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President, GAAPP

GINA 2022-Global Strategies

Global Asthma Burden

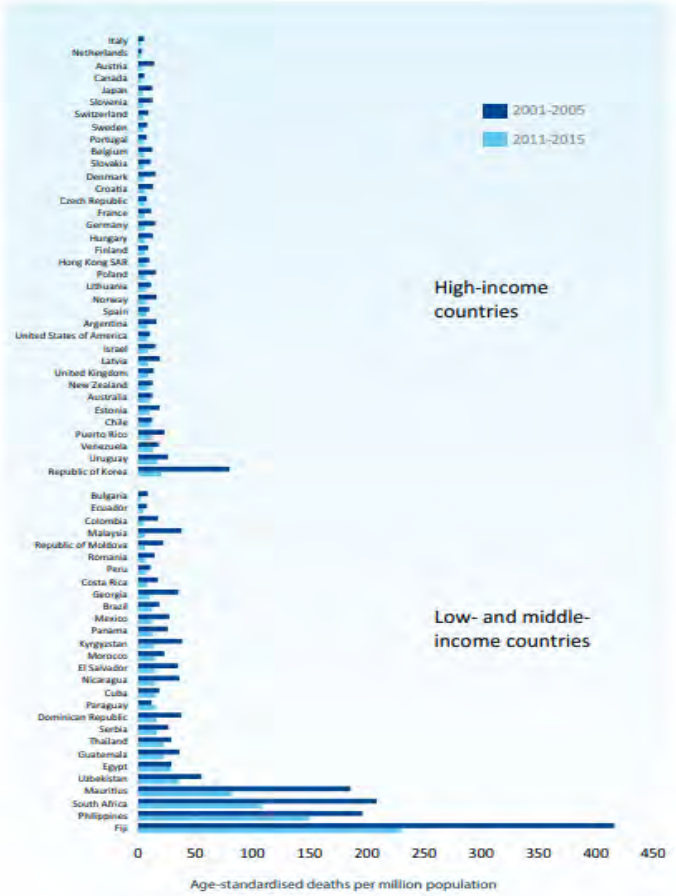
- >300 Million Living with Asthma
- 1 in 10 Children
- >50% uncontrolled
- >1000 people per day die from asthma
- Lack of access to EML's
- Climate Change Impact
- COVID Impact
- International Respiratory Coalition
- WHA Resolution

Figure 1:

Age-standardised asthma mortality rates (all ages) 2001-2005 and 2011-2015 by country, ranked by 2011-2015 age-standardised mortality rate within World Bank 2014 income group

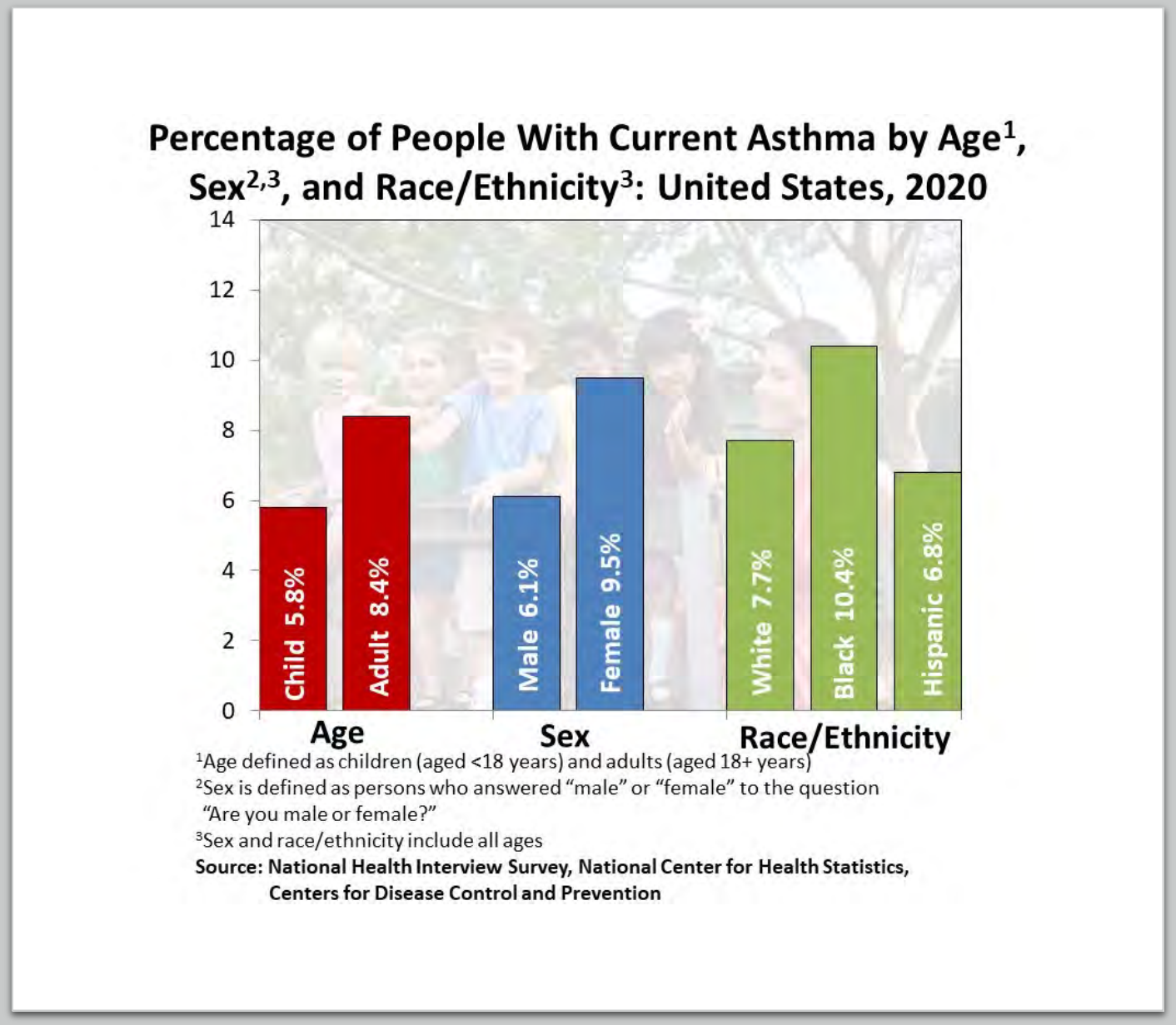
Source: WHO Mortality Database, October 2017 update. Population denominators from UN World Population Prospects, June 2017 revision. Income groups based on the World Bank 2014 definitions.

Restricted to countries where asthma is separately coded as a cause of death and rates were based on at least 100 asthma deaths (all ages) in each time period. Rates were calculated from the average number of deaths and average population for each 5-year age-group over the periods 2001-2005 and 2011-2015, using all available data for each country (the number of available years over each period ranged from 1 to 5). Rates were standardised to the age distribution of the World Standard Population.



CDC 2020 Data Highlights

- Asthma Prevalence on the Rise→25M
- Asthma Mortality Rose for first time in >20 years-4145
- 50% Below Poverty Limit



GINA treatment figure for adults and adolescents (≥12 years)

- Treatment options are shown in two tracks
  - This was necessary to clarify how to step treatment up and down with the same reliever
- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred strategy**
  - Preferred because of the evidence that using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and lung function
- **Track 2, with SABA as the reliever, is an 'alternative' (non-preferred) strategy**
  - Less effective than Track 1 for reducing severe exacerbations
  - Use Track 2 if Track 1 is not possible; can also consider Track 2 if a patient has good adherence with their controller, and has had no exacerbations in the last 12 months
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to continue to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- "Other controller options"
  - These have limited indications, or less evidence for efficacy and/or safety than Track 1 or 2 options
- Step 5
  - A new class of biologic therapy has been added (anti-TSLP)
  - A prompt added about the GINA severe asthma guide

Adults & adolescents 12+ years

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

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

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

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1
Take ICS whenever SABA taken

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed short-acting beta$_2$-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

Background - 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

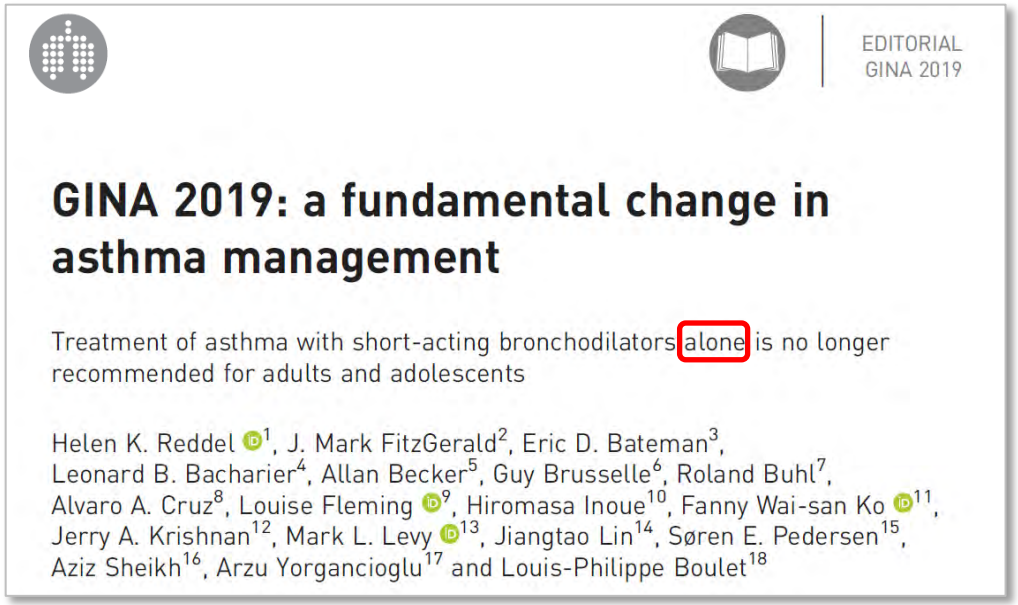
  } had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007; Bergstrom, 2008)*

- 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)*
- 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



EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

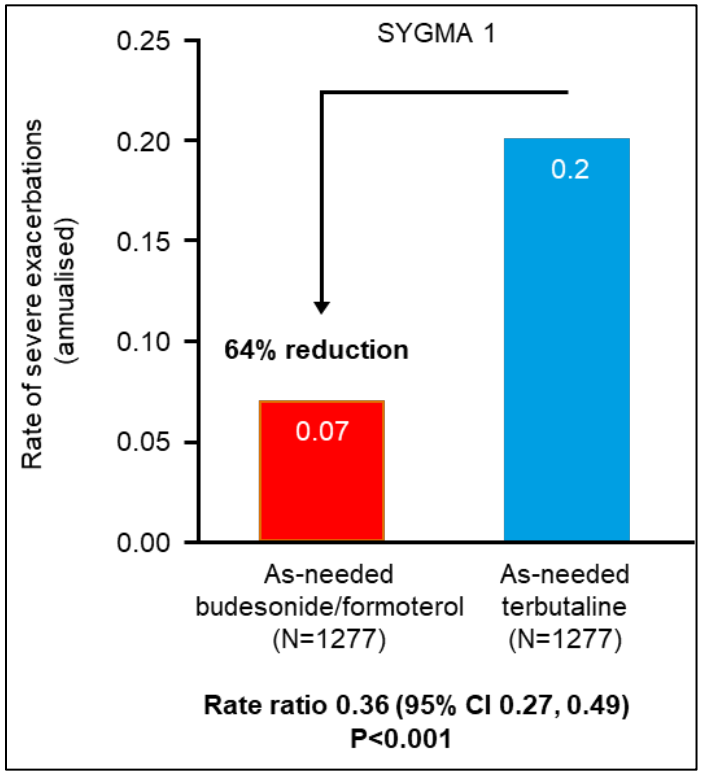
As-needed low dose ICS-formoterol in mild asthma (n=9,565)

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

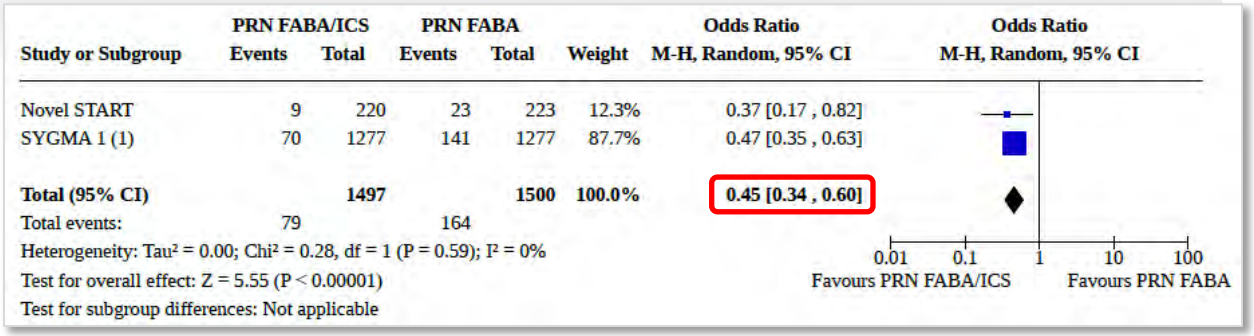


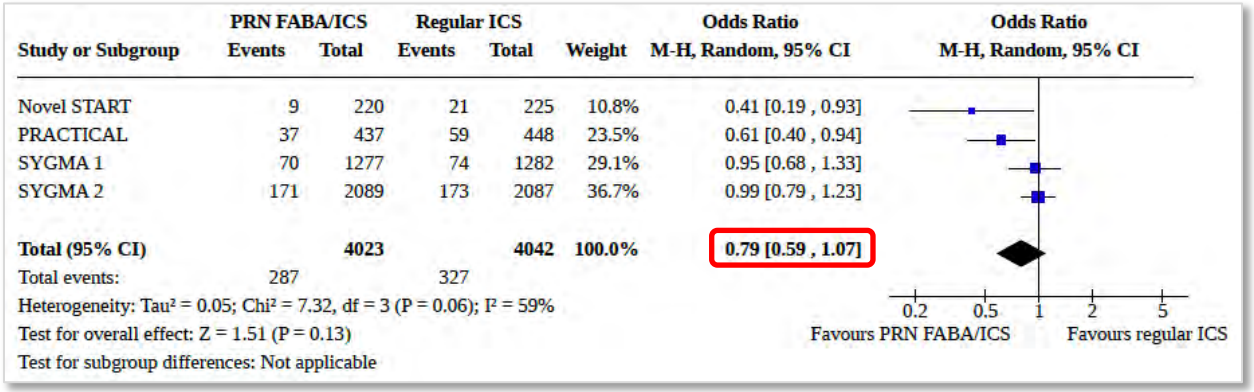
O'Byrne et al, NEJM 2018

*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





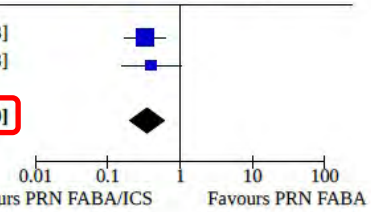
New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - 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			

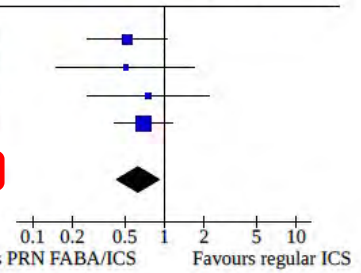
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
Test for subgroup differences: Not applicable



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

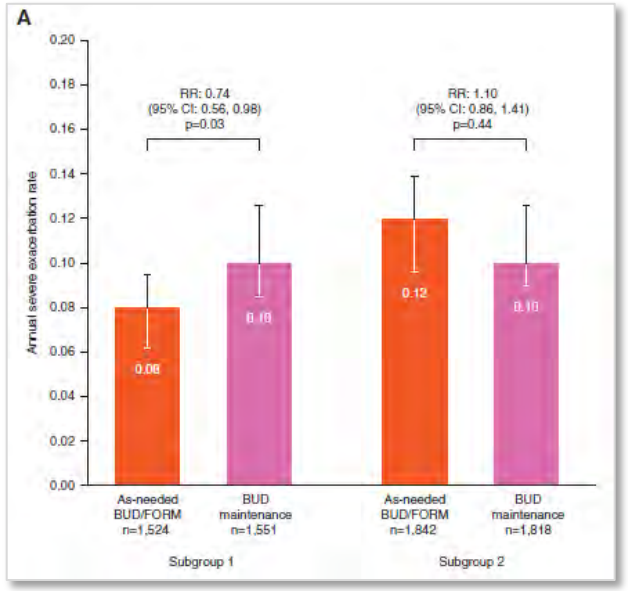
Study or Subgroup	PRN FABA/ICS Events	PRN FABA/ICS Total	Regular ICS Events	Regular ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	13	220	24	225	27.4%	0.53 [0.26 , 1.06]
PRACTICAL	4	437	8	448	9.3%	0.51 [0.15 , 1.70]
SYGMA 1	6	1277	8	1282	12.0%	0.75 [0.26 , 2.17]
SYGMA 2	25	2089	36	2087	51.3%	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

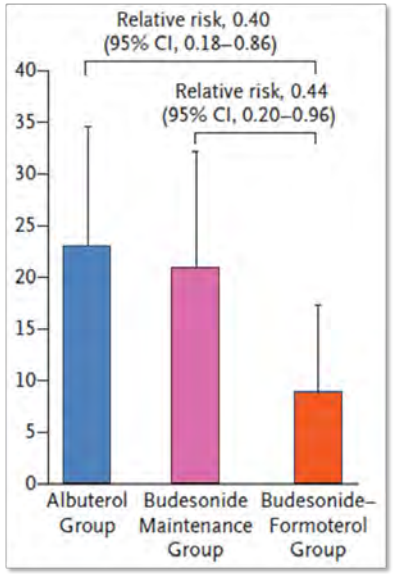


New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all 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
  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS
- 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

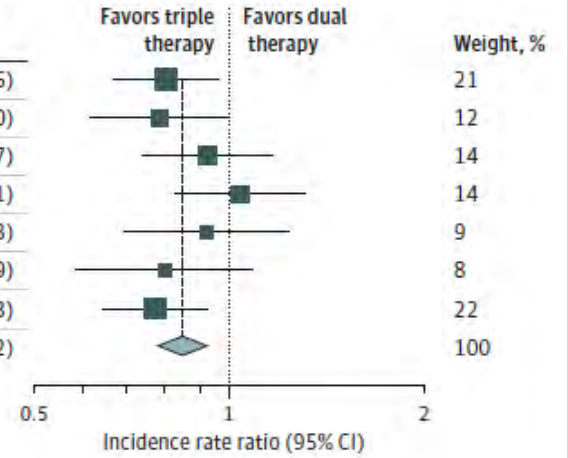


Beasley 2019

Other changes in medication recommendations for ≥12 years

- Long-acting muscarinic antagonists (LAMA) should not be used as monotherapy for asthma (i.e. without ICS) because of increased risk of severe exacerbations *(Baan, Pulm Pharmacol Ther 2021)*
- Adding LAMA to ICS-LABA: GRADE review and meta-analysis *(Kim, JAMA 2021)* confirms previous findings
  - Small increase in lung function (mean difference 0.08 L)
  - No clinically important benefits for symptoms or quality of life → don't prescribe for dyspnea
  - Modest overall reduction in exacerbations compared with ICS-LABA (risk ratio 0.83 [0.77, 0.90])

Source	Mean annualized exacerbation rate[a] Triple	Dual	Incidence rate ratio (95% CI)
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)



  - Patients with exacerbations should receive at least medium dose ICS-LABA before considering add-on LAMA
- Chromone pMDIs (sodium cromoglycate, nedocromil sodium) have been discontinued globally

Management of asthma in low- and middle-income countries

- 96% of asthma deaths are in low- and middle-income countries (LMIC) *(Meghji, Lancet 2021)*
  - Much of this burden is avoidable, especially with ICS *(e.g. Comaru, Respir Med 2016)*
  - Barriers include lack of access to essential medications, and prioritization of acute care over chronic care by health systems *(Mortimer, ERJ 2022)*
- Lack of access to affordable quality-assured inhaled medications *(Stolbrink, review for WHO 2022)*
  - Oral bronchodilators have slow onset of action and more side-effects than inhaled
  - OCS are associated with serious cumulative adverse effects (e.g. sepsis, cataract, osteoporosis) even with occasional courses *(Price, J Asthma Allerg 2018)*
- GINA supports the initiative by IUATLD towards a World Health Assembly Resolution on equitable access to affordable care for asthma, including inhaled medicines
  - In the meantime, if Track 1 is not available due to lack of access or affordability, Track 2 treatment may be preferable, although less effective in reducing exacerbations
  - If Track 2 options also not available, taking ICS whenever SABA is taken may be preferable to LTRA or maintenance OCS because of concerns about efficacy and/or safety
  - Greatest overall benefit at a population level would be from increasing access to ICS-formoterol

Key changes to GINA severe asthma guide in 2022

- Additional investigations
  - Consider screening for adrenal insufficiency if patient is on maintenance OCS or high dose ICS-LABA
  - For patients with eosinophils ≥300/µl, investigate for non-asthma causes including *Strongyloides* (often asymptomatic), before considering biologic therapy
  - For patients with hypereosinophilia, e.g. ≥1500/µl, investigate for conditions such as EGPA
- Assessment of inflammatory phenotype
  - If blood eosinophils or FeNO not elevated, repeat up to 3 times, at least 1–2 weeks after stopping OCS, or on lowest possible OCS dose
- Treatment options for patients with no evidence of Type 2 inflammation on repeated testing
  - Consider add-on treatment with LAMA or low-dose azithromycin if not already tried
  - Can also consider anti-IL4R* (if on maintenance OCS) or anti-TSLP* (but insufficient evidence with maintenance OCS)
- Consider maintenance OCS only as last resort, because of serious cumulative adverse effects

**Check local eligibility criteria for specific biologic therapies*

Key changes to GINA severe asthma guide in 2022 (continued)

- Anti-IL4R* (dupilumab) for severe eosinophilic/Type 2 asthma
  - Not suggested if blood eosinophils (current or historic) >1500/µl
  - Dupilumab now also approved for children ≥6 years with severe eosinophilic/Type 2 asthma, not on maintenance OCS *(Bacharier, NEJMed 2021)*
- Anti-TSLP* (tezepelumab) now approved for severe asthma (age ≥12 years)
  - Greater clinical benefit with higher blood eosinophils and/or higher FeNO
  - Insufficient evidence in patients taking maintenance OCS

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

**Check local eligibility criteria for specific biologic therapies; TSLP: thymic stromal lymphopoietin*

Other changes or clarifications in GINA 2022

- "Written" asthma action plans
  - Handwritten, printed, digital or pictorial instructions about what to do when asthma gets worse
  - Not just verbal instructions!
- Acute asthma in healthcare settings
  - At present, salbutamol (albuterol) is the usual bronchodilator in acute asthma management
  - Formoterol has similar efficacy and safety in ED studies *(Rodrigo, Ann Allerg Asthma Immunol, 2010)*
  - One study showed high dose budesonide-formoterol had similar efficacy and safety as SABA *(Balanag, Pulm Pharmacol Ther 2006)*
  - Patients admitted to hospital for an asthma exacerbation should continue, or commence, ICS-containing therapy
- Air filters can reduce fine particle exposure, but no consistent effect on asthma outcomes *(Park, Allergy Asthma Immunol Res 2021)*
- Use of e-cigarettes is associated with increased risk of respiratory symptoms and asthma exacerbations *(Cho, PLoSOne 2016; Wills, ERJ 2021)*

CDC EXHALE TECHNICAL PACKAGE

- **E** Education on asthma self- management
- **X** X-tinguishing smoking and second- hand smoke
- **H** Home visits for trigger reduction and asthma self- management education
- **A** Achievement of guidelines-based medical management
- **L** Linkages and coordination of care across settings
- **E** Environmental policies or best practices to reduce asthma triggers from indoor, outdoor and occupational sources

https://www.cdc.gov/asthma/exhale/index.htm

Topics to be addressed in future GINA reports

(Some were delayed from 2021 by COVID-19)

- Allergen immunotherapy for asthma
- Diagnosis, assessment and management of asthma in children 5 years and younger
- Further discussion about the definition of mild asthma, and assessment of symptom control
- Use of digital tools and communication in asthma management
- A pocket guide on management of severe asthma in children 6–11 years is in development
- Advice about COVID-19 and asthma will be updated as relevant new information emerges

- We will be seeking your feedback on how to improve GINA resources