Comparison of Asthma Guidelines

삼성서울병원 호흡기내과
임상 조교수 신 선 혜

Asthma guidelines

- GINA Global Strategy for Asthma Management and Prevention (2021)
- 대한결핵 및 호흡기학회 천식 진료지침 (2020)
- National Asthma Education and Prevention Program (NAEPP) Coordinating Committee Asthma Management Guidelines (2020)
- BTS/SIGN British guideline on the management of asthma (2019)
- National Institute for Health and Care Excellence (NICE) guidelines (2017, last update in 2021)

Causes for the differences

- Difference in time lines for the updates
- Selection of key questions
- Scope / Methodology
- National regulations

Guideline methodologies

Approach	GINA	NAEPP
Direction	Global	National
Composition	Primarily asthma specialists from representative countries	Multidisciplinary combination of asthma specialists, primary care physicians, health policy experts, implementation and dissemination experts, methodologists, and other health care personnel
Target audience	Template for application for countries to develop their national approach	Provides specific guidance for the national approach in the United States
Challenges	Must consider developing countries with limited resources and access to asthma specialists	Must consider federal regulations as limitations of recommendations
Revision	Annually	Periodically
Scope	Living document approach that regularly reviews current literature and decides on modifications	Decides which questions to address and then evaluates the literature to make evidence-based recommendations using detailed GRADE methodology
Support system	Previously from restricted education grants from the pharmaceutical industry and now from product sales. Commercial sales allow for widespread advertising with multiple products, such as handbooks, documents, and teaching slides	NIH-directed development and distribution, with limited budget for distribution

White J, et al. *Thorax* 2018;73:293–297

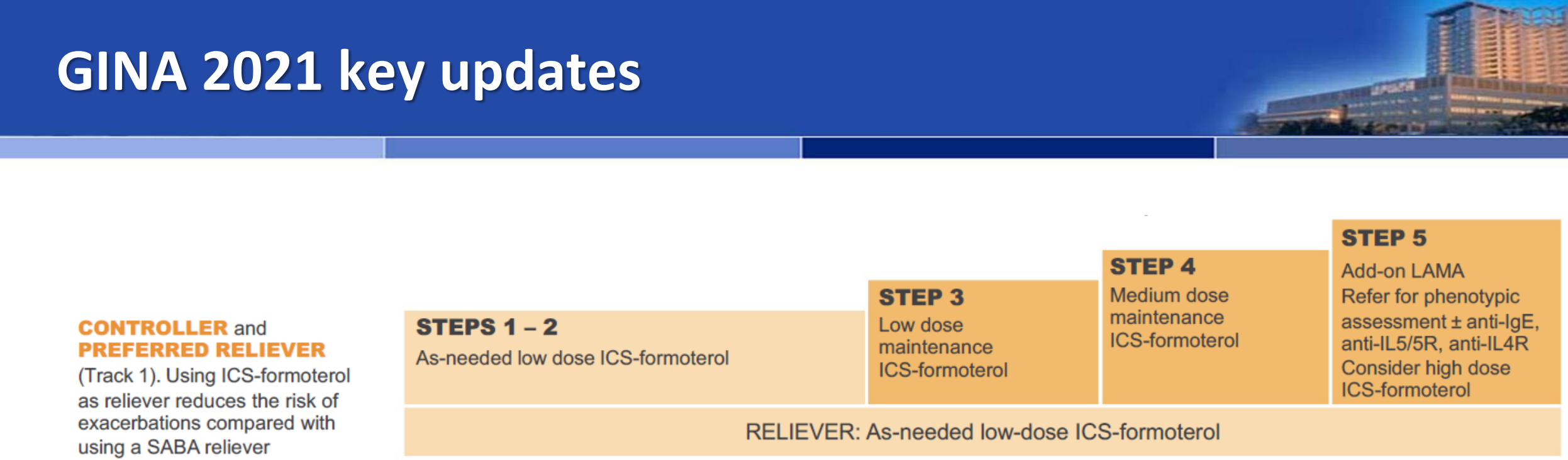
Szefler et al. *JACI* 2020;146:6:1275-1280

Contents

- Brief review of GINA 2021 updates

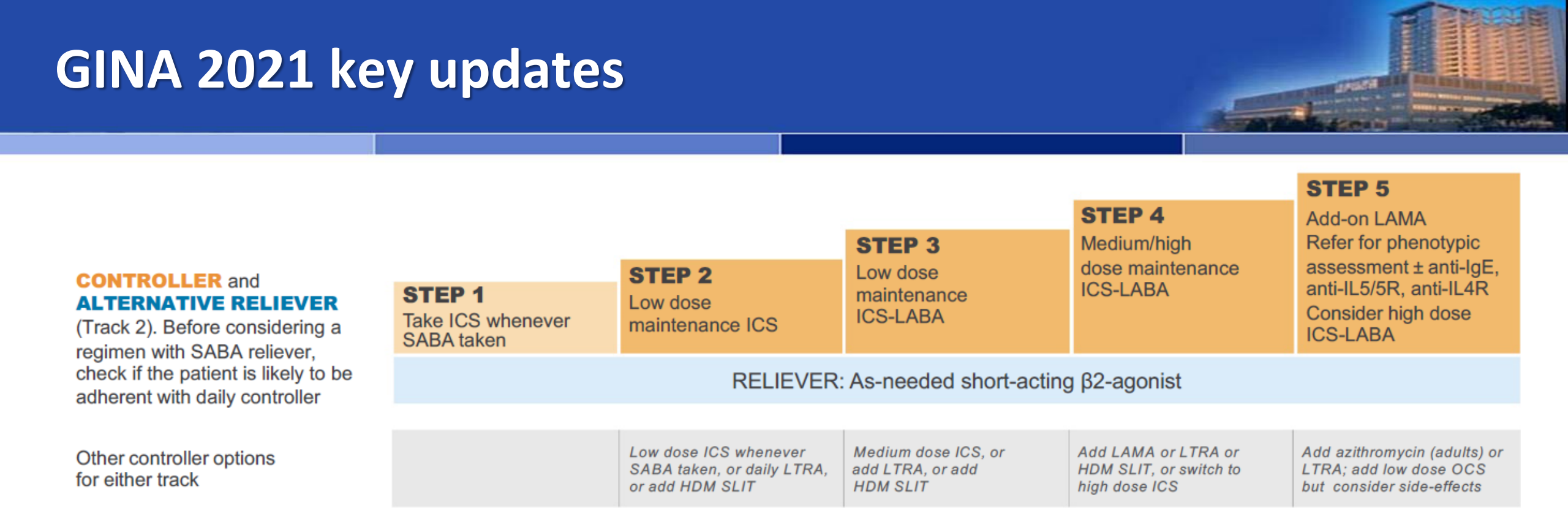
- Mild asthma : As-needed ICS-Formoterol (*vs.* Low-dose ICS + prn SABA)
- Moderate asthma : MART with ICS-Formoterol (*vs.* Regular dosing ICS-LABA + prn SABA)
- Severe asthma : Add-on LAMA (*vs.* High-dose ICS-LABA) and biologics

GINA 2021 key updates



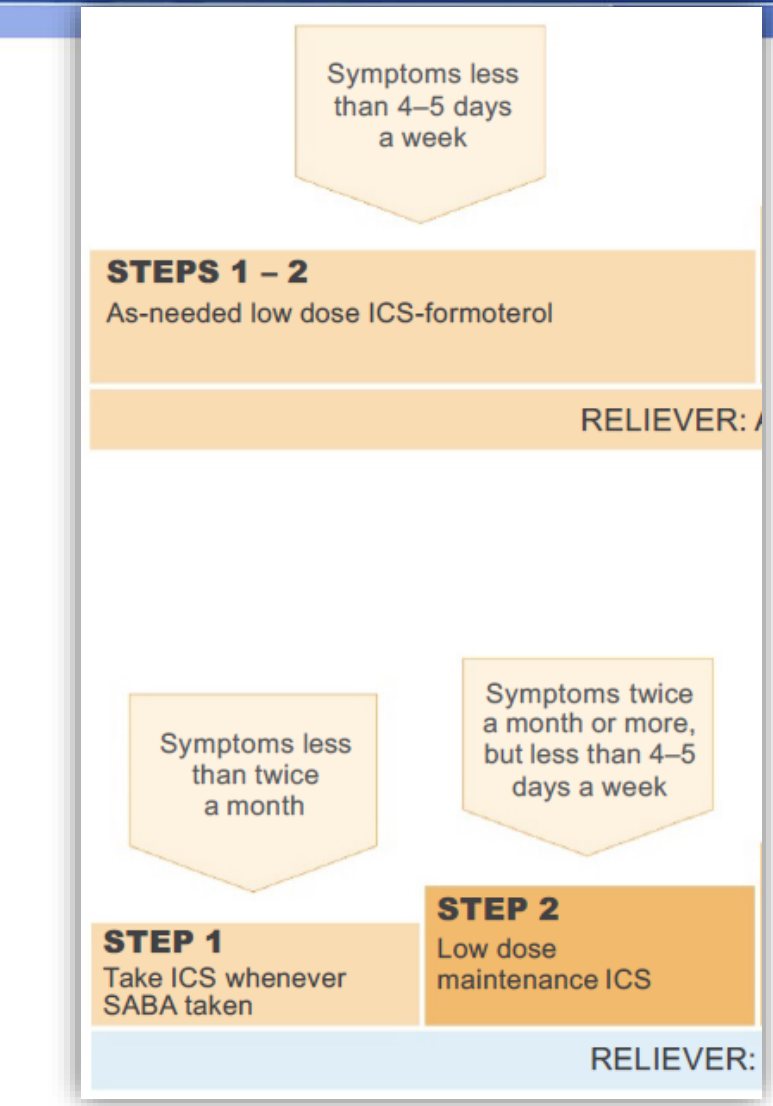
- **Track 1 (Preferred)** : Low dose ICS-formoterol as the reliever
  - ✓ Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and similar lung function
  - ✓ In steps 3-5, MART with ICS-formoterol (cannot use a different ICS-LABA for controller)

GINA 2021 key updates

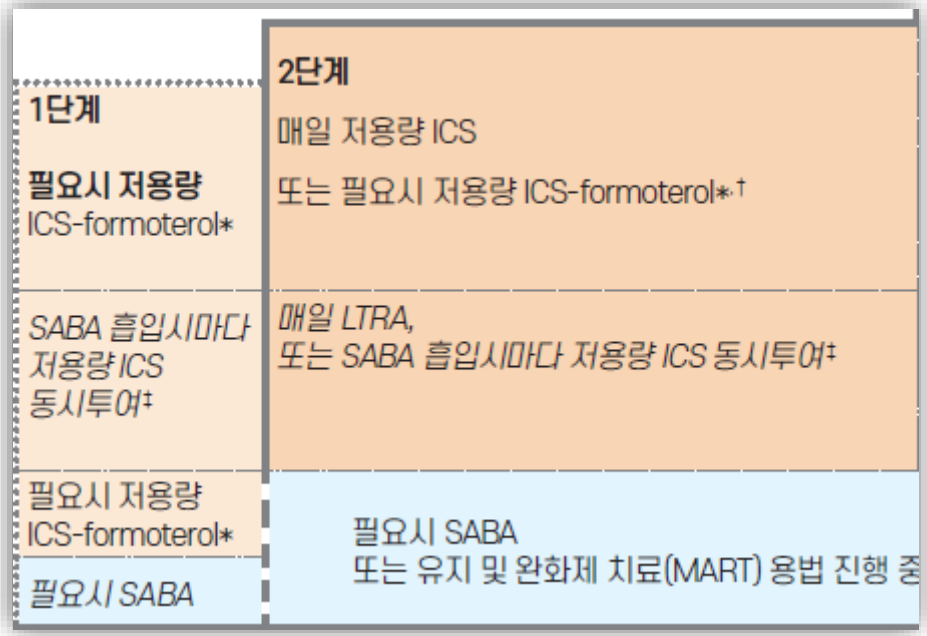


- **Track 2 (Alternative)** : SABA as the reliever
  - ✓ If track 1 is not possible or not preferred by a patient with no exacerbation on current controller therapy & <u>Patient is likely to adherent with daily controller</u>
  - ✓ In step 1, ICS right after SABA
  - ✓ In steps 2-5, ICS-containing controller everyday + SABA alone reliever

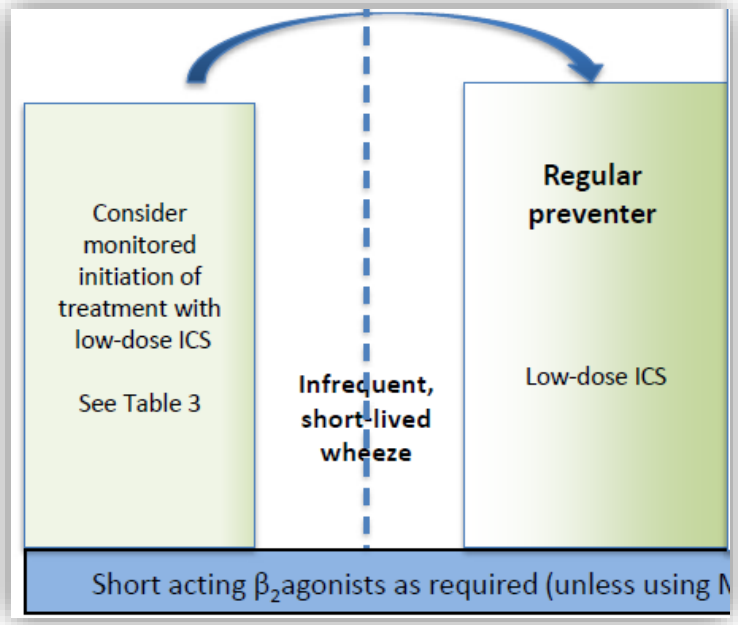
Mild Asthma



GINA

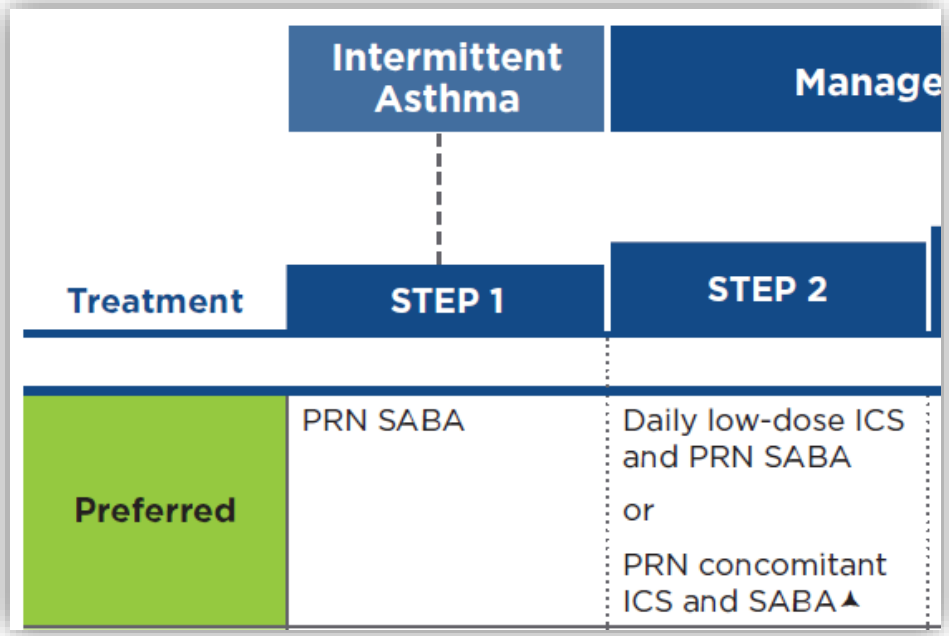


KATRD



BTS/SIGN

Mild Asthma



NAEPP

1.6.1 Offer a short-acting beta$_2$ agonist (SABA) as reliever therapy to adults (aged 17 and over) with newly diagnosed asthma. [2017]

1.6.2 For adults (aged 17 and over) with asthma who have infrequent, short-lived wheeze and normal lung function, consider treatment with SABA reliever therapy alone. [2017]

1.6.3 Offer a low dose of an ICS as the first-line maintenance therapy to adults (aged 17 and over) with:

- symptoms at presentation that clearly indicate the need for maintenance therapy (for example, asthma-related symptoms 3 times a week or more, or causing waking at night) **or**
- asthma that is uncontrolled with a SABA alone. [2017]

NICE

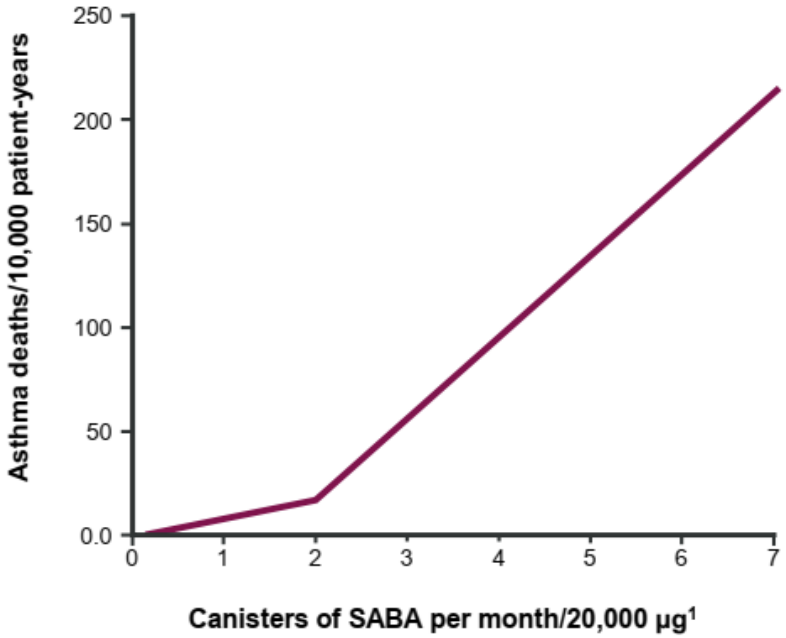
STEP 1 & 2 distinction

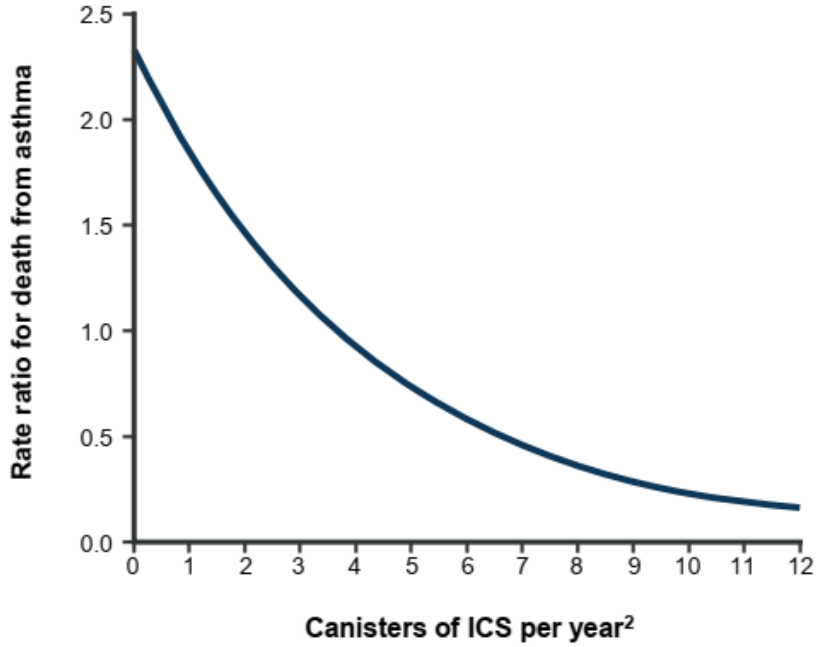
- GINA (track 1) does not distinguish between so-called “intermittent” and “mild persistent asthma”
  - Historical distinction was arbitrary, not evidence-based
  - Based on an untested assumption that “patients with symptoms twice a week or less” would not benefit from ICS

- But, intermittent asthma are still at risk of severe exacerbation → this risk is reduced by ICS.
- Exacerbation triggers (viruses, pollens, pollution, poor adherence) are unpredictable.

STEP 1 : as needed SABA alone?

- NAEPP and NICE recommends “SABA as needed” for intermittent asthma (STEP 1)
- SABA-only treatment → Overuse of SABA + Underuse of ICS → Risk of adverse clinical outcomes
- Starting with SABA *trains* the patient to regard it as their primary asthma treatment

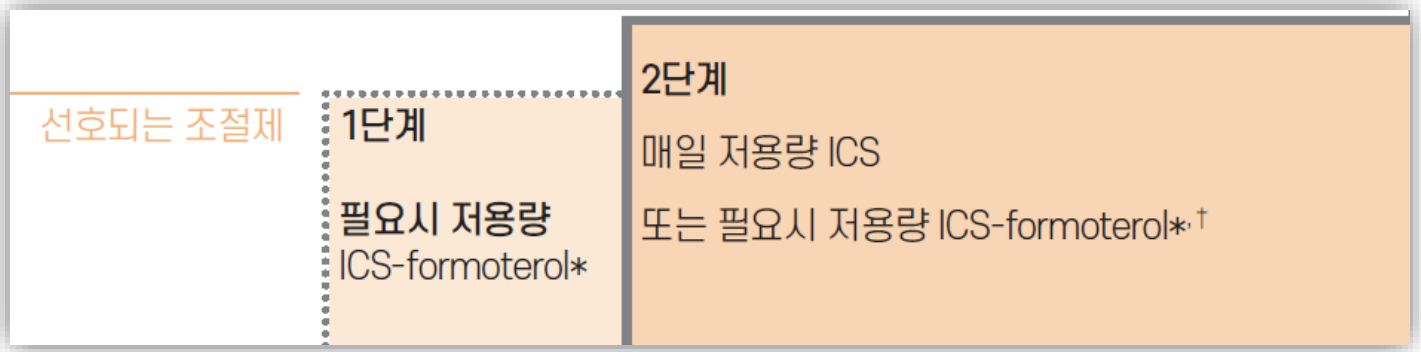




1. Suissa S et al. *Am J Respir Crit Care Med* 1994;149:604–10
2. Suissa S et al. *N Engl J Med* 2000;343:332–6

STEP 2 : as-needed ICS-Formoterol

- GINA recommends as-needed ICS-Form (**preferred** to low-dose ICS maintenance + prn SABA)
- NAEPP & BTS : No recommendations were made (not addressed in the latest updates)
- KATRD : 필요시 저용량 ICS-formoterol 에 대하여 충분한 주의가 필요함

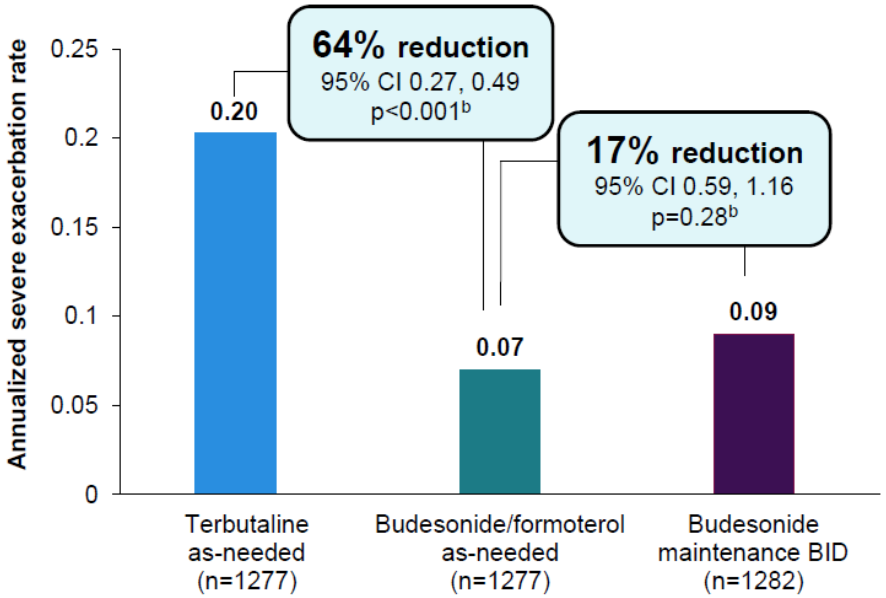


†국내 천식 진료 실정상 천식 치료 관련 순응도 저하 및 경과 관찰 등의 천식 관리 어려움과 진행 중인 천식 적정성 평가 결과에 부정적 영향을 미칠 가능성이 있어 충분한 주의가 필요함.

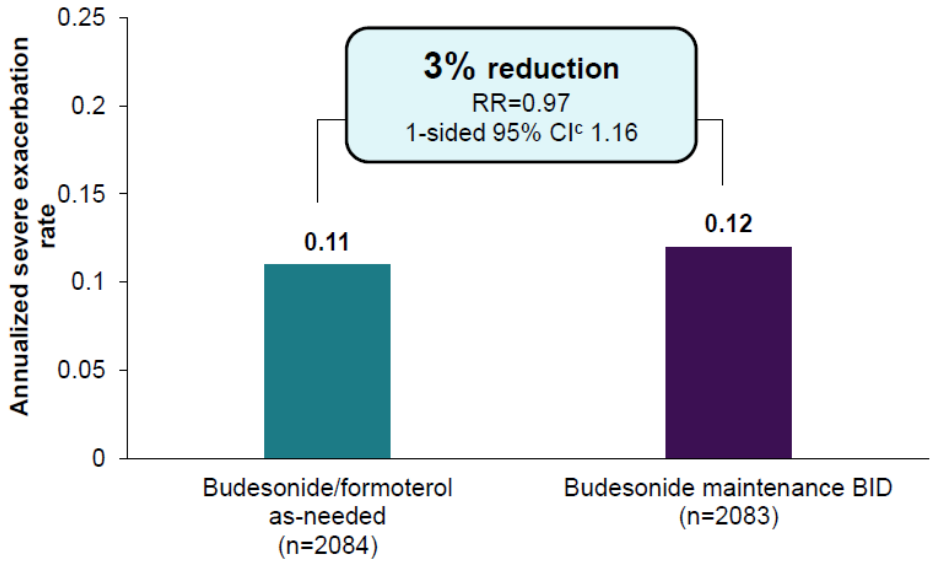
지속방문 환자비율
ICS 처방 환자비율

STEP 2 : as-needed ICS-Formoterol

- **SYGMA studies** : as-needed ICS-Form showed comparable risk of severe AE, to low-dose ICS maintenance, with a significantly lower steroid load.



SYGMA 1

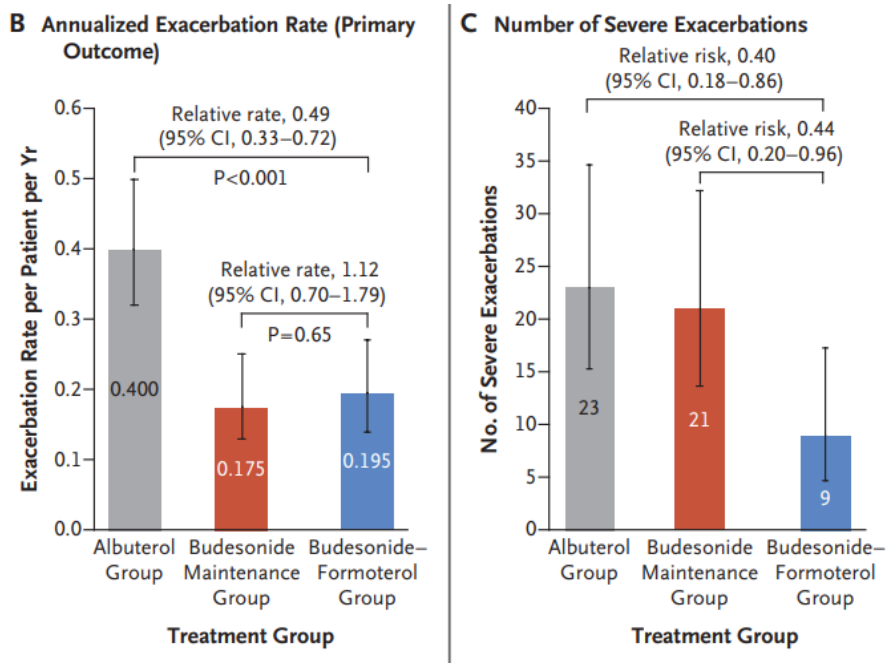


SYGMA 2

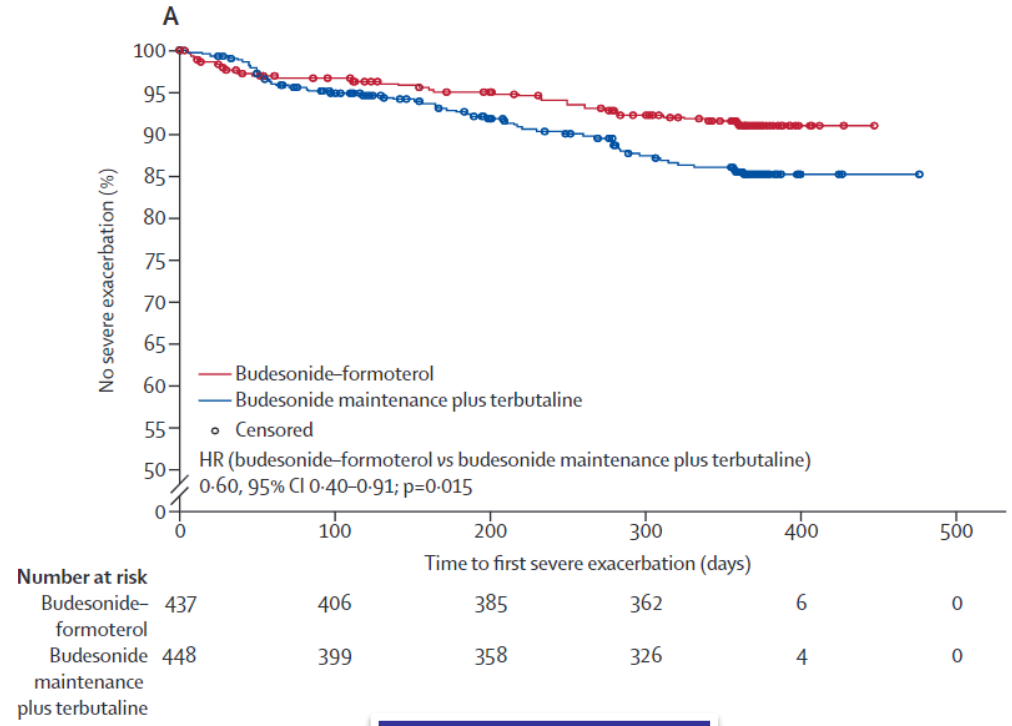
O'Byrne PM, et al. *N Engl J Med* 2018;378: 1865-1876
Bateman ED, et al. *N Engl J Med 2018*;378:1877-1887

STEP 2 : as-needed ICS-Formoterol

- **Novel START & PRACTICAL** : Open-label study with single inhaler → Superior to BUD maintenance



Novel START

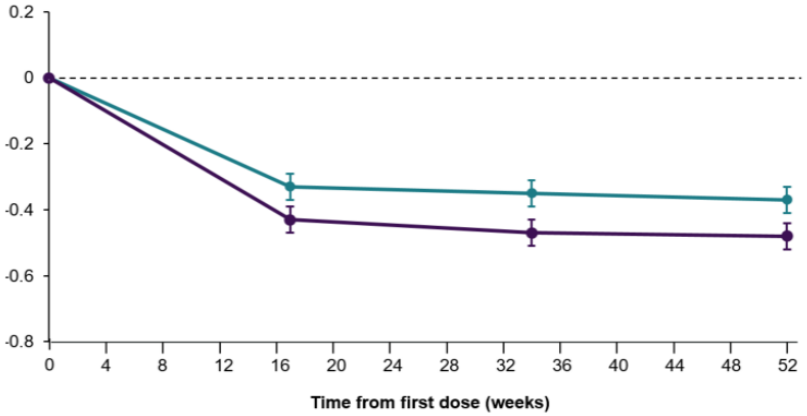


PRACTICAL

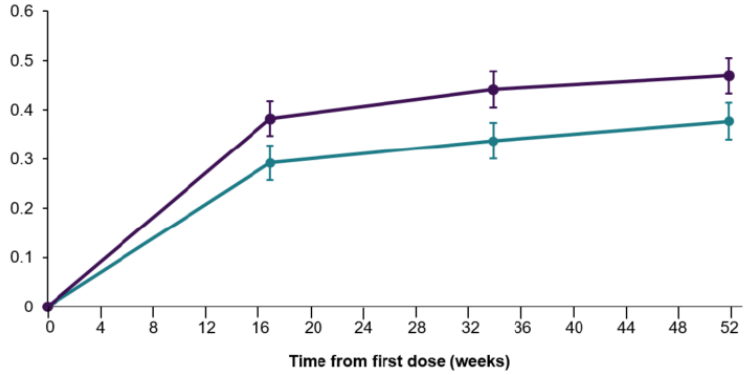
Beasley R, et al. *N Engl J Med* 2019; 380:2020-2030
Hardy J, et al. *Lancet* 2019; 394: 919–28

STEP 2 : as-needed ICS-Formoterol

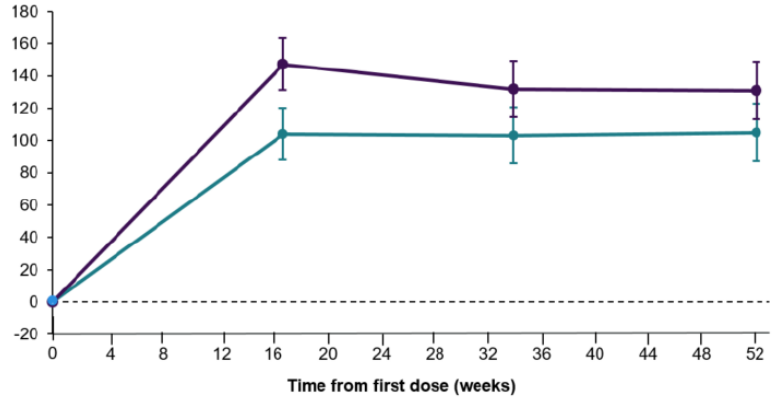
- However, **Low-dose ICS maintenance** > **as-needed ICS-Form**
  - ✓ Symptom control (ACQ-5) : Small difference (-0.1)
  - ✓ Quality of life (AQLQ) : Small difference (0.1)
  - ✓ Lung function improvement (FEV_1) : Small difference (30 ~ 50 mL)



Symptom



QoL



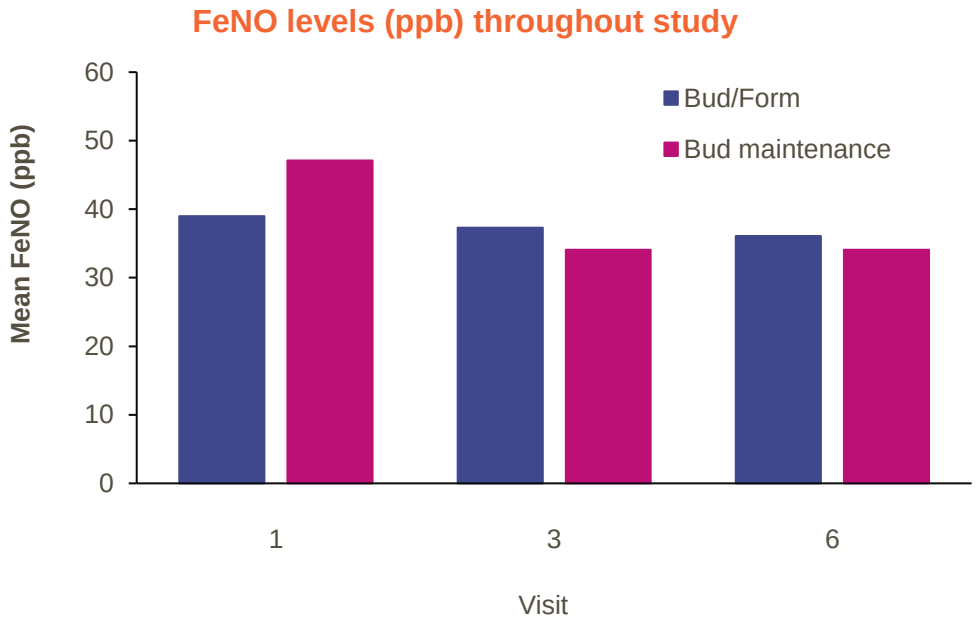
FEV_1

Bateman ED, et al. *N Engl J Med 2018*;378:1877-1887

STEP 2 : as-needed ICS-Formoterol

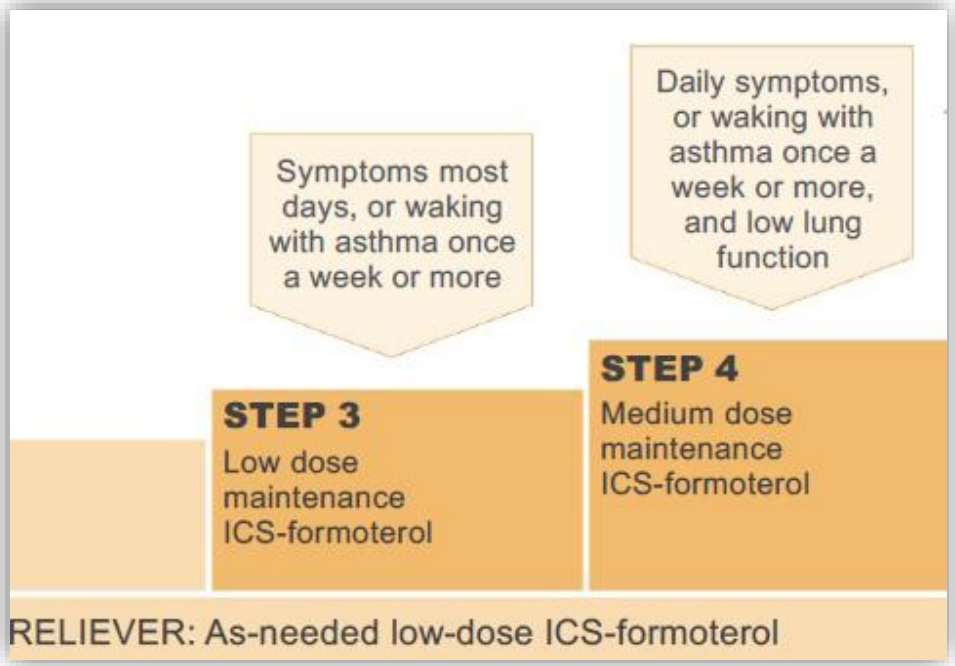
- Other issues with as-needed ICS-Formoterol
  - ✓ Rely on patient's accurate perception of asthma symptoms → Patients may over- or under- perceive
  - ✓ Ongoing inflammation even when symptoms are not present

    : Control of airway inflammation (FeNO in PRACTICAL study : median 5 PPB difference)[1]



1. Hardy J, et al. *Lancet* 2019; 394: 919–28

STEP 3-4 : MART with ICS-Formoterol

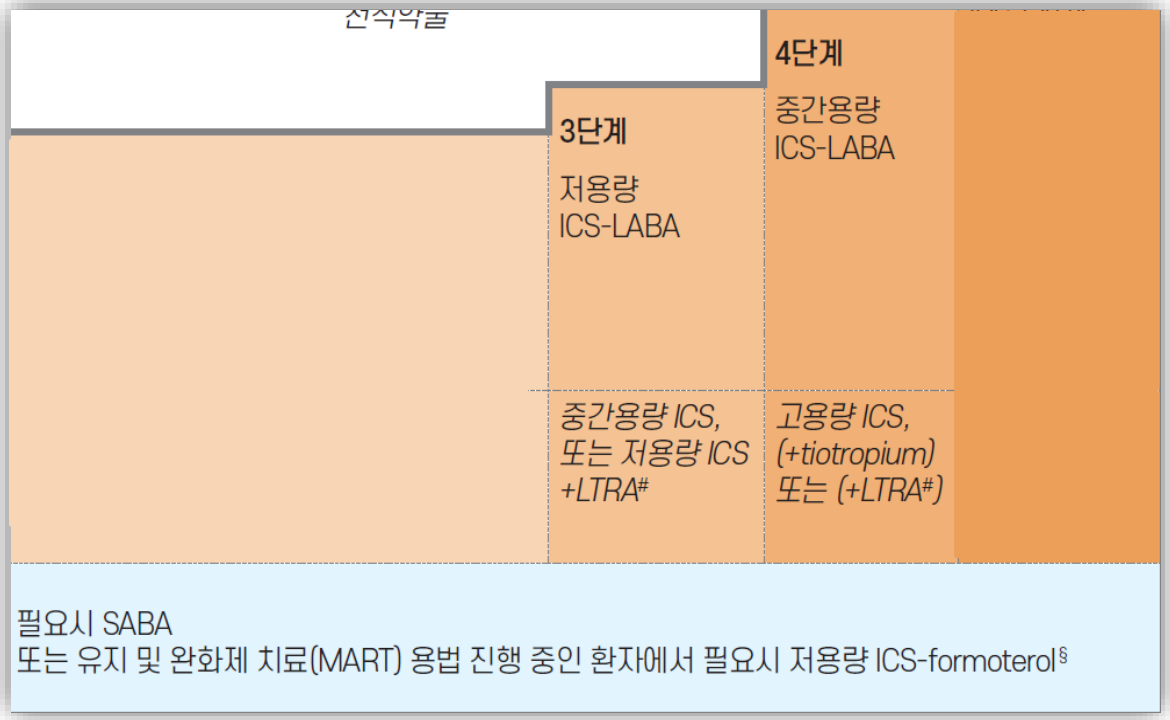


GINA

STEP 3	STEP 4
Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲

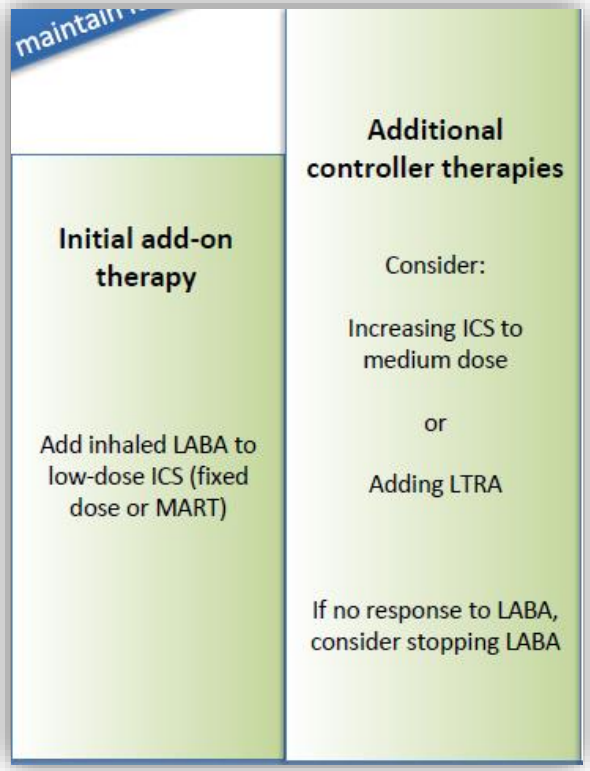
NAEPP

STEP 3-4 : MART with ICS-Formoterol



§저용량 ICS-form은 bud-form or BDP-form 유지 및 완화제 치료 (SMART 혹은 MART)의 경우 가능

KATRD



BTS/SIGN

STEP 3-4 : MART with ICS-Formoterol

- GINA & NAEPP recommends MART with ICS-Form (**preferred** to same or higher dose ICS-LABA + prn SABA)
  - ✓ Should not be used in patients taking different ICS-LABA for their controller therapy
  - ✓ Maintenance ICS-LABA does not need to be changed, if it is giving adequate control
  - ✓ Uncontrolled → Maintenance ICS-LABA should be changed to MART before increasing to a higher step

- KATRD & BTS : "low- or medium-dose ICS-LABA + prn SABA" **or** "MART with ICS-Form"

- 악화 병력이 있는 환자에서 규칙적 흡입스테로이드-흡입지속성베타작용제와 및 필요시 흡입속효성베타작용제 사용보다 흡입스테로이드-formoterol의 유지 및 완화 요법을 권고한다(근거수준: 높음, 권고강도: 강함).

- NICE : uncontrolled with low dose ICS-LABA (+/- LTRA) → change to MART (low to medium dose)

STEP 3-4 : MART with ICS-Formoterol

- Maintenance and reliever therapy (MART)
  - Only used with formoterol as LABA
  - Formoterol : rapid onset, can be used more than twice daily (every 4 hr, up to 12 puffs = 54mcg)
  - Primarily used with budesonide as ICS (beclomethasone in one study)

STEP 3-4 : MART with ICS-Formoterol

- MART vs. higher-dose ICS + prn SABA
  - Three large RCTs[1-3] (N = 4662) : MART with bud-form 160/9 to 320/9 vs. daily budesonide 320 to 640
  - Asthma exacerbation : RR 0.6 (0.53 – 0.68)
  - Asthma control (not validated measurements) : significantly favored MART
  - Overall ICS/OCS doses : significantly lower with MART

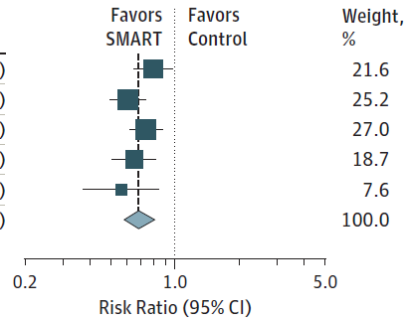
1. O'Byrne et al. *AJRCCM* 2005;171:129-36.
2. Rabe et al. *Chest* 2006;129:246-56.
3. Scicchitano et al. *Curr Med Res Opin* 2004;20:1403-18.

STEP 3-4 : MART with ICS-Formoterol

- MART vs. same-dose ICS-LABA

Source	SMART Group Total No. of Participants	SMART Group No. With Event	Control Group Total No. of Participants	Control Group No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
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: $t_4 = -6.44$, $P < .001$



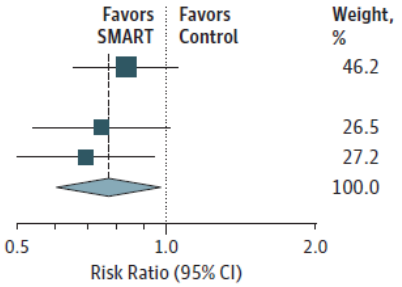
Severe exacerbation : RR 0.68

- ✓ Asthma control (ACQ-5) improved in only one blind RCT
- ✓ No significant differences in deaths, lung function, rescue med

- MART vs. higher-dose ICS-LABA

Source	SMART Group Total No. of Participants	SMART Group No. With Event	Control Group Total No. of Participants	Control Group No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)
Kuna et al,[33] 2007						
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$



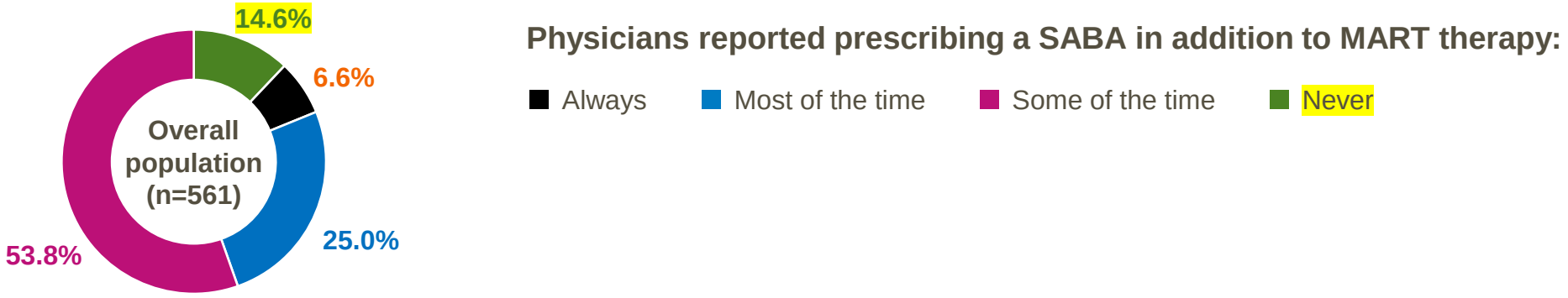
Severe exacerbation : RR 0.77

- ✓ No significant differences in asthma control, QoL, deaths, lung function, rescue med

Sobieraj et al. *JAMA.* 2018;319(14):1485-1496

STEP 3-4 : MART with ICS-Formoterol

- Issues with MART
  - MART is not currently approved by US FDA
  - Prescription of SABA with MART regimen



  - No comparison was made with once-daily ICS/LABA

Champman et al. *Respiratory Med.* 2021; 186:106524

STEP 5 : Add-on therapy

STEP 5

Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol

STEP 5

Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA

Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects

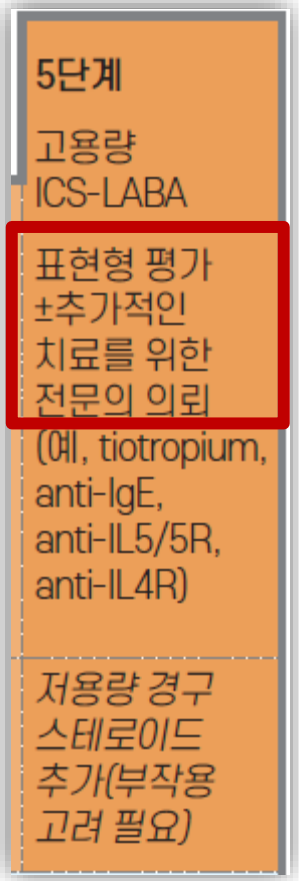
GINA

STEP 5	STEP 6 ■
Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

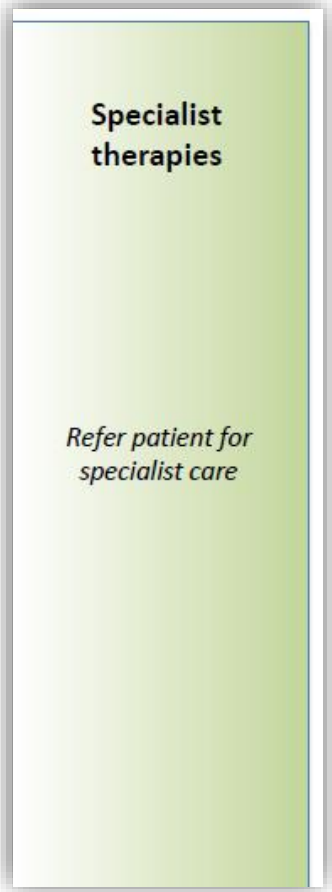
NAEPP

STEP 5 : Add-on therapy

선호



KATRD



BTS/SIGN

If asthma control remains inadequate on medium-dose (adults) or low-dose (children) of inhaled corticosteroid plus a long-acting β_2 agonist or a leukotriene receptor antagonist, the following interventions can be considered:

- increase the inhaled corticosteroids to high dose (adults)/ medium dose (children 5–12 years)* *or*
- add a leukotriene receptor antagonist (if not already trialled) *or*
- add tiotropium (adults) *or*
- add a theophylline.

Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden.

Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden.

STEP 5 : Add-on therapy

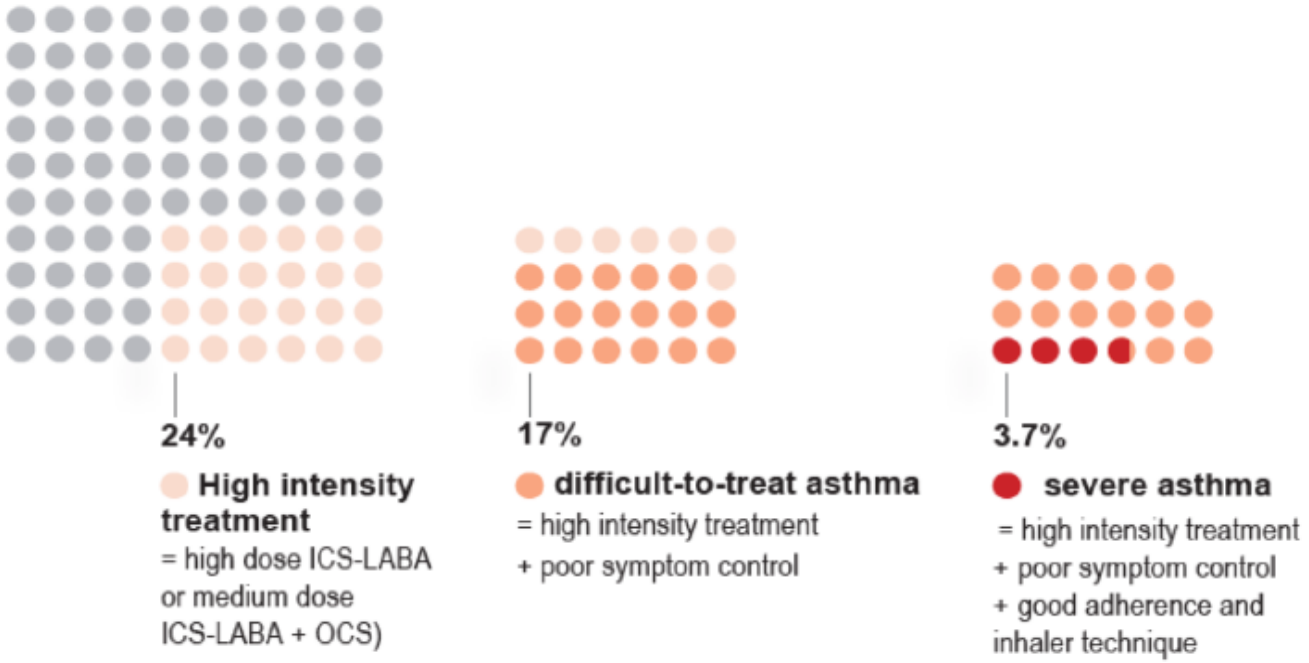
- GINA & NAEPP recommends adding LAMA to ICS-LABA (preferred to refer or high dose ICS-LABA)
  - ✓ Tiotropium SMI or Triple combinations (age ≥ 18 years)
  - ✓ Ensure that patient receives sufficient ICS (at least medium ICS-LABA) before adding a LAMA
  - ✓ GINA discuss biologics in severe asthma in detail, but not covered in NAEPP

- KATRD recommends specialist referral for phenotypic assess & add-on therapy (preferred)
  - ✓ Alternatives : High dose ICS-LABA, Tiotropium SMI (no other LAMA), Azithromycin, Biologics

- BTS recommends specialist therapies
  - ✓ High dose ICS-LABA, LTRA, Tiotropium SMI, Theophylline, Biologics

STEP 5 : Severe asthma in GINA

- Definition : uncontrolled despite adherence with optimized high dose ICS-LABA or that requires high dose ICS-LABA to remain controlled



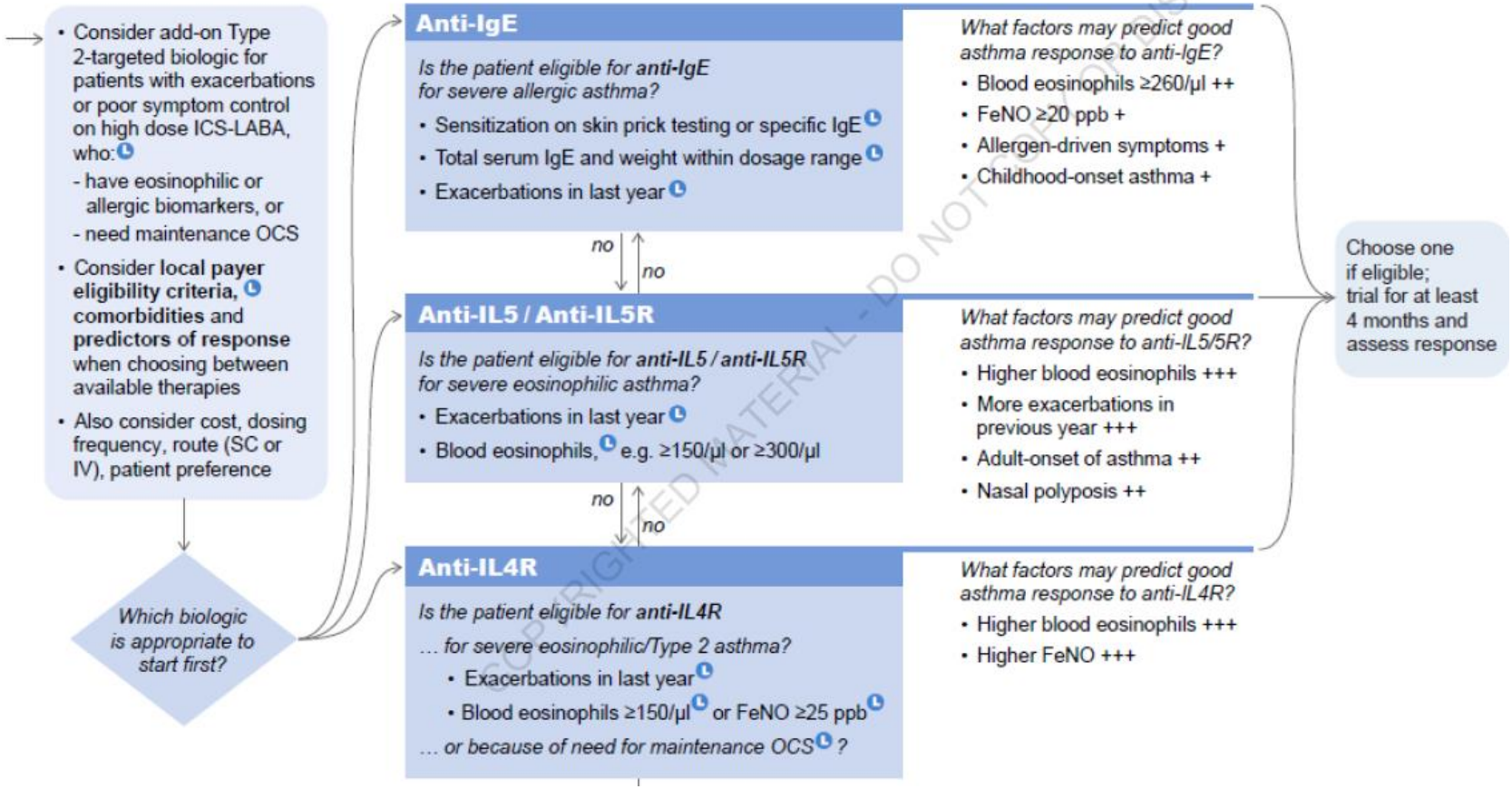
Hekking et al. *JACI* 2015; 135(4): 896-902

STEP 5 : Severe asthma in GINA

- Assessment for type 2 inflammation in patients taking high dose ICS or daily OCS
  - Blood eosinophils ≥ 150/µL
  - FeNO ≥ 20 ppb
  - Sputum eosinophils ≥ 2%
  - Asthma is clinically allergen-driven
- Tests should be performed before starting OCS or on the lowest possible OCS
- Repeat blood eosinophils and FeNO up to 3 times before assuming asthma is non-Type 2

STEP 5 : Severe asthma in GINA

- GINA included a greater evidence on biologic-specific advices



Summary

- Reason for the differences among major guidelines

  : Difference in time lines, key questions, scope / methodologies, national regulations

- Key differences (preference) in pharmacologic treatment
  - Mild asthma : As-needed ICS-Formoterol (*vs.* Low-dose ICS + prn SABA)
  - Moderate asthma : MART with ICS-Formoterol (*vs.* Regular dosing ICS-LABA + prn SABA)
  - Severe asthma : Add-on LAMA (*vs.* High-dose ICS-LABA) and biologics

경청해 주셔서 감사합니다.