Optimal therapy for treatment in all severity of Asthma

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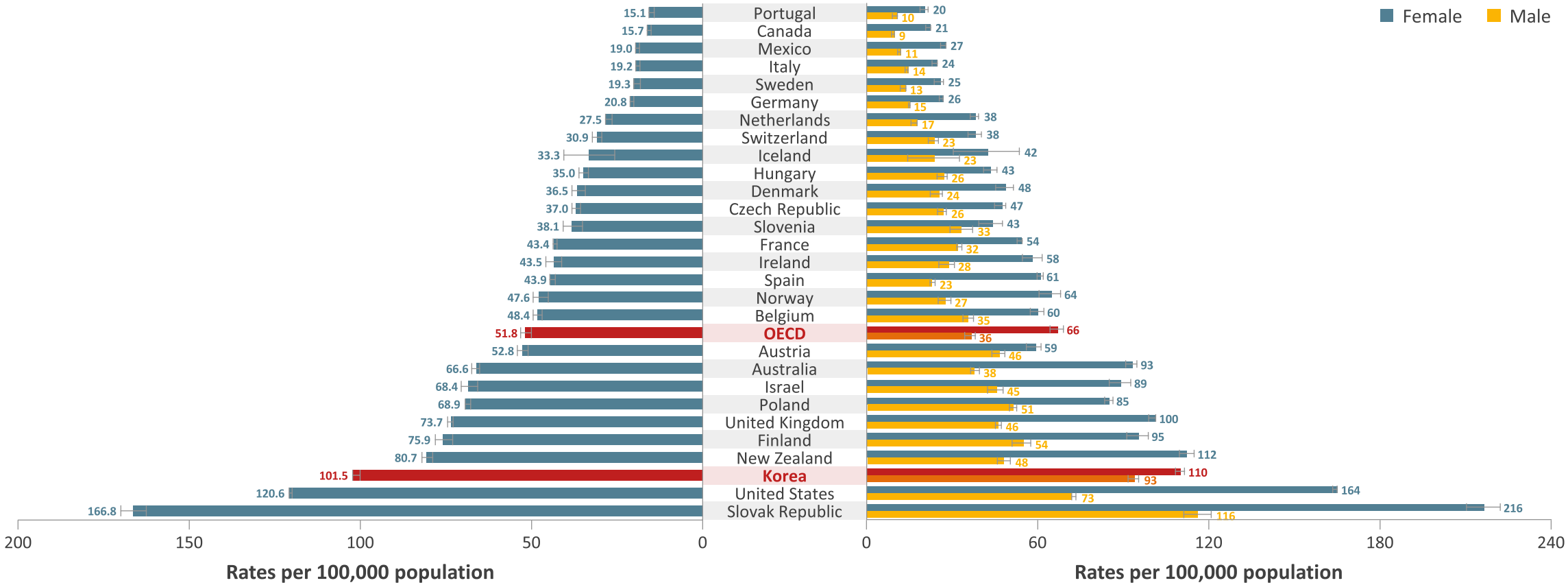
Outline

- Basics for Treatment Strategy in Asthma
  - Present data of asthma in Korea
  - Real World data of SABA use of asthma
  - Treatment tracks in updated GINA guideline
  - Roles of ICS/Formoterol

한국에서는 천식 치료가 잘 이루어지고 있을까요?
한국은 OECD 국가 평균보다 천식으로 인한 입원률 2배를 보이고 있습니다.

5.1.1 Asthma hospital admission rates, population aged 15 and over, 2009 (or nearest year)



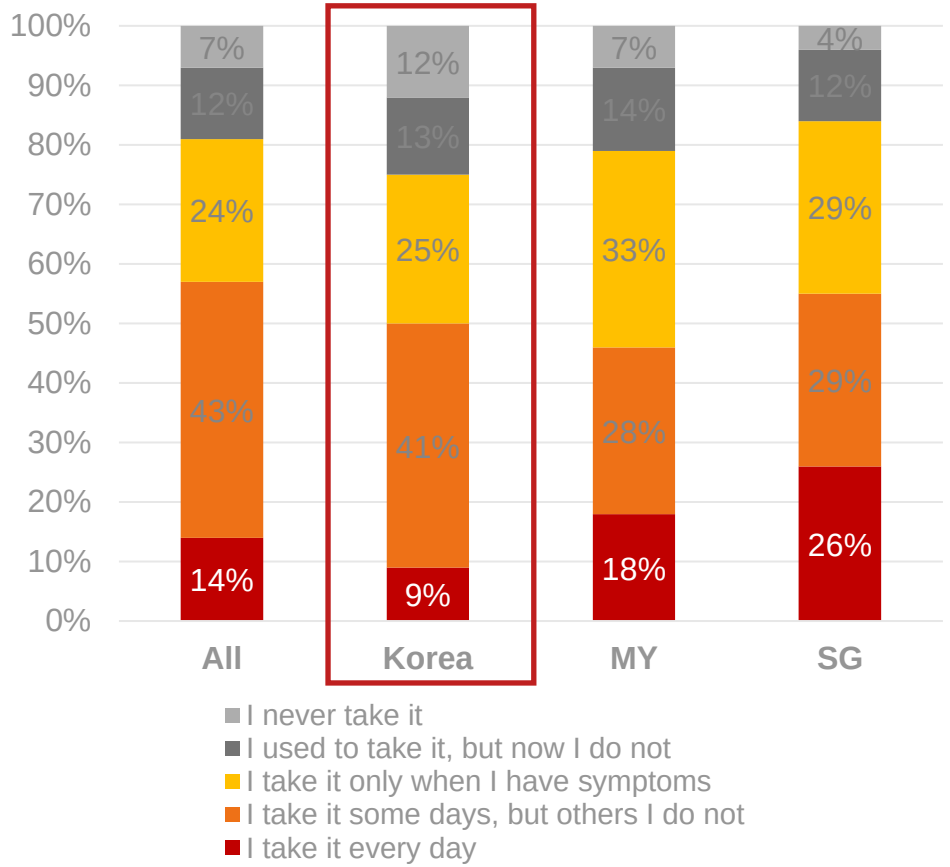
Note: Rates are age-sex standardized to 2005 OECD population. 95% confidence intervals are represented by ⊢⊣.

http://dx.doi.org/10.1787/888932315602

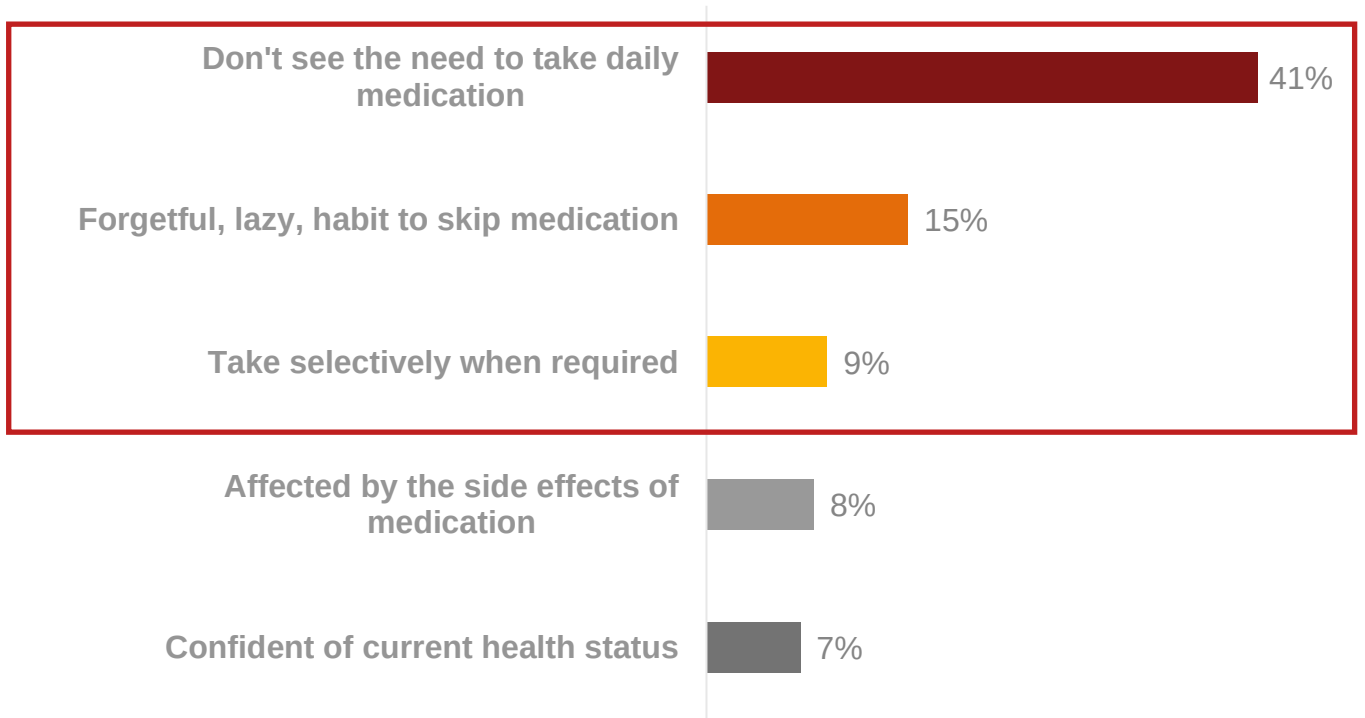
1. Health at a Glance 2011: OECD Indicators (available at: https://www.oecd.org/els/healthsystems/49105858.pdf, accessed on Jul 2019);

한국에서 Controller Inhaler 를 매일 사용하는 환자 비율은 단지 9% 였고, 증상이 있을 때에만 Inhaler 를 사용하려는 경향을 보였습니다.

Patients' perceptions of asthma control



Reasons for non-adherence to Controller Inhaler



REALISE study; Online survey of 2,467 patients with asthma from 8 Asian countries

Data are shown as percentage of all respondents with a controller inhaler (n=1072).
Q: Which of the statement best describes how you take your regular asthma treatment (controller inhaler, which is usually brown, orange, red, purple, or pink)? Respondents could select from the identified choices.

*REcognise Asthma and LInk to Symptoms and Experience (REALISE)

1. Price D et al., J Asthma Allergy 2015; 8:93-103

그리고 대부분의 천식 환자들은 즉각적으로 빠른 증상 조절 효과를 보이는 Reliever 의 사용을 선호합니다.

- **40%** 의 환자들은 증상 조절이 잘 되면 치료제를 매일 복용할 필요가 없다고 생각합니다[1].
- **90%** 의 환자들이 빠른 증상 조절 효과를 보이는 **Reliver** 를 원한다고 답했습니다[1].

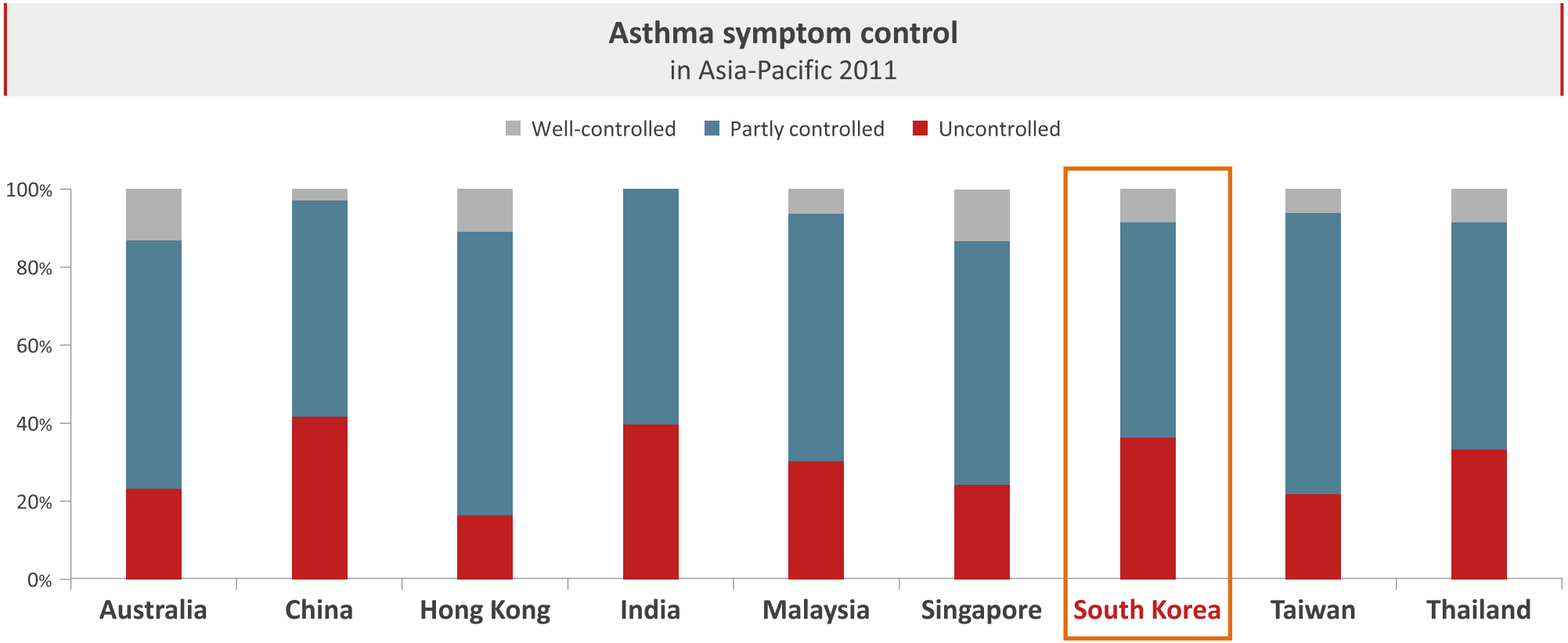
Patient attitudes to asthma management (n=3,415)

believe there is **no need to take medication** every day when they feel well

want treatments that provide **immediate relief**

The INSPIRE study examined the attitudes and actions of 3415 physician-recruited adults with asthma in 11 countries. Patients were prescribed regular maintenance therapy with ICS or ICS/LABA.
ICS = inhaled corticosteroid(s); INSPIRE = International Asthma Patient Insight Research; LABA = long-acting β2-agonist.
1. Partridge MR, et al. BMC Pulm Med. 2006;6:13.

한국 천식 환자들의 천식조절도를 보았을 때 Well-controlled는 불과 8%를 보였고, 이는 약 92%*가 조절이 안되고 있음을 뜻합니다.



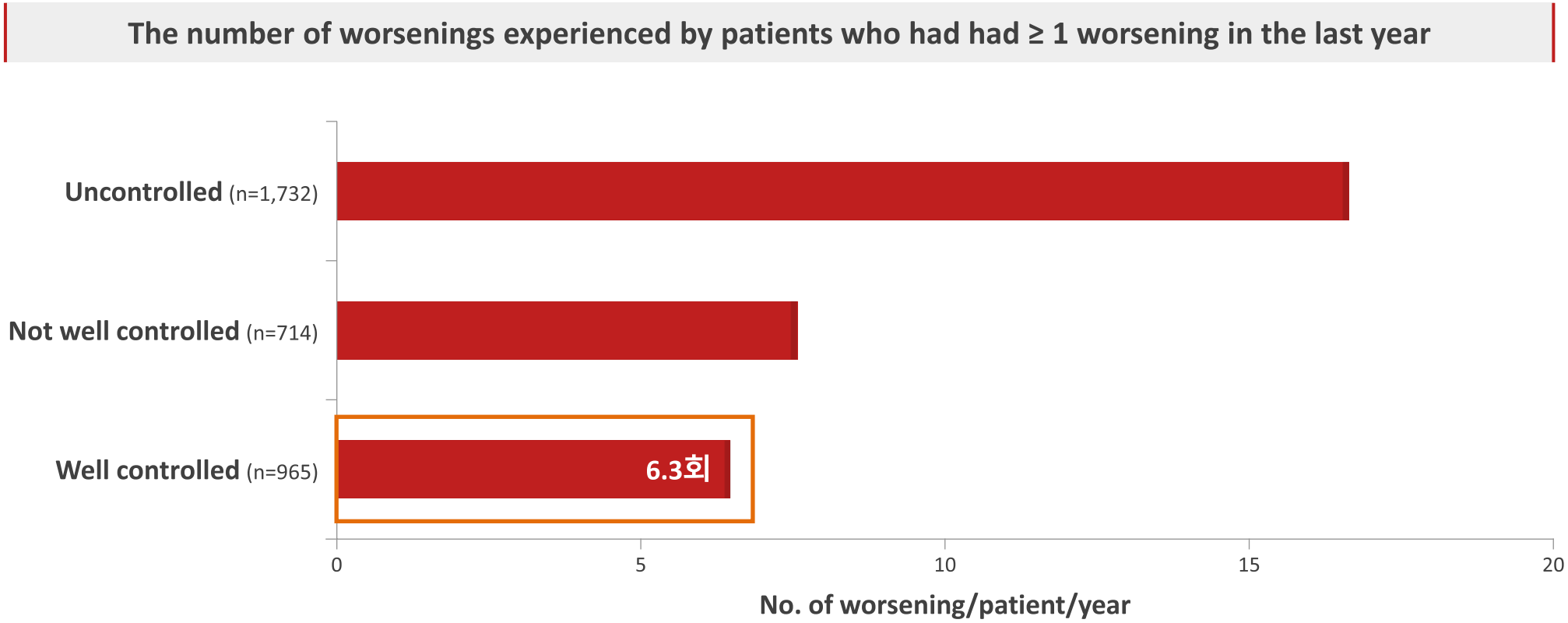
Overall AP	Total (n=3,630)	Well-controlled n=276 (7.6%)	Partly controlled n=2,271 (63%)	Uncontrolled n=1,083 (30%)
South Korea	400	33 (8%)	220 (55%)	147 (37%)

*Partly controlled 55%, Uncontrolled 37%

1. Gold *et al*. Respir Med. 2014 Feb;108(2):271-7

천식이 잘 조절되는 환자들도 1년에 평균 6.3회 증상 악화 (symptom worsening)를 경험합니다[1].

- 89% 환자가 1년에 평균 11.8회 '증상이 나빠지는 것*' 을 경험했습니다[1].
- 천식이 잘 조절되는 환자라도 1년에 평균 6.3회 증상이 나빠졌습니다[1].



*A worsening was defined as an occasion when asthma symptoms had become bothersome or hindering in the past year

1. Martyn RP, *et al*. BMC Pulmonary Medicine. 2006;1-9.

8th 천식적정성평가

평가영역		지표명	'19년(7차) (A)	'20년(8차) (B)	증감 (B-A)	결과 해석
평가지표	검사	폐기능검사시행률	36.9	42.4	5.5↑	높을수록 좋음
	치료지속성	지속방문 환자비율	74.0	77.1	3.1↑	
	처방	ICS 처방 환자비율	44.2	55.9	11.7↑	
		필수약제(ICS or LTRA) 처방 환자비율	74.4	82.6	8.2↑	
		ICS 없이 LABA 처방 환자비율	12.2	7.3	4.9↓	낮을수록 좋음
		ICS 없이 SABA 처방 환자비율	7.2	6.5	0.7↓	
		ICS 없이 OCS 처방 환자비율	21.8	15.1	6.7↓	
모니터링 지표	처방	(전체 평가대상자) ICS 처방일수율	17.6	**24.5**	**6.9↑**	높을수록 좋음
		(치료지속성 평가대상자) ICS 처방일수율	24.3	**30.6**	**6.3↑**	
	결과	천식으로 인한 입원경험 환자비율	2.5	**2.0**	**0.5↓**	낮을수록 좋음
		천식으로 인한 응급실 방문경험 환자비율	1.2	**1.0**	**0.2↓**	

주 1. ICS: Inhaled Corticosteroid, 흡입스테로이드
2. LTRA: Leukotriene Receptor Antagonist, 류코트리엔조절제
3. LABA: Long-Acting Beta2 Agonist, 지속성베타2항진제
4. SABA: Short-Acting Beta2 Agonist, 속효성베타2항진제
5. OCS: Oral Corticosteroid, 경구스테로이드

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study

Eric D. Bateman, David B. Price, Hao-Chien Wang, Adel Khattab, Patricia Schonffeldt, Angelina Catanzariti, Ralf J. P. van der Valk, Maarten J.H.I. Beekman

European Respiratory Journal 2021; **DOI:** 10.1183/13993003.01402-2021

SABINA III - An observational, cross-sectional study carried out in 24 countries in 8,351 patients

- Aim: To assess SABA prescriptions and associated outcomes in countries lacking robust national healthcare databases
- Real-world primary data was collected in local health care settings through eCRFs
- Unlike in database studies, this enabled assessment of additional endpoints such as assessment of asthma control

Primary Objectives:

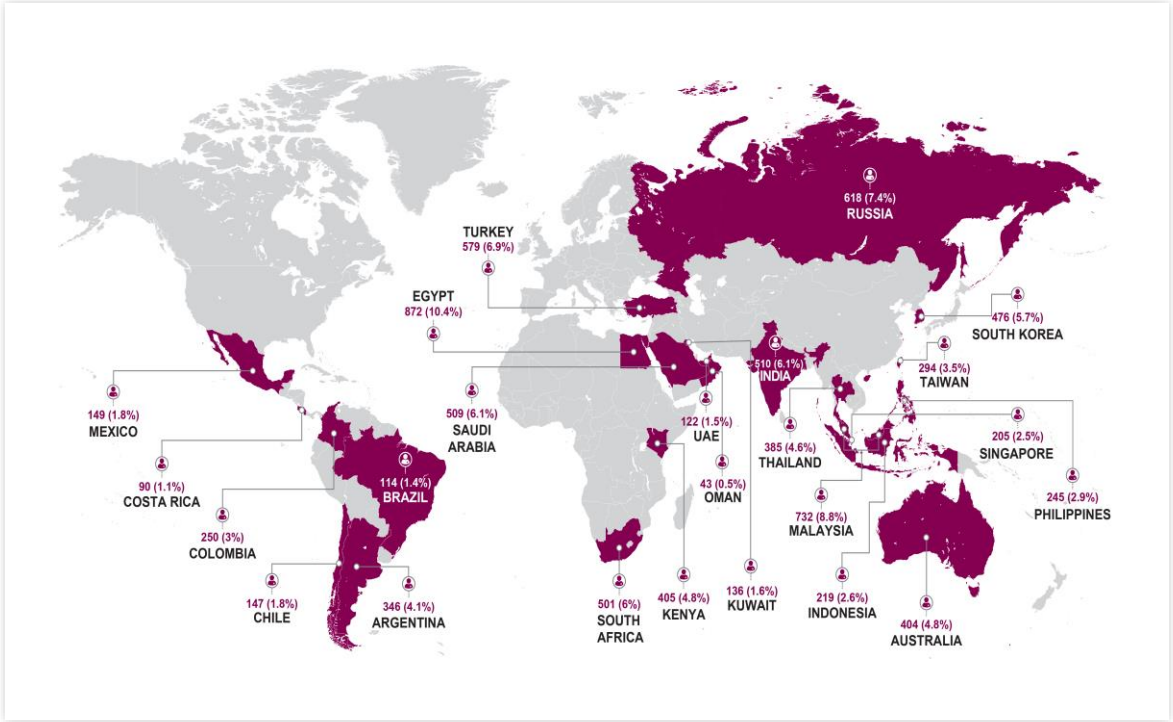
Describe the demographic and clinical features of the asthma population selected by prescriber type using (investigator-defined) GINA steps 1/2 (mild) and steps 3–5 (moderate/severe)

Estimate SABA canister prescriptions per patient in the previous 12 months

Estimate ICS prescriptions per patient (by average daily dose) in the previous 12 months

Secondary Objectives:

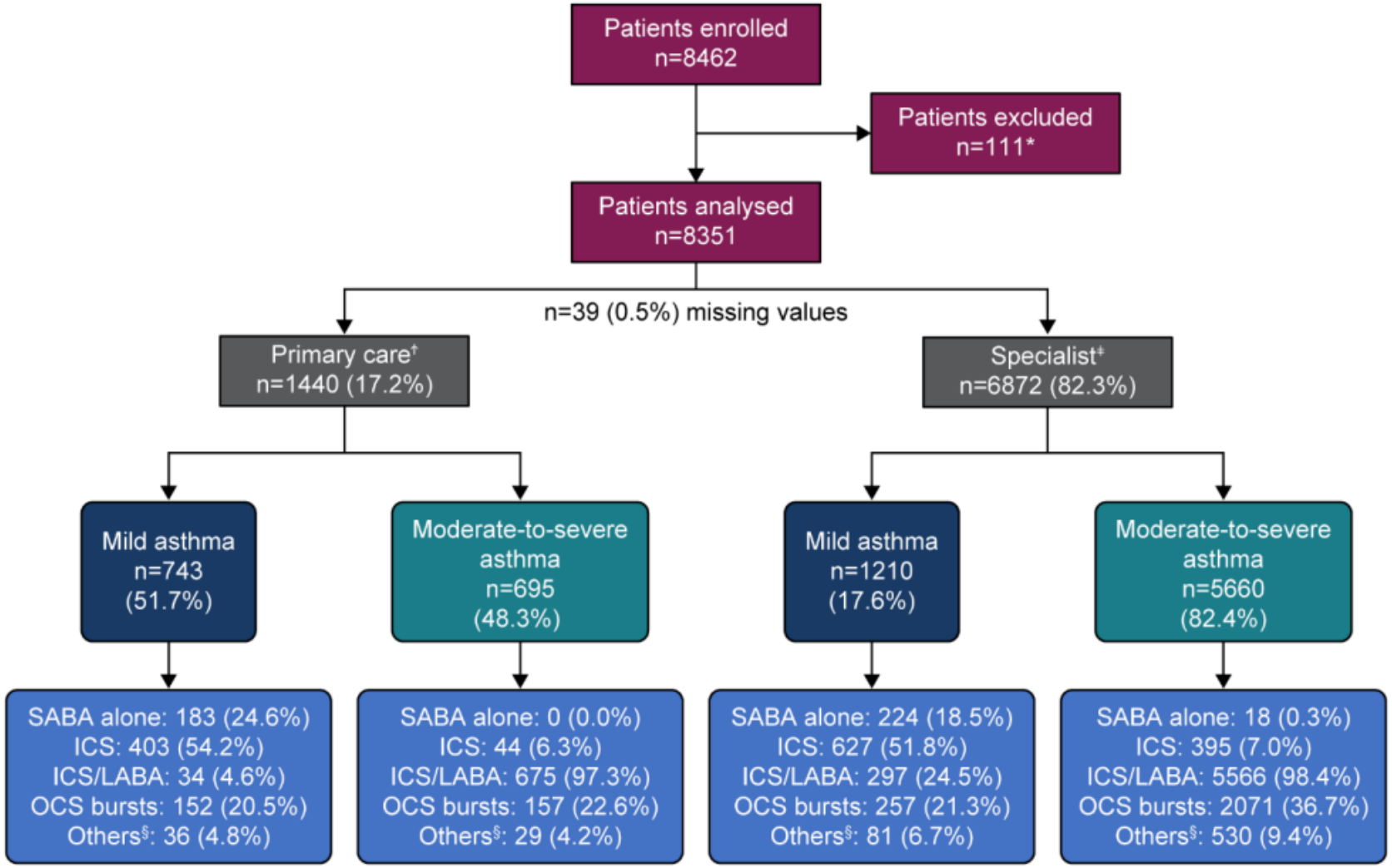
Describe the associations between SABA prescriptions and asthma symptom control level (as per 2017 GINA assessment of asthma control); number of severe exacerbations



SABINA International

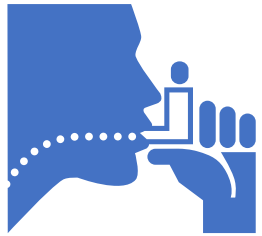
Bateman E, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

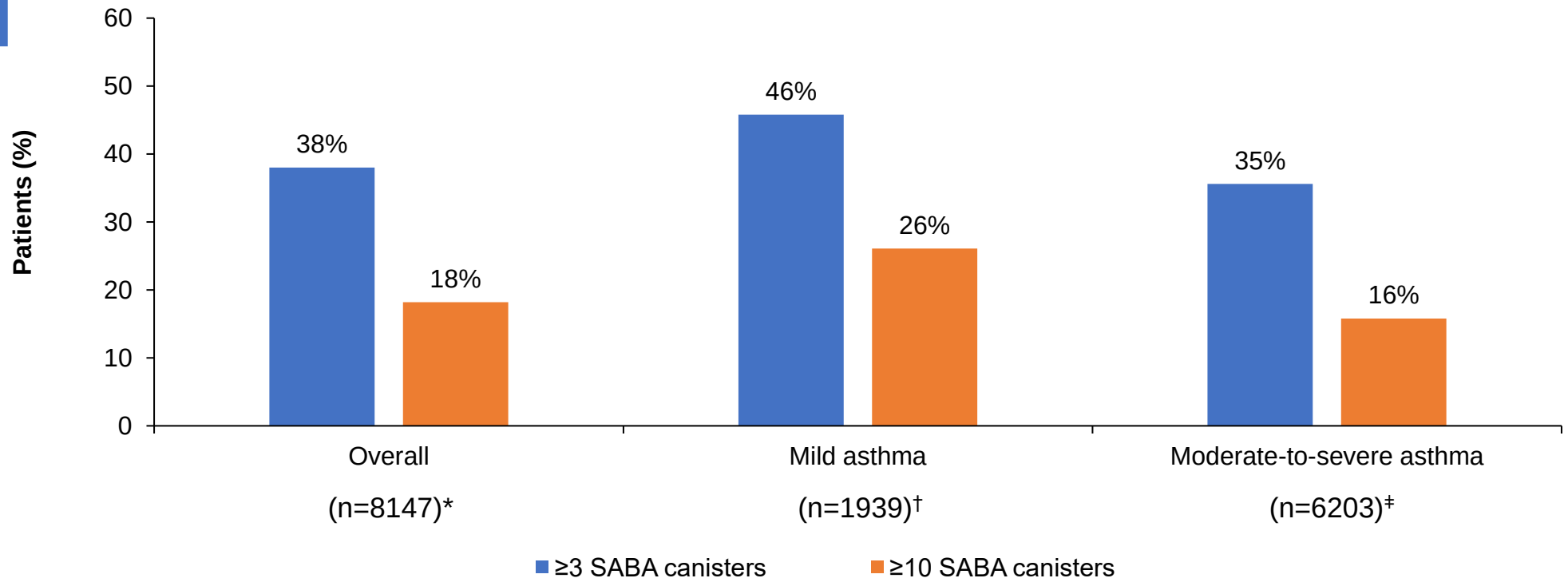
SABINA III - Patient population by practice type and asthma severity



Bateman E, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

Overall, 38% of patients were prescribed ≥3 SABA canisters in the previous year and almost one-fifth were prescribed ≥10 SABA canisters



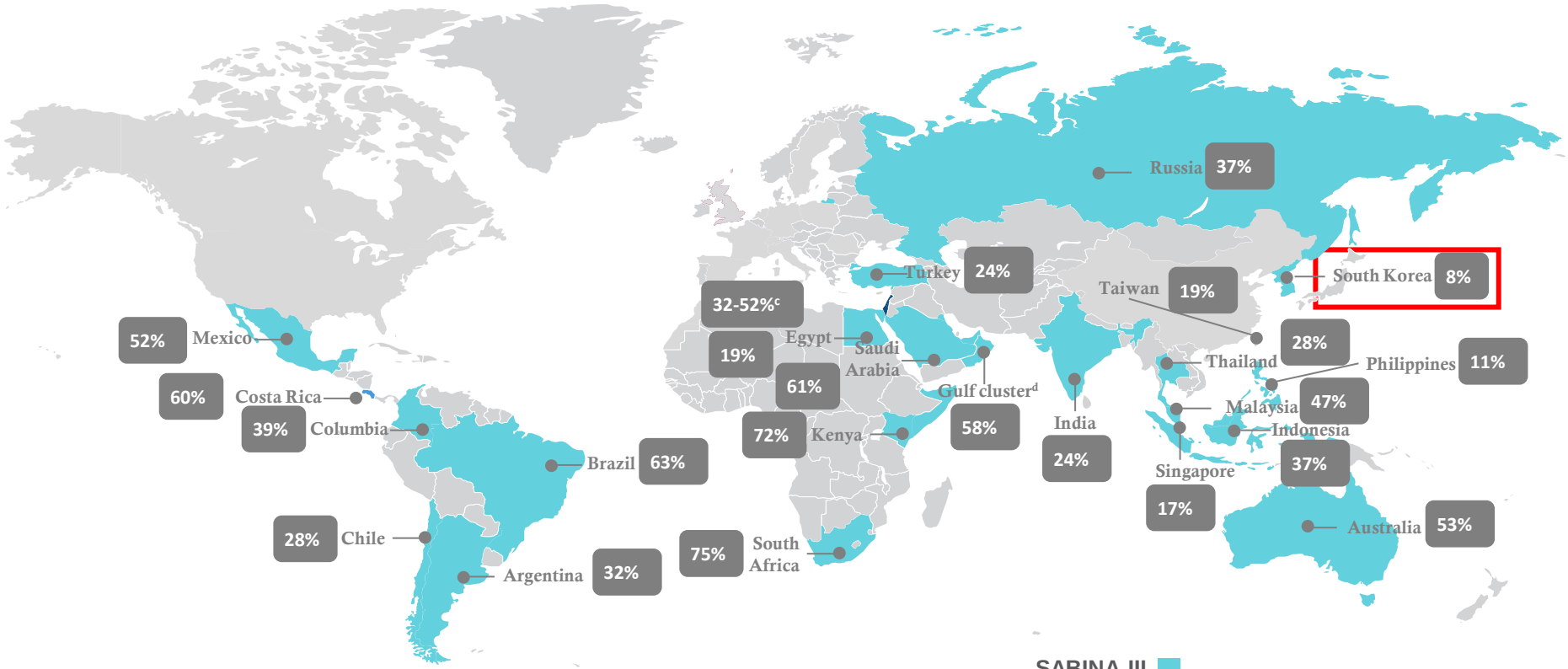


*Missing data for overall population: n=204; †missing data for mild asthma: n=19; ‡ missing data for moderate-to-severe asthma: n=185

Bateman E, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

SABINA International

SABINA-III: SABA over-prescriptions were widespread across regions and countries in the SABINA International study



Pan international	Latin America	Africa	Middle East	Asia
38%	40%	47%	47%	27%

Note: Country percentages are rounded to the nearest whole number

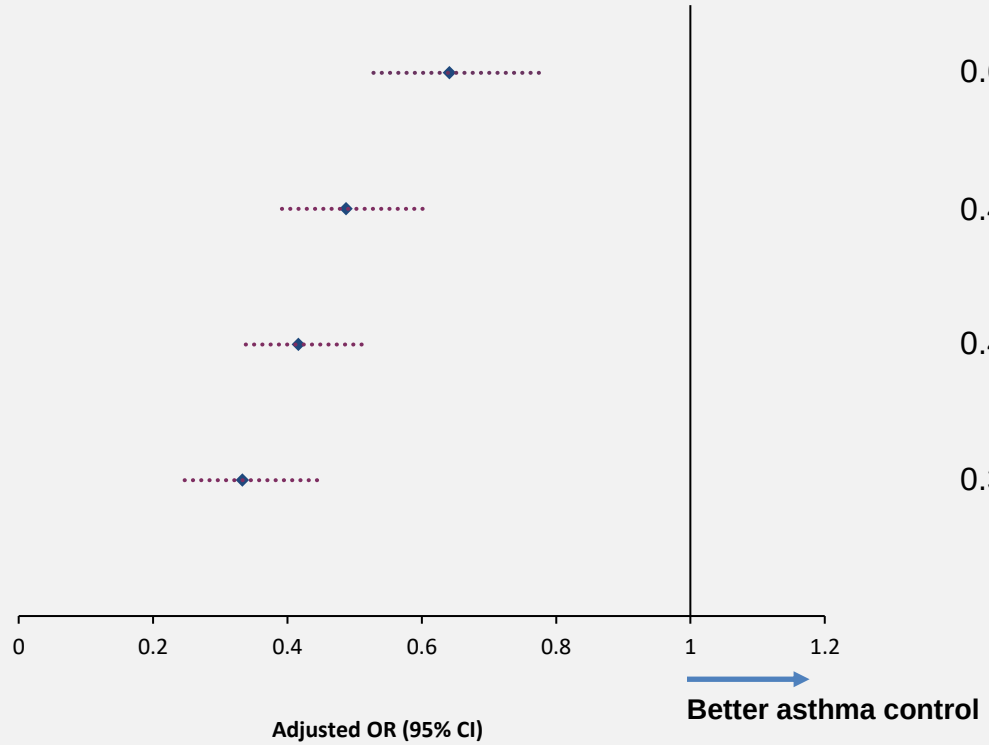
1.Quint JK, et al. Presented at: IPCRG 10th Virtual World Congress; 6-8 May 2021; 2. Bateman ED, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

SABINA International

The odds of having at least partly-controlled asthma were *significantly* lowered with increasing SABA canister prescriptions (vs. 1–2 canisters; n=1,796, reference OR 1.0)

Odds of at least partly controlled asthma (n=4,597)

SABA canister prescriptions	OR	95% CI	*p*
3–5 (n=842)	0.64	0.53–0.78	<0.0001
6–9 (n=627)	0.49	0.39–0.61	<0.0001
10–12 (n=1,062)	0.42	0.34–0.51	<0.0001
≥13 (n=270)	0.33	0.25–0.45	<0.0001

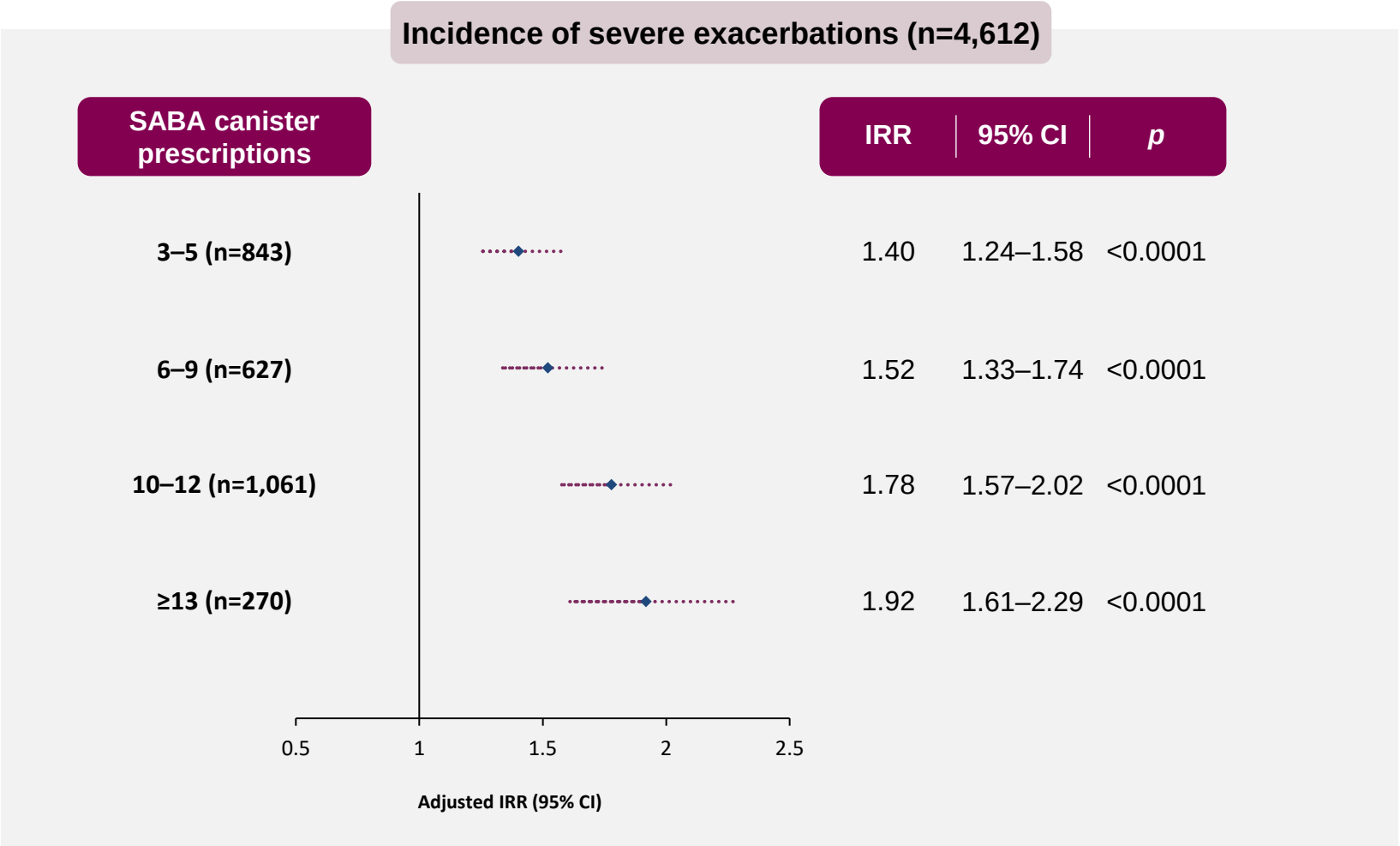


Analyses were adjusted for the following covariates: country, age (continuous), sex, smoking, GINA step by investigator, healthcare insurance, education level, prescriber type, co-morbidities, duration of asthma (continuous) and BMI (continuous).

Bateman E, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

SABINA International

Severe exacerbations significantly increased with the number of SABA prescriptions (vs. 1–2 SABA prescriptions; n=1,811, reference OR 1.0)

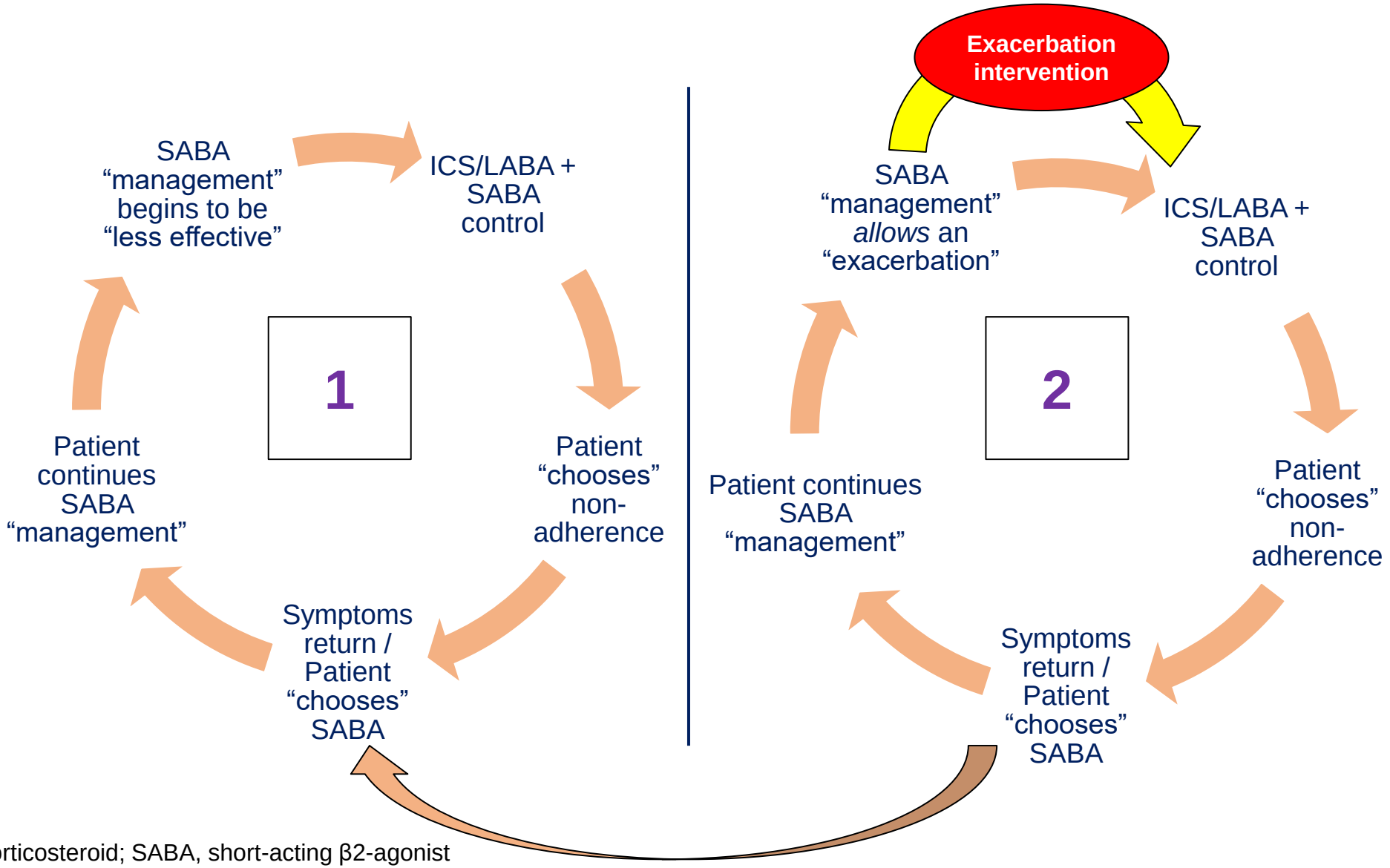


Analyses were adjusted for the following covariates: country, age (continuous), sex, smoking, GINA step by investigator, healthcare insurance, education level, prescriber type, co-morbidities, duration of asthma (continuous) and BMI (continuous).

Bateman E, et al. Eur Respir J 2021; In press (https://doi.org/10.1183/13993003.01402-2021).

SABINA International

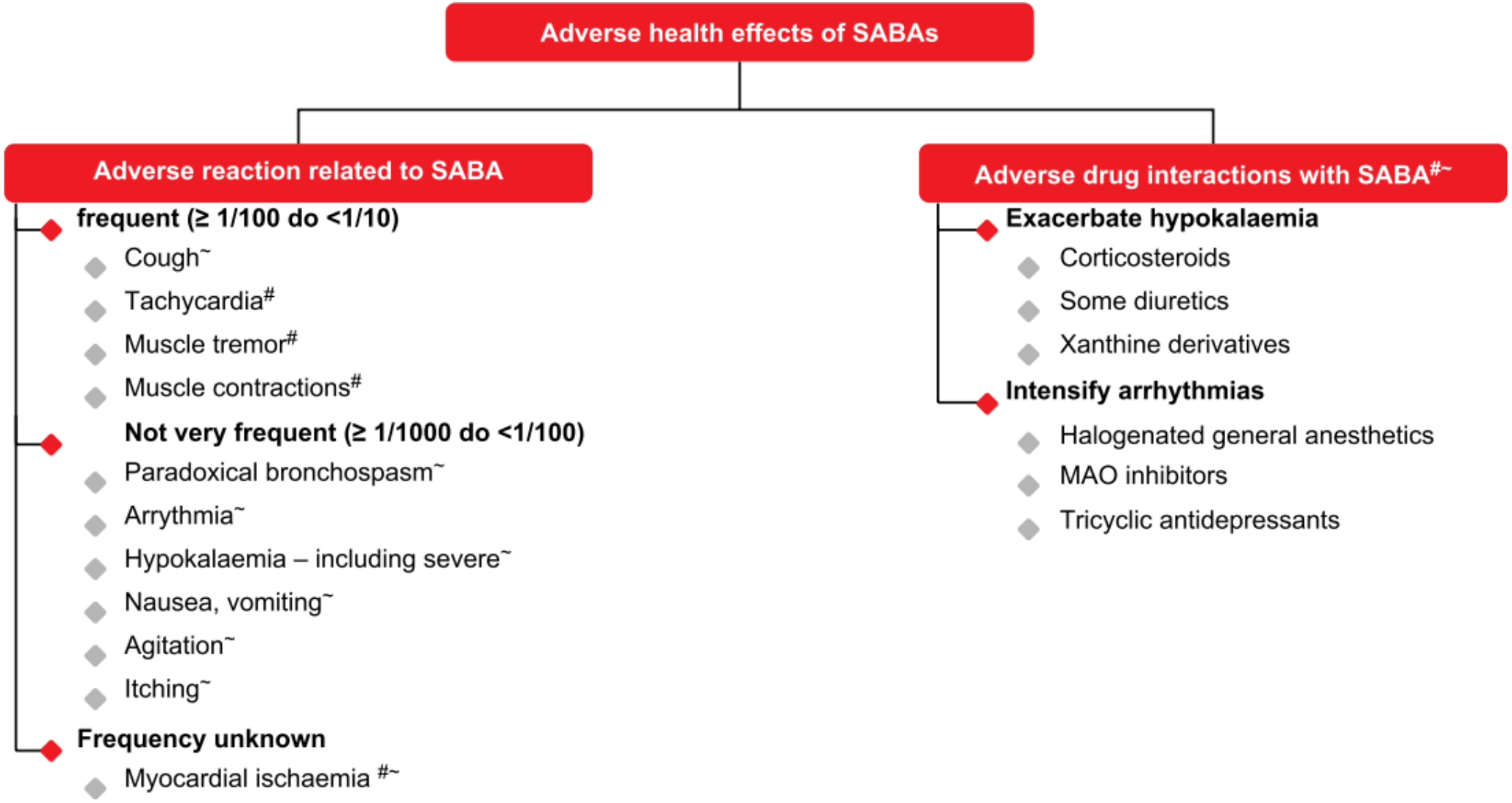
What patients really do…



ICS, inhaled corticosteroid; SABA, short-acting β2-agonist

Partridge, M et al. BMC Pulmonary Medicine 2006; 6: 13

Adverse Effects of SABA in Asthma



Kuprys-Lipinska et al. Clin Transl Allergy (2020) 10:19

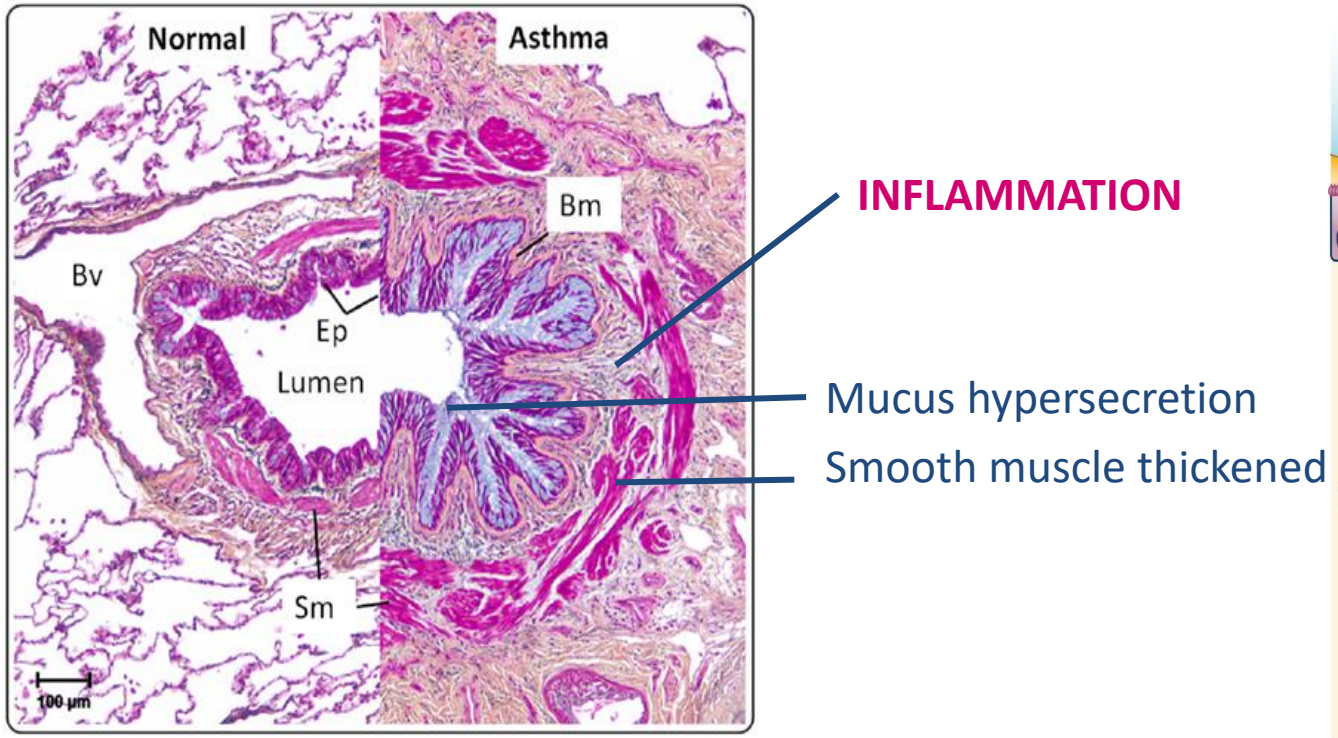
Proportion of patients agreeing with statements

	Total	BE	FR	DE	IT	NL	ES	SE	UK	AUS	CAN	USA
Base	(n=3415)	(n=300)	(n=307)	(n=298)	(n=300)	(n=300)	(n=300)	(n=300)	(n=301)	(n=308)	(n=301)	(n=400)
I want immediate relief	90%	89%	85%	90%	91%	87%	93%	92%	93%	90%	91%	91%
I am confident to intervene early	85%	85%	87%	65%	78%	83%	84%	89%	92%	91%	88%	90%
I use my medication as and when necessary	81%	74%	64%	62%	86%	92%	78%	86%	86%	89%	83%	90%
I prefer to adjust ICS to changes in my asthma	69%	75%	72%	50%	68%	58%	77%	86%	76%	73%	75%	52%
I manage my asthma myself	70%	76%	50%	66%	66%	82%	60%	89%	83%	70%	67%	67%

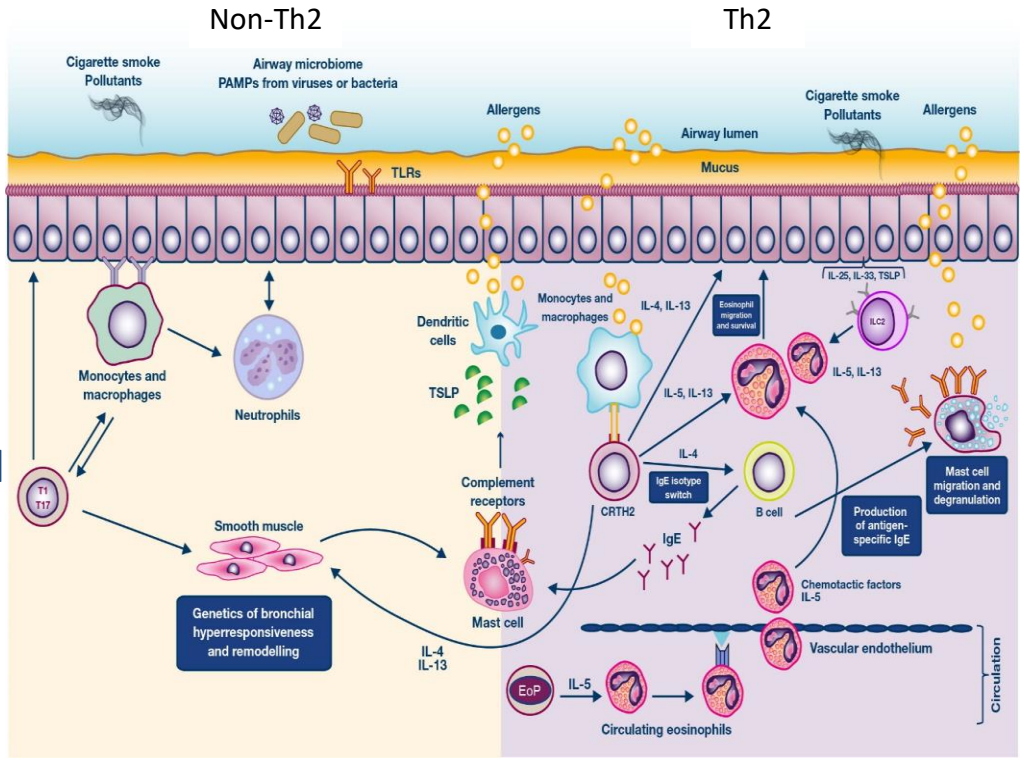
Partridge, M et al. BMC Pulmonary Medicine 2006; 6: 13

천식 증상의 발현과 악화는 염증 반응에 의해 나타나며, 증상 및 악화 조절을 위해 항염증 효과가 중요합니다.

Healthy versus severe asthmatic airway[2]



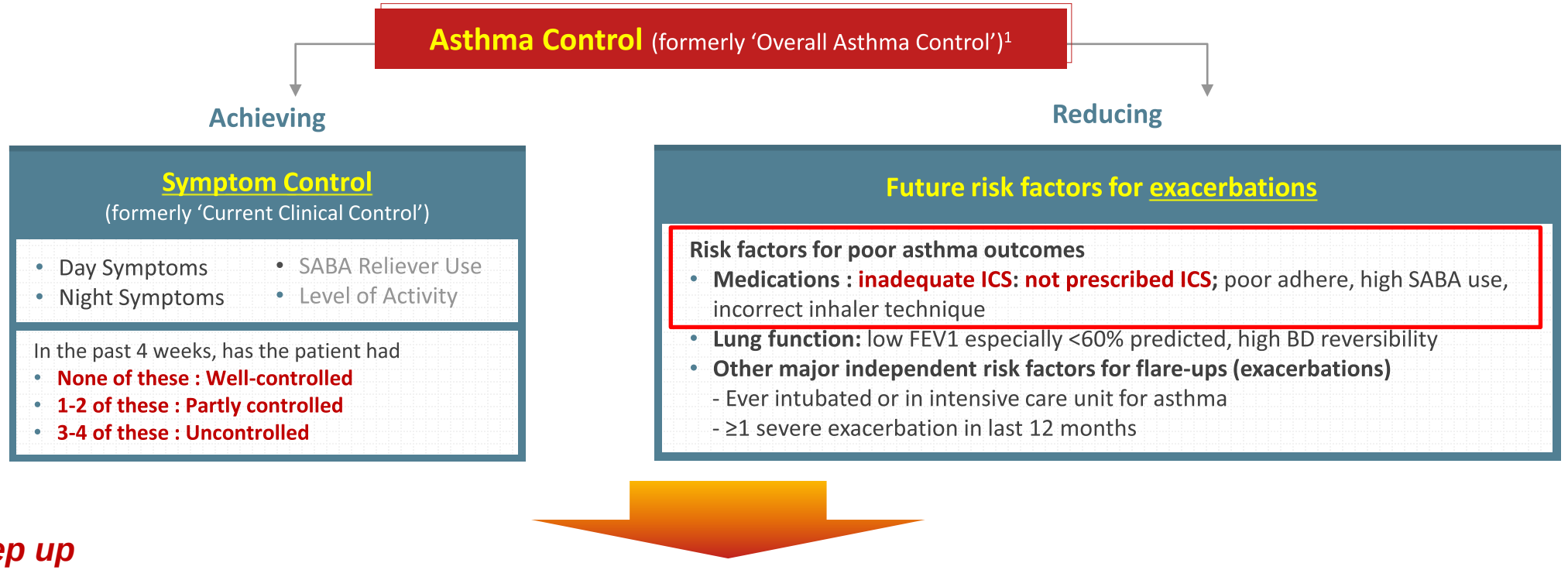
Key inflammatory pathways in asthma[3–4]



Bm = basement membrane; Bv = blood vessel; CRTH2 = chemoattractant receptor-homologous molecule expressed on Th2 cells; EoP = eosinophilopoiesis; Ep = epithelium; IgE = immunoglobulin E; IL = interleukin; ILC2 = type 2 innate lymphoid cells; SM = smooth muscle; T1 = Type 1 cell; T2 = Type 2 cell; T17 = Type 17 cell; TLR = toll-like receptor; TSLP = thymic stromal lymphopoietin.

1. Global Initiative for Asthma. 2019 GINA Report, Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org. Accessed 12 June 2019; 2. Holgate ST, et al. Nat Rev Dis Primers. 2015;1:15025; 3. Wenzel SE. Nat Med. 2012;18:716-725; 4. Peters SP, et al. J Allergy Clin Immunol Pract. 2017;5:S15-S24

천식 치료시 ICS 를 충분히 사용하지 않으면 exacerbation risk 가 증가하므로, 환자 개별 증상에 따른 적절한 ICS 치료가 필요합니다.



◆ *Step up*

- ✓ *Sustained step up (for at least 2–3 months)*: Response reviewed after 2–3 months.
- ✓ *Short-term step up (for 1–2 weeks)*: During viral infections or seasonal allergen exposure.
- ✓ *Day-to-day adjustment:* Adjusts the number of as-needed doses from day to day according to their symptoms.

◆ *Step down*

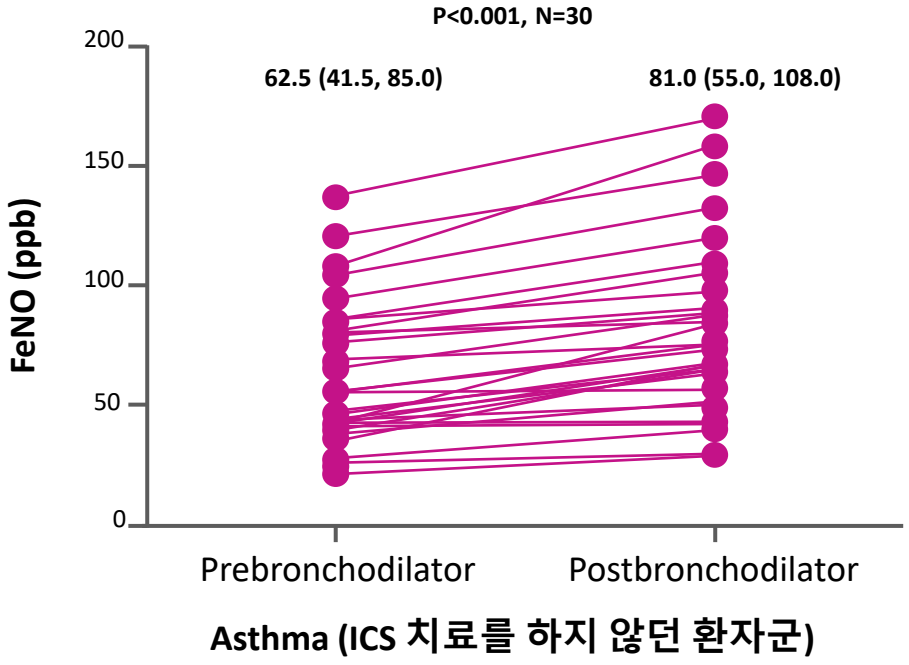
- ✓ *To find the patient's minimum effective treatment* : Minimize the costs of treatment and potential for side-effects
- ✓ *To encourage the patient to continue regular controller treatment* : Patients concern about the risks or costs of daily treatment.

1. Global Initiative for Asthma. Main report 2020.

ICS는 SABA와 달리 FeNO(기도염증반응을 확인하는 biomarker)를 감소시킵니다

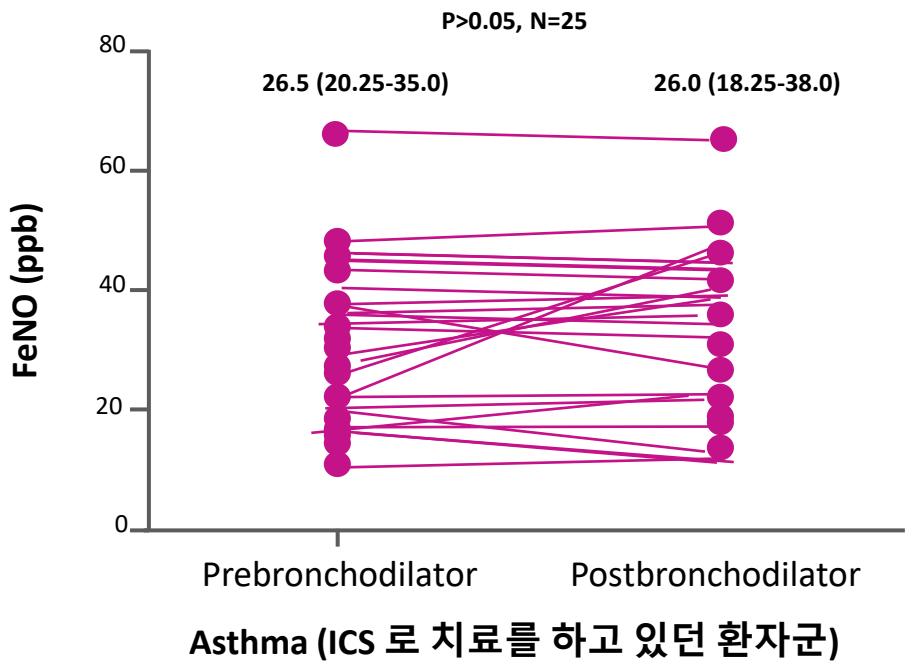
- **Steroid 를 사용하지 않은 천식 환자**는 Steroid 치료 하던 천식 환자와 달리 **SABA (albuterol) 흡입 후 FeNO 가 증가**했습니다.

Bronchodilator effects on FeNO levels in steroid-naïve patients



Asthma (ICS 치료를 하지 않던 환자군)

Bronchodilator effects on FeNO levels in ICS-treated patients

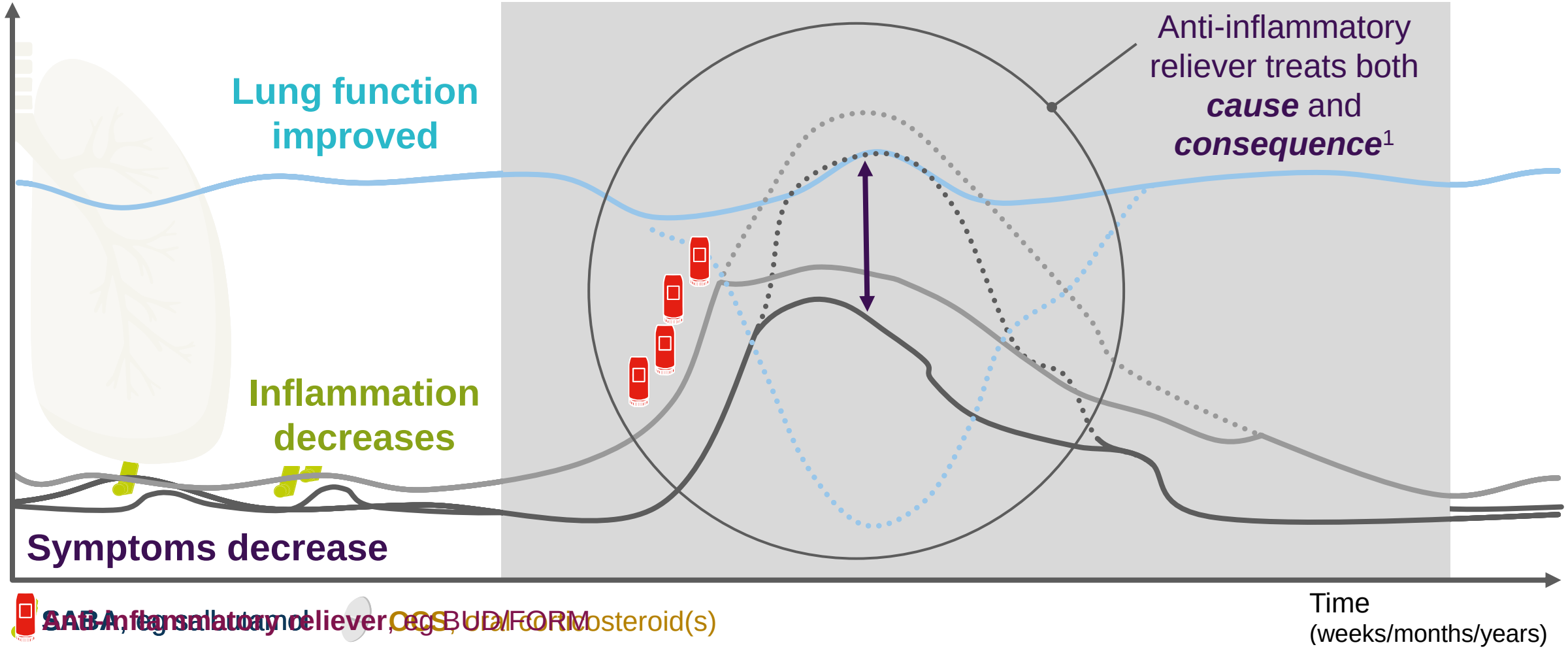


Asthma (ICS 로 치료를 하고 있던 환자군)

Disclaimer: The relationship between pharmacological properties and clinical efficacy has not been established.
An observational, prospective study was carried out in 30 steroid-naïve patients, 25 ICS-treated patients with asthma and 20 patients with COPD. The COPD population is not presented here.
COPD = chronic obstructive pulmonary disease; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid(s); ppb = parts per billion.

1. Zhao H, et al. Clin Respir J. 2017;11:328-336.

Anti Inflammatory reliever 는 증상의 원인인 염증반응과 폐기능 및 천식 증상을 모두 개선합니다.

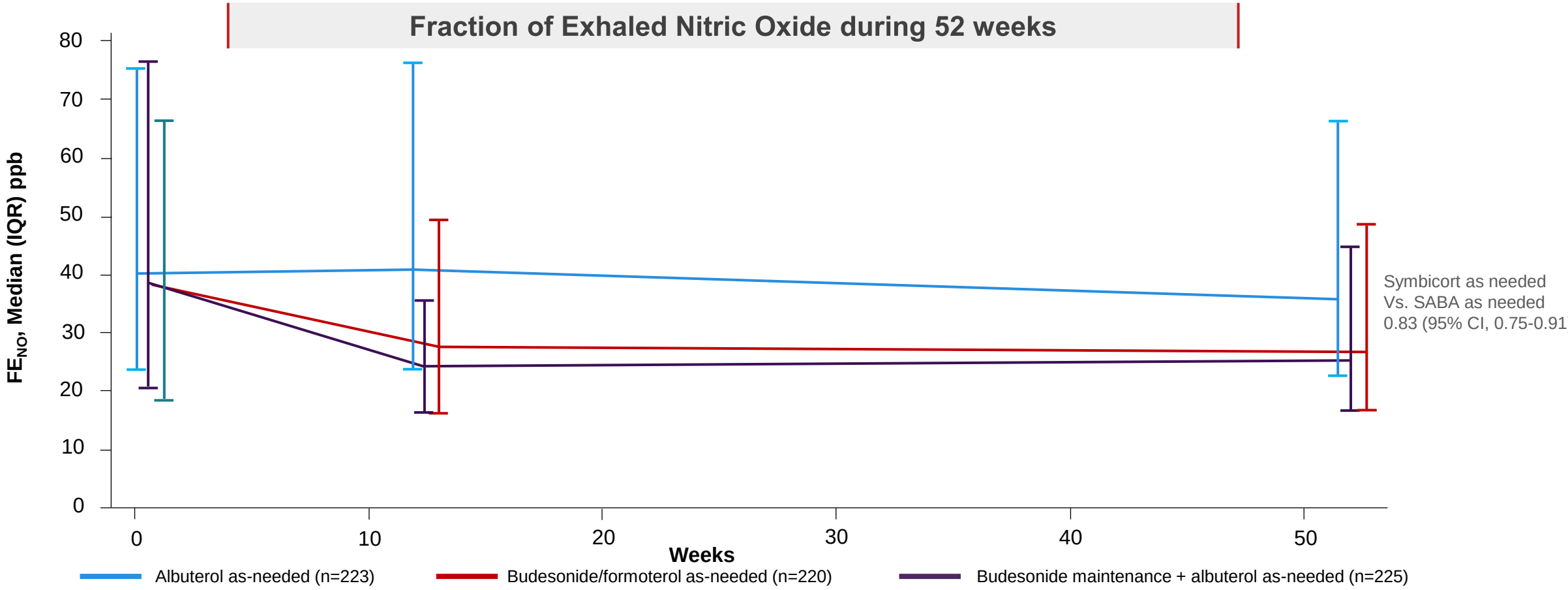


The animation is for descriptive/illustrative purposes only.
BUD = budesonide; FORM = formoterol.

1. Beasley R, et al. *N Engl J Med.* 2019;380:2020-2030.

증상 완화제로 사용 시에도 항염증 작용이 함께 나타나는 Anti Inflammatory Reliever*는 천식 조절 시작에 적합한 제제입니다.

- 심비코트는 NOVEL START 연구를 통해 SABA와 달리 FeNO 수치를 감소시켜 우수한 항염증 효과를 입증했습니다.[1]



Ratio of Geometric Mean FE_{NO} at 52 weeks:[a] BUD/FORM as-needed vs. albuterol as-needed, 0.83 (95% CI, 0.75-0.91); BUD/FORM as-needed vs. BUD maintenance, 1.13 (95% CI, 1.02-1.25)

[a]Secondary endpoints were not adjusted for multiplicity. BUD = budesonide; FENO = fraction of exhaled nitric oxide; FORM = formoterol; IQR = interquartile range; ppb = parts per billion.

1. Beasley R et al. N Engl J Med. 2019;380:2020-2030.

모든 천식 단계[1-4]에서 우수한 악화 감소 효과를 입증한 항염증 증상완화제, 하나로! 천식 치료 시작 가능합니다.

Mild asthma → Severe asthma

SYGMA1[1]
64%↓
vs. SABA
In Number of Severe Exacerbations

SYGMA2[2]
Non-inferior
vs. BUD maintenance
In Number of Severe Exacerbations

Novel Start[3]
56%↓
vs. BUD maintenance
In Number of Severe Exacerbations

COMPASS[4]
39%↓
vs. FLU/SAL
Rate of Severe Exacerbation

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose ICS, Or as-needed low dose ICS-formoterol	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy. e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options				
Low dose ICS taken whenever SABA is taken	*Leukotriene receptor antagonists (LTRA), or Low dose ICS taken whenever SABA taken*	*Medium dose ICS, or Low dose ICS+LTRA*	*High dose ICS, add-on tiotropium, or add-on LTRA*	*Add low dose OCS, but consider side-effects*

PREFERRED RELIEVER

As-needed low dose ICS/formoterol[1]

Other reliever option — *As-needed SABA*

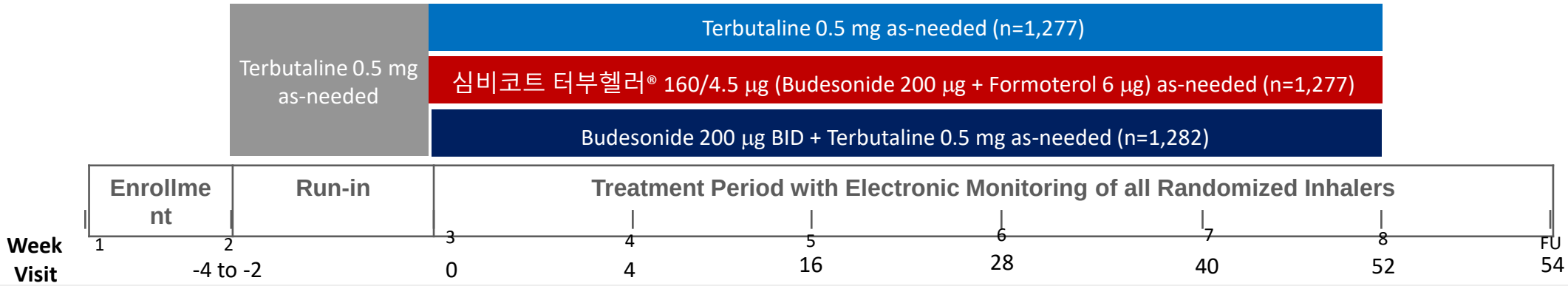
국내에서는 심비코트 터부헬러 160/4.5ug이 경증천식환자의 항염증 증상완화요법으로 허가를 받았습니다.

1. O'Byrne PM, et al. Supplementary material. N Engl J Med. 2018;378:1865-1876; 2. Bateman ED, et al. Supplementary material. N Engl J Med. 2018;378:1877-1887 3. Beasley R, et al. N Engl J Med. 2019;380:2020-2030.
4. Kuna P et al. Int J Clin Pract 2007;61:725–736 (COMPASS) 5. Bouaquet et al. Respiratory Medicine 2007 (AHEAD) 6. Global Initiative for Asthma. Main report 2020.

SYGMA 연구를 통해 경증 천식에서의 Anti Inflammatory Reliver 로써의 효과를 입증했습니다.

SYGMA 1 (n=3,836)

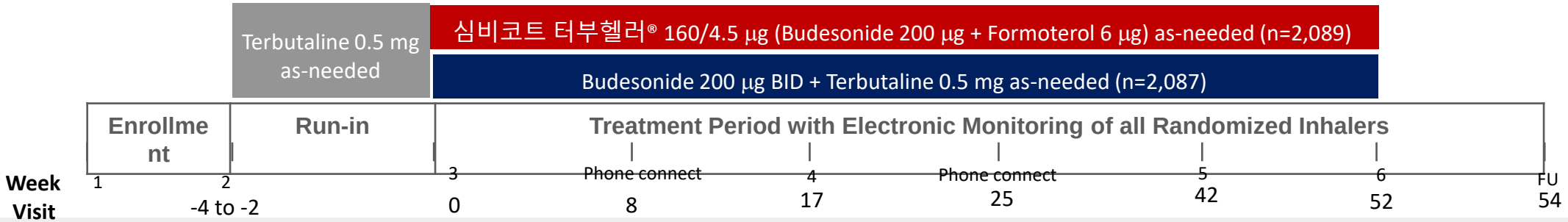
12-month, randomized, double-blind, parallel-group, multicenter study to access the long-term efficacy and safety of budesonide/formoterol and anti-inflammatory reliever in comparison to SABA as-needed or ICS maintenance + SABA as-needed in patients with mild asthma



Primary endpoint : Well-Controlled Asthma Week (WCAW) (superiority vs. terbutaline as-needed)
Secondary endpoints : WCAW (non-inferiority vs. budesonide maintenance + terbutaline as-needed), severe asthma exacerbation rate, FEV1, ACQ-5, ICS use, use of as-needed inhalations

SYGMA 2 (n=4,176)

12-month, randomized, double-blind, parallel-group, multicenter study to access the long-term efficacy and safety of budesonide/formoterol and anti-inflammatory reliever in comparison to ICS maintenance + SABA as-needed in a pragmatic trial of patients with mild asthma

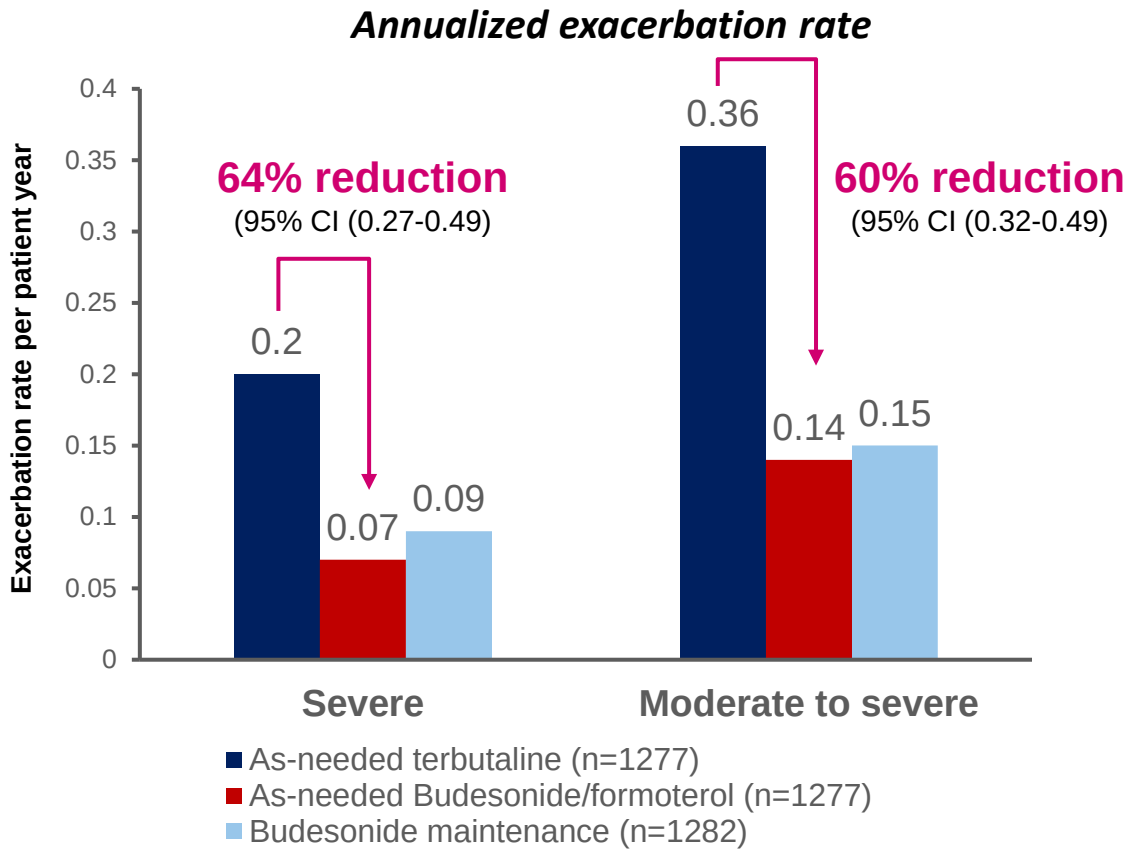


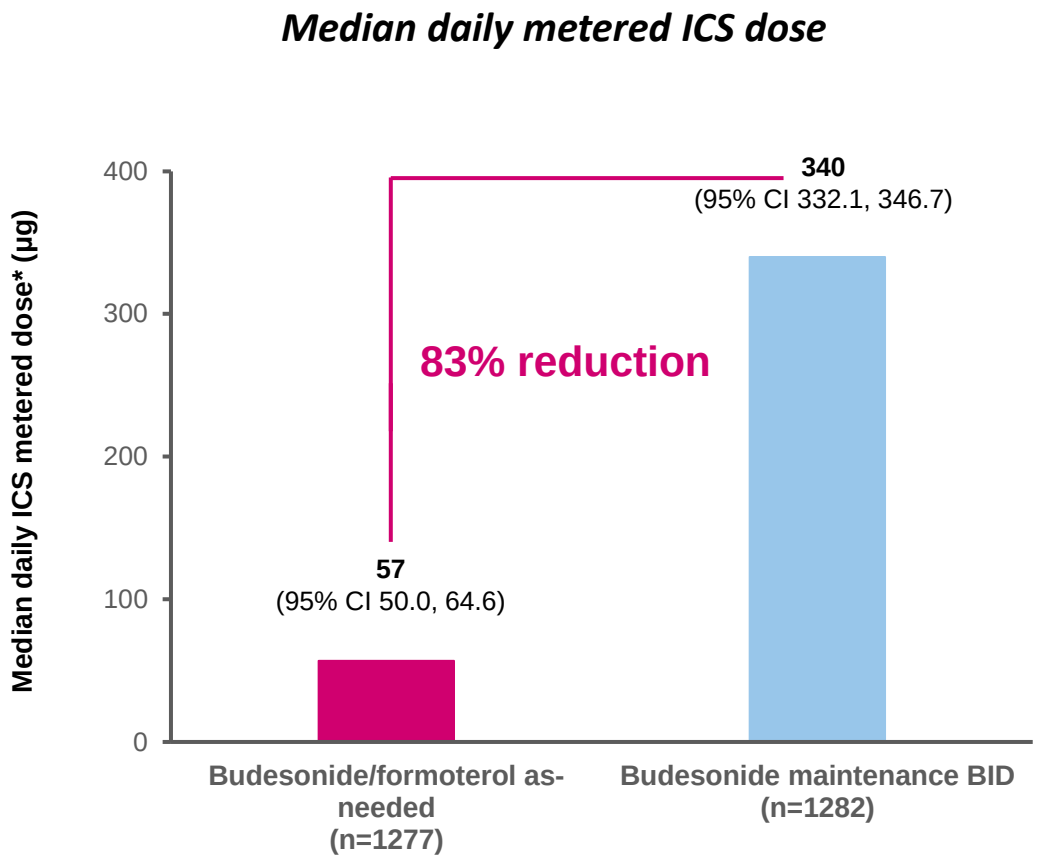
Primary endpoint : Annualized severe asthma exacerbation rate (non-inferiority)
Secondary endpoints : FEV1, ACQ-5, ICS use, use of as-needed inhalations

1. . O'Byrne PM, et al. Supplementary material. N Engl J Med. 2018;378:1865-1876; 2. Bateman ED, et al. Supplementary material. N Engl J Med. 2018;378:1877-1887

SYGMA 1 - 경증 천식에서의 악화 감소 효과 vs As needed SABA

심비코트 터부헬러 160/4.5 as-needed 사용시
- SABA 대비 **연간 중증 악화 비율 64% 감소 & 연간 중증도~중증 악화 비율 60% 감소**
- SABA 대비 **첫 중증 악화 & 첫 중등도~중증 악화 발생까지의 시간 더 지연**
- Budesonide 유지요법군 대비 **Median daily ICS dose 83% 감소**





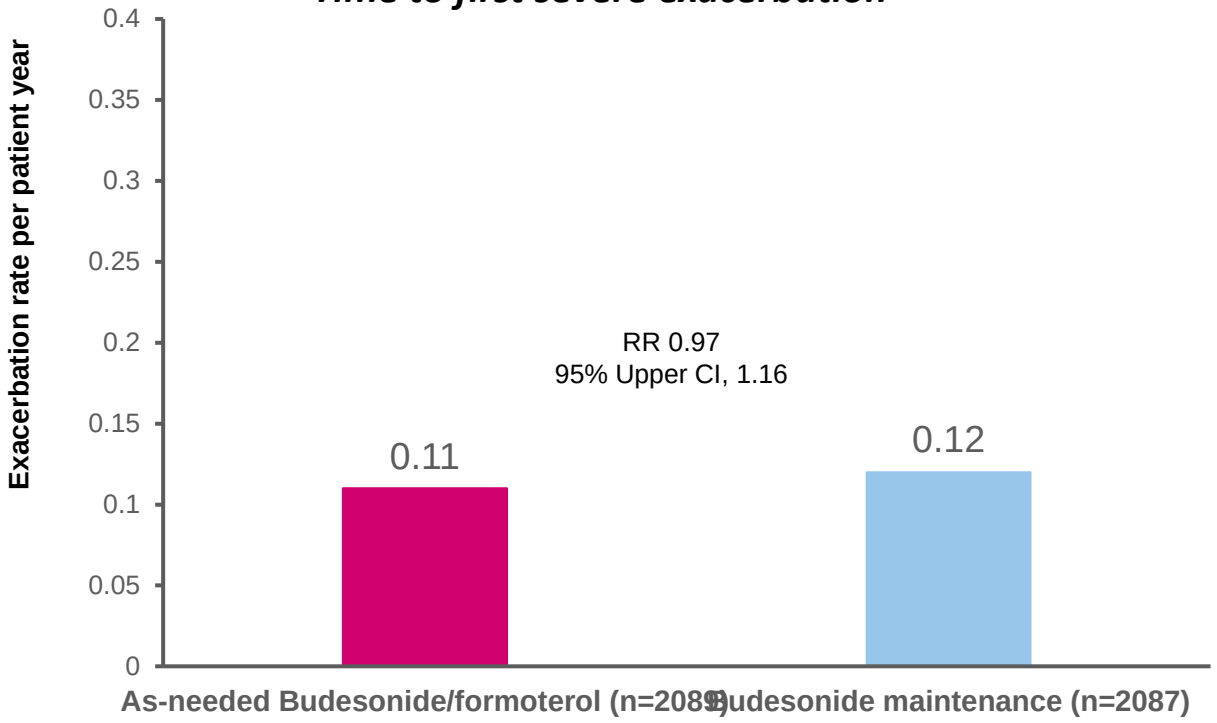
1. . O'Byrne PM, et al. Supplementary material. N Engl J Med. 2018;378:1865-1876

SYGMA 2 - 경증 천식에서의 악화 감소 효과
vs ICS maintenance + SABA

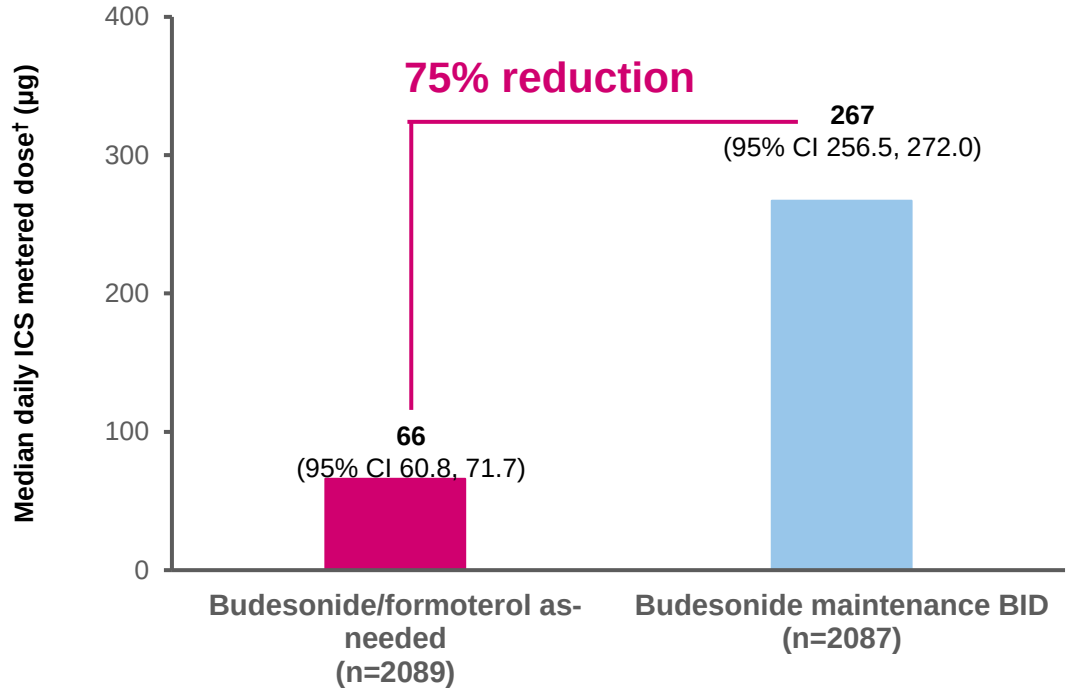
심비코트 터부헬러 160/4.5 as-needed 사용시 Budesonide 유지요법군 대비

- **연간 중증 악화 발생 빈도**에 있어 **비열등성** 통계학적으로 입증
- 첫 중증 악화 발생까지의 시간이 임상적으로 유의한 차이 없었음
- 흡입스테로이드를 사용한 일수의 비율이 더 낮았음 (심비코트 군 30.5% vs. Budesonide 유지요법 군 67.9%)
- **Median daily ICS dose 75%** 감소

Time to first severe exacerbation



Median daily metered ICS dose

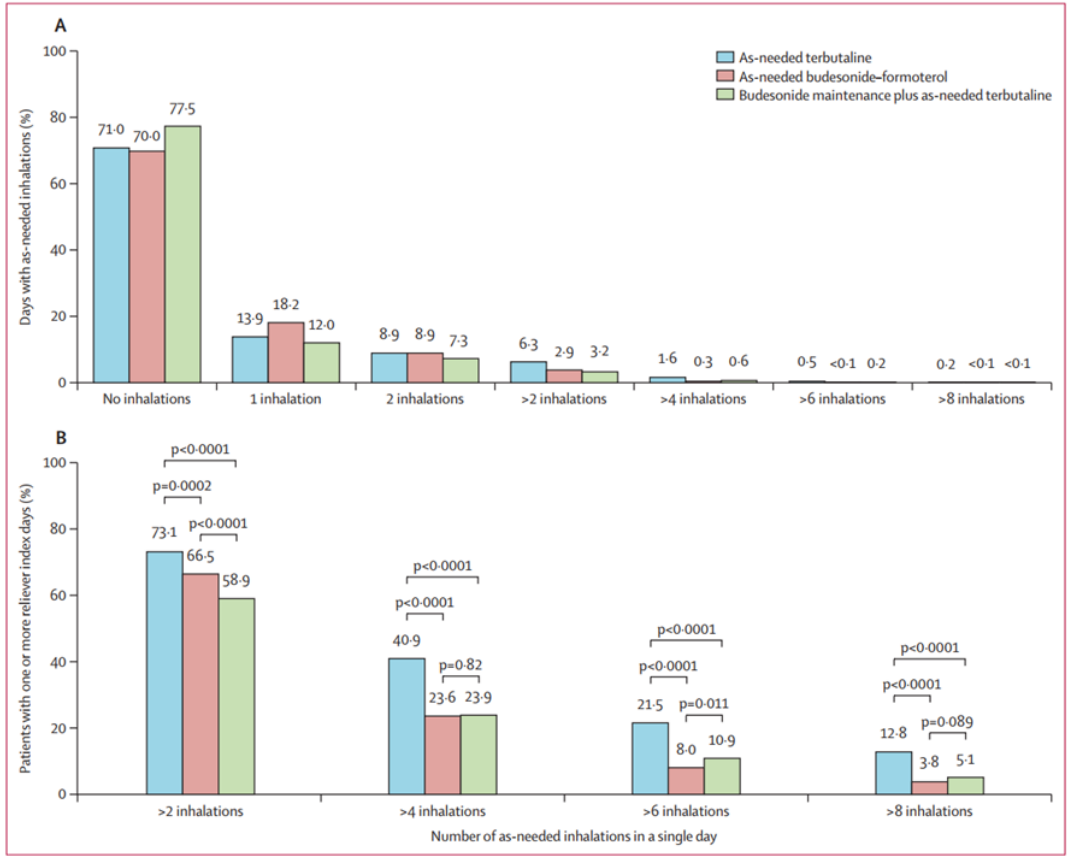


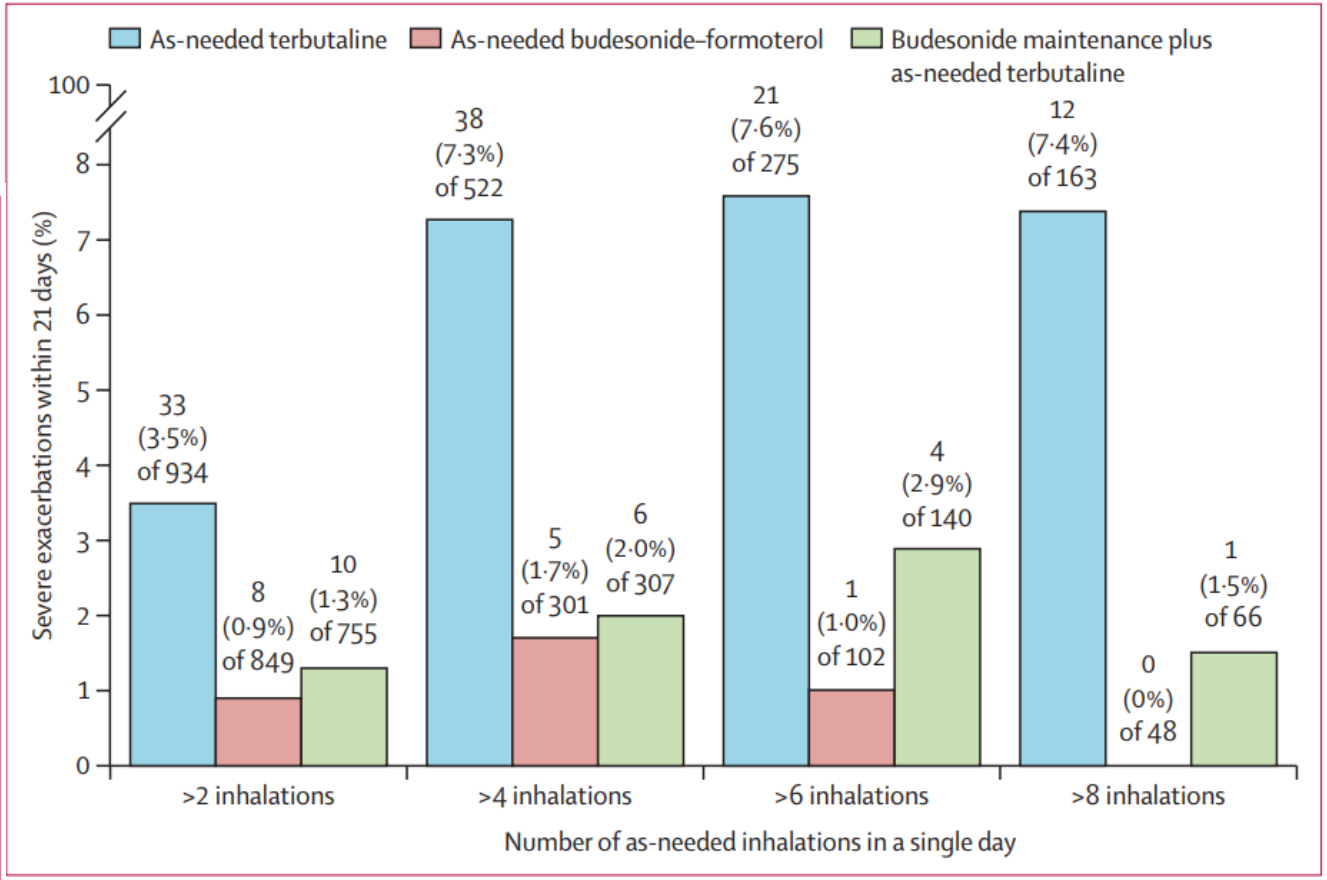
1. . Bateman ED, et al. N Engl J Med 2018;378:1877-87.

Increasing evidence for as-needed ICS-formoterol

A single day of small increased doses of ICS-formoterol significantly reduces the risk of severe exacerbations

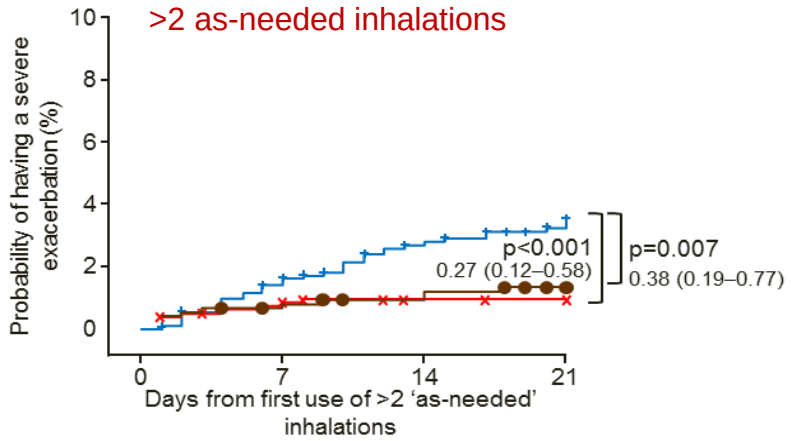
Effect of a single day of increased as-needed budesonide–formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study



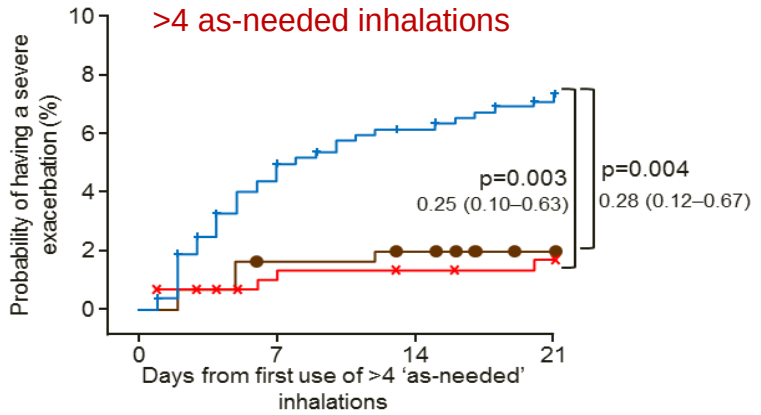


Lancet Respir Med 2021; 9: 149–58

SYGMA 1: Probability of a severe exacerbation during 21 days after a high reliever day (post hoc analysis)

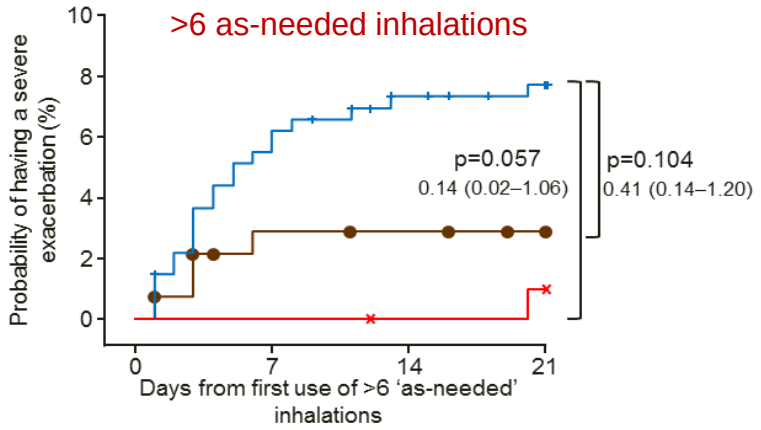


Number at risk (censored)				
As-needed terbutaline	934 (0)	916 (5)	898 (11)	888 (16)
As-needed budesonide–formoterol	849 (0)	841 (2)	835 (6)	834 (7)
Budesonide maintenance plus as-needed terbutaline	755 (0)	745 (5)	740 (8)	732 (13)

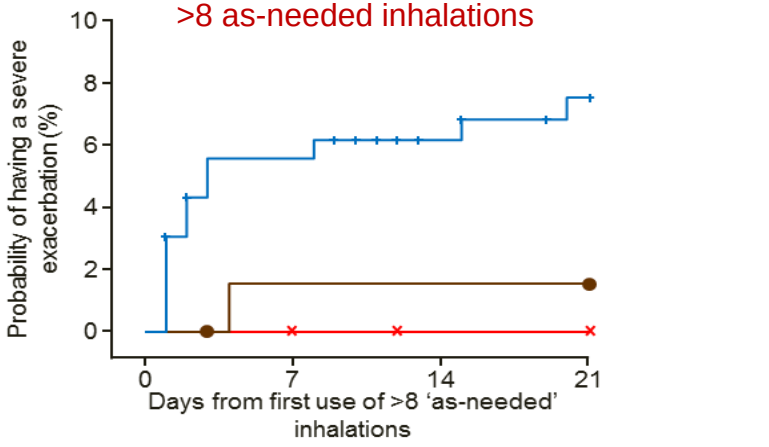


	522 (0)	494 (5)	478 (12)	470 (15)
	301 (0)	293 (5)	291 (6)	289 (7)
	307 (0)	299 (3)	295 (6)	289 (12)

As-needed terbutaline
As-needed BUD/FORM
BUD maintenance + as-needed terbutaline



Number at risk (censored)				
As-needed terbutaline	275 (0)	258 (2)	249 (6)	244 (10)
As-needed budesonide–formoterol	101 (0)	101 (0)	100 (1)	99 (1)
Budesonide maintenance plus as-needed terbutaline	140 (0)	133 (3)	131 (5)	129 (7)



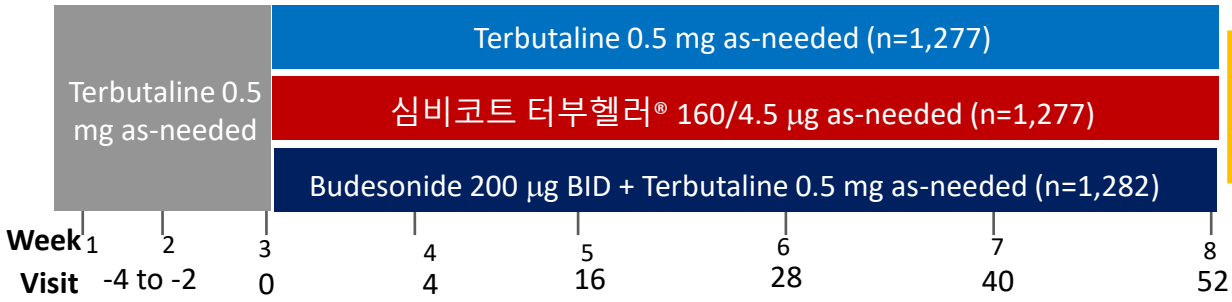
	163 (0)	152 (2)	143 (10)	138 (13)
	48 (0)	48 (0)	46 (2)	46 (2)
	66 (0)	64 (1)	64 (1)	64 (1)

O'Byrne PM, *et al. Lancet Respir Med,* 2021; 9(2):149-158.

RCT 뿐만 아니라 Real world study 에서도 경증 천식에서의 Anti Inflammatory Reliver 로써의 효과를 입증했습니다.

SYmbicort Given as needed in Mild Asthma

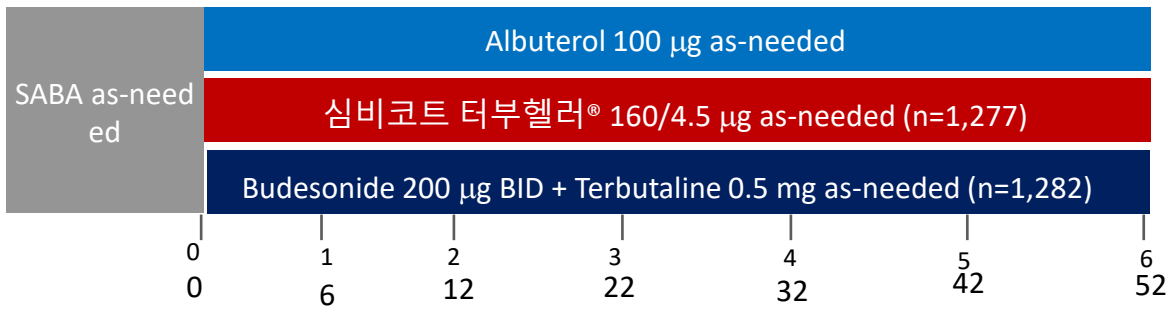
SYGMA 1 (n=3,836)[1]



Primary endpoint : Well-Controlled Asthma Week (WCAW) (superiority vs. terbutaline as-needed)
Secondary endpoints : WCAW (non-inferiority vs. budesonide maintenance + terbutaline as-needed), severe asthma exacerbation rate, FEV1, ACQ-5, ICS use, use of as-needed inhalations

Novel Symbicort Turbuhaler Asthma Reliever Therapy

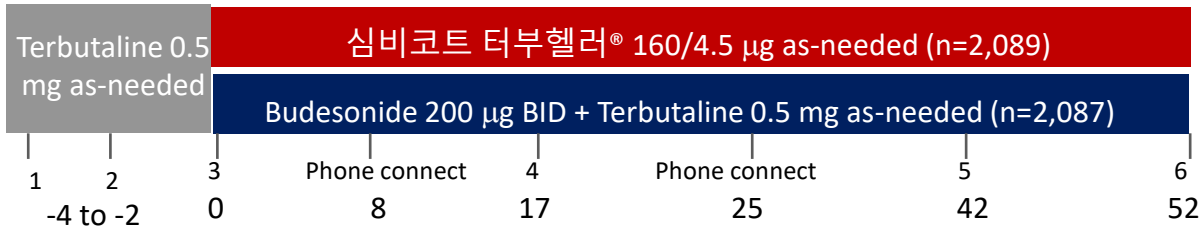
Novel START (n=675)[3]



Primary efficacy endpoint: Annualized rate of asthma exacerbations per patient
Secondary endpoints : Number of exacerbations by exacerbation treatment criteria and time to first exacerbation; number of severe exacerbations; percentage of patients withdrawn due to treatment failure; ACQ-5; FENO; on-treatment FEV1; electronically-recorded ICS use and SABA use; OCS use.

SYmbicort Given as needed in Mild Asthma

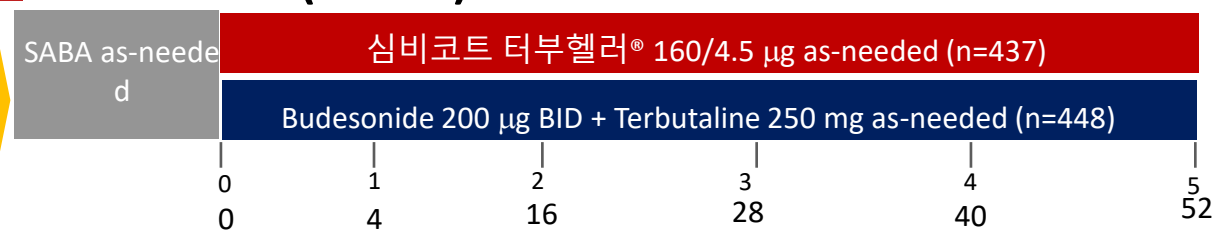
SYGMA 2 (n=4,176)[2]



Primary endpoint : Annualized severe asthma exacerbation rate (non-inferiority)
Secondary endpoints : FEV1, ACQ-5, ICS use, use of as-needed inhalations

The PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And Fast Onset Long-acting β2-agonist

PRACTICAL (n=885)[4]



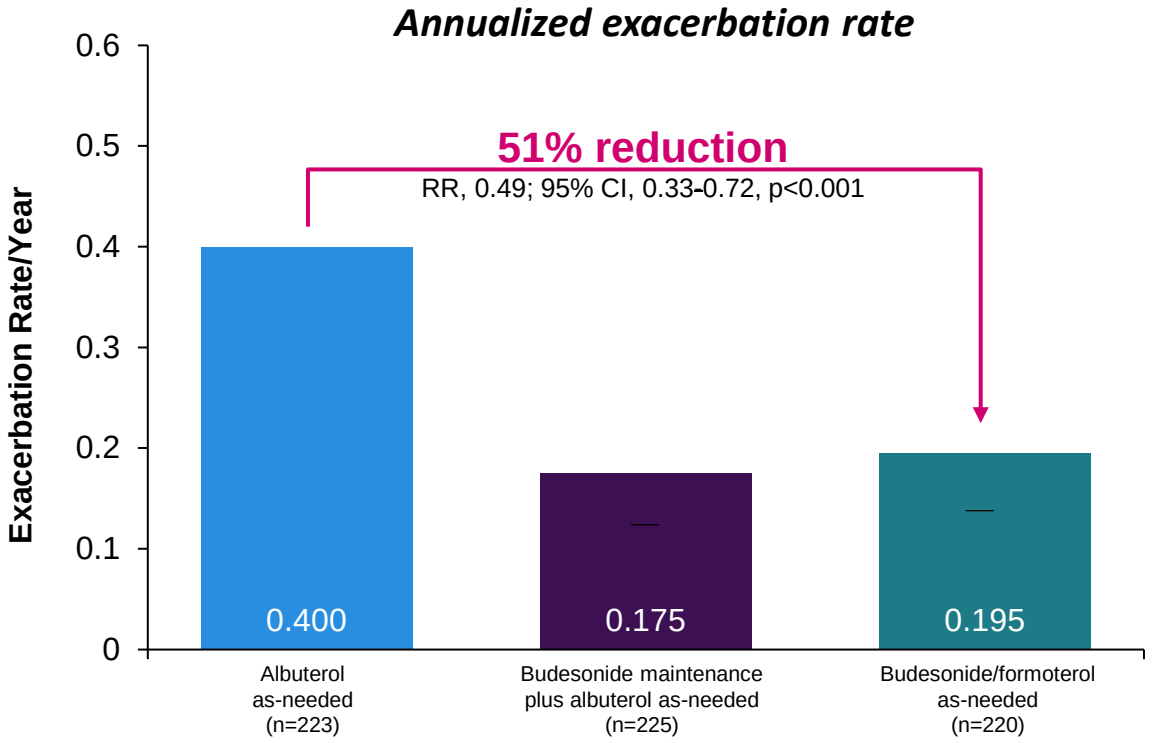
Primary endpoint : Number of severe asthma exacerbations per patient per year
Secondary endpoints : Severe asthma duration; time to first moderate or severe exacerbation, FEV1, ACQ-5, ICS use, use of as-needed inhalations

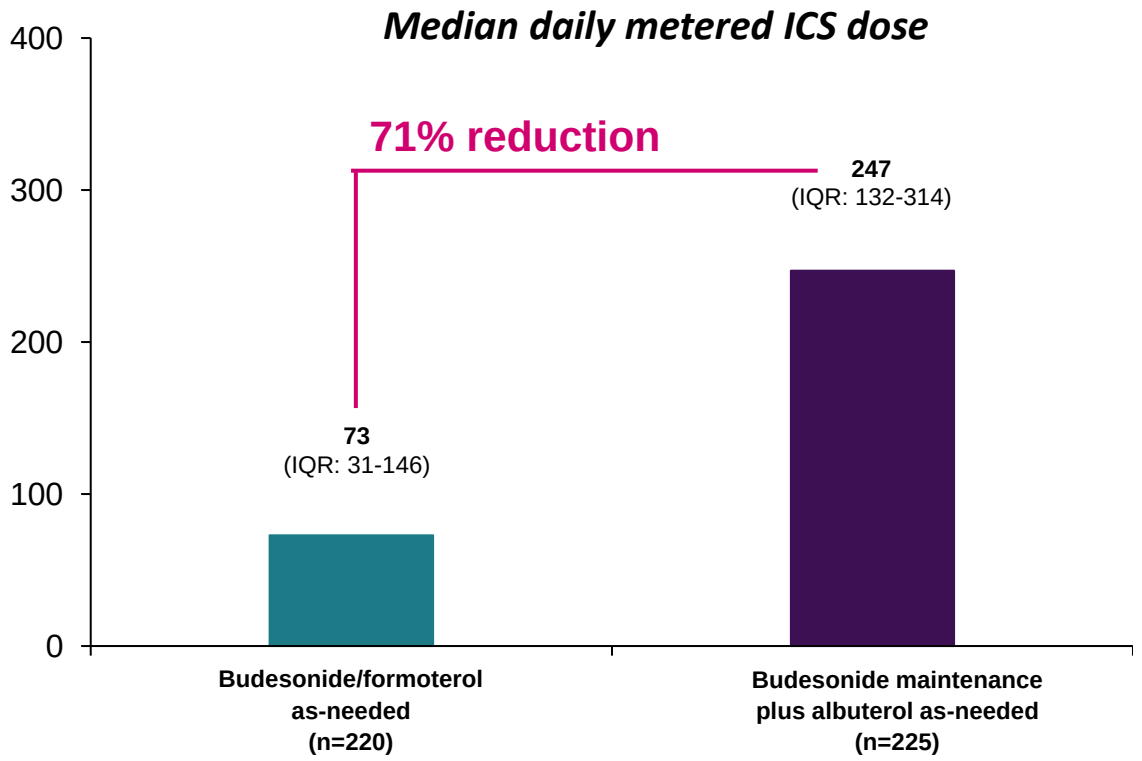
1. . O'Byrne PM, et al. Supplementary material. N Engl J Med. 2018;378:1865-1876; 2. Bateman ED, et al. Supplementary material. N Engl J Med. 2018;378:1877-1887 3. Beasley R, et al. N Engl J Med. 2019;380:2020-2030. 4. Hardy J, et al. Lancet. 2019 (ahead of print).

Novel START - Real world 에서 경증 천식 환자 대상 악화감소 효과

심비코트 터부헬러 160/4.5 as-needed 사용시

- Albuterol as-needed 군 대비 **연간 악화의 발생률 51% 감소 & 연간 중증 악화 발생률 60% 감소**
- Albuterol as-needed 군 대비 **첫 중증 악화 발생까지의 시간 더 지연**
- **Budesonide 유지요법군 대비 Median daily ICS dose 71% 감소**
- **악화로 인한 전신스테로이드 사용량에 있어 Albuterol as-needed 사용 대비 약 57% 감소, Budesonide 유지요법 대비 48% 감소**





A 52-week, open-label study assessing the effects of BUD/FORM Turbuhaler anti-inflammatory reliever in patients with mild asthma (n=220) compared with SABA as needed (n=223) and maintenance low-dose BUD BID + SABA as needed (n=225).
An exacerbation was defined as worsening asthma that resulted in ≥1 of the following: urgent medical consultation, use of systemic glucocorticosteroids or an episode of high β2-agonist use.
BID = twice daily; BUD = budesonide; FORM = formoterol; SABA = short-acting β2-agonist.

1. . Beasley R, et al. N Engl J Med. 2019;380:2020-2030.

Anti-Inflammatory Reliever로서 RWE에서 ICS mono therapy와 비교하여, 중증 악화 수를 56% 감소시켰습니다.[1]

이를 기반으로, 천식 환자들의 Inhaler Adherence가 떨어지는 Real World에서 BUD/FOR as-needed therapy가 좋은 치료 옵션이 될 수 있다고 말씀 드릴 수 있습니다[1].

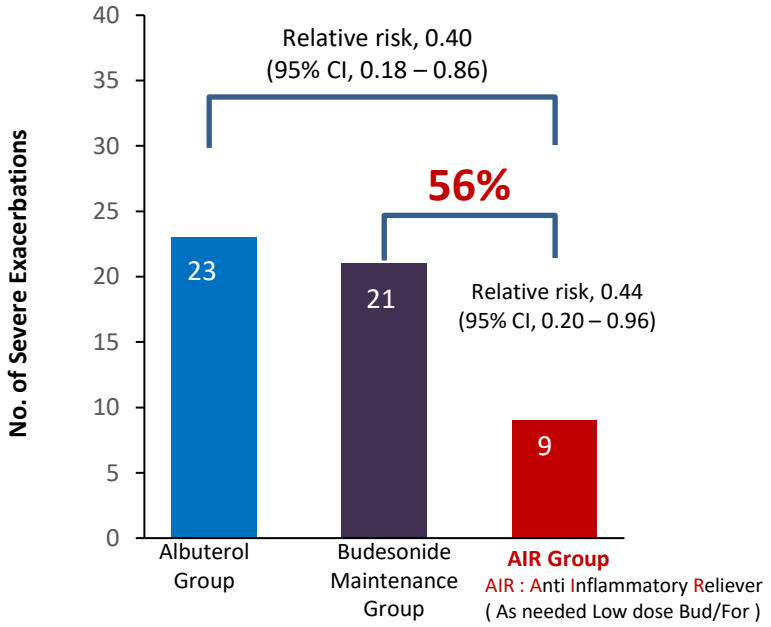
Pivotal Randomized Controlled Trials with Budesonide-Formoterol on Demand in Mild Asthma[2]

	Exacerbations* (vs budesonide-formoterol on demand)	ICS dose (budesonide-formoterol on demand vs budesonide, 200 µg twice daily)	Adherence to budesonide (200 µg twice daily)	ACQ** (vs budesonide-formoterol on demand)
NOVEL START	Albuterol on demand, 51% lower (p<0.001) Budesonide, 200 µg twice daily, 12% greater (p = 0.65)#	52% lower	56%	Albuterol on demand, -0.15 Budesonide, 200 µg twice daily, 0.14
SYGMA 1	Terbutaline on demand, 64% lower (p < 0.001) Budesonide, 200 µg twice daily, 17% lower (p = 0.28)#	83% lower	79%	Terbutaline on demand -0.15 Budesonide, 200 µg twice daily, 0.15
SYGMA 2	Budesonide, 200 µg twice daily, 3% lower (p = 0.75)#	75% lower	63%	Budesonide, 200 µg twice daily, 0.15

BUD, budesonide; **FOR**, formoterol; **SABA**: short-acting beta$_2$-agonis; **ACQ**, asthma control questionnaire; **ICS**, inhaled cortiosteroid; **Novel START**, Novel symbicort turbuhaler asthma reliever therapy; **SYGMA**, symbicort given as needed in mild asthma.
* Exacerbations were the secondary end point in SYGMA 1.
** The dose of budesonide-formoterol on demand was 200/6 µg in all 4 studies. Minimal clinically important difference in ACQ is 0.5.
# No significant difference

Novel START(n=668) RWE[2]

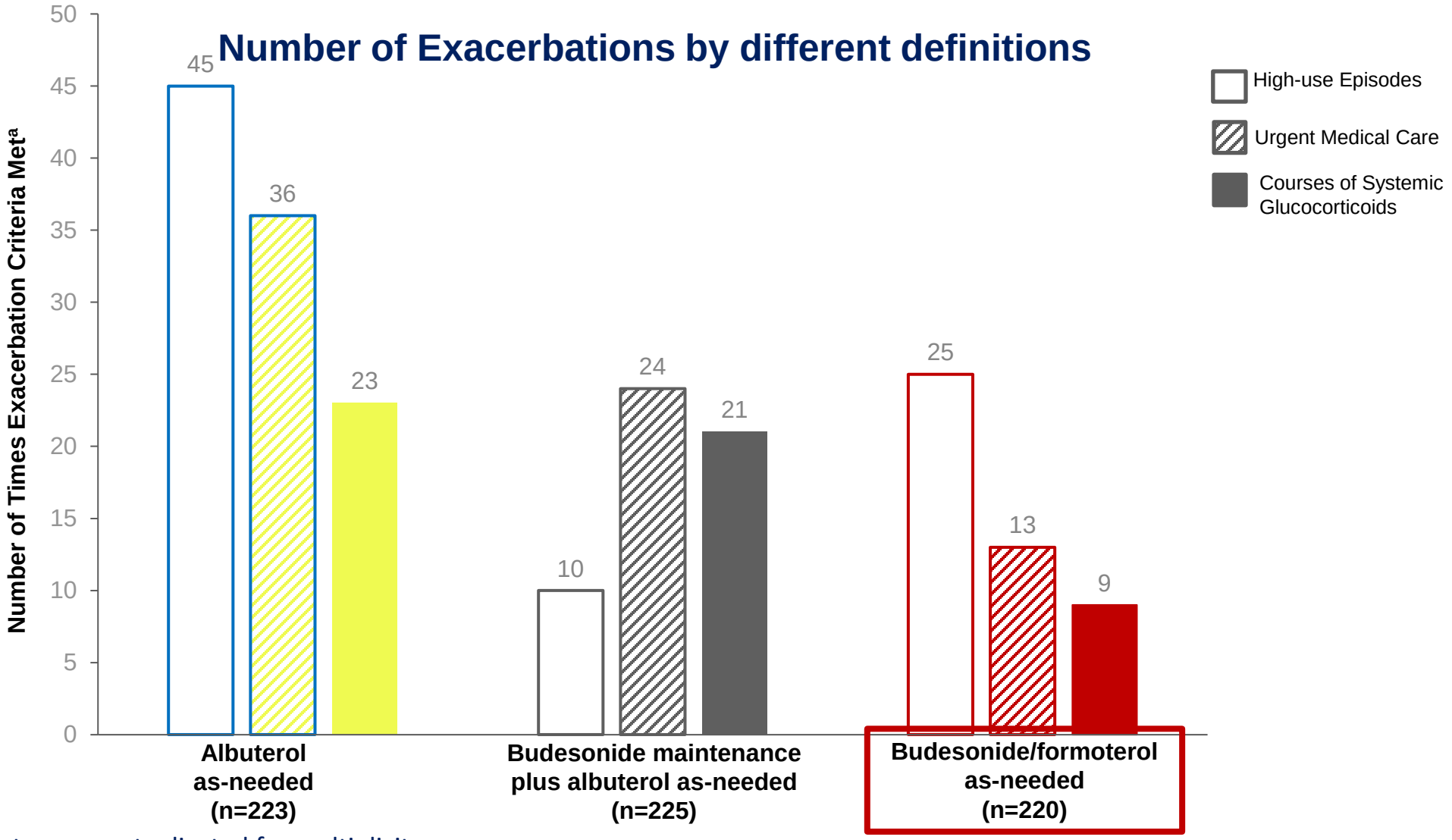
Number of Severe Exacerbations



52-week, randomized, open-label, parallel-group, controlled trial involving adults with mild asthma. The analysis included 668 of 675 patients who underwent randomization into the albuterol group, the budesonide maintenance group, and Anti Inflammatory Reliever group
Primary efficacy endpoint: Annualized rate of asthma exacerbations per patient
Secondary endpoints : Number of exacerbations and time to first exacerbation; number of severe exacerbations; percentage of patients withdrawn due to treatment failure; ACQ-5; FENO; on-treatment FEV1; electronically-recorded ICS use and SABA use; OCS use.

1. Beasley R, Holliday M, Reddel HK, *et al*. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med*. 2019;380(21):2020-2030. 2. Lipworth B, Chan R, Kuo CR. Anti-inflammatory reliever therapy for asthma. *Ann Allergy Asthma Immunol*. 2020;124(1):13-15.

"Real world", open-label trial of as-needed BUD/FORM in adults previously treated with as-needed SABA only

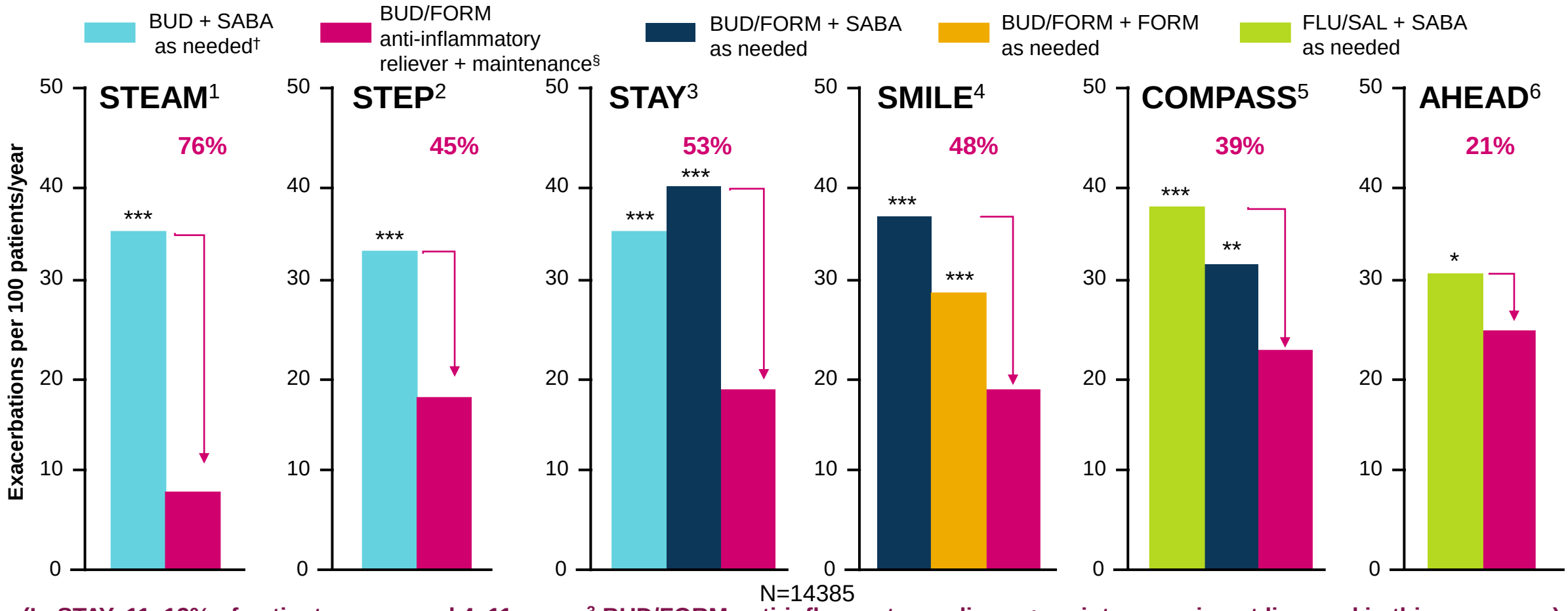


[a]Secondary endpoints were not adjusted for multiplicity.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Real-world clinical trials of Budesonide–Formoterol as Needed for Mild Asthma

	SYGMA 1	Novel START	SYGMA 2	PRACTICAL
Journal	NEJM 2018	NEJM 2019	NEJM 2018	Lancet 2019
Study type	RCT	**Real world**	RCT	**Real world**
Severity	Mild (Step 2)	Mild (**Step 1,2**)	Mild(Step 2)	Mild to Moderate(Step 1,2,3)
# of participants	3,836	668	4,176	885
Arm				
SABA Only	O	O	X	X
ICS maintenance + SABA	O	O	O	O
As needed ICS/FOR	O	O	O	O
Primary outcome	Symptom control	Exacerbation rate	Severe exacerbation rate	Severe exacerbation rate
Adherence (as needed ICS/FOR)	**79.1%**		**62.8%**	
ICS dose (day, median)	**57ug** vs 340ug	**73ug** vs 247ug	**66ug** vs 267ug	**164ug** vs 328ug
Severe exacerbation	(annualized rate)	(frequency)	(annualized rate)	(annualized rate)
SABA only	20%	23	X	X
ICS maintenance+ SABA	9%	21	12%	17.2%
As needed ICS/FOR	7%	9	11%	11.9%



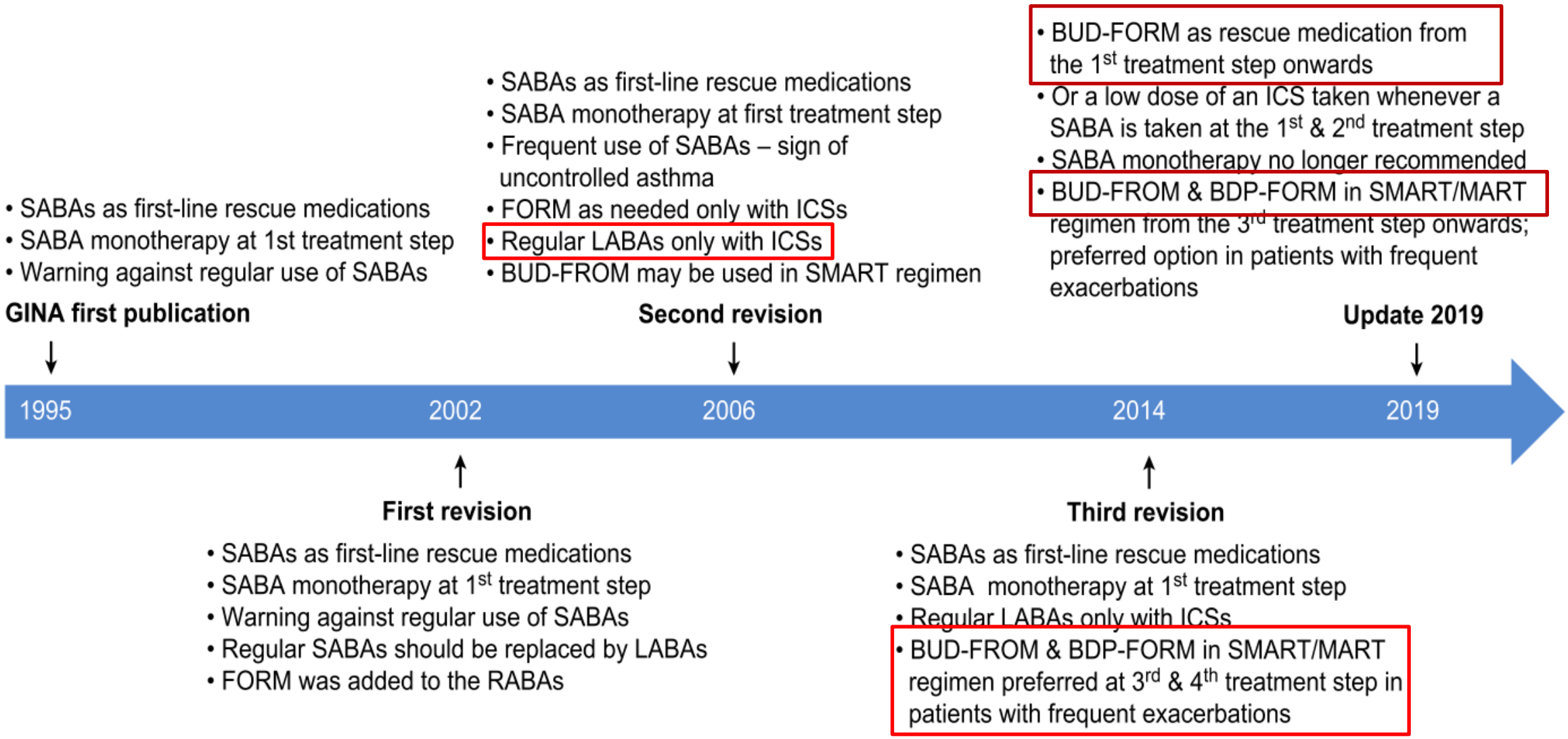
(In STAY, 11–13% of patients were aged 4–11 years;[3] BUD/FORM anti-inflammatory reliever + maintenance is not licensed in this age group)

*P=0.039 versus BUD/FORM anti-inflammatory reliever + maintenance. **P=0.0048 versus BUD/FORM anti-inflammatory reliever + maintenance. ***P<0.001 versus BUD/FORM anti-inflammatory reliever + maintenance. †BUD maintenance dose in each study was either one inhalation of 320 µg BID or two inhalations of 160 µg QD. §BUD/FORM was delivered via Turbohaler in all studies apart from STEAM; in STEAM BUD/FORM was delivered via DPI.

BID = twice daily; BUD = budesonide; DPI = dry powder inhaler; FLU = fluticasone; FORM = formoterol; ICS = inhaled corticosteroid(s); LABA = long-acting β_2-agonist; QD = once daily; SABA = short-acting β_2-agonist; SAL = salmeterol.

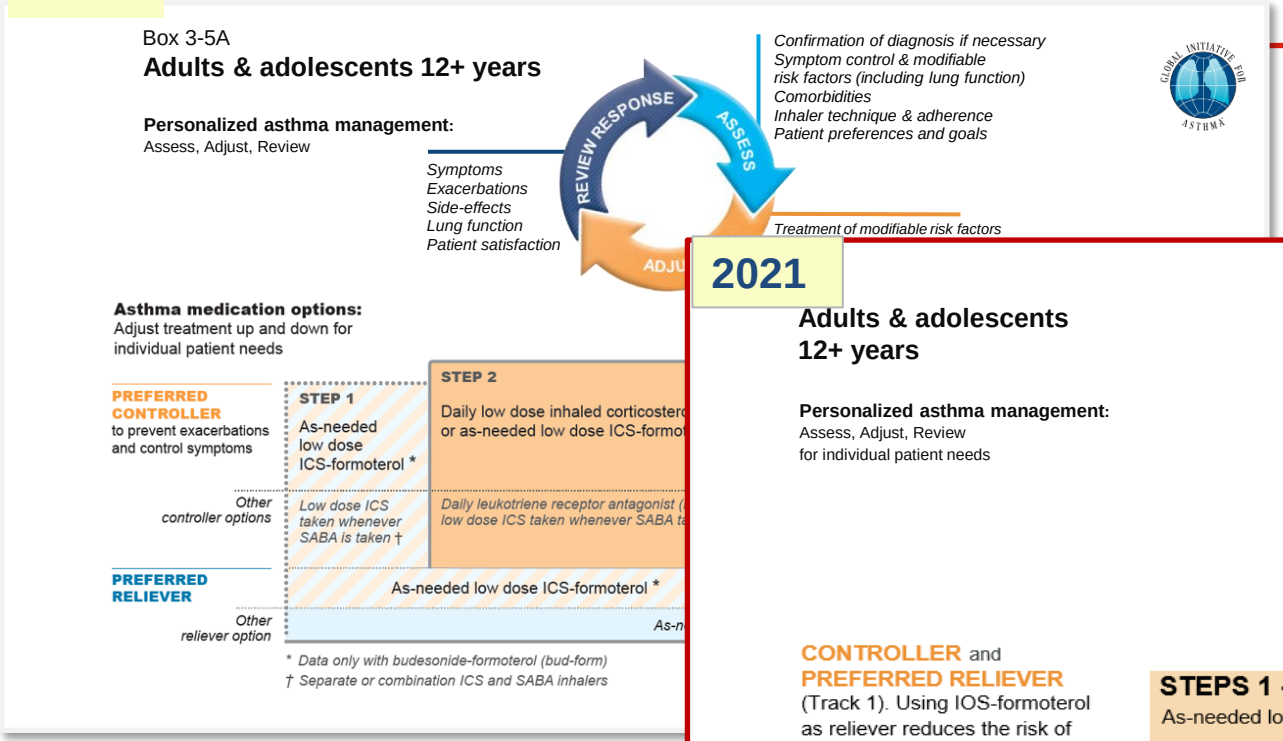
1. Rabe KF, et al. *Chest.* 2006;129:246-256; 2. Scicchitano R, et al. *Curr Med Res Opin.* 2004;20:1403-1418; 3. O'Byrne PM, et al. *Am J Respir Crit Care Med.* 2005;171:129-136; 4. Rabe KF, et al. *Lancet.* 2006;368:744-753; 5. Kuna P, et al. *Int J Clin Pract.* 2007;61:725-736; 6. Bousquet J, et al. *Respir Med.* 2007;101:2437-2446.

Introduction of anti-inflammatory reliever in GINA guidelines

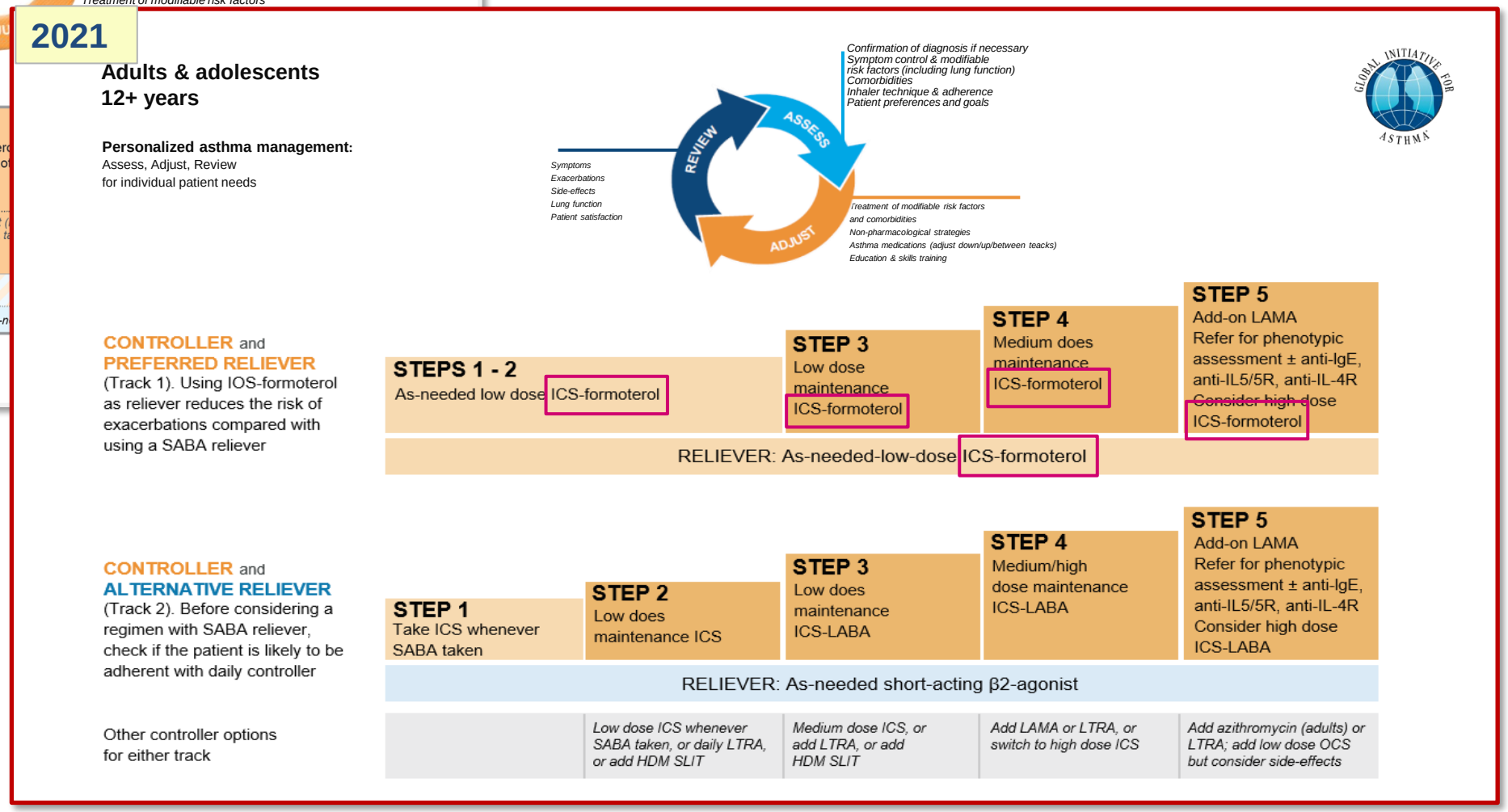


Modified management treatment algorithm (Box3-5A)

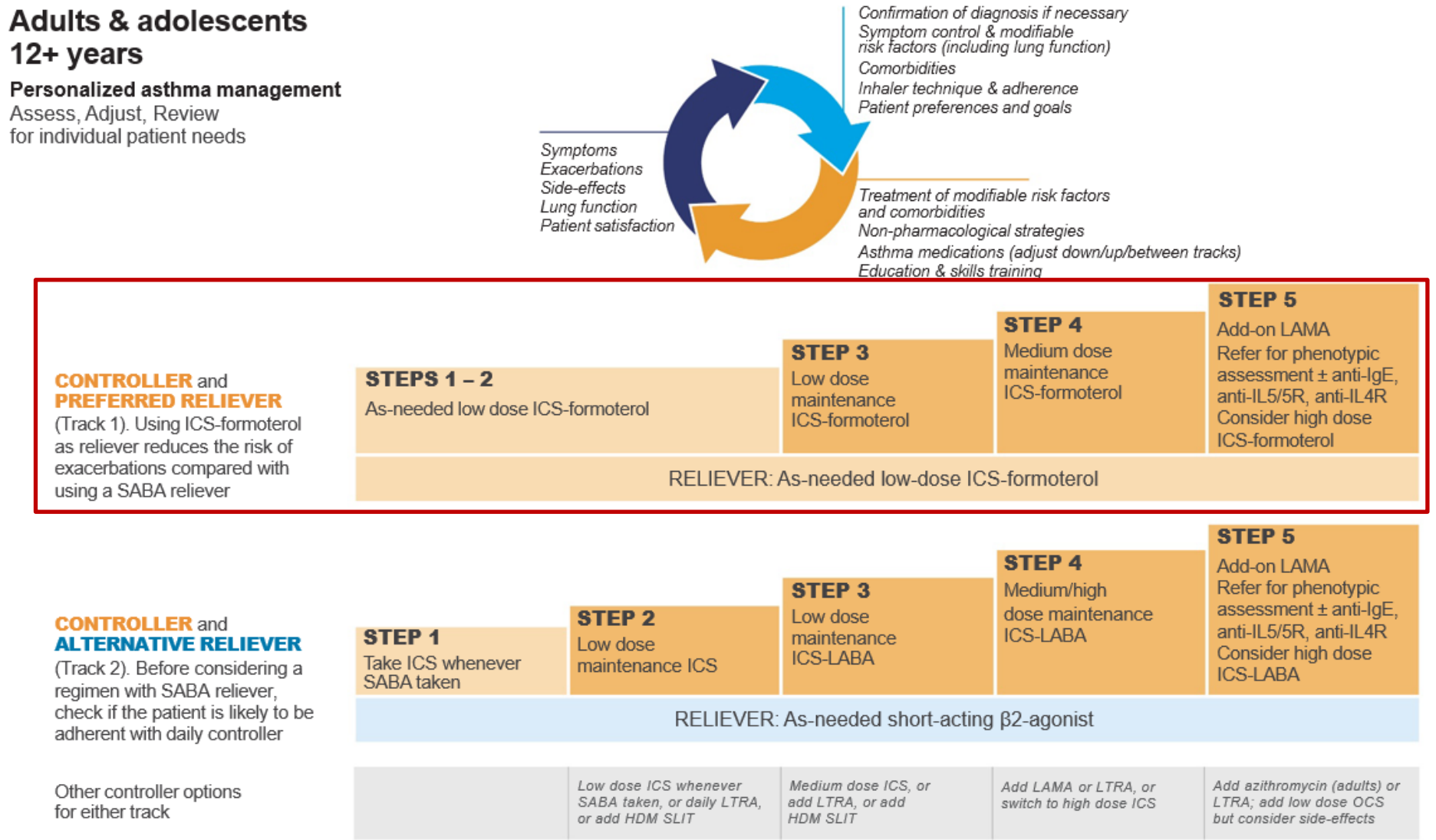
2020



2021



2021년 GINA 가이드라인에서는 모든 Step에서 ICS-formoterol를 controller 와 reliever로 우선권고하는 Track 1을 preferred treatment로 권고하였습니다



Global Initiative for Asthma. Main report 2021.

Initial asthma treatment – where to start?

"Starting treatment algorithm"

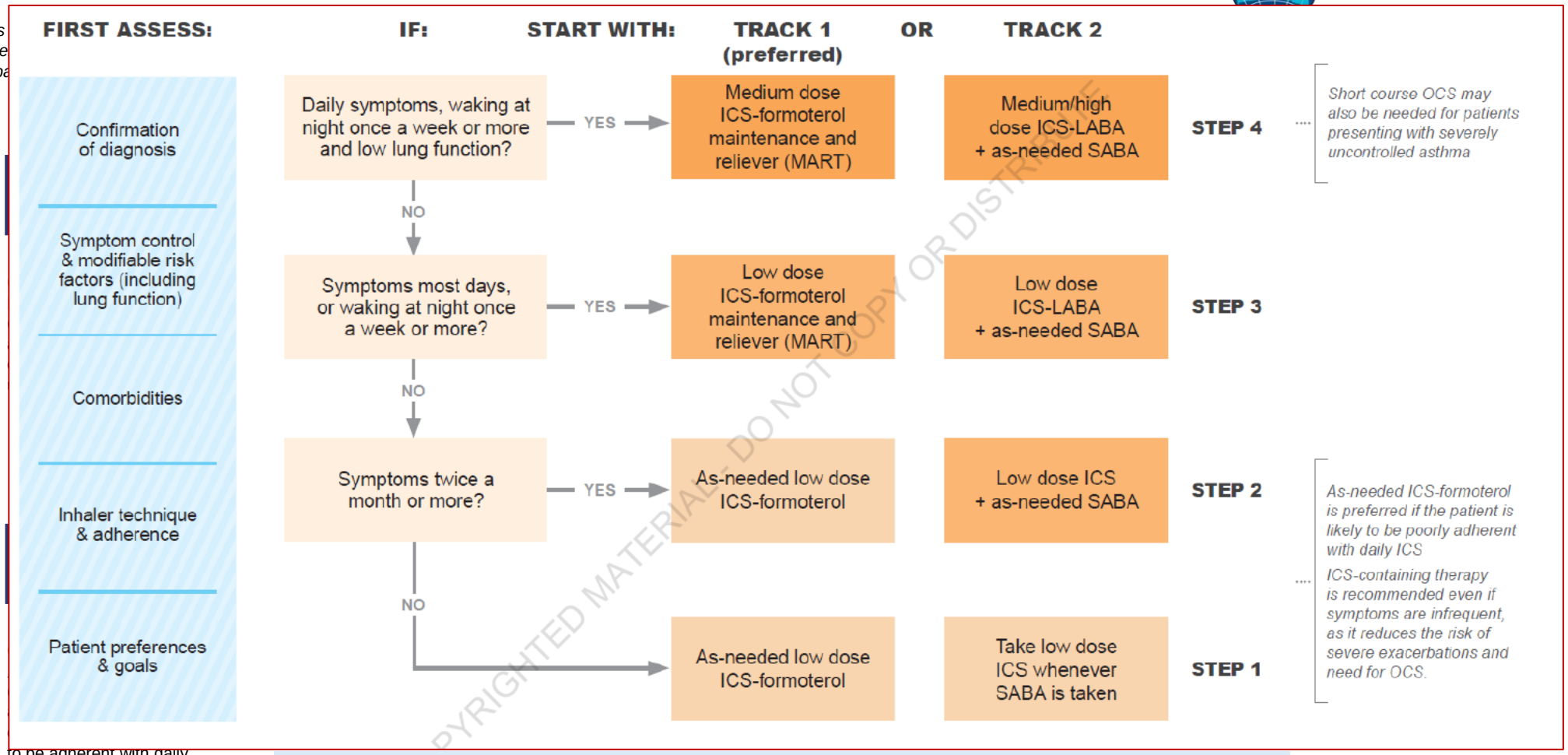
STARTING TREATMENT

in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is
ICS-containing therapy is recomme
reduces the risk of severe exacerba

FIRST ASSESS:

- Confirm diagnosis
- Symptom control and modifiable risk factors, including lung function
- Comorbidities
- Inhaler technique and adherence
- Patient preferences and goals



to be adherent with daily controller therapy

RELIEVER: As-needed short-acting β2-agonist

Step-down

Reduction in

1) Dose

2) Dosing Frequency

Current step	Current medication and dose	Options for stepping down	Evidence
Step 5	High dose ICS-LABA plus oral corticosteroids (OCS)	• Continue high dose ICS-LABA and reduce OCS dose • Use sputum-guided approach to reducing OCS • Alternate-day OCS treatment • Replace OCS with high dose ICS	D B D D
	High dose ICS-LABA plus other add-on agents	• Refer for expert advice	D
Step 4	Moderate to high dose ICS-LABA maintenance treatment	• Continue combination ICS-LABA with 50% reduction in ICS component, by using available formulations • Discontinuing LABA may lead to deterioration[301]	B A
	Medium dose ICS-formoterol* as maintenance and reliever	• Reduce maintenance ICS-formoterol* to low dose, and continue as-needed low dose ICS-formoterol* reliever	D
	High dose ICS plus second controller	• Reduce ICS dose by 50% and continue second controller[300]	B
Step 3	Low dose ICS-LABA maintenance	• Reduce ICS-LABA to once daily • Discontinuing LABA may lead to deterioration[301]	D A
	Low dose ICS-formoterol* as maintenance and reliever	• Reduce maintenance ICS-formoterol* dose to once daily and continue as-needed low dose ICS-formoterol* reliever	C
	Medium or high dose ICS	• Reduce ICS dose by 50%[300] • Adding LTRA† may allow ICS dose to be stepped down[302]	A B
Step 2	Low dose ICS	• Once-daily dosing (budesonide, ciclesonide, mometasone)[303,304] • Switch to as-needed low dose ICS-formoterol[168,169,171] • Switch to taking ICS whenever SABA is taken[196,197,199]	A A B
	Low dose ICS or LTRA	• Switch to as-needed low dose ICS formoterol[168-171] • Complete cessation of ICS in adults and adolescents is not advised as the risk of exacerbations is increased with SABA-only treatment[299]	A A

SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis

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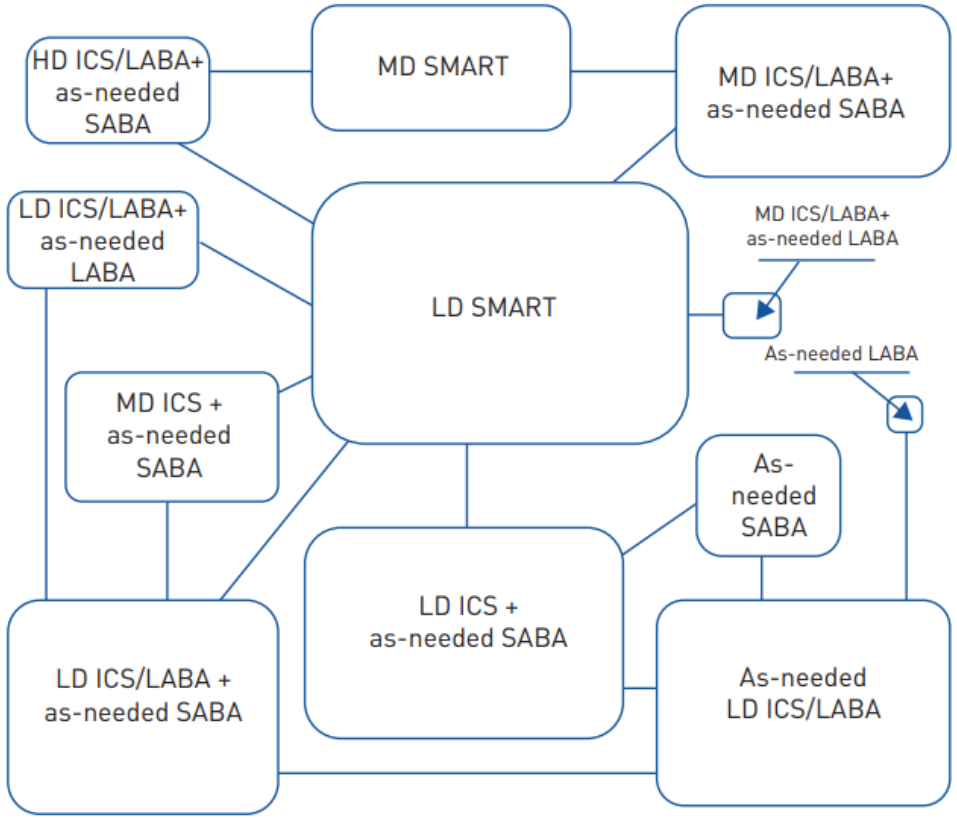
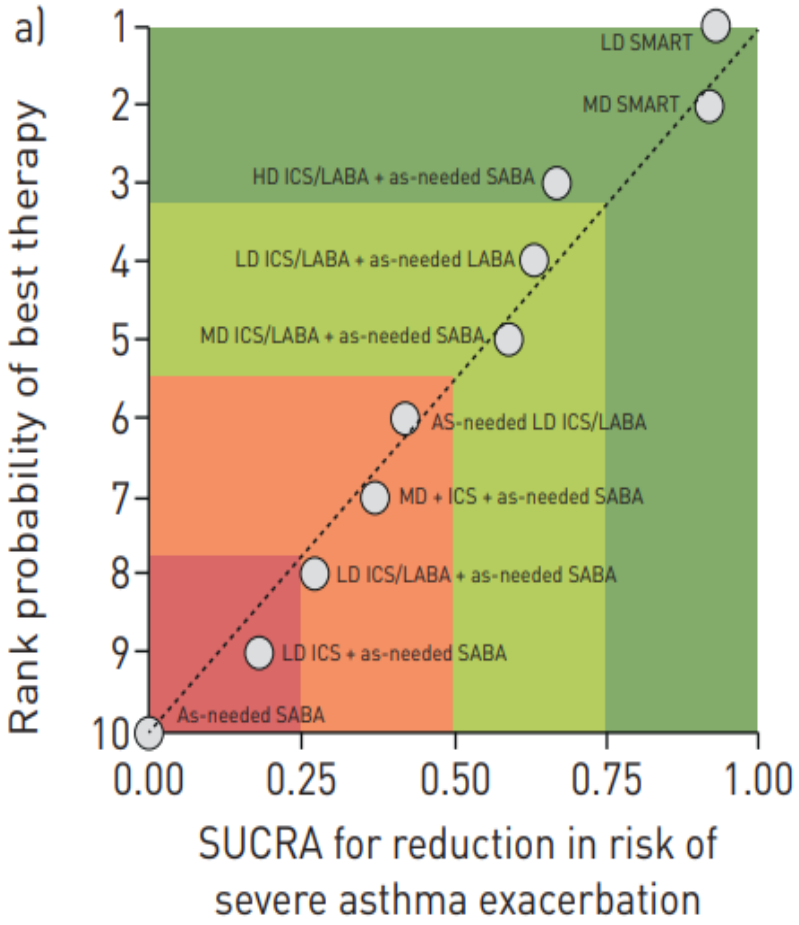


@ERSpublications
As-needed therapy represents a suitable therapeutic option in the treatment of asthma, with single maintenance and reliever therapy and as-needed ICS/LABA being the most effective therapeutic options https://bit.ly/3dEIXh4

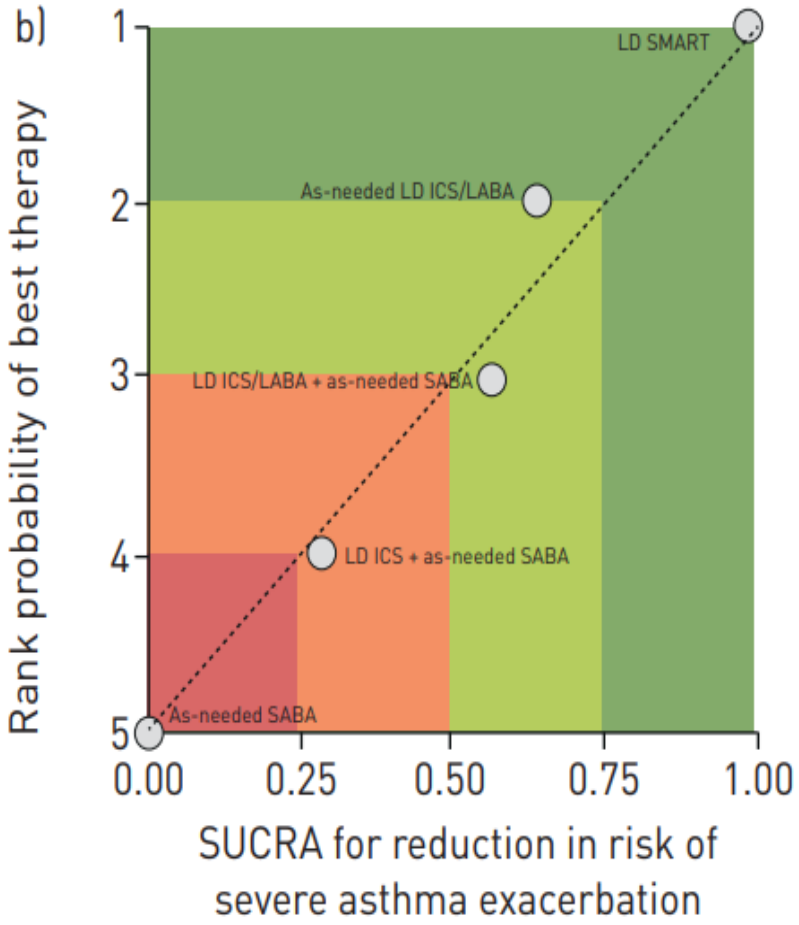
Cite this article as: Rogliani P, Ritondo BL, Ora J, *et al*. SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. *Eur Respir J* 2020; 56: 2000625 [https://doi.org/10.1183/13993003.00625-2020].

Ranking plot of the efficacy of as-needed therapies in preventing the risk of severe exacerbation

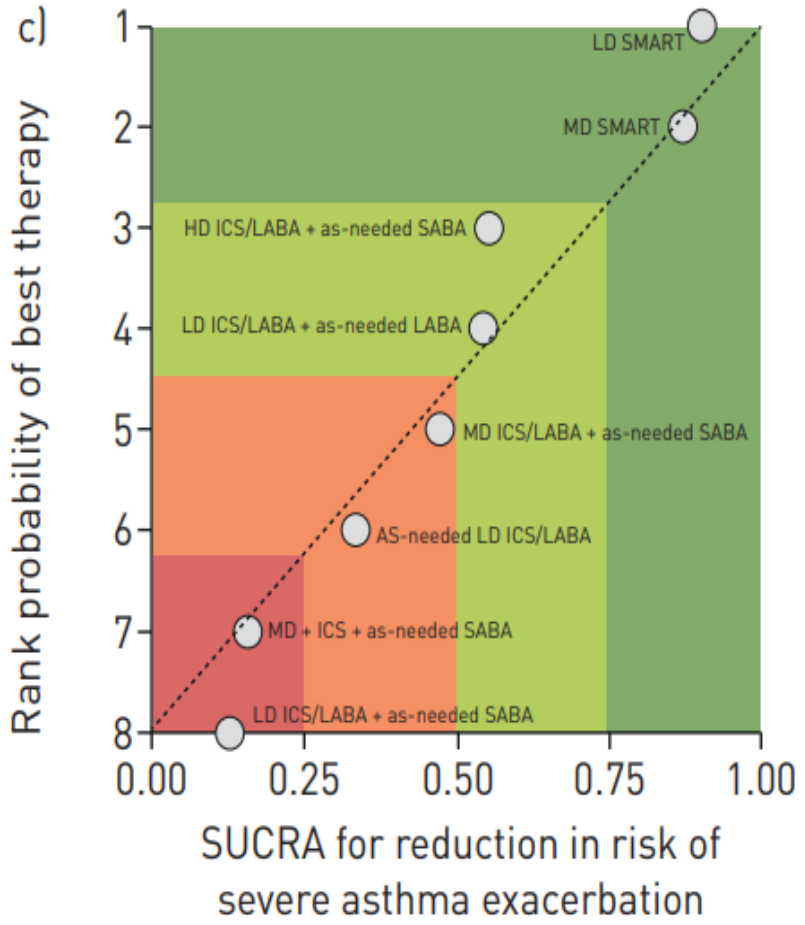
All patients



Mild to moderate



Moderate to severe



Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild to severe asthma: a network meta-analysis. Eur Respir J. 2020;2000625.

[결핵및호흡기학회] 2020 천식진료지침 4차 개정 ; 초기 조절 치료의 단계별 접근

증상에 따른 초기 조절제 치료 선택

- 한달에 2번 미만의 드문 천식 증상(악화 위험 인자 없을 경우) → 필요시 저용량 ICS-Formoterol
- **천식 증상 또는 Reliever 필요가 한달에 2번 이상** → 저용량 ICS + 필요시 SABA / **필요에 따른 저용량 ICS-Formoterol**
- **빈번한 천식 증상** 또는 **야간 증상**으로 일주일에 한번 이상 깨는 경우 **(특히 위험요소 동반하는 경우)** → **저용량 ICS-Formoterol 유지 및 완화요법** / 일반적인 ICS-LABA 유지용법 + 필요시 SABA/ 중간용량 ICS + 필요시 SABA
- **천식의 초기 증상이 중증의 조절 안되는 상태**이거나 **천식 급성 악화**가 있으면 → 단기간 OCS & 규칙적 조절제 (고용량 ICS or 중간용량 ICS-LABA) 치료 시작

	단계 1	단계 2	단계 3	단계 4	단계 5
선호되는 치료	**필요시 저용량 ICS-Formoterol** (증상완화 혹은 운동직전)	규칙적 저용량 ICS & 필요시 SABA 또는 **필요시 저용량 ICS-formoterol**	저용량 ICS-Formoterol을 유지치료로 사용 & 필요시 SABA 사용 또는 **저용량 ICS(BUD or BDP)-Formoterol 유지 및 완화요법**	**저용량 ICS-Formoterol 유지 및 완화요법** 또는 중간용량 ICS-LABA와 필요시 SABA 사용	전문가에게 의뢰하여 표현형 평가와 부가적 치료를 고려

BUD : Budesonide / BDP : Beclometasone dipropionate

1. 2020 천식진료지침 4차개정 - KATRD

[1, 2단계] 더 이상 SABA 단독치료는 권하지 않으며, ICS가 천식 조절에 가장 효과적인 약물로, 가능한 모든 천식 환자에서 사용할 것을 권고합니다.

	1단계	2단계
치료법	• **ICS는 전반적인 천식 조절에 가장 효과적인 약물로 가능한 모든 천식환자에서 사용할 것을 권고(근거수준: 높음, 권고강도: 강함)** • 성인 천식 치료에 있어 SABA 단독 치료는 안전성 문제로 권고되지 않음	• **ICS는 전반적인 천식 조절에 가장 효과적인 약물로 가능한 모든 천식환자에서 사용할 것을 권고(근거수준: 높음, 권고강도: 강함)**
선호되는 치료	**필요시 저용량 ICS-Formoterol (증상완화 혹은 운동 직전)** ① 매우 간헐적 증상을 보이는 환자에서도 중증 혹은 치명적 악화가 발생할 수 있음 ② 2단계 치료에서, 필요시 저용량 BUD/FOR 치료가 SABA 단독치료에 비해 중증악화발생을 2/3이상 감소시키고, ICS 매일 투여에 비해 평균 ICS 사용량을 20% 미만으로 감소시킴 ③ 증상이 드문 환자들에서 ICS 매일 투여에 대한 순응도가 매우 나쁘고, 이로인해 SABA 단독치료의 위험성이 높음 ④ 천식 치료 시작 시, 증상완화를 위한 SABA에 의존하는 위험을 피하기 위해, 모든 환자들에게 조절제(경증에서는 필요에 따라)를 증상완화와 악화 위험성 감소를 위해 처음부터 써야한다고 지속적으로 교육해야 함	규칙적 저용량 ICS와 필요시 SABA 또는, **필요시 저용량 ICS-Formoterol** → 경증천식에서 규칙적인 저용량 ICS와 증상발생 시 혹은, 운동전 SABA 치료와 필요에 따른 BUD-FOR 치료를 비교한 연구에서는 운동유발성 기관지수축의 경감효과가 동등했음
다른 치료	SABA 사용 시, 저용량 ICS를 동시에 사용하는 방법 고려 가능 → 증상이 적은 환자에서 저용량 ICS의 규칙적 사용은 순응도가 매우 낮음, SABA 단독치료의 위험을 막기 위해 저용량 ICS 단독 처방은 권고하지 않음	
권장되지 않는 치료	성인에서 SABA 단독 치료는 권고되지 않음 → 지속하는 경우, 증상조절이 잘 되는 경우에도 천식 연관 사망의 위험과, 천식악화로 인한 응급방문의 가능성이 높아짐	서방형테오필린과 크로몰린제와 같은 조절제는 일반적으로 사용하지 않음

1, 2단계 환자에서는 흡입순응도를 높이기 위해 필요시 저용량 ICS-Formoterol을 선호 치료제로 두었습니다.

1. 2020 천식진료지침 4차개정 - KATRD

BUD : Budesonide / BDP : Beclometasone dipropionate

[3, 4단계] 악화 병력이 있는 환자에서 규칙적 ICS-LABA와 필요시 SABA 사용보다 ICS-Formoterol의 유지 및 완화 요법을 권고합니다.(근거수준: 높음, 권고강도: 강함)

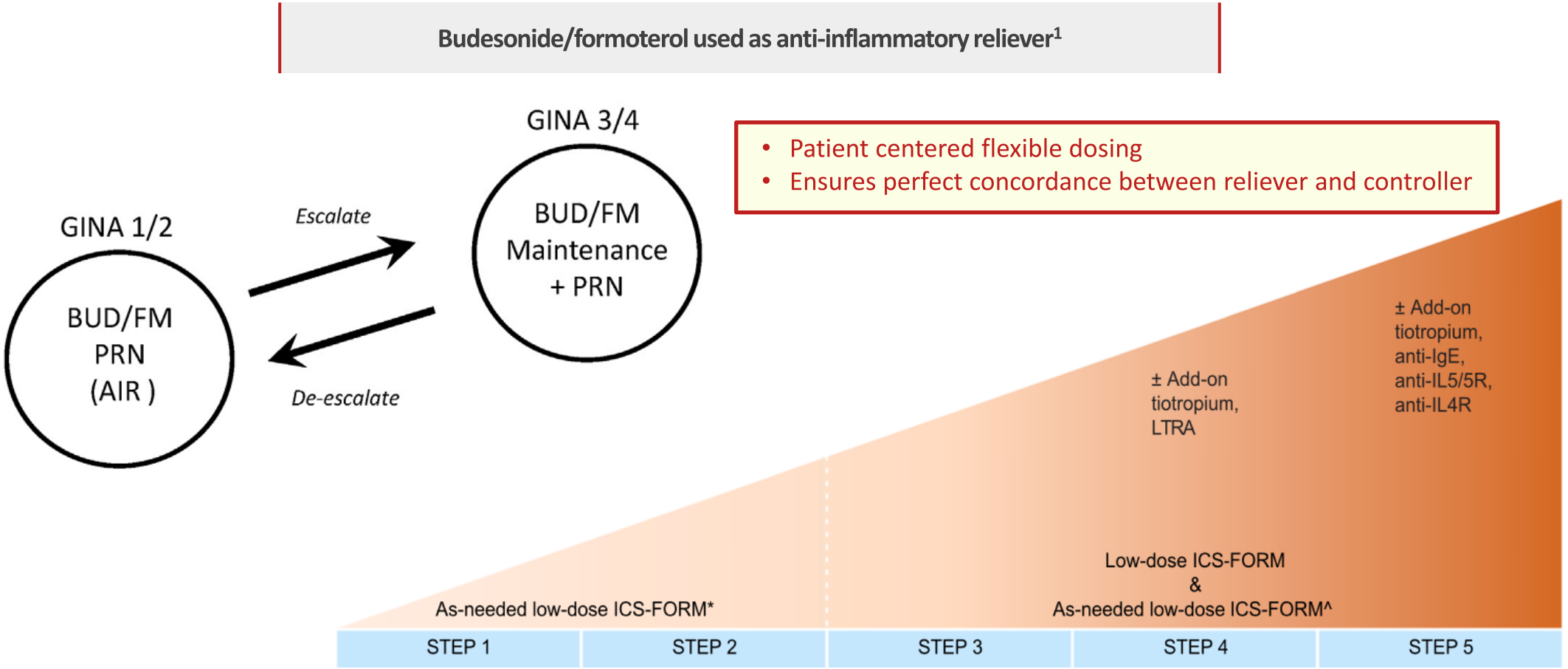
	3단계	4단계
치료법	•저용량 ICS 치료로 조절되지 않는 환자는 LABA를 우선적으로 추가할 것을 권고(근거수준 높음, 권고강도 강함) •저용량 ICS 치료로 조절되지 않는 환자는 Tiotropium을 추가하기 보다, LABA를 우선적으로 추가함 (근거수준:낮음, 권고강도:약함) •ICS 단독으로 조절되지 않는 천식환자에서 LABA 병합요법이 LTRA 추가하는 것보다 효과적임 (근거수준:높음, 권고강도:강함) •저용량 ICS로 조절되지 않는 환자는 ICS를 중간용량으로 증량할 것을 권고 (근거수준:높음, 권고강도:강함) •저용량 ICS 치료로 조절되지 않는 환자는 LTRA 추가할 것을 권고 (근거수준:높음, 권고강도:강함) •**BUD-FOR** 또는 BDP-FOR은 급성악화 감소와 증상 호전을 유도할 수 있어 **유지요법 및 증상완화제로 사용이 가능함(근거수준: 높음, 권고강도: 강함)** •**악화 병력이 있는 환자에서** 규칙적 ICS-LABA와 필요시 SABA 사용보다 **ICS-Formoterol의 유지 및 완화 요법을 권고함(근거수준: 높음, 권고강도: 강함)**	•**BUD-FOR** 또는 BDP-FOR은 급성악화 감소와 증상 호전을 유도할 수 있어 **유지요법 및 증상완화제로 사용이 가능함(근거수준: 높음, 권고강도: 강함)** •**악화 병력이 있는 환자에서 ICS-Formoterol 유지 및 완화 요법을** 규칙적 ICS-LABA와 필요시 SABA사용보다 **권고함(근거수준: 높음, 권고강도: 강함)**
선호되는 치료	저용량 ICS-LABA를 유지치료로 사용하면서 필요시 SABA 사용, 혹은 **저용량 ICS(BUD or BDP)-FOR 유지 및 완화요법** →BDP-FOR 혹은 BUD-FOR은 유지치료 및 증상완화의 두 가지 용도로 사용할 수 있음 →지난 1년 동안 1회 이상의 급성악화가 있었던 환자에서 ICS-formoterol의 유지 및 완화 치료 방법은 고정용량의 ICS-LABA 유지 치료 혹은 고용량 ICS와 필요시 SABA 치료와 비교하였을 때, 상대적으로 낮은 용량의 ICS 사용으로도 비슷한 정도의 증상 조절을 보이면서, 급성악화를 줄일 수 있음	**저용량 ICS-Formoterol 유지 및 완화요법이나** 중간용량 ICS-LABA와 필요시 SABA 사용 →지난 1년동안 1회 이상의 급성악화가 있었던 환자에서, 유지 및 완화제로 저용량 ICS-FOR의 사용은, 유지요법으로서 동일한 용량의 다른 ICS-LABA 혹은 고용량 ICS와 비교하였을 때, 급성악화의 빈도를 더 낮춤 → BDP-FOR 혹은 BUD-FOR 를 저용량으로 사용 환자의 경우 필요하면 유지용량을 중간용량으로 증량할 수 있음 →저용량 ICS-LABA와 필요시 SABA를 사용함에도 잘 조절되지 않으면, 중간용량 ICS-LABA를 고려할 수 있음 → 4단계에서 고용량 ICS는 더 이상 권장되지 않음

1. 2020 천식진료지침 4차개정 - KATRD

BUD : Budesonide / BDP : Beclometasone dipropionate

환자들은 Anti Inflammatory Reliever 치료법을 통해 하나의 디바이스로 천식 단계에 따른 용량 조절, Step up/down 을 편리하게 할 수 있습니다.[1,2]

- 실제로 여러 **Trigger factors** 로 인해, 혹은 시간이 지남에 따라 천식 환자에서 경증과 중증도 증상 변화가 나타나기 때문에 적절한 용량 조절이 필요합니다.[1]
- 또한 증상이 나타날 때만 흡입기를 사용하려는 환자들의 행동패턴에 맞춰 치료가 가능합니다.



1. Ann Allergy Asthma Immunol 124 (2020) 13e15 2. Kuprys-Lipinska et al. Clin Transl Allergy (2020) 10:19

효과적인 증상 조절을 위해 Medication adherence 를 높이도록 Controller 와 Reliever 를 동일한 device 로 사용하는 것이 권장됩니다.[1]

- 천식 치료시 **Same device** 사용 군이 **Mixed devices** 사용 군 보다 더 나은 천식 증상 조절, 중증 악화 감소 효과를 보였습니다.[2]
- 따라서 환자에게 **한 가지 흡입기**의 올바른 사용법을 교육하여 **적절한 천식 치료 시작**하는 것이 다양한 흡입기를 사용하는 것보다 **효과적**입니다.

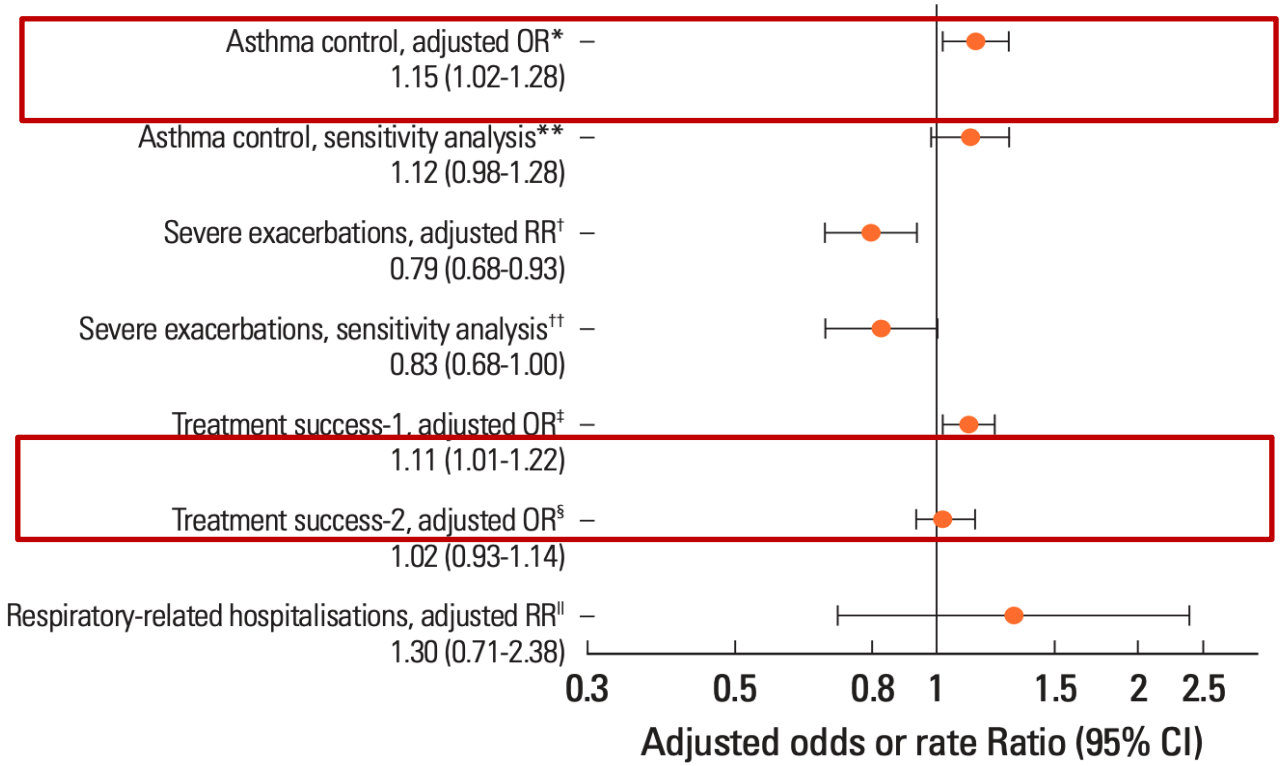
Poor medication adherence in asthma[1]

Factors contributing to poor adherence

Medication/regimen factors
- Difficulties using inhaler device (e.g. arthritis)
- Burdensome regimen (e.g. multiple times per day)
- Multiple different inhalers

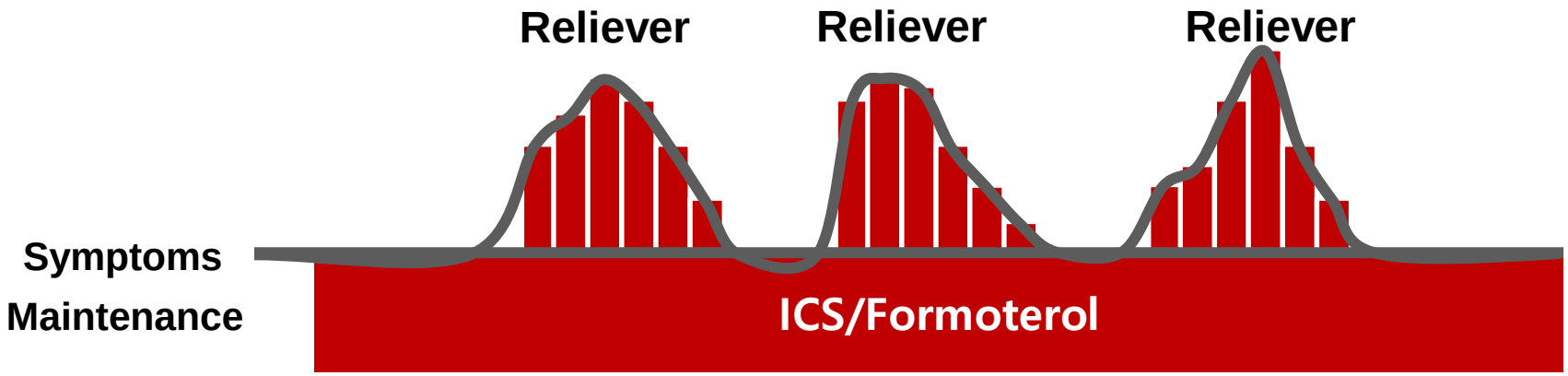
Unintentional poor adherence
- Misunderstanding about instructions
- Forgetfulness
- Absence of a daily routine
- Cost

Same device vs. Mixed devices[2]



1. Global Initiative for Asthma. Main report 2020. 2. David Price et al, Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care Allergy Asthma Immunol Res. 2012 July;4(4):184-191.

Device Preference for Maintenance/Stepping Therapy



	SMART	Step up/down With 1 device	Once Daily	Prevent exacerbation
BUD/FOR	O	O	O	O
Flu/Sal	X	X	X	O
Flu/Vil	X	X	O	O
Bec/For	O	X	X	O
Flu/For	X	X	X	O

*Benefit of ICS/Formoterol in preventing exacerbation appears to be due to intervention at a very early stage of worsening asthma: GINA 2020

Summary

- **Present of asthma in Korea**

  여전히 SABA 나 OCS 의 처방율이 높고 ICS 처방율이 낮다

- **RWS에서도 SABA 사용이 천식에서 나쁜 임상결과를 보여주었다.**

- **Anti-inflammatory therapy is essential in treatment of mild to severe asthma**
  - Anti-inflammatory treatment(BUD/FOR) is highly effective from mild to severe asthma
  - Anti-inflammatory reliever (MART) is the basement of the preferred track in managing asthma
  - Besides step-up therapy, step-down strategy is also important in managing mild to moderate asthma

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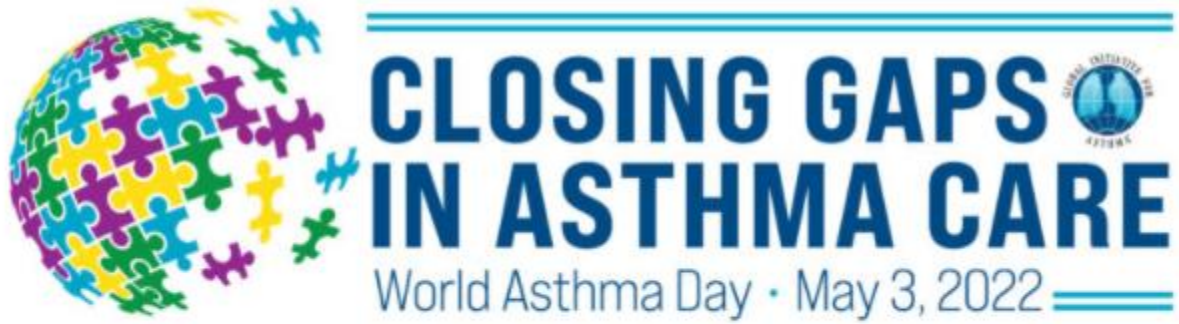

- in equal access to diagnosis and treatment (medicine)
- between care for different socioeconomic, ethnic and age groups
- between wealthy and poorer communities and countries;
- in communication and care across the primary/secondary/tertiary care interface
- in communication and education provided for people with asthma, (quality of asthma care plans vs)
- in asthma knowledge and asthma awareness between health care providers
- in prioritization between asthma and other long term conditions
- between prescribing inhalers and monitoring adherence and ability to use these devices;
- exist for the general public's (non-asthmatics) and health care professional's awareness and understanding that asthma is a chronic (not acute) disease.
- between scientific evidence and actual delivery of care for people with asthma.


감사합니다