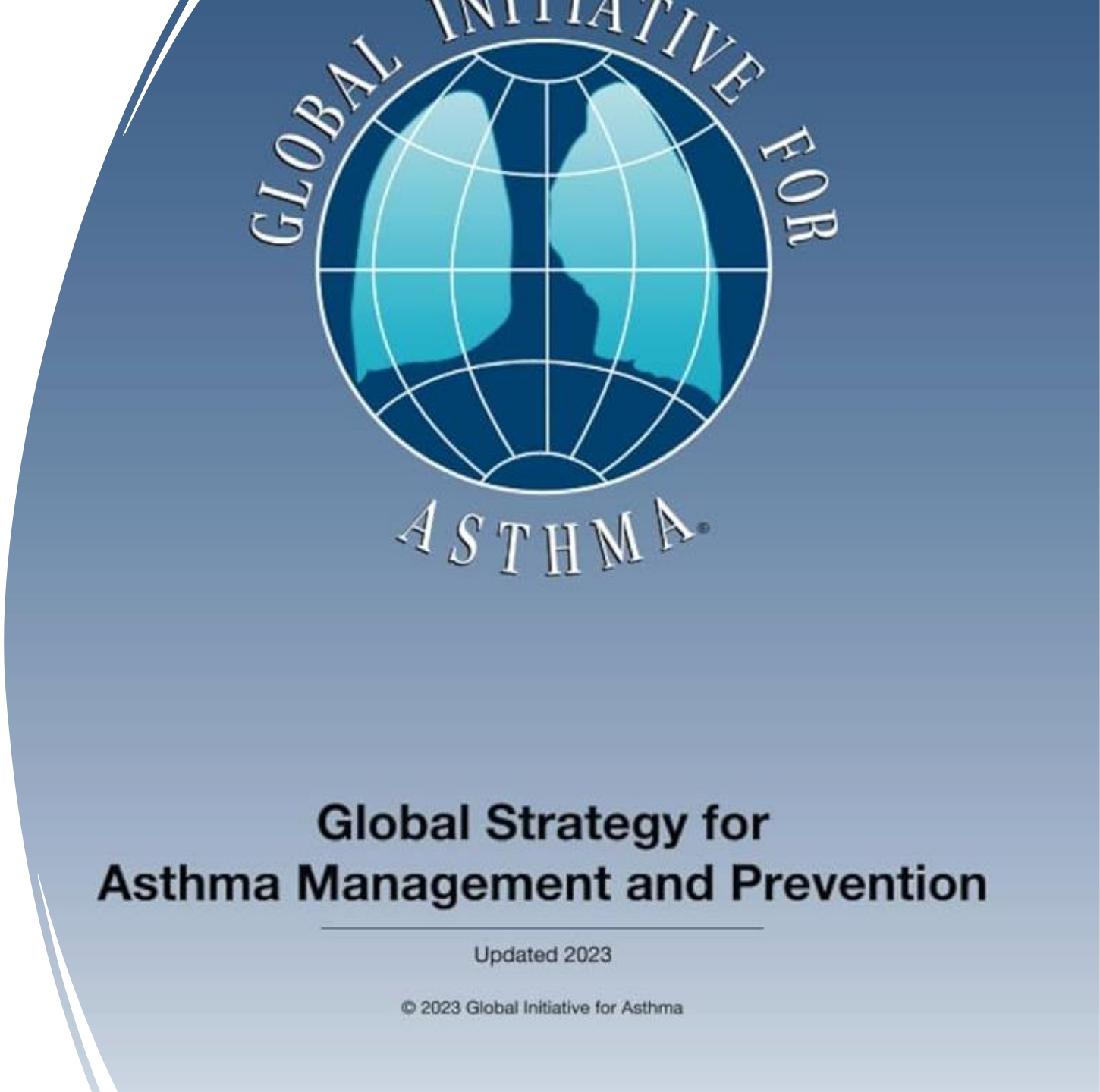
What's new in GINA 2023

양산부산대학교병원
호흡기알레르기내과
손은정



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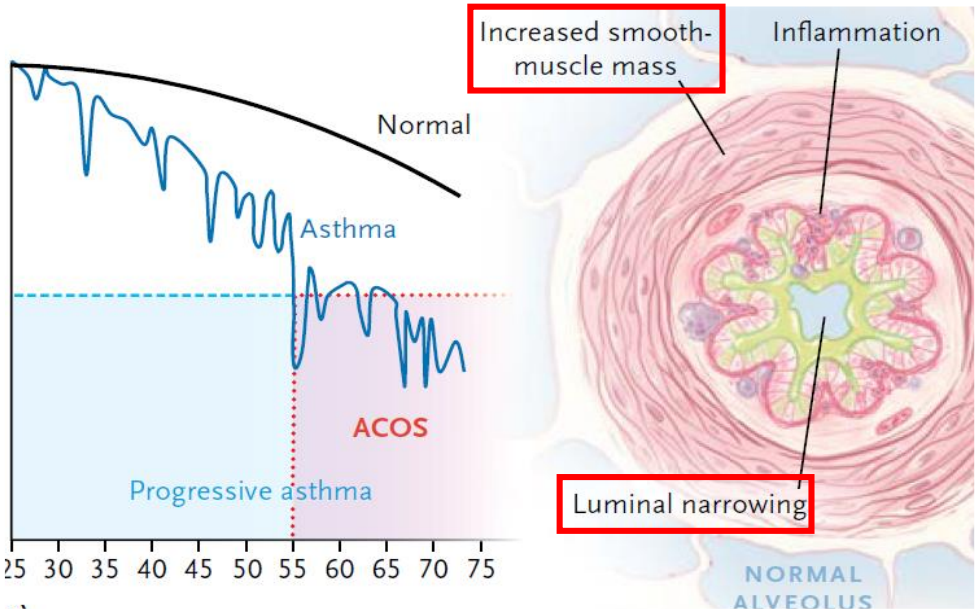
천식의 정의



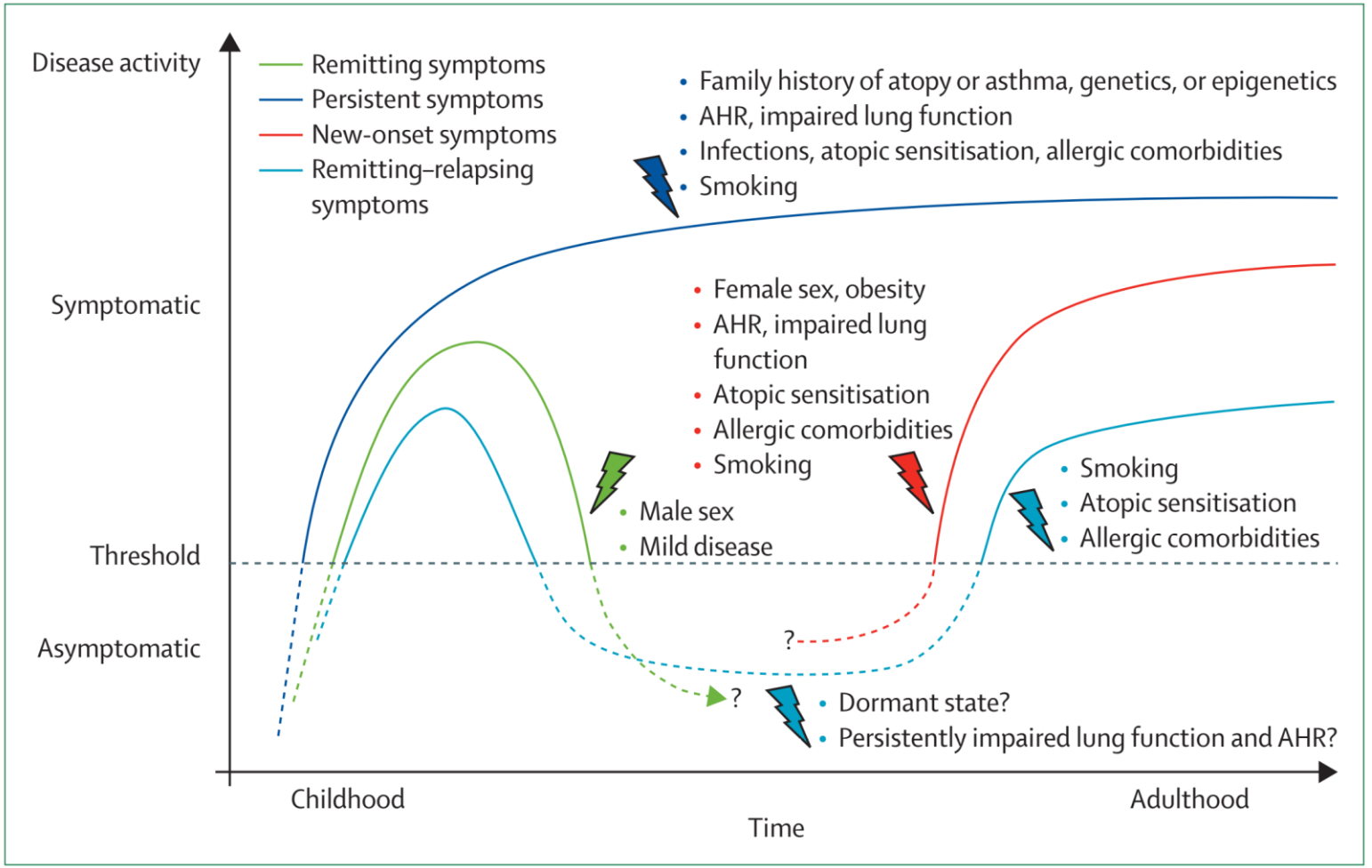
(1) Heterogeneous disease characterized by chronic airway inflammation

(2) History of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, cough, that vary over time and in intensity

(3) Variable expiratory airflow limitation

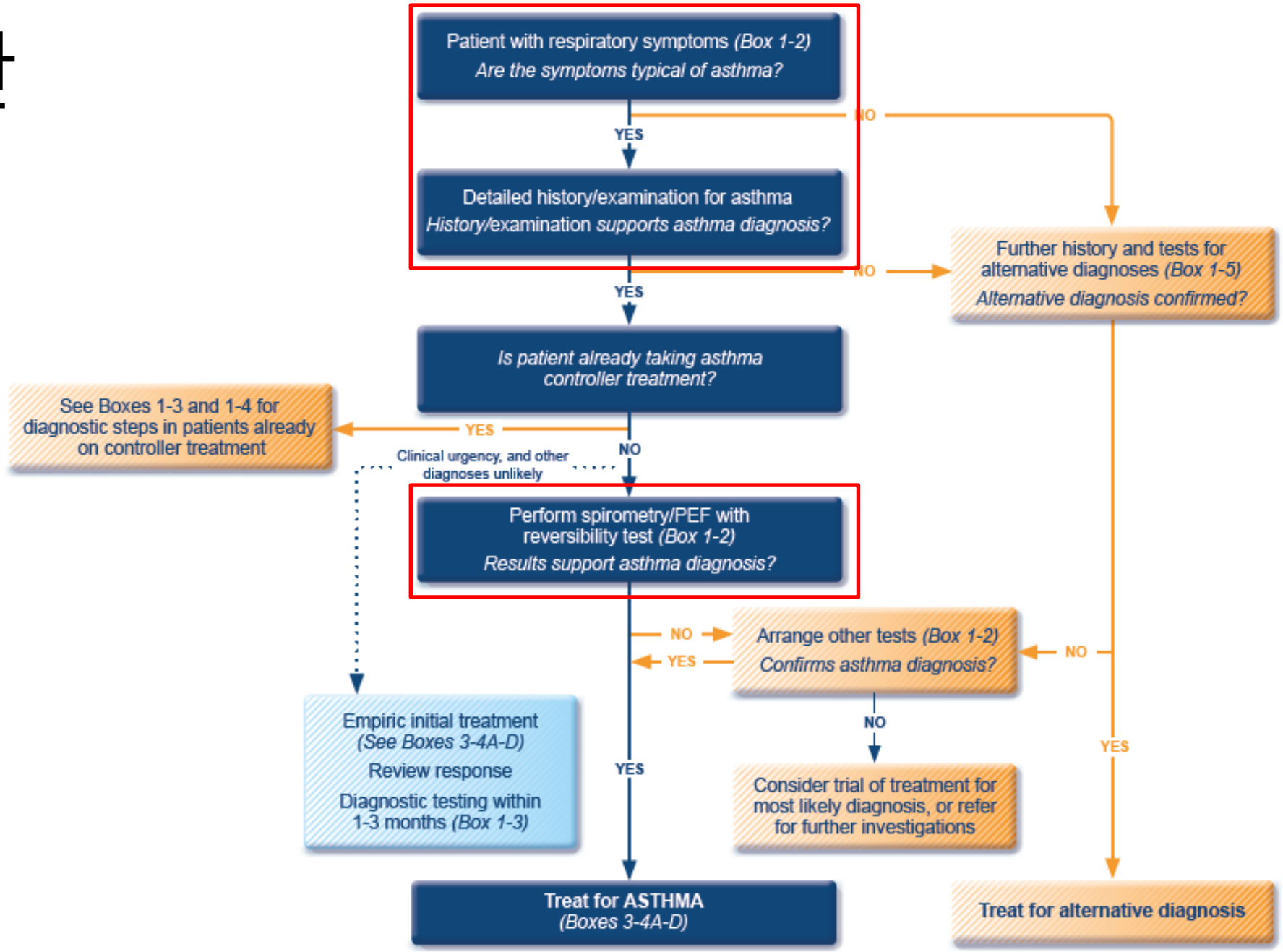
GINA 2023, PostmaDS, et al. N EnglJ Med 2015;373(13):1241-9.

천식의 자연경과



Fuchs O, et al. Lancet RespirMed 2017:5(3):224-234.

천식의 진단



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천식의 증상

Feature	Symptoms or features that support the diagnosis
Wheeze, **shortness of breath**, **chest tightness** and **cough**	• More than one type of respiratory symptom • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections

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천식의 진단

Documented excessive variability in lung function* (one or more of the following)

- Positive bronchodilator (BD) reversibility test
- Excessive variability in twice daily PEF over 2 wks
- Increase in lung function after 4 weeks of anti-inflammatory treatment
- Positive exercise challenge test
- Positive bronchial challenge test
- Excessive variation in lung function between visits

+

Documented expiratory airflow limitation

At a time when FEV1 is reduced, confirm that FEV1/FVC is also reduced compared with the lower limit of normal

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호기 기류제한의 변동성 검사

Documented excessive variability in lung function* (one or more of the following)	
Positive bronchodilator (BD) reversibility test	FEV1 of >12% and >200 mL Measure change 10-15 minutes after 200-400 mcg salbutamol.
Excessive variability in twice daily PEF over 2 wks	Average daily diurnal PEF variability >10%
Increase in lung function after 4 weeks of anti-inflammatory treatment	Increase in FEV1 by >12% and >200 mL (or PEF by >20%) from baseline

Peak expiratory flow

$$\text{일중 최대호기유량 변동값} = \frac{\text{최대호기유량} - \text{최소호기유량}}{(\text{최대호기유량} + \text{최소호기유량})/2} \times 100$$

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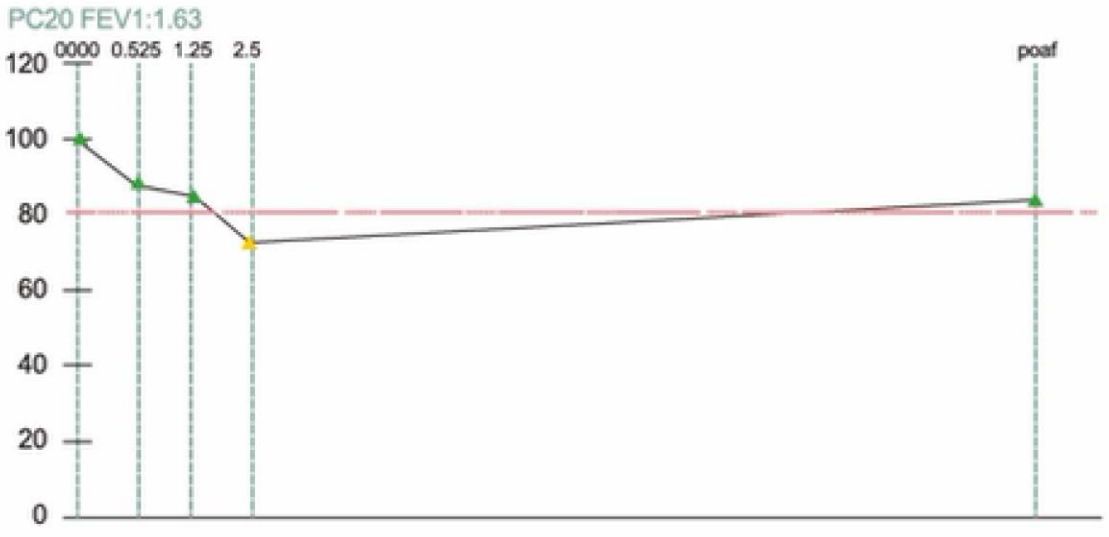
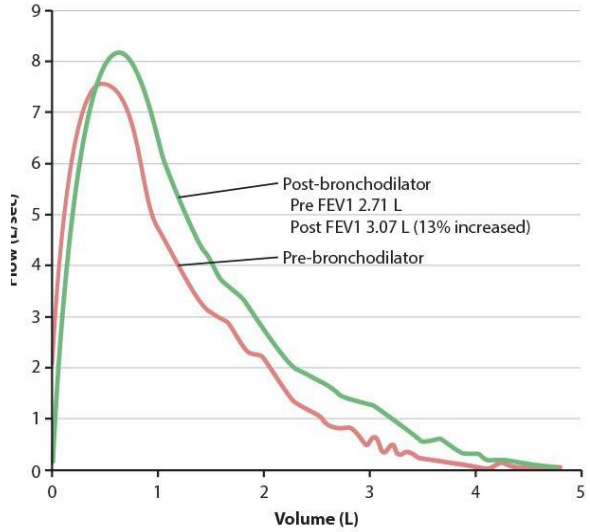
호기 기류제한의 변동성 검사

Documented excessive variability in lung function* (one or more of the following)	
Positive exercise challenge test	Fall in FEV1 of >10% and >200 mL from baseline
Positive bronchial challenge test	Fall in FEV1 from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits	Variation in FEV1 of >12% and >200 mL between visits





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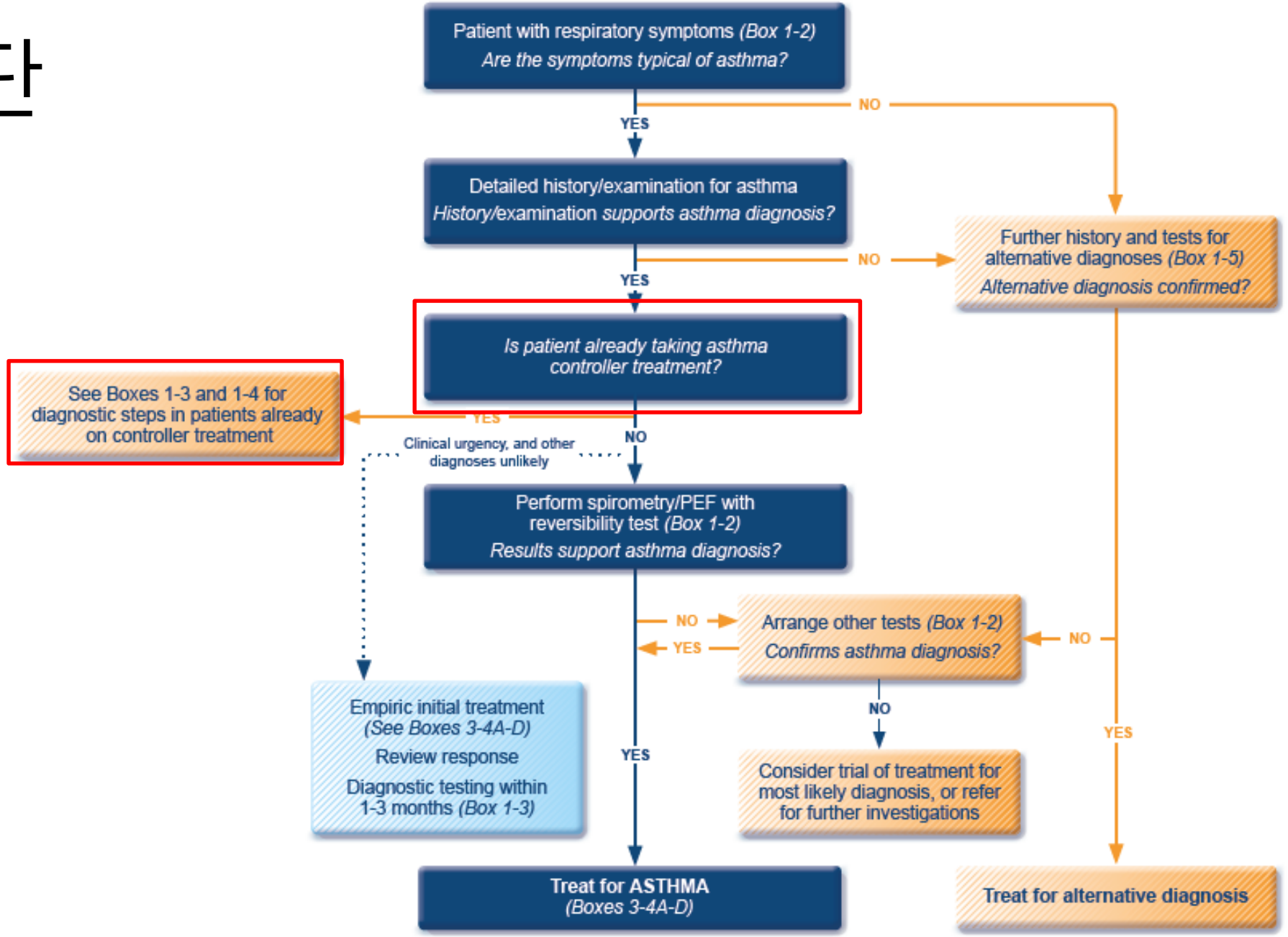
천식의 진단



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증상조절제 치료 받은 환자에서 진단

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding bronchodilator (4 hrs for SABA, 24 hrs for twice daily ICS-LABA, 36 hrs fore once-daily ICS-LABA) or during symptoms. If still normal, consider other diagnoses.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test after withholding BD. Consider stepping down ICS-containing treatment. If still normal, consider other diagnoses.
Persistent shortness of breath and persistent airflow limitation	Consider stepping up ICS-containing treatment for 3 months, then reassess symptoms and lung function. If no response, resume previous treatment and refer patients for diagnosis and investigation.

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천식의 감별진단

Box 1-5. Differential diagnosis of asthma in adults, adolescents and children 6–11 years

Age	Symptoms	Condition
6–11 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Sudden onset of symptoms, unilateral wheeze	Inhaled foreign body
	Recurrent infections, productive cough	Bronchiectasis
	Recurrent infections, productive cough, sinusitis	Primary ciliary dyskinesia
	Cardiac murmurs	Congenital heart disease
	Pre-term delivery, symptoms since birth	Bronchopulmonary dysplasia
	Excessive cough and mucus production, gastrointestinal symptoms	Cystic fibrosis
12–39 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Productive cough, recurrent infections	Bronchiectasis
	Excessive cough and mucus production	Cystic fibrosis
	Cardiac murmurs	Congenital heart disease
	Shortness of breath, family history of early emphysema	Alpha$_1$-antitrypsin deficiency
	Sudden onset of symptoms	Inhaled foreign body
40+ years	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Cough, sputum, dyspnea on exertion, smoking or noxious exposure	COPD*
	Productive cough, recurrent infections	Bronchiectasis
	Dyspnea with exertion, nocturnal symptoms, ankle edema	Cardiac failure
	Treatment with angiotensin-converting enzyme (ACE) inhibitor	Medication-related cough
	Dyspnea with exertion, non-productive cough, finger clubbing	Parenchymal lung disease
	Sudden onset of dyspnea, chest pain	Pulmonary embolism
	Dyspnea, unresponsive to bronchodilators	Central airway obstruction
All ages	Chronic cough, hemoptysis, dyspnea; and/or fatigue, fever, (night) sweats, anorexia, weight loss	Tuberculosis
	Prolonged paroxysms of coughing, sometimes stridor	Pertussis

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천식 증상 조절평가

A. 천식 증상 조절 평가		천식 증상 조절 수준		
지난 4주 동안 환자가 다음 사항을 경험했는가:		**잘 조절됨**	**부분 조절됨**	**조절되지 않음**
주간 증상이 주 3회 이상 발생했습니까?	예☐ 아니오☐	해당 없음	1–2개	3–4개
천식으로 밤중에 깬 적이 있습니까?	예☐ 아니오☐			
SABA* 완화제가 주 3회 이상 필요했습니까?	예☐ 아니오☐			
천식으로 활동이 제한되었습니까?	예☐ 아니오☐			

＊ 조절되지 않는 천식증상이 있는 것은 악화의 중요한 위험요소

불량한 천식 예후의 위험인자

천식증상이 거의 없는 환자라도 추가적으로 교정가능한 악화 위험인자

- 약물치료: SABA 과용량(1년에 캐니스터 3개[개당 200회분량]이상; 월간 캐니스터 1개 이상인 경우 사망률이 유의하게 증가), 부적절한 ICS (ICS가 처방되지 않은 경우; 낮은 순응도 또는 잘못된 흡입기 사용법)
- 동반질환: 비만, 만성부비동염, 위식도역류질환, 확진된 음식 알레르기, 불안, 우울증, 임신
- 노출: 흡연, 전자담배, 감작된 경우 알레르기항원 노출, 대기오염
- 환경: 중대한 사회경제적 문제
- 폐기능: 낮은 FEV1(예측치의 60% 미만인 경우), 높은 기관지확장제 반응성
- 제 2형 염증 표지자: 높은 혈액 호산구 수, ICS치료에도 높은 FENO

급성악화의 중대한 독립적 위험인자

- 천식으로 인한 기관삽관 또는 중환자실 치료력, 지난 12개월 간 1회 이상의 중증악화

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천식의 치료

필요한 경우 진단을 확인한다
증상 조절 및 교정 가능한 위험인자(폐기능 포함)
동반질환
흡입기 사용법 및 순응도
환자(및 부모)의 선호도 및 목표

교정 가능한 위험인자 및 동반질환 치료
비약물적 전략
천식 약물(단계 상향/하향, 트랙조정)
교육 및 사용법 훈련

증상
악화
부작용
폐기능
환자(및 부모)의
만족도

*** 천식 치료의 목표 (1) 악화와 천식으로 인한 사망예방**
(2) 증상의 완화와 조절

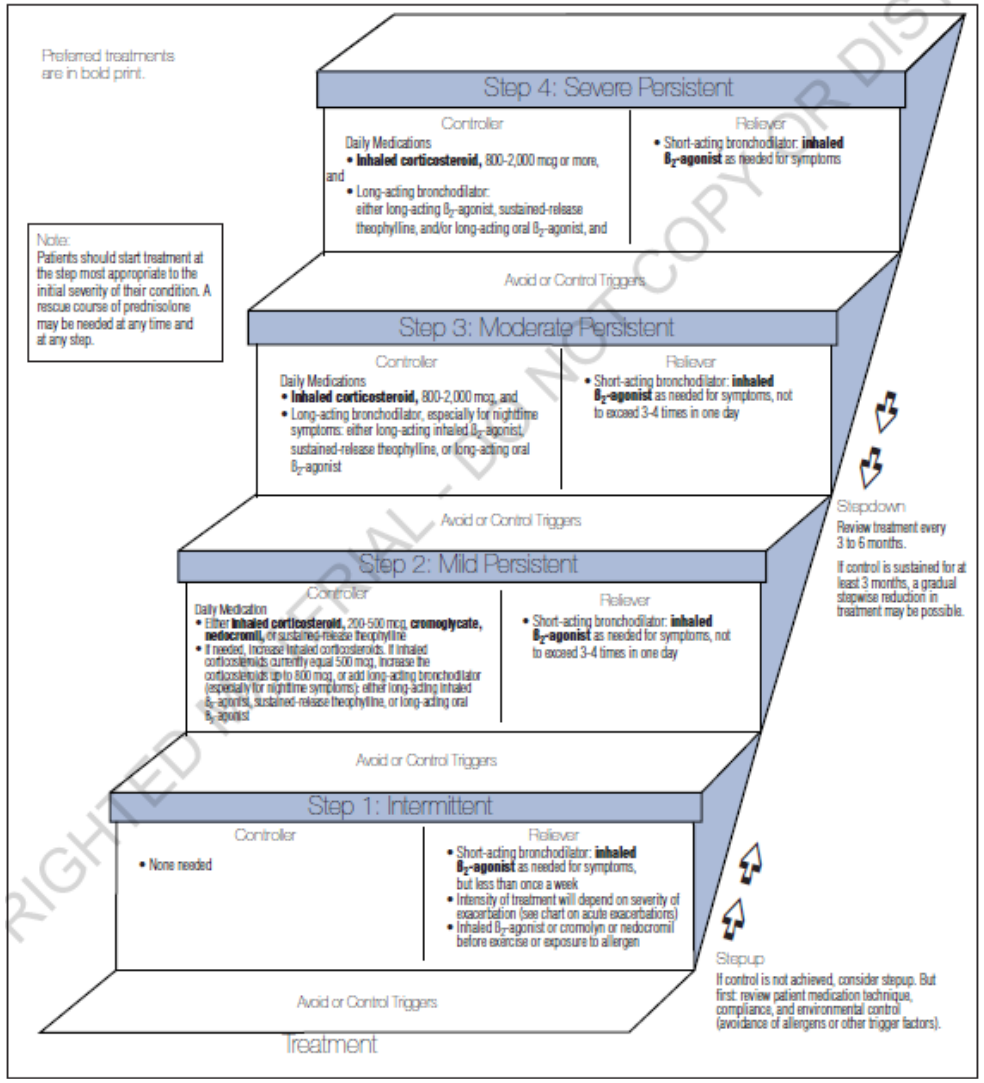
1995 GINA guideline

- Preferred treatment: ICS + SABA

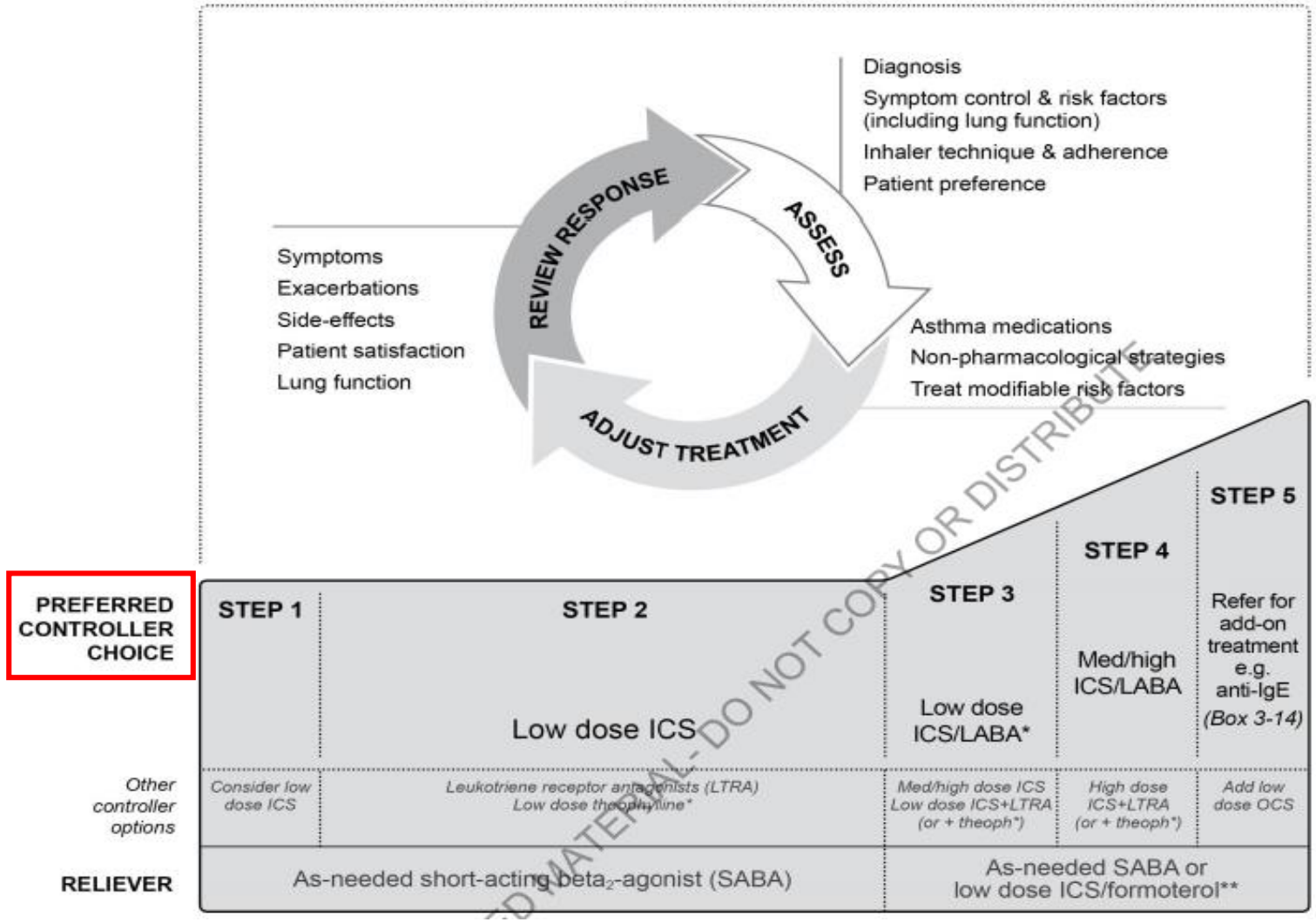
GLOBAL INITIATIVE FOR ASTHMA

GLOBAL STRATEGY FOR
ASTHMA MANAGEMENT AND PREVENTION
NHLBI/WHO WORKSHOP REPORT
(Based on a March 1993 Meeting)

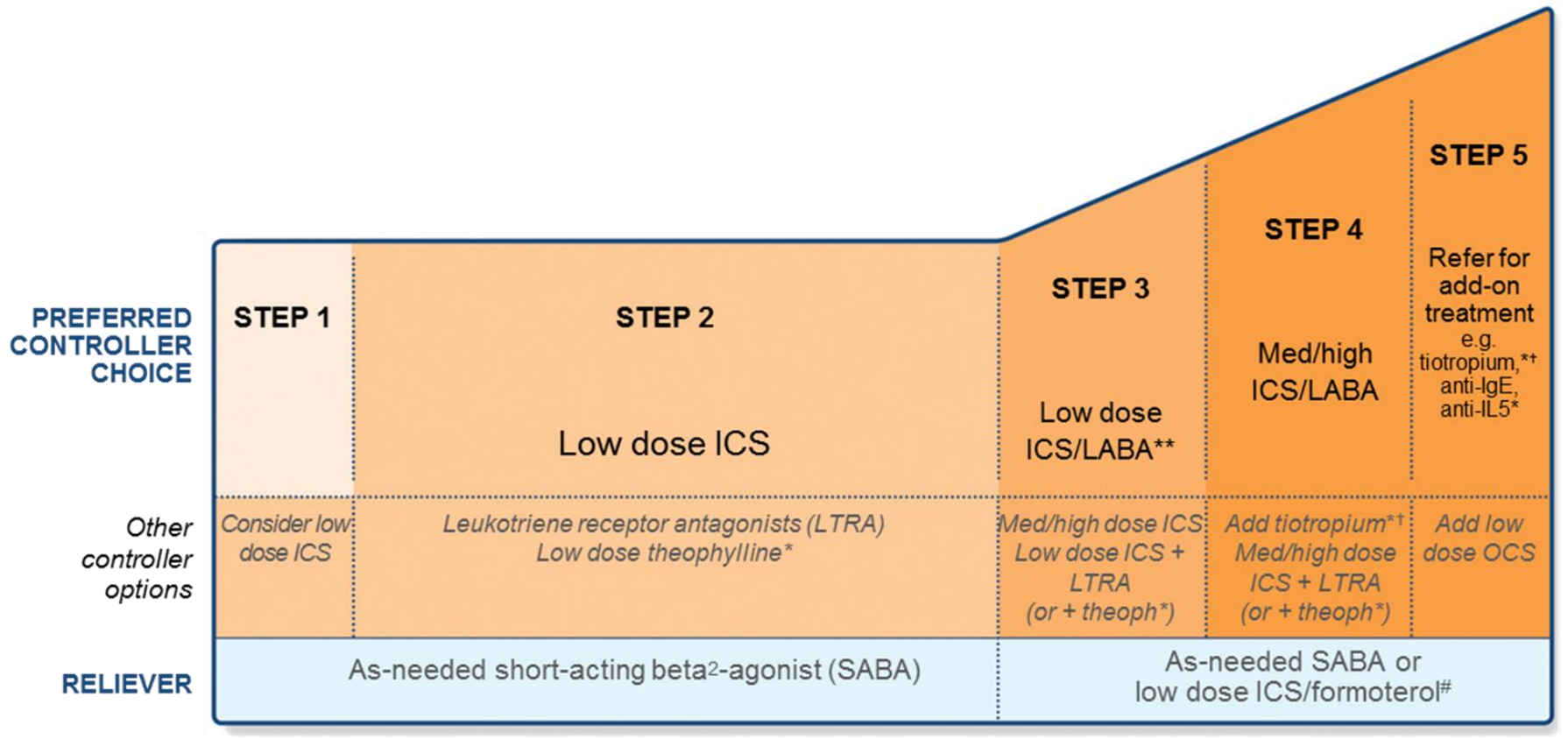
NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
Publication Number 95-3659
January 1995
Reprinted May 1996



2014 GINA guideline



2018 GINA guideline



GINA 2018

Safety of regular SABA

- 30,569 patients with asthma treatment, 5-44yr, population-based cohort (1975-1997)

TABLE 3. CRUDE AND ADJUSTED RATE RATIOS FOR DEATH FROM ASTHMA IN RELATION TO DISCONTINUATION OF INHALED CORTICOSTEROID USE.*

CORTICOSTEROID USE	CASE PATIENTS (N=66)	CONTROLS (N=2681)	CRUDE RATE RATIO	ADJUSTED RATE RATIO (95% CI)†
Uninterrupted (%)	4.6	7.9	1.0	1.0 (reference group)
Discontinued (%)				
1–3 mo before index date	19.7	9.0	3.9	4.6 (1.1–19.1)
4–6 mo before index date	4.6	6.3	1.3	1.8 (0.3–10.9)
7–9 mo before index date	4.6	5.3	1.7	1.6 (0.3–9.4)

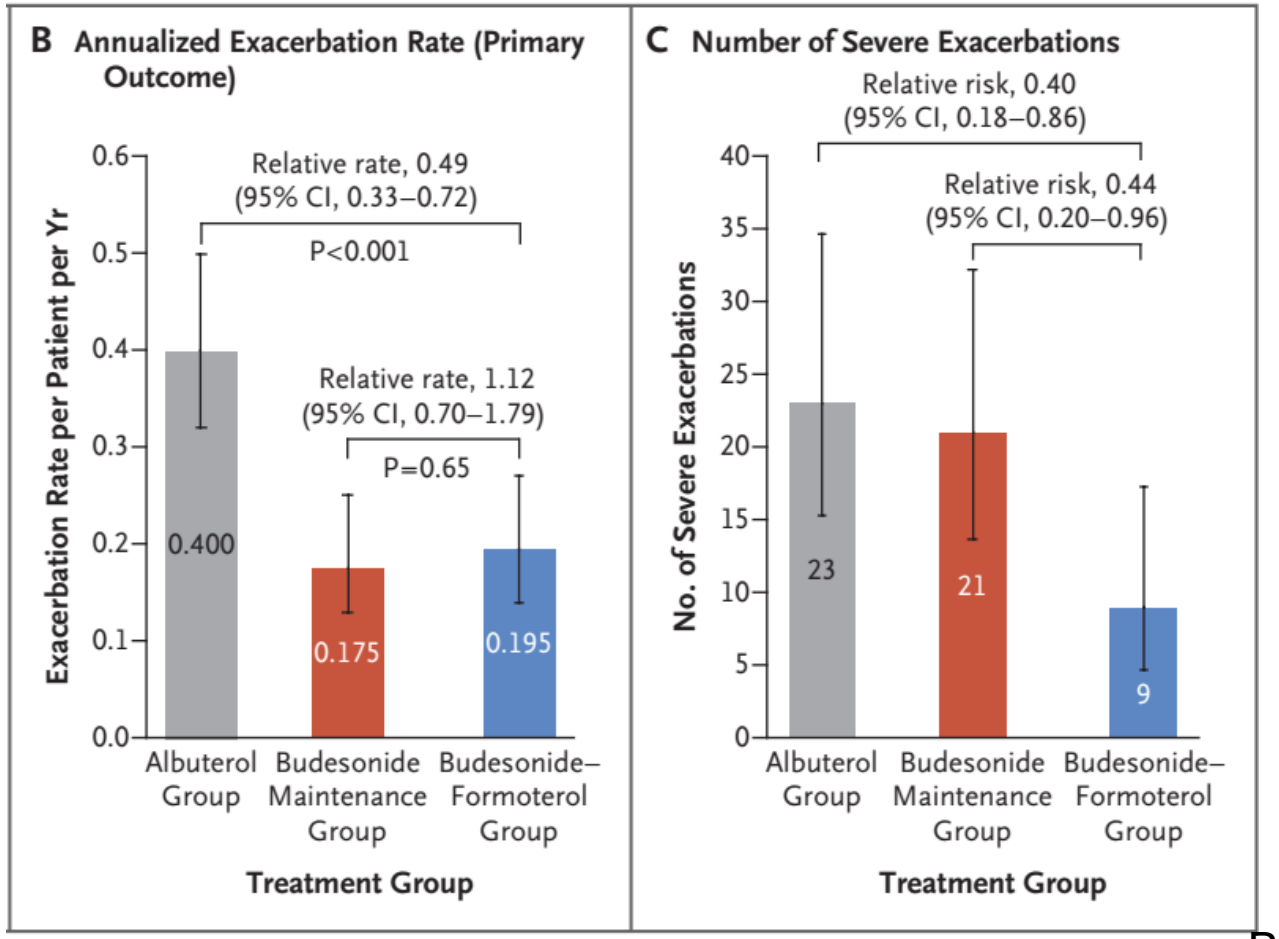
*The index date for case patients and matched controls was the date of the case patient's death from asthma. CI denotes confidence interval.

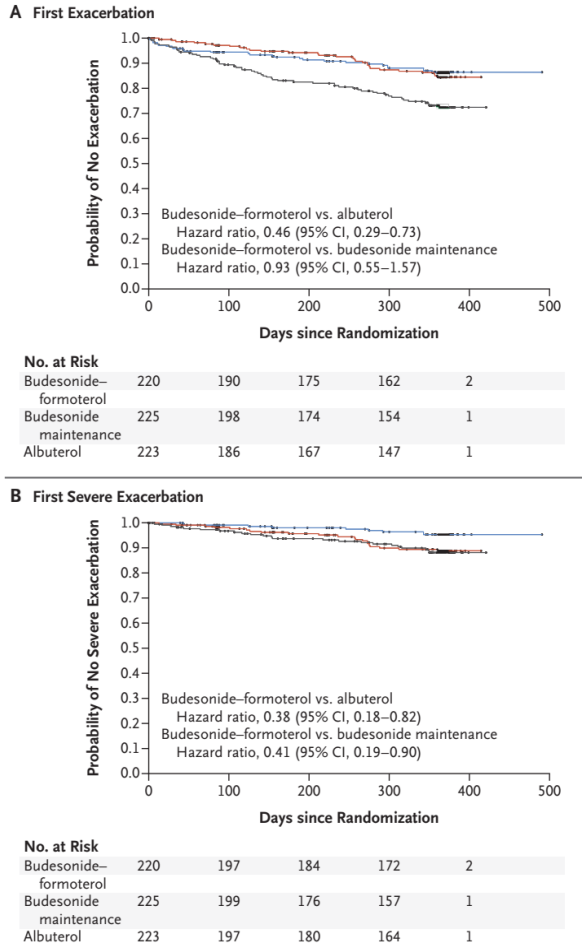
*** SABA 단독 치료를 받는 환자들이 천식관련사망의 위험이 높음**

SuissaS, et al. N EnglJ Med 2000;343:332-6.

ICS-LABA as needed vs. SABA as needed

- 668 patients with mild asthma, Novel START study





Beasley R, et al. N EnglJ Med 2019;380(21):2020-2030.

Beta-agonists monotherapy와 사망위험

- **Beta-agonist monotherapy**

– Providing constant bronchodilation

– Masking worsening asthma control and airway inflammation

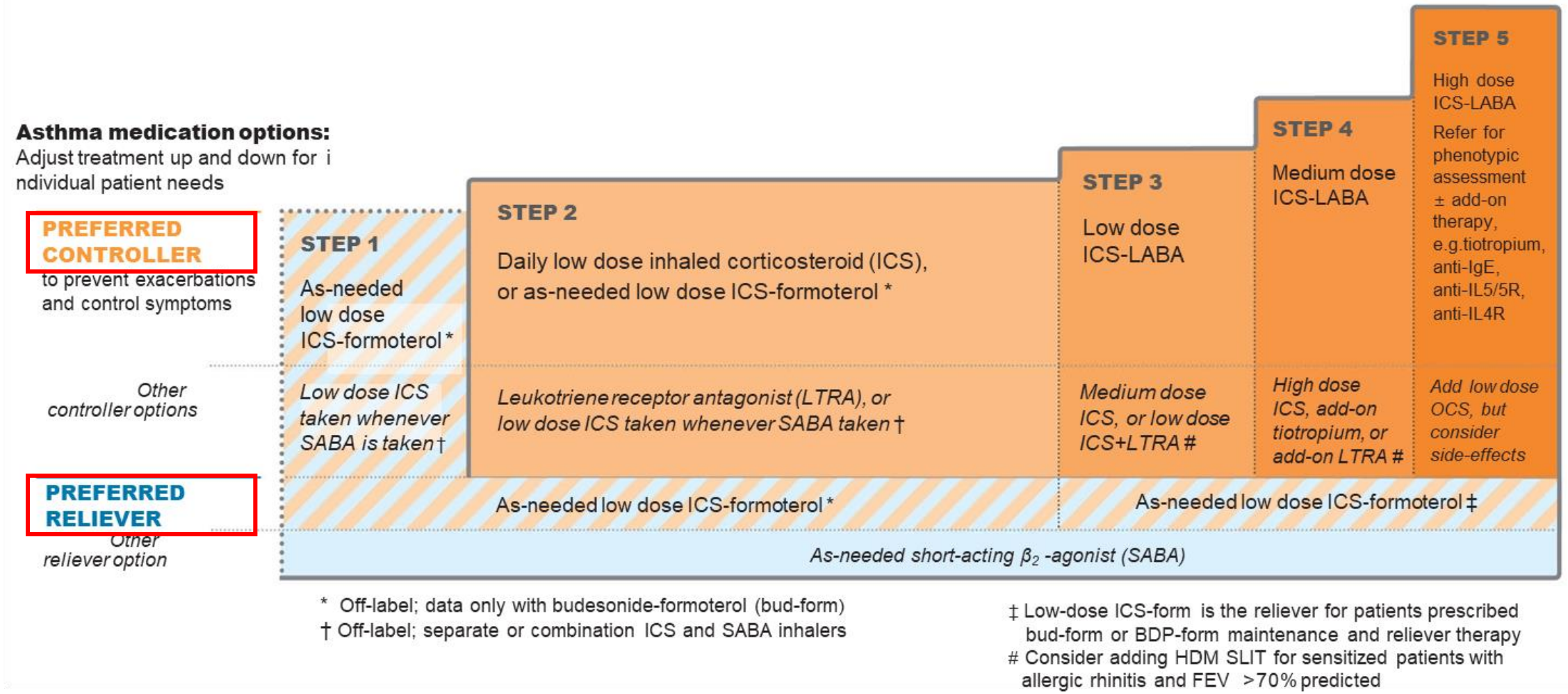
→ Greater risk for catastrophic asthma exacerbation

Regular SABA or LABA monotherapy → **Fatal asthma attack**

↑

Airway inflammation↑, Airway hypersensitivity↑, Tolerance induction↑

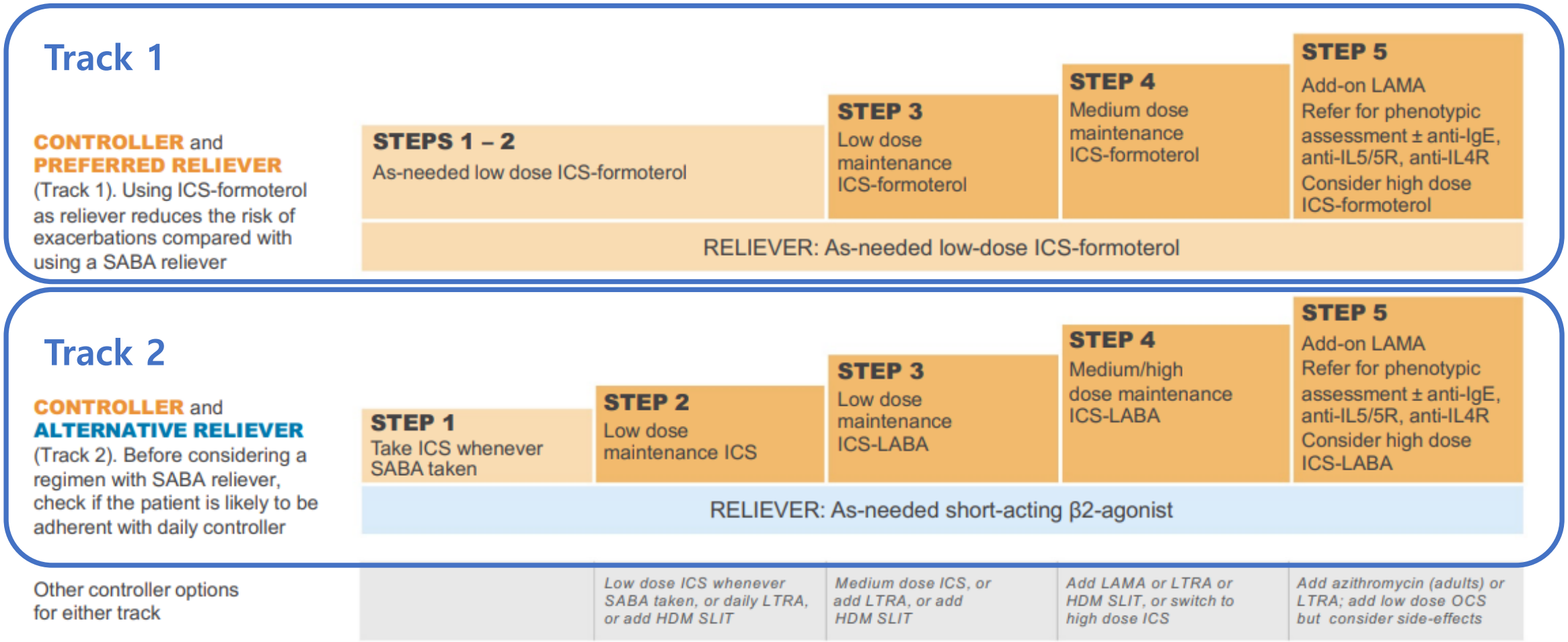
2019 GINA guideline



→ GINA **NO LONGER** recommends **SABA-only treatment for Step 1, ICS 강조!!**

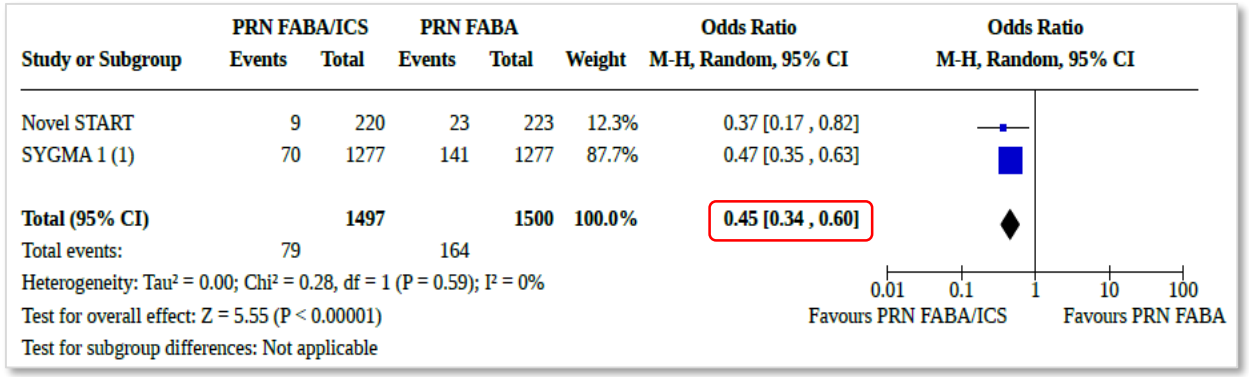
GINA 2019

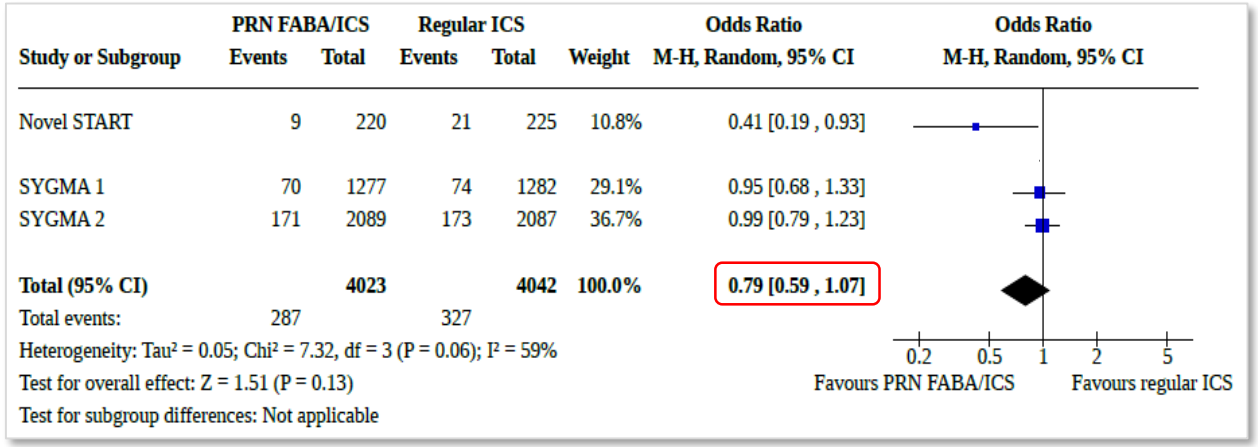
2021 GINA guideline



GINA 2021

Track 1, Steps 1-2: As-needed ICS-formoterol



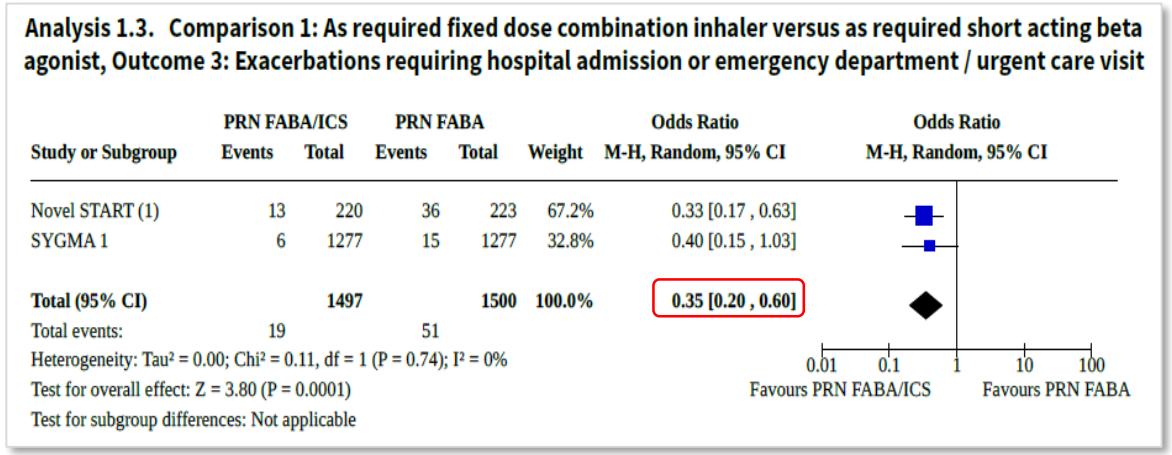


Risk of severe exacerbations

- Meta-analysis of four all RCTs, n=9,565
- Compared with as-needed SABA alone: 55% reduction (OR 0.45[0.34-0.60])
- Compared with daily ICS plus as-needed SABA: (OR 0.79[0.59-1.07])

Crossingham, Cochrane 2021

Track 1, Steps 1-2: As-needed ICS-formoterol

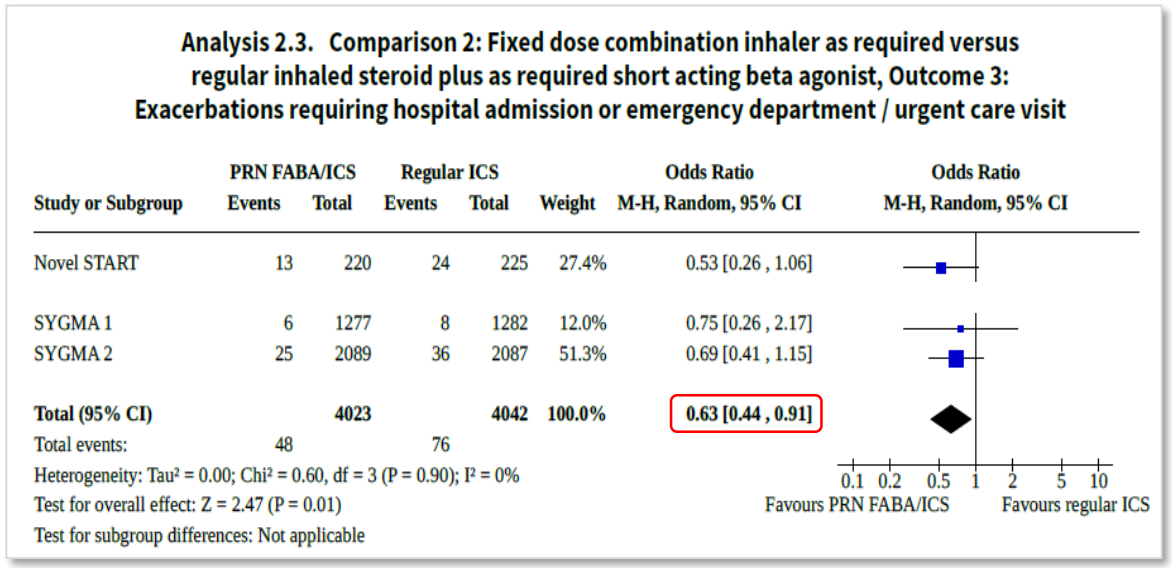


Analysis 1.3. Comparison 1: As required fixed dose combination inhaler versus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit

Study or Subgroup	PRN FABA/ICS Events	Total	PRN FABA Events	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

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours PRN FABA/ICS Favours PRN FABA



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	Total	Regular ICS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	13	220	24	225	27.4%	0.53 [0.26 , 1.06]
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

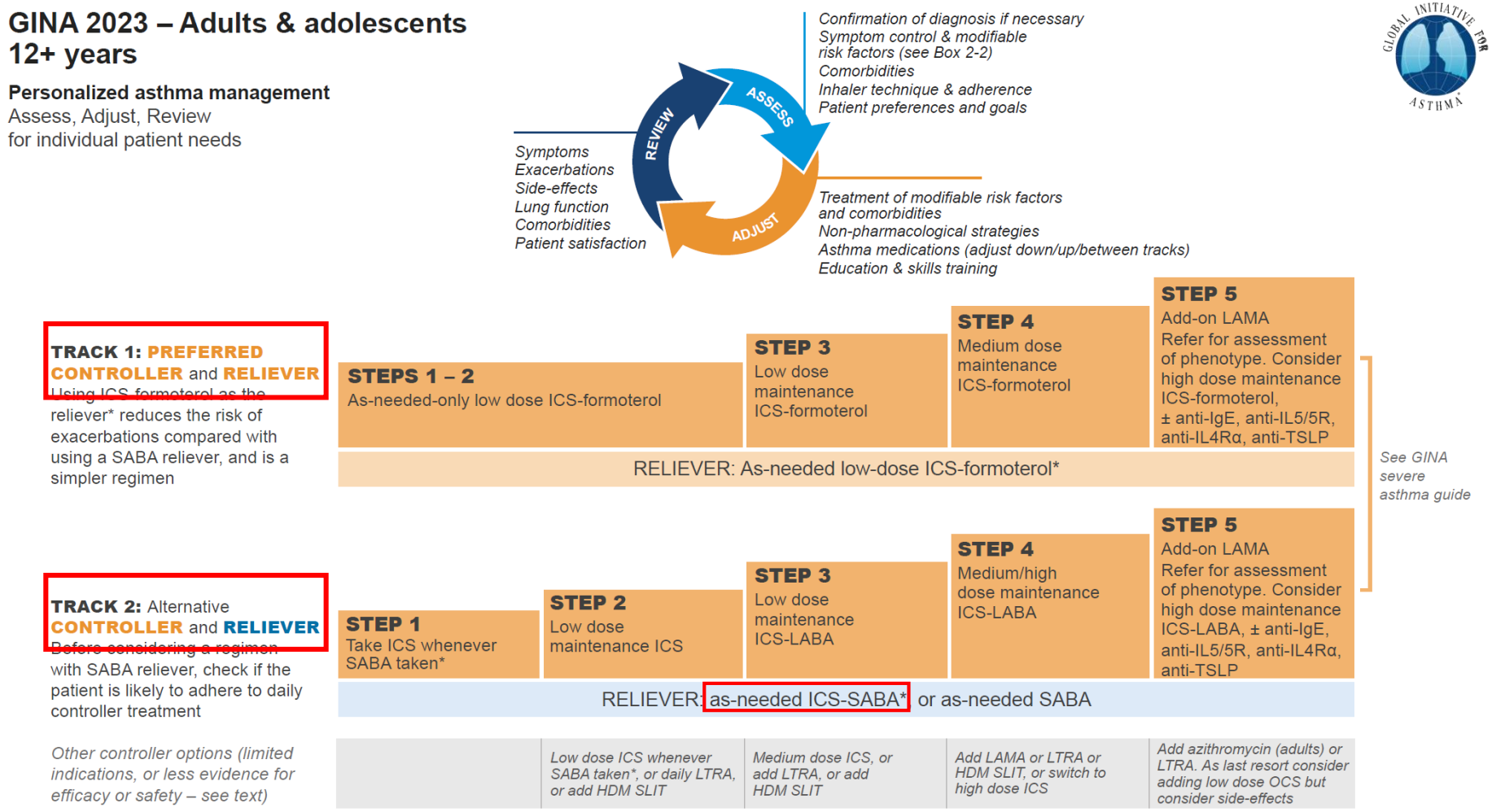
Odds Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours PRN FABA/ICS Favours regular ICS

Risk of emergency department visits or hospitalization

- Meta-analysis of four all RCTs, n=9,565
- Compared with as-needed SABA alone: 65% reduction
- Compared with daily ICS plus as-needed SABA: 37% reduction

Crossingham, Cochrane 2021

GINA 2023

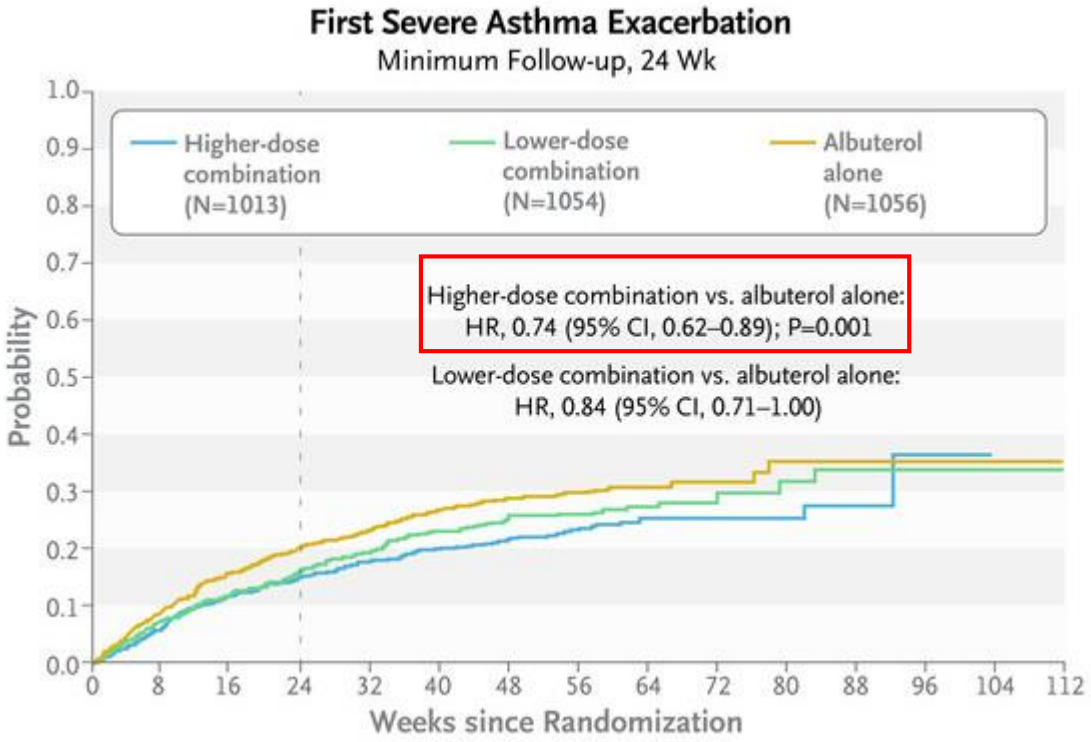


*Anti-inflammatory reliever (AIR)

Box 3-12 © Global Initiative for Asthma, www.ginasthma.org

As needed use of ICS-SABA

- Multinational, phase 3, double-blind, randomized trial
- patients with uncontrolled moderate-to-severe asthma
- Reliever: Albuterol 180 μg–budesonide 160 μg vs. Albuterol 180 μg–budesonide 80 μg vs. Albuterol 180 μg



Albuterol 180 μg–budesonide 160 μg vs albuterol 180 μg

-> severe asthma exacerbation : 26% ↓

N Engl J Med 2022;386:2071-83

천식의 약물치료

- **조절제(controller)**
  - 항염증 효과를 통해 증상이 조절되도록 장기간 매일 꾸준히 사용
  - 폐기능 개선, 기도과민성 감소, 기도 염증 조절
  - ICS, ICS+LABA, LTRA, theophylline, biologics

- **증상완화제(Reliever):**
  - 신속히 기도를 확장하여 증상을 개선시키는 약제로 필요할 때만 사용
  - 천식 급성악화 때 기도 폐쇄 완화
  - 운동 유발천식 환자에서 운동 전 처치로 일차적으로 사용
  - SABA, ICS-formoterol

대한결핵 및 호흡기 학회, 2022 천식진료지침, GINA 2023

GINA 2023 Terminology

- **A**nti-**I**nflammatory **R**eliever=**AIR**
  - ICS-formoterol, ICS-SABA
  - Provides rapid symptom relief
  - Reduces the risk of exacerbation, compared with using SABA

- Regimens with ICS-formoterol anti-inflammatory reliever
  - As-needed-only ICS-formoterol=**AIR-only**(step 1-2)
    The patient takes low-dose ICS-formoterol whenever needed for symptom relief
  - **M**aintenance **A**nd **R**eliever **T**herapy with ICS-formoterol=**MART**(Step3-5)
    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

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GINA 2023- starting treatment

Box 7B. 초기 치료: 천식이 진단된 성인 및 청소년 환자

GINA 2023 — 치료 시작

천식이 진단된 성인 및 청소년

ICS-formoterol 증상완화제를 이용하는 트랙 1이 추천된다. SABA 증상완화제를 이용한 경우에 비해 중증 악화 위험을 줄여주며, 증상완화 치료와 유지요법에 이용하는 약물이 동일하므로 환자가 이용하기에 더 간단하다.

The definition of mild asthma

- GINA suggest that the term 'mild asthma' should generally be avoided in clinical practice
- Patients and clinicians often interpret 'mild asthma' to mean that the patient is at low risk and does not need controller treatment.
- However, up to 30% of asthma exacerbations and deaths occur in people with infrequent symptoms, for example, less than weekly or only on strenuous exercise.

-> Always emphasize the need for and benefit from ICS-containing treatment in patients with asthma, regardless of their symptom frequency, and even if they have no obvious additional risk factors

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Doses for Track 1 (Preferred approach)

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 ≥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**, PLUS 1 inhalation whenever needed
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**1 inhalation once or twice daily,** 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**, PLUS 1 inhalation whenever needed
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	
Step 5 MART	6–11	(No evidence)	-	-	-
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, 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 nun

Investigating a patient with poor symptom control and/or exacerbations despite treatment

Box 2-4. Investigating a patient with poor symptom control and/or exacerbations despite treatment

Watch patient using their inhaler **Discuss adherence and barriers to use**	• Watch patient use their inhaler(s), check against inhaler checklist. Show correct method, and recheck, up to 3 times. Re-check each visit. • Have empathic discussion to identify poor adherence, e.g. *"Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you taken it?" (0 days, 1, 2, 3 etc)* and/or. *"Do you find it easier to remember your inhaler in the morning or the evening?"* Ask about beliefs, cost of medications, and refill frequency.
Confirm the diagnosis of asthma	• If no evidence of variable airflow limitation on spirometry or other testing *(Box 1-2)*, consider halving ICS dose and repeating lung function after 2–3 weeks *(Box 1-5)*; check patient has action plan. Consider referring for challenge test.
If possible, remove potential risk factors **Assess and manage comorbidities**	• For adults/adolescents, switch to GINA Track 1, if available, to reduce exacerbations and simplify regimen *(Box 3-5)* • Check for risk factors or inducers such as smoking, beta-blockers or NSAIDs, or occupational or domestic allergen exposure *(Box 2-2)*, and address as possible *(Box 3-17)*. • Check for and manage comorbidities (e.g. rhinitis, obesity, GERD, obstructive sleep apnea, depression/anxiety) that may contribute to symptoms
Consider treatment step-up	• Consider step-up to next treatment level or alternative option on present level *(Boxes 3-12, 3-13)*. • Use shared decision-making, and balance potential benefits and risks
Refer to a specialist or severe asthma clinic	• If asthma still uncontrolled after 3–6 months on high dose ICS-LABA, or with ongoing risk factors, refer to a specialist or severe asthma clinic, if available • Refer earlier than 6 months if asthma very severe or difficult to manage, or if doubts about diagnosis.

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Management of asthma if patient acquires COVID-19

- **Advice has been added about management of asthma if patients acquire COVID-19 because several key drug interaction websites are recommending that LABAs should be stopped if ritonavir-boosted nirmatrelvir (NMV/r) is prescribed, without advising that this could result in asthma exacerbation**
- **Be cautious if prescribing NMV/r for patients taking ICS-salmeterol or ICS-vilanterol**, as the **interaction may increase cardiac toxicity of the LABA**
- consider prescribing an alternative antiviral therapy or switching to **ICS alone** or **ICS-formotel** for the duration of NMV/r treatment and for a further 5 days afterwards

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Drug interaction in ABPA treatment

- Clinicians should be aware of the potential for drug interactions between **itraconazole (a cytochrome P450 inhibitor)** and asthma medications.
- These interactions may lead to increased risk of ICS adverse effects such as **adrenal suppression** and **Cushing' syndrome**, and may **increased the risk of cardiovascular adverse effects** of some LABAs (salmeterol and vilanterol)
- Concomitant use is not recommended, so it may be **appropriate to switch ICS-LABA treatment to an alternative product as budesonide-formoterol or mometasone-formoterol for the duration of treatment with itraconazole**.

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Other changes

- Pertussis : added as a differential diagnosis for asthma and for exacerbation
- ACQ-5 is advised again rather than ACQ6, ACQ7
- **Fragility fractures: the adverse effect of exposure to oral corticosteroid** include not just osteoporosis but also fragility fracture
- Outdoor air pollution: use of digital monitoring devices identified an impact of higher pollution on asthma medication utilization with a lag of 0-3 days
- Vaccination; **influenza vaccination** are advised, but insufficient evidence to recommend routine pneumococcal and pertussis vaccination in adults

GINA 2023 Key changes

- Updated advice on definition of mild asthma
- Clarification of terminology for asthma medications
- Practical guidance for GINA track1
- Advice about potential drug interactions

경청해 주셔서 감사합니다.