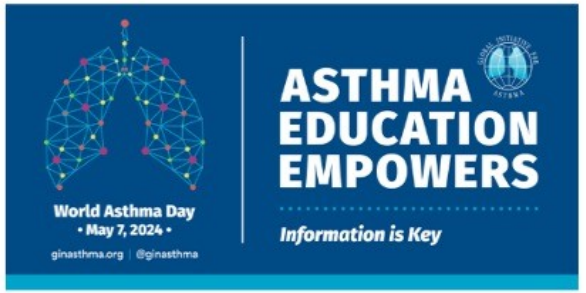
MANAGEMENT OF ASTHMA
ASTIM YÖNETİMİ

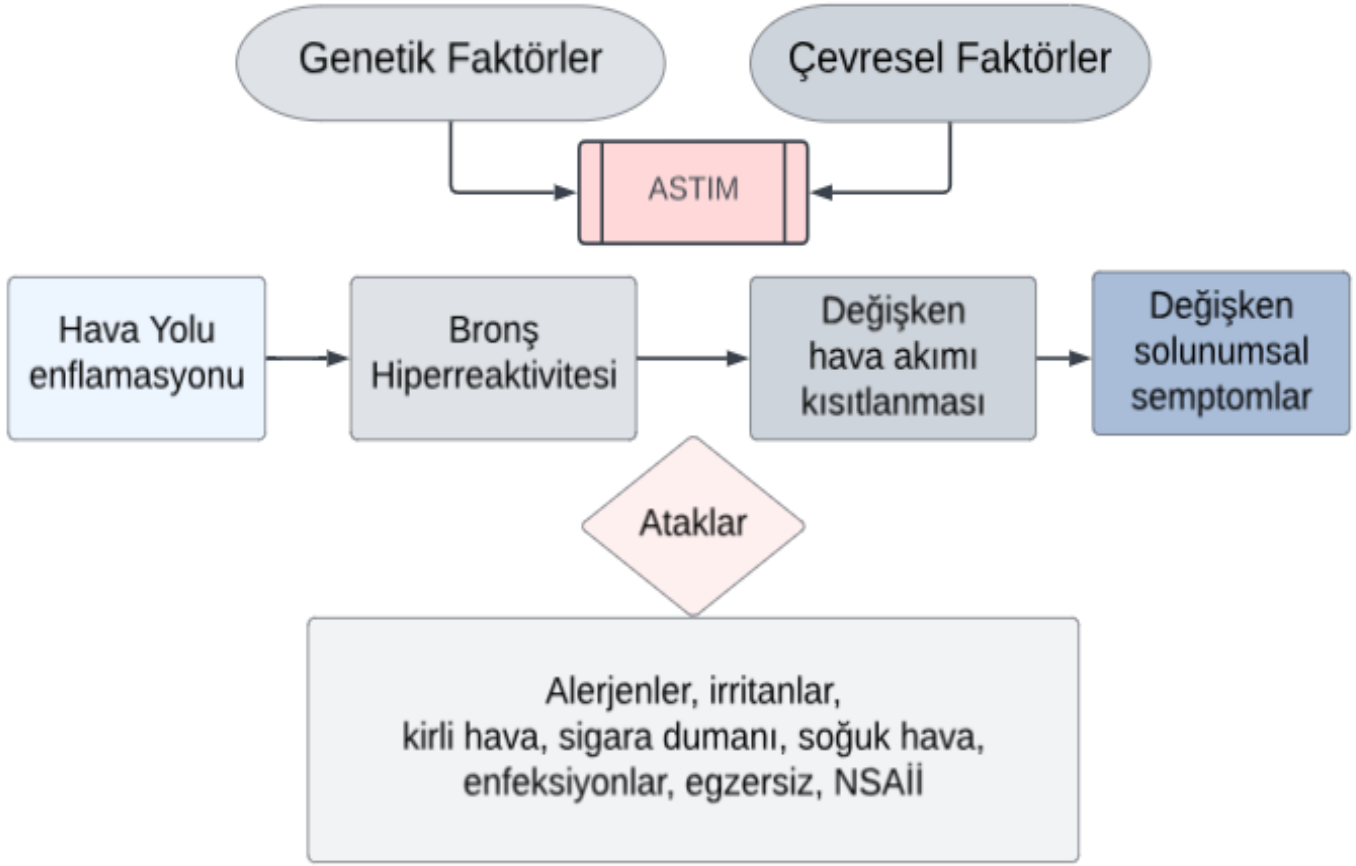
- **Assoc. Prof. Dr. F. Merve TEPETAM**
- **University of Health Sciences**
- **Süreyyapaşa Chest Diseases and Thoracic Surgery EAH**
- **Immunology and Allergy Clinic**

The Global Initiative for Asthma (GINA)

- The GINA Strategy Report is a global evidence-based strategy that can be adapted for local health systems and medicine availability
  - GINA 2024 report is available from www.ginasthma.org/reports
- The GINA Report is updated every year
  - Twice-yearly cumulative review and systematic evaluation of new evidence about asthma
  - Evidence integrated across the whole asthma strategy, not isolated PICOT questions
  - Careful attention to study design, populations, and clinical relevance
  - Extensive external review
  - Practical focus: not just 'what', but 'why' and 'how'
- Widely used
  - Downloaded from >200 countries
  - 2023 report downloaded >500,000 times
- GINA 2024 report was launched on World Asthma Day, May 7, 2024
  - See section on "What's new in GINA 2024?" for more details
  - Update published on 22 May, as we became aware that some medication doses in Box 4-8 were being misread



DEFINITION IN ASTHMA



TIPS IN DEFINING ASTHMA

Heterojen bir hastalık

- Çoğunlukla kronik hava yolu enflamasyonuyla karakterize
- Çoğunlukla bronşial hiperreaktivite ve kronik hava yolu enflamasyonu ile ilişkili
- Ama **şart değil**

Semptomlar veya hava akımı kısıtlanması olmadığında bile

- Bronşial hiperreaktivite ve kronik hava yolu enflamasyonu **persiste** olabilir

Çoğunlukla persiste olan bu özellikler

- Ancak tedaviyle normale dönebilir

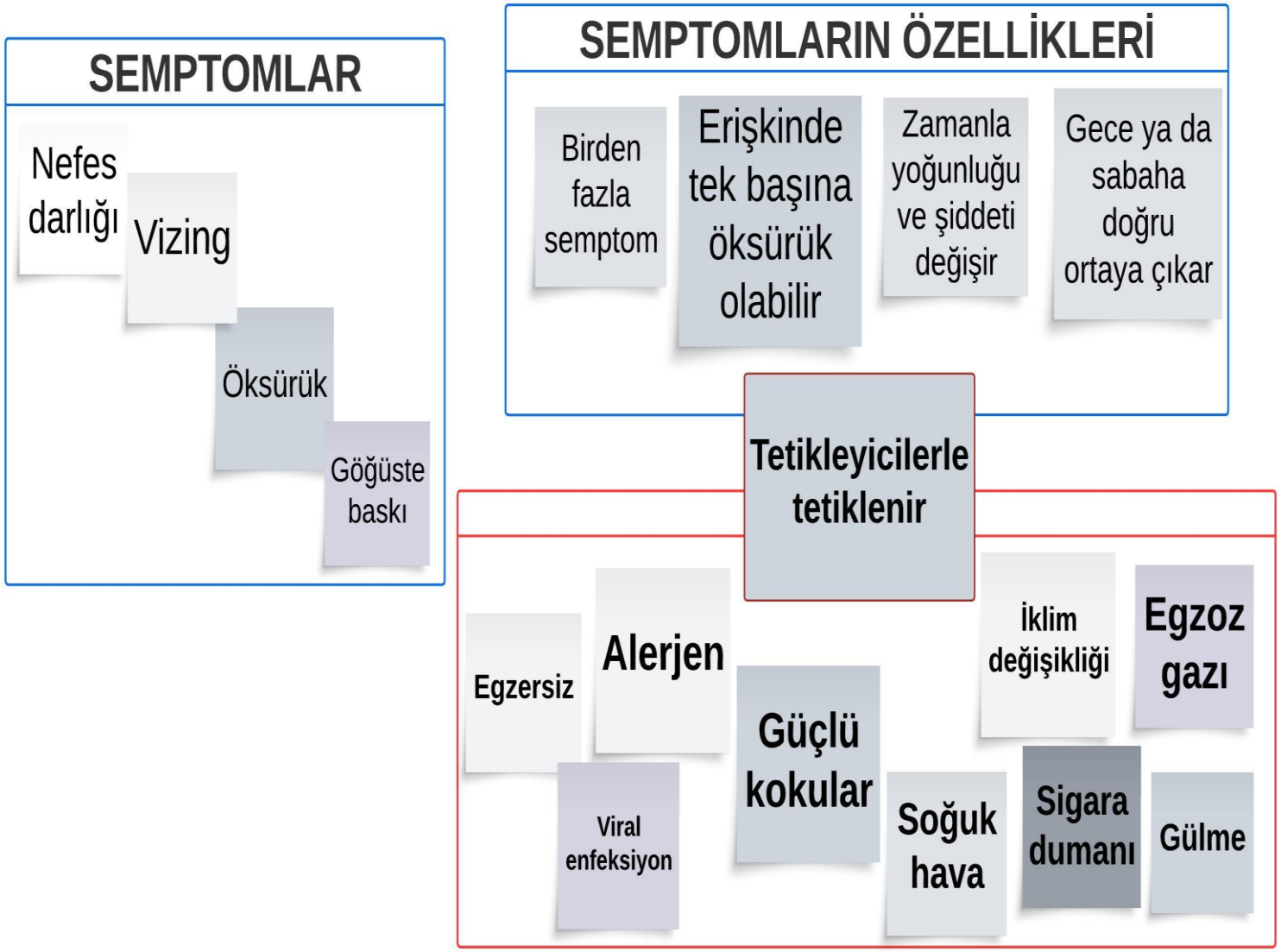
DIAGNOSIS IN ASTHMA

Diagnosis in Asthma

Presence of variable respiratory symptoms in the history

Verification of variable airflow obstruction

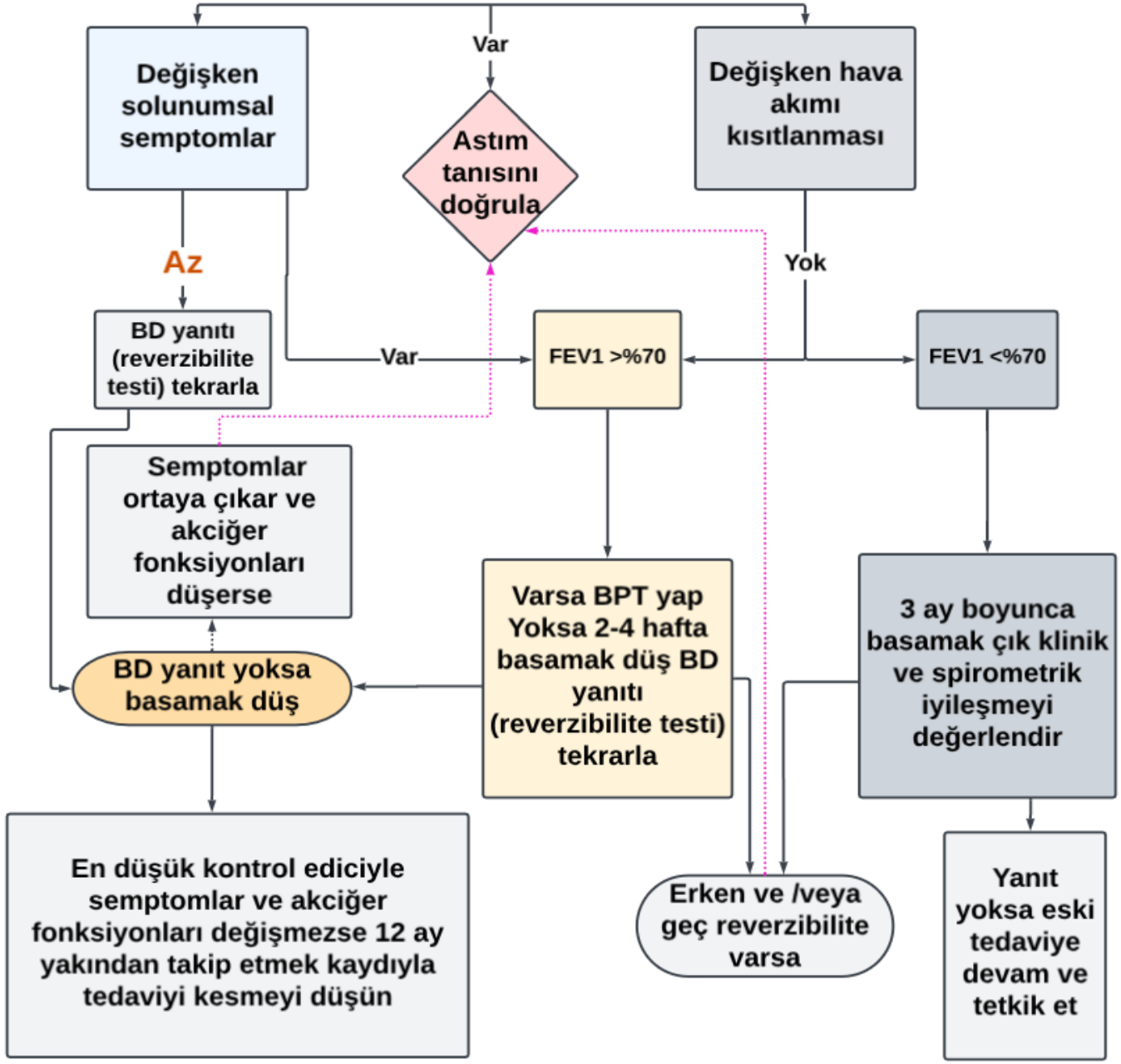
HISTORY OF VARIABLE RESPIRATORY SYMPTOMS



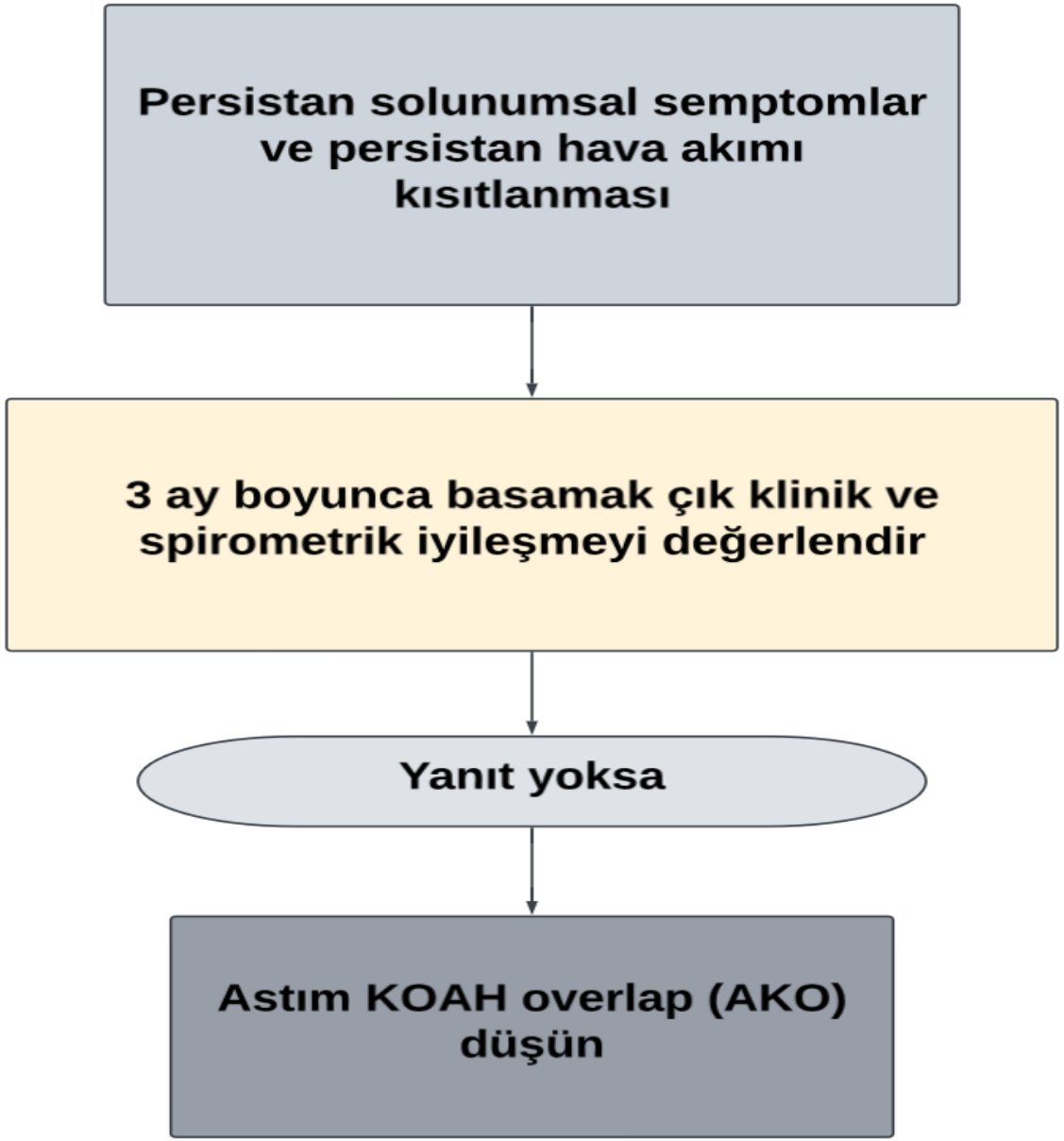
VARIABLE AIRFLOW OBSTRUCTION

AIRFLOW OBSTRUCTION: FEV1/FVC <75-80%
VARIABILITY
➢ Bronchodilator reversibility: >200 mL and 12% increase in FEV1 or FVC >, 20% increase in PEF
➢ Daily PEF variability >10%
➢ >200 mL and 12% increase in FEV1 after 4 weeks of anti-inflammatory treatment >
➢ Exercise test: 10> and >200 mL decrease in FEV1
➢ Bronchoprovocation test positivity: 20% in FEV1 and FEV1/FVC in provocation with methacholine or histamine ≥; 15% decrease in FEV1 in provocation with standard hyperventilation, hypertonic saline or mannitol ≥
➢ Inter-visit variability: 200 mL > and 12% in FEV1 > (less reliable)
*In practice, when evaluating reversibility in patients with high baseline FEV1, an increase in FEV1 of >200 mL; In patients with low baseline FEV1, a 12>% increase in FEV1 can be interpreted in favor of reversibility (>200 mL or >12% increase in FEV1)

Diagnostic Algorithm in Asthma Patient Undergoing Treatment



Diagnostic Algorithm in Asthma Patient Undergoing Treatment



CASE

A 47-year-old female patient.

Physician

No smoking.

For 33 years (since the age of 14) it has been increasing with exertional irritants, mostly in the morning.

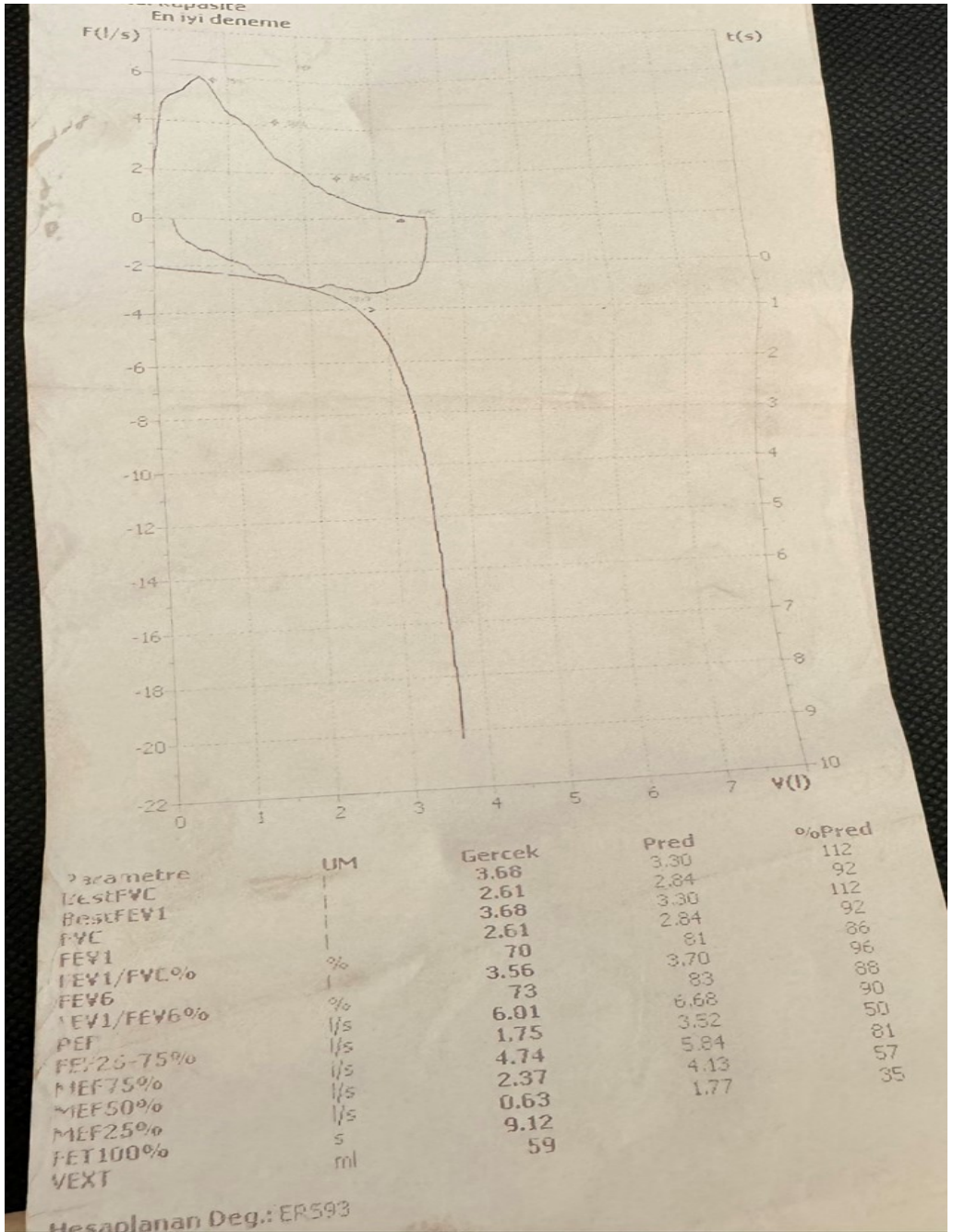
- wheezing,
- dyspnea
- cough and
- Feeling of pressure in the chest

33 years of PERENNIAL AND SEASONAL INCREASE

- runny nose,
- nasal congestion .

SFT

- FEV1:2,61 (%92)
- FVC:3,68 (%112)
- FEV1/FVC: %70
- FEF25-75:1,75 %50
- FET: 9,12 sn
- Vizitler arası değişkenlik 2610-2400=210 mL (+)



DO CLINICAL AND SPIROMETRIC SUPPORT ASTHMA

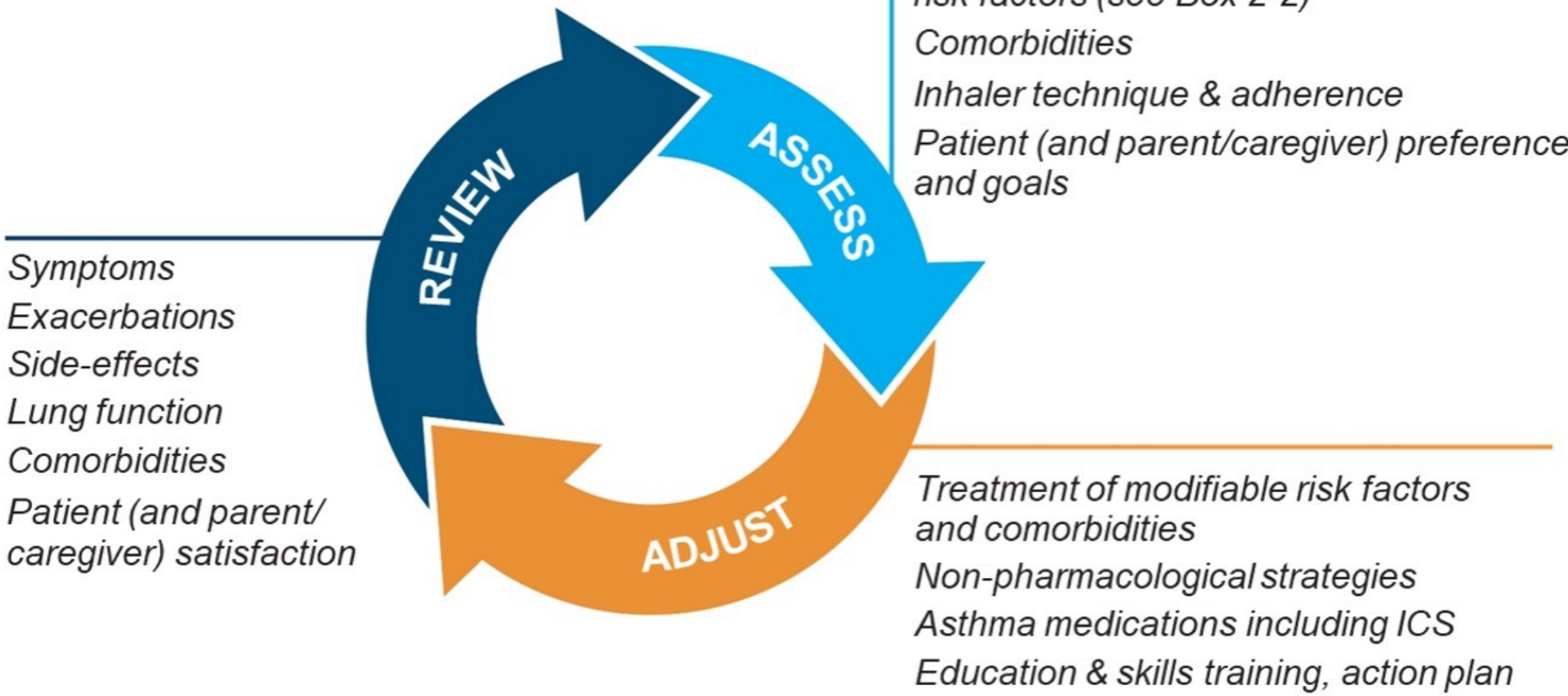
DIAGNOSIS IN ASTHMA

Diagnosis in Asthma

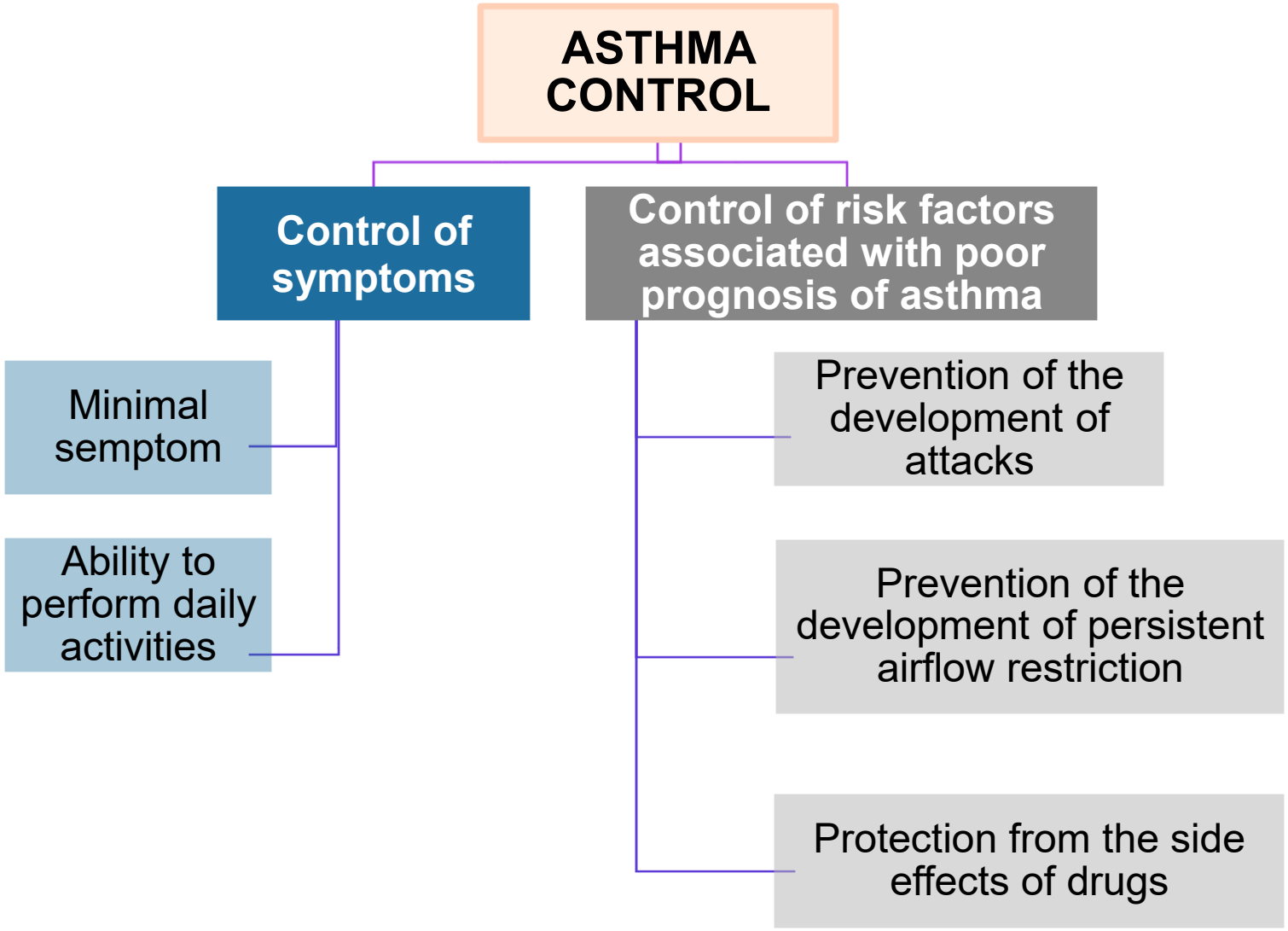
Presence of variable respiratory symptoms in the history

Verification of variable airflow restriction

Asthma treatment is not ‘set and forget’, and not just medications



PURPOSE IN THE SELECTION OF TREATMENT



GINA goal of asthma management

The goal is to achieve the **best possible long-term asthma outcomes** for each patient:

- Long-term symptom control, which may include:
  - Few/no asthma symptoms, quickly relieved
  - No sleep disturbance
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance oral corticosteroids
  - No medication side-effects

When discussing best possible long-term outcomes with a patient, consider:

- Their asthma phenotype
- Clinical features
- Multimorbidity
- Risk factors (e.g. poor adherence, smoking, persistent airflow limitation)
- Availability, cost and adverse effects of medications
- The patient's goals (these may be different from medical goals)

- Assessing symptom control is not enough! Patients with few asthma symptoms can still have severe or fatal exacerbations related to individual risk factors or external triggers (viruses, allergen, pollution)
- Encourage referral for expert advice for patients with difficult-to-treat or severe asthma

In the selection of treatment

At the Population Level

Treatment Selection

Patient Level

Treatment Selection

In the selection of Treatment Options

At the population level

Effect

Efficiency

Reliability

Accessibility and cost

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (2024)

Bireysel Kontrol edici seçimi

Symptom control	Risk attack	Phenotypes	Practical considerations
			• Accessibility • Inhaler technique • Adherence • Patient satisfaction • Cost • Minimal environmental damage

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (2024)

TREATMENT-TERMINOLOGY

Controller

- Treatment involving IKS to achieve symptom control and reduce the risk of attacks (as it is also used as a savior for confusion) 'Maintenance treatment with IKS' is more appropriate definition

Maintenance therapy

- **Frequency; regularly planned, e.g. 2 times a day IKS, IKS-LABA, IKS-LABA-LAMA, LTRA, Biological**

Reliever: SABA, SABA+IKS, Formeterol+IKS

- To relieve symptoms before exercise or allergen exposure

Anti-inflammatory reliever (AIR); örn: IKS-Formeterol, IKS-SABA

- IKS-Formeterol alone as needed
- (AIR only) digits 1-2

Maintenance and reliever treatment (MART); Maintenance and rescue treatment press 3-5 Formeterol+IKS

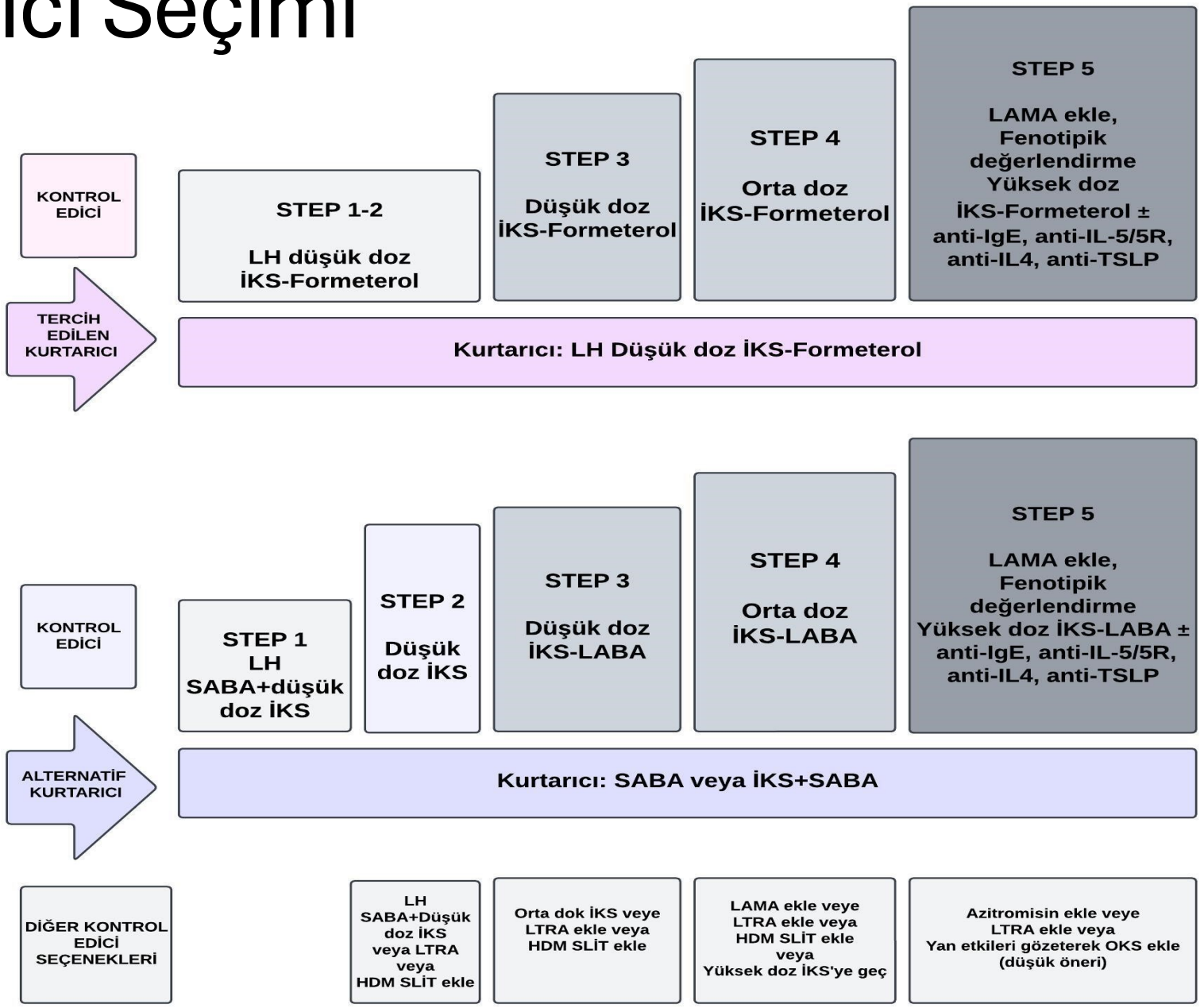
Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (2024)

GINA 2021
Two Crossroads in Population Level Rescuer Selection

Astımda Kurtarıcı Seçimi

KONTROL EDİCİ ve **TERCİH EDİLEN KURTARICI**
(1 Yol). İKS-formoterolü kurtarıcı olarak kullanmak atak riskini SABA'ya göre azaltır

KONTROL EDİCİ ve **ALTERNATİF KURTARICI**
(Yol 2). SABA ile bir rejime başlamadan hastanın günlük kontrol edici uyumunun iyi olduğuna bakın



Tepetam FM. Algoritmalarla Astım ve İmmunoloji Hastalarının Yönetiminide Poliklinik El Kitabı

REDUCING ATTACKS IS A HIGH PRIORITY

Development of patient burden, persistent airflow restriction

Burden on the health system

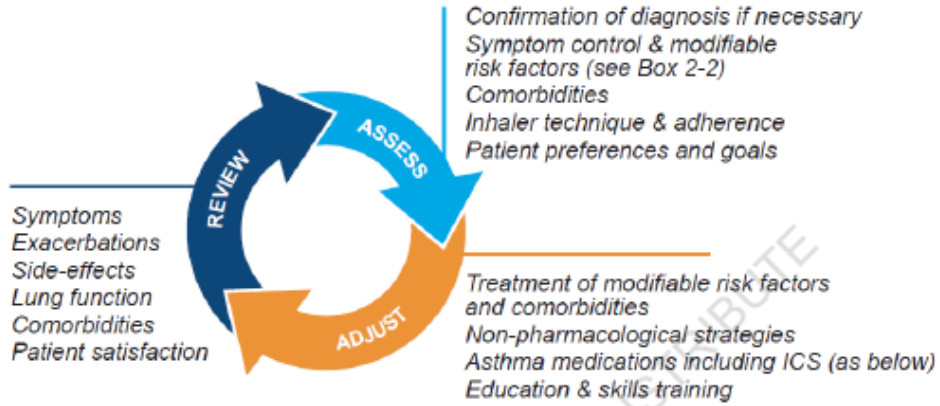
Risk of OCS side effects

ASTHMA TREATMENT STEPS IN ADULTS AND ADOLESCENTS

Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk

GINA 2024 – Adults & adolescents 12+ years

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



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

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

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

See GINA severe asthma guide

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

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

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

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

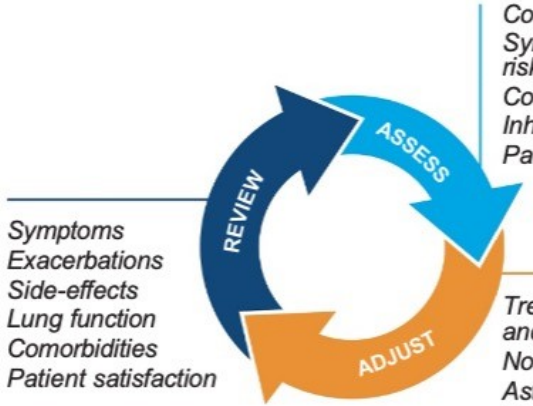
Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

GINA SAVIOR 1ST PATHWAY ADVANTAGES

Simple for Patients and Clinicians	To relieve symptoms	They don't have to wait for hours to be able to use it again like SABA
• The only preparation as a maintenance savior • It is sufficient to change the number of doses to go up or down the steps • In the written action plan, IKS and Formeterol dose increase are done together	• Exercise-they can take an inhalation before allergen exposure	• You can take it again after 1-3 seconds • All at once

GINA 2024 – 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 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

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See GINA severe asthma guide

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

WAY 2 WHEN CHOOSING AN ALTERNATIVE RESCUER

Attention to controlling drug adherence (no frequent SABA exposure)

Stable and patient satisfaction with current treatment

The last 1 year should not be offensive

INCREASED SABA USAGE RISKS

- Using SABA alone for 1 week
- Increased BHR, EIB
- Increased Inflammation
- Decreased BD response
- Increased attack (3 boxes)
- Increased mortality (12 boxes)

Eur Respir J 2020; 55: 1901872

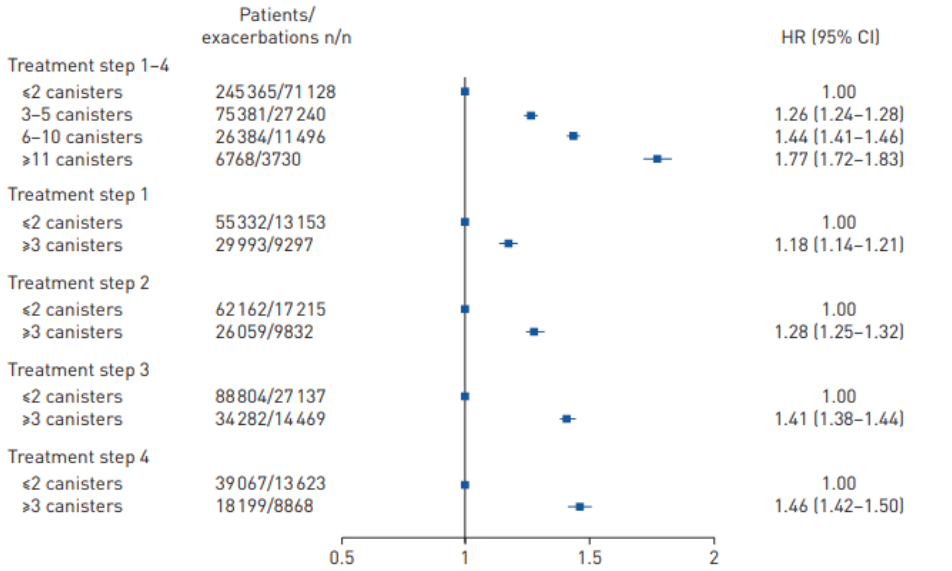


FIGURE 2 Associations between baseline short-acting β_2-agonist (SABA) use and treatment step and subsequent risk of asthma exacerbation. Adjusted for age at asthma diagnosis, sex, treatment step and comorbidity. ⩽2 canisters: patients collecting two or fewer SABA canisters during the baseline year; ⩾3 canisters: patients collecting three or more SABA canisters during the baseline year; HR: hazard ratio.

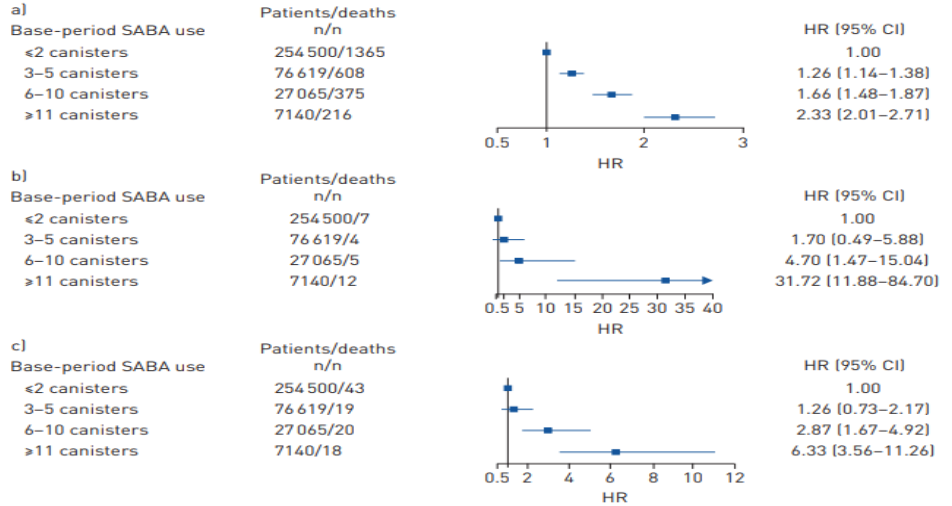


FIGURE 5 Association between baseline short-acting β_2-agonist (SABA) use and risk of mortality. a) Overall mortality; b) asthma-related mortality; c) respiratory-related mortality. Adjusted for treatment step, Charlson Comorbidity Index, sex and age. ⩽2 canisters: patients collecting two or fewer SABA canisters during the baseline year; ⩾3 canisters: patients collecting three or more SABA canisters during the baseline year; HR: hazard ratio.

ATAK RİSKİ VEYA ÖYKÜSÜ VARSA KURTARICI: AİR: IKS+ FORMETEROL/SABA

Box 3-5. Treating potentially modifiable risk factors to reduce exacerbations and minimize OCS use

Risk factor	Treatment strategy	Evidence
Any patient with one or more risk factors for exacerbations (including poor symptom control)	Ensure patient is prescribed an ICS-containing treatment.	A
	Switch to a regimen with an anti-inflammatory reliever (ICS-formoterol or ICS-SABA) if available, as this reduces the risk of severe exacerbations compared with if the reliever is SABA.	A
	Ensure patient has a written action plan appropriate for their health literacy.	A
	Review patient more frequently than low-risk patients.	A
	Check inhaler technique and adherence frequently; correct as needed.	A
	Identify and manage any modifiable risk factors (Box 2-2, p.37).	D
≥1 severe exacerbation in last year	Switch to a regimen with an anti-inflammatory reliever (as-needed ICS-formoterol or ICS-SABA) if available, as this reduces the risk of severe exacerbations compared with if the reliever is SABA.	A
	Consider stepping up treatment if no modifiable risk factors.	A
	Identify any avoidable triggers for exacerbations.	C

WHY DOES GINA PREFER PATHWAY 1 FOR MILD ASTHMA?

In steps 1-2

- Proof value of budesonide-formeterol efficacy and safety if required (n~10,000)
- İKS-SABA when necessary (n=455 Papi et al, NEJMed 2007)

CASE-Examinations

Serum Total IgE	40-75 IU/ml
Eosinophil	0-100/uL
Alerji deri testi	(skin prick testi)
Grass Ambrosia (ragweed)	7*9 13*11
Dermatophagoides p Dermatophagoides f	3*3 3*3

WHAT ARE THE PATIENT'S ATTACK RISKS?

a. Risk factors for exacerbations
Uncontrolled asthma symptoms: Having uncontrolled symptoms is an important risk factor for exacerbations.[85]
Factors that increase the risk of exacerbations even if the patient has few asthma symptoms†
SABA over-use: High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)[86-89]
Inadequate ICS: not prescribed ICS, poor adherence,[90] or incorrect inhaler technique[91]
Other medical conditions: Obesity,[92,93] chronic rhinosinusitis,[93] GERD,[93] confirmed food allergy,[94] pregnancy[95]
Exposures: Smoking,[96] e-cigarettes,[97] allergen exposure if sensitized,[96,98] air pollution[99-102]
Psychosocial: Major psychological or socioeconomic problems[103,104]
Lung function: Low FEV_1 (especially <60% predicted),[96,105] high bronchodilator responsiveness[93,106,107]
Type 2 inflammatory markers: Higher blood eosinophils,[93,108,109] high FeNO (adults with allergic asthma on ICS)[110]
Exacerbation history: Ever intubated or in intensive care unit for asthma;[111] ≥1 severe exacerbation in last year[112,113]
b. Risk factors for developing persistent airflow limitation
History: Preterm birth, low birth weight and greater infant weight gain,[114] chronic mucus hypersecretion[115,116]
Medications: Lack of ICS treatment in patient with history of severe exacerbation[117]
Exposures: Tobacco smoke,[115] noxious chemicals; occupational or domestic exposures[62]
Investigation findings: Low initial FEV_1,[116] sputum or blood eosinophilia[116]
c. Risk factors for medication side-effects
Systemic Frequent OCS, long-term, high-dose and/or potent ICS, P450 inhibitors[118]
Local: High-dose or potent ICS,[118,119] poor inhaler technique[120]

See list of abbreviations (p.11).*Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise (see Assessing asthma symptom control, p.38).

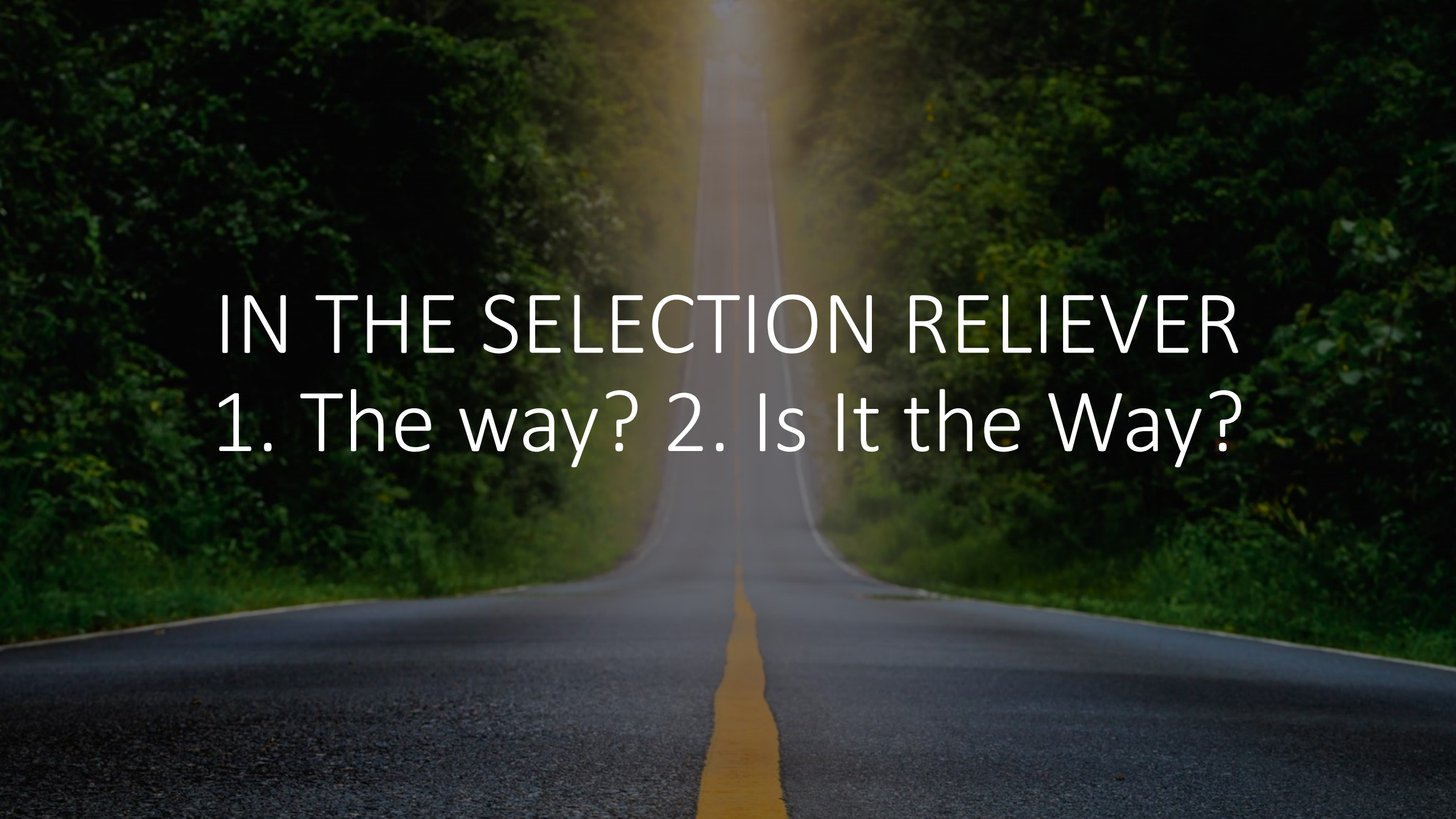
Risk factors for attack

ATAK RİSKİ:

SIK SEMPTOM

RİNİT

SEZONAL ALERJEN MARUZİYETİ DEVAM EDİYOR


IN THE SELECTION RELIEVER
1. The way? 2. Is It the Way?

ATAK RİSKİ VEYA ÖYKÜSÜ VARSA KURTARICI: AİR: IKS+ FORMETEROL/SABA

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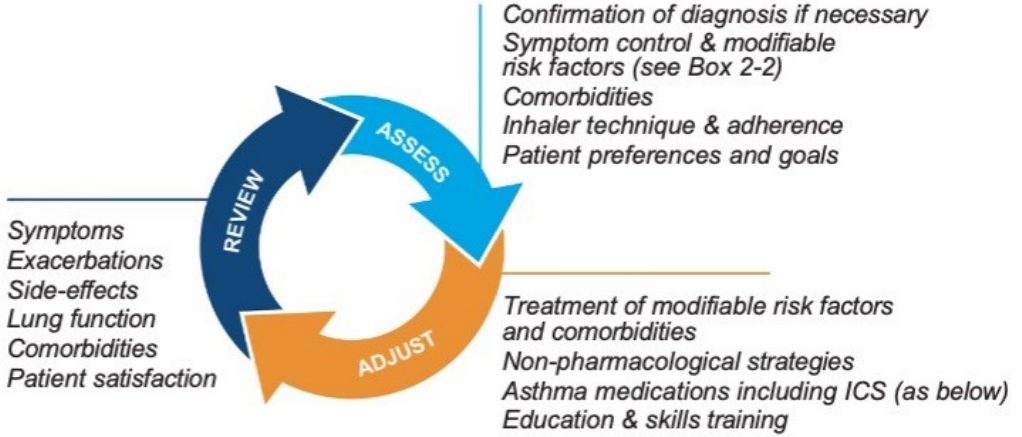
	Identify any avoidable triggers for exacerbations.	C

BASAMAK 3-5 MART ADAYLARI

- **For Track 1,** as-needed-only low-dose ICS-formoterol has been the preferred treatment option for both Step 1 and Step 2 since 2021, so together they are called 'Steps 1–2'. Accordingly, the descriptions of evidence and other considerations are now also presented for Steps 1–2 together. A common question is which patients should instead start treatment at Step 3, i.e., with low-dose ICS-formoterol being taken as maintenance-and-reliever therapy (MART) rather than as-needed-only. There is no specific evidence to guide this choice, but clinical factors that are suggested for consideration of starting with MART (if permitted by local regulators) include symptoms every day, current smoking, low lung function, a recent severe exacerbation or a history of life-threatening exacerbation, impaired perception of bronchoconstriction (e.g. low initial lung function but few symptoms), severe airway hyperresponsiveness, or current exposure to a seasonal allergic trigger (p.78).

GINA 2024 – Adults & adolescents 12+ years

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



TRACK 1: PREFERRED CONTROLLER and RELIEVER
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STEPS 1 – 2
As-needed-only low dose ICS-formoterol

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

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

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

See GINA severe asthma guide

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

STEP 1
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-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

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

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*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

KONTROL EDİCİ TEDAVİ SEÇİMİNDE

MILD ASTHMA

STEP 1-2

MILD PERSİSTAN STEP 3-4

SEVERE PERSİSTAN STEP 5

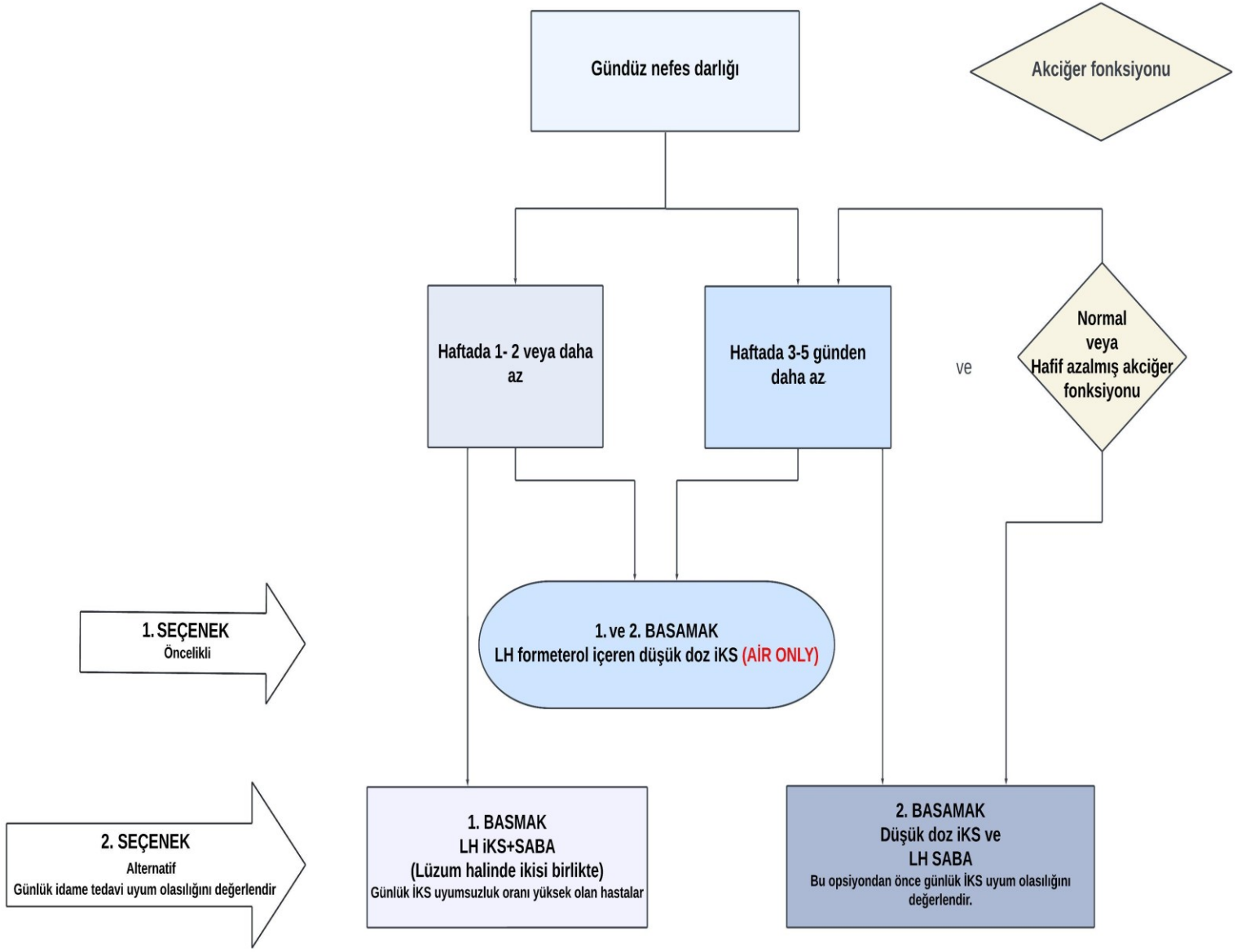
INITIATION OF CONTROLLING THERAPY

These recommendations are based on evidence, where available, and on consensus.

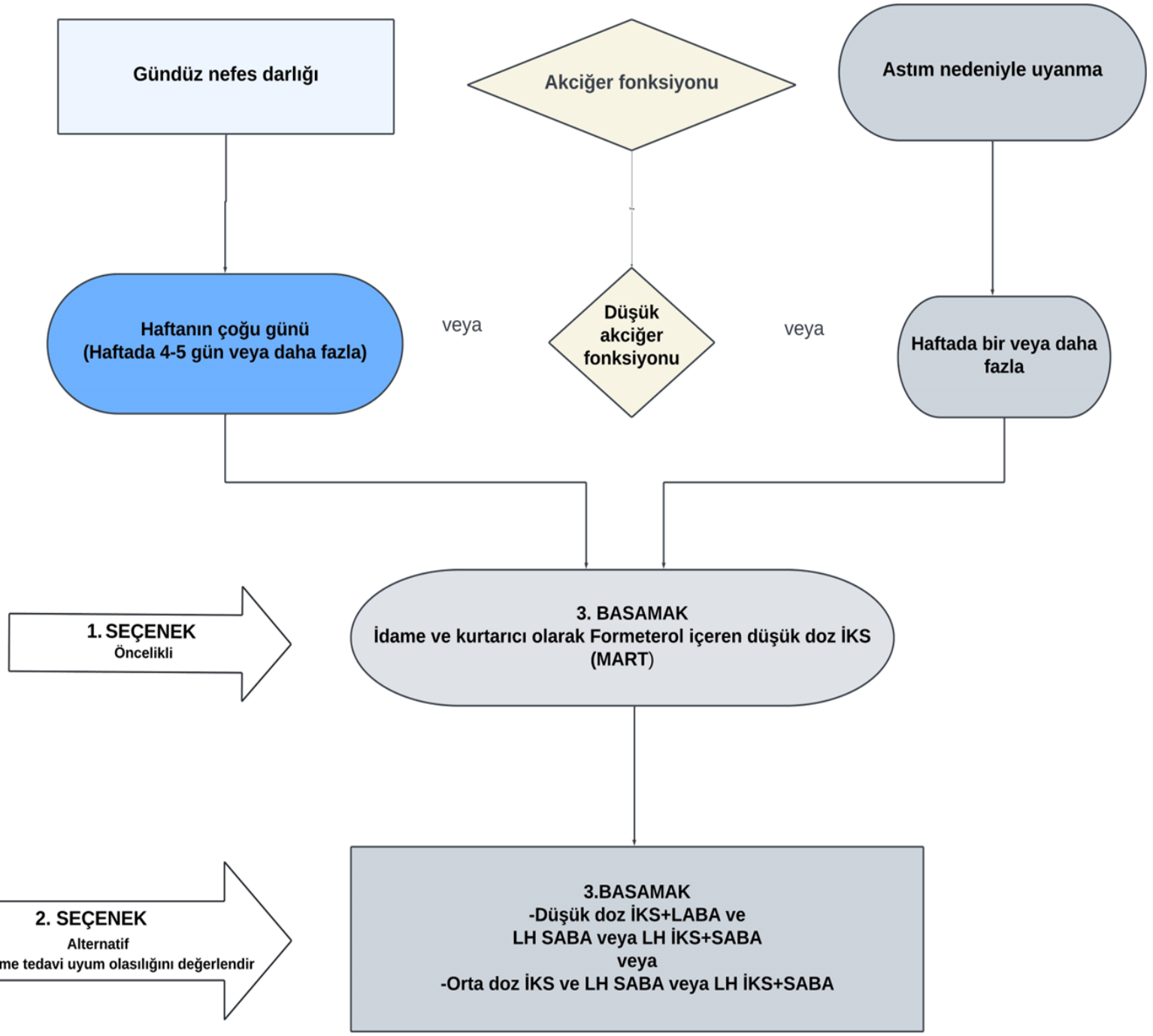
Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g., 1–2 days/week or less	**As-needed low-dose ICS-formoterol** (Evidence A)	**Low-dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B). Such patients are highly unlikely to be adherent with daily ICS.
Asthma symptoms less than 3–5 days/week, with normal or mildly reduced lung function		**Low-dose ICS plus as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Asthma symptoms most days (e.g., 4–5 days/week or more); or waking due to asthma once a week or more, or low lung function. See p.80 for additional considerations for starting at Step 3.	**Low-dose ICS-formoterol maintenance-and-reliever therapy** (MART) (Evidence A)	**Low-dose ICS-LABA plus as-needed SABA** (Evidence A) or plus as-needed ICS-SABA (Evidence B), **OR** Medium-dose ICS plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B). Consider likely adherence with daily maintenance treatment.
Daily asthma symptoms, waking at night with asthma once a week or more, with low lung function	**Medium-dose ICS-formoterol maintenance-and-reliever therapy** (MART) (Evidence D).	**Medium- or high-dose ICS-LABA** (Evidence D) plus as-needed SABA or plus as-needed ICS-SABA. Consider likely adherence with daily maintenance treatment. High-dose ICS plus as-needed SABA is another option (Evidence A) but adherence is worse than with combination ICS-LABA.
Initial asthma presentation is during an acute exacerbation	Treat as for exacerbation (Box 9-4, p.167 and Box 9-6, p171), including short course of OCS if severe; commence medium-dose MART (Evidence D).	Treat as for exacerbation (Box 9-4, p.167 and Box 9-6, p.171), including short course of OCS if severe; commence medium- or high-dose ICS-LABA plus as-needed SABA (Evidence D).

Tepetam FM. Algoritmalarla Astım ve İmmunoloji Hastalarının Yönetiminide Poliklinik El Kitabı

WHICH IS IN MILD ASTHMA LET'S CHOOSE THE CONTROLLING TREATMENT

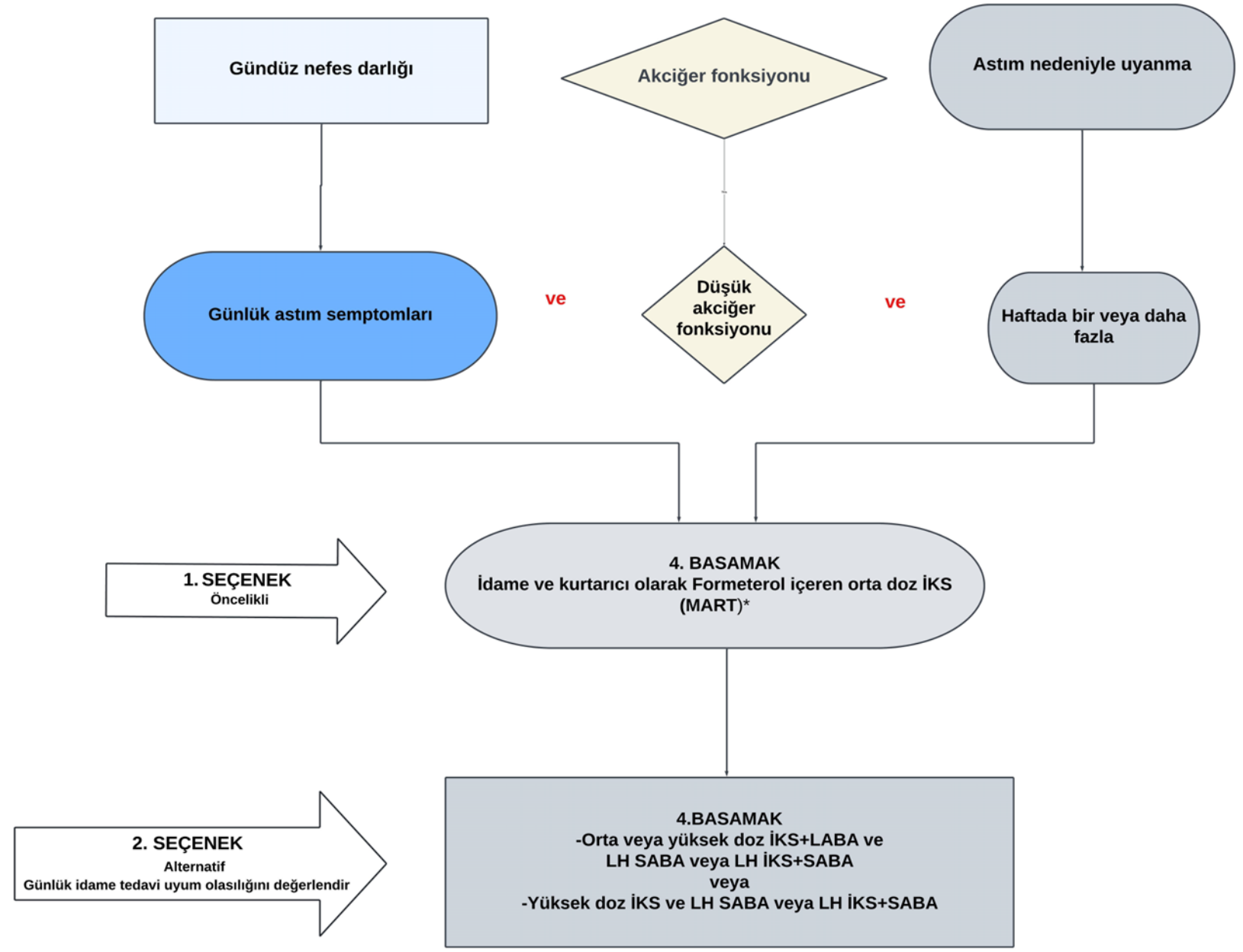


STEP 3 CONTROLLING TREATMENT OPTION



Tepetam FM. Algoritmalarla Astım ve İmmunoloji Hastalarının Yönetiminide Poliklinik El Kitabı

STEP 4 CONTROLLING TREATMENT OPTION



Tepetam FM. Algoritmalarla Astım ve İmmunoloji Hastalarının Yönetiminide Poliklinik El Kitabı

*Kurtarıcı düşük doz İKS-Formeterol

SUMMARIZE

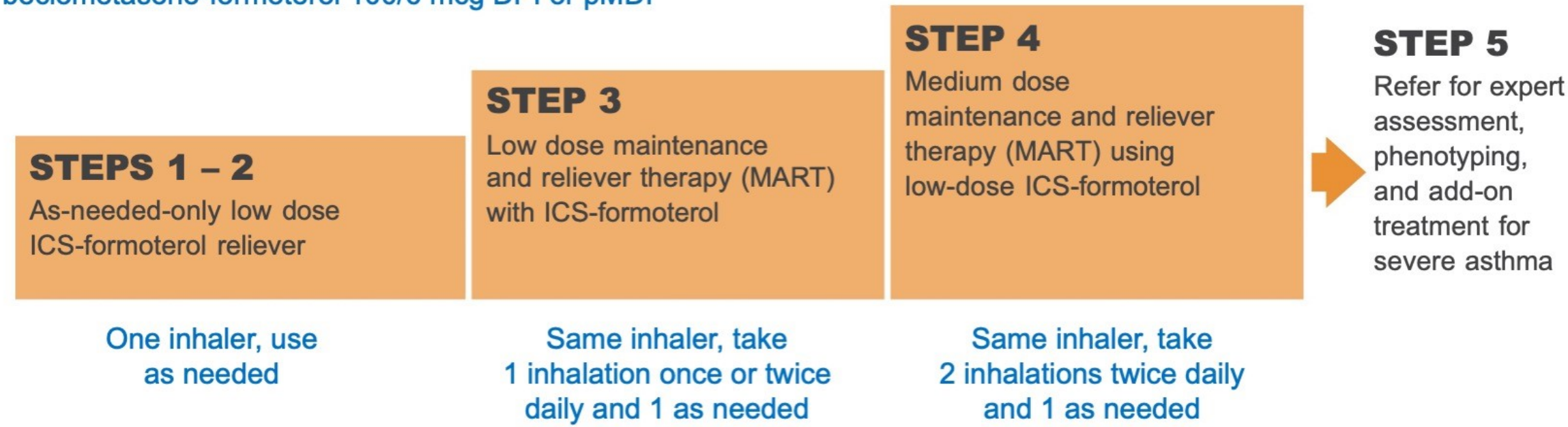
Nocturnal symptom 1 and more per week	And if there are daily symptoms and Sft is Low	Daytime Symptom

• Combination Preparations
• (STEPS 3-4)
	• Step 4
	• (Medium Dose Combination)
		• **Up to 2 per week**
		  • Basamak 1
		• **Less than 3-5 per week**
		  • Basamak 2
		• **4-5 and more per week (most days of the week)**
		  • Basamak 3
		• **Daily Symptom**
		  • Basamak 4

TRACK 1, Steps 1–4: PREFERRED CONTROLLER and RELIEVER for adults and adolescents.

Using ICS-formoterol as an anti-inflammatory reliever (AIR), with or without maintenance ICS-formoterol, reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen, with a single medication across treatment steps.

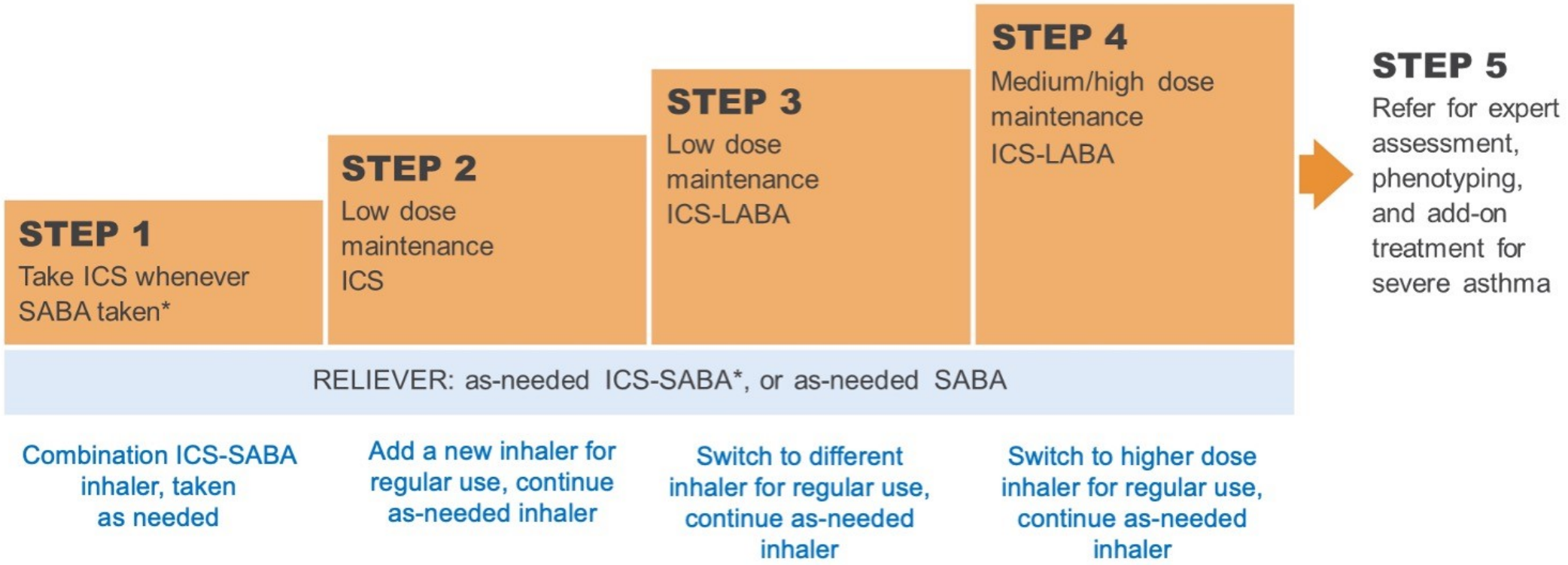
For budesonide-formoterol 200/6 mcg [160/4.5] DPI or pMDI*, or beclometasone-formoterol 100/6 mcg DPI or pMDI



*In some countries, a budesonide-formoterol pMDI with 100/3 [80/2.25] mcg per actuation is available for AIR-only or MART. For this pMDI, the recommended number of inhalations is double those shown above above.

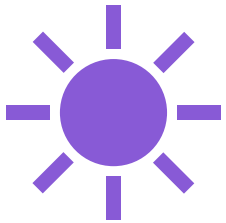
TRACK 2, Steps 1–4: Alternative CONTROLLER and RELIEVER for adults and adolescents, with ICS-SABA reliever

If maintenance and reliever medications are in different types of inhaler device, or if changing steps requires a change in device, train patient in correct inhaler technique. Make sure the patient knows which inhaler should be taken regularly, and which one as needed.



CASE NEWLY DIAGNOSED ASTHMA PATIENT CONTROL TREATMENT STEP?

WAKING UP WITH ND AT NIGHT PER WEEK1



DAYTIME ND

ALMOST EVERY DAY

LUNG FUNCTION

SMALL AIRWAYS AFFECTED

At which step should treatment be started?

- 1.STEP
- 2.STEP
- 3.STEP
- 4.STEP

MART DOSE

Adults 18 years and older	
Budesonide-formoterol **DPI** or **pMDI** 200/6 [160/4.5] (maximum total 12 inhalations in any day*)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed
Budesonide-formoterol **pMDI** 100/3 [80/2.25] (maximum total 24 inhalations in any day*) ***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol***	***These doses ONLY for pMDIs with 3 [2.25] mcg formoterol*** Step 1–2 (AIR-only): 2 inhalations as needed Step 3 MART: 2 inhalations twice (or once) daily plus 2 as needed Step 4 MART: 4 inhalations twice daily plus 2 as needed Step 5 MART: 4 inhalations twice daily plus 2 as needed
Beclometasone-formoterol **pMDI** or **DPI** 100/6 (GINA suggests maximum total 12 inhalations in any day*†)	Step 1–2 (AIR-only): 1 inhalation as needed Step 3 MART: 1 inhalation twice (or once) daily plus 1 as needed Step 4 MART: 2 inhalations twice daily plus 1 as needed Step 5 MART: 2 inhalations twice daily plus 1 as needed

For abbreviations, see p.11. *Maximum total inhalations in any day = as-needed doses plus maintenance doses, if used.

†Beclometasone (BDP)-formoterol has not been studied for as-needed-only use (Steps 1–2), but it may be suitable given its efficacy for MART in moderate-severe asthma.[316] GINA suggests that the maximum total dose of BDP-formoterol in any day should be 12 inhalations, based on extensive safety data with budesonide-formoterol.[322] For more details, see p.82.

#Budesonide-formoterol 400/12 [320/4.5] mcg should **not** be used as an anti-inflammatory reliever. For adults/adolescents, GINA does not suggest use of budesonide-formoterol 100/6 [80/4.5] as an anti-inflammatory reliever, since most evidence is with budesonide-formoterol 200/6 [160/4.5] mcg.

†For beclometasone (BDP)-formoterol, GINA suggests that the maximum total dose in any day should be 12 inhalations, based on extensive safety data with budesonide-formoterol; it has not been studied as-needed only but may be suitable (see p.82. The delivered dose for BDP-formoterol 100/6 mcg is 84.6/5 mcg for pMDI and 81.9/5 mcg for DPI. See next page for more inhaler doses.

INHALER SELECTION AND ENVIRONMENTAL FACTORS

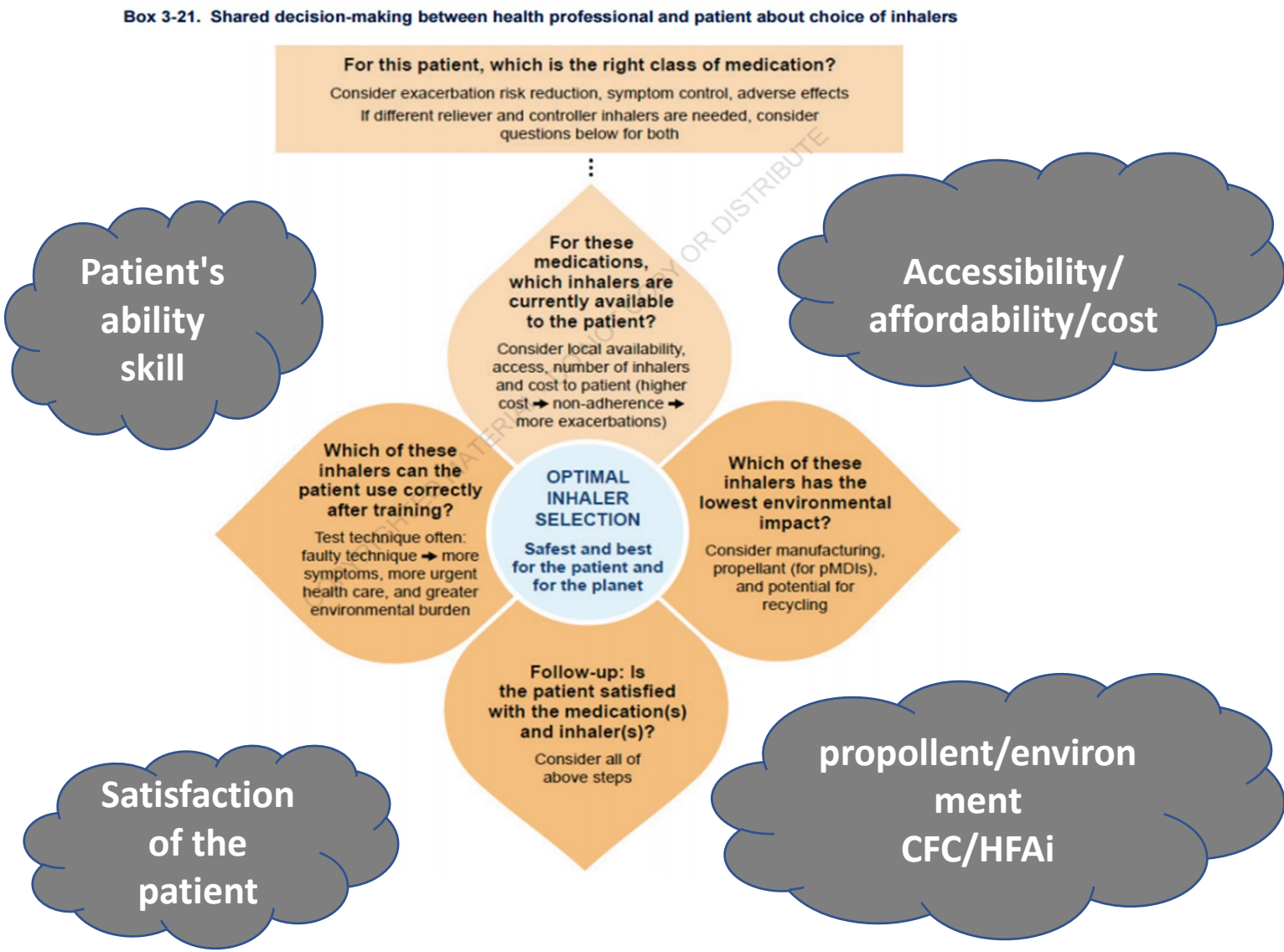
- IKS astımda atak riskini ve astımla ilgili mortaliteyi azaltır
- Farklı inhaler tipler; ÖDİ, KTİ, kapsül, breath actuated, mist inhaler, nebul.
- Farlı inhaler teknik
  - Prime/dont prime
  - Sallama /sallama gerektirmeyen
  - Twist/flip/press (Bükme, çevirme, basma)
  - Fast/slow
  - Haftalık yıkanan/nemlendirilmemesi gereken

Farklı farklı inhaler

Daha fazla hata

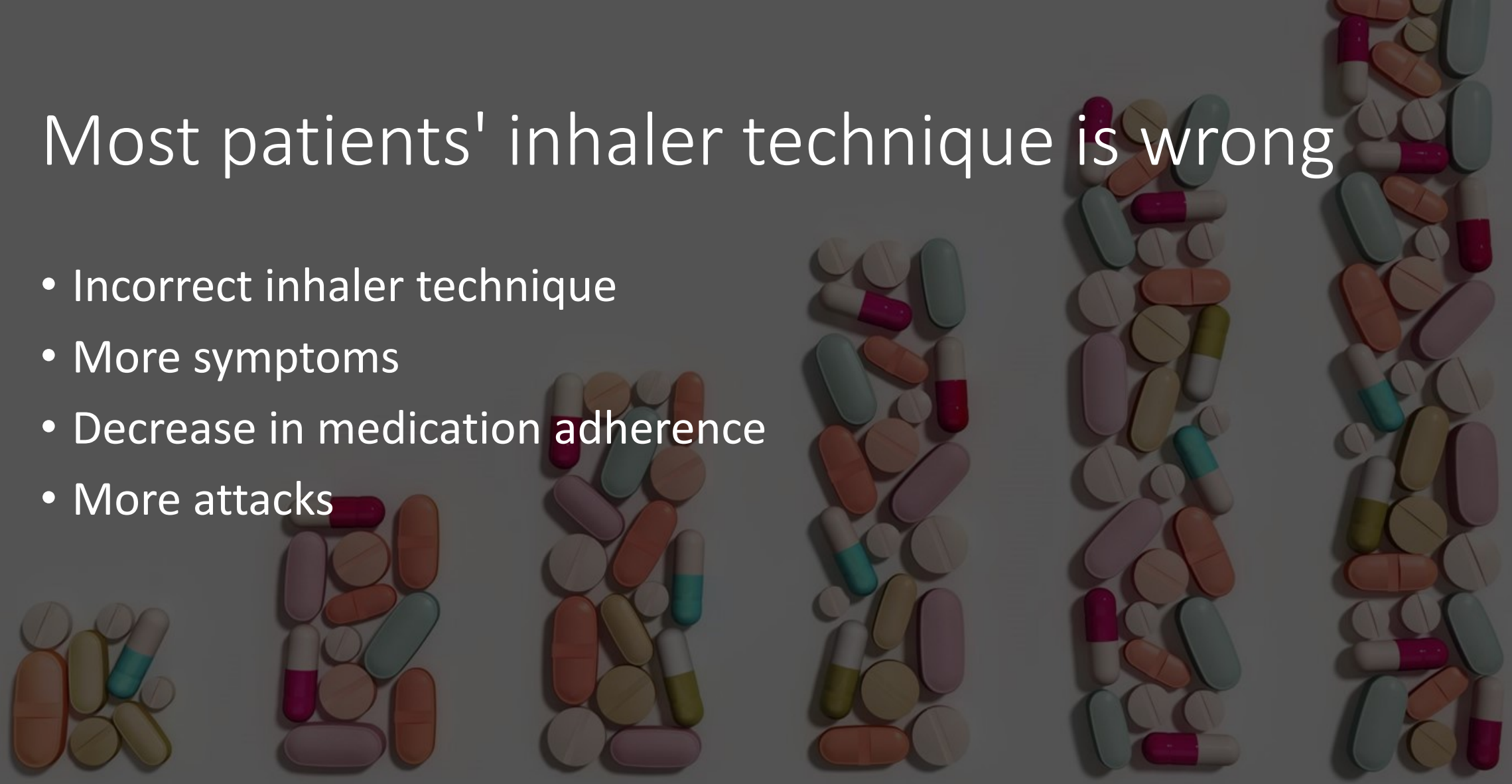
- Bazı inhalerler bazı hastalar için uygun değil ;kognigtif, tremor

CHOOSING AN INHALER



Most patients' inhaler technique is wrong

- Incorrect inhaler technique
- More symptoms
- Decrease in medication adherence
- More attacks

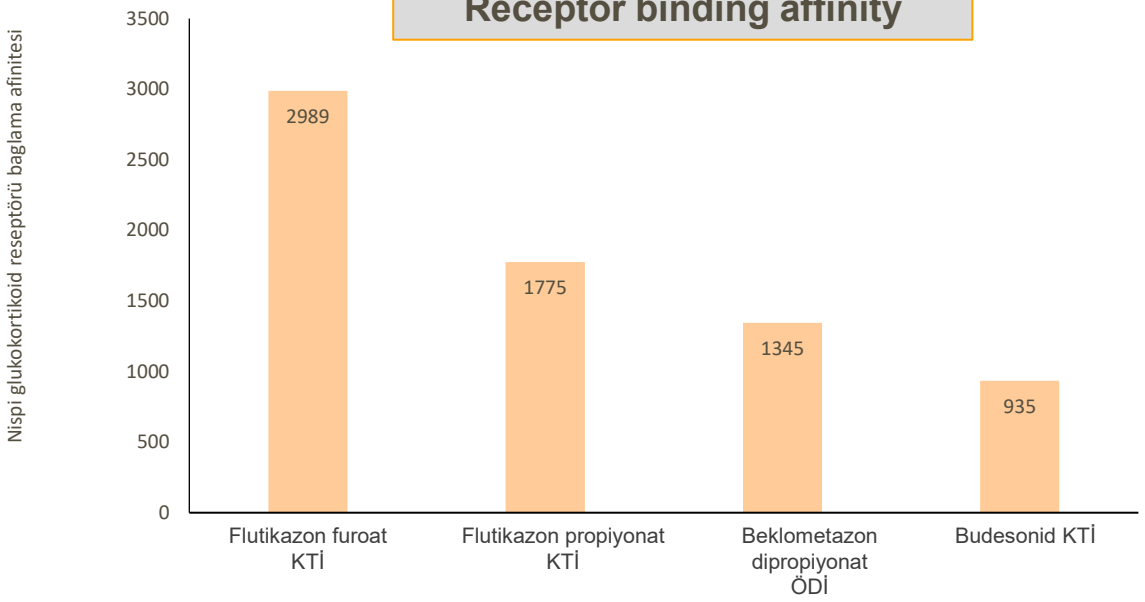


Are All IKS Molecules the Same?

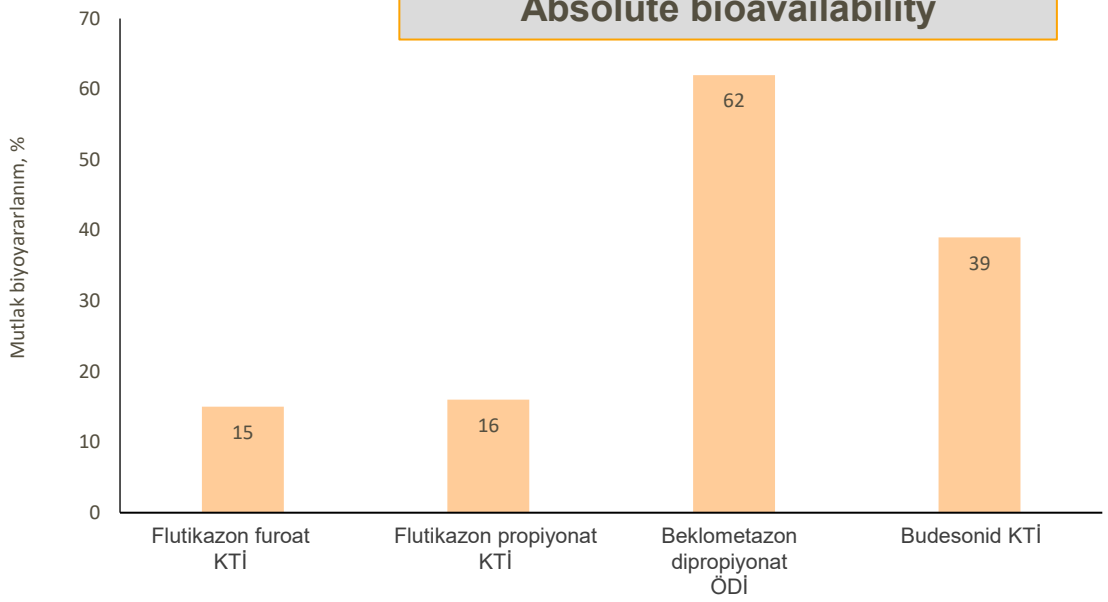
PHARMACOKINETIC AND PHARMACODYNAMIC DATA ON ICS

FLUTİKAZON FUROAT

Receptor binding affinity



Absolute bioavailability



FF'nin yüksek reseptör bağlama afinitesi düşük terapötik doz ile ilişkili olup, bu da düşük biyoyararlanımı ile birlikte diğer İKS'lere kıyasla sistemik etkiler potansiyelini azaltır

FF monoterapisi KOAH'ta kullanım için ruhsatlı değildir. Mutlak biyoyararlanım sağlıklı gönüllülerde belirlenmiştir.
Glukokortikoid reseptörü bağlama afinitesi, afinitesi = 100 olan deksametazona kıyasladır. Beklometazon dipropiyonat için AKAif metabolitler için reseptör bağlama afinitesi (beklometazon 17-monopropiyonat) gösterilmektedir.

KTİ, kuru toz inhaler; FF, flutikazon furoat; İKS, inhale kortikosteroid; ÖDİ, ölçülü doz inhaler

1. Daley-Yates PT. Br J Clin Pharmacol. 2015;80:372–380.

WHICH IKS

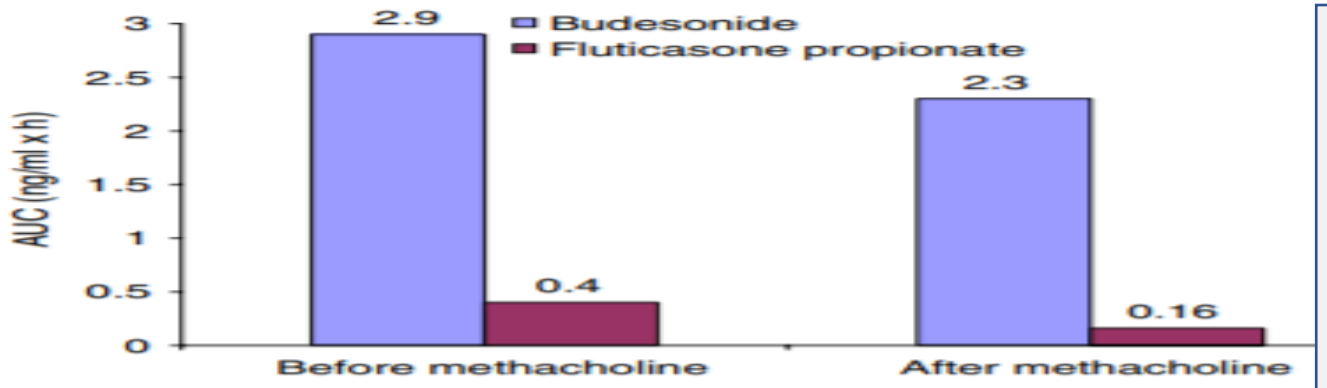


Figure 2 Mean areas under curves of plasma drug concen
tion vs. time (AUC) for single inhaled doses of budeso
(800 μg) and fluticasone (1000 μg) before and after challe
with methacholine.[52] The relative reduction in AUC caused by

- Budesonide: high solubility
- Fluticasone: lipophilic
- In airflow restriction
- Oropharyngeal accumulation
- Renal clearance is excessive

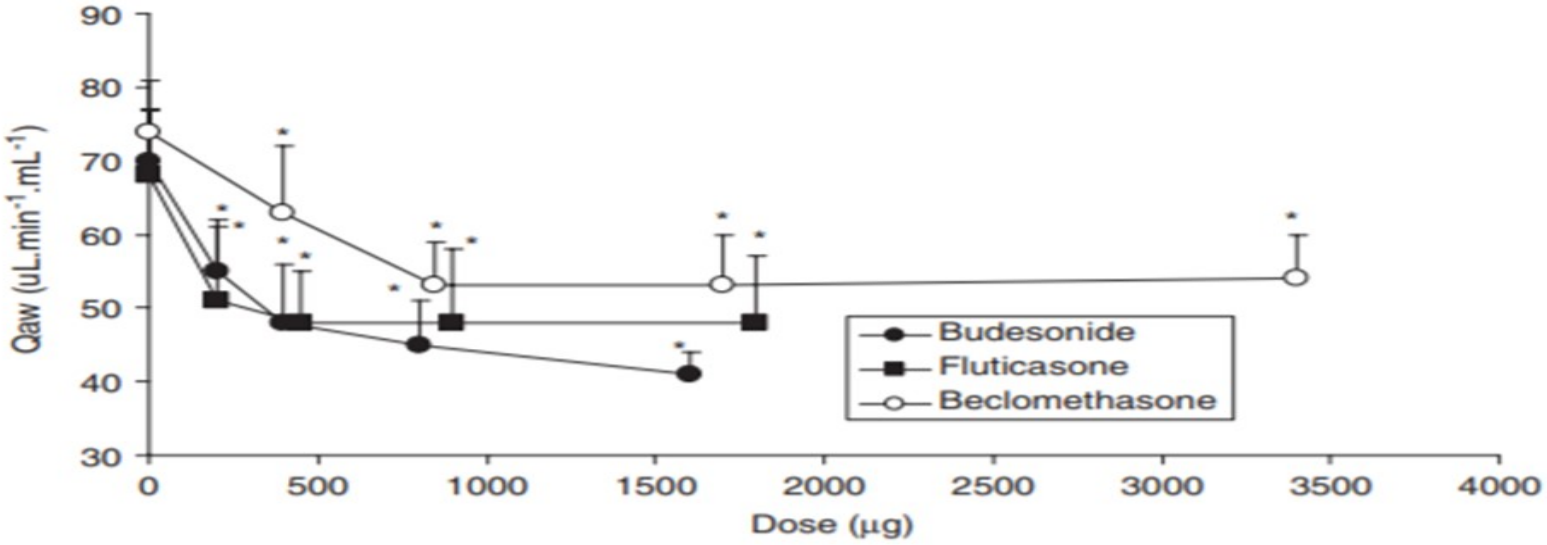


Figure 3 Comparative vasoconstrictor efficacy of three inhaled corticosteroids in 10 corticosteroid naïve patients with asthma.[41]

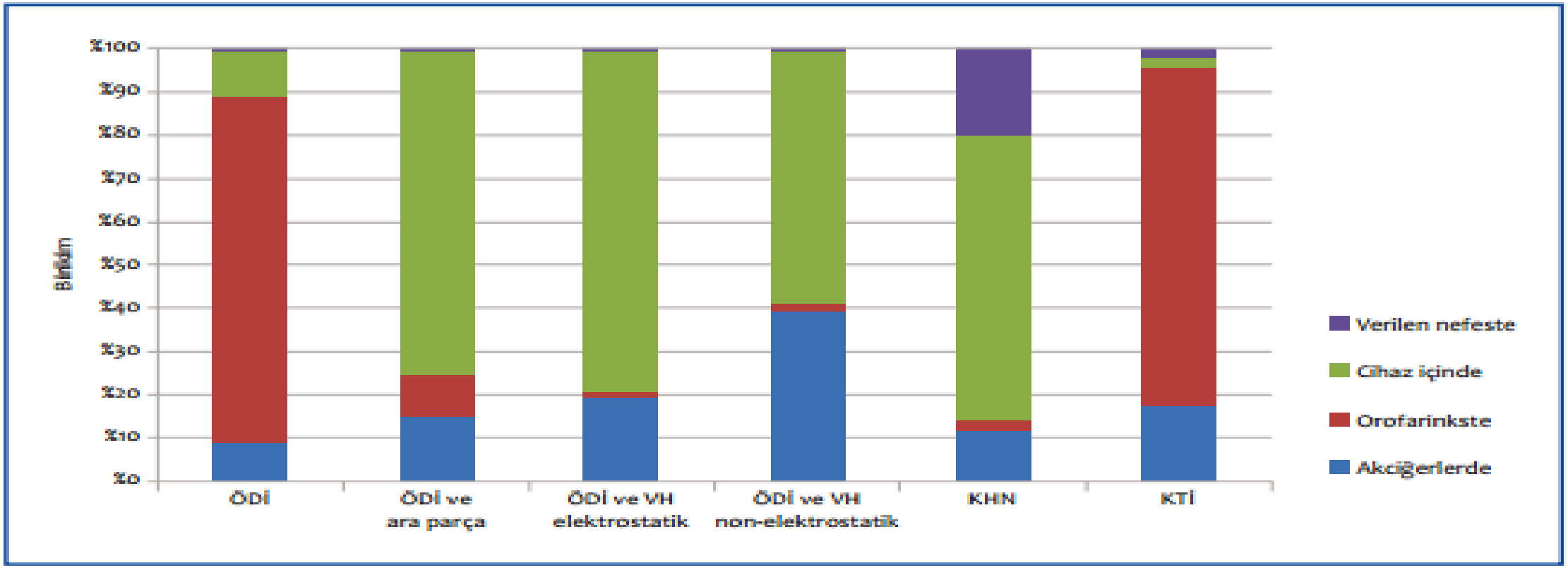
Yetişkin veya adölesan (12 yaş ve üzeri)

İnhale Kortikosteroid	Toplam günlük İKS dozu (mcg)			
	Düşük	Orta	Yüksek	Maksimum
Beklometazon dipropionat (pMDI, standart partikül, HFA)	200-500	>500-1000	>1000	2000
Beklometazon dipropionat (DPI veya pMDI, ekstra ince partikül, HFA)	100-200	>200-400	>400	800
Budesonid (DPI veya pMDI, standart partikül, HFA)	200-400	>400-800	>800	1600
Siklesonid (pMDI, ekstra ince partikül, HFA)	80-160	>160-320	>320	640
Flutikazon furoat (DPI)	100		200	
Flutikazon propiyonat (DPI)	100-250	>250-500	>500	1000
Flutikazon propiyonat (pMDI, standart partikül, HFA)	100-250	>250-500	>500	1000
Mometazon furoat (DPI)	DPI cihazına bağlı			
Mometazon furoat (pMDI, standart partikül, HFA)	200-400		>400	

Low, medium and high doses of ICS

Inhaled corticosteroid (alone or in combination with LABA)	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 11-3, p.191			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50–100	>100–200	>200
Budesonide (DPI, or pMDI, standard particle, HFA)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

- This is a table of low, medium and high doses of various ICS
- **It does NOT imply equivalent potency**
- For example, if you switch a patient from a 'medium' dose of one ICS to a 'medium' dose of another ICS, this may represent a *decrease* in potency, so their asthma may worsen, or it might represent an *increase* in potency and the patient may experience more adverse effects
- Always monitor patients after any change in medication, dose or device, to ensure they are stable



Şekil 2. Mevcut inhalasyon cihazlarında ilaç birikimleri. Akciğerlere ulaşan, orofarinkste ve cihaz içinde tutulan ve verilen nefesle kaybedilen ilaç yüzdelerindeki değişiklikler renklerle gösterilmiştir.
ÖDİ = ölçülü doz inhaler; VH = valfli hazne; KHN = küçük hacimli nebülizer; KTİ = kuru toz inhaler
(Kaynak 1 ve 7'den izinle yeniden düzenlenmiştir)

Solunum Tedavileri Uygulayanlar İçin Aerosol Tedavi Cihazları Rehberi, 2. Baskı American Association for Respiratory Care

Tüm LABA'lar Aynı mı?

LABA'LARA İLİŞKIN FARMAKOKINETIK VE FARMAKODINAMIK VERILER

LABA'LAR | ÖZELLİKLER | FARMAKOKİNETİK VE FARMAKODİNAMİK

	Potens (pEC_{50})	Başlangıç $t_{1/2}$ (min)	Seçicilik oranı (β_2 / β_1)	Doz aralığı (saat)
Vilanterol	8.62 ± 0.27	3.1 ± 0.5[2]	2400	24
Salmeterol	6.84 ± 0.03	15.2 ± 0.6	3000	12
İndakaterol	6.84 ± 0.16	4.0 ± 0.2	16†	24
Formoterol	8.56 ± 0.18	4.0 ± 0.1*	150†	12

Vilanterol hızlı etki başlangıcı ve ß$_1$'e karşı ß$_2$ reseptörleri için yüksek seçicilik gösteren, potent, günde bir kez uygulanan bir LABA'dır

VI monoterapisi KOAH'ta kullanım için ruhsatlı değildir.
*Salmeterole karşı P<0.001; † Vilanterole karşı P<0.0001. İn vitro veriler, klinik anlamı bilinmiyor.

LABA, uzun etkili β2-agonisti; pEC50, logaritmik dönüştürülmüş yarı maksimum etkili konsantrasyon; t1/2, ayrışma yarılanma ömrü

1. Slack RJ et al. J Pharmacol Exp Ther. 2013;344:218–230. 2. Cazzola M et al. Am J Respir Crit Care Med. 2013;187(7):690-6

WHICH ANTICHOLINERGIC-WHICH M BLOCKER?

TABLE 1 Binding affinities (pK_i) and dissociation half-lives ($t_{1/2}$) of anticholinergics against muscarinic M_1, M_2 and M_3 receptor subtypes

	pK_i			$t_{1/2}$ h		
	M_1	M_2	M_3	M_1	M_2	M_3
Ipratropium	9.40	9.53	9.58	0.1	0.03	0.22
Aclidinium	10.78	10.68	10.74	6.4	1.8	10.7
Glycopyrronium	10.09	9.67	10.04	2.0	0.37	6.1
Tiotropium	10.80	10.69	11.02	10.5	2.6	27
umeclidinium (GSK573719)	9.8	9.8	10.2			

Dissociation constants determined by analysing competition kinetics curves in the presence of [*N*-methyl-^{3}H]scopolamine and different concentrations of unlabelled antagonist. Data from [65].

Gosens et al., Eur Respir J 2018; 52: 1701247

Muscarinic Receptors

M1

Epitel hücreleri, periferik ac

Otonom sinir sistemi

Beyin

Gastrik Gland

M2

Kalp

Düz kas hücrelerinde otoreseptör (inhibitör)

M3

Düz kas

Salgı

Pupil

Vaskuler

The separation time of umeclidinium from M2 is 4 times faster than that of thiotroprium

TABLE 1

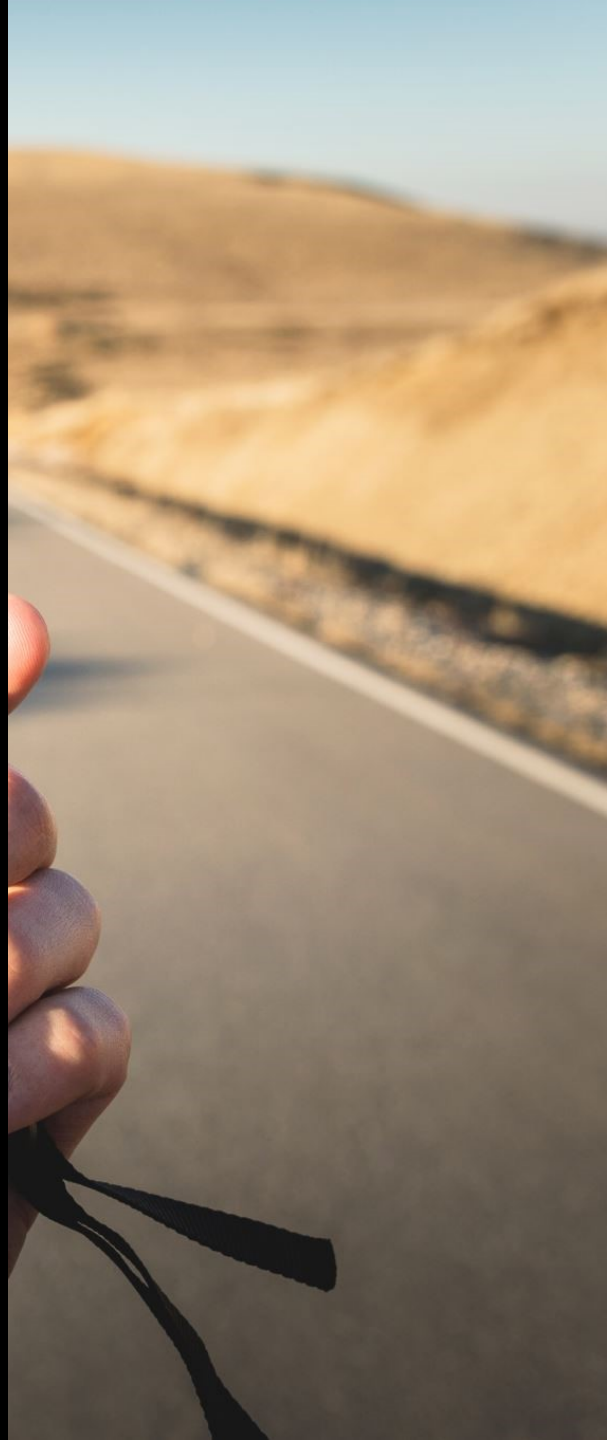
Receptor binding data

Data represent the mean ± S.E.M., where $N = 3$ for [^{3}H-NMS]-based experiments and $N = 4$ for [^{3}H]GSK5' kinetic parameters are k_{on} = $M^{-1} \cdot min^{-1}$, k_{off} = min^{-1}, and $t_{1/2}$ = minutes.

	mAChR Subtype		
Compound	M1	M2	M3
GSK573719 versus [^{3}H-NMS]			
Ki (nM)	0.16 ± 0.01	0.15 ± 0.01	0.06 ± 0.01
pK_i	9.8	9.8	10.2
[^{3}H]GSK573719			
pK_D		9.79 ± 0.08	10.5 ± 0.01
k_{on}		2.22 ± 0.11 $\times 10^9$	5.67 ± 0.45 $\times 10^8$
k_{off}		0.074 ± 0.004	0.0089 ± 0.0012
$t_{1/2}$		9.4 ± 0.5	82.2 ± 0.0012
[^{3}H]Tiotropium			
pK_D		10.3 ± 0.08	10.7 ± 0.07
k_{on}		1.26 ± 0.10 $\times 10^9$	4.09 ± 0.55 $\times 10^8$
k_{off}		0.023 ± 0.008	0.0026 ± 0.0003
$t_{1/2}$		39.2 ± 9.7	272.8 ± 27.6

J Pharmacol Exp Ther 345:260–270, May 2013

TAKİP EDERKEN NELERE DİKKAT EDELİM ?



SYMPTOM CONTROL RISK FACTORS

Box 2-2. GINA assessment of asthma control at clinical visits in adults, adolescents and children 6–11 years

A. Recent asthma symptom control (but also ask the patient/caregiver about the whole period since last review#)

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA* reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.

Measure FEV_1 at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

a. Risk factors for exacerbations

Uncontrolled asthma symptoms: Having uncontrolled symptoms is an important risk factor for exacerbations.[85]

Factors that increase the risk of exacerbations even if the patient has few asthma symptoms†

- *SABA over-use:* High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)[86-89]
- *Inadequate ICS*: not prescribed ICS, poor adherence,[90] or incorrect inhaler technique[91]
- *Other medical conditions:* Obesity,[92,93] chronic rhinosinusitis,[93] GERD,[93] confirmed food allergy,[94] pregnancy[95]
- *Exposures:* Smoking,[96] e-cigarettes,[97] allergen exposure if sensitized,[96,98] air pollution[99-102]
- *Psychosocial*: Major psychological or socioeconomic problems[103,104]
- *Lung function:* Low FEV_1 (especially <60% predicted),[96,105] high bronchodilator responsiveness[93,106,107]
- *Type 2 inflammatory markers:* Higher blood eosinophils,[93,108,109] high FeNO (adults with allergic asthma on ICS)[110]
- *Exacerbation history:* Ever intubated or in intensive care unit for asthma;[111] ≥1 severe exacerbation in last year[112,113]

b. Risk factors for developing persistent airflow limitation

- *History:* Preterm birth, low birth weight and greater infant weight gain,[114] chronic mucus hypersecretion[115,116]
- *Medications:* Lack of ICS treatment in patient with history of severe exacerbation[117]
- *Exposures:* Tobacco smoke,[115] noxious chemicals; occupational or domestic exposures[92]
- *Investigation findings:* Low initial FEV_1,[116] sputum or blood eosinophilia[116]

c. Risk factors for medication side-effects

- *Systemic* Frequent OCS, long-term, high-dose and/or potent ICS, P450 inhibitors[118]
- *Local:* High-dose or potent ICS,[118,119] poor inhaler technique[120]

SYMPTOM CONTROL

A. Recent asthma symptom control (but also ask the patient/caregiver about the whole period since last review#)

In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• SABA* reliever for symptoms more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			

ASTIMDA SEMPTOM KONTROLÜNÜN DEĞERLENDİRİLMESİ

Astım semptom kontrolü			**Astım semptom kontrol seviyesi**		
Son 4 hafta içinde			**Kontrol altında**	**Kısmi kontrol**	**Kontrolsüz**
Haftada ikiden fazla gündüz semptomları	**Evet**	**Hayır**	**Bu bulgulardan hiçbiri yok**	**1-2 tanesi var**	**3-4 tanesi var**
Astım nedeniyle gece uyanması	**Evet**	**Hayır**			
Haftada ikiden fazla kurtarıcı SABA kullanımı **FORMETEROL-IKS? SABA-İKS?**	**Evet**	**Hayır**			
Astıma bağlı aktivite kısıtlılığı	**Evet**	**Hayır**			

ASTHMA KONTROL TEST

FOR PATIENTS:

Take the Asthma Control Test™ (ACT) for people 12 yrs and older.

Know your score. Share your results with your doctor.

Step 1 Write the number of each answer in the score box provided.

Step 2 Add the score boxes for your total.

Step 3 Take the test to the doctor to talk about your score.

									SCORE
1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	
2. During the past **4 weeks**, how often have you had shortness of breath?	More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	
5. How would you rate your **asthma** control during the **past 4 weeks**?	Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	
									TOTAL		

If your score is 19 or less, your asthma may not be controlled as well as it could be. Talk to your doctor.

FOR PHYSICIANS:

The ACT is:

- A simple, 5-question tool that is self-administered by the patient
- Clinically validated by specialist assessment and spirometry[1]
- Recognized by the National Institutes of Health

a. Risk factors for exacerbations
Uncontrolled asthma symptoms: Having uncontrolled symptoms is an important risk factor for exacerbations.[85]
Factors that increase the risk of exacerbations even if the patient has few asthma symptoms†
SABA over-use: High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)[86-89]
Inadequate ICS: not prescribed ICS, poor adherence,[90] or incorrect inhaler technique[91]
Other medical conditions: Obesity,[92,93] chronic rhinosinusitis,[93] GERD,[93] confirmed food allergy,[94] pregnancy[95]
Exposures: Smoking,[96] e-cigarettes,[97] allergen exposure if sensitized,[96,98] air pollution[99-102]
Psychosocial: Major psychological or socioeconomic problems[103,104]
Lung function: Low FEV_1 (especially <60% predicted),[96,105] high bronchodilator responsiveness[93,106,107]
Type 2 inflammatory markers: Higher blood eosinophils,[93,108,109] high FeNO (adults with allergic asthma on ICS)[110]
Exacerbation history: Ever intubated or in intensive care unit for asthma;[111] ≥1 severe exacerbation in last year[112,113]
b. Risk factors for developing persistent airflow limitation
History: Preterm birth, low birth weight and greater infant weight gain,[114] chronic mucus hypersecretion[115,116]
Medications: Lack of ICS treatment in patient with history of severe exacerbation[117]
Exposures: Tobacco smoke,[115] noxious chemicals; occupational or domestic exposures[62]
Investigation findings: Low initial FEV_1,[116] sputum or blood eosinophilia[116]
c. Risk factors for medication side-effects
Systemic Frequent OCS, long-term, high-dose and/or potent ICS, P450 inhibitors[118]
Local: High-dose or potent ICS,[118,119] poor inhaler technique[120]

See list of abbreviations (p.11).*Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise (see Assessing asthma symptom control, p.38).

NASIL TAKİP EDELİM?

- İlk vizitten 1 ay sonra
- Kontrol sağlanırsa 3 ayda bir

Who, When should we fall the steps?

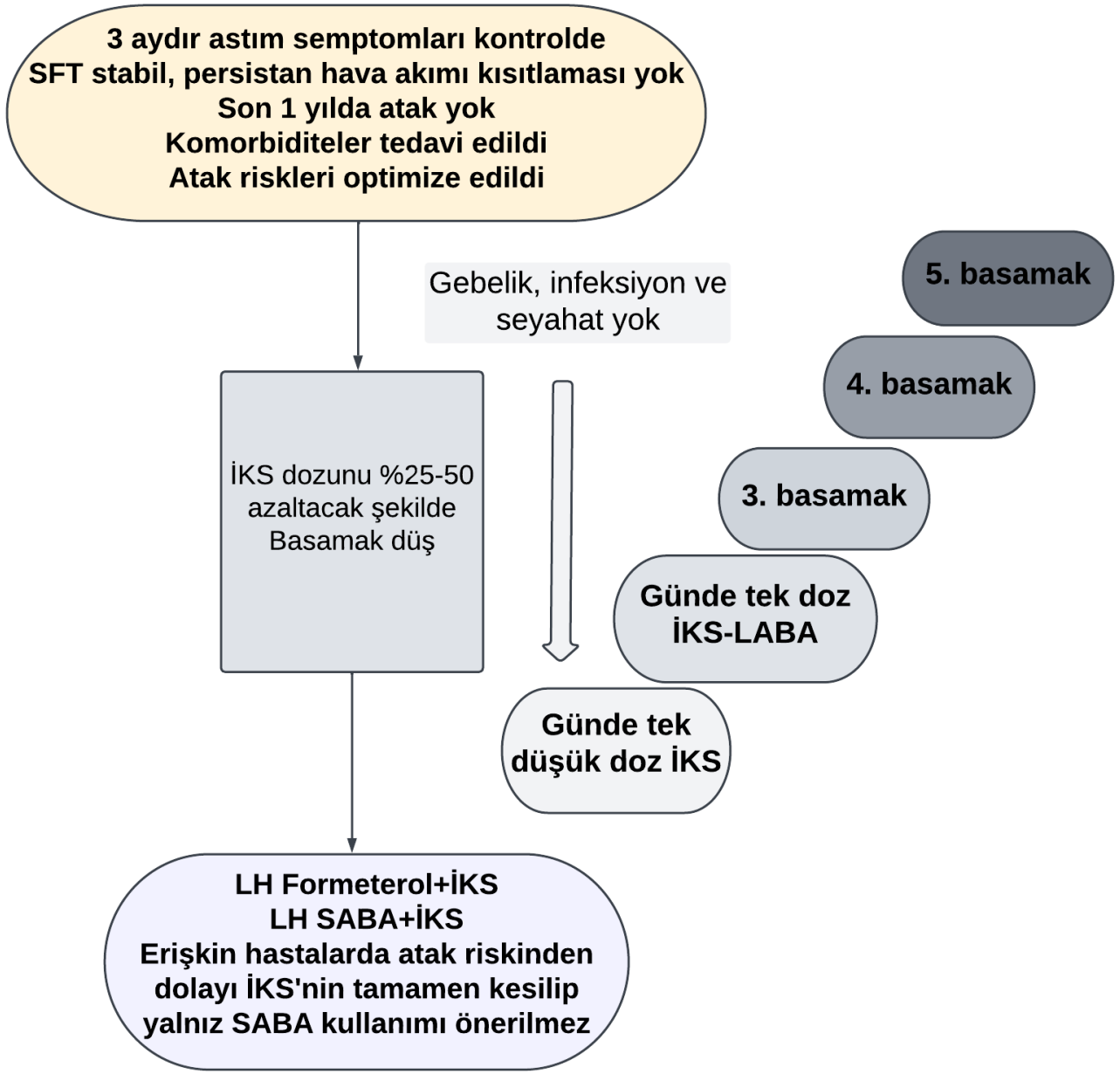
- Tedavi genellikle başarılı bir şekilde azaltılabilir;
  - **Good asthma control has been achieved**
  - **After being maintained for 2-3 months**
  - **After lung function reaches a plateau**
- Uygun bir zaman seçilmeli;
  - **no respiratory tract infections**
  - **The patient does not travel**
  - **Not pregnant**
  - **Not pollen season (if allergic)**

WHEN FALLING DOWN THE LADDER

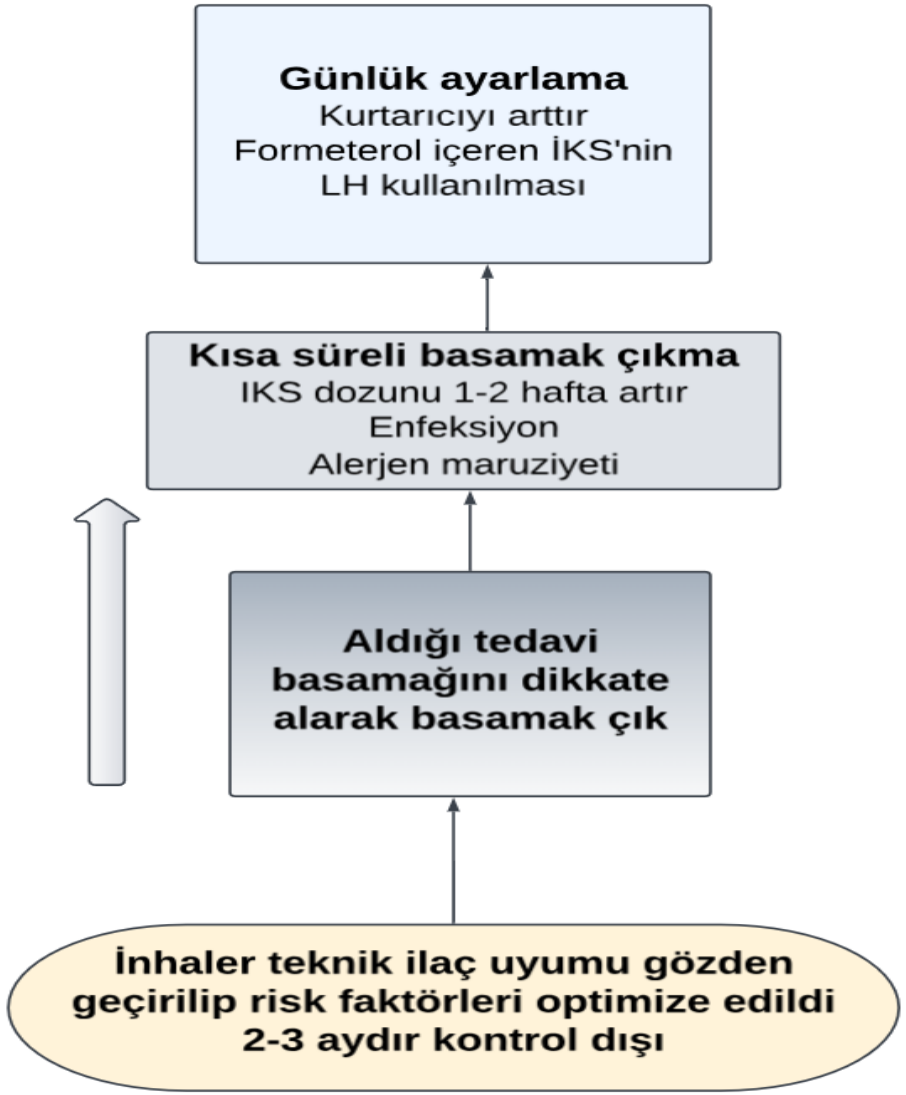
- Try reducing and discontinuing OCS first (by controlling adrenal insufficiency)
- Try discontinuing additional therapies (LAMAs)
- Try IKS/LABA dose reduction
- **IKS is not completely discontinued**

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024. Available from: www.ginasthma.org

STEP DROP IN ASTHMA



CLIMBING STEPS IN ASTHMA



WRITTEN ACTION PLAN

HASTANIN ALMAKTA OLDUĞU TEDAVİ	ASTIM KÖTÜLEŞMESİNDE KISA SÜRELİ DEĞİŞİKLİK	KANIT DÜZEYİ
Kurtarıcı kullanımını arttır		
Düşük doz İKS-formoterol (AİR)	İhtiyaca göre İKS-formoterol kullanım sıklığını arttır	A
Kısa etkili beta-agonist SABA	SABA kulanım sıklığını arttır, MDI için spacer ekle	A
Kontrol edici tedaviyi arttır		
Düzenli ve gerektiğinde İKS-formoterol (MART)	Düzenli İKS-formoterole devam et ve ihtiyaç halinde İKS-formoterolü arttır **Budesonid kombinasyonunda** Formeterol için maksimum günlük ölçülen doz 72 mcg, akciğere ulaşan doz 54 mcg **Beklometazon kombinasyonunda** Formeterol için maksimum günlük ölçülen doz 48 mcg, akciğere ulaşan doz 36 mcg olacak şekilde ayarlanır	A
Düzenli İKS, gerektiğinde SABA	İKS'yi dört katına çık	B
Düzenli İKS-formoterol, gerektiğinde SABA	İKS-formoterol'ü dört katına çık	B
Düzenli İKS-diğer LABA gerektiğinde SABA	Daha yüksek doz başka bir İKS-LABA kombinasyonuna geç veya ayrı olarak dört kat artacak şekilde ilave İKS ekle	B D
Oral kortikosteroid ekle, hekimini ara		
OKS	Ağır atak durumunda (PEF/FEV1 <%60 beklenenin veya kişisel en iyi değerin) veya 48 saat içinde tedaviye yanıt yoksa OKS ekle	A
	40-50 mg/gün prednizolon ya da eş değeri 5-7 gün	D
	İki haftadan kısa süreli kullanımlarda azaltarak kesmeye gerek yok	B

OLGU

AFTER 3 MONTHS, HE CAME FOR A CHECK-UP

SHE WAS RECEIVING TREATMENT 4 step

EVALUATION OF SYMPTOM CONTROL IN ASTHMA

Astım semptom kontrolü			Astım semptom kontrol seviyesi		
Son 4 hafta içinde			Kontrol altında	Kısmi kontrol	Kontrolsüz
Haftada ikiden fazla gündüz semptomları	Evet	Hayır	Bu bulgulardan hiçbiri yok	1-2 tanesi var	3-4 tanesi var
Astım nedeniyle gece uyanması	Evet	Hayır			
Haftada ikiden fazla kurtarıcı SABA kullanımı FORMETEROL-IKS? SABA-İKS?	Evet	Hayır			
Astıma bağlı aktivite kısıtlılığı	Evet	Hayır			

RISK FACTORS RELATED TO POOR PROGNOSIS ARE OPTIMIZED

- INHALER TECHNICAL DRUG COMPLIANCE IS GOOD
- APPLYING ALLERGEN PROTECTION METHODS
- RECEIVING TREATMENT FOR RHINITIS

HOW SHOULD WE APPROACH? SHALL WE CLIMB THE LADDER?

Yolak 1 (önerilen)

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

Kurtarıcı: Düşük doz İKS + formoterol

Yolak 2

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

Kurtarıcı: Düşük doz İKS + SABA / SABA

Diğer kontrol ediciler (sadece kısıtlı endikasyonlarda ana yolaklara alternatif olarak)

-Orta doz İKS

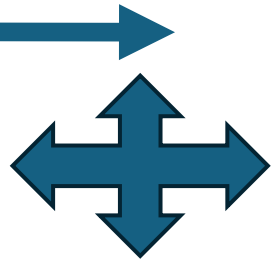
-Yüksek doz İKS

Ekleme tedavisi

-LAMA eklenmesi

-LTRA eklenmesi

-HDM SLIT eklenmesi (TR için SCİT??)



EFFECT/SIDE EFFECT AS THE IKS DOSE INCREASES

Inhaled Corticosteroid Therapy in Adult Asthma

Time for a New Therapeutic Dose Terminology

Richard Beasley[1,2,3], James Harper[1], Grace Bird[1], Ingrid Maijers[1], Mark Weatherall[3,4], and Ian D. Pavord[5]

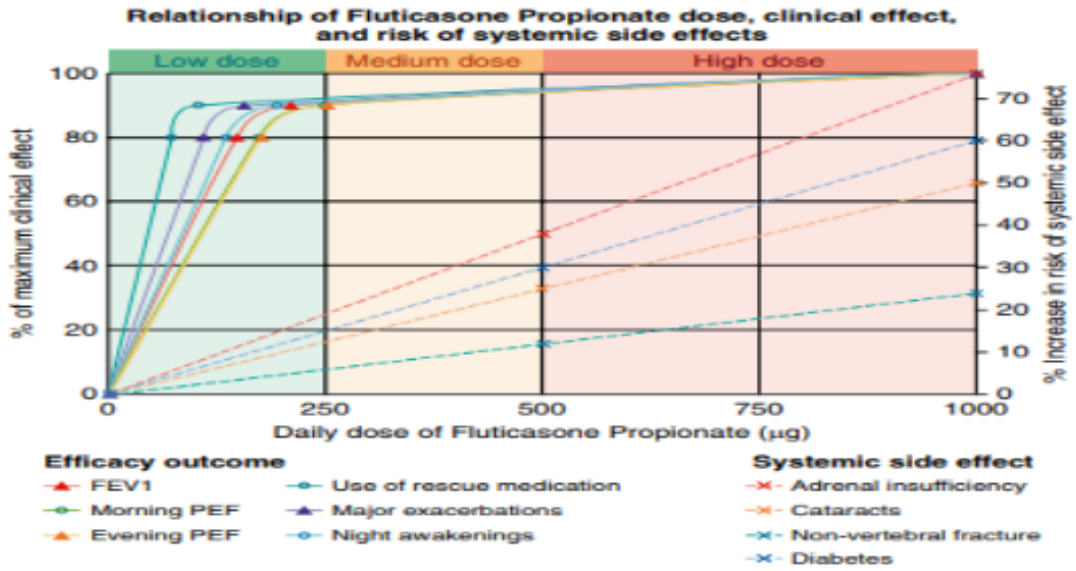
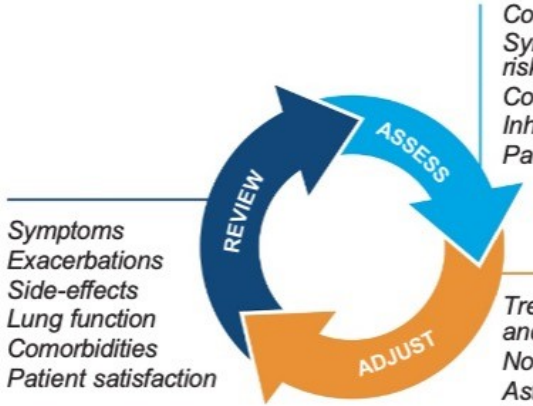


Figure 1. Schematic dose–response curves for different outcomes for efficacy and adverse effects with inhaled corticosteroids, expressed as fluticasone propionate in µg/d, derived from Tables 2 and 5. PEF = peak expiratory flow.

Am J Respir Crit Care Med Vol 199, Iss 12, pp 1471–1477, Jun 15, 2019 Originally Published in Press as DOI: 10.1164/rccm.201810-1868CI on January 15, 2019
Internet address: www.atsjournals.org

GINA 2024 – 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 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

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

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

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

See GINA severe asthma guide

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

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

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

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

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

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

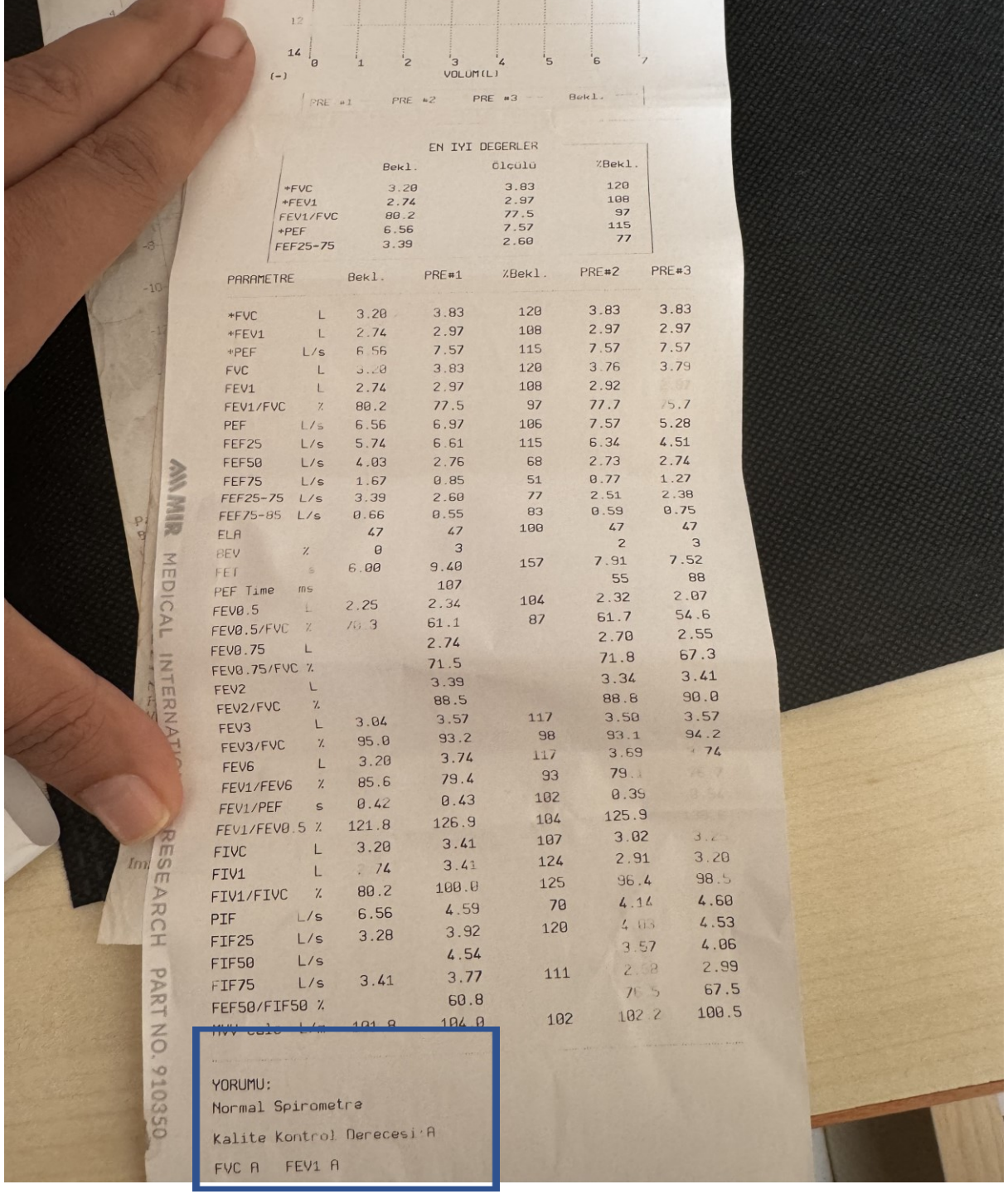
GINA 2024 Box 4-6

SFT FVC ve FEV1 A KALİTESİ 2019 ATS-ERS FVC KABUL EDİLEBİLİR

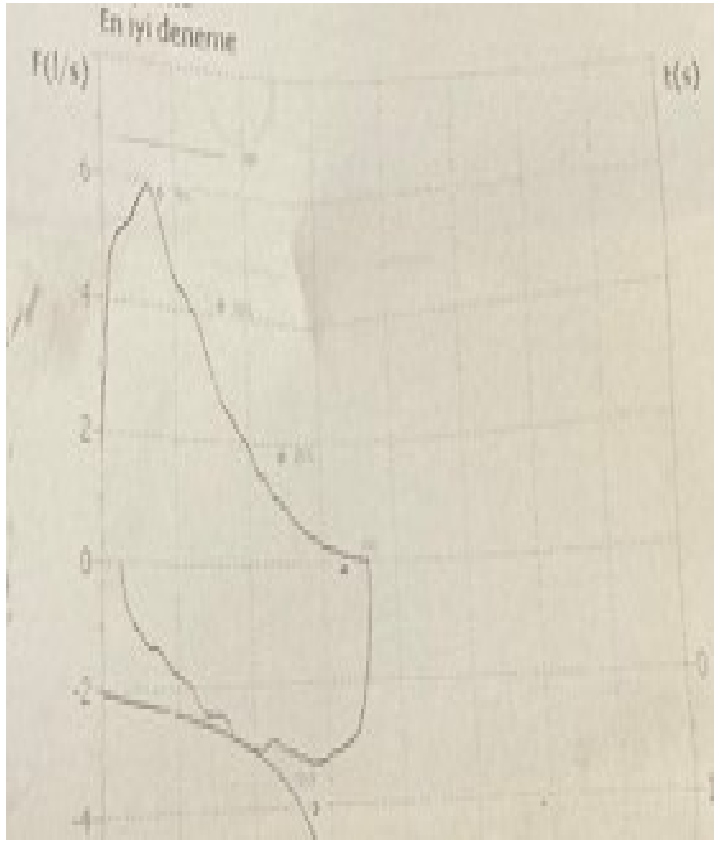
- FEV1:2.97 (%108)
- FVC:3.83 (%120)
- FEV1/FVC: %77.5
- FEF25-75: %71.8
- FET: 9.4 sn

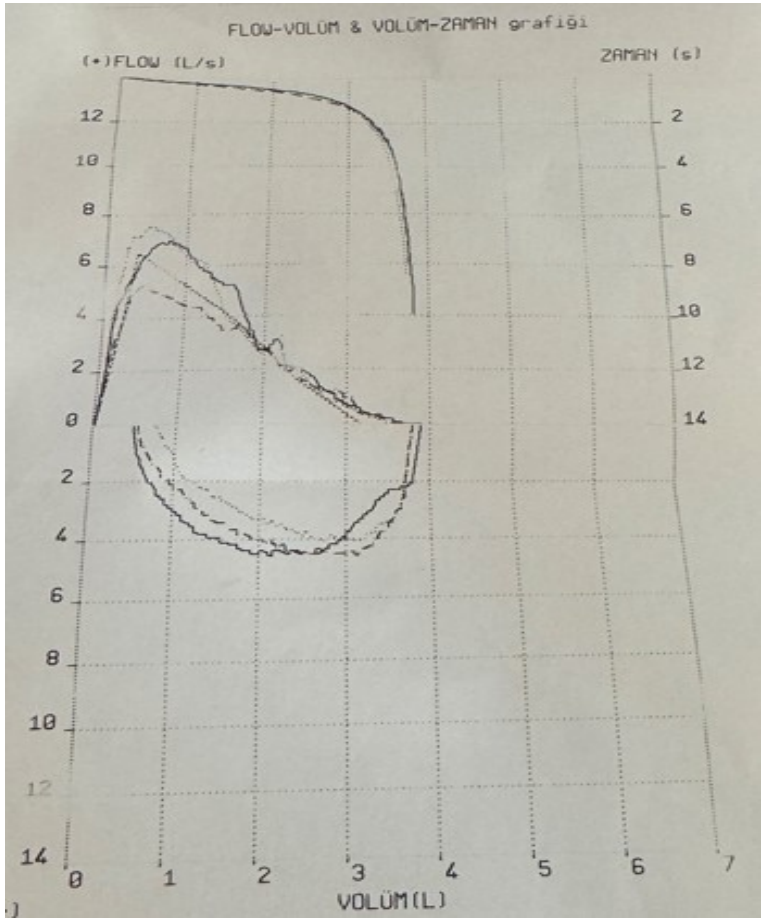
İyileşme

- FEV1:+360 ML
- FEF25-75:+%27.5



Pre-treatment and post-treatment Current Volume Curve





AFTER THE LLAMA IS STARTED

- No attacks
- Symptoms are under control
- ACT:22

ALWAYS AT 3-MONTH INTERVALS TO OPTIMIZE THE RISK OF ATTACK IN CONTROL

AFTER 3 MONTHS

- THE LAMA IS stopped

AFTER 3 MONTHS

- DOWN TO STEP 3

AFTER 3 MONTHS

- LOW-DOSE COMBINATION REDUCED TO SINGLE DOSE

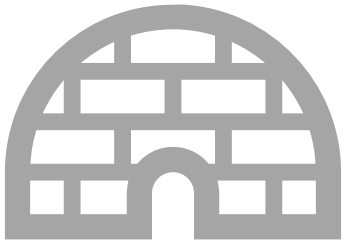
Hasta 2. basamak tedavi alıyorsa..

Düşük doz IKS idame → Günde bir kez (A) → Gereğinde düşük doz IKS/formoterol (A) → Gereğinde SABA ile düşük doz IKS (B)

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024. Available from: www.ginasthma.org

SHOULD WE STOP TREATMENT?

TREATMENT IS NOT INTERRUPTED



AIR TREATMENT CONTINUATION (LH IKS-FORMETEROL)

Remission of asthma

- Children vs adults
- Clinical vs complete remission
- “Off treatment” vs “on treatment”
- Multiple definitions, operationalized in many ways
  - Often assessed over only 12 months
  - “No exacerbations” and “no maintenance OCS” assessed from electronic medical record or patient interview
  - “No symptoms over 12 months” often assessed from Asthma Control Questionnaire (i.e. the last 7 days!)
- No validated tools for assessment of symptoms over periods longer than 4 weeks

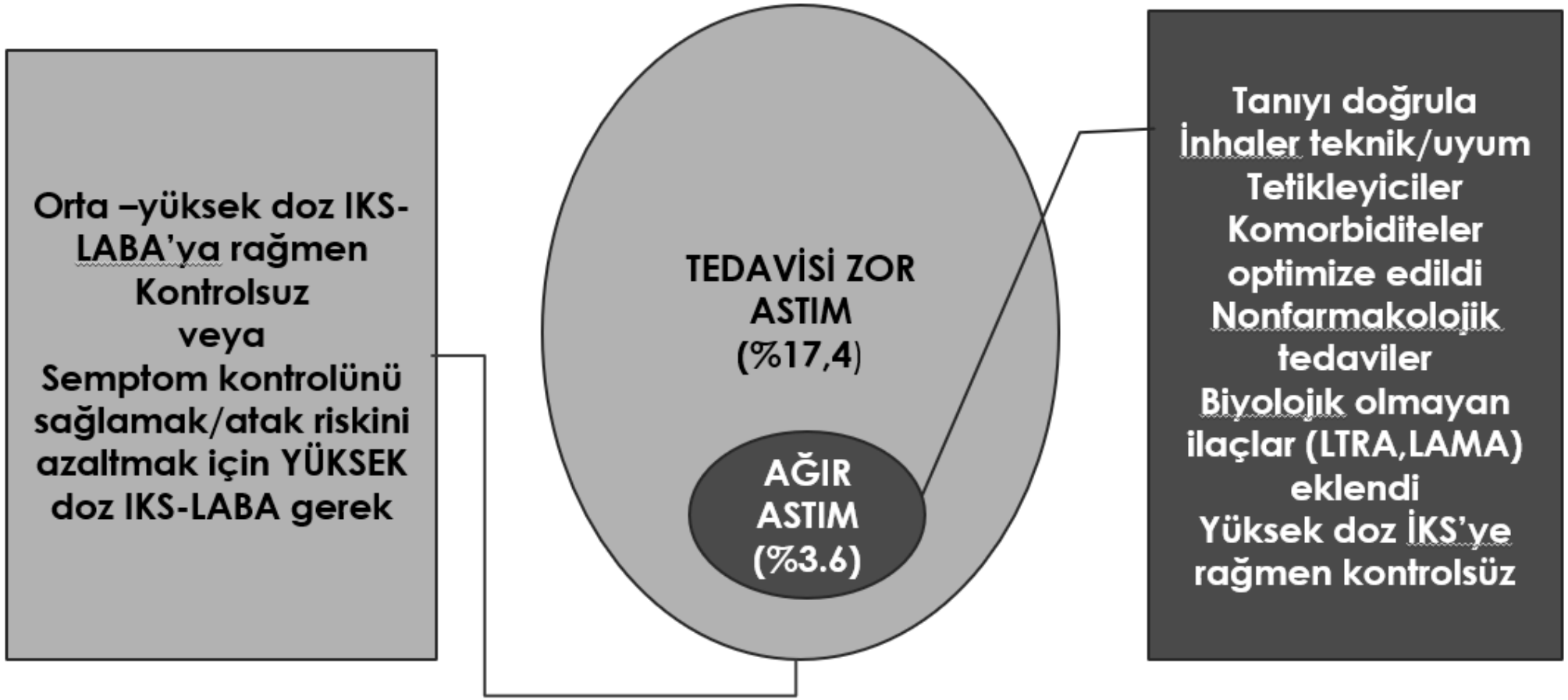
Remission of asthma

- Remission from childhood wheezing or asthma, off treatment
  - Parents/caregivers often ask if their child will 'grow out of their asthma'
  - Rates vary depending on population and age, e.g. 59% at age 6, 15% at age 26
  - Asthma often recurs: remission is not cure, and patients may develop persistent airflow limitation
  - Say to parent/caregiver 'Their asthma has gone quiet for a while'
- Remission in adults, on treatment
  - Current reports are mostly for patients with severe asthma treated with biologic therapy
  - Remission also seen in non-severe asthma with ICS-containing treatment, and sometimes spontaneously
  - Research needed to identify pathways in patients who have ongoing respiratory symptoms, e.g. multimorbidity, anxiety and/or depression, moderate or severe persistent airflow limitation
- Evidence about goal-setting tells us that treatment goals for patients should be personalized and achievable
- Avoid encouraging automatic step-up of therapy
  - Treat comorbidities and modifiable risk factors first (including poor inhaler technique and poor adherence); use non-pharmacologic strategies; if high-dose ICS or ICS-LABA is used, limit to 3–6 months whenever possible
  - Use GINA Track 1 regimen to reduce exacerbations using *lower* ICS doses

5.BASAMAK AĞIR ASTIM

KİME DİYELİM?

DIFFICULT ASTHMA - SEVERE ASTHMA DIFFERENTIATION



DEFINITION OF UNCONTROLLED ASTHMA

(4-5. basamak) Medium-high dose IKS-LABA

(Steps 4-5)

- **Tedaviye rağmen**

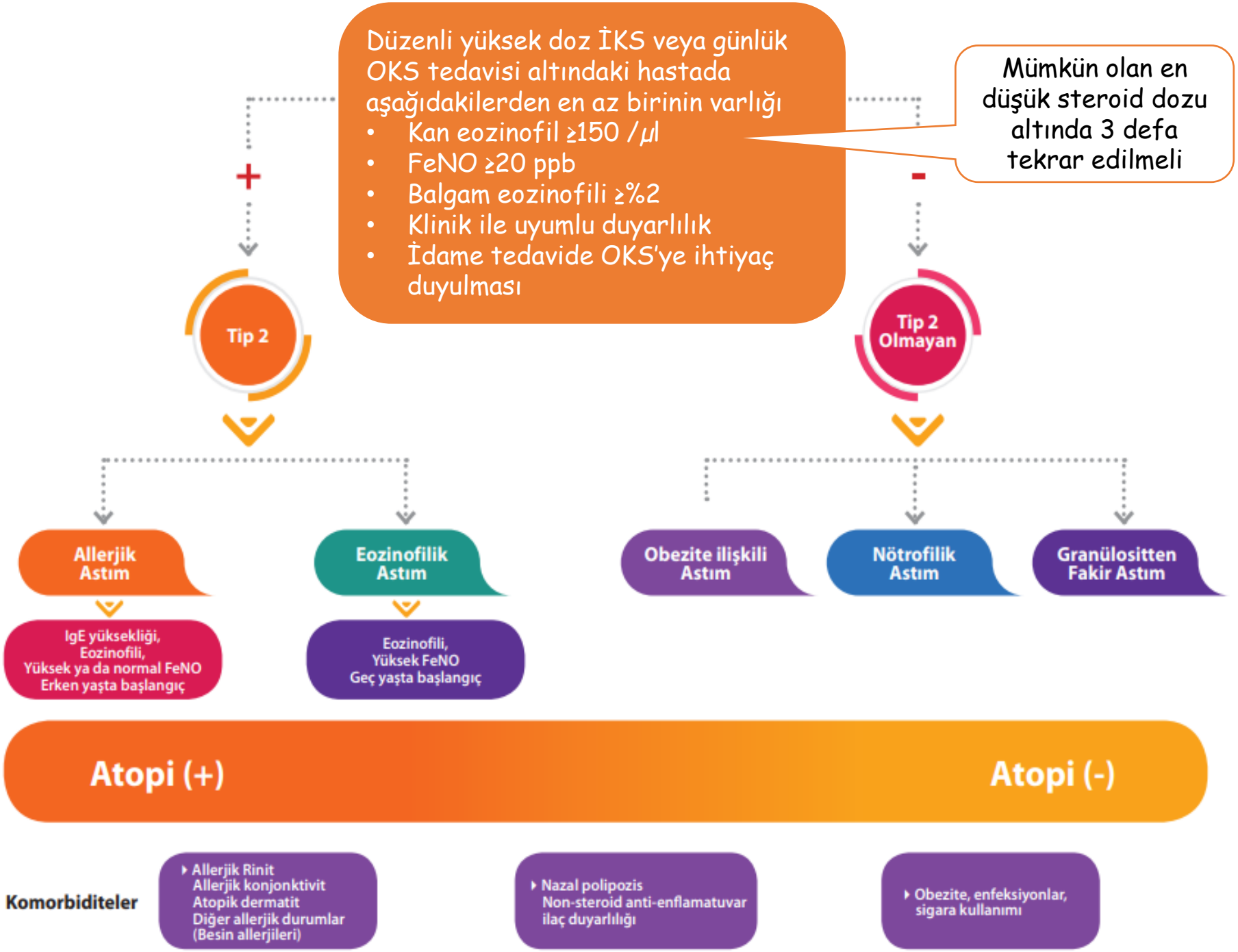
At least 1 of them

- **ACQ>1,5 veya AKT<20 veya GINA/NAEPP Out of control**
- **2≥ attack (3 days< systemic steroid use)**
- **1 ≥ serious attack: Hospitalization, ICU, mechanical ventilation**

FEV_1<%80 , FEV_1/FVC <LLN: Şart değil (ATS/ERS 2014 tanımında var)

Ağır Astımlı hastada yaklaşım

Fenotipik yaklaşım
- Astım başlangıç yaşı
- Klinik bulgular
- Hava yolu inflamasyonu dolaylı belirteçleri
- Tedaviye yanıt

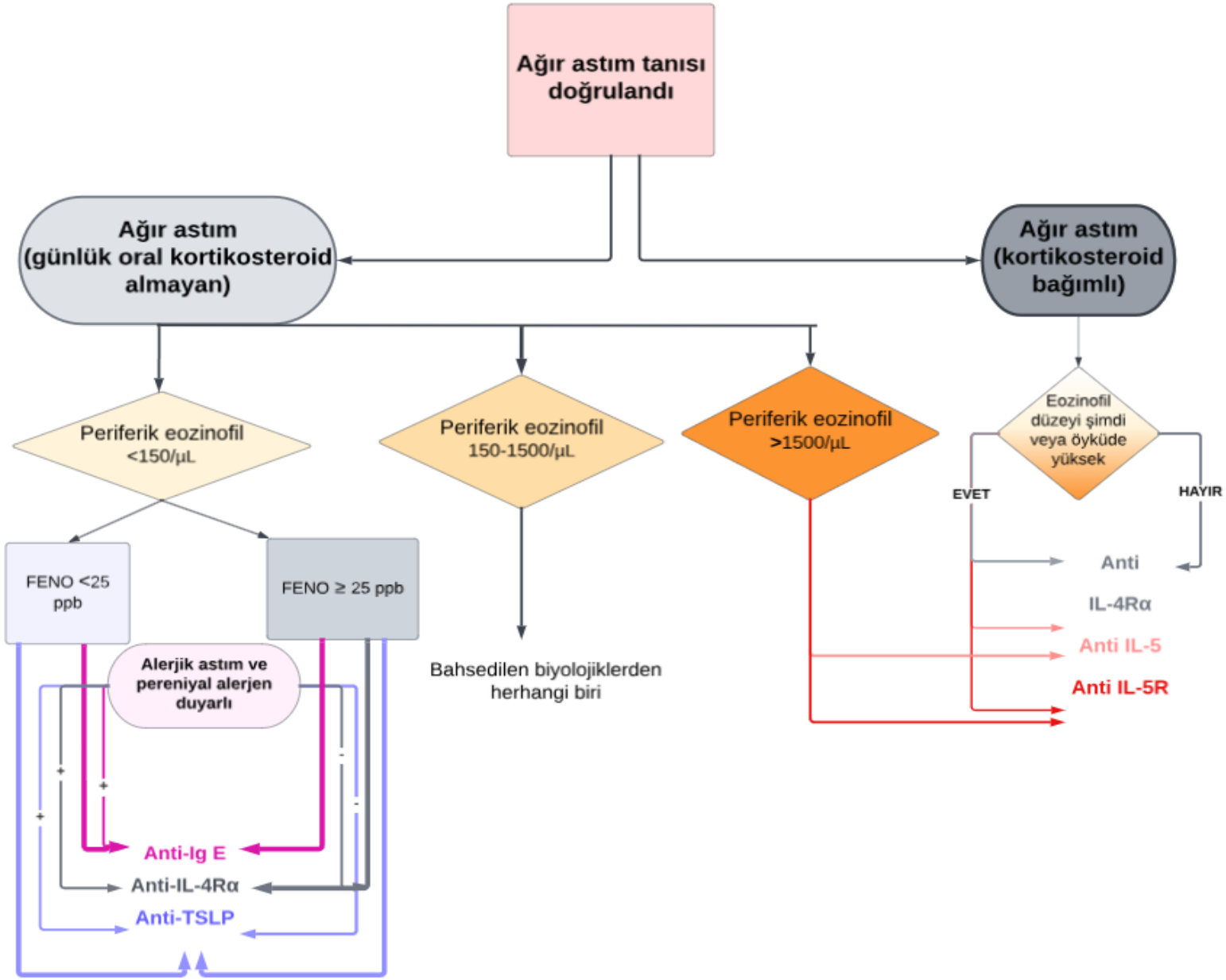


Erişkin ve çocuklarda ağır astım tanı ve tedavi rehberi el kitapçığı
www.aid.org.tr

FDA ONAYLI BİYOLOJİKLER

Biyolojik Ajan	Hedef Bölgesi	Doz/Uygulama Şekli	Endikasyon	Beklenen Yararlar	Riskler
Omalizumab (Novartis, Switzerland)	IgE	2-4 hafta ara ile her IgE IU/mL başına 0,016 mg/kg s.c.	≥6 yaş, pereniyal alerjen duyarlılığı olan yüksek doz İKS-LABA tedavisine rağmen sık gece gündüz semptomu olan, birden fazla ağır atak öyküsü olan, FEV_1<%80 Total IgE 30-1500 IU/mL, 20-150 kg ağırlığında olan hastalar	Astım ataklarında azalma (%44) ve semptomlarda ve yaşam kalitesinde önemli iyileşme, FEV_1'de yükseme ve steroid gereksiniminde hafif azalma	Anaflaksi
Mepolizumab (GlaxoSmithKline, Brentford, UK)	IL-5	4 haftada bir 100 mg s.c.	≥6 yaş, en az 6 aydır kortikosteroid bağımlı kontrollü veya kontrolsüz astım veya yüksek doz İKS-LABA ve 3. kontrol ediciye rağmen en az 3 gün sistemik steroid kullanmayı gerektiricek 2 ve üzeri atak öyküsü olan kontrolsüz ağır eozinofilik astım (Periferik eozinofil ≥150 hücre/µL, başvuru anında veya steroid altında; ≥300 hücre/µL, son 1 yılda)	Astım ataklarında azalma (%47-53) ve semptomlarda önemli iyileşme, FEV_1'de iyileşme ve steroid bağımlı astımda steroid kesilebilir	Herpes Zoster
Reslizumab (Teva Pharmaceuticals, Petah Tikva, Israel)	IL-5	4 haftada bir 3mg/kg i.v.	≥18 yaş, yüksek doz İKS-LABA tedavisine rağmen en az 1 kere sistemik steroid gerektiren atak öyküsü olan ağır eozinofilik astım (Periferik eozinofil ≥400 hücre/µL)	Astım ataklarında azalma (%55-61), FEV_1 ve semptomlarda hafif iyileşme, steroid bağımlı astımda düşünülebilir	Anaflaksi Geçici kreatinin fosfokinaz (CK) artışı
Benralizumab (MedImmune, Gaithersburg, USA; ve AstraZeneca, Cambridge, UK)	IL-5R α	İlk 3 doz 4 haftada bir 30 mg; daha sonra 8 hftada bir 30 mg s.c.	≥12 yaş, yüksek doz İKS-LABA tedavisine rağmen kontrolsüz ağır eozinofilik astım (Periferik eozinofil ≥300 hücre/µL)	Astım ataklarında azalma (%40-70), FEV_1'de iyileşme ve steroid bağımlı astımda steroid kesilebilir	Eozinofil sayısında uzun süreli azalma
Dupilumab (Regeneron, Tarrytown, USA ve Sanofi, Paris, France)	IL-4R α	2 haftada bir 200 mg veya 300 mg s.c. (İlk doz 400 mg veya 600 mg olarak verilir)	≥12 yaş, yüksek doz İKS-LABA tedavisine rağmen kontrolsüz ağır eozinofilik astım (Periferik eozinofil ≥ 150-1500 hücre/µL veya FeNO ≥25 ppb)	Astım ataklarında azalma (%56), FEV_1'de ve semptomlarda önemli iyileşme, steroid kullanımında hafif azalma	Eozinofili, Konjuktivit
Tezepelumab (AMG-157/ MEDI9929) (Amgen ve Medimmune)	TSLP	4 haftada bir 210 mg s.c.	≥12 yaş, son 1 yıl ağır atakları olan non tip 2 astımda da düşünülebilir	Astım ataklarında azalma (%30-70), FEV_1'de ve semptomlarda önemli iyileşme var ancak steroid kullanımında azalma yapmamış.	Bilgi yok

BIOLOGICAL SELECTION IN SEVERE ASTHMA



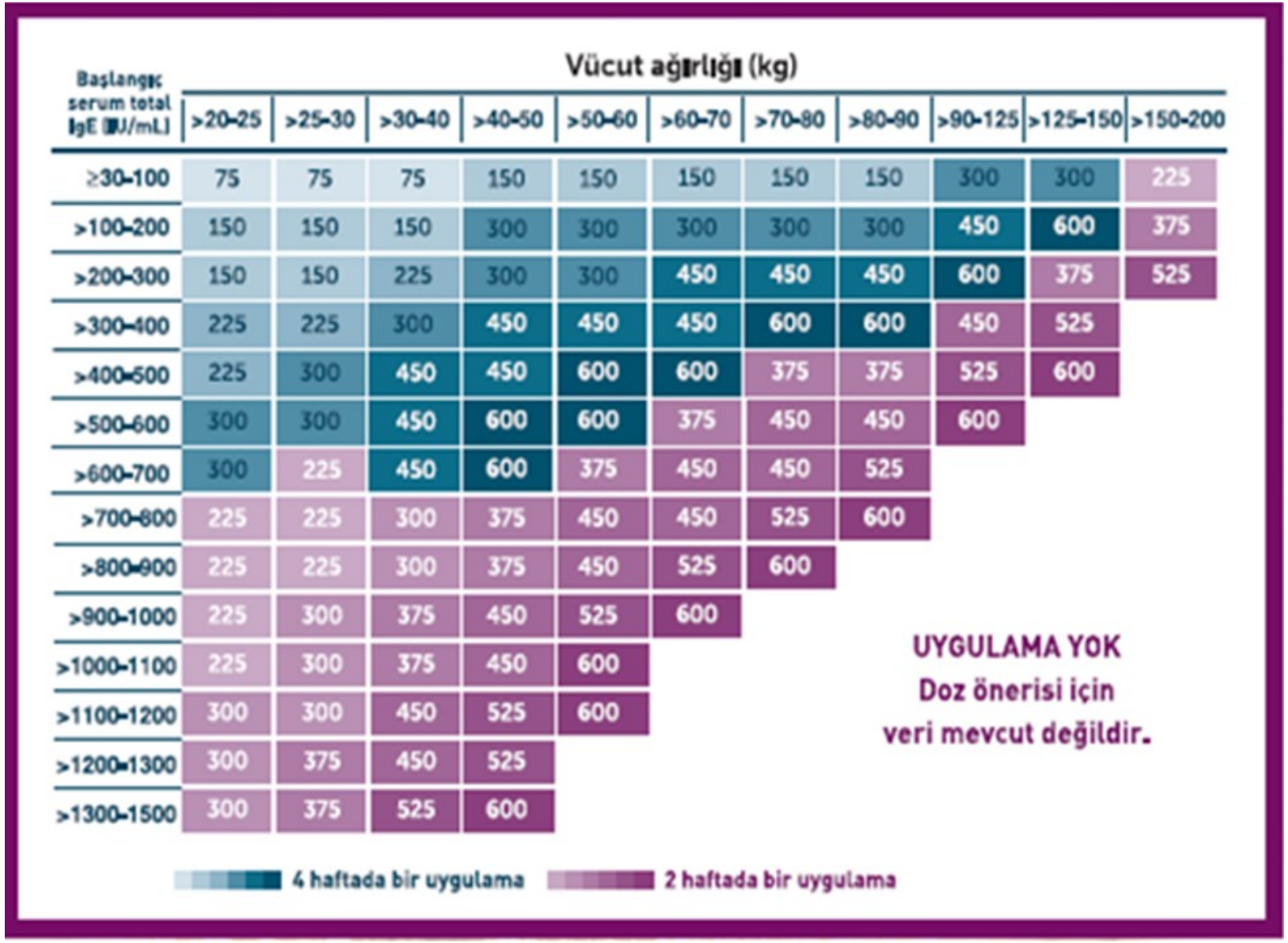
Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022 Jan 13;386(2):157-171.

IF CASE WAS SEVERE WHAT IS THE PHENOTYPE

- Childhood onset
- Atopic
- Noneoshinophilic (0-100/ul)
- Total IgE:70 IU/mL

WHİCH BIOLOGIC DO YOU PREFER?

OMALİZUMAB



Başlangıç serum total IgE (IU/mL)	Vücut ağırlığı (kg)										
	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150	>150–200
≥30–100	75	75	75	150	150	150	150	150	300	300	225
>100–200	150	150	150	300	300	300	300	300	450	600	375
>200–300	150	150	225	300	300	450	450	450	600	375	525
>300–400	225	225	300	450	450	450	600	600	450	525	
>400–500	225	300	450	450	600	600	375	375	525	600	
>500–600	300	300	450	600	600	375	450	450	600		
>600–700	300	225	450	600	375	450	450	525			
>700–800	225	225	300	375	450	450	525	600			
>800–900	225	225	300	375	450	525	600				
>900–1000	225	300	375	450	525	600					
>1000–1100	225	300	375	450	600						
>1100–1200	300	300	450	525	600						
>1200–1300	300	375	450	525							
>1300–1500	300	375	525	600							

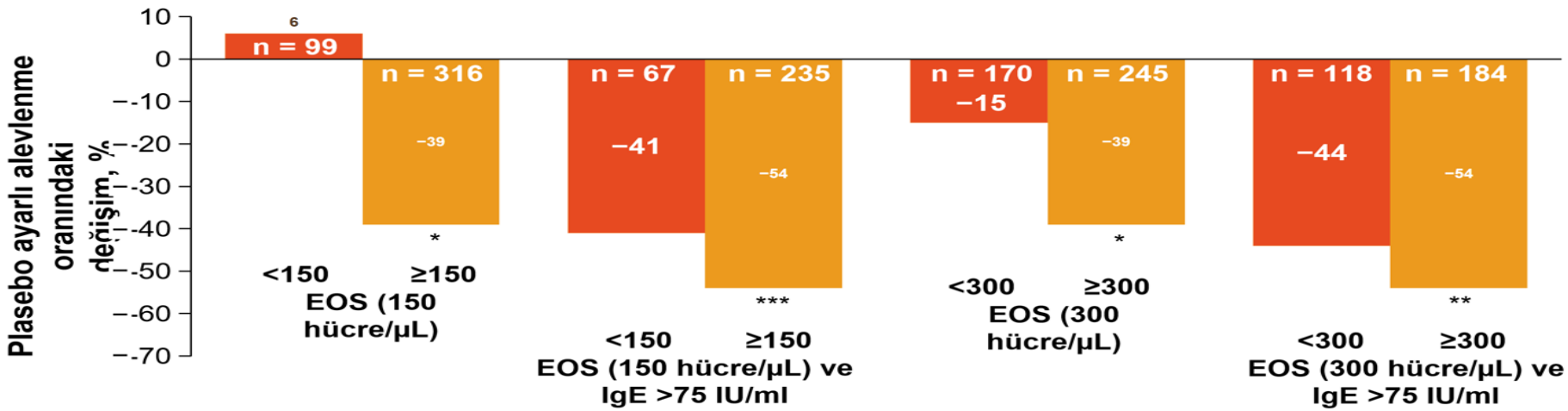
UYGULAMA YOK
Doz önerisi için
veri mevcut değildir.

4 haftada bir uygulama

2 haftada bir uygulama

INNOVATE çalışması

Hem IgE hem de EOS seviyeleri yüksek olan popülasyonlar omalizumab ile gelişmiş yanıt gösterebilir



INNOVATE çalışma verilerinin post - hoc analizi (N = 419)

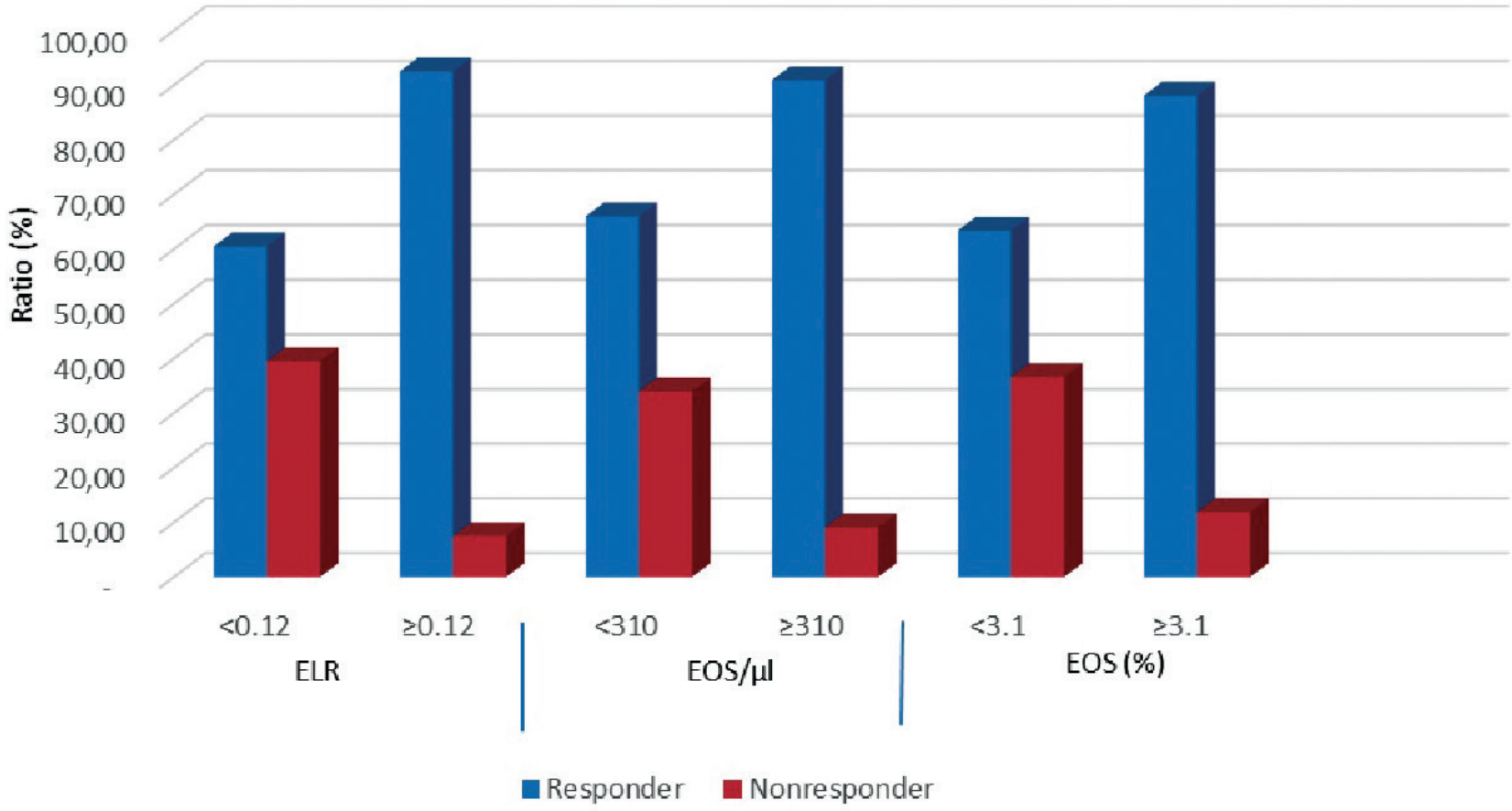
doi • 10.5578/tt.20219905
Tuberk Toraks 2021;69(1):39-48
Geliş Tarihi/Received: 22.02.2021 • Kabul Ediliş Tarihi/Accepted: 18.03.2021

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

The significance of eosinophil and eosinophil lymphocyte ratio (ELR) in predicting response to omalizumab treatment in patients with severe allergic asthma

Hasan ÖZGEN[1] (ID)
Fatma Merve TEPETAM[2] (ID)
İsmet BULUT[2] (ID)
Cihan ÖRÇEN[3] (ID)

[1] Clinic of Chest Diseases, Bartın S
[1] *Bartın Devlet Hastanesi, Göğüs H*
[2] Department of Immunology and Süreyyapaşa Chest Diseases and Hospital, Istanbul, Turkey
[2] *Sağlık Bilimleri Üniversitesi, Süre Cerrahisi Eğitim ve Araştırma Has İstanbul, Türkiye*
[3] Clinic of Chest Diseases, Univers and Research Hospital, Kocaeli, T
[3] *Sağlık Bilimleri Üniversitesi, Deri Göğüs Hastalıkları Kliniği, Kocael*



OMALİZUMAB-MEPOLİZUMAB

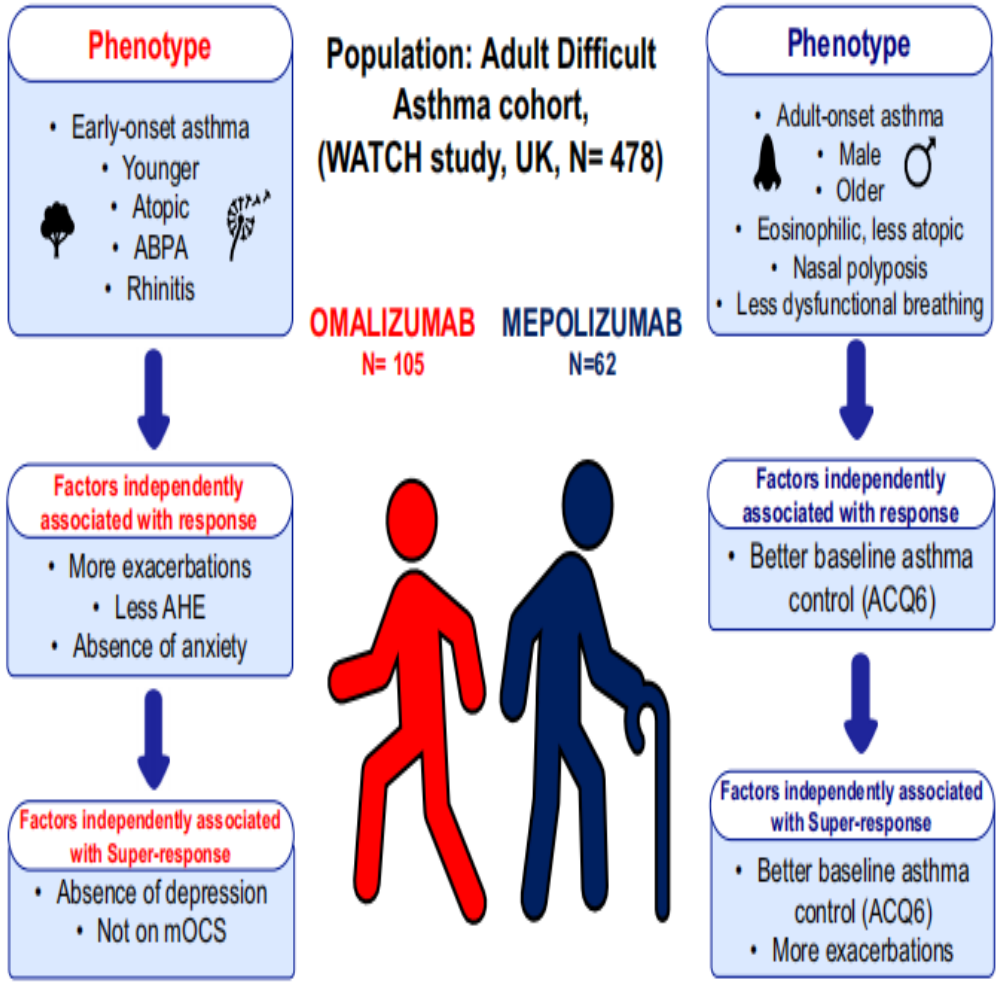


FIGURE 3 Summary of baseline phenotypic features of Omalizumab and Mepolizumab treated patients and factors independently associated with response and super-response to these drugs. ABPA: allergic bronchopulmonary aspergillosis. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. ACQ6: Asthma Control Questionnaire 6. mOCS: maintenance oral corticosteroids. WATCH: Wessex AsThma CoHort of difficult asthma

OMALIZUMAAB-MEPOLINIZIMAB IN PATIENTS WITH ATOPIC-EOSINOPHILIC OVERLAP

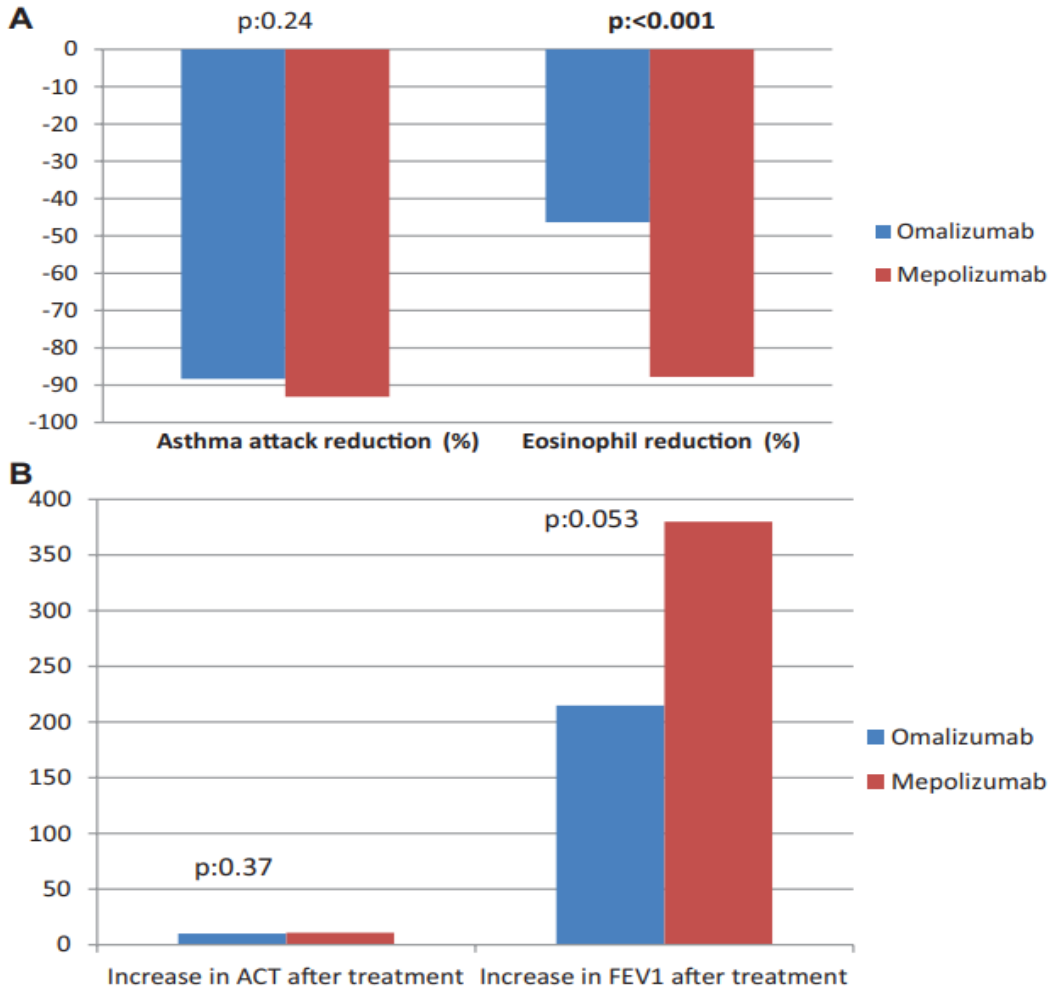
Observational Study

OPEN

Comparison of omalizumab and mepolizumab treatment efficacy in patients with atopic and eosinophilic "Overlap" severe asthma

Biological agent preference in atopic-eosinophilic severe asthma

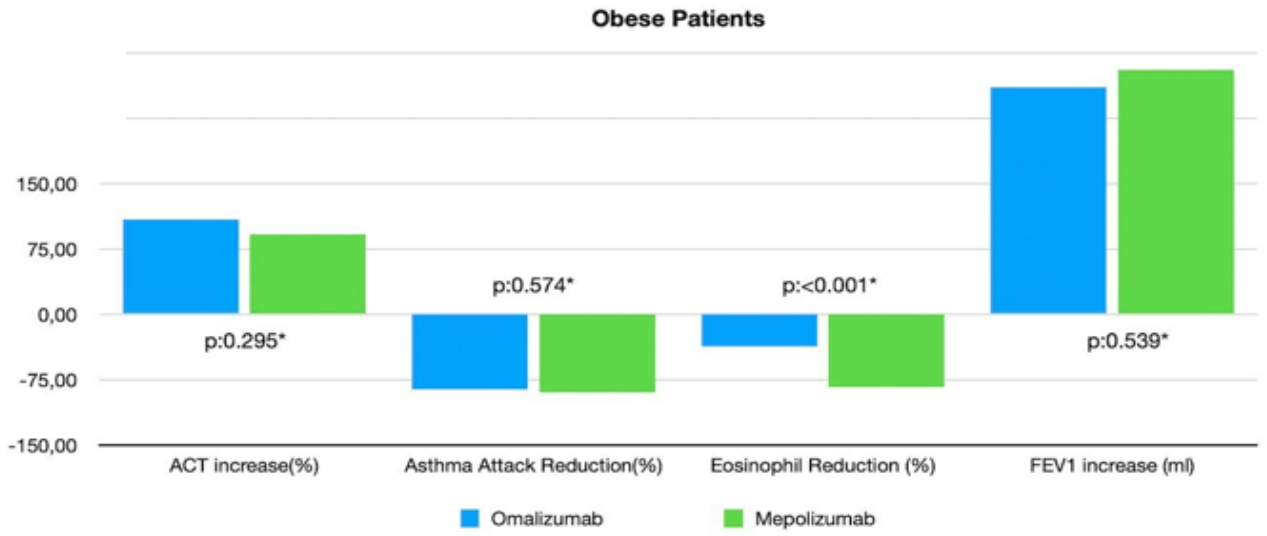
Fatma Merve Tepetam, MD[a,*], Ali Burkan Akyıldız, MD[a], Şeyma Özden, MD[a], Cihan Örcen, MD[b], Tuğçe Yakut, MD[c], Özge Atik, MD[a]

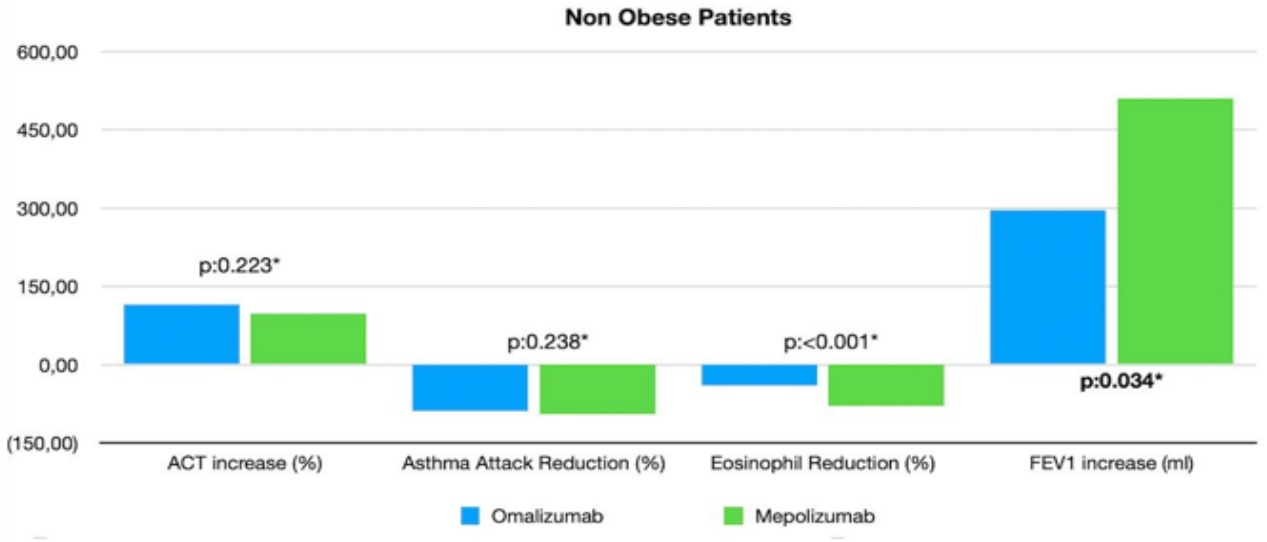


The phenotypic heterogeneity of obese and nonobese patients with severe asthma and comparison of omalizumab–mepolizumab treatment efficiency in these patients

Şeyma Özden, MD[a,*], Fatma Merve Tepetam, MD[a], Cihan Örçen, MD[b], Tuğçe Yakut, MD[c]

OUR EXPERIENCE
121 HASTA
OMALİZUMAB: 88
MEPOLİZUMAB: 33
OBEZ:44
NONOBEZ: 77





POTENTİAL PREDİCTORS

ANTI-IL5

ANTI-IL5 R

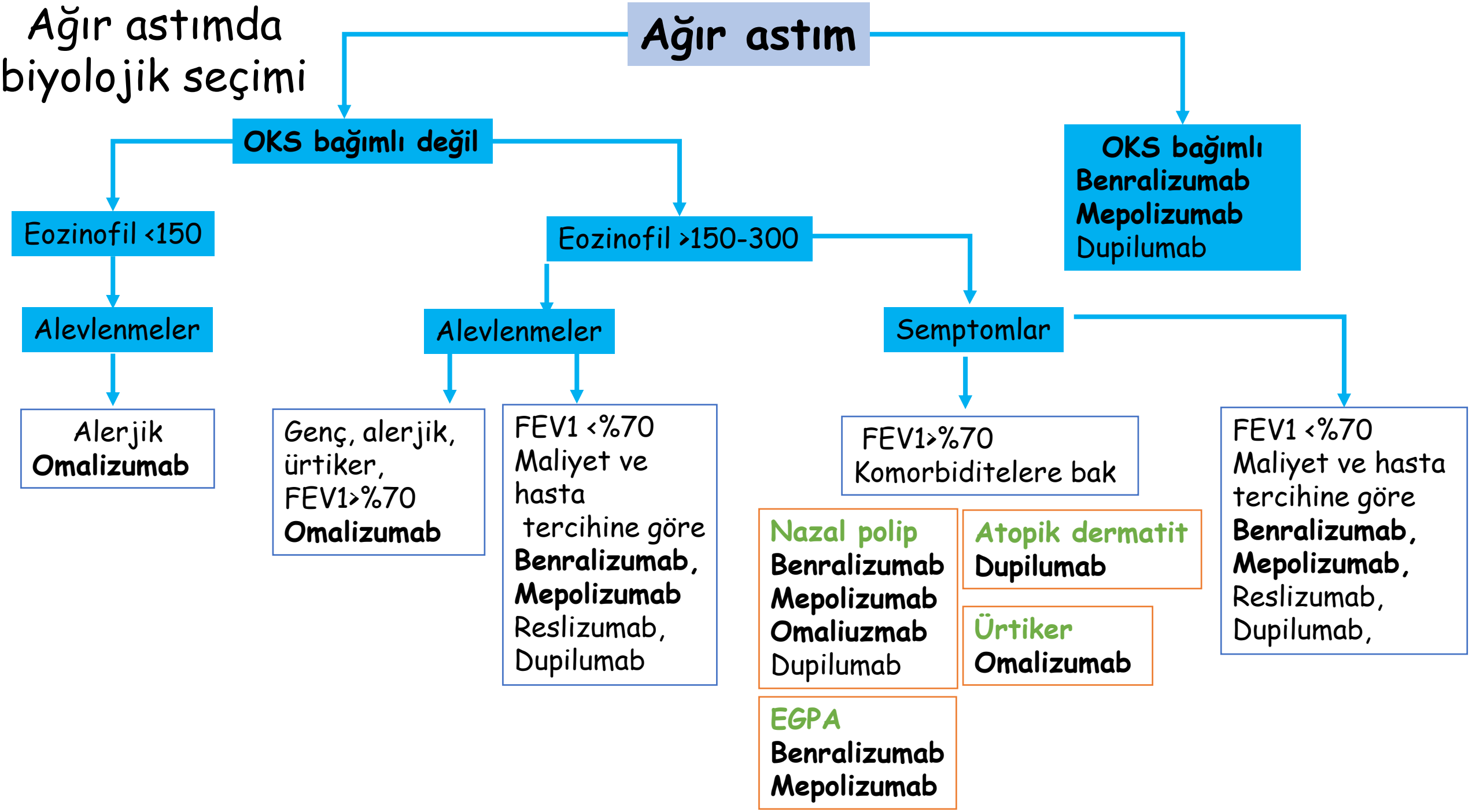
Potential predictors of good asthma response to anti-IL5 or anti-IL5Rα:

- Higher blood eosinophils (strongly predictive)[685]

- Higher number of severe exacerbations in previous year (strongly predictive)[685]
- Adult-onset asthma[686]
- Nasal polyps[682]
- Maintenance OCS at baseline[682]
- Low lung function (FEV_1 <65% predicted) in one study.[687]

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (2024)

Ağır astımda biyolojik seçimi



- *ASTIMDA EĞİTİM GÜÇ VERİR*
- *BİLGİ ANAHTARDIR*