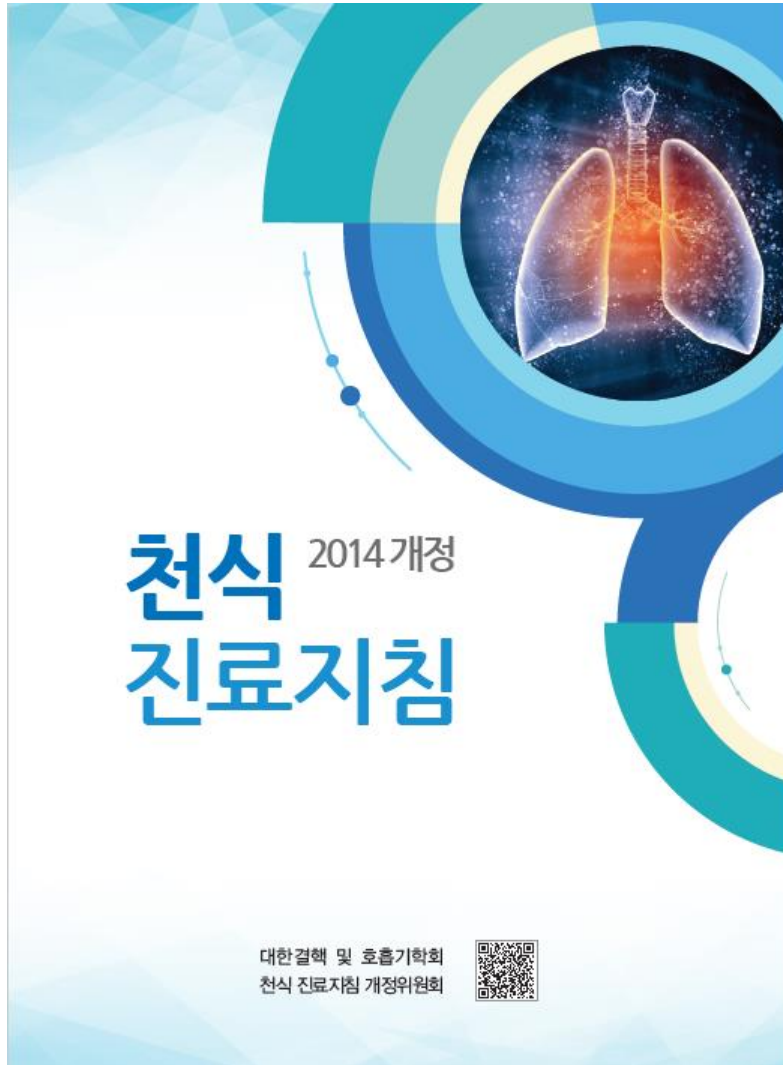


Asthma Guideline; 2018 update

동아대학교 호흡기 내과
엄수정

Asthma Guidelines



Global

NICE National Institute for
Health and Care Excellence

NICE
guideline

**Asthma: diagnosis, monitoring and
chronic asthma management**

NICE guideline

Published: 29 November 2017

[nice.org.uk/guidance/ng80](https://www.nice.org.uk/guidance/ng80)

DEFINITION

Definition of asthma

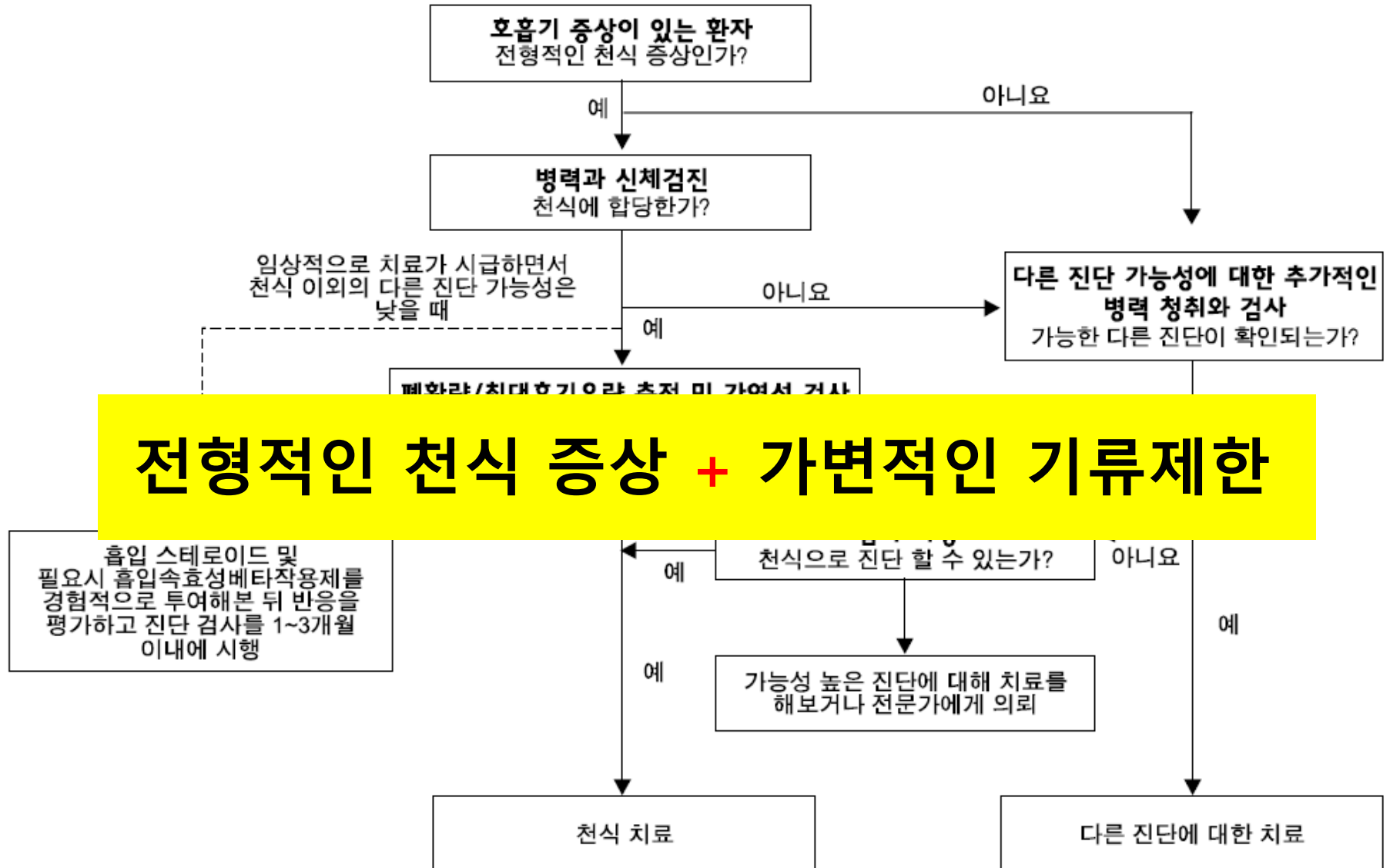


Asthma is a heterogeneous disease, usually characterized by **chronic airway inflammation**.

It is defined by the history of **respiratory symptoms** such as wheeze, shortness of breath, chest tightness and cough that **vary over time and in intensity**, together with **variable expiratory airflow limitation**.

DIAGNOSIS

Diagnosis of asthma (GINA and KOREA)



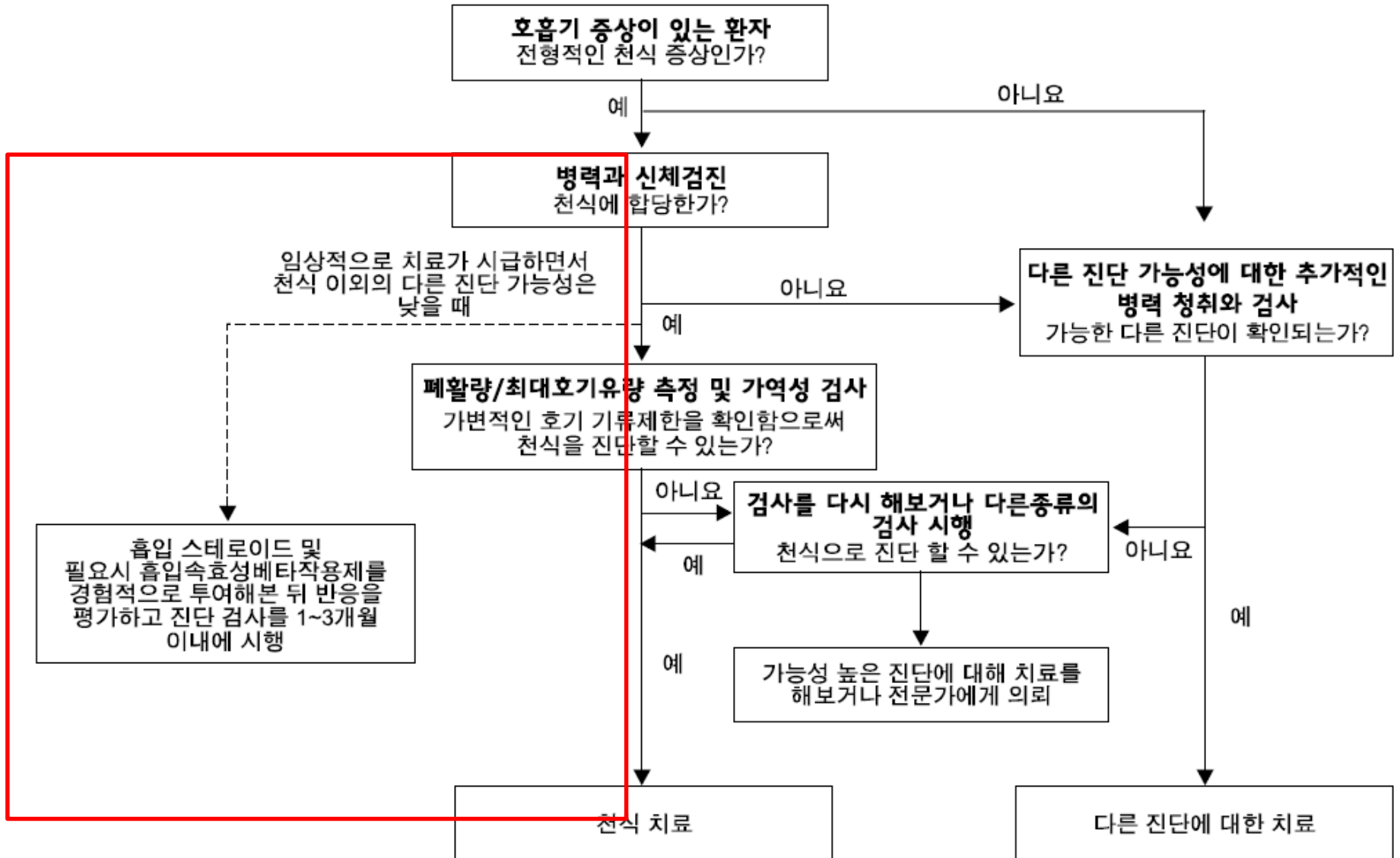
Diagnosis of asthma – variable airflow limitation



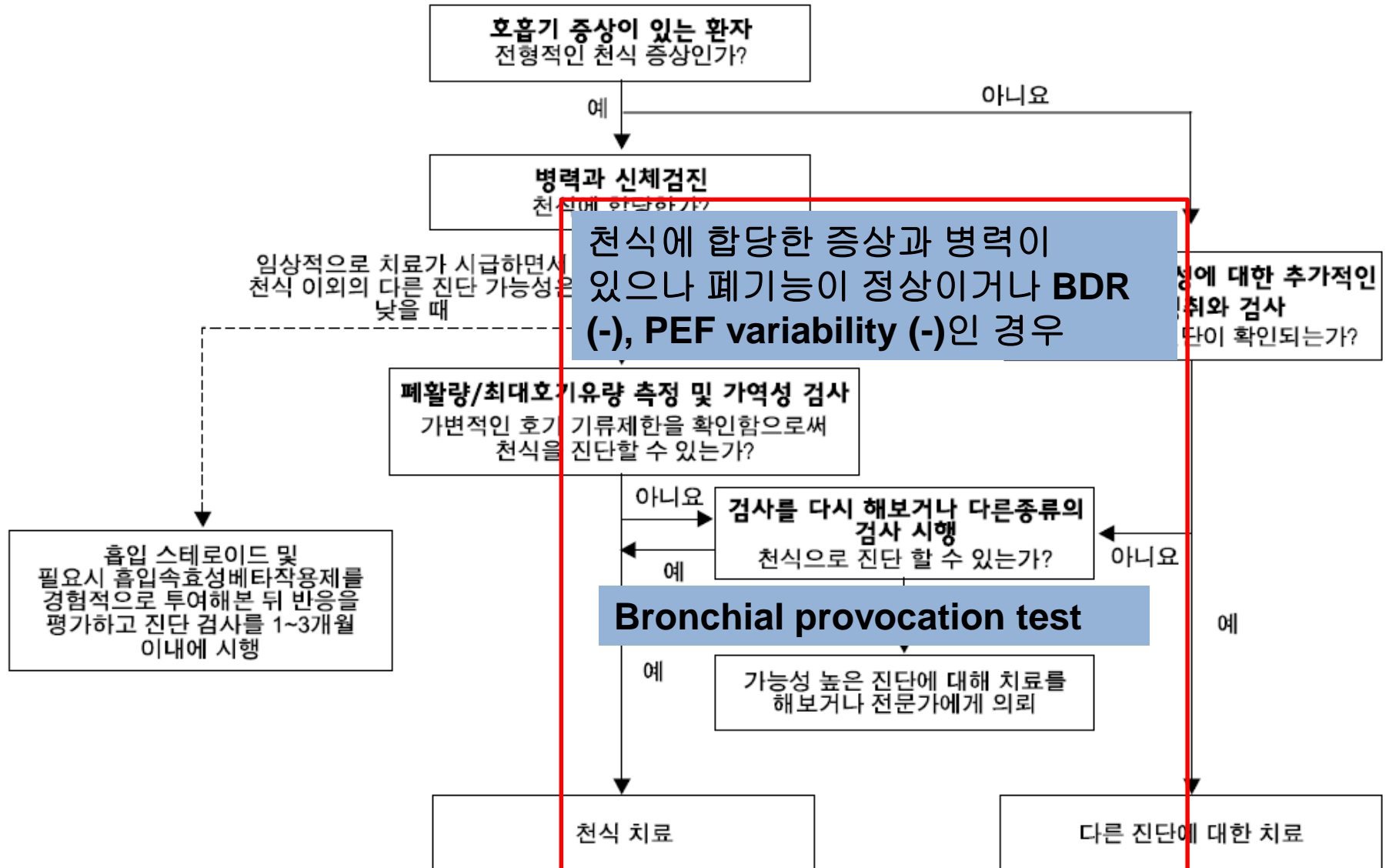
- Confirm presence of airflow limitation
 - $FEV_1/FVC < 0.75\sim 0.80$

- Confirm variation in lung function
 - Excessive bronchodilator reversibility (increase in $FEV_1 > 12\%$ and $> 200\text{mL}$)
 - Excessive diurnal variability from 1-2 weeks' twice-daily PEF monitoring
(daily amplitude x 100/daily mean, averaged)
 - Significant increase in FEV_{1_1} or PEF after 4 weeks of controller treatment

Diagnosis of asthma (GINA and KOREA)



Diagnosis of asthma (GINA and KOREA)



- Asthma is usually characterized by airway inflammation and airway hyperresponsiveness, but these are not necessary or sufficient to make the diagnosis of asthma.
 - Bronchial provocation test
 - Allergy test (Skin prick test, sIgE)
 - FeNO

Exhaled nitric oxide (FeNO)



- Modestly associated with levels of blood and sputum eosinophils
- Response to ICS
 - In adult steroid-naïve patients with non-specific respiratory symptoms ; **FeNO >50ppb** was associated with good short-term response to ICS
 - No long-term studies examining the safety of withholding ICS if FENO is low
 - FeNO cannot be recommended for deciding against treatment with ICS

FeNO High

- Asthma (Type 2 inflammation)
- eosinophilic bronchitis, atopy, allergic rhinitis, eczema
- Late response to allergen

FeNO Low

- Smokers
- Bronchoconstriction
- Early phases of allergic response
- neutrophilic asthma

Exhaled nitric oxide (FeNO)



- FeNO is becoming more widely available in some countries
- In patients with a diagnosis or suspected diagnosis of asthma, FeNO can support the decision to start ICS, but cannot safely be recommended for deciding against treatment with ICS
- FeNO-guided treatment is not recommended for the general asthma population at present

Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database Syst Rev 2016;9:Cd011440

Exhaled nitric oxide levels to guide treatment for adults with asthma (Review)

Decreased

- Rate of exacerbations
- % of Patients with ≥ 1 exacerbations

No effect

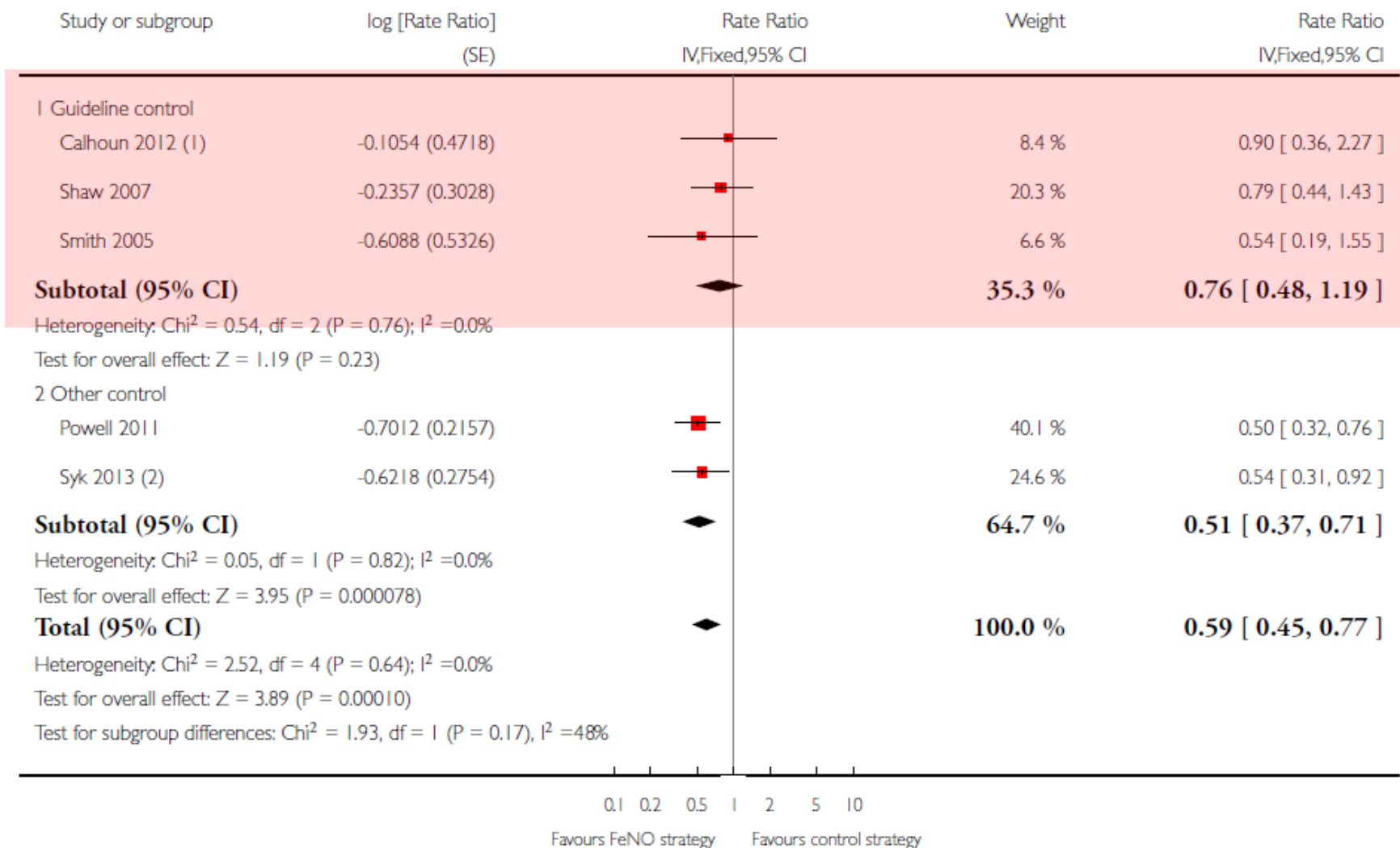
- OCS use
- Hospitalization
- Lung function
- End of Tx FeNO level
- ICS amount

Analysis 1.11. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 11 Subgroup (control guideline use): Number of exacerbations per 52 weeks (exacerbation rates).

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 11 Subgroup (control guideline use): Number of exacerbations per 52 weeks (exacerbation rates)



Accuracy of FE_{NO} for diagnosing asthma: a systematic review

Stefan Karrasch,^{1,2,3} Klaus Linde,¹ Gerta Rücker,^{4,5} Harriet Sommer,^{4,5}
Marlies Karsch-Völk,¹ Jos Kleijnen,^{6,7} Rudolf A Jörres,³ Antonius Schneider¹

Karrasch S, et al. Thorax 2017;72:109–116

- Sensitivity ; 0.65 (95% CI 0.58 to 0.72)
- Specificity ; 0.82 (95% CI 0.76 to 0.86)
- Diagnostic OR 9.23 (6.55 to 13.01), AUC 0.80 (0.77 to 0.85)

The overall specificity was higher than sensitivity, which indicates a higher diagnostic potential for ruling in than for ruling out the diagnosis of asthma; thus, FENO measurement might render bronchial provocation partially superfluous

Diagnose asthma

Asthmatic symptom plus

FeNO \geq 40 ppb + BDR (+)
or PEF variability
or Bronchial Hyperreactivity

FeNO 25~39 ppb + Bronchial Hyperreactivity

BDR (+) + PEF variability irrespective of FeNO

Suspect asthma

Asthmatic symptom, obstructive spirometry plus

BDR (-) + FeNO \geq 40 ppb
or FeNO 25~39 ppb + PEF variability

BDR (+) + FeNO 25~39 ppb + PEF variability (-)

Positive test thresholds

Obstructive spirometry	FEV1/FVC < 70% (or LLN)
FeNO	≥ 40ppb
BDR	Improvement of FEV ; ≥12% and ≥ 200mL
PEF variability	≥ 20%
Bronchial challenge test	PC20 < 8mg/mL

ASSESSMENT

1. Asthma control - two domains
 - Symptom control over the last 4 weeks
 - Risk factors for poor outcomes (including low lung function)

2. Treatment issues
 - Check inhaler technique and adherence
 - Side-effects
 - Written asthma action plan?
 - Patient's attitudes and goals for their asthma

3. Comorbidities
 - Rhinosinusitis, GERD, obesity, obstructive sleep apnea, depression, anxiety

GINA assessment of symptom control



A. Symptom control

Level of asthma symptom control

In the past 4 weeks, has the patient had:

- Daytime asthma symptoms more than twice a week? Yes No
- Any night waking due to asthma? Yes No
- Reliever needed for symptoms* more than twice a week? Yes No
- Any activity limitation due to asthma? Yes No

Well-controlled	Partly controlled	Uncontrolled
None of these	1-2 of these	3-4 of these

*Excludes reliever taken before exercise, because many people take this routinely

GINA assessment of asthma control



A. Symptom control

Level of asthma symptom control

In the past 4 weeks, has the patient had:

- Daytime asthma symptoms more than twice a week? Yes No
- Any night waking due to asthma? Yes No
- Reliever needed for symptoms* more than twice a week? Yes No
- Any activity limitation due to asthma? Yes No

Well-controlled

Partly controlled

Uncontrolled

None of these

1-2 of these

3-4 of these

B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV₁ at start of treatment, after 3 to 6 months of treatment to record the patient's personal best, then periodically for ongoing risk assessment

Risk factors for exacerbations include:

- Uncontrolled asthma symptoms

Additional risk factors, even if the patient has few symptoms:

- High SABA use (≥ 3 canisters/year)
- Having ≥ 1 exacerbation in last 12 months
- Low FEV₁; higher bronchodilator reversibility
- Incorrect inhaler technique and/or poor adherence
- Smoking
- Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia
- Elevated FeNO in adults with allergic asthma taking ICS
- Ever intubated for asthma



Risk factors for fixed airflow limitation include:

- No ICS treatment, smoking, occupational exposure, mucus hypersecretion, blood eosinophilia; pre-term birth, low birth weight

Risk factors for medication side-effects include:

- Frequent oral steroids, high dose/potent ICS, P450 inhibitors



Assessing Future Need for Acute Care in Adult Asthmatics*

Table 2—Summary of Multivariate Poisson Regression Models*

Factors†	PAR Model A: Questionnaire Data Only		PAR Model B: Questionnaire and Spirometry Data		PAR Model C: Questionnaire, Spirometry, and Skin-Prick Test Data	
	RR	95% CI	RR	95% CI	RR	95% CI
Age	0.98	0.97–1.00	0.97	0.95–0.98	0.97	0.95–0.98
Education‡	0.57	0.43–0.77	0.63	0.47–0.84	0.57	0.43–0.76
Double-pane windows in bedroom	0.71	0.52–0.97				
Caffeine consumption	1.16	1.01–1.33	1.15	1.01–1.33	1.19	1.04–1.37
Sensitive to indoor allergens§	2.07	1.17–4.08	1.97	1.11–3.88	1.92	1.08–3.77
Owens a cat or dog	1.66	1.16–2.43	1.71	1.19–2.50		
Owens and is skin-prick test positive for cat or dog					1.61	1.19–2.18
Nightly nighttime symptoms	1.99	1.40–2.80				
Perennial (as opposed to seasonal) asthma	1.78	1.15–2.87				
Impact of asthma on work/school attendance	1.45	1.16–1.80	1.53	1.23–1.90	1.57	1.27–1.94
Saw a physician for breathing problems in the past year	1.78	1.22–2.66	1.94	1.32–2.91	2.02	1.38–3.04
Ever seen in urgent care or the ER for breathing problems	3.36	1.81–6.98	3.16	1.70–6.54	3.63	2.00–7.41
Ever hospitalized for asthma	1.67	1.21–2.31	1.42	1.02–1.97		
%FEV ₁ 60 to 80%¶			2.43	1.59–3.65	2.47	1.63–3.72
%FEV ₁ < 60%¶			4.33	2.94–6.39	4.61	3.16–6.77

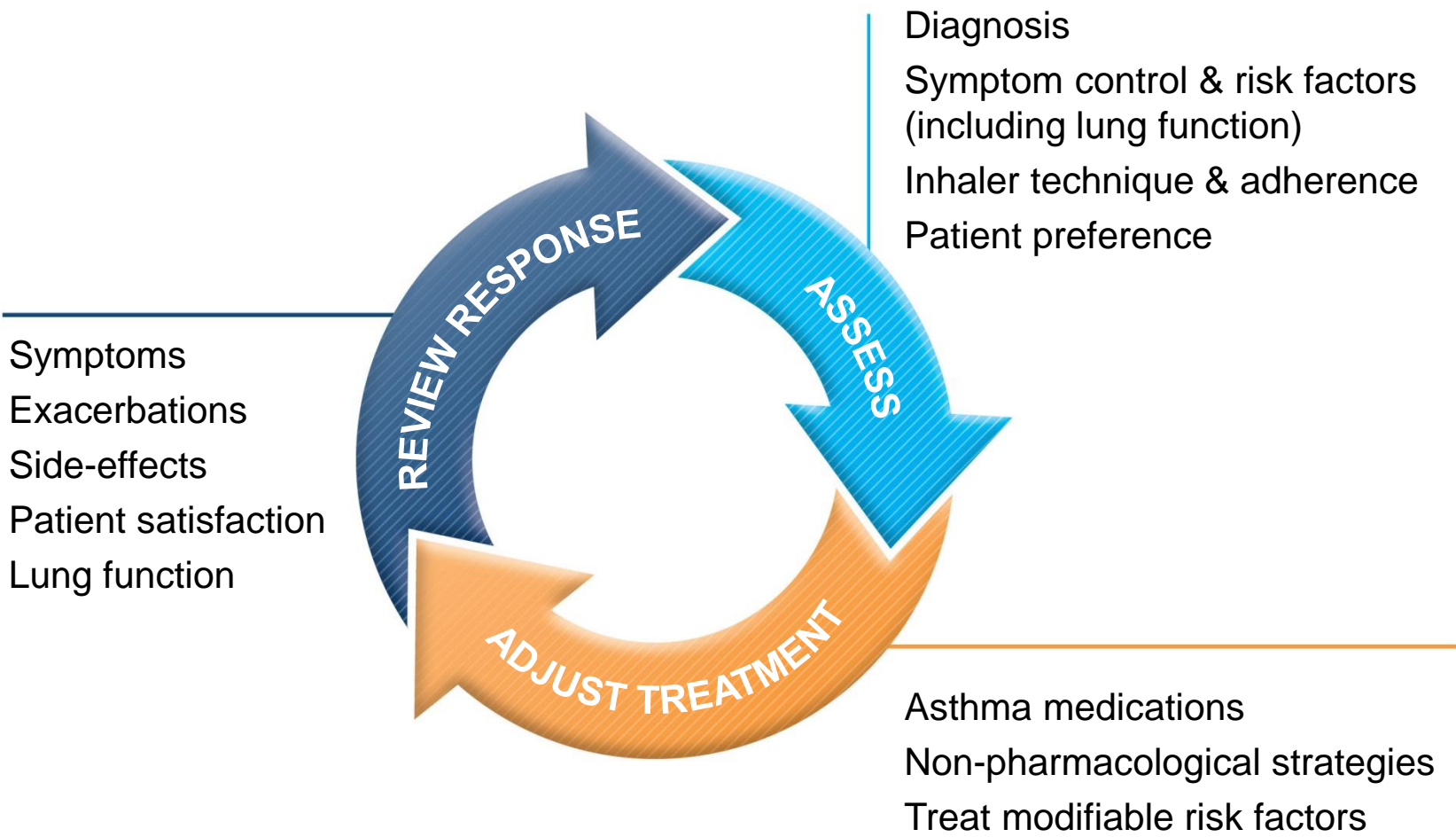
TREATMENT

Goals of asthma management

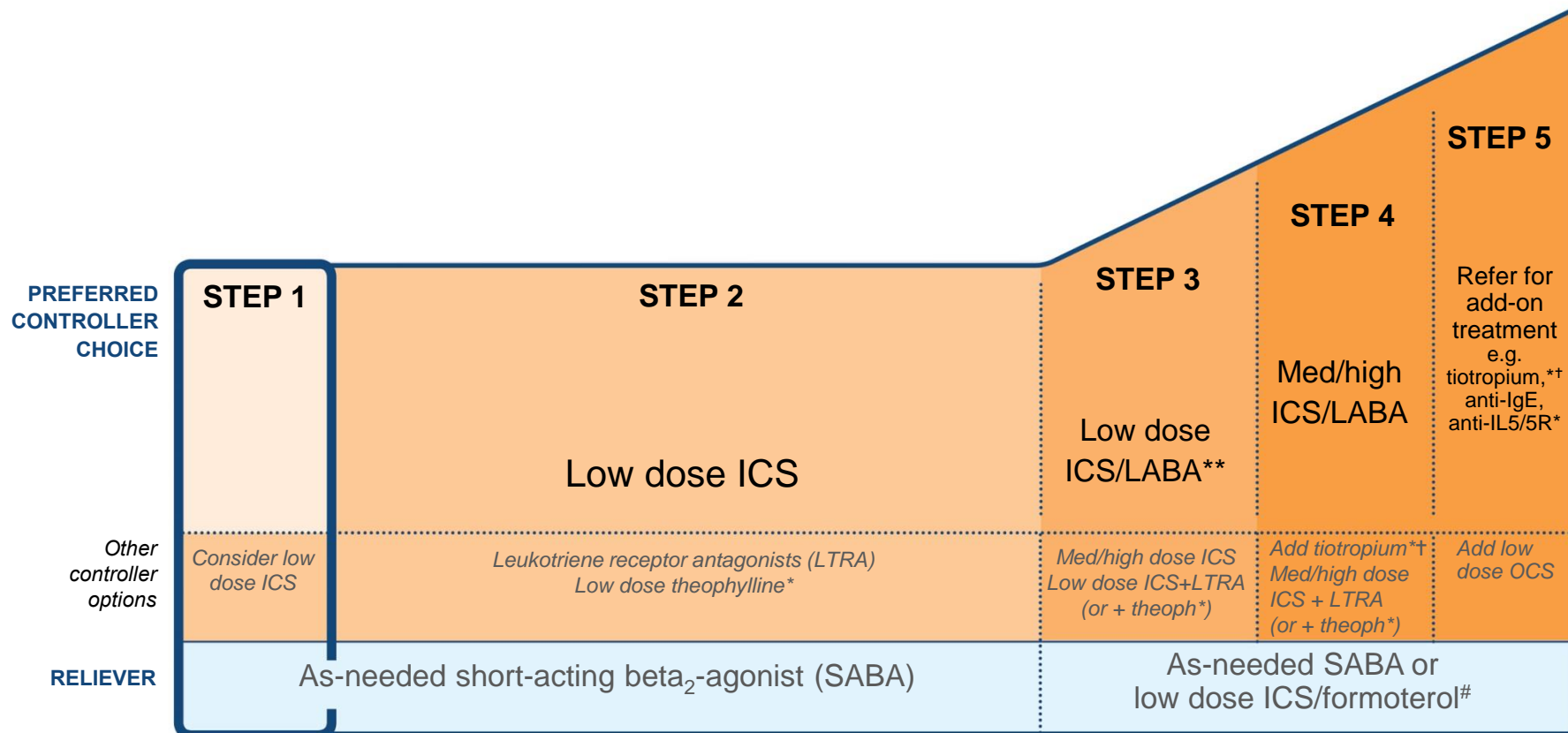


- 1. Symptom control:** to achieve good control of symptoms and maintain normal activity levels
- 2. Risk reduction:** to minimize future risk of exacerbations, fixed airflow limitation and medication side-effects

The control-based asthma management cycle



Step 1 – as-needed inhaled short-acting beta₂-agonist (SABA) (very few patients)



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 1 – as-needed reliever inhaler



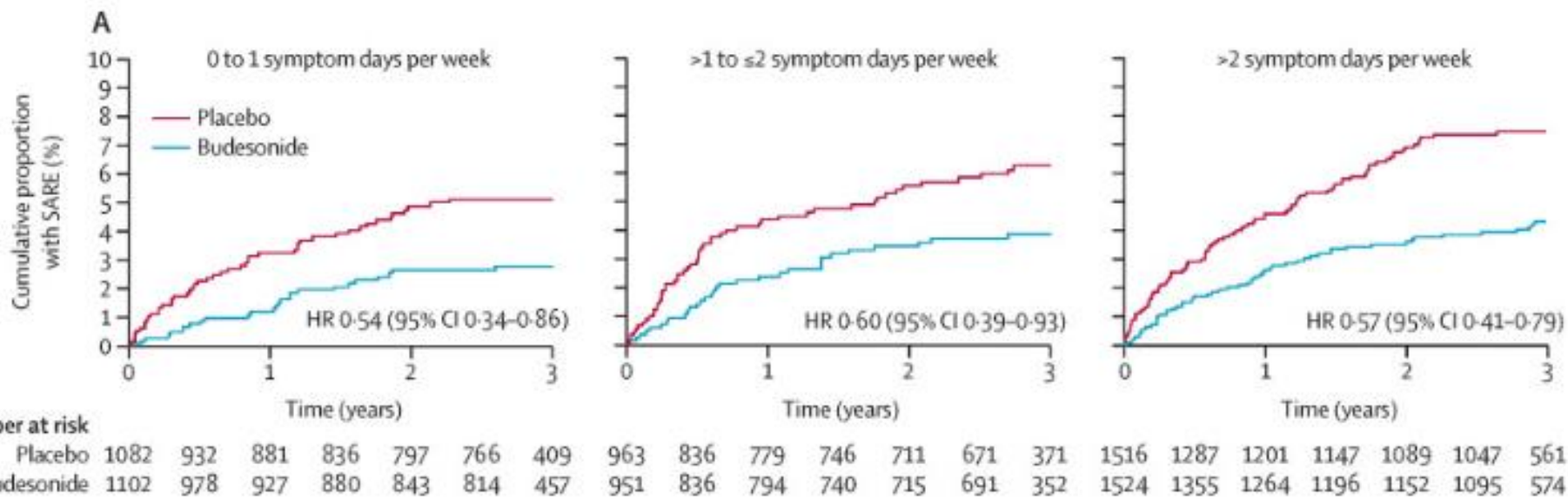
- Preferred option: as-needed SABA
 - This option should be reserved for patients with **infrequent symptoms (less than twice a month) of short duration, with no night waking due to asthma, and with no risk factors for exacerbations (Normal lung function)**
- Other options
 - Regular low dose ICS
(to reduce the risk of serious exacerbations)



Low dose ICS vs. As needed SABA in Mild Persistent Asthma

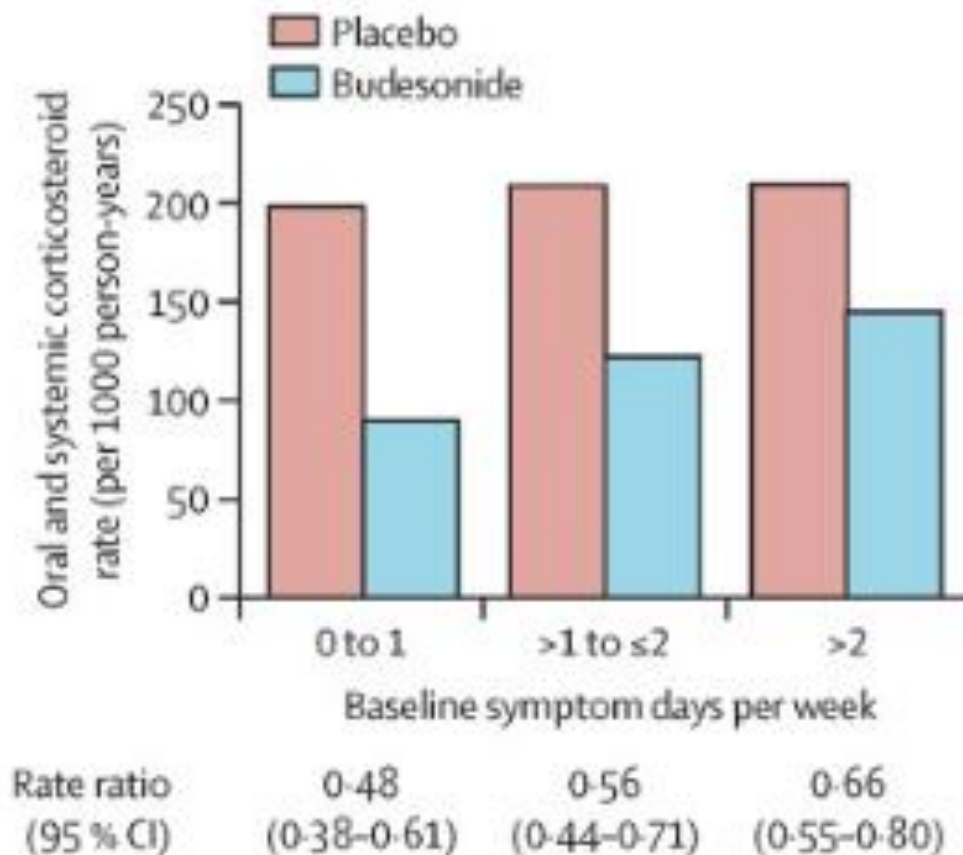
- Post-hoc analysis of START study
- 3yrs multinational pragmatic prospective RCT, N =7200
- New onset mild persistent asthma pts

Time to first SARE



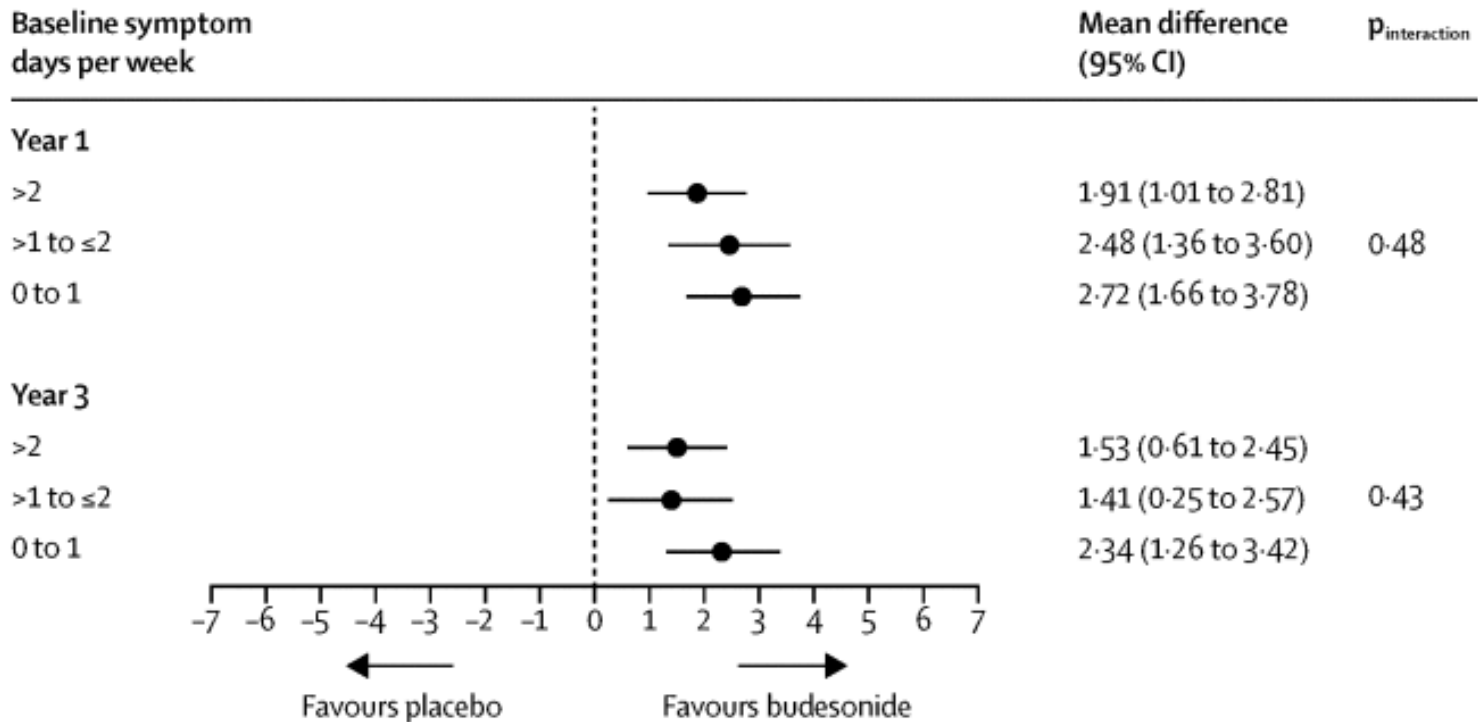
Low dose ICS vs. As needed SABA in Mild Persistent Asthma

Oral and systemic corticosteroid use rate

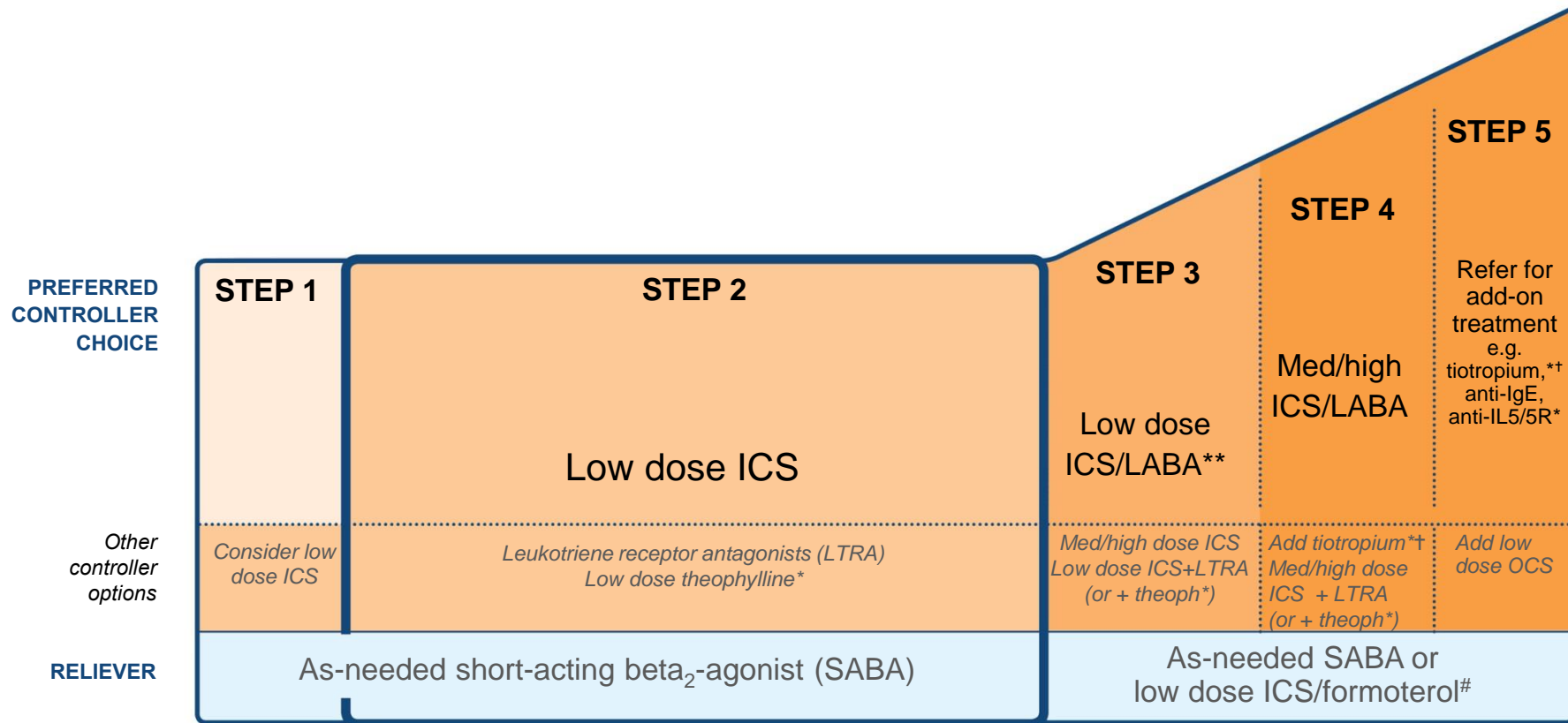


Low dose ICS vs. As needed SABA in Mild Persistent Asthma

PreBD FEV₁ (% pred)



Step 2 – low-dose controller + as-needed inhaled SABA



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

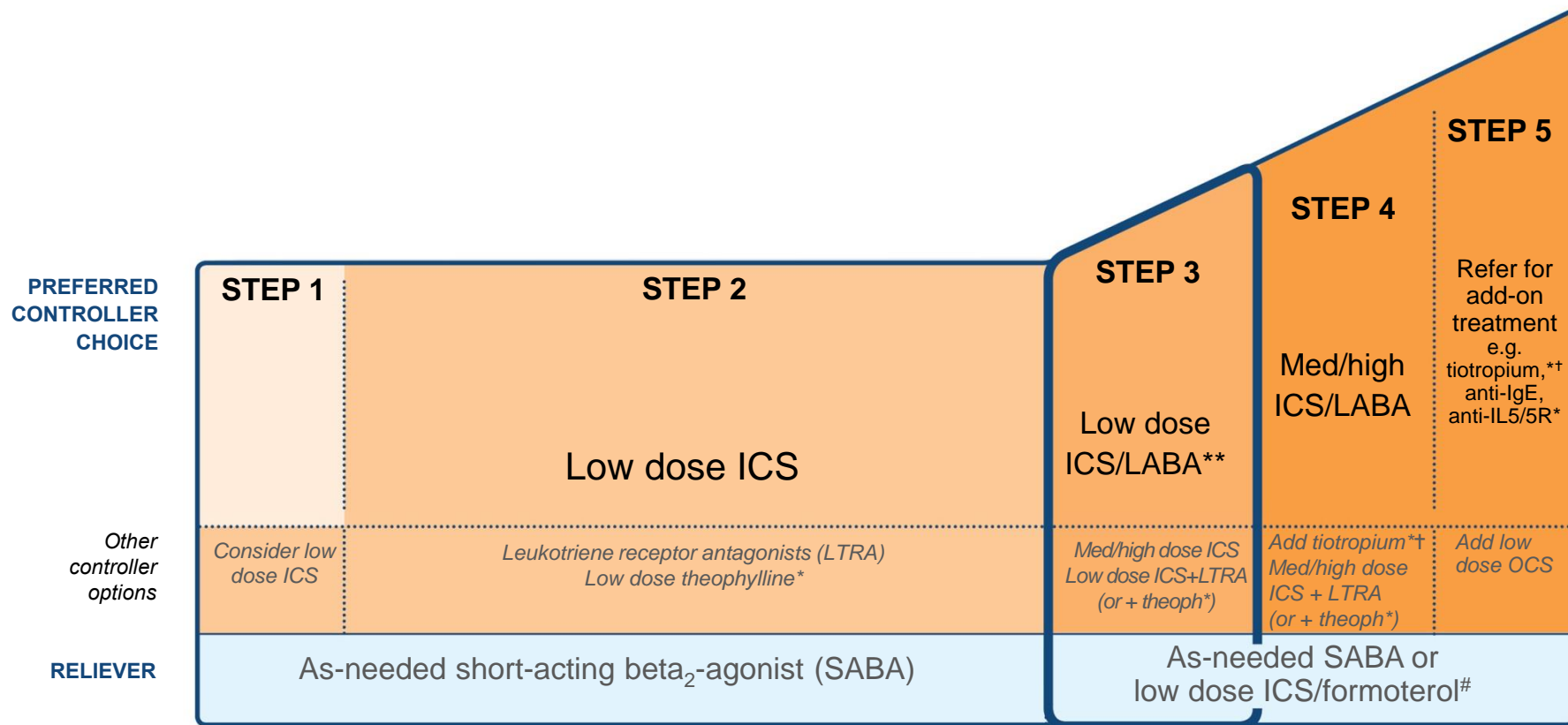
Step 2 – Low dose controller + as-needed SABA



- Preferred option: regular low dose ICS + as-needed SABA

- Other options
 - LTRA+ as-needed SABA
 - low dose ICS/LABA + as-needed SABA
 - Intermittent ICS + as-needed SABA
 - ;for purely seasonal allergic asthma with no interval symptoms
 - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

Step 3 – one or two controllers + as-needed inhaled reliever



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 3 – one or two controllers + as-needed inhaled reliever



- Before considering step-up
 - Check inhaler technique and adherence, confirm diagnosis

- Preferred options :
 - 1) Low dose ICS/LABA maintenance + as-needed SABA, OR
 - 2) Combination low dose ICS/formoterol maintenance and reliever regimen*

- Other options
 - Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
 - consider adding SLIT

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

ORIGINAL ARTICLE

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone

David A. Stempel, M.D., Ibrahim H. Raphiou, Ph.D., Kenneth M. Kral, M.S., Anne M. Yeakey, M.D., Amanda H. Emmett, M.S., Charlene M. Prazma, Ph.D., Kathleen S. Buaron, B.S.N., and Steven J. Pascoe, M.B., B.S.,
for the AUSTRI Investigators*

ORIGINAL ARTICLE

Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone

Stephen P. Peters, M.D., Ph.D., Eugene R. Bleecker, M.D., Giorgio W. Canonica, M.D., Yong B. Park, M.D., Ricardo Ramirez, M.D., Sally Hollis, M.Sc., Harald Fjallbrant, M.D., Ph.D., Carin Jorup, M.D., and Ubaldo J. Martin, M.D.

Add LABA to ICS vs. ICS alone

- Did not increase serious asthma related events.
- Reduce risk of exacerbations and improves symptoms and lung function

Step 3 – one or two controllers + as-needed inhaled reliever



- Before considering step-up
 - Check inhaler technique and adherence, confirm diagnosis

- Preferred options ;
 - 1) Low dose ICS/LABA maintenance + as-needed SABA, OR
 - 2) Combination low dose ICS/formoterol maintenance and reliever regimen*

- Other options
 - Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
 - consider adding SLIT

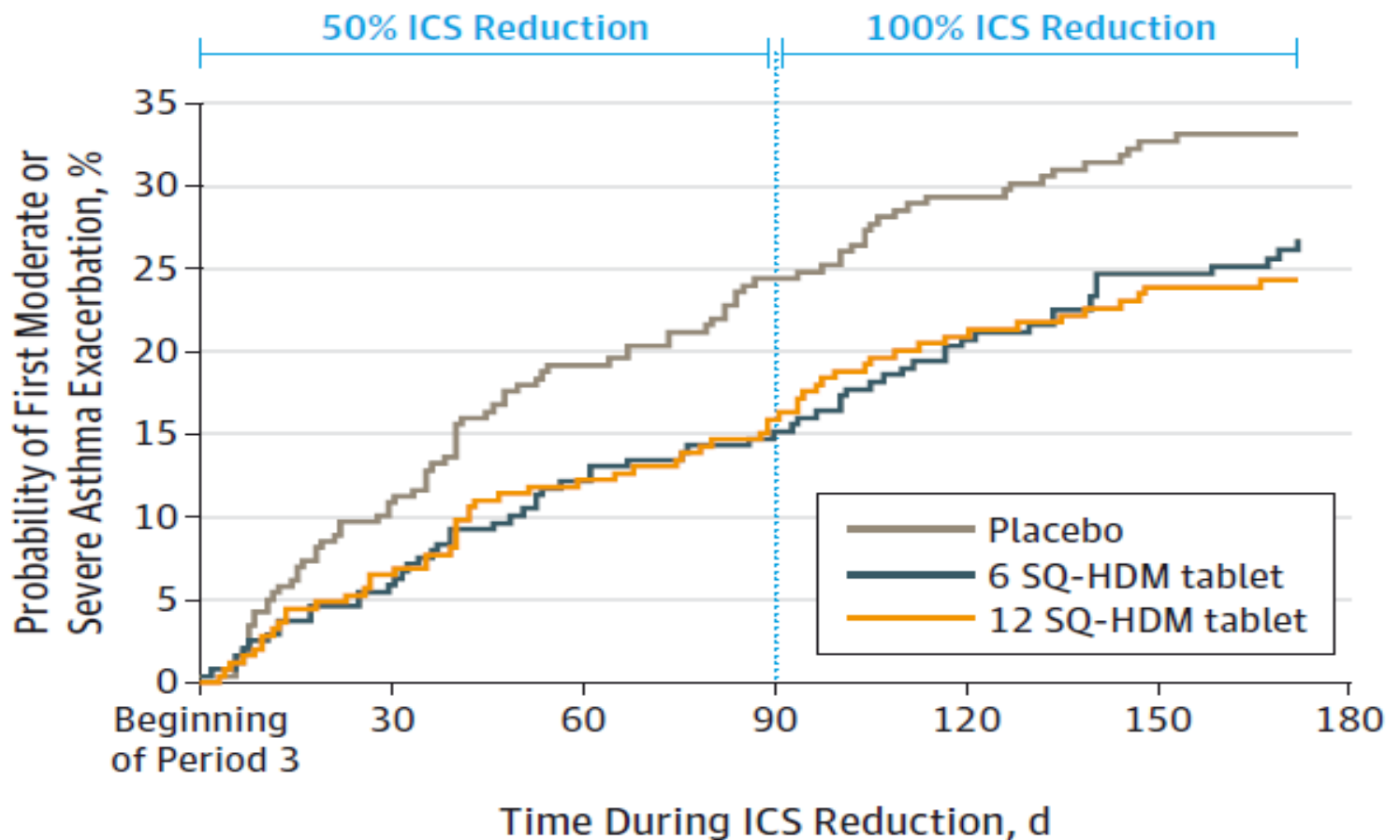
*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Original Investigation

Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma

A Randomized Clinical Trial

JAMA 2019;321:1715



Step 3 – one or two controllers + as-needed inhaled reliever



- Before considering step-up
 - Check inhaler technique and adherence, confirm diagnosis

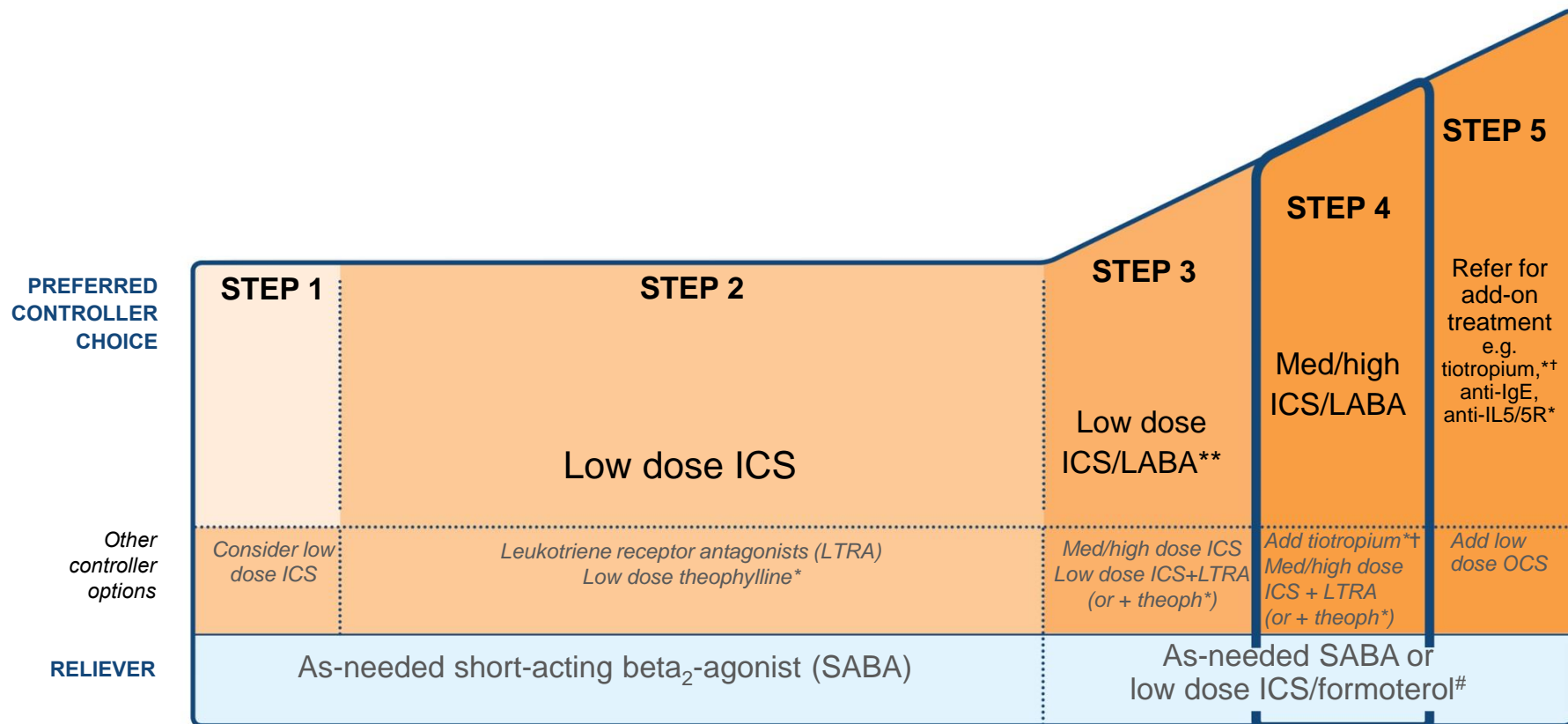
- Preferred options ;
 - 1) Low dose ICS/LABA maintenance + as-needed SABA, OR
 - 2) Combination low dose ICS/formoterol maintenance and reliever regimen*

- Other options
 - Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
 - consider adding SLIT

Consider as add-on therapy in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 4 – two or more controllers + as-needed inhaled reliever



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 4 – two or more controllers + as-needed inhaled reliever

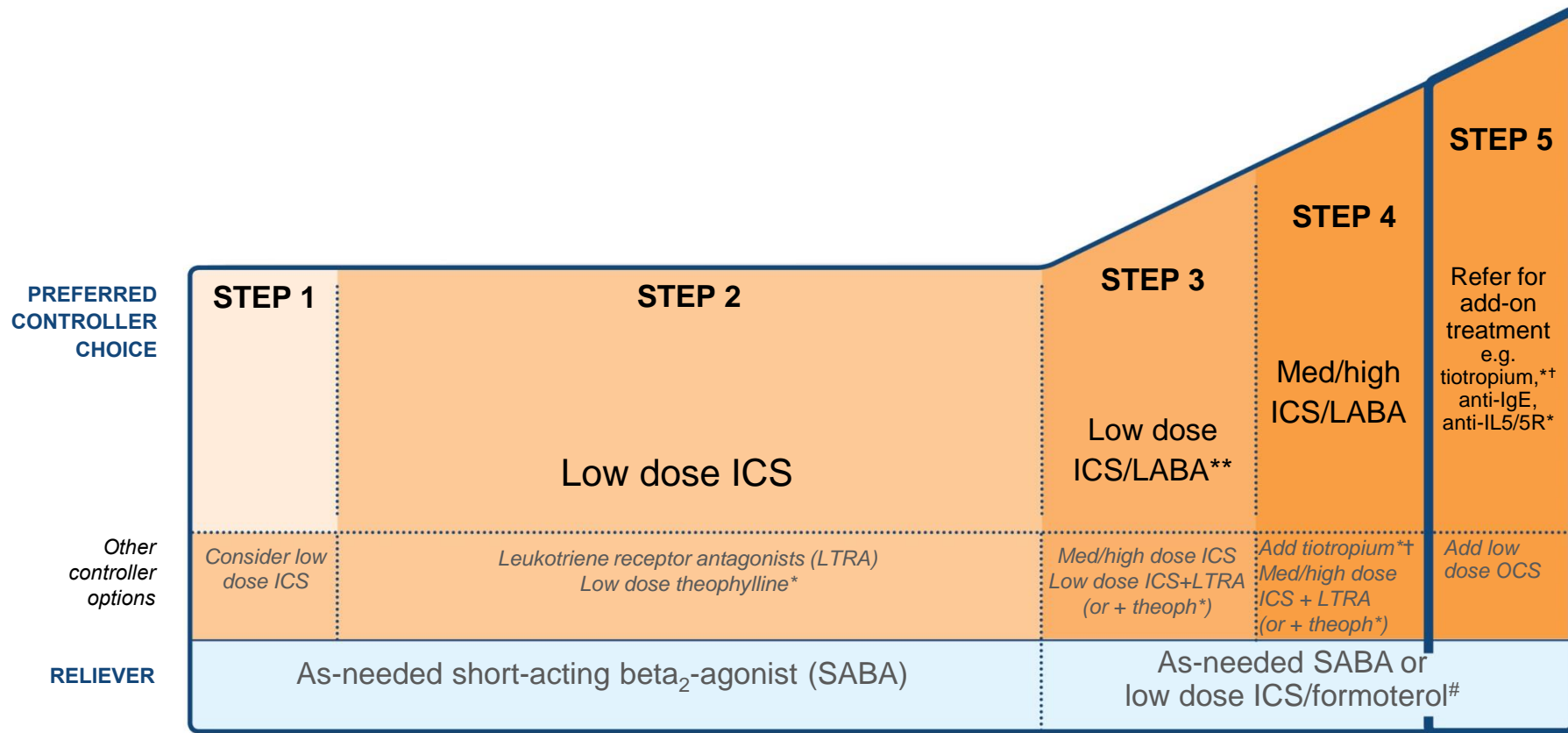
- Before considering step-up
 - Check inhaler technique and adherence

- Preferred option :
 - 1) Low dose ICS/formoterol as maintenance and reliever regimen
 - 2) Medium dose ICS/LABA + as-needed SABA

- Other options
 - Tiotropium by mist inhaler as add-on
 - Adults: consider adding SLIT
 - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
 - Increase dosing frequency (for budesonide-containing inhalers)
 - Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 5 – higher level care and/or add-on treatment



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 5 – higher level care and/or add-on treatment



- Preferred option is referral for specialist investigation and consideration of add-on treatment
 - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
 - Add-on tiotropium
 - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
 - Add-on anti-IL5 (mepolizumab (SC, ≥ 12 yrs) or reslizumab (IV, ≥ 18 yrs)) or anti-IL5R (benralizumab (SC, ≥ 12 yrs)) for severe eosinophilic asthma
- Other add-on treatment options at Step 5 include:
 - Sputum-guided treatment:
 - Add-on low dose oral corticosteroids (≤ 7.5 mg/day prednisone equivalent):

Low, medium and high dose inhaled corticosteroids

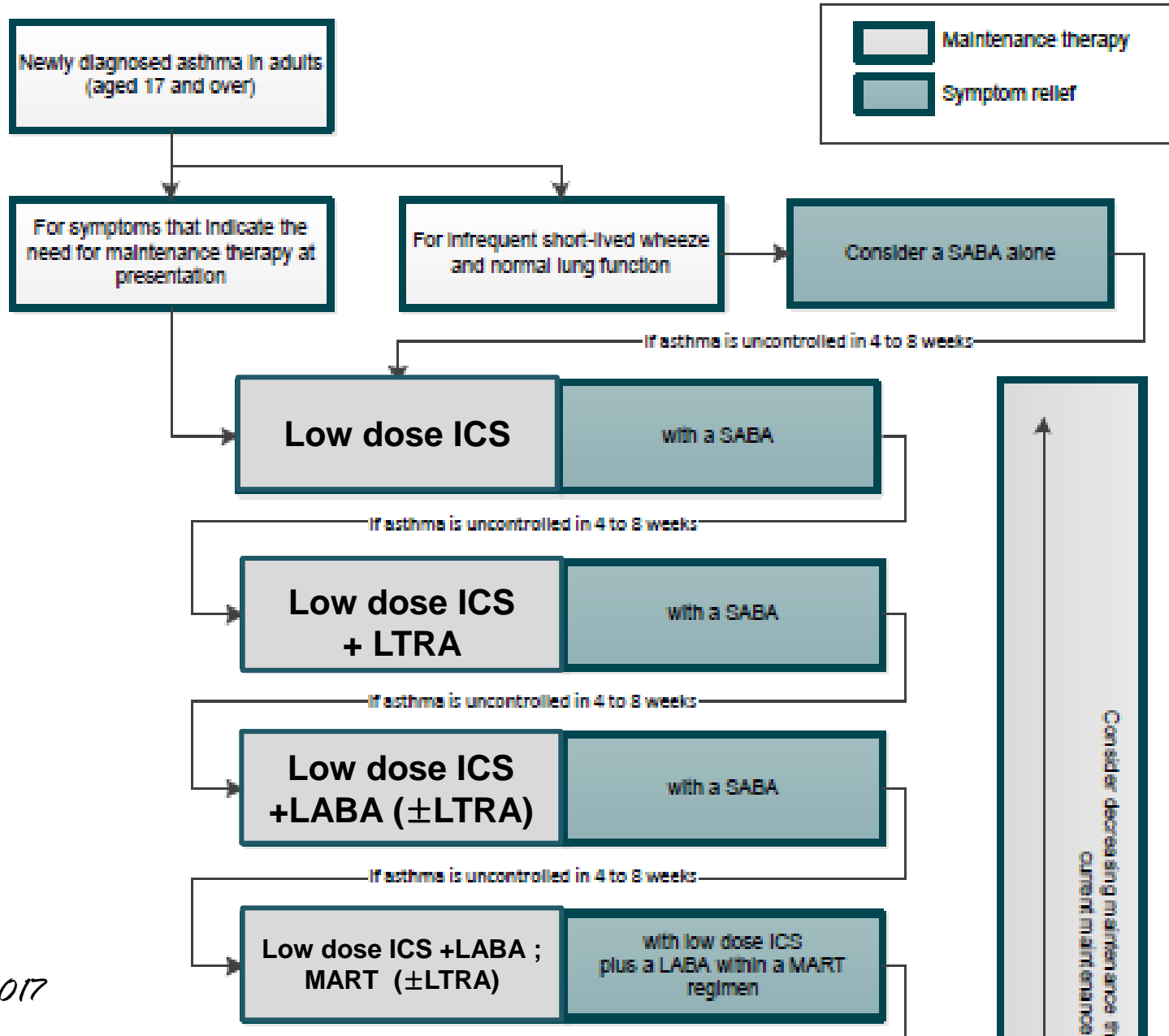
Adults and adolescents (≥ 12 years)



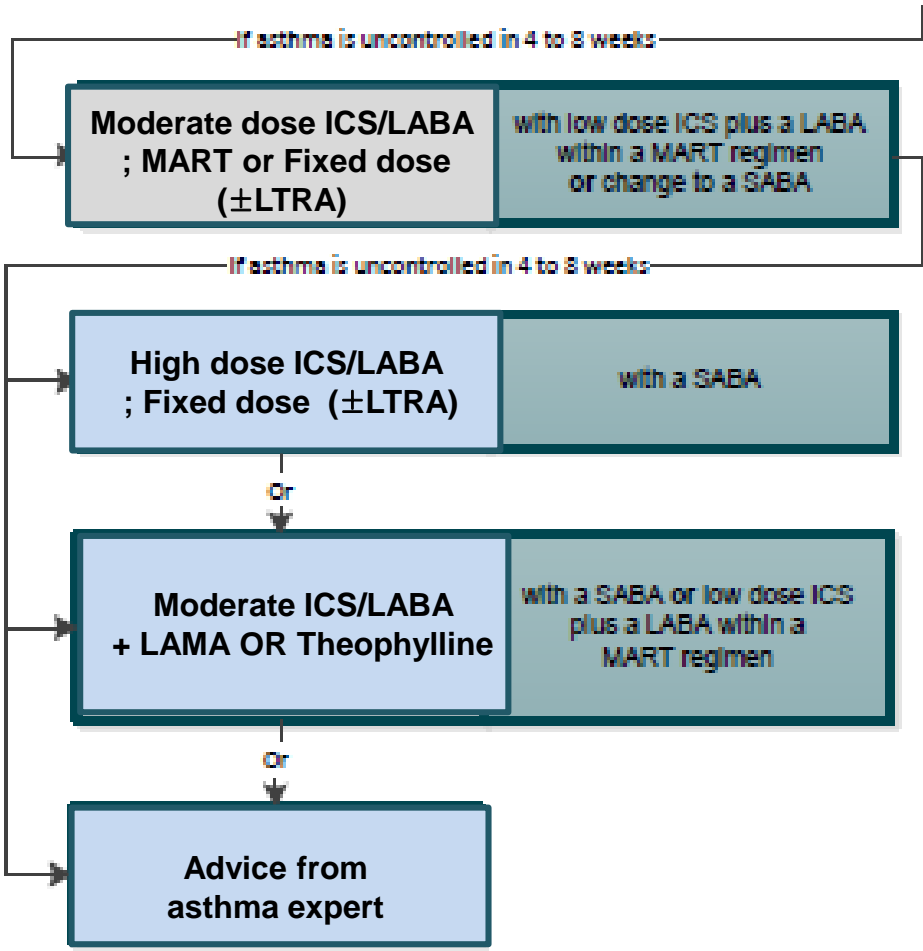
Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Algorithm F: Pharmacological treatment of chronic asthma in adults aged 17 and over

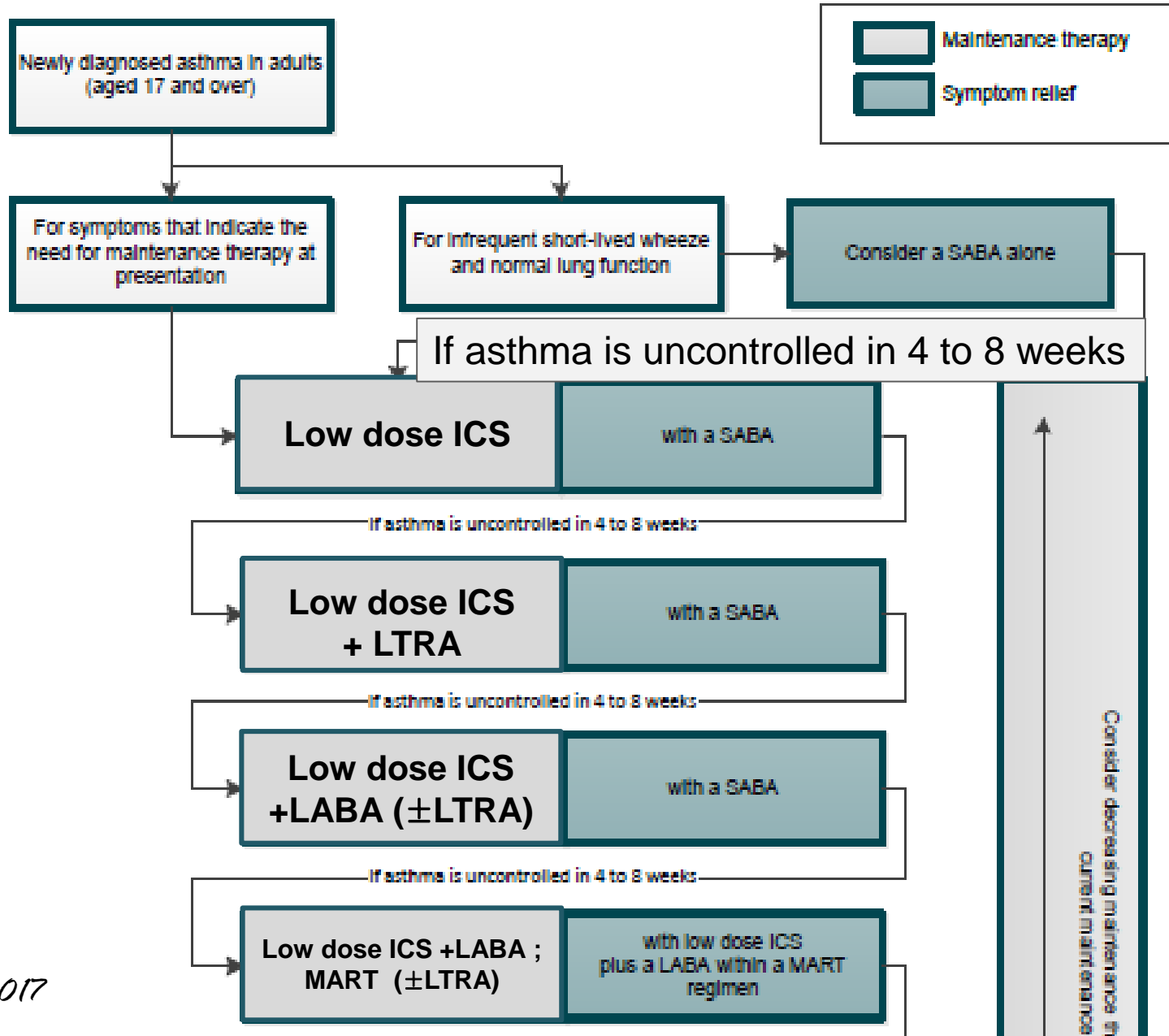


therapy when asthma has been controlled with
a therapy for at least 3 months

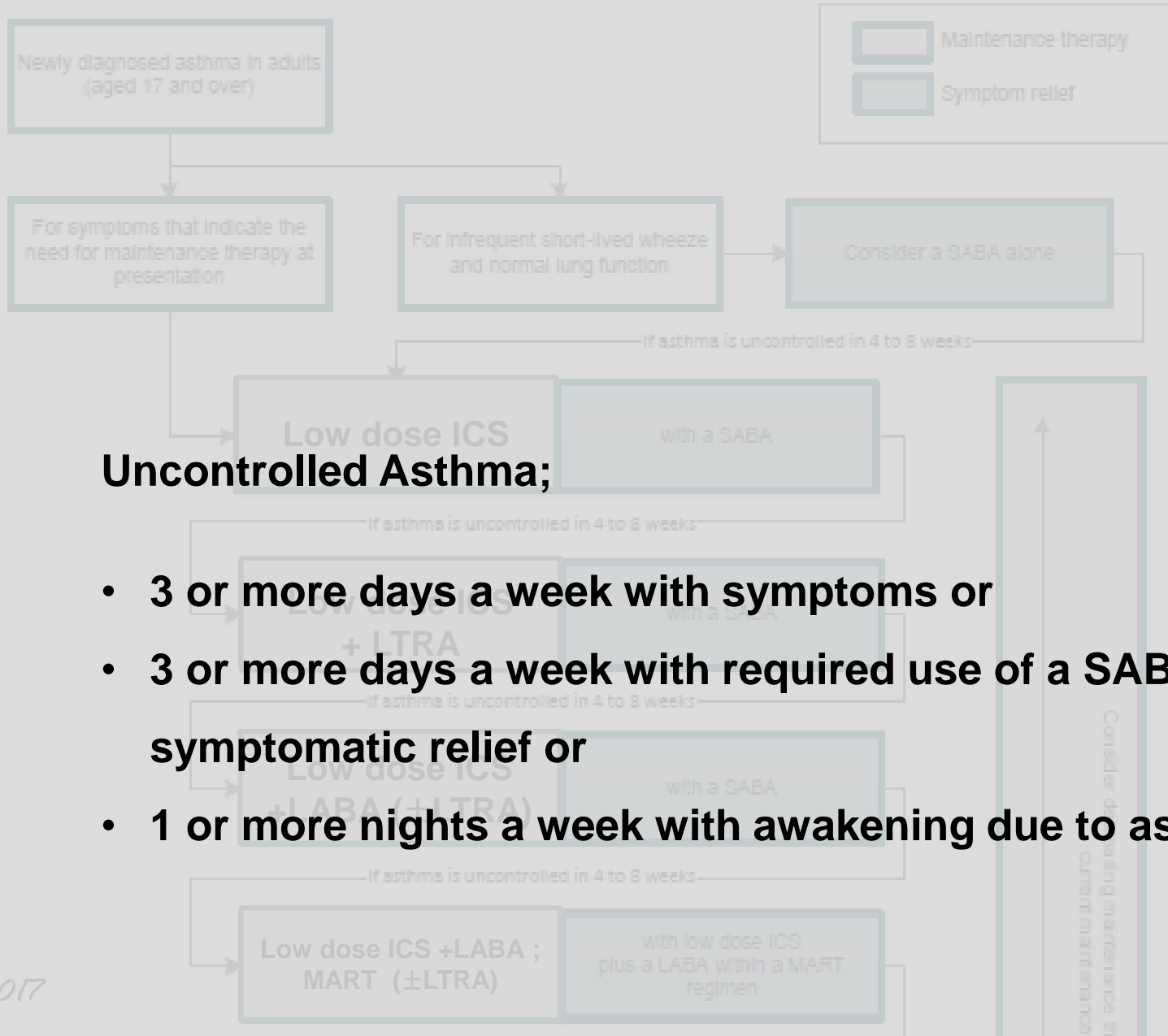


Abbreviations:
ICS, Inhaled corticosteroid
LABA, long-acting beta agonist
LTRA, leukotriene receptor antagonist
MART, maintenance and reliever therapy
SABA, short-acting beta agonist

Algorithm F: Pharmacological treatment of chronic asthma in adults aged 17 and over



Algorithm F: Pharmacological treatment of chronic asthma in adults aged 17 and over

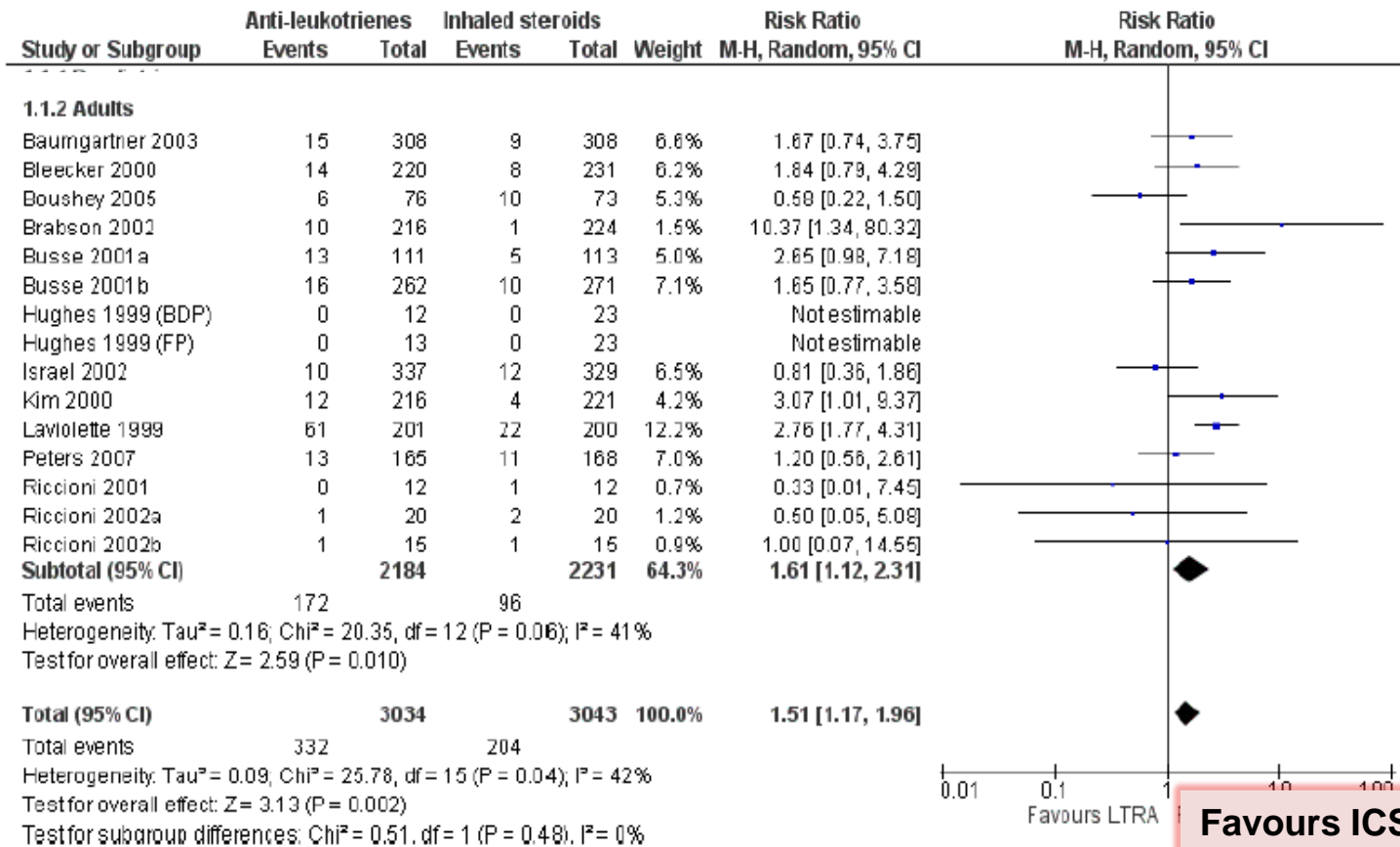


Uncontrolled Asthma;

- 3 or more days a week with symptoms or
- 3 or more days a week with required use of a SABA for symptomatic relief or
- 1 or more nights a week with awakening due to asthma

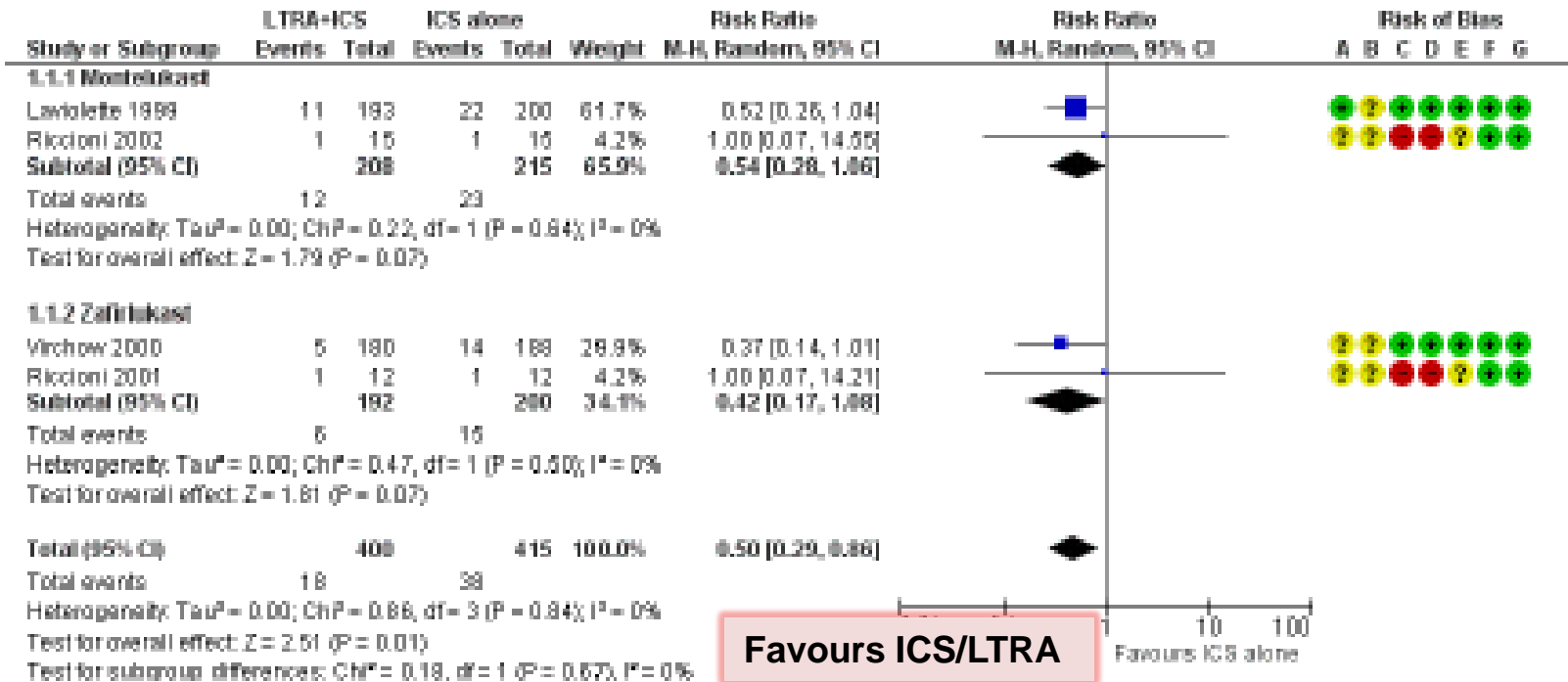
ICS vs LTRA

Risk of exacerbation requiring oral corticosteroid



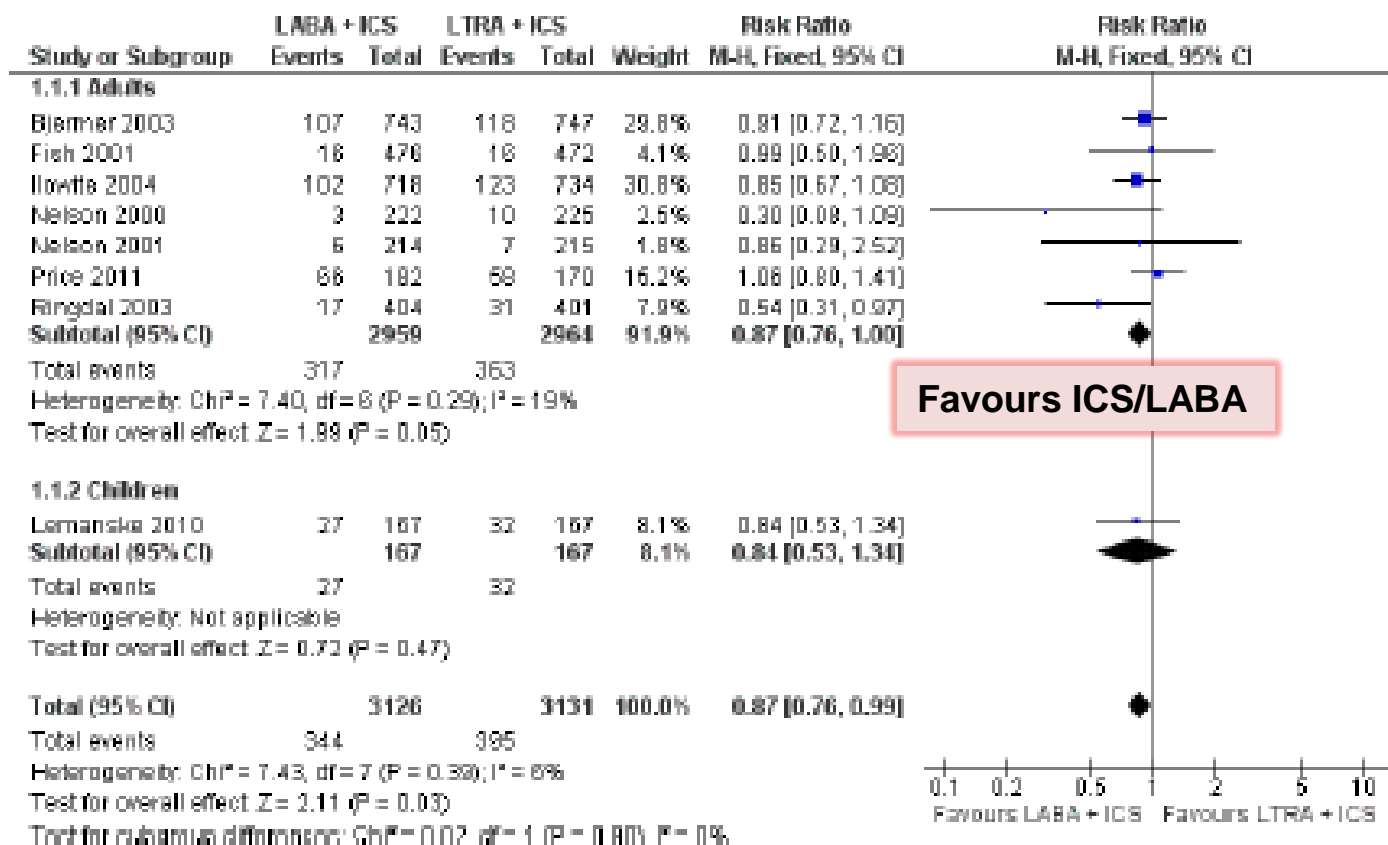
ICS/LTRA vs ICS

Risk of ≥ 1 exacerbation requiring oral corticosteroid



ICS/LABA vs ICS/LTRA

Risk of ≥ 1 exacerbation requiring oral corticosteroid



Investigations in patients with severe asthma



- Confirm the diagnosis of asthma
 - Consider alternative diagnoses or contributors to symptoms, e.g. upper airway dysfunction, COPD, recurrent respiratory infections
- Investigate for comorbidities
 - Chronic sinusitis, obesity, GERD, obstructive sleep apnea, psychological or psychiatric disorders
- Check inhaler technique and medication adherence
- Investigate for persistent environmental exposure
 - Allergens or toxic substances (domestic or occupational)

Management of severe asthma



- Optimize dose of ICS/LABA
 - Complete resistance to ICS is rare
 - Consider therapeutic trial of higher dose
- Add-on treatments without phenotyping
 - Tiotropium - reduces exacerbations (history of exacerbations, age ≥ 12 years)
 - Theophylline, LTRA – limited benefit
- Phenotype-guided treatment
 - Severe allergic asthma: add-on anti-IgE (omalizumab ≥ 6 yrs)
 - Severe eosinophilic asthma: add-on anti-IL 5 (mepolizumab ≥ 12 yrs or reslizumab ≥ 18 yrs), or anti-IL5R (benralizumab ≥ 12 yrs)
 - Sputum-guided treatment to reduce exacerbations and/or OCS dose
 - Aspirin-exacerbated respiratory disease: consider add-on LTRA
- Non-pharmacological interventions
 - Consider bronchial thermoplasty for selected patients (with registry)
 - Comprehensive adherence-promoting program
- Consider low dose maintenance oral corticosteroids
 - Monitor for and manage side-effects, including osteoporosis



OTHERS

Perimenstrual asthma, and asthma in pregnancy



- Perimenstrual (catamenial) asthma – new section added
 - Asthma worse premenstrually in ~20% women
 - More common in older women, higher BMI, longer duration and more severe asthma; often have dysmenorrhea, shorter cycles, longer bleeding; aspirin-exacerbated respiratory disease more common
 - Add-on treatment: oral contraceptives and/or LTRA may be helpful
- The recommendation against stopping ICS during pregnancy has been reinforced

Follow-up after an asthma exacerbation



- Follow up all patients regularly after an exacerbation, until symptoms and lung function return to normal

- The opportunity

- At follow-up visit(s), check:
 - The patient's understanding of the cause of the flare-up
 - Modifiable risk factors, e.g. smoking
 - Adherence with medications, and understanding of their purpose
 - **SABA is being taken only as-needed, not regularly**
 - Inhaler technique skills
 - Written asthma action plan

Check adherence with asthma medications



- Poor adherence:
 - >50% of adults do not take controller medications as prescribed
 - Contributes to uncontrolled asthma symptoms and risk of exacerbations and asthma-related death
- Contributory factors
 - Unintentional (e.g. forgetfulness, cost, confusion) and/or
 - Intentional (e.g. no perceived need, fear of side-effects, cultural issues, cost)
- How to identify patients with low adherence:
 - Ask an empathic question
 - Check prescription date, label date and dose counter
 - Ask patient about their beliefs and concerns about the medication

Strategies to improve adherence in asthma



- Only a few interventions have been studied closely in asthma and found to be effective for improving adherence
 - Shared decision-making
 - Comprehensive asthma education with nurse home visits
 - Inhaler reminders, either proactively or for missed doses
 - Reviewing patients' detailed dispensing records



THANK YOU