Asthma Management:
Track 2. ICS + non-formoterol SABA

Jong Geol Jang, MD

Assistant Professor
Division of Pulmonary, Allergy, and Critical Care Medicine
Department of Internal Medicine
Yeungnam University Medical Center
Yeungnam University of Korea

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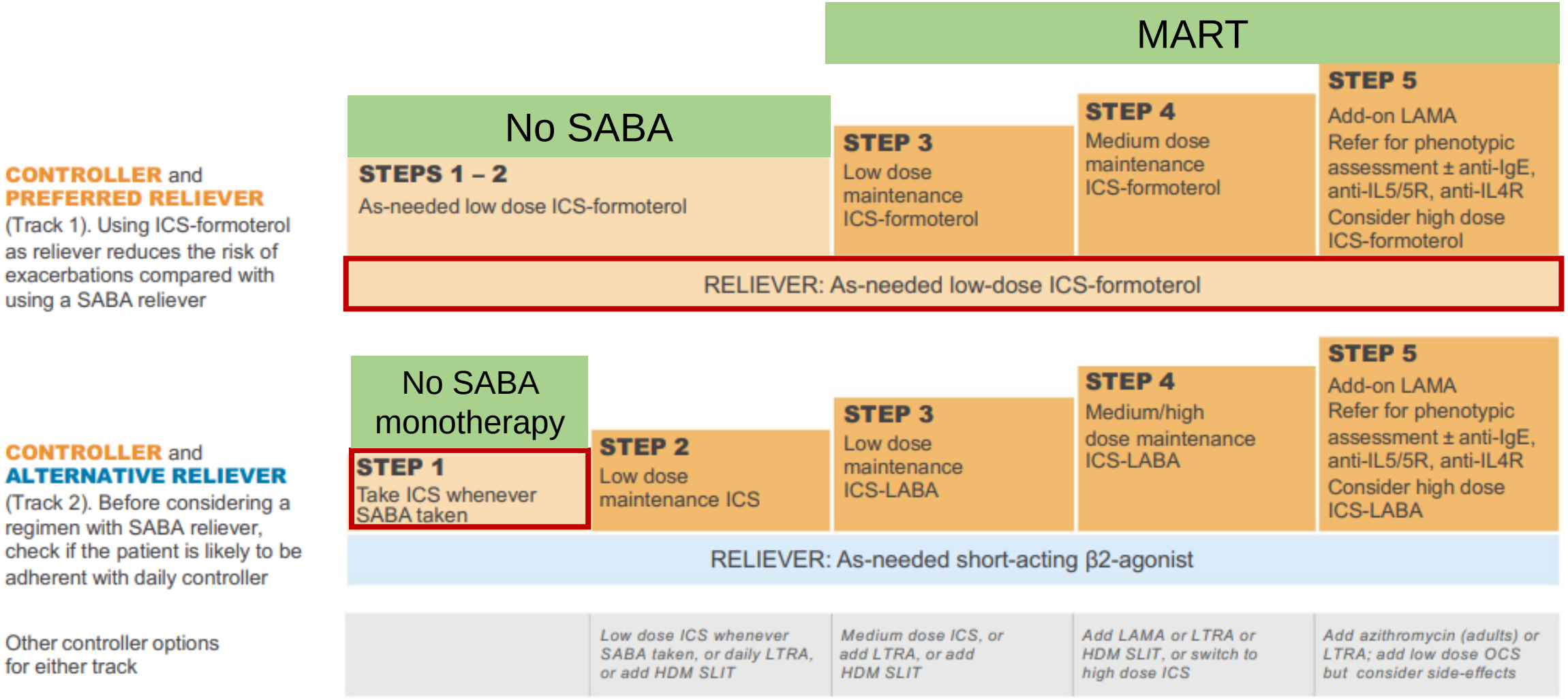
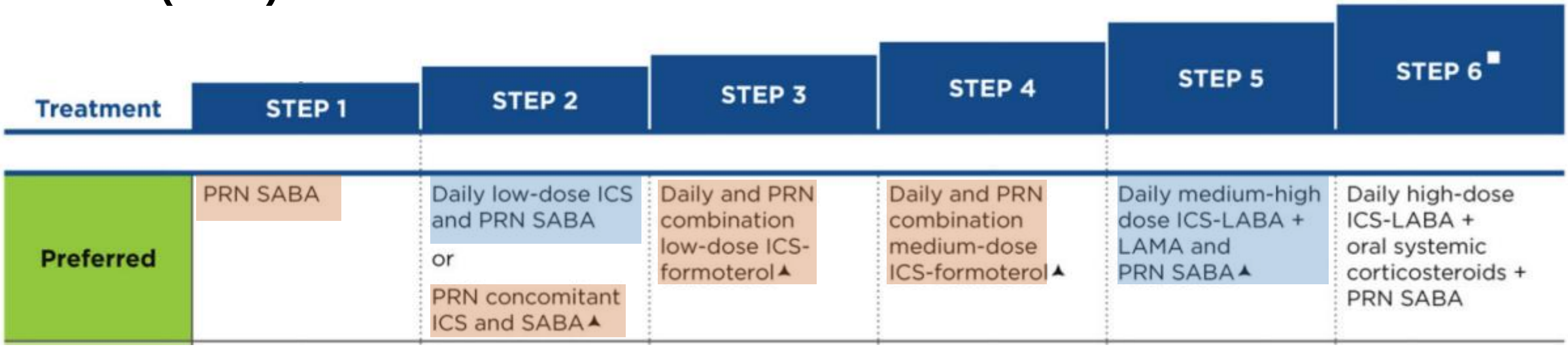
GINA: Stepwise asthma treatment 2021



KATRD (2020)

NAEPP (2020)



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The risks of SABA only in mild asthma

Dusser et al. Allergy 62:591-604, 2007; Hancox et al. Respir Med 8:767-71, 2000; Aldridge et al. AJRCCM 161:1459-64, 2000; Stanford et al. Ann Allergy Asthma Immunol 109(6):403-7, 2012; Suissa et al. Eur Respir J 7:1602-9, 1994

Short-Acting Beta2-Agonist Use in Asthma

	Italy	Germanya	Spain	Sweden	UK
Mean (SD) number of annual SABA canisters	3.1 (4.0)	1.6 (3.9)	3.3 (3.6)	1.9 (2.9)	4.2 (5.1)
Individuals with 0–2 SABA canisters/year (%)	91	84	71	70	62
Individuals with ≥3 SABA canisters/year (%)	9	16	29	30	38
Individuals with 3–6 SABA canisters/year (%)	6	10	19	25	24
Individuals with 7–12 SABA canisters/year (%)	2	3	6	5	11
Individuals with ≥13 SABA canisters/year (%)	1	2	4	1	4

Adv Ther (2020) 37:1124–1135 Allergy Asthma Immunol Res. 2021 Nov;13(6):945-953

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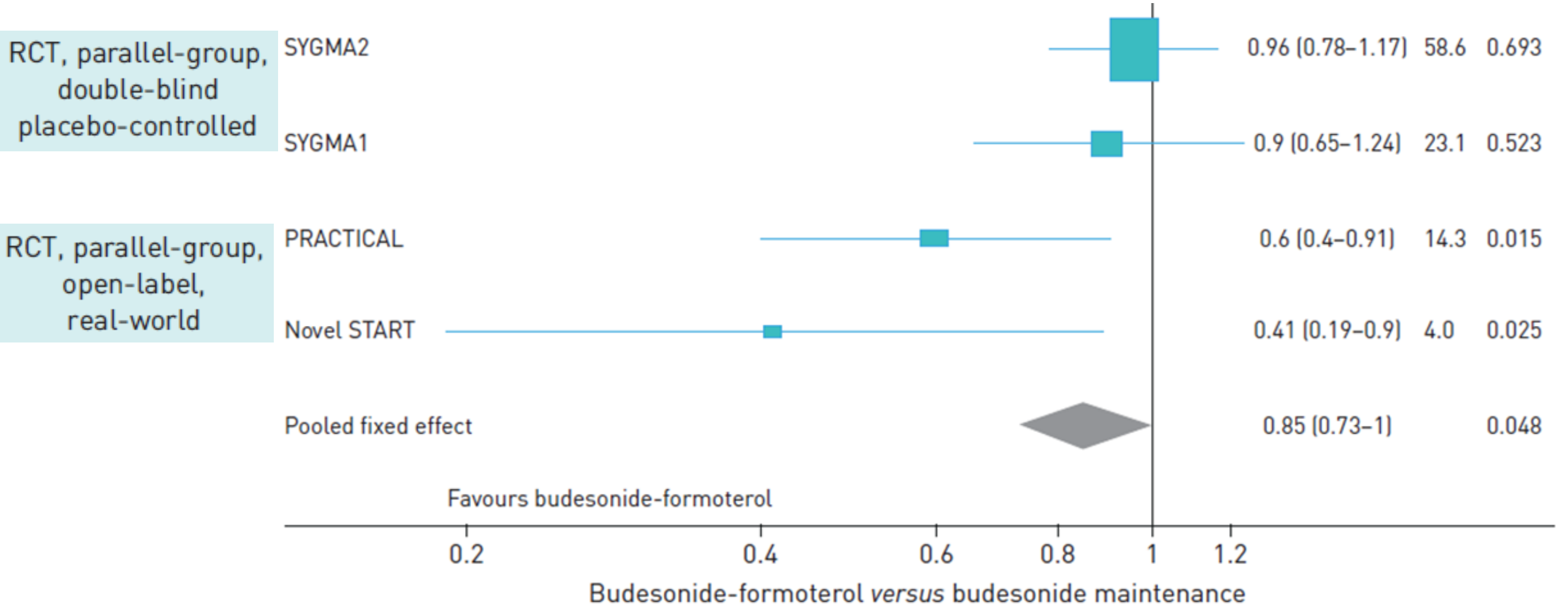
Mild asthma: step 1 (Symptoms less than twice a month)

Track 1	Controller	As-needed low dose-ICS-formoterol
	Preferred reliever	As-needed low dose-ICS-formoterol
Track 2	Controller	Take ICS whenever SABA taken
	Alternative reliever	As-needed SABA

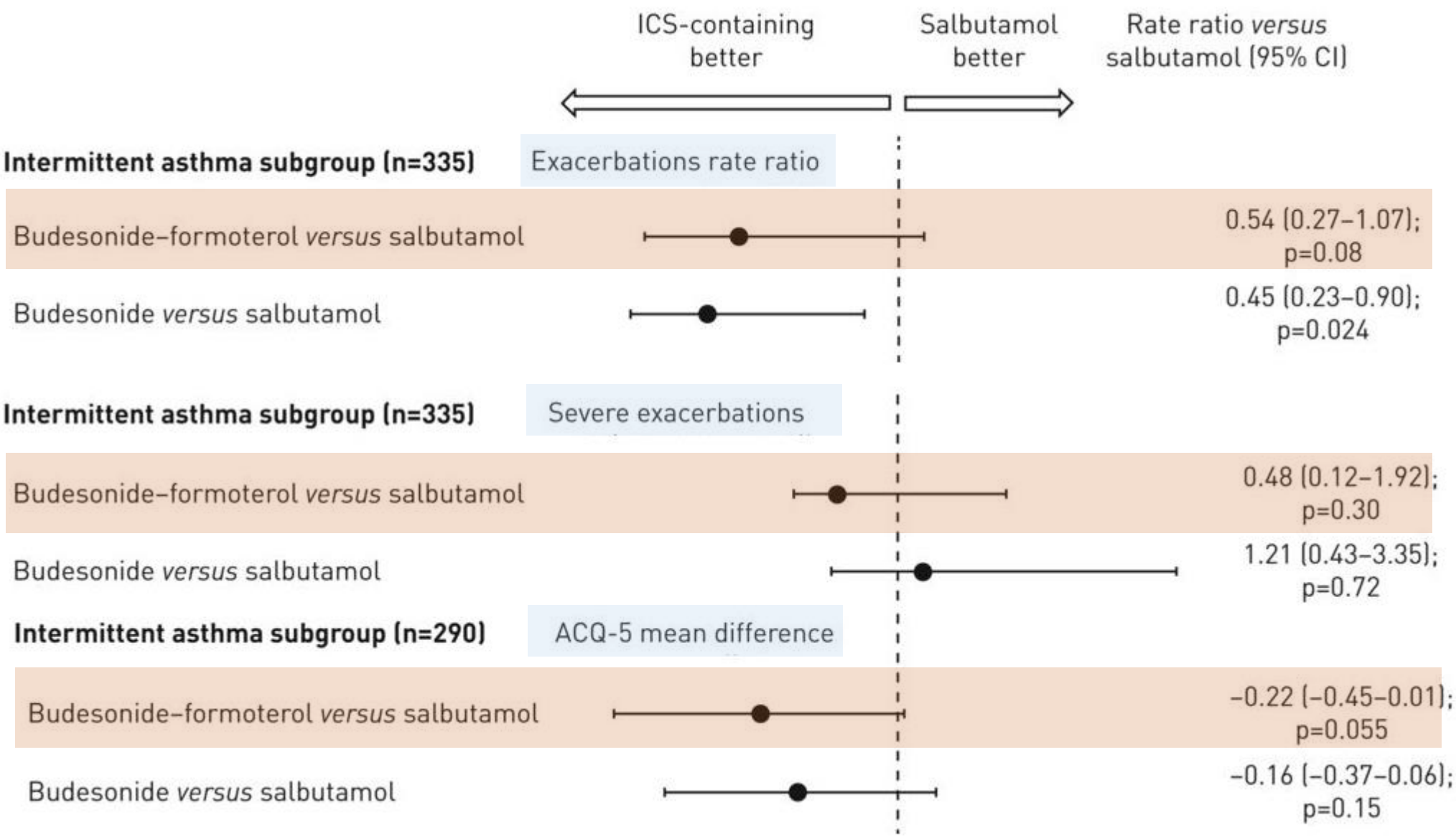
There is indirect evidence about safety and efficacy of as-needed ICS-formoterol from four large RCTs in patients eligible for Step 2 treatment

Mild asthma: step 1 (Symptoms less than twice a month)



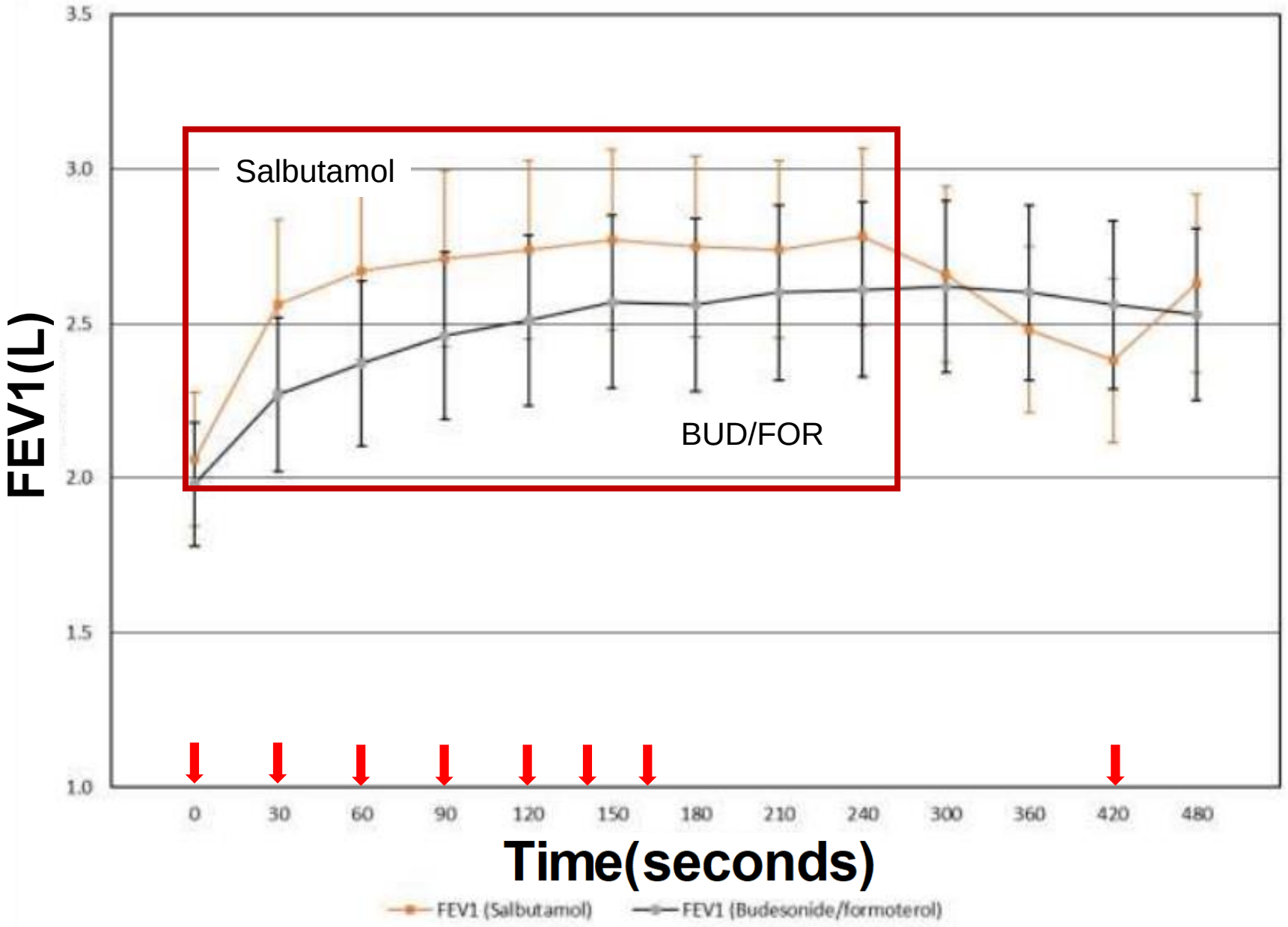
L. HATTER ET AL. ERJ Open Res 2021; 7: 00701-2020

Novel START post-hoc: Intermittent vs Mild persistent asthma



Papi et al. Eur Respir J 2021; 57: 2003064

Reliever in acute asthma: SABA vs ICS/Formoterol



European Respiratory Journal 2022; DOI: 10.1183/13993003.02309-2021

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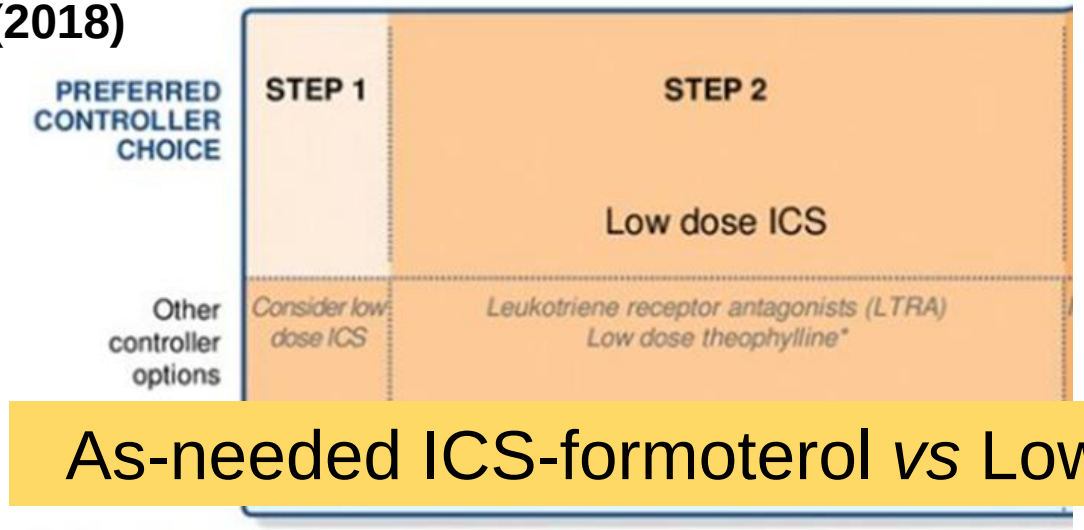
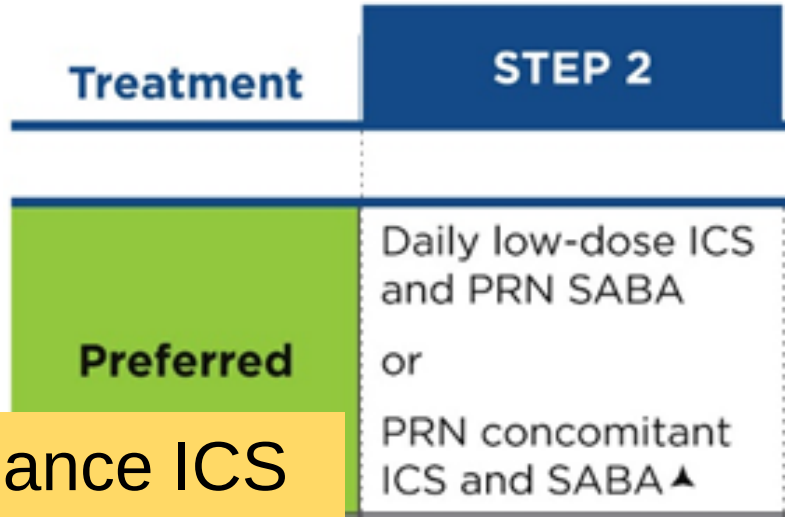
Mild asthma: step 2 (Symptoms less than 4-5 days a week)

GINA (2018)



NAEPP (2020)

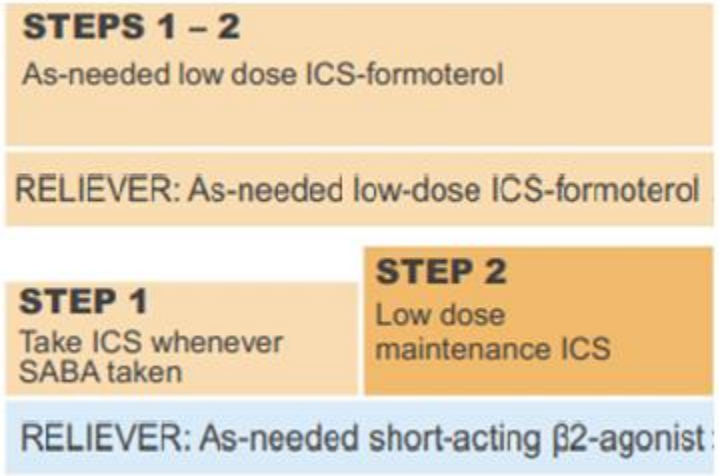


As-needed ICS-formoterol *vs* Low dose maintenance ICS

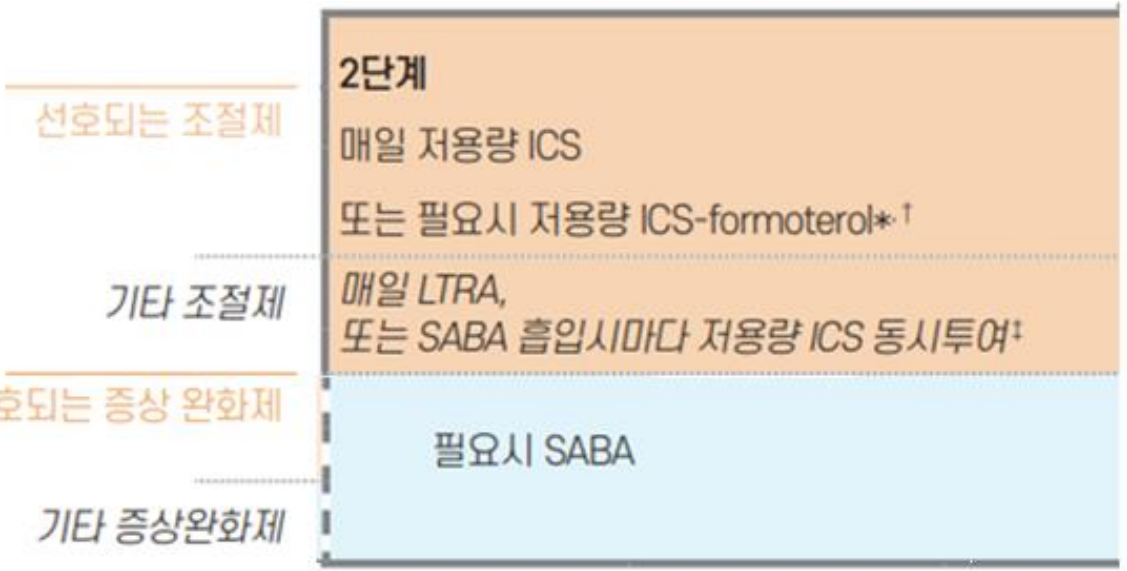
GINA (2021)

CONTROLLER and PREFERRED RELIEVER (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

CONTROLLER and ALTERNATIVE RELIEVER (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller



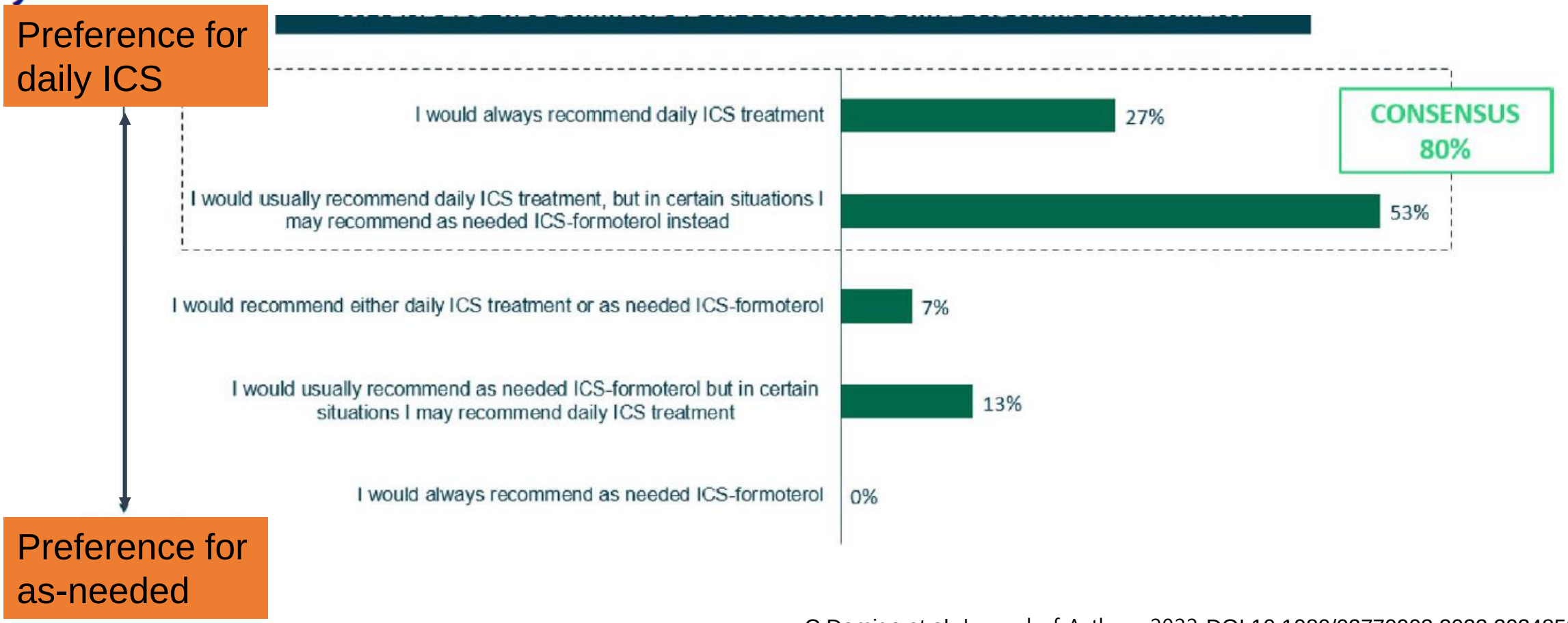
KATRD (2020)



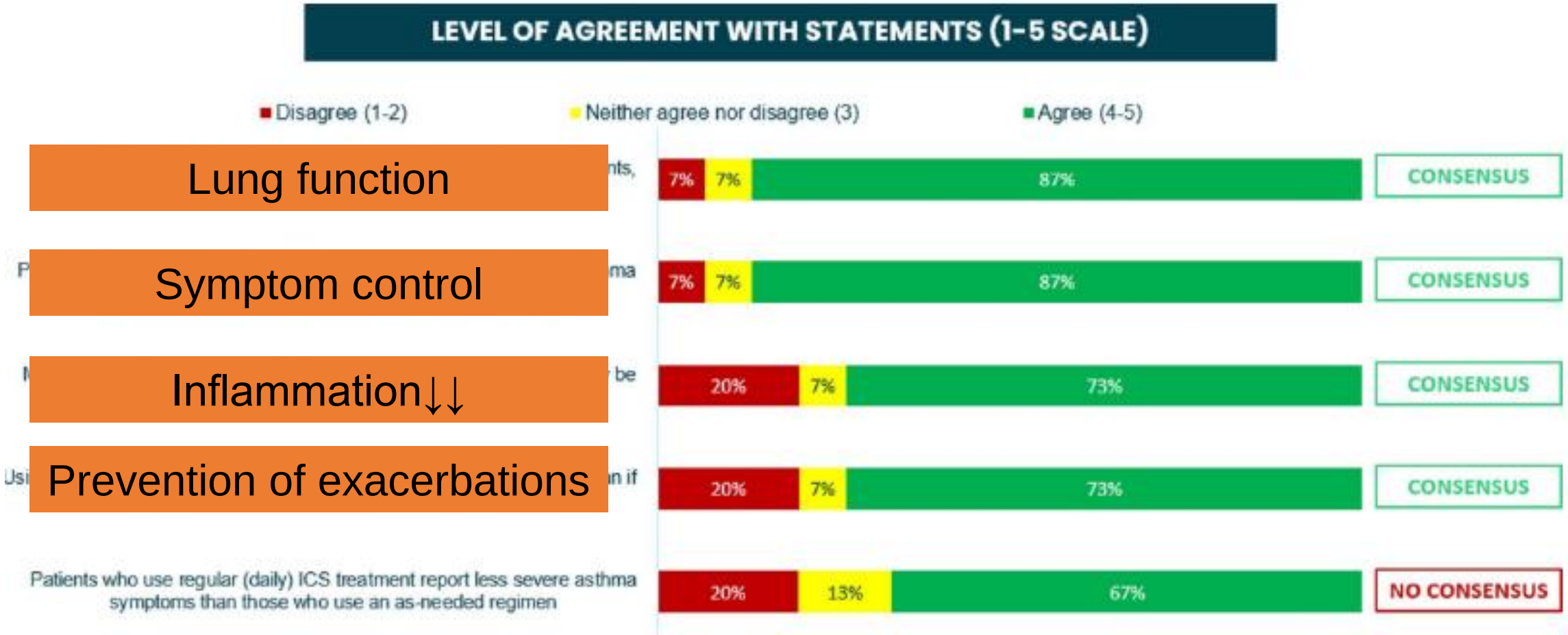
JOURNAL OF ASTHMA
https://doi.org/10.1080/02770903.2022.2034850

Taylor & Francis
Taylor & Francis Group

Consensus on mild asthma management: results of a modified Delphi study



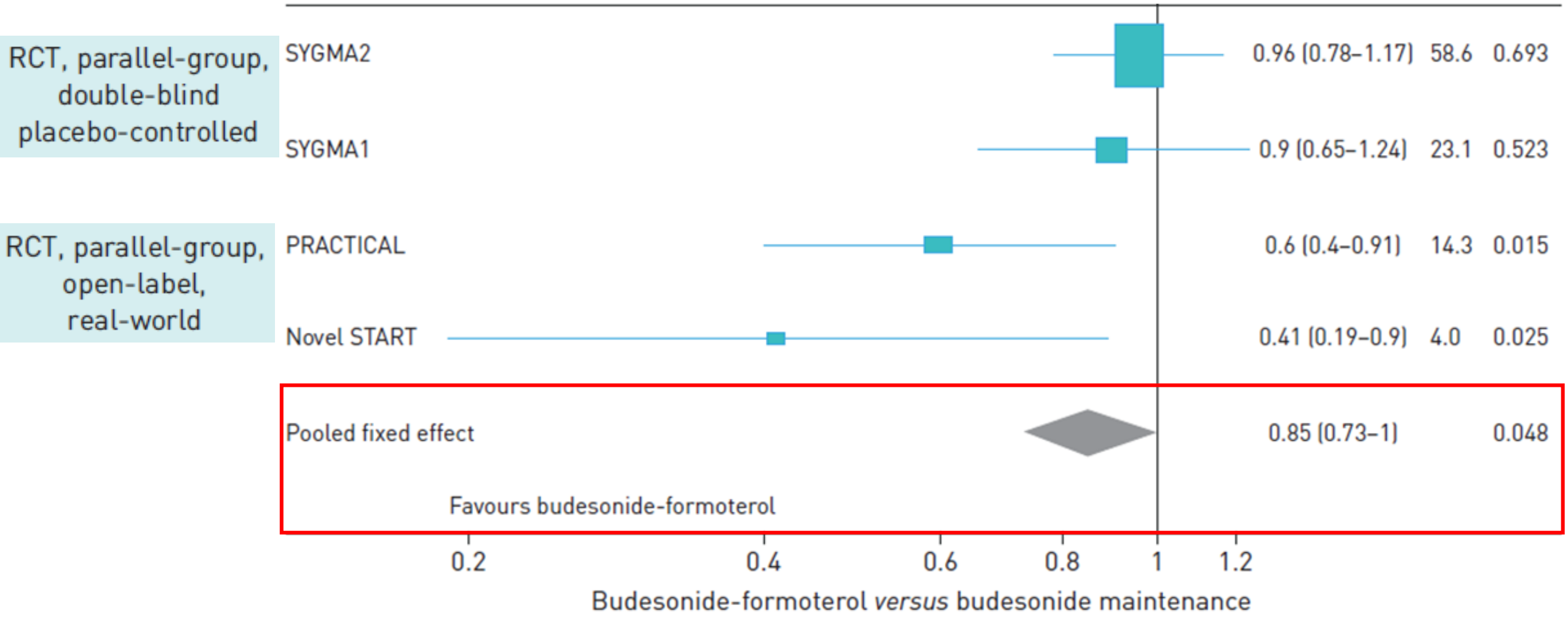
C Domigo et al. Journal of Asthma 2022 DOI:10.1080/02770903.2022.2034850



C Domigo et al. Journal of Asthma 2020 DOI:10.1080/02770903.2022.2034850

Track 2 vs Track 1

Severe exacerbations



L. HATTER ET AL. ERJ Open Res 2021; 7: 00701-2020

Track 2 vs Track 1

Severe exacerbations

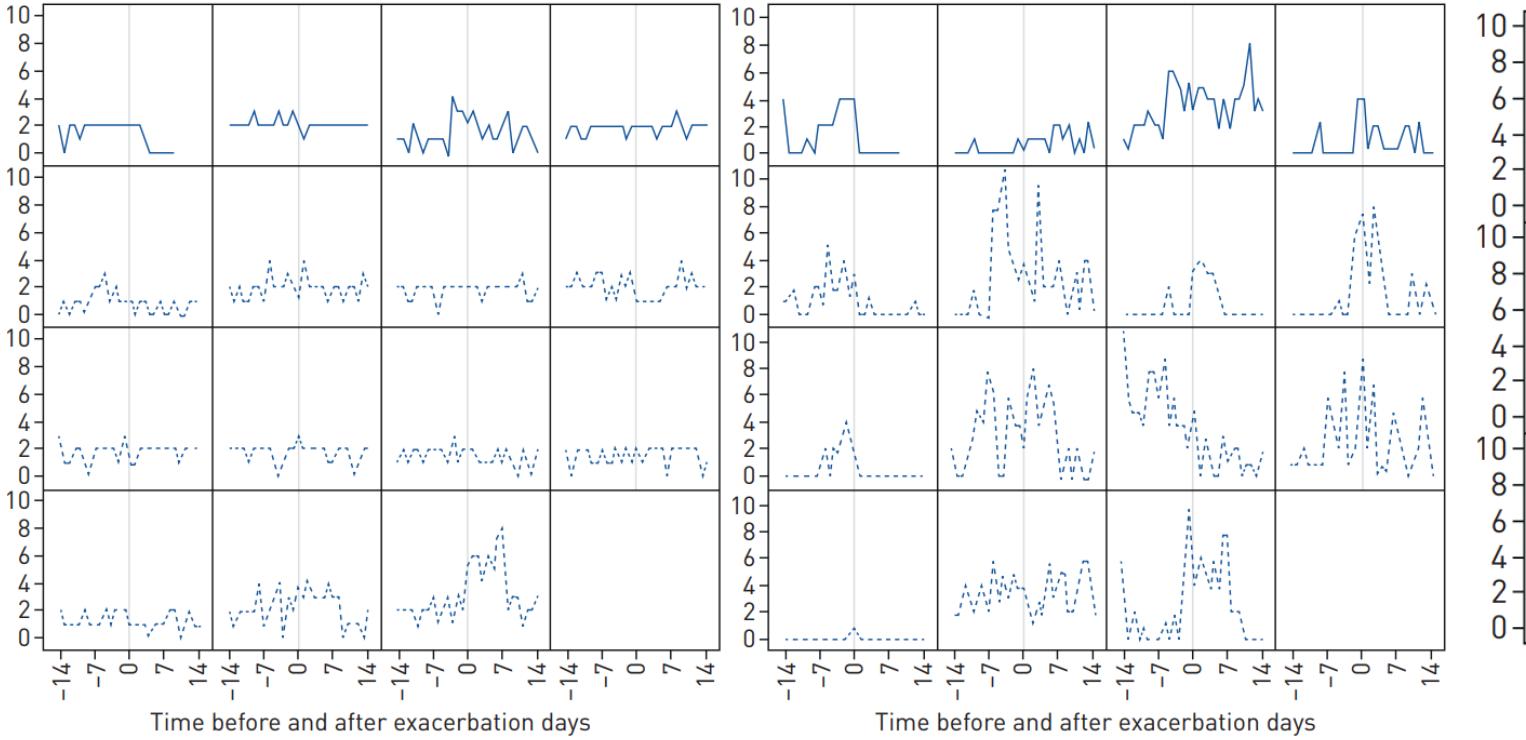
Timing of ICS use > Total ICS dose

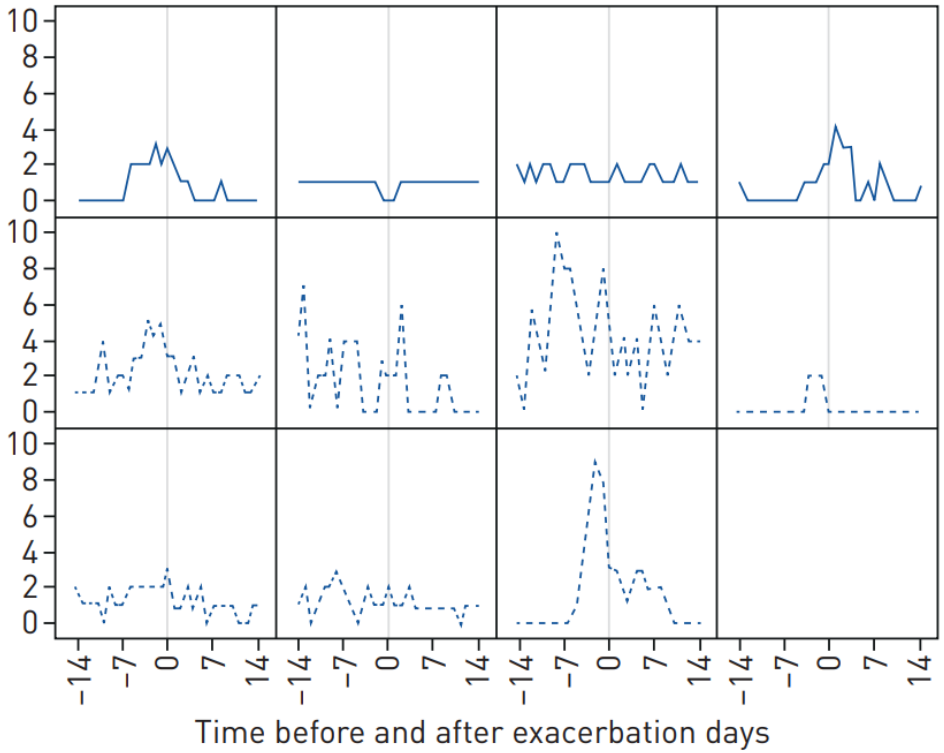
Maintenance ICS

As-needed ICS-Formoterol

ICS

SABA

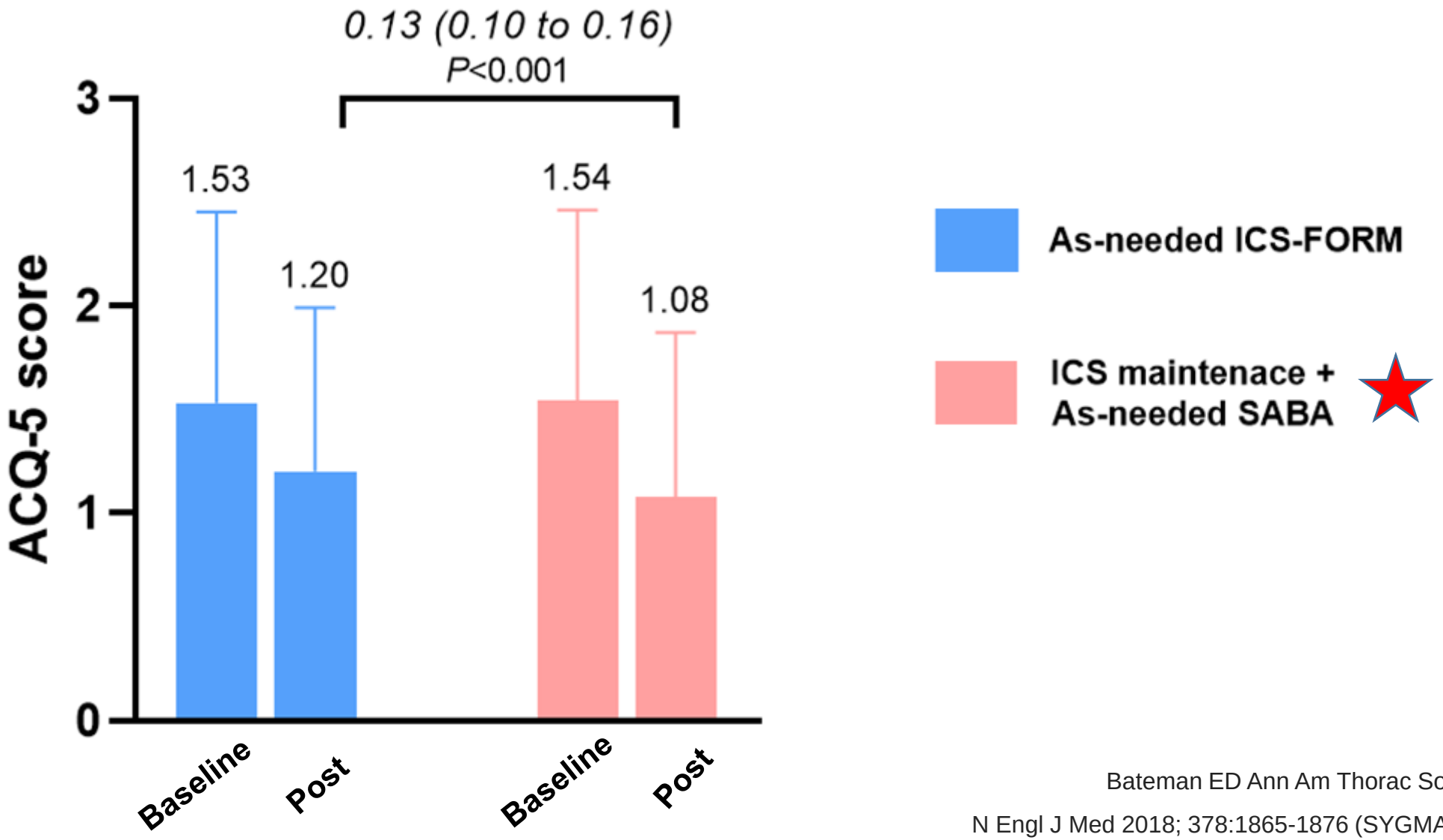




Eur Respir J 2020; 56: 2000170

Track 2 vs Track 1

Symptom control (Pooled analysis of SYGMA 1 and 2)

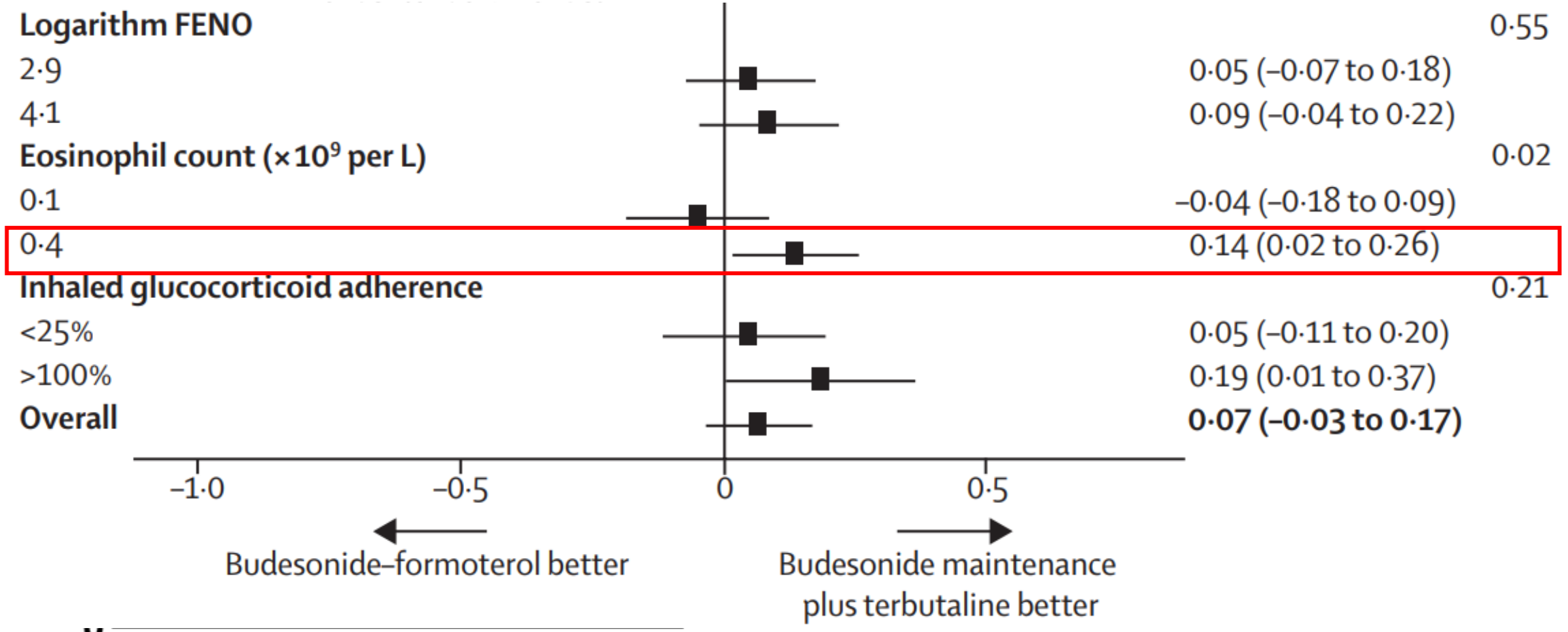


Bateman ED Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017.

N Engl J Med 2018; 378:1865-1876 (SYGMA 1) Lancet 2019; 394: 919–28

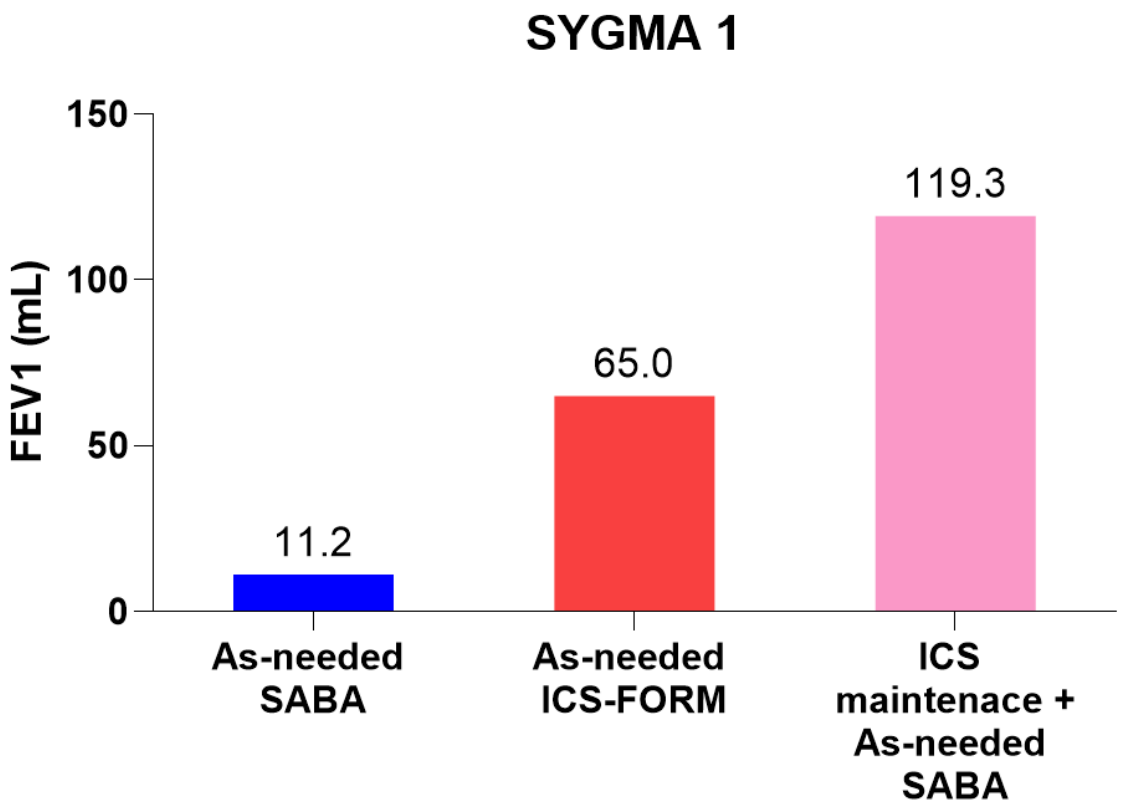
Track 2 vs Track 1

Symptom control (From PRACTICAL study)

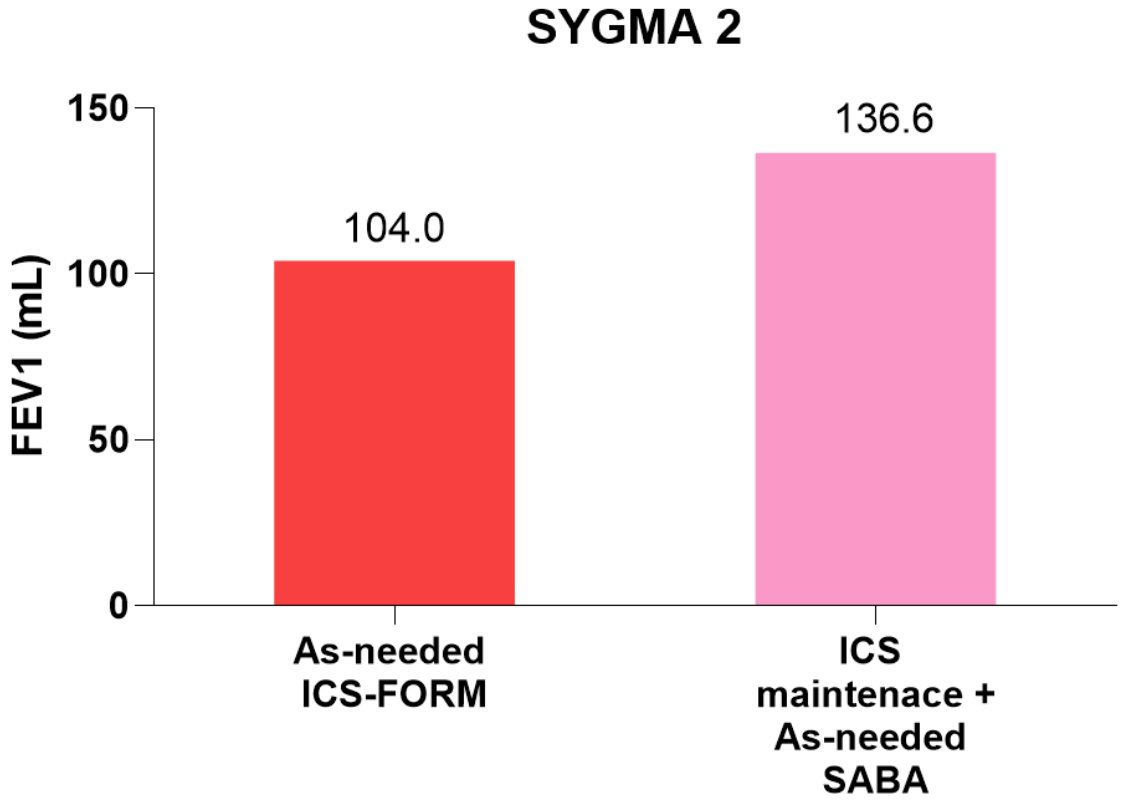


Lancet 2019; 394: 919–28

Lung function



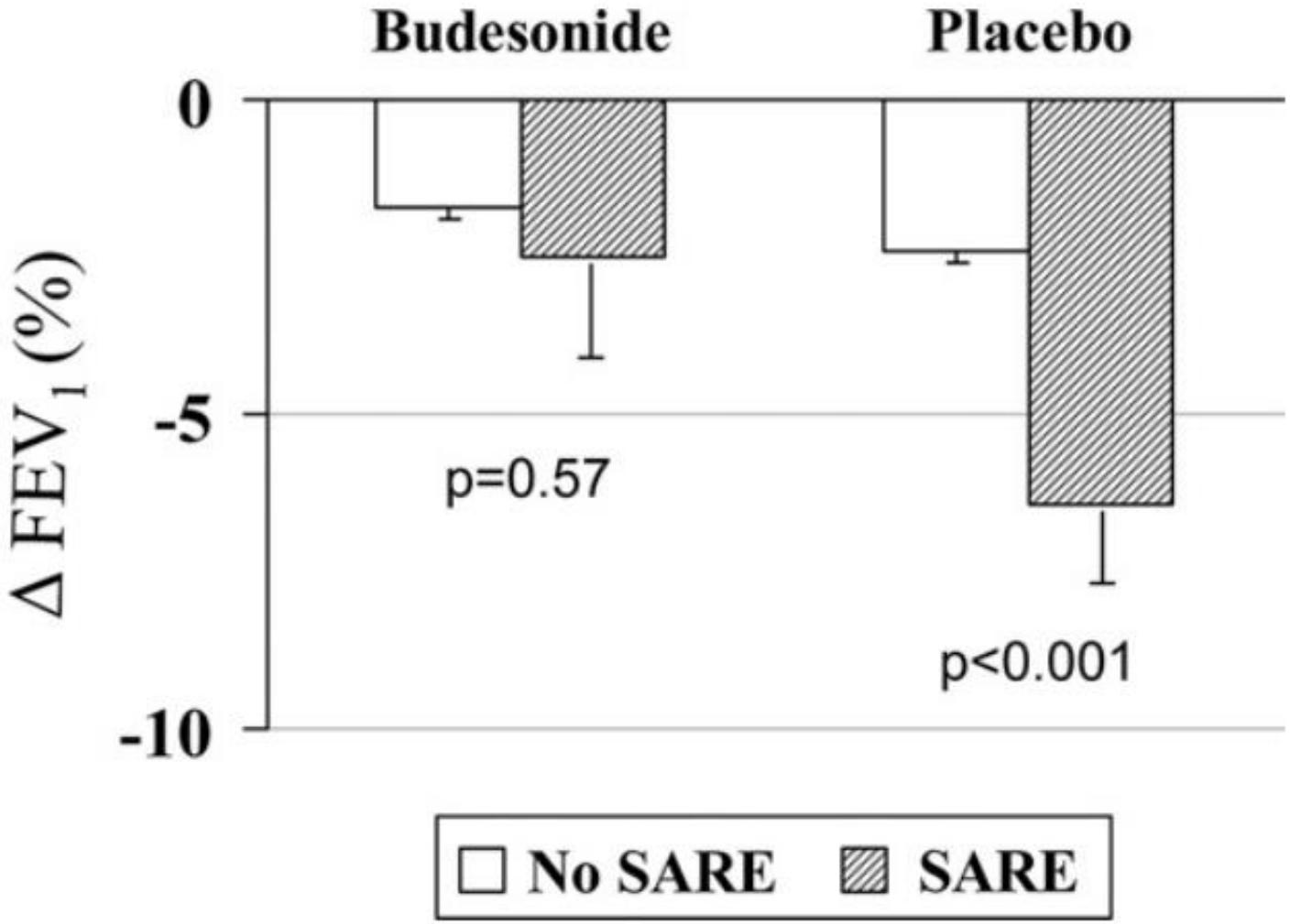
54.3 mL
95% CI (29.8 to 78.8)
P-value <0.001



32.6 mL
95% CI (11.4-53.7)
P-value = 0.003

Bateman ED Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017.

Lung function: Role of ICS maintenance in mild asthma



Am J Respir Crit Care Med Vol 179. pp 19–24, 2009

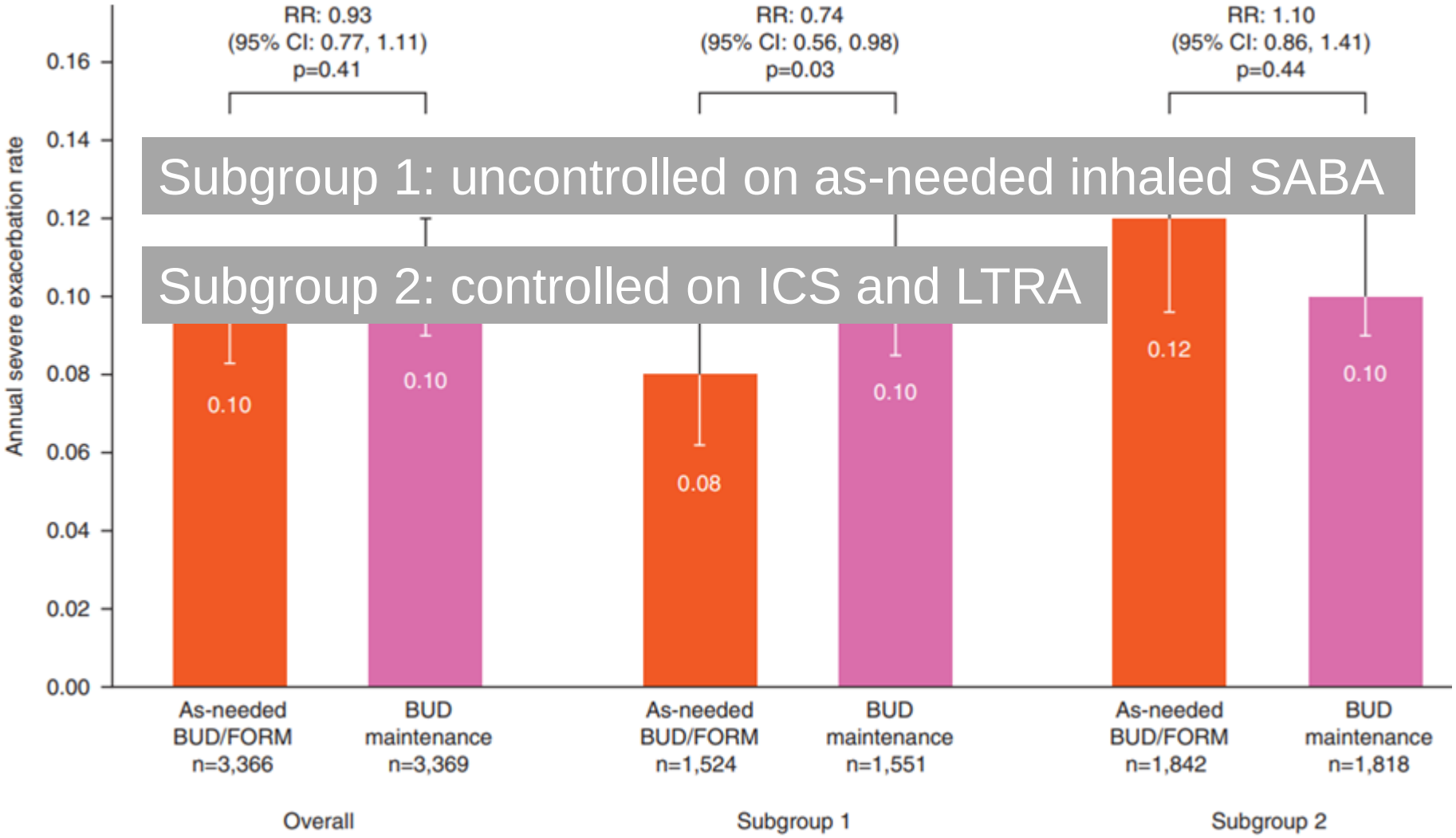
Track 2 vs Track 1

Severe exacerbations: Time of ICS use

Symptoms control: Track 2

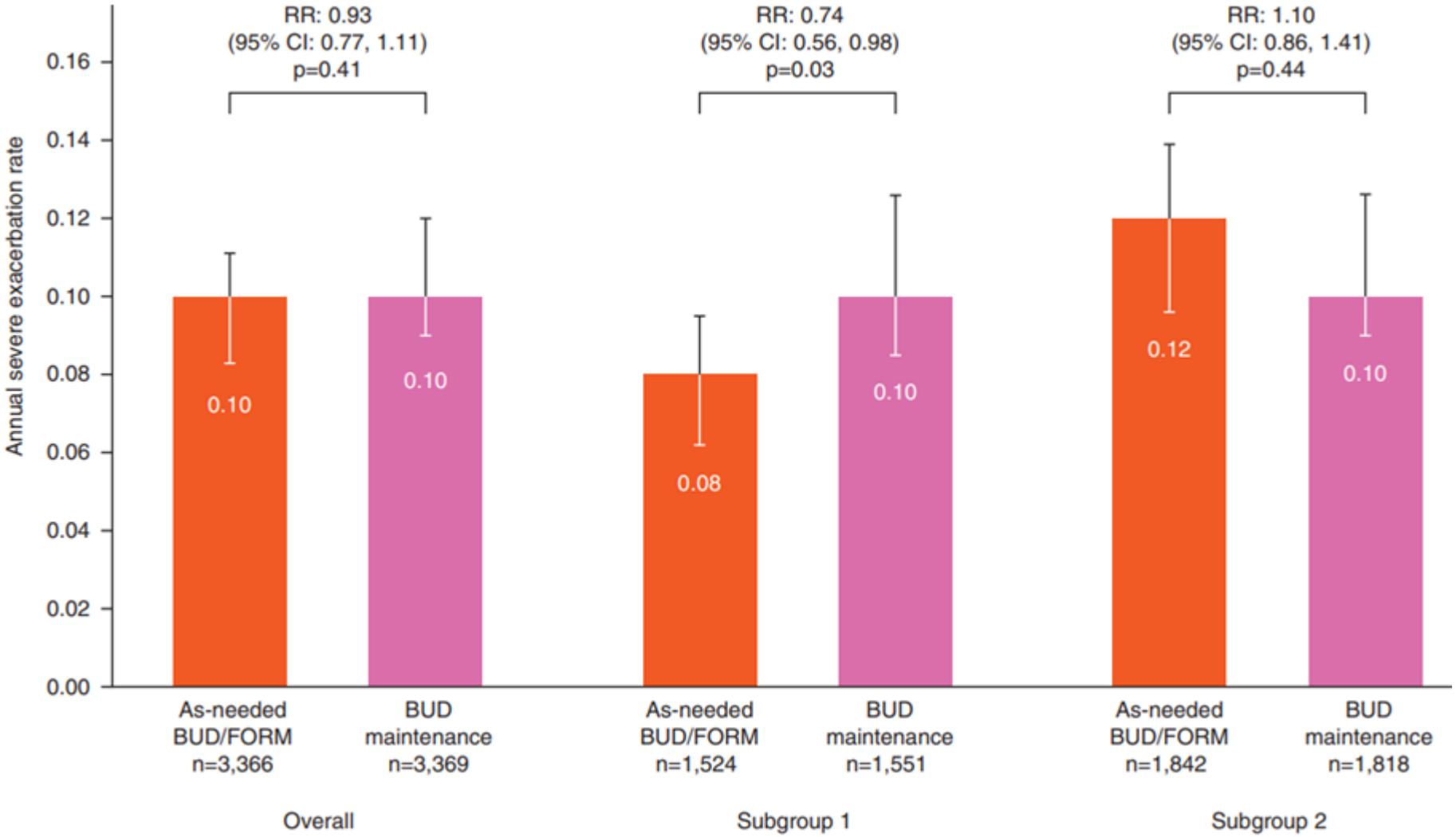
Lung function: Track 2

Severe exacerbation (Pooled analysis of SYGMA 1 and 2)



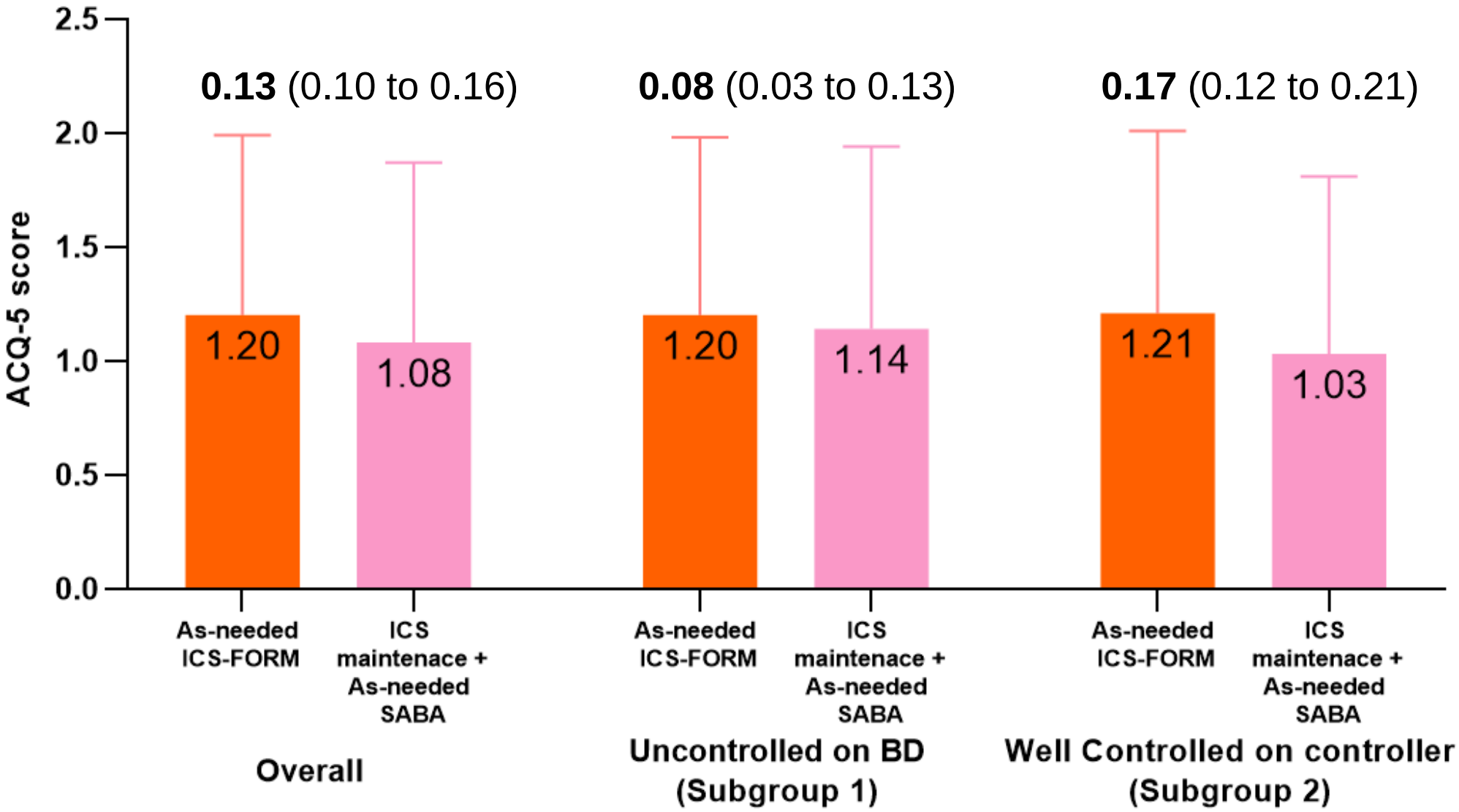
Bateman ED Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017. doi: 10.1513/AnnalsATS.202011-1386OC

Severe exacerbation (Pooled analysis of SYGMA 1 and 2)



Bateman ED Ann Am Thorac Soc. 2021 Dec;18(12):2007-2017. doi: 10.1513/AnnalsATS.202011-1386OC

Symptom control



Lung function

	Overall		Well Controlled on ICS or LTRA (*Subgroup 2*)	
	As-needed BUD–FORM	BUD Maintenance + As-needed Terbutaline	As-needed BUD–FORM	BUD Maintenance + As-needed Terbutaline
Lung function				
N	3,257	3,242	1,792	1,756
Pre-bronchodilator FEV_1% predicted, change from baseline to treatment average (95% CI)*	2.7 (2.4 to 3.1)	4.0 (3.7 to 4.3)	3.2 (2.8 to 3.7)	4.6 (4.2 to 5.1)
Difference (95% CI)*	—	−1.3 (−1.7 to −0.8)	—	−1.4 (−2.0 to −0.8)
P value	—	$P < 0.001$	—	$P < 0.001$

Track 2 → Track 1

Well controlled disease and Good adherence

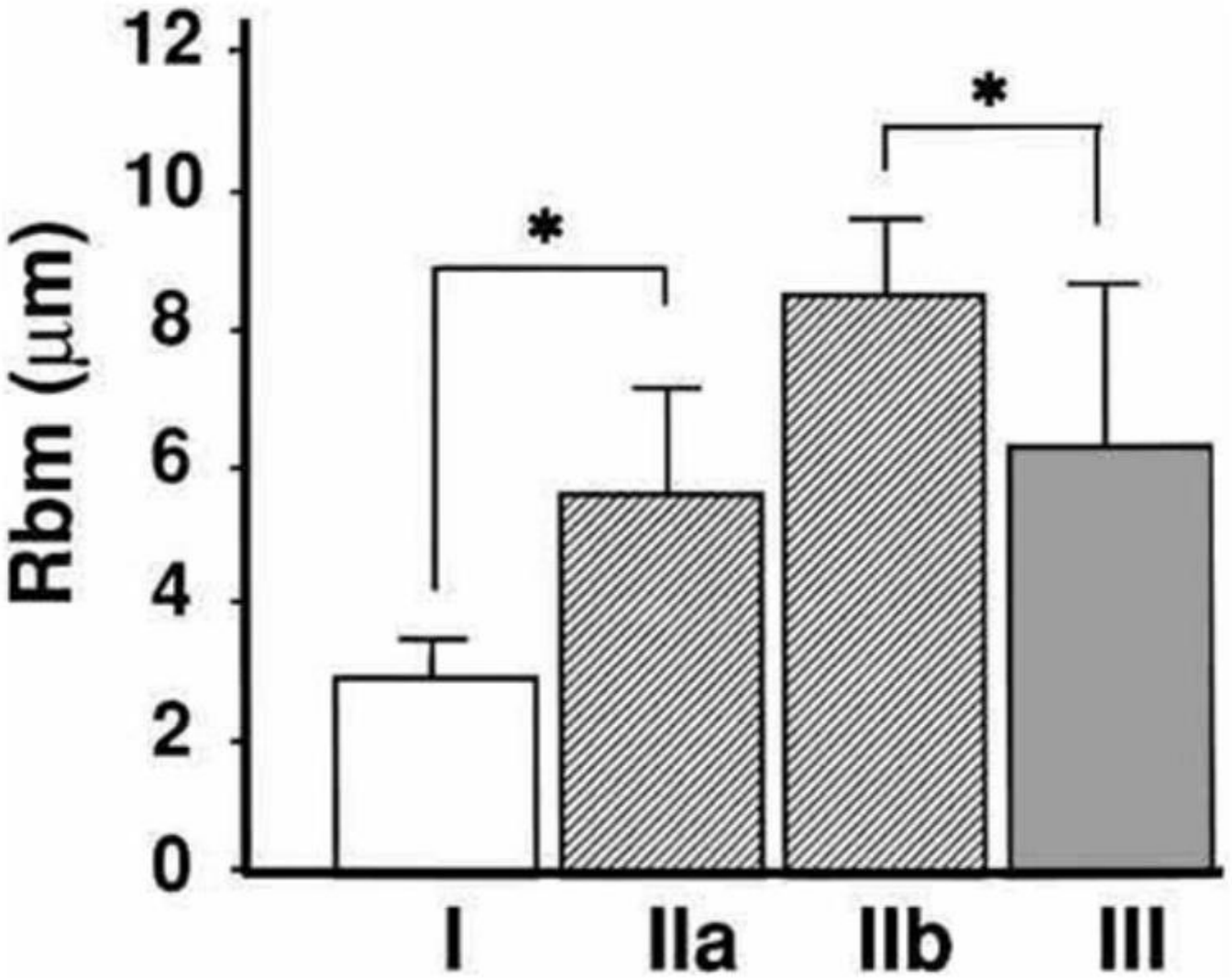
Severe exacerbations: no difference

Symptoms control: bad

Lung function: bad

Timing of ICS use < Total ICS dose

Airway remodeling in mild asthma



Group 1: healthy control subjects

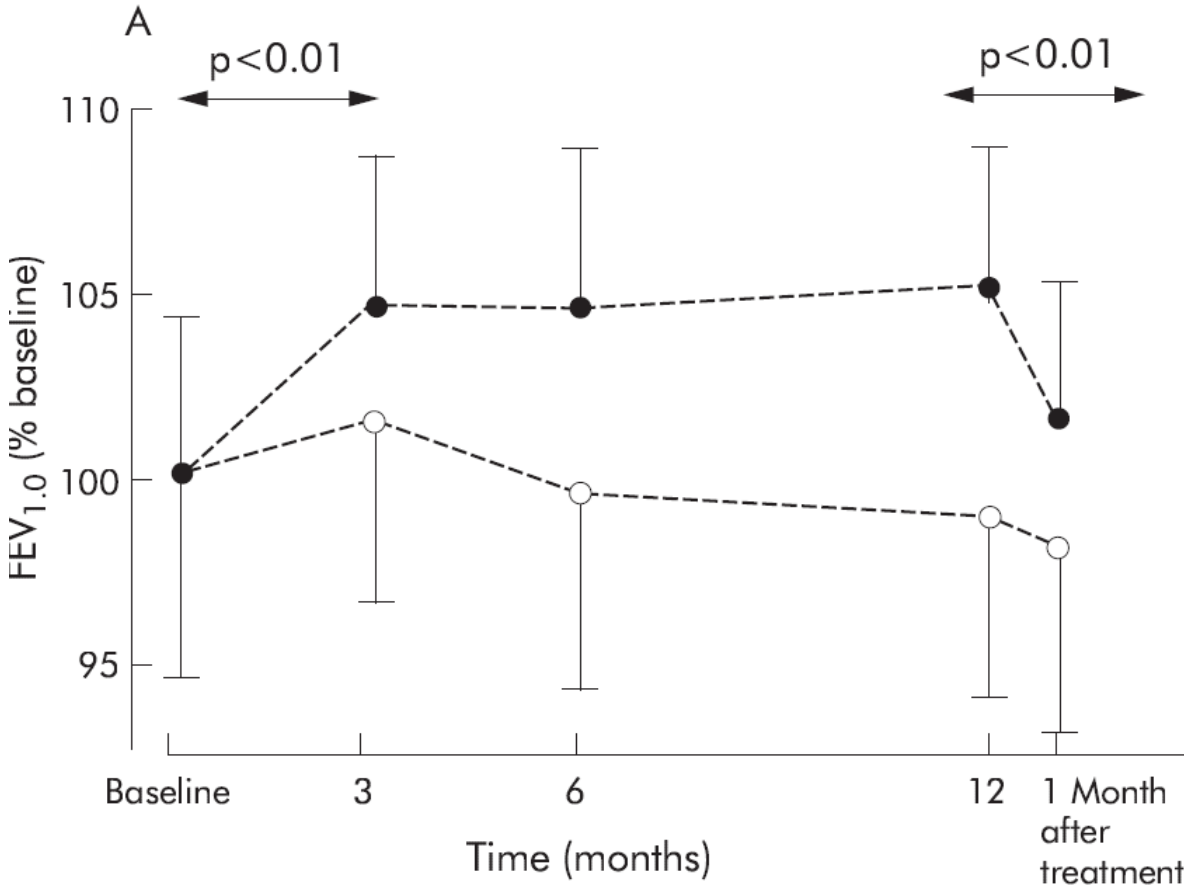
Group IIa: mild asthma (<12 months)

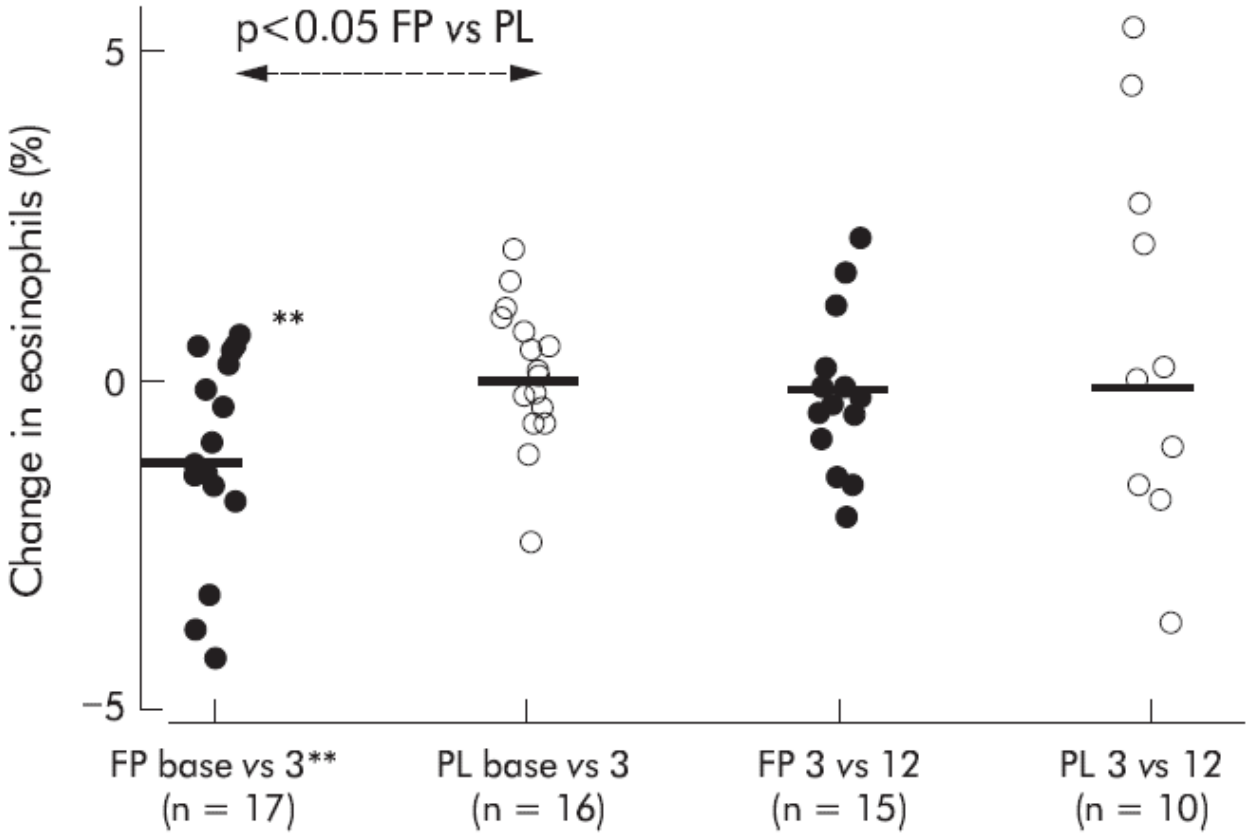
Group IIb: mild asthma (>12 months)

Group III: mild to moderate asthma treated with inhaled corticosteroids

CHEST 2002; 122:1622–1626

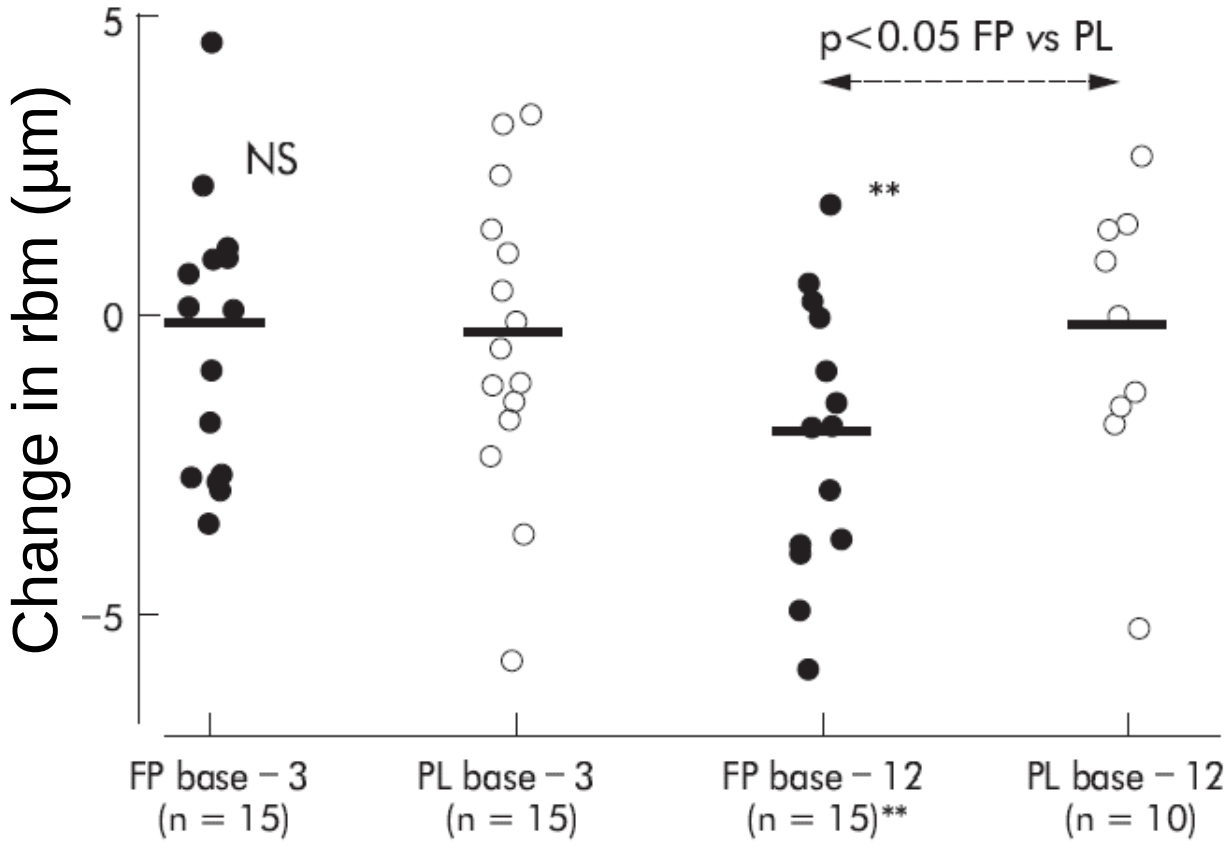
Role of ICS maintenance in Airway remodeling





Thorax 2002;57:309–316

Role of ICS maintenance in Airway remodeling



Thorax 2002;57:309–316

Track 1: Symptoms driven treatment

Perception of symptom

:may be affected by age, sex, smoking, airway inflammation, obese patients

Low symptom perception >> under treatment

Smoker, Old age, Airway inflammation, (Korean??)

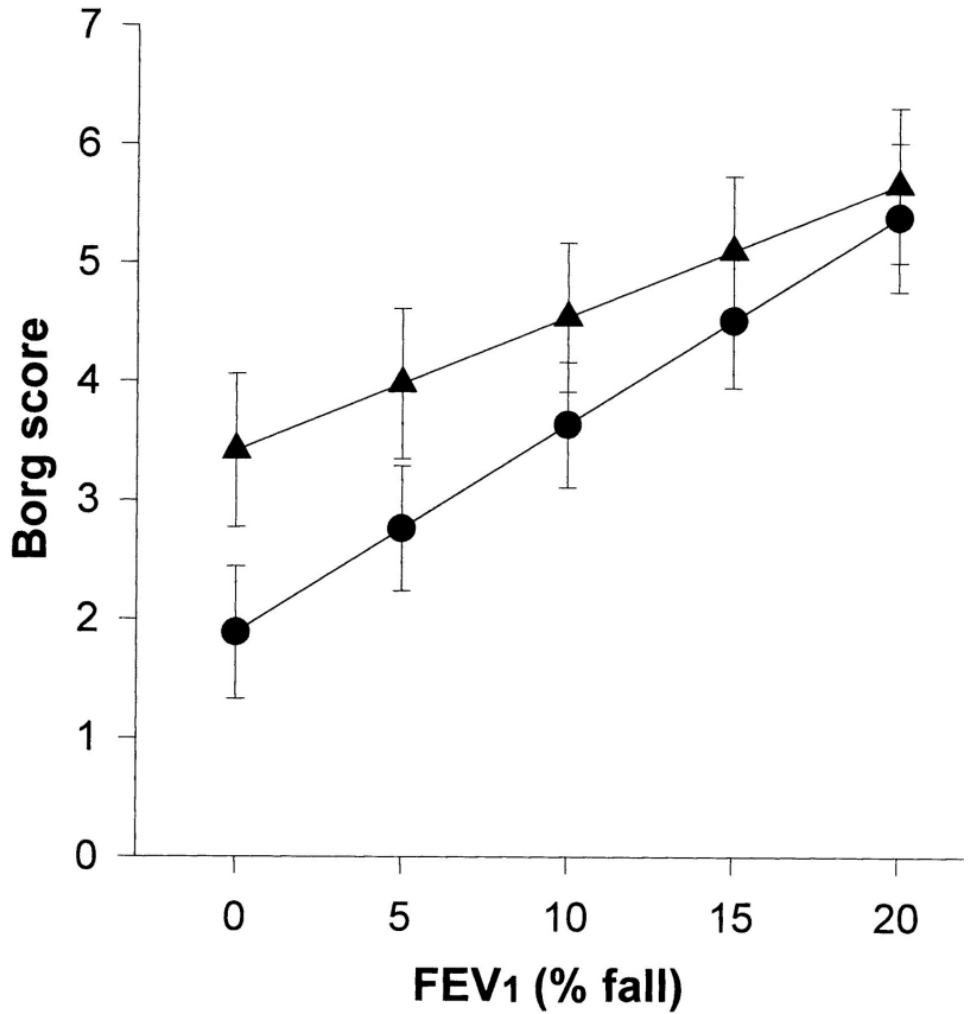
High symptom perception >> over treatment

Psychological disorder (panic, anxiety), Obese

J Allergy Clin Immunol2019;144:1180

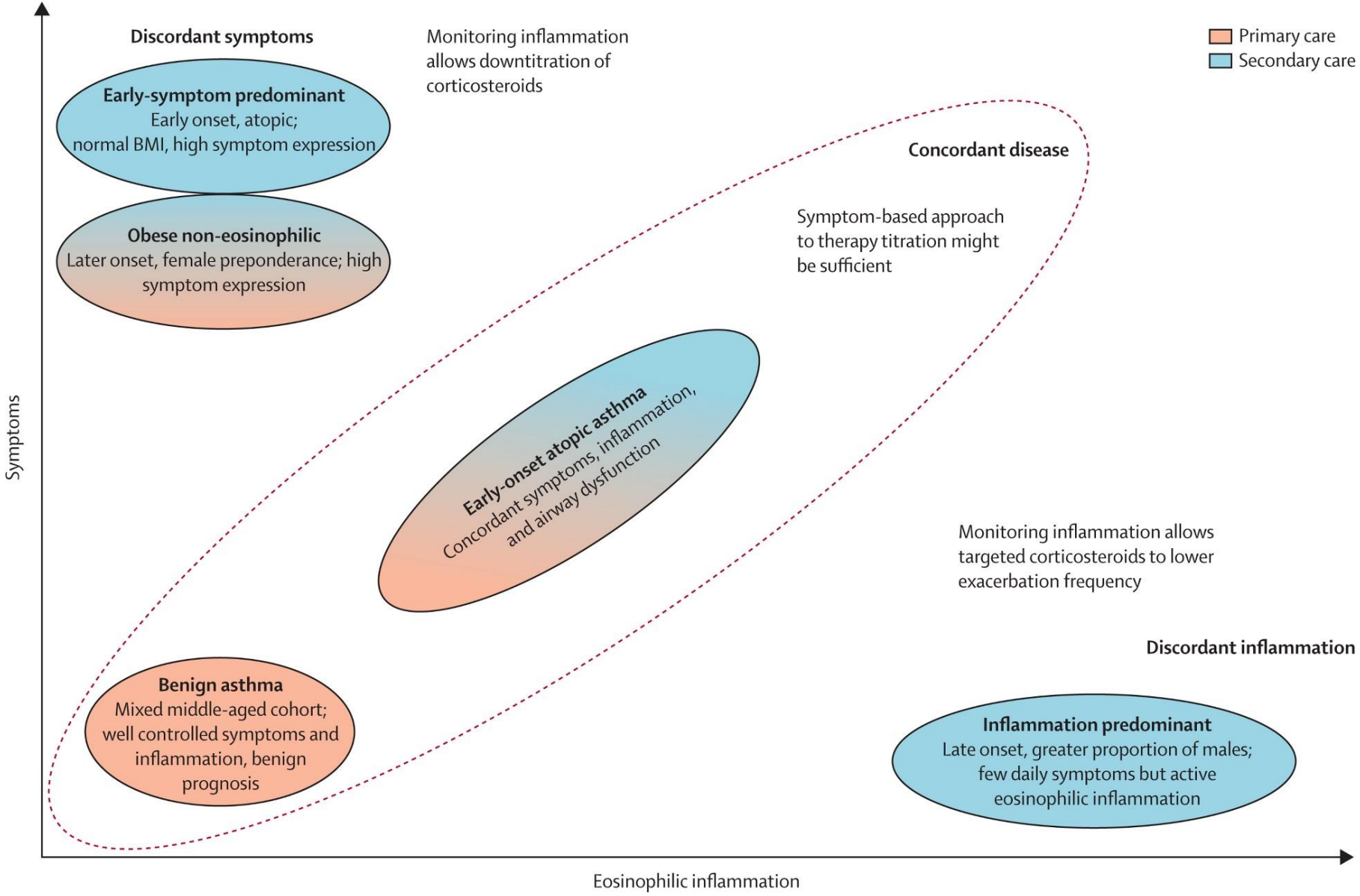
Effect of Budesonide on the Perception of Induced Airway Narrowing in Subjects with Asthma

CHERYL M. SALOME, HELEN K. REDDEL, SANDRA I. WARE, ALYSON M. ROBERTS, CHRISTINE R. JENKINS, GUY B. MARKS, and ANN J. WOOLCOCK†



Am J Respir Crit Care Med. 2002 Jan 1;165(1):15-21.

Discordance between symptoms and inflammation



Martinez, Lancet 2013; 382: 1360–72

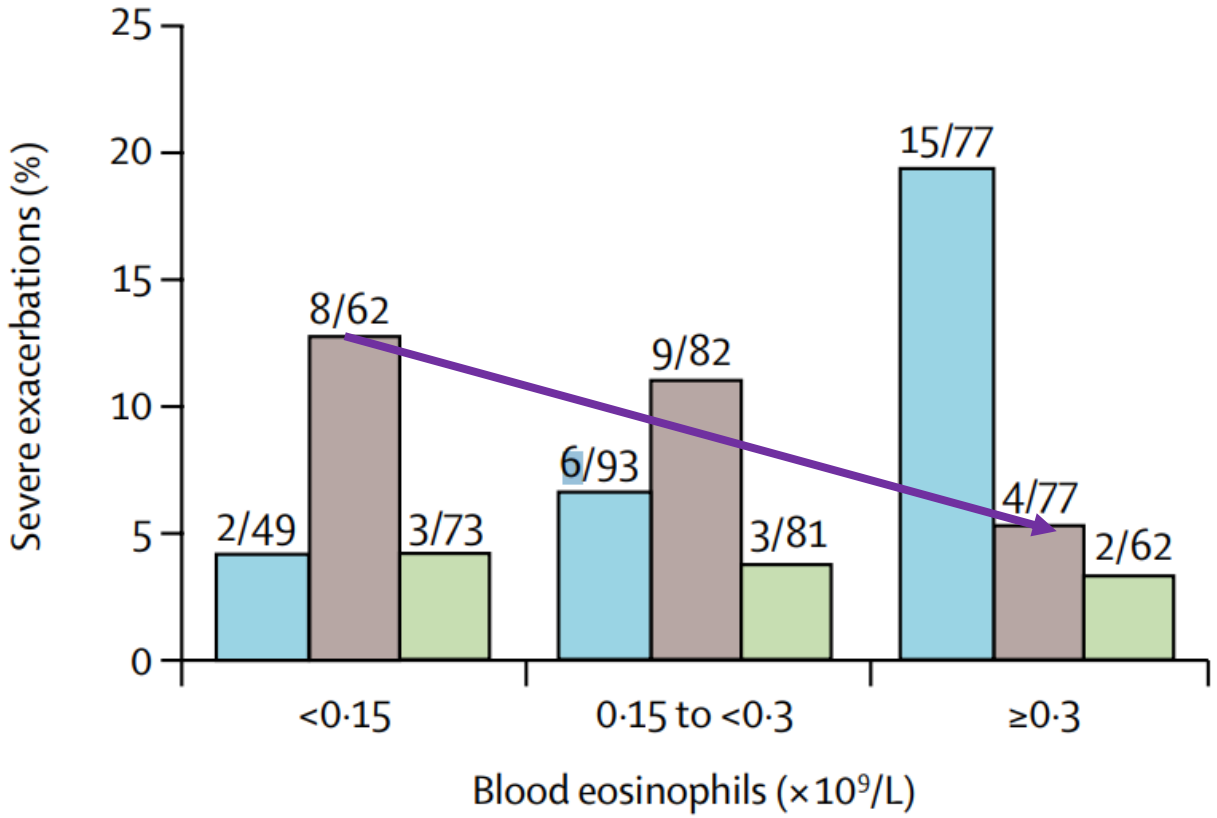
Other considerations for as-needed ICS-formoterol in Step 2

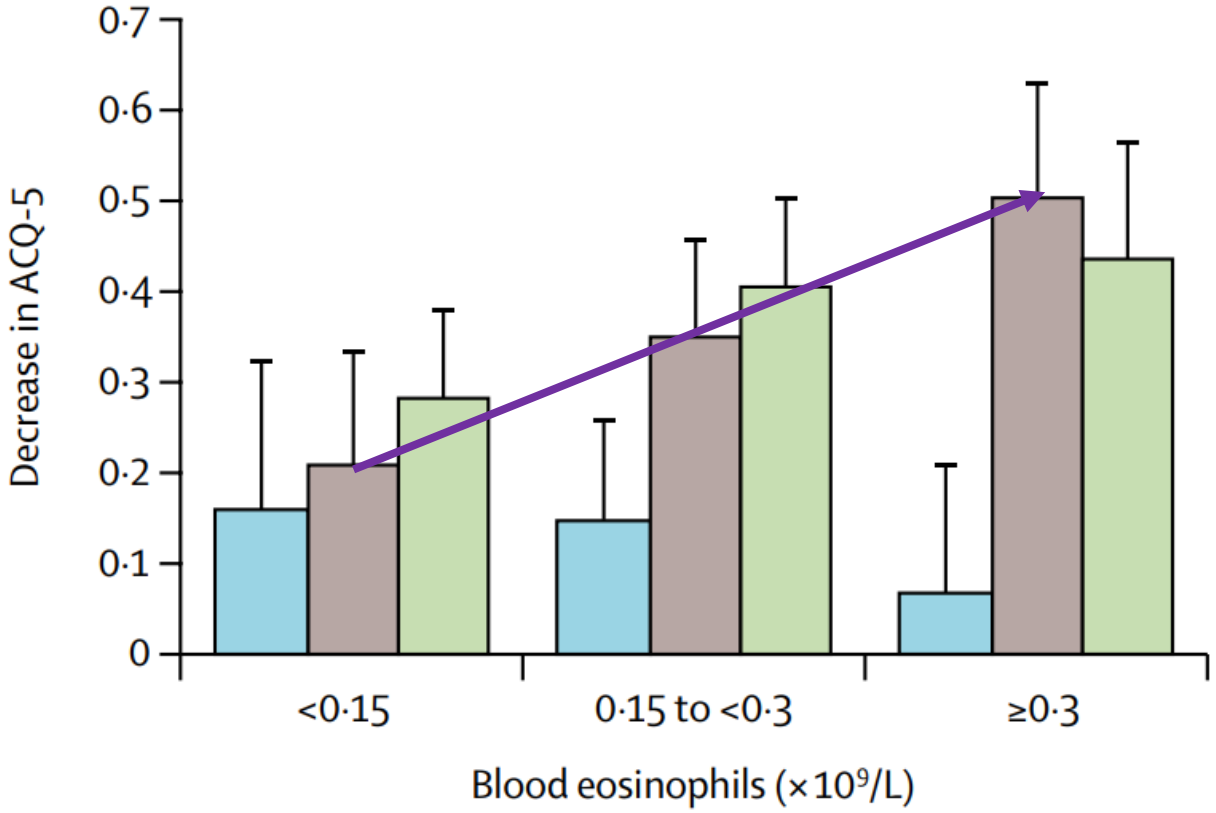
- Severe exacerbations can occur in mild asthma and are often unpredictable
  - Viral infections, allergen exposure, air pollution, stress
- ICS are highly effective in mild asthma, but patients are often poorly adherent
- Even occasional short courses of OCS are associated with increased risk
  - Osteoporosis, diabetes, cataract etc *(Price, J Asthma Allergy 2018)*
- Differences in symptom control and lung function were not clinically important
  - Primary outcome variable of one study *(O'Byrne NEJMed 2018)* was 'well-controlled asthma weeks', but this outcome was not considered reliable as it was based on an earlier concept of asthma control, and was systematically biased against the as-needed ICS-formoterol treatment group
- Phenotyping is not needed for treatment with as-needed ICS-formoterol
  - No significant difference in treatment effect compared with as-needed SABA or daily ICS with high vs low baseline eosinophils or FeNO *(Beasley NEJMed 2019; Hardy Lancet 2019)*

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SABA: short-acting $beta_2$-agonist

Phenotyping in mild asthma

Data from different treatment groups of Novel START trial





As-needed salbutamol

Maintenance budesonide and as-needed salbutamol

As-needed budesonide–formoterol

Lancet Respir Med 2020; 8: 671–80

Phenotyping in mild asthma

Data from different treatment groups of Novel START trial

	Exacerbation rate ratios (95% CI)			Severe exacerbation risk odds ratios (95% CI)		
	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$
Blood eosinophils count	..	..	0·014	..	..	0·009
High (≥0·3 × 10^9/L)	0·28 (0·12–0·63)	0·13 (0·05–0·33)	..	0·15 (0·03–0·79)	0·11 (0·03–0·45)	..
Low (<0·15 × 10^9/L)	0·63 (0·27–1·44)	1·15 (0·51–1·28)	..	1·42 (0·19–10·50)	5·72 (0·97–33·60)	..
p value (high *vs* low)	0·18	0·0006	..	0·10	0·0007	..

$p_{interaction}$ refers to the interaction between any treatment effect and the biomarker status. p values between treatment comparisons were only considered further if this interaction was significant. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

Table 3: Exacerbation and severe exacerbation interaction analysis for the change in treatment effect for treatments containing budesonide compared with as-needed salbutamol

Blood eosinophil counts ≥ 300/uL

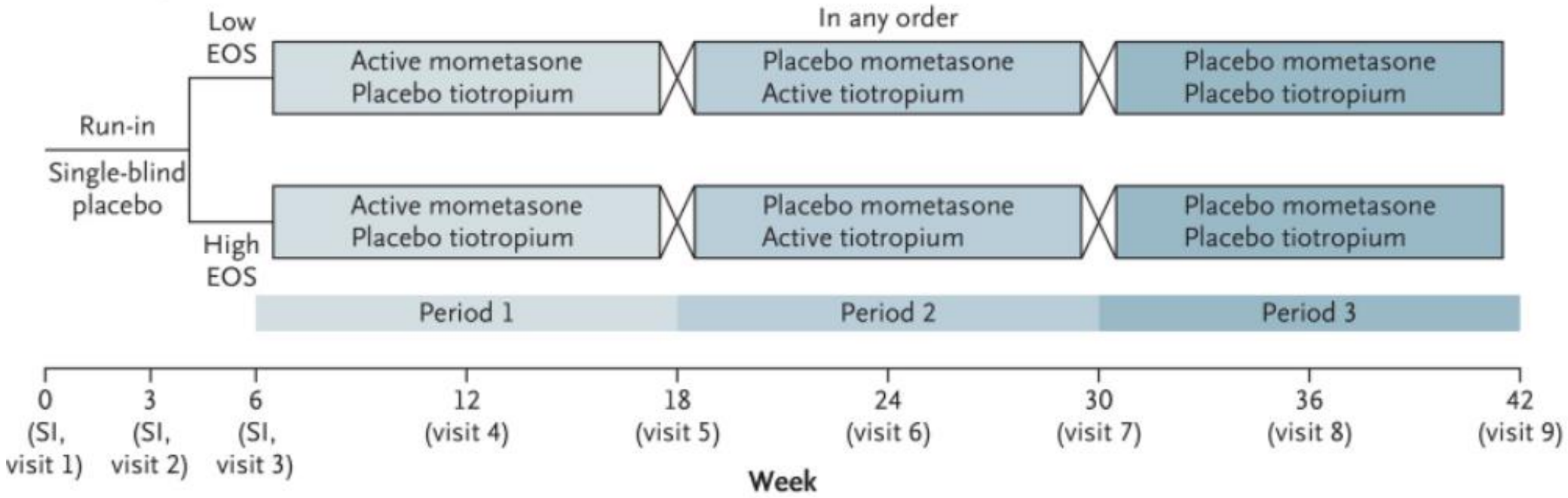
- As-needed salbutamol
- Maintenance budesonide and as-needed salbutamol ★
- As-needed budesonide–formoterol

Lancet Respir Med 2020; 8: 671–80

ORIGINAL ARTICLE

Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

Trial Design



N Engl J Med 2019;380:2009-19

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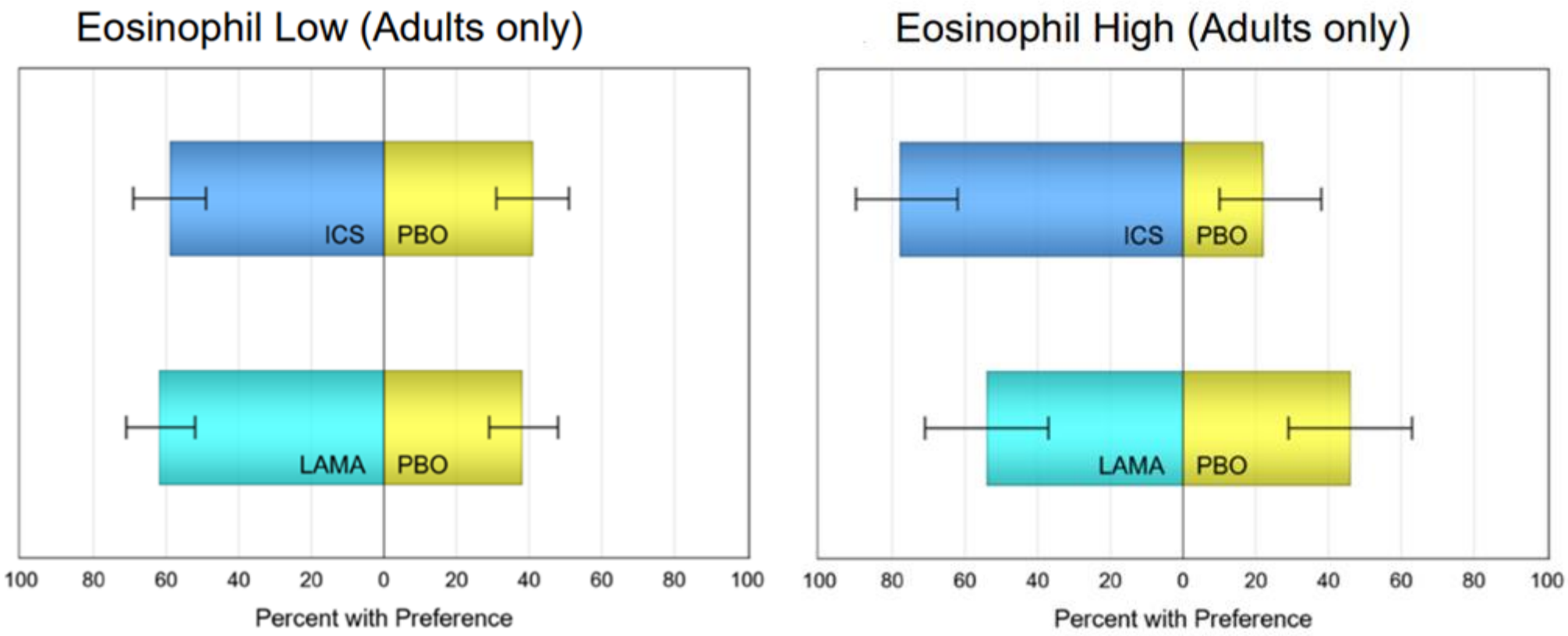


N Engl J Med 2019;380:2009-19

Phenotyping in mild asthma

Poor perception of symptom

Discordance between symptoms and inflammation

High eosinophil >> **Track 2**

Contents

Moderate to severe asthma: step 3-4

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

RELIEVER: As-needed low-dose ICS-formoterol

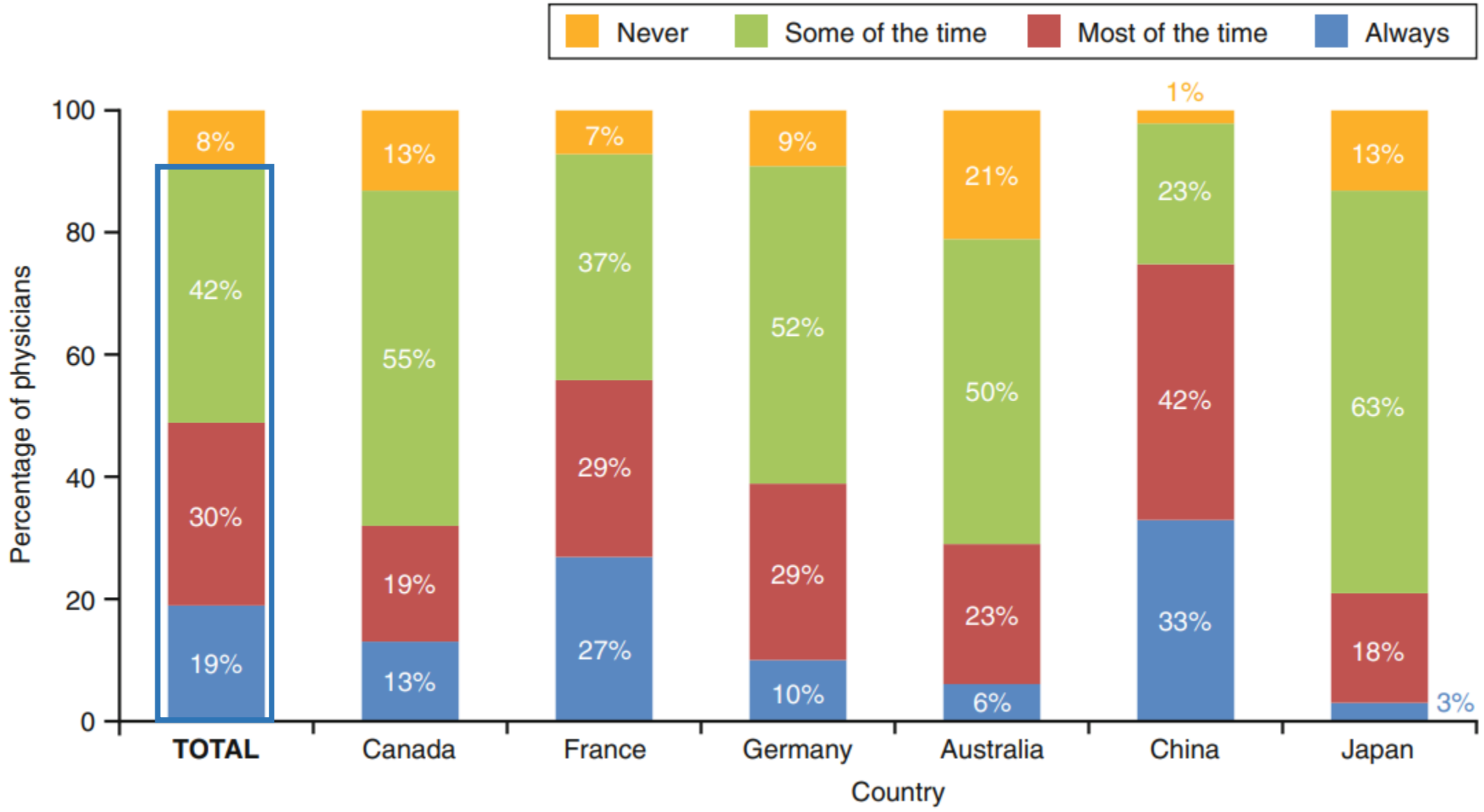
CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 3
Low dose maintenance ICS-LABA

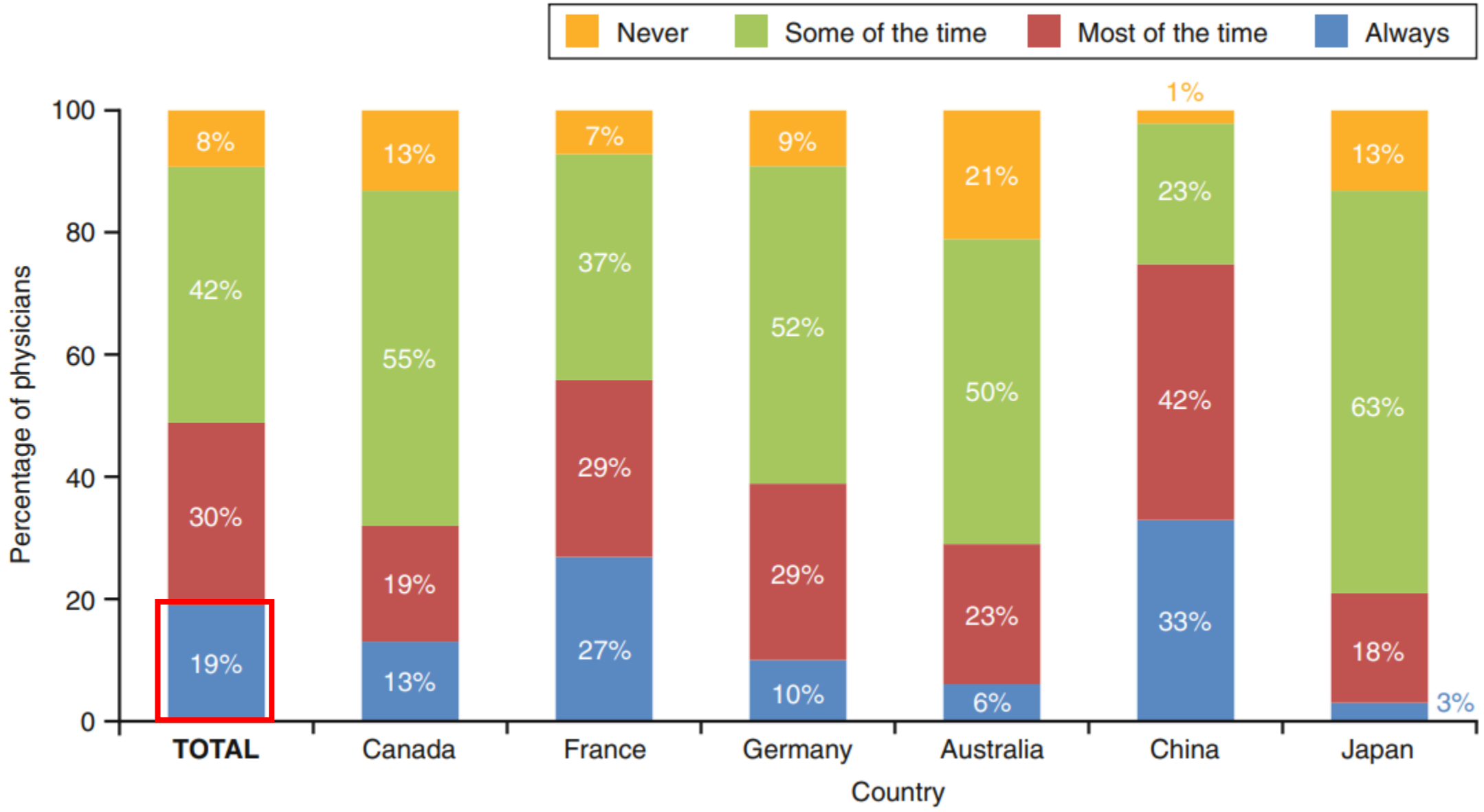
STEP 4
Medium/high dose maintenance ICS-LABA

RELIEVER: As-needed short-acting β2-agonist

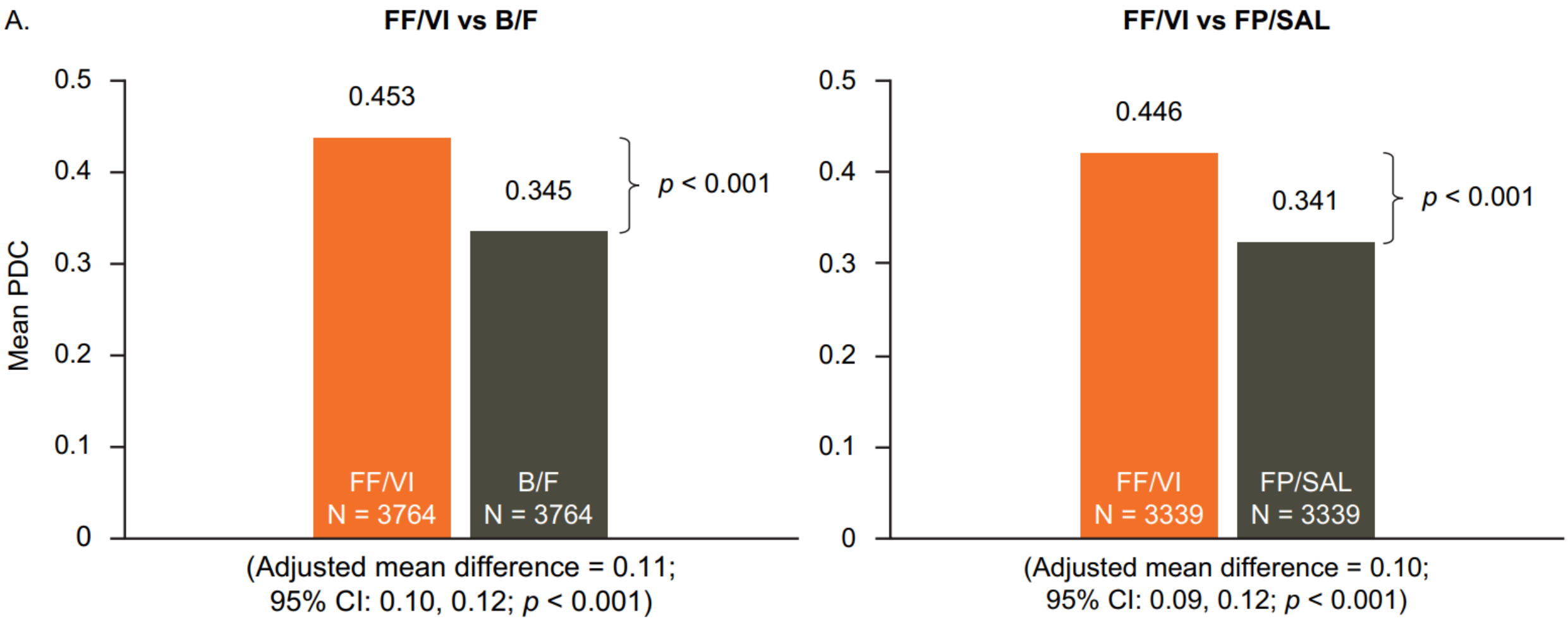
Prescription of SABAs in addition to MART



Prescription of SABAs in addition to MART



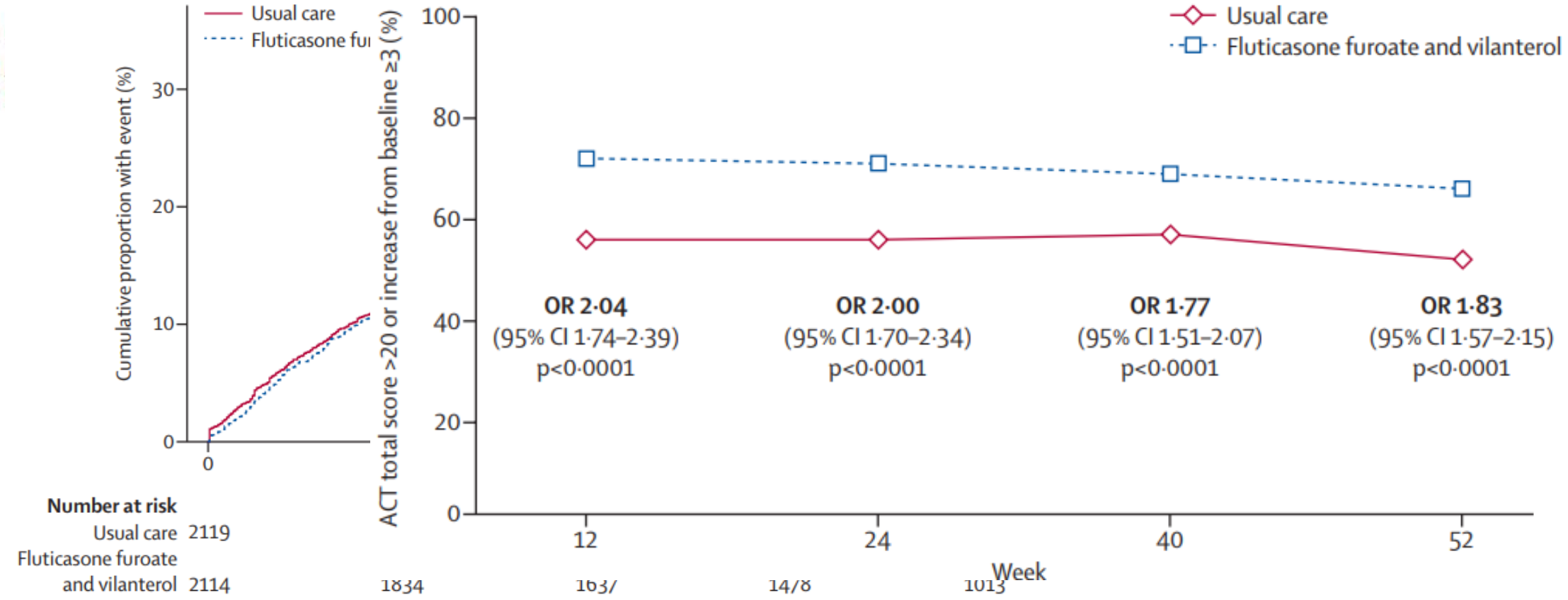
Once daily ICS/LABA



*proportion of days covered (PDC)

Once daily ICS/LABA

Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial



Moderate to severe asthma: step 5

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEP 5

Add-on LAMA

Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R

Consider high dose ICS-formoterol

RELIEVER: As-needed low-dose ICS-formoterol

No evidence of MART + LAMA

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 5

Add-on LAMA

Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R

Consider high dose ICS-LABA

RELIEVER: As-needed short-acting β2-agonist

Once daily SITT

MF/GLY/IND (Enerzair®, Novartis)

F/UMEC/VI (Trelegy®, GSK)

Summary

Choice of Track

Goals of asthma management

Perception of symptom

Phenotyping in mild asthma

Change of Track

Well controlled and good adherence

Conclusion

Low rate of SABA use in KOREA

Efficacy of ICS maintenance

Asthma Management:
Track 2. ICS + non-formoterol SABA

경청해 주셔서 감사합니다.