천식 환자에서 ICS는 끊으면 안 된다

: pro

2019. 7. 13.

이 창 훈

끊다 [끈타] ★★

[동사]

1. 실, 줄, 끈 따위의 이어진 것을 잘라 따로 떨어지게 하다.
2. 관계를 이어지지 않게 하다.
3. 하던 일을 하지 않거나 멈추게 하다.

[유의어] 그만두다, 발급하다, 사다

"천식 환자에서 ICS를 쓰다가 중단하면?"

P 천식 환자 에서

I ICS를 쓰다가 중단 하면

C ICS를 계속 투여 한 경우와 비교해서

O 천식 조절, 증상
기도과민성
폐기능
급성악화

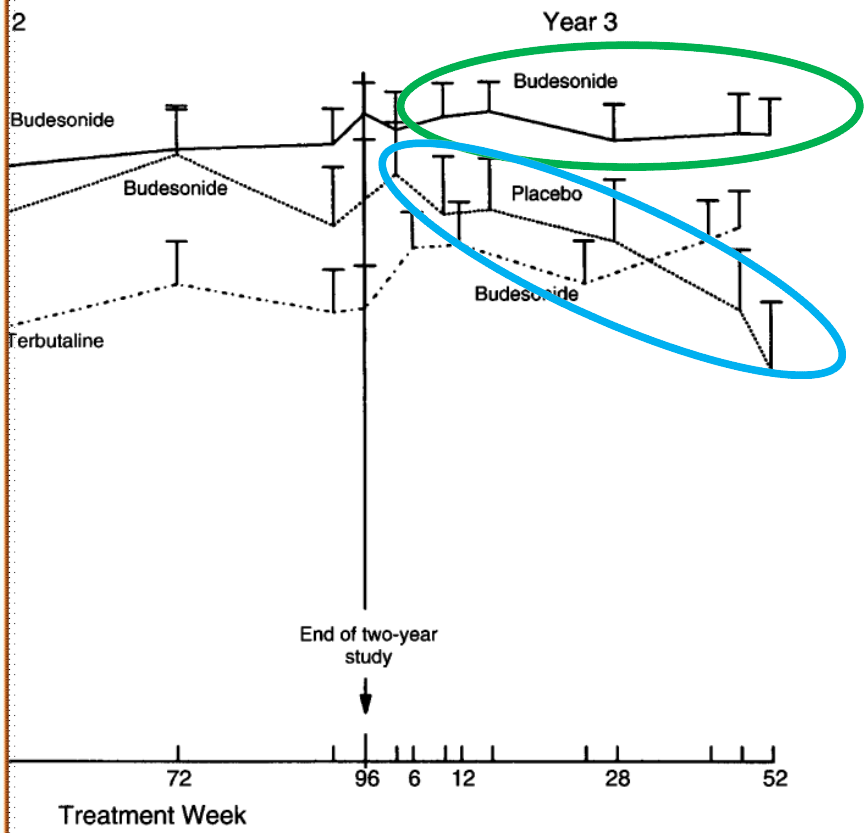
?

ICS 중단 ⇨ PC15, FEV1, PEF⇩ Sx

RCT. Newly diagnosed generally mild asthma pts. (FEV1, FVC ≥ 80%) (**N=74**)
BUD 600μg bid for 2yr → (1) Double-blind RCT: BUD 200μg bid (n=19) *vs* PLA (n=18)
Terbutaline for 2yr → *(2) Open-label: BUD 1,200μg/d.*
Outcome: **FEV1, FVC, PC15**

Table 2. Changes in Lung Function and Diary-Card Data during the Third Year of the Study.*

Variable	Double-Blind Budesonide, 400 μg/day (N = 19)	Double-Blind Placebo (N = 18)	Open-Label Budesonide, 1200 μg/day (N = 37)
FVC (liters)			
Base line	4.12±0.19	3.92±0.19	3.84±0.12
Change	+0.01±0.05	−0.16±0.09	−0.03±0.07
FEV$_1$ (liters) *			
Base line	3.31±0.14	3.16±0.16	3.02±0.10
Change	+0.01±0.04†	−0.25±0.09‡	+0.05±0.05
PC$_{15}$ (dose steps)			
Base line	5.0±0.3	4.7±0.4	3.7±0.3
Change *	±0.0±0.2§	−1.5±0.6¶	+0.5±0.3
Morning PEF (liters/min)			
Base line	487±19	481±20	438±11
Change	−5±7§	−22±6‖	+15±5‡
Evening PEF (liters/min)			
Base line	491±18	482±21	449±12
Change	−6±7	−13±5¶	+6±4
Asthma-symptom score			
Base line	1.2±0.3	1.8±0.4	2.4±0.3
Change	+0.2±0.2	+0.5±0.2¶	−0.6±0.2‡
Terbutaline dose (puffs/day)			
Base line	0.6±0.3	0.7±0.4	0.9±0.3
Change	+0.8±0.6	+1.6±1.0	−0.4±0.2‡



Haahtela T. N Engl J Med 1994;331:700.

ICS 중단 ⇨ PEF⇩

Double-blind RCT (BEST).

Mild persistent asthma pts (>6mo) **controlled during run-in (BDP 500μg/d 4wk)** (**N=466**)

BDP 250μg/AL prn *vs* AL prn *vs* BDP 250μg bid + AL prn *vs* BDP 250μg/AL bid+prn for 6mo.

Primary outcome: **morning PEF**.

	Value	Difference (95% CI)	P Value
Morning PEF (liters/min)			
As-needed combination	442.75±9.68	9.47 (0.83 to 18.11)	0.03
As-needed albuterol	428.52±10.49	−2.49 (−11.40 to 6.42)	
Regular beclomethasone	433.08±10.83	11.96 (2.96 to 20.97)	0.009
Regular combination	435.18±9.55	−1.36 (−10.13 to 7.42)	

Papi A. N Engl J Med

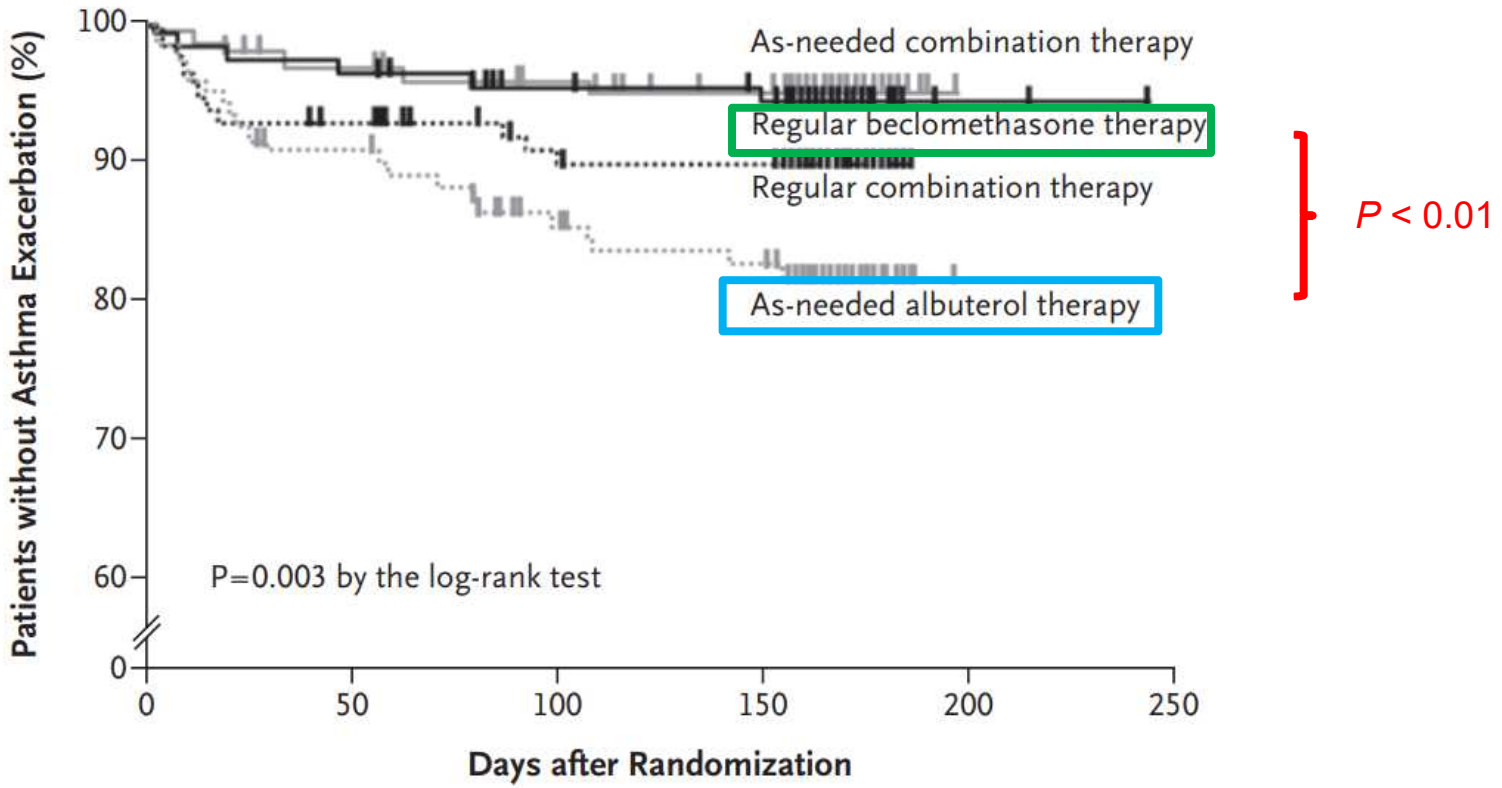
ICS 중단 ⇨ AE⇧

Double-blind RCT (BEST).

Mild persistent asthma pts (>6mo) **controlled during run-in (BDP 500μg/d 4wk)** (**N=466**)

BDP 250μg/AL prn *vs* AL prn *vs* BDP 250μg bid + AL prn *vs* BDP 250μg/AL bid+prn for 6mo.

Primary outcome: **morning PEF**.



Papi A. N Engl J Med

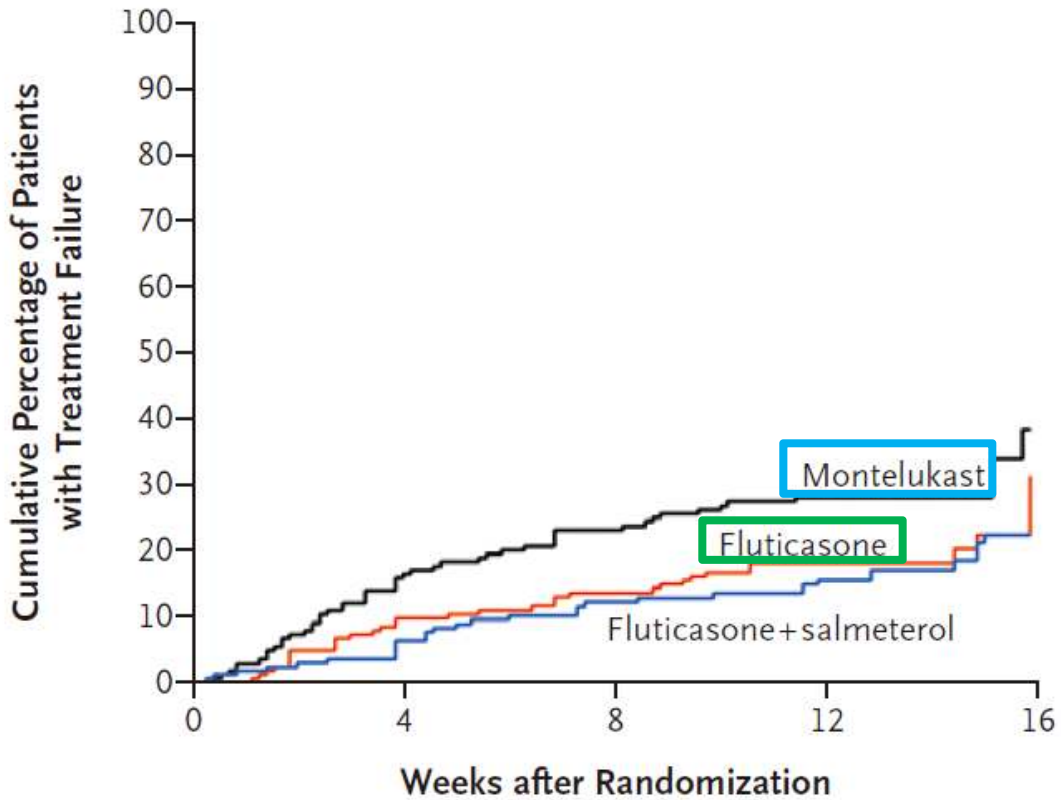
ICS 중단, LTRA ⇨ 치료실패⇧

Double-blind RCT. BA pts **well-controlled by FP 100μg bid** (**N=500**)

FP 100μg bid *vs* montelukast 5-10mg qd *vs* FP 100μg / SAL 50μg qd for 16wk.

Primary outcome: **time to treatment failure**.

Exacerbation, ICS↑, SABA↑ , FEV1 ↓, PEF ↓, …



HR, 1.6
(95% CI, 1.1-2.6)

American Lung Association Asthma Clinical Research Centers. N Engl J Med 2007;356:2027.

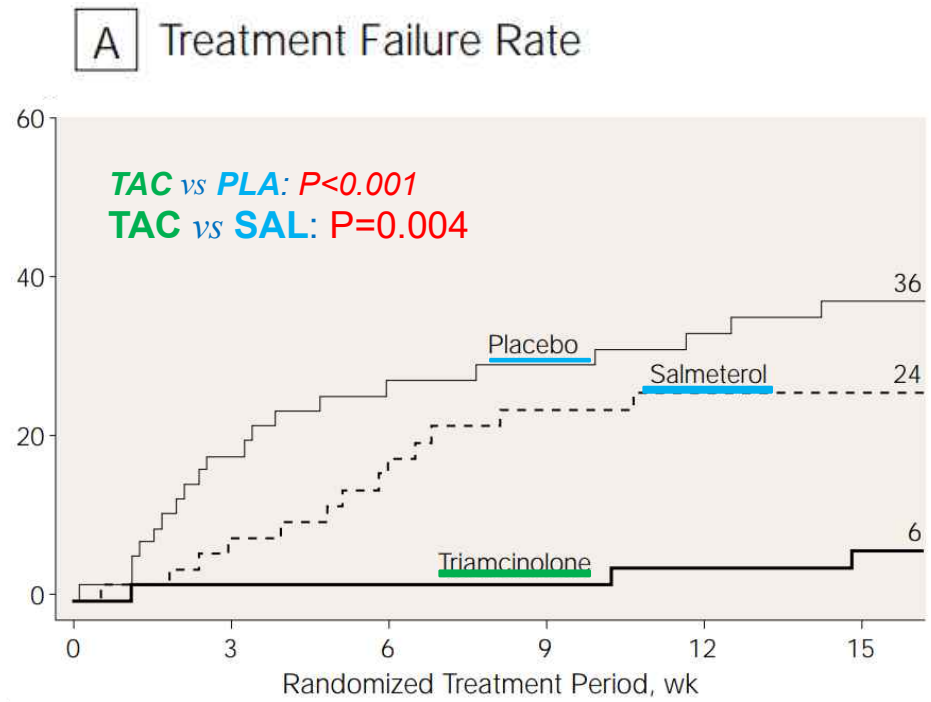
ICS 중단, LABA 치료실패, AE

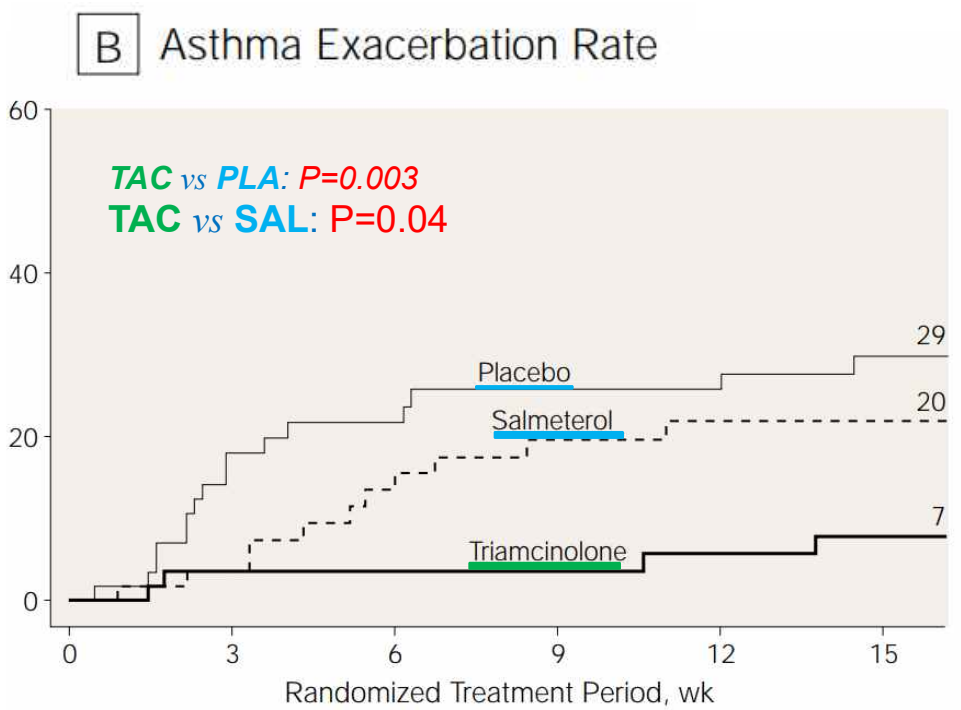
Double blind RCT (SOCS).

"well controlled"(FEV1>80%, PEF variability ≤20%) by TAC 400 μg/d (run-in 6 weeks) (N=164)

TAC 400 μg/d *vs* SAL *vs* PLA for 16 weeks.

Outcome: **PEF, FEV1, symptom scores, SABA use, treatment failure, AE, ...**





Lazarus SC. JAMA 2001;285:2583.

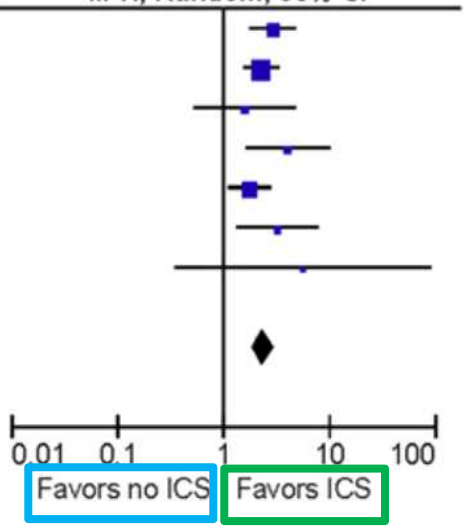
ICS 중단 ⇨ AE⇧, FEV1⇩

A

Study or Subgroup	Stopped ICS Events	Total	Continued ICS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Berger 2010	55	150	18	144	21.0%	2.93 [1.81, 4.74]
Condemi 1997	57	95	27	101	36.9%	2.24 [1.56, 3.22]
Hahhtela 1994	6	18	4	19	4.1%	1.58 [0.53, 4.70]
Lazaurs 2001	21	56	5	54	6.0%	4.05 [1.65, 9.97]
Martinez 2011	36	74	20	72	25.0%	1.75 [1.13, 2.72]
Papi 2007	21	119	6	110	6.4%	3.24 [1.36, 7.72]
Waalkens 1993	6	20	0	8	0.6%	5.57 [0.35, 88.77]
Total (95% CI)		**532**		**508**	**100.0%**	**2.35 [1.88, 2.92]**
Total events	202		80			

Heterogeneity: Tau² = 0.00; Chi² = 5.59, df = 6 (P = 0.47); I² = 0%

Test for overall effect: Z = 7.59 (P < 0.00001)

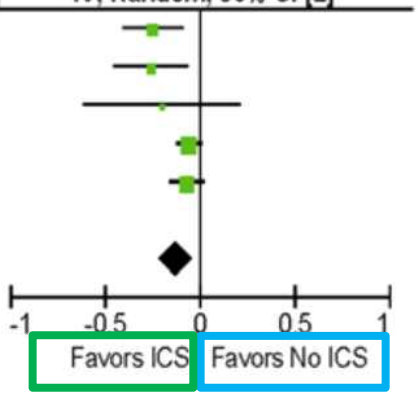


B

Study or Subgroup	no ICS Mean [L]	SD [L]	Total	ICS Mean [L]	SD [L]	Total	Weight	Mean Difference IV, Random, 95% CI [L]
Condemi 1997	-0.18	0.6	95	0.07	0.49	101	17.8%	-0.25 [-0.40, -0.10]
Hahhtela 1994	-0.25	0.38	18	0.01	0.17	19	13.5%	-0.26 [-0.45, -0.07]
Lazaurs 2001	-0.3	0.97	56	-0.1	1.2	54	3.9%	-0.20 [-0.61, 0.21]
Martinez 2011	0.04	0.19	74	0.1	0.19	72	35.4%	-0.06 [-0.12, 0.00]
Papi 2007	-0.03	0.23	119	0.04	0.42	110	29.4%	-0.07 [-0.16, 0.02]
Total (95% CI)			**362**			**356**	**100.0%**	**-0.13 [-0.21, -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 8.54, df = 4 (P = 0.07); I² = 53%

Test for overall effect: Z = 3.00 (P = 0.003)



Rank MA. J Allergy Clin Immunol 2013;131:724.

ICS 중단 ⇨ PEF⇩, Sx⇧

C

Study or Subgroup	no ICS Mean [L/min]	no ICS SD [L/min]	no ICS Total	ICS Mean [L/min]	ICS SD [L/min]	ICS Total	Weight	Mean Difference IV, Random, 95% CI [L/min]
Condemi 1997	-28	40	101	-6	39	95	20.1%	-22.00 [-33.06, -10.94]
Hahhtela 1994	-22	25	19	-5	31	18	15.4%	-17.00 [-35.21, 1.21]
Lazaurs 2001	-18	16	56	14	16	54	22.9%	-32.00 [-37.98, -26.02]
Martinez 2011	-17	42	74	-16	26	72	19.9%	-1.00 [-12.30, 10.30]
Papi 2007	-8	39	119	5	35	110	21.0%	-13.00 [-22.59, -3.41]
Waalkens 1993	-11	124	20	20	188	8	0.7%	-31.00 [-172.16, 110.16]
Total (95% CI)			**389**			**357**	**100.0%**	**-17.51 [-29.28, -5.75]**

Heterogeneity: $Tau^2 = 147.74$; $Chi^2 = 27.70$, df = 5 ($P < 0.0001$); $I^2 = 82\%$

Test for overall effect: $Z = 2.92$ ($P = 0.004$)

Mean Difference IV, Random, 95% CI [L/min]

-100 -50 0 50 100

Favors ICS | Favors no ICS

D

Study or Subgroup	no ICS Mean	no ICS SD	no ICS Total	ICS Mean	ICS SD	ICS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Condemi 1997	0.7	1.9	95	-0.1	1	101	27.0%	0.53 [0.24, 0.81]
Hahhtela 1994	0.5	0.8	18	0.2	0.9	19	5.2%	0.34 [-0.31, 0.99]
Lazaurs 2001	0.35	0.72	56	0.06	0.3	54	15.2%	0.52 [0.14, 0.90]
Martinez 2011	0.05	0.17	74	0.006	0.09	72	20.6%	0.32 [-0.01, 0.65]
Papi 2007	0.05	0.1	119	-0.33	1.4	110	32.0%	0.39 [0.13, 0.65]
Total (95% CI)			**362**			**356**	**100.0%**	**0.43 [0.28, 0.58]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.27$, df = 4 ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 5.69$ ($P < 0.00001$)

Std. Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Favors no ICS | Favors ICS

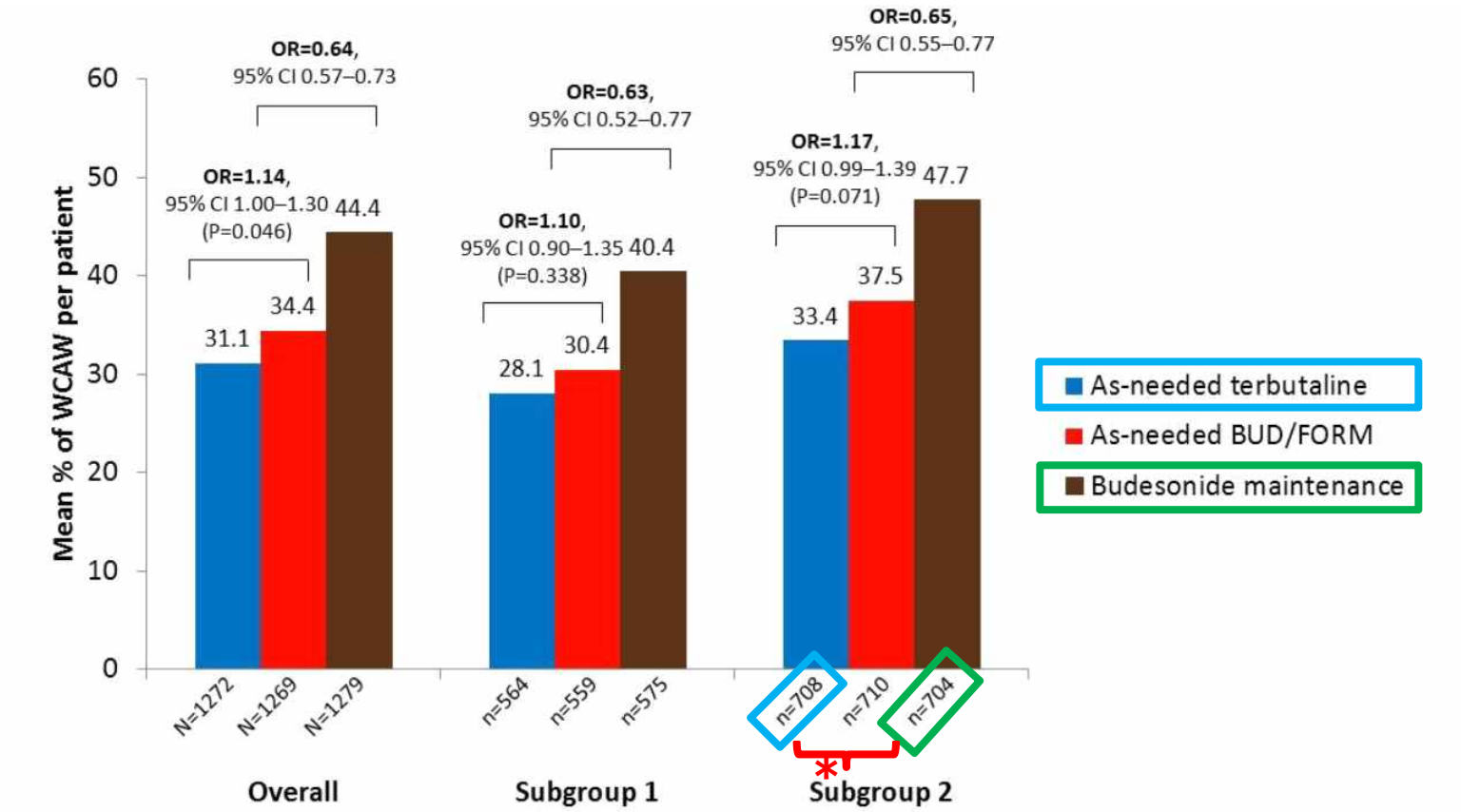
Rank MA. J Allergy Clin Immunol 2013;131:724.

ICS 중단 ⇨ control⇩

Double-blind RCT (SYGMA-1). **GINA step 2 asthma pts** (**N=3,849**)

TB prn *vs* BUD 200μg bid + TB prn *vs* BUD 250μg / FOR 6μg prn for 52 weeks.

Primary outcome: **asthma symptom control** (superior to TB prn).



O'Byrne PM. N Engl J Med 2018;378:1865.

"천식 환자에서 ICS를 쓰다가 중단하면?"

P 천식 환자 에서

I ICS를 쓰다가 중단 하면

C ICS를 계속 투여 한 경우와 비교해서

O 천식 조절, 증상
기도과민성
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} 성적이 나쁘다

"천식 환자에서 ICS maintenance 대신 as needed로 쓰면?"

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I ICS (± FOR, SABA)를 as needed 로 쓰면

C ICS maintenance 경우와 비교해서

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기도과민성
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?

PEF, AE: ICS ≈ high ICS or OCS prn

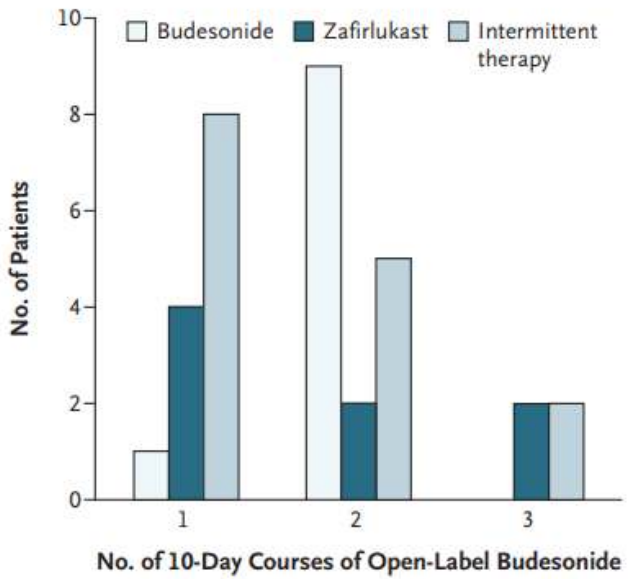
Double-blind RCT (IMPACT). **Mild persistent asthma pts** (**N=225**)

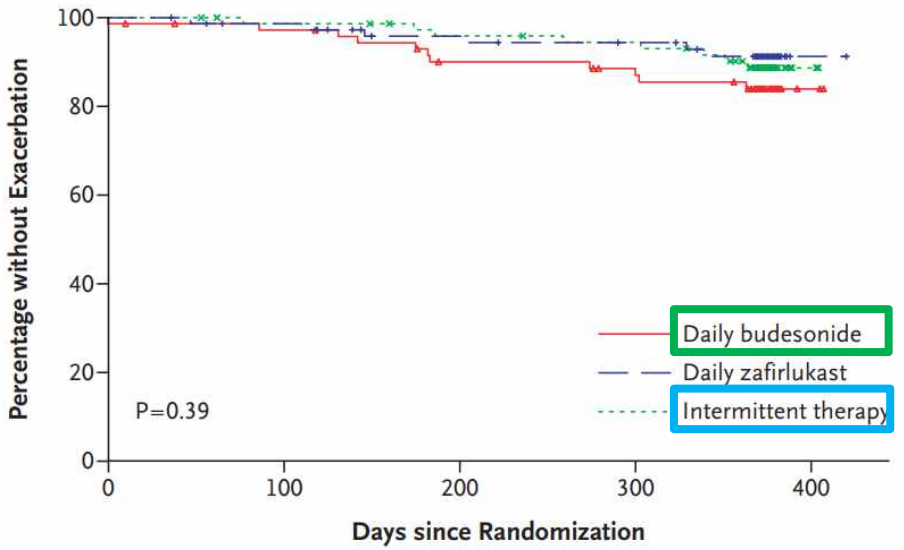
Run-in (BUD 800µg bid + ZLK 20mg bid + AL prn for 10-14days + Pd 0.5mg/kg x5d)

→ BUD 200µg bid *vs* ZLK 20mg bid *vs* PLA + BUD 800 bid or Pd 0.5mg/kg for 5 days as needed

Primary outcome: **Δ morning PEF**.

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
Morning PEF (%)	66	8.3±1.9	<0.001	62	7.9±2.1	<0.001	70	7.1±2.0	<0.001	0.90





Boushey HA. N Engl J Med

pre-FEV1⇩, sputum eosinophilia⇧, sx⇧: ICS > high ICS or OCS prn

Double-blind RCT (IMPACT). **Mild persistent asthma pts** (**N=225**)

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Primary outcome: **Δ morning PEF**.

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
FEV_1 (%)										
Pre-bronchodilator	67	4.0±1.2	0.001	62	−1.1±1.0	0.30	70	0.7±1.1	0.55	0.005
Post-bronchodilator	67	−1.7±0.5	0.002	61	−0.5±0.7	0.45	69	−1.0±0.5	0.04	0.29
Exhaled nitric oxide (%)	63		0.75	60		0.02	66		<0.001	0.006
Median		−14.4			12.4			26.6		
Asthma control score‡¶	70	−0.4±0.1	<0.001	70	−0.2±0.04	<0.001	73	−0.3±0.05	<0.001	<0.001
No. of symptom-free days‡	70	4.0±0.4	<0.001	70	3.1±0.4	0.001	73	2.9±0.4	<0.001	0.03

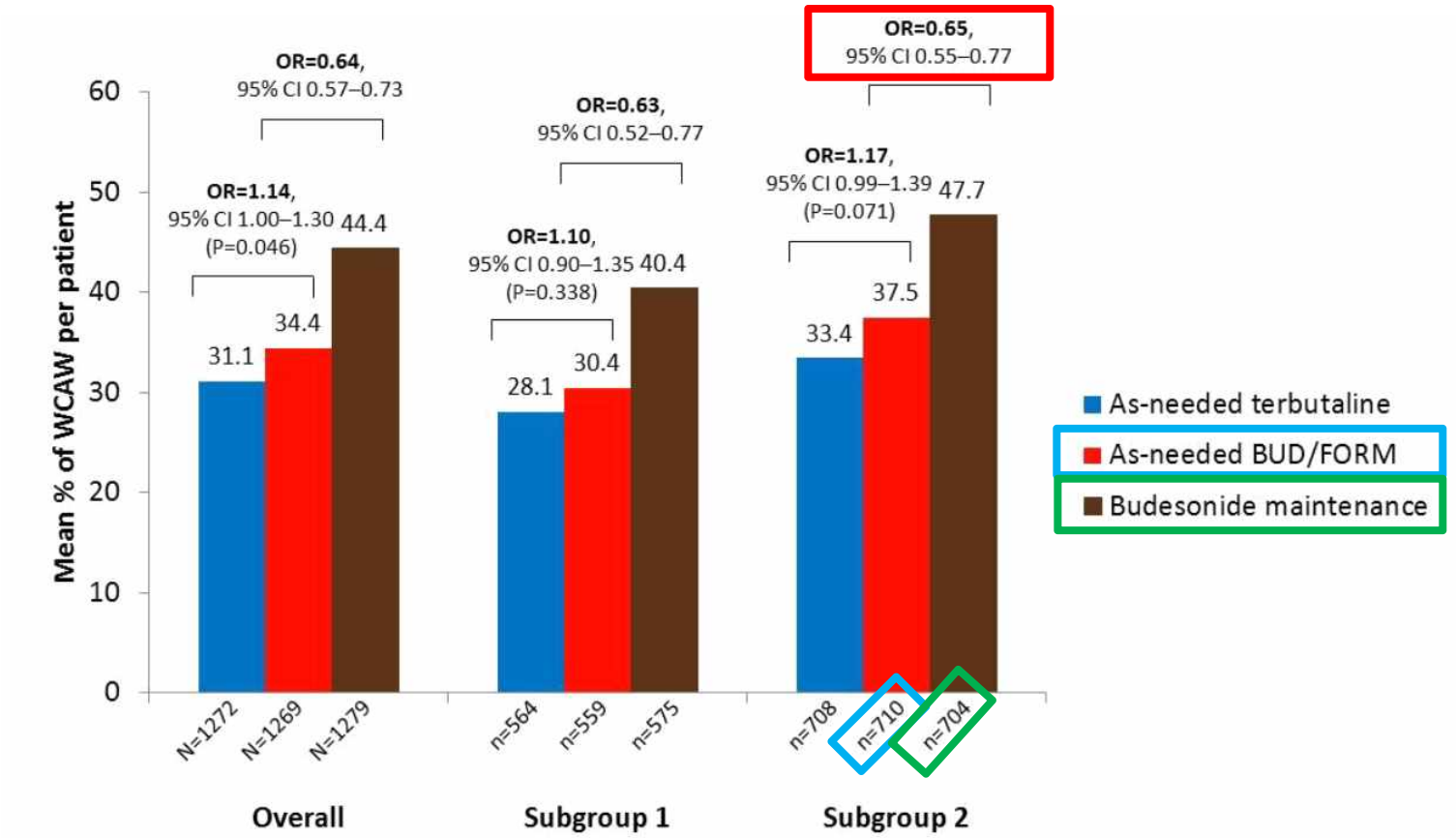
Boushey HA. N Engl J Med

Control : ICS > ICS/FOR prn

Double-blind RCT (SYGMA-1). **GINA step 2 asthma pts** (**N=3,849**)

TB prn *vs* BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.

Primary outcome: **asthma symptom control** (superior to TB prn).



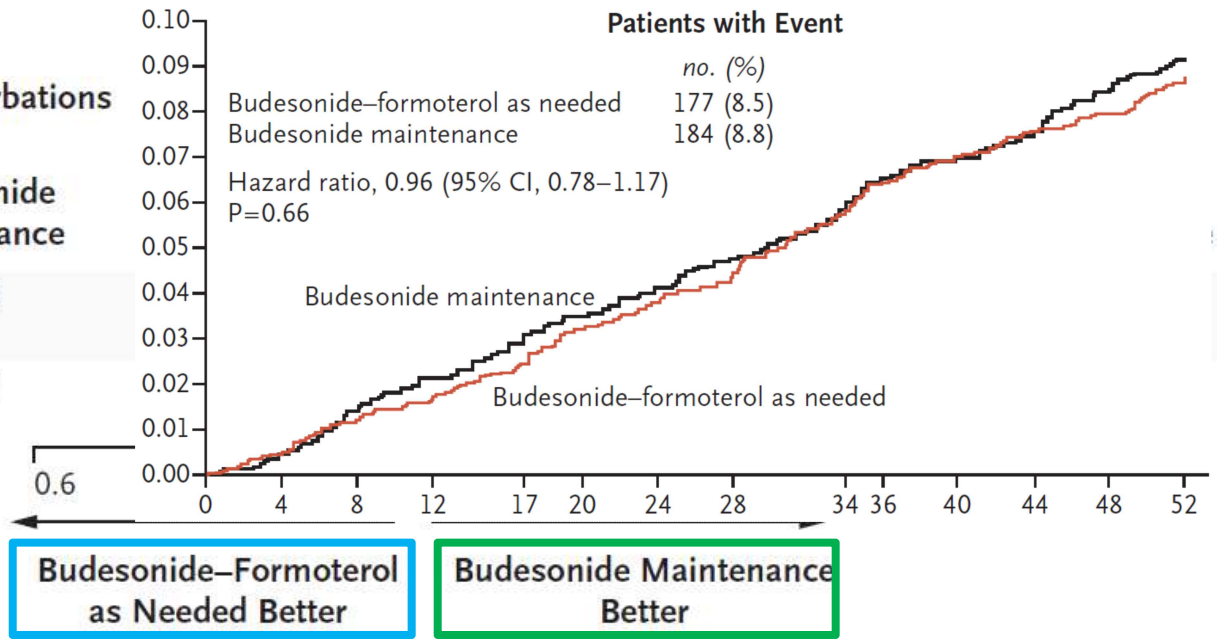
O'Byrne PM. N Engl J Med 2018;378:1865.

AE: ICS ≈ ICS/FOR prn

Double-blind RCT (SYGMA-2). **GINA step 2 asthma pts** (**N=4,176**)
BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.
Primary outcome: **severe AE rate**. (non-inferior)

A Annualized Rate of Severe Asthma Exacerbations

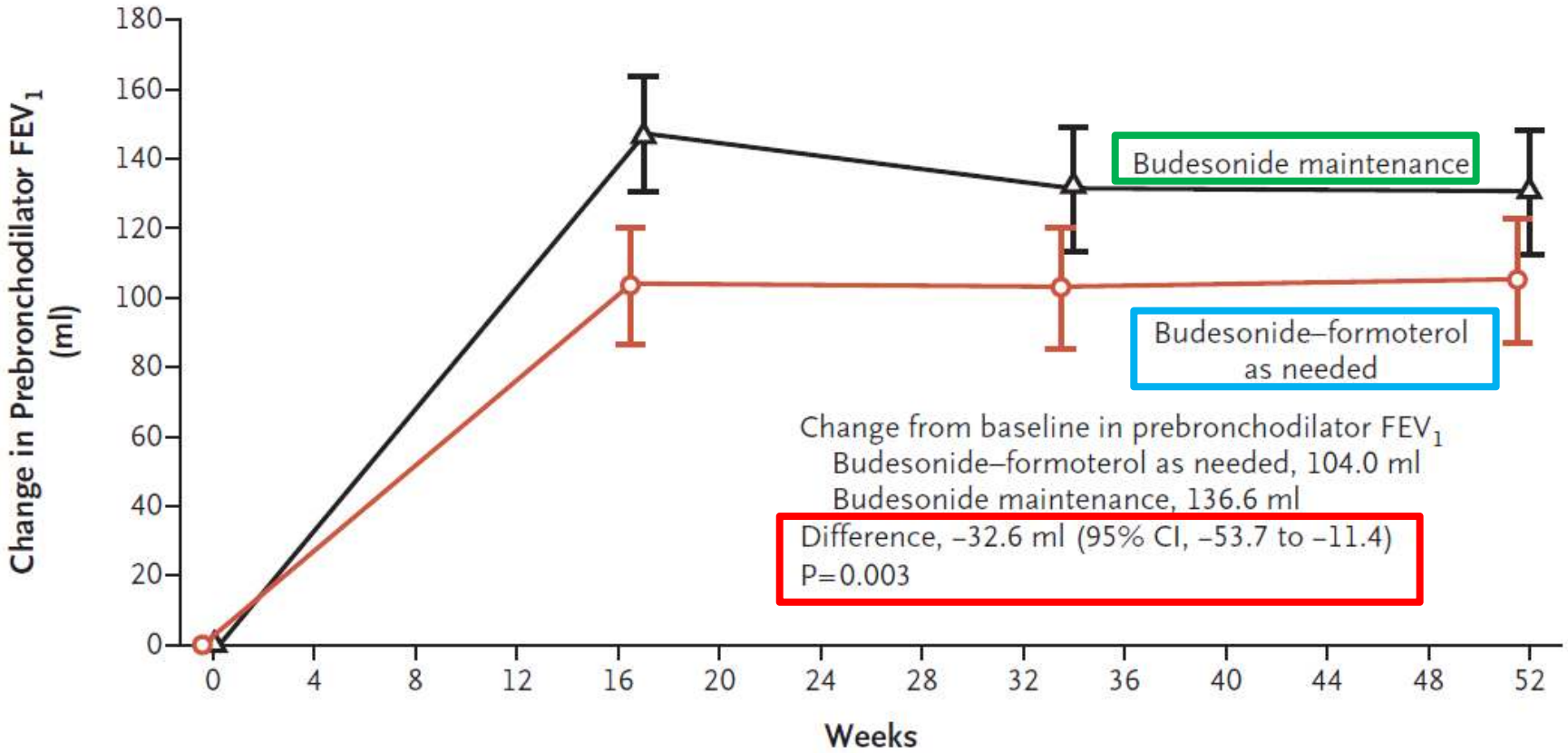
Test	Budesonide–Formoterol as Needed	Budesonide Maintenance
Noninferiority test	2084	2083
Superiority test	2089	2087



Bateman BD. N Engl J Med 2018;378:1877.

Pre-FEV1: ICS > ICS/FOR prn

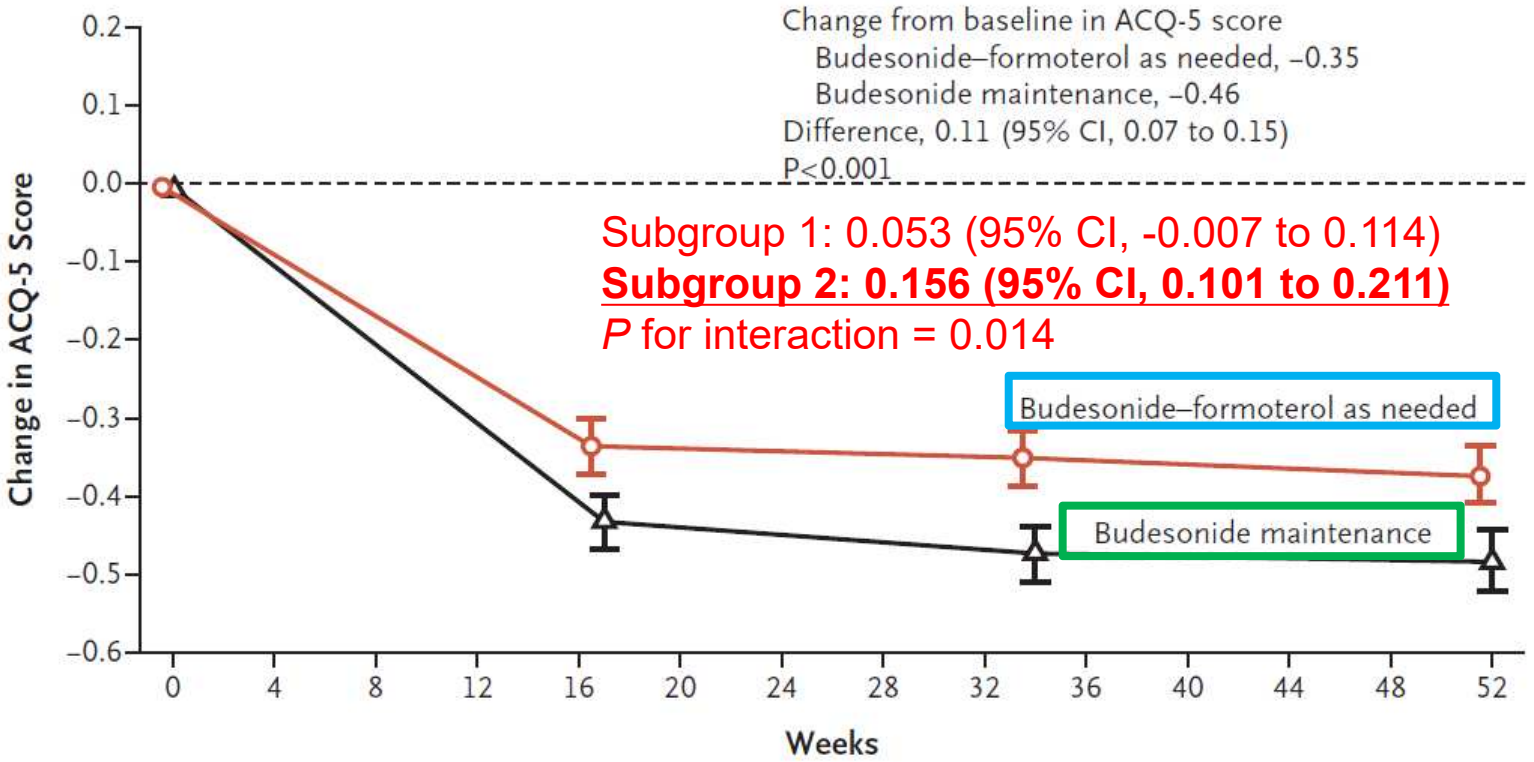
Double-blind RCT (SYGMA-2). **GINA step 2 asthma pts** (**N=4,176**)
BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.
Primary outcome: **severe AE rate**. (non-inferior)



Bateman BD. N Engl J Med 2018;378:1877.

ACQ-5: ICS > ICS/FOR prn

Double-blind RCT (SYGMA-2). **GINA step 2 asthma pts (N=4,176)**
BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.
Primary outcome: **severe AE rate**. (non-inferior)



Bateman BD. N Engl J Med 2018;378:1877.
Bateman BD. Am Thorac Soc 2019.

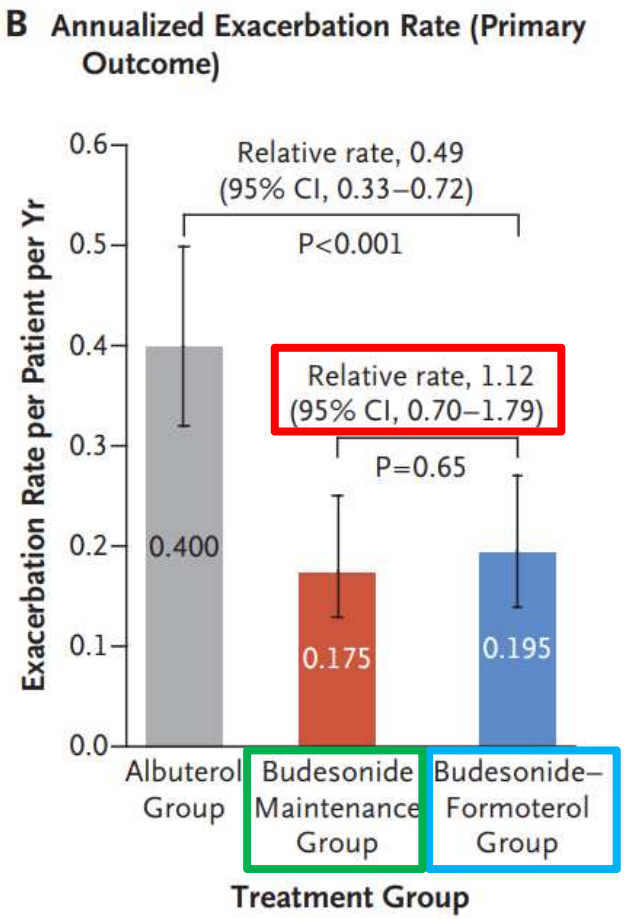
AE: ICS ≈ICS/FOR prn

Open-label RCT in NZ, UK, Italy, Australia (Novel START).

Mild (2/mo ≤ SABA ≤ 2/d) BA pts with no hospitalization within 12mo (**ACQ 1.1**) (**N=675**)

BUD 200µg bid + AL 100µg prn *vs* BUD 200µg / FOR 6µg as needed *vs* AL prn for 52 weeks.

Primary outcome: **exacerbation rate.**



easley R. N Engl J Med 2019;380:2020.

ACQ-5: ICS > ICS/FOR prn

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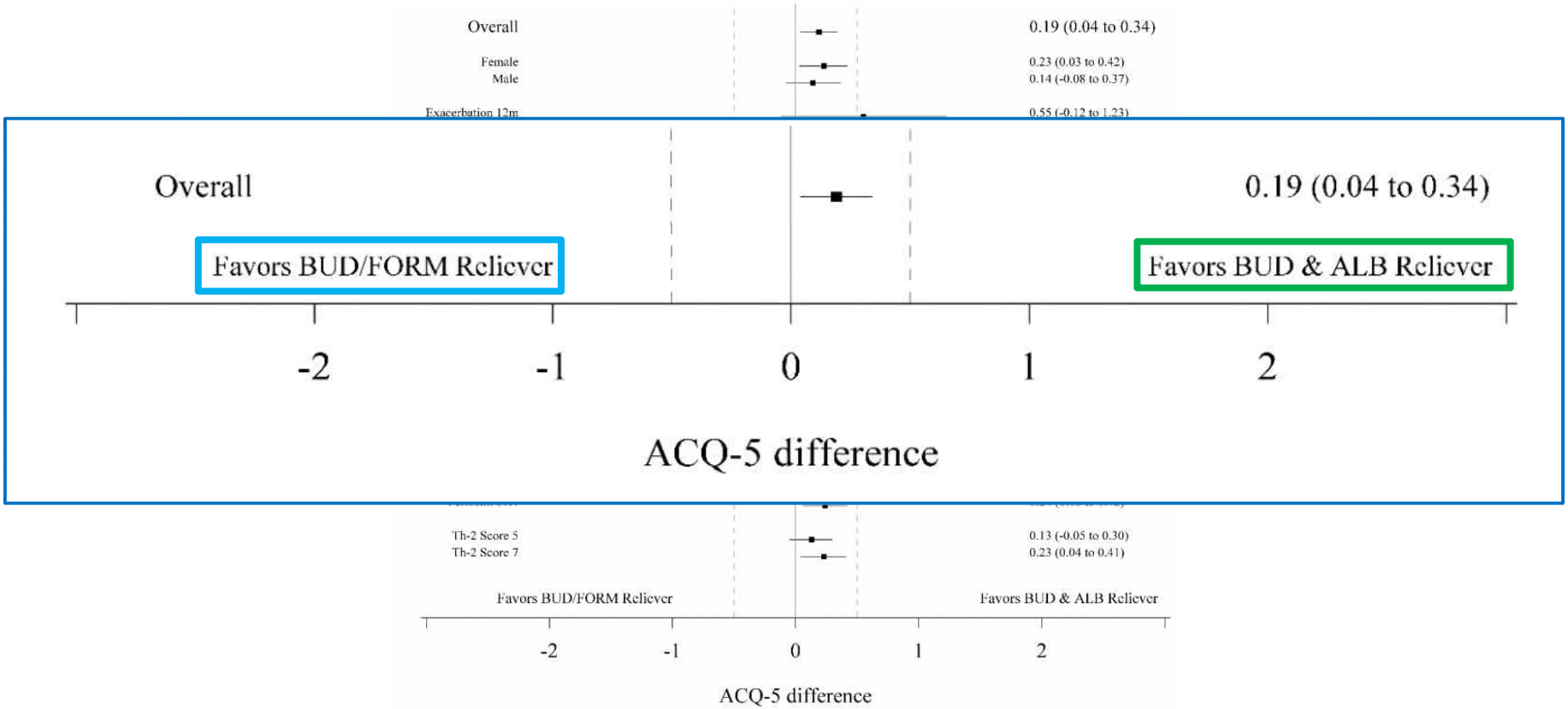
Primary outcome: **exacerbation rate.**



Beasley R. N Engl J Med 2019;380:2020.

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폐기능
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} 성적이 나쁘다

“천식 환자에서 첫 치료로 안 쓰면?”

P 천식 환자 첫 치료로

I ICS를 안 쓰면

C ICS를 쓰는 경우와 비교해서

O 천식 조절, 증상
기도과민성
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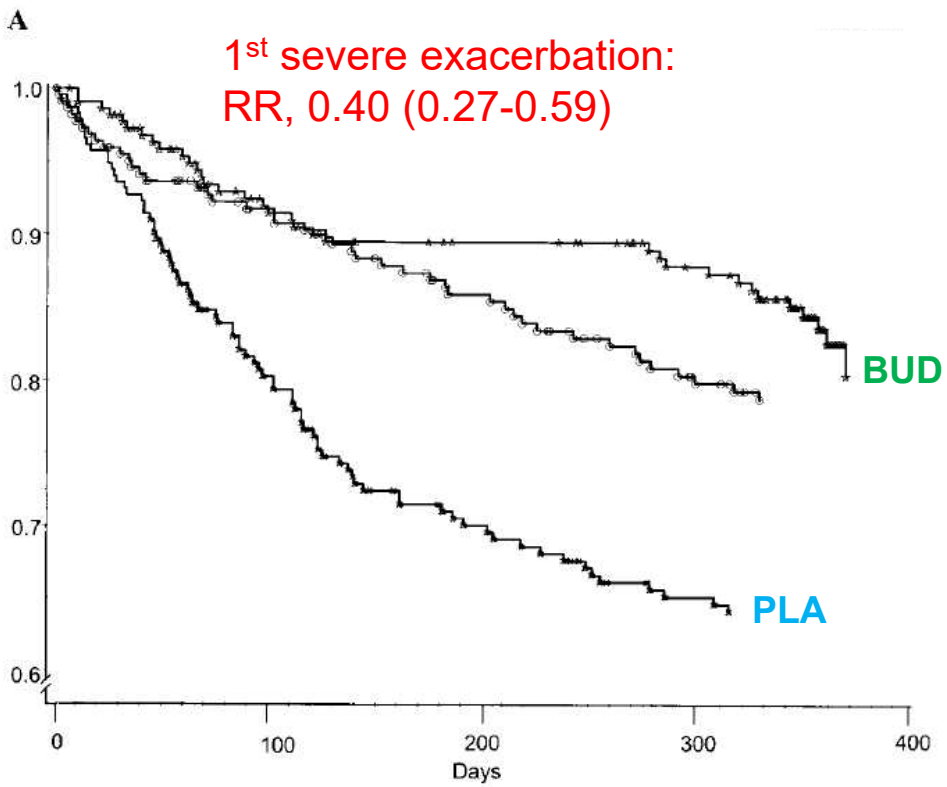
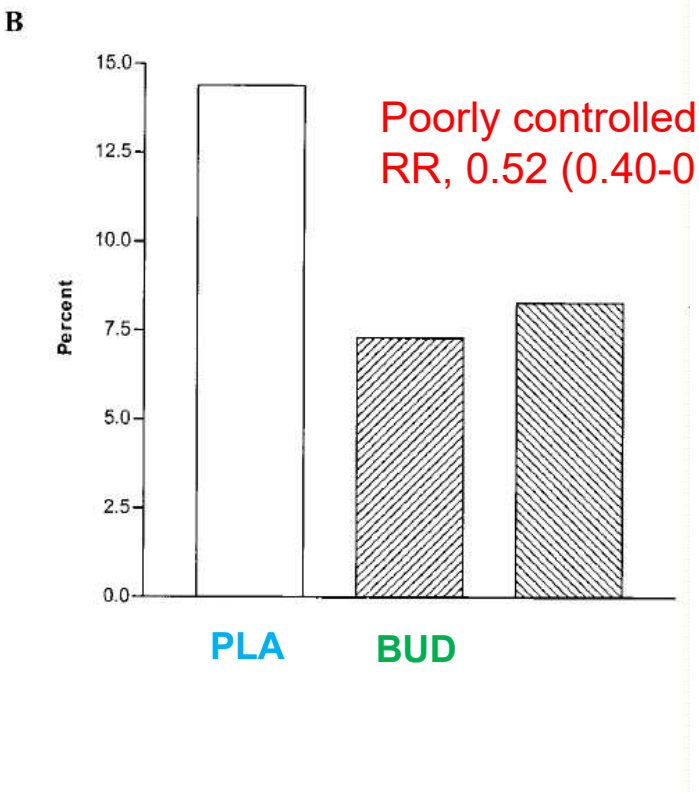
?

AE, control: ICS > PLA

Double-blinded multicenter RCT (OPTIMA). BA pts ≥ 12YO (**steroid-free** for at least 3mo) (**N=698**)
Run-in with PLA (pts need rescue tx ≥ 2/week) → BUD 100µg bid *vs* BUD 100µg + FOR 4.5µg bid *vs* PLA
Primary outcome: **time to 1st severe exacerbation**





O'Byrne PM. Am J Respir Crit Care Med

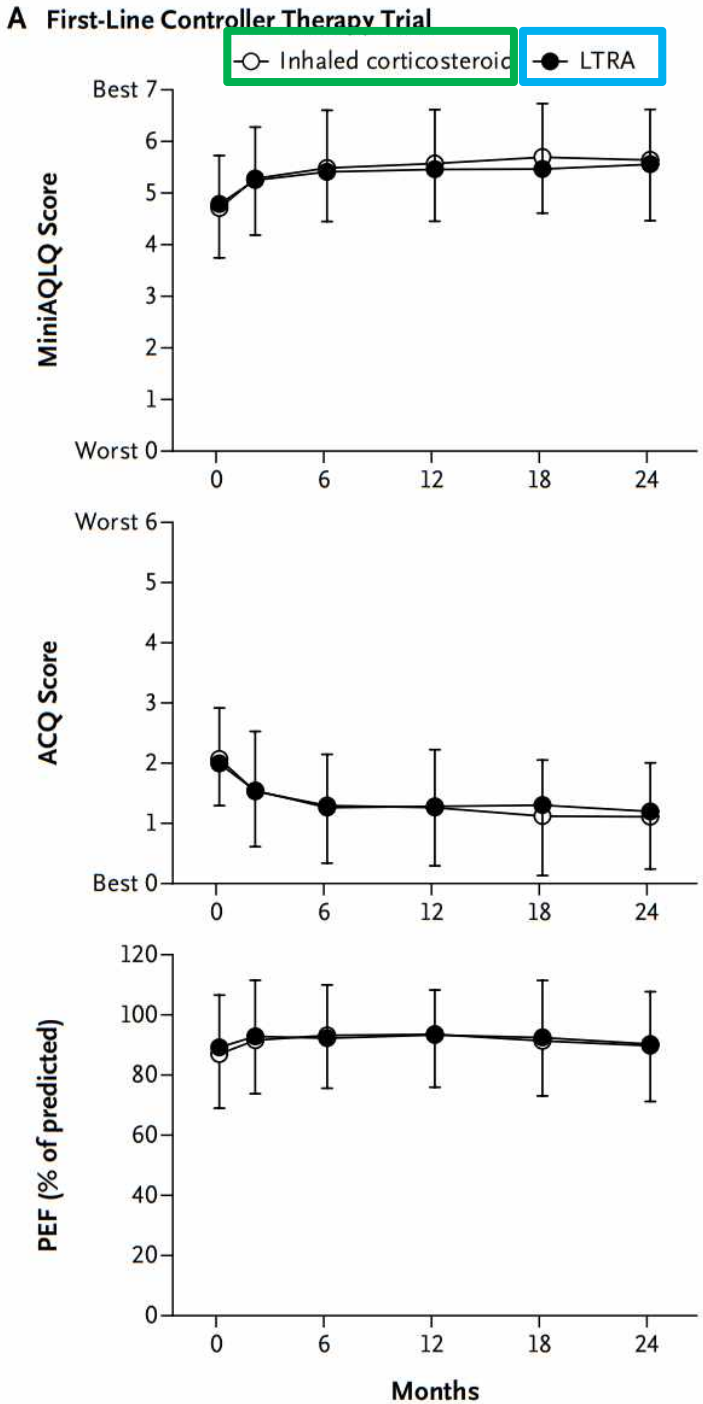
Mini-AQLQ, ACQ, PEF: ICS ≈ LTRA

UK multicenter pragmatic RCT.

BA pts with mini-AQLQ ≤ 6 or ACQ ≥ 1. (**N=306**)

ICS *vs* LTRA for 24 weeks

Primary outcome: **MiniAQLQ**



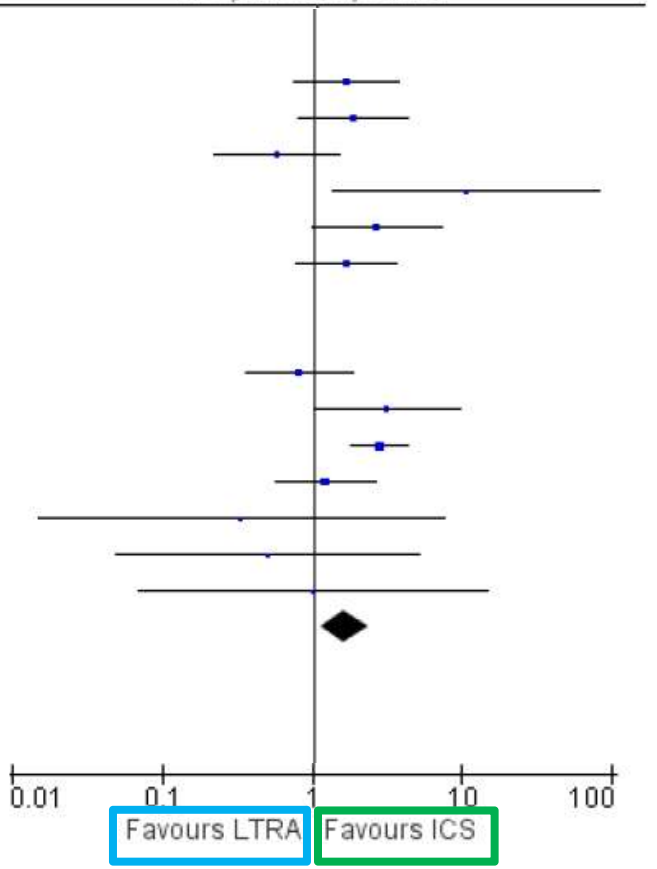
Price D. N Engl J Med

AE: ICS > LTRA

Study or Subgroup	Anti-leukotrienes Events	Total	Inhaled steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 Adults						
Baumgartner 2003	15	308	9	308	6.6%	1.67 [0.74, 3.75]
Bleecker 2000	14	220	8	231	6.2%	1.84 [0.79, 4.29]
Boushey 2005	6	76	10	73	5.3%	0.58 [0.22, 1.50]
Brabson 2002	10	216	1	224	1.5%	10.37 [1.34, 80.32]
Busse 2001a	13	111	5	113	5.0%	2.65 [0.98, 7.18]
Busse 2001b	16	262	10	271	7.1%	1.65 [0.77, 3.58]
Hughes 1999 (BDP)	0	12	0	23		Not estimable
Hughes 1999 (FP)	0	13	0	23		Not estimable
Israel 2002	10	337	12	329	6.5%	0.81 [0.36, 1.86]
Kim 2000	12	216	4	221	4.2%	3.07 [1.01, 9.37]
Laviolette 1999	61	201	22	200	12.2%	2.76 [1.77, 4.31]
Peters 2007	13	165	11	168	7.0%	1.20 [0.56, 2.61]
Riccioni 2001	0	12	1	12	0.7%	0.33 [0.01, 7.45]
Riccioni 2002a	1	20	2	20	1.2%	0.50 [0.05, 5.08]
Riccioni 2002b	1	15	1	15	0.9%	1.00 [0.07, 14.55]
Subtotal (95% CI)		**2184**		**2231**	**64.3%**	**1.61 [1.12, 2.31]**
Total events	172		96			

Heterogeneity: Tau² = 0.16; Chi² = 20.35, df = 12 (P = 0.06); I² = 41%

Test for overall effect: Z = 2.59 (P = 0.010)



Chauhan BF. Cochrane Database Syst Rev 2012;(5):CD002314.

“천식 환자에서 첫 치료로 안 쓰면?”

P 천식 환자 첫 치료로

I ICS를 안 쓰면

C ICS를 쓰는 경우와 비교해서

O 천식 조절, 증상
기도과민성
폐기능
급성악화

} 성적이 나쁘다

“천식 환자에서 ICS는 부작용이 더 많은가?”

P 천식 환자 첫 치료로

I ICS를 안 쓰면

C ICS를 쓰는 경우와 비교해서

O 폐렴
결핵
골밀도감소
당뇨
…

} ?

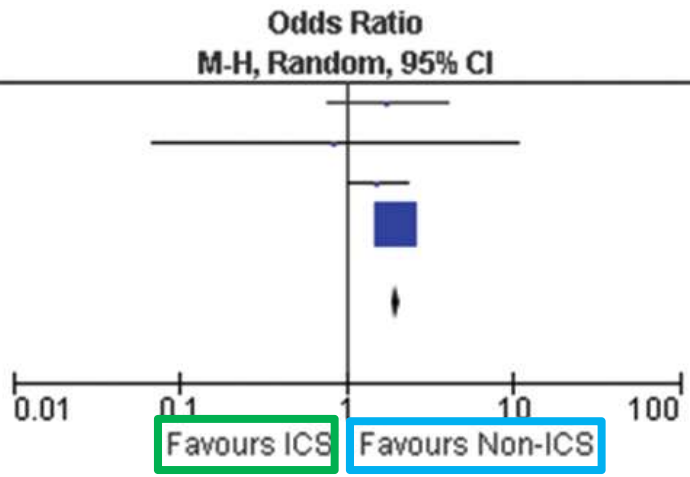
ICS ⇨ pneumonia

SR for **observational studies (N=44,016)**

Study or Subgroup	ICS Events	ICS Total	Non ICS Events	Non ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Almirall 2010	22	30	210	344	0.4%	1.75 [0.76, 4.06]
Andrejak 2013	9	30	1	3	0.0%	0.86 [0.07, 10.70]
Festic 2014	61	149	90	291	1.6%	1.55 [1.03, 2.33]
Mckeever 2013	3425	15594	3432	27575	98.0%	1.98 [1.88, 2.09]
Total (95% CI)		**15803**		**28213**	**100.0%**	**1.97 [1.87, 2.07]**
Total events	3517		3733			

Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (P = 0.60); I² = 0%

Test for overall effect: Z = 25.77 (P < 0.00001)



NNH ≈ 11

Bansal V. Acta Med Acad 2015;44:135.

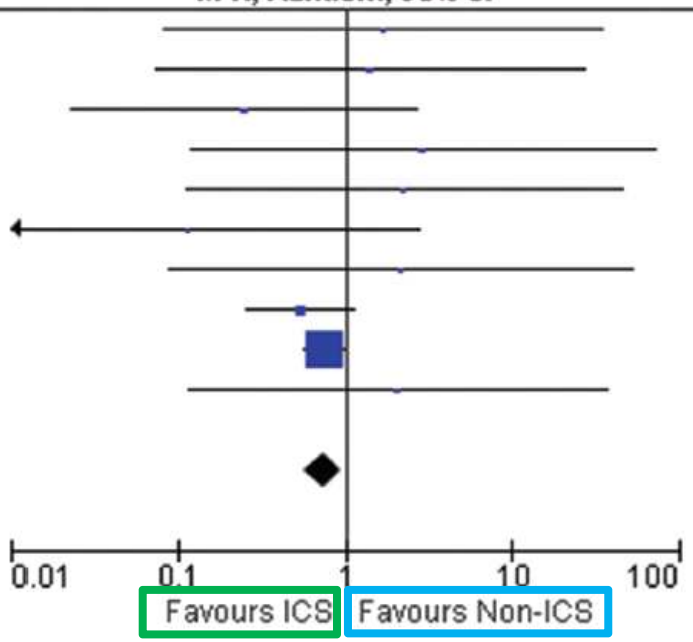
ICS ⇨ pneumonia⇩

SR for **14 RCTs (N=19,098)**

Study or Subgroup	ICS Events	ICS Total	Non ICS Events	Non ICS Total	Weight	Risk Ratio M-H, Random, 95% CI
ADA103575	2	544	0	181	0.7%	1.67 [0.08, 34.62]
Busse 2012	3	519	0	103	0.7%	1.40 [0.07, 26.90]
Busse 2014	1	232	2	115	1.1%	0.25 [0.02, 2.70]
Corren 2007	1	244	0	236	0.6%	2.90 [0.12, 70.88]
Karpel 2007	2	85	0	38	0.7%	2.27 [0.11, 46.12]
Maspero 2013	0	424	1	142	0.6%	0.11 [0.00, 2.74]
Noonan 2006	1	348	0	248	0.6%	2.14 [0.09, 52.32]
O'Byrne 2011	15	5437	12	2335	11.1%	0.54 [0.25, 1.15]
Sheffer 2005	86	3630	113	3591	83.1%	0.75 [0.57, 0.99]
Woodcock 2011	5	545	0	101	0.8%	2.05 [0.11, 36.88]
Total (95% CI)		**12008**		**7090**	**100.0%**	**0.74 [0.57, 0.95]**
Total events	116		128			

Heterogeneity: Tau² = 0.00; Chi² = 5.45, df = 9 (P = 0.79); I² = 0%

Test for overall effect: Z = 2.37 (P = 0.02)



NNT ≈ 119

Bansal V. Acta Med Acad 2015;44:135.

ICS ⇨ TB⇧

A nested case-control study based on HIRA database.
New pts treated with inhaled drugs. (**N=853,439 TB n=4,146**)

Table 4 Subgroup analysis according to asthma or COPD

			Unadjusted		Adjusted*	
Asthma	**Tuberculosis (N=484), n (%)**	**Control (N=2420), n (%)**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
ICS use						
Non-ICS users†	307 (63.4)	1614 (66.7)	1 (ref)		1 (ref)	
ICS users‡	177 (36.6)	806 (33.3)	1.22 (0.96 to 1.55)	0.105	1.46 (1.11 to 1.92)	0.008
COPD	Tuberculosis (N=1360), n (%)	Control (N=6791), n (%)				
ICS use						
Non-ICS users†	730 (53.7)	4214 (62.1)	1 (ref)		1 (ref)	
ICS users‡	630 (46.3)	2577 (37.9)	1.47 (1.3 to 1.66)	<0.001	1.20 (1.05 to 1.37)	0.007

P for interaction > 0.05

NNH ≈ 400

Lee CH. Thorax 2013;68:1105.

ICS ⇨ NTM-PD

A nested case-control study based on OPD pharmacy records.
(Treated cohort of pts with airway disease) (**N=279,333, NTM n=248**)

NNH ≈ 600

Table 3. Asso…roid use with risk of nontuberculous mycobacterial pulmonary infection, stratified by period of i…ohort entry and diagnosis at cohort entry

Any ICS use	*n*	Odds Ratios (95% Confidence Interval) for NTM Infection with ICS Use		
		Unadjusted OR	Medication-adjusted OR*	Fully Adjusted OR†
Within prior 120 d	2,728	3.88 (2.87–5.26)	2.86 (2.02–4.05)	2.74 (1.83–4.09)
Within past 1 yr	2,321	4.14 (2.80–6.13)	3.04 (1.97–4.68)	2.80 (1.79–4.37)
Within past 2 yr	1,829	4.49 (2.62–7.70)	2.82 (1.59–5.00)	2.51 (1.40–4.49)

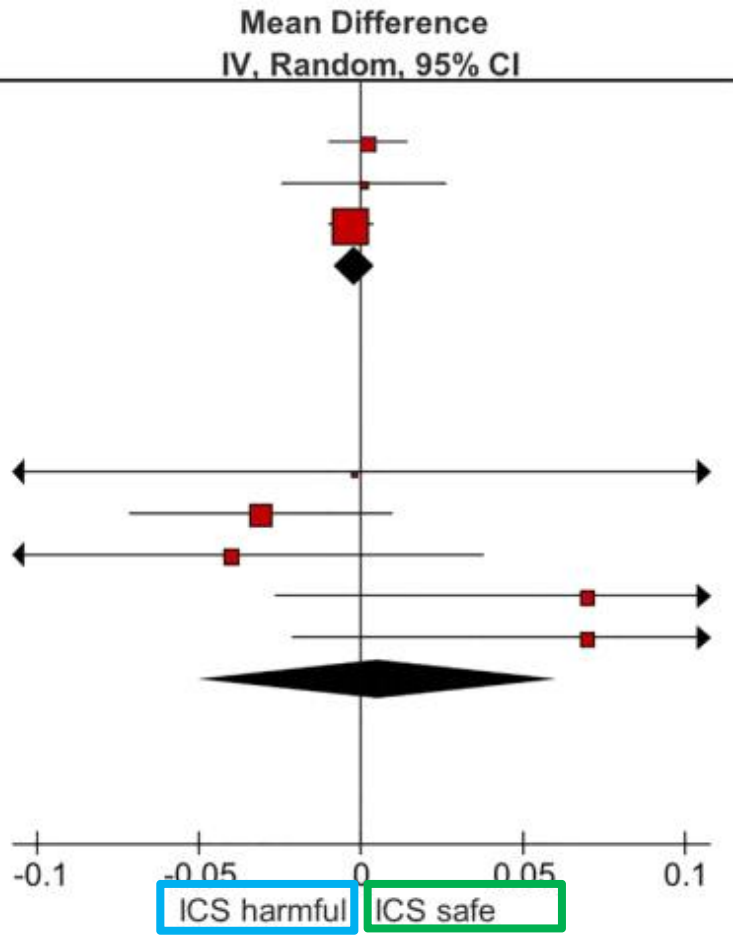
	NTM Cases	Control Subjects
Airway disease medication use in past 120 d		
ICS	187 (75.4)	1,111 (44.8)
Mixed ICS + LABA	42 (16.9)	161 (6.5)
SABA	108 (43.6)	725 (29.2)
LABA	39 (15.7)	201 (8.1)
Anticholinergic	104 (41.9)	437 (17.6)
Leukotriene antagonist	29 (11.3)	96 (3.9)
Oral corticosteroid	90 (36.3)	353 (14.2)

Liu V. Ann Am Thorac Soc 2018;15:1169.

ICS ⇨ 골밀도⇩☎

SR for 18 studies (**7 RCTs, 11 observational studies**)

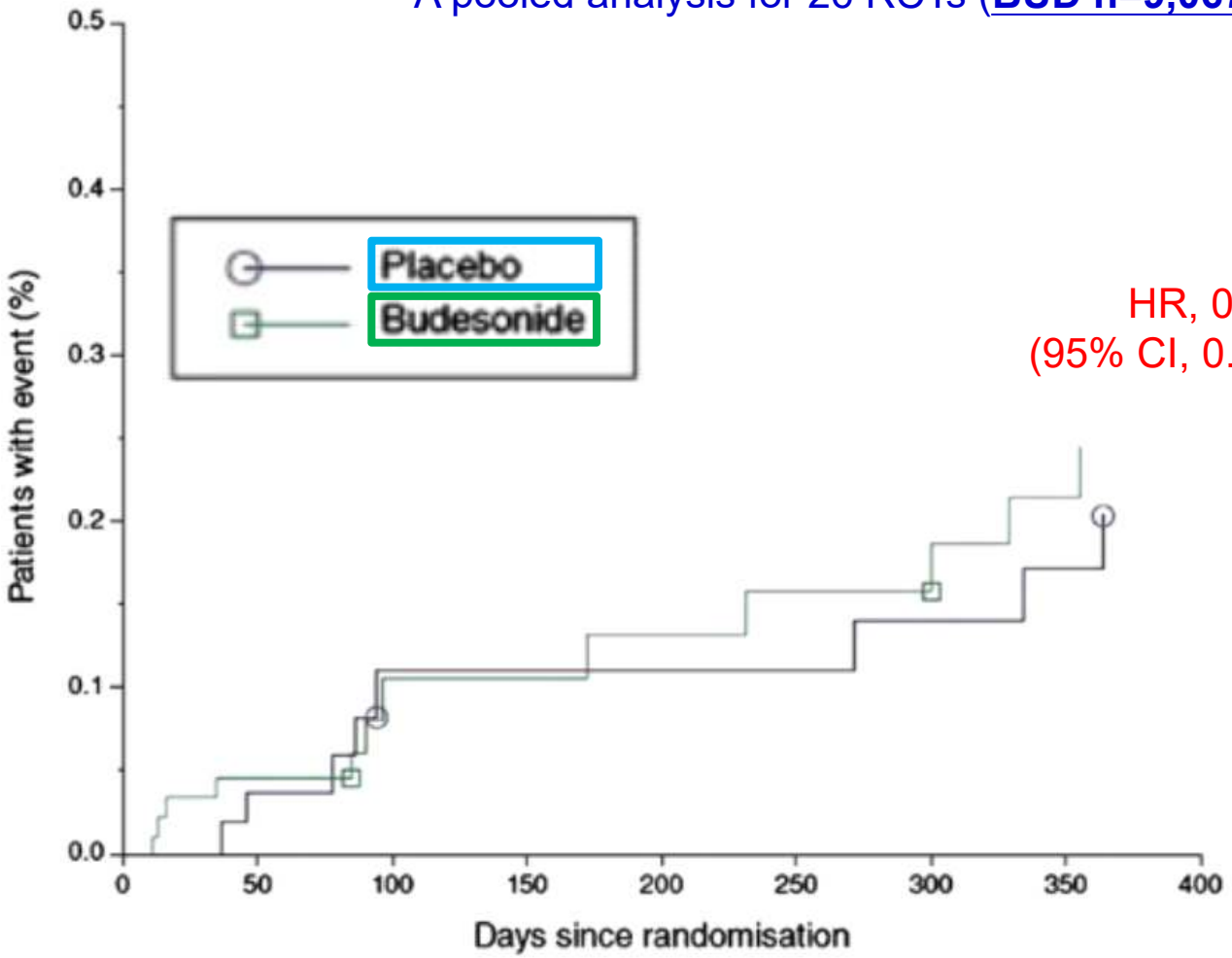
Study or Subgroup	Weight	Mean Difference IV, Random, 95% CI
RCTs		
Kemp All ICS 2004	22.5%	0.0021 [-0.0099, 0.0141]
Li 1999	5.1%	0.0010 [-0.0241, 0.0261]
Maspero All ICS 2013	72.4%	-0.0033 [-0.0100, 0.0034]
Subtotal (95% CI)	**100.0%**	**-0.0019 [-0.0075, 0.0038]**
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%		
Test for overall effect: Z = 0.64 (P = 0.52)		
Non-Randomised Studies		
El 2005	0.0%	-0.0020 [-5.9601, 5.9561]
Sosa 2006	38.1%	-0.0310 [-0.0714, 0.0094]
Wisniewski Female 1997	23.7%	-0.0400 [-0.1174, 0.0374]
Wisniewski Male 1997	18.5%	0.0700 [-0.0262, 0.1662]
Yanik 2009	19.8%	0.0700 [-0.0209, 0.1609]
Subtotal (95% CI)	**100.0%**	**0.0055 [-0.0468, 0.0578]**
Heterogeneity: Tau² = 0.00; Chi² = 7.24, df = 4 (P = 0.12); I² = 45%		
Test for overall effect: Z = 0.21 (P = 0.84)		



Loke YK. BMJ Open 2015;5:e008554.

ICS ⇨ DM/hyperGlc⇧(x)

A pooled analysis for 26 RCTs (**BUD n=9,067, PLA n=5,926**)



HR, 0.98
(95% CI, 0.38-2.50)

O'Byrne PM. Respir Med 2012;106:1487.

ICS ⇨  (x)

2 nested case control studies. **Pregnant women** (**N=1,306,281**)

TABLE 3. Risk of PIH According to ICS Use

	PIH (n = 43,908)	Control (n = 219,534)	Unadjusted		Model 1		Model 2		Model 3	
Category	**n (%)**	**n (%)**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Inhaler medication use*										
No ICS	43,821 (99.80%)	219,174 (99.84%)	1		1		1		1	
ICS	87 (0.20%)	360 (0.16%)	1.20 (0.78–1.85)	0.397	1.33 (1.02–1.72)	0.032	1.29 (0.99–1.68)	0.060	1.27 (0.98–1.66)	0.074

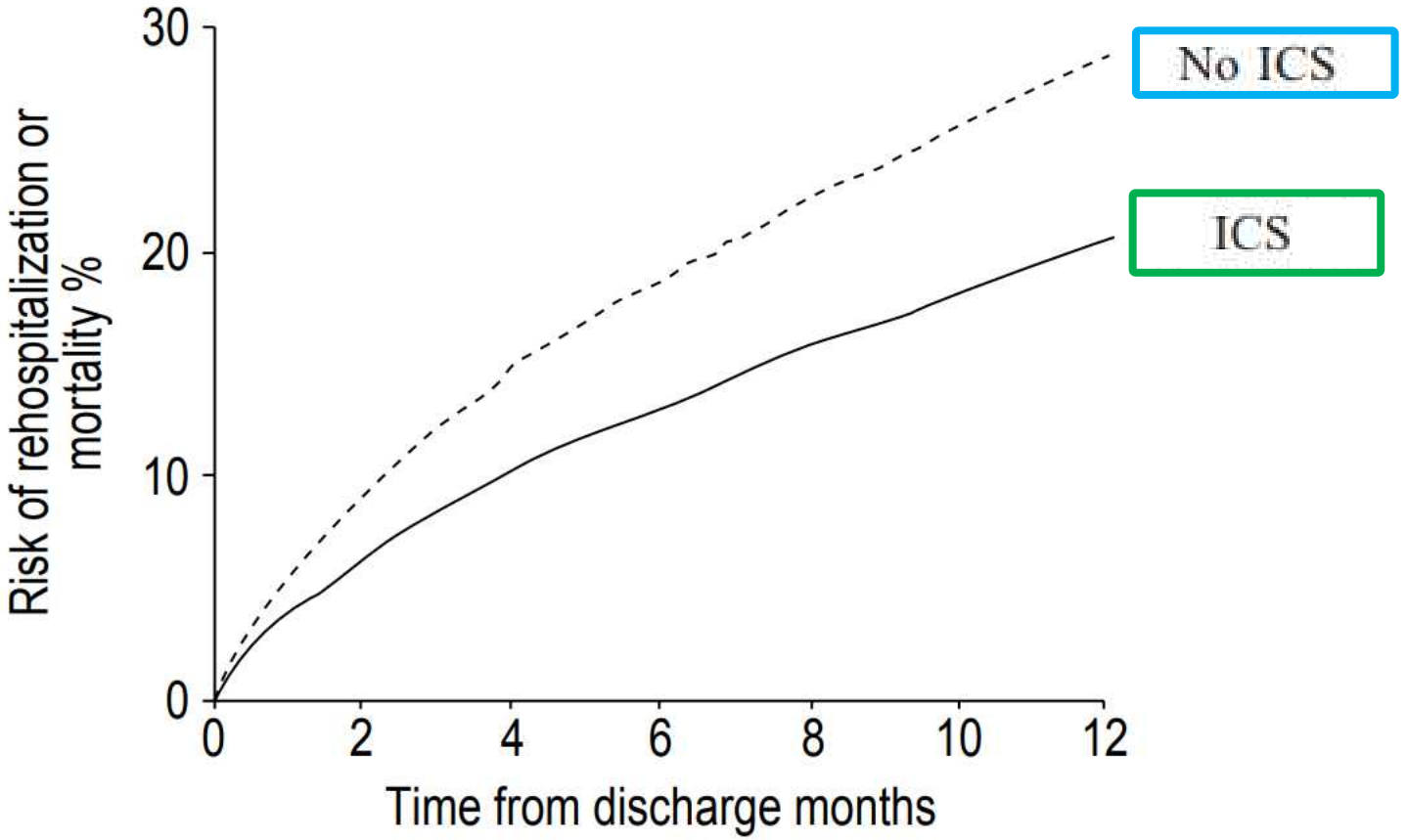
TABLE 4. Risk of GDM According to ICS Use

	GDM (N = 34,190)	Control (N = 170,934)	Unadjusted		Model 1		Model 2		Model 3	
Category	**n (%)**	**n (%)**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Inhaler medication use*										
No ICS	34,121 (99.80%)	170,580 (99.79%)	1		1		1		1	
ICS	69 (0.20%)	354 (0.20%)	0.9 (0.72–1.25)	0.710	1 (0.77–1.38)	0.818	1 (0.76–1.37)	0.904	1 (0.77–1.4)	0.823

Lee CH. Medicine 2016;95:e3627.

ICS ⇨ re-admission, mortality⇩

A retrospective database study. **Hospitalized elderly asthma patients**. (**N=6,254**)

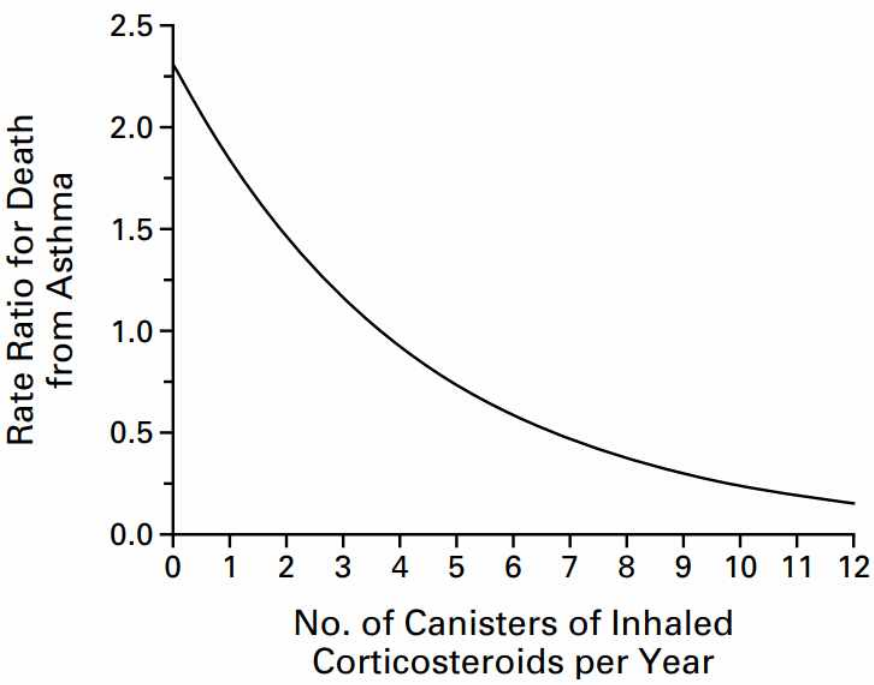


Sin DD. Eur Respir J 2001;17:380.

ICS ⇨ mortal-ity⇩

Use of Inhaled Corticosteroids	Case Patients (N=66)	Controls (N=2681)	Crude Rate Ratio	Adjusted Rate Ratio (95% CI)†
Previous 1 yr				
None (%)	47.0	53.8	1.0	1.0 (reference group)
Any use (%)	53.0	46.2	1.41	1.19 (0.66–2.14)
1–5 canisters	51.5	38.8	1.67	1.53 (0.83–2.80)
⩾6 canisters	1.5	7.4	0.25	0.15 (0.02–1.22)
Mean no. of canisters	1.18	1.57	0.82†	0.79 (0.65–0.97)‡
Previous 6 mo				
None (%)	56.1	65.7	1.0	1.0 (reference group)
Any use (%)	43.9	34.3	1.56	1.33 (0.74–2.37)
1 or 2 canisters	42.4	23.1	2.25	2.18 (1.18–4.02)
⩾3 canisters	1.5	11.2	0.16	0.13 (0.02–0.97)
Mean no. of canisters	0.62	0.79	0.50‡	0.46 (0.26–0.79)§

A retrospective database study.
Those who were using anti-asthma tx (N=30,569)



Suissa S. N Engl J Med 2000;343:332.

ICS 중단 ⇨ mortality⇧

A retrospective database study.
Those who were using anti-asthma tx (N=30,569)

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

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

Suissa S. N Engl J Med 2000;343:332.

“천식 환자에서 ICS는 부작용이 더 많은가?”

P 천식 환자 첫 치료로

I ICS를 안 쓰면

C ICS를 쓰는 경우와 비교해서

O 폐렴
결핵
골밀도감소
…

비스포스포네이트 추가도

사망 위험은 줄여

결 론

- **ICS를 쓰다가 중단하면?**
  - 성적이 나쁘다

그러므로, ICS를 끊으면 안된다.

- **ICS maintenance 대신 as needed로 쓰면?**
  - 성적이 나쁘다

- **첫 치료로 ICS를 안 쓰면?**
  - 성적이 나쁘다

- ICS는 부작용이 비슷하거나 좀 더 많을 수도 있다
  - 그러나, 사망 감소 등 harm이 benefit을 넘지 않는다.


Thank you

흡입용 스테로이드제
(ICS, inhaled corticosteroid)

Adults and adolescents (12 years and older)			
Drug	**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)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

GINA update 2018.

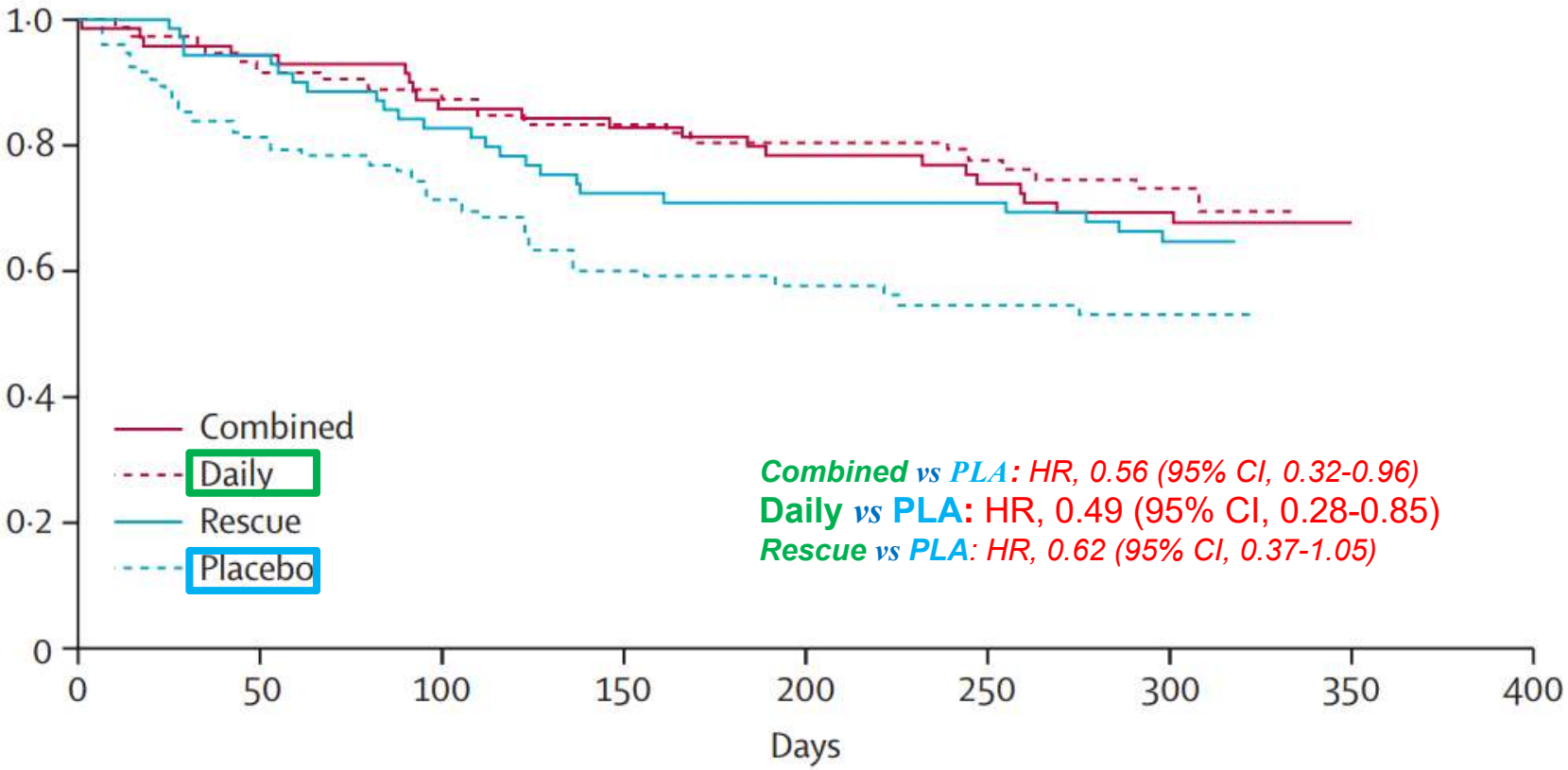
ICS 중단 ⇨ 급성악화⇧

Double blind RCT (TREXA).

Mild persistent BA children (5-18YO) **"well controlled" (NAEPP) with ≤ low dose ICS tx** (N=288)

BDP 80μg/d+BDP/AL prn *vs* BDP+PLA/AL prn *vs* PLA+BDP/AL prn *vs* PLA+PLA/AL prn for 44 weeks.

Primary outcome: **time to 1st AE requiring Pd**.



Martinez FD. Lancet 2011;377:650.

ICS 중단, LTRA ⇨ PEF, 급성악화 nc

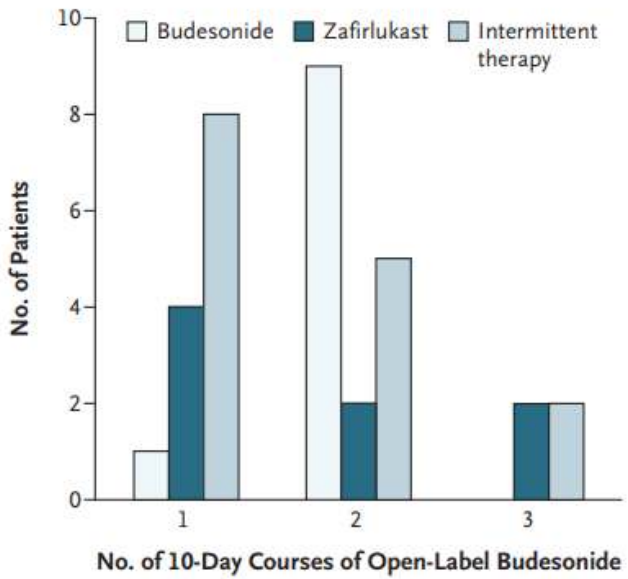
Double-blind RCT (IMPACT). **Mild persistent** asthma pts (N=225)

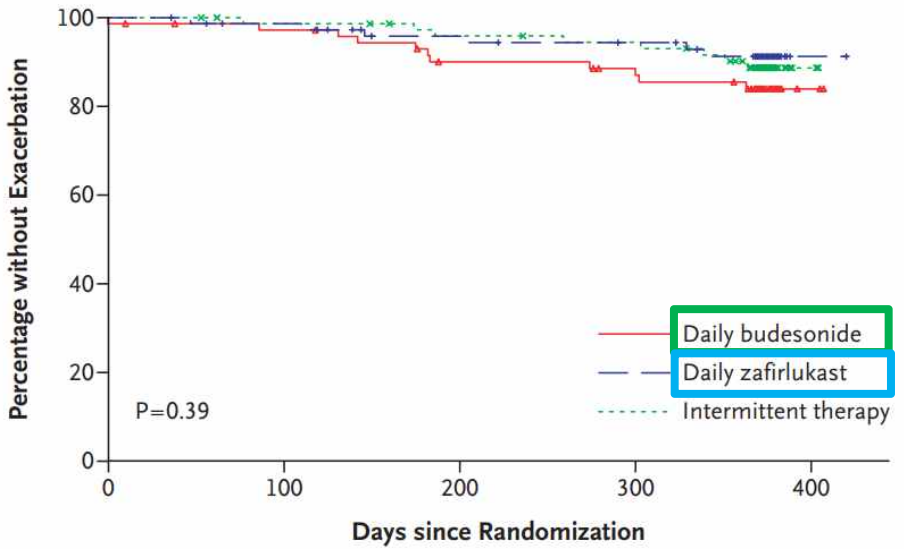
Run-in (BUD 800μg bid + ZLK 20mg bid + AL prn for 10-14days + Pd 0.5mg/kg x5d)

→ BUD 200μg bid *vs* ZLK 20mg bid *vs* PLA + BUD 800 bid or Pd 0.5mg/kg for 5 days as needed.

Primary outcome: **Δ morning PEF**.

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
Morning PEF (%)	66	8.3±1.9	<0.001	62	7.9±2.1	<0.001	70	7.1±2.0	<0.001	0.90





Boushey HA. N Engl J Med

ICS 중단, LTRA ⇨ pre-FEV1⇩, sputum eosinophilia⇧, symptom⇧

Double-blind RCT (IMPACT). **Mild persistent asthma pts** (N=225)

Run-in (BUD 800μg bid + ZLK 20mg bid + AL prn for 10-14days + Pd 0.5mg/kg x5d)

→ BUD 200μg bid *vs* ZLK 20mg bid *vs* PLA + BUD 800 bid or Pd 0.5mg/kg for 5 days as needed.

Primary outcome: **Δ morning PEF**.

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
FEV_1 (%)										
Pre-bronchodilator	67	4.0±1.2	0.001	62	−1.1±1.0	0.30	70	0.7±1.1	0.55	0.005
Post-bronchodilator	67	−1.7±0.5	0.002	61	−0.5±0.7	0.45	69	−1.0±0.5	0.04	0.29
Exhaled nitric oxide (%)	63		0.75	60		0.02	66		<0.001	0.006
Median		−14.4			12.4			26.6		
Asthma control score‡¶	70	−0.4±0.1	<0.001	70	−0.2±0.04	<0.001	73	−0.3±0.05	<0.001	<0.001
No. of symptom-free days‡	70	4.0±0.4	<0.001	70	3.1±0.4	0.001	73	2.9±0.4	<0.001	0.03

Boushey HA. N Engl J Med

ICS/LABA 쓰다 ICS 중단 ⇨ 치료실패 ⇧

Double-blind RCT (SLIC) Persistent asthma pts suboptimally controlled by TAC 400μg bid (**N=175**)

(1) PLA-minus (n=21) : TAC 200μg bid for 8weeks → D/C TAC for 8weeks *vs*

(2) SAL-minus (n=74) : TAC 400μg/SAL bid for 2weeks → TAC 200μg/SAL bid for 8weeks → SAL for 8weeks *vs*

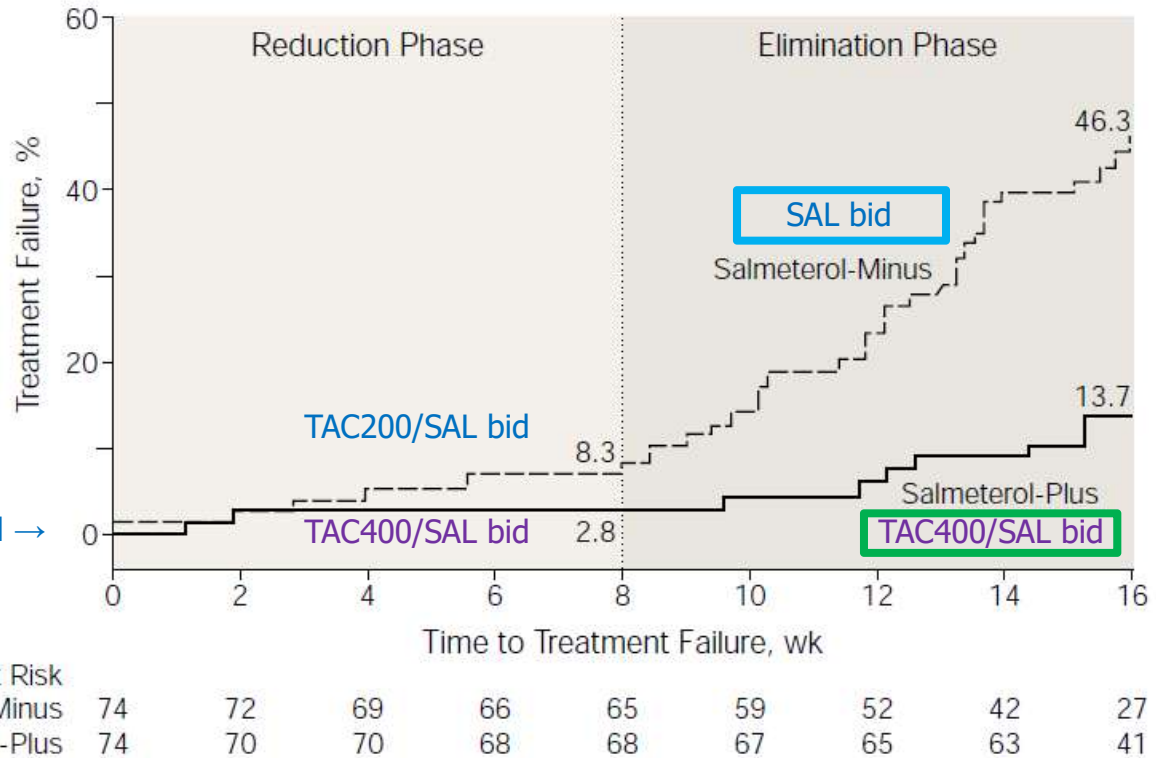
(3) SAL-plus (n=74) : TAC 400μg/SAL bid for 2weeks → TAC 400μg bid for 16weeks.

Primary outcome: **time to treatment failure**.

AE, SABA↑, FEV1 ↓, PEF ↓, …

(2), (3)

TAC400 bid → TAC400/SAL bid →



RR, 4.3 (95% CI, 2.0-9.2)

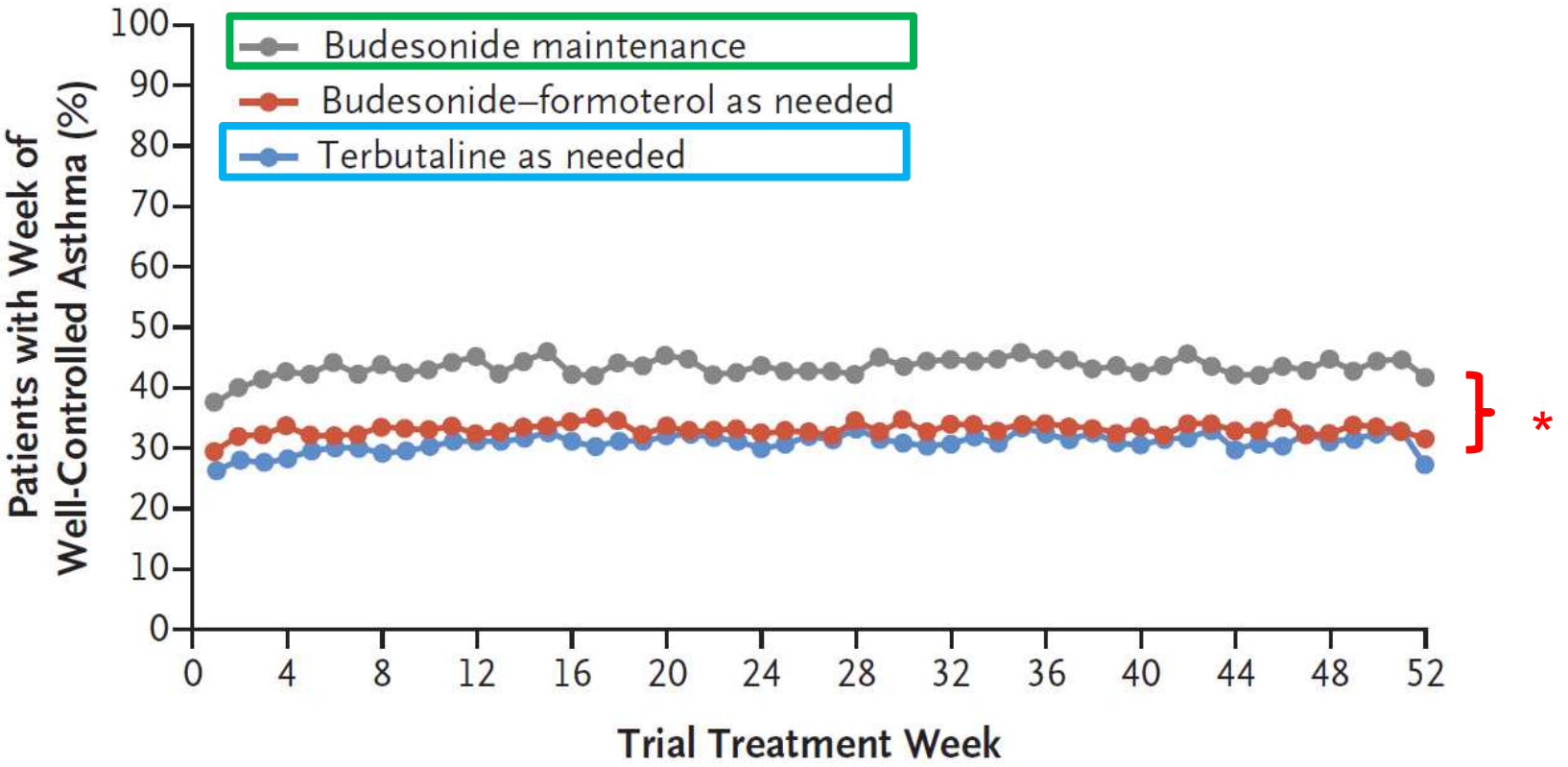
Lemanske RF. JAMA

ICS 중단 ⇨ Sx control⇩

Double-blind RCT (SYGMA-1). **GINA step 2 asthma pts** (**N=3,849**)

TB prn *vs* BUD 200μg bid + TB prn *vs* BUD 250μg / FOR 6μg prn for 52 weeks.

Primary outcome: **asthma symptom control** (superior to TB prn).



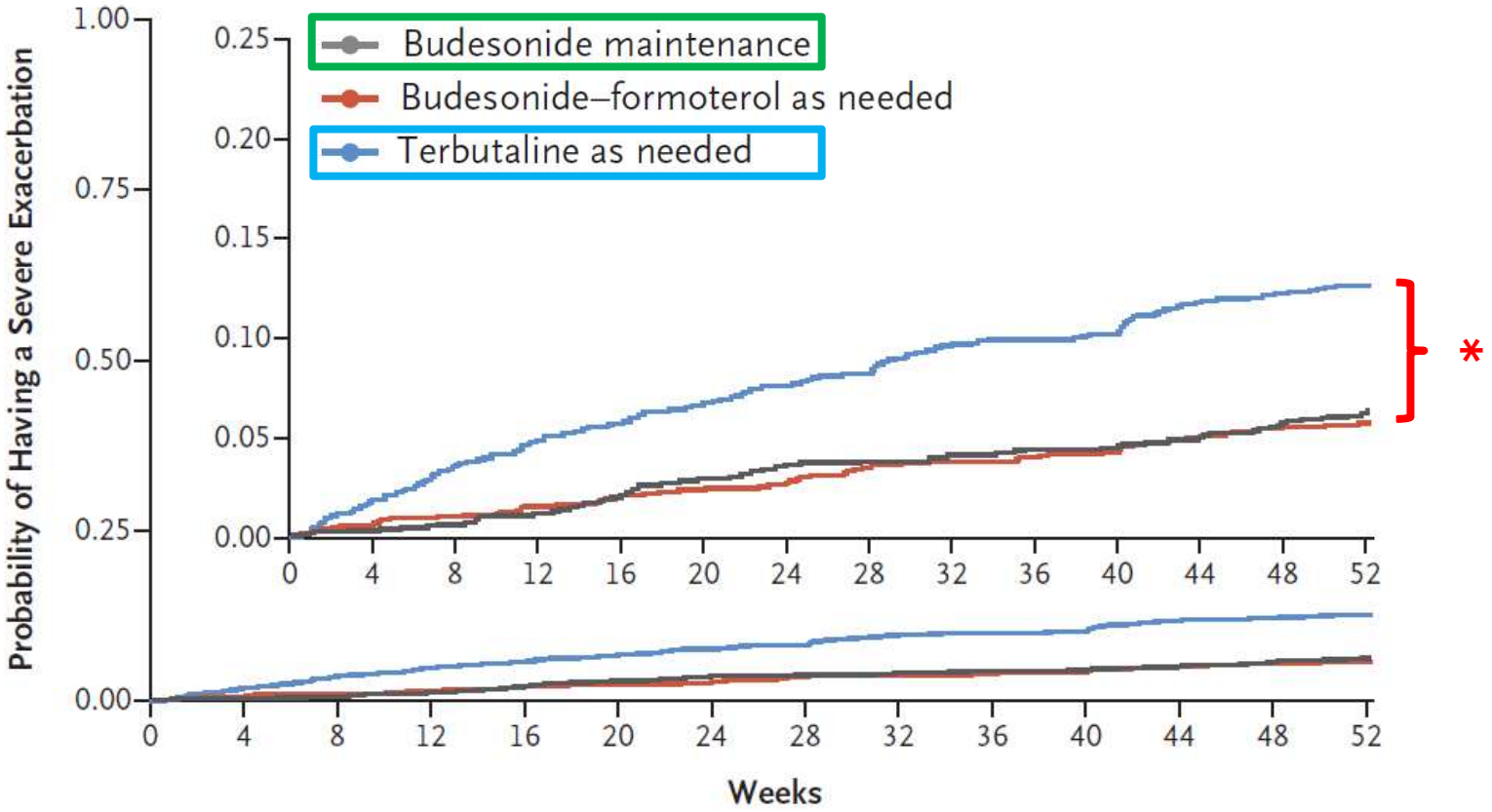
O'Byrne PM. N Engl J Med 2018;378:1865.

ICS 중단 ⇨ AE⇧

Double-blind RCT (SYGMA-1). **GINA step 2 asthma pts** (**N=3,849**)

TB prn *vs* BUD 200μg bid + TB prn *vs* BUD 250μg / FOR 6μg prn for 52 weeks.

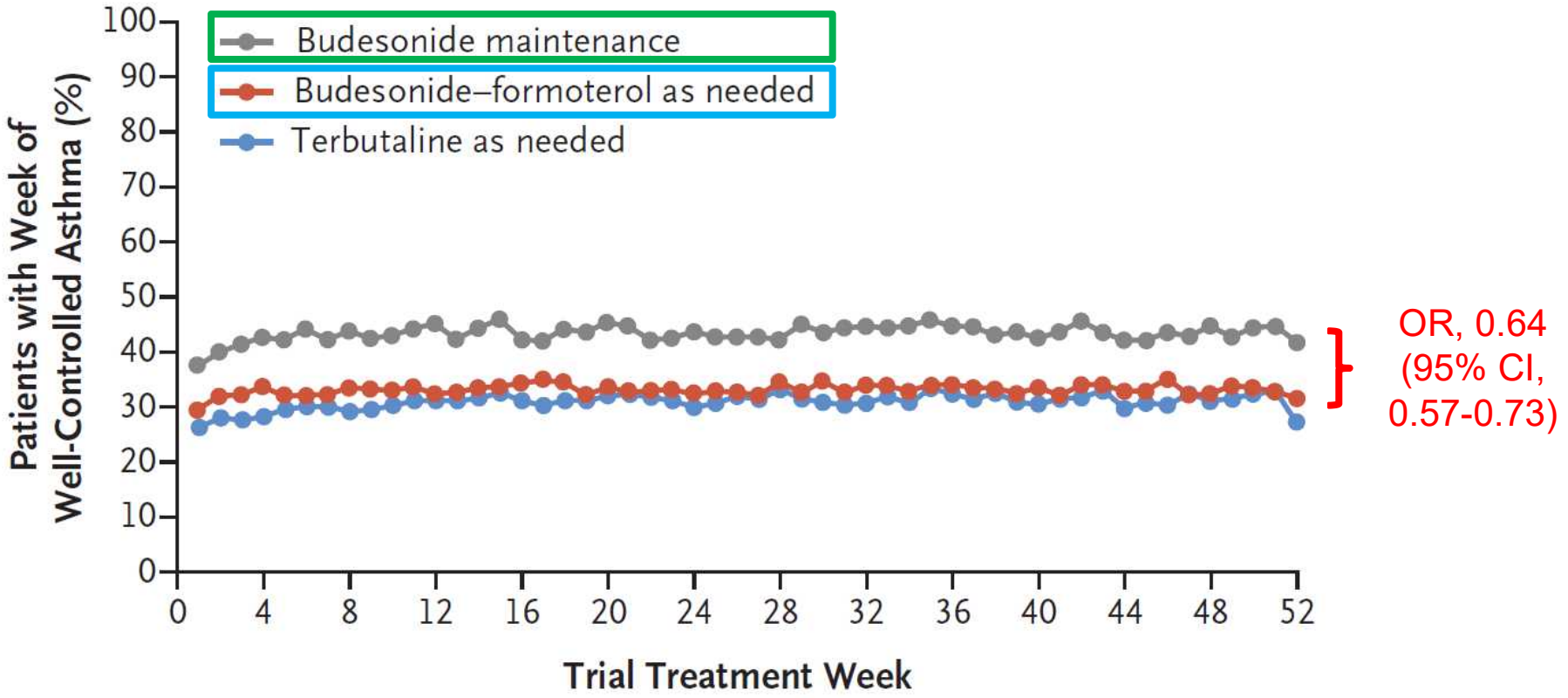
Primary outcome: **asthma symptom control** (superior to TB prn).



O'Byrne PM. N Engl J Med 2018;378:1865.

Control:
ICS > ICS/FOR prn

Double-blind RCT (SYGMA-1). **GINA step 2 asthma pts** (**N=3,849**)
TB prn *vs* BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.
Primary outcome: **asthma symptom control** (superior to TB prn).



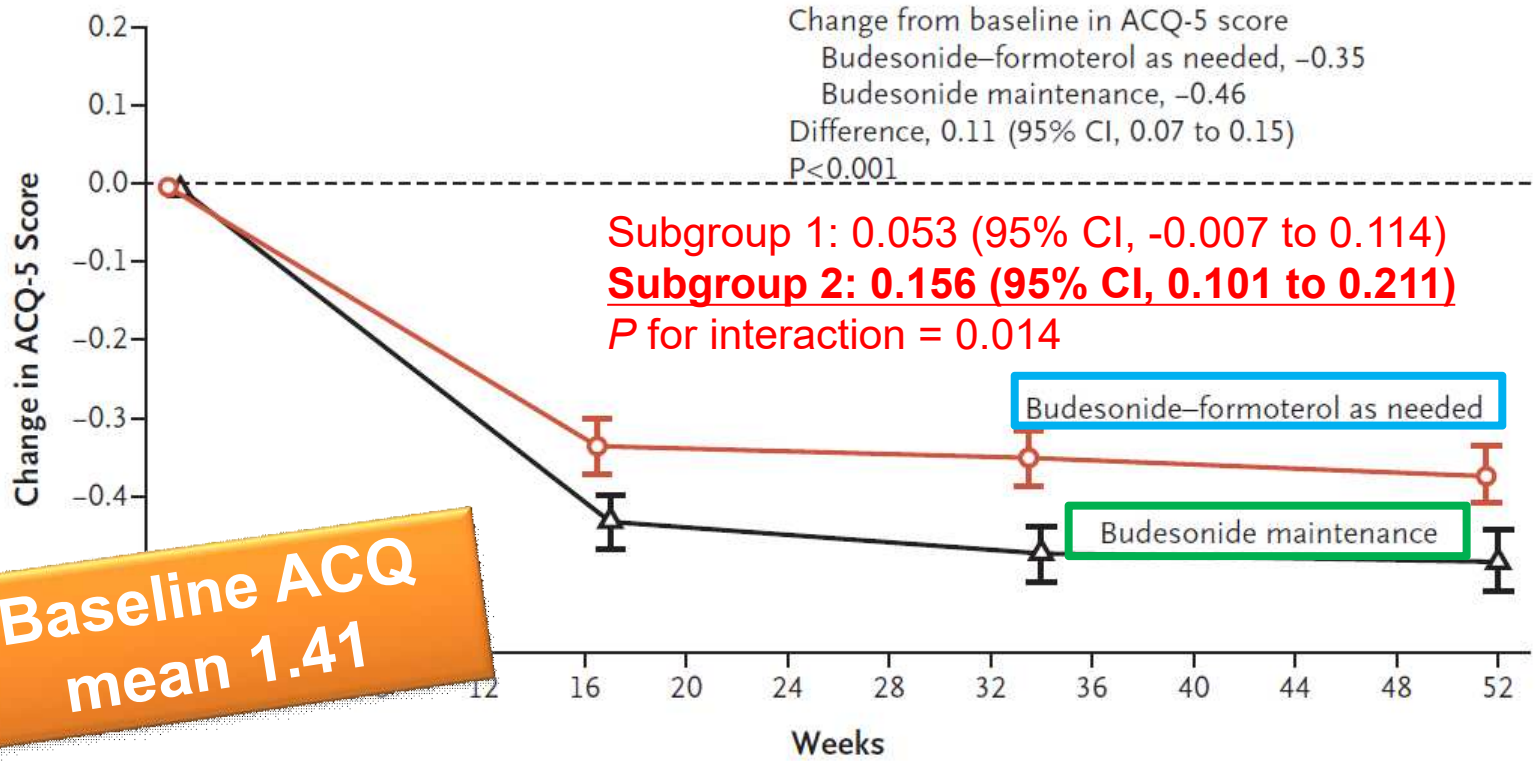
O'Byrne PM. N Engl J Med 2018;378:1865.

ACQ-5: ICS > ICS/FOR prn

Double-blind RCT (SYGMA-2). **GINA step 2 asthma pts (N=4,176)**

BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.

Primary outcome: **severe AE rate**. (non-inferior)



Subgroup 1: 0.053 (95% CI, -0.007 to 0.114)

Subgroup 2: 0.156 (95% CI, 0.101 to 0.211)

P for interaction = 0.014

Baseline ACQ mean 1.41

Bateman BD. N Engl J Med 2018;378:1877.

Bateman BD. Am Thorac Soc 2019.

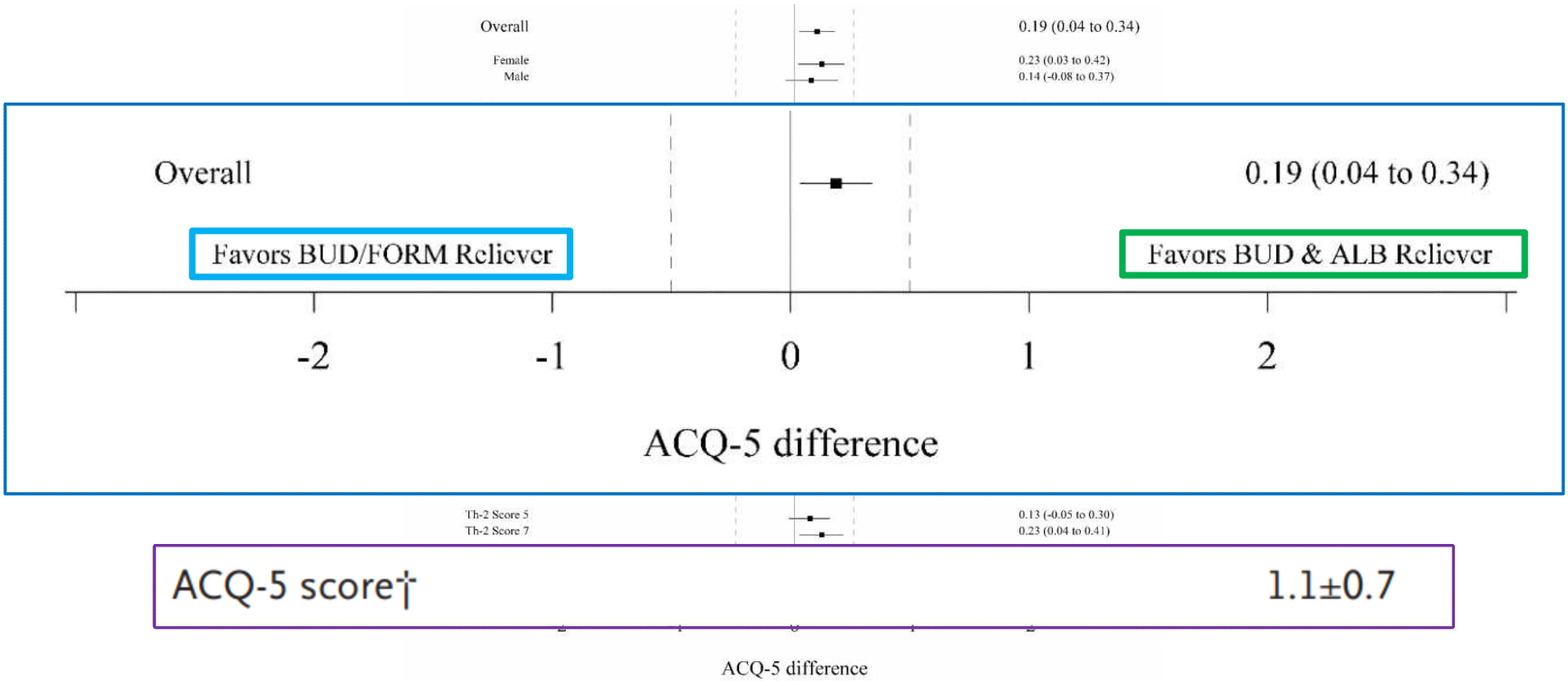
ACQ-5: ICS > ICS/FOR prn

Open-label RCT in NZ, UK, Italy, Australia (Novel START).

Mild (2/mo ≤ SABA ≤ 2/d) BA pts with no hospitalization within 12mo **(ACQ 1.1)(N=675)**

BUD 200µg bid + AL 100µg prn *vs* BUD 200µg / FOR 6µg as needed *vs* AL prn for 52 weeks.

Primary outcome: exacerbation rate



Beasley R. N Engl J Med 2019;380:2020.

ACQ-5 is a predictor of AE

A pragmatic trial. BA pts for 12 mo. (**N=611**)

Table 3 ORs and coefficients* of logistic prediction models for severe asthma exacerbations

	History		History+spirometry		History+spirometry+Fe_{NO}	
	OR(95% CI)	Coefficient	OR (95% CI)	Coefficient	OR (95% CI)	Coefficient
ACQ (per 0.5 score)	1.55 (1.22 to 1.98)	0.208	1.52 (1.19 to 1.94)	0.198	1.52 (1.19 to 1.94)	0.195
Current smoking	2.13 (1.08 to 4.17)	0.712	1.83 (0.93 to 3.62)	0.570	1.77 (0.89 to 3.50)	0.532
Chronic sinusitis	2.09 (1.02 to 4.28)	0.694	2.49 (1.17 to 5.31)	0.860	2.39 (1.11 to 5.14)	0.813
Ever admitted asthma	2.28 (1.16 to 4.49)	0.778	1.90 (0.95 to 3.82)	0.606	1.88 (0.94 to 3.79)	0.590
Oral steroids previous year	3.52 (1.68 to 7.36)	1.188	3.69 (1.74 to 7.80)	1.229	3.76 (1.79 to 7.94)	1.236
FEV1% predicted (per 10%)			0.97 (0.95 to 0.99)	−0.281	0.97 (0.95 to 0.99)	−0.270
Fe_{NO} (per 10 ppb)					1.01 (1.00 to 1.01)	0.059
Intercept		−4.595		−0.491		−0.737

*Coefficients of the models shown after shrinkage; shrinkage factors were 0.9440, 0.9407 and 0.9326 for the history, spirometry and Fe_{NO} model, respectively.
ACQ, Asthma Control Questionnaire.

Baseline ACQ mean 1.01

Loymans R. Thorax 2016;71:838.

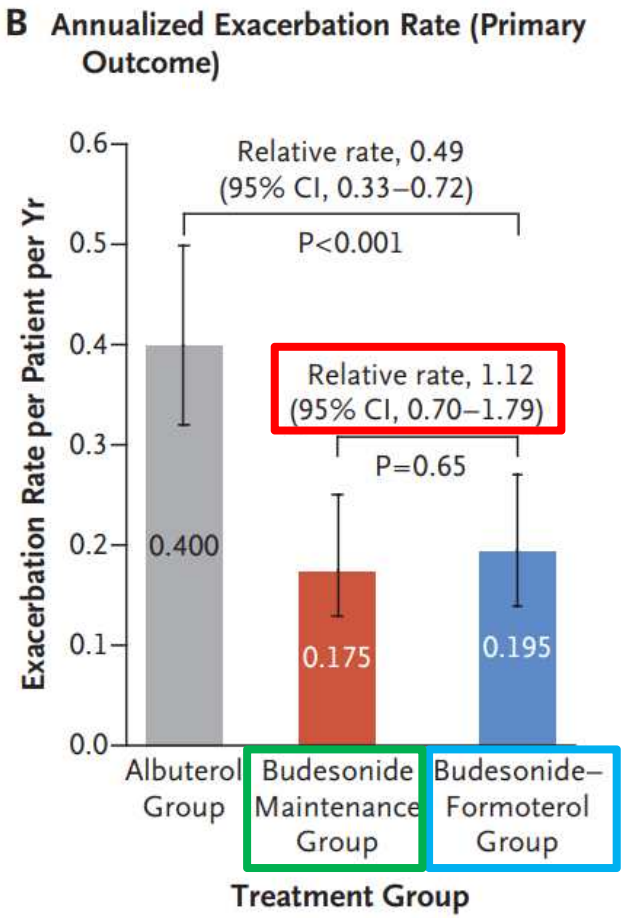
AE: ICS ≈ ICS/ FOR prn

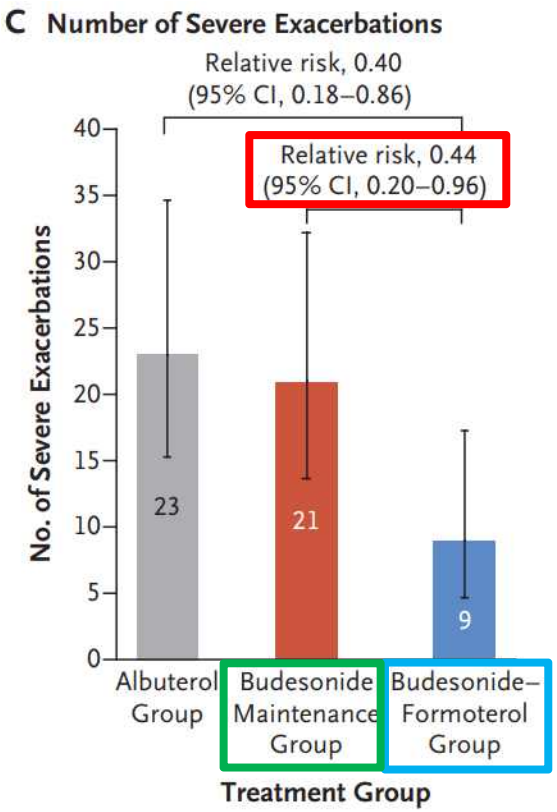
Open-label RCT in NZ, UK, Italy, Australia (Novel START).

Mild (2/mo ≤ SABA ≤ 2/d) BA pts with no hospitalization within 12mo **(ACQ 1.1) (N=675)**

BUD 200µg bid + AL 100µg prn *vs* BUD 200µg / FOR 6µg as needed *vs* AL prn for 52 weeks.

Primary outcome: **exacerbation rate**





easley R. N Engl J Med 2019;380:2020.

AE: ICS ≈ ICS/FOR prn

Open-label RCT in NZ, UK, Italy, Australia (Novel START).

Mild (2/mo ≤ SABA ≤ 2/d) BA pts with no hospitalization within 12mo **(ACQ 1.1) (N=675)**

BUD 200µg bid + AL 100µg prn *vs* BUD 200µg / FOR 6µg as needed *vs* AL prn for 52 weeks.

Primary outcome: **exacerbation rate**

Table 2. Medication Outcomes.*

Outcome	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Glucocorticoid use			
No. of inhaled glucocorticoid-containing actuations per day			
Mean	NA	1.11±0.56	0.53±0.54
Median (IQR)	NA	1.23 (0.66–1.57)	0.37 (0.15–0.73)
Range	NA	0–2.01	0–3.95

Beasley R. N Engl J Med 2019;380:2020.

AE: ICS ≈ ICS/FOR prn

Open-label RCT in NZ, UK, Italy, Australia (Novel START).

Mild (2/mo ≤ SABA ≤ 2/d) BA pts with no hospitalization within 12mo **(ACQ 1.1) (N=675)**

BUD 200µg bid + AL 100µg prn *vs* BUD 200µg / FOR 6µg as needed *vs* AL prn for 52 weeks.

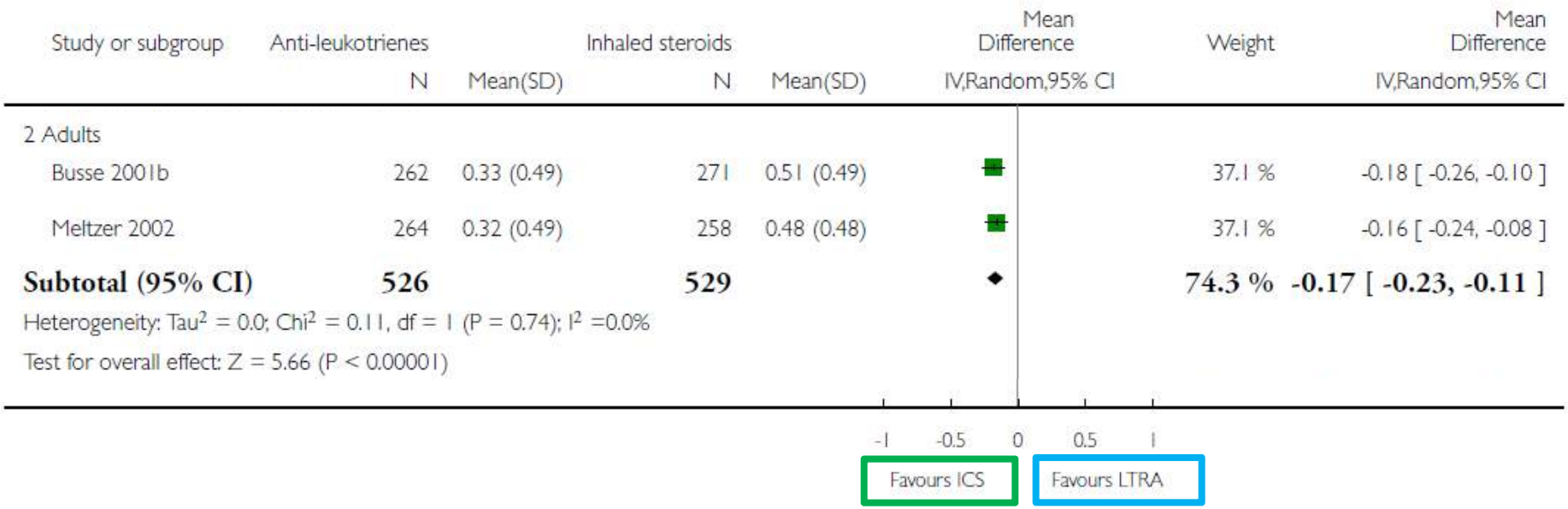
Primary outcome: **exacerbation rate**

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
No. of severe exacerbations in the previous 12 mo. — no. (%)			
0	203 (91.0)	208 (92.4)	208 (94.5)
1	20 (9.0)	15 (6.7)	12 (5.5)
2	0	2 (0.9)	0
Any	20 (9.0)	17 (7.6)	12 (5.5)

Beasley R. N Engl J Med 2019;380:2020.

FEV1: ICS > LTRA



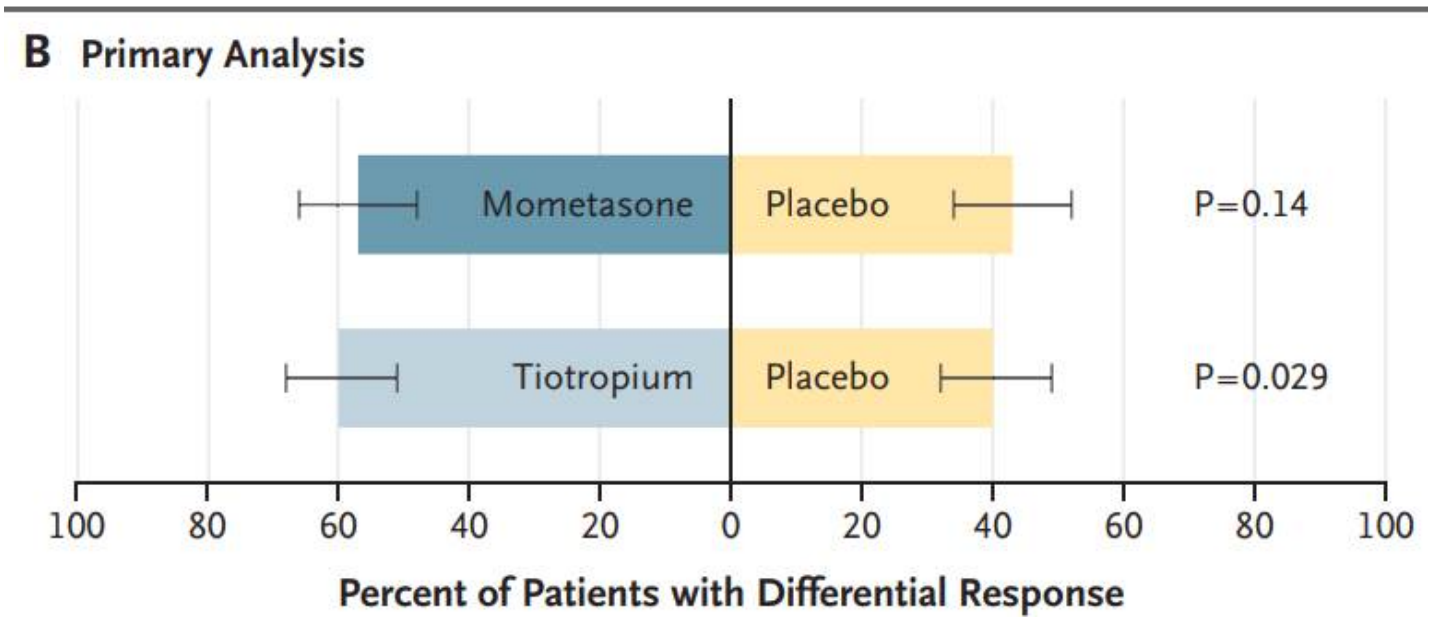
Chauhan BF. Cochrane Database Syst Rev 2012;(5):CD002314.

Response in low Eo group: ICS ≈ PLA, LAMA > PLA

Double-blind cross-over RCT (SIENNA). BA pts≥12YO with Sp Eo<2% (**ICS/LTRA-free** for at least 3wk) (**N=221**)

MOM 200µg bid *vs* TIO SMI 5 µg qd *vs* PLA for 12 weeks

Primary outcome: **Response (treatment failure > asthma control days > FEV1)**



Lazarus S. N Engl J Med 2019;380:2009.

Response in low Eo group: ICS ≈ PLA, LAMA > PLA

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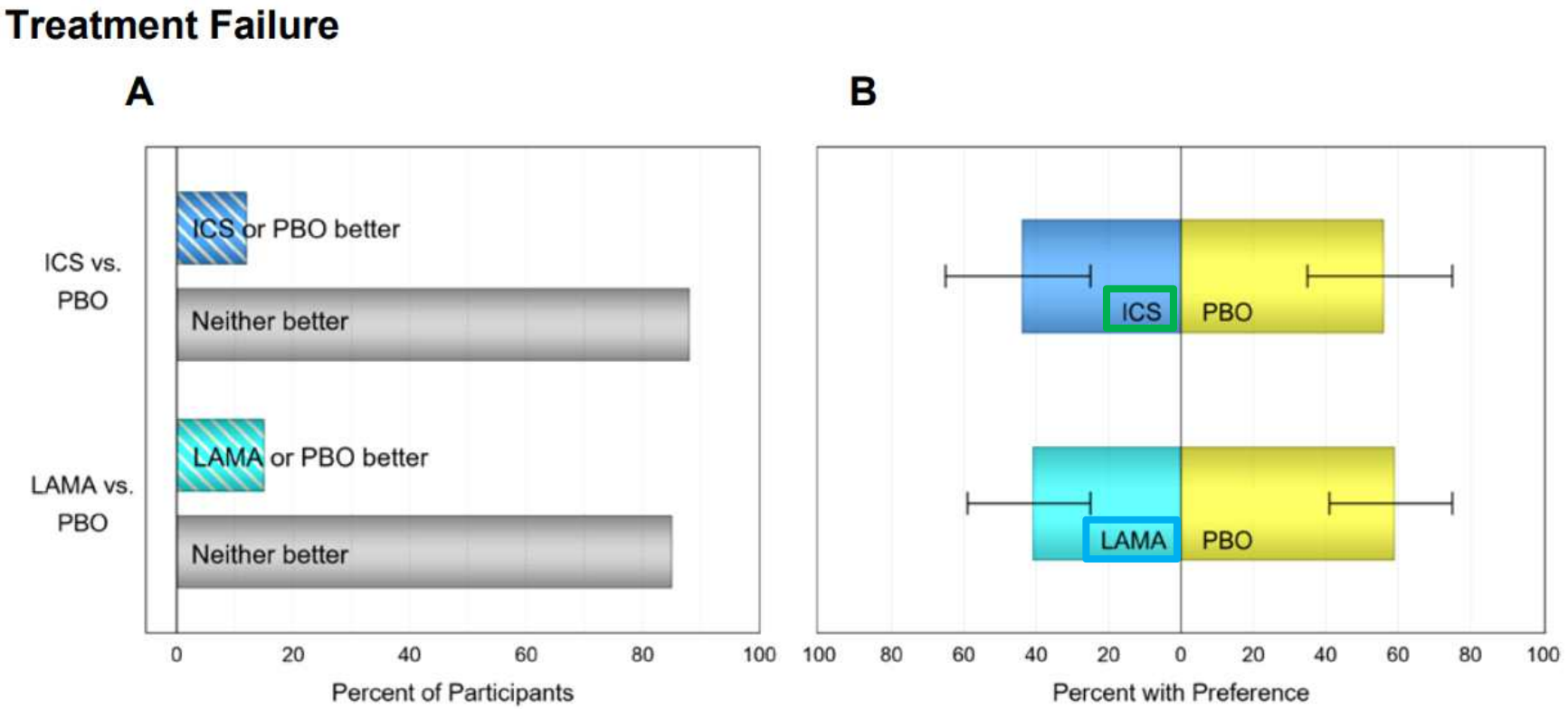
MOM 200µg bid *vs* TIO SMI 5 µg qd *vs* PLA for 12 weeks
Primary outcome: **Response (treatment failure > asthma control days > FEV1)**



Lazarus S. N Engl J Med 2019;380:2009.

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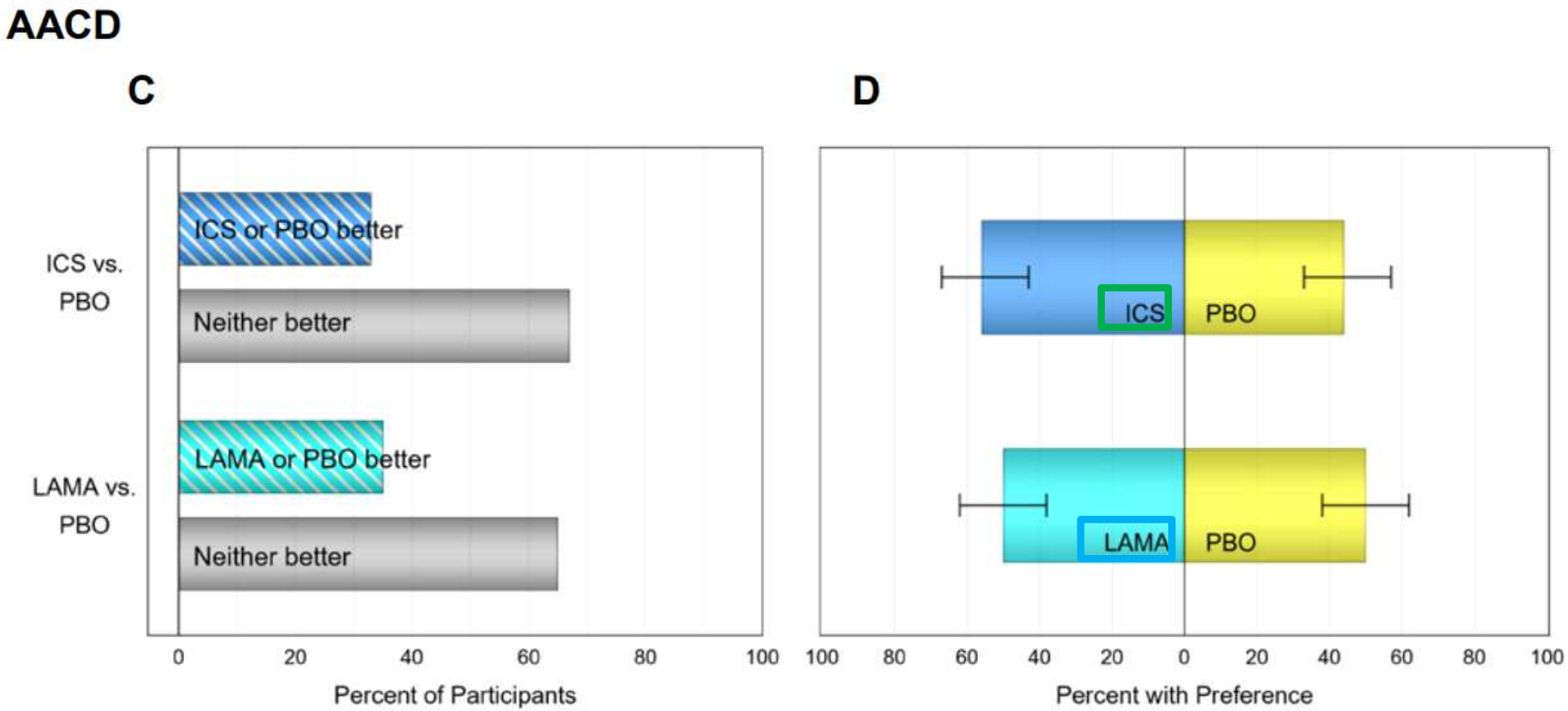
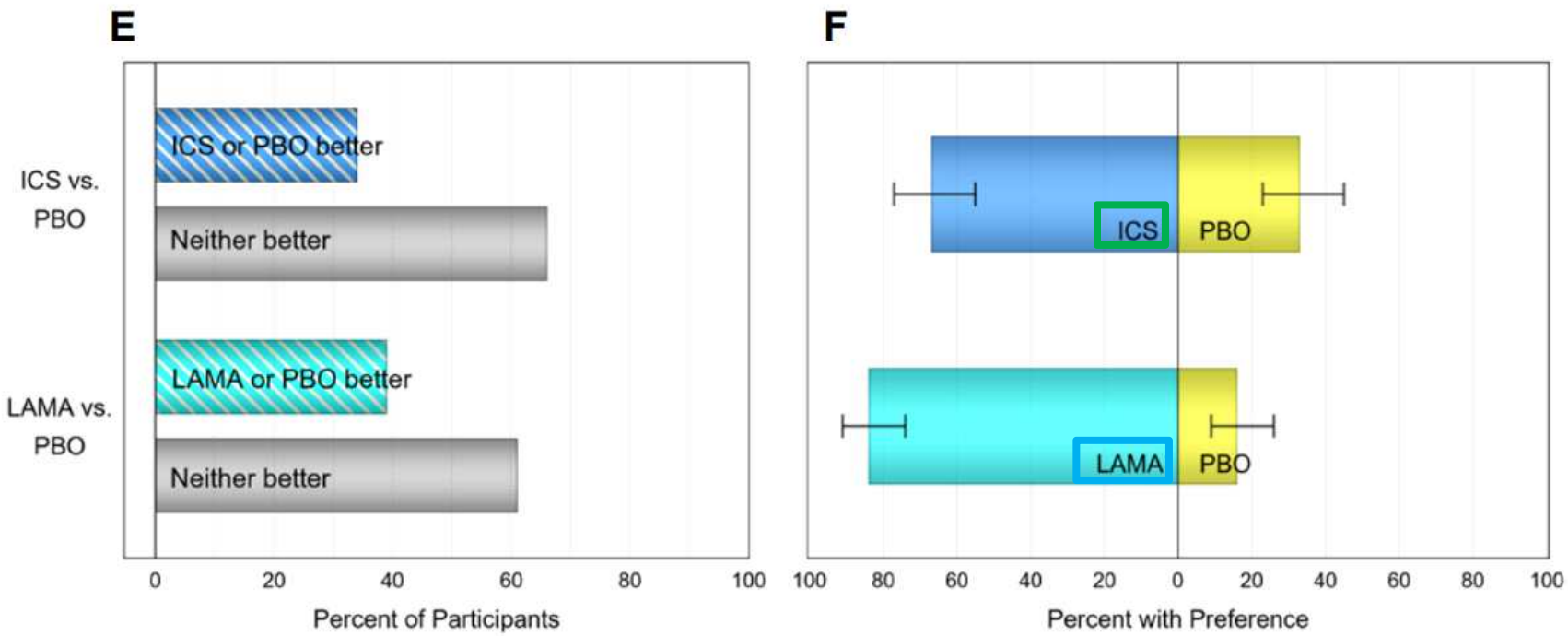


Lazarus S. N Engl J Med 2019;380:2009.

Response in low Eo group: ICS ≈ PLA, LAMA > PLA

Double-blind cross-over RCT (SIENA). BA pts≥12YO with Sp Eo<2% (**ICS/LTRA-free** for at least 3wk) (**N=221**)
MOM 200µg bid *vs* TIO SMI 5 µg qd *vs* PLA for 12 weeks
Primary outcome: **Response (treatment failure > asthma control days > FEV1)**

FEV1



Lazarus S. N Engl J Med 2019;380:2009.

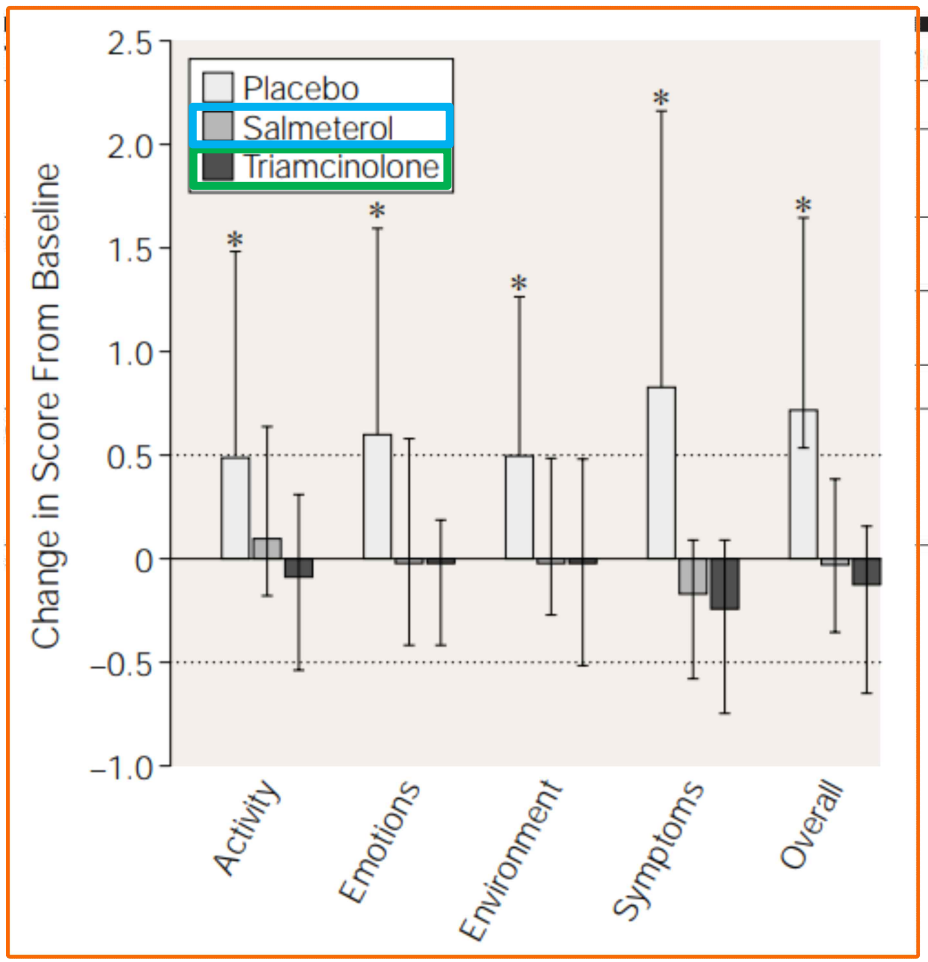
ICS 중단, SAL ⇨ PEF, 천식 관련 QoL nc

Double blind RCT (SOCS).

"well controlled" (FEV1>80%, PEF variability ≤20%) **by TAC 400 μg/d (run-in 6 weeks) (N=164)**

TAC 400 μg/d *vs* SAL *vs* PLA for 16 weeks.

Outcome: PEF, FEV1, symptom scores, SABA use, treatment failure, AE, ...



AM PEF*

Treatment Group			
Triamcinolone	Placebo vs Salmeterol	Placebo vs Triamcinolone	Salmeterol vs Triamcinolone
460.4 (17.1)			
474.6 (14.3)			
449.4 (15.7)			
14.2 (−17.5 to 46.0) [.38]	−39.7 (−85.2 to 5.8) [.09]	−32.6 (−77.5 to 12.2) [.15]	7.1 (−38.4 to 52.6) [.76]

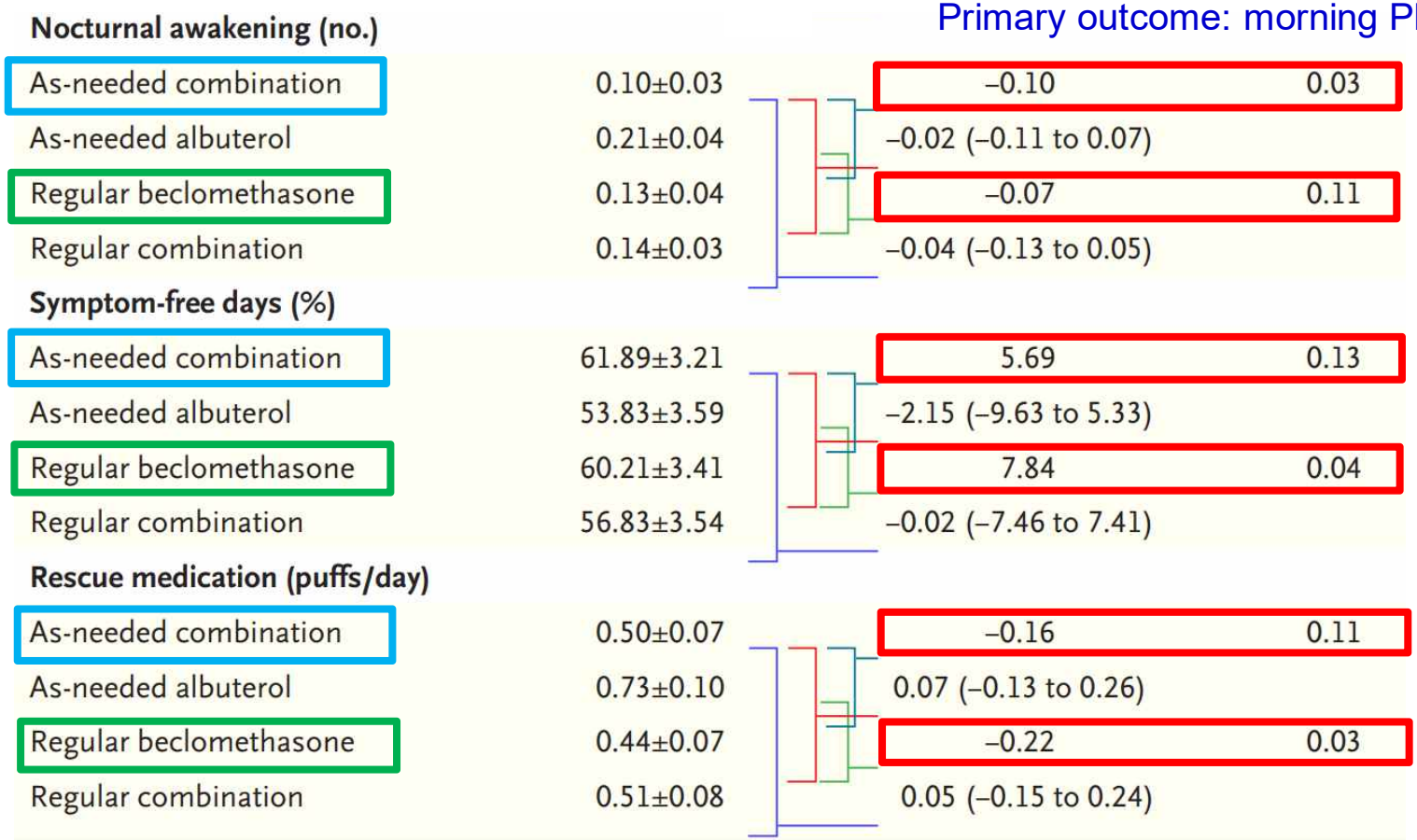
Lazarus SC. JAMA 2001;285:2583.

Sx-free days, rescue medication: regular ICS > SABA prn, ICS/SABA prn ≈ SABA prn

Double-blind RCT (BEST). Mild persistent BA pts controlled in run-in (BDP 500µg/d 4wk) (N=466)

BDP 250µg/AL prn *vs* Albuterol prn *vs* BDP 250µg bid + AL prn *vs* BDP 250µg + AL bid+prn for 6mo.

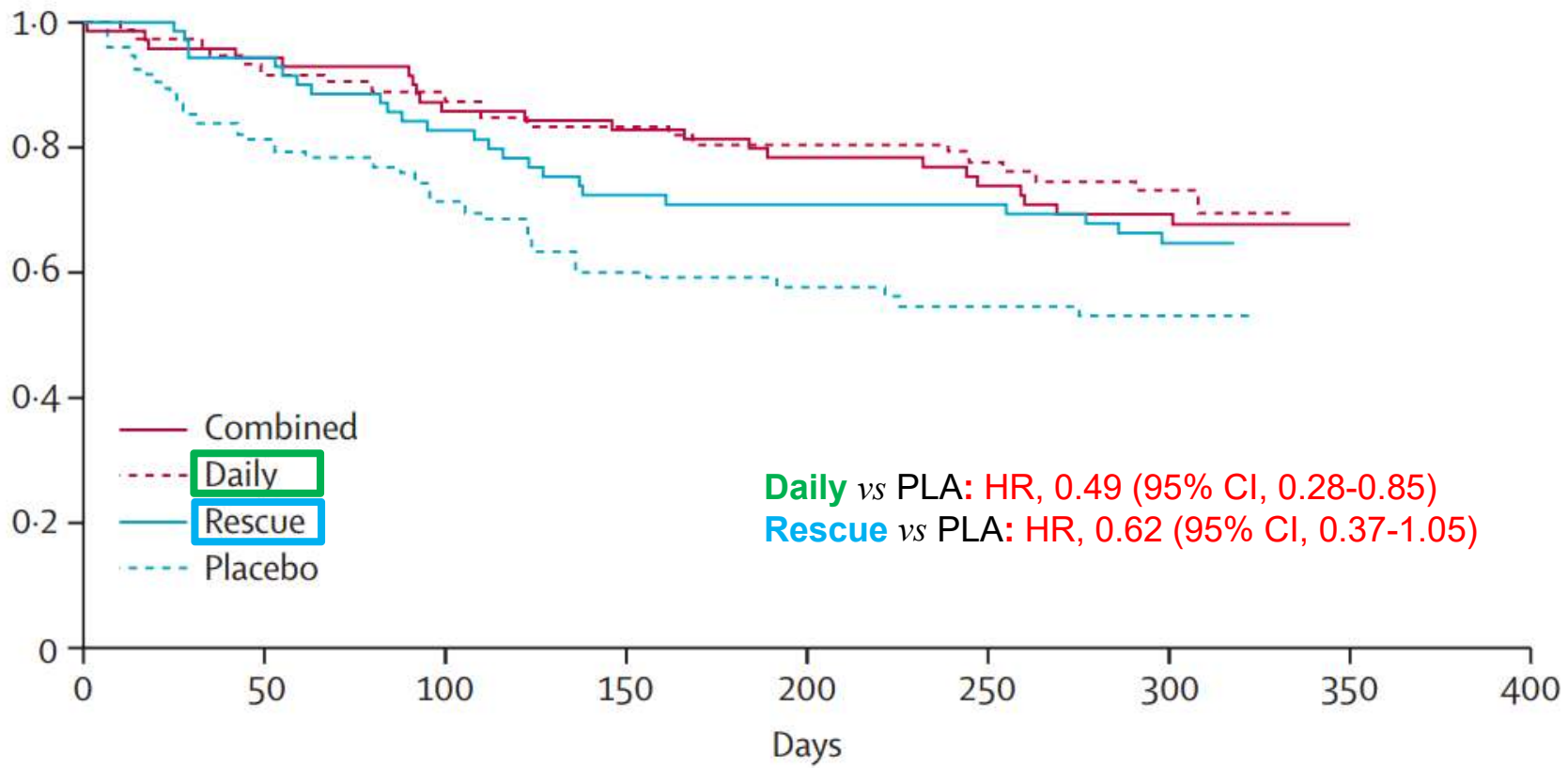
Primary outcome: morning PEF.



Papi A. N Engl J Med

AE: regular ICS > SABA prn, ICS/SABA prn ≈ SABA prn

Double blind RCT (TREXA).
Mild persistent BA children (5-18YO) "well controlled" (NAEPP) with ≤ low dose ICS tx (N=288)
BDP 80µg/d+BDP/AL prn *vs* BDP+PLA/AL prn *vs* PLA+BDP/AL prn *vs* PLA+PLA/AL prn for 44 weeks.
Primary outcome: time to 1st AE requiring Pd.



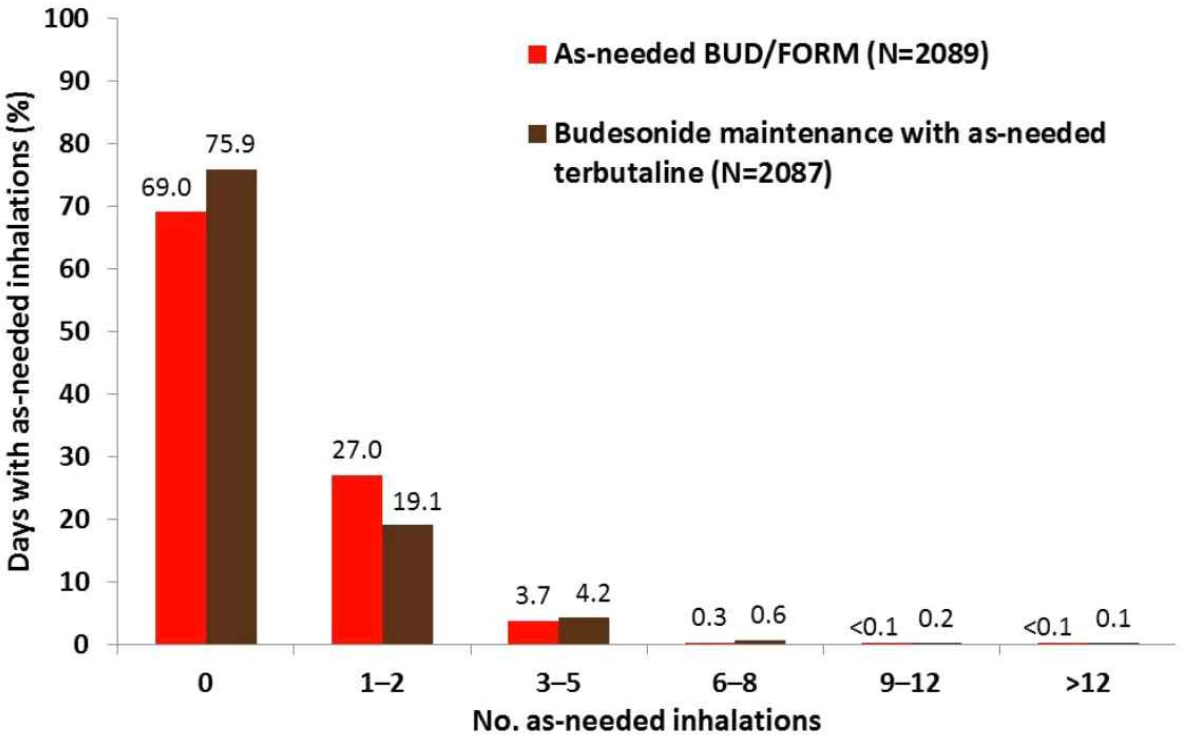
Daily *vs* PLA: HR, 0.49 (95% CI, 0.28-0.85)
Rescue *vs* PLA: HR, 0.62 (95% CI, 0.37-1.05)

Martinez FD. Lancet 2011;377:650.

No as-needed tx in 70%

Double-blind RCT (SYGMA-2). GINA step 2 asthma pts (N=4,176)
BUD 200µg bid + TB prn *vs* BUD 250µg / FOR 6µg prn for 52 weeks.
Primary outcome: severe AE rate. (non-inferior)

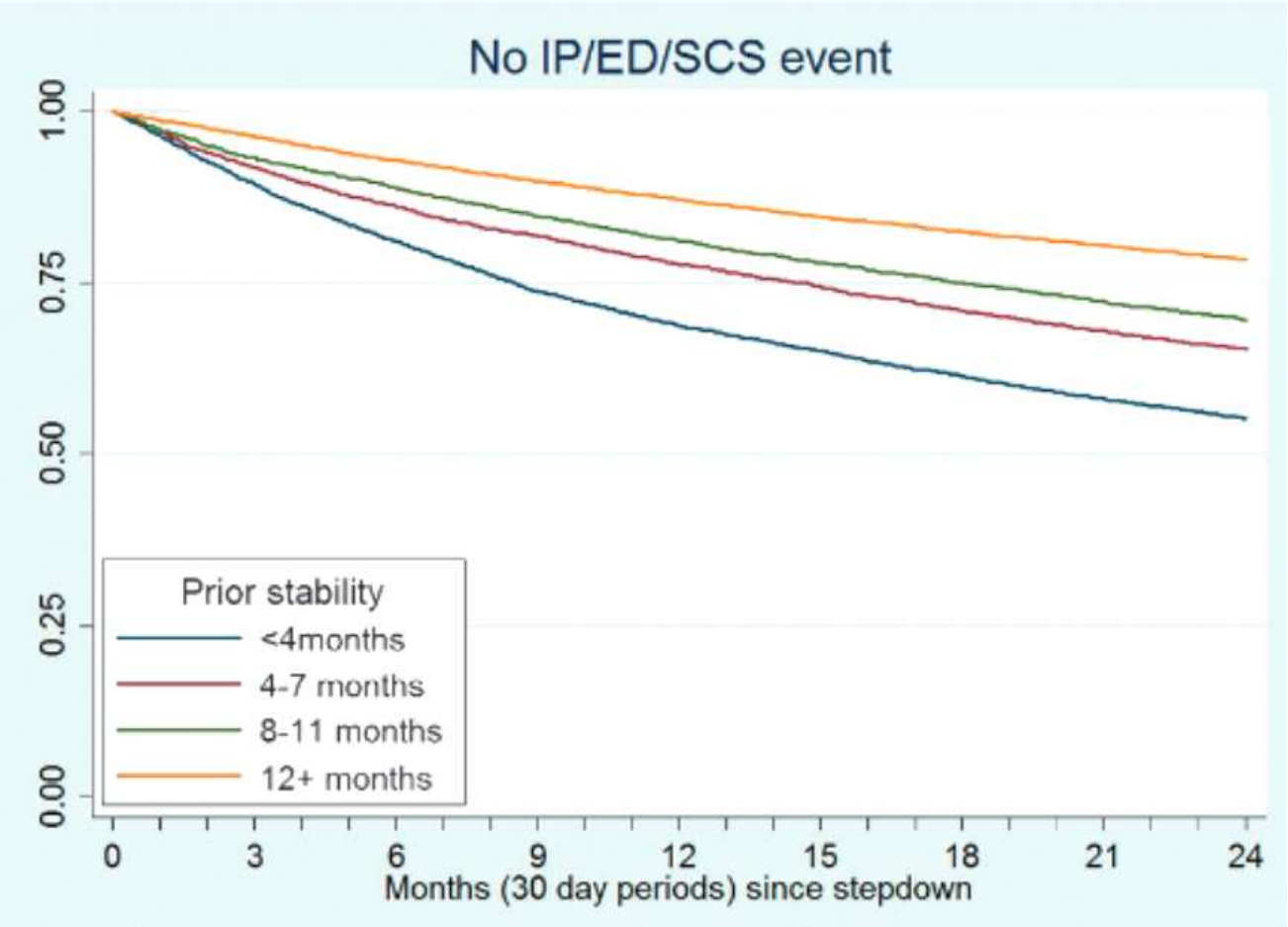
Figure S4. Proportion of Patient Days by Frequency of As-Needed Reliever Use, and by Treatment Group



Bateman ED. N Engl J Med 2018;378:1877.

ICS 감량 >50% ⇨ 급성악화⇧

A retrospective claims data analysis in US. Asthma pts (N=26,292)
Primary outcome: time-to-first AE.

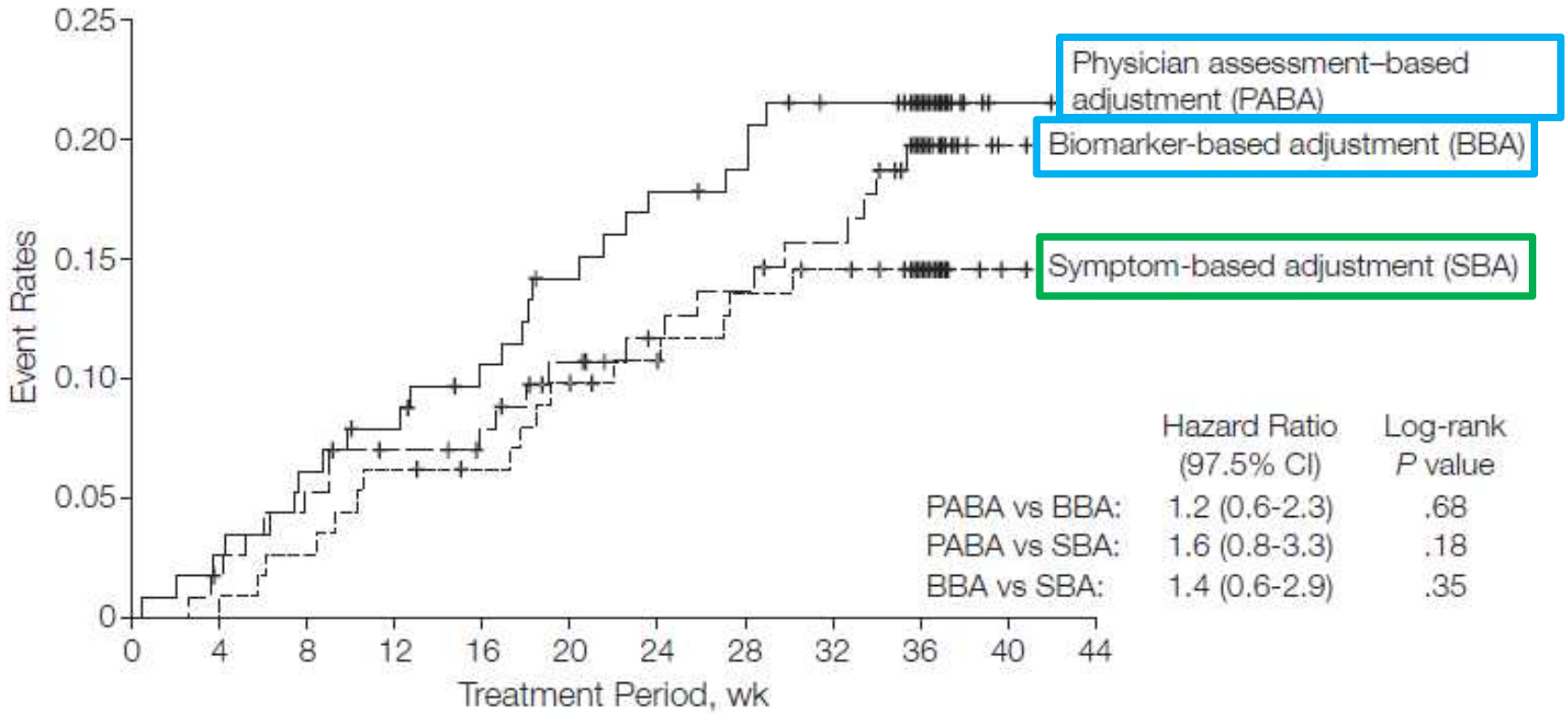


Rank MA. Chest 2015;148:630.

ICS maintain ≈ dose adjust

Double-blind RCT (BASALT). Mild-to-mod asthma pts controlled by BDP HFA 80µg/d (run-in) (N=342)
sician assessment-based (PABA) *vs* FeNO-based (BBA) *vs* Symptom-based (SBA) prn for 52 weeks.
Primary outcome: severe AE rate. (non-inferior)

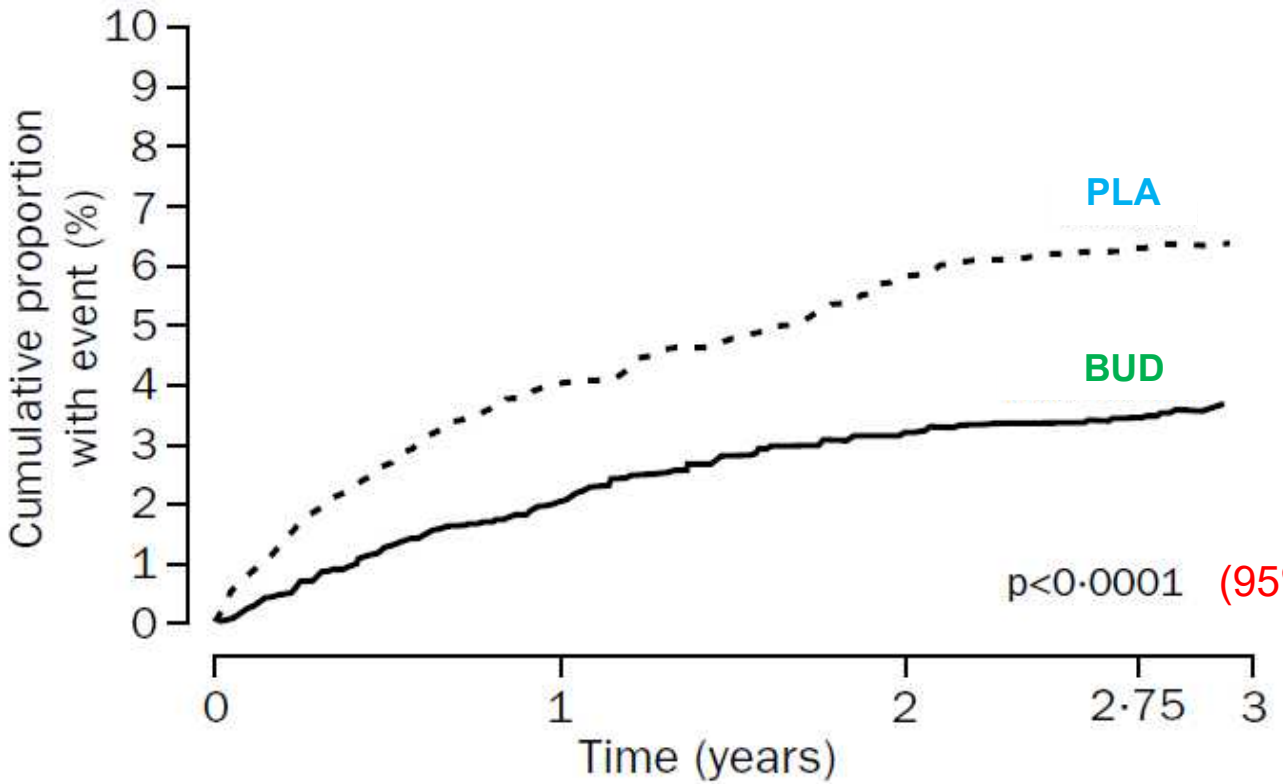
Figure 2. Time to First Treatment Failure



Galhoun WJ. JAMA 2012;308:987.

AE: ICS > PLA

Double-blind RCT (START). **Mild-persistnet (≥2yr) BA pts** (**N=7,241**)
BUD 400μg (<11YO, 200μg) qd *vs* PLA for 3yr.
Primary outcome: **time to 1st severe asthma-related event**.



Pauwels RA. Lancet 2003;361:1071.

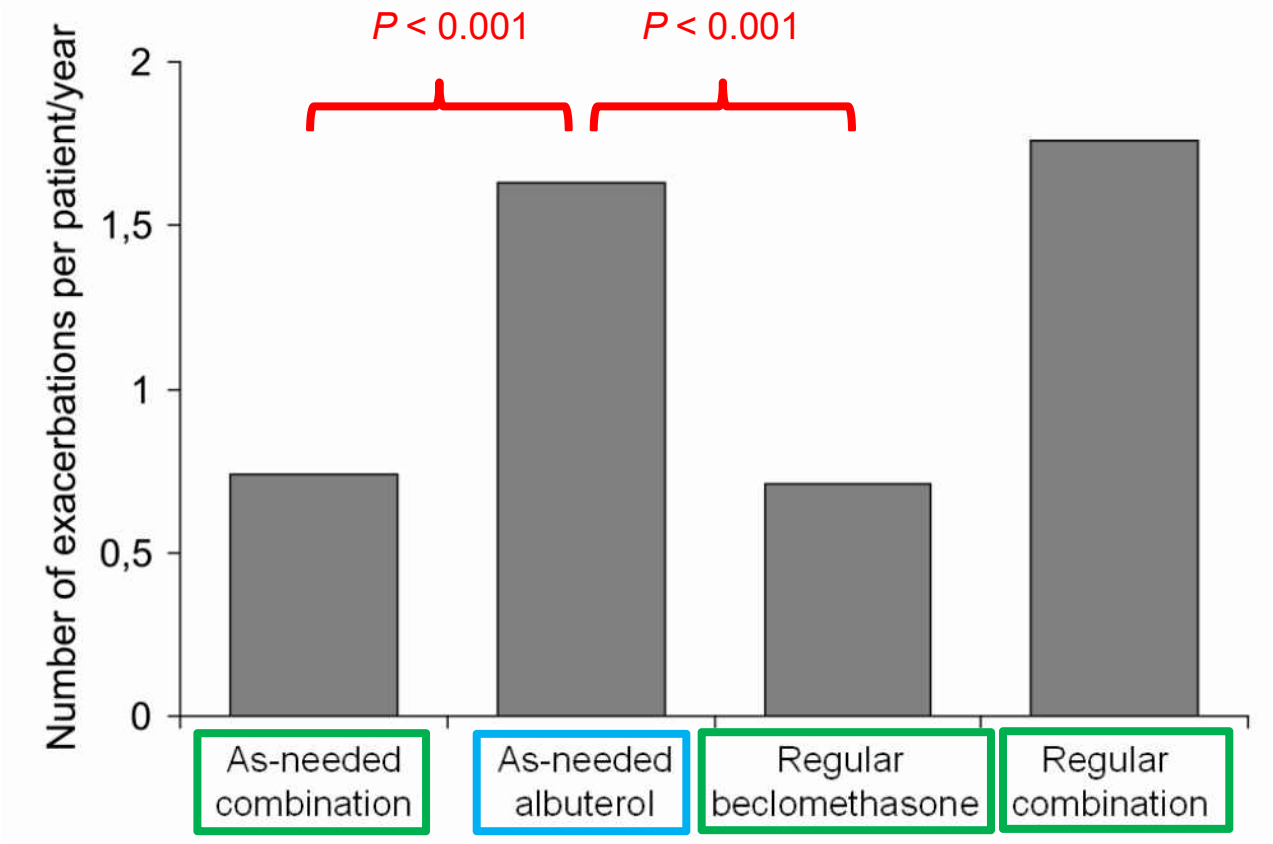
ICS 중단 ⇨ 급성악화⇧

Double-blind RCT (BEST).

Mild persistent asthma pts (>6mo) controlled during run-in (BDP 500μg/d 4wk) (N=466)

BDP 250μg/AL prn *vs* Albuterol prn *vs* BDP 250μg bid + AL prn *vs* BDP 250μg + AL bid+prn for 6mo.

Primary outcome: morning PEF.



Papi A. N Engl J Med