Asthma Management

ICS/formoterol vs ICS/non-formoterol SABA

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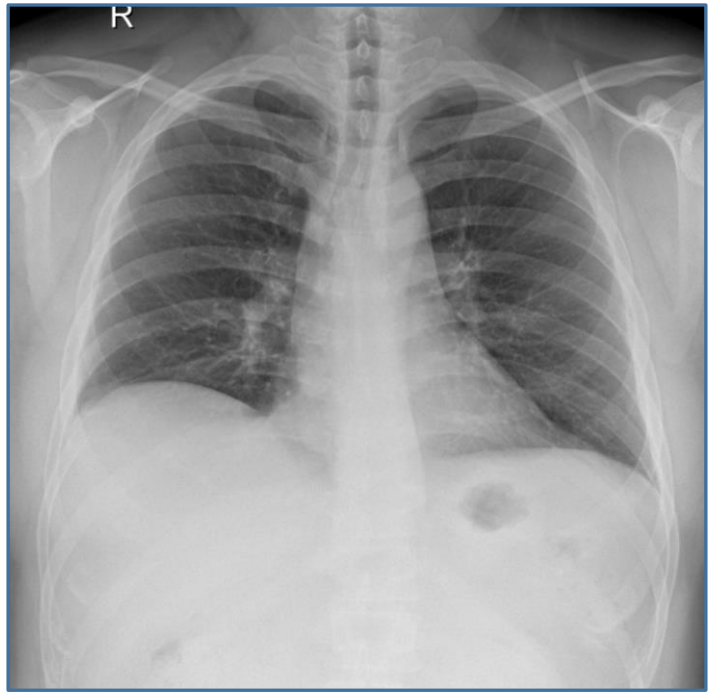
CASE M/33		
	주 호소	**만성 기침**으로 의뢰 **거의 매일 기침**, 자다 깨지는 않음
	사회력, 직업력	Never-smoker, 편의점에서 근무
	혈액검사	Blood eosinophil 6.2% (480/μL)



PFT	Liter	% Predicted
FEV_1/FVC	79	
FEV_1	**2.66**	**65**
FVC	3.36	64

ASTHMA
STEP 3
T2 inflammation

MBPT	FEV_1 (L)	% Change
Baseline	2.66	0
1 mg/mL	2.45	-7
2 mg/mL	2.37	-10
3 mg/mL		**-20**
4 mg/mL	1.95	-26

Low dose ICS/formoterol
Single inhaler Maintenance & Reliever Therapy
(**SiMART**)

vs.

ICS/other LABA
plus
as-needed **SABA**

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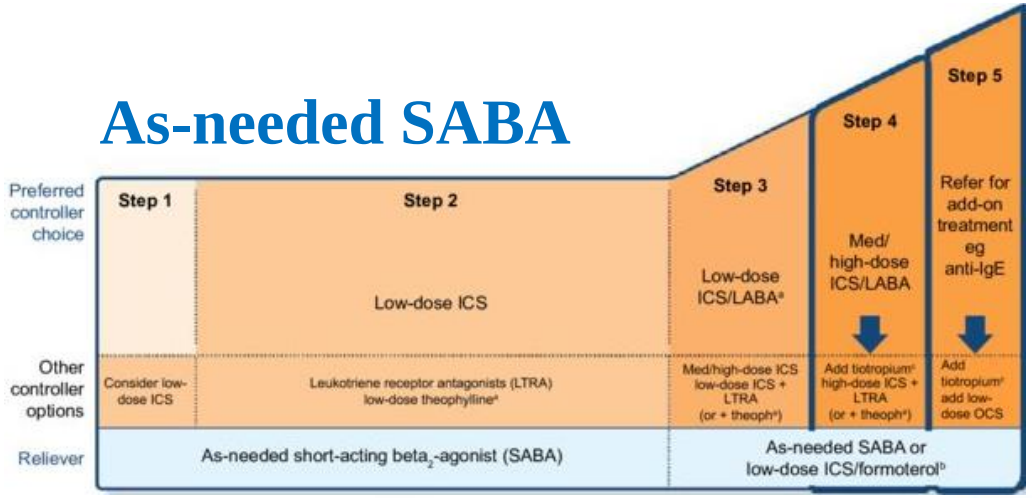
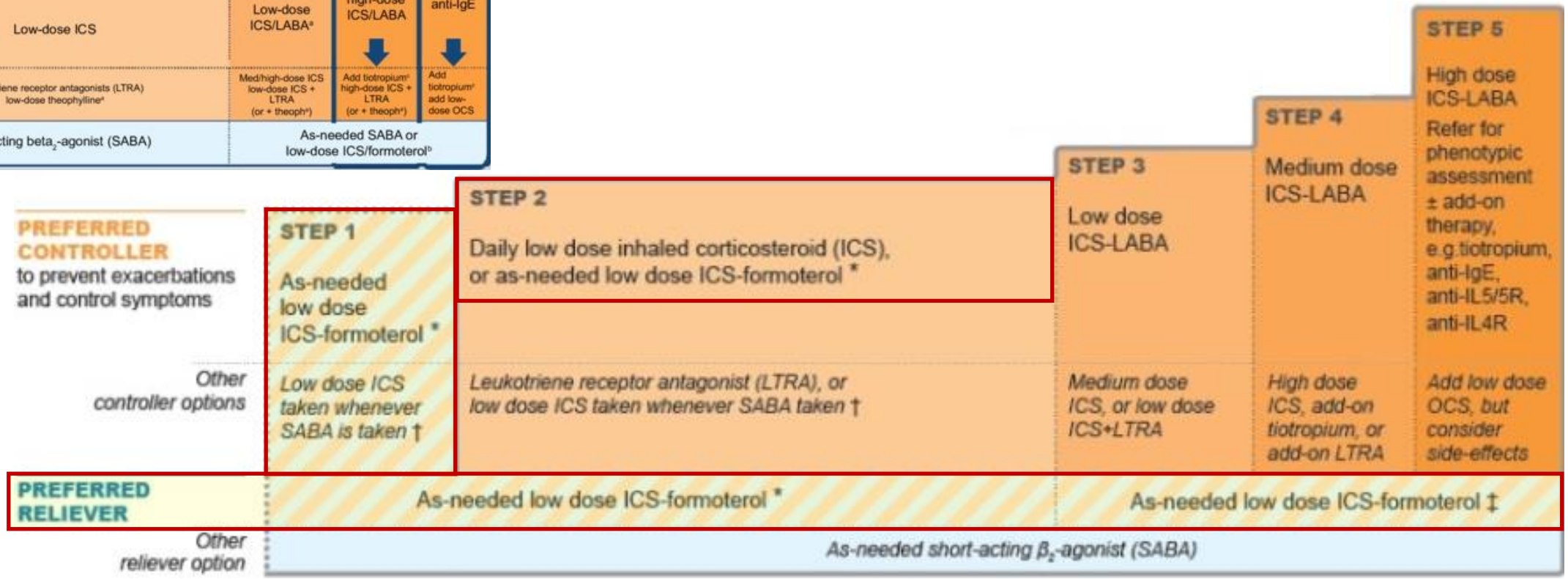
GINA 2019 Landmark Changes in Asthma Management

As-needed SABA

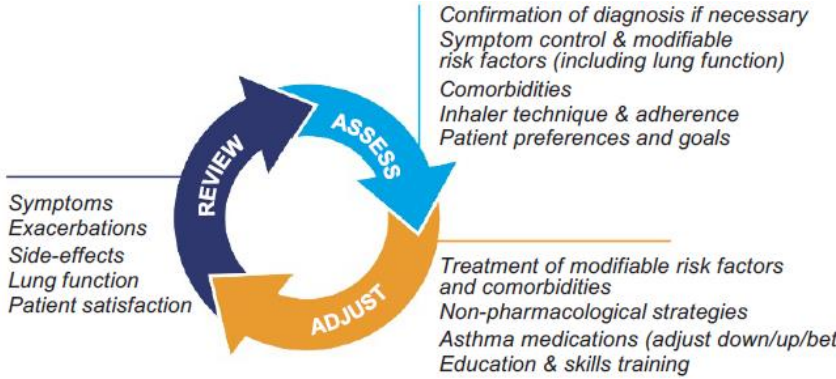




GINA 2021 Options for Asthma Treatment for Adults

Adults & adolescents 12+ years

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



Track 1, Preferred

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

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	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

Track 2, Alternative

(T1 impossible, not preferred by a patient with no AE on current controller)

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 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 phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA

RELIEVER: As-needed short-acting β2-agonist

GINA 2021 Options for Asthma Treatment for Adults

Track 1 : Preferred Approach for Most Patients

Based on 1) Evidence of Overall Lower Exacerbation Risk & Similar Symptom Control c/w Track 2
2) Availability & Cost at the **Population Level**

Track 2 : Alternative

If Track 1 is Impossible, or Not Preferred by a Patient with No Exacerbation on Current Medication
Consider 1) Patient Charactersistics : Smoker, History of Exacerbation, Blood Eosinophilia…
2) Patient's Preference : Goals, Beliefs, Concerns about Asthma & Medications
3) Practical Issues : Inhaler Technique, Adherence, Cost

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Paradoxes in Current Asthma Management

Paradox	Description
1	천식은 만성 기도 염증이 있는 질환이고 악화시 기도 염증도 증가하지만, **STEP 1**에서는 **항염증작용이 없는 SABA** 단독 치료를 권고하고 있음.
2	STEP 1에서는 필요시 자율적으로 SABA를 이용해 증상을 조절하도록 권고하지만, 이후 STEP에서는 규칙적인 fixed dose ICS 사용을 권함. '**필요시**'에서 '**규칙적**' 사용으로의 변화에 따른 혼란스러움이 있음.
3	STEP 1에서 **STEP 2**로 전환하는 목표 중 하나는 SABA 사용을 최소화하는 데에 있음. 하지만 사용을 권고하는 **ICS** 흡입제에 환자가 **즉각적인 benefit**을 감지하지 못함. 따라서 SABA의 빠른 증상 완화에 익숙한 환자들은 ICS 보다 **SABA를 보다 자주 선택**함 (**INSPIRE, REALISE**).
4	LABA는 단독으로 사용하면 안되고 ICS와 함께 사용해야 함을 강조하지만, **SABA 단독** 사용은 지침상 표준치료이고 **위험에 대한 언급이 없어** 안전하다는 착각을 유발할 수 있음.

O'Byrne & Bateman, Eur Respir J 2017; 50: 1701103. Modified.

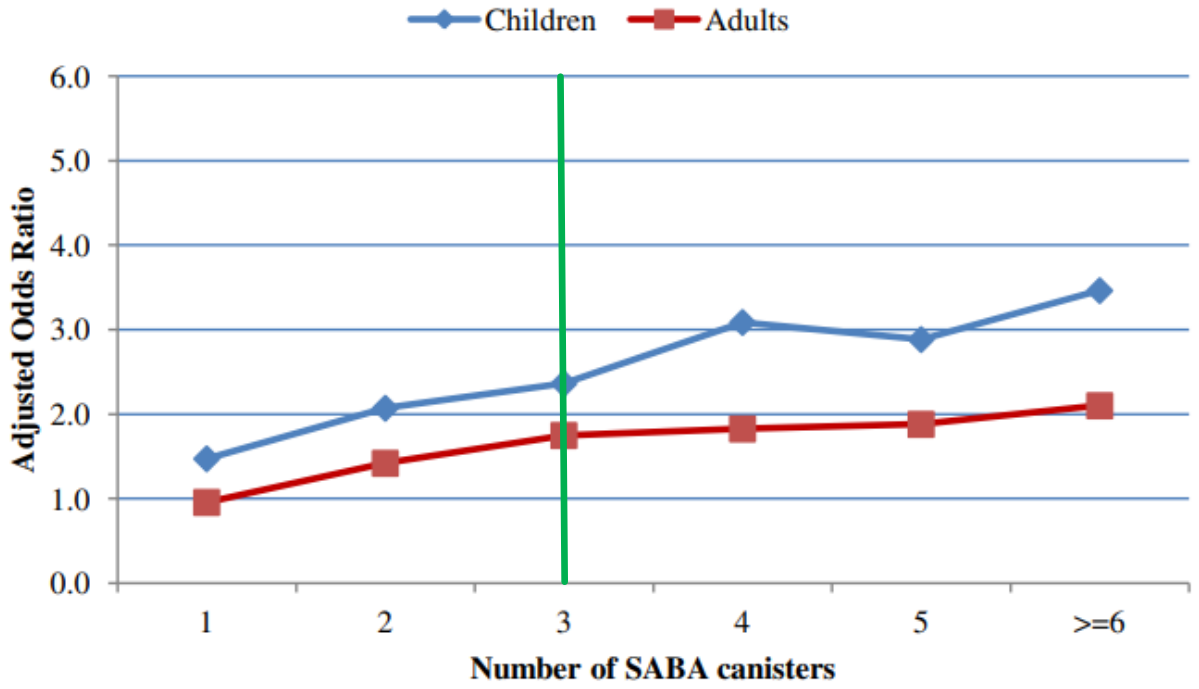
Severe Exacerbation in Mild Asthma

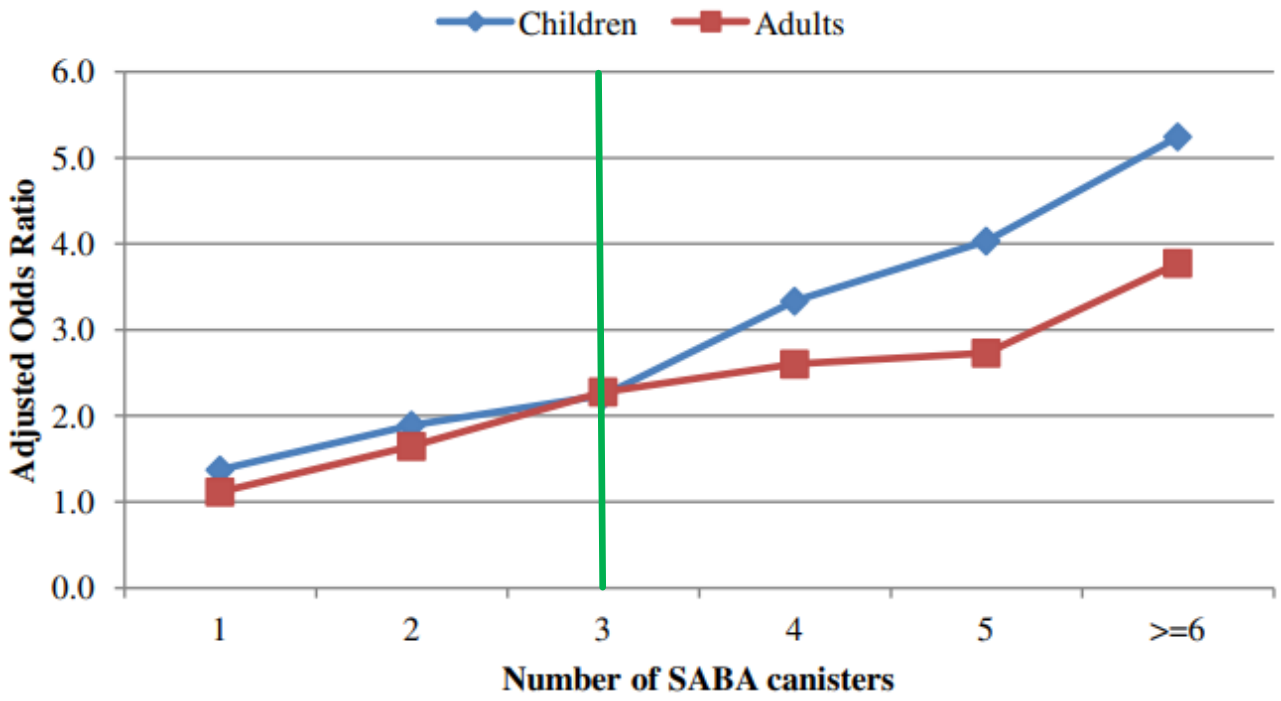
Author	Publication	Population	Definition of Mild asthma	Number (%) of Mild Asthma
Salmeron et al.	Lancet 2001;358:629	French multicenter cohort **ER admissions for acute asthma** (n=4,087)	< 1 symptoms per week during preceding 3 months	1211 (**29.6%**)
Mitchell et al.	Chest 2002;121:1407	Canada Alberta **ER admissions for acute asthma** (n=197)	Self-reported severity	73 (**37.6%**)
			Symptom only with exercise	94 (**51.7%**)
Sailly et al.	Eur J Health Econ 2005;6:94	French multicenter study **ER admissions for acute asthma** (n=169)	Intermittent asthma	51 (**30.2%**)
			Mild persistent asthma	38 (**22.5%**)

Allergy 2007; 62: 591-604.

SABA Use & Asthma-Related Hospitalization or ER Visit

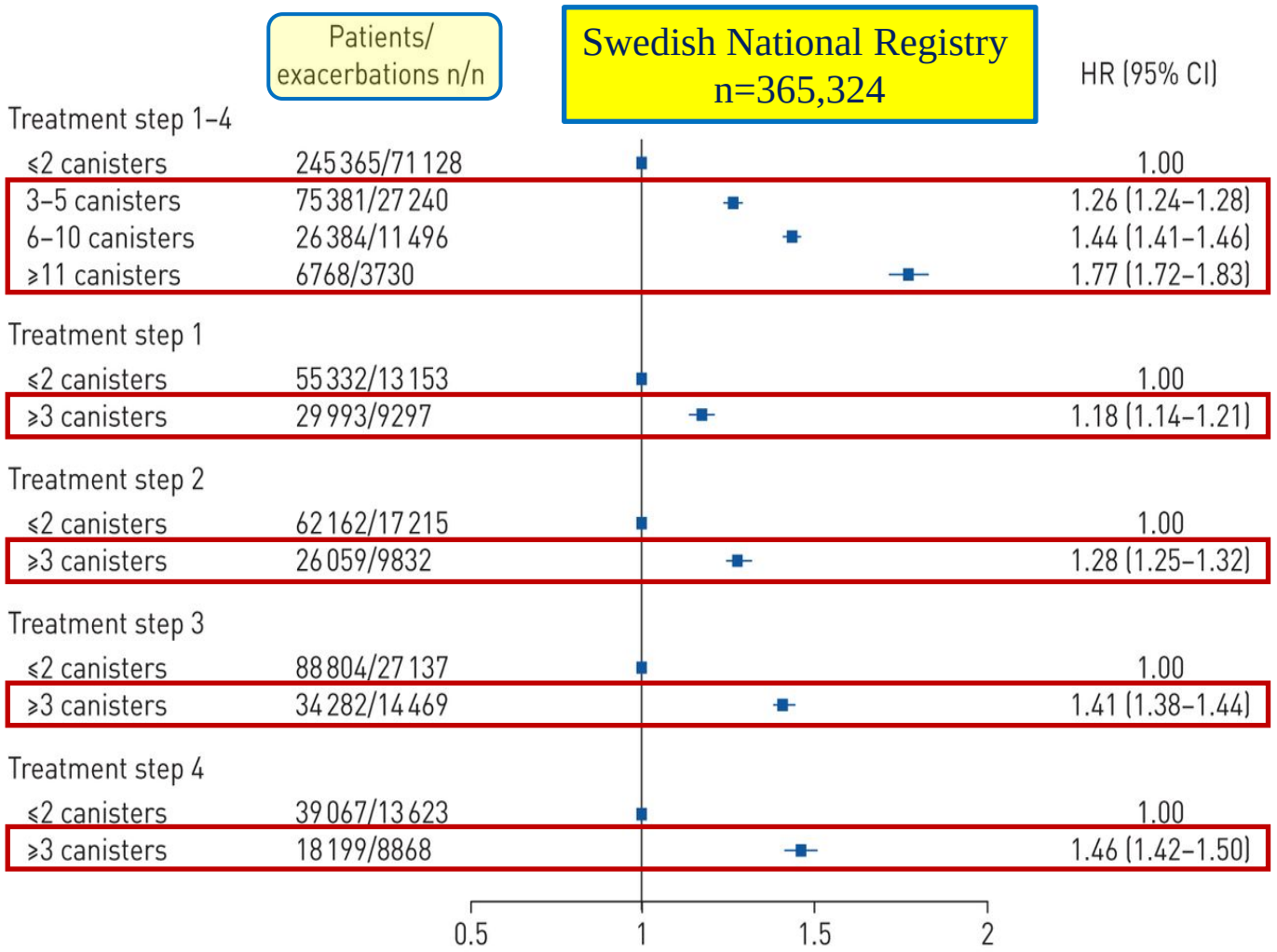
Medicaid		Commercial	
Chidren, n = 25,048	Adults, n = 8,745	Chidren, n = 41,753	Adults, n = 59,684

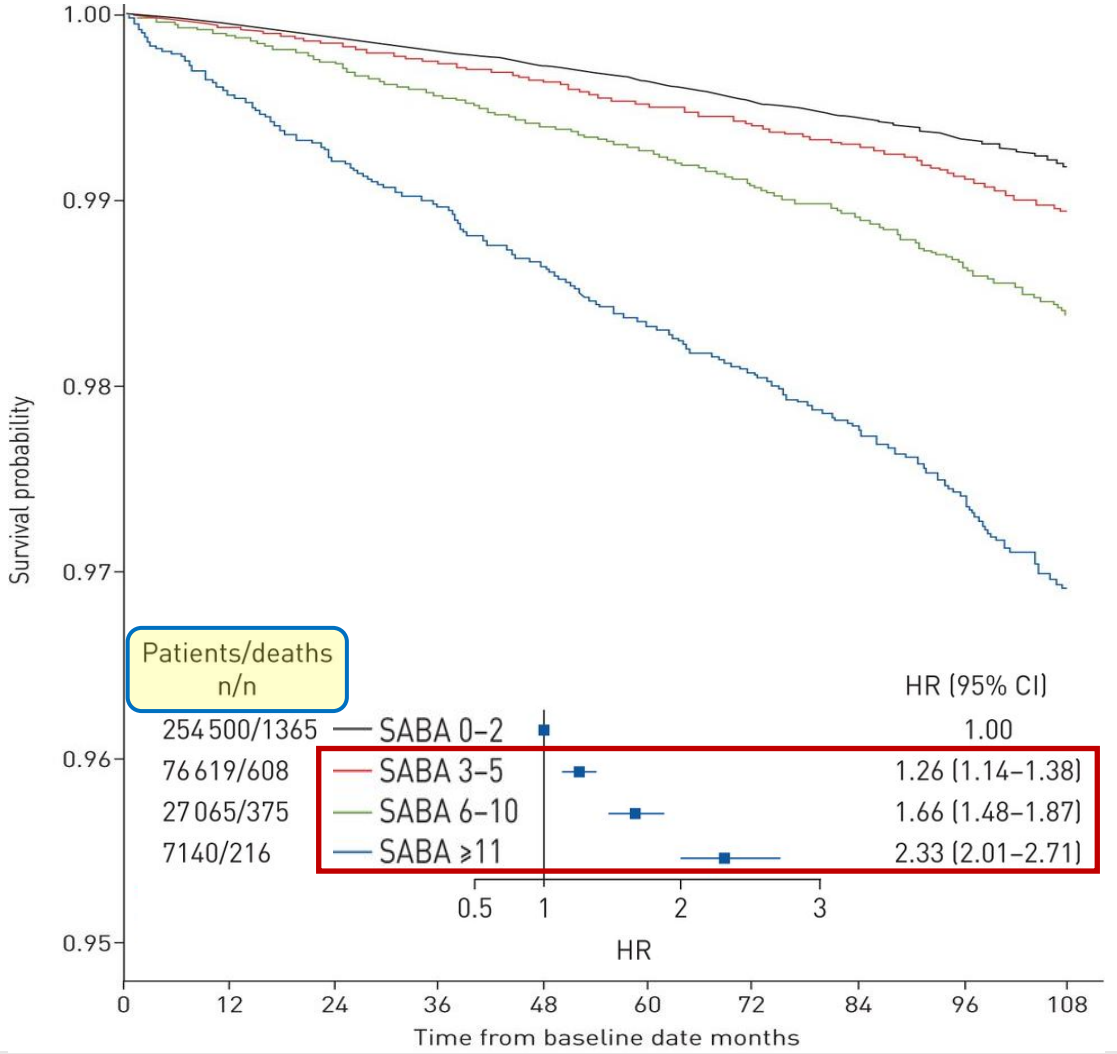




Ann Allergy Asthma Immunol 2012; 109: 403-7.

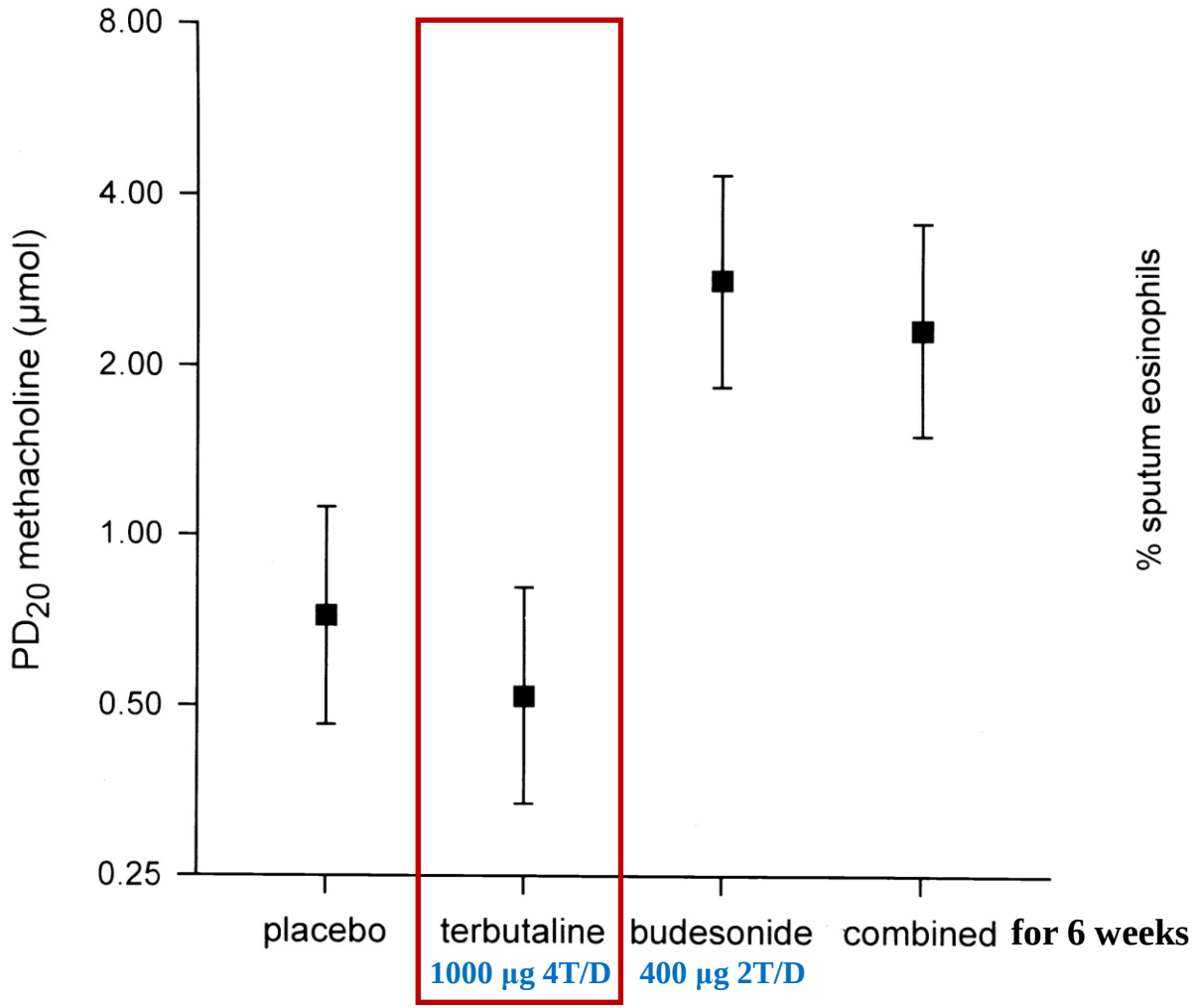
SABA Overuse in Asthma and Exacerbation & Mortality

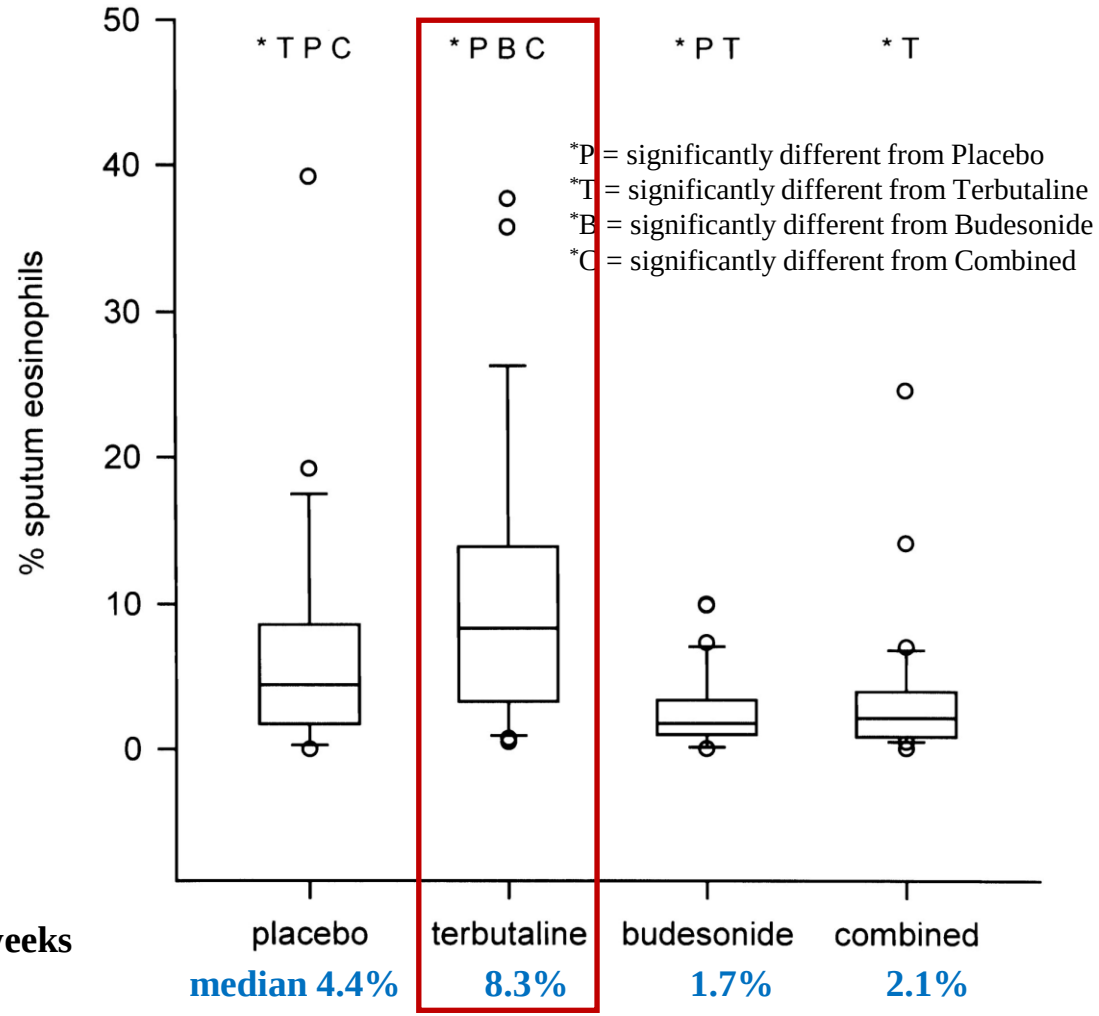




Eur Respir J 2020; 55: 1901872.

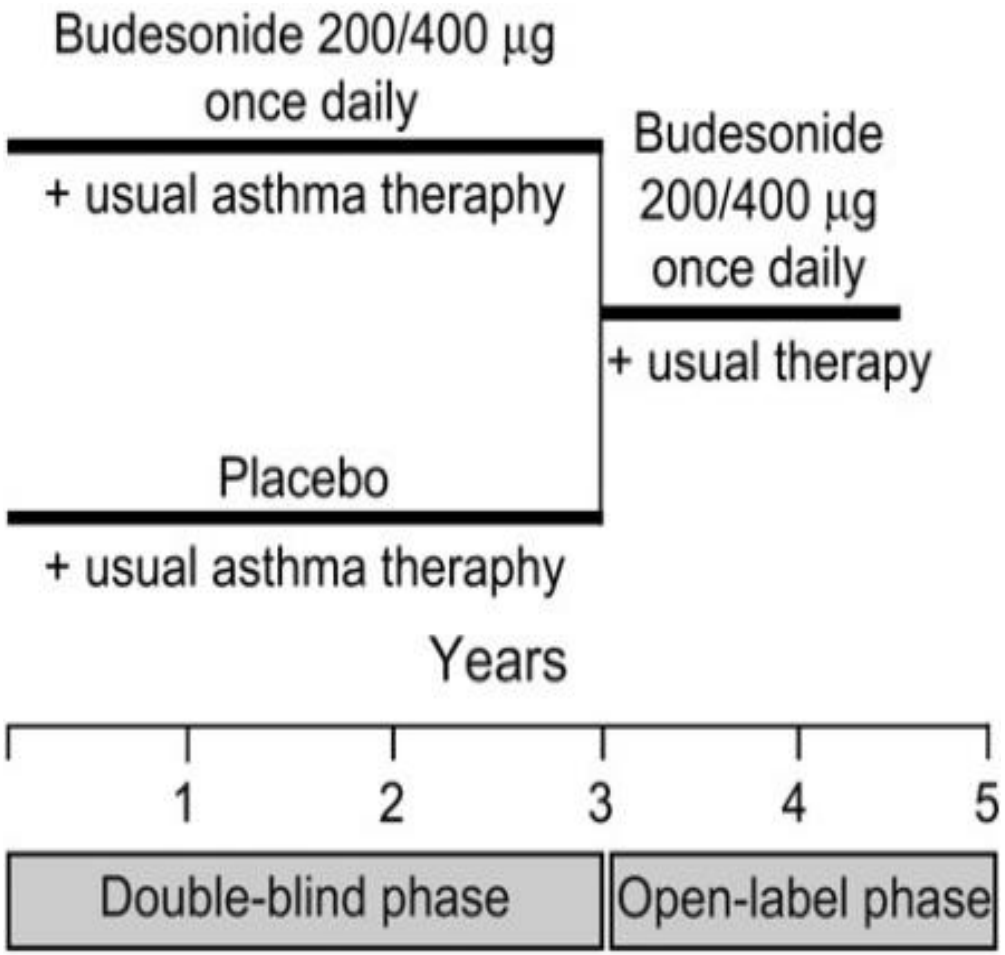
Permissive Effect of SABA on Airway Inflammation

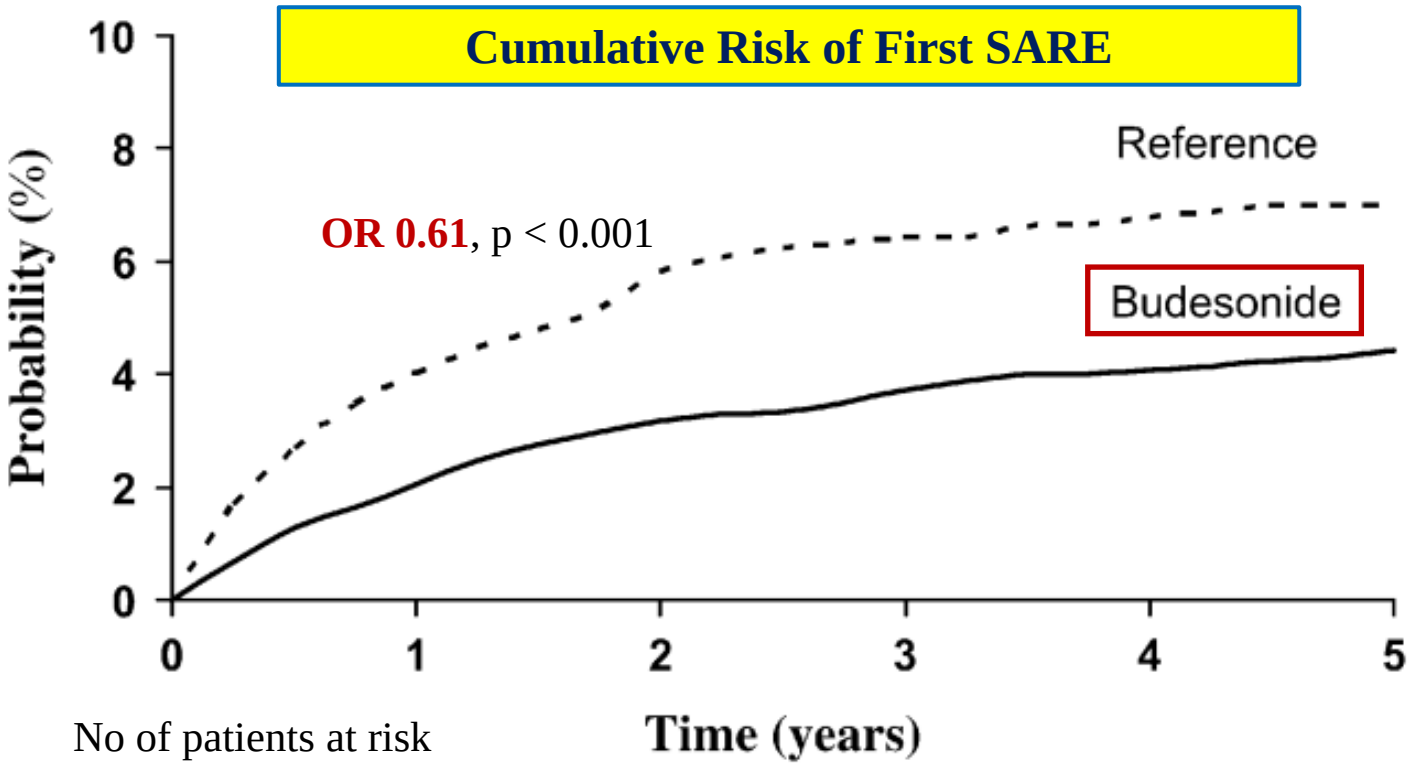




Am J Respir Crit Care Med 2000; 161: 1459-64.

ICS in Mild Asthma & Prevention of Severe Event : START





No of patients at risk

	Baseline	2.5 year	4.5 year
BUD	3,597	2,613	2,337
Placebo	3,568	2,486	2,195

J Allergy Clin Immunol 2008;121:1167-74.

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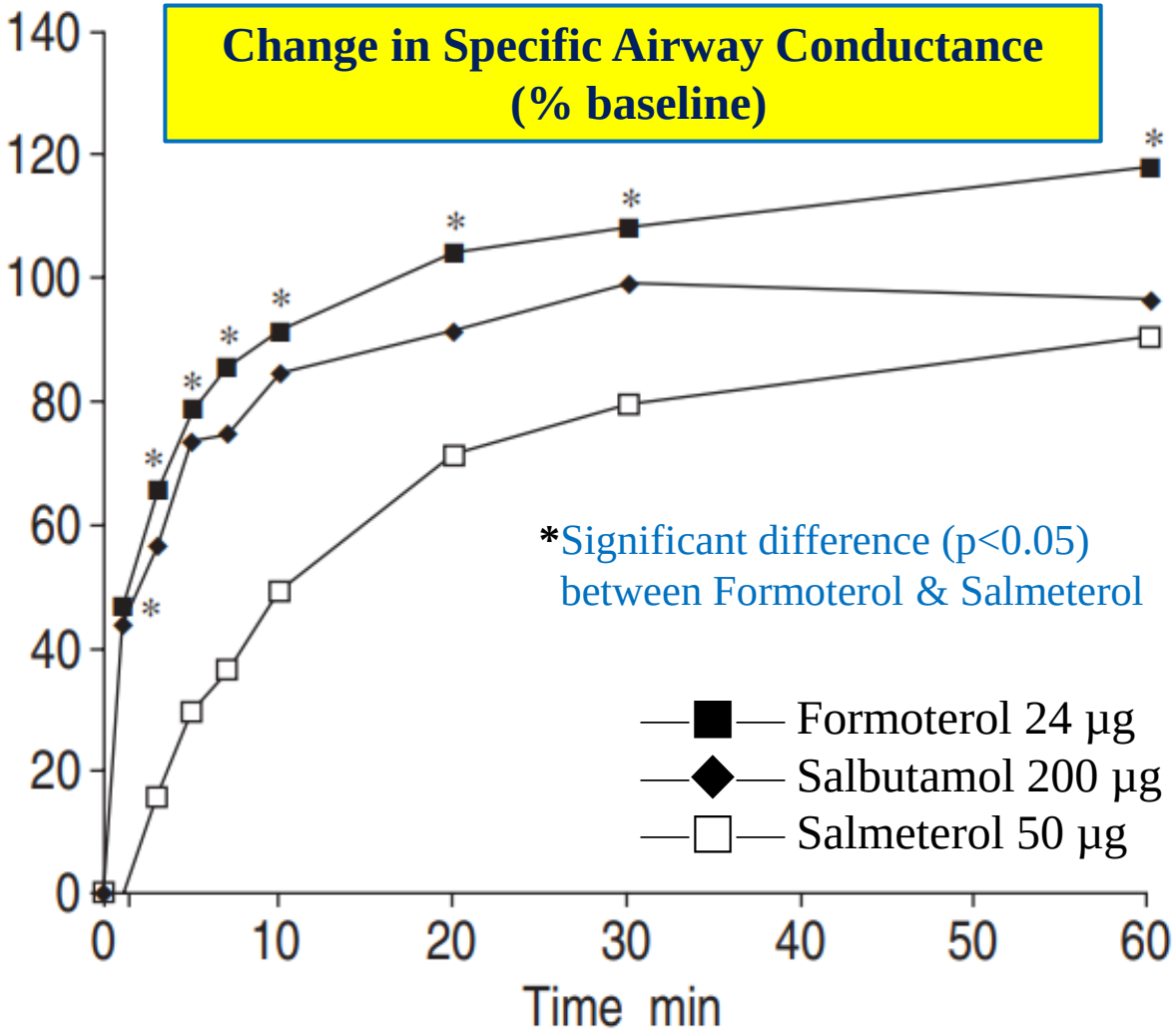
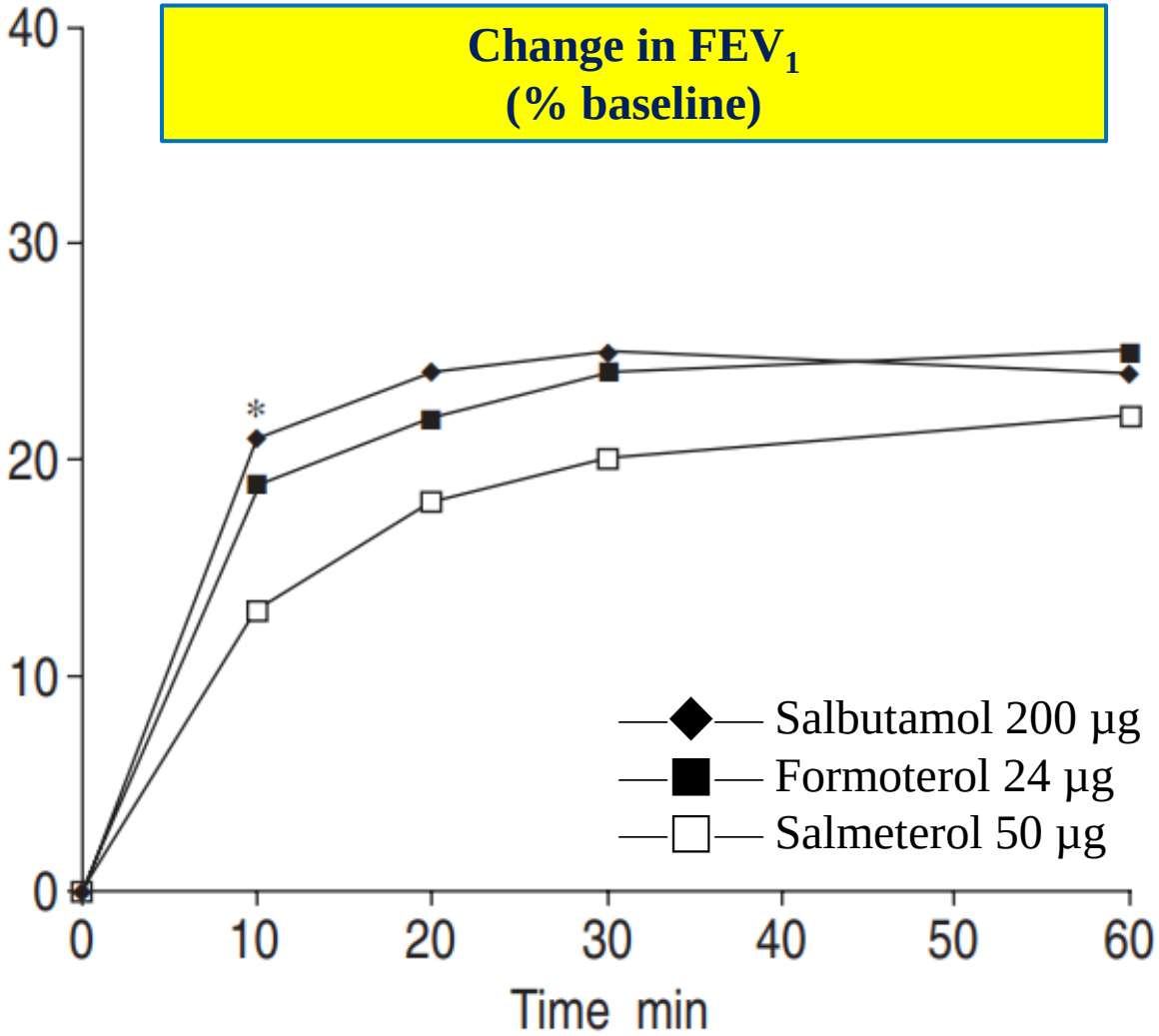
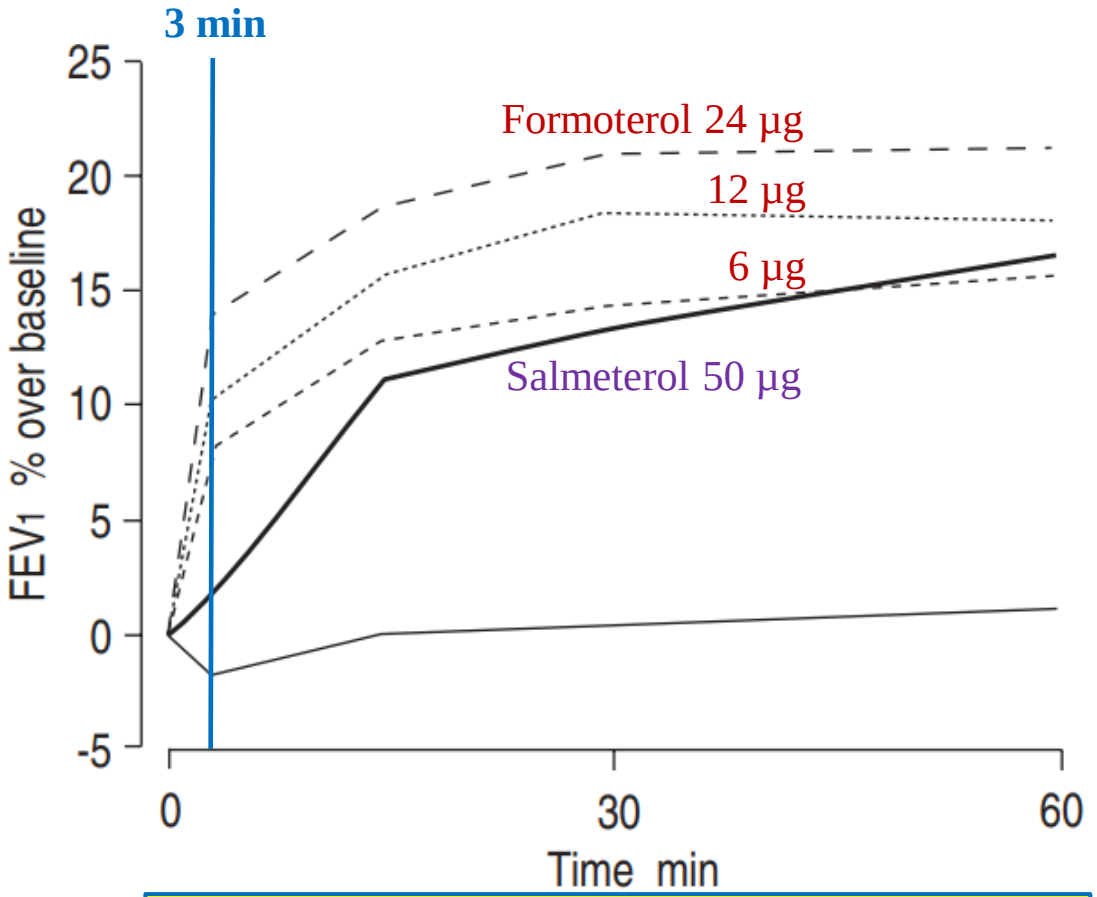
Formoterol vs. Salmeterol & Salbutamol in Asthma: Onset



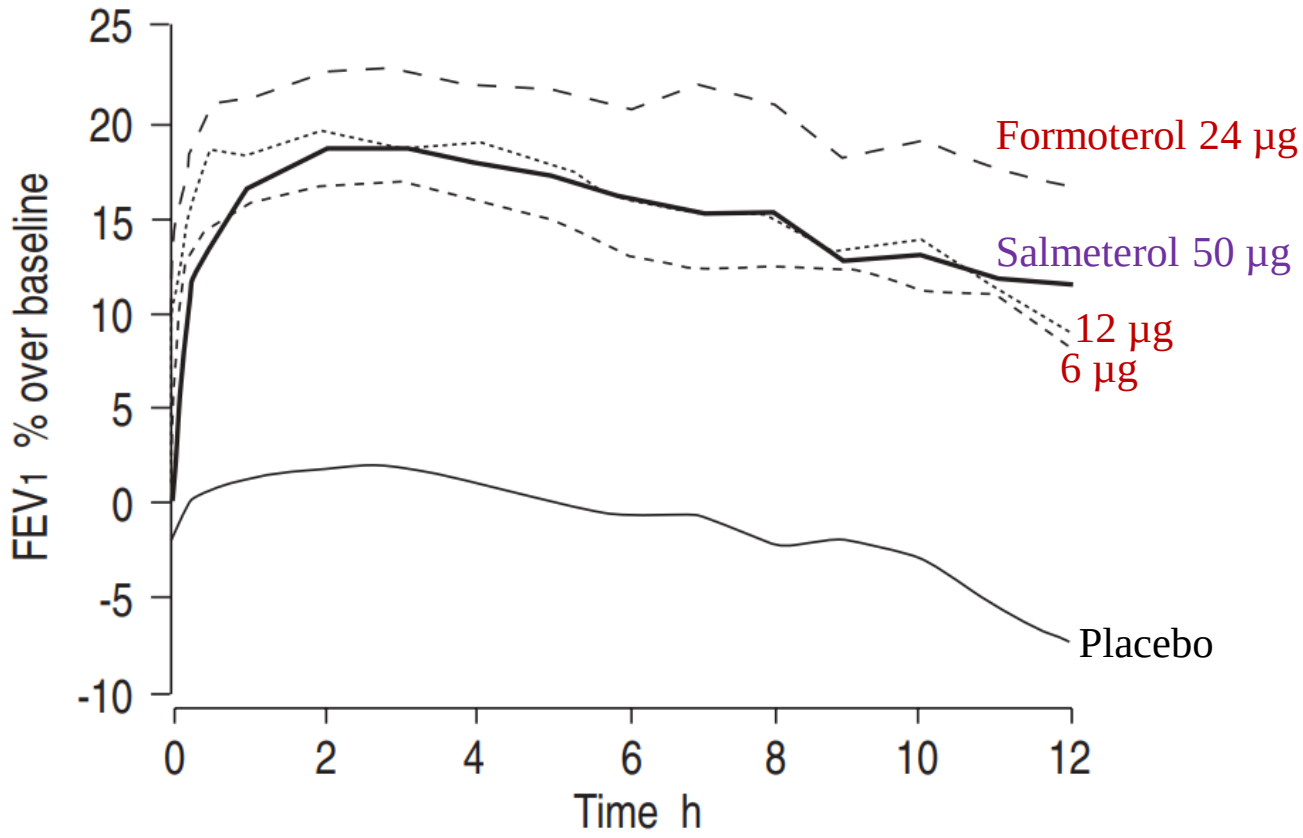


Eur Respir J 1996; 9: 1684-8.

Formoterol vs. Salmeterol in Asthma: Onset & Duration



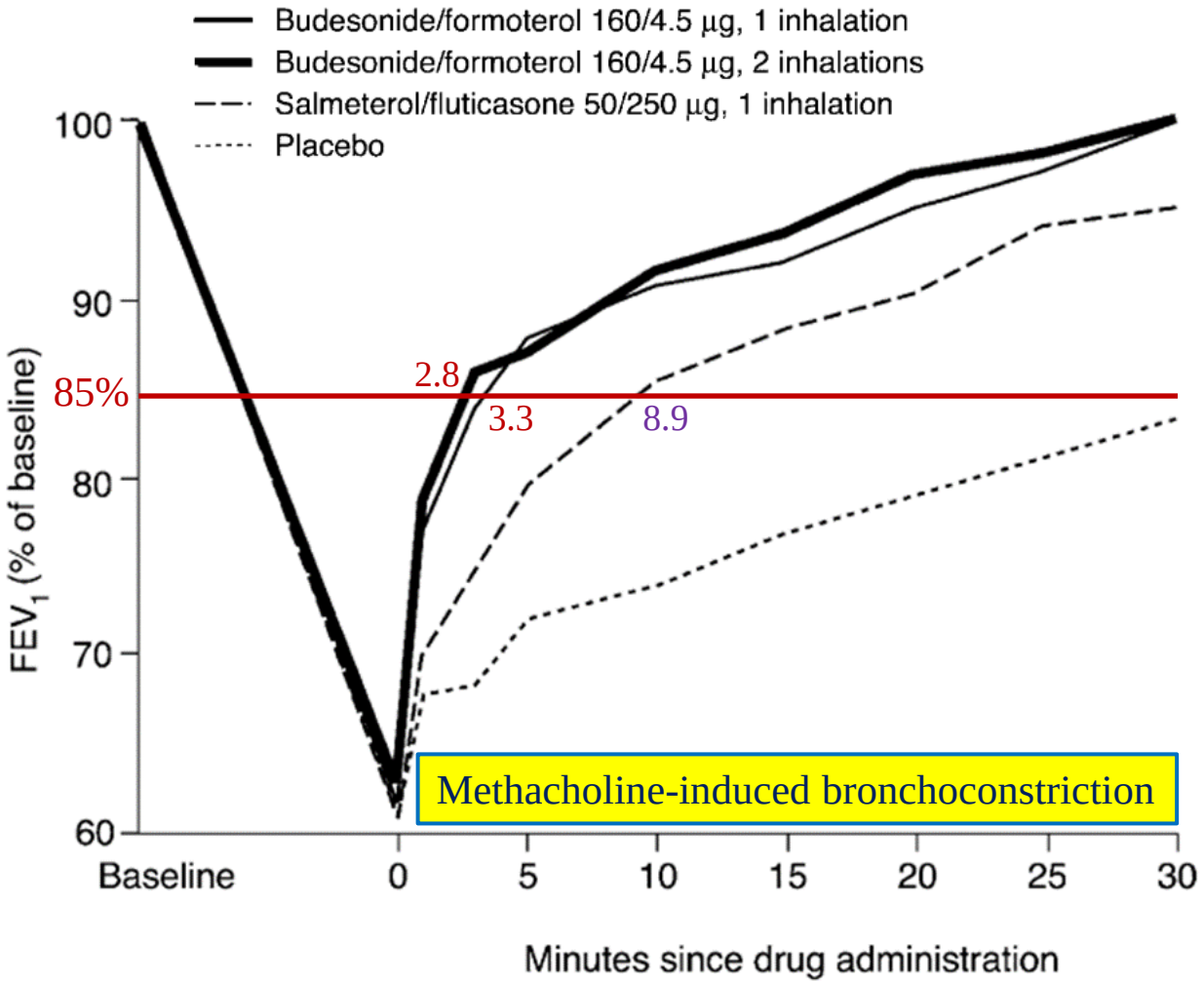
Formoterol, more rapid onset than Salmeterol

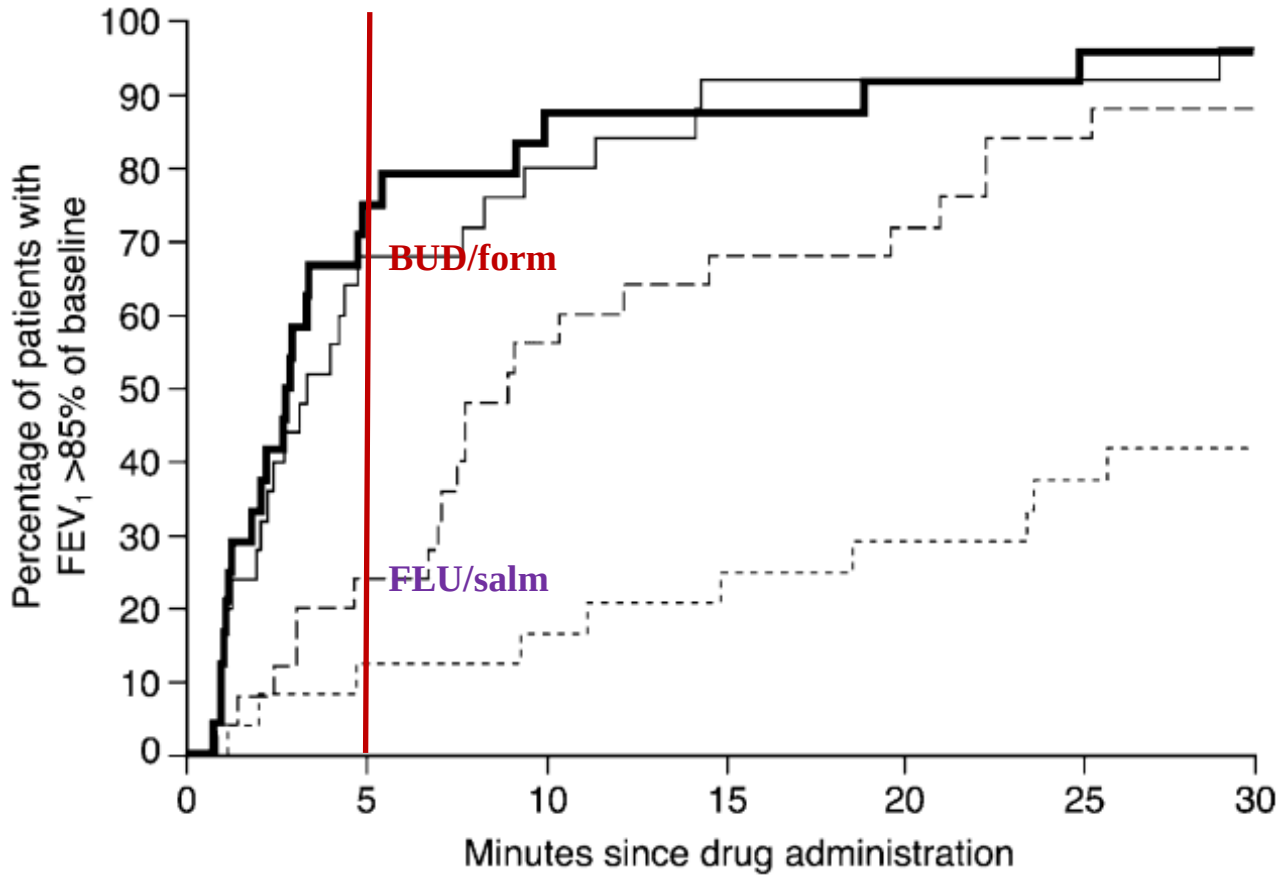


Formoterol, similar duration to Salmeterol

Eur Respir J 1997; 10: 2484-9.

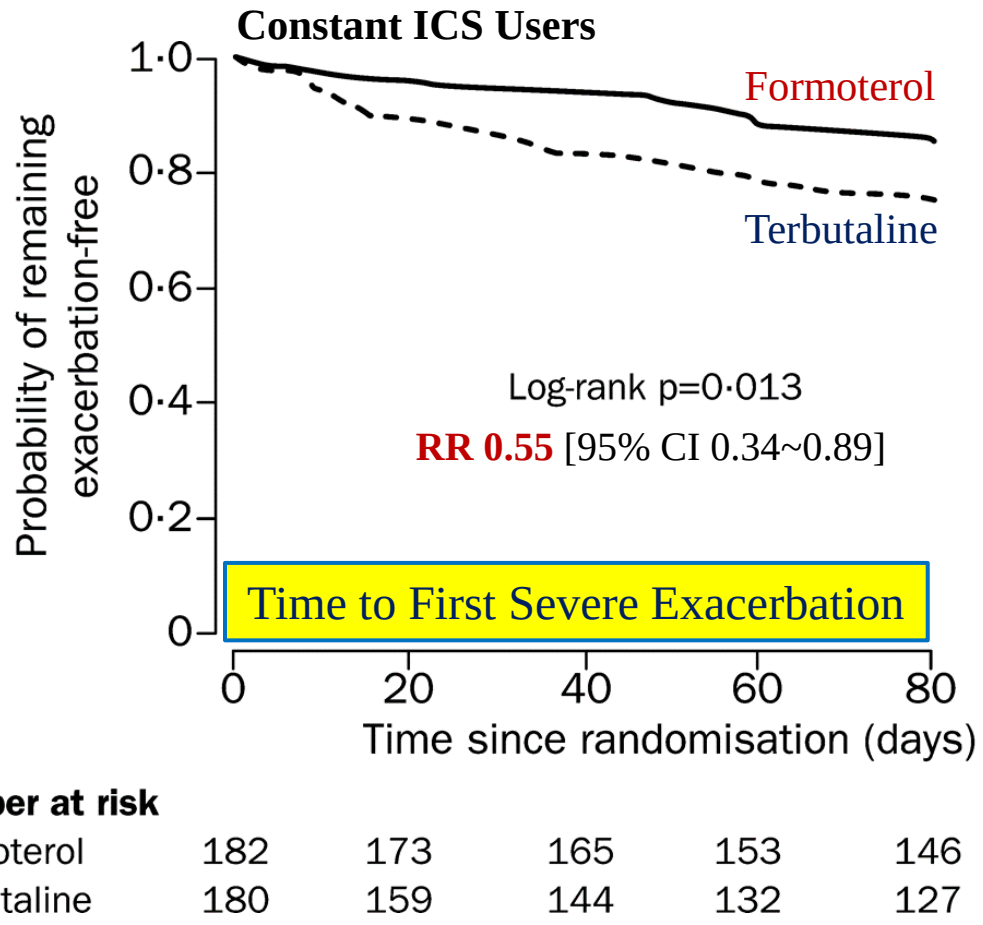
BUD/form Rapidly Relieves Bronchoconstriction





Pulm Pharmacol Ther 2004; 17: 89-95.

Comparison of Formoterol & Terbutaline as Relievers



Variable	Form 4.5 µg		Terbutaline 0.5 mg		Mean Difference in Change (95% CI)	P value
	Run-in	Change	Run-in	Change		
No. Inhalations	Maximum/Day **54 µg**		Maximum/Day **6 mg**			
Total	5.07	-1.15	5.29	-0.40	-0.76 (-1.18~-0.33)	**0.0005**
Daytime	4.24	-0.99	4.47	-0.36	-0.63 (-0.97~-0.29)	**0.0003**
Night-time	0.84	-0.13	0.81	+0.01	-0.14 (-0.35~0.06)	0.17
Morning PEF (L/min)	369	+8	357	-4	11 (3~20)	**0.009**
Heart Rate	74.4	-0.31	70.8	+0.59	-0.9	**0.12**
Serum K^+ (mmol/L)	4.28	+0.03	4.30	+0.03	0	**0.77**

Lancet 2001; 357: 257-61.

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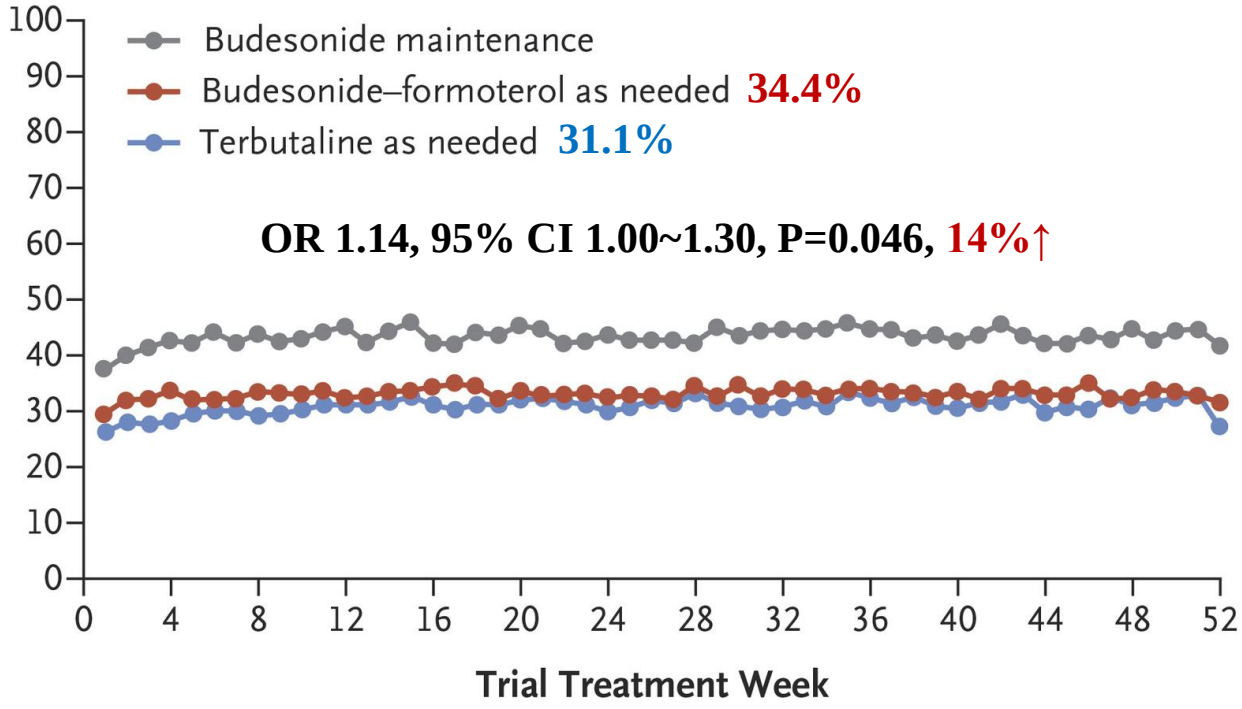
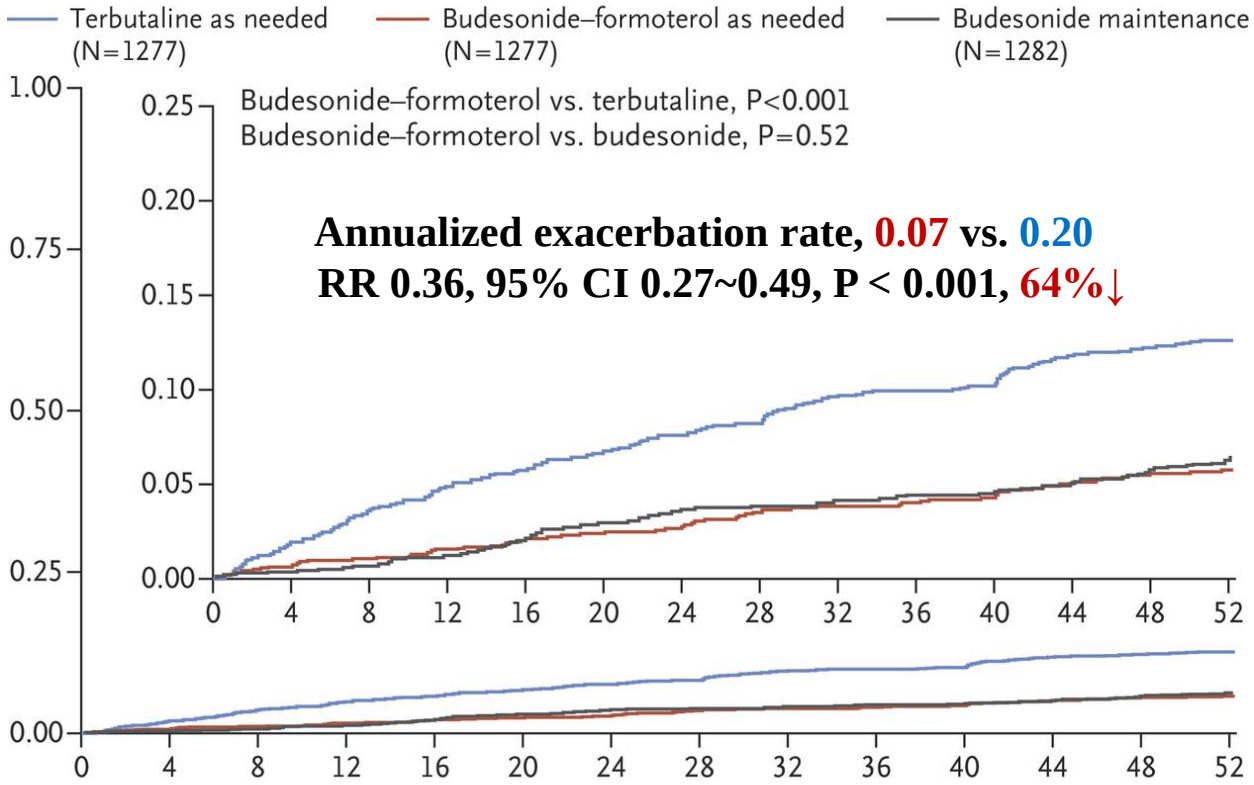
As-Needed BUD/form in Mild Asthma : SYGMA 1



Patients with Week of Well-Controlled Asthma (%)



Time to First Exacerbation

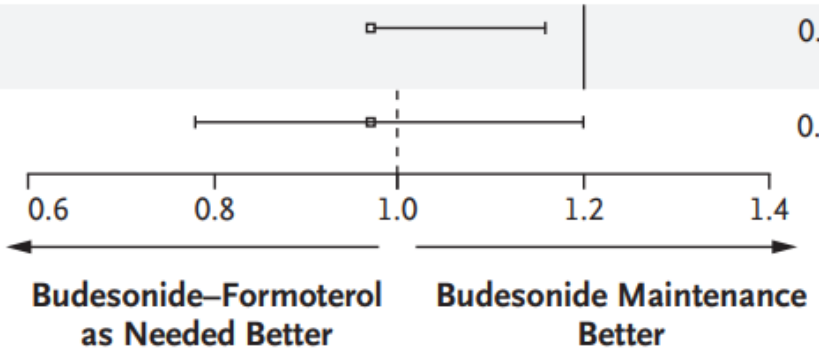
BUD/form as-needed 57 μg vs. BUD maintenance 340 μg → **83% Lower Median Daily Dose of ICS**

N Engl J Med 2018; 378: 1865-76.

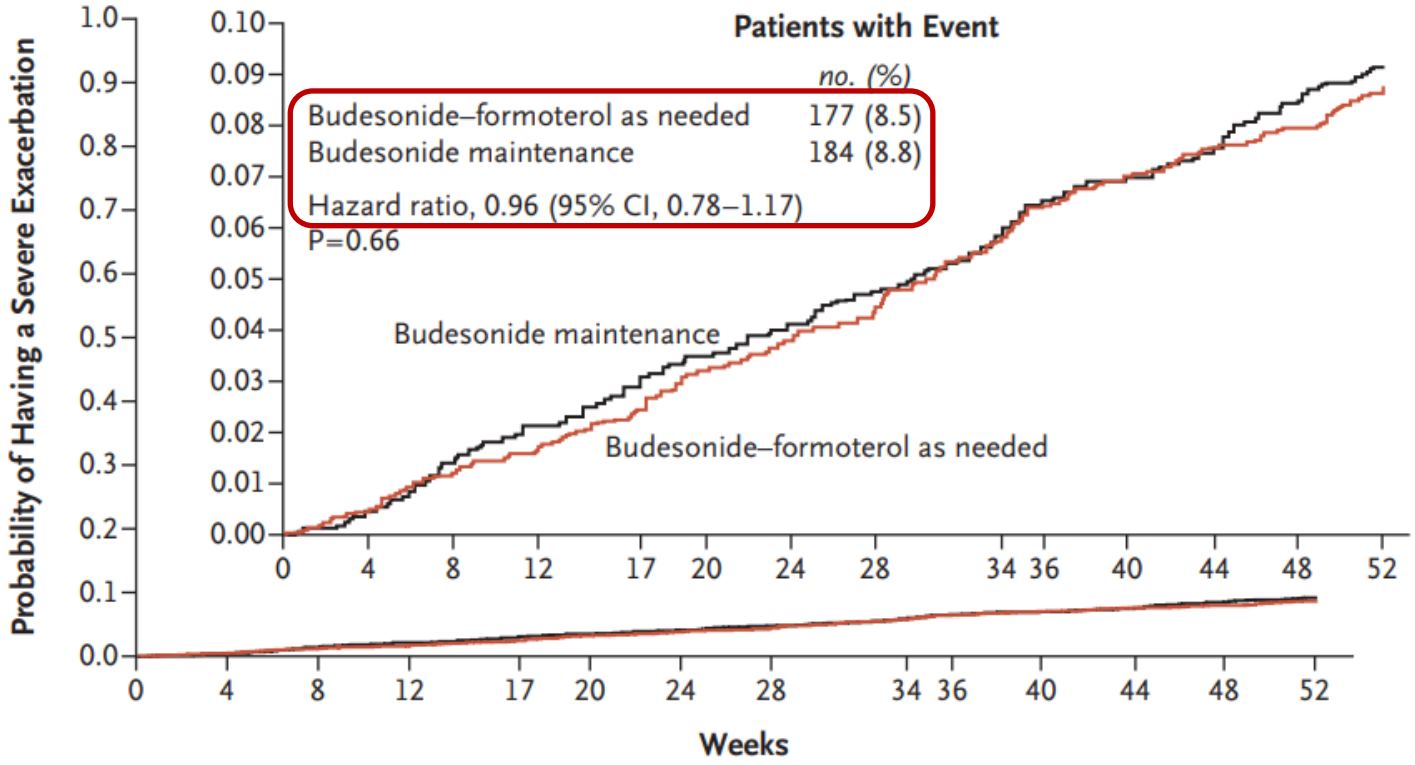
As-Needed BUD/form in Mild Asthma : SYGMA 2

Annualized Rate of Asthma Exacerbations

Test	Budesonide–Formoterol as Needed	+Terbutaline Budesonide Maintenance	Rate Ratio (95% CI)
Noninferiority test	2084	2083	0.97 (NA–1.16)
Superiority test	2089	2087	0.97 (0.78–1.20)



Time to First Asthma Exacerbation

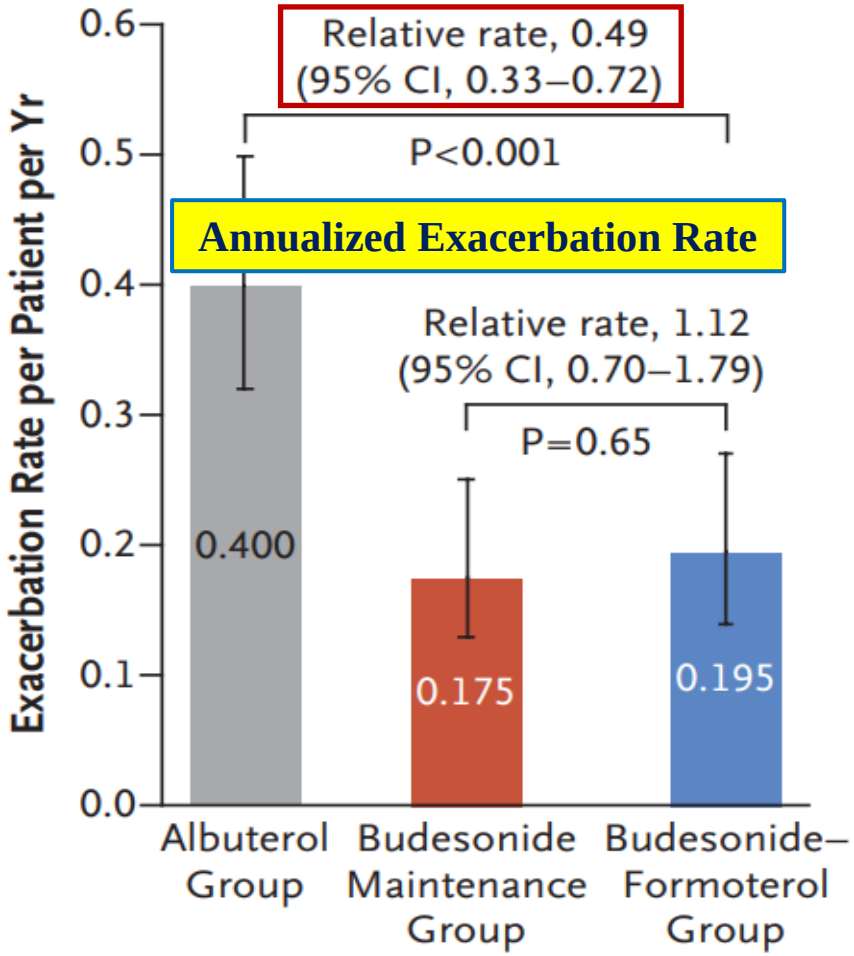


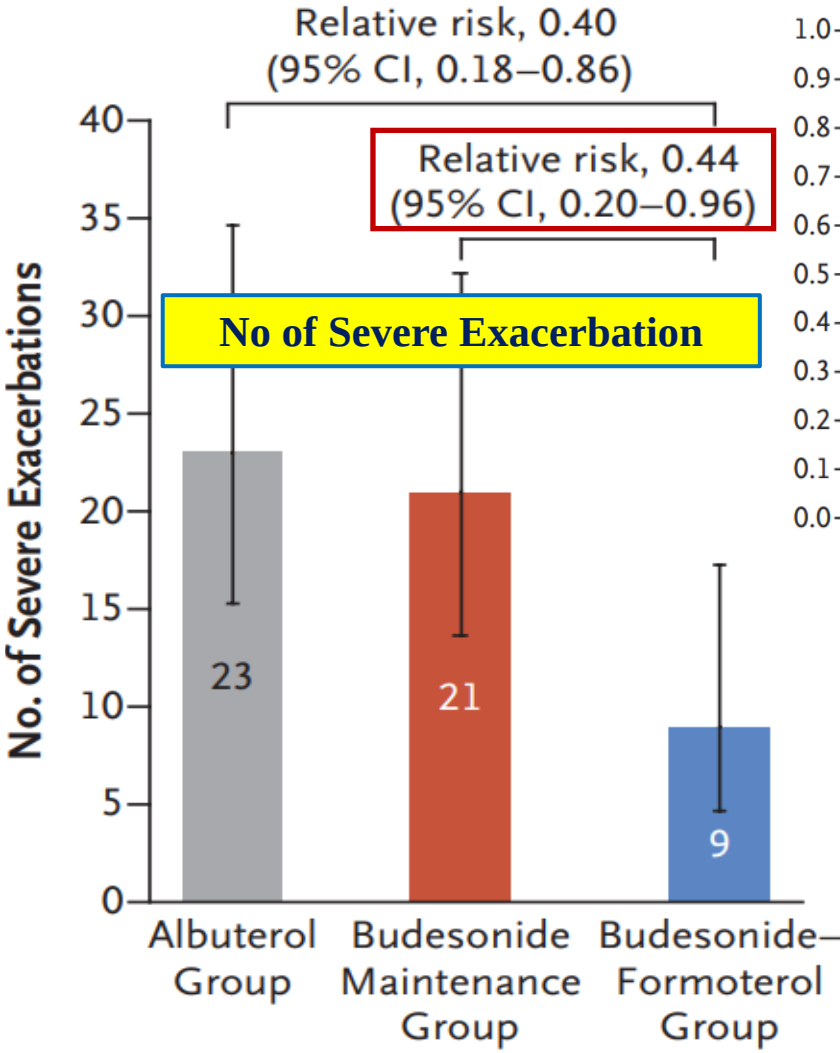
75% Lower Median Daily Dose of ICS

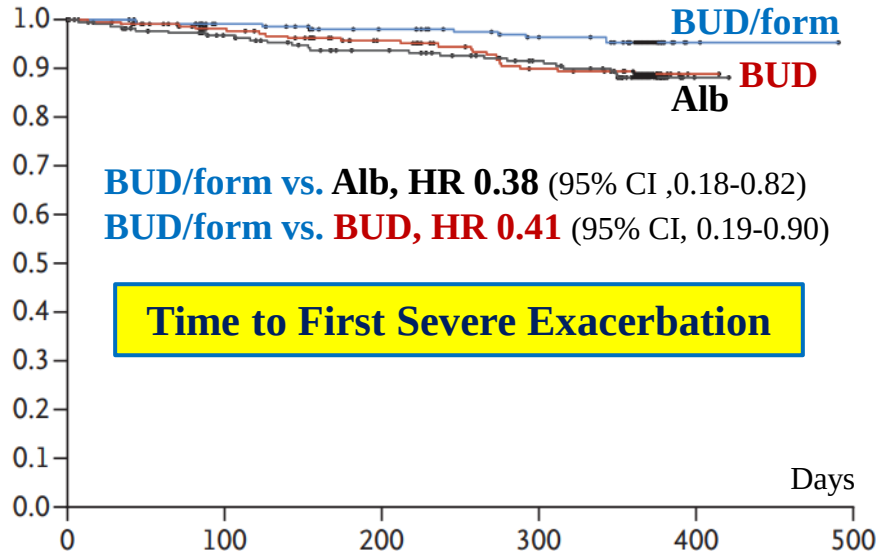
BUD/form as-needed 66 μg
vs. BUD maintenance 267 μg

N Engl J Med 2018; 378: 1877-87.

As-Needed BUD/form in Mild Asthma : Novel START



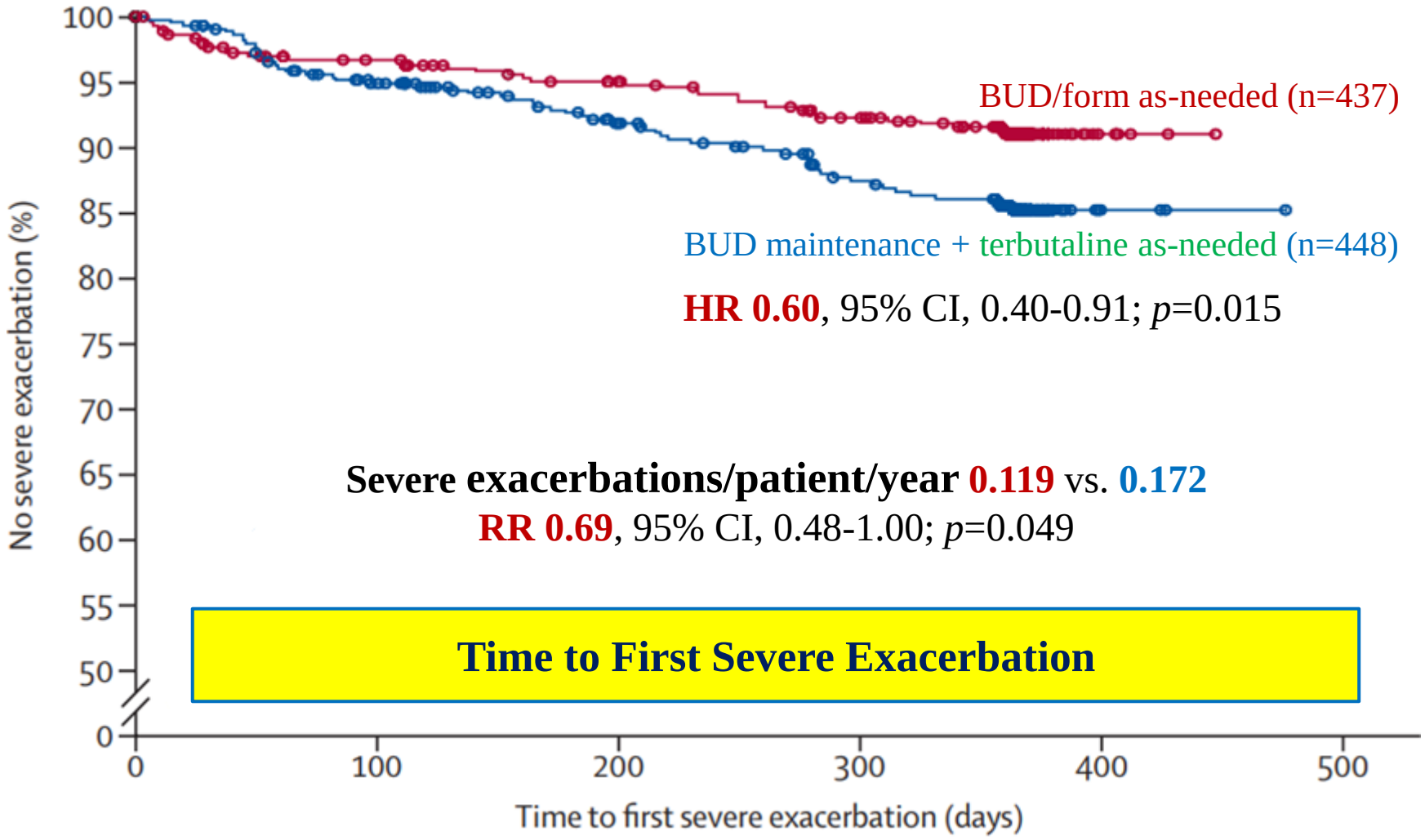




	BUD/form (n=220)	BUD+alb (n=225)
BUD dose/D, μg	**107**±109	**222**±113
Oral PD use, mg	7.5±40.2	14.5±51.0

N Engl J Med 2019; 380: 2020-30.

As-Needed BUD/form in Mild Asthma : PRACTICAL



Lancet 2019; 394: 919-28.

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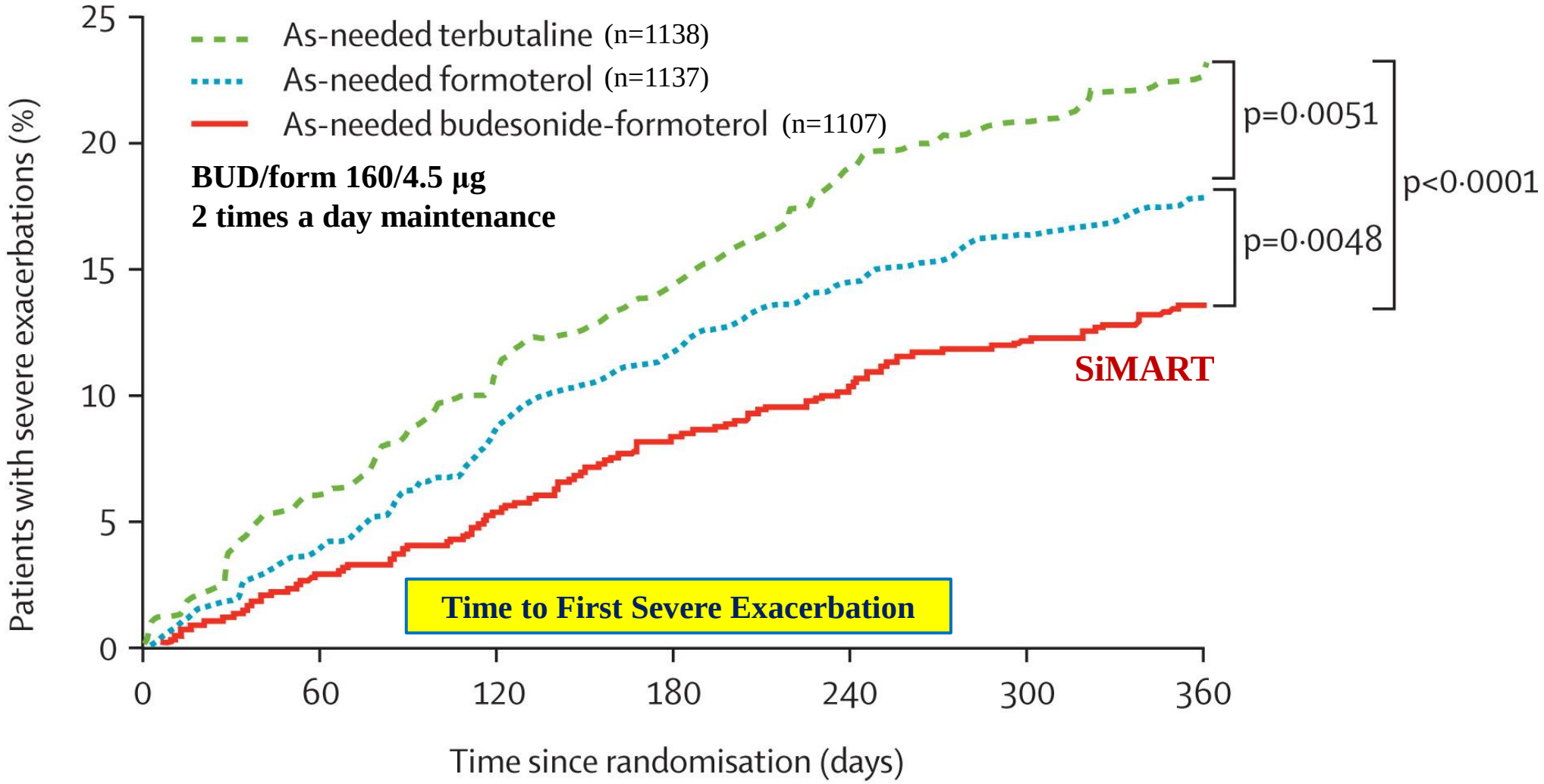
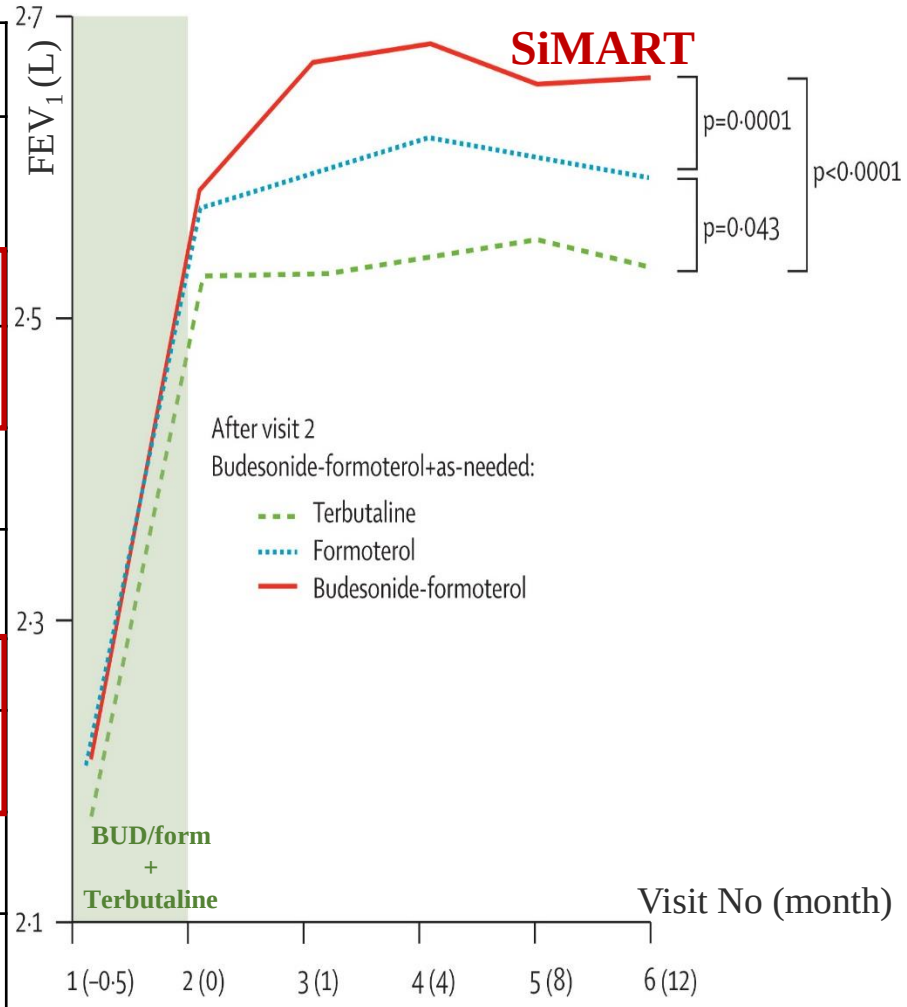
BUD/form as Maintenance & Reliever Therapy in Asthma (1)



Rabe et al., Lancet 2006; 368: 744-53.

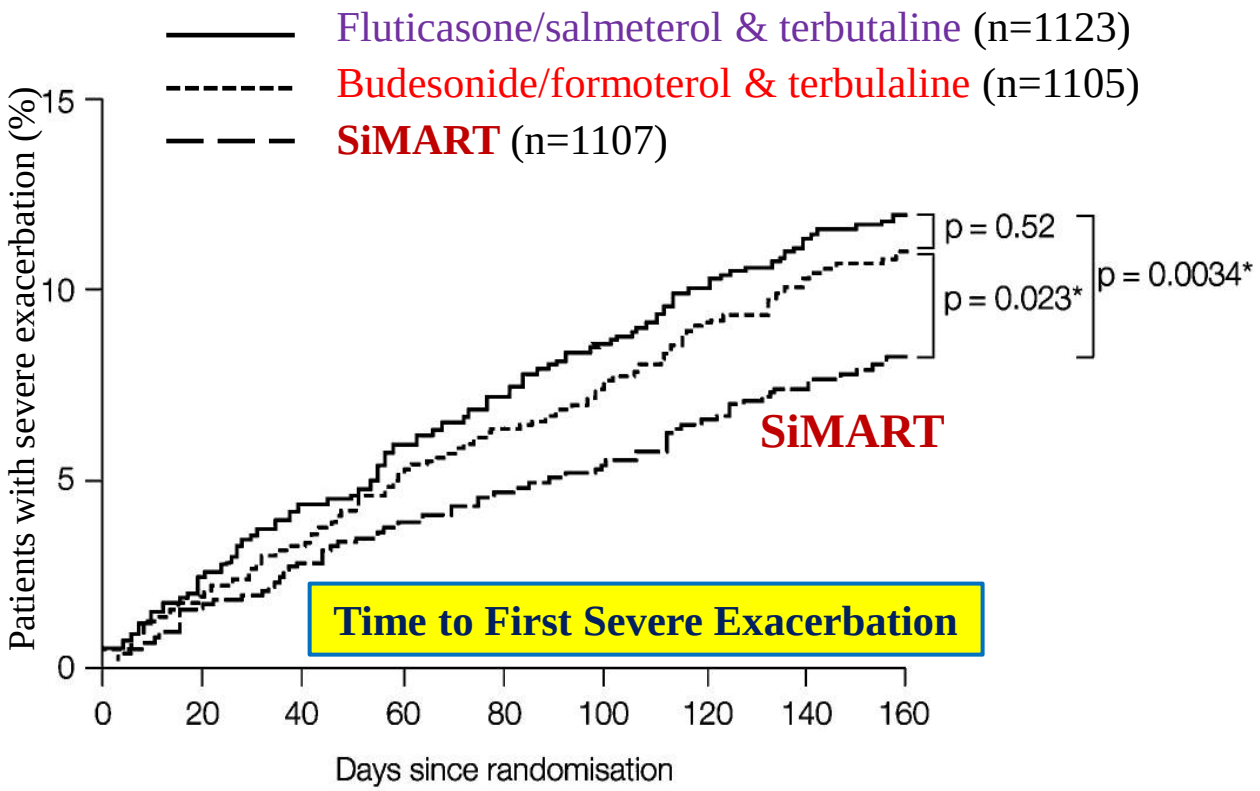
BUD/form as Maintenance & Reliever Therapy in Asthma (1)

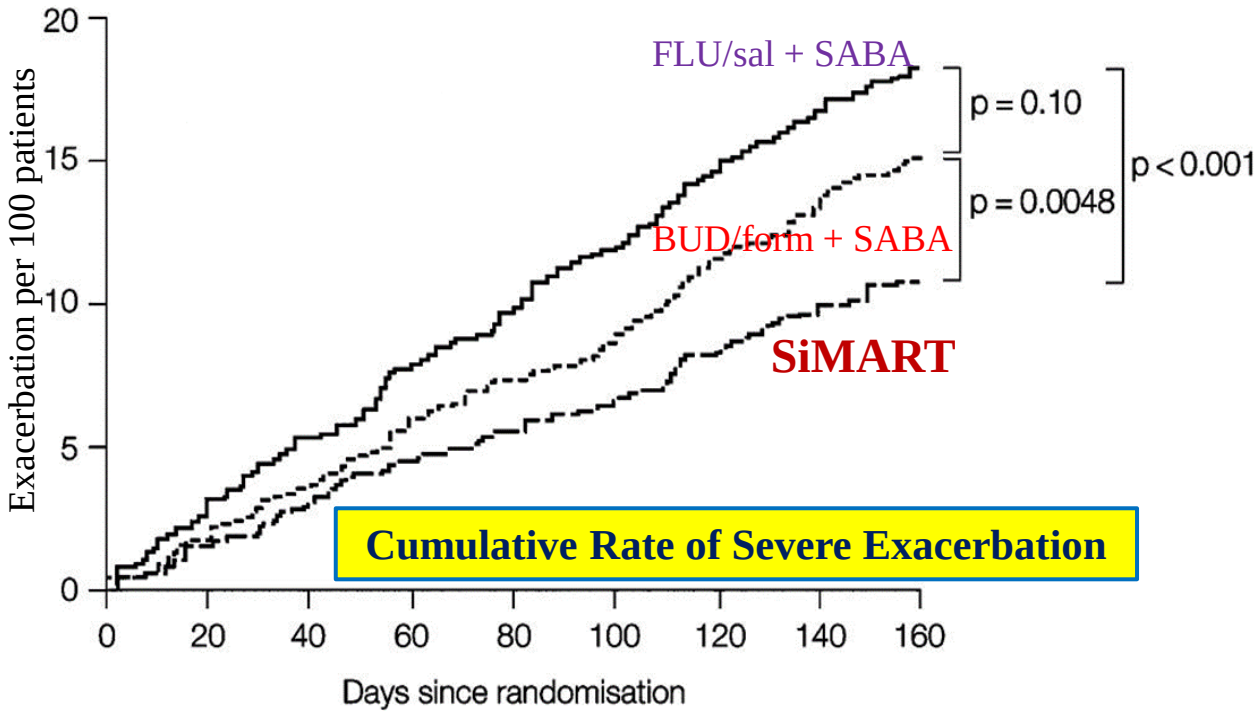
	Reliever Groups			Hazard Ratios (95% CI)		
	Terbutaline (n=1138)	Formoterol (n=1137)	SMART (n=1107)	Formoterol vs Terbutaline	SMART vs Terbutaline	SMART vs Formoterol
Severe Exacerbations (All Definitions)						
Patients with Event n (%)	245 (22%)	195 (17%)	143 (13%)	0.76 (0.63–0.92) p=0.004	**0.55** (0.45–0.68) p<0.0001	**0.73** (0·59–0·90) p=0.0038
Total Events (Days with Events)	377 (3030)	296 (2214)	194 (1353)			
Rate Events /100 Pts / Year	37	29	19	0.78 (0.67–0.91) p=0.0012	**0.52** (0.44–0.62) p<0.0001	**0.67** (0.56–0.80) p<0.0001
ER Visits or Hospitalisations						
Patients with Event n (%)	91 (8%)	75 (7%)	54 (5%)	0.79 (0.58–1.07) p=0.12	**0.57** (0.41–0.81) p=0.0013	0.73 (0.51–1.04) p=0.079
Total Events (Days with Events)	115 (392)	98 (282)	70 (218)			
Rate Events /100 Pts / Year	7	5	4	0.83 (0.63–1.08) p=0.17	**0.61** (0.45–0.82) p=0.0010	**0.73** (0.54–0.99) p=0.046



Rabe et al., Lancet 2006; 368: 744-53.

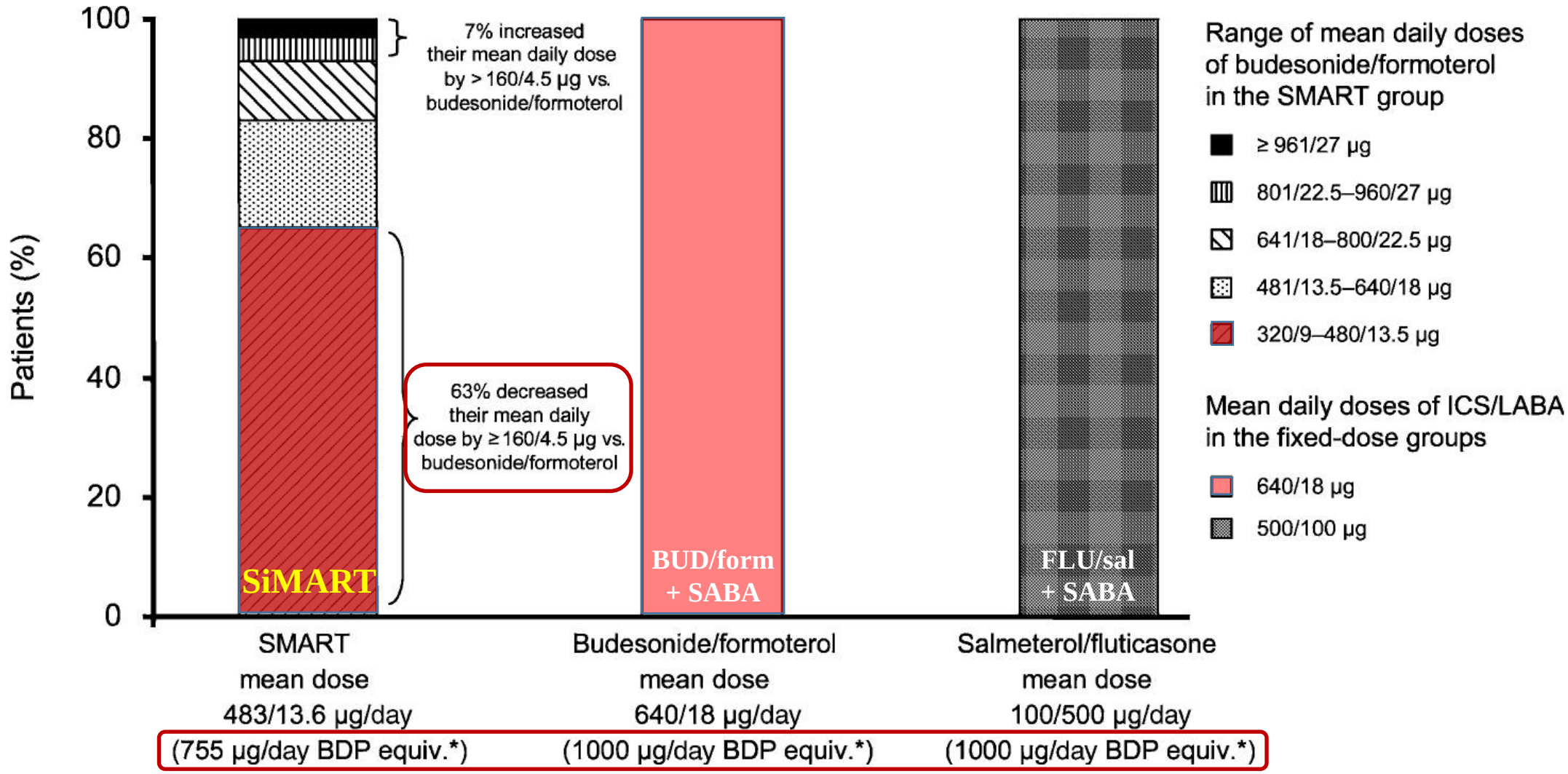
BUD/form as Maintenance & Reliever Therapy in Asthma (2)





Kuna et al., Int J Clin Pract 2007; 61: 725-36.

BUD/form as Maintenance & Reliever Therapy in Asthma (2)



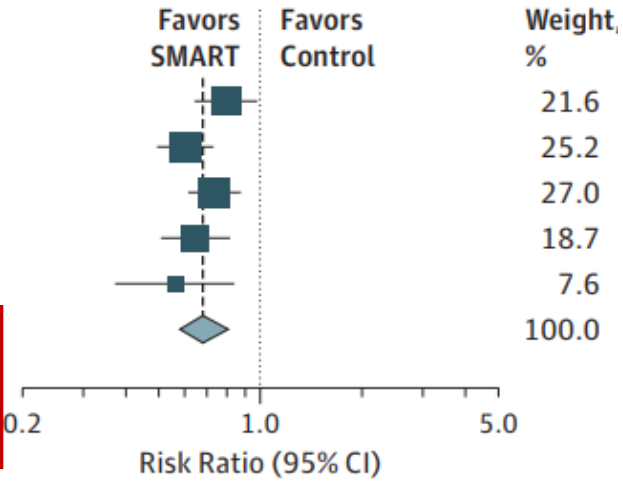
Kuna et al., Int J Clin Pract 2007; 61: 725-36.

Single Inhaler MART vs ICS/LABA in Persistent Asthma

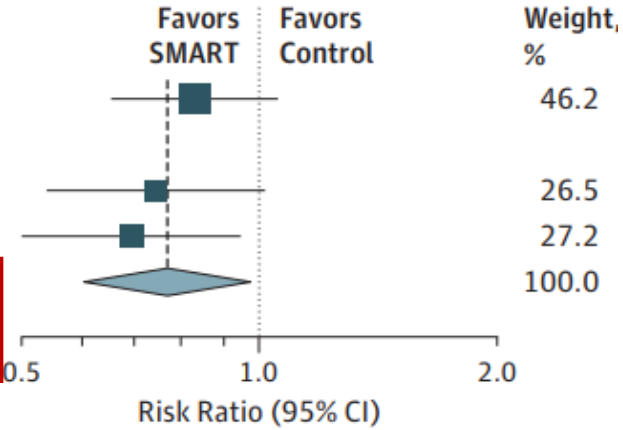
Severe Exacerbation

BEC/form

Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Vogelmeier et al,[23] 2012	1067	132	1076	167	-3.1 (-6.1 to -0.2)	0.80 (0.64 to 0.99)
Rabe et al,[25] 2006	1107	143	1138	245	-8.6 (-11.7 to -5.5)	0.60 (0.50 to 0.72)
Atienza et al,[24] 2013	1049	170	1042	229	-5.8 (-9.1 to -2.4)	0.74 (0.62 to 0.88)
Papi et al,[26] 2013	852	99	849	152	-6.3 (-9.6 to -2.9)	0.65 (0.51 to 0.82)
Patel et al,[27] 2013	151	28	152	50	-14.4 (-24.1 to -4.6)	0.56 (0.38 to 0.84)
Overall (random-effects model)	4226	572	4257	843	-6.4 (-10.2 to -2.6)	0.68 (0.58 to 0.80)
Heterogeneity: $I^2 = 29\%$, $P = .23$						
Test for overall effect: $t_4 = -6.44$, $P < .001$						



Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)
Kuna et al,[33] 2007						
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)
Heterogeneity: $I^2 = 0\%$, $P = .64$						
Test for overall effect: $t_2 = -4.71$, $P = .04$						



JAMA 2018; 319: 1485-96.

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GINA 2021 Initial Asthma Treatment

	Presenting symptoms	Preferred (Track 1)	Alternative (Track 2)
STEP 1	Symptoms < 2/m, no risk for AEs	**As-needed low dose ICS/form**	**Low dose ICS whenever SABA** is taken
STEP 2	Symptoms ≥ 2/m, but < **4-5 days/w**	**As-needed low dose ICS/form**	**Low dose ICS + as-needed SABA** Consider likely adherence with daily ICS

GINA 2021, Box 3-4A, 3-4Bi, 3-4Bii, modified.

As-needed ICS/form vs. ICS maintenance & SABA

Budesonide /formoterol	
Beclometasone /formoterol	

Budesonide		
Fluticasone		
Ciclesonide		

GINA 2021 Initial Asthma Treatment

	Presenting symptoms	Preferred (Track 1)	Alternative (Track 2)
STEP 3	Symptoms **most days**, or Waking due to asthma ≥ 1/w	**Low dose ICS/form MART**	**Low dose ICS/LABA + as-need SABA** Medium dose ICS + as-needed SABA Consider likely adherence with daily ICS
STEP 4	**Daily symptoms**, or Waking due to asthma ≥ 1/w, and **Low lung function**	**Medium dose ICS/form MART** Short course of oral PD may also be needed	**Medium dose ICS/LABA + as-needed SABA** High dose ICS c as-needed SABA Consider likely adherence with daily ICS Short course of oral PD may also be needed

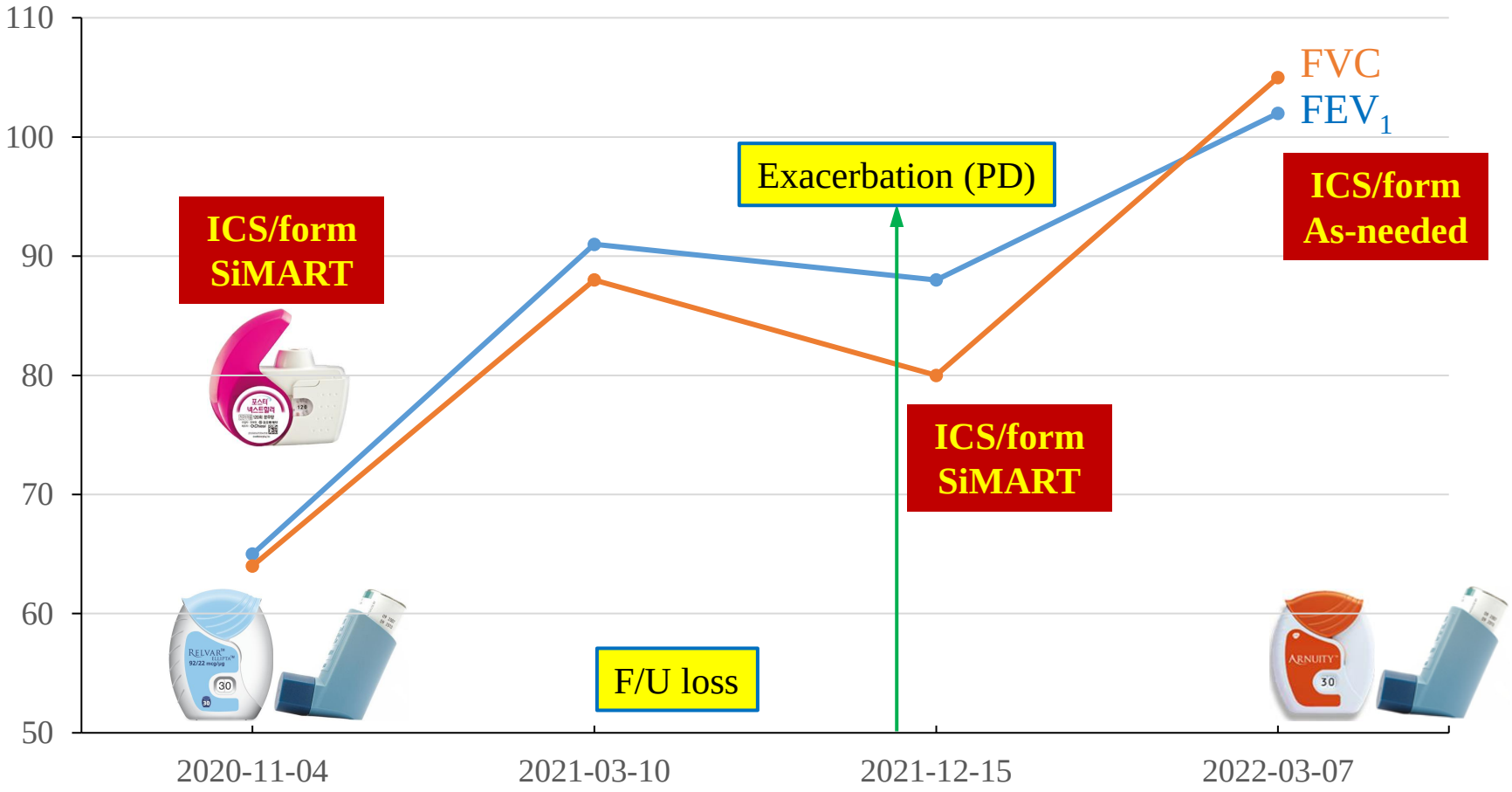
GINA 2021, Box 3-4A, 3-4Bi, 3-4Bii, modified.

Single ICS/form MART vs. ICS/other LABA & SABA

Budesonide /formoterol	
Beclometasone /formoterol	

Fluticasone /salmeterol		
Fluticasone /vilanterol		
Mometasone /indacaterol		

A Case of Asthma, Initially STEP 3



SUMMARY (1)

- 경증 천식에서도 중증 악화가 드물지 않게 발생함
- STEP 1 & 2에서 실제 환자들은 ICS에 즉각적인 효과를 느끼지 못하여 SABA를 자주 사용함
- 일정량 이상의 SABA 사용은 천식 악화와 천식 관련 사망 위험을 증가시킴

- Formoterol은 다른 LABA보다 빠르고 SABA와는 대등한 작용시간을 나타냄
- ICS 유지 중인 천식 환자에서 완화제로 formoterol을 사용하는 것이 SABA에 비해 악화를 줄임

SUMMARY (2)

STEP 1 & 2	
ICS/form as-needed > ICS (maintenance) + SABA as needed	**중증 악화**를 **감소**시킴
	ICS 사용량을 현저히 **감소**시킴 (1/2~3/4)
STEP 3 & 4	
ICS/form SiMART > ICS/LABA + SABA as-needed	**중증 악화**를 **감소**시킴
	ICS 사용량을 **감소**시킴 (1/4~1/2)
Track 1. ICS/form as-needed or SiMART	
Track 2.에 비해 **악화 위험을 감소**시키고 ICS 사용량도 줄일 수 있어 **우선적으로 선택하는 것을 권고**