Acute exacerbation

[제15차 천식연구회 · COPD연구회 공동 심포지엄]

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이현

Contents (1) – COPD AE

- Inhaler
  - LAMA vs. LABA
  - LAMA vs. ICS/LABA
  - LAMA/LABA vs. TIO
  - LAMA/LABA vs. ICS/LABA
  - LAMA/LABA/ICS vs. LAMA/LABA
  - LAMA/LABA/ICS vs. ICS/LABA
- Intensified ICS/LABA
- Low dose theophylline as adjunct to ICS
- Roflumilast
- Beta-blocker therapy
- Blood eosinophil
- Home-based ds-management program

Contents (2) – Asthma AE

- Dupilumab
- As needed ICS/LABA in mild asthma
- Escalating ICS to prevent AE
- LAMA use in uncontrolled persistent asthma
- Interventions for autumn exacerbations of asthma in children
- Prolonged use of oral corticosteroid
- Indoor allergen control

COPD

COPD AE

- **Inhaler**
  - **LAMA vs. LABA**
  - LAMA vs. ICS/LABA as an initial treatment
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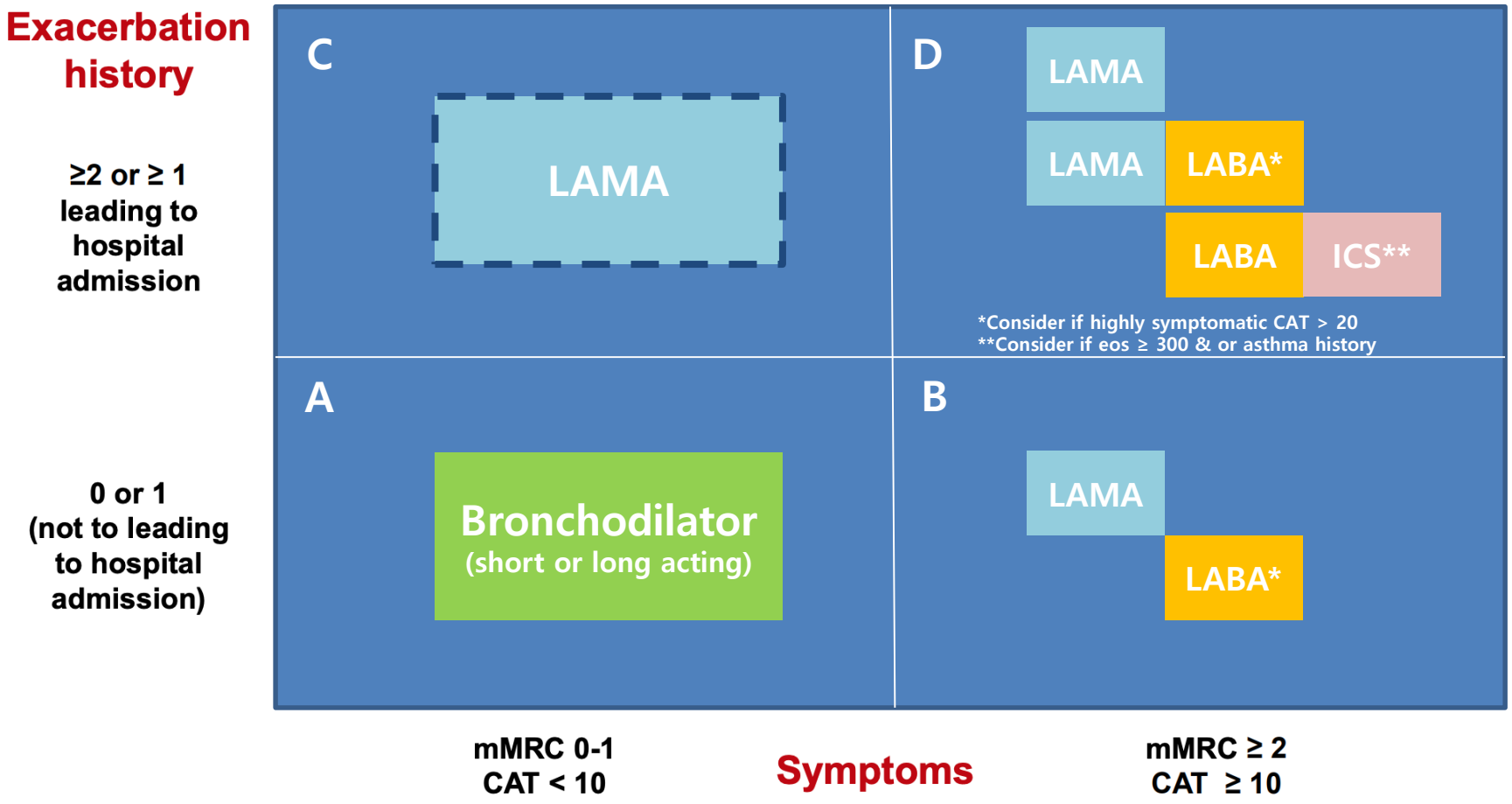
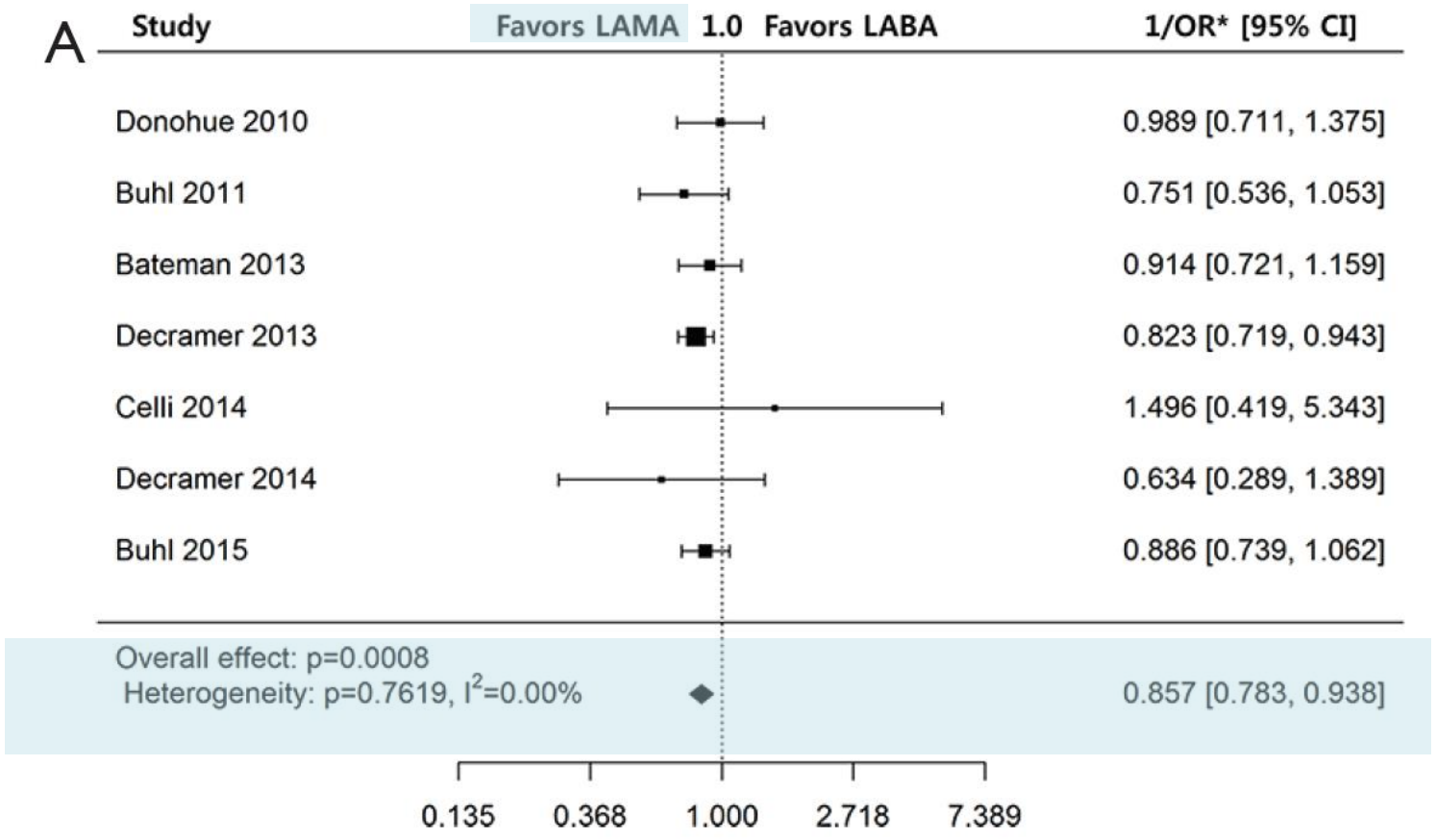
GOLD 2019


Exacerbation history
≥2 or ≥ 1 leading to hospital admission
0 or 1 (not to leading to hospital admission)
C
LAMA
D
LAMA
LAMA
LABA*
LABA
ICS**
*Consider if highly symptomatic CAT > 20
**Consider if eos ≥ 300 & or asthma history
A
Bronchodilator
(short or long acting)
B
LAMA
LABA*
mMRC 0-1
CAT < 10
Symptoms
mMRC ≥ 2
CAT ≥ 10

Once-daily LAMAs vs once-daily LABAs

Metanalysis of 7 studies comparing uLAMA vs. uLABA



Cho and Kim, J Thoracic Dis 2018;10:6522-6530

Inhalers

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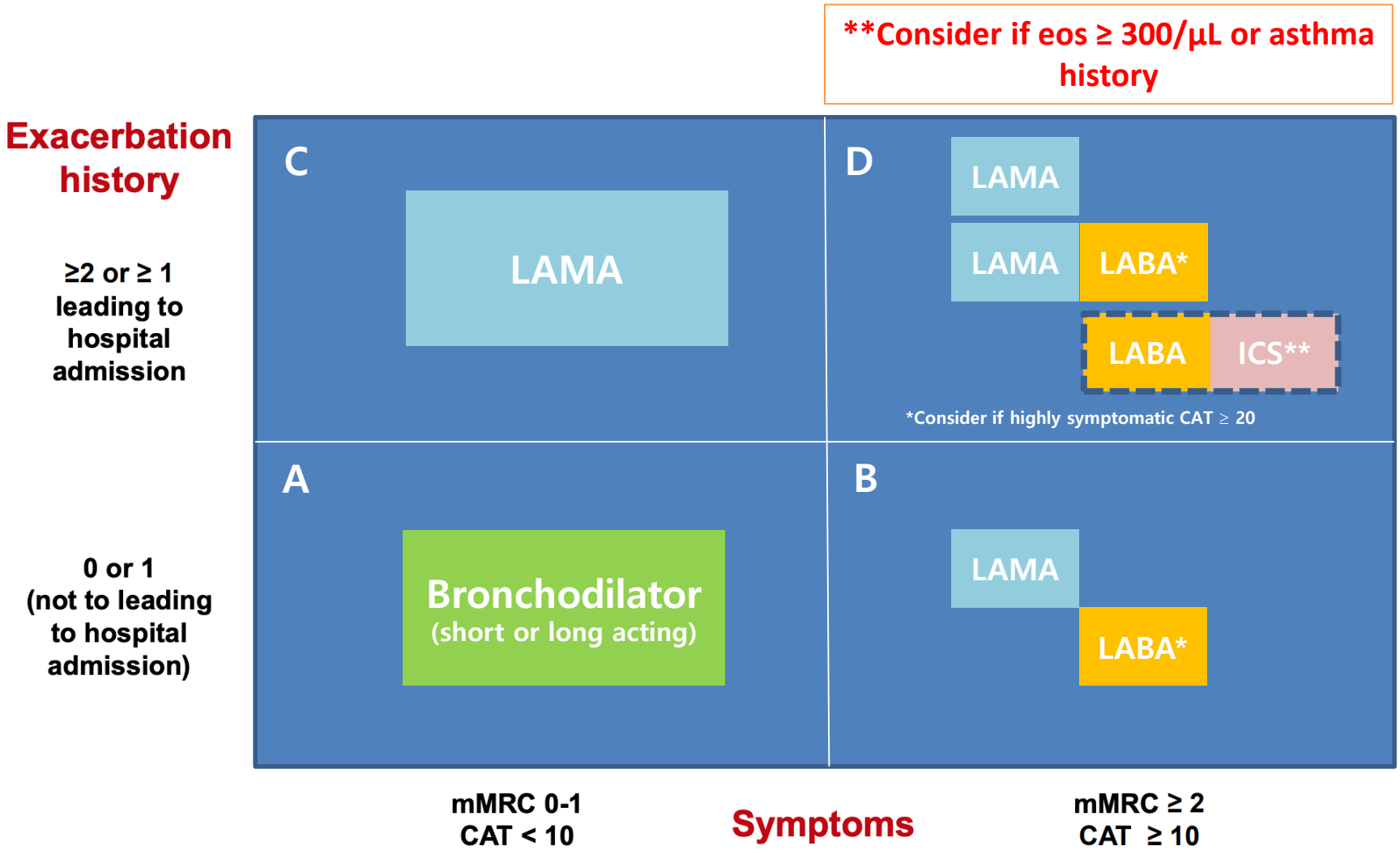
GOLD 2019


**Consider if eos ≥ 300/µL or asthma history
Exacerbation history
≥2 or ≥ 1 leading to hospital admission
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C
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Bronchodilator
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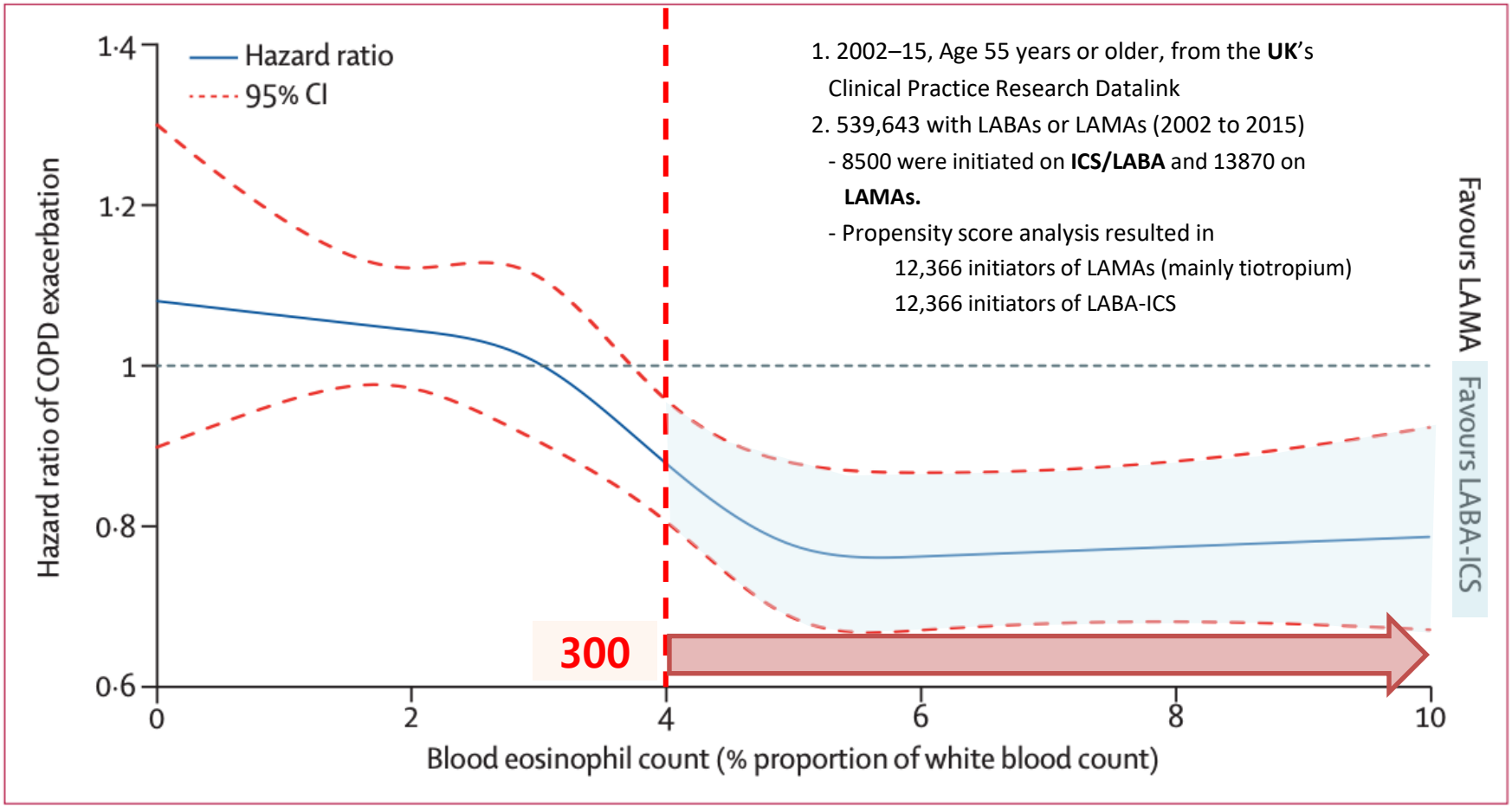
mMRC 0-1
CAT < 10
Symptoms
mMRC ≥ 2
CAT ≥ 10

LAMA vs. ICS/LABA for AE

as an initial treatment



Sussia, Lancet Respir Med 2018; 6: 855–62

COPD AE

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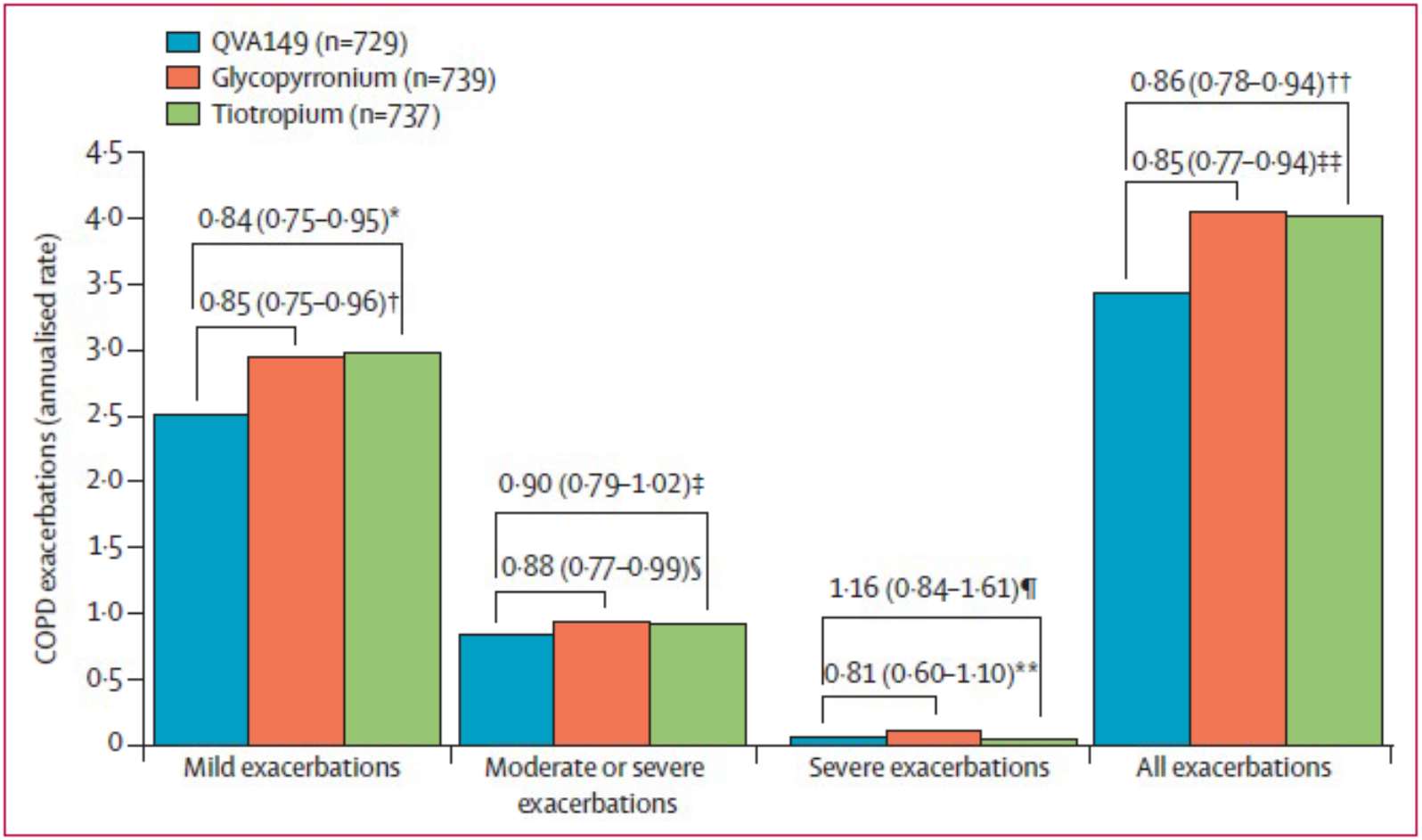
LAMA/LABA vs. TIO

	IND/GLY (110/50)	VI/UMEC (25/62.5)	OLO/TIO (5/5)	FOR/ACLI (12/400)	FF/GP (9.8/18)
Annualized rate of All AE, RR	**0.86***	**NS**			
Time to fist AE	**NS**	**NS-0.5****	-	-	-
Annualized rate of mod-severe AE, RR	**NS**	-	**0.90 (NS for 99% CI)**	-	-
Time to first mod-to-severe AE, HR	**NS**	-	**0.95 (NS for 99% CI)**	-	**NS**

Modified from Miravitlles, Tuberc Respir Dis 2018;81:198-215
*Wedzicha, Lancet Respir Med, 2013;1:199-209 (SPARK study)
**Maleki-Yazdi, Respir Med 2013;107:1538-1546
Calvery, Lancet Respir Med 2018;6:337-44

SPARK study

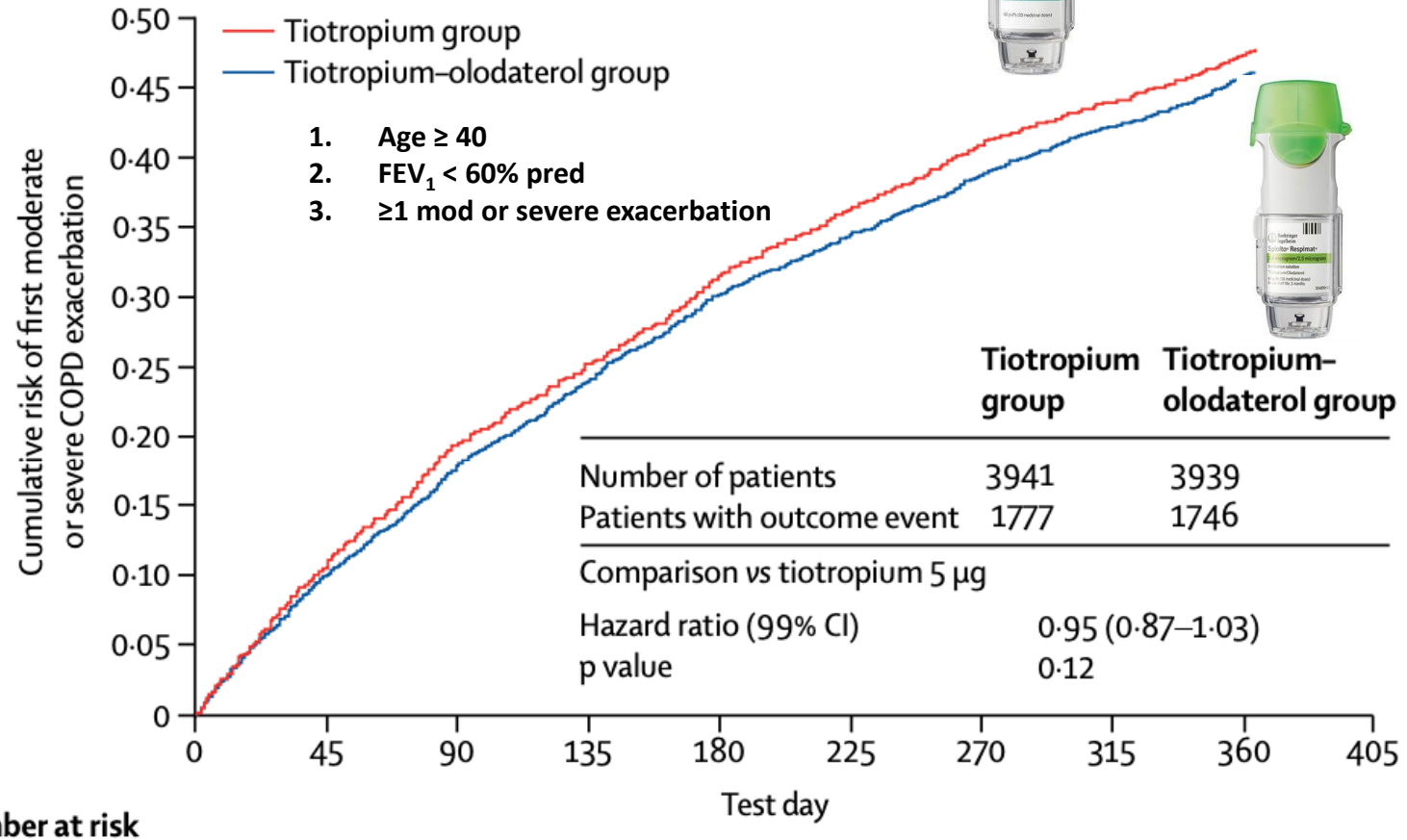
IND/GLY vs. TIO



Wedzicha Lancet Respir Med, 2013;1:199-209 (SPARK study)

DYNAGITO study

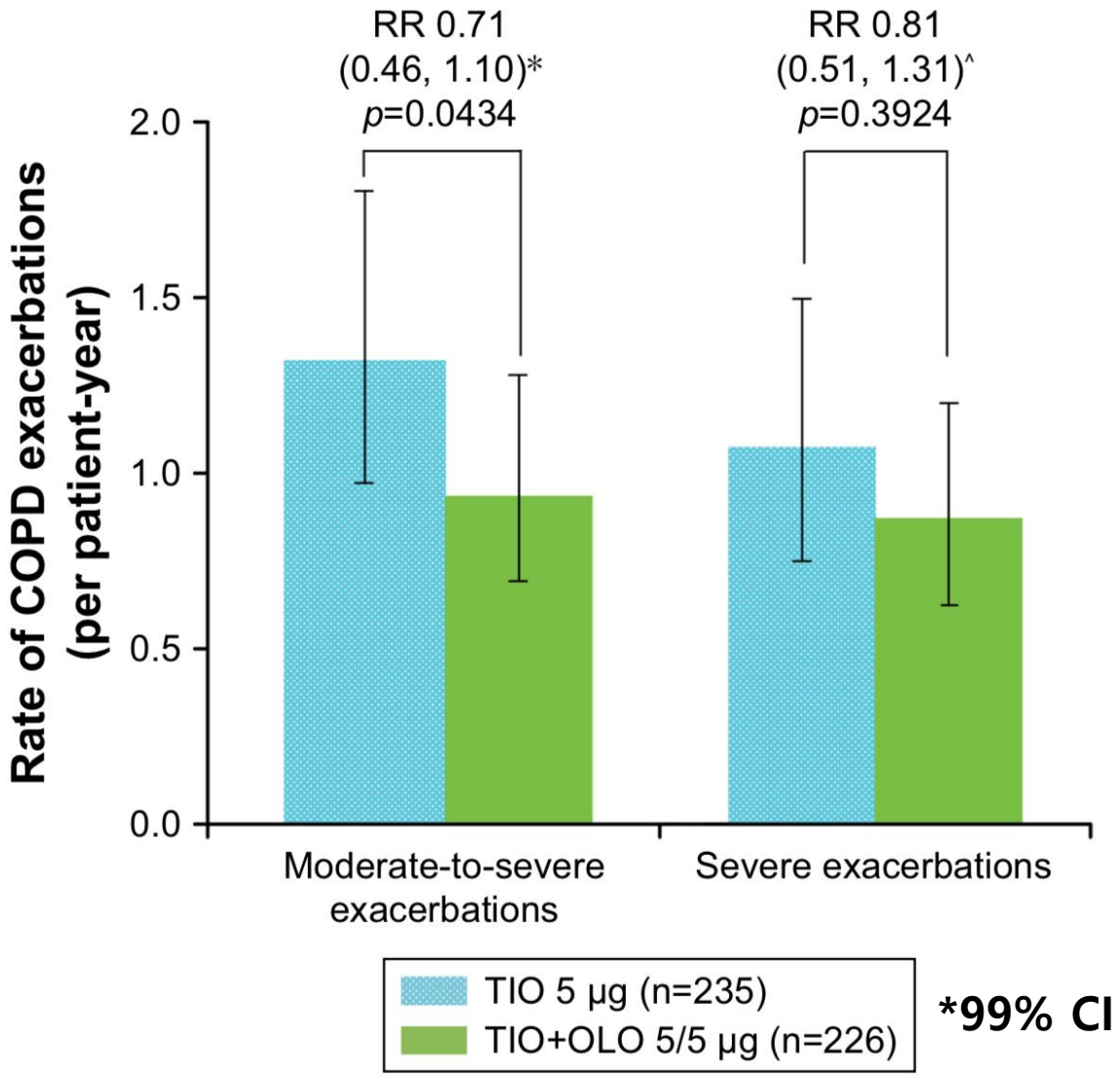
OLO/TIO vs. TIO



Number at risk

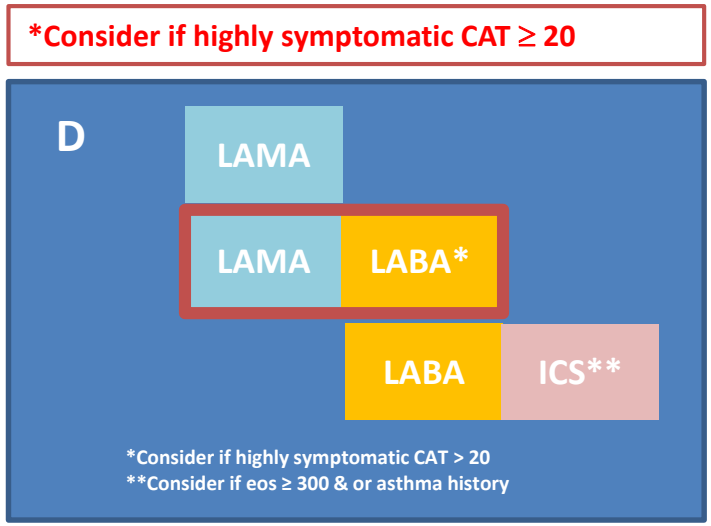
Tiotropium group	3941	3418	3020	2764	2503	2296	2109	1985	1537	0
Tiotropium–olodaterol group	3939	3485	3132	2859	2600	2424	2242	2101	1631	2

Calvery, Lancet Respir Med 2018;6:337-44

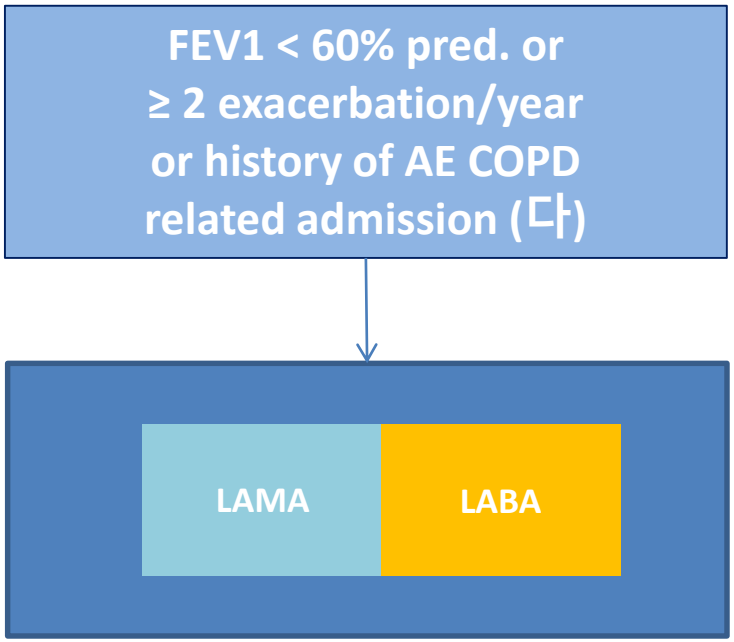

RR 0.71
(0.46, 1.10)*
p=0.0434
RR 0.81
(0.51, 1.31)^
p=0.3924
Rate of COPD exacerbations (per patient-year)
2.0
1.5
1.0
0.5
0.0
Moderate-to-severe exacerbations
Severe exacerbations
TIO 5 µg (n=235)
TIO+OLO 5/5 µg (n=226)
*99% CI

LAMA/LABA as an initial treatment in frequent exacerbators ?

GOLD 2019



COPD 진료지침 2018 개정



GOLD 2019
COPD 진료지침 2018 개정

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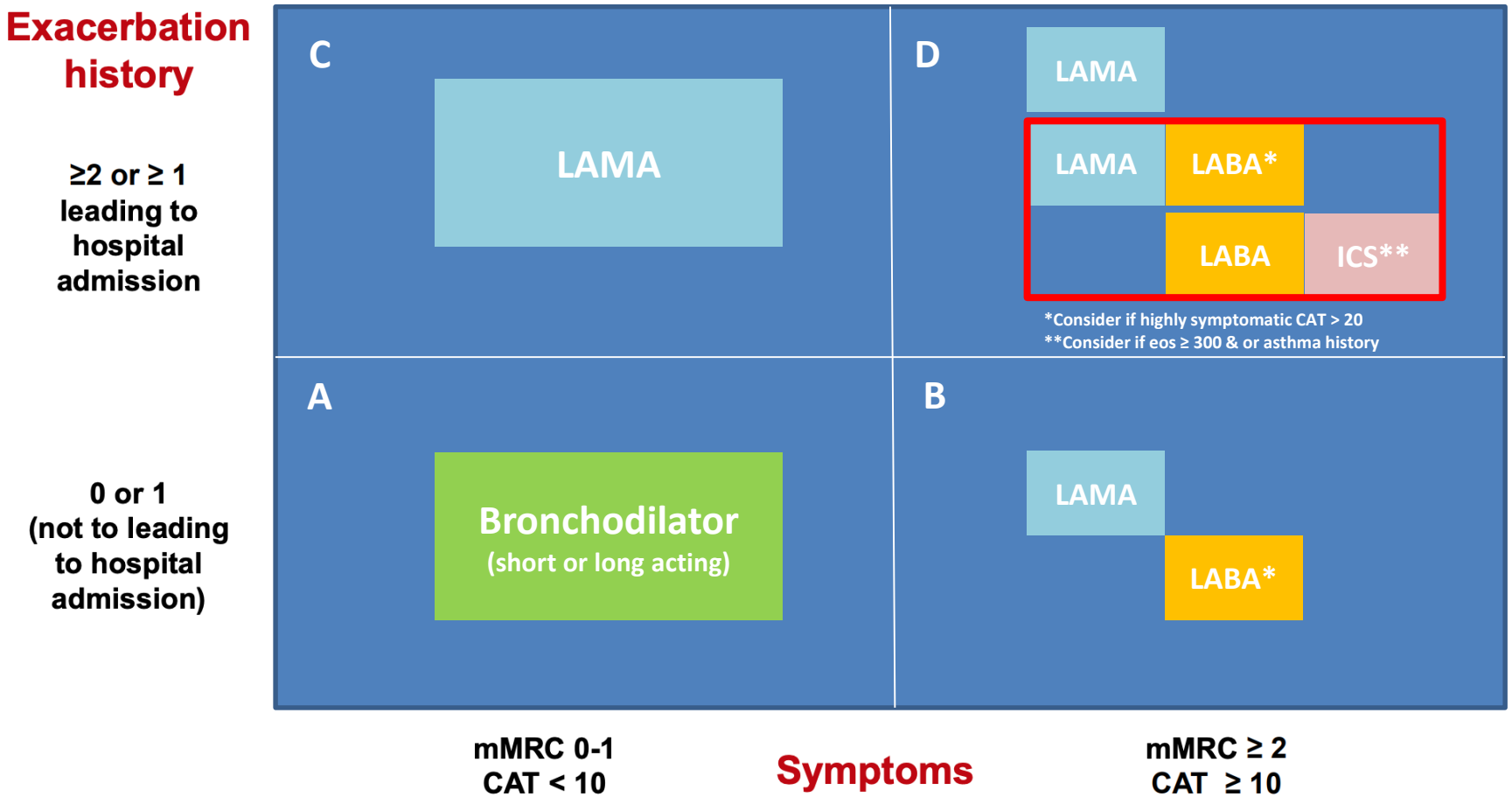
LAMA/LABA vs. ICS/LABA as an initial Tx in Group D ?



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FLAME study

Time to first mod or severe AE

(Subgroup analyses from the FLAME study)

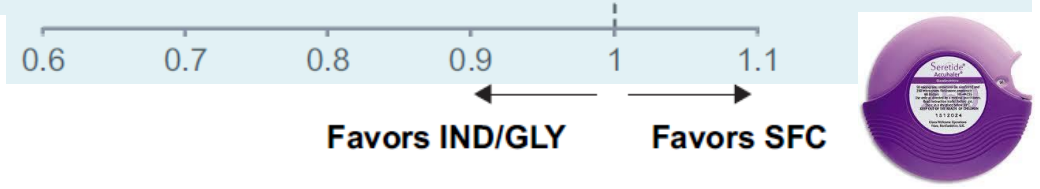
1. FMALE study (N = 3,362)
2. FEV1 25-59%
3. mMRC ⩾ 2
4. AE ⩾ 1

LAMA/LABA vs. ICS/LABA

RR - 0.89; 95% CI, 0.83-0.96

Subgroup analysis of FLAME study

Exacerbation in the previous year	Number of patients IND/GLY	SFC	Rate ratio (95% CI)
1 exacerbation	1,329	1,335	0.85 (0.70–0.93)
≥2 exacerbations	321	320	0.85 (0.70–1.03)
≥2 exacerbations or an exacerbation that led to hospitalization	531	503	0.86 (0.74–1.00)



Group D

Vogelmeier, International Journal of COPD 2018;13:1125–1134

IMPACT study

	≥2 Moderate/Severe Exacerbations In Prior Year		
	FF/UMEC/VI (N=4151)	**FF/VI (N=4134)**	**UMEC/VI (N=2070)**
Number of patients in each subgroup	2296	2222	1137
Number of patients	2292	2222	1137
Model estimated exacerbation rate	0.94	1.06	1.32
(95% CI)	(0.89 to 1.00)	(1.00 to 1.12)	(1.21 to 1.43)
FF/UMEC/VI vs. column			
Percentage reduction in annual rate (95% CI)		11%** (3% to 18%)	28%*** (21% to 35%)

Lipson, N Engl J Med 2018;378:1671-1680

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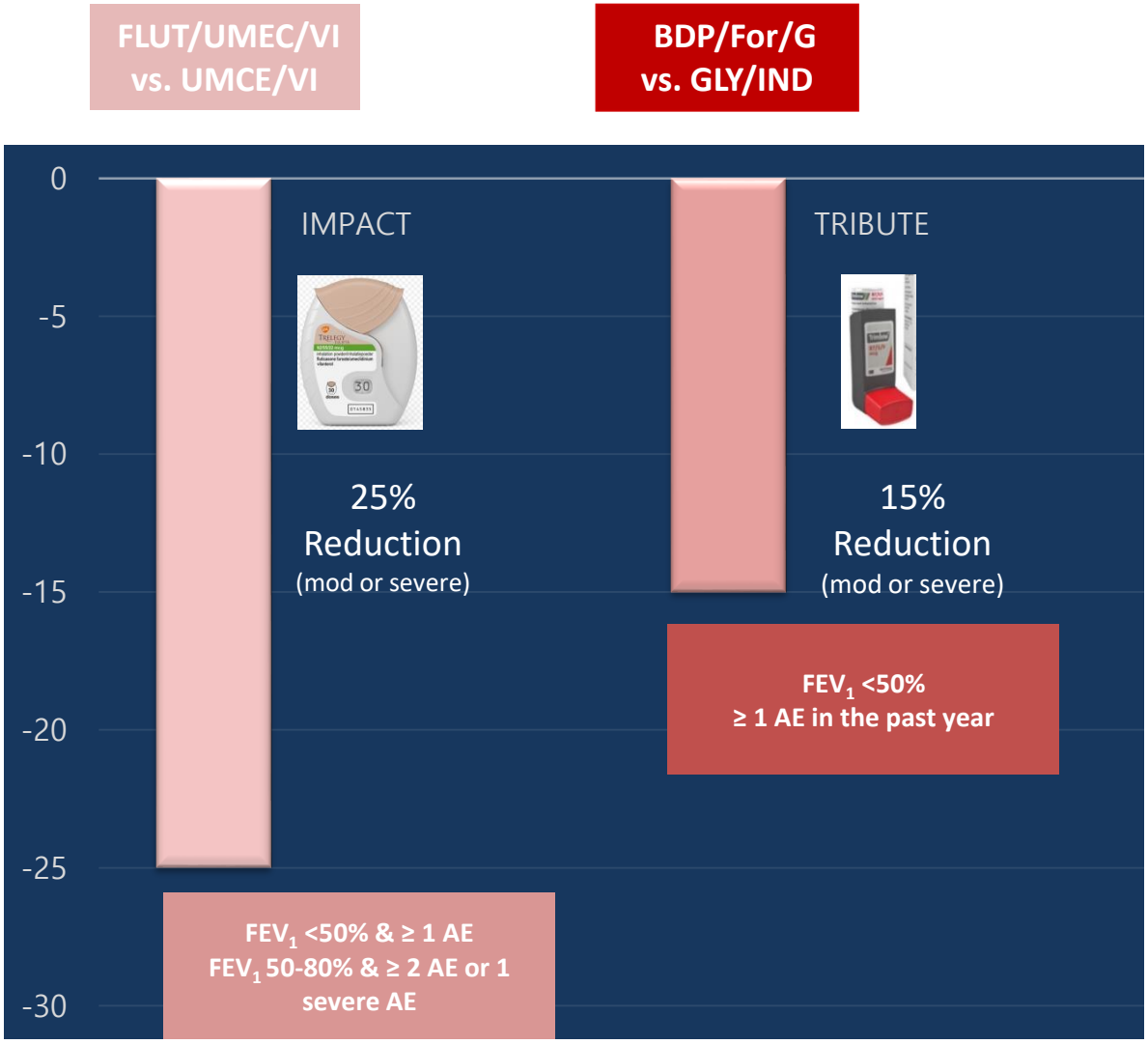
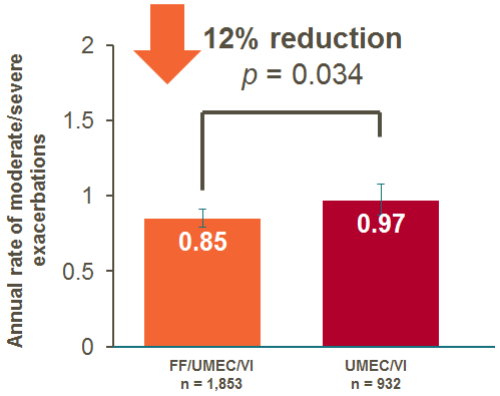


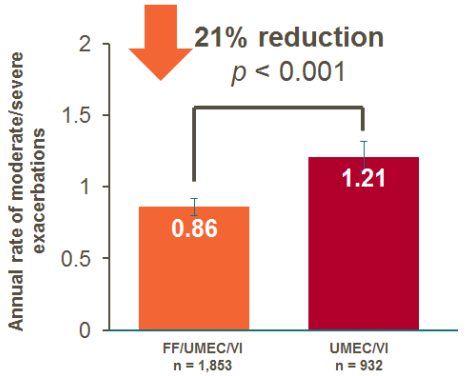
Lipson, N Engl J Med 2018;378:1671-1680
Papi, Lancet 2018;391:1076-1084

IMPACT study

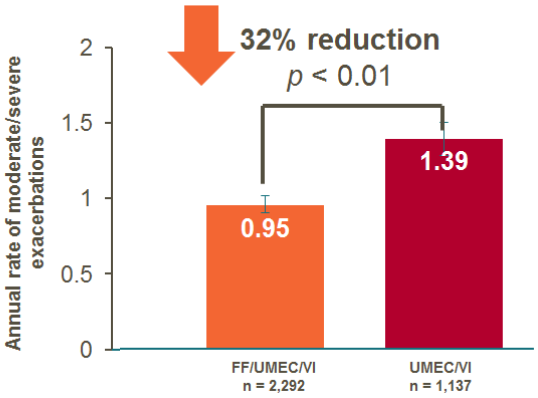
Eos < 150 cells/µL



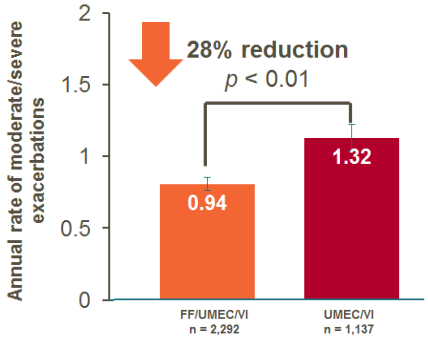
One or less mod-to-severe AE In the prior year



Eos ⩾ 300 cells/µL



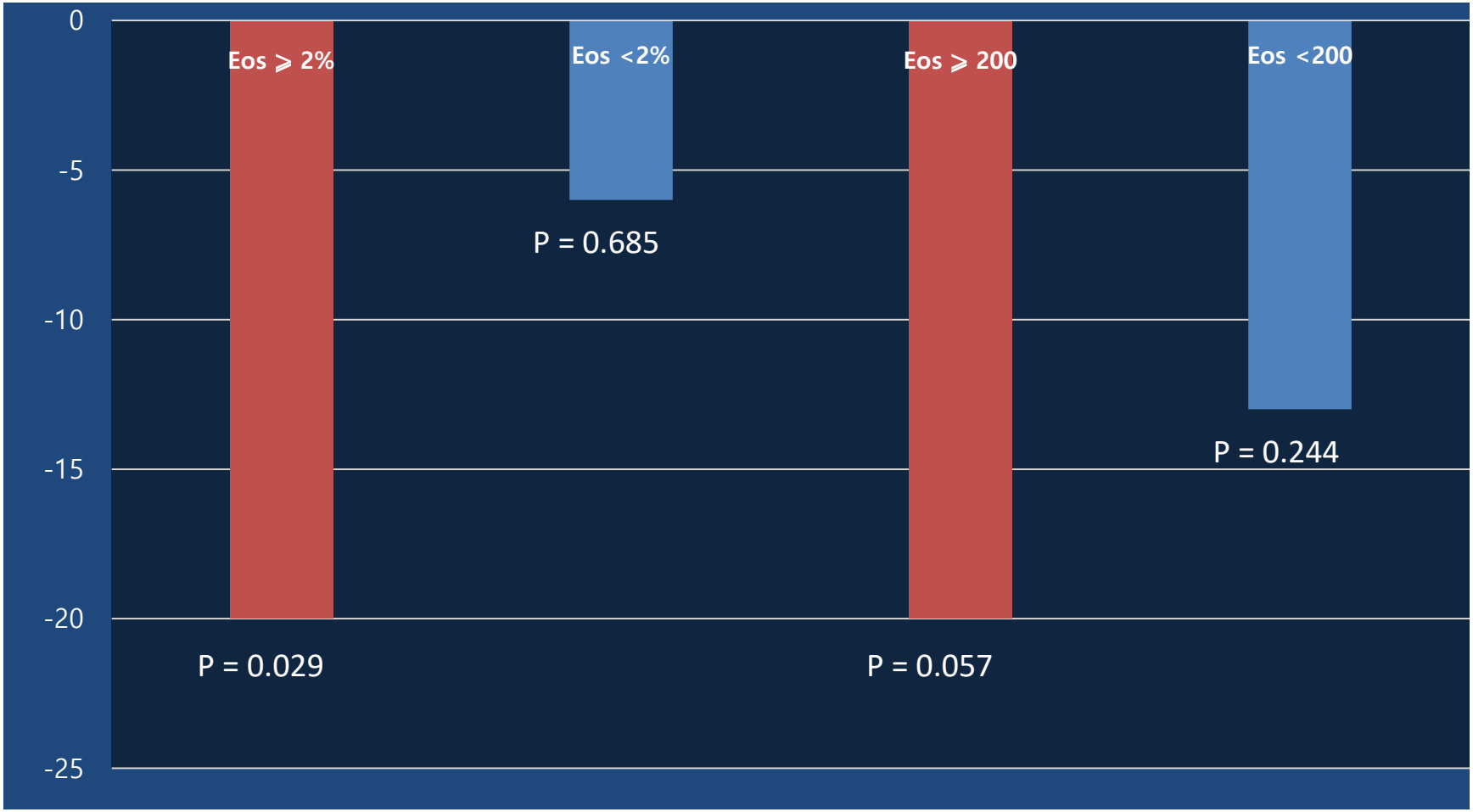
⩾ 2 mod/severe AE in the prior year



Lipson, N Engl J Med 2018;378:1671-1680

TRIBUTE study

BDP/FF/G vs. GLY/IND

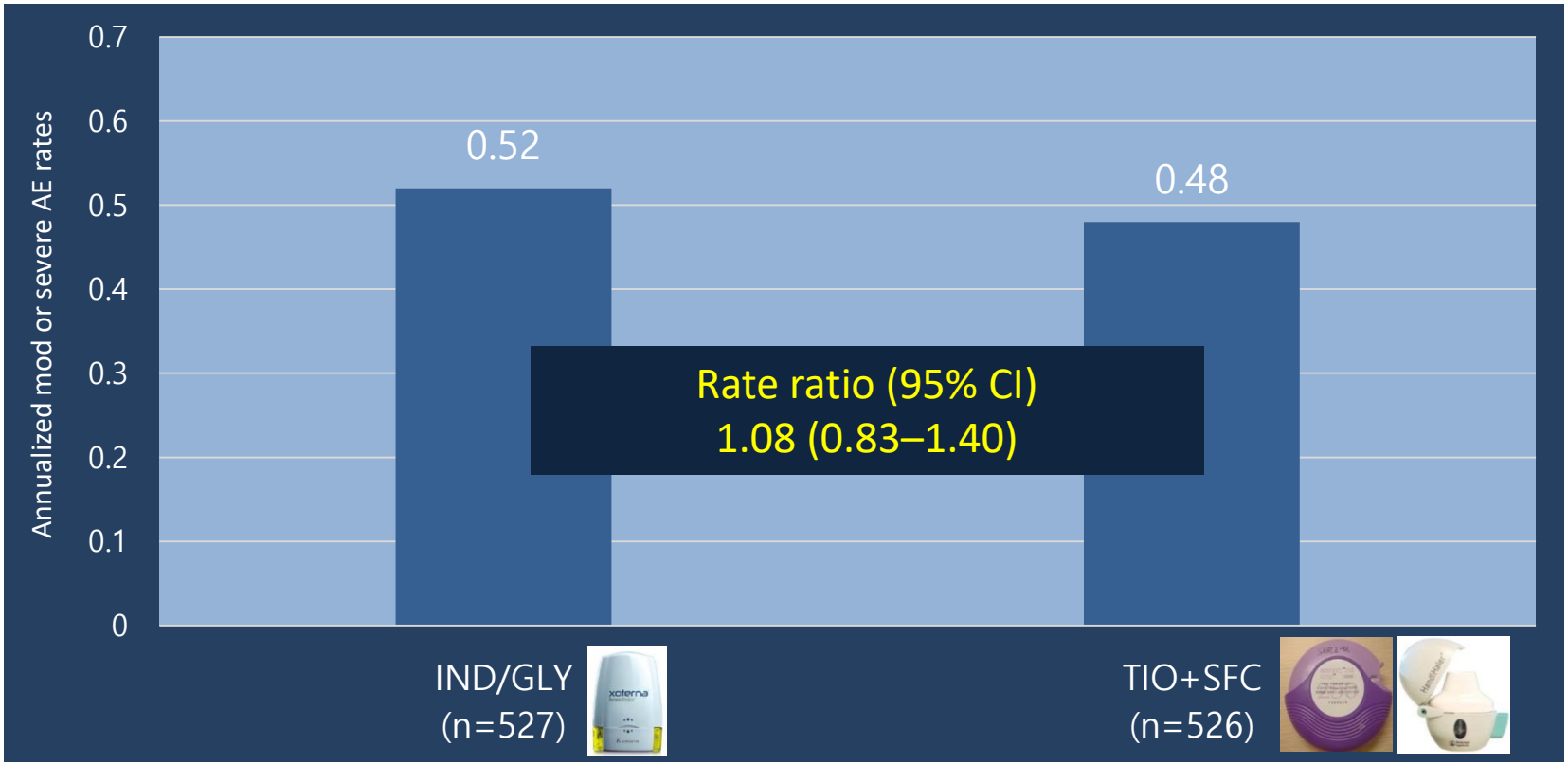


Papi, Lancet 2018;391:1076-1084

SUNSET study

TIO+SFC → **IND/GLY**
TIO+SFC
26 wks

1. 26-week randomized double-blind, triple-dummy study
2. 1,093 Pts with nonfrequent AE



Chapman, Am J Respir Crit Care Med 2018;3:329-339

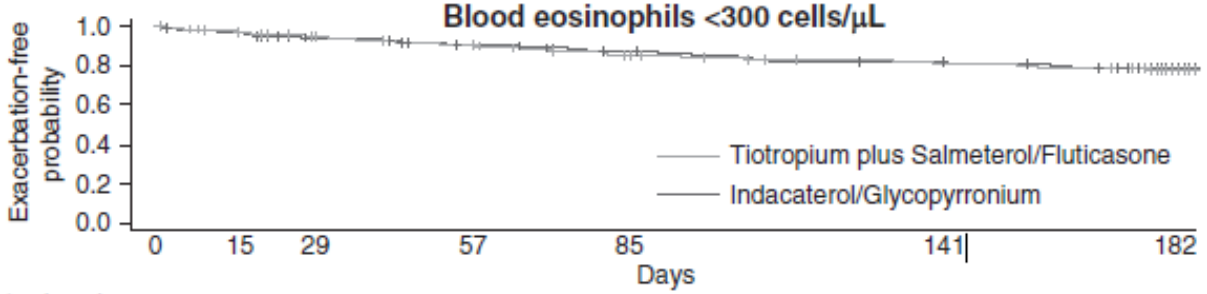
SUNSET study

Rate Ratio of COPD Exacerbations

Indacaterol/Glycopyrronium Better

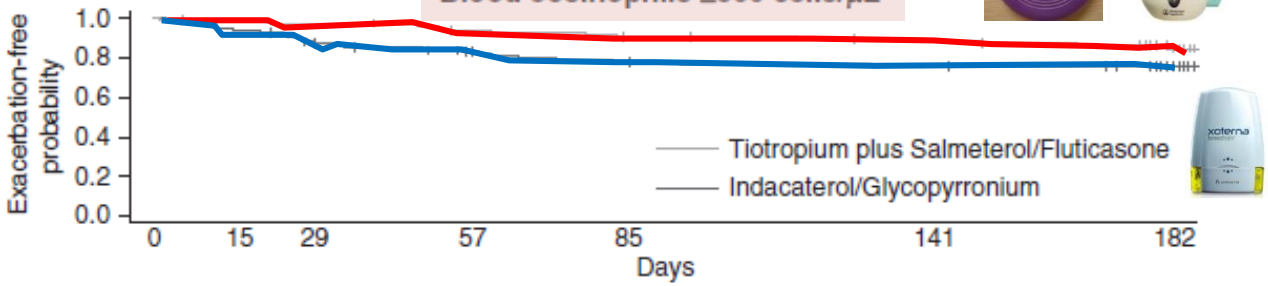
Tiotropium plus Salmeterol/Fluticasone Better

D



Tiotropium plus Salmeterol/Fluticasone	406	392	375	355	326	305	250
Indacaterol/ Glycopyrronium	401	387	369	347	331	305	231

E



Tiotropium plus Salmeterol/Fluticasone	119	117	115	109	104	99	78
Indacaterol/ Glycopyrronium	125	118	108	95	88	85	66

Chapman, Am J Respir Crit Care Med 2018;3:329-339

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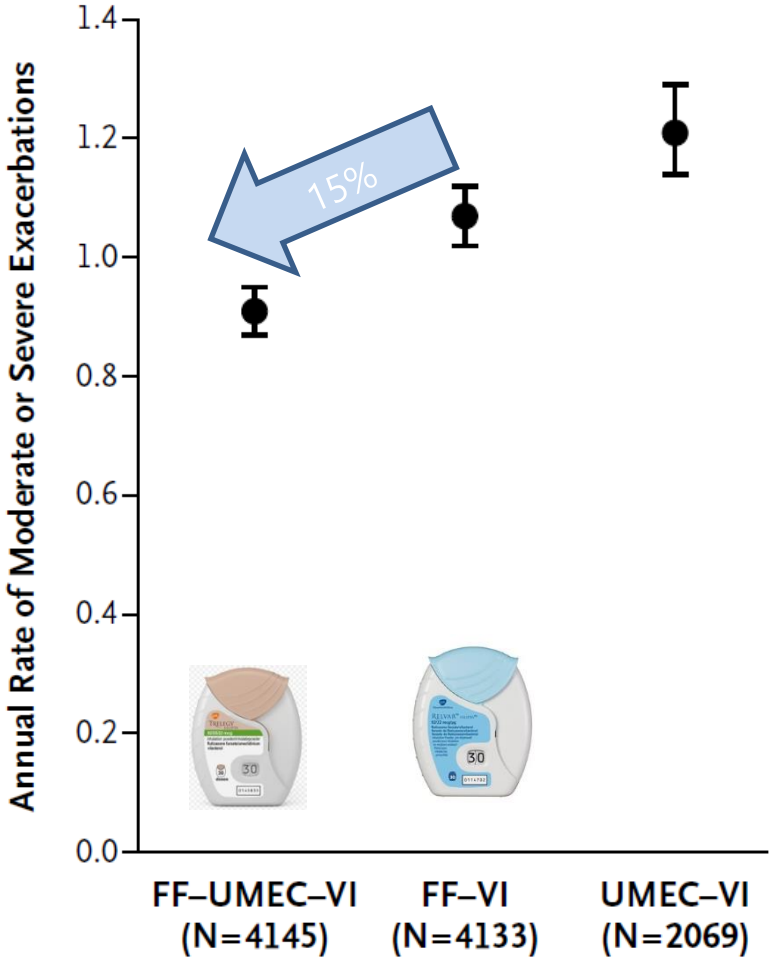
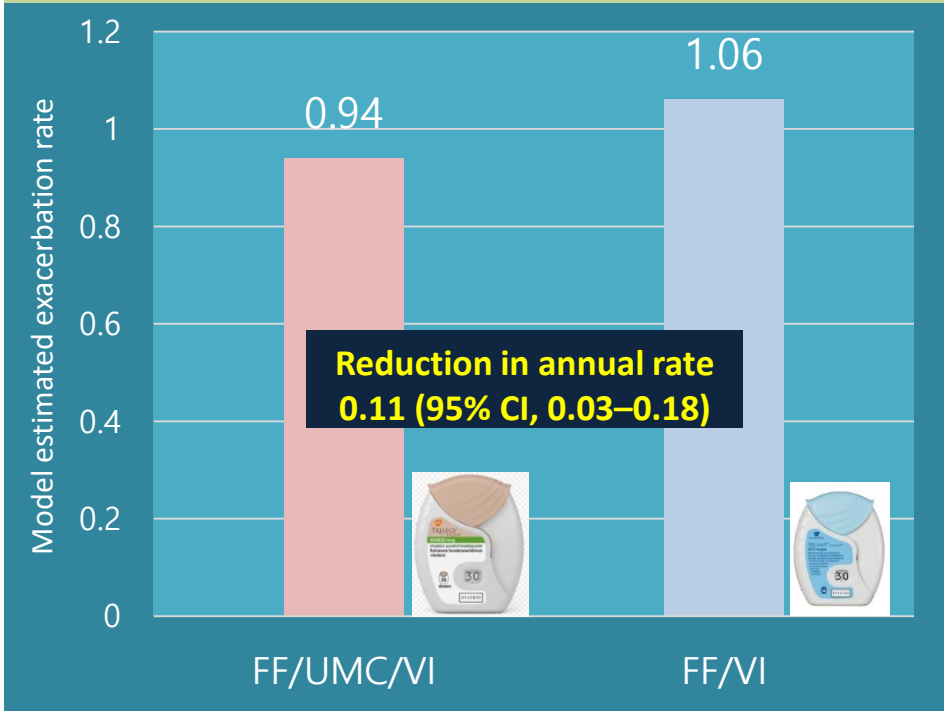
IMPACT study



⩾ 2 mod/severe AE in the prior year



Lipson, N Engl J Med 2018;378:1671-1680

FULFIL study

FF/UMC/VI vs. BUD/F

1. Aged ⩾40 years with advanced symptomatic COPD
2. FEV_1 <50 %pred and CAT score ⩾10, or
3. FEV_1 50–80 %pred & CAT ⩾10 with either ⩾2 mod AE or 1 severe AE/year

AE rate ratio
0.65 (95% CI, 0.49–0.86)

TABLE 2 Mean annual moderate/severe exacerbation rates by subgroup (intent-to-treat (ITT) population; up to week 24)

Subgroup	FF/UMEC/VI		BUD/FOR		Rate reduction % (95% CI)
	n	Rate	n	Rate	
Patients	911		899		
Prior medication					
ICS+LABA	266	0.10	258	0.27	63 (29–80)***
BUD+FOR	87	0.05	83	0.10	54 (−74–88)
ICS+LABA+LAMA	256	0.28	254	0.53	47 (13–67)*
LAMA alone	79	0.12	79	0.23	49 (−42–81)
TIO alone	65	0.15	67	0.20	24 (−125–74)
LAMA+LABA	100	0.38	83	0.26	−44 (−194–29)
Disease severity					
FEV_1 % pred <50%, no moderate/severe exacerbations	311	0.22	315	0.33	33 (−4–57)
FEV_1 % pred <50%, ⩾1 moderate/severe exacerbation	299	0.22	290	0.41	45 (11–66)*
FEV_1 % pred 50– <80%, ⩾2 moderate or ⩾1 severe exacerbations	296	0.22	289	0.30	27 (−21–56)
Exacerbation history					
0/1 moderate exacerbations	599	0.25	609	0.40	36 (11–54)**
⩾2 moderate exacerbations	308	0.24	283	0.32	25 (−23–55)
⩾1 severe exacerbations	185	0.13	198	0.32	59 (17–80)*

Halpin, ERJ Open Res 2018; 4: 00119-2017

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- **Intensified ICS/LABA in case of an upper respiratory tract infection (URTI)**
- Theophylline as adjunct to ICS
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Intensified ICS/LABA

in case of an URTI

Budesonide/Formoterol (200mcg/6mcg) TWD

URTI

Budesonide/Formoterol (200mcg/6mcg) TWD

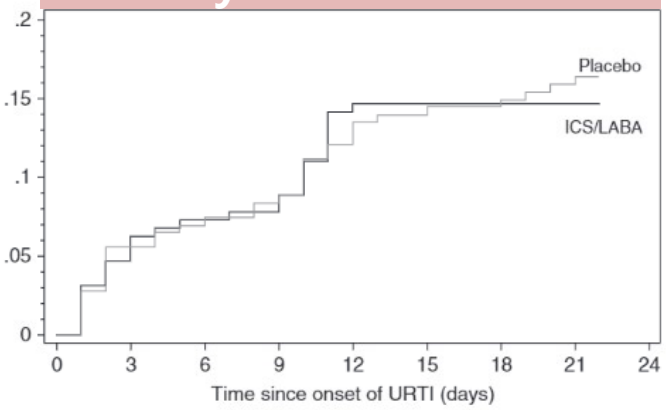
Budesonide/Formoterol (400mcg/12mcg) TWD

Budesonide/Formoterol (200mcg/6mcg) TWD

Stolz, Am J Respir Crit Care Med, 2018;197:1136-1136

Intensified ICS/LABA
in case of an URTI

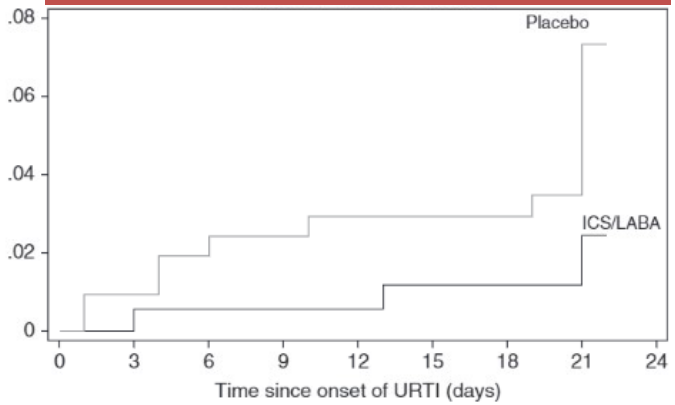
Any exacerbation



Patients at risk*								
Placebo	216	203(1)	199	195(1)	184(1)	180	179(2)	175(1)§
ICS/LABA	192	180	177(1)	173(1)	162	159(3)	159	159§

Hazard ratio = 0.77 (p = 0.312)

Severe exacerbation

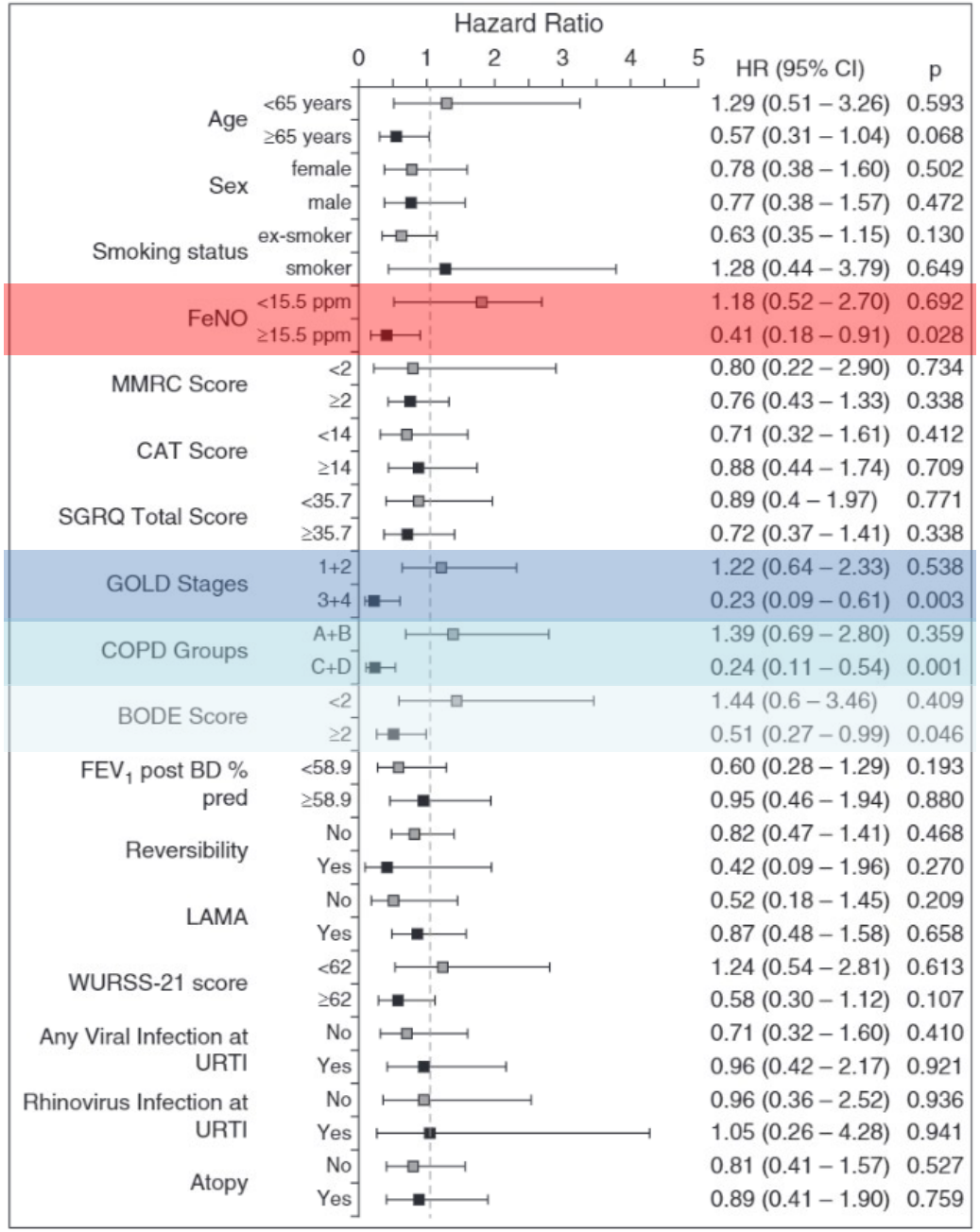


Patients at risk*								
Placebo	212	200(10)	196(1)	193(3)	183(9)	179(4)	178(1)	167(3)§
ICS/LABA	188	176(11)	173(3)	170(3)	159(11)	156(2)	156(0)	153(1)§

Hazard ratio = 0.28 (p = 0.010)

Stolz, Am J Respir Crit Care Med, 2018;197:1136-1136

A



Stolz, Am J Respir Crit Care Med, 2018;197:1136-1136

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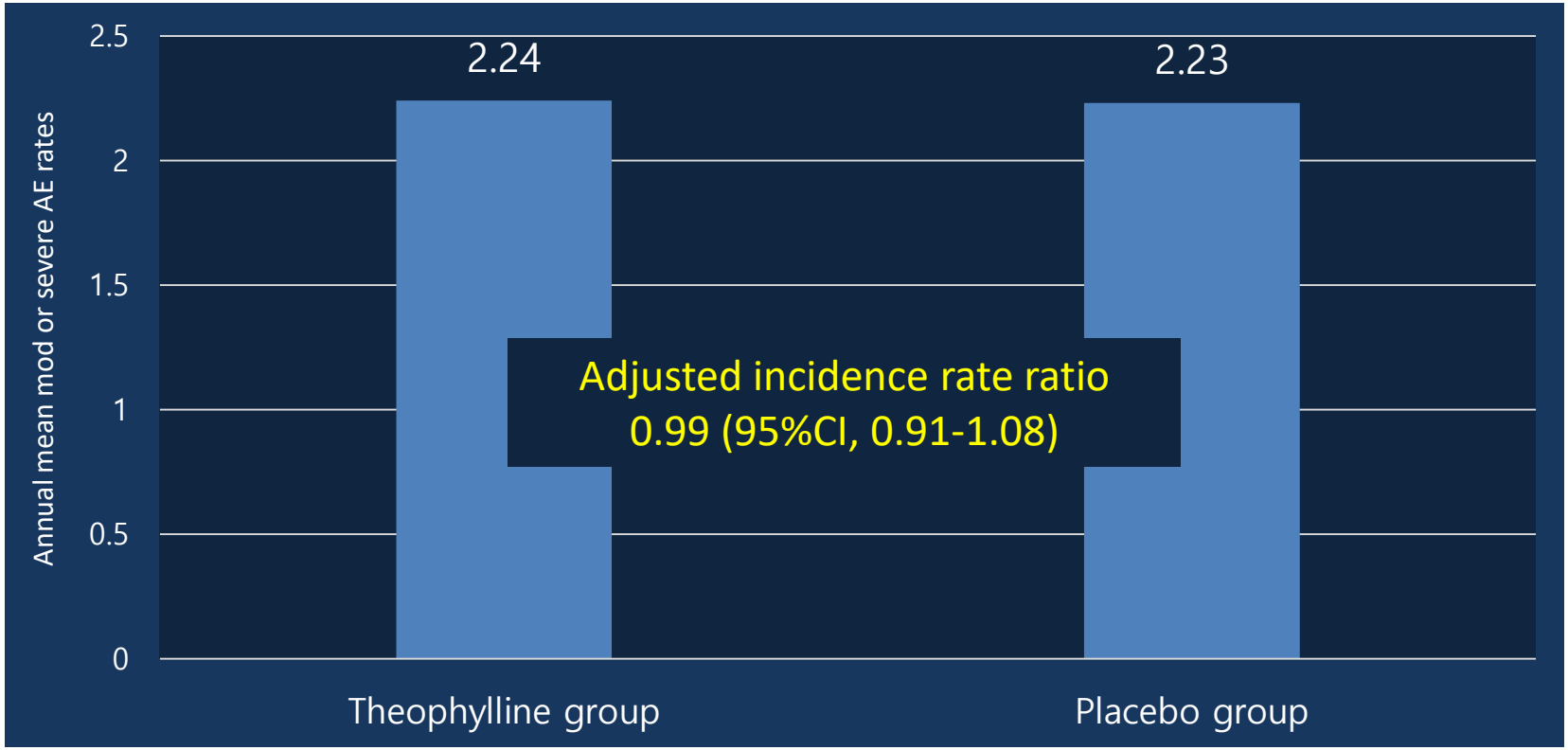
TWICS trial

Low-dose theophylline as adjunct to ICS
on the AE of COPD

1. 1578 with COPD in 121 **UK** primary and secondary care using **ICS**
2. At least **2 mod AE** in the previous year
3. Low-dose theophylline dose: 200 mg once or twice per day



Devereux, JAMA. 2018;320:1548-1559

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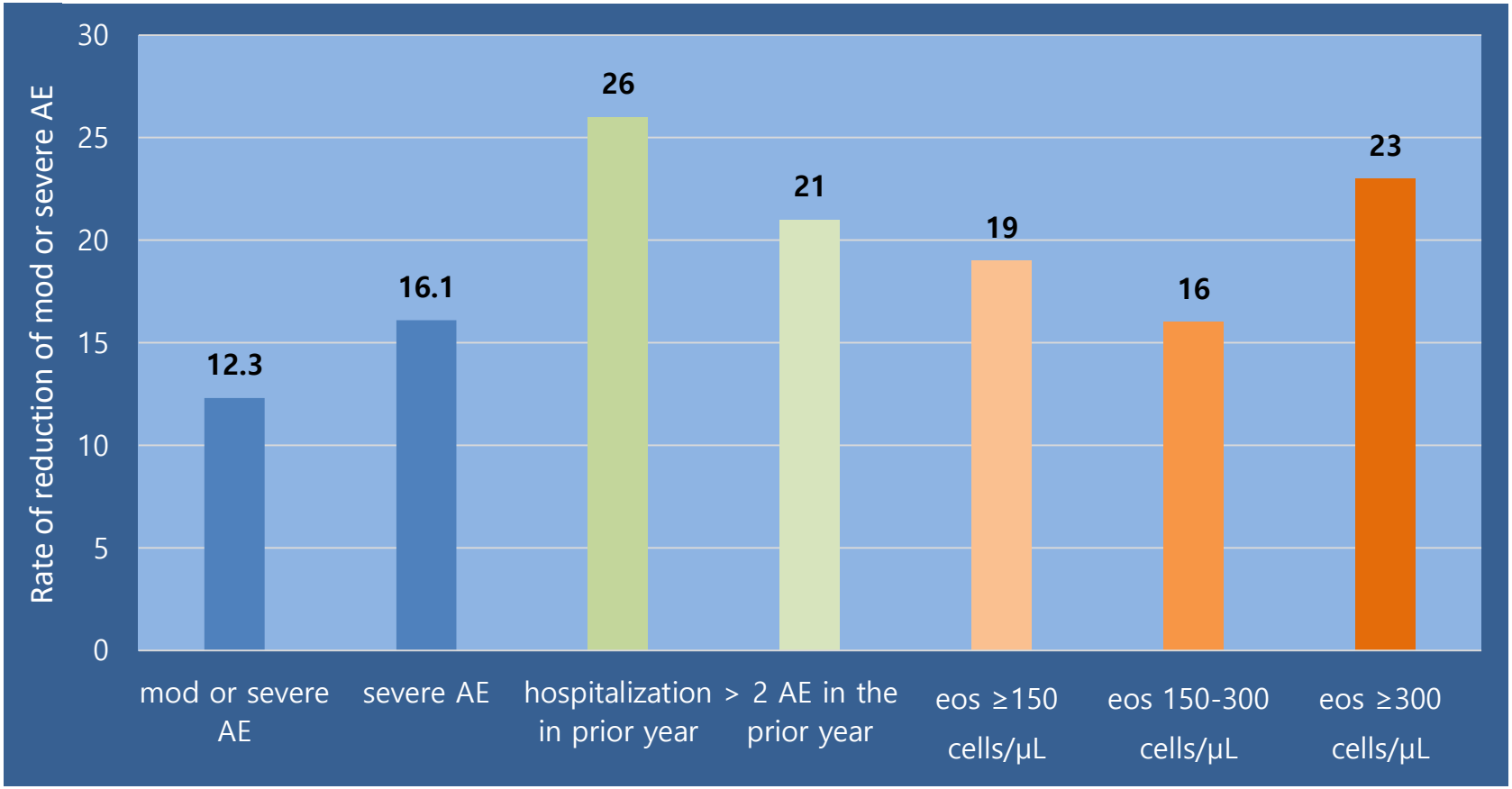
- Multicomponent home-based ds-management program

Roflumilast

1. Subject aged ⩾ 40 years with severe or very severe COPD
2. **Chronic bronchitis**
3. **⩾ 2 AE and/or hospitalizations due to AE** within 1 yr
4. receiving **ICS/LABA** ± LAMA (at least 3 mon)

REACT and RE$_2$SPOND



Martinez, Am J Respir Crit Care Med. 2018;198:1268-1278

COPD AE

- Inhaler
  - LAMA vs. LABA
  - LABA vs. ICS/LABA
  - LAMA/LABA vs. TIO
  - LAMA/LABA vs. ICS/LABA
  - LAMA/LABA/ICS vs. LAMA/LABA
  - LAMA/LABA/ICS vs. ICS/LABA
- Intensified ICS/LABA
- Theophylline as adjunct to ICS
- Roflumilast
- **Beta-blocker therapy**
- Biomarker
- Multicomponent home-based ds-management program

Time to first AE according to treatment allocation and use of beta-blocker therapy at Baseline

1. 16,485 of SUMMIT participants
2. Baseline beta-blocker therapy was used by 31% (n=5,159)

	Placebo N=4,111	Fluticasone Furoate N=4,135	Vilanterol N=4,118	Fluticasone Furoate/ Vilanterol N=4,121
(A) Time to first exacerbation of chronic obstructive pulmonary disease				
No Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		0.95 (0.86, 1.04)	0.94 (0.85, 1.03)	0.83 (0.75, 0.91)
Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		1.00 (0.87, 1.15)	0.86 (0.75, 1.00)	0.73 (0.63, 0.85)
Treatment by Beta-blocker Interaction p-value	0.18			

Dransfield, MT, Ann Am Thorac Soc 2018, **15,** 5, 608.

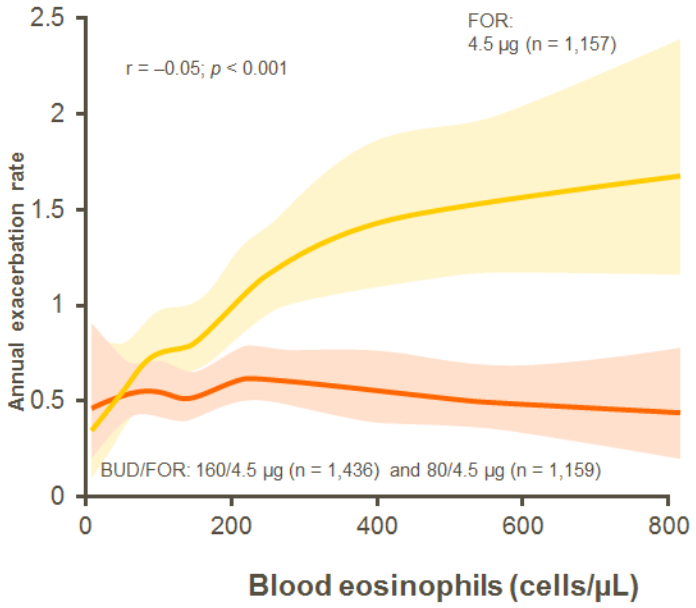
COPD AE

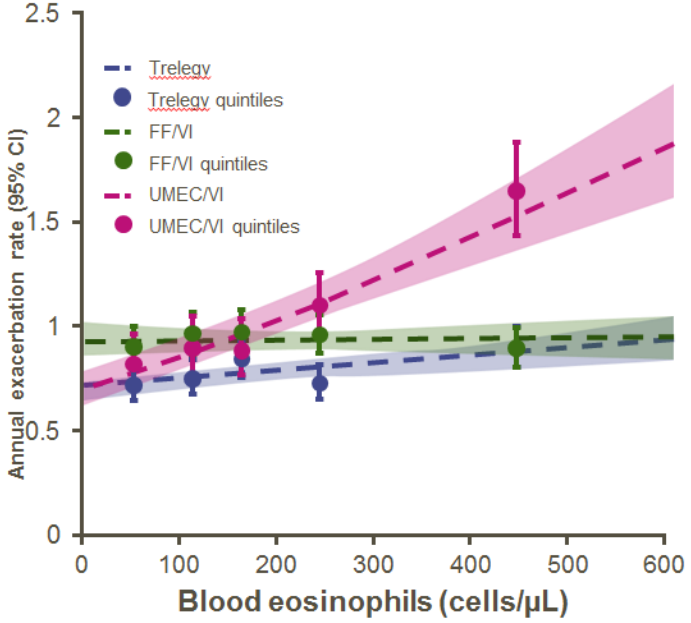
- Inhaler
  - LAMA vs. LABA
  - LABA vs. ICS/LABA
  - LAMA/LABA vs. TIO
  - LAMA/LABA vs. ICS/LABA
  - LAMA/LABA/ICS vs. LAMA/LABA
  - LAMA/LABA/ICS vs. ICS/LABA
- Intensified ICS/LABA
- Theophylline as adjunct to ICS
- Beta-blocker therapy
- Roflumilast
- **Blood eosinophil**
- Multicomponent home-based ds-management program

Blood eosinophil counts predicts future exacerbations and ICS response

- IMPACT study (2018)/Analysis of three Astrazeneca RCT with BUD/F
- Wisdom study (2016) / Sunset study (2018)
  - ICS discontinuation in pts with Eos ⩾ **300 cells/μL**

    → RR for AE 1.73 (1.15-2.62)/1.86 (1.06-3.28)





Lipson, N Engl J Med 2018;378:1671-1680
Bafadhel, Lancet Respir Med. 2018;6:117-126
Chapman, Am J Respir Crit Care Med 2018;3:329-339

Factors affecting AE

in cases with eosinophil count ⩾ 300 cells/μL

AE history

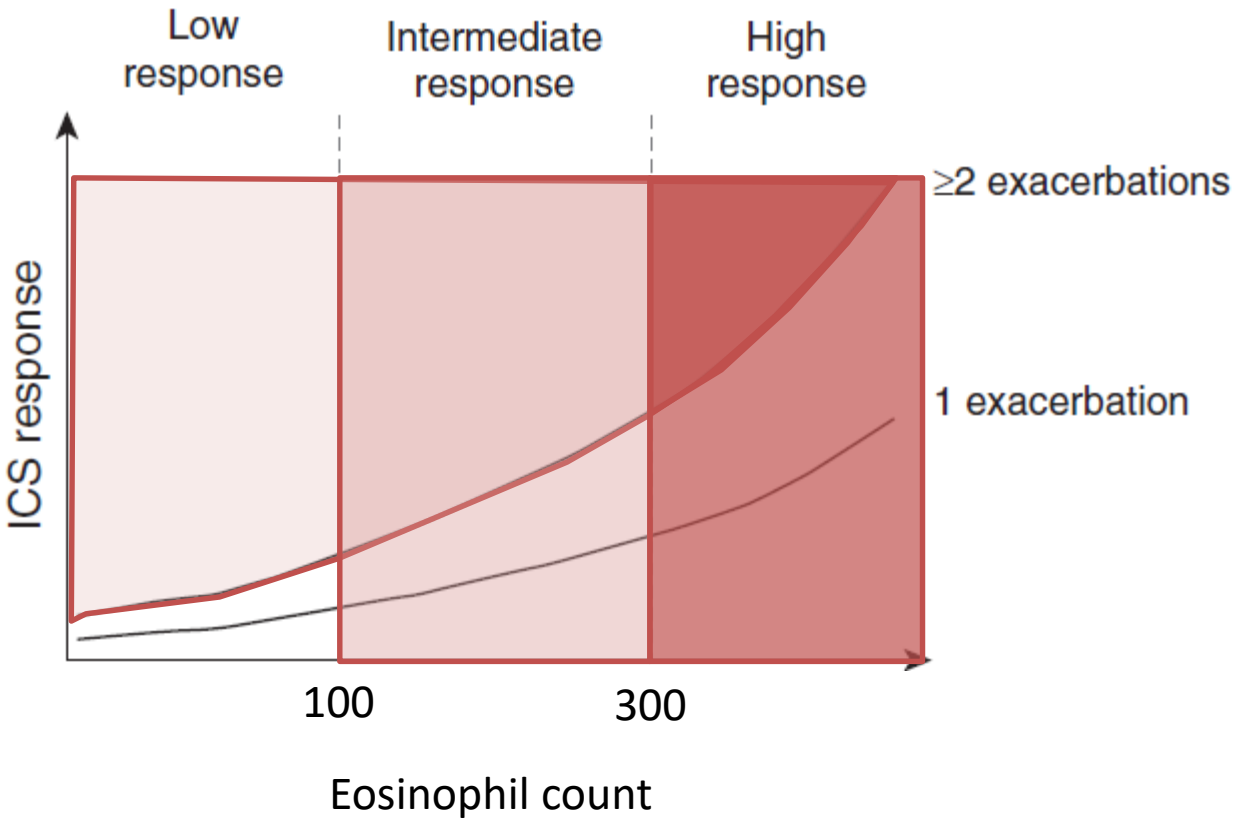
Risk of increased blood eos on future AE stratified by prior AE history

Non-eos vs. eos	Study	RR	0 AE	1 AE	2 or more AE
Eos ⩾ 300 cells/μL at screening	COPDgene cohort	IRR	1.12 (0.57-2.28)	1.02 (0.48-2.20)	**1.96 (1.21-3.21)**
	ECLIPSE cohort	IRR	1.03 (0.57-2.28)	1.15 (0.87-1.51)	**1.40 (1.15-1.70)**
	WISDOM study	RR (ICS/ICS withdrawal)	-	1.45 (0.96-2.17)	**1.75 (1.09-2.80)**

Yun, J Allergy Clin Immunol. 2018;141:2037-2047
Calverley Am J Respir Crit Care Med. 2017;196:1219-1221

ICS response

Frequent exacerbator +
High blood eosinophils (≥ 300 cells/μL)



Singh, Am J Respir Crit Care Med 2017;196:1098-1100

COPD AE

- Inhaler
  - LAMA vs. LABA
  - LABA vs. ICS/LABA
  - LAMA/LABA vs. TIO
  - LAMA/LABA vs. ICS/LABA
  - LAMA/LABA/ICS vs. LAMA/LABA
  - LAMA/LABA/ICS vs. ICS/LABA
- Intensified ICS/LABA
- Theophylline as adjunct to ICS
- Beta-blocker therapy
- Biomarker
- **Multicomponent home-based ds-management program**

A multicomponent home-based disease-management program

COMET study

1) Age ⩾35 years
2) FEV_1 < 50%pred

Intervention

1) Self-management program
2) Home monitoring
3) E-health telephone/web platform

Primary outcomes

1) Number of unplanned all-cause **hospitalisation days**

Secondary outcomes

1) Acute care hospitalisation days
2) BODE index
3) **Exacerbations**
4) Safety events (adverse events and deaths)

PIC COPD⁺ study

1) Age ⩾50 years
2) ⩾1 ER visit or admission for AE in prev 12 mon
3) ⩾2 prognostically-important COPD comorbidities

Intervention

1) Individualized care/ action plans
2) Telephone consults
   (12-weekly then 9-monthly)

Primary outcomes

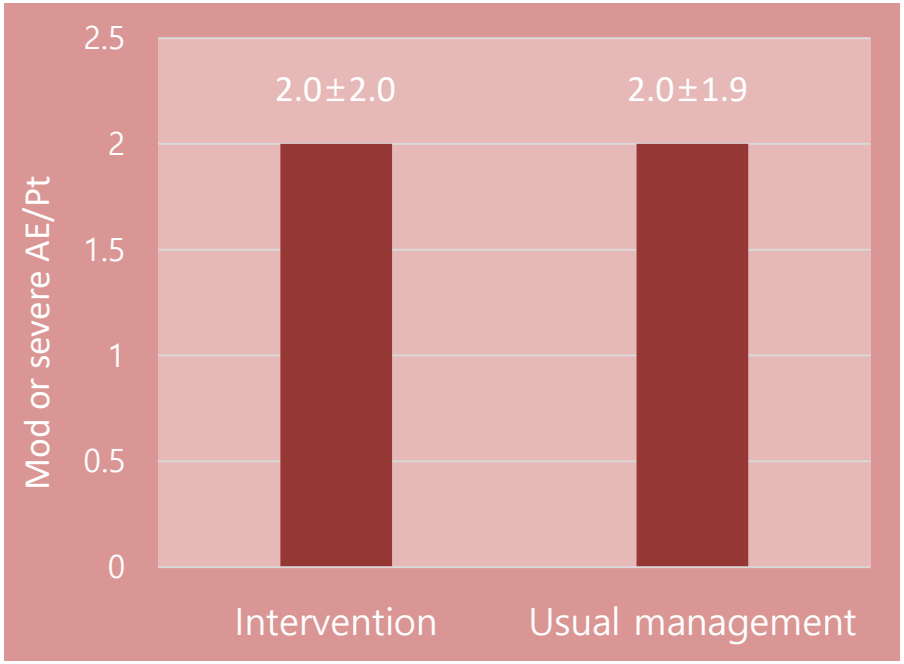
1) Emergency department visits

Secondary outcomes

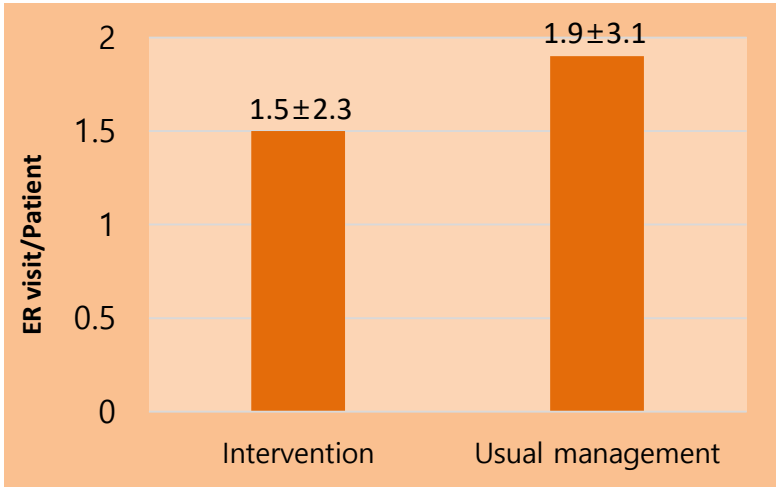
1) Hospitalisation, mortality
2) Health-related quality of life, chronic obstructive pulmonary disease (COPD) severity, COPD self-efficacy, anxiety and depression

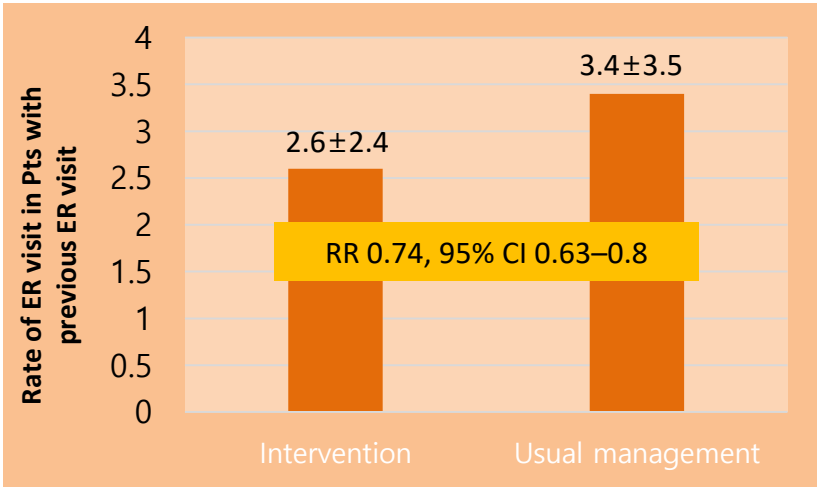
Kessler, Eur Respir J 2018; 51: 1701612
Rose, Eur Respir J 2018; 51: 1701567

COMET study



PIC COPD+ study





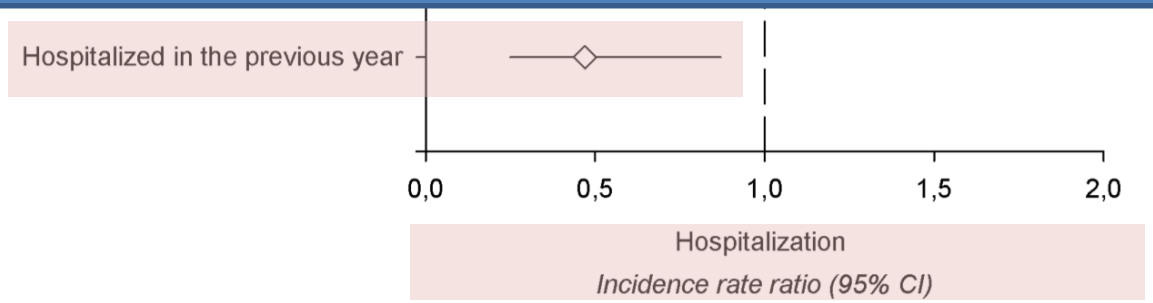
Kessler, Eur Respir J 2018; 51: 1701612
Rose, Eur Respir J 2018; 51: 1701567

Telemonitoring

(Monitoring of lung function by forced oscillation technique)

1) GOLD II-IV
2) ⩾1 ER visit or admission for AE in prev 12 mon
3) ⩾1 COPD comorbidity

Intervention might be useful to prevent severe AE for COPD patients with severe AE in prior yr



Walker, Am J Respir Crit Care Med. 2018;198:620-628

Summary (1)

- **Inhaler**
  - **LAMA** > LABA
  - **ICS/LABA** vs. LAMA as an initial Tx
    - ICS/LABA favors if **Eos ⩾ 4%** (300 cells/μL)
    - LAMA favors if Eos < 4% (300 cells/μL)
  - LAMA/LABA vs. TIO
    - OLO/TIO >= TIO (did not meet primary endpoint)

Summary (2)

- **Inhaler**
  - **Triple** vs. LAMA/LABA or ICS/LABA
    - **Triple** > LAMA/LABA → IMPACT, TRIBUTE
    - **Triple** > ICS/LABA → IMPACT, FUIFIL, TRILIGY

- **Triple → LAMA/LABA**
  - **Eos ⩾ 300 cells/μL → Triple** > LAMA/LABA
  - Eos < 300 cells/μL → No difference in the rate of AE

Summary (3)

- **Roflumilast**
  - Effective in **Group D patients receiving ICS**
- **Blood eosinophil**
  - Predicts **AE and ICS response** in COPD patients
- **Multicomponent ds-management program**
  - Maybe effective in patients with **previous severe AE** (previous hospitalization)

Asthma

Asthma AE

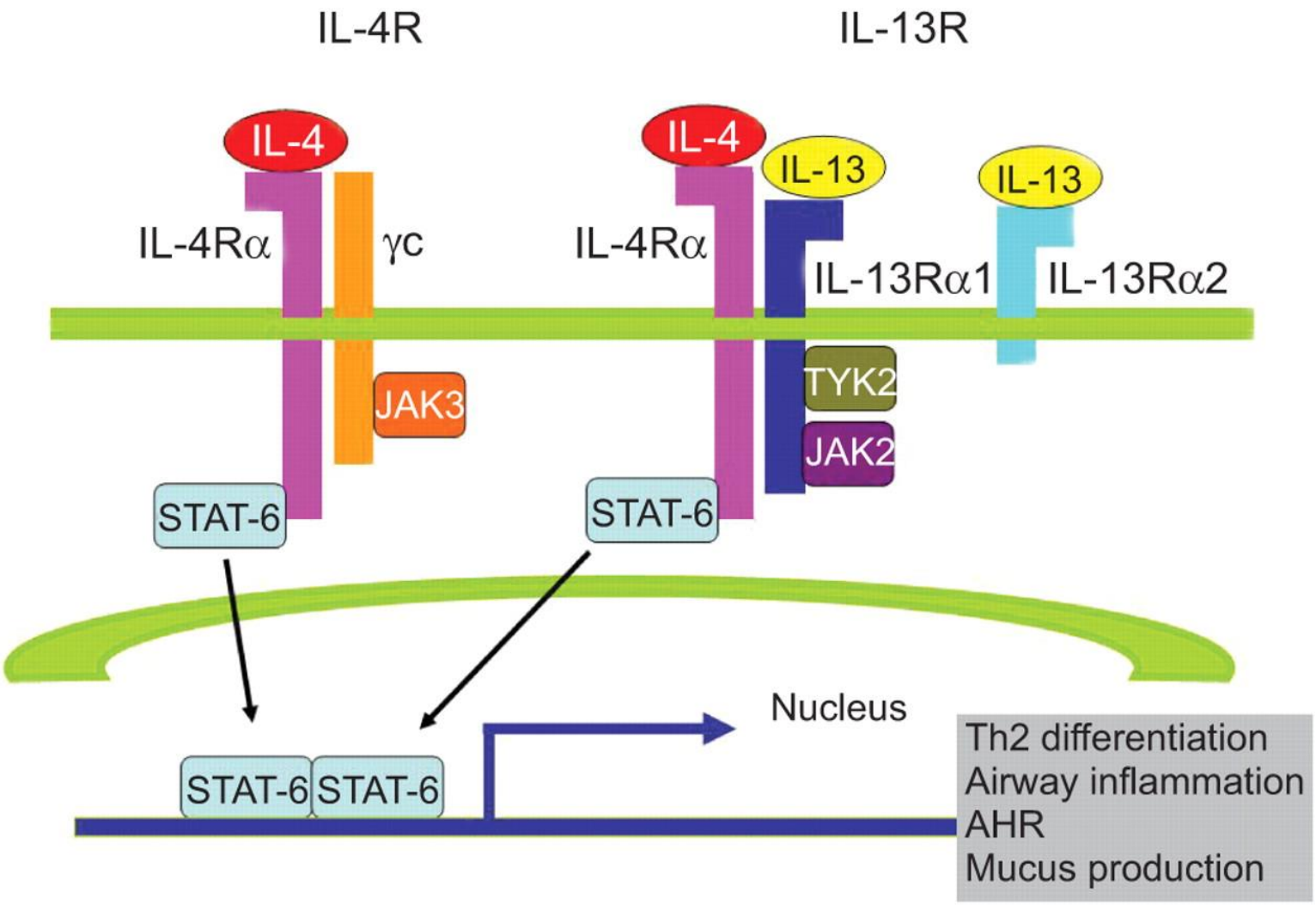
- Dupilumab
- As needed ICS/LABA in mild asthma
  - As needed SABA vs. as needed ICS/LABA vs. ICS maintenance
- Escalating ICS to prevent AE at the time of asthma control loss
- LAMA in uncontrolled persistent asthma
- Prolonged use of OCS
- Indoor allergen control

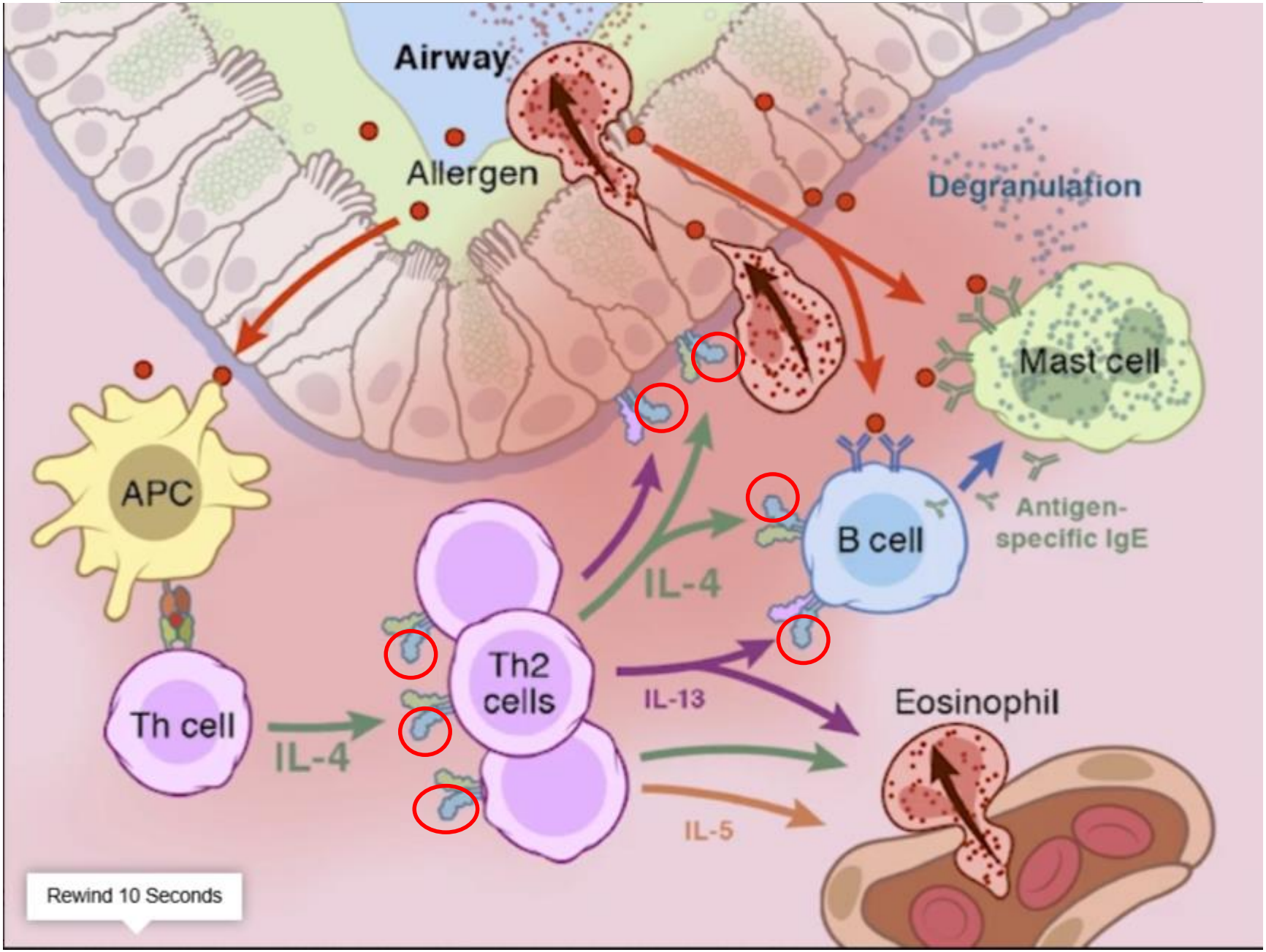
Asthma AE

- **Dupilumab**
- As needed Tx in mild asthma
  - As needed SABA vs. as needed ICS/LABA vs. ICS maintenance
- Escalating ICS to prevent AE
- LAMA in uncontrolled persistent asthma
- Prolonged use of corticosteroid
- Indoor allergen control

Dupilumab

- **A fully human anti–IL-4 receptor α monoclonal antibody**
  - Blocks IL-4 and IL-13 signaling

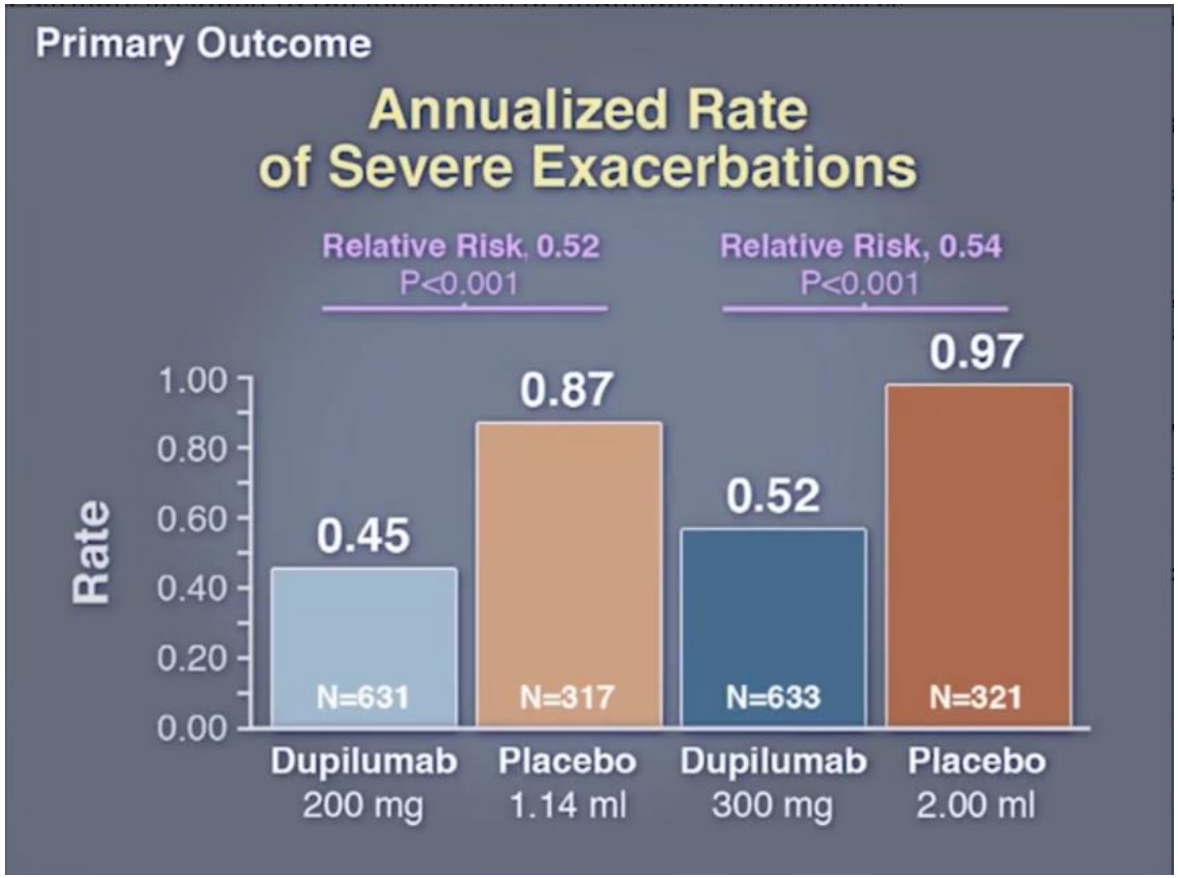

IL-4R
IL-13R
IL-4
IL-4Rα
γc
JAK3
STAT-6
IL-4
IL-13
IL-13
IL-4Rα
IL-13Rα1
IL-13Rα2
TYK2
JAK2
STAT-6
Nucleus
STAT-6
STAT-6
Th2 differentiation
Airway inflammation
AHR
Mucus production



https://www.nejm.org/doi/full/10.1056/NEJMoa1804092

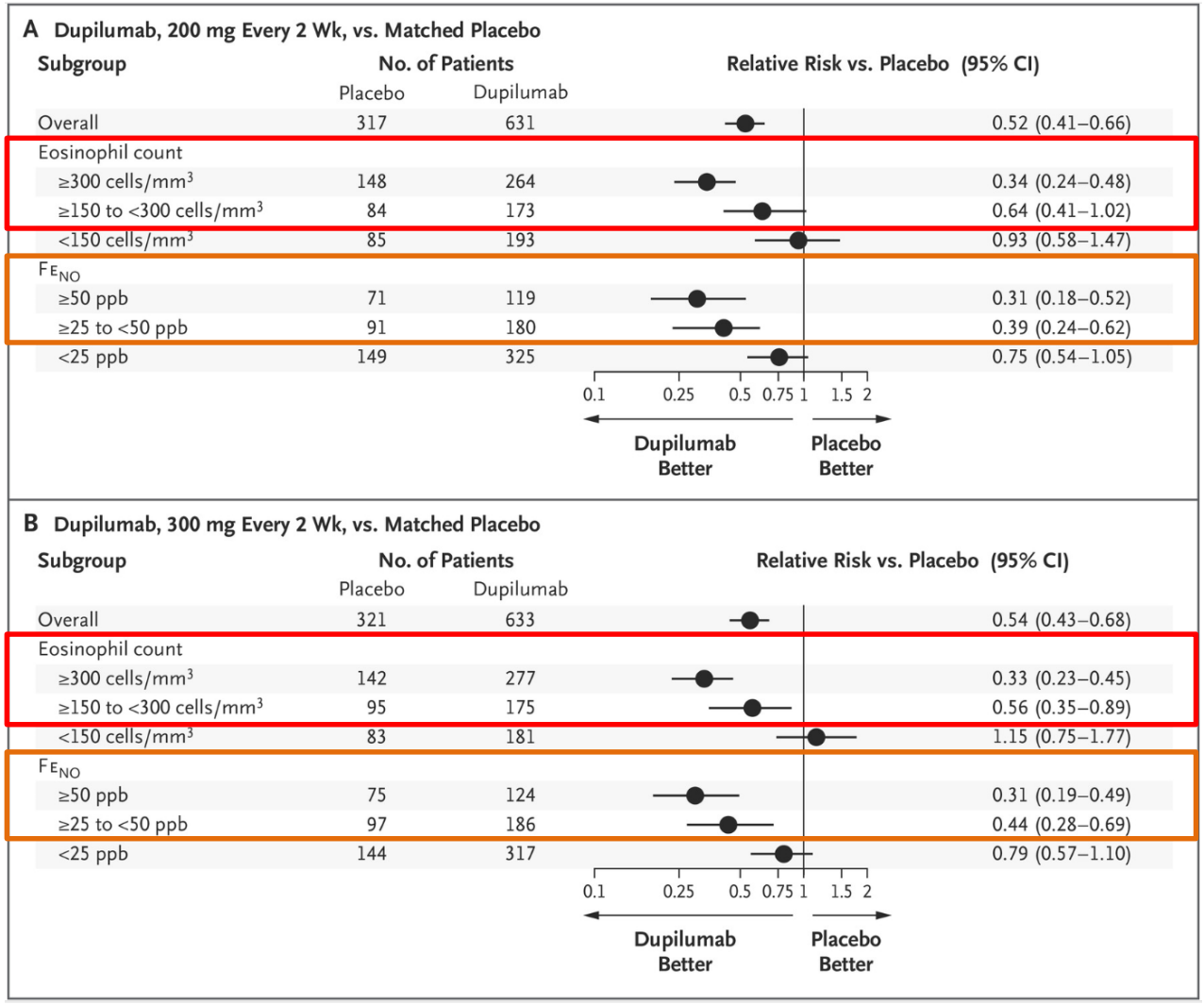
Dupilumab vs. placebo

1 . Refractory to maximized standard-of-care controller therapy
2. 1,902 patients with moderate-to-severe asthma



Rabe, N Engl J Med 2018;378:2475-85

Severe AE by Eos/FE_{NO}

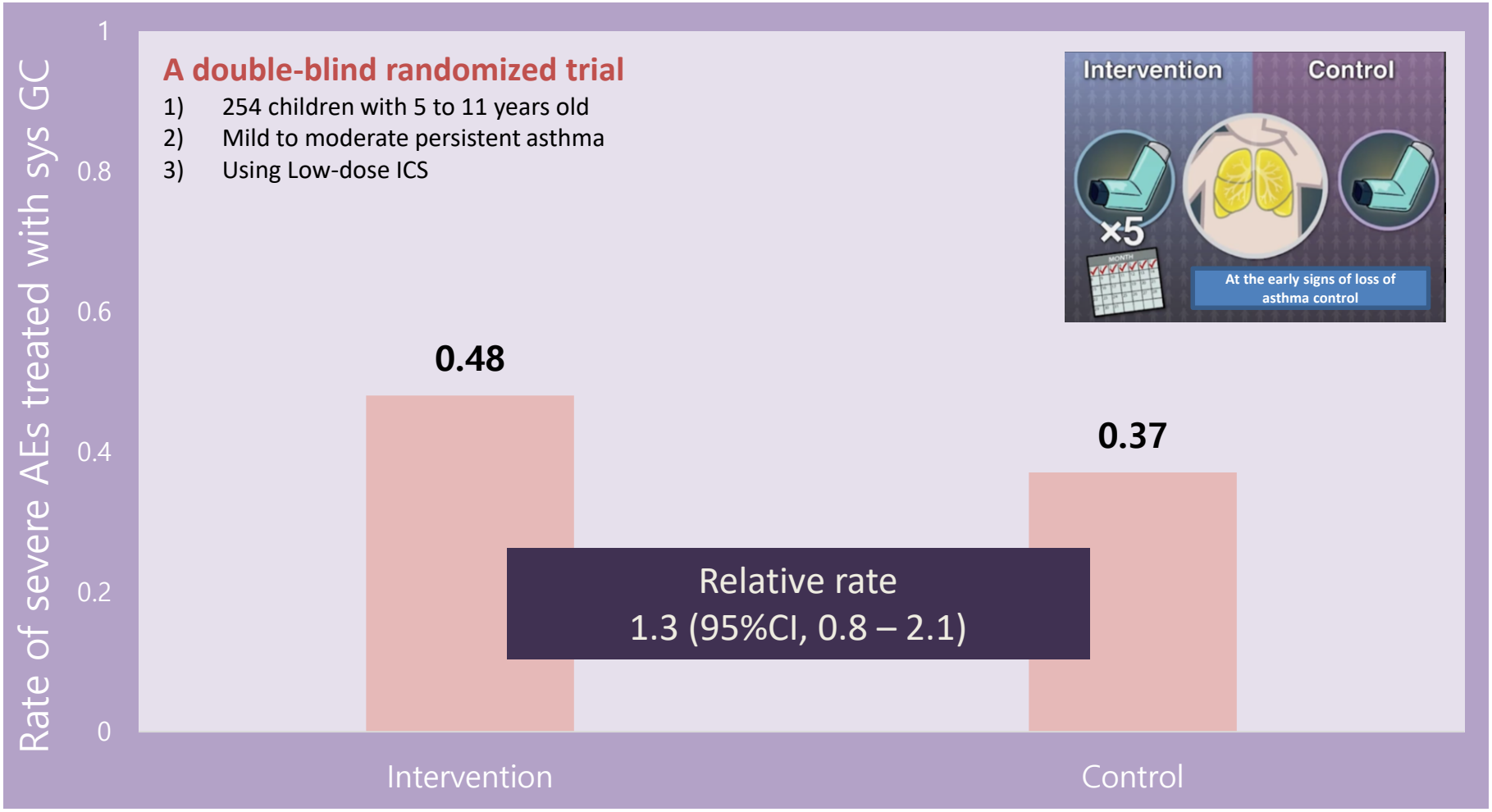


Rabe, N Engl J Med 2018;378:2475-85.

Asthma AE

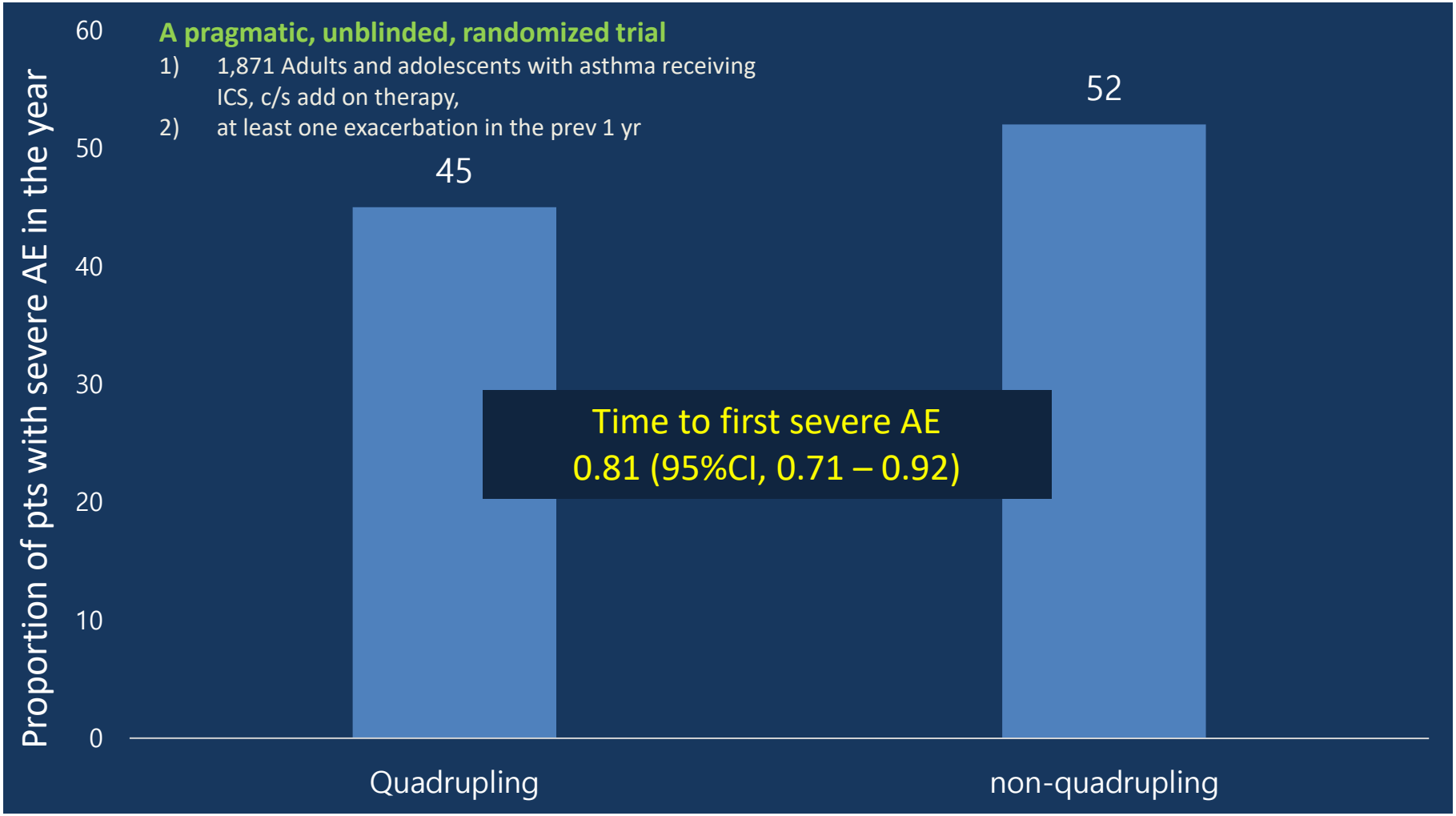
- Dupilumab
- **Escalating ICS to prevent AE** **at the time of loss of asthma control**
  - **Adolescent and adults**
  - **Children**
- As needed Tx in mild asthma
  - SABA vs. ICS/LABA vs. ICS maintenance
- LAMA use in uncontrolled persistent asthma
- Prolonged use of corticosteroid
- Indoor allergen control

Quintupling ICS to Prevent Childhood Asthma Exacerbations



Jackson, N Engl J Med 2018; 378:891-901

Quadrupling ICS Dose to Abort Asthma AE in adolescents and adults

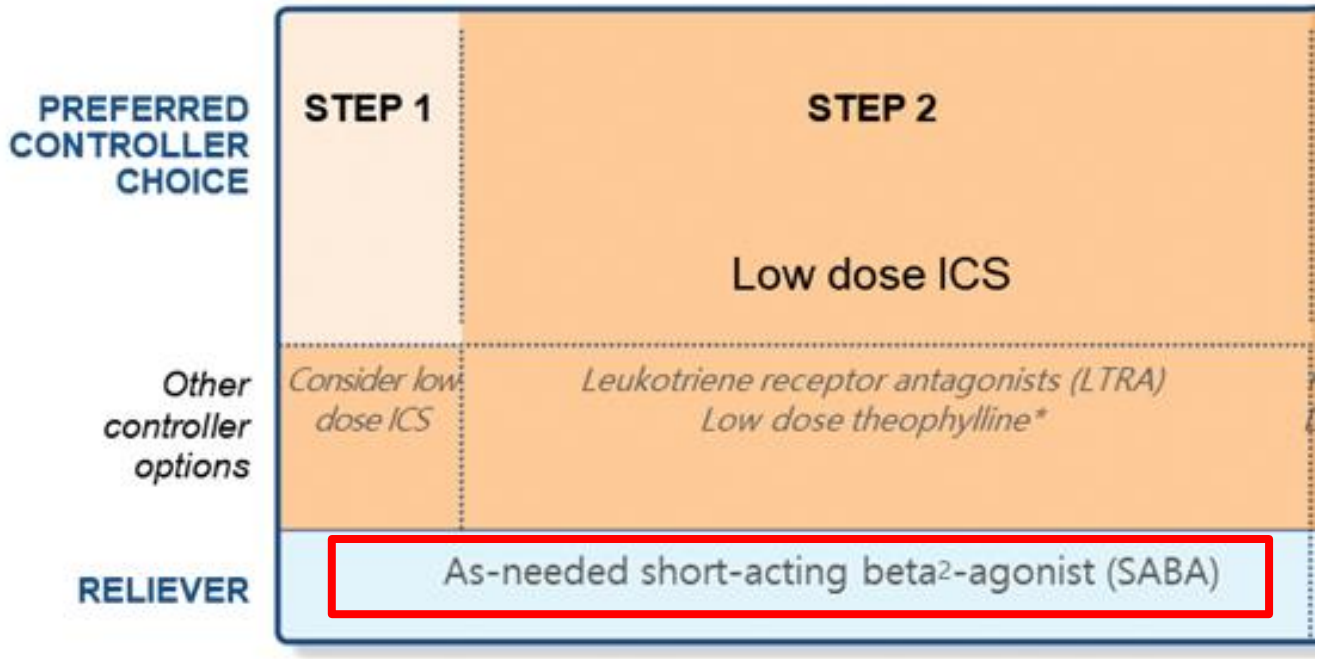


McKeever, N Engl J Med 2018;378:902-10

Asthma AE

- Dupilumab
- Escalating ICS to prevent AE
- **As needed ICS/LABA in mild asthma**
  - **As needed SABA vs. as needed ICS/LABA vs. ICS maintenance**
- LAMA use in uncontrolled persistent asthma
- Prolonged use of corticosteroid
- Indoor allergen control

Recommended Treatment in Mild asthma



The Global Initiative for Asthma 2018, www.ginasthma.org

동상이몽

(As needed ICS/LABA ?)

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma [SYGMA 1]

1. 12 years of age or older
2. Needing GINA step 2 treatment
   (regular, low-dose inhaled glucocorticoid)

52 weeks (n=3836)

As-needed SABA

Placebo + Terbualine as needed
(n=1,277)

As-needed ICS/LABA

Placebo + **BUD/F as needed**
(n=1277)

ICS maintenance

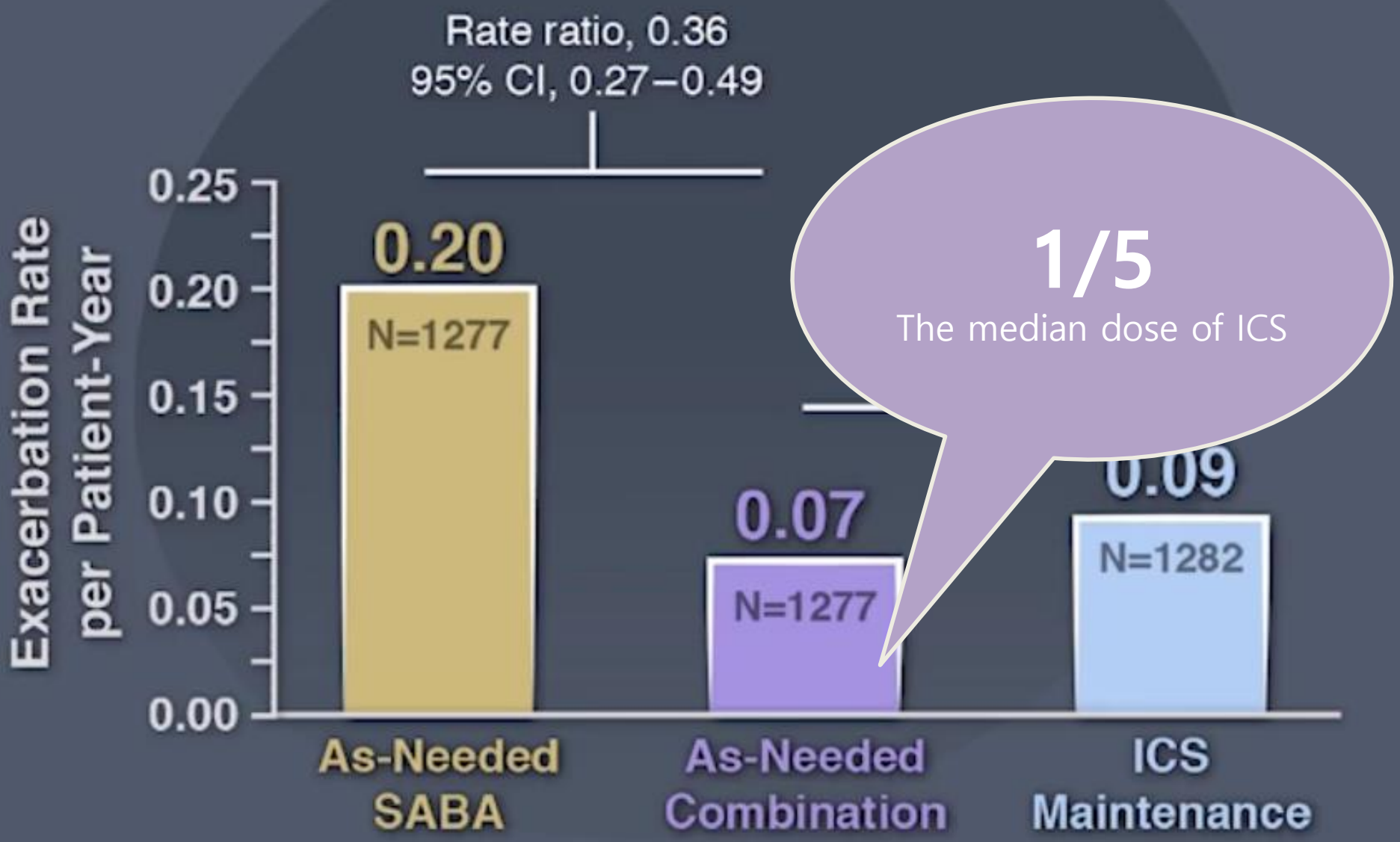
BUD + Turbutaline as needed
(n=1282)

Well-controlled Asthma Weeks

Severe AE

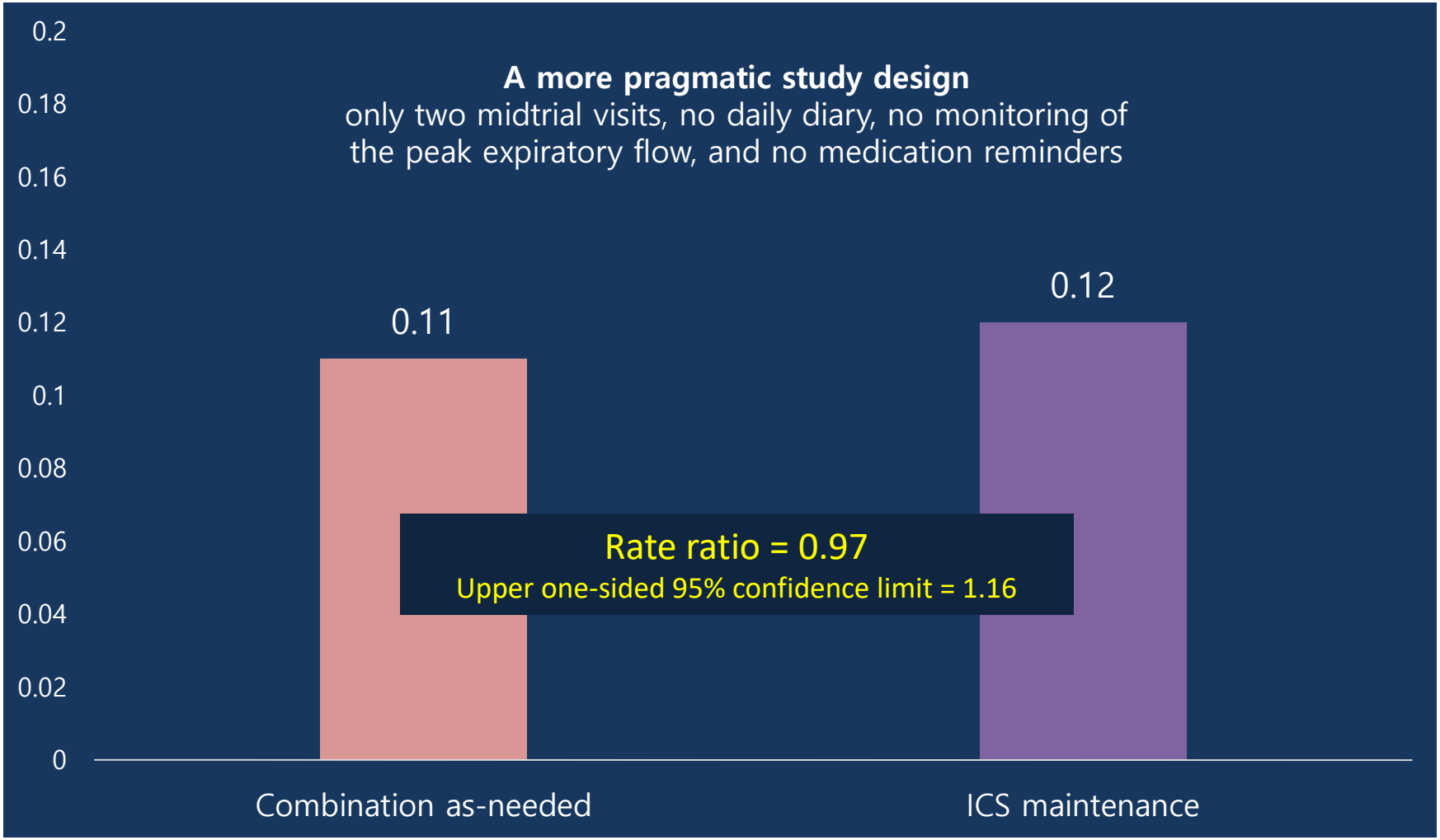
O'Byrne, N Eng J med 2018;378:1865-76

Rate of Severe Exacerbation



O'Byrne, N Eng J med 2018;378:1865-76

As-Needed Budesonide–Formoterol vs. Maintenance Budesonide in Mild Asthma [SYGMA II study]

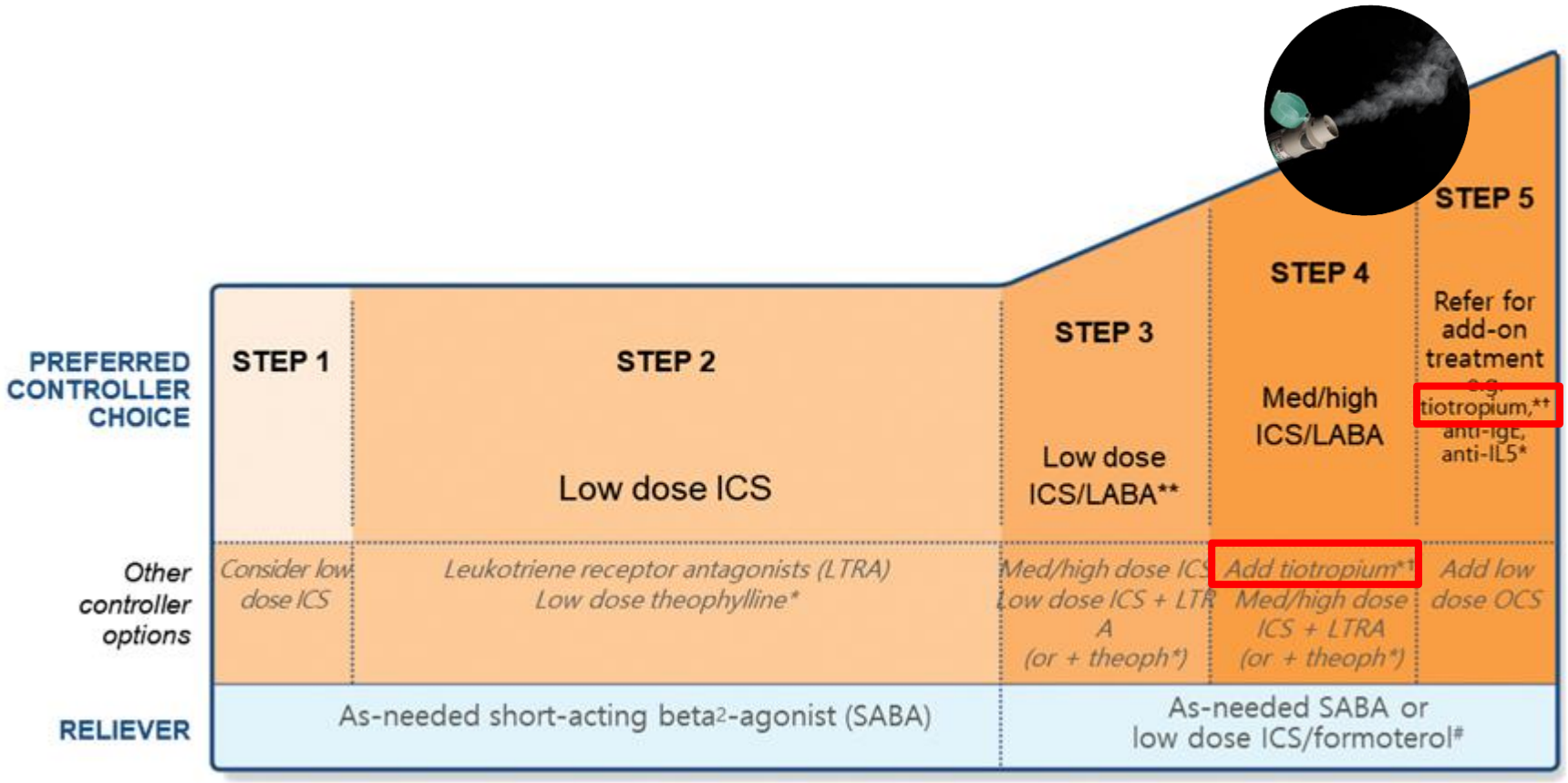


Bateman, N Eng J med 2018;378:1877-87

Asthma AE

- Dupilumab
- Escalating ICS to prevent AE
  - Adolescent and adults
  - Children
- As needed ICS/LABA in mild asthma
  - SABA vs. ICS/LABA vs. ICS maintenance
- **LAMA use in uncontrolled persistent asthma**
- Prolonged use of corticosteroid
- Indoor allergen control

LAMA in the treatment of asthma



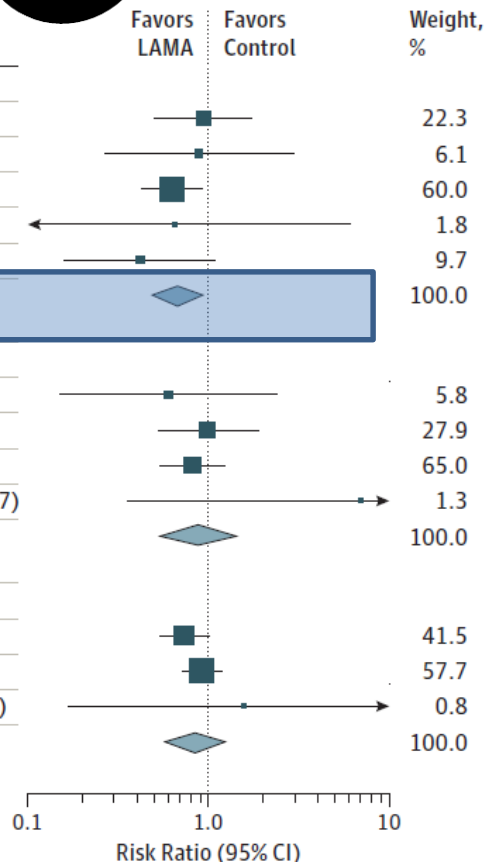
The Global Initiative for Asthma 2018, www.ginasthma.org

ICS + LAMA vs. ICS +placebo

1. **Meta-analysis of 15 randomized clinical trials**
2. **7122 participants 12 years or older**
3. **Uncontrolled, persistent asthma**

Exacerbations requiring systemic corticosteroid

Source	LAMA Add-on Therapy: No. With Events	LAMA Add-on Therapy: Total No. of Participants	Control: No. With Events	Control: Total No. of Participants	Absolute Risk Difference, % (95% CI)	Risk Ratio (95% CI)	Weight, %
ICS + LAMA vs ICS + placebo (control)							
Bateman et al,[17] 2011	16	128	17	126	-1.0 (-9.3 to 7.3)	0.93 (0.49 to 1.75)	22.3
Paggiaro et al,[21] 2016	7	309	4	155	-0.3 (-3.3 to 2.7)	0.88 (0.26 to 2.95)	6.1
Kerstjens Trial 1 and 2,[18] 2015	53	1036	43	523	-3.1 (-5.8 to -0.4)	0.62 (0.42 to 0.92)	60.0
Lee et al,[19] 2015	3	298	1	64	-0.6 (-3.8 to 2.7)	0.64 (0.07 to 6.09)	1.8
Hamelmann et al,[22] 2016	7	259	9	138	-3.8 (-8.4 to 0.7)	0.41 (0.16 to 1.09)	9.7
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.69$	86	2030	74	1006	-1.7 (-3.7 to 0.3)	0.67 (0.48 to 0.92)	100.0
ICS + LAMA vs ICS + LABA (control)							
Peters et al,[29] 2010	3	71	5	71	-2.8 (-10.4 to 4.8)	0.60 (0.15 to 2.42)	5.8
Bateman et al,[17] 2011	16	128	17	134	-0.2 (-8.2 to 7.8)	0.99 (0.52 to 1.87)	27.9
Kerstjens Trial 1 and 2,[18] 2015	53	1036	341	541	-1.2 (-3.6 to 1.3)	0.81 (0.54 to 1.24)	65.0
Lee et al,[19] 2015	3	298	0	295	1.0 (-0.3 to 2.3)	6.93 (0.36 to 133.57)	1.3
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.49$	75	1533	56	1041	0.1 (-2.1 to 2.3)	0.87 (0.53 to 1.42)	100.0
ICS and LABA + LAMA vs ICS and LABA (control)							
Kerstjens Trial 1,[26] 2012	53	237	68	222	-8.3 (-16.3 to -0.2)	0.73 (0.54 to 0.99)	41.5
Kerstjens Trial 2,[26] 2012	69	216	81	232	-3.0 (-11.7 to 5.8)	0.91 (0.70 to 1.19)	57.7
Hamelmann et al,[28] 2017	3	257	1	135	0.4 (-1.5 to 2.4)	1.58 (0.17 to 15.00)	0.8
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.47$	125	710	150	589	-0.5 (-8.1 to 7.0)	0.84 (0.57 to 1.22)	100.0



Sobieraj, JAMA. 2018;319(14):1473-1484

Asthma AE

- Dupilumab
- Escalating ICS to prevent AE
  - Adolescent and adults
  - Children
- As needed Tx in mild asthma
  - SABA vs. ICS/LABA vs. ICS maintenance
- LAMA use in uncontrolled persistent asthma
- **Prolonged use of oral corticosteroid (OCS)**
- Indoor allergen control

OCS exposure and AE in asthmatic patients

1. A retrospective cohort study of asthmatic patients 18 years and older in the 2000-2014 MarketScan claim data set
2. Propensity score matching was used at baseline
   - 72,063 OCS cohort vs. matching cohort

TABLE III. Regression results: Odds ratios of incident (new) AEs (combined end point)

	OR	SE	*P* value	95% CI
Current OCS, 1-3 prescriptions	1.04	0.01	.01	1.01-1.06
Current OCS, ≥4 prescriptions	1.29	0.04	<.01	1.20-1.37
No. of prior years with 1-3 prescriptions	1.10	0.01	<.01	1.08-1.13
No. of prior years with ≥4 prescriptions	1.11	0.03	<.01	1.05-1.17
No. of years with 1-3 OCS prescriptions	1.07	0.01	<.01	1.05-1.08
No. of years with 4 or more OCS prescriptions	1.20	0.02	<.01	1.15-1.24

Logistic regression controlling for age, sex, geographic region, years since the index date, insurance type, use of immunosuppressive medication (yes/no; not OCS) and general comorbidity burden (NCC).

Current, Year in which the AE occurred; *OR*, odds ratio; *prior*, year or years before the year in which the AE occurred.

Sullivan, J Allergy Clin Immunol 2018;141:110-6

Asthma AE

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- LAMA use in uncontrolled persistent asthma
- Prolonged use of corticosteroid
- **Indoor allergen control**

Creation of an environmentally safe sleeping zone

Allergen-impermeable covers on the mattress, box spring, and pillows

HEPA air purifier

Professional pest control

children sensitized and

to cockroach

HEPA filter cleaner

Intervention

N Engl J Med 2004; 351:1068-1080

Indoor allergen reduction

TABLE III. Allergen-reduction interventions: Summary results and SOE*

Intervention (no. of studies)	Asthma control	Exacerbations	Health care use	Absenteeism	Pulmonary physiology	Quality of life	Symptoms	Allergen reduction
Acaricide only (n = 7)[12-18]	No studies	No studies	No studies	No studies	No effect (moderate)	Inconclusive	Inconclusive	Inconclusive
Acaricide multicomponent (n = 6)[51,65,67-70]	No studies	Inconclusive	Inconclusive	No studies	No effect (moderate)	No studies	No effect (high)	Improved (low)
Air purification only (n = 9)[19-27]	Inconclusive	No effect (low)	No effect (low)	No studies	No effect (low)	Improved (low)	Inconclusive	No effect (low)
Air purification multicomponent (n = 5)[49,50,59,61,78]	No effect (low)	No effect (high)	No studies	Improved (low)	Inconclusive	No effect (high)	Improved (low)	Improved (moderate)
Carpet removal only (n = 0)	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Carpet removal multicomponent (n = 8)[51,52,54,58,68,71,72,77]	No studies	Inconclusive	Inconclusive	No studies	Inconclusive	Inconclusive	Inconclusive	Improved (moderate)
HEPA vacuum only (n = 1)[28]	No studies	No studies	No studies	No studies	Inconclusive	No studies	No studies	Inconclusive
HEPA vacuum multicomponent (n = 8)[50,53,55,60,61,64,75,76]	Inconclusive	Improved (moderate)	No effect (high)	Improved (low)	Inconclusive	Improved (moderate)	Improved (low)	Improved (moderate)
Mattress cover only (n = 17)[29-45]	No effect (moderate)	No effect (moderate)	No effect (high)	Improved (low)	No effect (high)	No effect (high)	No effect (high)	Improved (moderate)
Mattress cover multicomponent (n = 19)[49-52,54,55,58,59,61,62,65-71,74,76]	Inconclusive	No effect (high)	Inconclusive	Improved (low)	No effect (high)	No effect (moderate)	Improved (high)	Improved (low)
Mold removal only (n = 0)	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Mold removal multicomponent (n = 6)[56-58,76-78]	No studies	Inconclusive	Inconclusive	No studies	Inconclusive	Inconclusive	Improved (low)	Inconclusive
Pest control only (n = 2)[46,47]	Inconclusive	Inconclusive	No studies	Inconclusive	Inconclusive	No studies	Improved (low)	Inconclusive
Pest control multicomponent (n = 13)[49,52,54,55,58-62,66,74-76]	Inconclusive	Improved (moderate)	Inconclusive	Improved (low)	Inconclusive	Improved (low)	Improved (low)	Improved (low)
Pet removal only (n = 1)[48]	No studies	Inconclusive	Inconclusive	No studies	No studies	No studies	No studies	No studies
Pet removal multicomponent (n = 2)[51,58]	No studies	No studies	No studies	No studies	No studies	No studies	No studies	No studies

Leas, J Allergy Clin Immunol. 2018;14:1854-1869

Summary (1)

- **Dupliumab vs. placebo to prevent AE**
  - Associated with lower severe AE
    - Greater benefits with higher eosinophils
- **Escalating ICS to prevent AE at the time of loss of asthma control**
  - No evidence in children
  - Reduced AE in adolescent and adults with some limitation in study design

Summary (2)

- **As needed ICS/LABA in mild asthma to prevent AE**
  - As needed SABA < **As needed ICS/LABA** = ICS maintenance + SASA
- **Prolonged use of OCS**
  - OCS dependent asthma is associated with AE
- **Indoor allergen control**
  - Multicomponent intervention is needed

Thank you for your attention