In What Patients Should I Use Fixed LABA-LAMA Combination in COPD ?

동아대학교 호흡기 내과
엄수정

Contents

1. LABA/LAMA FDC
2. Lessons from Guidelines
3. Lessons from Clinical trials
4. Safety Issues
5. What about ICS?
6. Summary

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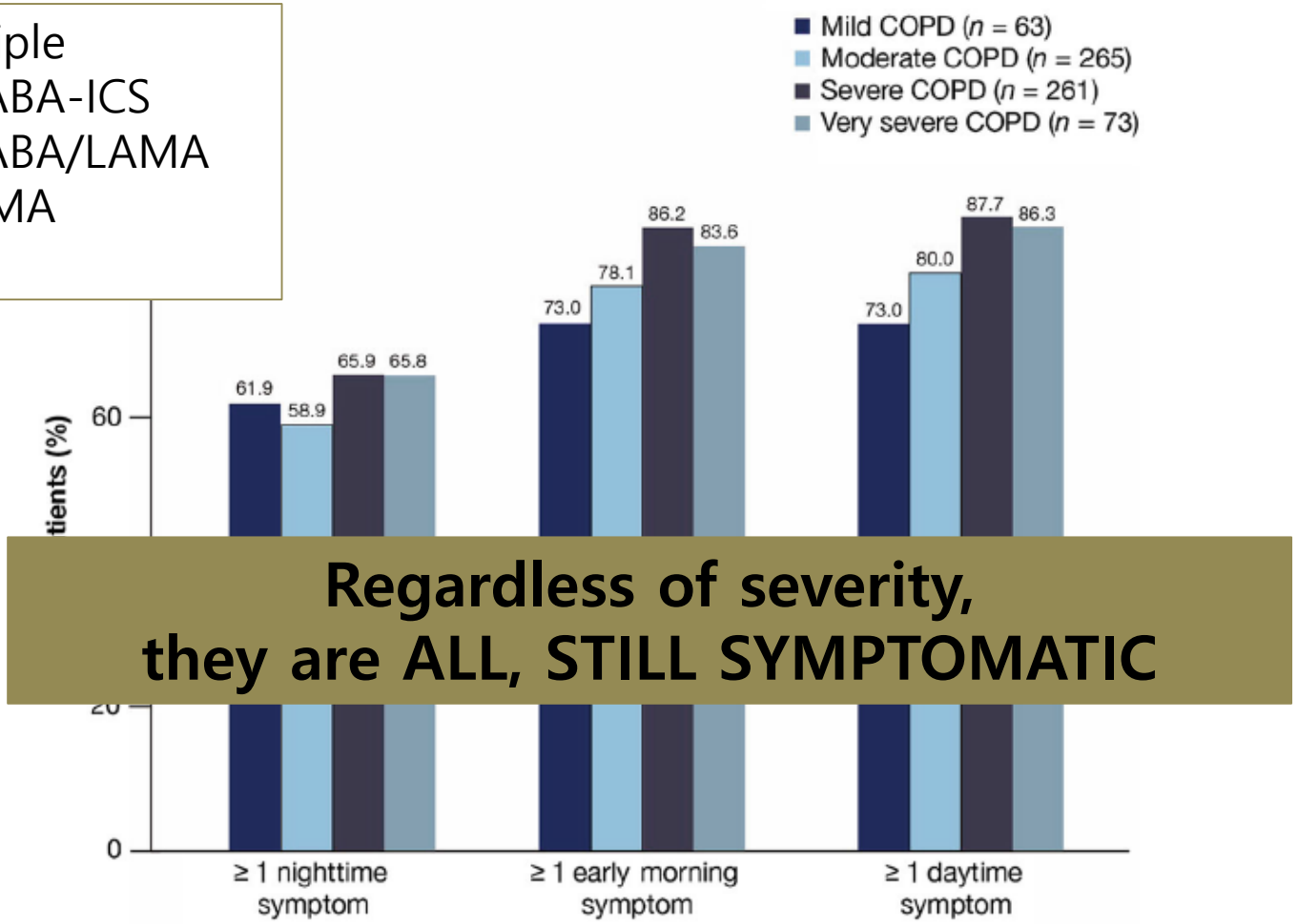
Prevalence of symptoms

50% on Triple
13% on LABA-ICS
10% on LABA/LAMA
7% on LAMA
.....



Regardless of severity,
they are ALL, STILL SYMPTOMATIC

Miravitlles M, et al. Respir Res. 2014;15:122.

Impact of Dyspnea on COPD

COPD disease process including air trapping leads to **dyspnea with activities**

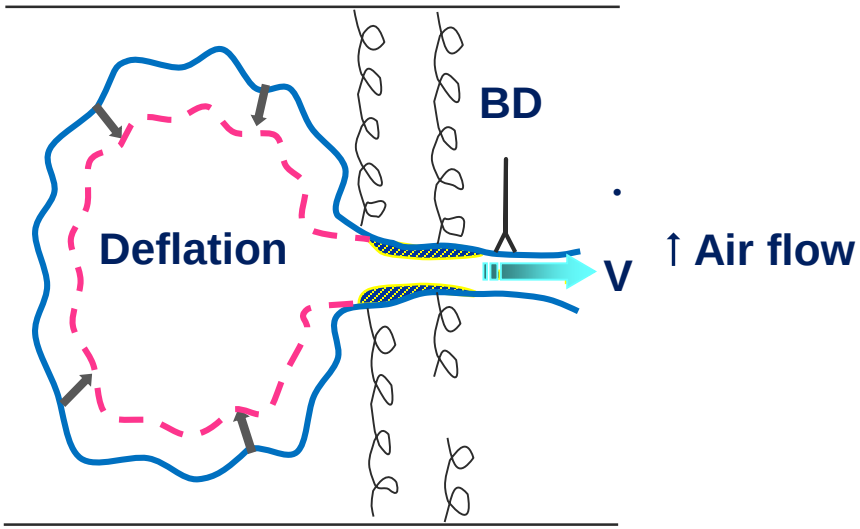
Becomes more sedentary to avoid dyspnea-producing activity **(decreases activity)**

Deconditioning aggravates dyspnea; patients adjust by reducing activity further

Adapted from Reardon, et al. Am J Med 2006

ZuWallack. COPD 2007

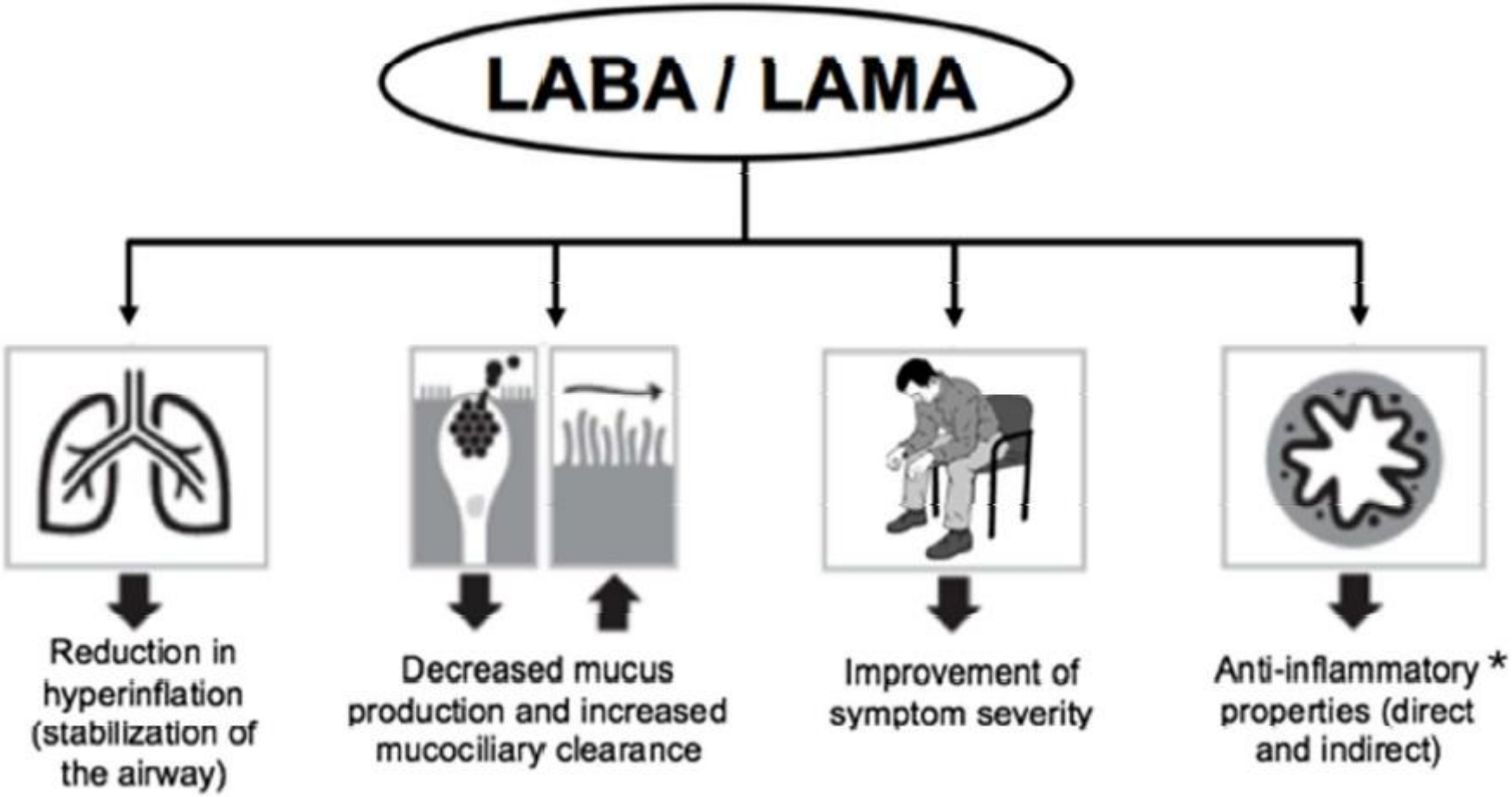
Bronchodilator therapy deflates the lung



→ Improvement in flow – FEV_1

→ Improvement in volumes – FVC and IC

BD = bronchodilator; V = ventilation; FEV_1= forced expiratory volume in 1 second;
FVC= forced vital capacity; IC = inspiratory capacity



Beeh KM, et al. Am J Respir Crit Care Med. 2016 Dec 6. [Epub ahead of print].

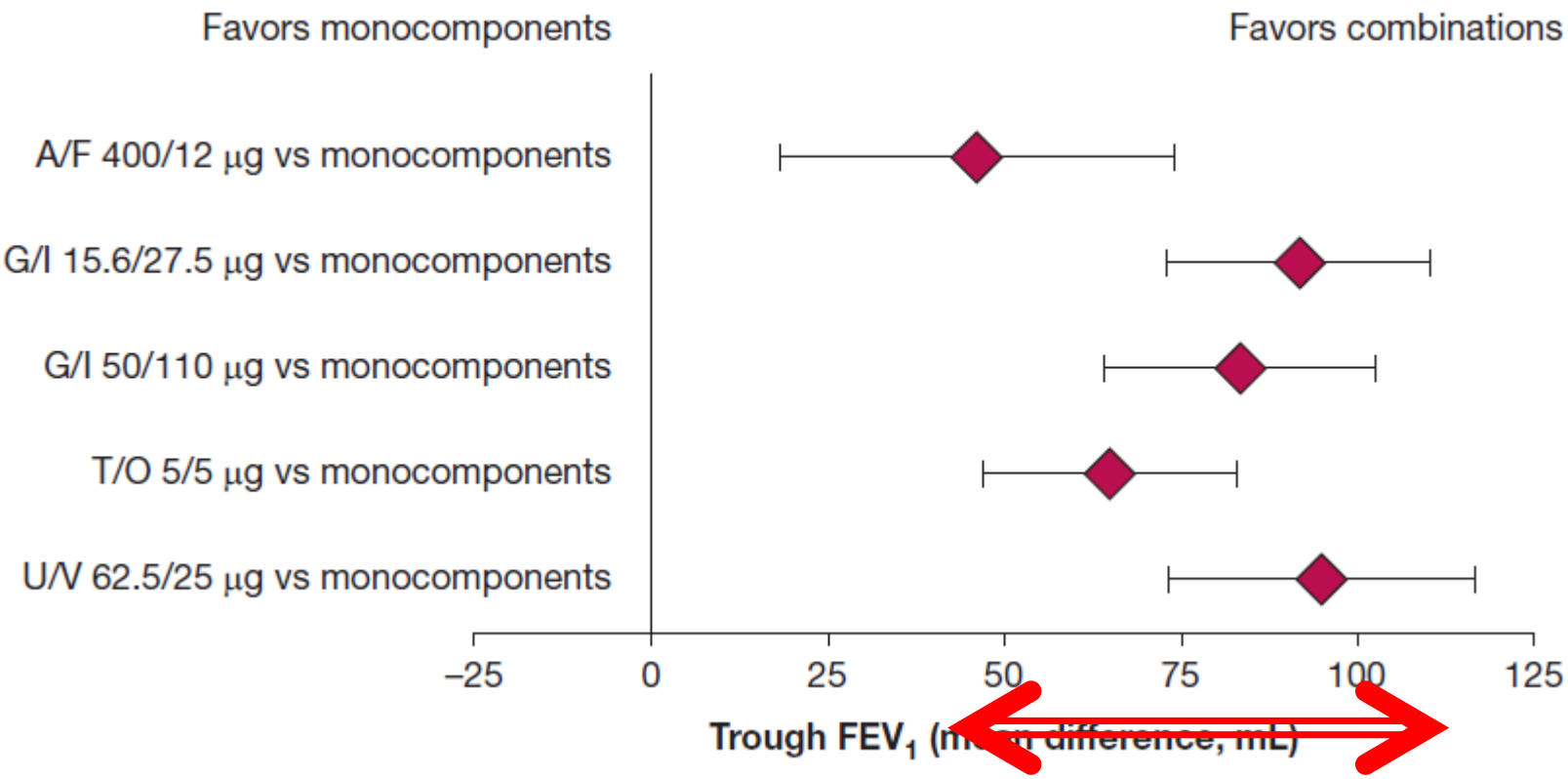
Potential Benefit of LABA/LAMA

- Maximize Bronchodilation
- Synergistic Effect
- Simplify treatment regimen

LABA/LAMA FDCs

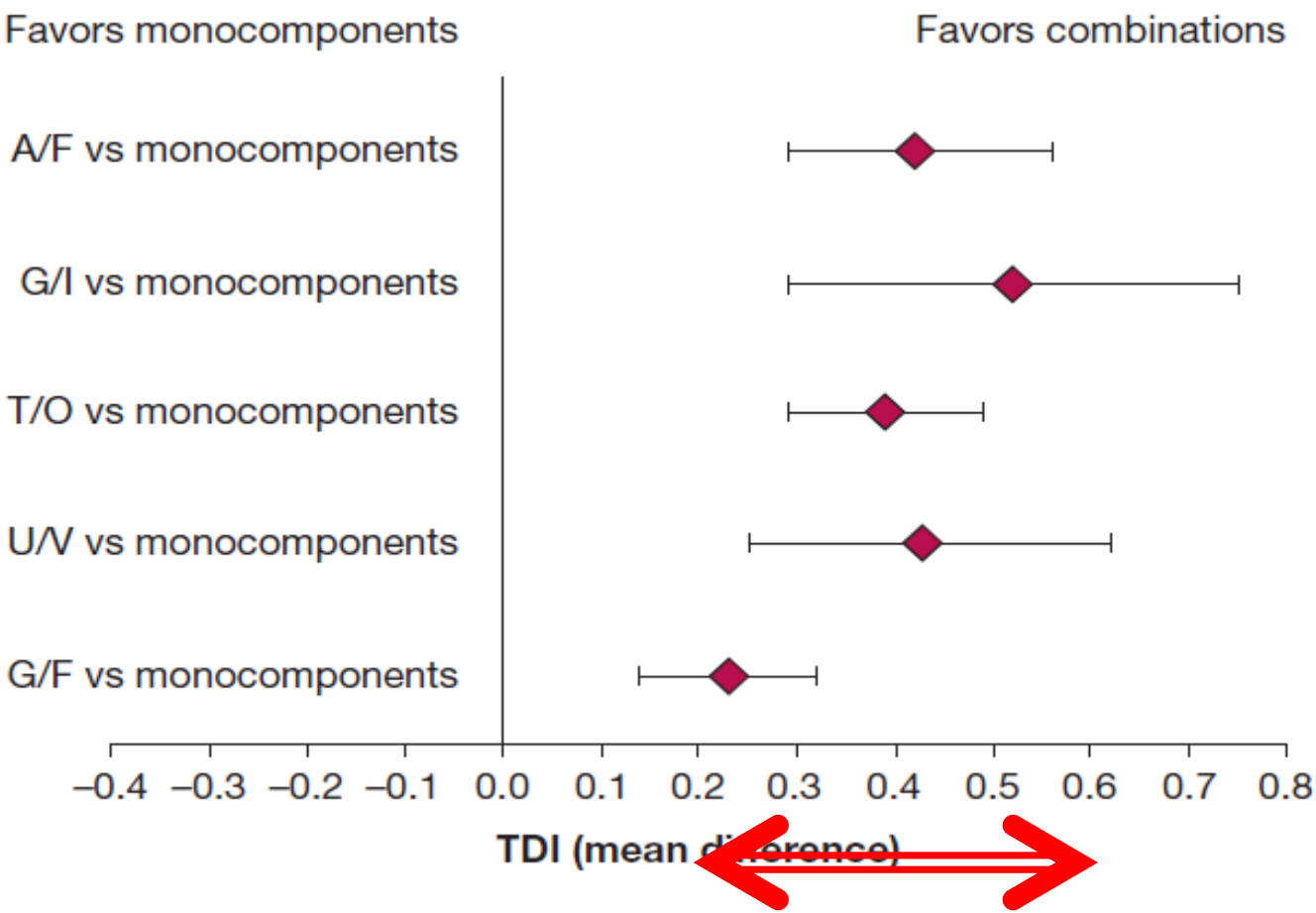
Drug	Approved dose		Trade name /Device
Umeclidinium/Vilanterol	62.5/25 μg QD	DPI	Anoro/ Ellipta
Glycopyrronium/Indacaterol	50/110 μg QD 15.6/27.5 μg BID	DPI	Ultibro (Xoterna) /Breezhaler
Aclidinium/Formoterol	400/12 μg BID	DPI	Brimica (Duaklir) /Genuair
Tiotropium/Olodaterol	2.5/2.5 μg 2puff QD	SMI	Stiolto (Vahelva) /Respimat
Glycopyrronium/Formoterol	18/9.8 μg BID	MDI	

Impact on Trough FEV_1



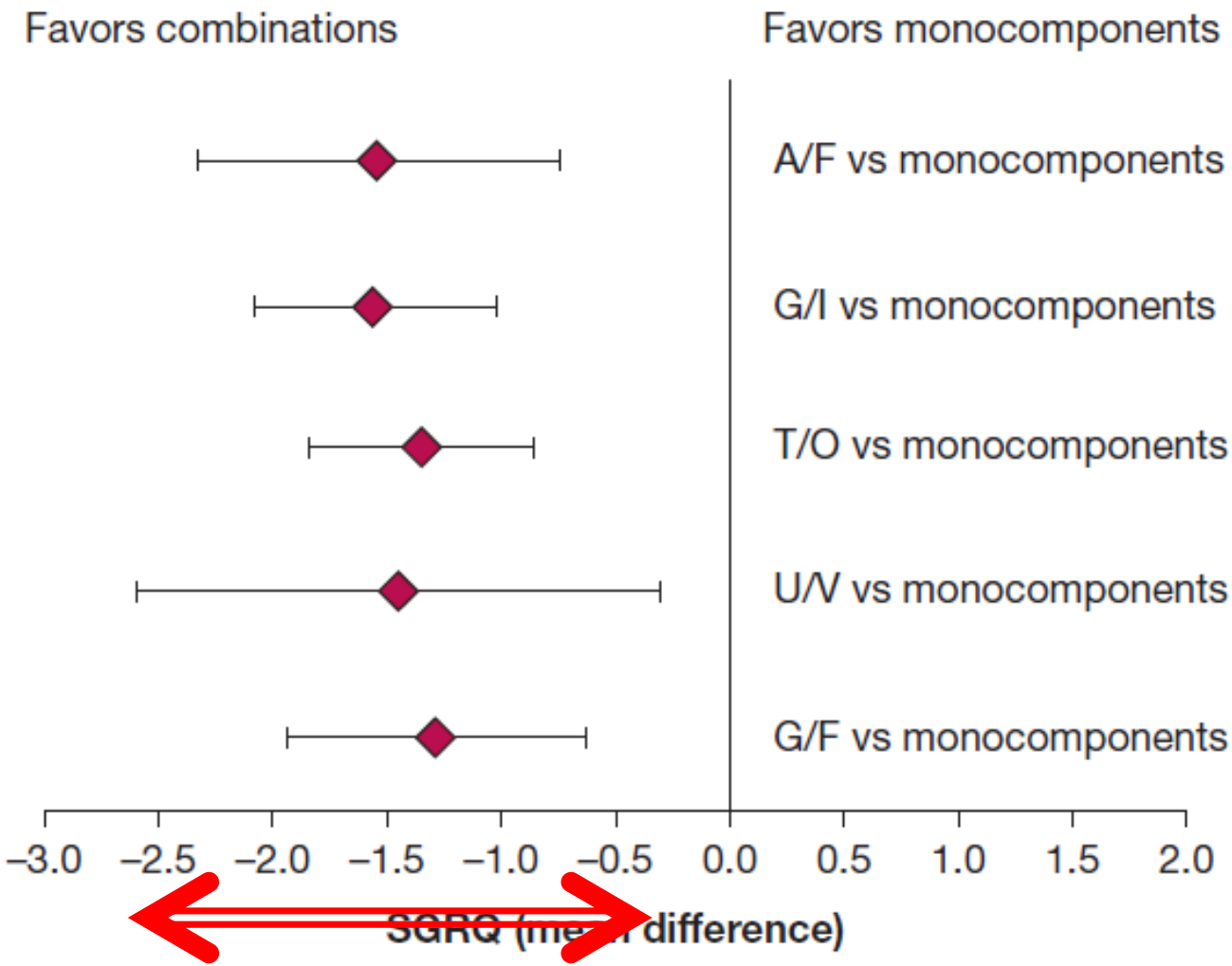
Calzetta L, et al. Chest. 2016 May;149(5):1181-96

Impact on Dyspnea(TDI)



Calzetta L, et al. Chest. 2016 May;149(5):1181-96

Impact on SGRQ



Calzetta L, et al. Chest. 2016 May;149(5):1181-96

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Initial Pharmacologic Management GOLD 2016

Patient Group	First Choice	Alternative Choice	Other possible
A	SAMA or SABA prn	LAMA LABA SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS+LABA or LAMA	LAMA and LABA LAMA and PDE4 (-) LABA and PDE4 (-)	SAMA and/or SABA Theophylline
D	ICS+LABA and/or LAMA	ICS+LABA and LAMA ICS+LABA and PDE4 (-) LAMA and LABA LAMA and PDE4 (-)	Carbocysteine N-acetylcysteine SAMA and/or SABA Theophylline

Initial Pharmacologic Management GOLD 2016

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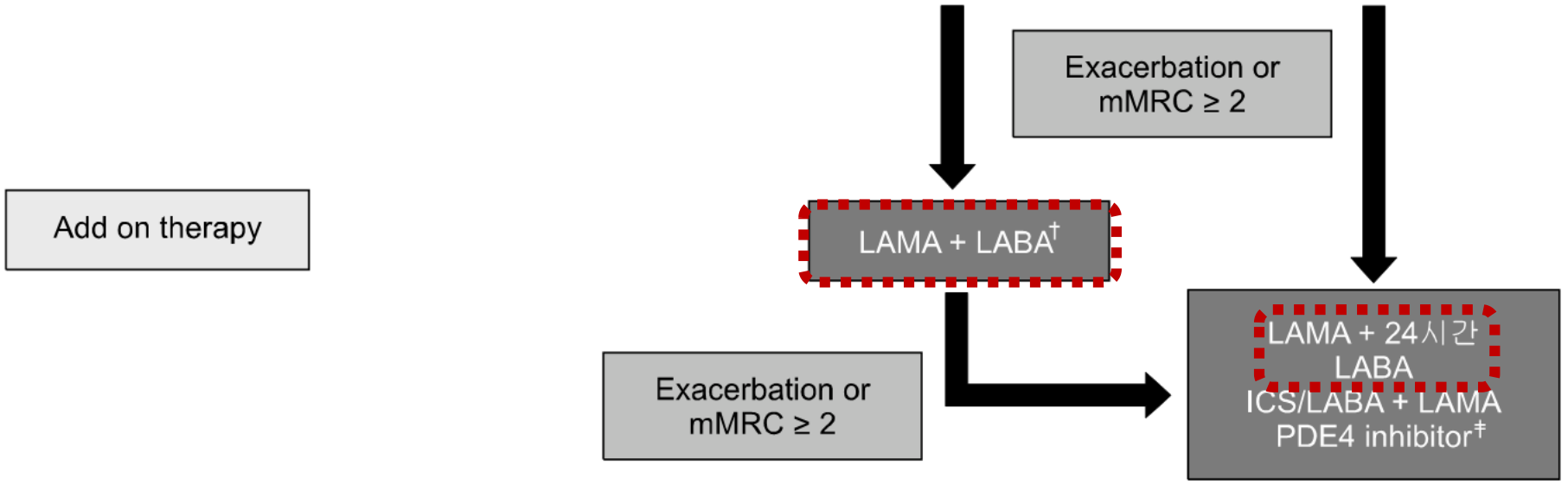
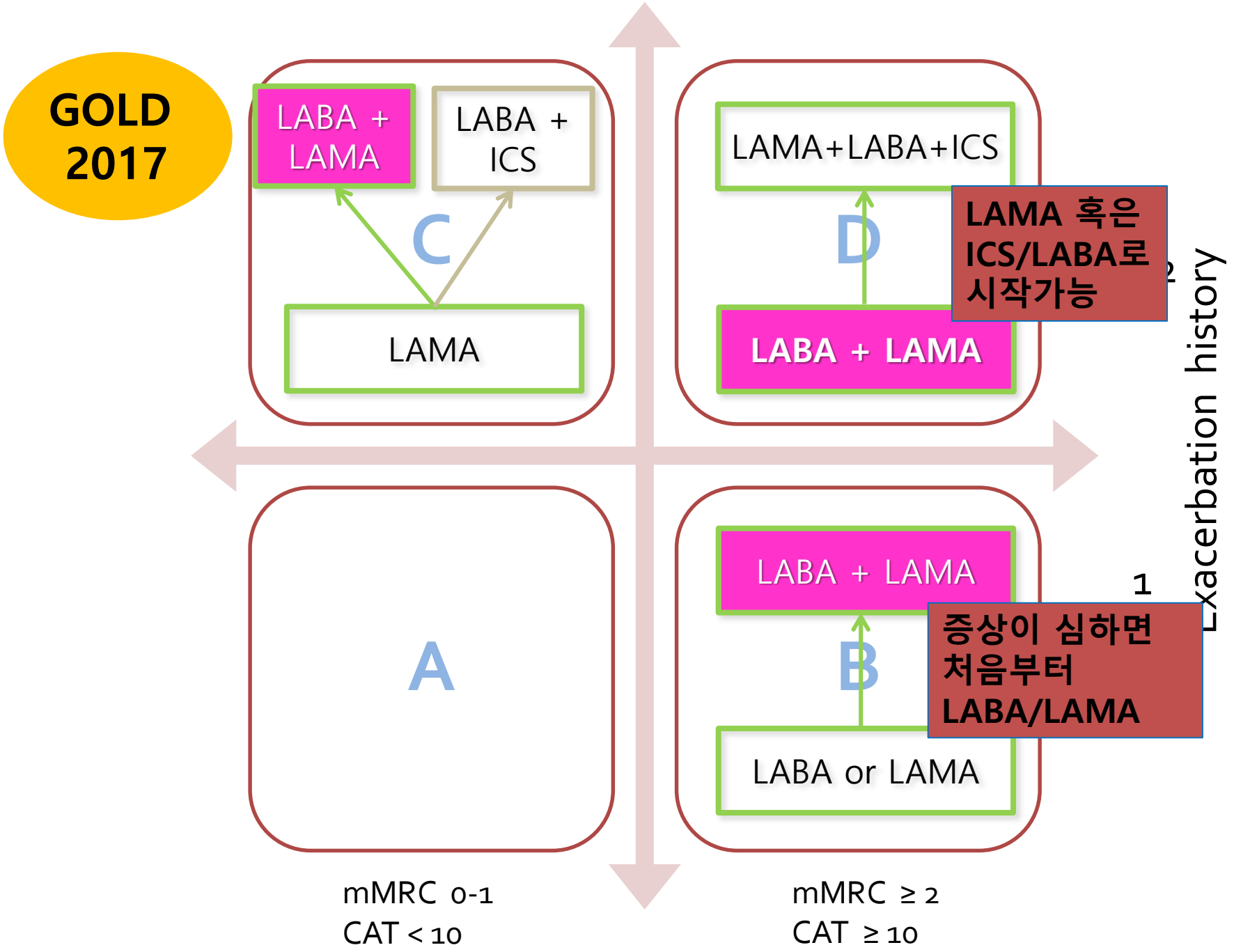
D	ICS+LABA and/or LAMA	ICS+LABA and LAMA ICS+LABA and PDE4 (-) LAMA and LABA LAMA and PDE4 (-)	Carbocysteine N-acetylcysteine SAMA and/or SABA Theophylline

안정시 COPD 약물 단계치료 2014

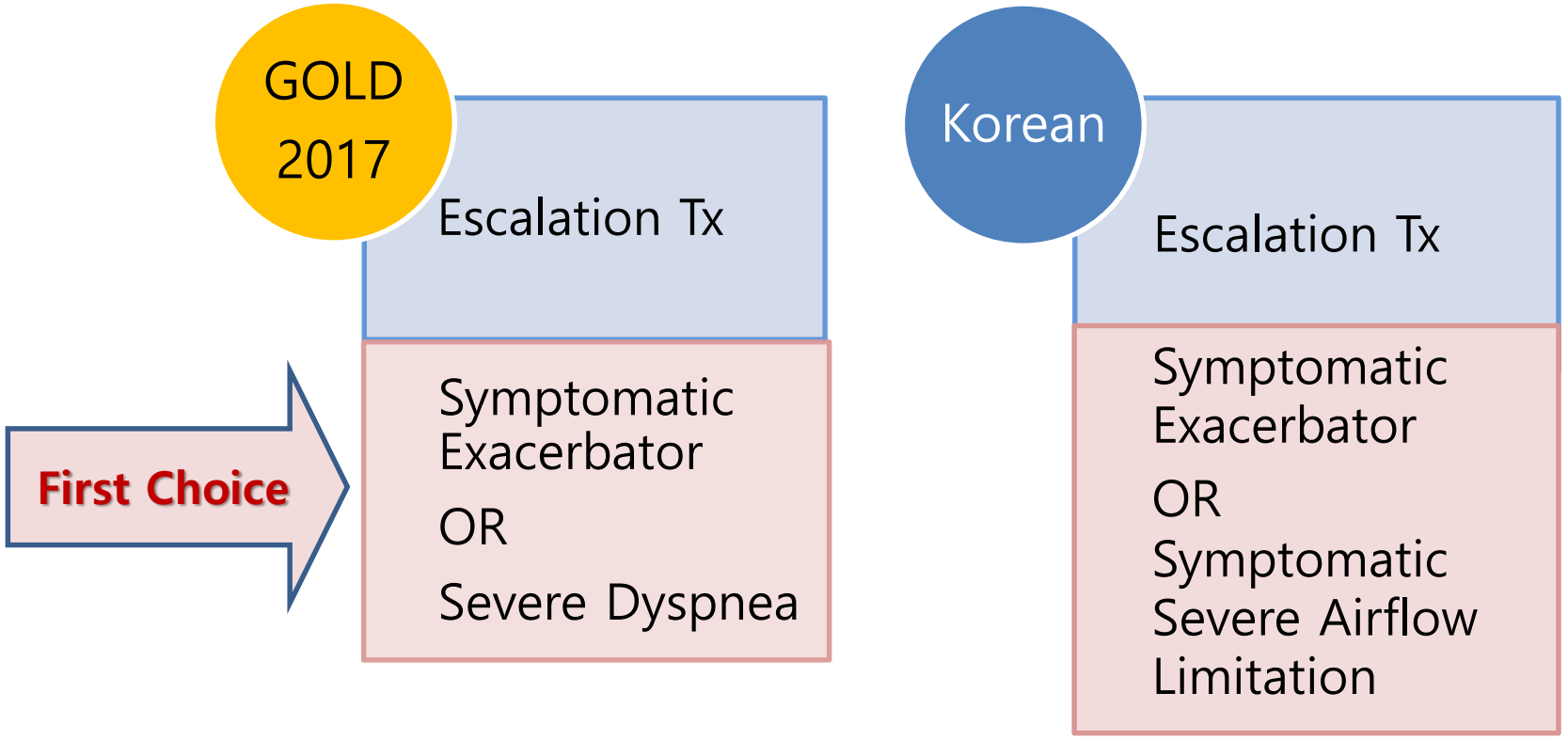
	FEV_1 ≥ 60% pred. and 0~1 exacerbation/year		FEV_1 < 60% pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA



대한 결핵 및 호흡기학회, 2014


GOLD 2017
LABA + LAMA
LABA + ICS
C
LAMA
LAMA+LABA+ICS
D
LABA + LAMA
LAMA 혹은 ICS/LABA로 시작가능
A
LABA + LAMA
B
LABA or LAMA
증상이 심하면 처음부터 LABA/LAMA
1
Exacerbation history
mMRC 0-1
CAT < 10
mMRC ≥ 2
CAT ≥ 10

Summary of Guideline



* Exacerbator : Frequent Exacerbator or hospitalized experience

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Efficacy Endpoints

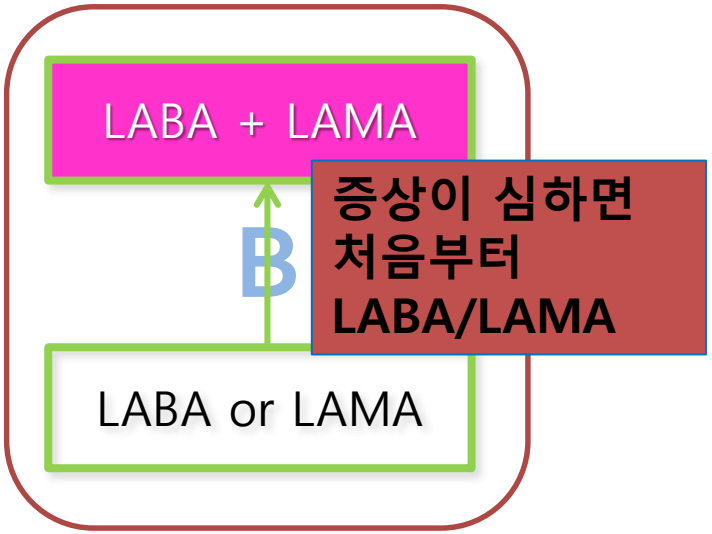
- FEV1
- Symptom scales
- Health-related quality of life
- COPD exacerbations

Group B

GOLD 2011

1) FEV_1 ≥ 50% **&** Exacerbation ≤ 1

2) Symptomatic



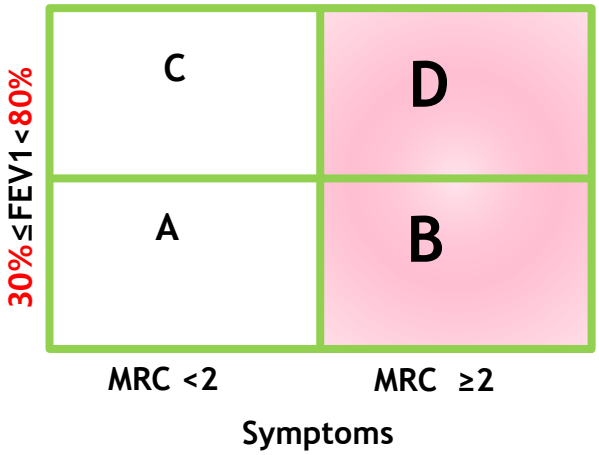
GOLD 2017

1) Exacerbation ≤ 1

2) Symptomatic

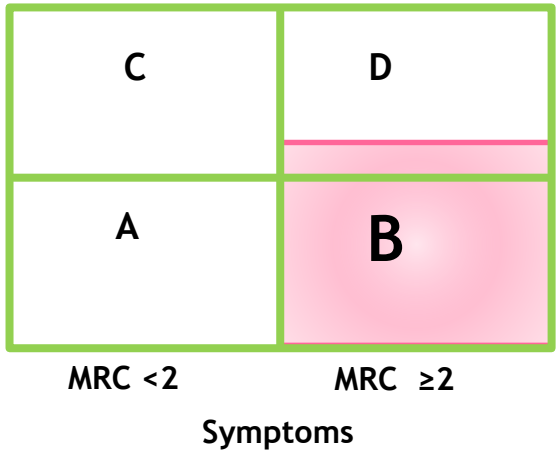
LABA/LAMA vs Mono

Aclidinium/Formoterol vs Mono
24wks, DB RCT PCB controlled



Exacerbation = 0.5

GOLD 2011



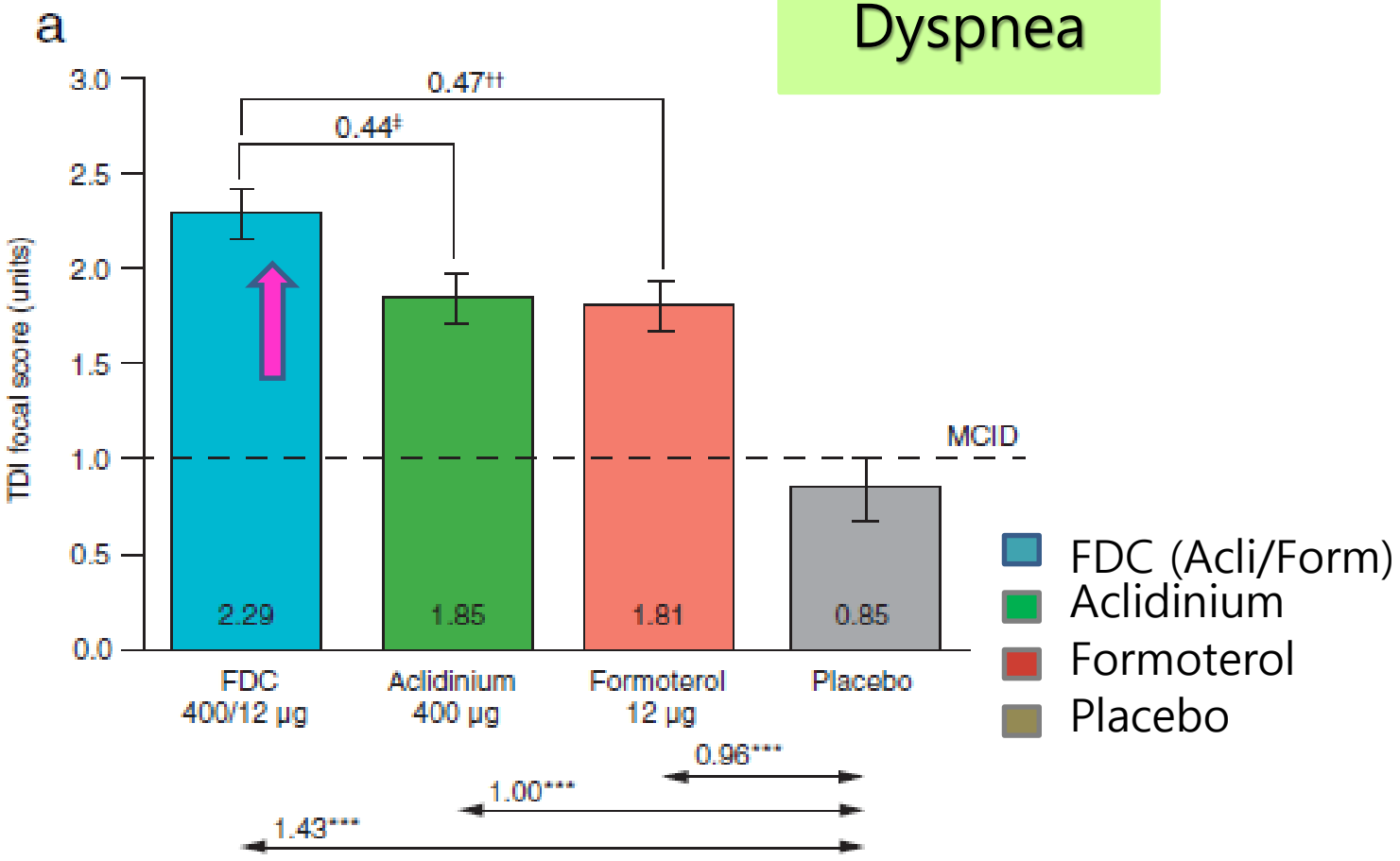
Exacerbation =0.5

GOLD 2017

Bateman et al. Respiratory Research (2015) 16:92

LABA/LAMA vs Mono

Dyspnea

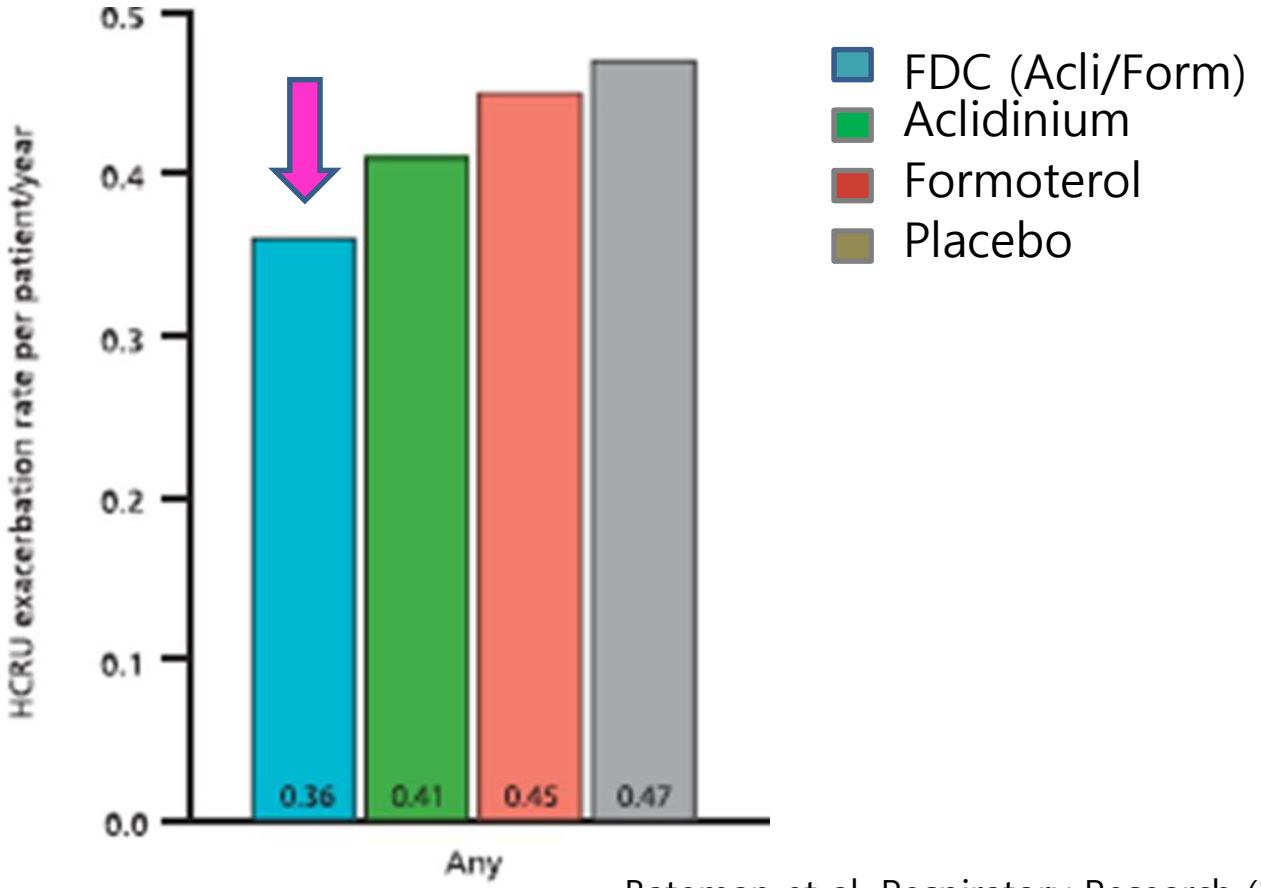


Bateman et al. Respiratory Research (2015) 16:92

LABA/LAMA vs Mono

Aclidinium/Formoterol vs Mono
24wks, DB RCT PCB controlled

Exacerbation



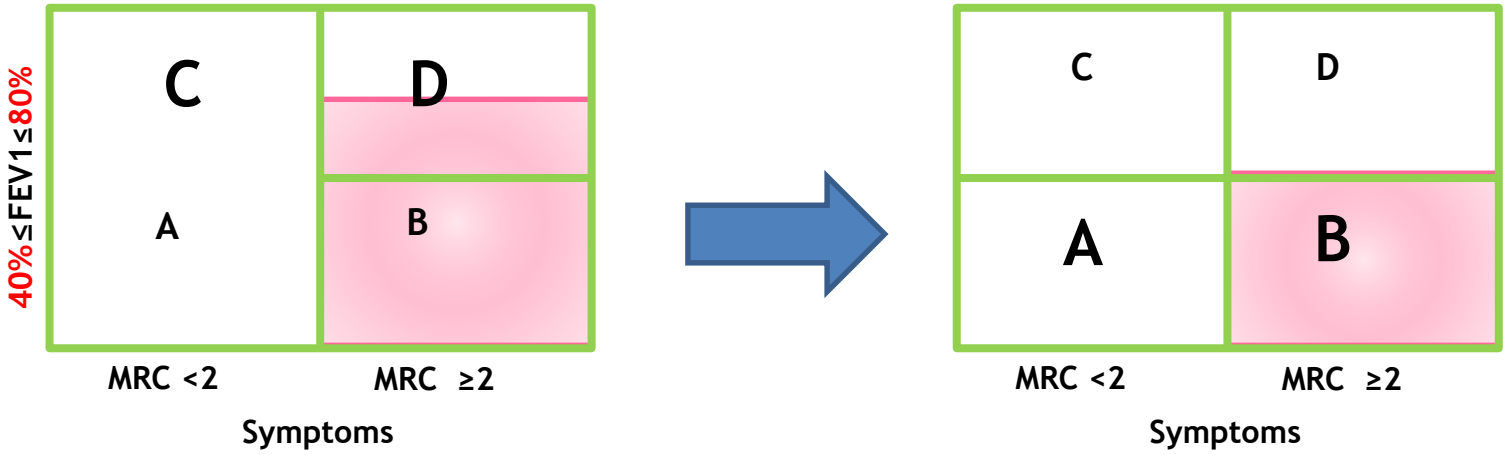
Bateman et al. Respiratory Research (2015) 16:92

LABA/LAMA vs ICS/LABA

ILLUMINATE

26-week, multicentre, randomised, double-blind, parallel-group, double-dummy study

QVA149 vs ICS/LABA



Exacerbation = 0

GOLD 2011

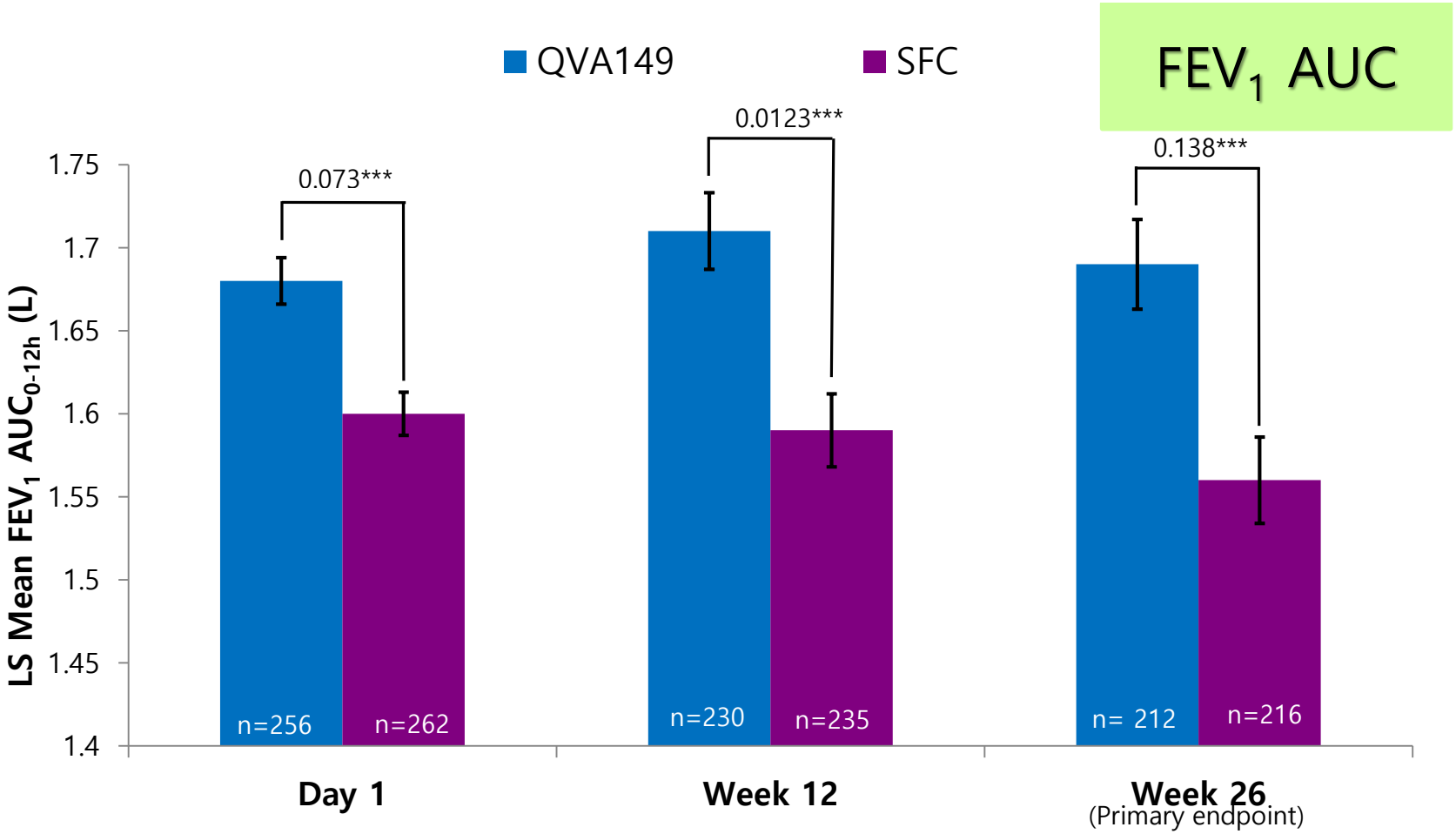
Exacerbation =0

GOLD 2017

Vogelmeier CF, et al. Lancet Resp Med. 2012

LABA/LAMA, better than ICS/LABA?

ILLUMINATE



Vogelmeier CF, et al. Lancet Resp Med. 2012

LABA/LAMA, better than ICS/LABA!!

	Day 1		Week 26	
	Treatment difference QVA149 versus SFC (LSM [95% CI])	p value for treatment comparison	Treatment difference QVA149 versus SFC (LSM [95% CI])	p value for treatment comparison
FEV_1 AUC_{0-12h} (L)*	0·073 (0·051 to 0·0		to 0·176)	<0·0001
Peak FEV_1 (L)*	0·066 (0·043 t		194)	<0·0001
Pre-dose trough FEV_1 (L)*	..		41)	<0·0001
FEV_1 (L) 5 min post-dose	0·081 (0·064		01)	<0·0001
FEV_1 (L) 30 min post-dose	0·075 (0·054		01)	<0·0001
FVC AUC_{0-12h} (L)	0·086 (0·036 t		·271)	<0·0001
Peak FVC (L)	0·062 (0·010 to 0·1		to 0·292)	<0·0001
Pre-dose trough FVC (L)	..		96 (0·131 to 0·261)	<0·0001
TDI focal score*	..	..	0·76 (0·26 to 1·26)	0·0031
SGRQ-C total score	..	..	−1·24 (−3·33 to 0·85)	0·25
Change from baseline in rescue medication use, puffs/day	..	..	−0·39 (−0·71 to −0·06)	0·019
Change from baseline in daytime rescue medication use, puffs/day	..	..	−0·32 (−0·52 to −0·13)	0·0013

Patient Reported Outcomes

*Minimum clinically important difference is 100 mL (FEV_1)[11] and 1-point (TDI score)ares mean. FEV_1=forced expiratory volume in 1 second. AUC_{0-12h}=area under the curve from 0 to 12 h. FVC=forced vital capacity. eorge's Respiratory Questionnaire for COPD patients (a reduction indicates improvement).

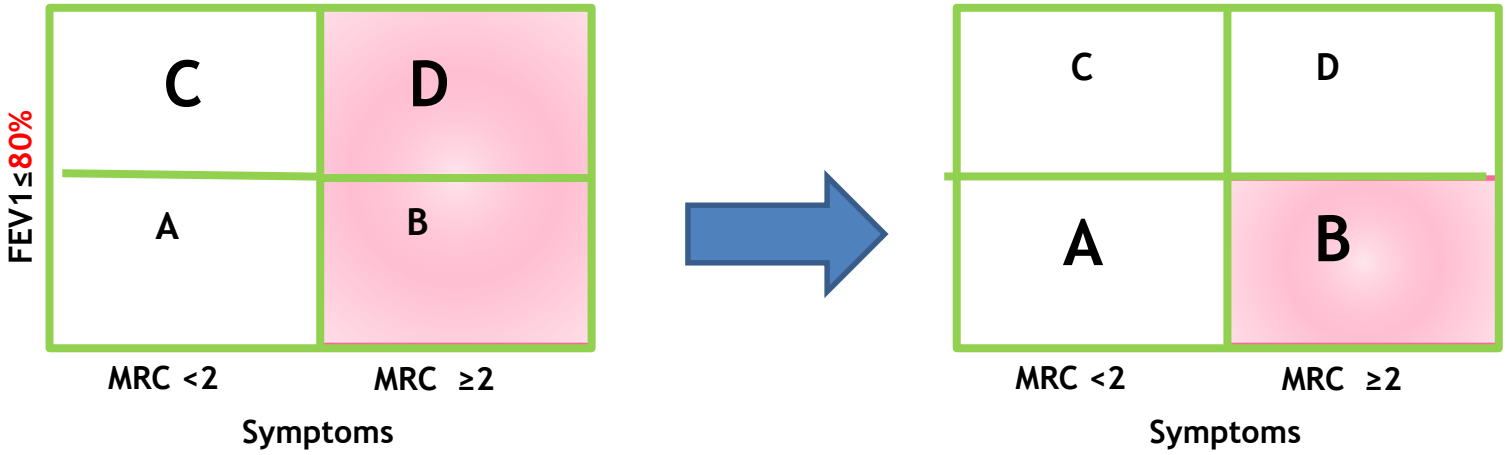
Table 2: Primary and secondary efficacy outcomes in the ILLUMINATE stud

LABA/LAMA vs ICS/LABA

LANTERN

26-week, multicentre, randomised, double-blind, parallel-group, double-dummy study

QVA149 vs ICS/LABA



Exacerbation ≤ 1

GOLD 2011

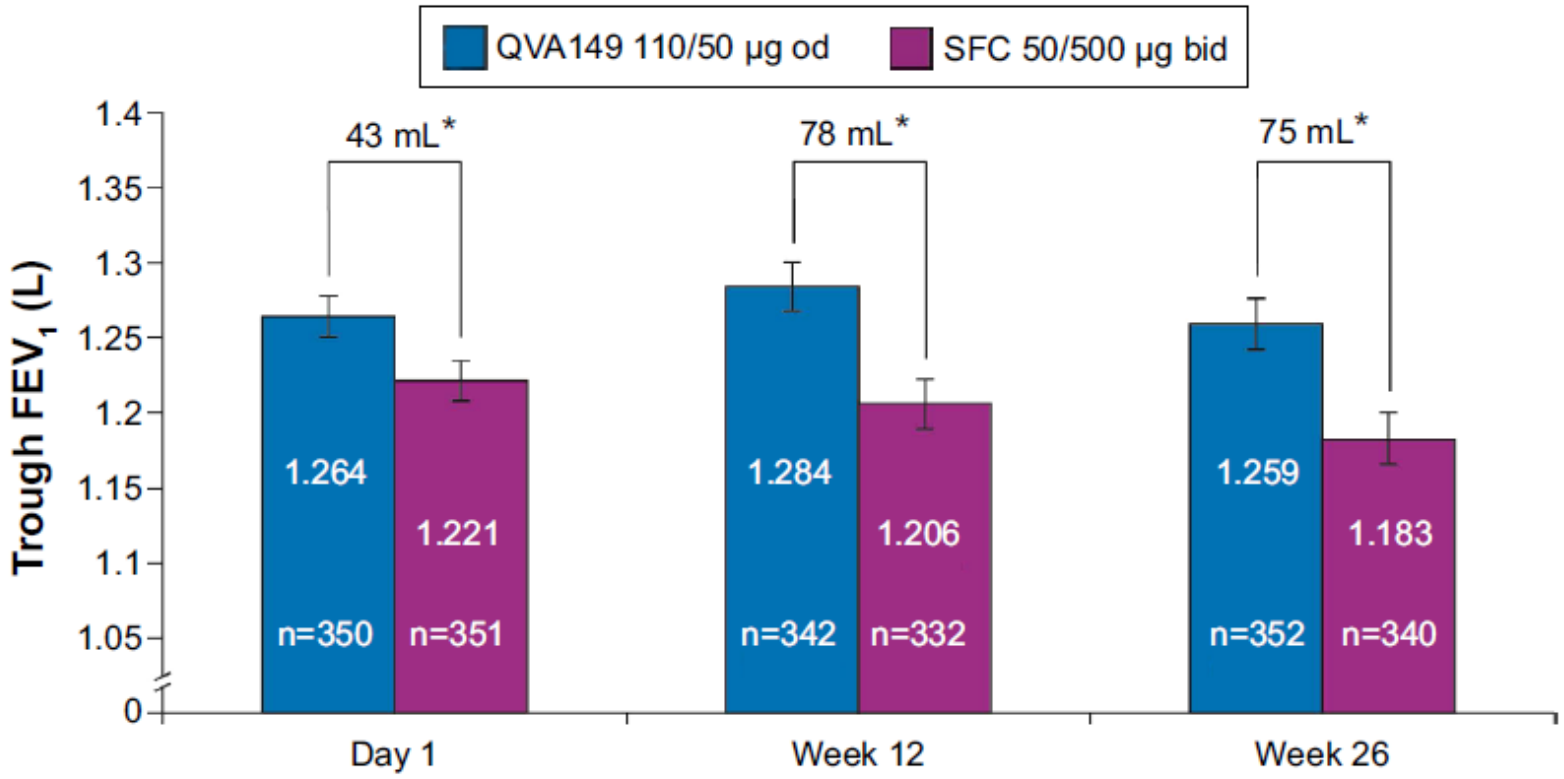
Exacerbation ≤ 1

GOLD 2017

Vogelmeier CF, et al. Lancet Resp Med. 2012

LABA/LAMA, better than ICS/LABA?

LANTERN

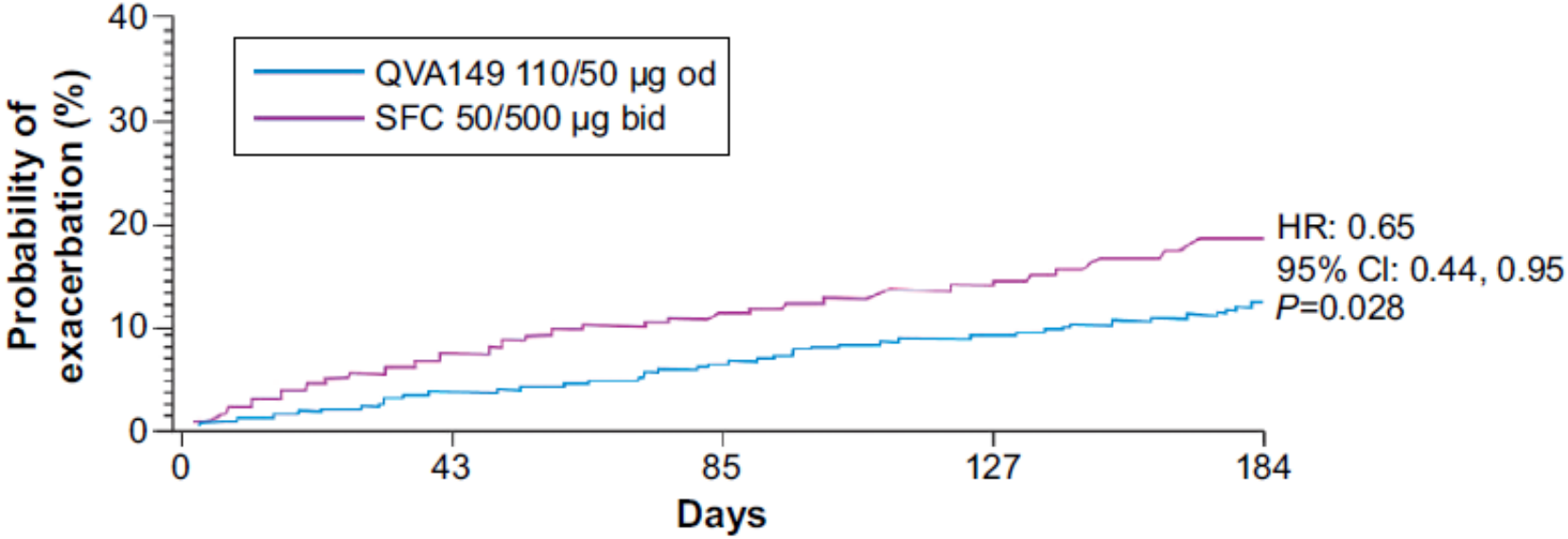


Zhong et al. Int J COPD 2015:10

LABA/LAMA, better than ICS/LABA!

LANTERN

Exacerbation



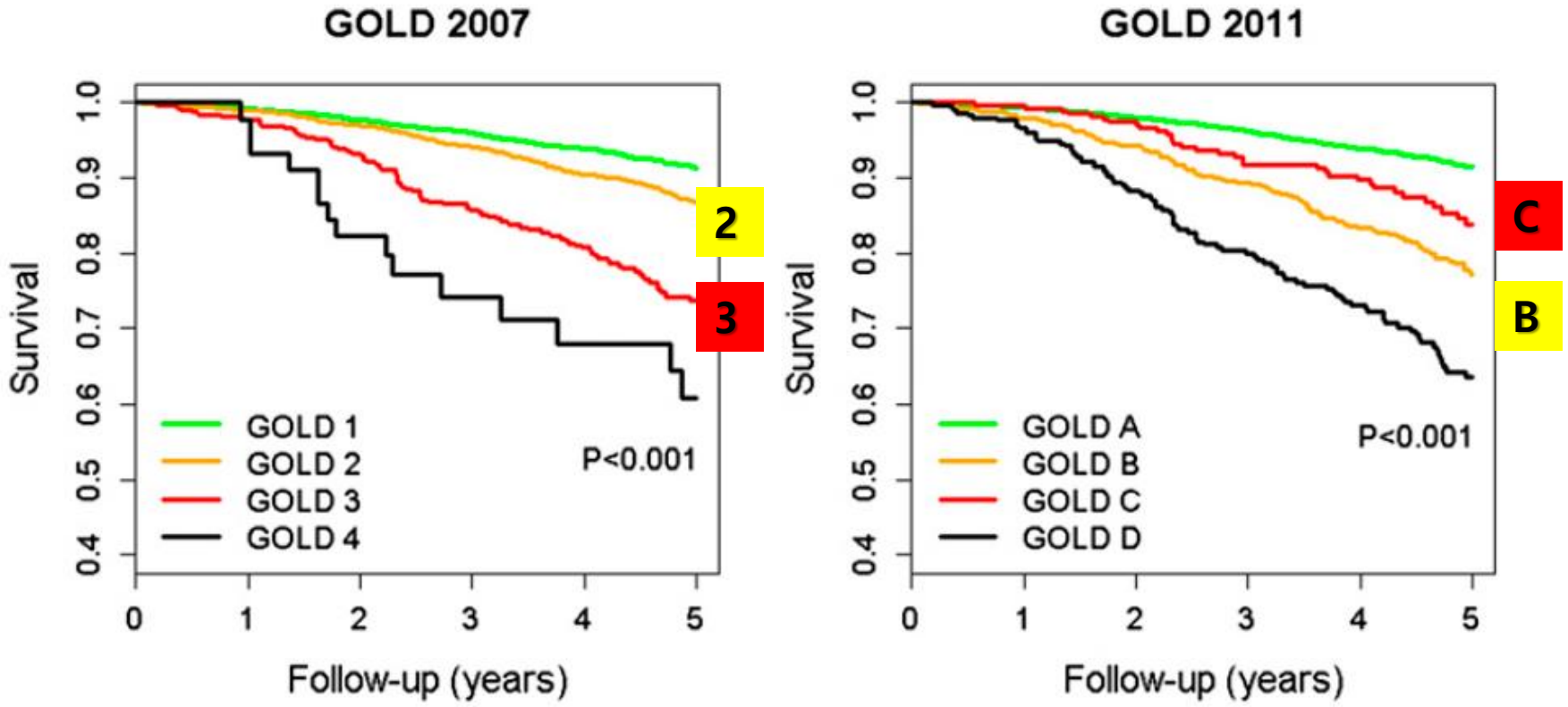
Patients with exacerbation (%)				
QVA149: 0 (0.0%)	12 (3.3%)	20 (5.5%)	31 (8.6%)	43 (12.1%)
SFC: 0 (0.0%)	24 (6.6%)	38 (10.5%)	48 (13.4%)	67 (18.9%)

Zhong et al. Int J COPD 2015:10

Single Agent or FDC LABA/LAMA as Initial Tx ?

Survival Prediction

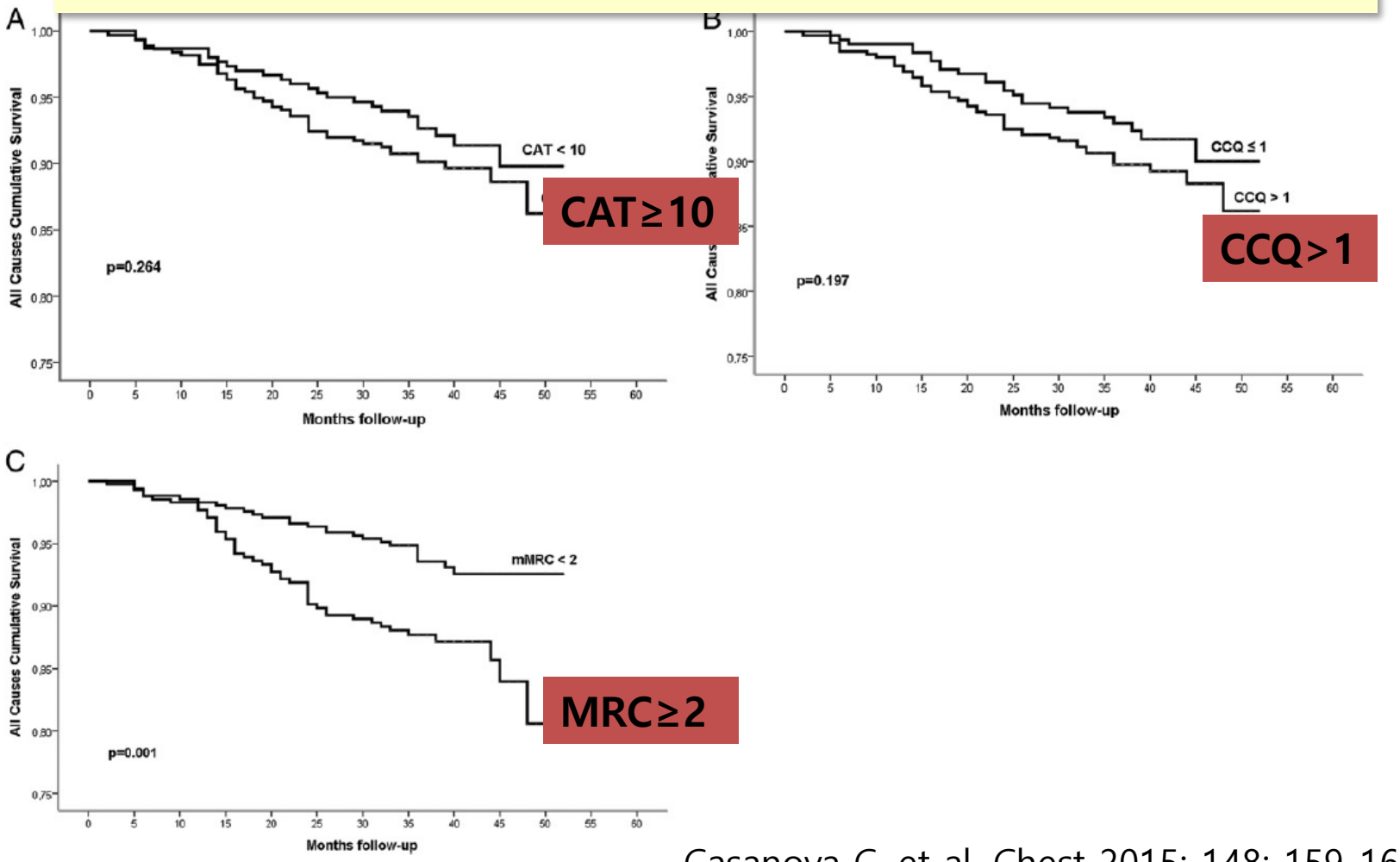
증상 조절이 중요하다



Lange P, et al. Am J Respir Crit Care Med 2012; 186: 975-981.

Survival Prediction

호흡곤란은 중요한 예후 예측인자이다



Casanova C, et al. Chest 2015; 148: 159-168.

Group B 요약

- LABA/LAMA FDC 는 Mono component보다 Trough FEV1, 호흡곤란, 삶의 질을 향상시키고 악화를 감소시킨다.
- 악화 감소효과는 ICS/LABA와 비교할때에도 뛰어나다.

In What Patients Should I Use Fixed LABA-LAMA Combination in COPD ?

- Step up from LABA or LAMA
- 악화 위험이 적은 환자에서, CAT ≥10, MRC≥2 인 환자 중 호흡곤란이 심한 환자는 처음부터 처방 가능

Efficacy Endpoints

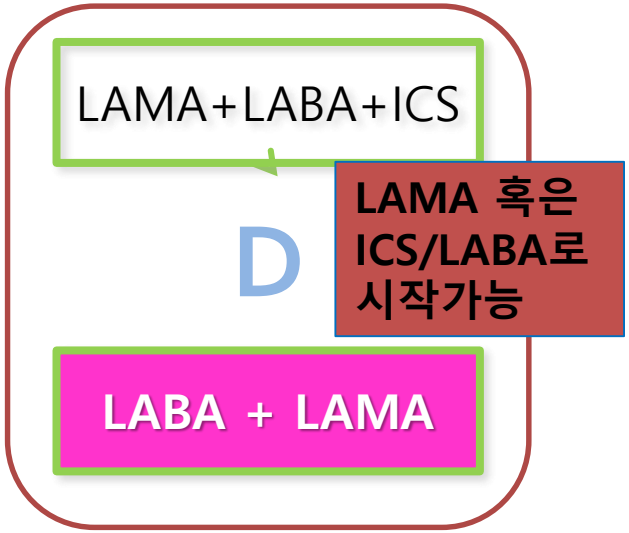
- FEV1
- Symptom scales
- Health-related quality of life
- COPD exacerbations

Group D

GOLD 2011

1) FEV_1 < 50% **&** Exacerbation ≥ 2

2) Symptomatic

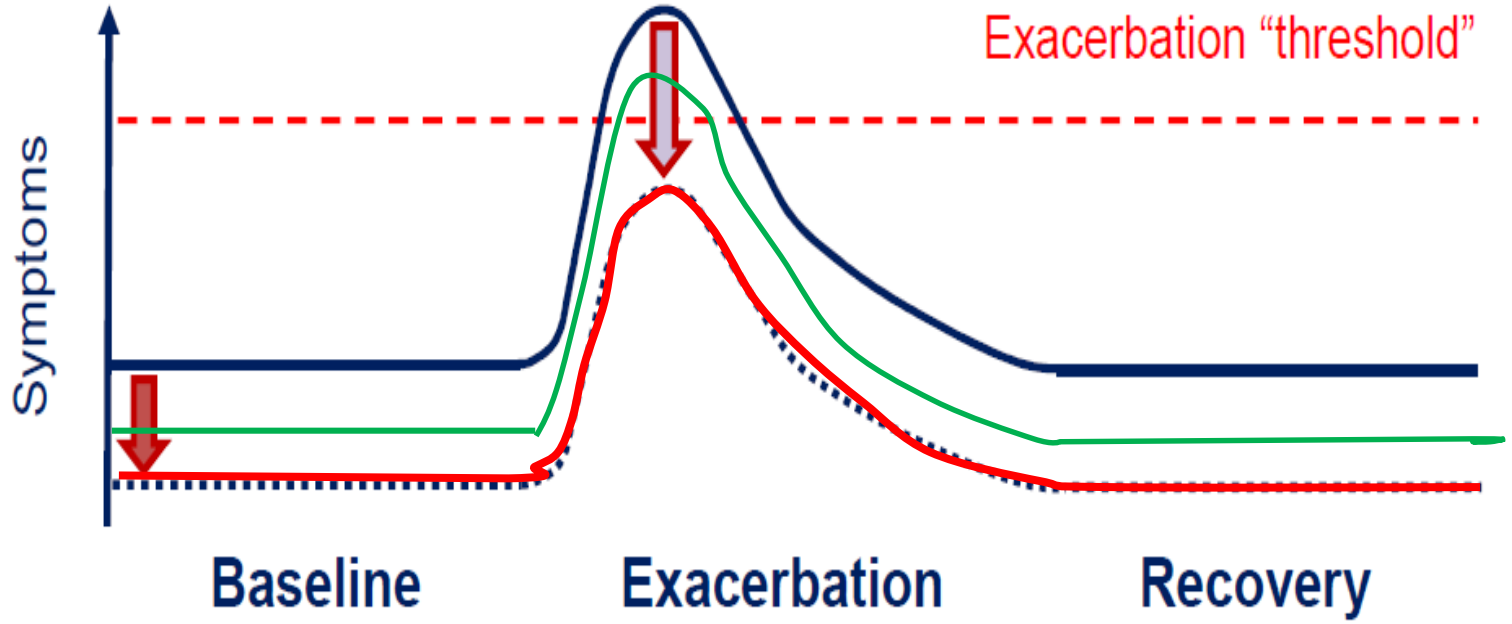


GOLD 2017

1) Exacerbation ≥ 2

2) Symptomatic

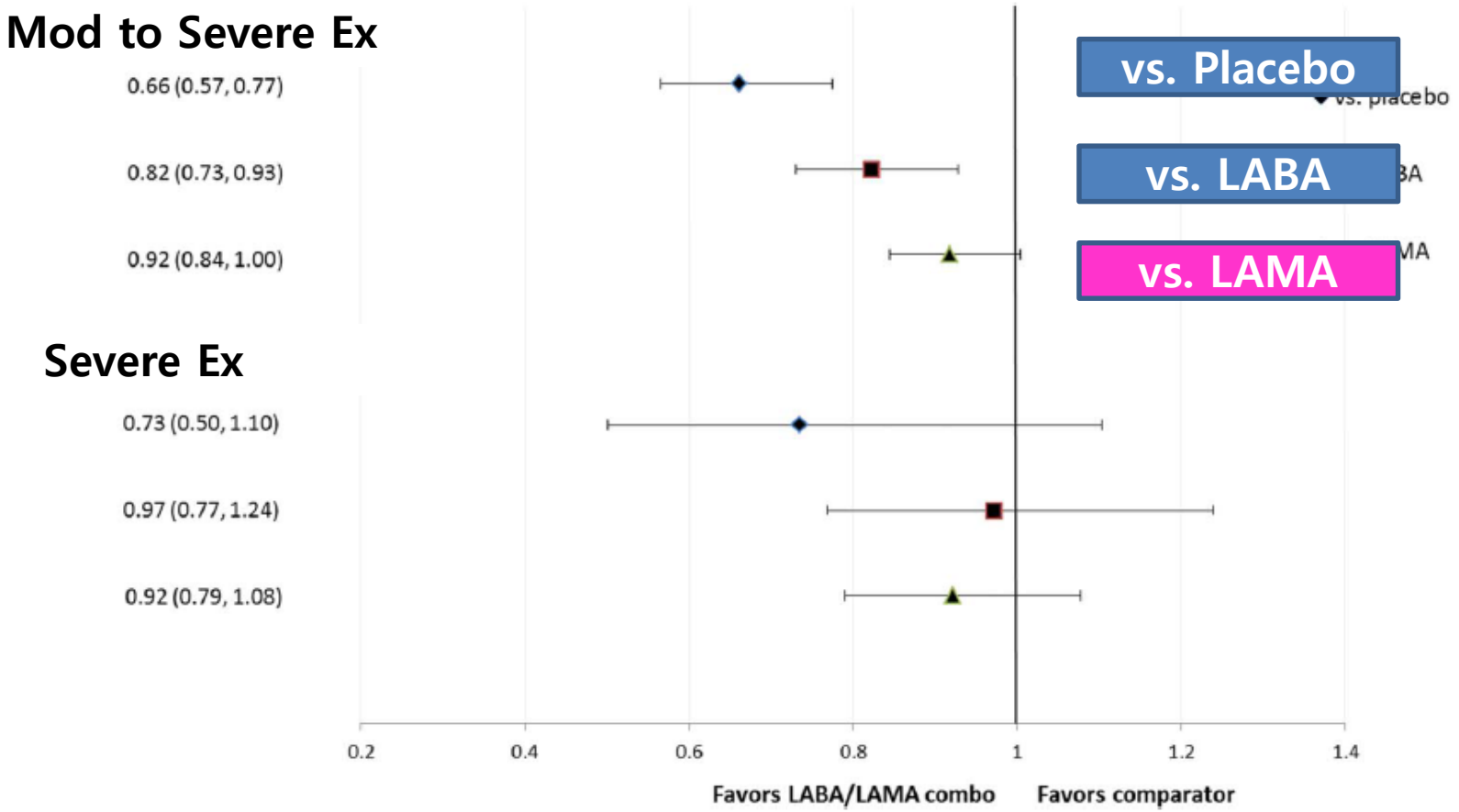
LABA/LAMA and Exacerbation Control



Beeh KM, et al. Am J Respir Crit Care Med. 2016 Dec 6. [Epub ahead of print].

LABA/LAMA vs Mono

Network Meta Analysis of 23 Trials

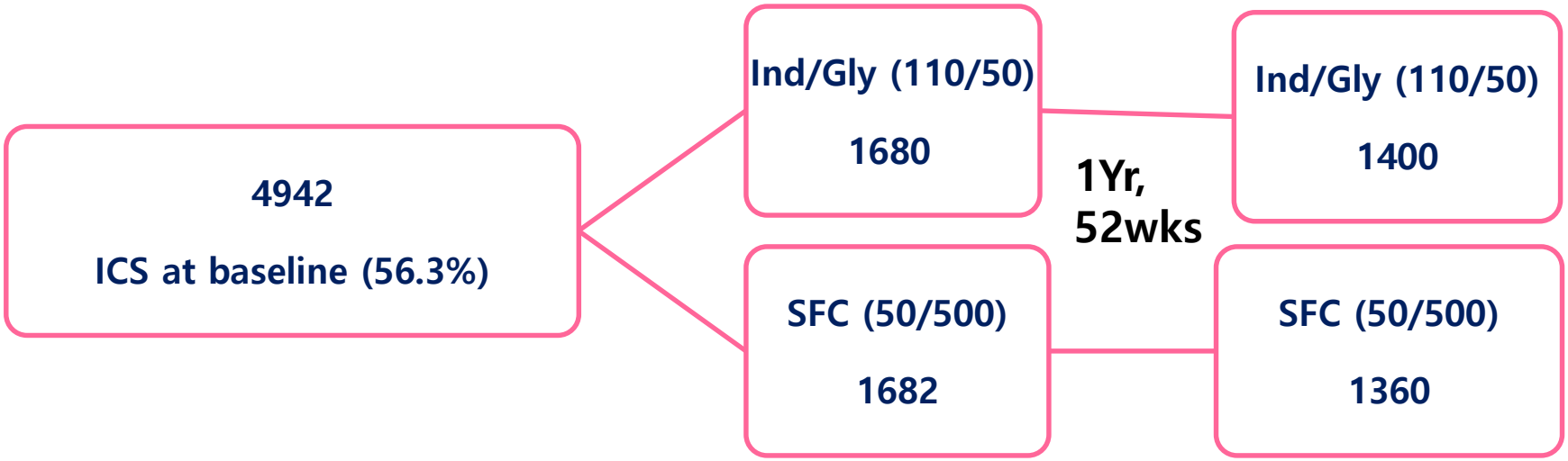


Oba Y, et al. Thorax 2016;71:15–25.

LABA/LAMA or ICS/LABA ?

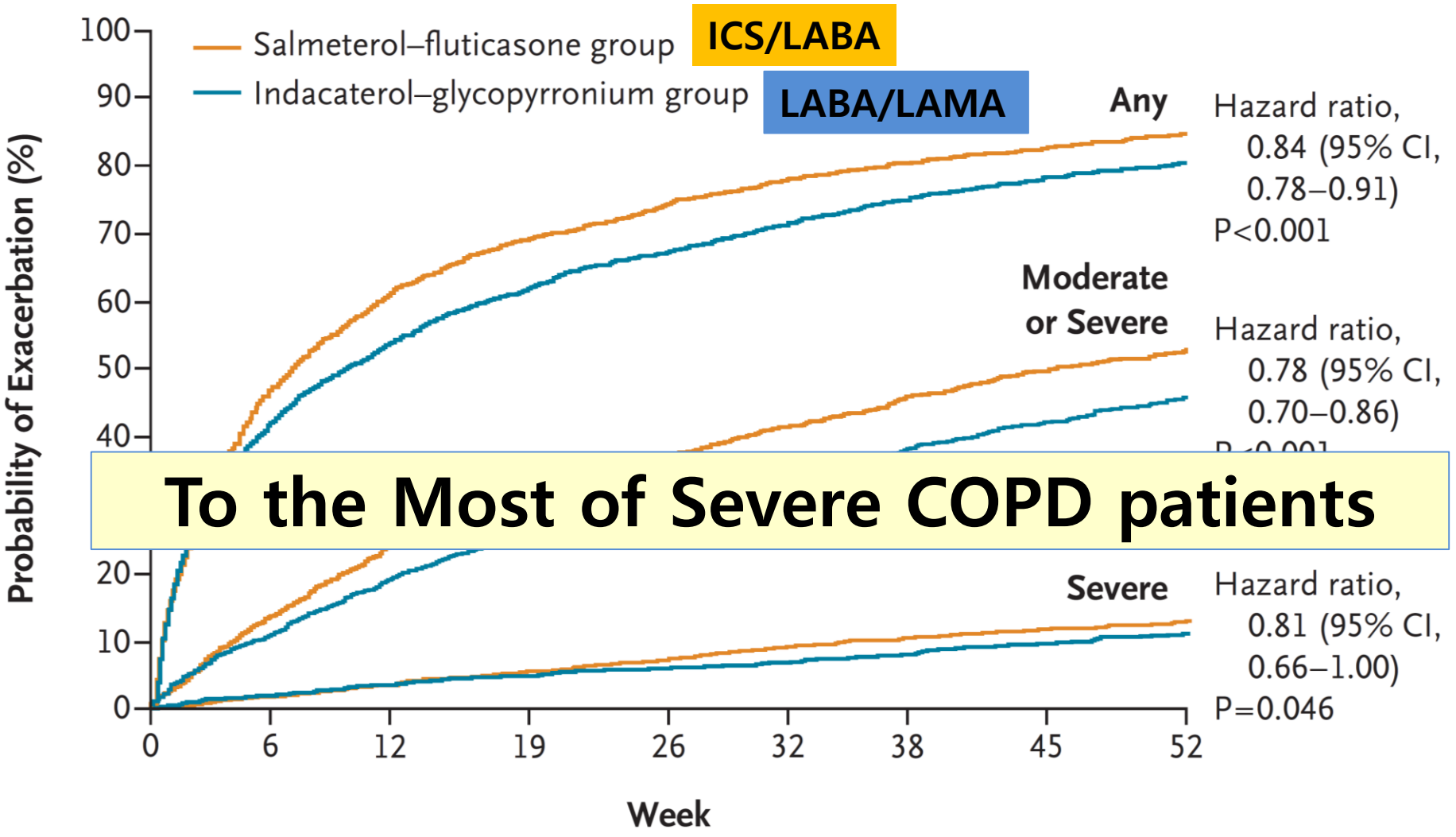
FLAME study

- ✓ FEV1≥25% and <60%
- ✓ Exacerbation ≥1



Wedzicha JA et al. NEJM 2016

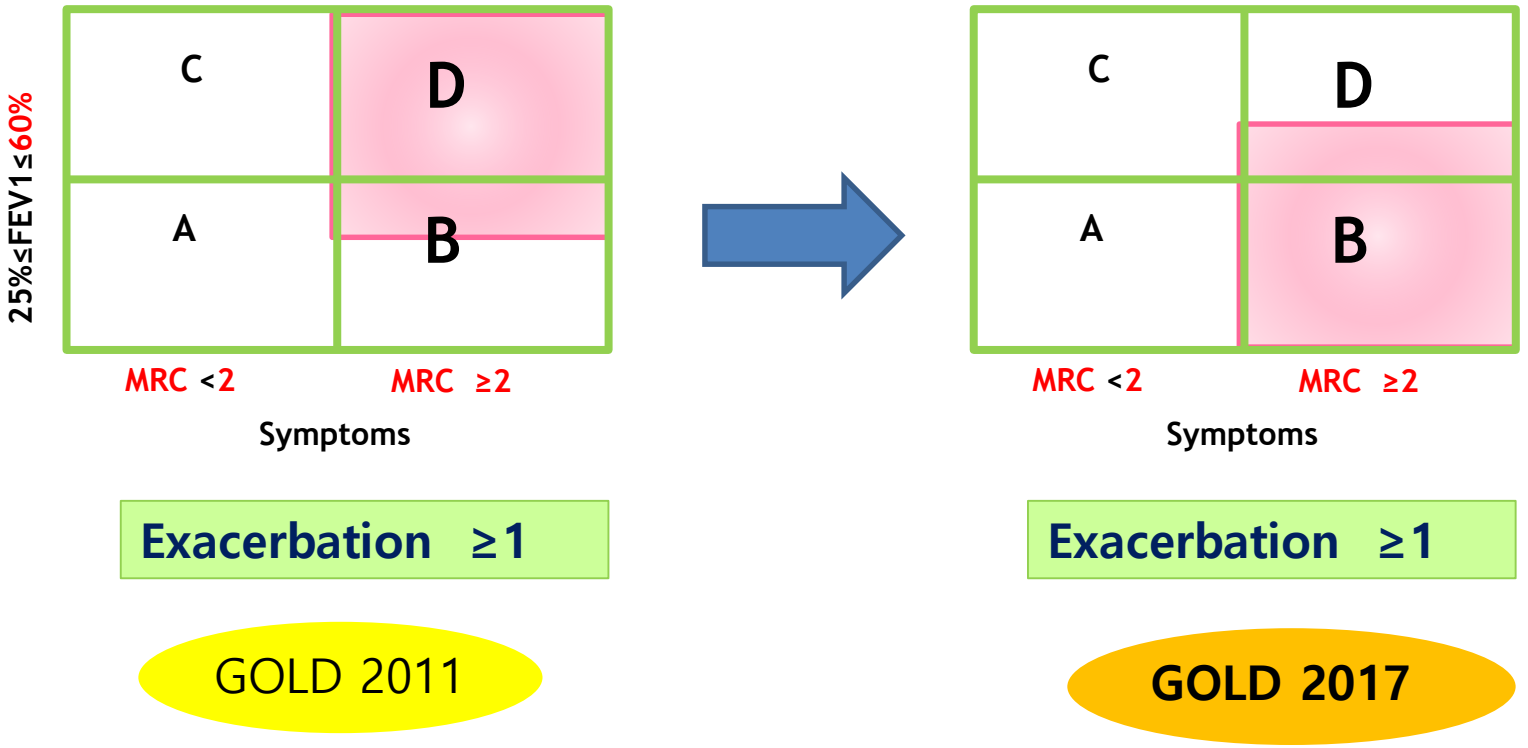
LABA/LAMA, Better Than ICS/LABA?



To the Most of Severe COPD patients

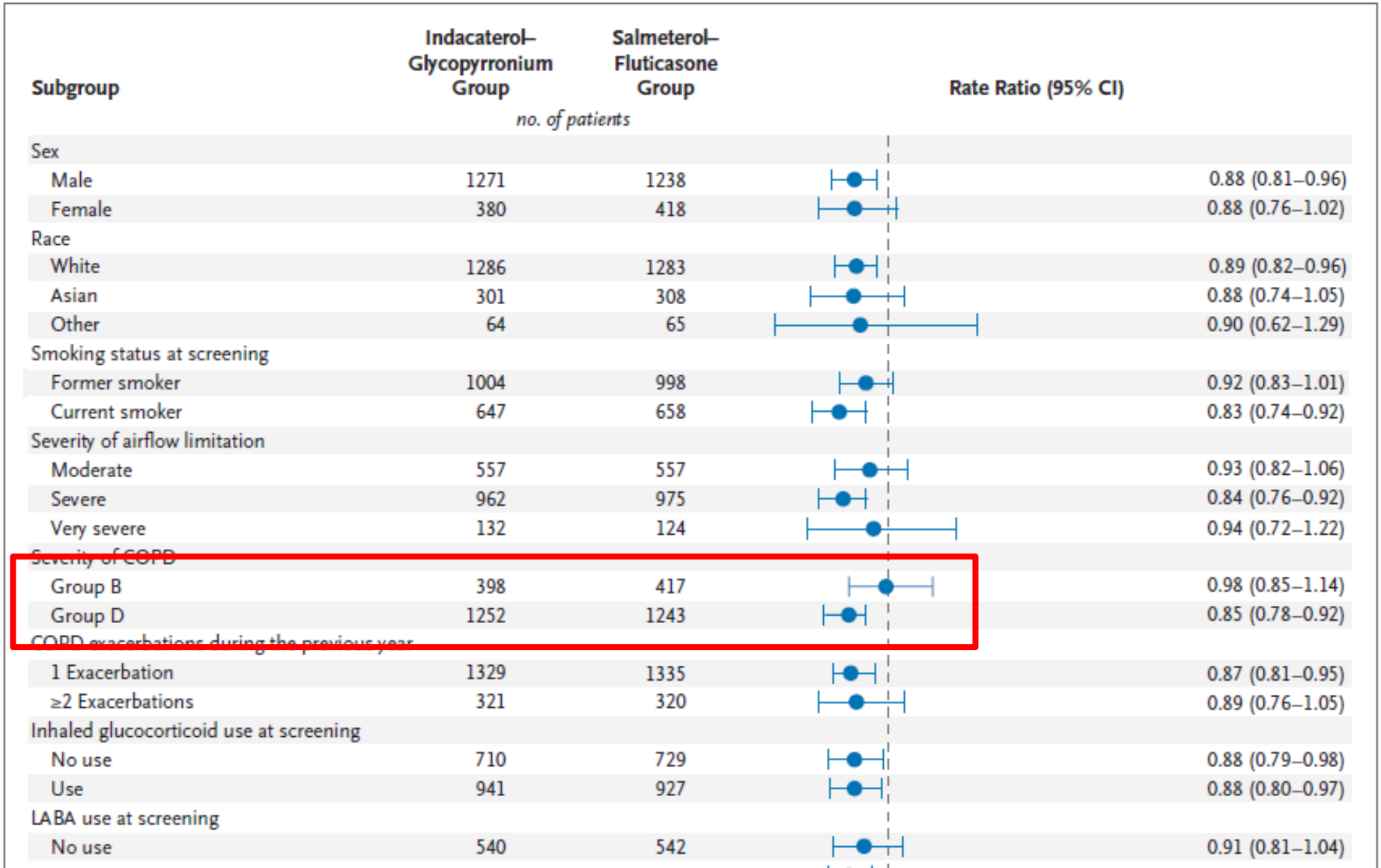
Wedzicha JA et al. NEJM 2016

FLAME
Inclusion criteria



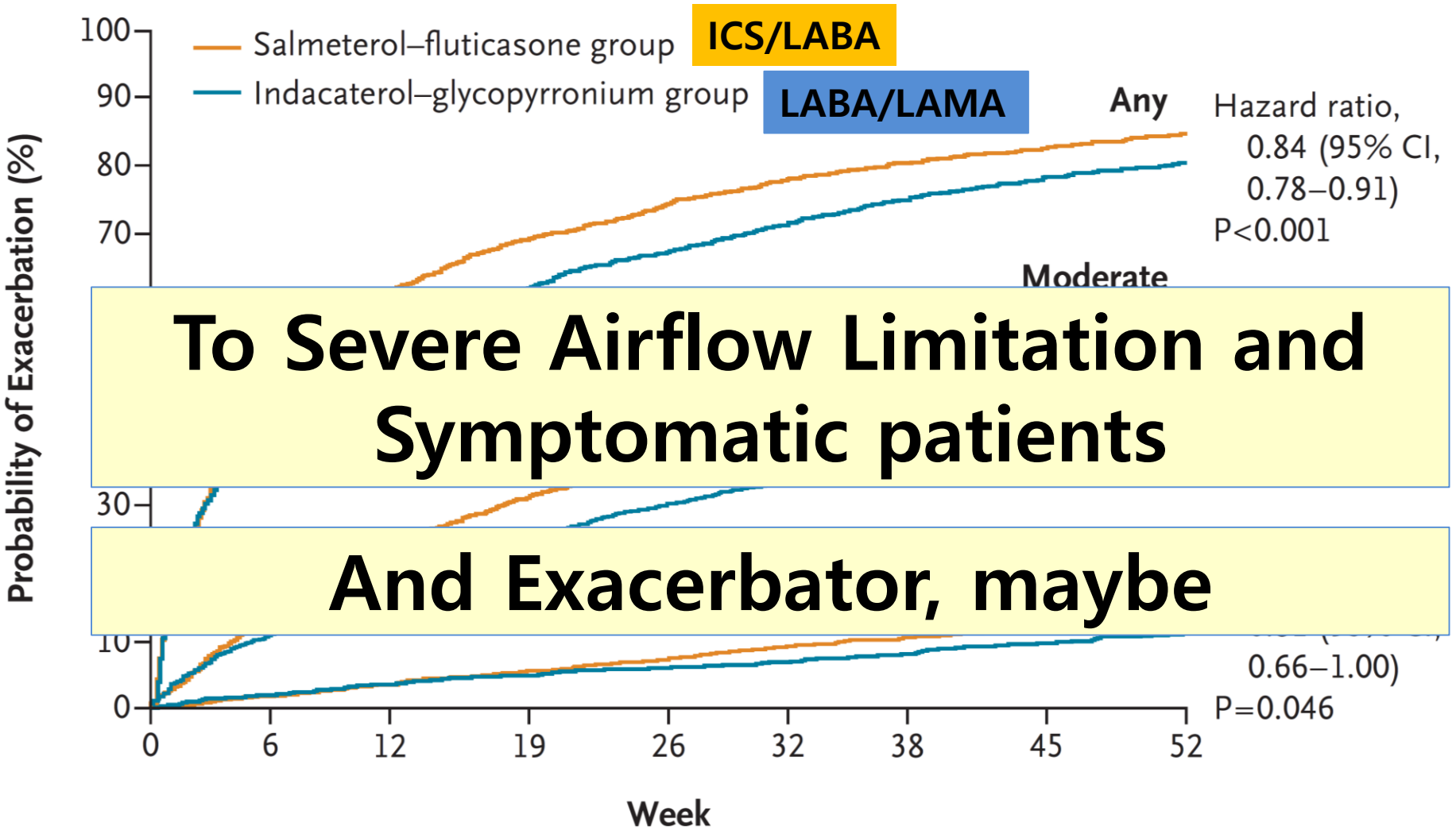
Wedzicha JA et al. NEJM 2016

Subgroup analysis



Subgroup	Indacaterol–Glycopyrronium Group	Salmeterol–Fluticasone Group	Rate Ratio (95% CI)
	no. of patients		
Sex			
Male	1271	1238	0.88 (0.81–0.96)
Female	380	418	0.88 (0.76–1.02)
Race			
White	1286	1283	0.89 (0.82–0.96)
Asian	301	308	0.88 (0.74–1.05)
Other	64	65	0.90 (0.62–1.29)
Smoking status at screening			
Former smoker	1004	998	0.92 (0.83–1.01)
Current smoker	647	658	0.83 (0.74–0.92)
Severity of airflow limitation			
Moderate	557	557	0.93 (0.82–1.06)
Severe	962	975	0.84 (0.76–0.92)
Very severe	132	124	0.94 (0.72–1.22)
Severity of COPD			
Group B	398	417	0.98 (0.85–1.14)
Group D	1252	1243	0.85 (0.78–0.92)
COPD exacerbations during the previous year			
1 Exacerbation	1329	1335	0.87 (0.81–0.95)
≥2 Exacerbations	321	320	0.89 (0.76–1.05)
Inhaled glucocorticoid use at screening			
No use	710	729	0.88 (0.79–0.98)
Use	941	927	0.88 (0.80–0.97)
LABA use at screening			
No use	540	542	0.91 (0.81–1.04)

LABA/LAMA, better than ICS/LABA?

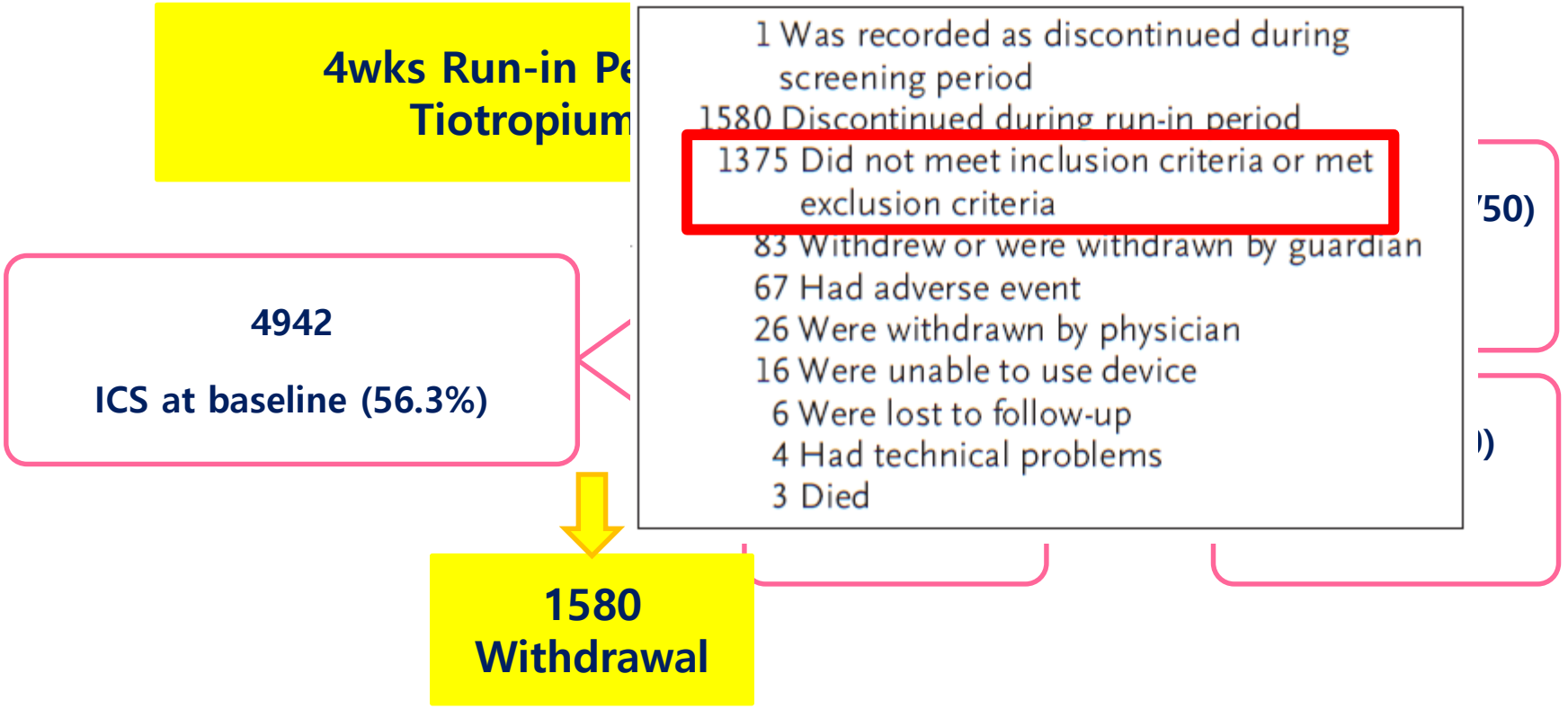


To Severe Airflow Limitation and Symptomatic patients

And Exacerbator, maybe

Wedzicha JA et al. NEJM 2016

FLAME



Wedzicha JA et al. NEJM 2016

Exclusion Criteria of FLAME

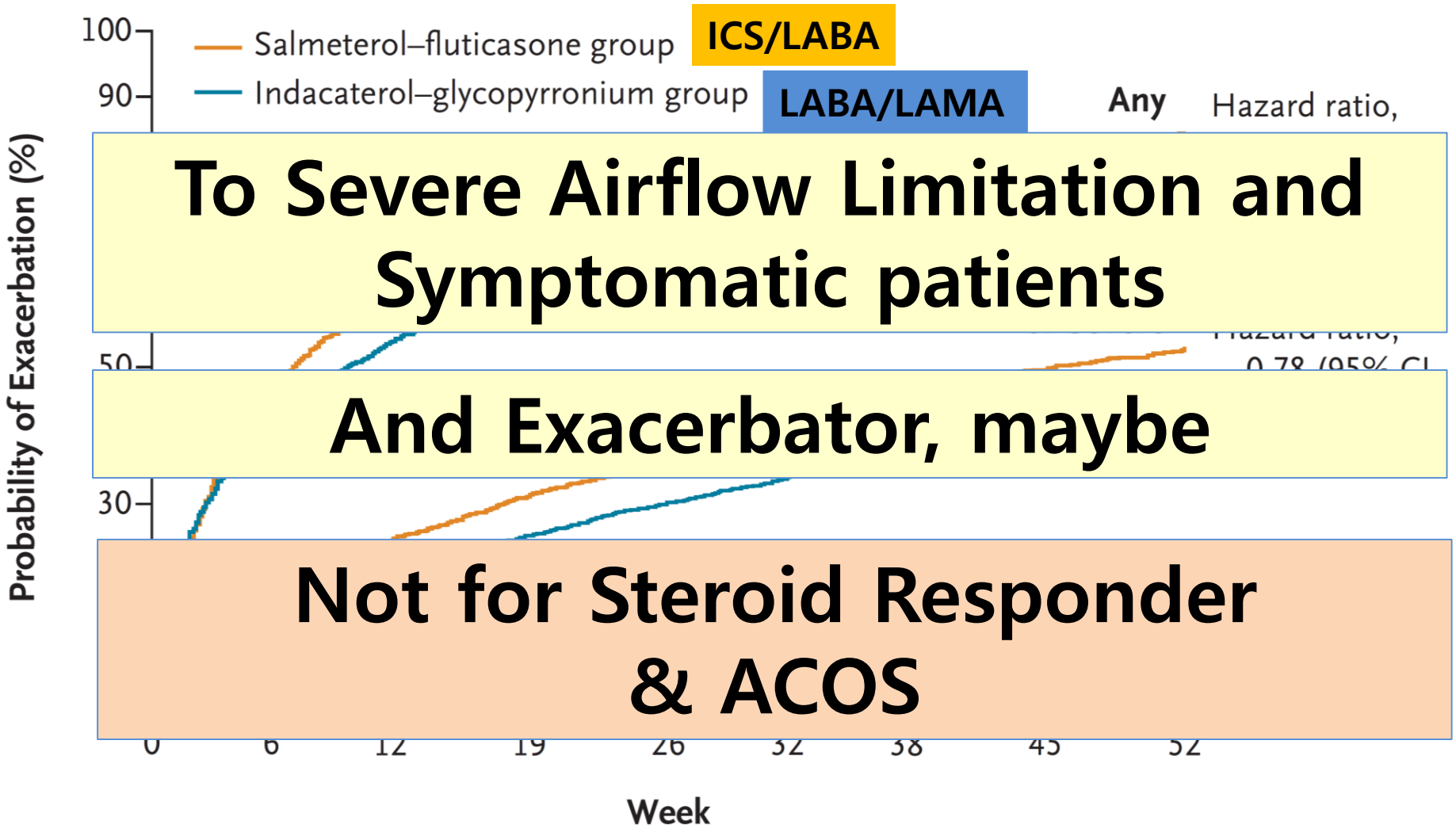
14. Patients who developed a COPD exacerbation of any severity (mild/moderate/severe) between screening (Visit 1) and treatment epoch (Visit 201) were not eligible but were permitted to be re-scr after the resolution of the COPD exacerbation.

Steroid Responder

18. Patients with any history of asthma.
19. Patients with an onset of respiratory symptoms, includi g a COPD diagnosis prior to age 40 years.
20. Patients with a blood eosinophil count >600/mm^3 at the st (Visit 101).
21. Patients with allergic rhinitis who used an H_1-antagonis or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen as permitted).

ACOS

LABA/LAMA, better than ICS/LABA?



To Severe Airflow Limitation and Symptomatic patients

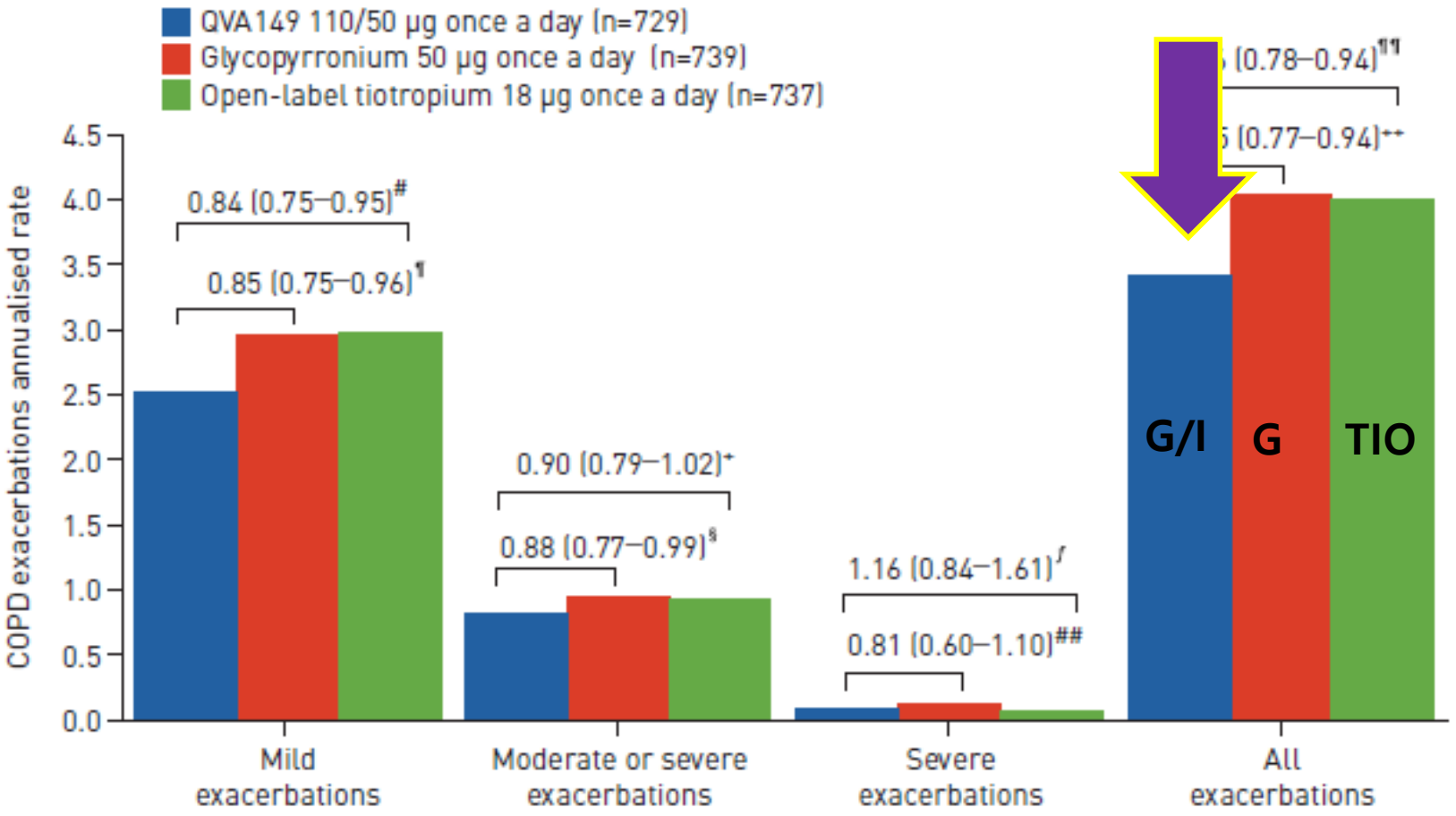
And Exacerbator, maybe

Not for Steroid Responder & ACOS

Wedzicha JA et al. NEJM 2016

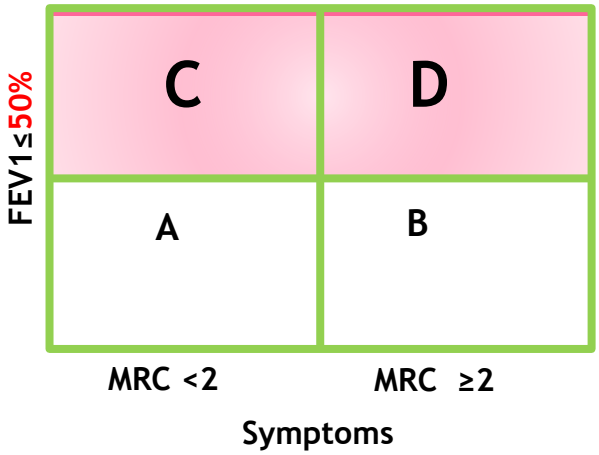
LABA/LAMA, better than Mono?

SPARK study (64wks)



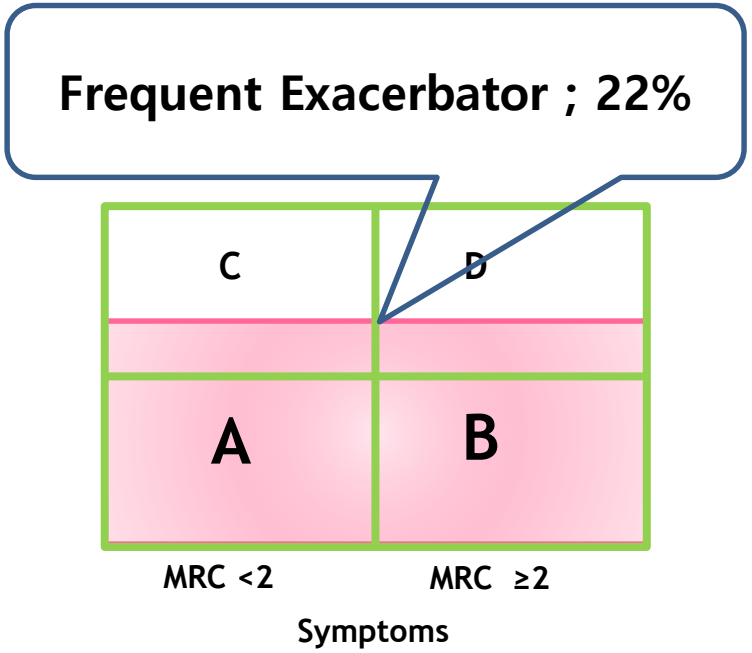
Wedzicha JA, et al. *Lancet Respir Med.* 2013 May;1(3):199-209

SPARK



Exacerbation ≥1

GOLD 2011



Exacerbation ≥1

GOLD 2017

Wedzicha JA, et al. *Lancet Respir Med.* 2013 May;1(3):199-209

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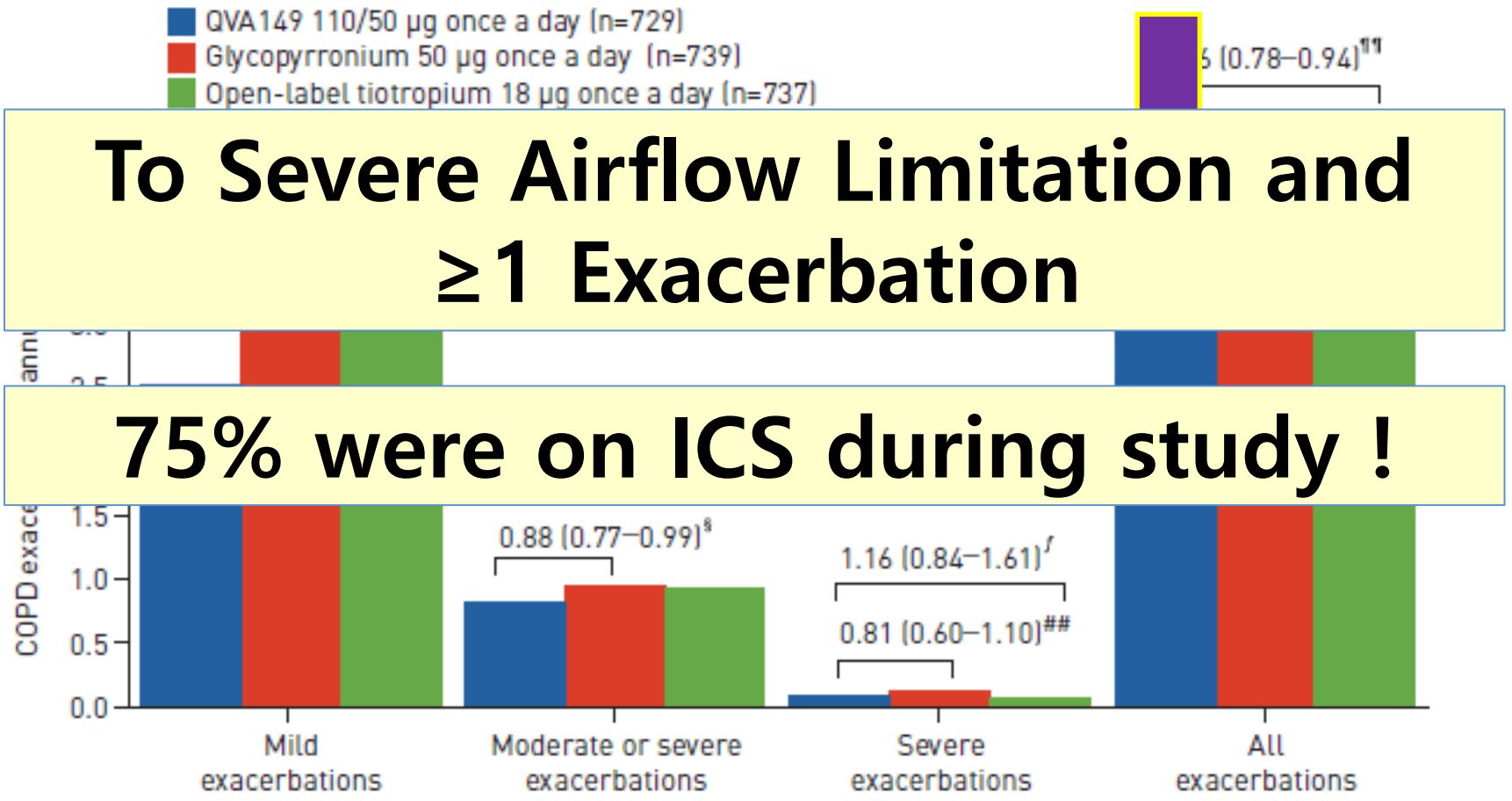

To Severe Airflow Limitation and ≥1 Exacerbation

75% were on ICS during study !

Wedzicha JA, et al. *Lancet Respir Med.* 2013 May;1(3):199-209

In What Patients Should I Use Fixed LABA-LAMA Combination in COPD ?

- Step up from LABA or LAMA
- 악화 위험이 적은 환자에서, CAT ≥10, MRC≥2 인 환자 중 호흡곤란이 심한 환자는 처음부터 처방 가능
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Network Meta-analysis: LAMA/LABA Combinations vs Comparators on Adverse Events

Network Meta Analysis of 23 Trials

	Mortality HR	Total SAEs HR	Cardiac SAEs HR	Dropouts due to AEs, HR
FDC vs placebo	1.95 (0.73, 7.71)	1.10 (0.89, 1.38)	1.65 (0.81, 3.35)	0.95 (0.71, 1.28)
FDC vs LABA	0.99 (0.61, 1.66)	0.96 (0.84, 1.10)	0.82 (0.46, 1.35)	0.92 (0.72, 1.19)
FDC vs LAMA	0.87 (0.64, 1.16)	1.04 (0.95, 1.14)	0.87 (0.59, 1.27)	1.03 (0.84, 1.26)
Number of studies	15	20	16	16
Number of patients	24,041	27,172	25,913	23,529

Oba Y, et al. *Thorax*. 2016;71:15-25.

Umeclidinium/Vilanterol C-V Safety

	Placebo (n = 109)	UMEC/VI 125/25 µg (n = 226)	UMEC 125 µg (n = 227)
Any cardiovascular AEs of special interest	23%	15%	22%
Acquired long QT	0	0	0
Cardiac arrhythmias	16%	12%	17%
Cardiac failure	<1%	<1%	2%
Cardiac ischemia	4%	2%	2%
Hypertension	6%	4%	3%
Sudden death	0	0	0
Stroke	0	0	< 1%

Naccarelli G, et al. *AJRCCM*. 2014;189:A3766.

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GOLD 2017

Pharmacologic treatment algorithms

A proposed model for the initiation, and then subsequent escalation and/or de-escalation of pharmacologic management of COPD according to the individualized assessment of symptoms and exacerbation risk is shown in **Figure 4.1.**

In past versions of the GOLD Report, recommendations were only given for initial therapy. However, many COPD patients are already on treatment and return with persistent symptoms after initial therapy, or less commonly with resolution of some symptoms that subsequently may require less

It should be noted that there is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D. These recommendations will be re-evaluated as additional data become available

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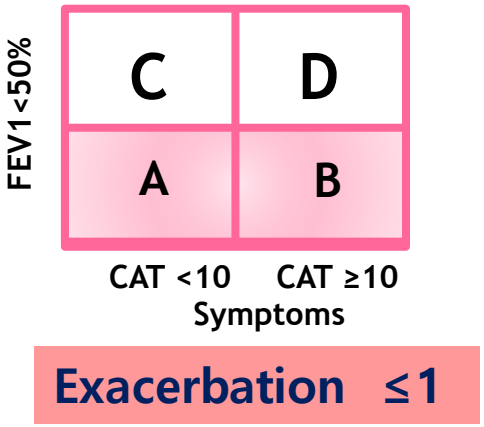
OPTIMO: Withdrawal of ICS in COPD Patients at Low Risk of Exacerbation

- Multicenter, real-life study
- 914 COPD patients recruited
  - On maintenance therapy with bronchodilators and ICS
  - **FEV_1 > 50% predicted**
  - **< 2 exacerbations/year**
- Outcomes (baseline and 6 months)
  - FEV_1
  - CAT score (symptoms)
  - Exacerbations



Rossi A, et al. *Respir Res*. 2014;15:77.

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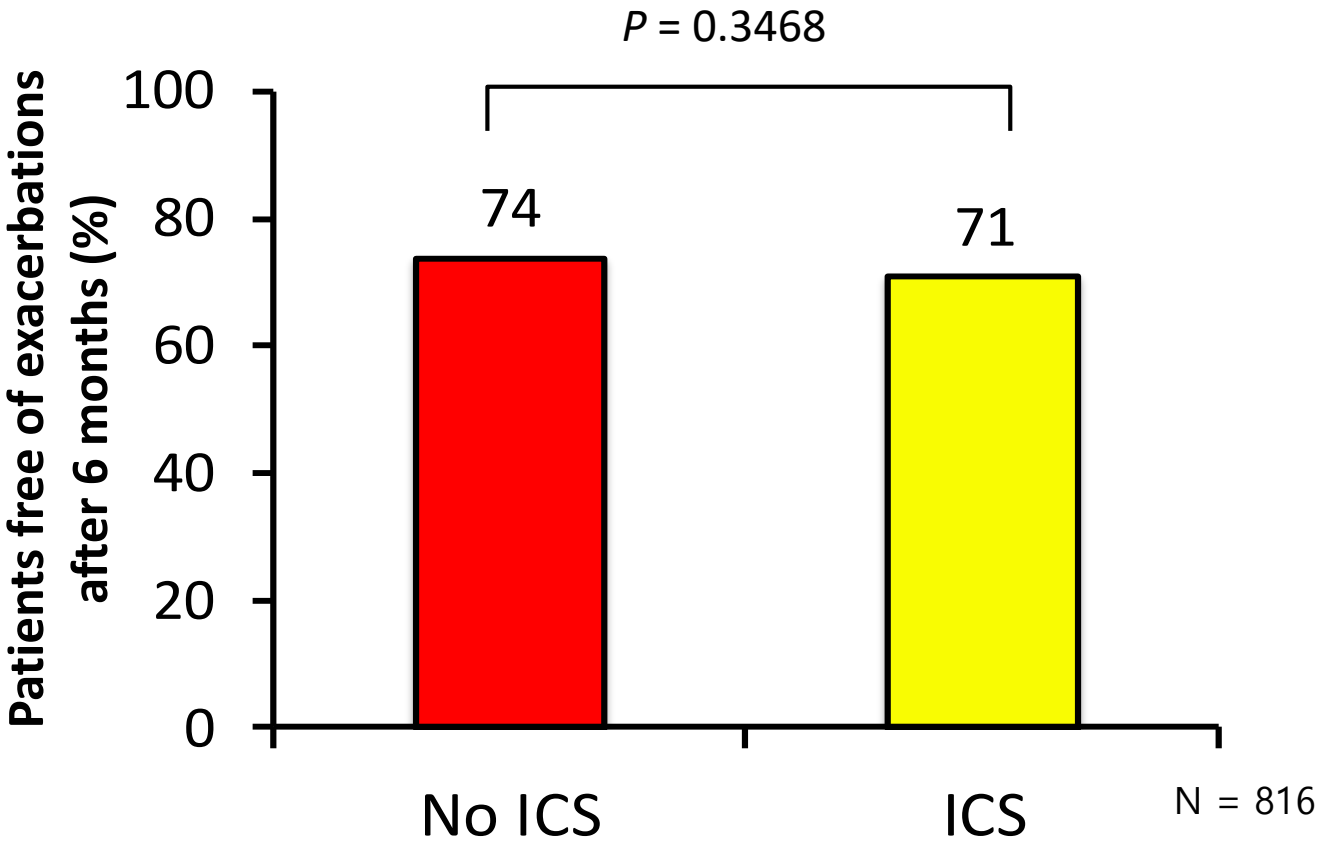
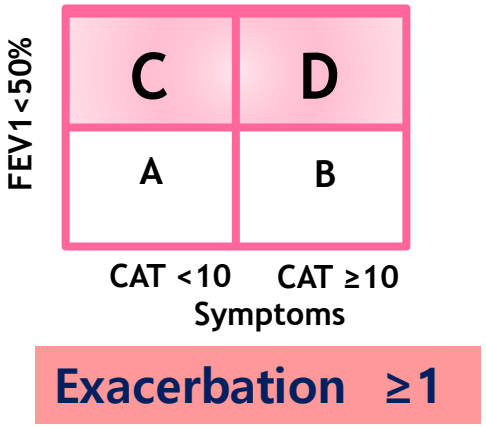


Rossi A, et al. *Respir Res*. 2014;15:77.

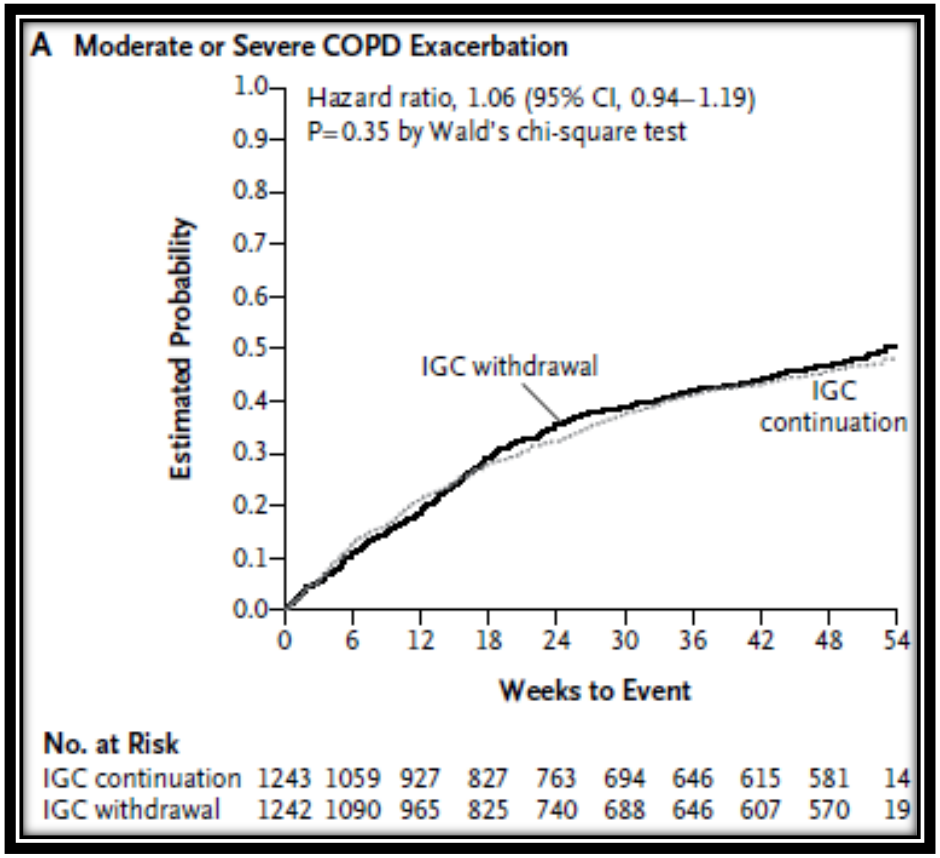
WISDOM: Withdrawal of ICS in Patients on Maintenance Therapy with LABA/LAMA

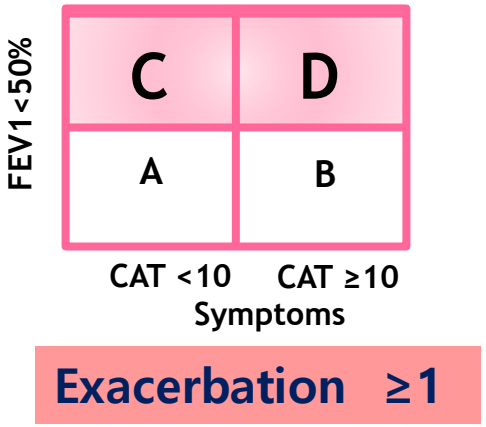
- 12-month, double-blind, parallel group study
- 2485 patients randomized
  - **FEV1 ≤ 50%**
  - **Exacerbation ≥ 1**
- Outcomes (baseline and 6 months)
  - Time to first moderate or severe COPD exacerbation
  - Change from baseline in lung function
  - Health status
  - Dyspnea



NEJM 2014;371:1285-94

WISDOM: Withdrawal of ICS in Patients on Maintenance Therapy with LABA/LAMA





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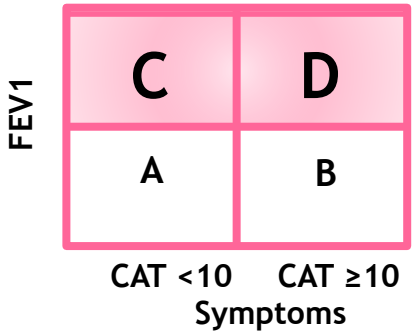
WISDOM



6wks Run-in Period
All participants received Triple therapy

2488 GOLD C/D with ≥1 exacerbation

Over 60% : NOT on TRIPLE at baseline

riple
1243 (ITT)

52wks

Triple
1016 (PP)

ICS step down
2 (ITT)

52wks

ICS step down
1011 (PP)

NEJM 2014;371:1285-94

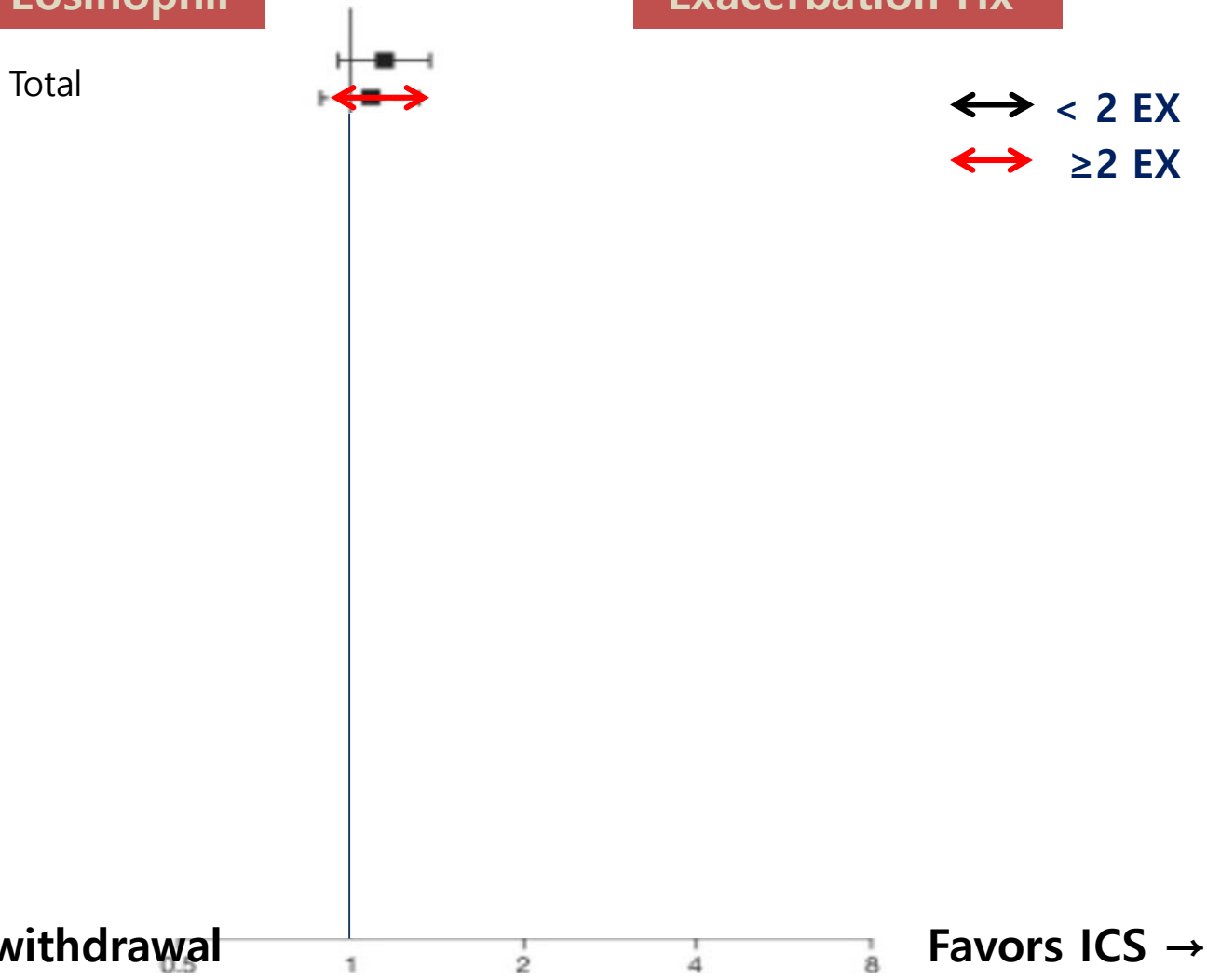
- **Frequent Exacerbation은 ICS 사용의 biomarker일 수 있을까?**

2016 ERS

WISDOM post hoc analysis

Blood Eosinophil

Exacerbation Hx

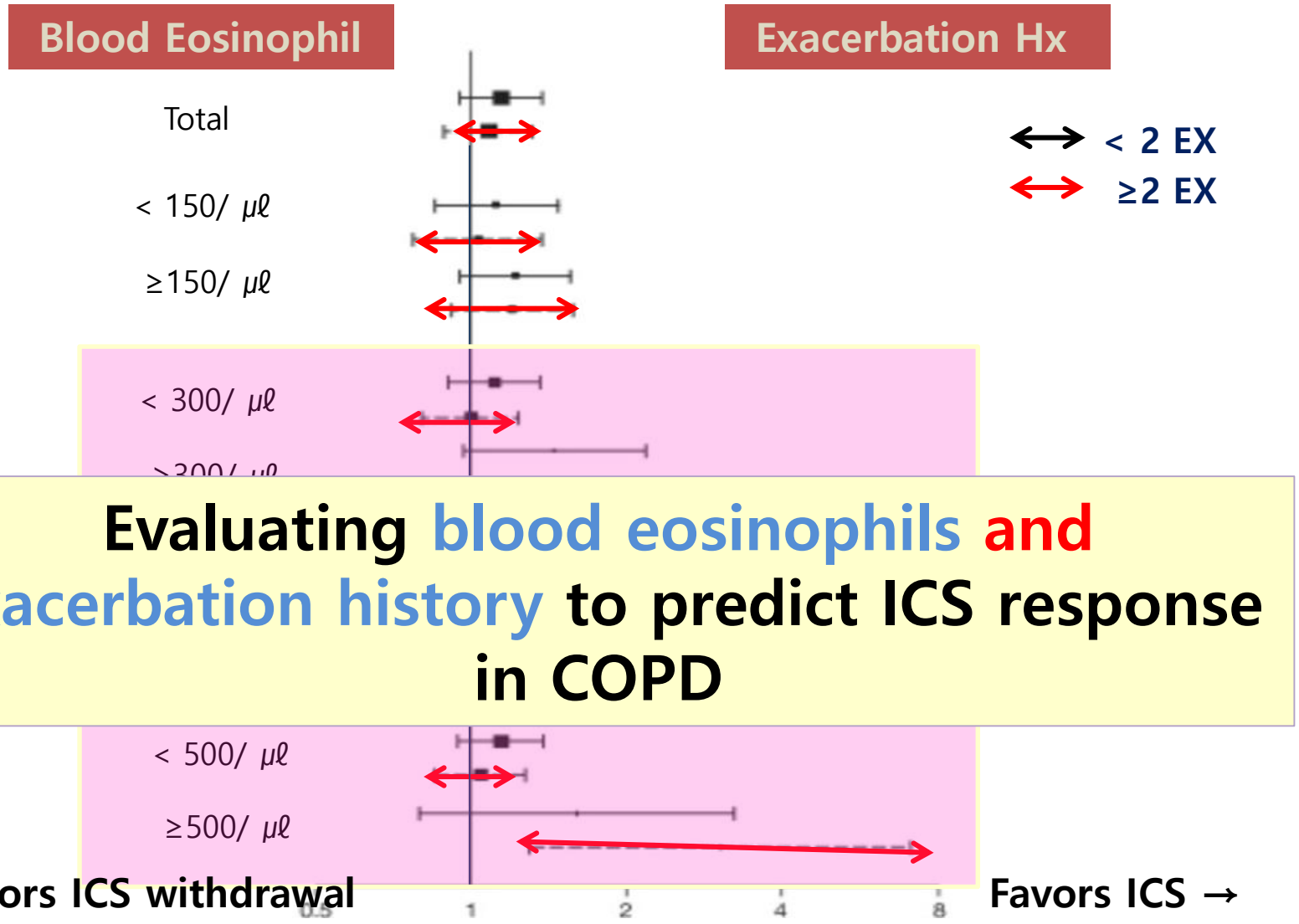


← Favors ICS withdrawal

Favors ICS →

2016 ERS

WISDOM post hoc analysis



Evaluating blood eosinophils and exacerbation history to predict ICS response in COPD

← Favors ICS withdrawal

Favors ICS →

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  -- Eosinophil count가 높고

  과거 악화 병력이 2회 이상은 ICS 고려

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COPD exacerbation & inhaler device handling: Real-life assessment

ORIGINAL ARTICLE
COPD

Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients

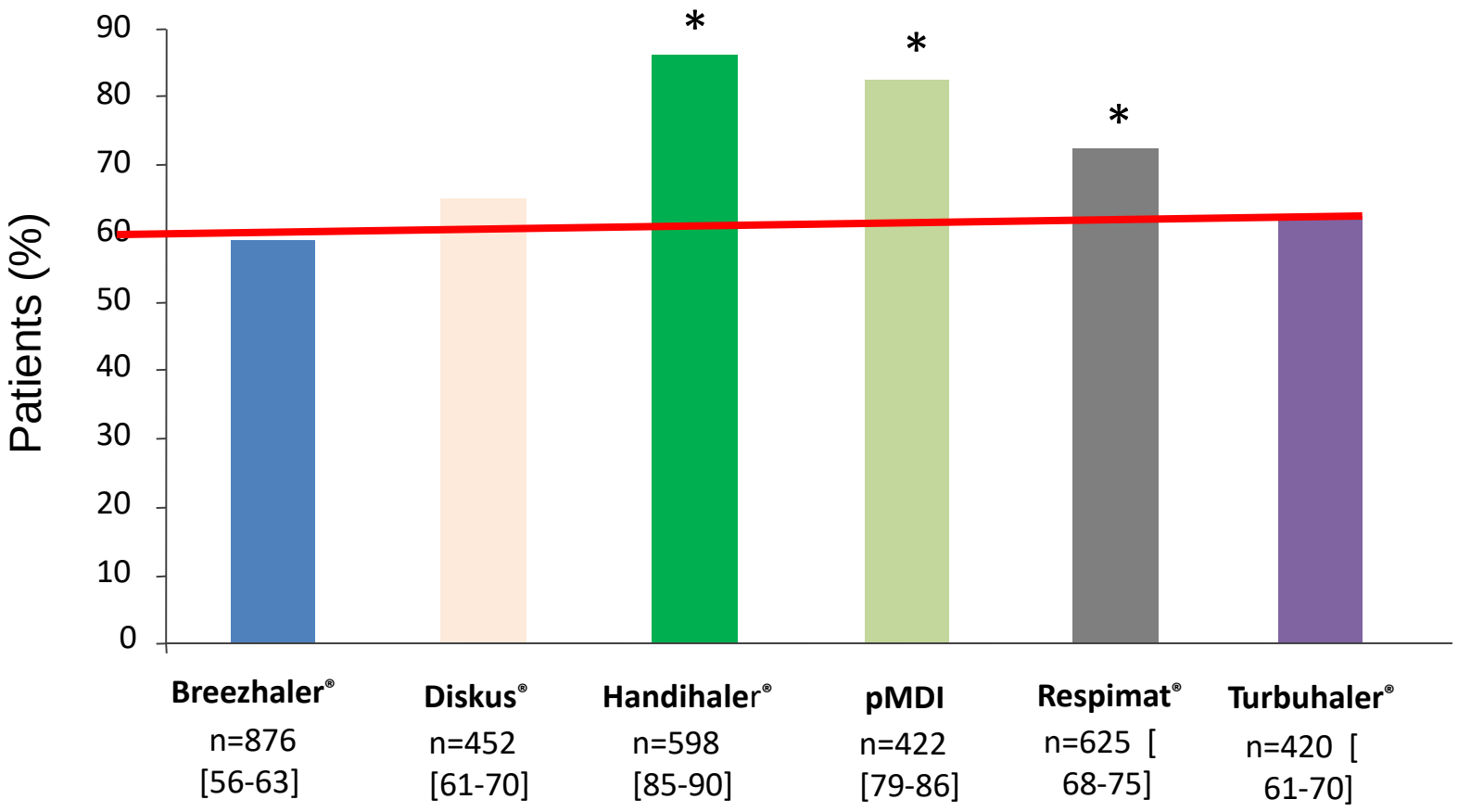
Mathieu Molimard[1,2], Chantal Raherison[2,3], Severine Lignot[1,4,5], Aurelie Balestra[1,4,5], Stephanie Lamarque[1,4,5], Anais Chartier[1,4,5], Cecile Droz-Perroteau[1,4,5], Regis Lassalle[1,4,5], Nicholas Moore[1,2,4] and Pierre-Olivier Girodet[1,4]

Affiliations: [1]Dépt de Pharmacologie, University Bordeaux, Bordeaux, France. [2]INSERM U1219, Bordeaux, France. [3]Service des Maladies Respiratoires, Hôpital du Haut Lévèque, Pessac, France. [4]Bordeaux PharmacoEpi, INSERM CIC Bordeaux CIC1401, Bordeaux, France. [5]ADERA, Pessac, France.

Correspondence: M. Molimard, Dépt de Pharmacologie, CHU Pellegrin Carreire, 33076 Bordeaux cedex, France. E-mail: mathieu.molimard@u-bordeaux.fr

Molimard et al., Eur Respir J 2017; 49: 1601794

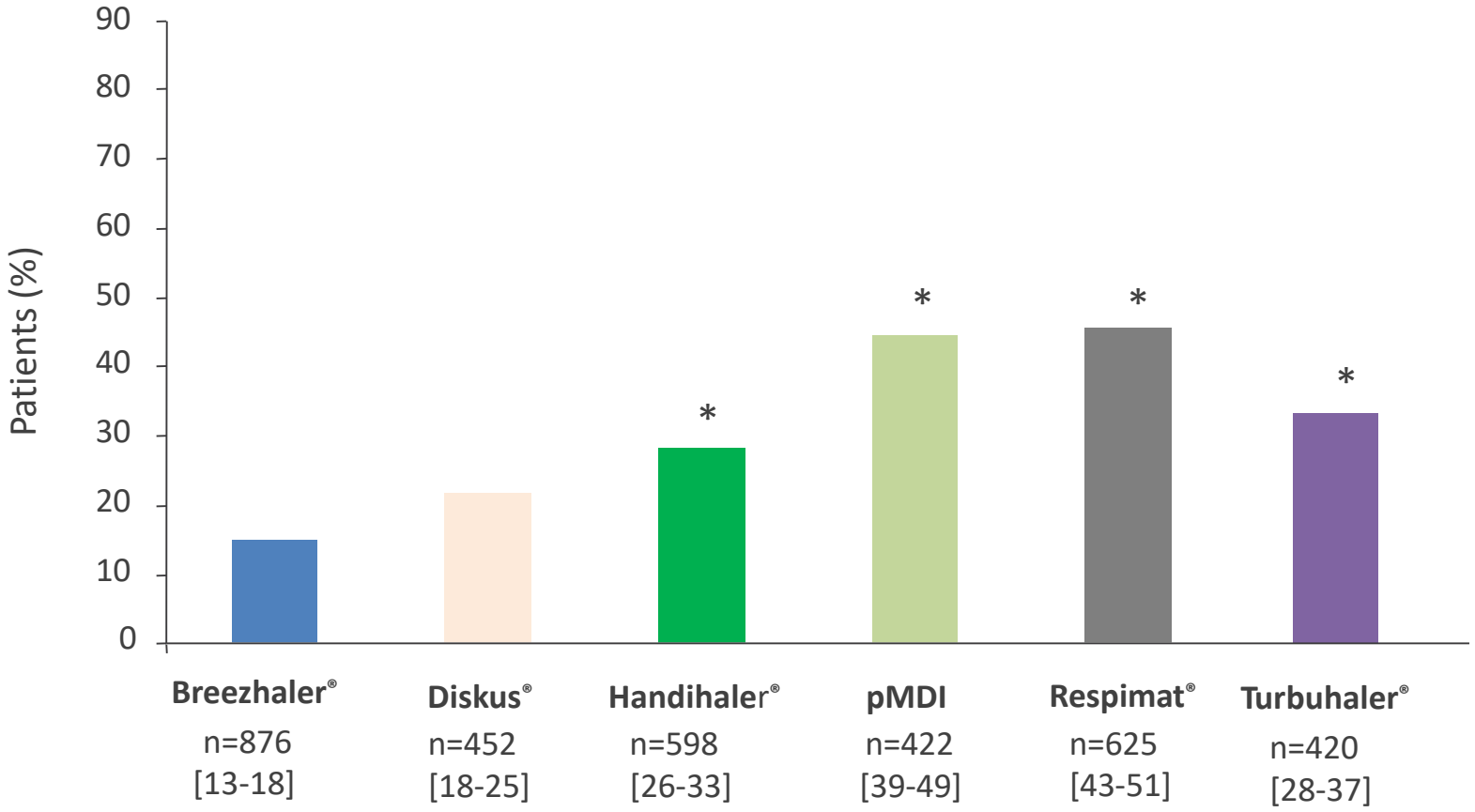
At Least One Error



* no overlap of [95% CI] with the best result

Molimard et al., Eur Respir J 2017; 49: 1601794

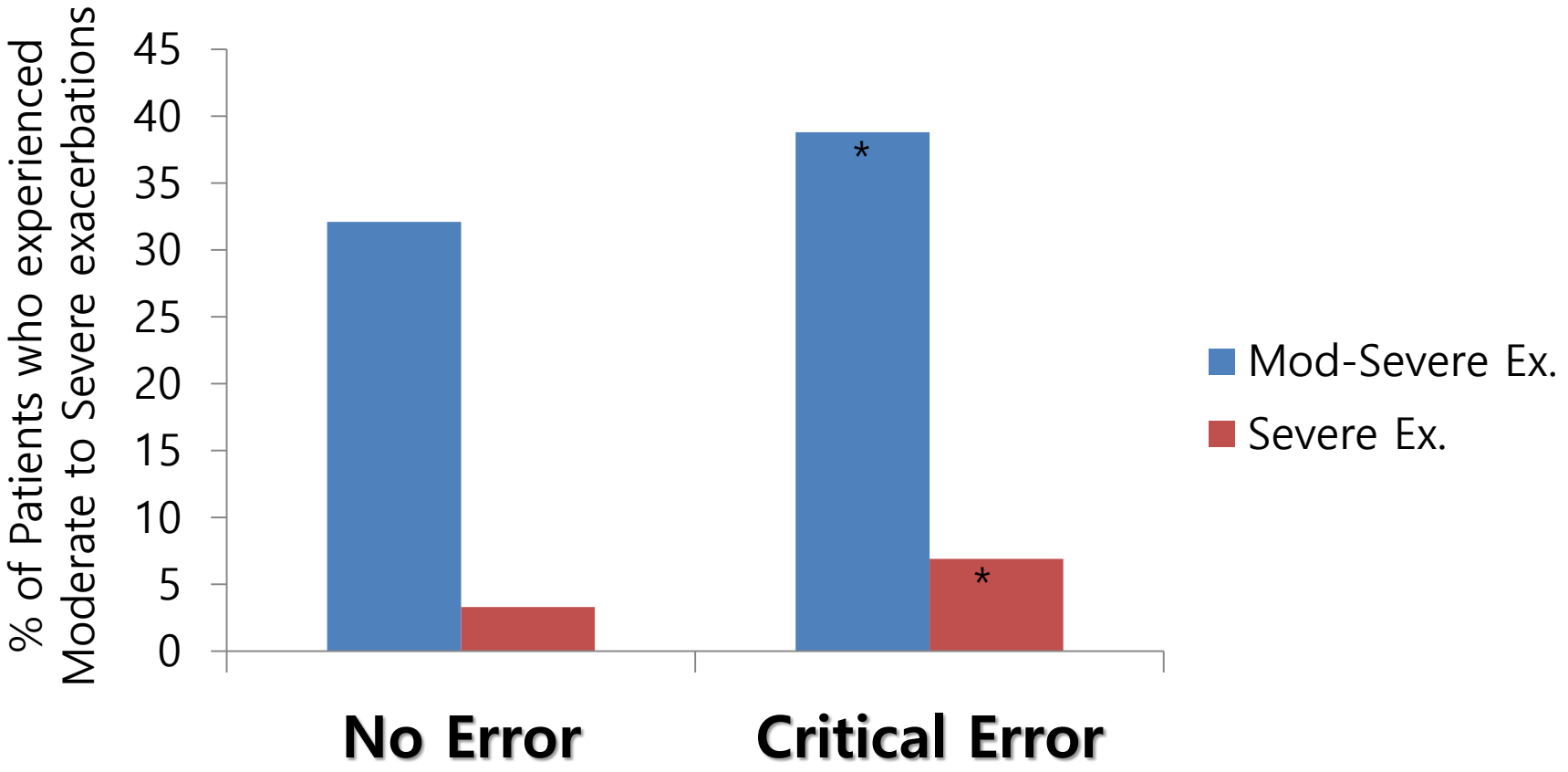
At least One Critical Error



* no overlap of [95% CI] with the best result

Molimard et al., Eur Respir J 2017; 49: 1601794

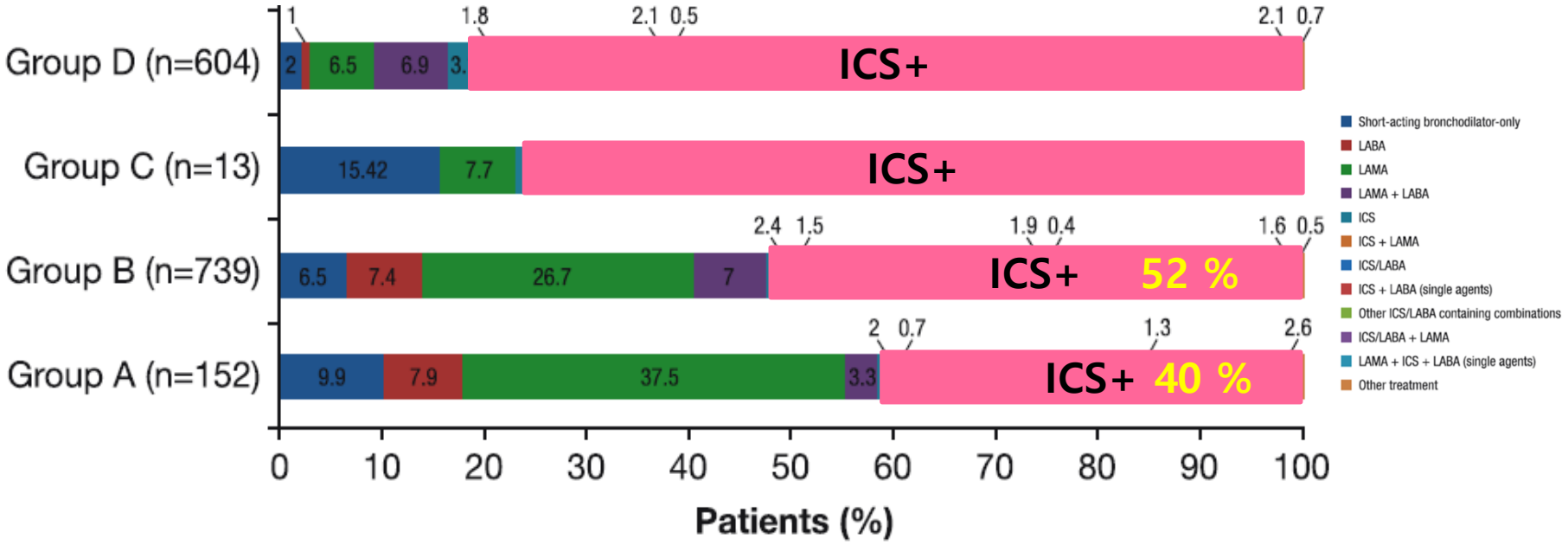
Inhaler Handling Error and Moderate to Severe Exacerbation



* p<0.05, compared with no error

Molimard et al., Eur Respir J 2017; 49: 1601794

Real World Treatment according to GOLD 2011



Resp Med 2014;108:729~736

Conclusion

- 기관지확장제 병합치료는 COPD 의 병인과 일치하는 치료로서 증상 호전, 삶의 질 호전, 악화 예방 효과가 있다.
- 흡입 스테로이드는 여전히 COPD 환자, 특히 ACOS 환자나 악화가 잦은 환자 중 steroid 반응군에게 유효하지만 부작용을 고려하여 적응이 되는 환자에게 투약하는 것이 좋겠다.
- 흡입스테로이드에 반응하는 환자를 쉽게 찾을 수 있는 biomarker 에 대한 연구가 요구된다.
- 흡입기를 제대로 잘 사용하는 것이 더욱 중요하다.