Importance of Maximal Bronchodilation from the start

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박 혜 윤

Contents

For lung function improvement

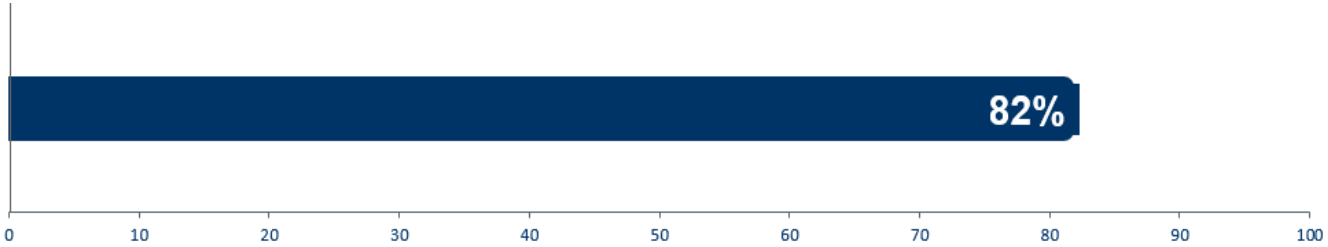
For Maintenance-naïve patients

LAMA/LABA >> LAMA or LABA

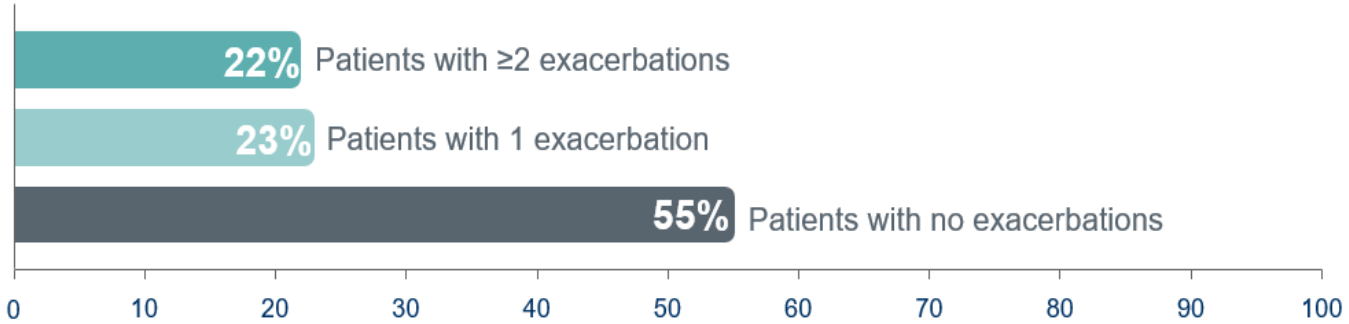
호흡곤란/악화

Dyspnea is a common experience in COPD patients whereas exacerbation rate may vary

Proportion of patients with any MRC dyspnoea grade recorded (N=40,425)[1]

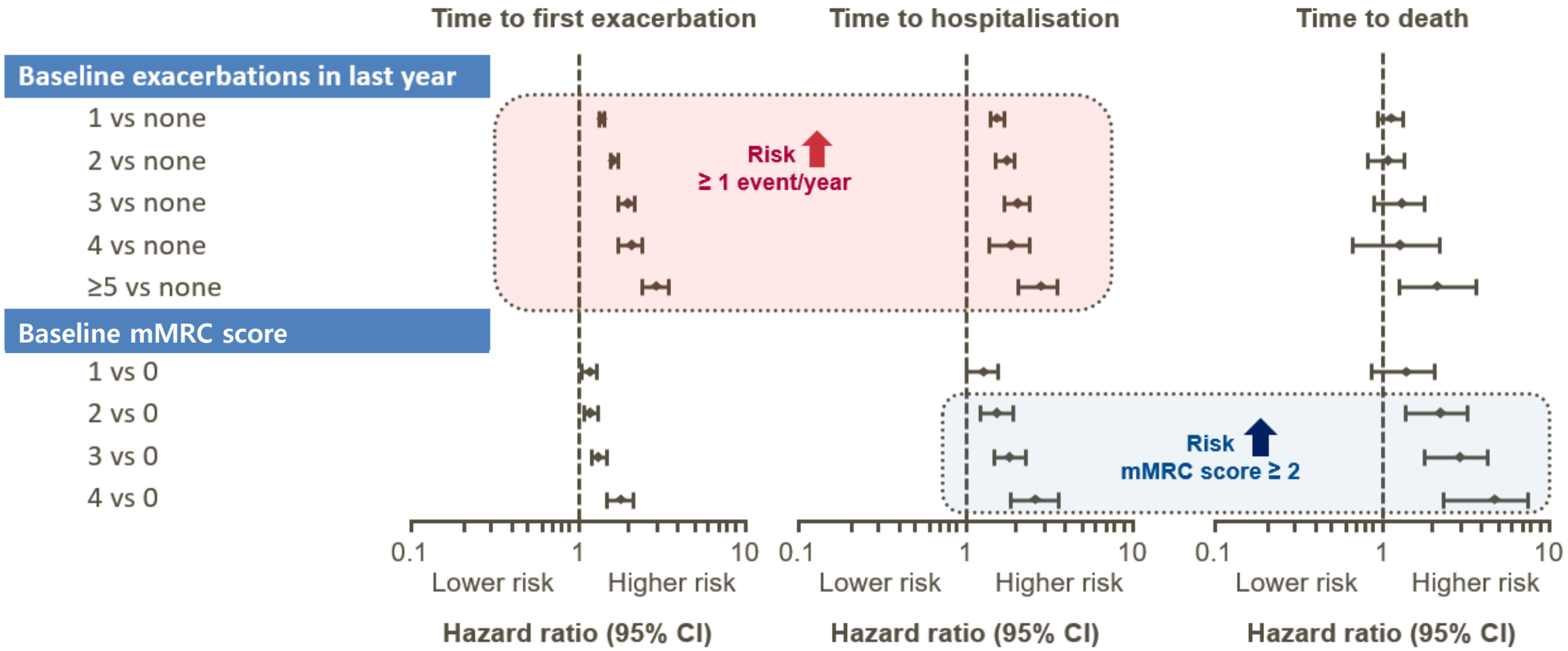


1-year exacerbation rates in GOLD stage 2 patients (N=945)[2]



1. Müllerová H, et al. PLoS One 2014; 9: e85540; 2. Hurst JR, et al. N Engl J Med 2010; 363: 1128–1138

향후 COPD 결과



Calverley PMA, et al. Int J Chron Obstruct Pulmon Dis. 2017;12:3391–3405.

COPD 치료 목표

증상 완화

- 증상 완화
- 운동 능력 향상
- 삶의 질 향상

위험 감소

- 질병 진행 예방
- 급성 악화 치료 및 감소
- 사망률 감소

Bronchodilator

LABA or LAMA vs. LABA/LAMA

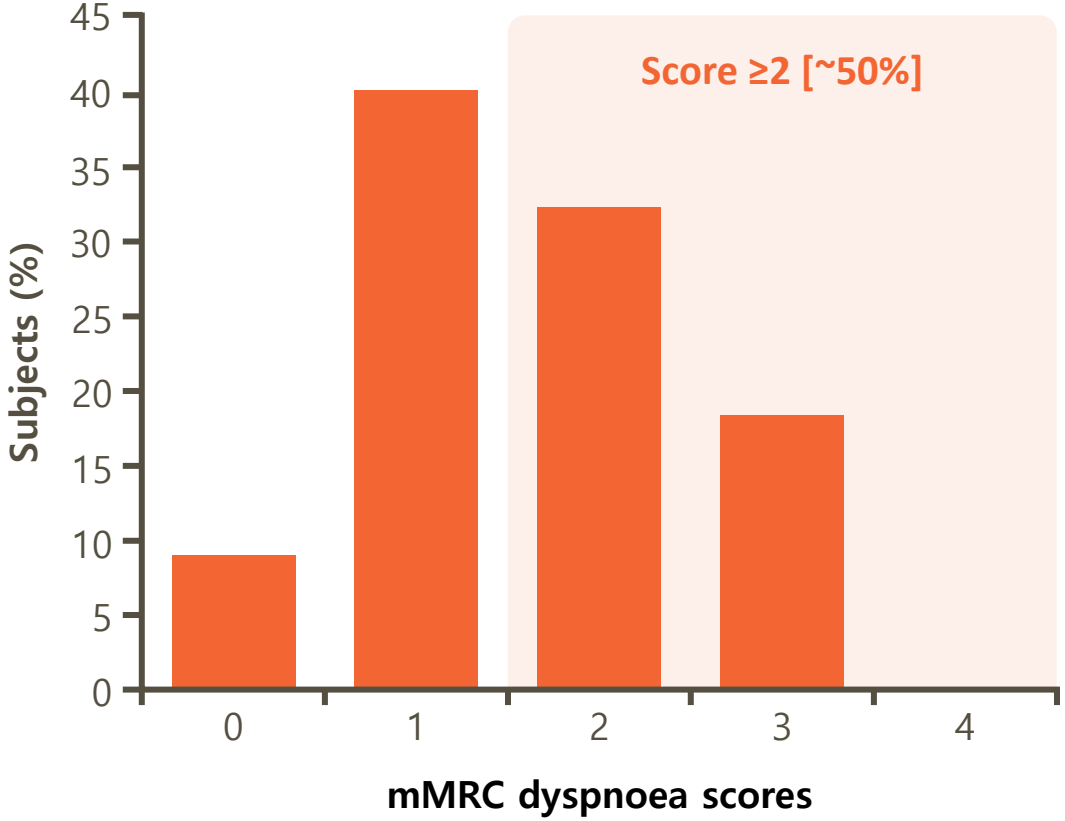
LAMA or LABA

Genuair | Breezhaler | Respimat | Ellipta

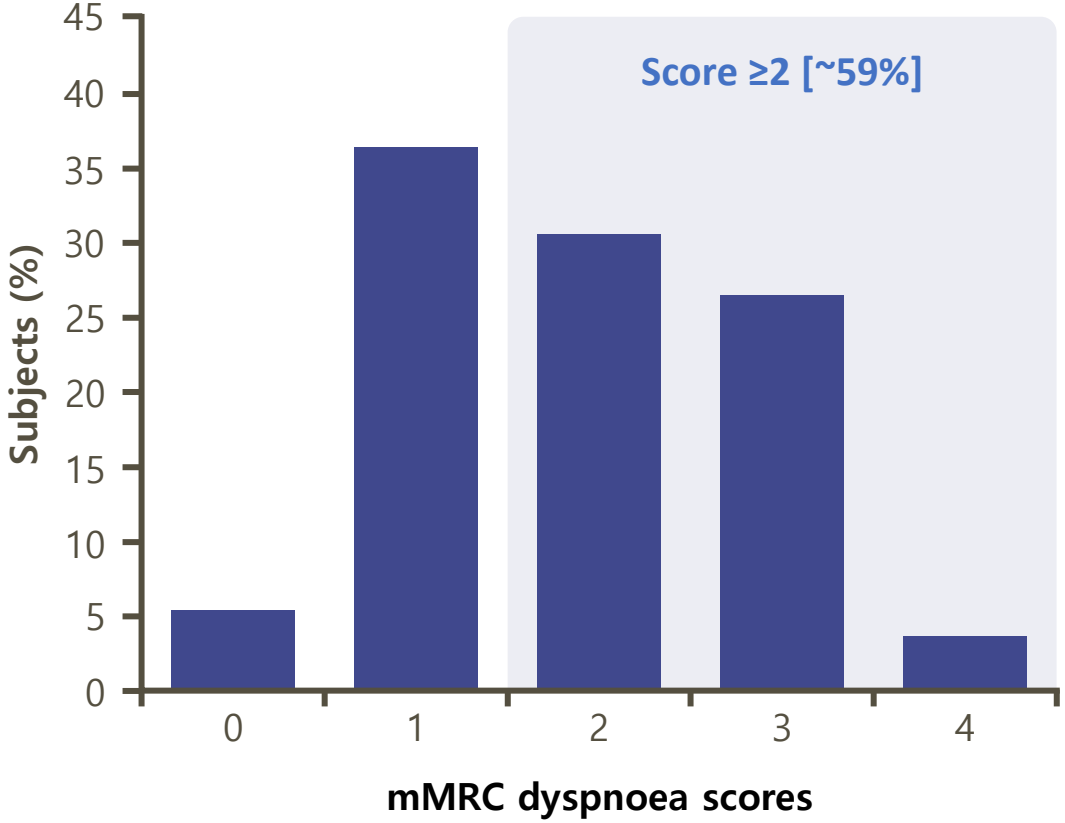
LAMA & LABA

A high symptom burden persists in most patients when using a mono-bronchodilator

Mild/moderate COPD patients (n = 454)*

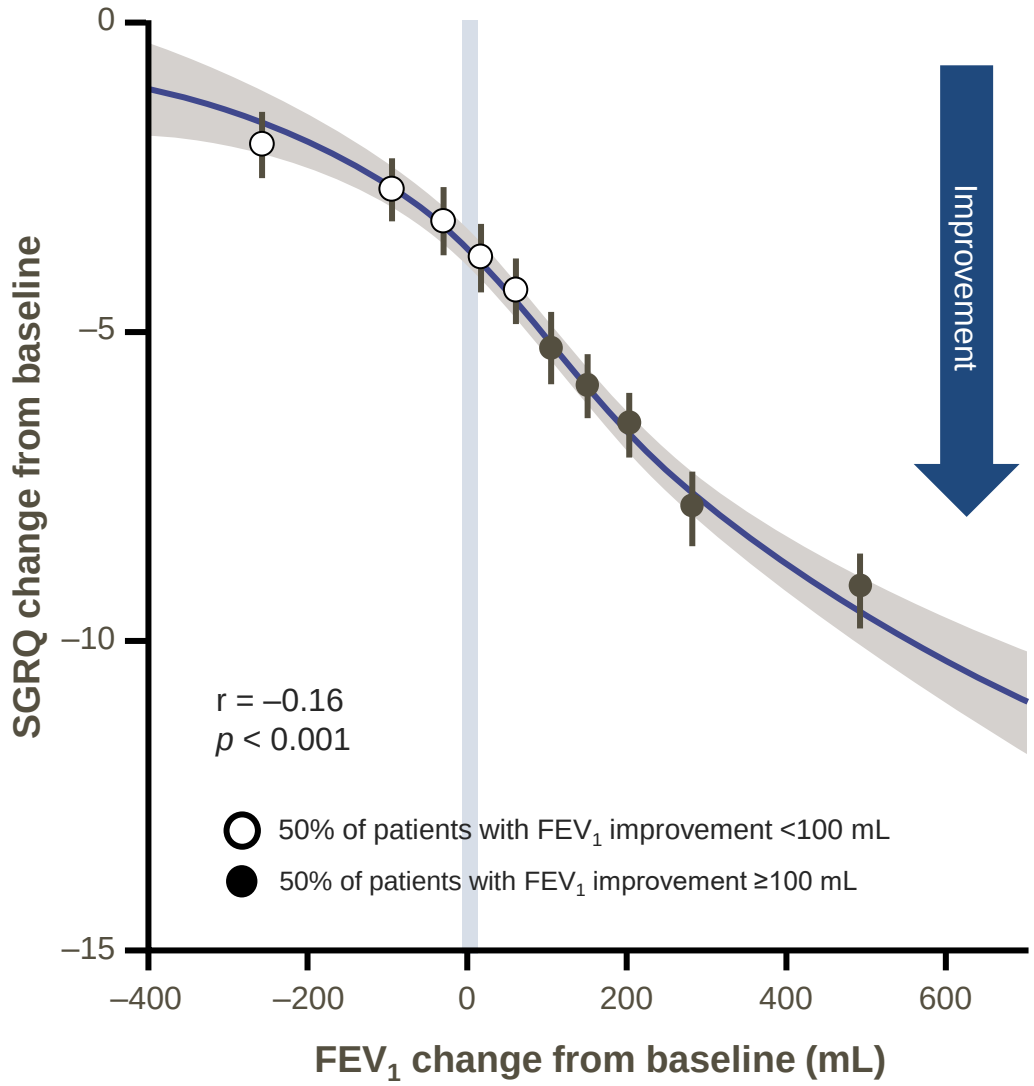


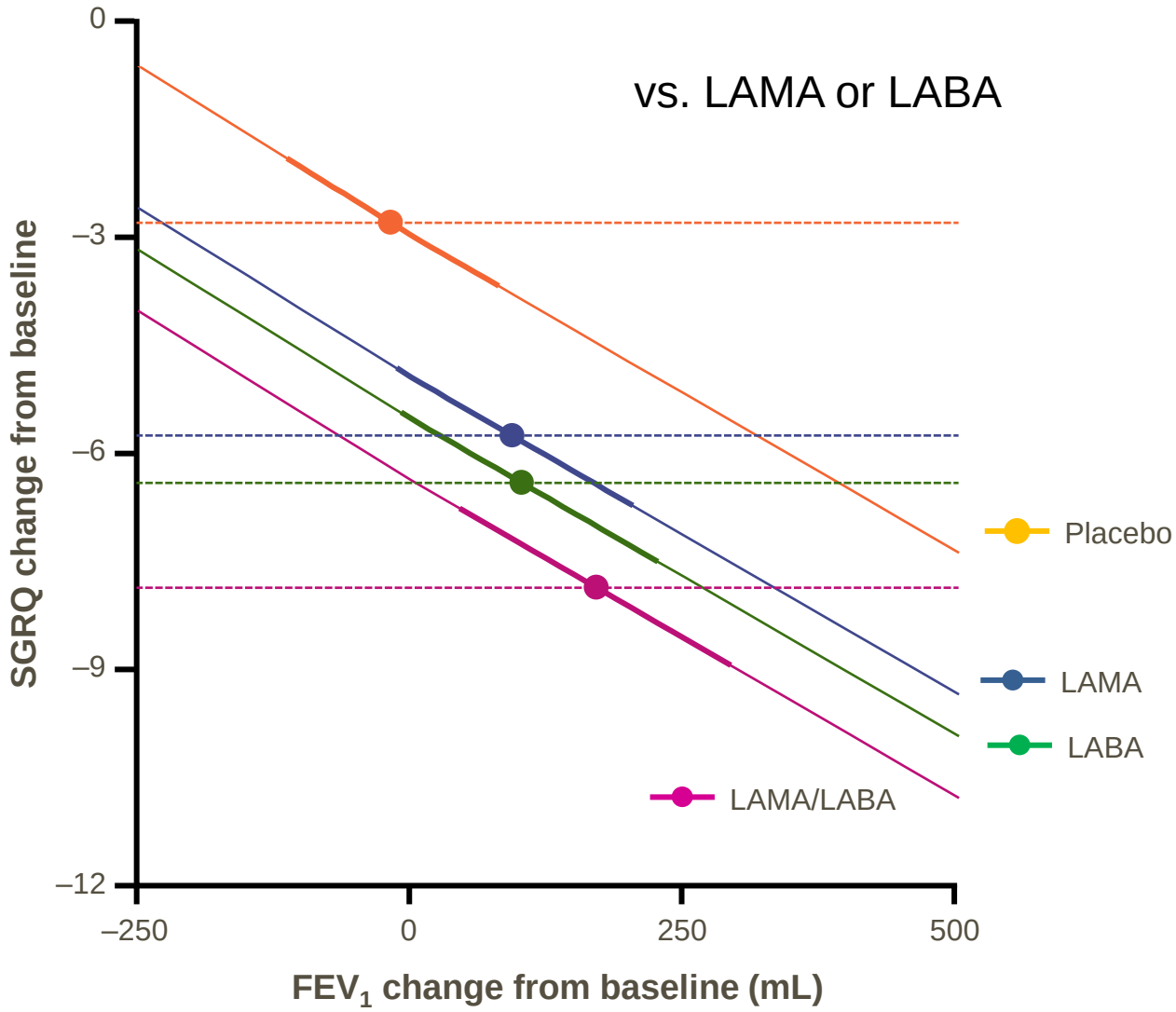
Severe/very severe COPD patients (n = 235)*



Dransfield MT, et al. Prim Care Respir J. 2011;20:46-53.

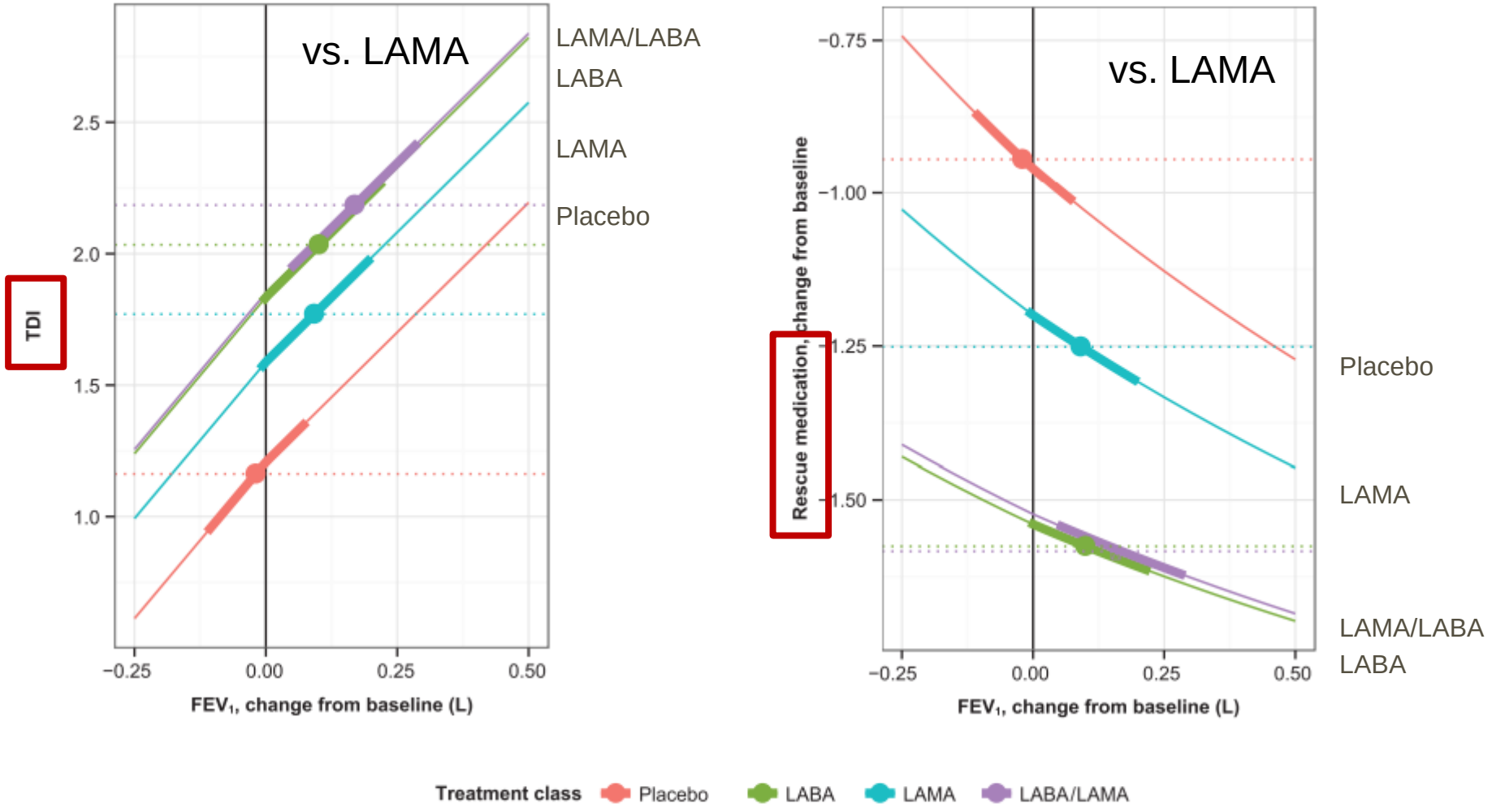
Correlations between FEV_1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with COPD





Donohue JF, et al. Pulm Pharmacol Ther. 2018

Correlations between FEV_1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with COPD

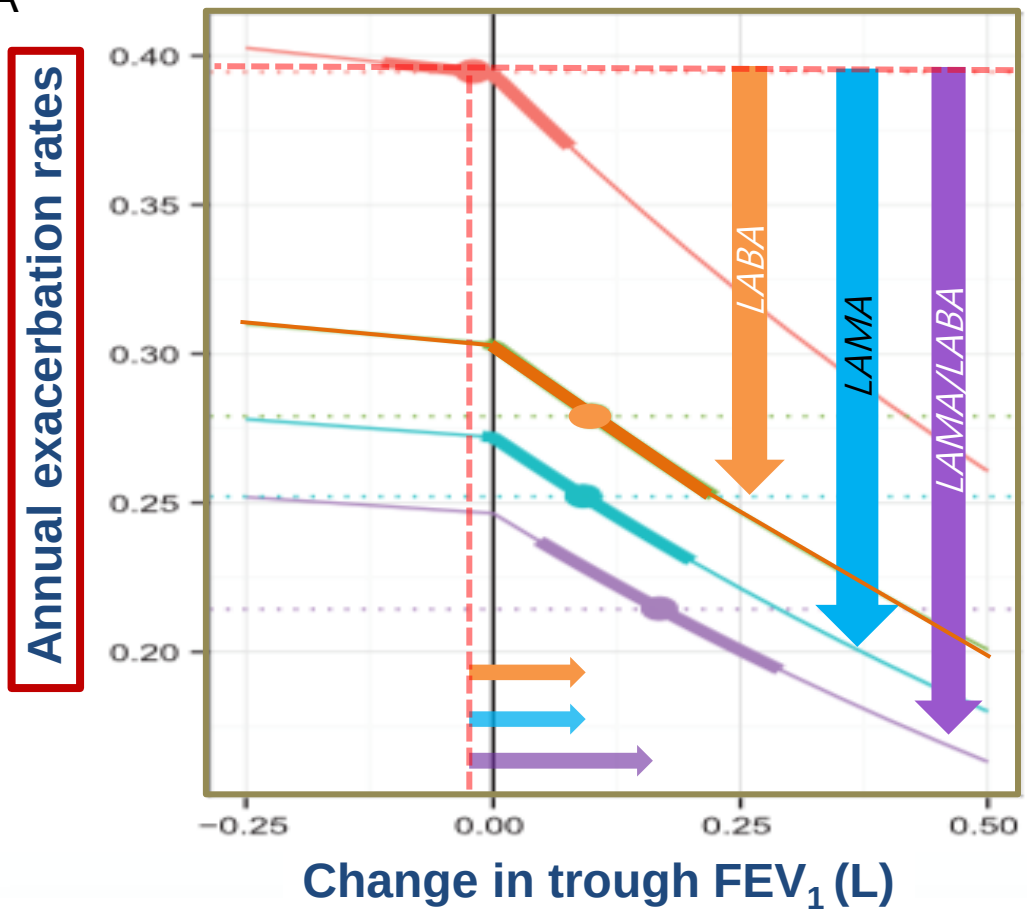


Donohue JF, et al. Pulm Pharmacol Ther. 2018

Correlations between FEV1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with COPD

vs. LABA

Annual exacerbation rates vs. change in trough FEV_1



Pooled analysis of 23 trials (6-64 weeks duration) with 23,213 patients on all long-acting bronchodilator types or placebo.

* Only 35% of patients in these studies had ≥1 exacerbation in the last year

- Placebo
- LABA
- LAMA
- LAMA/LABA

Donohue JF, et al. Pulm Pharmacol Ther. 2018

Adverse Events

Summary of effects of LAMA/LABA combinations versus LAMA, LABA and placebo on adverse events

	Mortality FE HR (95% CrI)	Total SAEs FE HR (95% CrI)	Cardiac SAEs RE HR (95% CrI)	Dropouts due to AE RE HR (95% CrI)
Number of studies	15	20	16	16
Number of patients	24,041	27,172	25,913	23,529
versus 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)
versus 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)
versus 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)

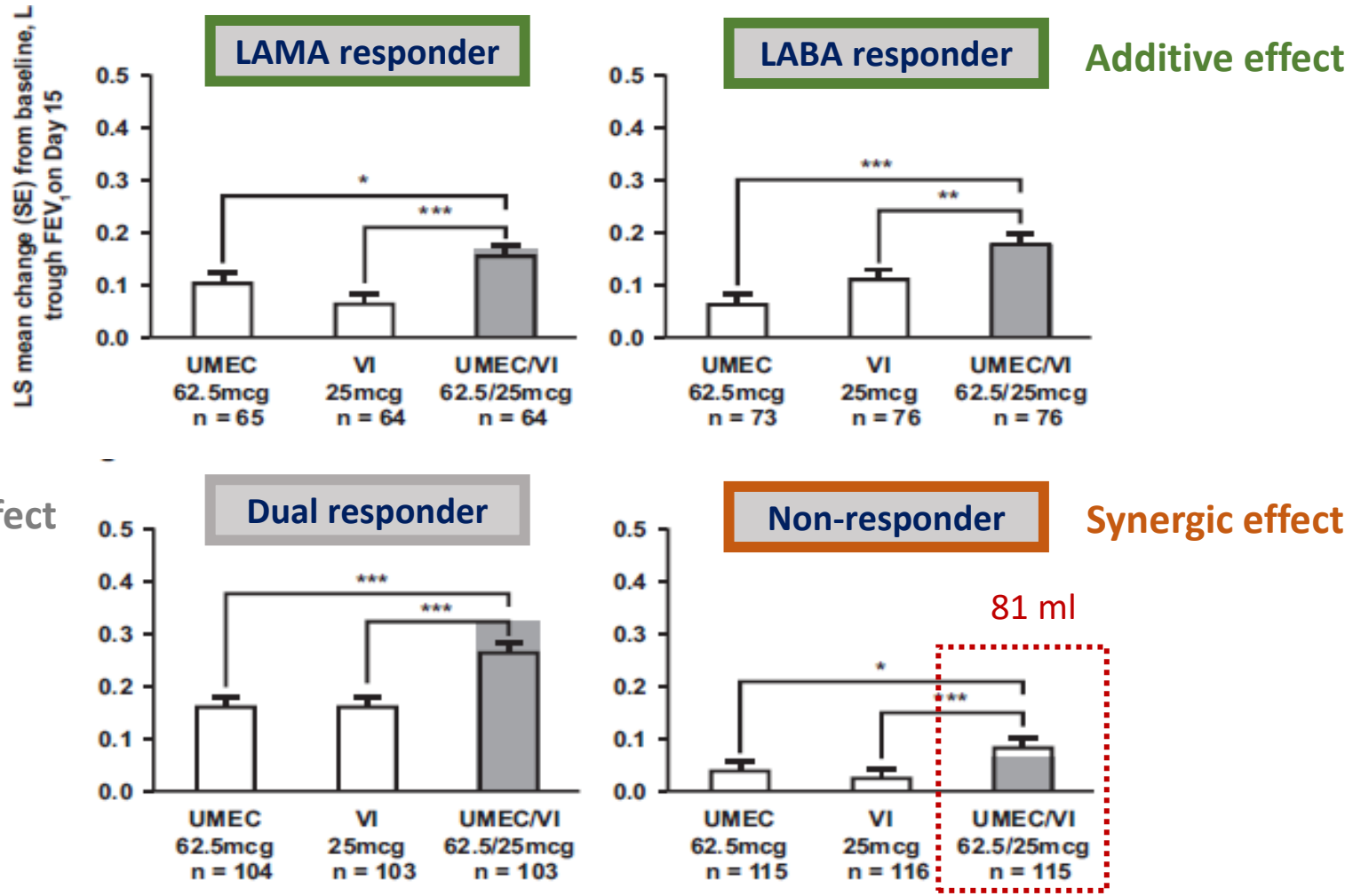
All hazard ratios with LAMA/LABA vs. LABA or a LAMA are equal to 1.00

FE fixed-effects

RE random-effects

Oba Y, et al. Thorax. 2016

Changes of trough FEV_1 on day 15

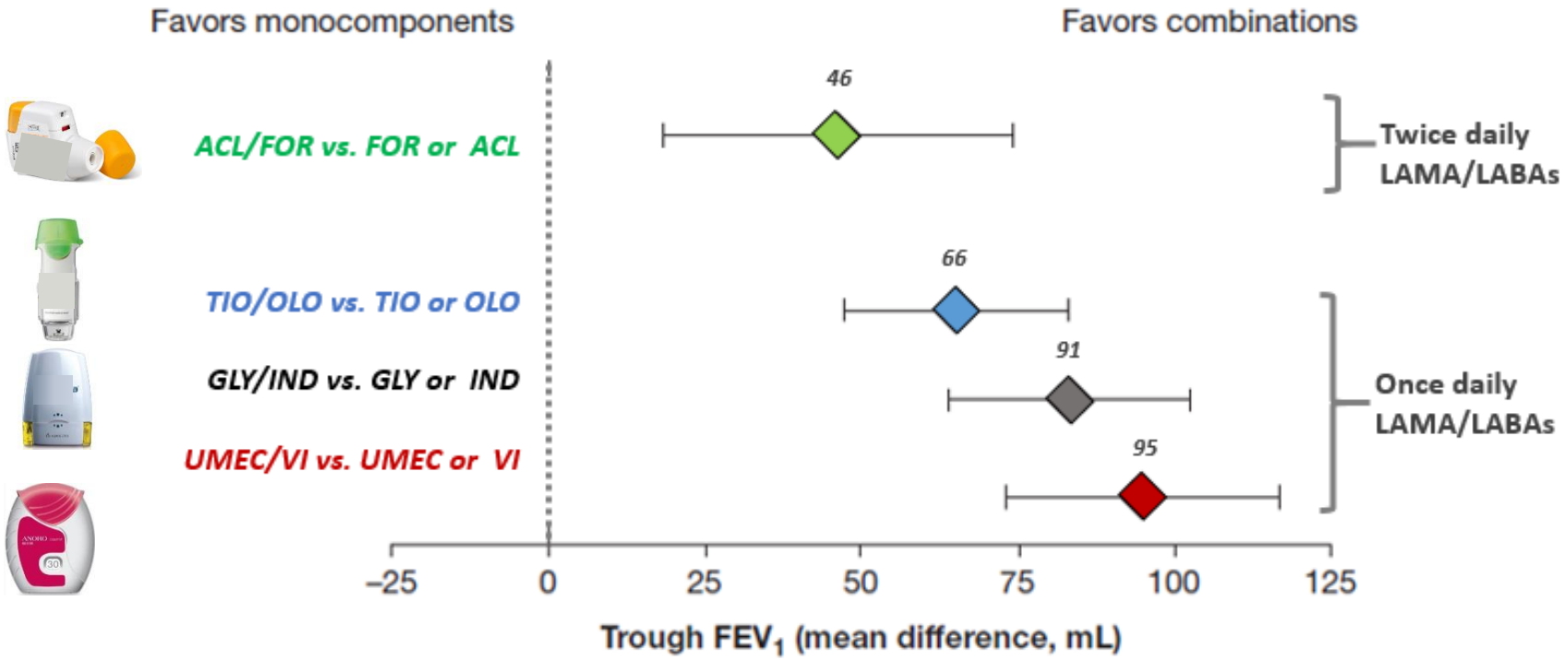


Grey bars: expected fully additive effect of both monotherapies

Donohue et al, Respir Med 2016:112:65

Efficacy (FEV_1) Gradient in LAMA/LABAs

A network meta-analysis (NMA); n=23,168; 15 RCTs ≥12 weeks in length: Endpoint Trough FEV_1

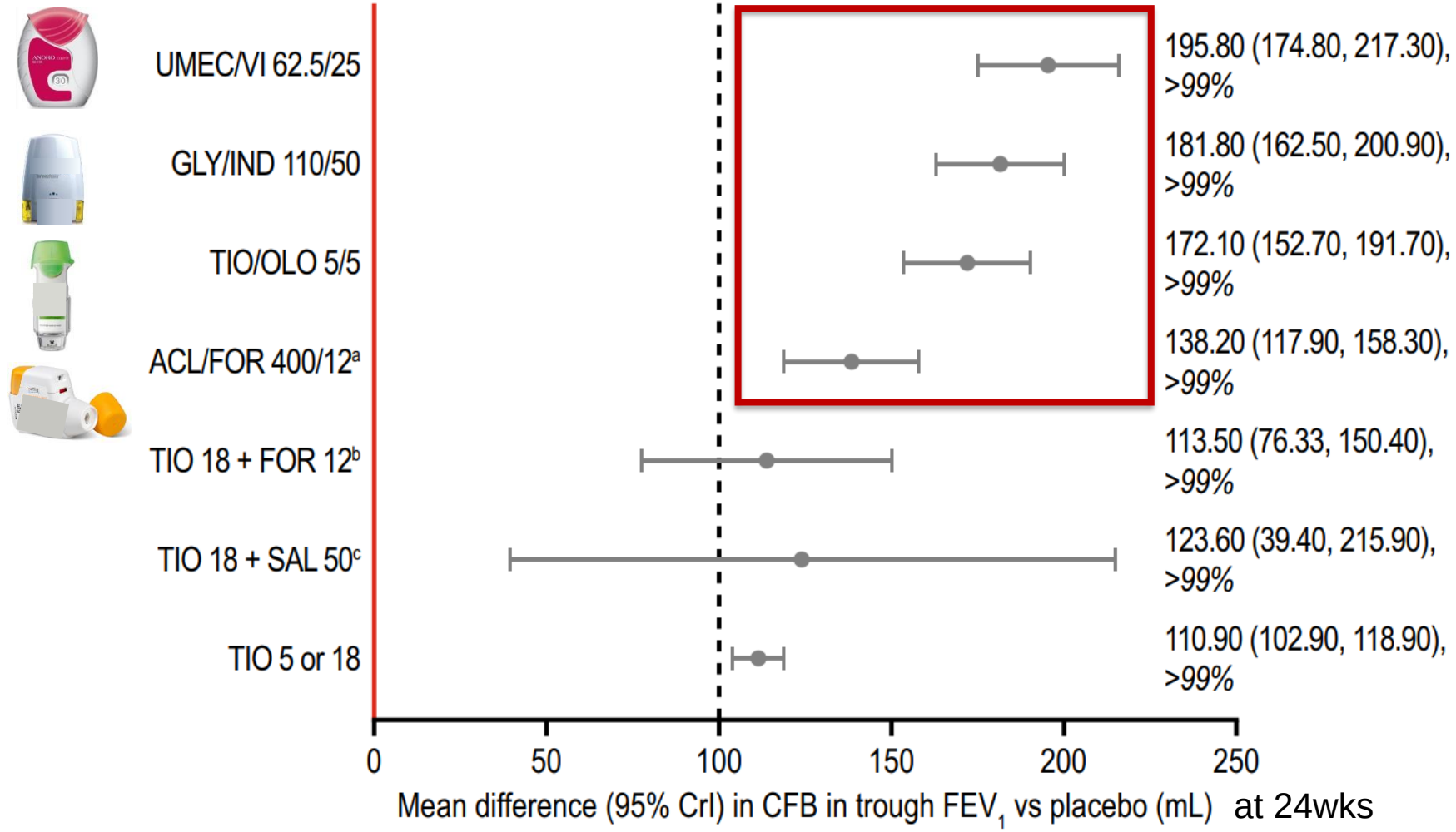


All LAMA/LABAs are superior to their LAMA and LABA components on average by 46 - 95 ml

Adapted from Calzetta L et al. Chest 2016:149 (5)

Efficacy (FEV_1) Gradient in LAMA/LABAs

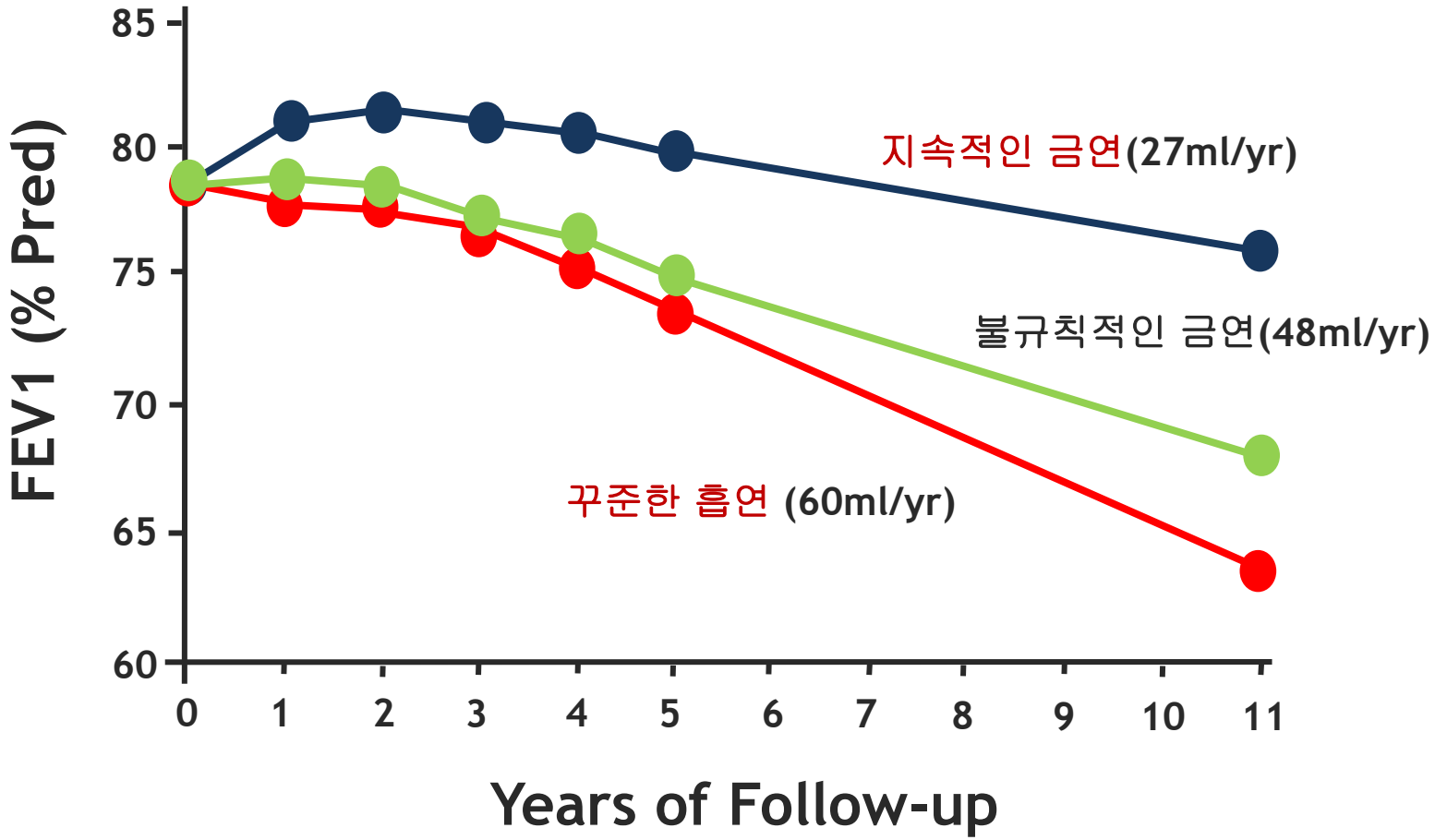
Data from 44 RCTs in network meta-analysis



Sion KYJ et al. Pul Ther, 2017

금연

흡연가



Anthonisen et al. AJRCCM 2002

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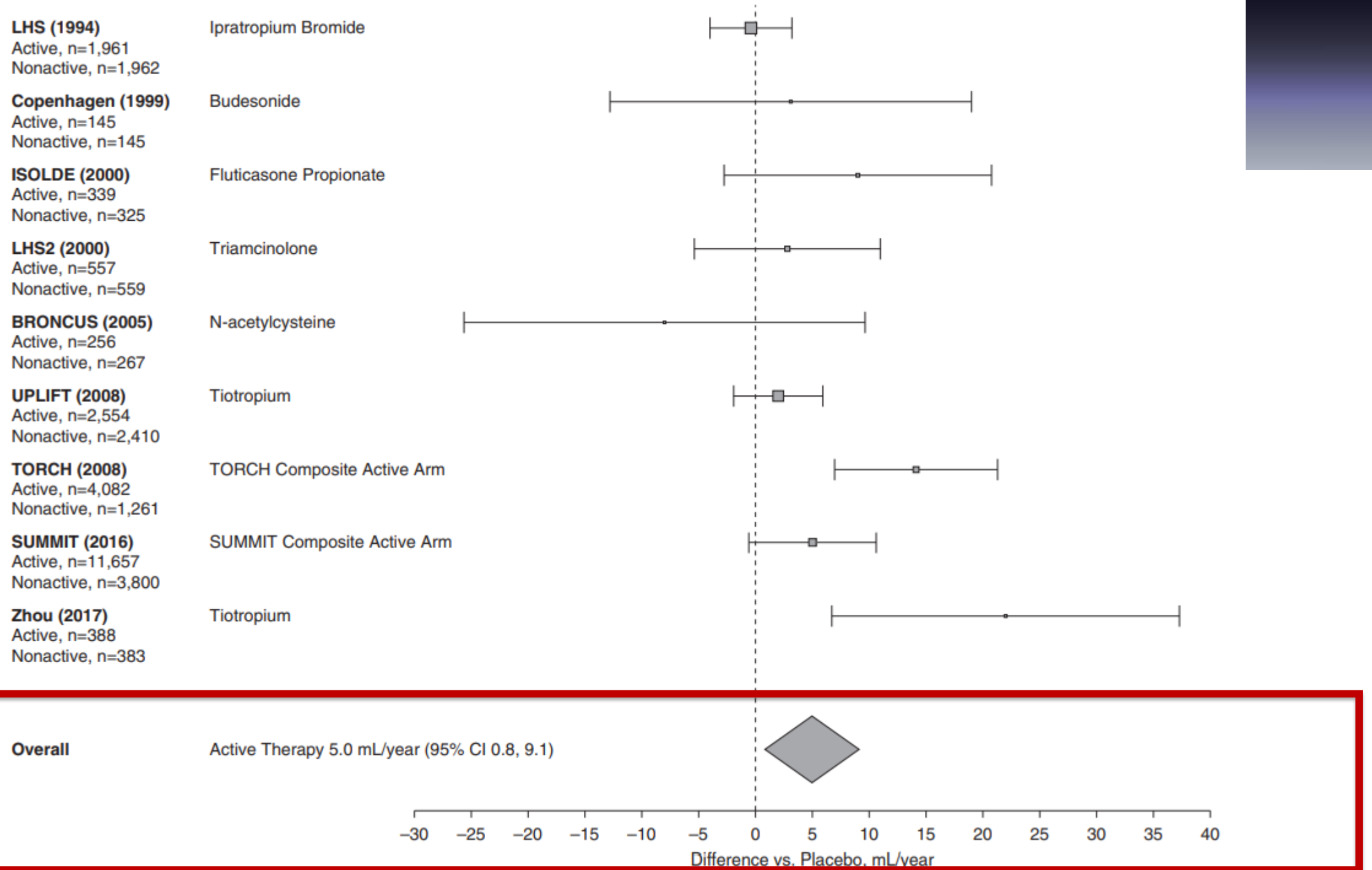
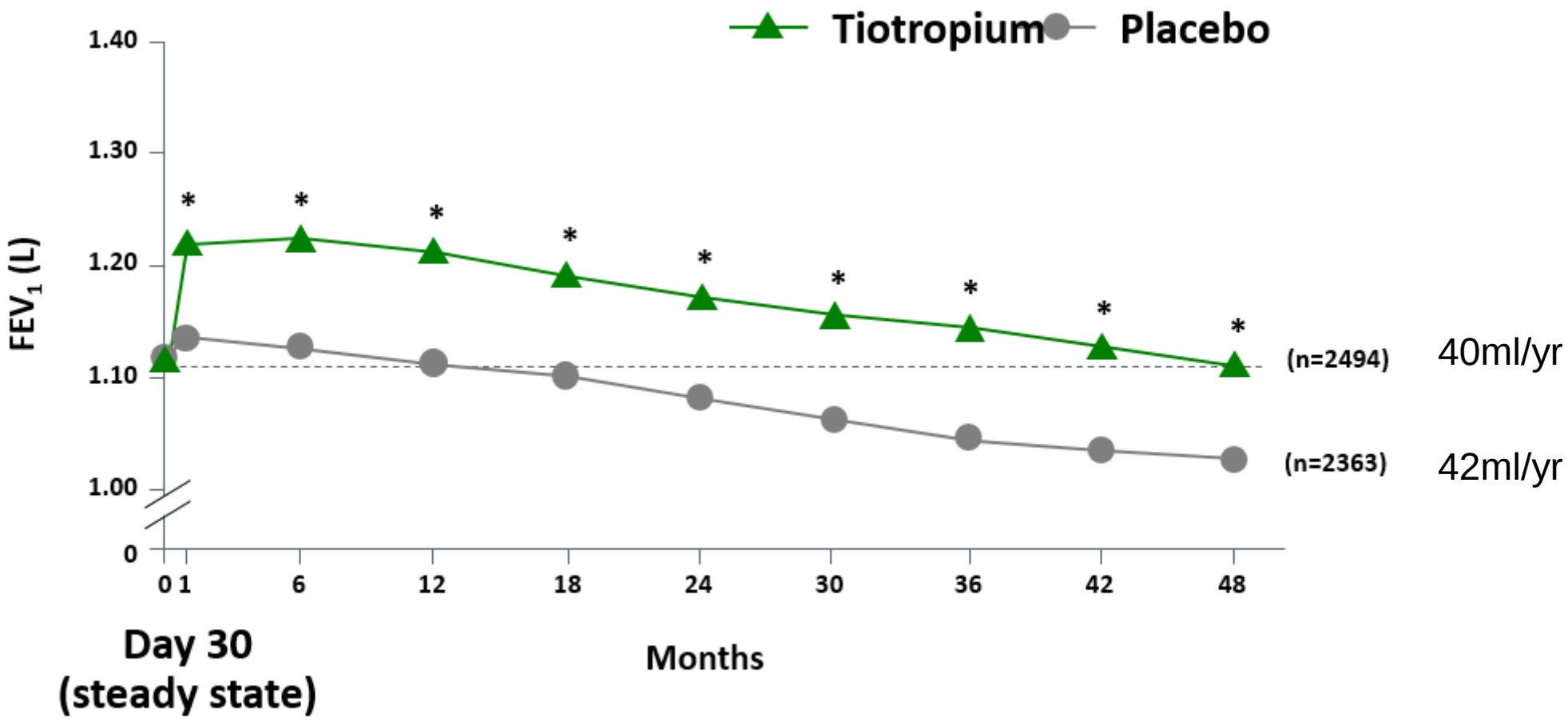


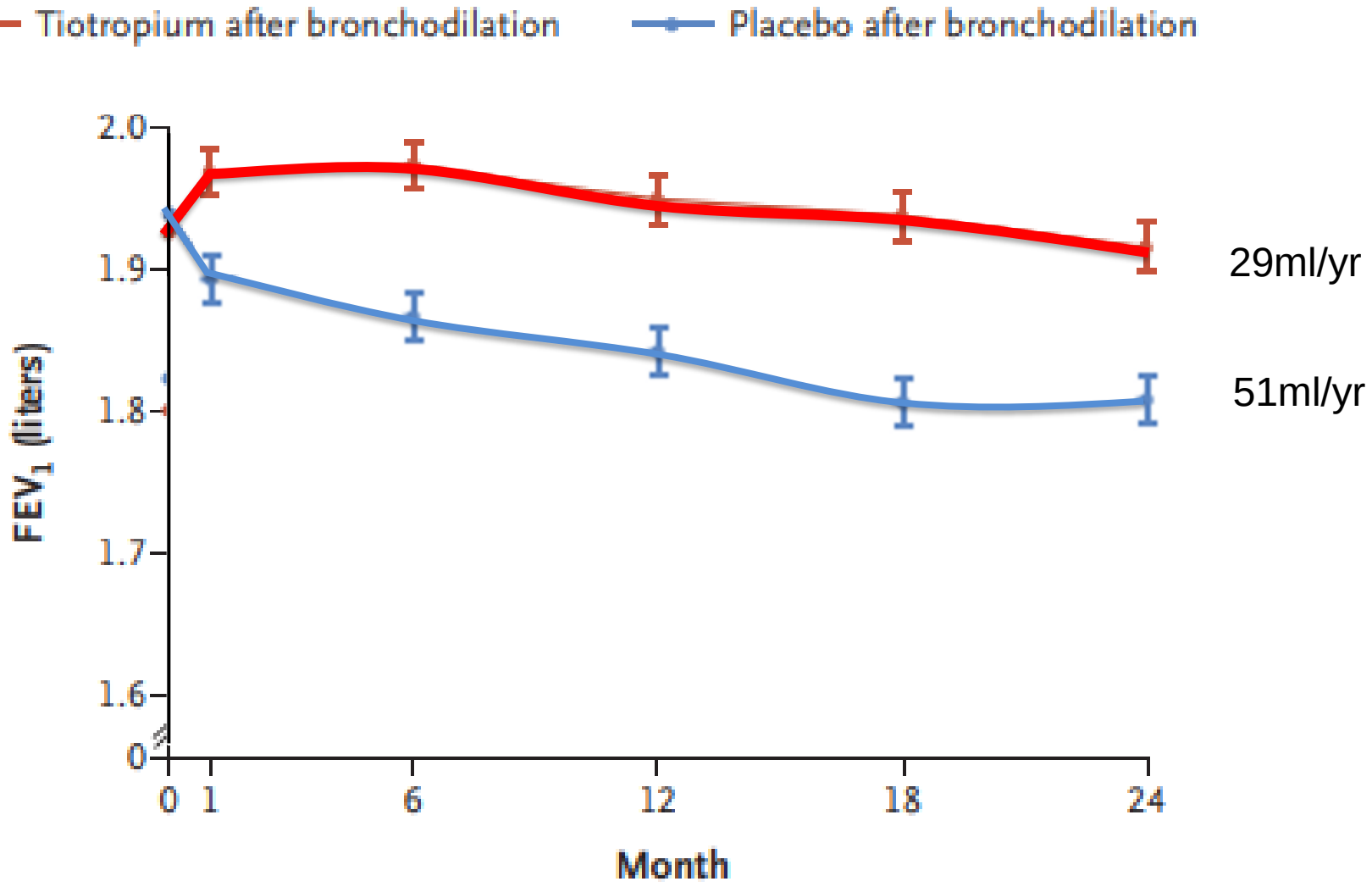
UPLIFT (FEV_1 of 70% less)

Tiotropium HandiHaler® significantly improved trough FEV_1 over 4 years



Tashkin DP et al. N Eng J Med. 2008;359:1543-1554.

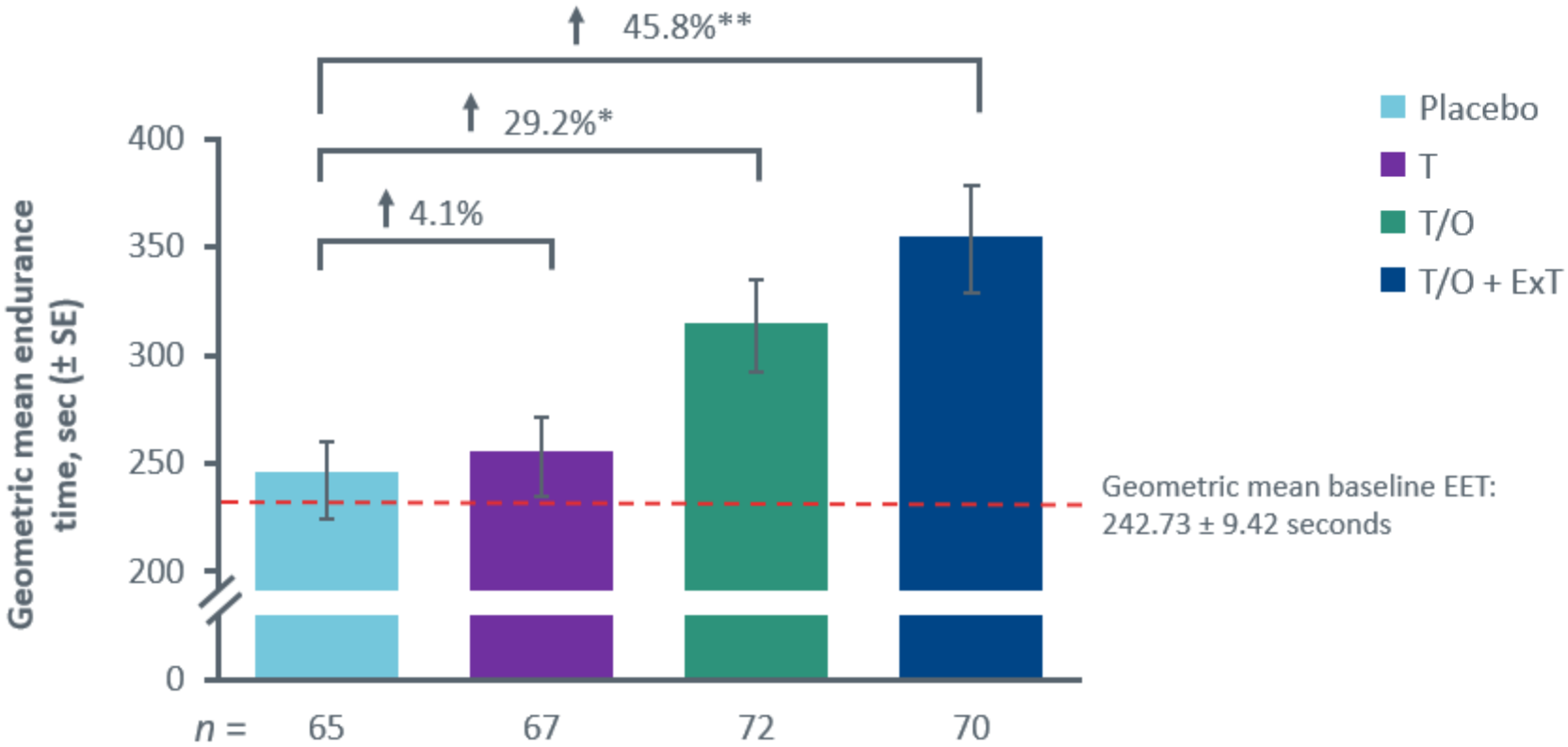
Tiotropium in Early-Stage COPD



Zhou et al. N Eng J Med. 2017;377:923-935.

Tiotropium/olodaterol plus behaviour modification increased EET vs placebo

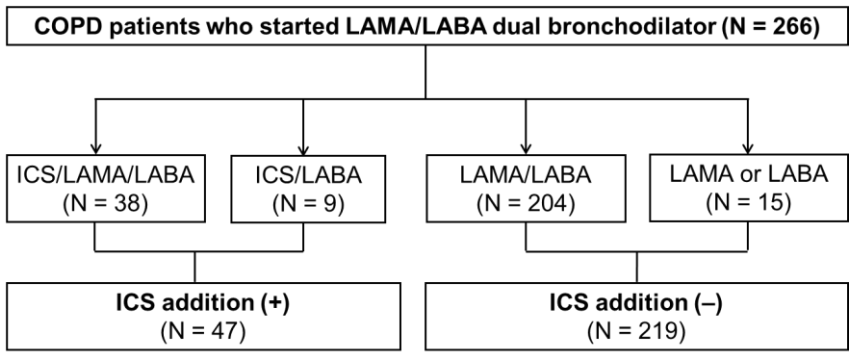
Mean exercise endurance time (EET) during Endurance shuttle walk test results after 8 weeks

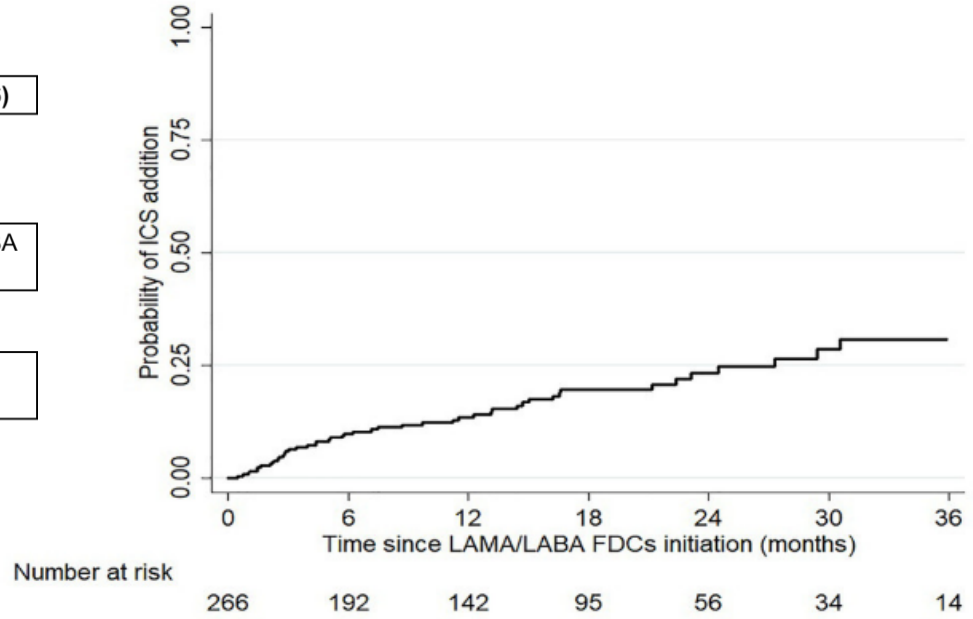


Troosters T, et al. AJRCCM 2018

Stable clinical course with LAMA/LABA

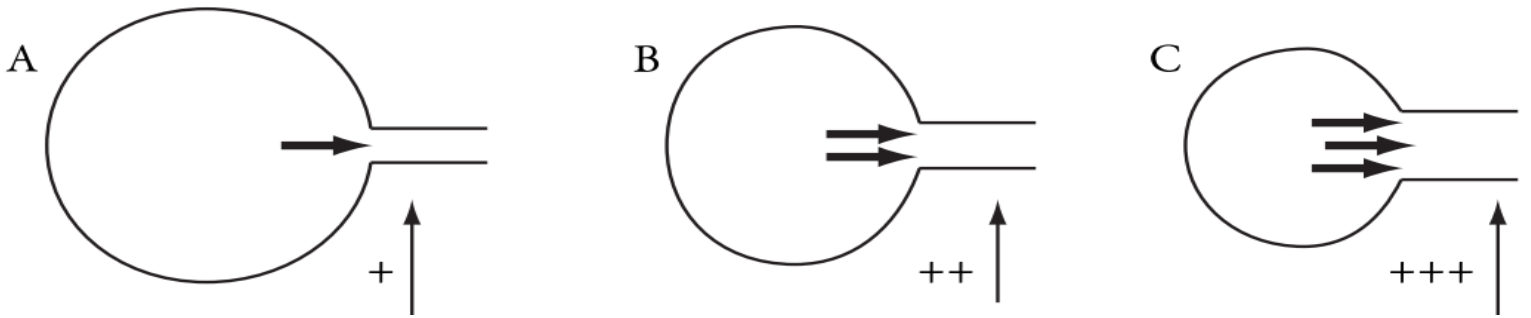
- Median follow-up : 12.4 (5.6 – 22.2) months
  - 266 patients received dual bronchodilator at Samsung Medical Center
  - 87% and 78% remained without adding ICS at 12 and 24 months





Shin & Park et al. J Clin Med. 2020, 9(8), 2547

Bronchodilator 치료의 약물 효과



A: short-acting
B: twice-daily
C: once-daily

Airway obstruction
Air-trapping
Hyperinflation

삶의 질 향상

호흡곤란 ↓

운동 능력 장애

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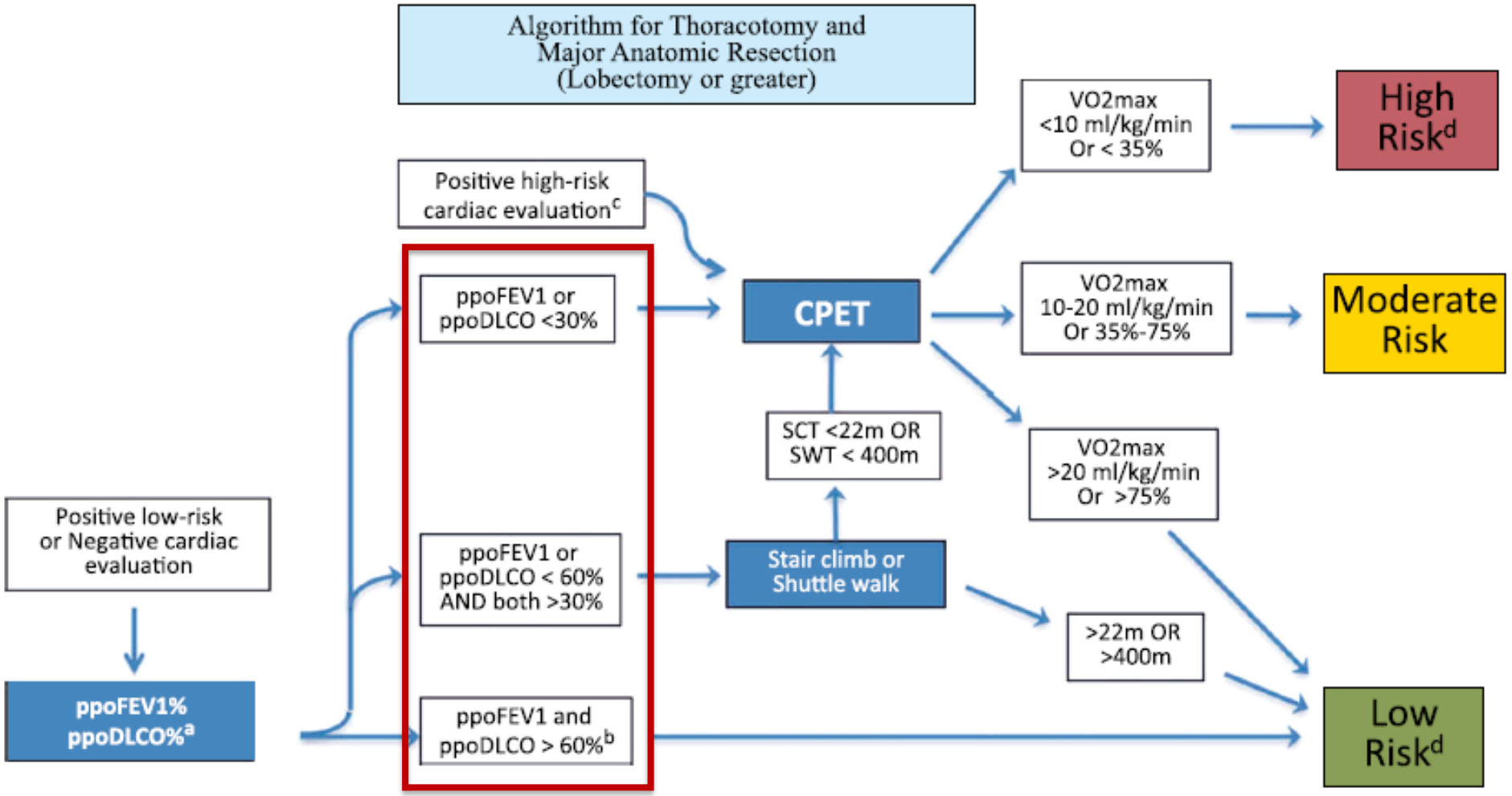
폐암 수술 전 초기 평가

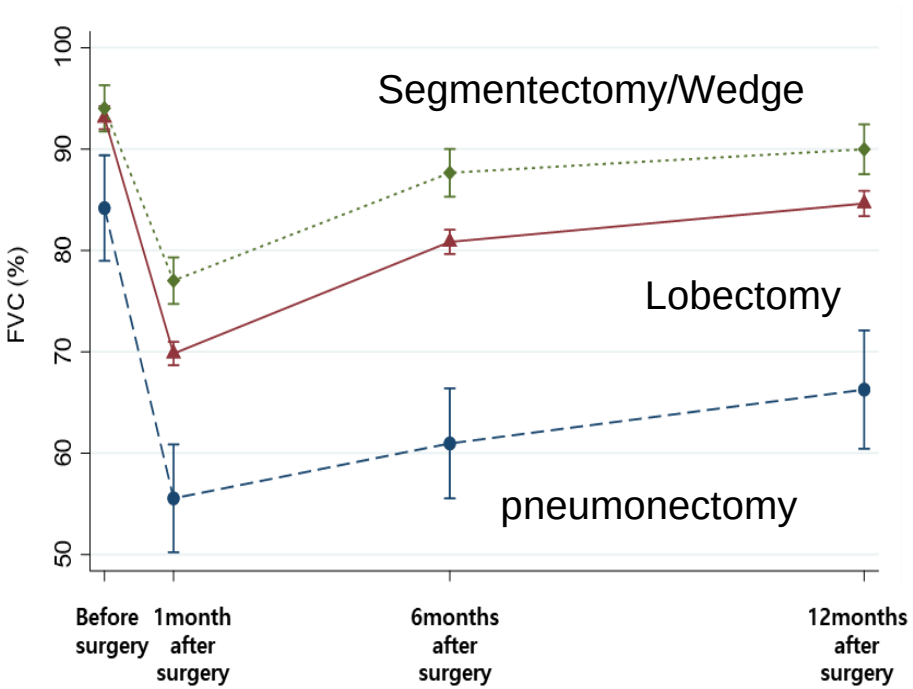


CHEST 2013; 143(5)(Suppl):e166S-e190S

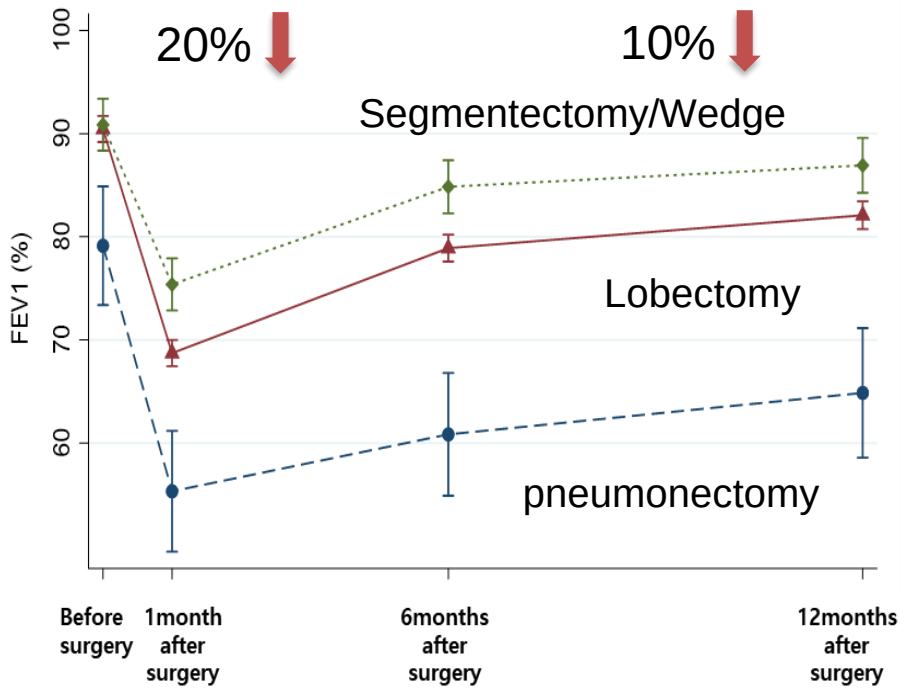
폐기능의 변화

CATCH-LUNG cohort between March 2015 and Oct 2018 (n=620)
For this analysis, 555 patients were included.

FVC (%)



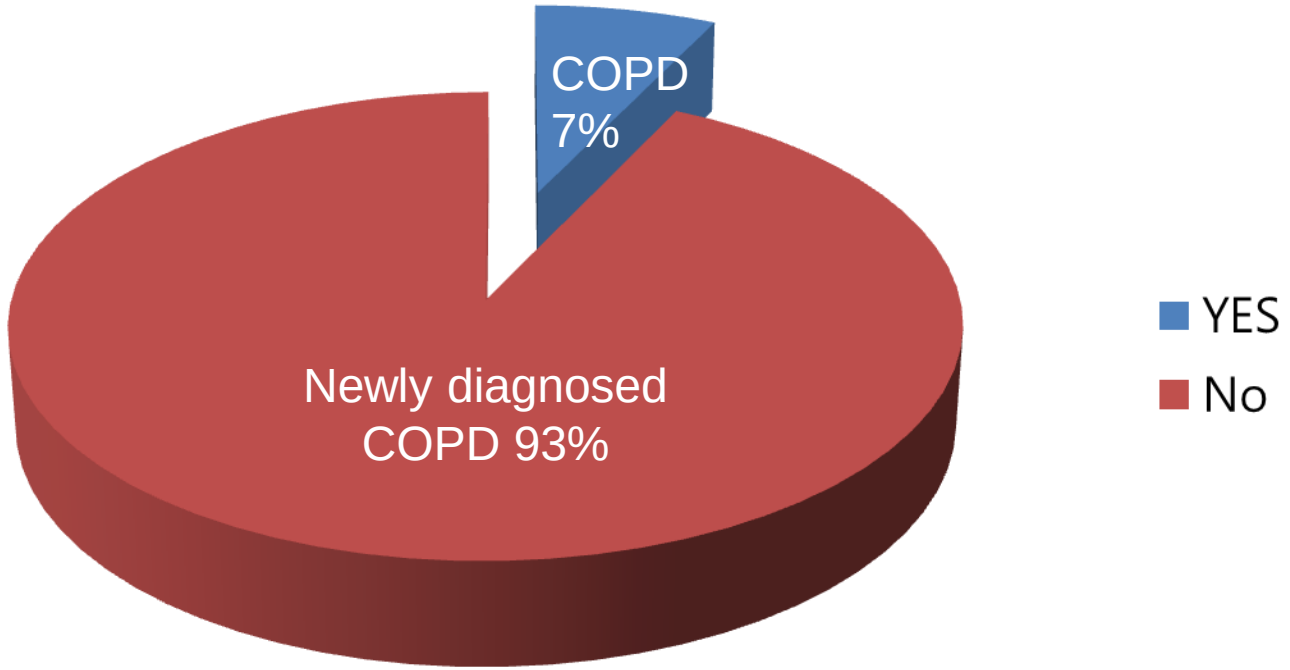
FEV_1 (%)



Pneumonectomy, Bilobectomy Lobectomy Segmentectomy, Wedge resection

진단이 안 된 COPD

N=221 LCA, 111 COPD vs. 110 non-COPD, COPD : post-BD $FEV_1/FVC < 70\%$

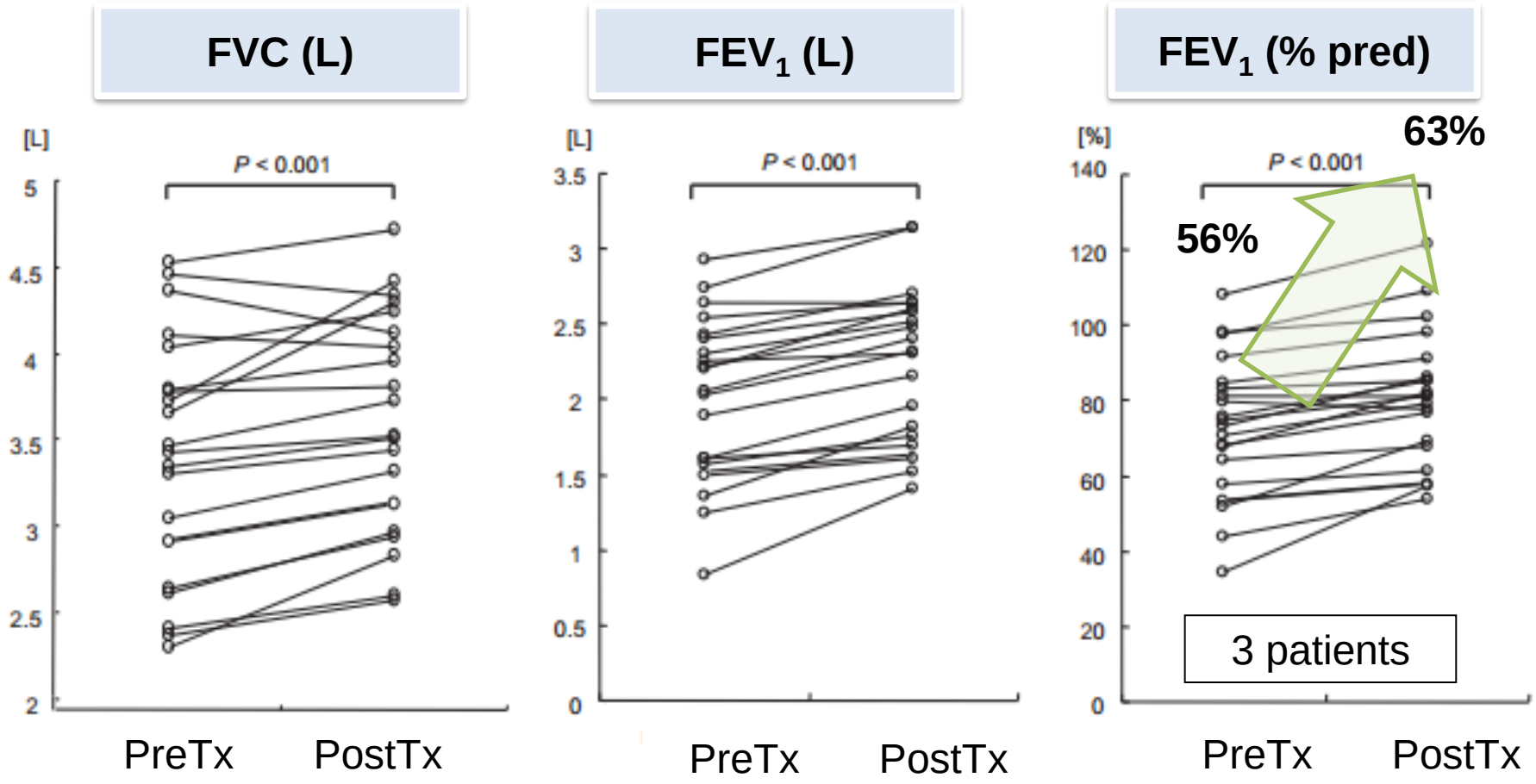


흡입제 사용?

Lee et al. Journal of Thoracic Oncology 2014; 6

Effect of Tiotropium in LCA patients with untreated COPD

Two-week preoperative treatment with TIOT
(n=21, untreated COPD)



Kobayashi et al. Respirology 2009;14:675-79

Inhalers

2014




2015
2016

LAMA +LABA

Glycopyrronium
Indacaterol

Aclidinium
Formoterol

Umeclidinium
Vilanterol

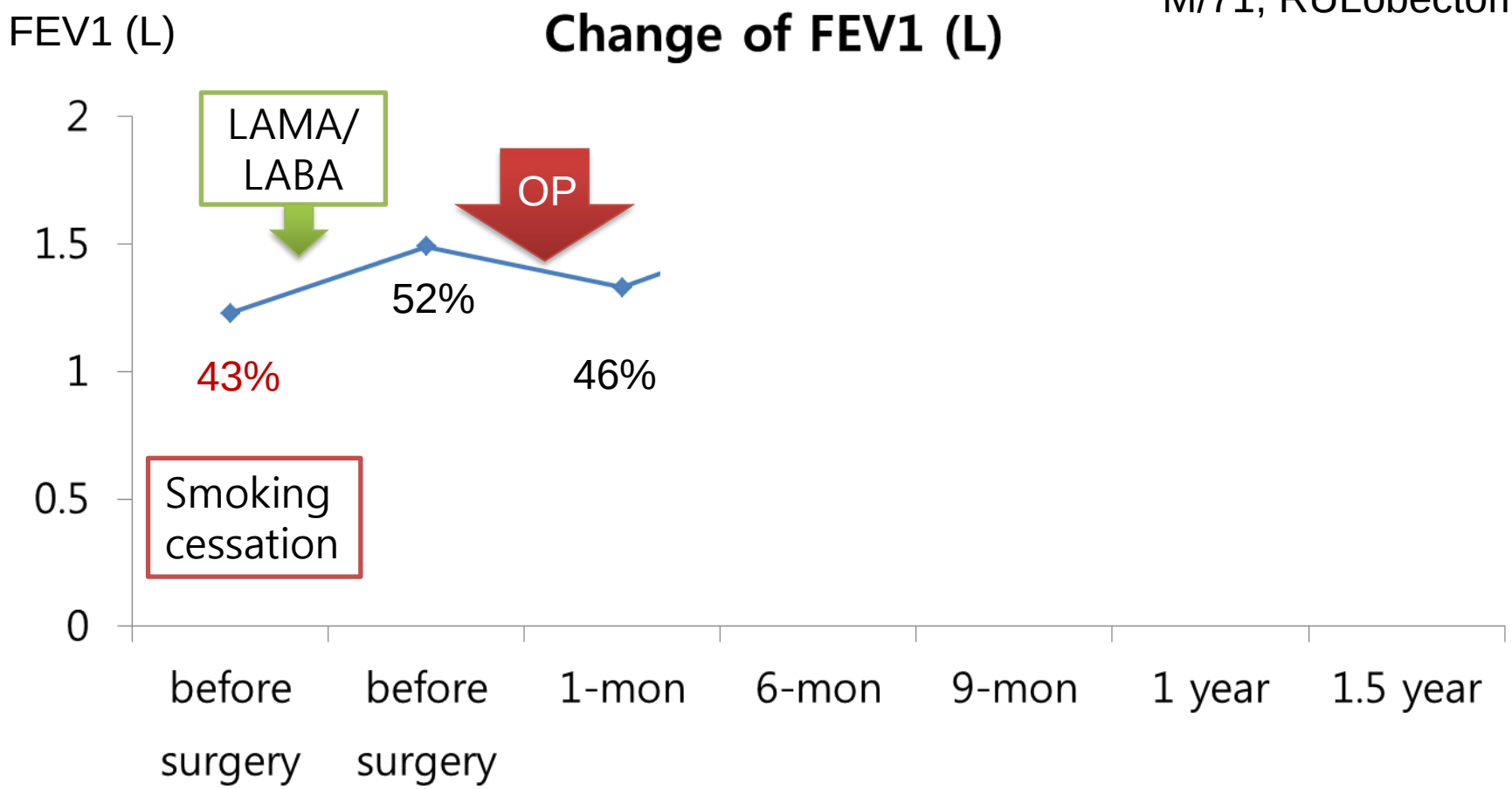
Tiotropium
Olodaterol

Aclidinium
(에클리라®)

Fluticasone furoate /Vilanterol
(렐바®)

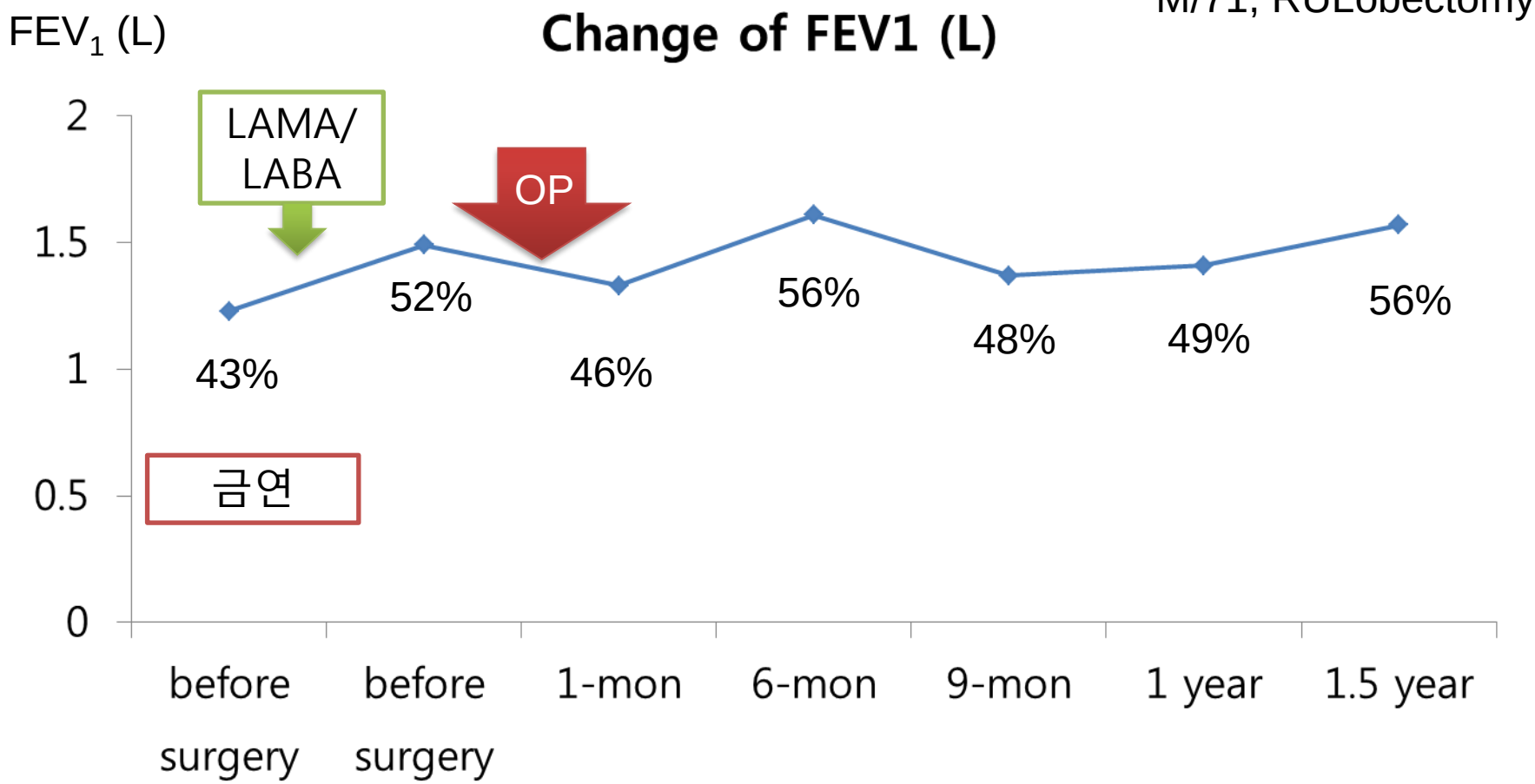
COPD management in LCA

M/71, RULobectomy



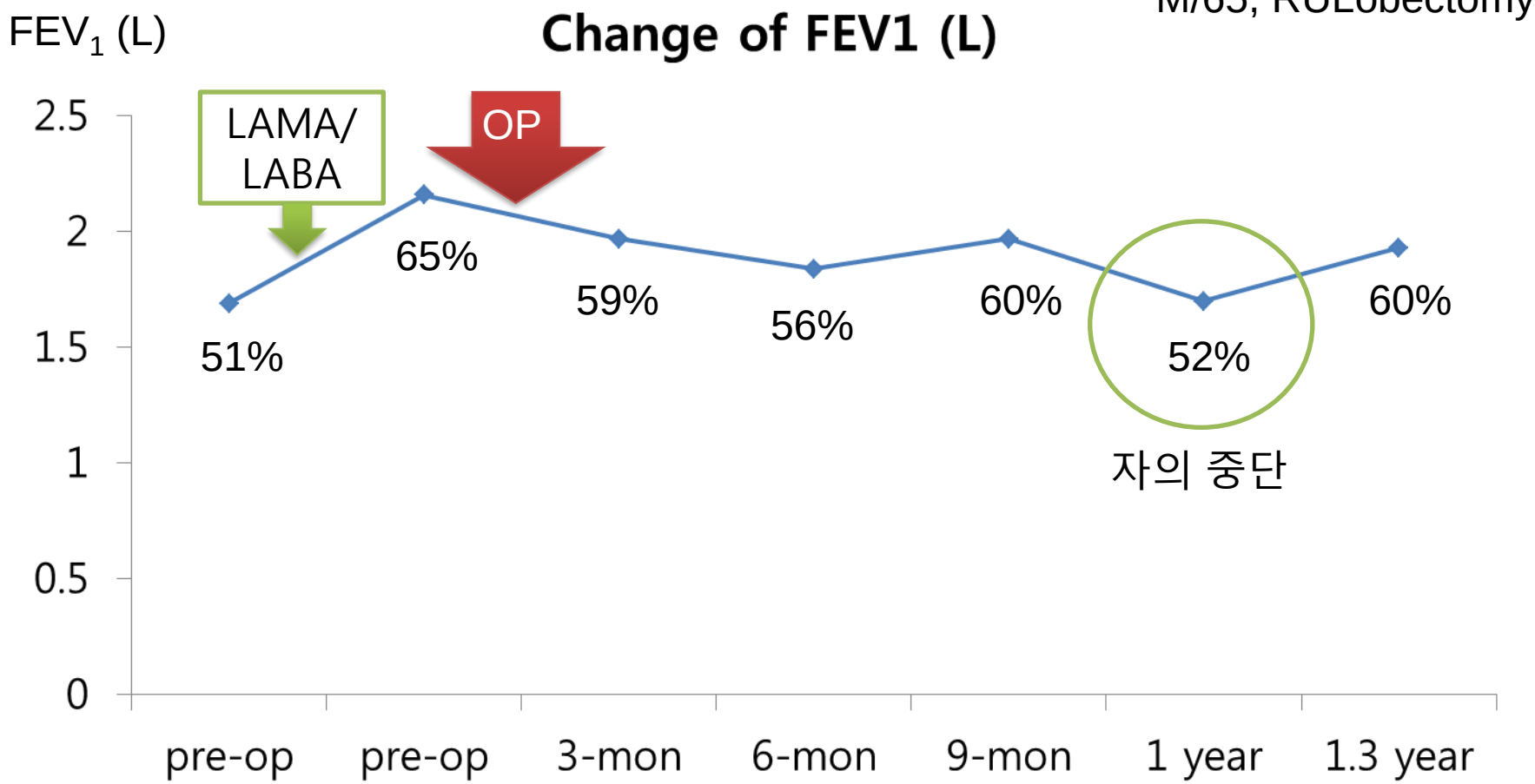
COPD management in LCA

M/71, RULobectomy



COPD management in LCA

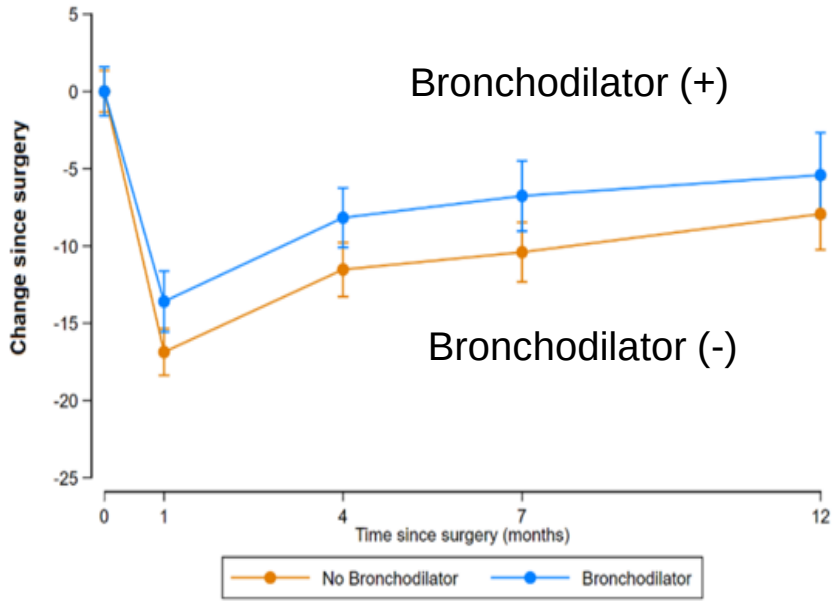
M/65, RULobectomy



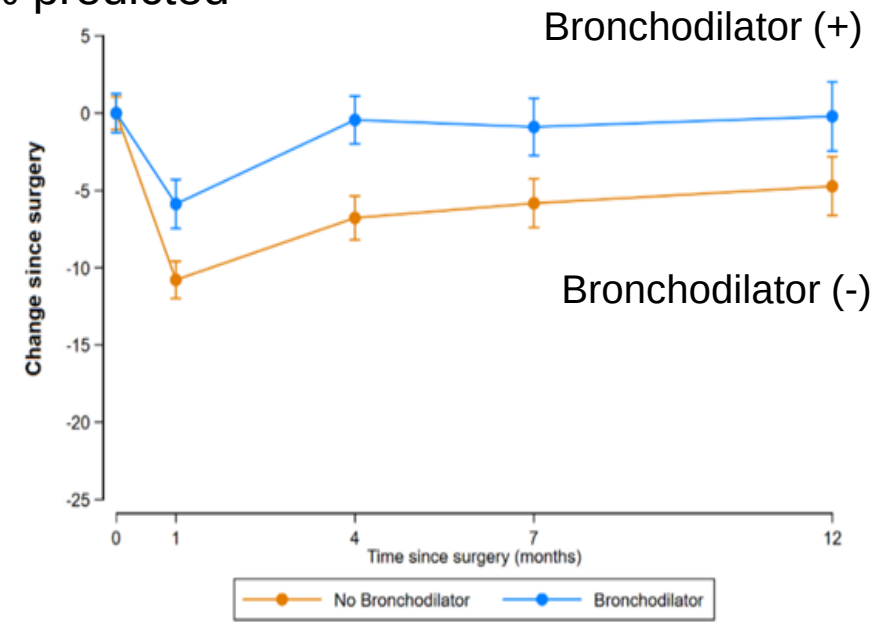
COPD management in LCA

Patients with curative intent resection for NSCLC between 2016 and 2018 and pre-bronchodilator FEV_1/FVC <70% and FEV_1 < 80% pred

FVC, % predicted



FEV_1, % predicted



n=156 n=112 (42%)

Newly diagnosis of COPD : 75%

n=156 n=112 (42%)

Shin, Im, Park et al. Sci Report 2021

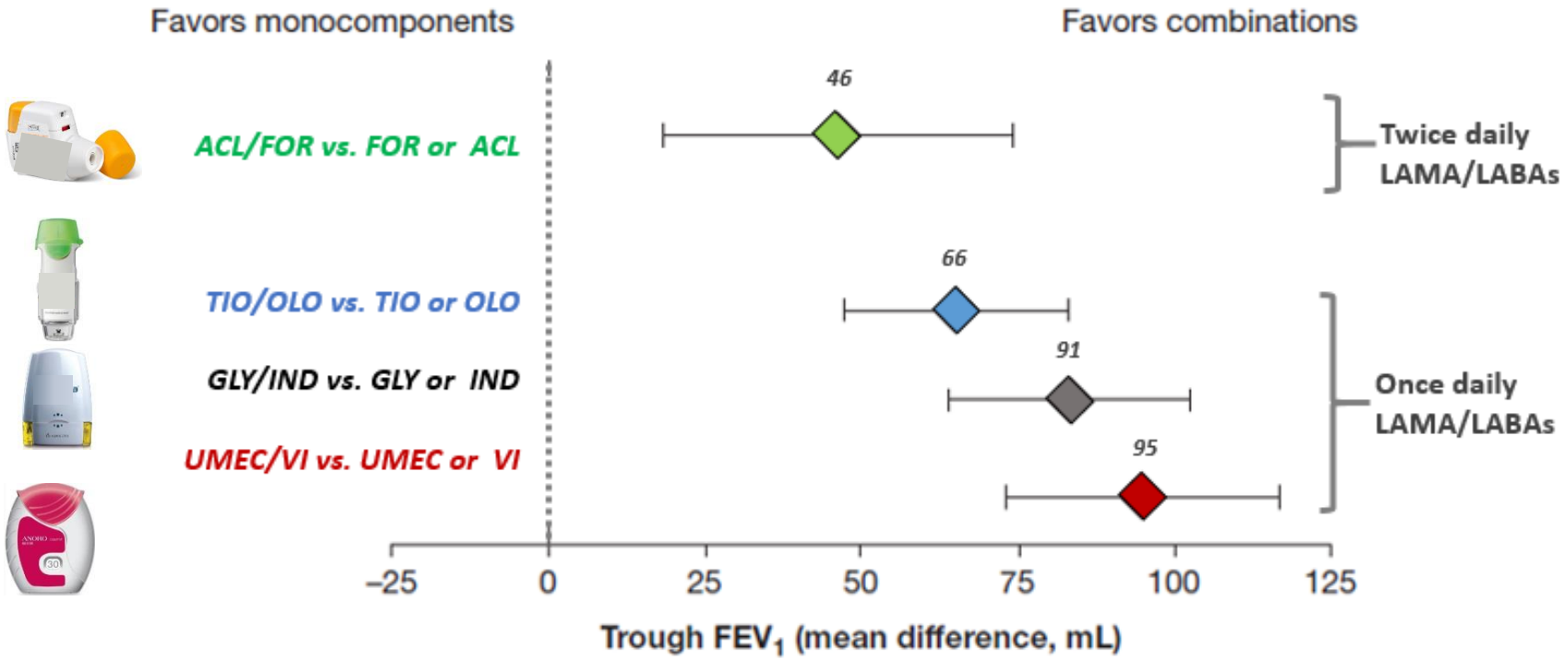
Effect of peri-operative bronchodilator

	No Perioperative Bronchodilator (N = 156)	Mono bronchodilator (N = 36)	Dual bronchodilator (N = 76)	*P* for trend
FEV_1 (mL)				
Change from baseline to 1 months after surgery	-345.7 (-394.0, -297.5)	-148.0 (-268, -28)	-195.3 (-268.7, -122.0)	<0.001
Change from baseline to 4 months after surgery	-219.9 (-269.2, -170.6)	-50.1 (-141.2, 41)	-36.9 (-103.4, 29.5)	<0.001
Change from baseline to 12 months after surgery	-154.5 (-195.9, -113.2)	-32.9 (-119.3, 53.6)	-22.5 (-82.7, 37.7)	<0.001
FEV_1, % predicted				
Change from baseline to 1 months after surgery	-10.9 (-12.5, -9.3)	-4.4 (-8.3, -0.5)	-5.8 (-8.2, -3.4)	<0.001
Change from baseline to 4 months after surgery	-6.8 (-8.4, -5.1)	-0.4 (-3.5, 2.6)	-0.9 (-3.1, 1.4)	<0.001
Change from baseline to 12 months after surgery	-4.4 (-5.9, -2.9)	0.5 (-2.6, 3.7)	0.1 (-2.1, 2.2)	<0.001

Shin, Im, Park et al. Sci Report 2021

Efficacy (FEV_1) Gradient in LAMA/LABAs

A network meta-analysis (NMA); n=23,168; 15 RCTs ≥12 weeks in length: Endpoint Trough FEV_1



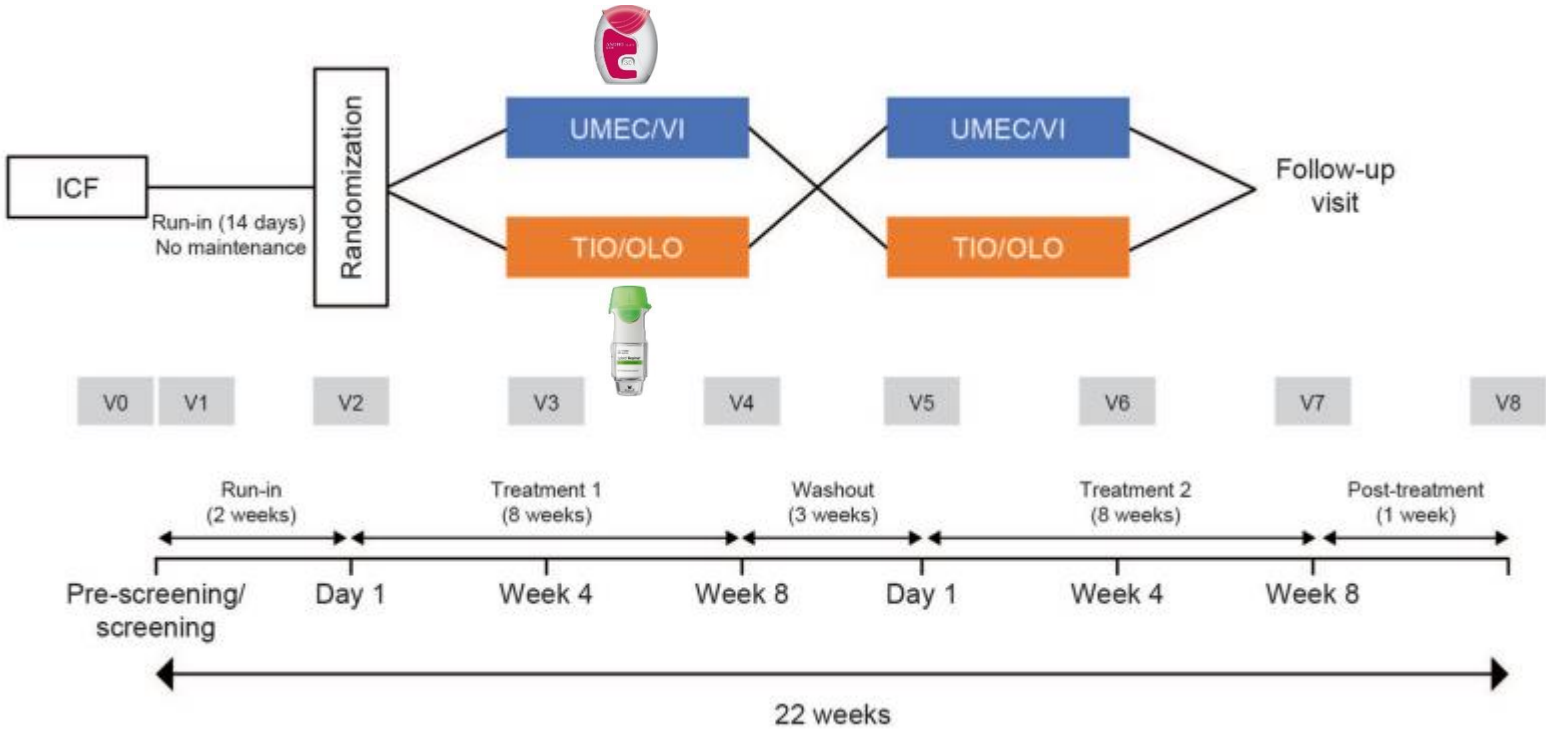
All LAMA/LABAs are superior to their LAMA and LABA components on average by 46 - 95 ml

Adapted from Calzetta L et al. Chest 2016:149 (5)

Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study

Gregory J. Feldman, Ana R. Sousa, David A. Lipson, Lee Tombs, Neil Barnes, John H. Riley, Sadhana Patel, Ian Naya, Chris Compton, Bernardino Alcazar Navarrete

Non-inferiority, randomised, two-period 8 week crossover study



Feldman et al. Adv Ther, 2017

Study Design

Key eligibility criteria

- Age ≥ 40 years
- COPD diagnosis (ATS & ERS definition)
- Smoking history ≥ 10 pack-years
- Post-bronchodilator FEV_1/FVC ratio < 0.70
- mMRC dyspnoea score ≥ 2
- **Post-BD FEV_1 50%-70%**
- **Not receiving ICS-containing therapy at inclusion**

Primary endpoint

- **Change from baseline in trough FEV_1 at Week 8**

Other endpoints

- FEV_1 **responders%** (≥ 100 mL change from baseline) at week 4 and 8
- Trough FVC and IC at week 4 and 8
- CAT score and **responders*%** at week 4 and 8
- Weekly mean E-RS $_{COPD}$ symptom score and weekly **responders**%**
- Rescue use and % rescue-free days (weeks 1-8)
- Inhaler ease-of-use

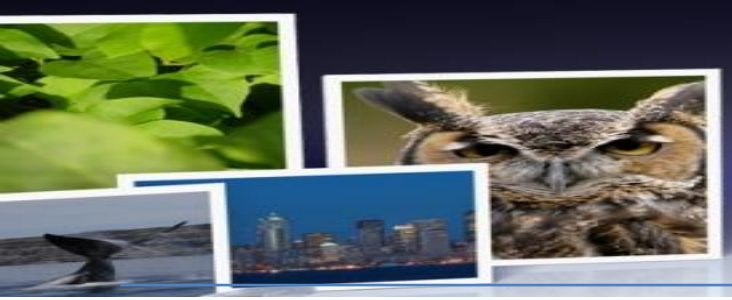
Safety endpoints

- Incidence of adverse events and serious adverse events
- Incidence of COPD exacerbations

* Responders defined as patients with a reduction of ≥2 units from baseline CAT score;
** Responders defined as patients achieving a reduction from baseline E-RS score of ≥2 units

CAT = COPD assessment tool; E-RS EXACT-Respiratory Symptoms; = FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; ICS = inhaled corticosteroids; MDI = metered dose inhaler; mMRC = modified Medical Research Council

Reference. Feldman G et al, Comparative efficacy of once-daily umeclidinium/vilanterol and tiotropium/olodaterol therapy in symptomtic chronic obstructive pulmonary disease: a randomized study, Advances in Therapy 2017; vol.34: DOI 10.1007/s12325-017-0626-4



Baseline characteristics

	Total (N = 236)
Mean age, y (SD)	64.4 (8.5)
Male, %	60
Current smoker at screening, %	53
COPD exacerbation history (12 months prior to screening) %	
≥1 requiring OCS/antibiotics	14
2 requiring OCS/ antibiotics	2
Requiring hospitalisation	3
Mean post-bronchodilator FEV_1, % predicted (SD)	59.6 (5.6)
GOLD 2017 mMRC / Exacerbation category, %	
Group B	**95**
Group D	5
mMRC score, %	
2 (moderate)	66
3 (severe)	30
4 (very severe)	4
Respiratory maintenance meds used prior to run-in, %*	
LAMA	16
LABA	12
LAMA/LABA	13
ICS	4
None**	**63**

Screened; n = 421

ITT; n = 236

PP; n = 227 (97%)

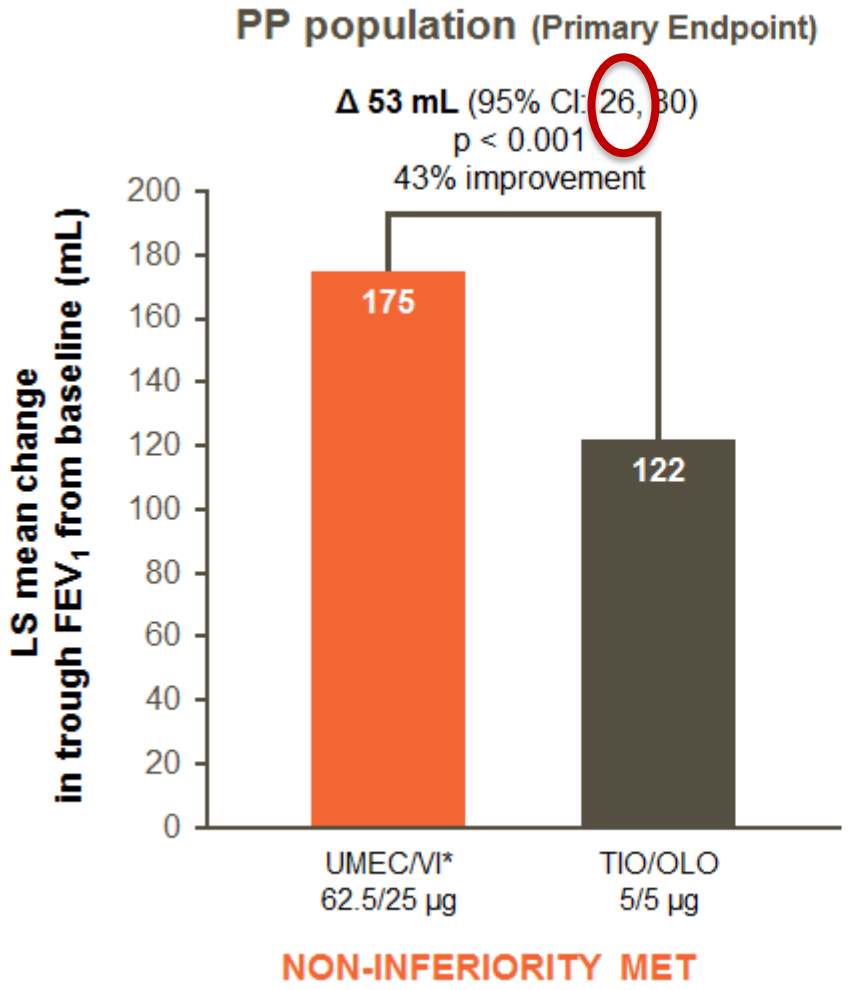
Competed study n = 225 (95%)

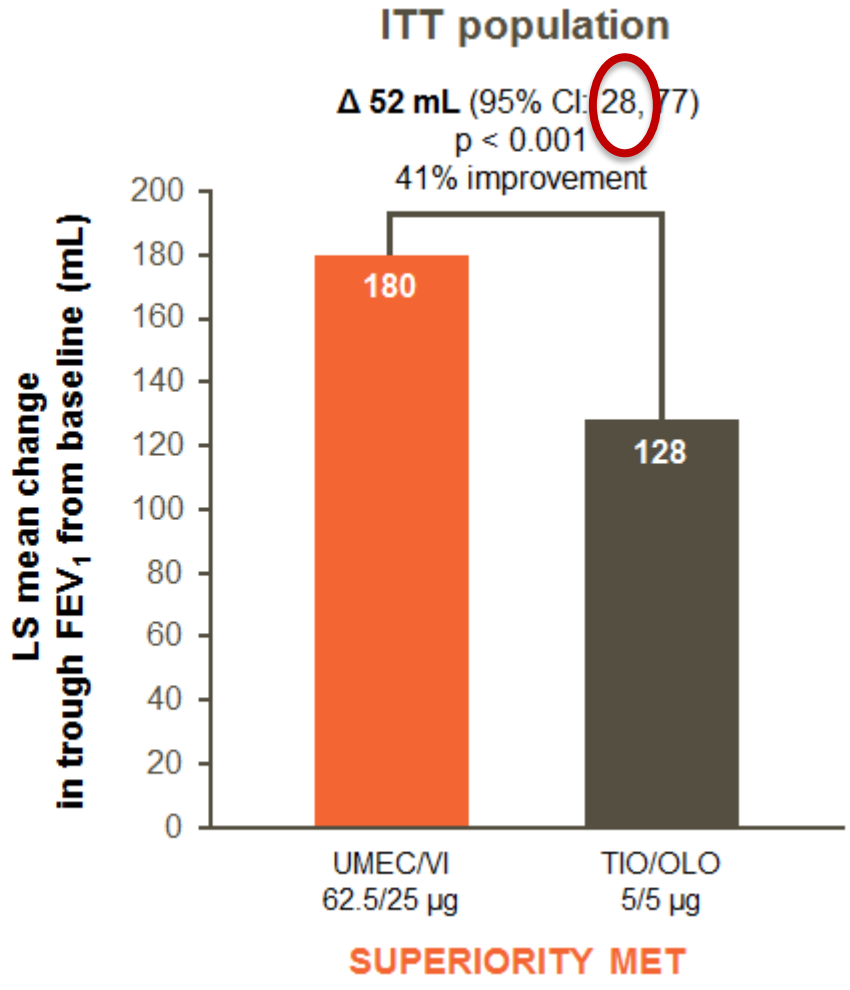
Inhaler naïve n = 75

* Removed prior to run-in.

** **No maintenance for ≥ 6 weeks** prior to randomization and including 30 days prior to run-in.

Trough FEV_1 at Week 8 Primary Endpoint

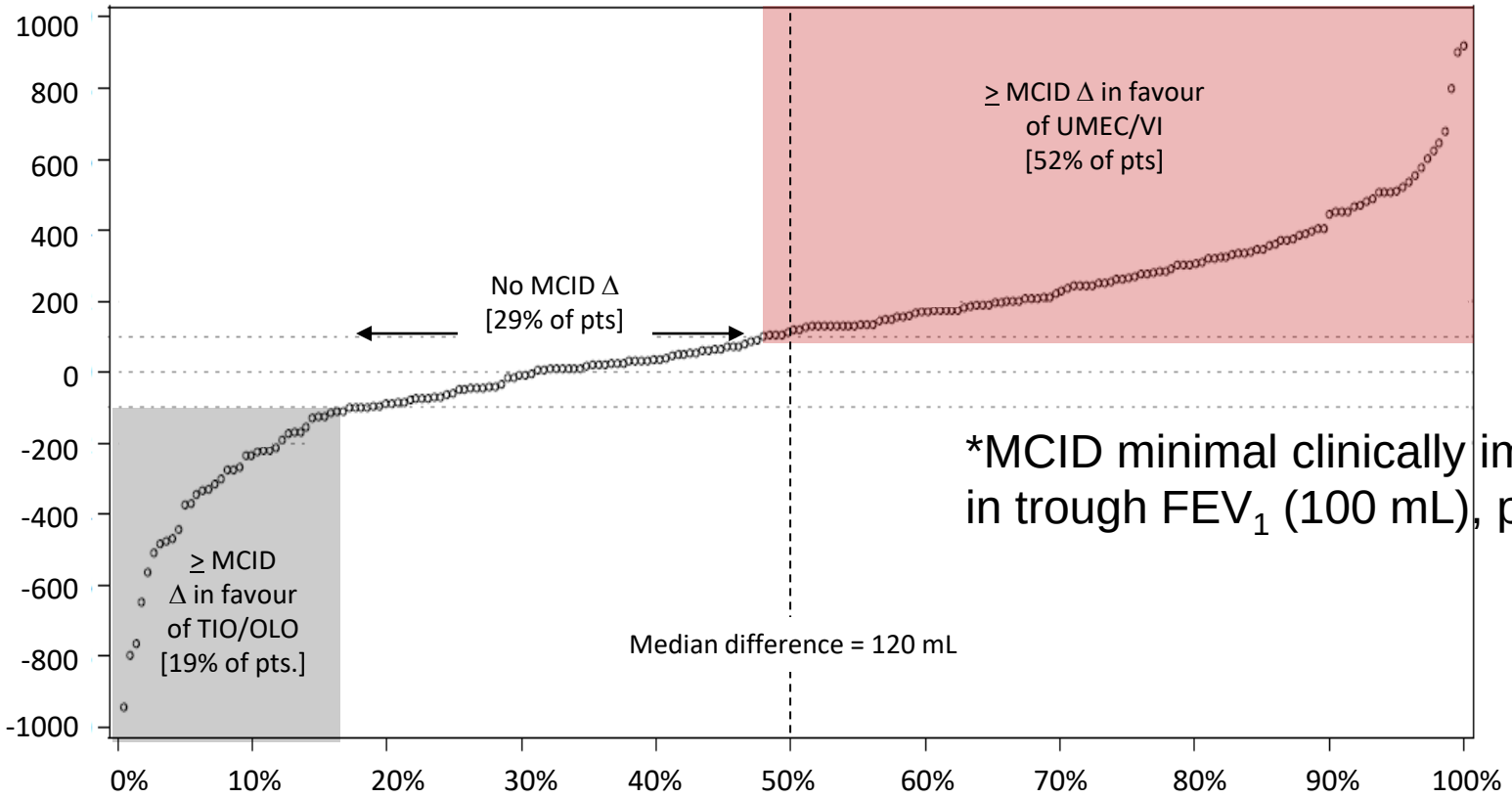




Reference. Feldman G et al, Comparative efficacy of once-daily umeclidinium/vilanterol and tiotropium/olodaterol therapy in symptomtic chronic obstructive pulmonary disease: a randomized study, Advances in Therapy 2017; vol.34: DOI 10.1007/s12325-017-0626-4

Different efficacy between the LAMA/LABAs

- ITT population after 8-weeks treatment (descriptive data of the cumulative within patient comparisons)



*MCID minimal clinically important difference in trough FEV_1 (100 mL), pts patients

Δ = treatment difference;

ITT population (n=221) with 8-week trough FEV_1 data for UMEC/VI and TIO/OLO

엘립타는 사용하기 편리한 디바이스입니다

엘립타는 COPD 조절을 간편하게 만들어줍니다

- 엘립타는 간편하고 직관적인 breath-actuated 흡입기입니다.[1,2]
- 엘립타 건조분말 흡입기 (DPI)는 사전충전 방식으로 환자들이 실수로 삼키거나 캡슐을 흡입할 위험성이 없습니다.[1]
- 필요한 약물의 양을 흡입하는데 어렵거나 힘들지 않습니다. (PIFR of 42–129L/min tested in-vitro)[2]

1 열고 → **2 흡입하고** → **3 닫고**

1. Anoro Ellipta Prescribing Information. 2. Hamilton M et al. Journal of Aerosol Med. and Pulm. Drug Delivery 2015; 28(6):498-506.

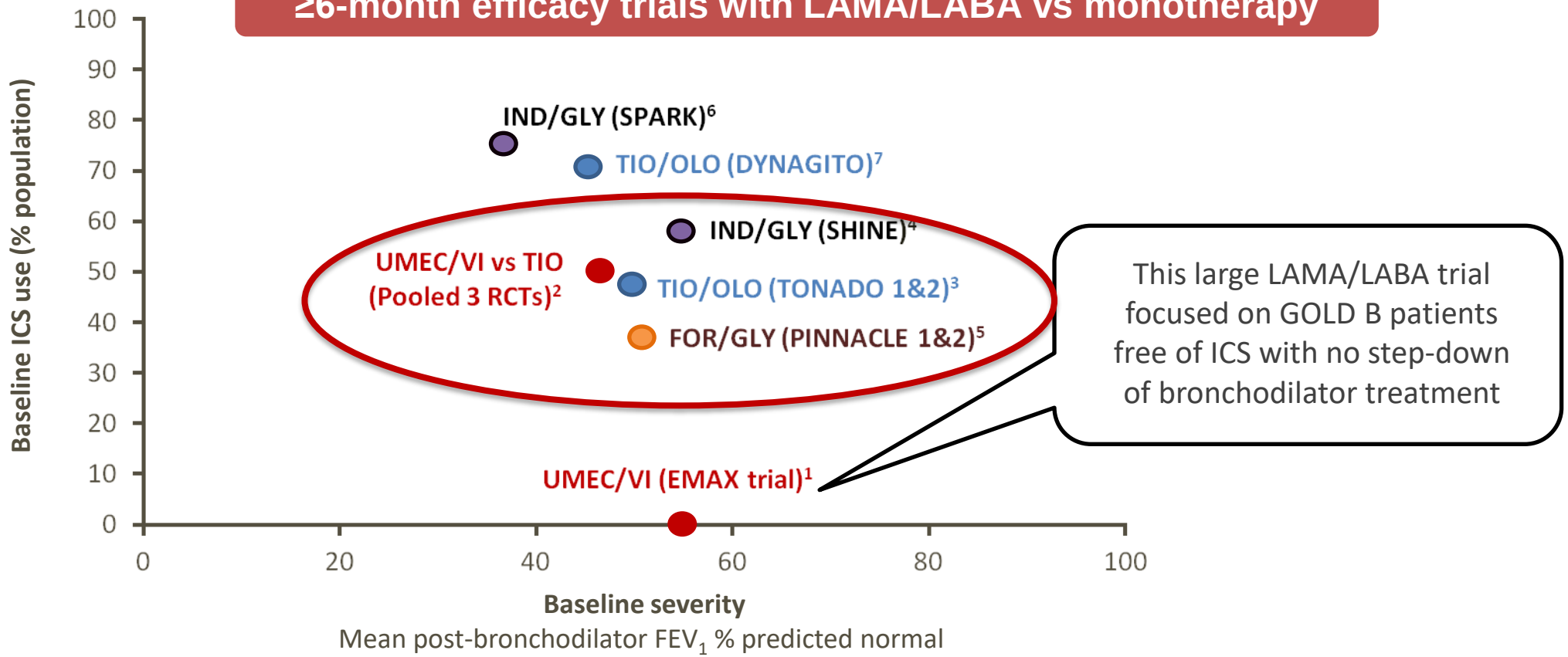
Contents

For lung function improvement

For Maintenance-naïve patients

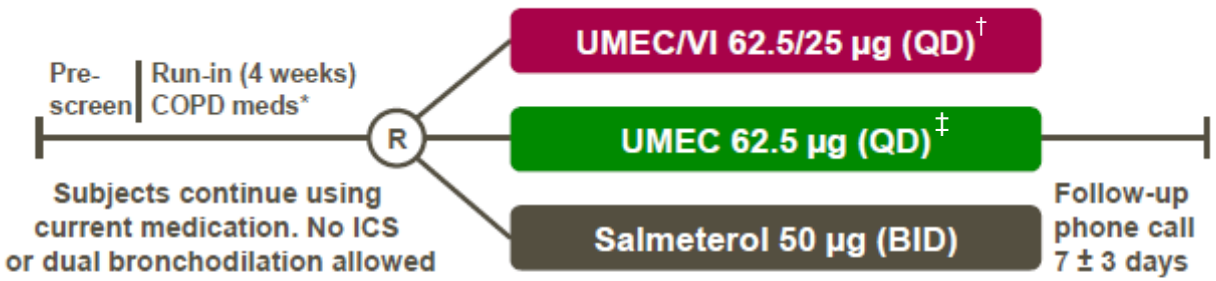
LAMA/LABA >> LAMA or LABA

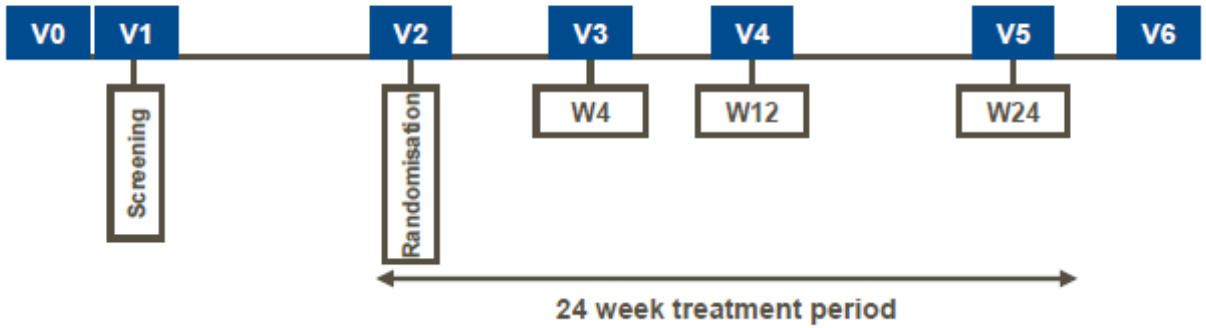
LAMA/LABA RCTs in COPD patients



EMAX study design

24-week randomised, double-blind, double-dummy, parallel-group study





2,431 patients randomised
(Analysed ITT population, n = 2,425)

- Aged 40+ years
- CAT ≥ 10
- Post-bronchodilator FEV_1 30–80%
- ≤ 1 moderate exacerbation in past year
- Not receiving ICS, LAMA/LABA

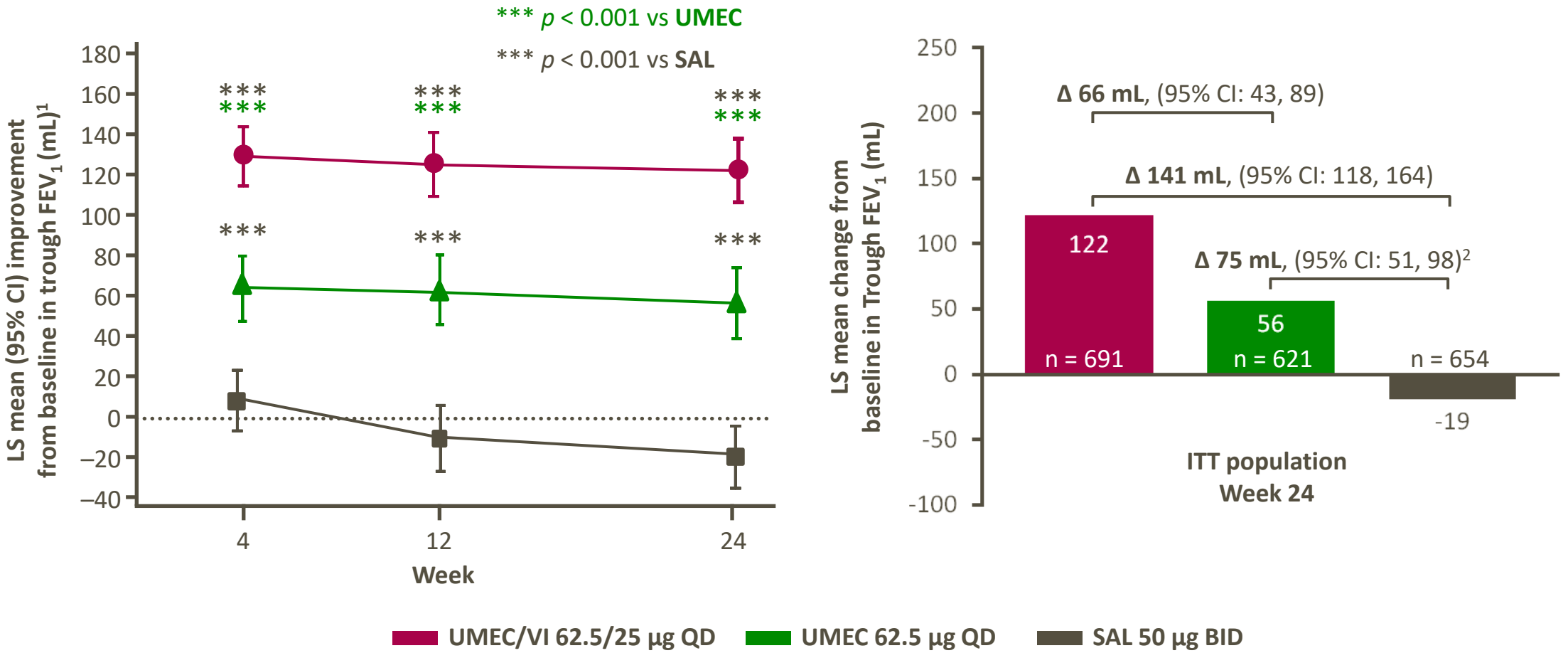
- **Primary endpoint**: trough FEV_1 at Week 24§
- **Key secondary endpoint**: TDI (trial powered for TDI)
- Other secondary endpoints include: daily symptoms E-RS, rescue medication use, CAT, SGRQ, time to first exacerbation, time to first clinically important deterioration (CID)
- Safety

Francois Maltais, et al. Respiratory research. 2019

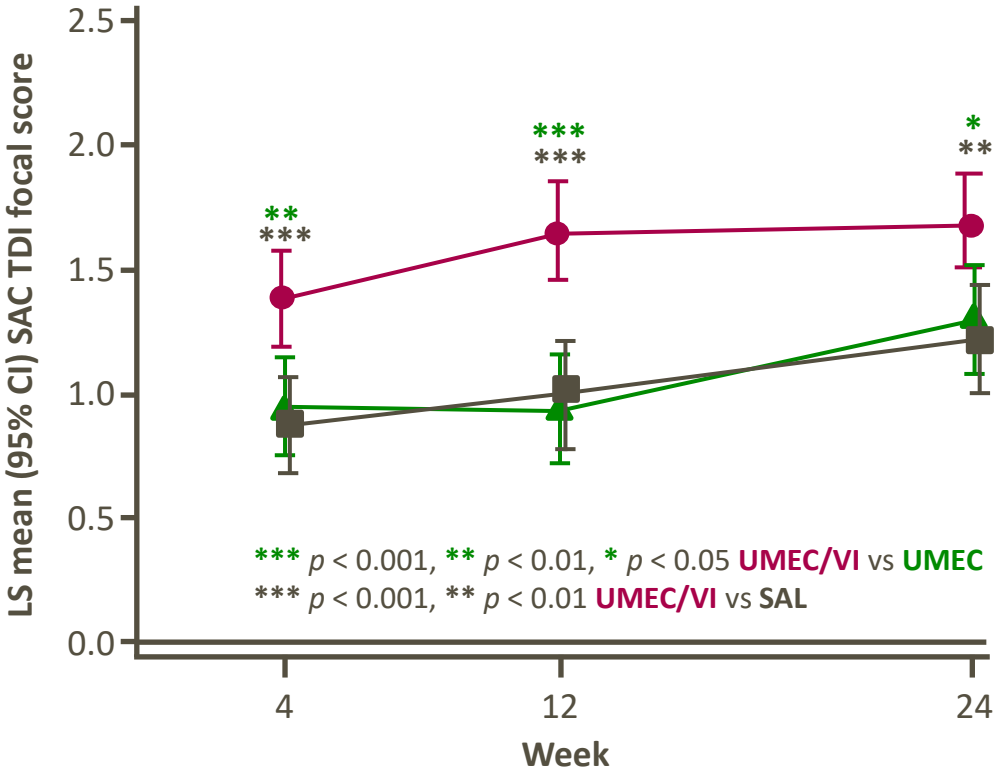
EMAX: Demographics and baseline characteristics

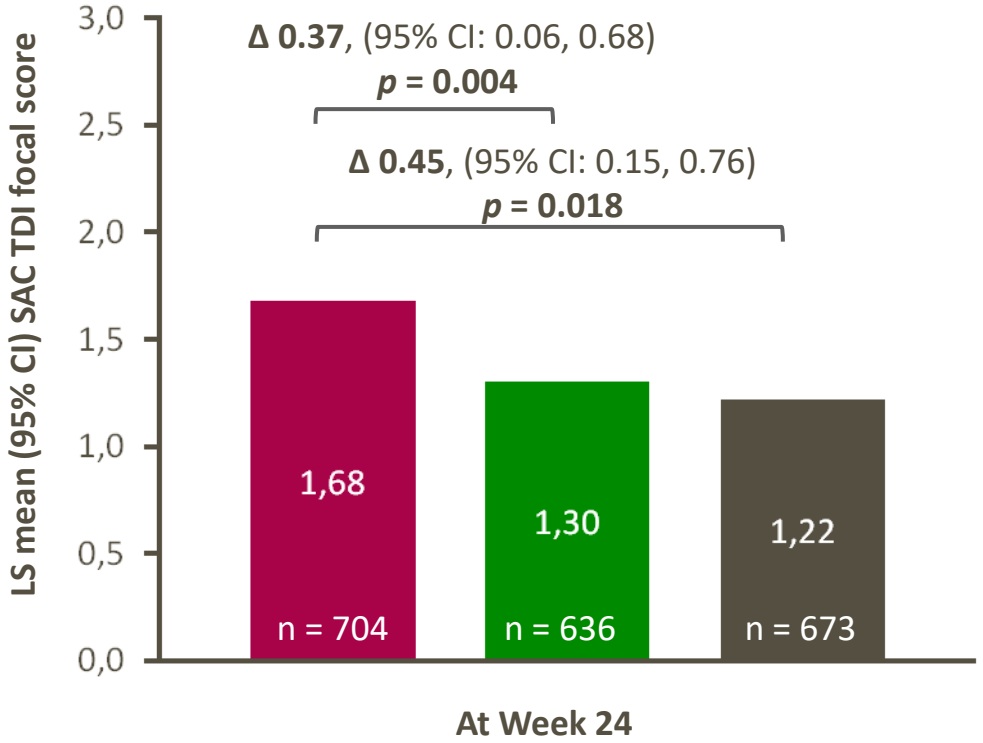
	UMEC/VI 62.5/25 µg (n = 812)	UMEC 62.5 µg (n = 804)	SAL 50 µg (n = 809)	Total (N = 2,425)
Age (y), mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39%)	327 (41%)	342 (42%)	988 (41%)
Current smoker at screening, n (%)	394 (49%)	396 (49%)	413 (51%)	1203 (50%)
Smoking pack years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
Duration of COPD (y), mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Post BD % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
Reversibility to salbutamol*, mean % (SD)	10.4 (12.8)	10.2 (13.3)	10.7 (13.3)	10.5 (13.1)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)	7.0 (1.9)
Baseline CAT score, mean (SD)[2]	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)	19.2 (6.1)
Baseline rescue medication use, mean puffs/day (SD)	2.2 (2.6)	2.1 (2.3)	2.2 (2.5)	2.2 (2.5)
One moderate exacerbation in last year†, n (%)	123 (15%)	124 (15%)	146 (18%)	393 (16%)
Maintenance-naive‡, n (%)[3]	250 (31%)	250 (31%)	249 (31%)	749 (31%)

EMAX: Primary endpoint: Trough FEV_1



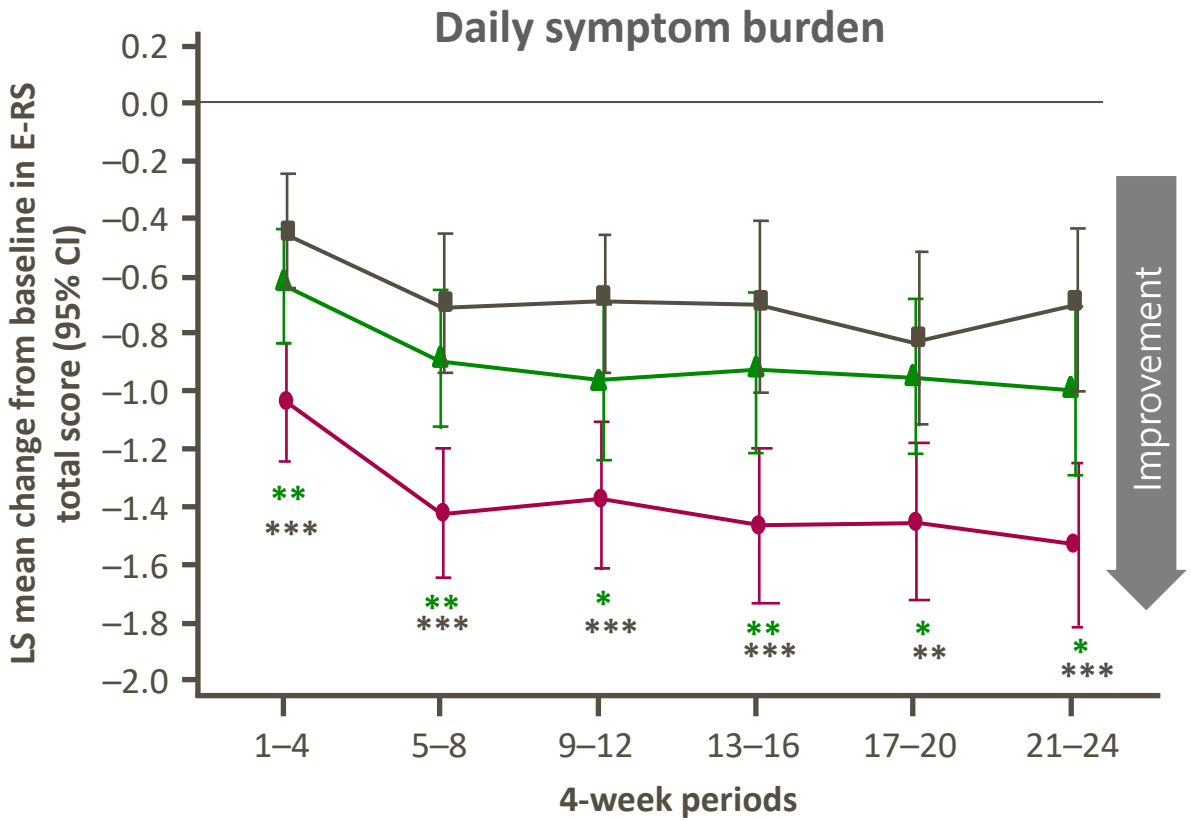
EMAX: Breathlessness (TDI)

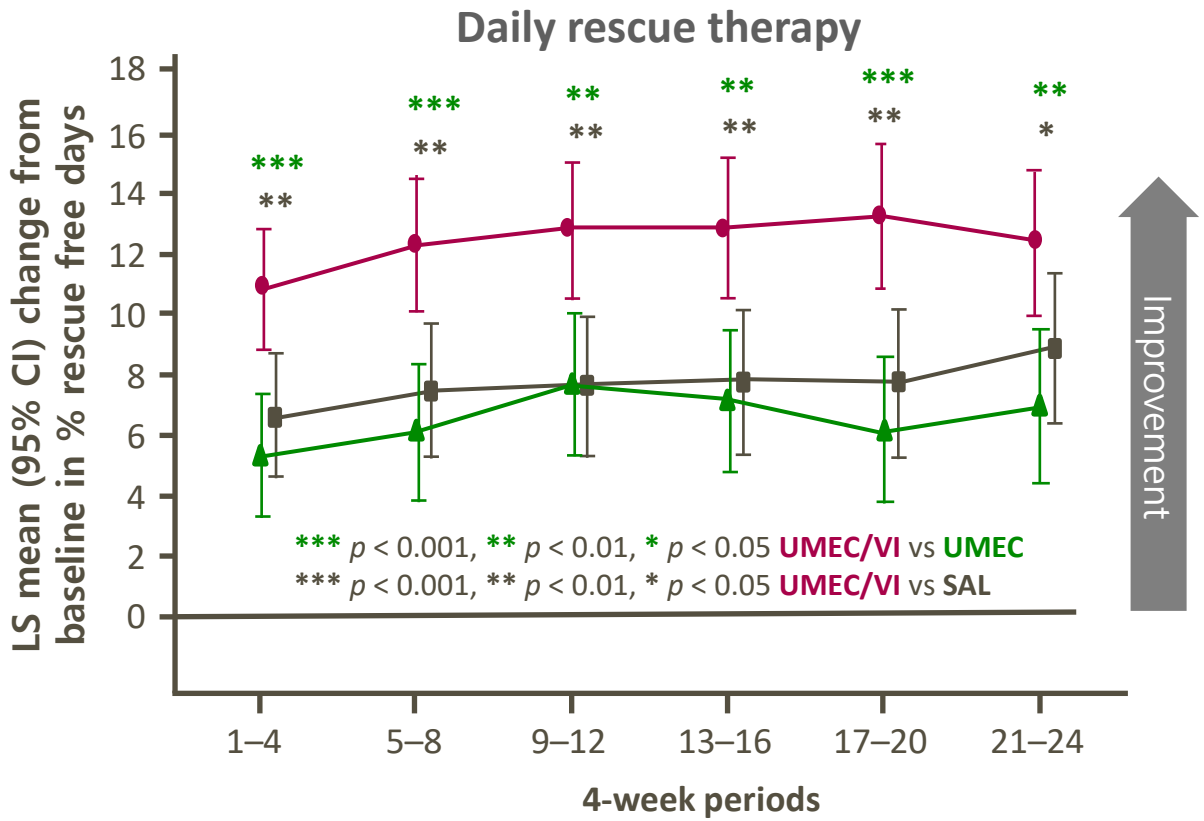




UMEC/VI 62.5/25 µg QD UMEC 62.5 µg QD SAL 50 µg BID

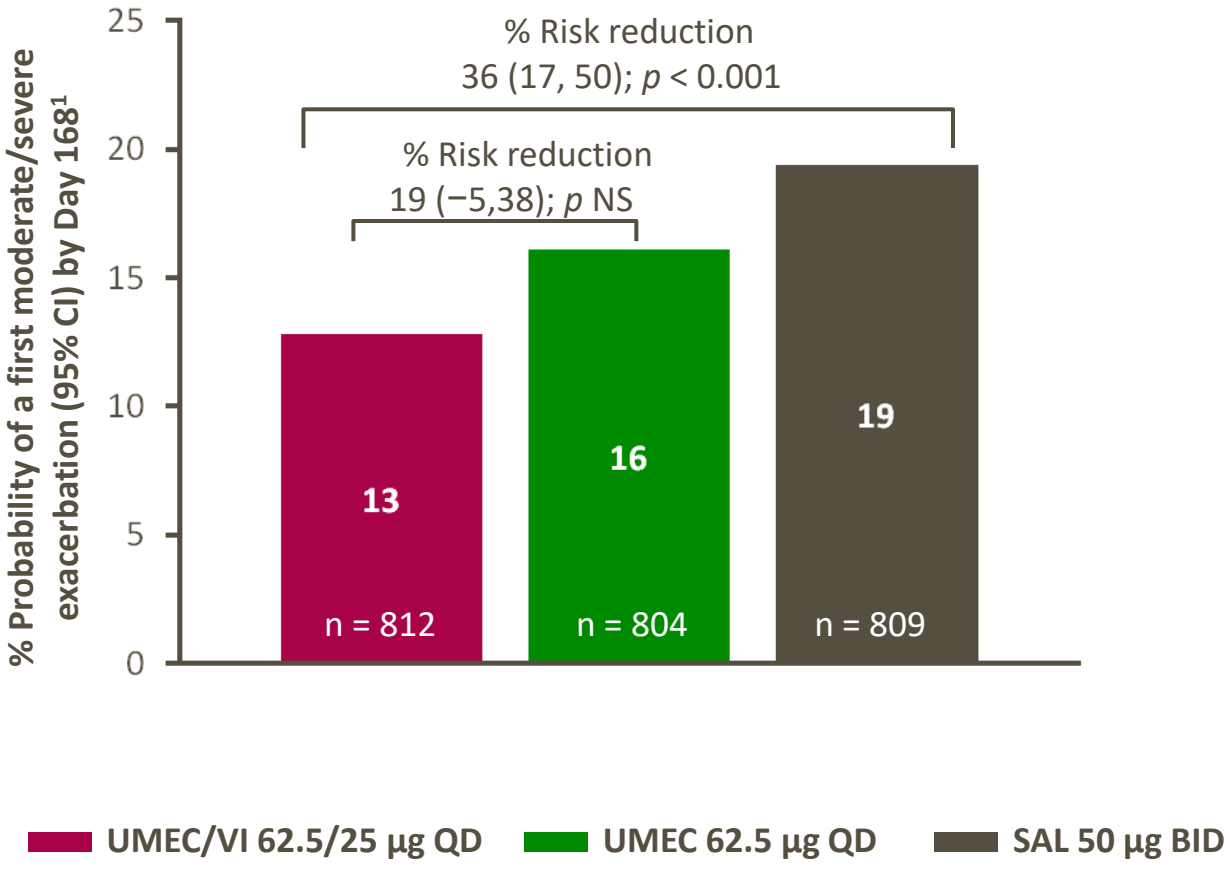
EMAX: Daily respiratory symptoms and rescue medication

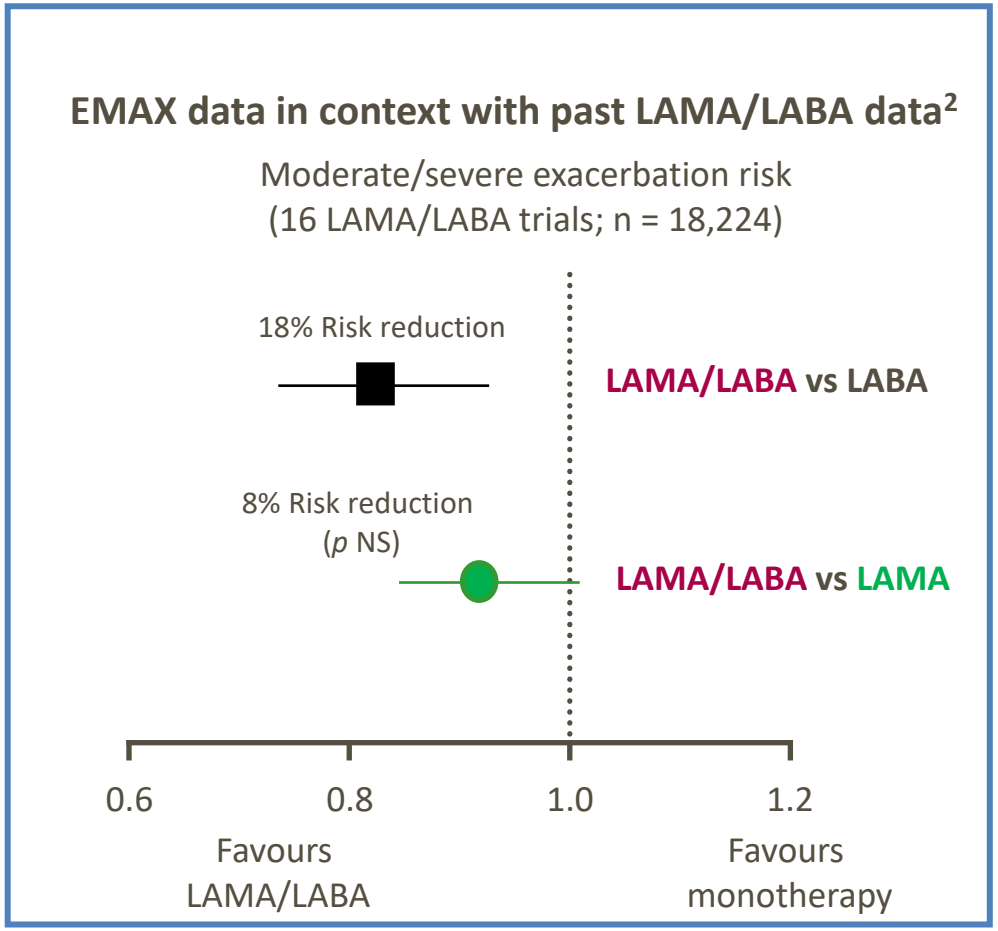




UMEC/VI 62.5/25 µg QD UMEC 62.5 µg QD SAL 50 µg BID

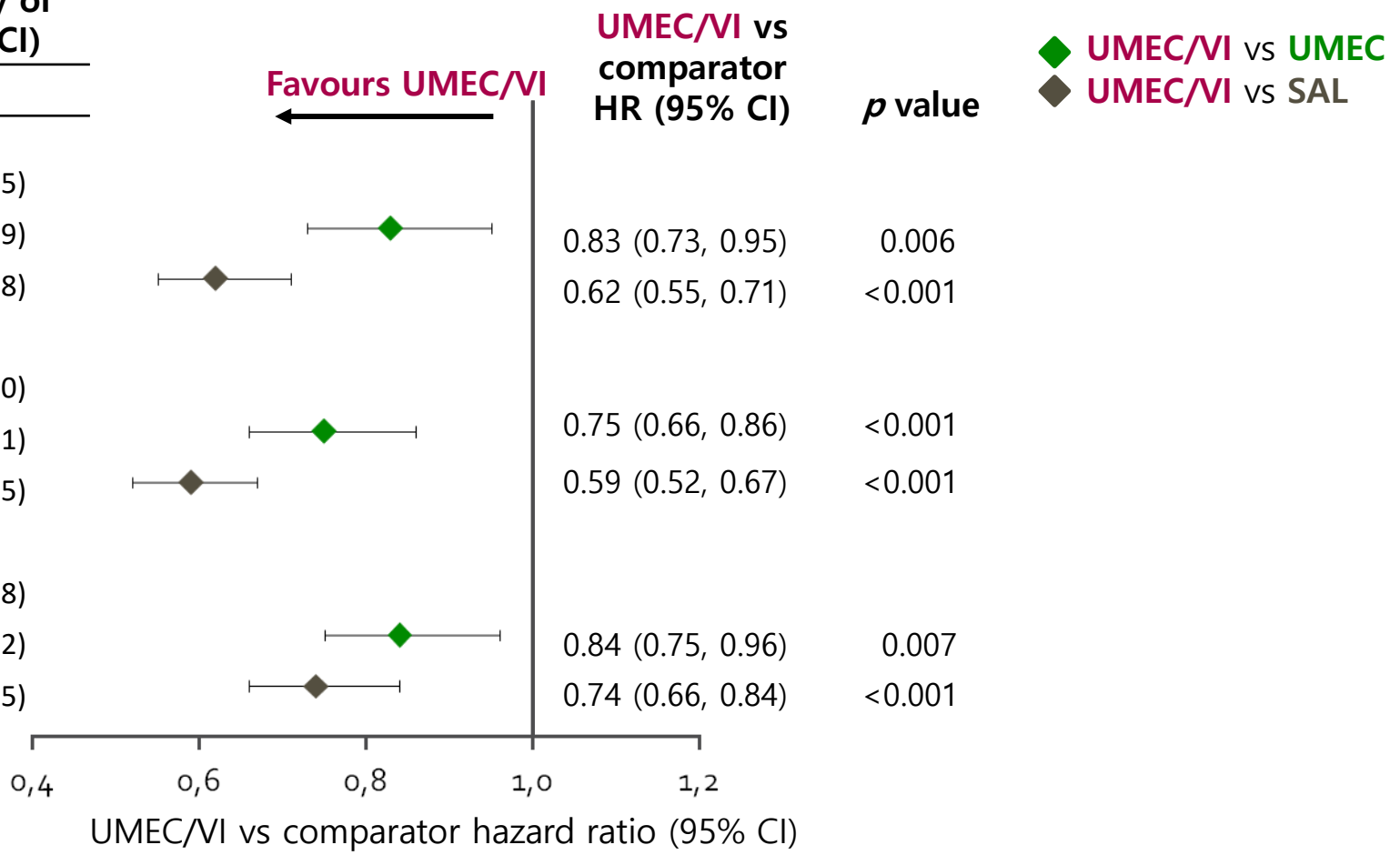
EMAX:
Risk of a first moderate/severe exacerbation





EMAX: Risk of a first CID over 6 months of tre atment across multiple composite definitions

Treatment	Incidence of CID n/N* (%)	% Probability of event (95% CI)	UMEC/VI vs comparator HR (95% CI)	*p* value
Composite CID definitions				
A) Exacerbation†, FEV_1, SGRQ				
UMEC/VI	430/780 (55)	52.8 (49.3, 56.5)		
UMEC	439/741 (59)	60.2 (56.5, 63.9)	0.83 (0.73, 0.95)	0.006
SAL	545/758 (72)	69.5 (66.1, 72.8)	0.62 (0.55, 0.71)	<0.001
B) Exacerbation†, FEV_1, CAT				
UMEC/VI	402/781 (51)	49.3 (45.8, 53.0)		
UMEC	449/743 (60)	60.4 (56.7, 64.1)	0.75 (0.66, 0.86)	<0.001
SAL	530/758 (70)	67.1 (63.7, 70.5)	0.59 (0.52, 0.67)	<0.001
C) Exacerbation†, CAT, SGRQ, TDI‡				
UMEC/VI	500/791 (63)	61.3 (57.8, 64.8)		
UMEC	524/761 (69)	69.8 (66.3, 73.2)	0.84 (0.75, 0.96)	0.007
SAL	578/775 (75)	73.4 (70.1, 76.5)	0.74 (0.66, 0.84)	<0.001



CID: clinically important deterioration

EMAX: Overview of adverse events

	UMEC/VI 62.5/25 µg (n = 812)	UMEC 62.5 µg (n = 804)	SAL 50 µg (n = 809)
Adverse events (AE), n (%)			
AE	315 (39)	316 (39)	314 (39)
Drug-related AE	29 (4)	37 (5)	27 (3)
AE leading to study withdrawal	32 (4)	36 (4)	26 (3)
Serious adverse events (SAE), n (%)			
Non-fatal SAE	46 (6)	31 (4)	38 (5)
Fatal SAE*	4 (<1)	4 (<1)	0
Drug-related SAE	0	0	0
Most frequent AEs†, n (%)			
Nasopharyngitis	68 (8)	87 (11)	84 (10)
Upper respiratory tract infection	19 (2)	12 (1)	20 (2)
Influenza	20 (2)	9 (1)	18 (2)
Back pain	10 (1)	13 (2)	15 (2)
Cough	14 (2)	11 (1)	10 (1)
Headache	10 (1)	17 (2)	6 (<1)

GOLD Guideline

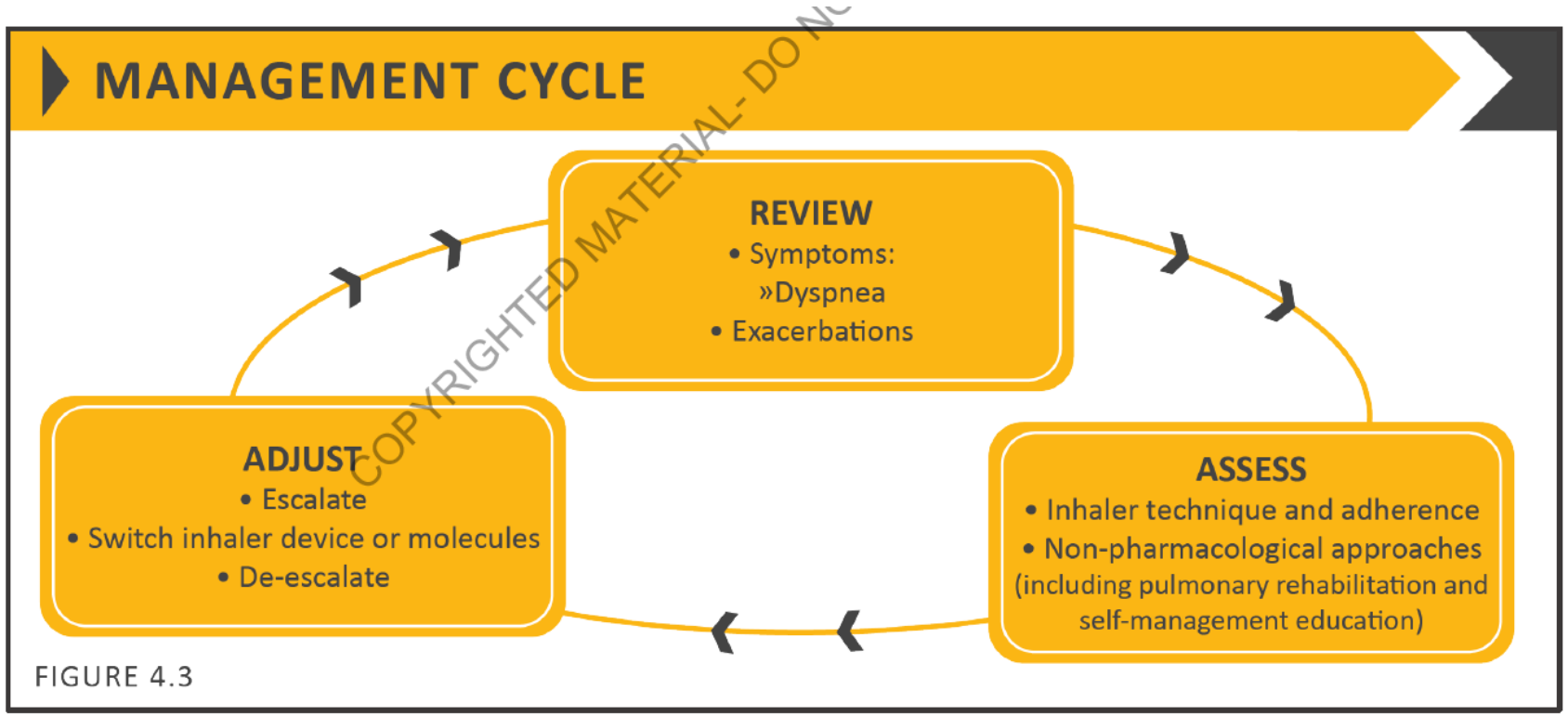
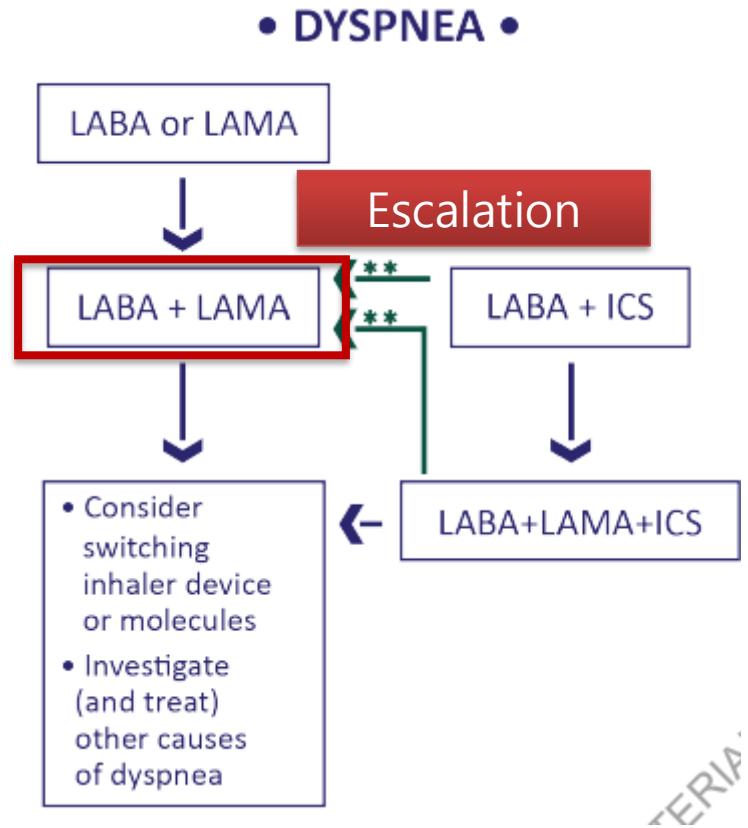
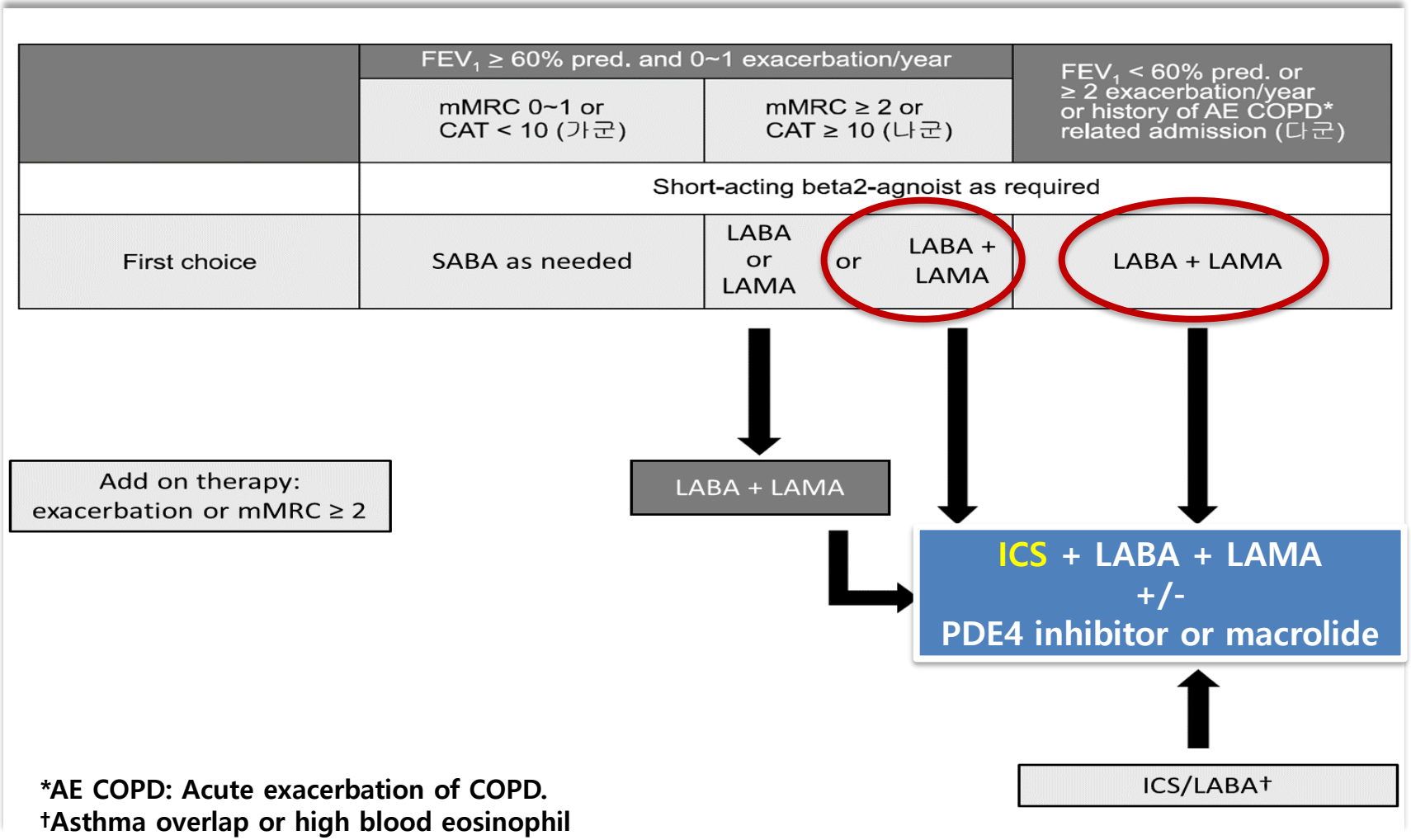


FIGURE 4.3



2018, Korean Guideline



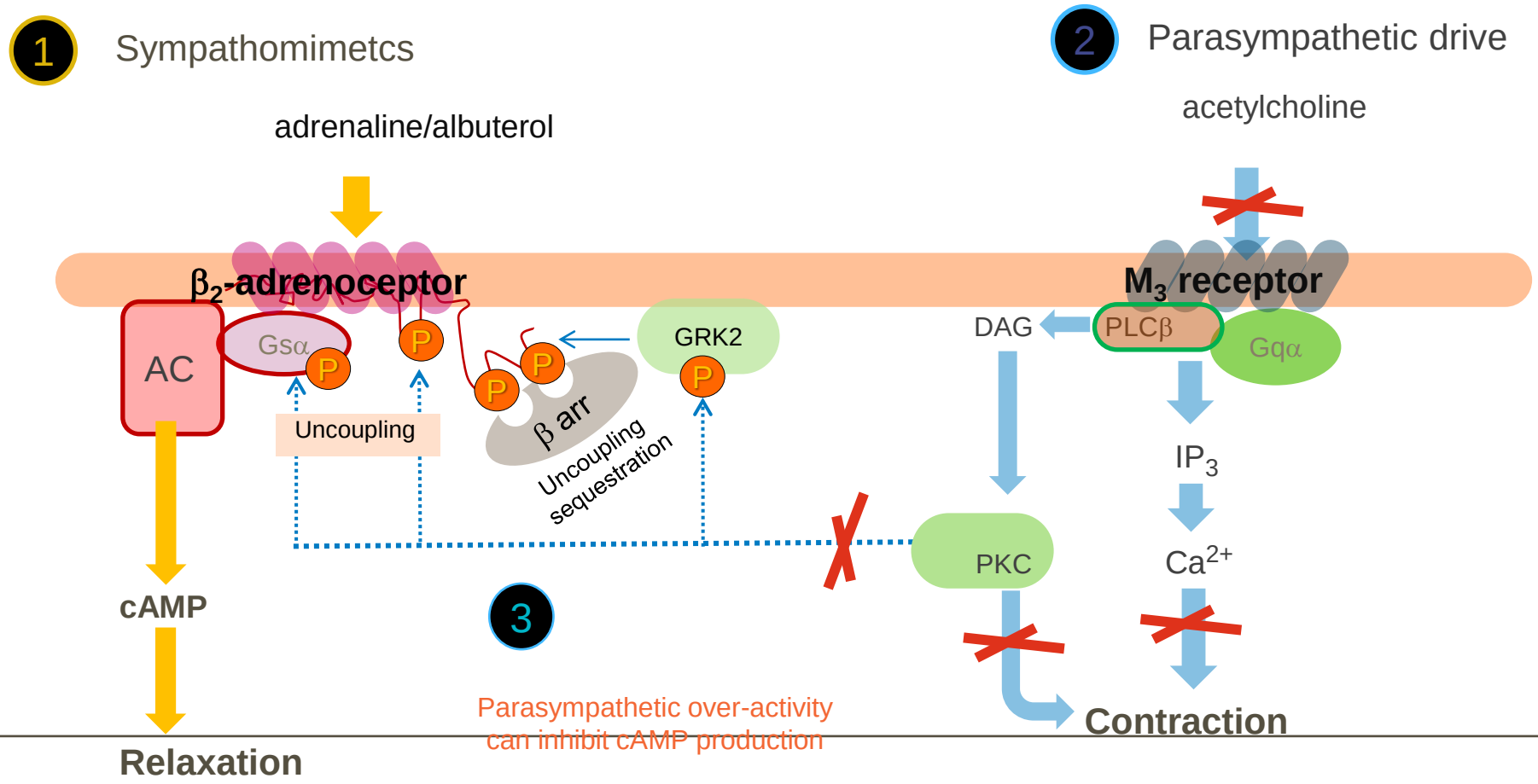
*AE COPD: Acute exacerbation of COPD.
†Asthma overlap or high blood eosinophil
‡급성악화 병력이 있고 만성기관지염을 수반한 COPD: 1) FEV1 < 50% 정상예측치 또는 흡입지속성베타-2작용제나 흡입지속성항콜린제 등의 지속 투여에도 연 2회 이상 급성악화가 발생한 경우

경청해 주셔서

감사합니다.

Dual bronchodilation

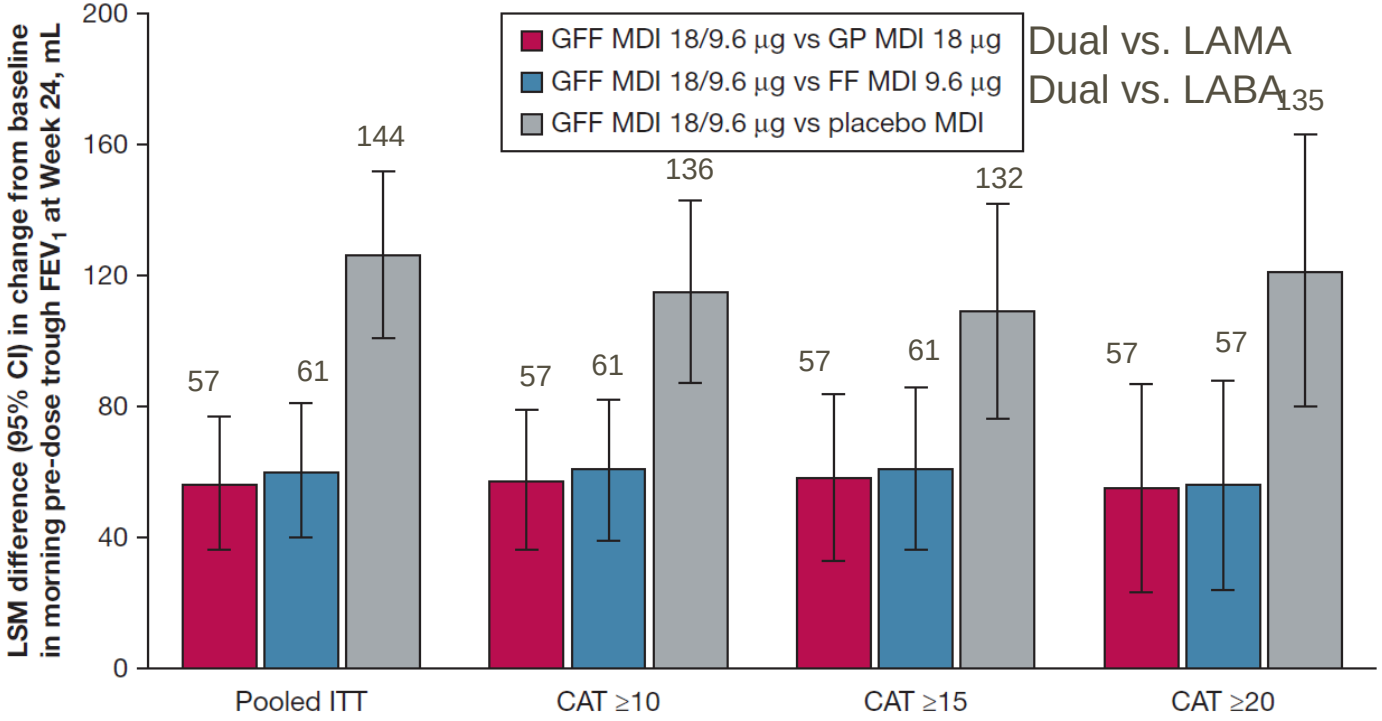
Mechanism of action of relieving airway obstruction in human airway smooth muscle



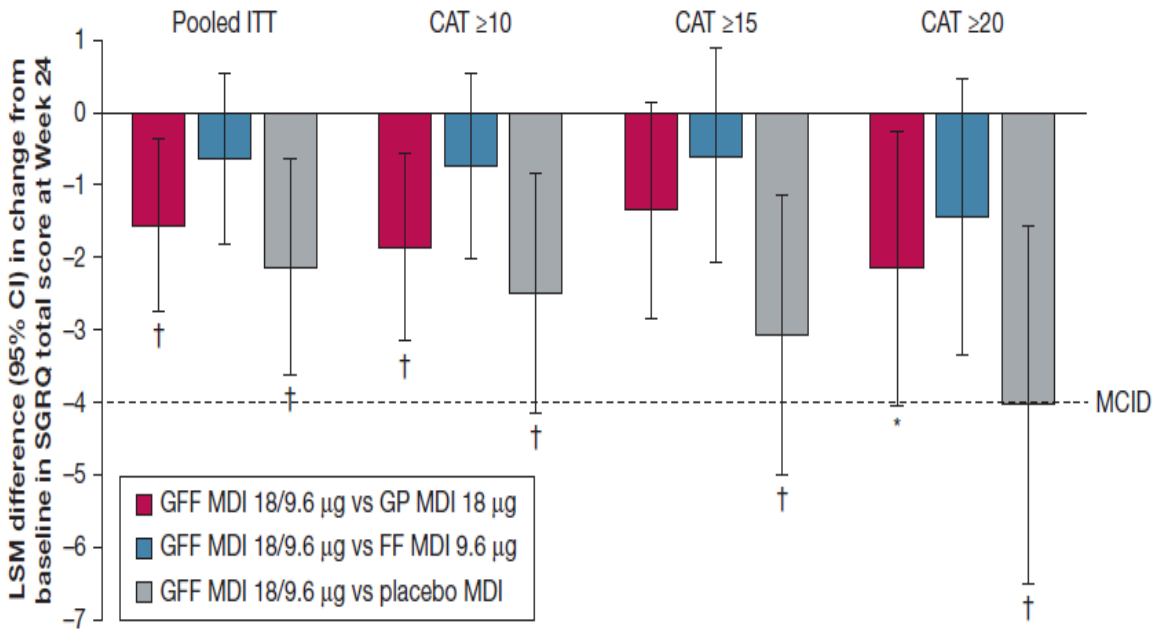
Adapted from Meurs H et al Pulmonary Pharmacology & Therapeutics (2013)

Baseline CAT & dual bronchodilators

FEV_1



SGRQ total



GFF glycopyrrolate/formoterol fumarate
GP glycopyrrolate
FF formoterol fumarate

Martinez et al. Chest 2017;152: 1169-1178

Baseline CAT & dual bronchodilators

TABLE 2] Rates and Rate Ratios (GFF MDI vs Comparator [95% CI]) of Moderate or Severe COPD Exacerbations Stratified by Baseline CAT Score

	Pooled PINNACLE-1 and PINNACLE-2			
Rate of Moderate or Severe COPD Exacerbations	GFF MDI 18/9.6 µg	GP MDI 18 µg	FF MDI 9.6 µg	Placebo MDI
ITT				
Adjusted[a] annual rate	0.511	0.591	0.568	0.649
Treatment incidence rate ratio (95% CI)[b]	...	0.87 (0.69-1.08)	0.90 (0.72-1.13)	0.79 (0.60-1.04)
Baseline CAT ≥ 10				
Adjusted[a] annual rate	0.509	0.624	0.594	0.647
Treatment incidence rate ratio (95% CI)[b]	...	0.82 (0.65-1.03)	0.86 (0.68-1.08)	0.79 (0.59-1.05)
Baseline CAT ≥ 15				
Adjusted[a] annual rate	0.512	0.669	0.658	0.707
Treatment incidence rate ratio (95% CI)[b]	...	0.77[c] (0.60-0.98)	0.78 (0.61-1.00)	0.72[c] (0.53-0.99)
Baseline CAT ≥20				
Adjusted[a] annual rate	0.503	0.734	0.657	0.770
Treatment incidence rate ratio (95% CI)[b]	...	0.69[c] (0.50-0.94)	0.77 (0.55-1.06)	0.65[c] (0.44-0.97)

GFF glycopyrrolate/formoterol fumarate
GP glycopyrrolate
FF formoterol fumarate

Martinez et al. Chest 2017;152: 1169-1178

Case

M/78세 Anoro 사용중
악화 없음