# A dual bronchodilator of LAMA & LABA as a primary therapy for symptomatic moderate COPD patients (나 군)

# Pro

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최혜숙

# 질문 1

75세 남자

3개월 전부터 진행하는 호흡곤란 mMRC IV, 기침(-), 가래(-)

흡연력-30갑년, 알러지 병력(-)

$FEV_1$/FVC 63%, $FEV_1$은 예측치의 75%, BD(-)

**첫 치료로 어떤 처방을 하시겠습니까?**

① ICS+LABA

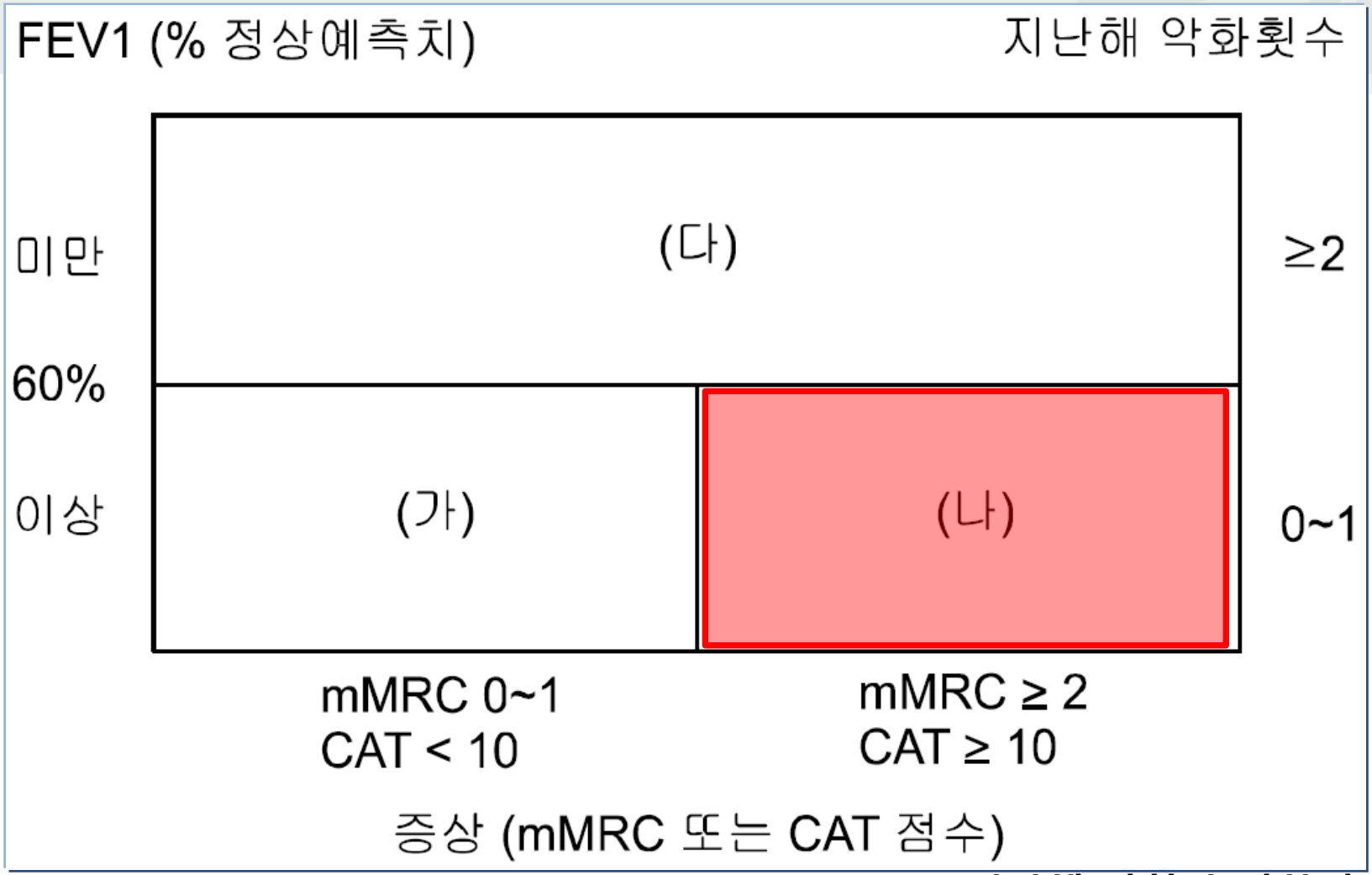
② LAMA+LABA

③ LAMA 또는 LABA

④ ICS+LABA+LAMA

⑤ Oral corticosteroid

# COPD의 한국분류(가, 나, 다군)




mMRC, CAT : 뒤 슬라이드 참고

**지난해 악화가 심하여 입원 하였으면 1번이라도 다 군임.**

# COPD 치료의 목표

- 증상 완화
- 폐기능향상
- 운동 능력 향상
- 삶의 질 향상

증상 호전
(기관지 확장제)

- 급성악화 감소
- 질병진행 예방
- 사망률 감소

위험 감소
(기관지 확장제 + 항염증 치료)

GOLD. COPD guidelines 2014. Available at http://www.goldcopd.org (Accessed December 2014)

# 국내 COPD "나" 군 환자의 치료

| | $FEV_1 \geq 60\%$ 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 |

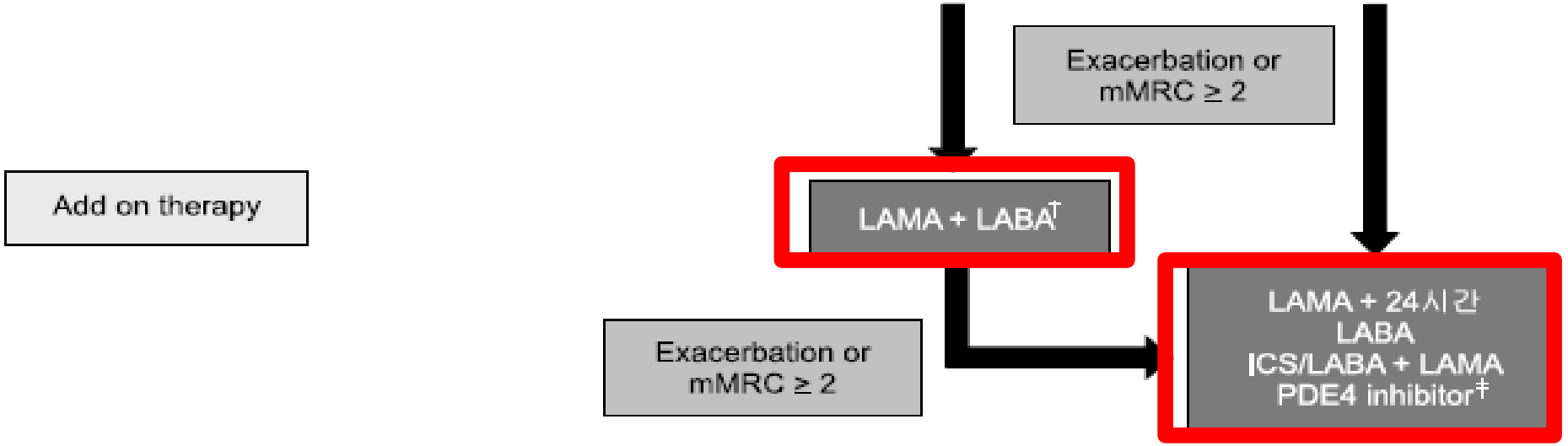
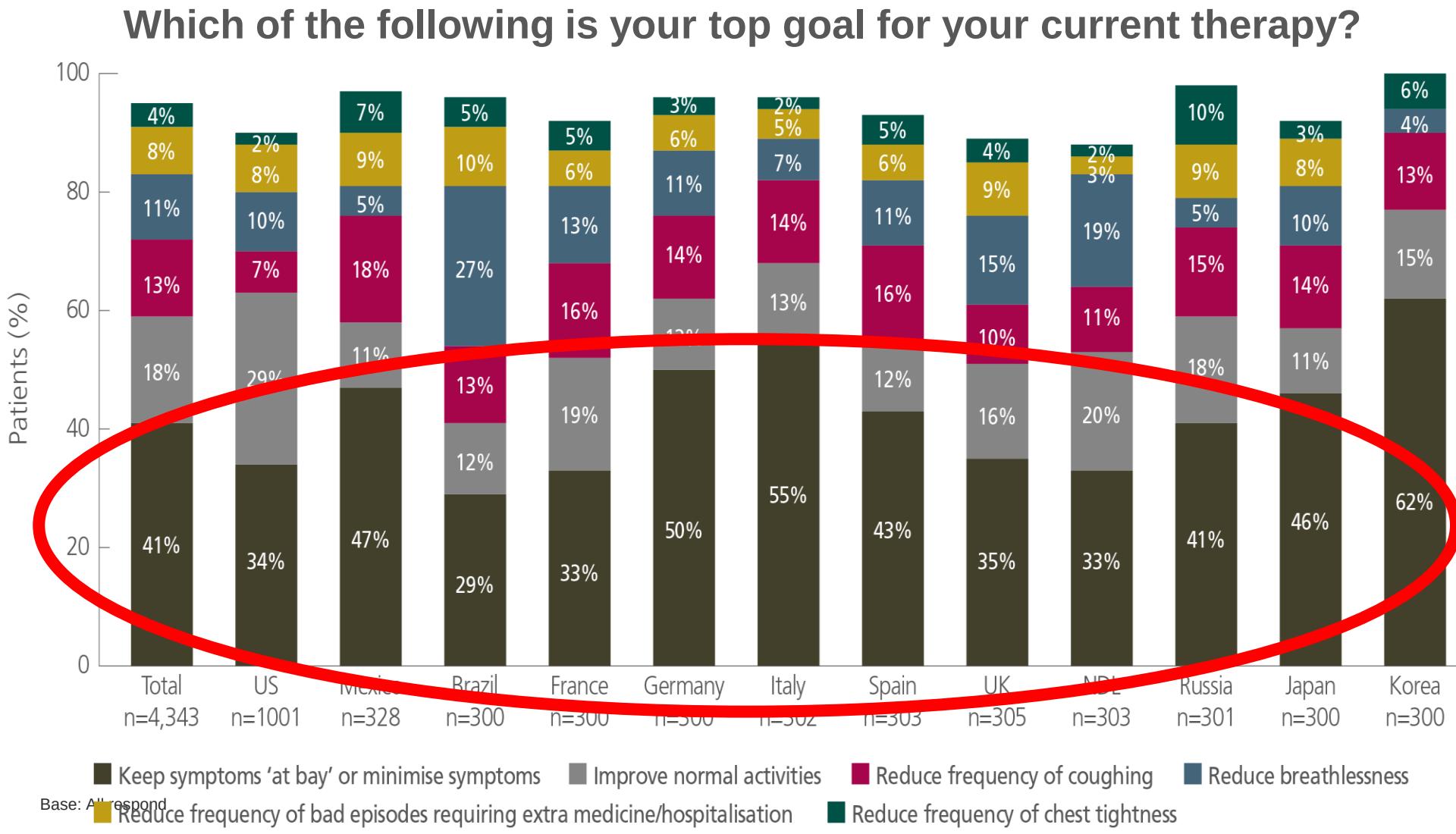



그림 3-2. 안정 시 COPD의 약물 단계치료.
*AE COPD: Acute exacerbation of COPD.
†24시간 LABA 포함.
‡$FEV_1$ <50% 정상예측치, 만성기침, 악화병력이 있는 환자군.
LABA: Long Acting Bronchodilator, LAMA: Long Acting Muscarinic antagonist.

지침서대로 기관지확장제를 사용하는 환자들은 증상조절이 잘 될까?

# COPD patients' top goal for current therapy is to minimise symptoms[1]

*'Continuing to Confront COPD'- patients survey across 12 countries[1]*



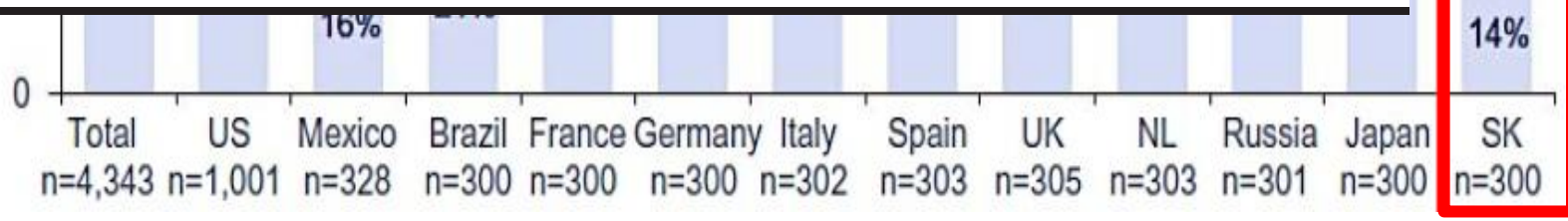

Base: All respond

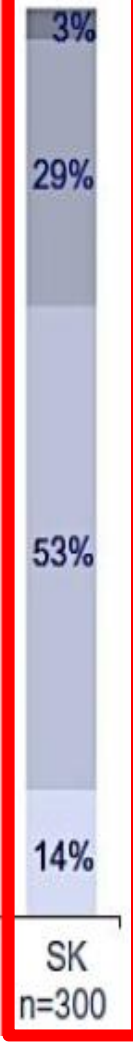
1. C2C selection for Anoro MedAffairs. GSK. Data on File.

# Patient-reported COPD severity.

: Continuing to Confront COPD International Patient Survey

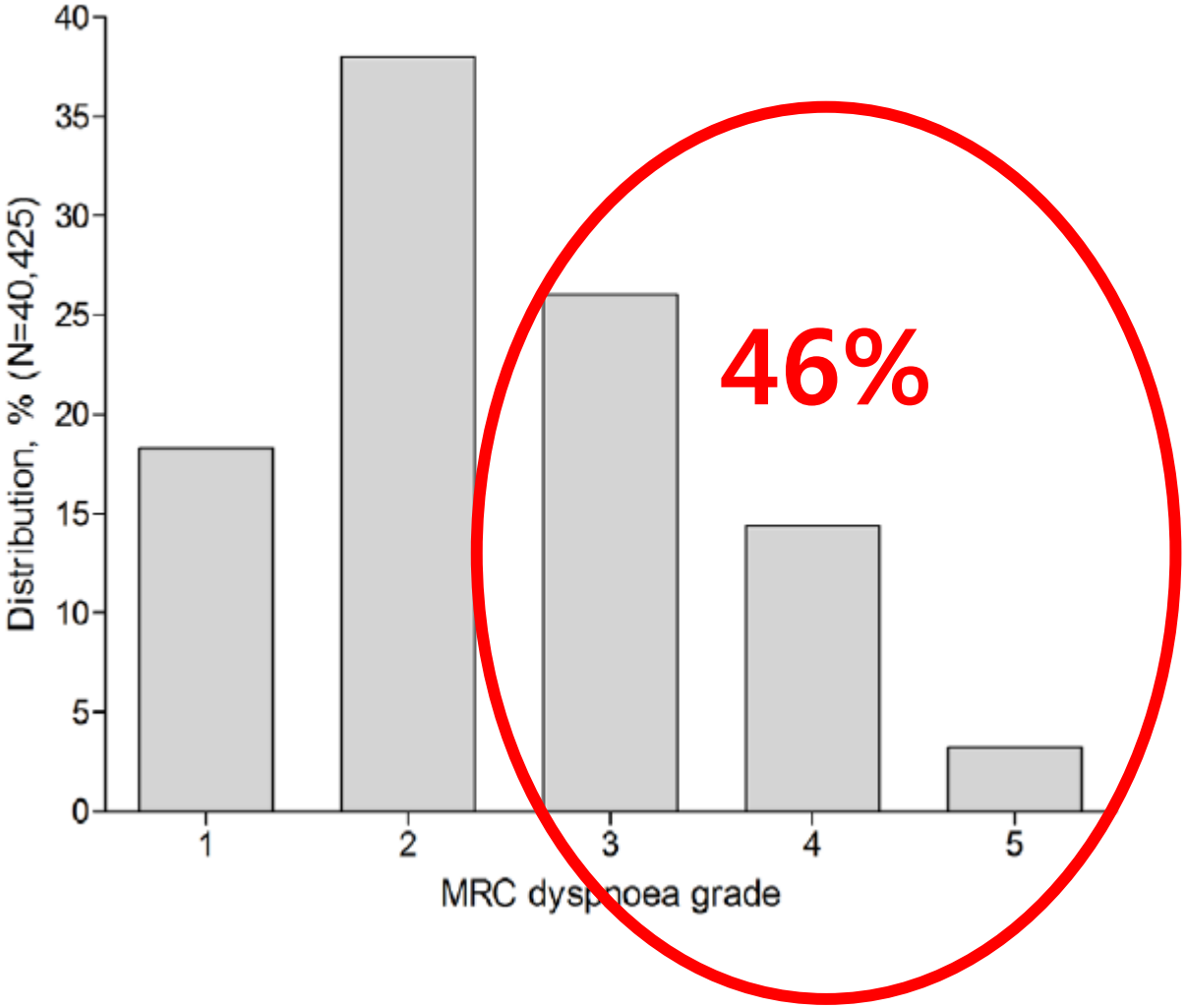
| | Total n=4,343 | SK n=300 |
|---|---|---|
| CAT score, mean (SD) | 21.5 (9.2) | 24.2 (7.7) |
| mMRC grade | | |
| 0–1 | 53 | 52 |
| ≥2 | 47 | 48 |



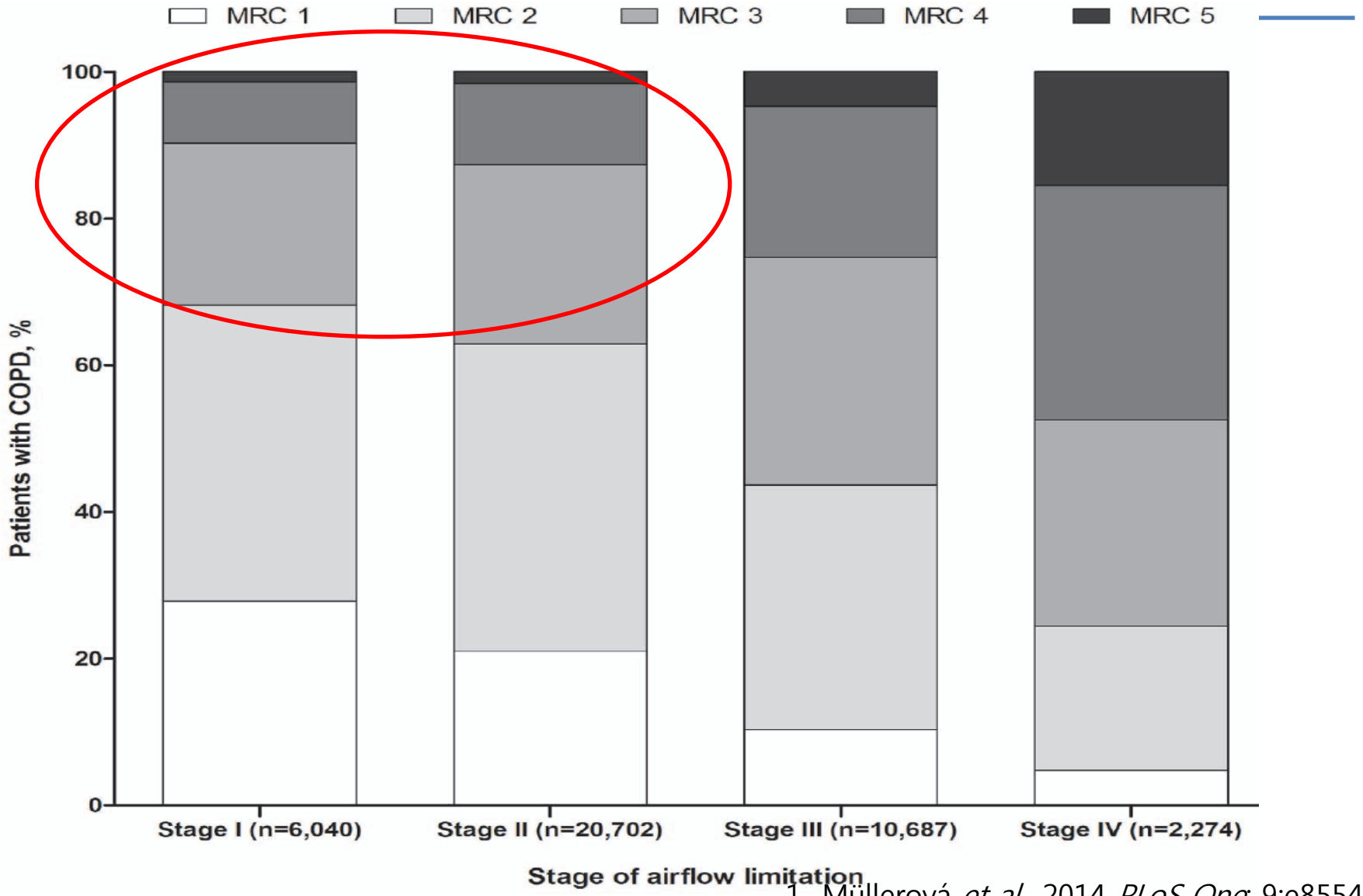

International Journal of COPD 2014:9 597–611

# Moderate-to-severe dyspnoea **(MRC ≥ 3)** was reported by **>40%** of patients diagnosed with COPD in primary care



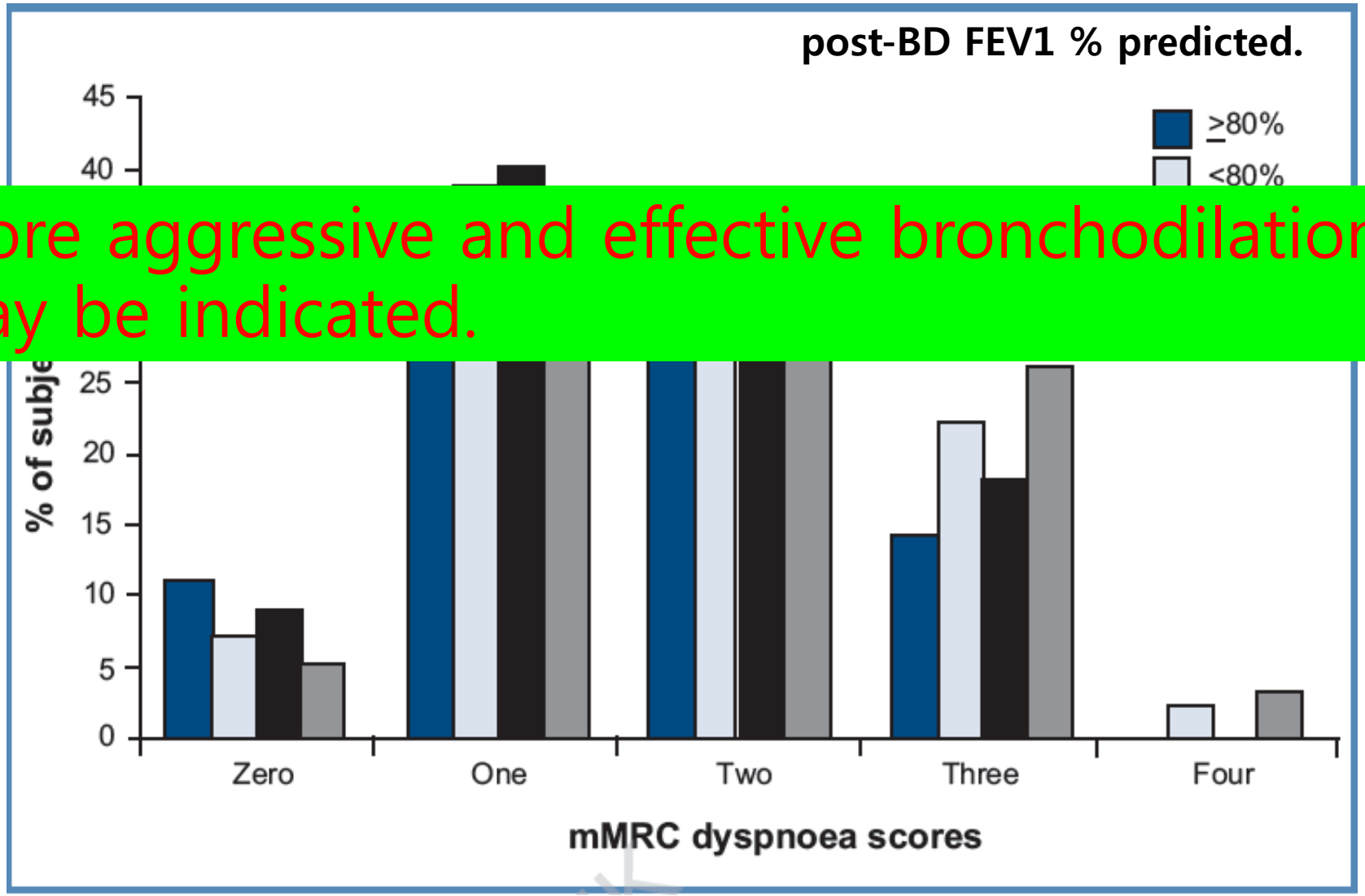

1. Müllerová *et al.*, 2014 *PLoS One*; 9:e85540

# Dyspnoea severity increased with increasing severity of airflow




1. Müllerová *et al.*, 2014 *PLoS One*; 9:e85540

# Many patients continue to experience breathlessness on mono-LABD therapy, USA, N=1084




More aggressive and effective bronchodilation may be indicated.

*Primary Care Respiratory Journal* (2011); 20(1): 46-53

# COPD patients treated with ICS/LABA still have moderate-to-severe dyspnoea

| Variable | Total cohort | MRC grade (N = 40,425) | | | | | p-value across MRC grades |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | |
| Medication, n (%) | | | | | | | |
| ICS | 10,451 (21.1) | 1664 (19.2) | 3454 (39.8) | | | | <0.001 |
| LABA | 4823 (9.8) | 532 (13.4) | 1508 (37.9) | | | | 0.169 |
| ICS/LABA combination product | 25,611 (51.8) | 2769 (13.3) | 7169 (34.5) | 5912 (28.5) | 3923 (18.9) | 983 (4.7) | <0.001 |
| LAMA | 19,374 (39.2) | 1610 (10.3) | 5109 (32.7) | 4753 (30.4) | 3324 (21.3) | 834 (5.3) | <0.001 |
| Theophyllines | 2976 (6.0) | 179 (7.9) | 533 (23.4) | 627 (27.5) | 692 (30.4) | 248 (10.9) | <0.001 |
| SABD | 40,270 (81.5) | 5130 (15.6) | 12,311 (37.4) | 9009 (27.3) | 5281 (16.0) | 1218 (3.7) | <0.001 |
| Oral corticosteroid, long-term treatment[a] | 3163 (6.4) | 198 (8.6) | 567 (24.6) | 640 (27.8) | 644 (28.0) | 254 (11.0) | <0.001 |

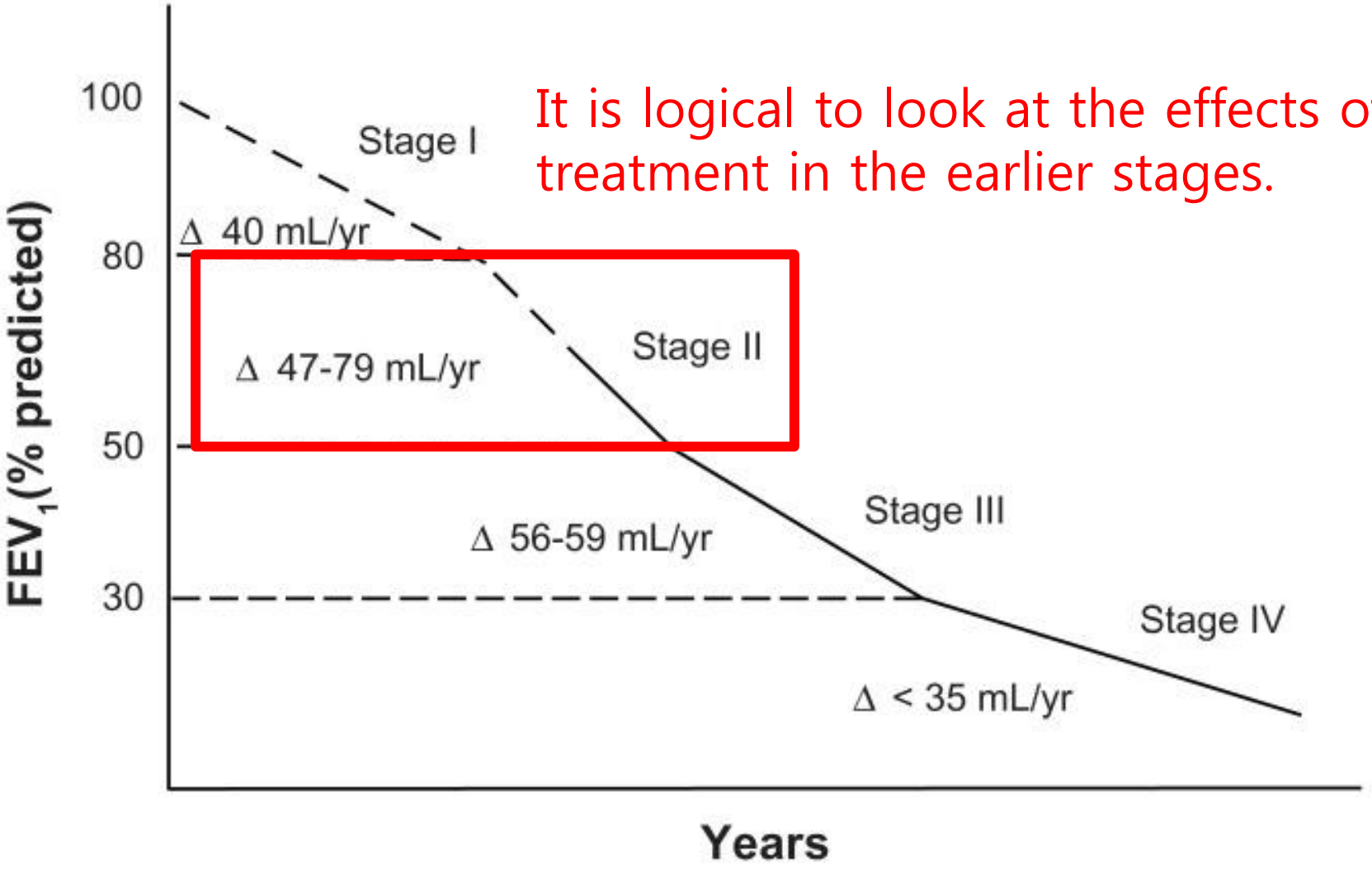
**52%**

1. Müllerová *et al.*, 2014 *PLoS One*; 9:e85540

# 폐기능 저하가 심하지 않은 조기 COPD 환자 적극적인 치료가 필요할까?

네

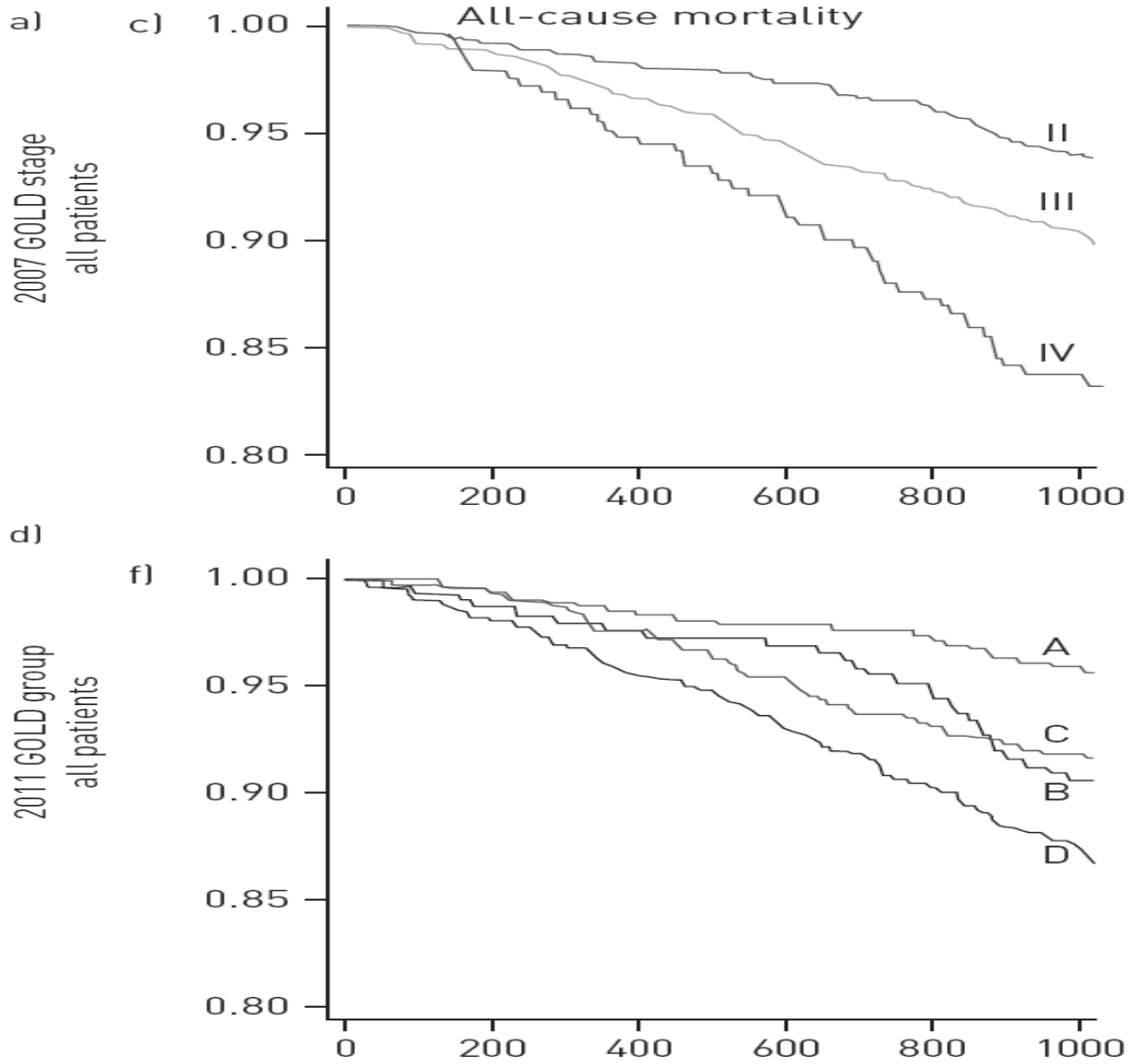
# The loss of lung function seems more accelerated in the initial phases of COPD




It is logical to look at the effects of treatment in the earlier stages.

Int J Chron Obstruct Pulmon Dis. 2012;7:95-9

# Mortality rates for COPD patients: GOLD A-D



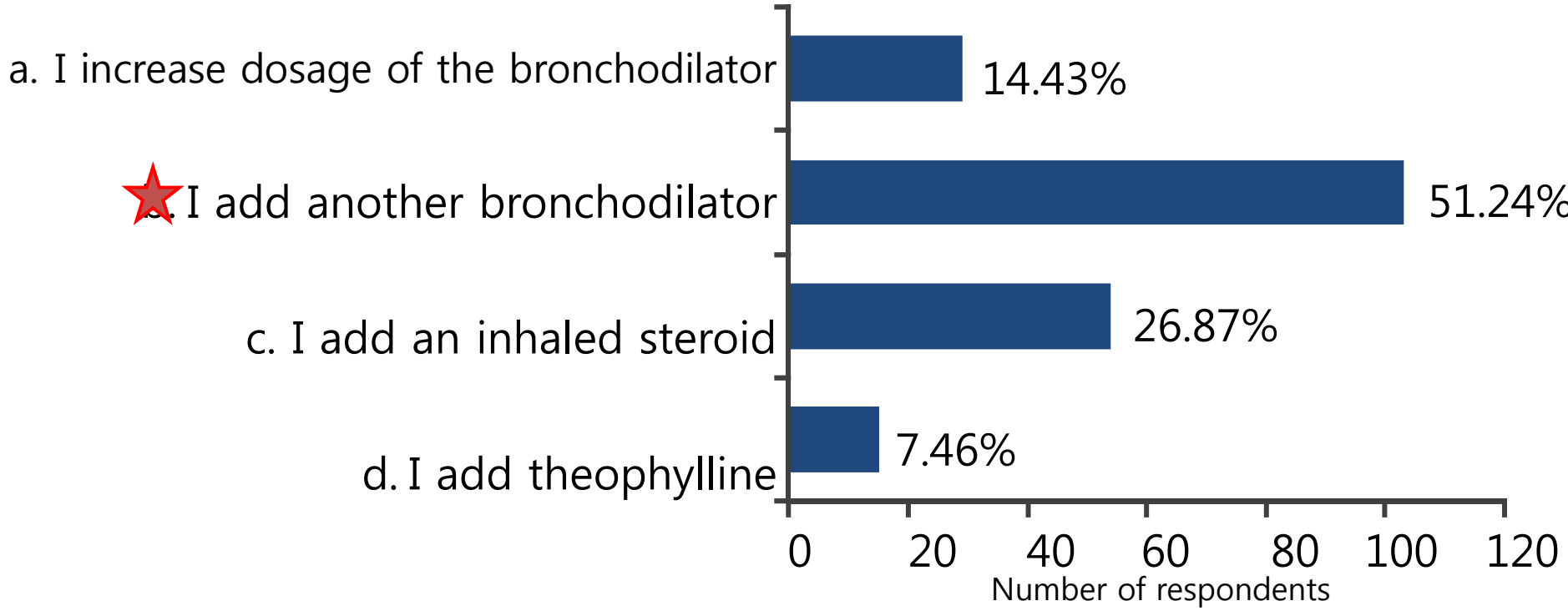

*Eur Respir J 2013; 42:636–646.*

- 현재 우리는 지침서대로 치료하고 있는가?

# The majority of respirologists would add a second bronchodilator to symptomatic patients, The Delphi Primo survey, Italy, n=208

**Doctors were asked:**

**"In the follow-up, what measures do you use when a patient, already under treatment with a single bronchodilator, returns with persistent symptoms?"**



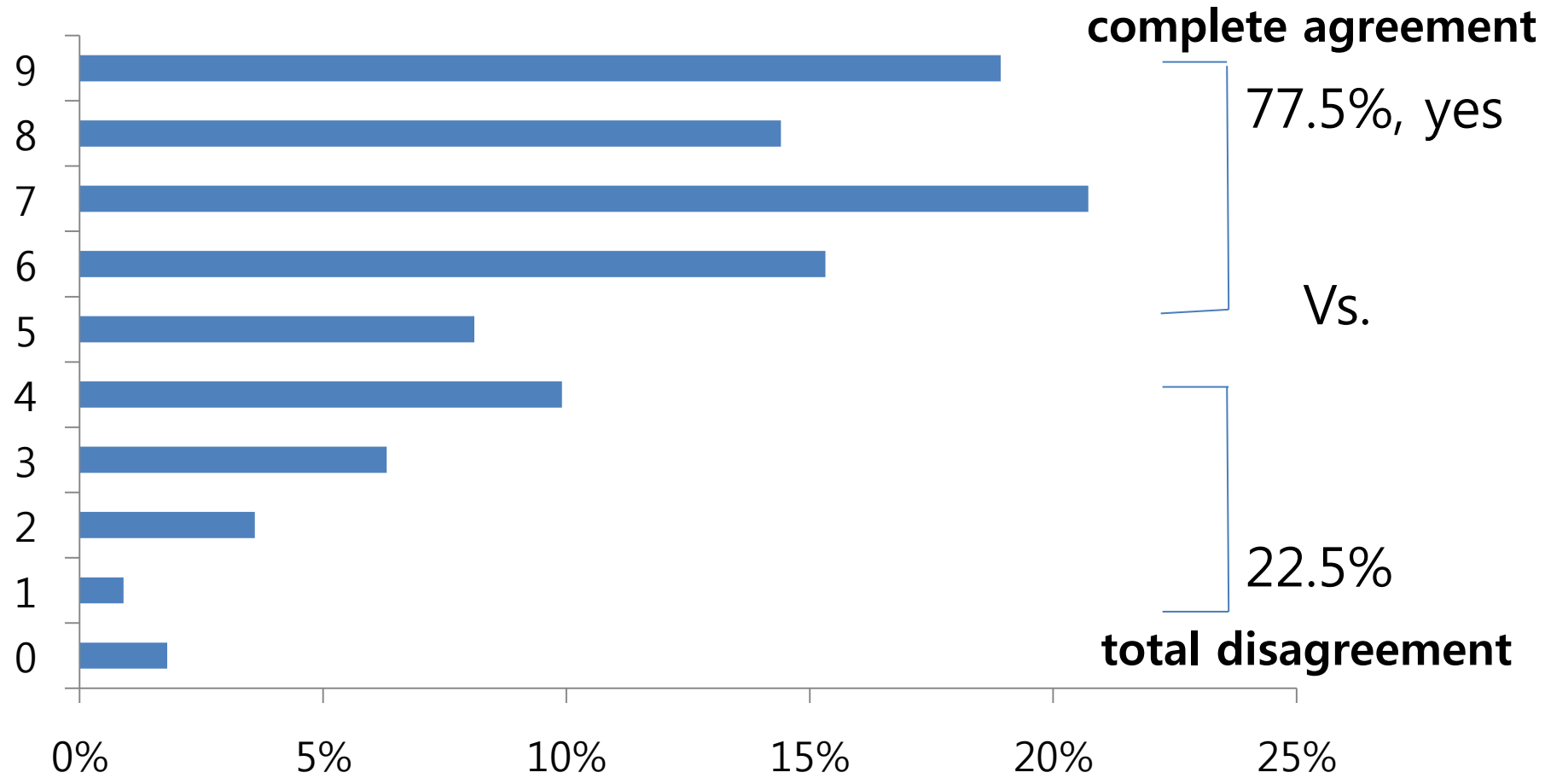

Cazzola et al. Pulm Pharmacol Ther. 2013 Apr;26(2):218-28

# The majority of respirologists thought the use of bronchodilators is effective in the prevention of exacerbations,

The Delphi Primo survey, Italy, n=208

**Doctors were asked:**

**Do you think the use of bronchodilators is effective in the prevention of exacerbations?**




Pulm Pharmacol Ther. 2013 Apr;26(2):218-28

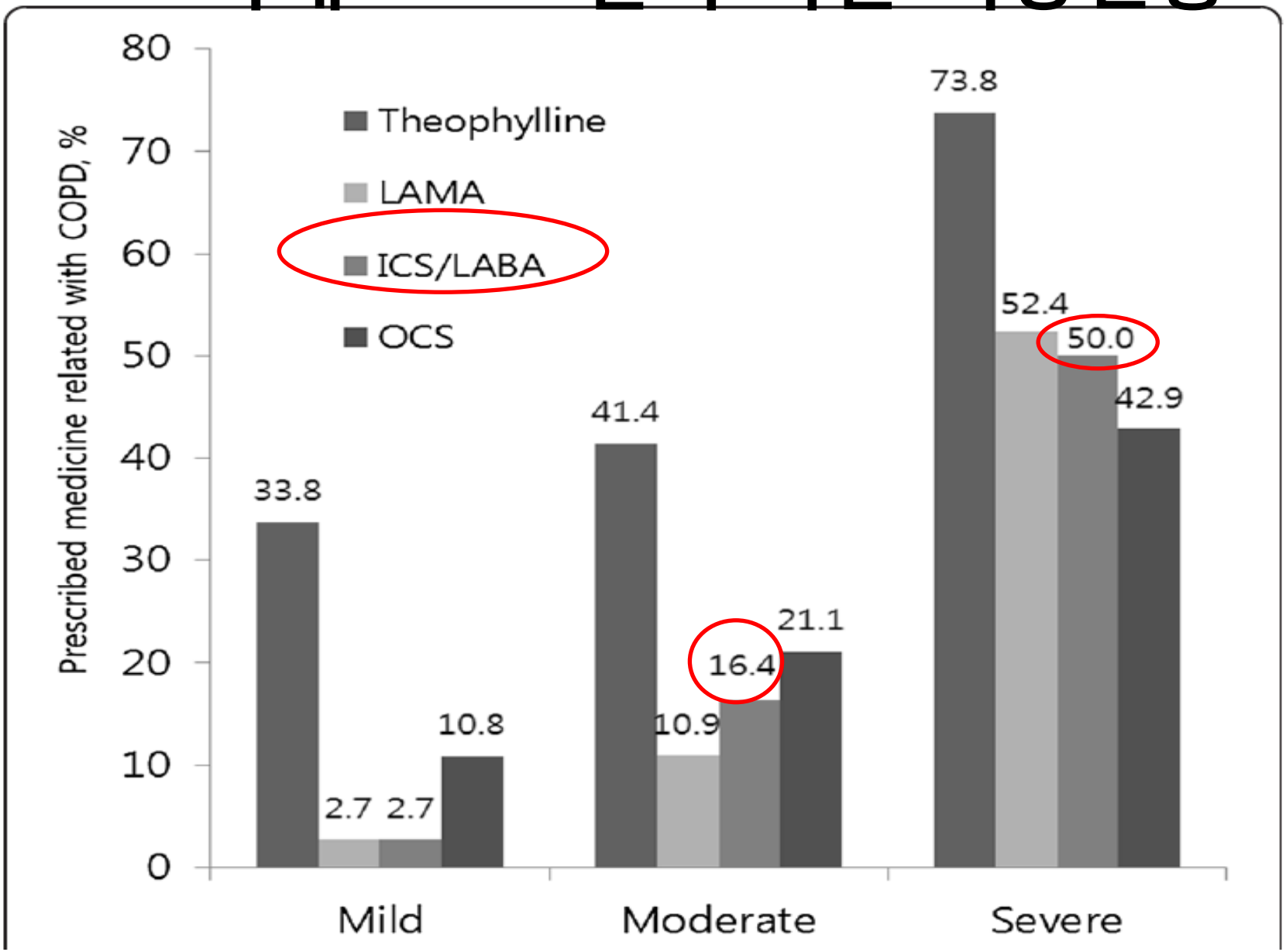
Currently free combination(LABD) is utilized much less frequently than LAMA monotherapy (tiotropium), LABA/ICS combinations, and the triple combination of LAMA +LABA/ICS in clinical practice

| Regimen | Mean monthly patient volume[a] | | |
|---|---|---|---|
| | Total COPD | COPD only | COPD + asthma |
| Tiotropium monotherapy | 310,423 | 279,530 | 30,893 |
| ICS/LABA | 451,019 | 360,760 | 90,259 |
| LABA + LAMA | 5,888 | 5,479 | 410 |
| Tiotropium + ICS/LABA | 193,137 | 170,063 | 23,074 |

aData from IMS Health, LifeLink solutions, calculated from US CMS-1500 medical claims and NCPDP prescription claims during period May 2011-April 2012.

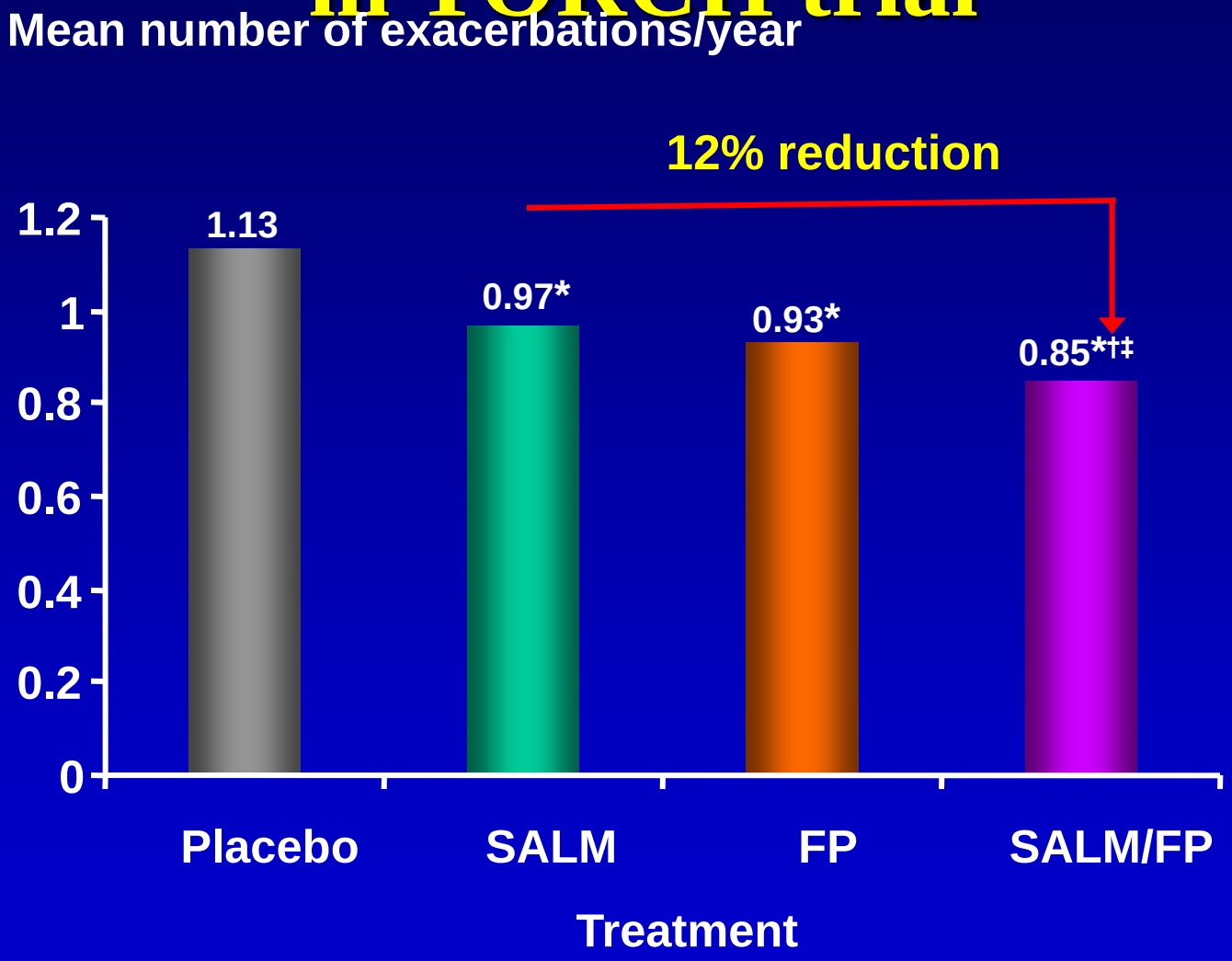
Tashkin and Ferguson Respir Res. 2013; 14(1): 49.

# 국내 COPD환자 약물 처방현황




Chung et al. BMC Pulmonary Medicine 2014, 14:27

# Moderate and severe exacerbations in TORCH trial

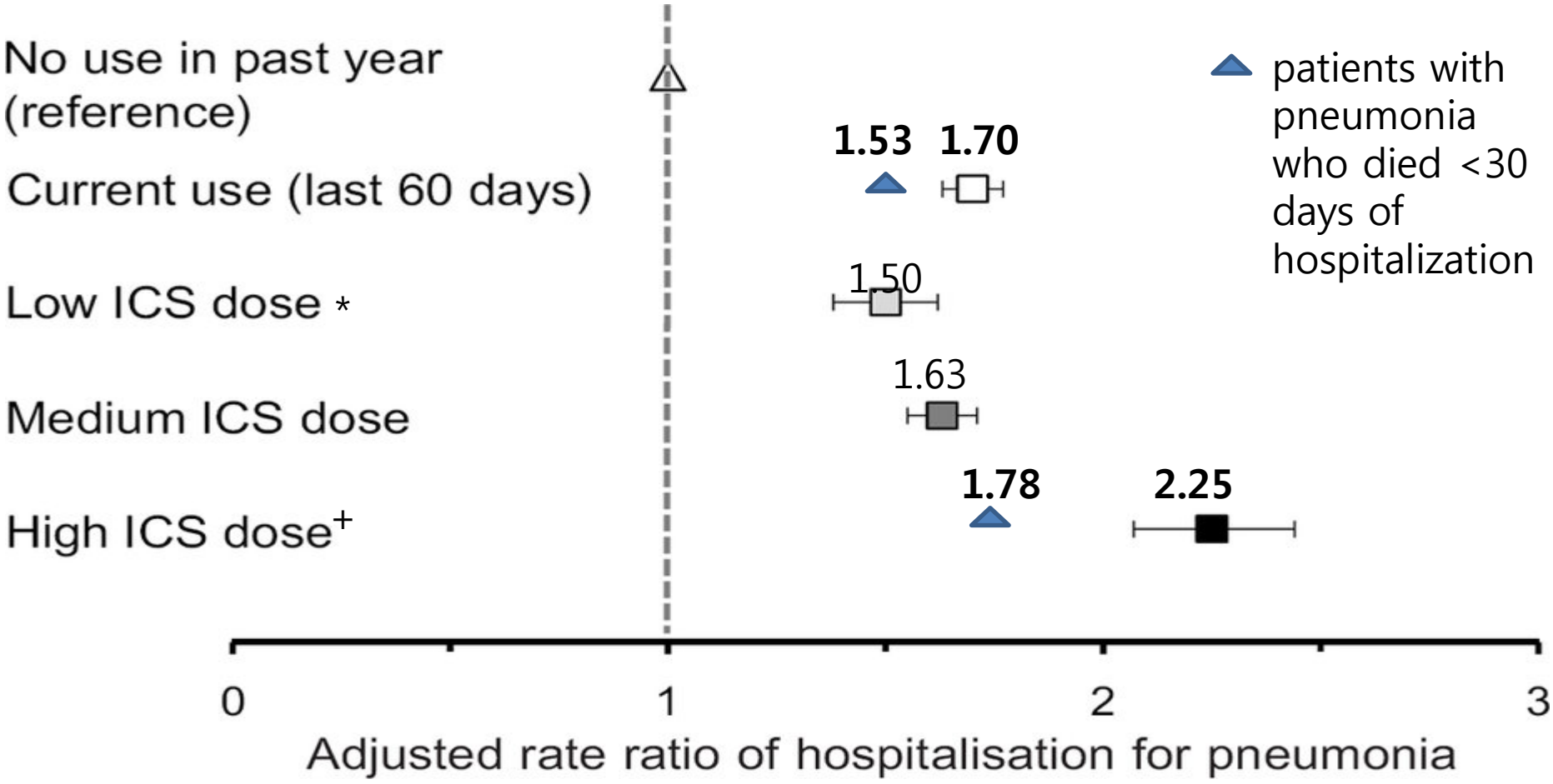



*p < 0.001 vs placebo; †p = 0.002 vs SALM; ‡p = 0.024 vs FP

**25% reduction**

Calverley et al. N Engl J Med. 2007 22;356(8):775–89.

# The use of ICS is associated with an excess risk of pneumonia hospitalization




*Fluticasone<500 μg
+ Fluticasone>1000 μg

*Prim Care Respir J 2013; 22(1): 92-100*
*adapted from AJRCCM 2007:176(2):162-166*

# 무슨 의미인가?

- Benefits must be balanced against risks
- For breathless subjects at low risk of exacerbations optimal bronchodilation manages symptoms whilst minimizing risks of treatment related side effects

# 그렇다면, 어떻게 해야하는가?

# Dual bronchodilation may offer enhanced efficacy

- "Bronchodilator medications are central to symptom management in COPD"

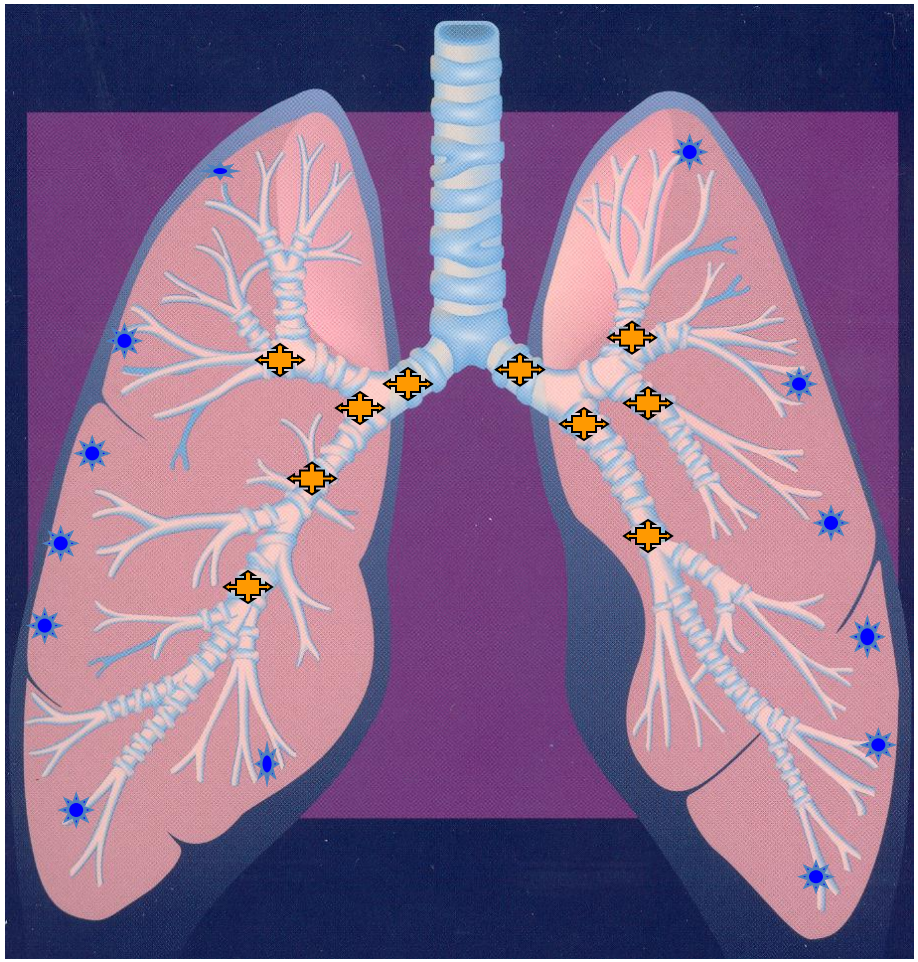
- *"Combining bronchodilators of different pharmacological classes may **improve efficacy** and **decrease the risk of adverse effects** compared to increasing the dose of a single bronchodilator."*

- The current GOLD strategy recommends **adding a second bronchodilator to therapy in stable COPD** in order to optimize the symptom benefit for patients

*GOLD 2014*

# 왜, dual bronchodilator인가?

# Antimuscarinic and $\beta_2$-agonist bronchodilators affect different airways in the lung



**β-adrenoreceptor**

- The density is higher in lung tissues
- **β-agonists are relatively more effective in the di stal airways**

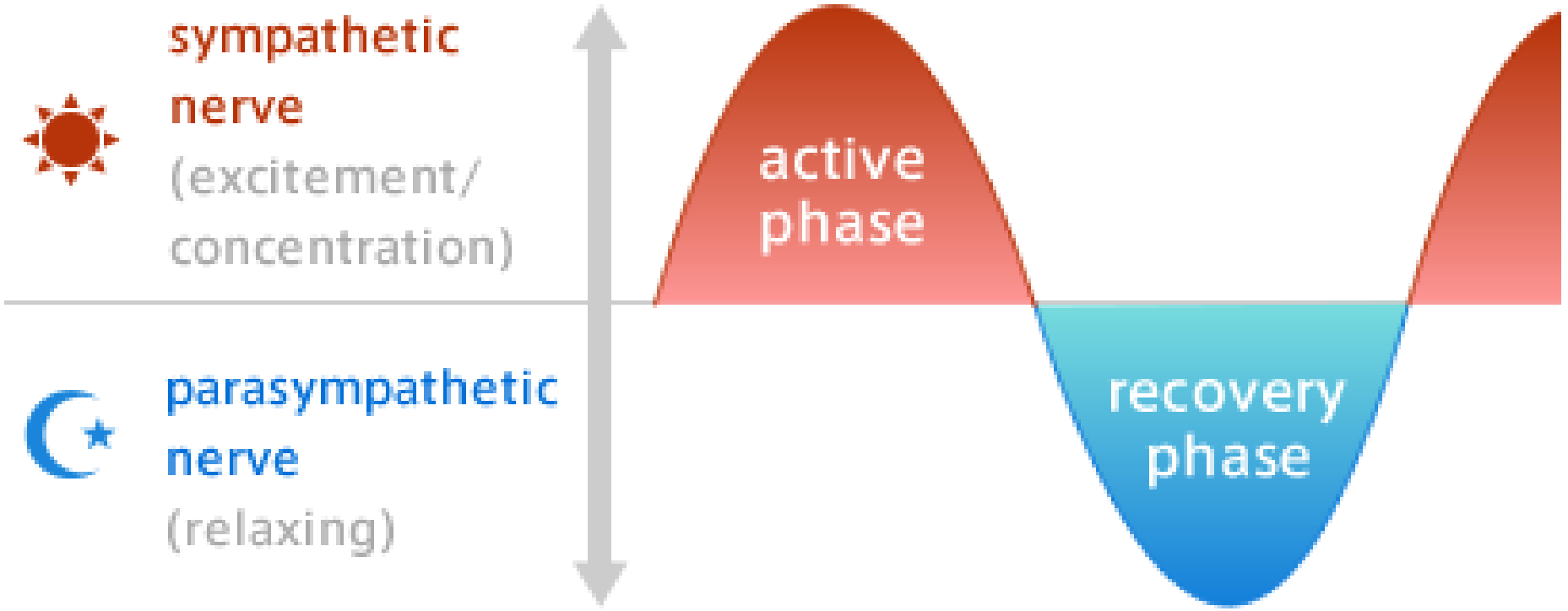
muscarinic receptor

- The density is higher in larger airways
- **Anticholinergic agents are more effective in t he proximal airways**

Data on file: Novartis KR1503311638

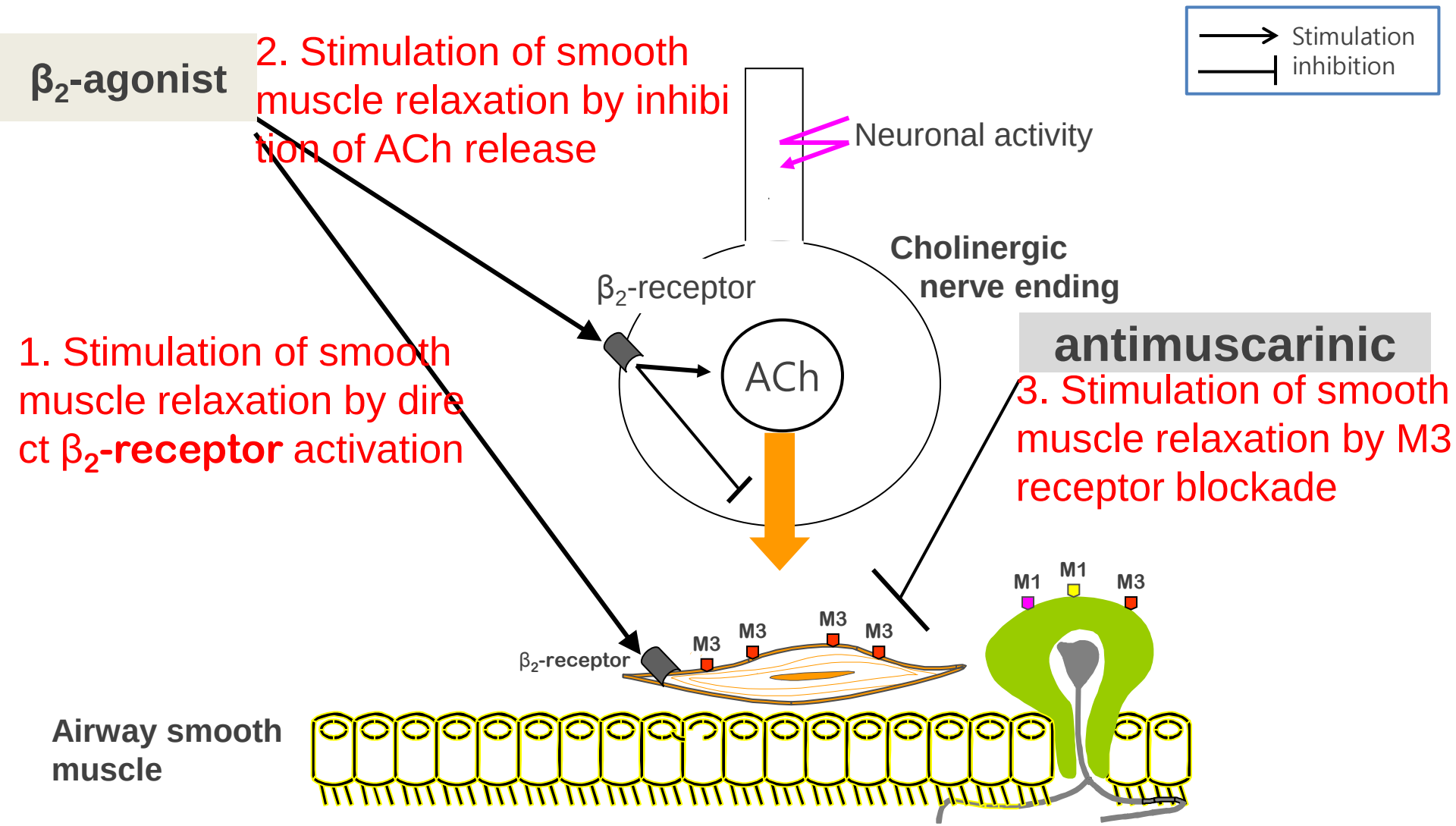
Proc Am Thorac Soc. 2004;1(4):345-51

# Targeting two bronchodilatory pathways may also address daily variations in symptoms




Circulation. 1990 Feb;81(2):537-47.

# $\beta_2$-agonists may amplify smooth muscle relaxation induced by antimuscarinics by reducing aceytlcholine release from cholinergic nerve endings

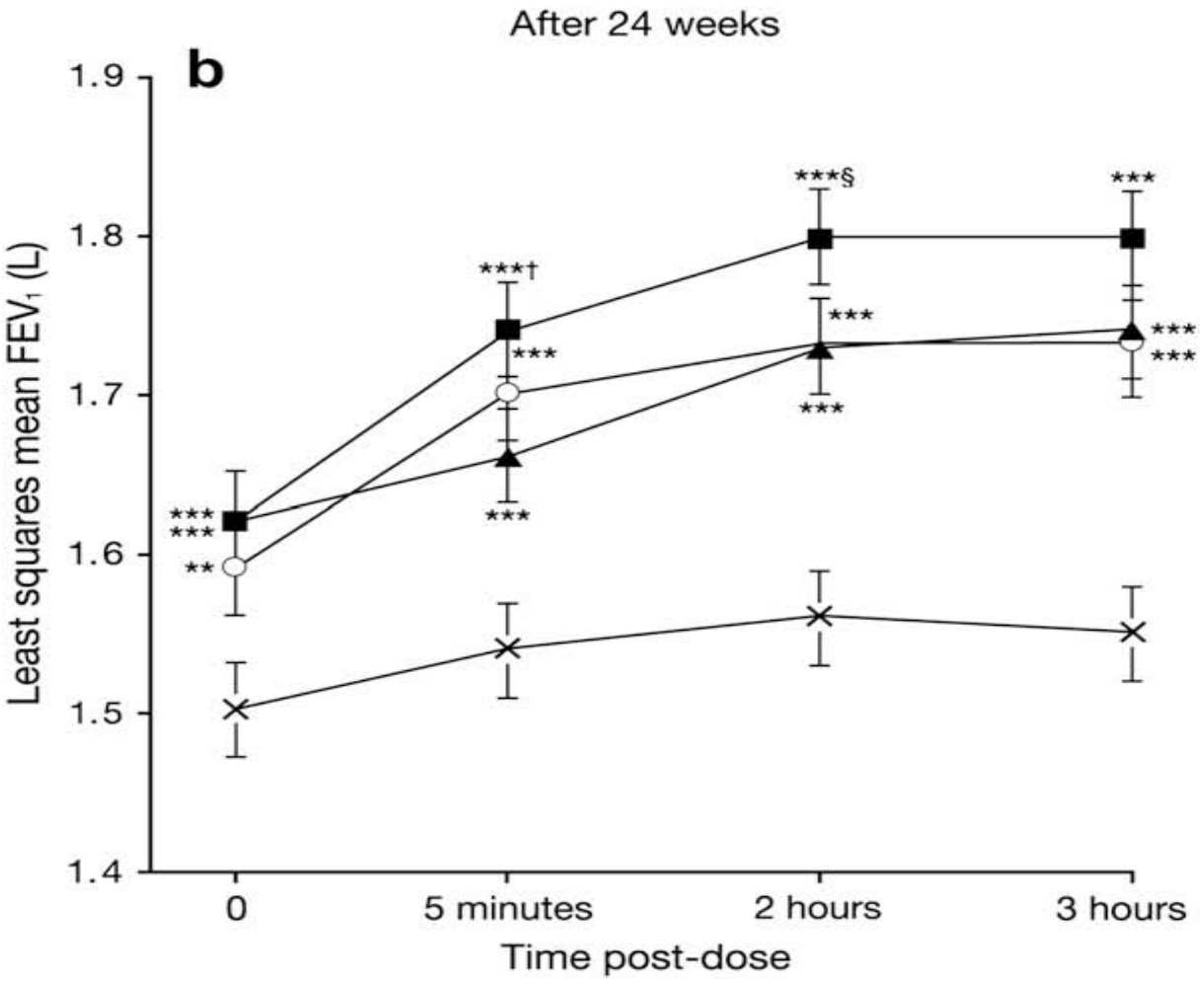



ACh = acetylcholine


1. Cazzola et al. Arch Bronconeumol 2005
2. Cazzola M and Matera MG. Drug Discov Today: Ther Strateg 2006

# Additional Bronchodilatation

Formoterol (10*μg* b.i.d) mono- and combination therapy with tiotropium(18 *μg* o.d) in patients with COPD: A 6-month study, n=847 (mean FEV1 52% predicted; FEV1/FVC 53%



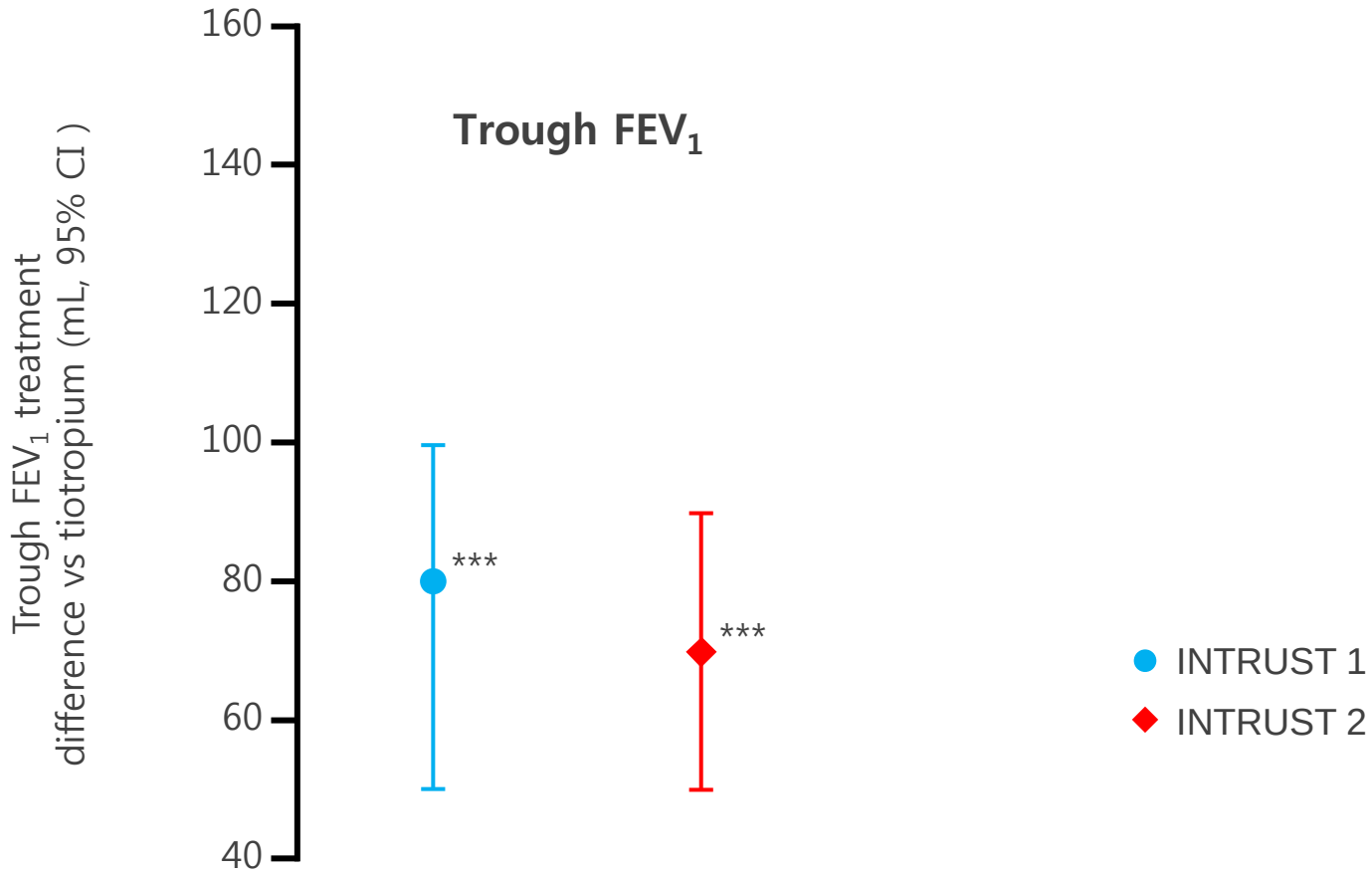

formoterol (O),
tiotropium (▲),
tiotropium
+formoterol (■)
or placebo (X).

+p < 0.05 vs.tiotropium,
§p < 0.05 vs. formoterol

Medicine (2008) 102, 1511e1520

# Indacaterol plus tiotropium improved trough $FEV_1$ vs tiotropium alone

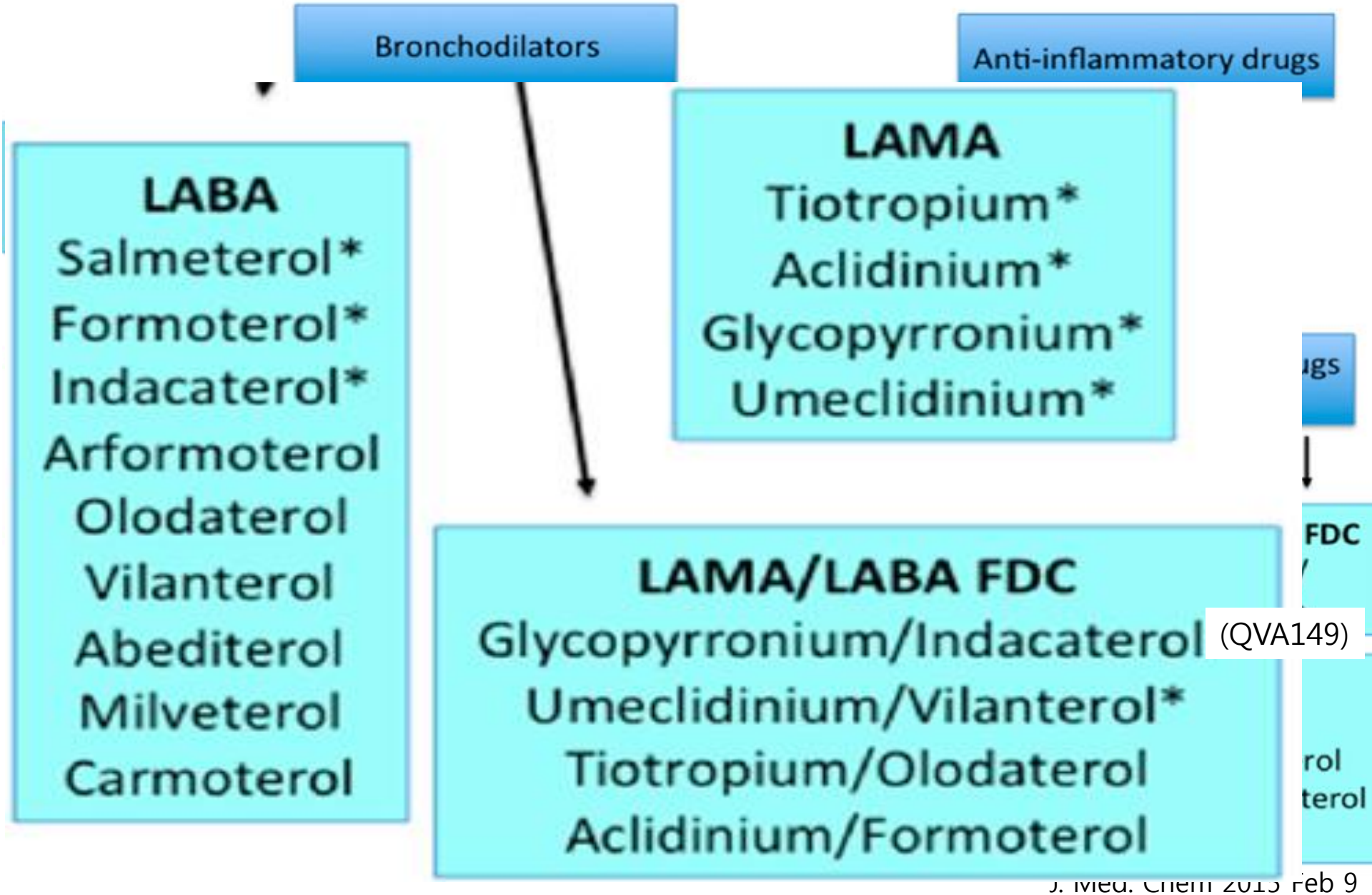
- **Difference between treatments (indacaterol 150 µg q.d. plus tiotropium 18 µg q.d. vs tiotropium 18 µg q.d.) in trough at Week 12**




***p<0.001

Mahler et al. Thorax 2012;67(9):781-8

# Drugs for stable COPD

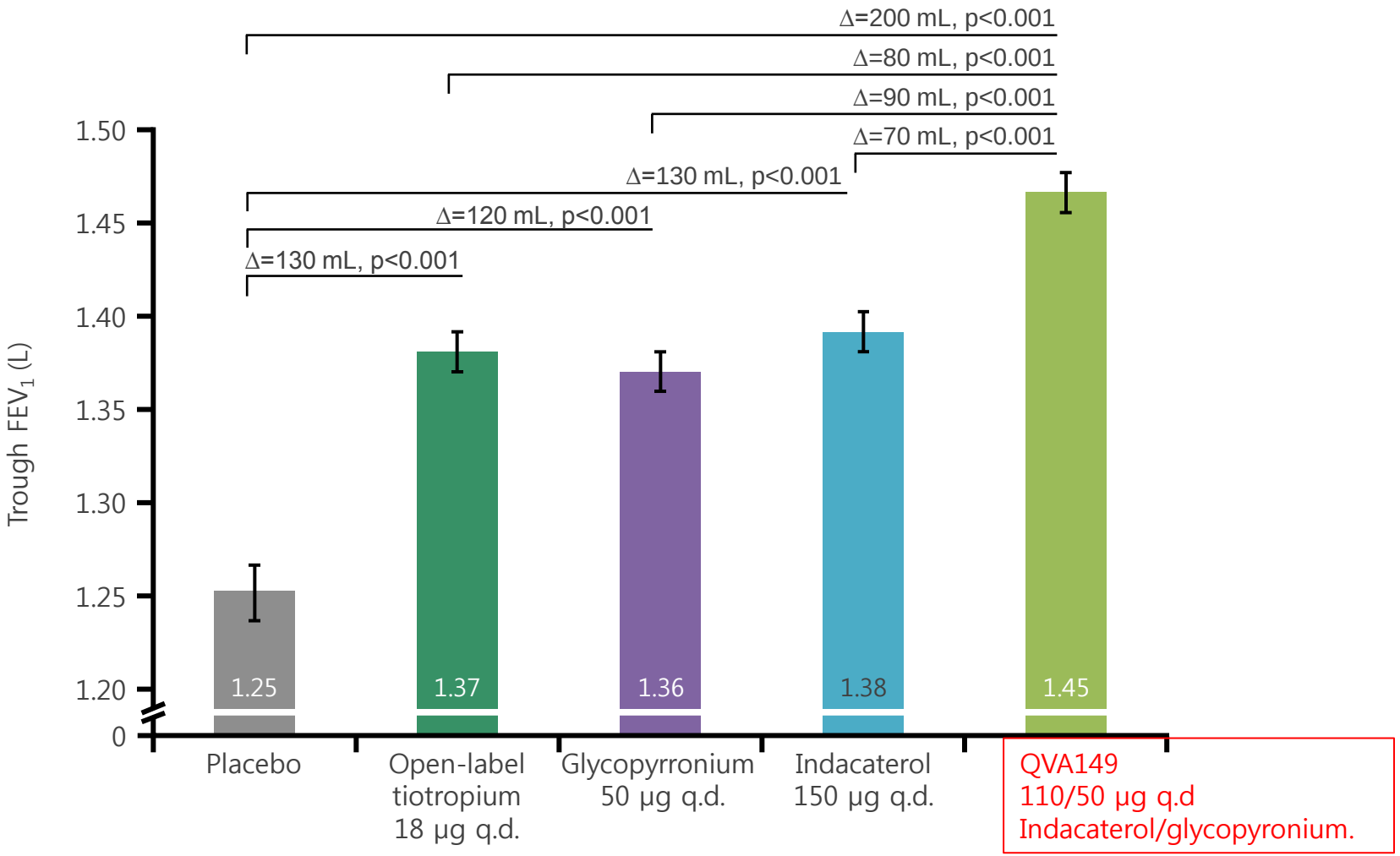



J. Med. Chem 2013 Feb 9

# Effects of dual bronchodilation on lung function

SHINE

# QVA149 significantly improved mean trough $FEV_1$ at Week 26 (primary endpoint), Pivotal safety and efficacy study (USA, EU, Latin America, Asia) 2,144 COPD patients randomized; 2,135 full analysis set, >80%$FEV_1$≥30%




Data are least-squares mean ± standard error

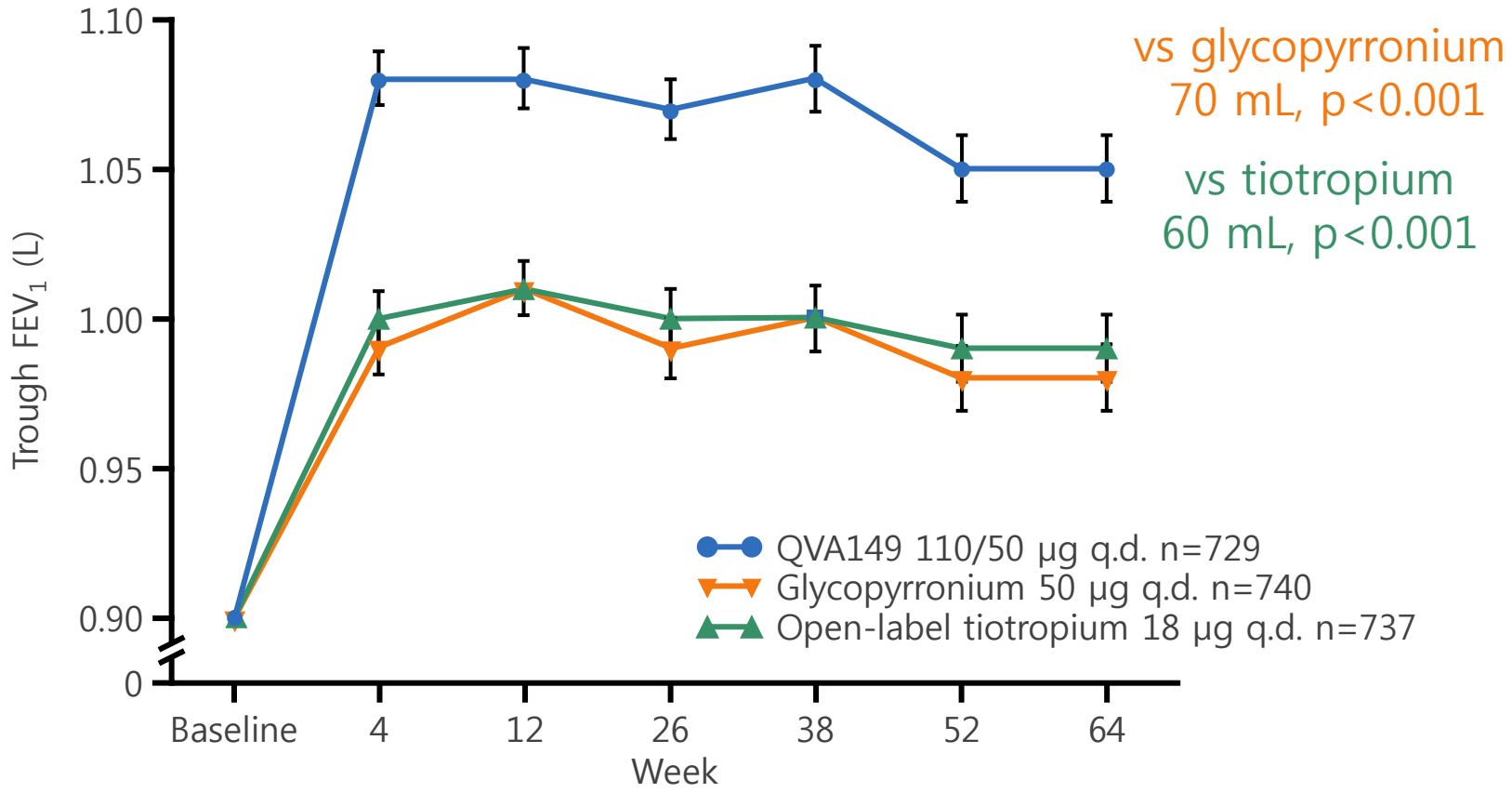
$FEV_1$ = forced expiratory volume in 1 second; q.d. = once daily

KR1503311638

Bateman et al. Eur Respir J 201342(6):1484-94

# QVA149 improved trough $FEV_1$ over 64 weeks vs glycopyrronium and open-label tiotropium, N=2224, FEV1<50%

- At all time points, QVA149 was superior to glycopyrronium and open-label tiotropium (p<0.001)



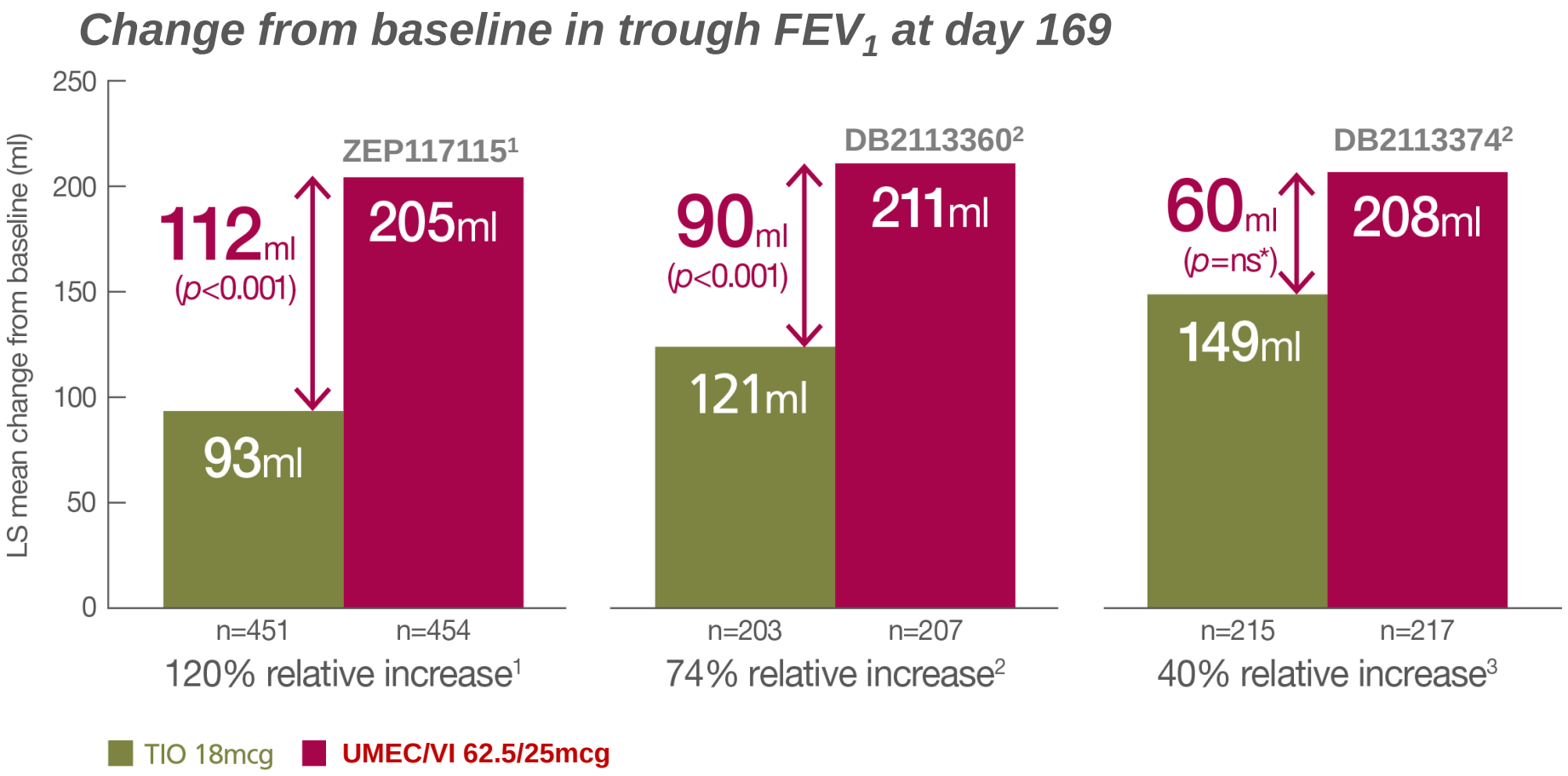

Data are least-squares mean ± standard error
$FEV_1$ = forced expiratory volume in 1 second; q.d. = once daily

KR1503311638

Wedzicha et al. Lancet Respir Med 2013

# Umeclidinium/vilanterol vs. Tiotropium

## Primary endpoint: Trough $FEV_1$ at day 169



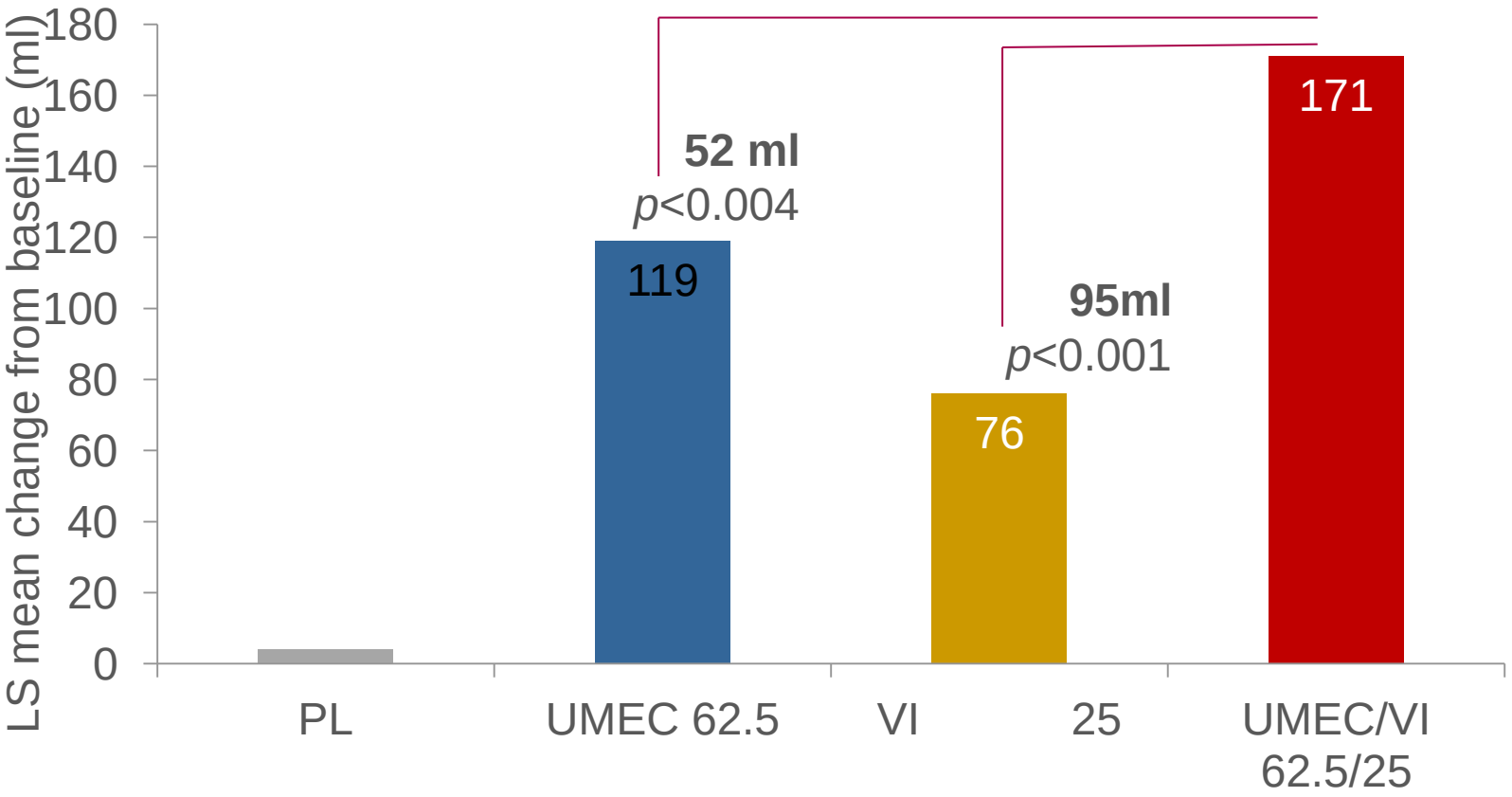

*Not statistically significant due to hierarchical testing

1. Maleki-Yazdi MR et al. Respir Med. 2014;108(12):1752-1760. 2. Decramer M et al. Lancet Respir Med. 2014;2(6):472-86

# Umeclidinium/vilanterol vs. *UMEC and VI*

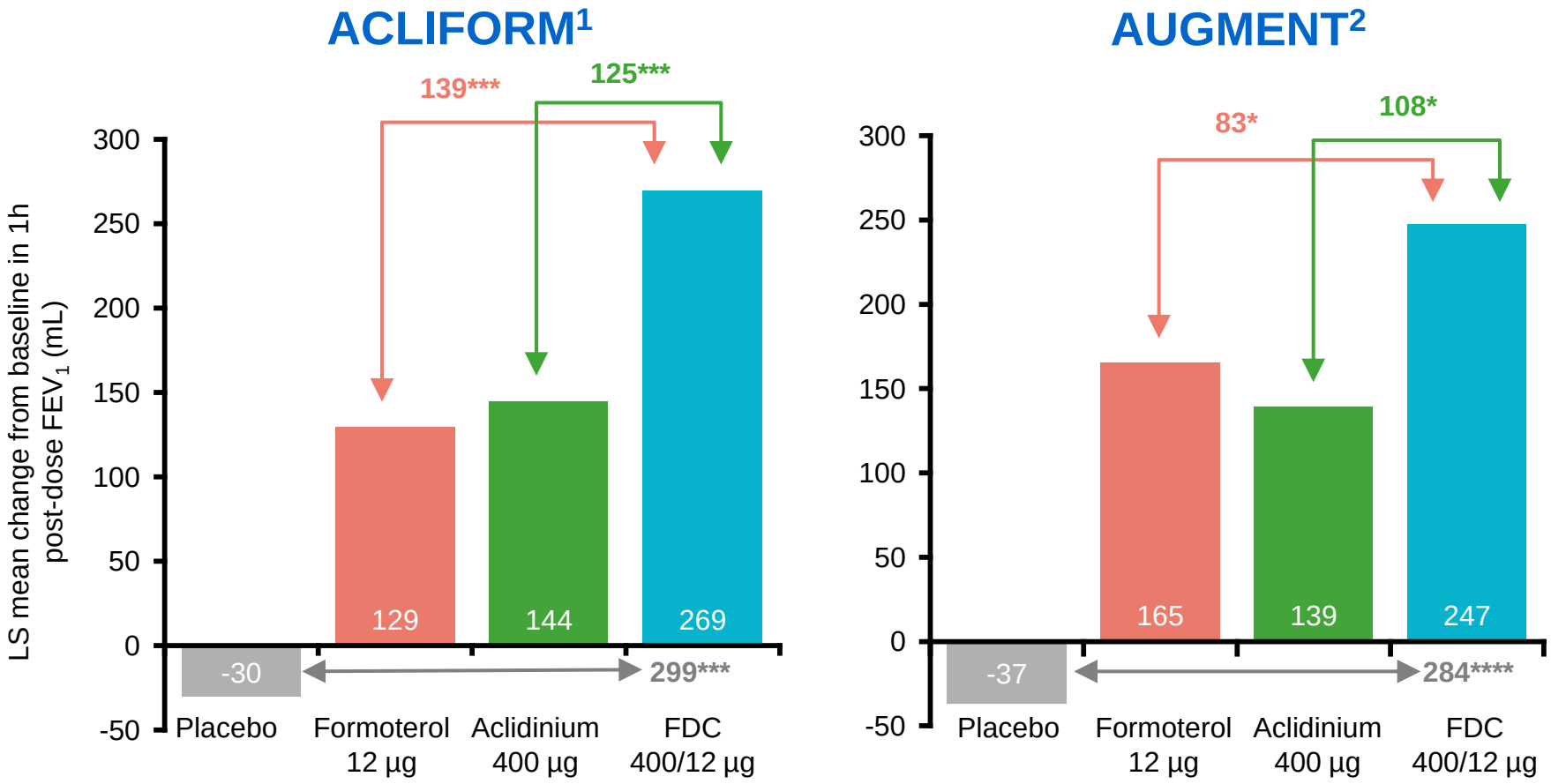
**Primary endpoint: Trough $FEV_1$ at day 169**

***Change from baseline in trough $FEV_1$ at day 169***




*Donohue et al Respir Med 2013; 107: 1538-1546*

# Aclidinium/Formoterol: change from baseline in 1-hour morning post-dose $FEV_1$ at Week 24

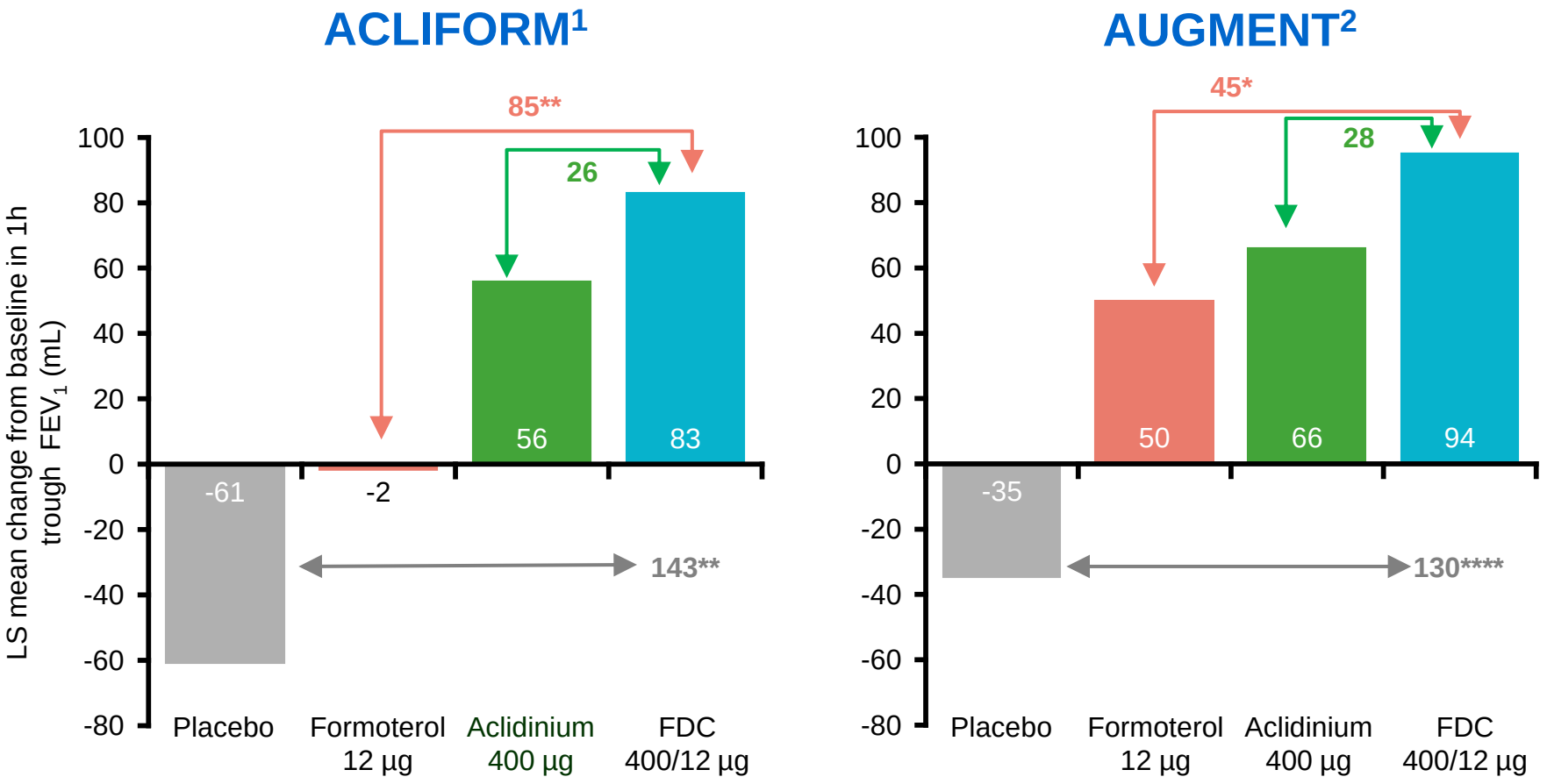



- FDC 400/12 µg significantly improves 1 hour morning post-dose $FEV_1$ vs placebo and monotherapy components at Week 24

[1]Singh et al. *BMC Pulm Med* 2014;14:178. doi:10.1186/1471-2466-14-178.
[2]D'Urzo et al. *Respir Med* 2014;15:123.

*p<0.05; ***p<0.001; ****p<0.0001

# Aclidinium/Formoterol: co-primary endpoint: change from baseline in morning pre-dose (trough) $FEV_1$ at Week 24

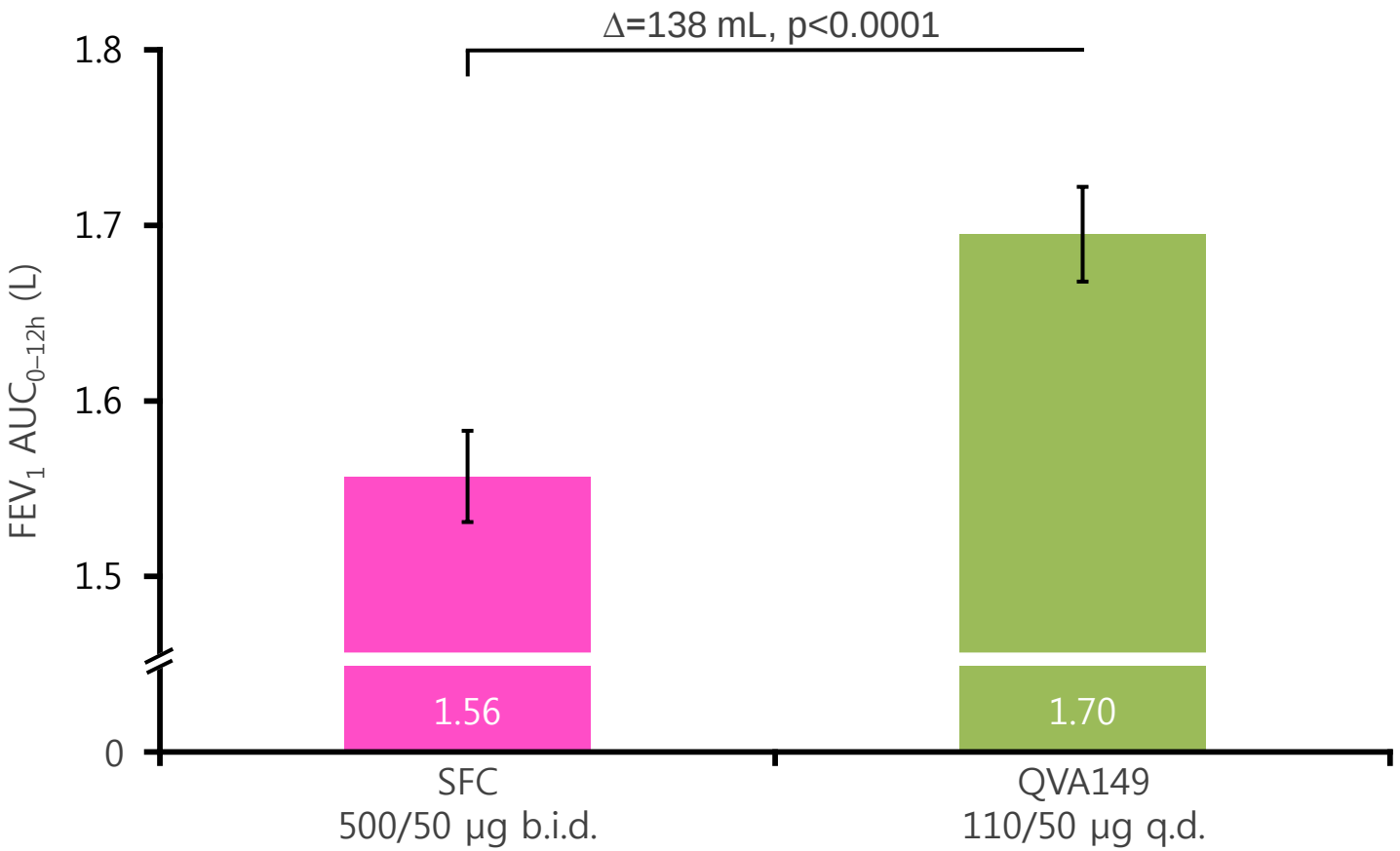



- FDC 400/12 µg significantly improves trough $FEV_1$ vs placebo and formoterol monotherapy at Week 24

[1]Singh et al. *BMC Pulm Med* 2014;14:178. doi:10.1186/1471-2466-14-178.
[2]D'Urzo et al. *Respir Med* 2014;15:123.

*p<0.05; **p<0.001; ****p<0.0001

# QVA149 significantly improved $FEV_1$ $AUC_{0–12h}$ at Week 26 (primary endpoint) vs **SFC.** $FEV_1$ 80-30%



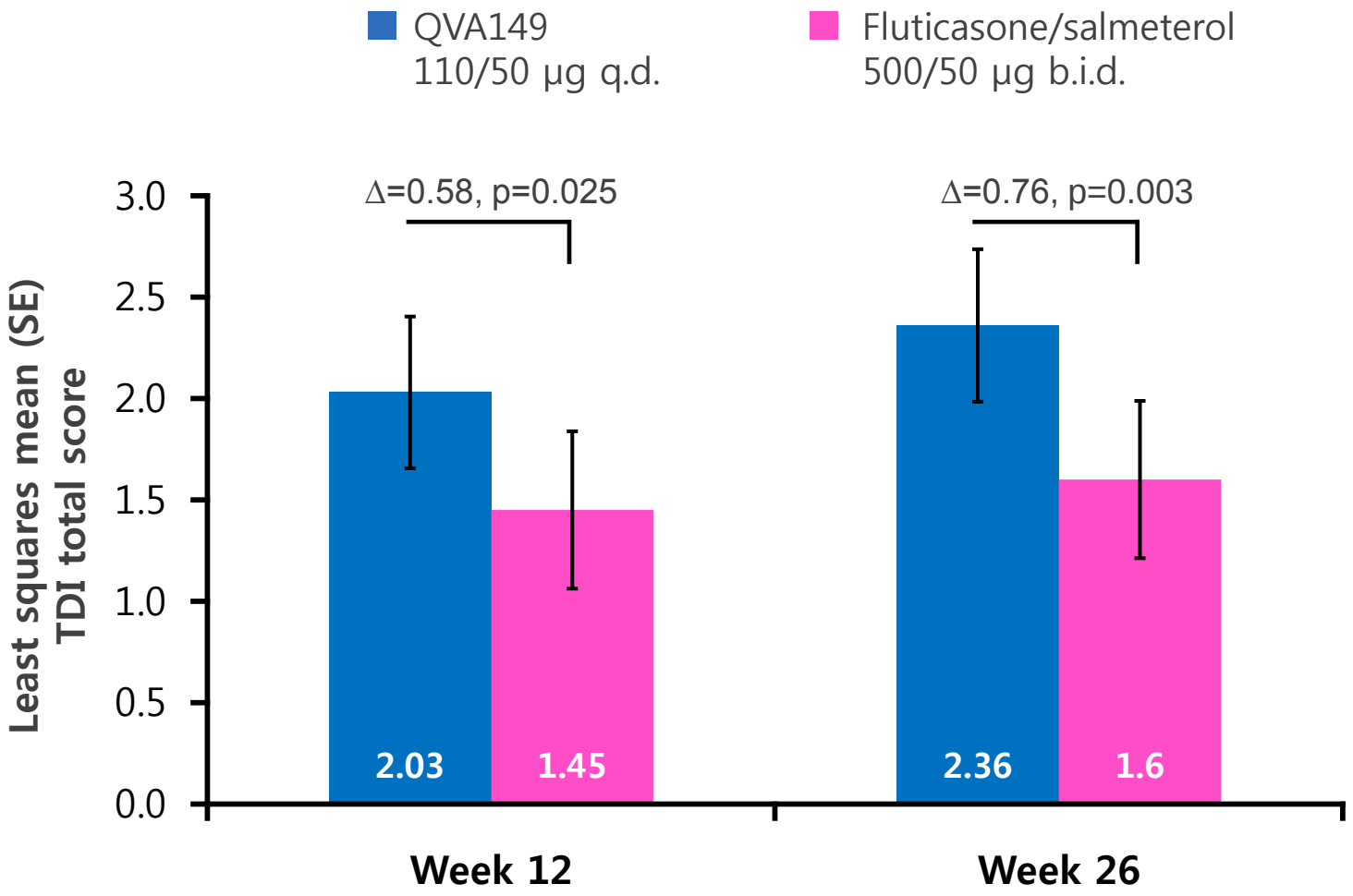

Data are least-squares mean ± standard error
AUC = area under the curve; b.i.d. = twice daily
$FEV_1$ = forced expiratory volume in 1 second; q.d. = once daily
SFC = salmeterol/fluticasone propionate

Vogelmeier et al. Lancet Respir Med 2013

KR1503311638

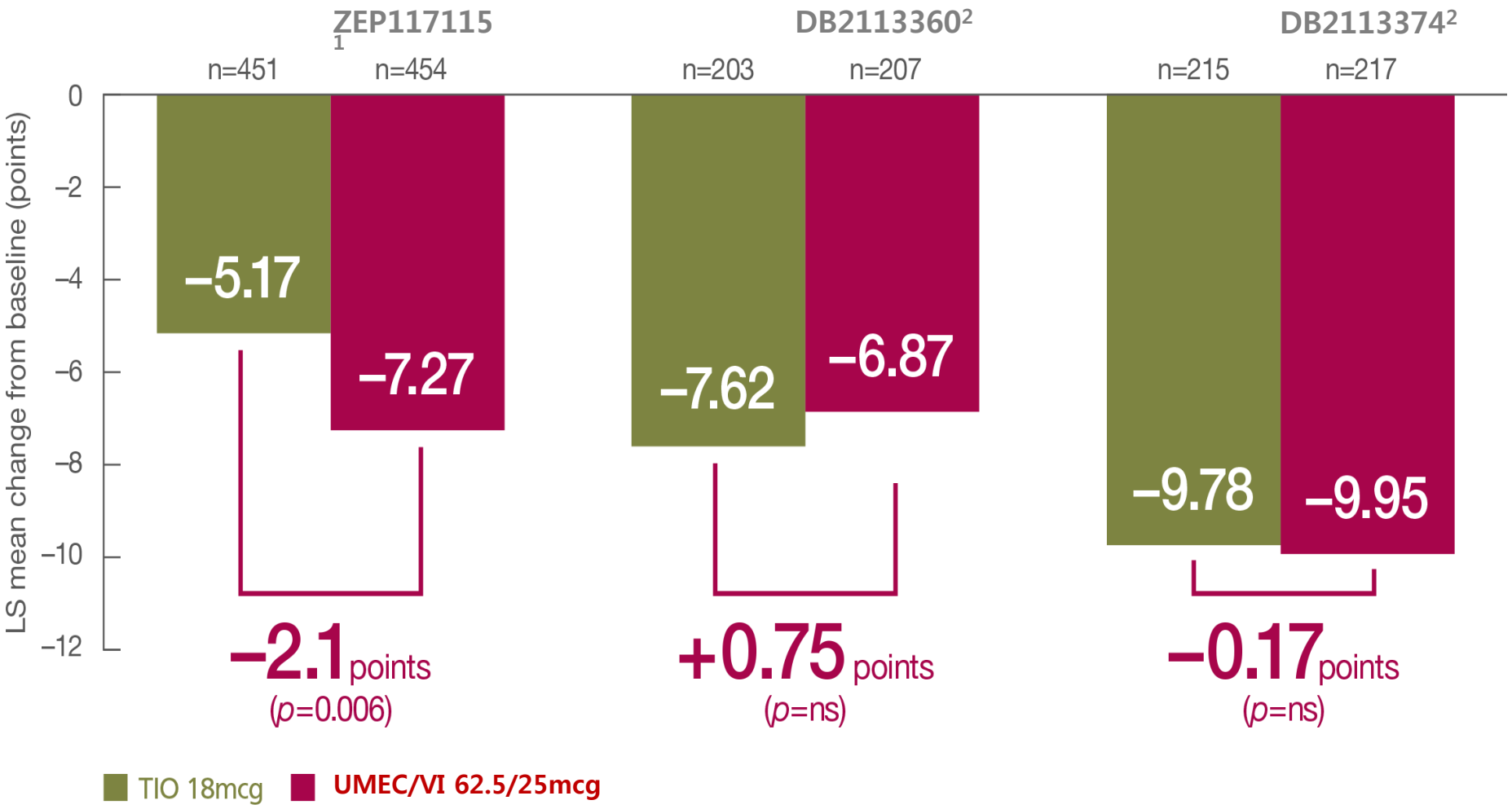
# Effects of dual bronchodilation on COPD symptoms

# QVA149 significantly improved TDI total score vs ICS/LABA



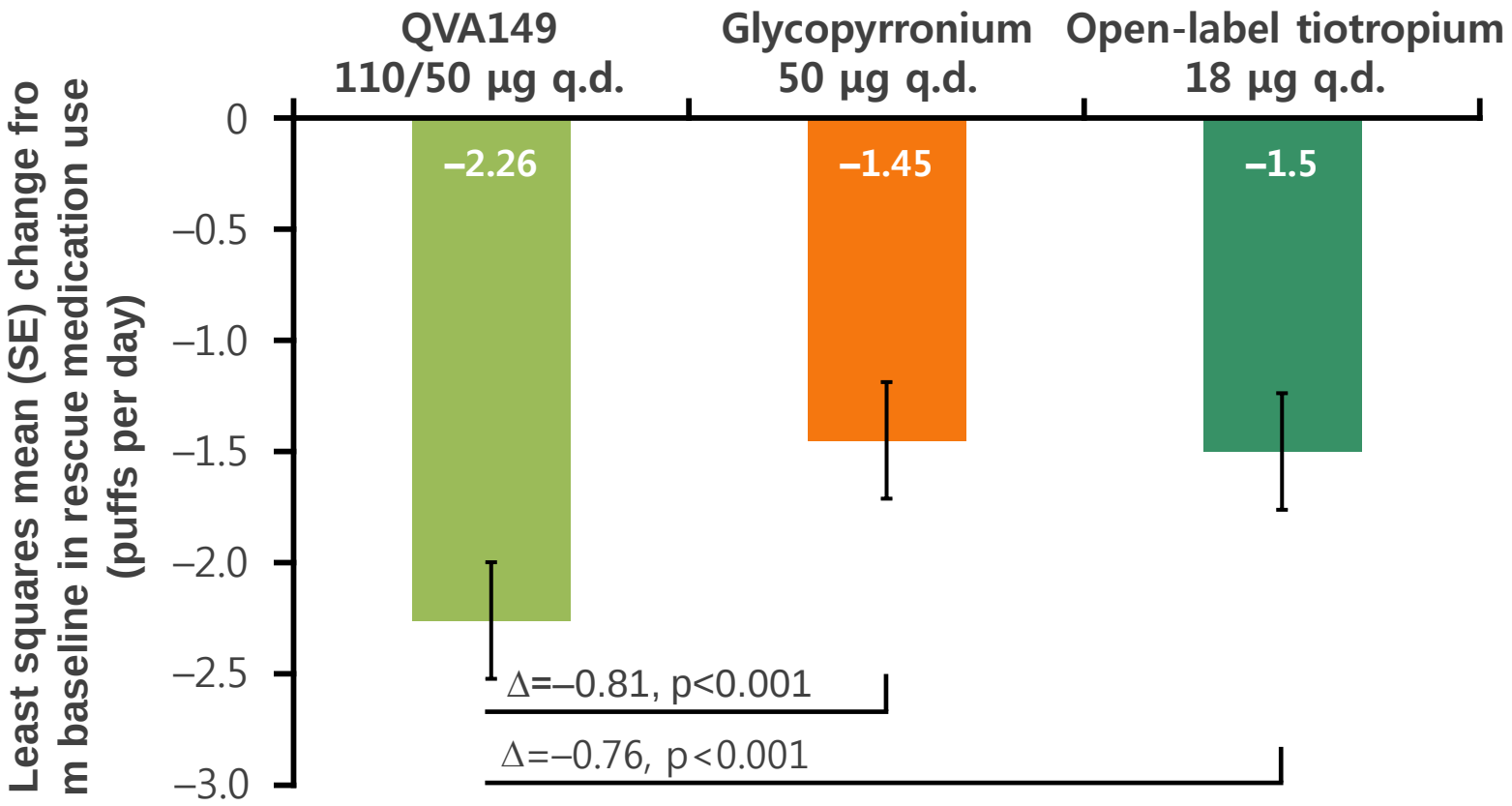

Vogelmeier et al. Lancet Respir Med 2013

# SGRQ: Umec/VI vs. Tiotropium




*References: 1. Maleki-Yazdi MR et al. Respir Med. 2014;108(12):1752-1760. 2. Decramer M et al. Lancet Respir Med. 2014;2(6):472-86*

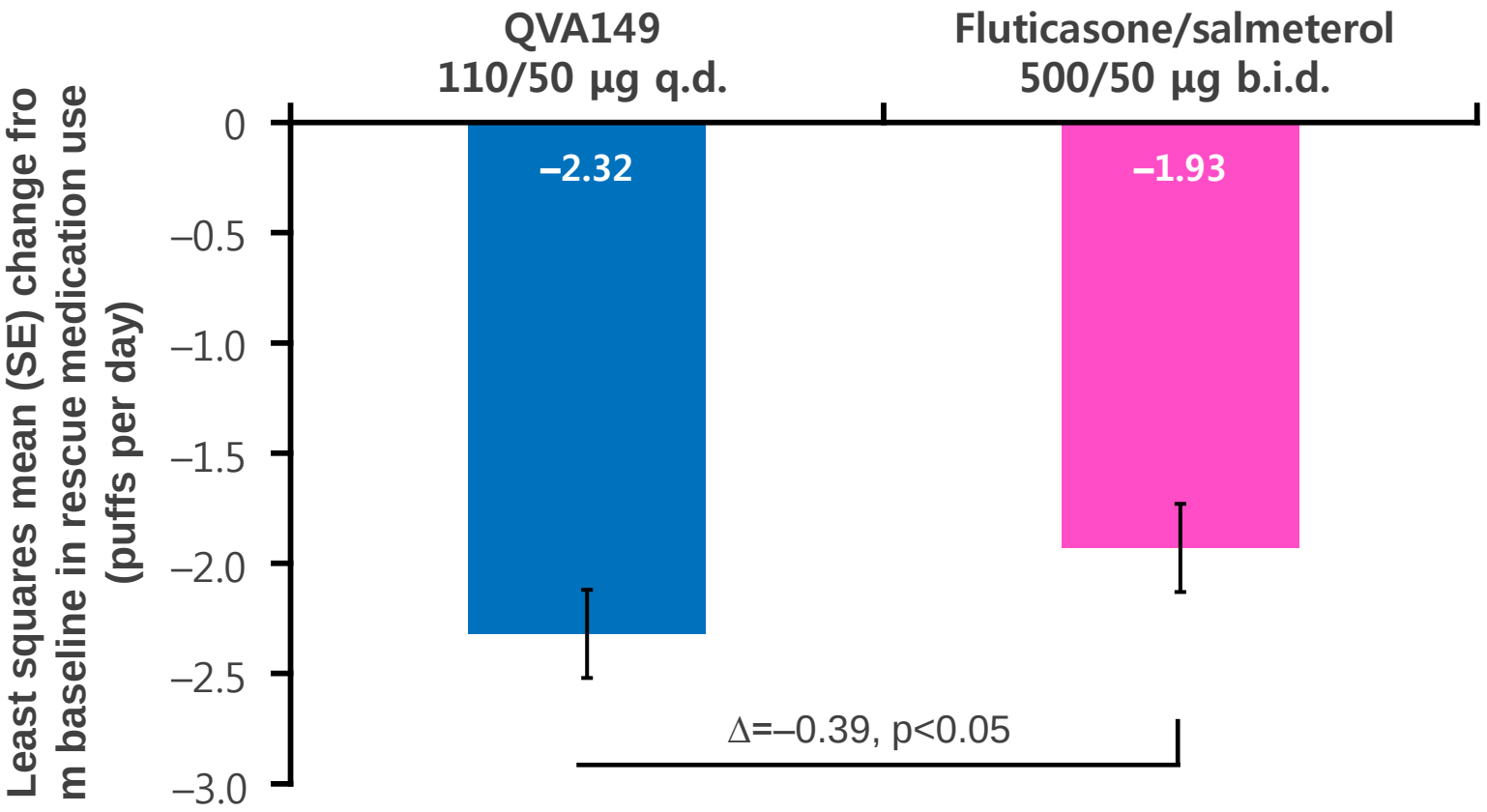
# QVA149 significantly reduced daily use of rescue medication vs glycopyrronium and tiotropium over 64 weeks




Wedzicha et al. Lancet Respir Med 2013

KR1503311638

# QVA149 significantly reduced daily use of rescue medication vs LABA/ICS over 26 weeks

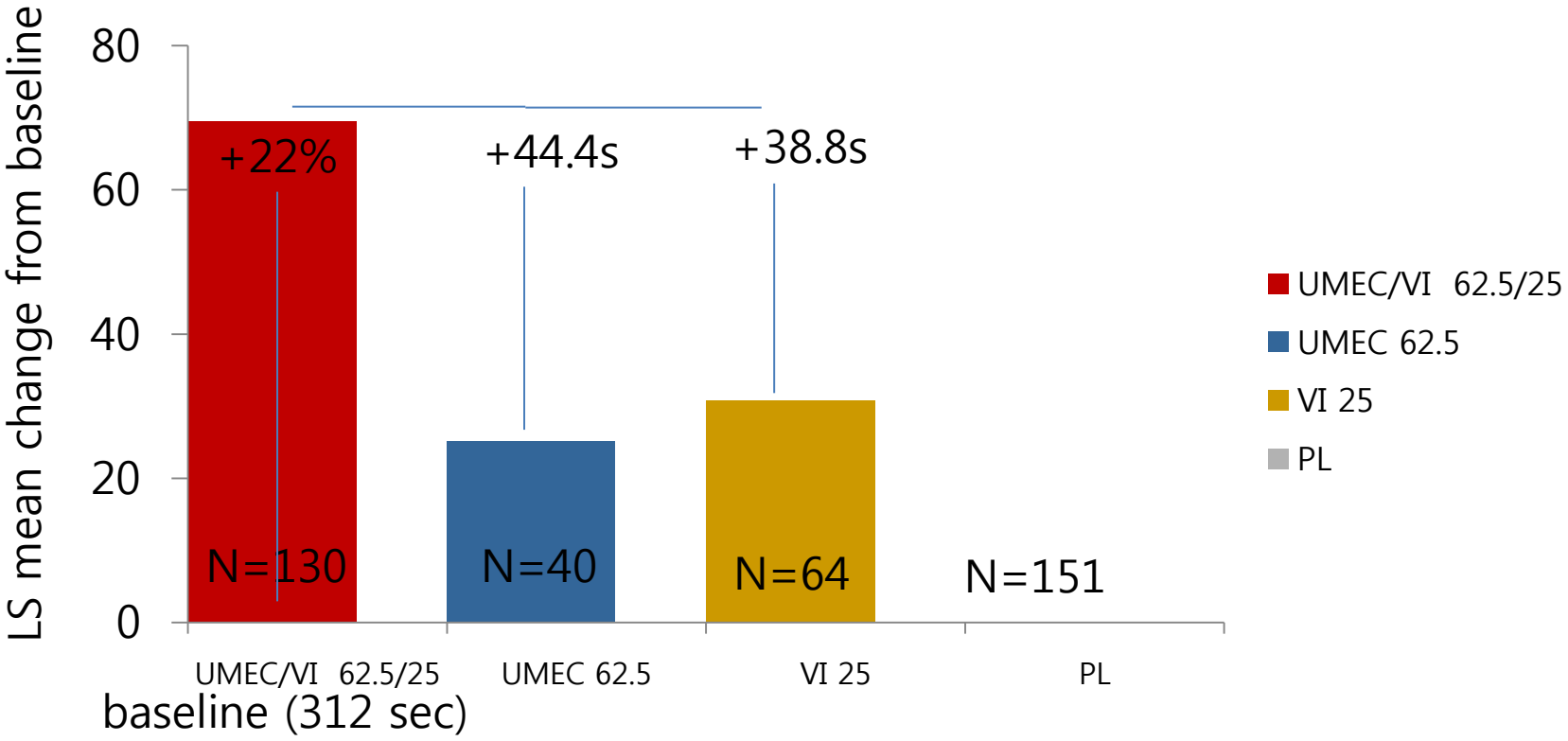



Vogelmeier et al. Lancet Respir Med 2013

# Effect of UMEC/VI 62.5/25mcg on exercise endurance:

FEV1 ⩾35% and ⩽70% predicted

EET change from baseline at 3 hrs post-dose at Week 12, DBDB2114418




A minimal clinically important difference (MCID) of 45–85 seconds in response to a bronchodilator

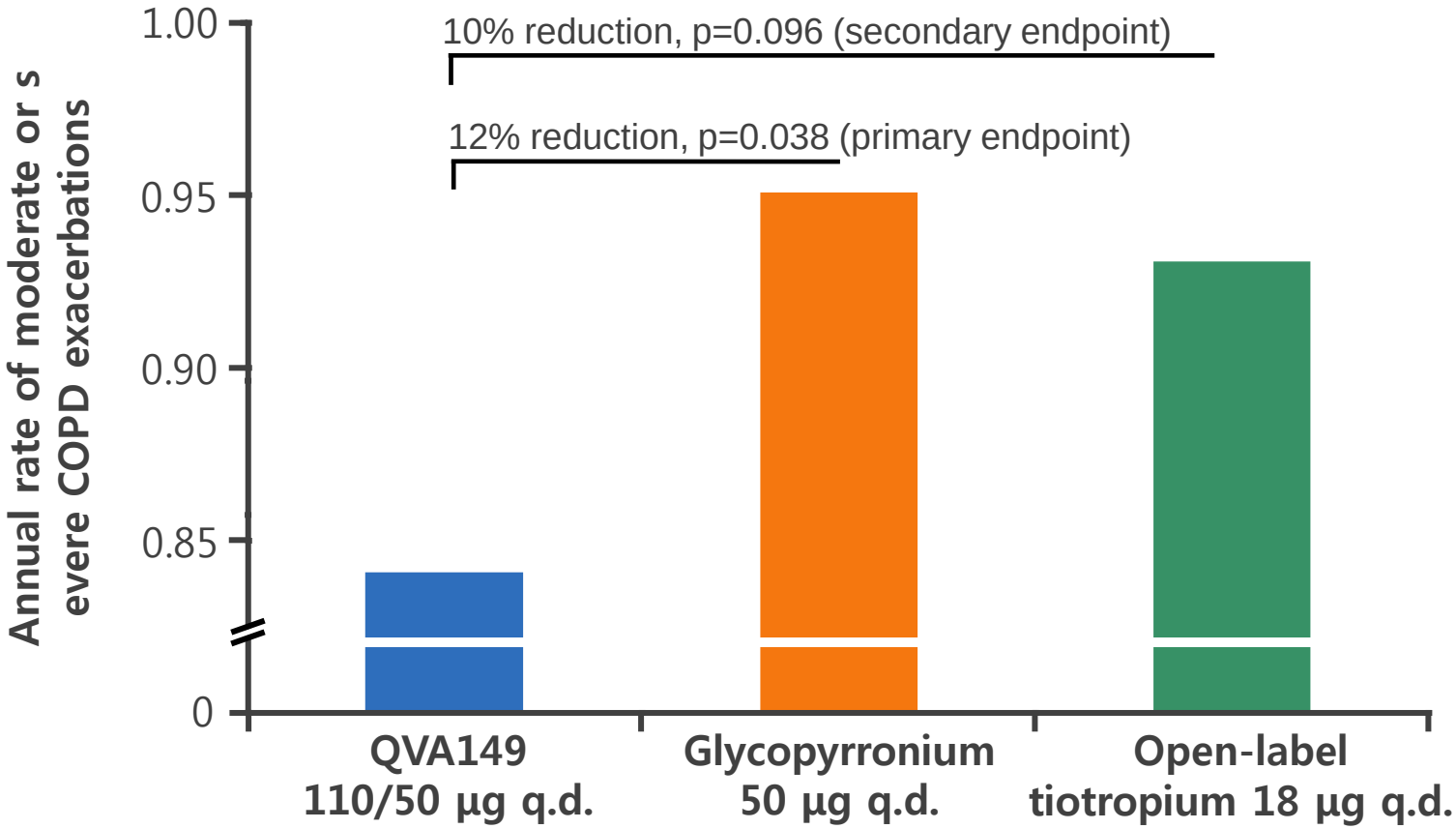
*Maltais F et al. Ther Adv Respir Dis. 2014 Dec;8(6):169-81*

# Effects of dual bronchodilation on exacerbations

# QVA149 significantly reduced the rate of moderate or severe COPD exacerbations vs glycopyrronium over 64 weeks

A2304 SPARK

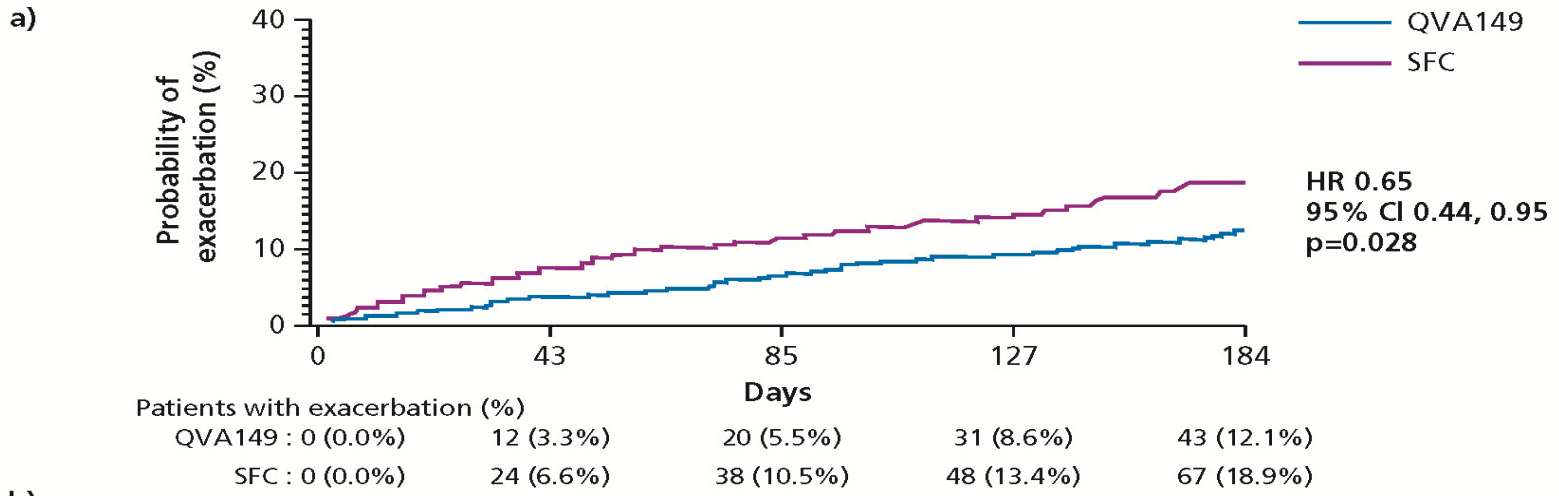
- SPARK met its primary endpoint, demonstrating that QVA149 was superior to glycopyrronium with regard to rate of moderate or severe COPD exacerbation s

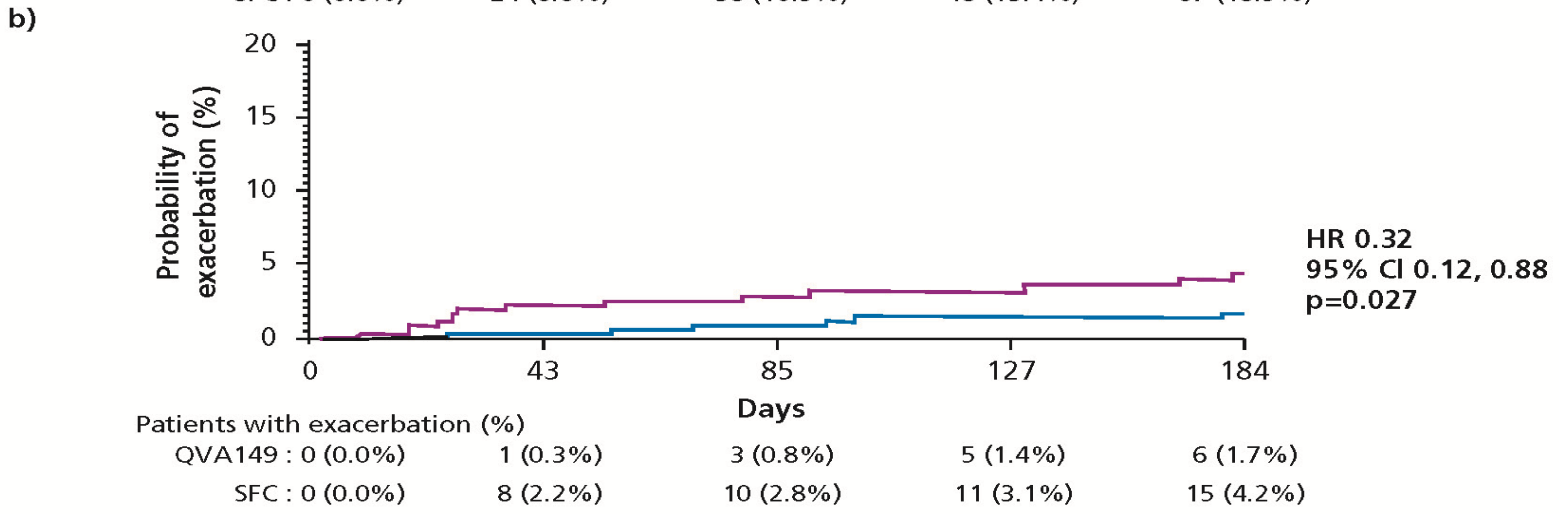



Wedzicha et al. Lancet Respir Med 2013

# QVA149 significantly reduced the rate of moderate to severe COPD exacerbations vs. SFC

**Figure 5. Kaplan-Meier plots of the time to first a) moderate or severe COPD exacerbation; b) severe COPD exacerbation over 26 weeks of treatment**



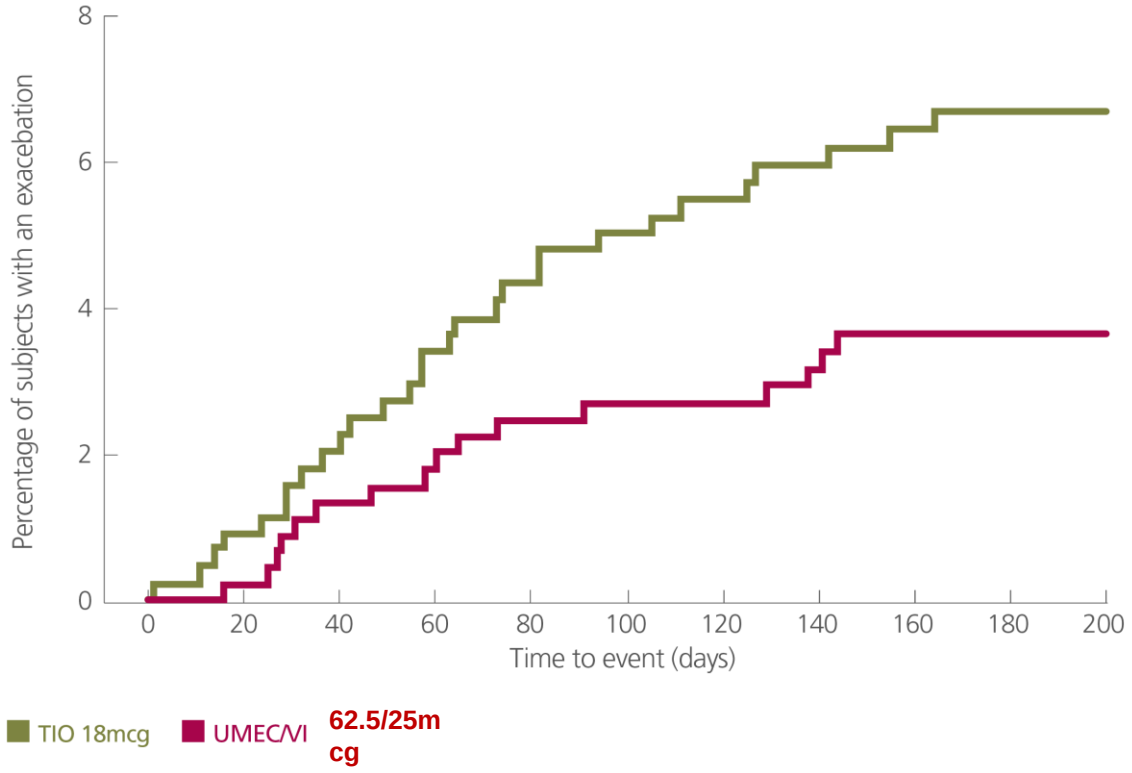

CI, confidence interval; HR, hazard ratio; SFC, salmeterol/fluticasone combination

Zhong et al. ERS 2014

# Umec/Vl vs tiotropium
# Time to first exacerbation

**Time to first on-treatment COPD exacerbation**

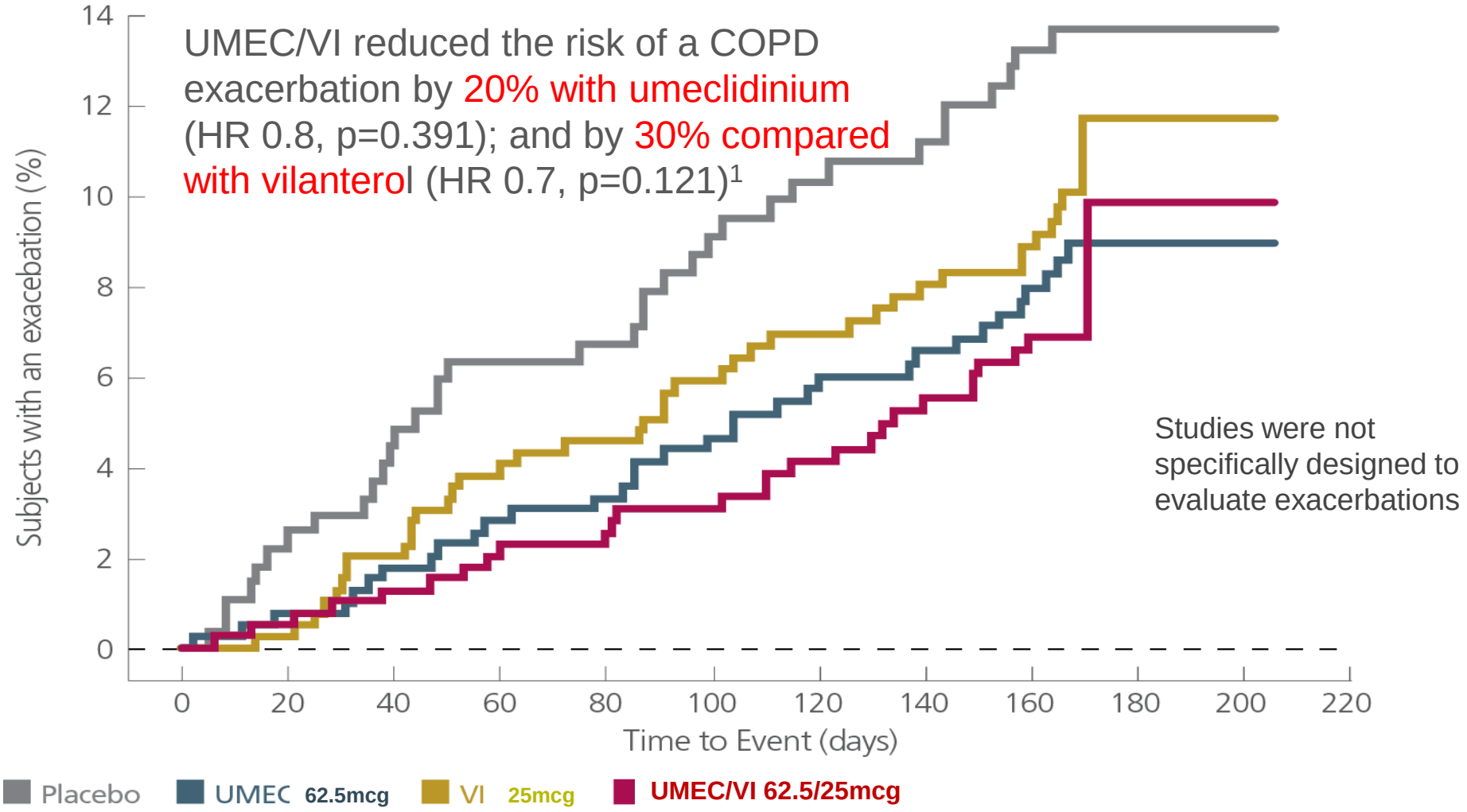
Studies were not specifically designed to evaluate exacerbations




UMEC/VI showed a significant delay in time to first exacerbation compared to tiotropium in 1 study[1] [HR: 0.5 (95% CI: 0.3-1; *p*=0.044)], but not in the other 2 studies where there was no signifiacnt difference in time to first exacerbations[2].

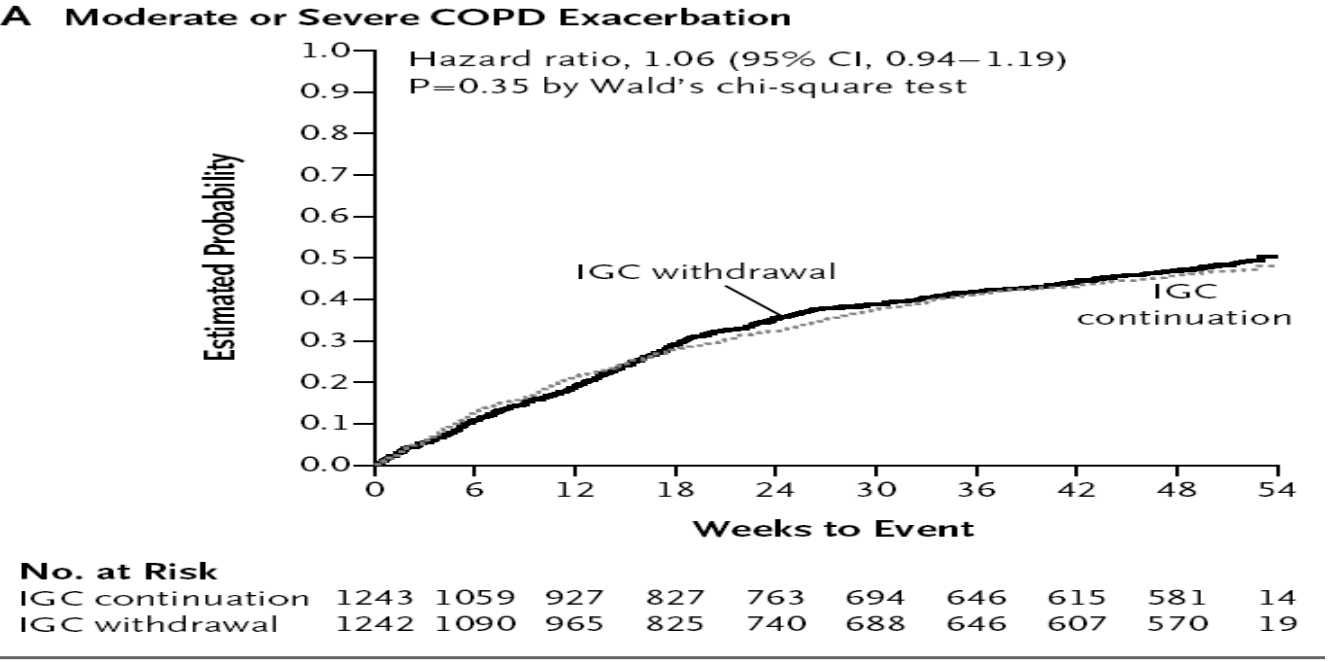
*References: 1. Maleki-Yazdi MR et al. Respir Med. 2014;108(12):1752-1760 2. Decramer M et al. Lancet Respir Med. 2014;2(6):472-86*

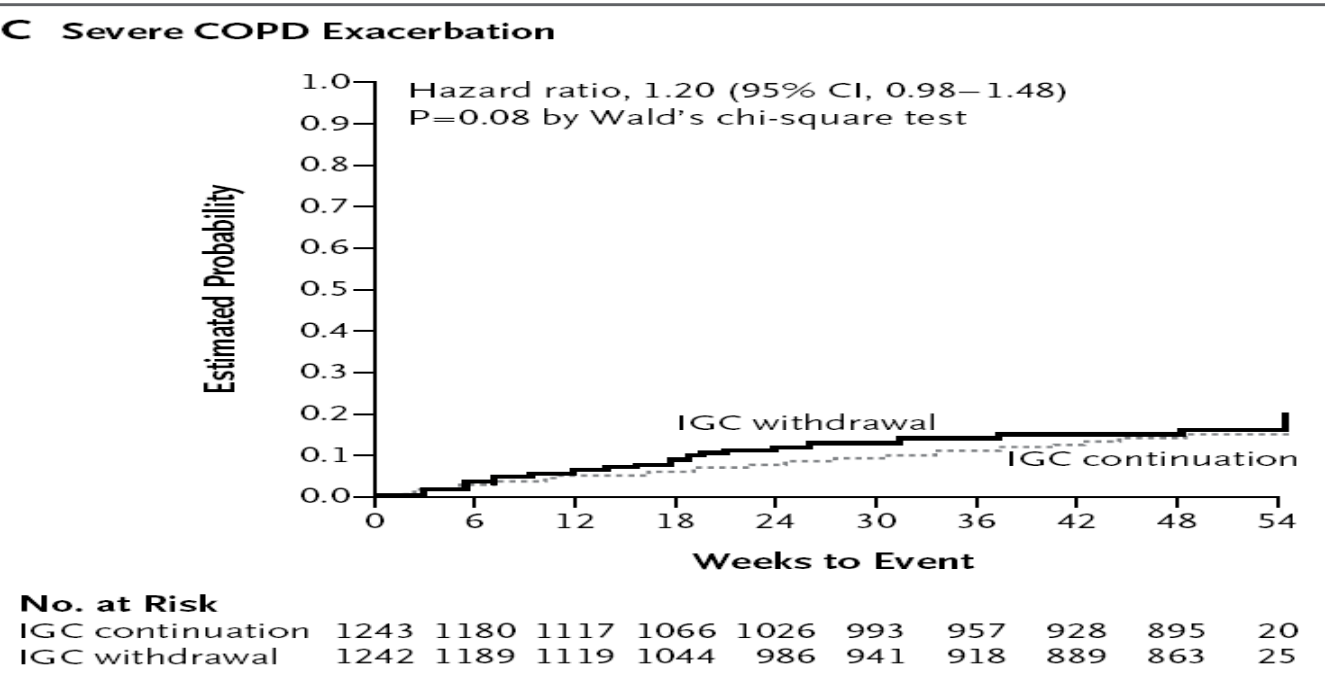
# Umec/VI vs Umec and VI
# Time to first exacerbation




*1. Anoro Ellipta SmPC, April 2014. 2. Donohue et al Respir Med 2013; 107: 1538-1546* :

(WISDOM) trial



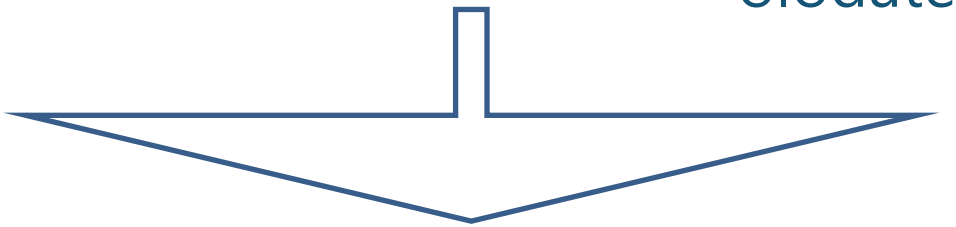




withdrawal of ICS in COPD patients receiving dual bronchodilation *met the inferiority margin (HR 1.20), hazard ratio 1.06.*

N Engl J Med. 2014 Oct 2;371(14):1285-94

# Safety data of Dual bronchodilator

| Dual bronchodilator | vs | Monotherapy |
| --- | --- | --- |
| glycopyronium/indacaterol | | Glycopyronium<br>Indacaterol |
| umeclidinium/vilanterol | | Umeclidinium<br>Vilanterol |
| aclidinium/formoterol | | Aclidinium<br>Formoterol |
| Tiotropium/olodaterol | | Tiotropium<br>olodaterol |



Similar safety profile without an increase in AEs

# Compliance and costs

# Two drugs in one inhaler

# Inhaler mishandling remains common in real life and is associated with reduced disease control

- Large observational study in 24 chest clinics in Italy
- (N=1664, 52% COPD, 42% asthma; 843 MDI, 1113 DPI)

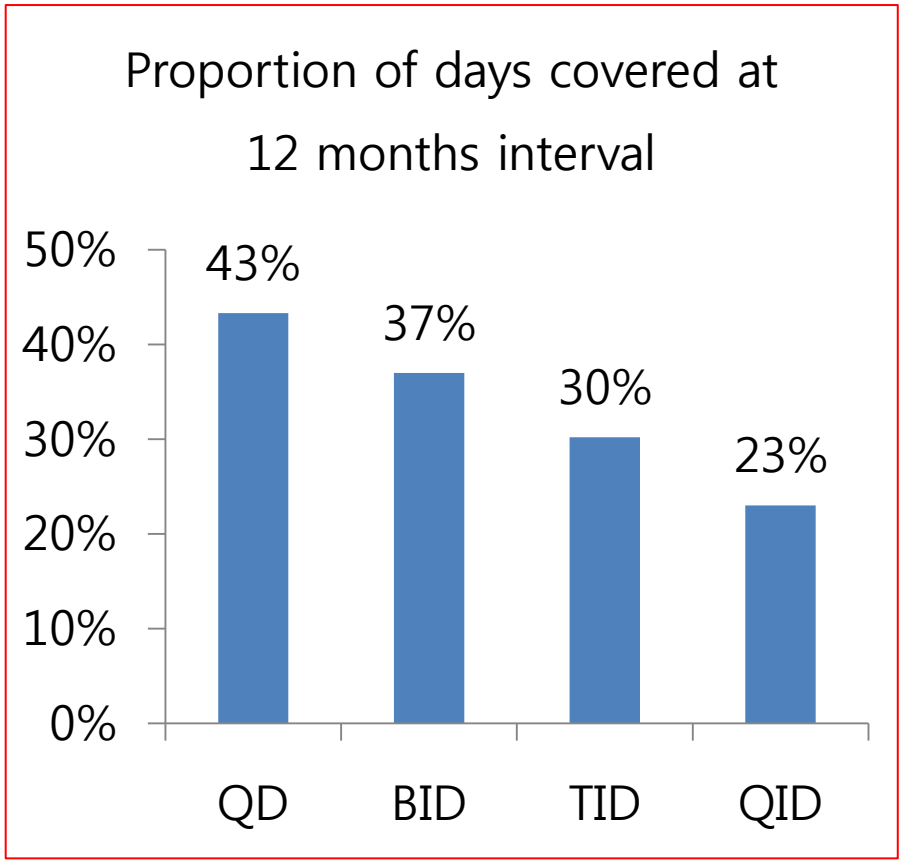
Critical mistakes
- 12% for MDIs,
- 35% for Diskus and HandiHaler
- 44% for Turbuhaler

Percentage of observations of inhaler technique according to some unscheduled health-care resources use in the last year

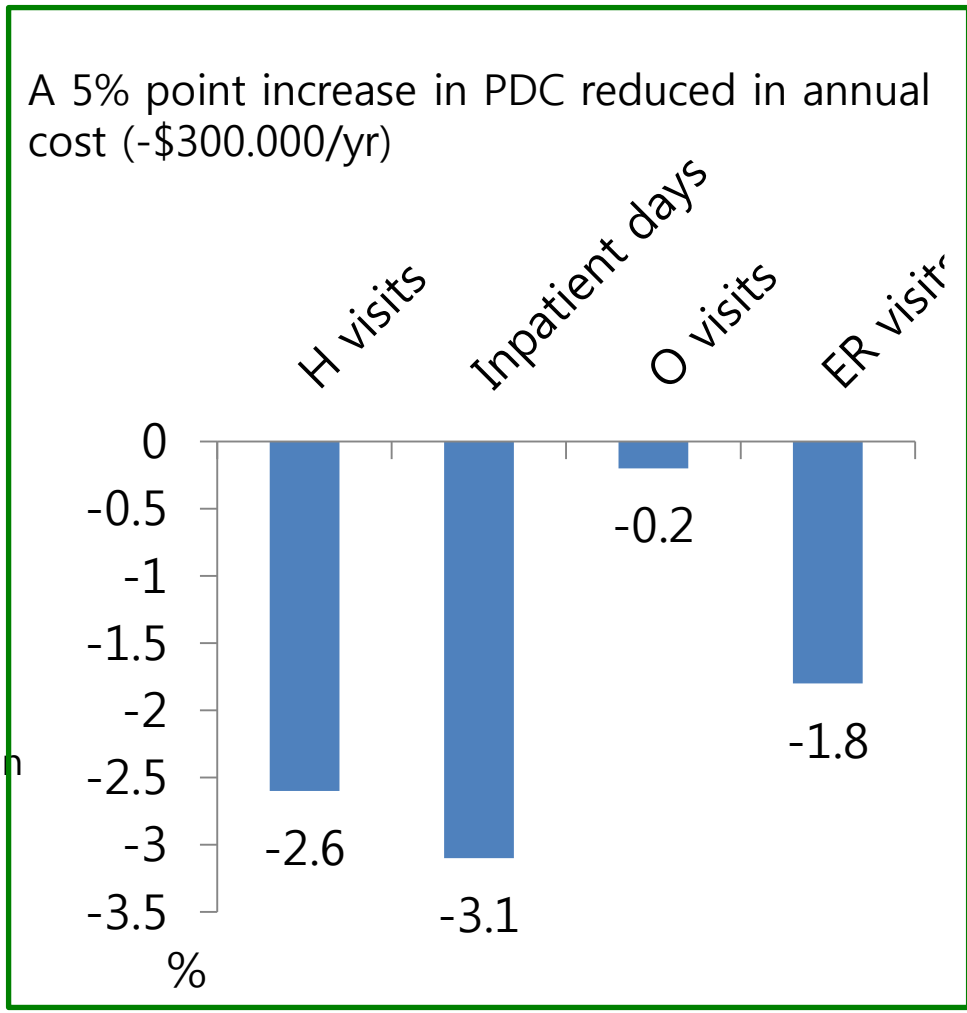
| | OR | P |
|---|---|---|
| Hospital admissions | 1.47 | 0.001 |
| Emergency department visits | 1.62 | 0.0006 |
| Antimicrobic courses, | 1.50 | 0.00004 |
| Corticosteroid courses | 1.54 | 0.00003 |

Respir Med. 2011 Jun;105(6):930-8.

# Adherence by dosing class of first COPD treatment from1999 to 2006, 55,076 COPD patients



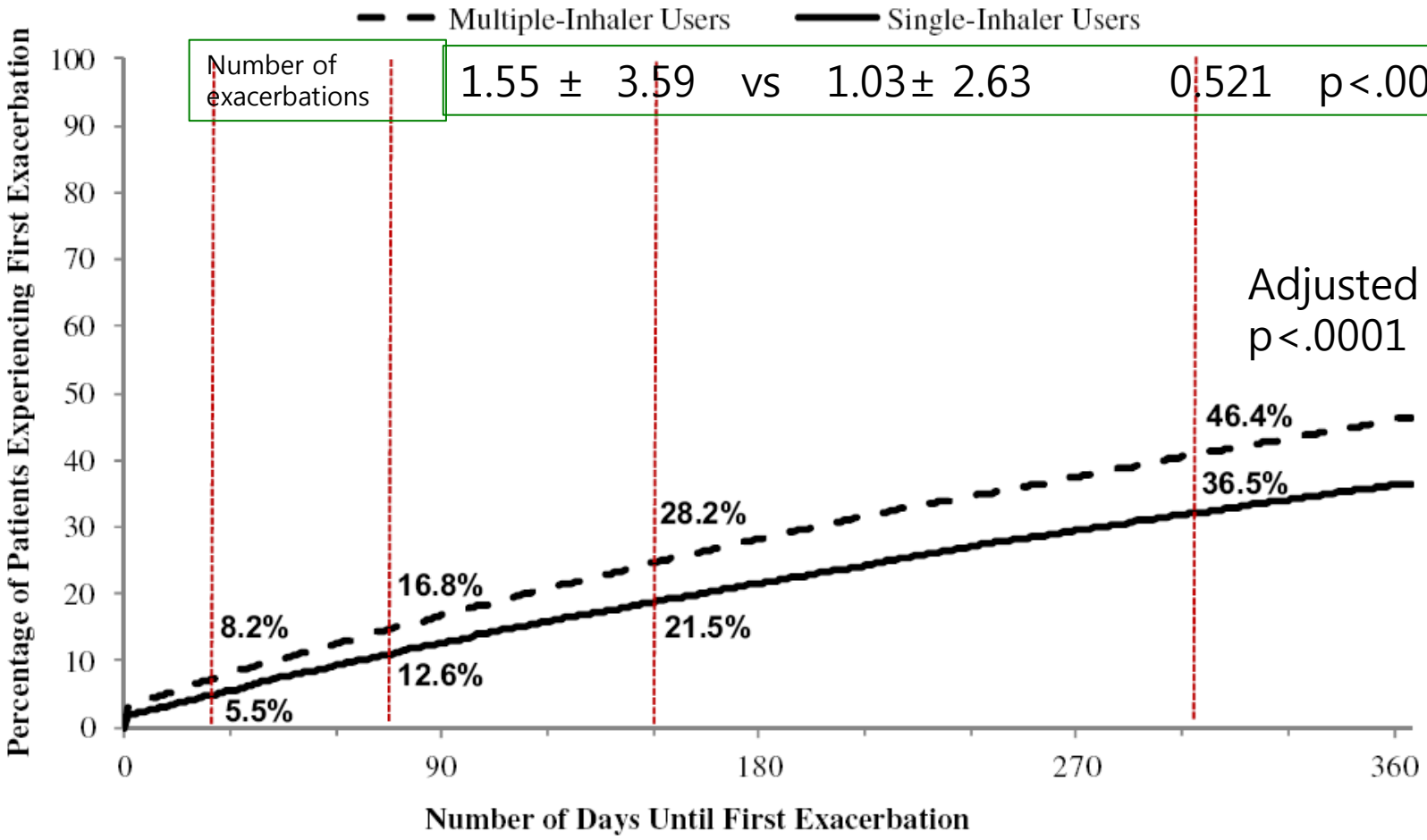

PDC is defined as the ratio of the days supply a given drug during the observation period to the total number of days in the observation period




Toy EL et al. Respir Med. 2011 Mar;105(3):435-41.

# **Multiple-inhaler** users experienced significantly **more exacerbations** and had a higher risk of exacerbation than single-inhaler users

N=23,494 2004-2008




Yu AP et al. Respir Med. 2011 Dec;105(12):1861-71

# SUMMARY

1. Patients with stable COPD on **single LABD**

- may still be breathless and suffer from exacerbations.

2. **Dual Bronchodilator** Therapy

- Combining different mechanisms of actions

  → additive effects, increasing efficacy

  (lung function, Sx., AE, vs. monotherapy)

- Convenience ➔ improve compliance, reduce medical cost
- Reducing the dose of individual components

  → reduced risk for side effects

  → improve drug safety and tolerability
- May help avoid the inappropriate use of ICS in '나" patients

# 질문 1

75세 남자

3개월 전부터 진행하는 호흡곤란 mMRC IV, 기침(-), 가래(-)

흡연력-30갑년, 알러지 병력(-)

$FEV_1$/FVC 63%, $FEV_1$은 예측치의 75%, BD(-)

**첫 치료로 어떤 처방을 하시겠습니까?**

① ICS+LABA

② LAMA+LABA

③ LAMA 또는 LABA

④ ICS+LABA+LAMA

⑤ Oral corticosteroid

# Conclusions

*Which patients can be treated with dual bronchodilator, '나'군?*

- ✓ Drug naive patients (maximal bronchodilation)
- ✓ LAMA or LABA monotherapy
- ✓ ICS/LABA
- ✓ ICS/LABA/LAMA triple therapy (if, ICS is not needed)
- ✓ LABA, LAMA free combination (compliance ↑)

- The trend is moving toward dual bronchodilator therapy (LAMA/LABA) to achieve "maximal" bronchodilation

J. Med. Chem 2015 Feb 9

# 질문 2

“나”군 환자의 증상조절과 악화예방에 기관지확장제 단일요법보다 병합요법이 더 효과적이라고 생각하십니까?

① 예

② 아니오