I nuovi broncodilatatori nella BPCO

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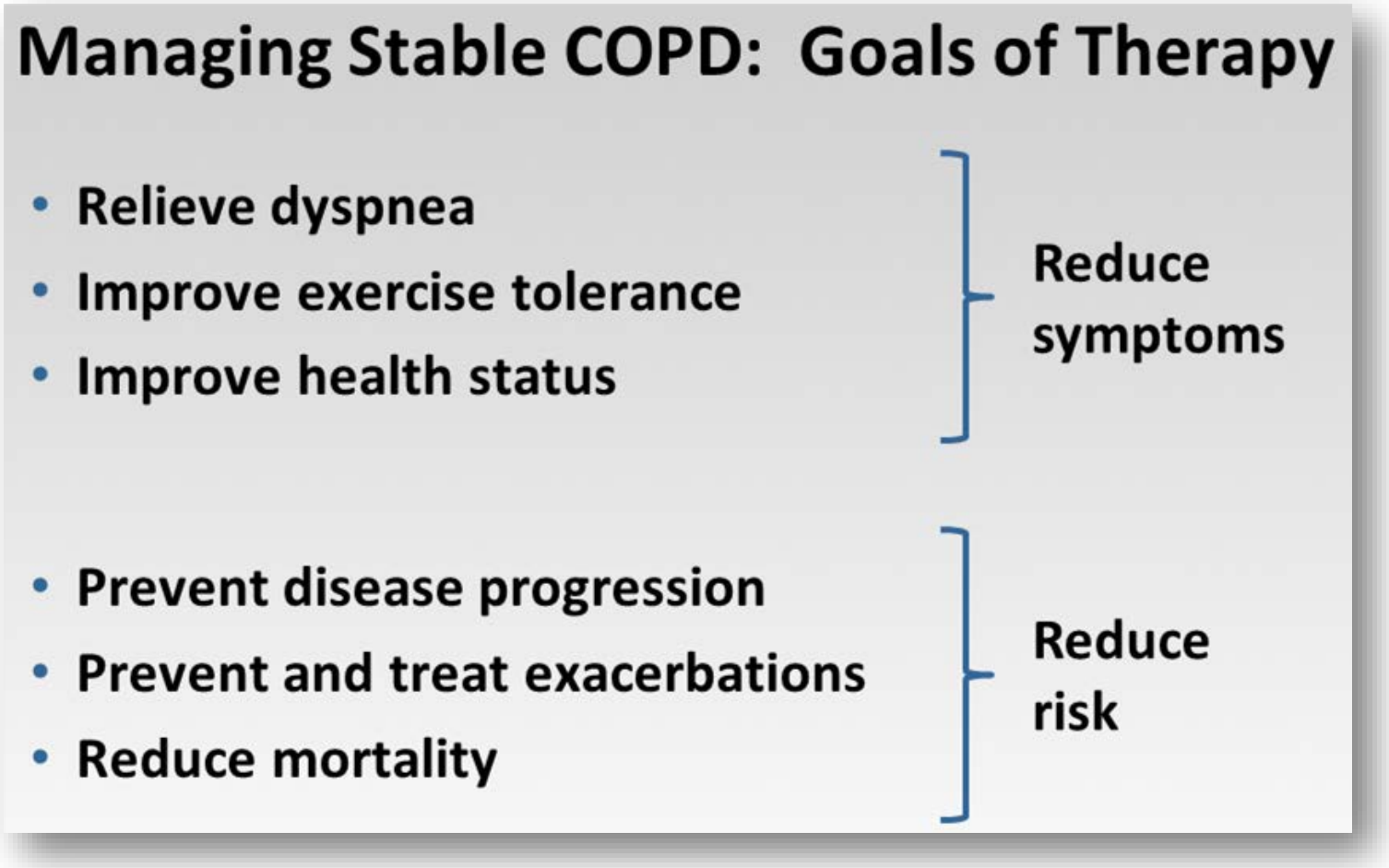
ULSS21 LEGNAGO

The scientific rationale for combining long-acting β_2-agonists and muscarinic antagonists in COPD

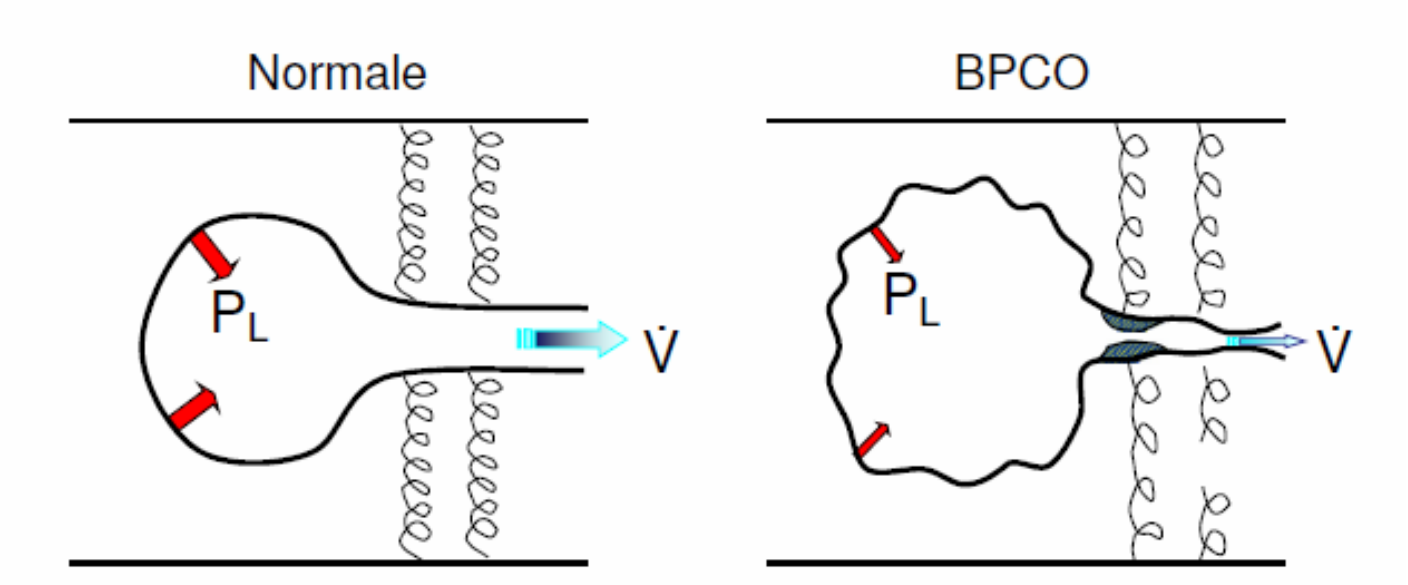
I broncodilatatori sono il cardine della terapia farmacologica per la malattia polmonare ostruttiva cronica (BPCO) e sono raccomandati dalle attuali linee guida nazionali e internazionali come la prima linea della terapia nei pazienti sintomatici e quelli che dimostrano limitazione del flusso aereo.

Cazzola M, Molimard M. Pulmonary Pharmacology & Therapeutics 2010, 23: 257-267

Managing stable COPD: goals of therapy



Ostruzione al flusso aereo espiratorio



Ipersecrezione di muco

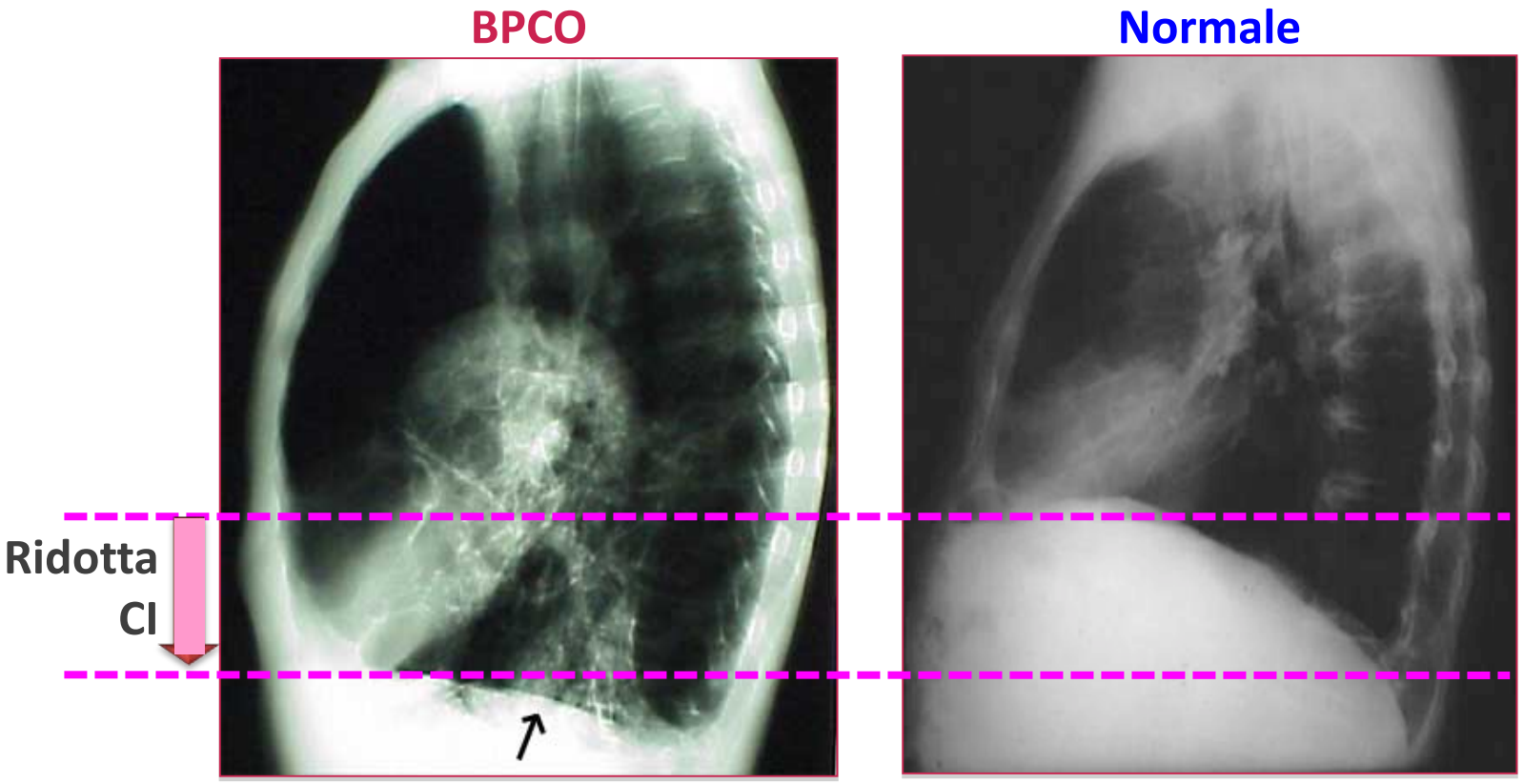
Maggiore tono broncomotore colinergico

Iperreattività bronchiale

Aumento dell'ostruzione bronchiale (rimodellamento)

Ridotto ritorno elastico
Ridotte connessioni parenchimali
Aumento delle resistenze

Ostruzione al flusso aereo nella BPCO il ridotto ritorno elastico determina iperinflazione

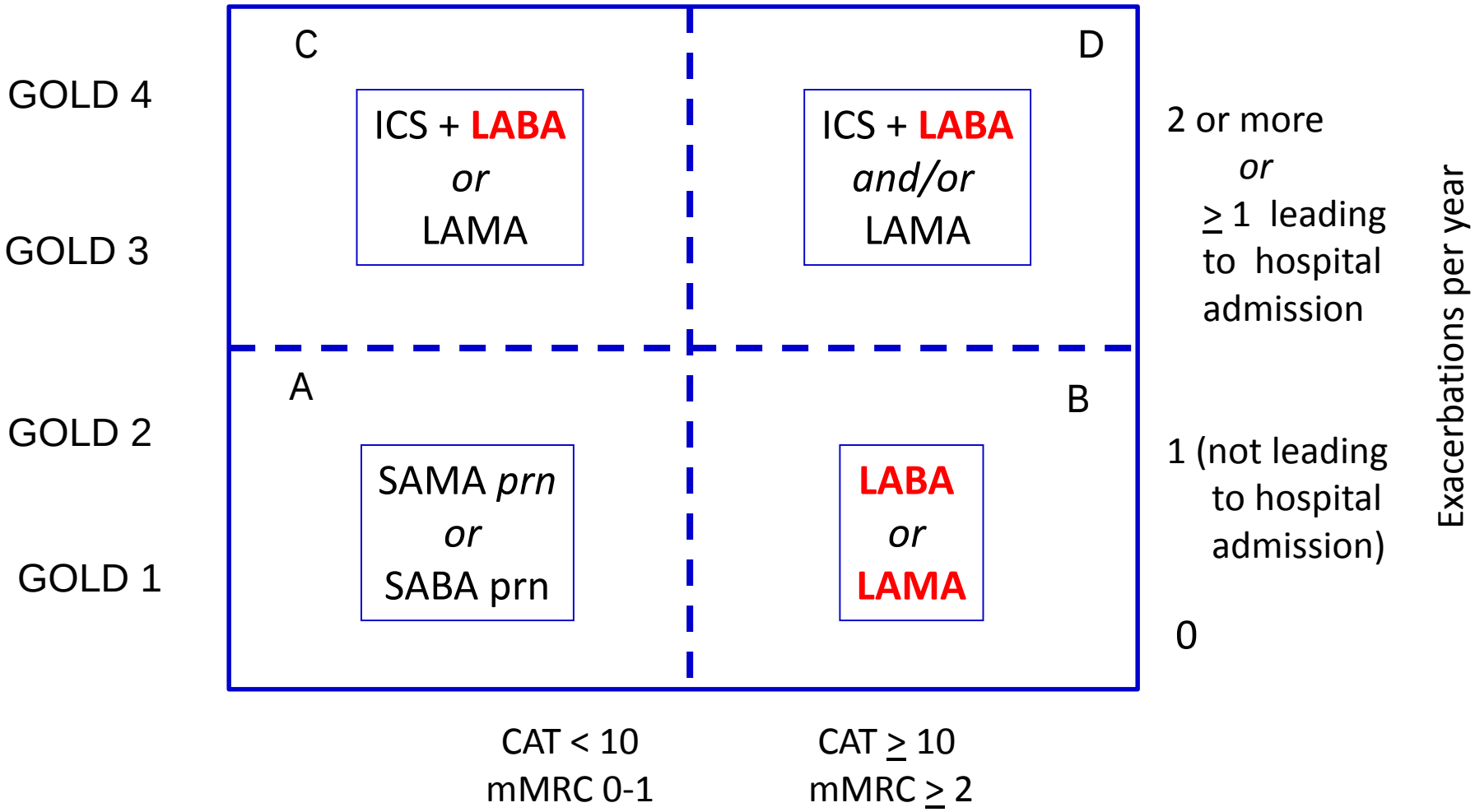


- Alterazione della parete toracica e dei meccanismi diaframmatici
- Lavoro della respirazione ↑ Dispnea ↑

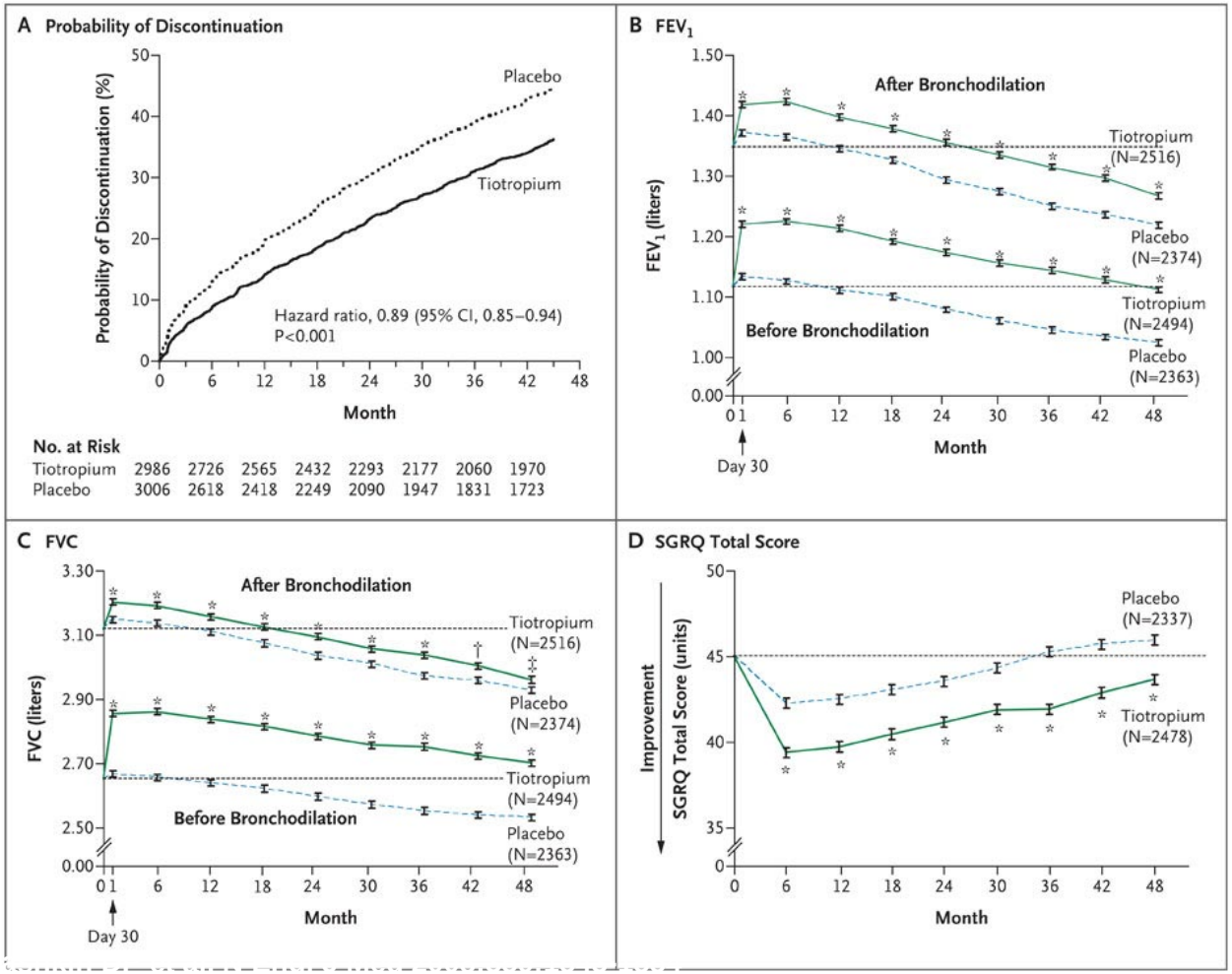
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE



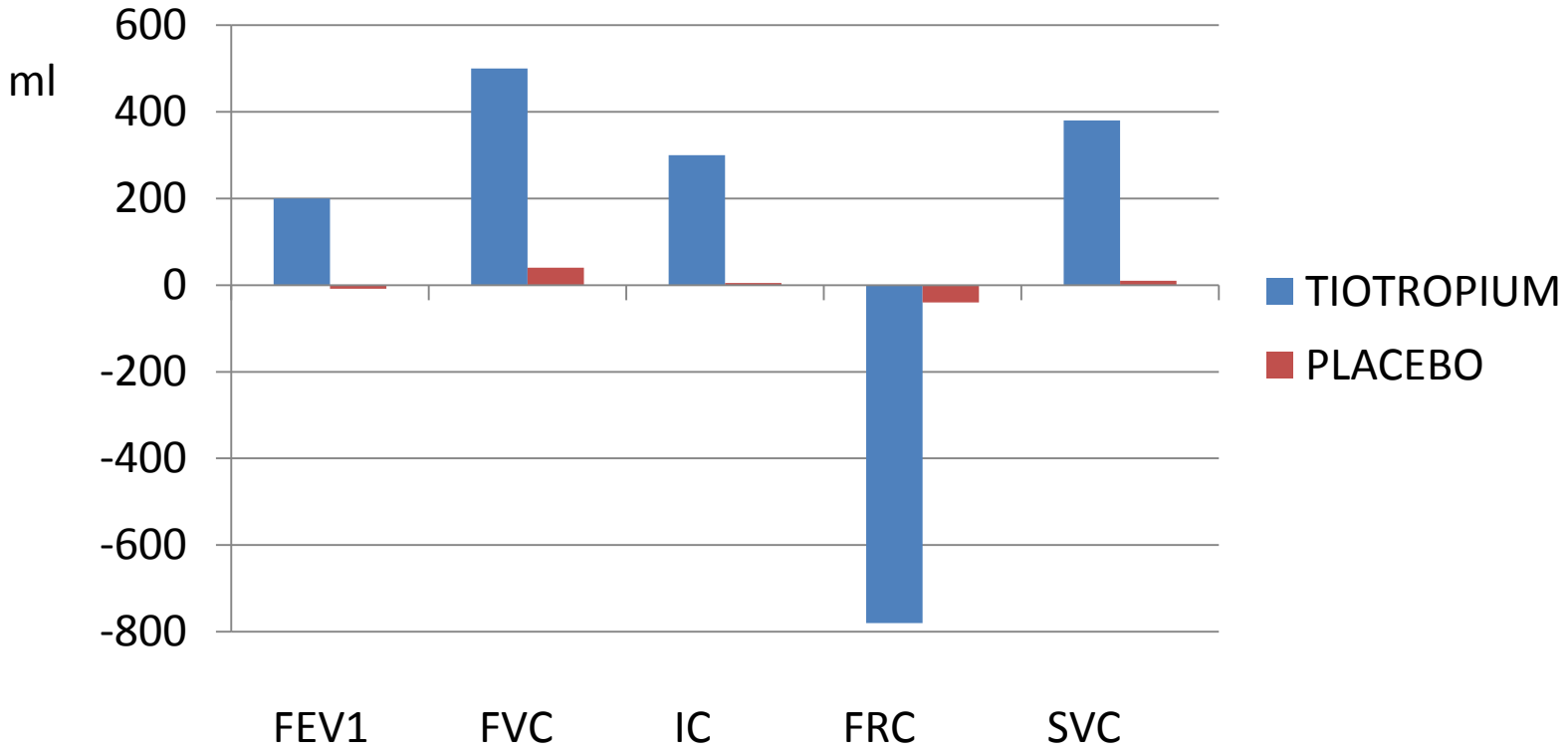
Probability of Treatment Discontinuation, Mean FEV_1 and FVC before and after Bronchodilation, and Scores for Health-Related Quality of Life



NEJM 2008

Effect of tiotropium on lung volumes

COPD patients: FEV_1 45% predicted
Lung function 4 weeks after treatment



Changes in lung volumes and spirometry following 4 weeks of treatment with tiotropium or placebo

Celli B et al: Chest 2003

Efficacy and safety of once-daily NVS237 in patients with Mild to Moderate COPD: the GLOW1 trial.

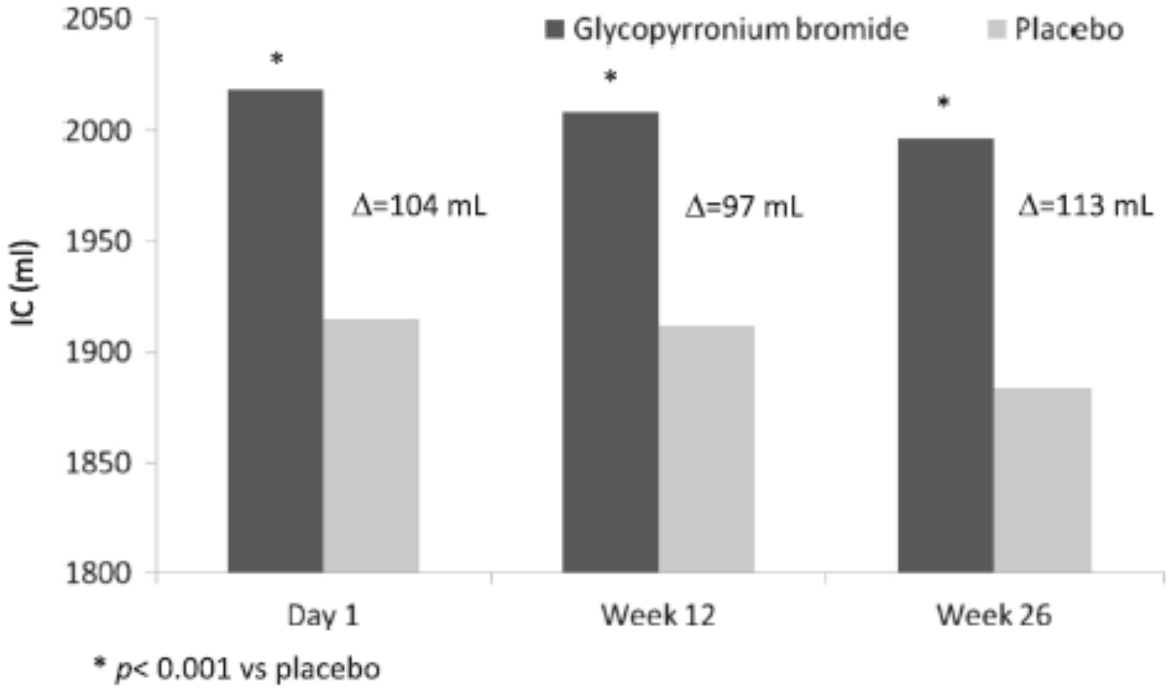


Figure 3 Difference of inspiratory capacity (IC) values between glycopyrronium bromide and placebo at the end of the first day and at 12th and 26th week of therapy before the administration of the active drug or placebo. Δ = Difference between glycopyrronium bromide and placebo.

D'Urzo A, et al. Resp Res 2011

Aclidinium improves exercise endurance, dyspnea, lung hyperiflation in COPD patients

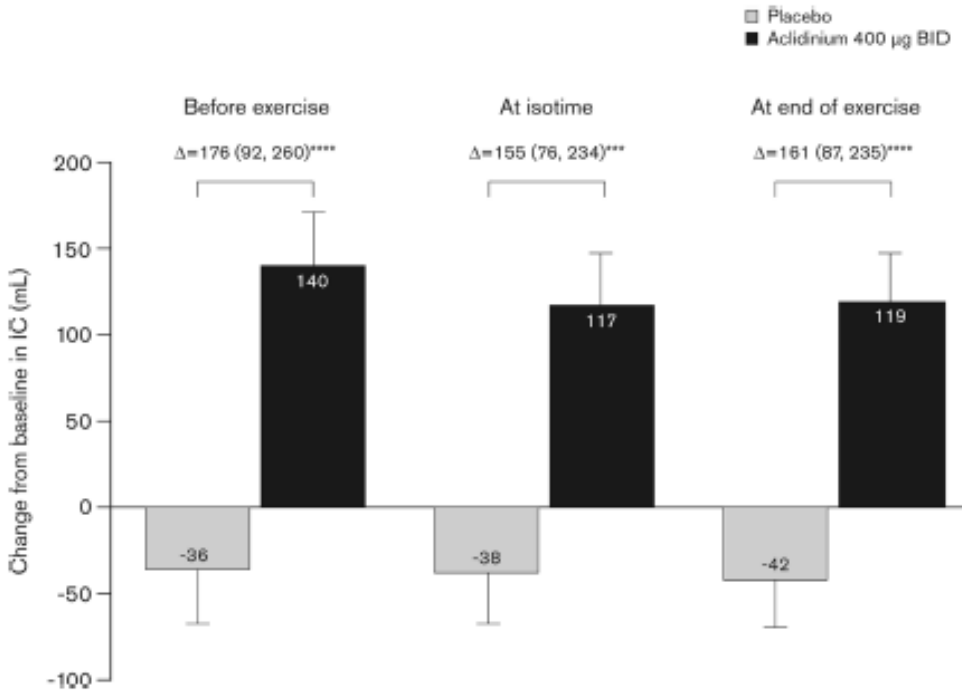


Figure 4 Change from baseline in dynamic IC at end of exercise at Week 3. Change from baseline in dynamic IC measured before exercise, at isotime, and at end of exercise was assessed at Week 3 (ITT population). Data reported as least squares means change from baseline (analysis of covariance) + standard error; Δ = least squares means difference (95% confidence intervals). *** $p < 0.001$, **** $p < 0.0001$ versus placebo. BID, twice daily; IC, inspiratory capacity; ITT, intent-to-treat.

Beeh KM, et al. BMC Pulm Med 2014

Acute effects of indacaterol on lung hyperinflation in moderate COPD: A comparison with tiotropium

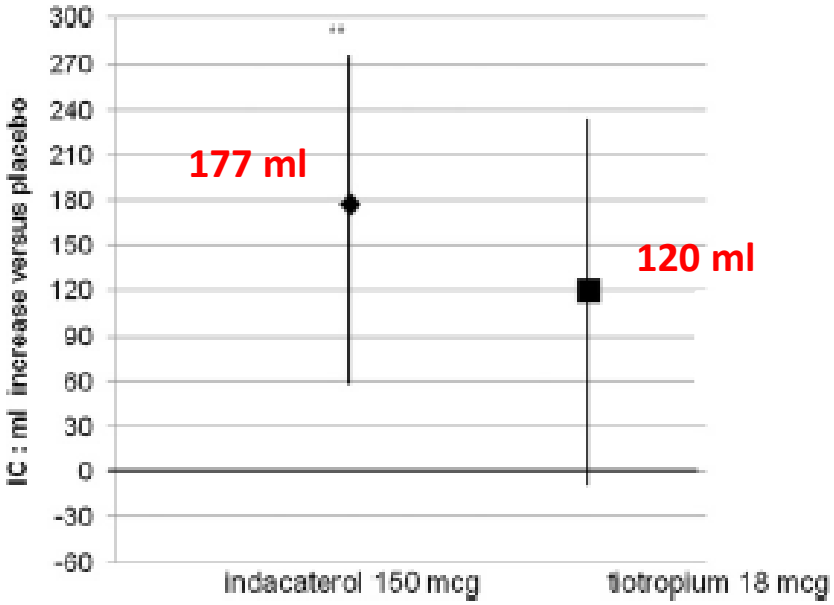


Figure 2 Difference in peak inspiratory capacity (IC). Data are mean ± 95% CI. $^{**}p < 0.01$ versus placebo.

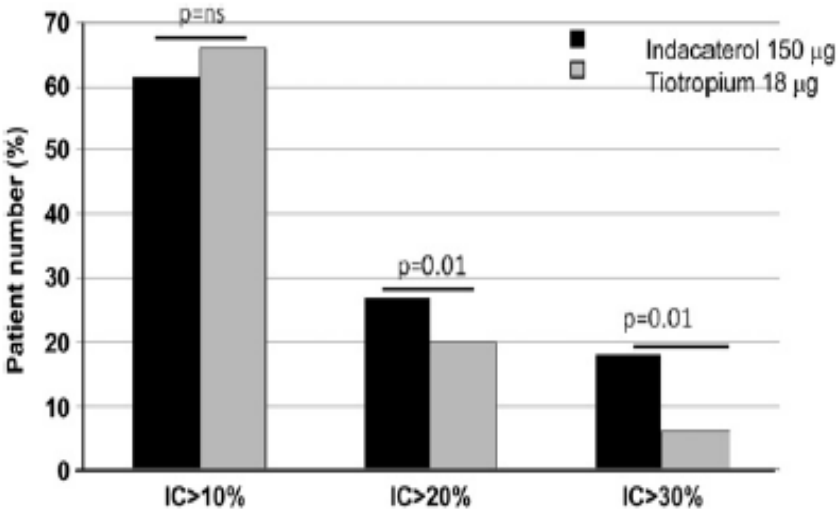


Figure 4 Distribution of patients with significant improvements in inspiratory capacity (IC) over 4 h. *P*-values denote significant differences between indacaterol and tiotropium.

Rossi A, et al. Resp Med 2011

Acute effects of indacaterol on lung hyperinflation in moderate COPD: A comparison with tiotropium

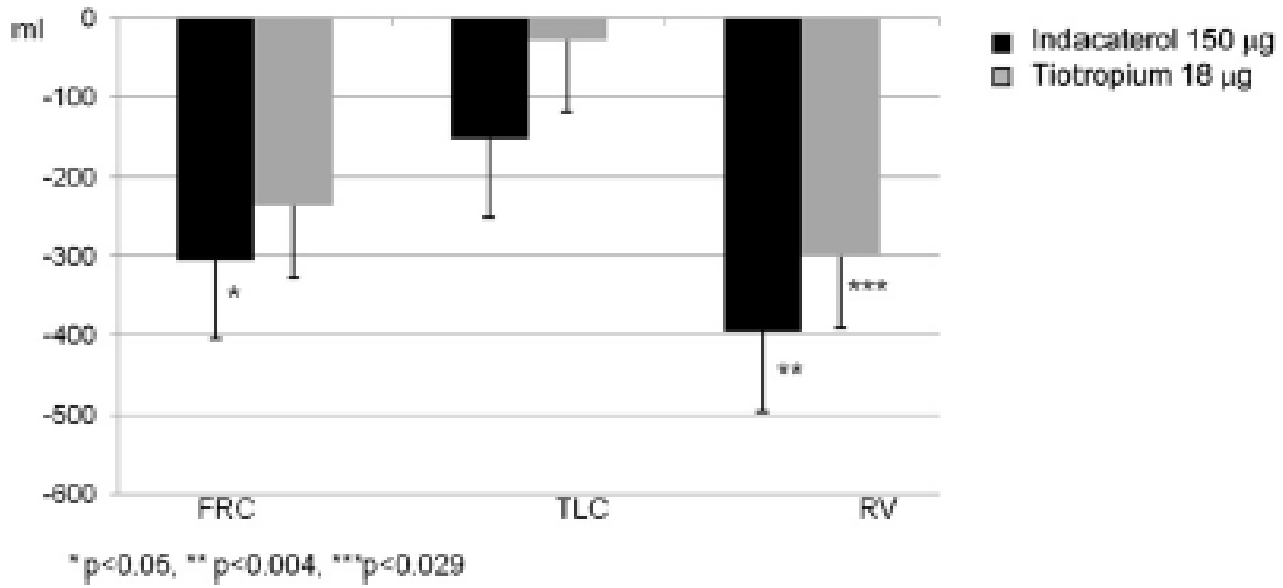
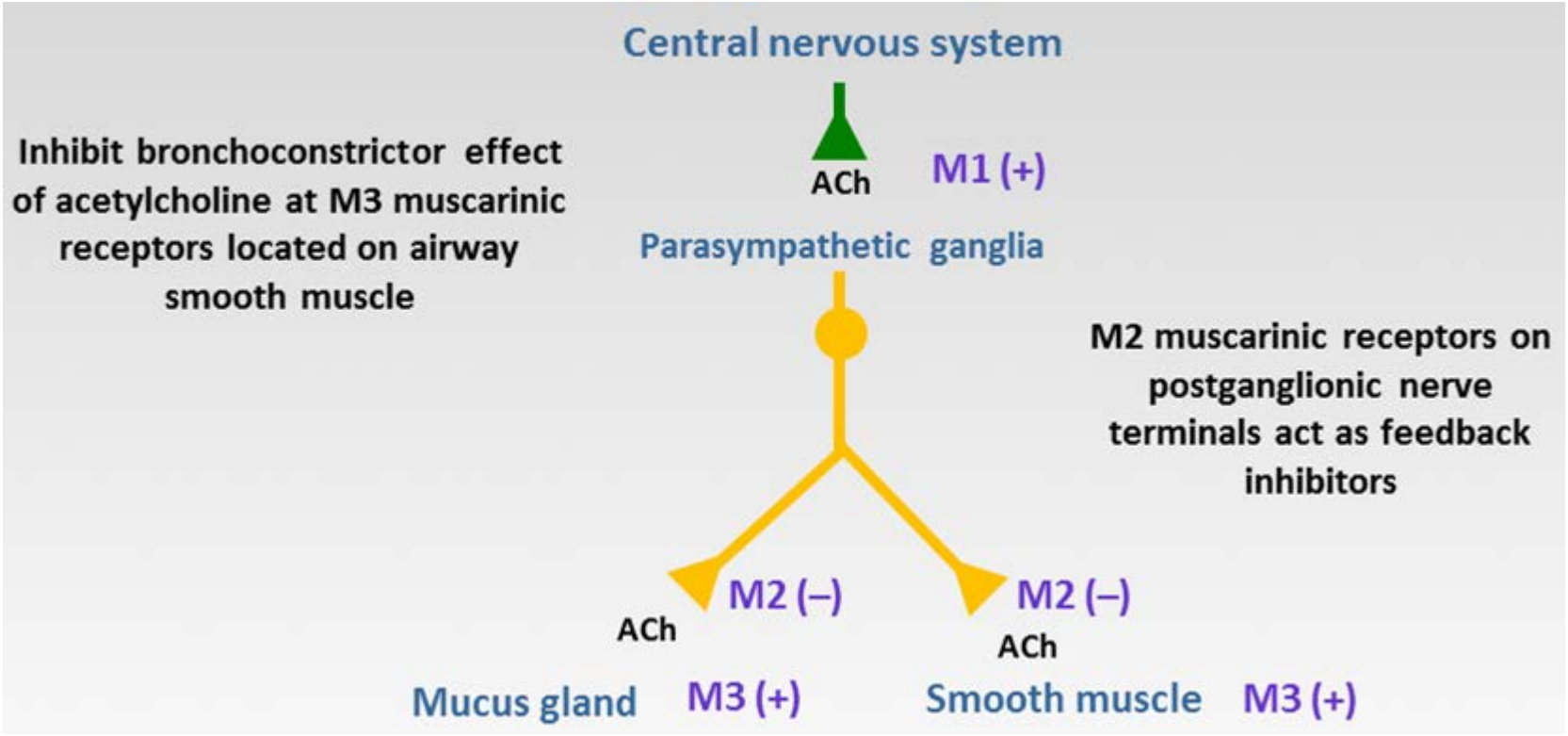


Figure 6 Changes in FRC, TLC and RV at the 4th hours after administration.FRC was decreased compared to pre-dose by 305 ± 100 ml with indacaterol ($p = 0.01$) and by 236 ± 88 ml with tiotropium ($p = 0.053$); TCL by 152 ± 0.114 ml with indacaterol ($p = 0.208$) and by 28 ± 85 ml with tiotropium.($p = 0.806$); RV by 396 ± 0.125 ml with indacaterol ($p = 0.004$) and by 301 ± 0.106 ml with tiotropium ($p = 0.029$) Data are expressed as mean ± SE.

Rossi A, et al. Resp Med 2011

Rationale for dual bronchodilation

Why combine bronchodilating therapies ?
Mechanism of action of muscarinic antagonists



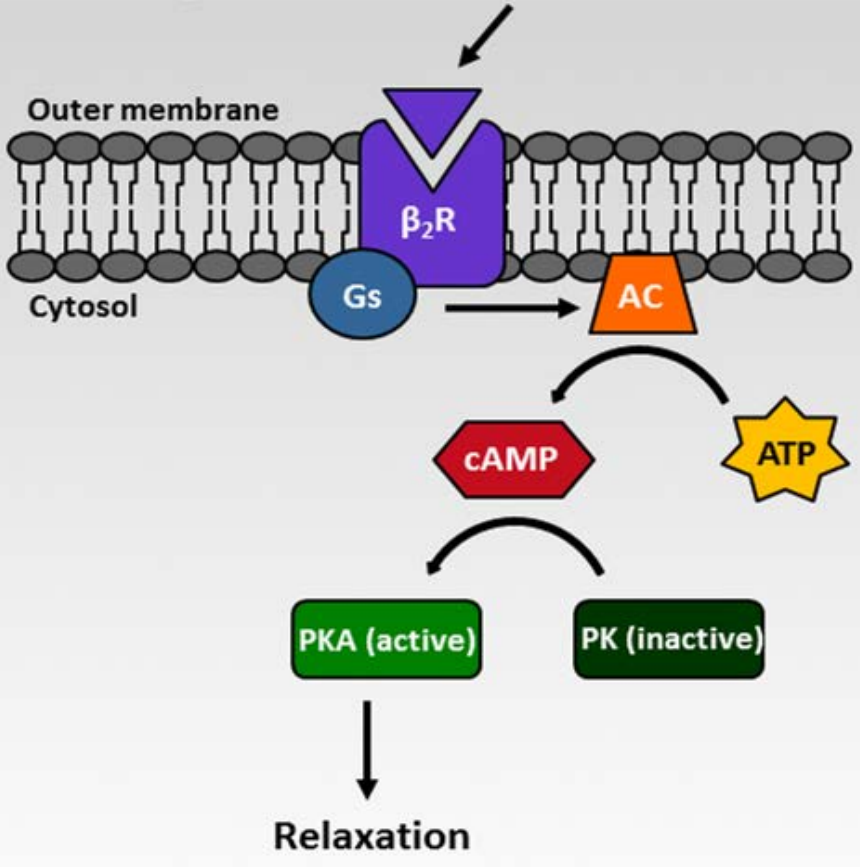
Muscarinic antagonists block M_1 and M_3 receptors to prevent binding of acetylcholine and inhibiting airway smooth muscle contraction.

Roux et al. Gen Pharmac 1998

Why combine bronchodilating therapies ? Mechanism of action of β_2-agonists

B_2-agonist

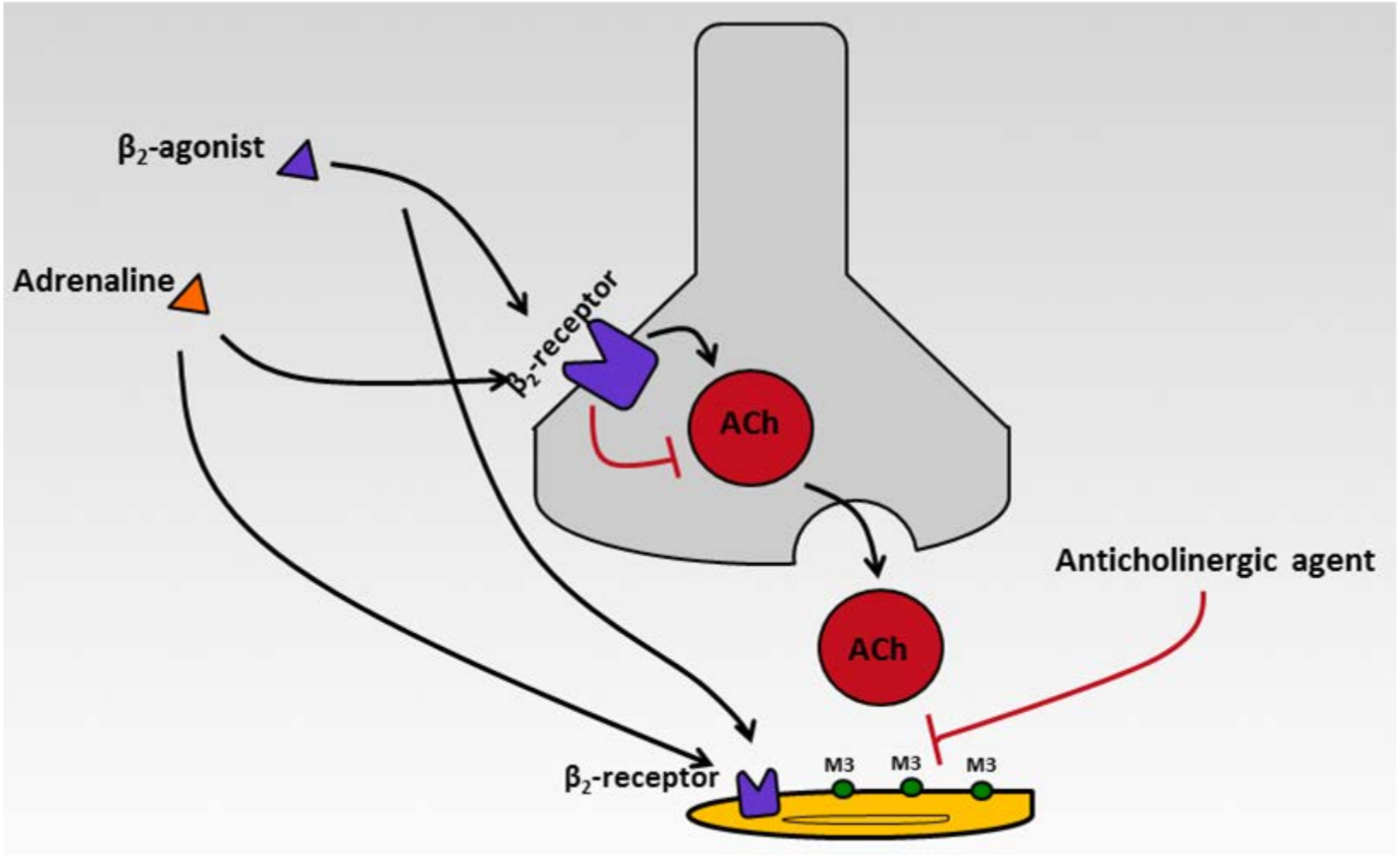
Directly activate β_2 receptors in bronchioles, leading to increase in cAMP, relaxation of smooth muscle, and bronchodilation



AC = adenylate cyclase; ATP = adenosine triphosphate; β2R = β2 receptor; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A

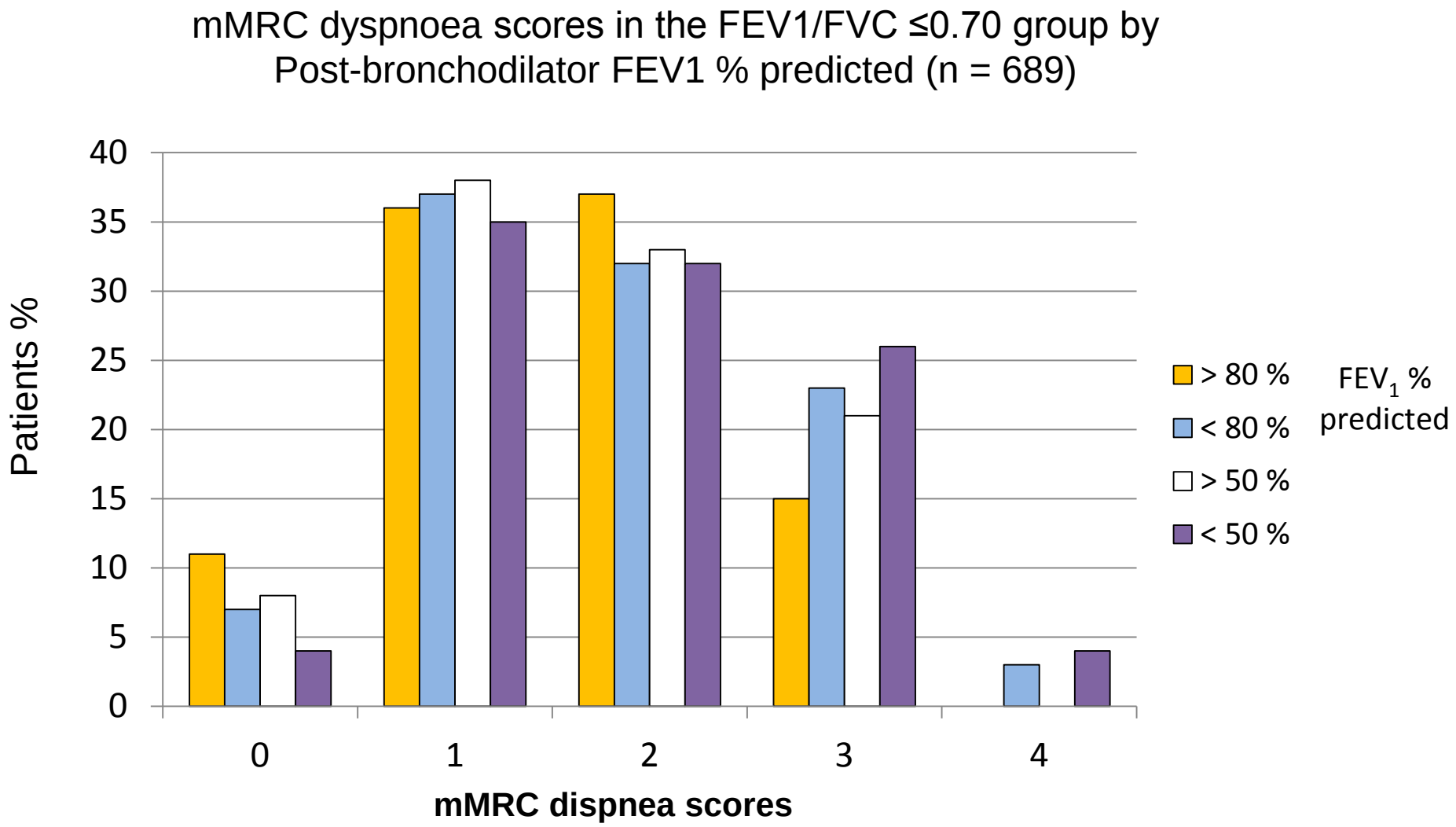
Johnson M. *Am J Respir Crit Care Med*. 1998;158(5 Pt 3):S146-153.

LABA/LAMA combination: interaction between Receptors and Neurotransmission pathways



Cazzola M, et al. Arch Bronconeumol 2005

Real world study: patients can still be breathless with long acting bronchodilator monotherapy



Dransfeld MT, et al. Prim care Resp J 2011

LABA/LAMA combination therapy

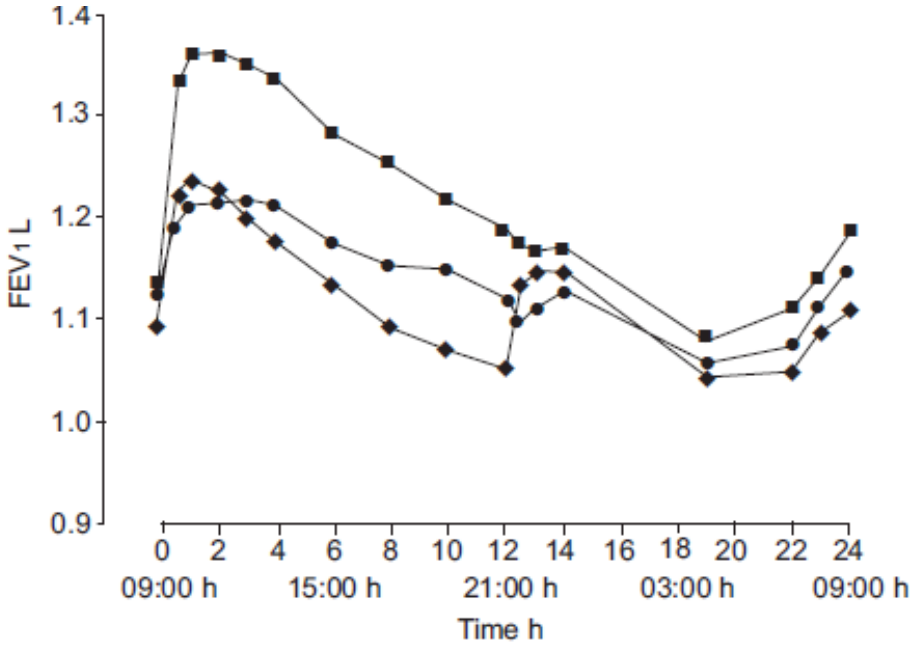


FIGURE 2. Mean forced expiratory volume in one second (FEV_1; adjusted for period, centre and patient within centre) before and during 24 h after the inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

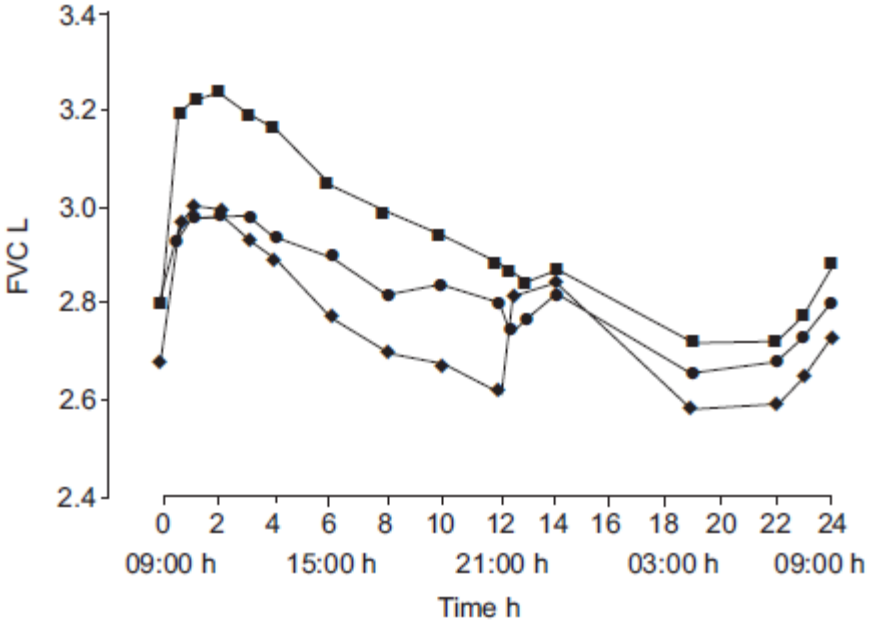
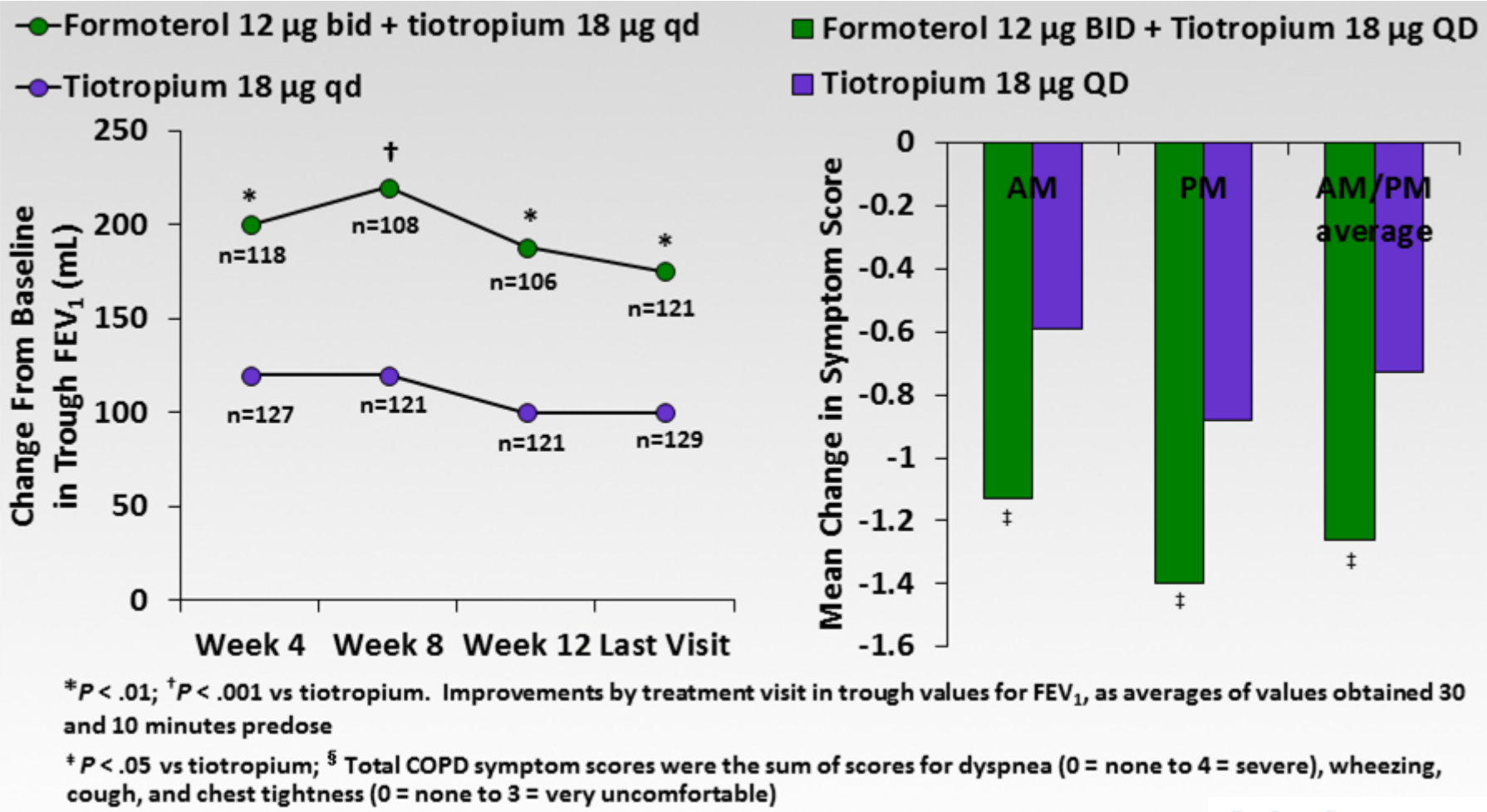


FIGURE 3. Mean forced vital capacity (FVC; adjusted for period, centre and patient within centre) before and during 24 h after inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

JA van Noord, et al . Eur Resp J 2005; 26: 214-22

LABA/LAMA combination: improved lung function and symptoms vs LAMA alone



*$P < .01$; †$P < .001$ vs tiotropium. Improvements by treatment visit in trough values for FEV_1, as averages of values obtained 30 and 10 minutes predose

‡ $P < .05$ vs tiotropium; § Total COPD symptom scores were the sum of scores for dyspnea (0 = none to 4 = severe), wheezing, cough, and chest tightness (0 = none to 3 = very uncomfortable)

Tashkin DP, et al COPD 2009

Available and emerging bronchodilators for COPD

Agents

- LABAs (twice daily)
  - formoterol
  - salmeterol
- LAMAs (twice daily)
  - aclidinium
- LABAs (once daily)
  - indacaterol
  - olodanterol
  - vilanterol
- LAMAs (once daily)
  - glycopyrronium
  - tiotropium
  - umeclidinium

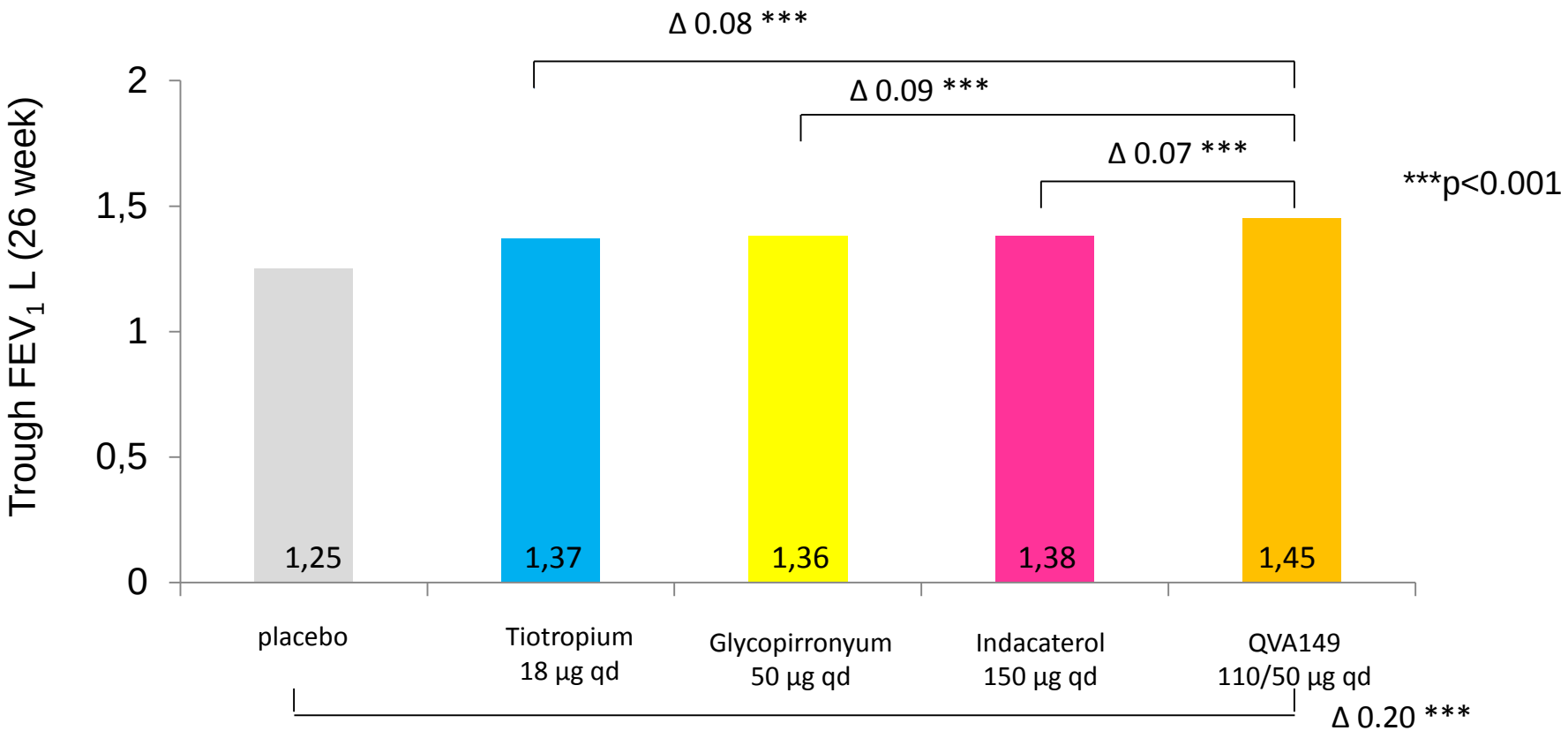
LABA/LAMA combinations

- Once daily
  - indacaterol/glycopyrronium
  - vilanterol/umeclidinium
  - olodaterol/tiotropium
- Twice daily
  - formoterol/aclidinium
  - formoterol/glycopyrrolate*

* under investigation in Europe

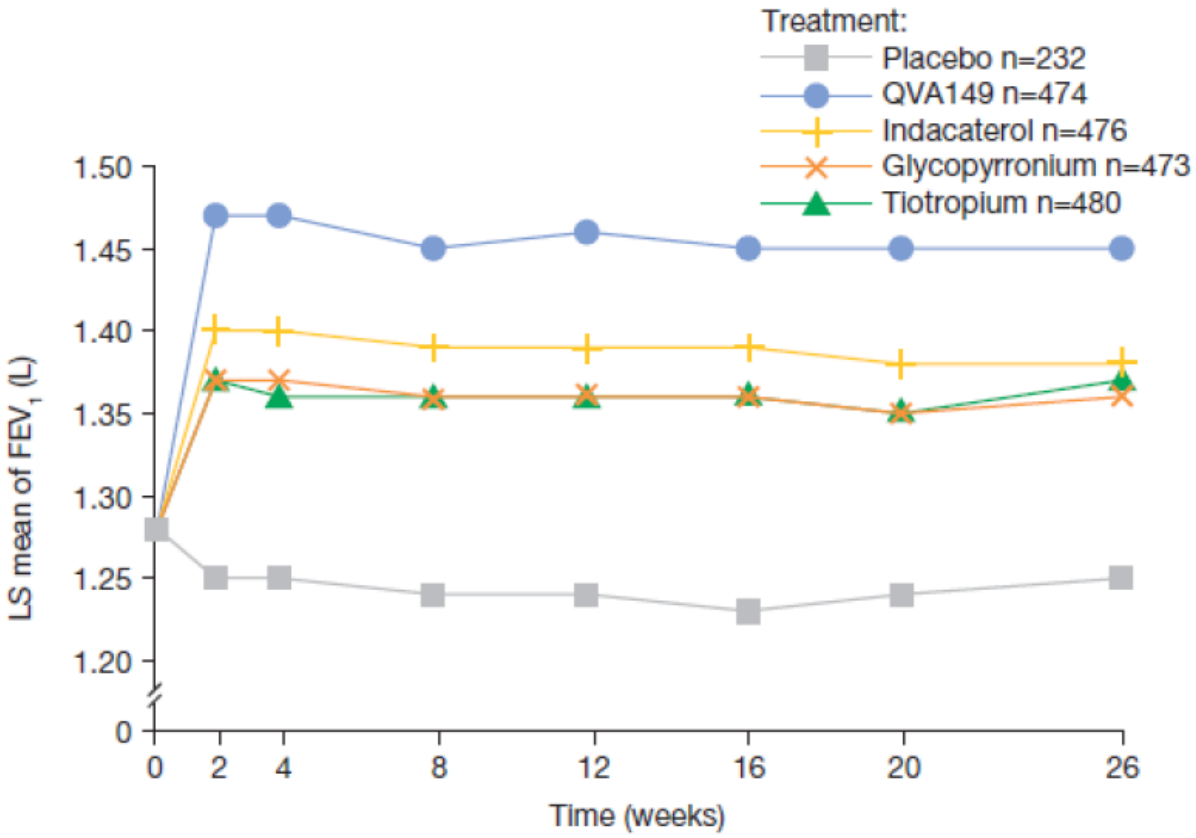
Improved lung function with QVA 149 (glycopyrronium plus indacaterol) versus monotherapy and placebo

SHINE: 26-week randomized, controlled study in patients with moderate to severe COPD (n= 2144).



Bateman E, et al. Eur Resp J 2013

Dual bronchodilation with QVA149: the SHINE study

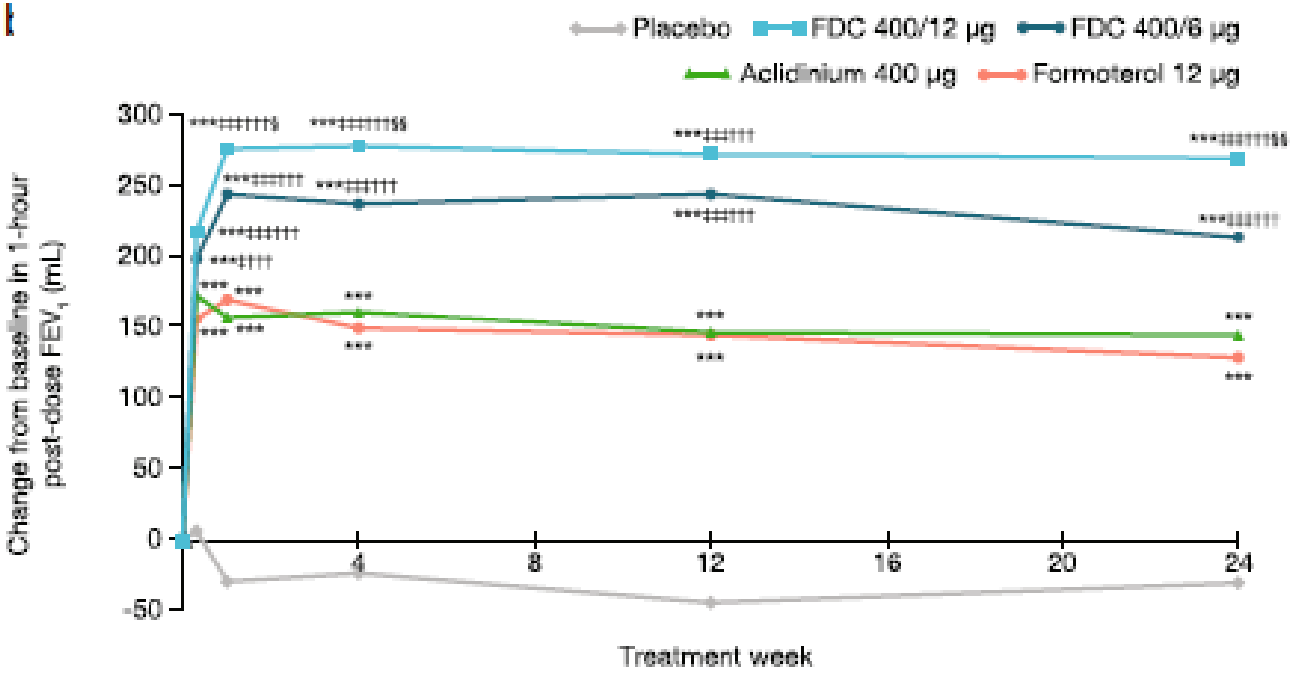


QVA149 was superior to all active treatments and placebo at all time points (all $p < 0.001$).

- 2/3 of the subjects moderate;
- 80% no exacerbations
- entry SGRQ >40

Bateman et al Eur Respir J. 2013

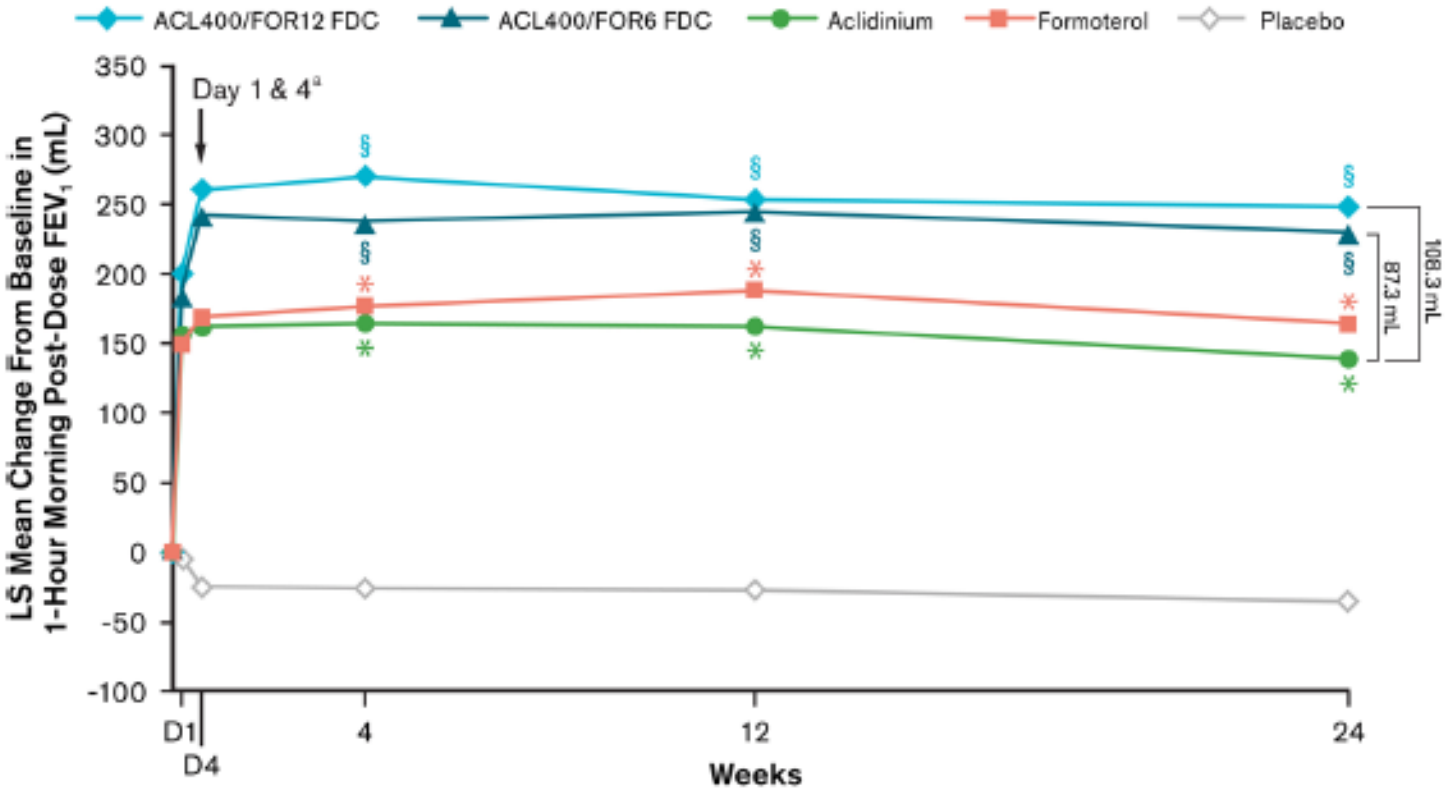
Efficacy and safety of aclidinium/formoterol fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD)



Mean treatment differences for change from baseline in 1-hour **post-dose** FEV_1
***p < 0.001 vs placebo; ‡ p < 0.05; ‡‡‡ p < 0.001 vs aclidinium;
††† p < 0.001 vs formoterol; § p < 0.05; §§ p < 0.01 vs FDC 400/6 µg.

Singh et al. BMC Pulmonary Medicine 2014, 14:178

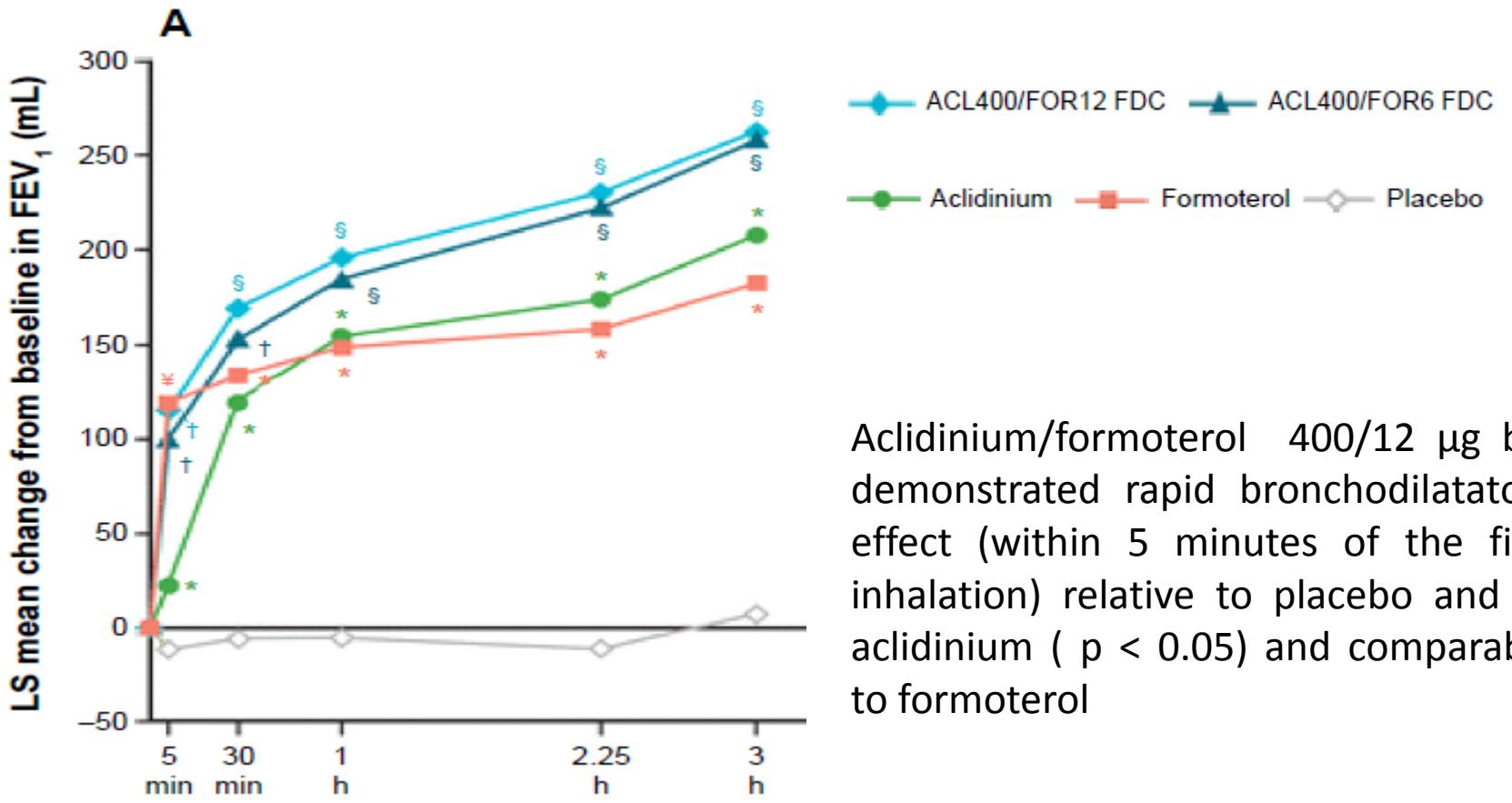
Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study



*p < 0.05 versus placebo; §p < 0.05 versus aclidinium, formoterol, and placebo

D'Urzo et al. Respiratory Research 2014

Aclidinium/formoterol: FEV_1 improvement on Day 1

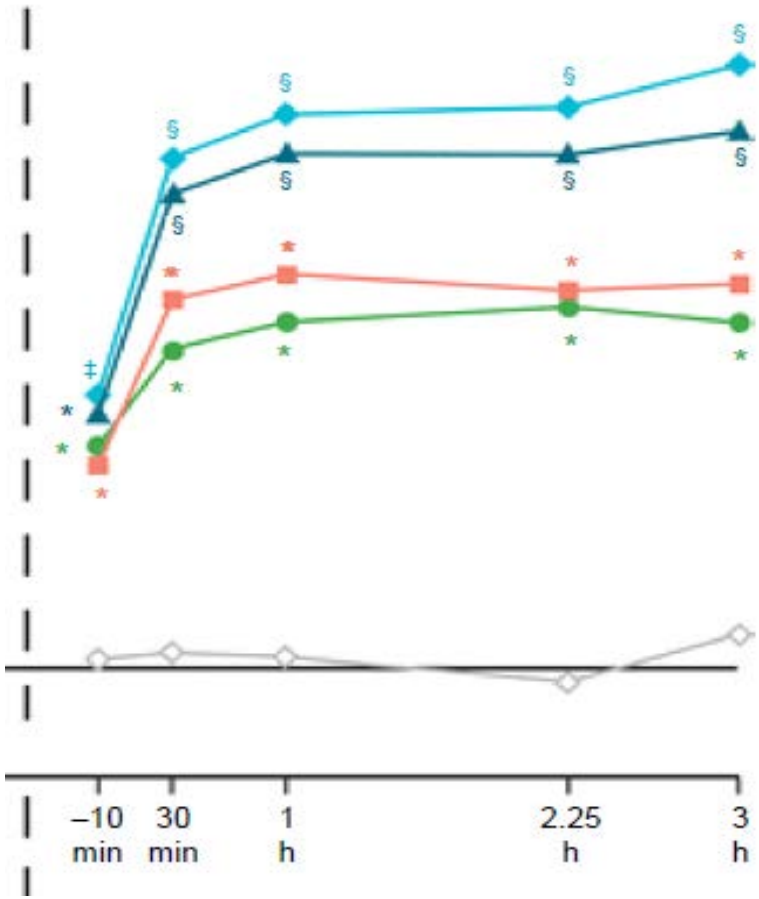


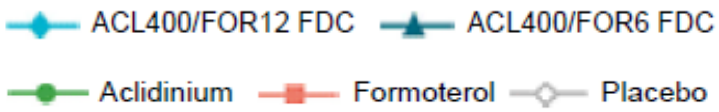
Aclidinium/formoterol 400/12 µg bid demonstrated rapid bronchodilatatory effect (within 5 minutes of the first inhalation) relative to placebo and to aclidinium ($p < 0.05$) and comparable to formoterol

*$P < 0.05$ vs placebo; † $P < 0.05$ vs aclidinium and placebo; § $P < 0.05$ vs aclidinium, formoterol, and placebo; ¥ $P < 0.05$ vs aclidinium/formoterol FDC 400/6 µg and placebo

D'Urzo AD et al. Resp Res 2014

Aclidinium/formoterol: FEV_1 improvement at week 24



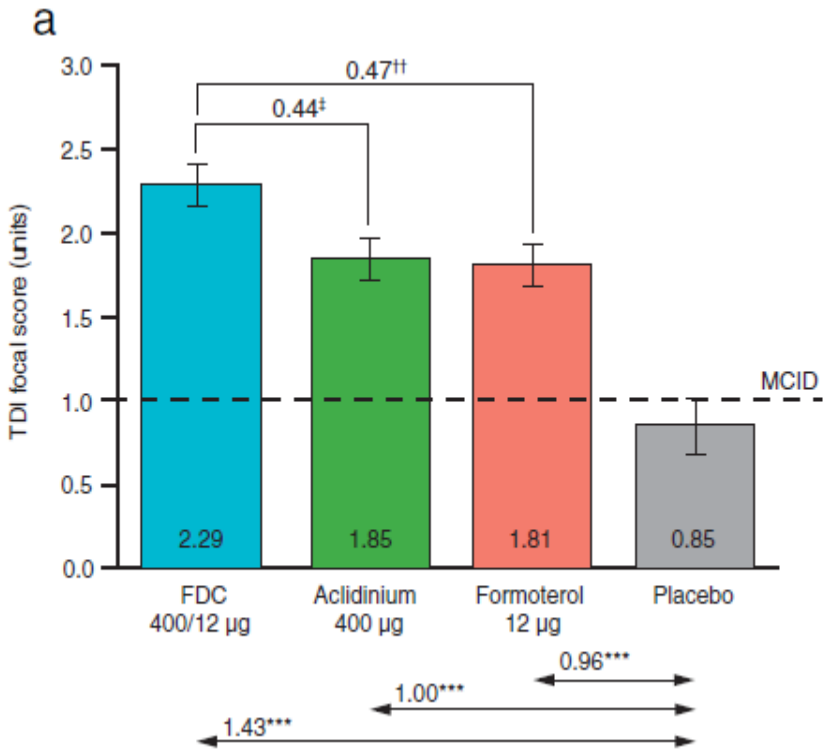


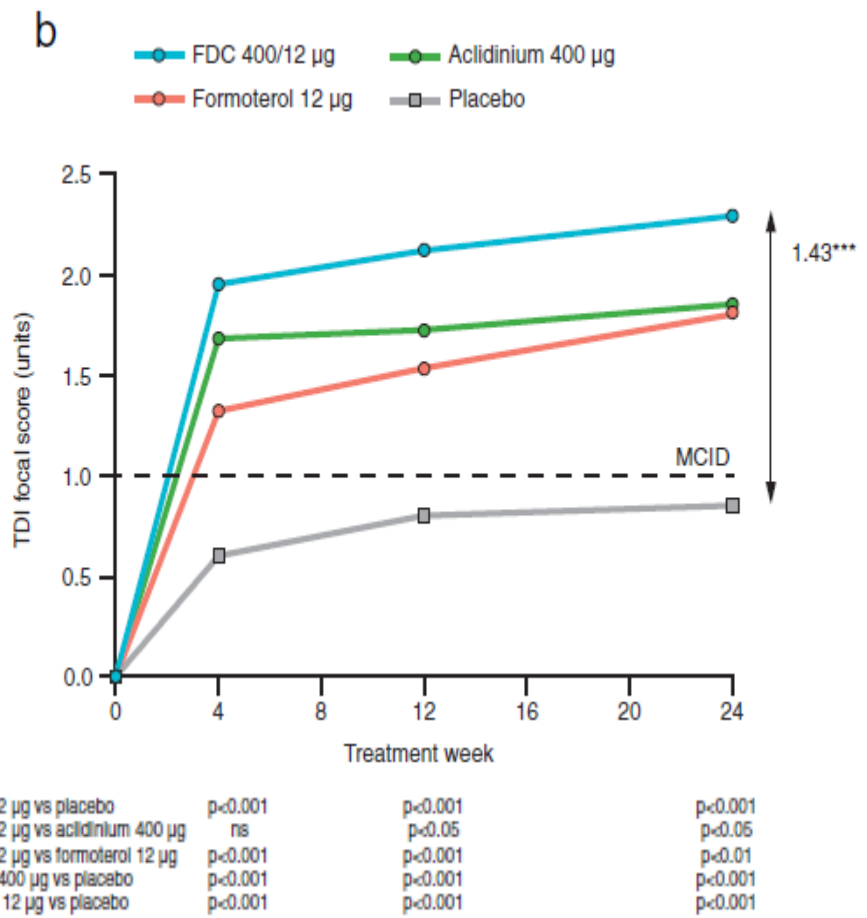
Aclidinium/formoterol 400/12 µg bid demonstrated rapid bronchodilatatory effect over the first 3 hours post-dose compared with placebo and monotherapy components at week 24

D'Urzo AD et al. Resp Res 2014

*P < 0.05 vs placebo; †P <0.05 vs aclidinium and placebo; §P< 0.05 vs aclidinium, formoterol, and placebo; ¥P <0.05 vs aclidinium/formoterol FDC 400/6 µg and placebo

Pooled Analysis: Improvement in TDI focal score at Week 24 and over 24 weeks

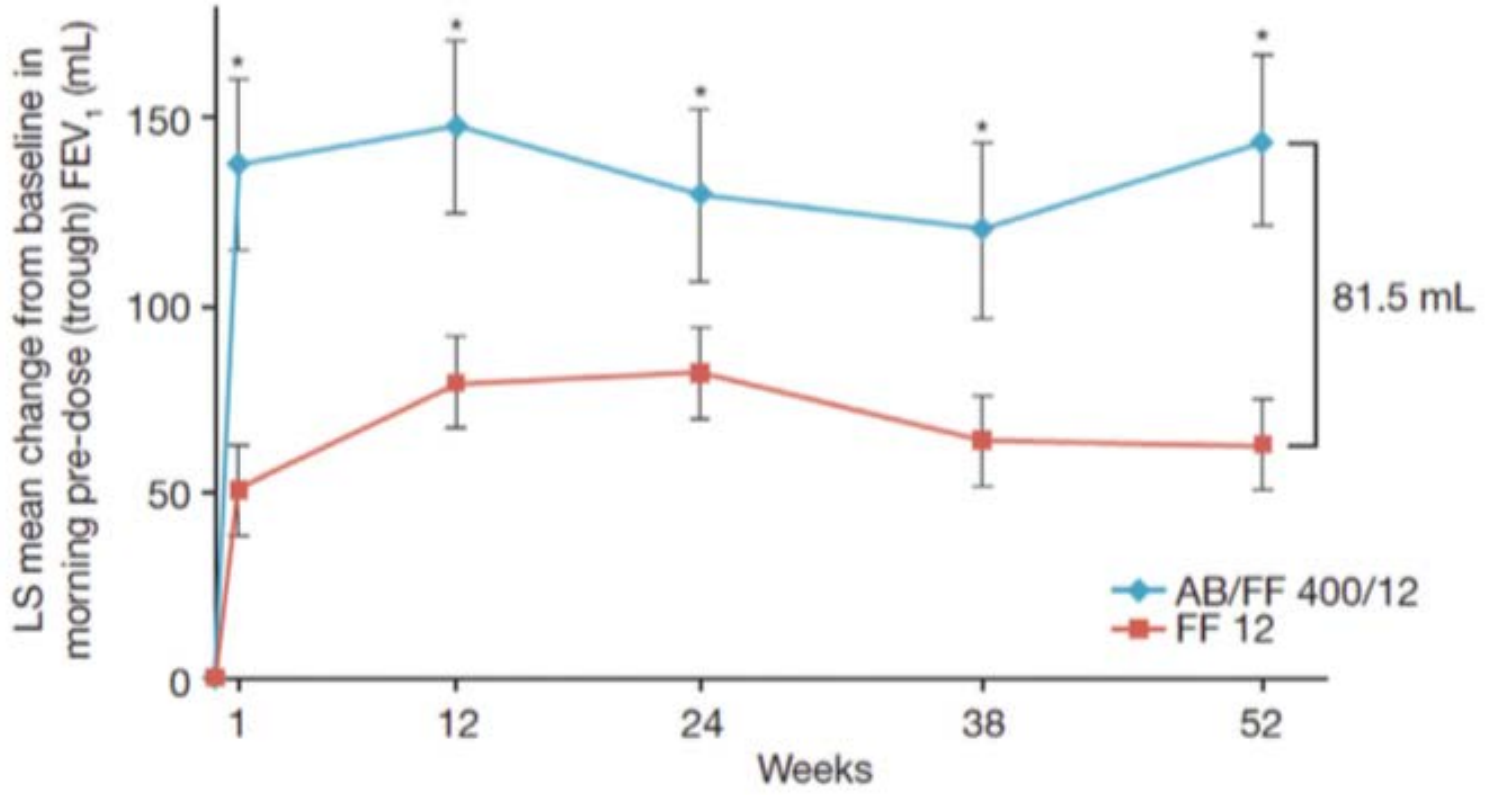




FDC 400/12 µg vs placebo	p<0.001	p<0.001	p<0.001
FDC 400/12 µg vs aclidinium 400 µg	ns	p<0.05	p<0.05
FDC 400/12 µg vs formoterol 12 µg	p<0.001	p<0.001	p<0.01
Aclidinium 400 µg vs placebo	p<0.001	p<0.001	p<0.001
Formoterol 12 µg vs placebo	p<0.001	p<0.001	p<0.001

Bateman et al. Resp Research 2015

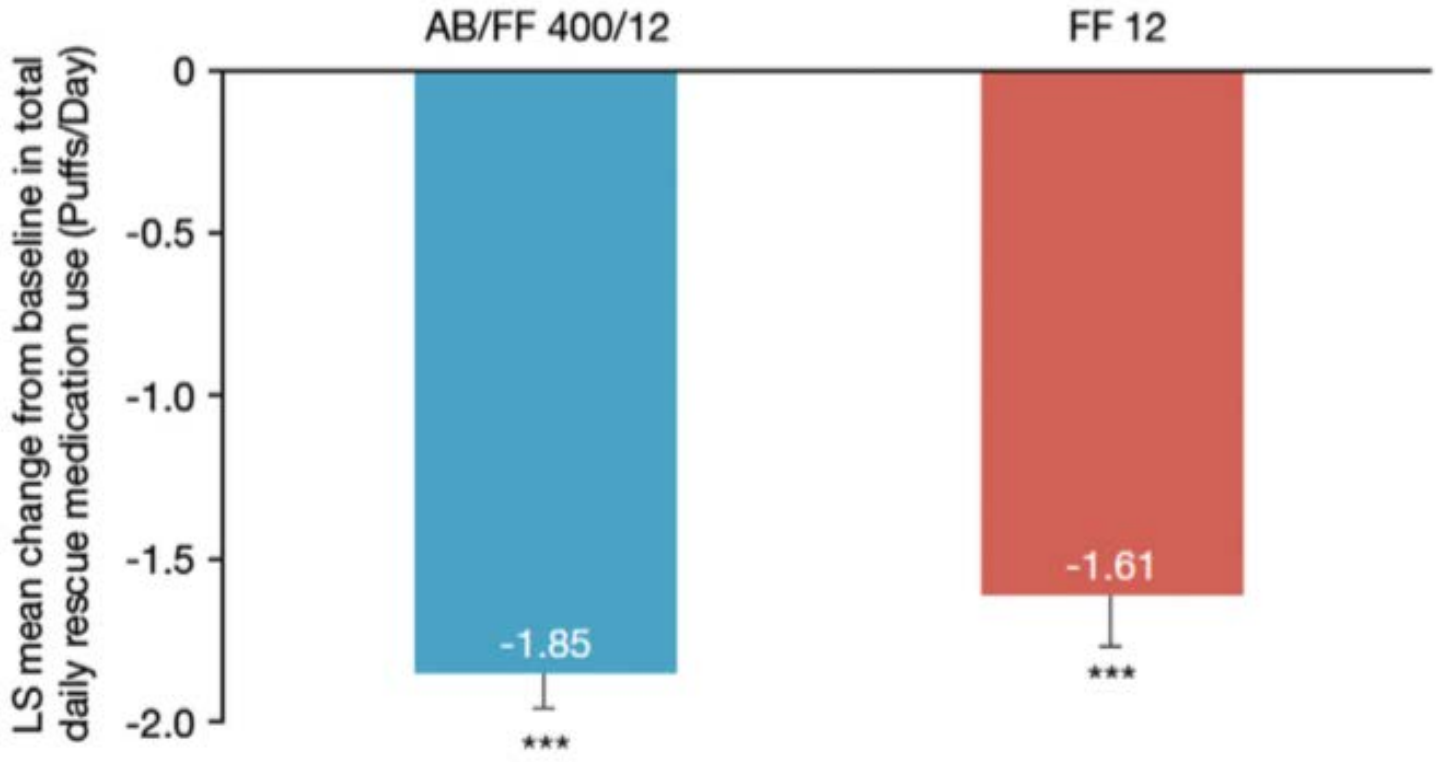
Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: Results of a randomized 1-year trial in patients with COPD



*p < 0.05 vs formoterol 12 mg

Donohue J, et al. Resp Medicine 2016

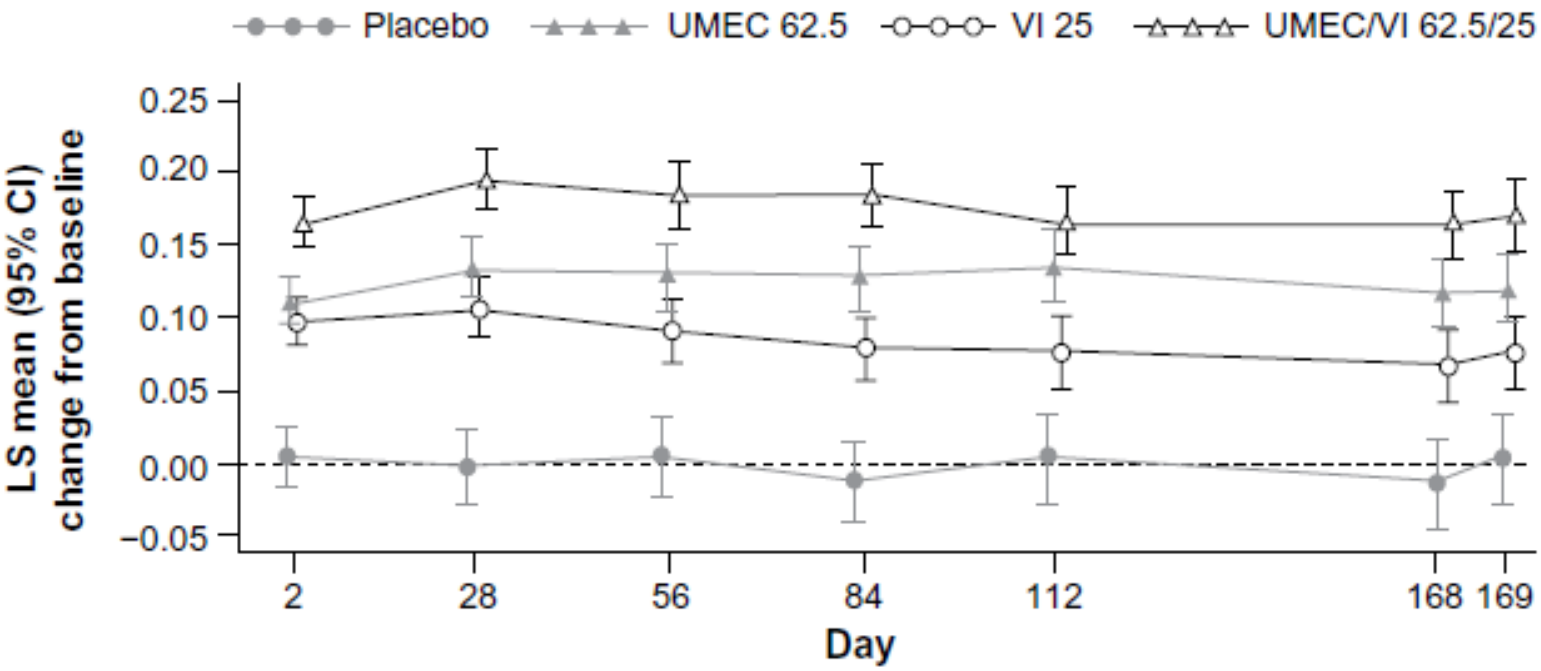
Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: Results of a randomized 1-year trial in patients with COPD



***p < 0.0001 vs baseline

Donohue J, et al. Resp Medicine 2016

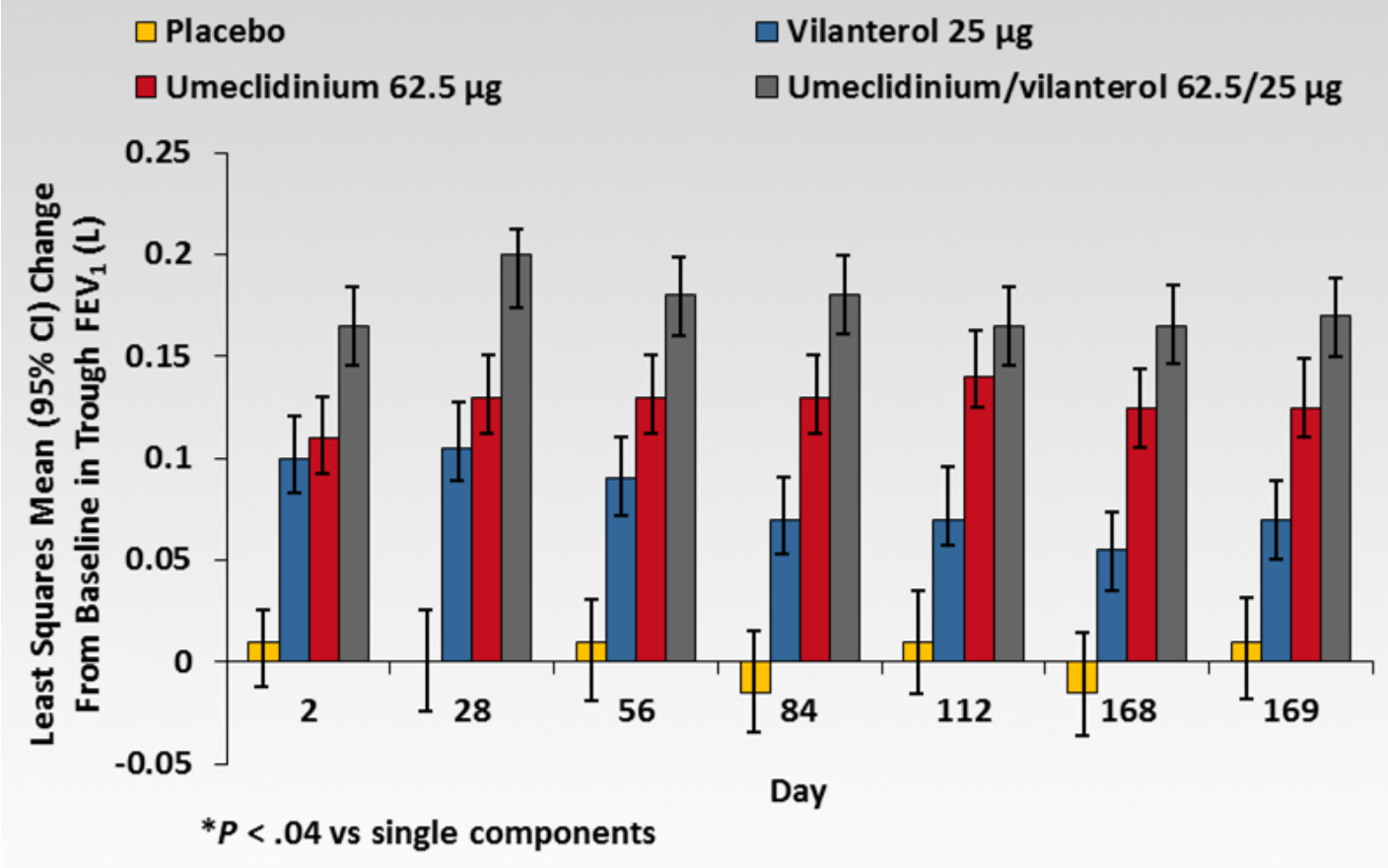
Efficacy and safety of once daily umeclidinium/vilanterol 62.5/25 mcg in COPD



All active treatments produced statistically significant improvements in trough FEV_1 compared with placebo on Day 169 (0.072-0.167 L, all $p < 0.001$); increases with UMEC/VI 62.5/25 mcg were significantly greater than monotherapies (0.052-0.095 L, $p < 0.004$).

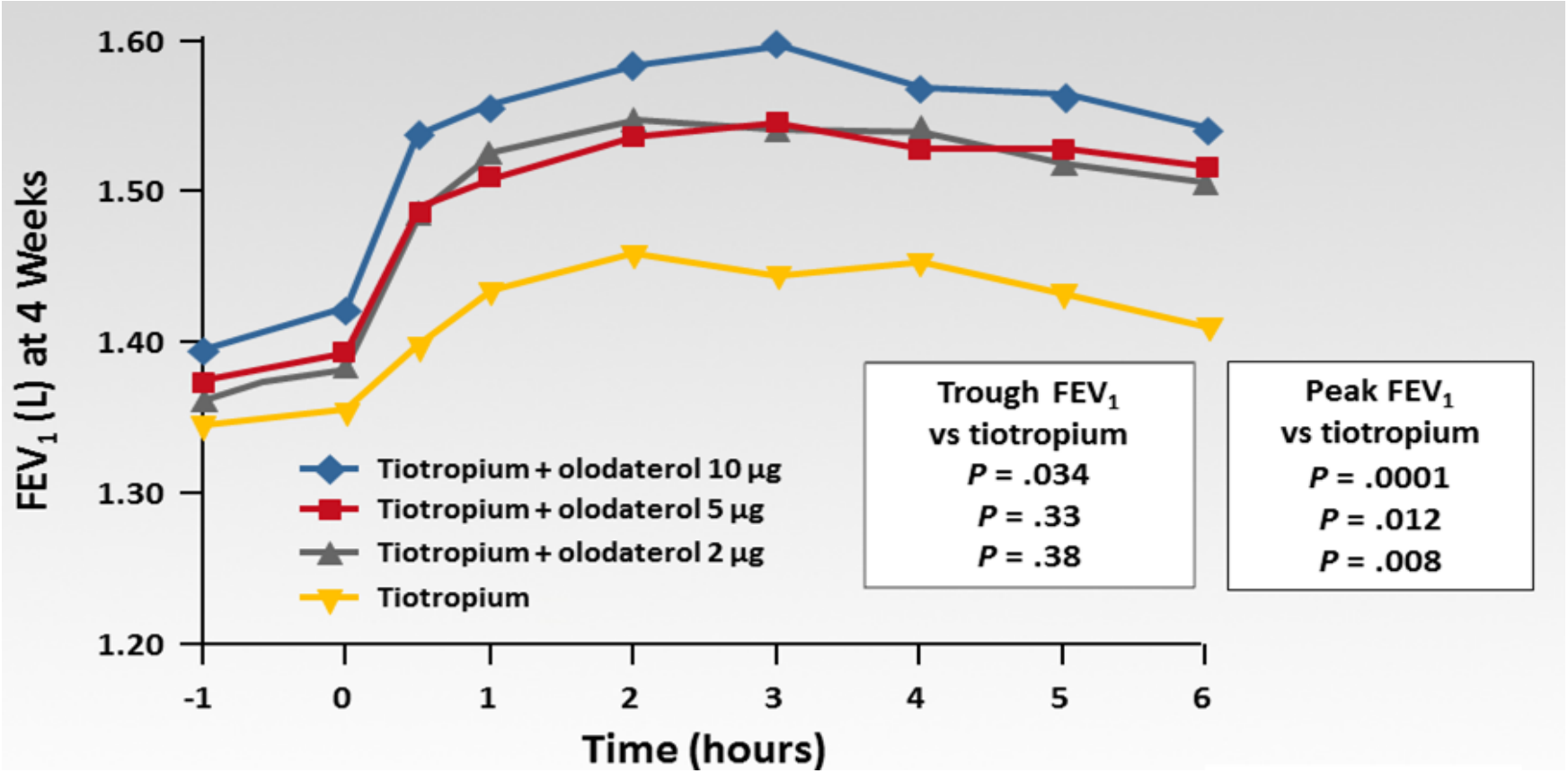
Donohue JF, et al. Respir Med 2013

Efficacy and safety of once daily umeclidinium/vilanterol 62.5/25 mcg in COPD



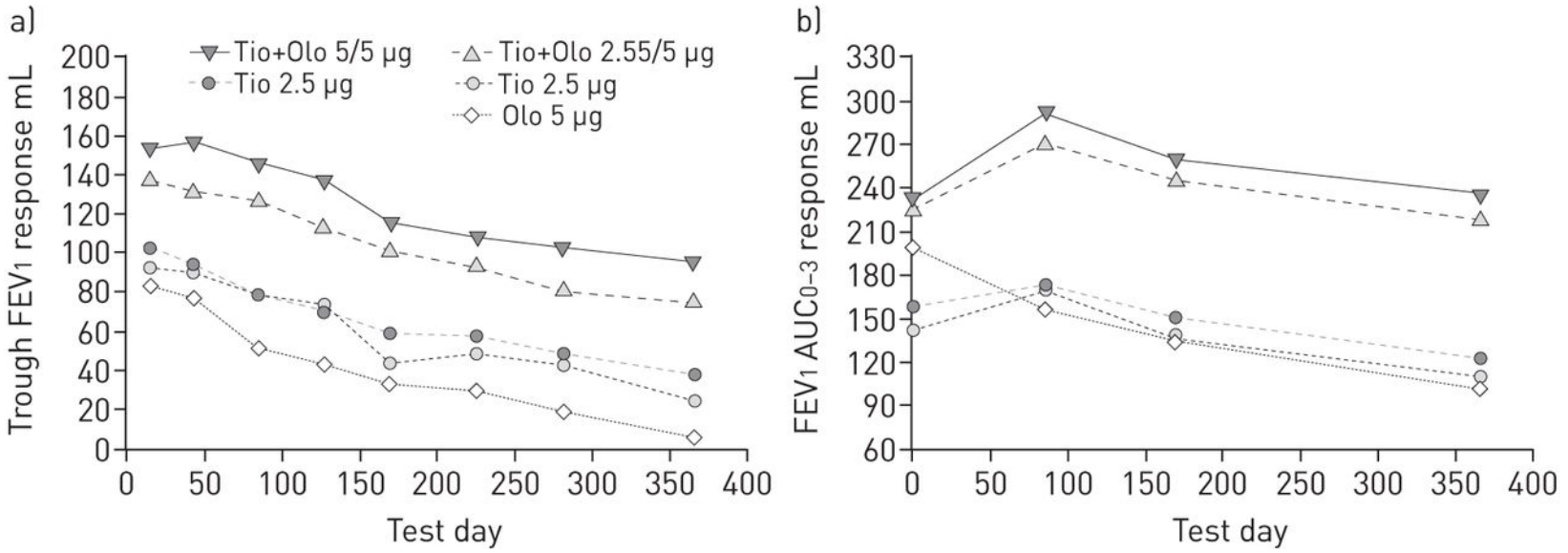
Donohue JF, et al. Respir Med 2013.

3 doses of olodaterol/tiotropium vs tiotropium alone



Maltais F, et al. ERS 2010

Tiotropium and olodaterol combination versus mono/components COPD GOLD 2 /4

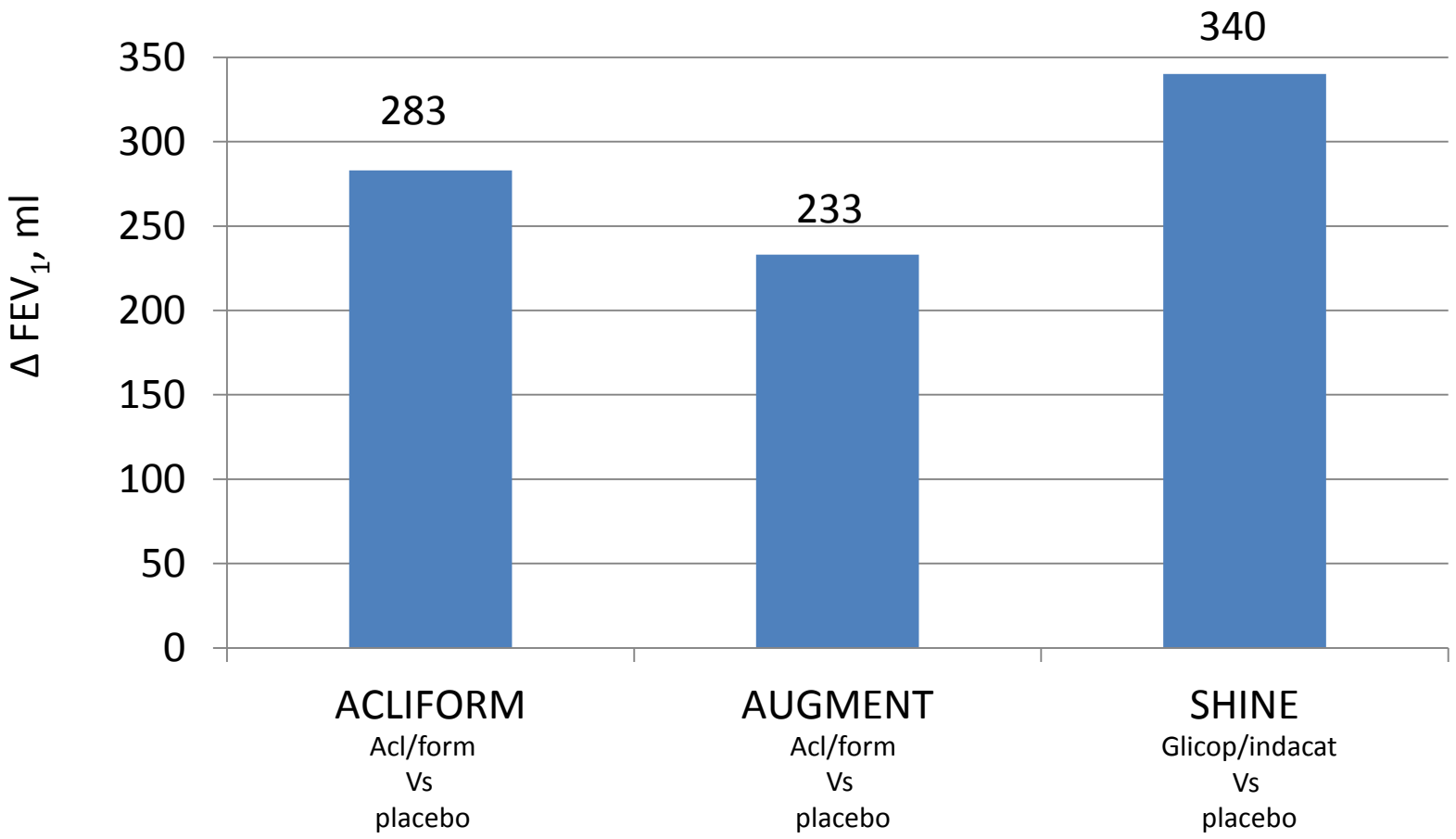


Lung function end points (combined data set) over 52 weeks: full analysis set. a) adjusted mean trough forced expiratory volume in 1 s (FEV1); b) area under the curve from 0 to 3 hours

Buhl R, et al. Eur Respir J 2015 45(6):1763

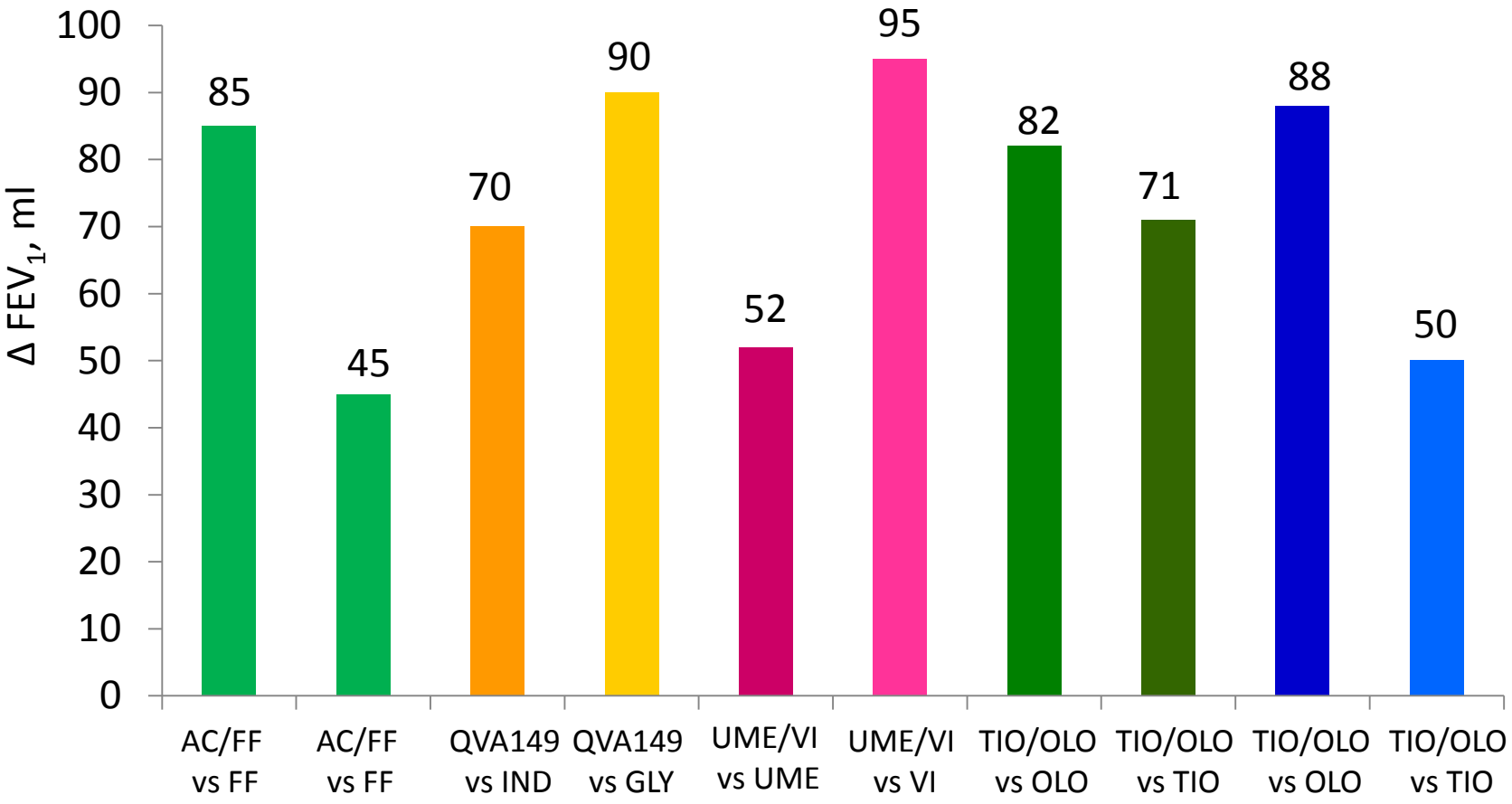
Combination treatments cause large FEV_1 changes immediately post-dose

1) Singh D et al. BMC Pulm Med 2014 2) D'Urzo AD et al. Resp Res 2014 3) Bateman et al Eur Respir J. 2013



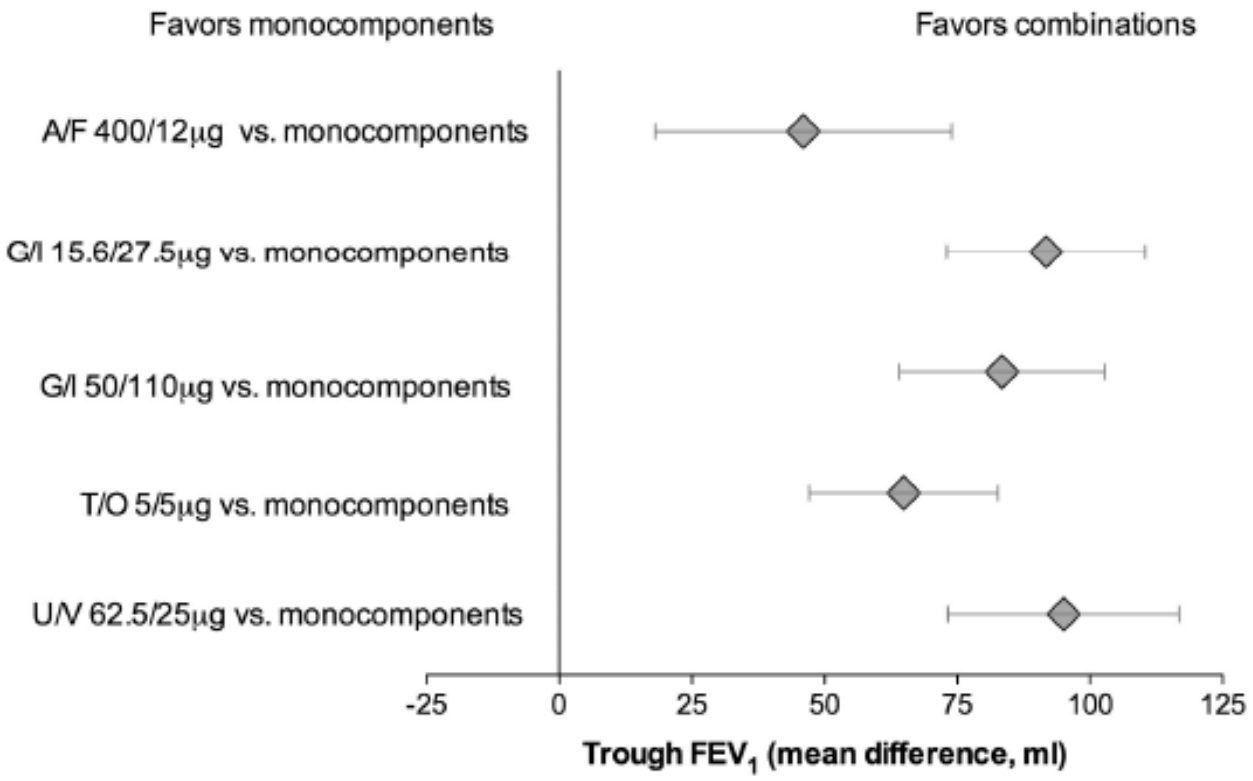
Changes in trough FEV_1: Combination vs monotherapy

Changes in trough FEV1 for combination vs monotherapy from all studies (range 45-95 ml)



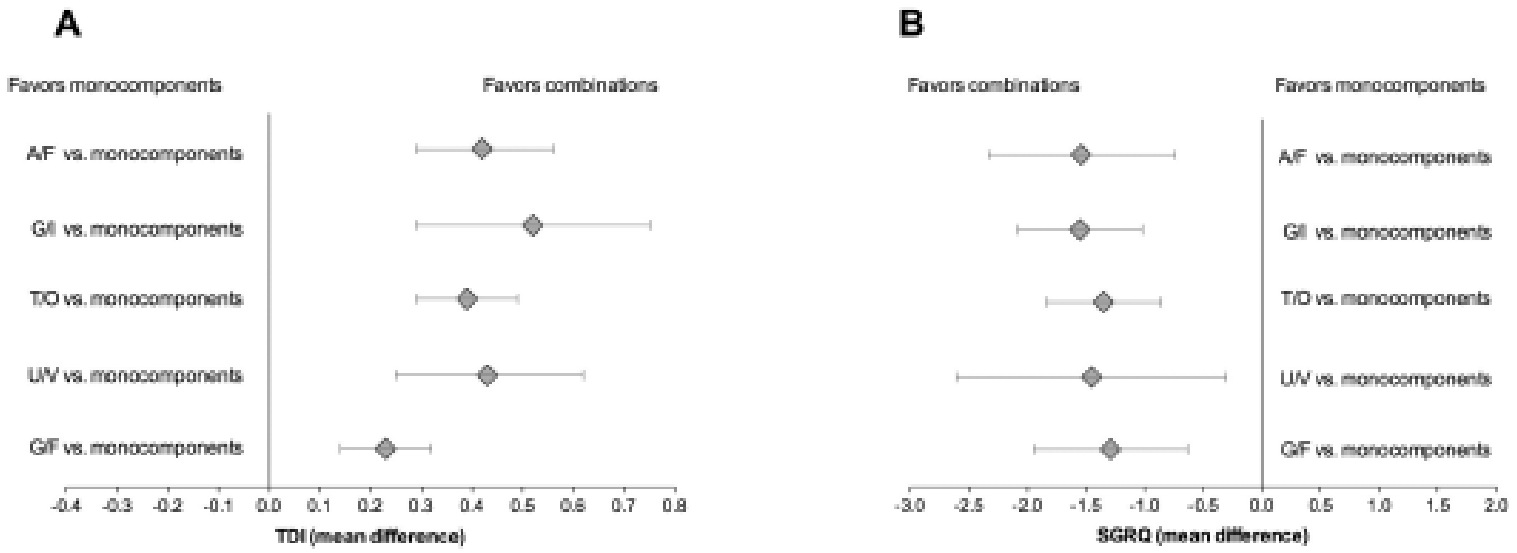
1) Singh D et al. BMC Pulm Med 2014 2) D'Urzo AD et al. Resp Res 2014 3) Bateman et al Eur Respir J. 2013 4) Donohue J et al. 5) Buhl R et al. Eur Resp J 2015.

A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD



Calzetta L, et al. Chest 2016

A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD



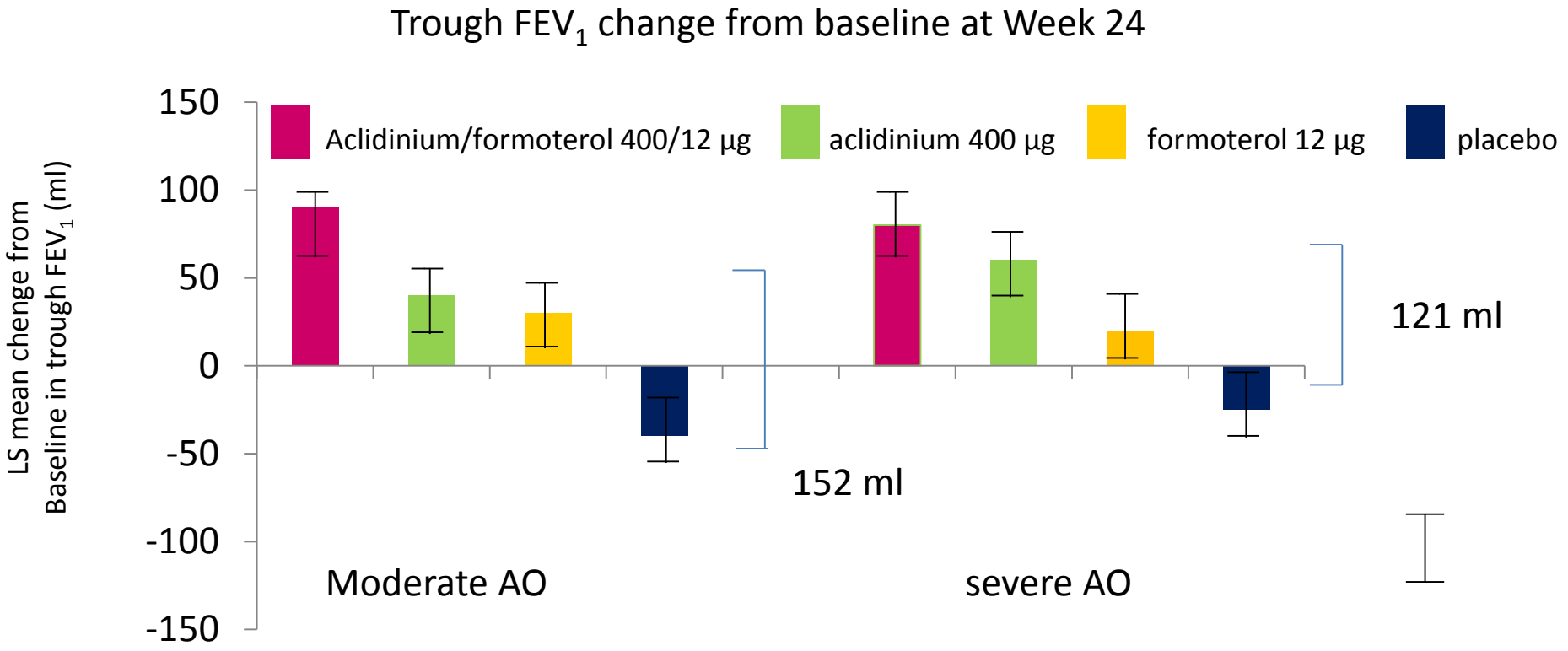
Calzetta L, et al. Chest 2016

Response to LABA/LAMA combination by patient subgroup

- Is there a change in response to LABA/LAMA due to:

- Severity of airflow obstruction
- Concomitant ICS
- Patient age

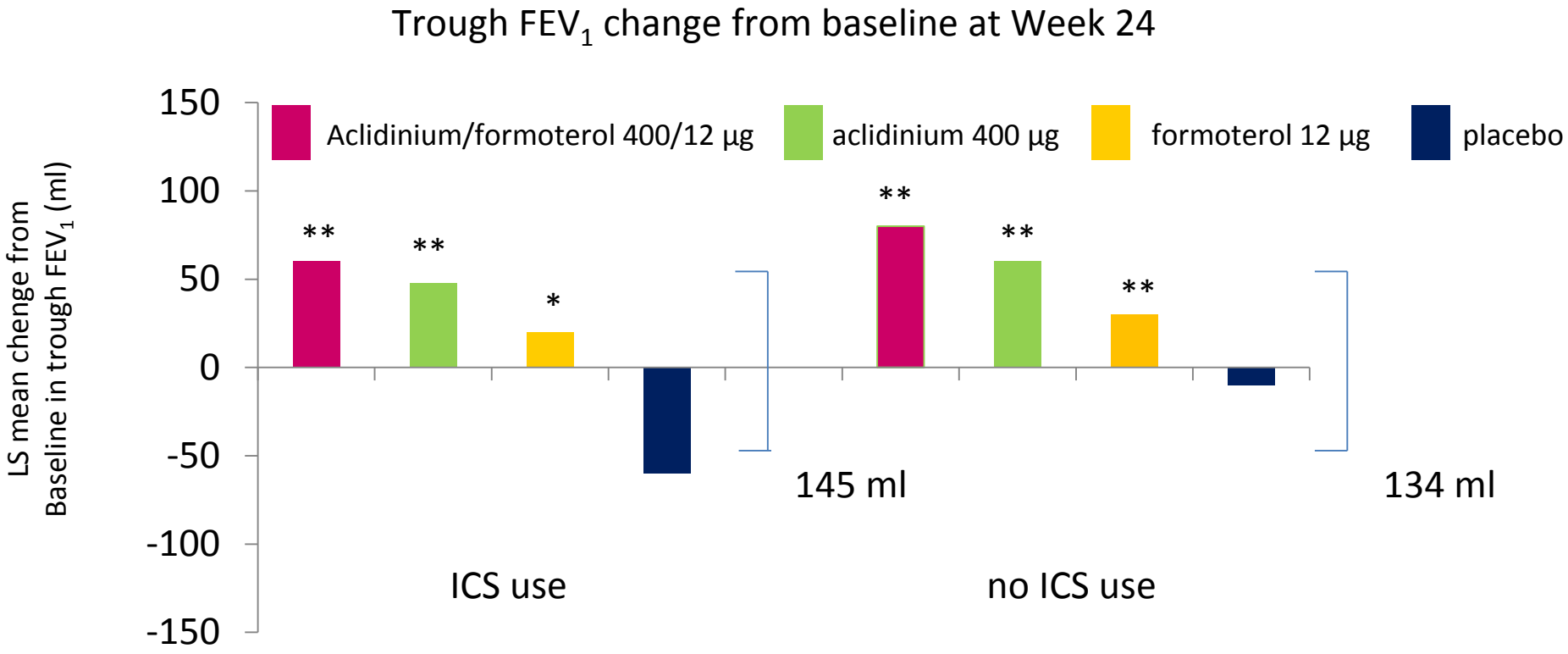
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by COPD severity



- Aclidinium/formoterol 400/12 µg BID:
  - improved morning pre-dose (trough) FEV1 versus Formoterol $p < 0.001$ regardless of AO severity
  - improved morning pre-dose (trough) FEV1 versus Aclidinium $p < 0.05$ in patients with moderate AO

Pooled data ACLIFORM-AUGMENT. Bateman E, et al. ATS 2015

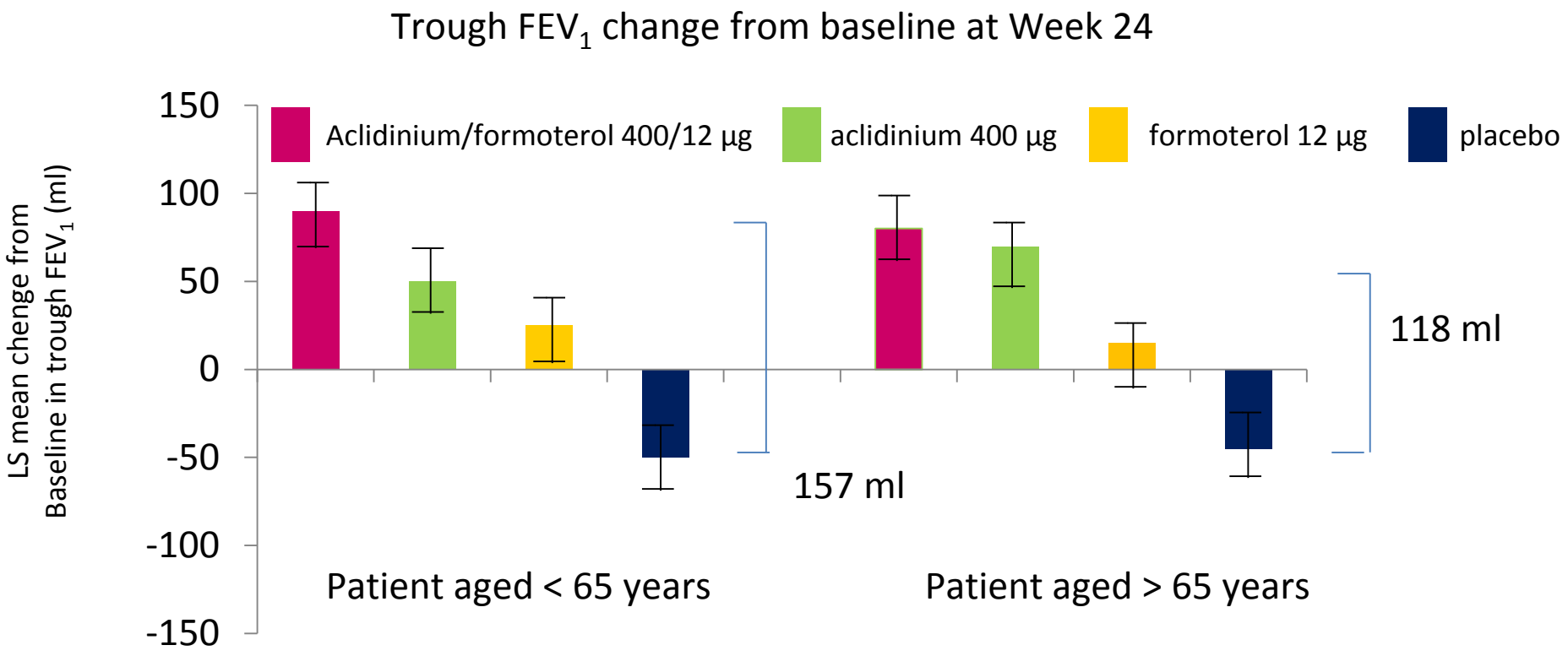
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by ICS use



- Aclidinium/formoterol 400/12 µg BID improved trough FEV_1 by 71 ml versus Formoterol alone ($p < 0.001$) and by 54 ml vs Aclidinium alone ($p < 0.05$) in patients using concomitant ICS.
- Trough FEV_1 was significantly greater with all active treatments vs placebo, regardless of ICS use.

Pooled data ACLIFORM-AUGMENT. Bateman E, et al.ATS 2015.

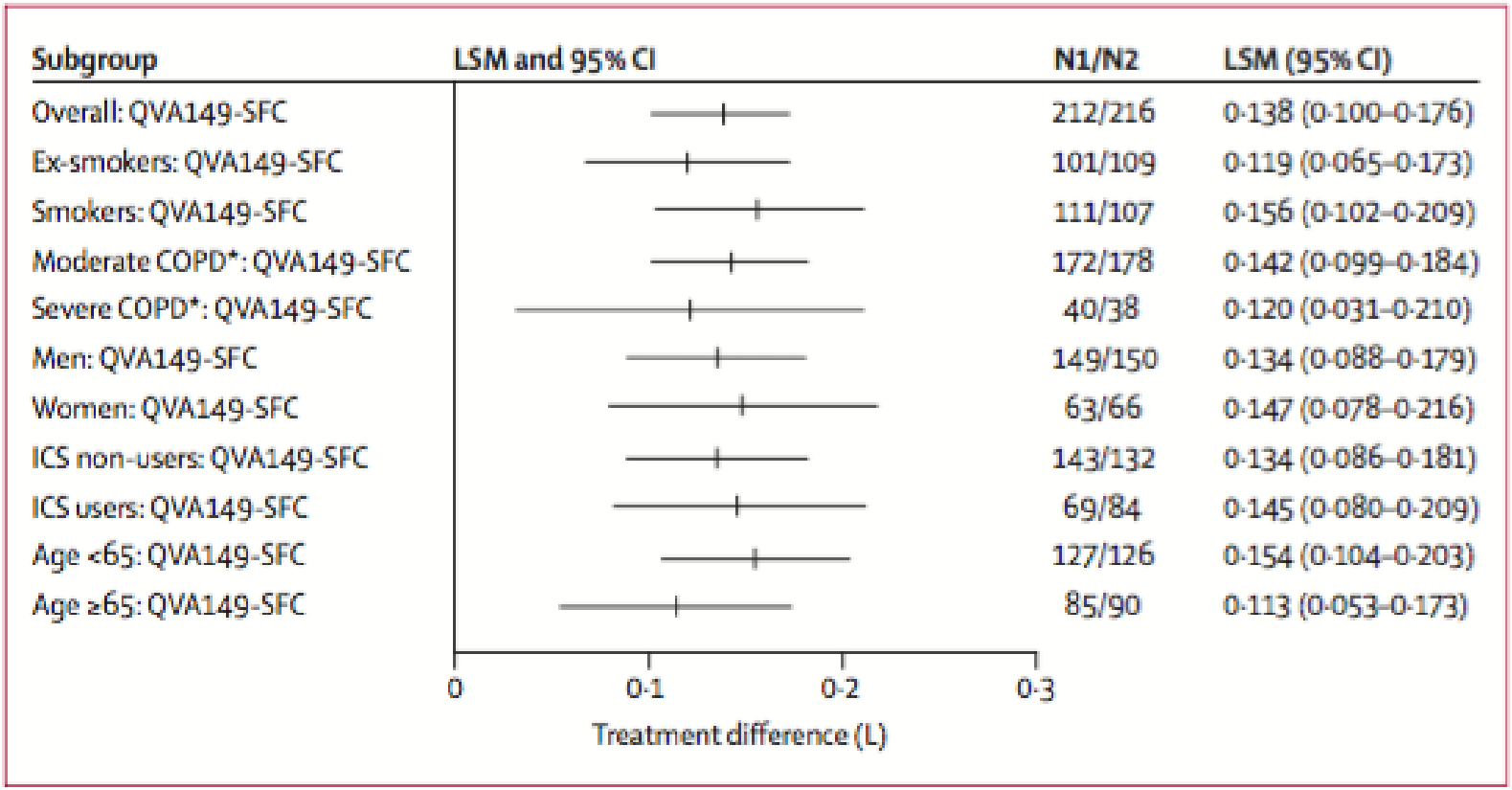
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by patient age



- Regardless of patient age, Aclidinium/formoterol 400/12 µg BID:
  - improved morning pre-dose (trough) FEV1 versus Formoterol $p < 0.001$
  -improved morning pre-dose (trough) FEV1 versus Aclidinium $p < 0.05$ in patients aged < 65 years

Pooled data ACLIFORM-AUGMENT. Bateman E, et al.ATS 2015.

Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol–fluticasone in patients with COPD



Vogelmeier C, et al. Lancet 2012

Risks and benefits of LABA/LAMA combination therapy

- Compared with separated monotherapy inhalers, LABA/LAMA combination may offer:[1]

  - superior bronchodilation

  - reduced symptom burden and relief medication use

  - improved inhaler compliance

1) Tashkin DP, Ferguson GT. Respir Res 2013

Safety and tolerability profiles of LABA/LAMA combination therapies

The safety and tolerability profiles of the approved LABA/LAMA combinations are similar in those of the individual monotherapy components

Most common AEs by preferred term

Aclidinium/ formoterol[1]

- Nasopharyngitis (7.9 %)
- Headhache (6.8 %)

Glycopyrronyum/ indacaterol[2]

3 % incidence

- Cough
- Oropharingeal pain

Umeclidinium/ vilanterol[3]

- Nasopharyngitis (9 %)

Tiotropium/ olodaterol[4]

- Dry mouth (1.7 %)

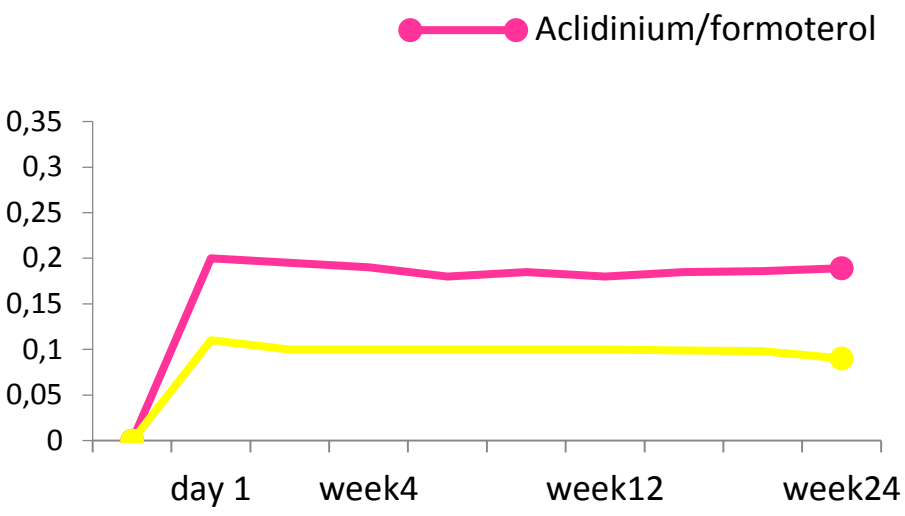
1 Duaklir Genuair Summary of Product Characteristics 2014 2) Ultibro Breezhaler Summary of Product Characteristics 2015 3) Anoro Ellipta Summary of Product Characteristics 2015 4) Spiolto Respimat Summary of Product Characteristics 2015

LABA/LAMA vs LABA/ICS

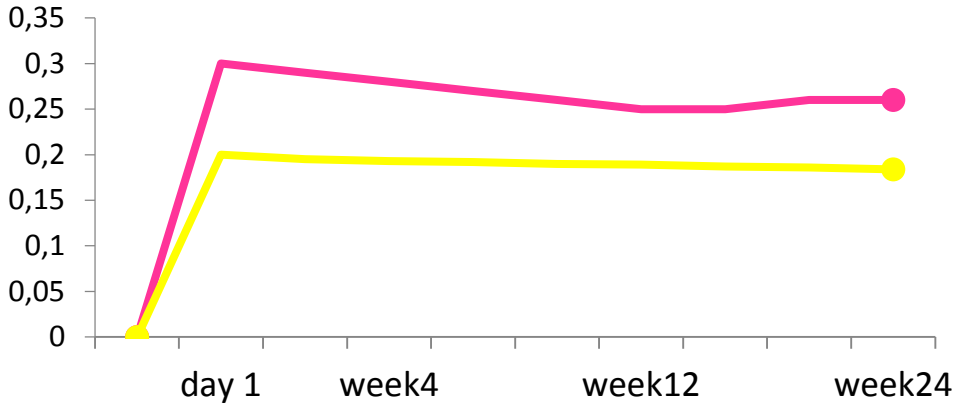
AFFIRM: Aclidinium/formoterol vs salmeterol/fluticasone

- Phase III AFFIRM study demonstrated improvements in bronchodilatation with aclidinium/formoterol 400/12 µg BID vs salmeterol/fluticasone 50/500 µg BID. Patients with stable symptomatic COPD (n= 933)

Change from baseline in FEV_1 AUC_{0-3h} (ITT population)[a]



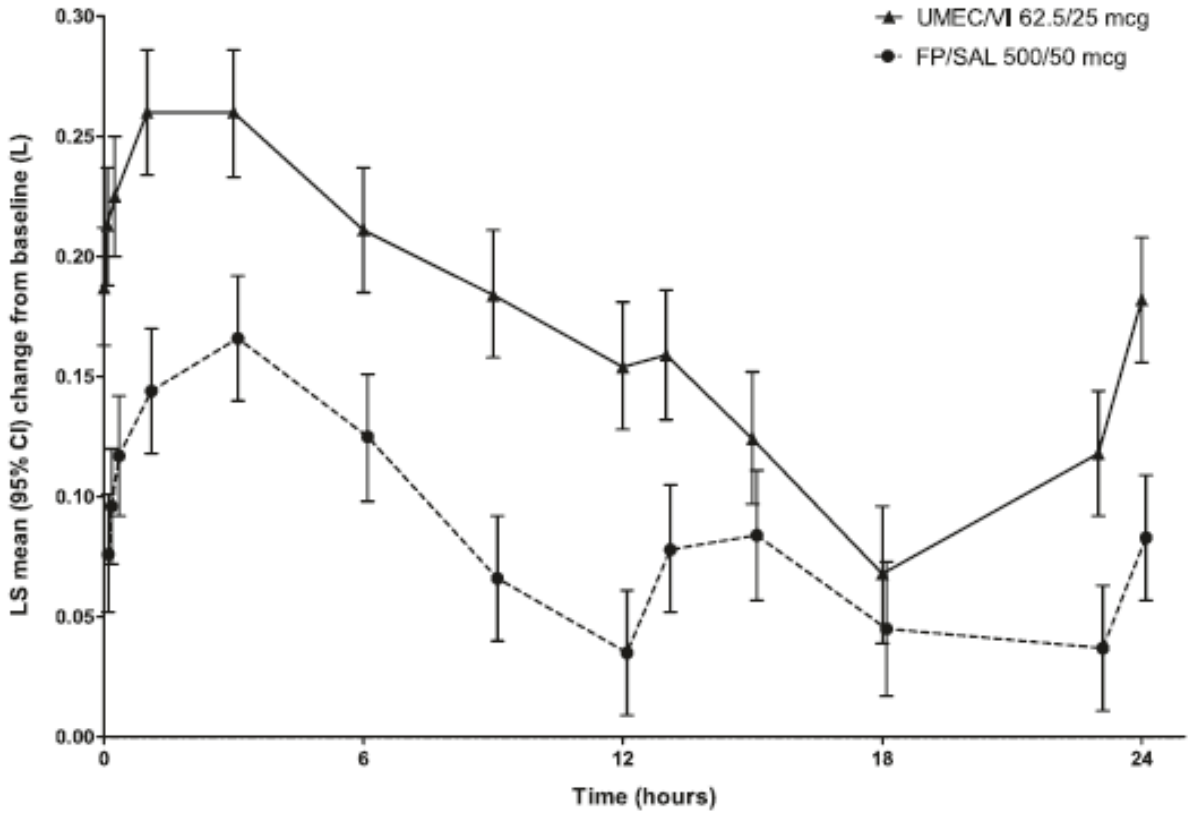
Change from baseline in peak FEV_1 (ITT population)[a]



Singh D, et al. ERS International Congress, Amsterdam 2015

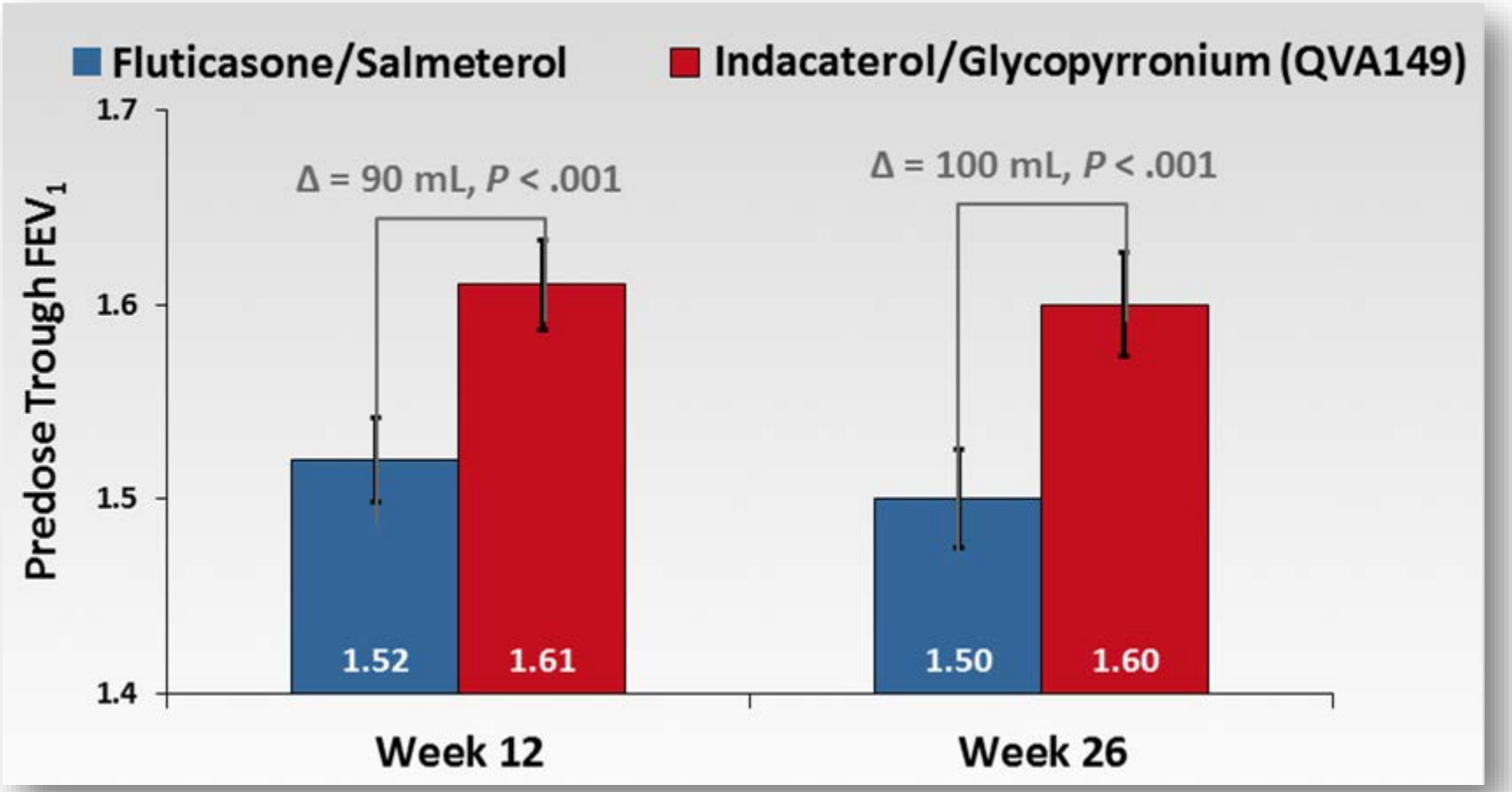
Umeclidinium/vilanterol vs salmeterol/fluticasone

- Umeclidinium/vilanterol 62.5/25 µg QD over 12 weeks improved lung function compared with salmeterol/fluticasone 50/500 µg BID in patients with moderate-to-severe COPD with infrequent exacerbations (n = 717)



Singh D, et al. BMC Pulm Med 2015

ILLUMINATE: indacaterol/glycopyrronium vs fluticasone/salmeterol



Vogelmeier C, et al. Lancet Resp Med 2013; 1 (1): 51-60

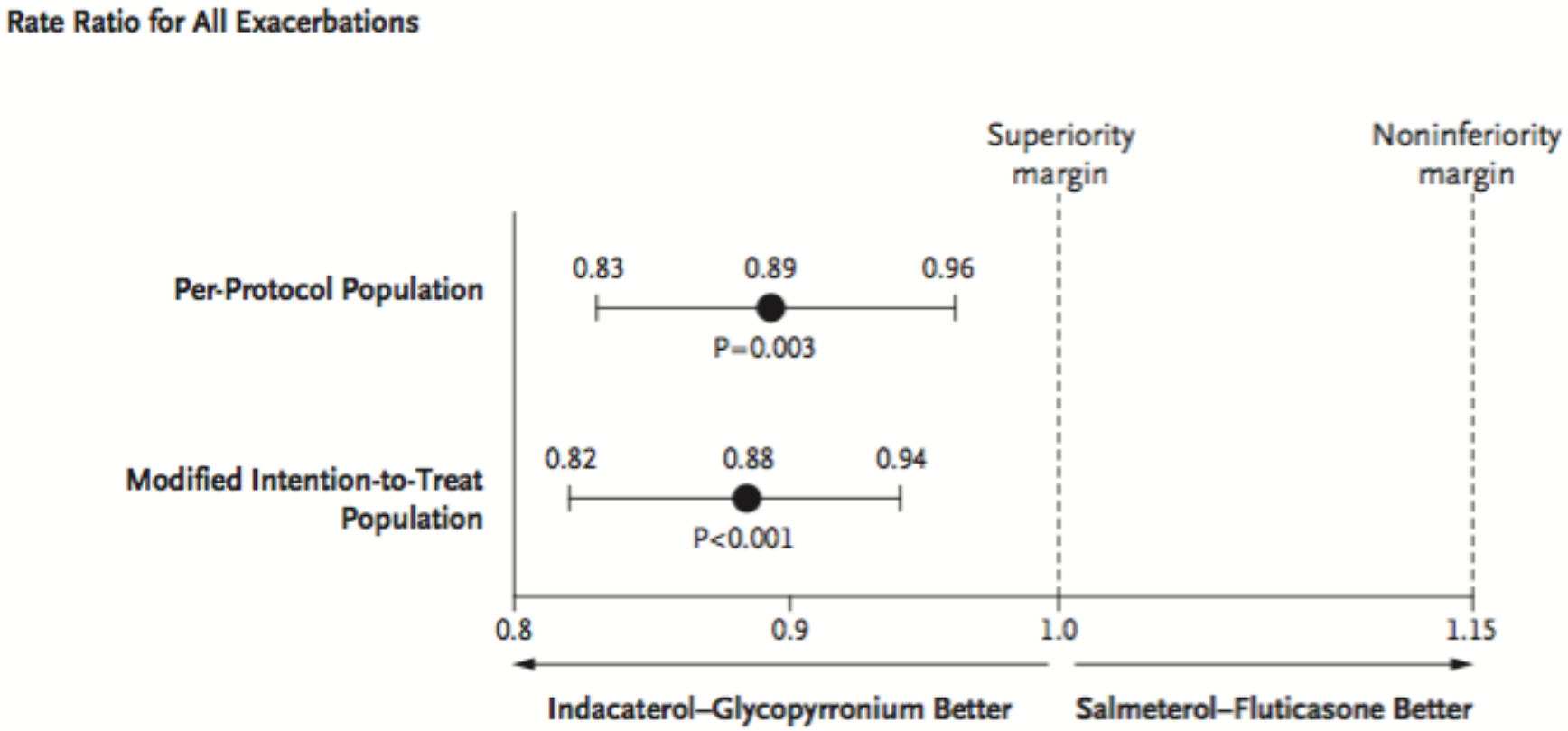
Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Primary outcome

In the per-protocol population, the annual rate of all COPD exacerbations was **3.59** (95% confidence interval [CI], 3.28 to 3.94) in the indacaterol–glycopyrronium group and **4.03** (95% CI, 3.68 to 4.41) in the salmeterol–fluticasone group (rate ratio, 0.89 [95% CI, 0.83 to 0.96], representing an **11%** lower rate; P = 0.003)

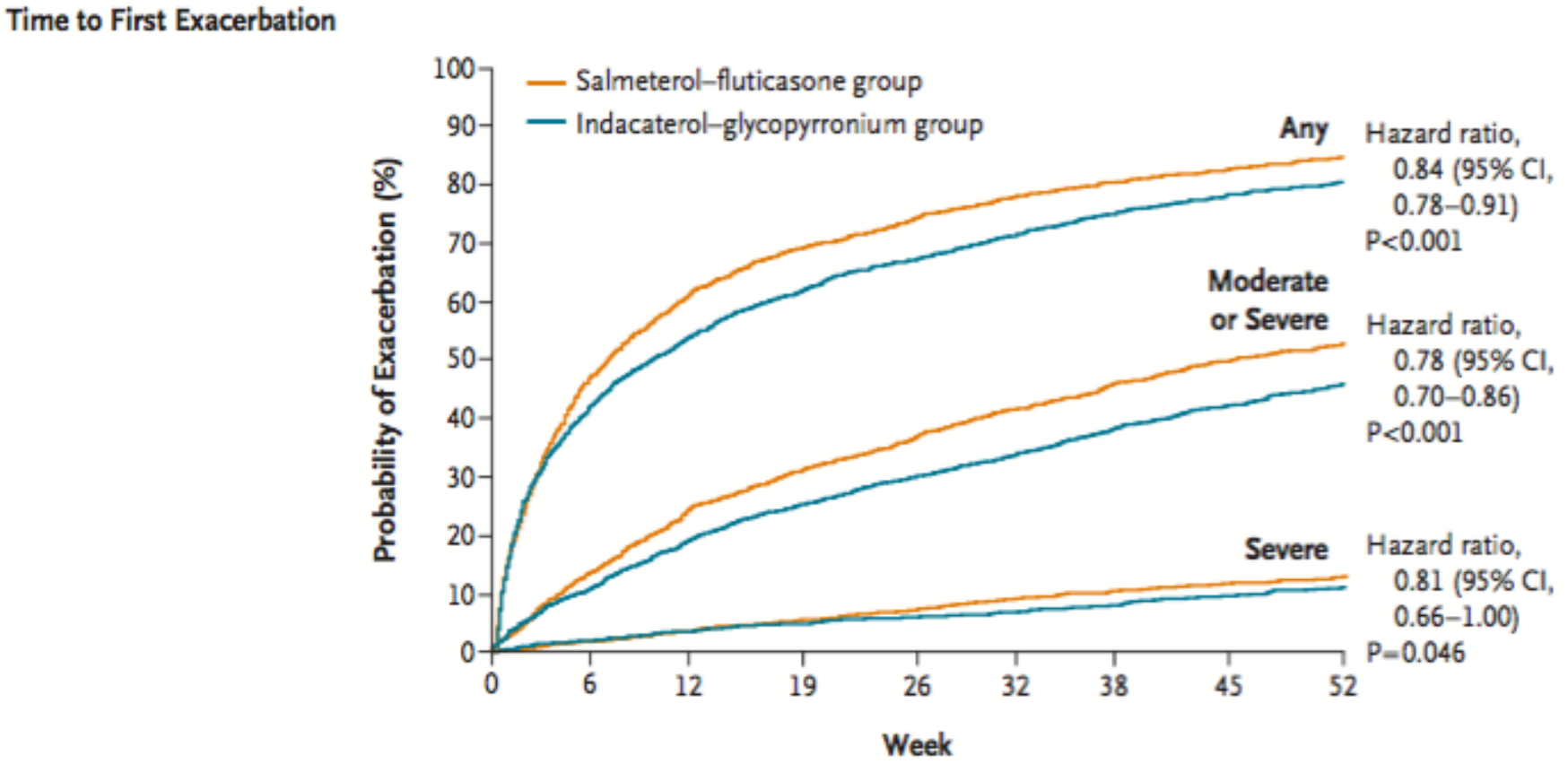
Jadwiga A. Wedzicha, et al. New Engl J Med 2016

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD



Jadwiga A. Wedzicha, et al. New Engl J Med 2016

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD



Jadwiga A. Wedzicha, et al. New Engl J Med 2016

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Table 2. Adverse Events and Serious Adverse Events.*

Variable	Indacaterol–Glycopyrronium Group (N=1678)	Salmeterol–Fluticasone Group (N=1680)
	number (percent)	
Patients with ≥1 adverse event	1459 (86.9)	1498 (89.2)
Adverse events that occurred in ≥3% of either treatment group†		
Worsening of chronic obstructive pulmonary disease	1299 (77.4)	1374 (81.8)
Nasopharyngitis	197 (11.7)	195 (11.6)
Viral upper respiratory tract infection	132 (7.9)	138 (8.2)
Bacterial upper respiratory tract infection	125 (7.4)	168 (10.0)
Lower respiratory tract infection	82 (4.9)	98 (5.8)
Upper respiratory tract infection‡	81 (4.8)	83 (4.9)
Pneumonia	53 (3.2)	80 (4.8)
Cough	50 (3.0)	51 (3.0)
Dyspnea	49 (2.9)	51 (3.0)
Influenza	35 (2.1)	56 (3.3)
Oral candidiasis	20 (1.2)	71 (4.2)
Serious adverse event§	308 (18.4)	334 (19.9)
Death	24 (1.4)	24 (1.4)
Patients who discontinued because of adverse event	126 (7.5)	143 (8.5)
Patients who discontinued because of serious adverse event	85 (5.1)	87 (5.2)
Patients who discontinued because of nonserious adverse event	49 (2.9)	70 (4.2)

Jadwiga A. Wedzicha, et al. New Engl J Med 2016

Conclusioni

- Le terapie di combinazione LABA/LAMA migliorano la broncodilatazione, confrontate con i monocomponenti ed il placebo.

- Gli effetti positivi delle terapie di combinazione LABA/LAMA sono osservati immediatamente nel post-dose
- L'effetto broncodilatante è presente in tutti i sottogruppi

- Il profilo di sicurezza e tollerabilità della duplice terapia LABA/LAMA è confrontabile a quello delle monoterapie.

- Il rapporto rischio/beneficio dovrebbe essere considerato nella gestione ottimale della terapia per ogni singolo paziente.