Up-to-date sulle terapie di associazione della BPCO

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REGIONE DEL VENETO
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Introduzione

- La terapia di combinazione LABA/LAMA potenzia la broncodilatazione

  - Evidenti benefici delle combinazioni LABA/LAMA
  - I benefici della broncodilatazione sono evidenti in tutti i sottogruppi

- Profilo di tollerabilità dei LABA/LAMA

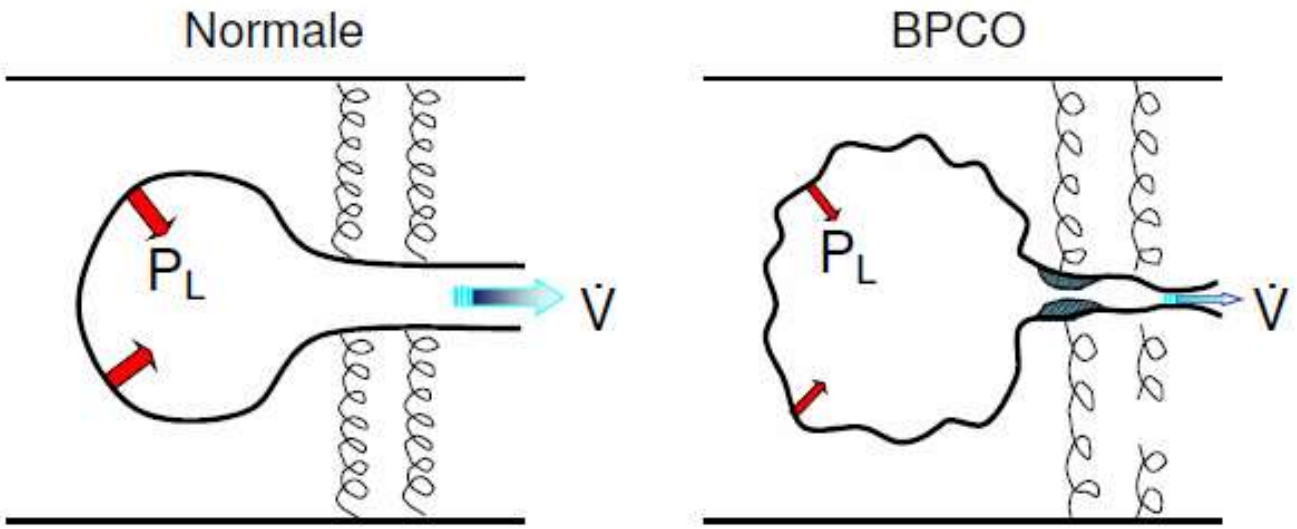
- Rapporto rischio/beneficio

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

Ostruzione al flusso aereo espiratorio



Ipersecrezione di muco

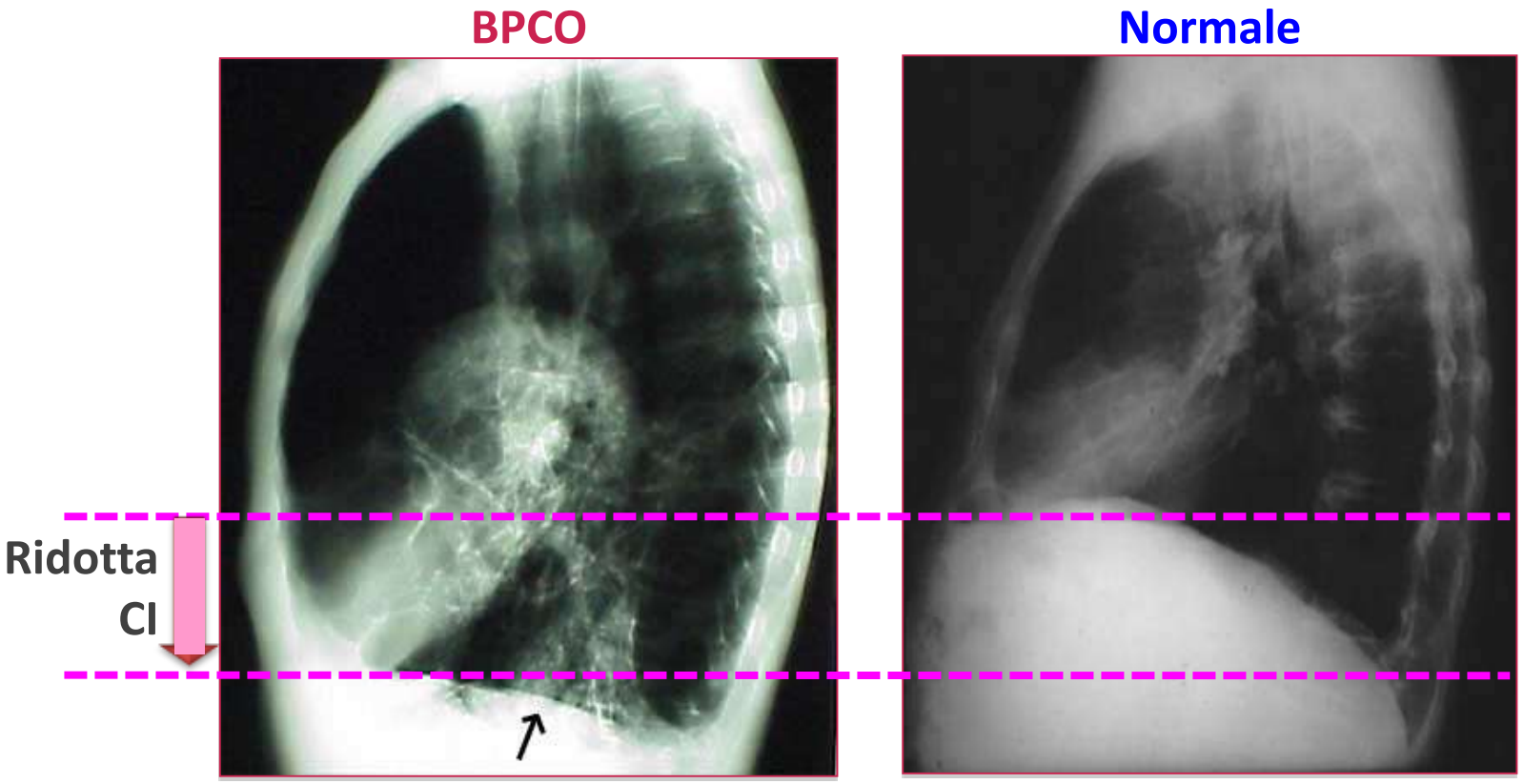
Maggiore tono broncomotore colinergico

Iperreattività bronchiale

Aumento dell'ostruzione bronchiale (rimodellamento)

Ridotto ritorno elastico
Ridotte connessioni parenchimali
Aumento delle resistenze

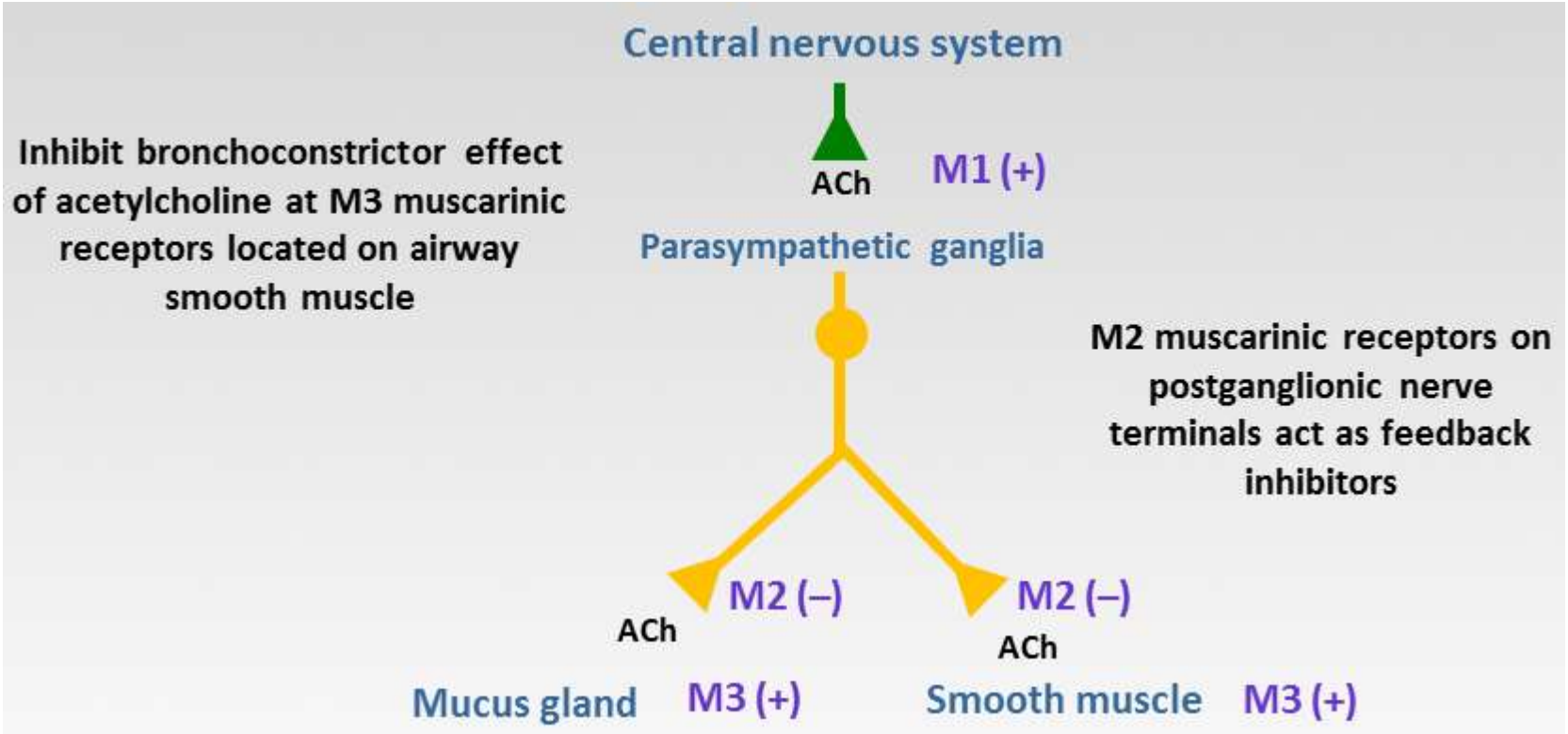
Ostruzione al flusso aereo nella BPCO il ridotto ritorno elastico determina iperinflazione



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

Razionale della doppia broncodilatazione

Perché combinare le terapie bronco-dilatanti ?
Meccanismo d'azione degli antagonisti muscarinici



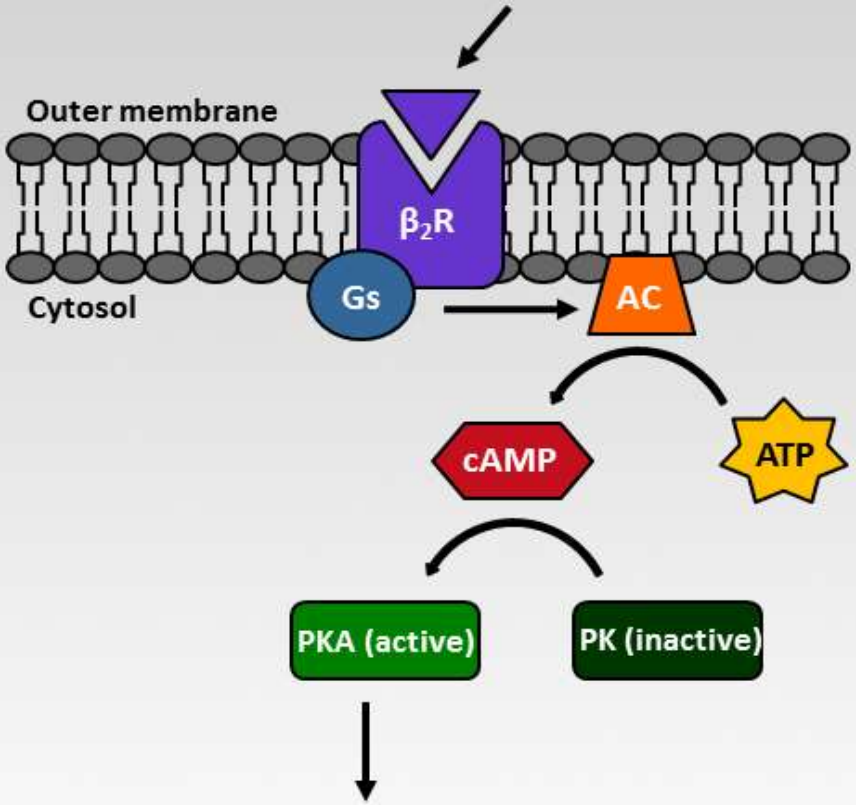
Gli antagonisti muscarinici bloccano i recettori M_1 e M_3 per prevenire il legame dell'acetilcolina ed inibire la contrazione della muscolatura liscia delle vie aeree

Roux et al. Gen Pharmac 1998

Perché combinare le terapie bronco-dilatanti ?
Meccanismo d'azione dei β_2-agonisti

B_2-agonist

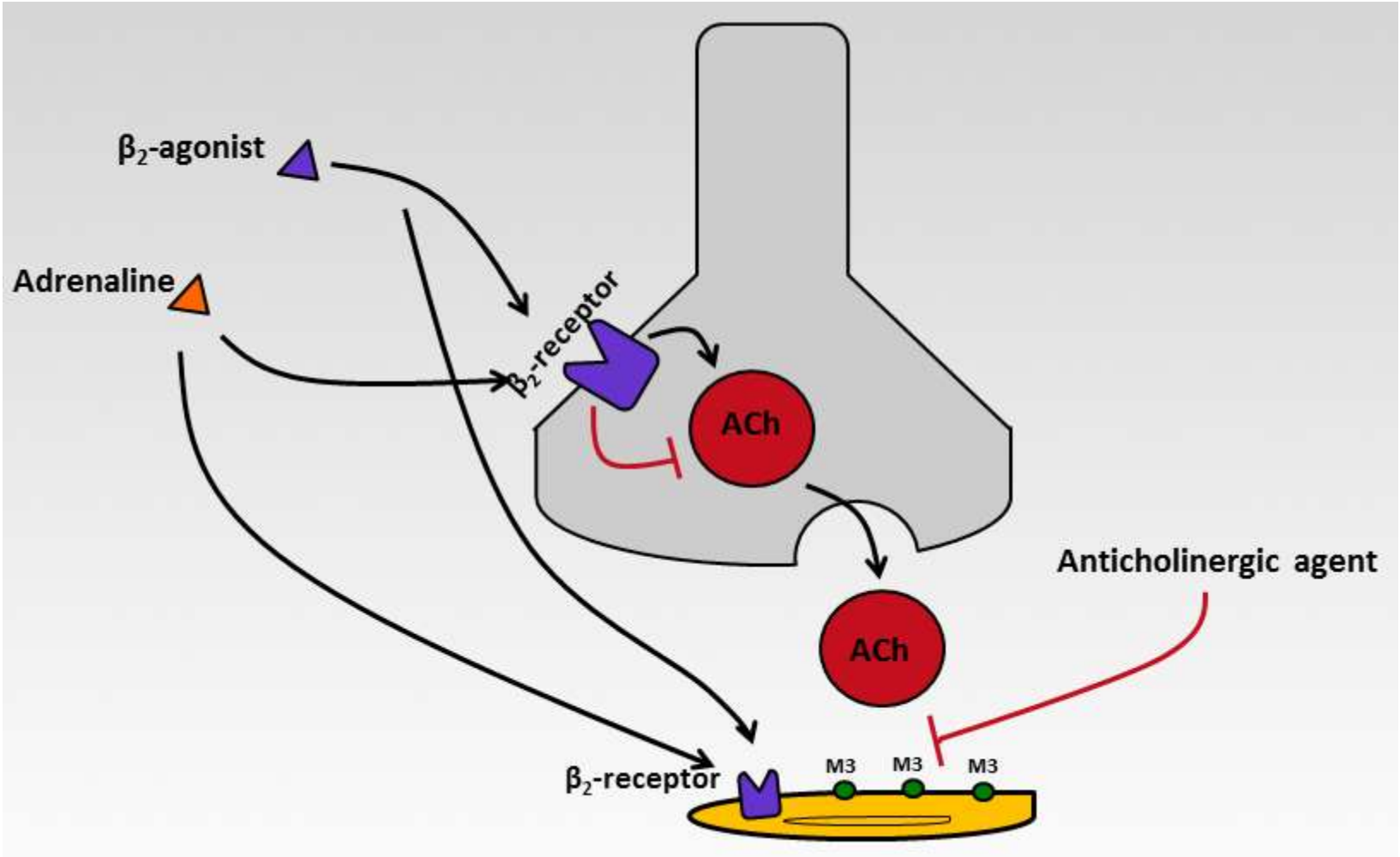
Directly activate β_2 receptors in bronchioles, leading to increase in cAMP, relaxation of smooth muscle, and bronchodilation



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

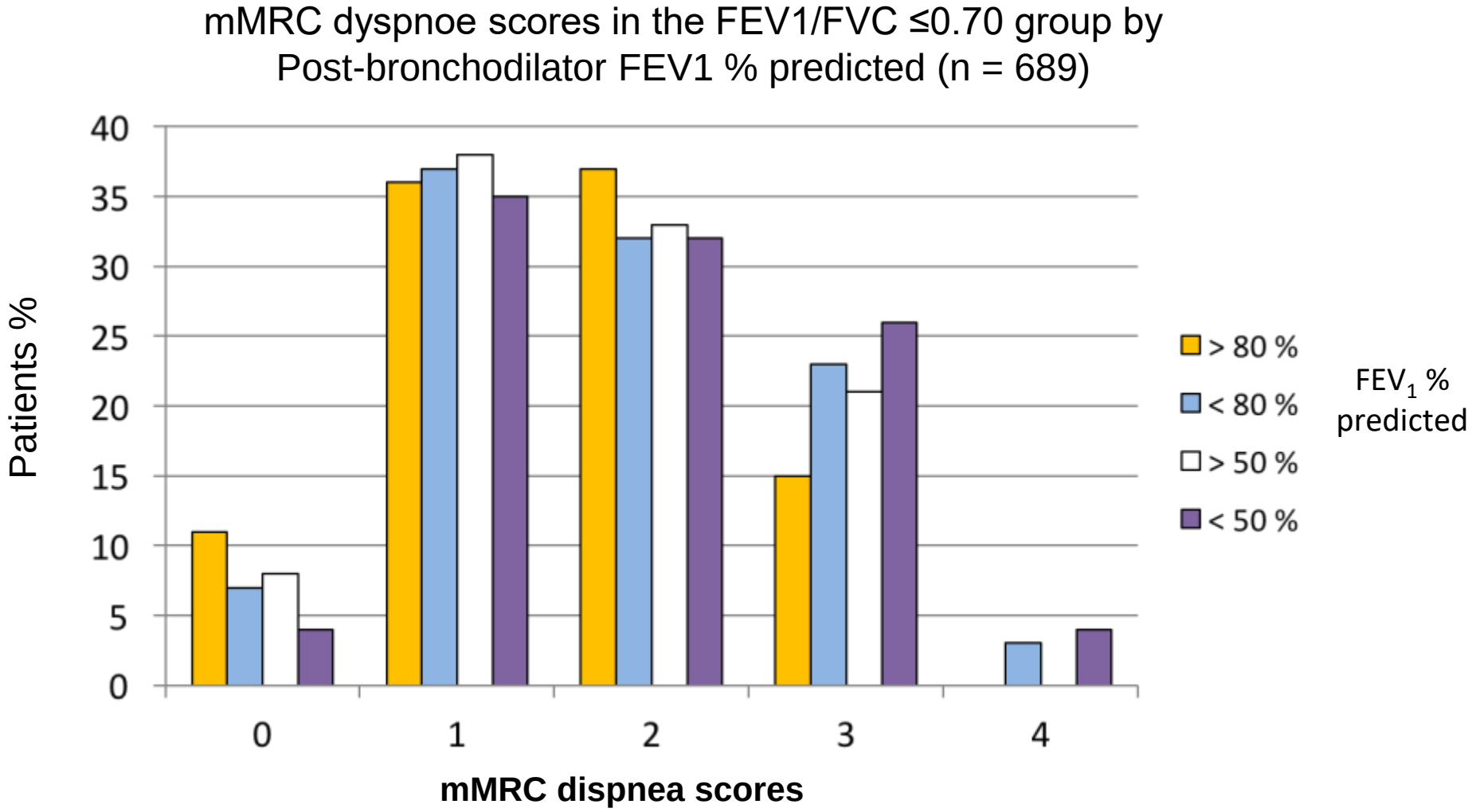
Johnson M. *Am J Respir Crit Care Med*. 1998;158(5 Pt 3):S146-153.

LABA/LAMA combination: interaction between Receptors and Neurotransmission pathways



Cazzola M, et al. Arch Bronconeumol 2005

Studio in real-life: i pazienti riferiscono ancora dispnea con un broncodilatatore in monoterapia



Dransfeld MT, et al. Prim care Resp J 2011

Terapia di combinazione LABA/LAMA

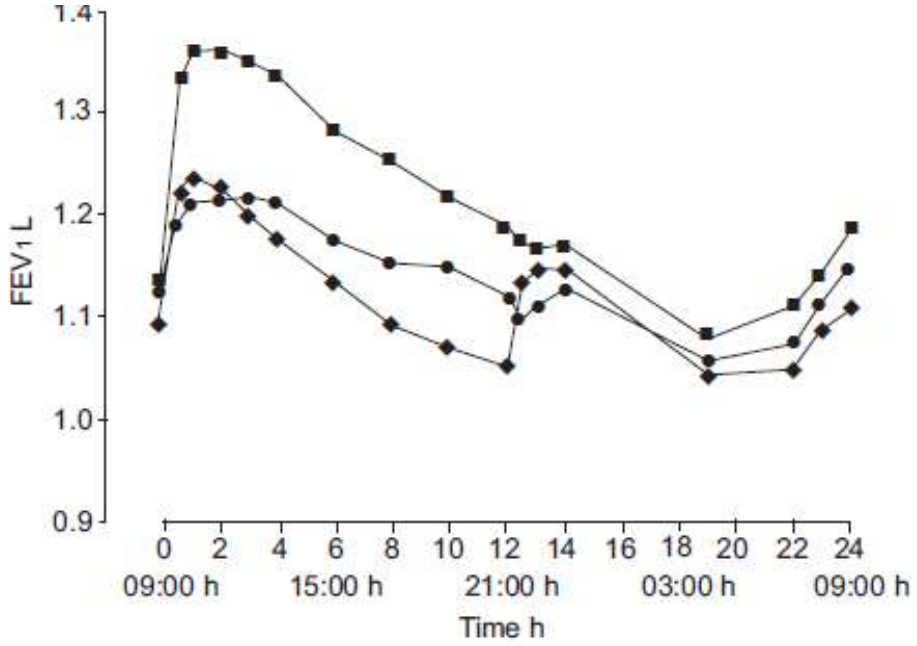


FIGURE 2. Mean forced expiratory volume in one second (FEV_1; adjusted for period, centre and patient within centre) before and during 24 h after the inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

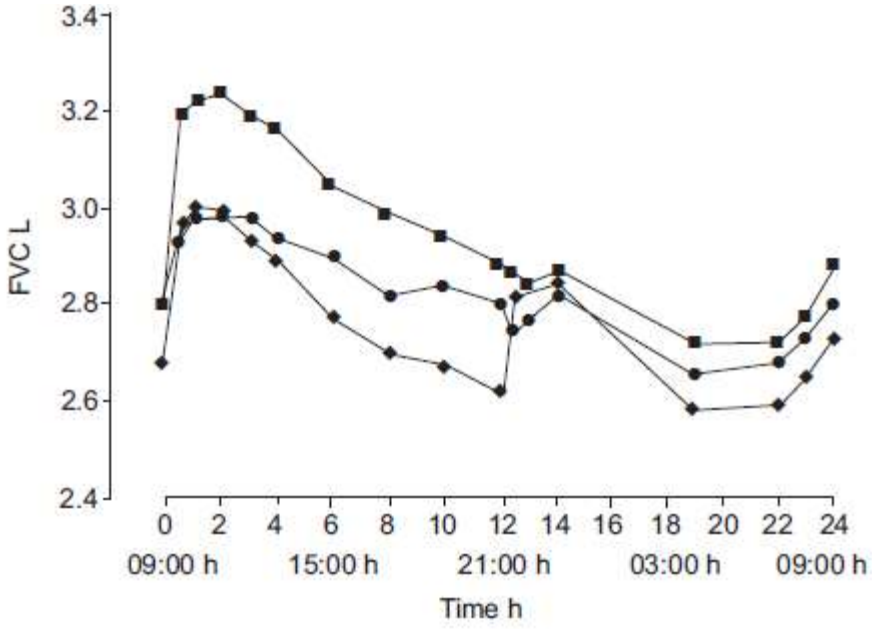
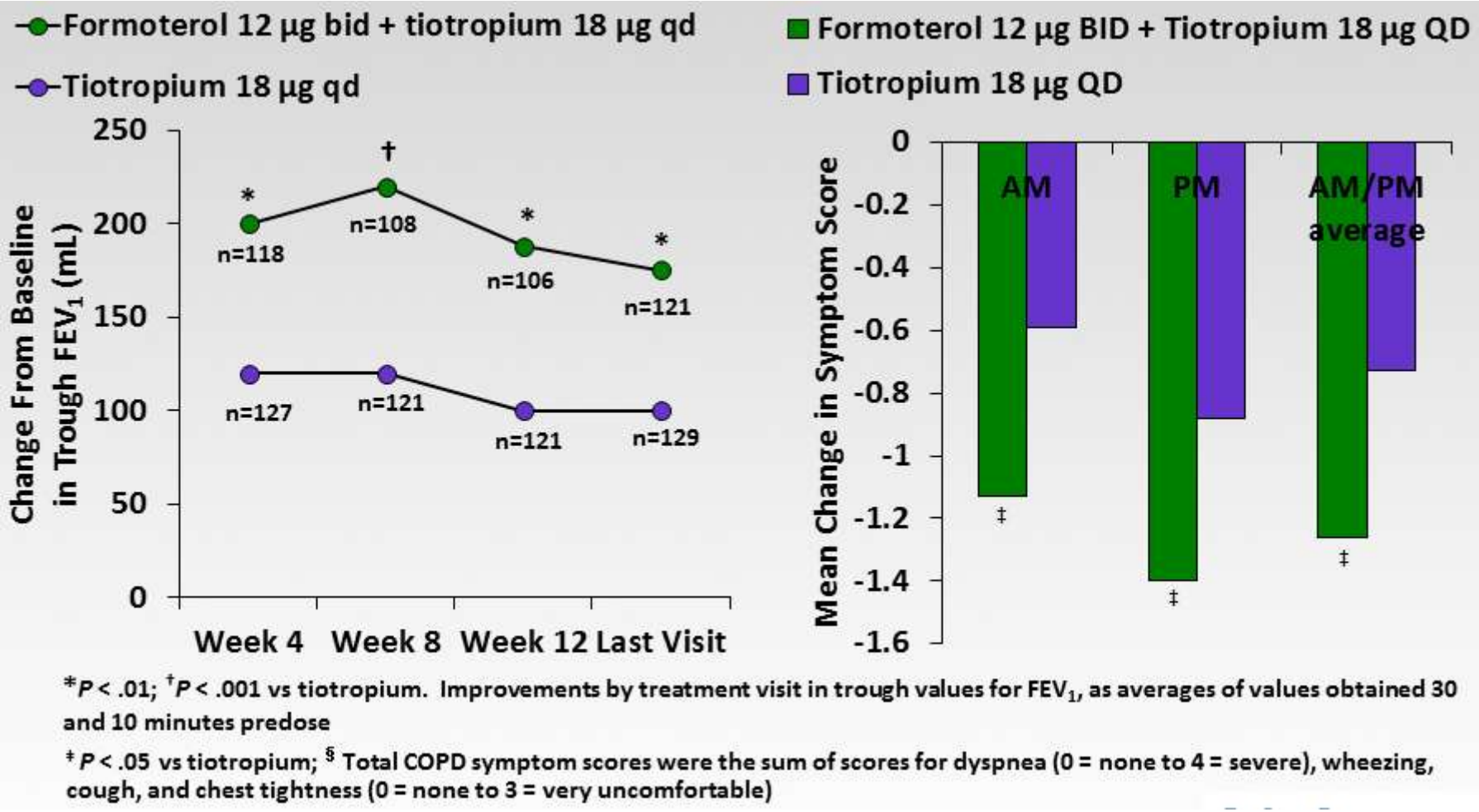


FIGURE 3. Mean forced vital capacity (FVC; adjusted for period, centre and patient within centre) before and during 24 h after inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

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

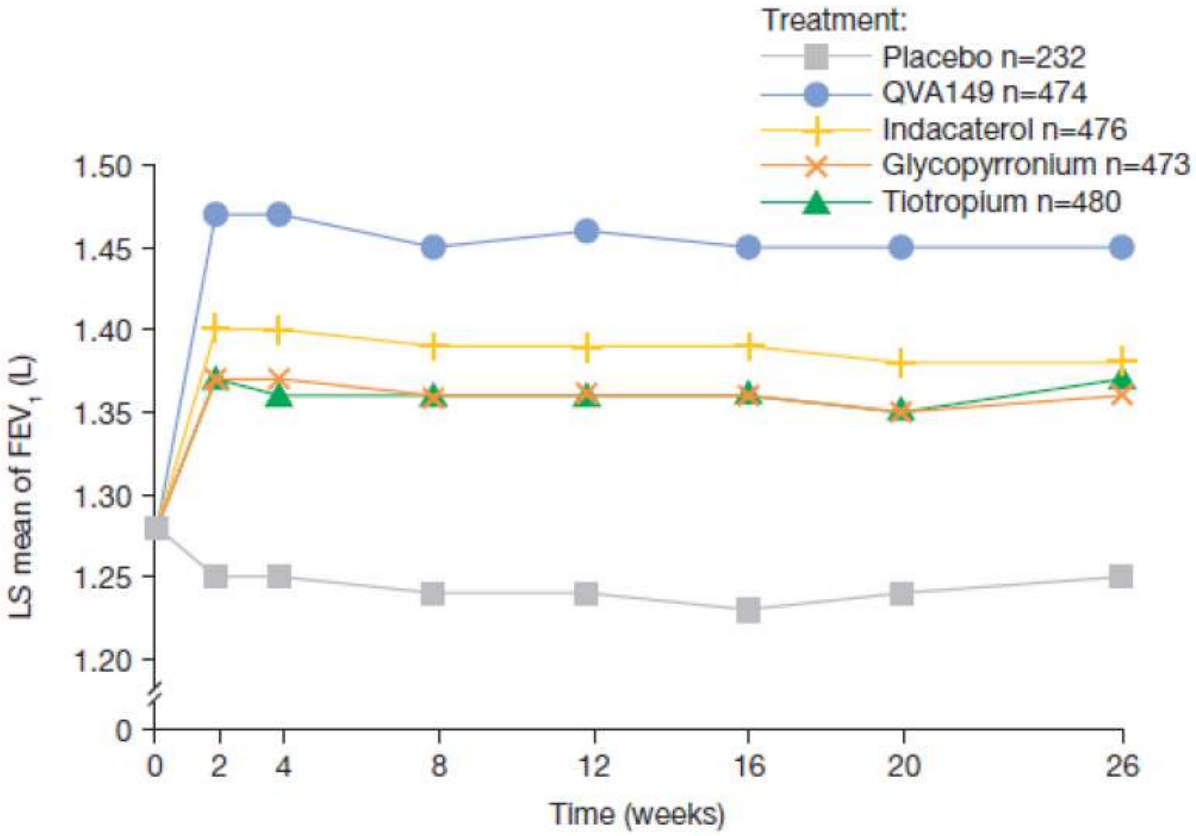
- LABAs (twice daily)
  - formoterol
  - salmeterol
- LAMAs (twice daily)
  - aclidinium
- LABAs (once daily)
  - indacaterol
  - olodanterol
  - vilanterol
- LAMAs (once daily)
  - glycopyrronium
  - tiotropium
  - umeclidinium

LABA/LAMA combinations

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

* under investigation in Europe

Dual bronchodilation with QVA149: the SHINE study

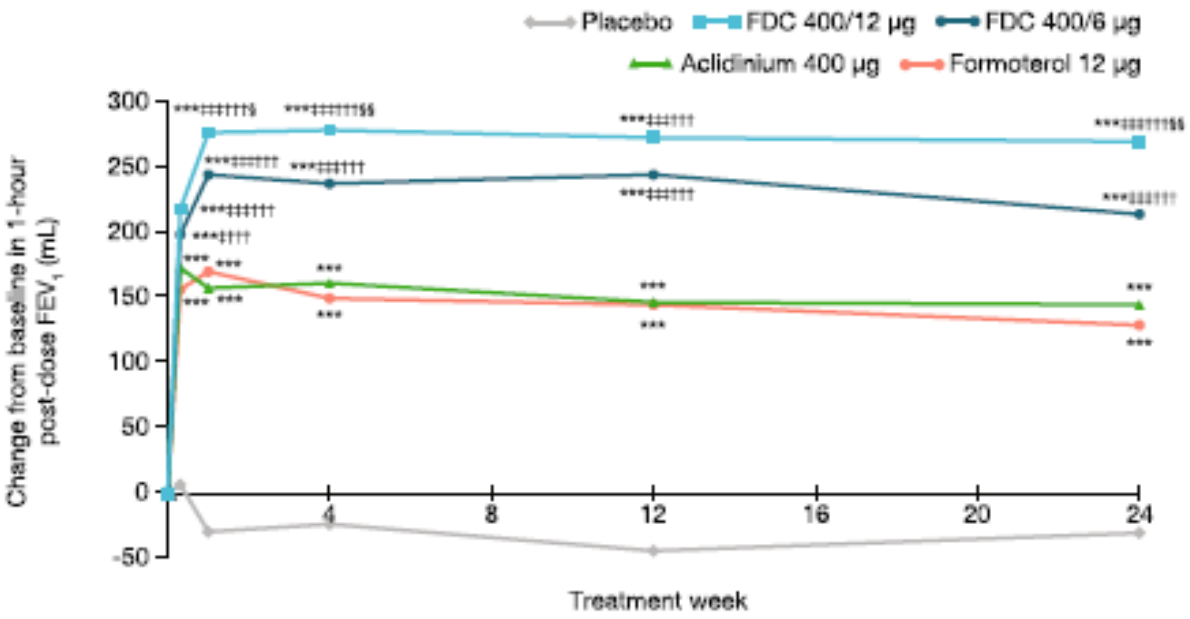


QVA149 was superior to all active treatments and placebo at all timepoints (all $p < 0.001$).

- 2/3 soggetti inclusi moderati;
- quasi 80% no riacutizzazioni
- sintomatici per entry (SGRQ >40)

Bateman et al Eur Respir J. 2013

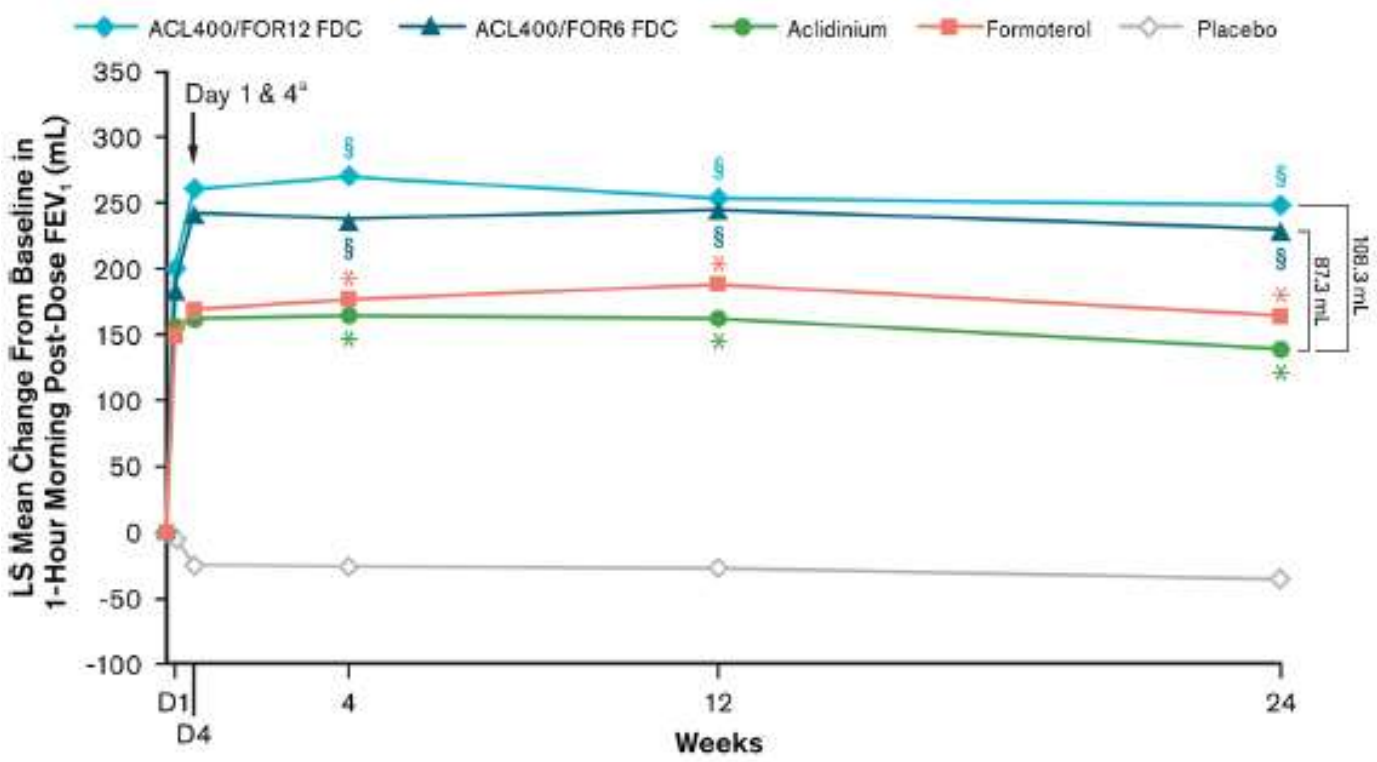
Efficacy and safety of aclidinium/formoterol fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD)



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

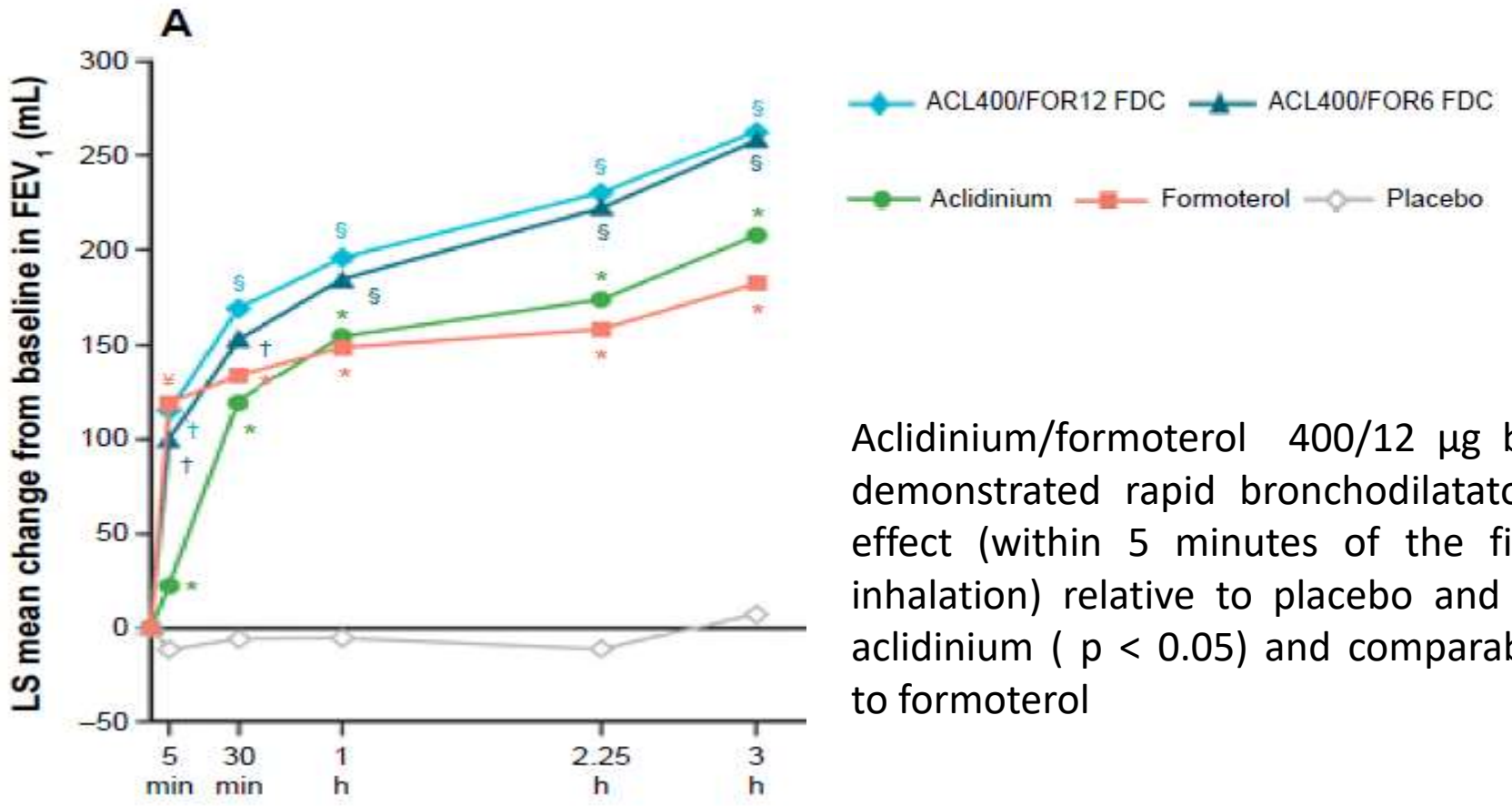
Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study



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

D'Urzo et al. Respiratory Research 2014

Aclidinium/formoterol: FEV1 improvement on Day 1

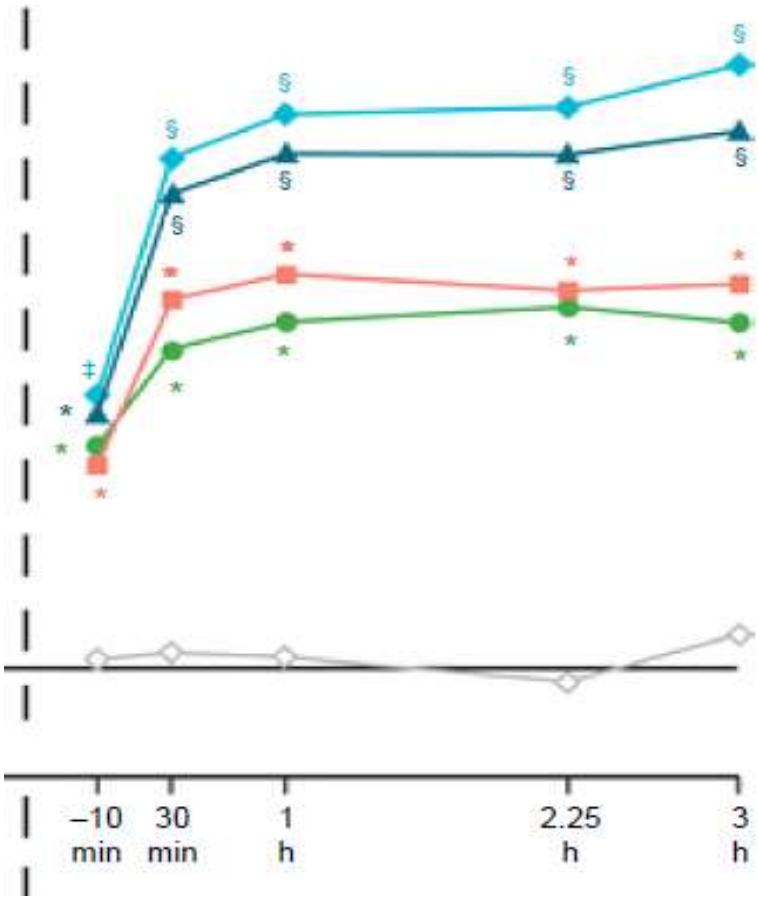


Aclidinium/formoterol 400/12 µg bid demonstrated rapid bronchodilatatory effect (within 5 minutes of the first inhalation) relative to placebo and to aclidinium ($p < 0.05$) and comparable to formoterol

*$P < 0.05$ 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: FEV1 improvement at week 24

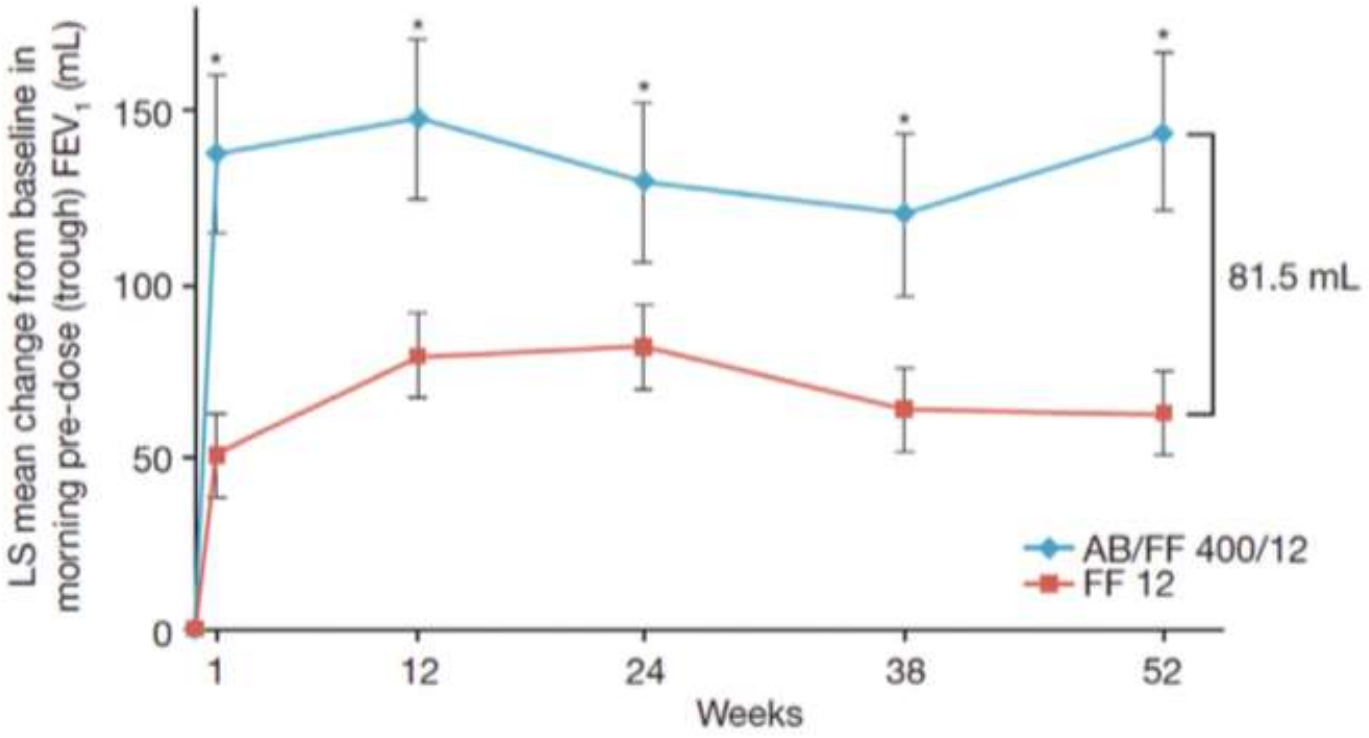


Aclidinium/formoterol 400/12 µg bid demonstrated rapid bronchodilatatory effect over the first 3 hours post-dose compared with placebo and monotherapy components at week 24

*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

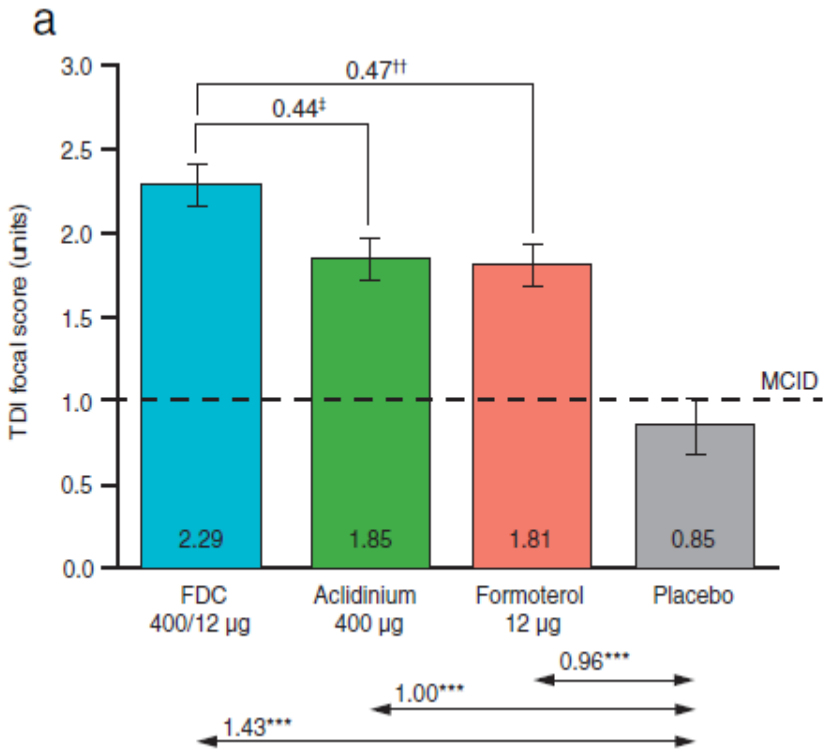
Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: Results of a randomized 1-year trial in patients with COPD

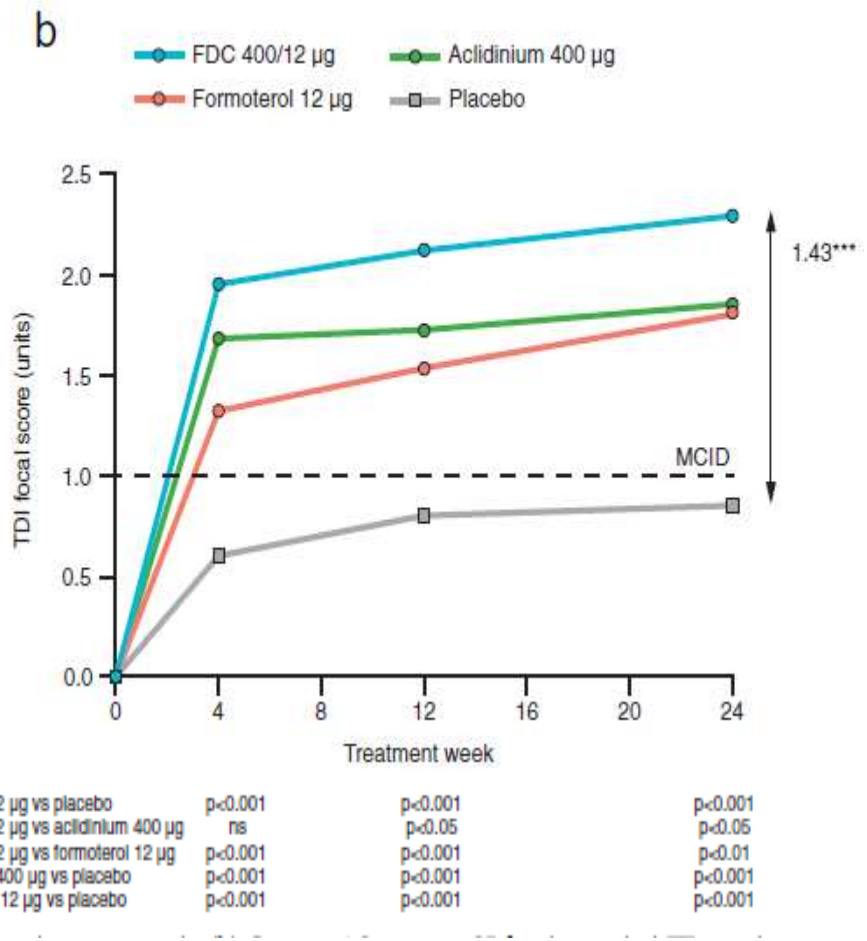


*p < 0.05 vs formoterol 12 mg

Donohue J, et al. Resp Medicine 2016

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

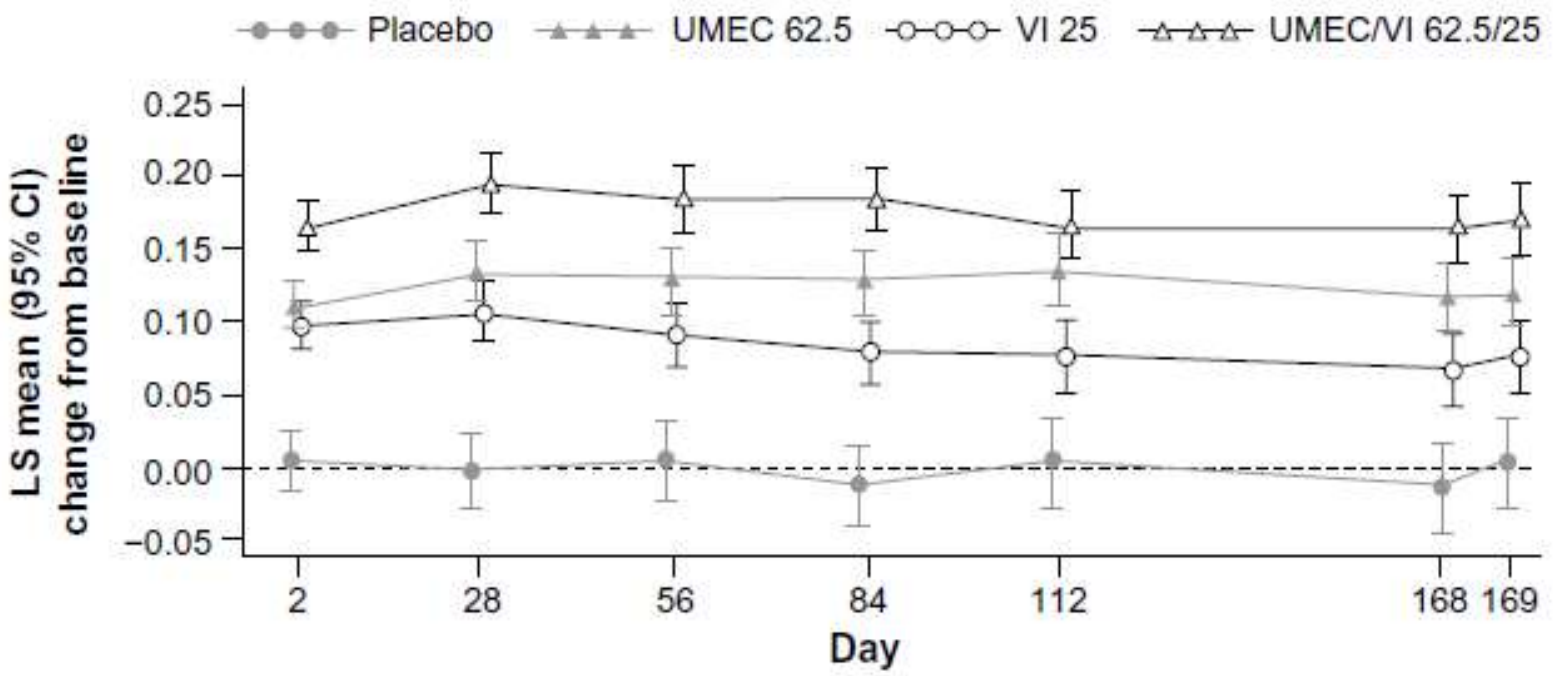




FDC 400/12 µg vs placebo	p<0.001	p<0.001	p<0.001
FDC 400/12 µg vs aclidinium 400 µg	ns	p<0.05	p<0.05
FDC 400/12 µg vs formoterol 12 µg	p<0.001	p<0.001	p<0.01
Aclidinium 400 µg vs placebo	p<0.001	p<0.001	p<0.001
Formoterol 12 µg vs placebo	p<0.001	p<0.001	p<0.001

Bateman et al. Resp Research 2015

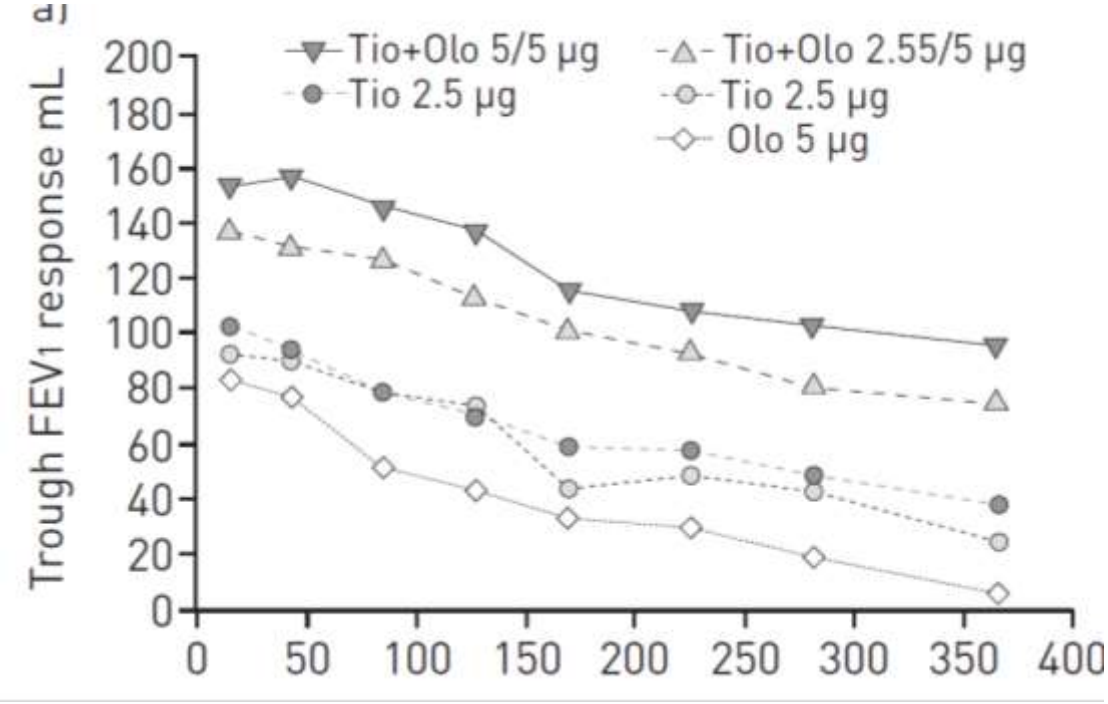
Efficacy and safety of once daily umeclidinium/vilanterol 62.5/25 mcg in COPD



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, $p < 0.004$).

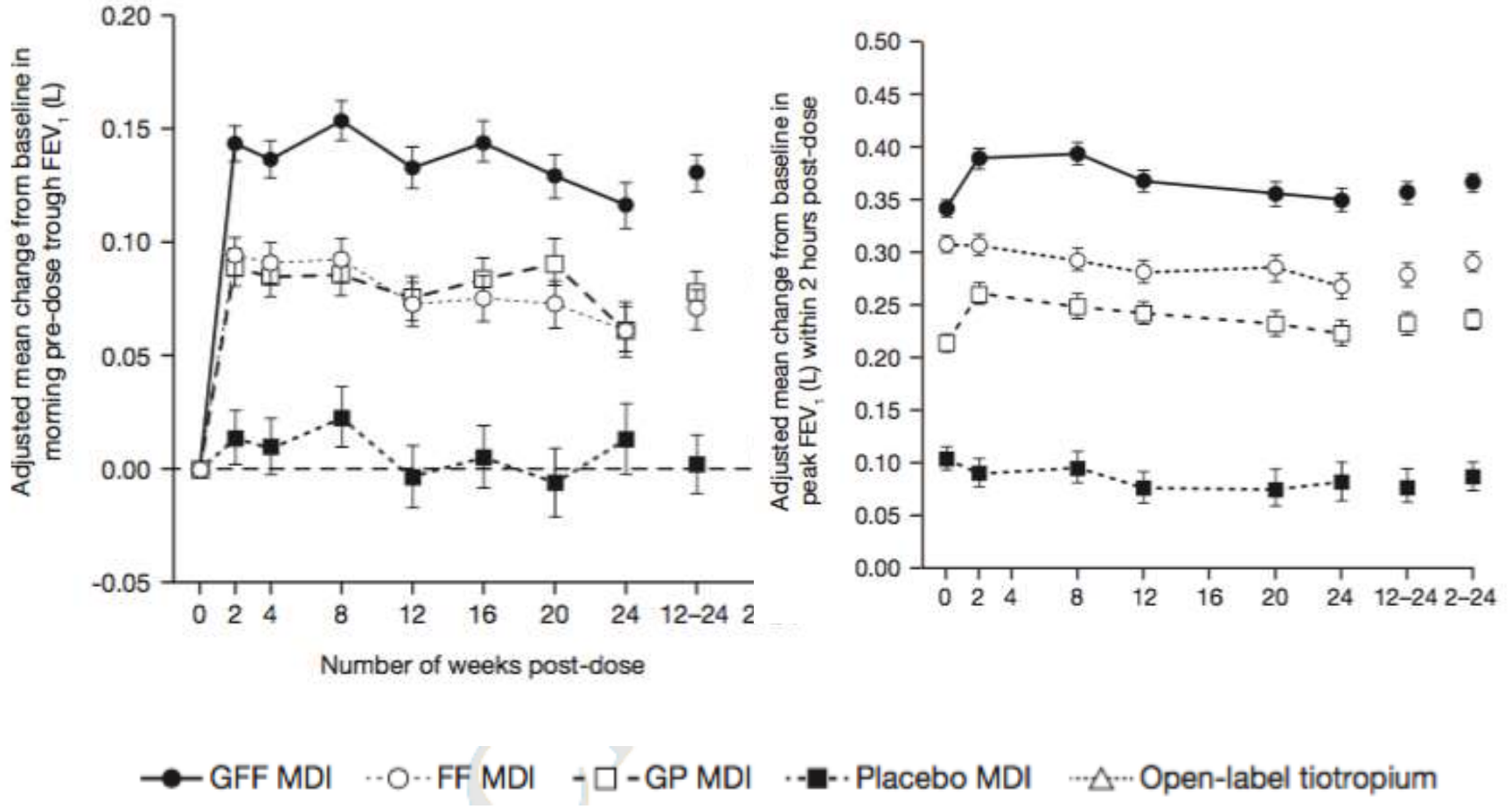
Donohue JF, et al. Respir Med 2013.

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



Buhl R, et al. Eur Respir J 2015

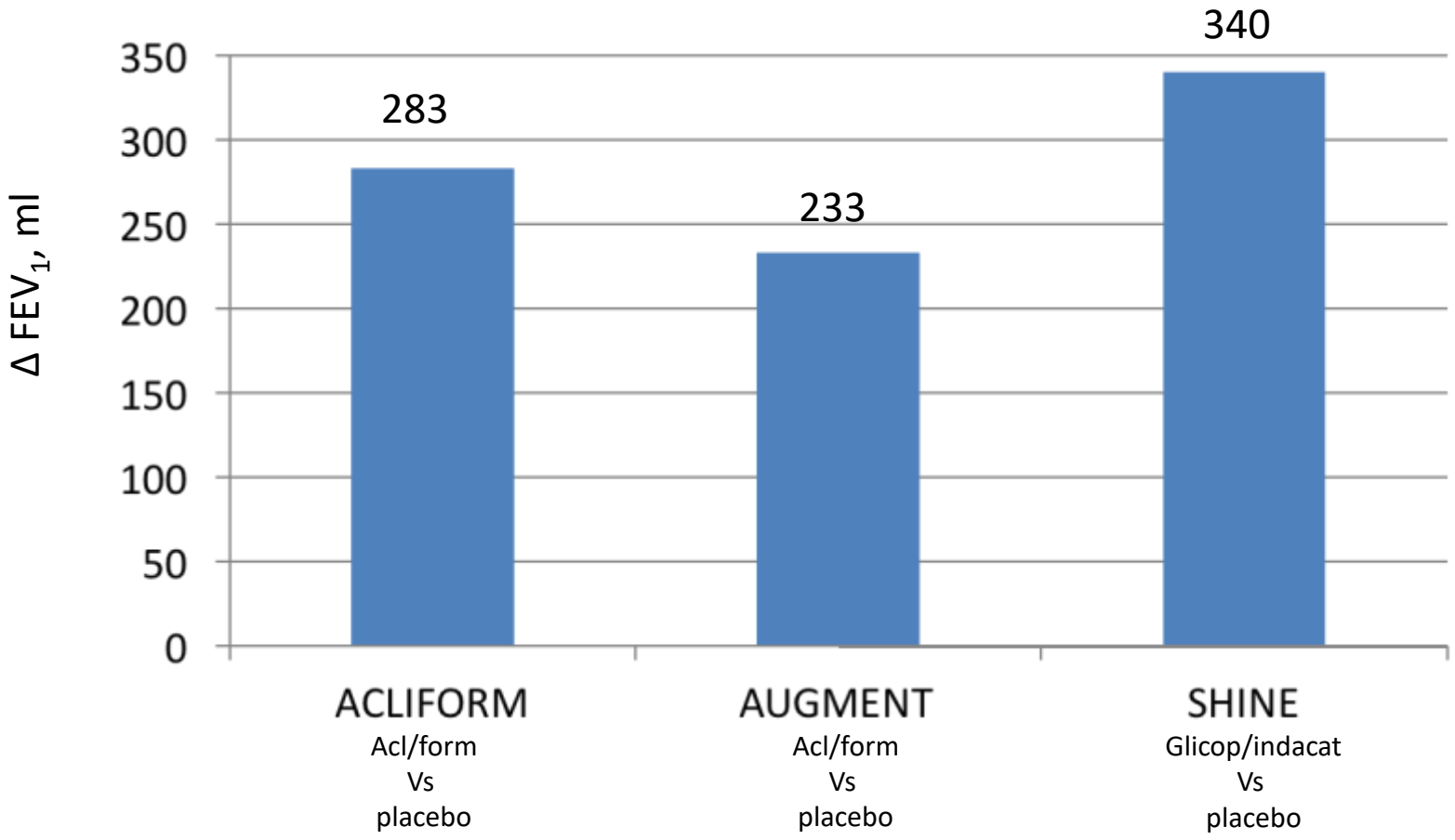
Efficacy and Safety of Glycopyrrolate/Formoterol MDI Formulated using Co-Suspension™ Delivery Technology in Patients with COPD



Martinez FJ, et al. Chest 2016

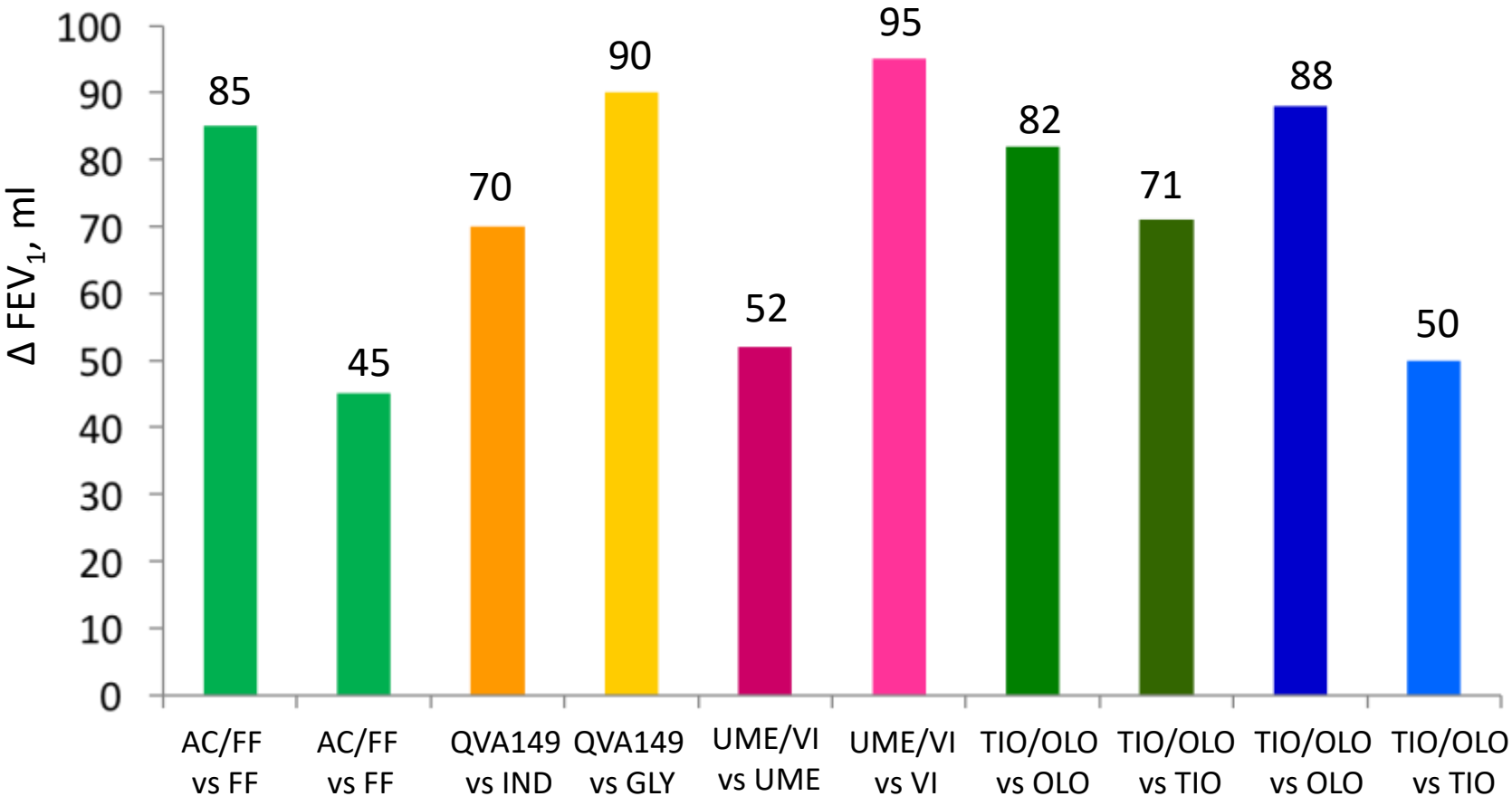
Combination treatments cause large FEV_1 changes immediately post-dose

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



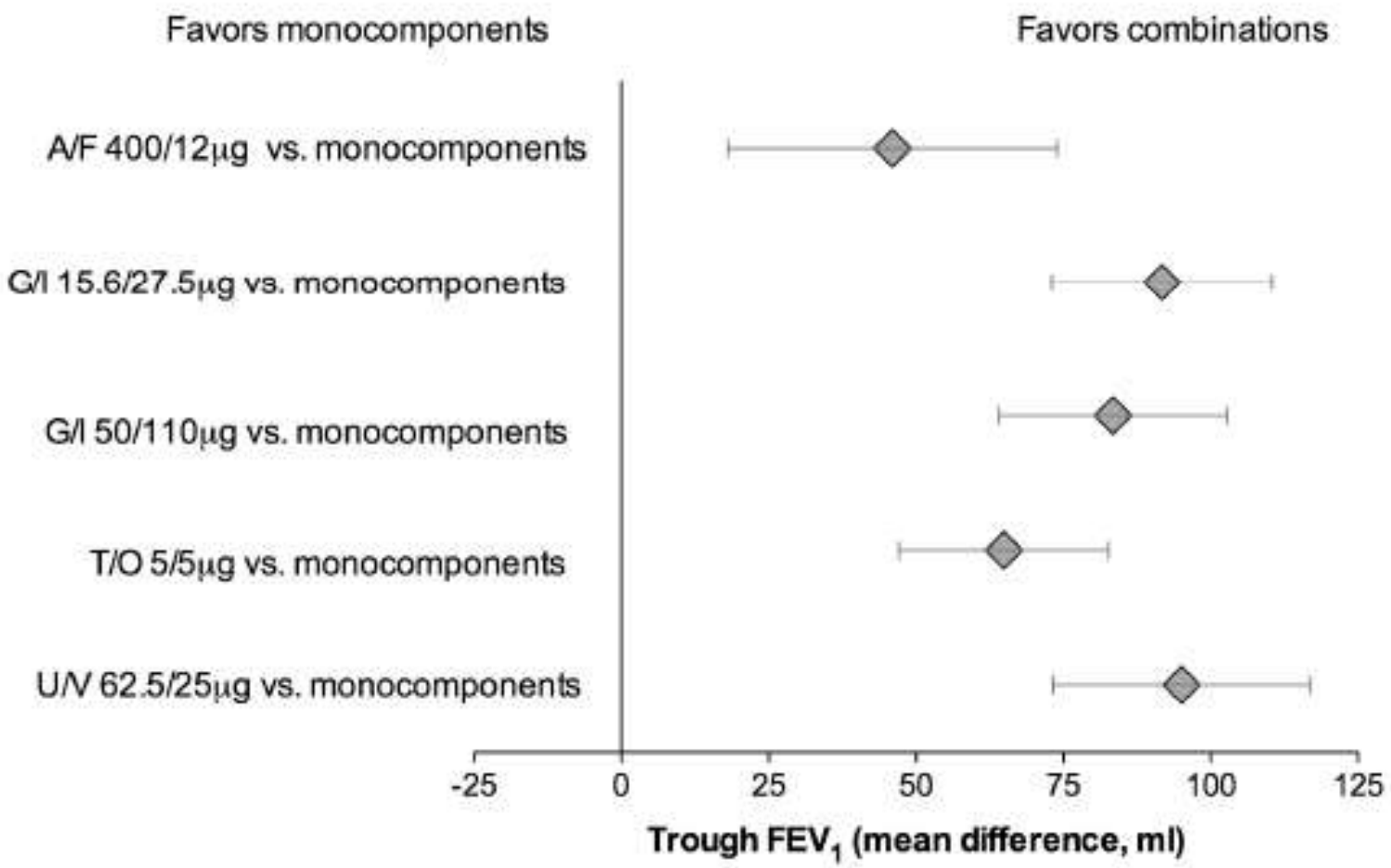
Changes in trough FEV_1: Combination vs monotherapy

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



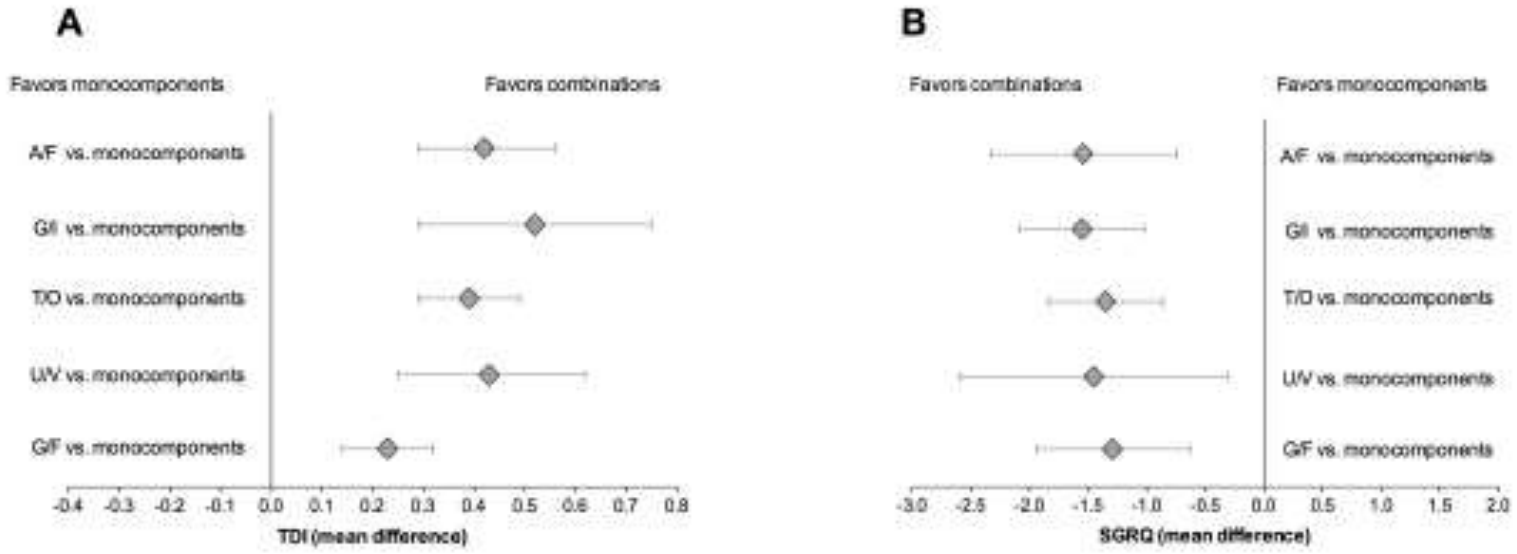
1) Singh D et al. BMC Pulm Med 2014 2) D'Urzo AD et al. Resp Res 2014 3) Bateman et al Eur Respir J. 2013 4) Donohue J et al. 5) Buhl R et al. Eur Resp J 2015.

A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease



Calzetta L, et al. Chest 2016

A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease



Calzetta L, et al. Chest 2016

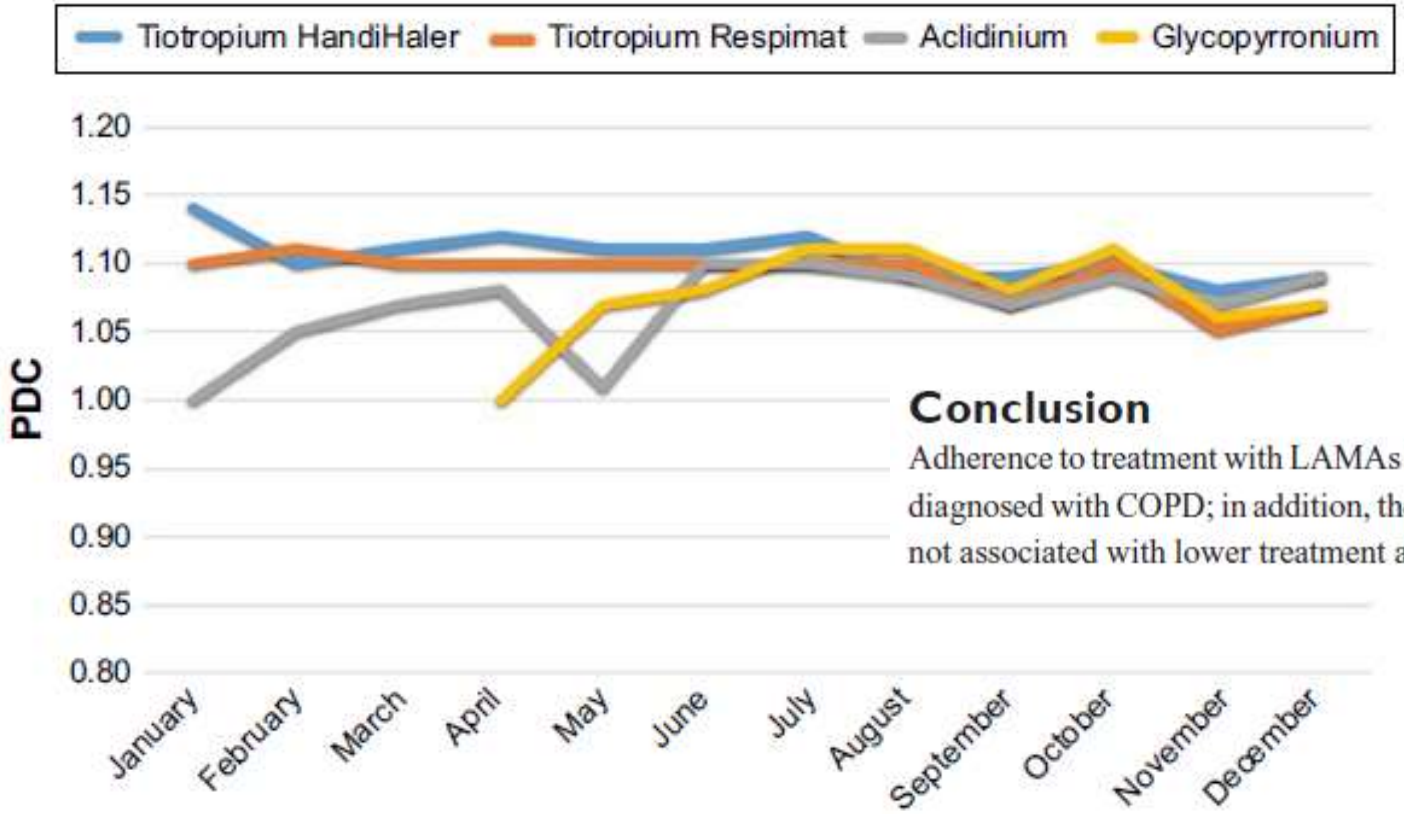
Qual’è il broncodilatatore ideale ?

1. Mono-somministrazione giornaliera per migliorare la compliance

2. Duplice somministrazione giornaliera per controllare meglio i sintomi diurni e notturni

3. L’elemento fondamentale per la scelta è il device

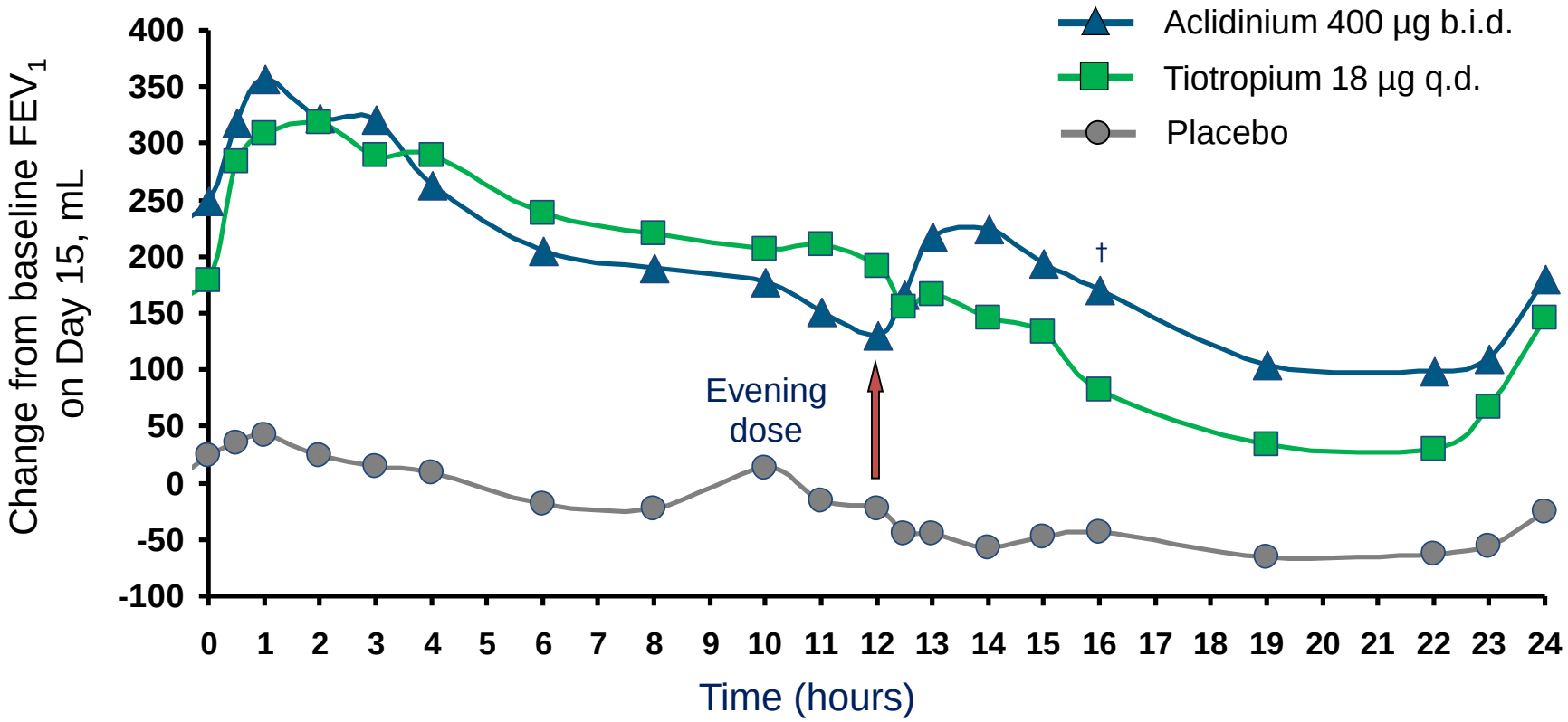
Relevance of dosage in adherence to treatment with long-acting anticholinergics in patients with COPD



Conclusion

Adherence to treatment with LAMAs is very high in patients diagnosed with COPD; in addition, the twice-daily dosage is not associated with lower treatment adherence.

Izquierdo JL, et al. Int J COPD 2016

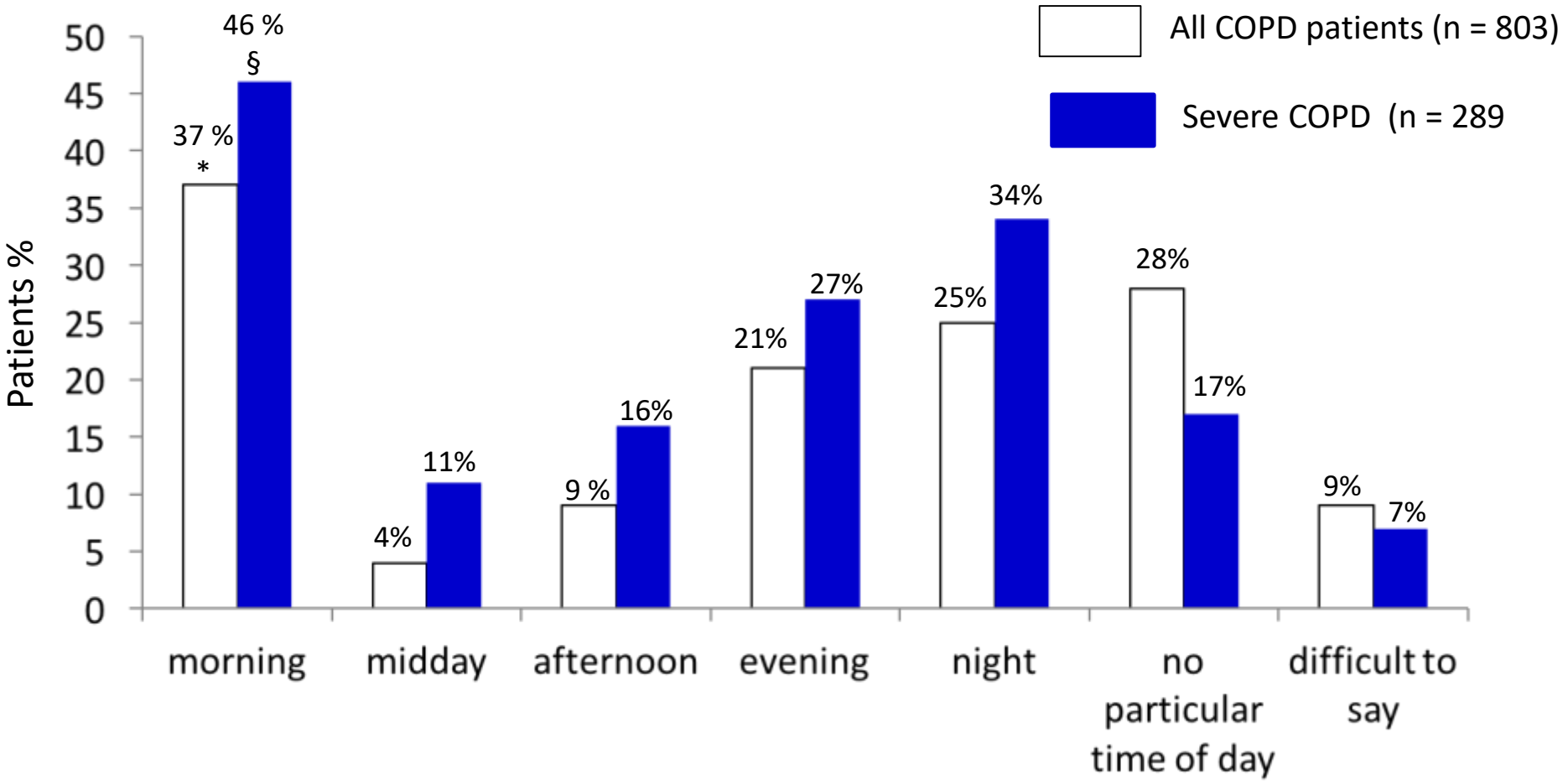


FEV_1 $AUC_{(12\text{-}24)}$ on Day 15 was significantly greater for aclidinium compared with tiotropium (207 vs 129 mL, respectively; $p<0.05$)

$p<0.01$ for aclidinium vs placebo at all time points
$p<0.01$ for tiotropium vs placebo at all time points except 22 h
†$p<0.05$ vs tiotropium

Fuhr et al, Chest 2011

Time when COPD symptoms are worse than usual



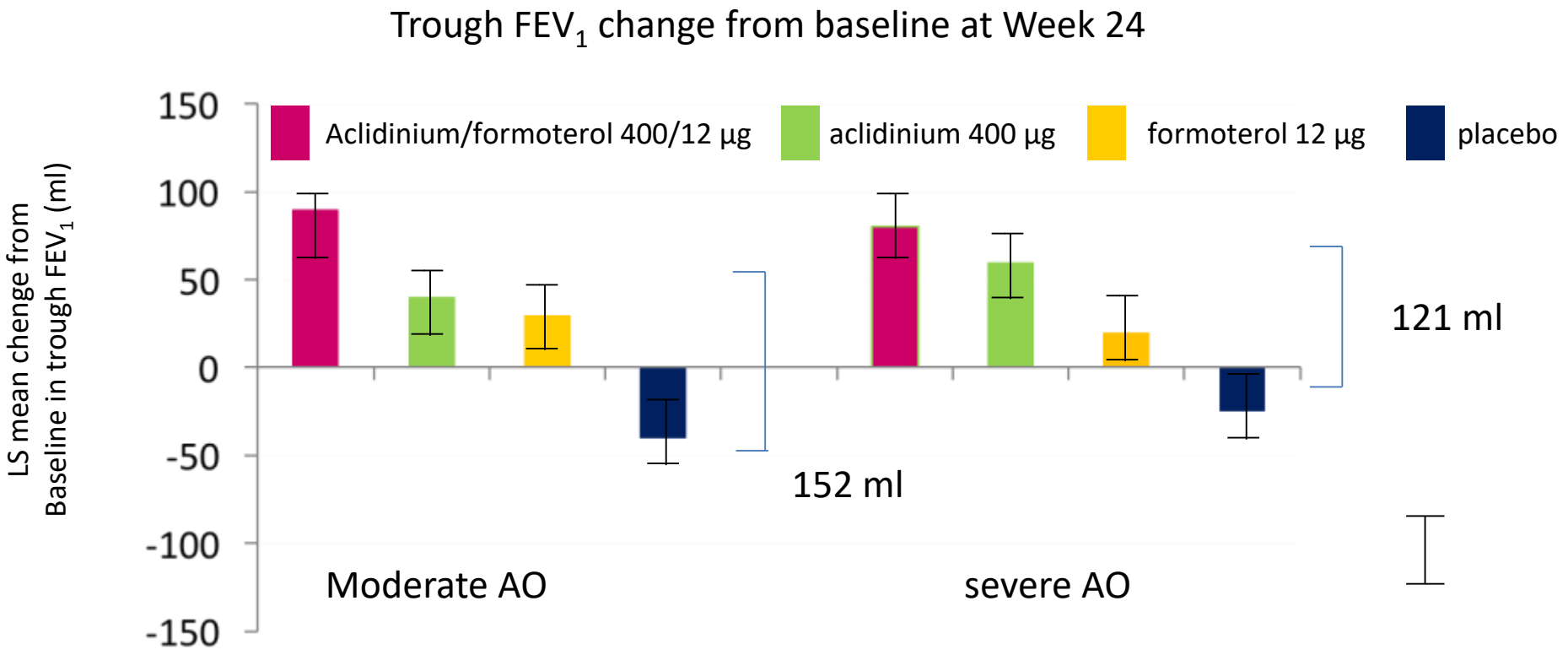
Partridge et al. Curr Med Res Opin 2009

Risposta alle combinazioni LAMA/LABA per sottogruppo di pazienti

- Vi è una variazione nella risposta ai LABA/LAMA dovuta a:

- Severità dell’ostruzione
- Uso concomitante degli ICS
- Età dei pazienti

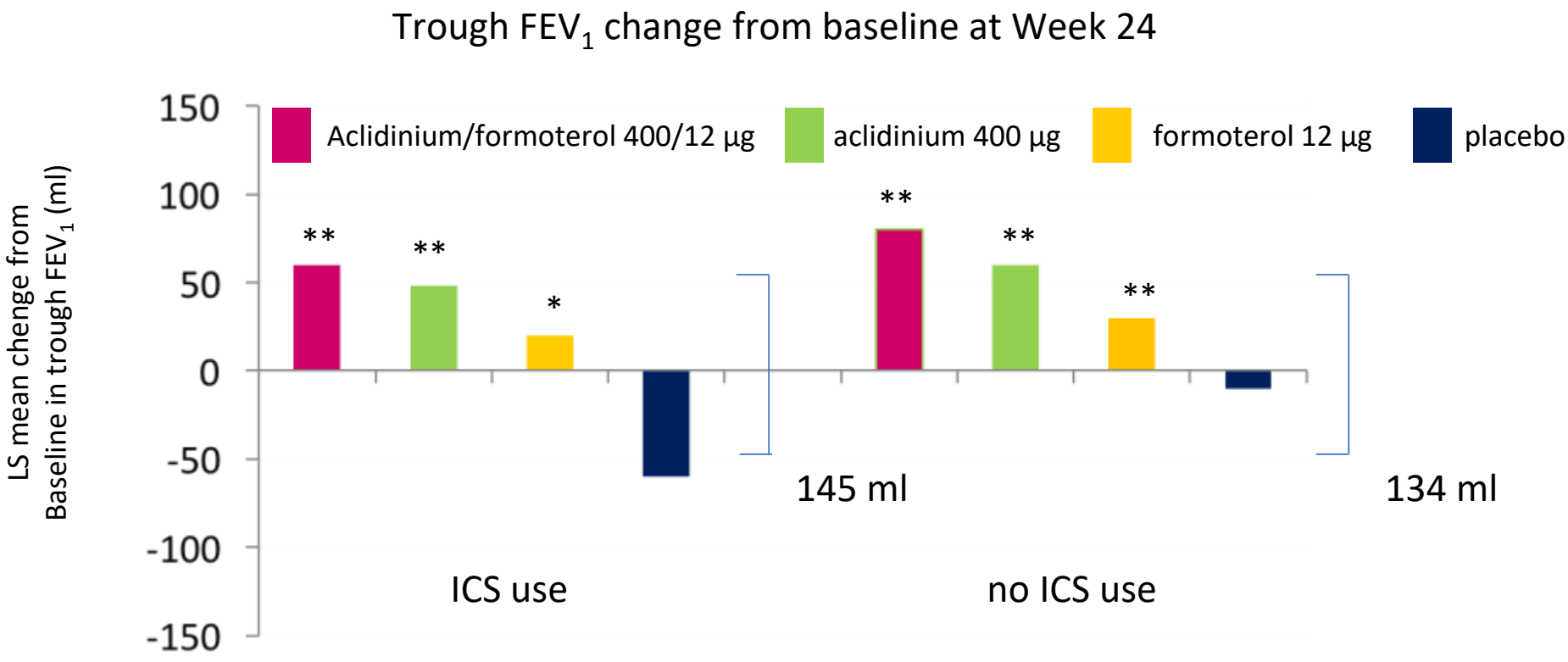
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by COPD severity



- 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.

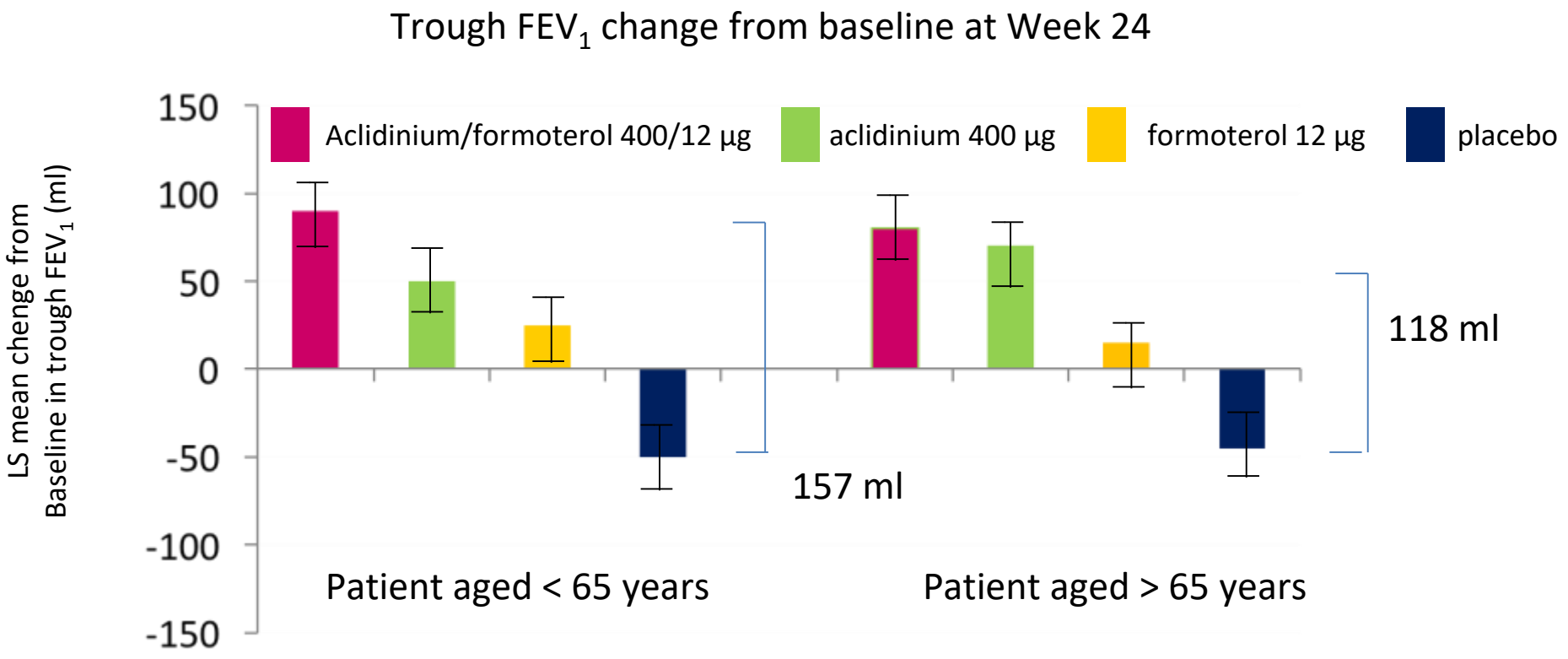
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by ICS use



- 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.

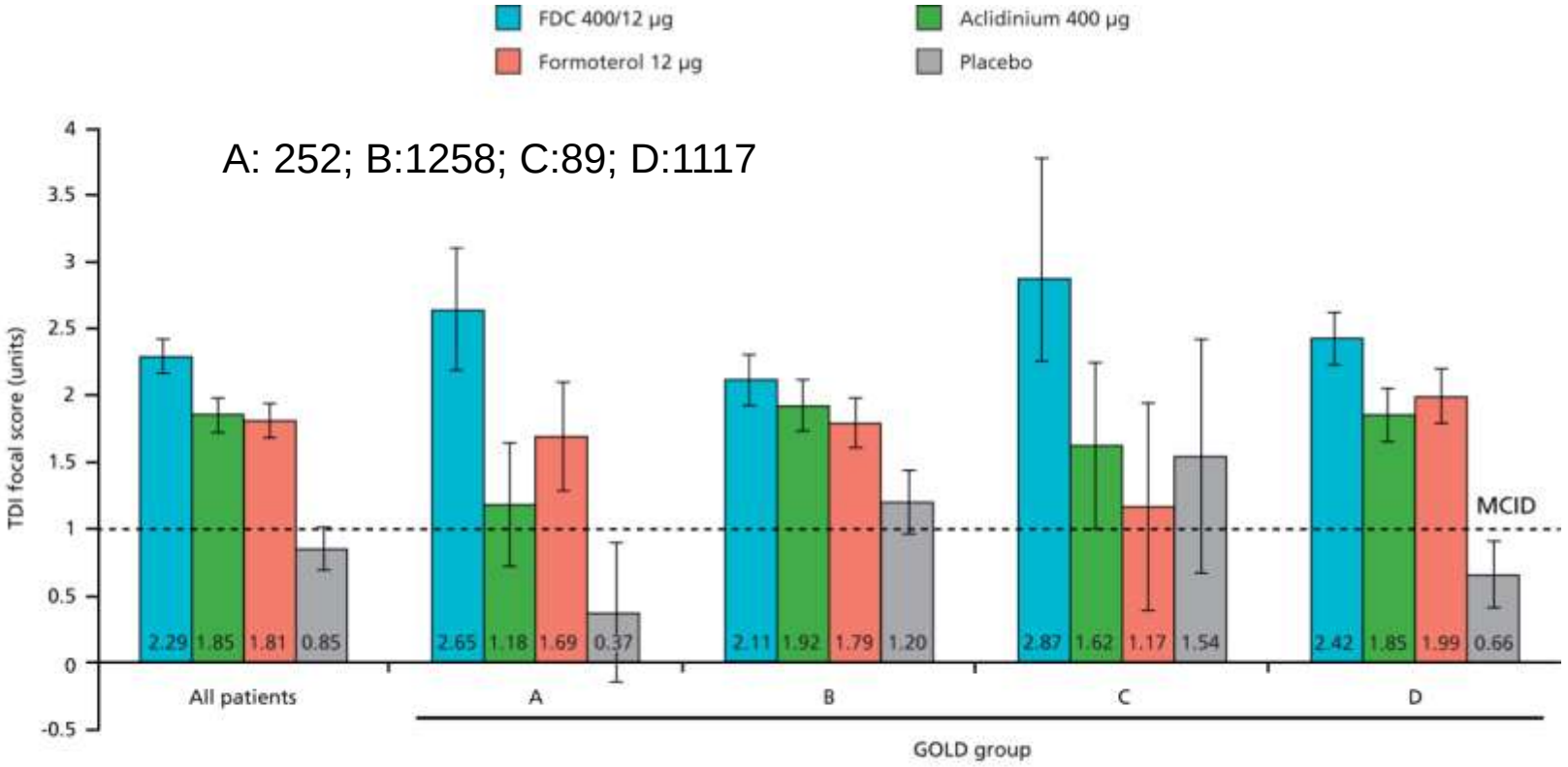
ACLIFORM/AUGMENT pooled post-hoc analysis stratified by patient age



- 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.

Improvement in TDI at Week 24, stratified by GOLD group



	All patients	A	B	C	D
FDC 400/12 µg vs placebo	1.43***	2.27***	0.91**	1.33	1.76***
FDC 400/12 µg vs aclidinium 400 µg	0.44‡	1.47‡	0.19	1.25	0.57‡
FDC 400/12 µg vs formoterol 12 µg	0.47††	0.96	0.32	1.71	0.43
Aclidinium 400 µg vs placebo	1.00***	0.81	0.72*	0.08	1.19***
Formoterol 12 µg vs placebo	0.96***	1.32*	0.59*	-0.38	1.33***

*****p<0.001, **p<0.01, *p<0.05 vs placebo, ‡p<0.05 vs aclidinium, ††p<0.01 vs formoterol**

T. Welte et al, Pulmonary Pharmacology & Therapeutics, 2015

International Journal of COPD

Dovepress

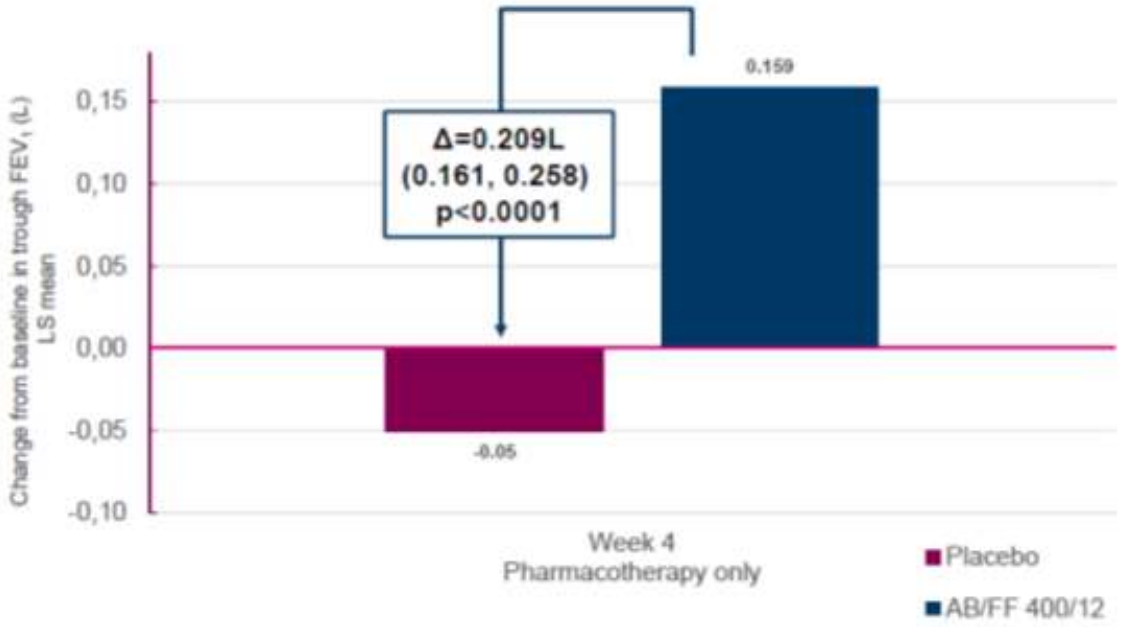
ORIGINAL RESEARCH

ACTIVATE: the effect of aclidinium/formoterol on hyperinflation, exercise capacity, and physical activity in patients with COPD

Lo studio ACTIVATE ha valutato gli effetti di aclidinio/formoterolo 400/12 µg BID sulla funzione polmonare, sul tempo di resistenza all'esercizio e sull' attività fisica in un gruppo di pazienti con BPCO moderata-severa

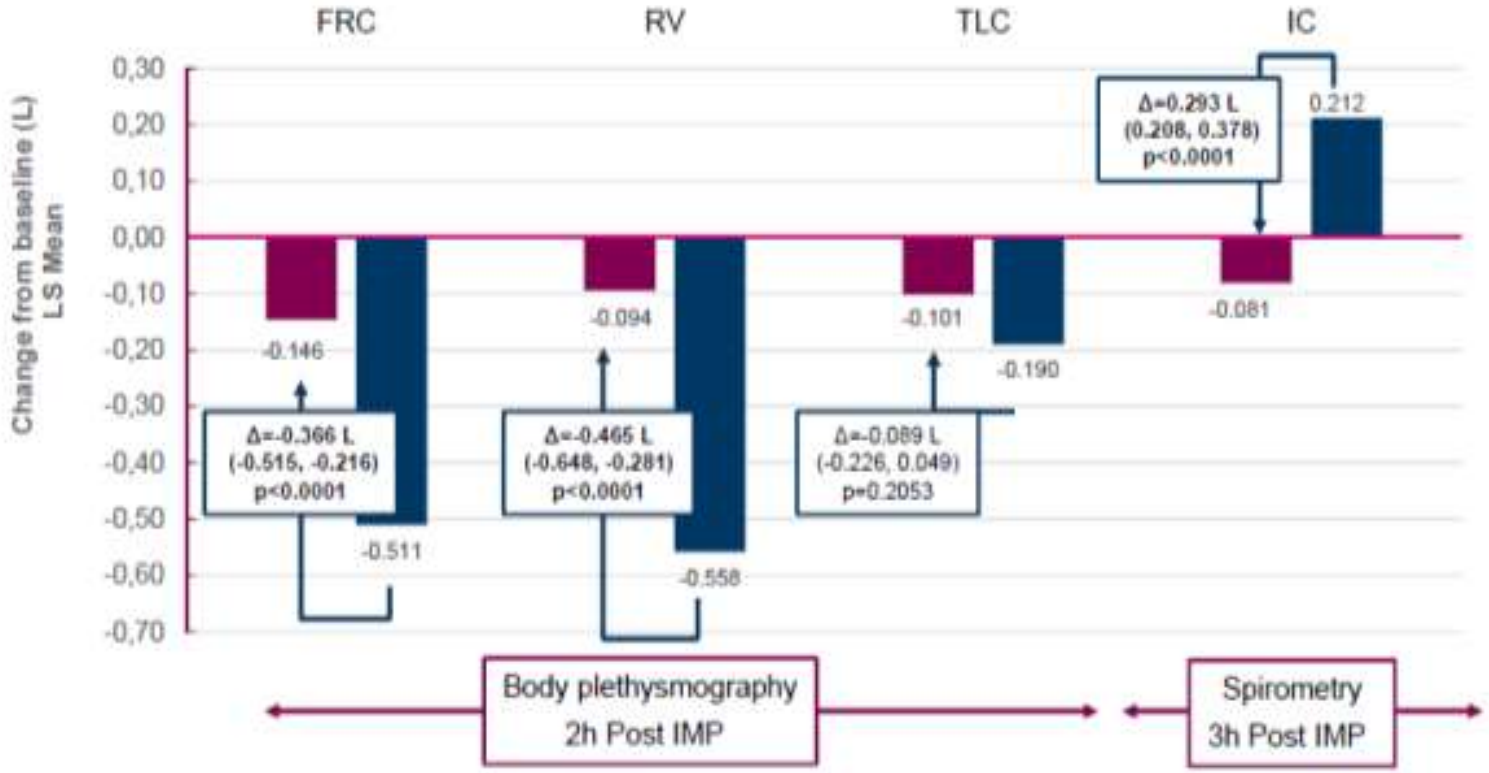
Watz H, et al. Int J COPD 2017

Variazione FEV1 di valle alla settimana 4



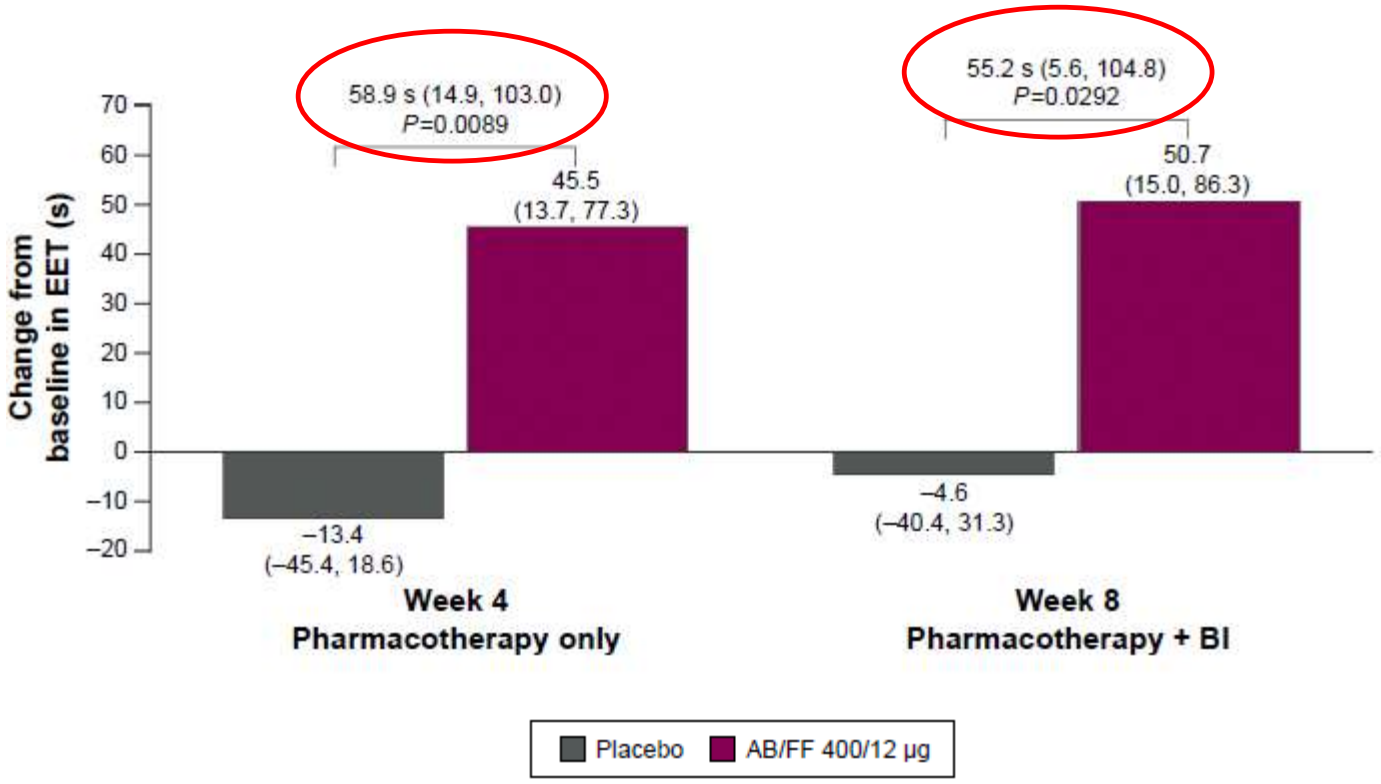
Watz H et al.. Int J Chron Obstruct Pulmon Dis. 2017

Parametri di iperinsufflazione



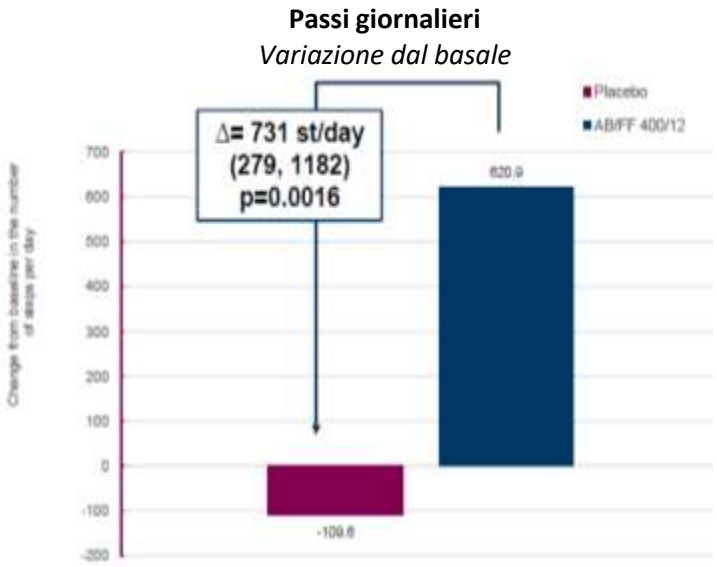
Watz H, et al. Int J COPD 2017

Tempo di resistenza all'esercizio fisico



Watz H, et al. Int J COPD 2017

Endpoint 2°: n° di passi giornalieri



- AB/FF ha anche aumentato il numero di passi giornalieri **(+621**) a **4 settimane** vs una **riduzione di 110 passi** osservata con placebo (*P*=0,0016).
- La differenza tra il farmaco attivo e il placebo era pari a **731 passi in più** al giorno con AB/FF.

Aclidinio/ formoterolo è l'unico LABA/LAMA ad aver dimostrato un aumento dell'attività fisica superiore a 600 passi giornalieri nei pazienti con BPCO.

Watz H, et al. Int J COPD 2017

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]

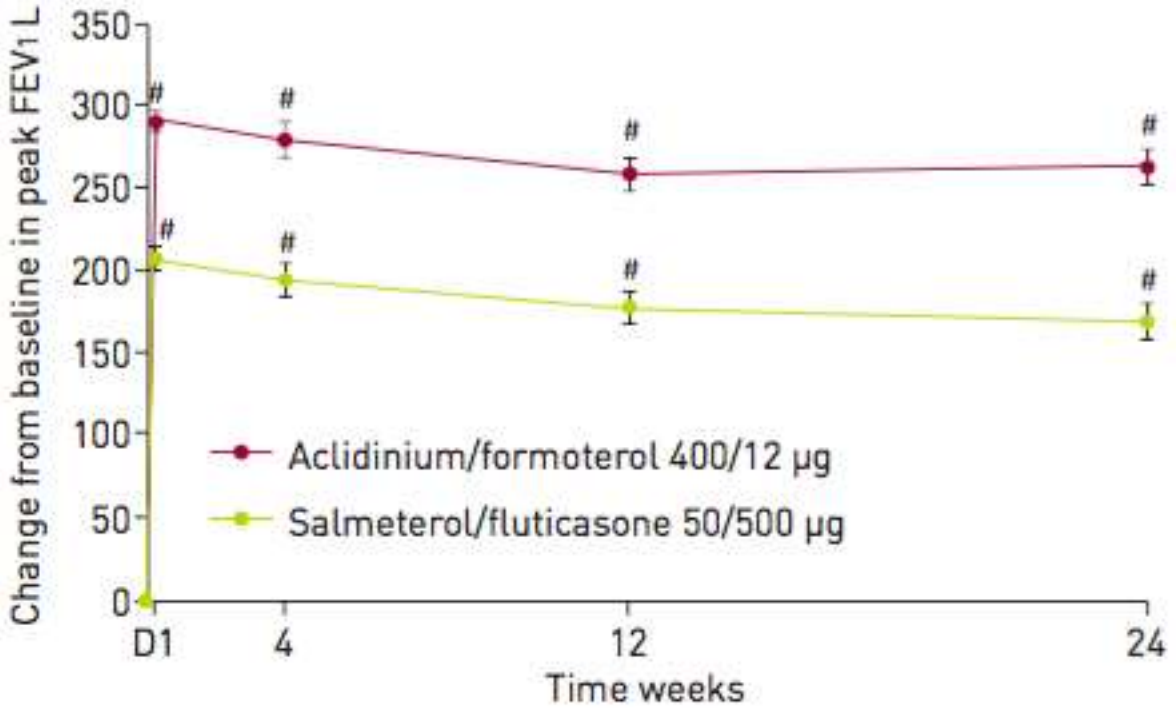
- Dry mouth (1.7 %)

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)

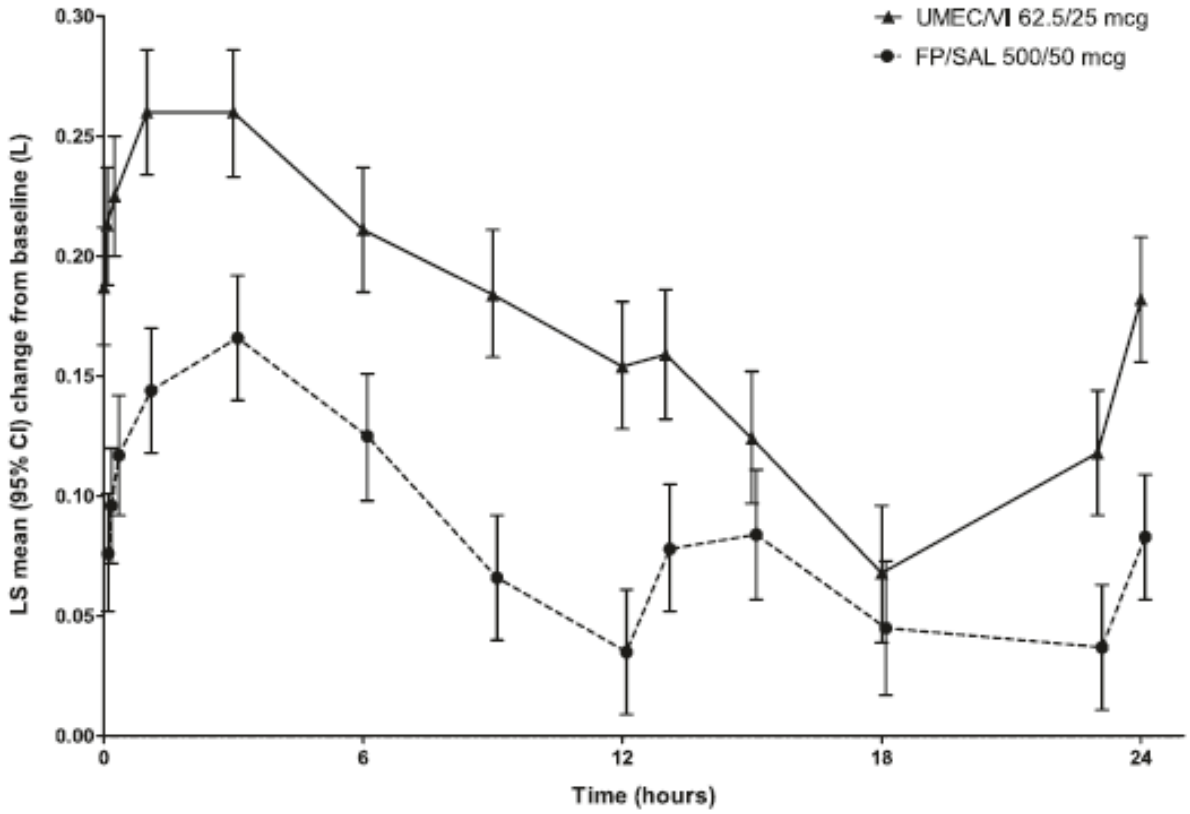


#: p<0.0001 for aclidinium/formoterol versus salmeterol/fluticasone.

Vogelmeier C, et al Eur Respir J 2016; 48: 972–975.

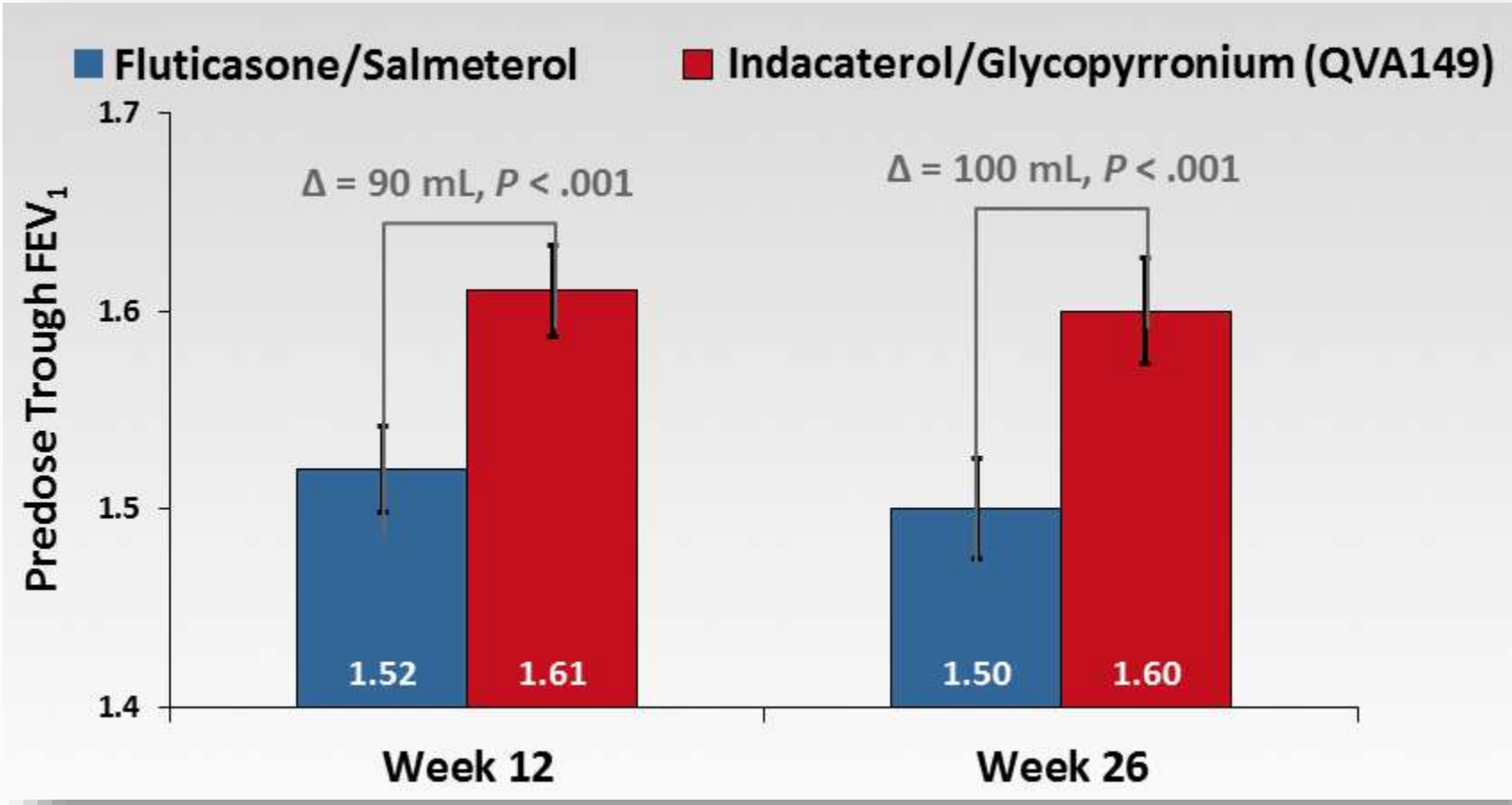
Umeclidinium/vilanterol vs salmeterol/fluticasone

- 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)



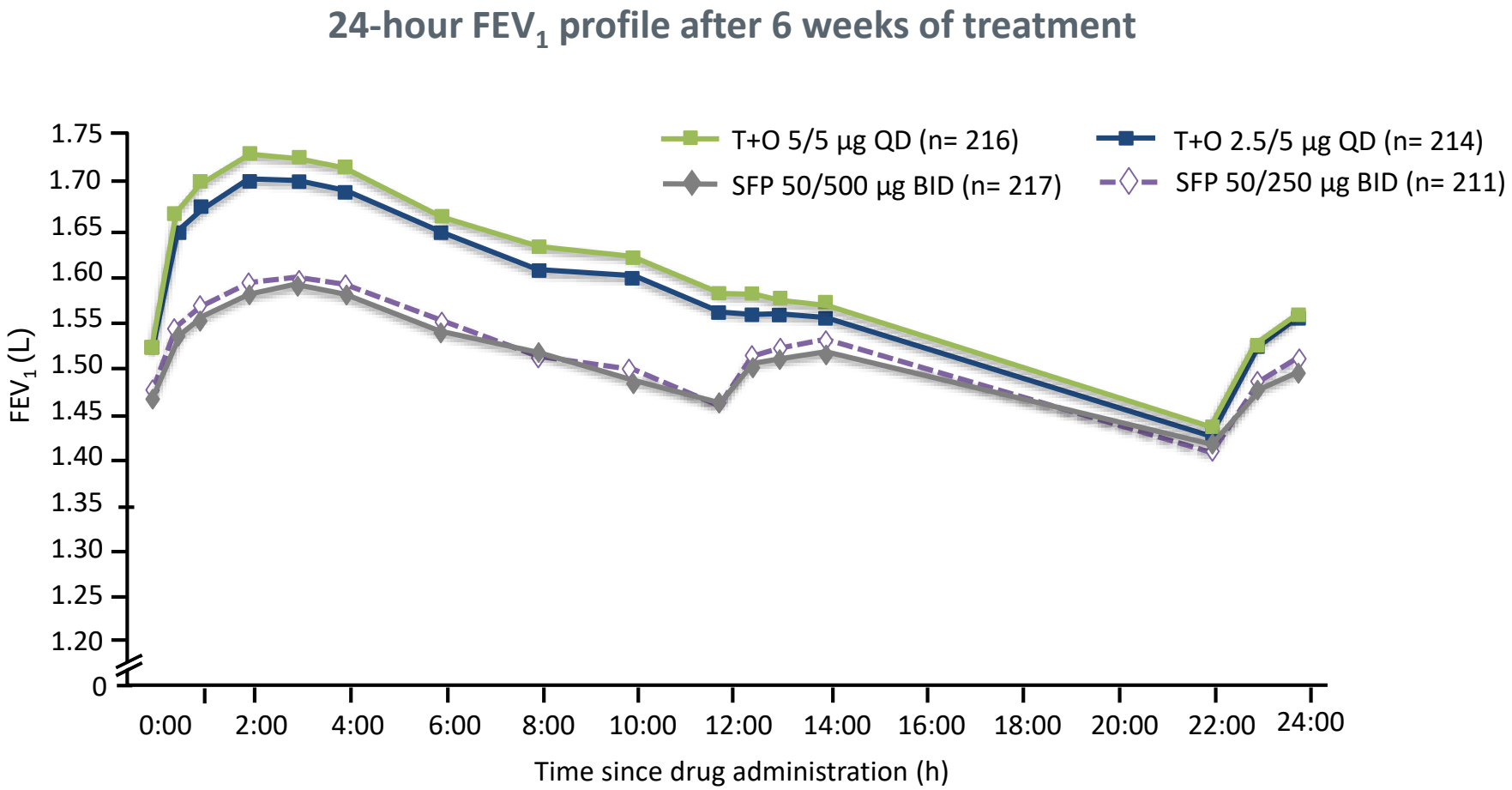
Singh D, et al. BMC Pulm Med 2015

ILLUMINATE: indacaterol/glycopyrronium vs fluticasone/salmeterol



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

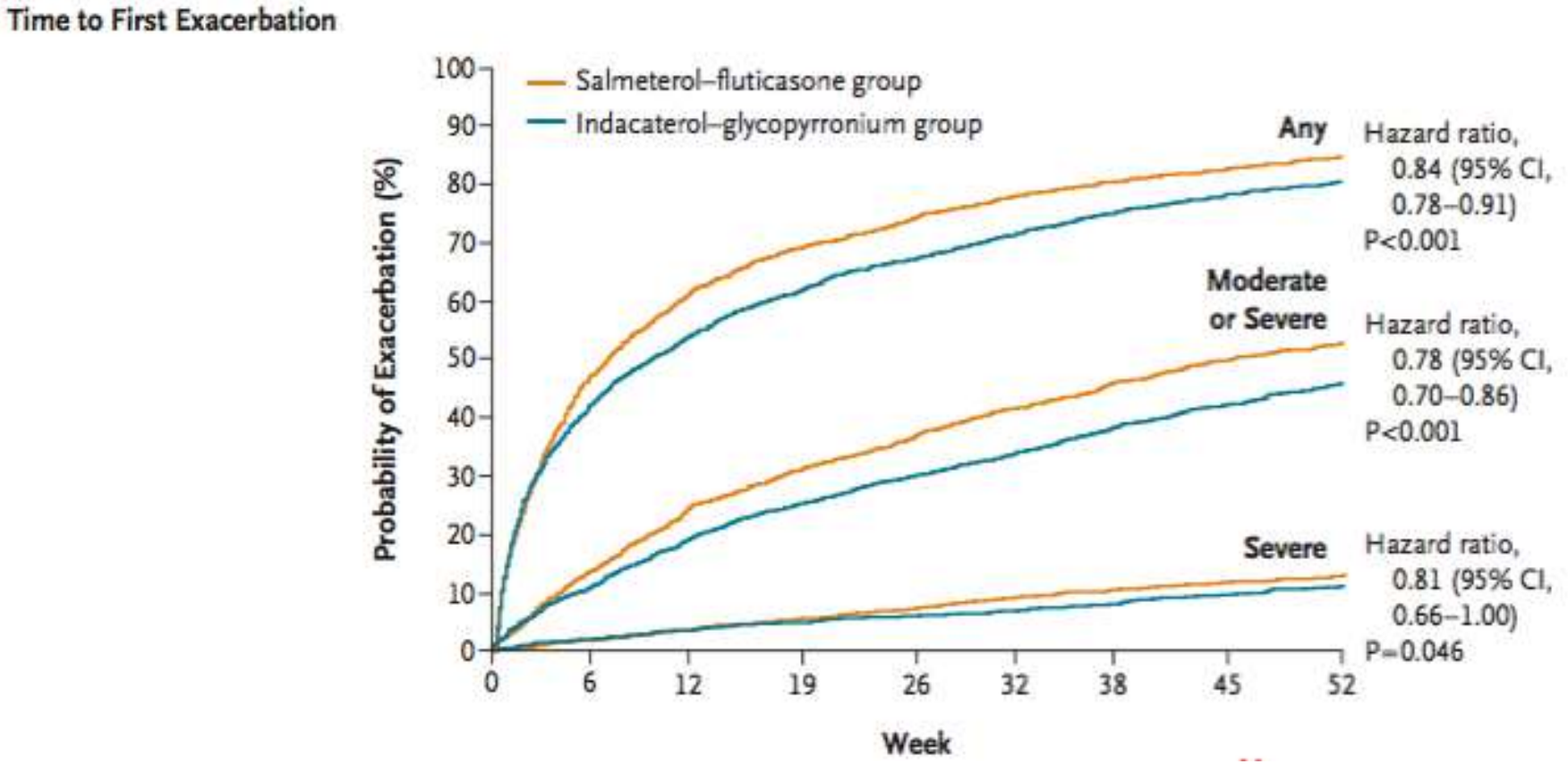
Once-daily Tiotropium + Olodaterol increases 24h FEV_1 compared to twice-daily SFP



Primary endpoint: T+O showed greater increases for both doses as compared to twice-daily SFP. The improvement of FEV_1 AUC_{0-12} was statistically significant for all dose levels, ranging from +103 mL to +129 mL ($p<0.0001$ for all comparisons).

Beeh KM et al. Int J COPD. 2016;11:193-205

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD



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

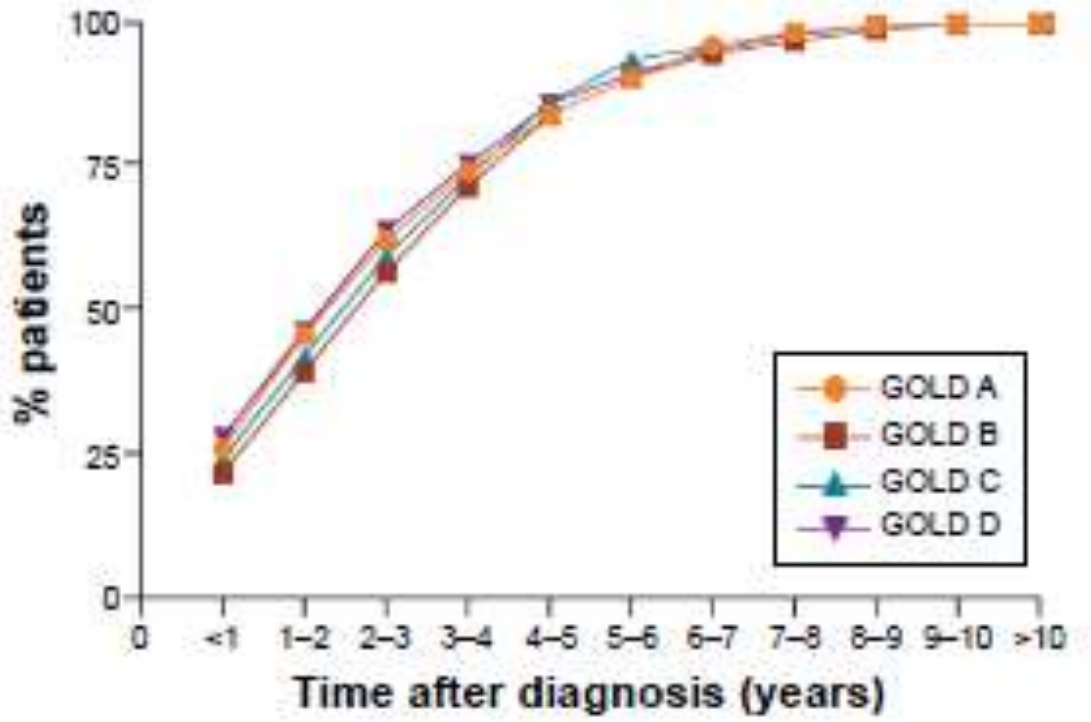
Pharmacologic treatment algorithms

In past GOLD Reports, 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 may subsequently require less therapy. Therefore, we now suggest **escalation** and **de-escalation** strategies.

The recommendations are based on available efficacy and safety data. We acknowledge that treatment escalation has not been systematically tested; trials of de-escalation are also limited and only include ICS.

AJRCCM Articles in Press. Published on 27-January-2017 as 10.1164/rccm.201701-0218PP

The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK

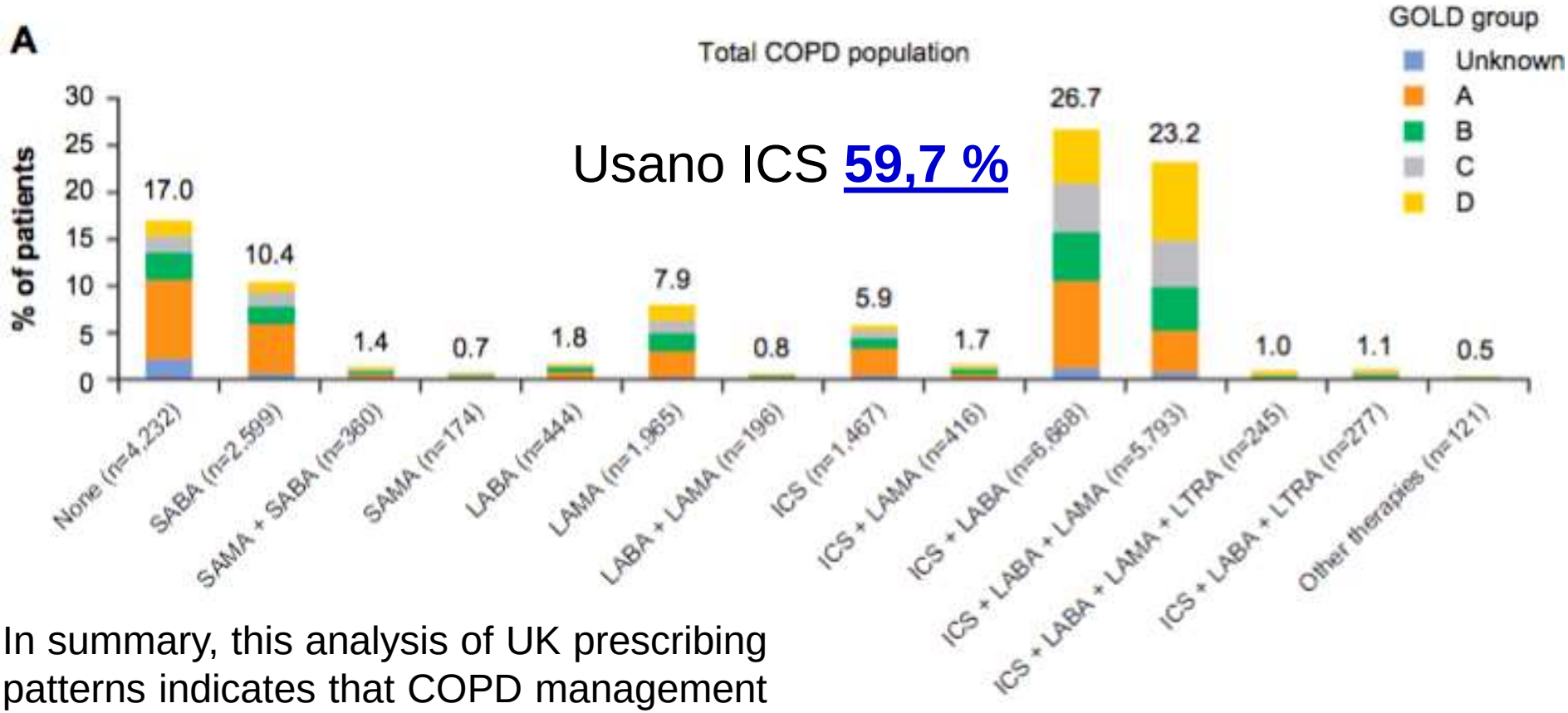


Circa il **100 %** dei pazienti considerati usano **ICS**

Cumulative proportion of patients receiving triple therapy by GOLD group (2002-2010)

Brusselle G, et al. Int J COPD 2015; 10, 2207-17

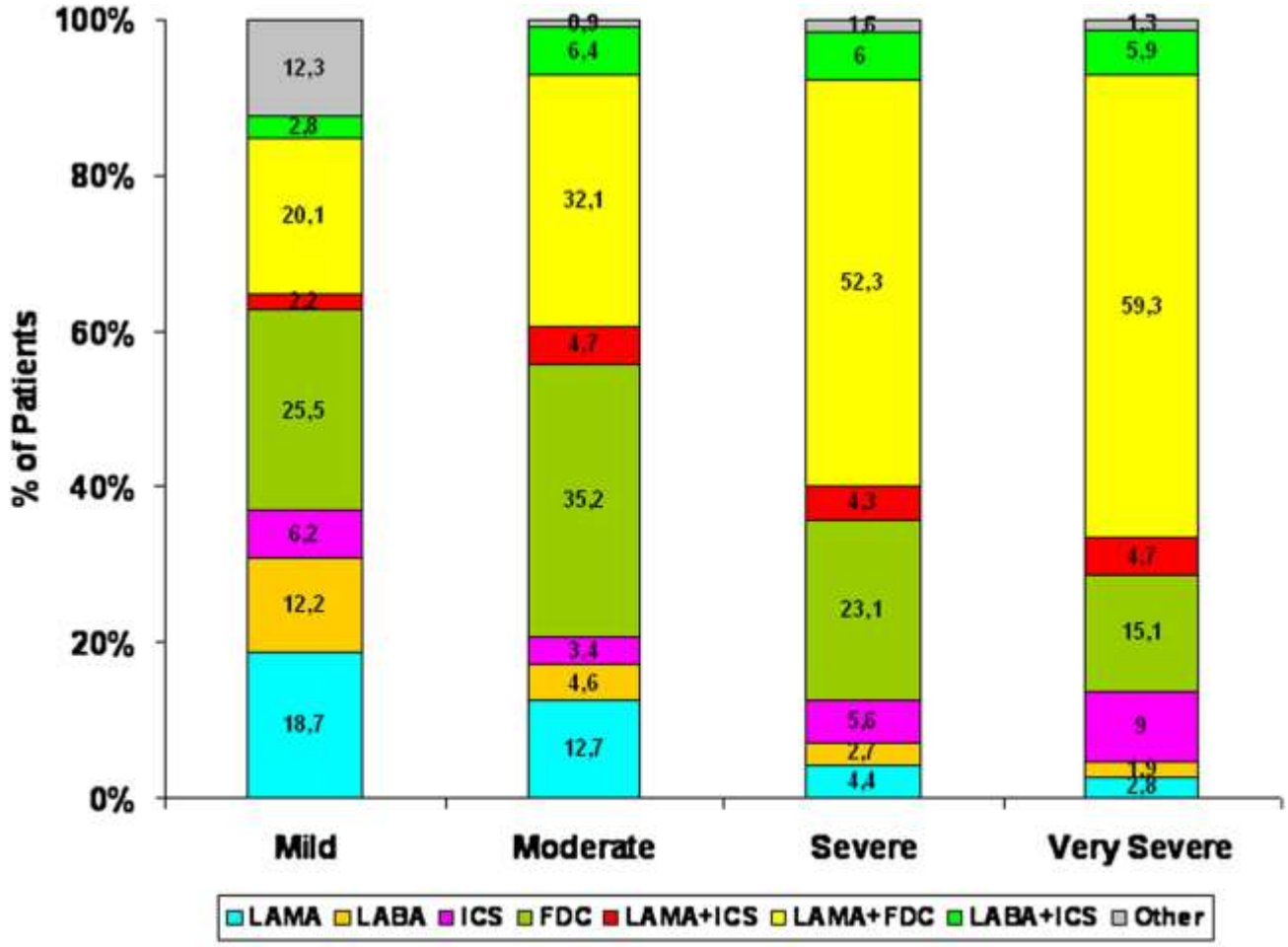
Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns



Usano ICS **59,7 %**

In summary, this analysis of UK prescribing patterns indicates that COPD management choices do not usually follow GOLD recommendations and NICE guidelines, in particular those relating to the use of ICS.

Price D. Int J Copd 2014



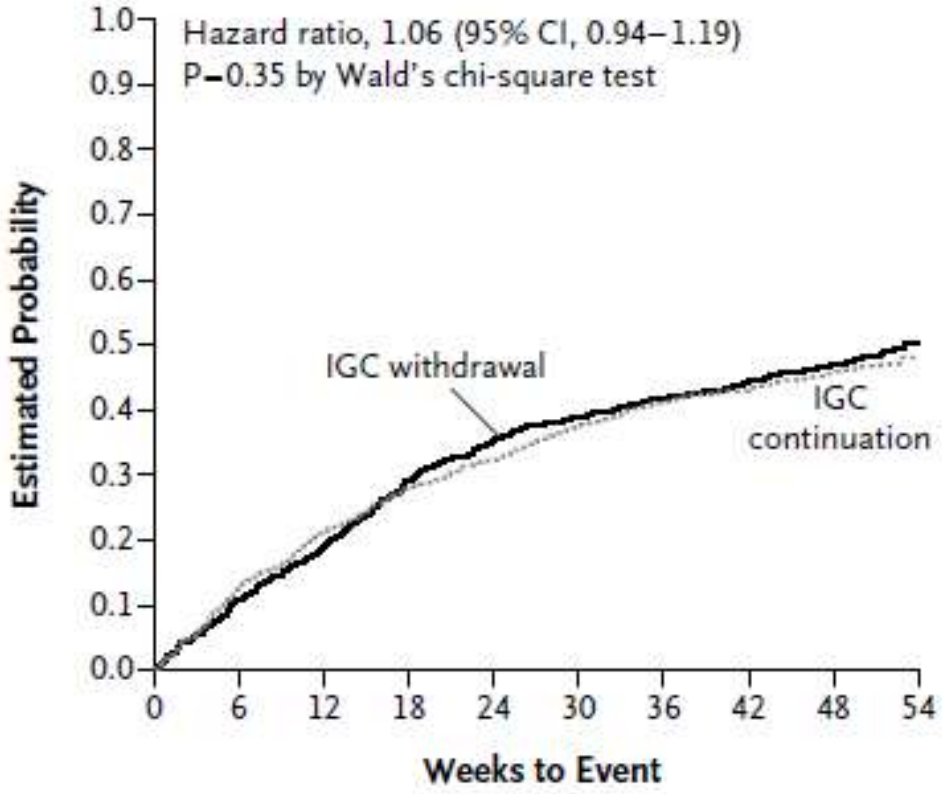
LAMA: Long-acting antimuscarinic agents; LABA: Long-acting beta2 agonists;
ICS: Inhalec corticosteroids; FDC: Fixed Dose Combination

Respiratory Medicine 2012

I nuovi LEA possono essere l'occasione per mettere ordine nella gestione della BPCO ?

057	BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO) NEGLI STADI CLINICI "MODERATA", "GRAVE" E "MOLTO GRAVE"	
	PRESTAZIONI	**FREQUENZA**
	VISITA DI CONTROLLO necessaria al monitoraggio della malattia, delle complicanze più frequenti ed alla prevenzione degli ulteriori aggravamenti (* NOTA)	ogni 6 mesi
90.25.5	GAMMA GLUTAMIL TRANSPEPTIDASI (gamma GT)	ogni 6 mesi
90.27.1	GLUCOSIO	ogni 6 mesi
90.44.1	UREA	ogni 6 mesi
90.44.3	URINE ESAME COMPLETO. Incluso: sedimento urinario	ogni 6 mesi
90.62.2	EMOCROMO: ESAME CITOMETRICO E CONTEGGIO LEUCOCITARIO DIFFERENZIALE Hb, GR, GB, HCT, PLT, IND. DERIV. Compreso eventuale controllo microscopico	ogni 6 mesi
91.49.2	PRELIEVO DI SANGUE VENOSO	ogni 6 mesi
91.48.5	PRELIEVO DI SANGUE ARTERIOSO	ogni 6 mesi
91.49.1	PRELIEVO DI SANGUE CAPILLARE	ogni 6 mesi
89.37.2	SPIROMETRIA GLOBALE [con tecnica di diluizione, pletismografia o altra metodica]	ogni 6 mesi
89.44.2	TEST DEL CAMMINO CON VALUTAZIONE DELLA SATURAZIONE ARTERIOSA [WALKING TEST]	ogni 6 mesi
87.44.1	RX DEL TORACE. Radiografia standard del torace in 2 proiezioni posteroanteriore e laterolaterale	ogni 12 mesi
89.52	ELETTROCARDIOGRAMMA	ogni 12 mesi
89.65.1	EMOGASANALISI ARTERIOSA SISTEMICA Emogasanalisi di sangue capillare o arterioso. Inclusa determinazione di pH ematico e Carbossiemoglobina.	ogni 6 mesi
	OPPURE	
89.66	EMOGASANALISI DI SANGUE MISTO VENOSO	ogni 6 mesi
89.65.5	MONITORAGGIO INCRUENTO DELLA SATURAZIONE ARTERIOSA / PULSOSSIMETRIA	ogni 12 mesi
93.18.2	RIEDUCAZIONE MOTORIA CARDIO-RESPIRATORIA DI GRUPPO relativa alle "funzioni dell'apparato cardiovascolare, ematologico, immunologico e respiratorio" secondo ICF dell'OMS. Per seduta di 60 minuti caratterizzata prevalentemente dall'esercizio terapeutico motorio, indipendentemente dalla tecnica utilizzata, dal mezzo in cui viene realizzato e dalle ortesi ed ausili utilizzati. Max 6 pazienti. Ciclo fino a 10 sedute	ogni 12 mesi

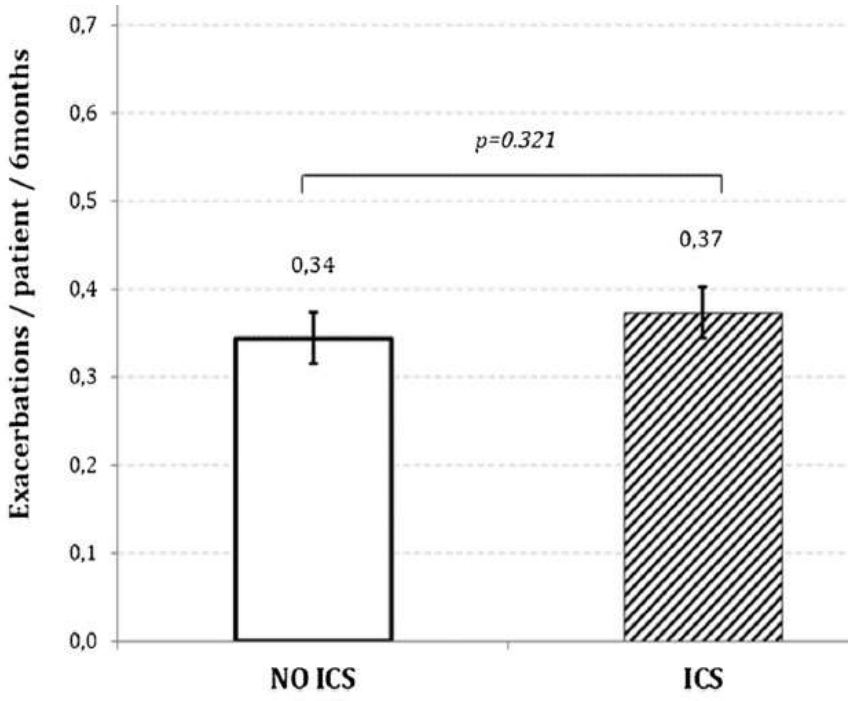
A **Moderate or Severe COPD Exacerbation**

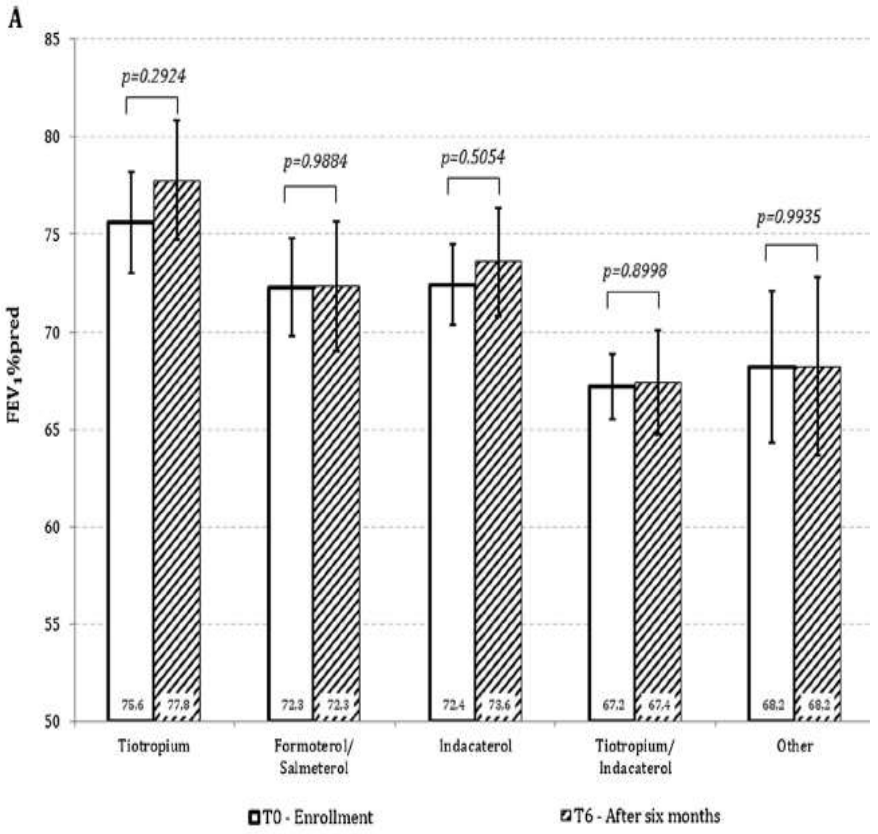


No. at Risk

IGC continuation	1243	1059	927	827	763	694	646	615	581	14
IGC withdrawal	1242	1090	965	825	740	688	646	607	570	19

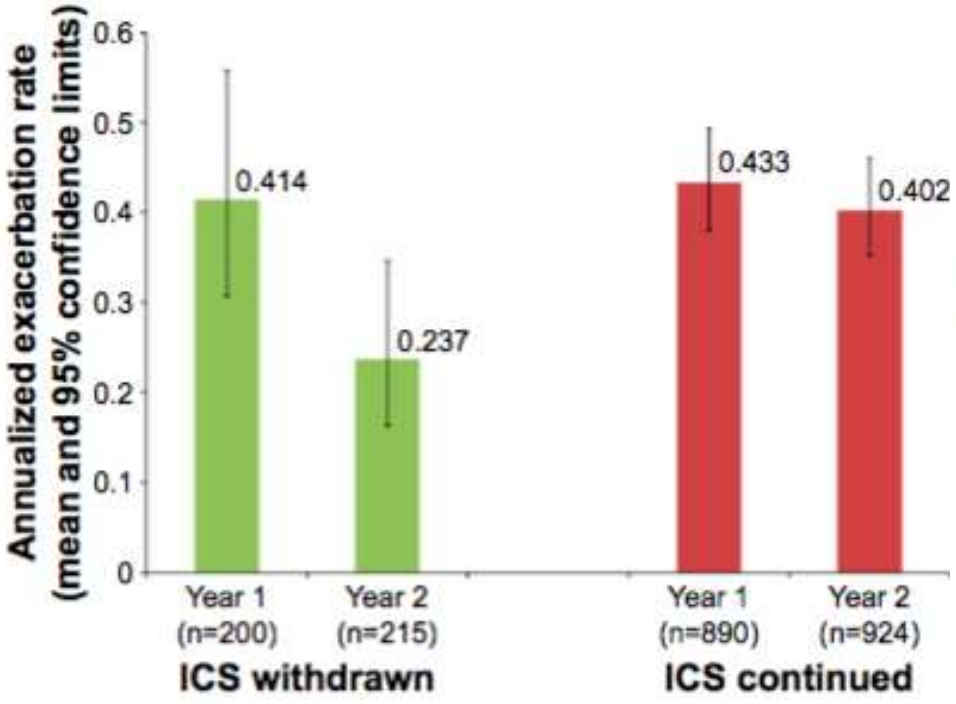
Magnussen H, et al. New Engl J Med 2014

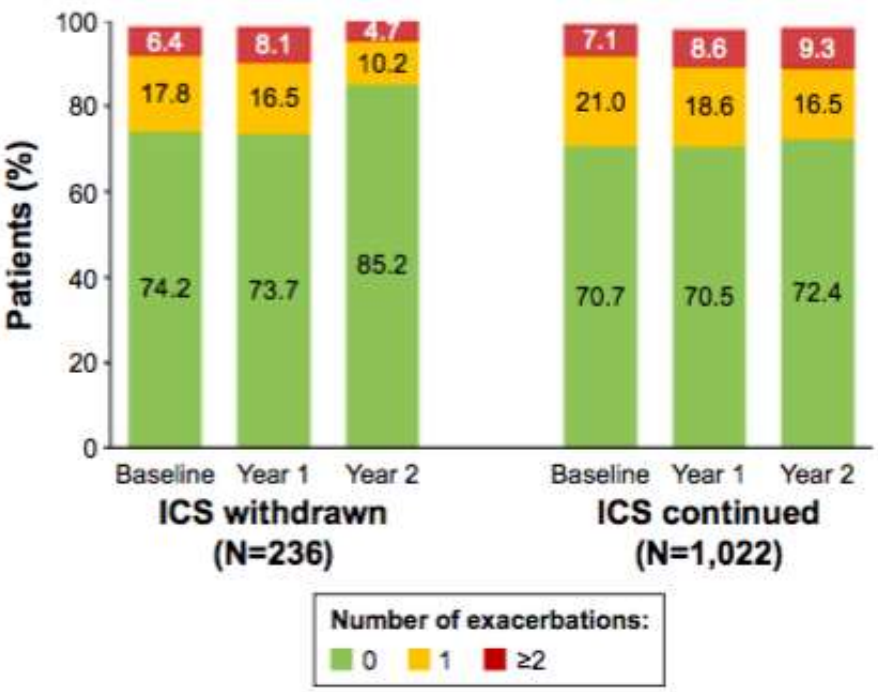




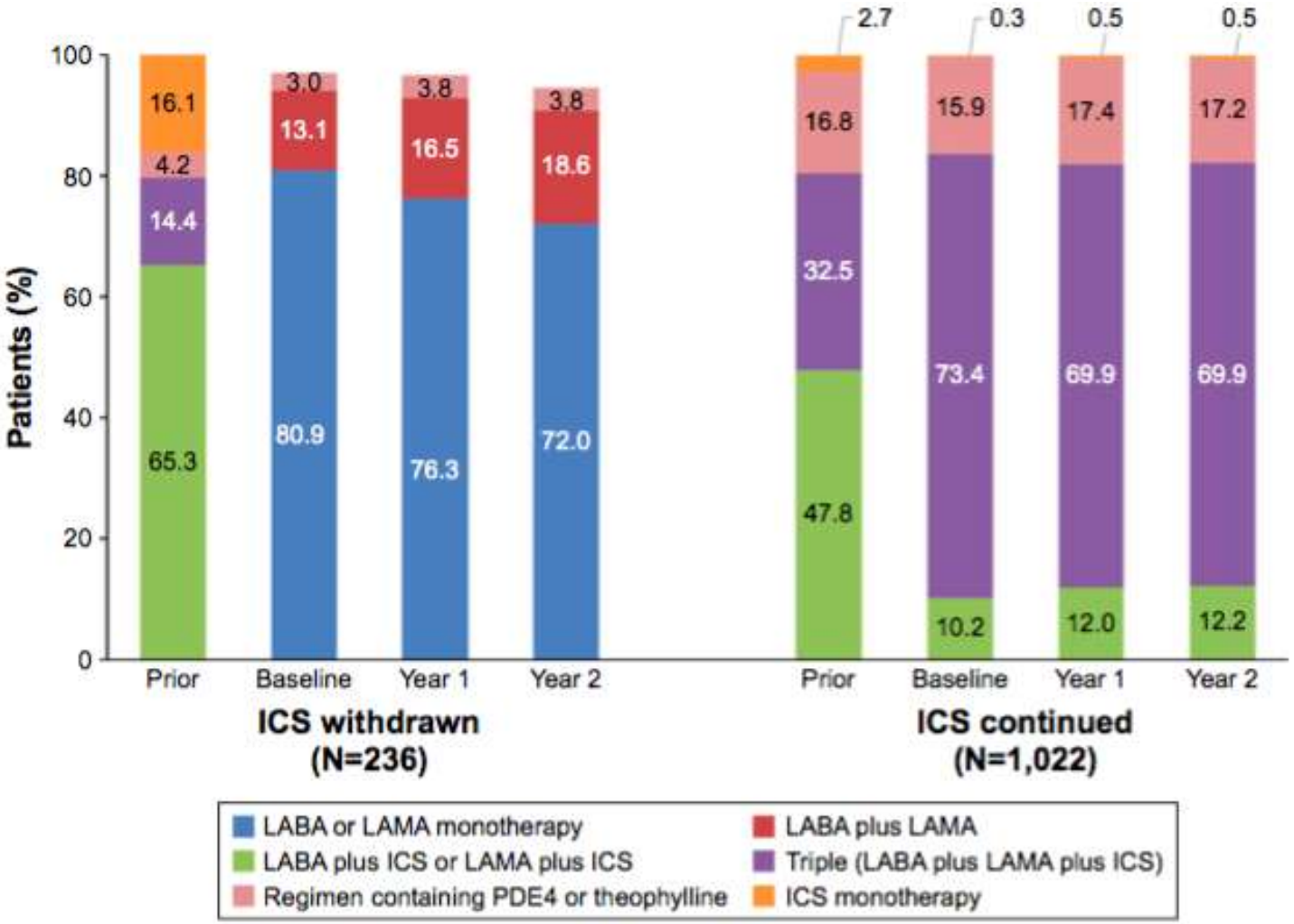
Rossi A, et al. Resp Research 2014

“Real-life” inhaled corticosteroid withdrawal in COPD: a subgroup analysis of DACCORD

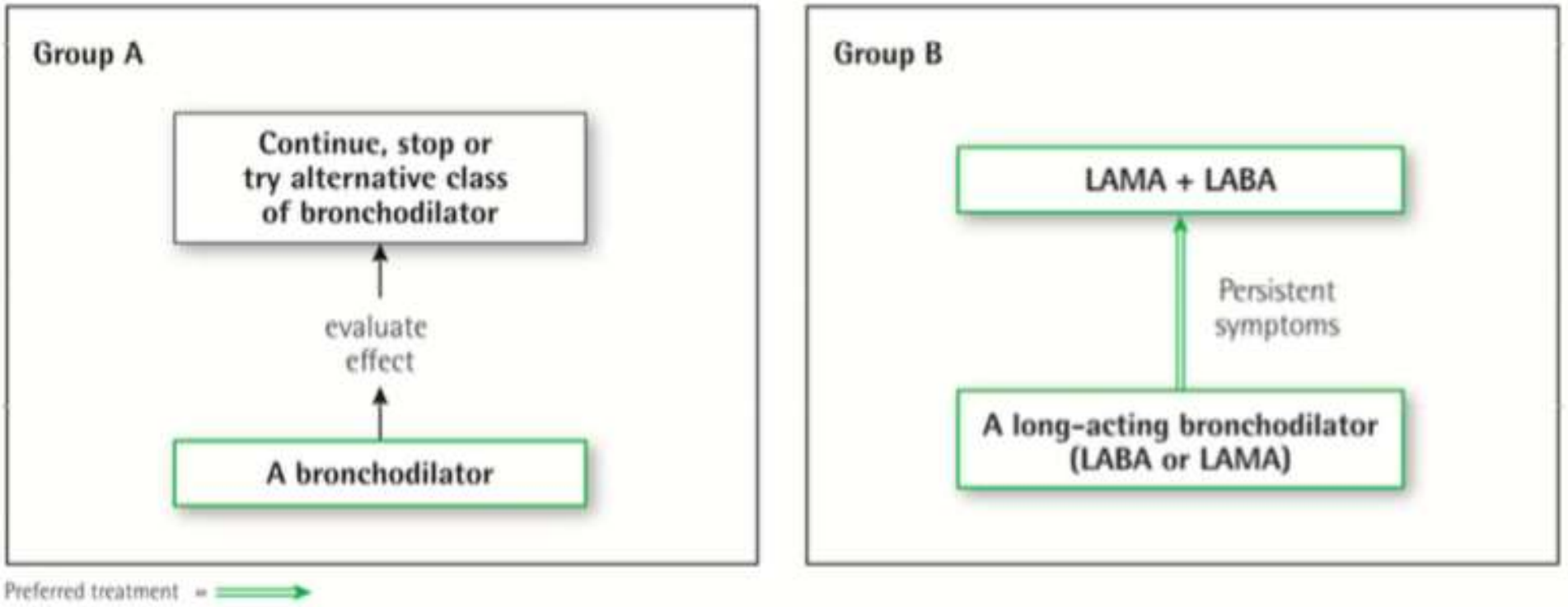




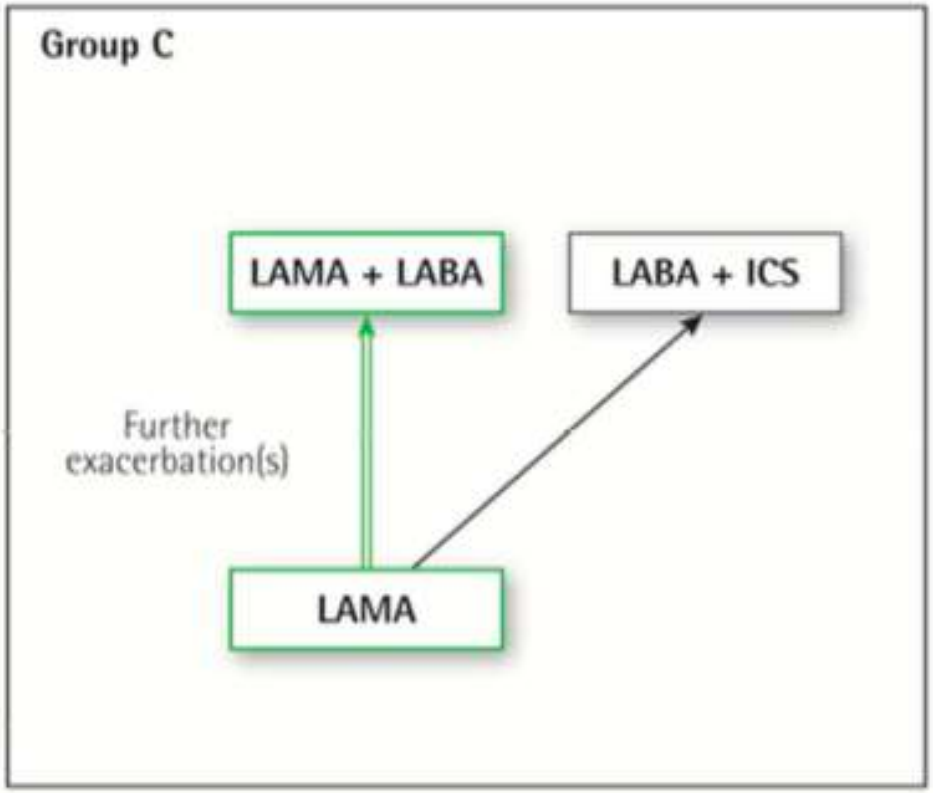
Vogelmeier C, et al. Int J COPD 2017

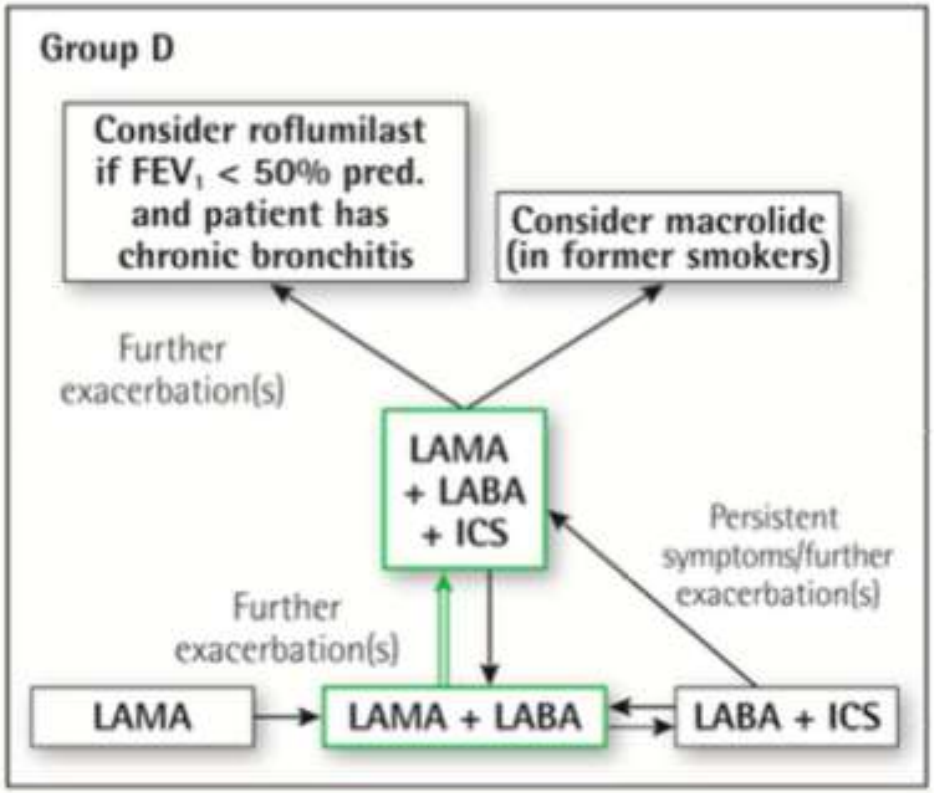


Vogelmeier C, et al. Int J COPD 2017


Group A
Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)
Preferred treatment

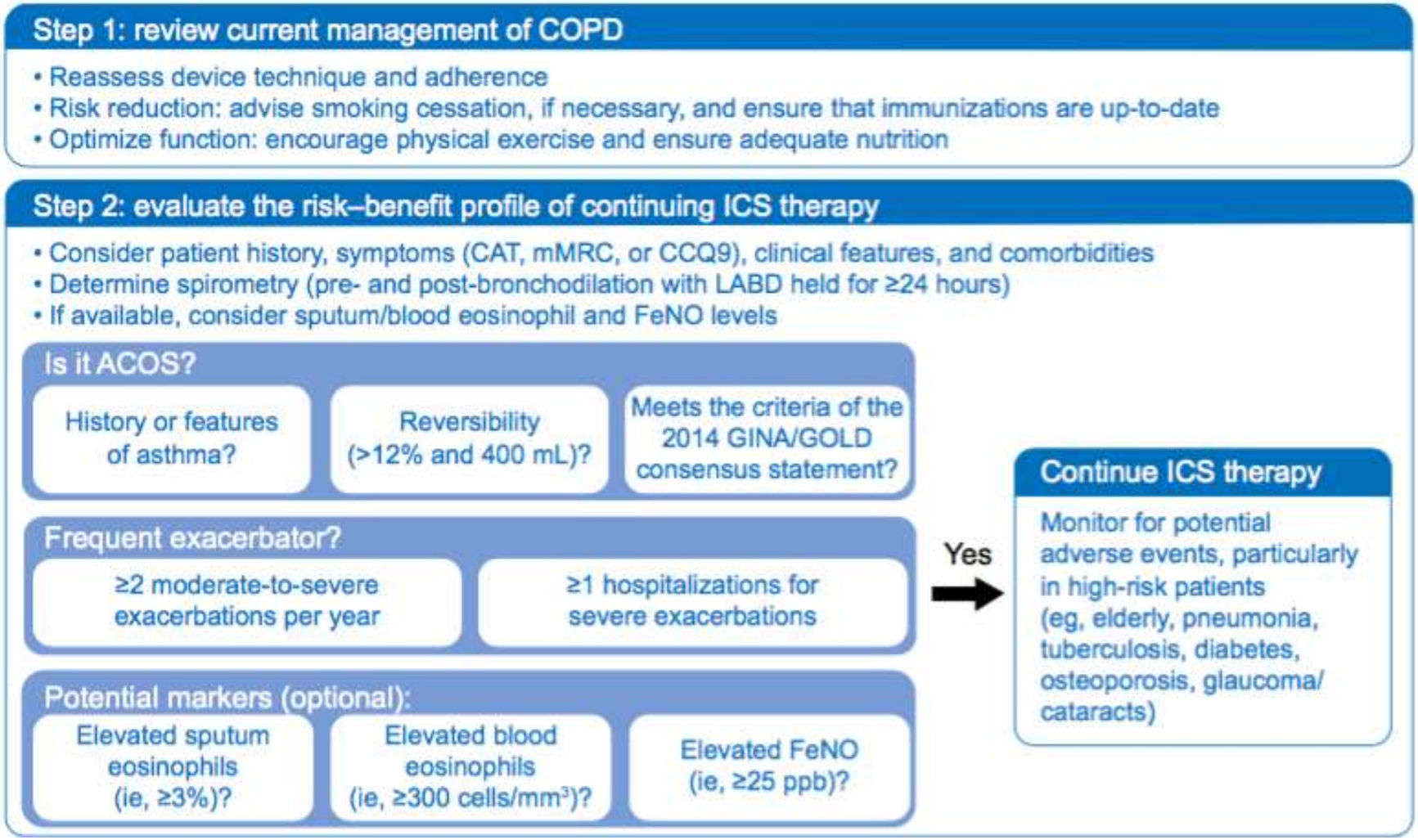
GOLD 2017


Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA

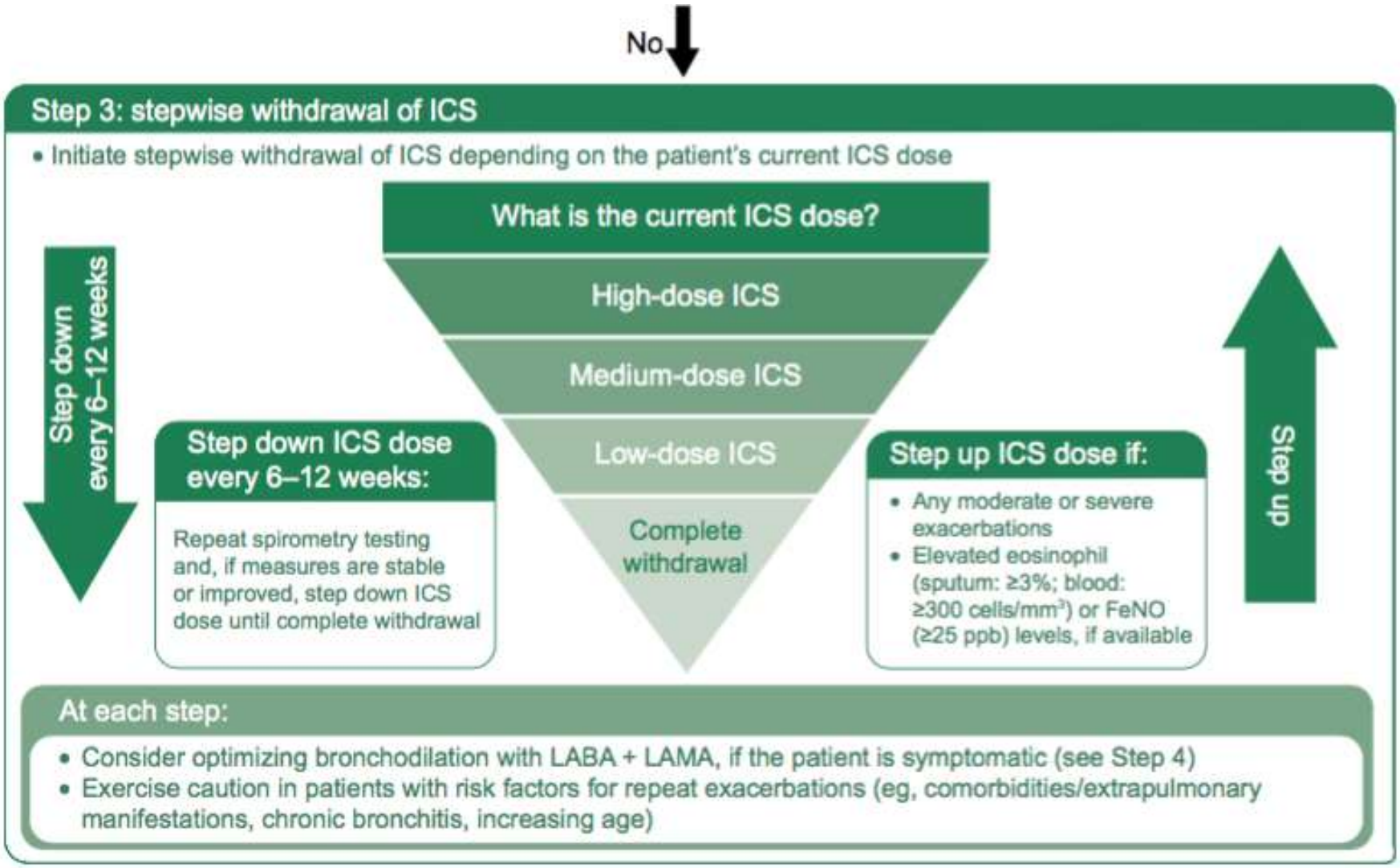

Group D
Consider roflumilast if FEV1 < 50% pred. and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS

GOLD 2017

Sospensione steroidi: proposta operativa



Alan G Kaplan. Int J COPD 2015



Alan G Kaplan. Int J COPD 2015

Step 4: optimize bronchodilation with LABA + LAMA

- Once ICS is completely withdrawn (ie, at last step down from lowest dose of ICS available), consider optimizing bronchodilation with LABA + LAMA (ie, fixed-dose combination, if coverage is available, or separate devices), if not already done so in Step 3
- Choose a device that the patient is able to use effectively

Step 5: follow-up

- See patient every 3 months in the first year, followed by an annual review, if COPD is stable and exacerbation-free

Alan G Kaplan Int J COPD 2015

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.