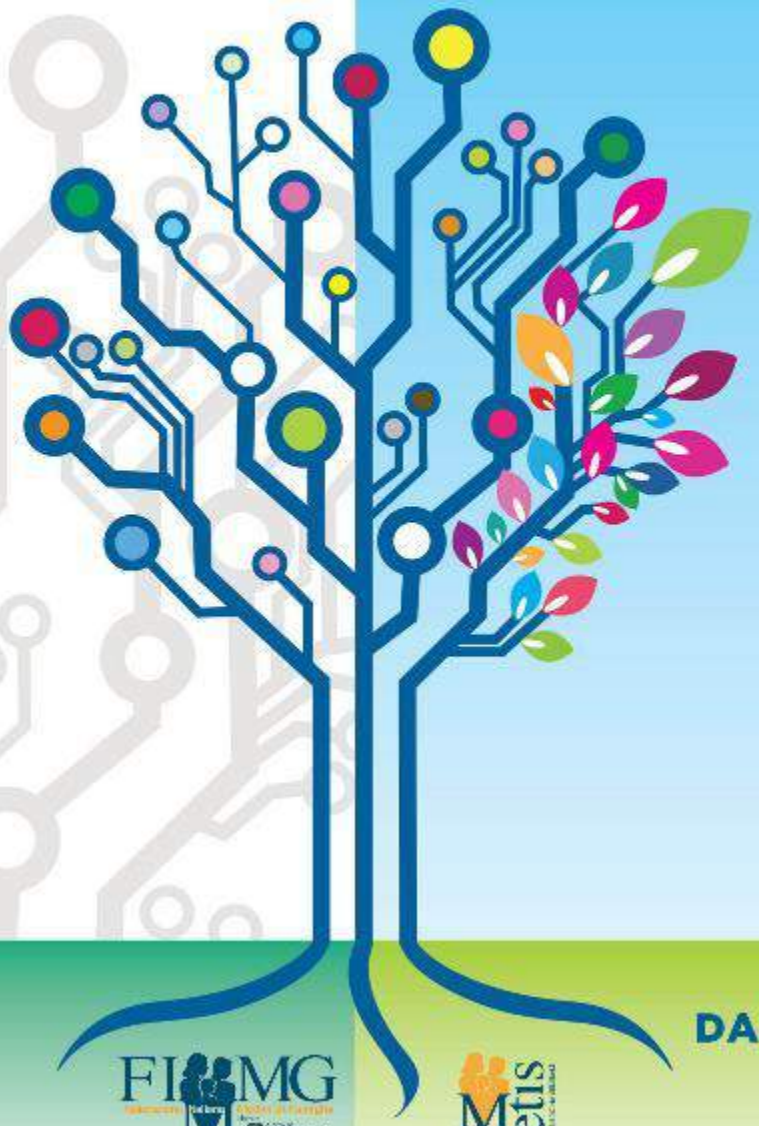

Il Paziente con BPCO: la personalizzazione della terapia

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DALLA PRESTAZIONE ALLA PERFORMANCE
74° Congresso Nazionale
2-7 ottobre 2017

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary

TASK FORCE REPORT
GOLD EXECUTIVE SUMMARY

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report

GOLD Executive Summary

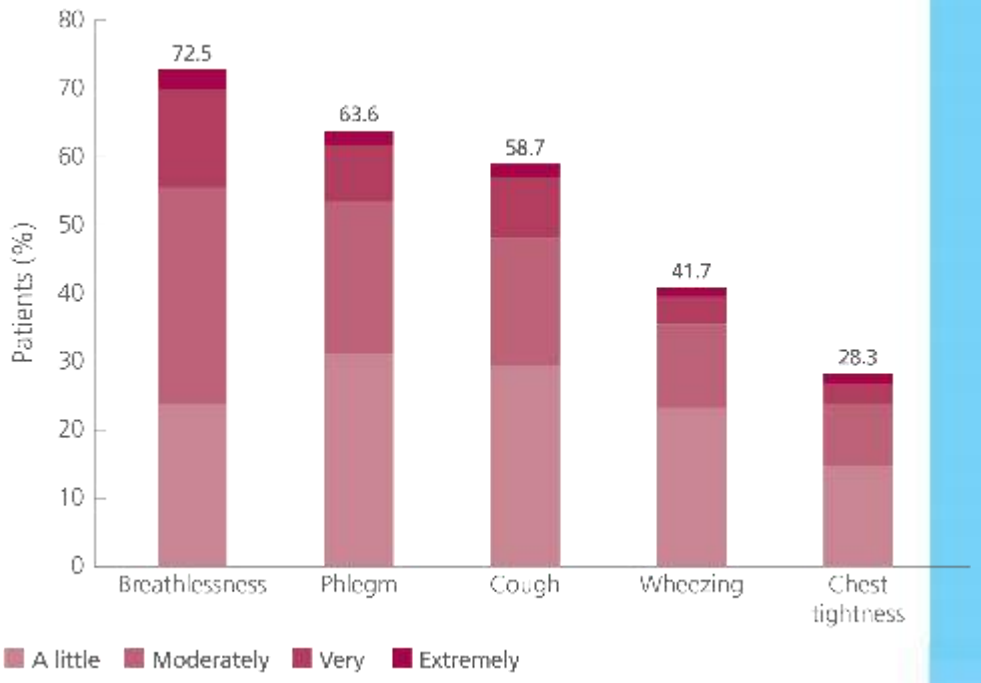
This Executive Summary of the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) 2017 Report focuses primarily on the revised and novel parts of the document. The most significant changes include: i) the assessment of COPD has been refined to separate the spirometric assessment from symptom evaluation. ABCD groups are now proposed to be derived exclusively from patient symptoms and their history of exacerbations; ii) for each of the groups A to D, escalation strategies for pharmacological treatments are proposed; iii) the concept of de-escalation of therapy is introduced in the treatment assessment scheme; iv) nonpharmacologic therapies are comprehensively presented and; v) the importance of comorbid conditions in managing COPD is reviewed.

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

La dispnea è il sintomo prevalente e rilevante nel paziente BPCO

- La dispnea è uno dei sintomi principali della BPCO ed è una delle maggiori cause di disabilità ed ansietà legata alla patologia[1]
- La dispnea è un sintomo che deriva da un complesso meccanismo fisiopatologico[2,3]
- La dispnea contribuisce in modo significativo al peso della malattia e alla bassa qualità di vita dei pazienti[3]
- In uno studio su 2,441 pazienti affetti da BPCO in 17 paesi europei, la dispnea è stata riferita come il sintomo più frequente lamentato dai pazienti (72.5%)

Variabilità dei sintomi in pazienti con BPCO grave: Studio cross-sectional paneuropeo[1]



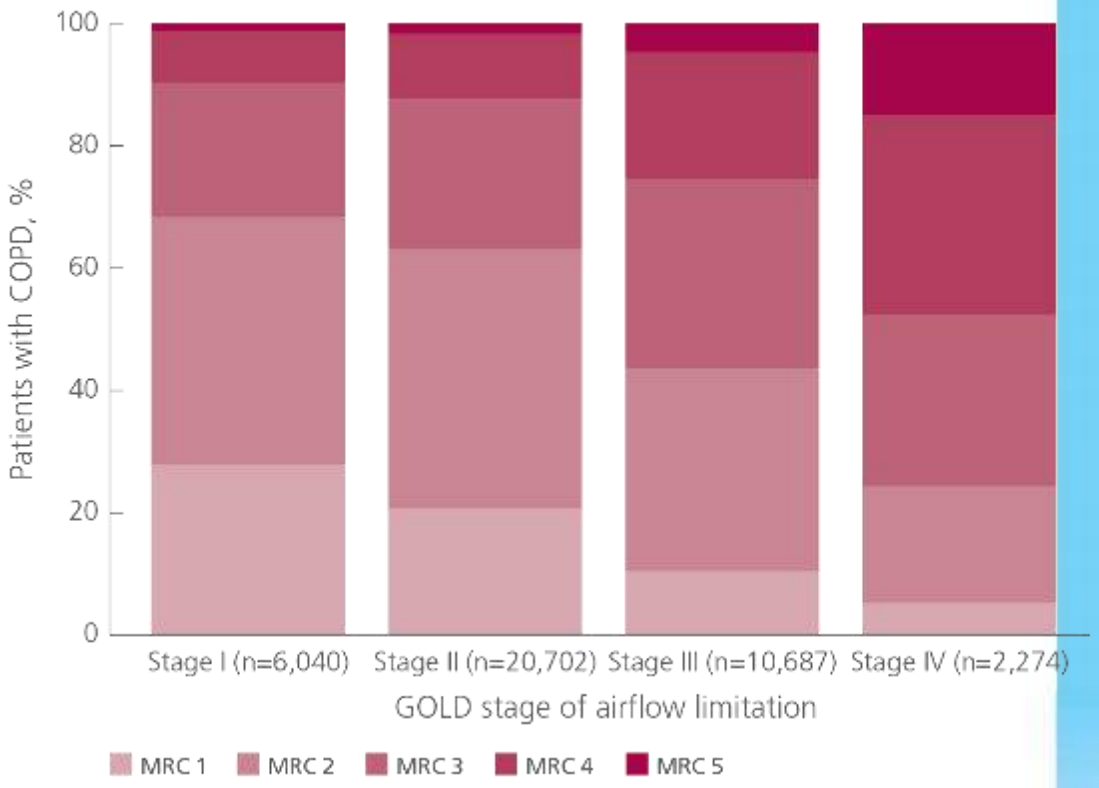
La dispnea è un sintomo frequente che impatta negativamente sulla vita del paziente BPCO

1 Jolley CJ & Moxham J. Eur Respir Rev 2009; 18: 66−79. 2. Booth S et al. Expert Rev Respir Med 2009; 3: 21−36. 3. Burgel PR et al. Respir Med 2013; 107: 233−241..

Una alta prevalenza di dispnea è presente in tutti i gradi di severità di BPCO

- In uno studio su 49,438 pazienti affetti da COPD, il 46% dei pazienti (pari a 22,770 unità) lamentano un livello di dispnea da moderato a grave (mMRC≥3)
- La dispnea aumenta con la maggiore limitazione broncostruttiva
- Inoltre una dispnea moderata-grave è stata osservata nel 32% dei pazienti con una ostruzione lieve

Punteggio del MRC: distribuzione sulla base della severità del grado di ostruzione[1]



La dispnea è frequente anche nei pazienti che presentano una ostruzione lieve-moderata

Müllerová H et al. PLoS One 2014; 9: e85540.

Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD

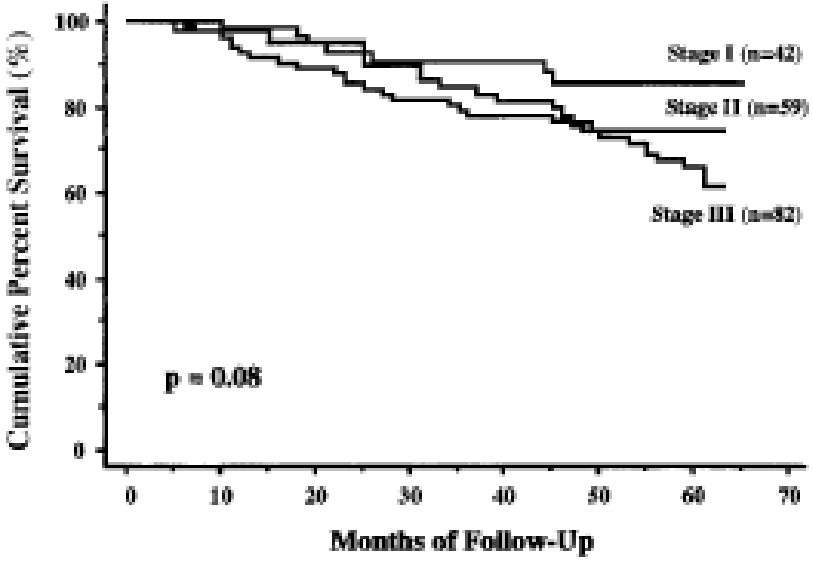


FIGURE 1. Five-year survival according to the staging of disease severity as defined by the ATS guideline evaluated by the percentage of predicted FEV_1.

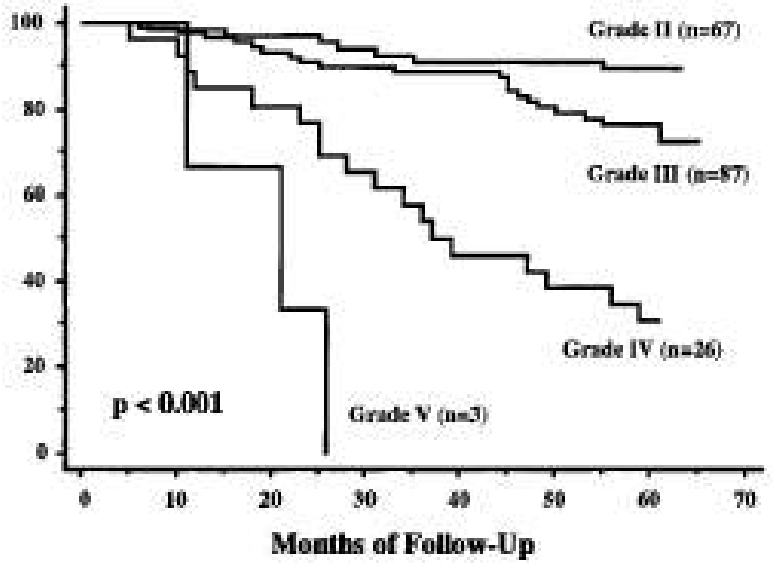
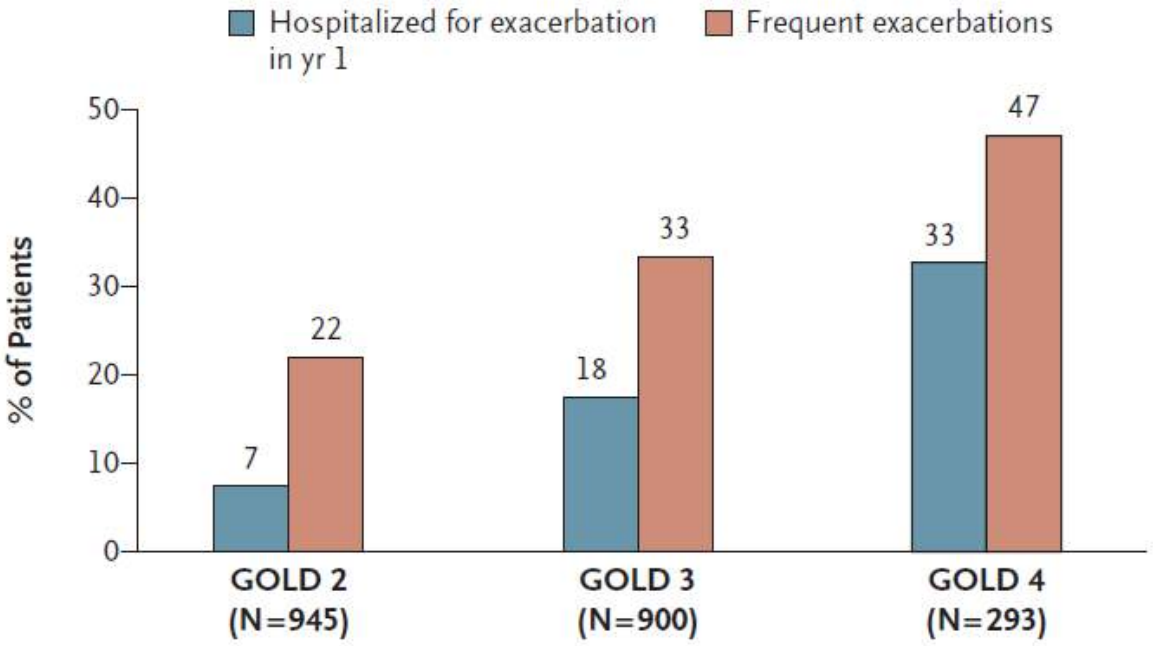


FIGURE 2. Five-year survival according to the level of dyspnea as evaluated by the modified 5-point grading system of Fletcher et al.[10]

Conclusions: The categorization of patients with COPD on the basis of the level of dyspnea was more discriminating than staging of disease severity using the ATS guideline with respect to 5-year survival. Dyspnea should be included as one of the variables, in addition to airway obstruction, for evaluating patients with COPD in terms of mortality.

Nishimura K, et al. Chest 2002; 121: 1434-1440



30%

Paziente Frequente Riacutizzatore

70%

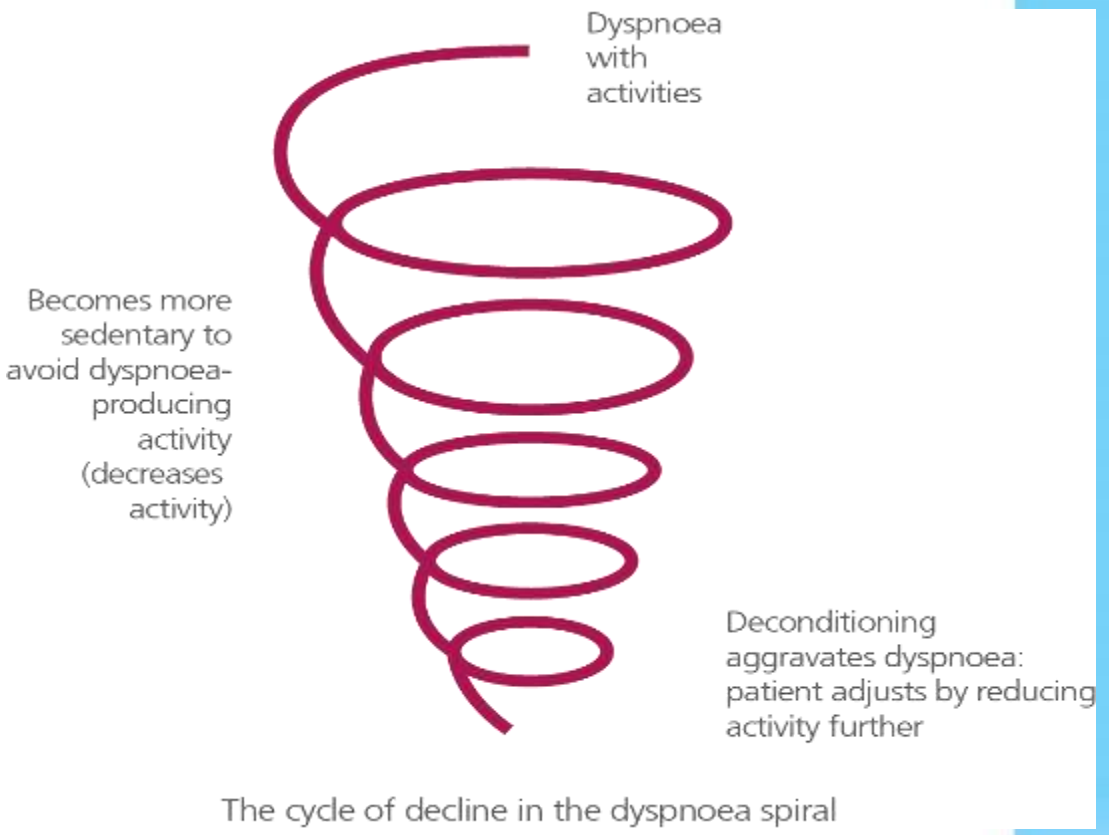
Paziente Sintomatico (prevalentemente limitazione alle attività quotidiane, dispnea da sforzo)

Hurst et al, N Engl J Med 2010;363:1128-38.

La dispnea è legata ad una spirale negativa per la salute

- I pazienti con BPCO, spesso inconsciamente, riducono le loro attività fisiche per ridurre l'intensità dei sintomi[1,2]

- Tale riduzione dell'attività fisica porta ad una vita sedentaria e questo aumenta ulteriormente la dispnea[1,2] per un effetto di decondizionamento dell'abitudine all'esercizio fisico

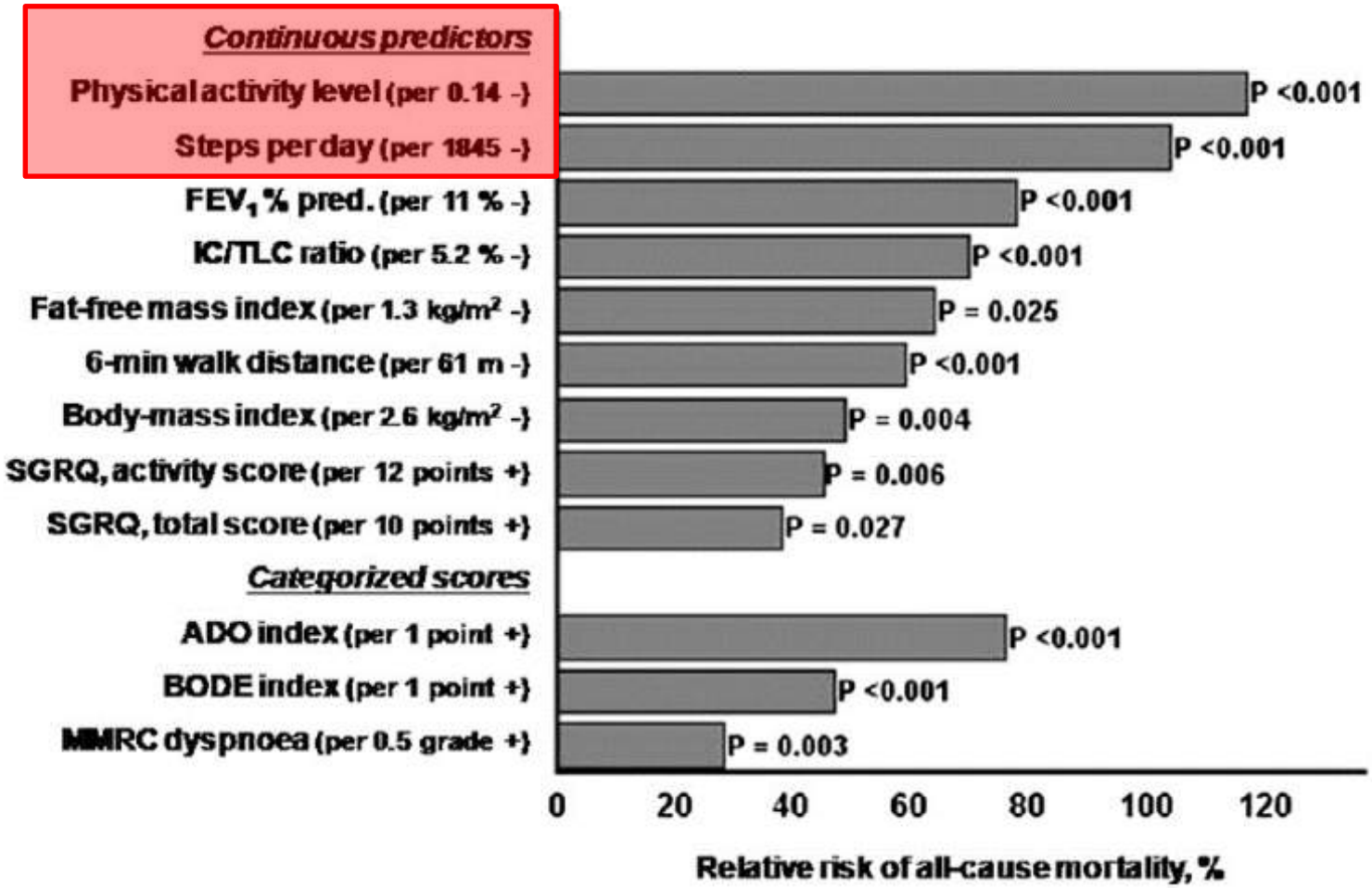


The cycle of decline in the dyspnoea spiral

La dispnea porta al decondizionamento all'attività fisica

1. Reardon JZ, Lareau SC, ZuWallack R. Am J Med 2006: 119; S32-S37. 2. ZuWallack R. COPD 2007: 4; 293–297.

Chi si ferma è perduto?



La riduzione della capacità fisica è un predittore del rischio di mortalità da tutte le cause nel paziente BPCO

Waschki B et al, Chest. 2011 Aug;140(2):331-42

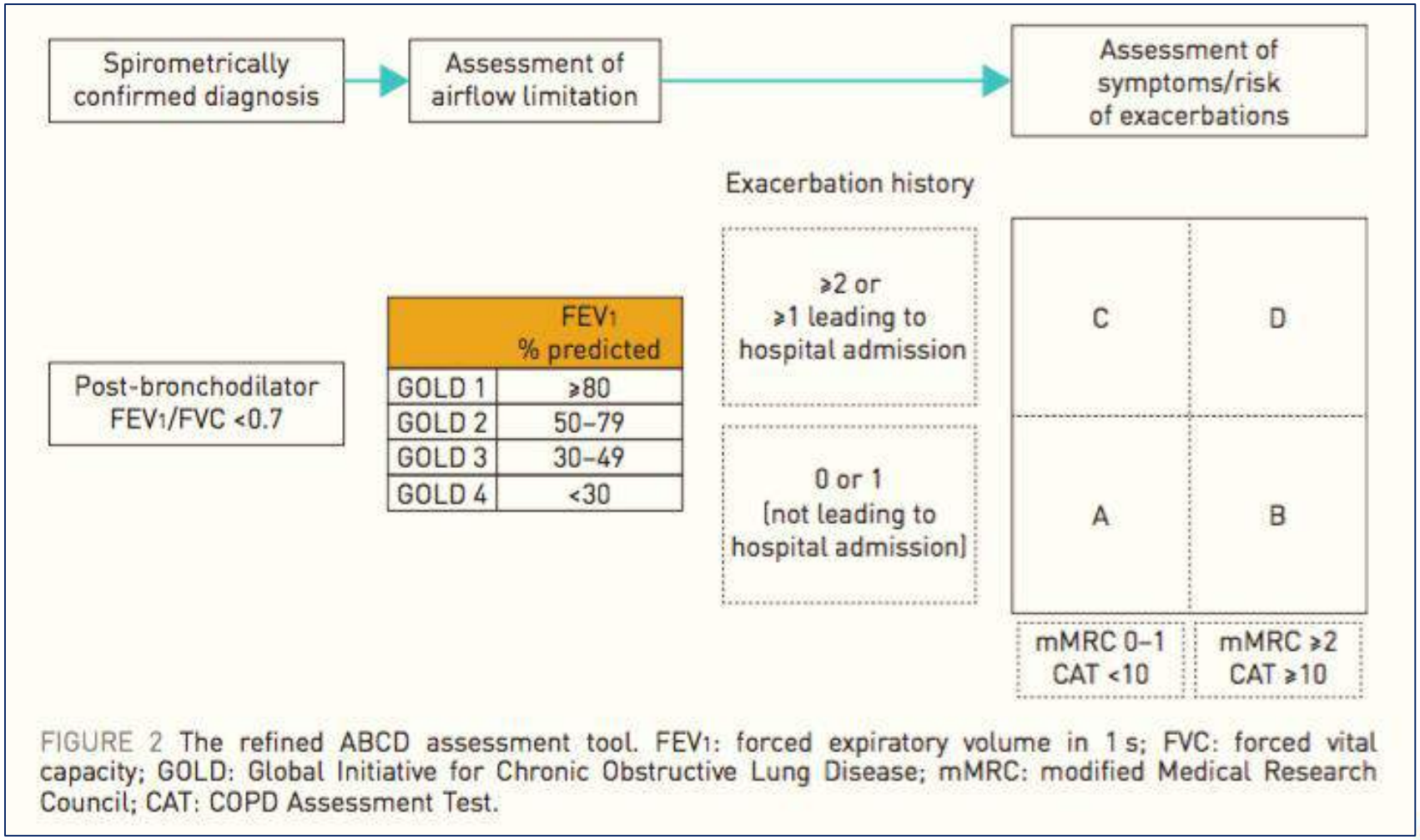


FIGURE 2 The refined ABCD assessment tool. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; CAT: COPD Assessment Test.

GOLD 2017

È ampiamente dimostrato che la terapia farmacologica regolare nella BPCO può:

- Migliorare la funzione respiratoria
- Migliorare la dispnea e la tolleranza all'esercizio fisico
- Rallentare il progressivo declino funzionale
- Diminuire la frequenza e la gravità delle riacutizzazioni
- Diminuire il numero delle ospedalizzazioni

La broncodilatazione rappresenta la priorità nella terapia farmacologica della BPCO in fase di stabilità.

I farmaci broncodilatatori a lunga durata d'azione, somministrati per via inalatoria rappresentano la prima scelta per la terapia regolare della BPCO in fase di stabilità.

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

La scelta terapeutica deve essere adeguata per la singola persona e guidata dalle caratteristiche e dalla gravità del quadro clinico considerato nel suo insieme di sintomi, funzione respiratoria, complicanze, comorbilità e delle peculiarità individuali (fenotipo) della persona che ne è affetta.

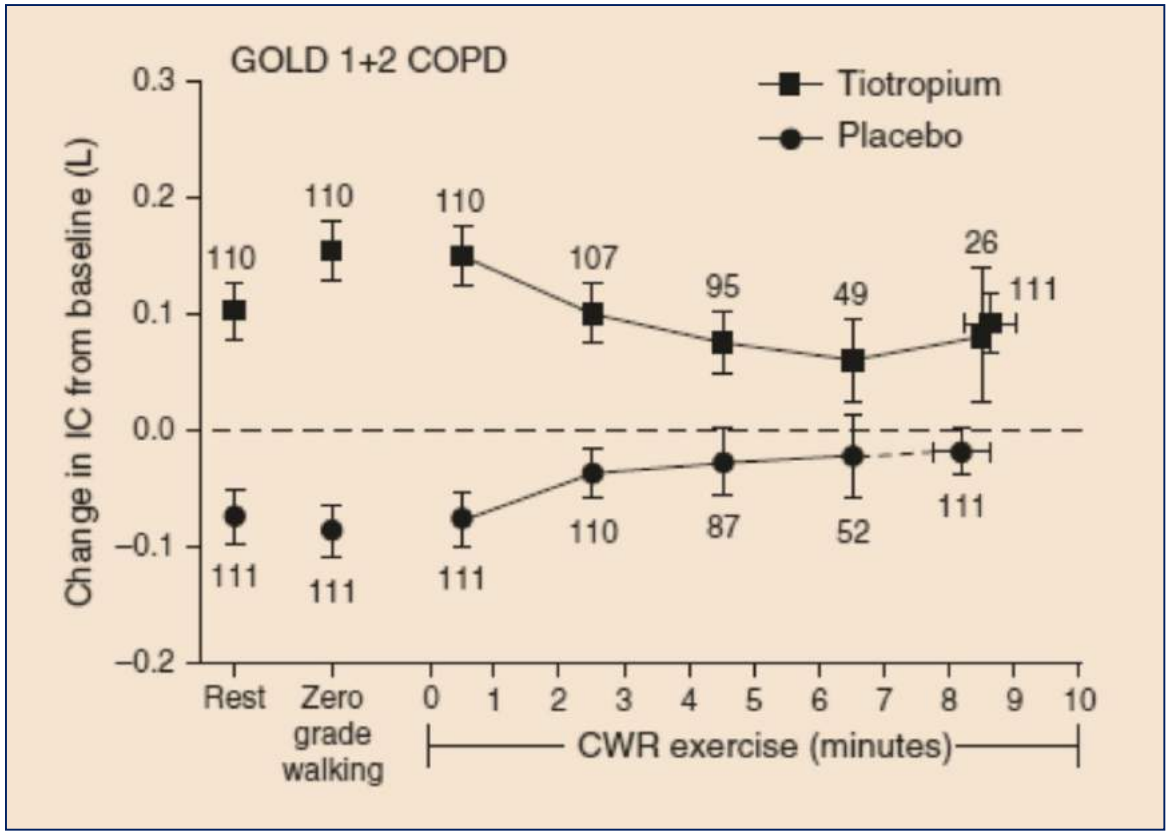
The scientific rationale for combining long-acting β_2-agonists and muscarinic antagonists in COPD

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

Nelle persone con diagnosi di BPCO che abbiano sintomi quali ad esempio la ridotta tolleranza all'esercizio fisico e/o dispnea da sforzo (≥ grado 1 MMRC), anche in presenza di un VEMS o FEV_1 pre-broncodilatatore ≥ 80% del valore teorico si può considerare il trattamento con farmaci broncodilatatori.

Effects of Tiotropium on Hyperinflation and Treadmill Exercise Tolerance in Mild to Moderate COPD

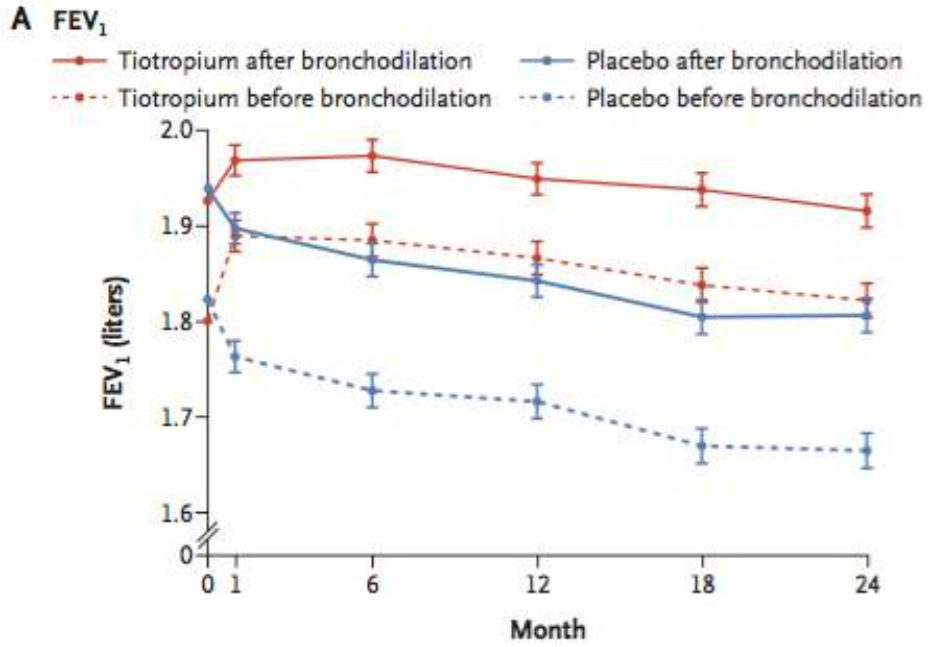


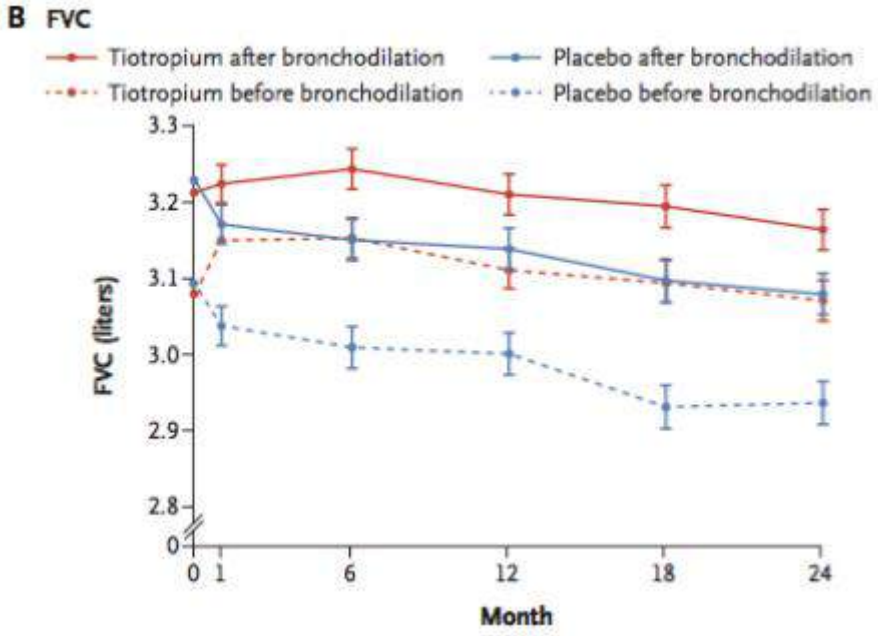
GOLD 1 and **GOLD 2** COPD who experienced IC decrease greater than 100 ml during incremental and constant work treadmill exercise

CWR = constant work rate

Casaburi R, et al. Ann Am Thorac Soc 2014

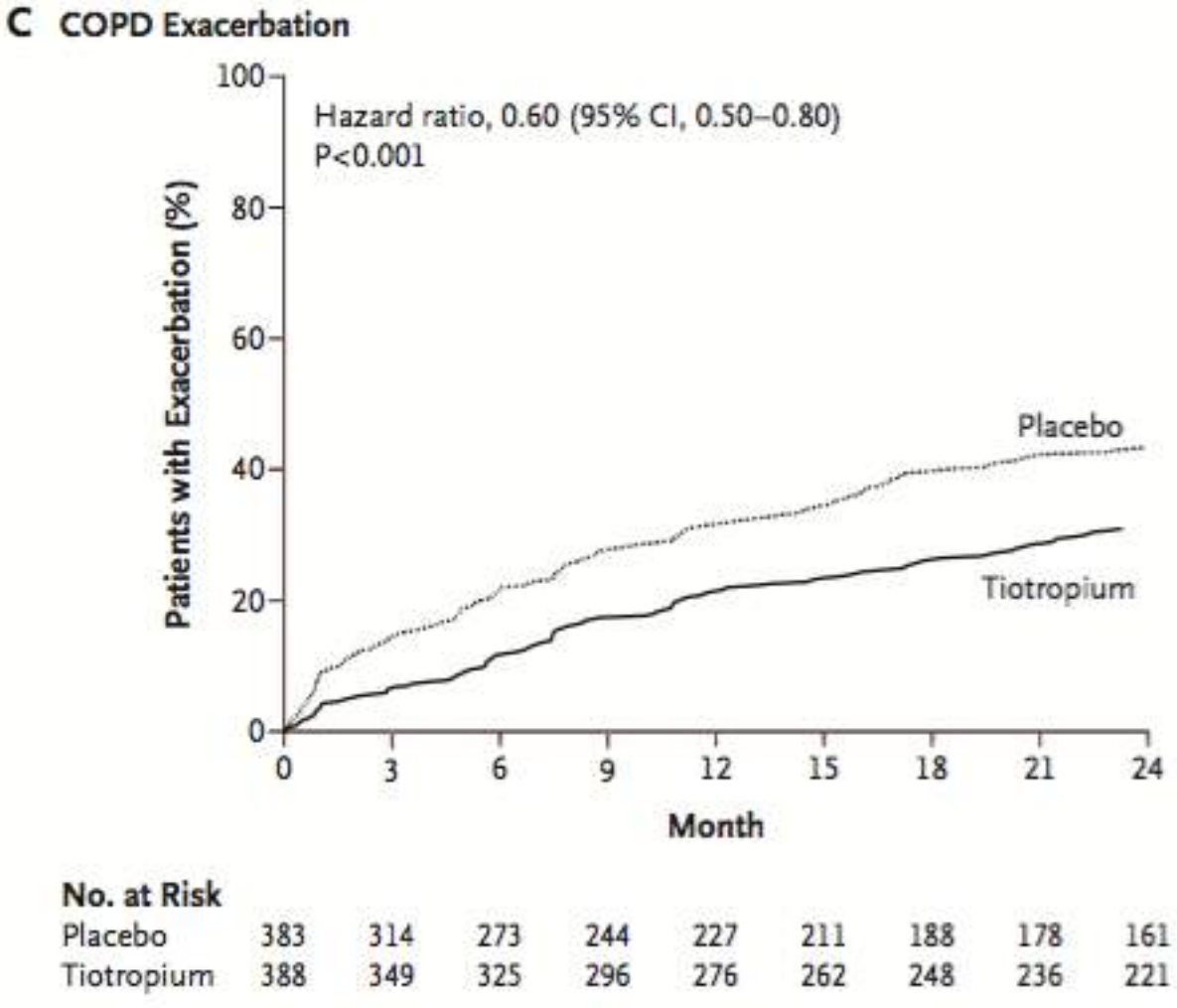
Tiotropium in Early-Stage COPD





Zhou Y, et al. N J Med 2017;377:923-35. Engl

Tiotropium in Early-Stage COPD



Zhou Y, et al. N J Med 2017;377:923-35. Engl

Nelle persone con sintomi e diagnosi di BPCO e VEMS o FEV_1 pre-broncodilatatore < 80% del valore teorico, attuare il trattamento regolare continuativo con un broncodilatatore a lunga durata d'azione per via inalatoria.

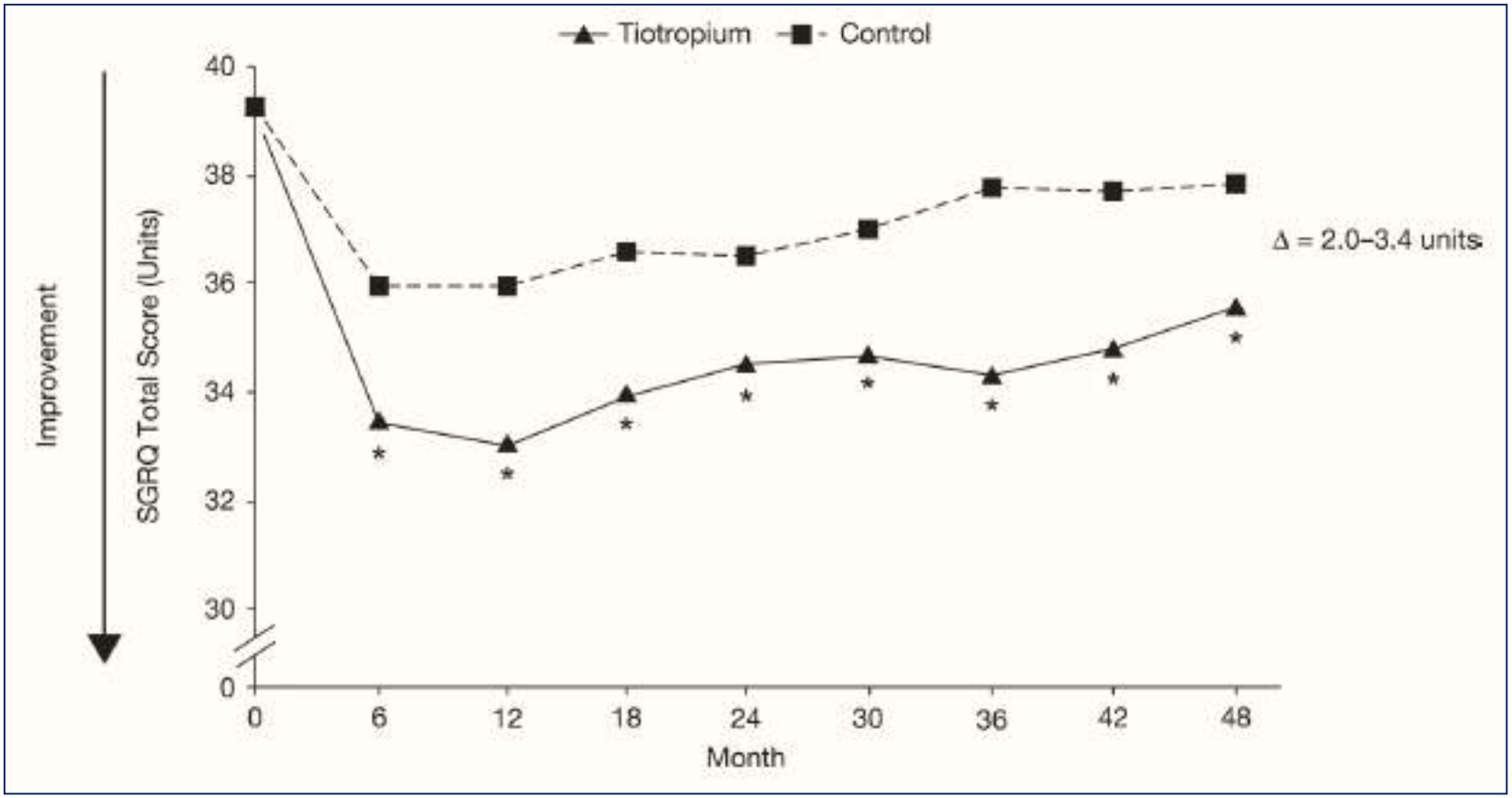
LABA: Long Acting Betadrenergic Agonists

indacaterolo, formoterolo, salmeterolo

LAMA: Long Acting Muscarinic Antagonists

tiotropio, glicopirronio, aclidinio

Efficacy of Tiotropium in COPD Patients with $FEV_1 \geq 60\%$ participating in the UPLIFT® Trial - *SGRQ~40*



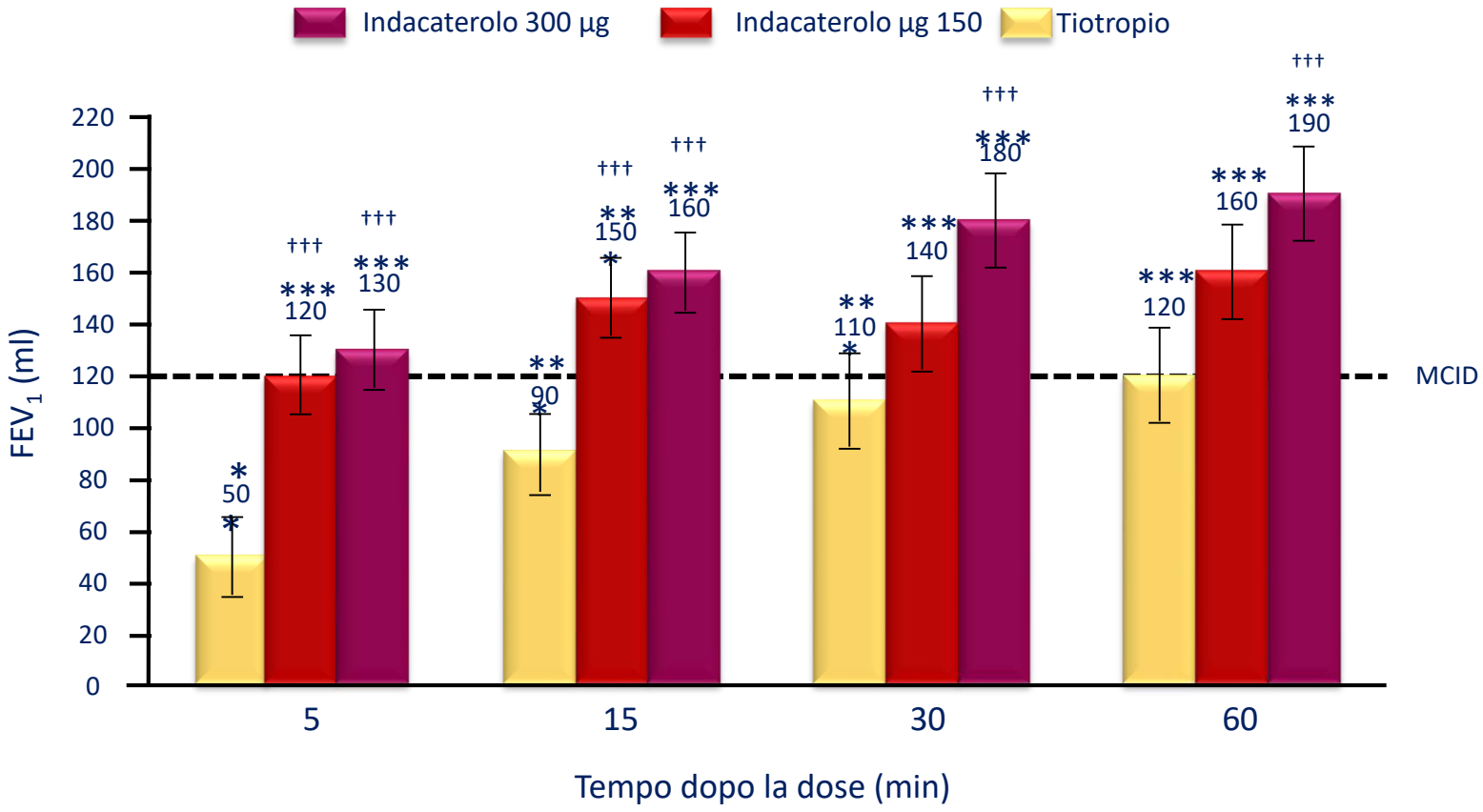
Tashkin DP, et al J COPD 2012

GOLD Stage II: Exacerbations

	Tiotropium (n=1384)	Control (n=1355)	Ratio (95% CI)	*P*-value
Time to first exacerbation (month)	23.1 (21.0, 26.3)	17.5 (15.9, 19.7)	0.82 (0.75, 0.90)*	<0.0001*
Mean number of exacerbations/pt yr (95% CI)	0.56 (0.52, 0.60)	0.70 (0.65, 0.75)	0.80 (0.72, 0.88)†	<0.0001†
Mean number of hospitalizations for exacerbations/ pt yr (95% CI)	0.08 (0.07, 0.09)	0.10 (0.08, 0.12)	0.80 (0.63, 1.03)†	0.082†

*Hazard ratio (control vs. tiotropium) and *P*-value were estimated using Cox regression.
†Rate ratio (tiotropium/control) and *P*-value were estimated using the Poisson with Pearson overdispersion model adjusting for treatment exposure.

Decramer et al. Lancet 2009; 374: 1171-78

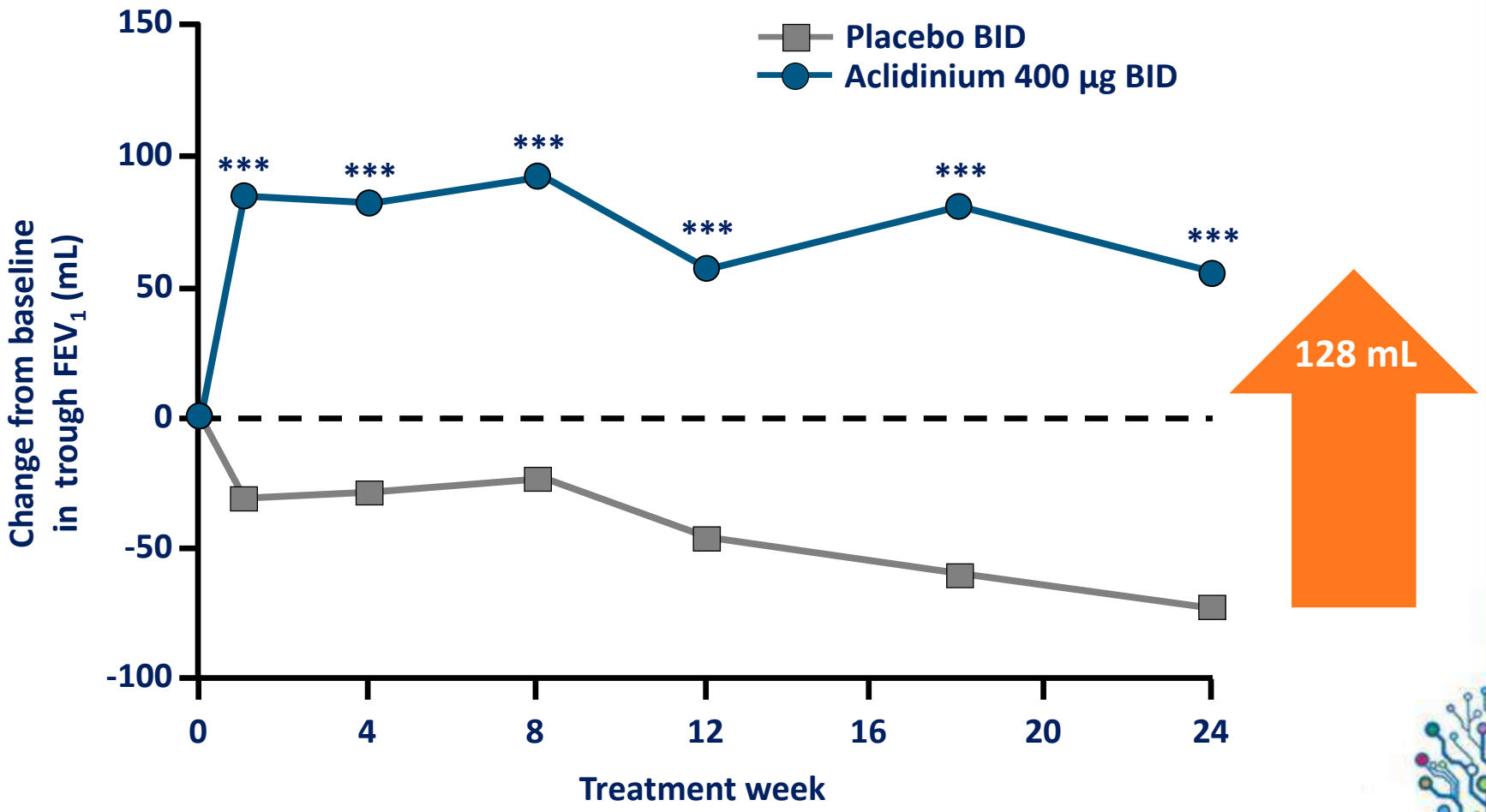


**p<0,01; ***p<0,001 vs placebo. †††p<0,05 vs tiotropio

Aumenti rispetto al basale a 5 min post-dose: 60 ml (4,4%) con tiotropio, 130 ml (9,7%) con indacaterolo 150 µg e 140 ml (10,2%) con indacaterolo 300 µg.

Vogelmeier et al. Respiratory Research 2010

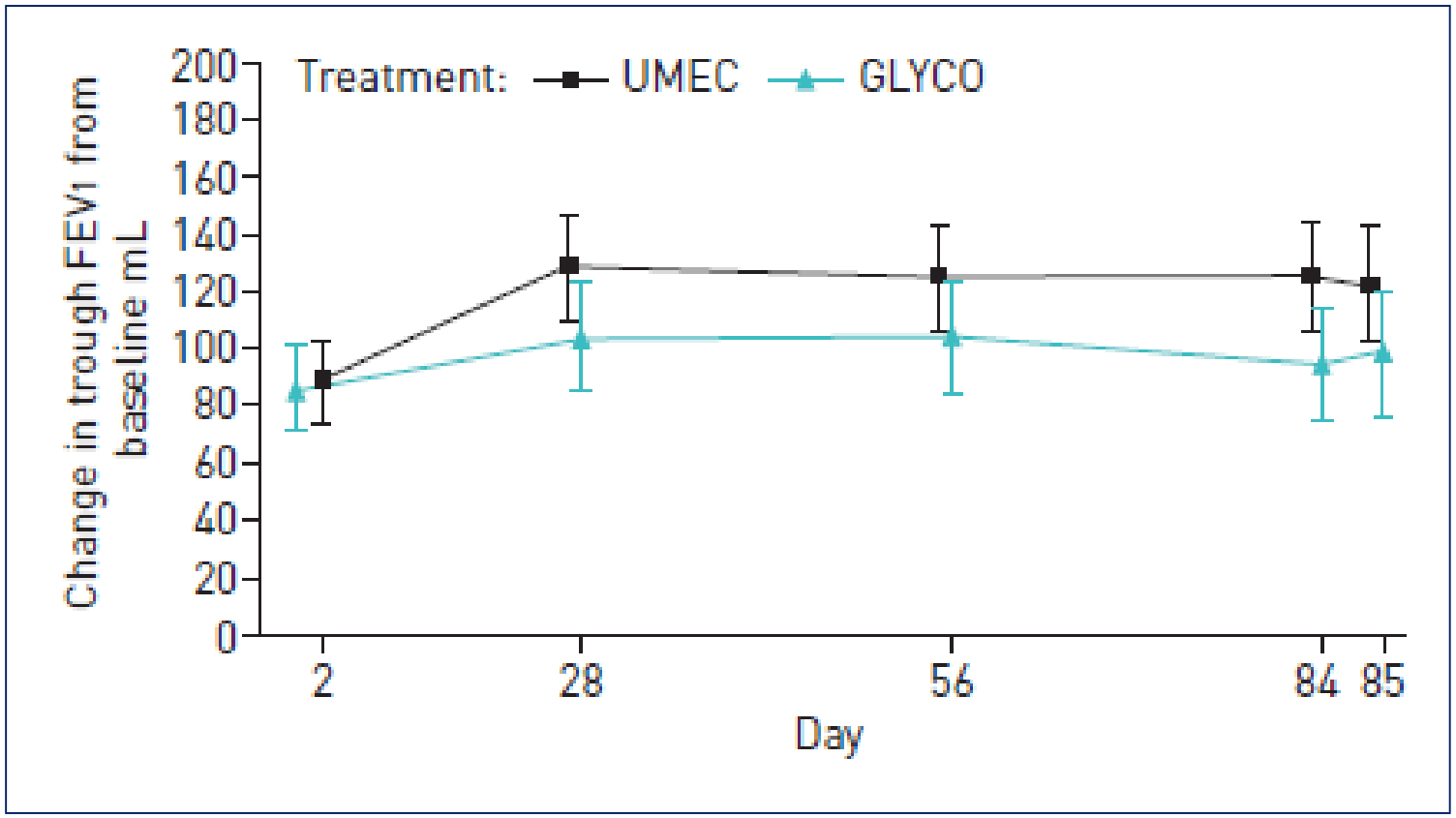
Aclidinium improves trough FEV_1:



***p < 0.001 vs placebo

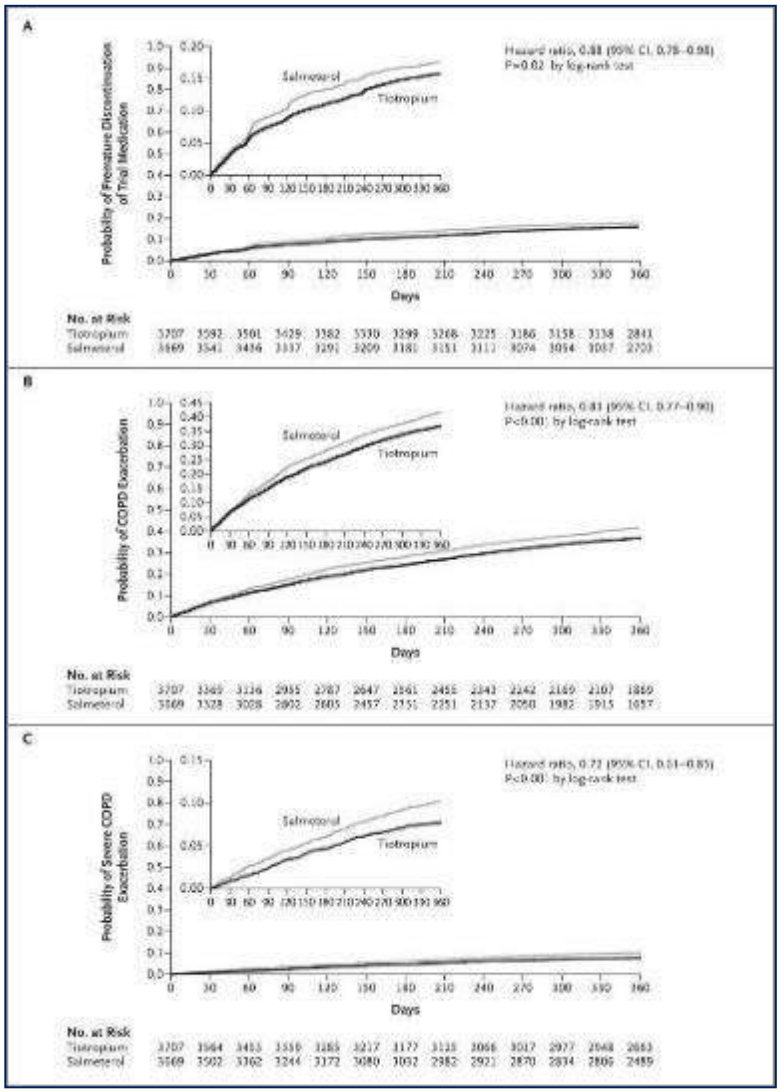
Jones et al, Eur Respir J 2012

A randomised, open-label study of umeclidinium versus glycopyrronium in patients with COPD



Eur Resp J Open research 2016

Kaplan–Meier Curves for the Primary and Selected Secondary Outcomes.



These results show that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations.

LAMA per riacutizzatori

Vogelmeier C et al. N Engl J Med 2011;364:1093-1103

Nelle persone in regolare trattamento farmacologico, valutare ad ogni visita programmata:

- la corretta e regolare assunzione della terapia
- la valutazione dei sintomi ed in particolare, la tolleranza all'esercizio fisico e la dispnea da sforzo
- le modificazioni della funzione polmonare non solo in termini di FEV_1 ma anche di altri parametri come i volumi polmonari e la DLCO
- la frequenza con la quale la persona ricorre a broncodilatatori a breve durata d'azione come supporto occasionale

- la frequenza e gravità degli episodi di riacutizzazione
- la frequenza e la durata degli episodi di ospedalizzazione
- la frequenza e la gravità di eventuali eventi collaterali e/o avversi

Nel caso di risultato giudicato insoddisfacente da parte della persona con BPCO e/o dal medico curante in termini di:

- sintomatologia
- funzionalità respiratoria
- riacutizzazioni e ospedalizzazioni
- eventi avversi

<u>considerare</u>:

- l'aumento della dose del singolo broncodilatatore se e come previsto nella scheda tecnica del farmaco in uso;
- l'aggiunta di un secondo broncodilatatore a lunga durata d'azione, con meccanismo d'azione differente;
- l'aggiunta di un cortisteroide per via inalatoria in presenza di frequenti riacutizzazioni.

Group B

Initial therapy should be a long acting bronchodilator. Long-acting bronchodilators are superior to short-acting bronchodilators taken intermittently.

There is no evidence to recommend one class of long-acting bronchodilators over another for symptom relief; the choice should depend on individual patient response.

For patients with persistent breathlessness on monotherapy the use of two bronchodilators is recommended. For patients with severe breathlessness, initial therapy with two bronchodilators may be considered.

GOLD 2017

Group C

Initial therapy should be a single long-acting bronchodilator. In two head-to-head comparisons the LAMA tested superior to the LABA regarding exacerbation prevention, therefore we recommend initiating a LAMA in this group.

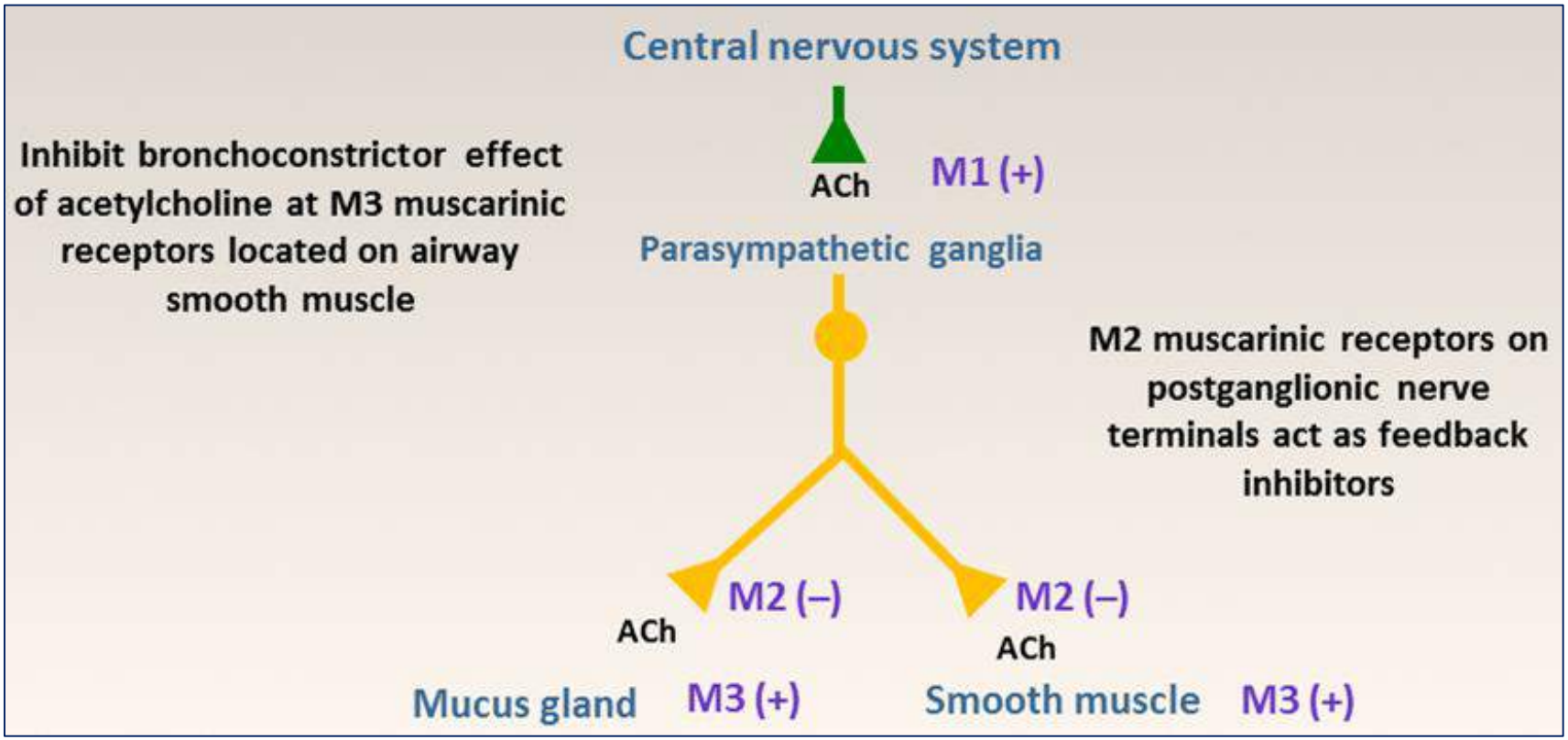
Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LABA/LAMA), or using LABA/ICS.

As ICS increases the risk for developing pneumonia, our primary choice is LABA/LAMA.

GOLD 2017

Razionale della doppia broncodilatazione

Perché combinare le terapie broncodilatanti? Meccanismo d'azione degli antagonisti muscarinici

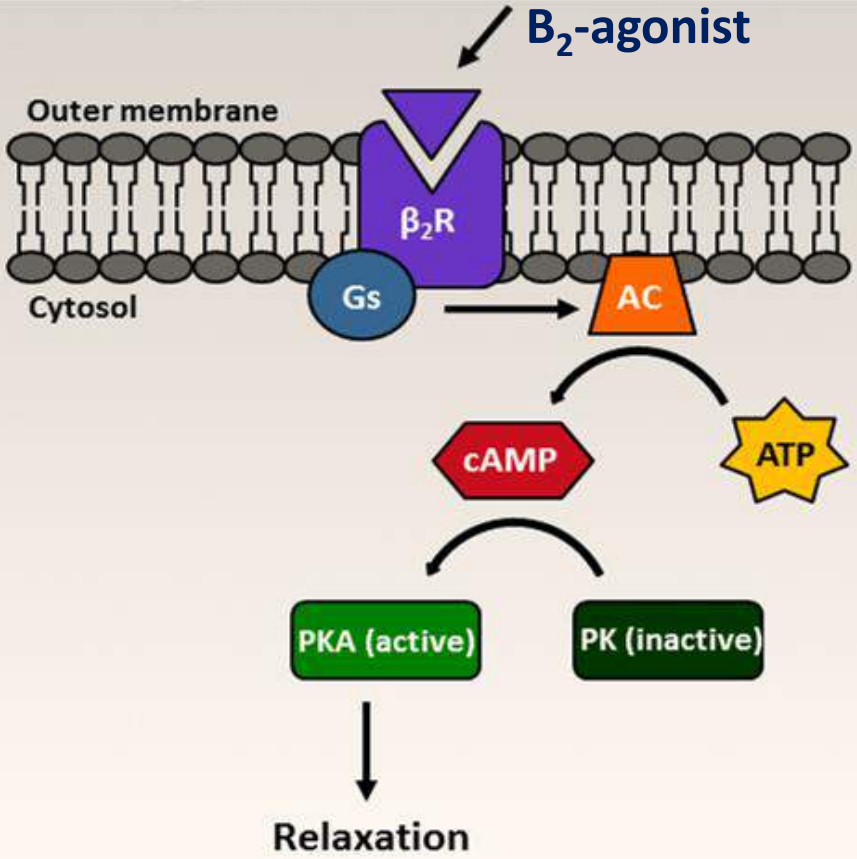


Gli antagonisti muscarinici bloccano i recettori M_1 e M_3 per prevenire il legame dell'acetilcolina ed inibire la contrazione della muscolatura liscia delle vie aeree.

Roux et al. Gen Pharmac 1998

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

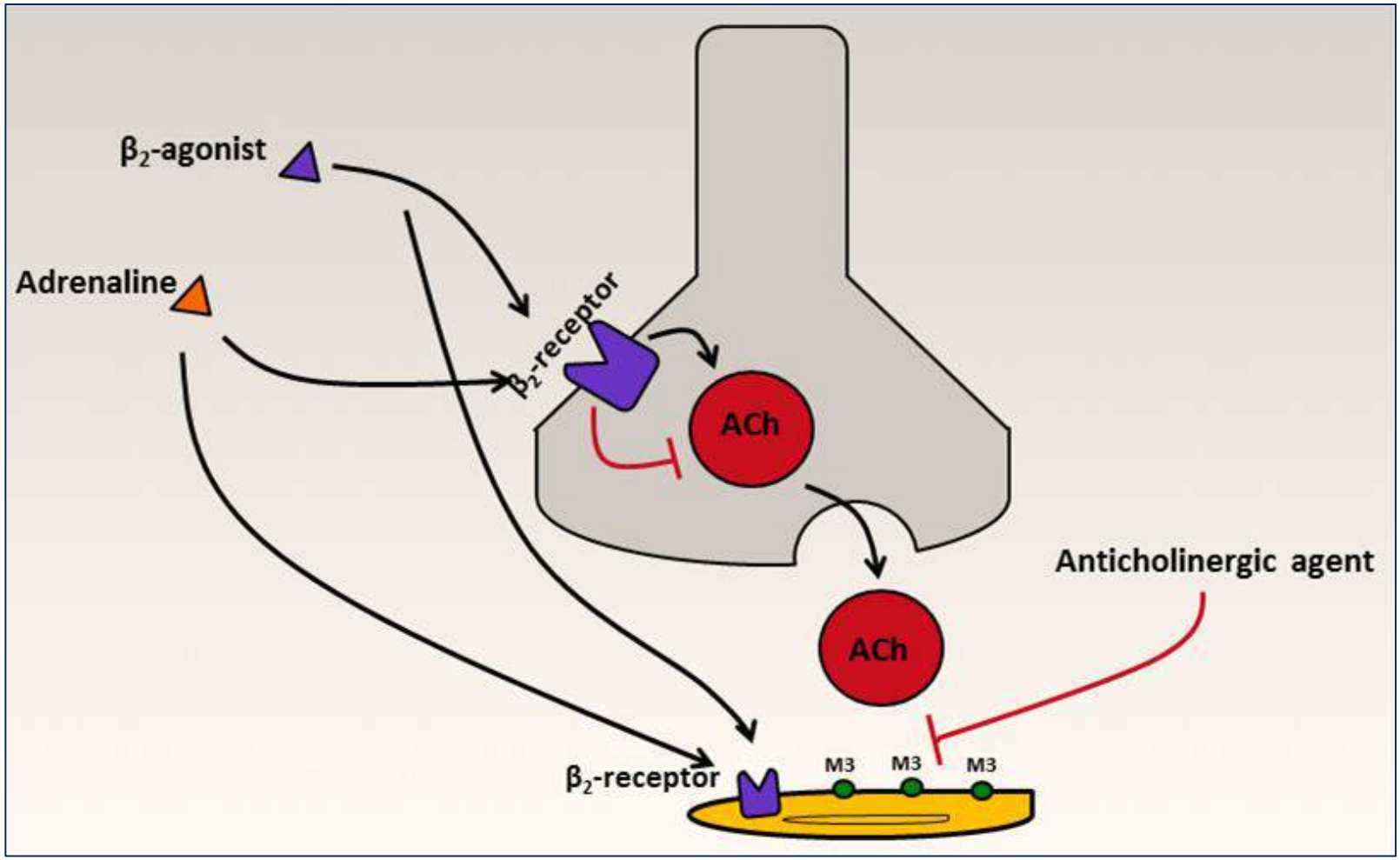
Directly activate β_2 receptors in bronchioles, leading to increase in cAMP, relaxation of smooth muscle, and bronchodilation



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

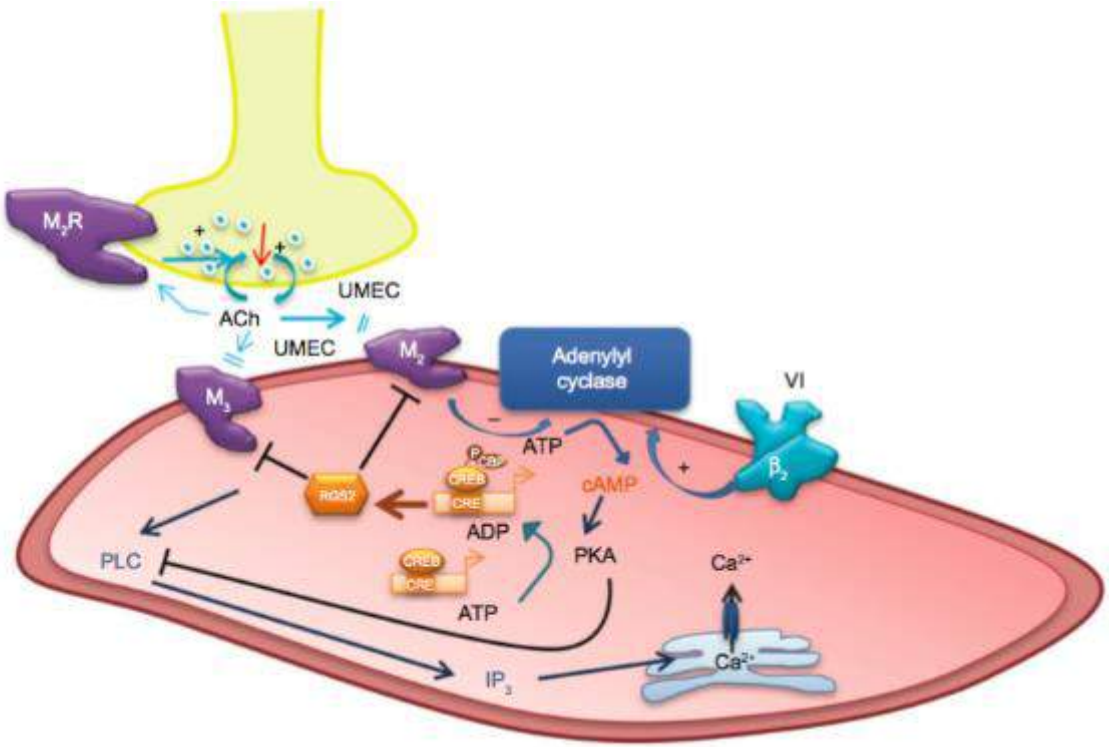
Johnson M. *Am J Respir Crit Care Med*. 1998;158(5 Pt 3):S146-153.

LABA/LAMA combination: interaction between Receptors and Neurotransmission pathways



Cazzola M, et al. Arch Bronconeumol 2005

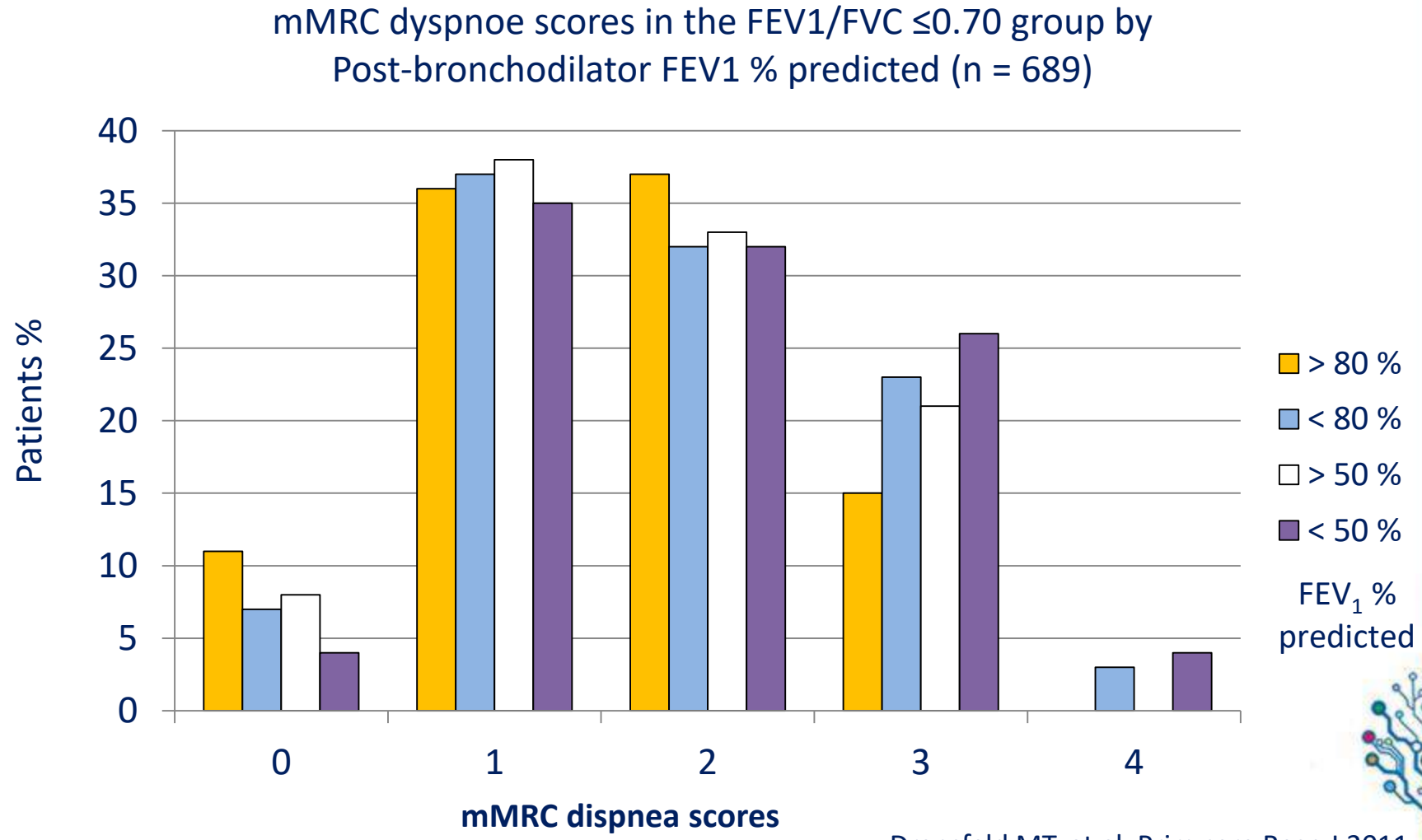
Intracellular interactions of umeclidinium and vilanterol in human airway smooth muscle



Conclusion: These data indicate that UMEC reverses cholinergic inhibition of VI-induced cAMP production, and is a more potent muscarinic receptor antagonist when in combination with VI versus either alone.

Nooreen Shaikh, et al. Int J COPD 2017

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

Terapia della combinazione LABA/LAMA

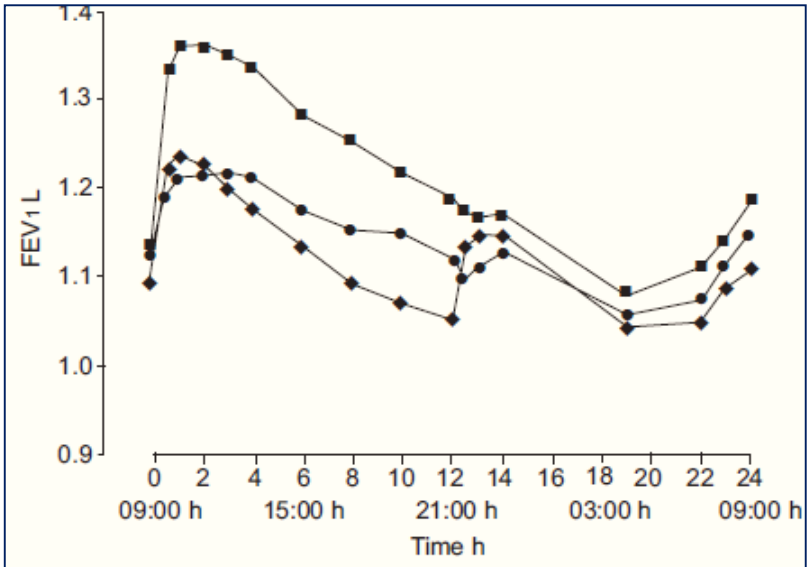


FIGURE 2. Mean forced expiratory volume in one second (FEV_1; adjusted for period, centre and patient within centre) before and during 24 h after the inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

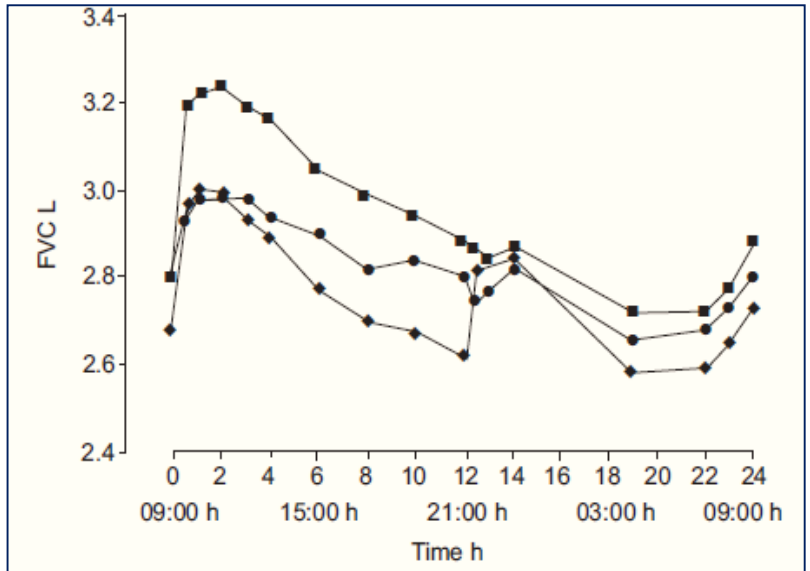
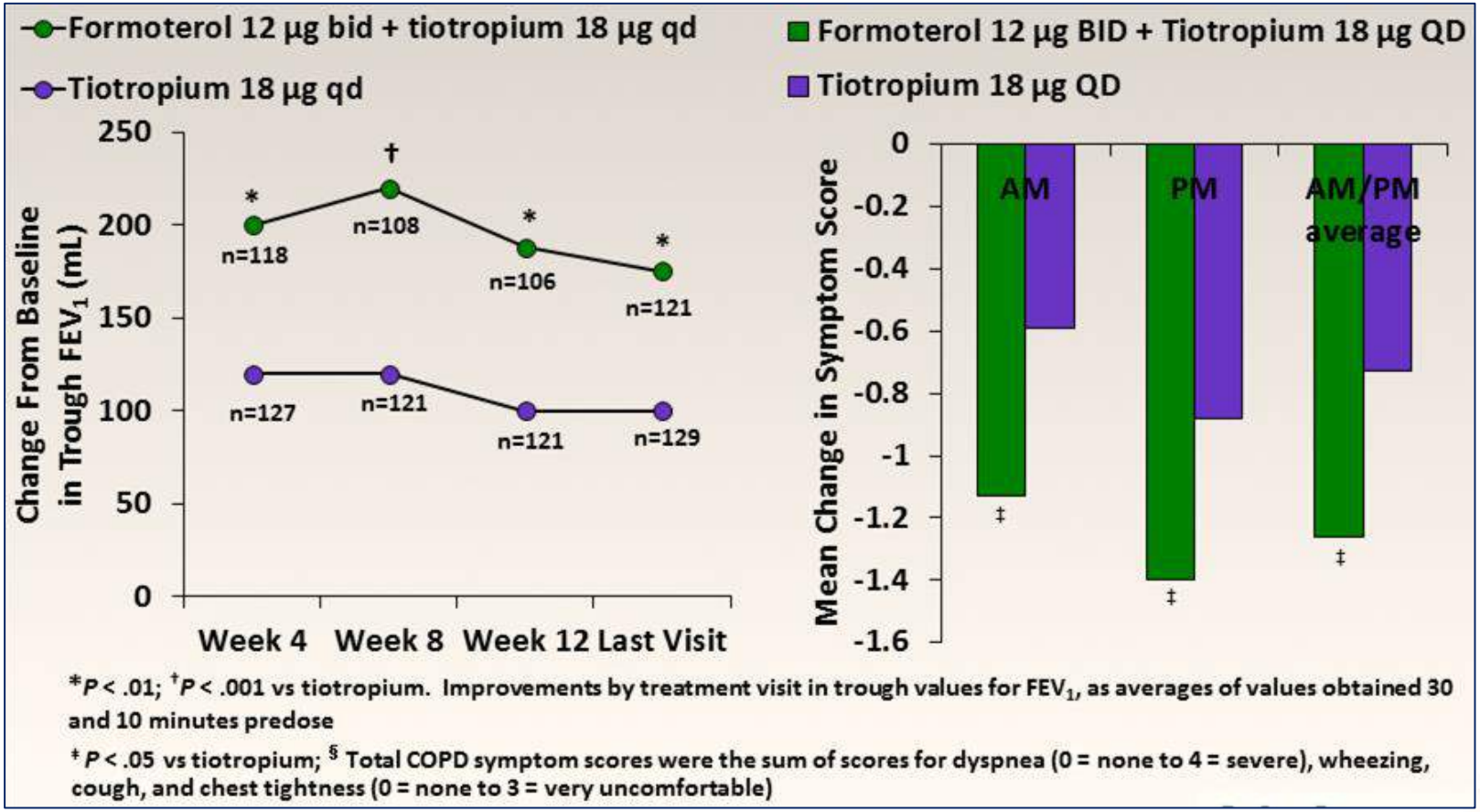


FIGURE 3. Mean forced vital capacity (FVC; adjusted for period, centre and patient within centre) before and during 24 h after inhalation of tiotropium *q.d.* (●), formoterol *b.i.d.* (◆), and tiotropium plus formoterol *q.d.* (■) at the end of the 6-week treatment periods.

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

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

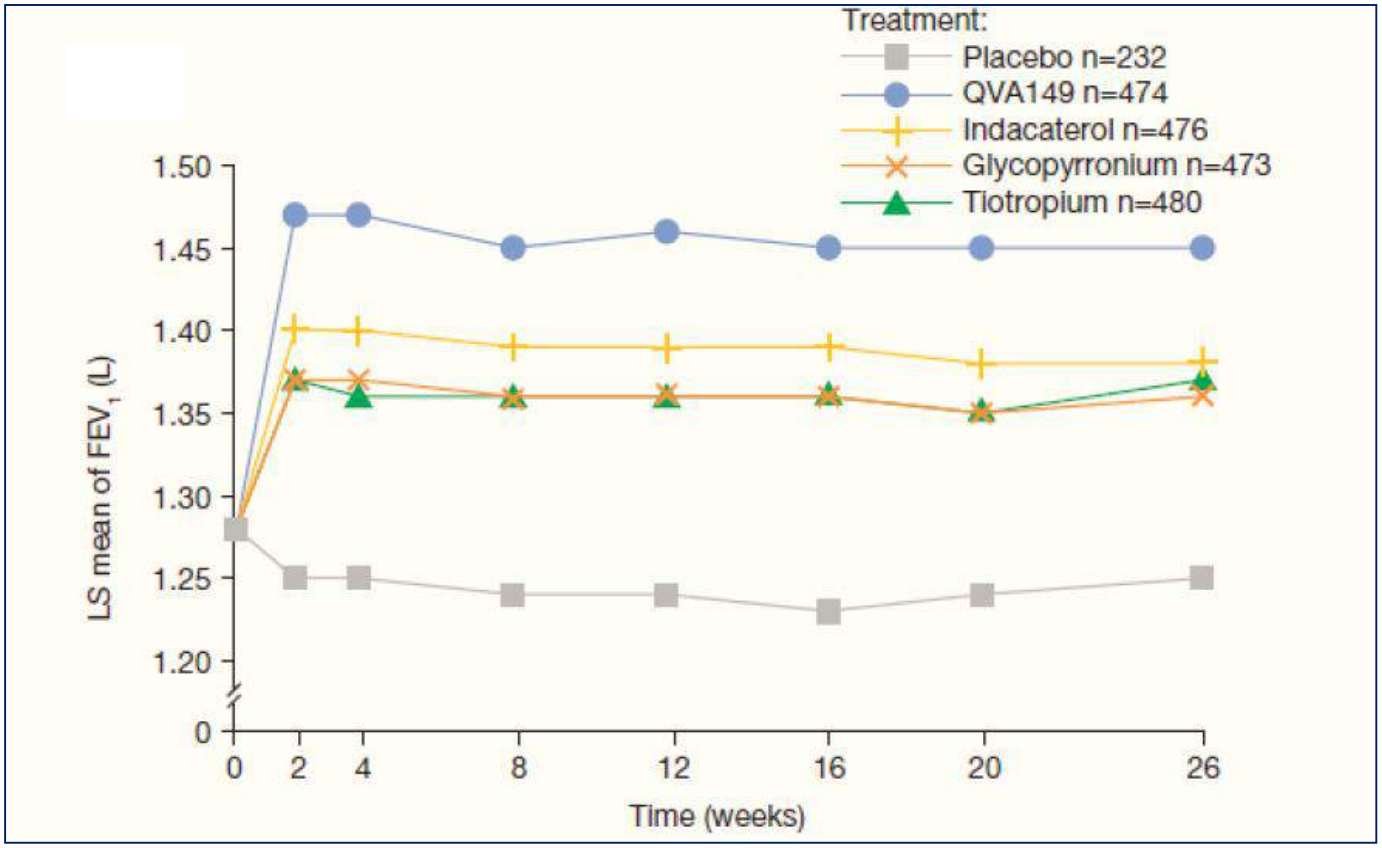


*$P < .01$; †$P < .001$ vs tiotropium. Improvements by treatment visit in trough values for FEV_1, as averages of values obtained 30 and 10 minutes predose

‡$P < .05$ 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

Dual bronchodilation with QVA149: the SHINE study

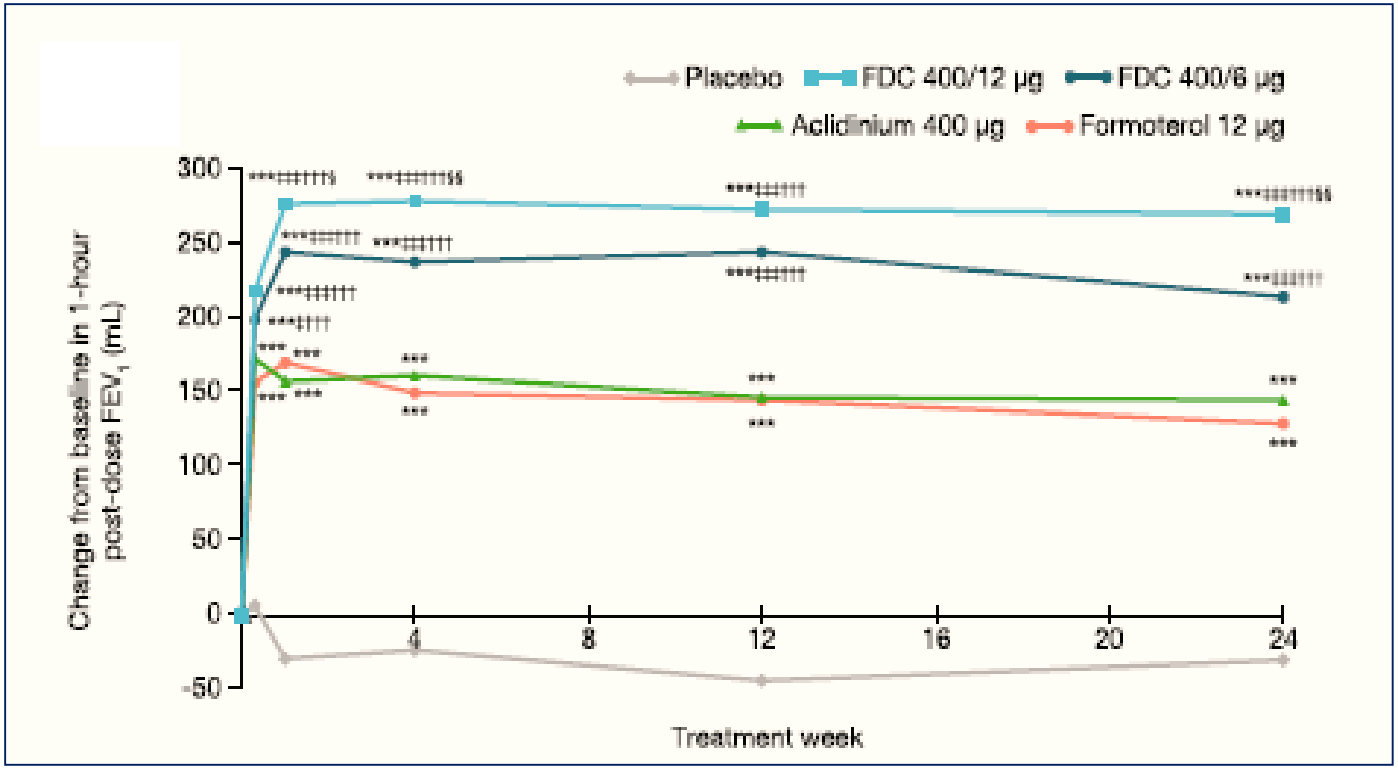


QVA149 was superior to all active treatments and placebo at all timepoints (all $p < 0.001$).

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

Bateman et al Eur Respir J. 2013

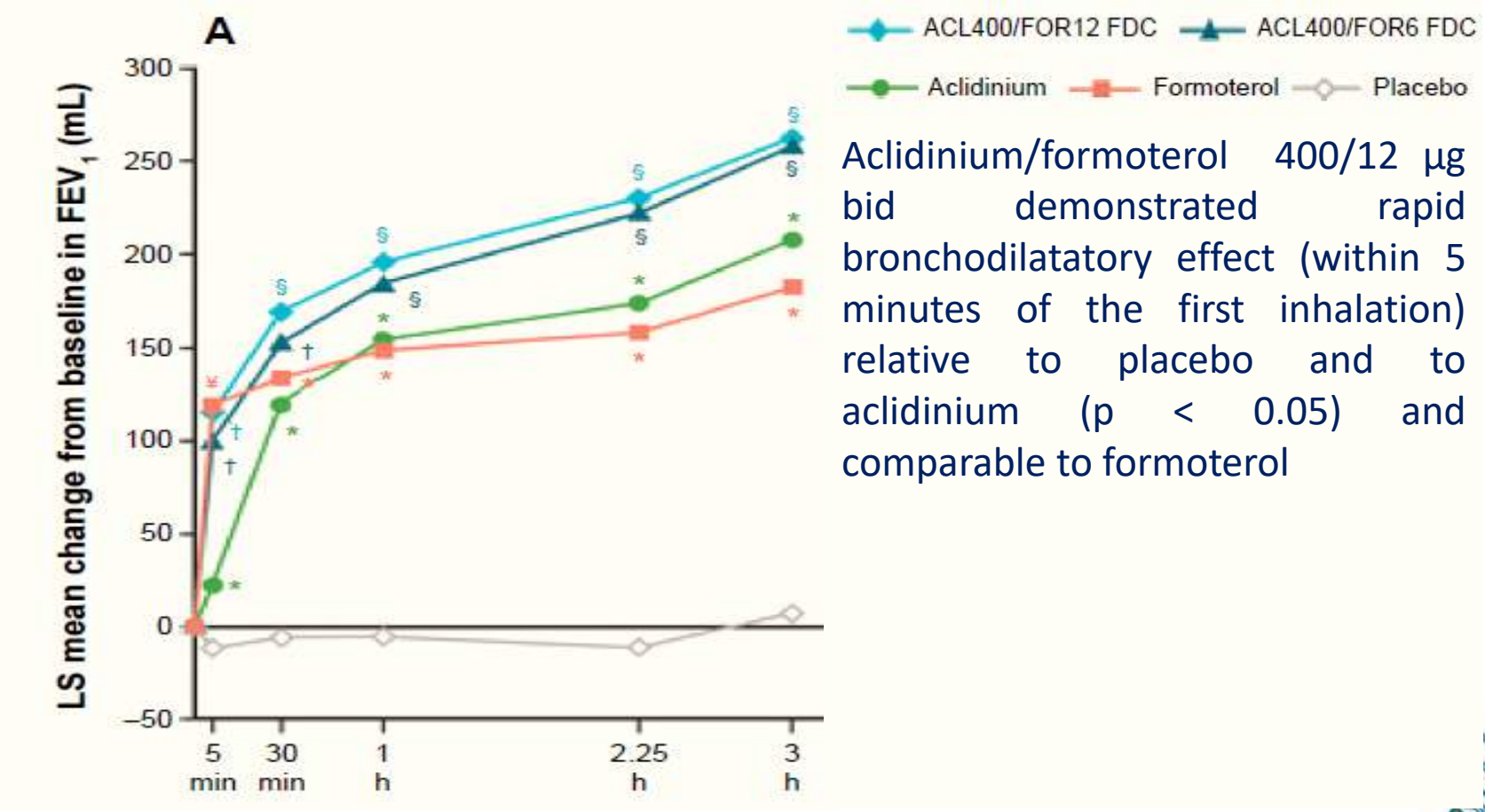
Efficacy and safety of aclidinium/formoterol fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD)



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

Aclidinium/formoterol: FEV1 improvement on Day 1

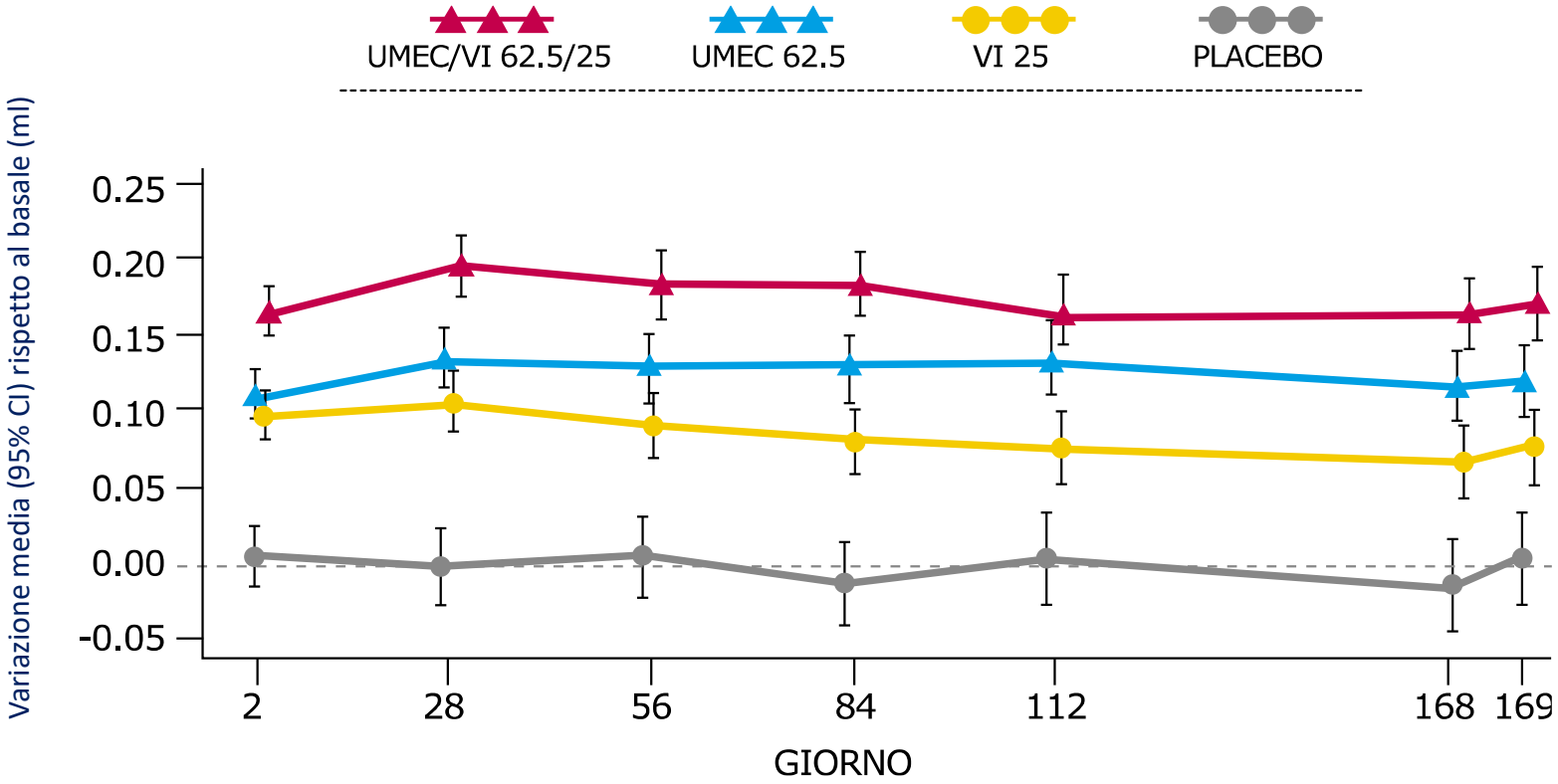


Aclidinium/formoterol 400/12 µg bid demonstrated rapid bronchodilatatory effect (within 5 minutes of the first inhalation) relative to placebo and to aclidinium ($p < 0.05$) and comparable to formoterol

*$P < 0.05$ 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

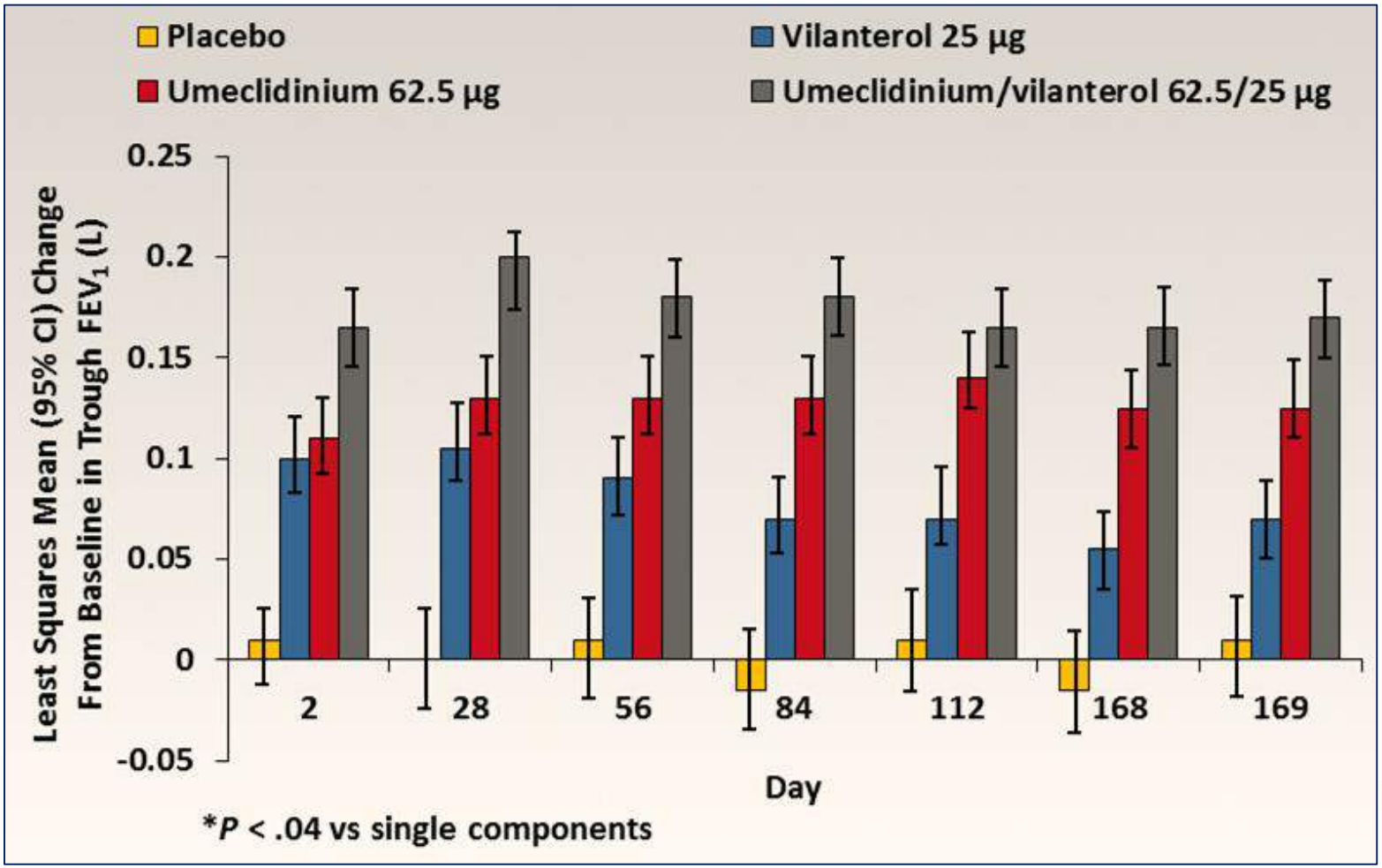
Efficacy and safety of once daily umeclidinium/vilanterol 62.5/25 mcg in COPD



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, $p < 0.004$).

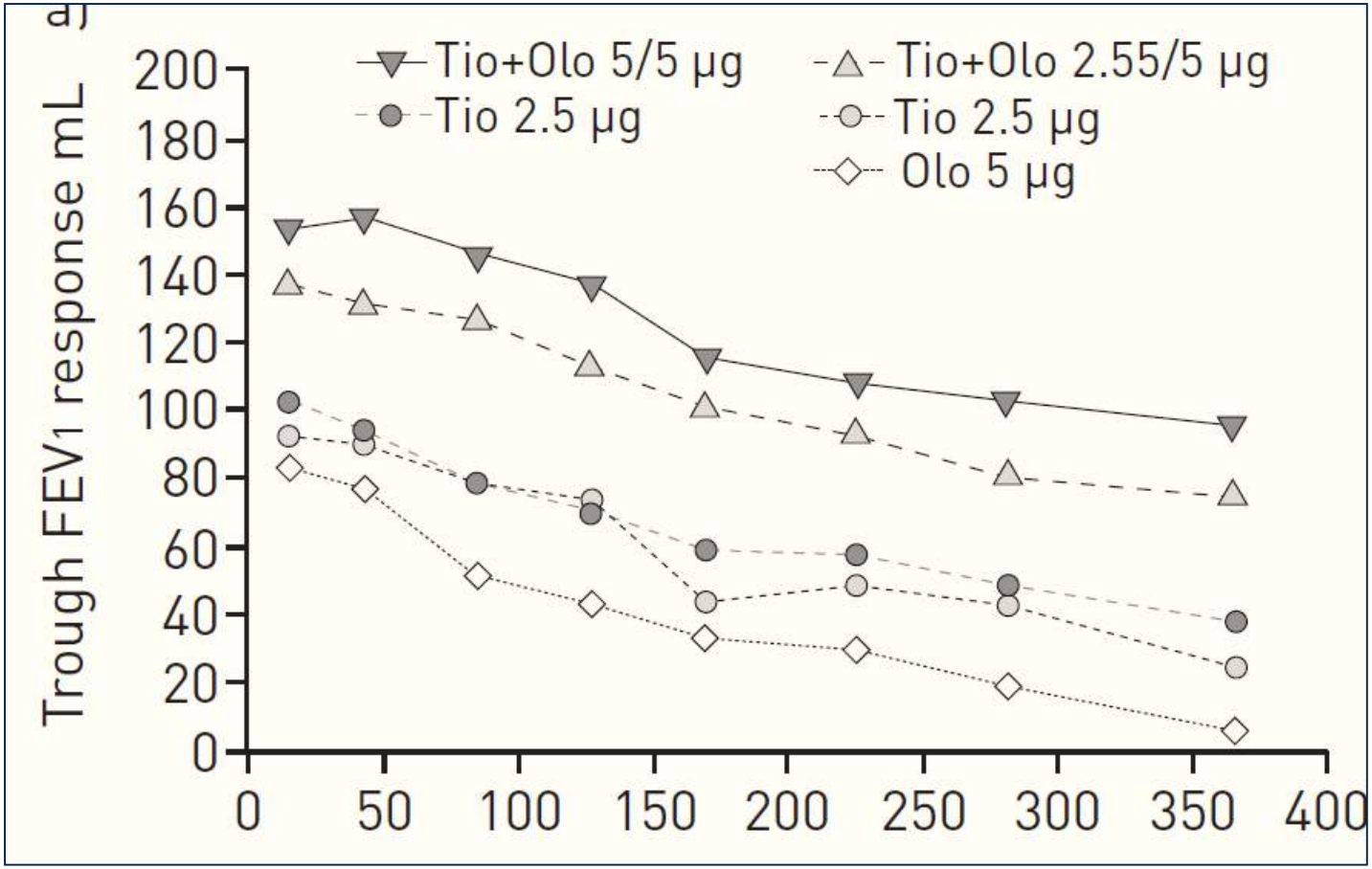
Donohue JF, et al. Respir Med 2013.

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



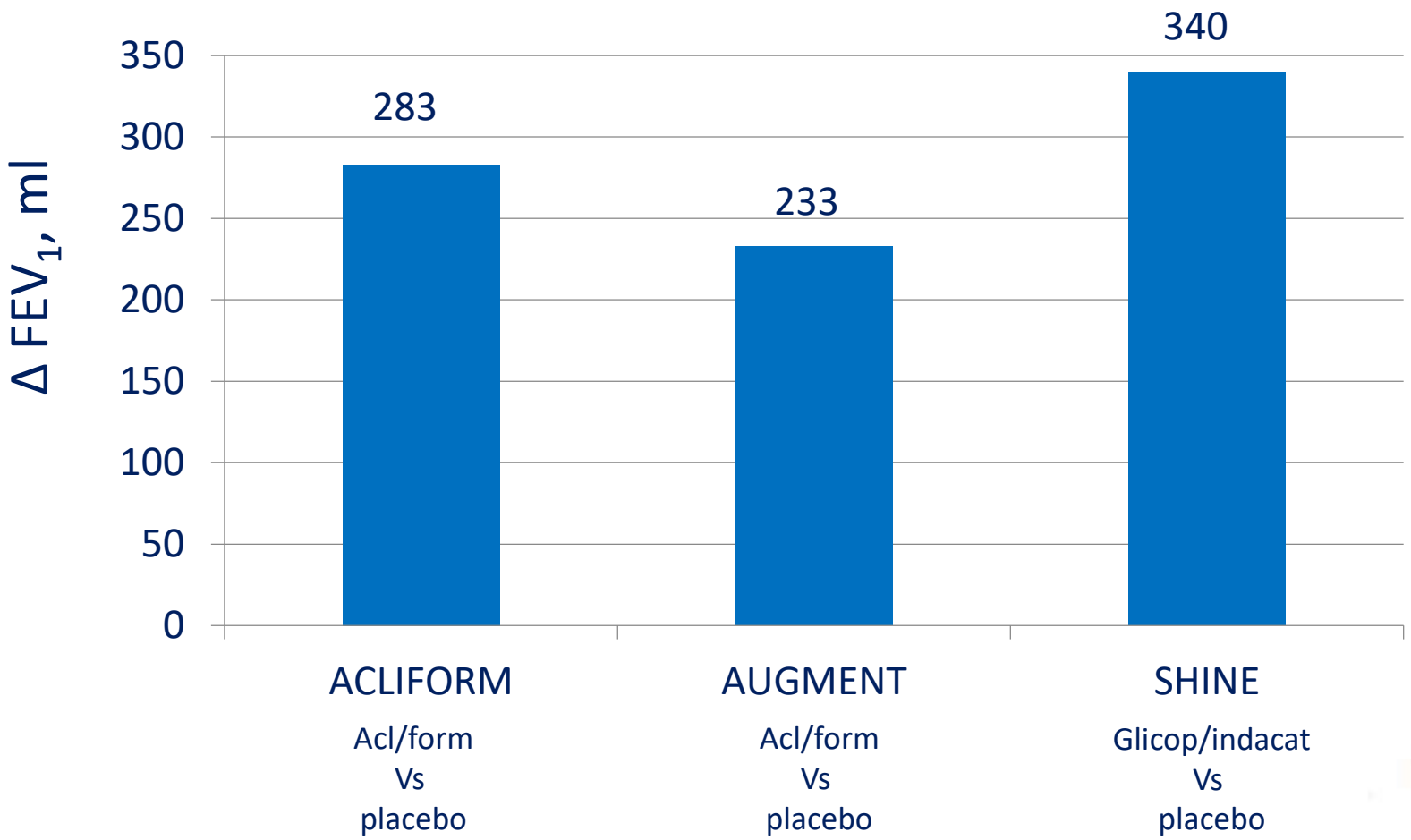
Donohue JF, et al. Respir Med 2013.

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



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

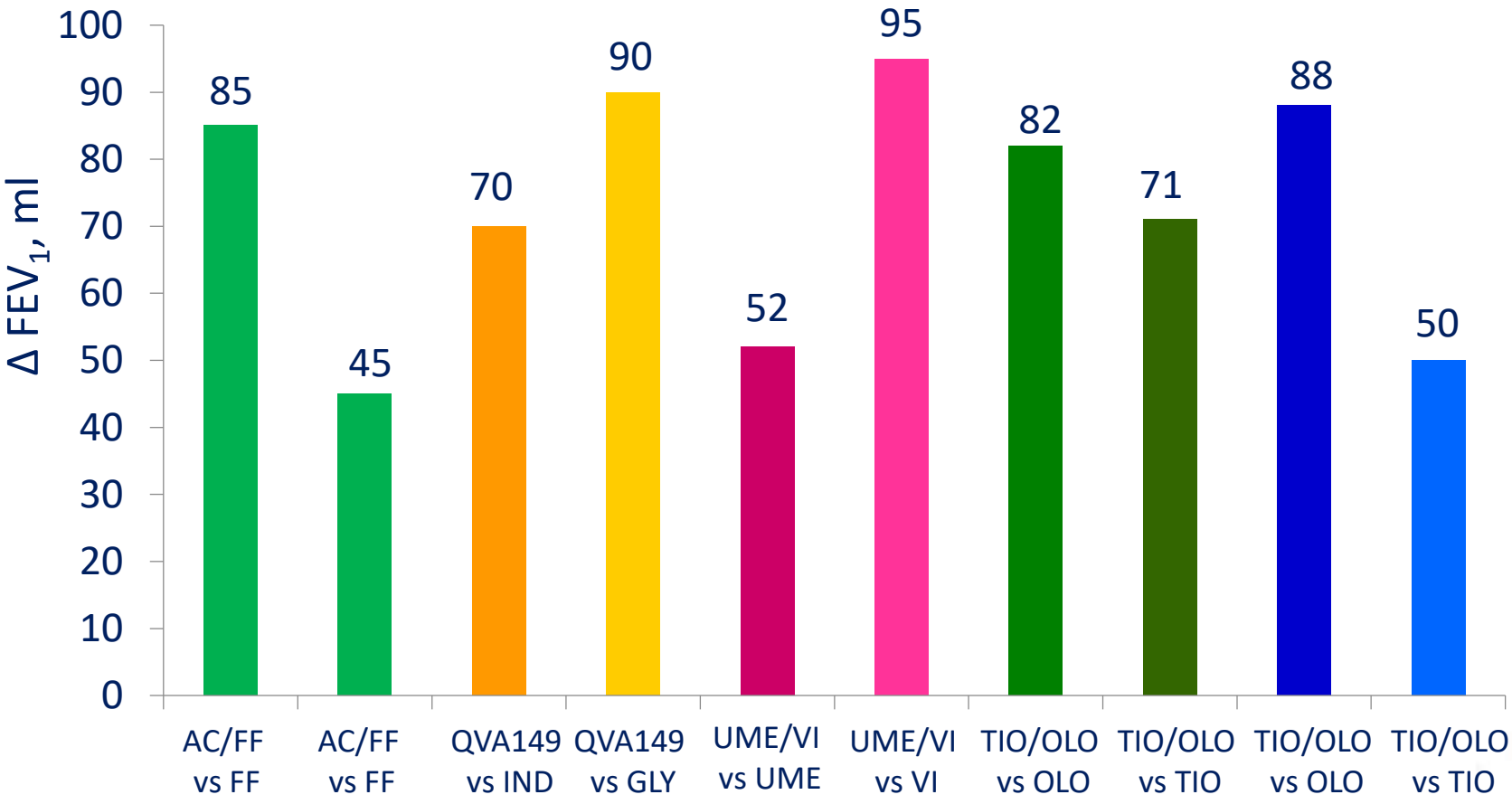
Combination treatments cause large FEV_1 changes immediately post-dose



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

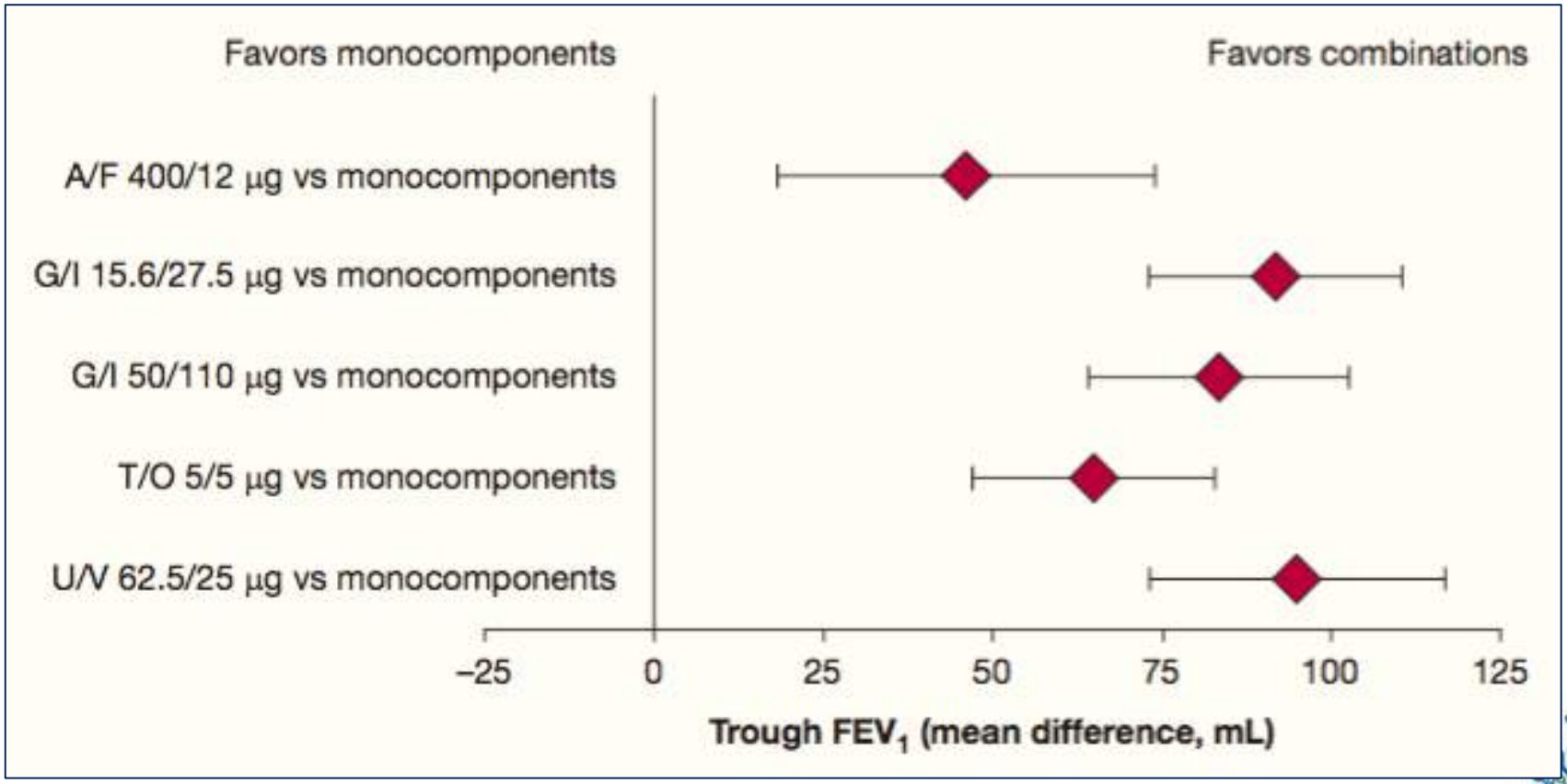
Changes in trough FEV_1: Combination vs monotherapy

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



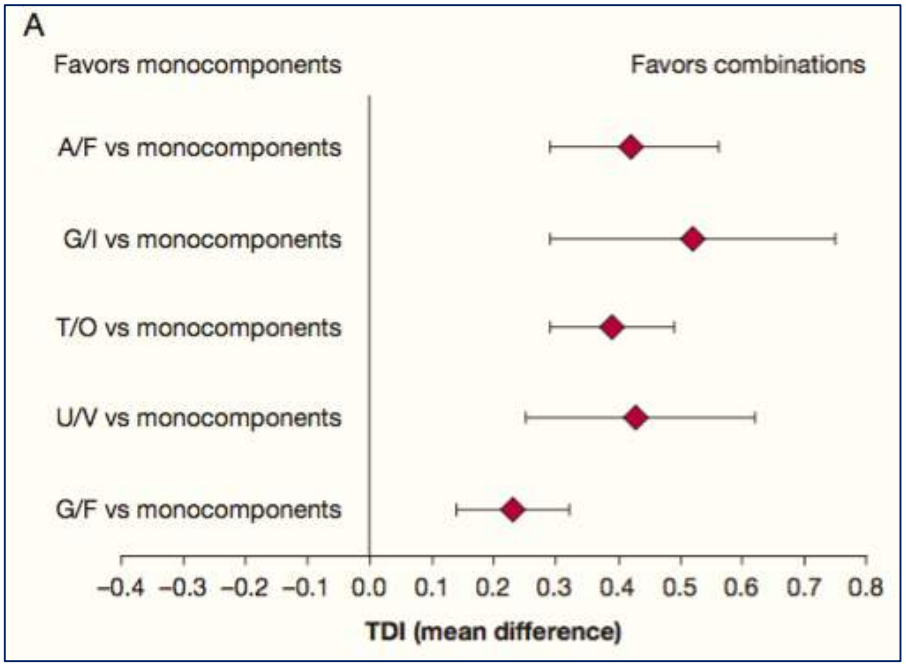
1) Singh D et al. BMC Pulm Med 2014 2) D'Urzo AD et al. Resp Res 2014 3) Bateman et al Eur Respir J. 2013
4) Donohue J et al. 5) Buhl R et al. Eur Resp J 2015.

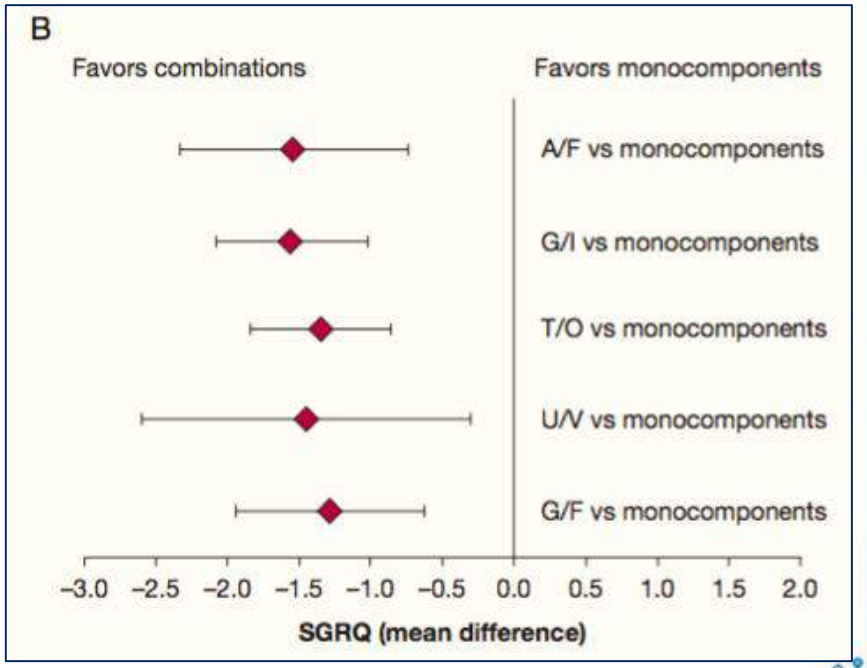
A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease



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

Confronto vs Tiotropio

Primary efficacy endpoint: Trough FEV1 on day 169

Endpoint di efficacia primario

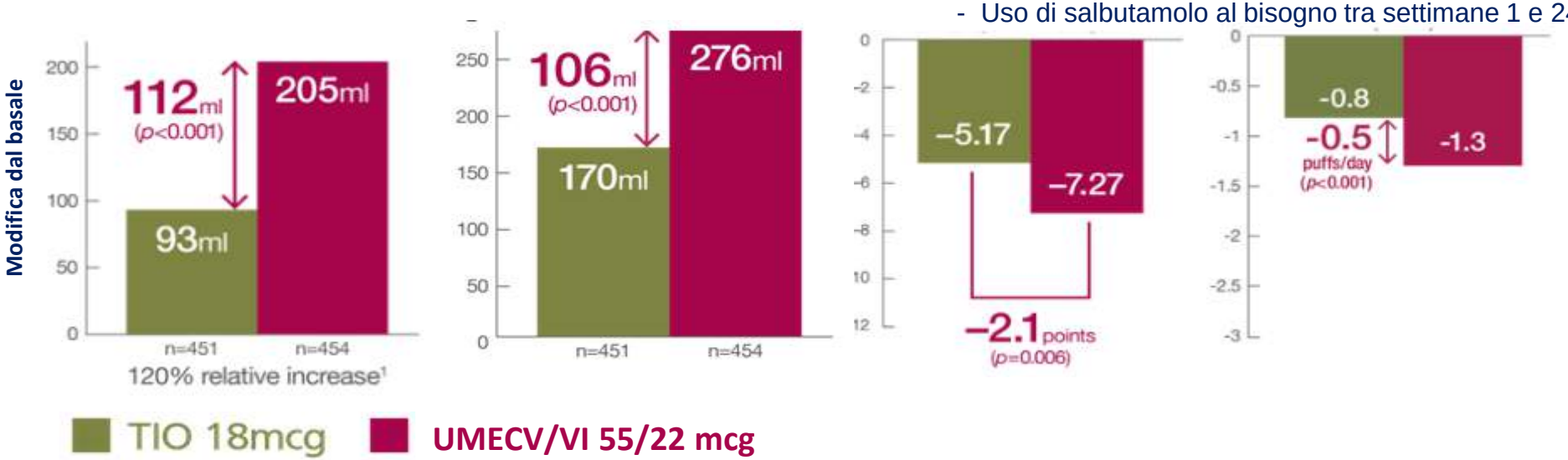
FEV_1 a valle al giorno 169

Endpoint di efficacia secondario:

FEV_1 0–6 h post dose alla settimana 24

Altri endpoints di efficacia:

- SGRQ total score alla settimana 24
- Uso di salbutamolo al bisogno tra settimane 1 e 24



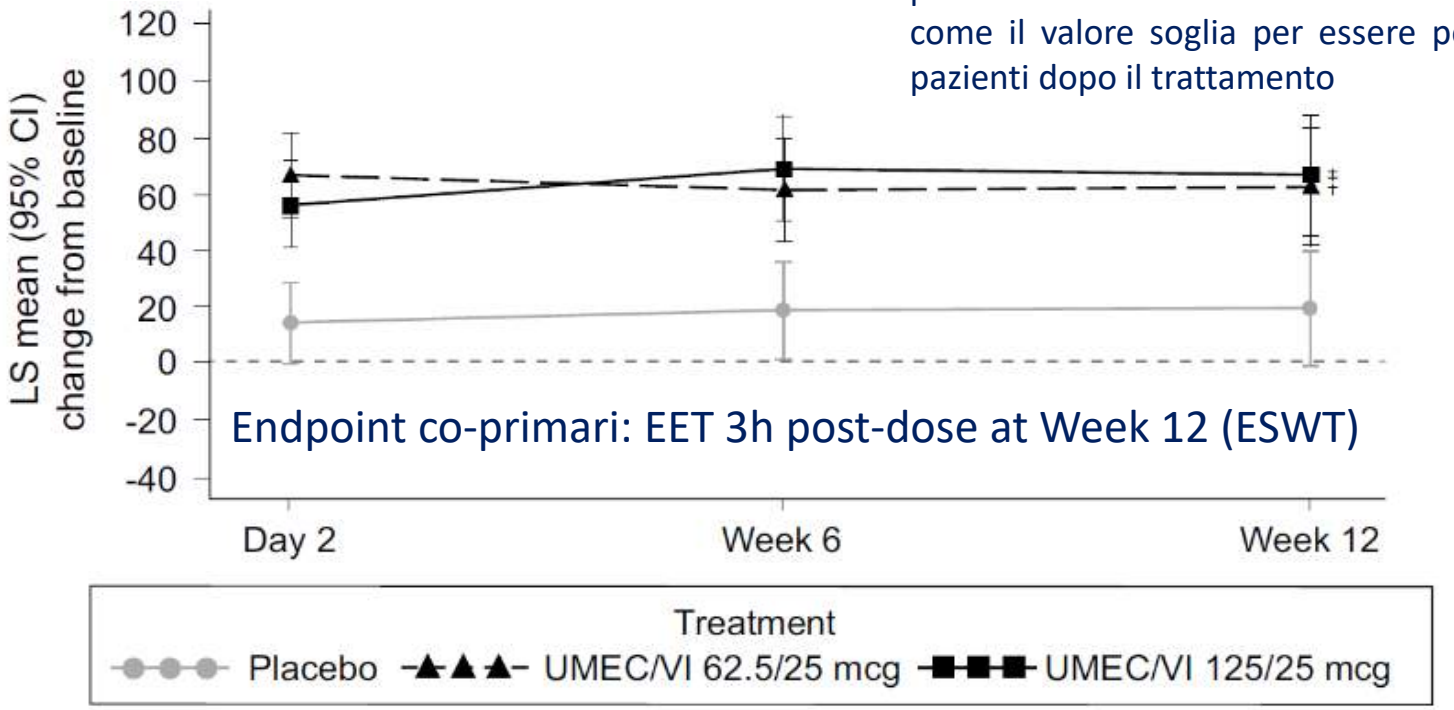
UMEC/VI ha indotto miglioramenti della funzionalità polmonare statisticamente e clinicamente significativi rispetto TIO. Inoltre UMEC/VI ha migliorato la qualità della vita e ridotto l'uso di farmaci al bisogno rispetto a TIO.

Maleki-Yazdi MR et al. Respir Med. 2014;108(12):1752-1760

Tolleranza all'esercizio fisico (EET) in comparazione con placebo

Mentre una valida stima della differenza minima clinicamente importante deve ancora essere stabilita, un cambiamento nelle prestazioni di 45-85 secondi viene considerato come il valore soglia per essere percepito dai pazienti dopo il trattamento

Post-Hoc Analisi Accorpata

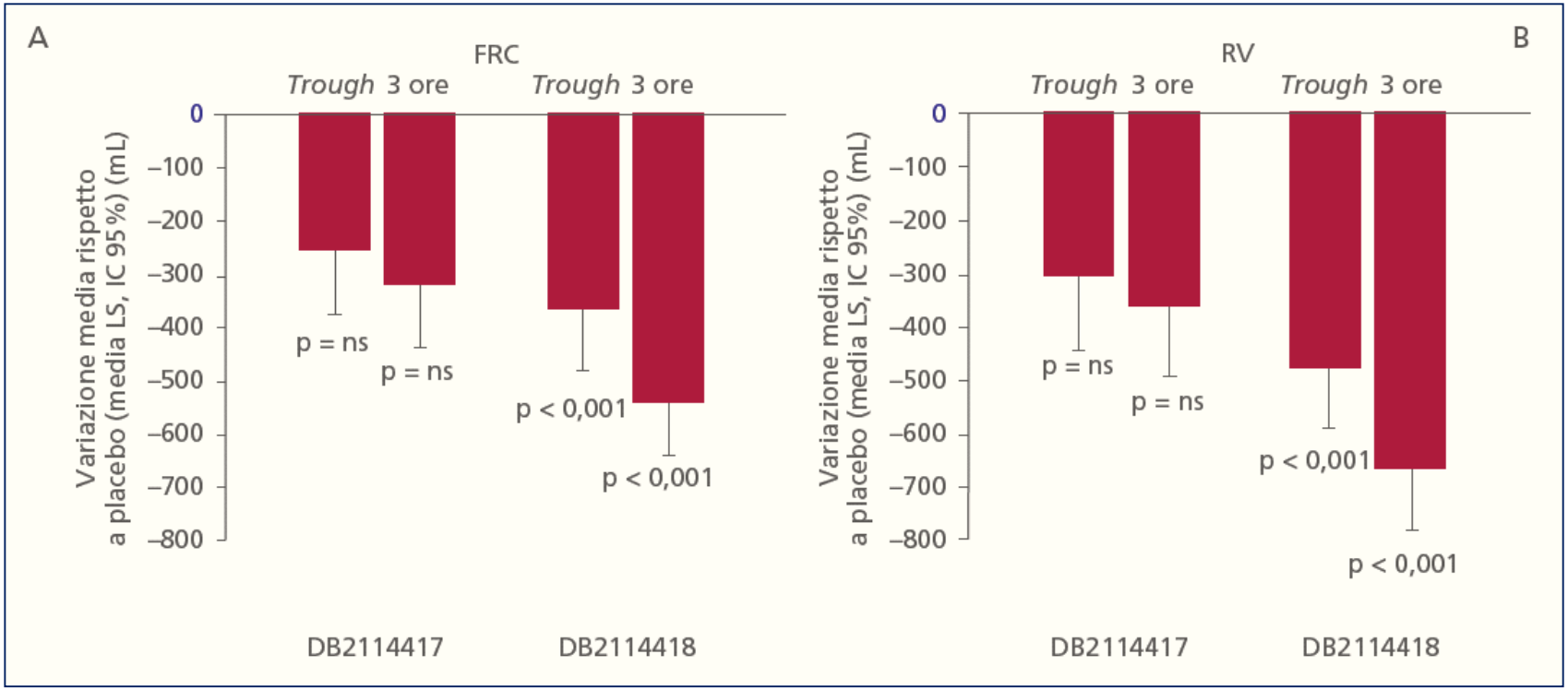


UMEC/VI 55/22 ha migliorato l'EET di 62,9 sec dal basale e 43,7 sec vs placebo

1. Maltais et al Ther Adv Respir Dis. 2014;8(6):169-81. 2. Pepin V et al. Thorax 2011; 66: 115–120.

Iperinsufflazione polmonare verso placebo

Capacità Funzionale Residua (FRC) & Volume Residuo (RV) alla settimana 12



*Non statisticamente significativo per il mancato rispetto della gerarchia statistica

UMEC/VI è in grado di desufflare il paziente già dalla prima somministrazione

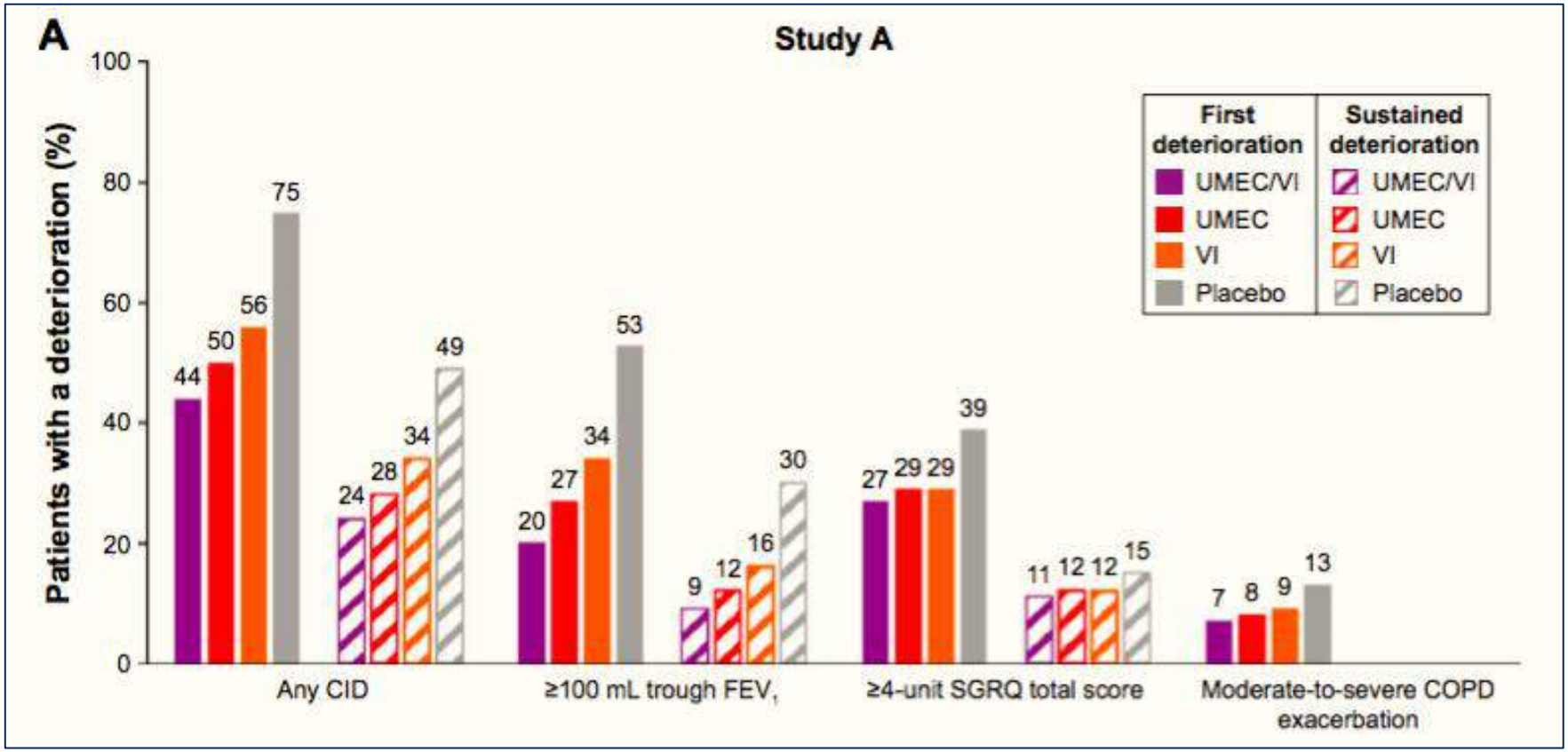
Maltais et al Ther Adv Respir Dis. 2014 Dec;8(6):169-81

Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol

Deterioration was assessed as the time to a first clinical important deterioration (CID), a composite measure defined as a:

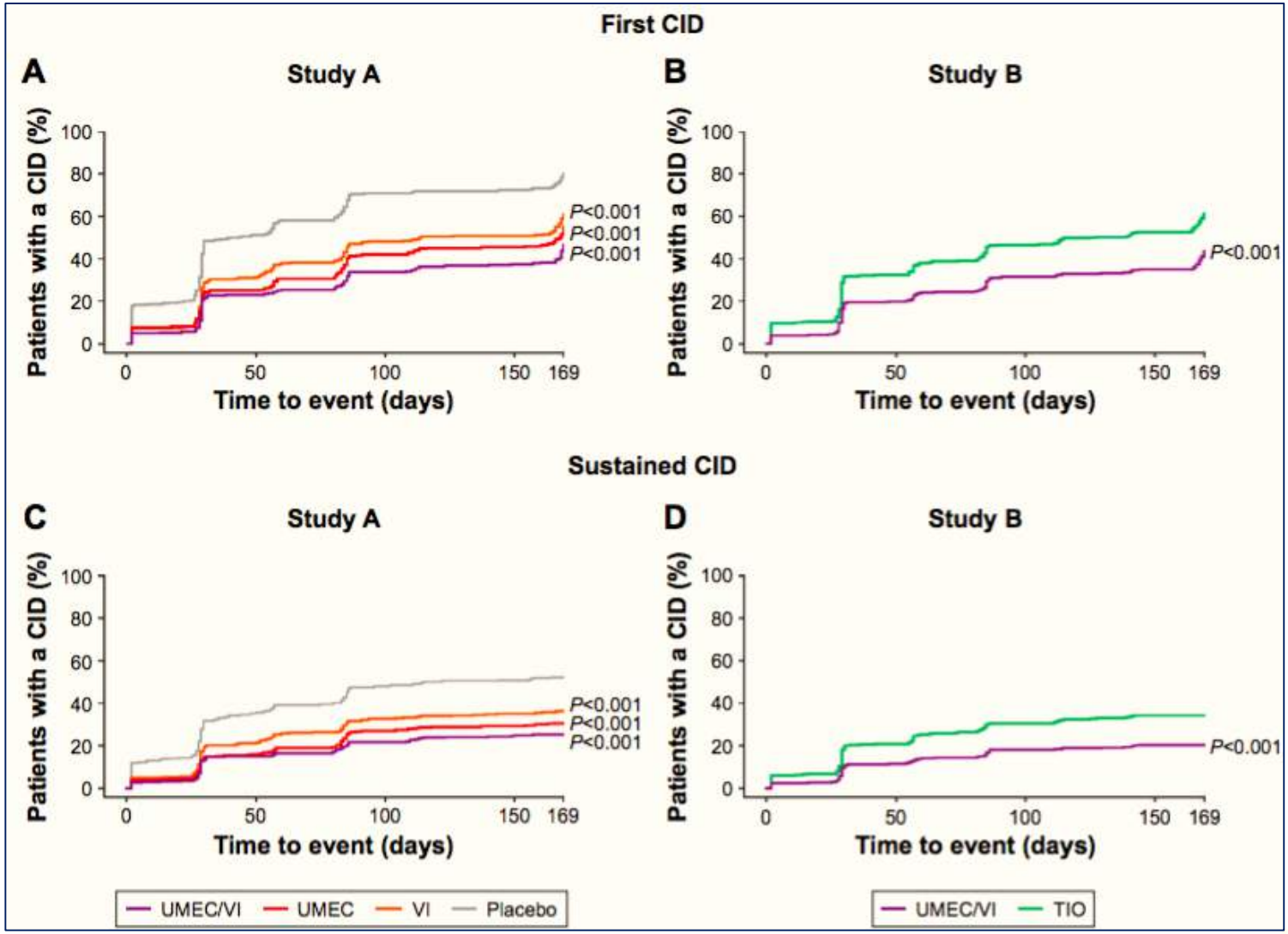
- decrease of > 100 mL in trough FEV_1 or
- > 4-unit increase in St George's Respiratory Questionnaire total score or
- an on-treatment moderate-to-severe COPD exacerbation.

Sing D, et al. Int J COPD 2016



CID = clinically important deterioration

Sing D, et al. Int J COPD 2016



CID = clinically important deterioration

Sing D, et al. Int J COPD 2016

Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD

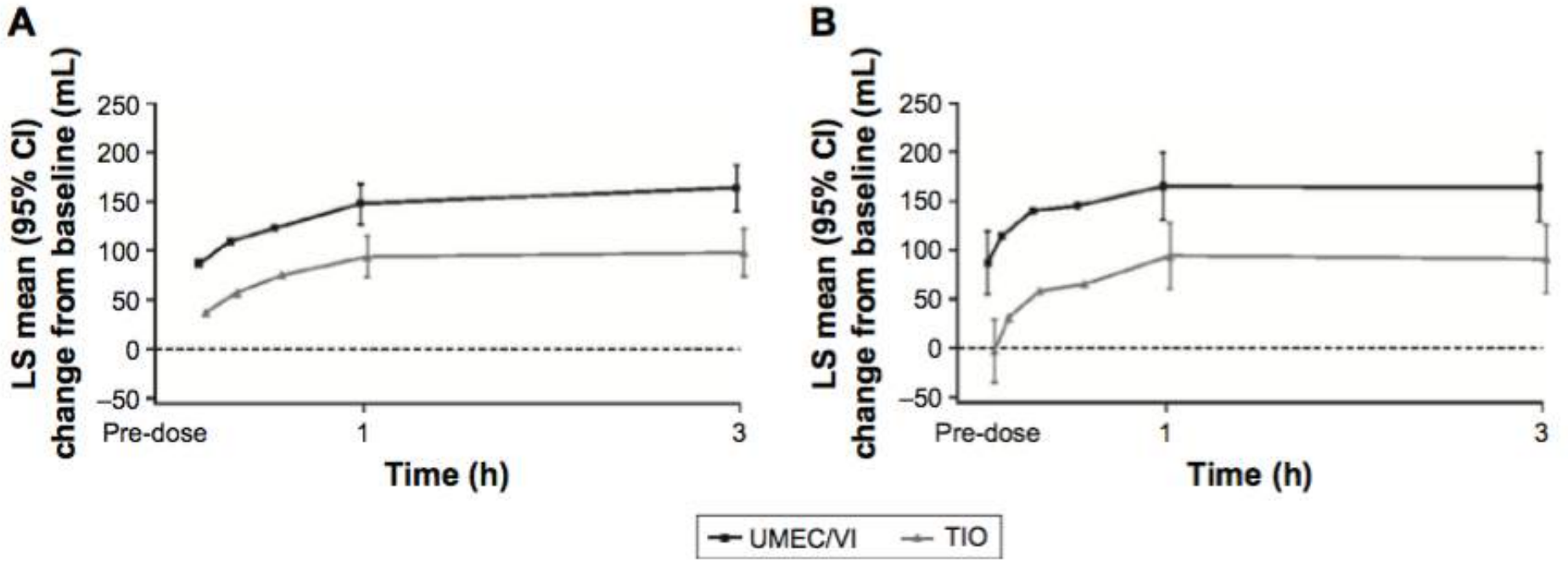


Figure 3 Serial LS mean change (95% CI) from baseline in FEV_1 over 0–3 h on Day 1 (**A**) and Day 84 (**B**; ITT population).
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ITT, intent-to-treat; LS, least squares; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Kervin E, et al. Int J COPD

Nelle persone con BPCO, sintomatiche nonostante l'uso regolare di broncodilatatori a lunga durata d'azione, con VEMS o FEV_1 pre-broncodilatatore < 60% del valore teorico e storia di frequenti riacutizzazioni (≥ 2/anno), considerare l'associazione LABA+CSI. L'utilizzo della combinazione fissa può migliorare significativamente l'aderenza della persona alla terapia.

Nelle persone con BPCO, sintomatiche con VEMS o FEV_1 <60% del valore teorico l'associazione LAMA+LABA+CSI:

- ha migliorato i parametri spirometrici e la qualità della vita
- ha ridotto il numero di ospedalizzazioni

Group D

We recommend initiating a LABA/LAMA combination because:

- In studies with patient reported outcomes as the primary endpoint, LABA/LAMA combinations showed superior results compared to a single bronchodilator.
- LABA/LAMA combination was superior to LABA/ICS combination in preventing exacerbations and improving other patient reported outcomes in Group D patients.
- Group D patients are at higher risk for pneumonia when receiving ICS treatment. If a single bronchodilator is initially chosen, a LAMA is preferred for exacerbation prevention based on comparison to LABAs.

GOLD 2017

Group D

LABA/ICS may be the first choice for initial therapy in some patients. These patients may have a history and/or findings suggestive of asthma–COPD overlap and/or high blood eosinophil counts.

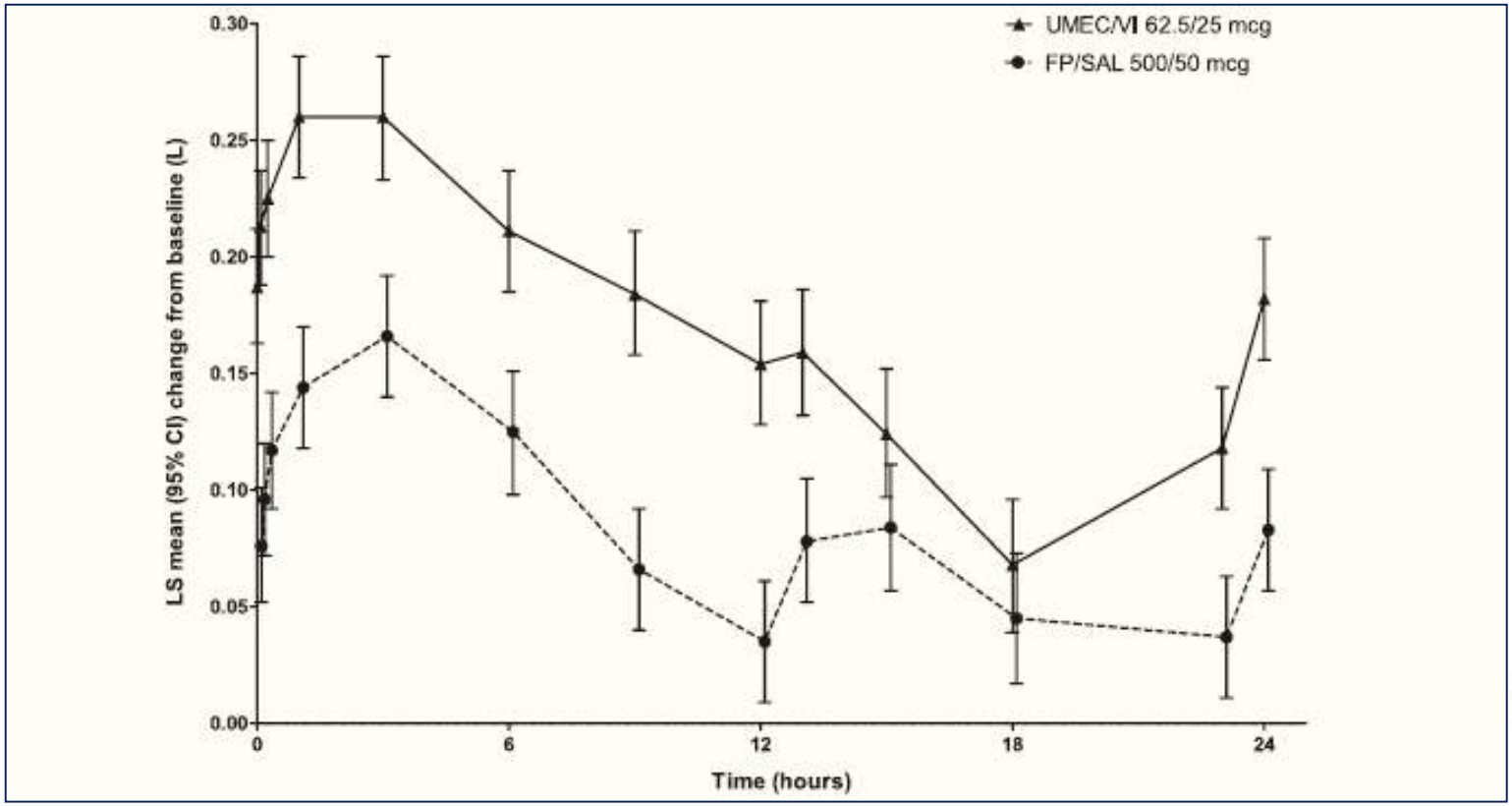
In patients who develop additional exacerbations on LABA/LAMA therapy we suggest two alternative pathways:

- Escalation to LABA/LAMA/ICS.
- Switch to LABA/ICS. If LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added.

GOLD 2017

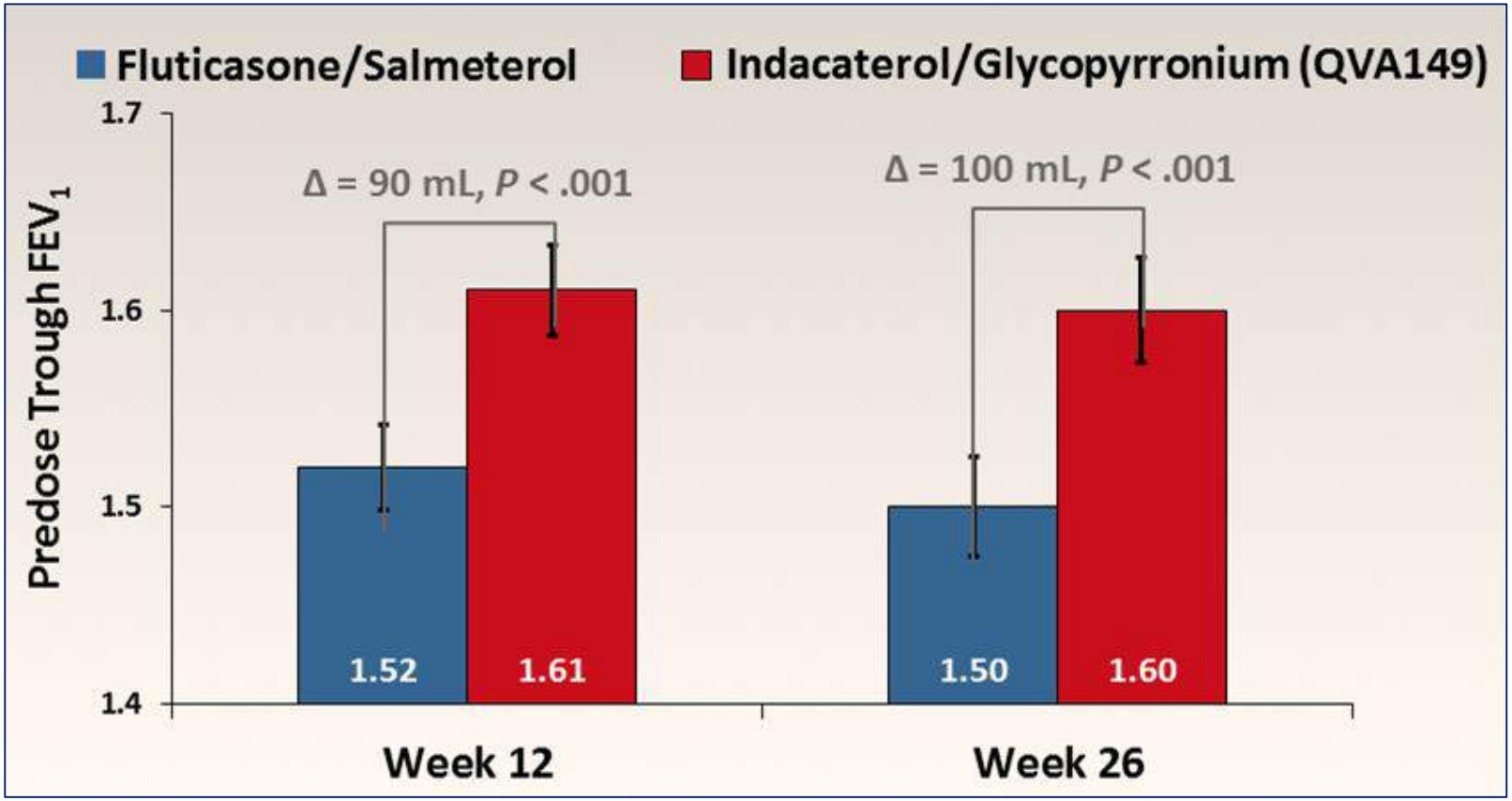
Umeclidinium/vilanterol vs salmeterol/fluticasone

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

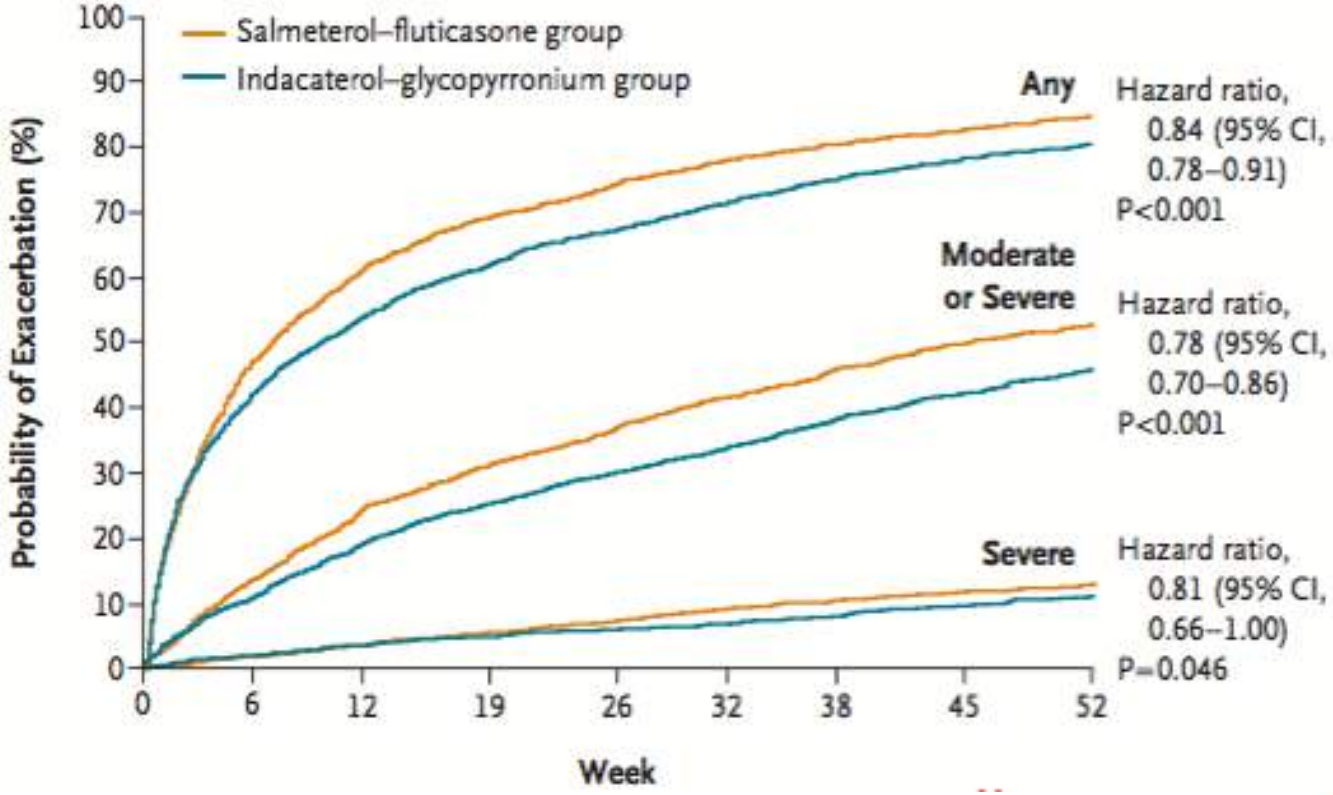
Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

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)

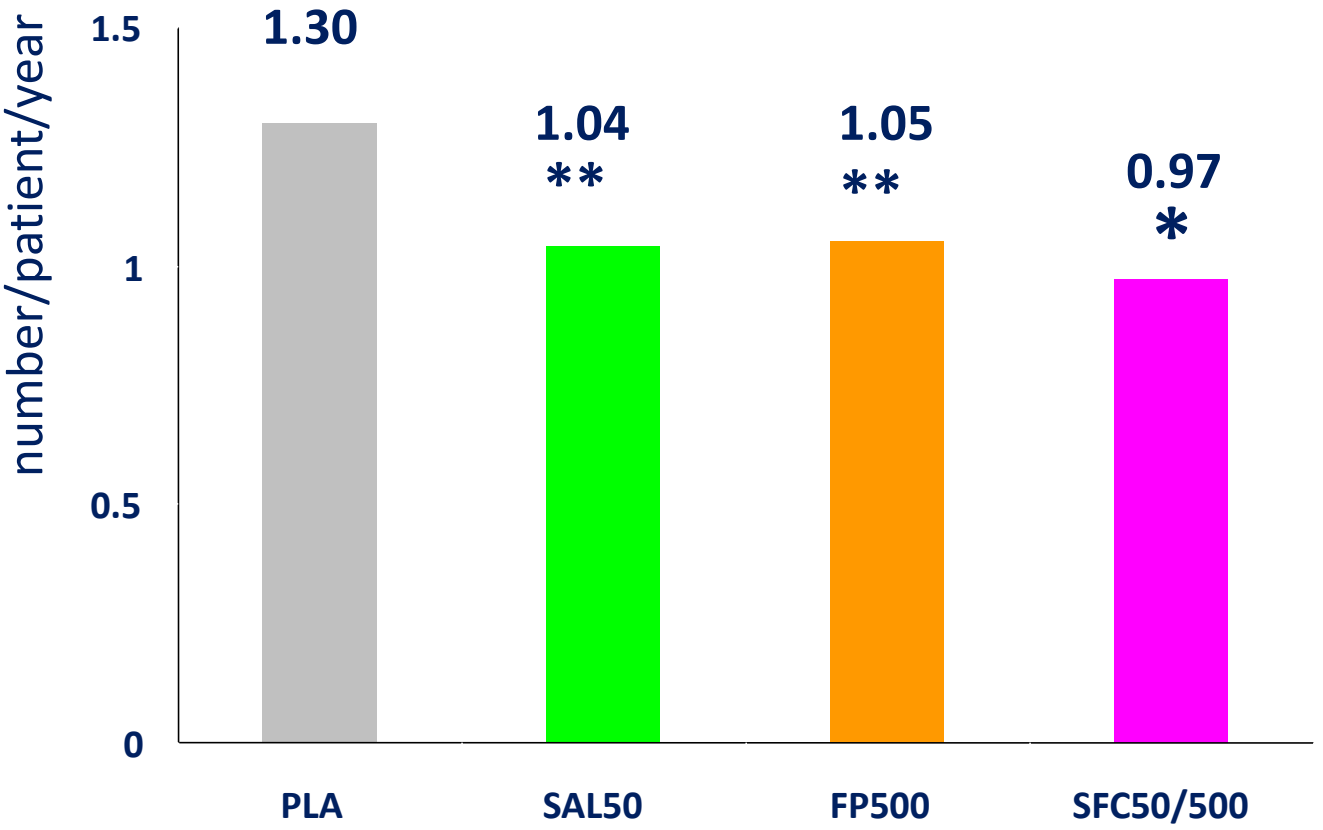
Jadwiga A. Wedzicha, et al. New Engl J Med 2016

Time to First Exacerbation



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

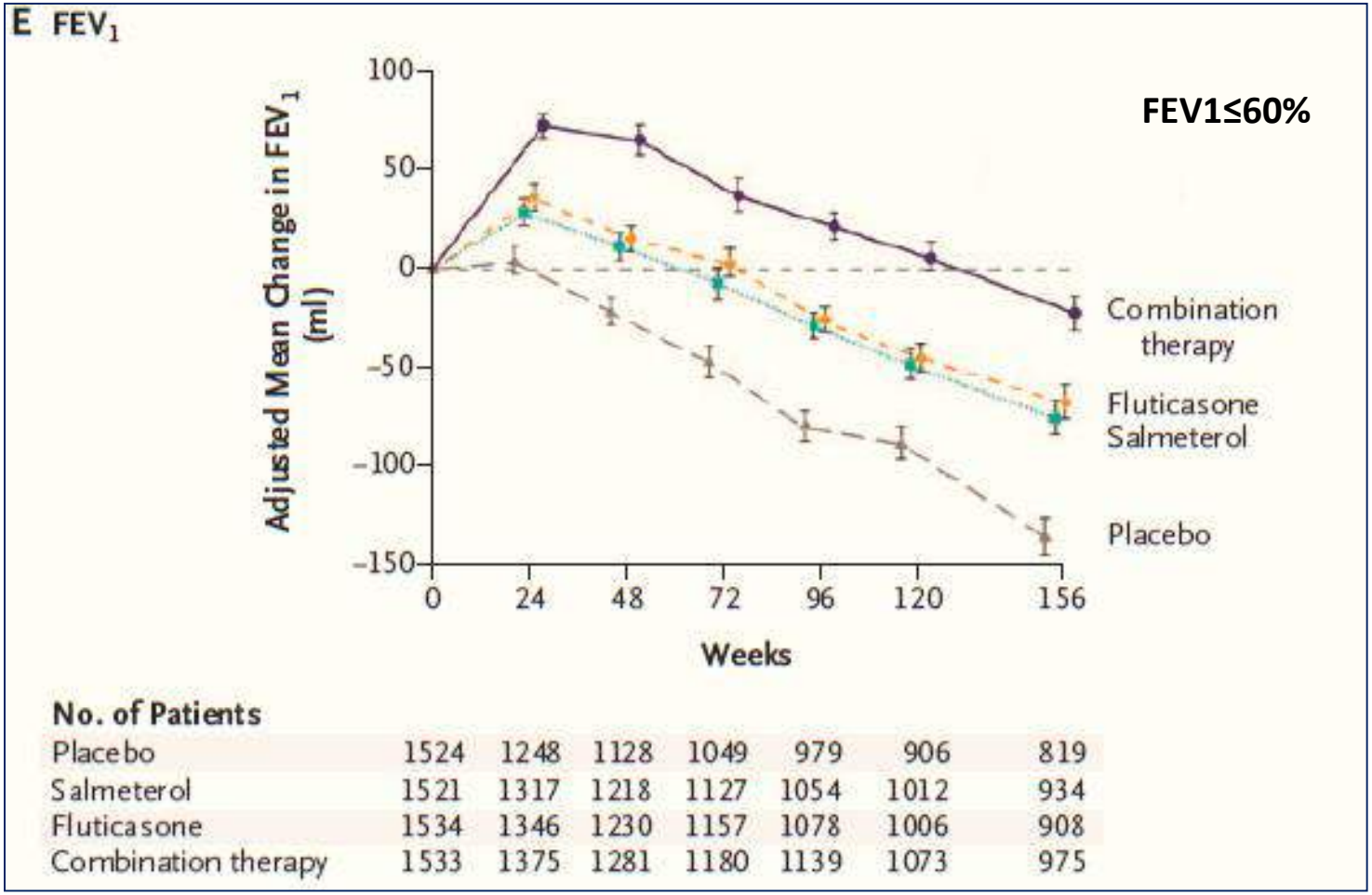
In the TRISTAN study, FP/Salm combination reduced the number of severe exacerbations



* p< 0.001 vs PLA ** p = 0.003 vs PLA

Calverly et al, Lancet 2003

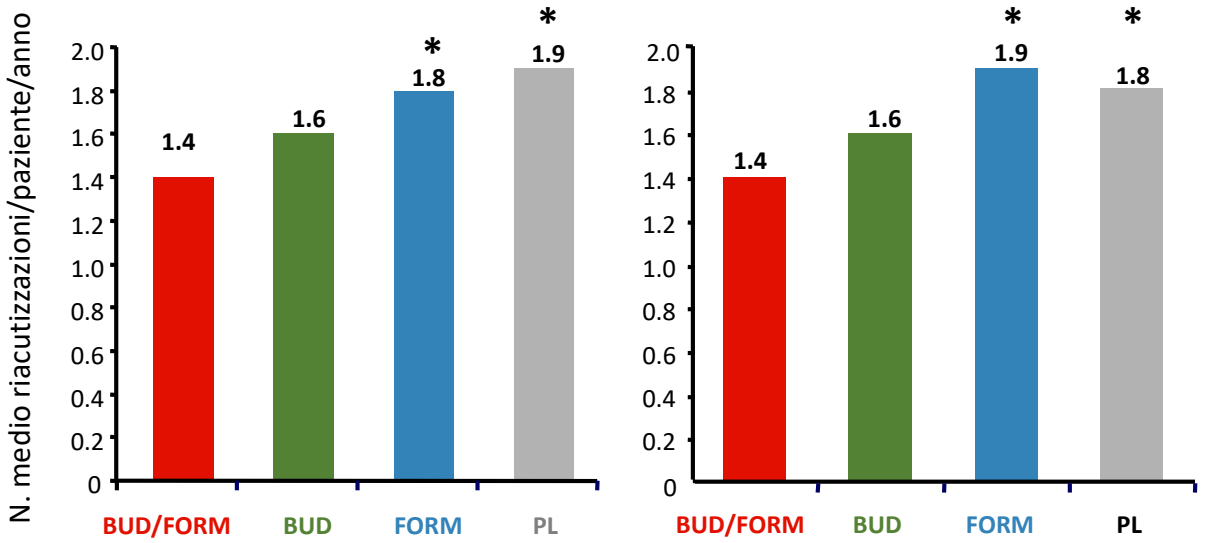
TORCH Study: additional effect of salmeterol/fluticasone vs both monotherapies



No. of Patients							
Placebo	1524	1248	1128	1049	979	906	819
Salmeterol	1521	1317	1218	1127	1054	1012	934
Fluticasone	1534	1346	1230	1157	1078	1006	908
Combination therapy	1533	1375	1281	1180	1139	1073	975

Calverley MD, et al. New Eng J Med 2007, Vol.356 (8): 775-210

Bud/Form: reduction of exacerbations



	Numero medio di riacutizzazioni/paziente/anno[1]	
Trattamento	Szafranski	Calverley
BUD/FORM	1,4*	1,4(*)
BUD	1,6	1,6
FORM	1,8	1,9
PL	1,9	1,8

*p<0,05 vs BUD/FORM
(*)p<0,05 vs BUD/FORM

1. Szafranski W et al. Eur Respir J 2003; 21: 74-81;
2. Calverley PM et al. Eur Respir J 2003; 22: 912-919

Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice

CONCLUSIONS

In patients with COPD and a history of exacerbations, a once-daily treatment regimen of combined fluticasone furoate and vilanterol was associated with a lower rate of exacerbations than usual care, without a greater risk of serious adverse events. (Funded by GlaxoSmithKline; Salford Lung Study ClinicalTrials.gov number, NCT01551758.)

Vestbo et al. New England J Med 2016

Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice

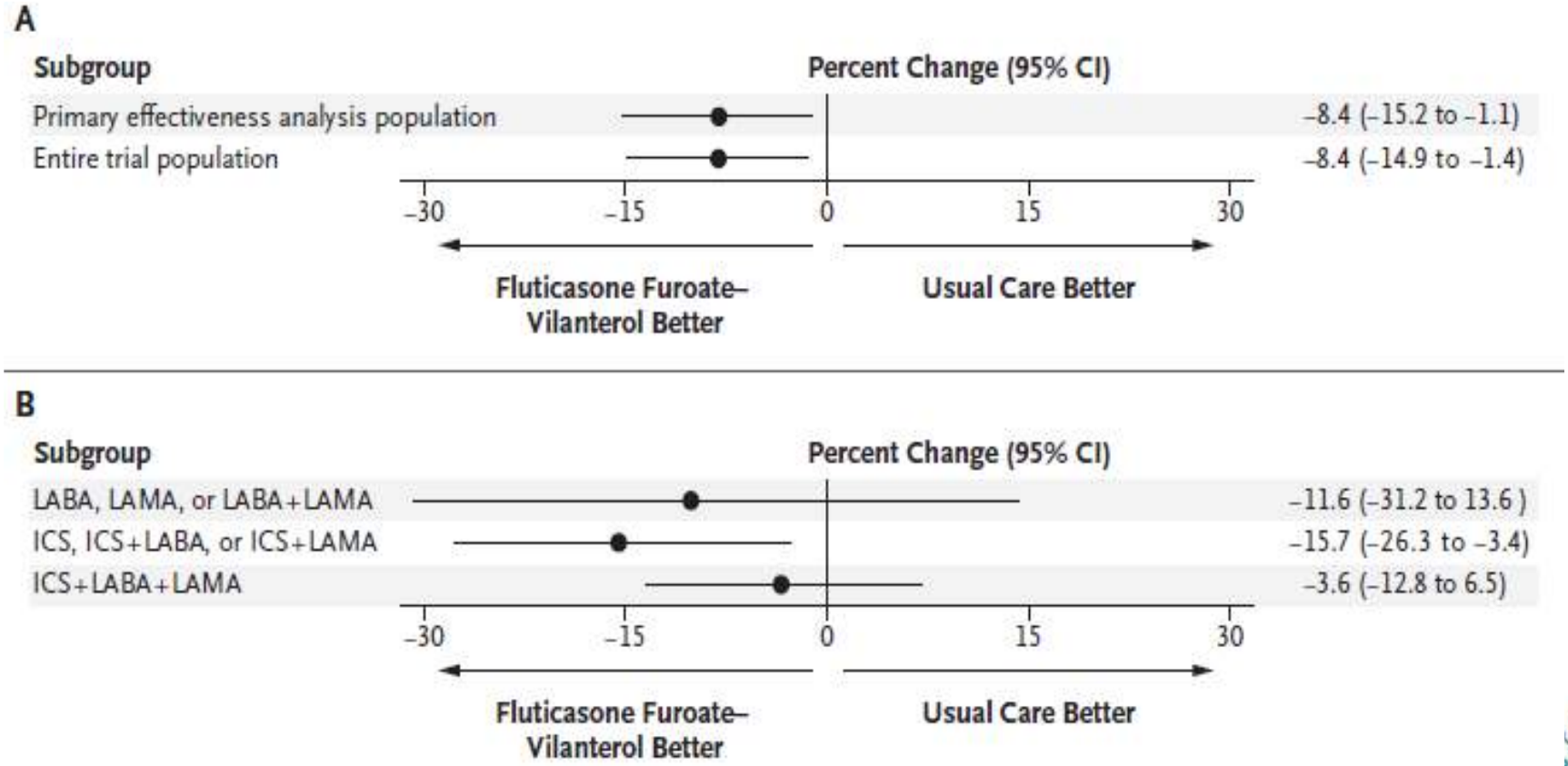
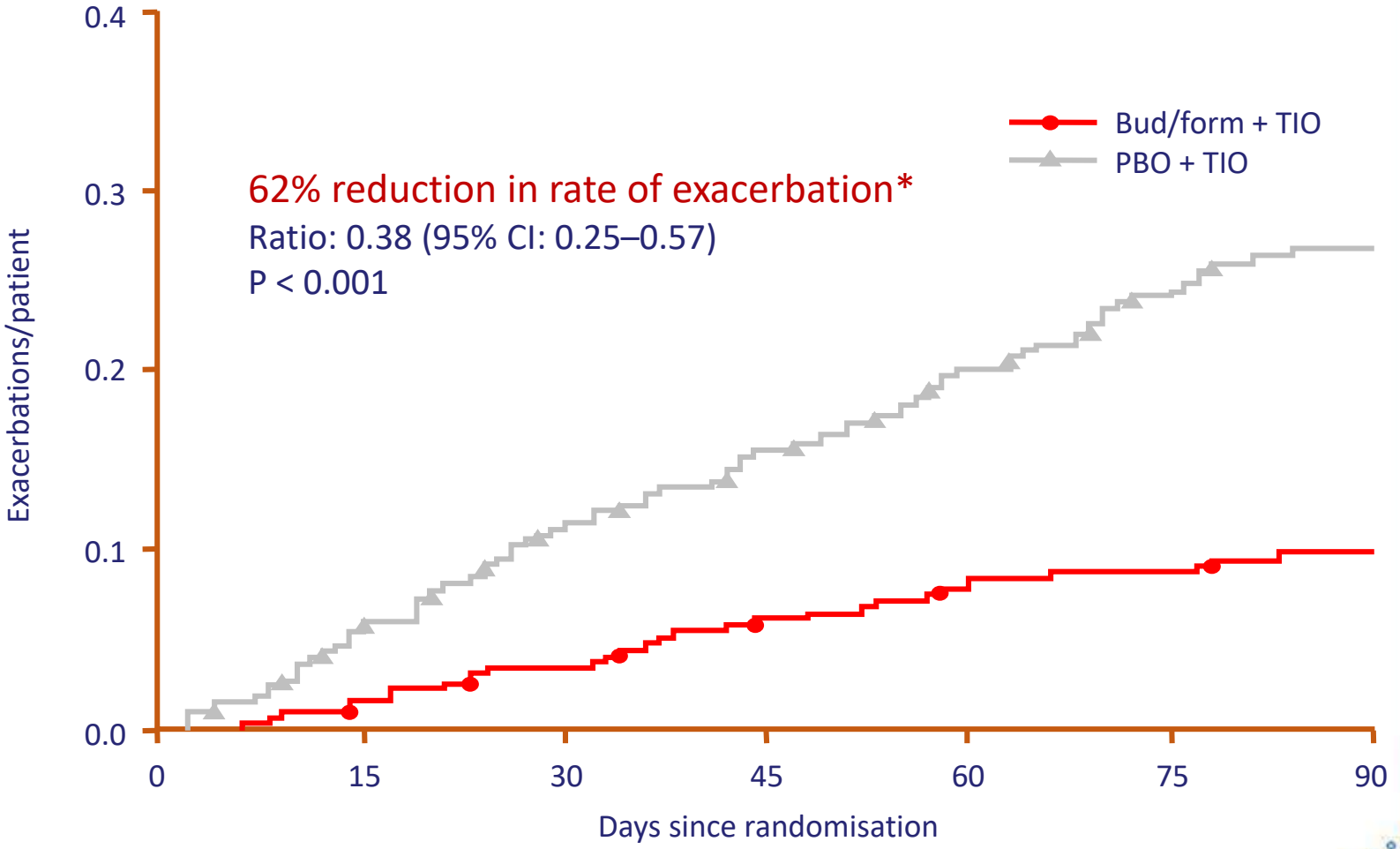


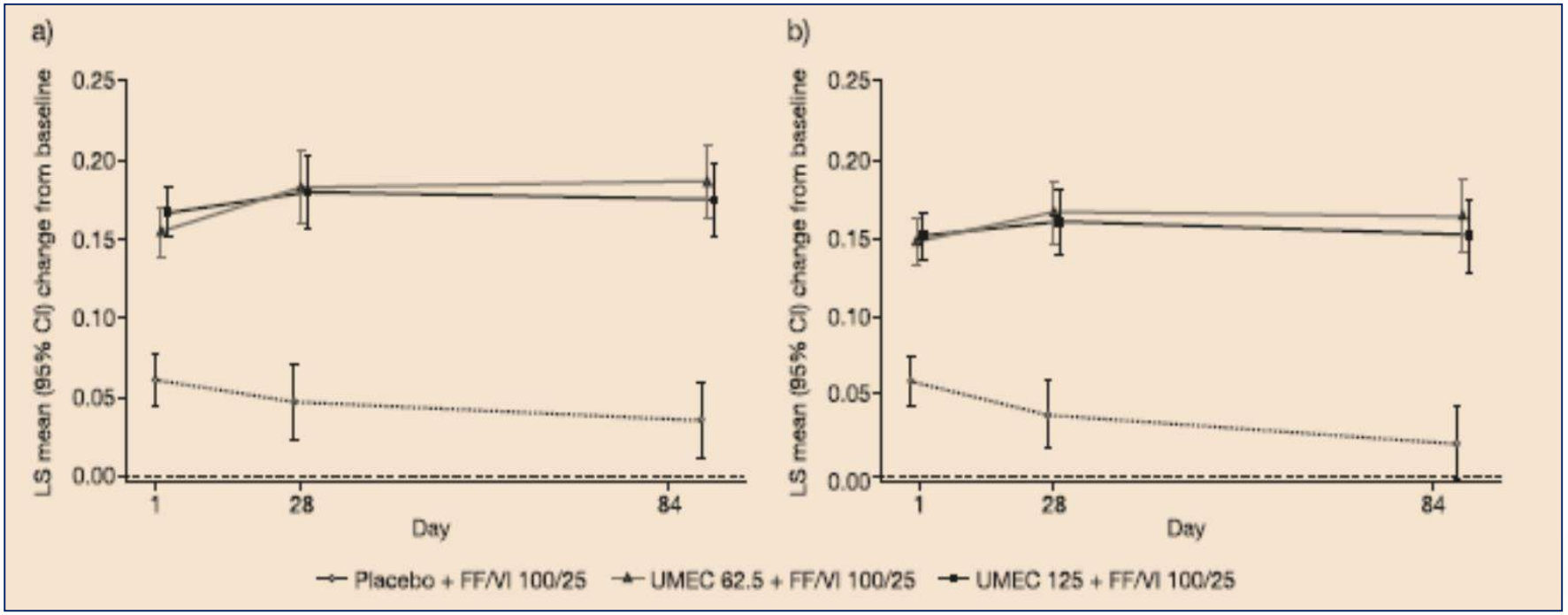
Figure 1. Treatment Effect on Moderate or Severe Exacerbations.

Vestbo et al. New England J Med 2016



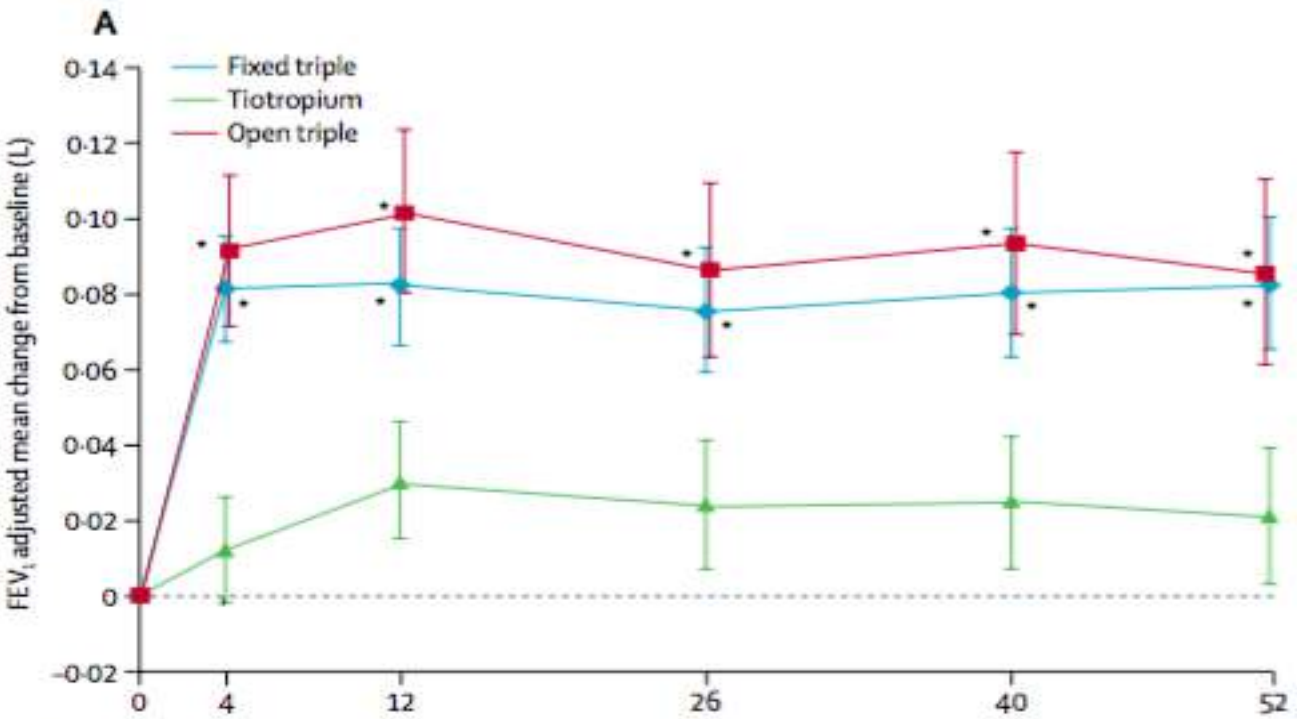
Welte T, et al. Am J Respir Crit Care Med 2009

Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in COPD



Siler et al. Resp Med 2015

Single inhaler extrafine triple therapy versus long-acting muscarinic antegonist therapy for COPD



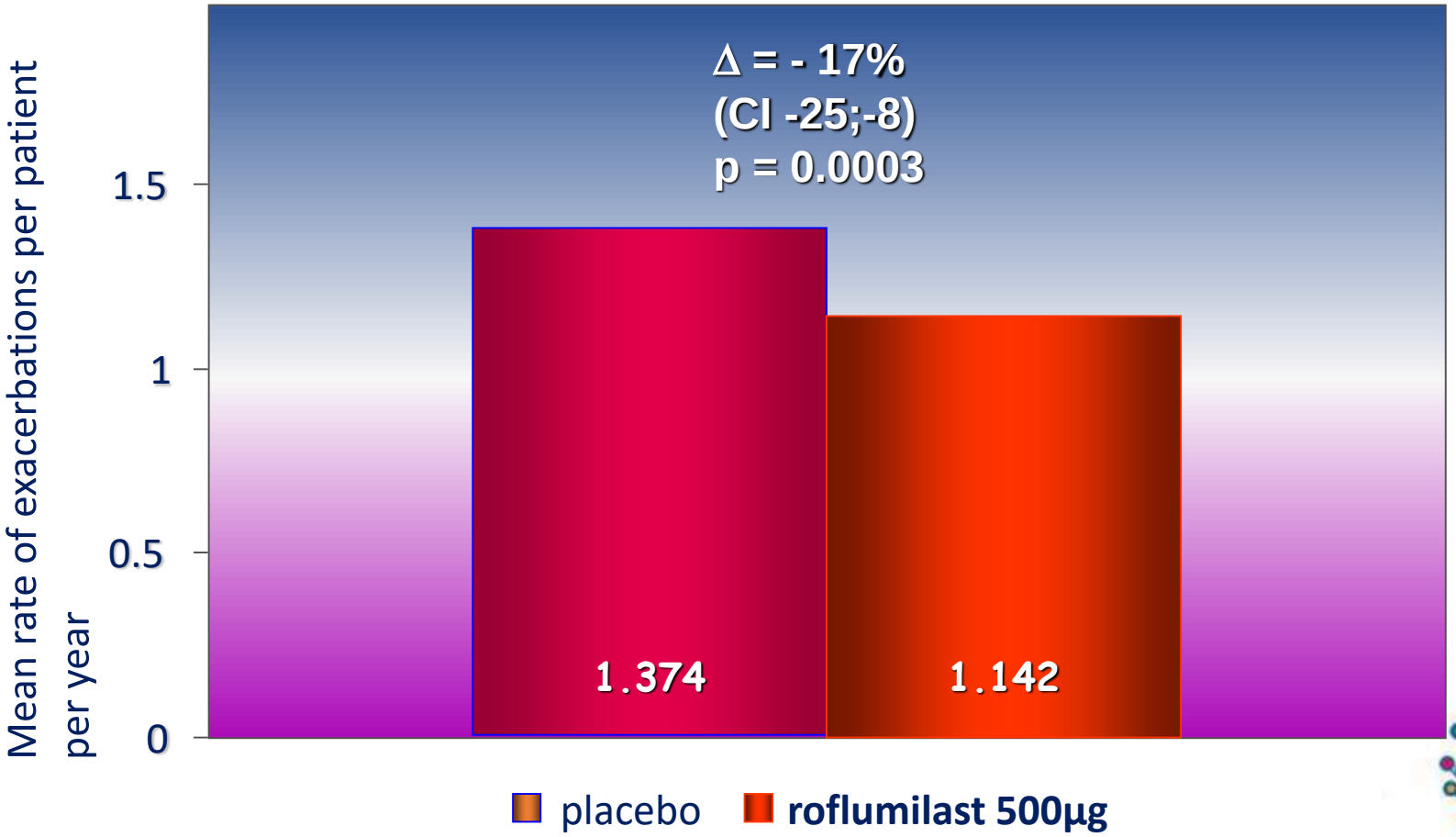
Number with available measurements						
Fixed triple	1077	1067	1047	1027	998	985
Tiotropium	1074	1052	1019	977	944	921
Open triple	538	536	526	510	502	495

Vestbo J, et al Lancet 2017

Nelle persone con BPCO, sintomi di bronchite cronica, VEMS o FEV_1 < 50% del valore teorico e frequenti riacutizzazioni (≥ 2), l'aggiunta di un inibitore delle fosfodiesterasi-4 (roflumilast) alla terapia regolare con broncodilatatori a lunga durata d'azione (LAMA o LABA):

- migliora i parametri spirometrici
- riduce la frequenza delle riacutizzazioni

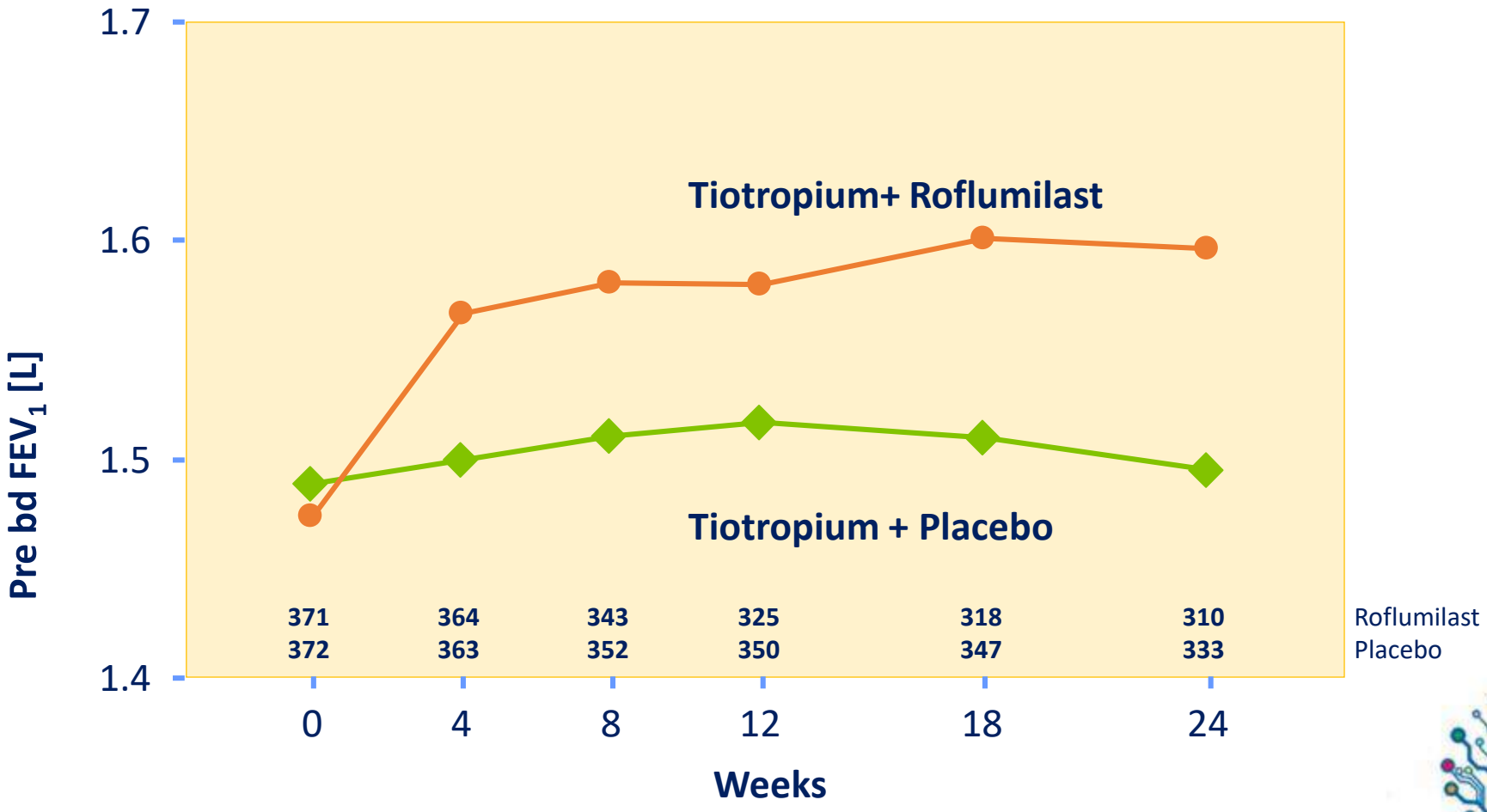
COPD Exacerbations (Moderate or Severe) M2-124 & M2-125 pooled analysis



Calverley PMA, Rabe, KF ,et al. Lancet 2009;374:685–94

Roflumilast as Add-On Therapy in COPD

Pre-bronchodilator FEV_1



Fabbri LM, Calverley PMA *et al*. *Lancet* 2009;374:695–703

Anti-inflammatory therapy in stable COPD

Antibiotics

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year (**Evidence A**).
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance (**Evidence A**) and hearing test impairment (**Evidence B**).

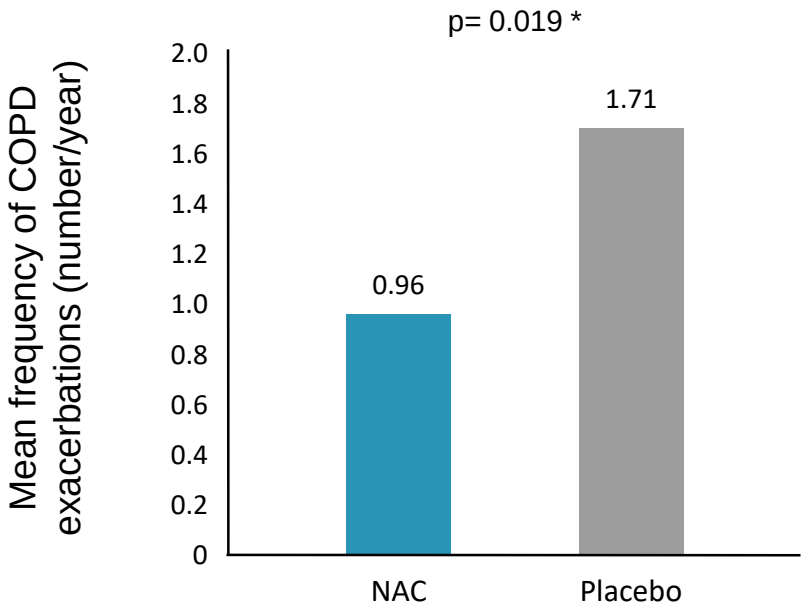
Mucolytics/antioxidants

- Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations (**Evidence B**).

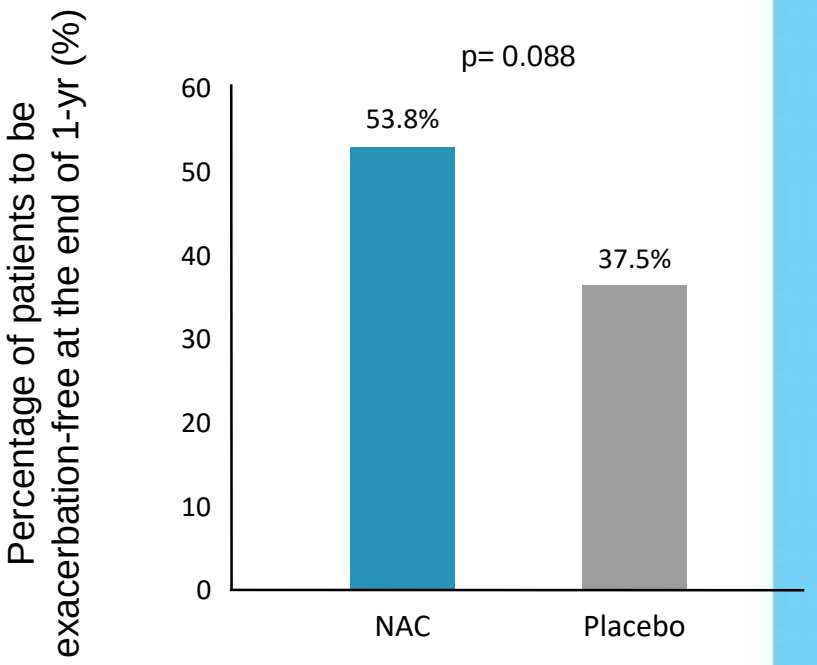
Other anti-inflammatory agents

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy (**Evidence A**). However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (**Evidence C**).
- Leukotriene modifiers have not been tested adequately in COPD patients.

NAC reduces the rate of AECOPD



Frequency of COPD exacerbation in NAC and placebo groups in the one-year follow-up period



Kaplan-Meier survival curves by severity of exacerbations in patients with COPD: (1) no acute exacerbations of COPD; (2) patients with acute exacerbations of COPD requiring emergency service visits without admission; (3) patients with acute exacerbations of COPD requiring one hospital admission; (4) patients with readmissions

Tse et al. Chest 2013


Il FEV_1 va molto bene

Grazie per l'attenzione

claudio.micheletto@aulss9.veneto.it