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# GOLD 2017: cosa c'è di nuovo

Istituti Clinici Scientifici Maugeri

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**Dipartimento di Medicina e Riabilitazione Cardiorespiratoria**

# Summary of new recommendations GOLD 2017

1. **Definition**
   - Impact of respiratory symptoms
2. **Risk factors**
3. **Spirometry**
4. **ABCD assessment tool**
   - Symptoms + Exacerbations

# COPD definition

GOLD 2011

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

GOLD 2017

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

# COPD definition: some aspects regarding symptoms

Symptoms (dyspnea, cough and/or sputum production)

- may precede the development of airflow limitation
- can exist in individuals with normal spirometry

Currently unclear if these patients have “chronic bronchitis” or an earlier presentation of what will eventually become COPD

# COPD definition – old and new

GOLD 2011

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that ~~is usually progressive~~ and ~~associated with an enhanced chronic inflammatory response in the airways and the lung~~ to noxious particles or gases.

GOLD 2017

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

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# Risk factors

- The main risk factor for COPD is **tobacco** smoking but other environmental exposures such as **biomass fuel exposure** and **air pollution** may contribute.

- Besides exposures, **host factors** predispose individuals to develop COPD. These include **genetic abnormalities, abnormal lung development and accelerated aging**.

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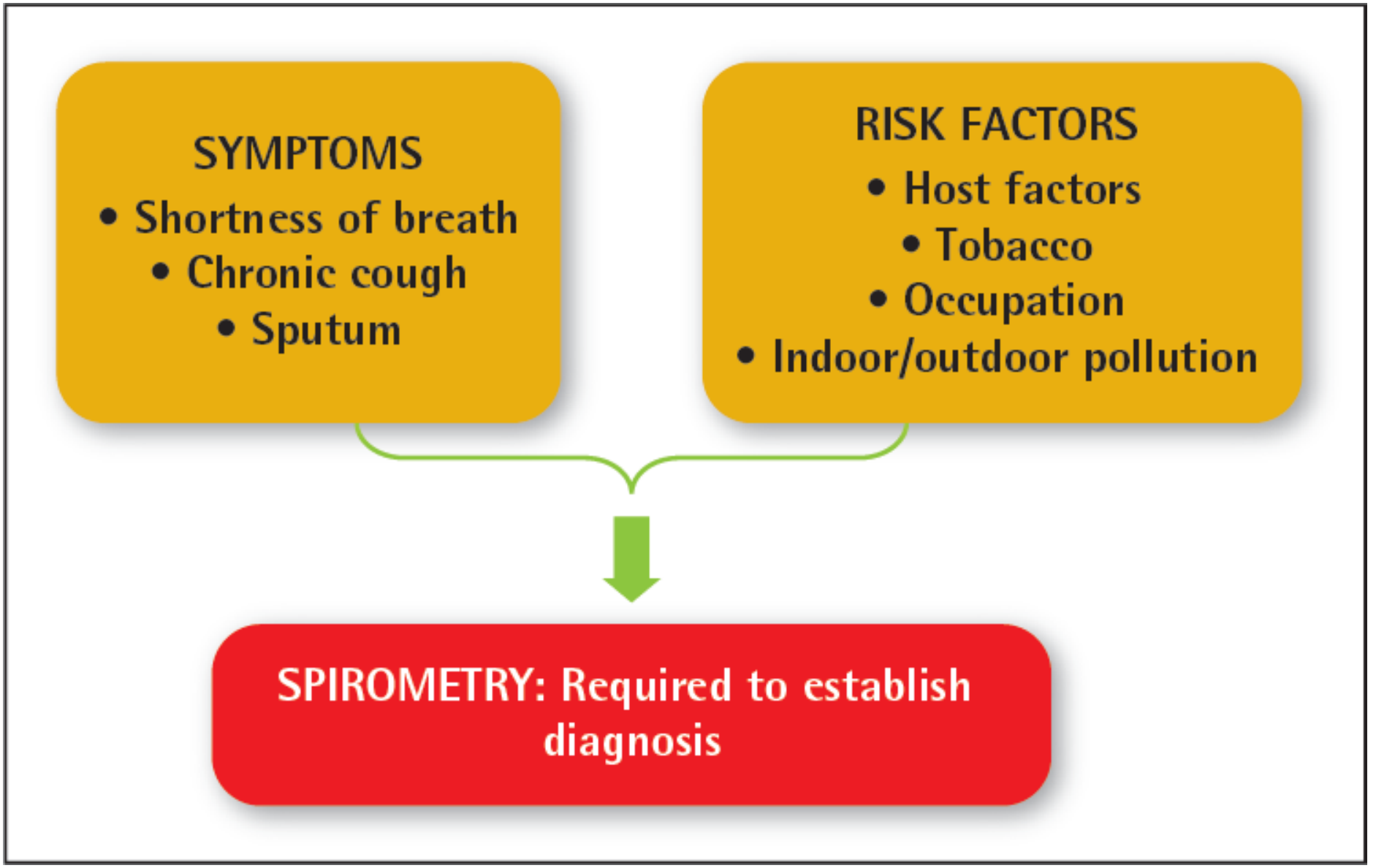
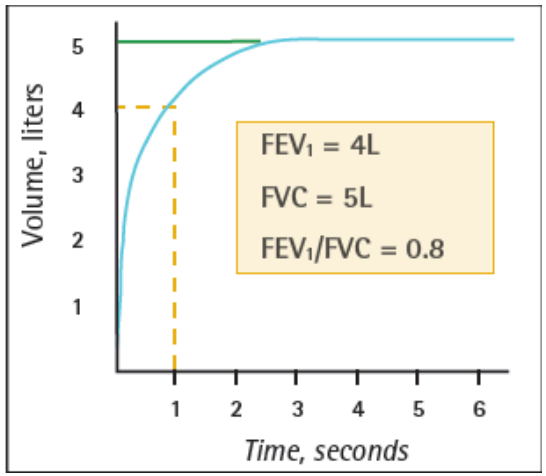



**Post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation**

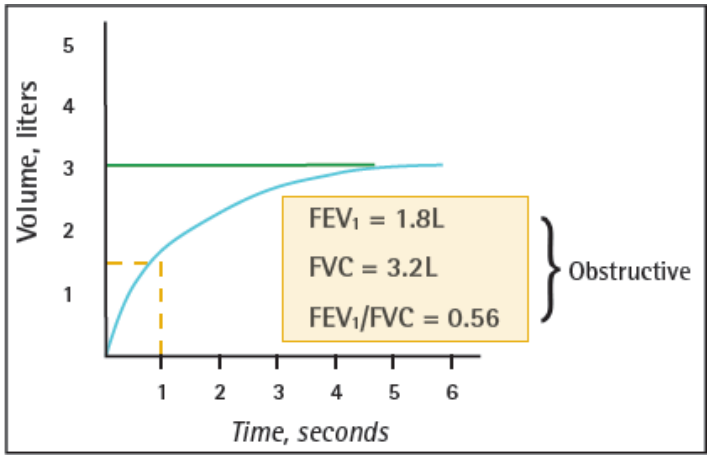
# Classification of airflow limitation severity in COPD

| Grade | $FEV_1$ (% predicted) |
|---|---|
| GOLD 1 | ≥ 80 |
| GOLD 2 | 50–79 |
| GOLD 3 | 30–49 |
| GOLD 4 | < 30 |




FVC =

$FEV_1$ =




1. **Diagnosis** essential

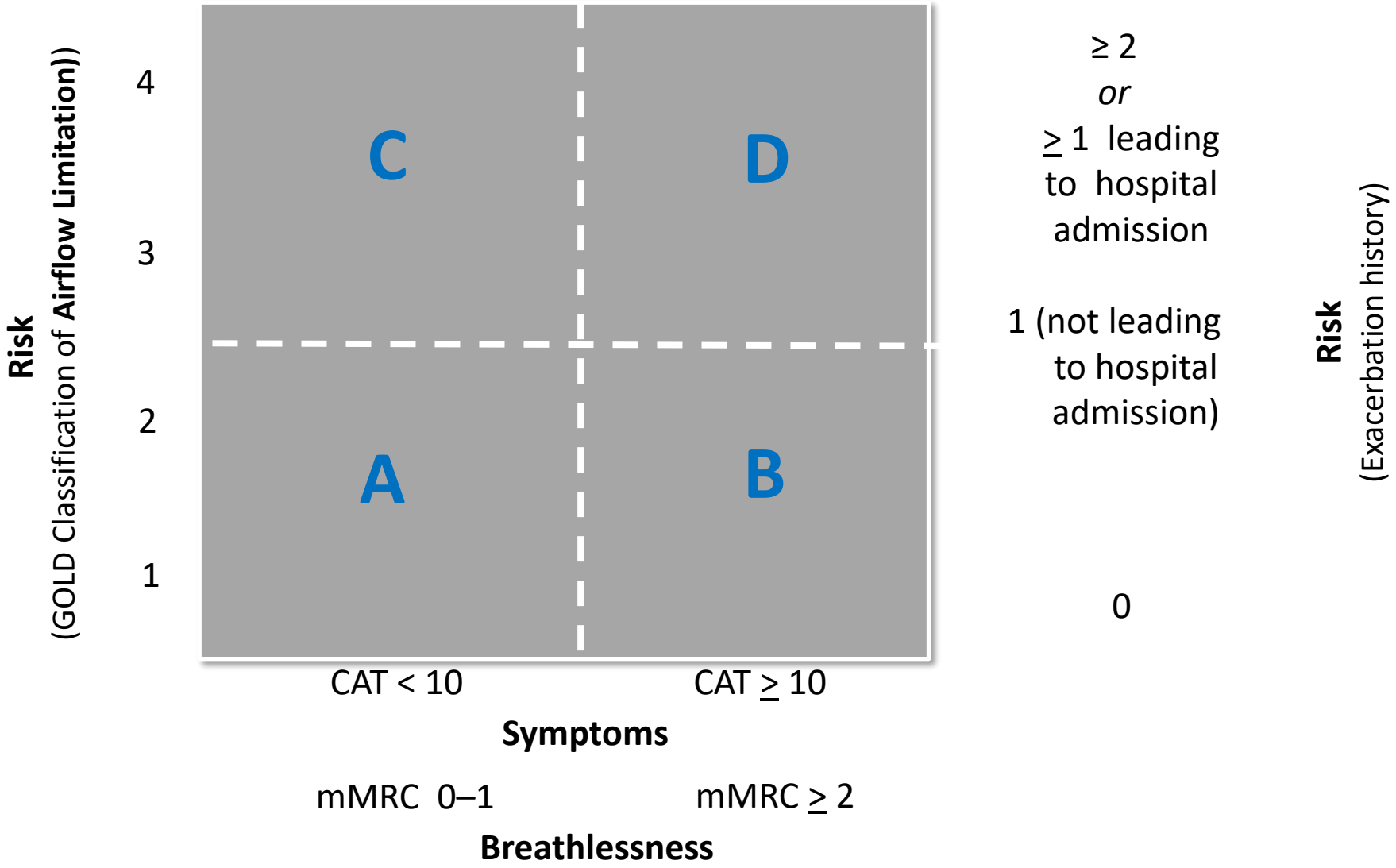
2. **Prognosis** essential

3. **Follow-up** identification of rapid decliners

# Summary of new recommendations GOLD 2017

1. **Definition**
   - Impact of respiratory symptoms
2. **Risk factors**
   - Environmental exposures
   - Host factors (early-life events)
3. **Spirometry**
4. **ABCD assessment tool**
   - Symptoms + Exacerbations

# 2011


Risk
(GOLD Classification of Airflow Limitation))
4
3
2
1
C
D
A
B
CAT < 10
CAT ≥ 10
Symptoms
mMRC 0–1
mMRC ≥ 2
Breathlessness
≥ 2
or
≥ 1 leading to hospital admission
1 (not leading to hospital admission)
0
Risk
(Exacerbation history)

Eur Respir J 2017; 49: 1700214

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

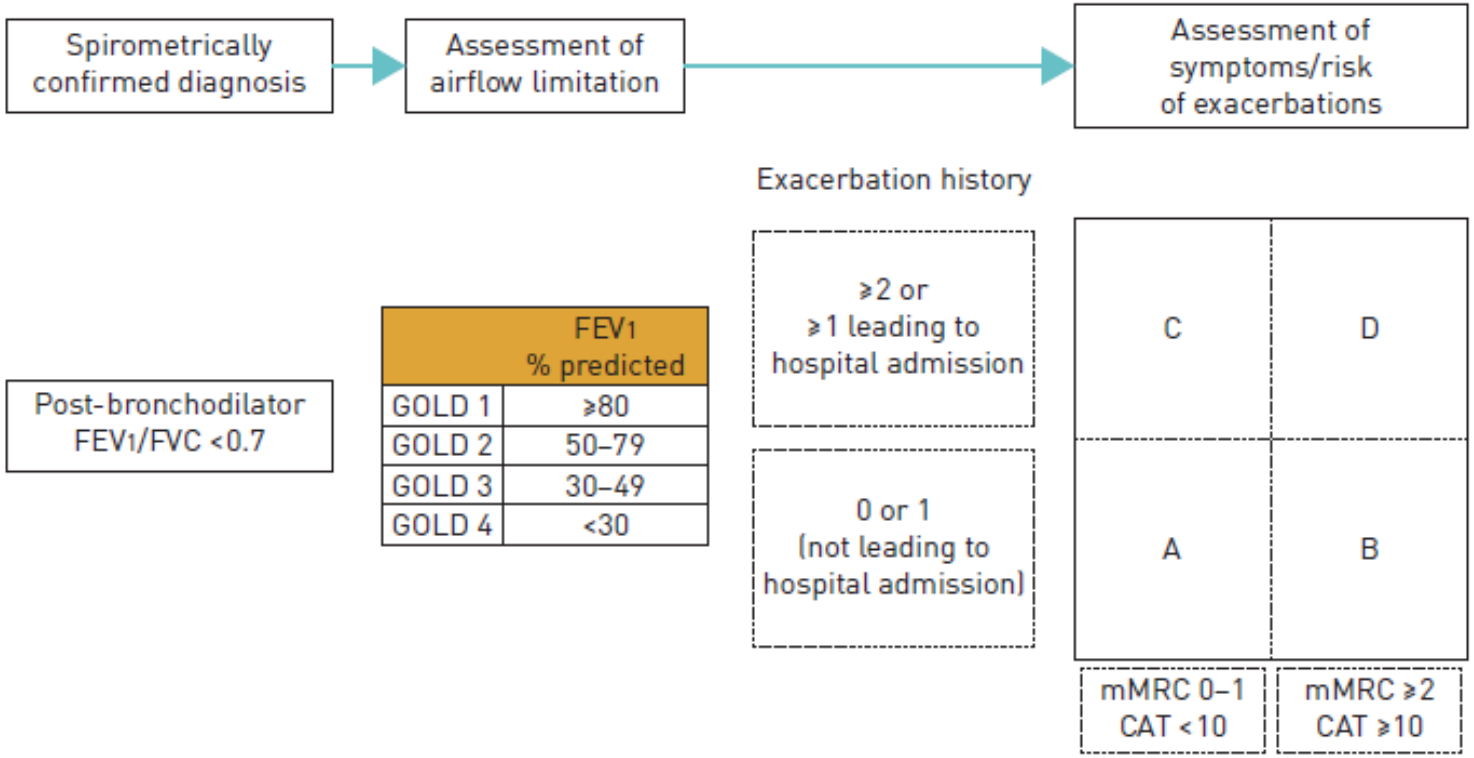
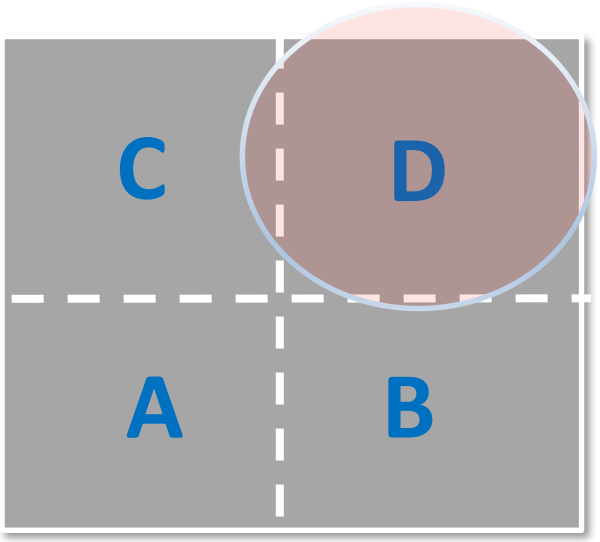



FIGURE 2 The refined ABCD assessment tool. $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; CAT: COPD Assessment Test.

## Two Patients

- Both with $FEV_1$ < 30% and CAT scores of 15
- One no AECOPD / the other 2 AECOPD

**(GOLD 2011)**




Both labelled GOLD D

**(GOLD 2017)**

| Grade | $FEV_1$ (% pred.) |
|---|---|
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| **2** | 50-79 |
| **3** | 30-49 |
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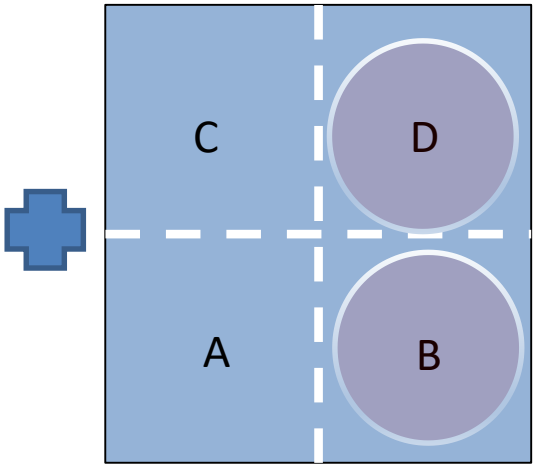
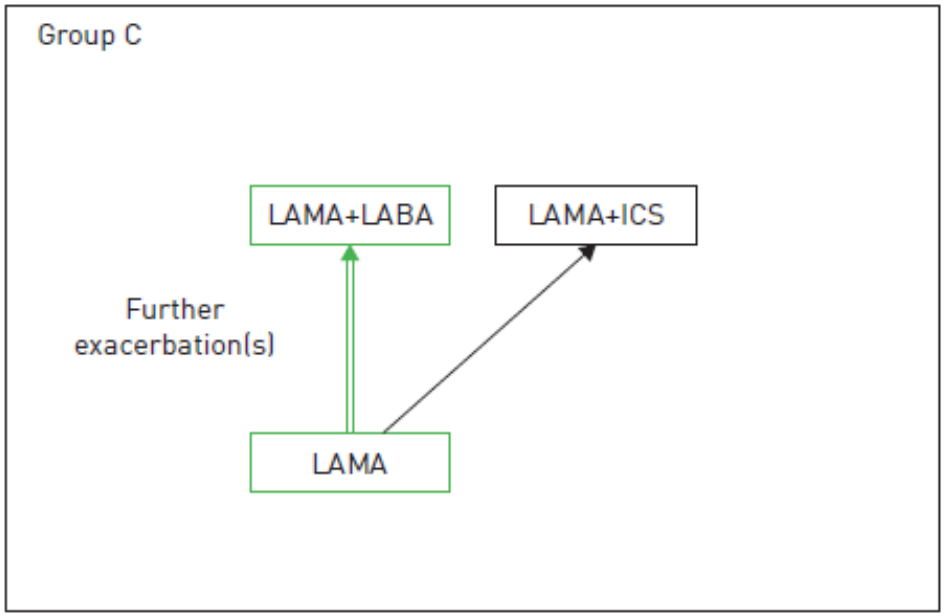
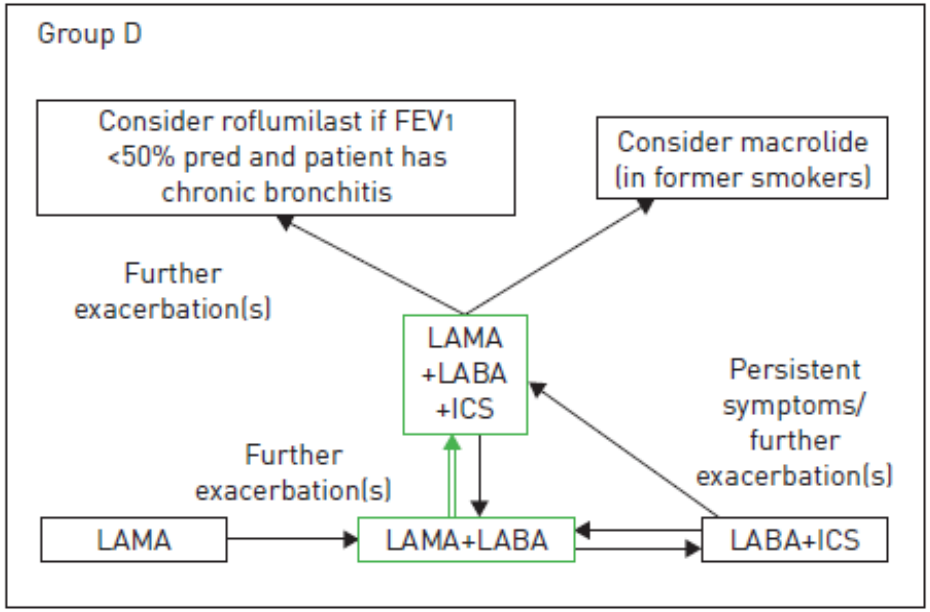
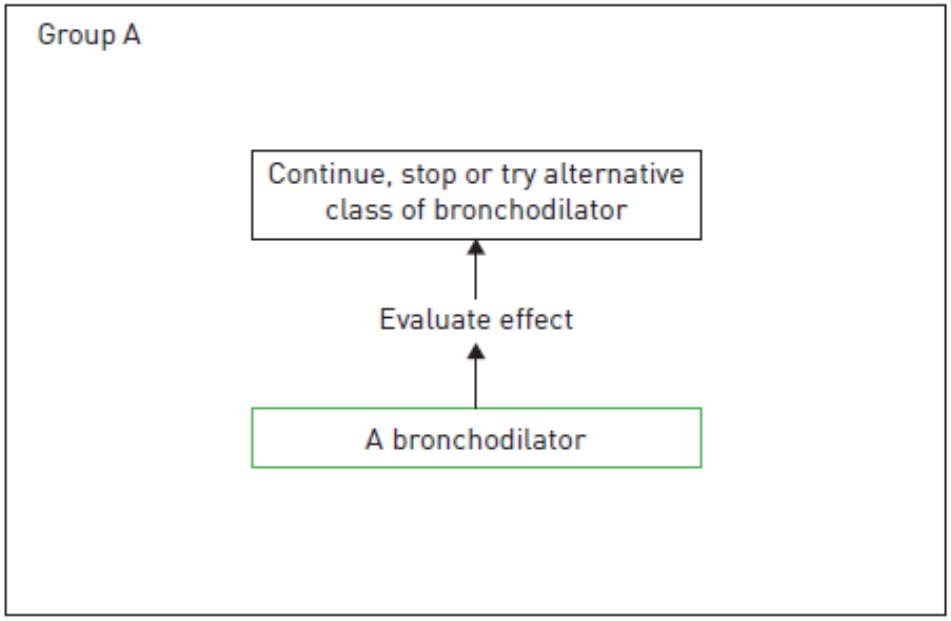
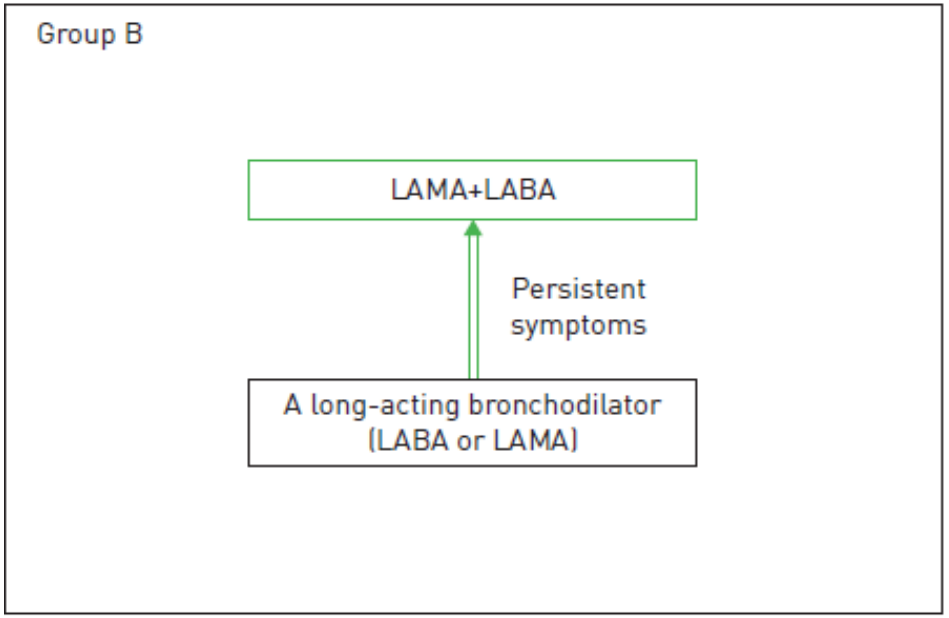


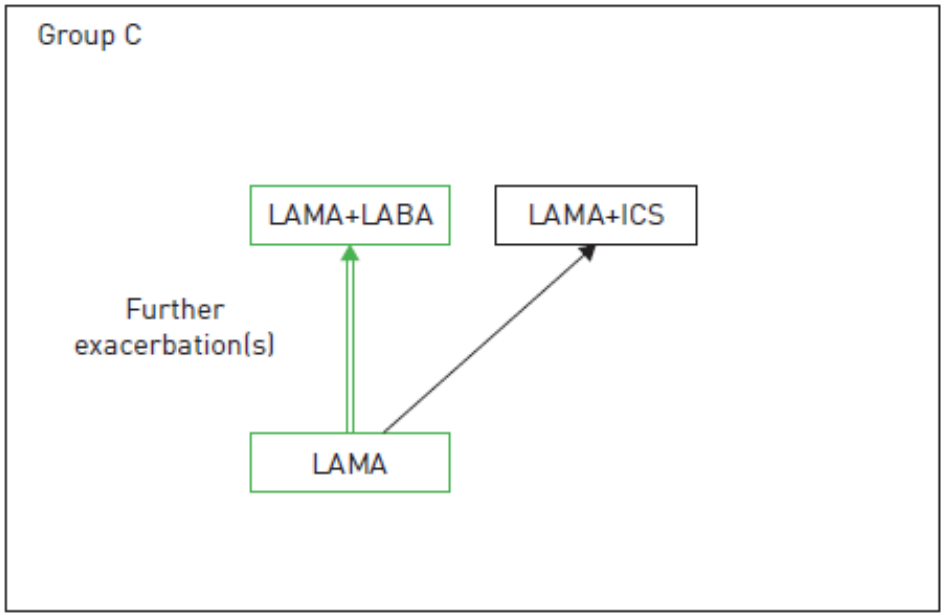

2 AECOPDs - GOLD 4, Category D
No AECOPDs- GOLD 4, Category B


Group C
LAMA+LABA
LAMA+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


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)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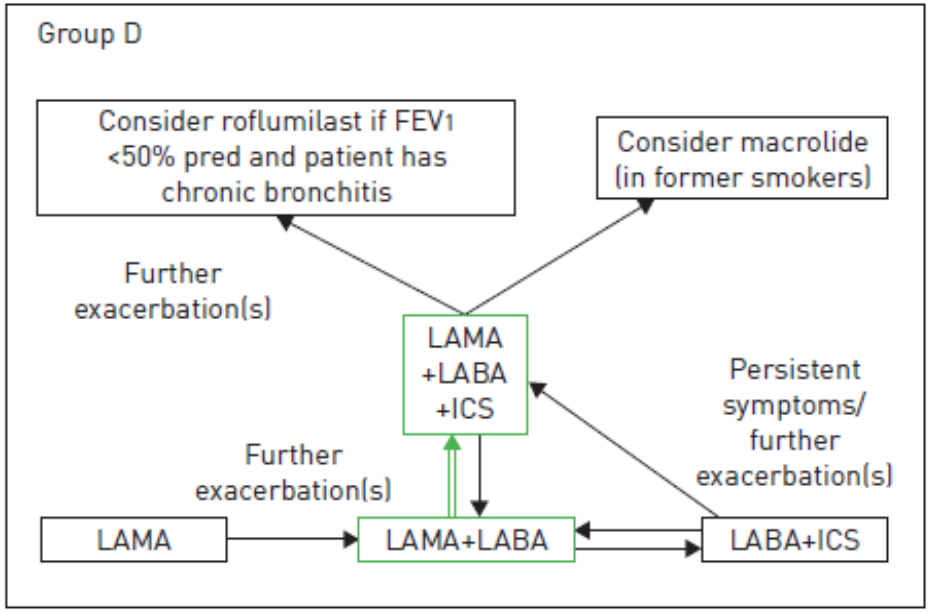
Further exacerbation(s)
LAMA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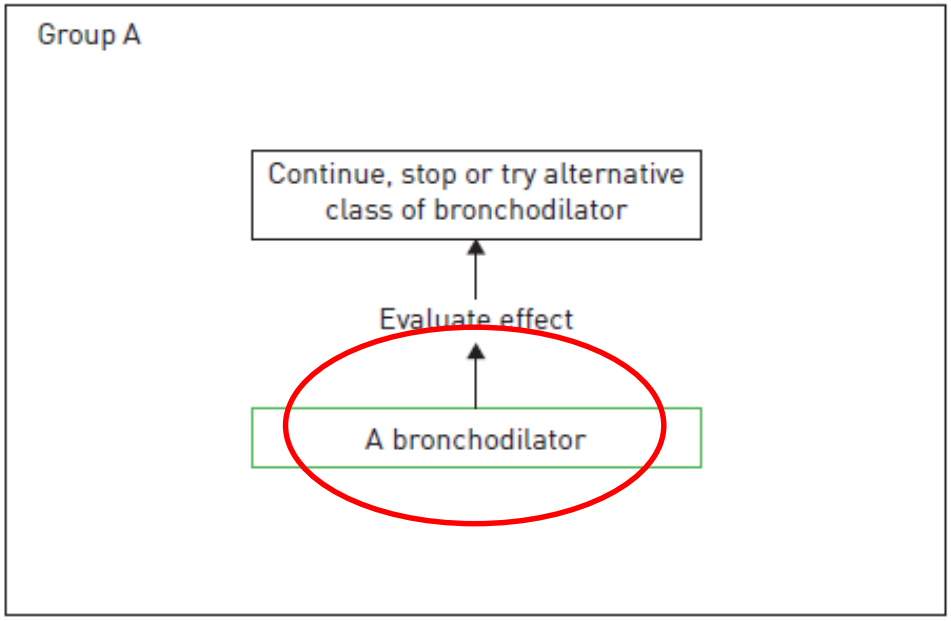
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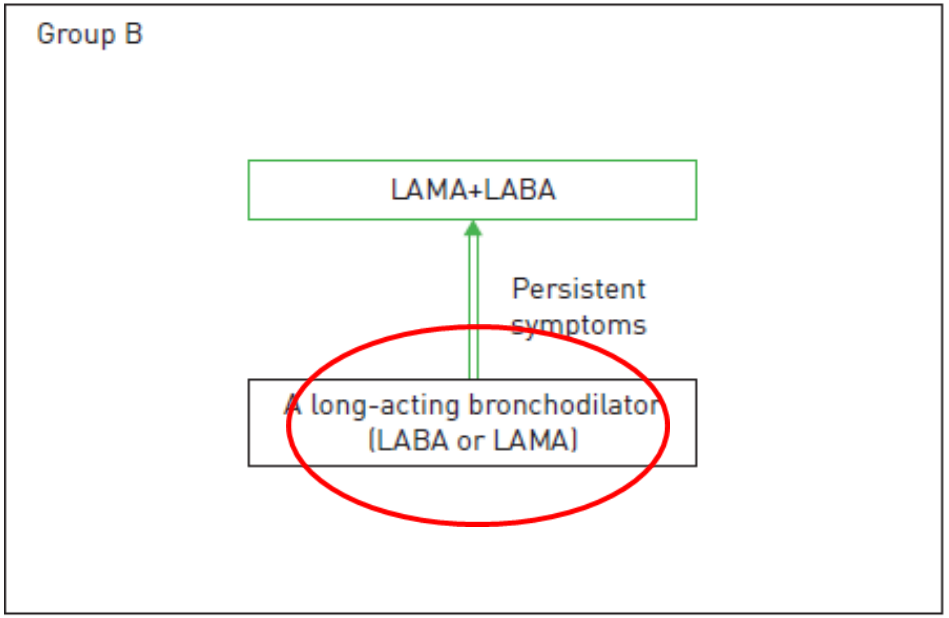
Group B
LAMA+LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

# Therapeutic Options: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

© 2013 Global Initiative for Chronic Obstructive Lung Disease

# Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis

International Journal of COPD 2017:12 367–381

James F Donohue[1]
Keith A Betts[2]
Ella Xiaoyan Du[2]
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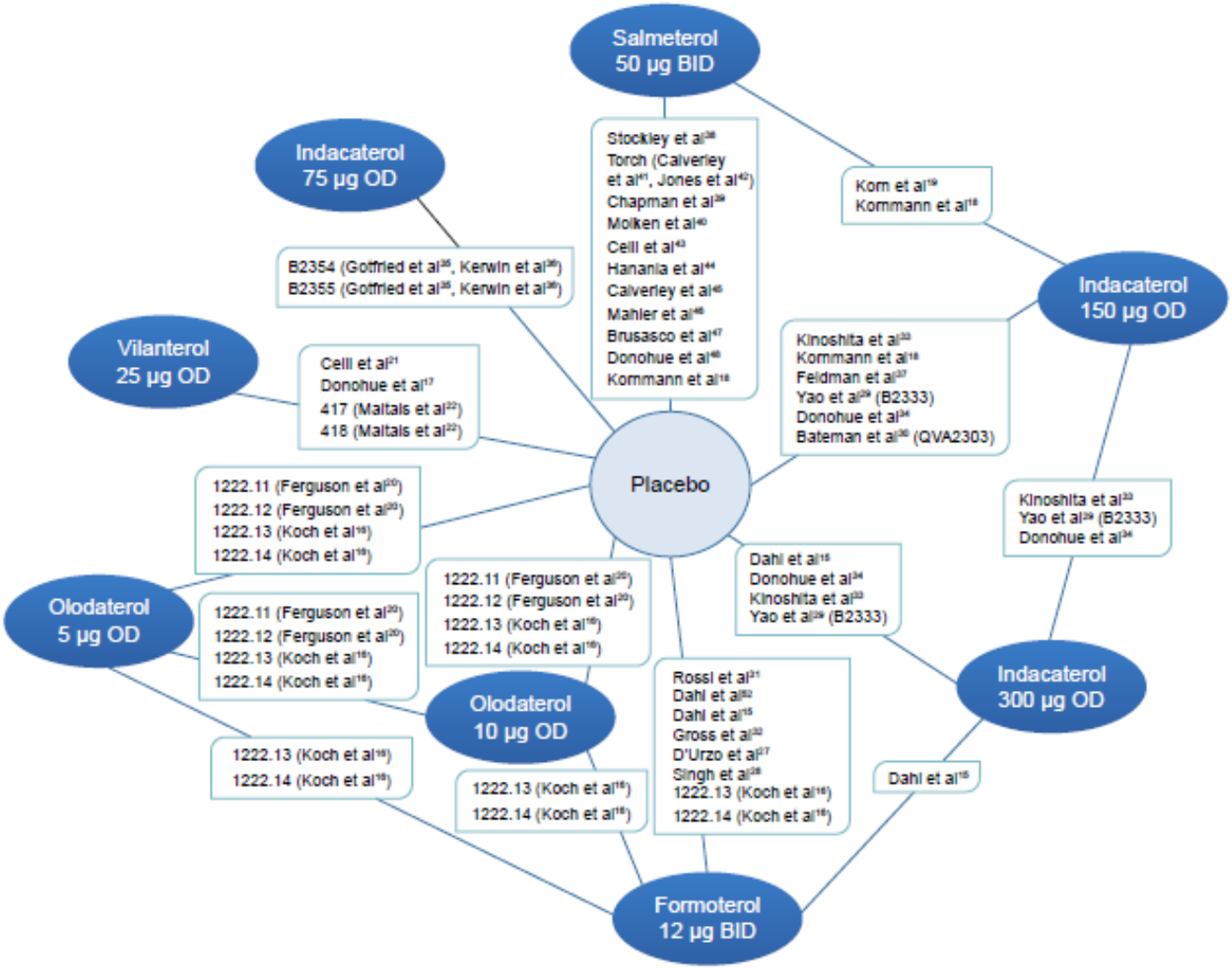


**Figure 2** Network diagram of LABA monotherapy trials included in network meta-analysis.
**Note:** N=33 total randomized controlled trials.
**Abbreviations:** BID, twice daily; OD, once daily; LABA, long-acting beta agonist.

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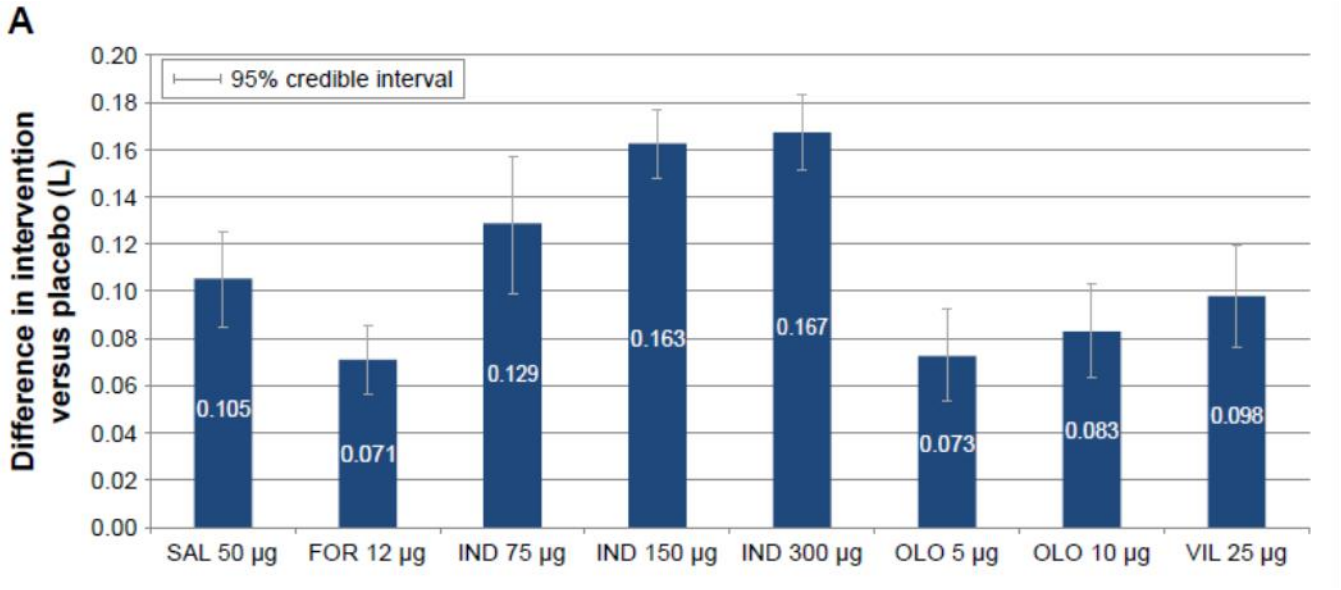


$FEV_1$

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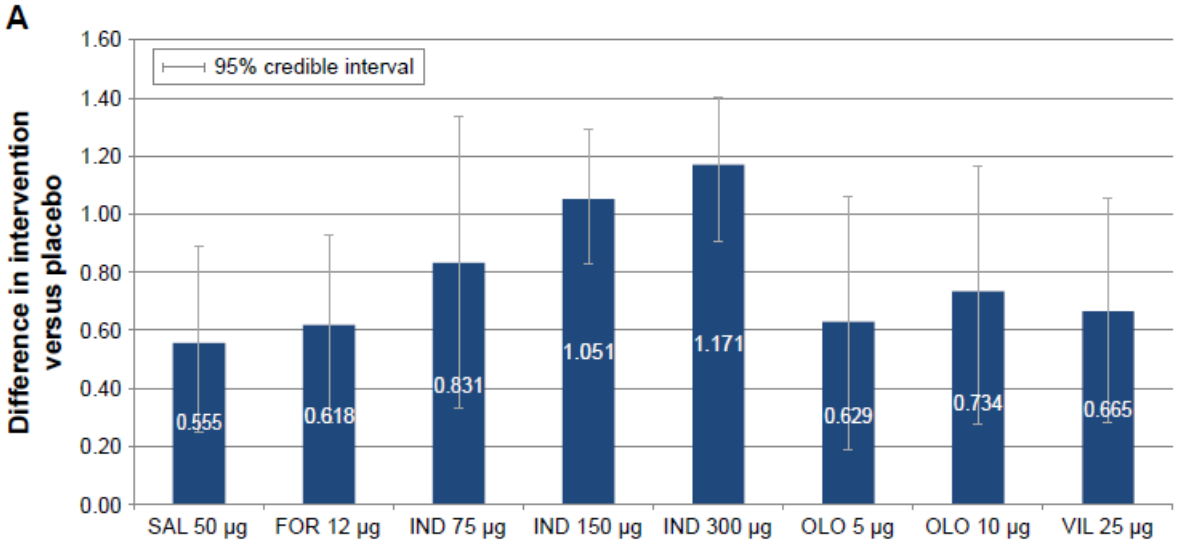


TDI

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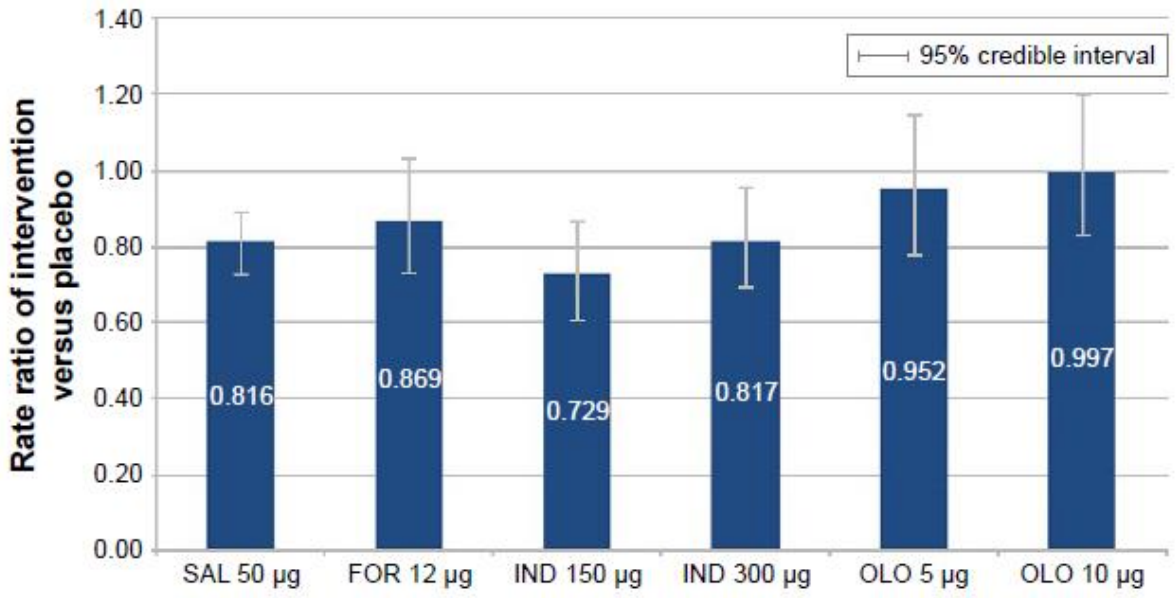
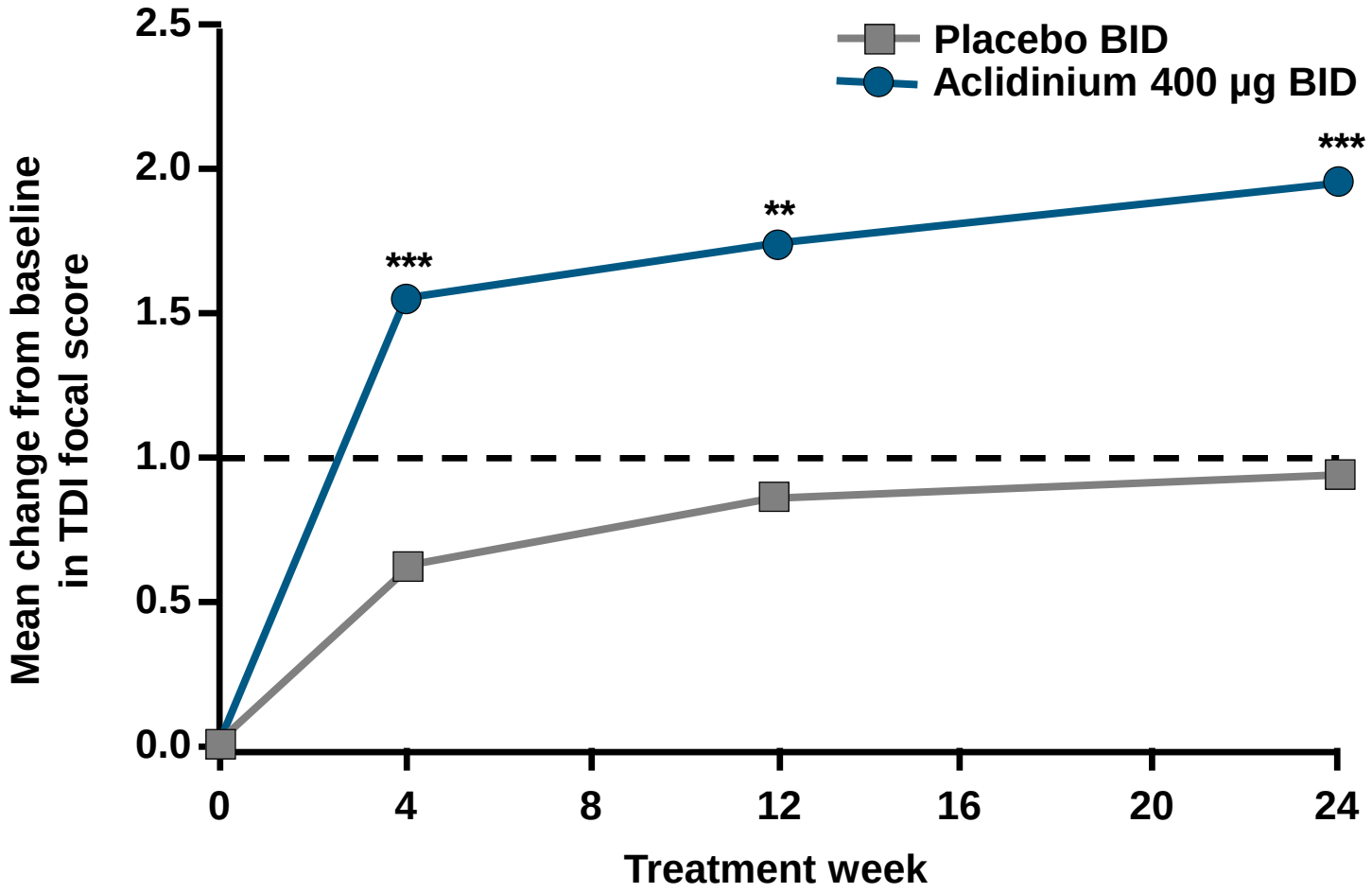



Exacerbations

# Aclidinium improves patient breathlessness
## ATTAIN

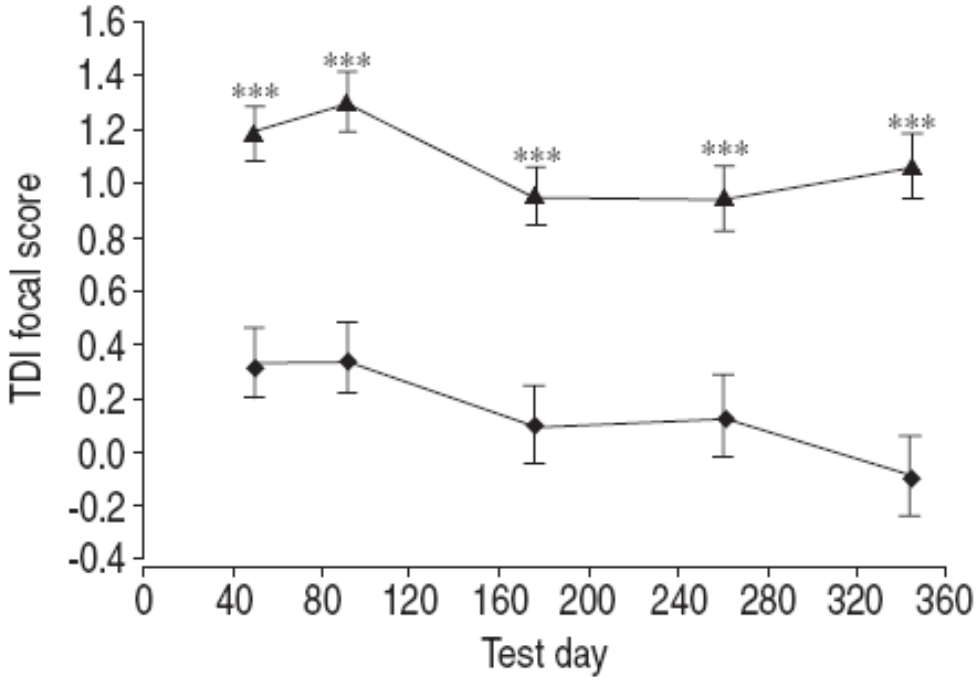



**p<0.01, ***p<0.001 vs placebo

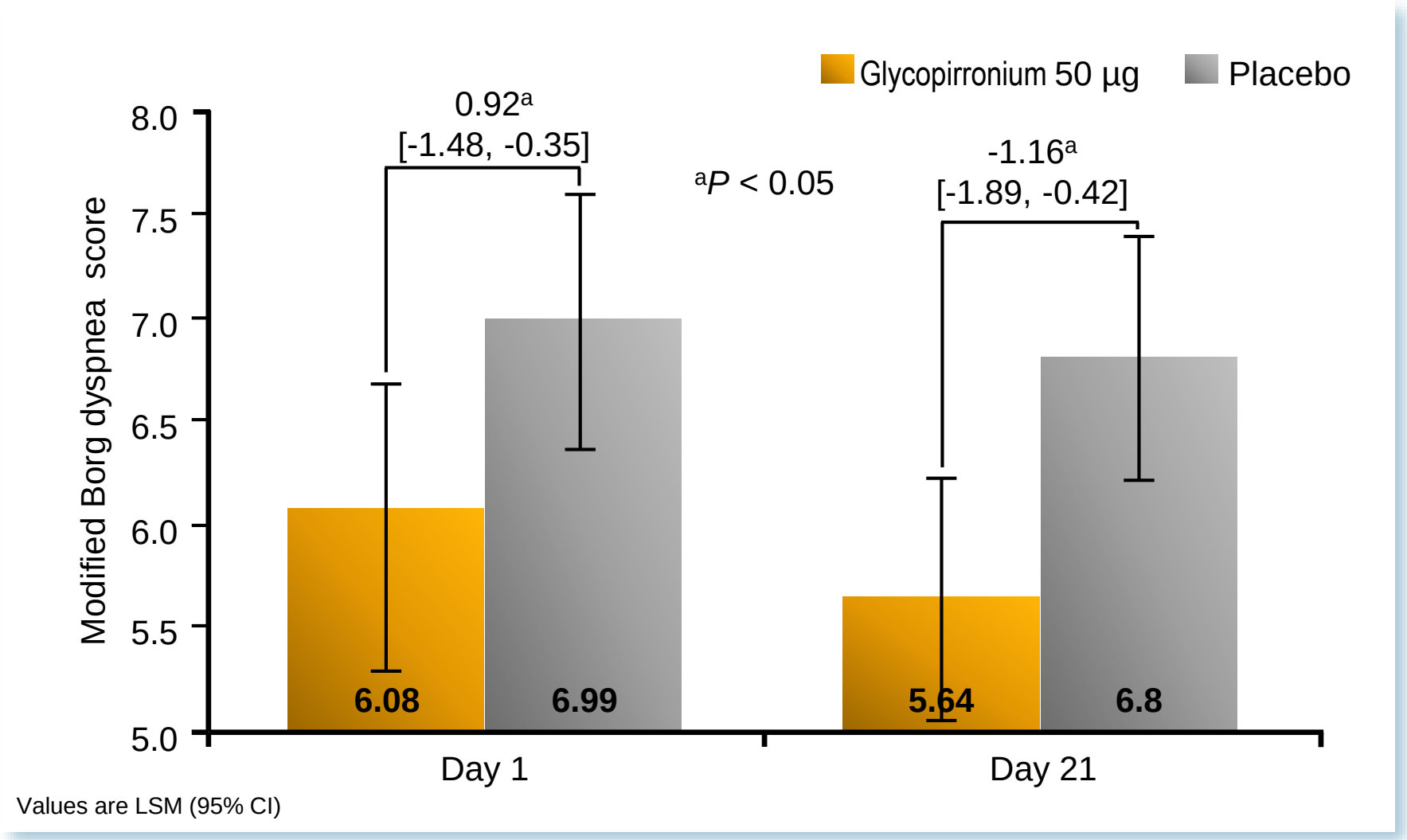
Jones et al, *Eur Respir J* 2012

# A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease

R. Casaburi*, D.A. Mahler#, P.W. Jones¶, A. Wanner+, G. San Pedro§, R.L. ZuWallackƒ, S.S. Menjoge**, C.W. Serby**, T. Witek Jr**

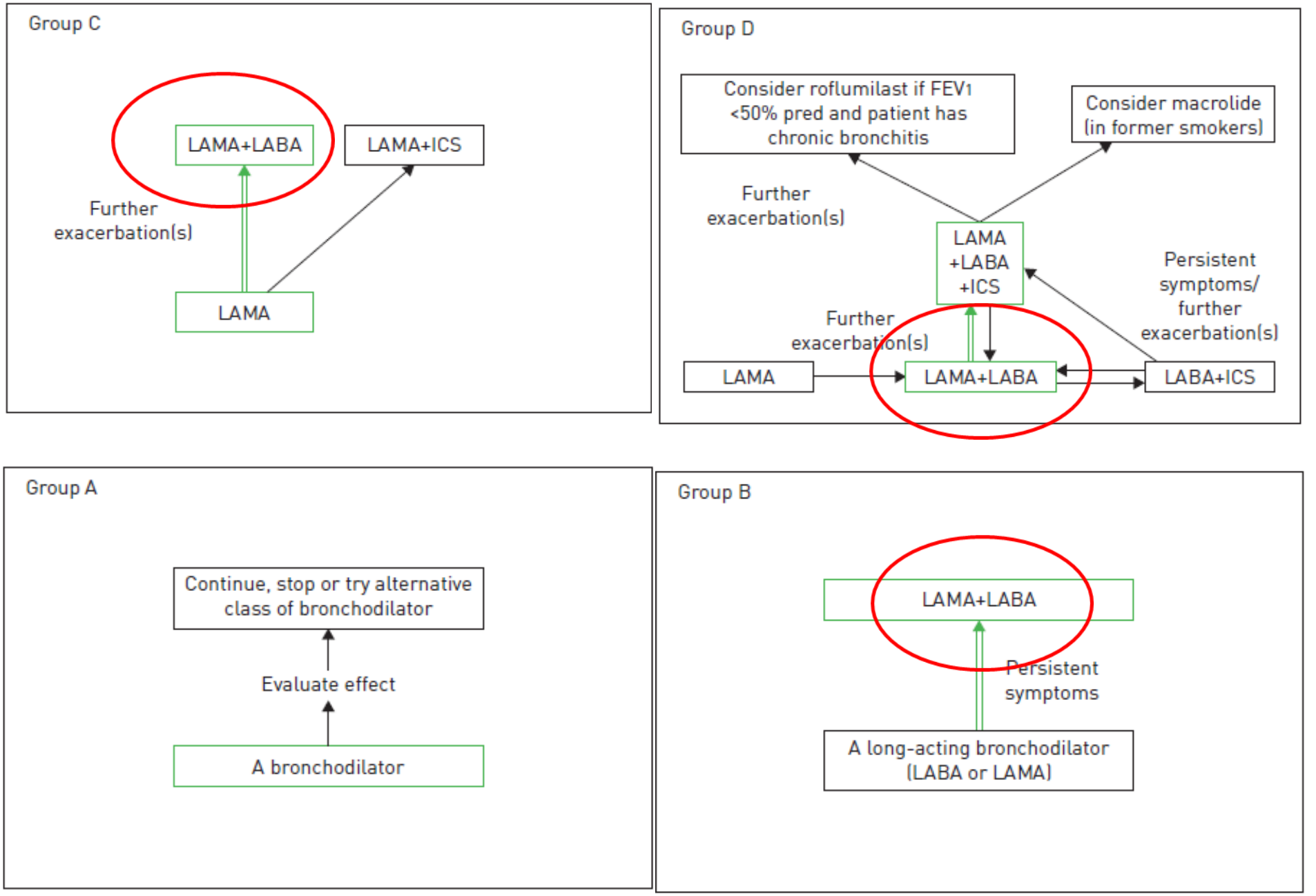



Eur Respir J 2002; 19: 217–224




Values are LSM (95% CI)

*Beeh KM et al. Int J Chron Obstruct Pulmon Dis 2012; 7:503–513*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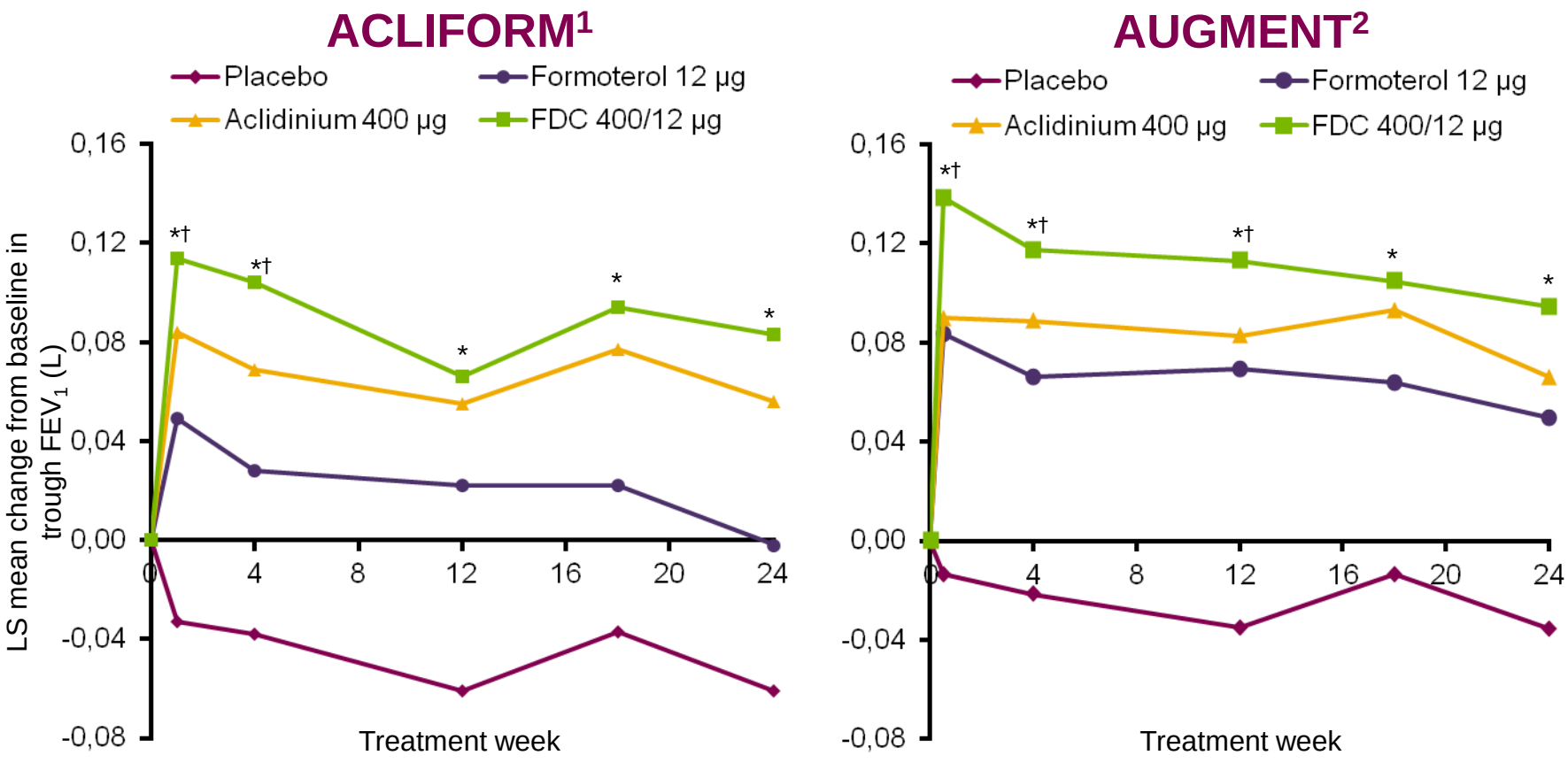



- FDC 400/12 µg significantly improves trough $FEV_1$ vs placebo and formoterol monotherapy at every measured time point

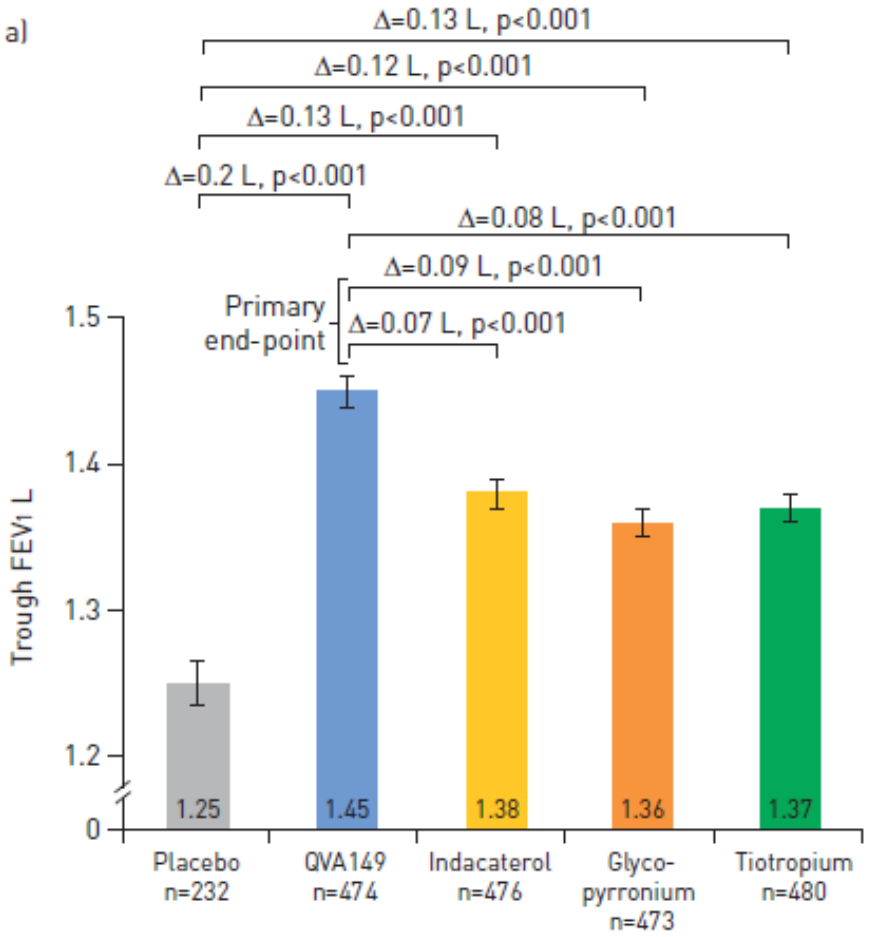
*p<0.05 vs placebo and formoterol; †p<0.05 vs aclidinium

[1]Singh et al. *BMC Pulm Med* 2014;14:178;
[2]D'Urzo et al. *Respir Res* 2014;15:123

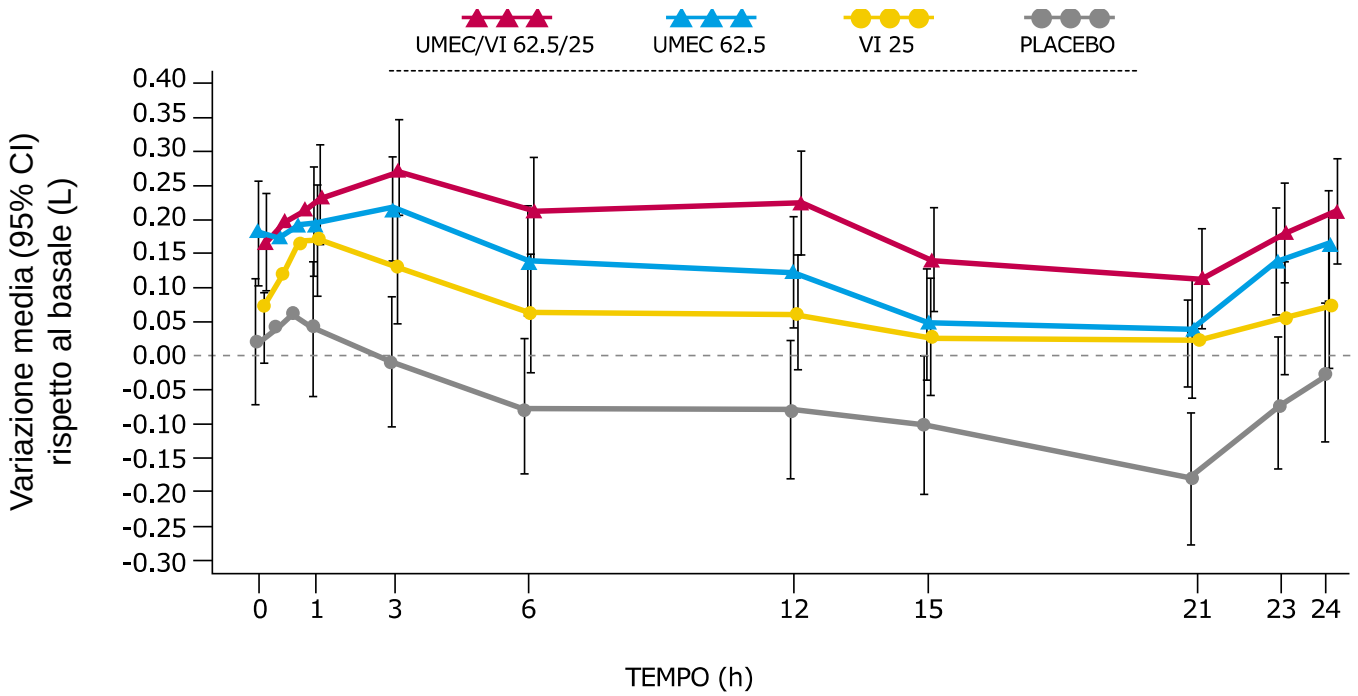
# Dual bronchodilation with QVA149 *versus* single bronchodilator therapy: the SHINE study

Eur Respir J 2013; 42: 1484–1494 | DOI: 10.1183/09031936.00200212

Eric D. Bateman[1], Gary T. Ferguson[2], Neil Barnes[3], Nicola Gallagher[4], Yulia Green[4], Michelle Henley[4] and Donald Banerji[5]



# Broncodilatazione efficace per 24 h




Giorno 168

Valori di $FEV_1$ seriale nelle 24h

*Donohue JF et al Respiratory Medicine 2013*

# The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease

Kai-Michael Beeh [a,*], Jan Westerman [b], Anne-Marie Kirsten [c], Jacques Hébert [d], Lars Grönke [e], Alan Hamilton [f], Kay Tetzlaff [e,g], Eric Derom [h]

Pulmonary Pharmacology & Therapeutics 32 (2015) 53–59

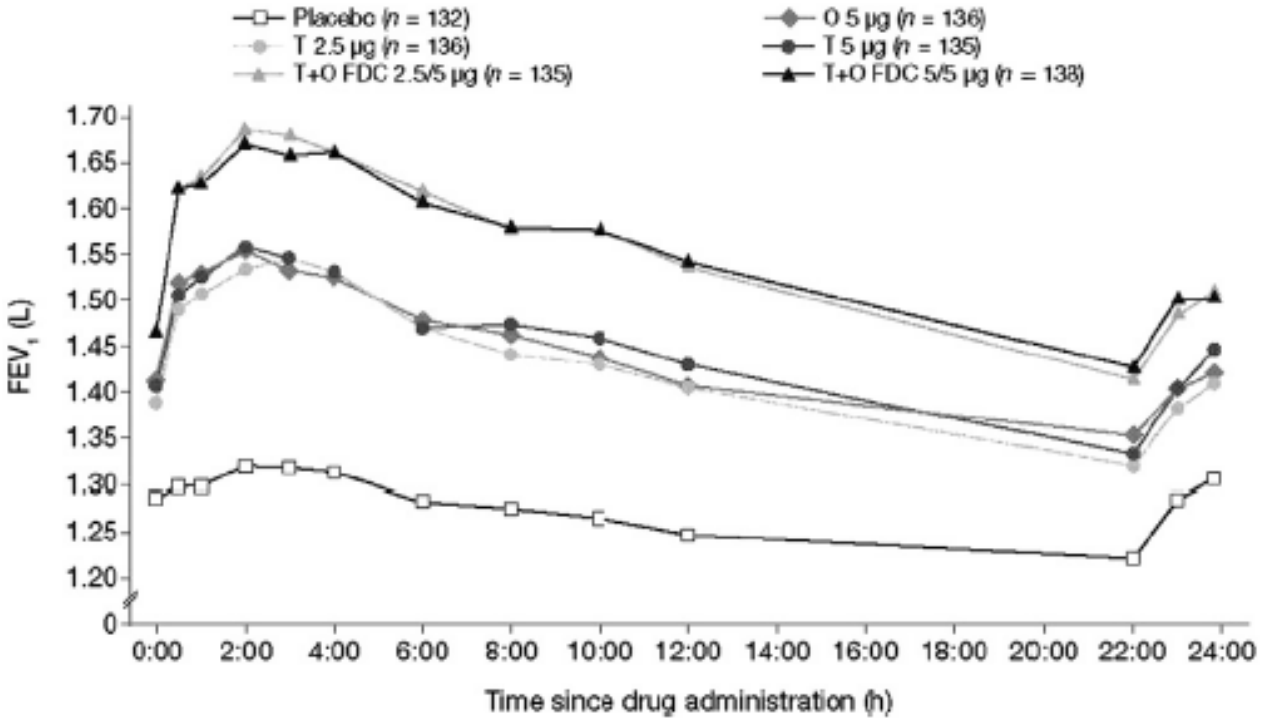



**Fig. 3.** Adjusted mean 24-h $FEV_1$ profile after 6 weeks of treatment (full analysis set). $FEV_1$, forced expiratory volume in 1 s; T, tiotropium; O, olodaterol; FDC, fixed-dose combination.

improvements in lung function over 24 h with an FDC of tiotropium + olodaterol over tiotropium or olodaterol alone, with no observed difference in tolerability

CHEST

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

CHEST 2016; 149(5):1181-1196

*Luigino Calzetta, PhD; Paola Rogliani, MD; Maria Gabriella Matera, MD; and Mario Cazzola, MD*

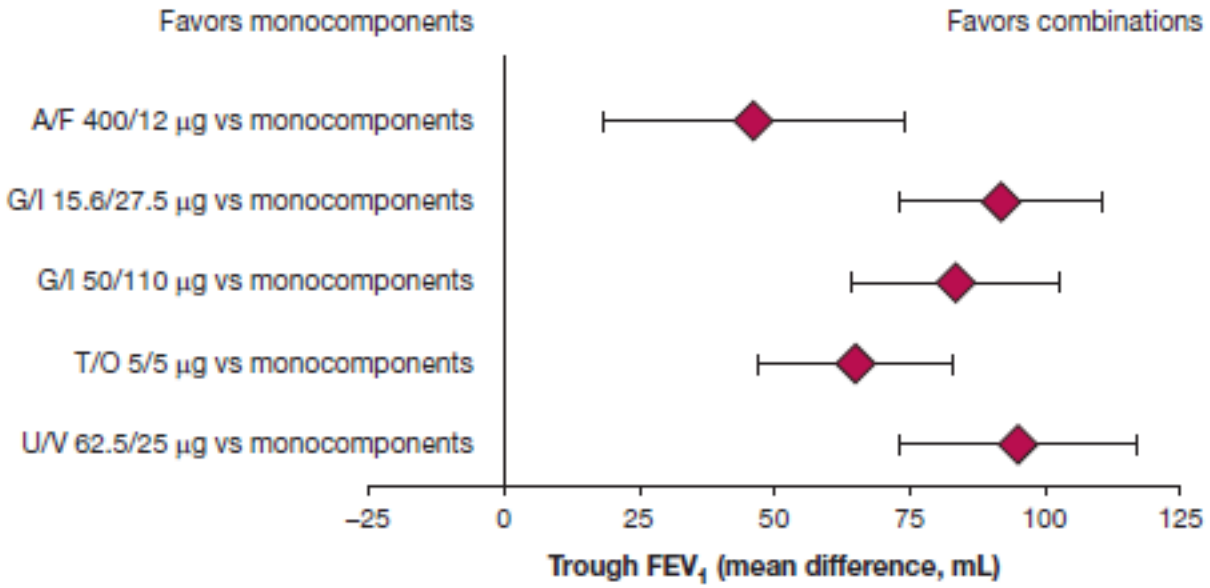



Figure 3 – *Forest plot meta-analysis of the impact of approved doses of long-acting muscarinic antagonist/long-acting β2-agonist combinations on trough FEV₁. Data are expressed as mean difference (mL) vs monocomponents. See Figure 2 legend for expansion of abbreviations.*

CHEST

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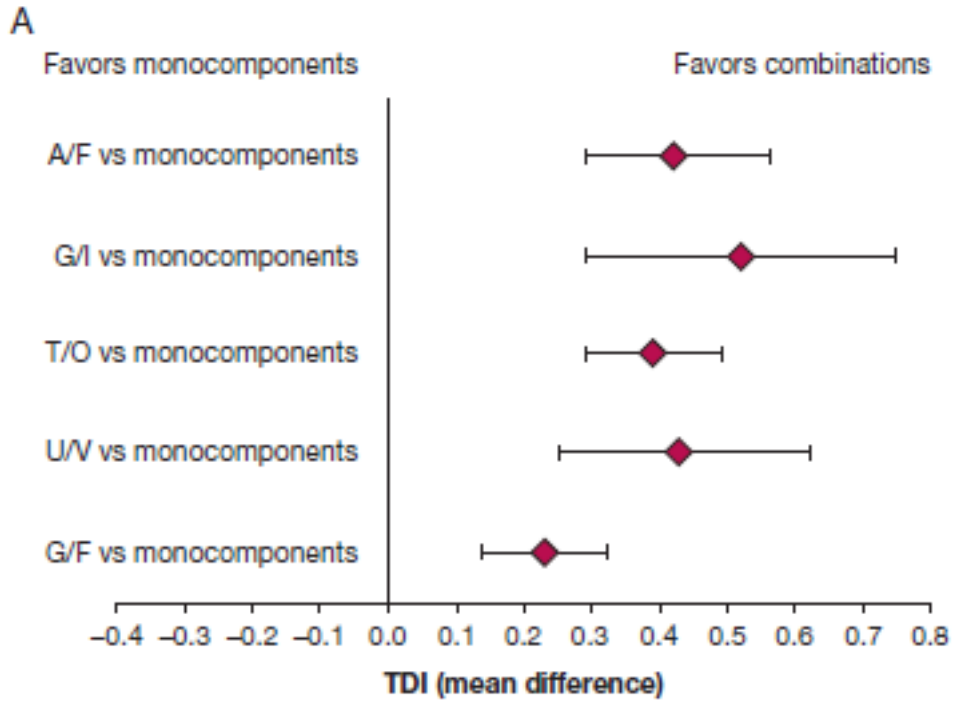
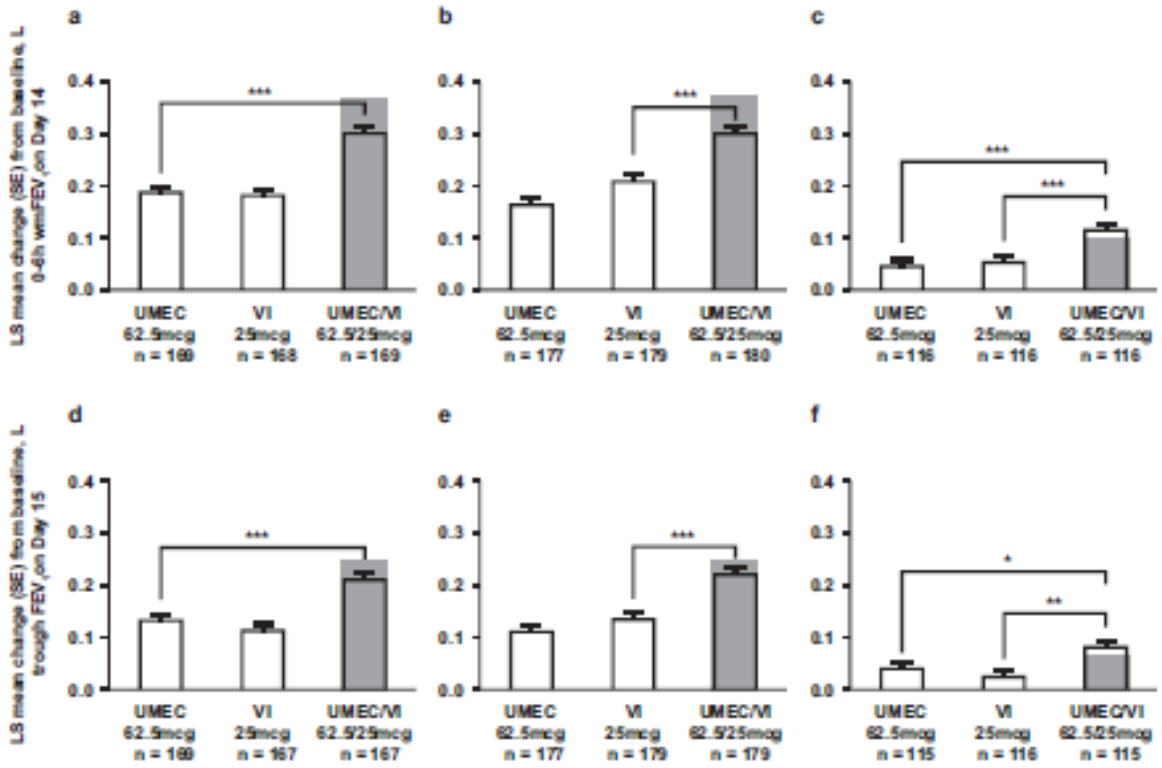
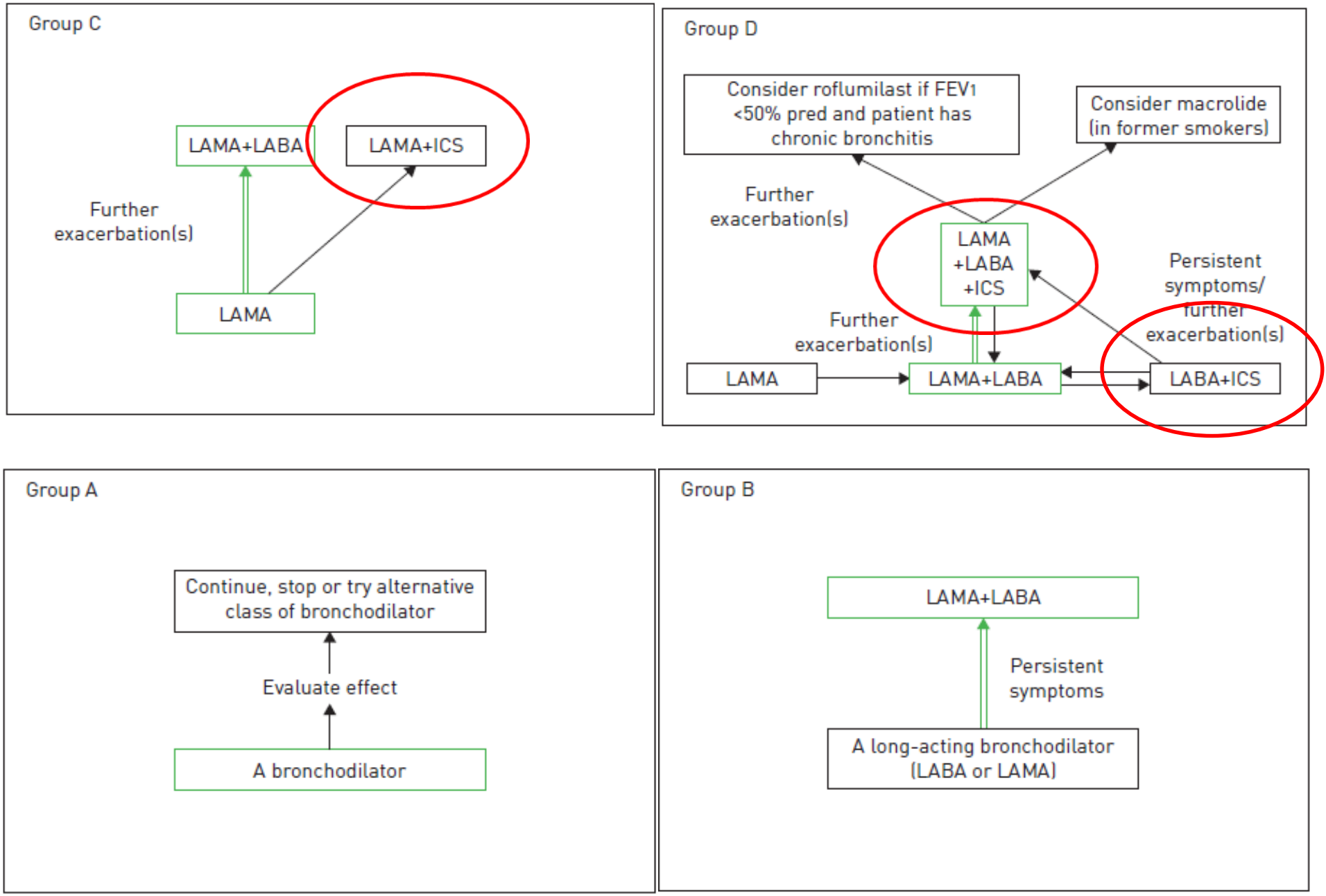


# Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: Results from two randomised controlled trials

James F. Donohue [a,*], Dave Singh [b], Clara Munzu [c], Sally Kilbride [d], Alison Church [e]




Our data suggests a more than additive phenomenon of UMEC/VI in patients who are non-responders to monotherapy. The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Group A
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Group B
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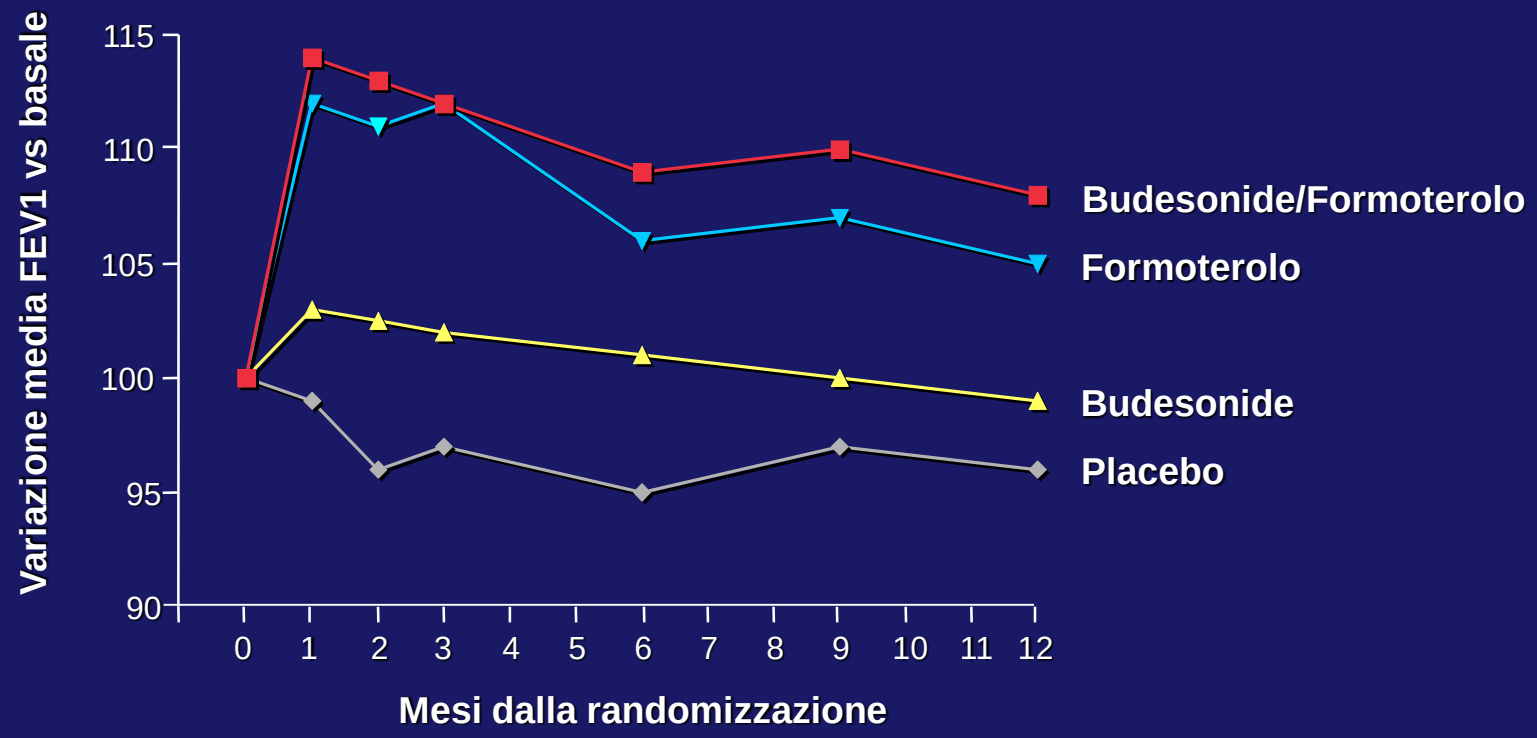
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

# Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease

W. Szafranski*, A. Cukier#, A. Ramirez¶, G. Menga+, R. Sansores§, S. Nahabedianƒ, S. Peterson**, H. Olsson**

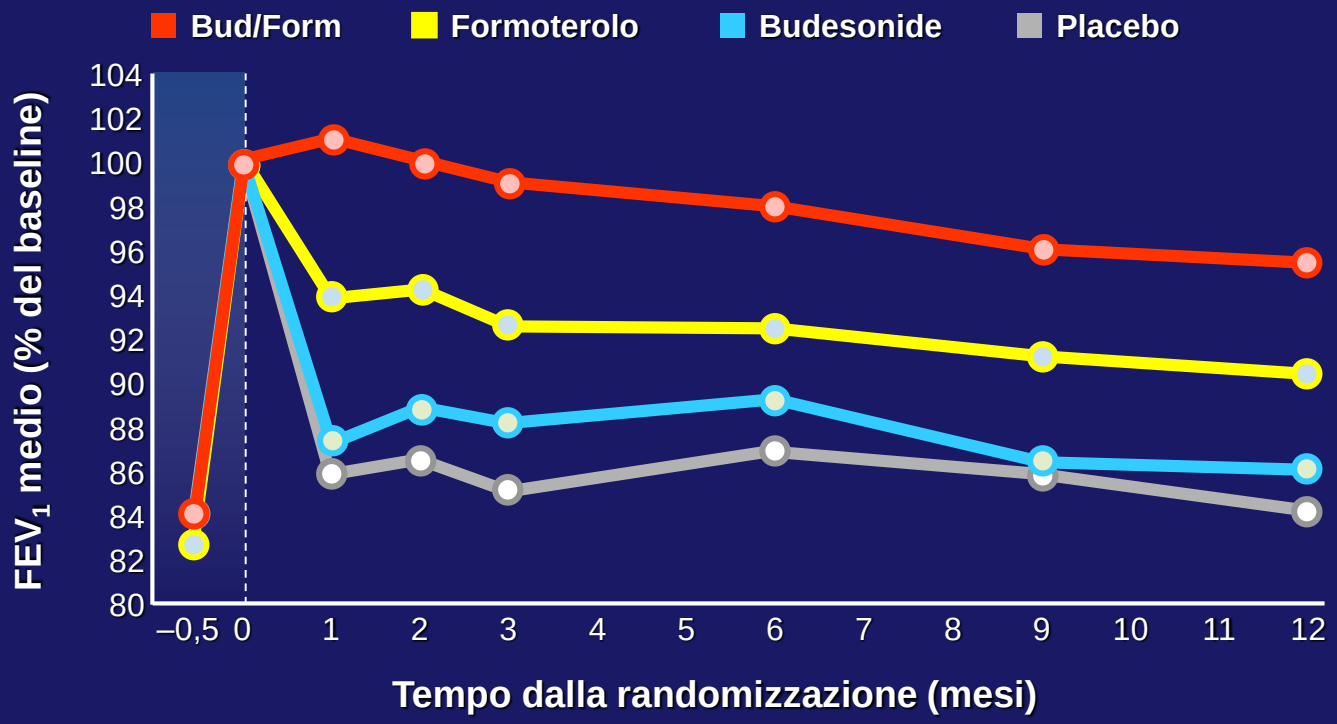



p<0.001 Budesonide/Formoterolo vs placebo e Budesonide
p<0.001 Formoterolo vs placebo
p<0.05 Budesonide vs placebo

Szafranski et al, Eur Respir J 2003; 21:74-81

# Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease

P.M. Calverley*, W. Boonsawat#, Z. Cseke¶, N. Zhong+, S. Peterson§, H. Olsson§

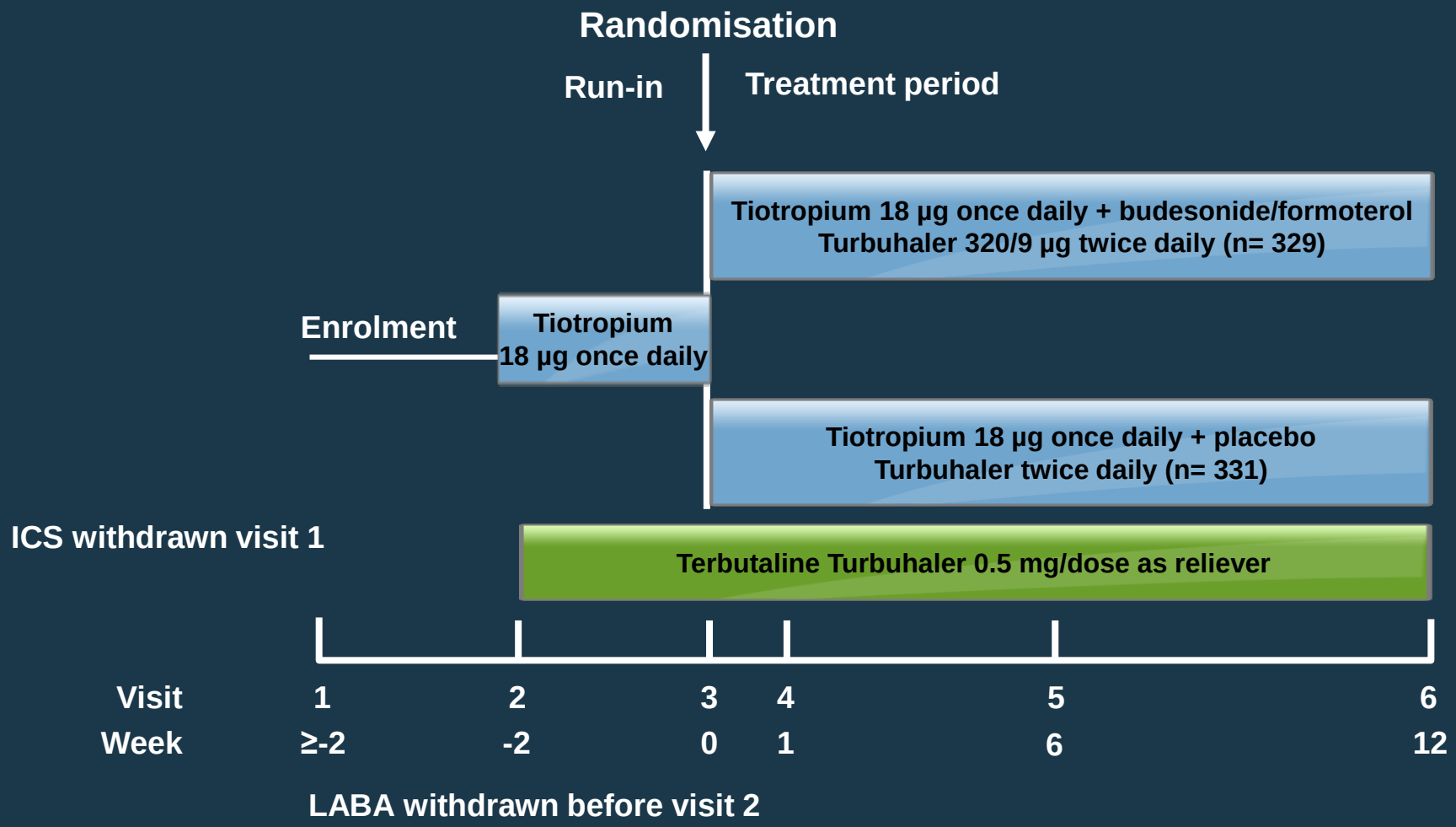



p<0,001 Bud/Form vs placebo e budesonide;
p=0,002 Bud/Form vs formoterolo;
p<0,001 formoterolo vs placebo

Calverley PM et al. Eur Respir J 2003; 22: 912-919

# The CLIMB study design

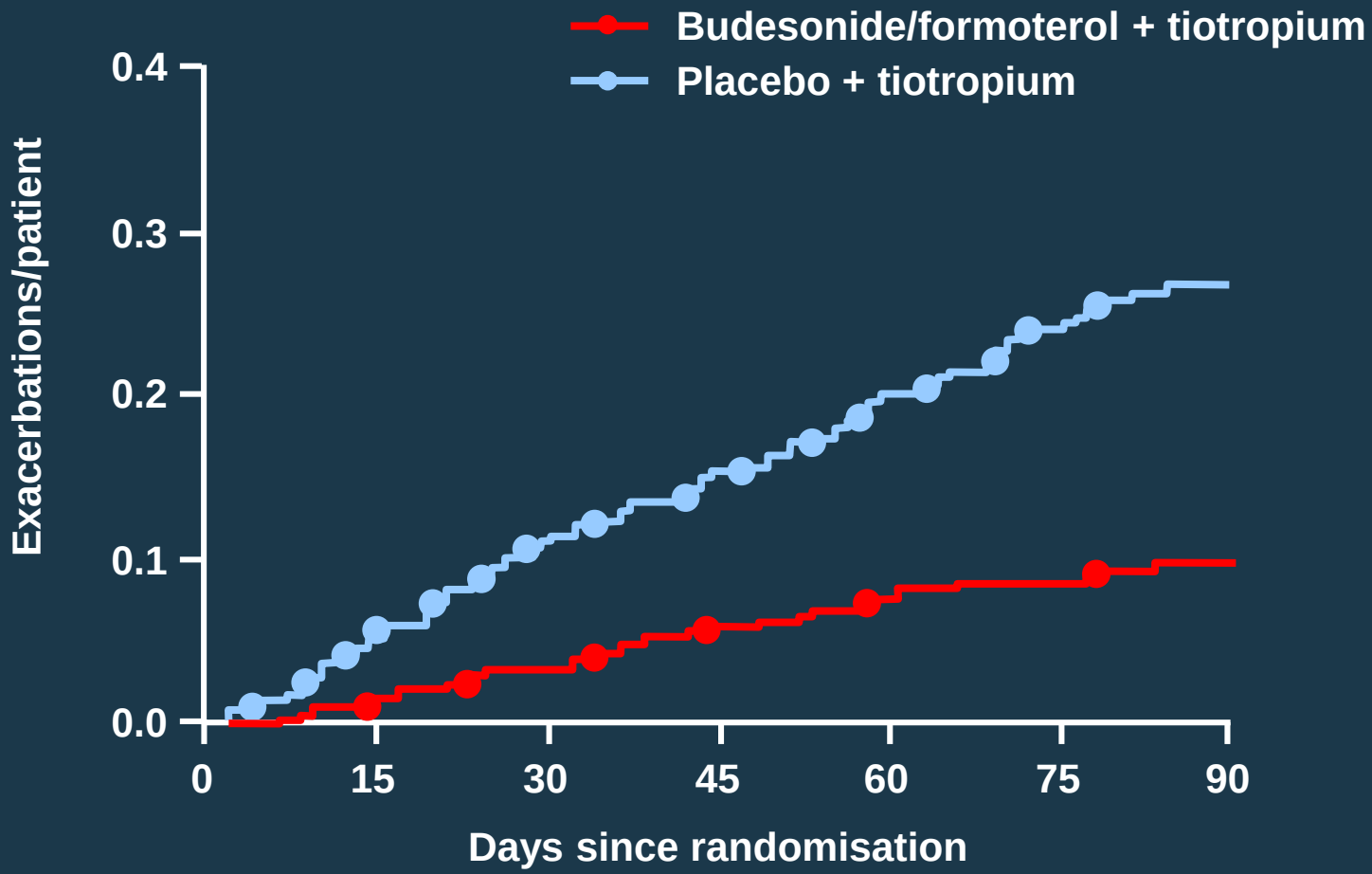
## A 12-week randomised double-blind parallel-group study




CLIMB

Figure reproduced from Welte T et al. Am J Respir Crit Care Med 2009; 180: 741–750. Official Journal of the American Thoracic Society. © American Thoracic Society.

# Rate of severe exacerbations reduced by 62% with budesonide/formoterol plus tiotropium compared with tiotropium alone




Cox-proportional hazards: rate ratio 0.38 (95% CI 0.25, 0.57, p<0.001)

Figure reproduced from Welte T et al. Am J Respir Crit Care Med 2009; 180: 741–750. Official Journal of the American Thoracic Society. © American Thoracic Society.

CLIMB

# LABA / ICS

# Why??

# Addressing the Complexity of Chronic Obstructive Pulmonary Disease

Alvar Agusti[1,2], Patricia Sobradillo[2], and Bartolomé Celli[3]

Am J Respir Crit Care Med Vol 183. pp 1129–1137, 2011

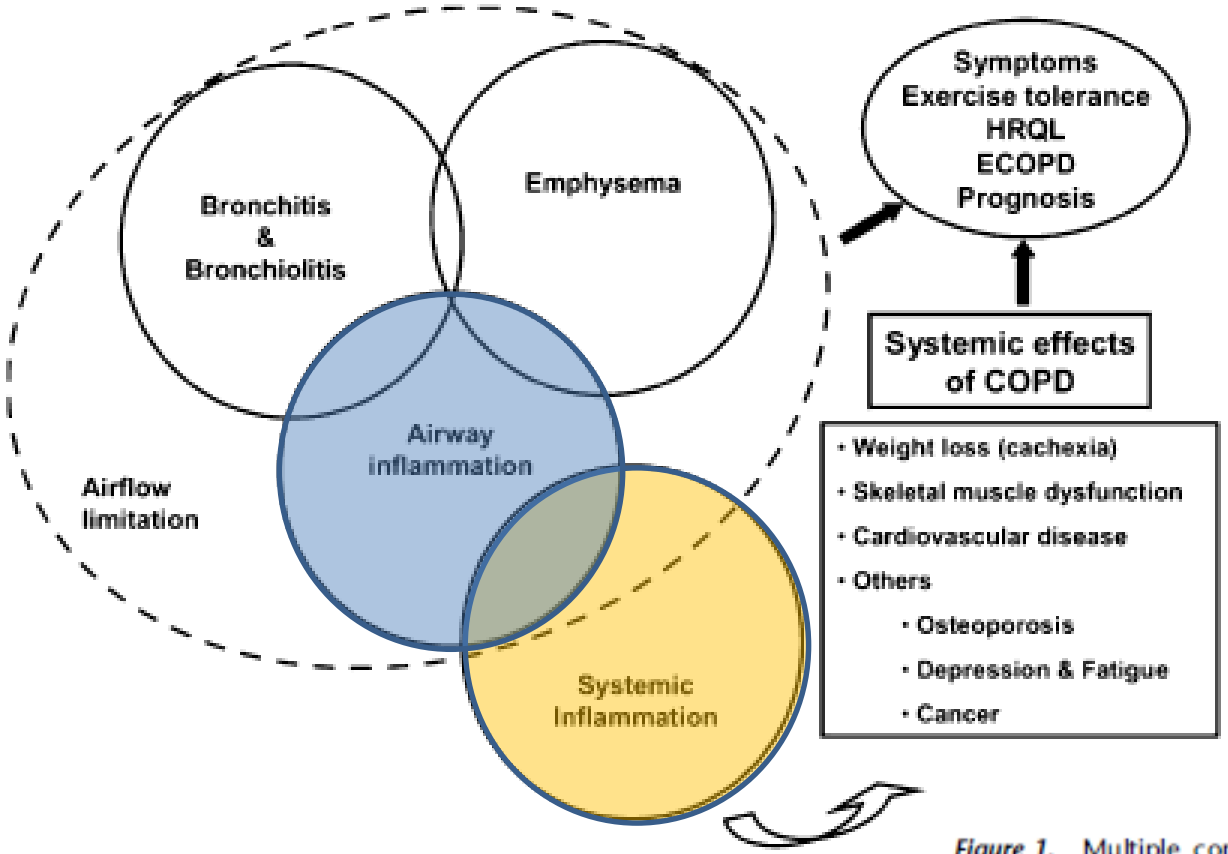


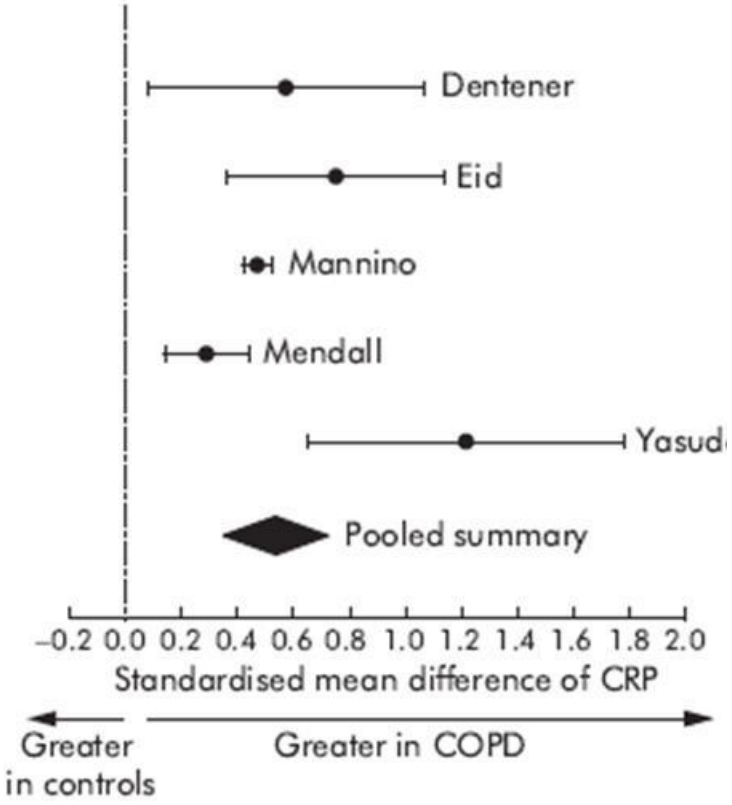

*Figure 1.* Multiple components of chronic obstructive pulmonary disease (COPD). For more explanation, *see* text. (Reprinted by permission from Reference 72.) HRQL = health-related quality of life; ECOPD = COPD exacerbation.

# Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis

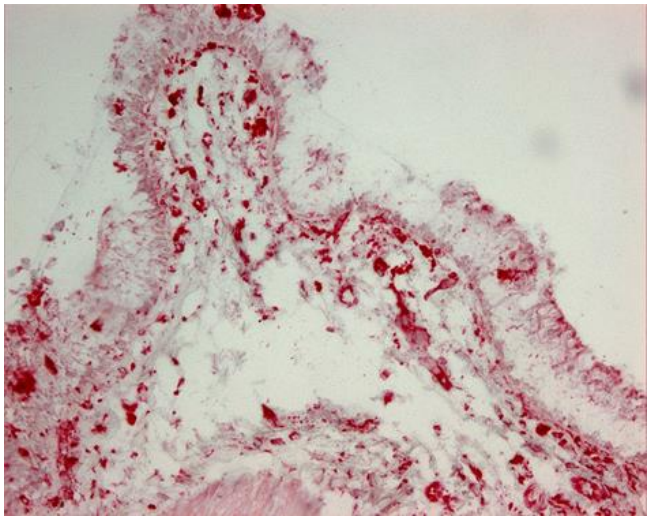
W Q Gan, S F P Man, A Senthilselvan, D D Sin

*Thorax* 2004;**59**:574–580.

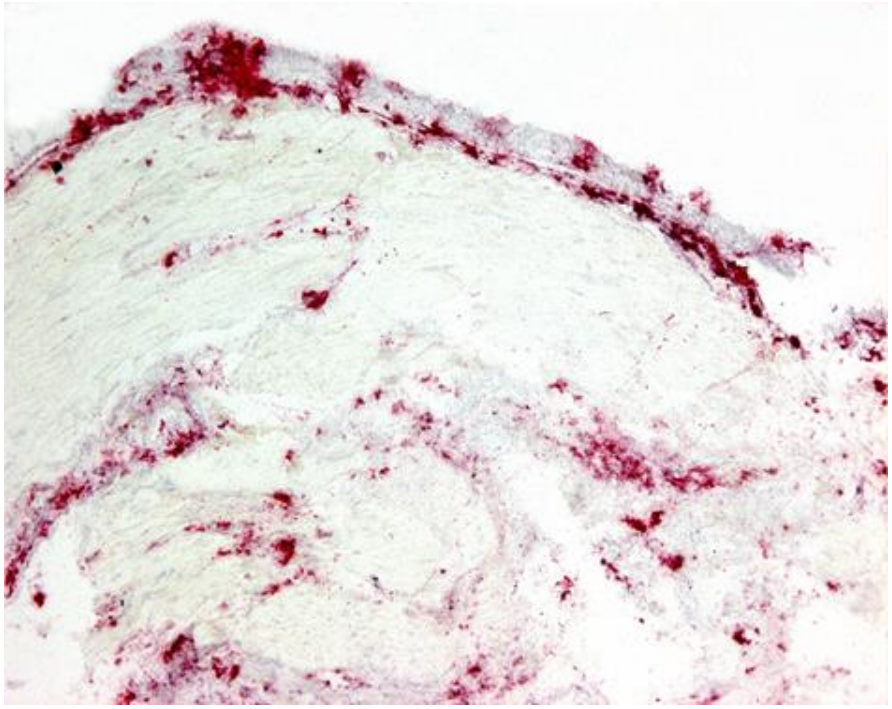
**CRP**



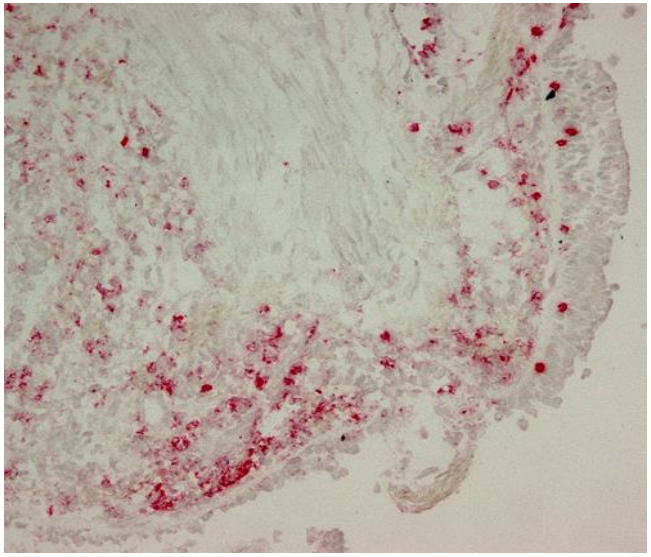

Patients with COPD had higher levels of CRP than control subjects in all studies



**Macrophages in mild/moderate COPD**



**Neutrophils in severe COPD**



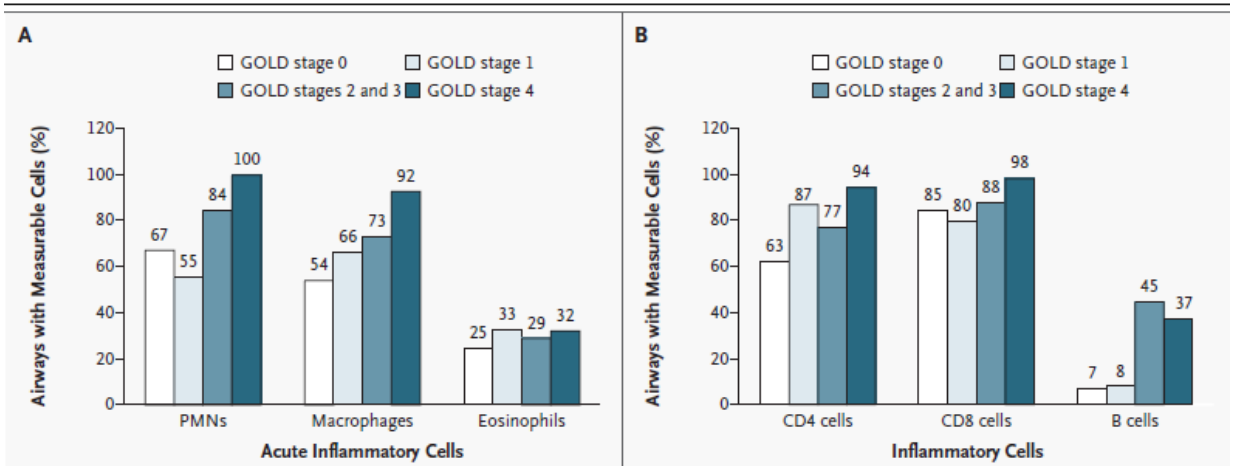
**CD8+ cells  in mild/moderate COPD**

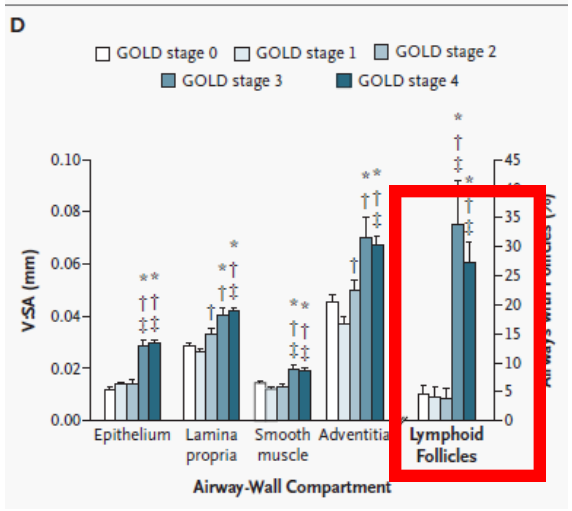

1 Zhu J. et al; AJRCCM 2001;164:2220-8
2 Saetta M. et al; AJRCCM 1997;156:1633-9
3 Mullen JBM. et al; BMJ 1985;291:1235-9
4 Saetta M. et al; AJRCCM 1998; 157:822-6

# The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease

James C. Hogg, M.D., Fanny Chu, B.Sc., Soraya Utokaparch, B.Sc., Ryan Woods, M.Sc., W. Mark Elliott, Ph.D., Liliana Buzatu, M.D., Ruben M. Cherniack, M.D., Robert M. Rogers, M.D., Frank C. Sciurba, M.D., Harvey O. Coxson, Ph.D., and Peter D. Paré, M.D.

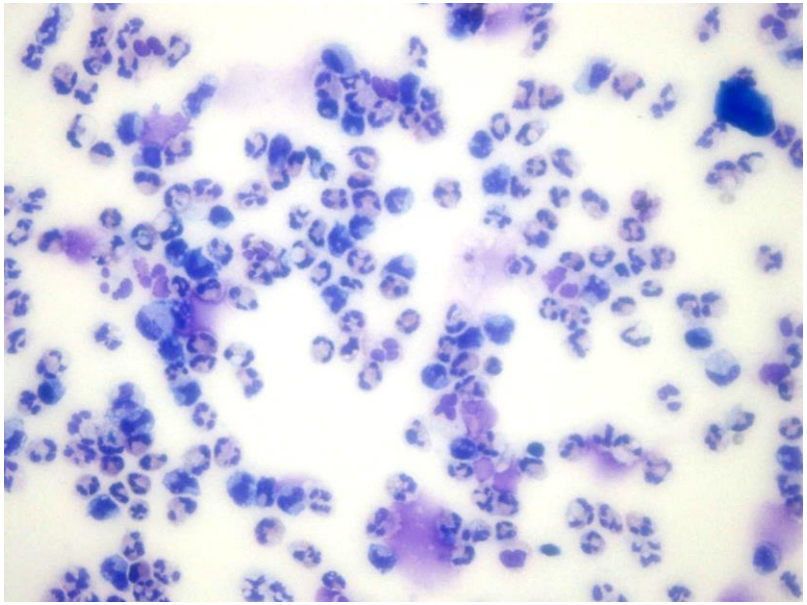
N Engl J Med 2004;350:2645-53.

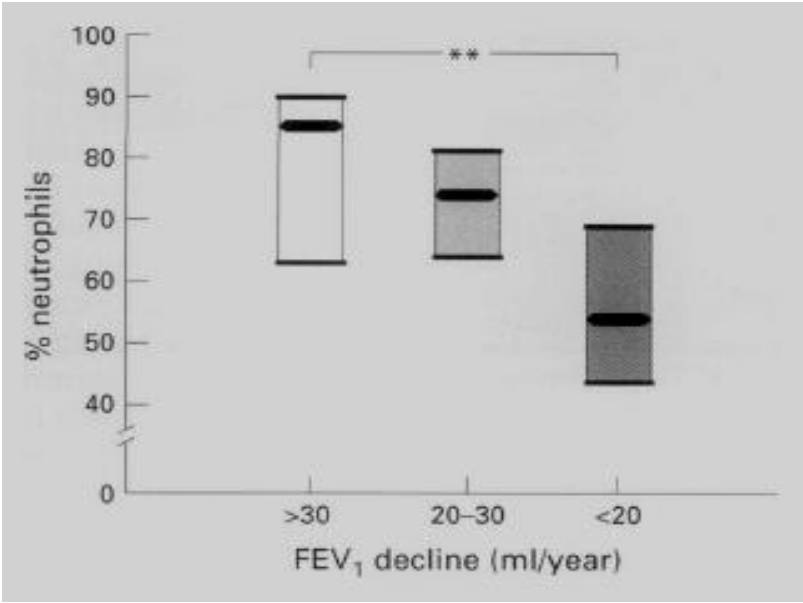


Airways obstruction, chronic expectoration, and rapid decline of $FEV_1$ in smokers are associated with increased levels of sputum neutrophils

Stanescu D, et al. Thorax 1996;51:267-271

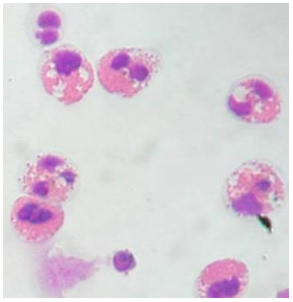


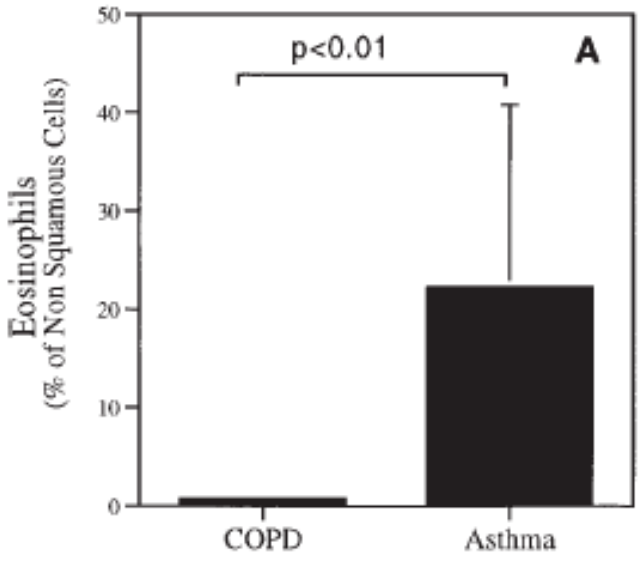


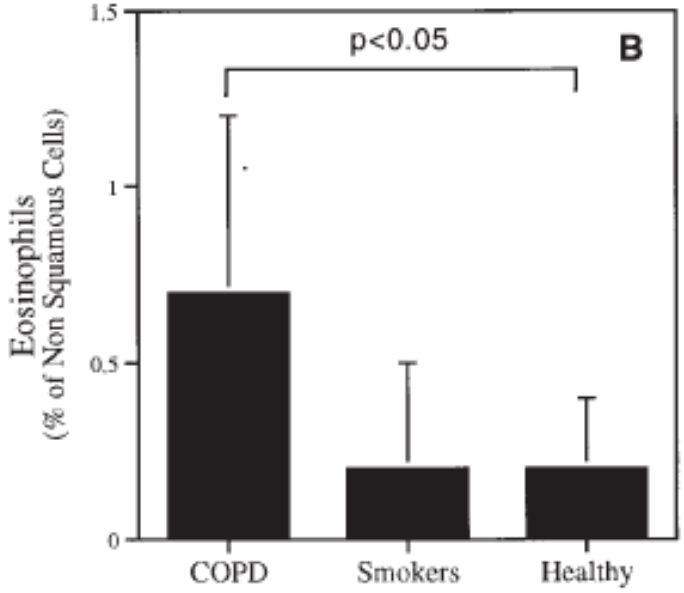
# Eosinophilic Inflammation in Stable Chronic Obstructive Pulmonary Disease

## Relationship with Neutrophils and Airway Function

**G. Balzano et al. AJRCCM 1999; 160: 1486-1492**






A significant increase in sputum eosinophils was found in patients with COPD as compared with healthy subjects, although the sputum eosinophilia in COPD was several orders of magnitude less versus the asthmatics

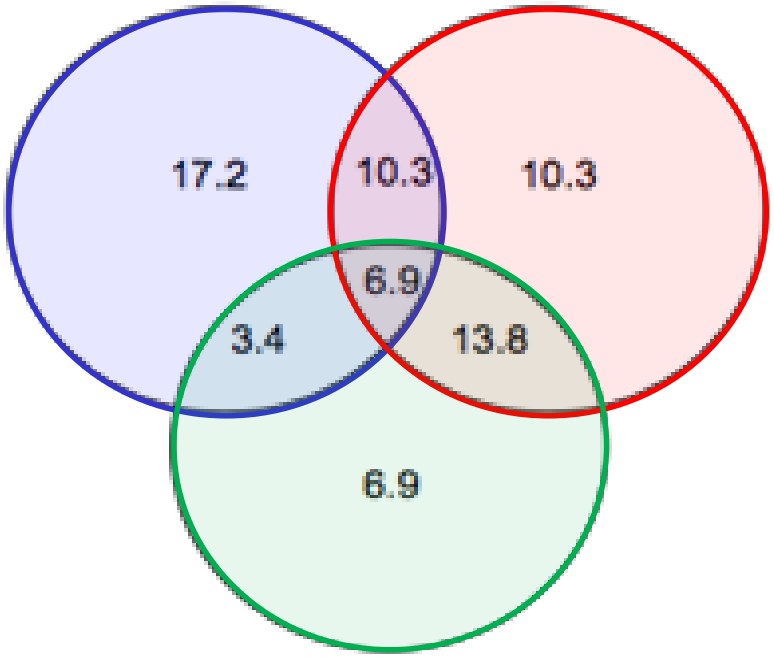
# Bronchial hyperresponsiveness, airway inflammation, and reversibility in patients with chronic obstructive pulmonary disease

International Journal of COPD 2015:10 1155–1161

Andrea Zanini[1]
Francesca Cherubino[1]
Elisabetta Zampogna[1]
Stefania Croce[2]
Patrizia Pignatti[2]
Antonio Spanevello[3]

**Reversibilità bronchiale**

**37.8%**




**Iperreattività bronchiale**

**41.3%**

**Eosinofilia dell'espettorato**

**31.0%**

- Effect of steroids on COPD inflammation

# C-reactive protein in patients with COPD, control smokers and non-smokers

Pinto-Plata VM et al. Thorax 2006

**CRP**

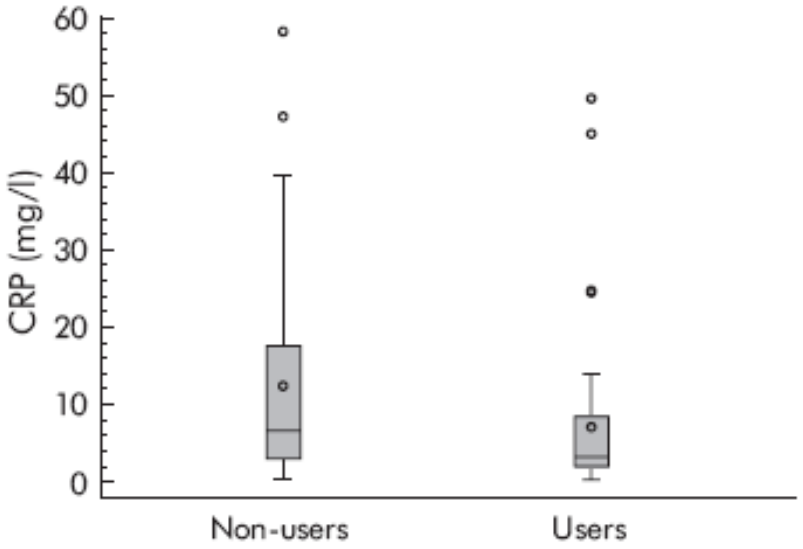



**Figure 4** Geometric mean C-reactive protein (CRP) levels with interquartile range in users and non-users of inhaled corticosteroids (ICS). The CRP level was lower in users of ICS than in non-users.

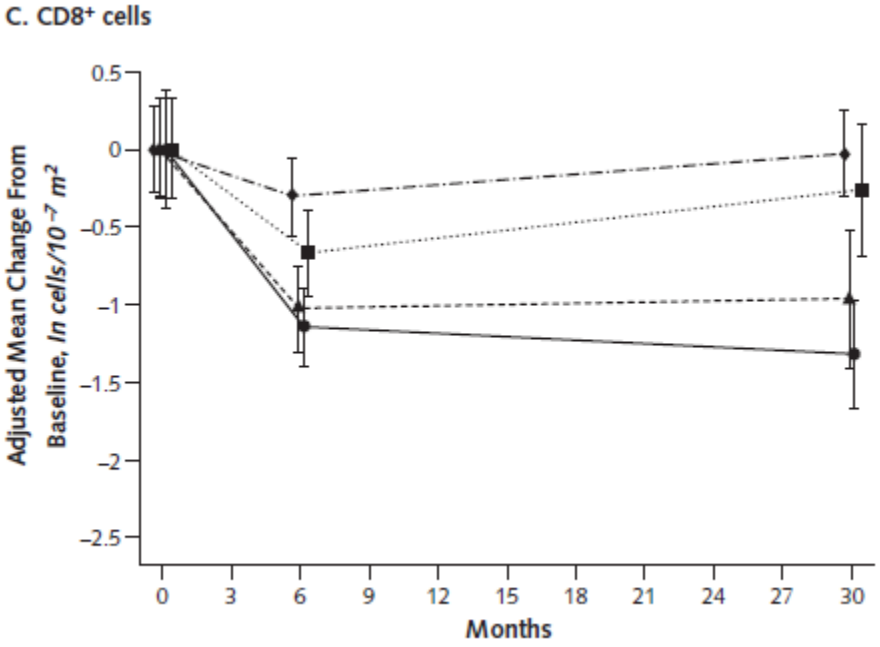
CRP levels were lower in COPD patients treated with ICS than in those not treated (3.7 (3.0) mg/l v 6.3 (3.6) mg/l)

# Effect of Fluticasone With and Without Salmeterol on Pulmonary Outcomes in Chronic Obstructive Pulmonary Disease

## A Randomized Trial

Lappere TS, Ann Intern Med 2009

**GLUCOLD study**




- Biopsie bronchiali : 114 pazienti con BPCO moderata o grave
- FP riduce significativamente l'infiammazione bronchiale
- La sospensione dello steroide inalatorio determina una recrudescenza della flogosi bronchiale

# Survival after Lung Volume Reduction in Chronic Obstructive Pulmonary Disease

## Insights from Small Airway Pathology

Am J Respir Crit Care Med Vol 176. pp 454–459, 2007

James C. Hogg[1], Fanny S. F. Chu[1], Wan C. Tan[1], Don D. Sin[1], Sanjay A. Patel[2], Peter D. Pare[1], Fernando J. Martinez[3], Robert M. Rogers[2], Barry J. Make[4], Gerard J. Criner[5], Reuben M. Cherniack[4], Amir Sharafkhaneh[6], James D. Luketich[2], Harvey O. Coxson[1], W. Mark Elliott[1], and Frank C. Sciurba[2]

TABLE 2. COMPARISON OF UNTREATED AND CORTICOSTEROID-TREATED GROUPS

| Parameter | Nontreated ($n = 16$) | Inhaled Steroids ($n = 45$) | Oral ± Inhaled Steroids ($n = 33$) | $P$ Value |
|---|---|---|---|---|
| Small airway wall dimensions | | | | |
| Lumen content of collapsed airway, % | 32.4 ± 3.9 | 30.2 ± 3.0 | 30.4 ± 3.8 | 0.931 |
| Lumen content of expanded airway, % | 8.20 ± 1.73 | 8.02 ± 1.13 | 7.89 ± 1.76 | 0.993 |
| Airways containing lymphoid follicles, % | 40.2 ± 6.4 | 26.1 ± 3.7 | 21.3 ± 4.5† | 0.051 |
| Total wall thickness, mm | 0.16 ± 0.008 | 0.15 ± 0.005 | 0.15 ± 0.006 | 0.913 |
| Epithelial thickness, mm | 0.035 ± 0.003 | 0.035 ± 0.001 | 0.035 ± 0.002 | 0.971 |
| Lamina propria, mm | 0.041 ± 0.002 | 0.040 ± 0.002 | 0.040 ± 0.002 | 0.801 |
| Smooth muscle, mm | 0.020 ± 0.001 | 0.018 ± 0.001 | 0.019 ± 0.001 | 0.320 |
| Adventitia, mm | 0.078 ± 0.006 | 0.077 ± 0.004 | 0.078 ± 0.005 | 0.971 |

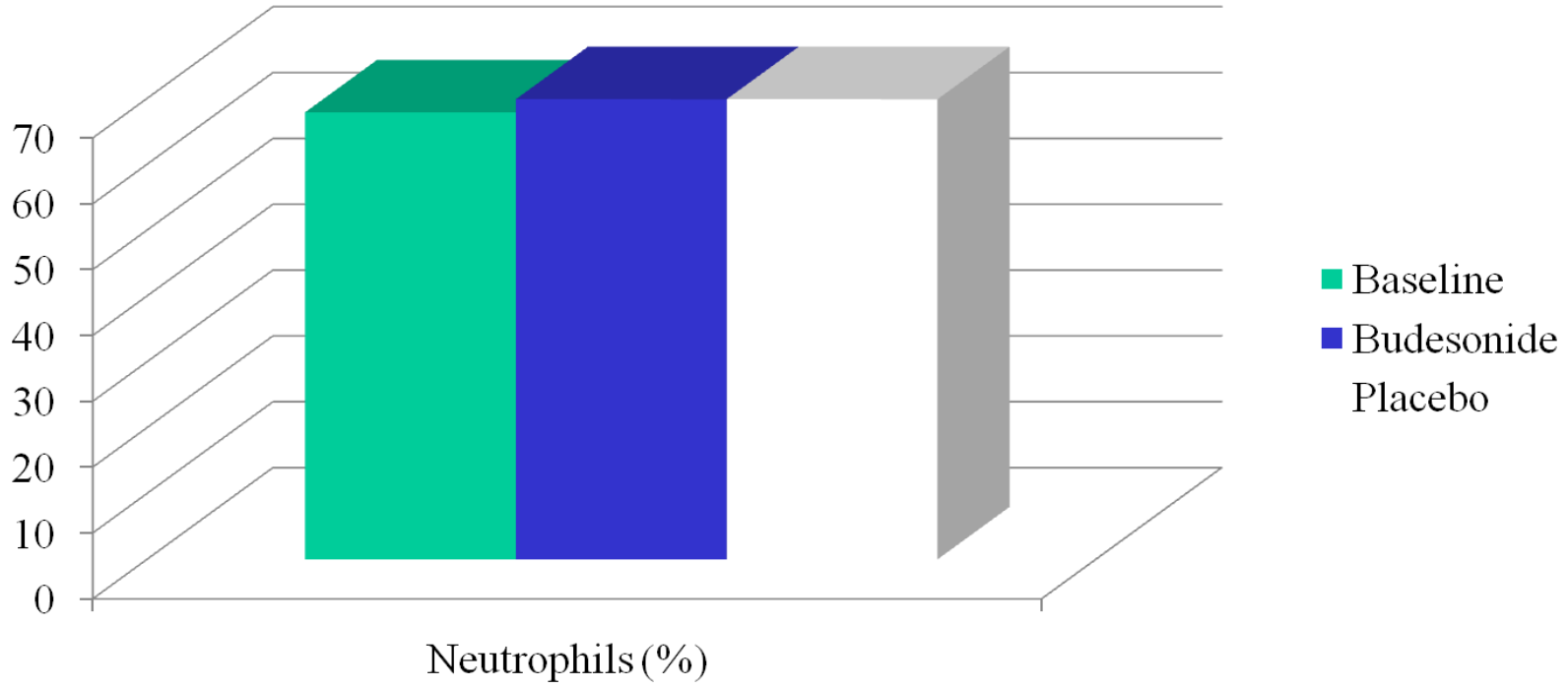
For definition of abbreviations, *see* Table 1.
Values are mean ± SEM.
† $P < 0.05$ versus nontreated group.
* $P < 0.05$ versus inhaled steroids group.

There was a trend toward the reduction in the number of airways containing lymphoid follicles

# Effects Of Inhaled and Oral Glucocorticoids on Inflammatory Indices in Asthma and COPD

Keatings VM, et al. AJRCCM 1997;155:542-548

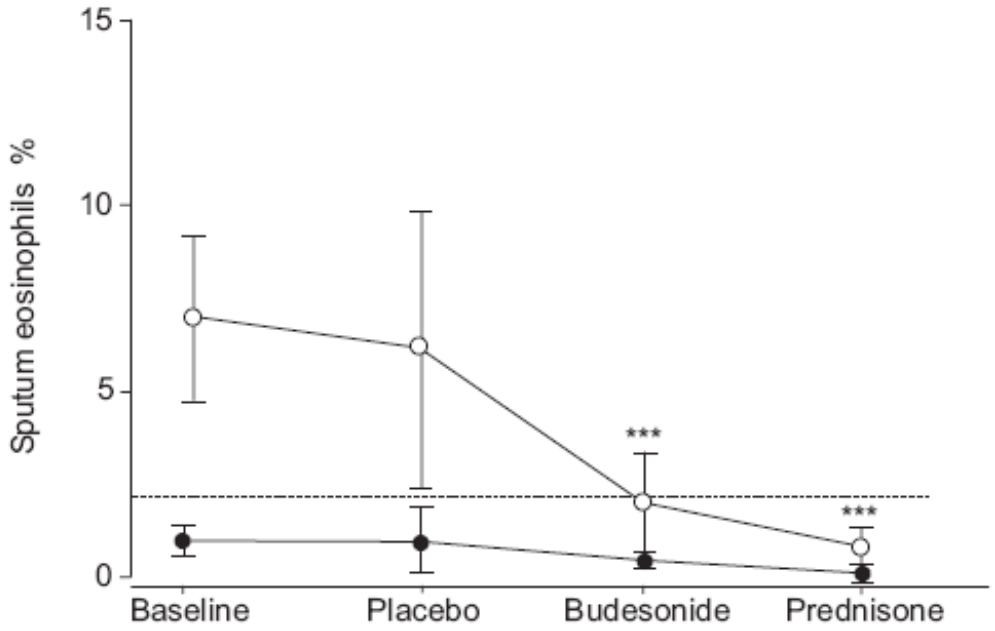
## Inflammatory indices in induced sputum in COPD after 2 weeks treatment with budesonide and placebo.




The treatment of COPD patients with budesonide did not determine an improvement of neutrophil airway inflammation

# Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment

**Leigh R et al. Eur Respir J 2006;27:964-971**




In stable COPD the presence of sputum eosinophils predicts, as occurs in asthmatic patients, a response to inhaled corticosteroid treatment.

# Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial

**R. Siva et al. Eur Resp J 2007; 29: 906-913**

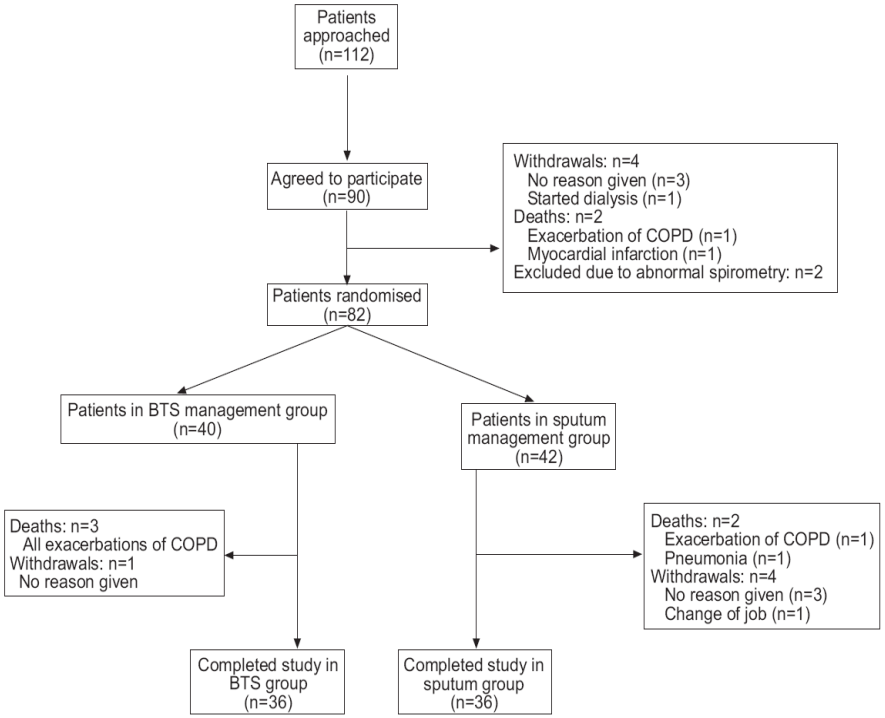



**FIGURE 1.** Flow chart of the trial profile. COPD: chronic obstructive pulmonary disease; BTS: British Thoracic Society.

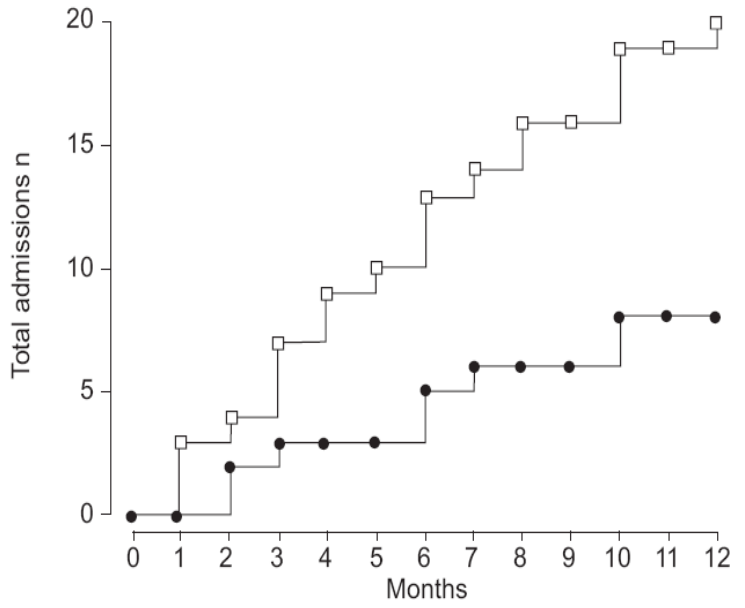



**FIGURE 3.** Hospital admissions in the British Thoracic Society (□) and sputum (●) groups. p=0.037.

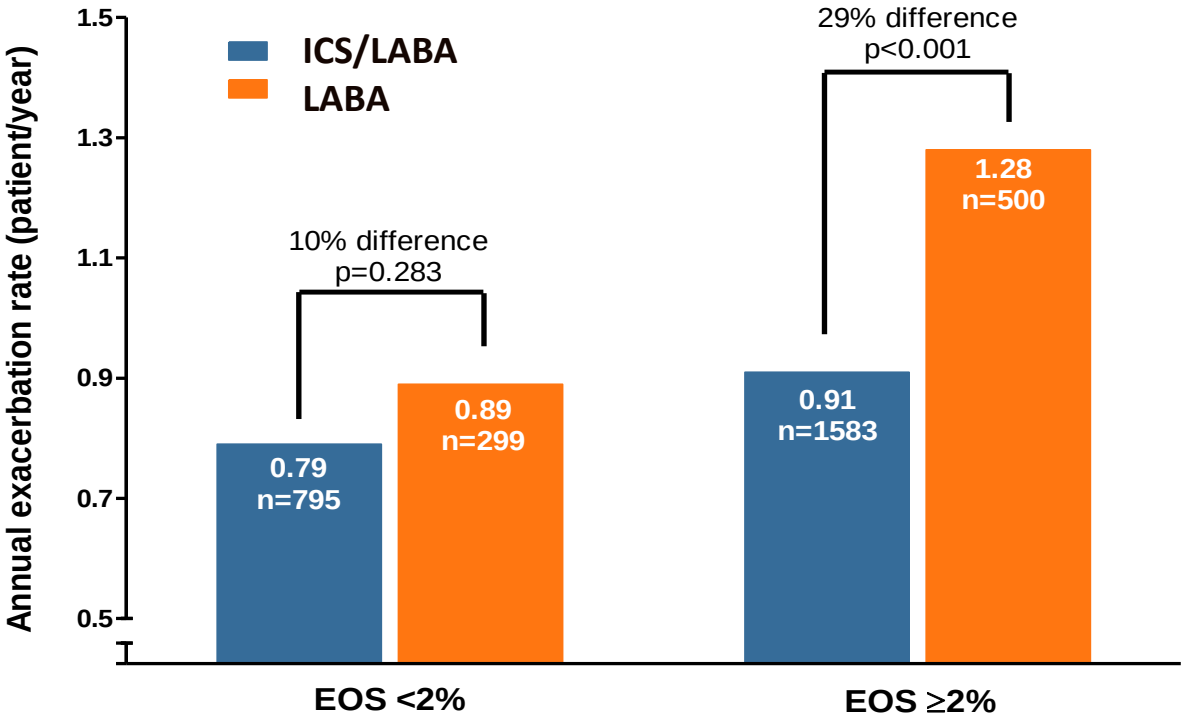
The management of COPD patients, according to sputum eosinophilia, allows to reduce the number of exacerbations

Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials

Steven Pascoe, Nicholas Locantore, Mark T Dransfield, Neil C Barnes, Ian D Pavord

Lancet Respir Med 2015; 3: 435–42

# Is blood eosinophil count a predictor of response to ICS in COPD?




- In the presence of plasmatic EOS≥2%, the percentage of exacerbations is 29% lower (p<0.01) in patients treated with combination compared to only LABA.
- No difference in the patients with EOS < 2%

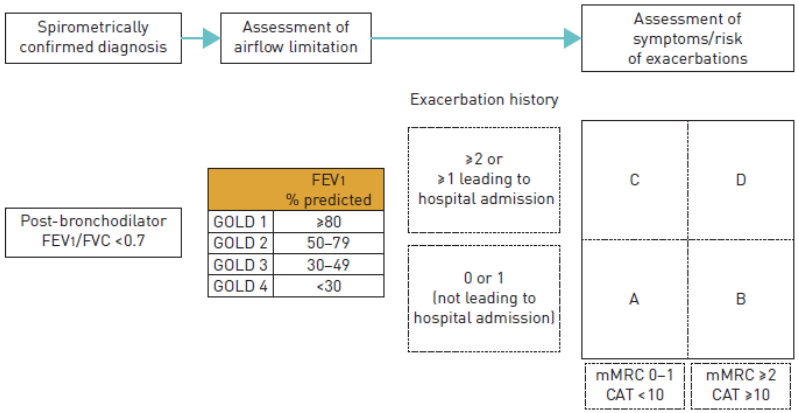
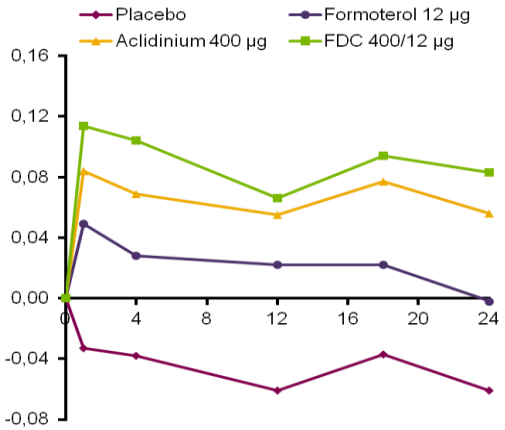
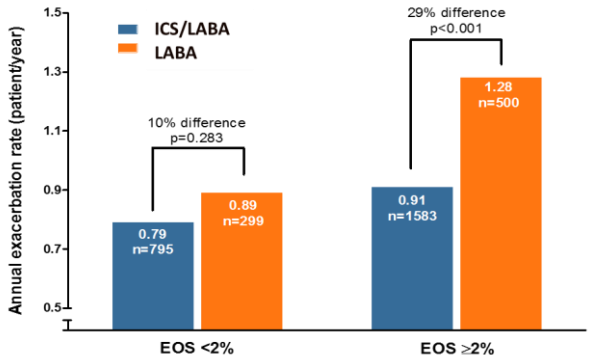
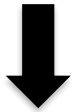



FIGURE 2 The refined ABCD assessment tool. $FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; CAT: COPD Assessment Test.



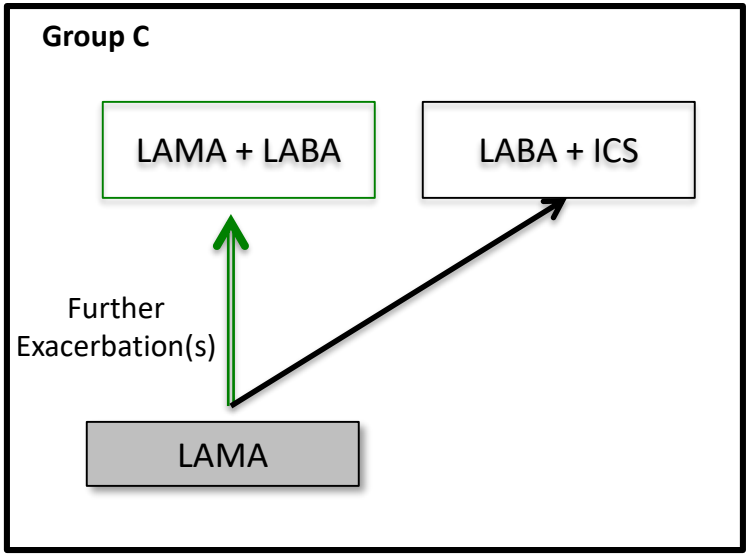
Symptoms and exacerbations guide therapy

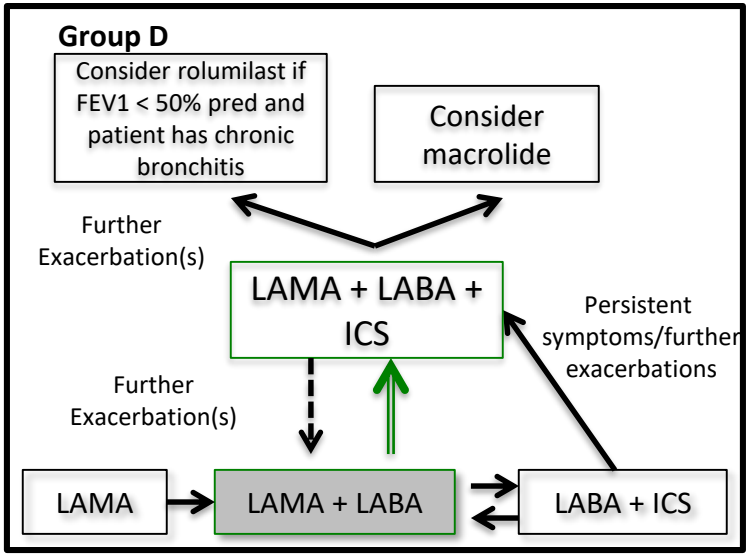


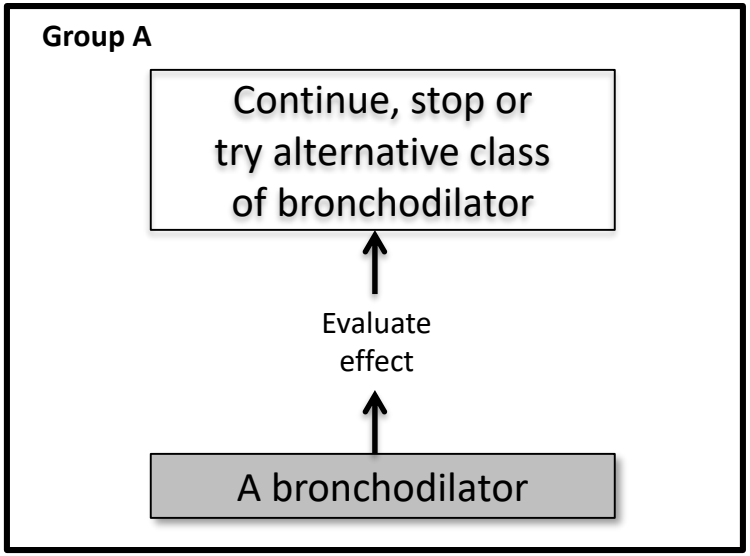
The separation of airflow limitation from clinical parameters makes it clearer what is being evaluated and ranked. This should facilitate more precise treatment recommendations based on parameters that are driving the patient's symptoms at any given time.

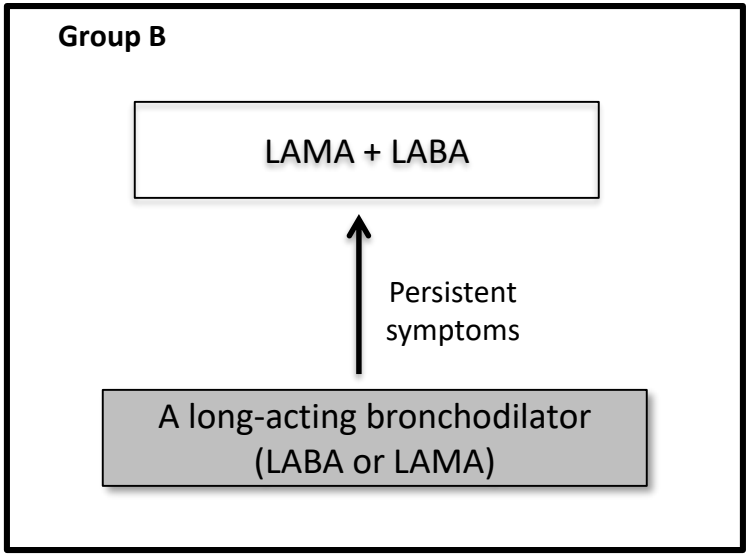
≥ 2 ECOPD or ≥1 leading to hospitalization

0 or 1 ECOPD (not leading to hospital admission)




mMRC 0-1
CAT < 10

mMRC 2+
CAT 10+

# The refined ABCD "GOLD 2017"

**Diagnosis** = **Assessment of airflow limitation** + **Assessment of symptoms/risk of exacerbations**

**FEV1/FVC<0.7**

| Grade | $FEV_1$ (% pred.) |
|---|---|
| **1** | ≥80 |
| **2** | 50-79 |
| **3** | 30-49 |
| **4** | <30 |

| | | |
|---|---|---|
| ≥ 2 or ≥1 leading to hospitalization | **C** | **D** |
| 0 or 1 (not leading to hospital admission) | **A** | **B** |
| | mMRC 0-1<br>CAT < 10 | mMRC 2+<br>CAT 10+ |

PULMONARY PERSPECTIVE

# Chronic Respiratory Symptoms with Normal Spirometry
## A Reliable Clinical Entity?

Roberto Rodriguez-Roisin[1], MeiLan K. Han[2], Jørgen Vestbo[3], Jadwiga A. Wedzicha[4], Prescott G. Woodruff[5], and Fernando J. Martinez[6]

Am J Respir Crit Care Med Vol 195, Iss 1, pp 17–22, Jan 1, 2017