Ferrara 6-7 novembre 2015

COPD. Terapia Farmacologica

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Università di Ferrara

COPD. Terapia Farmacologica

- COPD Definizione e inquadramento:
  - il Vecchio e il Nuovo
- Broncodilatazione
- Nuovi concetti nella prevenzione
  - Le riacutizzazioni

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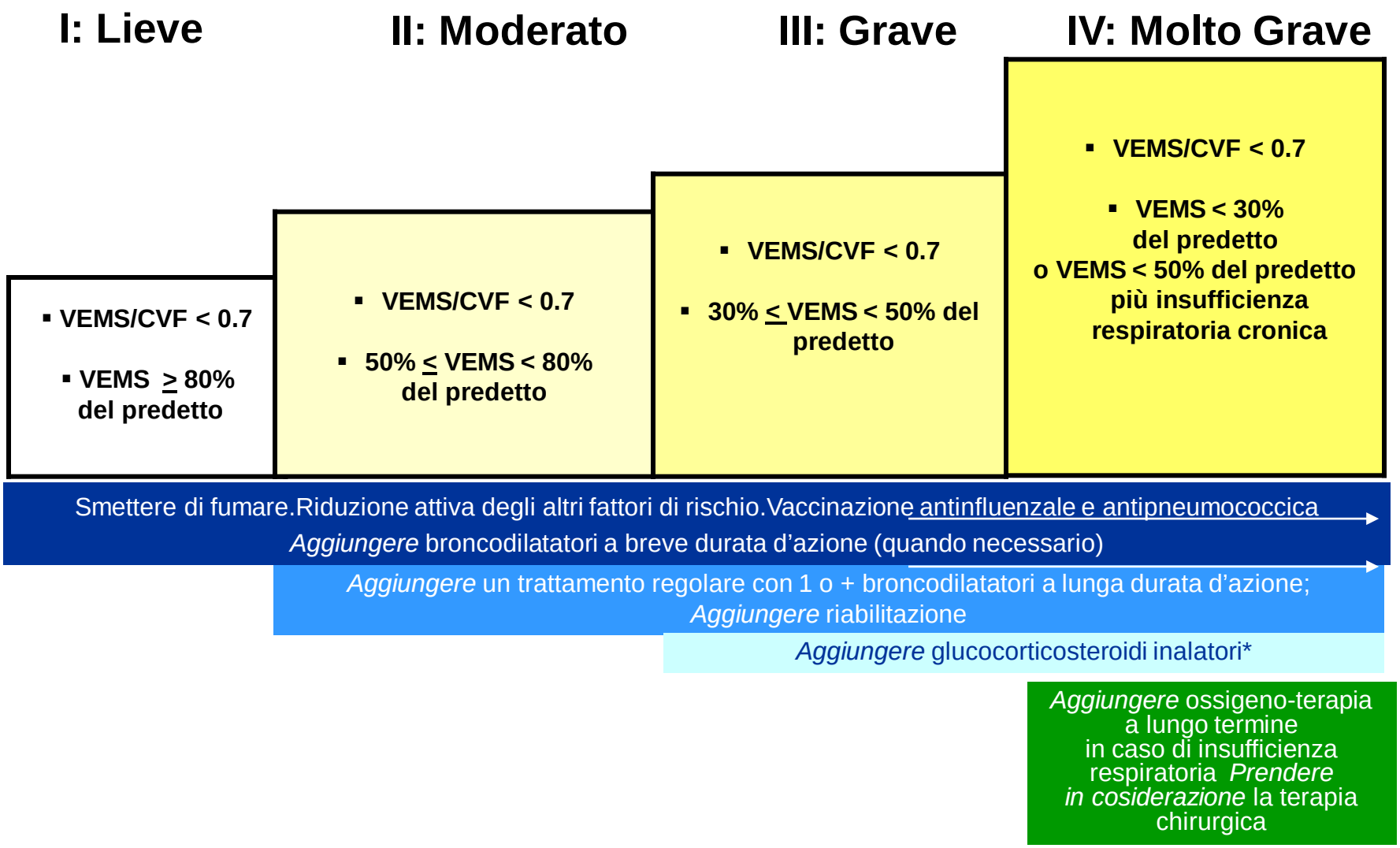
BPCO - Definizione

•***La Broncopneumopatia Cronica Ostruttiva (BPCO) è*** *condizione clinica prevenibile e trattabile* ***caratterizzata da una persistente limitazione al flusso aereo*** *solitamente evolutiva e* ***associata ad una aumentata risposta infiammatoria*** *cronica delle vie aeree e del polmone a particelle nocive o gas.*

• Le riacutizzazioni e le comorbidità contribuiscono alla complessiva severità clinica della BPCO

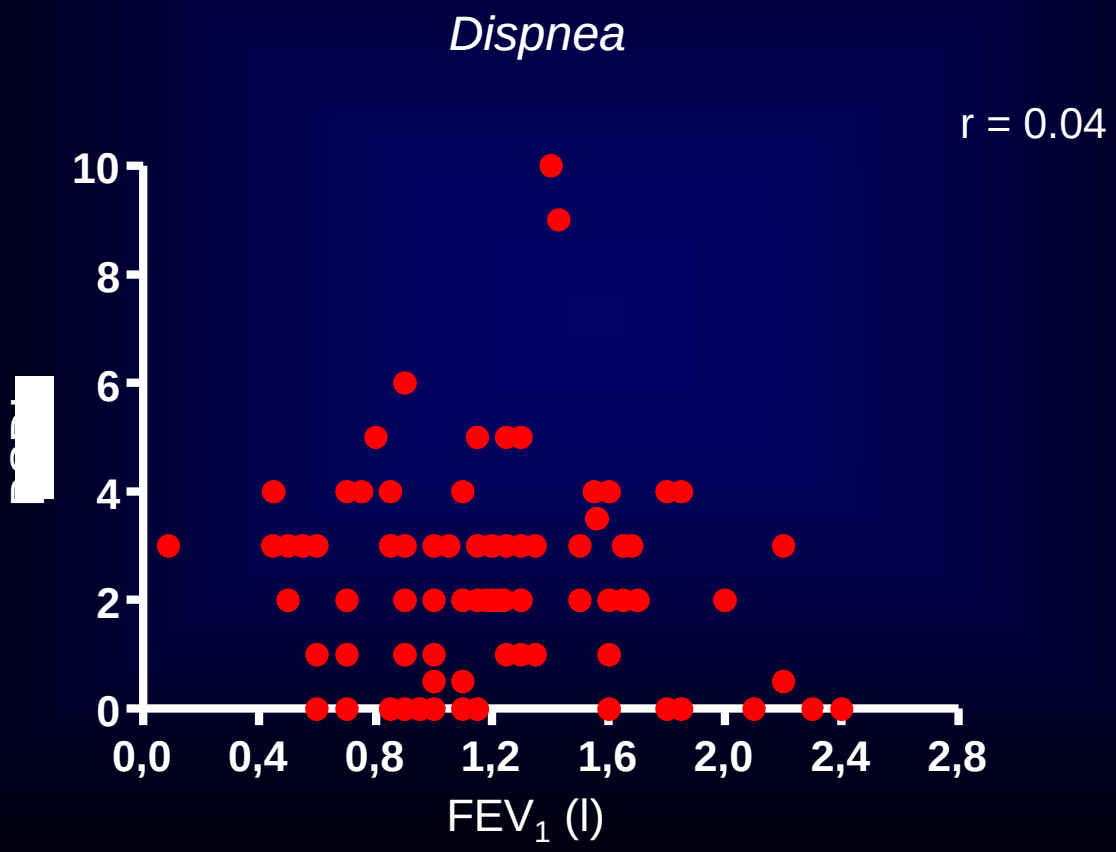
GOLD 2015

Terapia della BPCO in base allo stadio di gravità **in prima visita**



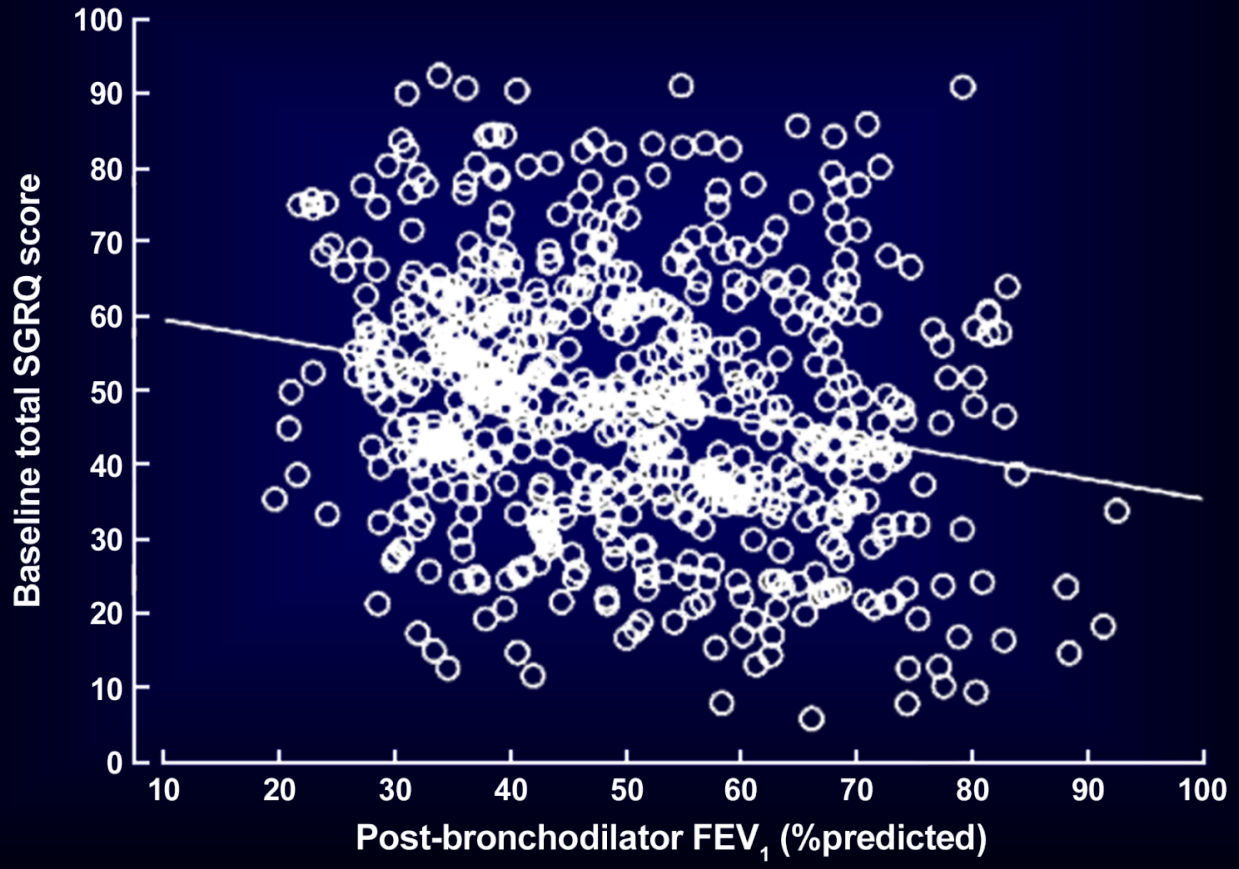
* Le autorità regolatorie Europea (EMEA) e Italiana (AIFA) hanno approvato l'uso della combinazione salmeterolo fluticasone in pazienti sintomatici con VEMS pre-broncodilatatore <60%.

Relazione tra funzionalità polmonare e sintomi nella broncopneumopatia ostruttiva



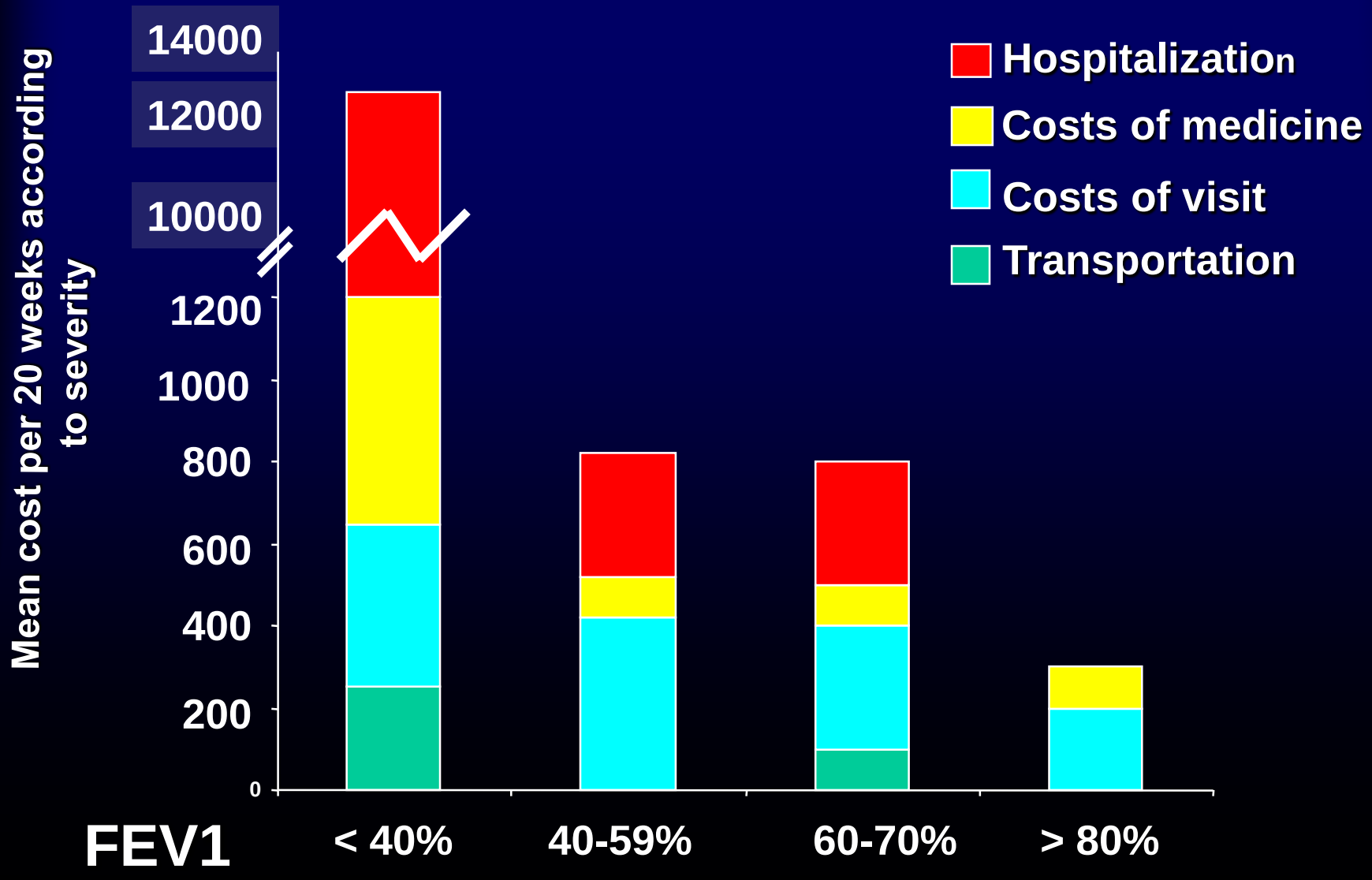
Wolkove N, Chest, 1989

Relazione tra QoL e FEV1 nella broncopneumopatia ostruttiva



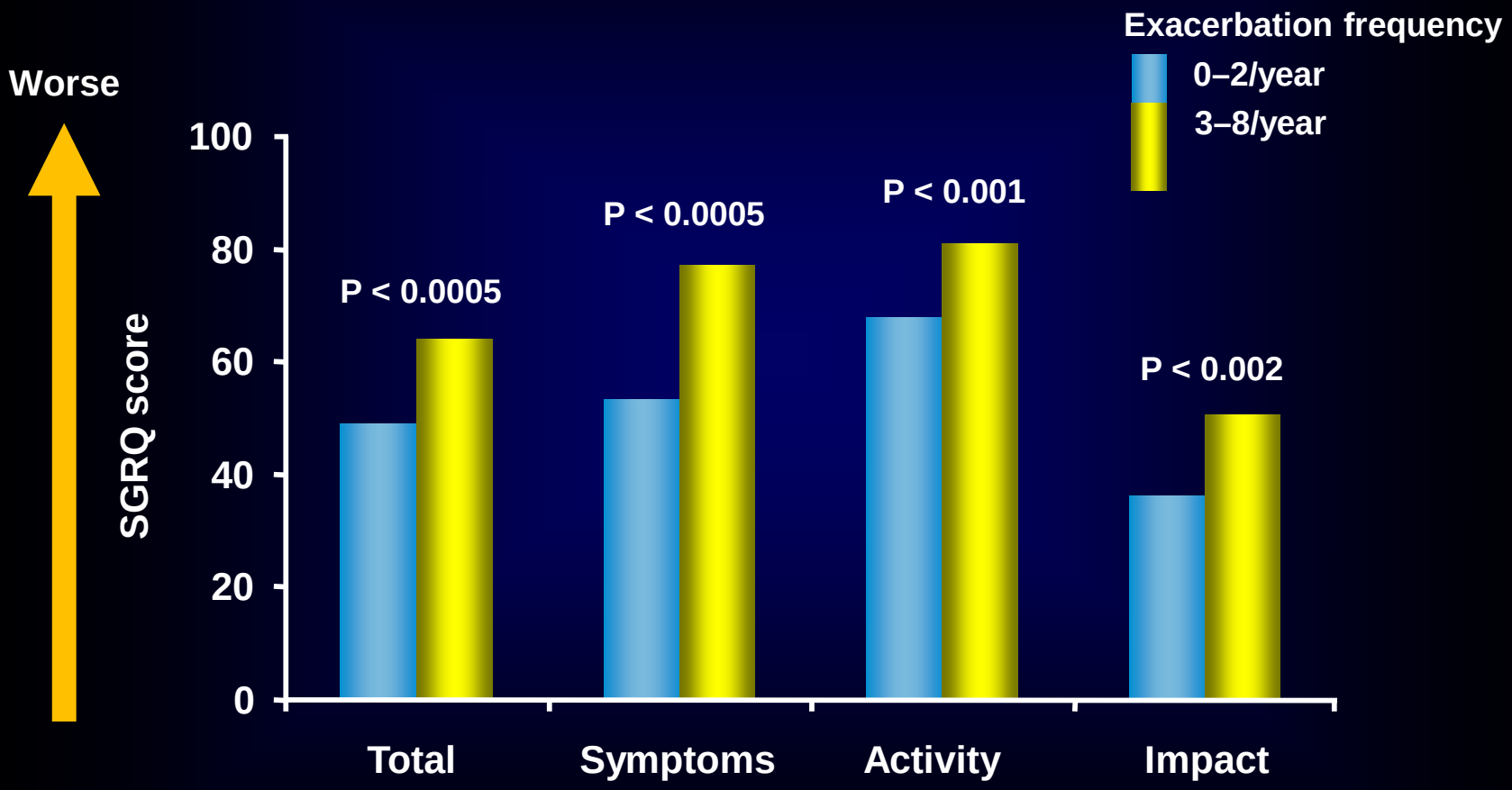
Burge PS, BMJ 2000

Costs of COPD

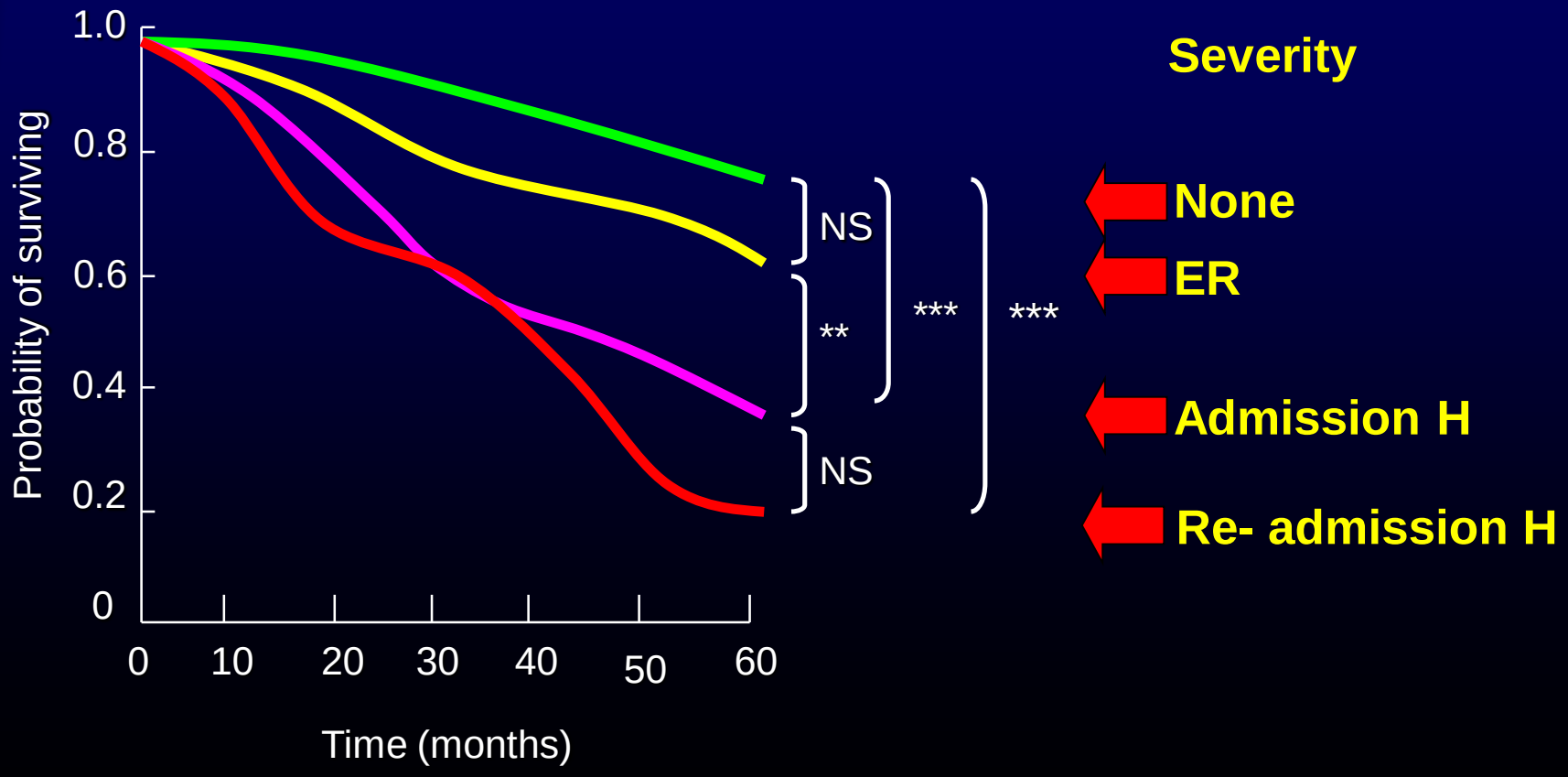


(Andersson et al, Repir Med 2002)

Frequent exacerbations impair health status in COPD

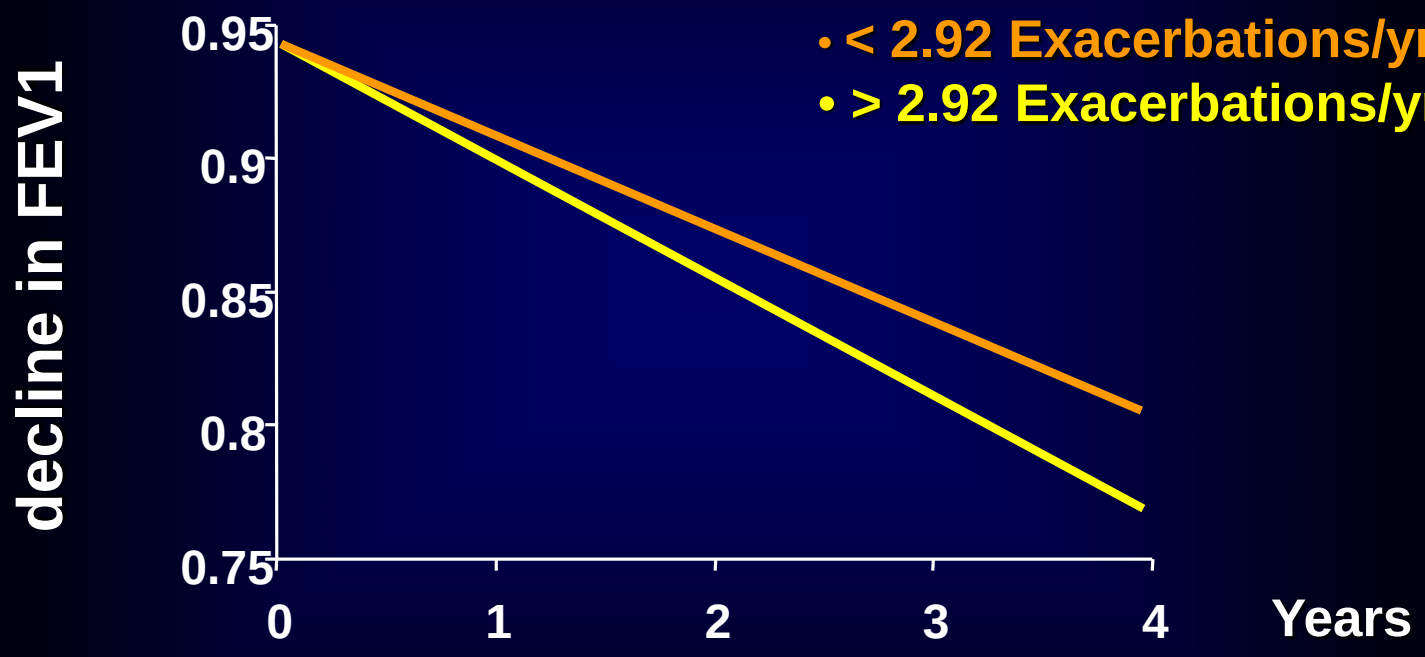


COPD exacerbations and mortality



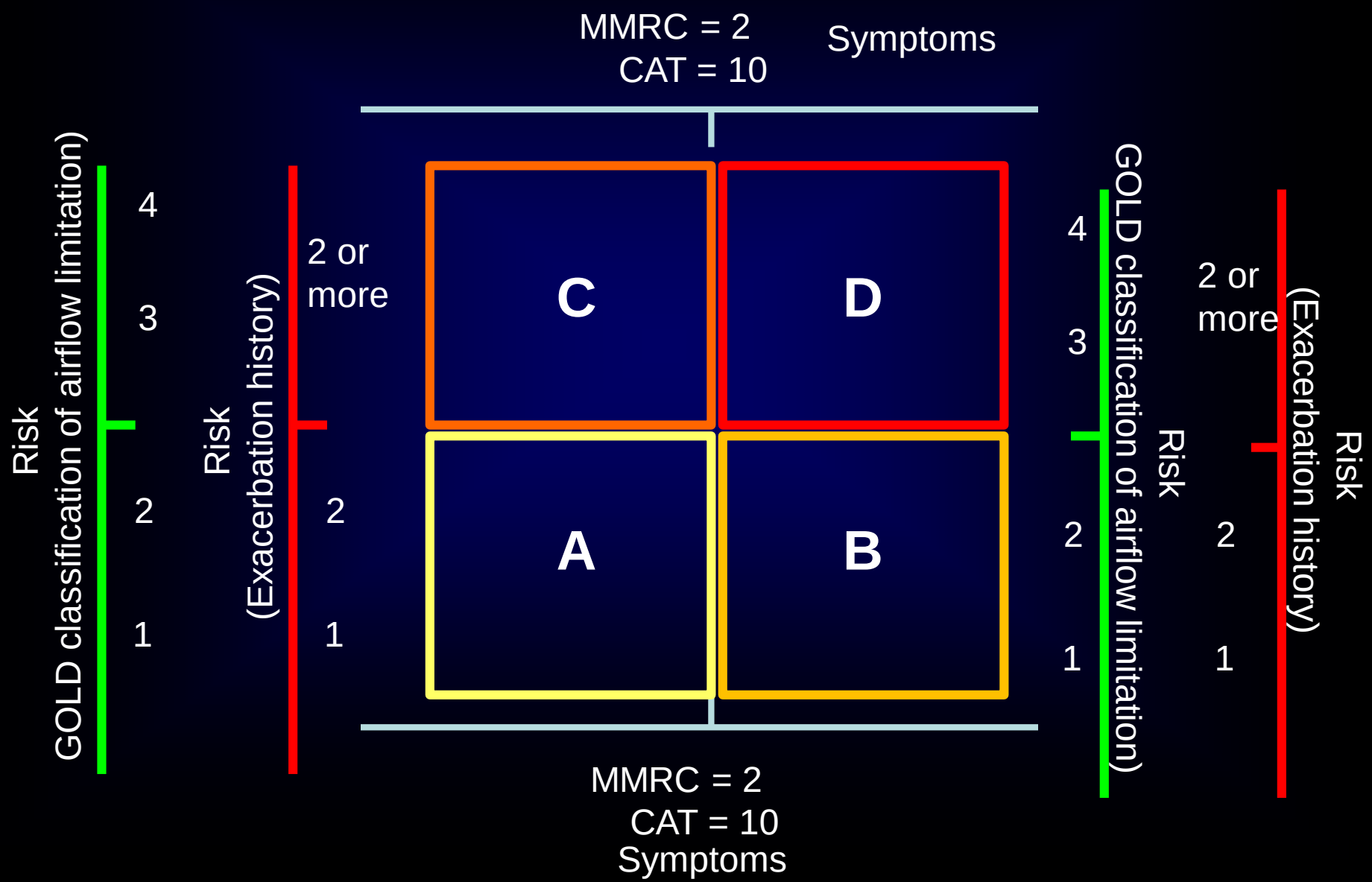
Soler-Cataluna JJ et al. Thorax 2005; 60: 925-931

Exacerbations and lung function decline

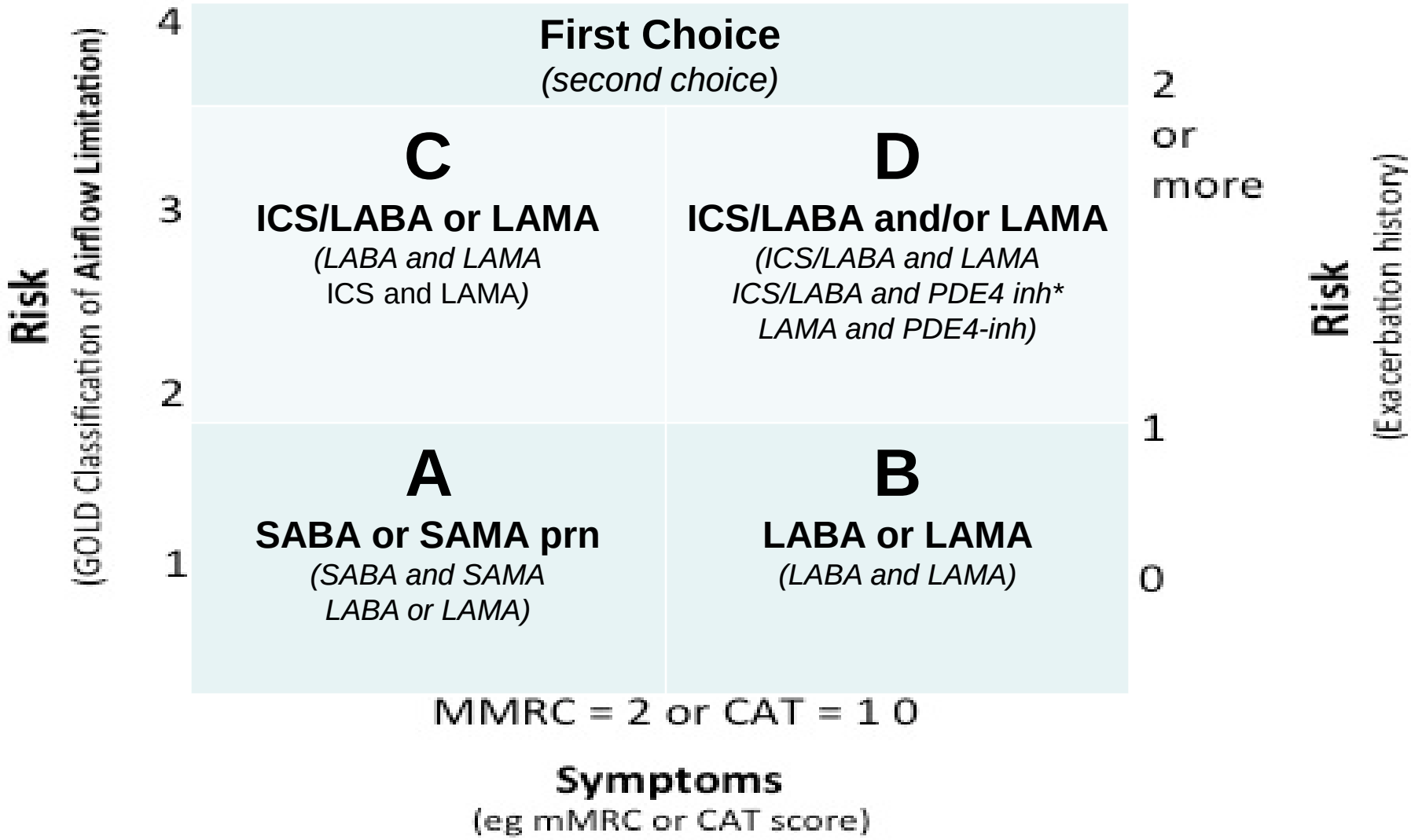


(Donaldson et al, Thorax 2002)

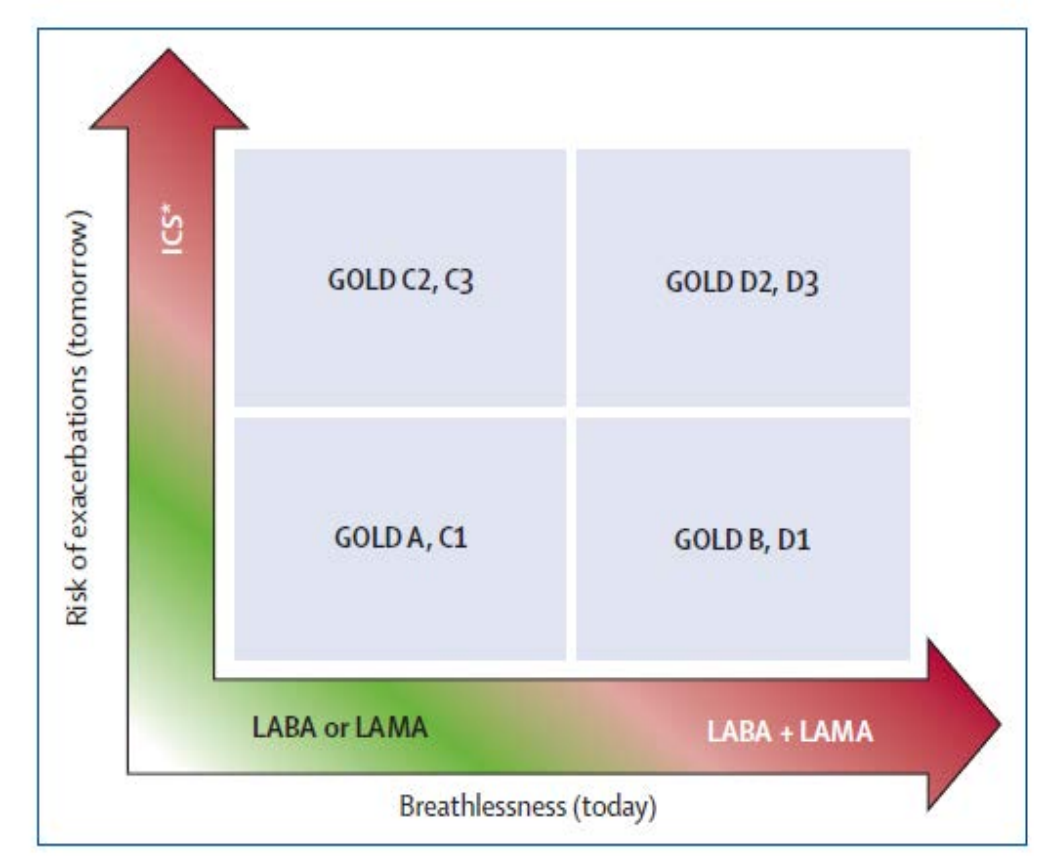
Association Between Symptoms, Spirometric Classification and Future Risk of Exacerbations



Initial pharmacological COPD management according to Symptoms / Risk Assessment



Current GOLD Paradigm



Agusti Lancet
Resp Med 2014

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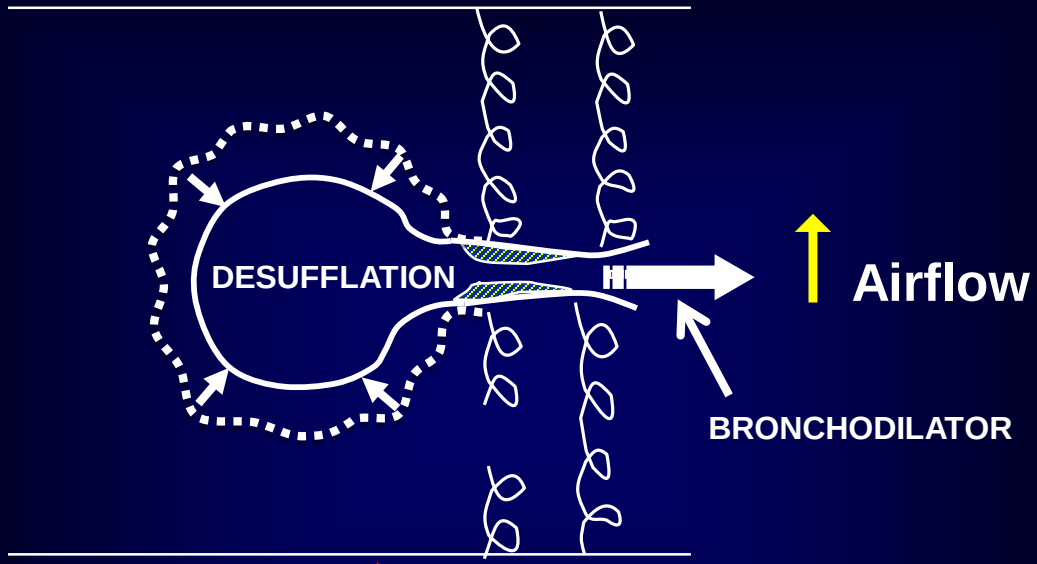
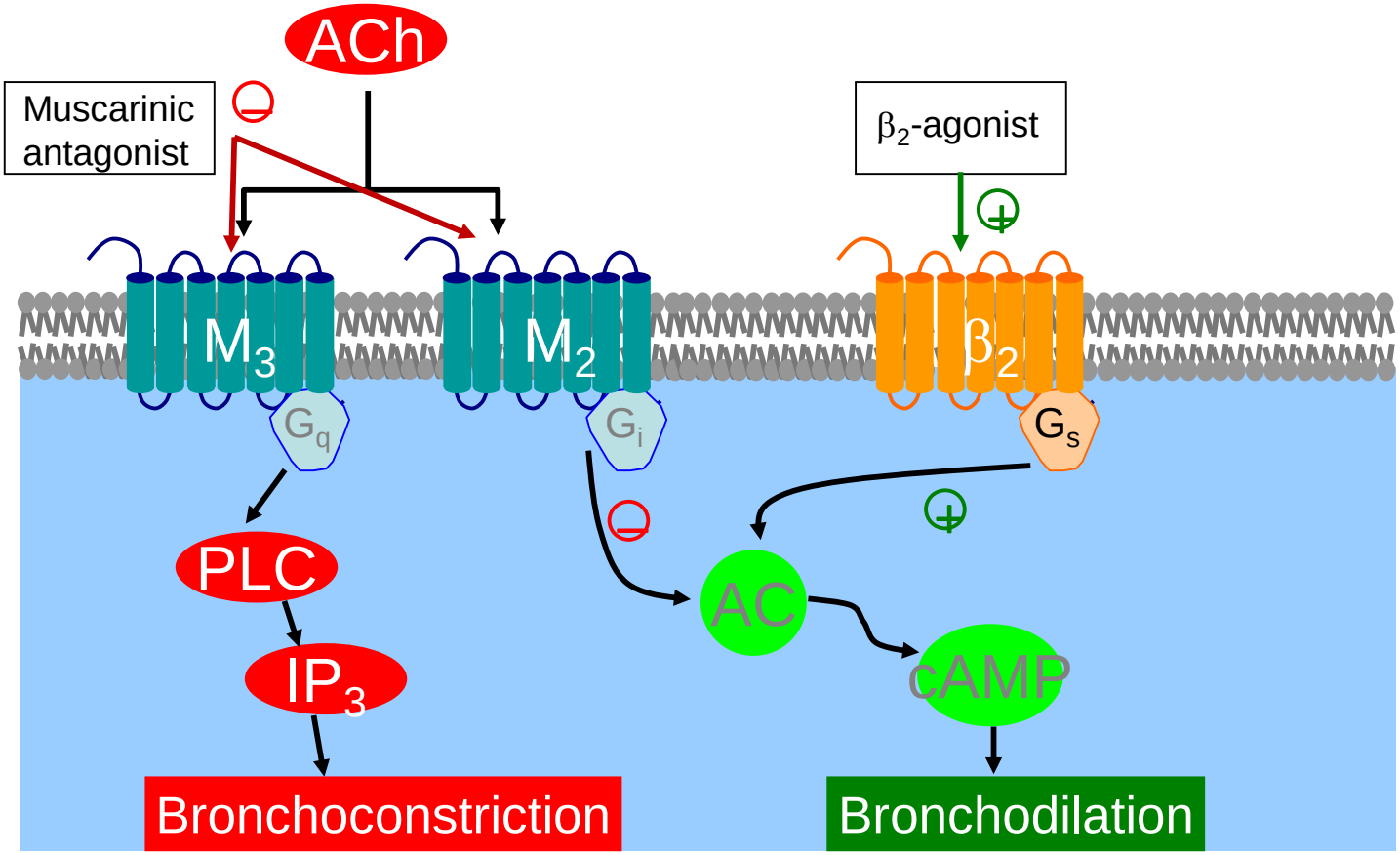
Bronchodilators & “desufflation”



- Increase: time integrate flow: ↑ FEV_1
- Lung volumes: ↓ RV, FRC, PEEPi
  ↑ VC, IC
- Decreased dyspnea (chronic and exercise)
- Increased exercise tolerance

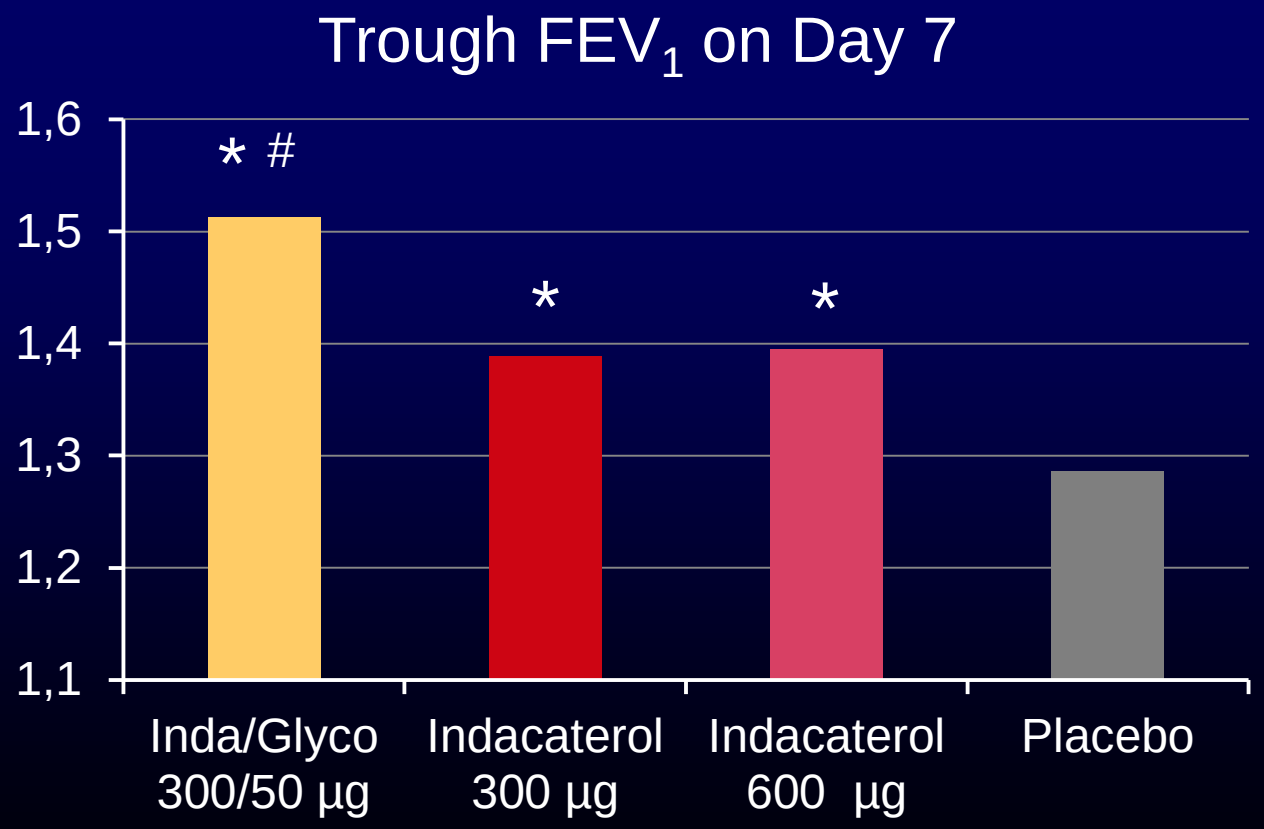
Schematic representation of the MA and BA bronchodilation of airway smooth muscle.

Two distinct and complementary mechanisms of inducing bronchodilation



+/- signs denote relaxation/constriction influences respectively

Bronchodilator: Increasing the doses versus combination



* P < 0.001 vs Placebo

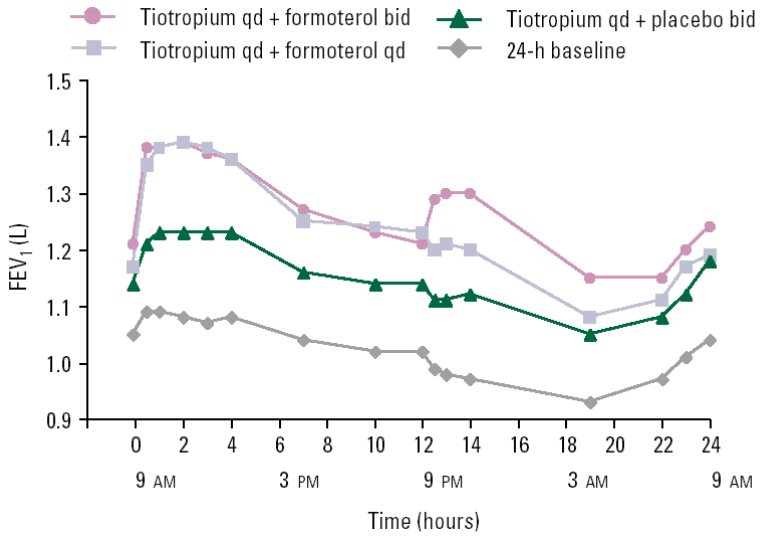
# P < 0.001 vs Indacaterol 300 and vs Indacaterol 600 µg

Van Noord, et al. *Thorax* 2010;65:1086–1091.

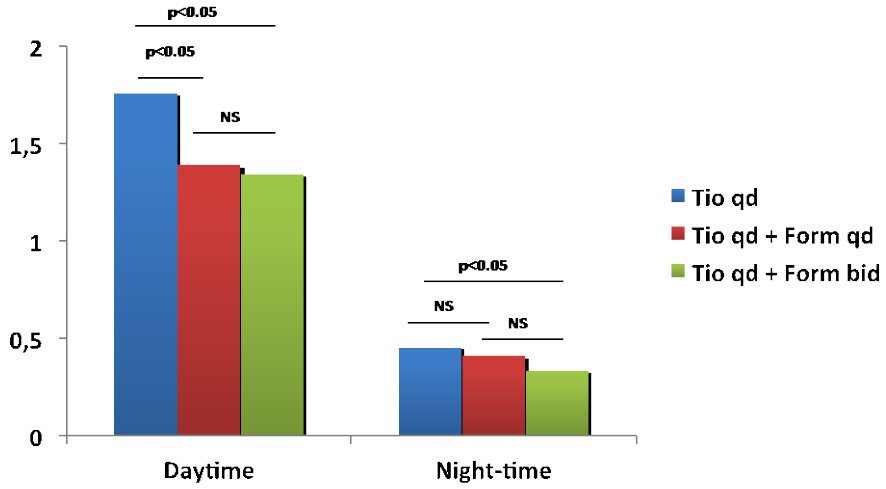
Formoterol twice daily in addition to tiotropium

2-week treatment periods

Time course of bronchodilators



As-needed salbutamol use

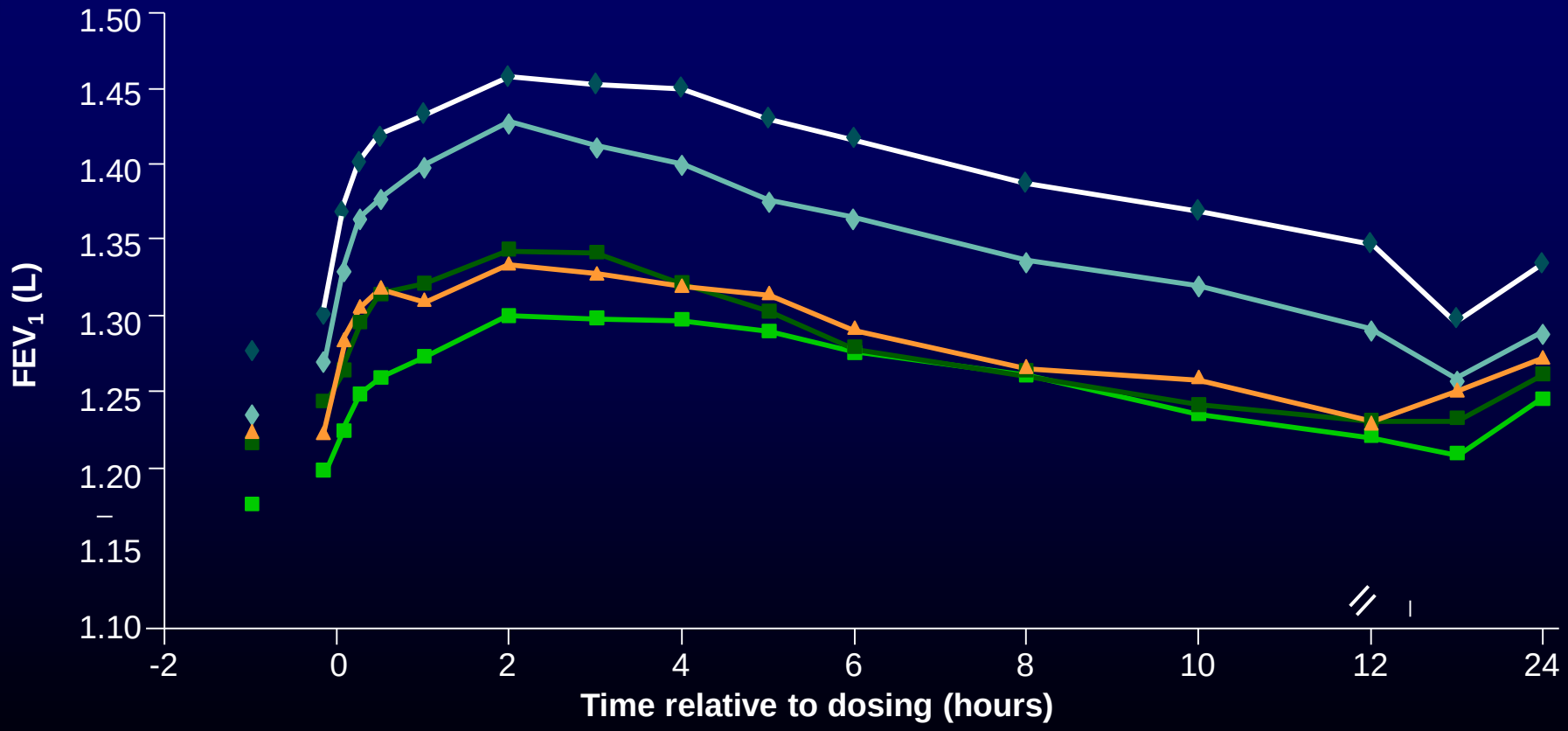


van Noord et al, Chest 2006;129:509-17

LABA/LAMA FDCs approved or in Clinical Development

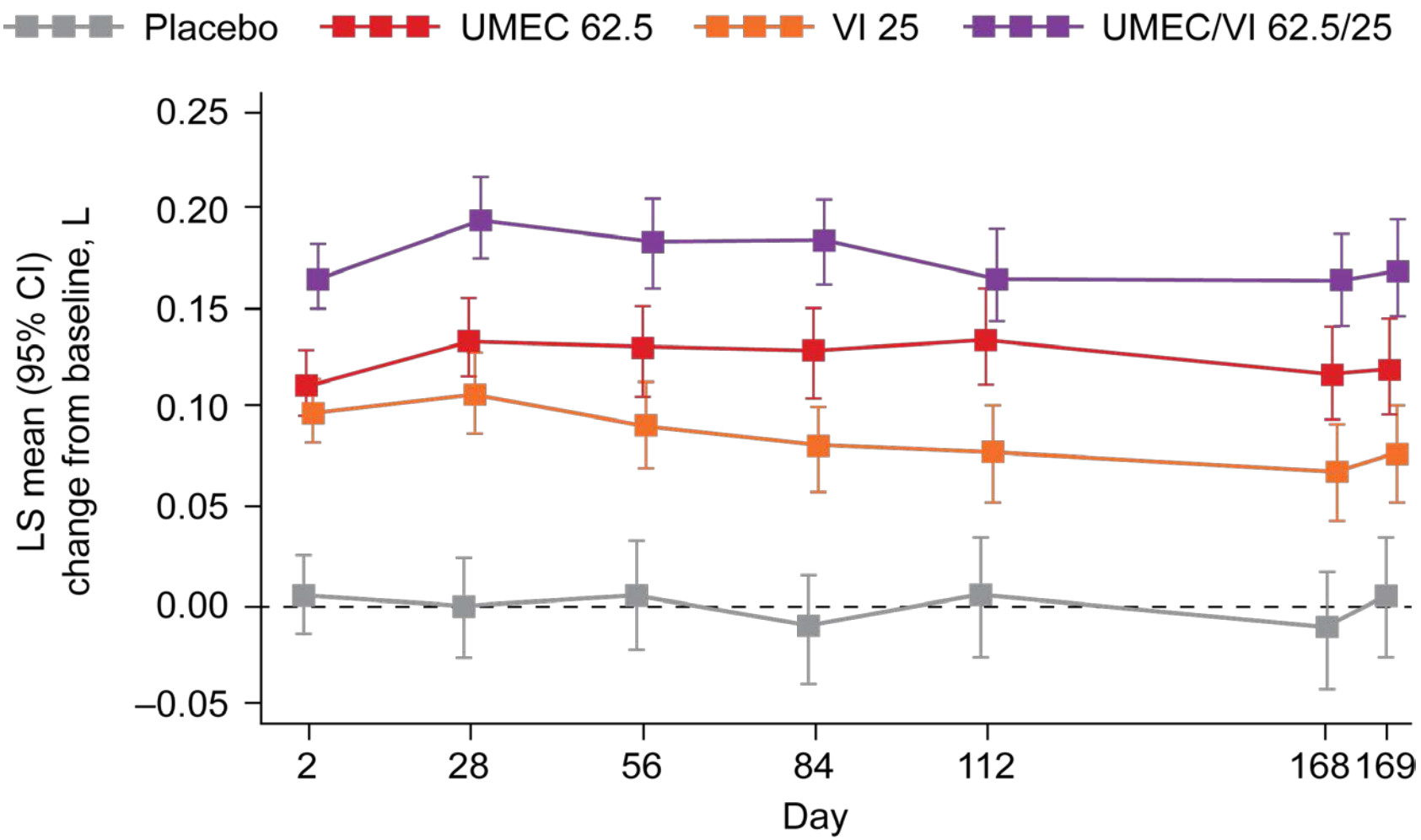
LABA	LAMA	Dosing	Inhaler
Indacaterol	Glycopyrronium	110/50 μg o.d. 27.5/15.6 μg b.i.d.	Breezhaler
Vilanterol	Umeclidinium	62.5/25 μg o.d.	Ellipta
Formoterol	Aclidinium	400/12 μg b.i.d.	Genuair
Olodaterol	Tiotropium	5/5 μg o.d.	Respimat
Formoterol	Glycopyrronium	Twice daily	HFA pMDI

FEV_1 improved over 24 hours after 24 weeks' treatment for T+O FDC 5/5 and 2.5/5 µg versus monotherapy



Buhl 2015.

Efficacy: trough FEV_1 (ITT population)

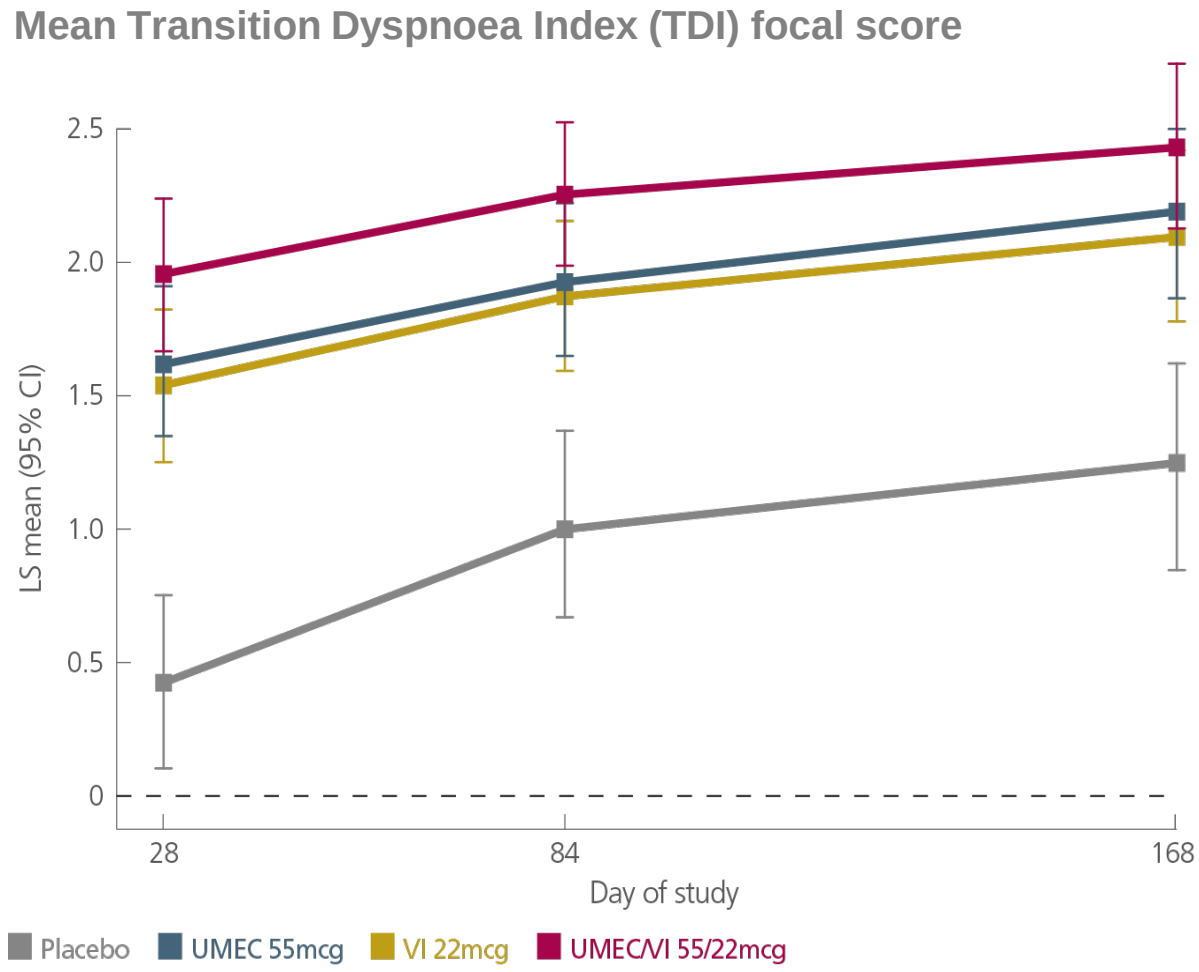


Statistically significant improvement for UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg (0.052 L; p = 0.004), VI 25 mcg (0.095 L; p < 0.001) and placebo (0.167L; p< 0.001) at Day 168

Donohue et al. Respir Med 2013; 107: 1538–46

Note: VI is not currently licensed as a monotherapy for COPD

UMEC/VI vs placebo and individual components Dyspnoea (TDI)



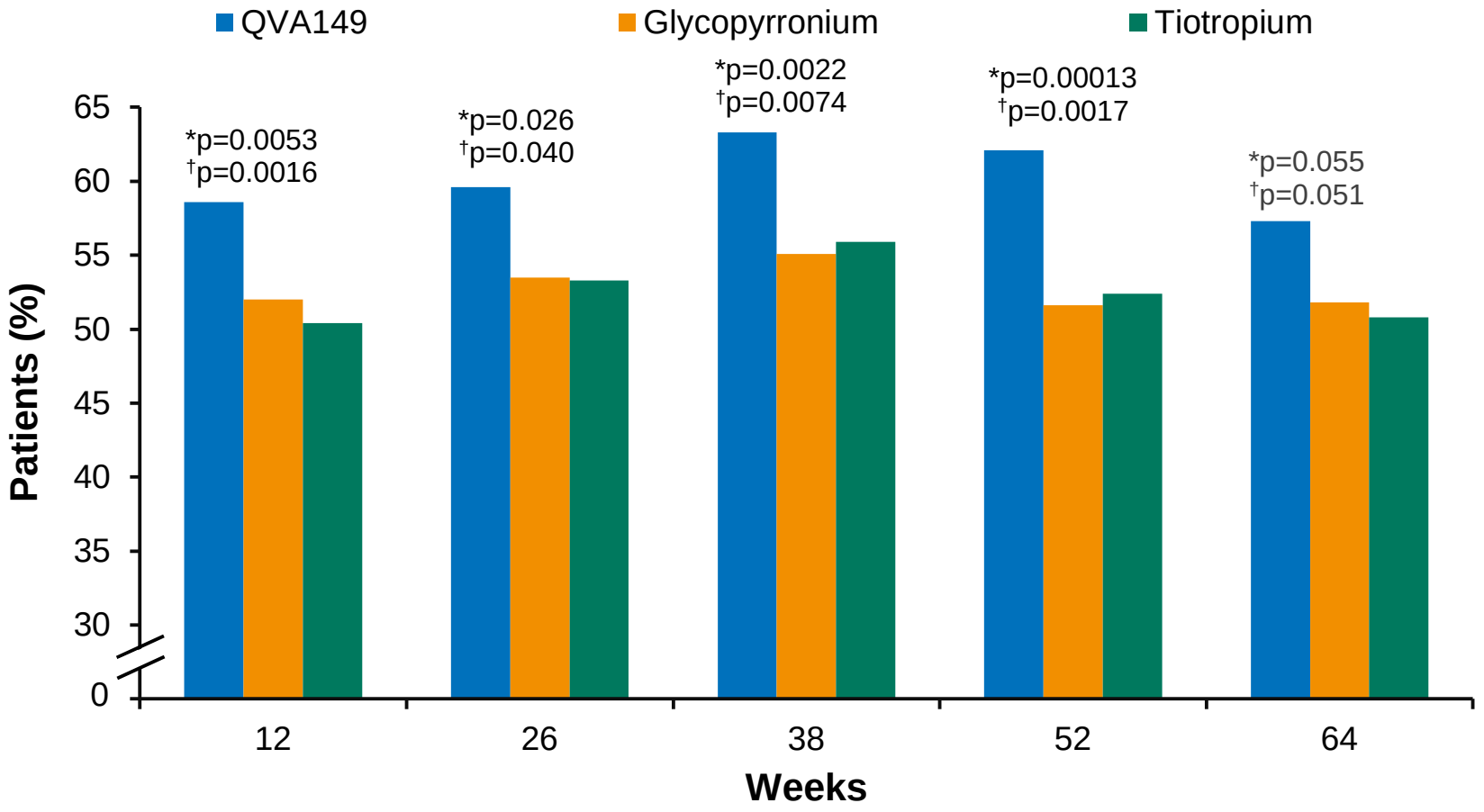
UMEC/VI 55/22mcg

1.2 unit increase over placebo (p<0.001)

Donohue et al. Respir Med 2013; 107: 1538–46

Note: VI is not currently licensed as monotherapy for COPD

Percentages of patients achieving the minimum clinically important difference (≥4 units) in SGRQ score



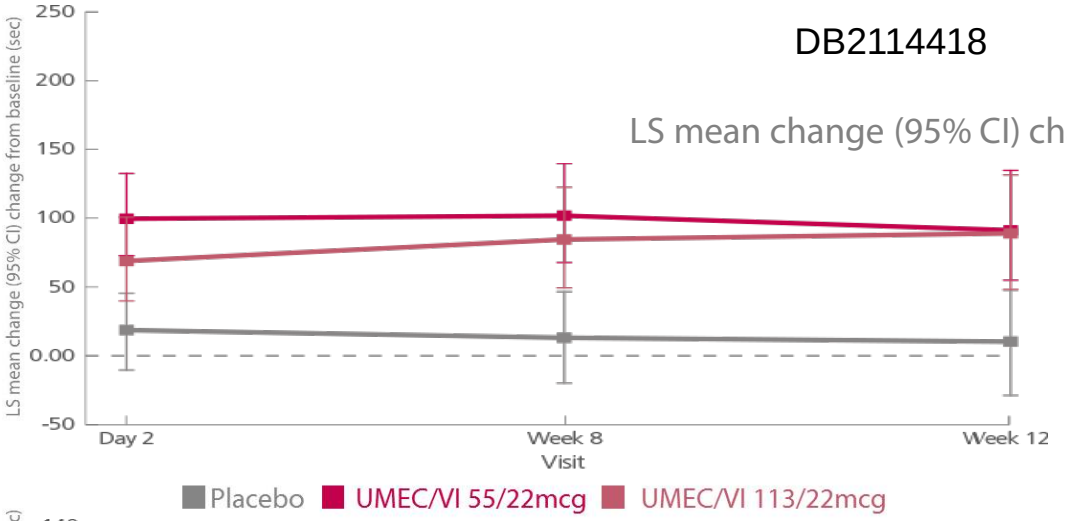
p-values are calculated for odds ratios. *QVA149 vs glycopyrronium; †QVA149 vs tiotropium

Wedzicha JA, et al. Lancet Resp Med 2013 1 (3): 199-209

Exercise endurance

3-hour post-dose exercise endurance times (EETs) at Week 12[1-3]

DB2114418

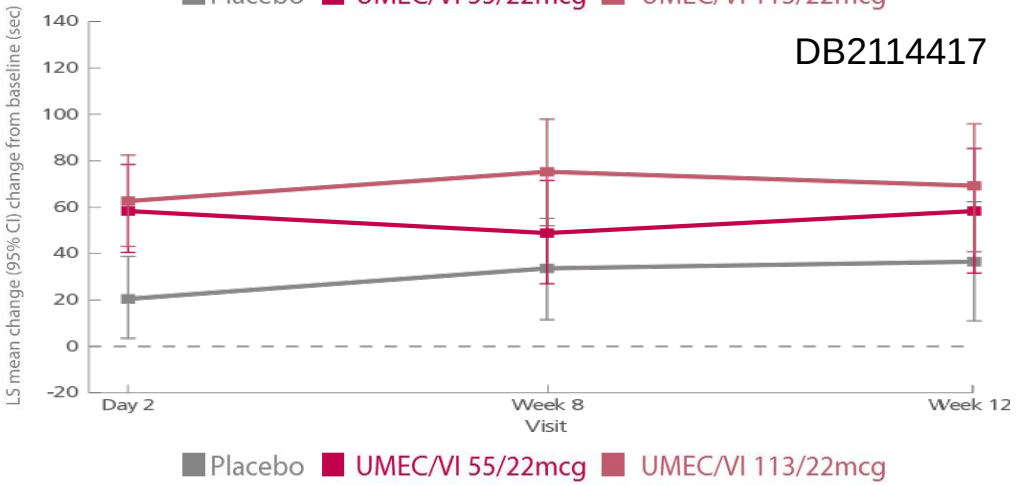


Endurance shuttle walk test (ESWT)

LS mean change (95% CI) change from baseline (sec)

UMEC/VI 55/22mcg
69.4 sec (*p= 0.003)*
and **21.9 sec** (NS)
increase over placebo

DB2114417

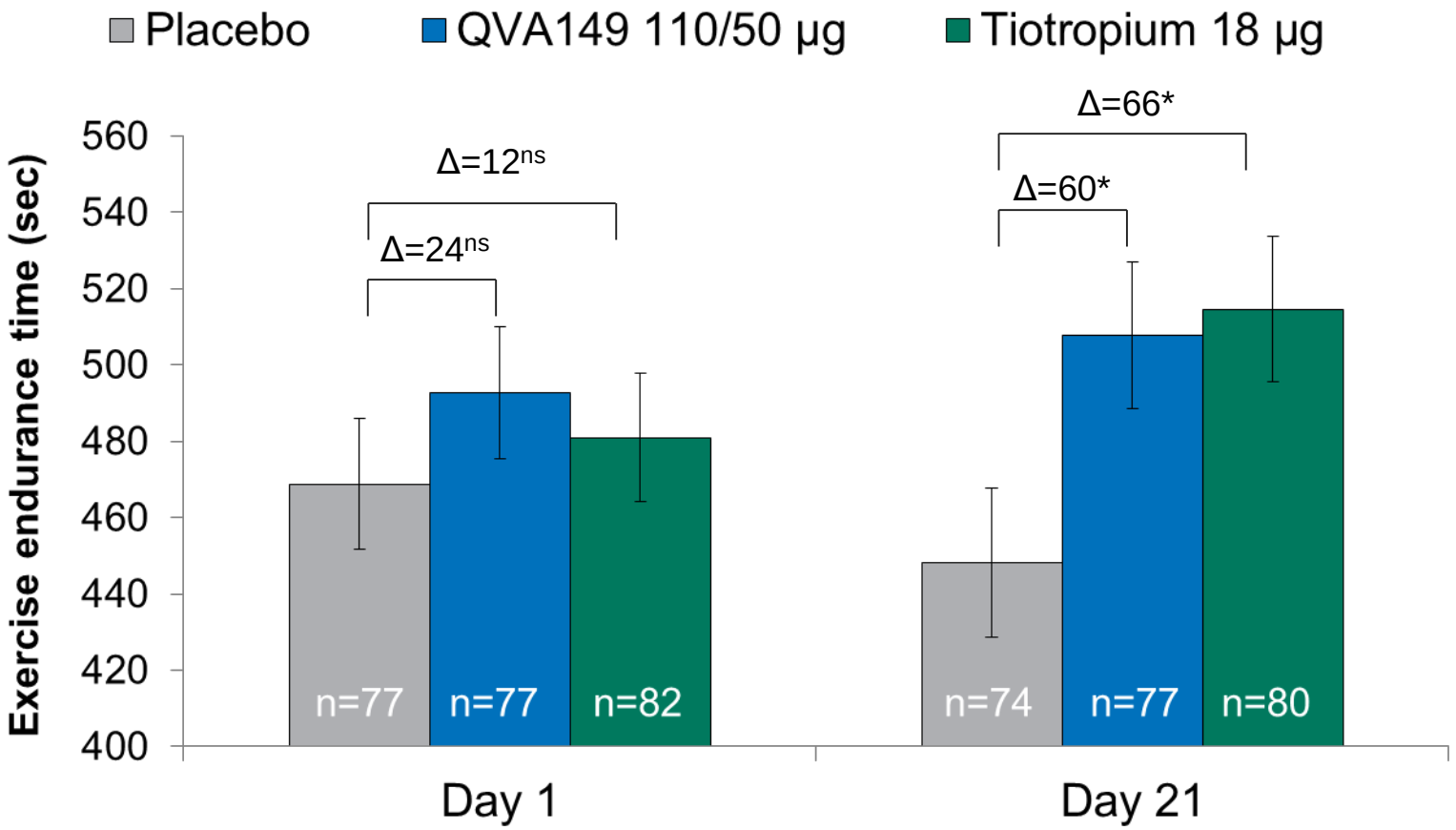


While a valid estimation of the minimal important difference has yet to be established, a change in performance of 45-85 seconds is likely to be perceived by patients following treatment.[2]

1. Data on file: CSR-DB2114418. 2. Data on file: CSR-DB2114417. 3. Anoro Ellipta SmPC, 2014.

Note: VI as monotherapy and UMEC/VI 113/22 mcg are not licensed for COPD

QVA significantly improved exercise endurance time at Day 21 compared with placebo



Full analysis set; values are least squares mean±standard error; ns, non-significant; **p<0.01

- Although it was an exploratory objective, a similar magnitude of improvement was seen for tiotropium compared with placebo

Beeh KM et al. Respir Med 2014

QVA149 significantly improved lung function parameters compared with placebo and tiotropium on Day 21

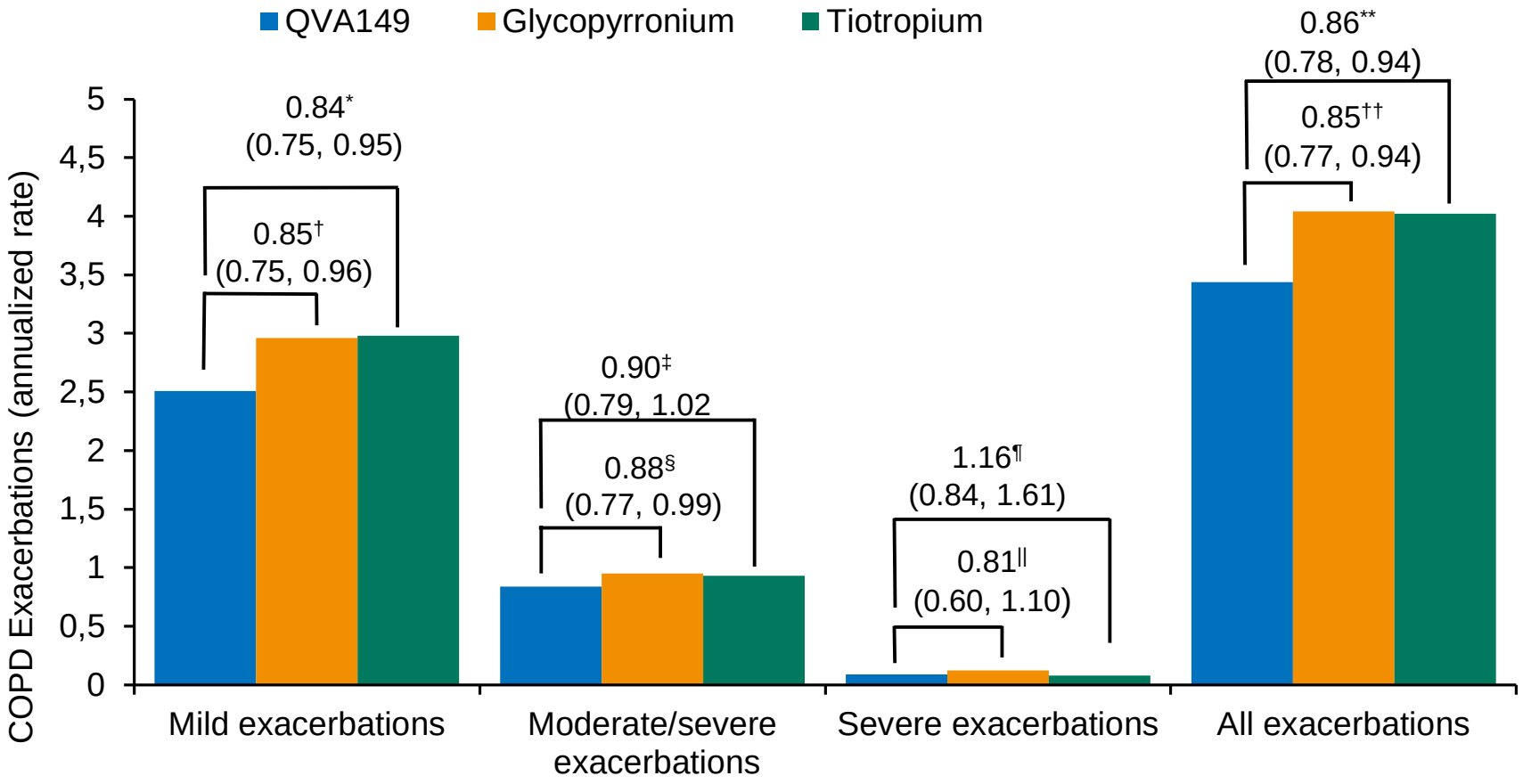
	LS mean treatment difference (95% CI) on Day 21		
	QVA149 110/50 µg – placebo	QVA149 110/50 µg – tiotropium 18 µg	Tiotropium 18 µg – placebo
IC pre-exercise, L	0.34 (0.25, 0.42)***	0.15 (0.07, 0.23)***	0.18 (0.10, 0.27)***
IC at isotime, L	0.32 (0.23, 0.40)***	0.14 (0.05, 0.22)**	0.18 (0.10, 0.27)***
IC at peak exercise, L	0.21 (0.13, 0.30)***	0.09 (0.00, 0.17)*	0.13 (0.04, 0.21)**
IC post-exercise, L	0.31 (0.20, 0.41)***	0.18 (0.08, 0.29)***	0.12 (0.01, 0.23)*
Trough IC, L	0.19 (0.09, 0.29)***	0.15 (0.06, 0.25)**	0.04 (–0.06, 0.13)^{ns}
Trough FEV_1, L	0.20 (0.15, 0.26)***	0.10 (0.05, 0.15)***	0.10 (0.05, 0.15)***
Trough FVC, L	0.28 (0.19, 0.37)***	0.11 (0.02, 0.20)*	0.17 (0.08, 0.27)***

Full analysis set; CI=confidence interval; IC=inspiratory capacity; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ns=non-significant; *p<0.05; **p<0.01; ***p<0.001

Beeh KM et al. Respir Med 2014

NCT number: NCT01294787

Rate reduction of COPD exacerbations



Values are rate reduction (95% CI); n numbers per treatment group: QVA149 n=729; glycopyrronium n=739; tiotropium n=737.
*p=0.0052,†p=0.0072,‡p=0.096,§p=0.038,¶p=0.36,‖p=0.18,**p=0.0017,††p=0.0012.

Wedzicha JA, et al. Lancet Resp Med 2013 1 (3): 199-209

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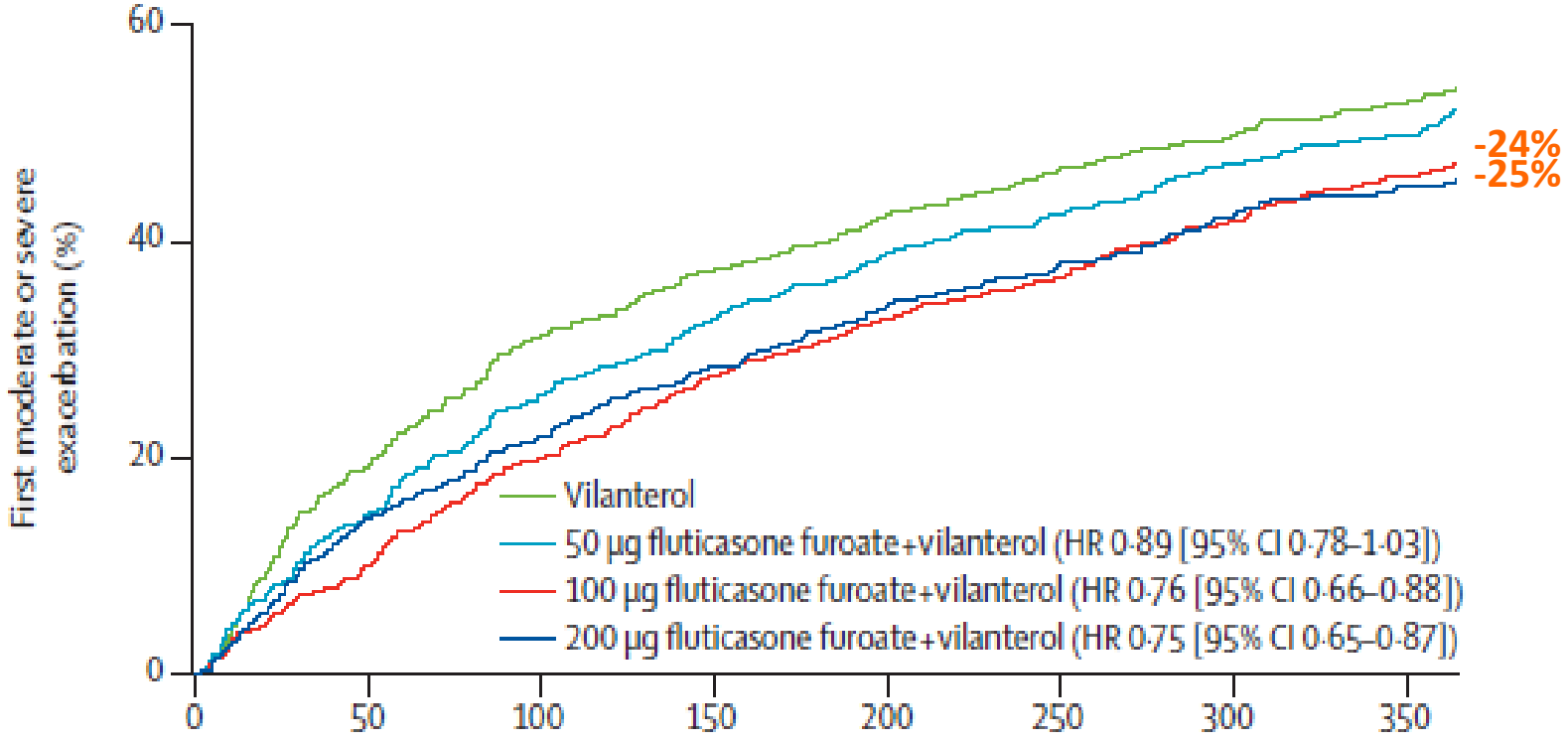
FF/VI in BPCO: Riduzione riacutizzazioni di BPCO a 12 mesi (Tempo alla prima riacutizzazione, Analisi accorpata)



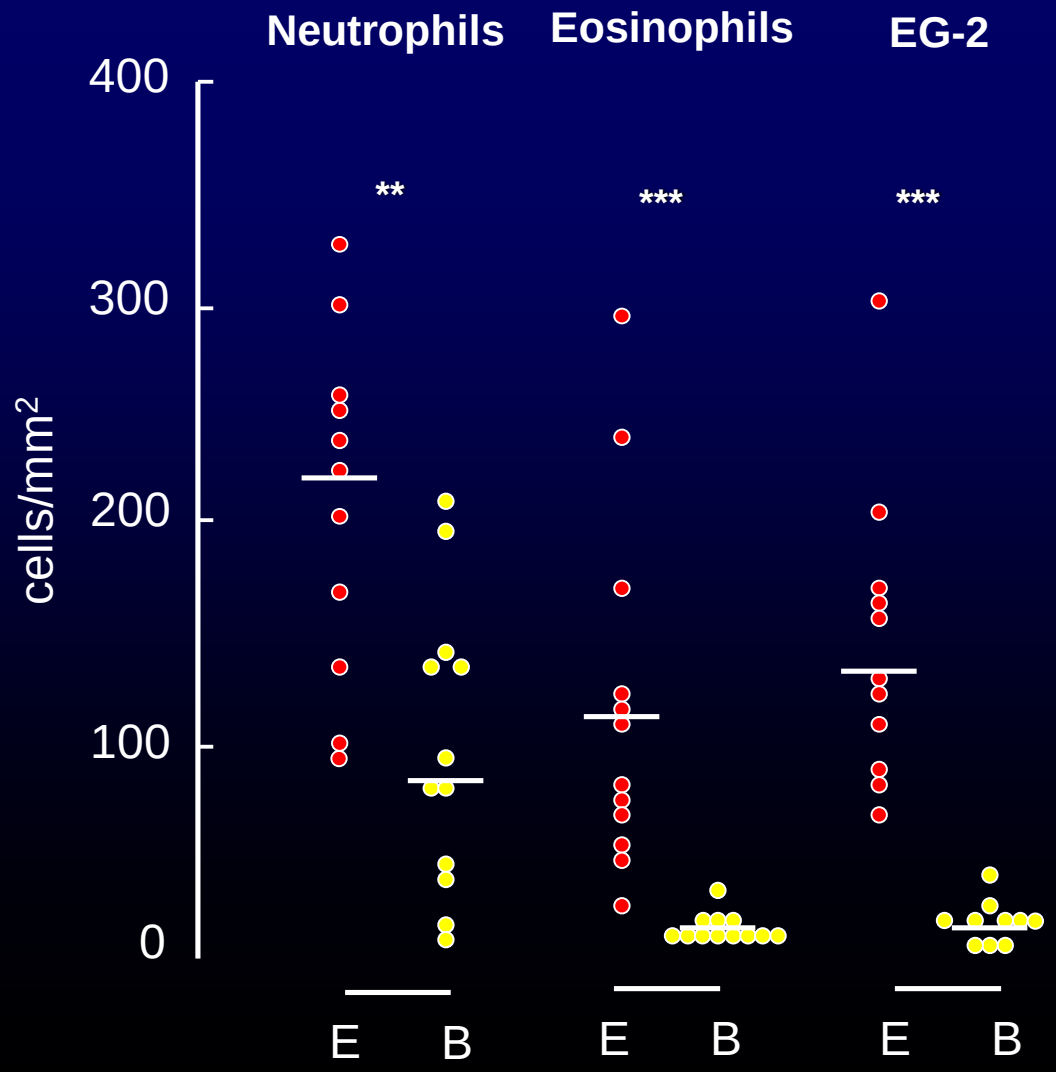
Il Tempo alla prima riacutizzazione moderata-grave era significativamente più lungo con Relvar 92/22 e 184/22 rispetto a Vilanterolo

Dransfield M et al., Lancet Respir Med 2013; 1: 210–23

Bronchial inflammation in COPD exacerbations

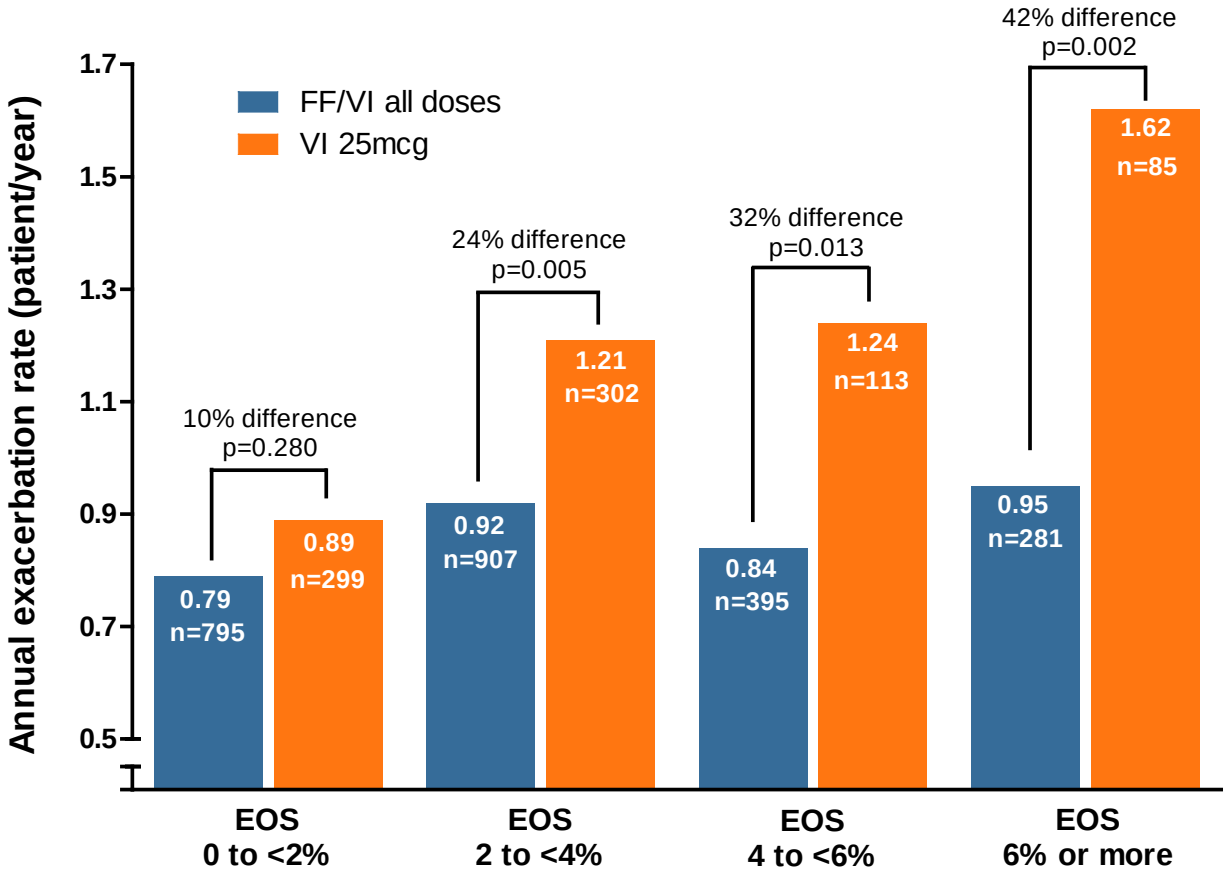
Increased Neutrophils and Eosinophils in COPD exacerbations

(Saetta 1994, Zhu 2001)



(Saetta, 1994)

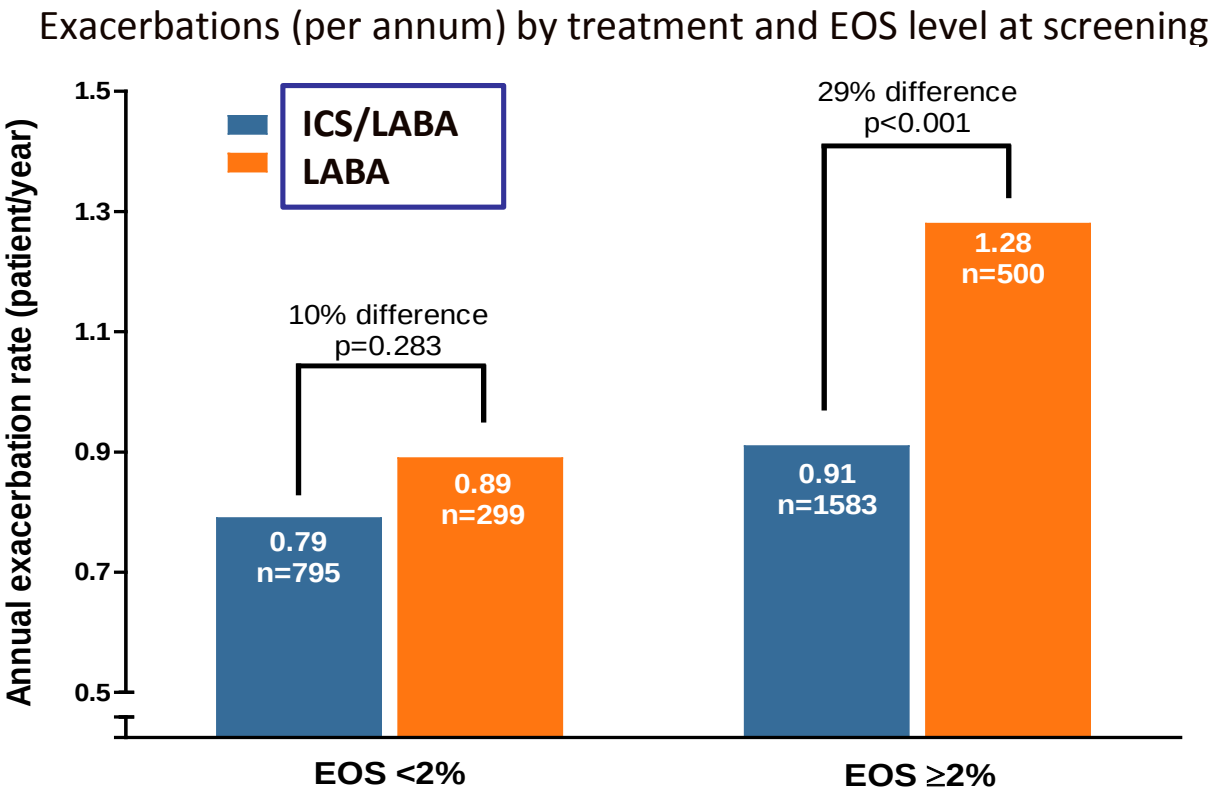
Treatment effect for FF/VI vs VI alone based on increasing levels of blood eosinophils



Dransfield MT *et al*. 2013. Lancet Respir Med 2013; 1: 210-223.
Data shown adapted from: Pascoe S, *et al. ERS 2014, Poster P2817*

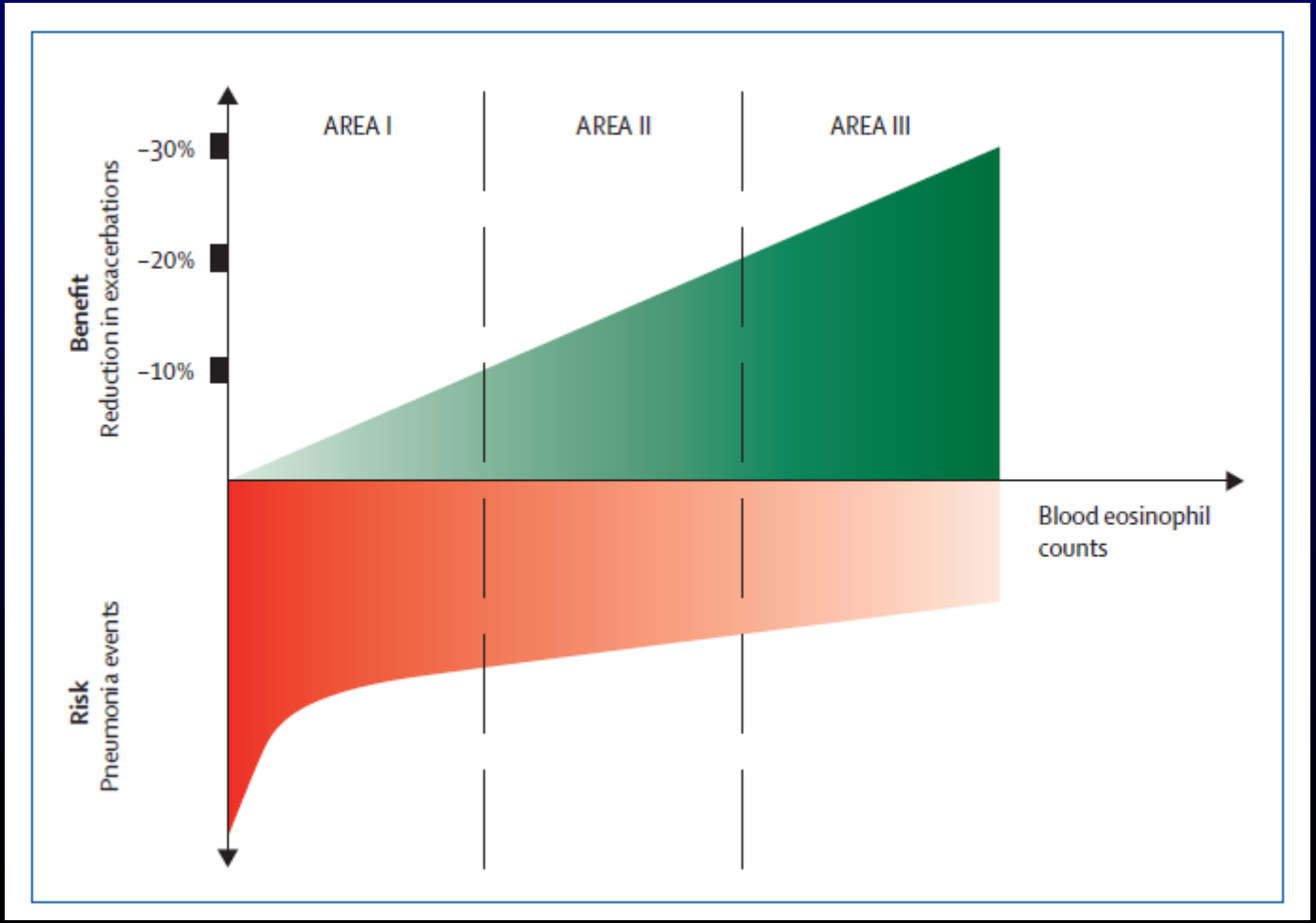
Risultati dello Studio (Pascoe S et al)

- In presenza di EOS. plasmatica ≥2%, il tasso di riacutizzazioni è del 29% inferiore (p<0.01) nei pazienti trattati con la combinazione rispetto al solo LABA.
- Nessuna differenza nei pazienti con EOS < 2%



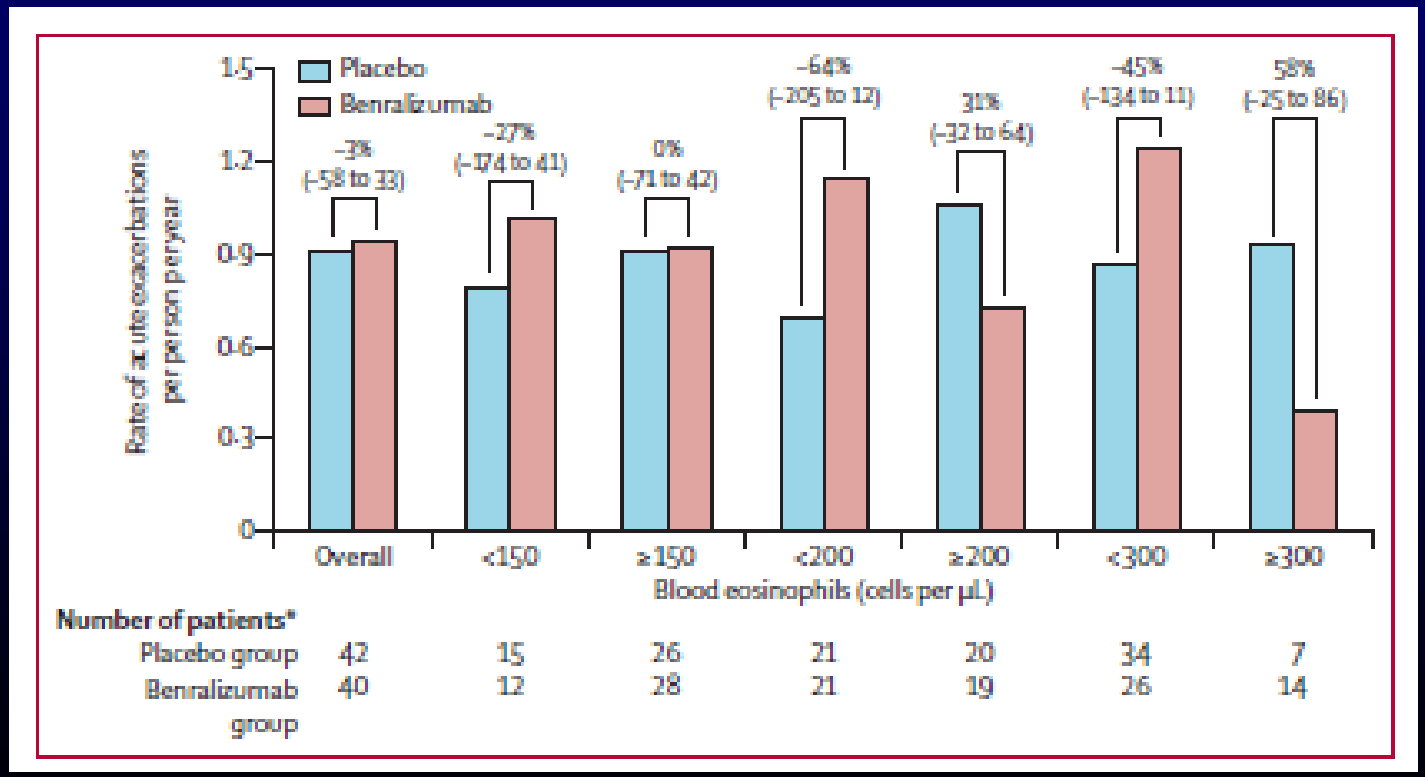
1. Pascoe S et al., Poster No P 2817, European Respiratory Society (ERS) International Congress, Munich, Germany, 6–10 September 2014 (abstract http://www.ers-education.org/events/international-congress.aspx?idParent=132584)

Benefit–risk ratio of inhaled corticosteroids in patients with COPD according to the level of blood eosinophils in stable disease



Brusselle G *Lancet Respir Med* 2015

Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study



Brightling CE, *et al. ERS 2014, Lancet Resp Med, 2015*

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