Girolamo Pelaia

OTTICA RESPIRO

VERONA 2017

CROWNE PLAZA

Clinically important deteriorations: un nuovo target di trattamento?

Clinically important deteriorations (CIDs)

- **Deterioration in health-related quality of life defined as ≥ 4-unit increase from baseline in SGRQ total score.**
- **Decrease of ≥ 100 mL from baseline in trough FEV_1.**
- **Occurrence of an on-treatment moderate-to-severe COPD exacerbation.**

St George's University of London

ST GEORGE'S RESPIRATORY QUESTIONNAIRE

MANUAL

Professor Paul Jones
Division of Cardiac and Vascular Science
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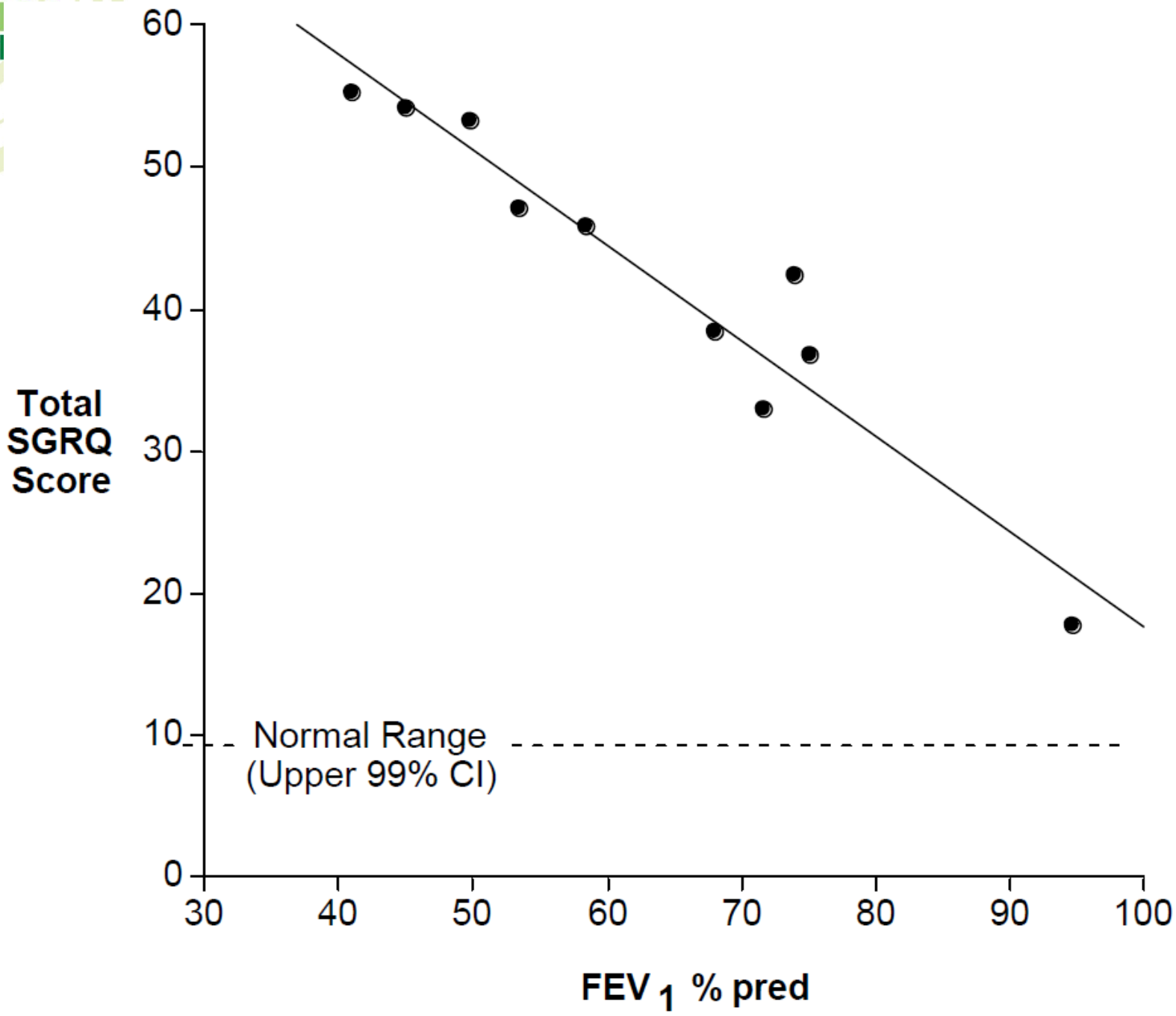
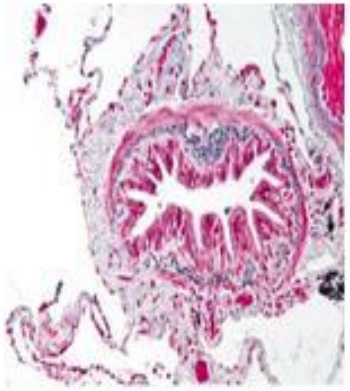
London SW17 0RE
UK

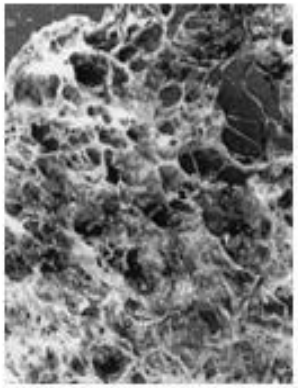

Total SGRQ Score
60
50
40
30
20
10
0
Normal Range
(Upper 99% CI)
30
40
50
60
70
80
90
100
FEV 1 % pred

Heterogeneity of COPD

Airways



Lung



Small airway remodeling and obstruction

Alveolar destruction: loss of lung recoil

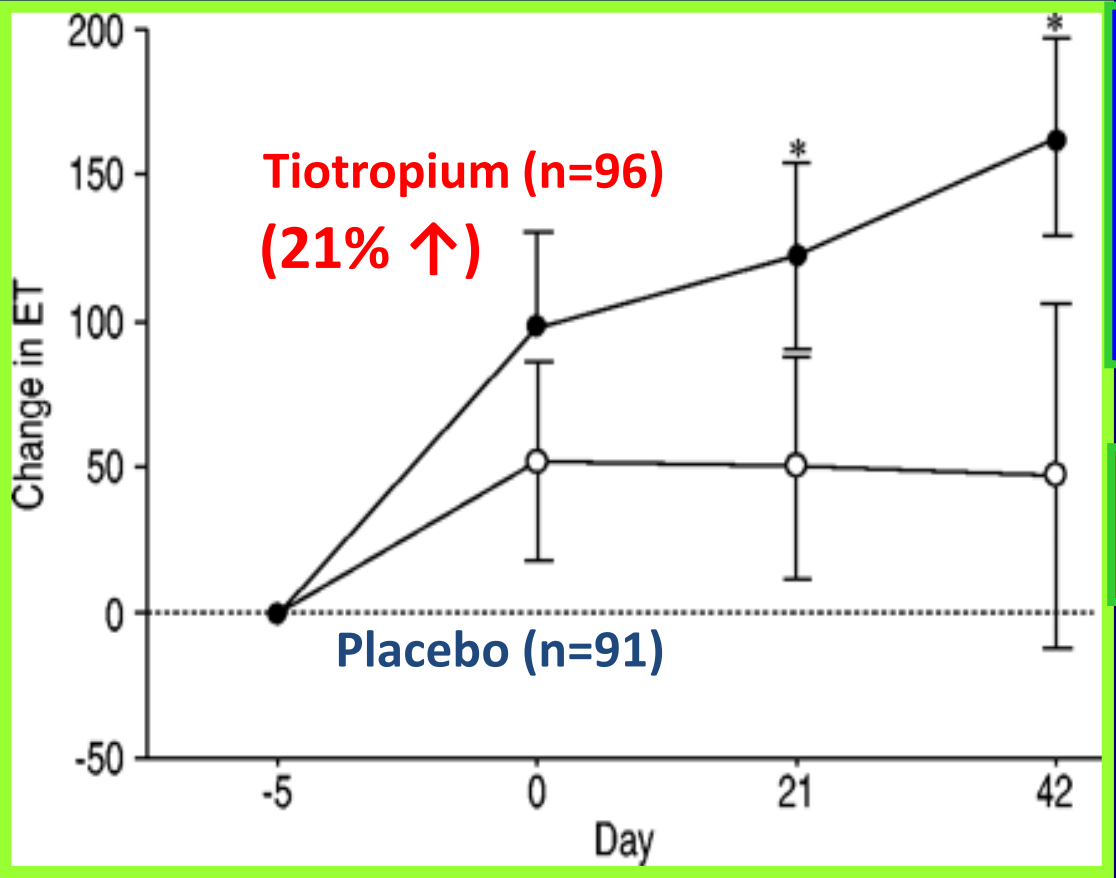
Airflow limitation

FEV_1 ↓

EFFECT OF TIOTROPIUM ON LUNG FUNCTION

Exercise endurance

O'Donnell D et al: Eur Respir J 2004

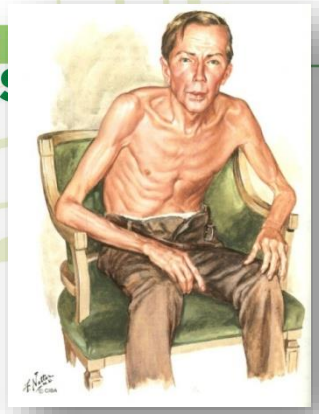


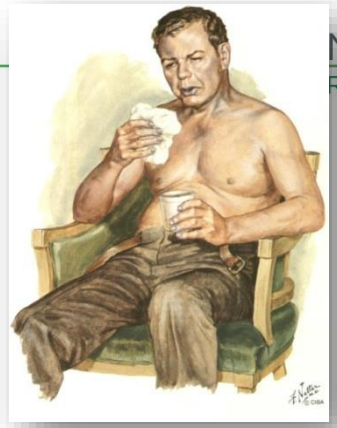
Other effects

- ↓ Dyspnea (Borg score)
- ↑ Inspiratory capacity
- ↓ Residual volume
- ↓ FRC

Does <u>not</u> correlate with ↑ FEV_1

Clinical Course of COPD
Disease Progression





COPD

Expiratory flow limitation

Air trapping

Hyperinflation

DYSPNEA

Activity limitation

Decrease in quality of life

Gas exchange impairment

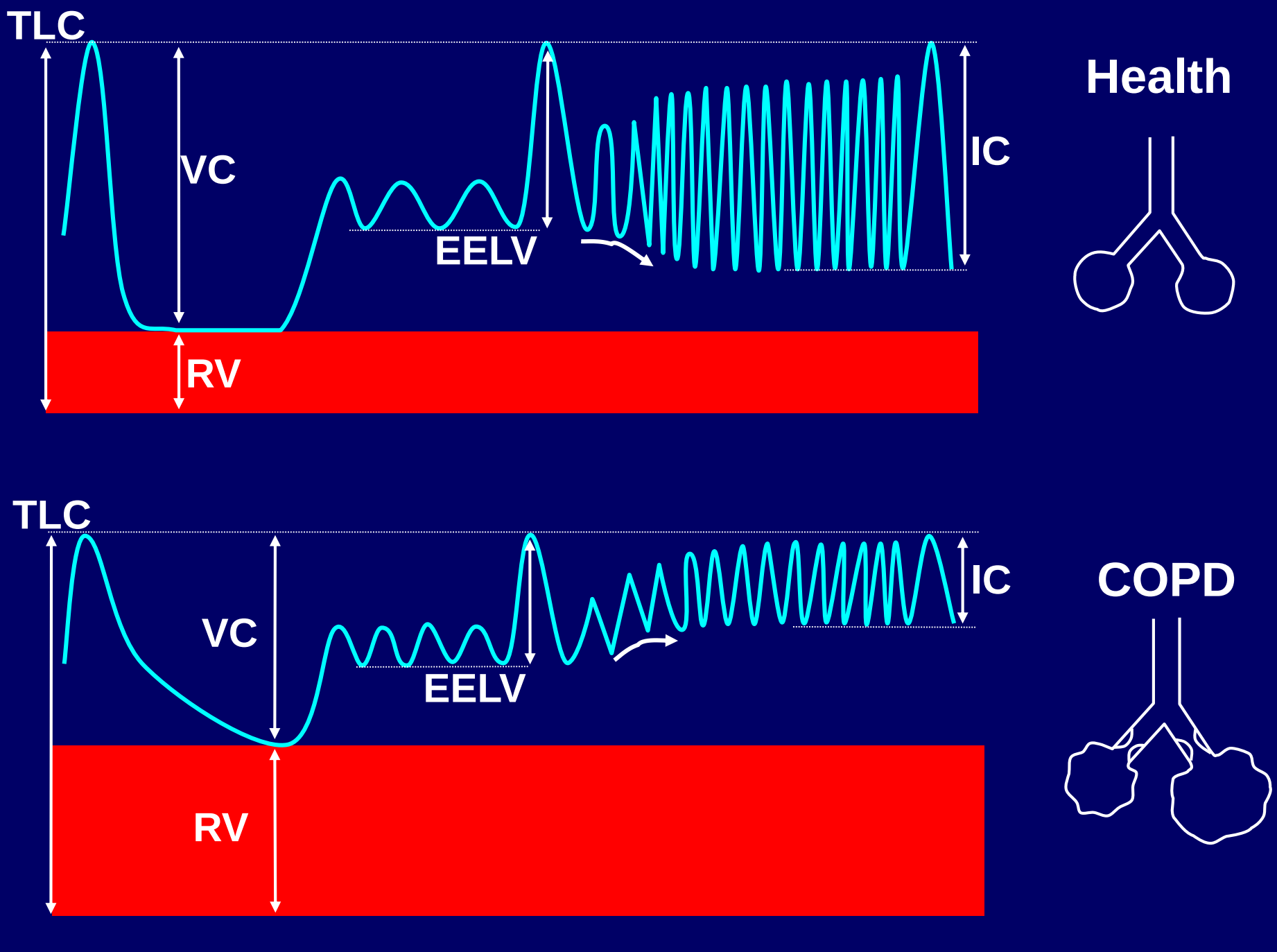
Pulmonary hypertension

Exacerbations

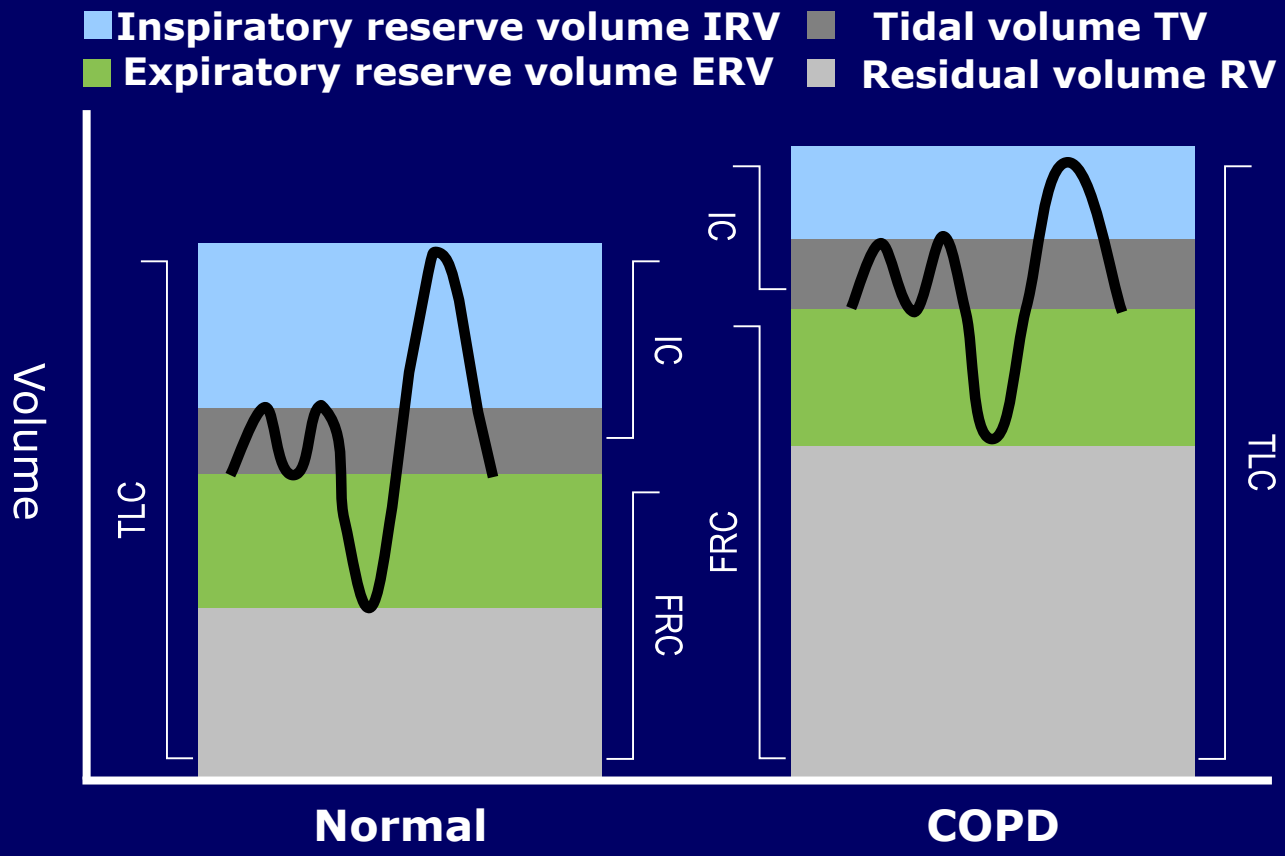
Deconditioning

Reduced exercise endurance

Modified from Cooper CB. *Am J Med* 2006; 119:S21-S31.


TLC
VC
EELV
IC
RV
Health
TLC
VC
EELV
IC
RV
COPD

Hyperinflation in patients with COPD: increased residual volume and reduced inspiratory capacity



TLC = Total lung capacity FRC = Functional residual capacity IC = Inspiratory capacity

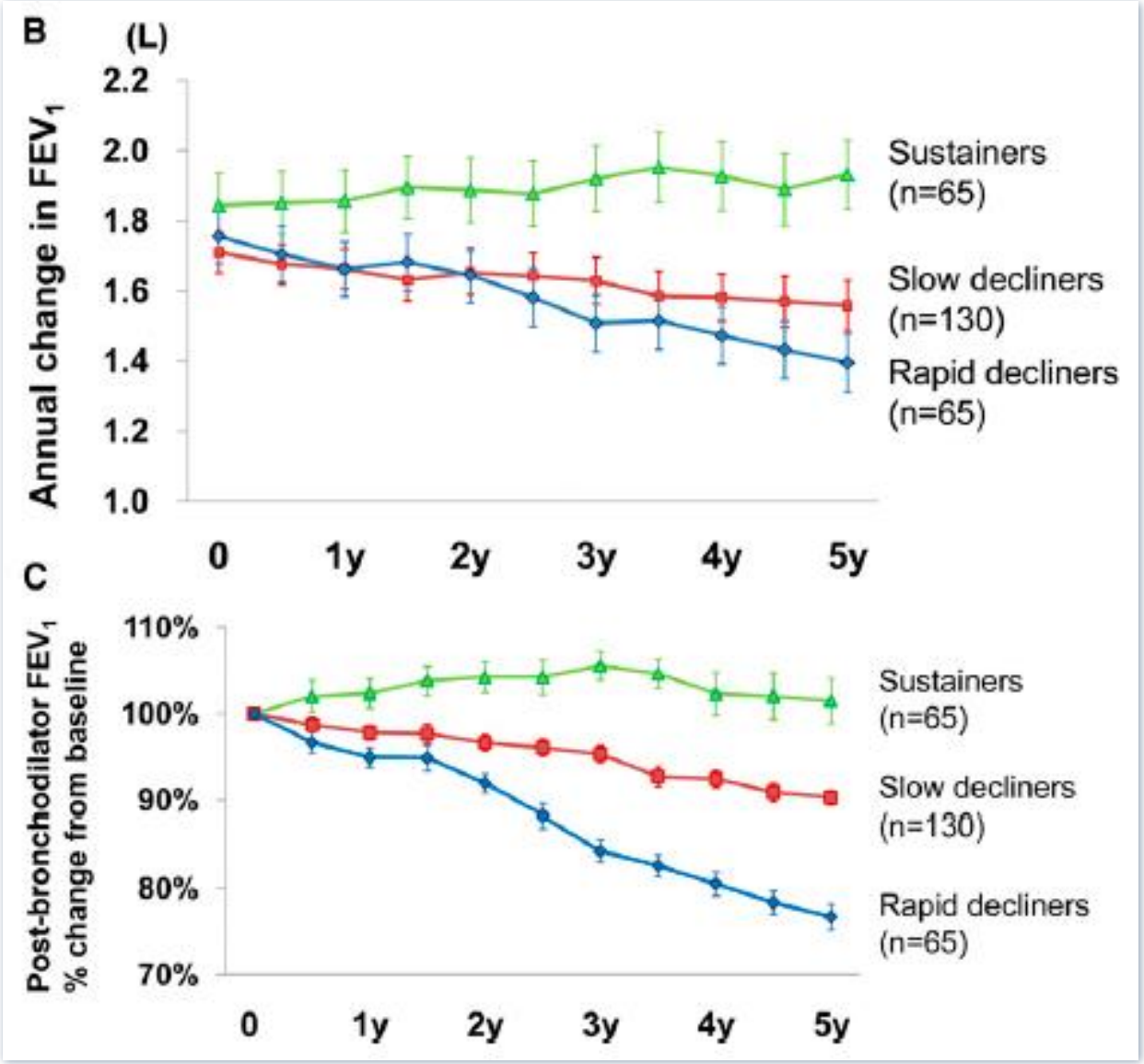
Casaburi et al., Am J Med 2004

AIR TRAPPING

An increase in RV is one of the first functional abnormaliteis in chronic bronchitis. As the disease progresses and RV increases more than TLC, VC falls and FEV_1 falls with it. The primary event, gas trapping, is a major reason for a progressive decline in FEV_1. The new paradigm would emphasise the role of gas trapping, with the decrease in FEV_1 secondary to it.

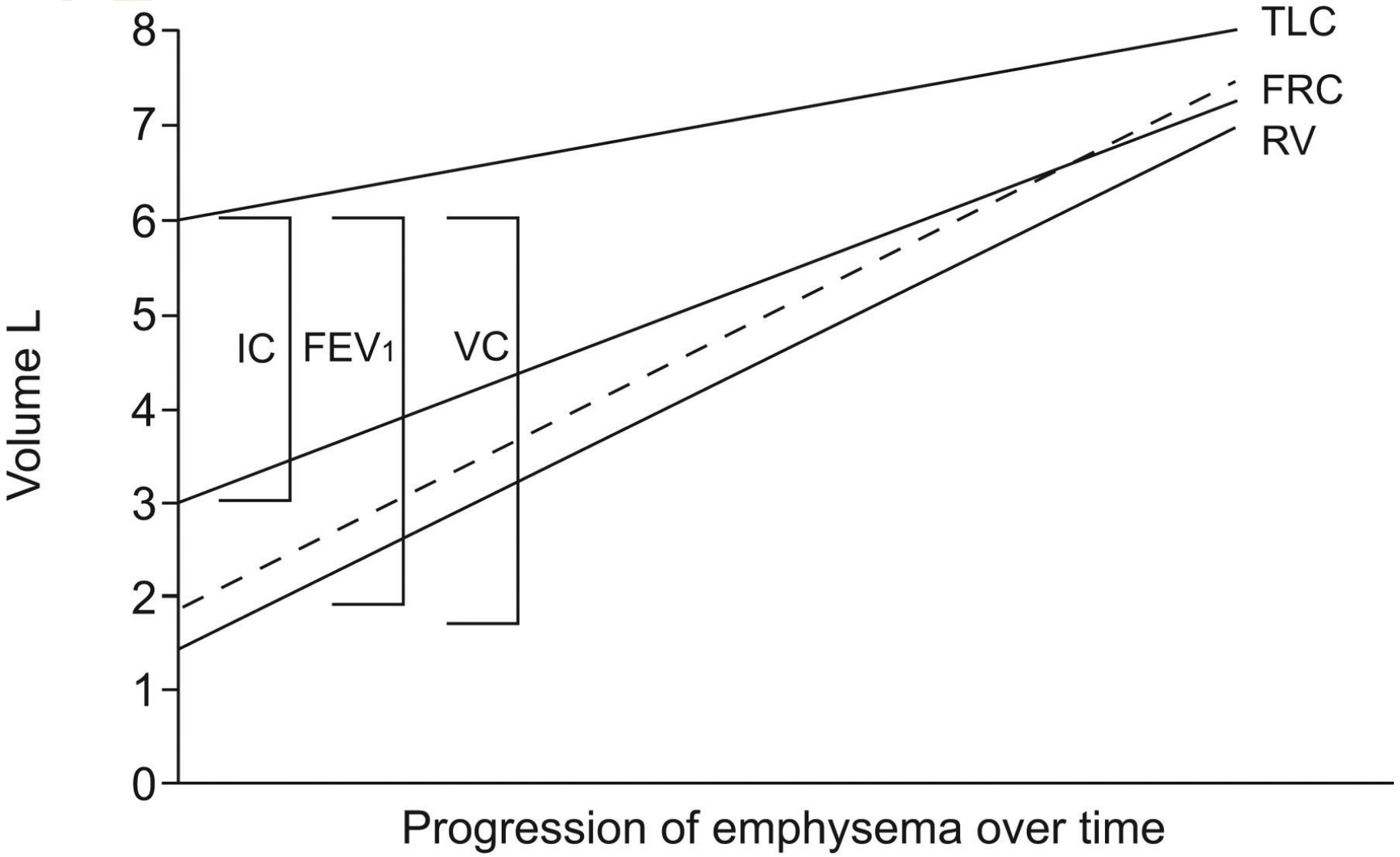
Macklem PT. *Eur Respir J* 35:676-680, 2010

ANNUAL CHANGES IN FEV_1



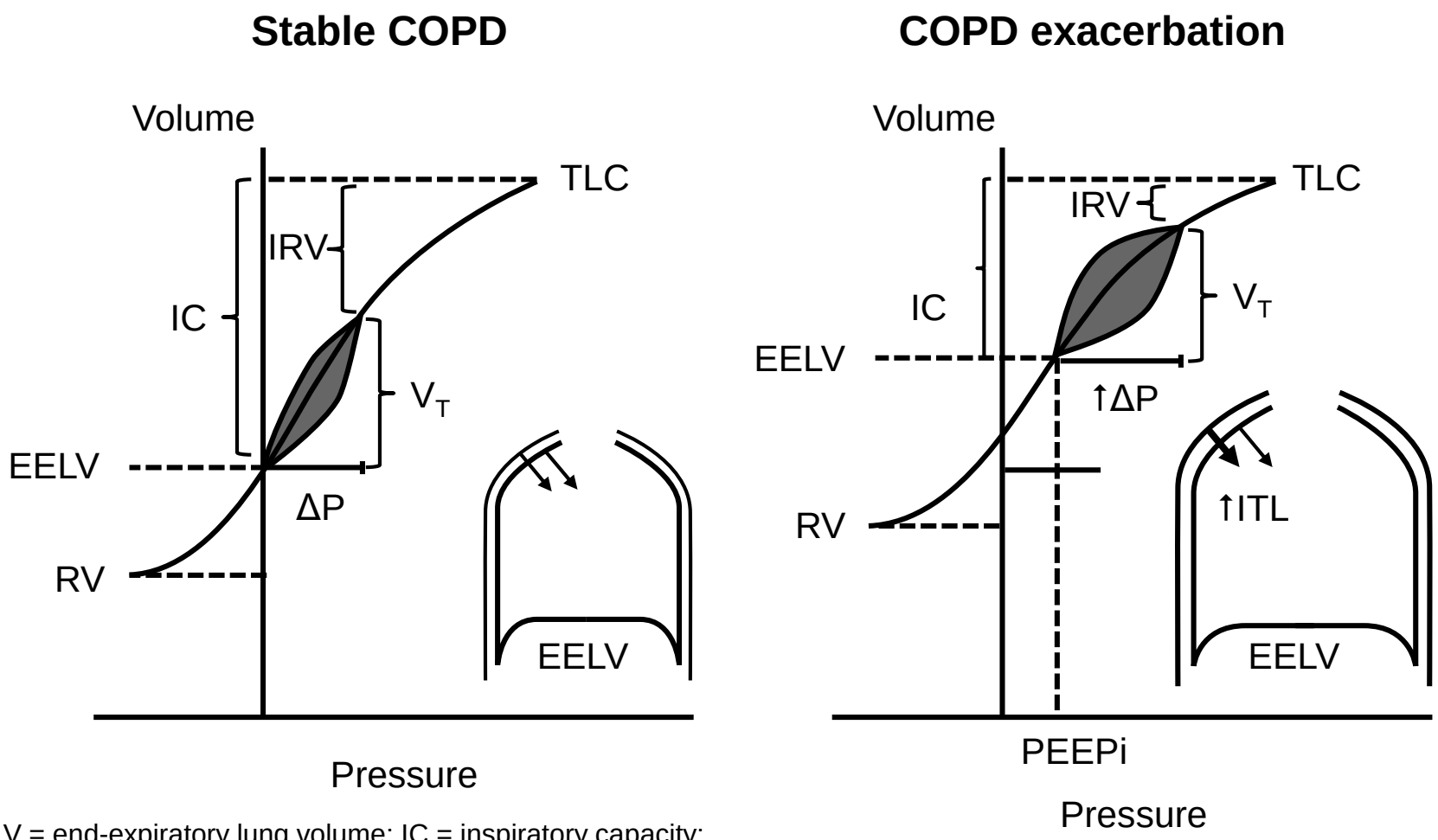
Nishimura M et al. *Am J Respir Crit Care Med* 185:44-52, 2012

PROGRESSIVE INCREASE IN RESIDUAL VOLUME (RV)



Macklem PT. *Eur Respir J* 35:676-680, 2010

Mechanical effects of an exacerbation



EELV = end-expiratory lung volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; PEEPi = intrinsic positive and expiratory pressure; RV = residual volume; TLC = total lung capacity; V_T = tidal volume

Wedzicha JA, Decramer M, Seemungal TAR. *Eur Respir J* 40:1545-1554, 2012

EFFECT OF LVRS ON COPD EXACERBATIONS

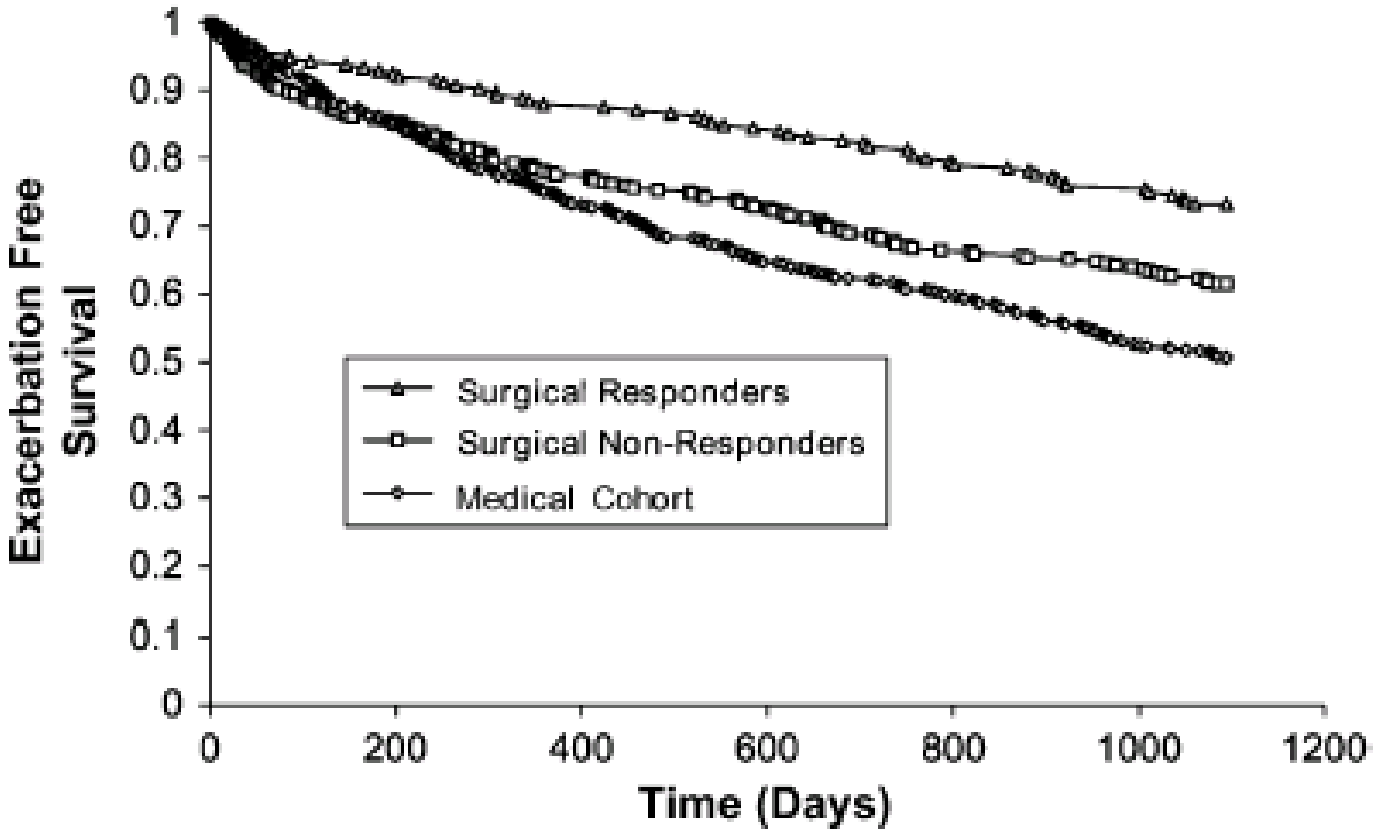
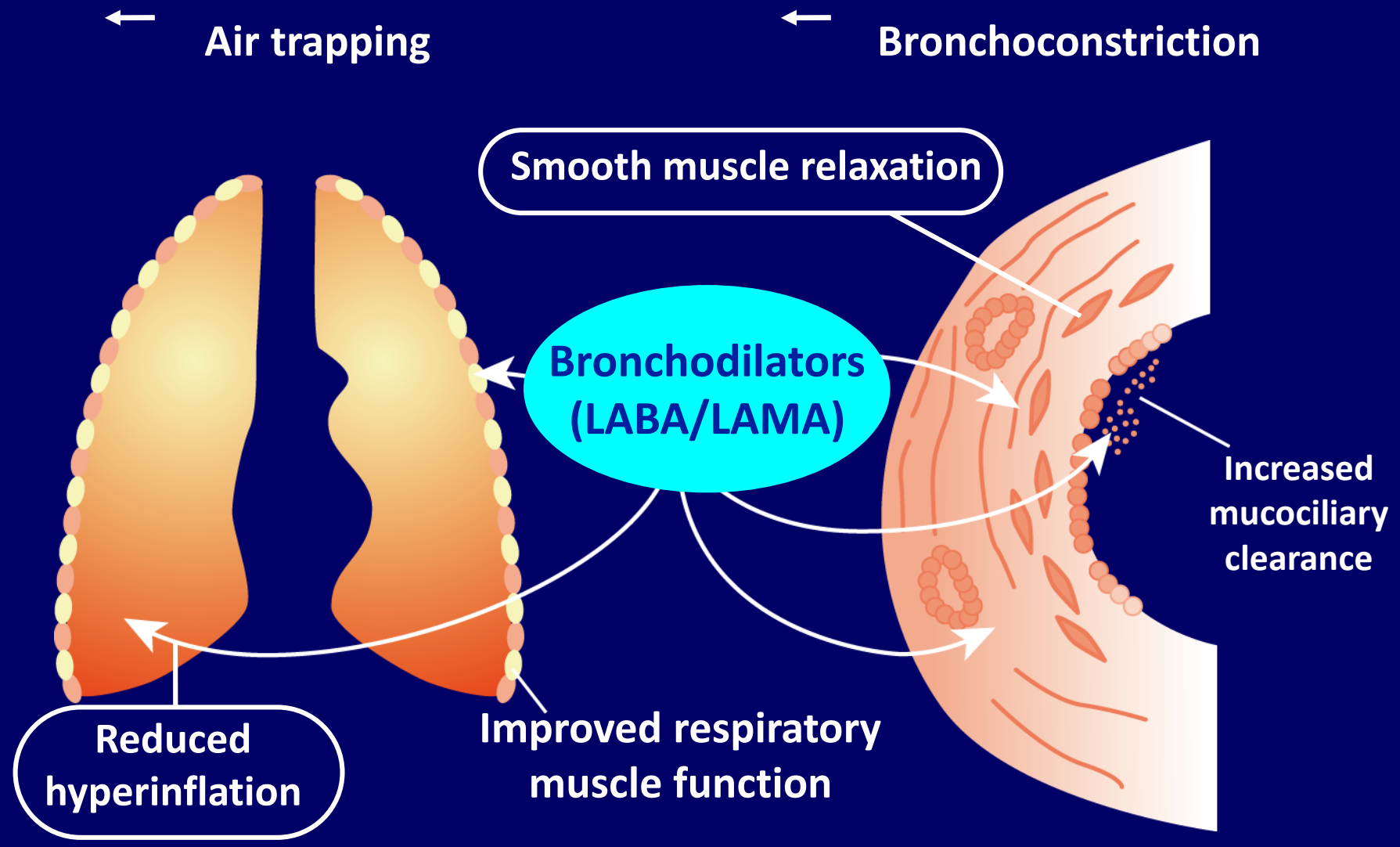


Figure 3. Time to event analysis of surgical responders defined as 6-month improvement in FEV_1 greater than 0.200 L and the surgical nonresponders defined as those with less than a 0.200-L improvement in FEV_1 over the same time period.

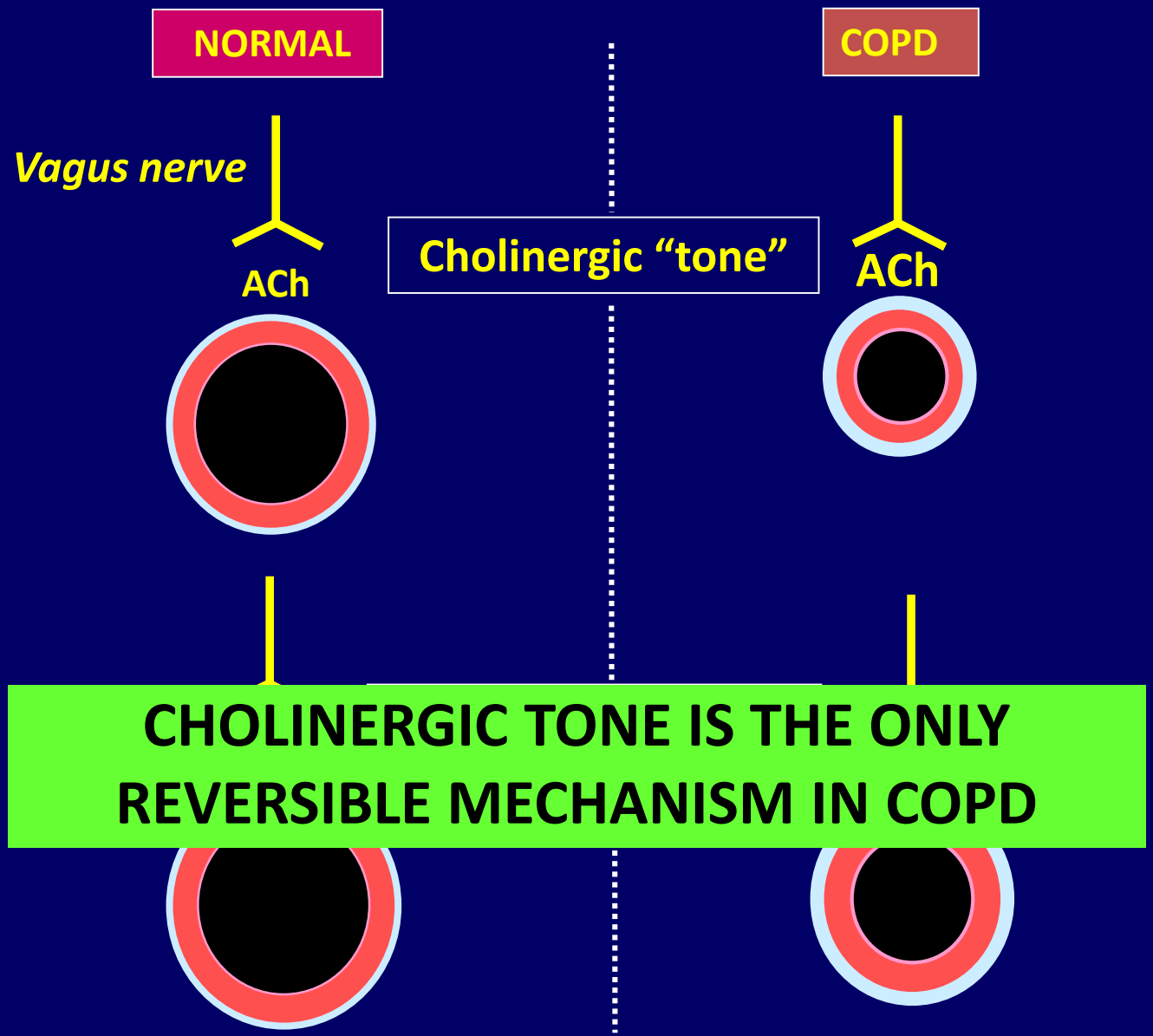
Washko GR et al, for the National Emphysema Treatment Trial Research Group.
***Am J Respir Crit Care Med* 177:164-169, 2008**

Long-acting bronchodilators are essential to symptom management in COPD

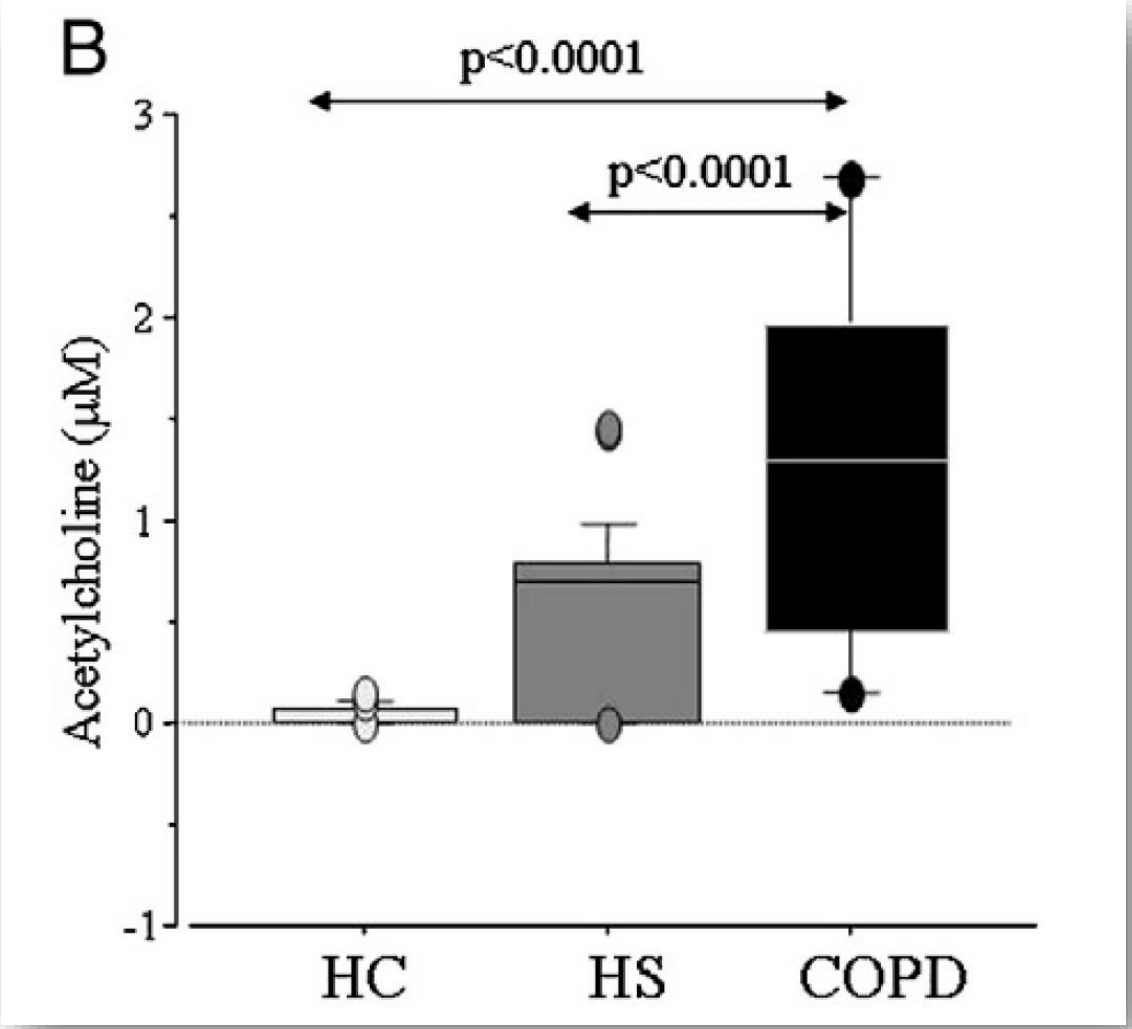


GOLD 2011

COUNTERACTING CHOLINERGIC TONE IN COPD

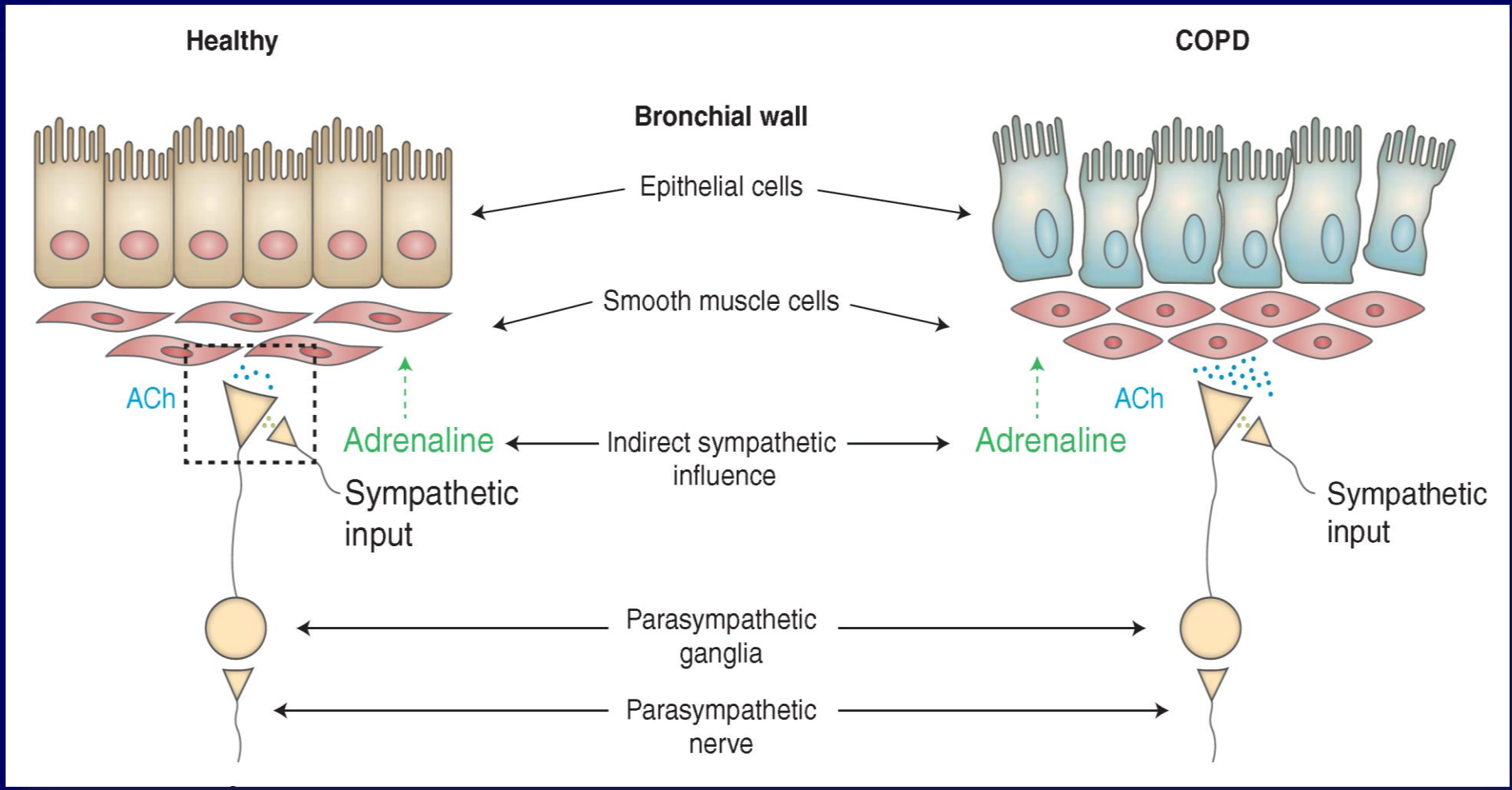


Acetylcholine concentration is increased in induced sputum from COPD patients



Profita M et al. *Biochim Biophys Acta* 1822:1079-1089, 2012

NEURAL INPUT TO AIRWAY SMOOTH MUSCLE CELLS



Panettieri RA. *Postgrad Med J* 127:771-780, 2015

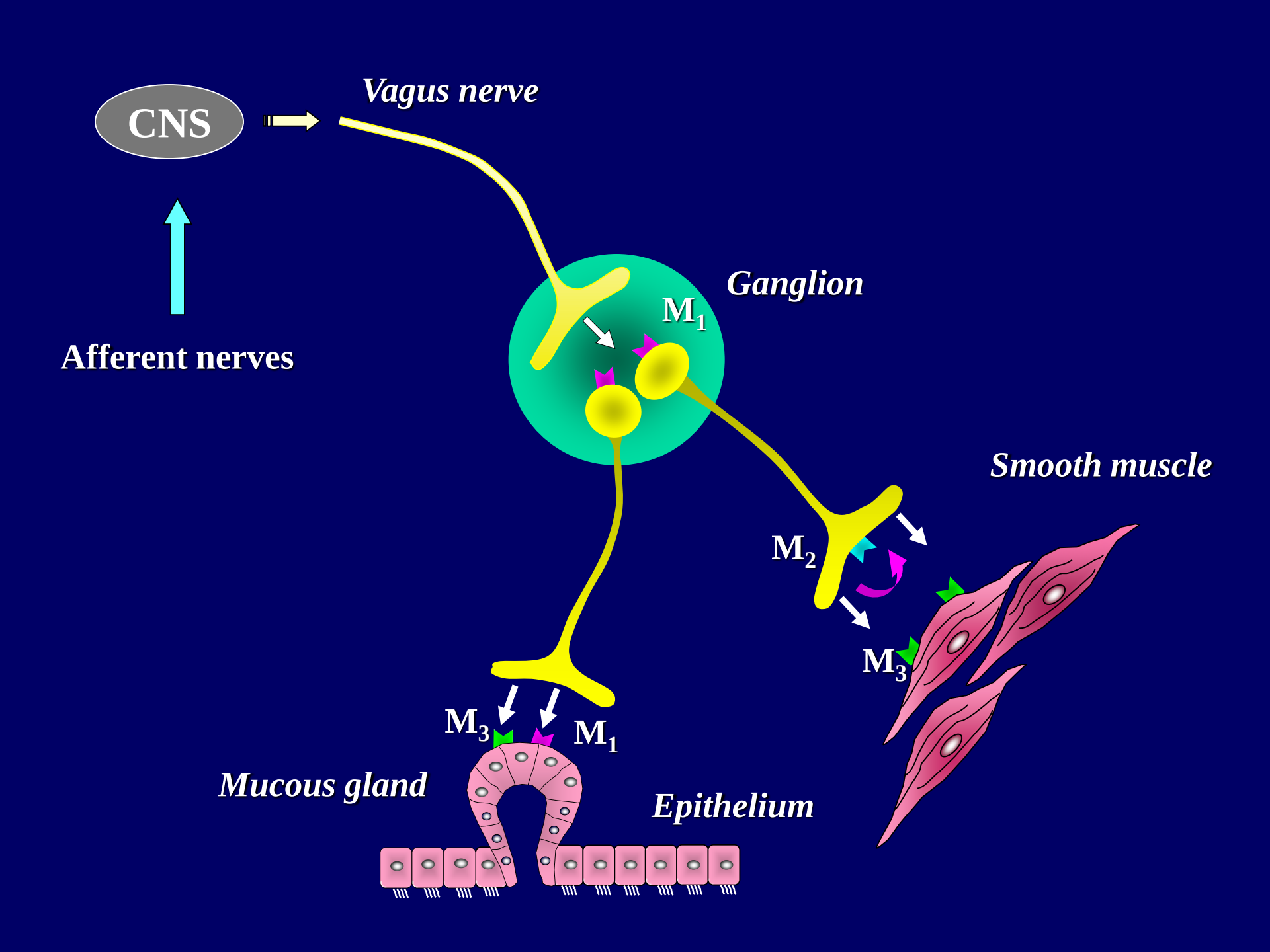
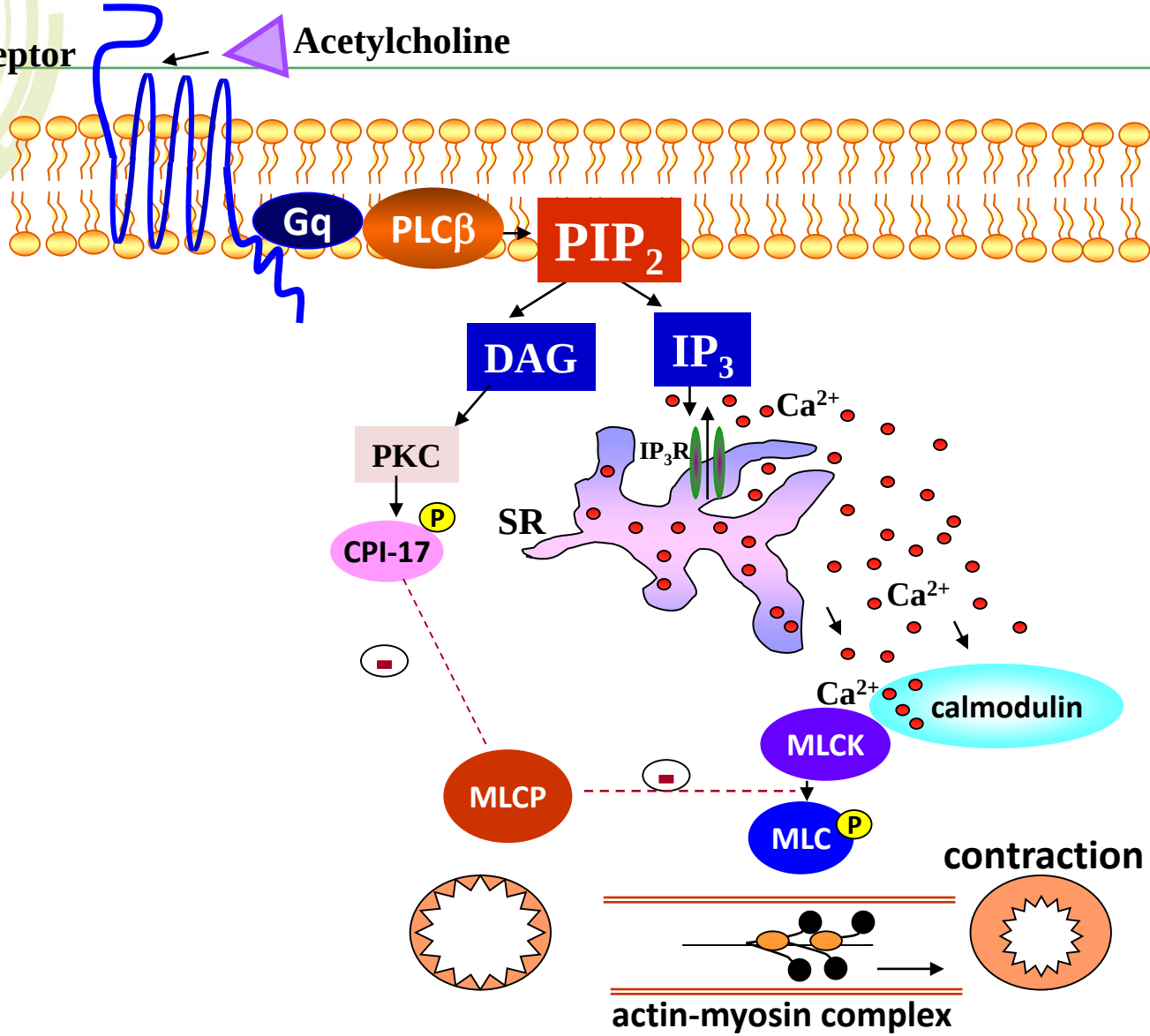

CNS
Vagus nerve
Afferent nerves
Ganglion
M1
Smooth muscle
M2
M3
M3
M1
Mucous gland
Epithelium

Table 1 Function of muscarinic receptor subtypes in lung

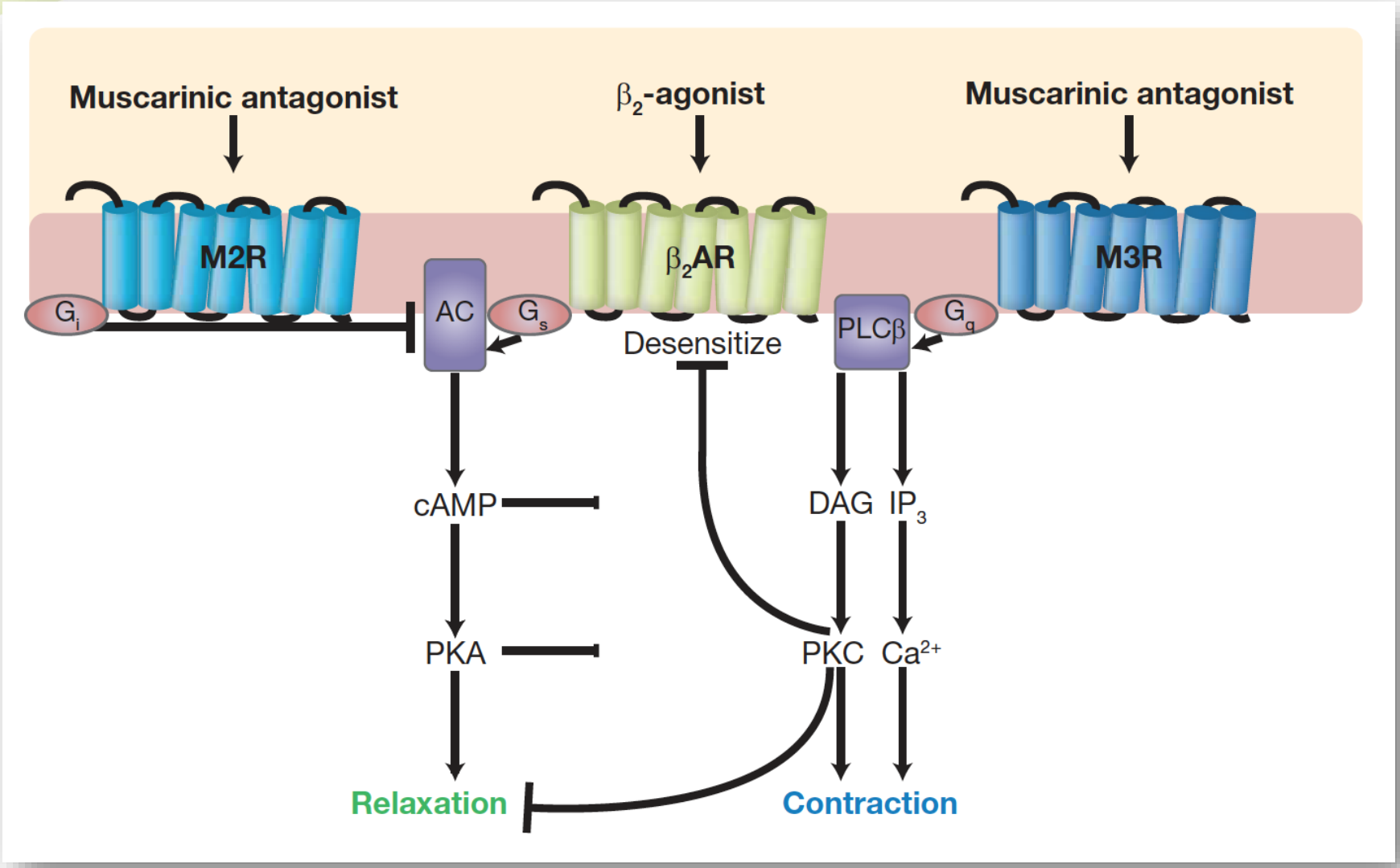
	M_1	M_2	M_3
Parasympathetic nerves	Increase neurotransmission at ganglia	Limit acetylcholine release	
Smooth muscle		Inhibit relaxation[a]	Contraction
Submucosal glands	Unknown		Mucus secretion
Endothelial cells		Unknown	Vasodilation[a]
Airway epithelium	Increase ciliary beat frequency[a] (if M_2 and M_3 blocked)	Reduce ciliary beat frequency[a]	Increase ciliary beat frequency
Immune function	Limit evoked histamine release from mast cells		Induce release of chemotactic factors from alveolar macrophages[a]
Airway remodeling		Increase proliferation in fibroblasts	Enhance proliferation induced by growth factors in smooth muscle

Buels KS, Fryer AD. *Handb Exp Pharmacol* 208:317-341, 2012



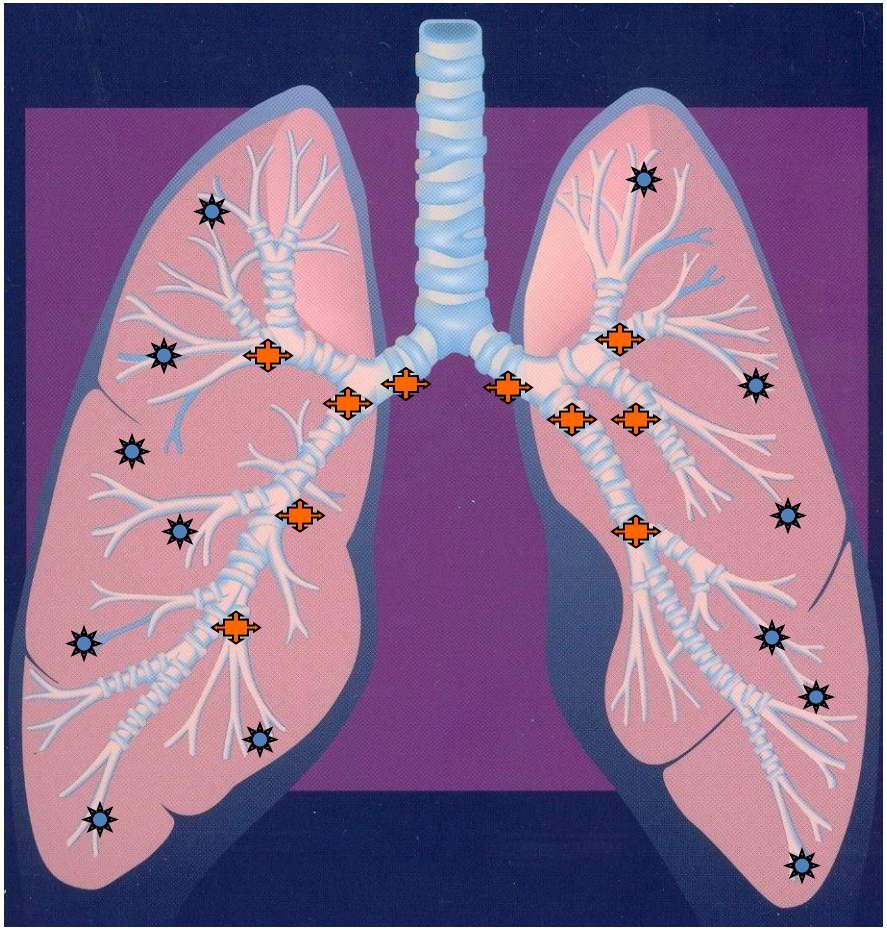
Pelaia G, Maselli R, Matera MG. *Pharmacology* 94:249-258, 2014

Interactions between muscarinic and β-adrenergic pathways in airway smooth muscle cells



Panettieri RA. *Postgrad Med J* 127:771-780, 2015

Different distribution of muscarinic and β_2-adrenergic receptors along the bronchial tree



Muscarinic receptors are more abundant in central airways

β_2-adrenergic receptors are more abundant in peripheral airways

Moving from short-acting to ultralong-acting bronchodilators

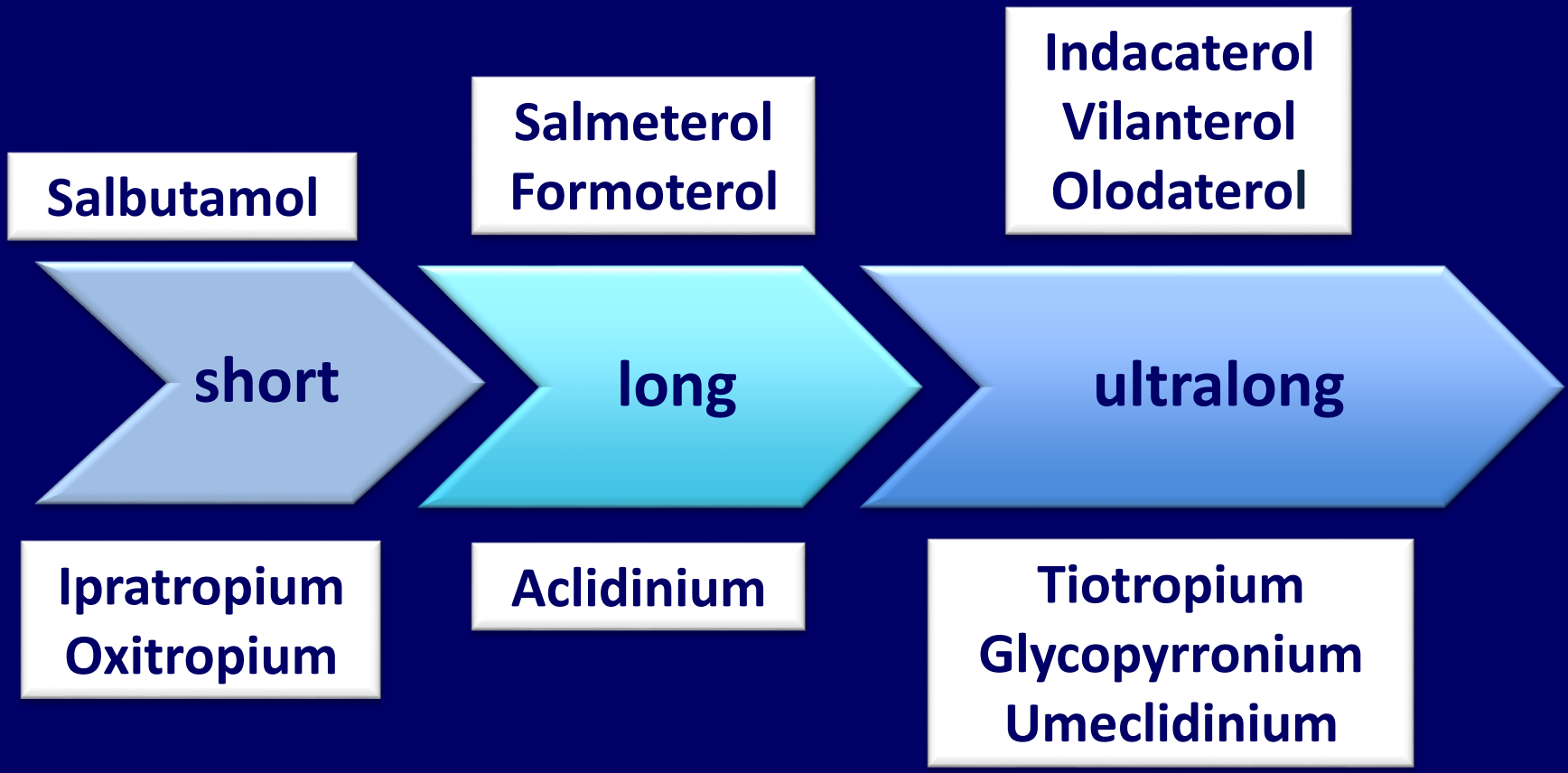


Table I LABA/LAMA fixed dose combinations

LABA	LAMA	Inhaler	Company
Olodaterol	Tiotropium	Respimat Soft Mist	Boehringer Ingelheim
Indacaterol	Glycopyrronium	Breezhaler	Novartis
Vilanterol	Umeclidinium	Ellipta	GlaxoSmithKline
Formoterol	Aclidinium	Genuair	Almirall

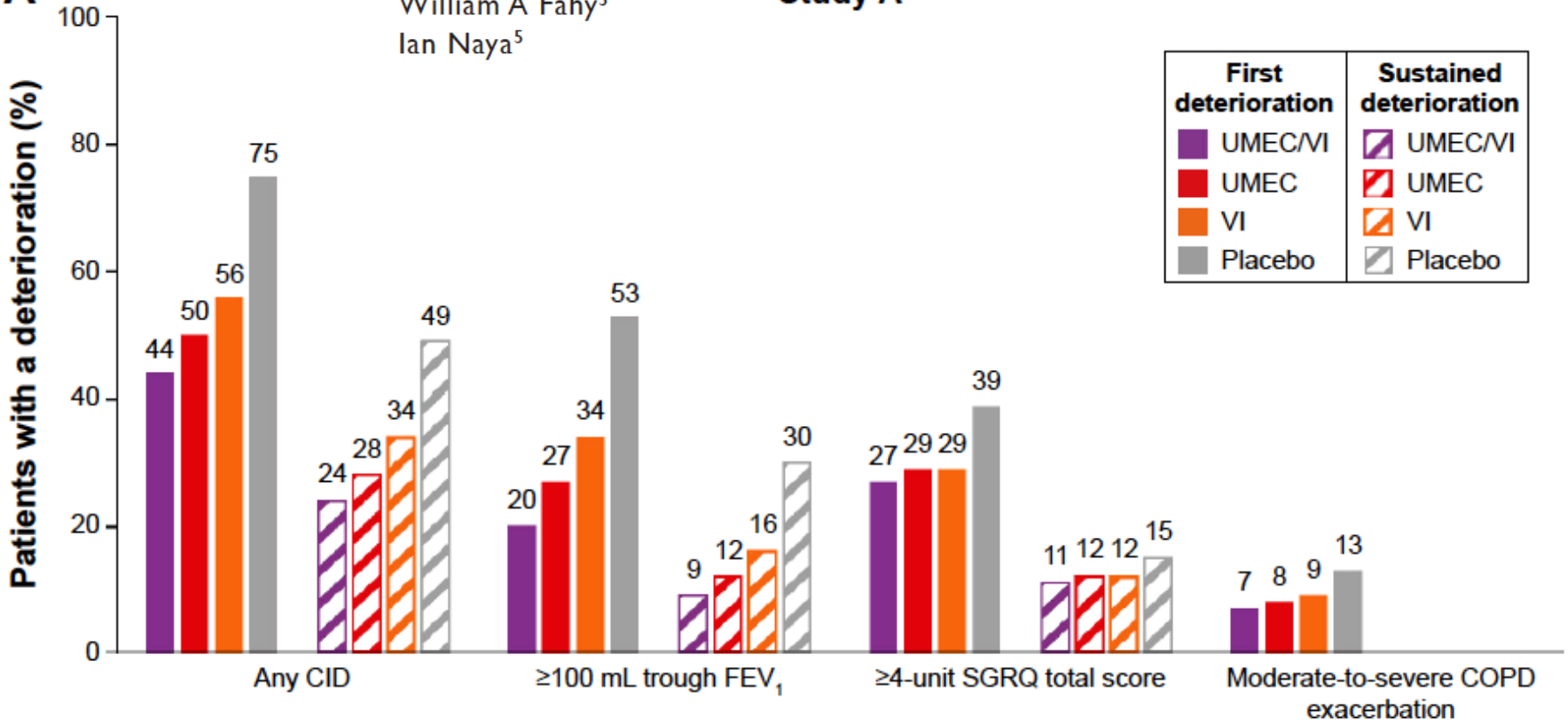
Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, Lombardo N, Maselli R. *Ther Clin Risk Manag* 11:1563-1572, 2015

Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol

Dave Singh[1]
M Reza Maleki-Yazdi[2]
Lee Tombs[3]
Ahmar Iqbal[4]
William A Fahy[5]
Ian Naya[5]

A

Study A



International Journal of COPD 2016:11 1413–1424

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M Reza Maleki-Yazdi[2]
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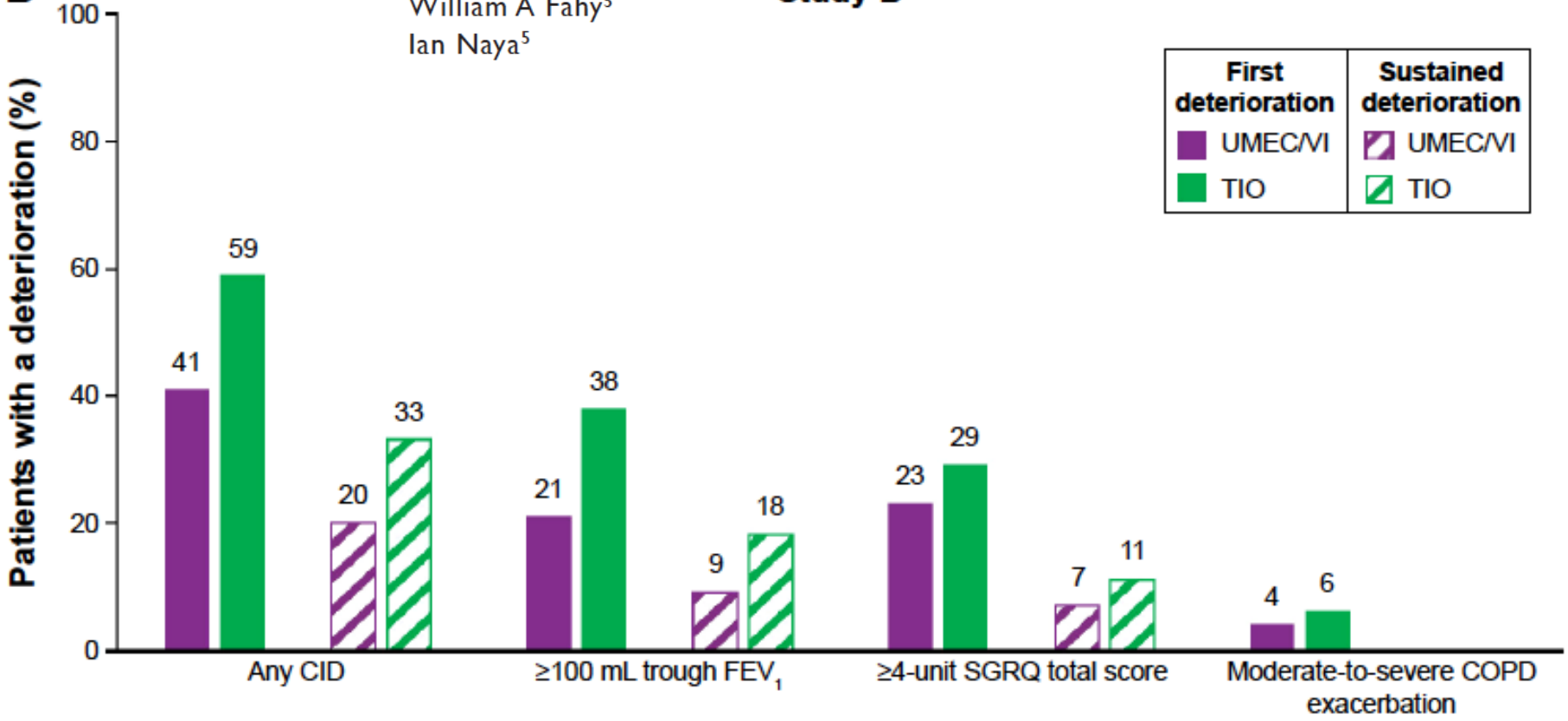
Ahmar Iqbal[4]
William A Fahy[5]
Ian Naya[5]

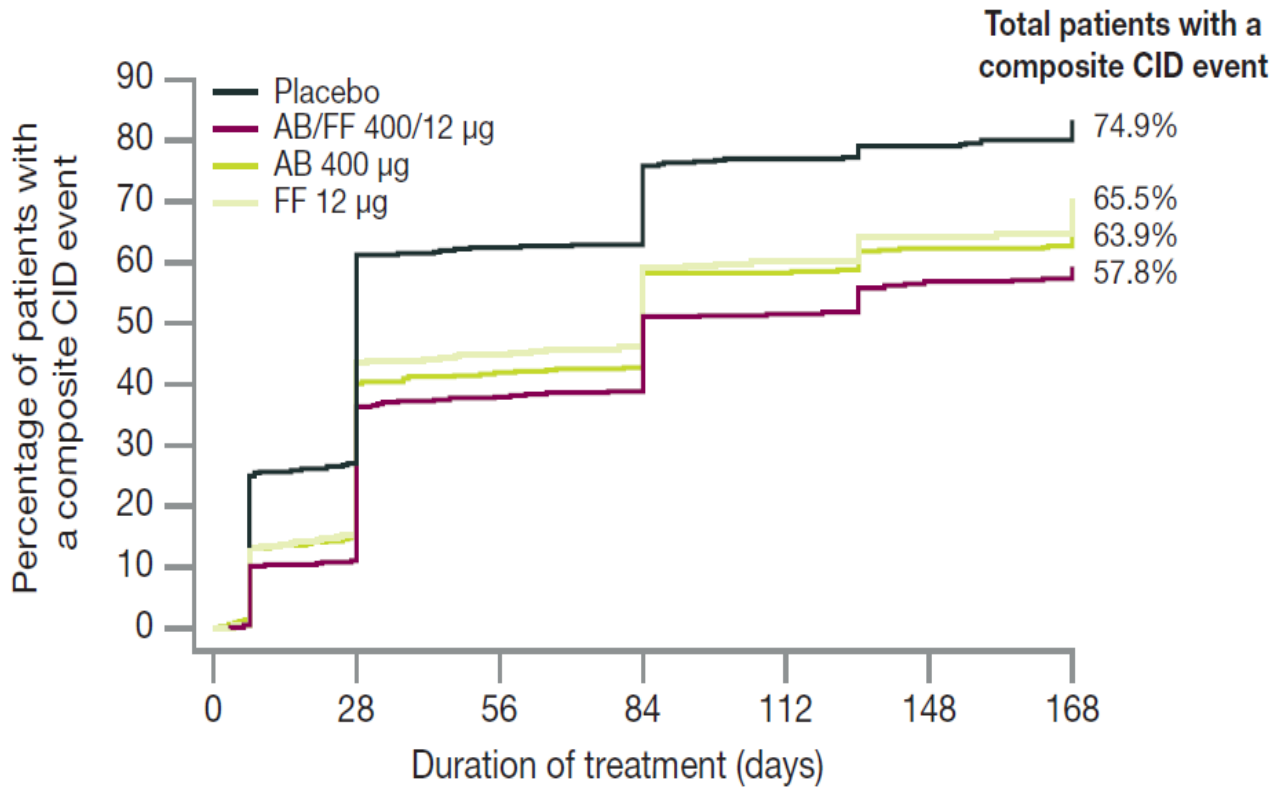
B **Study B**



International Journal of COPD 2016:11 1413–1424

Aclidinium/Formoterol combination is also effective in reducing the risk of clinically important deteriorations vs monotherapy

Figure 1. Incidence of composite CID events over 24 weeks



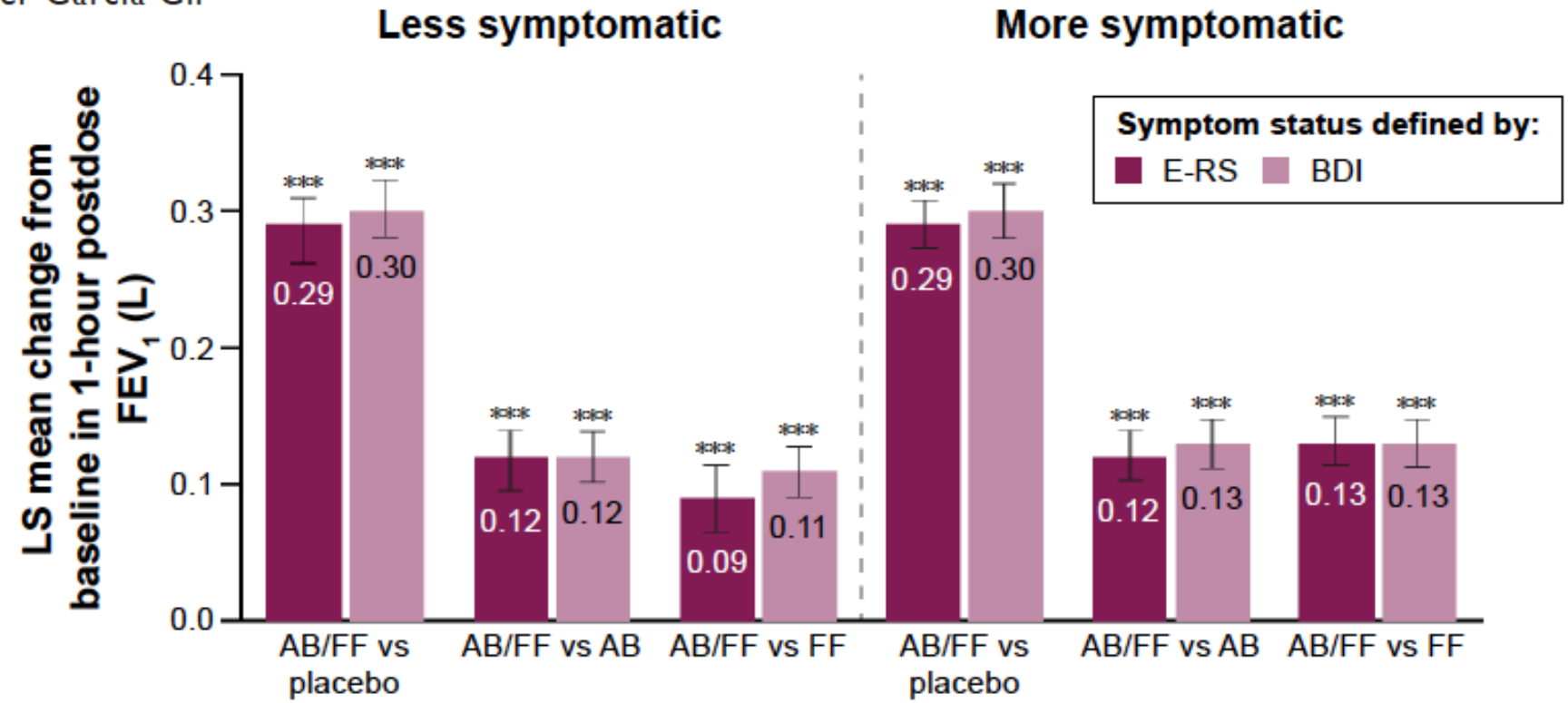
AB, aclidinium bromide; CID, clinically important deterioration; FF, formoterol fumarate

N= 2684. Pooled *post-hoc* analysis from ACLIFORM (NCT01462942) and AUGMENT (NCT01437397), two 24-week, randomized, double-blind, placebo- and active-controlled parallel-group clinical trials; assessing the ability of aclidinium/formoterol 400/12 µg to reduce the risk of CID versus placebo and monotherapies in patients with moderate to severe stable COPD.

Singh *et al*, ATS 2016.

The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis

Marc Miravitlles[1]
Kenneth R Chapman[2]
Ferran Chuecos[3]
Anna Ribera[4]
Esther Garcia Gil[3]



International Journal of COPD 2016:11 2041–2053

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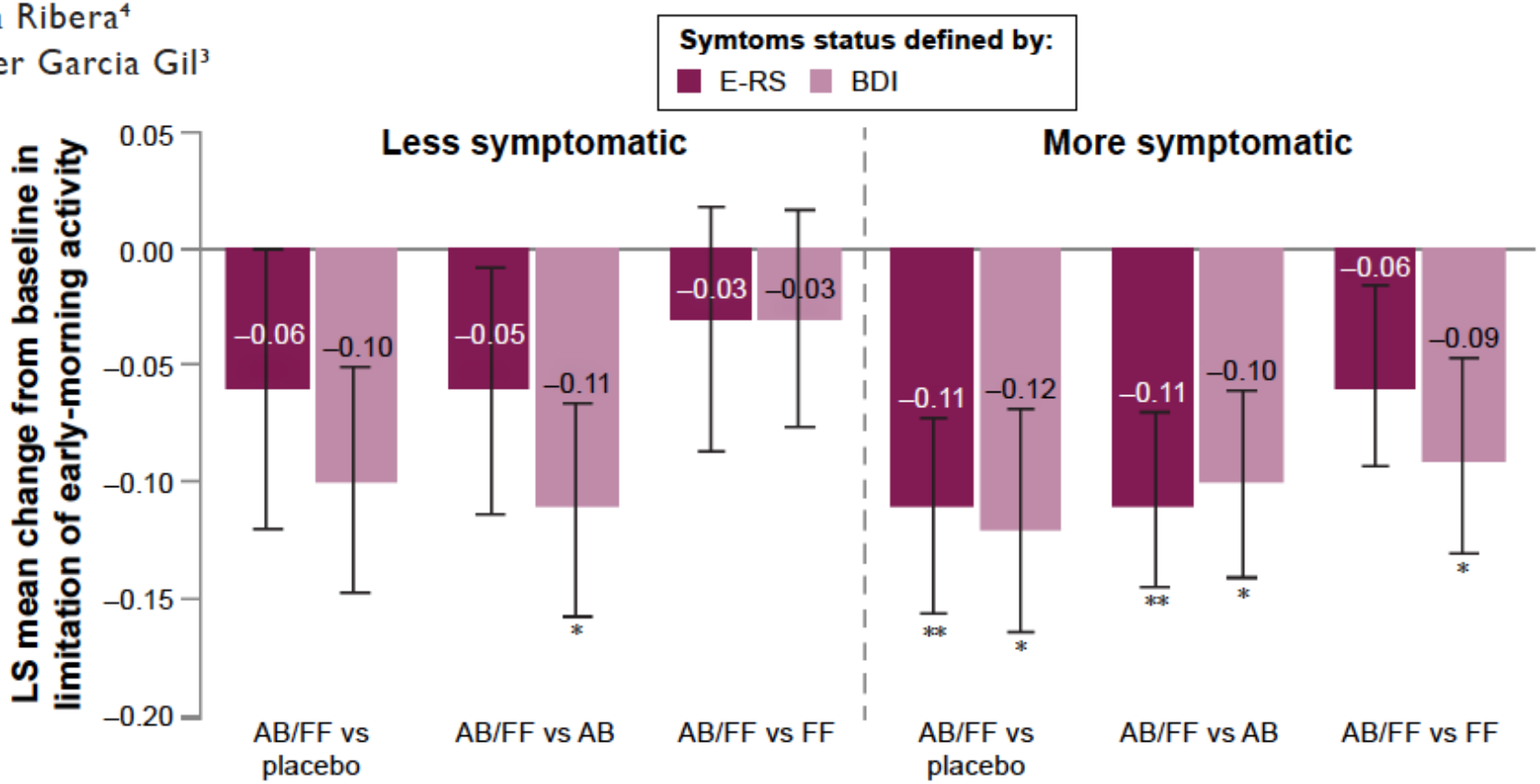
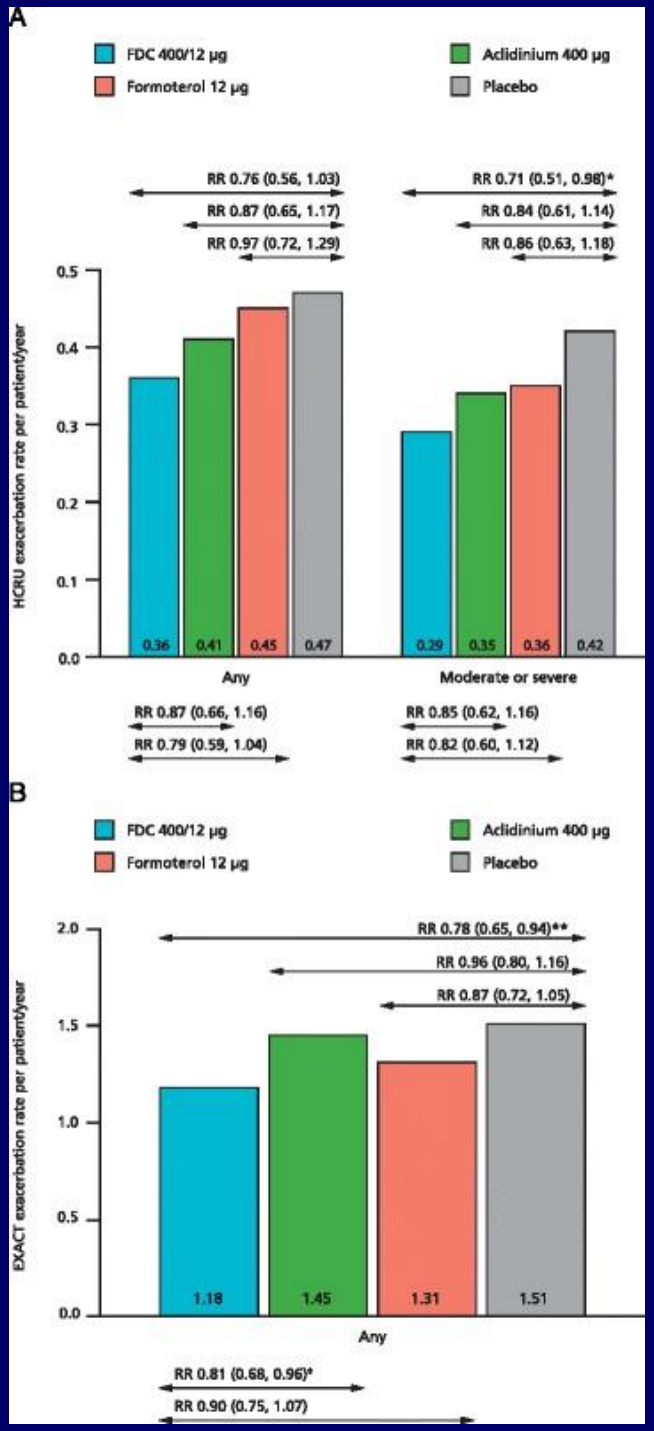


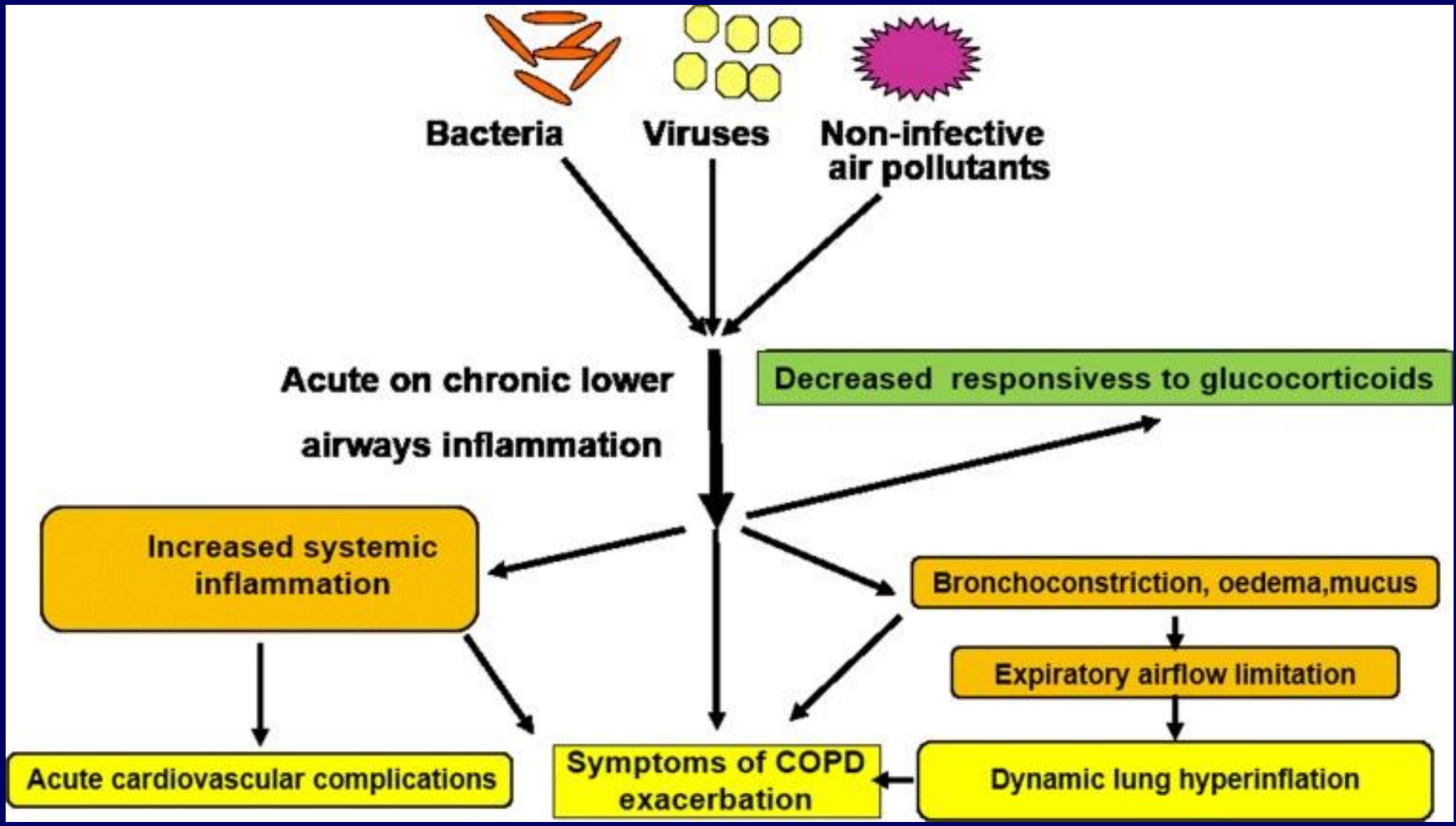
International Journal of COPD 2016:11 2041–2053



Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomized studies (ACLIFORM and AUGMENT)

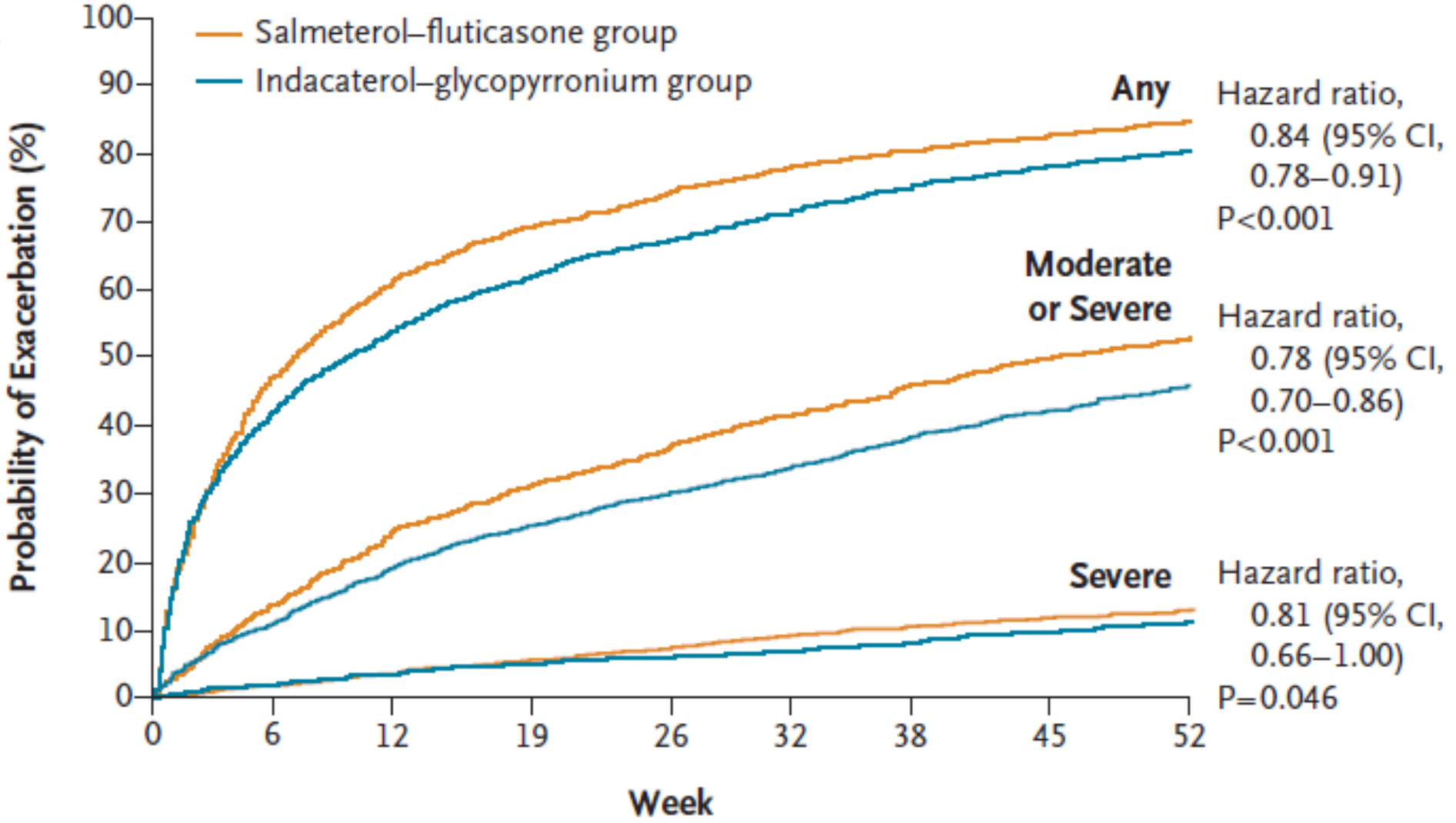
Bateman ED, Chapman KR, Singh D, D'Urzo AD, Molins E, Leselbaum A, Gil EG.
Respir Res 16:92, 2015

Bacteria, viruses and air pollutants can drive COPD exacerbations by causing an acute-on-chronic inflammation within the airways



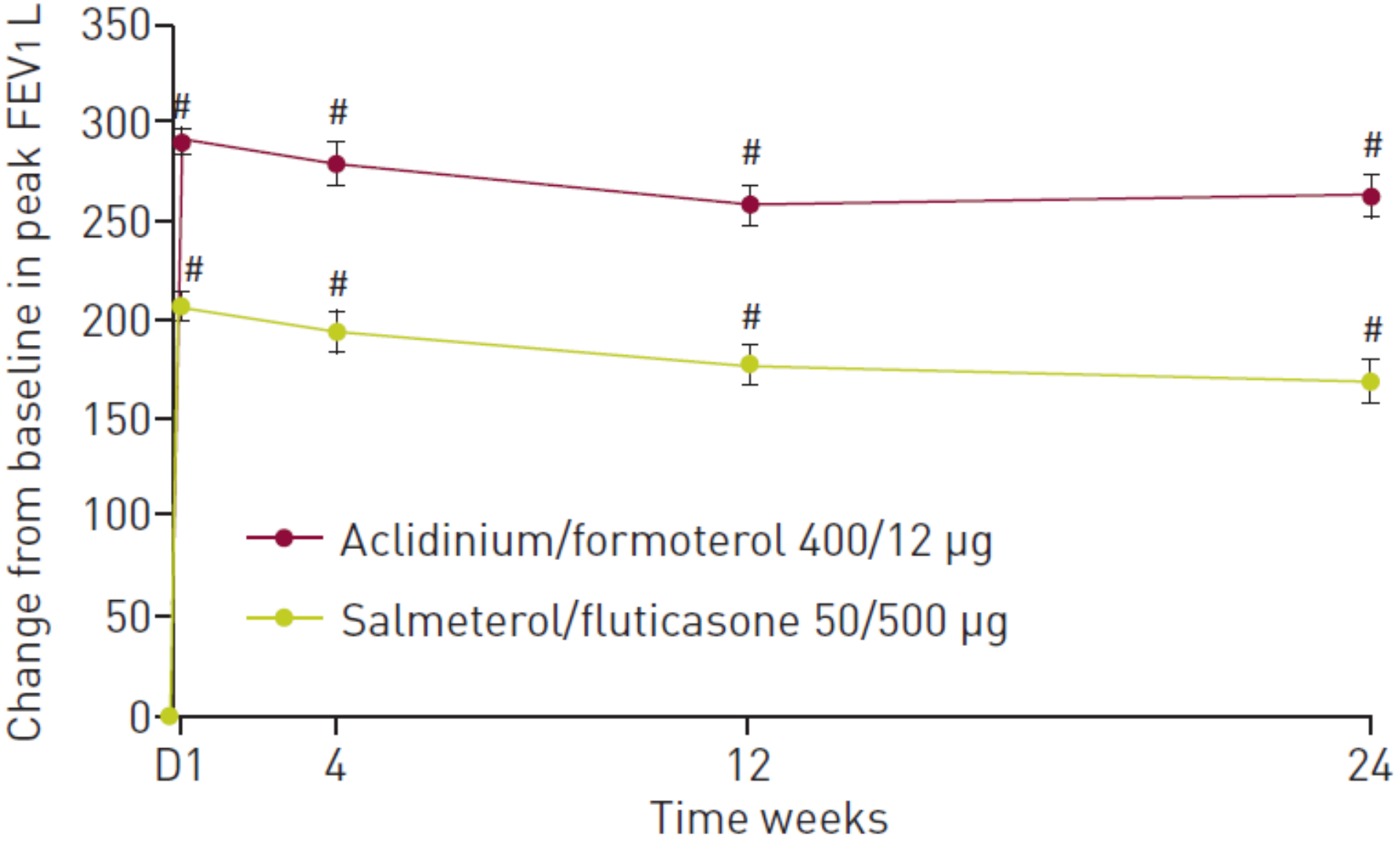
Caramori G, Casolari P, Barczyk A, Durham AL, Di Stefano A, Adcock I. *Semin Immunopathol* 38:497-515, 2016

FLAME



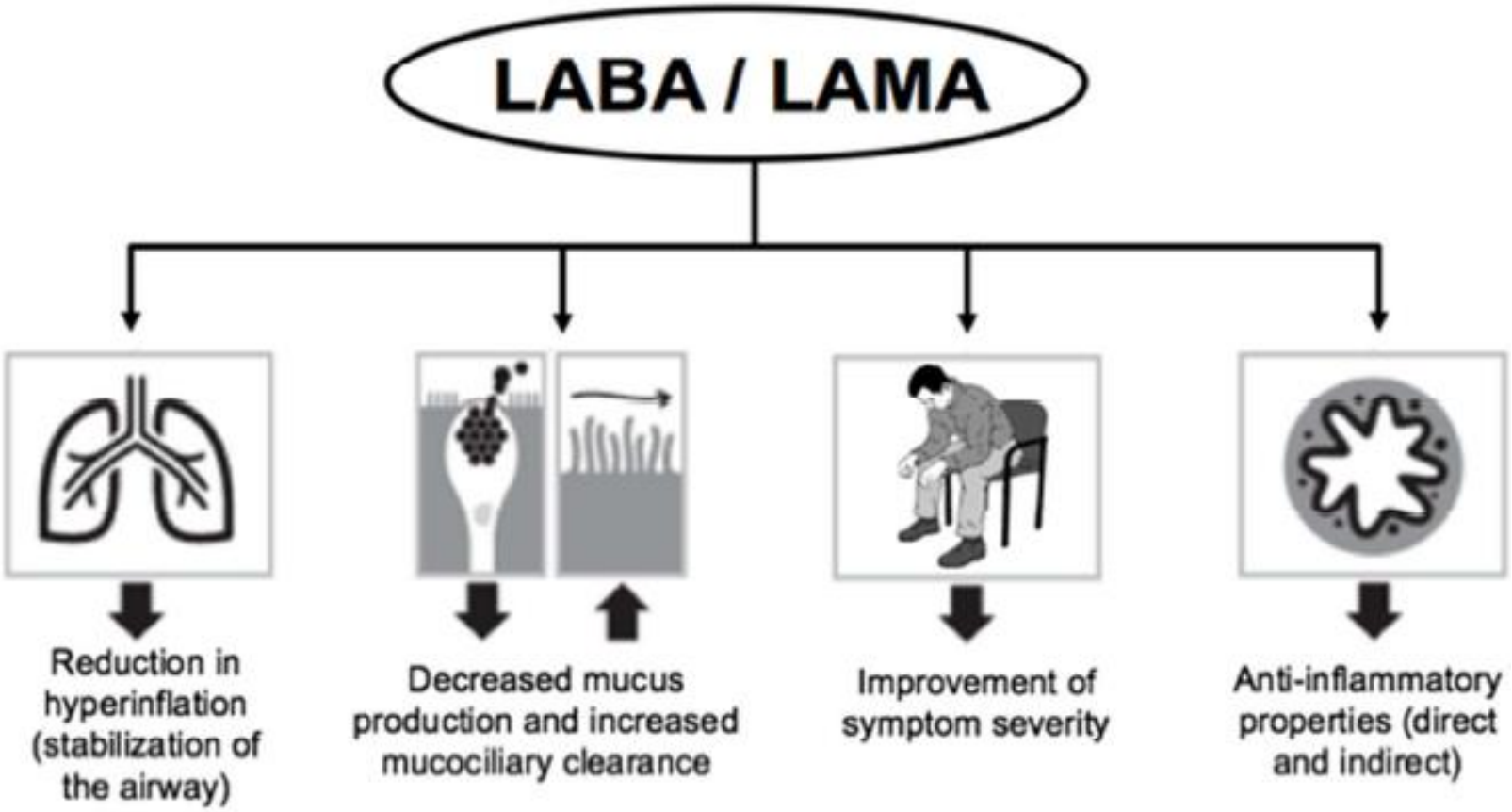
Wedzicha JA et al. *N Engl J Med* 374:2222-2234, 2016

AFFIRM



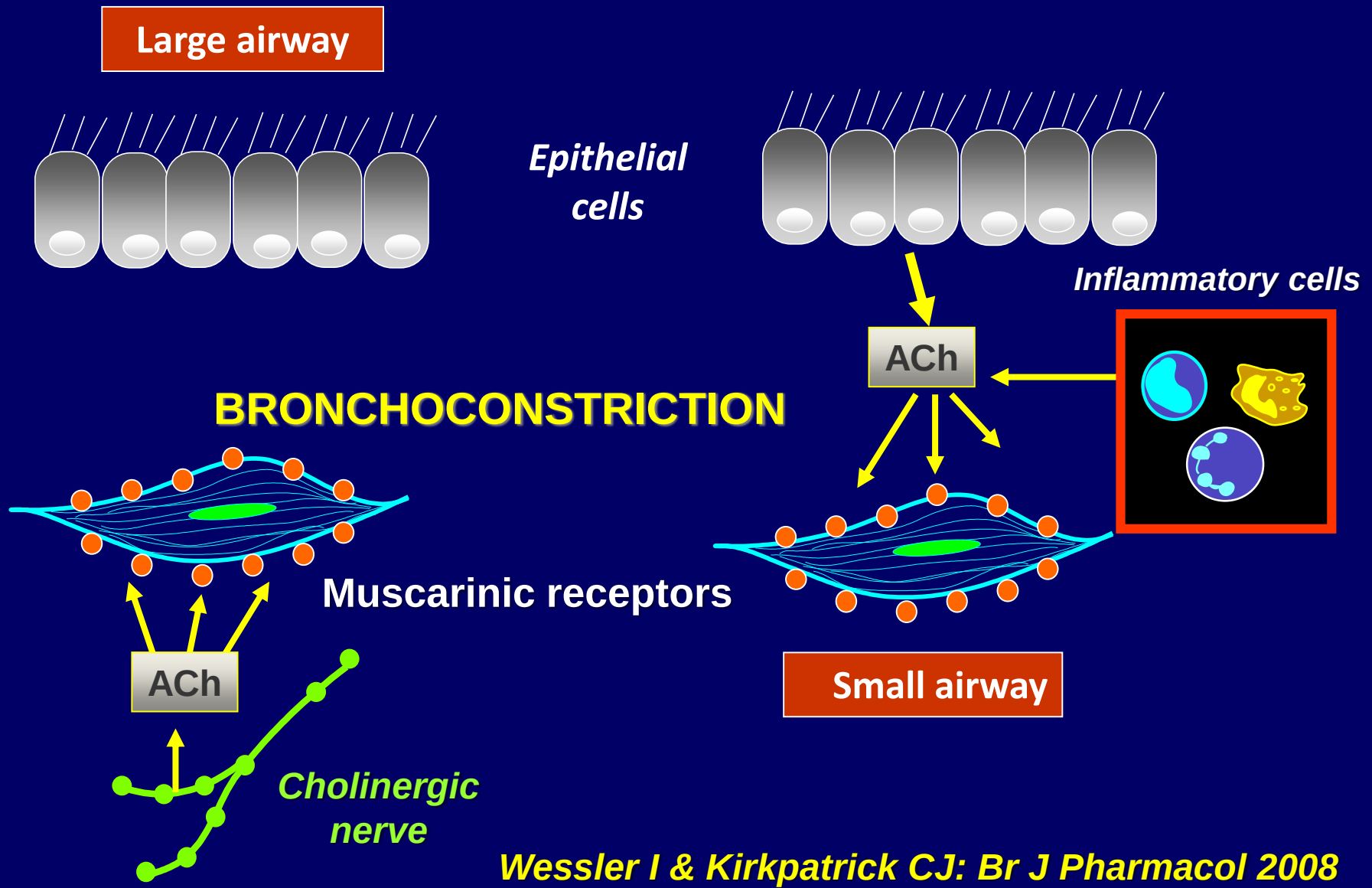
Vogelmeier C, et al. *Eur Respir J* 48:1030-1039, 2016

MECHANISMS BY WHICH LABA/LAMA MAY DECREASE THE FREQUENCY OF COPD EXACERBATIONS



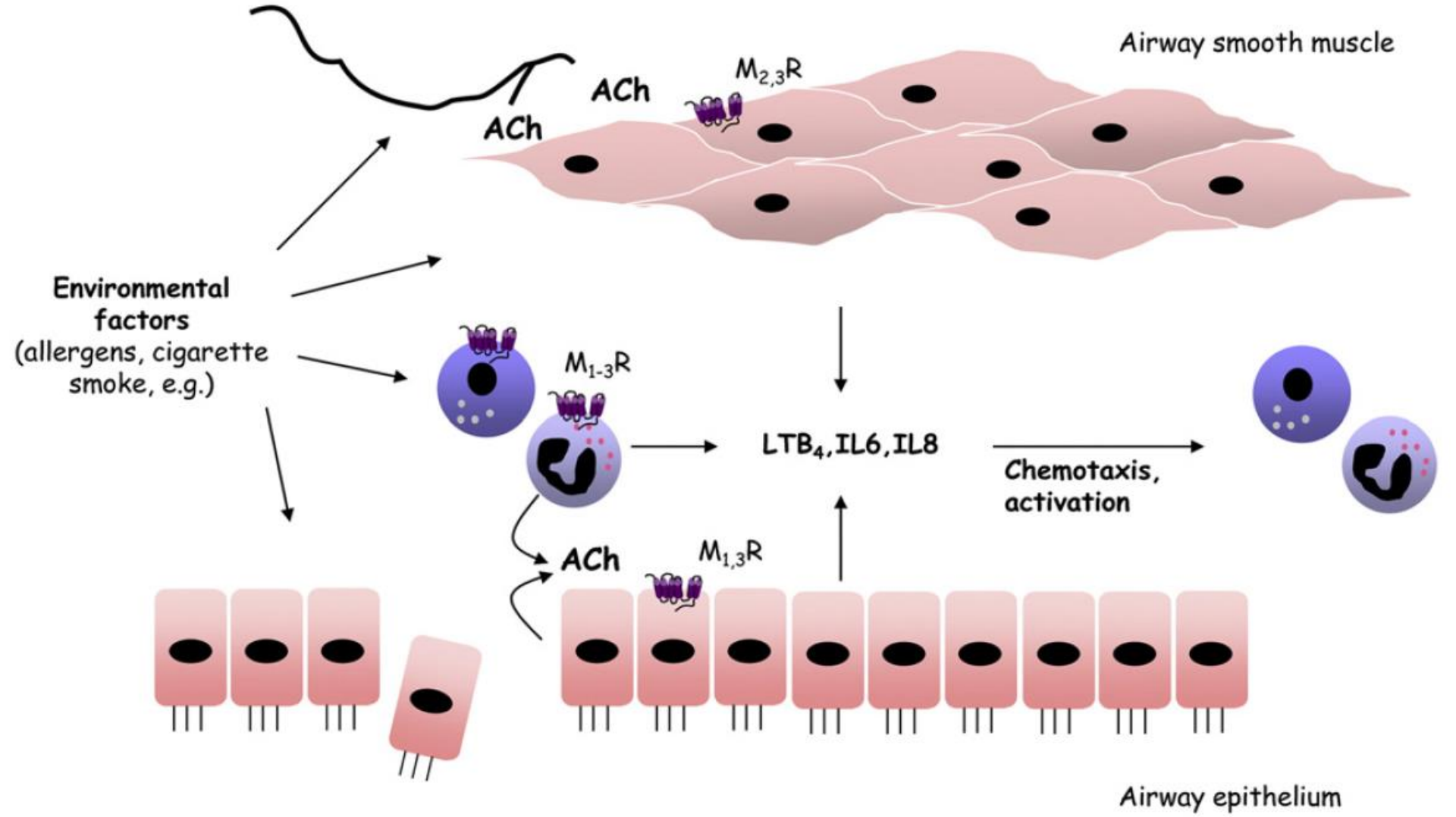
Beeh KM et al. *Am J Respir Crit Care Med* 2017, *in press*

CHOLINERGIC CONTROL OF AIRWAYS



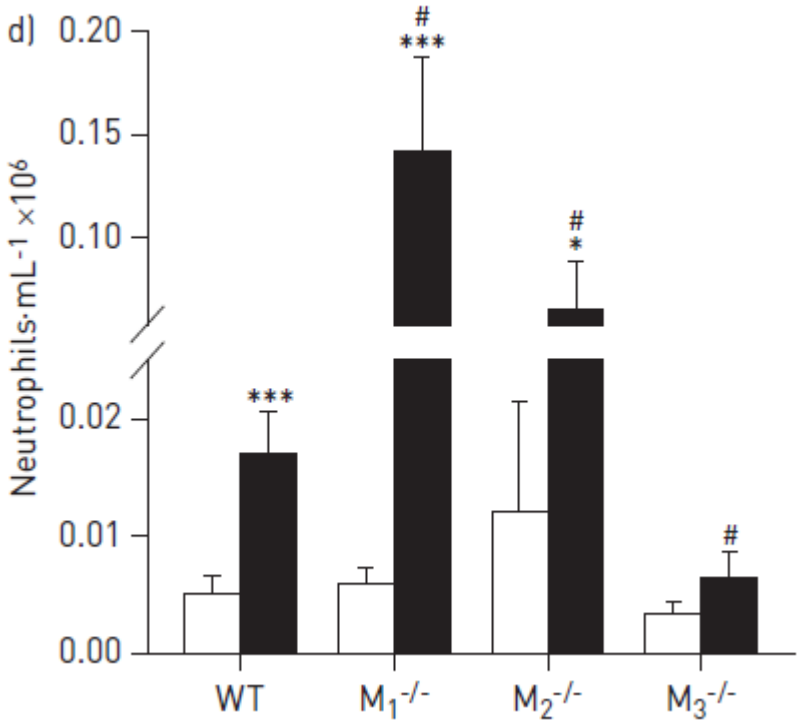
Wessler I & Kirkpatrick CJ: Br J Pharmacol 2008

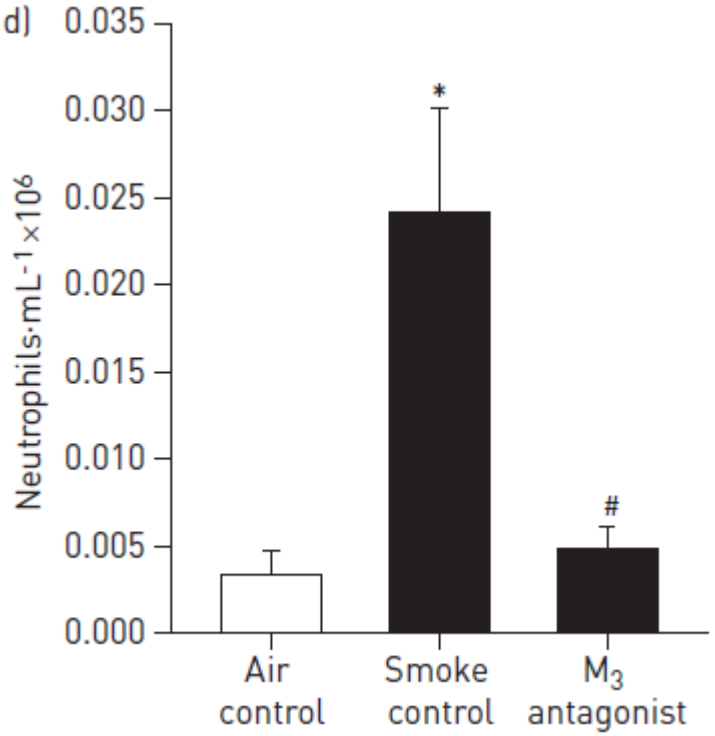
The regulatory role of acetylcholine in inflammatory cell chemotaxis and activation



Kistemaker LEM, Oenema TA, Meurs H, Gosens R. *Life Sci* 91:1126-1133, 2012

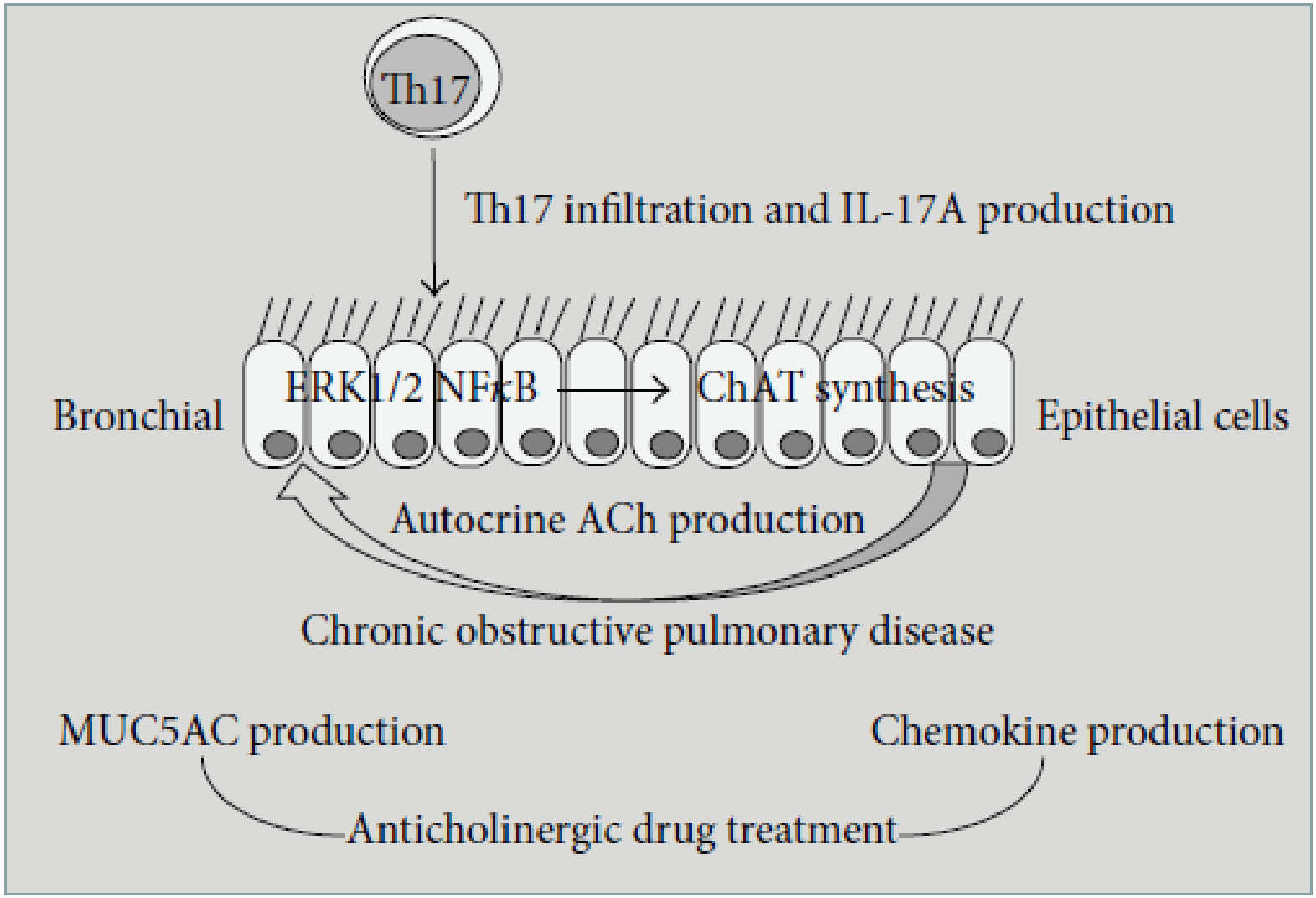
Muscarinic receptor subtype-specific effects on cigarette smoke-induced airway inflammation in mice





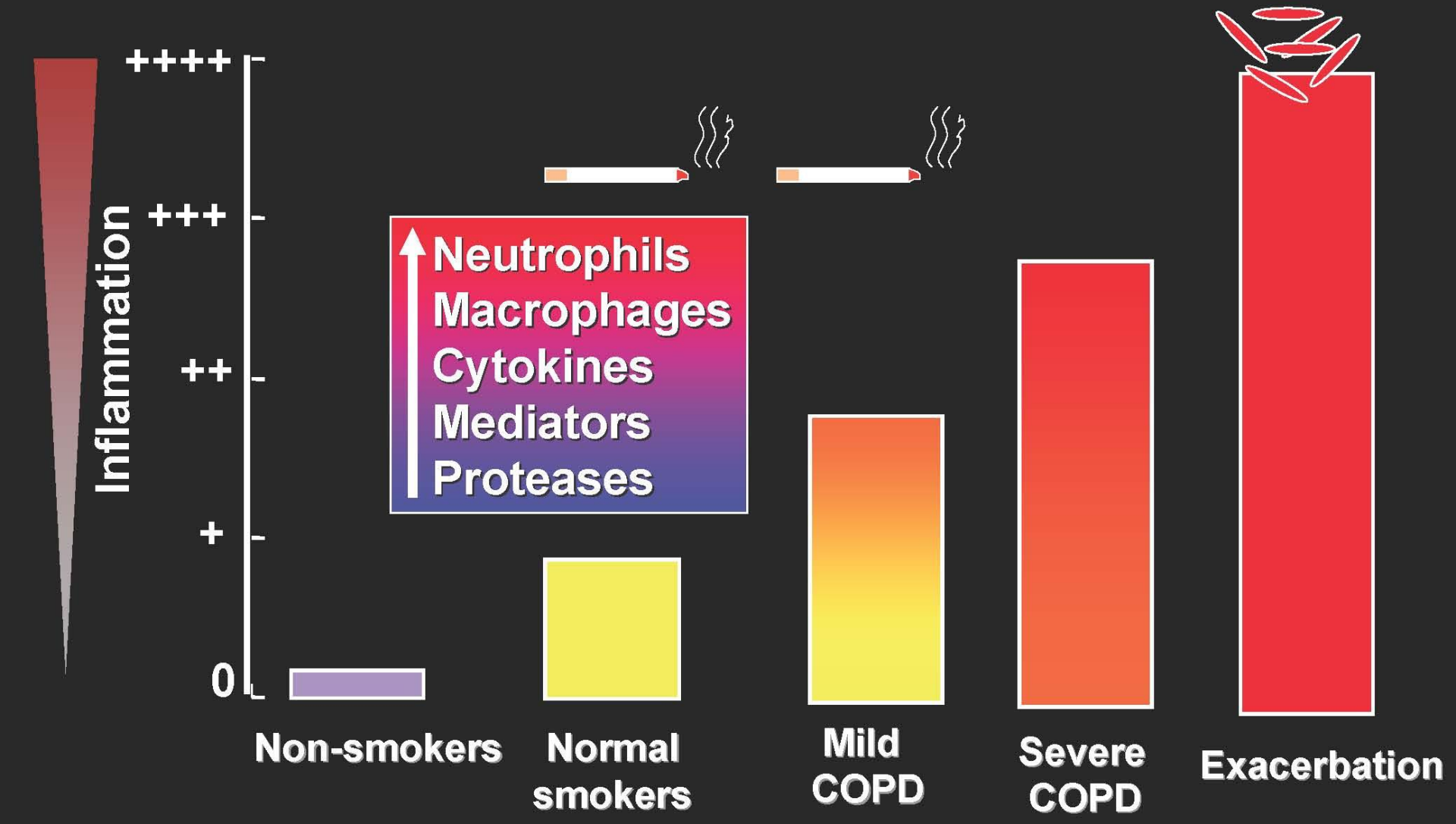
Kistemaker LEM et al. *Eur Respir J* 42:1677-1678, 2013

Effects of anticholinergic drugs on lung neutrophilic inflammation

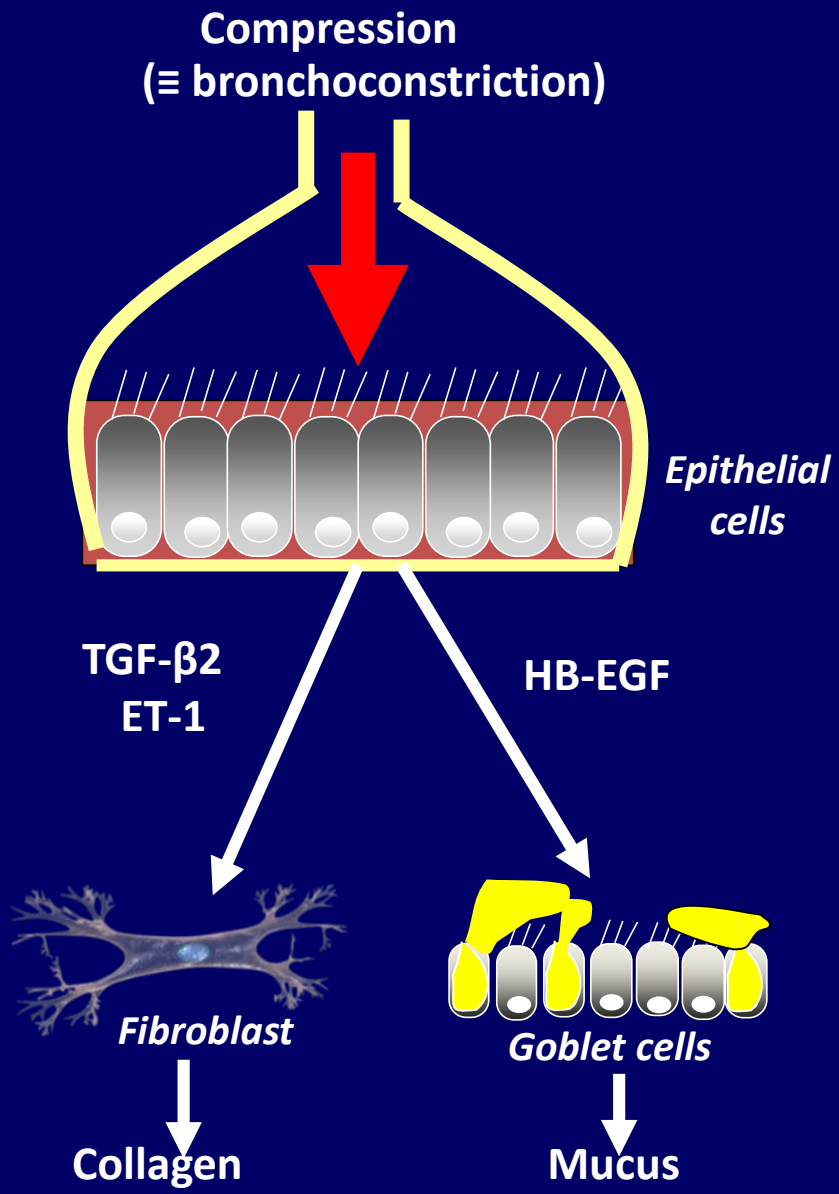


Montalbano AM et al. *Mediators Inflamm* 9063842, 2016

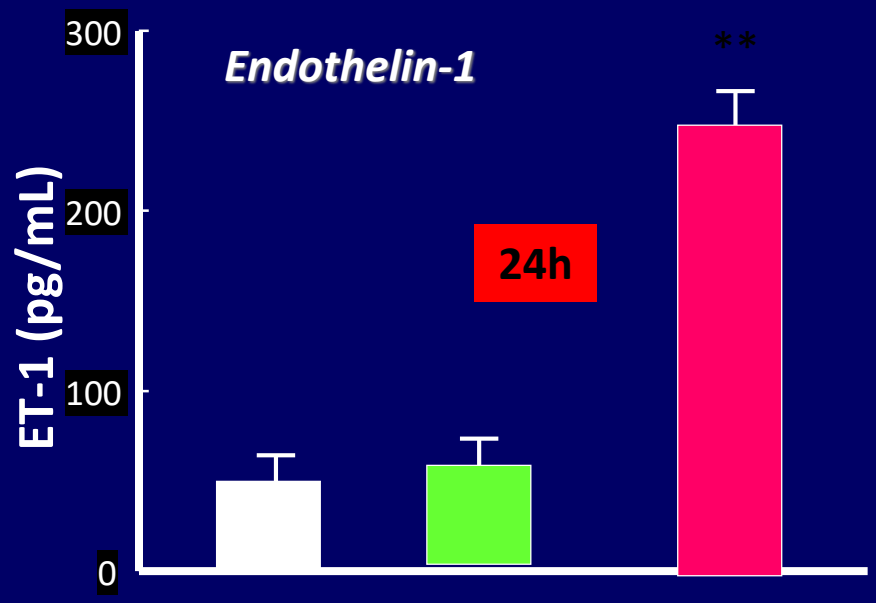
AMPLIFICATION OF INFLAMMATION IN COPD

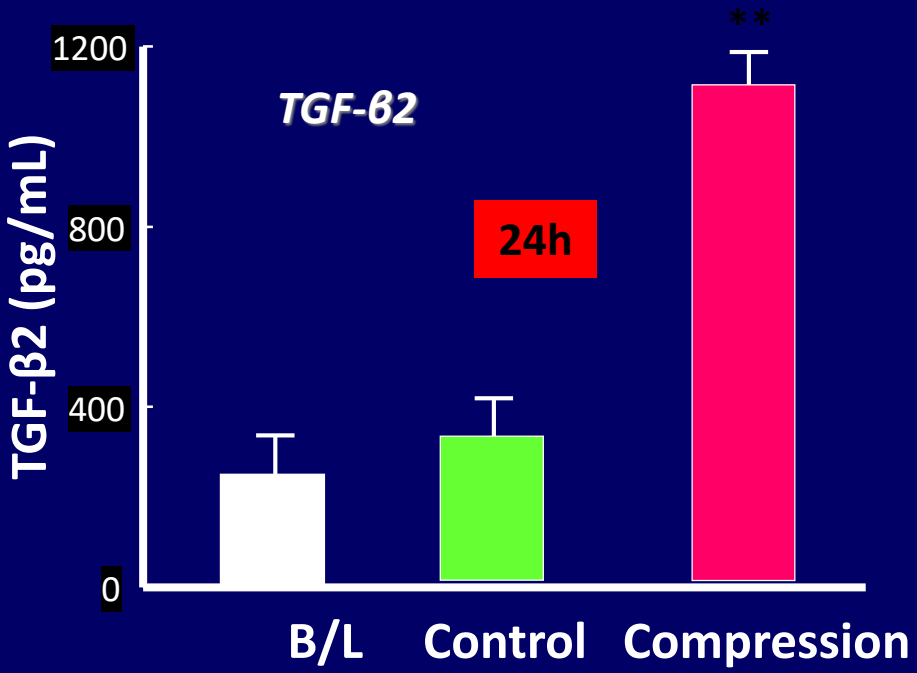


AIRWAY EPITHELIAL COMPRESSION

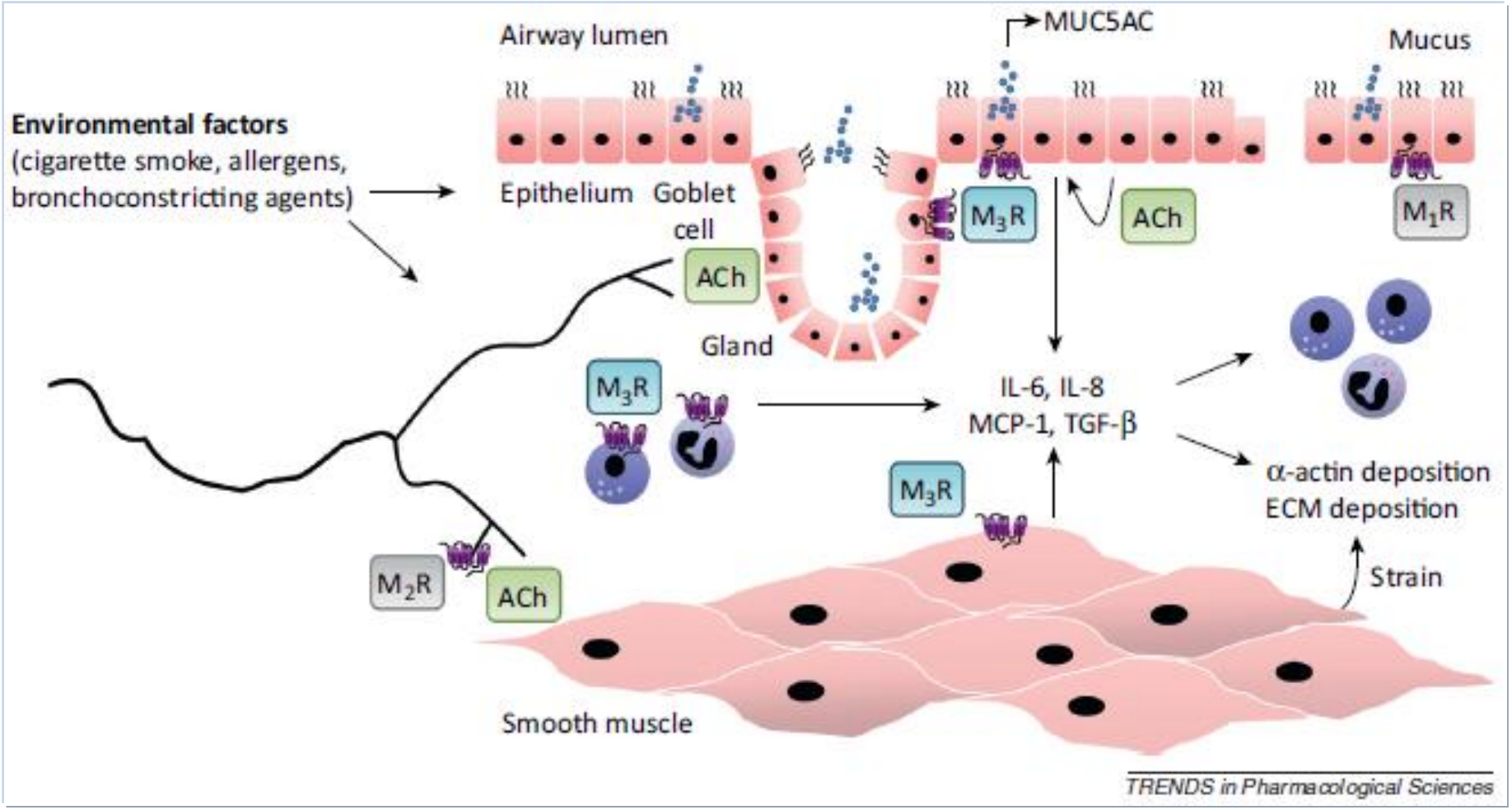


Tschumperlin DJ et al: AJRCMB 2003





Acetylcholine contributes to inflammation and remodeling of the airways via M_3 receptors



Kistemaker LEM, Gosens R. *Trends Pharmacol Sci* 36:164-171, 2015

Pharmacological Research 102 (2015) 310–318

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Aclidinium bromide combined with formoterol inhibits remodeling parameters in lung epithelial cells through cAMP

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ABSTRACT

Combined muscarinic receptor antagonists and long acting β_2-agonists improve symptom control in chronic obstructive pulmonary disease (COPD) significantly. In clinical studies aclidinium bromide achieved better beneficial effects than other bronchodilators; however, the underlying molecular mechanisms are unknown. This study assessed the effect of aclidinium bromide combined with formoterol on COPD lung ($n = 20$) and non-COPD lung ($n = 10$) derived epithelial cells stimulated with TGF-β_1 + carbachol on: (i) the generation of mesenchymal cells in relation to epithelial cells, (II) extracellular matrix (ECM) deposition, and (iii) the interaction of ECM on the generation of epithelial and mesenchymal cells. TGF-β_1 + carbachol enhanced the generation of mesenchymal cells, which was significantly reduced by aclidinium bromide or formoterol. The effect of combined drugs was additive. Inhibition of p38 MAP kinase and Smad by specific inhibitors or aclidinium bromide reduced the generation of mesenchymal cells. In mesenchymal cells, TGF-β_1 + carbachol induced the deposition of collagen-I and fibronectin which was prevented by both drugs dose-dependently. Formoterol alone reduced collagen-I deposition via cAMP, this however, was overruled by TGF-β_1 + carbachol and rescued by aclidinium bromide. Inhibition of fibronectin was cAMP independent, but involved p38 MAP kinase and Smad. Seeding epithelial cells on ECM collagen-I and fibronectin induced mesenchymal cell generation, which was reduced by aclidinium bromide and formoterol. Our results suggest that the beneficial effect of aclidinium bromide and formoterol involves cAMP affecting both, the accumulation of mesenchymal cells and ECM remodeling, which may explain the beneficial effect of the drugs on lung function in COPD.

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Efficacy and safety of long-acting β-agonist/ long-acting muscarinic antagonist combinations in COPD: a network meta-analysis

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What is the bottom line?

- The combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates, and had similar effects on safety outcomes and severe exacerbations as compared with monotherapies.

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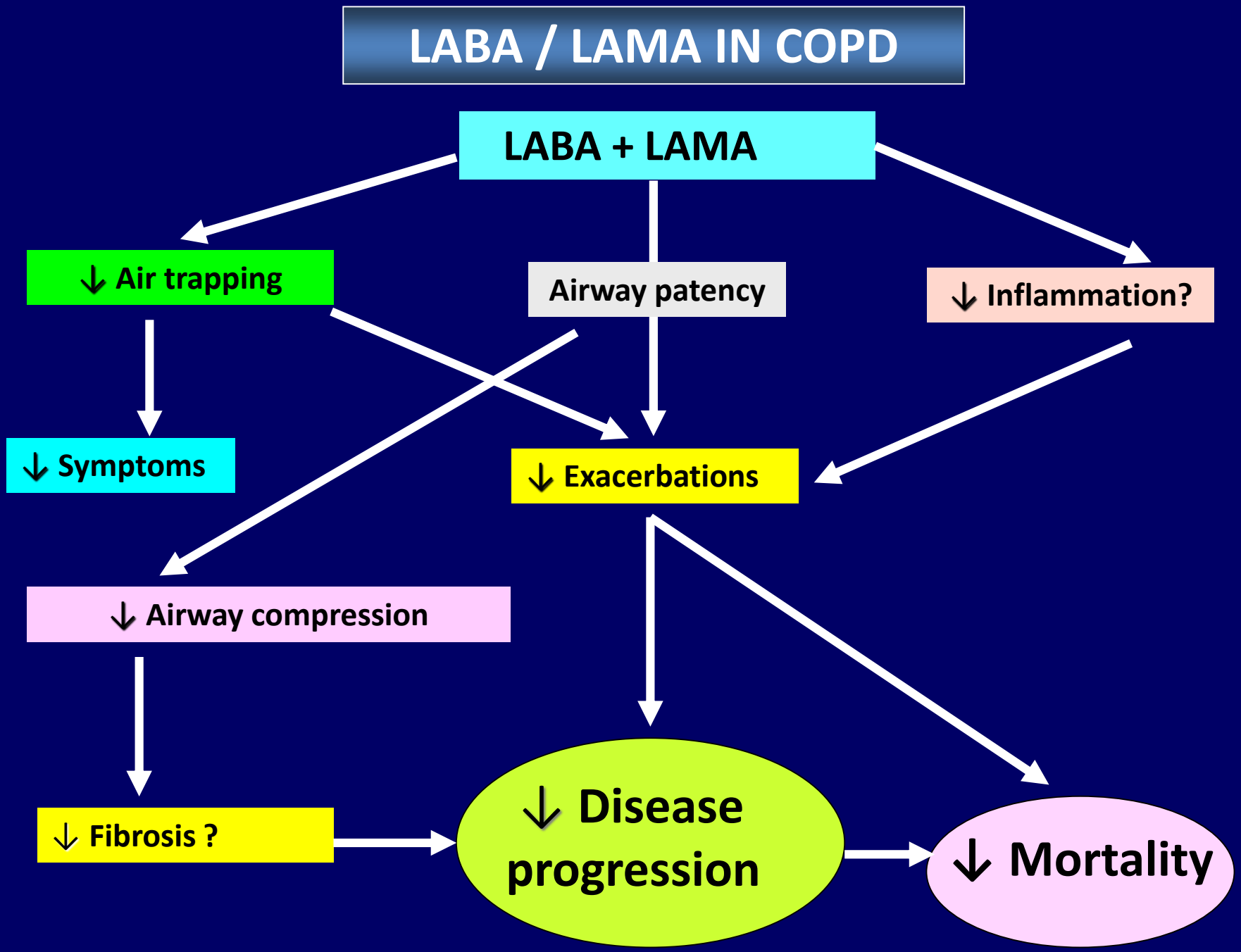
LABA / LAMA IN COPD
LABA + LAMA
↓ Air trapping
Airway patency
↓ Inflammation?
↓ Symptoms
↓ Exacerbations
↓ Airway compression
↓ Fibrosis ?
↓ Disease progression
↓ Mortality

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