58° Congresso Nazionale SIGG
Torino 27-30 novembre 2013

GLICOPIRRONIO: IL NUOVO ANTICOLINERGICO PER LA BPCO

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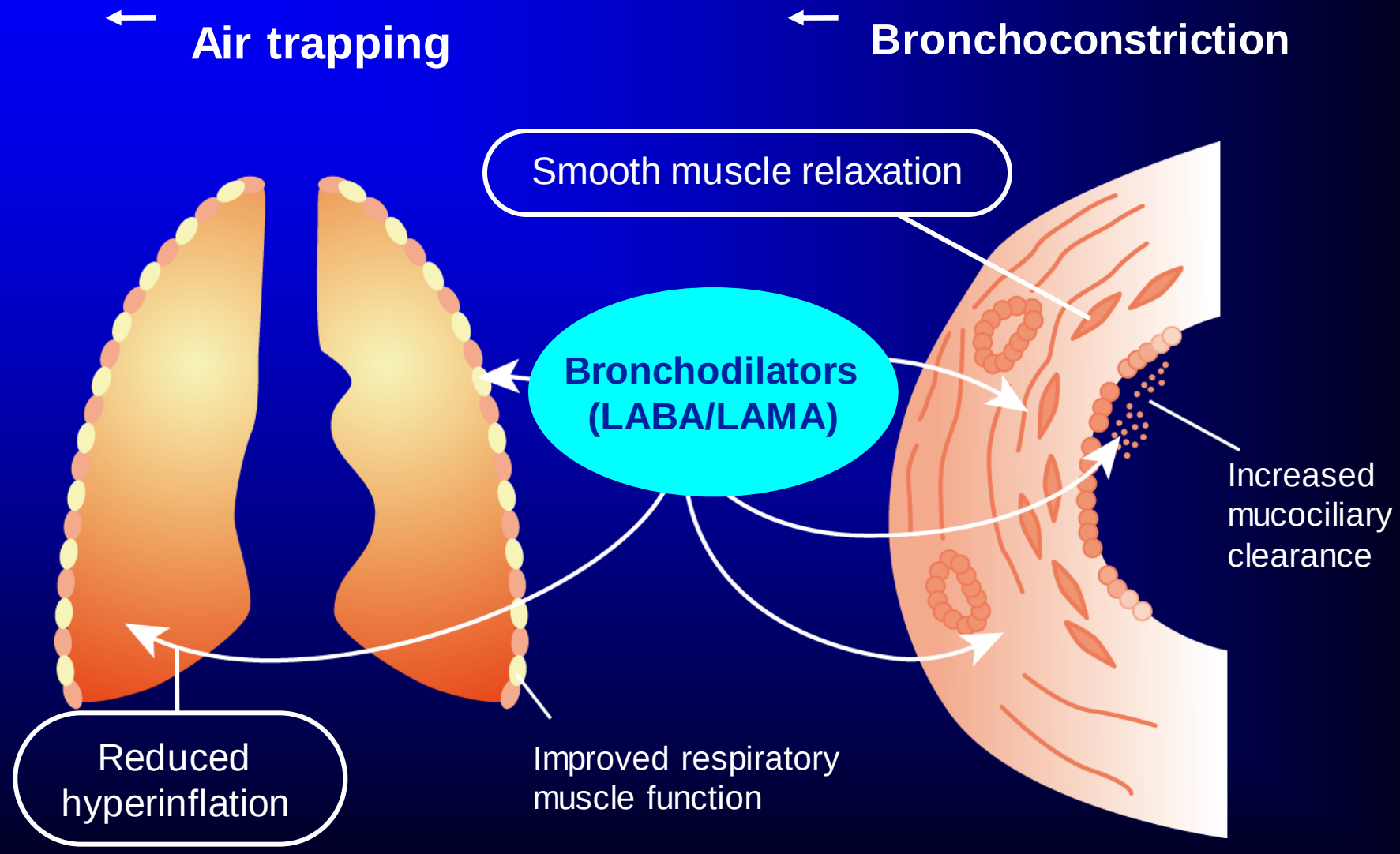
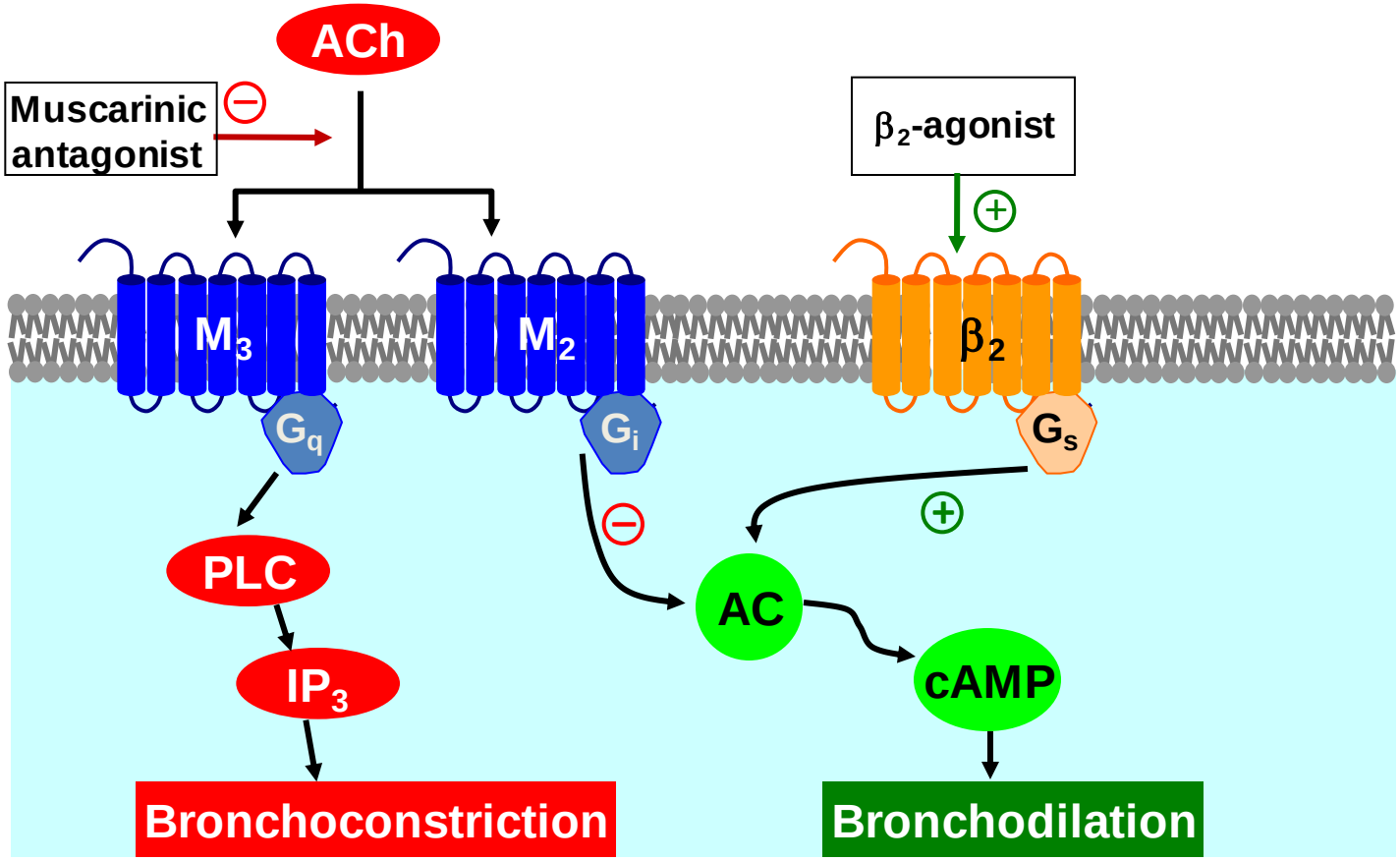
Università Magna Graecia di Catanzaro

Bronchodilators are essential to symptom management in COPD

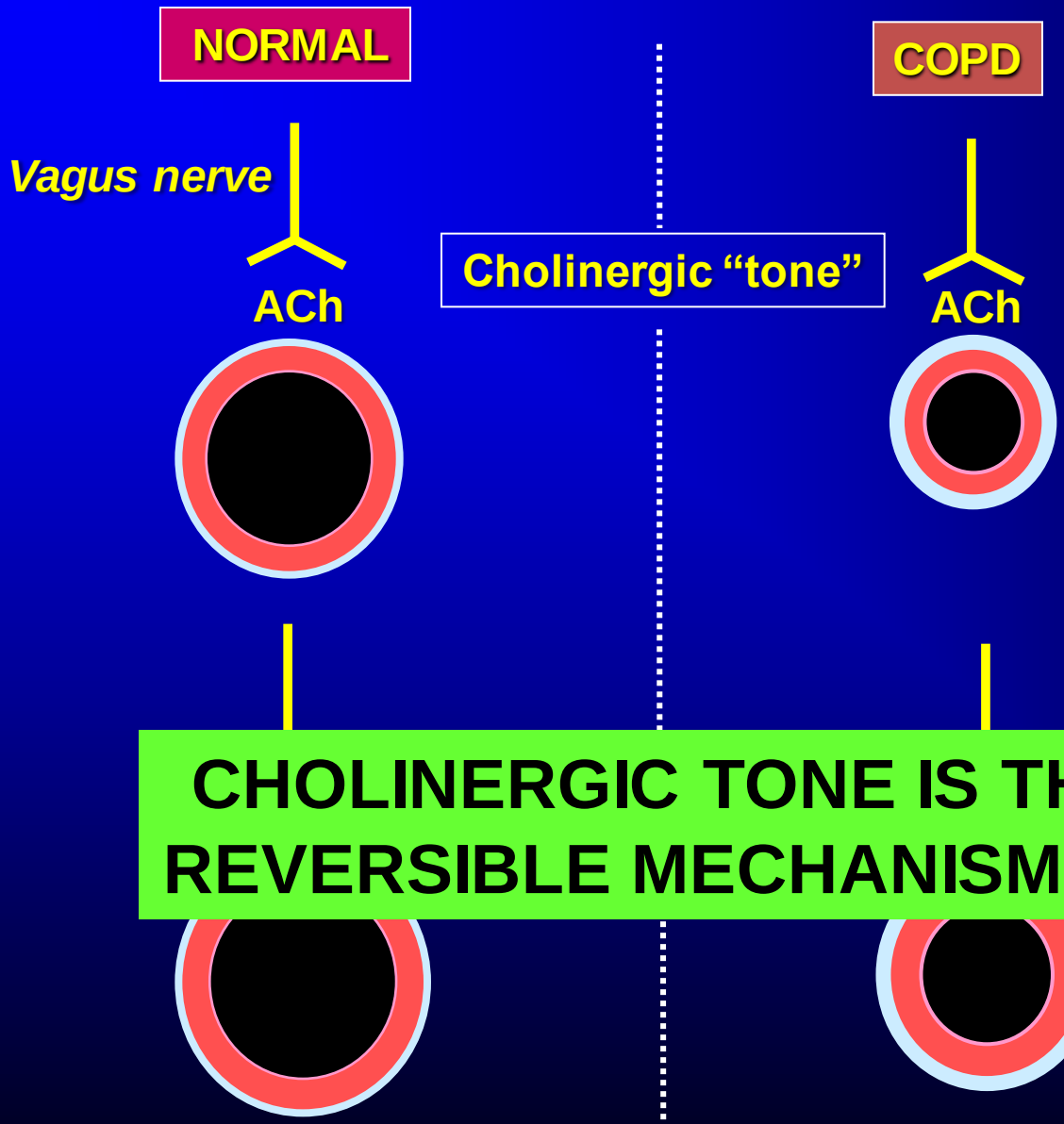


GOLD 2011

Basic representation of pharmacologically-induced airway smooth muscle relaxation

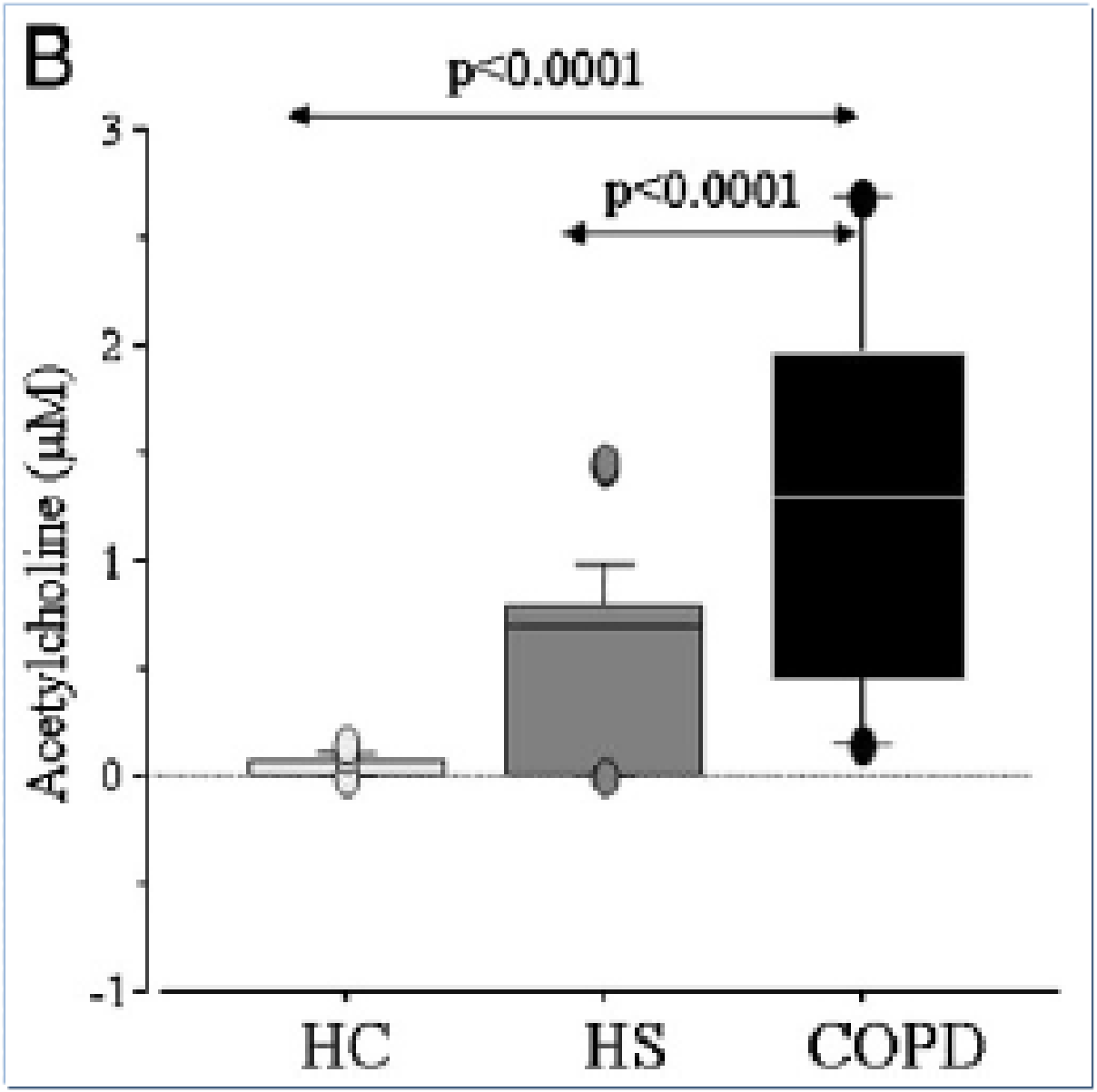


COUNTERACTING CHOLINERGIC TONE IN COPD



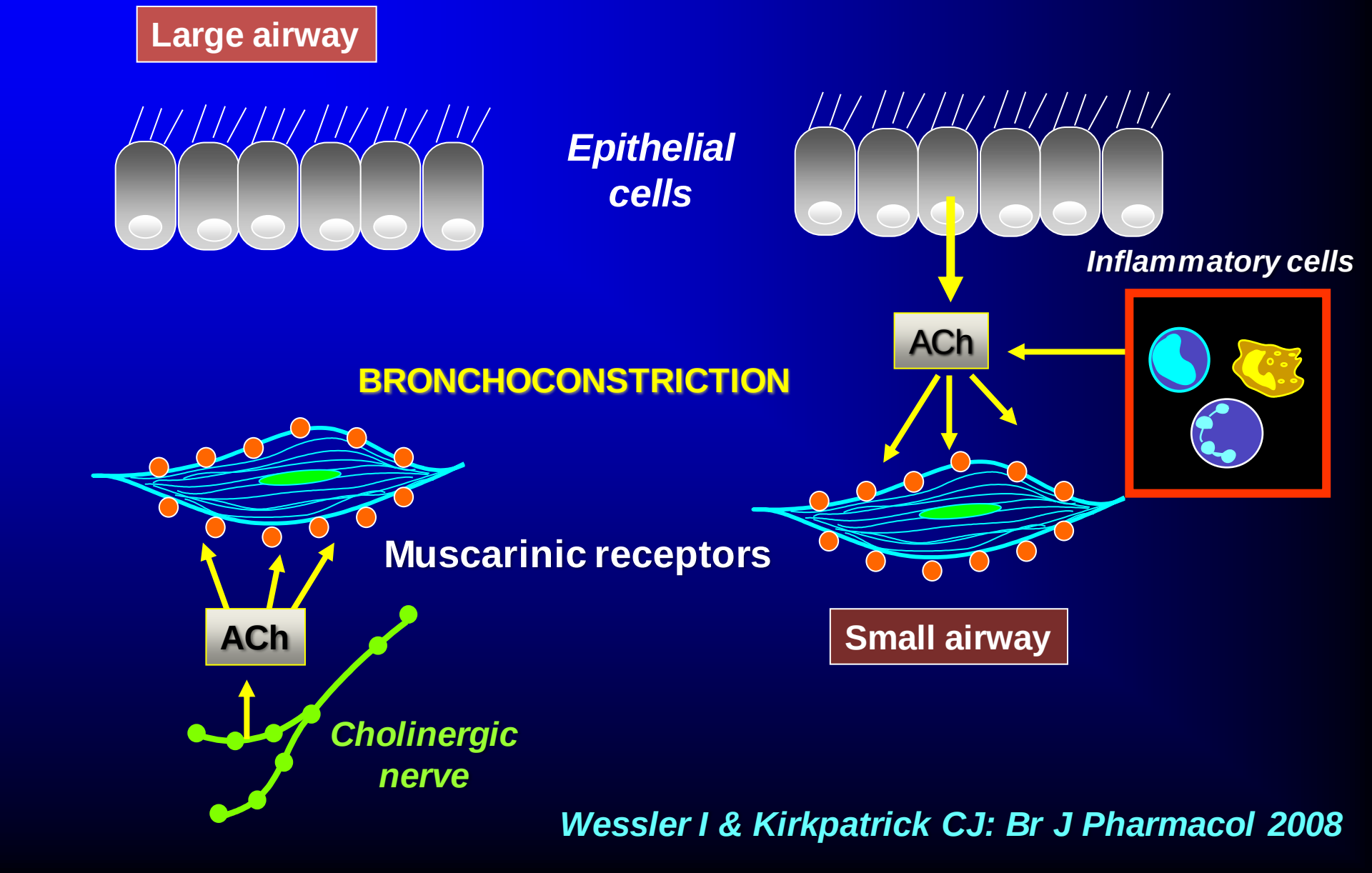
CHOLINERGIC TONE IS THE ONLY REVERSIBLE MECHANISM IN COPD

Acetylcholine concentration is increased in induced sputum from COPD patients



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

CHOLINERGIC CONTROL OF AIRWAYS



Wessler I & Kirkpatrick CJ: Br J Pharmacol 2008

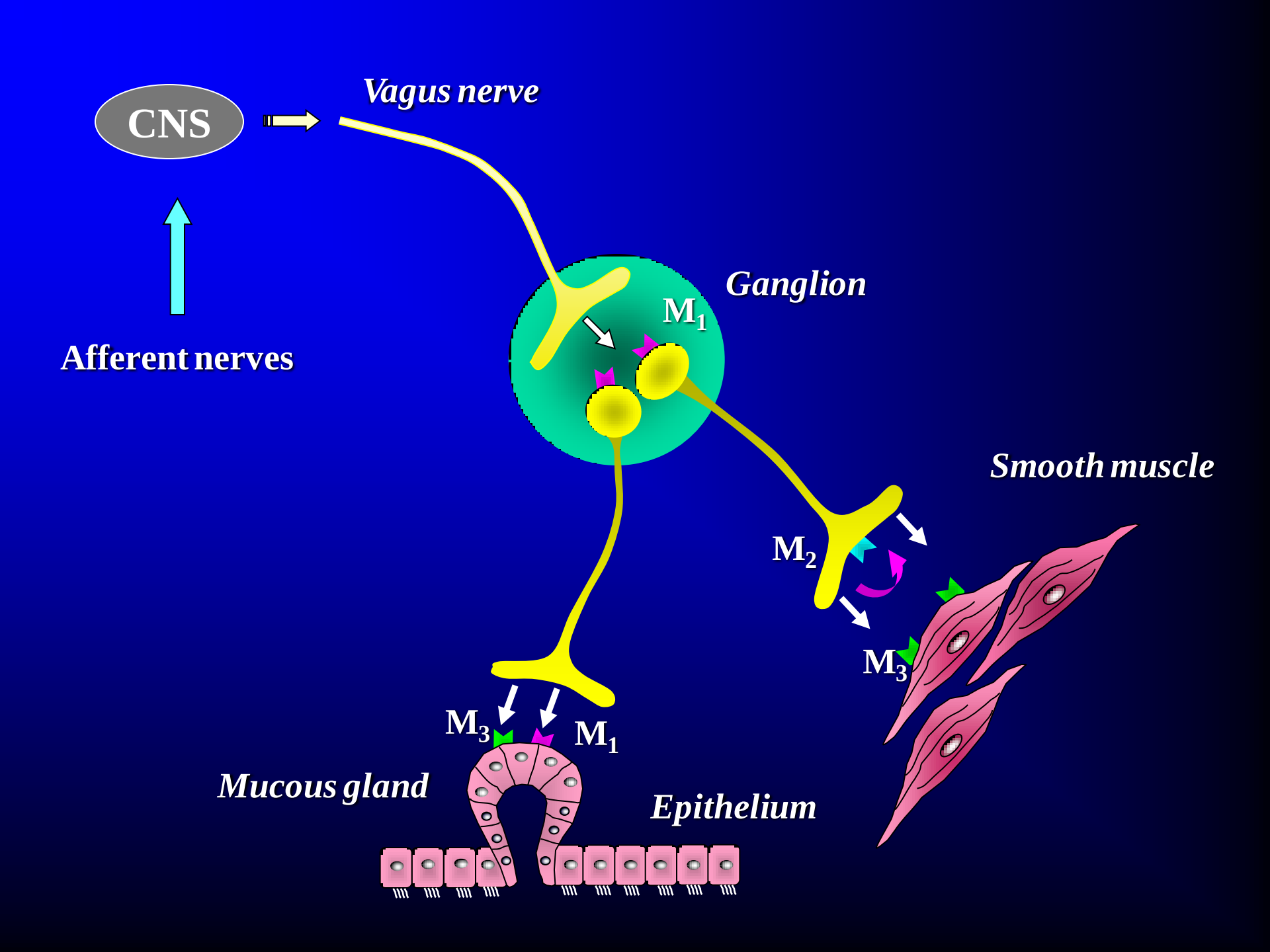
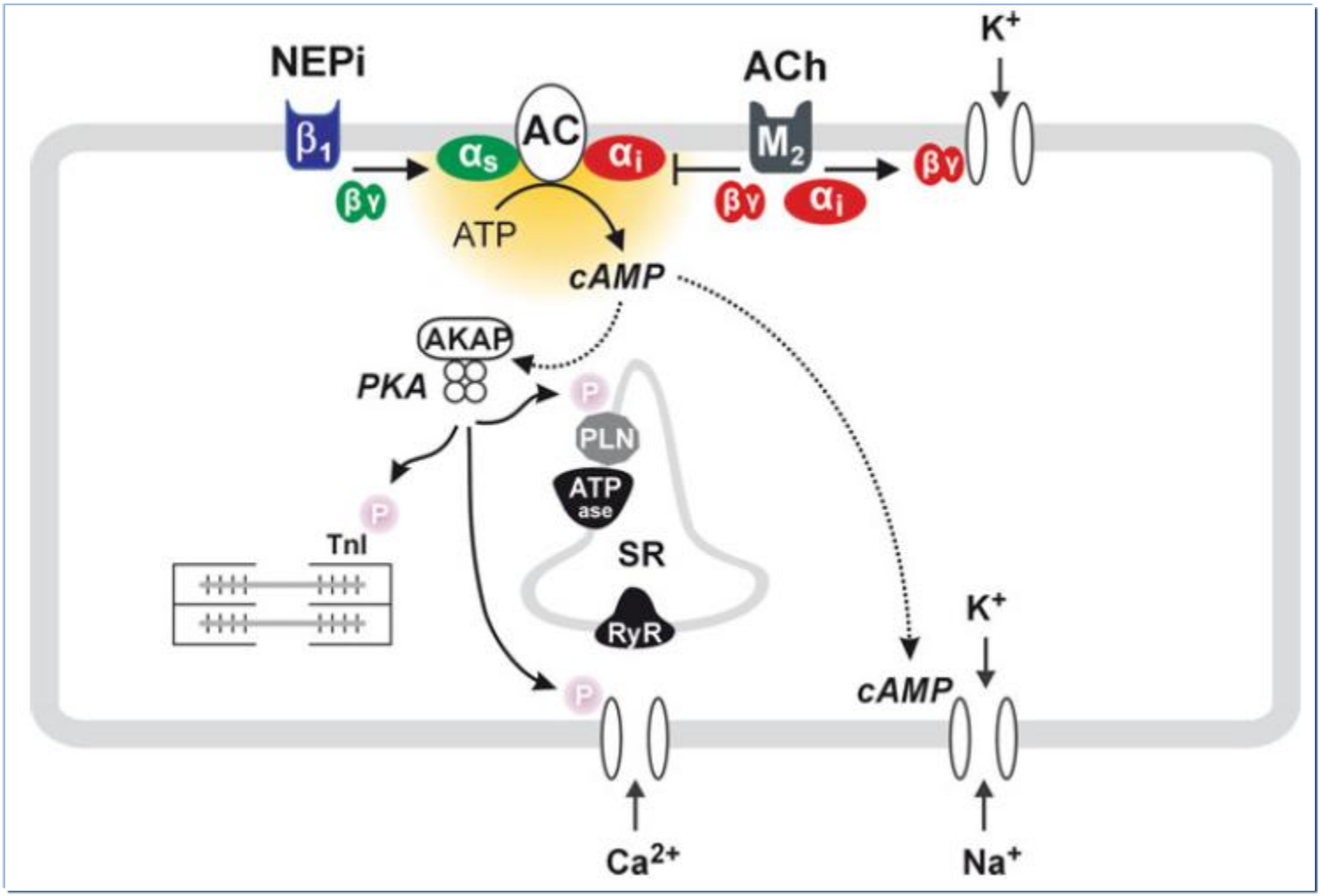

CNS
Vagus nerve
Afferent nerves
Ganglion
M1
M2
M3
Smooth muscle
M3
M1
Mucous gland
Epithelium

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

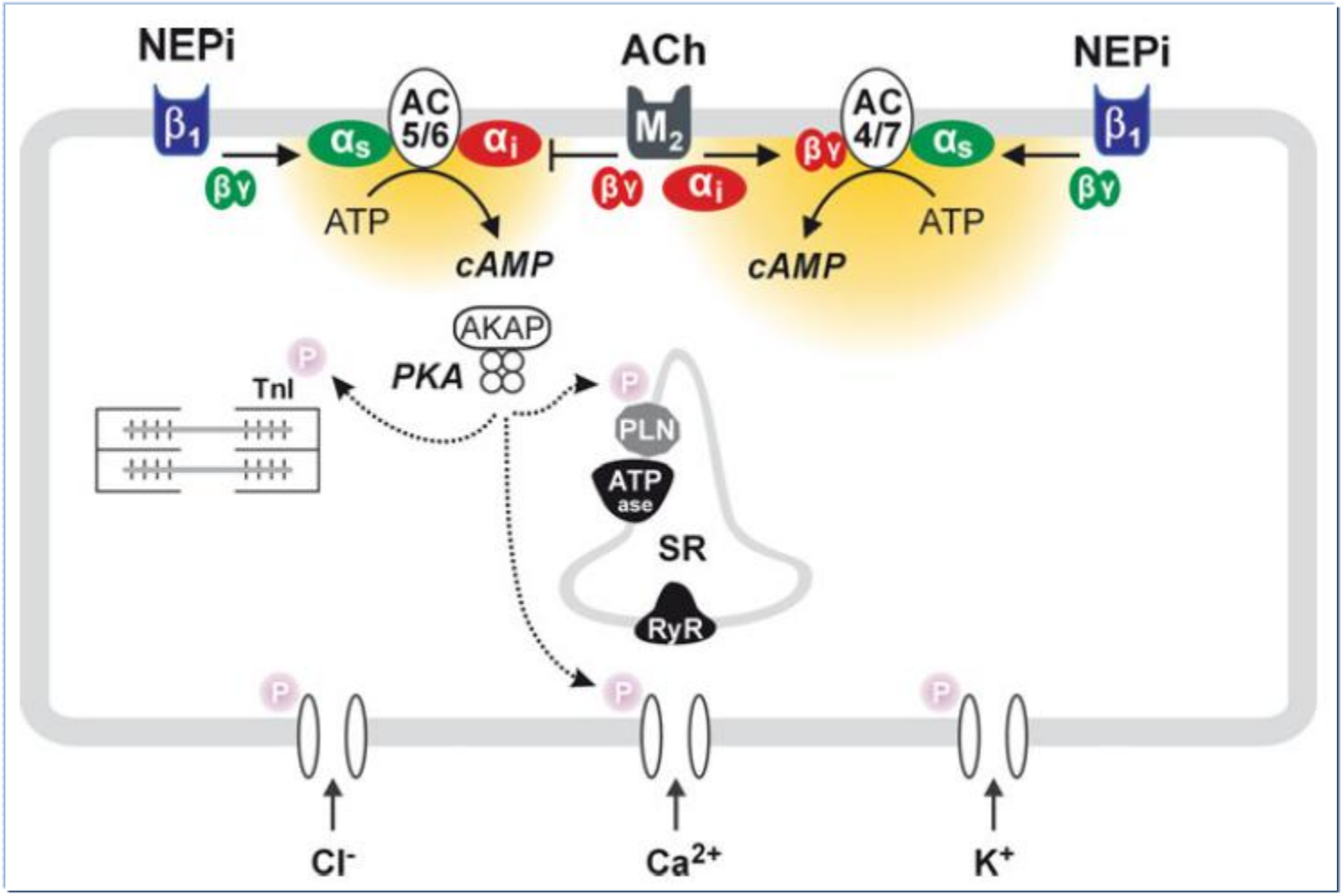
Buels KS, Fryer AD. *Handb Exp Pharmacol* 208:317-341, 2012

Muscarinic signaling pathways in supraventricular (sinoatrial, atrial and atrioventricular) myocytes



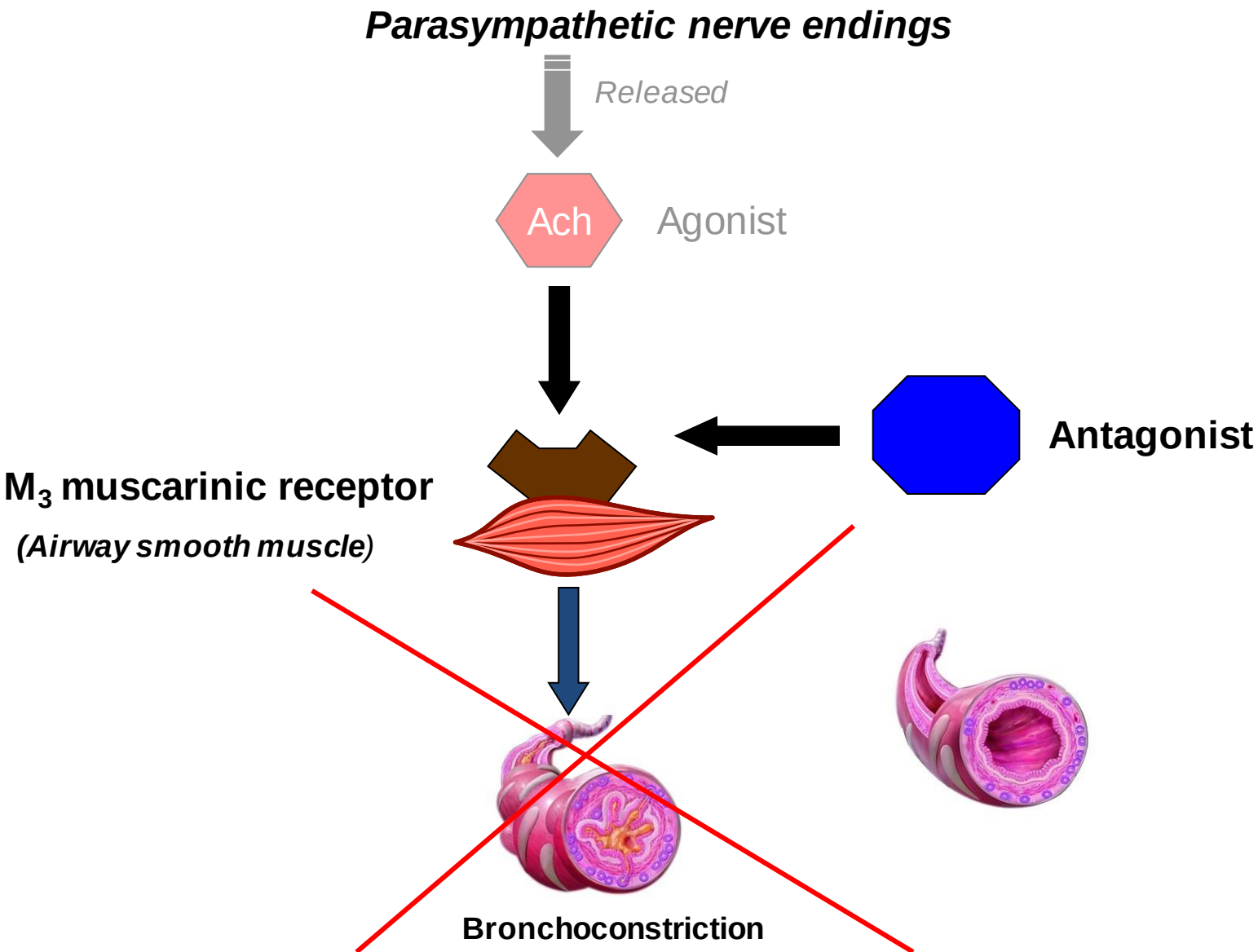
Harvey RD. *Handb Exp Pharmacol* 208:299-316, 2012

Muscarinic signaling pathways in ventricular myocytes

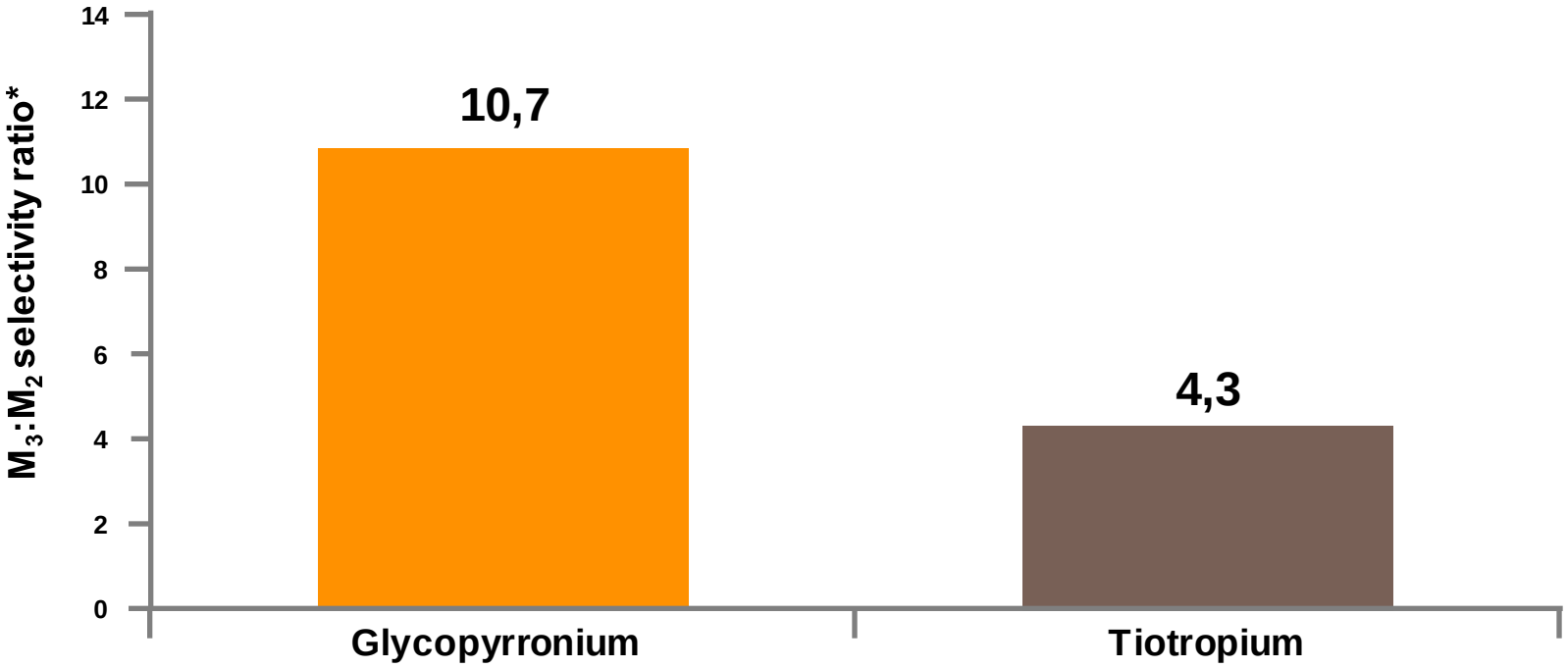


Harvey RD. *Handb Exp Pharmacol* 208:299-316, 2012

Mode of action: High affinity for M_3 muscarinic receptors and slow dissociation from them



Glycopyrronium shows greater M_3/M_2 receptor kinetic selectivity than tiotropium *in vitro*



*Ratio of occupancy versus time over 24 hours

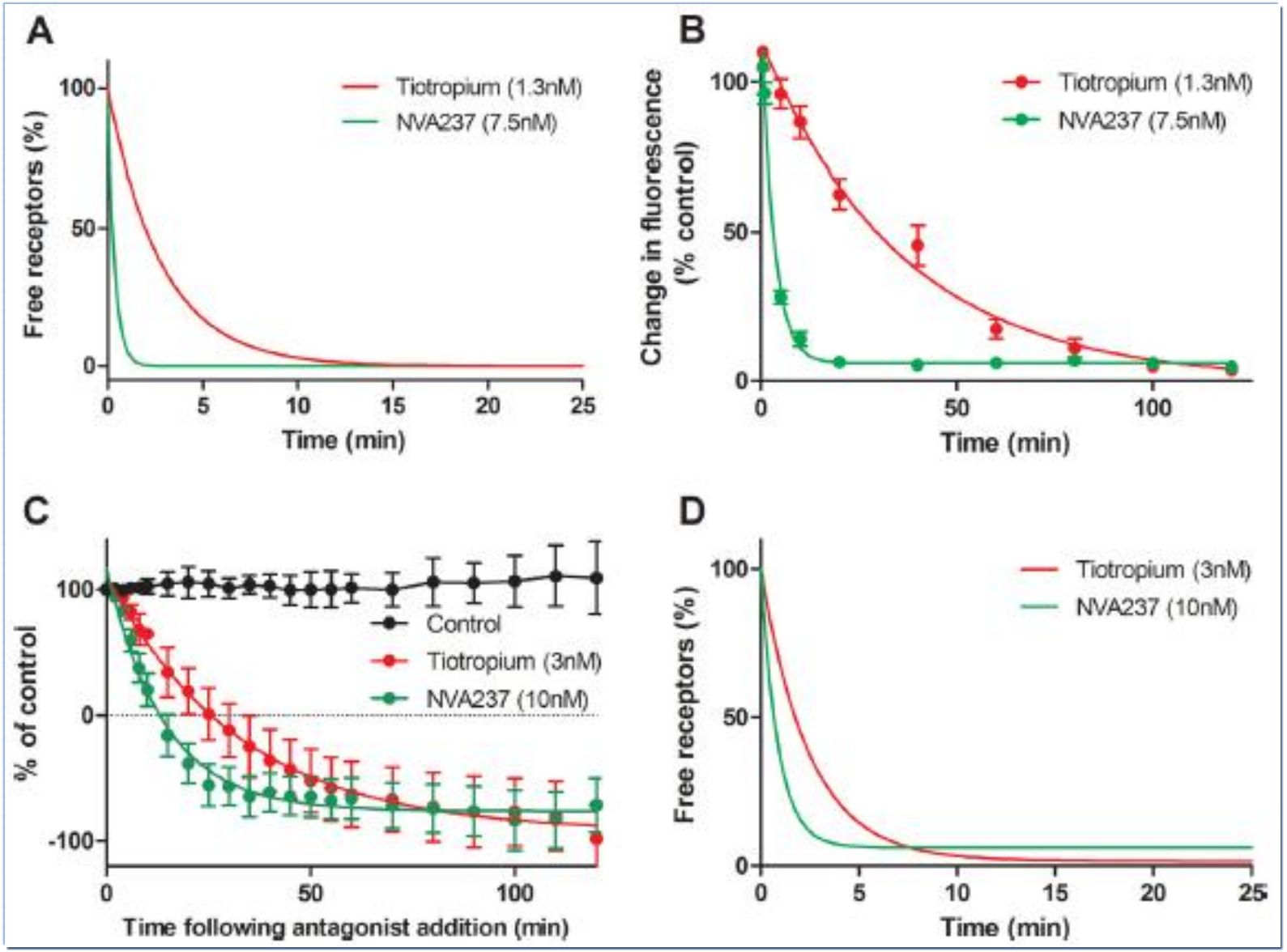
Sykes D et al. *J Pharmacol Exp Ther* 343:520-528, 2012

Half-life ratio for dissociation from M_3 and M_2 receptors

	$t_{1/2}$ Ratio M_3/M_2
Ipratropium	7.3
Tiotropium	10.4
Glycopyrronium	16.5

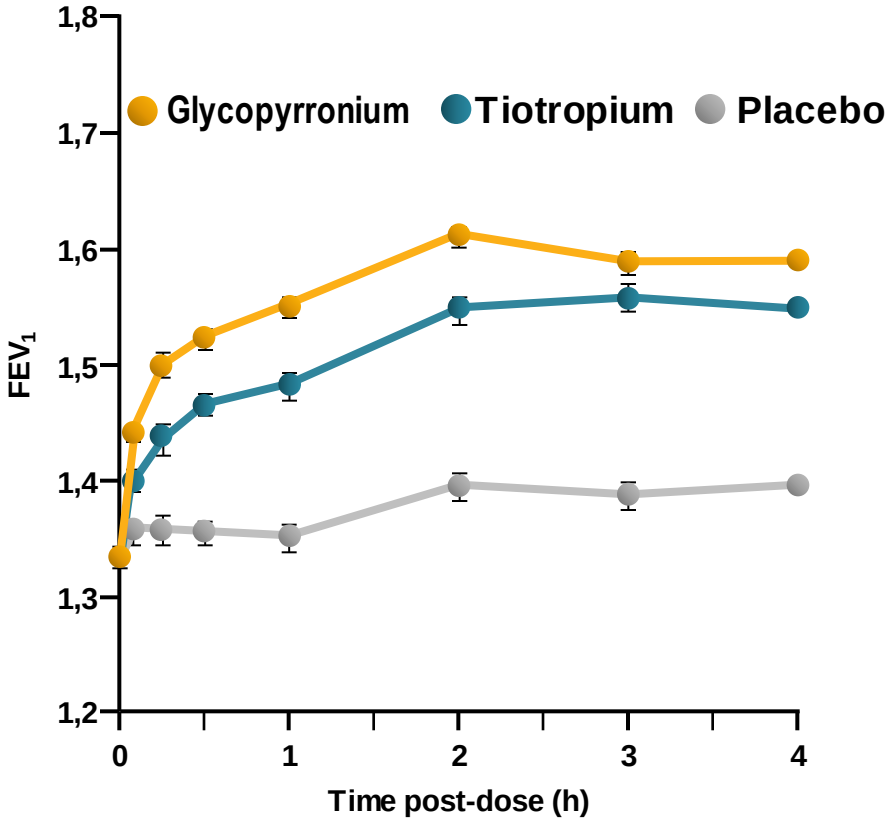
Casarosa P, Bouyssou T, Germeyer S, Schnapp A, Gantner F, Pieper M. *J Pharmacol Exp Ther* 330:660-668, 2012

When compared to tiotropium, glycopyrronium displays a faster onset of action

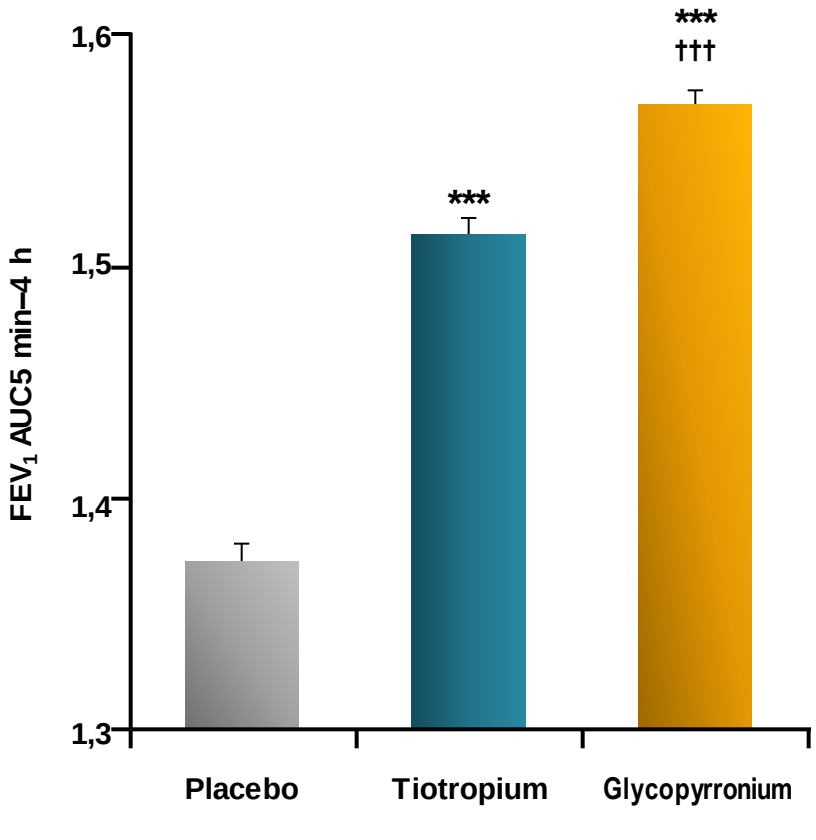


Sykes D et al. *J Pharmacol Exp Ther* 343:520-528, 2012

GLOW2 STUDY: FEV_1 from 5 minutes to 4 hours post-dose on Day 1



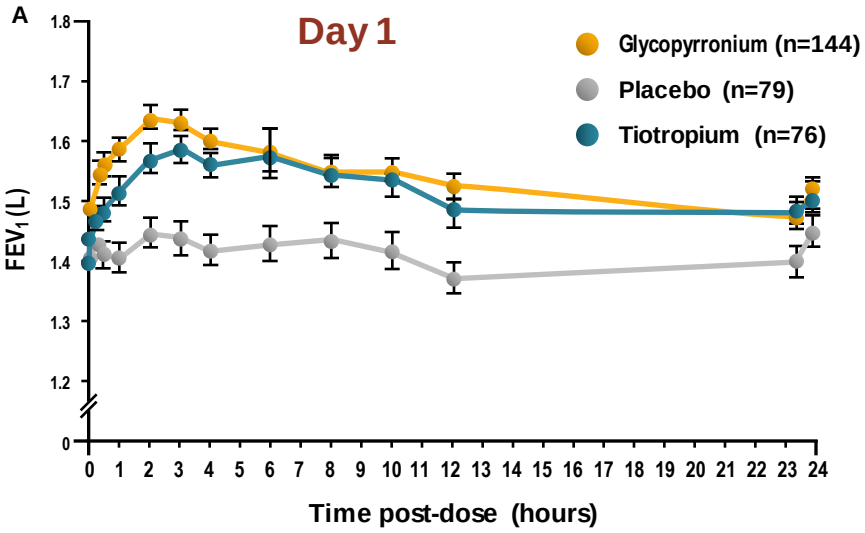
At all time points: p<0.001 Glycopyrronium vs placebo and tiotropium; p<0.01 tiotropium vs placebo

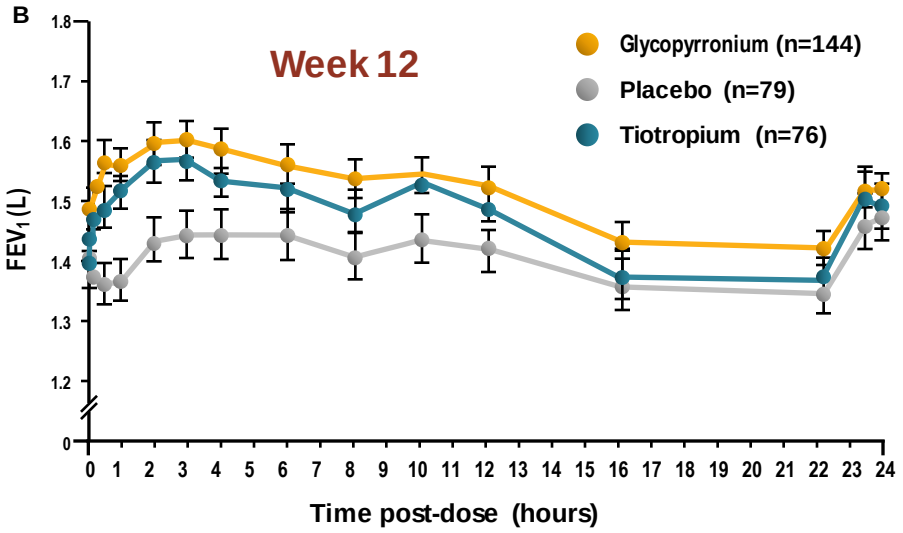


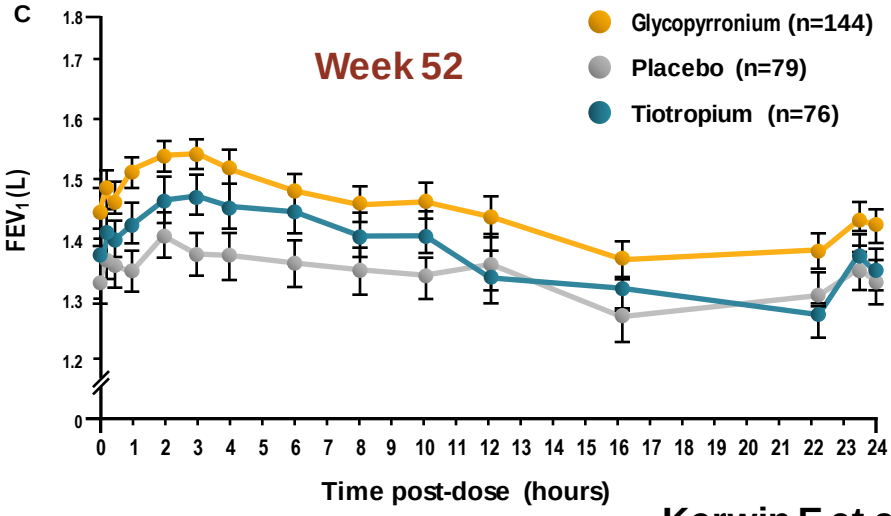
***p<0.001 versus placebo, †††p<0.001 versus tiotropium; data are LSMs SE. AUC = area under curve

Kerwin E, Hébert J, Gallagher N, Martin C, Overend T, Alagappan VKT, Lu Y, Banerji D
***Eur Respir J* 40:1106-1114, 2012**

EFFECTS OF GLYCOPYRRONIUM ON FEV_1







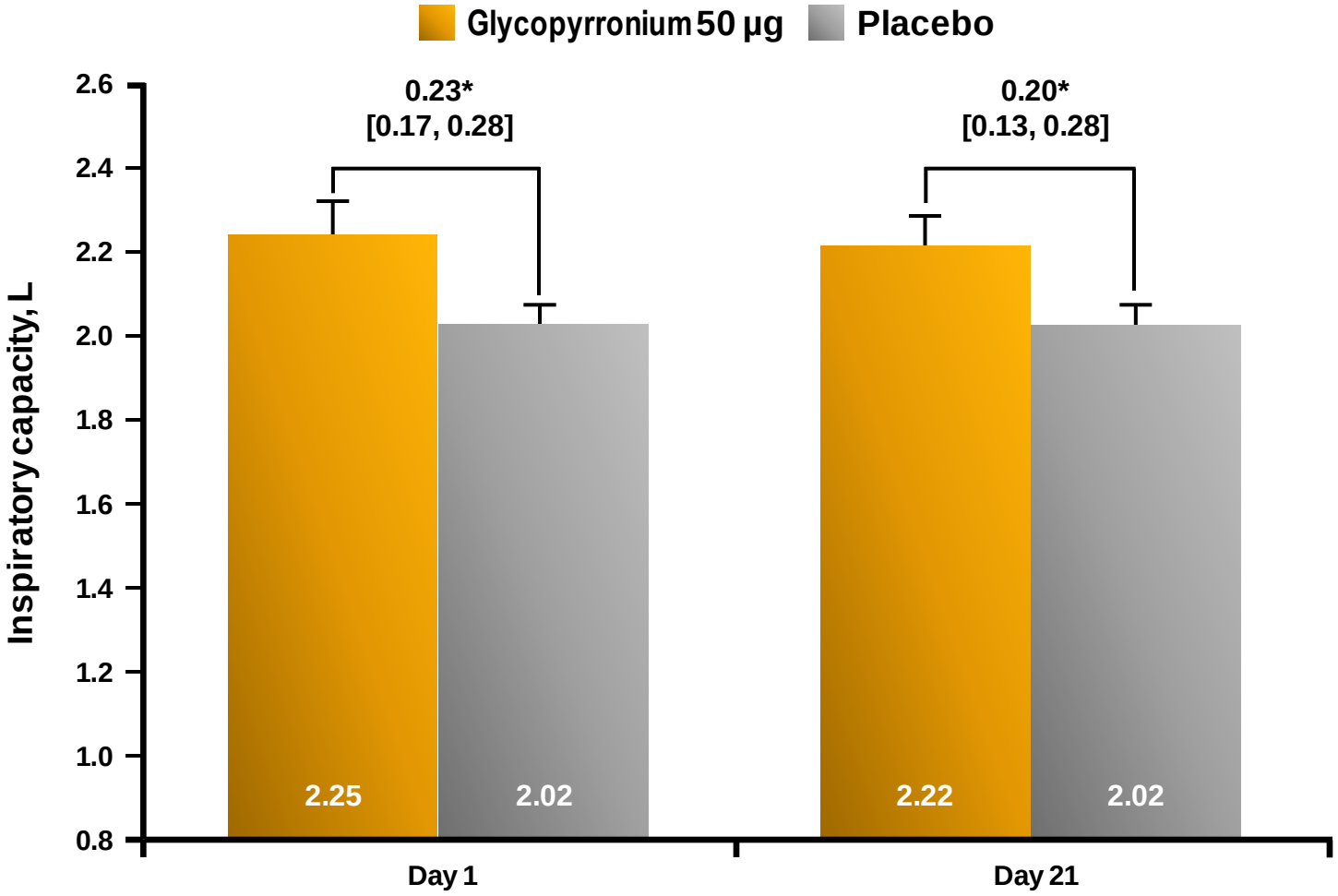
Kerwin E et al. GLOW 2 *Eur Respir J* 2012

Cardiovascular mortality in COPD

For every 10% decrease in FEV_1, cardiovascular mortality increases by approximately 28% and non-fatal coronary events increase by approximately 20% in mild to moderate COPD.

Lung Health Study, Anthonisen et al, Am J Respir Crit Care Med 2002

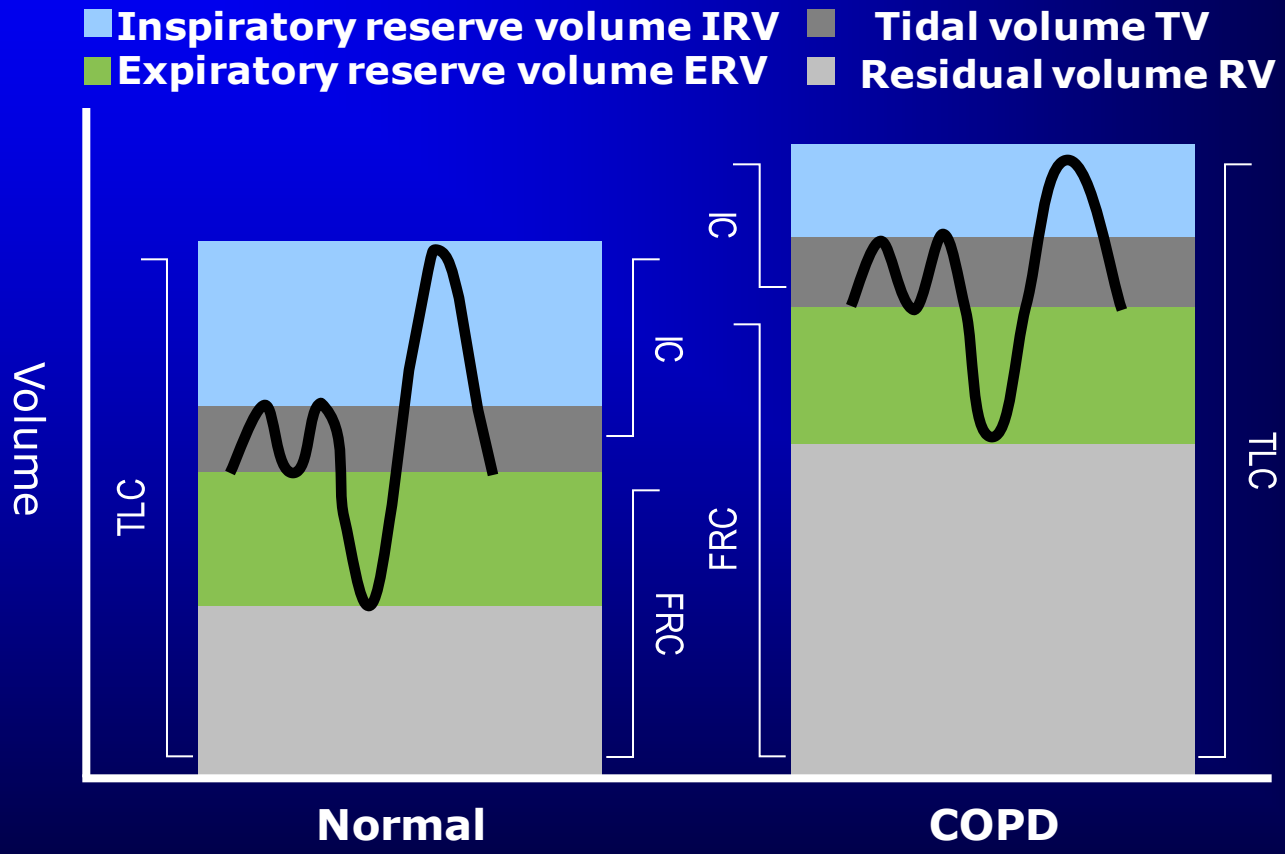
GLOW 3 STUDY:
effects of glycopyrronium on inspiratory capacity



Values are LSM (95% CI). *P <0.001

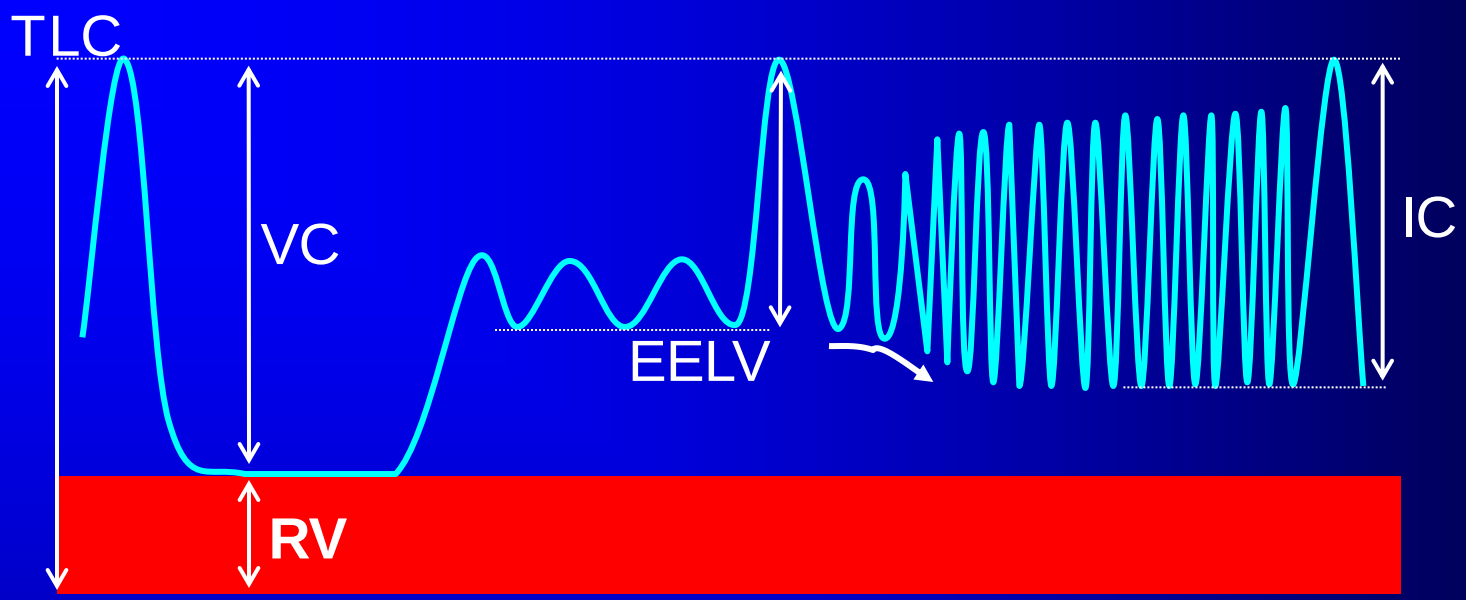
Beeh KM et al. ***Int J Chron Obstruct Pulm Dis*** **2012; 7:503–513**

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

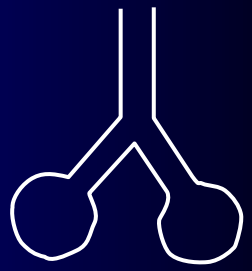


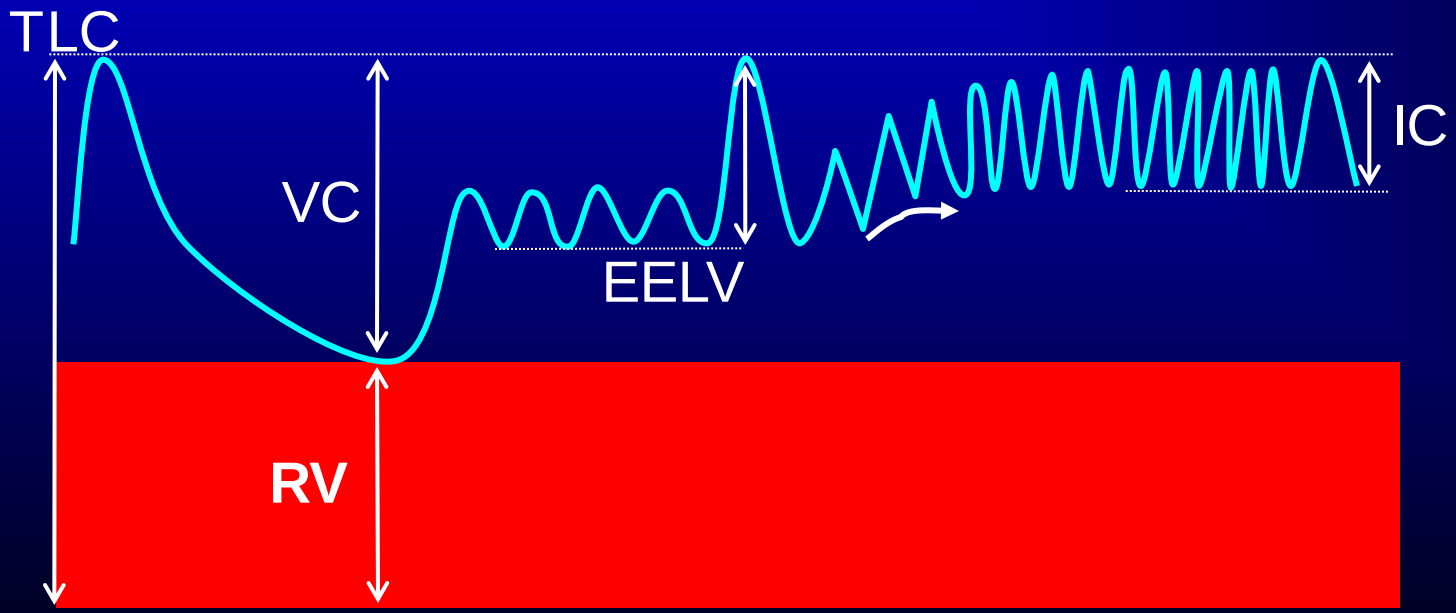
TLC = Total lung capacity FRC = Functional residual capacity IC = Inspiratory capacity

Casaburi et al., Am J Med 2004

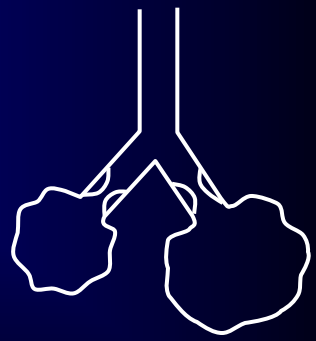


Health

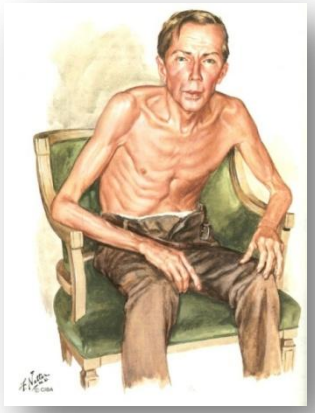


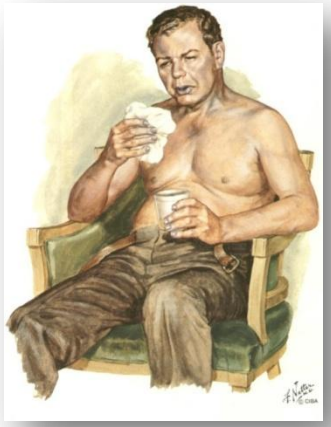


COPD



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

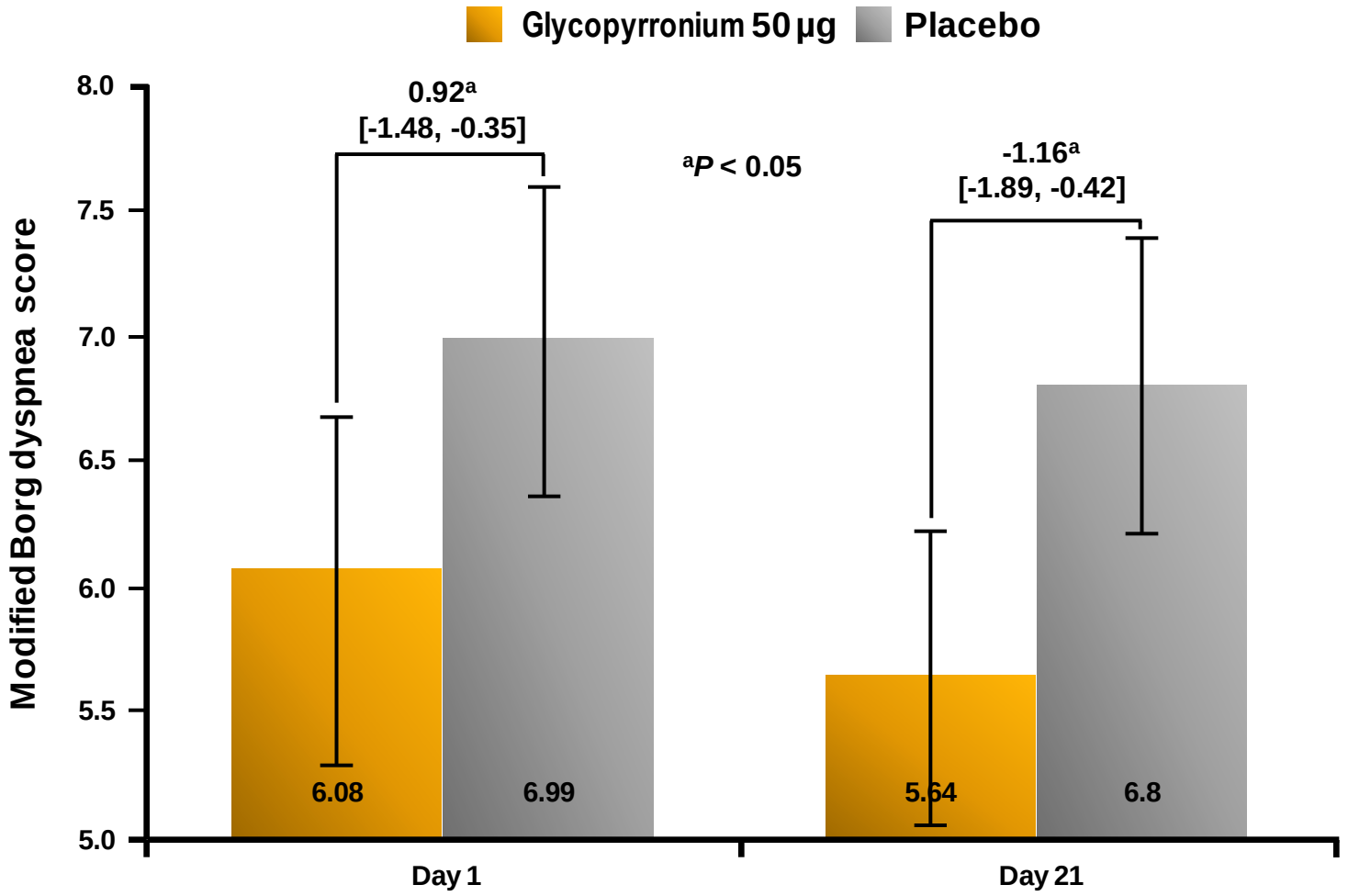
Exacerbations

Deconditioning

Reduced exercise endurance

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

GLOW3 STUDY: effects of glycopyrronium on dyspnea

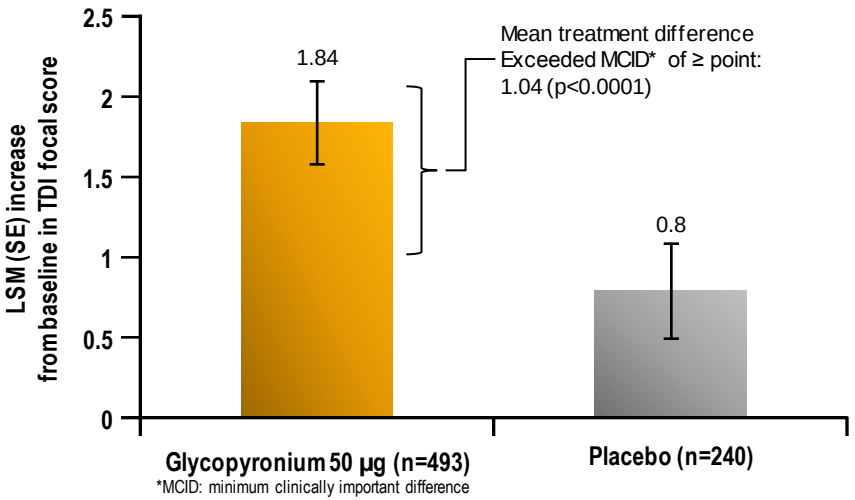


Values are LSM (95% CI)

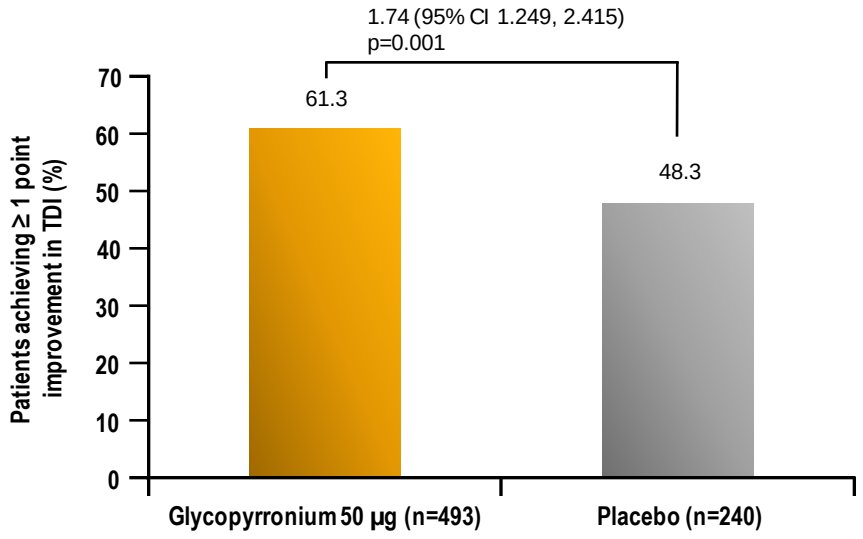
Beeh KM et al. *Int J Chron Obstruct Pulm Dis* 2012; 7:503–513

GLOW 1 TRIAL: OUTCOME IMPROVEMENT

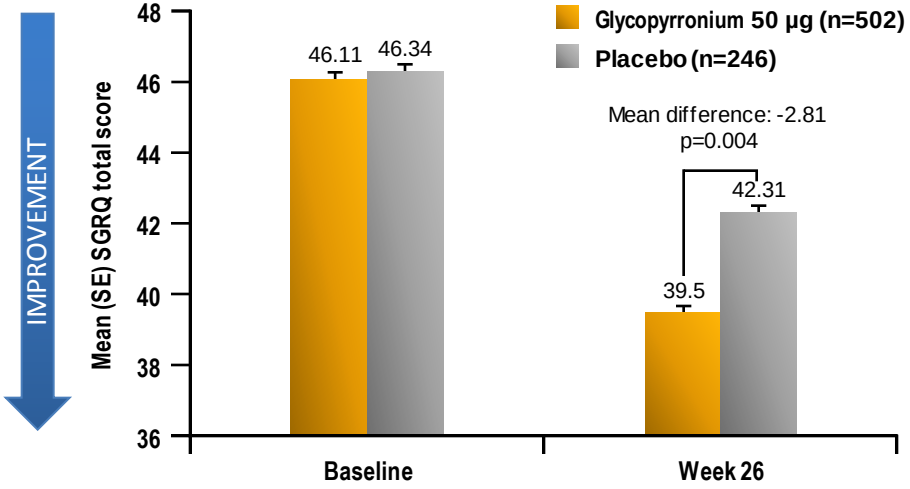
TDI focal score at Week 26



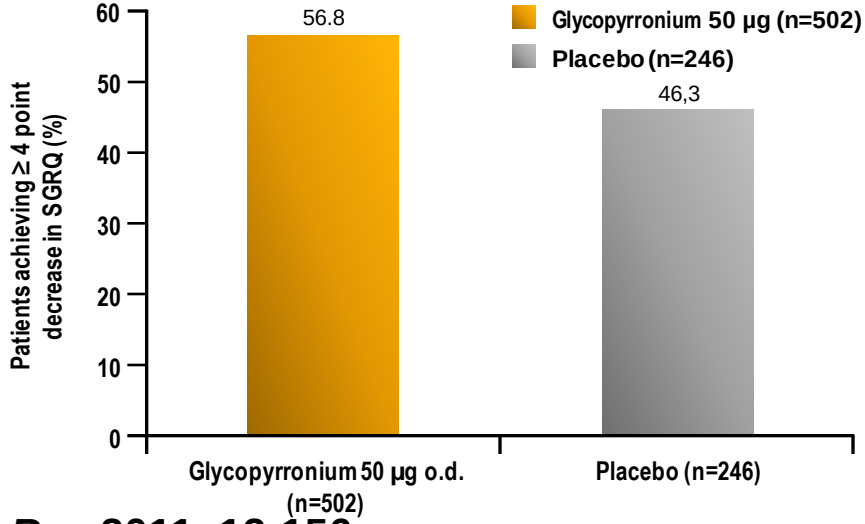
Patients achieving a clinically important improvement in dyspnea at Week 26



SGRQ total score at Week 26

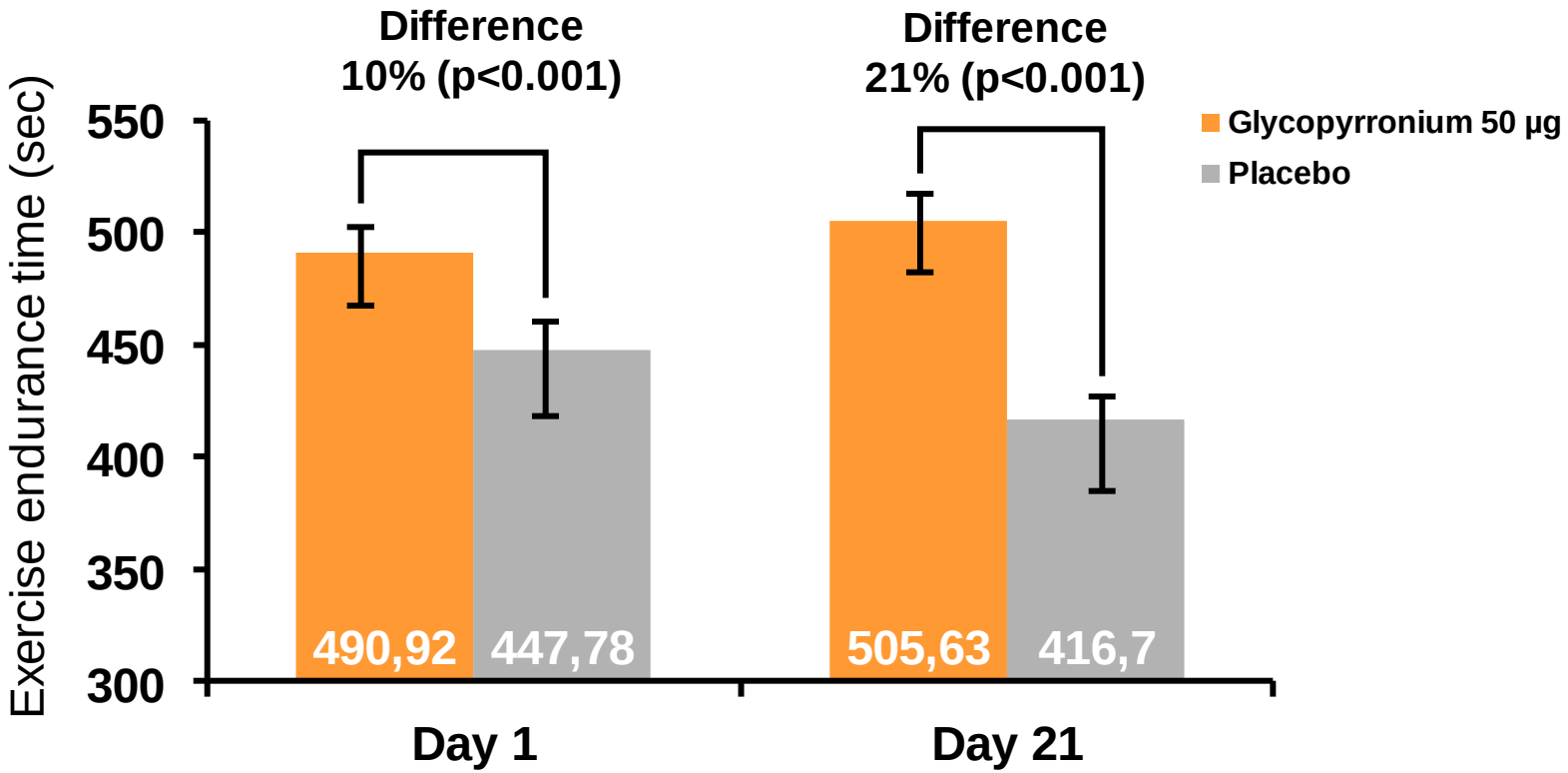


Patients achieving a clinically important improvement in HRQoL at Week 26



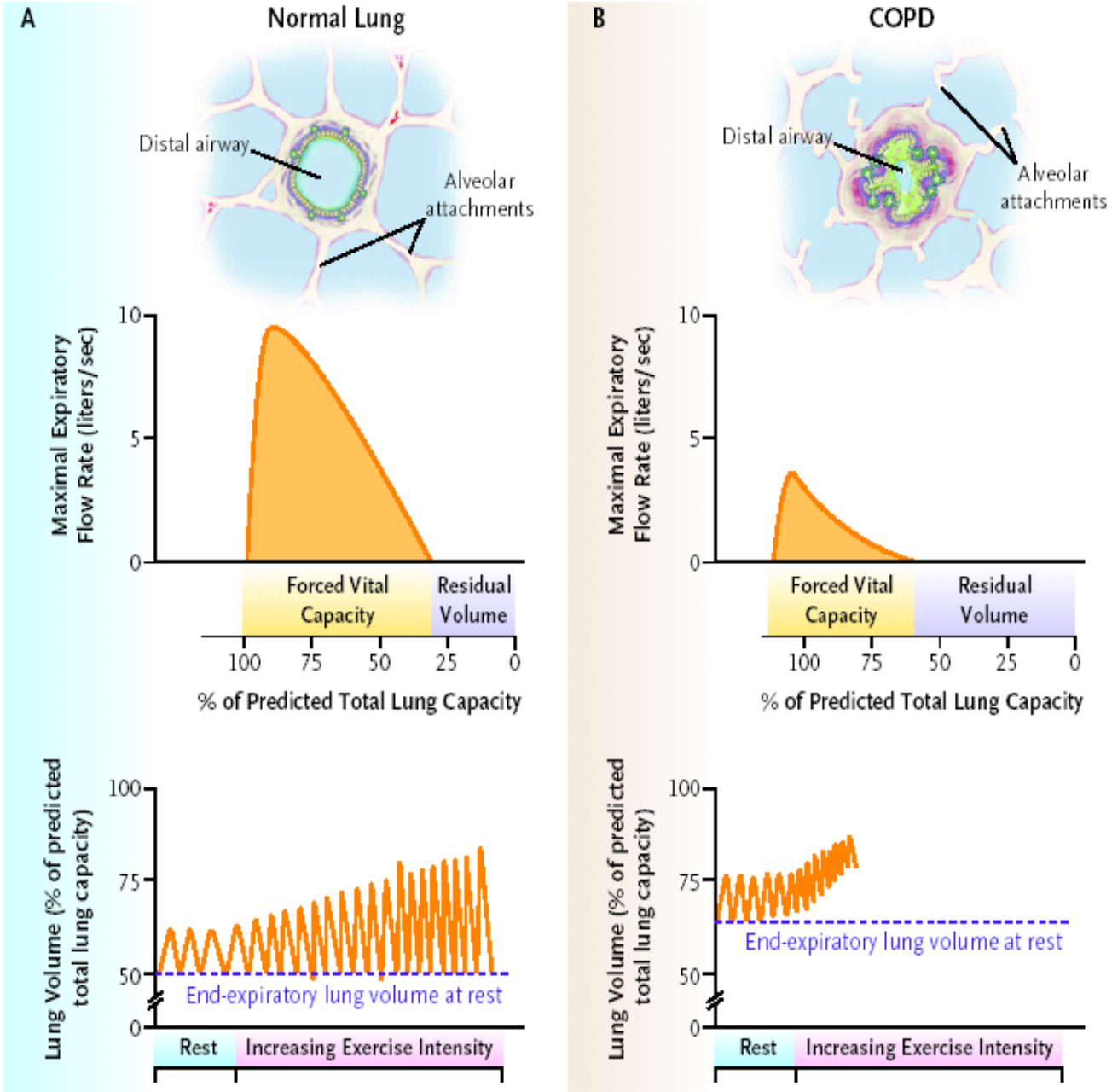
D'Urzo A et al. *Respir Res* 2011; 12:156

GLOW3 STUDY: Glycopyrronium significantly improved exercise endurance time vs placebo (Days 1 and 21)



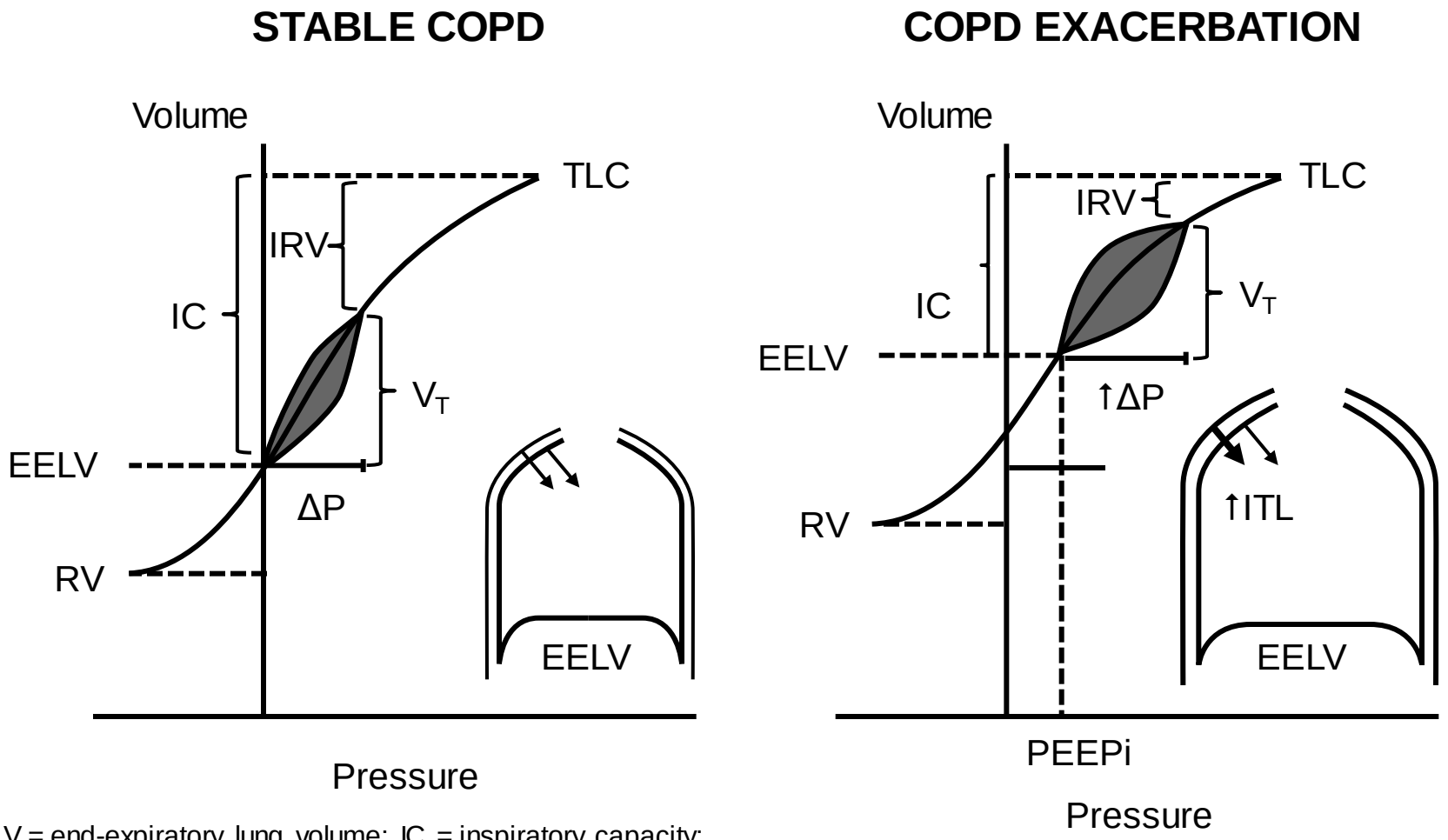
*p<0.001, Values are LSM±SE

Beeh et al. *Int J COPD* 2012



Niewoehner DE. *N Engl J Med* 362:1407-1416, 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

O'Donnell et al. *Thorax* 2006

EFFECT OF LVRS ON COPD EXACERBATIONS

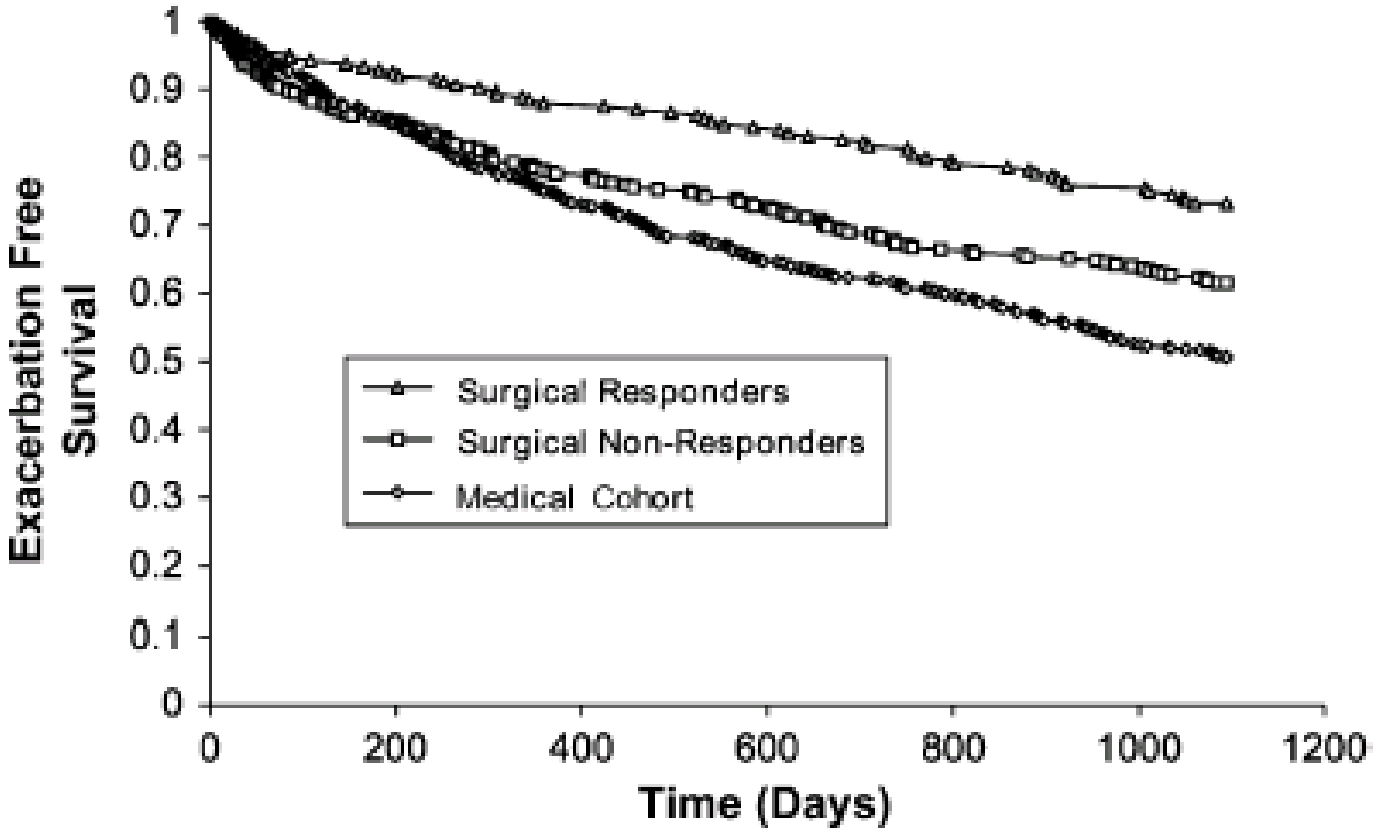
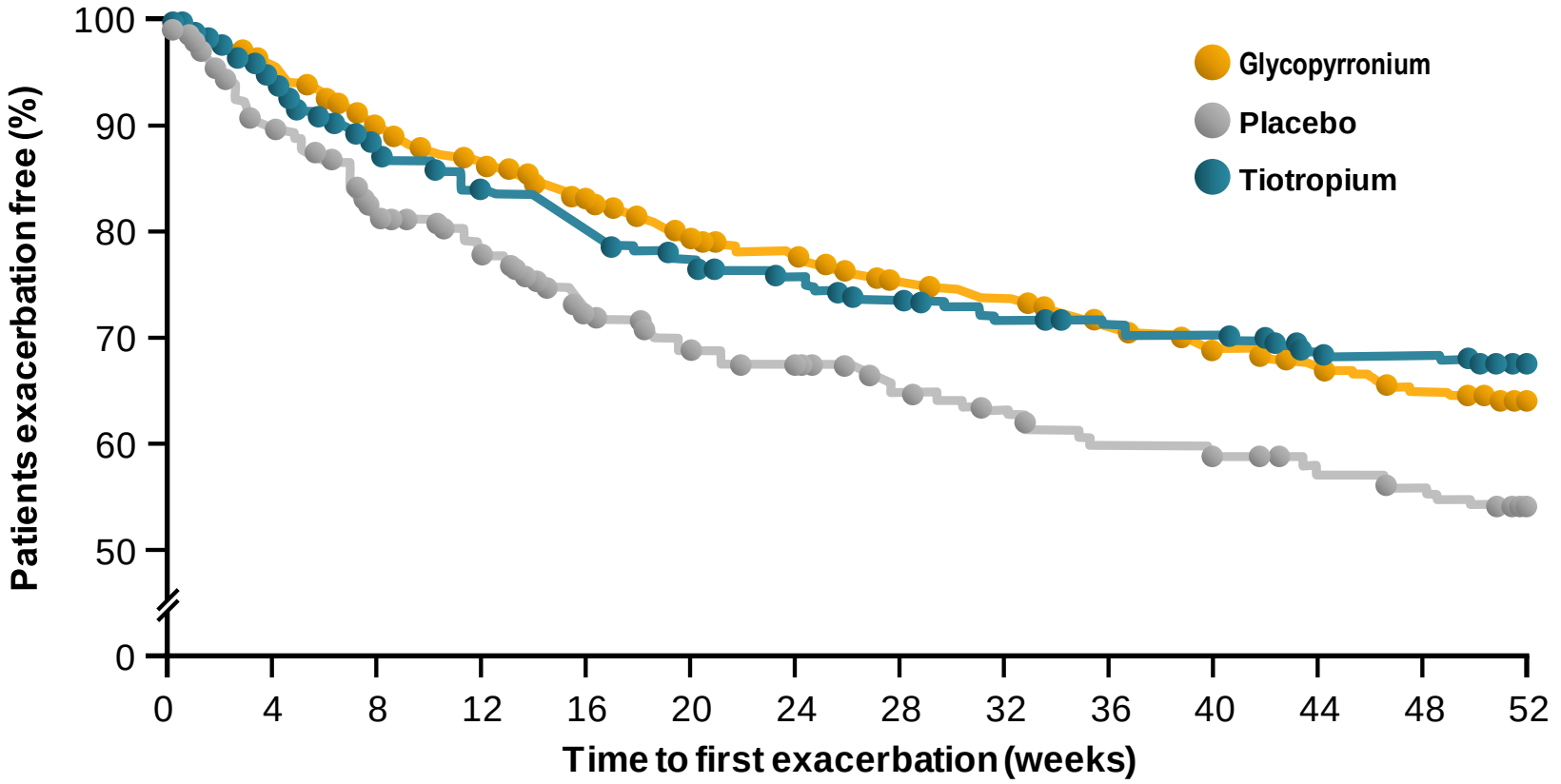


Figure 3. Time to event analysis of surgical responders defined as 6-month improvement in FEV_1 greater than 0.200 L and the surgical nonresponders defined as those with less than a 0.200-L improvement in FEV_1 over the same time period.

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

GLOW 2: glycopyrronium induces a 34% rate decrease of moderate and severe exacerbations

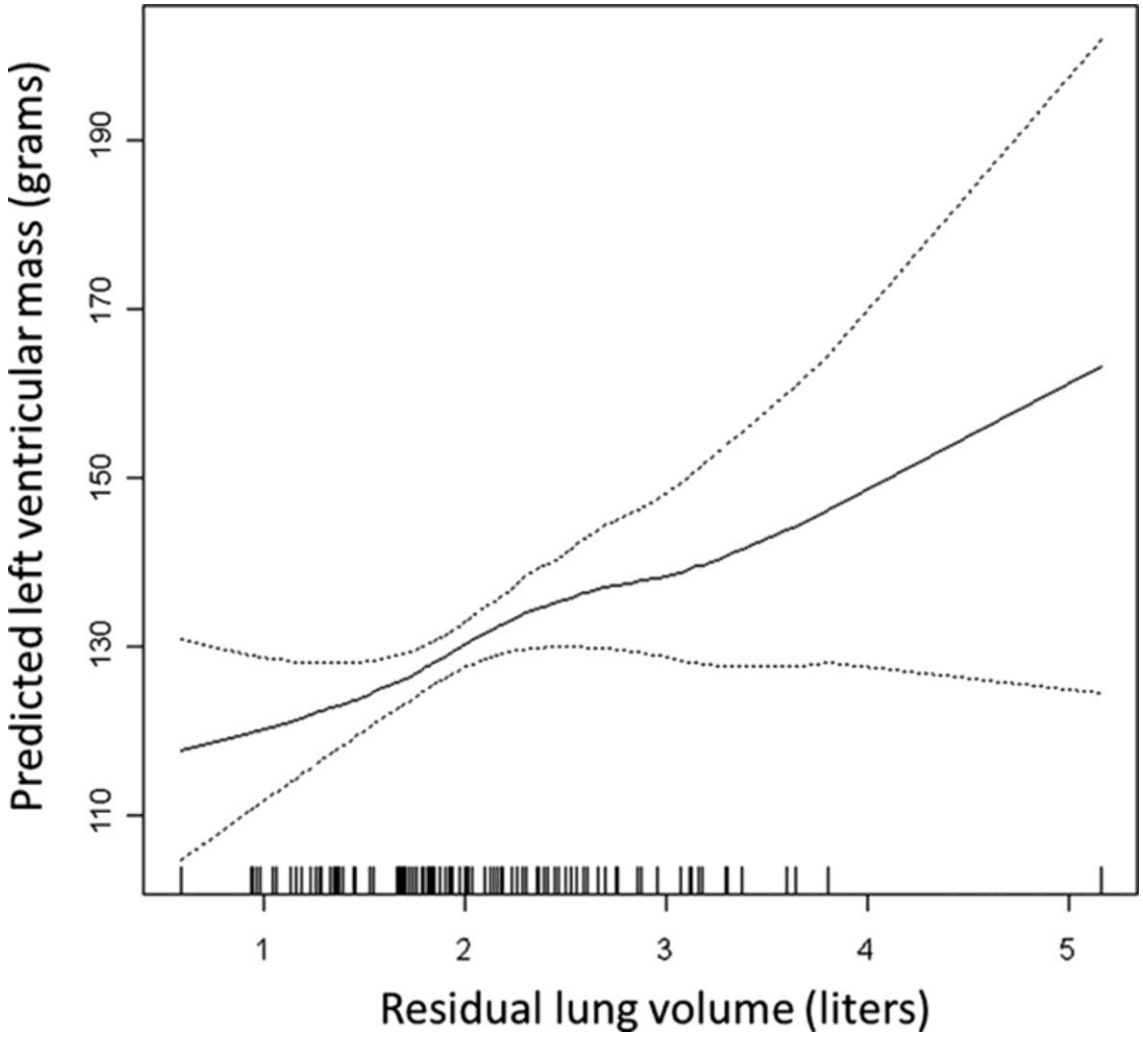


Number at Risk													
Glycopyrronium	495	451	426	394	370	360	341	335	318	310	296	282	239
Placebo	229	202	188	168	159	153	142	137	129	129	122	116	98
Tiotropium	245	222	209	200	190	184	176	169	166	163	157	155	129

p=0.001 for glycopyrronium or tiotropium versus placebo

Kerwin E et al. *Eur Respir J* 2012

Relationship between residual lung volume and left ventricular mass in the Multi-Ethnic Study of Atherosclerosis (MESA) chronic obstructive pulmonary disease (COPD) study.



Smith BM et al. *Circulation* 127:1503-1511, 2013

American Heart Association
Learn and Live

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CHEST

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Left ventricular hypertrophy in COPD without hypoxemia

Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD, George J. *Chest* 143:91-97, 2013

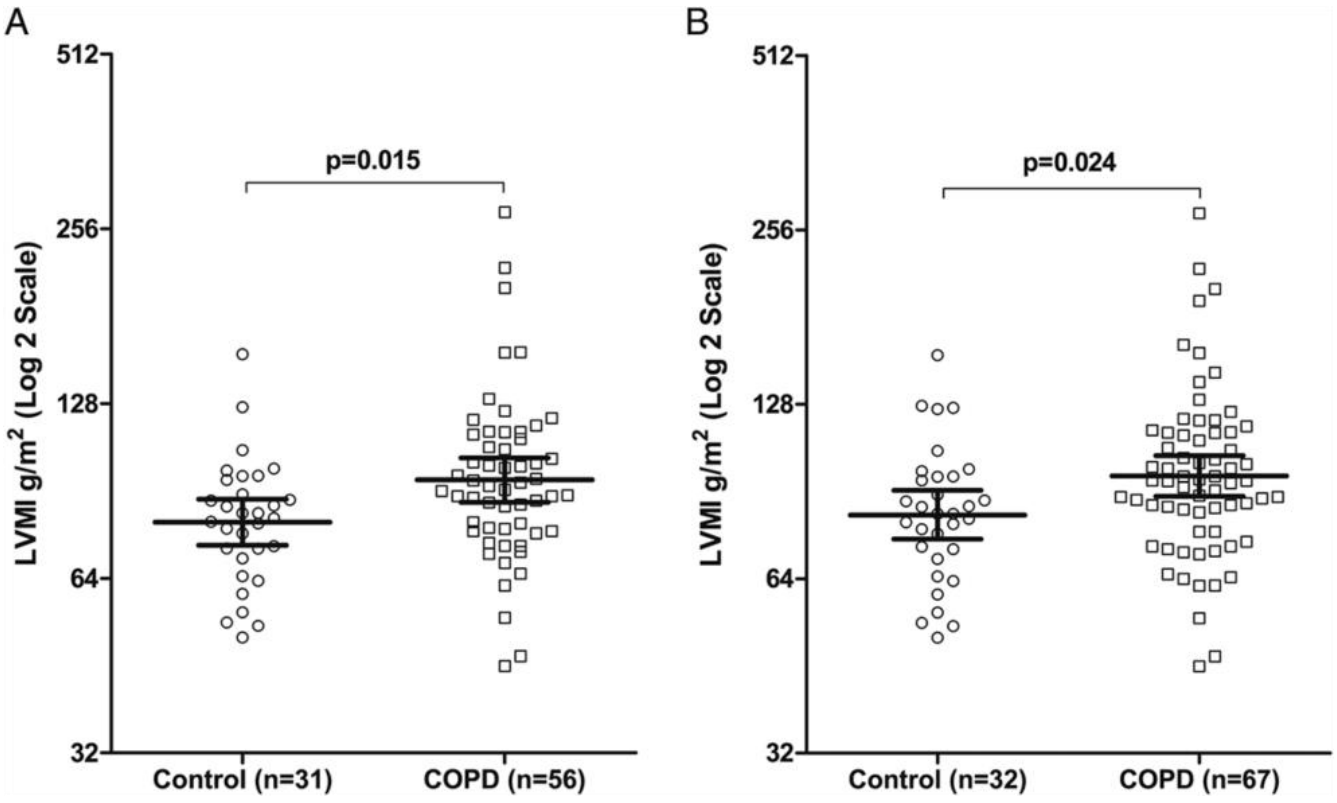


Figure Legend:

LVMI between groups without hypertension. Presented as scatterplots of all data points, with solid lines representing respective geometric means and 95% CIs. Means comparison with Student t test for unpaired samples (two tailed). Significance set at P < .05. A, Patients without a history of hypertension. B, Patients with 24-h systolic BP < 135 mm Hg. See Figure 1 legend for expansion of abbreviations.

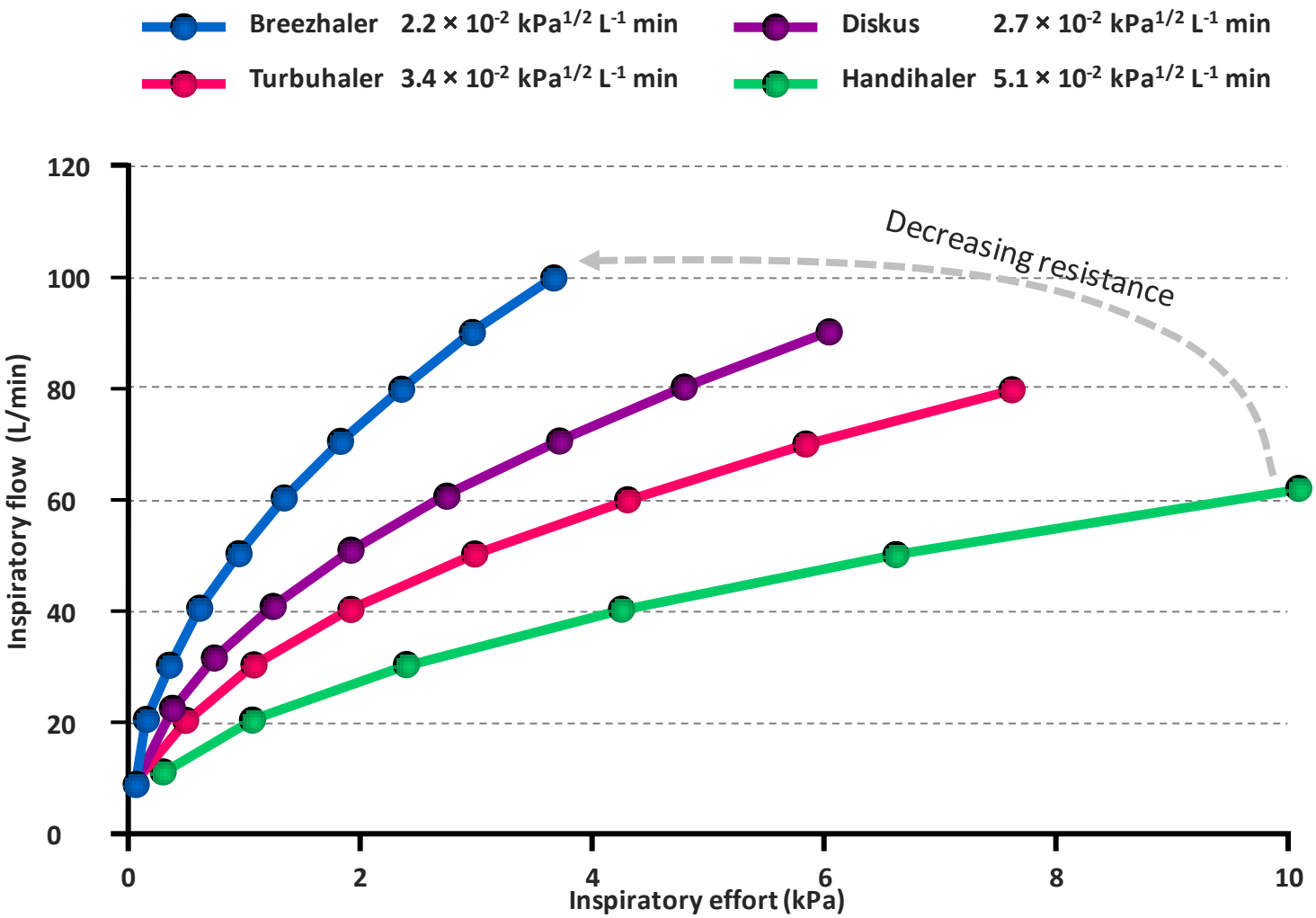
TABLE 3 Most frequent adverse events (≥3% in any treatment group), serious adverse events occurring in ≥3 patients in either group, deaths and discontinuations due to adverse events and electrocardiographic abnormalities

	NVA237 50 µg *q.d.*	Placebo	Tiotropium 18 µg *q.d.*
Subjects n	525	268	267
Patients with adverse events	402 (76.6)	205 (76.5)	198 (74.2)
COPD worsening#	191 (36.4)	116 (43.3)	90 (33.7)
Upper respiratory tract infection	57 (10.9)	33 (12.3)	30 (11.2)
Nasopharyngitis	47 (9.0)	15 (5.6)	21 (7.9)
Sinusitis	28 (5.3)	14 (5.2)	10 (3.7)
Upper respiratory tract infection, bacterial	28 (5.3)	28 (10.4)	21 (7.9)
Back pain	25 (4.8)	10 (3.7)	12 (4.5)
Headache	25 (4.8)	14 (5.2)	12 (4.5)
Lower respiratory tract infection	23 (4.4)	9 (3.4)	10 (3.7)
Bronchitis	22 (4.2)	10 (3.7)	12 (4.5)
Cough	21 (4.0)	13 (4.9)	12 (4.5)
Hypertension	21 (4.0)	12 (4.5)	14 (5.2)
Dry mouth	16 (3.0)	5 (1.9)	4 (1.5)
Dyspnoea	14 (2.7)	13 (4.9)	6 (2.2)
Pneumonia	14 (2.7)	12 (4.5)	7 (2.6)
Urinary tract infection	14 (2.7)	8 (3.0)	16 (6.0)
Peripheral oedema	9 (1.7)	6 (2..2)	8 (3.0)
Upper respiratory tract infection viral	9 (1.7)	13 (4.9)	11 (4.1)
Patients with serious adverse events	66 (12.6)¶	43 (16.0)	41 (15.4)¶
COPD worsening#	19 (3.6)	16 (6.0)	13 (4.9)
Pneumonia	7 (1.3)	7 (2.6)	4 (1.5)
Atrial fibrillation	4 (0.8)	0	0
Dehydration	4 (0.8)	2 (0.7)	0
Syncope	3 (0.6)	1 (0.4)	0
Transient ischemic attack	3 (0.6)	1 (0.4)	0
Bronchitis	3 (0.6)	1 (0.4)	0
Deaths	3 (0.6)+	2 (0.7)	2 (0.7)
Discontinuation due to adverse events	42 (8.0)	31 (11.6)	20 (7.5)
Electrocardiographic abnormalities			
Total notable	23 (4.4)	16 (6.0)	14 (5.3)
QTc >500 ms	2 (0.4)	2 (0.7)	0
Increase from baseline of 30–60 ms	83 (15.8)	39 (14.6)	43 (16.2)
Increase from baseline of >60 ms	1 (0.2)	1 (0.4)	0

Data are presented as n (%), unless otherwise stated. #: includes chronic obstructive pulmonary disease (COPD) exacerbation; ¶: includes one serious adverse event in the 30-day follow-up period; +: includes one death in the 30-day follow-up period.

Kerwin E et al. *Eur Respir J* 40:1106-1114, 2012

When compared to other devices, Breezhaler is characterized by a low resistance to inspiratory flow



Singh D et al. ATS 2010

LABA-LAMA COMBINATIONS

Once daily:

- Indacaterol + glycopyrronium (Novartis)
- Olodaterol + tiotropium (Boehringer)
- Vilanterol + umeclidinium (GSK)

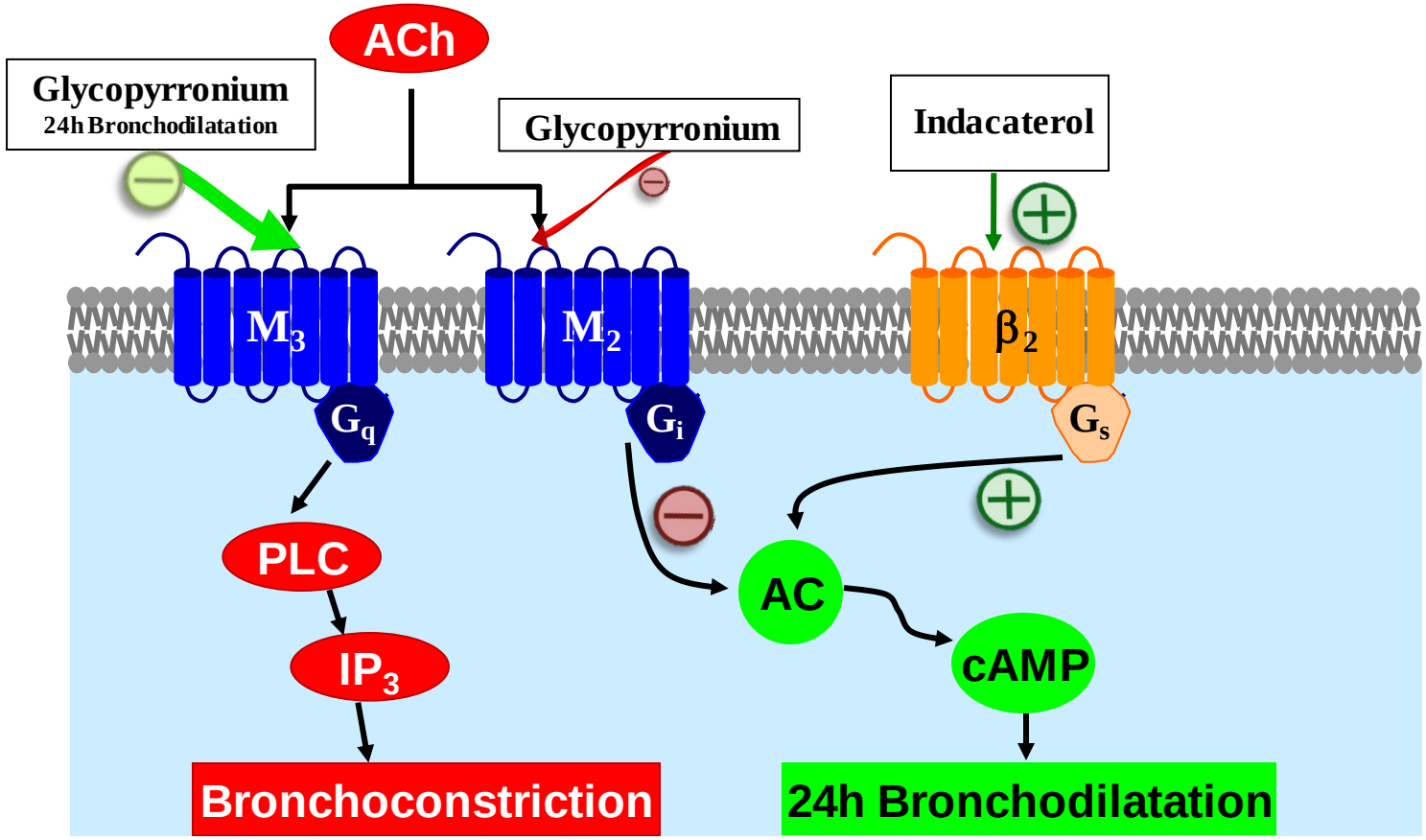
Twice daily:

- Formoterol + tiotropium (Cipla)
- Formoterol + aclidinium (Almirall)
- Formoterol + glycopyrrolate (Pearl)

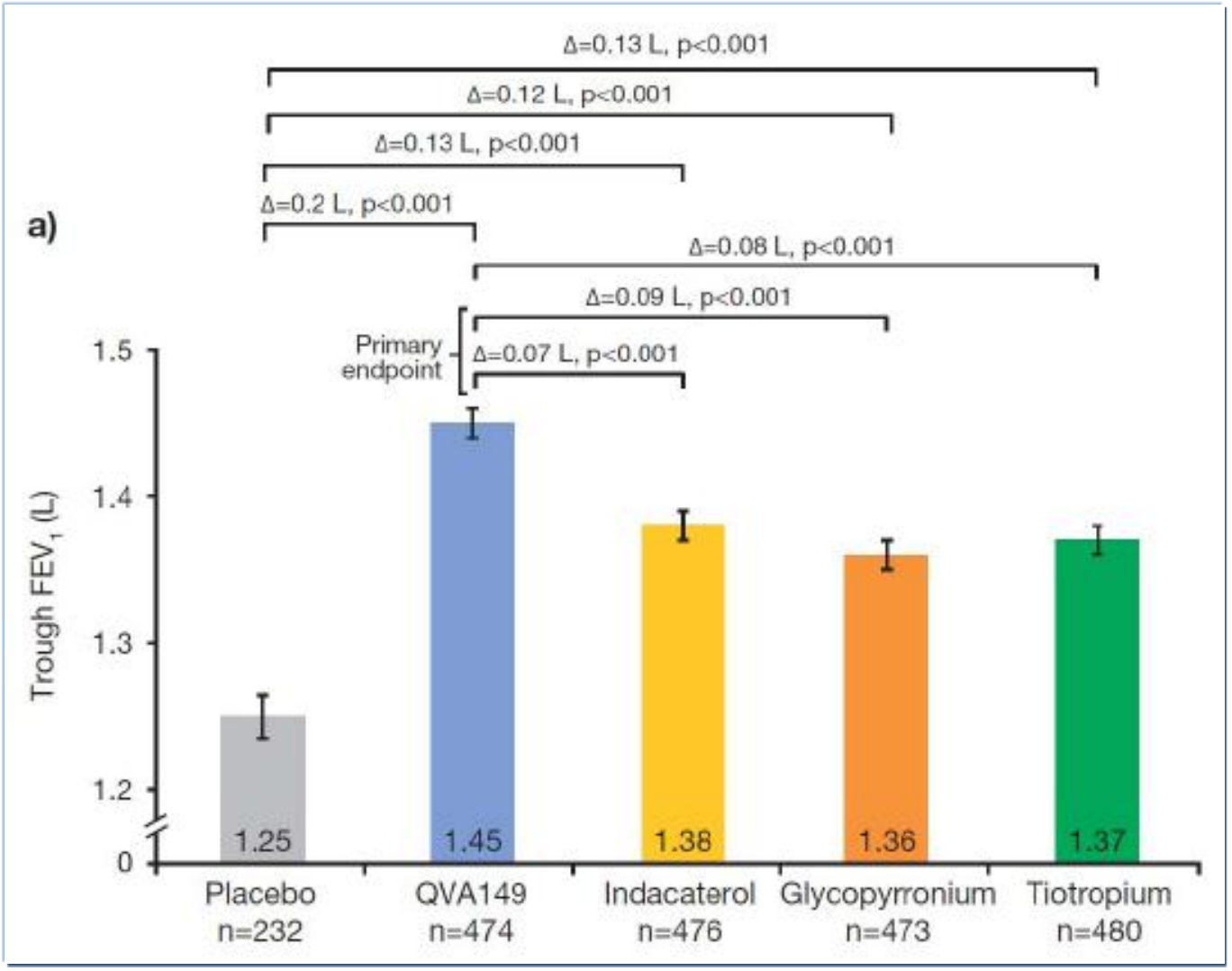
MABAs: difficult to balance activities

Triple: formoterol+tiotropium+budesonide (Triohale)
formoterol+glycopyrronium+budesonide (Chiesi)

Dual bronchodilatation with glycopyrronium/indacaterol

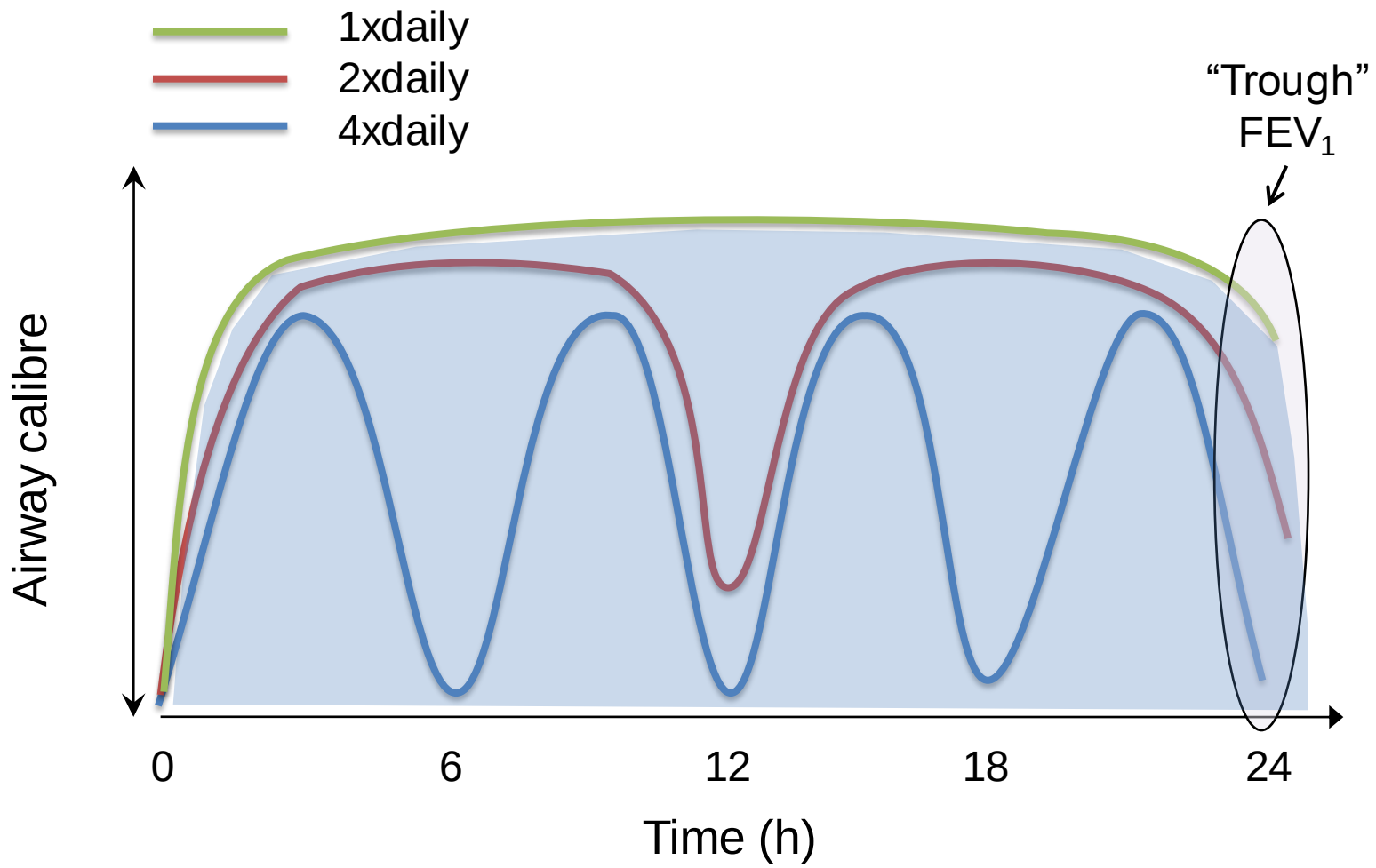


SHINE



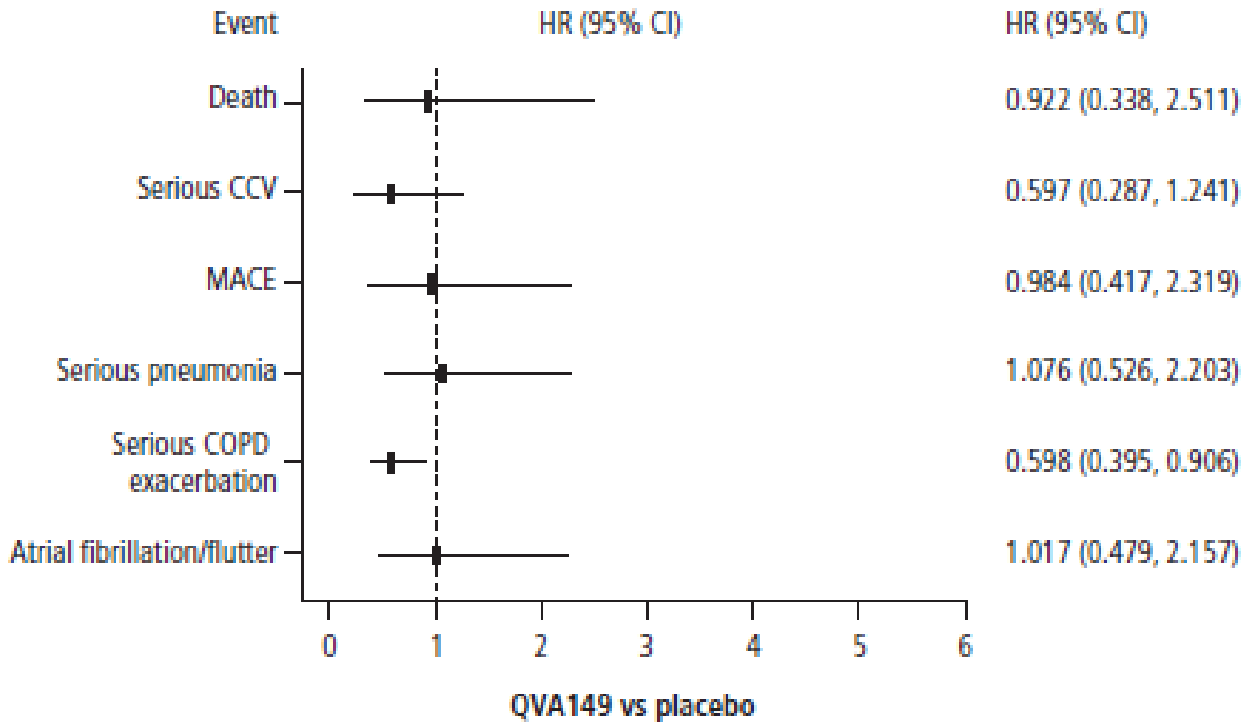
Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D
Eur Respir J* 2013, *in press

Airway pharmacological stenting



QVA149 does not increase the risk of cardio- and cerebro-vascular events, pneumonia and exacerbation events compared with placebo

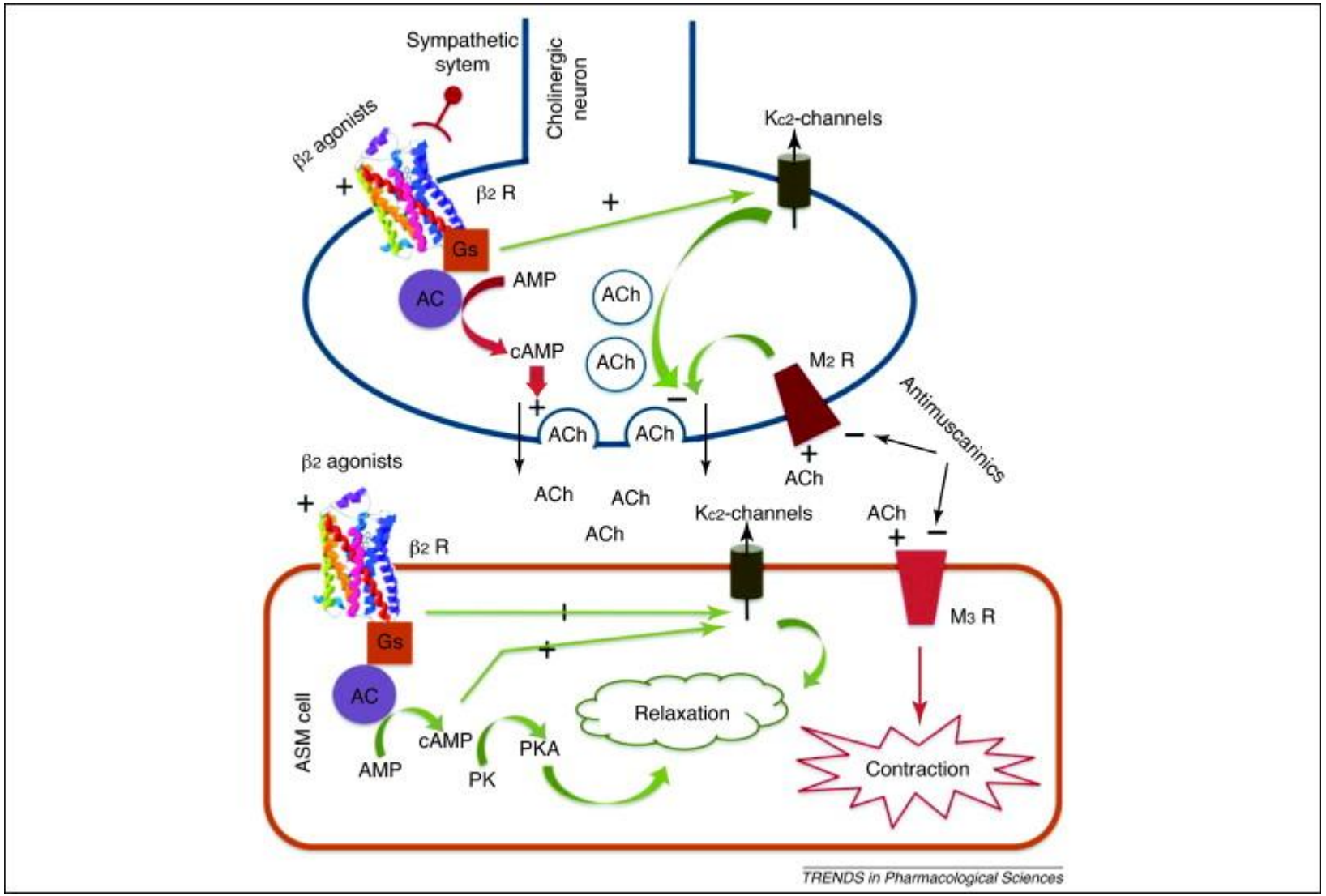
Figure 1. Forest plot of HRs for QVA149 110/50 µg (n=1,547) versus placebo (n=2,141) deaths, serious CCV events, MACE, serious pneumonia, serious COPD exacerbation and atrial fibrillation/flutter



MACE events included non-adjudicated events from the indacaterol and glycopyrronium studies, and adjudicated events from the QVA149 program; all atrial fibrillation/flutter events were adjudicated.
CCV=cardio- and cerebro-vascular; CI=confidence interval; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; MACE=major adverse cardiovascular events

Chen H, D'Andrea P, Banerji D. *ERS* 2013

LABA/LAMA COMBINATION



Matera MG, Page CV, Cazzola M. ***Trends Pharmacol Sci*** **32:495-506, 2011**

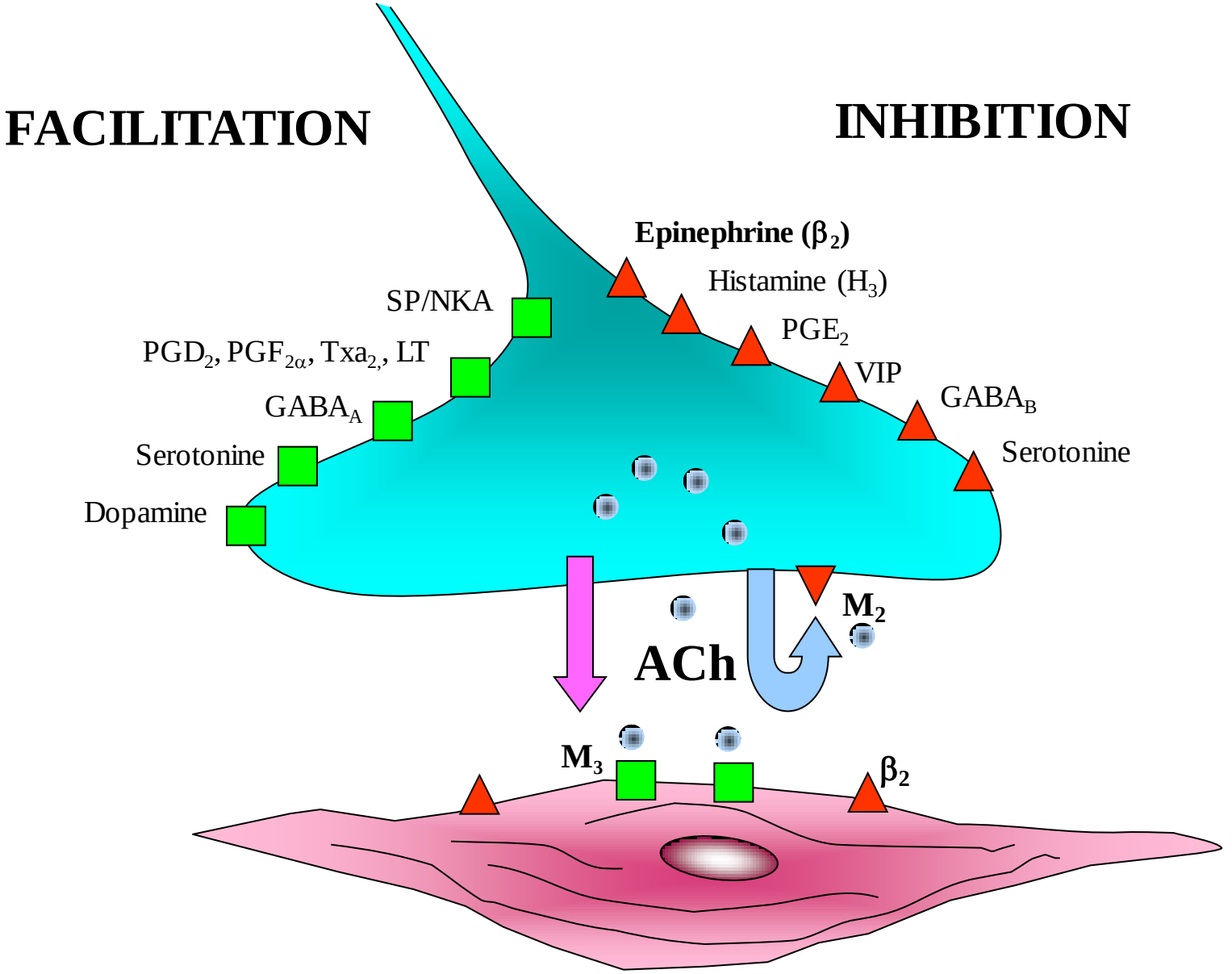
COPD is not a contraindication to beta-blockade

European Heart Journal (2008) 29, 2388–2442
doi:10.1093/eurheartj/ehn309

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

The majority of patients with HF and COPD can safely tolerate β-blocker therapy. Initiation at a low dose and gradual up-titration is recommended. Mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation. If symptoms worsen, a reduction of the dosage or withdrawal may be necessary. Selective β-blockade may be the preferable option.[188–190]


FACILITATION
INHIBITION
Epinephrine (β2)
Histamine (H3)
PGE2
VIP
GABAB
Serotonine
SP/NKA
PGD2, PGF2α, Txa2, LT
GABAA
Serotonine
Dopamine
M2
ACh
M3
β2

The main therapeutic characteristics of glycopyrronium

- **High kinetic selectivity** for M_3 muscarinic receptor (it means optimal bronchodilator efficacy and a low risk of cardiovascular adverse events, mainly due to blockade of muscarinic M_2 receptor).
- **Fast onset of the bronchodilator effect** (5' vs 30' when compared with tiotropium).
- **Maximal bronchodilation during the first 4 hrs after inhalation** (morning dyspnea relief).
- **Long duration of action** (24h): airway pharmacological stenting.
- **Improvement of all lung function parameters** (FEV_1, FVC, inspiratory capacity).
- **Symptomatologic improvement** (prolonged dyspnea and cough relief, decreased rescue medication, better health status).
- **Reduction of exacerbation rate.**
- **Favourable safety profile**, comparable with placebo.
- **Prolonged efficacy** without evidence of tolerance during 52 wks of treatment.
- **Ideal partnership** for therapies based on ultra-LABA/LAMA combinations.

Università Magna Græcia di Catanzaro
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