

COPD: 2009 Update

**American College of Osteopathic
Internists**

Tucson, Arizona

Stephen Rennard

University of Nebraska Medical Center

Disclosures (since 2007)

- **Consultancy:** Abbott, Able, Almirall, Altana, Anthera, APT, Aradigm AstraZeneca, BoehringerIngelheim, Britnall, COPD Forum, Defined Health, Dunn Group, Easton, Gerson, GSK, Infomed, Johnson and Johnson, KOL Connection, Leerink Swann, MedaCorp, Mpex, Novartis, Nycomed, Otsuka, Pfizer, Pharmaxis, Propagate, Pulmatrix, Quintiles, Roche, Scimed TargeGen, Theravance, UBS, Uptake, VantagePoint
- **Lecture fees:** ACCP, Adams, AstraZeneca, BoehringerIngelheim, Creative Educational Concepts, France Foundation, GSK, Network for Continuing Education, Novartis, Pfizer, Soma

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- **Physiology**
 - **Natural history**
 - **Clinical approach**
- **Systemic disease**
- **Treatments**

- **New directions**



GOLD Guidelines

Assess and Monitor Disease

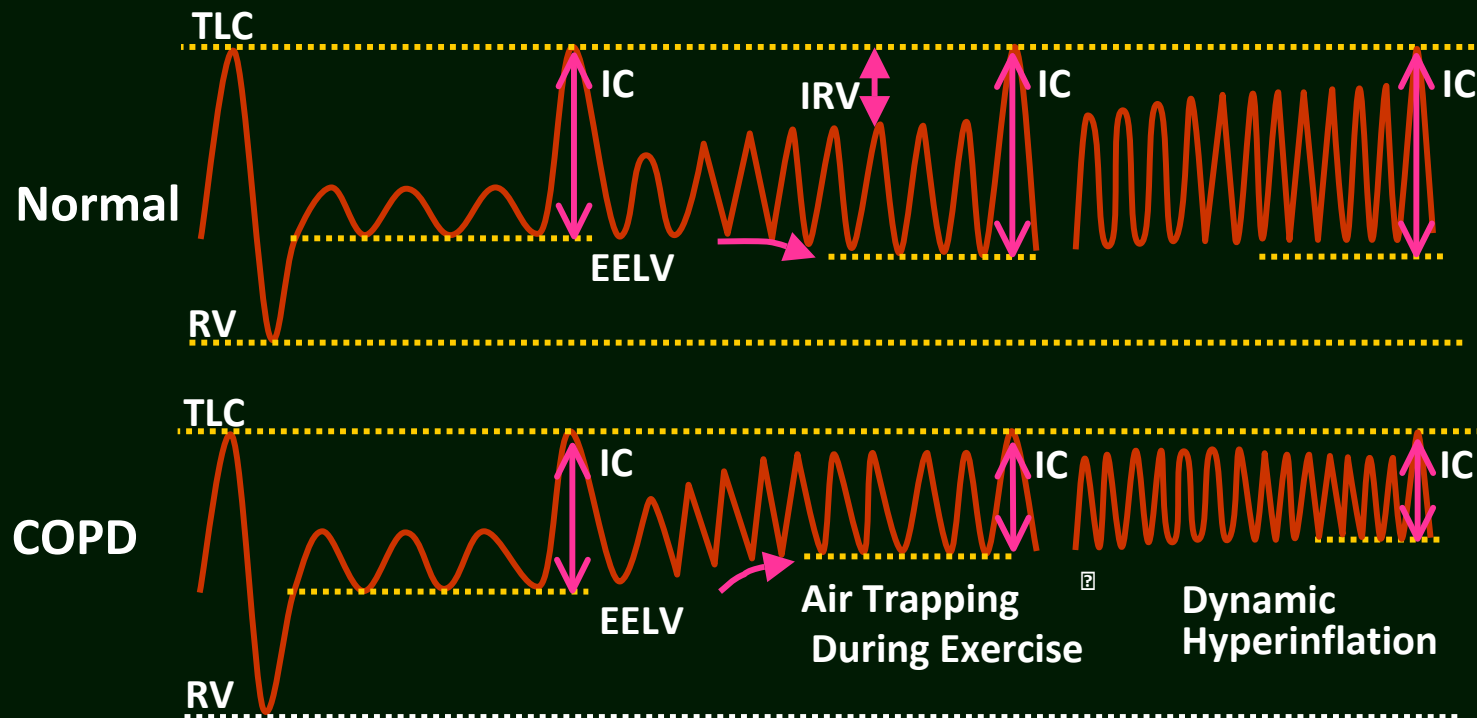


The GOLD Standard

CPT Codes for Spirometry

- **Spirometry** **94010**
- **Spirometry with bronchodilator** **94070**
- **Exercise test with spirometry
before and after**
94070

Hyperinflation: Increase in Lung Volume Due to Increased Expiratory Flow Limitation



Hyperinflation

- Limits inspiratory capacity¹
- Worsens with activity^{1,2}
- Increases work of breathing^{1,2}

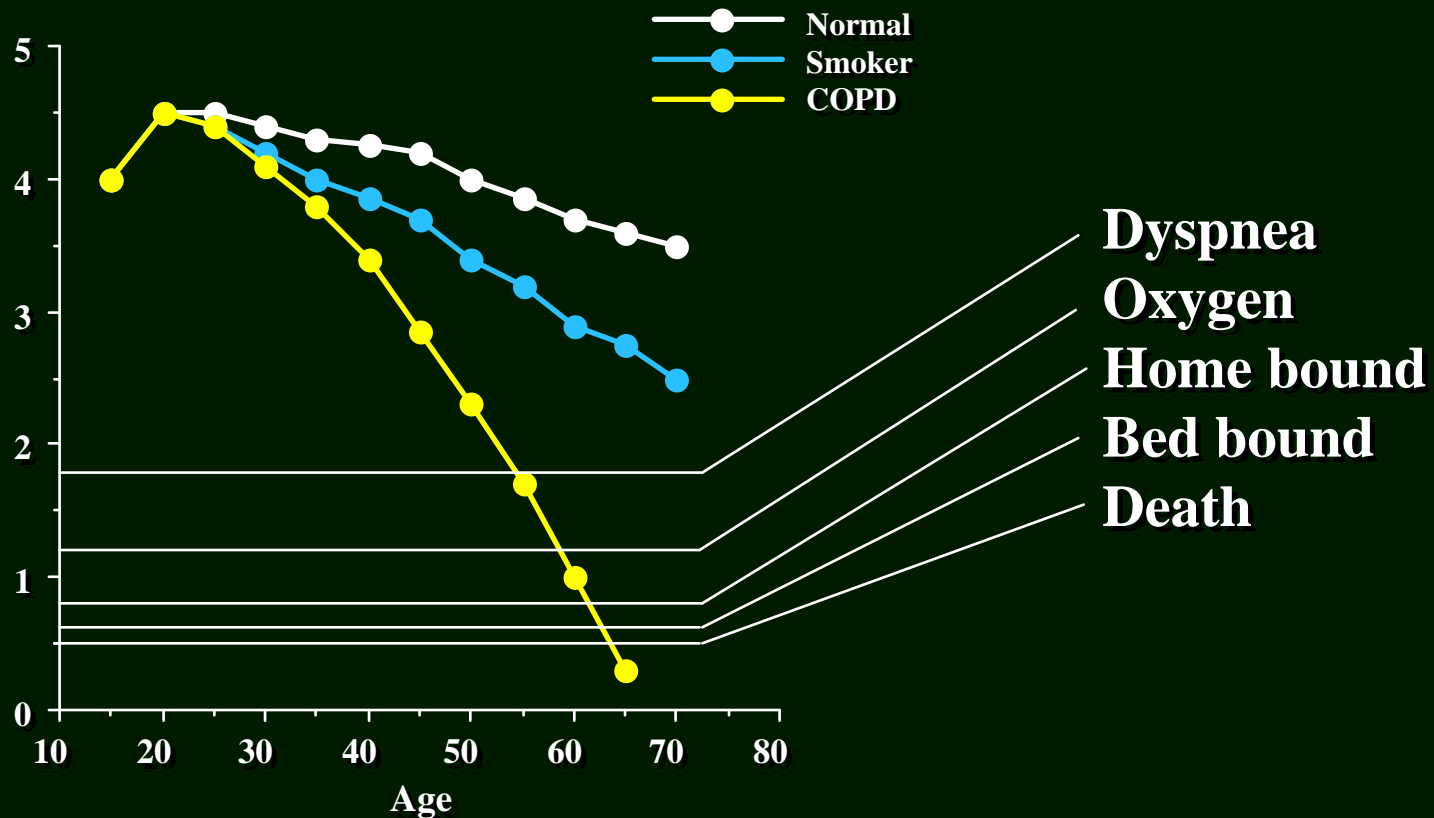
1. O'Donnell DE, et al. *Am J Respir Crit Care Med*. 2001;164:770-777.

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

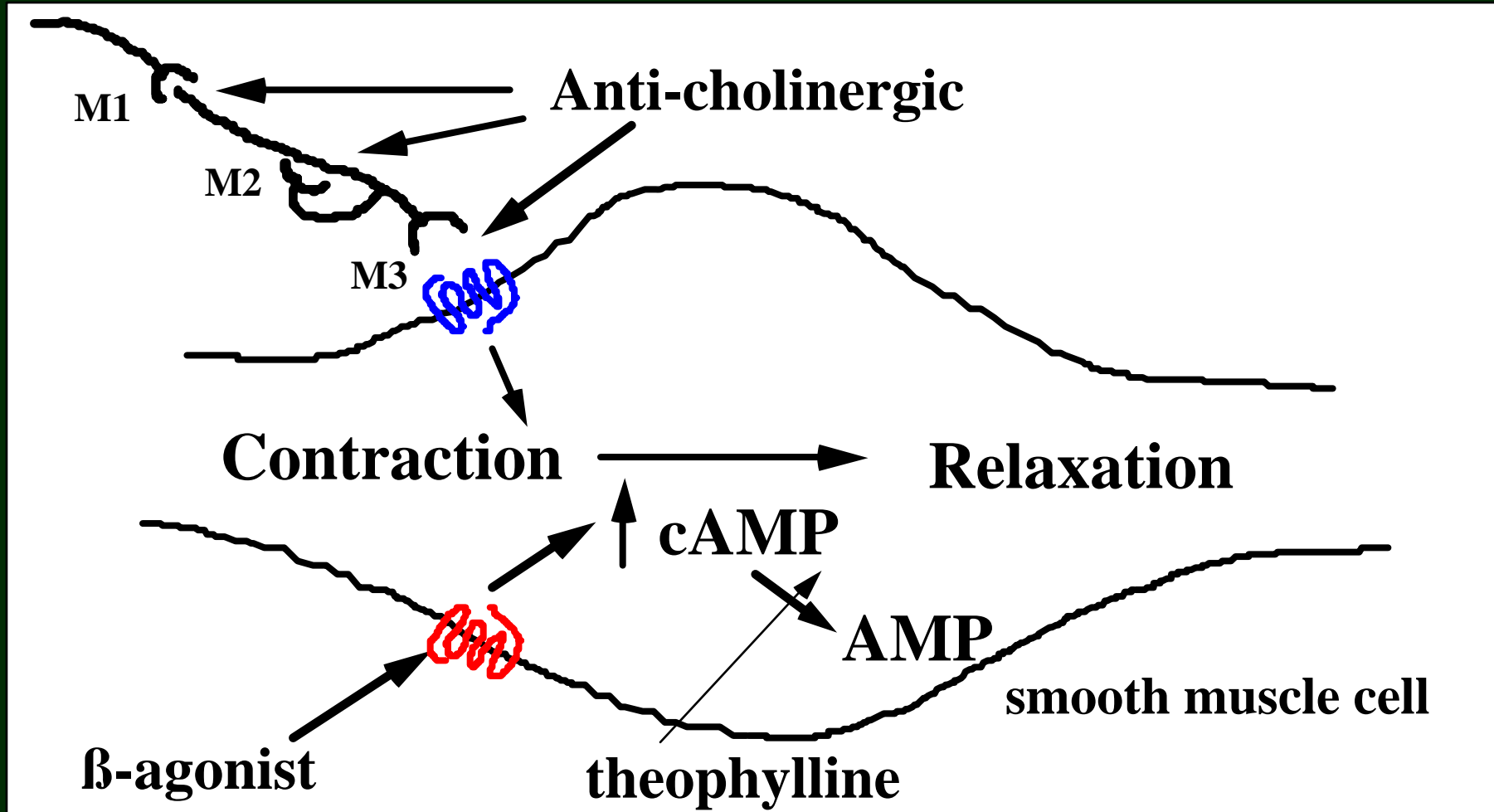
NATURAL HISTORY OF COPD

modified from Fletcher and Peto

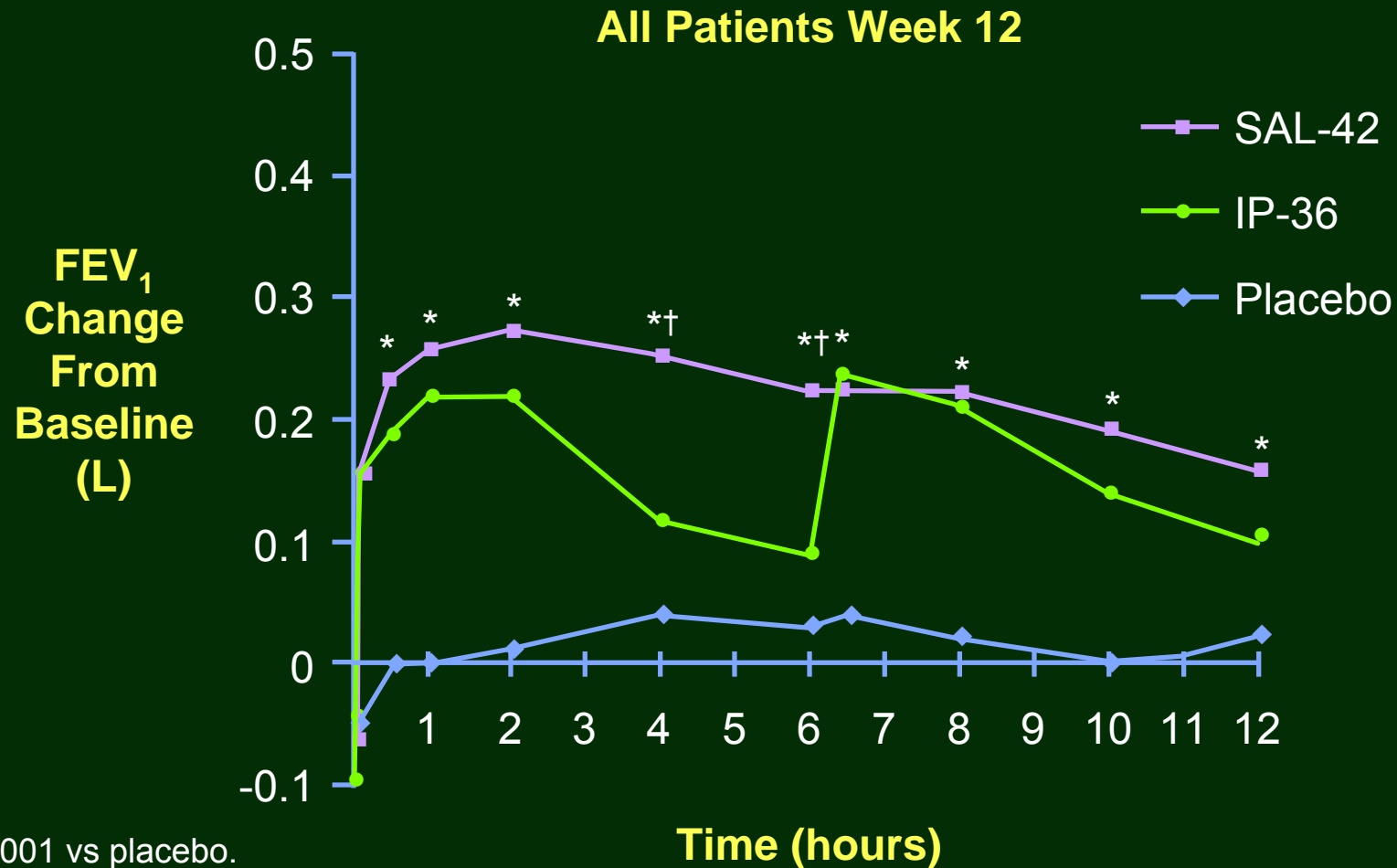
FEV-1 (liters)



BRONCHODILATORS: *mechanisms of action*



SALMETEROL OR IPRATROPIUM VS PLACEBO IN COPD: CHANGES IN PULMONARY FUNCTION



* $P=.001$ vs placebo.

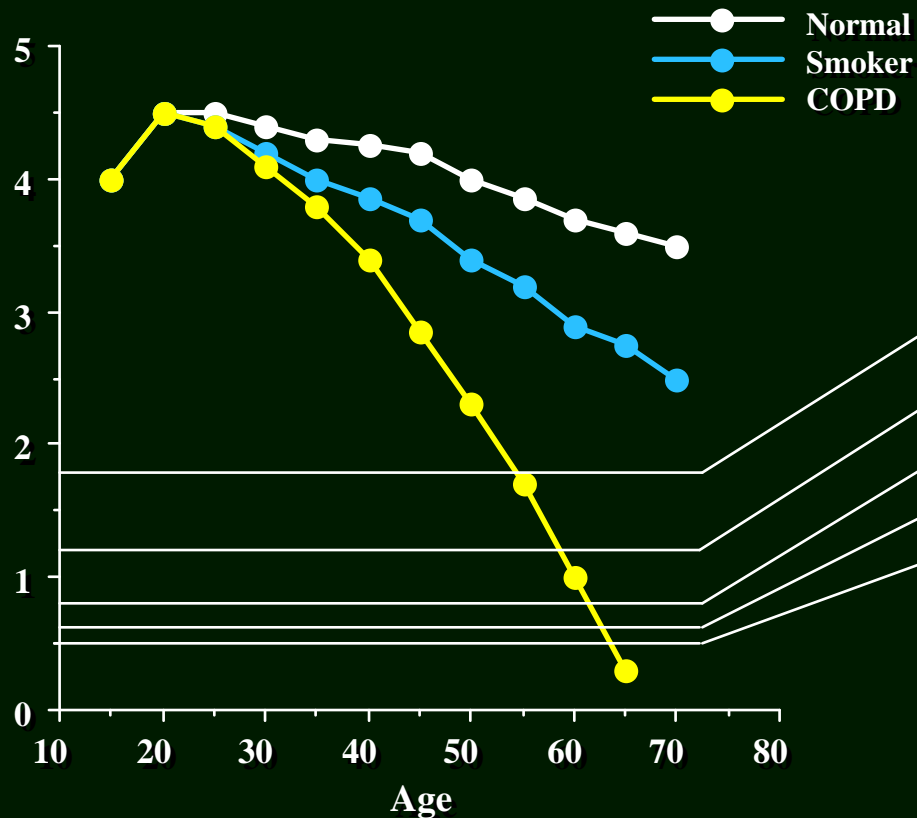
† $P<.001$ vs IP.

Adapted with permission from Mahler DA et al. *Chest*. 1999;115:957-965.

NATURAL HISTORY OF COPD

modified from Fletcher and Peto

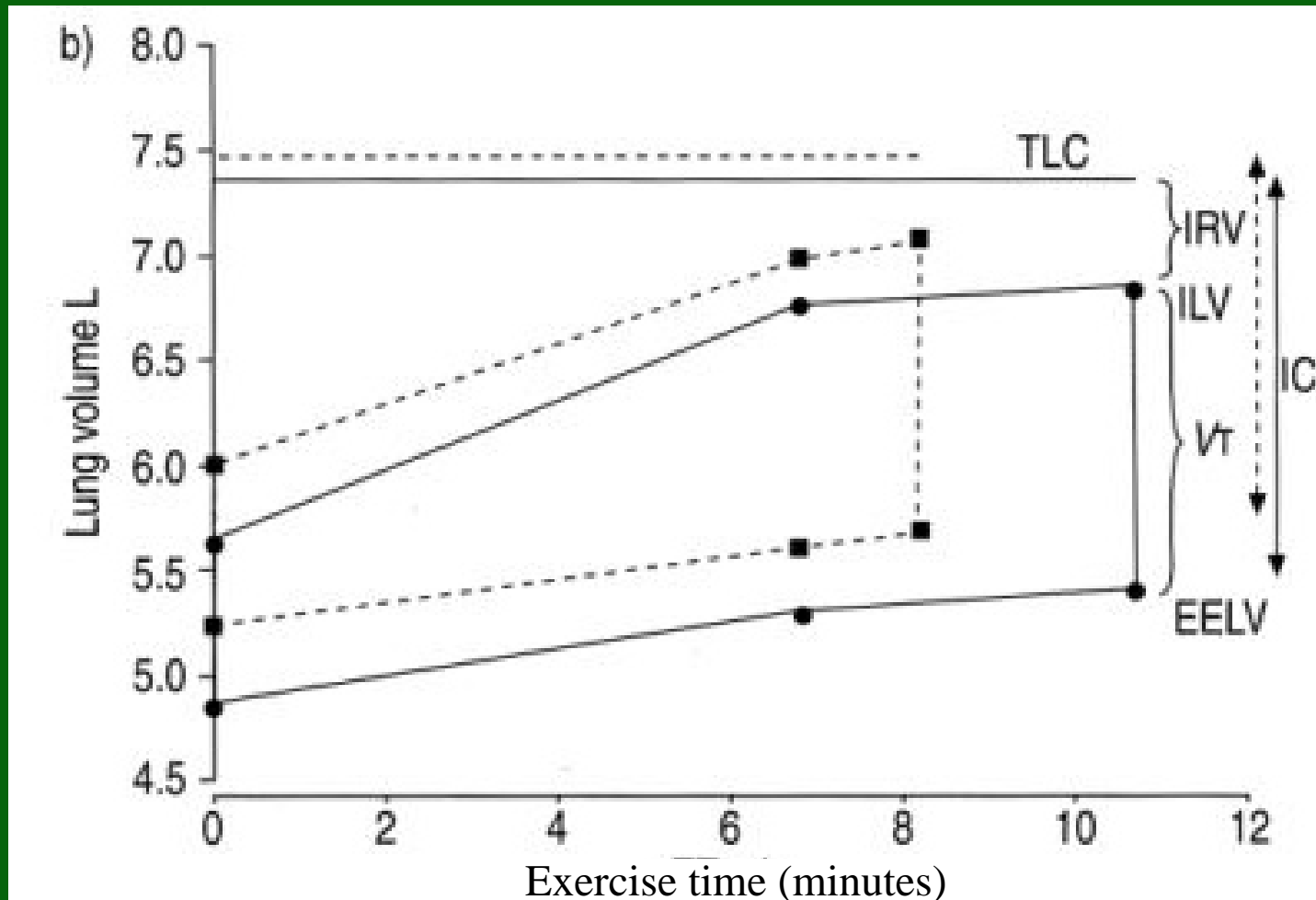
FEV-1 (liters)



Dyspnea
Oxygen
Home bound
Bed bound
Death

Effect of Tiotropium on Dynamic Hyperinflation

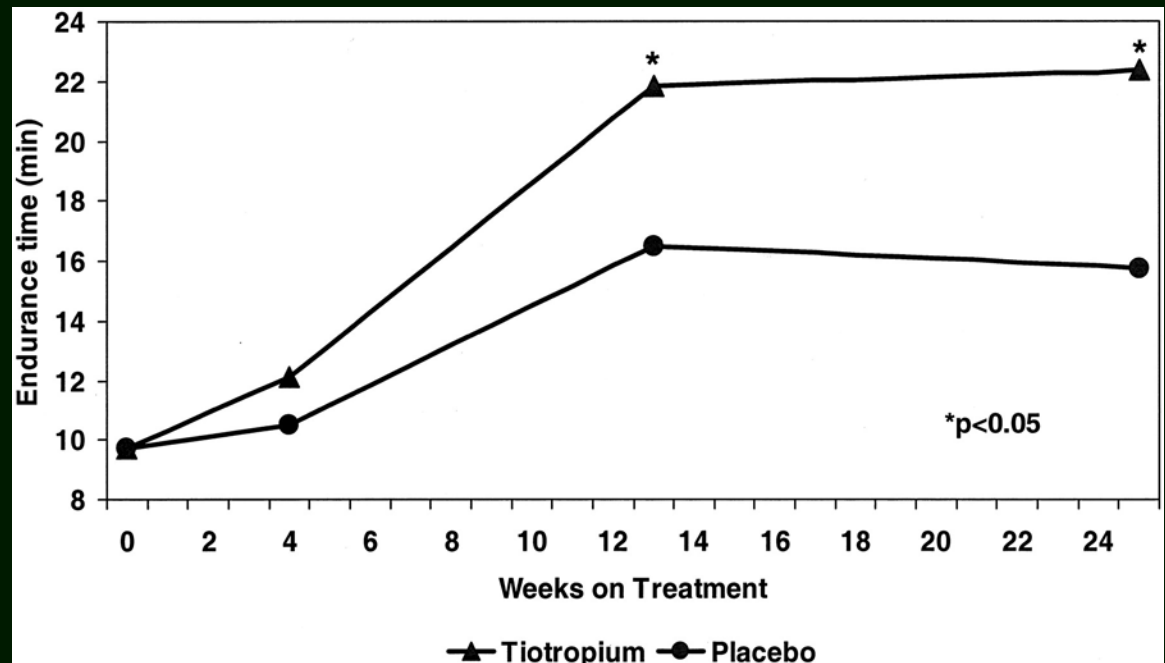
O'Donnell et al. 2004



Benefits of Combined Tiotropium and Pulmonary Rehabilitation

Casaburi et al. Chest 127: 809, 2005

- 91 COPD subjects
 - Tiotropium N=47
 - Placebo N=44
- Initiate therapy
- After 4 weeks, initiate rehabilitation
- Monitor
 - Exercise performance
 - Dyspnea
 - Health status (QoL)



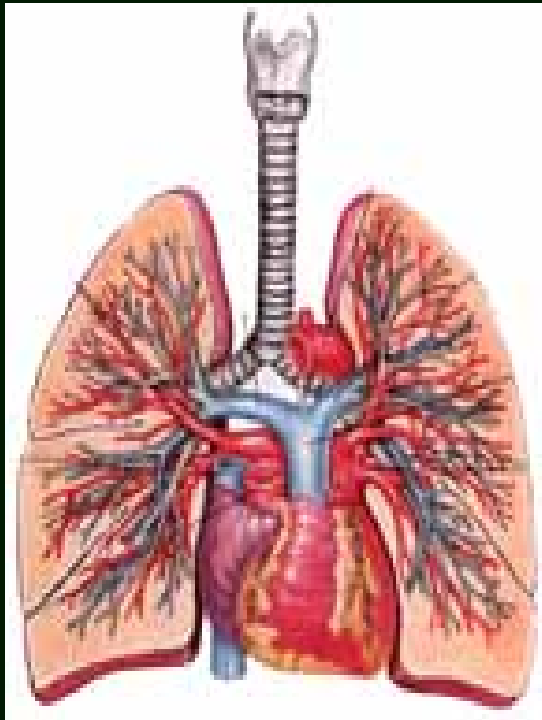
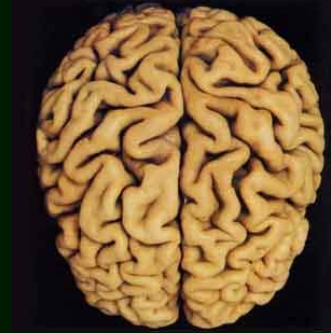
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Target organs

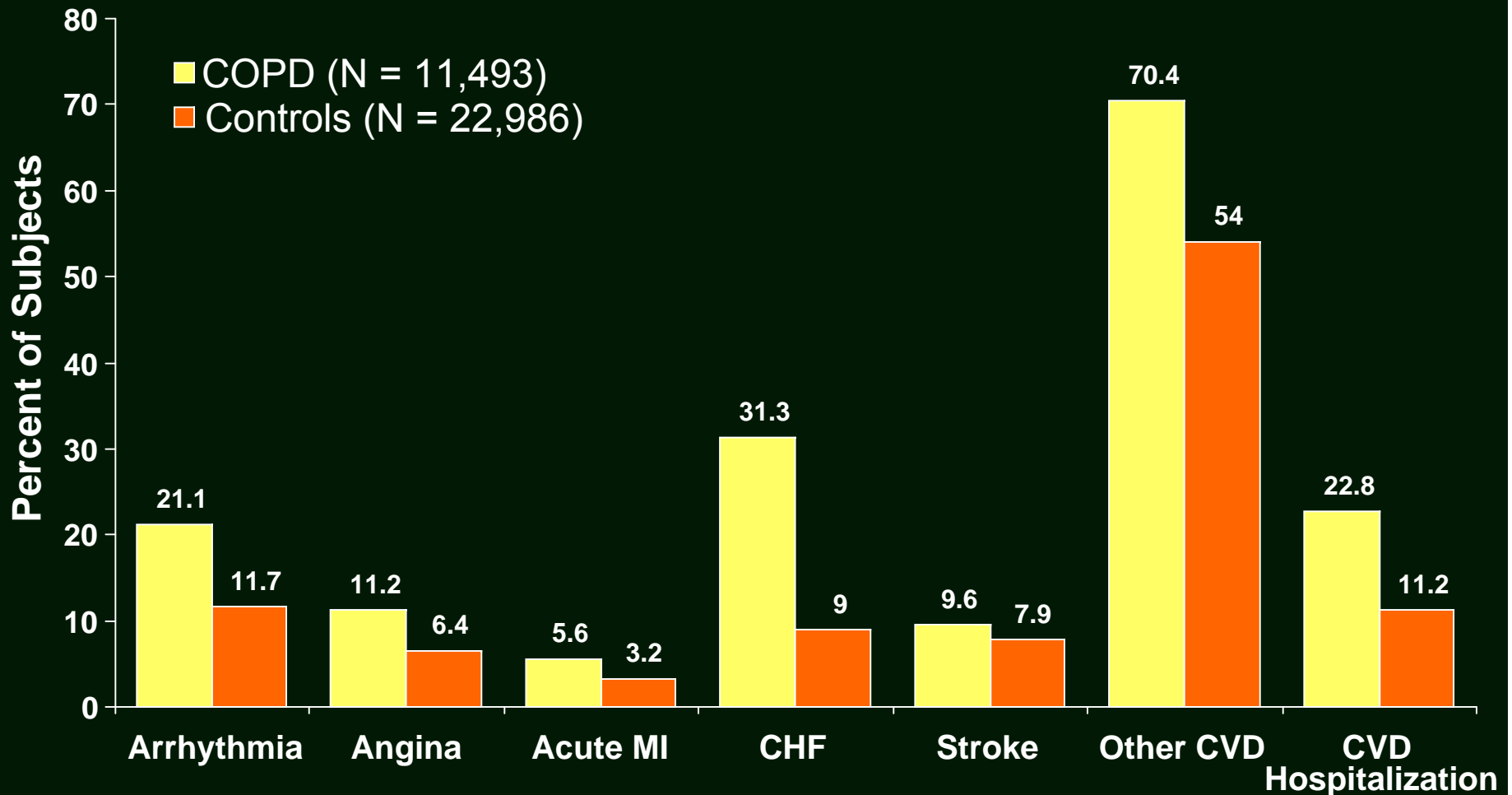
Respiratory system



**Systemic
inflammation**



Increased Risk for Cardiovascular Disease in COPD

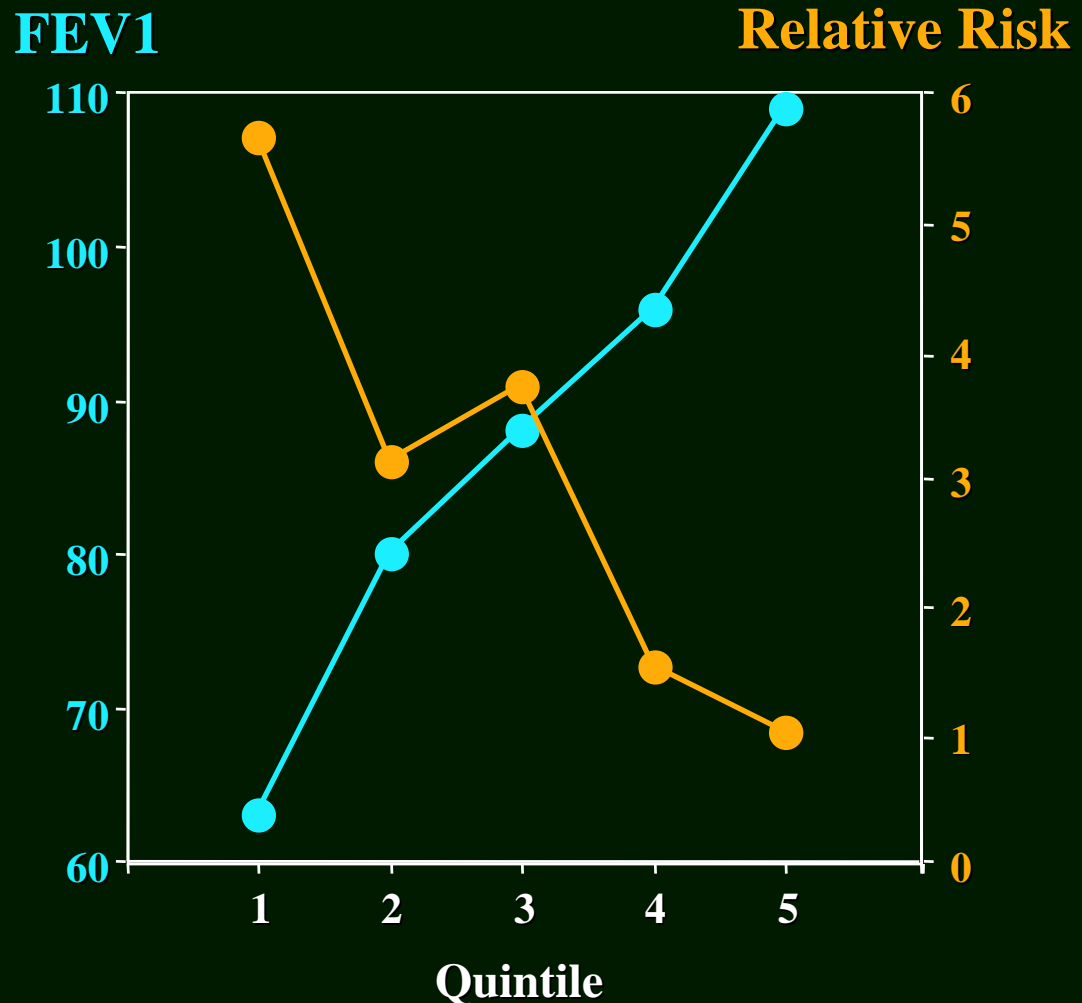


MI = myocardial infarction, CHF = congestive heart failure, CVD = cardiovascular disease;
All between-group differences $P < 0.05$ – adjusted for CV risk

Relationship of FEV1 to Cardiac Risk: *hospitalization or death*

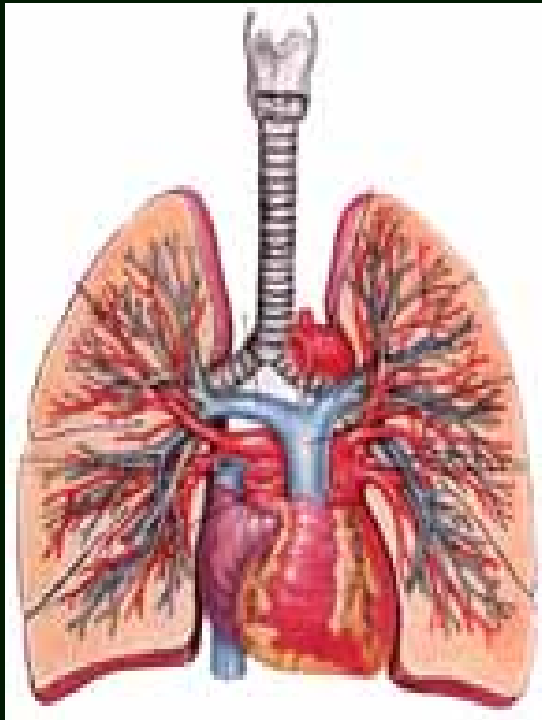
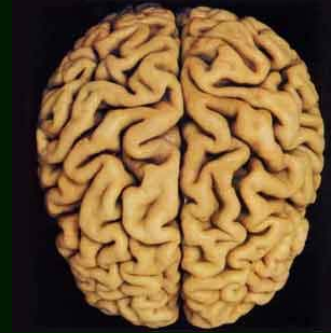
Sin et al. Chest 127: 1952, 2005

- NHANES follow up dataset
- Age 40-60
- 1861 subjects
- Assess cardiac events
- FEV1

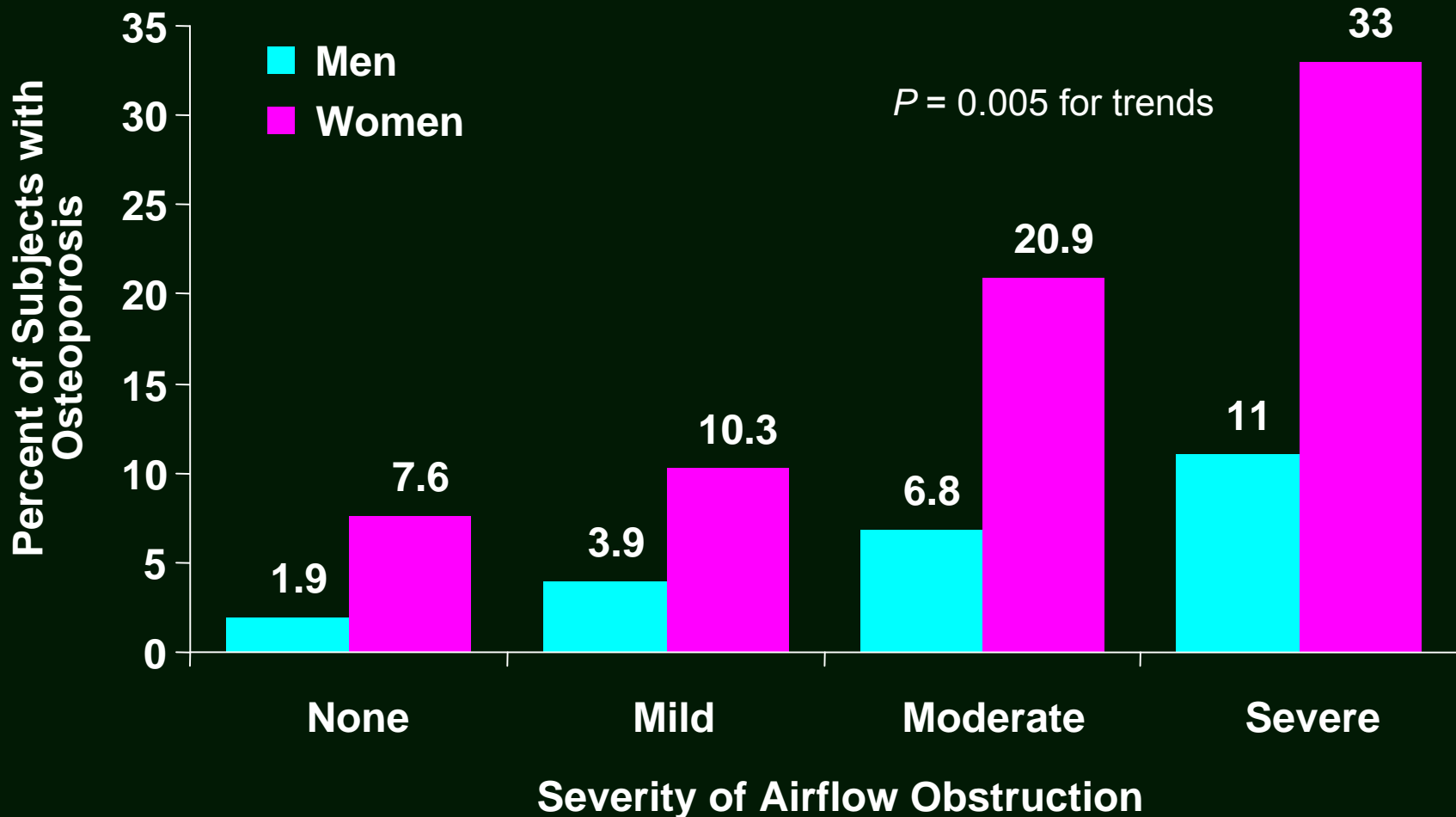


Target organs

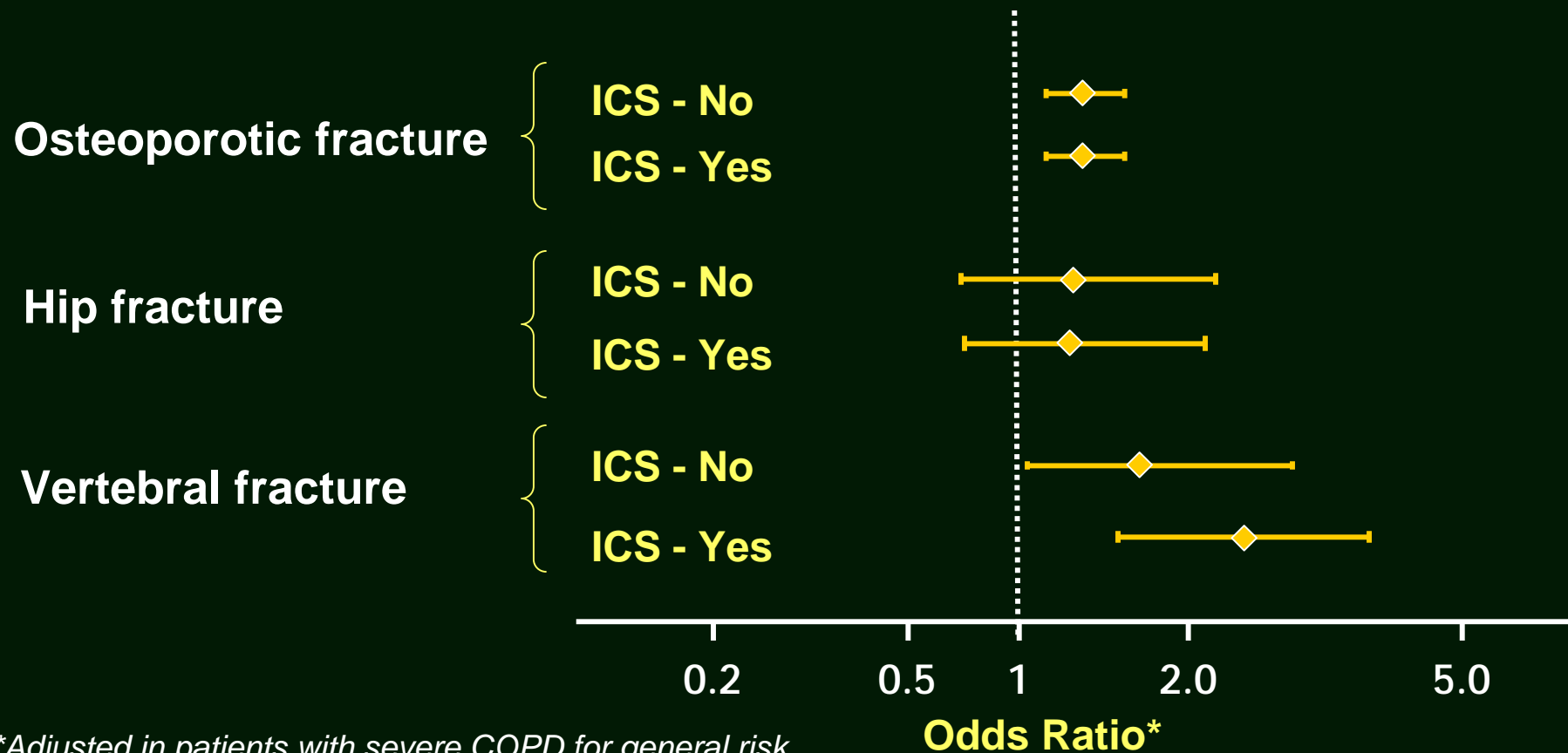
Respiratory system



The Risk of Osteoporosis in Caucasians With Obstructive Airways Disease



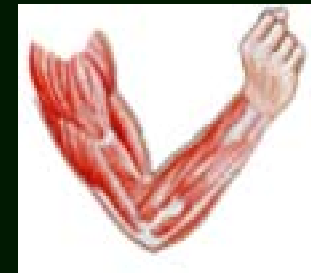
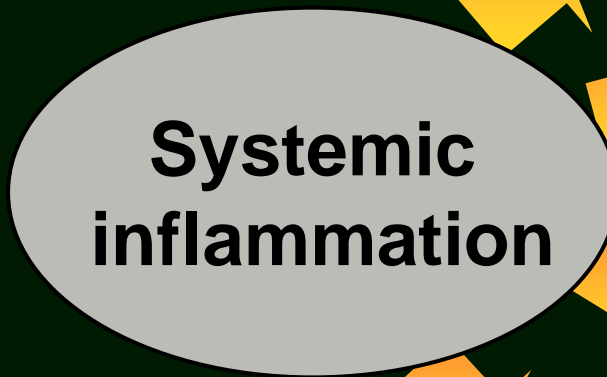
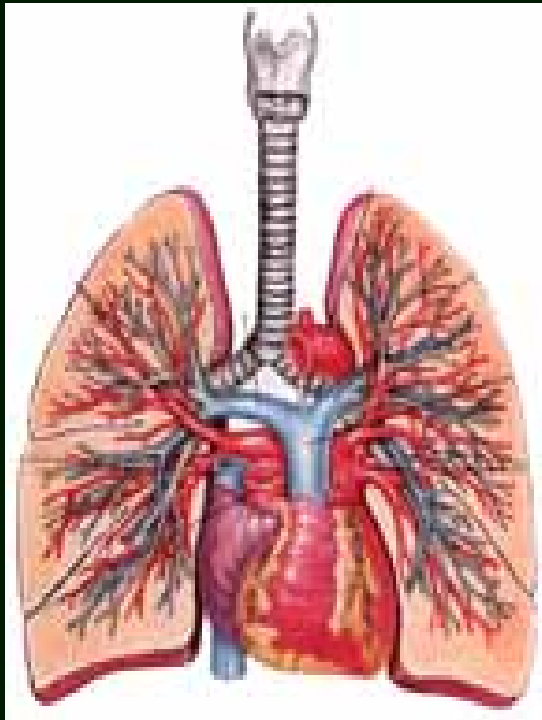
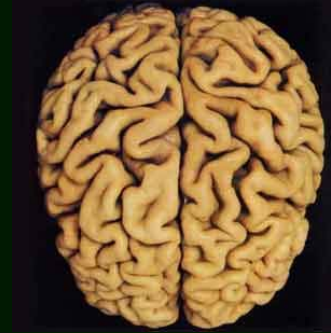
Severe Obstructive Airway Disease Is Associated With Greater Risk of Fracture



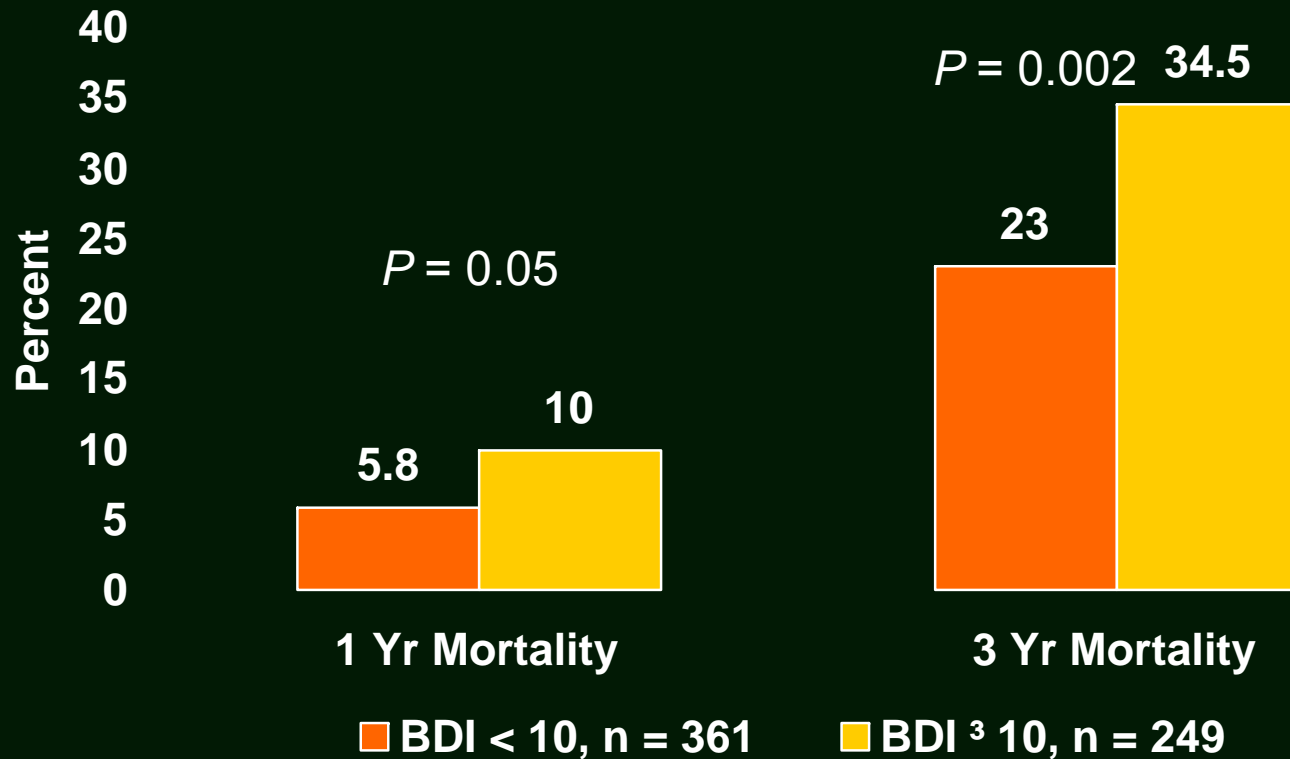
**Adjusted in patients with severe COPD for general risk factors, smoking status, duration of enrollment, and exposure to bronchodilators*

Target organs

Respiratory system



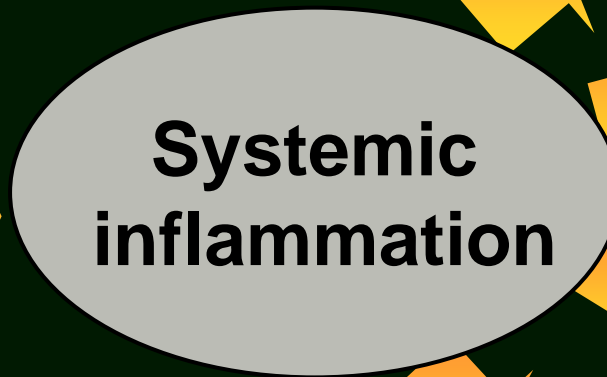
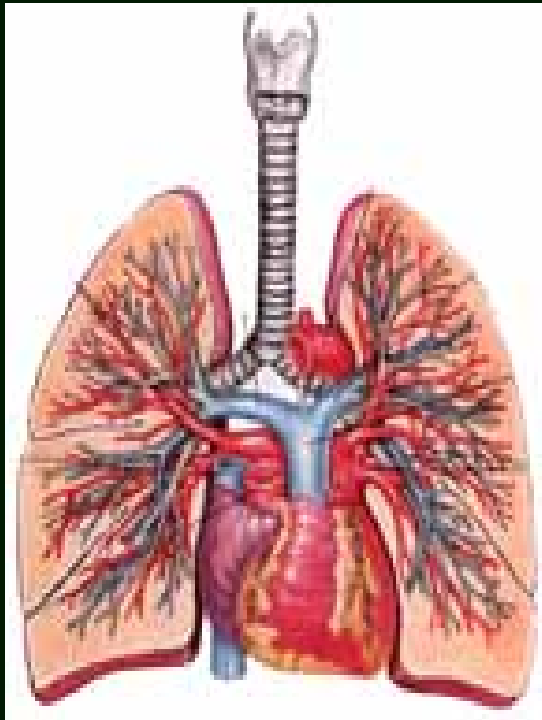
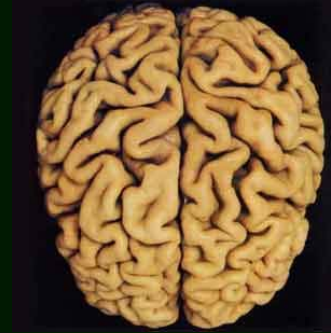
In NETT, 41% of Patients Were Depressed, and Depressed Patients Had Higher Mortality



BDI = Beck Depression Index; ≥ 10 = mild to moderate depression
Adjusted OR for mortality = 2.74 for BD ≥ 15 vs BD < 5

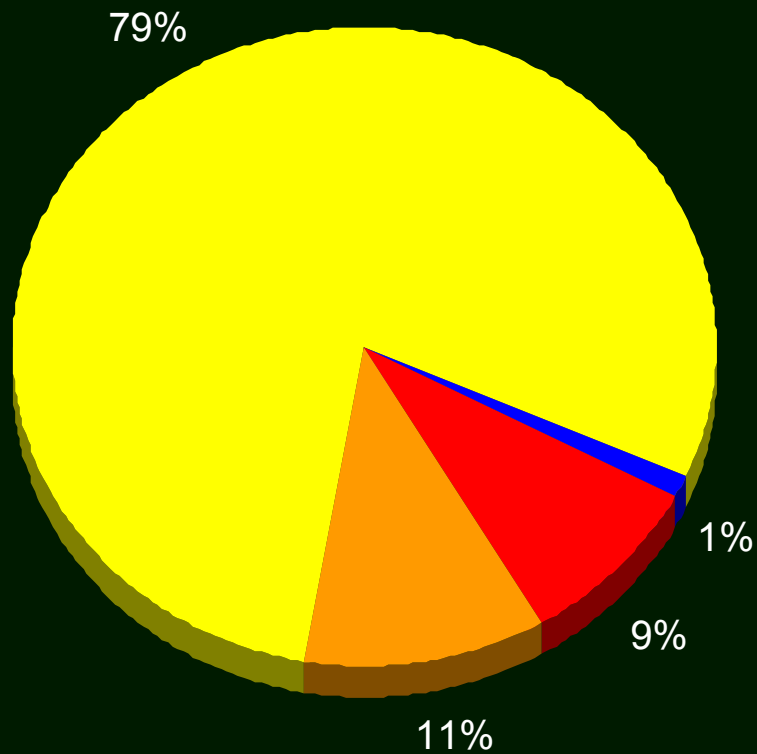
Target organs

Respiratory system

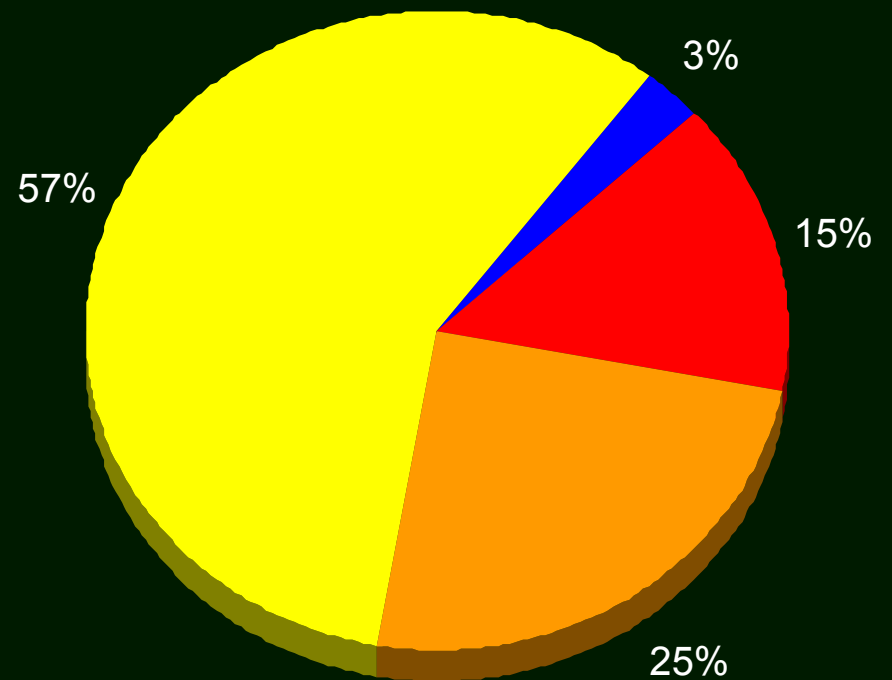


Body composition in COPD

Male



Female



Normal BMI and normal FFMI

low BMI and normal FFMI

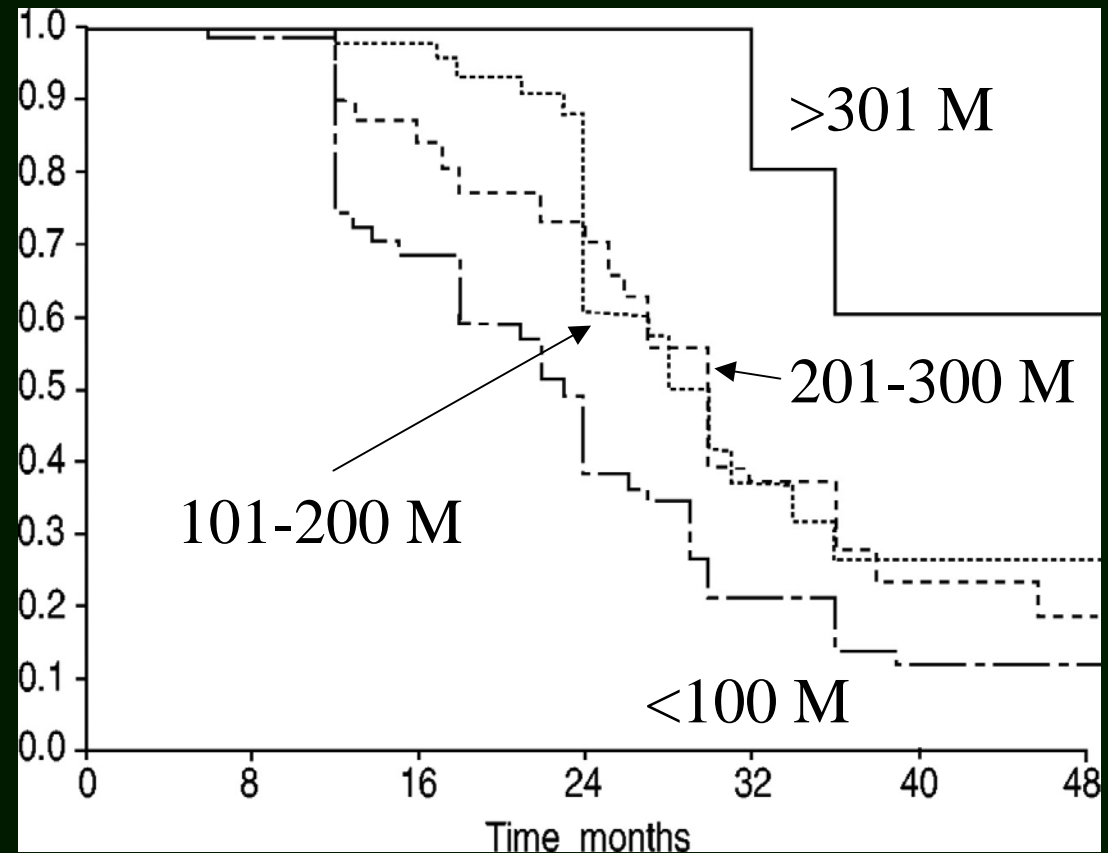
low BMI and low FFMI

Normal BMI and low FFMI

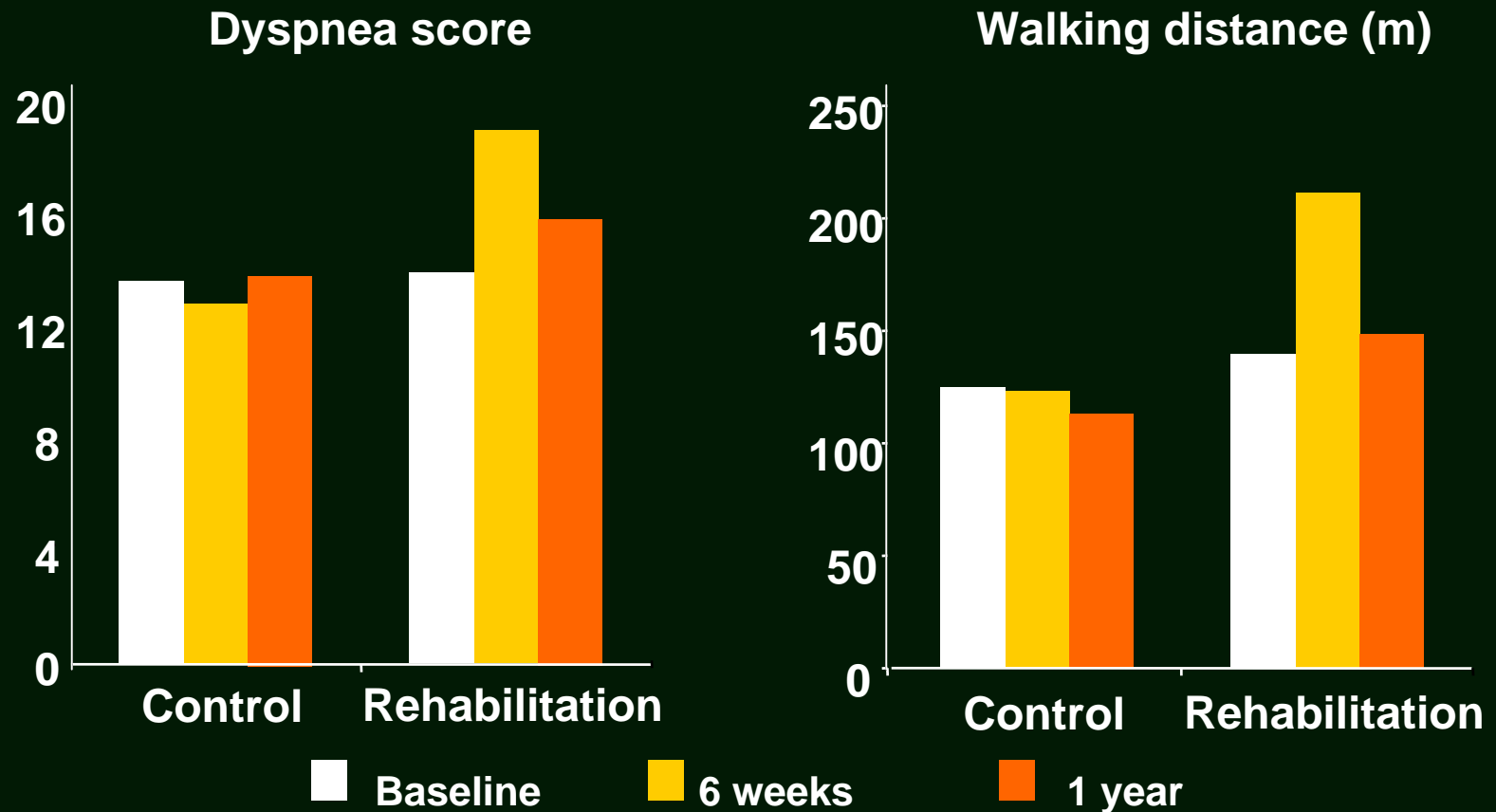
6-minute Walking Distance and Survival in COPD

Pinto-Plata et al. Eur. Resp. J. 23: 28-33, 2004

- **Subjects**
 - COPD N=198
 - Controls N=41
- **Assessments**
 - Lung function
 - Anthropometrics
 - 6-minute walk distance
- **Follow-up**
 - 2 years repeat
 - Survival



Efficacy of Pulmonary Rehabilitation



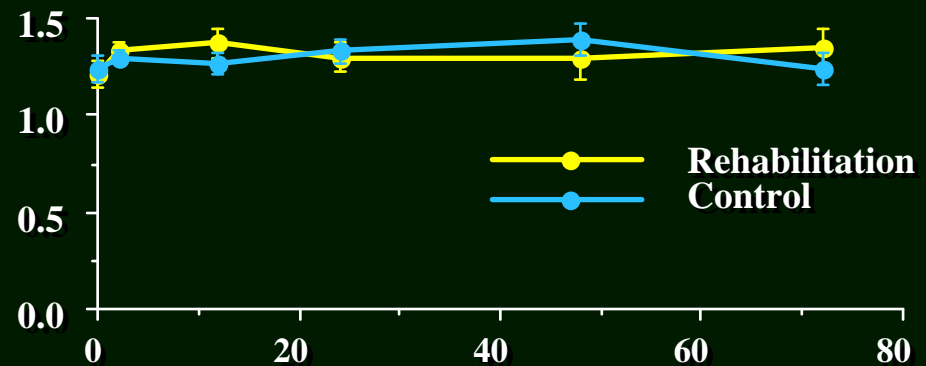
Griffiths TL, et al. *Lancet*. 2000;355:362-368.

BENEFITS OF A PULMONARY REHABILITATION PROGRAM

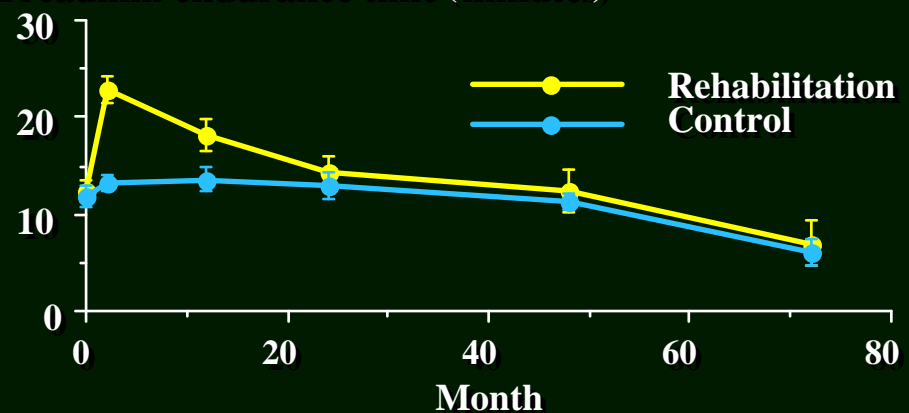
Ries et al. *Ann. Int. Med.* 122:823, 1995

- 128 COPD patients
- Randomize
 - education (control)
 - comprehensive rehabilitation
- Monitor
 - lung function
 - exercise
 - symptoms

FEV-1 (liters)



Treadmill endurance time (minutes)



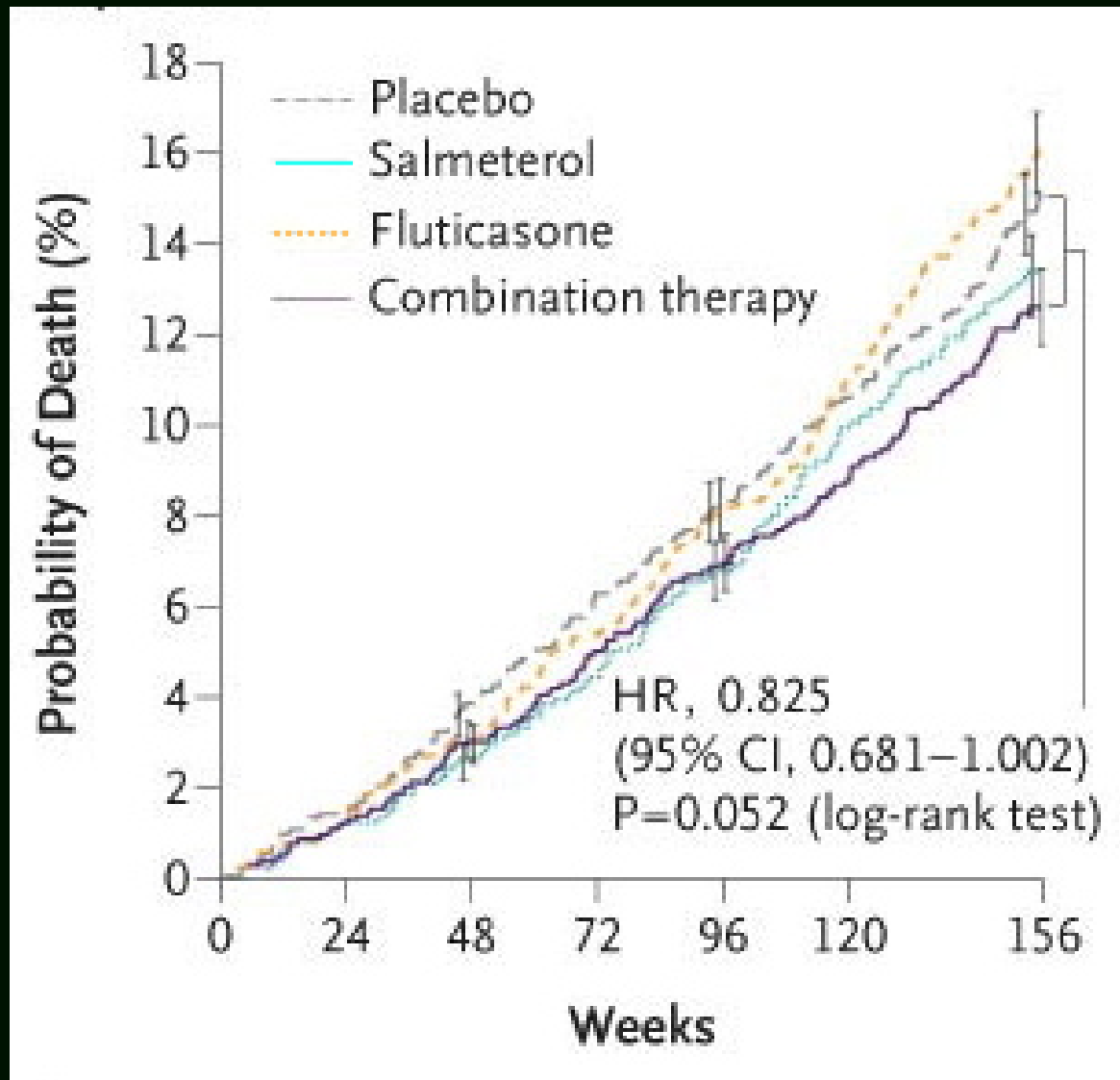
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TORCH

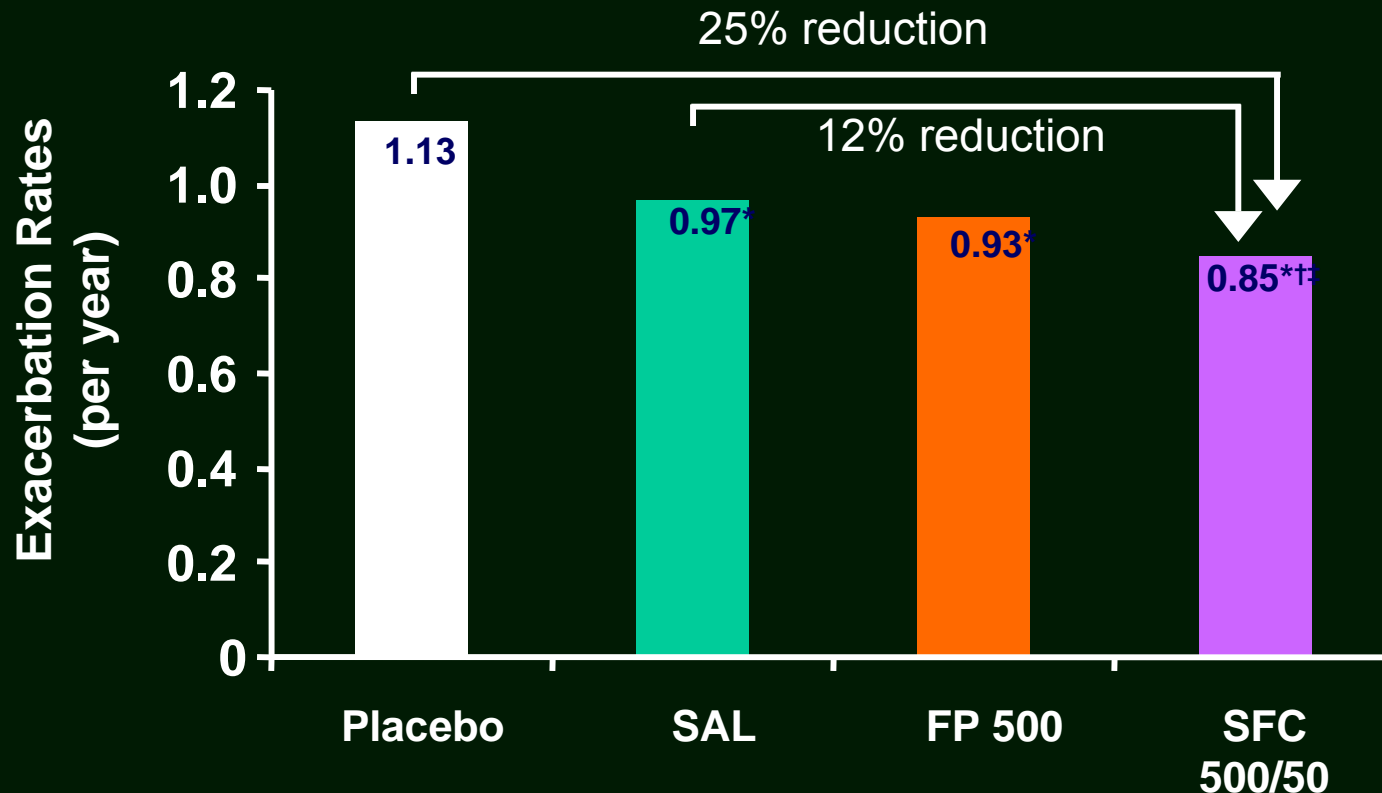
Calverley et al. *New Engl. J. Med.* 366: 775, 2007



TORCH

p = 0.052

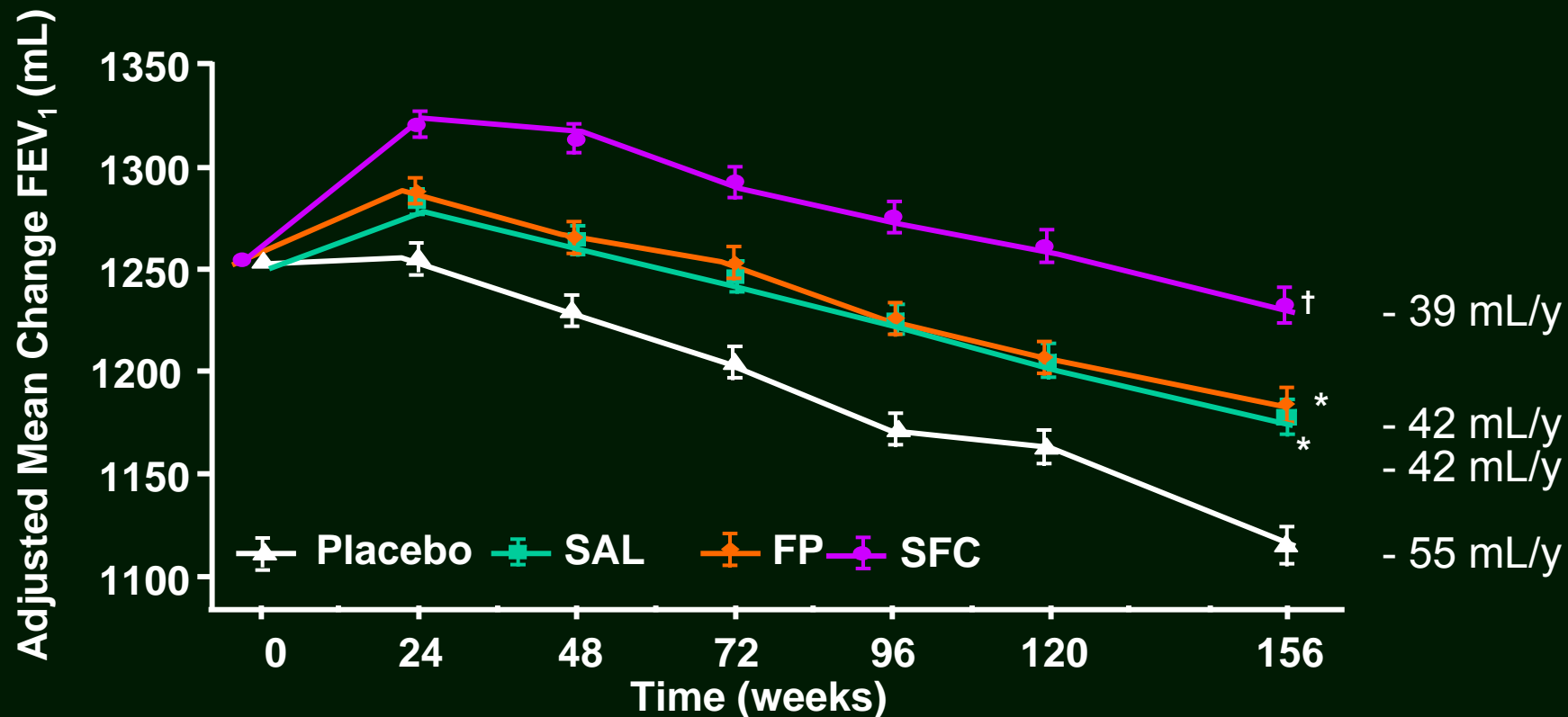
SFC 500/50 and Moderate-to-Severe COPD Exacerbations (Three-Year Data)



Exacerbations were defined as symptomatic deterioration requiring treatment with antibiotics or systemic corticosteroids (**moderate**), or hospitalization (**severe**)

* $P < 0.001$ vs placebo; † $P = 0.002$ vs SAL; ‡ $P = 0.024$ vs FP

Therapy Reduces the Rate of Decline of Post-bronchodilator FEV₁ (TORCH)

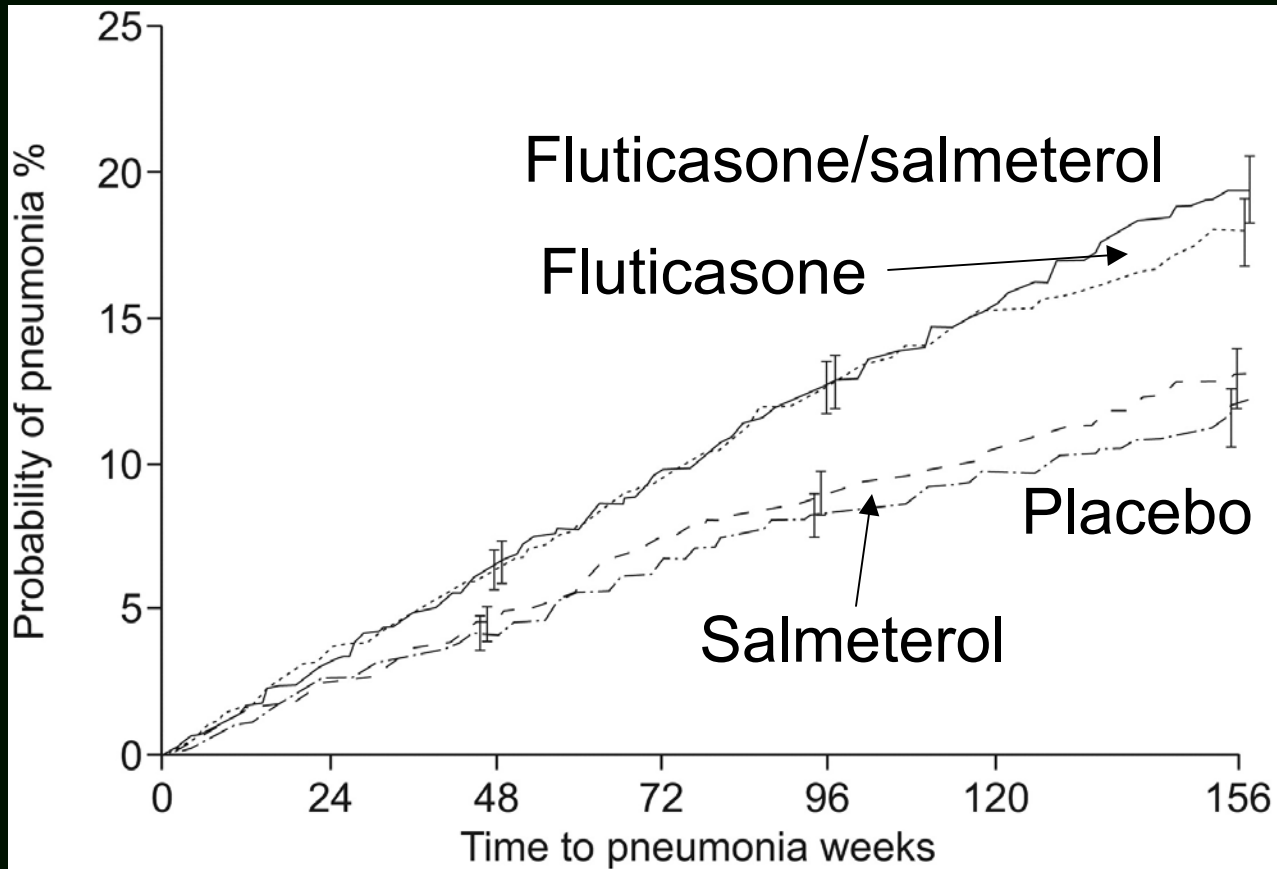


* $P = 0.003$ vs placebo

† $P < 0.001$ vs placebo

TORCH

Crim Eur. Resp. J. 34: 641, 2009



Patients n				
SFC	1546	1231	1034	631
FP	1552	1189	992	574
SAL	1542	1214	1024	645
P	1544	1117	947	587

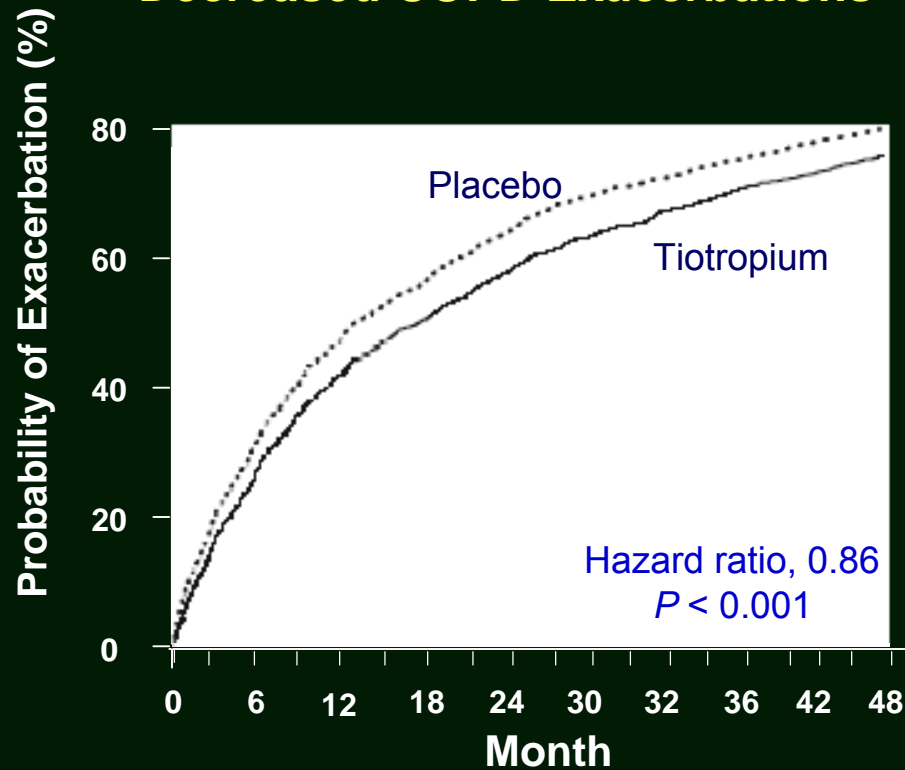
Rate of Decline of FEV₁ Compared to Previous Trials

Study (Duration) (order: year of publication)	Current smokers	Baseline FEV ₁ % predicted	Study drug	Annual decline in FEV ₁ (mL/year)		
				Study drug	Placebo only	Placebo* +
EUROSCOP (3 years)	100%	~ 79%	Budesonide	57	69	-
ISOLDE (3 years)	36 – 39%	~ 50%	Fluticasone	50	59	-
LHS II (3.3 years)	90%	~ 68%	Triamcinolone	44	47	-
BRONCUS (3 years)	41- 51%	~ 57%	NAC	54	47	-
TORCH (3 years) post hoc analysis	43%	~ 48%	S / F / SFC	42 / 42 / 39	55	-
UPLIFT (3 years)	30%	~ 47%	Tiotropium	37	-	42
UPLIFT (4 years)	30%	~ 47%	Tiotropium	40	-	42

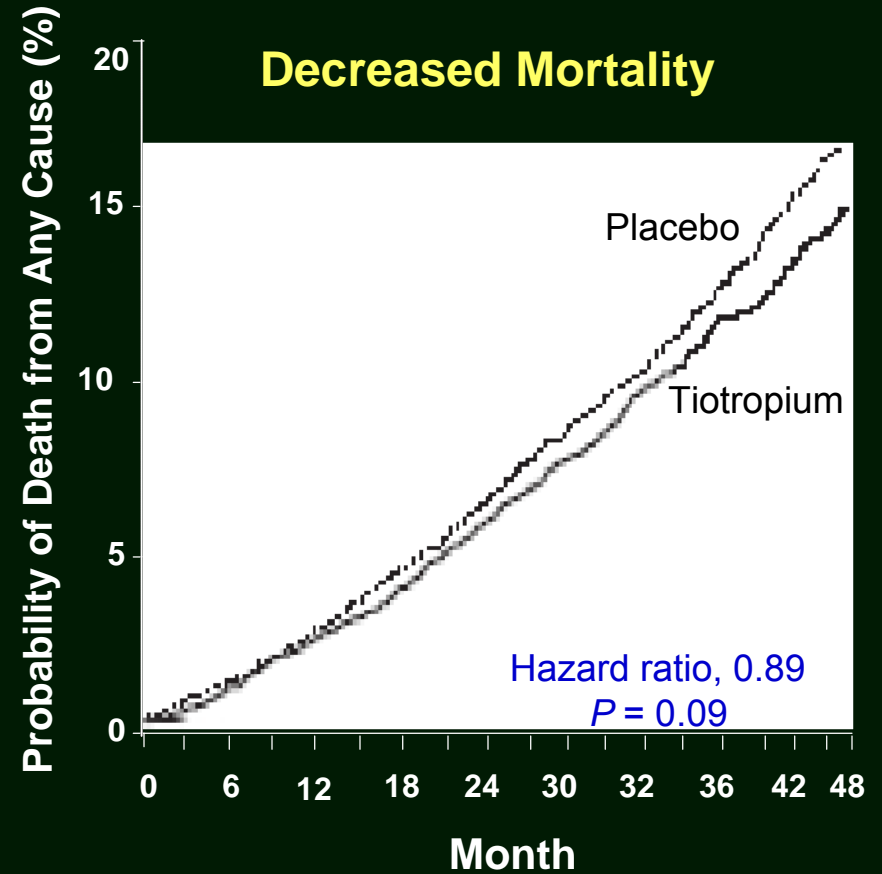
* All respiratory medications permitted throughout the trial,
other than inhaled anticholinergics

UPLIFT: Tiotropium Effects

Decreased COPD Exacerbations



Decreased Mortality



Recent Lessons from BIG COPD Studies

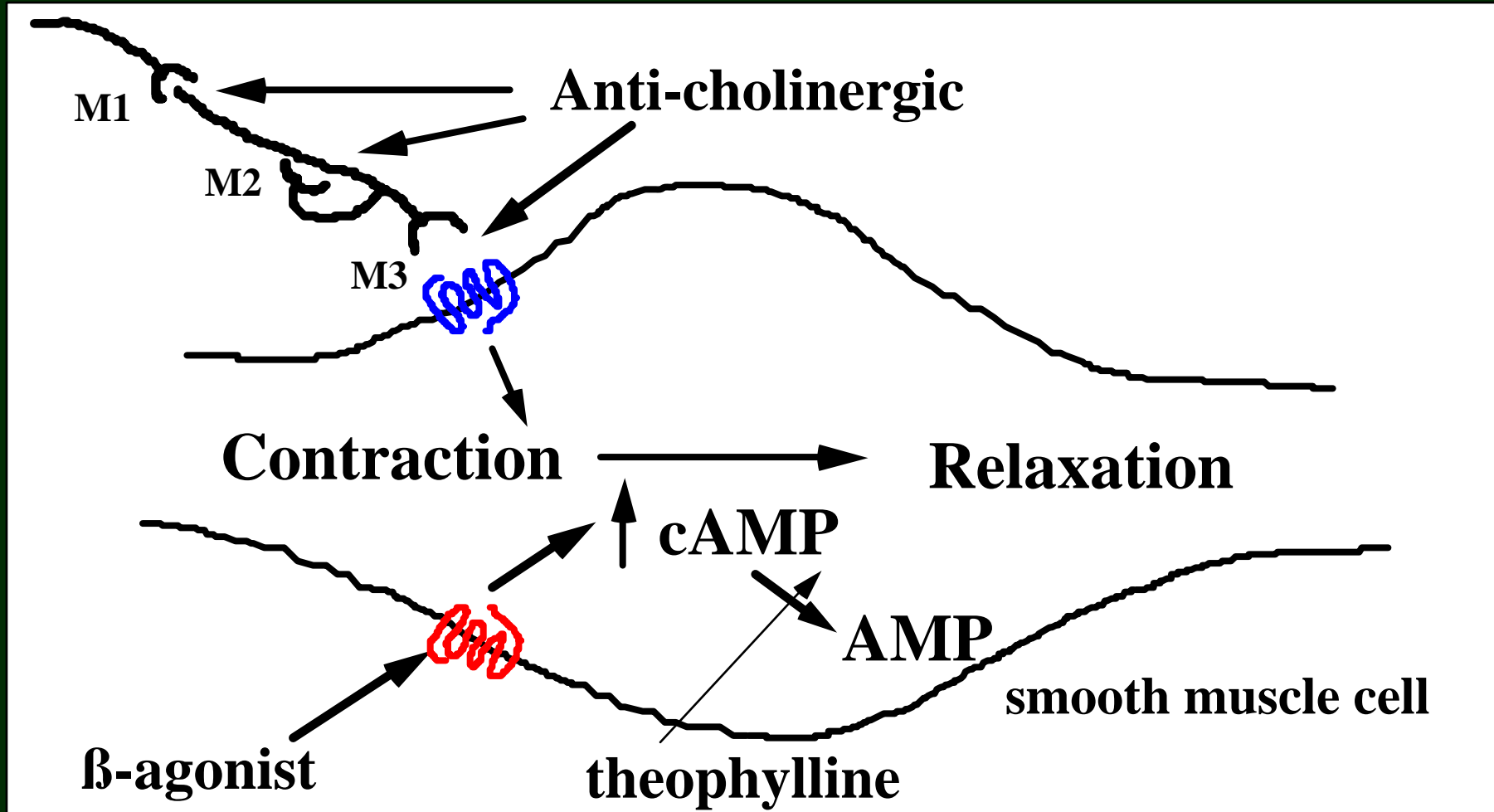
- Reduce exacerbations
- Improve lung function decline (?important)
- Non-significant numerical reduction in mortality
- No issues with mortality/stroke (tiotropium/UPLIFT)
- Pneumonia (fluticasone)

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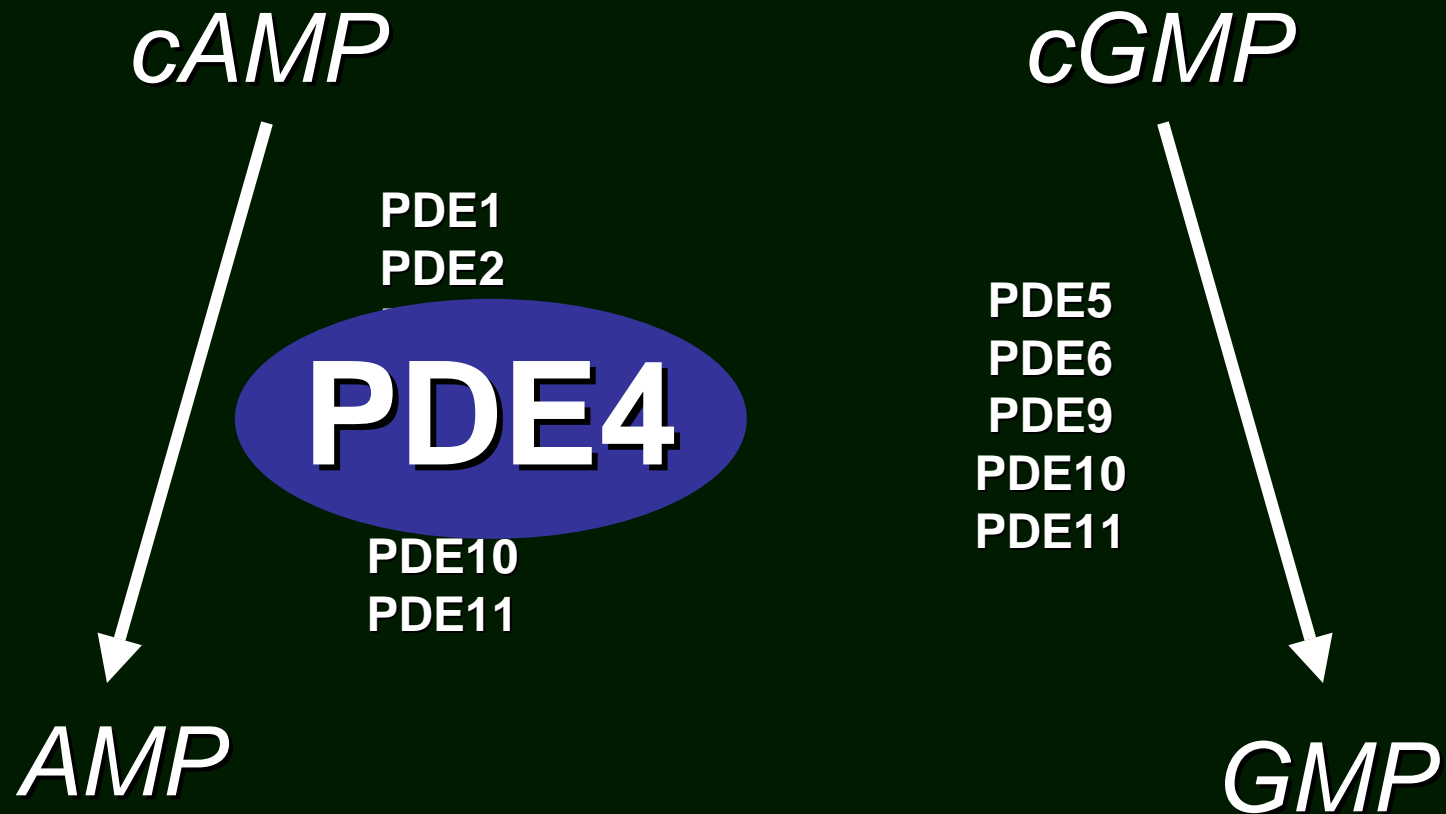
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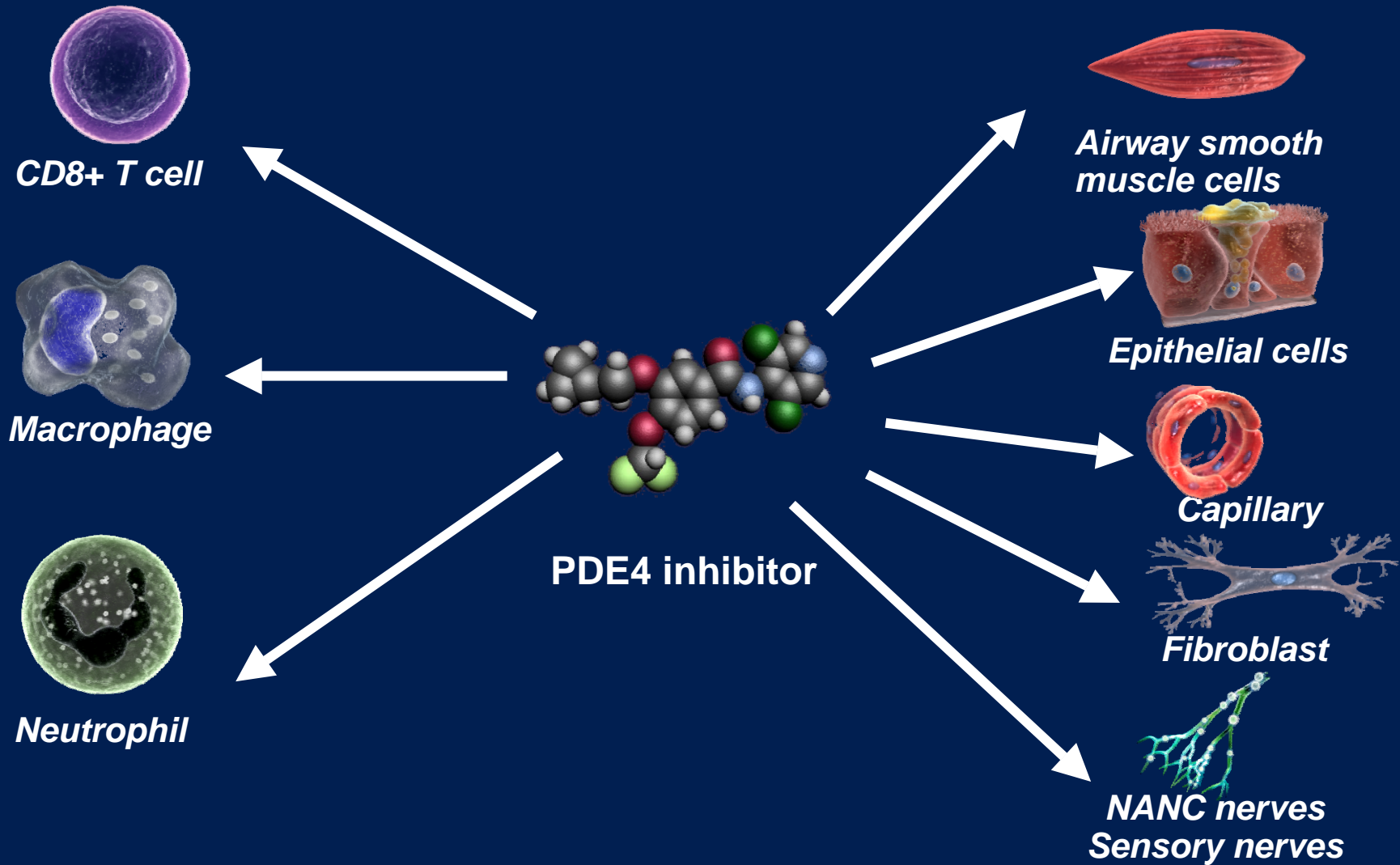
BRONCHODILATORS: *mechanisms of action*



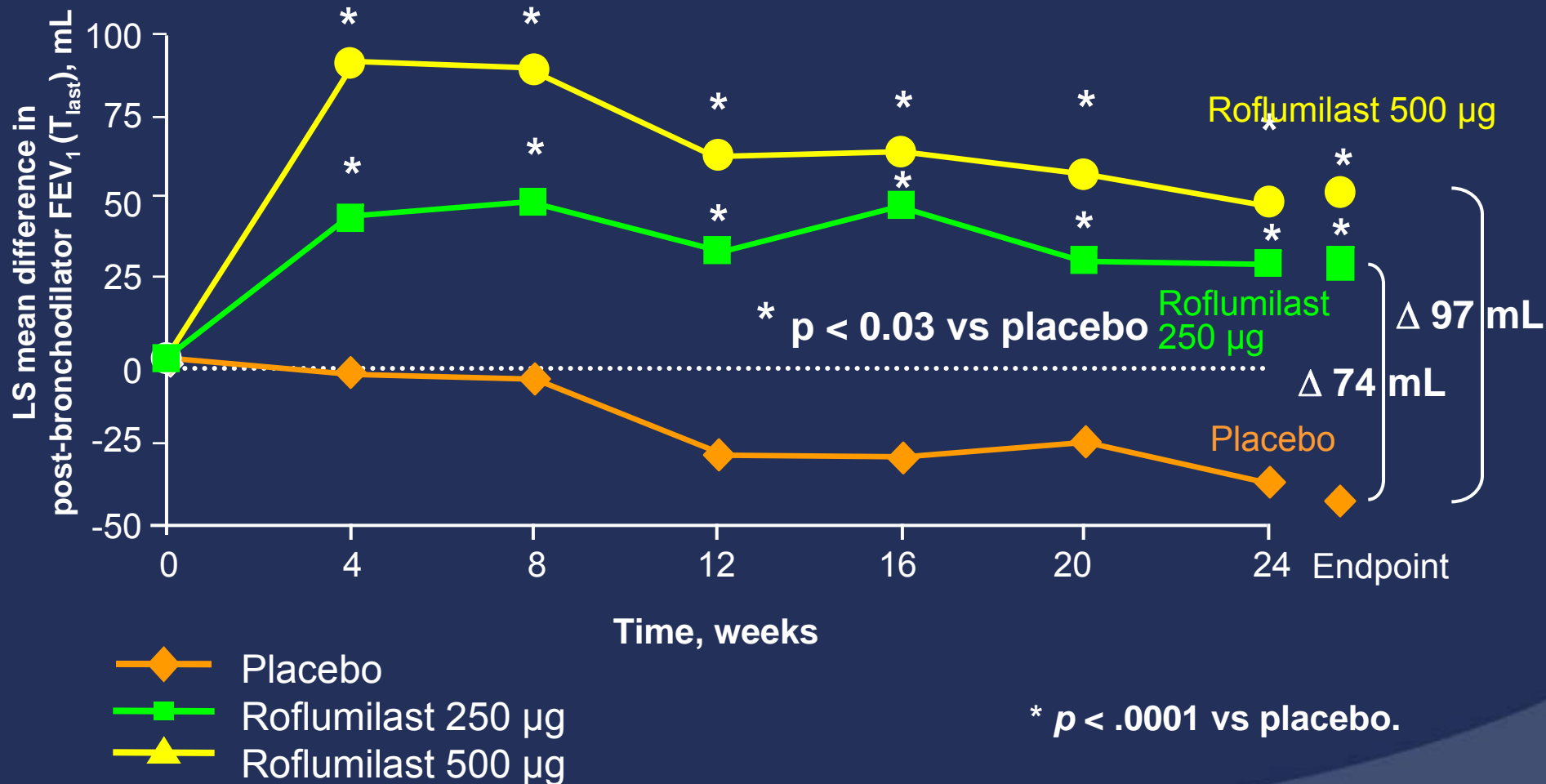
Phosphodiesterases



PDE4 Inhibitors in COPD



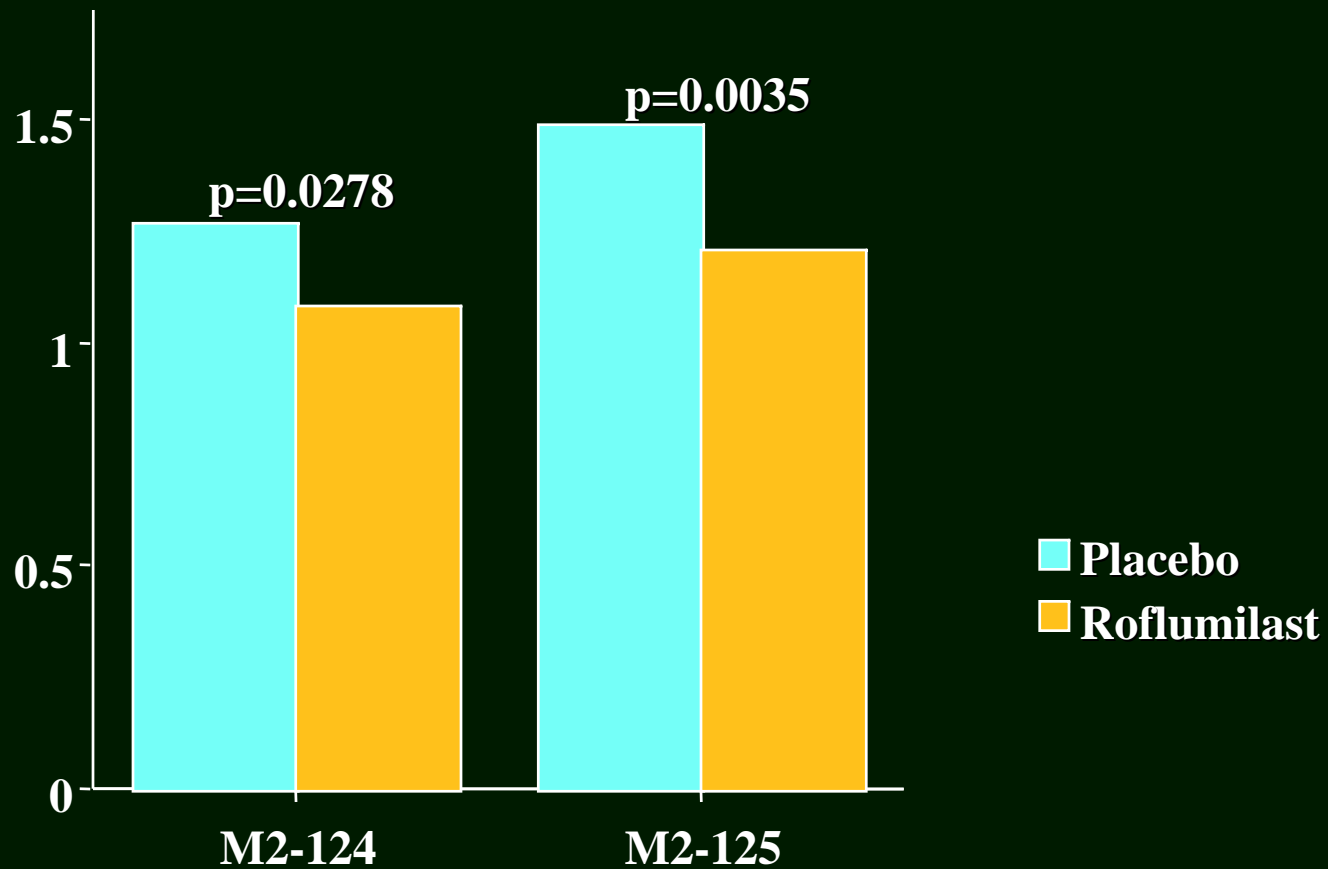
Roflumilast Improves FEV₁ in COPD Patients



Effect of Roflumilast in COPD: 1 year trials

Calverley et al. Lancet 374: 685, 2009

Moderate or Severe Exacerbations



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