Phenotype of COPD

서울의대 윤호일

A brief history

- Hippocrates (460B.C.-370B.C.) Asthma
- 1679 Theophile Bonet (1620-1689)
  - Description of ‘voluminous lungs’
- 1769 Giovanni Morgagni – 19 cases of ‘turgid’ lungs

- 1784 Dr. Samuel Johnson died of asthma
- 1793 Matthew Ballie published 'The morbid anatomy of some of the most important parts of the human body'

  The lungs are sometimes, …, formed into pretty large cells … this accumulation (of air) may break down two or three contiguous cells into one, thereby, form a cell of very large size.

- 1814 Charles Badham first used the term 'bronchitis'
  - 'inflammatory changes in the mucous membrane'

A treatise on the diseases of the chest and on mediate auscultation (Laennec, 1837)

The disease….. by no means infrequent. I consider many cases of asthma, …. as depending on this cause.

In opening the chest, it is not unusual to find that the lungs do not collapse,…… The bronchus of the trachea are often at the same time a good deal filled with mucous fluid.

Fig. 1. PLATE I.

Fig 2.

EXPLANATION OF THE PLATES.

PLATE I.

Fig. 1. This represents a section of the superior lobe of the lung, containing tubercles in different stages, and a vast tuberculous excavation. There are also, here and there, some pulmonary spots, more numerous between the excavation and top of the lung.

a. Very large anfractuous excavation, produced by the softening of the tuberculous matter, which still lines it partially.

b. Columnar bands crossing from one side of the excavation to the other, composed of the pulmonary tissue condensed, and covered with a thin layer of tuberculous matter.

c. Masses formed by the reunion of several immature tubercles, exhibiting, in the section of their substance, an infiltrated appearance. The shaded parts represent the grey and semitransparent matter of the incipient tubercle, and the inner white portions point out the same where it has become yellow and opaque.

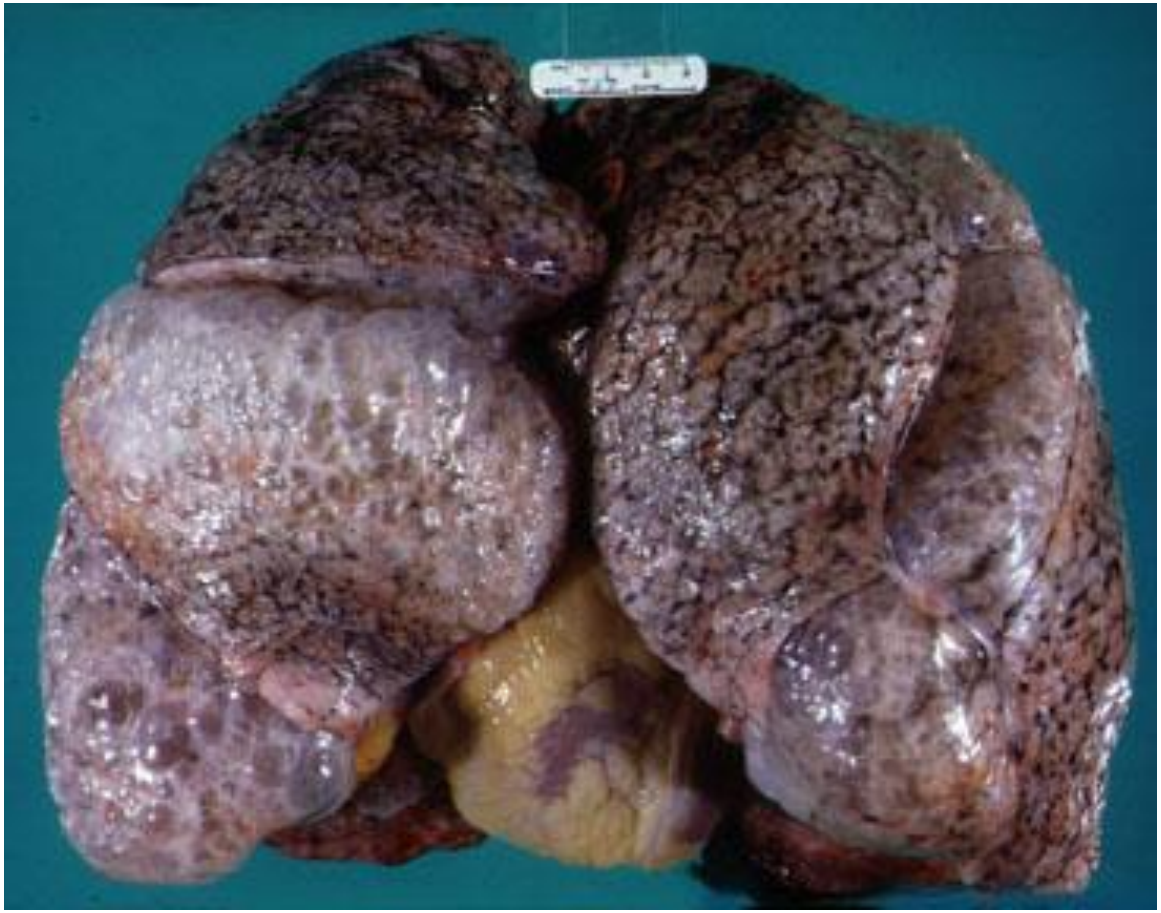
d. The miliary granulations of M. Bayle.

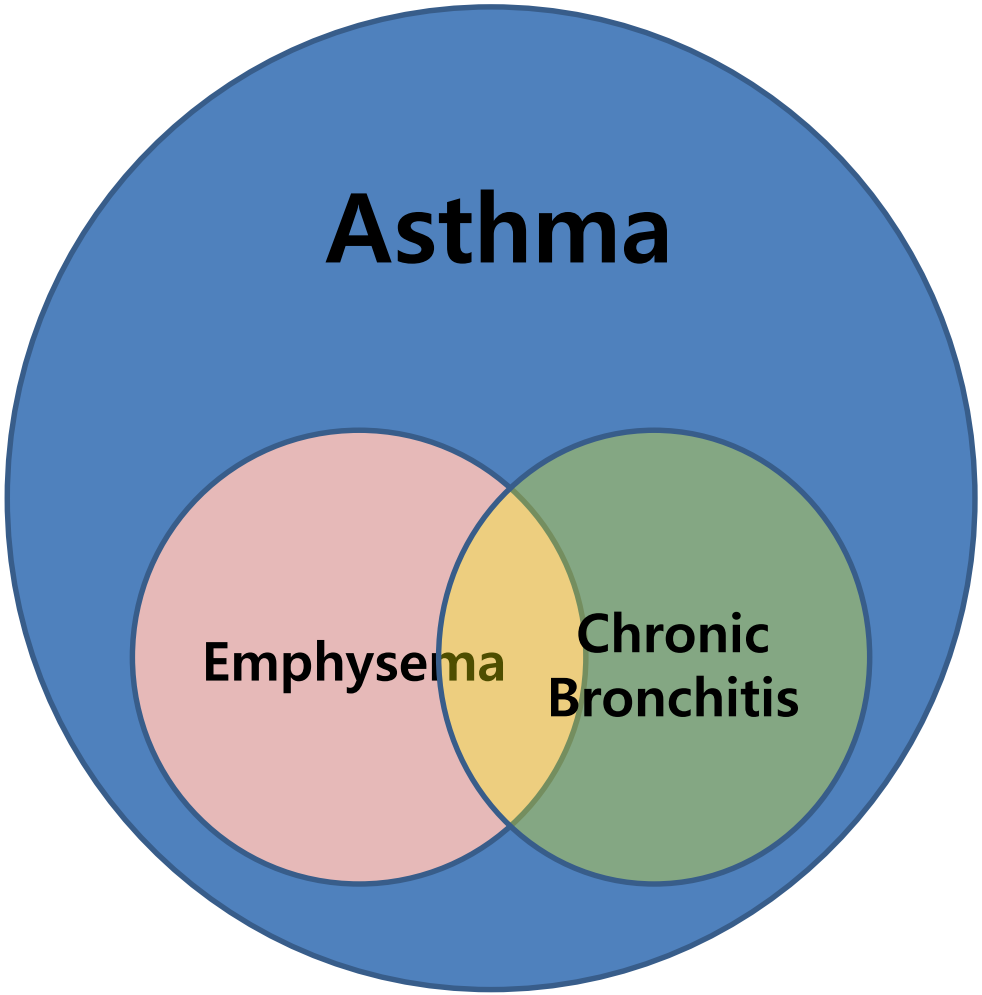
e. Bronchial tubes opening into the excavation.

f. Part of the exterior surface of the lungs.

Fig. 2. A section of the upper lobe of the left lung, exhibiting a vast and very antient pulmonary fistula, traversed by obliterated blood vessels, and lined by a thin mucous membrane. Between this cavity and the top of the lung are seen spots of black pulmonary matter, tinging the substance of the lung quite black.

Pathology

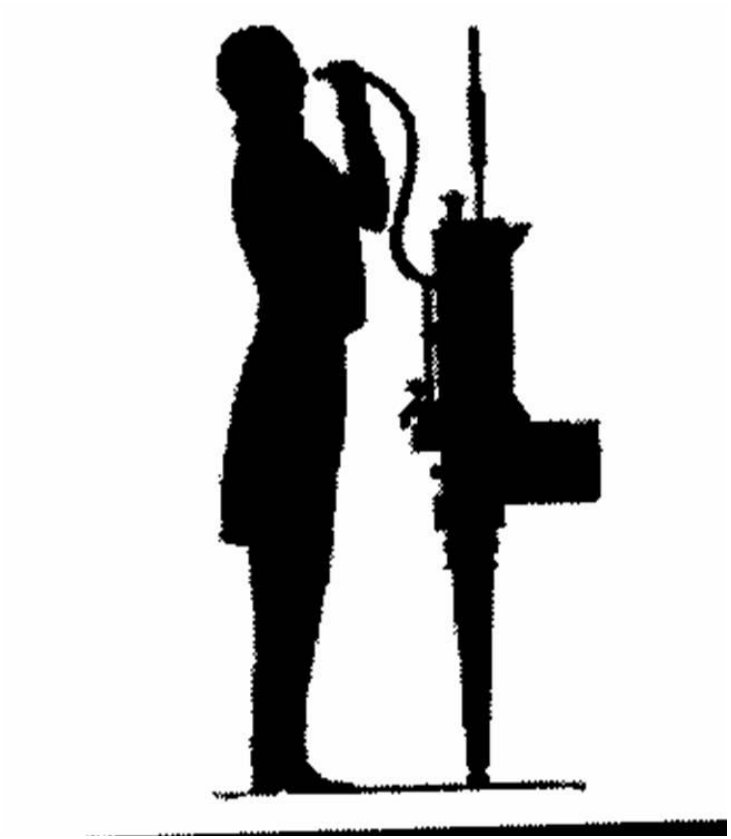



Asthma
Emphysema
Chronic
Bronchitis

Definition

- The CIBA Guest Symposium (1959)
- ATS committee on Diagnostic Standards (1962)
  - Chronic bronchitis
    - Sputum production lasting at least 3 months for at leat 2 years (clinical term)
  - Emphysema
    - Enlarged alveolar spaces and loss of alveolar walls (anatomical term)

Physiology

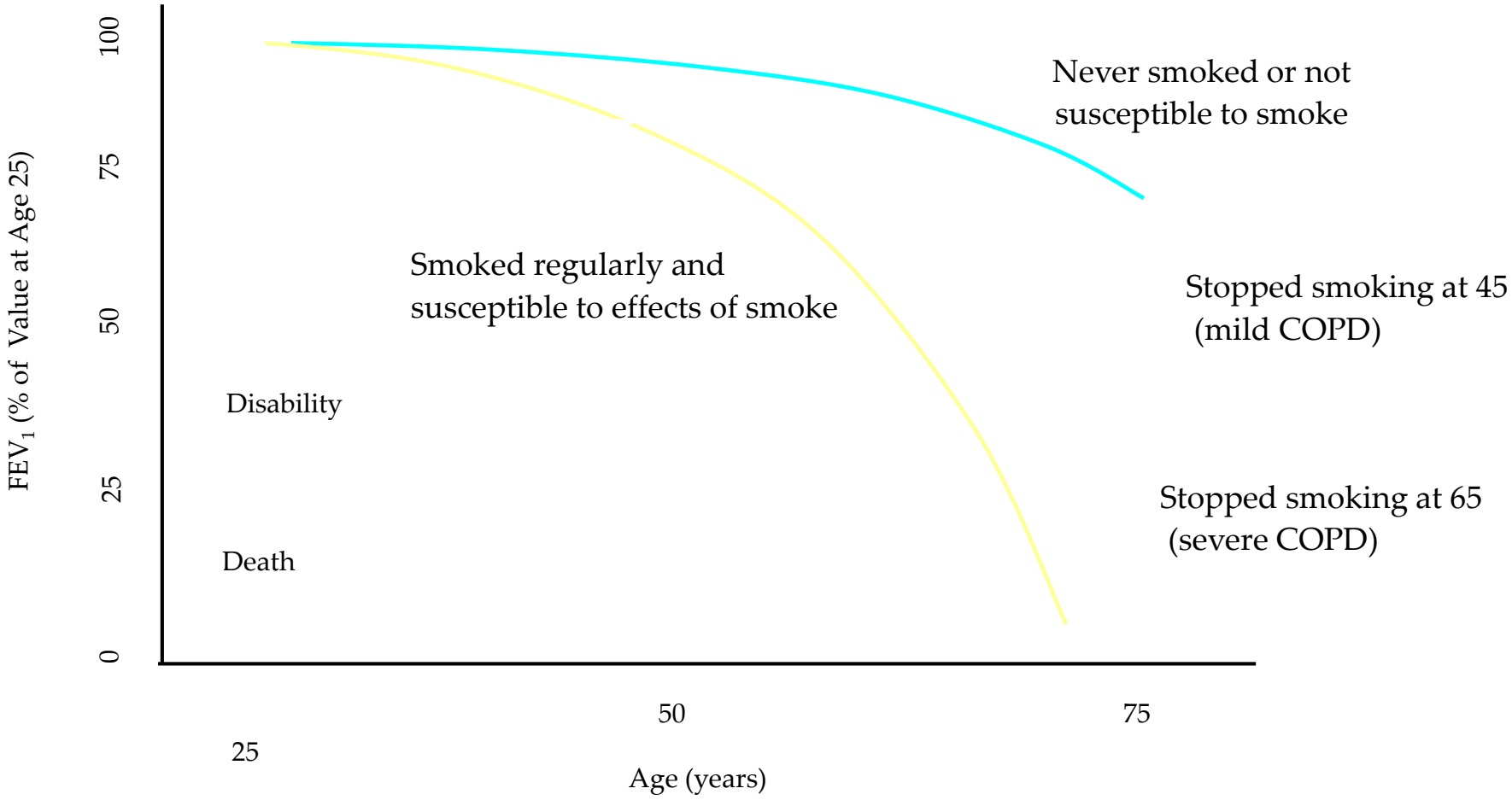


- 1846 Hutchinson invented spirometer
- 1947 Tiffeneau
  - the concept of timed vital capacity as a measure of airflow.
- 1950 Baensler FEV1, FEV1/FVC

Natural History

- 1976 Fletcher and Peto
- 1983 Peto smoking cessation

FEV_1 over time



Natural History

- 1976 Fletcher and Peto
- 1983 Peto smoking cessation
- 1987 Burrows
  - low FEV1/FVC predicted the onset of rapid decline in FEV1 “the horse riding effect”

Acronyms…

- Chronic obstructive bronchopulmonary disease
- Chronic airflow obstruction
- Chronnic obstructive lung disease
- Nonspecific chronic pulmonary disease
- Diffuse obstructive pulmonary syndrome
- Chronic obstructive pulmonary disease
  - (Briscoe, 1965, 9th Aspen Emphysema Conference)

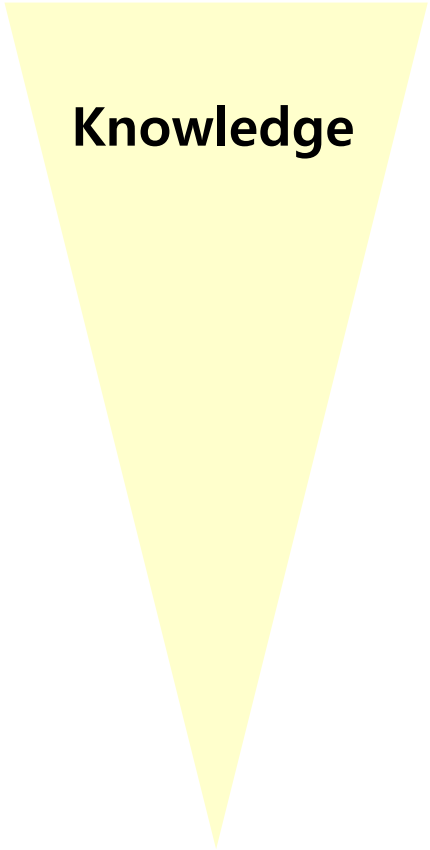
Definition of COPD

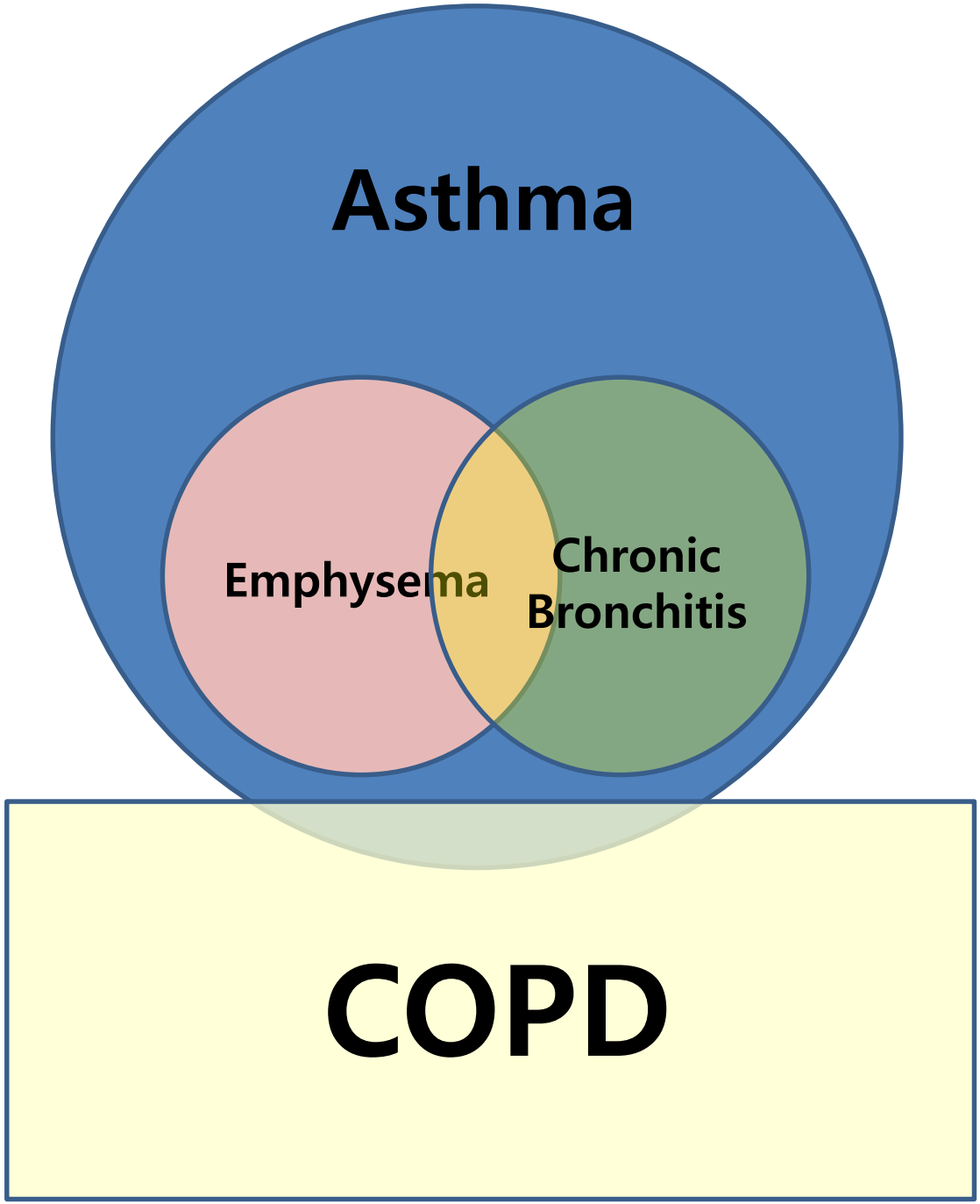
COPD is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema.

The airflow obstruction is generally progressive, may be accompanied by airflow hyperreactivity, and may be partially reversible

Defining Characteristics

- Cause
- Change in
  - Structure — emphysema
  - Function — COPD
- Clinical Finding(s)
  - Multiple — … syndrome
  - Single — chronic bronchitis

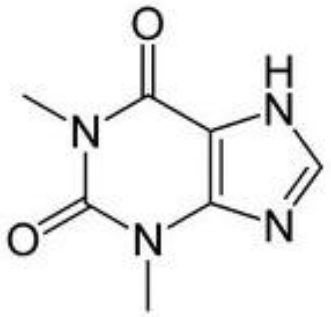



Asthma
Emphysema
Chronic
Bronchitis
COPD

British vs. Dutch

- Dutch (Orie and Sluiter, 1960)
  - Genetically determined bronchial hyperreactivity
- British (Stuart-Harris, 1953)
  - Repeated infection and air pollution

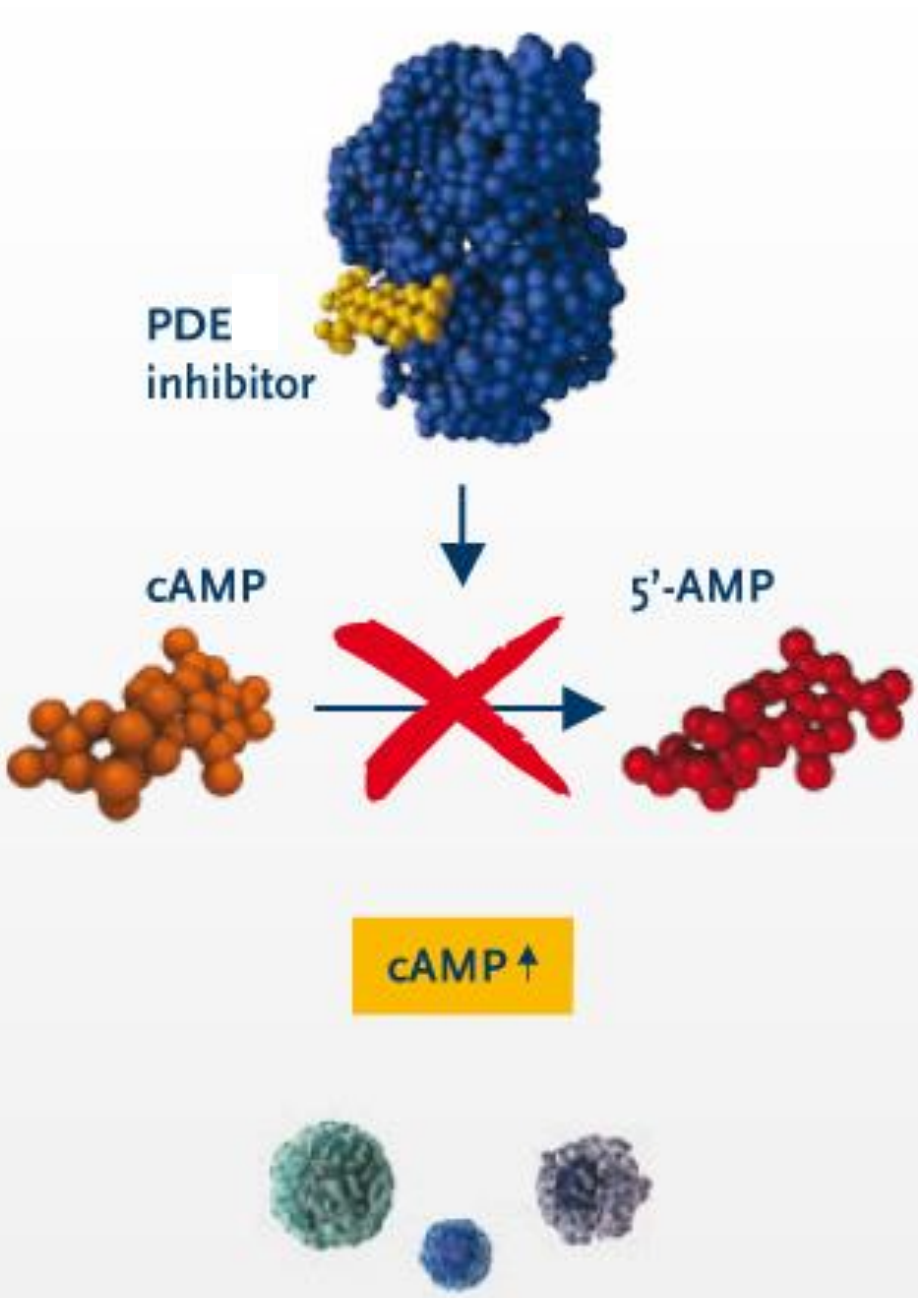
Theophylline



- 1888 Albrecht Kossei
  - Extraction of theophylline from tea leaves
- 1895 chemical synthesis
- 1902 First clinical use as diuretic
- 1922 First description in asthma treatment ‘bronchospasmolytic action’

Inflammatory modulation?

- 1990s Anti-inflammatory action of theophylline
  - Inhibit LAR and hyperresponsiveness
  - Reduced eosinophilic infiltration of airway
  - Decreased BAL CD4+ cells


PDE
inhibitor
cAMP
5'-AMP
cAMP ↑

THE PDE4 ENZYME EXPRESSION

LEUKOCYTE	PDE ISOFORM
Mast cells	4, 7
Eosinophils	4, 7
Neutrophils	4, 7
Monocytes	1, 3, 4, 7
Macrophages	1, 3, 4, 5, 7
T-cells ($CD4^+$ and $CD8^+$)	3, 4, 7

Structural Cells	PDE isoform
Airway smooth muscle	1, 2, 3, 4, 5, 7
Epithelial cells	1, 2, 3, 4, 5, 7, 8
Endothelial cells	2, 3, 4, 5
Sensory nerve	1, 3, 4
Cholinergic nerves	1, 3, 4

: Giembycz MA. *Monaldi Arch Chest Dis* **2002**;57:48-64

The effect of a novel orally active selective PDE4 isoenzyme inhibitor (CDP840) on allergen-induced responses in asthmatic subjects

P.L. Harbinson*, D. MacLeod**, R. Hawksworth+, S. O'Toole**, P.J. Sullivan*, P. Heath++, S. Kilfeather*, C.P. Page*, J. Costello*, S.T. Holgate**, T.H. Lee+

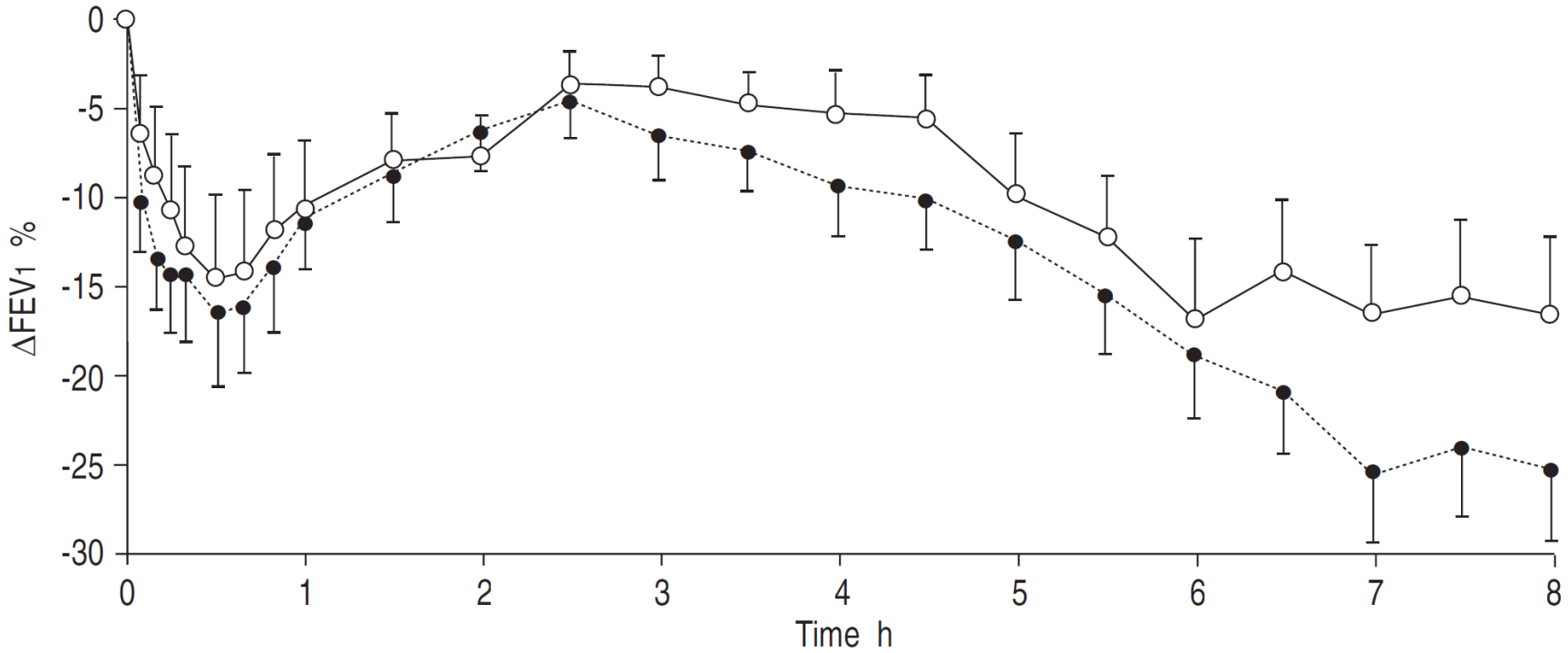
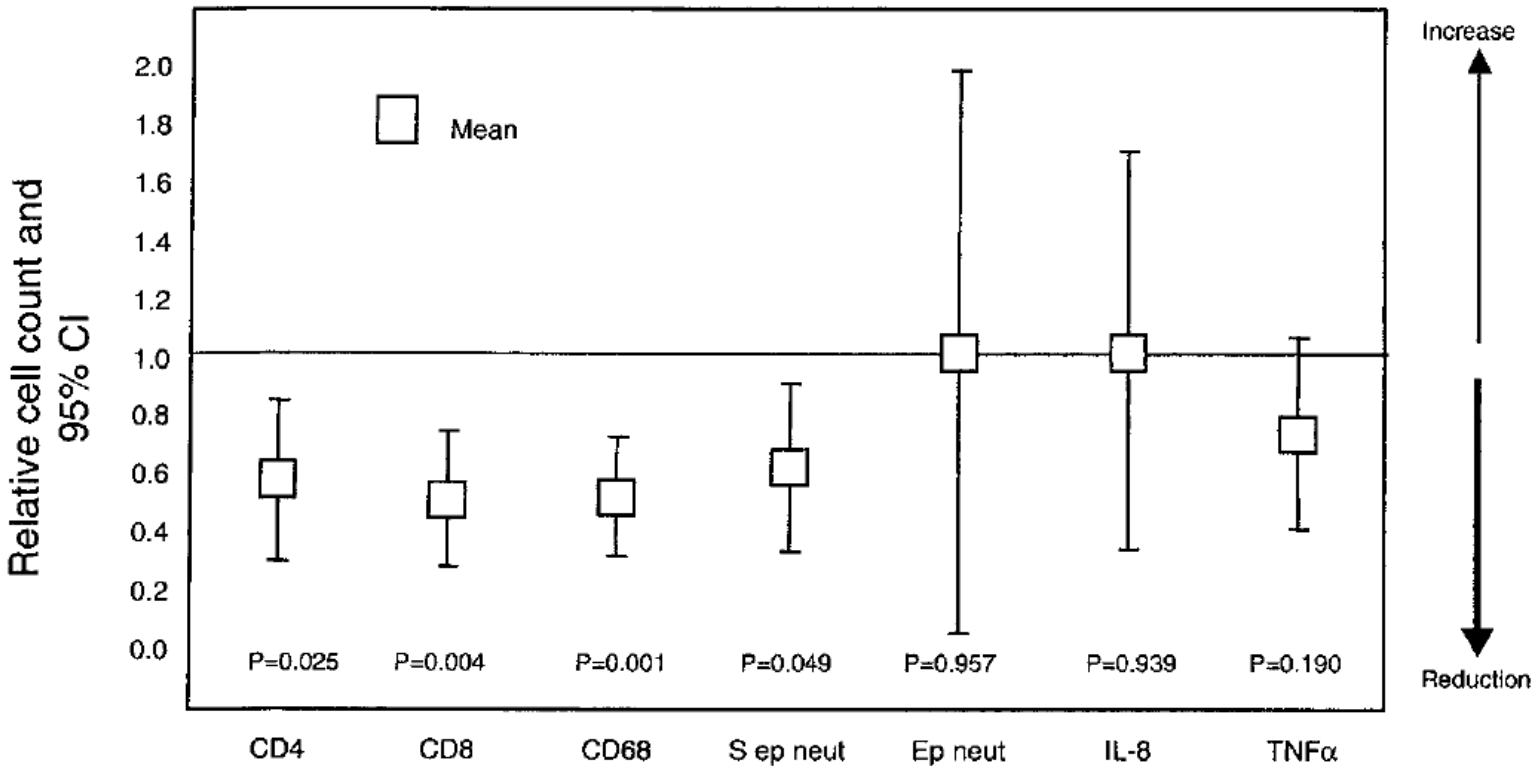


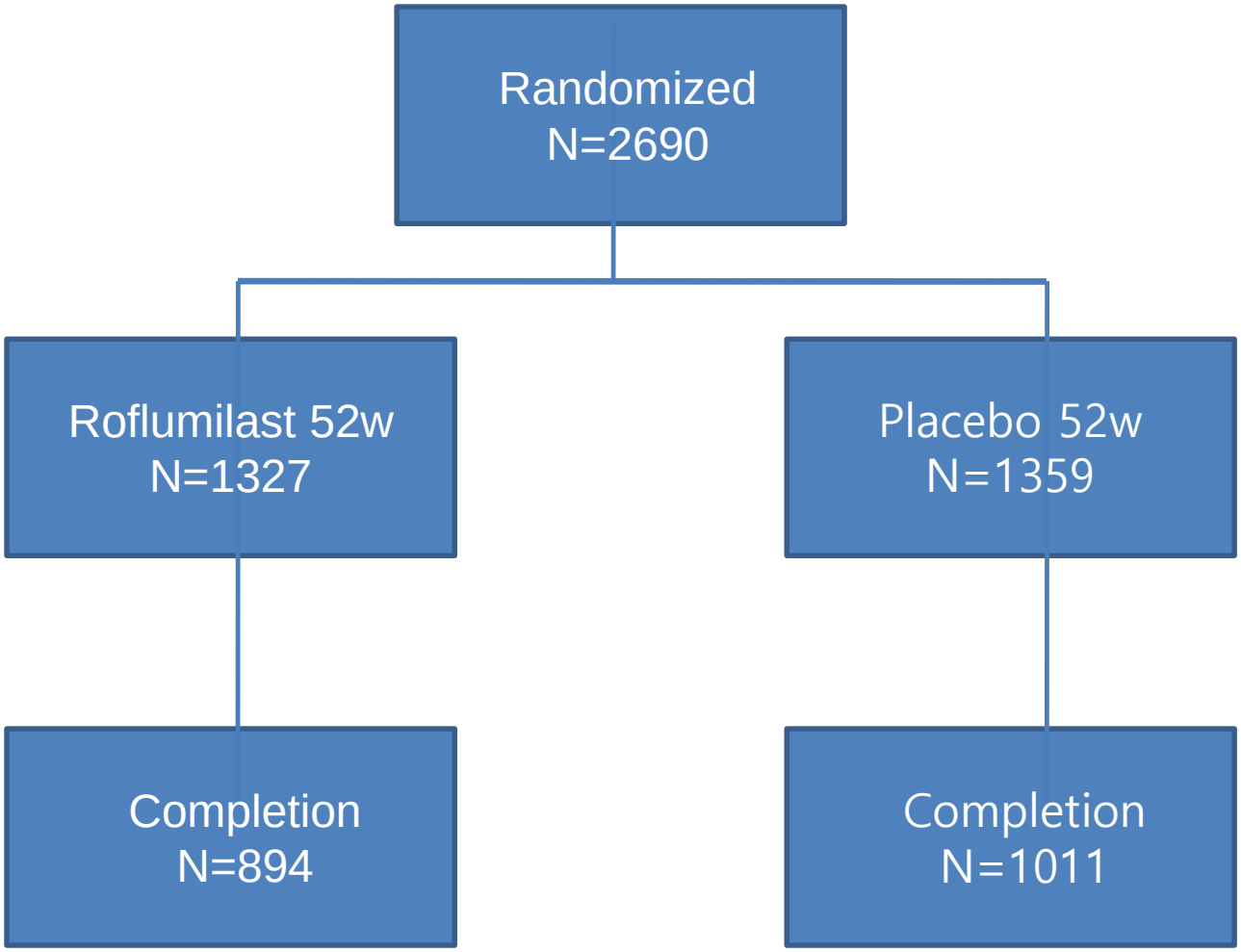
Fig. 1. – Effect of 9.5 days of treatment with CDP840 15 mg *b.i.d.* on the response to allergen, expressed as the percentage fall in FEV1 over the 8 h period following exposure (n=13). Values are expressed as mean±SEM. CDP840 : phosphodiesterase 4 inhibitor; ΔFEV1: change in forced expiratory volume in one second. ·····●·····: placebo; —○—: CDP840 15 mg *b.i.d.*

ERJ 1997;10:1008

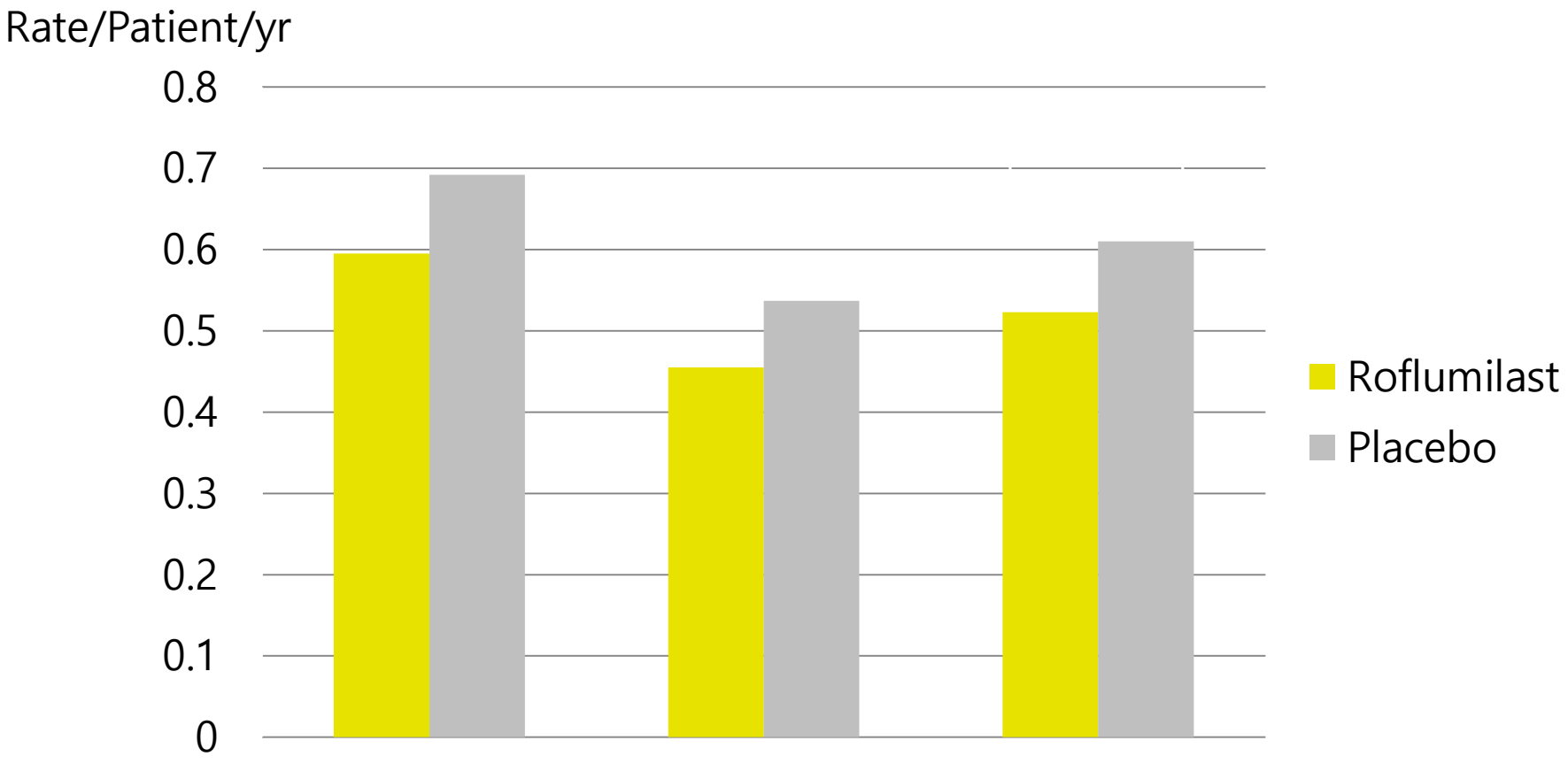
Cilomilast reduced CD8+ cells



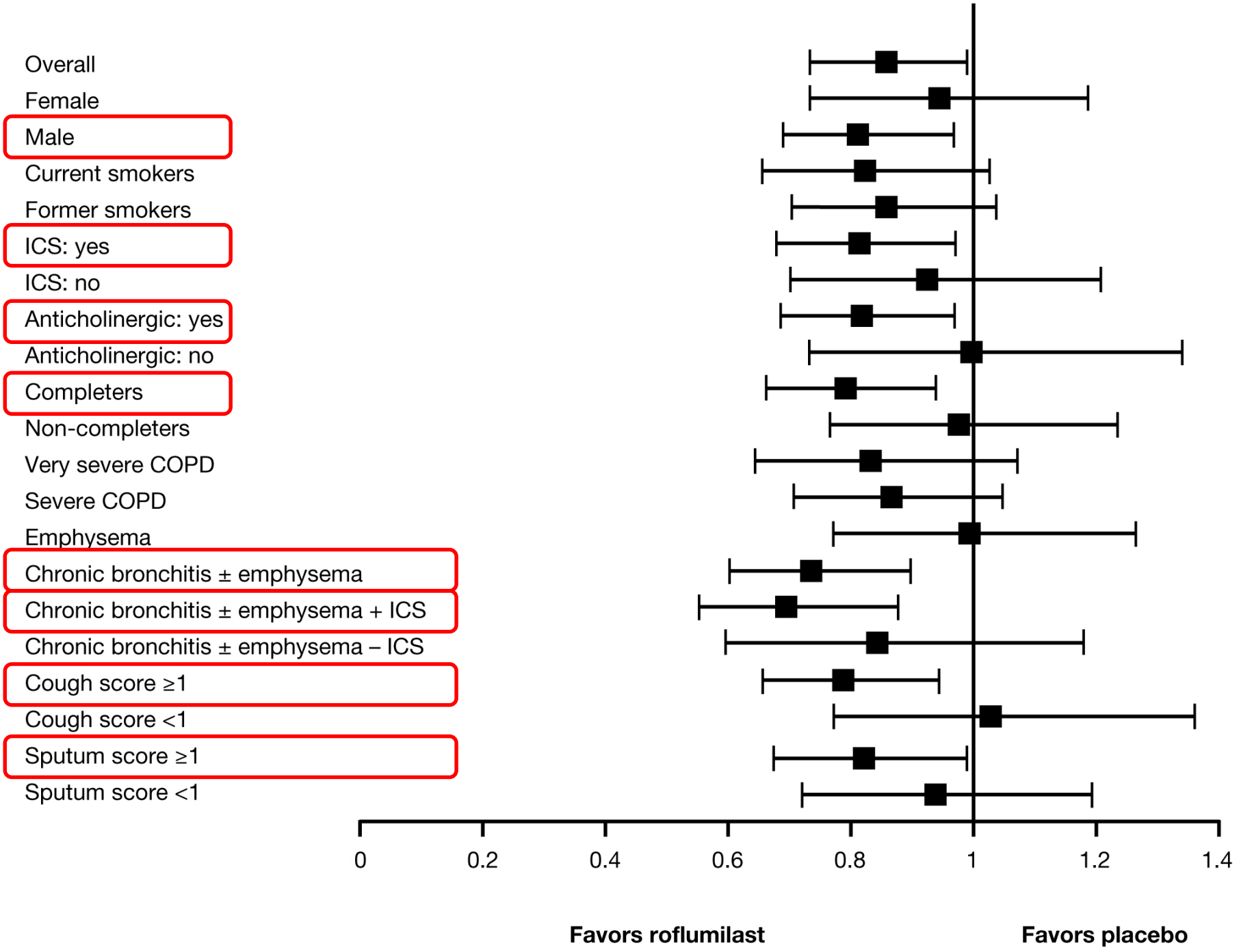
Pooled Analysis of M2-111, M2-112



Moderate or Severe Exacerbation



Rennard SI et al. Respiratory Research 2011;12:18


Overall
Female
Male
Current smokers
Former smokers
ICS: yes
ICS: no
Anticholinergic: yes
Anticholinergic: no
Completers
Non-completers
Very severe COPD
Severe COPD
Emphysema
Chronic bronchitis ± emphysema
Chronic bronchitis ± emphysema + ICS
Chronic bronchitis ± emphysema – ICS
Cough score ≥1
Cough score <1
Sputum score ≥1
Sputum score <1
0
0.2
0.4
0.6
0.8
1
1.2
1.4
Favors roflumilast
Favors placebo

Summary of post-hoc, pooled analysis

- Roflumilast reduced exacerbation
- Especially good in some subgroups
  - Chronic bronchitis
  - ICS user

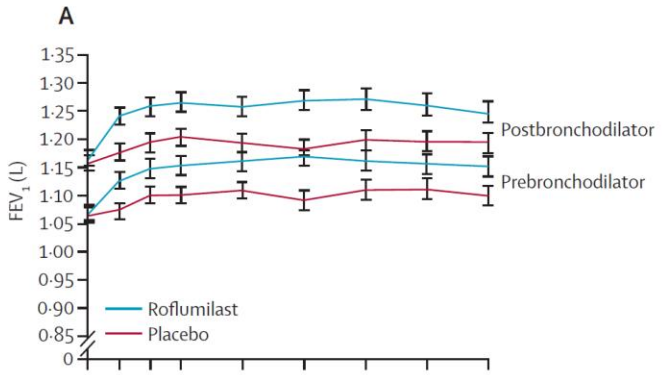
Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

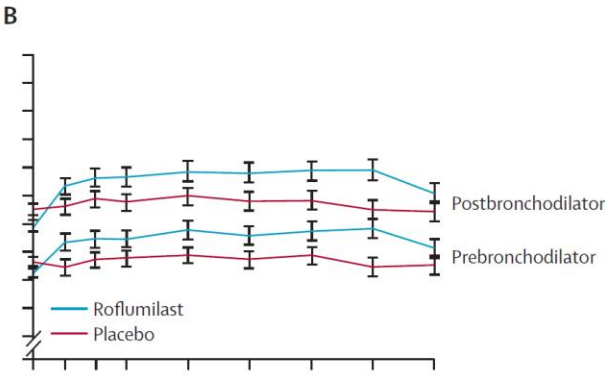
Peter M A Calverley, Klaus F Rabe*, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri†, Fernando J Martinez†, for the M2-124 and M2-125 study groups‡*

Lancet 2009; 374: 685-94

Study Outline of M2-124,125

- Multicenter, multinational, double blind RCT
- COPD (<FEV1 50%)
- Bronchitic Sx, History of exacerbation
- 500 μg Roflumilast qd vs. placebo for 1 yr
- N=3,000
- Coprimary endpoints – FEV1 and exacerbation rates



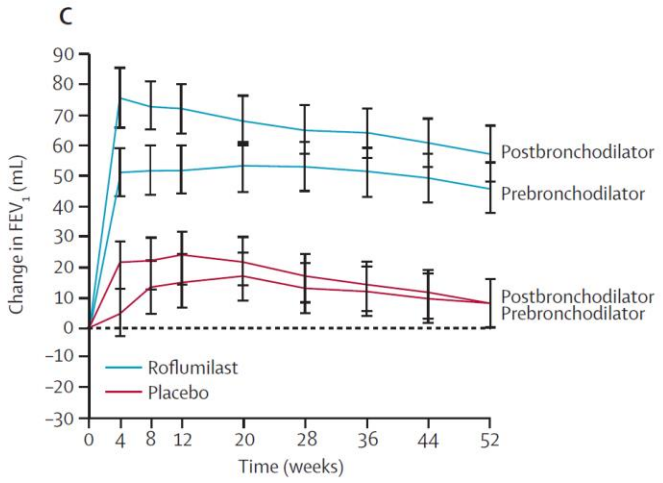


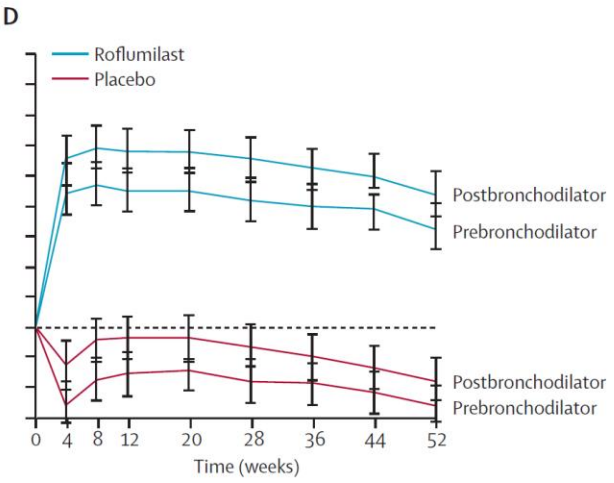
Number at risk*

Prebronchodilator									
Roflumilast	764	743	667	625	604	571	542	517	499
Placebo	758	744	694	667	633	600	566	537	521
Postbronchodilator									
Roflumilast	757	728	661	622	598	569	540	510	497
Placebo	753	733	691	662	626	597	562	532	513

Number at risk*

Prebronchodilator									
Roflumilast	772	730	669	637	606	581	558	544	525
Placebo	796	762	725	708	673	641	601	565	551
Postbronchodilator									
Roflumilast	769	725	666	635	604	577	554	543	525
Placebo	794	761	723	706	670	638	599	562	546





Calverley PMA et al. Lancet 2009; 374: 685-94

Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Peter M A Calverley, Klaus F Rabe*, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri†, Fernando J Martinez†, for the M2-124 and M2-125 study groups‡*

Summary

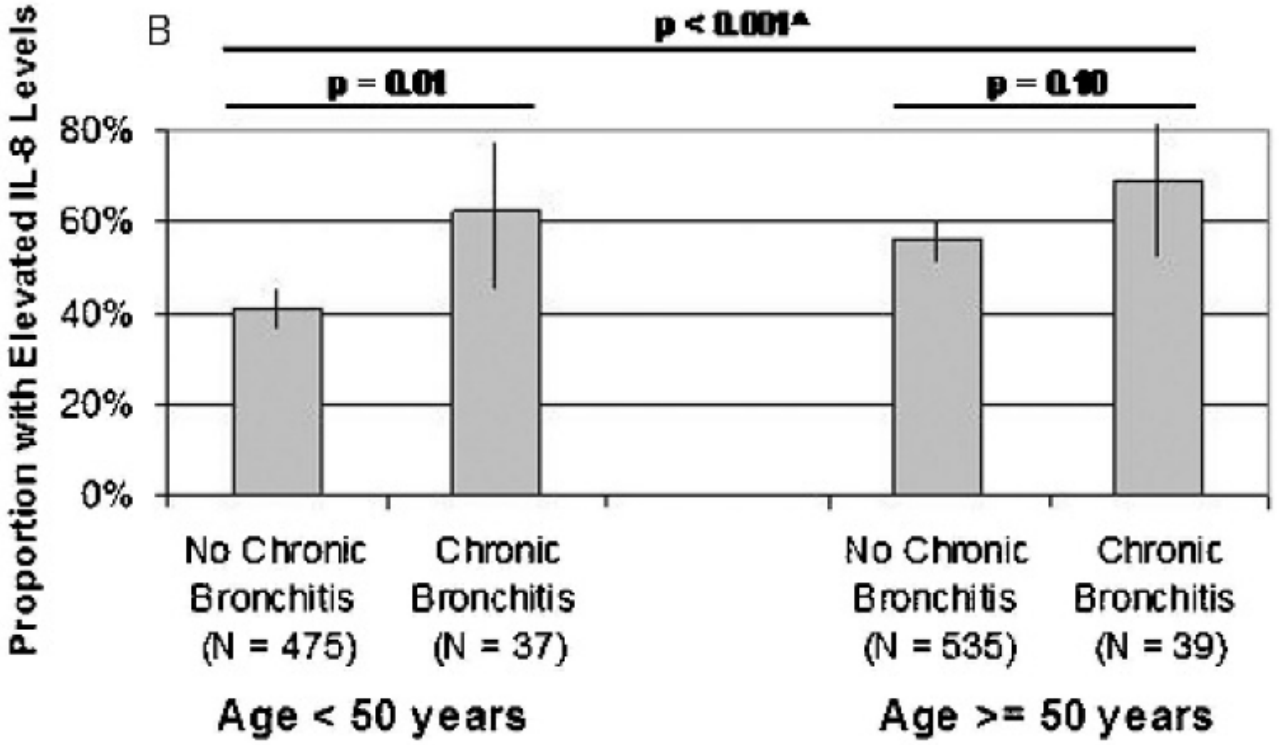
Background The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.

Methods In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 µg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV_1) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Findings Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β_2 agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo ($p<0\cdot0001$). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], $p<0\cdot0003$). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was –2·17 kg.

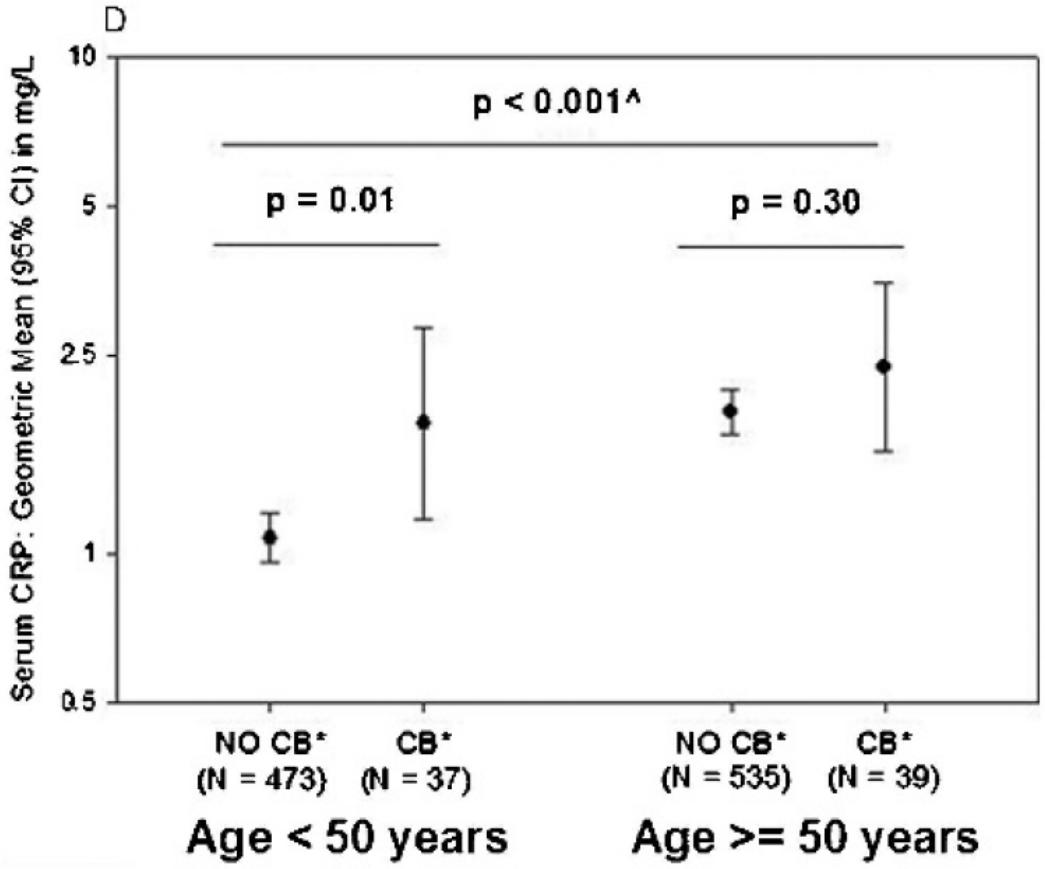
Interpretation Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management. This possibility should be explored further in prospective studies.

Chronic bronchitis and Inflammatory Markers



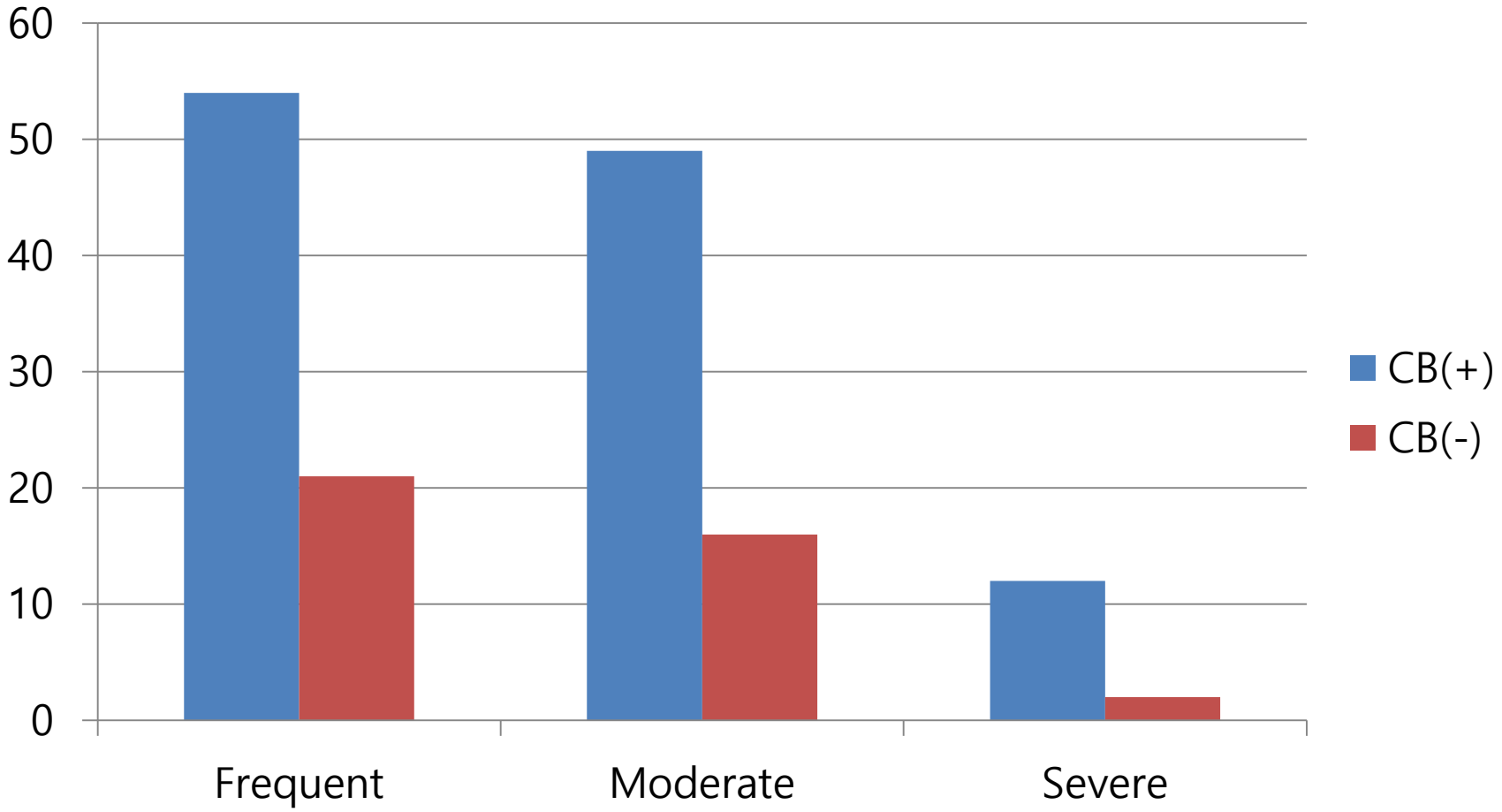
Guerra S. et al. Thorax 2009;64:894

Chronic bronchitis and Inflammatory Markers



Guerra S. et al. Thorax 2009;64:894

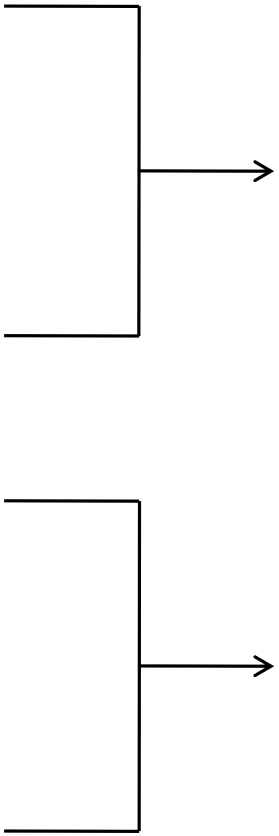
Chronic bronchitis and exacerbations



Burgel PR et al. Chest 2009;135:975

치료의 목표

- 증상의 완화
- Exercise intolerance개선
- Health status 개선
- 합병증/급성악화 예방
- 질병의 진행 억제
- 사망률 감소

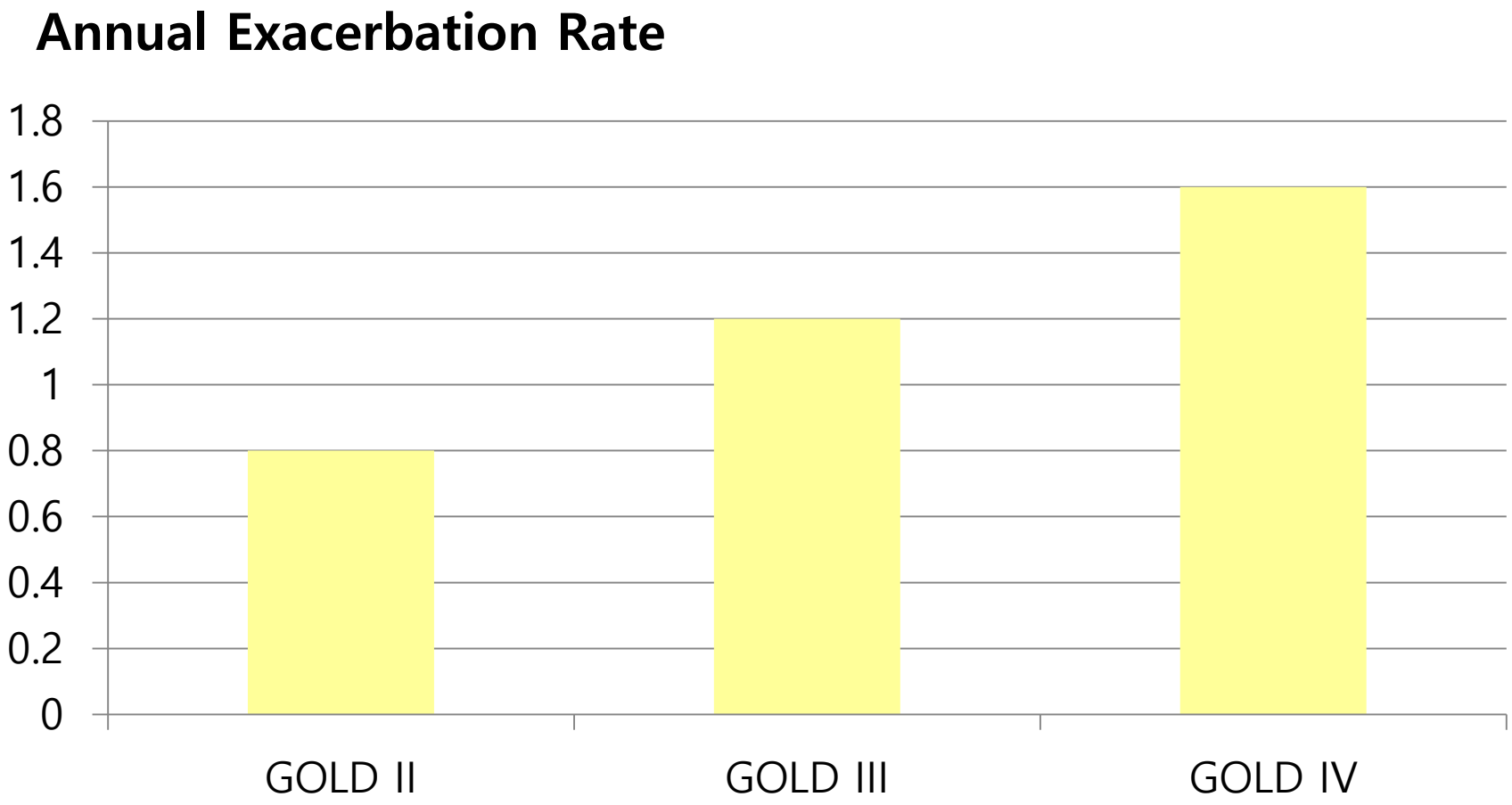


Reduce
SYMPTOM

Reduce
EXACERBATION

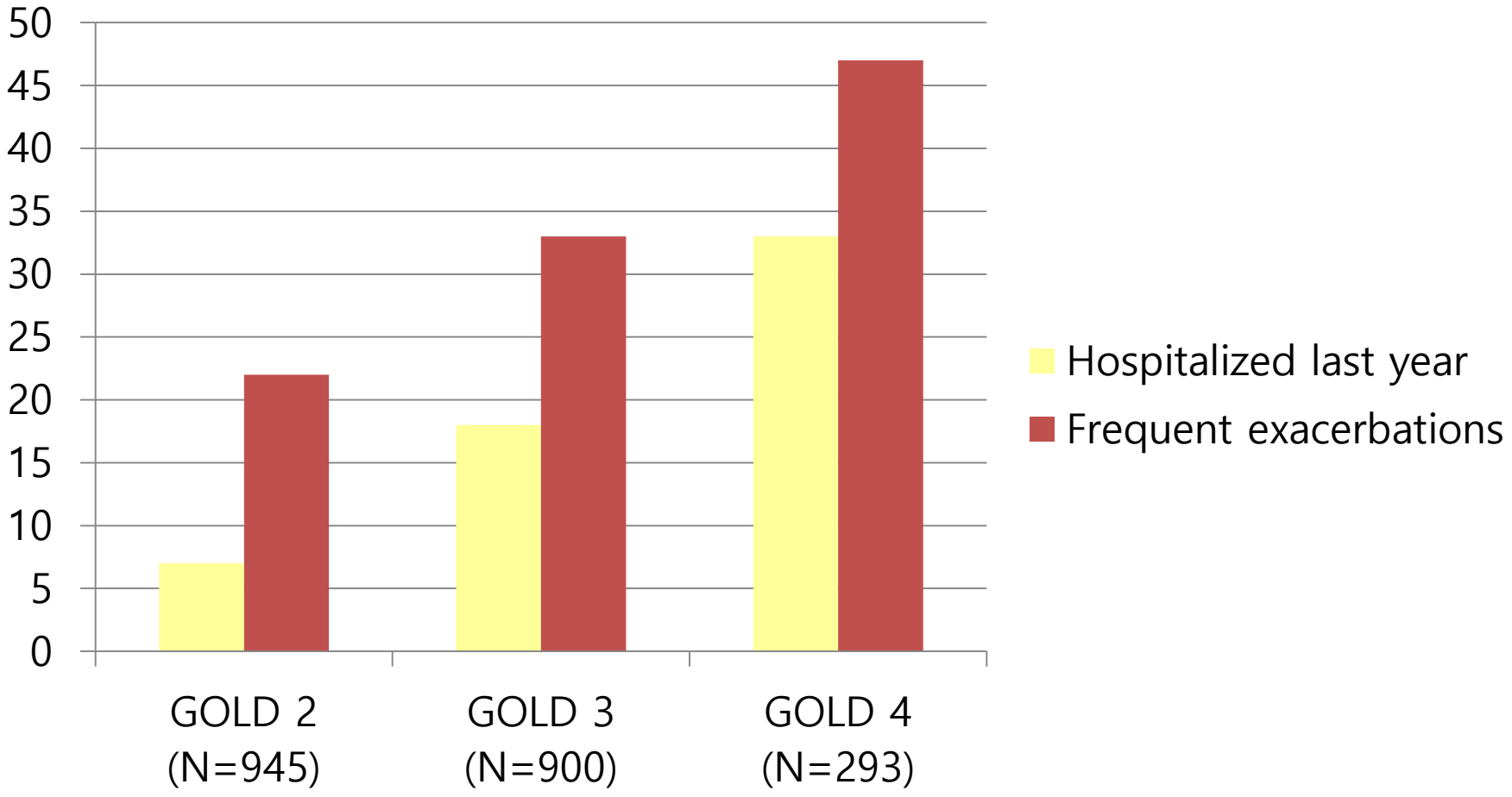
GOLD, 2011

Who's at risk?



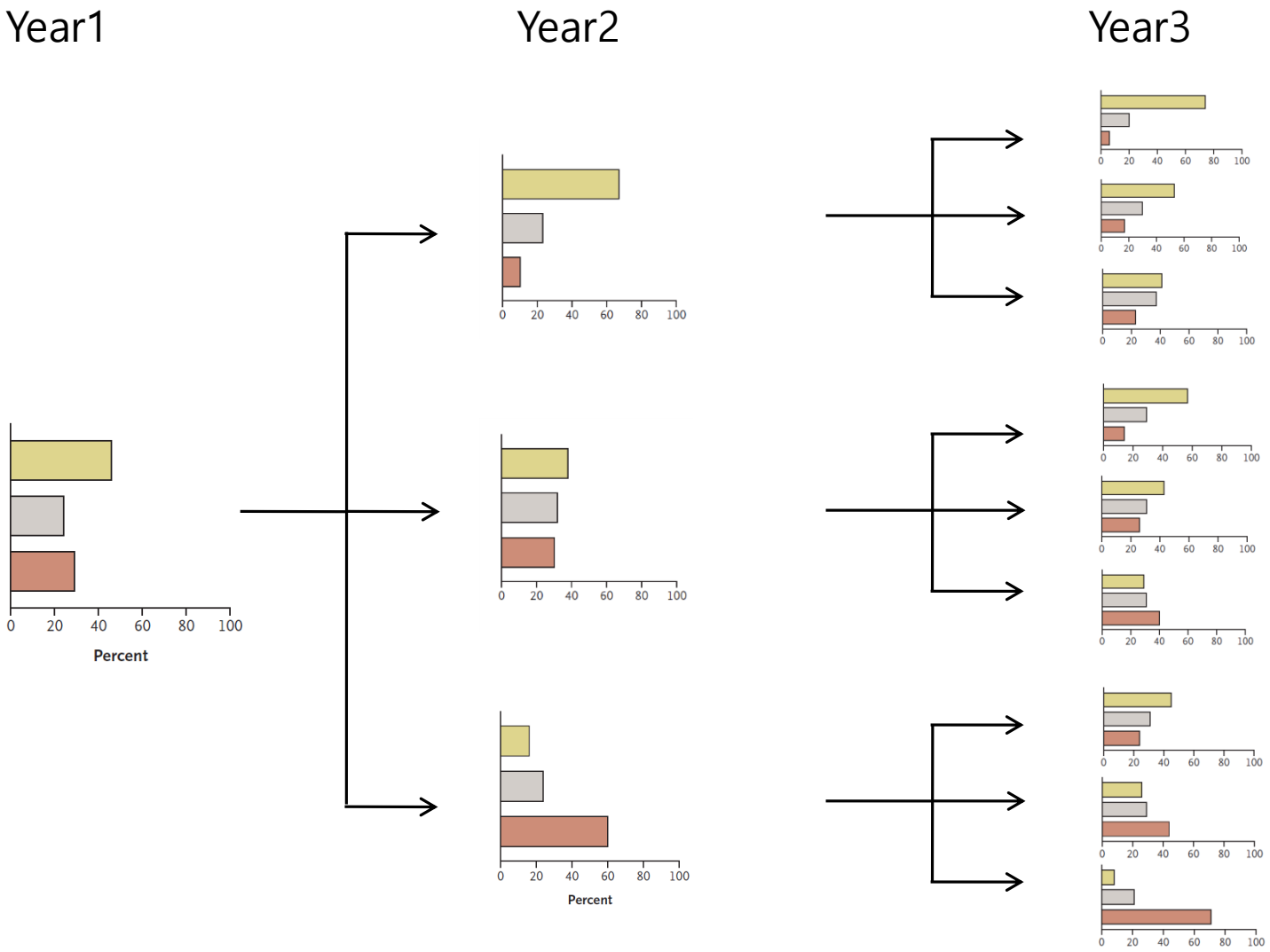
GOLD 2011. Adapted from TORCH, UPLIFT

Exacerbation and Severity



Hurst JR et al. N Engl J Med 2010;363:1128-1138

Tendency to exacerbate is a PHENOTYPE



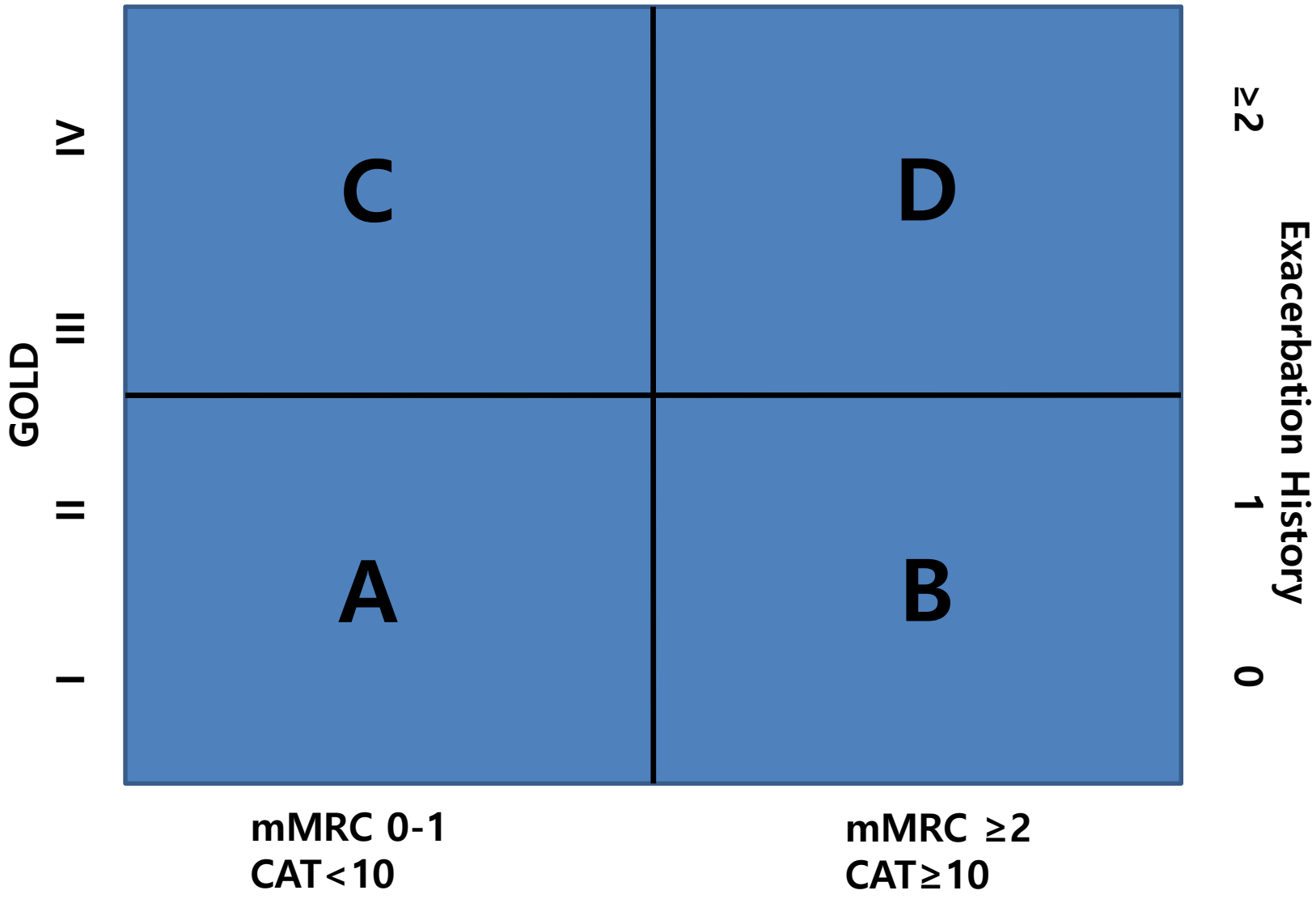
Hurst JR et al. N Engl J Med 2010;363:1128-1138

Factors associated with exacerbation risk

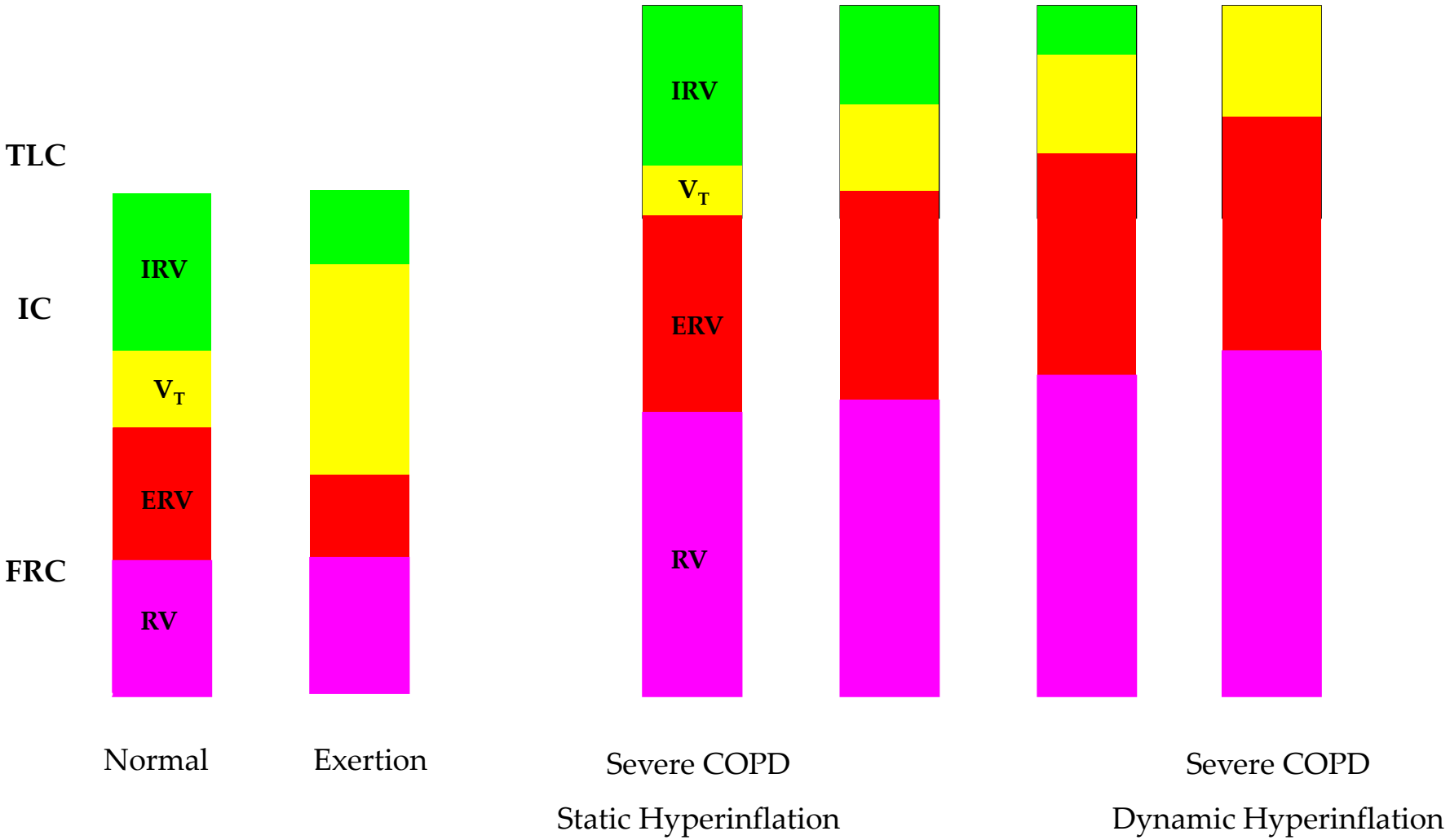
	OR (≥2 vs. 0)	P value
Women(n=376)		
History of exacerbation during prev. year	8.89	<0.001
History of asthma	3.38	<0.001
Fibrinogen	1.95	<0.002
Men(n=569)		
History of exacerbation during prev. year	7.38	<0.001
FEV1 (per 100ml decrease)	1.20	<0.001
Chronic wheezing	2.56	<0.001

Hurst JR et al. N Engl J Med 2010;363:1128-1138

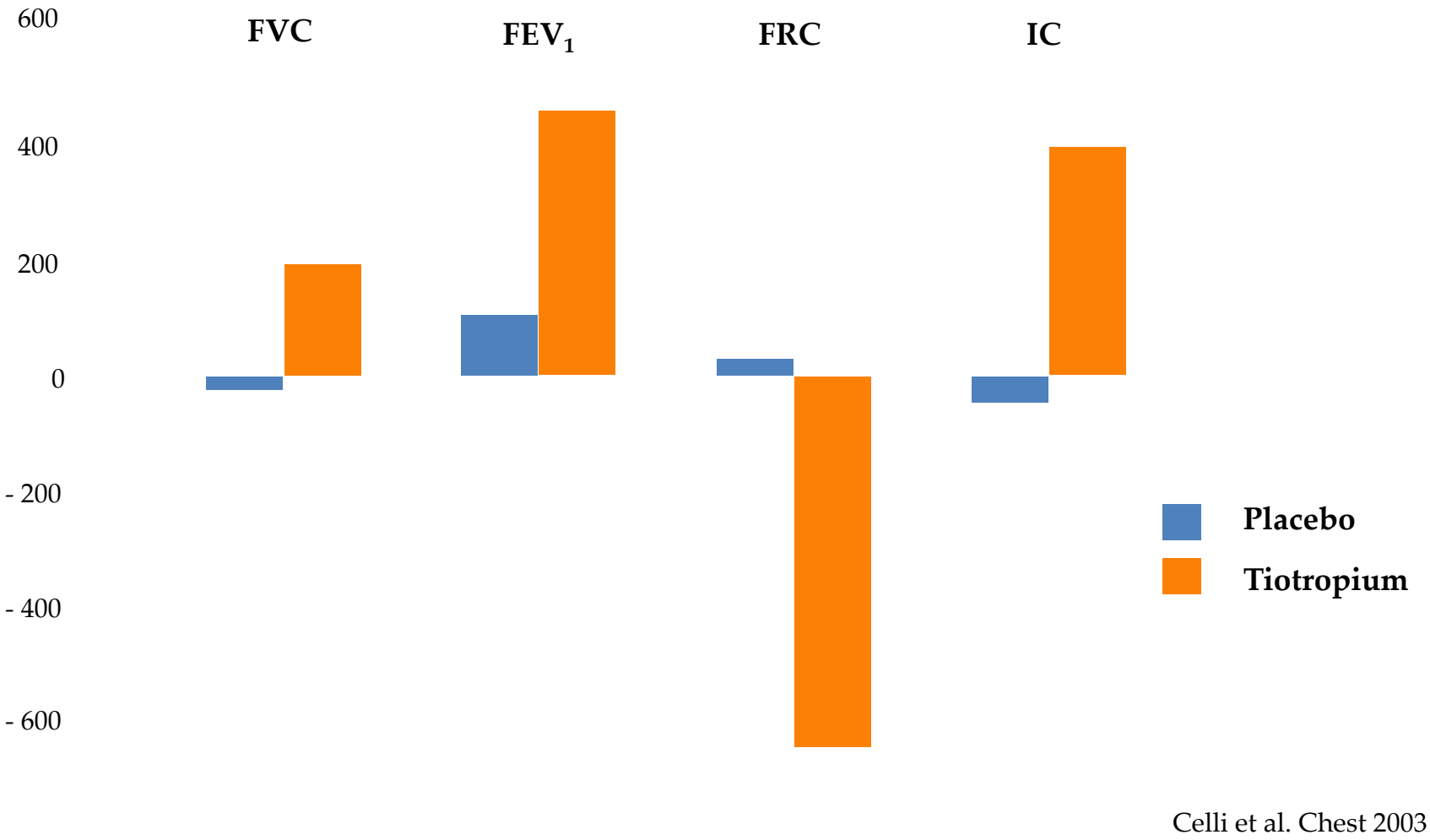
Stable COPD의 치료



What is hyperinflation?



Lung volume change after bronchodilator therapy

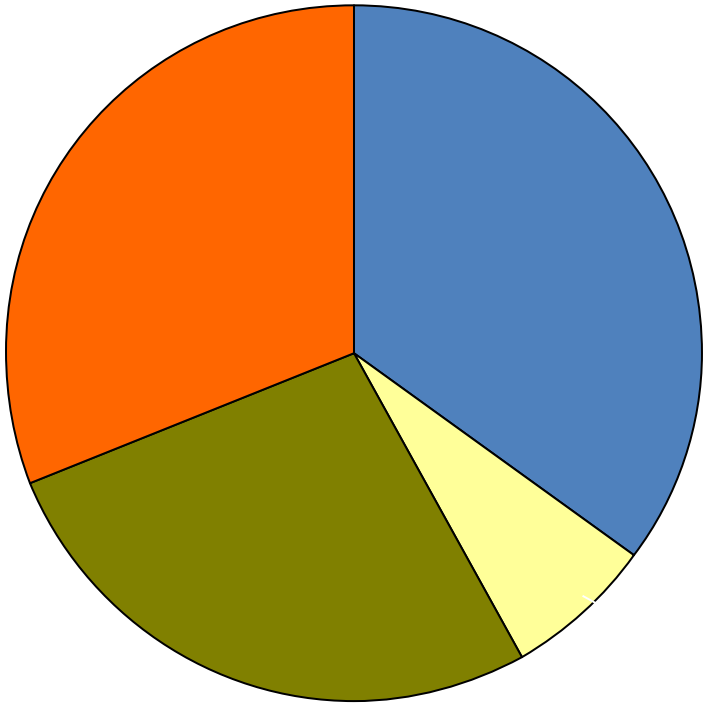


Celli et al. Chest 2003

Bronchodilator responses : Volume vs. Airflow

IC response

124 (31%)



No response

140 (35%)

Combined response

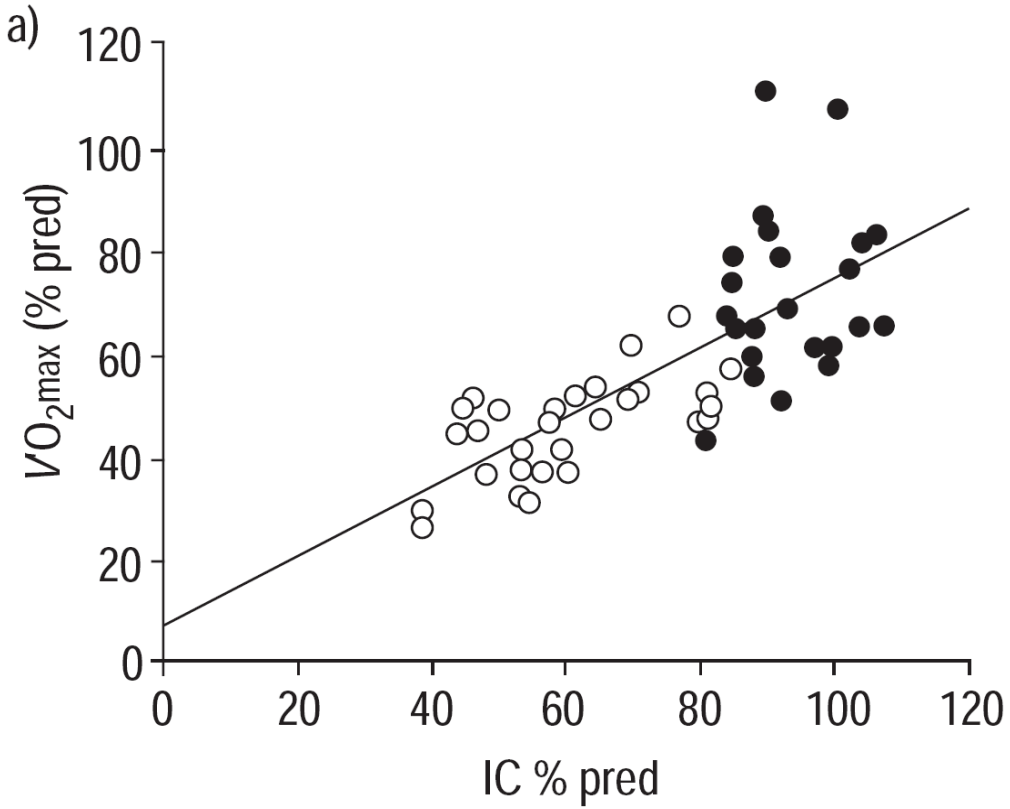
109 (27%)

FEV_1 response

29 (7%)

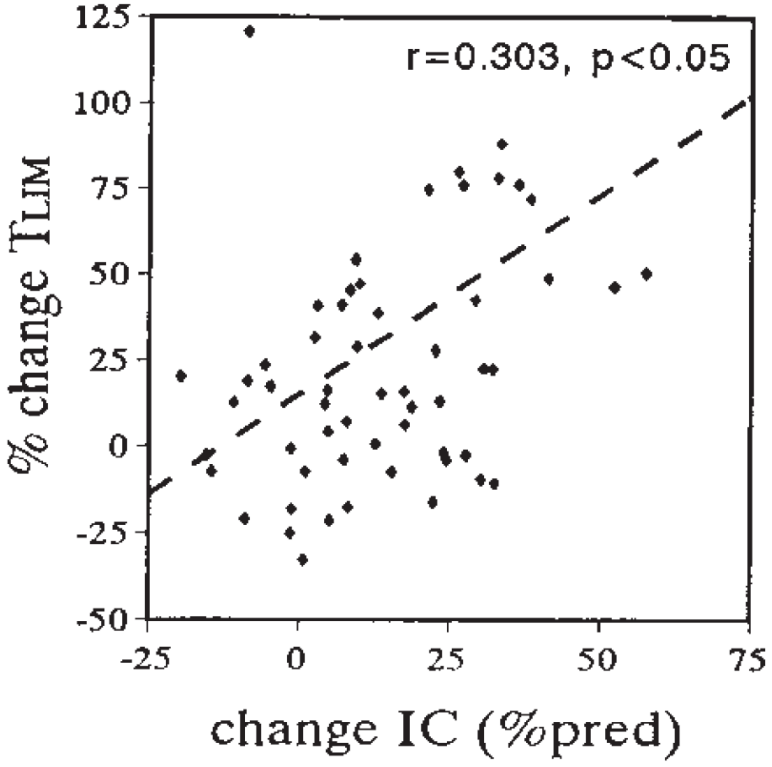
Newton et al. Chest 2002

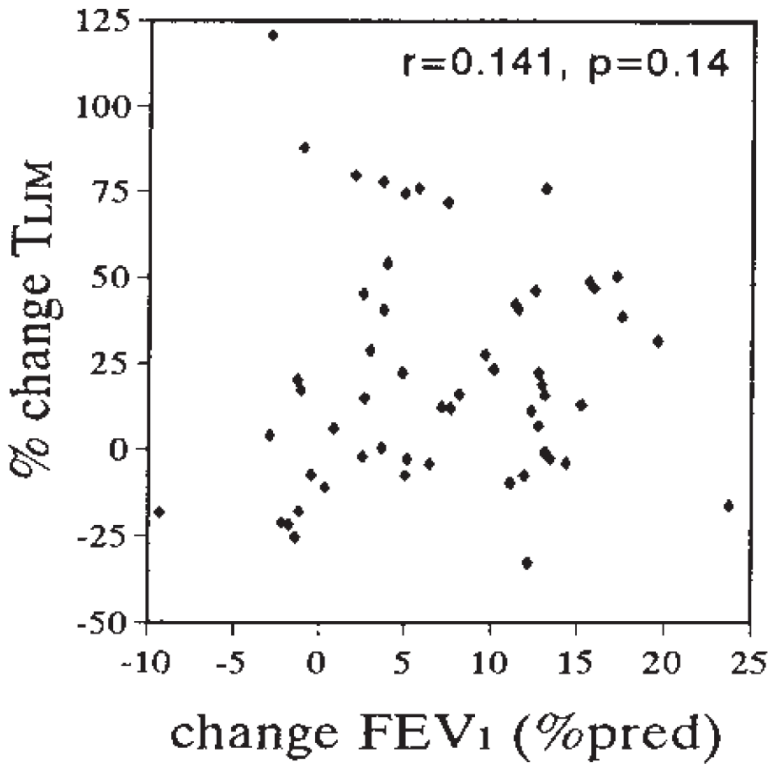
Lung volume and $VO_{2\ max}$



Diaz et al. ERJ 2000

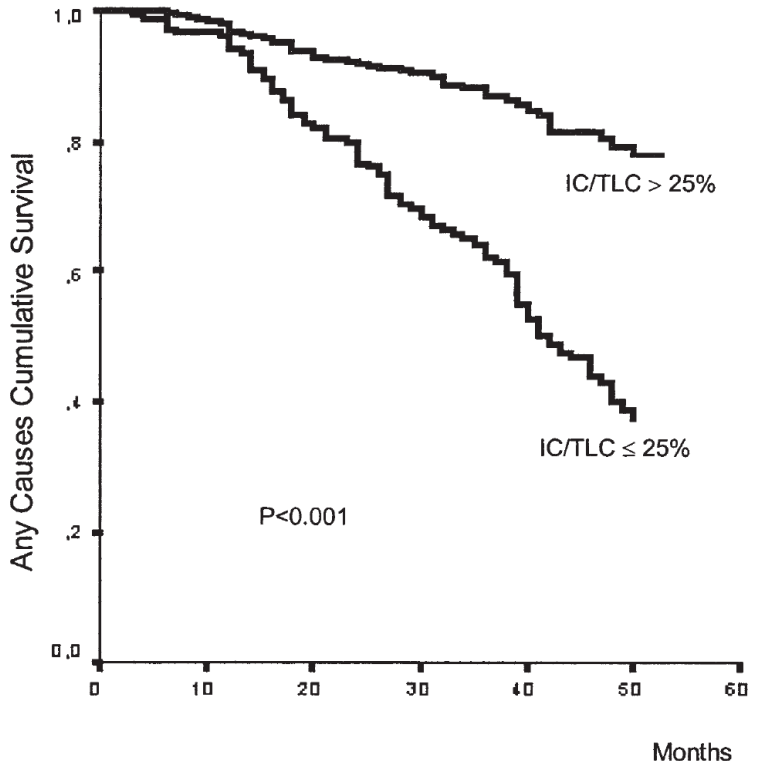
Lung volume correlates with exercise endurance

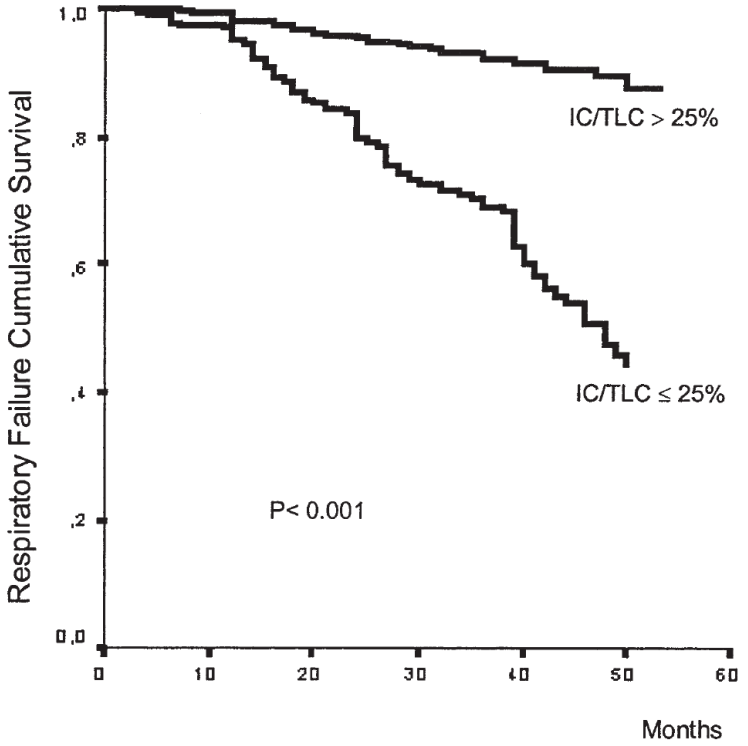




O'Donnel et al. AJRCCM 1999

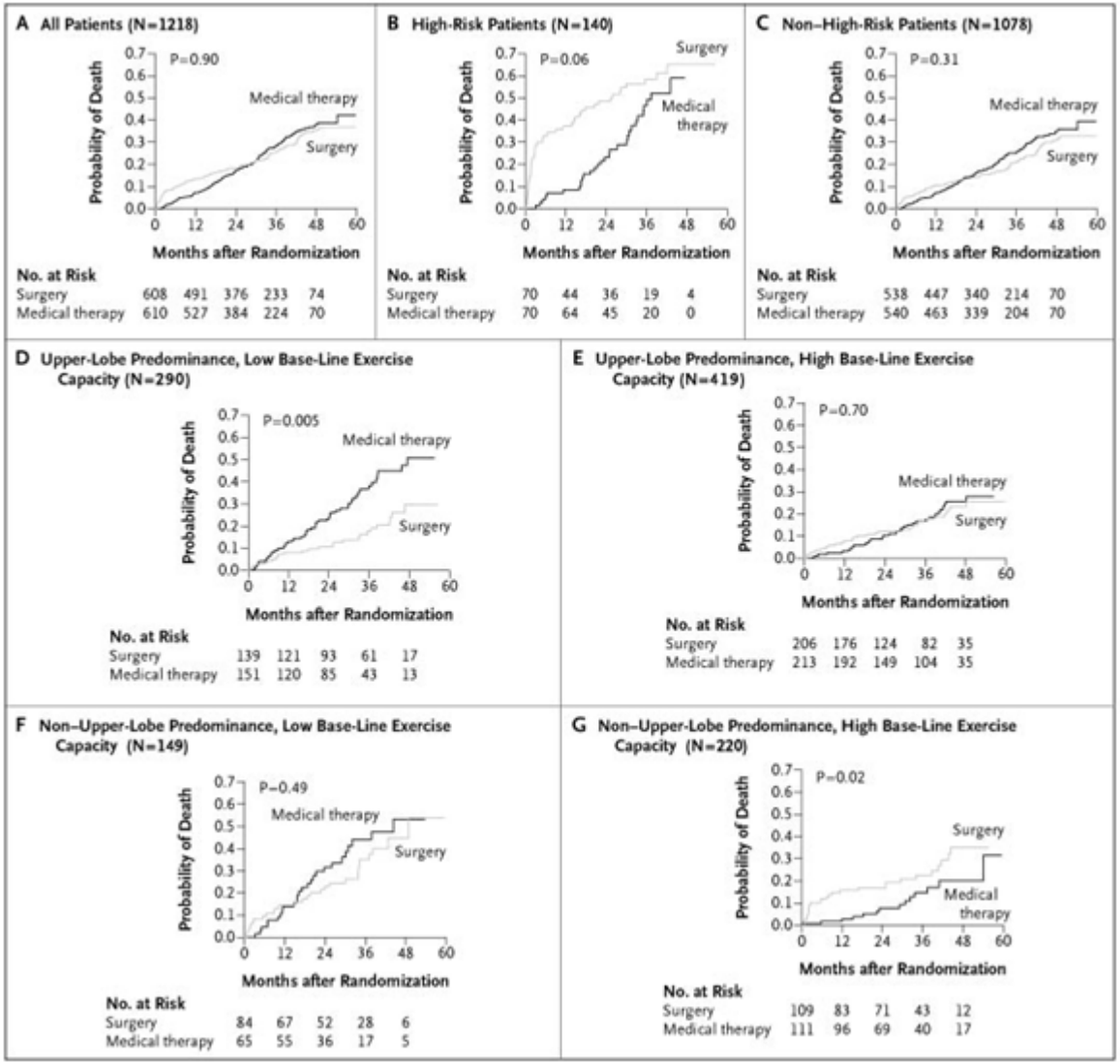
Lung volume correlates with survival



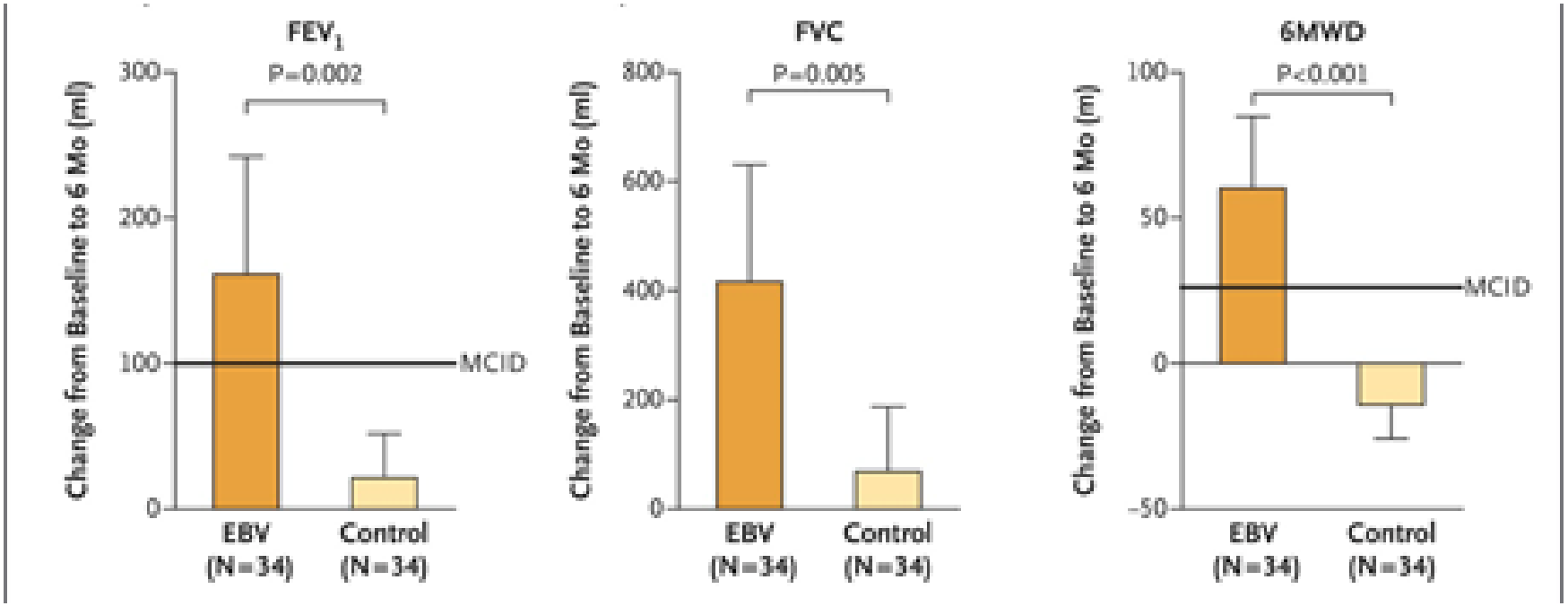


Casanova et al. AJRCCM 2005

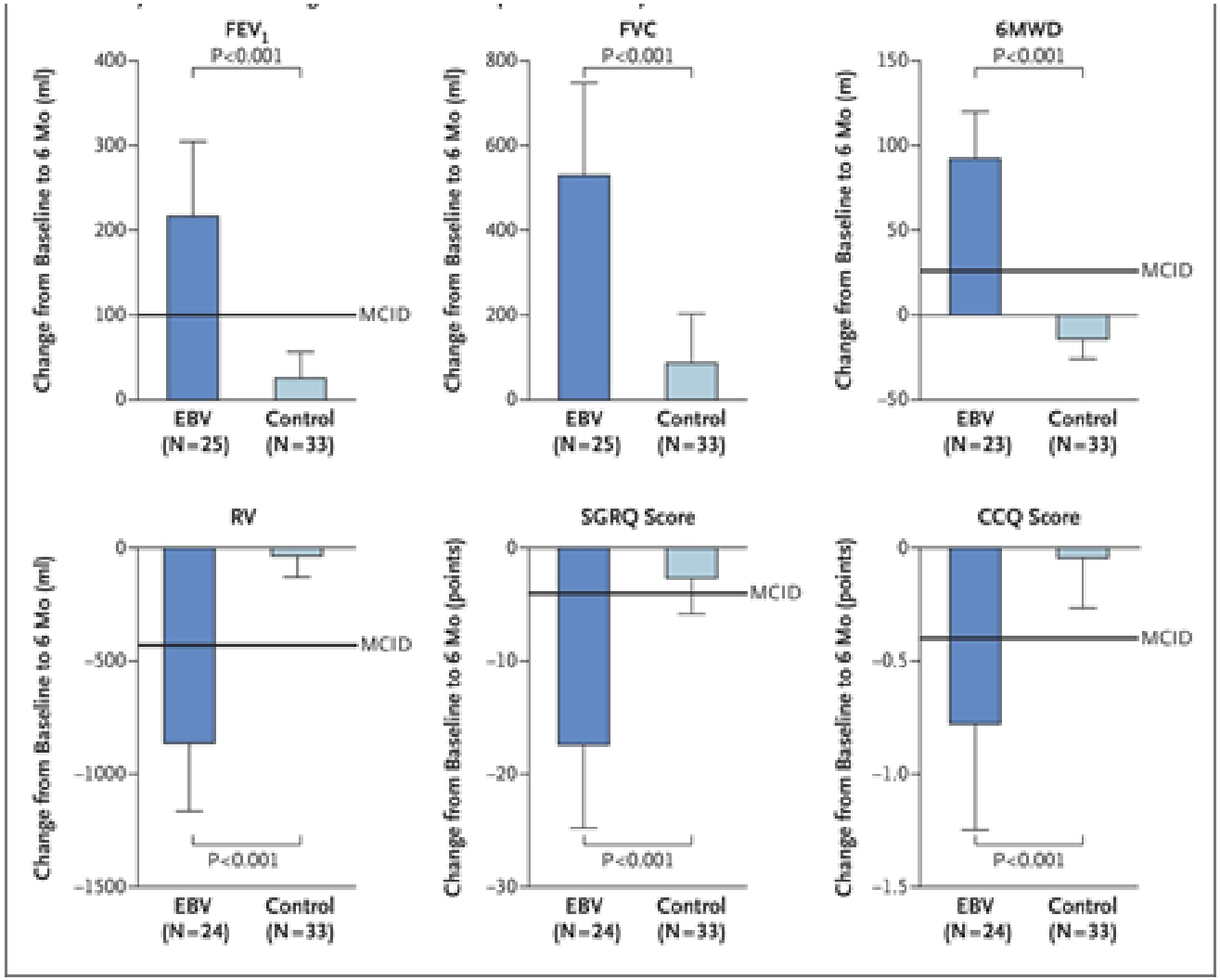
NETT trial


A All Patients (N=1218)
P=0.90
Medical therapy
Surgery
Probability of Death
Months after Randomization
No. at Risk
Surgery 608 491 376 233 74
Medical therapy 610 527 384 224 70
B High-Risk Patients (N=140)
P=0.06
Surgery
Medical therapy
Probability of Death
Months after Randomization
No. at Risk
Surgery 70 44 36 19 4
Medical therapy 70 64 45 20 0
C Non–High-Risk Patients (N=1078)
P=0.31
Medical therapy
Surgery
Probability of Death
Months after Randomization
No. at Risk
Surgery 538 447 340 214 70
Medical therapy 540 463 339 204 70
D Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)
P=0.005
Medical therapy
Surgery
Probability of Death
Months after Randomization
No. at Risk
Surgery 139 121 93 61 17
Medical therapy 151 120 85 43 13
E Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=419)
P=0.70
Medical therapy
Surgery
Probability of Death
Months after Randomization
No. at Risk
Surgery 206 176 124 82 35
Medical therapy 213 192 149 104 35
F Non–Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=149)
P=0.49
Medical therapy
Surgery
Probability of Death
Months after Randomization
No. at Risk
Surgery 84 67 52 28 6
Medical therapy 65 55 36 17 5
G Non–Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=220)
P=0.02
Surgery
Medical therapy
Probability of Death
Months after Randomization
No. at Risk
Surgery 109 83 71 43 12
Medical therapy 111 96 69 40 17

EBV for emphysema without CV



EBV for emphysema without CV



Conclusion

- Patients with symptoms of chronic bronchitis
- Patients with history of frequent exacerbations
- Patients with emphysema with exercise intolerance