EXCEL IN PULMONOLOGY
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3

The many clinically relevant phenotypes of Chronic Bronchitis and Emphysema

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Conflicts of Interest

- None

The history so far…

Sailor Travel Co.

The first “voluminous lungs” is described by Theophile Bonet.

1679

Rene Laennec, the physician who invented the stethoscope, coined the term 'emphysema'.

1837

John Hutchinson invented the spirometer.

1846

Dr. William Briscoe uses the term COPD at the 9th Aspen Emphysema Conference

1965

A1-AT

GAMA

1969

COPD

GOLD 1

2001

Big Marketing LTD

GOLD 3

2023

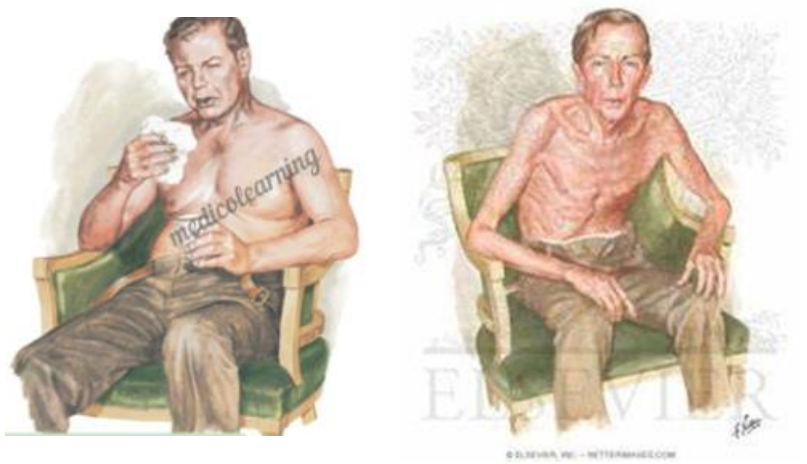
COPD@ATHENS

Oct 4th and 11th 2023, 6-8 pm CEST

ed training program in Respiratory Medicine

The ‘Stone Ages’

- It was only 15-20 years ago when COPD was still considered as an ‘orphan’ disease.
- Treatment relied on ‘borrowed’ drugs from asthma and theophylline
- Basically, nothing could be done except persuasion for smoking cessation
- FEV1 – centric categorization of severity in GOLD 1 guidelines (2001)
- Only two phenotypes of COPD, the ‘blue bloater’ and the ‘pink puffer’.



Alvar Agusti, 2014

Phenotyping: What is it and why bother?

- Phenotype refers to an individual's observable traits, such as height, eye colour and blood type. A person's phenotype is determined by both their genomic makeup (genotype) and environmental factors.
- But it's important to remember that phenotypes are equally, or even sometimes more greatly influenced by environmental effects than genetic effects.
- They allow us to classify patients into groups with different needs and different prognosis that require a different **treatment strategy.**

Blue Bloater (Chronic Bronchitis)

Symptoms

- Chronic, productive cough
- Purulent sputum
- Hemoptysis
- Mild dyspnea initially
- Cyanosis (due to hypoxemia)
- Peripheral edema (due to cor pulmonale)
- Crackles, wheezes
- Prolonged expiration
- Obese
- Complications
- Secondary polycythemia vera due to hypoxemia
- Pulmonary hypertension due to reactive vasoconstriction from hypoxemia
- Cor pulmonale from chronic pulmonary hypertension

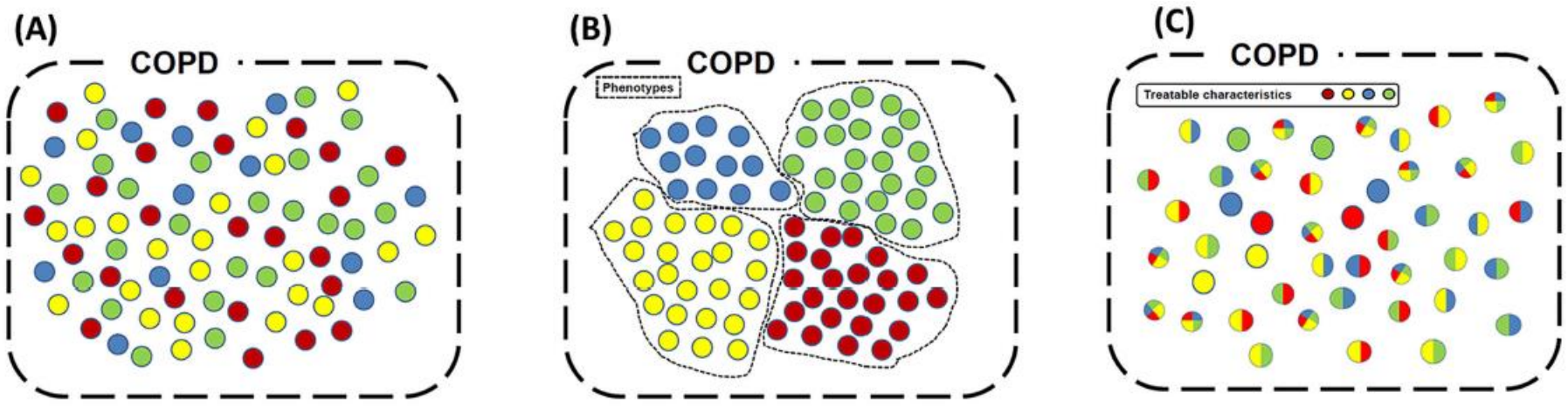
Pink Puffer (Emphysema)

Symptoms

- Dyspnea
- Minimal cough
- Increased minute ventilation
- Pink skin, Pursed-lip breathing
- Accessory muscle use
- Cachexia
- Hyperinflation, barrel chest
- Decreased breath sounds
- Tachypnea
- Complications
- Pneumothorax due to bullae
- Weight loss due to work of breathing

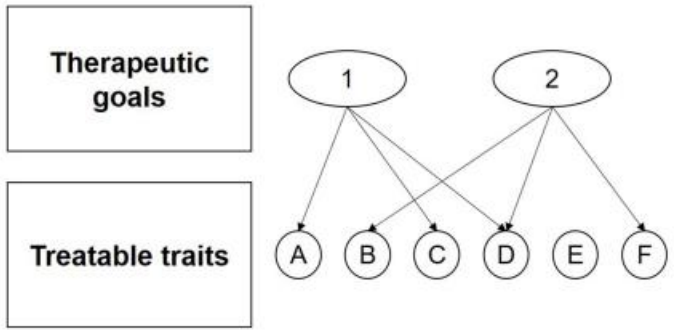
The ‘Renaissance of COPD’

- GOLD 3 in 2011 took into account exacerbation rates and dyspnoea scale (MRC).
- Spirometry is NOT correlated with patients’ symptoms or mortality.
- Phenotyping – Stratified medicine.



Alvar Agusti, 2014

Personalized Medicine and Treatable Traits

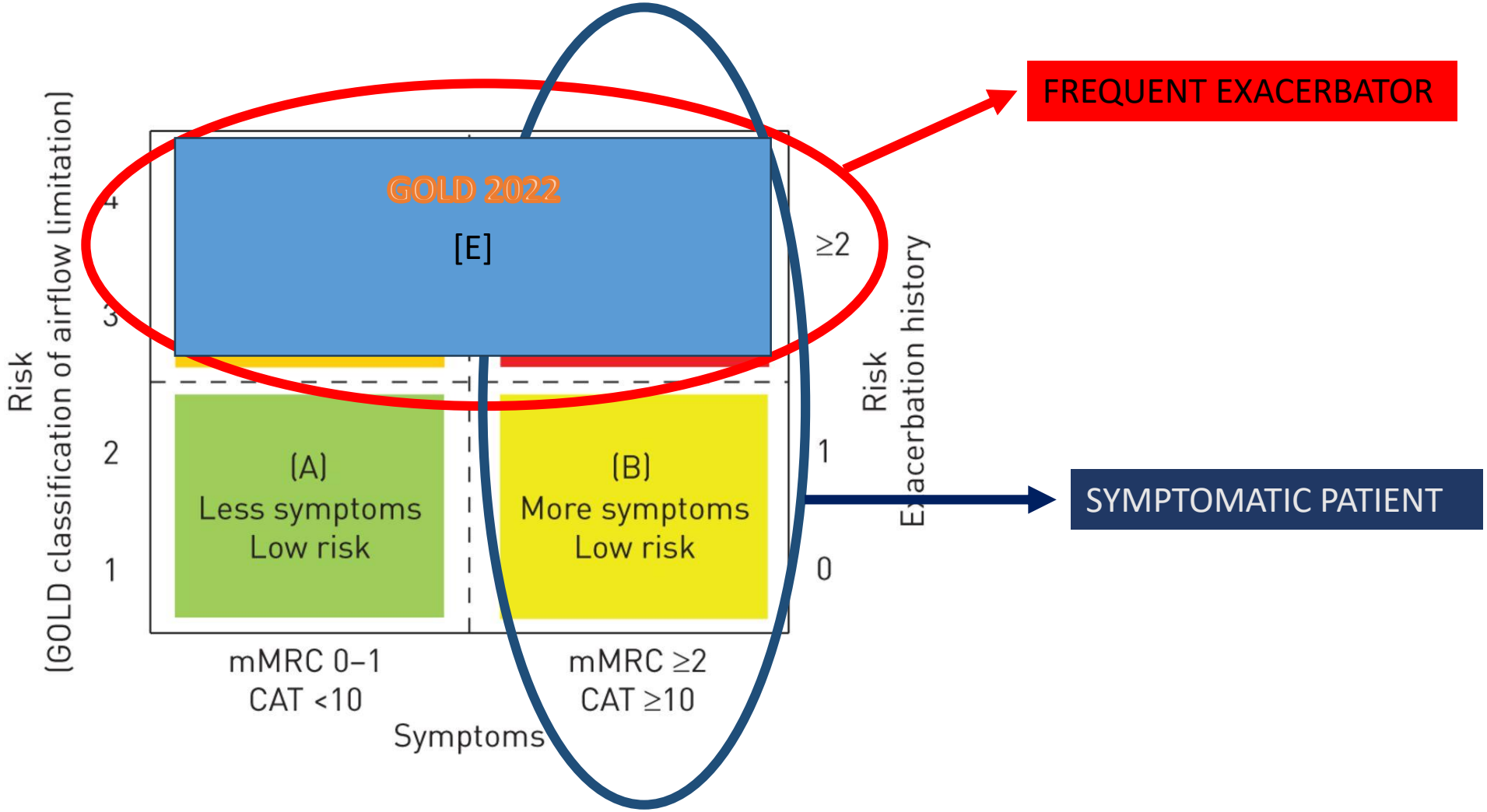


Pulmonary treatable trait

- Airflow limitation / Exacerbations
- Eosinophilic inflammation
- Chronic Bronchitis
- Emphysema
- A1-Insufficiency
- Exercise intolerance
- Chronic respiratory failure

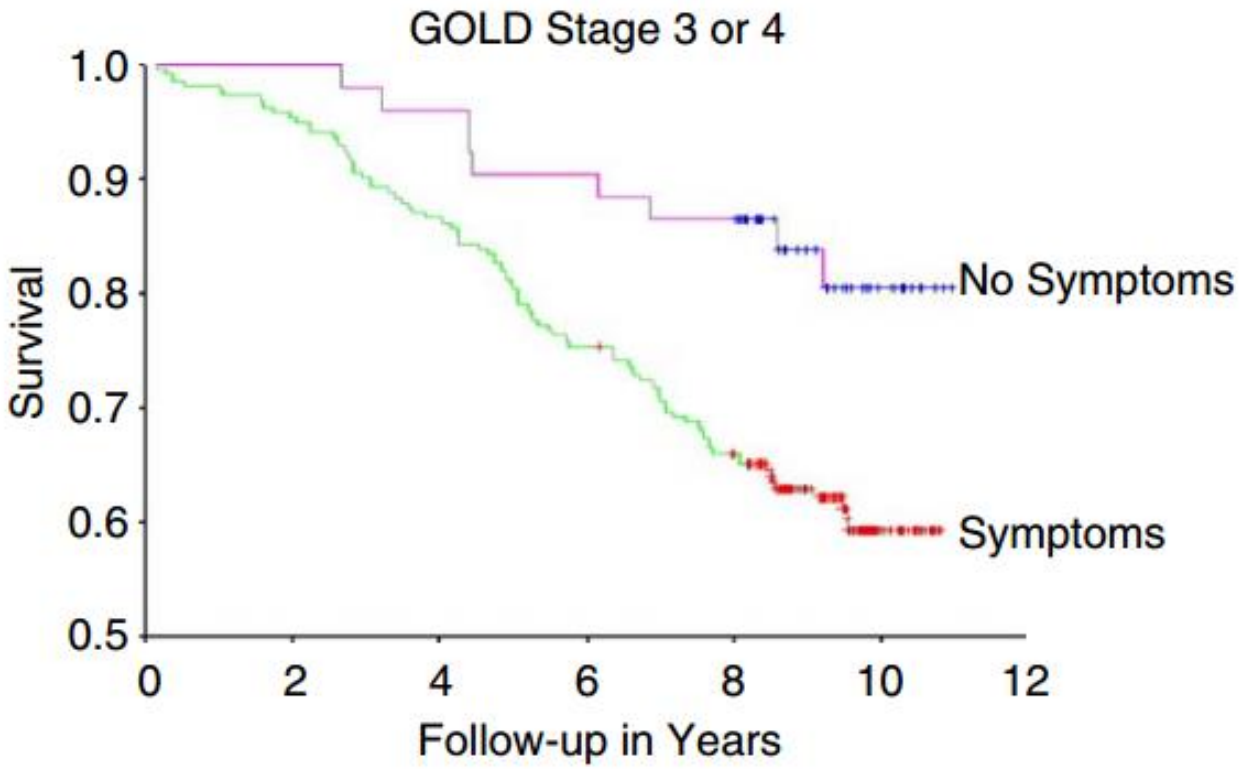
Extrapulmonary treatable trait

- Deconditioning
- Comorbidities
- Obstructive sleep apnea
- Osteoporosis
- Systemic inflammation
- GERD

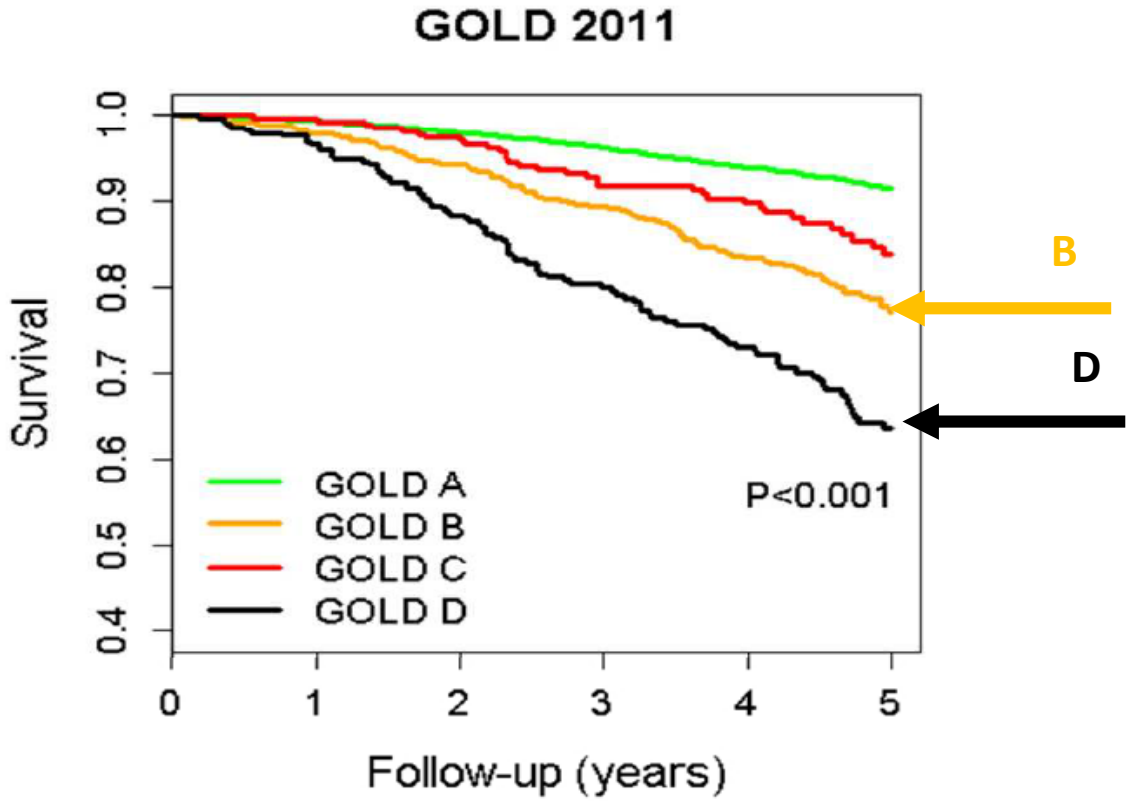

GOLD 2022
[E]
FREQUENT EXACERBATOR
SYMPTOMATIC PATIENT
Risk
(GOLD classification of airflow limitation)
4
3
2
1
(A)
Less symptoms
Low risk
(B)
More symptoms
Low risk
mMRC 0–1
CAT <10
mMRC ≥2
CAT ≥10
Symptoms
≥2
1
0
Risk
Exacerbation history

The symptomatic patient in stable COPD

Symptoms is the key!!!



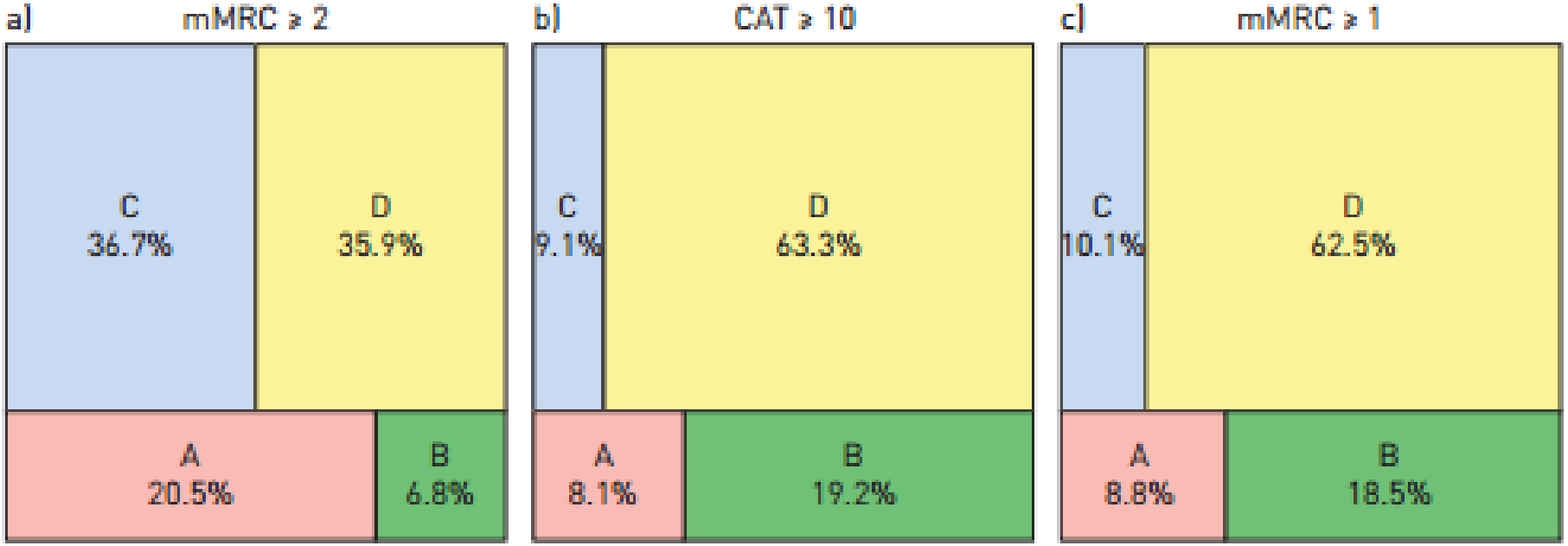
Manino DM et al Resp Med 2006



Lange P, AJRCCM 2012

Definition of the symptomatic patient mMRC≥2 or 1?

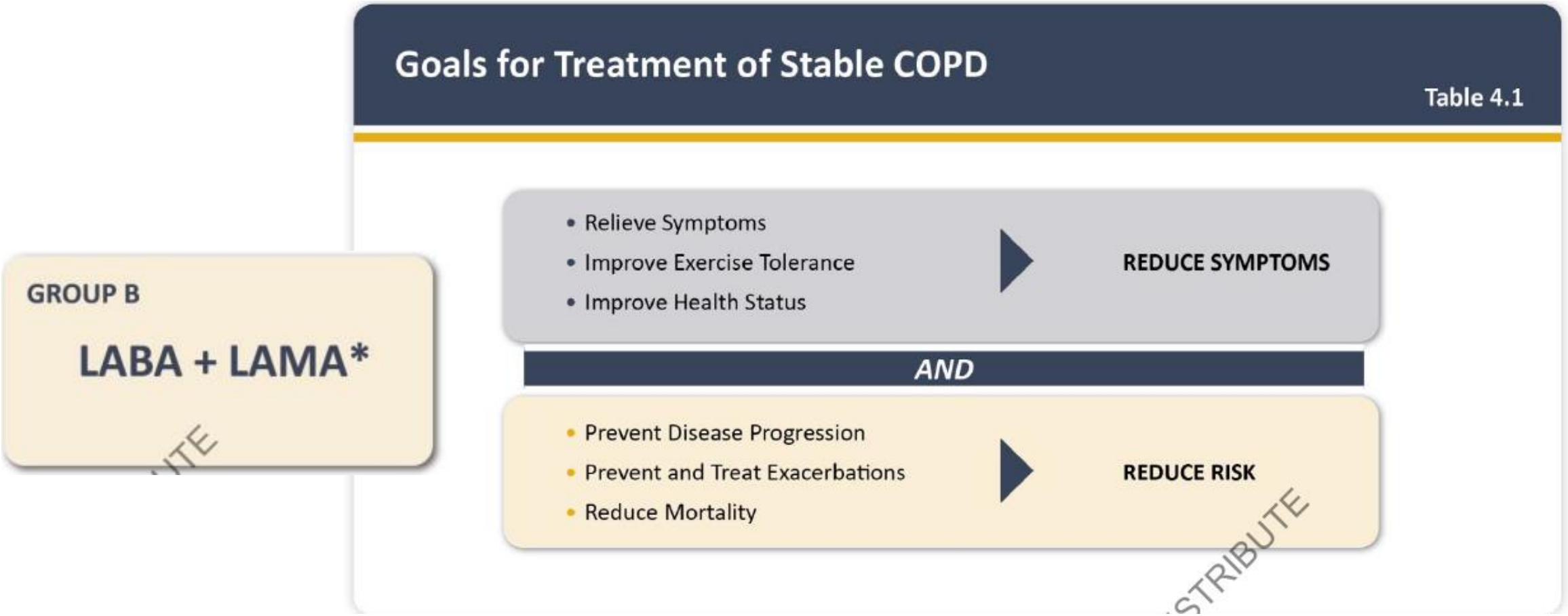
1817 COPD patients



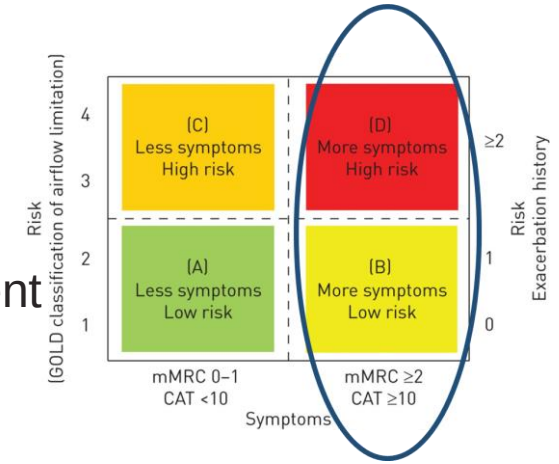
Low symptom group=57.2% **Low symptom group=17.2%** **Low symptom group=18.9%**

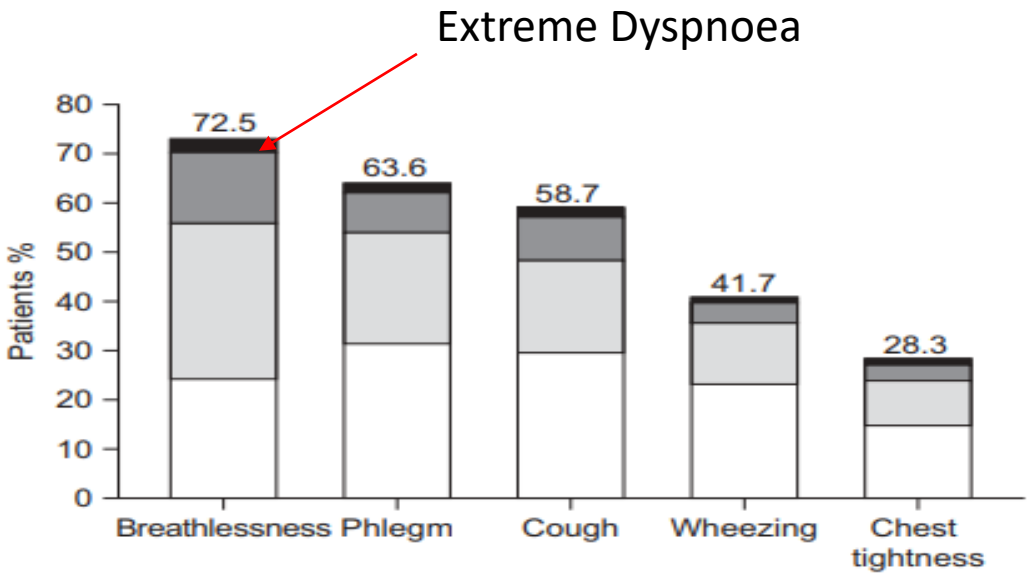
<u>mMRC ≥2 appears not to be equivalent to CAT ≥10</u>

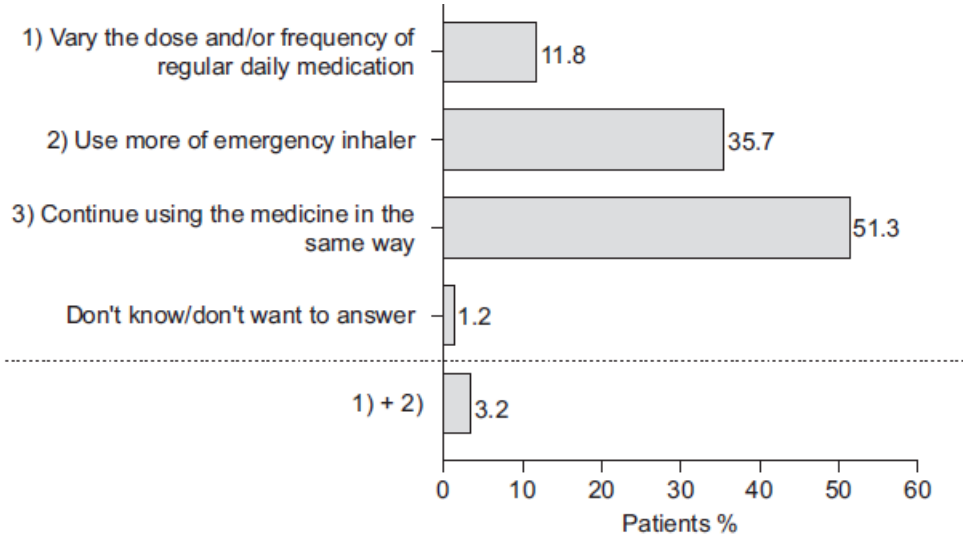
Jones P et al. ERJ 2013


Goals for Treatment of Stable COPD
Table 4.1
GROUP B
LABA + LAMA*
• Relieve Symptoms
• Improve Exercise Tolerance
• Improve Health Status
REDUCE SYMPTOMS
AND
• Prevent Disease Progression
• Prevent and Treat Exacerbations
• Reduce Mortality
REDUCE RISK

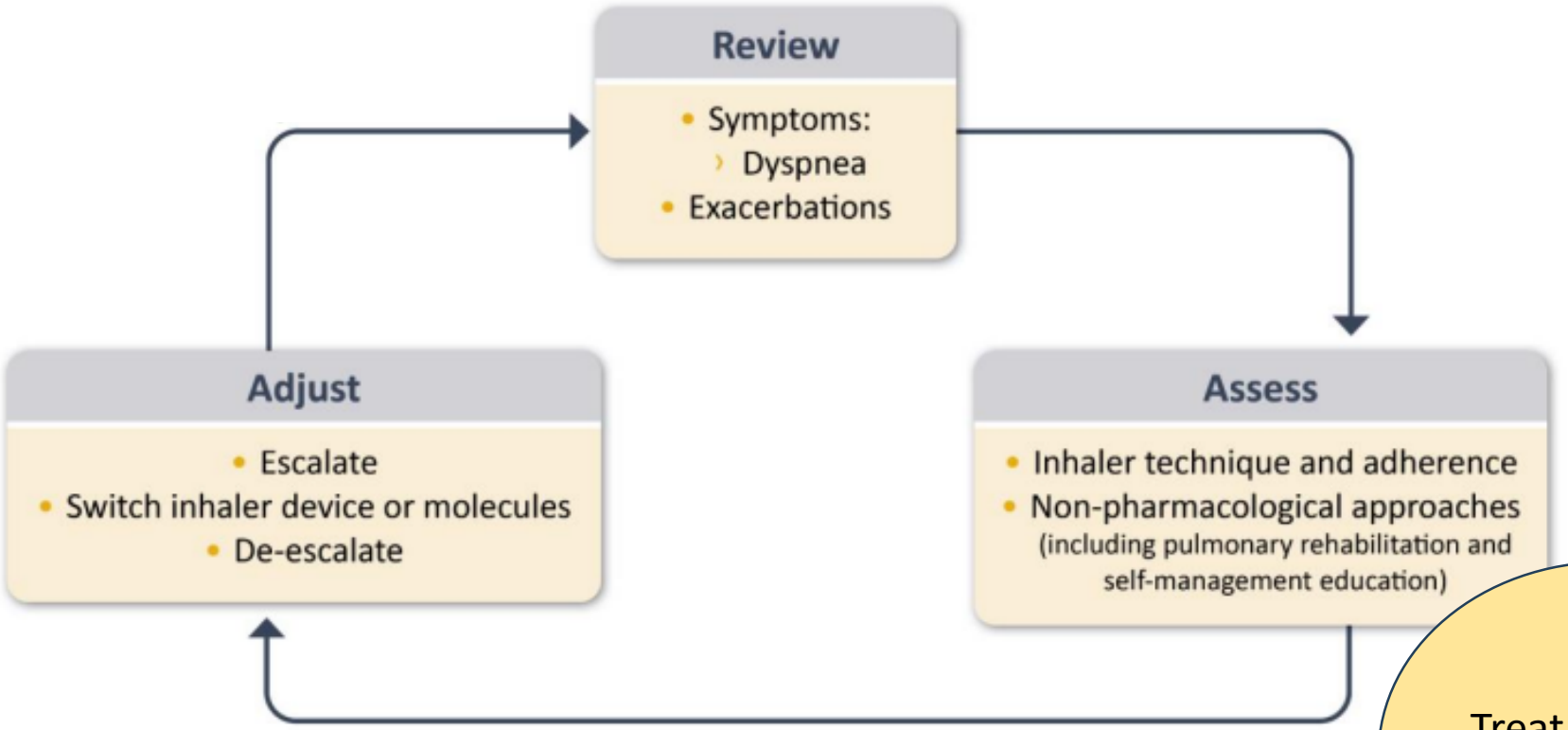
- The most common symptom is shortness of breath.
- More prominent in the early morning.
- High daily and weekly variability.
- The majority of patients appear not to adjust treatment when symptoms worsen.







Kessler 2011.



Treat Treatable Traits!!!

The frequent exacerbator

- Exacerbations are related to higher mortality rates and more exacerbations in the future.
- Frequent exacerbators are defined as those with more than 2 per/year.
- Frequent exacerbators have a more rapid decline in FEV1.

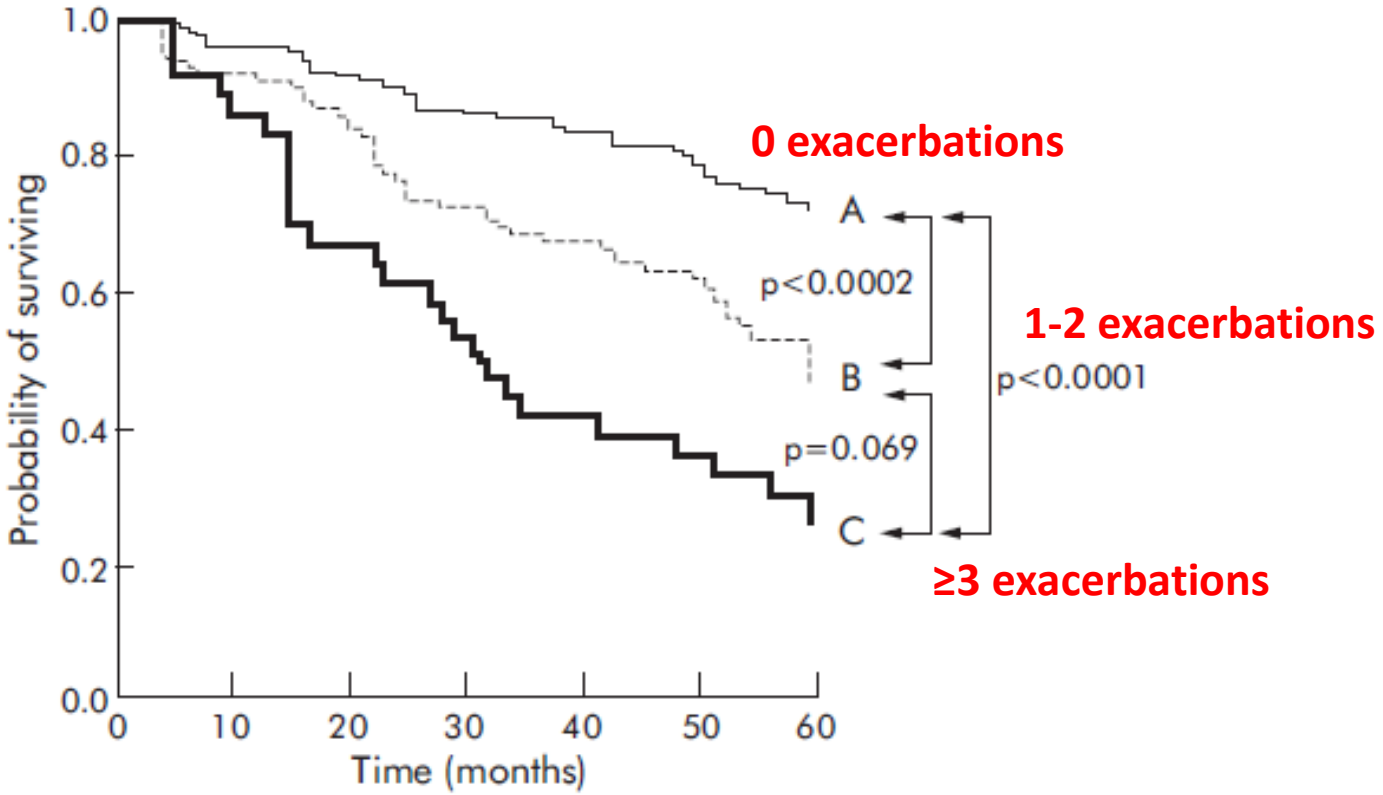
Table 3 Initial and annual change in lung function in patients with infrequent and frequent exacerbations

	Starting value		Annual change	
	Infrequent	Frequent	Infrequent	Frequent
Exacerbations (reported and unreported)			<50% percentile, <2.92 per year (n=63)	> 50% percentile >2.92 per year (n=46)
PEF (l/min)	214	232	–0.72 (n=16)	–2.94*** (n=16)
FEV_1 (ml)	893	950	–32.1	–40.1*

PEF=peak expiratory flow; FEV_1=forced expiratory volume in 1 second.
*p<0.05, ***p<0.001 annual rates of change between infrequent and frequent exacerbators.

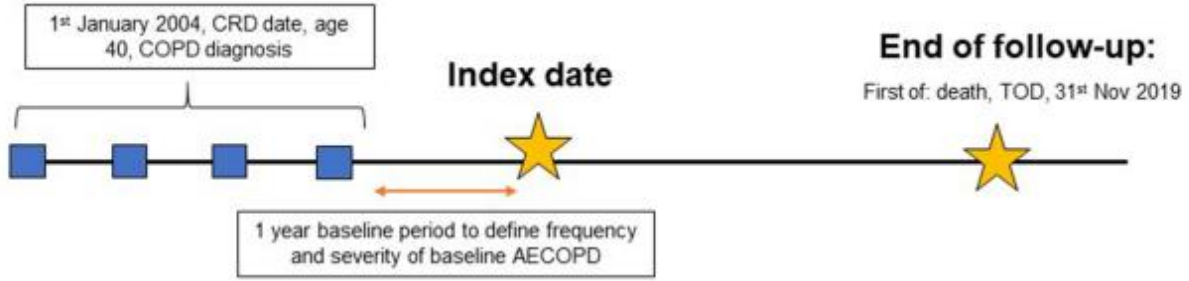
Donaldson GC et al Thorax 2002

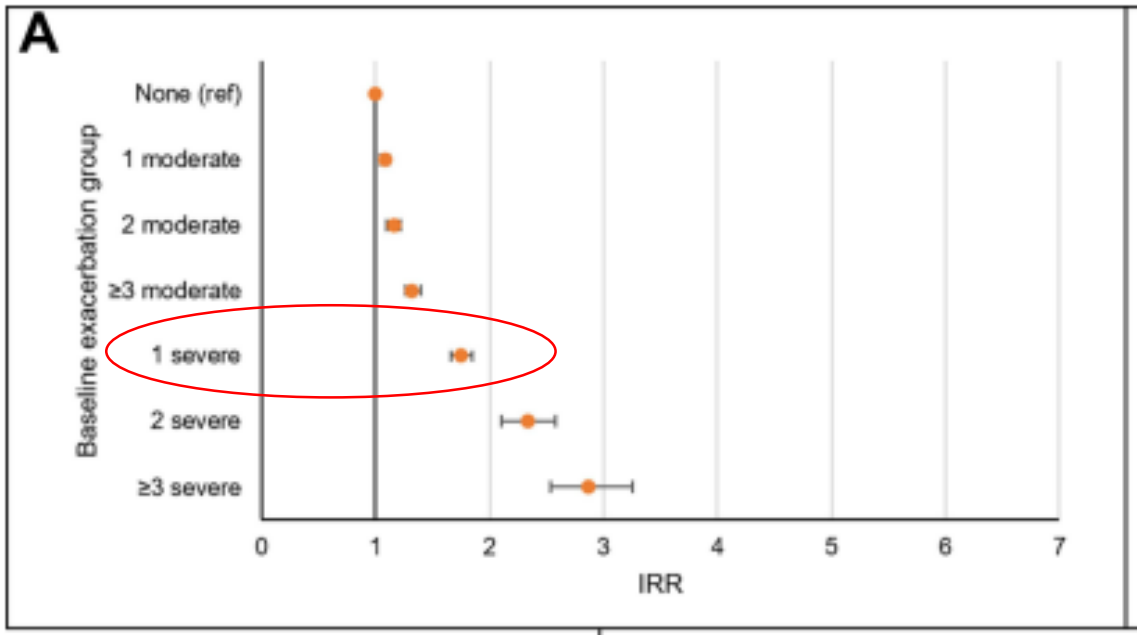
Frequent exacerbators display higher mortality

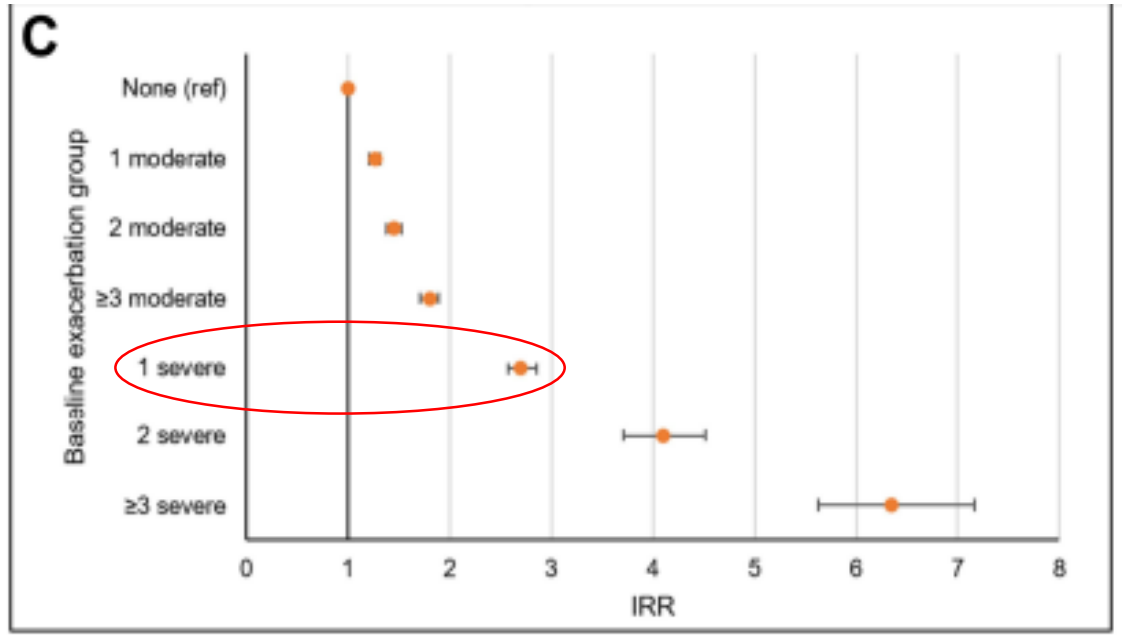


EXACOS-UK STUDY

340,515 patients







Hannah Whittaker et al. 2022

Treat Treatable Traits!!!

NO

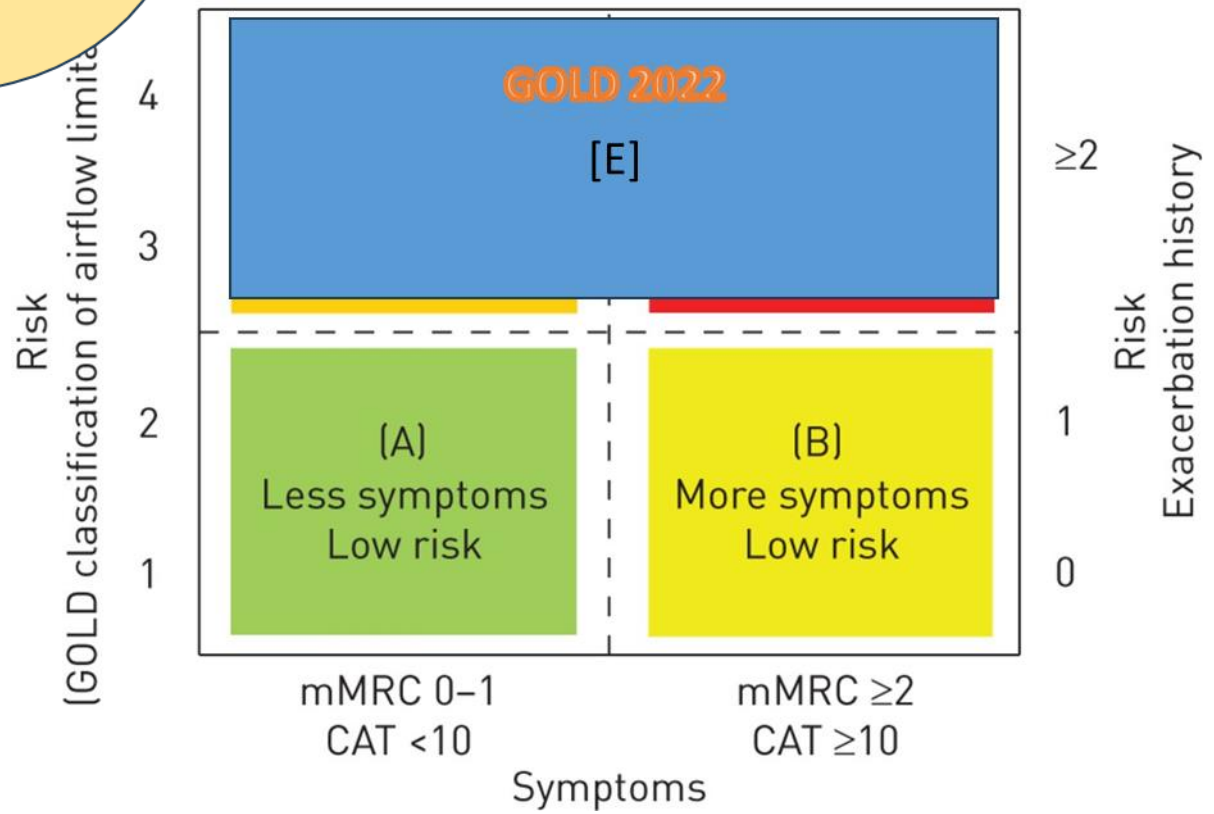
Eos > 300

YES

LABA/LAMA/ICS

lower rate of moderate or severe COPD exacerbations BY 25% (FF/UMEC/VI)

IMPACT Study



Miravitlles M et al Arch Bronc 2014

Astha - COPD overlap and eosinophilic inflammation

Eosinophilic airway inflammation

‘…In contrast to asthma, COPD was traditionally regarded as a mainly neutrophilic inflammatory disease. However, increased numbers of eosinophils have been detected in the airways of COPD patients, from sputum to bronchoalveolar lavage.’

Why is eosinophilic inflammation a treatable trait?

- An increased blood eosinophil count (BEC) in stable phase is related to an increased risk of exacerbations.
- It has been shown to predict therapeutic response to inhaled ICS.

Cardoso et al, 2021

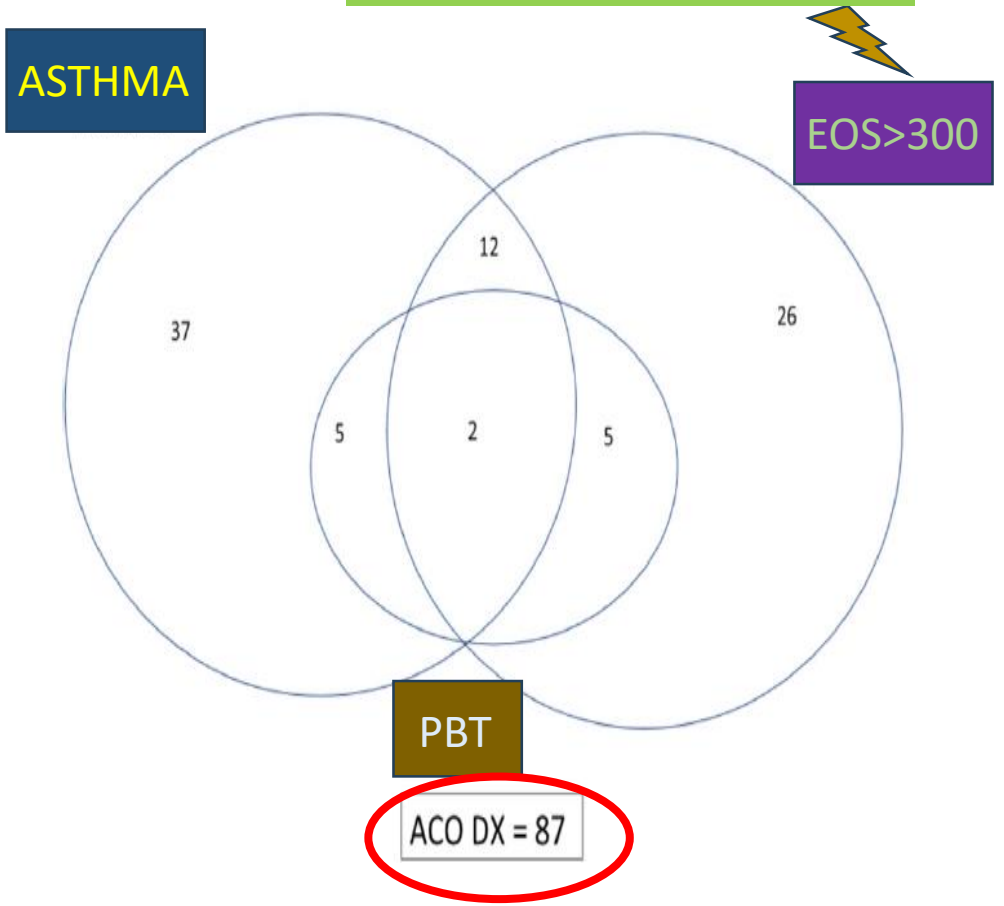
ACO

Table 2. Different diagnostic criteria of ACO used in clinical observational studies.

Study	Diagnostic criteria of ACO	*N* (total)	ACO *N* (%)
Hardin et al.(7) COPDGene	• Age: 45–80 years old • Smoking history ≥10 pack-years • Post BDT FEV_1/FVC <0.70 • History of asthma (defined as diagnosis reported by a physician before 40 years of age)	915	119 (13%)
Miravitlles et al. (8) EPI-SCAN	• Age: 40–80 years old • Post BDT FEV_1/FVC <0.70 • Previous diagnosis of asthma	385	67 (17.4%)
Menezes et al. (9) PLATINO	• COPD diagnosis (post BDT FEV_1/FVC <0.70) • Concomitant diagnosis of asthma: wheezing in the last 12 months + post BDT increase in FEV_1 or FVC of 200 ml and 12% *or* previous diagnosis of asthma	767	89 (11.6%)
Barrecheguren et al. (23) FyCEPOC	• Age ≥40 years old • Smoking history ≥10 pack-years • Post BDT FEV_1/FVC<0.70 **ACOS 1:** • ACOS diagnostic criteria of the Spanish consensus 2012 (12): 1) Major criteria: very positive bronchodilator test (improvement in FEV_1 400 mL and 15%); sputum eosinophilia or a previous diagnosis of asthma before the age of 40 years. 2) Minor criteria: increased total serum immunoglobulin (Ig)E; and previous history of atopy or a positive bronchodilator test (200 mL and 12% in FEV_1) on at least two occasions.	3125	158 (5.1%)
	ACOS 2: • Previous diagnosis of asthma before the age of 40 years		338 (10.8%)
Wurst et al. (24) ECLIPSE	• COPD diagnosis (FEV_1/FVC <0.70) • Self-reported previous diagnosis of asthma	1483	493 (25%)
Pérez de Llano et al. (40) CHACOS	GESEPOC- GEMA algorithm (17): • Age ≥35 years old • Tobacco exposure ≥10 pack-years • Post BDT FEV_1/FVC <0.70 • History of asthma and/or other features of asthma (atopy and/or respiratory symptoms: wheezing, cough, chest oppression) • In absence of asthma diagnosis: • very positive BDT (≥400 mL and 15%) and/or Blood eosinophilia ≥300 eosinophils/μL	292	87 (29.8%)

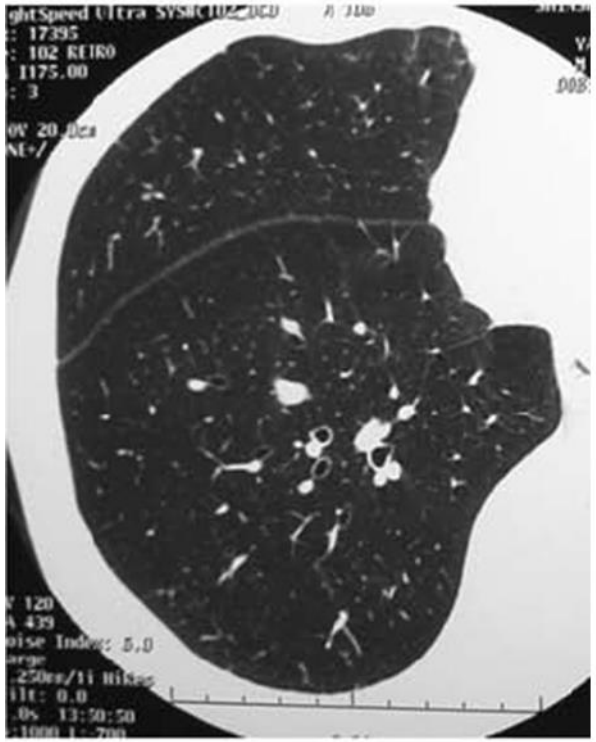
BDT: bronchodilator test; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity.

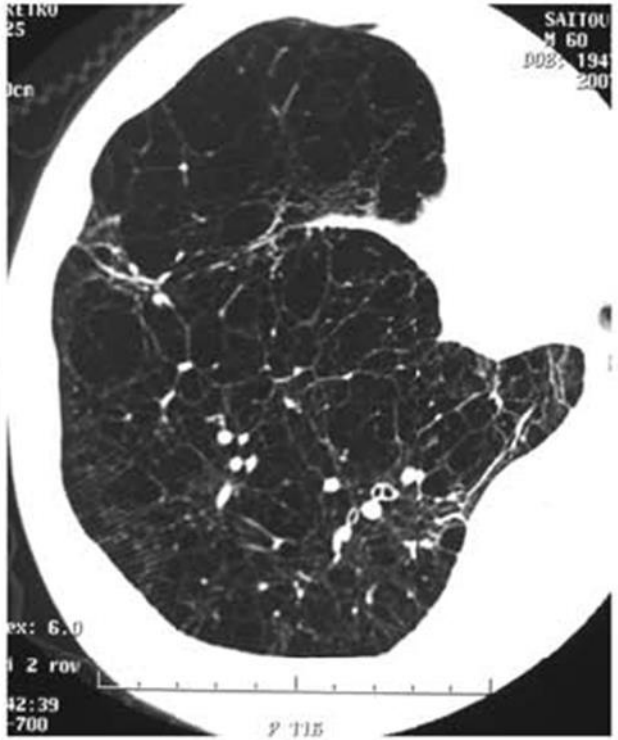
Type 2 inflammation :
- FeNO?,
- Sputum Eosinophils?

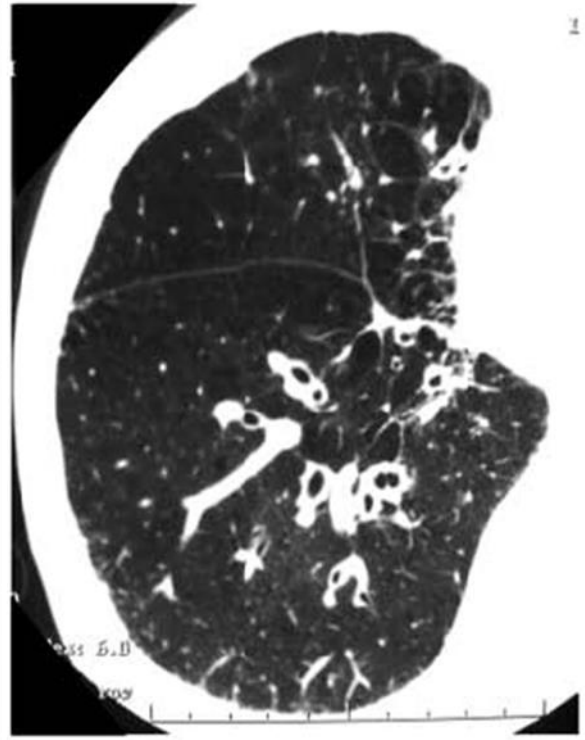


Nuñez et al 2019

Chronic Bronchitis







‘Airway’ Phenotype

- Thickness/Diameter of airway ratio
- Chronic bronchitis association
- Better BMI, less dyspnoea
- Increased sputum

‘Emphysema’ Phenotype

- More dyspnoea
- Hyperinflation
- Worst DLCO

‘Mixed’ Phenotype

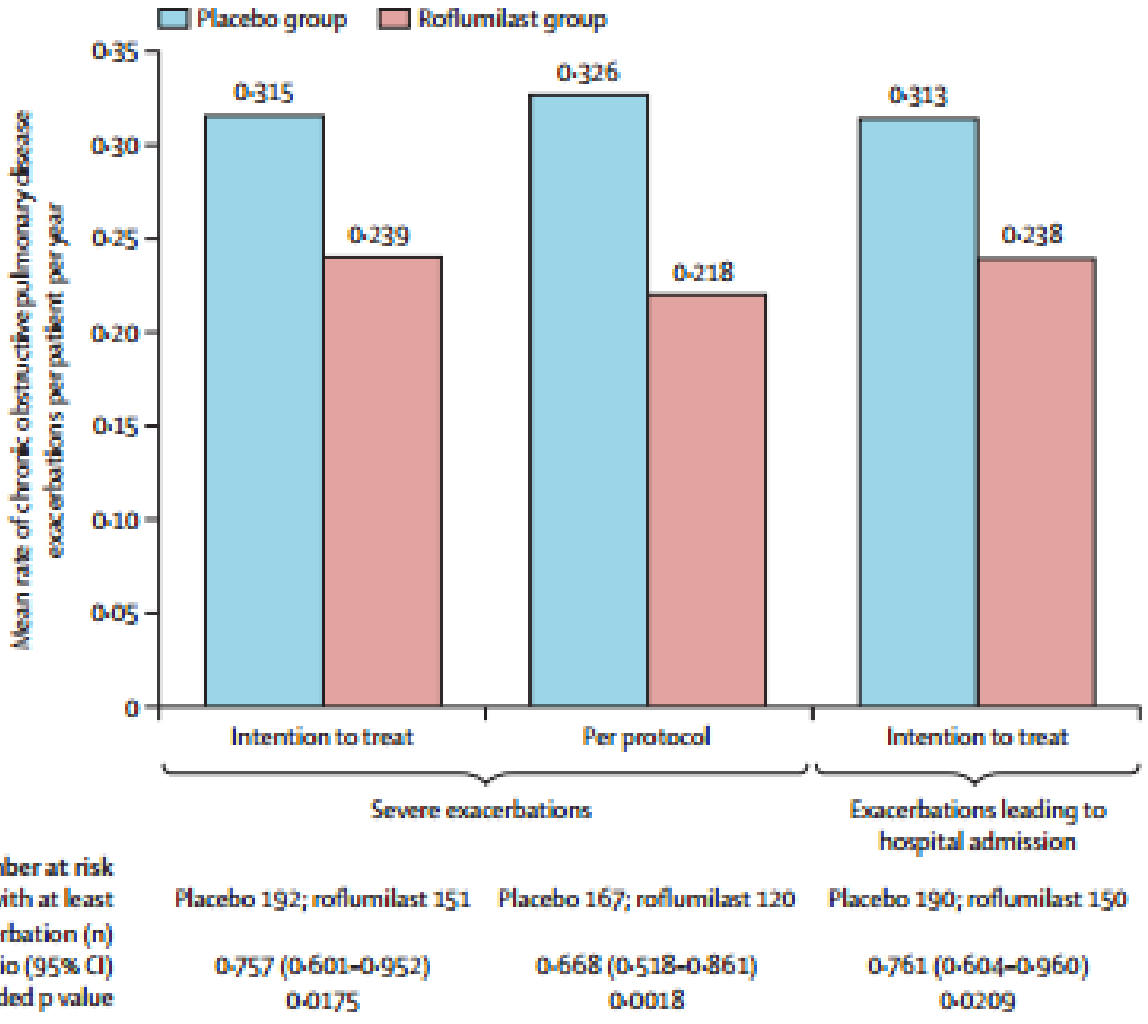
Homori H. et al Curr Op Pulm Med 2008
Boscetto P et al Thorax 2006

Chronic bronchitis and airway microbiome

- It has been shown that the composition of the lung microbiota differs in healthy individuals and in COPD patients, both in richness and diversity.
- More severe COPD is associated with reduced microbial diversity.
- In the absence of symptoms of acute infection, the isolation of microorganisms has been regarded as bacterial colonization.
- Persistence of these bacteria leads to maladaptive immune responses
- The use of long-term antibiotics (azithromycin), mucolytics and vaccinations has been shown to reduce exacerbations and improve quality of life.
- ICS should be avoided in those patients, especially with low eosinophil blood count.

Cardoso et al, 2019

Roflumilast and exacerbation rate in chronic bronchitis



Martinez FJ et al, Lancet 2015

Martinez FJ et al, Lancet 2015

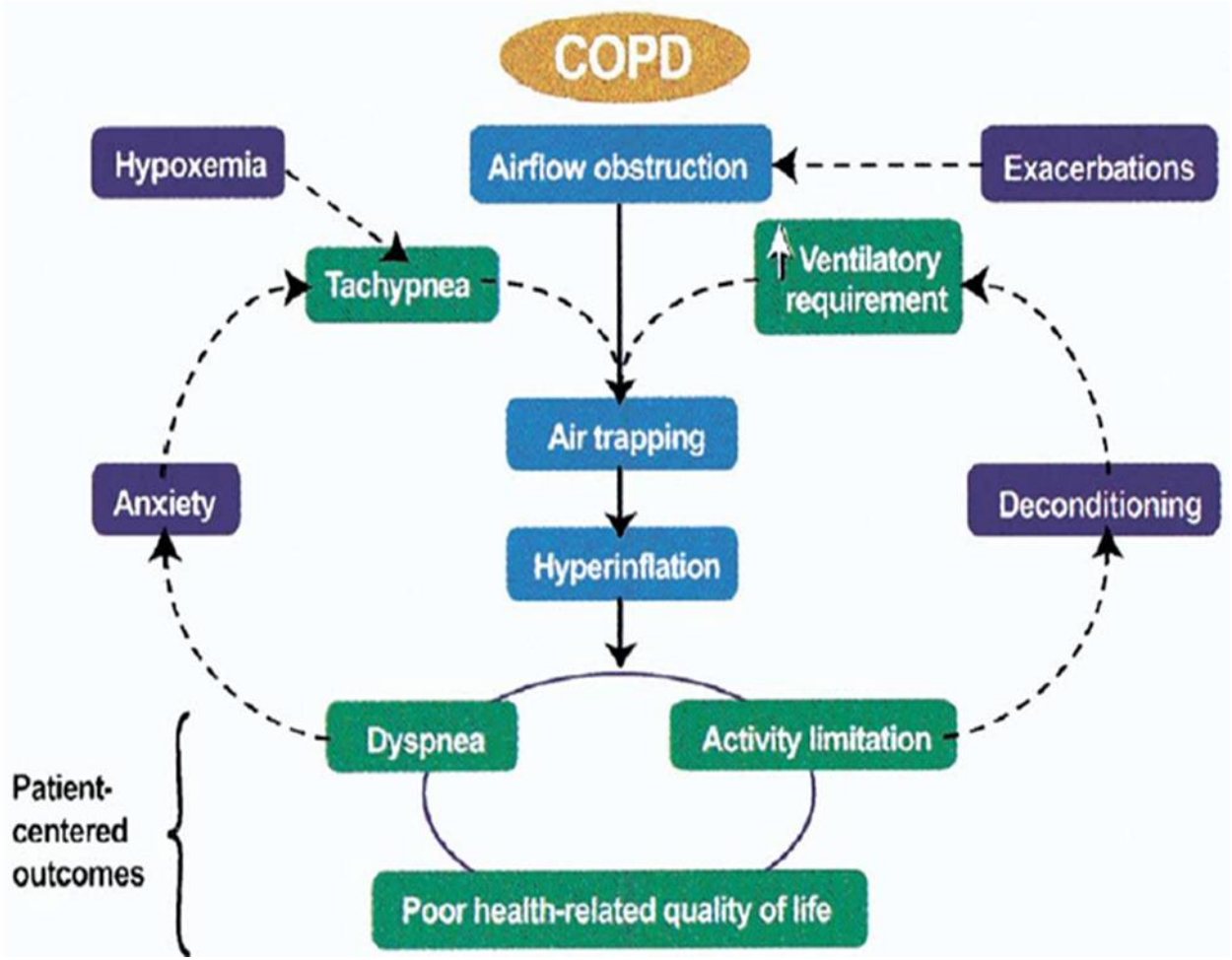
Review > Eur Respir Rev. 2015 Sep;24(137):451-61. doi: 10.1183/16000617.00002215.

Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis

Mario Cazzola [1], Luigino Calzetta [2], Clive Page [3], Josè Jardim [4], Alexander G Chuchalin [5], Paola Rogliani [2], Maria Gabriella Matera [6]

‘The strong signal that comes from this meta-analysis leads us to state that if a patient suffering from chronic bronchitis presents a documented airway obstruction, NAC should be administered at a dose of ≥ 1200 mg per day to prevent exacerbations, while if a patient suffers from chronic bronchitis, but is without airway obstruction, a regular treatment of 600 mg per day seems to be sufficient.’

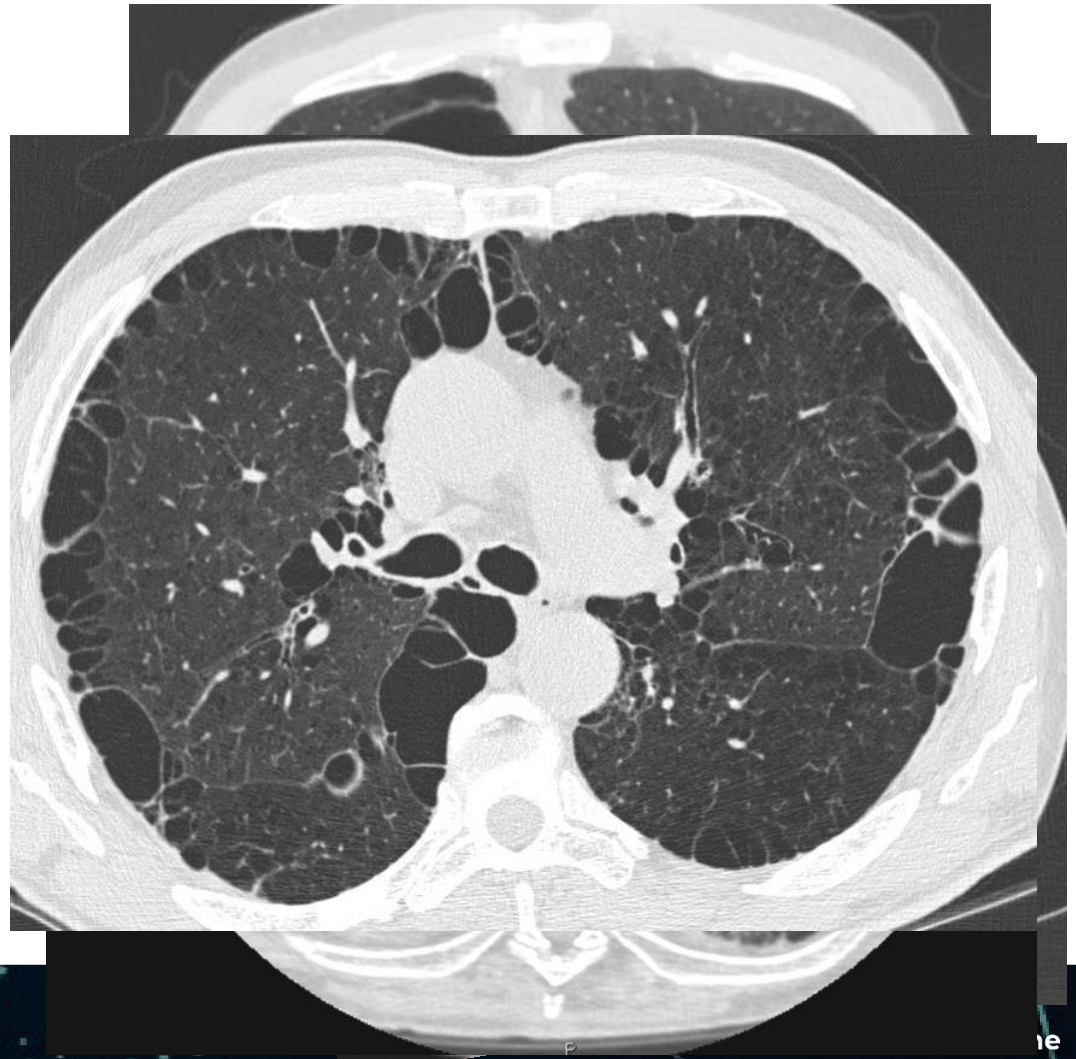
Emphysema and Hyperinflation



Cooper CB. 2006

Defining emphysema phenotypes
FEV1/FVC<70, >5% (-950HU) without other specific disease

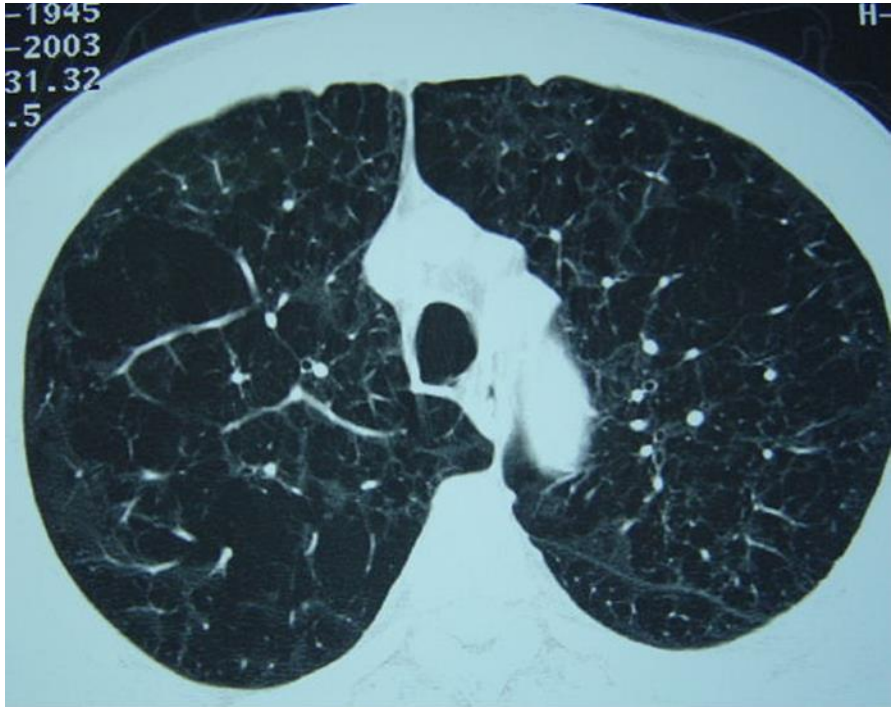
- A_1AT deficiency
- Bullous Disease
- Paraseptal Emphysema
- CPFE

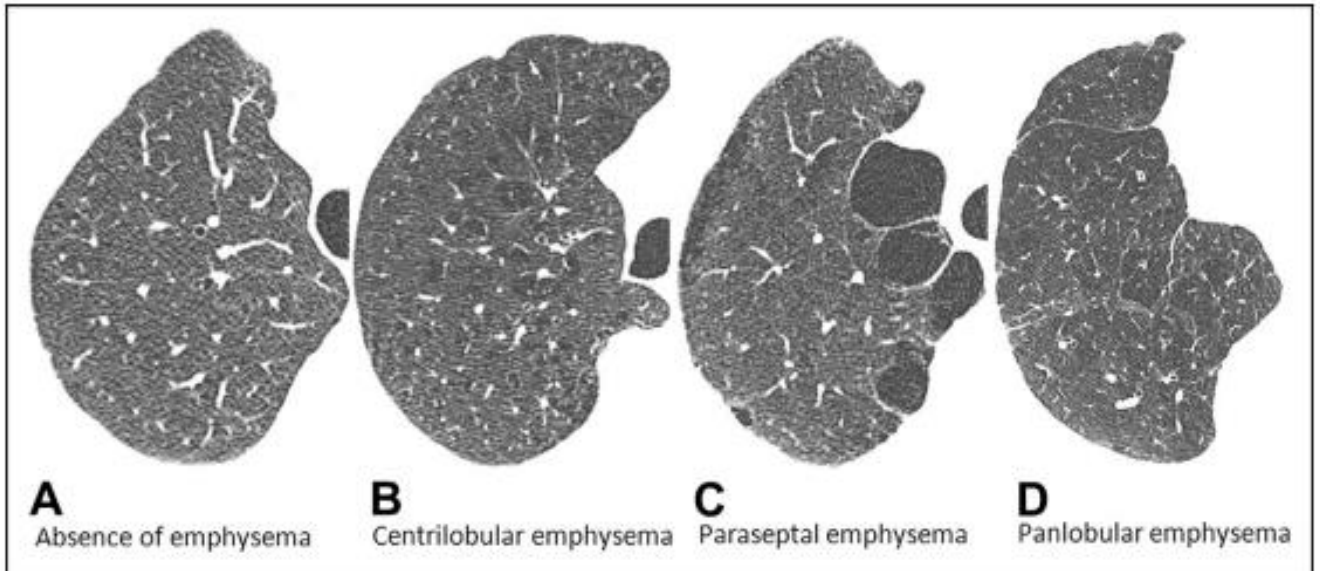


RADIOLOGICAL PHENOTYPING

HRCT IN THE DIAGNOSIS OF COPD

- Slices of 0,5mm – 1mm
- Can identify structures of 200-300µm
- Can identify up to 9th generation airways
- Early changes (emphysema or thickening of airways) can be identified BEFORE abnormalities in PFTs and symptom onset.
- Hounsfield Units < -950 indicative of emphysema

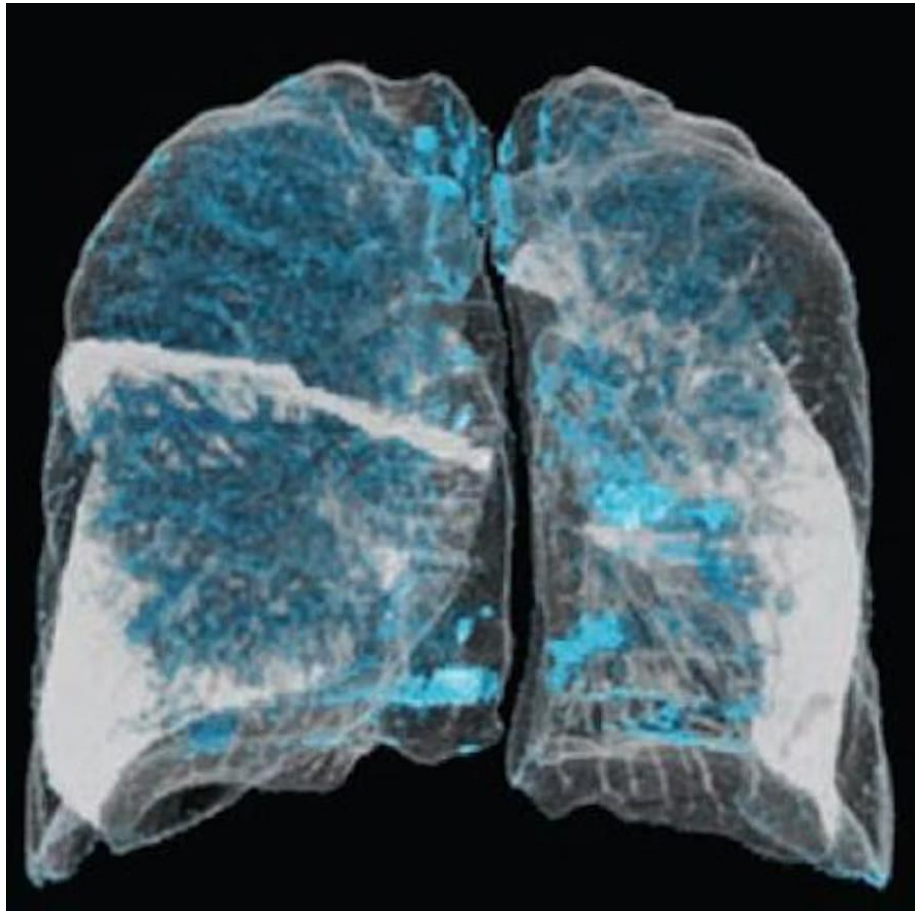


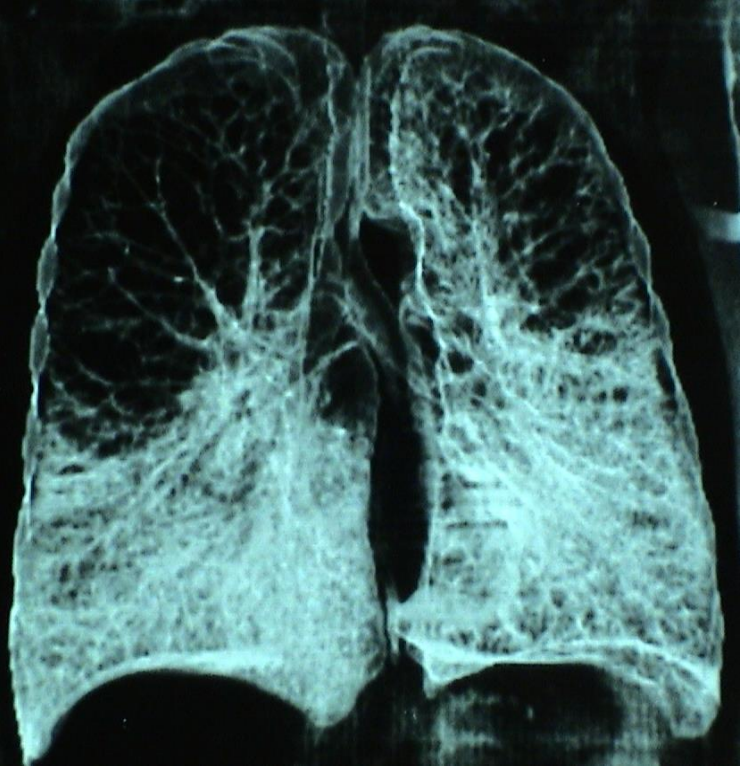


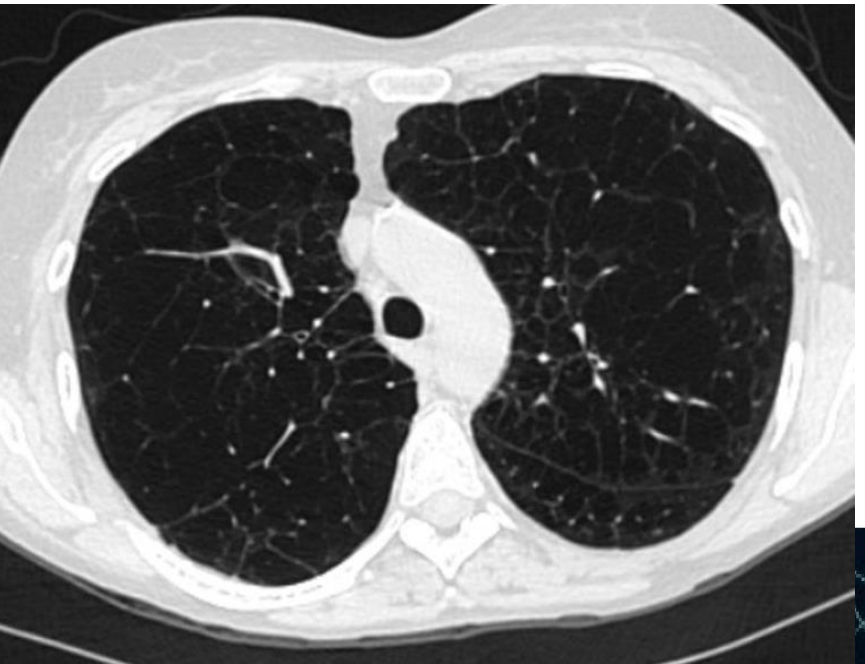
- Centrilobular and panlobular emphysema detected visually on computed tomography (CT) were associated with increased symptoms and reduced exercise capacity.
- Paraseptal emphysema, although common, was of little physiologic significance.
- Emphysema on CT was also observed among 17% of participants without spirometry-defined chronic obstructive pulmonary disease and was associated with functional impairment.
- Centrilobular, but not panlobular or paraseptal, emphysema was associated with greater smoking history
- Panlobular, but not other types of emphysema, was associated with reduced body mass index.
- Other than for dyspnea, these findings were independent of the forced expiratory volume in 1 second.

Benjamin M. Smith, 2020

ARTIFICIAL INTELLIGENCE IN EMPHYSEMA



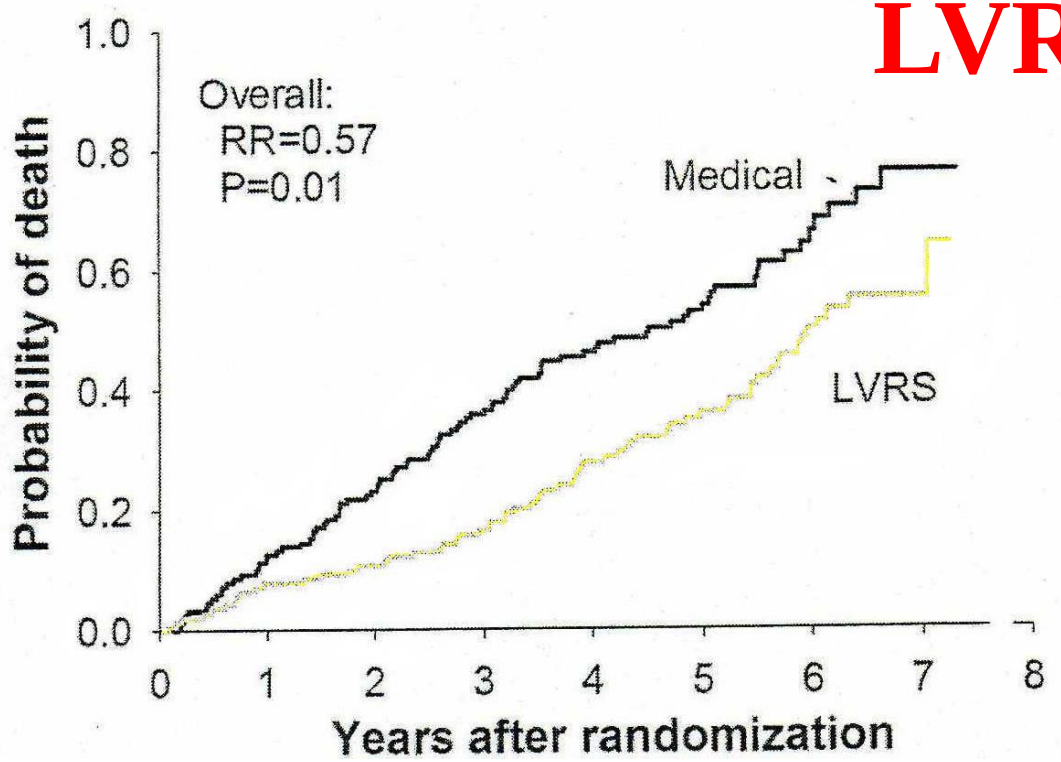




Targeting Lung Hyperinflation
Centrilobular, upper lobe predominance emphysema with marked hyperinflation (TLC>100%, RV>150%, DLCO> 20% and reduced exercise capacity: post rehab baseline max work of ≤ 25 watts for women and ≤ 40 watts for men.

Nationa Emphysema Treatment Trial 1218 pts

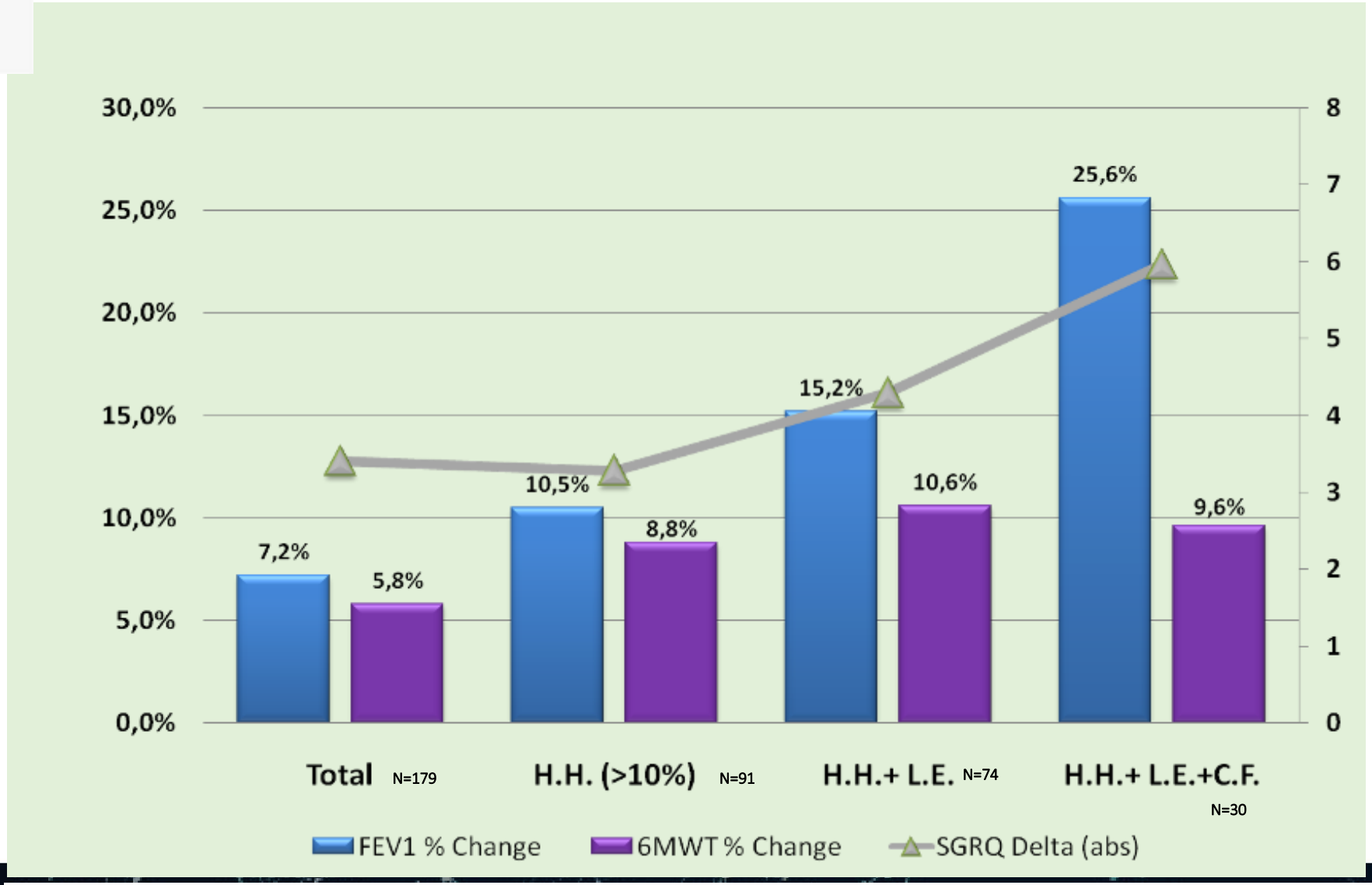
LVRS

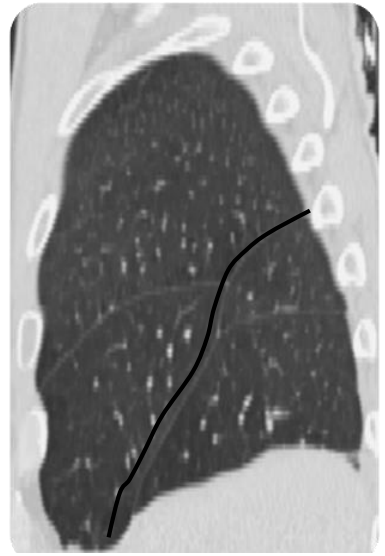


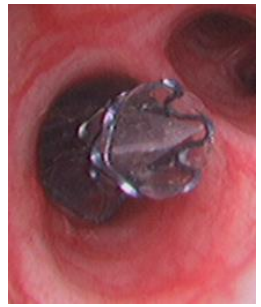
Ann Thorac Surg 2006;82:431-3

VENT Responder Summary

(Delta Treatment & Control @ 6mons)





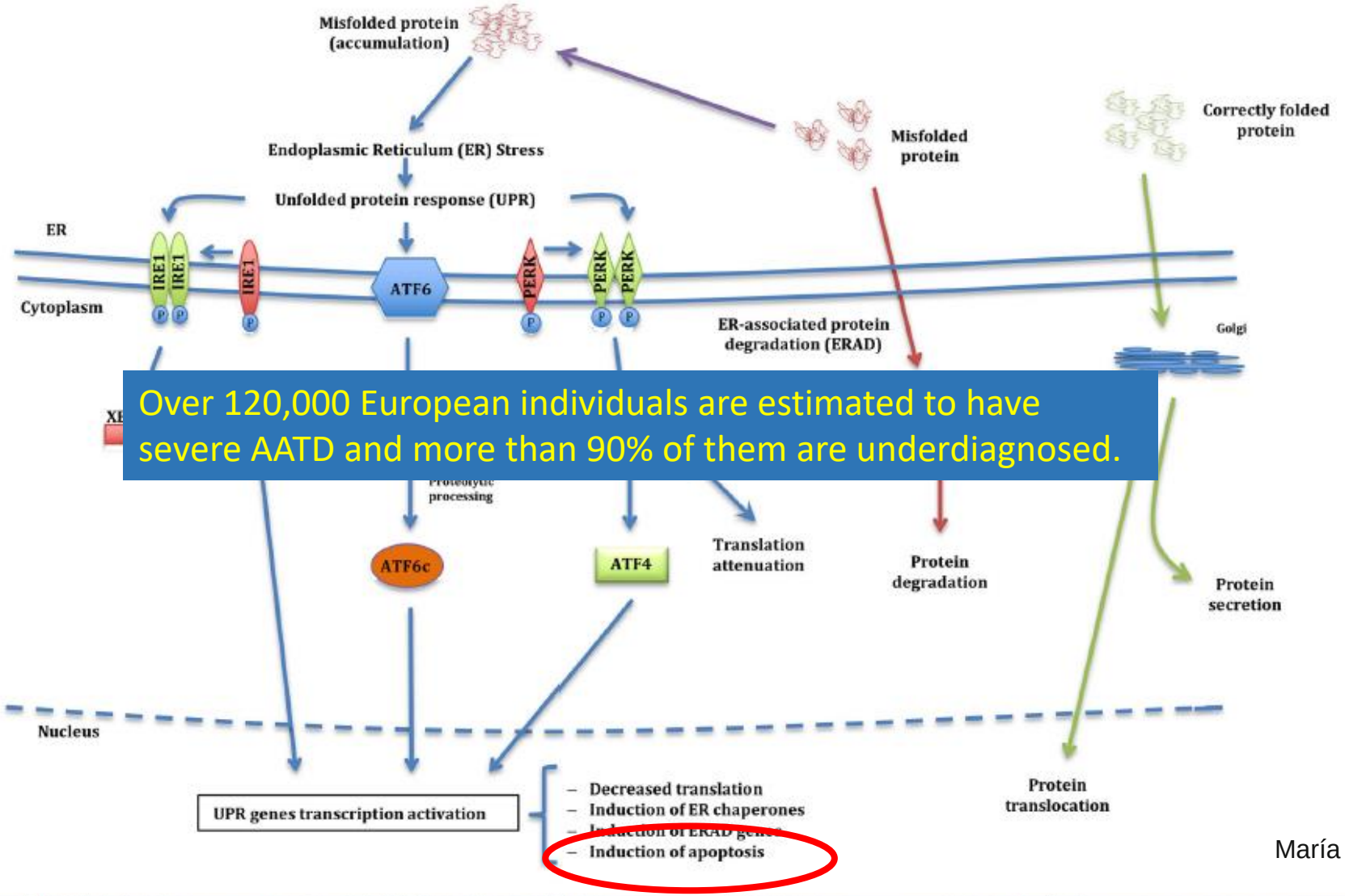


Eur Respir J 2012

H.H. – High Heterogeneity, L.E. – Lobar Exclusion Achieved, C.F. – Low Collateral Flow

A1-AT Deficiency

A1-AT DEFICIENCY



María Torres-Durán et al, 2020

AUGMENTATION THERAPY

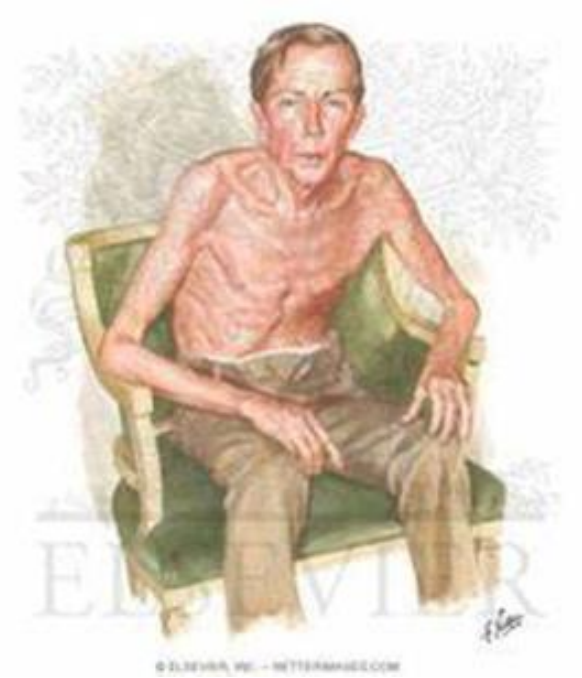
- Intravenous infusion of AAT in AATD individuals protects the lungs from the action of uncontrolled neutrophil elastase, and hence, slows the progression of emphysema.

- AAT augmentation therapy resulted in a slower decline in FEV1 and a reduction in mortality compared to those not receiving this treatment.

- However, the reduction in lung function loss was observed mainly for patients with a FEV1 between 35 and 60%, so this treatment was only recommended in patients that fall within this lung function-impairment range.

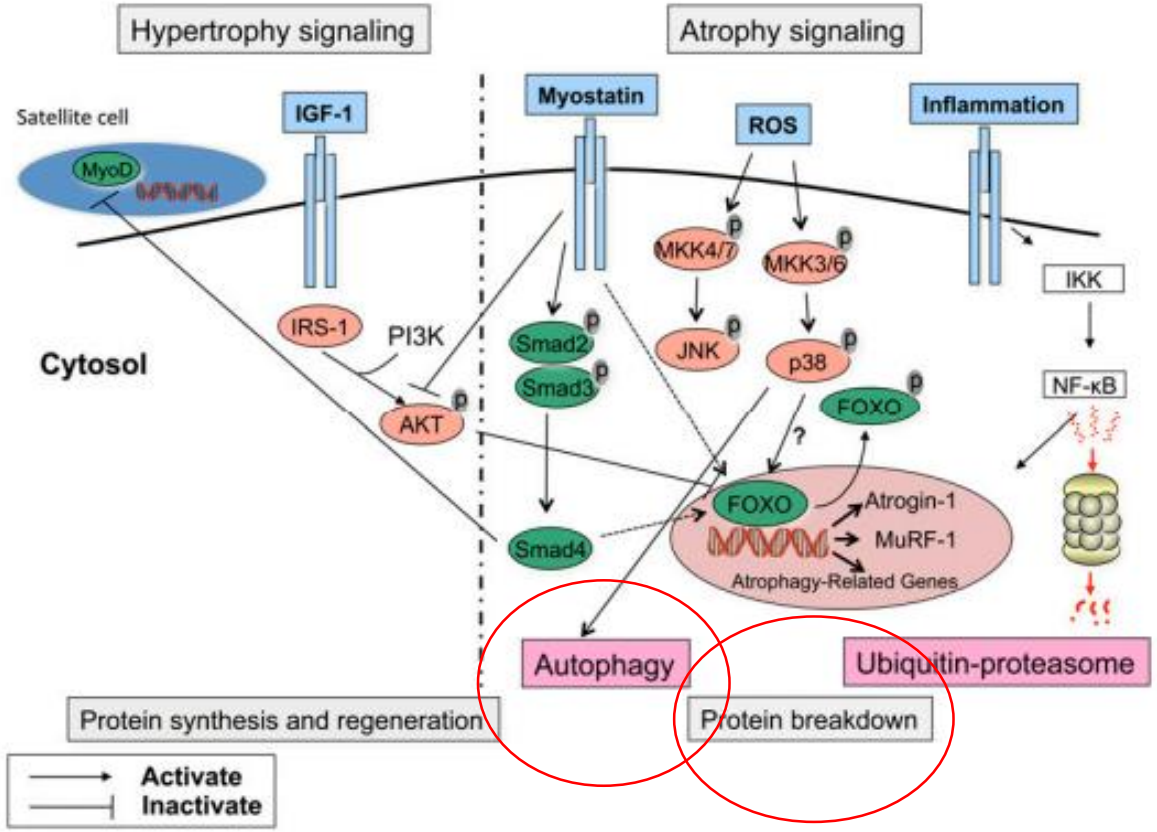
- Alternative strategies are currently being investigated, including the use of gene therapy or induced pluripotent stem cells, and non-augmentation strategies to prevent AAT polymerisation inside hepatocytes.

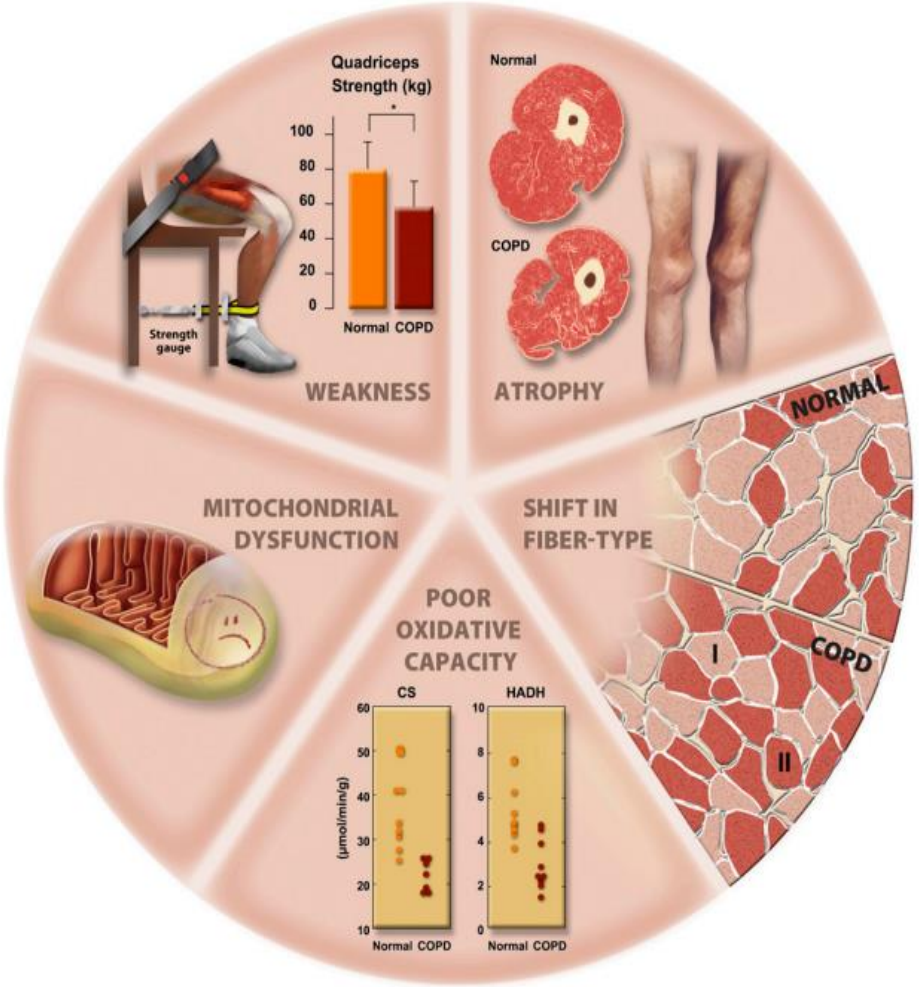
The deconditioned patient



- Usually low BMI.
- Dyspnea on minimal exercion.
- Usage of accessory respiratory muscles.
- Peripheral myopathy.
- Respiratory failure.
- Sendetary lifestyle, low physical activity.
- Bedridden, unable to perform daily routines.
- High prevalence of depression.

REHABILITATION





Am J Respir Crit Care Med. 2014 May 1;189(9):e15-62.

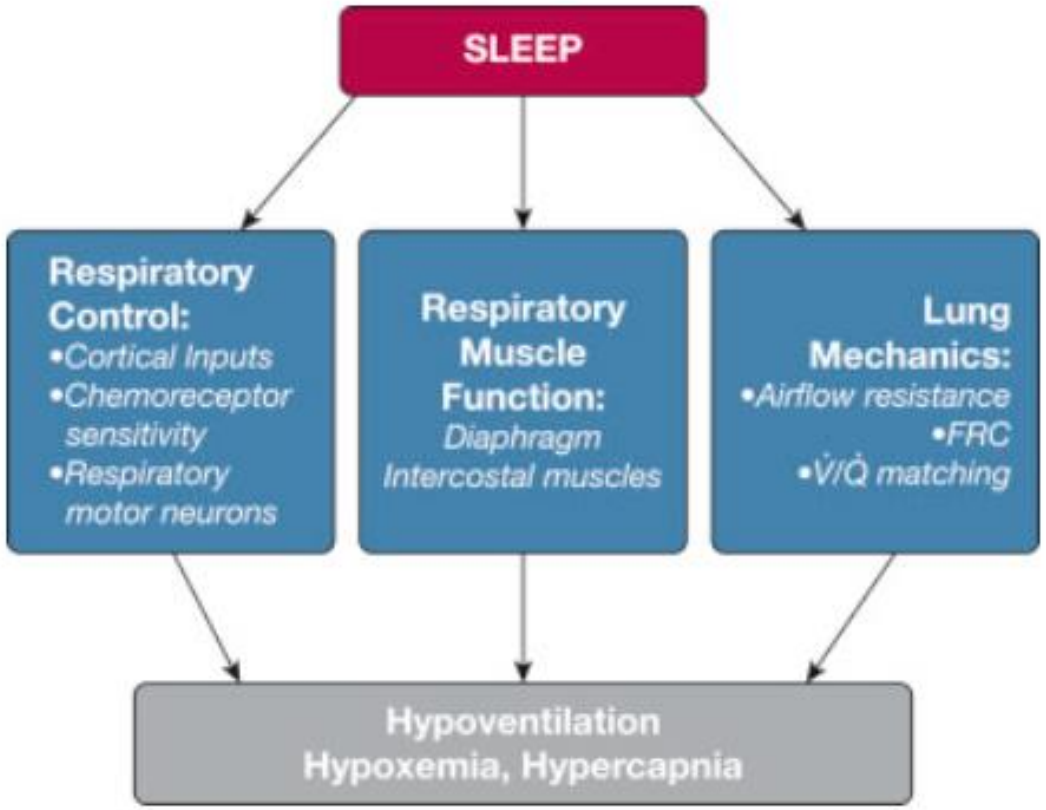
Table 2: Summary of Existing Evidence on Pulmonary Rehabilitation Interventions for Stable COPD*

Study (Type)	Number of Trials Search Years	Conclusions
CADTH, 2010 (HTA) (6)	102 1998 onwards	Pulmonary rehabilitation improves short-term exercise capacity, HRQOL, and mental health outcomes for patients with COPD.
Lacasse et al, 2006 (MA) (8)	31 1966–2004	Pulmonary rehabilitation including at least 4 weeks of exercise training leads to clinically and statistically significant improvements in important domains of quality of life including dyspnea, fatigue, emotional function, and mastery.
Viera et al, 2010 (SR) (7)	8	Self-monitored, home-based pulmonary rehabilitation is useful and, if properly done, may be an equivalent alternative to outpatient pulmonary rehabilitation. Many programs with endurance training have been found beneficial in improving HRQOL and exercise capacity.

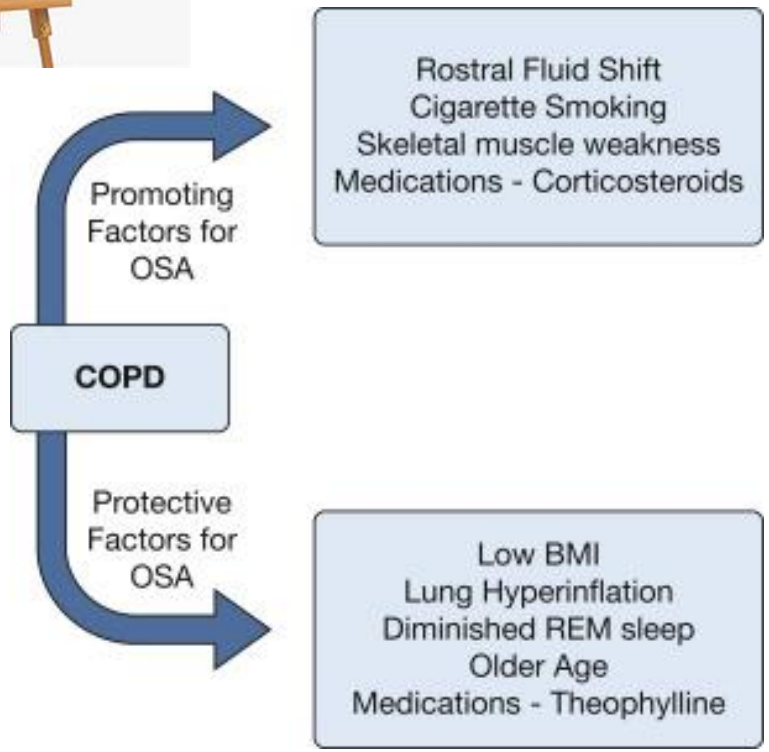
Outcome	Number of Studies	Number of Participants	Effect Size Mean Difference (95% CI)	GRADE
Quality of Life – Change in SGRQ				
Total Score	8	514	-8.40 (-13.30, -3.50)	Moderate
Symptoms	8	514	-3.40 (-7.85, 1.04)	
Impacts	8	514	-3.41 (11.03, 4.21)	
Activity	8	514	-7.73 (-14.24, -1.22)	
Quality of Life – Change in CRQ				
Fatigue	8	507	0.83 (0.62, 1.04)	Moderate
Emotional Function	8	507	0.70 (0.45, 0.95)	
Mastery	8	507	0.85 (0.63, 1.06)	
Dyspnea	8	507	0.97 (0.77, 1.17)	
Functional Exercise Capacity (6MWT)	15	659	54.83 (35.63, 74.03)	Moderate

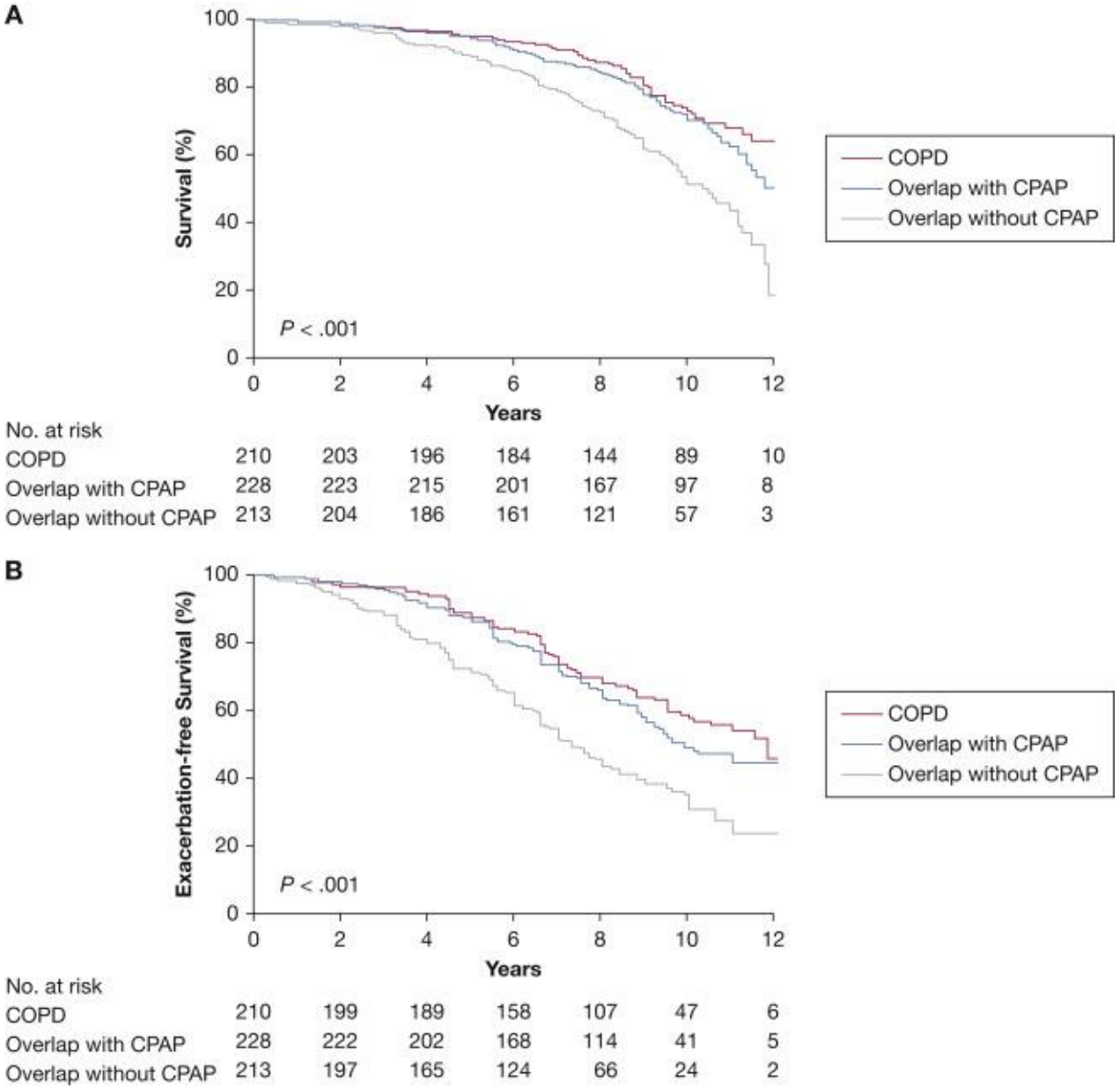
*Abbreviations: 6MWT, 6 Minute Walking Test; CI, confidence interval; CRQ, Chronic Respiratory Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

COPD and OSA - OHS



- Increasing BMI and smoking history positively correlate with the likelihood of OSA in patients with COPD.
- The predominant emphysema phenotype, with relatively low BMI, may predispose to a lower likelihood of OSA, and there is recent evidence that lung hyperinflation is protective against the development of OSA by lowering the critical closing pressure of the upper airway during sleep.
- the patient with higher BMI and cor pulmonale (right-sided heart failure) who typically presents with productive cough and hypoxemia may predispose to a higher likelihood of OSA


Promoting Factors for OSA
Rostral Fluid Shift
Cigarette Smoking
Skeletal muscle weakness
Medications - Corticosteroids
COPD
Protective Factors for OSA
Low BMI
Lung Hyperinflation
Diminished REM sleep
Older Age
Medications - Theophylline

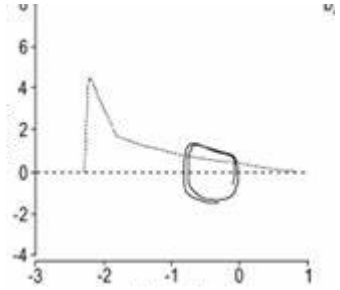

A
Survival (%)
100
80
60
40
20
0
P < .001
0 2 4 6 8 10 12
Years
COPD
Overlap with CPAP
Overlap without CPAP
No. at risk
COPD 210 203 196 184 144 89 10
Overlap with CPAP 228 223 215 201 167 97 8
Overlap without CPAP 213 204 186 161 121 57 3
B
Exacerbation-free Survival (%)
100
80
60
40
20
0
P < .001
0 2 4 6 8 10 12
Years
COPD
Overlap with CPAP
Overlap without CPAP
No. at risk
COPD 210 199 189 158 107 47 6
Overlap with CPAP 228 222 202 168 114 41 5
Overlap without CPAP 213 197 165 124 66 24 2

The end-stage patient

END - STAGE COPD?

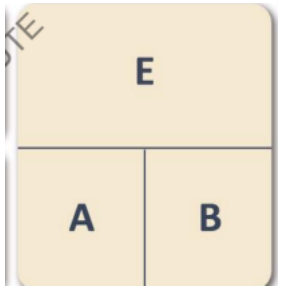
- ARTERIAL BLOOD GASSES?
- PULMONARY FUNCTION TESTS?
- BREATHLESSNESS SCORING?
- GOLD STAGING?
- USE OF LTOT?
- USE OF NIMV?
- QUALITY OF LIFE QUESTIONAIRE?
- SOCIOECCONOMIC STATUS?

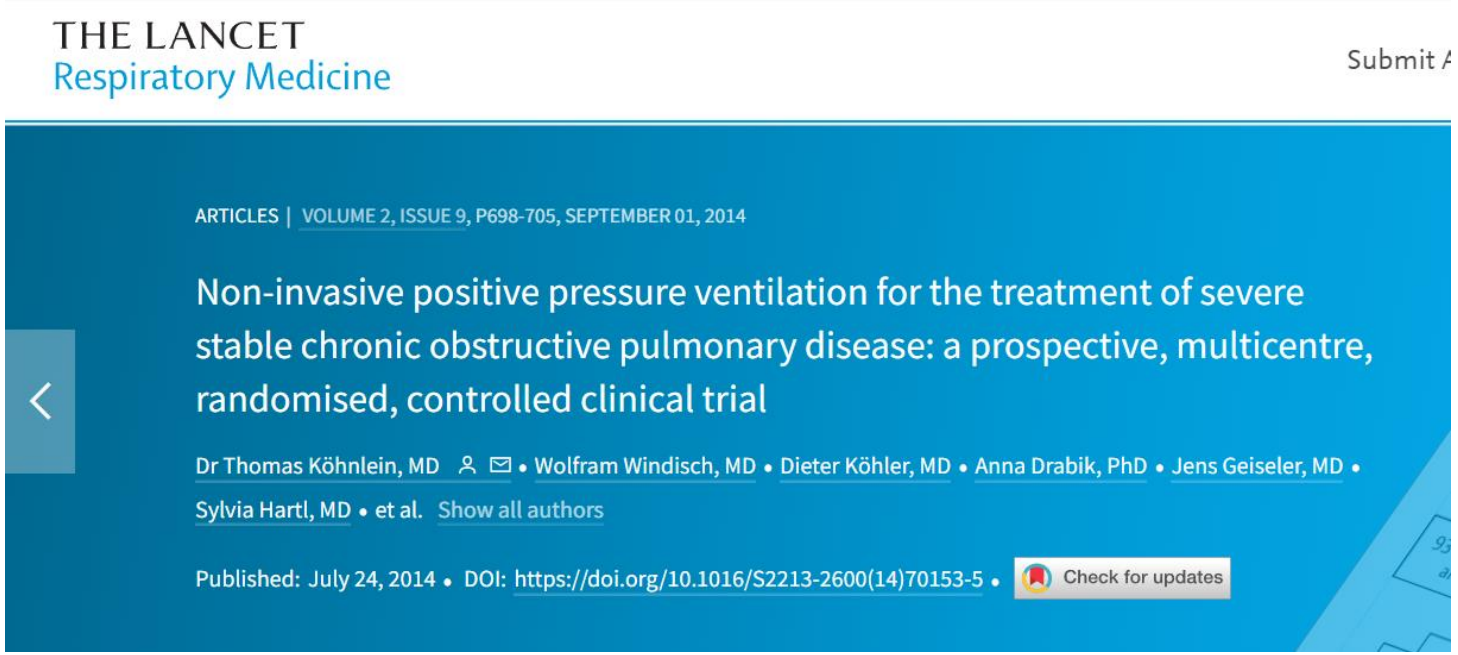
Normal Arterial Blood Gas Values*	
pH	7.35 - 7.45
$PaCO_2$	35 - 45 mm Hg
PaO_2	70 - 100 mm Hg **
SaO_2	93 - 98%
HCO_3^-	22 - 26 mEq/L
%MetHb	< 2.0%
%COHb	< 3.0%
Base excess	-2.0 to 2.0 mEq/L
CaO_2	16 - 22 ml O_2/dl



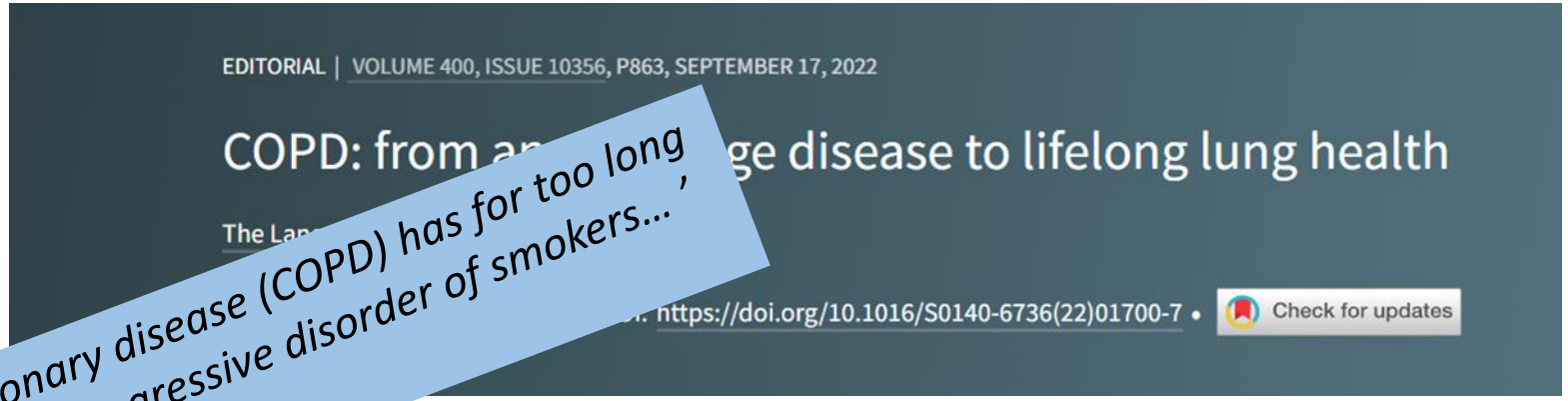
COPD severity	Characteristics	
	FEV1/ FVC	FEV1
GOLD Stage I (mild)	<70%	–
GOLD Stage II (moderate)	<70%	<50%–70%
GOLD Stage III (severe)	<70%	<30%–50%
GOLD Stage IV (very severe)	<70%	<30% or < insufficiency

CAT
COPD Assessment Test





- 195 patients with GOLD IV stable COPD with PCO2 > 52mmHg and PH >7,35
- 1:1 Randomization to standard care (control group, n=93) Vs NPPV for 12 months (intervention group, n=103)
- Primary endpoint: 1-year mortality 12% in the NPPV group Vs 33% in control group (HR:0,24)

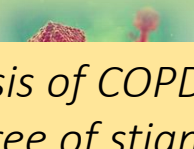


'Chronic obstructive pulmonary disease (COPD) has for too long been seen as a self-inflicted progressive disorder of smokers…'

GENETICS

EARLY LIFE EVENTS

RESPIRATORY INFECTIONS



TOBACCO

'Currently, a diagnosis of COPD is often accompanied by a sense of futility and a degree of stigma…[This Commission] aims for nothing less than to transform the way COPD is thought of. Lifelong lung health for all is the goal to aspire to.'

THANK YOU


HAVE YOU EVER TRIED BLIND-FOLDED ARCHERY?
YOU DON'T KNOW WHAT YOU'RE MISSING