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# **ACUTE EXACERBATION OF COPD: DIAGNOSIS, MANAGEMENT & PREVENTION**

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## **LPS Annual Meeting 2023**





# Outline

- Burden of COPD
- Pathophysiology to Diagnosis of AECOPD
- Management of AECOPD
- Impact of AECOPD
- Prevention of the AECOPD



# Attitude



“It is a disease on which a good deal of wholly, unmerited sympathy is frequently wasted....

It is a disease of the gluttonous, bibulous, otiose and obese and represents a well-deserved nemesis for the unlovely indulgences”

From “Middle and Old age”, Williams



# World's Top Ten Killers

# 1990





# World's Top Ten Killers





# Class Prediction

No/Mild COPD

Severe COPD





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# Diagnosis





## COPD exacerbation :GOLD

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) **defines an exacerbation of chronic obstructive pulmonary disease (COPD)** as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication".

This includes an acute change in one or more of the following cardinal symptoms:

- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character
- Dyspnea increases





## COPD exacerbation :GOLD

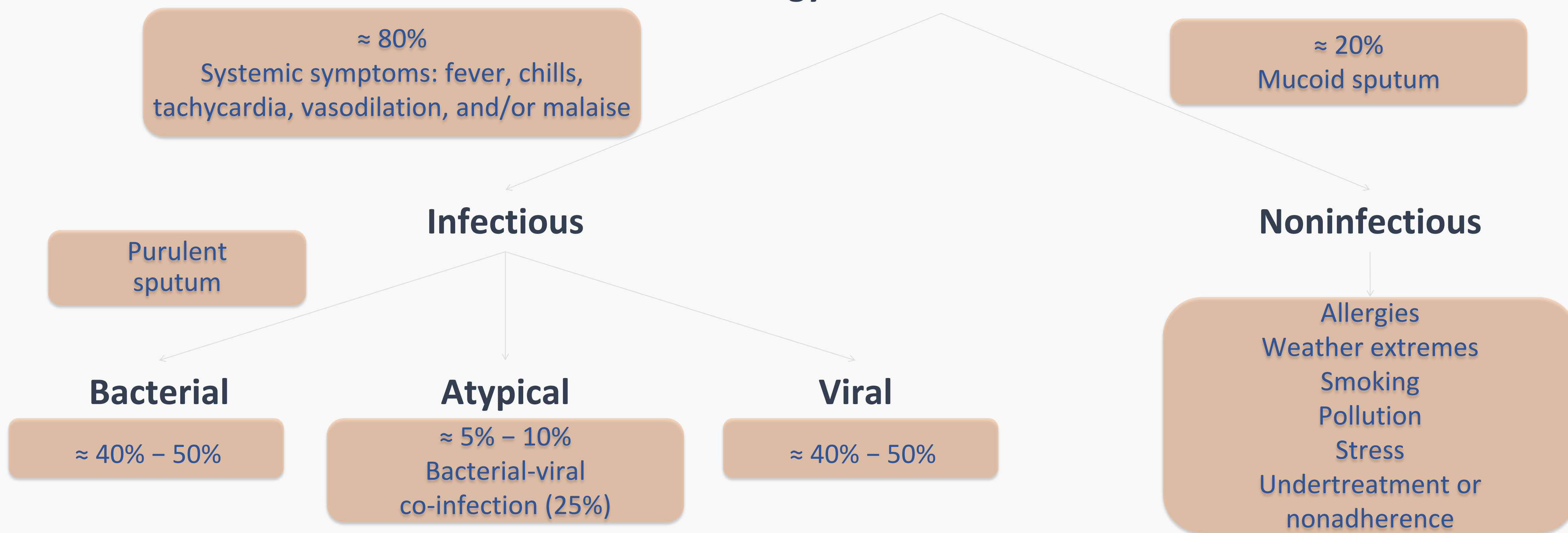
- Symptoms usually last 7 to 10 days.
- At 8 weeks, 20% of patients have not recovered to their pre-exacerbation state.
- COPD exacerbation contributes to disease progression.
- Exacerbations cluster in time, and once a patient experiences an exacerbation, they will show increased susceptibility to another event.
  
- The strongest predictor of future exacerbation frequency remains the number they have had in the prior year.
- Other risk factors: ratio >1 of pulmonary artery to aorta cross sectional dimension, greater % of emphysema or airway wall thickness on CT chest, presence of chronic bronchitis.
  
- \*frequent :2 or more per year



## Exacerbations are Commonly Caused by Infection and Air Pollution

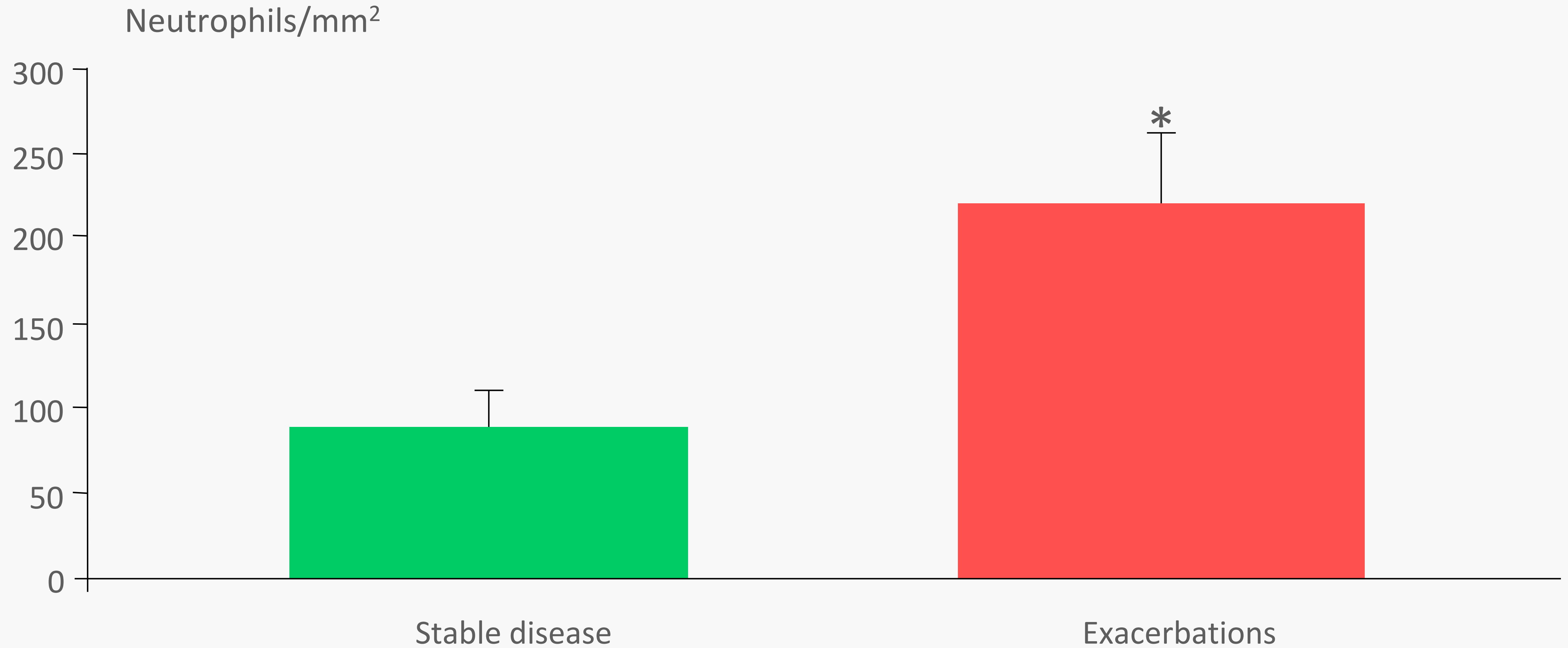
The cause of one-third of severe exacerbations cannot be identified

### Aetiology of COPD exacerbations<sup>2</sup>





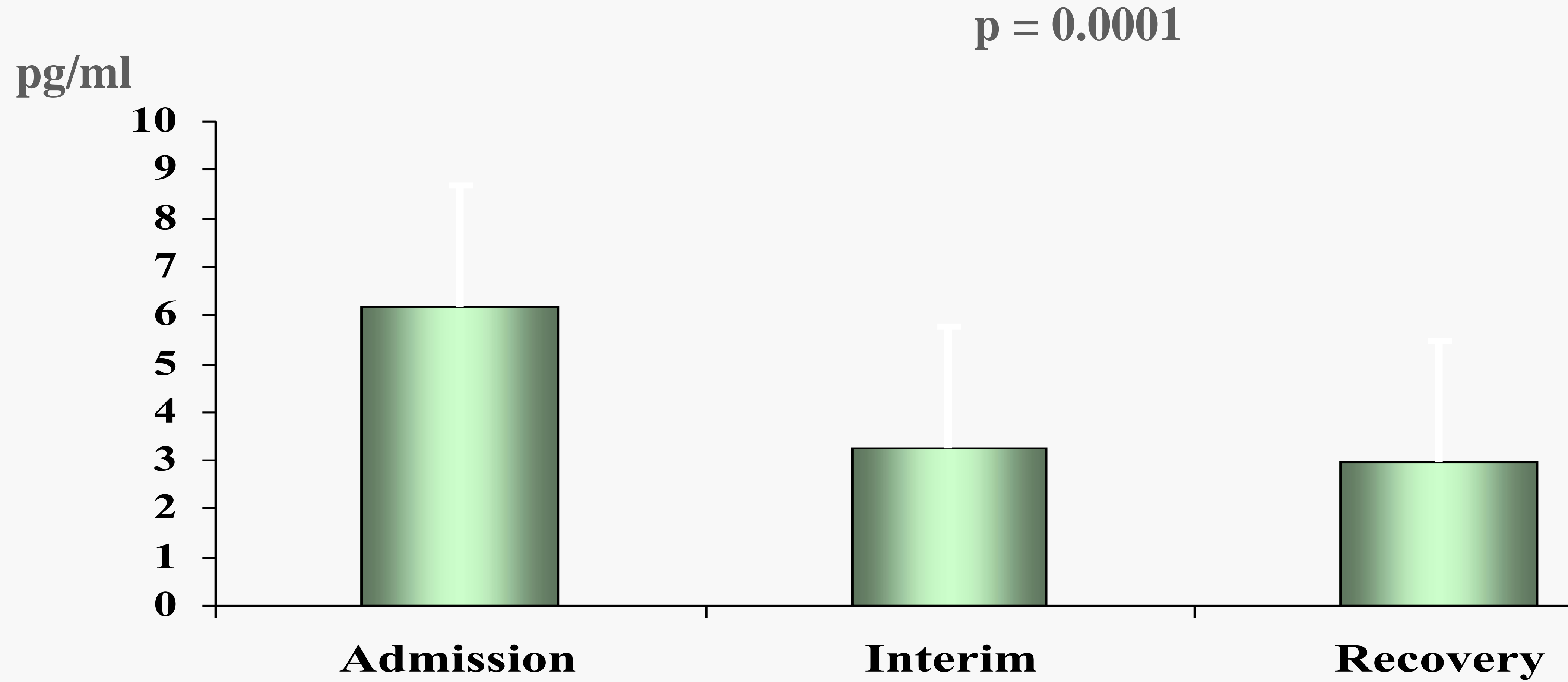
## Increased Neutrophils during Exacerbations of COPD



\*p<0.01



# IL-6 in the Exacerbation

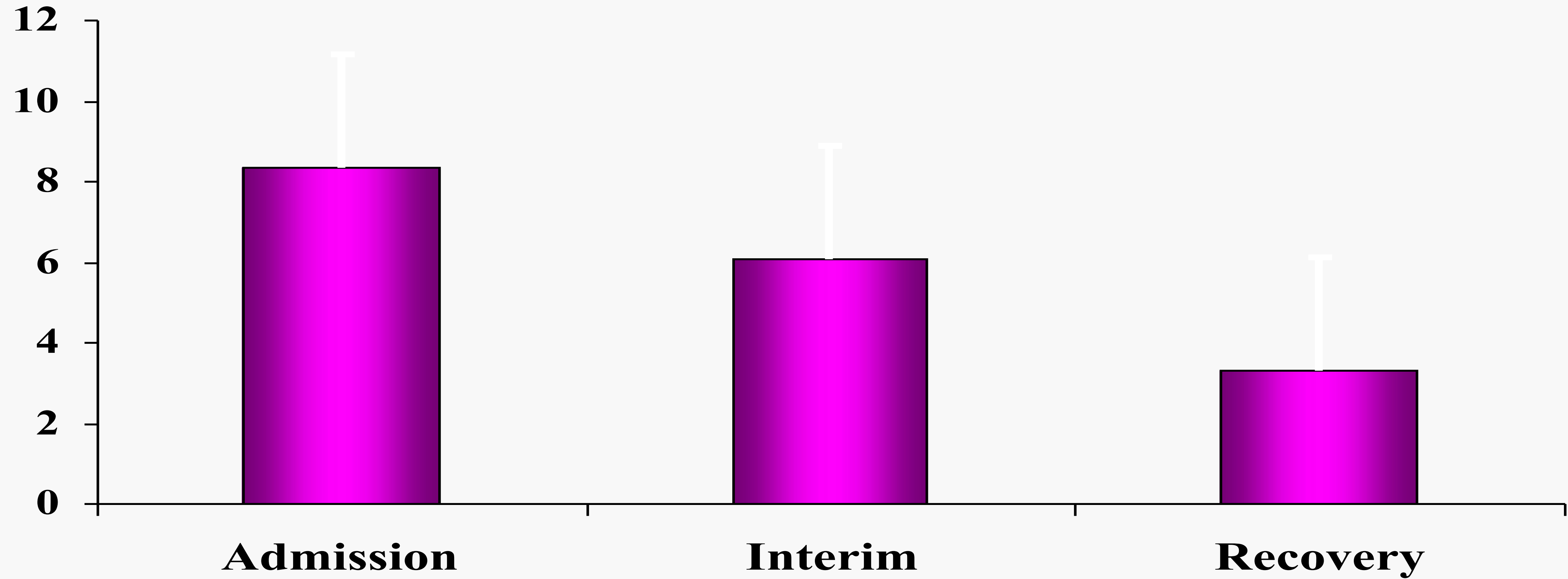




## IL-8 in the Exacerbation

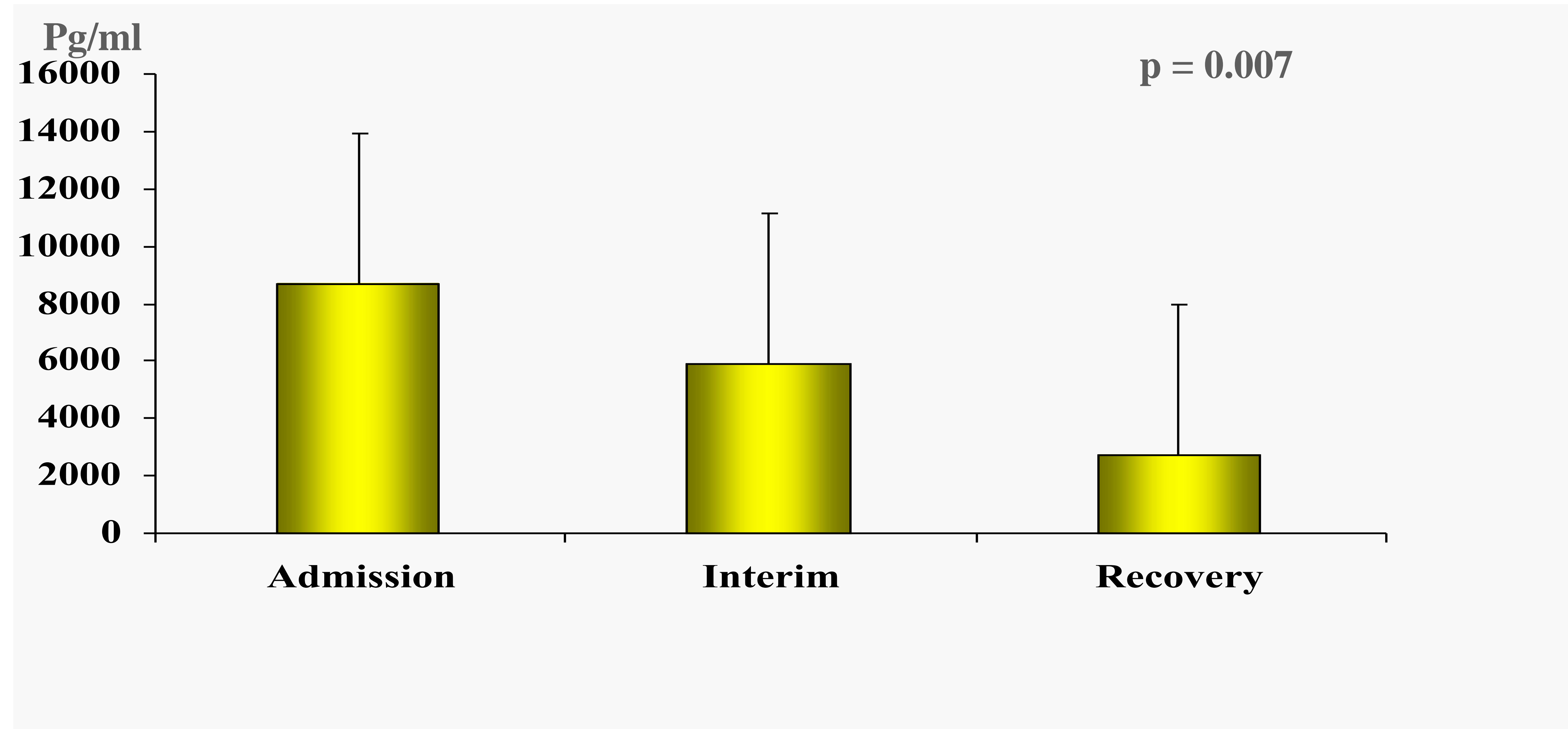
$p = 0.002$

pg/ml





## LTB4 in the Exacerbation





# Diagnosing an Exacerbation

An acute worsening of the patient's usual pattern of respiratory symptoms beyond normal day-to-day variability:

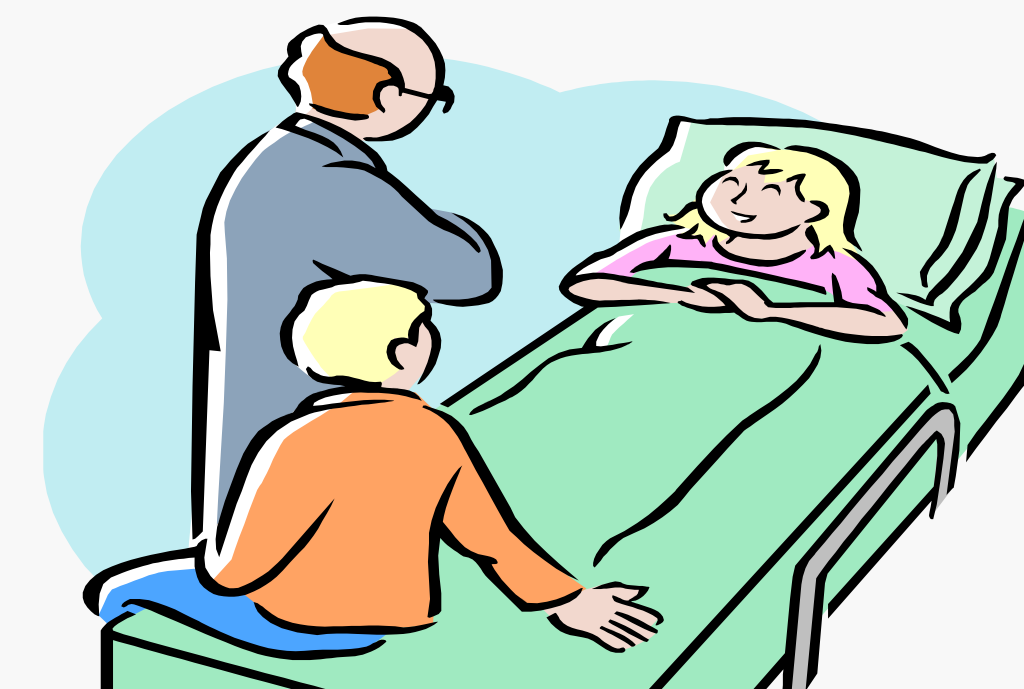
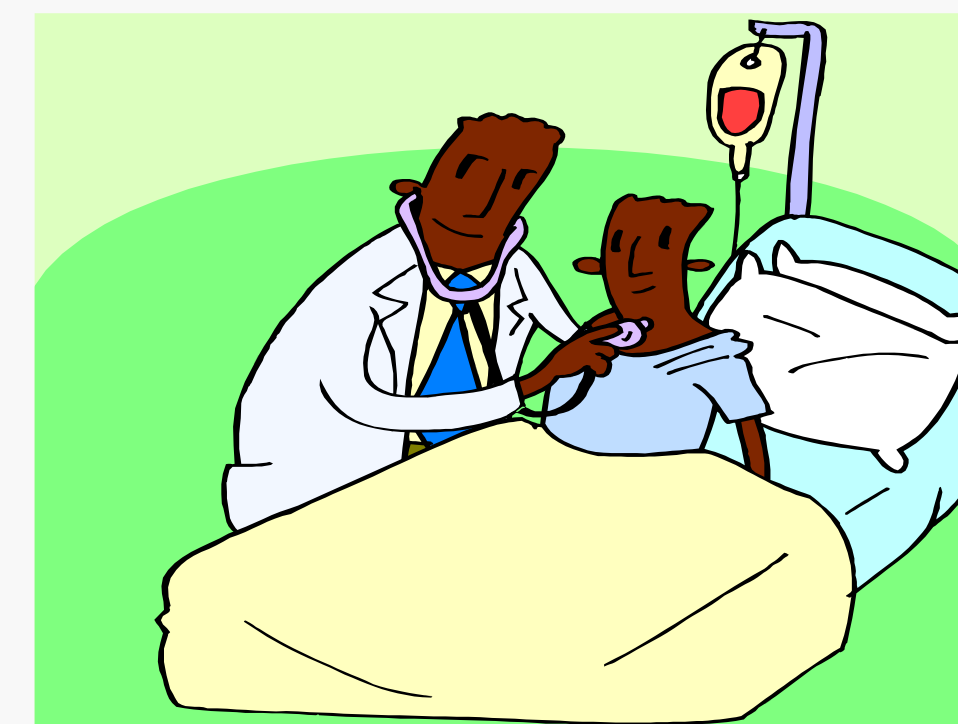
- Increased dyspnoea
- Worsening cough
- Increased sputum volume
- Sputum purulence

**No Biomarkers of an exacerbation as of yet**



## Who is at Risk of Exacerbating?

- Patients on no medication
- Patients with severe disease
- Patients with high MRC score
- Patients with low BMI
- Patients with cardiac arrhythmias
- Patients on high levels of medication







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# Management





# First Step(s)

- Oxygen As Needed
- SABA / SAMA



## Systemic Glucocorticoids

For patients requiring ED or hospital-based treatment for a COPD exacerbation, Oral glucocorticoids are rapidly absorbed (peak serum levels achieved at one hour after ingestion) with virtually complete bioavailability and appear equally efficacious to intravenous glucocorticoids for treating most exacerbations of COPD.

**In a systematic review, parenteral glucocorticoids were compared with oral glucocorticoids and no significant differences were noted in the primary outcomes of treatment failure, relapse, or mortality or for any secondary outcomes.**

However IV glucocorticoids are typically administered to patients who present with a severe exacerbation, who have not responded to oral glucocorticoids at home, who are unable to take oral medication, or who may have impaired absorption due to decreased splanchnic perfusion (eg, patients in shock).



## Steroids in GOLD COPD/ERS ATS

The GOLD guidelines suggest that glucocorticoids (eg, prednisone 30 to 40 mg/day) be given for five days, while the European Respiratory Society/American Thoracic Society guidelines suggest a course of therapy up to 14 days in duration. Thus, a range of 5 to 14 days appears reasonable.

The ***Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial*** randomly assigned 314 patients with exacerbations of COPD, of whom 289 required hospitalization, to prednisone 40 mg daily for 5 or 14 days;

- A. No difference was noted in the time to the next exacerbation, the likelihood of an exacerbation in the subsequent 180 days, or the recovery of lung function.
- B. The mean cumulative prednisone dose was significantly higher in the 14-day group, but treatment-related adverse effects, such as hyperglycemia and hypertension, were not different between the groups.



# Antibiotics



- Their use remains controversial.
- A course of 5-7 days.
- They should be given to patients with exacerbations who have three cardinal symptoms:
  - Increase in dyspnea, sputum volume, and sputum purulence.
  - or have two including sputum purulence.
  - or require mechanical ventilation.



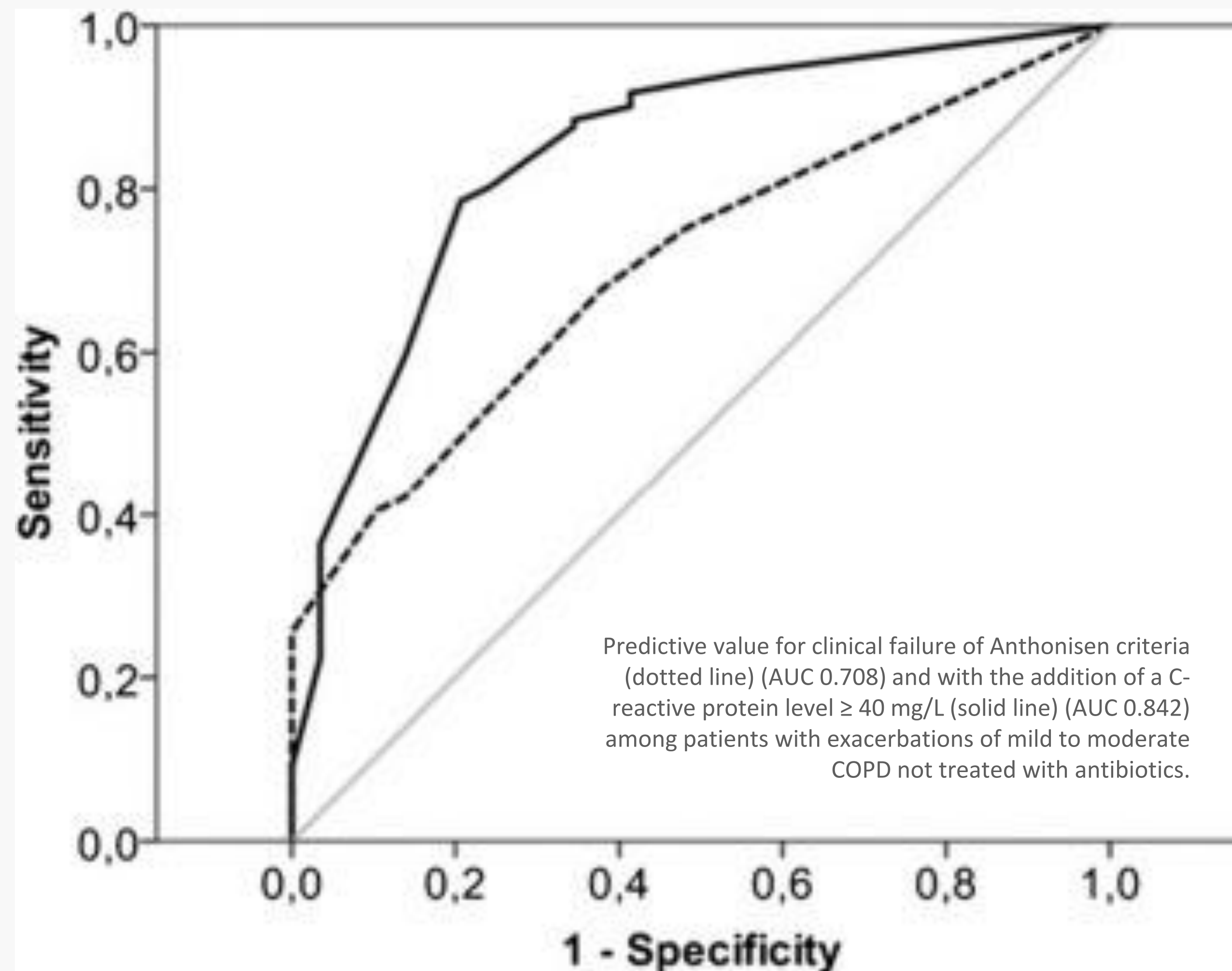
## ERS/ATS Statement 2017:

- Antibiotic therapy decreased treatment failure from 42% to 28% (RR 0.67) therefore NNT to prevent one treatment failure is 7.
- The majority (58%) of patients improved without antibiotics, suggesting not all exacerbations require antibiotics.



# Antibiotics

The only factors significantly associated with an increased risk of failure without antibiotics were the increase in sputum purulence (OR, 6.1) and a CRP concentration  $\geq 40$  mg/L (OR, 13.4). When both factors were present, the probability of failure without antibiotics was 63.7%.





# Antibiotics



- Regimens are designed to target the most likely pathogens:
  - *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.
- Should be broadened to target drug-resistant pathogens and difficult-to-eradicate pathogens in those at risk for poor outcomes:
  - Macrolide-resistant *S. pneumoniae*, non-typeable strains of *H. influenzae*.





- $\geq 2$  exacerbation/yr
- Compliant patient
- Pulse  $< 100$
- QT  $< 450$  msec.
- SGOT & SGPT  $< 3X$  normal
- No QT drugs
- Normal Hearing (Audiogram...)
- Exclude high cardiac risk patient



# Magnesium sulfate



For patients who present with a severe exacerbation that is not responding promptly to short-acting inhaled bronchodilators, we suggest intravenous administration of a single dose of magnesium sulfate (2 g infused over 20 minutes).

Intravenous magnesium sulfate has bronchodilator activity thought to arise from inhibition of calcium influx into airway smooth muscle cells .

The best evidence for benefit in COPD exacerbations comes from a systematic review (3 studies, 170 participants) that found a decrease in hospitalizations with intravenous magnesium compared with placebo (odds ratio [OR] 0.45, 95% CI 0.23-0.88) , which is similar to or better than the effect seen in severe asthma exacerbations.



- AECOPD patients with Vit D Deficiency were recruited and randomly allocated to receive either 300,000 IU of intramuscular vitamin D ( $n = 35$ ) or placebo ( $n = 35$ ).
- IL-6 levels significantly decreased in the vitamin-D vs. placebo group on the 6<sup>th</sup> day ( $P = 0.02$ ).
- No significant differences were observed in IL-8, CRP, mMRC, LOS and mortality.



- Vitamin D supplementation (immune modulating role) in subjects with severe deficiency results in 50% reductions in episodes and hospital admission.
- Randomized controlled trials (RCTs) showed that vitamin D supplementation reduced the rate of COPD exacerbation in patients with vitamin D deficiency.
- However, the association between COPD clinical outcomes and vitamin D levels remains controversial, therefore, vitamin D is not yet considered as a representative biomarker for COPD phenotypes.



# Hospital Admissions

## • Major Criteria

- Inability to cope at home
- Hypoxia, saturations  $< 90\%$  or  $> 5\%$  drop on mild exertion
- Severe breathlessness
- Altered mental state
- Worsening peripheral edema

## • Minor Criteria

- Decreased level of activity
- LTOT
- Rapid onset
- Poor general condition

Suspicion of presence of differential such as pneumonia, pneumothorax, pulmonary emboli, myocardial infarction



# Ventilatory Support; Non-Invasive



Respiratory distress:

Moderate to severe dyspnea

Accessory muscle use

Paradoxical movement of abdominal muscles

$\text{pH} < 7.35$  with  $\text{PaCO}_2 > 45$

Respiratory rate  $> 25$  breaths/min

At least two criteria should be present



## Contraindications to NIV:

- Inability to protect the airway or clear secretions
- Severely impaired consciousness
- Non-respiratory organ failure that is acutely life-threatening
- High aspiration risk
- Inability to cooperate
- Facial surgery, trauma, or deformity
- Recent esophageal anastomosis



# Severe COPD exacerbation



## Indications for ICU admission:

- Hemodynamic instability requiring vasopressor support
- Unstable cardiac events (eg, acute myocardial infarction, complex arrhythmias, cardiogenic shock)
- Severe neurologic complications (eg, major acute intracranial hemorrhage or stroke, status epilepticus)
- Persistent or worsening hypoxemia (eg,  $\text{PaO}_2 < 50$  mmHg despite supplemental oxygen)
- Need for monitoring or nursing care that exceeds the capacity of non-ICU settings





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# Impact





# Exacerbation Frequency Worsens with COPD Severity, but Can Occur at Any GOLD Level

Exacerbations become more frequent and more severe as the severity increases

Annual estimated frequencies of exacerbations

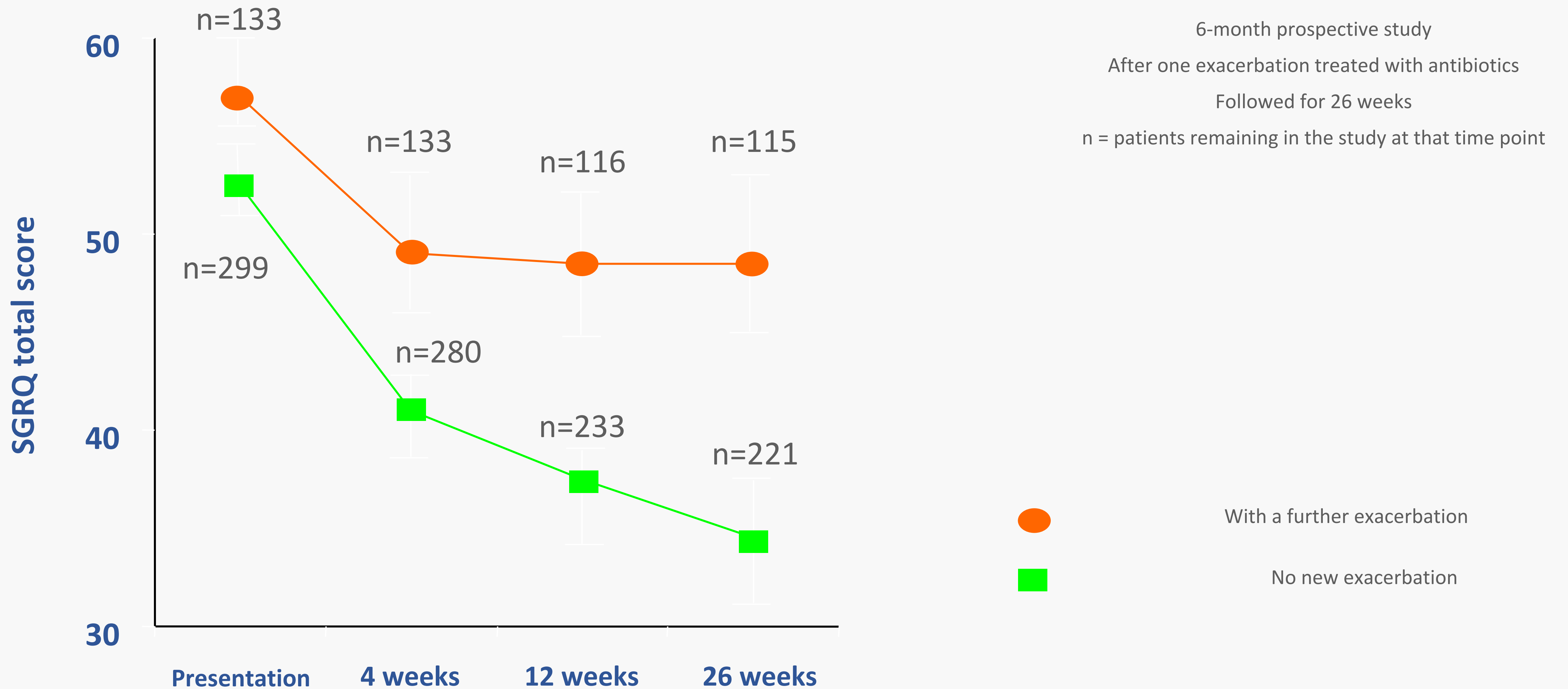
**In the ECLIPSE study (2,138 patients) the single best predictor of exacerbations was a History of Exacerbations**

GOLD spirometric level <sup>3</sup>	ECLIPSE study <sup>1</sup>			
	FEV <sub>1</sub> predicted	Total	Exacerbations requiring hospitalization	Frequent exacerbators
		Number exacerbations in year 1/patient		Patients with ≥2 exacerbations/yr
<b>GOLD 1: Mild</b>	≥80%			
<b>GOLD 2: Moderate</b>	≥50% to <80%	0.85	0.11	22%
<b>GOLD 3: Severe</b>	≥30% to <50%	1.34	0.25	33%
<b>GOLD 4: V. Severe</b>	<30%	2.00	0.54	47%

**Two-thirds of exacerbations are not reported by patients**

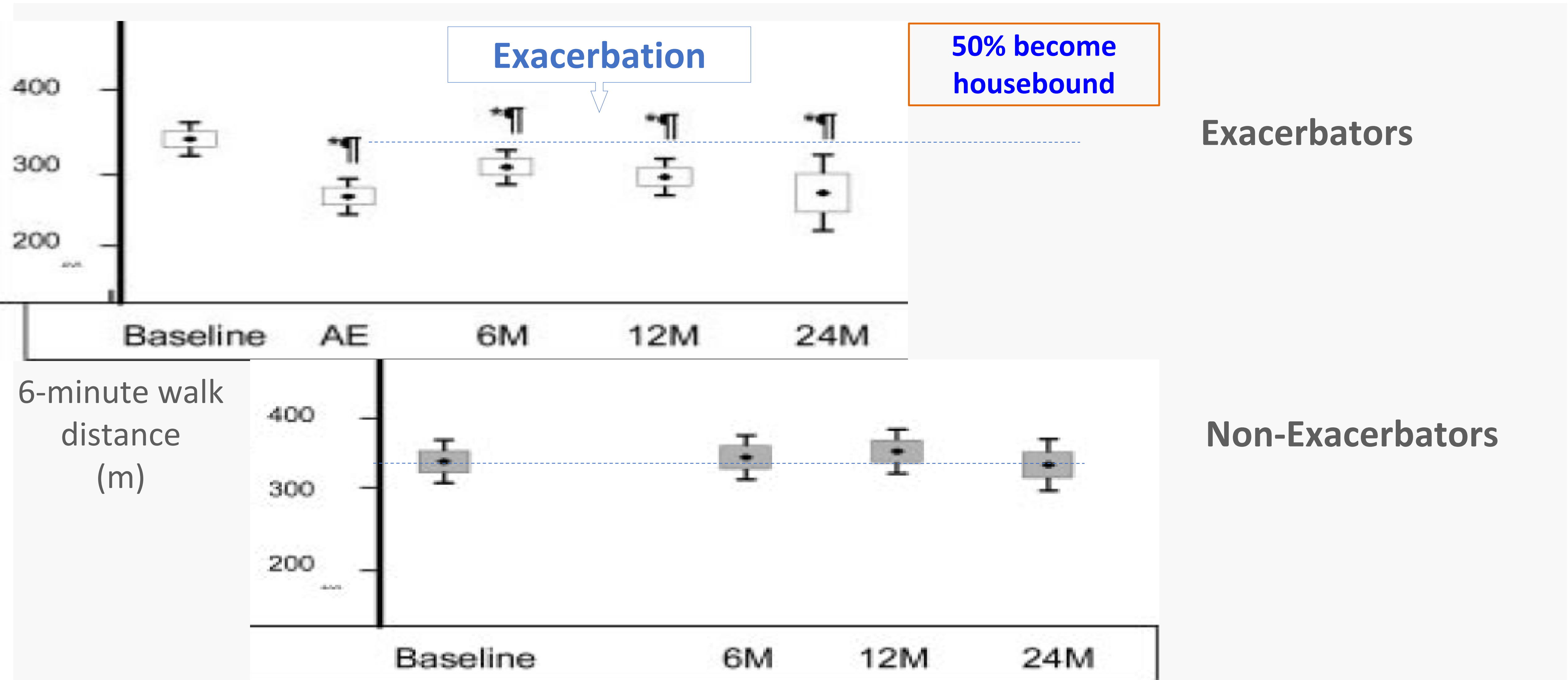


## Repeated Exacerbations Slow Recovery in Quality of Life



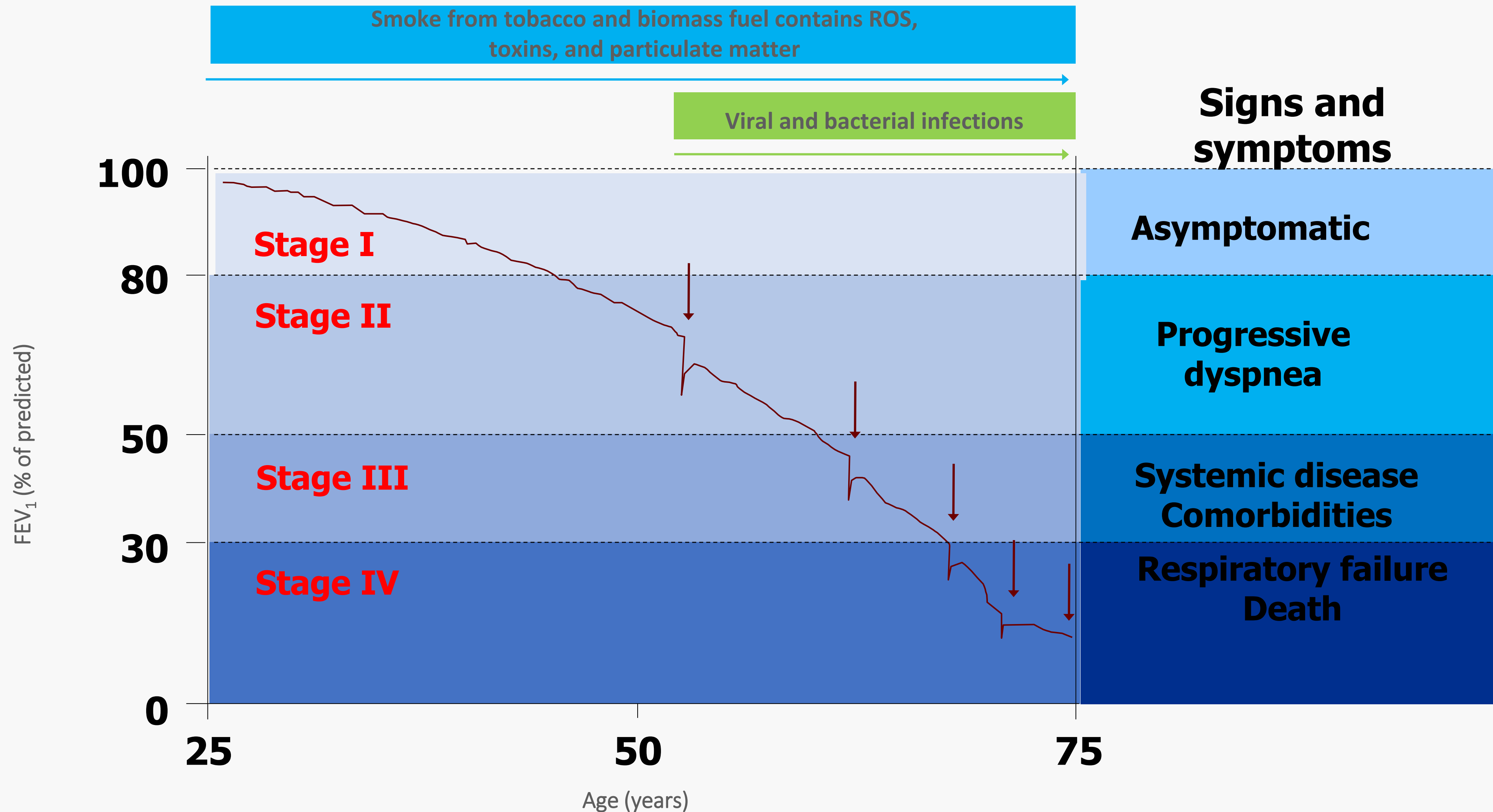


# Effect of exacerbation on 6-minute walk distance



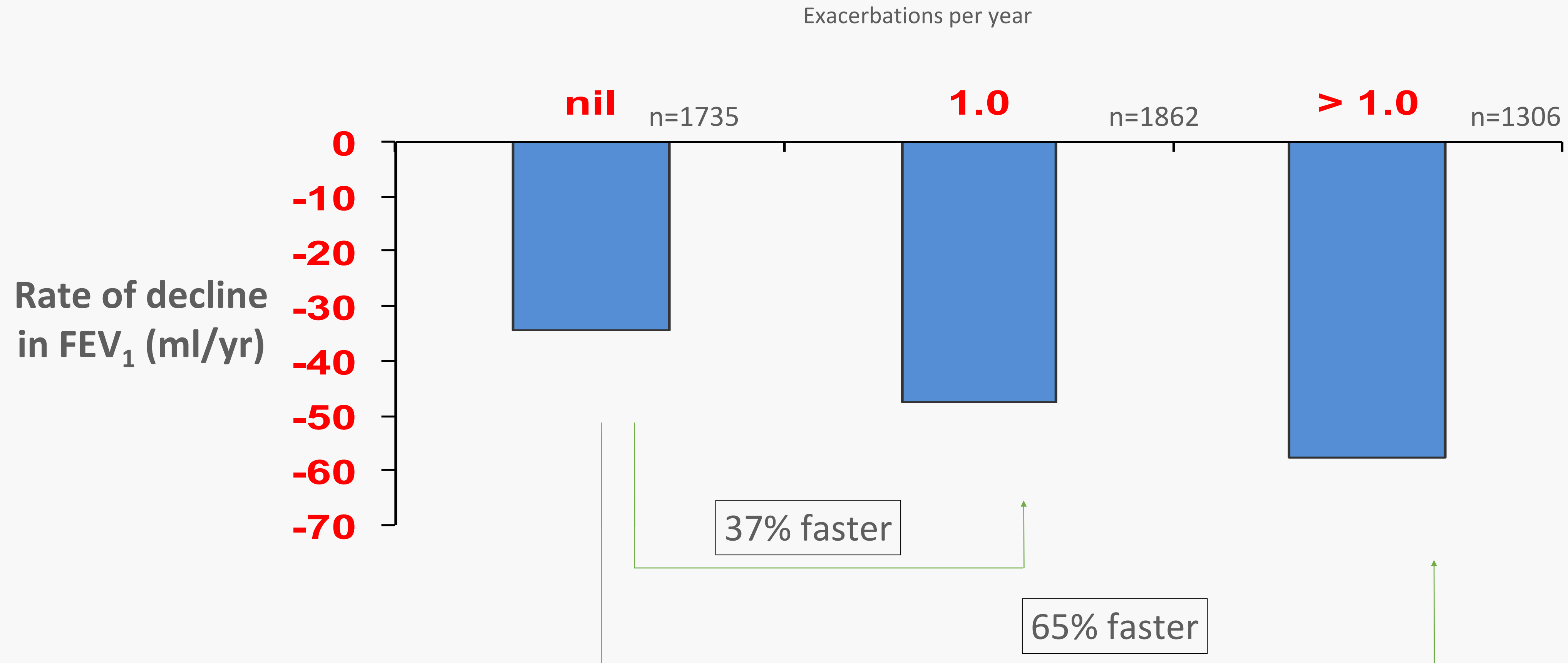


# Effect of Exacerbations on Disease Progression





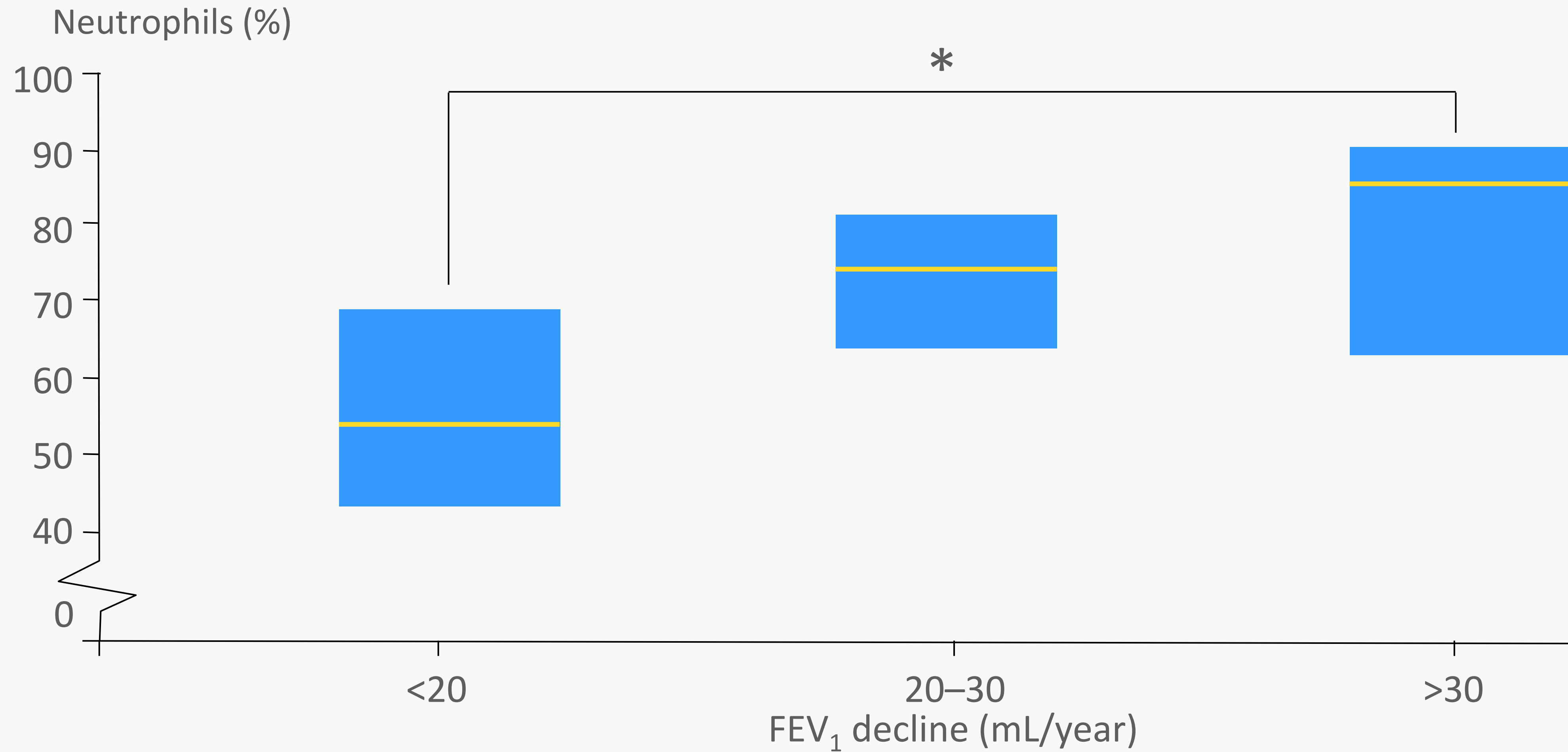
# Exacerbation rate and FEV<sub>1</sub> decline (all treatment arms)



Adjusted for smoking status, gender, baseline FEV<sub>1</sub> region, BMI, prior exacerbations, treatment, time, time by treatment and covariate by time

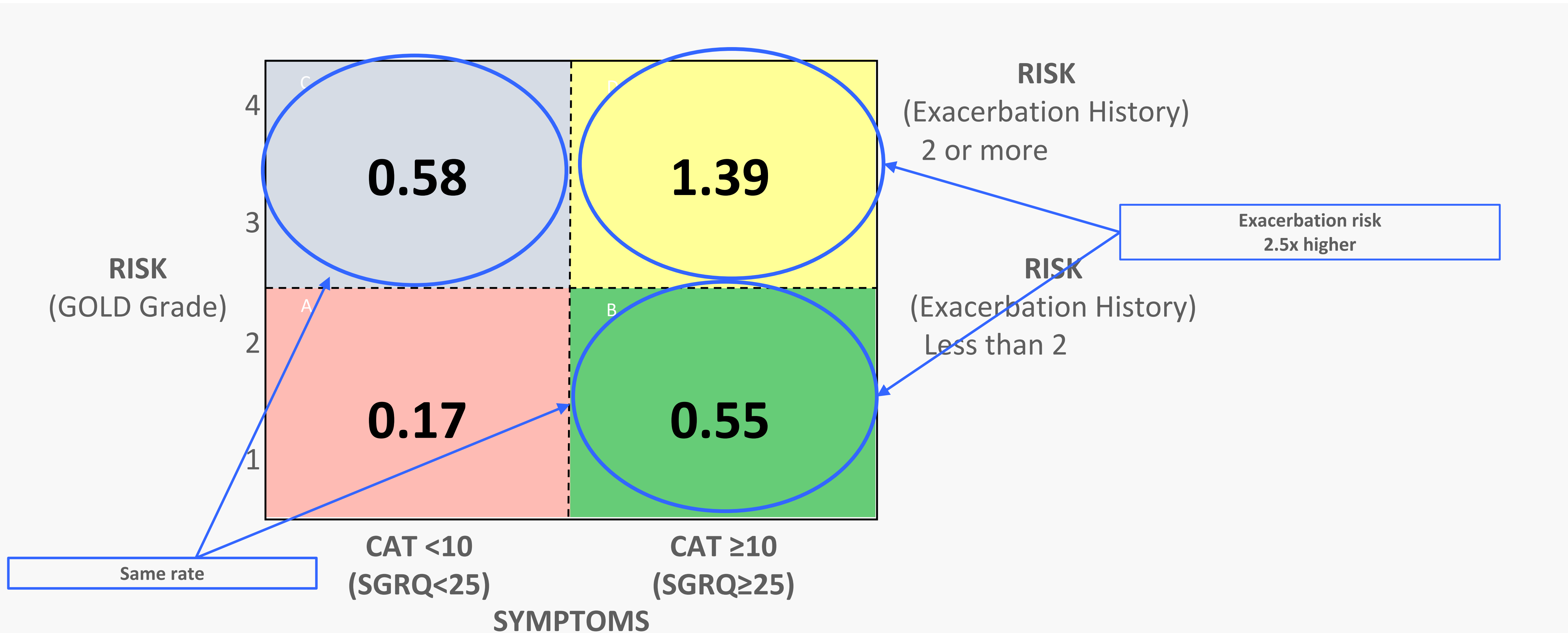


## Rapid decline of FEV<sub>1</sub> is associated with increased levels of sputum neutrophils





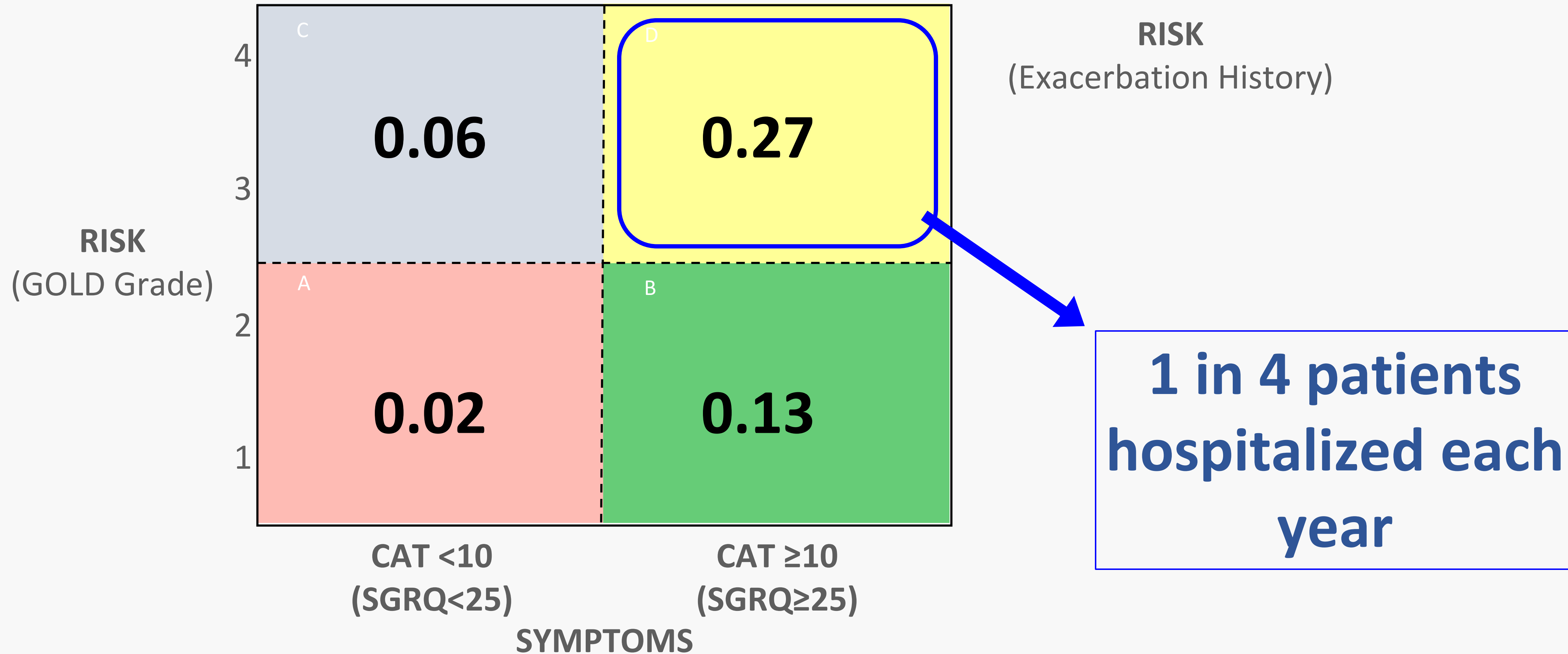
# Exacerbation rate per year





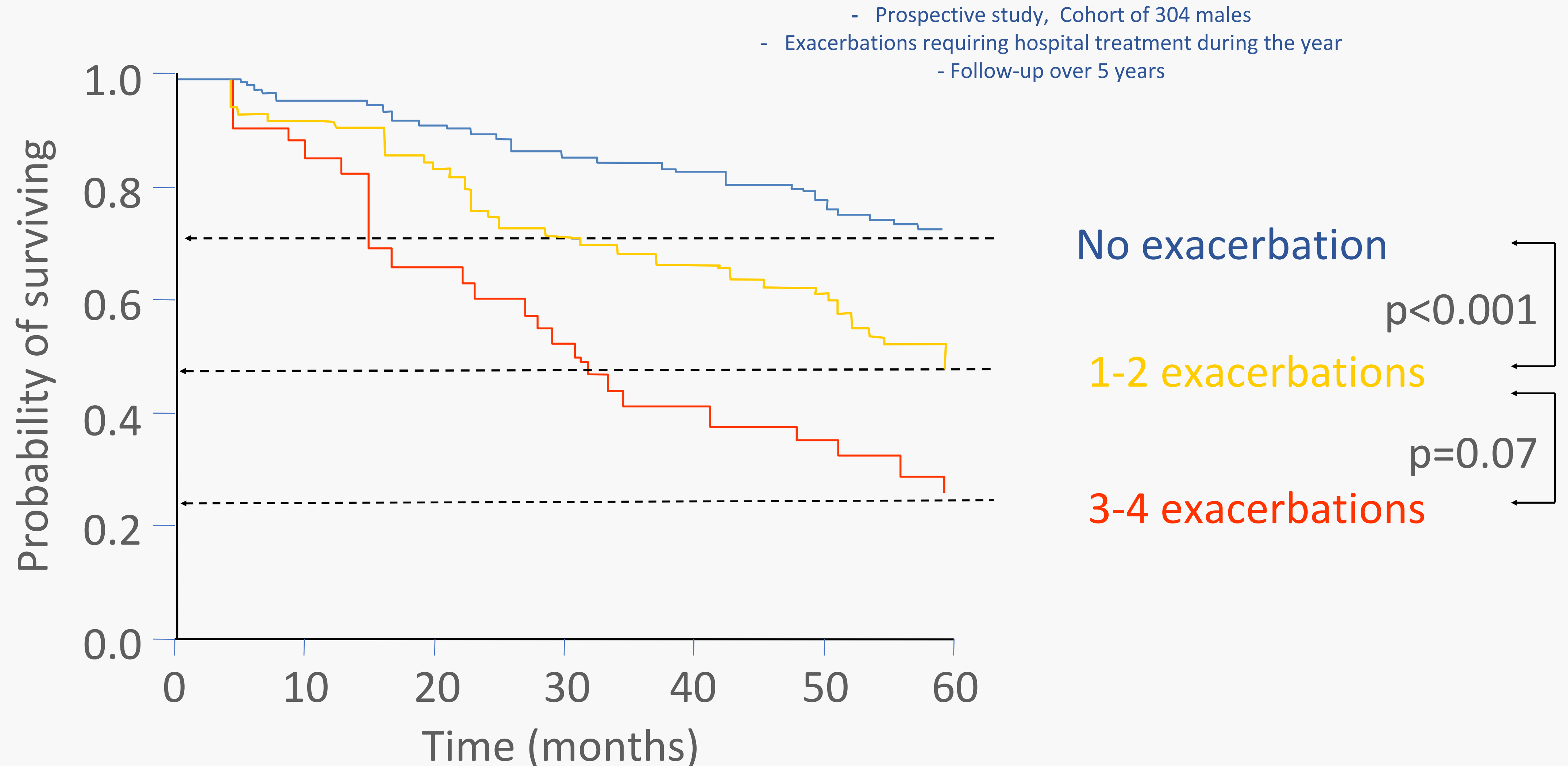


# Hospitalization rate per year



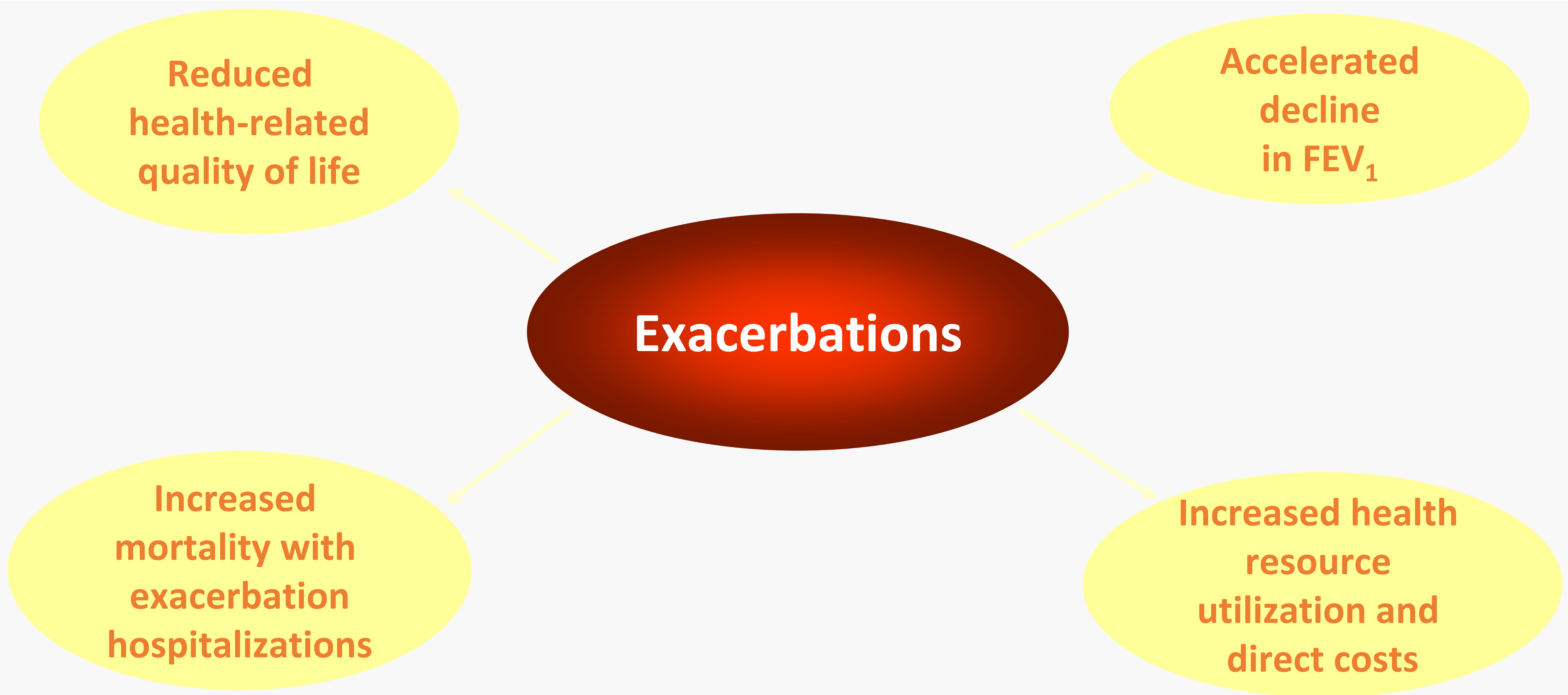


# Repeated Exacerbations Reduce the Probability of Survival





# Consequences of Exacerbations





# What does an Exacerbation mean to a Patient?

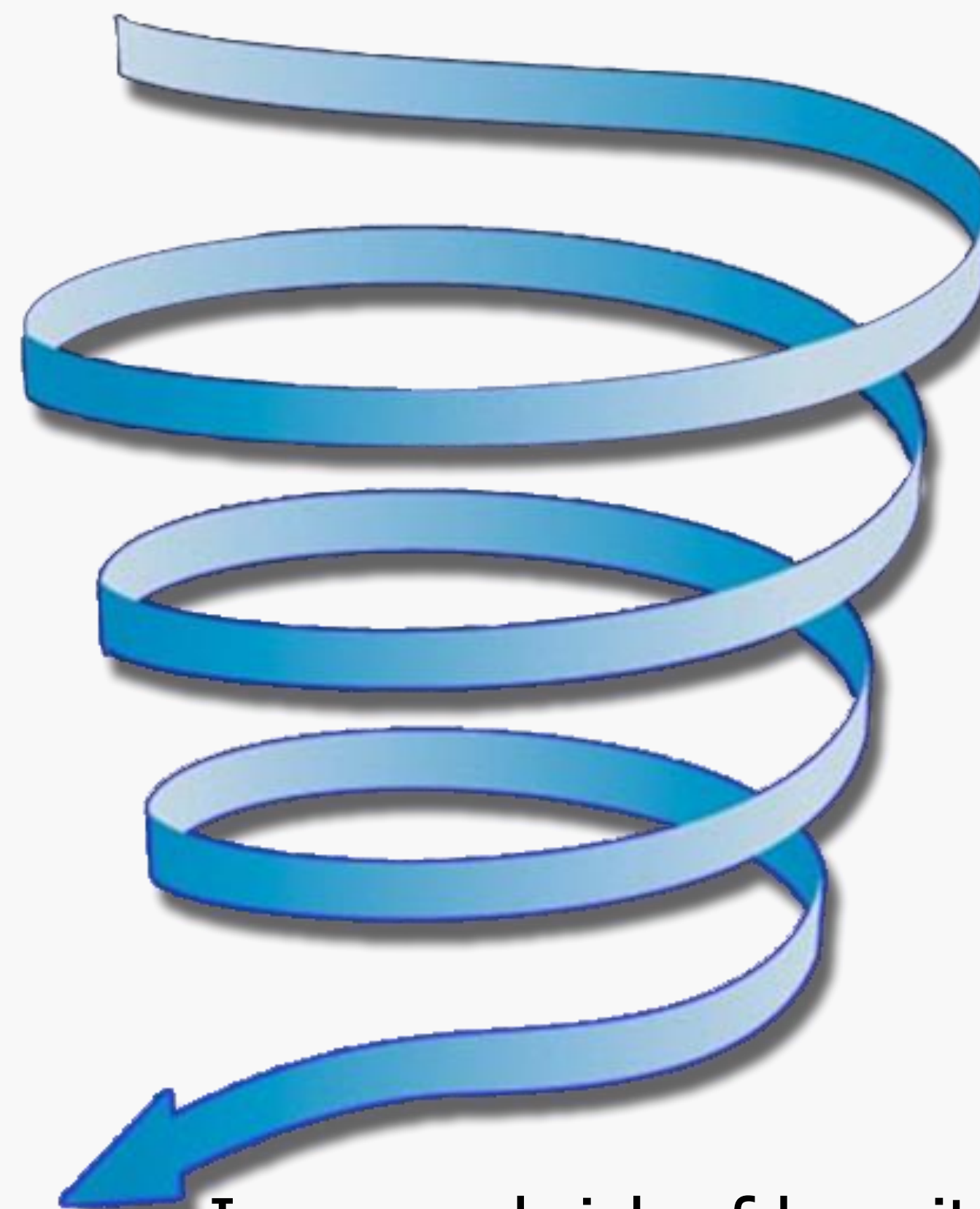


Decline in lung function<sup>1,2</sup>

Greater anxiety<sup>3</sup>

Social withdrawal

Increased risk of mortality<sup>8</sup>



Increased risk of hospitalisation<sup>1,2</sup>

Increased symptoms  
(I.e. breathlessness)<sup>6</sup>

Worsening quality of life<sup>4,5</sup>

More exacerbations<sup>6,7</sup>

1. Garcia-Aymerich J *et al.* 2001
2. Donaldson D *et al.* 2002
3. Gore JM *et al.* 2000
4. Seemungal T *et al.* 1998
5. Pauwels P *et al.* 2001
6. Seemungal T *et al.* 2000
7. Garcia-Aymerich J *et al.* 2003
8. Anto JM *et al.* 2001



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# Prevention



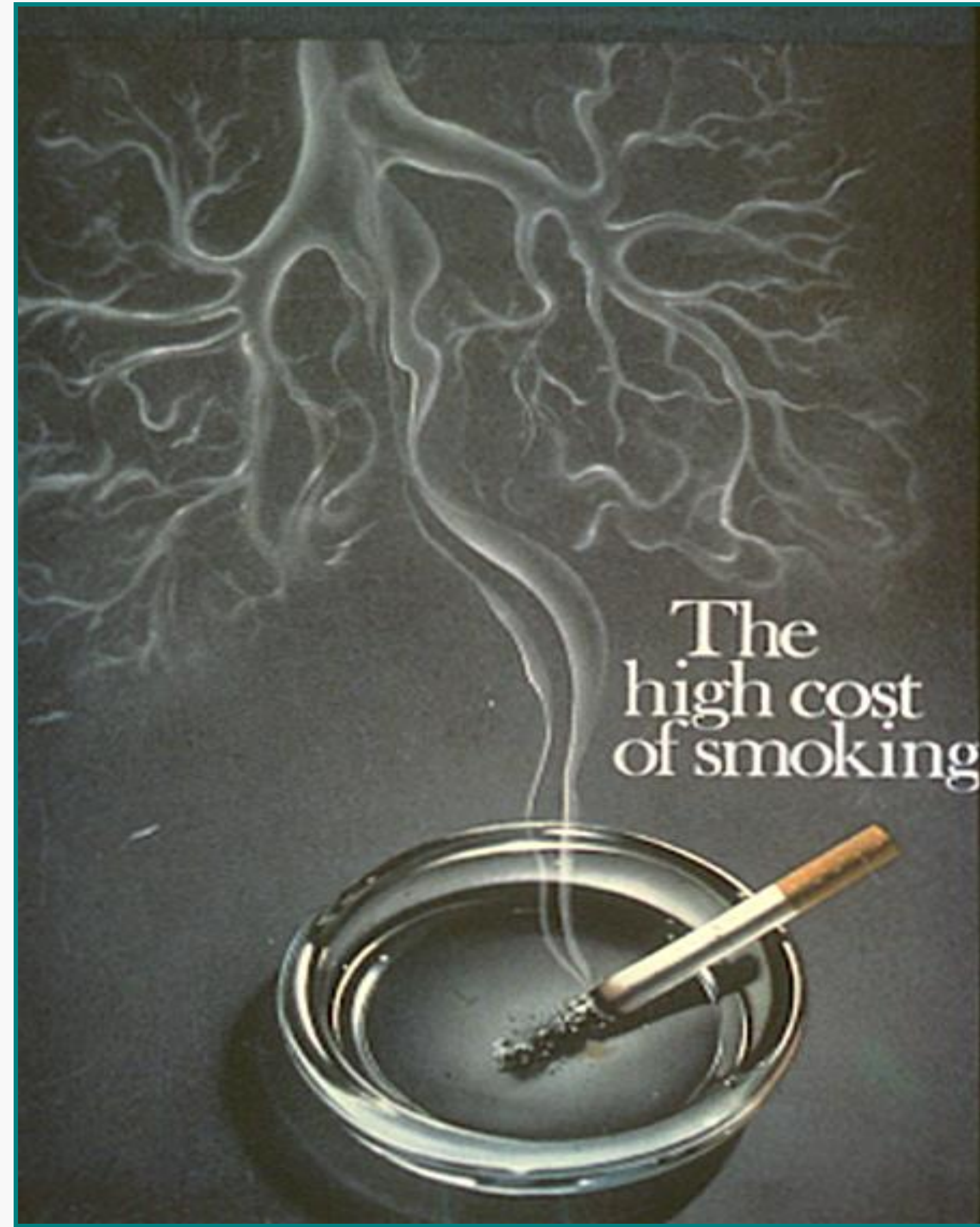


# Prevention of COPD Exacerbations

Smoking cessation	
Influenza vaccination	<b>Annually</b>
Pneumococcal vaccination	<b>Every 5–10 years</b>
Pulmonary rehabilitation	
Self-management education	
Optimize maintenance bronchodilator therapy	
Combination therapy	<b>Moderate to severe COPD with &gt;1 exacerbation/yr</b>
Roflumilast <sup>1</sup>	<b>Chronic productive cough</b>
Mucolytics	



# Cigarettes Can Take Your Breath Away



# THANK YOU



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