Brigham and Women's Hospital
Founding Member, Mass General Brigham

Chronic Obstructive Pulmonary Disease

Craig P. Hersh, MD, MPH
Associate Physician
Channing Division of Network Medicine
and Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School

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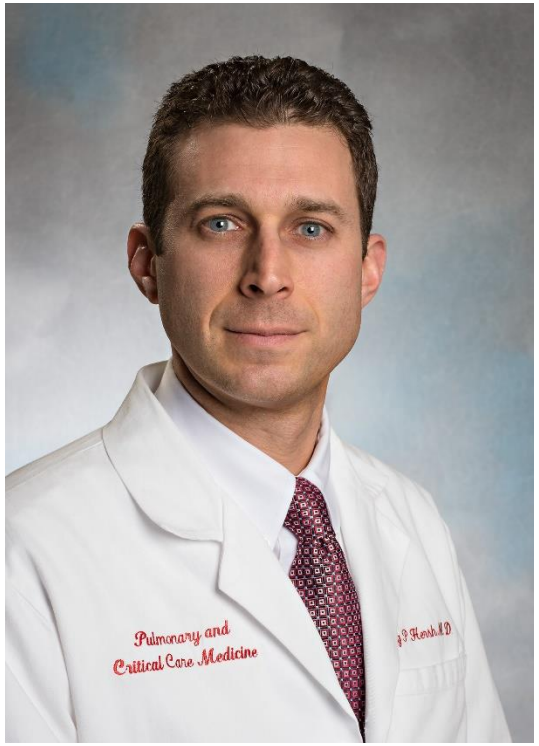

- Medical School: Univ of Pennsylvania
- Medical Residency: Univ of Pennsylvania
- Pulmonary and Critical Care fellowship: Harvard combined program
- Respiratory epidemiology fellowship: BWH
- Professor of Medicine at BWH
  - Clinical focus: COPD, Alpha-1 antitrypsin deficiency
  - Research focus: COPD epidemiology and genetics

Disclosures

- Consulting fees:
  - Apogee Therapeutics, AstraZenece, Chiesi, Genentech, Ono Pharma, Sanofi, Verona Pharma

Learning Objectives

- Review the assessment and current treatments for stable COPD
- Describe the evaluation and management of COPD exacerbations
- Highlight new concepts in COPD diagnosis

Case

A 70 year old woman with no prior respiratory diagnosis sees you after a hospital admission for a COPD exacerbation. She was discharged on triple inhaled therapy (LAMA/LABA/ICS). She stopped smoking 20 years ago but still has daily cough and sputum.

Which of the following tests should you order:

a) Spirometry
b) Chest CT scan
c) Blood eosinophil count
d) All of the above
e) (a) and (c) only

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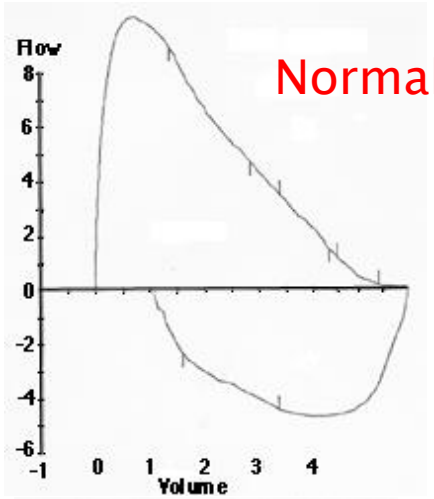
Chronic obstructive pulmonary disease

- Heterogeneous lung condition
- Chronic respiratory symptoms
- Abnormalities of the airways and/or alveoli
- Persistent airflow obstruction, often progressive

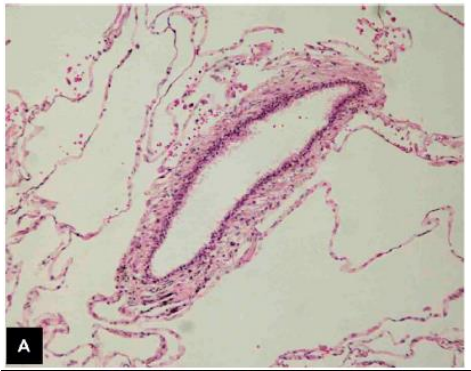
Global Initiative for Chronic Obstructive Lung Disease 2025
www.goldcopd.org

Multiple pathologies of COPD

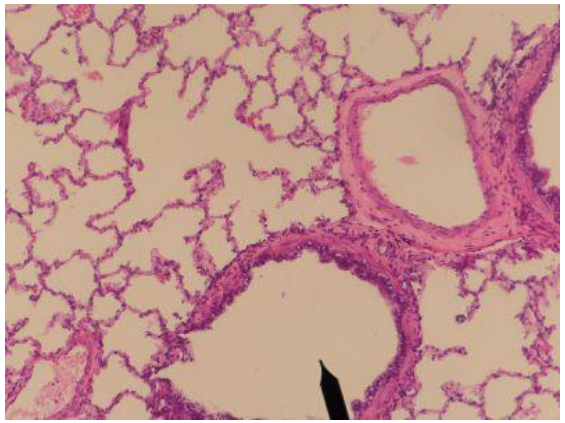


Normal spirometry

Emphysema

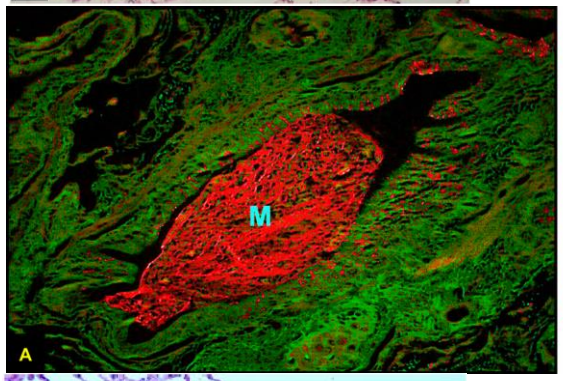


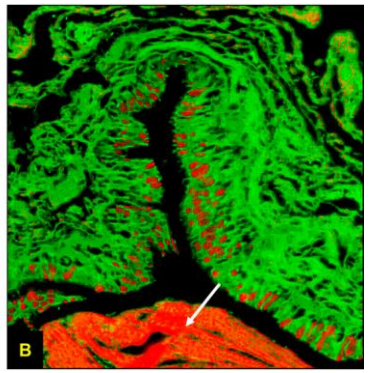
Normal

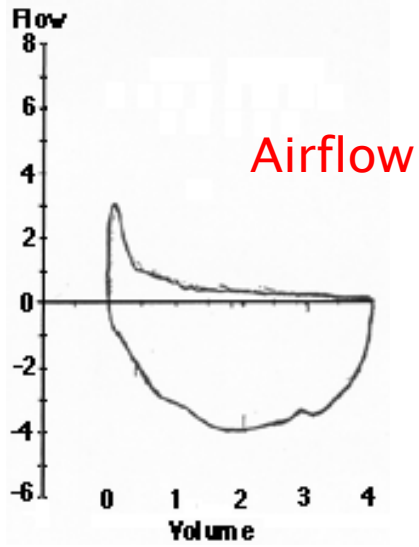


histology-world.com

Mucus metaplasia

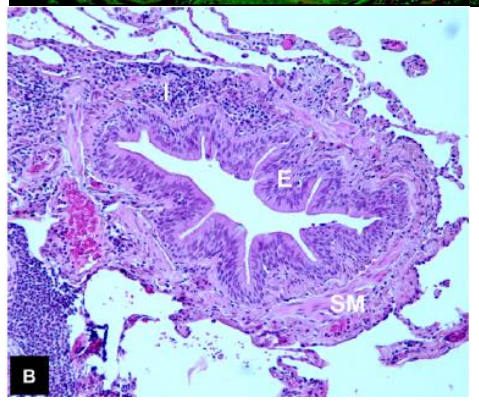






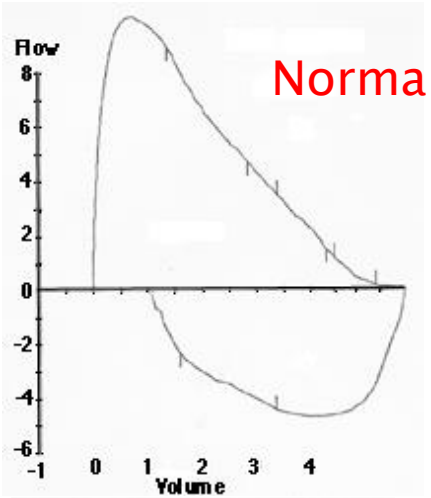
Airflow obstruction

Small airway disease



Kim V, Proc Am Thorac Soc 2008;5:478

Mechanisms of airflow limitation



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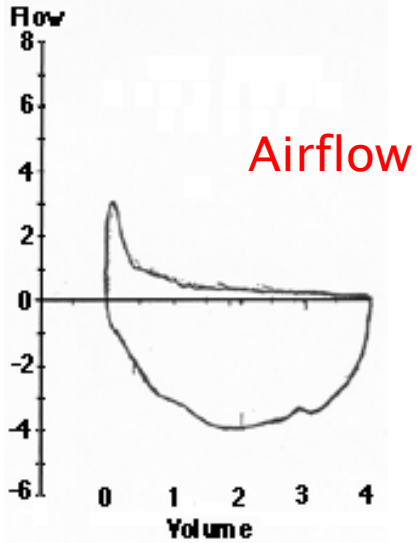
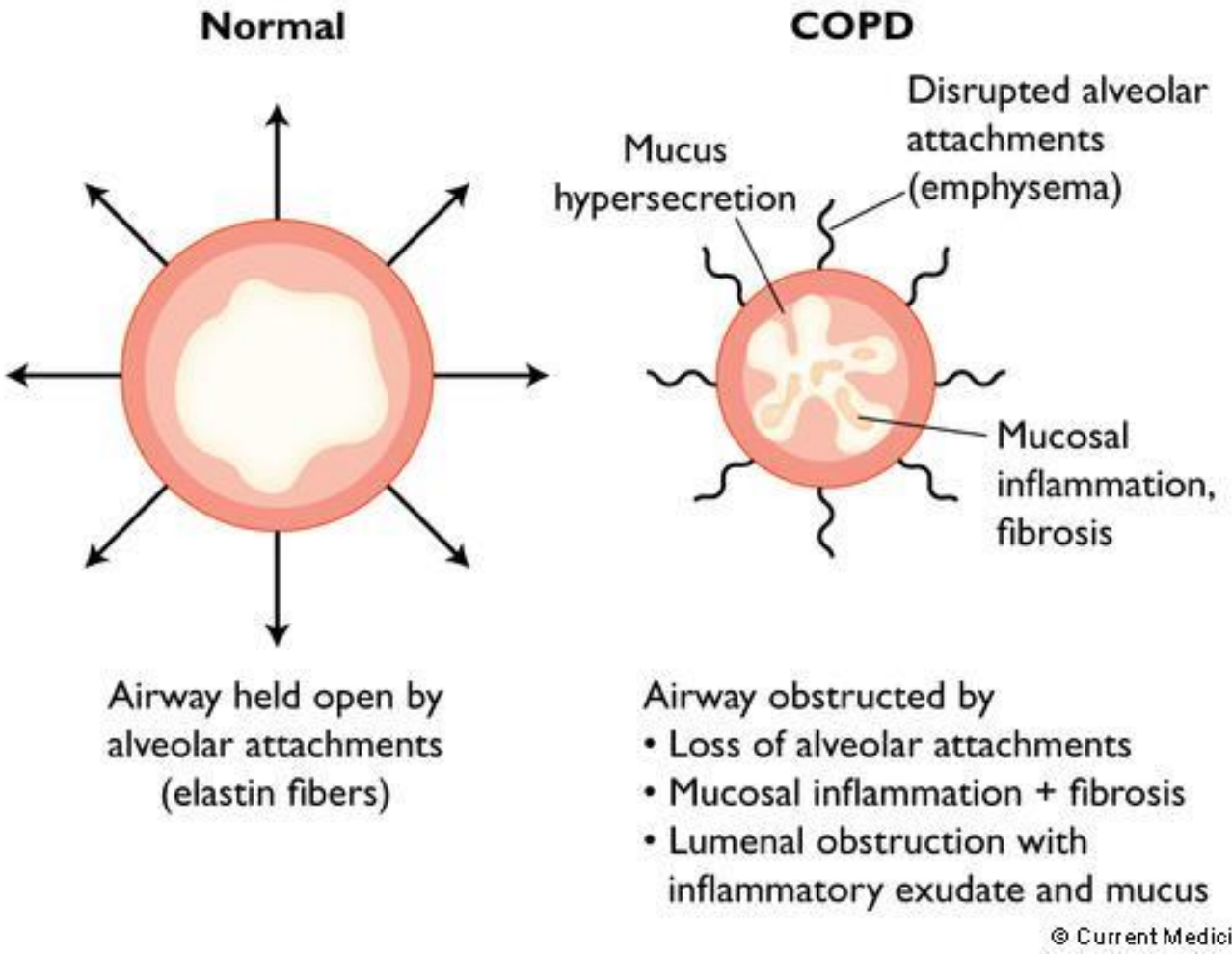


Airflow obstruction



Crapo J, ed. Atlas of COPD, 2009

Assessment: Symptoms and Signs of COPD

Symptoms

Cough
Sputum
Dyspnea
Wheeze
Chest tightness
Weight loss
Muscle weakness
Edema
Depression

Physical Exam

Tripod posture
Skin: cyanosis
Breathing: tachypnea, pursed lip breathing, prolonged expiration, accessory muscle use
Barrel Chest
Breath Sounds: distant, wheezes
Cardiac: distant, increased P2, JVD, edema
Cachexia

COPD Assessment Test (CAT)

I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all

Modified MRC Dyspnea scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Mahler DA, Chest 1988;93:580
Jones P, ERJ 2009;34:648

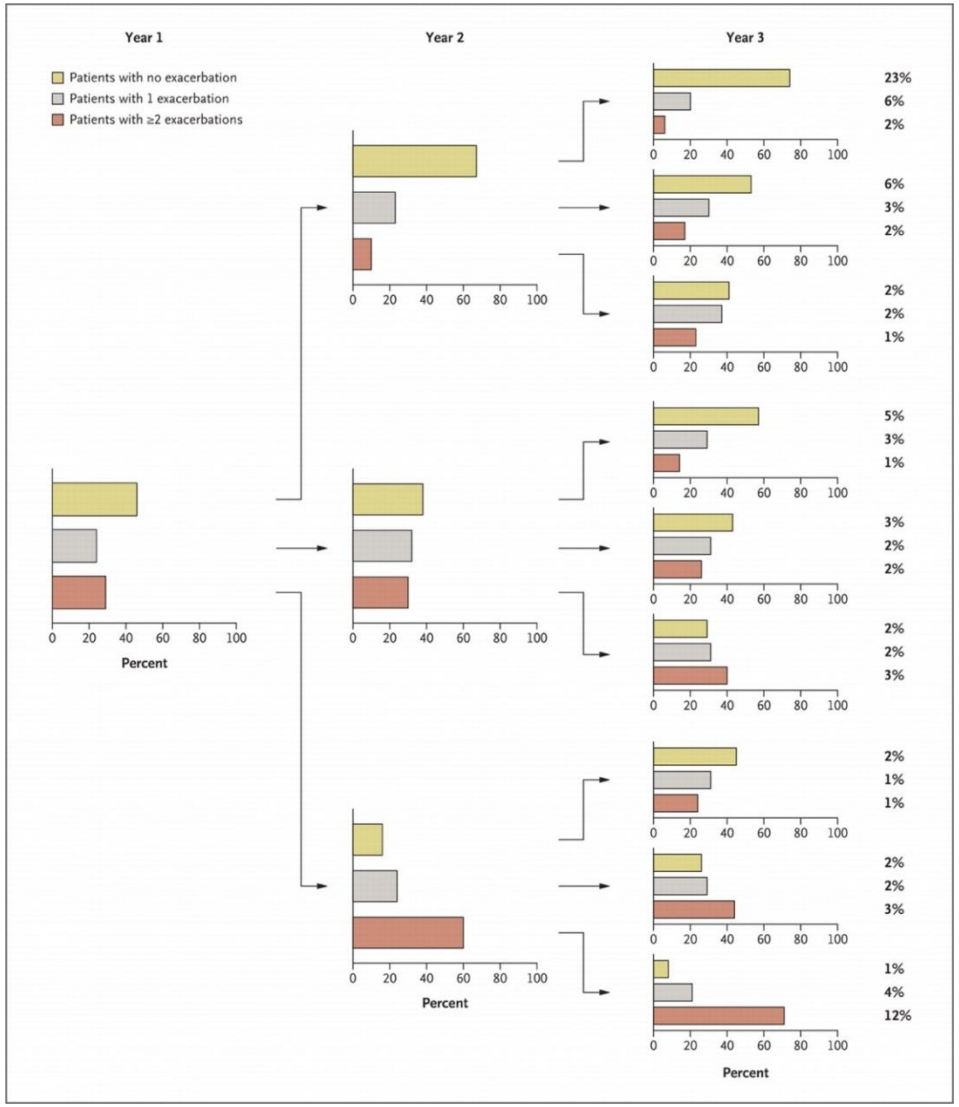
Classification of Severity of Airflow Limitation in COPD*

In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

**Based on Post-Bronchodilator FEV_1*

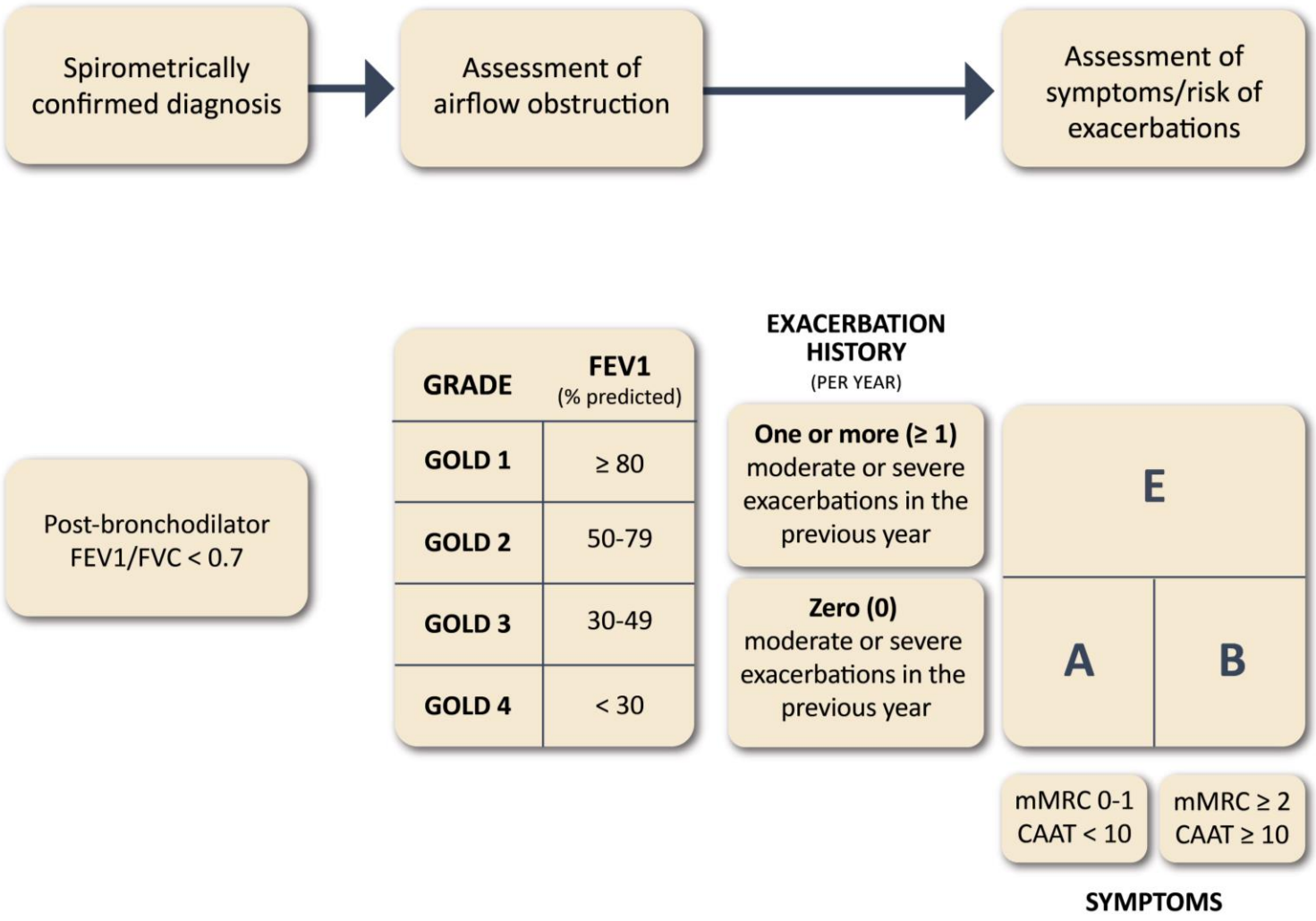
Exacerbation Risk: Past exacerbations are the best predictor of future exacerbations



Hurst JR, NEJM 2010; 363:1128

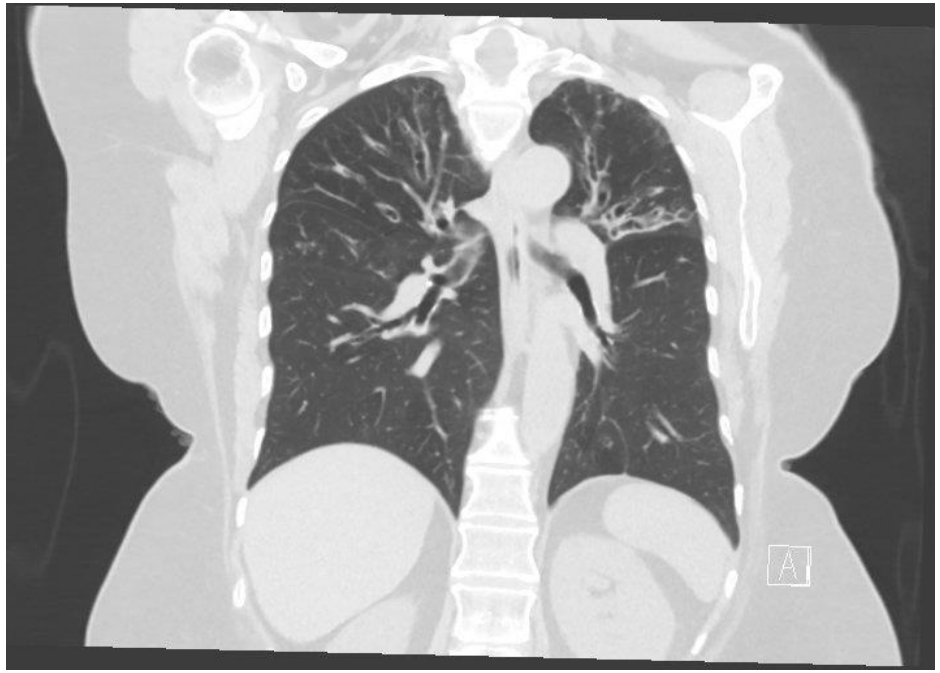
GOLD ABE Assessment Tool

Figure 2.13



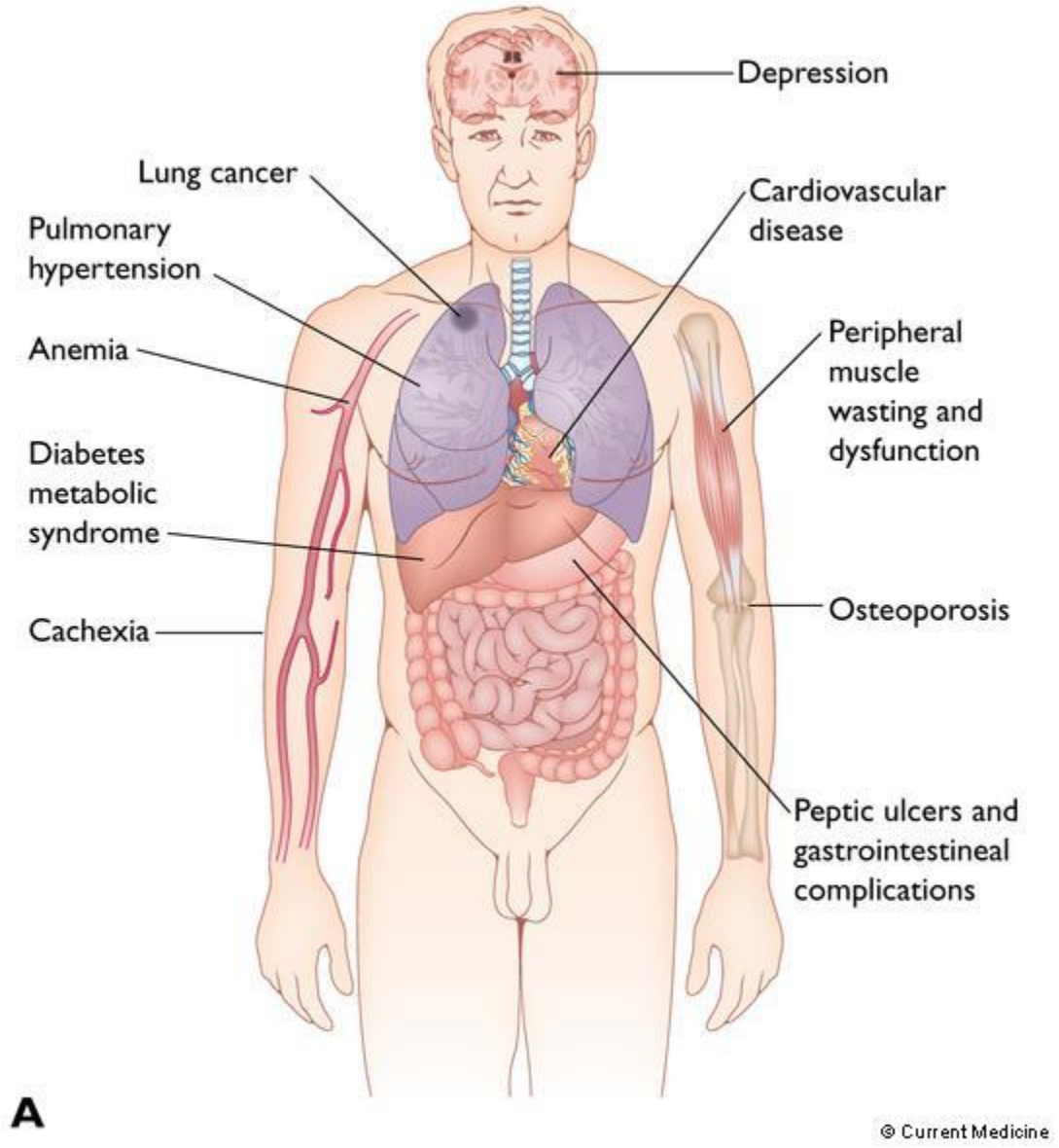
Other assessments

- Chest CT scan
  - Differential diagnosis
    - Bronchiectasis
    - “symptoms out of proportion”
  - Lung cancer screening
  - Lung volume reduction
- CBC with differential
- Alpha-1 antitrypsin deficiency
  - 1-2% of COPD in USA
  - AAT level +/- genotype or protein phenotype



Sandhaus RA, JCOPDF 2016; 3(3): 668-682

Comorbidities: COPD is a systemic disease



Crapo J, ed.,
Atlas of COPD, 2009

Case, 2 month follow-up

Spirometry: FEV_1 55% predicted, FEV_1/FVC 0.6.
Blood eosinophils 350 cells/µl
In the interim, she was treated with antibiotics for bronchitis.
What would you add to her regimen?

a) Roflumilast
b) Azithromycin 250mg daily
c) Dupilumab or mepolizumab
d) Ensifentrine

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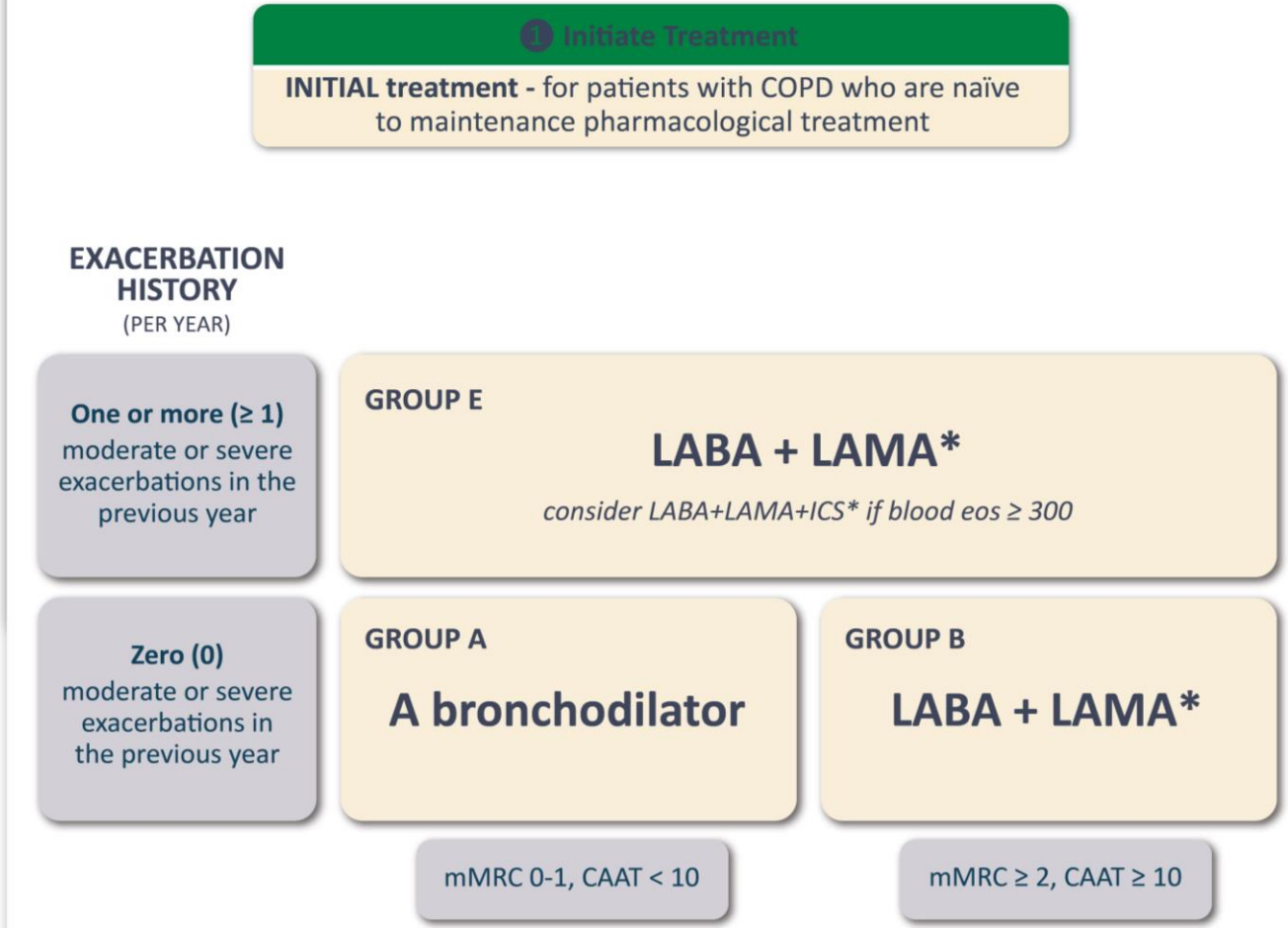
Initial Pharmacological Treatment

Figure 3.8



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment

Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAAT™: Chronic Airways Assessment Test™.

Follow-up Pharmacological Treatment

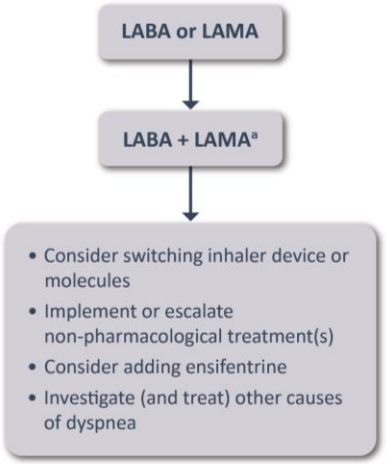
Figure 3.9

2 Adjust Treatment

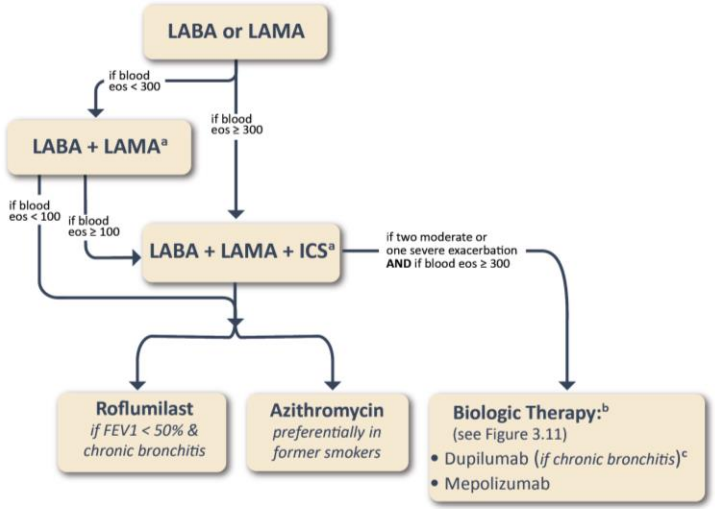
CONTINUE CURRENT TREATMENT

unless dyspnea or exacerbation(s) require optimization

• IF PERSISTENT DYSPNEA



• IF ONE OR MORE MODERATE OR SEVERE EXACERBATION



[a]Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

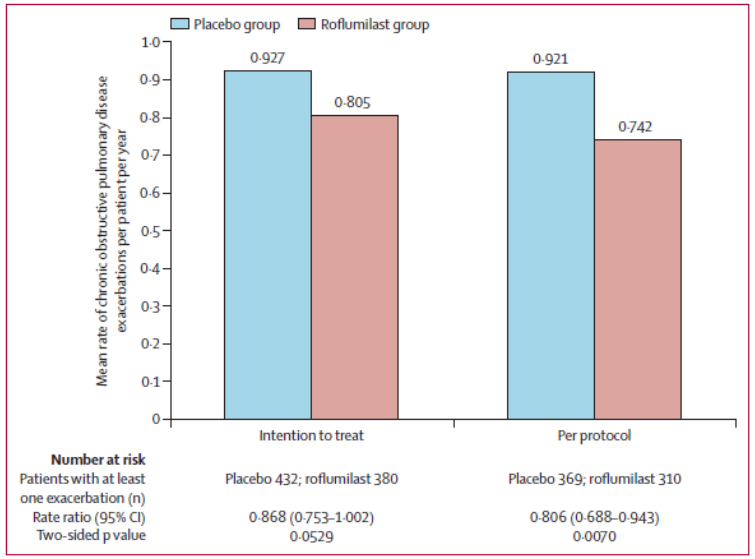
[b]Listed in order of approval in the US.

[c]Patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes.

Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eosinophils ≥ 300 cells/μl de-escalation is more likely to be associated with the development of exacerbations.

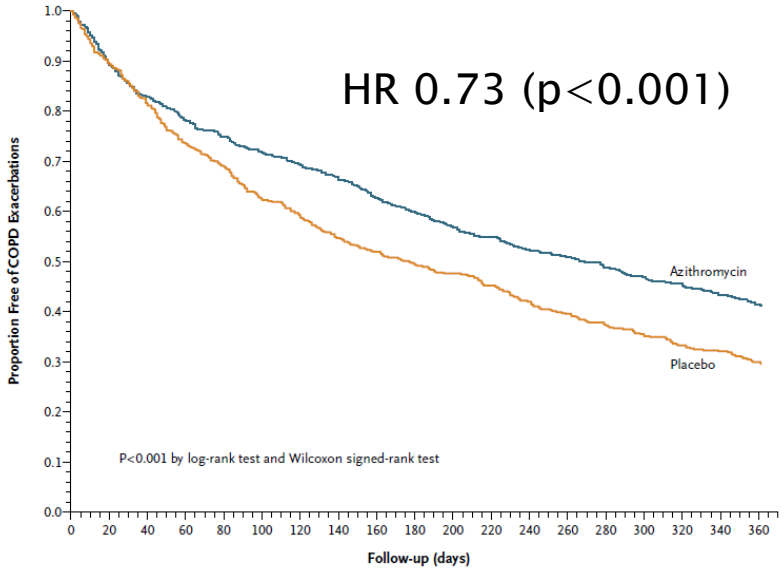
Oral therapies to decrease exacerbation risk

Roflumilast



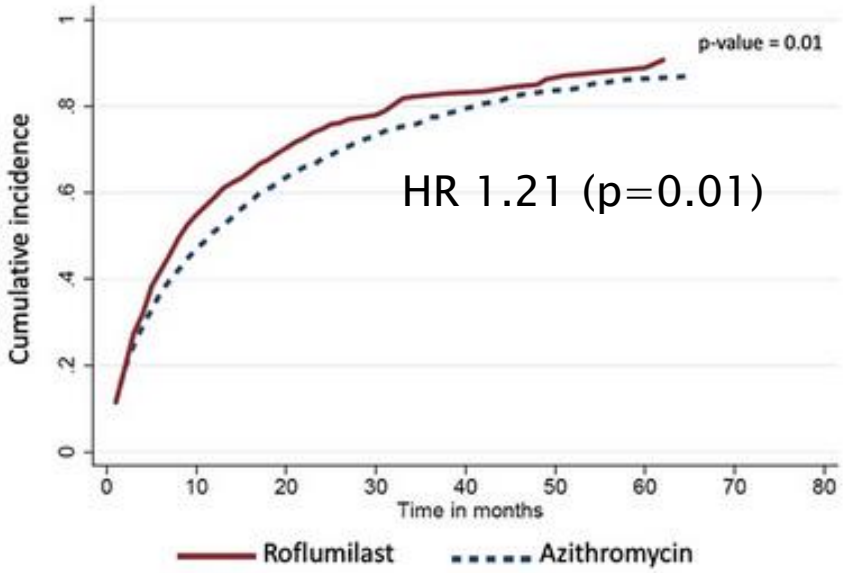
Severe COPD (FEV_1<50%)
chronic bronchitis
exacerbation history
GI side effects

Azithromycin 250mg daily



More effective: older, ex-smokers, milder COPD
Adverse effect: hearing loss

Comparison



VA database study:
Prefers azithromycin

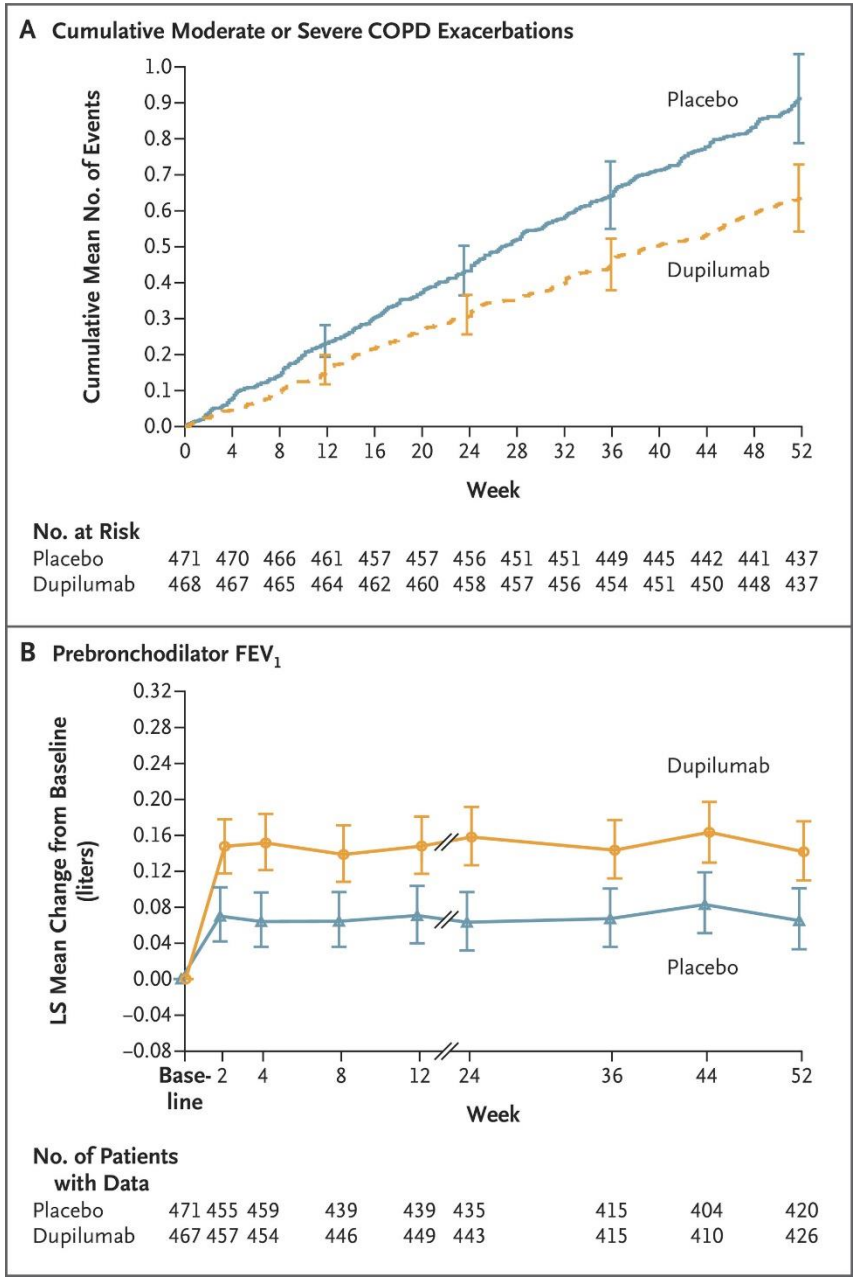
Martinez, Lancet 2015;385:857
Albert, NEJM 2011;365:689
Lam, JCOPDF 2021;8:450

Dupilumab

- Anti-IL4/13 mAb
- BOREAS trial
  - FEV_1 30-80%
  - Blood eos ≥ 300
  - Exacerbation history
  - On LABA/LAMA/ICS
- 300mg sc q2wks vs. placebo

Reduced exacerbations RR 0.70

Improved FEV1

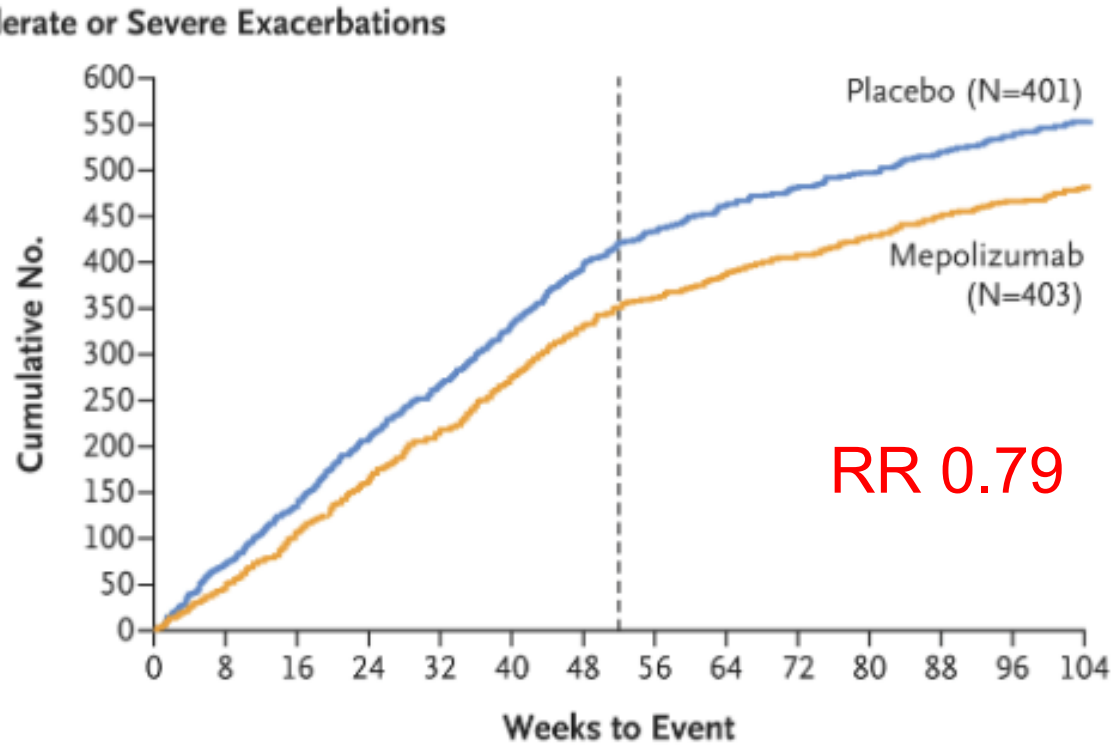


Bhatt SP, NEJM 2023;389:205

Mepolizumab: anti-IL5

- MATINEE trial
- Current/former smokers (n=804)
  - FEV1 20-80%
  - Blood eos ≥300
  - Exacerbation history
  - On triple therapy
- Mepo 100mg sc q4wks vs placebo
- Approval for eos ≥150 based on METREX trial

Pavord, NEJM 2017;377:1613

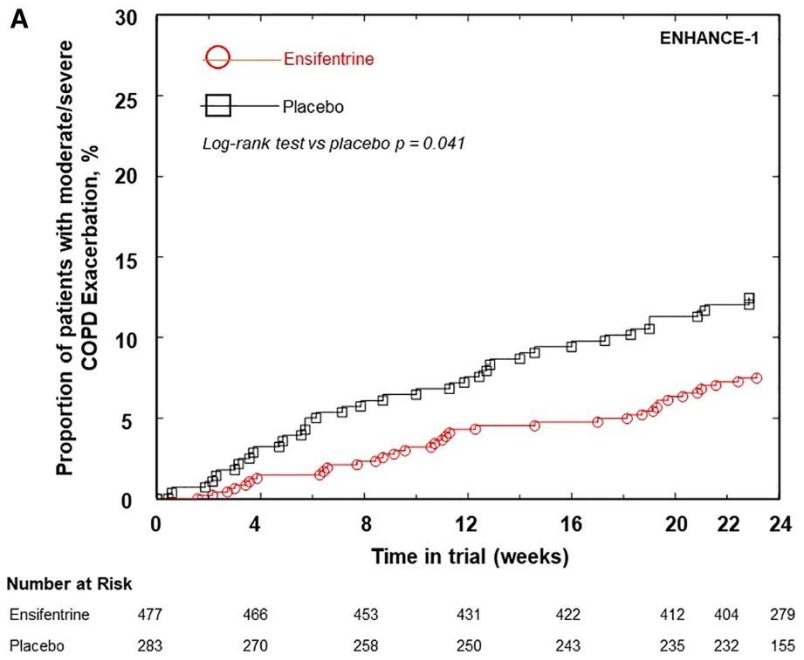


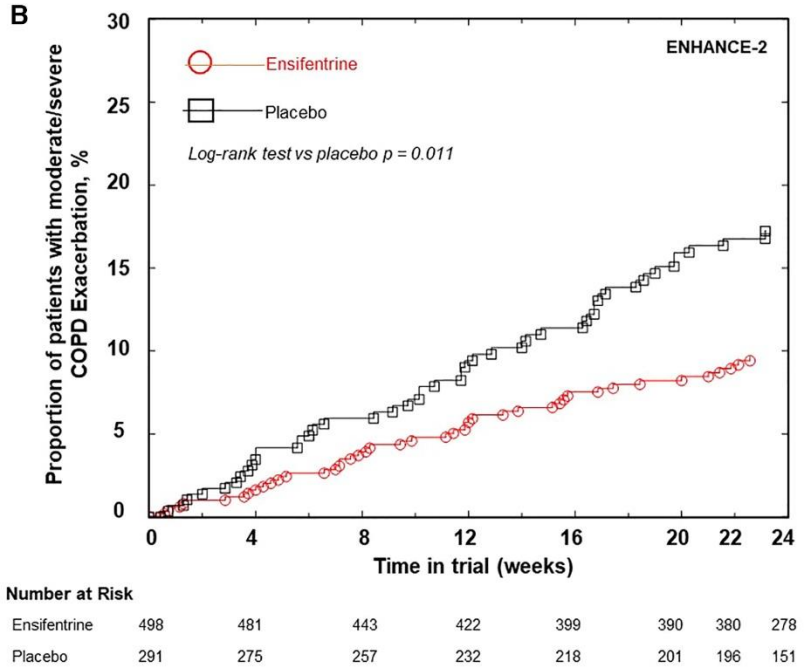
No effect on FEV1 or PROs

Sciurba, NEJM 2025;392:1710

Ensifentrine

- Nebulized PDE3/4 inhibitor
  - Bronchodilator and anti-inflammatory
- ENHANCE 1 and 2 trials
  - FEV1 increase ~90ml
  - Improved symptoms
  - Reduced exacerbations
- Caveat:
  - Maintenance therapy 68%, 55%
  - None on triple therapy

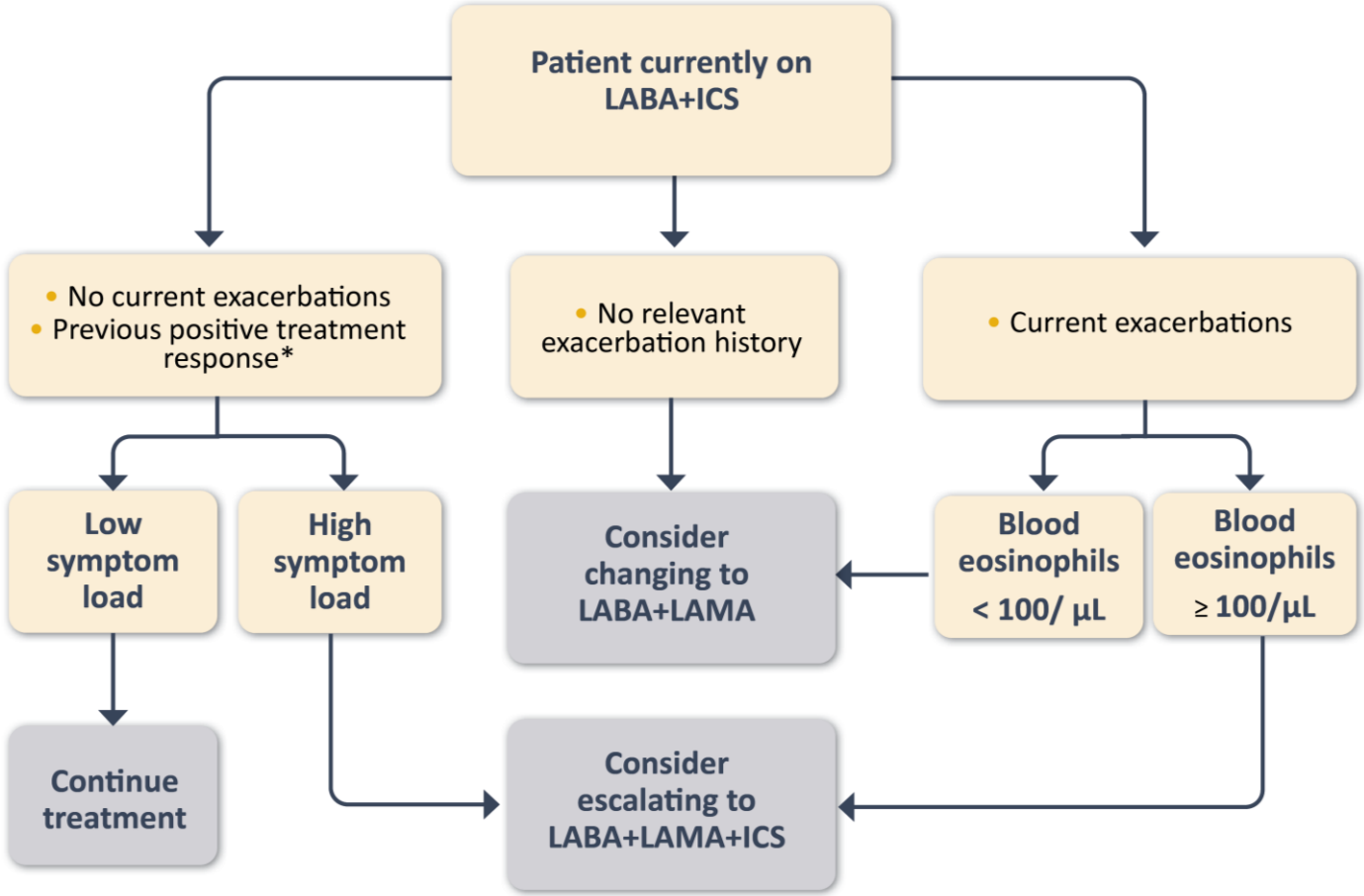




Anzueto, AJRCCM 2023;208:406

Management of Patients Currently on LABA+ICS

Figure 3.22



*Patient previously had exacerbations and responded to LABA+ICS treatment

Case, a few years later

She notes progressive dyspnea. O_2 sat is 88% on room air at rest. To reduce future adverse events, you prescribe supplemental O_2

A. 24 hours/day

B. 15 hours/day (e.g. nighttime)

C. Either A or B

D. No supplemental O_2

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B. 15 hours/day (e.g. nighttime)

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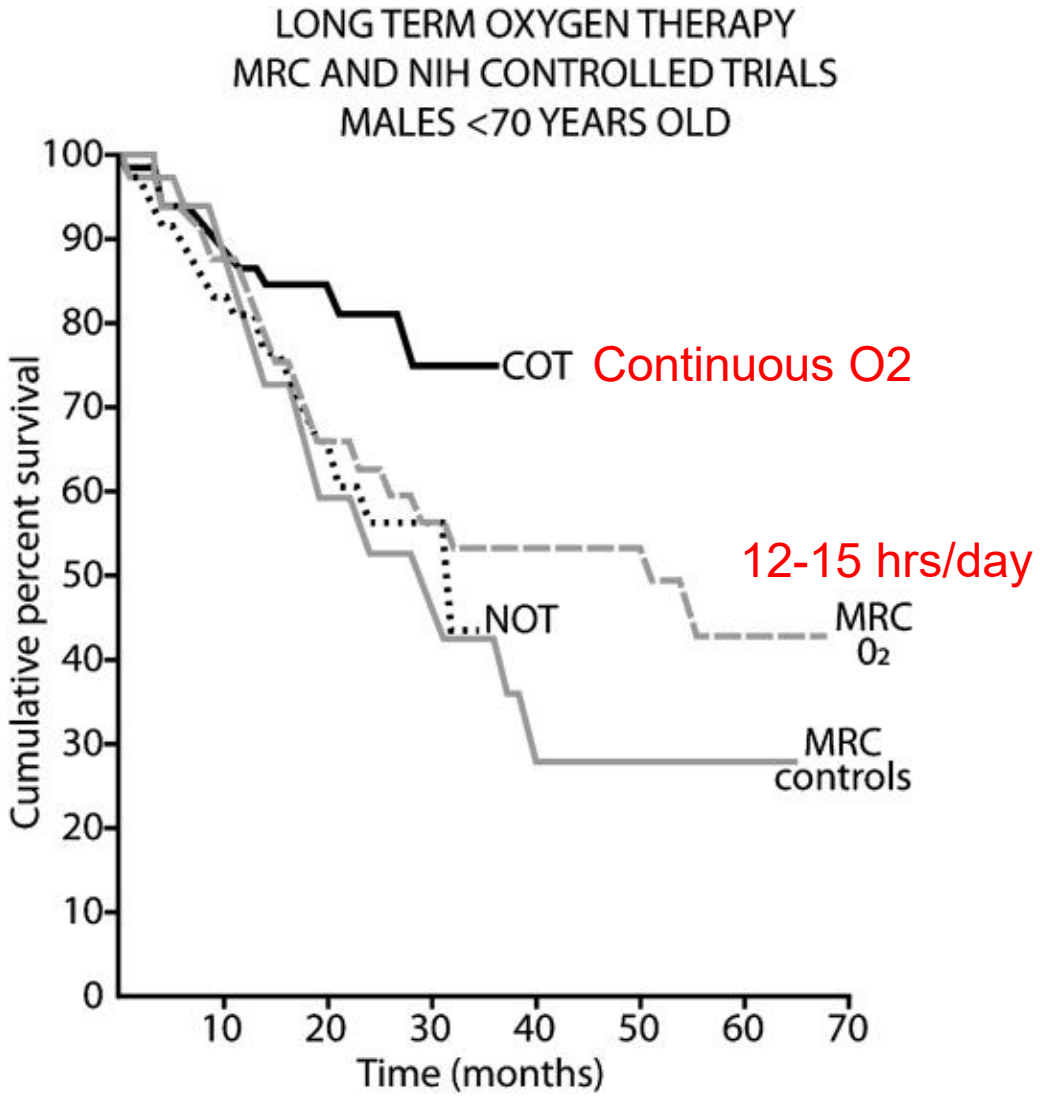
Supplemental oxygen reduces mortality in hypoxemic COPD patients

Criteria, at rest:

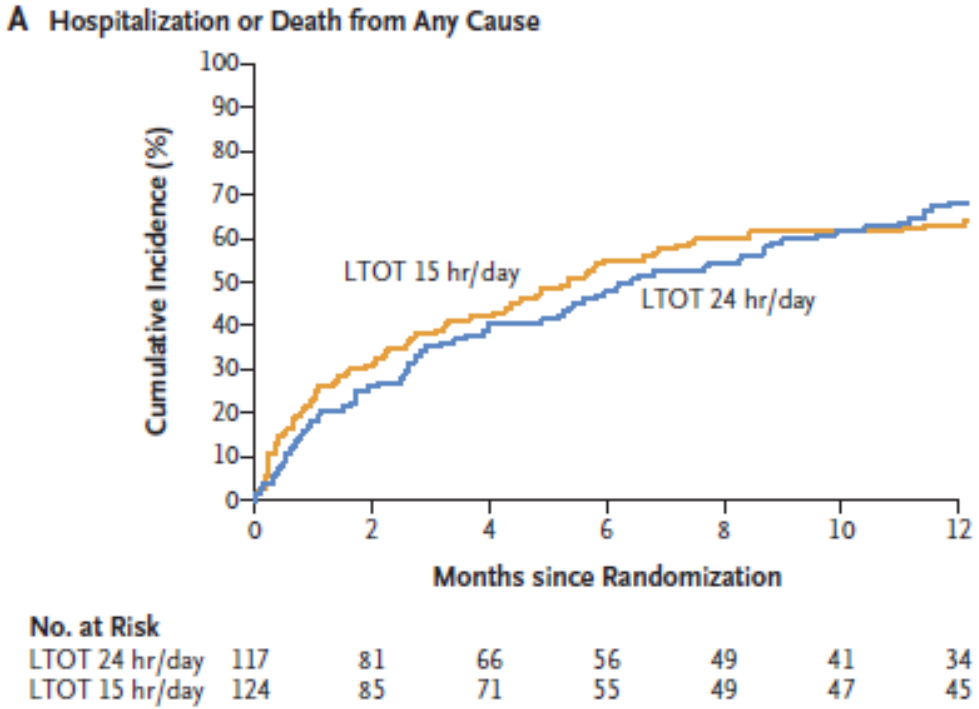
- PaO_2 ≤55 mmHg or SaO_2 ≤88% or
- PaO_2 ≤60mmHg or SaO_2 ≤89%
  - with cor pulmonale, right heart failure or polycythemia



Stoller J, Chest 2010

Do you need supplemental O_2 24hrs/day?

- REDOX trial
- N=241
- ~70% COPD
- Randomized O_2 24 vs 15 hr/d



Ekstrom M, NEJM 2024;391:977

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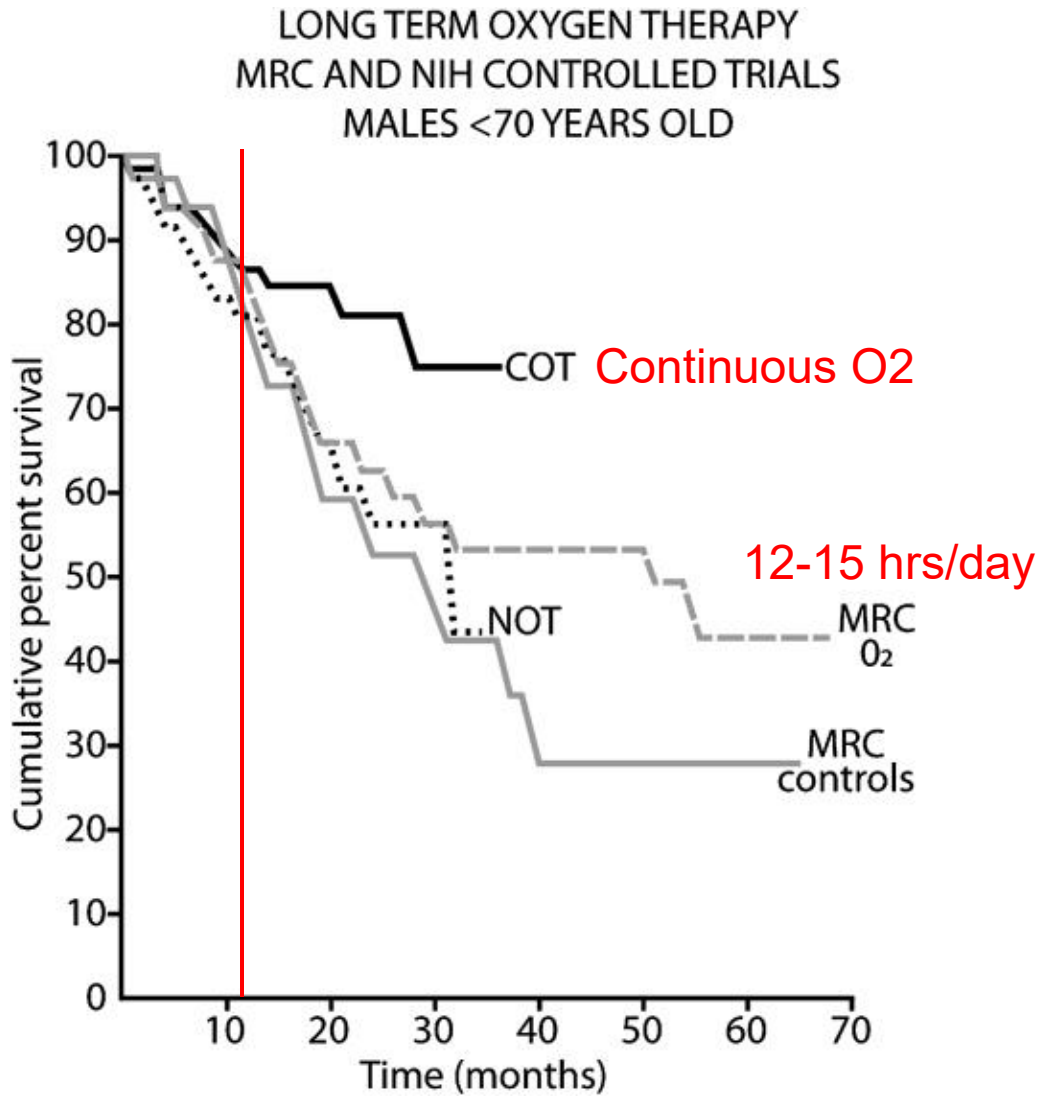
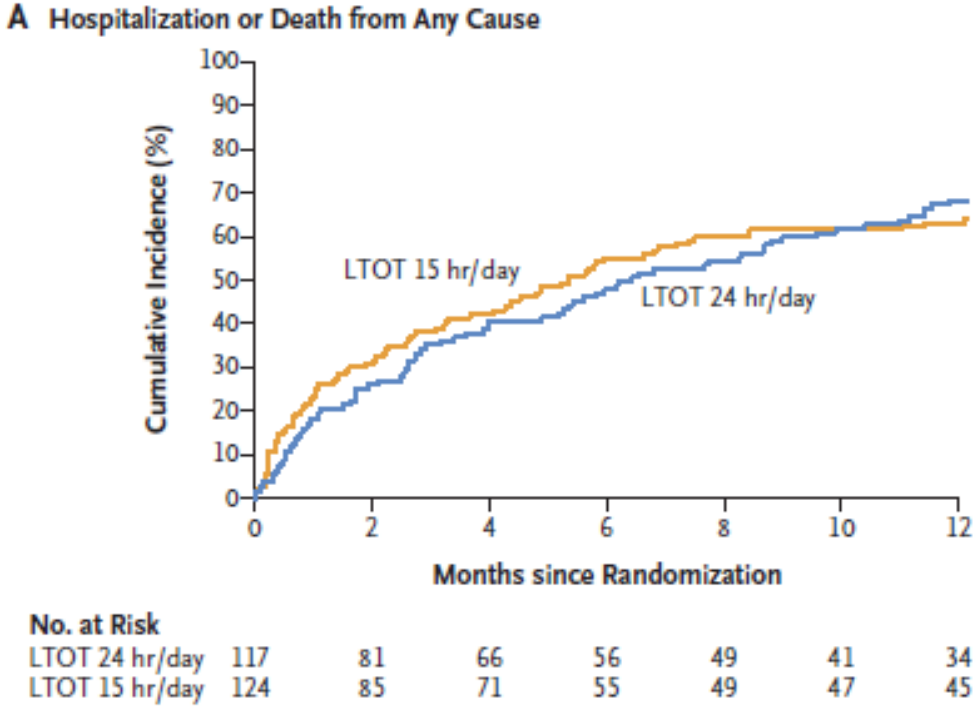
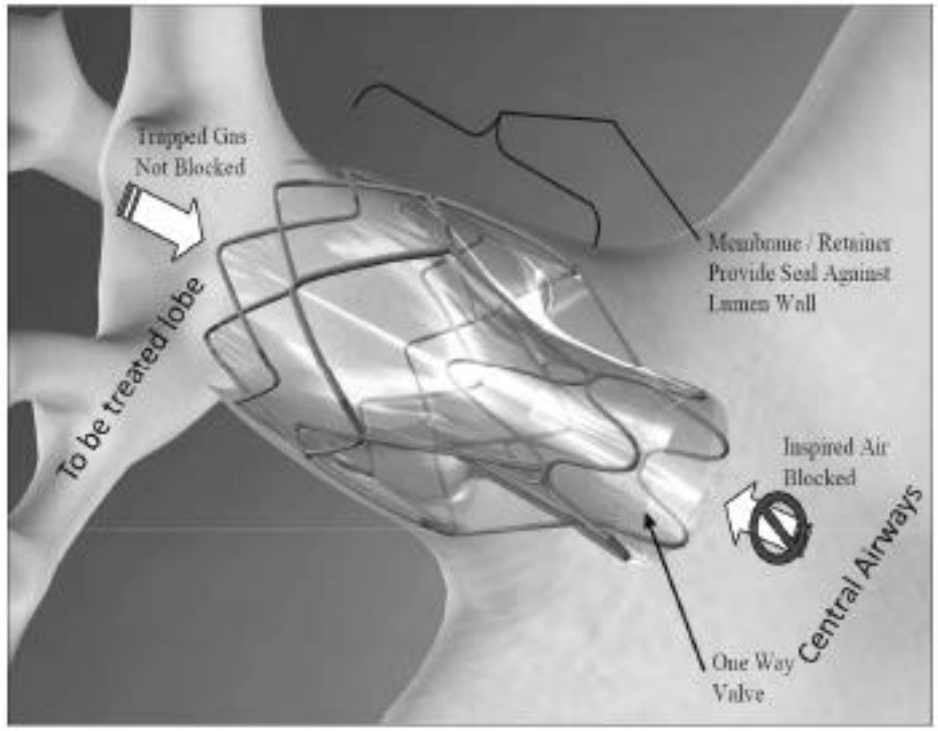




Ekstrom M, NEJM 2024;391:977

Surgical or interventional treatments

- Lung volume reduction surgery
  - Upper lobe predominant
  - Low exercise capacity
- Bronchoscopic lung volume reduction
- Lung transplantation



NETT, NEJM 2003;348:2059
*Klooster K, NEJM 2015;373:2325
Davey C, Lancet 2015;386:1066
Yusen R, J Heart Lung Transplant 2015;34:1264

Case, urgent visit

She has 3 days of dyspnea, productive cough, and chest tightness. She is tachycardic, tachypneic, O_2 sat 87% on her baseline 2 lpm, and she is wheezing on exam.

Besides COPD exacerbation, the differential diagnosis includes:

A. Community acquired pneumonia
B. Pulmonary embolism
C. Acute decompensated heart failure
D. (A) and (C) only
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COPD exacerbation: definitions

Symptom-based (Anthonisen)

- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

- Mild → Moderate → Severe
  - 1 → 2 → 3 symptoms

- Limitations
  - subjective
  - non-specific

Utilization-based

- Acute worsening of symptoms
- Requires additional therapy
  - Mild: short-acting bronchodilators
  - Moderate: antibiotics and/or systemic corticosteroids
  - Severe: ED visit or hospitalization

- Limitations
  - post-hoc
  - healthcare access
  - local medical practices

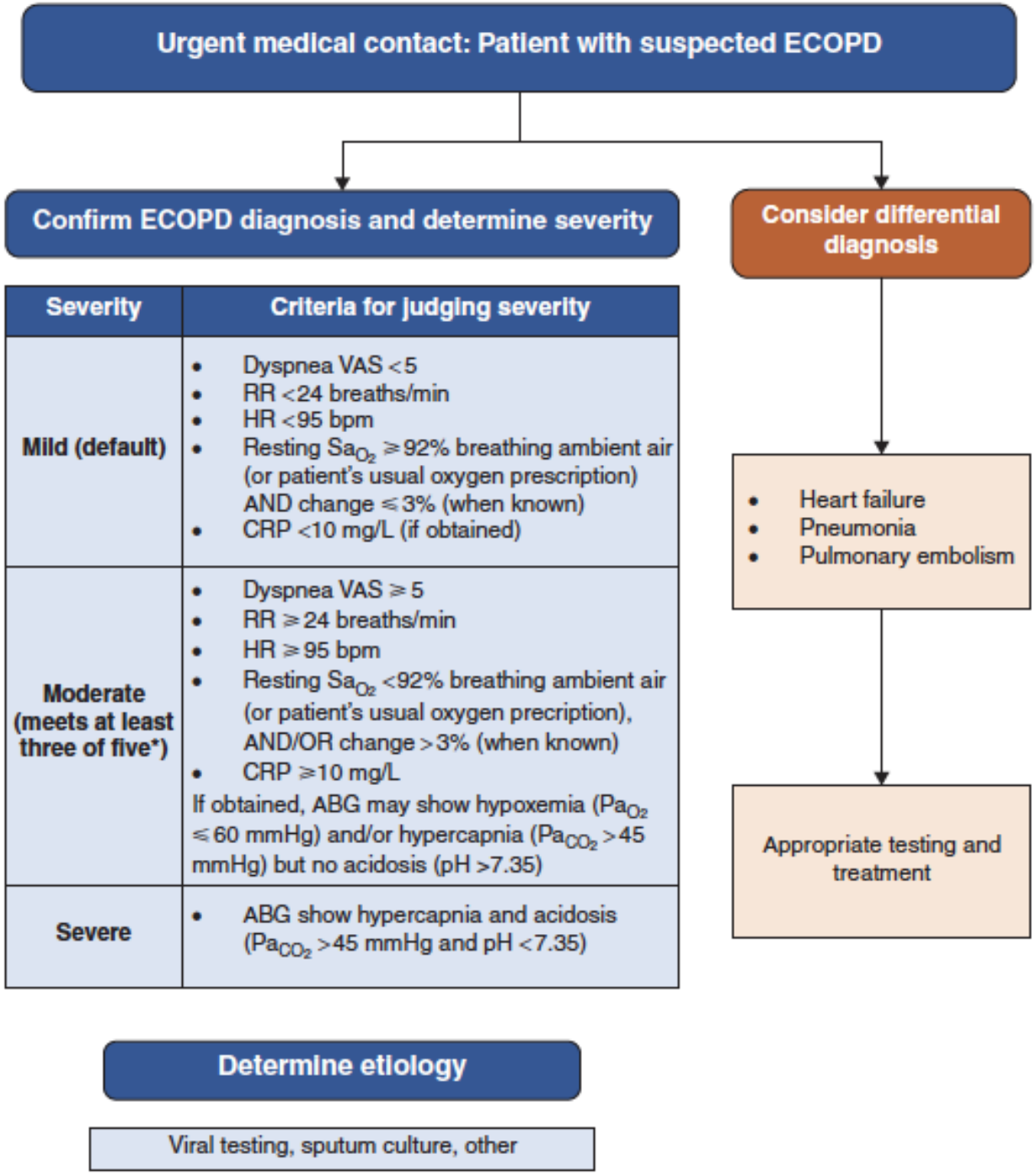
Anthonisen NR, Ann Intern Med 1987;106:196

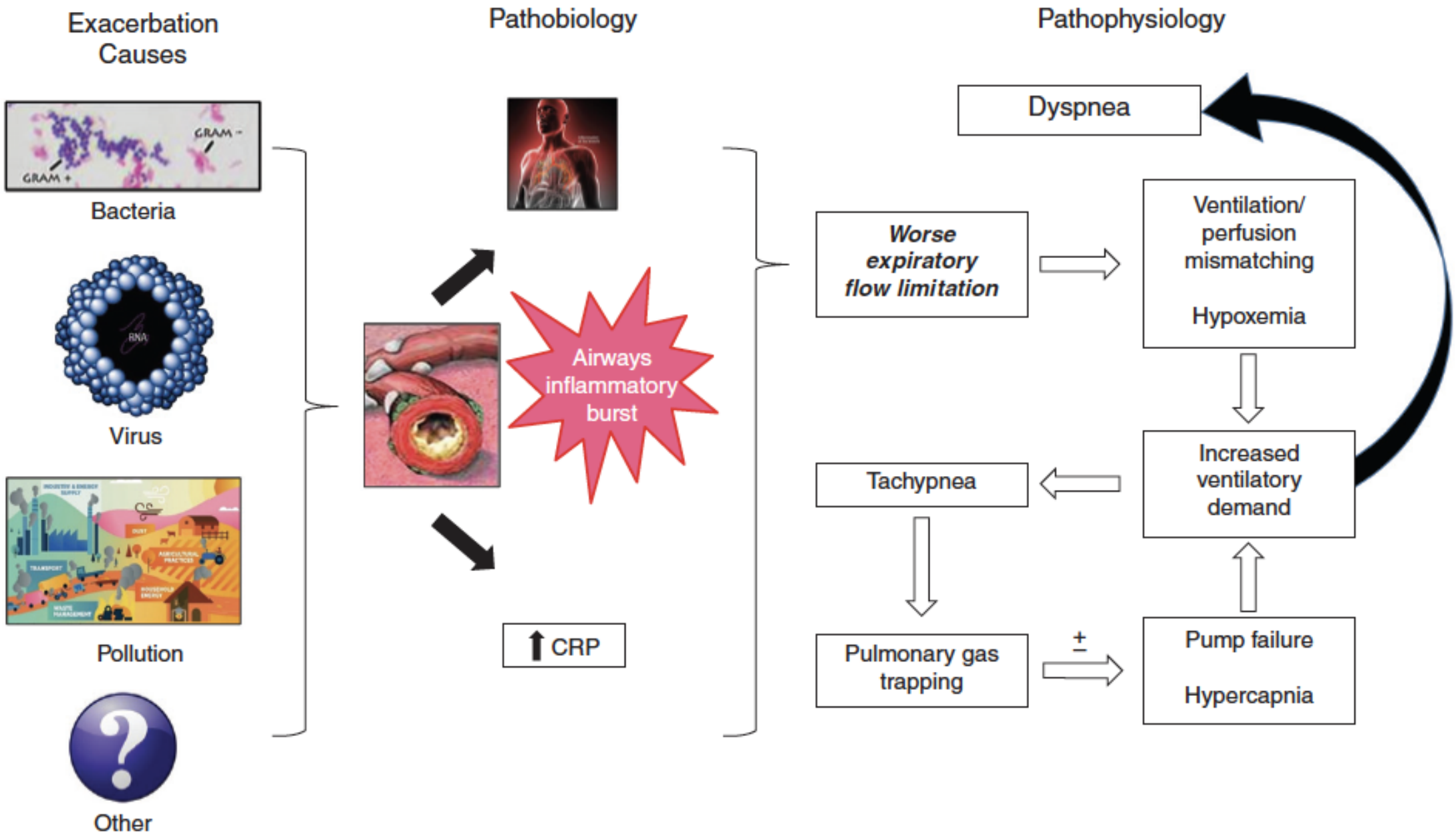
Calverley P, COPD 2005;2:143

Rome proposal

Celli BR et al, AJRCCM 2021;204:1251

- Modified Delphi method
- Goal: more objective
- Limitations
  - Arbitrary cutoffs
    - Change from baseline?
  - Discounts some symptoms
  - ED/hospital-based
  - No clinical validation



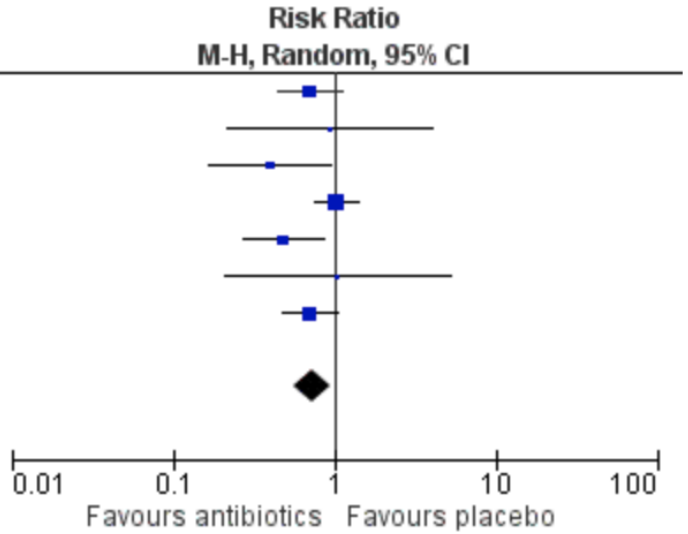


Celli BR et al, AJRCCM 2021;204:1251

Exacerbations treatment: Antibiotics

Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anthonisen 1987 (1)	19	57	28	59	19.8%	0.70 [0.45, 1.11]
Brusse-Keizer 2009 (2)	3	18	3	17	3.0%	0.94 [0.22, 4.05]
Hassan 2015 (3)	6	50	15	50	7.8%	0.40 [0.17, 0.95]
Jørgensen 1992 (4)	49	132	49	136	28.8%	1.03 [0.75, 1.41]
Llor 2012 (5)	15	158	30	152	14.5%	0.48 [0.27, 0.86]
Sachs 1995 (6)	4	40	2	21	2.5%	1.05 [0.21, 5.27]
van Velzen 2017 (7)	32	150	46	151	23.6%	0.70 [0.47, 1.03]
Total (95% CI)		**605**		**586**	**100.0%**	**0.72 [0.56, 0.94]**
Total events	128		173			

Heterogeneity: Tau² = 0.04; Chi² = 8.76, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 2.42 (P = 0.02)



Vollenweider DJ, Cochrane Database Syst Rev 2018:CD010257

- Reduce treatment failure
- Usually 5-7 days
- Respiratory flora: *H.influenzae, S.pneumoniae, M.catarrhalis*
  - E.g., Amox/clav, macrolides, doxycycline, quinolones
- Risk factors for pseudomonas
  - Previous sputum isolate, severe COPD, bronchiectasis, prior hospitalization

CRP to guide antibiotic prescription

- Primary care, N=653
- Point of case testing
  - < 20 mg/L should not use antibiotics
  - 20-40 mg/L may be beneficial
  - > 40 mg/L likely to be beneficial

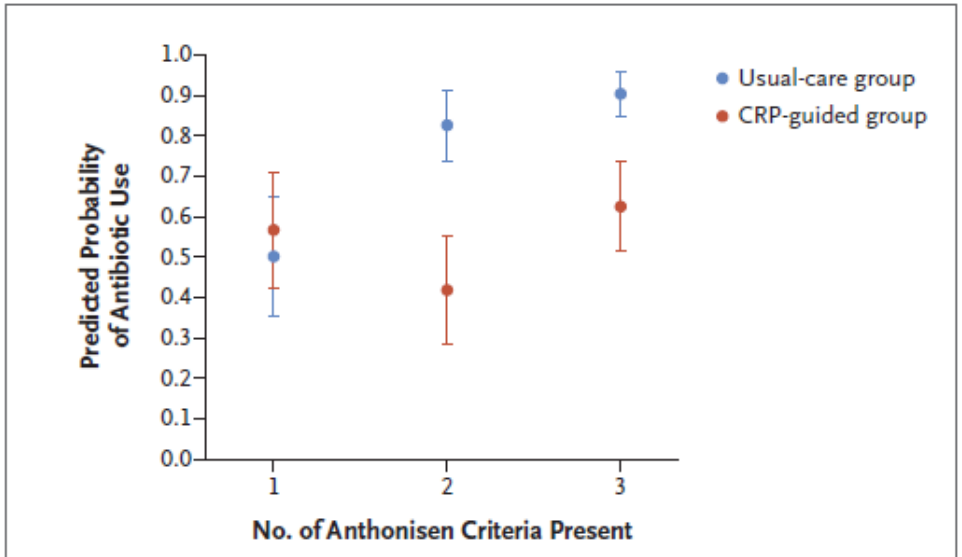


Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.

Less antibiotic use
No evidence of harm

Butler et al, NEJM 2019;381:111

Exacerbations treatment: Systemic steroids

Benefits:

↓ treatment failure, symptoms, LOS

↑ FEV_1

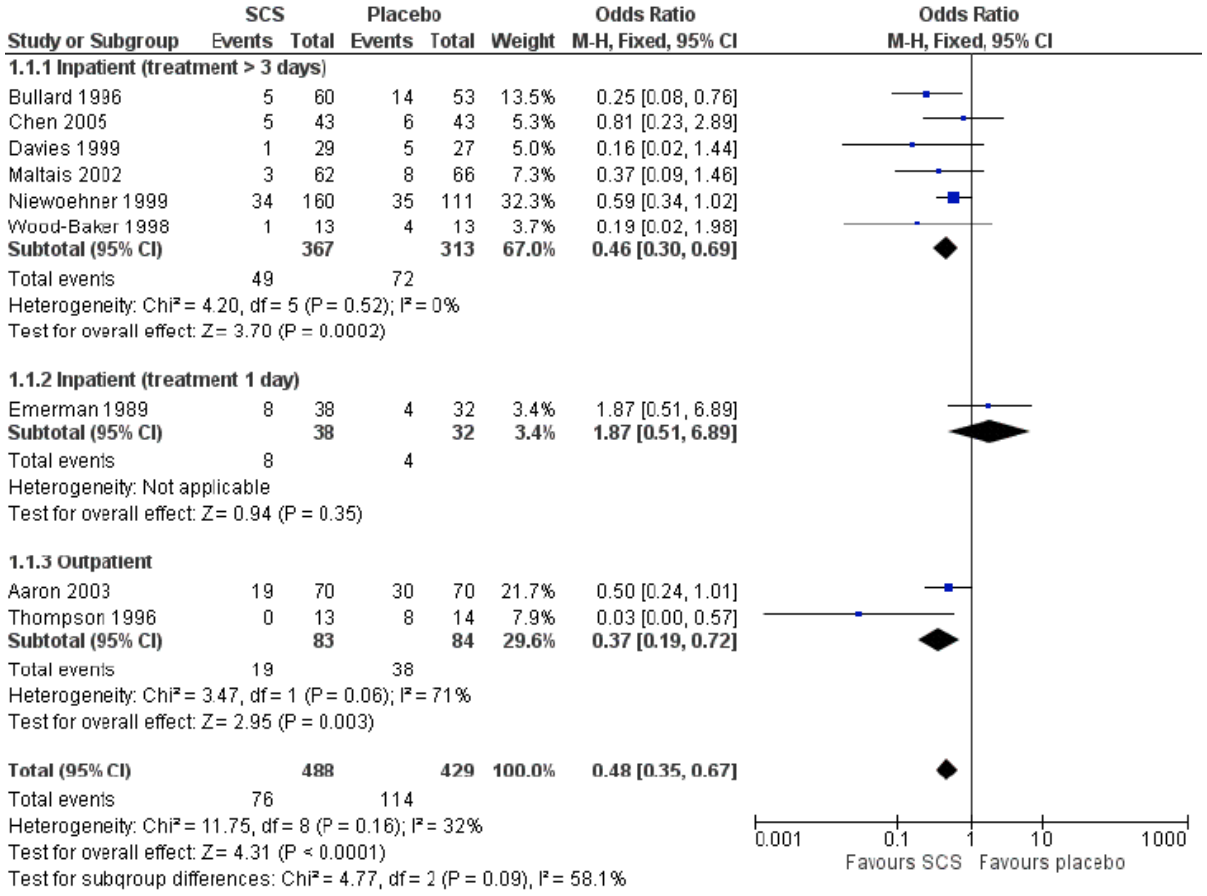
Dose/duration:

Benefit of lower doses

No difference in oral vs IV

Prednisone 40 mg x 5d non-inferior to 14d

Side effects: hyperglycemia, etc.

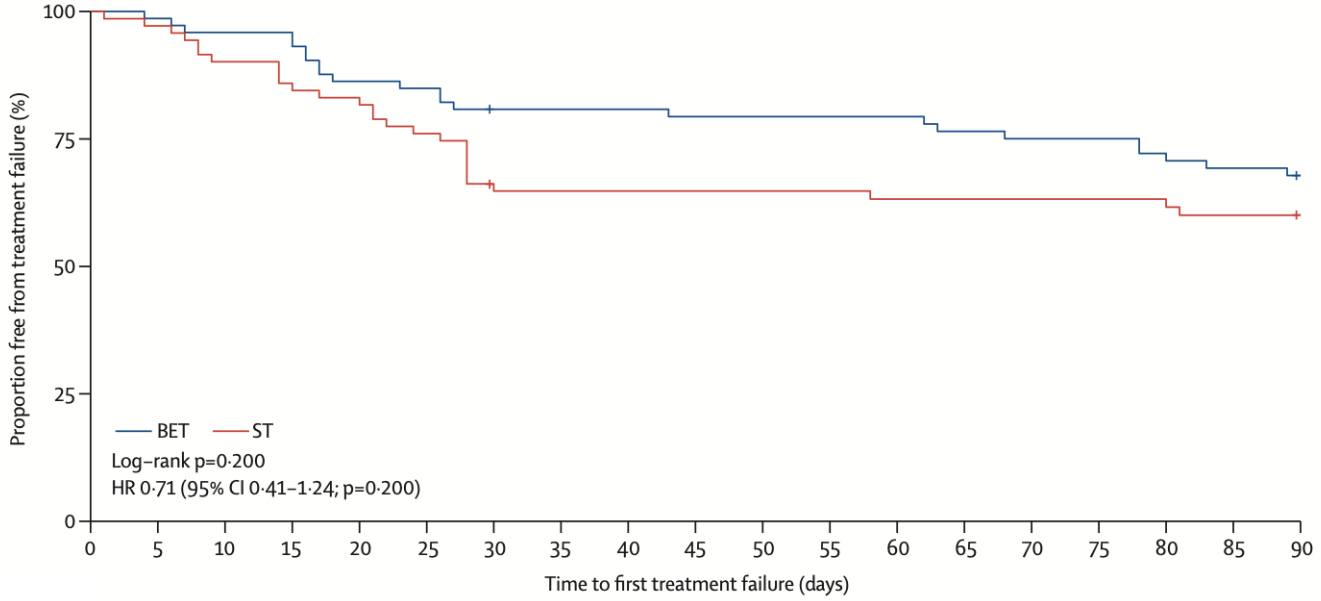


Walters JAE, Cochrane Database Syst Rev 2014:CD001288.
Davies L, Lancet 1999;354:456. Leuppi JD, JAMA 2013;309:2223.
Sivapalan P, Lancet Respir Med 2019;7:699

Eosinophil-guided oral steroid use

- STARR2: UK primary care practices
- 144 exacerbations, 93 subjects
- Point of care blood eos count
  - >2% prednisolone 30mg daily x 14d
  - <2% placebo
- Compared to standard care
  - prednisolone 30mg daily x 14d
- All received antibiotics

33% reduction in prednisolone Rx
Non-inferior



Ramakrishnan S, Lancet Respir Med 2024

Case #2

You see a 70 male former smoker after admission for “COPD exacerbation”.

At baseline, he has daily cough, sputum, and exertional dyspnea. He has no history of asthma. Work-up includes normal spirometry and a blood eosinophil count of 50 cells/μl. Lung screening CT scan within the past year showed mild bronchial wall thickening.

Which of the following is most likely to improve his symptoms?

A. LAMA-LABA inhaler
B. Triple therapy (LAMA-LABA-ICS)
C. Azithromycin 250mg daily
D. Roflumilast
E. None of the above

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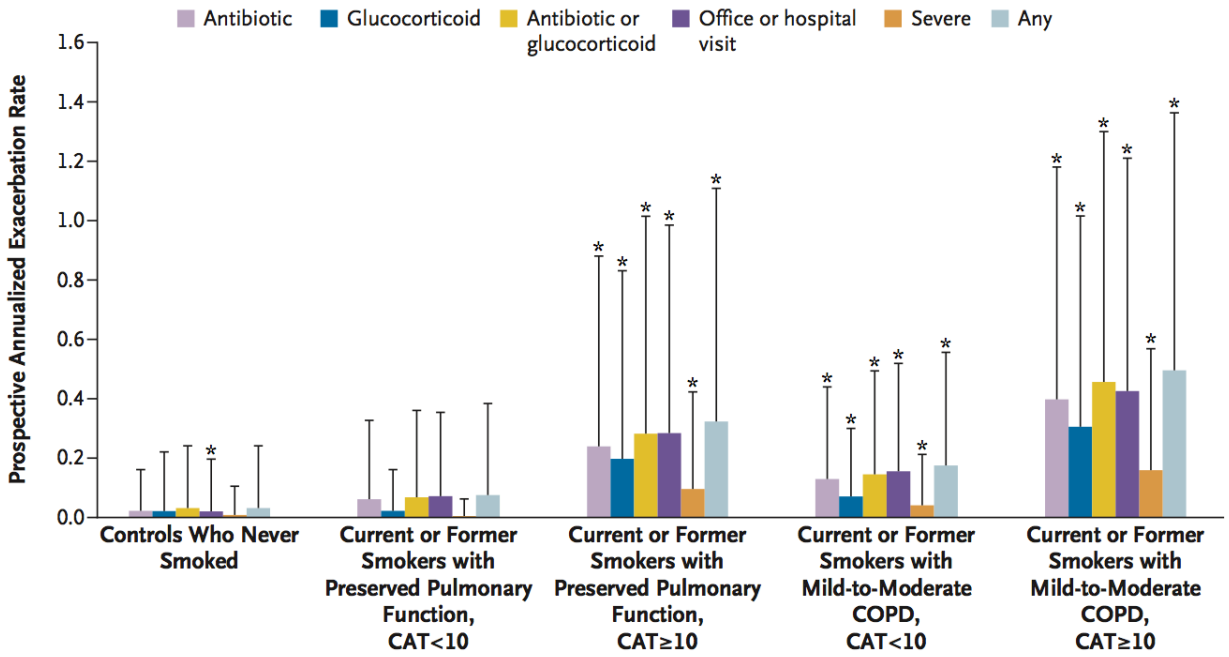
D. Roflumilast
E. **None of the above**

Current/former smokers with normal spirometry

Variable	No. (%) Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)
Individual Scores			
Chronic bronchitis, by criteria	0	552 (12.6)	125 (15.7)
History of ≥1 severe exacerbation	0	190 (4.3)	39 (4.9)
St George's Respiratory Questionnaire total score >25	4 (3.7)	1143 (26.0)	226 (28.5)
Six-minute walk distance <350 m	4 (3.7)	674 (15.4)	109 (13.7)
Modified Medical Research Council dyspnea score ≥2	4 (3.7)	1029 (23.5)	175 (22.0)
Emphysema >5%	9 (8.3)	428 (9.8)	273 (34.4)
Gas trapping >20%	11 (10.2)	536 (12.2)	319 (40.2)
Sums			
Any impairment	26 (24.1)	2375 (54.1)	585 (73.7)

COPD-like symptoms
CT scan changes

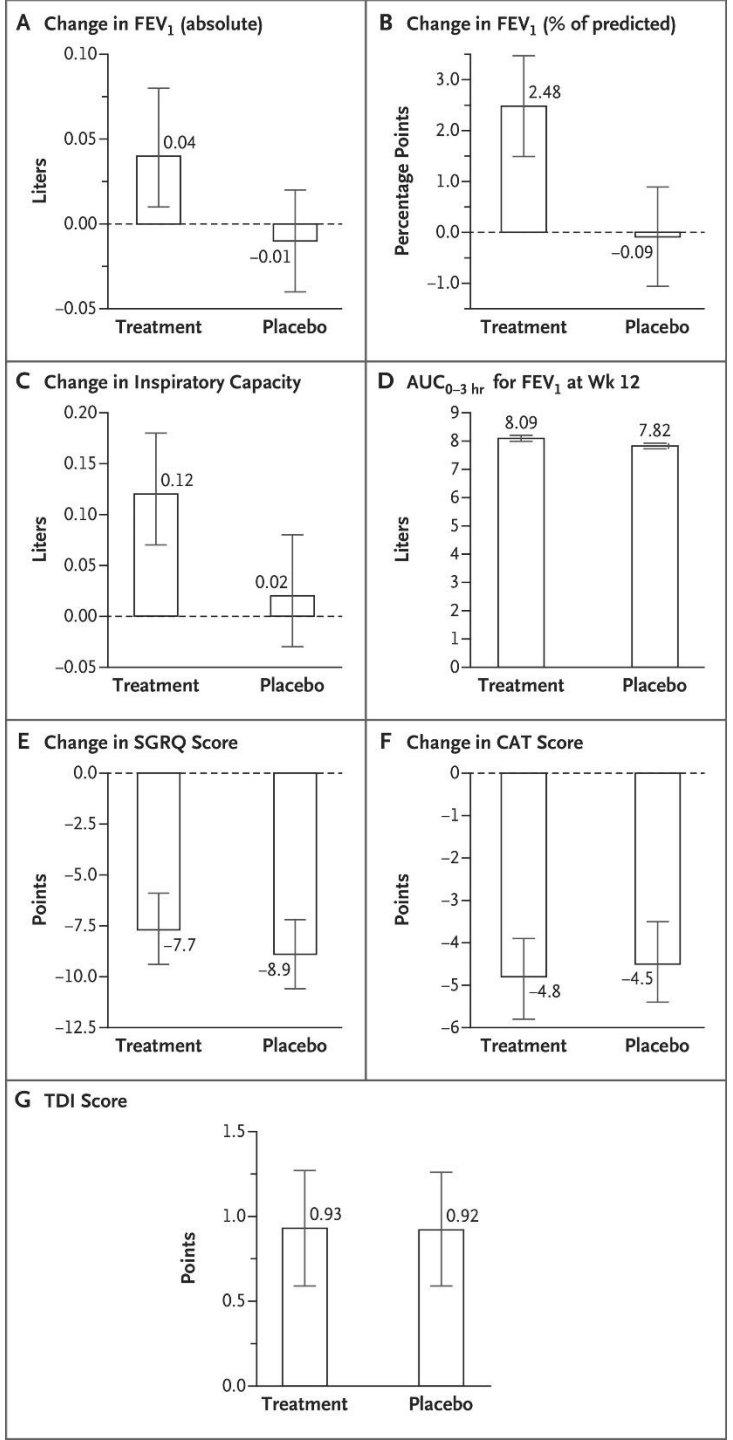


Increased exacerbation risk

COPDGene: Regan, JAMA Intern Med 2015;175:1539
SPIROMICS: Woodruff, NEJM 2016;374:1811

“Tobacco-exposed persons with symptoms and preserved lung function”

- How to treat?
  - Symptoms
    - CAT score ≥ 10
  - No airflow obstruction
    - $FEV_1/FVC \geq 0.7$
  - Asthma excluded
- LAMA-LABA inhaler did not improve symptoms vs placebo



Han MK, NEJM 2022;387:1173

Is the “O” required?

DIAGNOSTIC CRITERIA

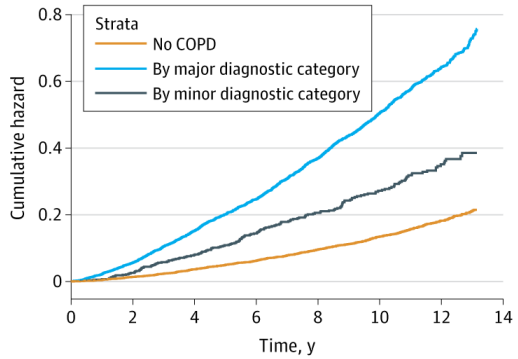
Major	Minor: imaging	Minor: symptoms
Airflow obstruction FEV_1/FVC <0.70 *or* FEV_1/FVC <LLN	**Emphysema** ≥Mild visual emphysema **Bronchial wall thickening**	**Dyspnea** mMRC score ≥2 **Quality of life** SGRQ score ≥25 *or* CAT score ≥10 **Chronic bronchitis**

DIAGNOSIS

Chronic obstructive pulmonary disease

Major diagnostic category	Minor diagnostic category
Major criterion *plus* ≥1 Minor criterion	≥3 Minor criteria *If symptoms are explained by other diseases, both imaging criteria should be met.*

A Multivariable cumulative hazards plot of all-cause mortality by COPD category

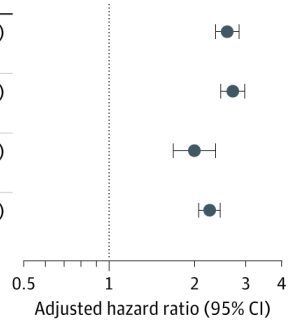


No. at risk

No COPD	4721	4183	3986	3612	3276	2932	1820
By major diagnostic category	3884	3495	3100	2626	2160	1763	1015
By minor diagnostic category	811	670	598	517	423	354	201

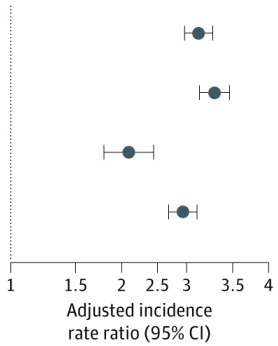
B Adjusted hazard ratio for all-cause mortality by COPD category

	Adjusted hazard ratio (95% CI)
Overall COPD by new diagnostic schema	2.58 (2.35-2.84)
COPD by major diagnostic category	2.70 (2.45-2.97)
COPD by minor diagnostic category	1.98 (1.67-2.35)
COPD per GOLD criteria	2.24 (2.05-2.44)



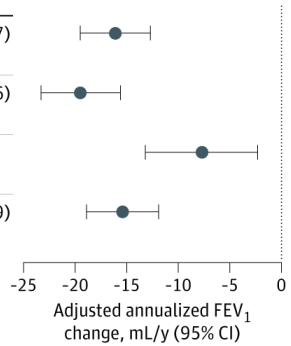
C Adjusted incidence rate ratio for exacerbations

	Adjusted incidence rate ratio (95% CI)
Overall COPD by new diagnostic schema	3.23 (2.96-3.53)
COPD by major diagnostic category	3.57 (3.25-3.92)
COPD by minor diagnostic category	2.09 (1.79-2.44)
COPD per GOLD criteria	2.93 (2.68-3.20)



D Adjusted annualized change in FEV_1

	Adjusted annualized FEV_1 change, mL/y (95% CI)
Overall COPD by new diagnostic schema	-16.1 (-19.5 to -12.7)
COPD by major diagnostic category	-19.5 (-23.3 to -15.6)
COPD by minor diagnostic category	-7.7 (-13.2 to -2.3)
COPD per GOLD criteria	-15.4 (-18.9 to -11.9)



COPDGene 2025 Diagnosis Working Group and CanCOLD Investigators, JAMA 2025;333:2164

COPD Summary

- Multidimensional assessment
  - Symptoms and exacerbation risk
  - Assessment and management of comorbidities
- Non-pharmacologic treatments
  - Smoking cessation, pulmonary rehab, vaccines, supplemental O_2
- Medications
  - Bronchodilators are first line therapy: LAMA-LABA
  - Inhaled steroids are add-on - elevated blood eosinophils
  - Daily azithromycin or roflumilast for frequent exacerbators
  - New therapies: dupilumab, mepolizumab, ensifentrine

COPD Summary (2)

- Lung volume reduction
  - Selected patients, specialized centers
- Acute exacerbations
  - No objective definition or biomarkers
  - Consider differential diagnosis
  - Antibiotics and systemic steroids have small effects
- New concepts in COPD diagnosis
  - Tobacco-exposed persons with symptoms and preserved lung function

References

- Global Initiative for Chronic Obstructive Lung Disease, Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, available at www.goldcopd.org
- COPD Foundation, www.copdfoundation.org
  - Patient information, including inhaler instructional videos
- Nici L, et al., Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020;201:e56-e69
- Celli B, et al., An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. Am J Respir Crit Care Med 2021; 204:1251-1258.