COPD Assessment and Management: a 2022 Update

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Disclosures

- Grant support:
  - NIH

Objectives

- Review risk factors for COPD
- Understand some of the disparities in COPD
- Review the diagnosis and assessment of the COPD patient
- Highlight current challenges in COPD management
- Discuss treatment strategies for stable COPD

Outline

- Epidemiology of COPD
  - Prevalence, risk factors and disparities
- Assessment of COPD
  - GOLD Guidelines
- Medical therapy for stable COPD
- Other interventions for COPD

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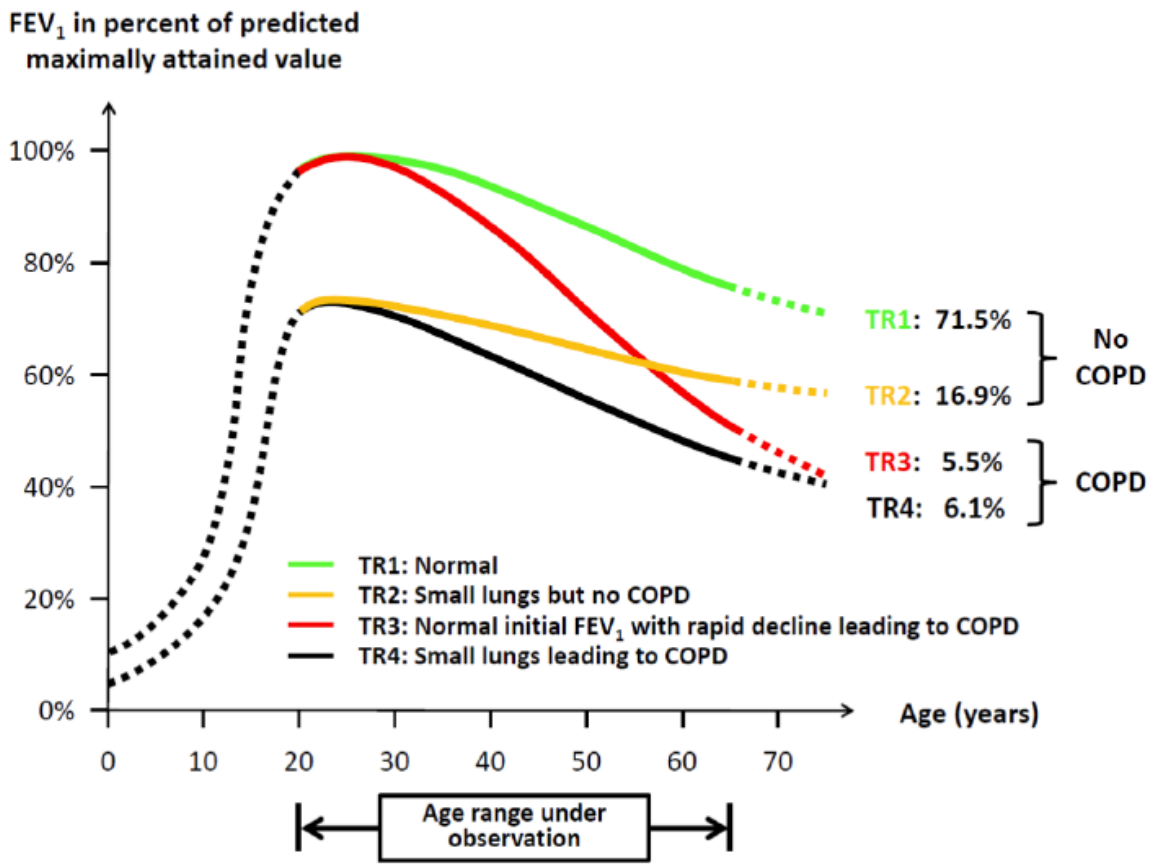
Epidemiology

- Globally there are nearly 400 million cases of COPD
  - Differs by country and region
  - Cases are expected to *increase through 2060* due to:
    - Increasing prevalence of smoking in developing countries
    - Aging populations in high income countries
  - **Deaths** attributable to COPD *are increasing* due to:
    - Increased smoking, aging populations, as well as reduced death due to heart disease and infectious disease, and lack of effective therapies

GOLD Guidelines, 2021.

Lung function trajectories and COPD

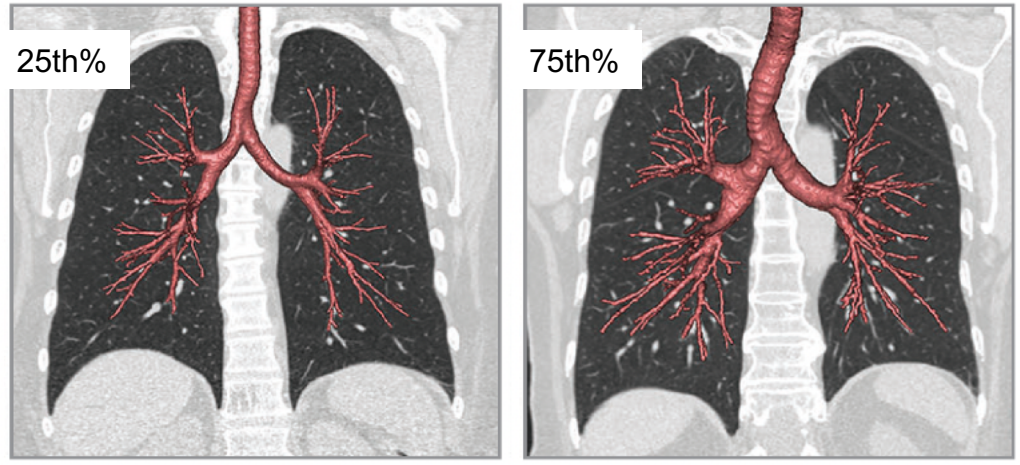
- Two main lung function trajectories can lead to COPD
  1) A normal “peak” lung function and a rapid decline
  2) A lower “peak” lung function and a normal rate of decline



Lange P, NEJM 2015.

Dysanapsis and COPD

- Dysanapsis is a mismatch of airway size to lung size
  - Using CT-based lung and airway measures, those in the lowest quartile of airway to lung size had a 3.3 times higher risk of having COPD compared to those in the lowest quartile (RR 3.3)
  - In a sample of adults 20 to 60 years old, a lower airway to lung size was associated with a lower FEV_1/FVC, and this finding was not modified by age



Smith BM et al. JAMA 2020. Smith BM et al. Chest 2021.

Smoke Exposure and COPD

- **Tobacco smoke** is a risk factor, but…
  - Only 20% of smokers develop COPD, and
  - More than 25% of patients with COPD are non-smokers
- Secondhand smoke exposure, including in children
- Household air pollution from burning wood, coal or biomass fuels inside
  - Characterized by a greater burden of airways disease, more symptoms and less emphysema

Terzikhan, Eur J Epidemiol, 2016. Assad et al. Semin Respir Critic Care Med, 2015.

Air Pollution and COPD

- Short-term increases in NO_2, $PM_{2.5}$ and PM_{10} have been linked to higher rates of COPD hospitalizations
- In the Framingham Heart Study, traffic-related air pollution was linked to a more rapid decline in FEV_1
- In 6 U.S. cities, long-term exposure to ozone, $PM_{2.5}$, black carbon and NO_X were associated with faster progression of percent emphysema over 10 years

DeVries, COPD, 2017. Wang M et al. JAMA, 2019. Rice MB et al. AJRCCM, 2015.

Occupational Exposures and COPD

- Occupational exposure to **vapor, gas, dust or fumes**
  - With any exposure they found a 2.1 times increased odds of developing COPD, when combined with tobacco smoke **OR 14.1**
- High risk occupations include
  - Sculptors, engravers
  - Groundskeepers, gardeners ➡ strong link to pesticide use
  - Plastics processors and molders
- Cadmium exposure has been linked to COPD, is used in batteries, steel plating and plastics
  - Cadmium is also found in cigarettes *and in the lungs of smokers*

Blanc, Thorax, 2009. De Matteis et al. ERJ 2019. De Matteis et al. Thorax, 2022. Fu, Am J Physiol Lung Cell Met Physiol, 2022.

Racial and Gender Disparities in COPD

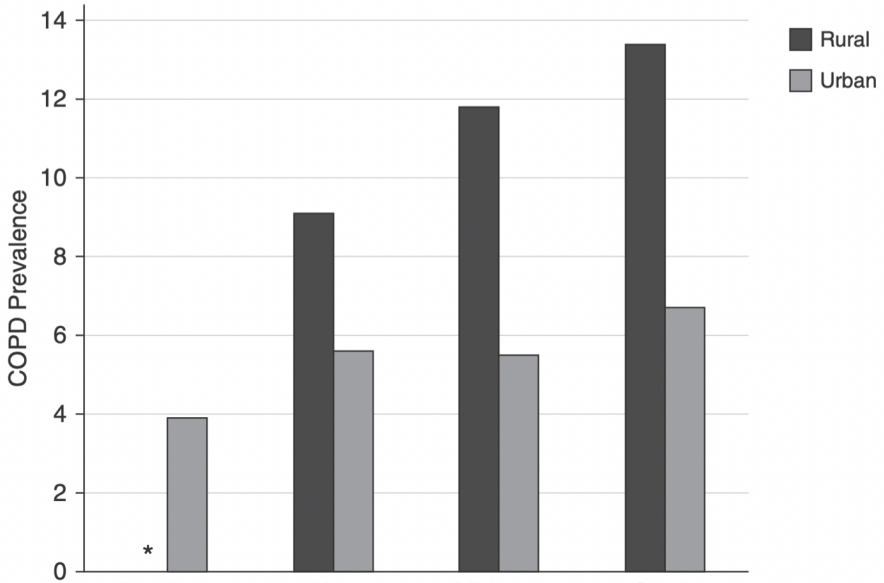
- Racial, ethnic disparities exist in COPD
  - Among nearly 2,700 SPIROMICS participants, ***blacks had greater burden*** of symptoms, worse quality of life and greater risk of exacerbations after accounting for COPD risk factors

    ➡ not fully explained by individual and neighborhood socioeconomic status
- Gender disparities exist as well, with higher rates of COPD in non-smokers who are women
- In part, this appears to be due to differences in susceptibility to cigarette smoke and differences in airway wall thickness and inflammation

Ejike et al, AJRCCM 2021. Barnes PJ, AJRCCM 2016. Dransfield M, Resp Med 2006.

Rural Disparities in COPD

- In the U.S., using NHANES data, those living in rural parts of the country had a greater risk of developing COPD
  - Among individuals with COPD, living in a rural area was associated with more symptoms and greater risk of having moderate and severe disease
- Chronic lower respiratory disease mortality *increased* in rural areas from 1999 to 2018, while it decreased in urban areas



	Northeast	West	Midwest	South
Rural	*	9.2 (6.9–12.3)	11.8 (9.9–14.1)	13.4 (8.7–19.9)
Urban	3.9 (1.8–8.1)	5.6 (3.9–8.0)	5.5 (3.6–8.3)	6.7 (4.9–9.2)

Raju et al. AJRCCM, 2020. Iyer et al. AJRCCM, 2021.

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COPD: the basics

- Chronic obstructive pulmonary disease is a common, preventable and treatable disease
- Patients have persistent symptoms (dyspnea, cough or sputum), recurrent exacerbations and/or risk factors
- Diagnosis is by *post-bronchodilator* spirometry

  ➡ airflow obstruction that is incompletely reversible

GOLD Guidelines 2021

Multidimensional Patient Assessment

- Symptoms
- Degree of airflow limitation
- History of exacerbations
- Comorbidities

GOLD Guidelines, 2021.

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

http://www.catestonline.org/

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.

GOLD Classification of Disease Severity

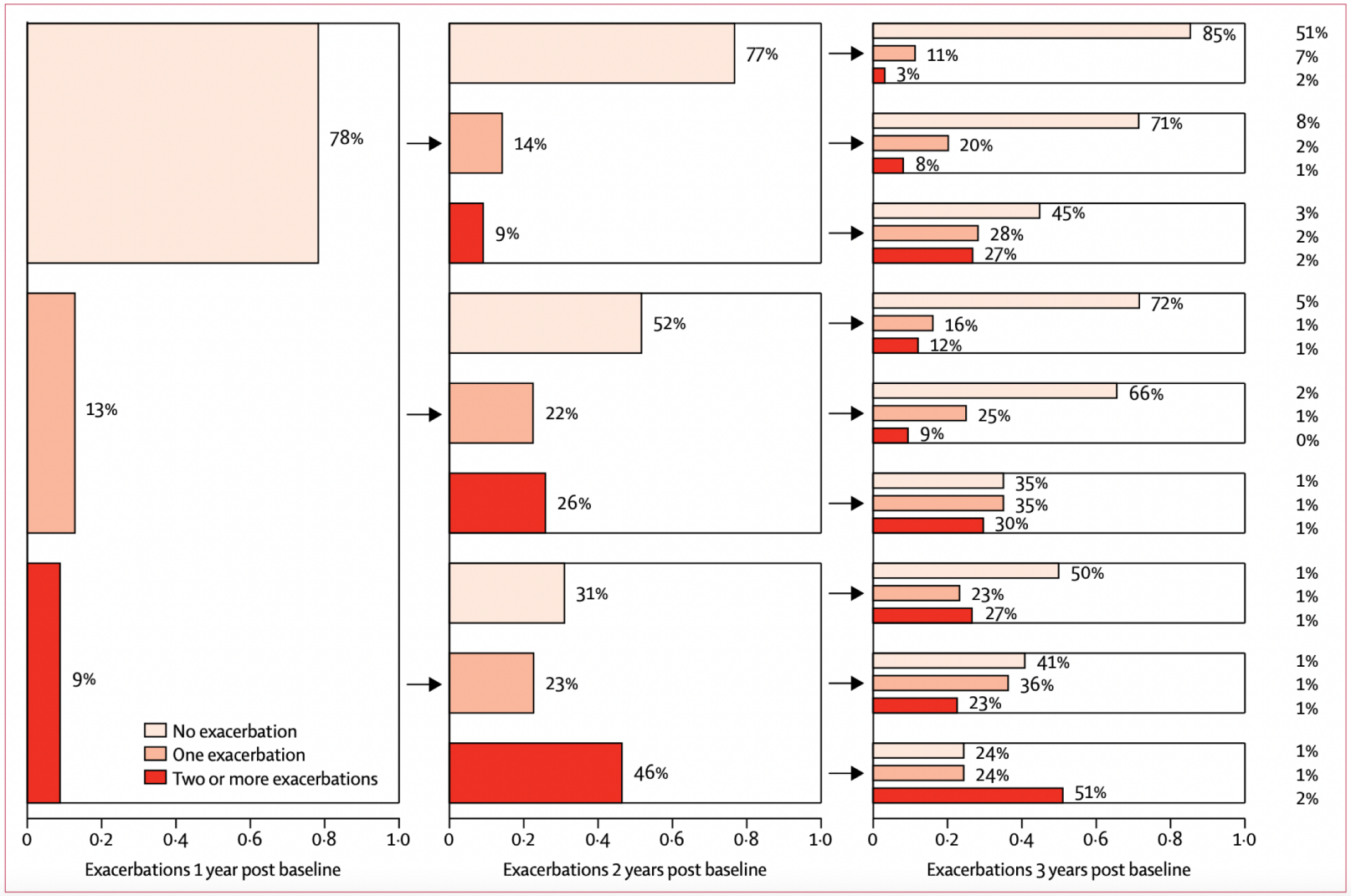
In patients with $FEV_1/FVC < 0.70$

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*

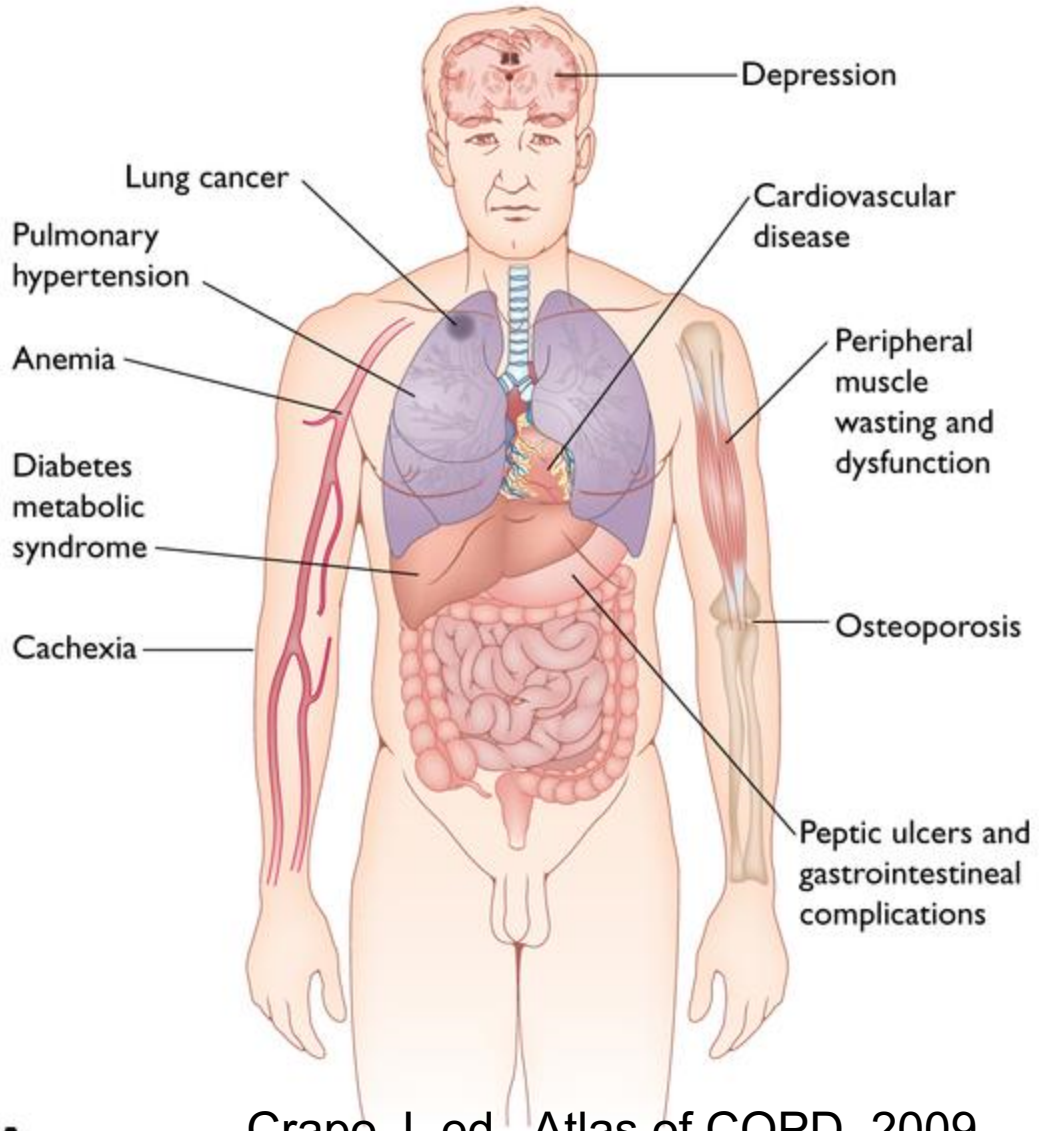
Prior exacerbations predict future ones

- This was found in both ECLIPSE and SPIROMICS (Figure)
- The number of exacerbations in the past year is the best predictor of future exacerbations



Hurst JR, NEJM 2010.
Han MK, Lancet Resp Med 2017.

COPD is a systemic disease

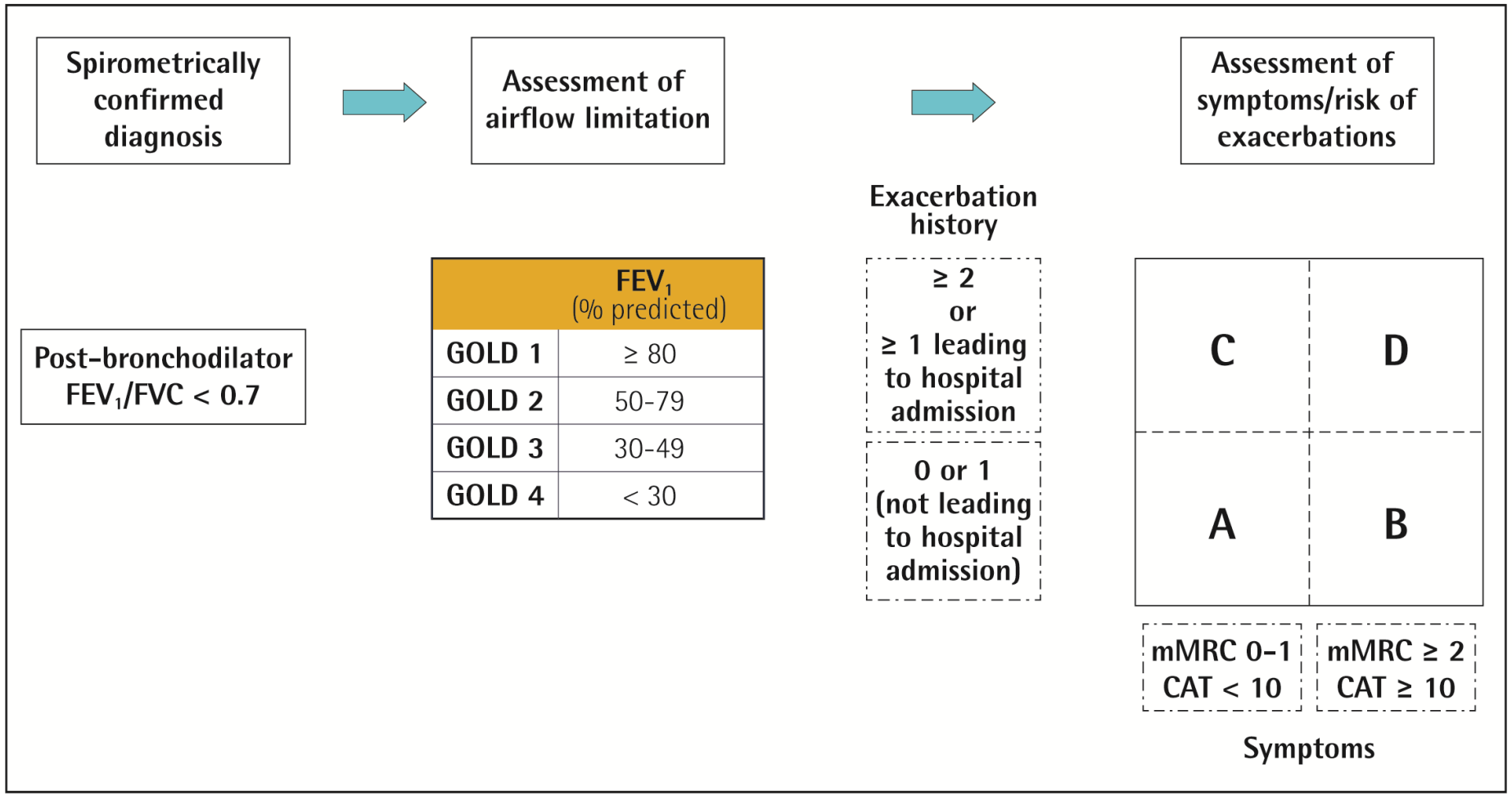


Comorbidities[a, b] n (%)	Group A (≤2 Comorbidities) N=439	Group B (>2 Comorbidities) N=854
Hypertension	129 (29.4)	645 (75.5)
High cholesterol	82 (18.7)	605 (70.8)
Osteoarthritis	62 (14.1)	414 (48.5)
GERD	49 (11.2)	410 (48.0)
Depression[c]	38 (8.7)	400 (46.8)
Obesity	70 (15.9)	376 (44.0)
Anxiety[c]	26 (5.9)	316 (37.0)
Insomnia	34 (7.7)	284 (33.3)
Diabetes	11 (2.5)	210 (24.6)
Sleep apnea	9 (2.1)	181 (21.2)
Osteoporosis	14 (3.2)	92 (10.8)
CHD	2 (0.5)	179 (21.0)
PVD	1 (0.2)	54 (6.3)
CHF	3 (0.7)	45 (5.3)

Crapo J, ed., Atlas of COPD, 2009. Putcha N, Int J COPD, 2021.

Combined Algorithm

Figure 2.4. The refined ABCD assessment tool



INITIAL PHARMACOLOGICAL TREATMENT

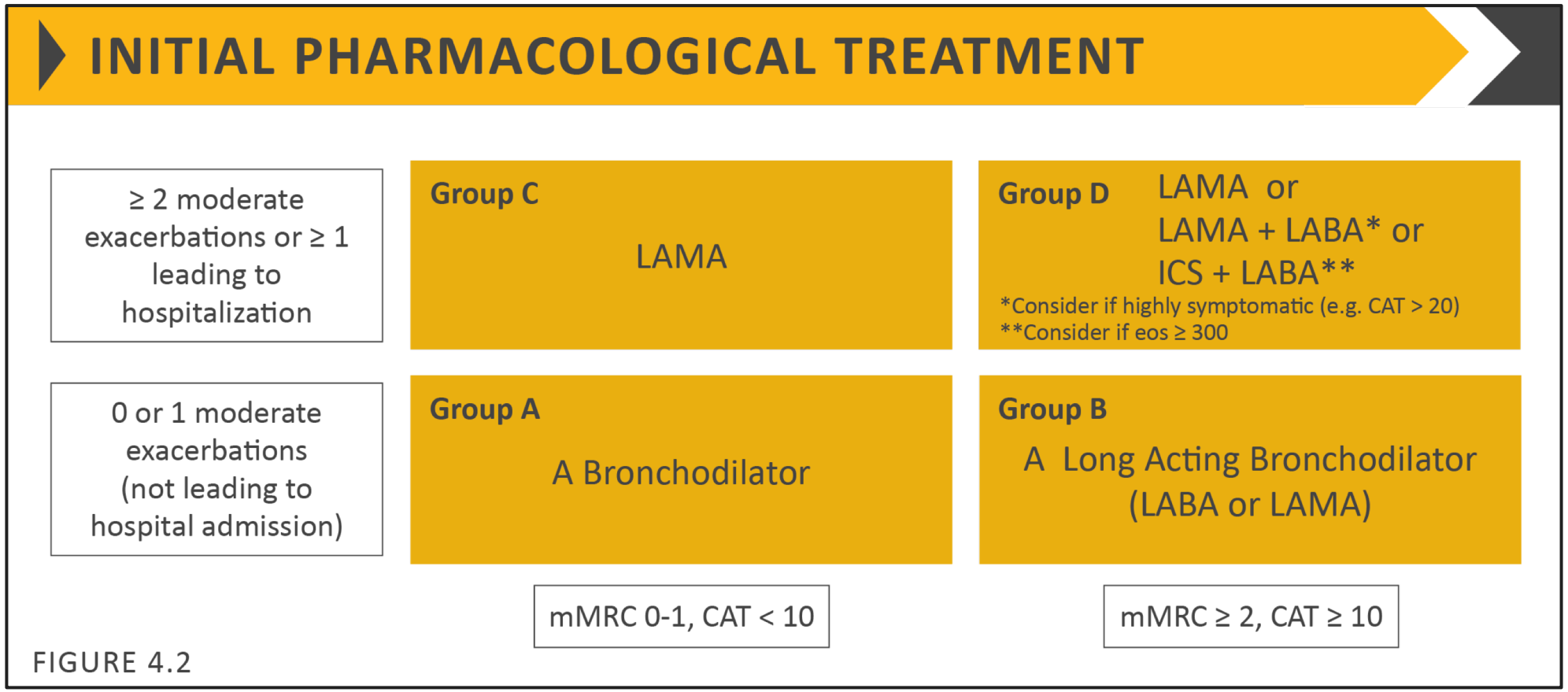
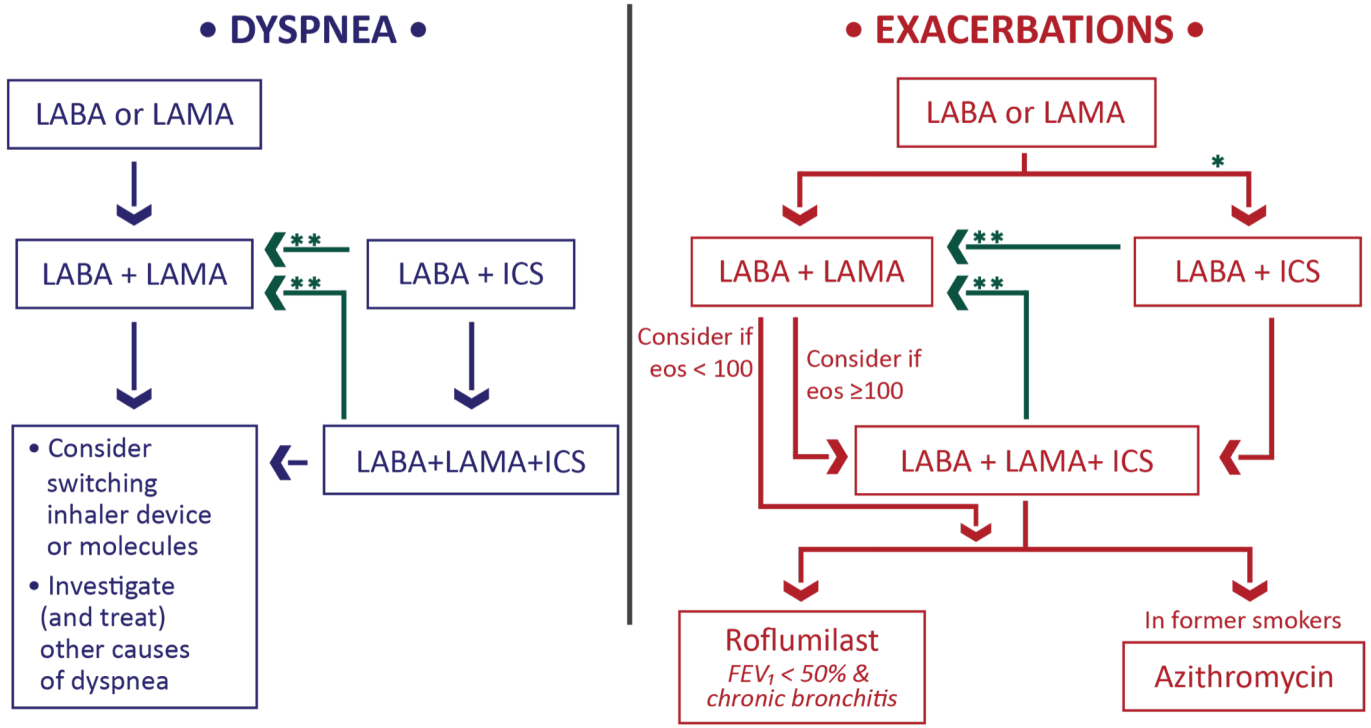


FIGURE 4.2

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.4

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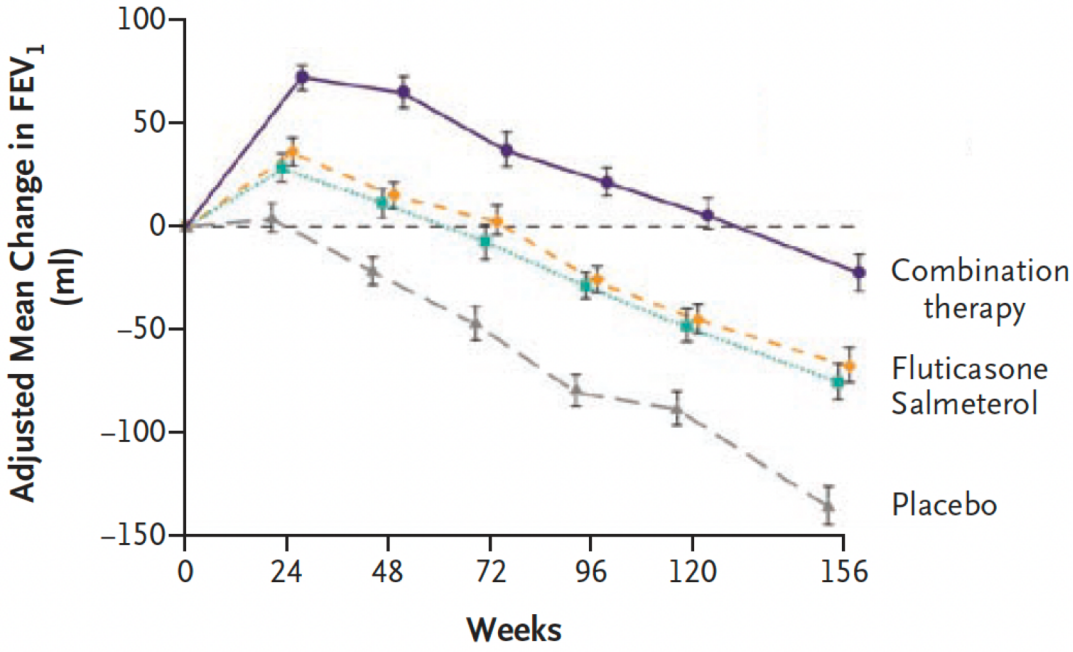
Inhaled corticosteroids + LABA

- Benefit of ICS
  - ICS+LABA reduces exacerbations
  - May reduce FEV_1 decline
- Side effects of ICS
  - Increased risk of pneumonia
  - Dysphonia, hoarseness, oral candidiasis
- GOLD: Consider if blood eosinophils >300 or >100 with exacerbation history



Calverley, NEJM 2007. Magnussen, NEJM 2014. Vestbo, NEJM 2016. Vestbo, Lancet 2016.

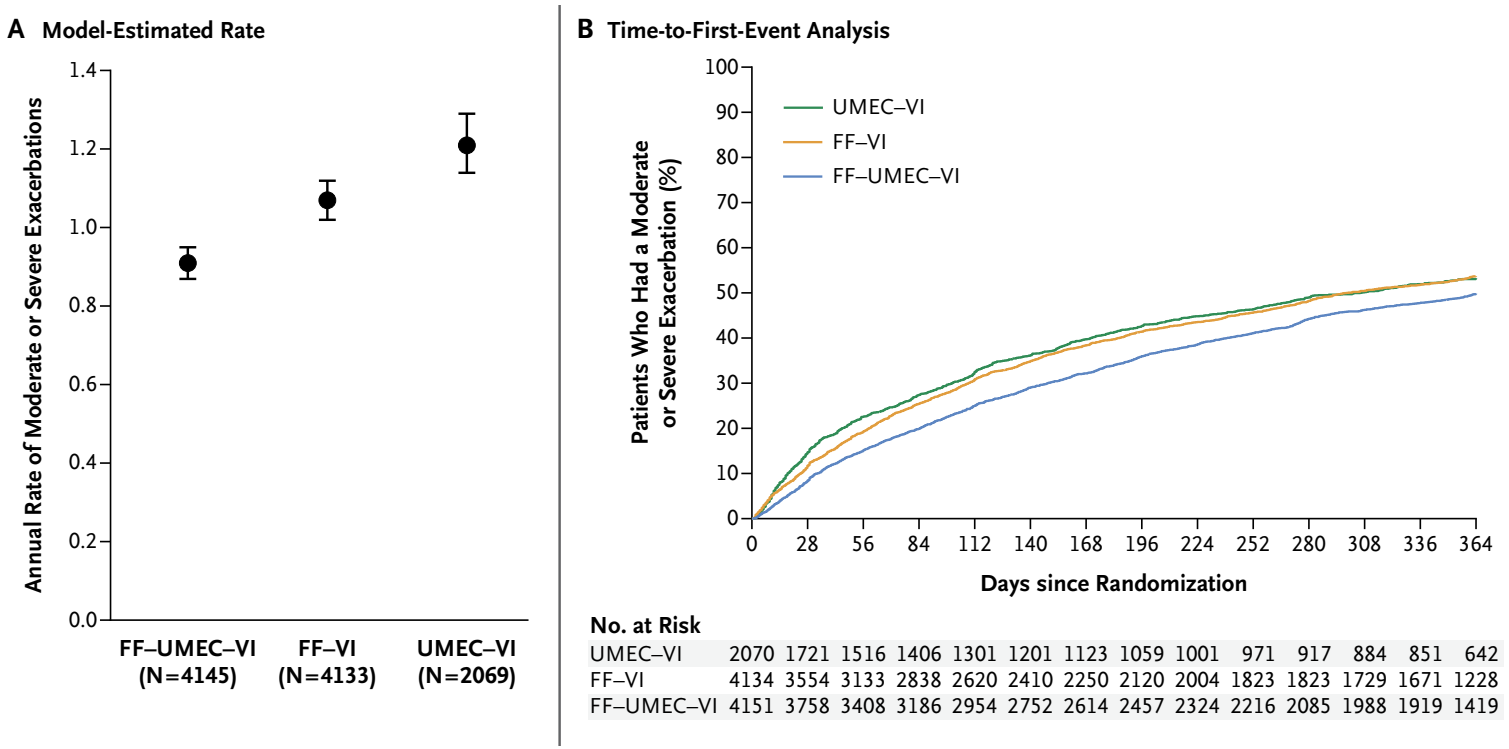
Routine blood tests in COPD

- Alpha-1 antitrypsin level +/- protein phenotype
  - 1-2% of COPD in USA
  - Recommended for all adults with:
    - COPD
    - Emphysema
    - Asthma with irreversible airflow obstruction
- CBC with differential
- IgE level was associated with exacerbations, HR 1.43 for > 76 IU/mL vs. < 76 IU/mL over 14 years in Copenhagen

Silverman EK, N Engl J Med 2009. Miravitlles M, ERJ 2017. Sandhaus RA, JCOPDF 2016. Colak, Ann All Asth Immun 2022.

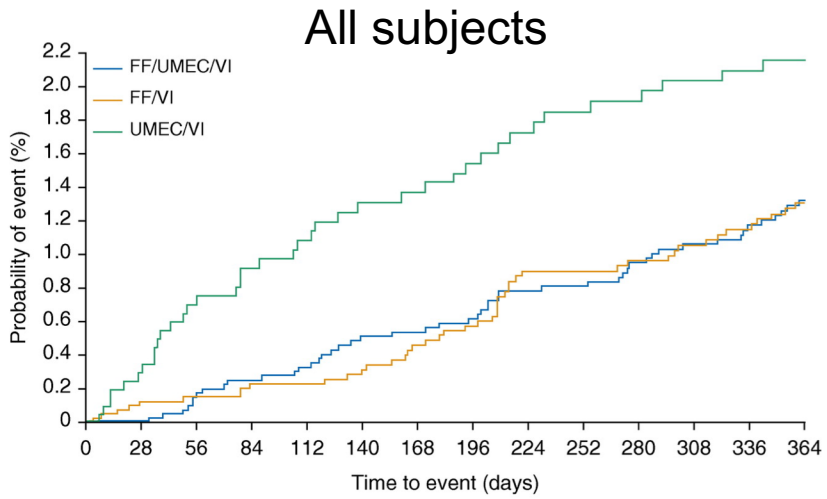
IMPACT: “closed” triple therapy

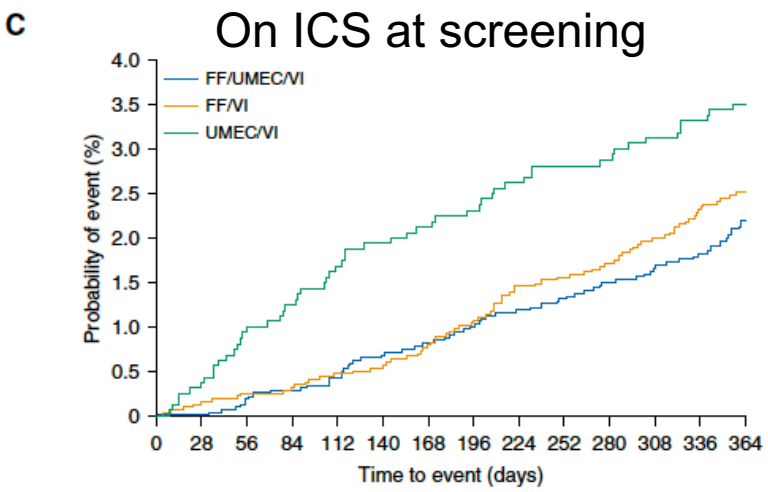
- RCT with 10,355 participants
- Inclusion criteria: FEV_1<50% and ≥1 exacerbation in last yr or FEV_1 50-80% and ≥2 exacerbations
- CAT ≥10, athsma excluded
- Protective if eos >150
- Pneumonia risk confirmed
  - prevented 225 AECOPDs
  - caused 35 pneumonias

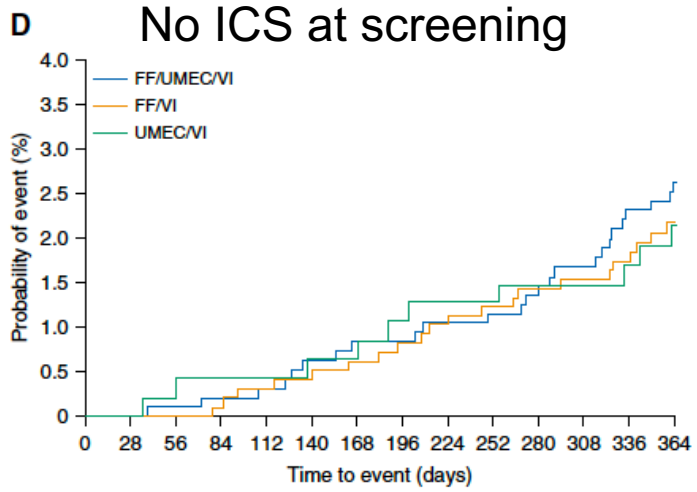


Lipson, NEJM 2018.

Do ICS reduce mortality? IMPACT Results



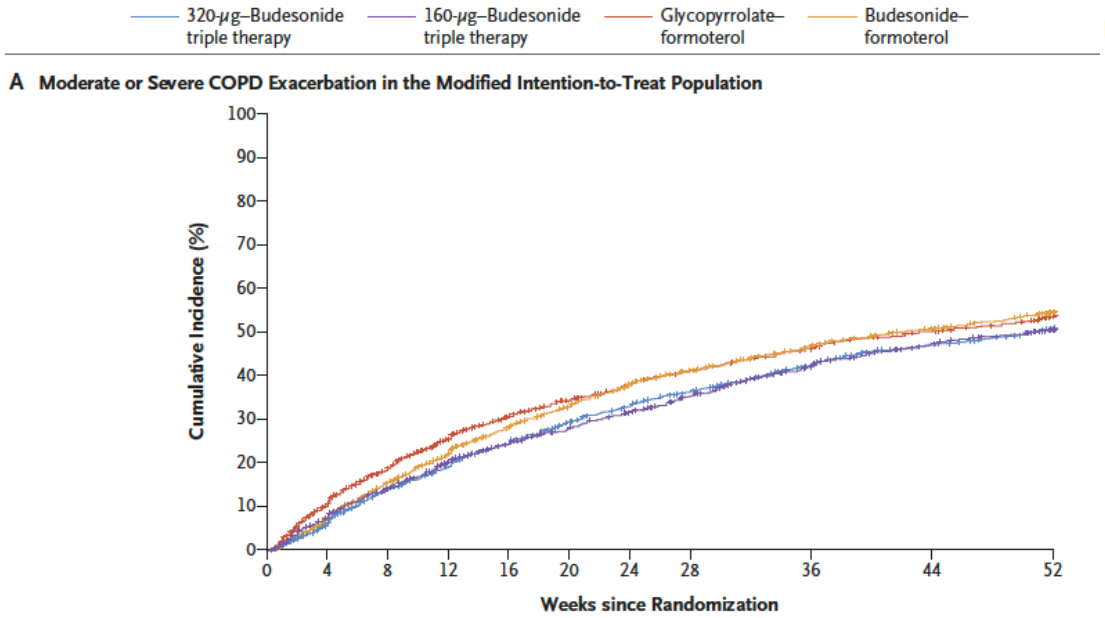


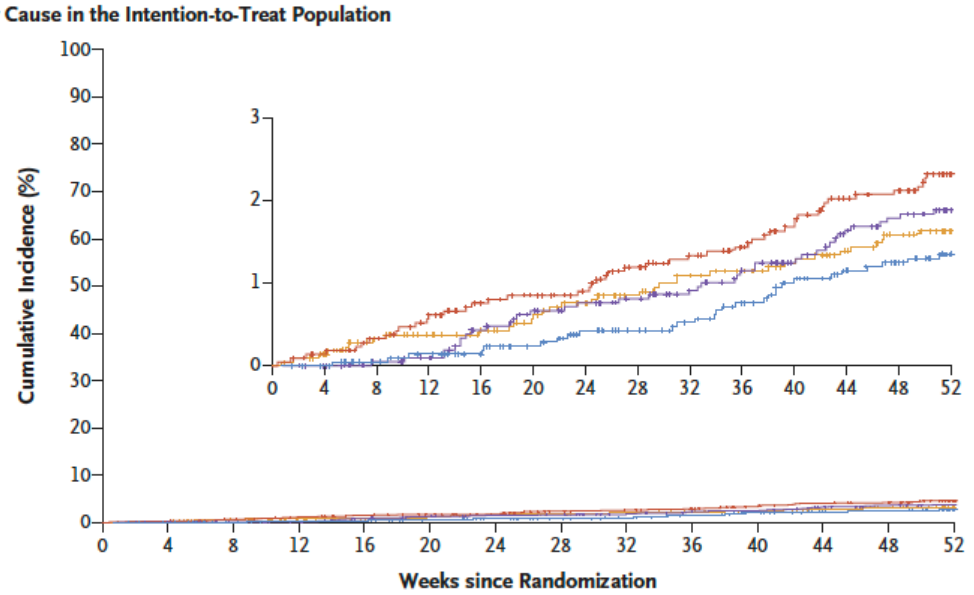


Lipson DA, AJRCCM 2020.

ETHOS trial

budesonide/glycopyrrolate/formoterol



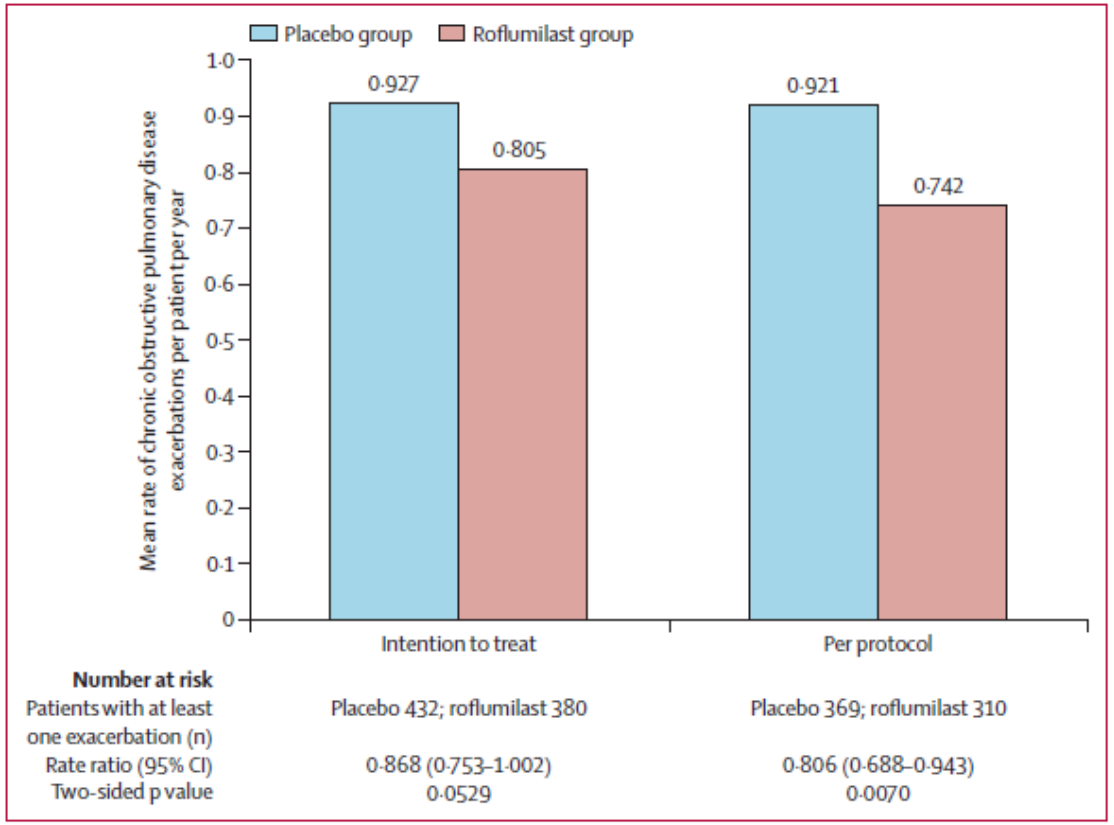


- RCT with 8,509 participants
- CAT ≥10, FEV_1 25-65%, excluded current asthma (not past)
- FEV_1<50% and ≥1 exacerbation in last yr or FEV_1 ≥50% and ≥2 exacerbations

Rabe KF, NEJM 2020.

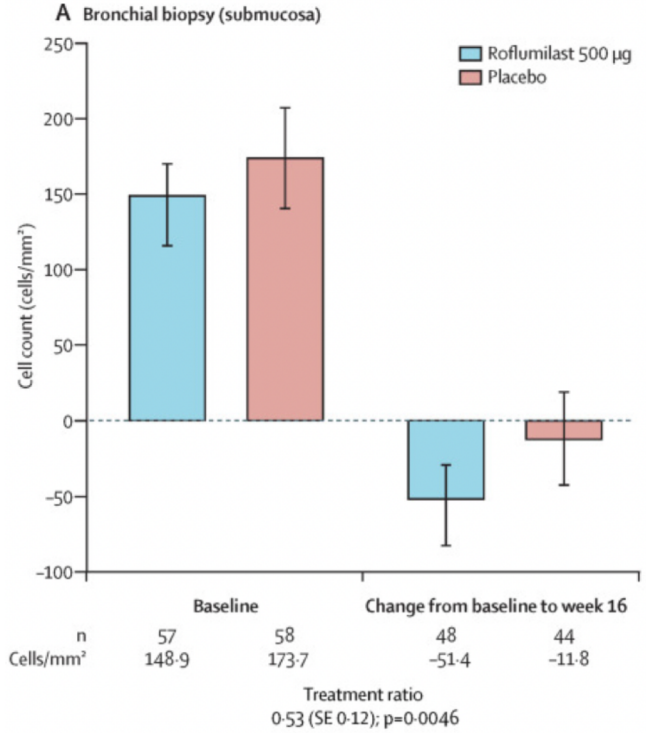
Roflumilast to reduce exacerbations

Roflumilast



Participants had severe COPD, FEV_1<50%
Chronic bronchitis and exacerbation history

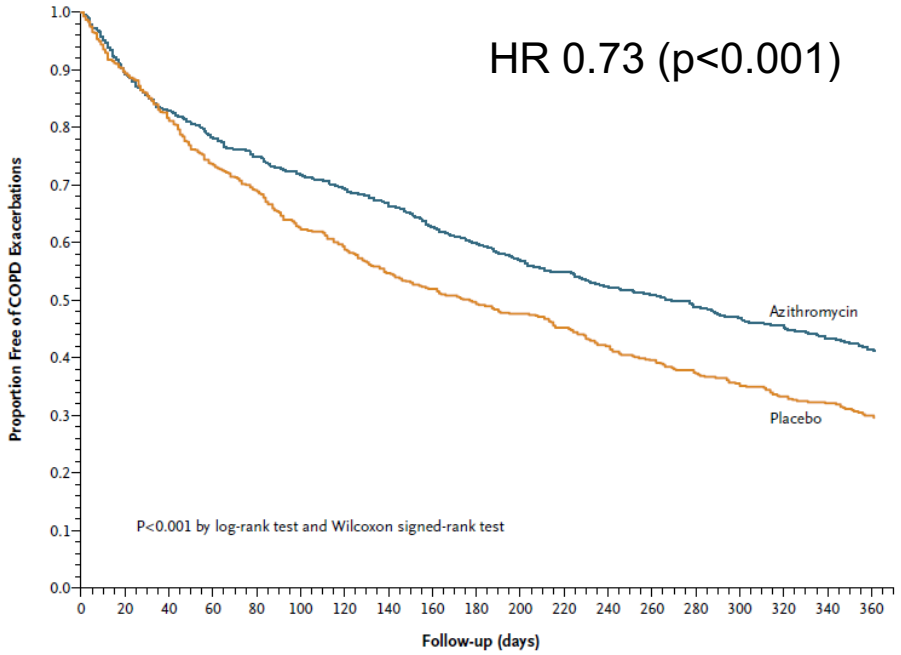
- Bronchial biopsies after 16 weeks showed significantly reduced eosinophils



Martinez, Lancet 2015. Rabe, Lancet Resp Med 2018.

Azithromycin to reduce exacerbations

Azithromycin 250mg daily



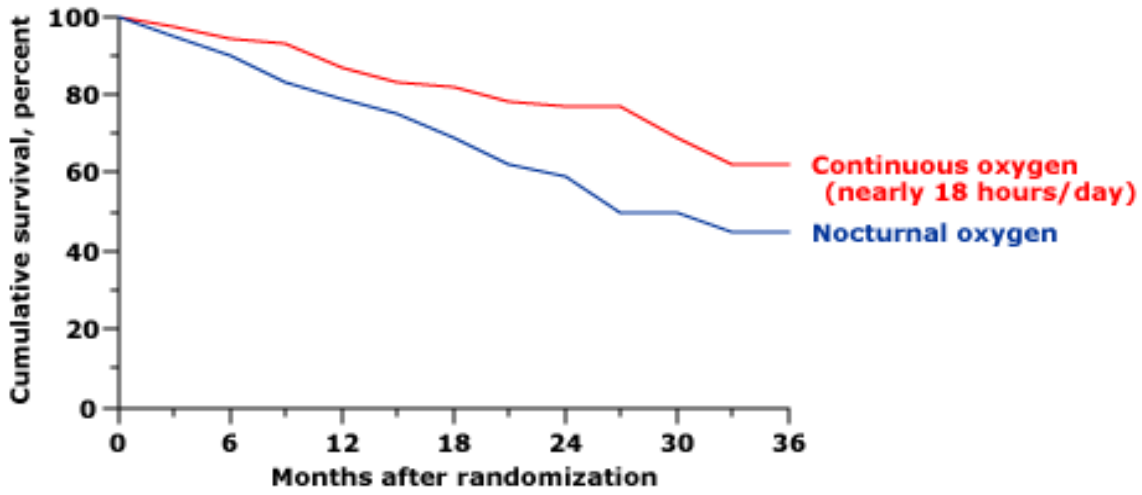
More effective in older, former smokers, milder COPD

- Simulation models incorporating reduction in COPD exacerbation with CV events, hearing loss, GI upset and bacterial resistance
- Any exacerbations QALY 17.9/100
- Frequent exacerbations QALY 22.8/100

Albert RK, NEJM 2011.
Han MK, AJRCCM 2014.
Ahmadian S, Thorax 2022.

Supplemental oxygen reduces mortality in hypoxemic COPD patients

NOTT trial, Ann Intern Med 1980.



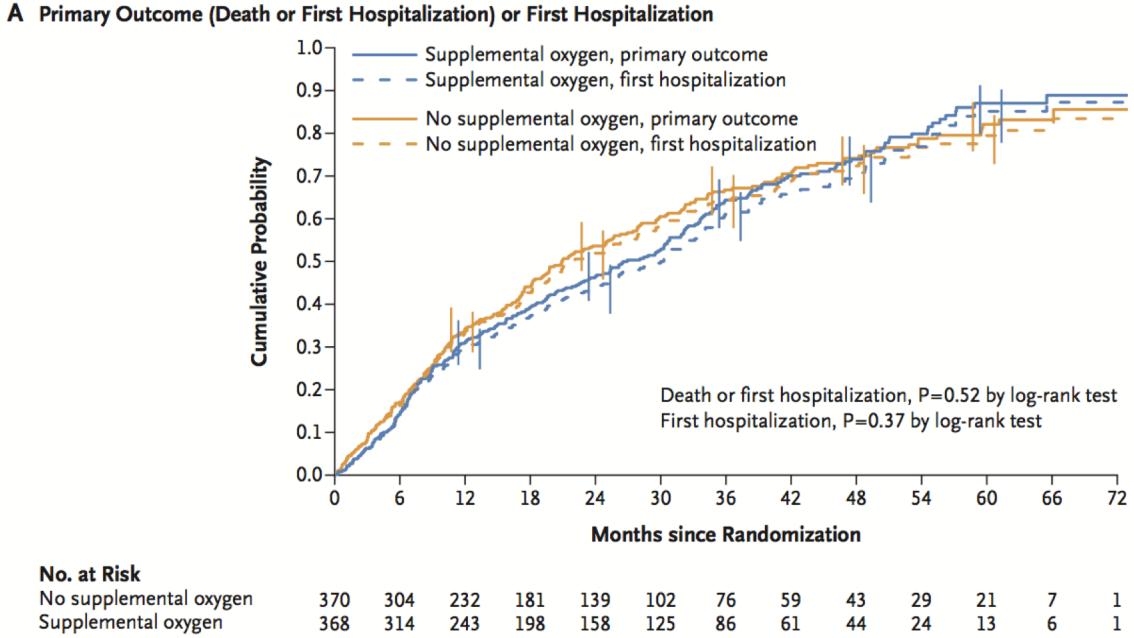
- PaO_2 ≤55mmHg or SaO_2 ≤88% on room air at rest, or
- PaO_2 ≤60mmHg or SaO_2 ≤89%,
  - with cor pulmonale, right heart failure or polycythemia

Long Term Oxygen Treatment Trial

NEJM 2016.

1) Moderate hypoxemia
   - SpO_2 89-93%
   - Randomized to 24 hr O_2
2) Exertional hypoxemia
   - SpO_2 <90%
   - Randomized to O_2 with exercise and sleep

- N=738
  - 57% / 43%



No change in secondary outcomes:

- 6-min walk distance
- Quality of life
- Exacerbations
- Lung function

Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic COPD

- ATS Practice Guideline
- Hypercapnic respiratory failure: $PaCO_2$>45
- Suggest nocturnal NIV
  - Stable, not exacerbation
  - Screen for OSA prior to starting
  - Target normal $PaCO_2$
- Benefit: improve QoL, possibly reduce exacerbations and mortality
- Barriers to implementation

Macrea et al. AJRCCM 2020.

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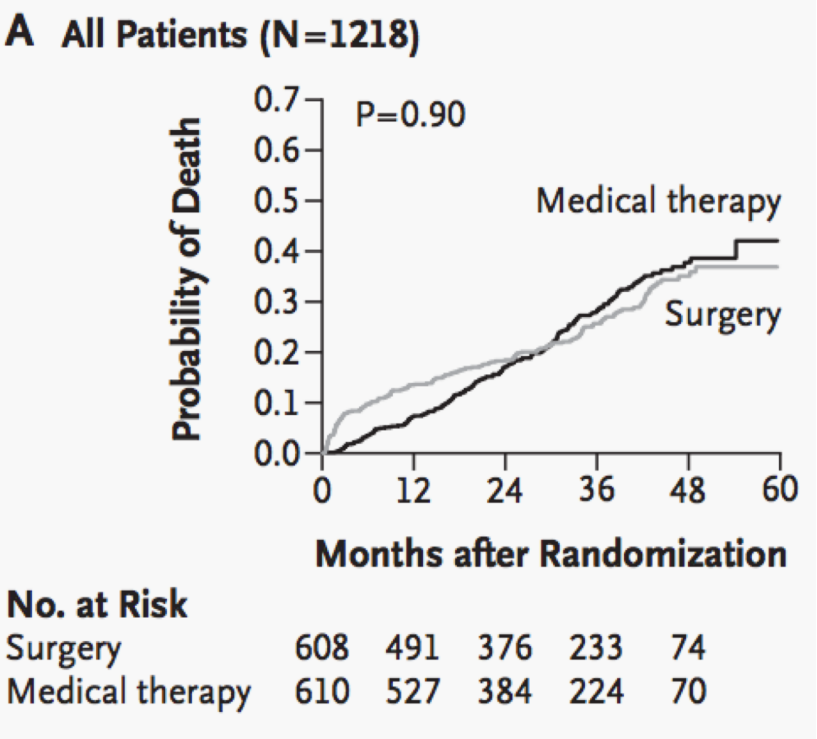
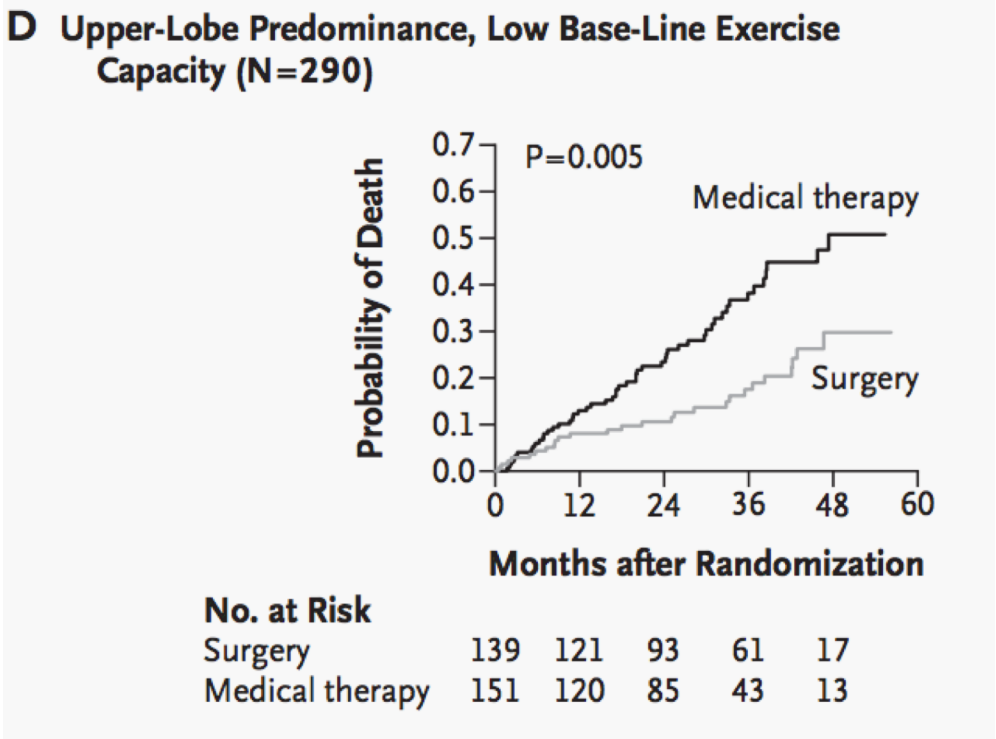
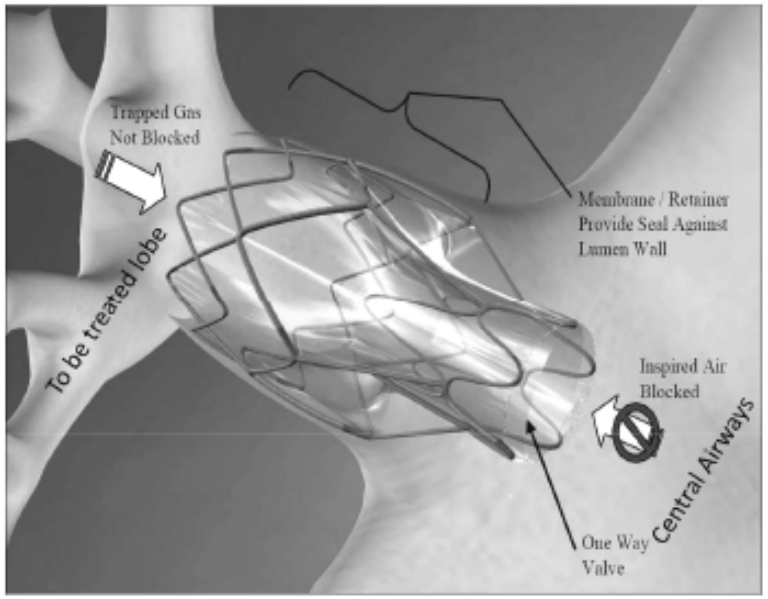
Lung volume reduction surgery

National Emphysema Treatment Trial, NEJM 2003

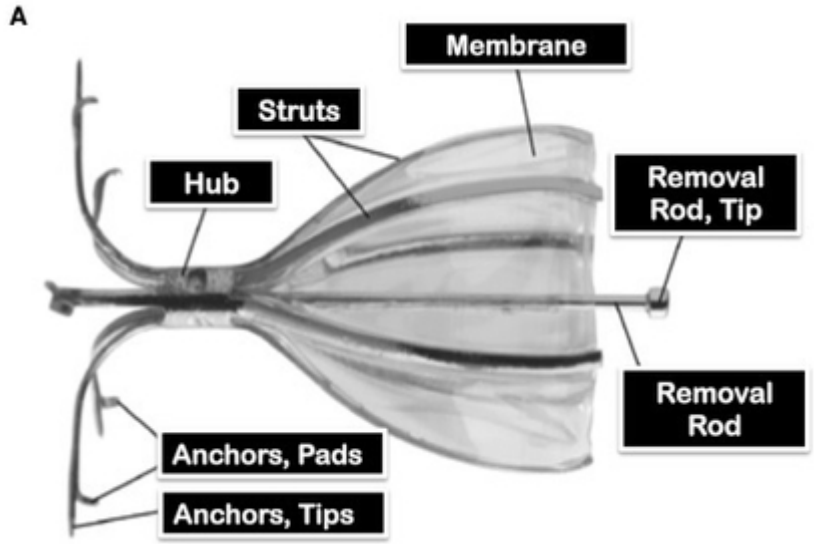




Bronchoscopic lung volume reduction

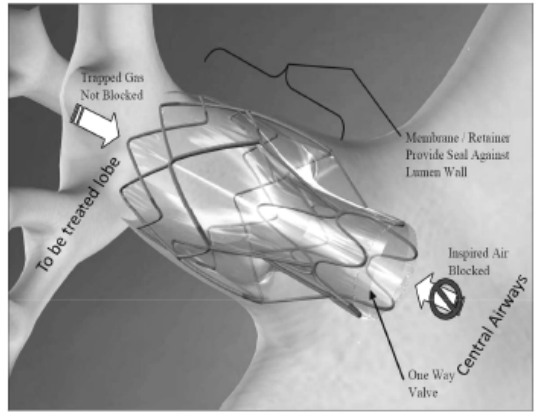


Klooster, NEJM 2015.



Criner, AJRCCM 2019.

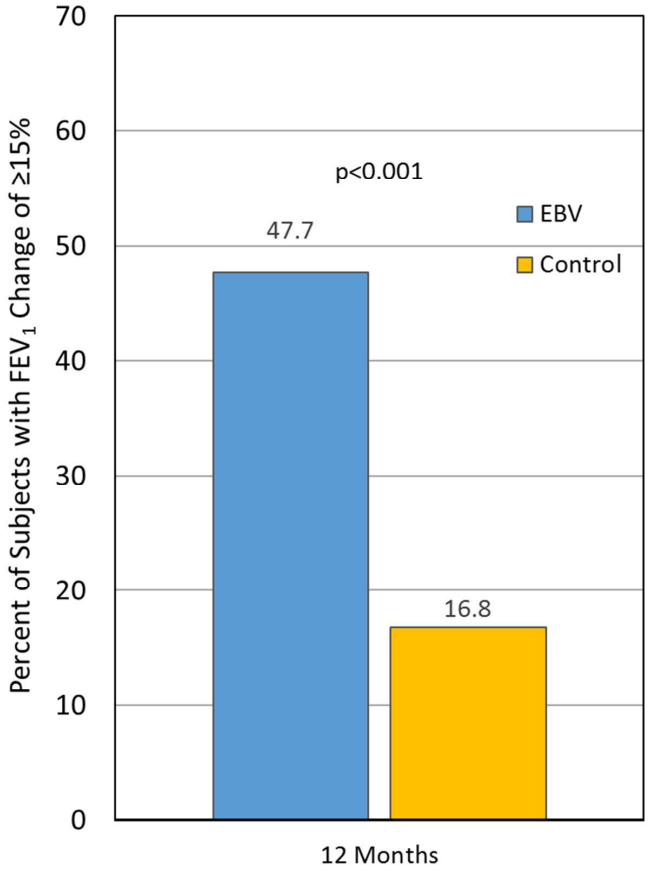
LIBERATE Trial

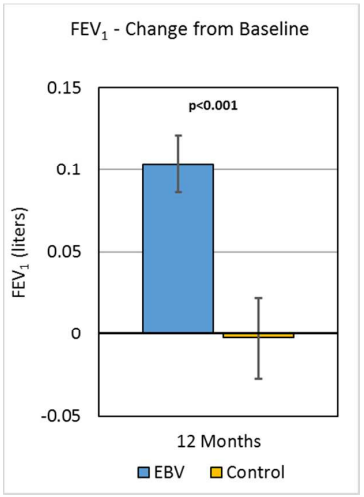


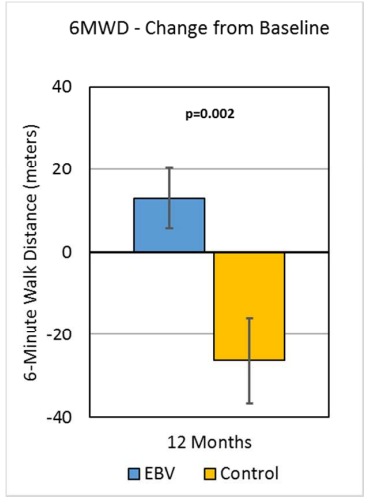
- RCT with 190 participants at 24 centers
- 2:1 to intervention
- Heterogeneous emphysema
- Low FEV_1 - 15-45%
- TLC >100%, RV >175%
- Completed pulmonary rehab
- Intraprocedure device to ensure absence of collateral ventilation

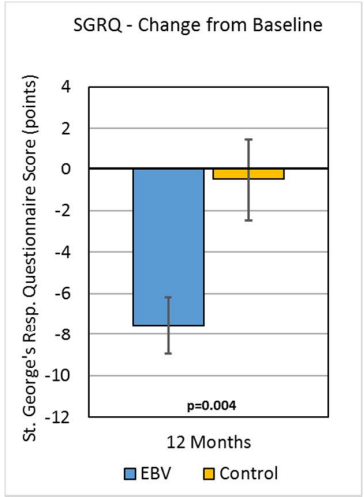
Criner, AJRCCM 2018.

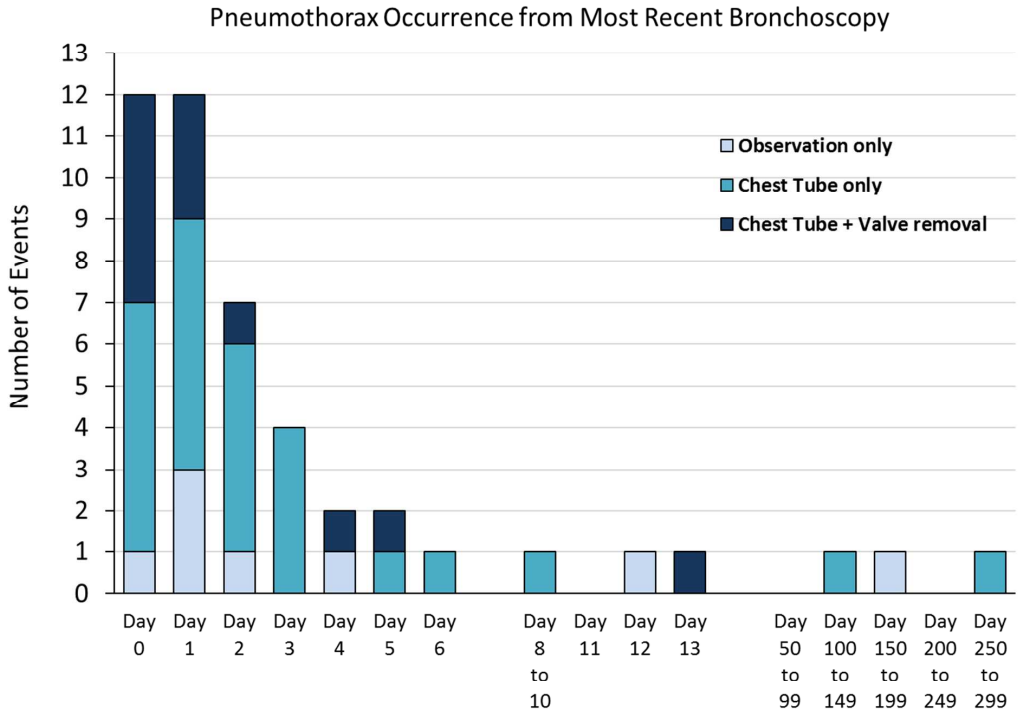
LIBERATE trial







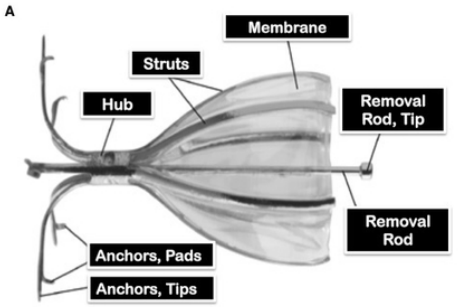


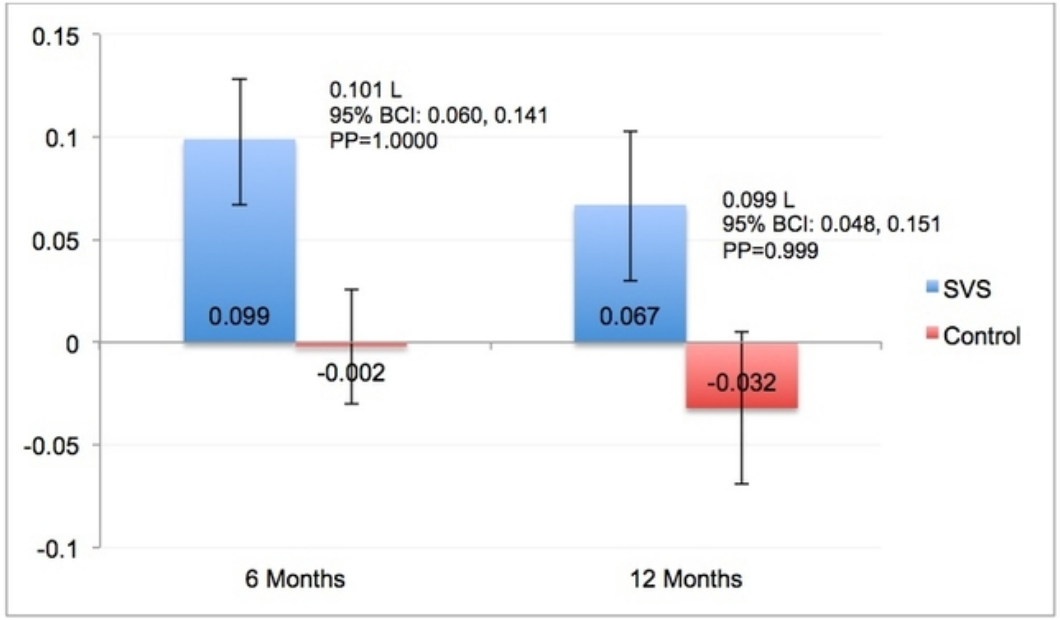


Criner, AJRCCM 2018.

EMPROVE trial

- N=172 randomized
- 31 sites
- FEV_1<45%
- TLC>100%, RV>175%
- Heterogeneous emphysema
- No assessment for collateral ventilation
- 12% pneumothorax

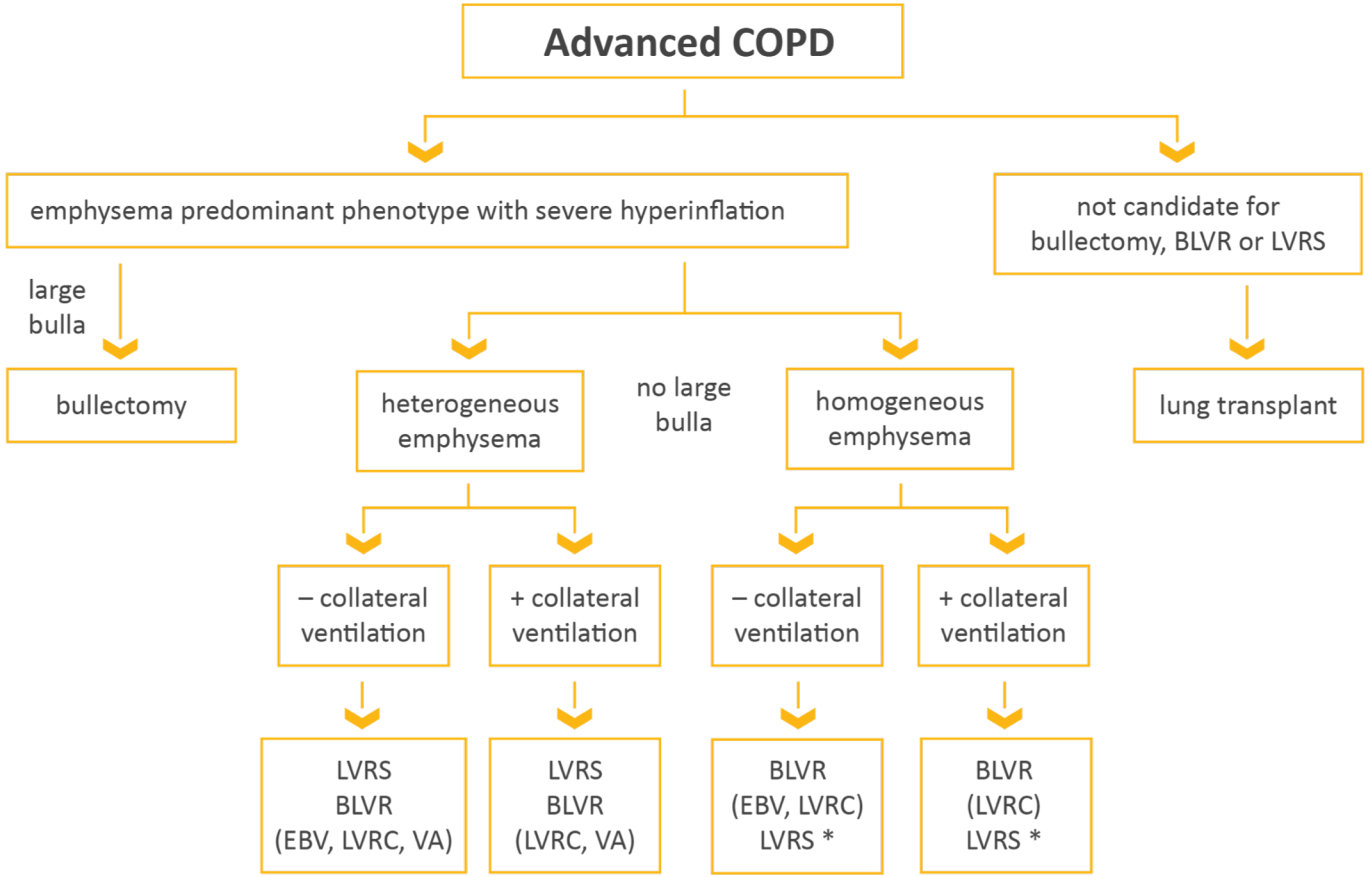




Criner, AJRCCM 2019.

INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.



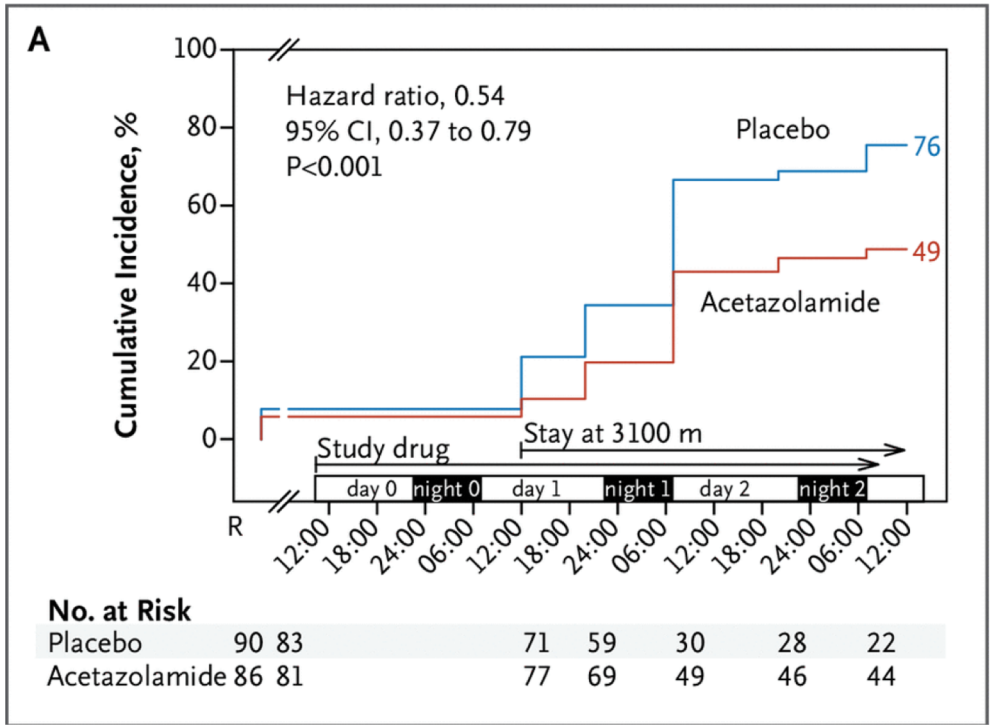
Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

*at some but not all centers

FIGURE 4.6

Acetazolamide for COPD at Altitude

- COPD patients traveling to high altitude
  - Resting O2 sat 92% or greater, PaCO2 <45 mmHg, average FEV_1 63% pred
  - Took acetazolamide 375 mg 24 hours before arriving at high altitude
  - Significantly reduced the risk of altitude-related adverse health effects



Furian, NEJM 2021.

COPD take-home points

- Risk factors for COPD in addition to cigarettes include dysanapsis, occupational exposures, indoor and outdoor air pollution
- Disparities exist in COPD by race, sex and rural/urban divide
- Assessment is multidimensional – symptoms, exacerbations
- Bronchodilator first strategy
  - Minimize → target ICS use
- Roflumilast or azithromycin for frequent exacerbations
- Unclear benefit of supplemental O_2 for desaturation with exercise
- Lung volume reduction – bronchoscopic valves or surgery

Review question

A 65 year old woman is referred for COPD management after being hospitalized for an exacerbation. She reports she is on antibiotics for “bronchitis” twice most years, she has dyspnea on exertion (walks slower than people her age; mMRC 2).

- She smokes 1/2 pack cigarettes per day.
- She takes LAMA/LABA, albuterol PRN, stopped ICS due to thrush.
- FEV_1 58% predicted, O_2 sat 92% at rest, 88% with exertion
- CT chest shows moderate bilateral upper lobe emphysema
- Eosinophil count 150/ul

In addition to smoking cessation counseling and pharmacotherapy, what would you do next?

A. Prescribe supplemental oxygen with ambulation
B. Start roflumilast
C. Start azithromycin daily
D. Re-start ICS
E. Refer for endobronchial valves

In addition to smoking cessation counseling and pharmacotherapy, what would you do next?

A. Prescribe supplemental oxygen with ambulation – no benefit on exacerbations, may reduce exertional dyspnea symptoms
B. Start roflumilast – indicated if FEV_1<50%
C. Start azithromycin daily – ex-smokers
D. <u>Re-start ICS</u>
E. Refer for endobronchial valves – FEV_1<45%