Management of COPD

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HARVARD MEDICAL SCHOOL

Disclosures

- Grant support:
  - Bayer
  - Boehringer-Ingelheim
  - Vertex
- Consultant:
  - Takeda
  - Astra-Zeneca

Objectives

- Review the diagnosis and assessment of the patient with COPD
- Highlight current treatment strategies for stable COPD

Outline

- GOLD guidelines
- Medications
  - Inhaled corticosteroids and Triple therapy
  - “non-inhaled” therapies
- Oxygen and non-invasive ventilation
- Bronchoscopic Lung Volume Reduction
- Redefining COPD

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Chronic obstructive pulmonary disease

- Common, preventable, treatable
- Persistent symptoms and airflow limitation
- Airway and/or alveolar abnormalities
- Exposure to noxious particles or gases
- Host factors, abnormal lung development
- Comorbidities

Global Initiative for Chronic Obstructive Lung Disease 2020
www.goldcopd.org

Multidimensional assessment

- Symptoms
- Airflow limitation
- Exacerbation risk
- Comorbidities

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;93:580

Global Strategy for Diagnosis, Management and Prevention of COPD

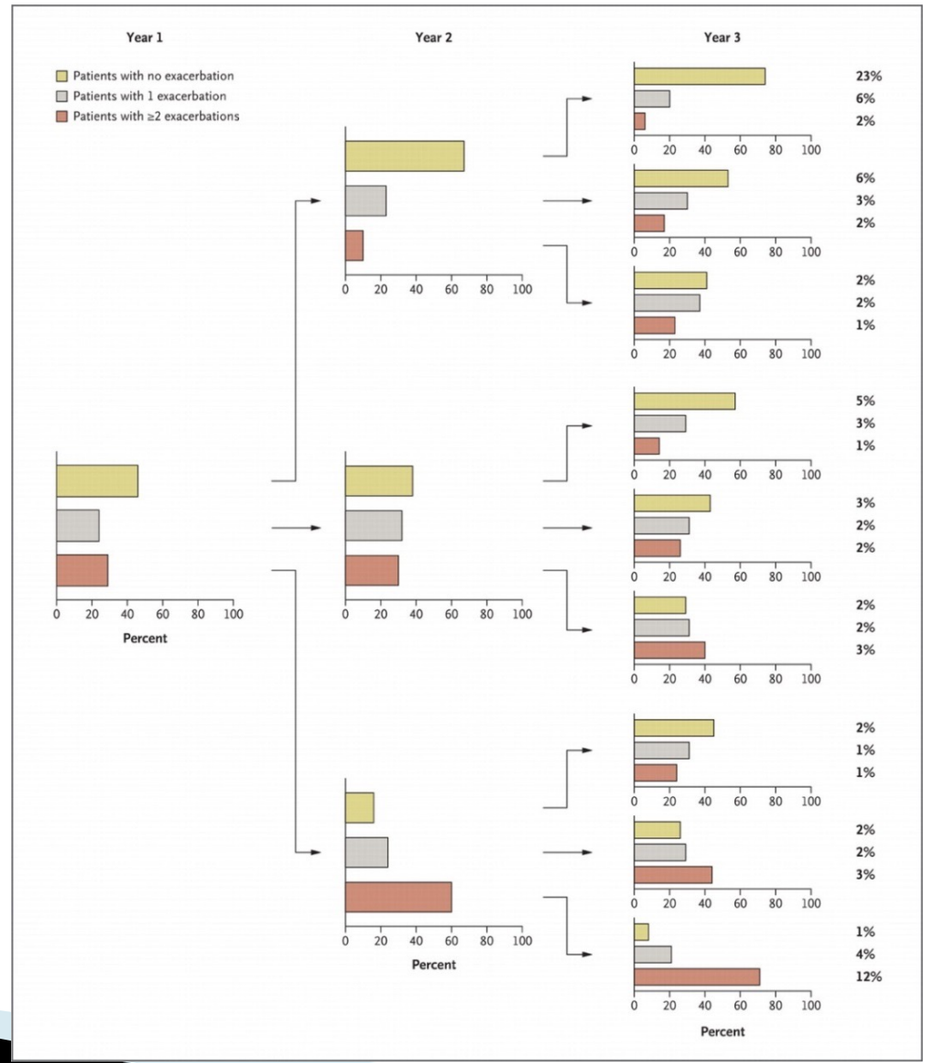
Classification of Severity of Airflow Limitation in COPD*

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

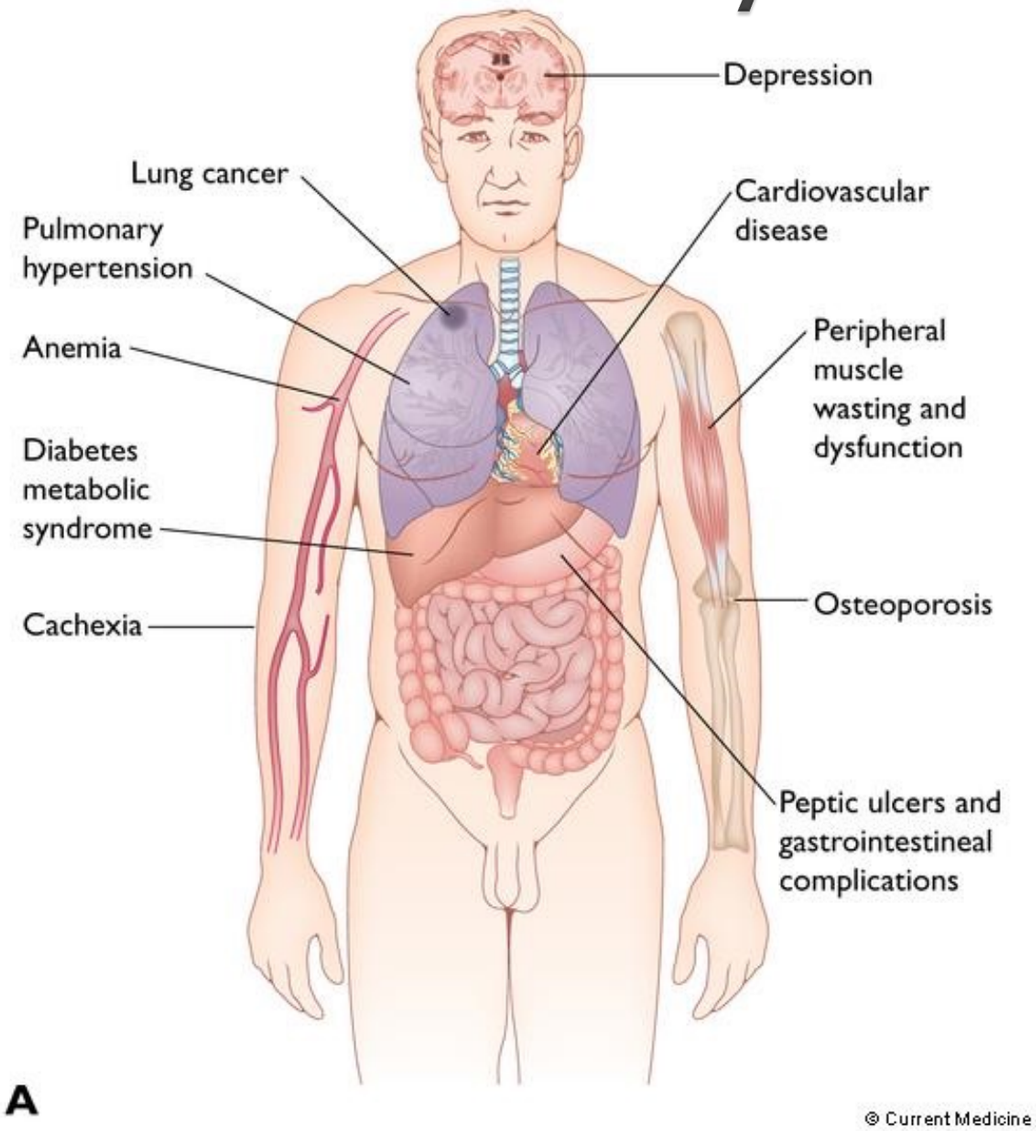
**Based on Post-Bronchodilator FEV_1*

Past exacerbations are best predictor of future exacerbations



Hurst JR, NEJM 2010; 363:1128.

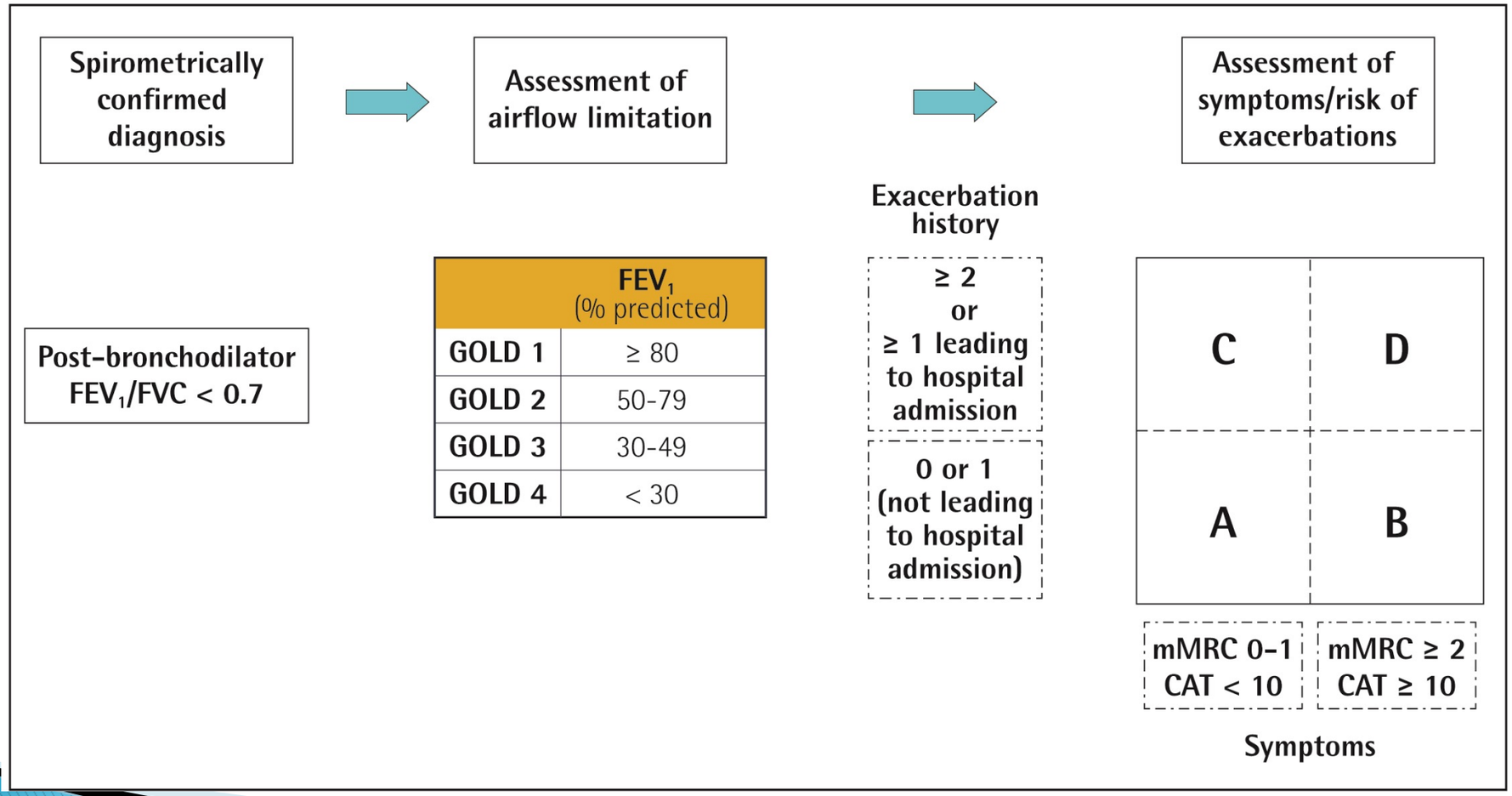
Comorbidities: COPD is a systemic disease



Crapo J, ed.,
Atlas of COPD, 2009

Combined Assessment

Figure 2.4. The refined ABCD assessment tool



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INITIAL PHARMACOLOGICAL TREATMENT

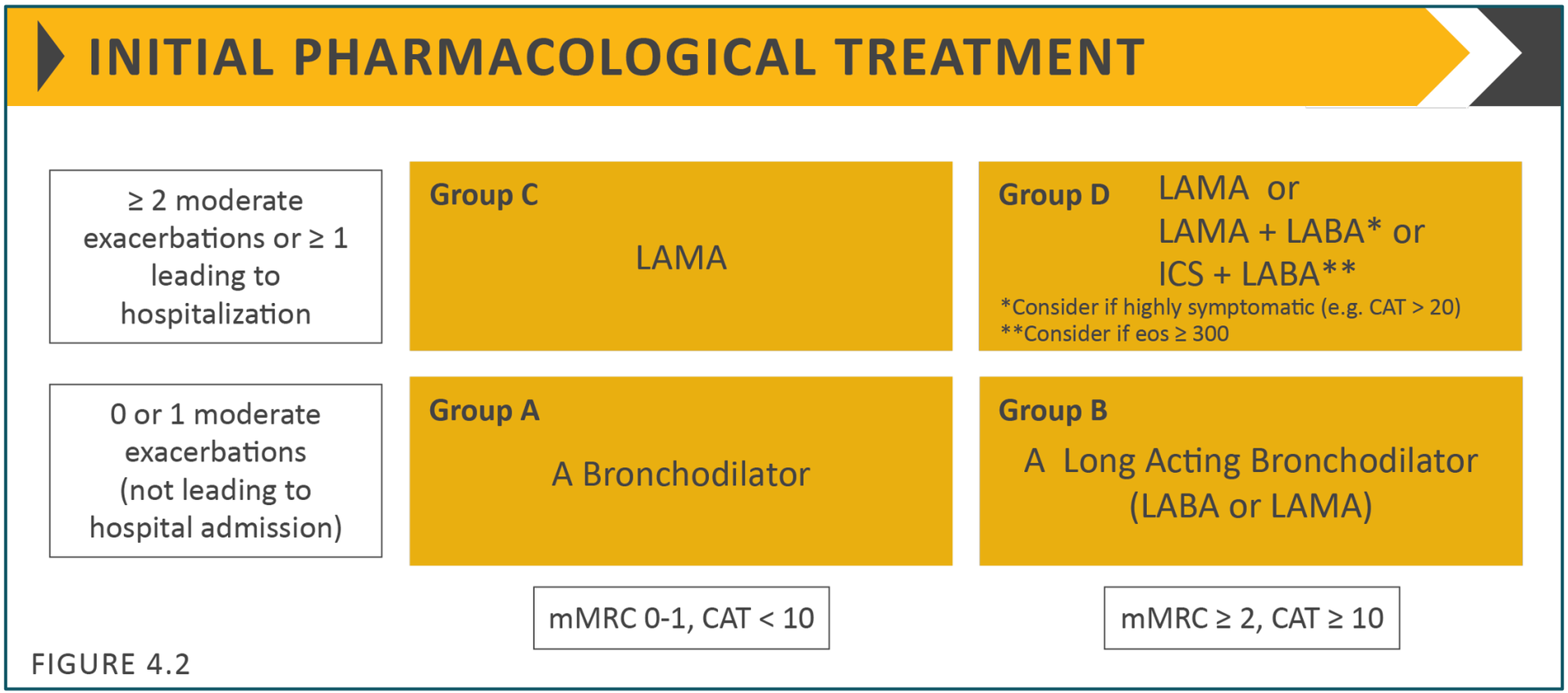
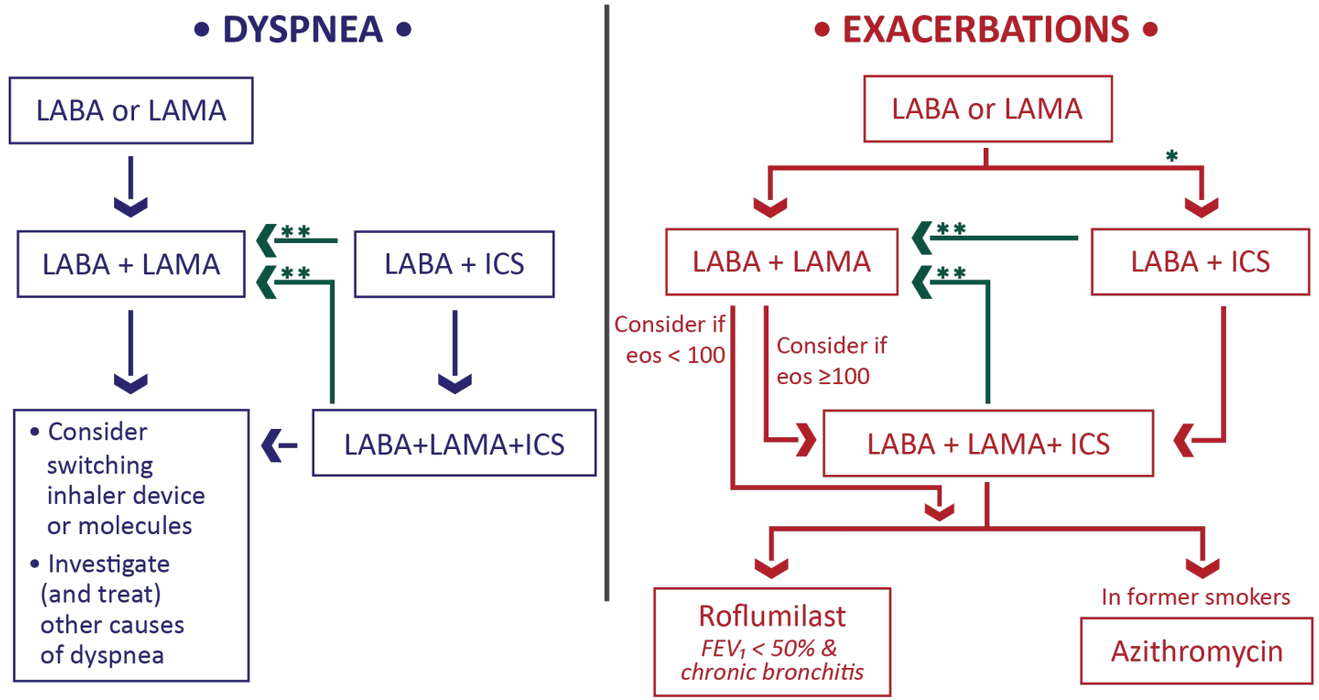


FIGURE 4.2

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

- Earlier studies:
  - Reduce exacerbations
  - May reduce FEV_1 decline
- Side effects
  - Increase risk of pneumonia
  - Dysphonia, hoarseness, oral candidiasis
- GOLD: Consider if blood eosinophils>300 or >100 with exacerbation history

Calverley, NEJM 2007;356:775
Magnussen, NEJM 2014;371;1285
Vestbo, NEJM 2016;375:1253
Vestbo, Lancet 2016;387:1817

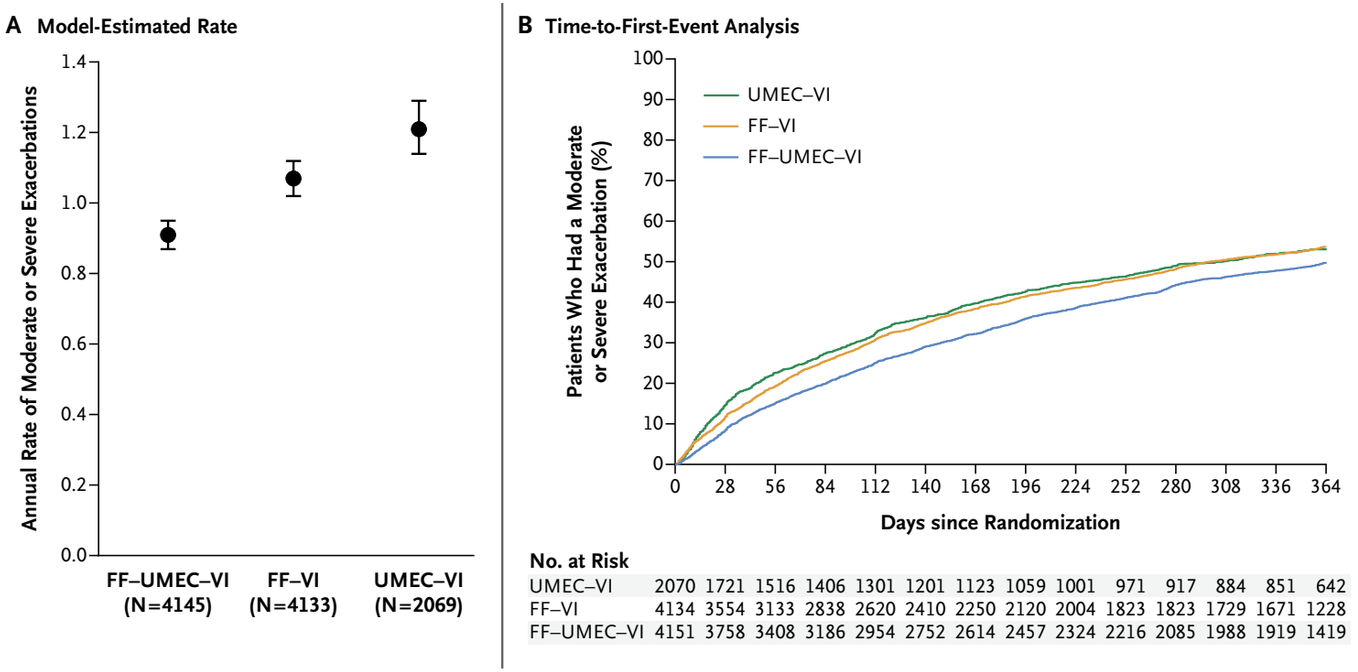
Routine blood tests in COPD?

- CBC with differential
- Alpha-1 antitrypsin deficiency
  - 1-2% of COPD in USA
  - AAT level +/- genotype or protein phenotype
- All adults with:
  - COPD
  - Emphysema
  - Asthma with irreversible airflow obstruction

Silverman EK, N Engl J Med 2009; 360:2749-2757
Miravitlles M, ERJ 2017; 50: 1700610
Sandhaus RA, JCOPDF 2016; 3(3): 668-682

IMPACT: “closed” triple therapy

- N=10,355
- FEV_1<50% and ≥1 exacerbation in last yr or FEV_1 50–80% and ≥2 exacerbations
- CAT ≥10
- Asthma not excluded

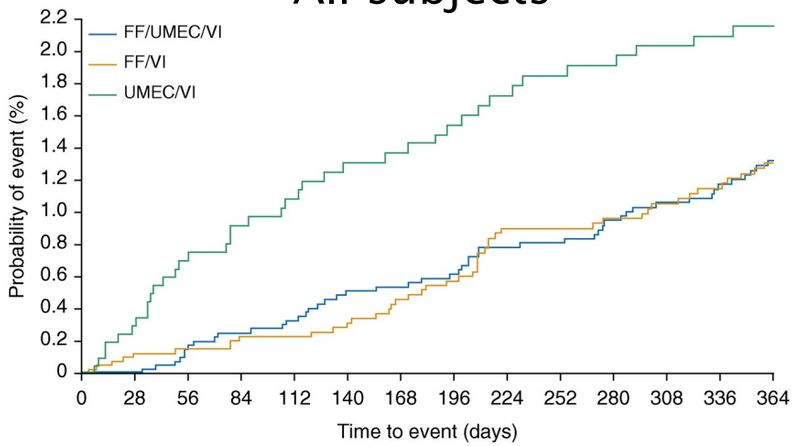


Greater effect if eosinophils ≥ 150 cells/ul
Pneumonia rate 50% higher in ICS arms

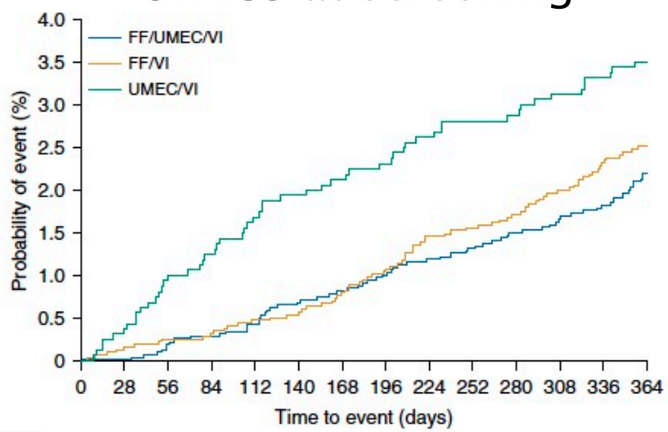
Lipson, NEJM 2018;378:1671

Do ICS reduce mortality? IMPACT trial

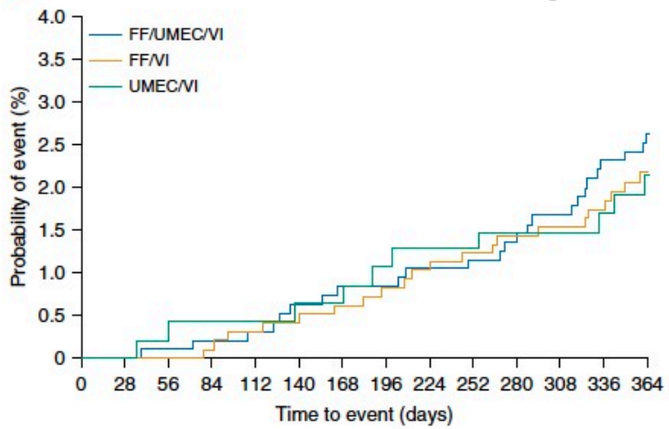
All subjects



C On ICS at screening



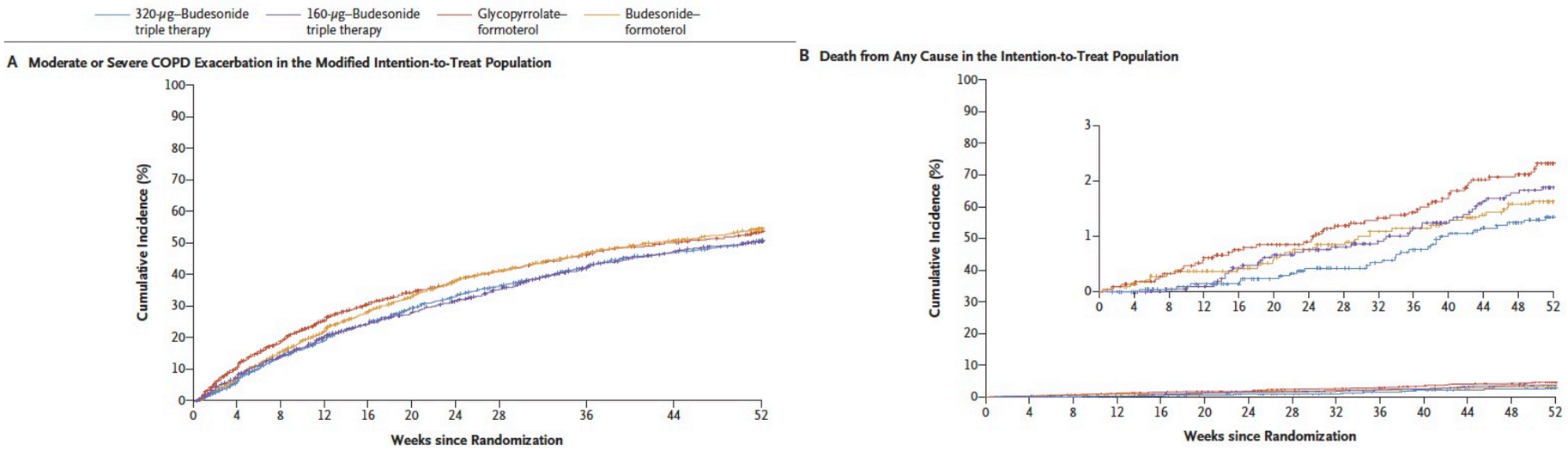
D No ICS at screening



Lipson DA, AJRCCM 2020;201:1508

ETHOS trial

budesonide/glycopyrrolate/formoterol

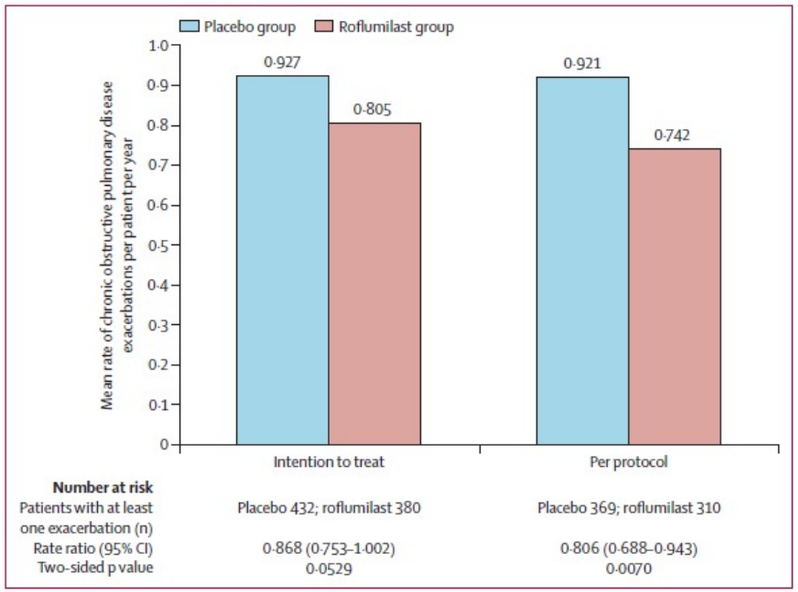


- N=8509
- CAT ≥10
- FEV1 25-65%
- FEV_1<50% and ≥1 exacerbation in last yr or FEV_1 ≥50% and ≥2 exacerbations
- Exclude current asthma (not past)

Rabe KF, NEJM 2020;383:35

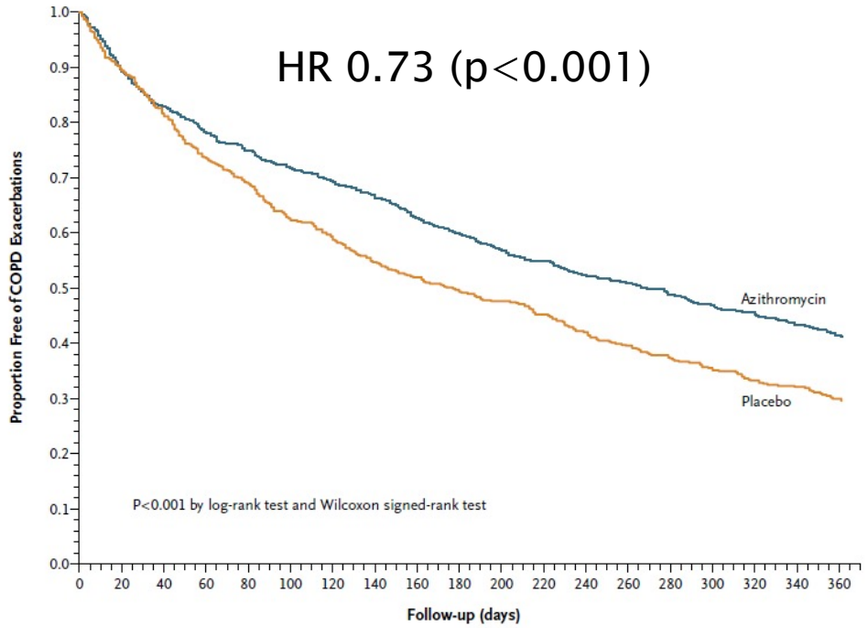
Oral therapies to decrease exacerbation risk

Roflumilast



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

Azithromycin 250mg daily



More effective: older, ex-smokers,
milder COPD

Martinez, Lancet 2015;385:857
Albert, NEJM 2011;365:689
Han, AJRCCM 2014;189:1503

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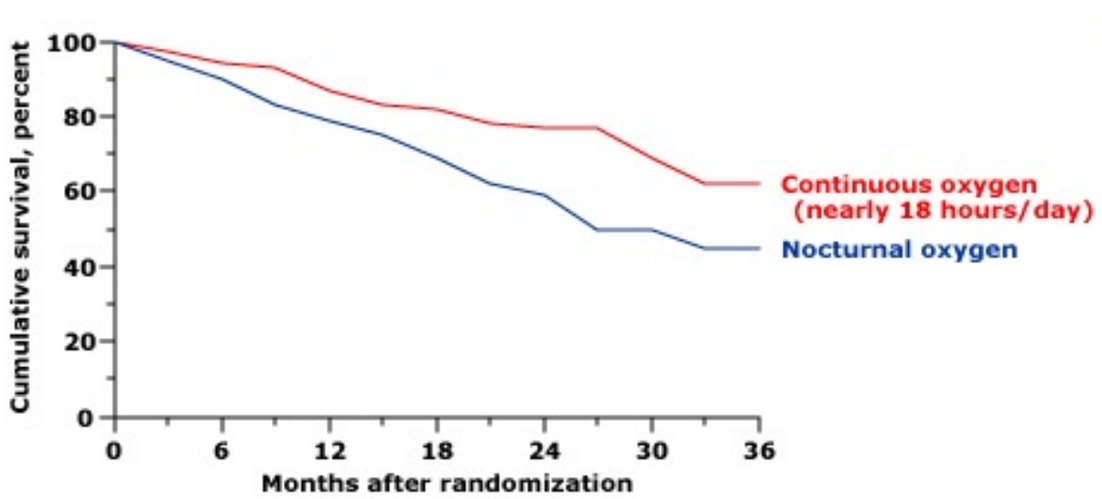
Supplemental oxygen reduces mortality in hypoxemic COPD patients

NOTT trial, Ann Intern Med 1980;93:391



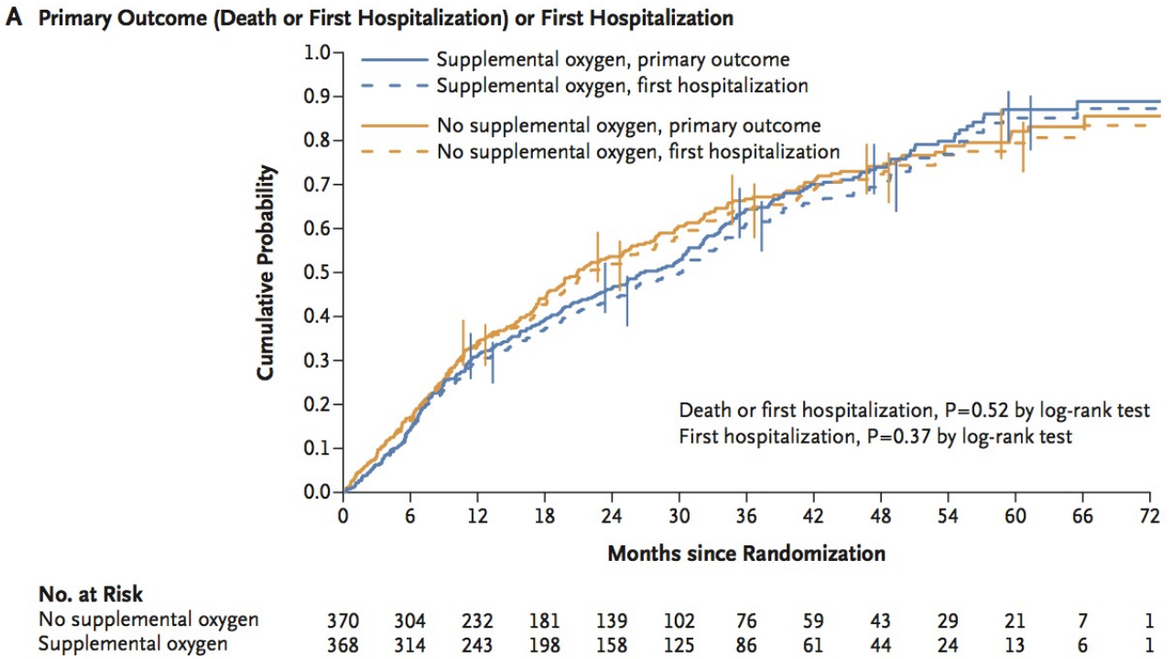
- PaO_2 ≤55mmHg or SaO_2 ≤88%, or
- PaO_2 ≤60mmHg or SaO_2 ≤89%,
  - with cor pulmonale, right heart failure or polycythemia

Long Term Oxygen Treatment Trial

NEJM 2016;375:1617-27

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 Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Guideline

Madalina Macrea, Simon Oczkowski, Bram Rochwerg, Richard D. Branson, Bartolome Celli, John M. Coleman III, Dean R. Hess, Shandra Lee Knight, Jill A. Ohar, Jeremy E. Orr, Amanda J. Piper, Naresh M. Punjabi, Shilpa Rahangdale, Peter J. Wijkstra, Susie Yim-Yeh, M. Bradley Drummond, and Robert L. Owens; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

- 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

AJRCCM 2020;202:e74-87

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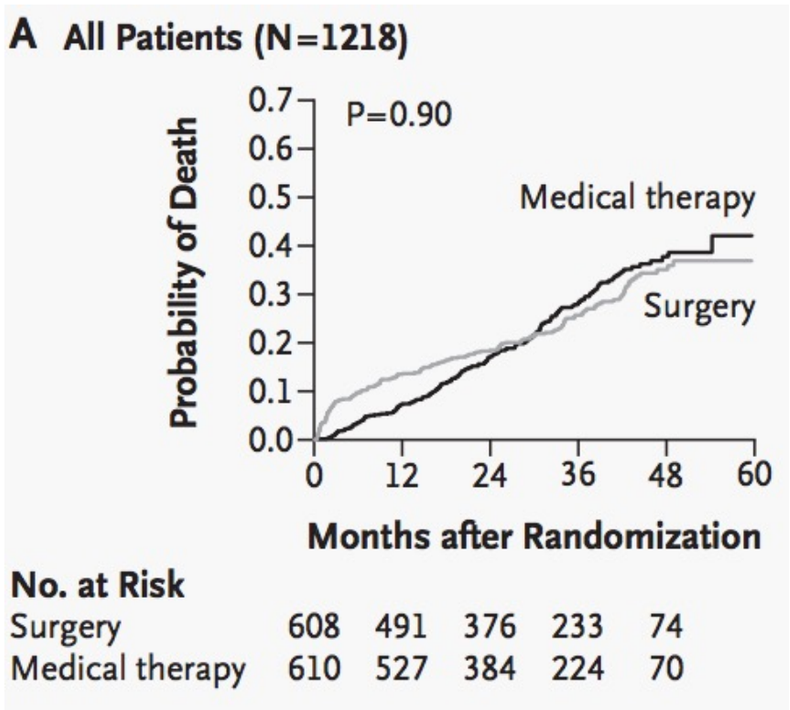
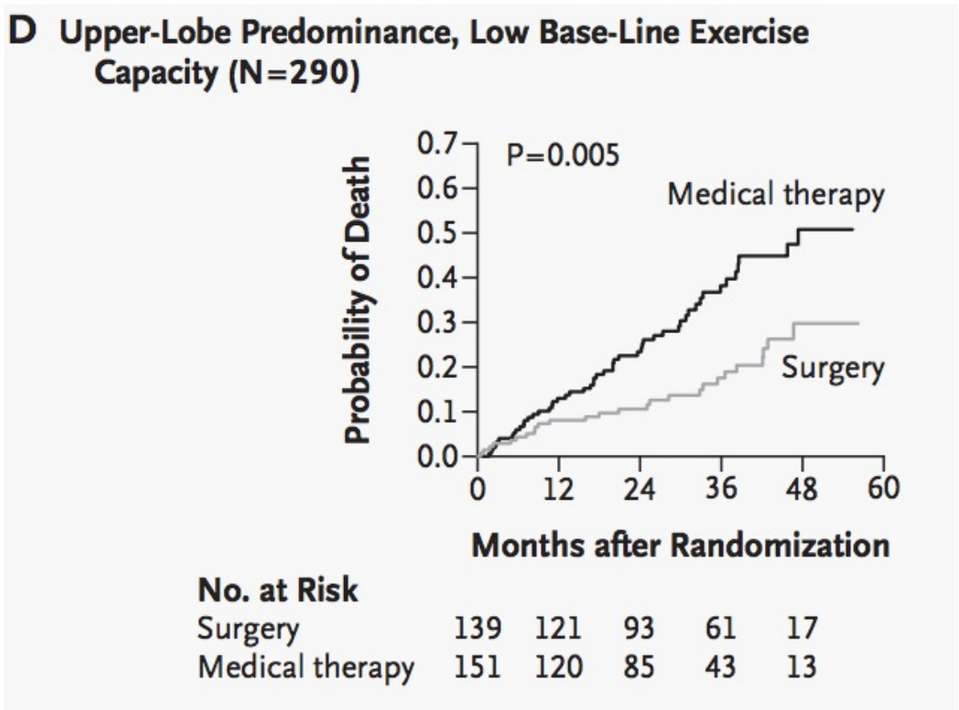
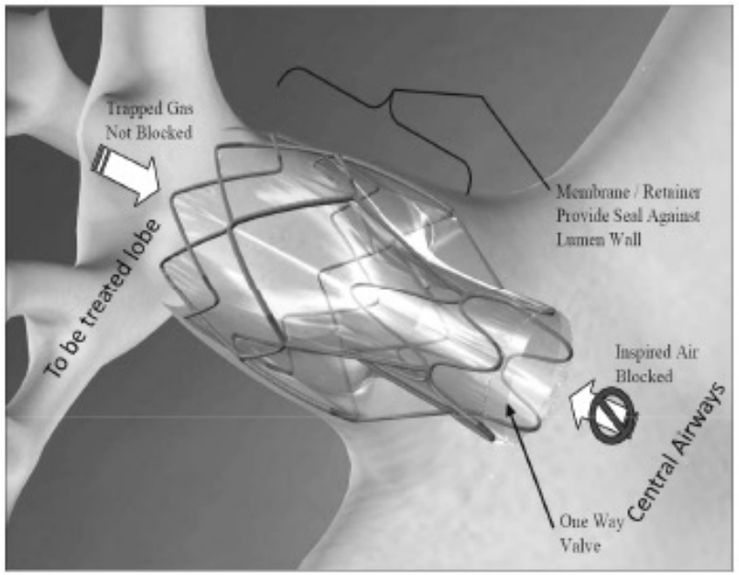
Lung volume reduction surgery

NETT, NEJM 2003;348:2059–73

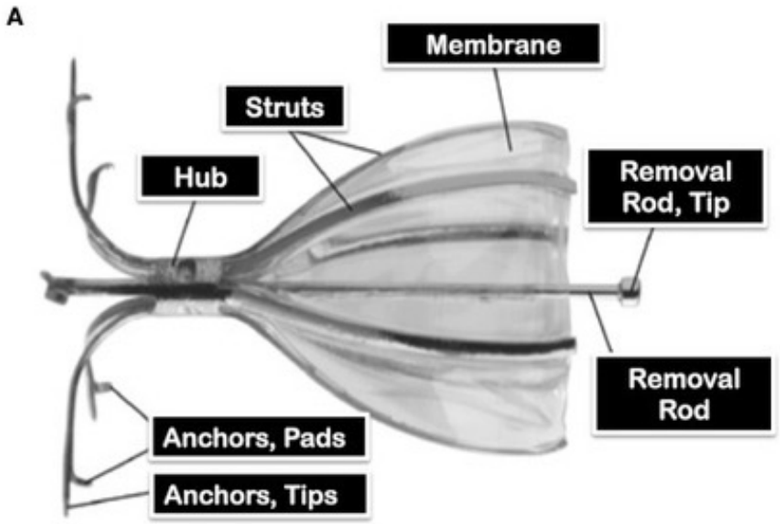




Endobronchial valves

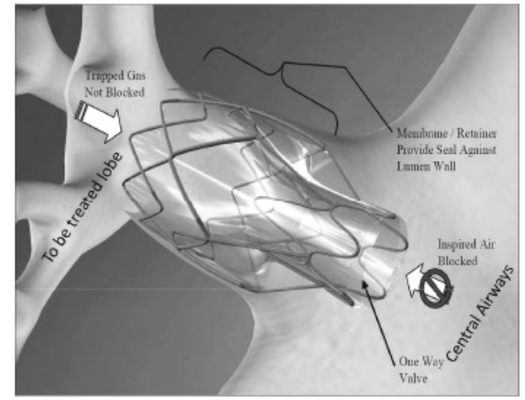


Klooster, NEJM 2015;373:2325



Criner, AJRCCM 2019;200;1354

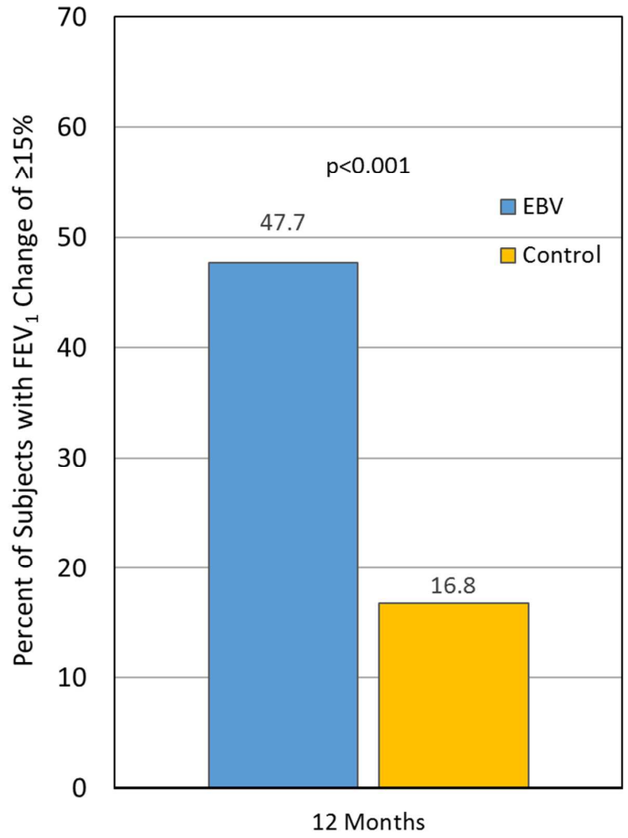
LIBERATE trial

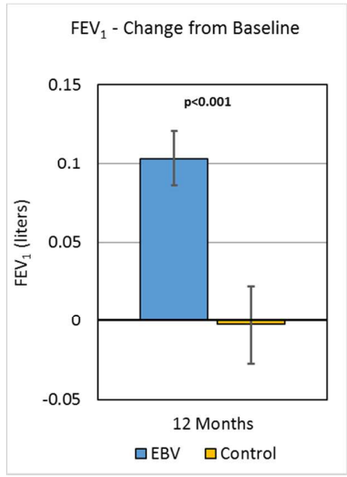


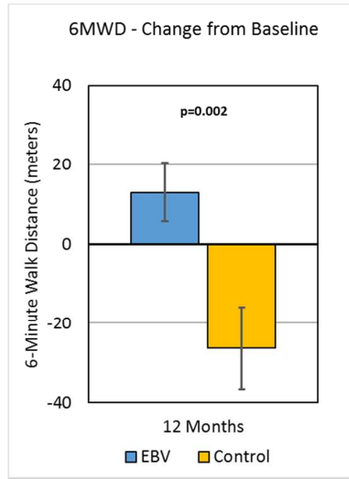
- N=909 consented, 190 randomized
- 24 centers
- FEV_1 15-45%
- TLC>100%, RV>175%
- Heterogeneous emphysema
- Completed pulmonary rehab
- 2:1 randomization
- Bronchoscopic device to ensure absence of collateral ventilation

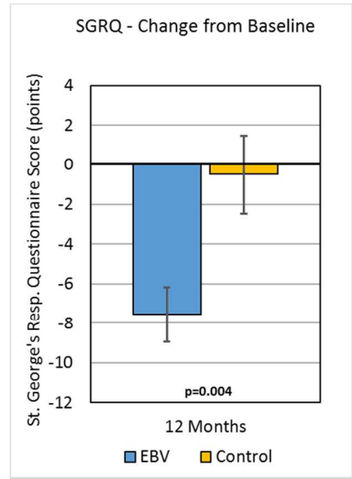
Criner, AJRCCM 2018;198:1151

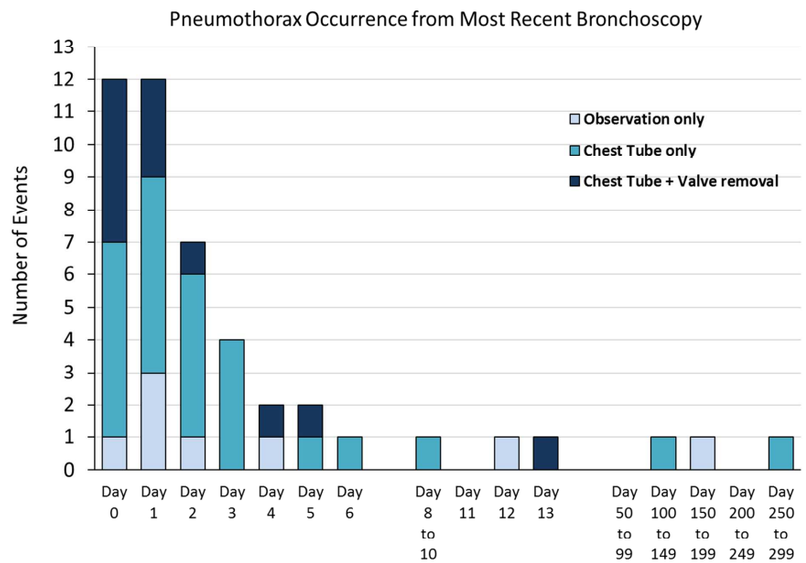
LIBERATE trial







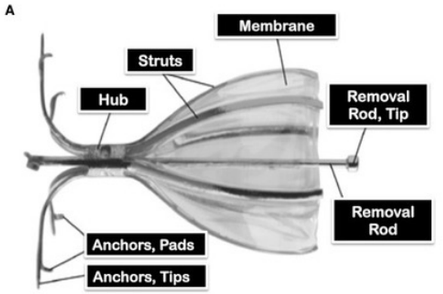


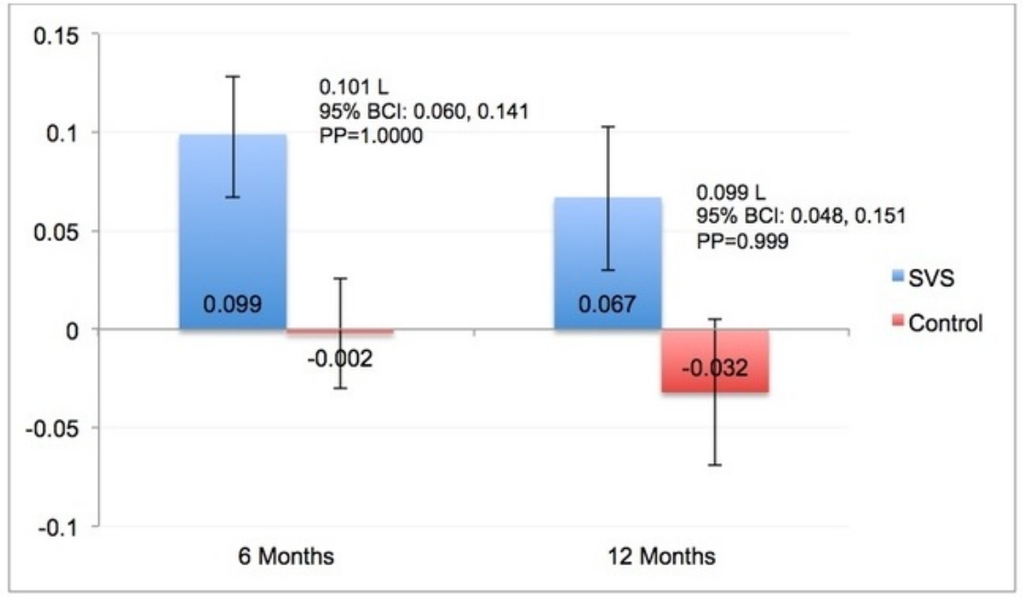


Criner, AJRCCM 2018;198:1151

EMPROVE trial

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

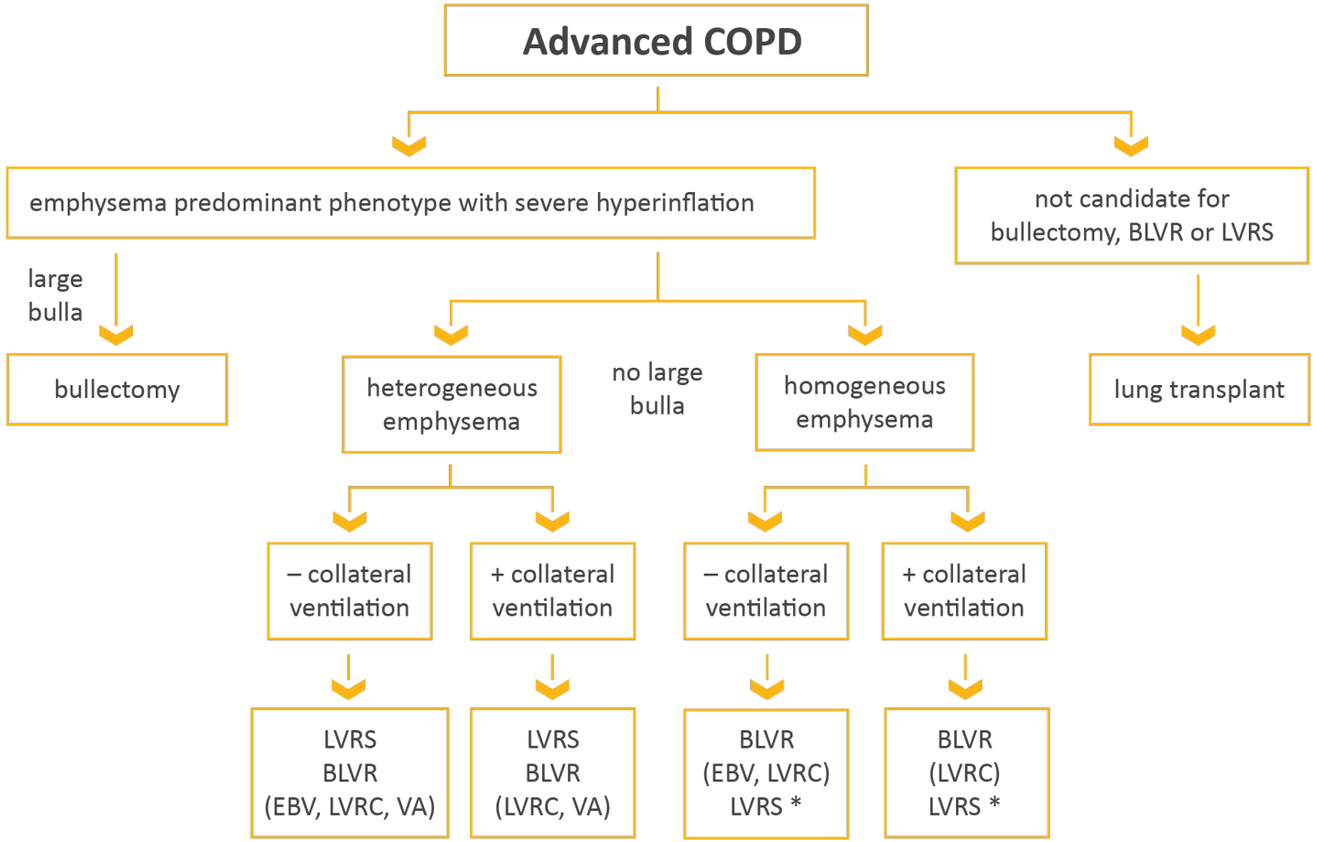




Criner, AJRCCM 2019;200:1354

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

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- GOLD guidelines
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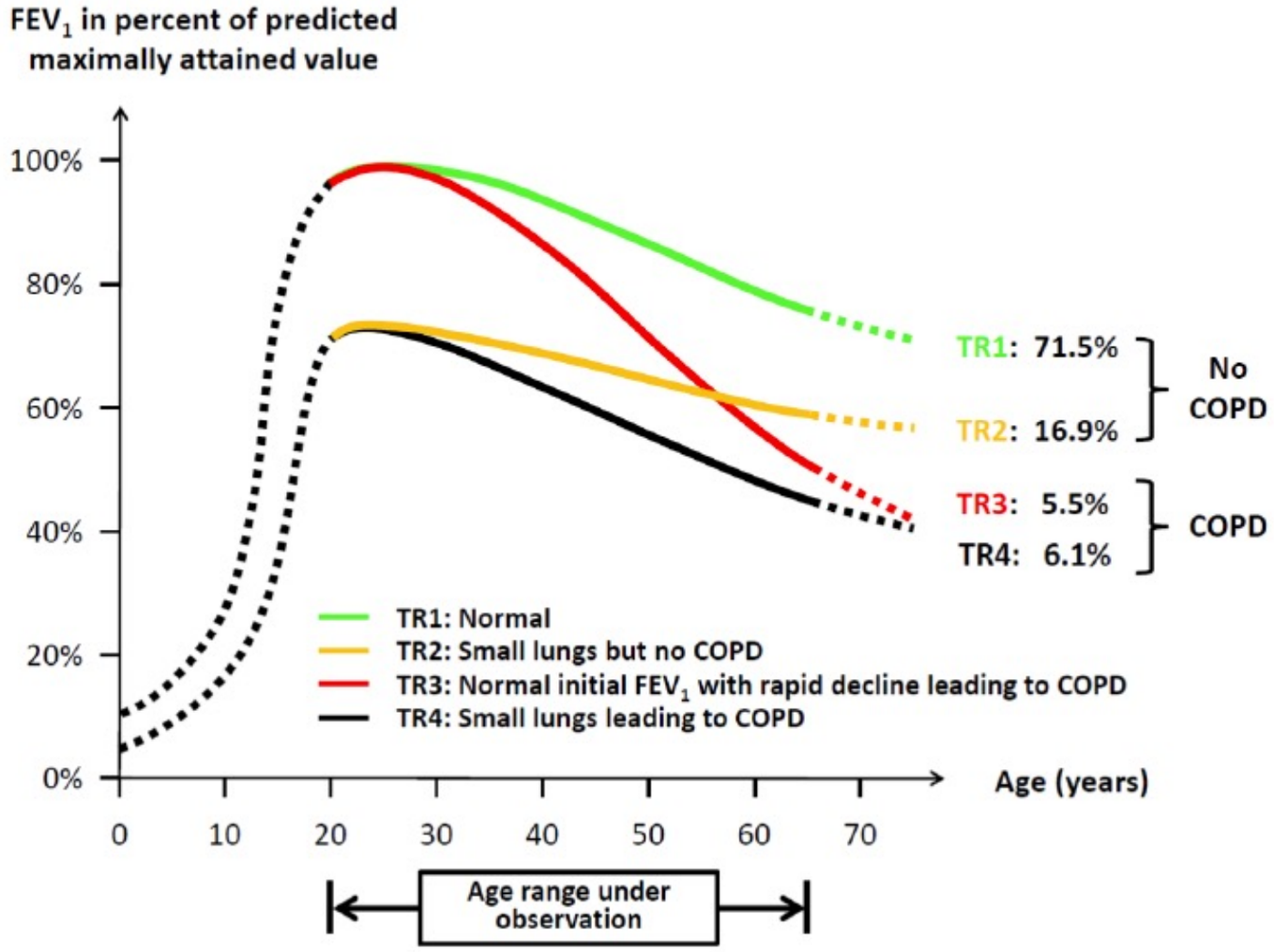
Lung development and COPD



Lange P, NEJM 2015;373:111

Smokers with Normal Spirometry: COPDGene Study

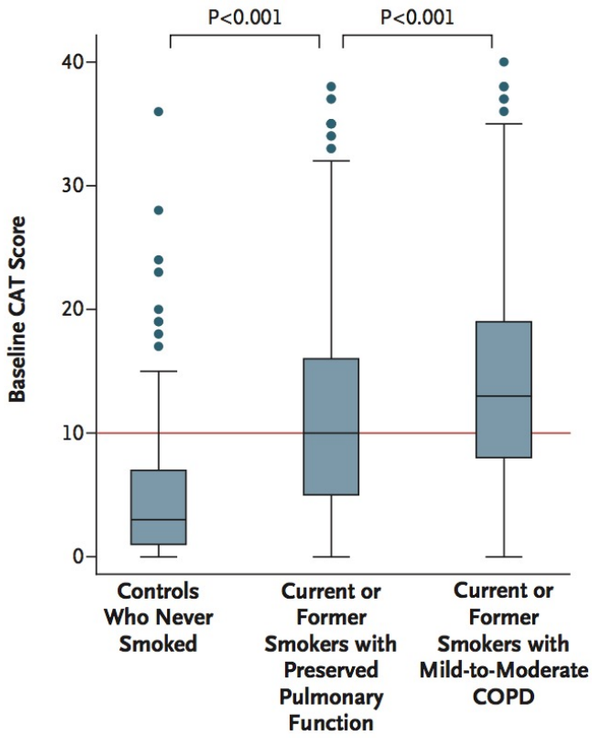
Respiratory impairments are common

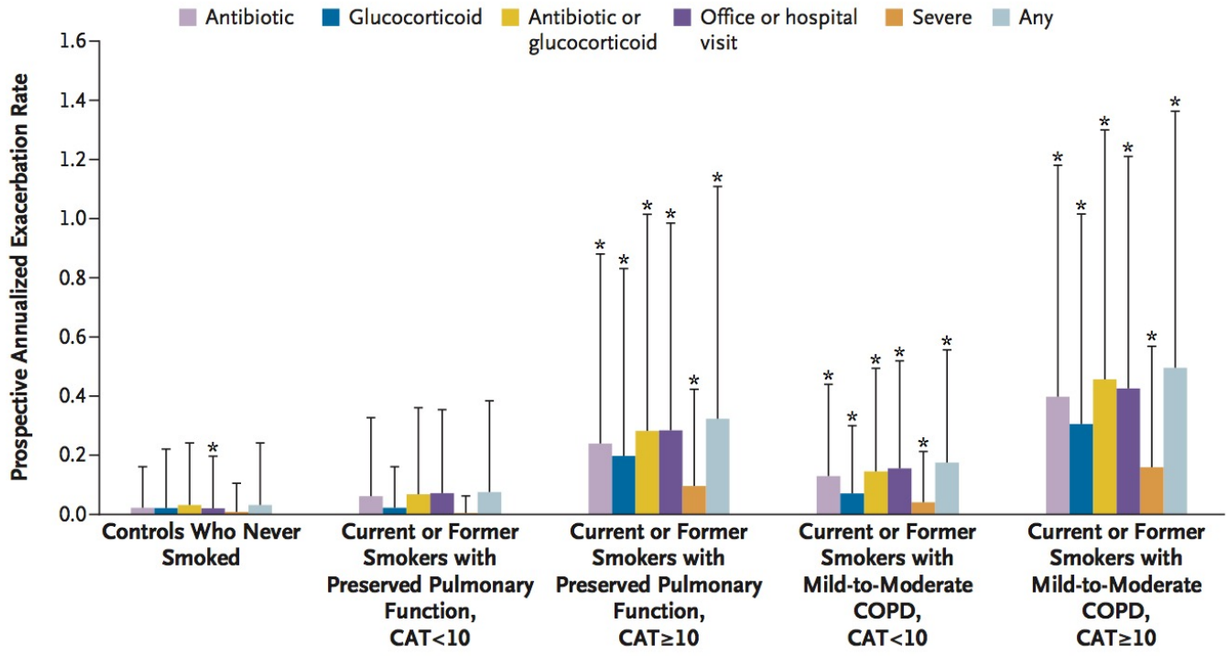
Variable	No. (%)		
	Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)
Individual Scores			
Chronic bronchitis, by criteria	0	552 (12.6)	125 (15.7)
History of ≥1 severe exacerbation	0	190 (4.3)	39 (4.9)
St George's Respiratory Questionnaire total score >25	4 (3.7)	1143 (26.0)	226 (28.5)
Six-minute 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)

Regan, JAMA Intern Med 2015;175:1539

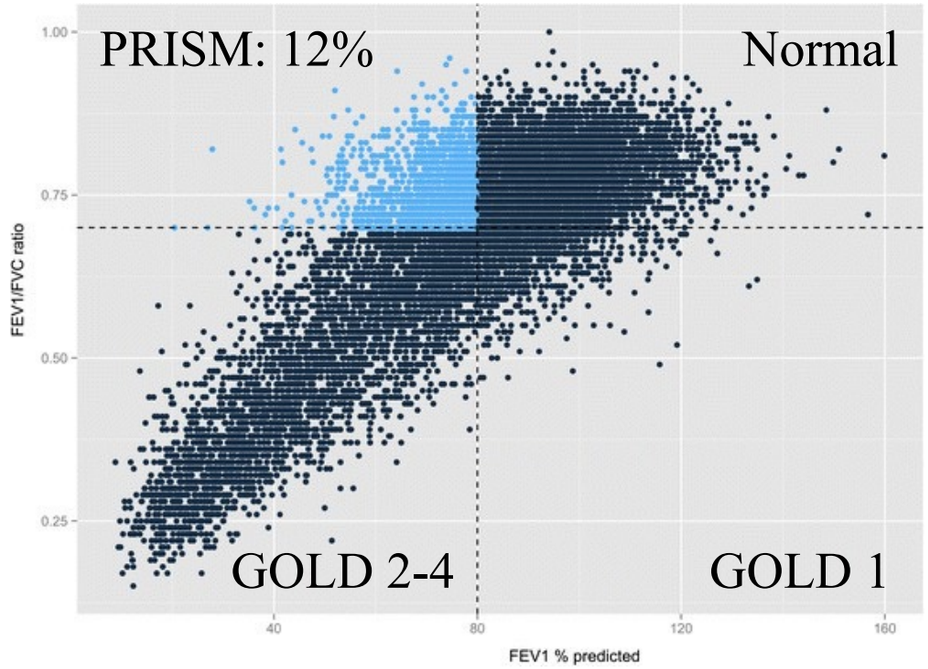
SPIROMICS study

Woodruff, NEJM 2016;374:1811–21





PRISM: Preserved ratio, impaired spirometry



45% with TLC(CT scan)<LLN

COPDGene

Phase 1*	Phase 2*	N	%
PRISm →	GOLD 0	152	22.2%
PRISm →	COPD (GOLD 1–4)	172	25.1%
PRISm →	PRISm	360	52.6%

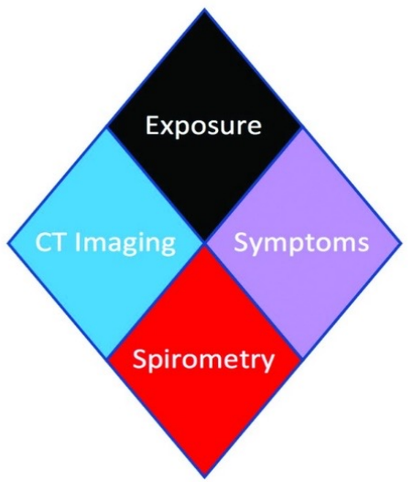
Rotterdam

135 PRISm →
- 14 (10.4%) NL
- 31 (23.0%) PRISm
- 44 (32.6%) COPD
- 46 (34.1%) deaths

Wan E, Resp Res 2014;15:89
Wan E, AJRCCM 2018;198:1397
Wijnant SRA, ERJ 2020;55:1901217

Redefining COPD? COPDGene 2019

Figure 1. Features Used to Define COPD in the COPDGene® Study



Exposure in the COPDGene® study includes individuals with a total of ≥ 10 pack years smoking. **CT Imaging** includes individuals with quantitative assessment showing ≥ 5% emphysema, a Pi10 ≥ 2.5 mm or ≥ 15% gas trapping. **Symptoms** include individuals with an mMRC dyspnea score ≥ 2 or chronic bronchitis. **Spirometry** includes individuals with FEV_1 < 80% predicted or FEV_1/FVC < 0.70.

COPDGene®=COPD Genetic Epidemiology study; COPD=chronic obstructive pulmonary disease; CT=computed tomography; Pi10=square root of airway wall area for a standardized airway of 10 mm internal perimeter; mMRC=modified Medical Research Council; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity

Figure 2. Logistic Regression and Cox Regression Models for Forced Expiratory Volume in One Second Progression and All-Cause Mortality (respectively) With the Proposed COPDGene 2019® Classification of Categories

	Category	Odds of Change >350 ml in FEV_1 (95% CI)[a]	Hazard Ratio for All-Cause Mortality (95% CI)[b]	COPDGene 2019® Classification
	A	1.0 (ref.)	1.0 (ref.)	NO COPD
	B	**1.31 (1.04-1.65)**	1.05 (0.76-1.44)	Possible COPD
	C	**1.42 (1.07-1.88)**	**1.55 (1.09-2.19)**	
	D	0.92 (0.64-1.30)	**1.48 (1.03-2.12)**	
	E	**1.74 (1.28-2.36)**	**1.90 (1.33-2.71)**	Probable COPD
	F	1.02 (0.66-1.60)	**2.62 (1.84-3.72)**	
	G	**2.11 (1.66-2.68)**	**1.76 (1.36-2.27)**	
	H	**2.82 (2.18-3.66)**	**5.18 (4.15-6.48)**	Definite COPD

[a]Change in FEV_1 assessment was done on 4925 participants who returned for Phase 2 clinical follow-up. Adjusted for age at first visit, sex, race, pack years, current smoking status, and baseline FEV_1.
[b]Mortality assessment was done on 8784 participants in the Phase 1 cohort. Data are implicitly adjusted for age, additionally adjusted for sex, race, pack years, and current smoking.

Bolded numbers indicate categories where the 95% CI did not include 1.0.

COPDGene®=COPD Genetic Epidemiology study; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory in 1 second; HR=hazard ratio; CI=confidence interval

Key:
Black diamond=exposure
Blue diamond=abnormal CT imaging
Red diamond=abnormal spirometry
Purple diamond=symptoms

Lowe KE, et al. *Chronic Obstr Pulm Dis*. 2019;6:384

COPD take-home points

- Multidimensional assessment
  - Symptoms and exacerbation risk
- Bronchodilator first strategy
  - Dual vs. mono?
  - Minimize → target ICS use
- Roflumilast or azithro for recurrent exacerbations
- Unclear benefit of supplemental O_2 for desaturation with exercise
- Lung volume reduction – valves or surgery
- Redefining COPD
  - PRISM
  - Symptoms – consider screening?
  - CT abnormalities (e.g. LDCT)

Review question

- 65yo woman referred for COPD management following hospitalization for an exacerbation
- Antibiotics for “bronchitis” twice per year
- Dyspnea on exertion (MMRC 2)
- Current smoker ½ pack daily
- Medications: LAMA/LABA daily, albuterol PRN
  - She developed thrush on LABA-ICS
- FEV_1 58% predicted
- O_2 sat 92% at rest, 88% with exertion
- CT chest: moderate-severe bilateral upper lobe predominant 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. Re-start ICS
E. Refer for endobronchial valves – $FEV_1 < 45\%$