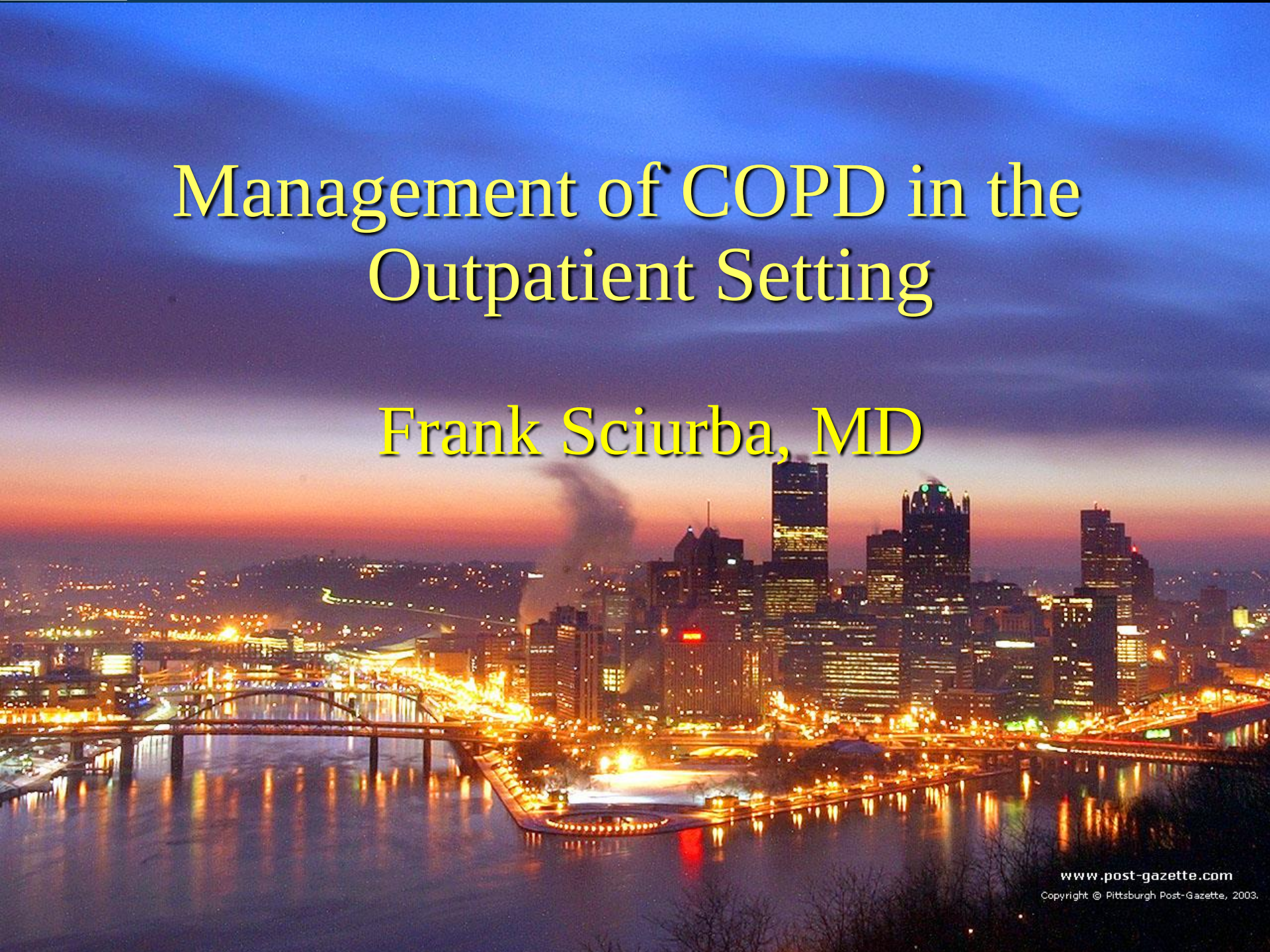
Management of COPD in the Outpatient Setting

Frank Sciurba, MD



Disclosures

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AstraZeneca, Pulmonx, Nuvaira, Gala Therapeutics, Sanofi

Diagnosis and Treatment of COPD

- Impact and Diagnosis
- Outpatient Treatment
  - General
  - “Precision” (Pulmonology Referral)

Definition and Early Symptoms of COPD

- **Common, preventable, treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases**
- **Umbrella term for progressive lung diseases, including**
  - Emphysema
  - Chronic bronchitis
  - Refractory (nonreversible) asthma/asthma-COPD overlap syndrome
  - Some forms of bronchiectasis…….ETC.
- **Most common early symptoms[3]**
  - Dyspnea on exertion
  - Chronic cough
  - Abnormal sputum production

[1]Global Initiative for Chronic Obstructive Lung Disease. 2017 Report.
Available at http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/
[2]COPD Foundation. http://www.copdfoundation.org/What-is-COPD/Understanding-COPD/What-is-COPD.aspx
[3]Fromer L. *Intern J Gen Med*. 2011;4:729-739.

Epidemiology of COPD

United States[1,2]

- ~~3rd~~ ~~4th~~ 5th leading cause of death
- Number affected: 13.7 million
- Now affects more women than men

Worldwide[3,4]

- 4th leading cause of death
- Number affected: 384 million
- Prevalence among individuals ≥30 y: 11.4%
- Prevalence is expected to increase with increasing prevalence of smoking in developing countries and increasing age of populations in high-income countries

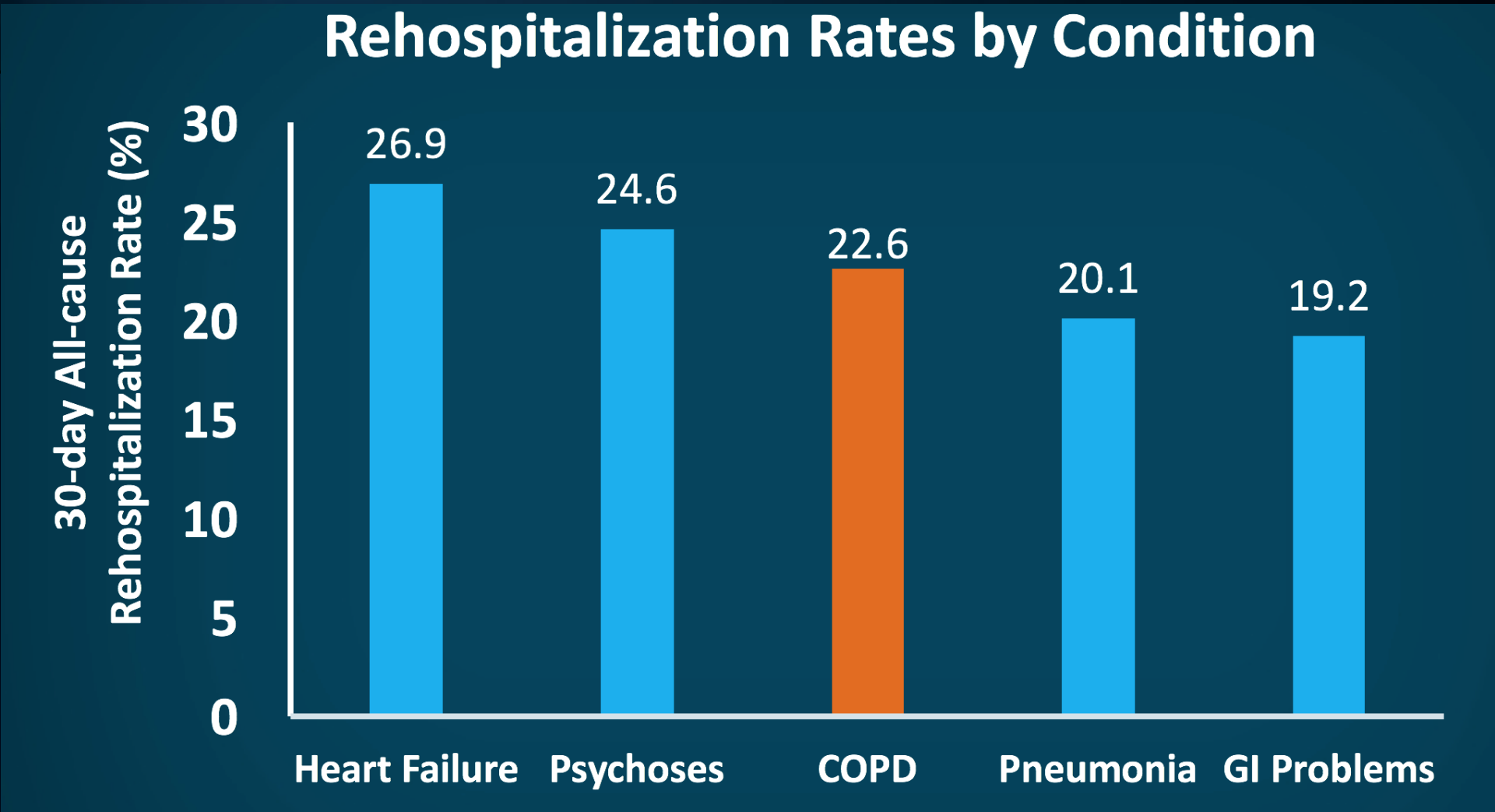
[1]Ford ES et al. *CHEST.* 2013:144:284-305.
[2]Akinbami LJ and Liu X. NCHS data brief, no. 63. 2011.
[3]Adeloye D, et al. *J Global Health.* 2015 5:02415.
[4]World Health Organization. http://www.who.int/mediacentre/factsheets/fs310/en/

The Patient Burden of COPD

- Declining lung function
- Symptoms
- Activity
- Exacerbations/hospitalizations
- Quality of life
- Mortality
- Costs

Vestbo J, et al. Am J Respir Crit Care Med. 2013;187(4):347-65.
Benton M, et al. Respirology. 2018 Mar 4. doi: 10.1111/resp.13285.

Conditions Most Commonly Associated with Hospital Readmission



- Reducing hospitalizations is a primary target of health care organizations and agencies

Jencks SF, et al. NEJM. 2009;360(14):1418-1428.

Spirometry Necessary for COPD Screening and Diagnosis

Consider COPD in patients with *any* symptoms and history of exposure to risk factors

SYMPTOMS
Shortness of breath
Chronic cough
Sputum

RISK FACTORS
Host factors
Tobacco smoke
Occupation
Indoor/outdoor air pollution

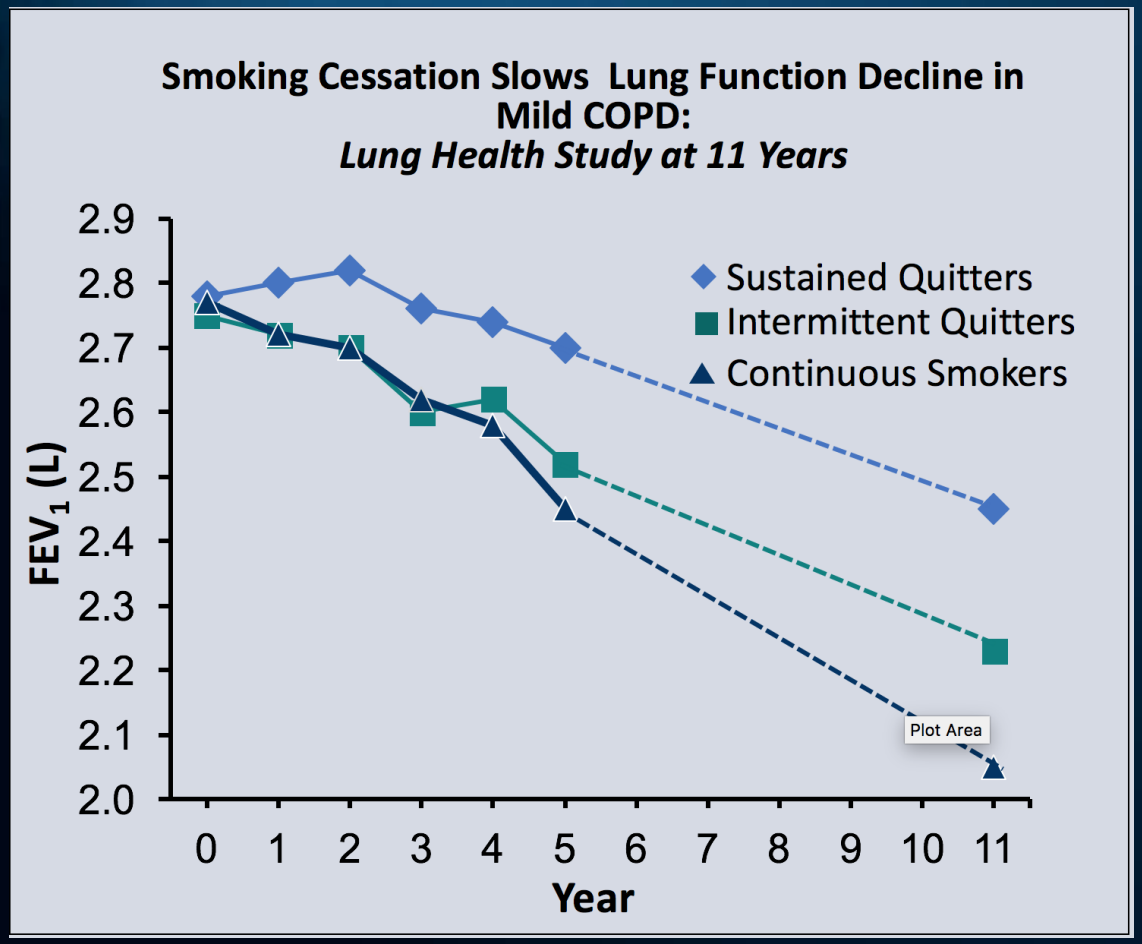
Spirometry is ***required*** to make diagnosis

Post-bronchodilator $FEV_1/FVC < 0.70$ confirms presence of *persistent* airflow limitation*

*Post-bronchodilator FEV_1/FVC measured 10-15 min after 2-4 puffs of a short-acting bronchodilator.
FEV_1, forced expired volume in 1 second; FVC, forced vital capacity.

Global Initiative for Chronic Obstructive Lung Disease. 2017 Report.
Available at http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/.

Does Early Diagnosis Improve Outcomes?



- Smoking cessation even at early stages of disease slows the decline of lung function.
- Does early detection of COPD with spirometry increase likelihood of smoking cessation?

Figure adapted from Anthonisen NR, et al. *Am J Respir Crit Care Med.* 2002;166:675-679. Calverley et al. *Lancet.* 2003;362:1053-1061. BMJ Publishing Group.

GOLD 2018: Classification of COPD Severity

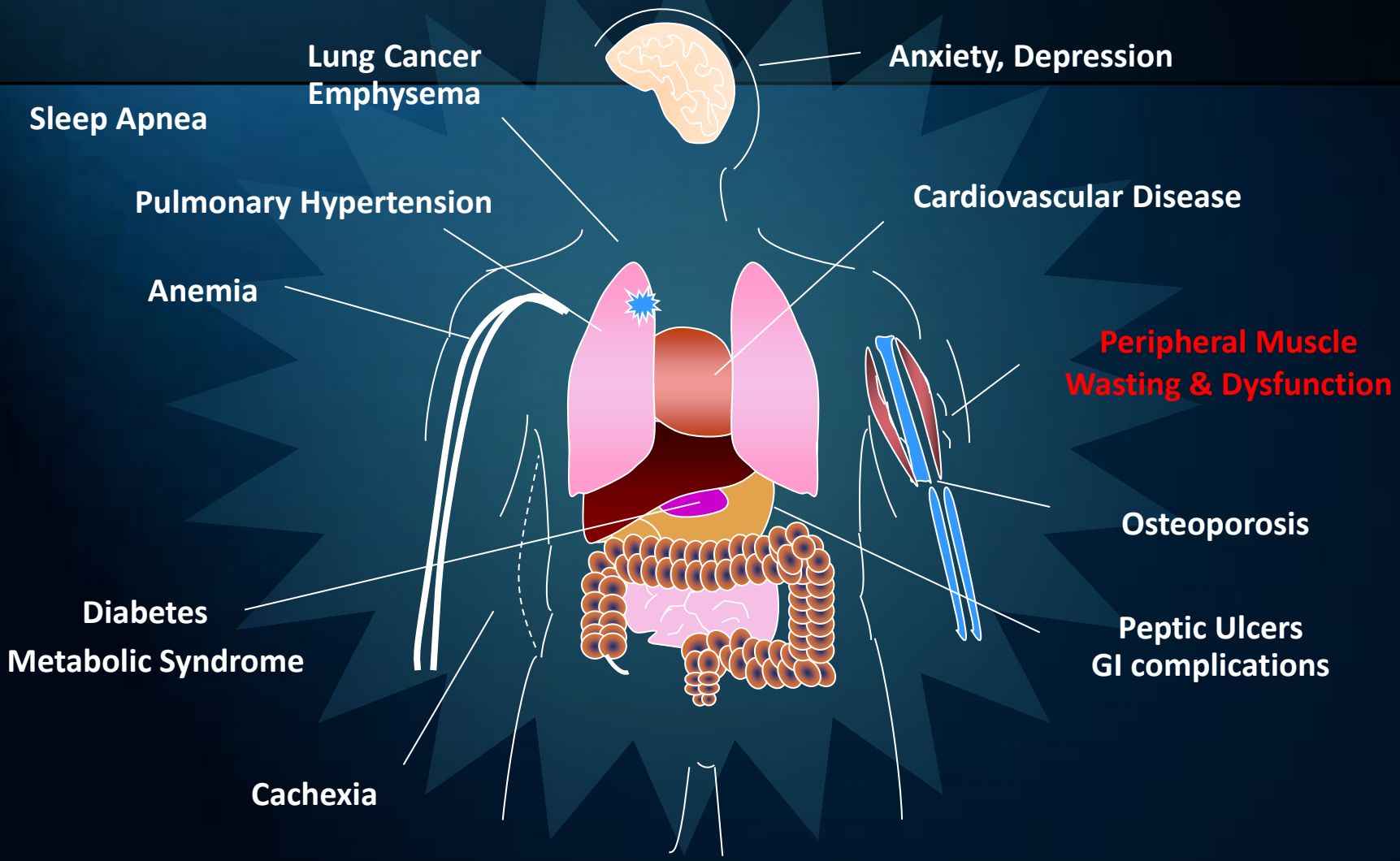
In patients with $FEV_1/FVC < 0.70$:

Category	Classification	FEV_1
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

- **Note: spirometry is generally used for diagnostic purposes; it is one element of measuring COPD severity**
- **Other measures (MRC dyspnea scale, exacerbation frequency, BMI; QoL assessment, and exercise capacity) build a more complete picture of severity**

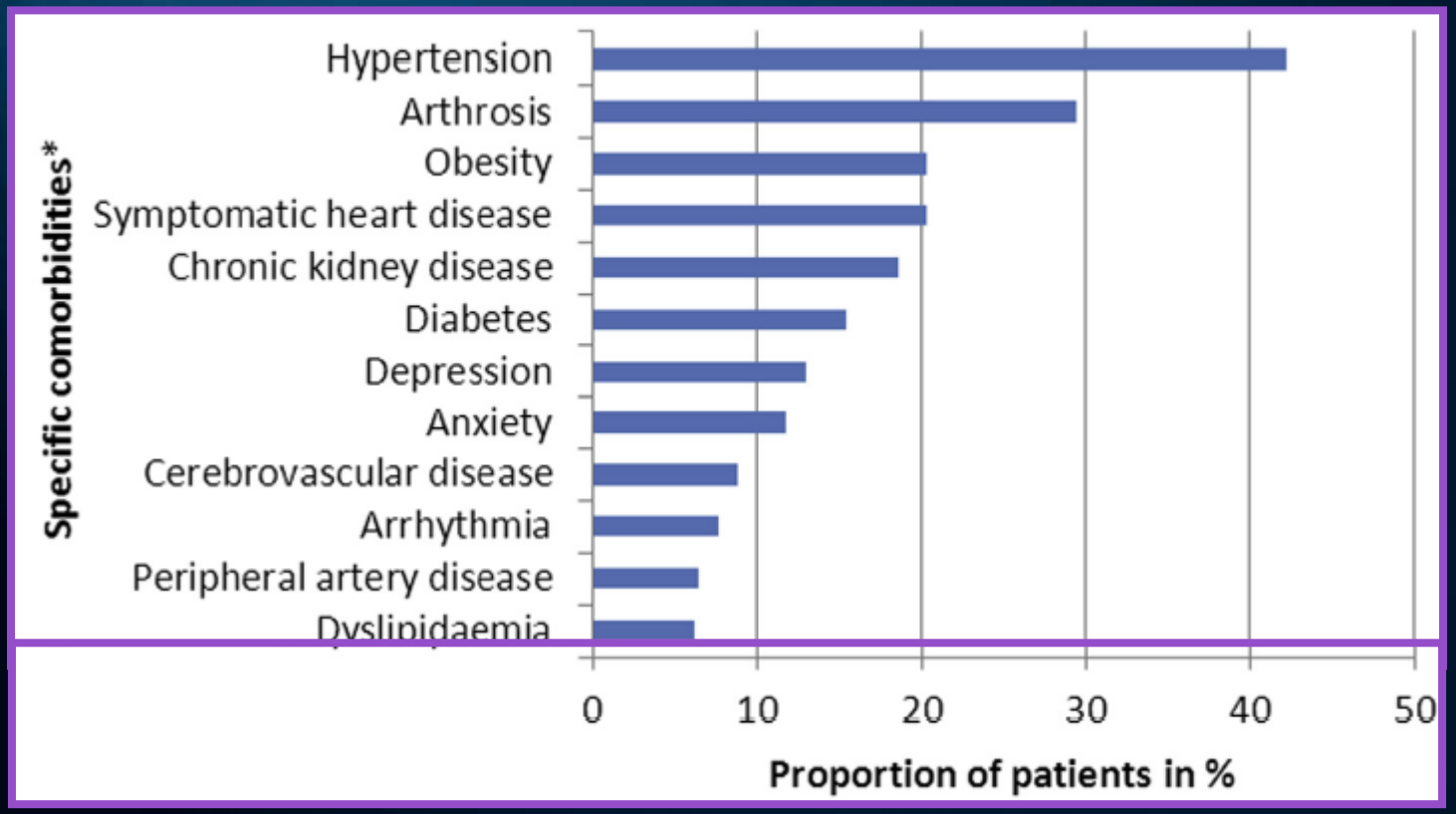
Agusti A, et al. GOLD 2018 update. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.

Comorbidities Are Common in COPD



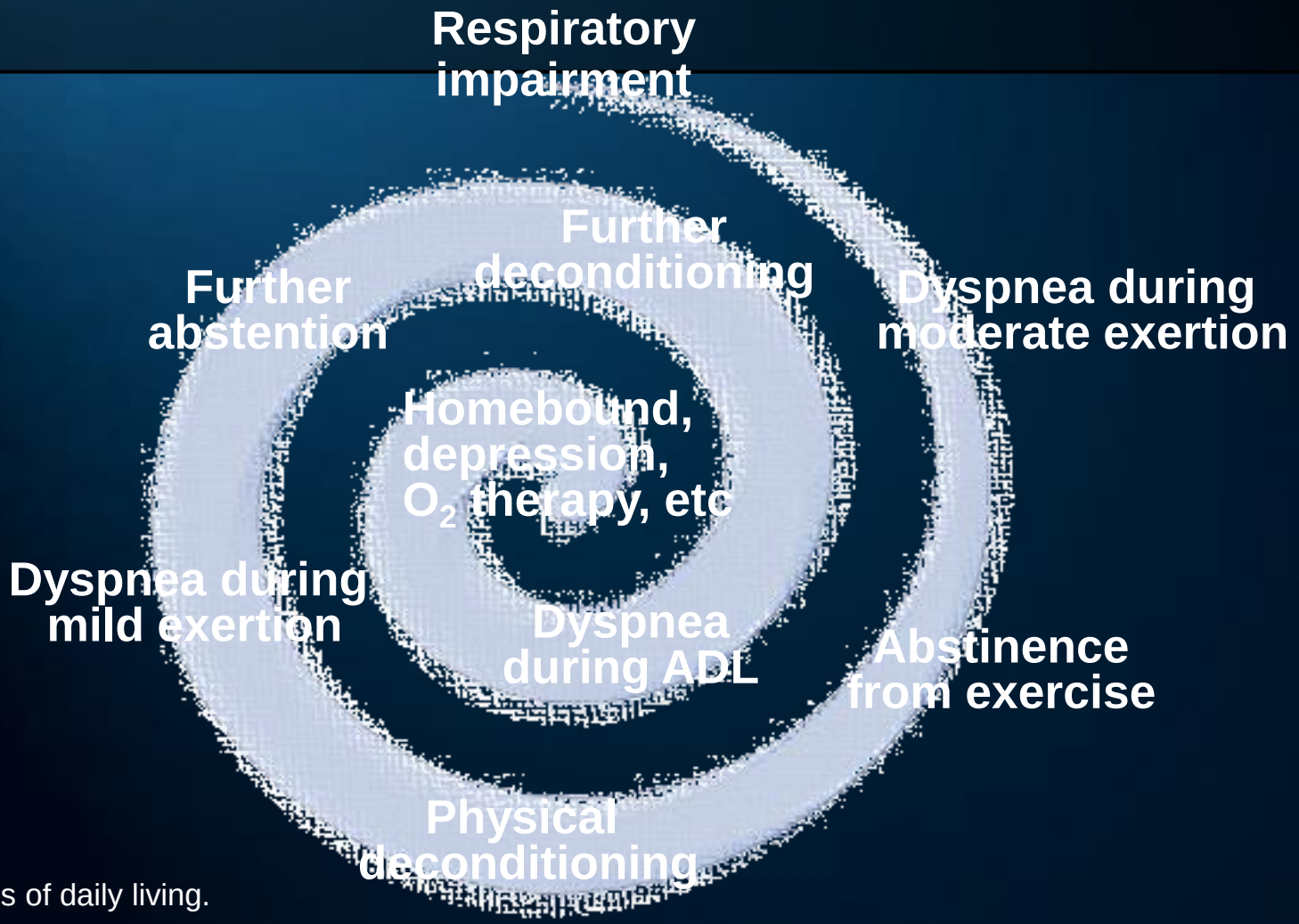
Adapted from Kao C et al. *Atlas of COPD*. 2008.
Barnes PJ et al. *Eur Respir J*. 2009;33:1165-1185.
Fishman A et al. *N Engl J Med*. 2003;348:2059-2073.

Comorbidities in COPD Disproportionate to Age Adjusted Population



Frei *J Clin Epi* '14

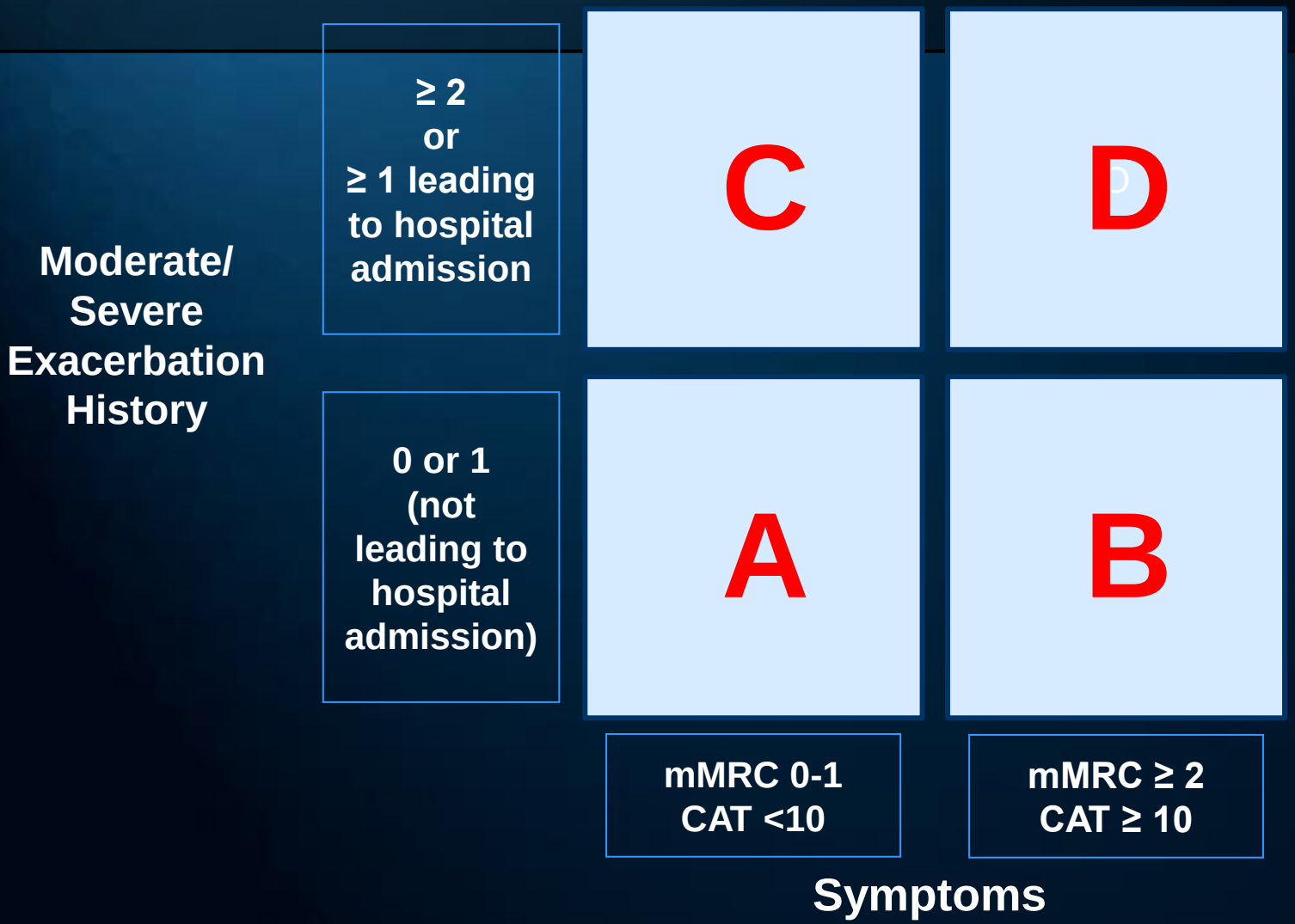
The Inactivity-Dyspnea Spiral



ADL, activities of daily living.

Adapted from Denis O´Donnell, MD.

GOLD Categories



mMRC: Modified Medical Research Council dyspnea scale; CAT: COPD Assessment Scale

Agusti A, et al. GOLD 2018 update. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.

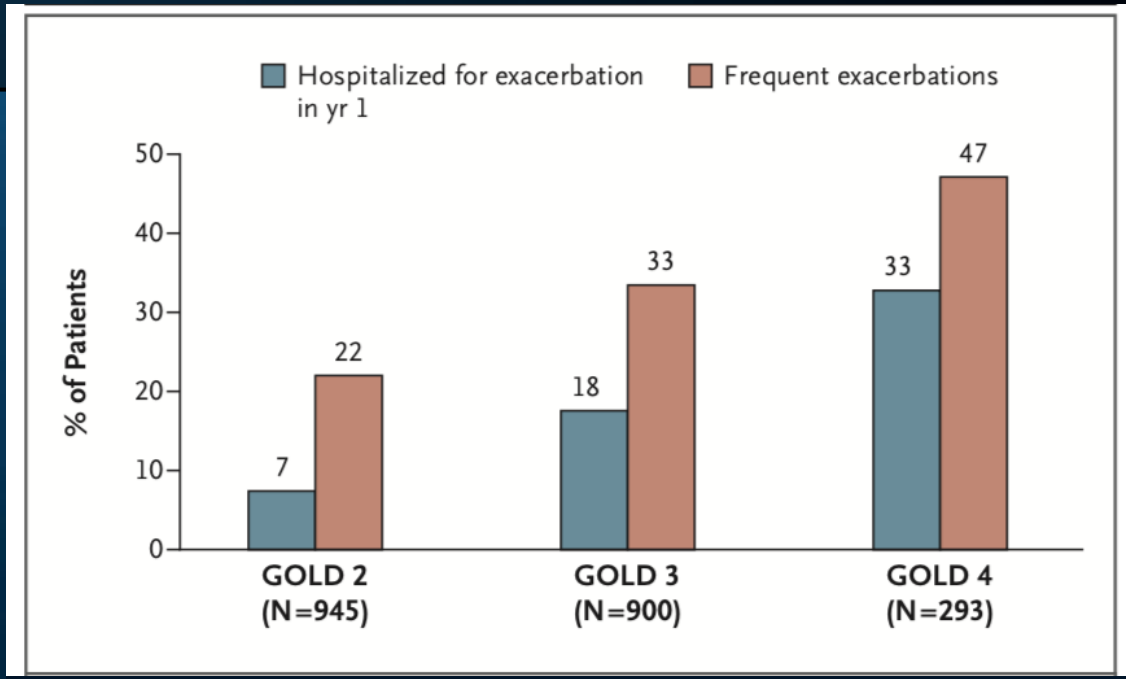
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

John R. Hurst, M.B., Ch.B., Ph.D., Jørgen Vestbo, M.D., Antonio Anzueto, M.D., Nicholas Locantore, Ph.D., Hana Müllerova, Ph.D., Ruth Tal-Singer, Ph.D., Bruce Miller, Ph.D., David A. Lomas, Ph.D., Alvar Agusti, M.D., Ph.D., William MacNee, M.B., Ch.B., M.D., Peter Calverley, M.D., Stephen Rennard, M.D., Emiel F.M. Wouters, M.D., Ph.D., and Jadwiga A. Wedzicha, M.D., for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators*

ABSTRACT



"Since moderate COPD is much more prevalent than very severe COPD, the overall burden of exacerbations may be greater in moderate disease."

IMPACT of PRIOR EXACERBATIONS in MODERATE COPD on FUTURE RISK

ORIGINAL ARTICLE

Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice–based Population with Chronic Obstructive Pulmonary Disease

Kieran J. Rothnie[1,2], Hana Müllerová[3], Liam Smeeth[2], and Jennifer K. Quint[1,2]

[1]Respiratory Epidemiology, Occupational Medicine and Public Health, National Heart and Lung Institute, Imperial College London, London, United Kingdom; [2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; and [3]Respiratory Epidemiology, GlaxoSmithKline R&D, Uxbridge, United Kingdom

ORCID ID: 0000-0003-4279-1624 (K.J.R.).

- 99,574 COPD patients from UK Clinical Practice Research Database
  - mean 67 yo
  - 70% GOLD 2/3
  - 52% smoker
- 10 years of follow-up, 2004 - 2015

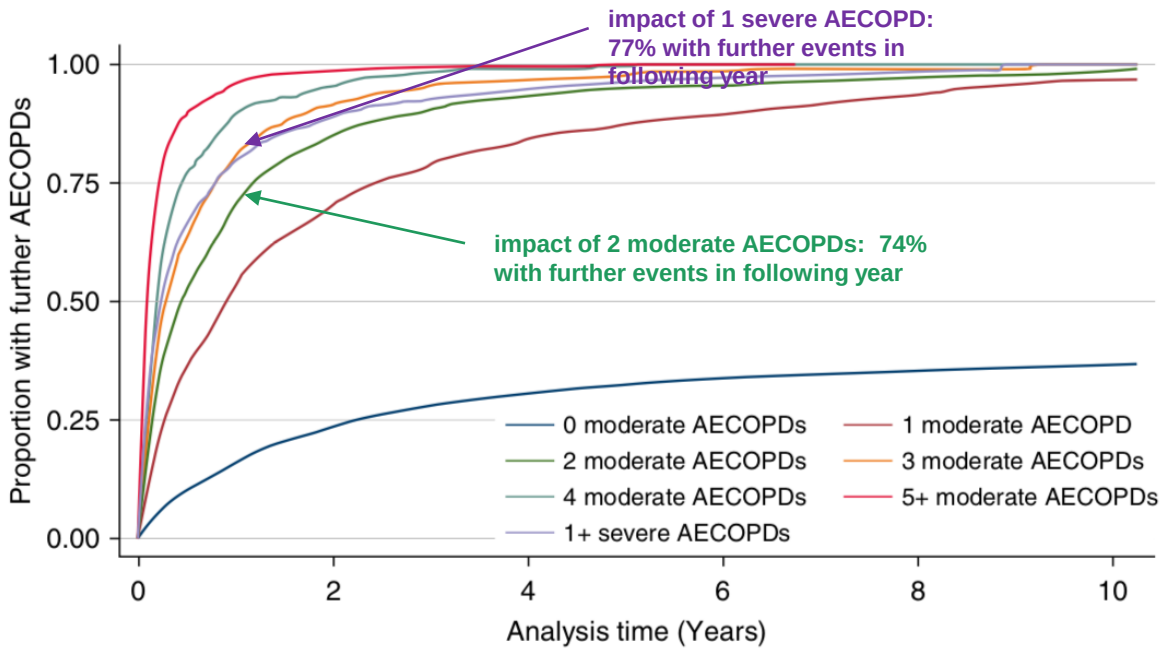


Figure 1. Time to first acute exacerbation of chronic obstructive pulmonary disease (AECOPD) by baseline AECOPD frequency and severity, established patients with chronic obstructive pulmonary disease.

Diagnosis and Treatment of COPD

- Impact and Diagnosis

- Treatment
  - General
  - “Precision” (Pulmonology Referral)

Therapeutic Goals in COPD

- Declining lung function: Slow ?
- Symptoms: Lessen
- Activity: Increase
- Exacerbations/hospitalizations: Reduce
- Quality of life: Improve
- Mortality: Reduce ?
- Costs: Lessen

Agusti A, et al. GOLD 2018 update. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.
Vestbo J, et al. Am J Respir Crit Care Med. 2013;187(4):347-65.

Management of COPD: Initial Focus on Prevention and Maintenance

Nonpharmacologic interventions

- **Smoking cessation**
- **Influenza**
- **Pneumococcal (Recommend PCV-13 and PPSV-23 in most per CDC recs)**
- **Avoidance of indoor/outdoor air pollution**
- **Reduce occupational exposure to irritants**
- **Encourage Physical activity/exercise training**

Pharmacologic Options in COPD

Bronchodilators

Short-Acting

Anticholinergic (SAMA):
Ipratropium

β-agonists (SABA):
Albuterol
Levalbuterol
Metaproterenol

SAMA + SABA:
Ipratropium + albuterol

Long-Acting

Anticholinergic (LAMA):
Tiotropium
Aclidinium (BID)
Umeclidinium
Revefenacin (nebulized)
Glycopyrrolate

β-agonists (LABA)
Salmeterol (BID)
Formoterol (BID, nebulized)
Arformoterol (BID, nebulized)
Indacaterol (QD)
Olodaterol (QD)

LAMA + LABA
Umeclidinium + vilanterol
Tiotropium + olodaterol
Indacaterol + glycopyrrolate (BID)
Formoterol + glycopyrrolate (BID)

Theophylline (pill)

Anti-Inflammatory

ICS + LABA

Fluticasone + salmeterol (bid)
Budesonide + formoterol (bid)
Fluticasone + vilanterol (qd)

ICS + LAMA + LABA

Fluticasone + vilanterol + Umeclidinium (qd)

Budesonide + Formoterol + Glycopyrrolate (bid)

PDE-4 inhibitors

Roflumilast (pill)

Antibiotic

Azithromycin* (pill)

Oral steroids

Prednisone*
Methylprednisolone*

*Not FDA-approved for use in COPD specifically.
SAMA, short-acting antimuscarinic agent; SABA, short-acting β2 andrenergic agent; LAMA, long-acting antimuscarinic agent; LABA, long-acting β2 andrenergic agent; ICS, inhaled corticosteroid; PDE-4, phosphodiesterase 4.

Clinical Review & Education

JAMA | Review

Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease
A Review

Craig M. Riley, MD; Frank C. Sciurba, MD

Pharmacologic Options in COPD

Table 1. Pharmacotherapy for COPD

Source	Class	Mechanism of Action	Medication Dose	Frequency	Device	Benefits[a]	Adverse Effects, %[b]
Short-Acting Inhaled Rescue Medications							
Combivent Inhalation Aerosol Study Group,[29] 1994	β_2-Agonist	Bronchodilation via airway smooth muscle β_2 receptor stimulation	Albuterol 180 or 200 µg	Every 4-6 h	pMDI, DPI	Mean peak effect vs placebo ↑FEV_1 170 mL	Headache, 3-5 Tachycardia, 2-3 Nasopharyngitis, 0-5 Muscle pain, 0-3 Dizziness, 0-3
			Albuterol 2.5 mg	Every 4-6 h	Nebulizer		
			Levalbuterol 90 µg	Every 4-6 h	pMDI		
			Levalbuterol 0.63 mg	Every 4-6 h	Nebulizer		
	Muscarinic antagonist	Inhibition of bronchoconstriction via airway smooth muscle M_1 and M_3 receptor blockade	Ipratropium 34 µg	4/d	pMDI	Mean peak effect vs placebo ↑FEV_1 170 mL	Dry mouth, 2 Nausea, 2 Flu-like symptoms, 2
			Ipratropium 0.5 mg	4/d	Nebulizer		
	Muscarinic antagonist and β_2-agonist combination	Bronchodilation via combination β_2 agonism and M_1 and M_3 receptor antagonism	Albuterol 100 µg and ipratropium 20 µg	4/d	SMI	Mean peak effect vs placebo, ↑FEV_1 240 mL	No difference vs monocomponents
			Albuterol 2.5 mg and ipratropium 0.5 mg	Every 4-6 h	Nebulizer		
Long-Acting Inhaled Maintenance Medications							
Karner et al,[32] 2014; Kew et al,[33] 2014	Muscarinic antagonist	Inhibition of bronchoconstriction via airway smooth muscle M_1 and M_3 receptor blockade	Aclidinium 400 µg	2/d	DPI	Mean peak effect vs placeb ↑FEV_1, 104 mL (82-125) ↓SGRQ, 2.6 U (2.0-3.5) ↓AE risk, 0.78 (0.70-0.87)[d]	Nasopharyngitis, 1-2 Dry mouth, 0-2
			Glycopyrrolate 15.6 µg	2/d[c]	DPI		
			Glycopyrrolate 25 µg	2/d	Nebulizer		
			Tiotropium 18 µg	Daily	DPI		
			Tiotropium 5 µg	Daily	SMI		
			Umeclidinium 62.5 µg	Daily	DPI		
			Revefenacin 88 µg	Daily	Nebulizer		
Kew et al,[33] 2014; Kew et al,[34] 2013	β_2-Agonist	Bronchodilation via airway smooth muscle β_2 receptor stimulation	Arformoterol 15 µg	2/d	Nebulizer	Mean peak effect vs placebo ↑FEV_1, 99 mL (72-128) ↓SGRQ, 2.3 U (1.5-3.2) ↓AE risk, 0.88 (0.76-1.02)	Nasopharyngitis, 1-3 Headache, 0-3 Muscle cramp, 1-2 Arthralgia, 0-2
			Formoterol 12 µg	2/d	DPI		
			Formoterol 20 µg	2/d	Nebulizer		
			Indacaterol 75 µg	Daily	DPI		
			Olodaterol 5 µg	Daily	SMI		
			Salmeterol 50 µg	2/d	DPI		
Oba et al,[35] 2016	Muscarinic Antagonist and β_2-agonist combination	Bronchodilation via combination β_2 agonism and M_1 and M_3 receptor antagonism	Glycopyrrolate 18 µg and formoterol 9.6 µg	2/d	pMDI	Mean peak effect vs placeb ↑FEV_1, 210 mL (190-230) ↓SGRQ, 4.6 U (3.3-5.9) ↓AE risk, 0.66 (0.57-0.77) vs LABA ↑FEV_1, 100 mL (80-130) ↓SGRQ, 2.3 U (1.3-3.3) ↓AE risk, 0.82 (0.73, 0.93) vs LAMA ↑FEV_1, 60 mL (50-80) ↓SGRQ, 2.3 U (1.7-2.9) ↓AE risk, 0.92 (0.84-1.00)	Nasopharyngitis, 1-2
			Indacaterol 27.5 µg and glycopyrrolate 15.6 µg	2/d[c]	DPI		
			Olodaterol 5 µg and tiotropium 5 µg	Daily	SMI		
			Umeclidinium 62.5 µg and vilanterol 25 µg	Daily	DPI		

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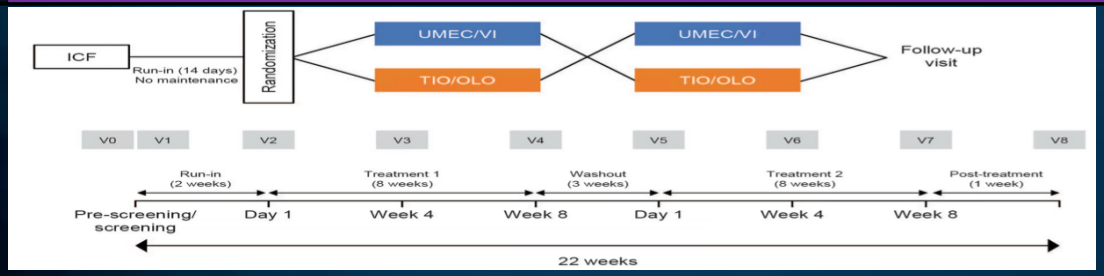
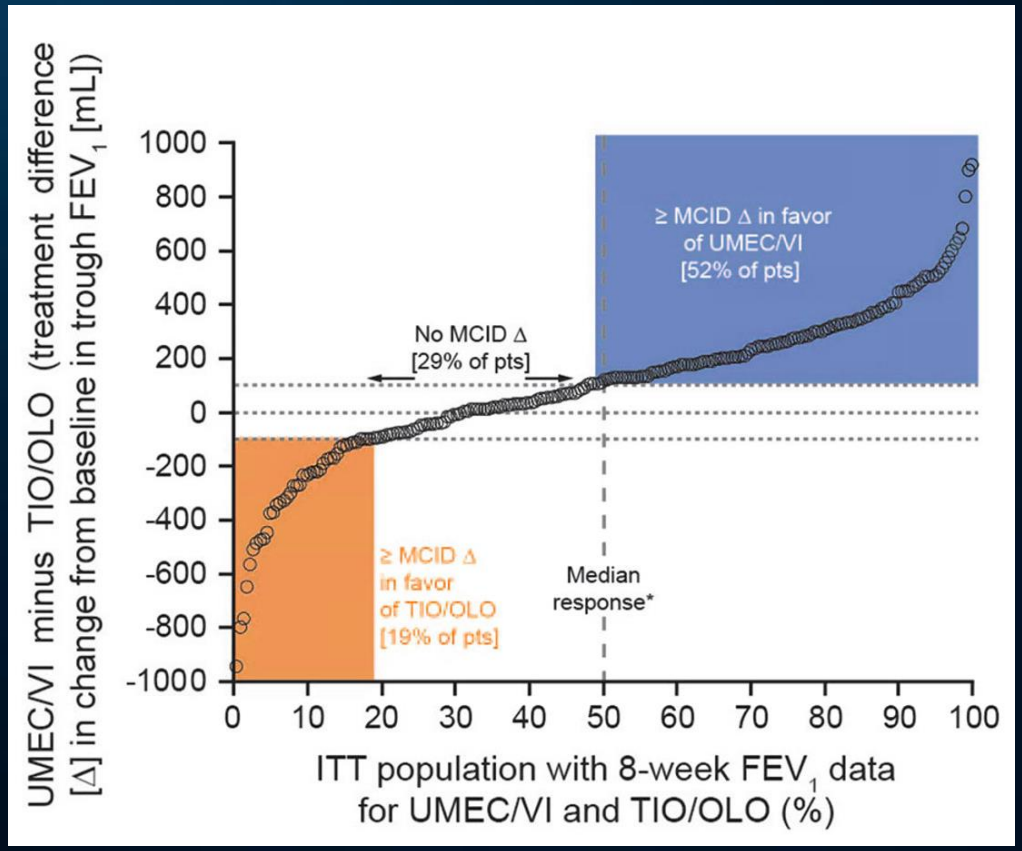
Comparative Efficacy of Two Dual Maintenance Bronchodilators: Individual Variation





Feldman et. al. Adv. Ther. 2017

Pharmacologic Options in COPD

Table 1. Pharmacotherapy for COPD (continued)

Source	Class	Mechanism of Action	Medication Dose	Frequency	Device	Benefits[a]	Adverse Effects, %[b]
Kew et al,[33] 2014; Rodrigo et al,[36] 2017; Nannini et al,[37] 2013	β_2-Agonist and ICS combination	Bronchodilation via airway smooth muscle β_2 receptor stimulation and decreased airway inflammation	Budesonide 320 µg and formoterol 9 µg	2/d	pMDI[e]	Mean peak effect vs placebo ↑FEV_1, 133 mL (101-164) ↓SGRQ, 3.9 U (3.0-4.7) ↓AE risk, 0.73 (0.69-0.78) vs combination LAMA and LABA ↓FEV_1, 60 mL (0-120) ↑SGRQ, 1.13 U (0.5-1.8) ↓AE risk, 1.22 (1.10-1.33)	Pneumonia, 3 Candidiasis, 1-9 Dysphonia, 1-5 Headache, 1-4 Nasopharyngitis, 1-2
			Fluticasone propionate 250 µg and salmeterol 50 µg	2/d	DPI		
			Fluticasone furoate 100 µg and vilanterol 25 µg	Daily	DPI		
Zeng et al,[38] 2018	Muscarinic antagonist, β_2-agonist, and ICS combination (Triple)	Combination bronchodilation via β_2 agonism and M_1 and M_3 receptor antagonism and decreased airway inflammation	Fluticasone furoate 100 µg, umeclidinium 62.5 µg and vilanterol 25 µg	Daily	DPI	Mean peak effect vs combination LAMA and LABA ↑FEV_1, 40 mL (20-70) ↓SGRQ, 1.81 U (1.04-2.57) ↓AE risk, 0.78 (0.70-0.88) Vs combination LABA and ICS ↑FEV_1, 110 mL (100-130) ↓SGRQ, 1.81 U (1.35-2.28) ↓AE risk, 0.77 (0.66-0.91)	Increase in event rate vs non-ICS regimens pneumonia: 3 vs combination LABA and ICS back pain, 2 Diarrhea, 1-2
Oral Medications							
Chong et al,[39] 2017	PDE4 inhibitors	Decreased airway inflammation and increased bronchodilation via inhibition of cAMP breakdown in inflammatory and airway smooth muscle cells	Roflumilast 500 µg	Daily	Tablet	Mean peak effect vs placebo ↑FEV_1, 52 mL (43-60) ↓SGRQ, 1.1 U (0.4-1.7) ↓AE risk, 0.78 (0.73-0.83)	Diarrhea, 7 Weight loss, 6 Any psychiatric disorder, 4 Nausea, 3 Headache, 2
Albert et al,[40] 2011	Macrolides	Decreased airway inflammation from decreased bacterial burden +/− impaired neutrophil chemotaxis	Azithromycin 250 mg[f]	Daily	Tablet	Mean peak effect vs placebo ↓SGRQ, 2.2 U (0.7-3.7) ↓AE risk, 0.83 (0.72-0.96)	Hearing impairment, 6

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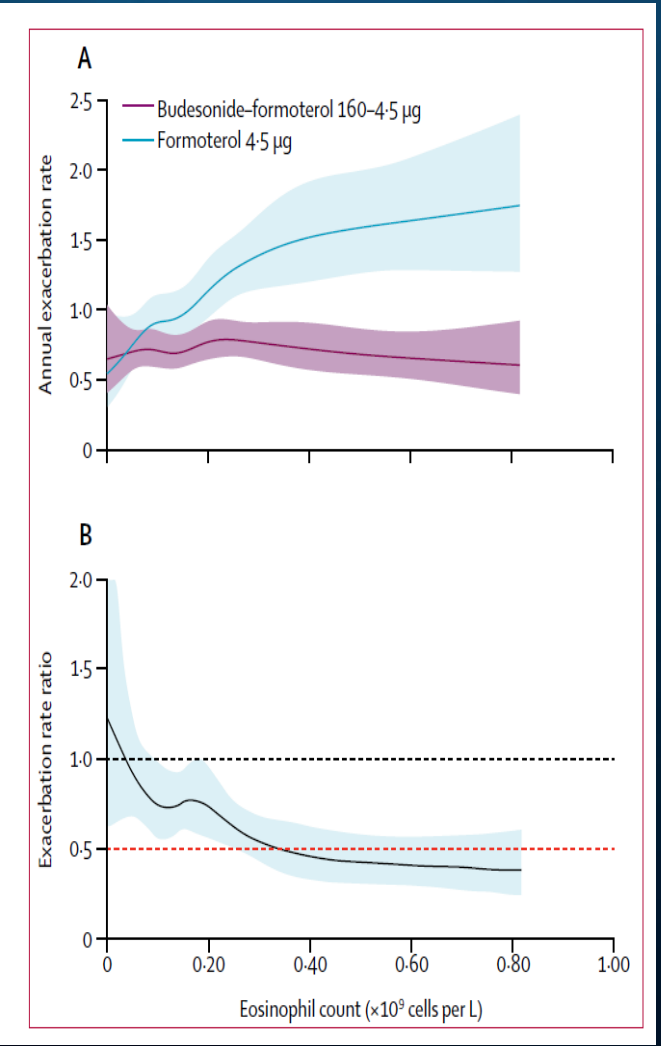
Eosinophils in COPD as a Predictor of Exacerbation Frequency and Response to ICS

n=4528



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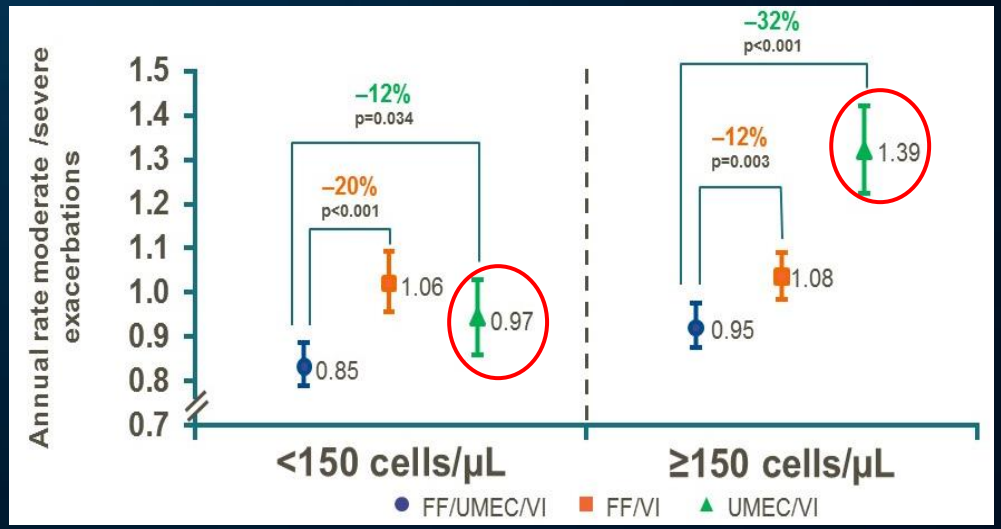


Bafadhel et al. Lancet Resp Med 2018;6:117-126

Lipson et al. NEJM 2018;378:1671-80

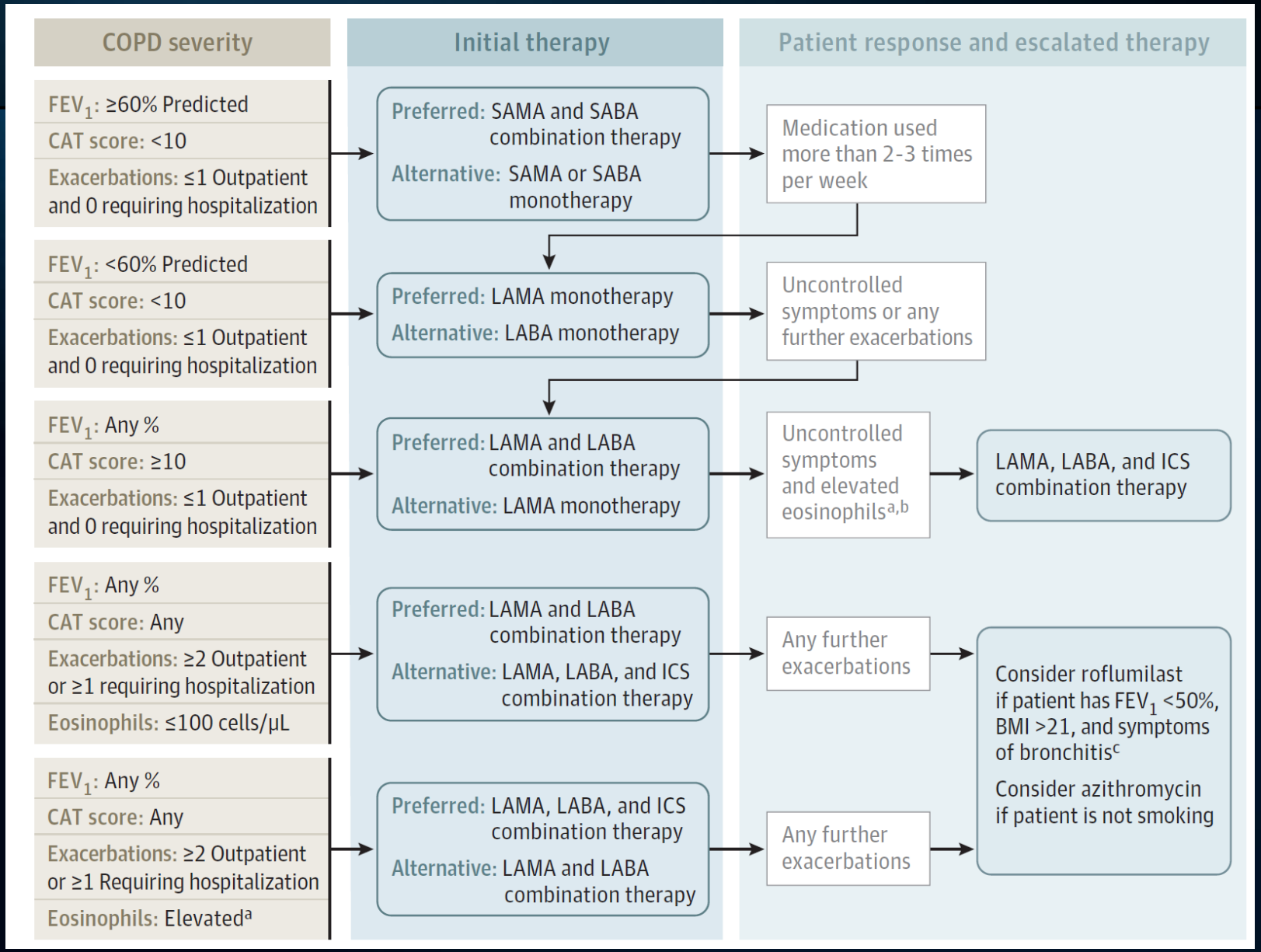
ICS Triple therapy vs. ICS/LABA vs LAMA/LABA Impact Trial

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

From *N Engl J Med.*, Lipson et. Al. 2018

Pharmacologic Options in COPD



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Considering Device Types

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Devices and Maintenance Inhalers.

	Powered Metered Dose Inhaler (pMDI)	Soft Mist Inhaler (SMI)	Dry Powder Inhaler (DPI): Single Dose	Dry Powder Inhaler (DPI): Multi-Dose	Nebulizer
Description	Medication and propellant contained in a pressurized cannister and propelled through a nozzle for inhalation.	Medication is propelled by a spring-loaded mechanism through a nozzle for inhalation.	Encapsulated medication is loaded prior to each dose, which is pierced by the device and delivered by patient inspiratory effort.	Doses of pre-loaded medication are delivered by patient inspiratory effort.	Medication is aerosolized by an air jet, ultrasonic energy or vibrating mesh and can be inhaled during normal tidal breathing.
Advantages	Patient familiarity (error rates (87%)	No spacer required Easier coordination of breath and actuation	Ease of use	Ease of use (error rates 61%)	No coordination or special breathing techniques
Pitfalls	Requires coordination of inhalation and actuation (improved with spacer)	Device assembly Limited medication options	Inadequate inspiratory flow rate Mishandling of capsules	Inadequate inspiratory flow rate Exposure to moisture	Less portable Requires frequent cleaning Limited medication options

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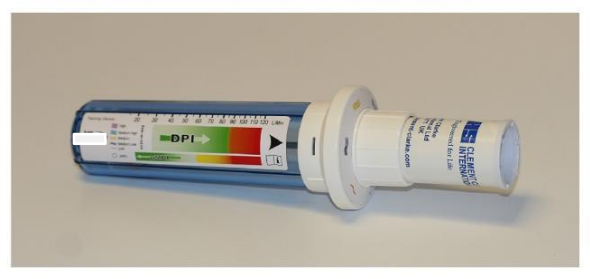
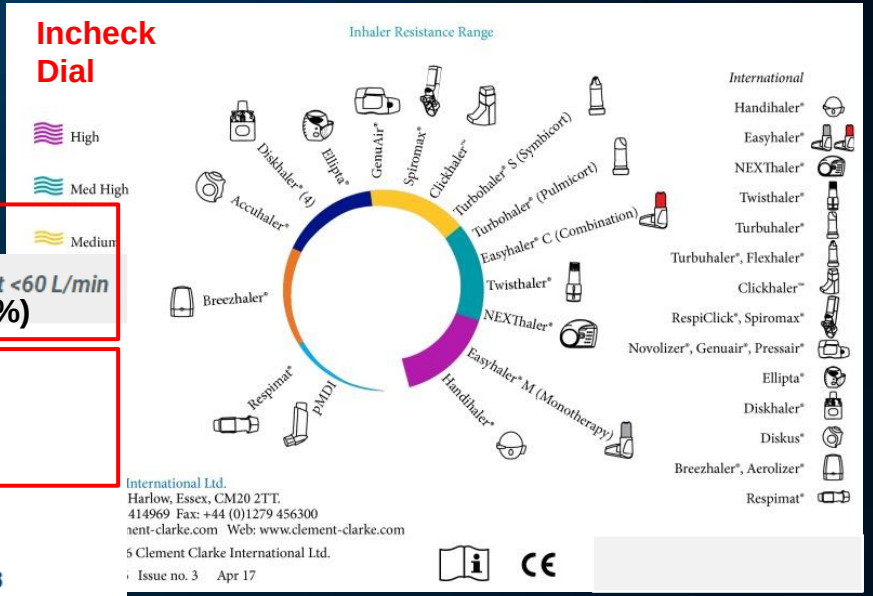
Global Initiative for Chronic Obstructive Disease (GOLD) 2014. www.goldcopd.com. Accessed 3/10/14.

COPD Phenotype for a Suboptimal Peak Inspiratory

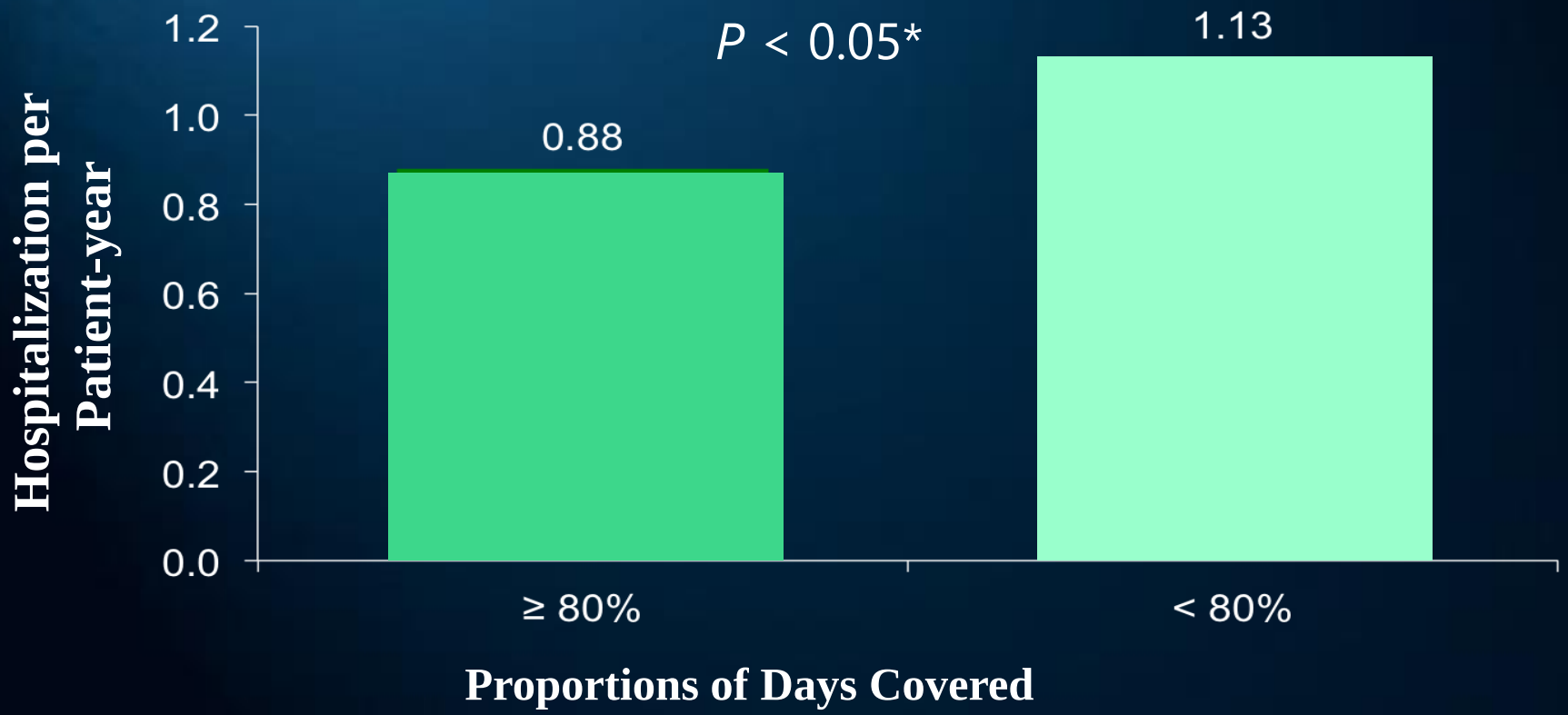




	Total	PIFRresist ≥60 L/min	PIFRresist <60 L/min (19%)
Number of subjects	213	172	41
Female/male	115/98	82/90	33/8
Age (yr)	70.1±6.9	69.9±7.1	71.3±6.0
Height (cm)	164.4±9.0	165.6±8.5	159.0±9.3
Weight (kg)	75.1±20.0	76.0±19.0	70.0±23.4
FEV1 (L)	0.92±0.26 (37±9%)	0.95±0.26 (38±8%)	0.77±0.23 (36±10%)
FVC (L)	2.51±0.84 (75±17%)	2.66±0.82 (77±16%)	1.91±0.64 (66±15%)

Mahler. J Aerosol Med Pulm Drug Deliv 2013;26:174–179

Higher Adherence to Therapy Lowers Risk for Hospitalization in COPD



Medicare Data: N = 33,816 patients

*Based on 95% CI for relative risk

Simoni-Wastila L, et al. Am J Geriatr Pharmacother. 2012;10:201-210.

Rationale for a Redundant Formulary

The Hawthorne Effect and the Art of Medicine

…it is likely that the heterogeneous population that comprises patients with COPD will include individuals who, in fact, will respond better to one than to another similar medication….

The ability to switch medications and to use all the available agents within a class may be best management for symptomatic support of the patient with COPD.

Sciurba & Rennard. AJRCCM 191:124, 2015

Hospital Discharge Planning

- In general, the use of maintenance bronchodilator therapy for COPD is lacking1
- At discharge only 45% were prescribed maintenance bronchodilators
- At discharge, 23% were not prescribed an inhaled therapy at all

Make B, et al. Int J Chron Obstruct Pulmon Dis. 2012;7:1-9.

Yip NH, et al. COPD. 2010;7(2):85-92.

Pharmacotherapy Management of COPD
HEDIS® metrics

Description: The percentage of COPD exacerbations for members 40 years of age and older who had an acute inpatient discharge or ED visit with a principal diagnosis of COPD, emphysema, or chronic bronchitis and who were dispensed appropriate medications.

Two rates are reported:

- **1. Dispensed a Systemic Corticosteroid (or there was evidence of an active prescription) within 14 days of the event.**
- **2. Dispensed a Bronchodilator (or there was evidence of an active prescription) within 30 days of the event.**

Nonpharmacologic Treatments

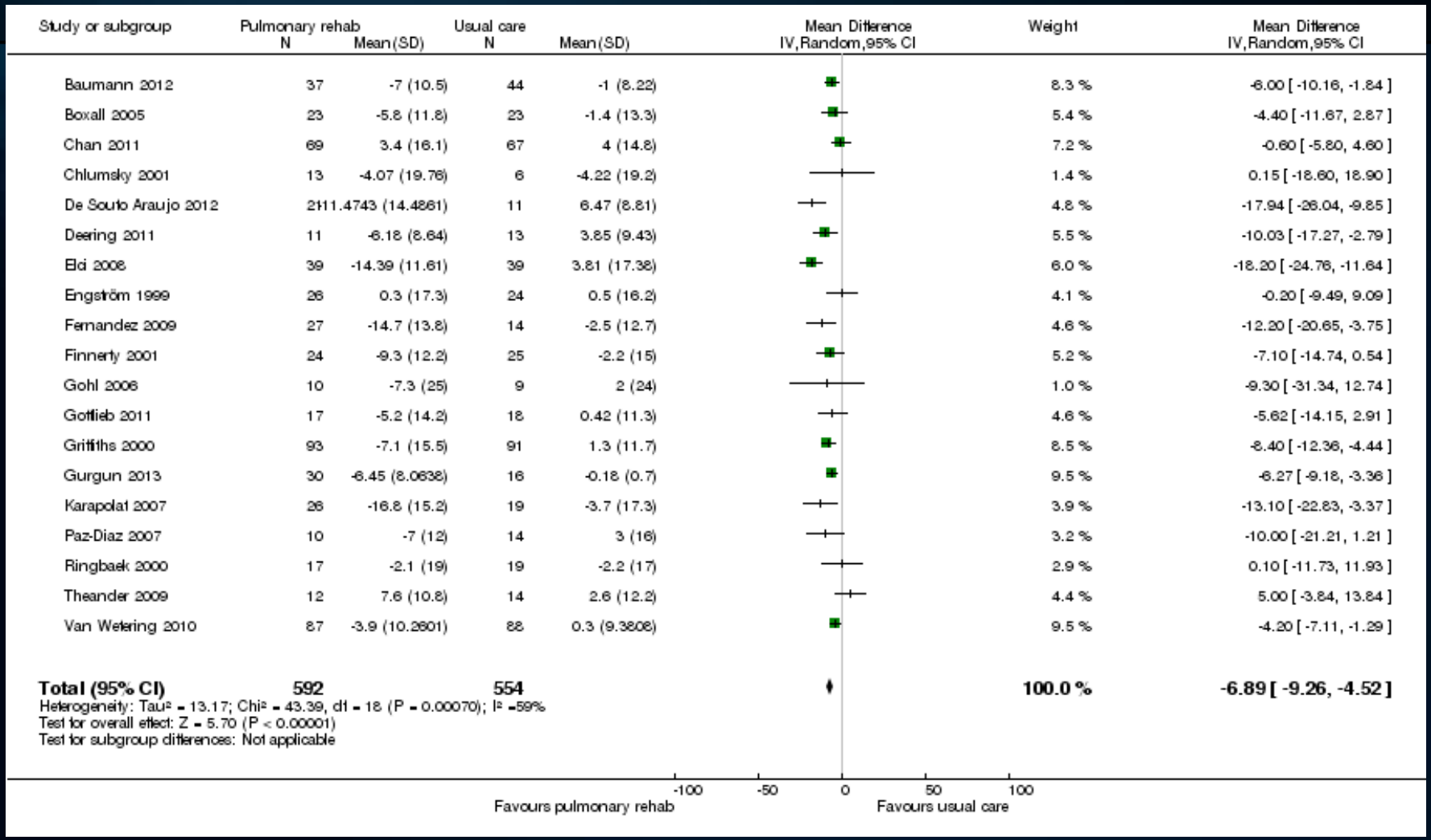
Pulmonary Rehabilitation

Global Initiative for Chronic Obstructive Disease (GOLD) 2014. www.goldcopd.com. Accessed 3/10/14.

Comparison of Different COPD Treatments

	Bronchodilator	Oxygen	Rehabilitation
Exercise Tolerance	↑	↑↑	↑↑↑
Dyspnea	↑	↑↑	↑↑↑
Quality of Life	↑	↑↑	↑↑↑
Duration of Benefit after Withdrawal	Days	Minutes	Months-years

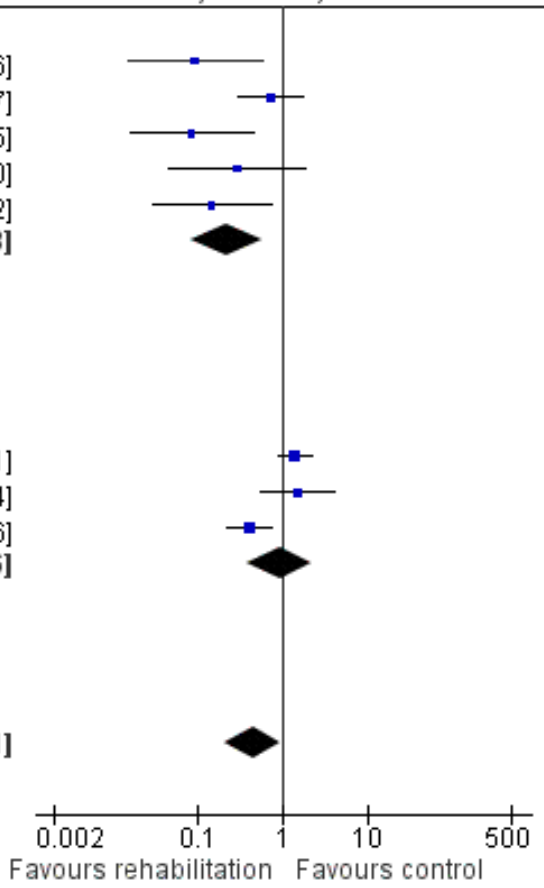
Pulmonary rehabilitation improves Quality of Life



McCarthy et al. Cochrane Database of Systematic Reviews 2015, issue 2.

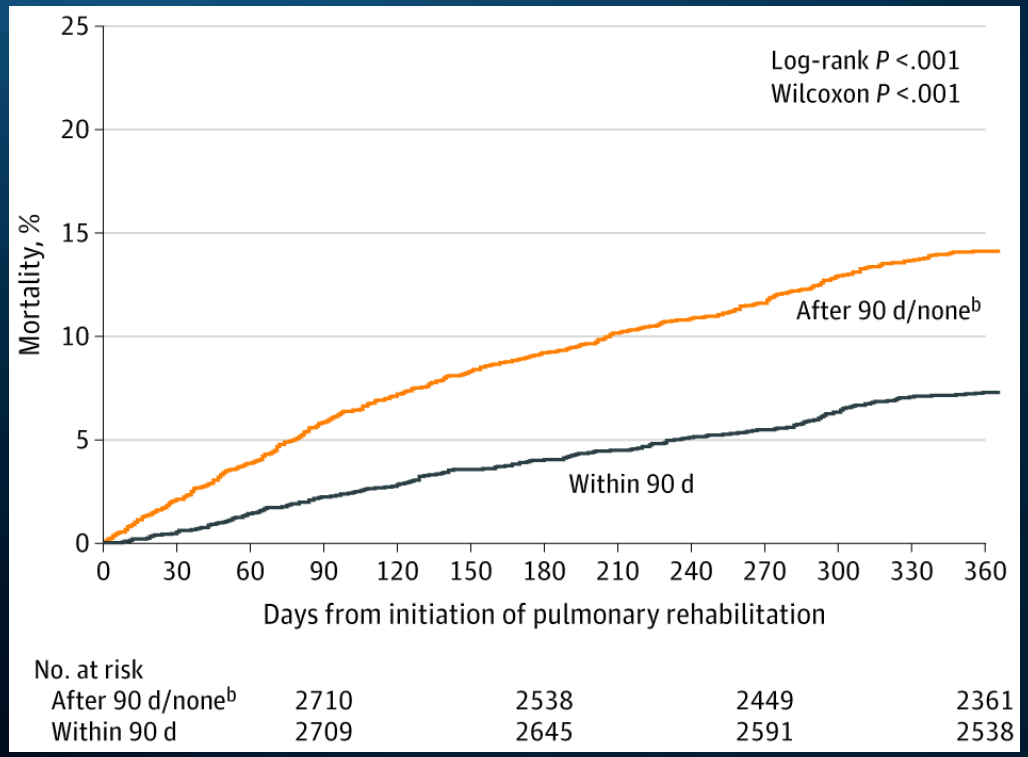
Pulmonary rehab decreases hospital admissions

Study or Subgroup	Pulmonary rehab Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.37.1 Existing trials						
Behnke 2000	3	14	9	12	8.8%	0.09 [0.01, 0.56]
Eaton 2009	11	47	15	50	14.8%	0.71 [0.29, 1.77]
Man 2004	2	20	12	21	9.5%	0.08 [0.02, 0.45]
Murphy 2005	2	13	5	13	8.5%	0.29 [0.04, 1.90]
Seymour 2010	2	30	10	30	9.9%	0.14 [0.03, 0.72]
Subtotal (95% CI)		**124**		**126**	**51.4%**	**0.22 [0.08, 0.58]**
Total events	20		51			
Heterogeneity: Tau² = 0.61; Chi² = 8.15, df = 4 (P = 0.09); I² = 51%						
Test for overall effect: Z = 3.06 (P = 0.002)						
1.37.2 New trials added						
Greening 2014	108	169	84	151	17.8%	1.41 [0.90, 2.21]
Ko 2011	16	30	13	30	14.0%	1.49 [0.54, 4.14]
Ko 2016	44	90	63	90	16.8%	0.41 [0.22, 0.76]
Subtotal (95% CI)		**289**		**271**	**48.6%**	**0.93 [0.38, 2.26]**
Total events	168		160			
Heterogeneity: Tau² = 0.49; Chi² = 11.00, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**413**		**397**	**100.0%**	**0.44 [0.21, 0.91]**
Total events	188		211			
Heterogeneity: Tau² = 0.74; Chi² = 29.80, df = 7 (P = 0.0001); I² = 77%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Test for subgroup differences: Chi² = 4.65, df = 1 (P = 0.03), I² = 78.5%						



Puhan et al. Cochrane Database of Systematic Reviews 2016, issue 12.

Association Between Initiation of Pulmonary Rehabilitation After Hospitalization for COPD and 1-Year Survival (Restrospective)



JAMA. 2020;323(18):1813-1823. doi:10.1001/jama.2020.4437

Barriers to PR uptake and referral

- Travel distance and transportation
- Health system resources
- Illness burden
- Physician knowledge
- Patient knowledge
- Beliefs about consequences

Cox et al. Journal of Physiotherapy 2017; 63(2).
Keating et al. Journal of Physiotherapy 2011; 57(3).

Managing Chronic Respiratory Failure

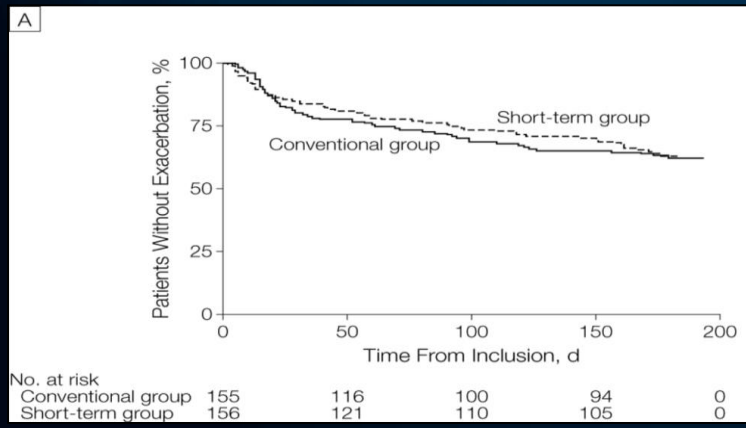
- **Hypoxemia**
  - At rest
  - With exertion
  - Overnight
- **Hypercapnia**
  - NIV in COPD without OSA

Acute Exacerbations of COPD

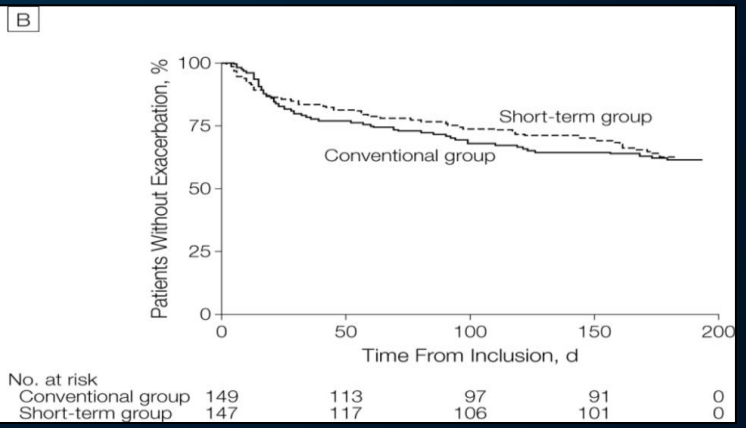
A 5-day Course of Oral CS May Be Appropriate after COPD Exacerbations

Re-exacerbations in the REDUCE Trial

Proportion of patients without re-exacerbation
ITT analysis
HR, 0.95 (90% CI, 0.70-1.29)
***P* for noninferiority = 0.006**



Proportion of patients without re-exacerbation
Per-protocol analysis
HR, 0.93 (90% CI, 0.68-1.26)
***P* for noninferiority = 0.005**



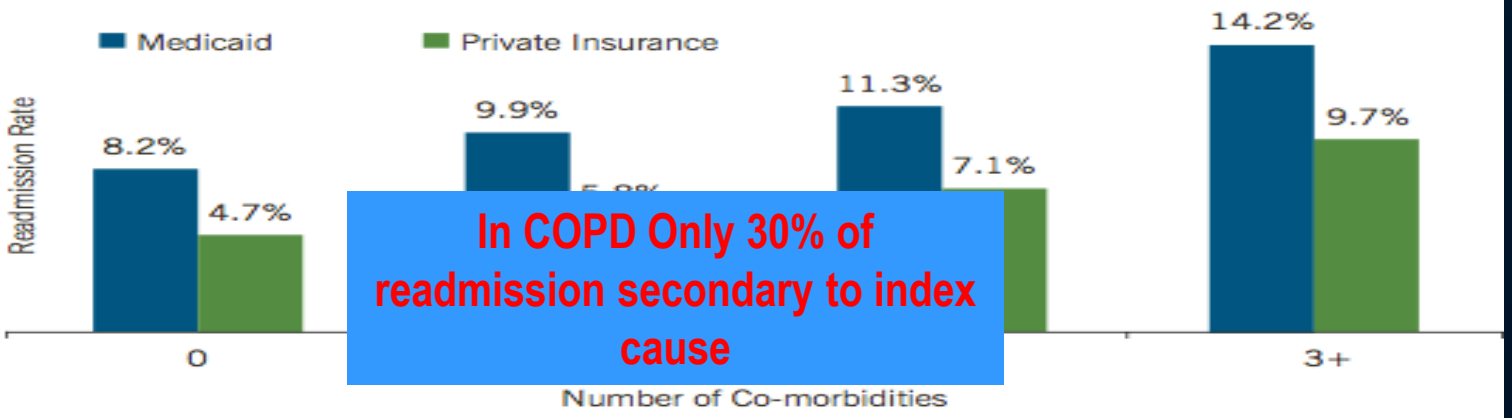
ITT = intention to treat; REDUCE = Reduction in the Use of Corticosteroids in Exacerbated COPD

Lueppi JD et al. *JAMA.* 2013;309:2223-2231.

Comorbidities and Social Issues Have a Significant Impact on Readmissions

Medicaid beneficiaries are consistently at greater risk of readmission than privately insured adults.

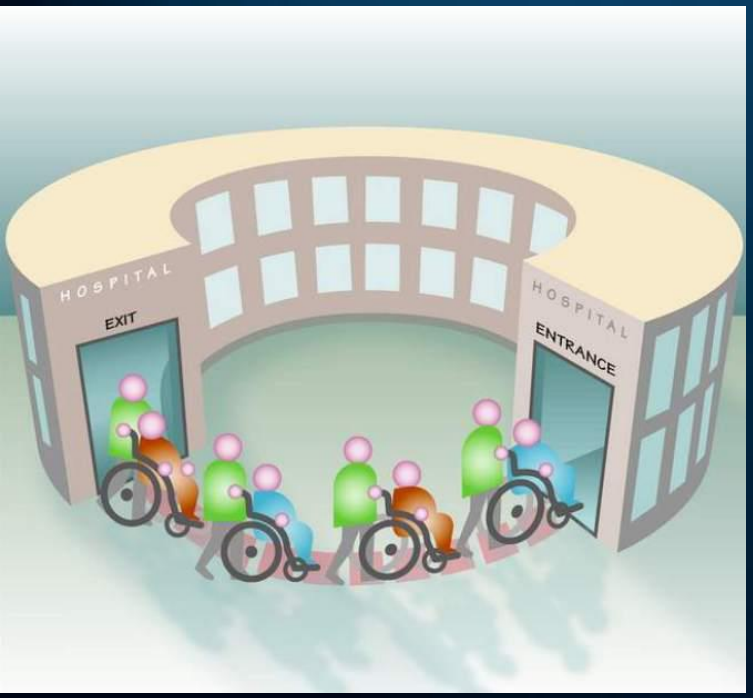
Chart 5: Non-obstetric, Adult 30-day Readmission Rates by Insurance Coverage and Number of Co-morbidities, 2007



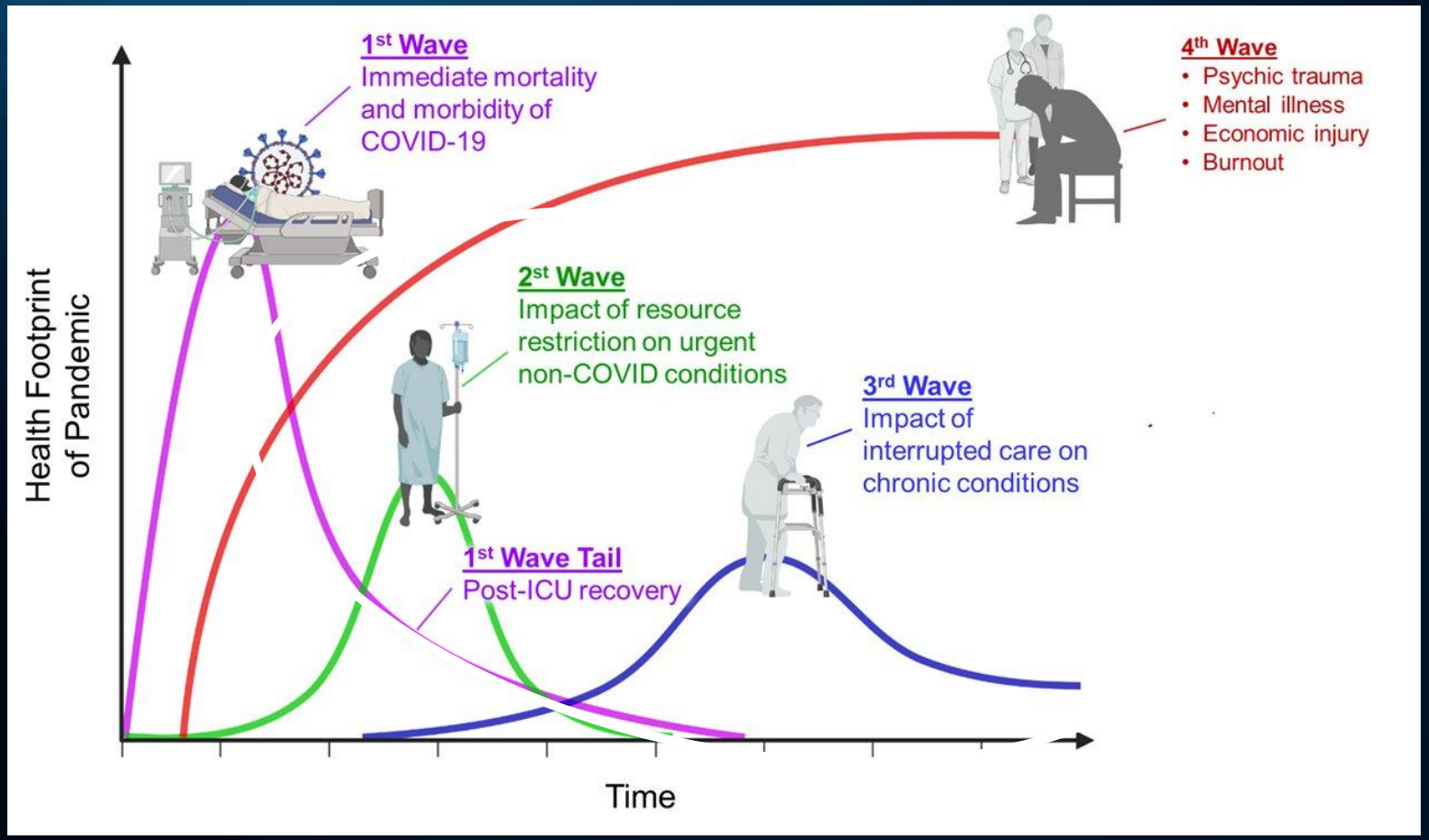
In COPD Only 30% of readmission secondary to index cause

Source: Jiang, H.J., and Wier, L.M. (April 2010). *All-cause Hospital Readmissions among Non-elderly Medicaid Patients, 2007.* HCUP Statistical Brief #89. Rockville, MD: Agency for Healthcare Research and Quality.

Preventing Readmission/The Next Admission



- **When to schedule follow up?**
  - Preferably within 1 week
  - At most, within 2 weeks
- **Who should see pulmonary?**
  - Multiple hospitalizations within 12 months
  - High baseline symptoms despite maximal inhaled therapy and pulmonary rehab
  - Severe obstruction in younger patients and/or rapid FEV1 decline



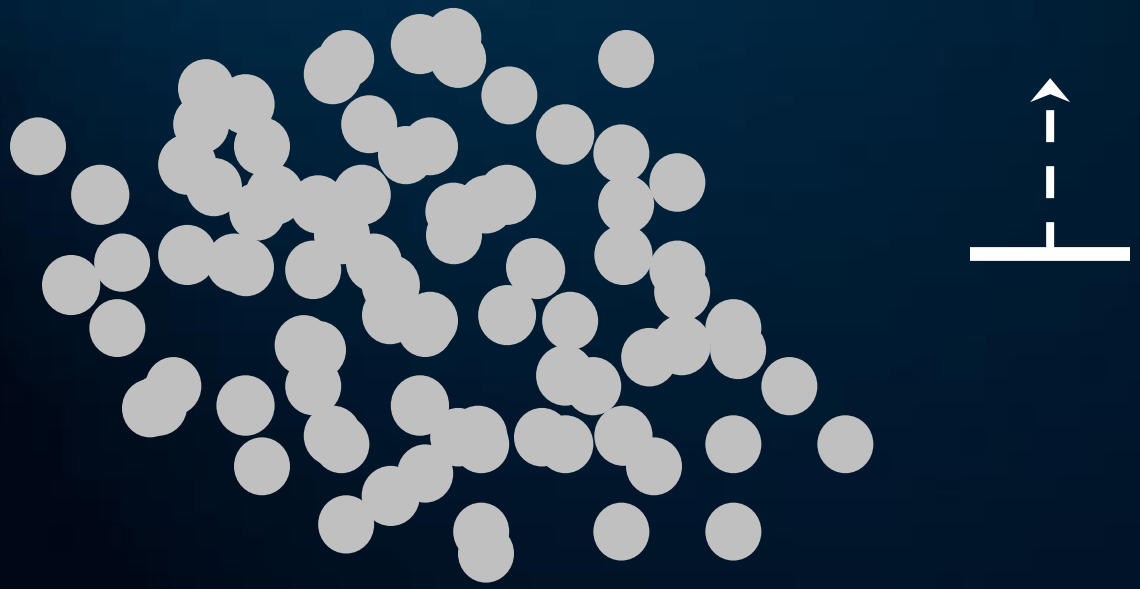
Victor Tseng, @VectorSting
Twitter 3/30/2020

Diagnosis and Treatment of COPD

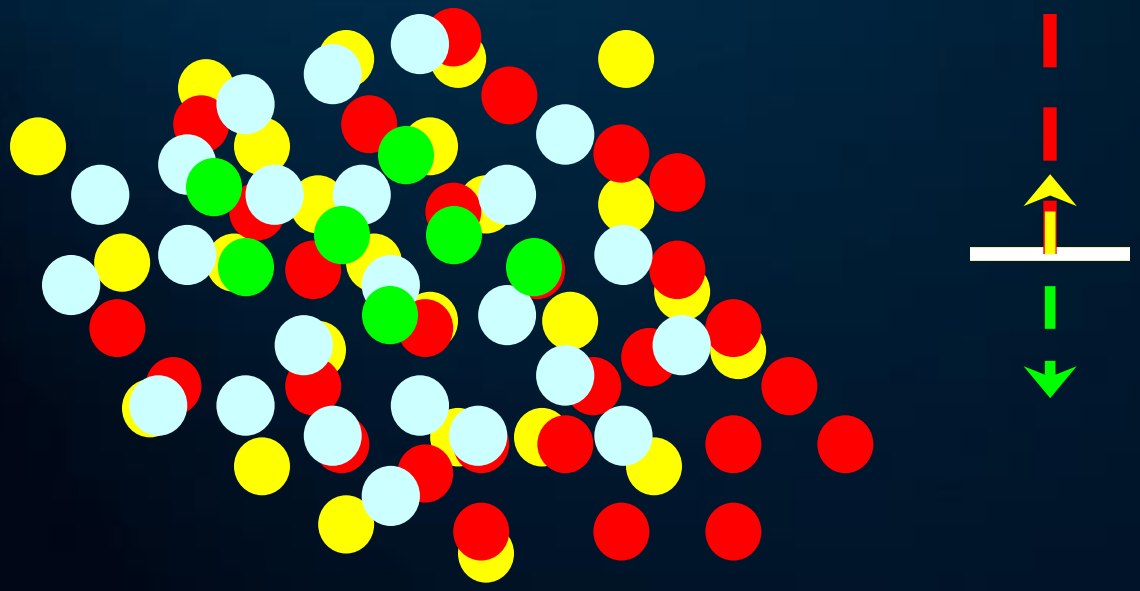
- Impact and Diagnosis

- Treatment
  - General
  - “Precision” (Pulmonology Referral)

Response of a Population to an Intervention: Blind to Phenotype



Response of a Population to an Intervention: Precision Approach



COPD Foundation Guideline Clinical Phenotype Based Reclassification of COPD

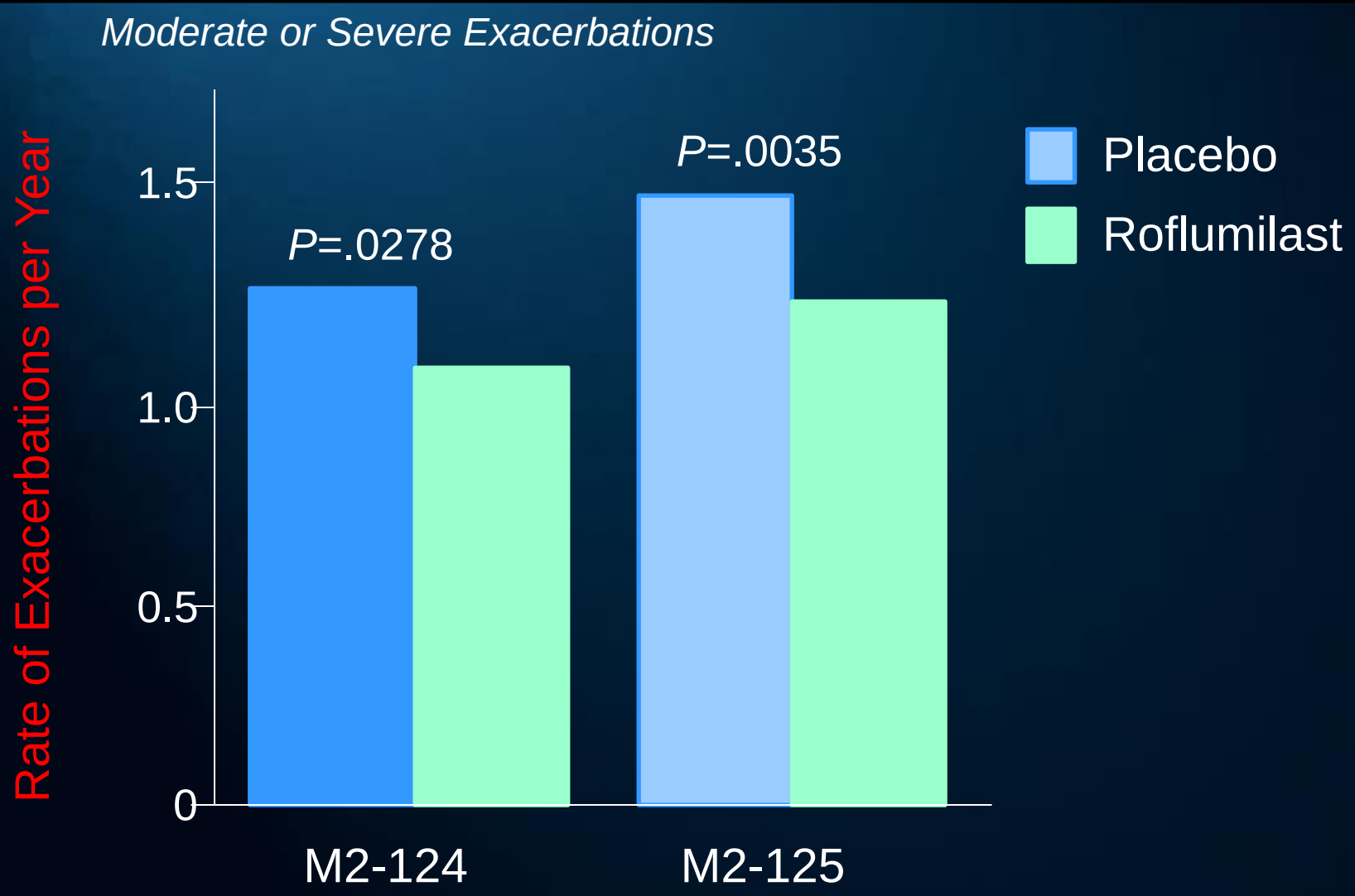
All patients should receive: Smoking cessation; vaccination for influenza, pneumococcus, pertussis, alpha-1 testing

	short acting bronchodilator (as needed)	LAMA or LABA or LAMA plus LABA	ICS/LABA	roflumilast	oxygen	exercise/ pulmonary rehabilitation	lung volume reduction surgery	azithromycin
Spirometry Grade SG1 Mild	✓	✓+						
SG 2/3 Moderate/Severe	✓	✓	✓	✓*				
Regular symptoms	✓	✓	✓			✓**		
Exacerbation risk high		✓++	✓++	✓*				✓++
Oxygenation severe hypoxemia					✓			
episodic hypoxemia					✓			
Emphysema							✓‡	
Chronic bronchitis				✓*				
Comorbidities	✓ Evaluate and treat identified comorbid conditions							

*Indicated if chronic bronchitis, high exacerbation risk, and spirometry grades 2/3 all present
**Suggest regular exercise program for all with COPD; those with SG2/3 should be considered for pulmonary rehab
+Recommended in select cases with upper lobe predominant emphysema
++Off label, consider potential cardiac risks and resistance concerns

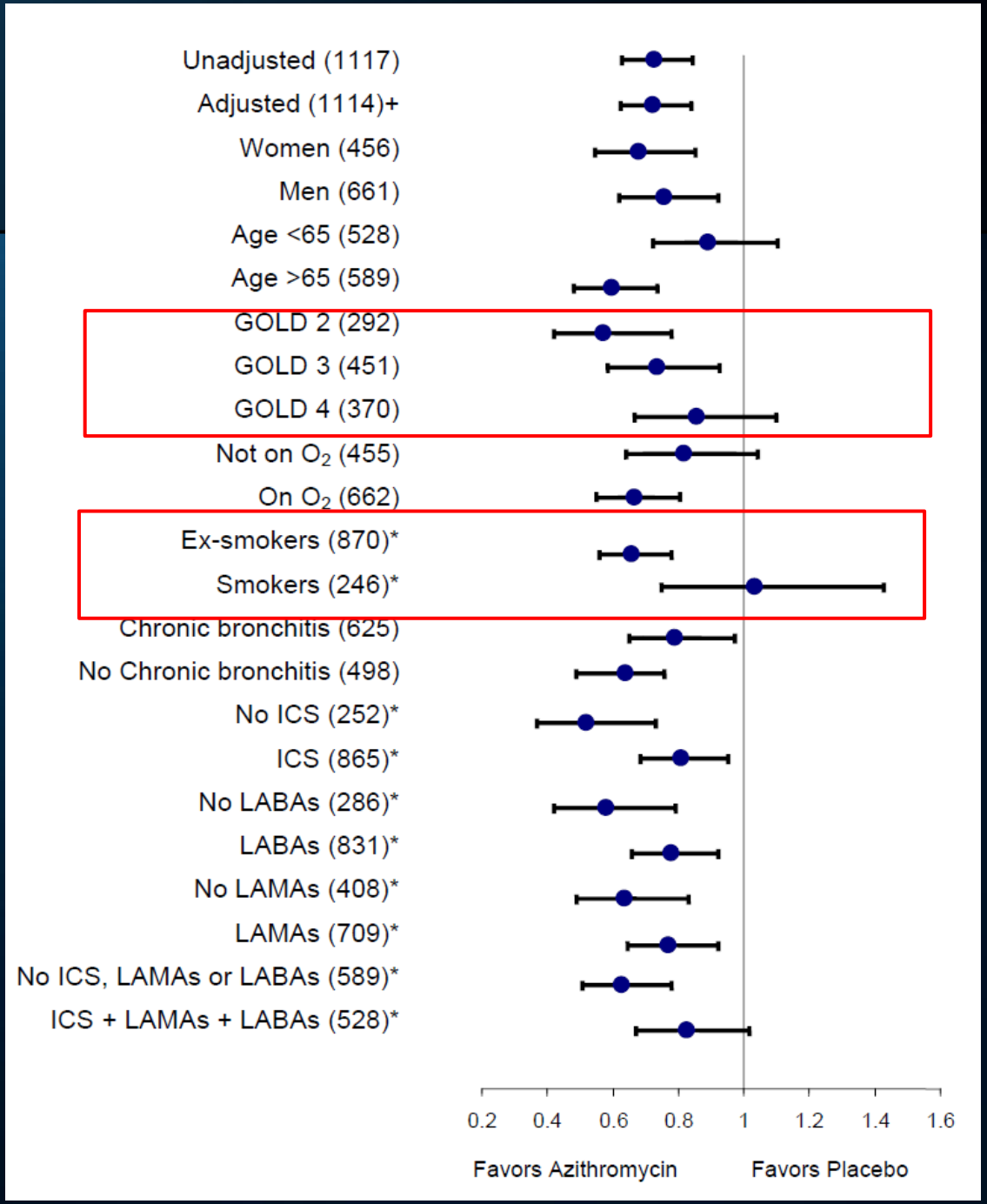
COPD Foundation. COPD Treatment. www.copdfoundation.org/Learn-More/For-Medical-Professionals/Treatment.aspx. Accessed 2/8/14.

Effect of PDE4 Inhibitor (Roflumilast) in Chronic Bronchitic Frequent Exacerbators (FEV1 < 50%pr.)

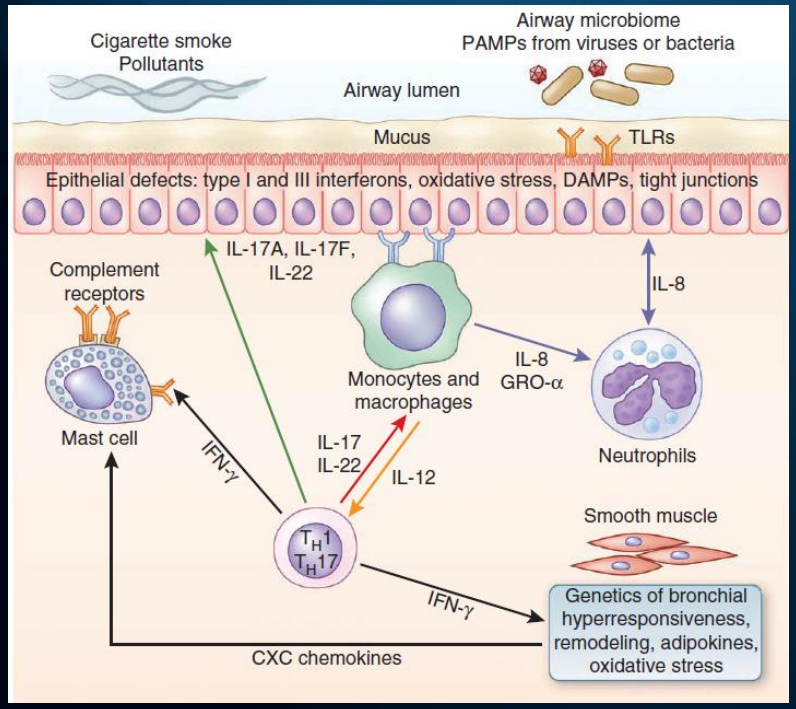


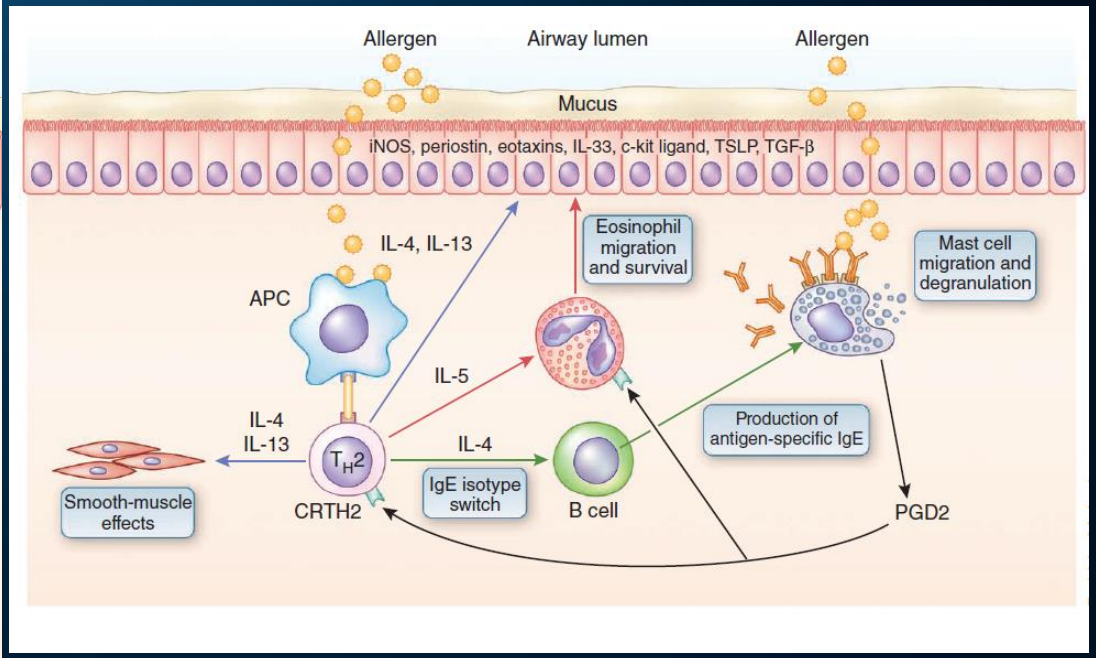
Calverley PM, et al. *Lancet.* 2009;374(9691):685-694.

Azithromycin in COPD: Subgroup analyses.



Inflammatory Pathways in Obstructive Lung Disease: Opportunities for Precision Therapy



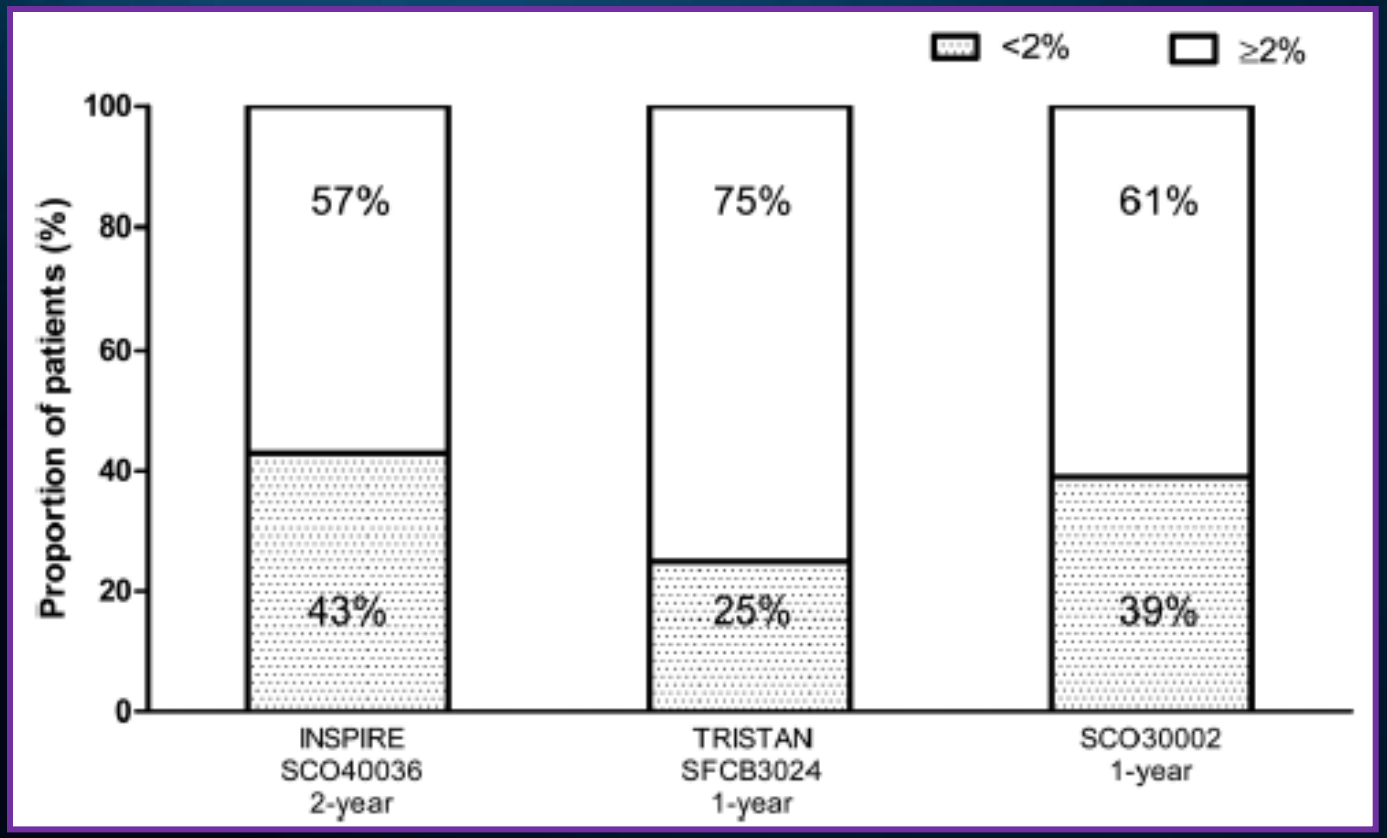


TH1 (Traditional COPD pathways)

TH2 (Traditional Asthma pathways)
?COPD Overlap

Wenzel. Nature Med 2012

Eosinophil Predominant Phenotype In COPD



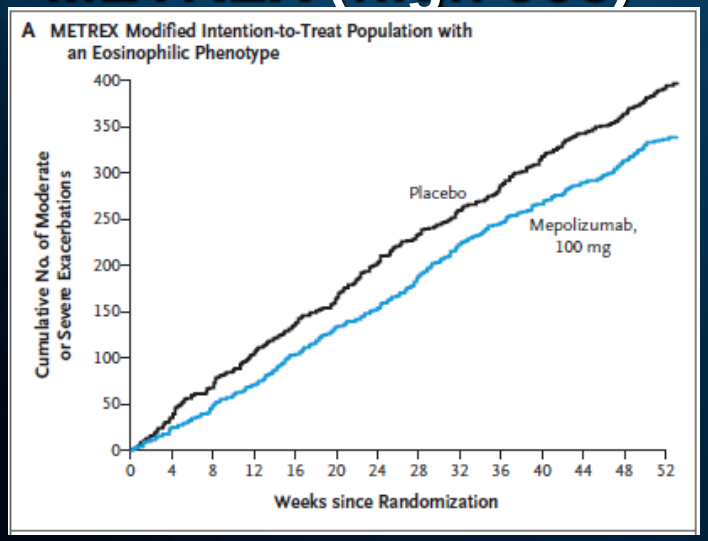
Pavrod et. al. Thorax 2016;71:118–125.

ORIGINAL ARTICLE

Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

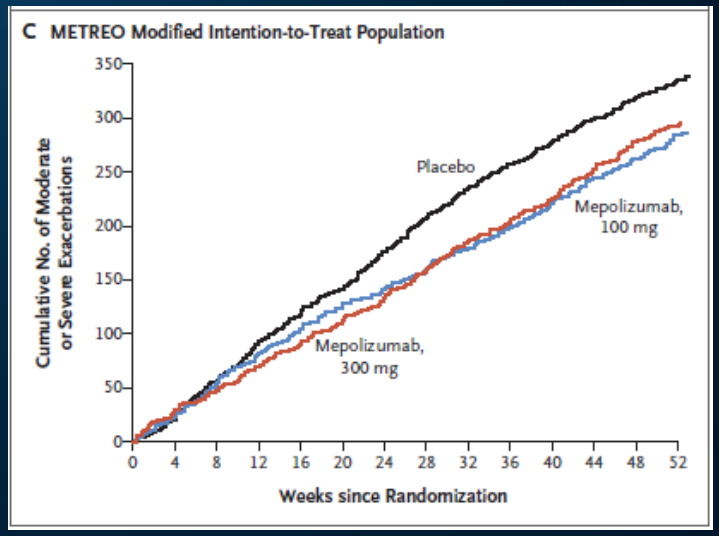
I.D. Pavord, P. Chanez, G.J. Criner, H.A.M. Kerstjens, S. Korn, N. Lugogo, J.-B. Martinot, H. Sagara, F.C. Albers, E.S. Bradford, S.S. Harris, B. Mayer, D.B. Rubin, S.W. Yancey, and F.C. Sciurba

- **METREX (high eos)**



- **RR 0.82 (0.68-0.94) adjusted p=0.04**

- **METREO**

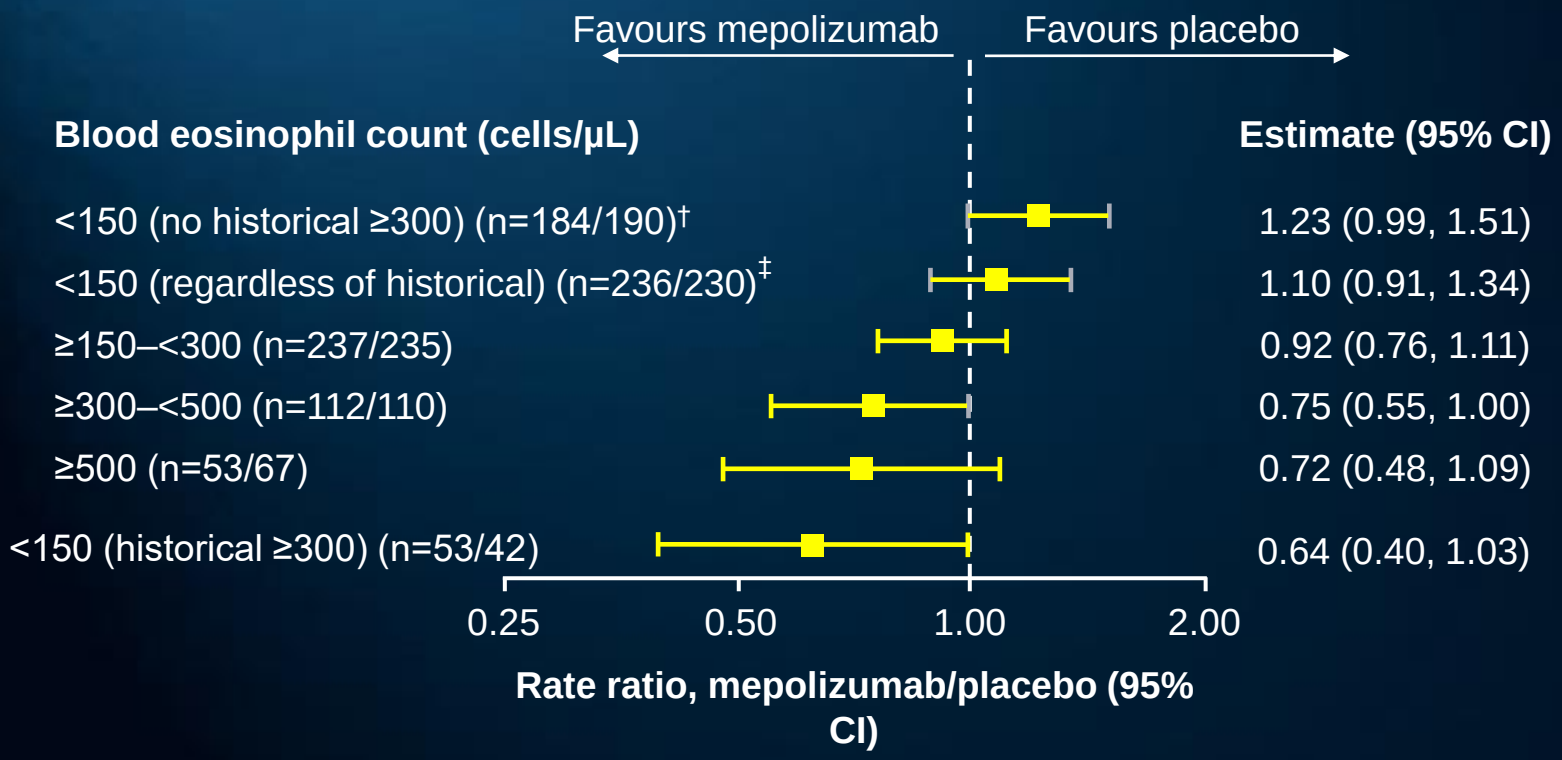


- **RR 0.80 (0.65-0.98) adjusted p=0.07**

- Rejected by FDA, One reason cited by panel is that in fact subset of responsive subjects may have asthma, need to improve selection.

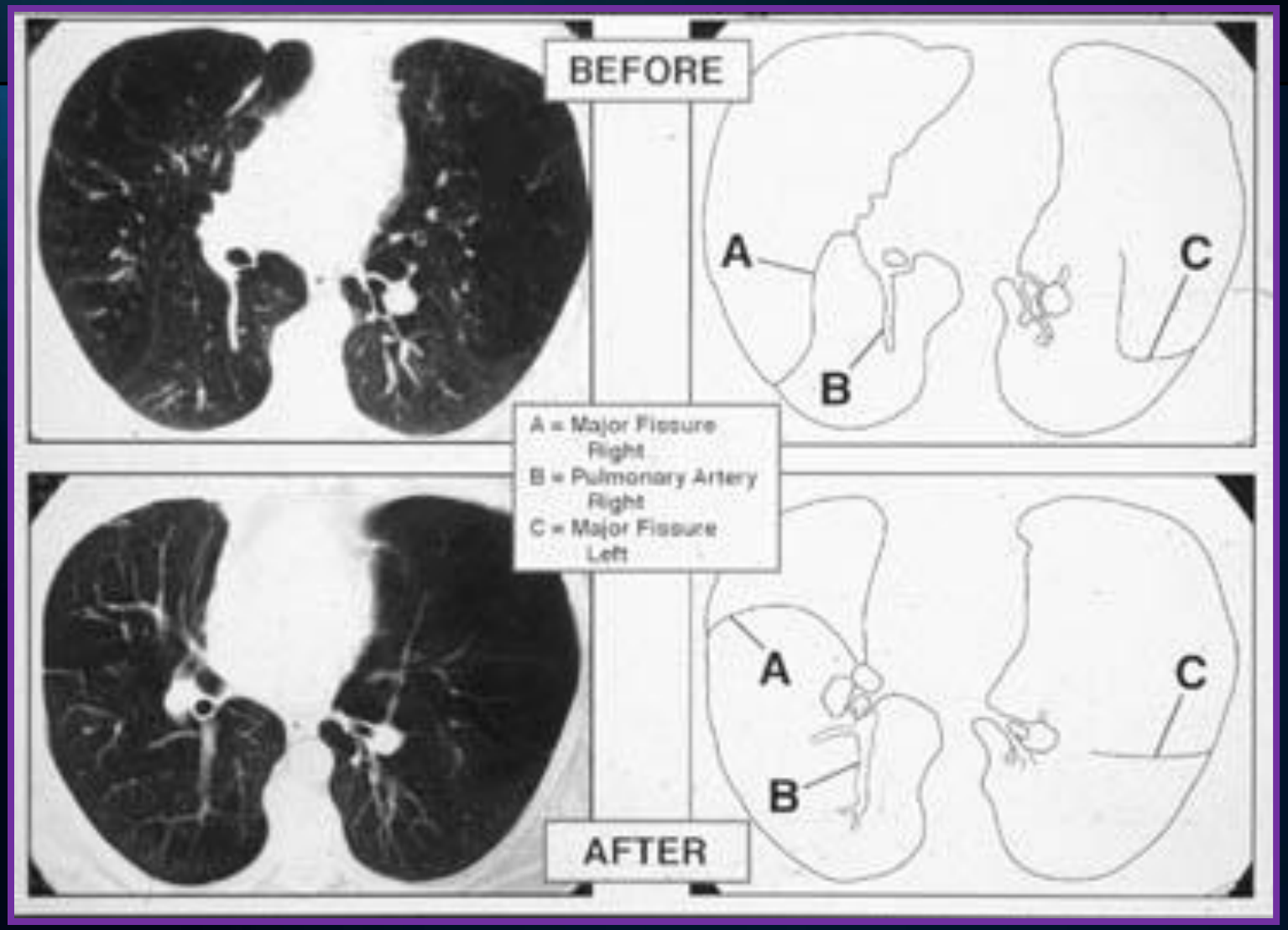
Pavord ID, et al. NEJM 2017

METREX and METREO meta-analysis: Annual rate of moderate/severe* exacerbations by blood eosinophil categories at screening



*Moderate exacerbation: requiring either SCS and/or antibiotics; severe exacerbation: requiring hospitalisation/resulting in death; †data from METREX mITT population patients without an eosinophilic phenotype; ‡post hoc analysis of METREX mITT-All and METREO mITT includes patients with an eosinophil count ≥300 cells/µL in previous year; all others are the METREX mITT-Eos plus METREO mITT

Surgical and Bronchoscopic Volume Reduction Approaches



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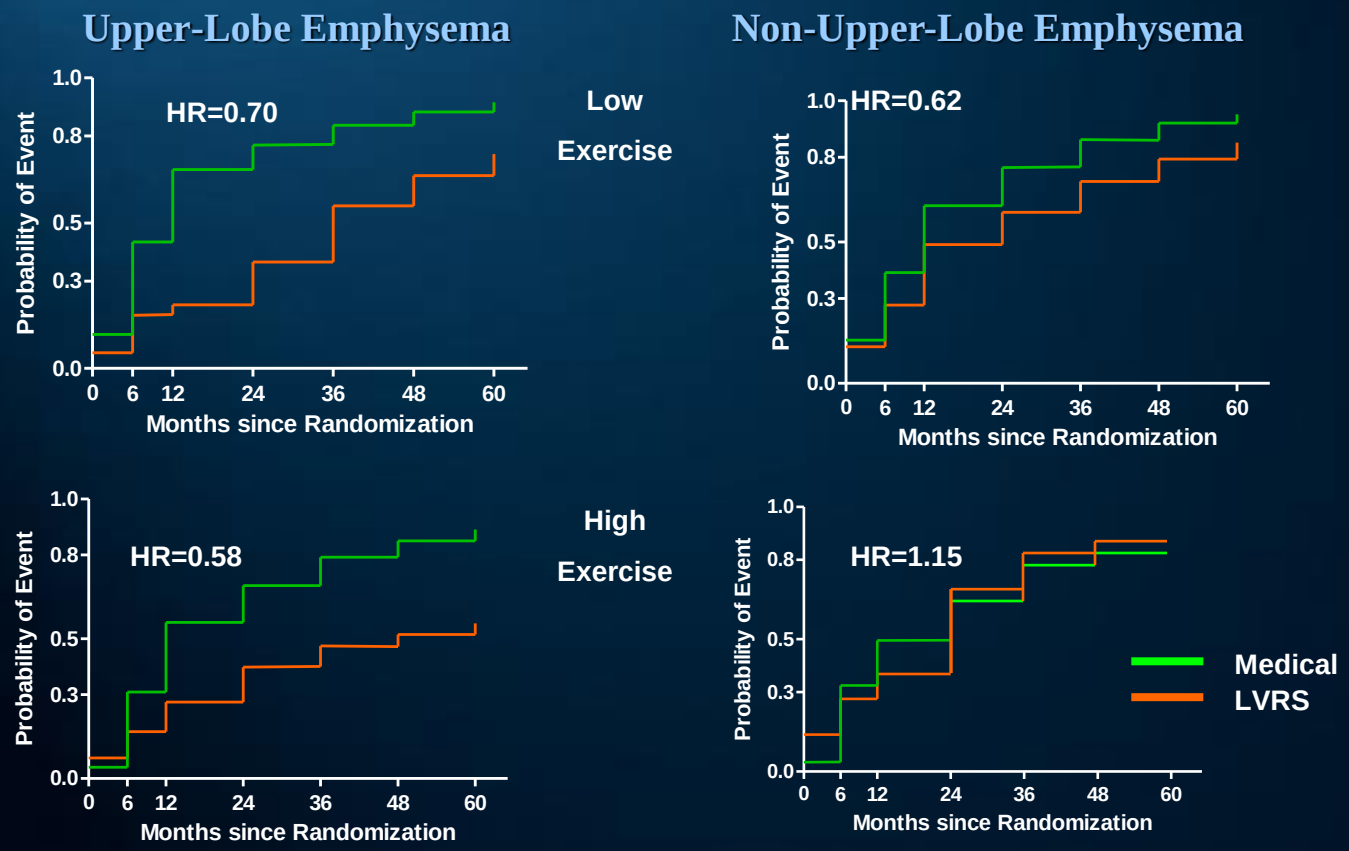
Lung Volume Reduction Surgery (NETT)

Composite Endpoint (Mortality or QOL Decline)



(HR at 3 yrs)

57

Benzo et al. *Am J Respir Crit Care Med*. 2009;180: 239-46

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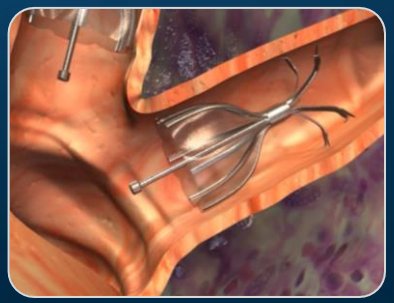
EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

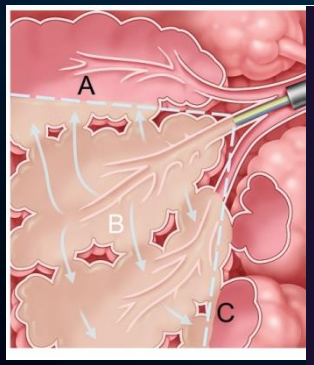
Bronchoscopic Lung Volume Reduction in COPD
Lessons in Implementing Clinically Based Precision Medicine

Frank C. Sciurba, MD; Divay Chandra, MD, MS; Jessica Bon, MD, MS

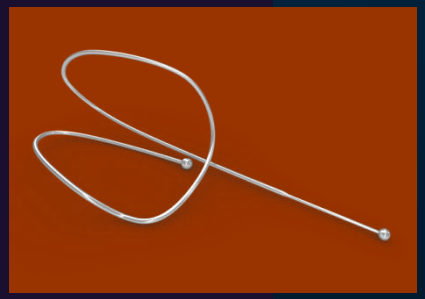
Valves



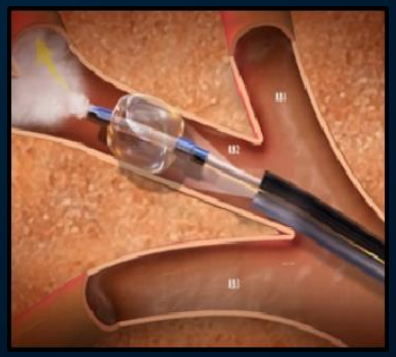
Foam



Coils



Steam



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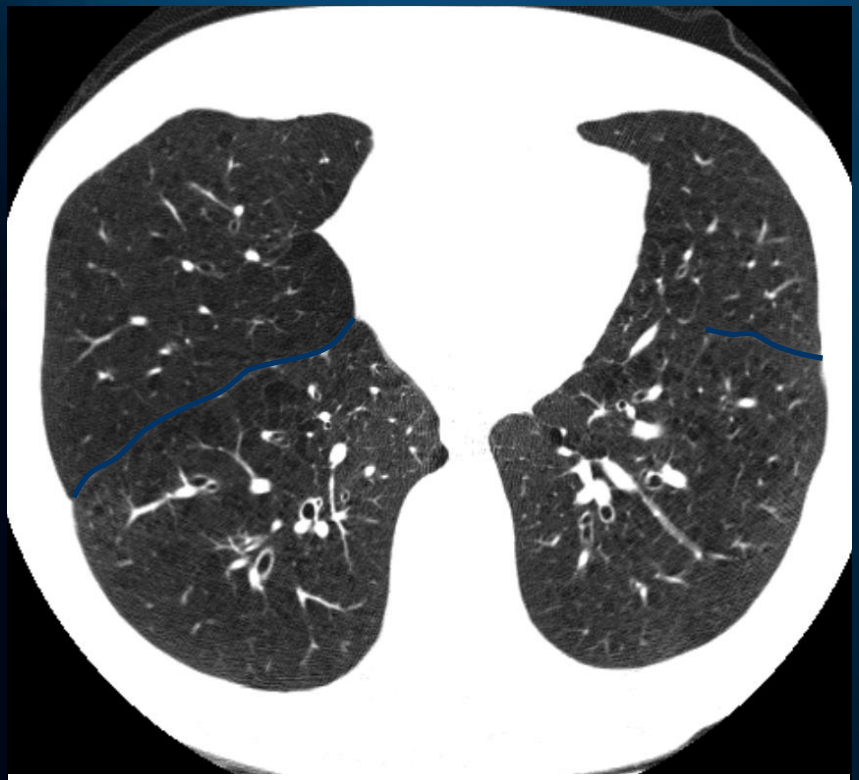
Impact of Fissure Integrity Phenotype



Complete Incomplete

- **Incomplete fissures**
  - Proxy for inter-lobar Collaterals
  - Attenuates volume reduction
- **Categorized by HRCT Core lab as:**
  - Complete
  - Incomplete
- **Rates of Incomplete Fissure:**

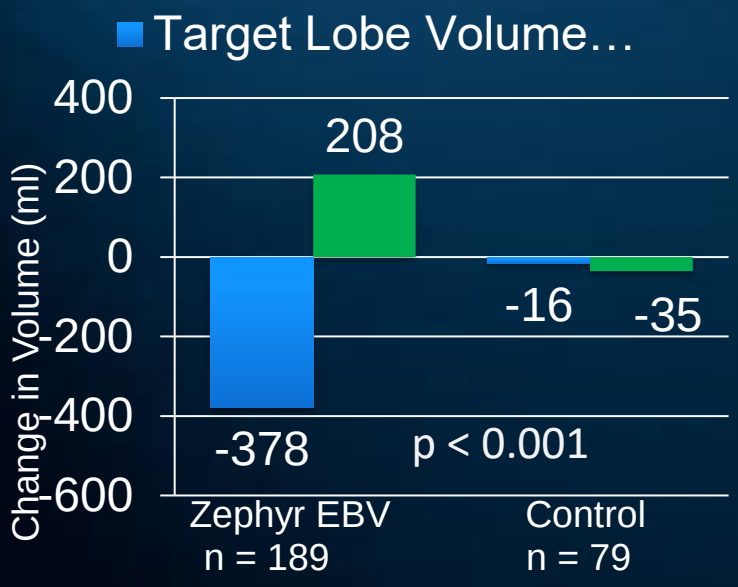
  - Right Oblique = 46%
  - Right Horizontal = 61%
  - Left Oblique = 38%

Lukose et al. Morphology of the lungs: Variations in the lobes and fissures. Biomedicine 1999;19:227-32.

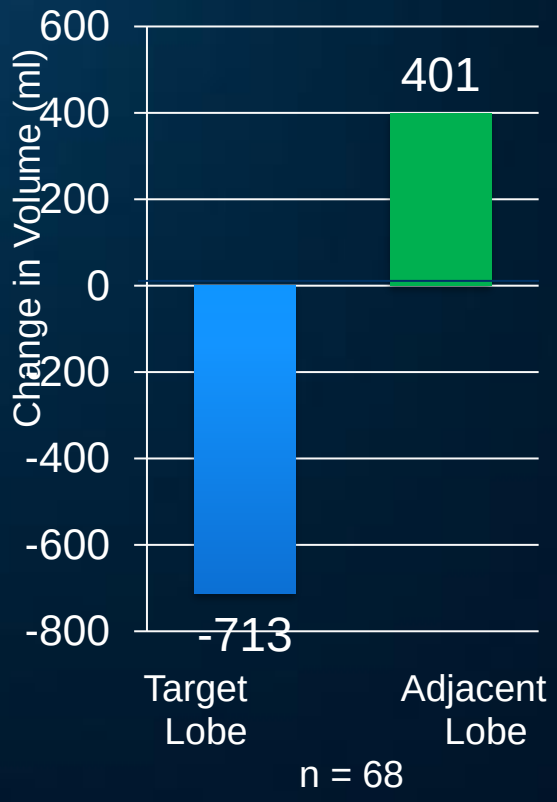
59

Greater Target Lobe Volume Reduction
Complete Fissure Subgroup at 6 Months (CC)

All Patients



Treated Group with Complete Fissures



- **High correlation between Lobar Volume change and FEV1 Improvement P=0.001**

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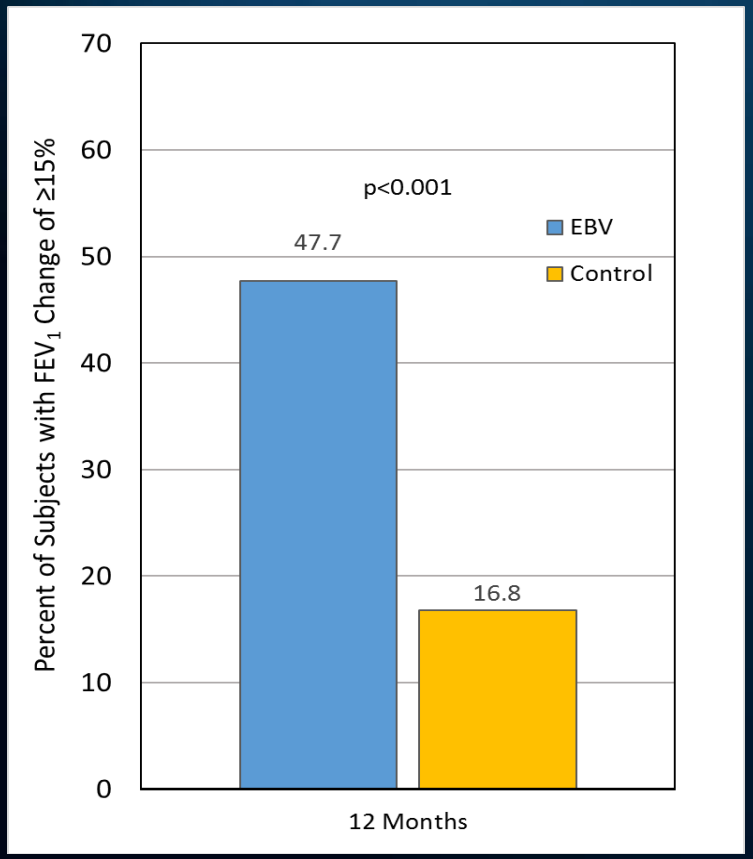
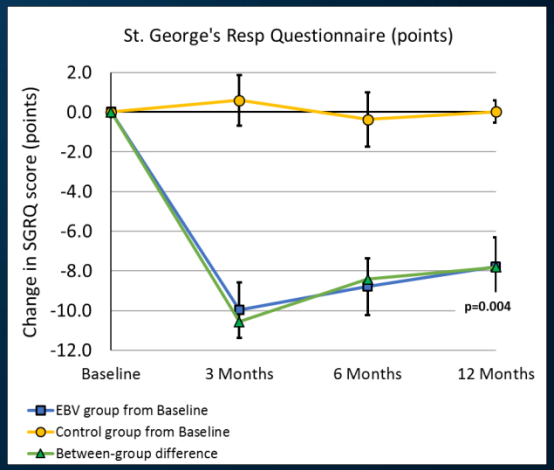
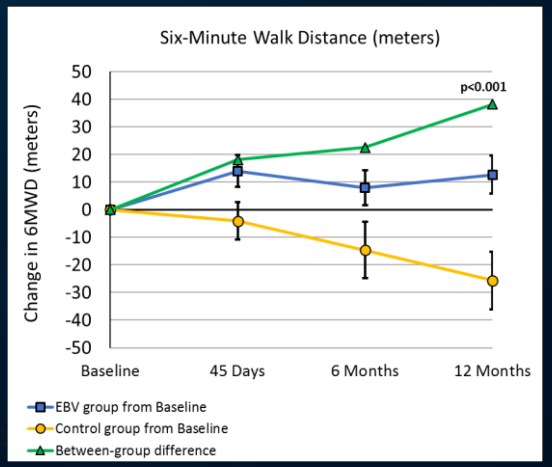
Zephyr Endobronchial Valve Pivotal Outcome: LIBERATE

Percent of Subjects with FEV_1 Change from Baseline to 12-months of ≥15%







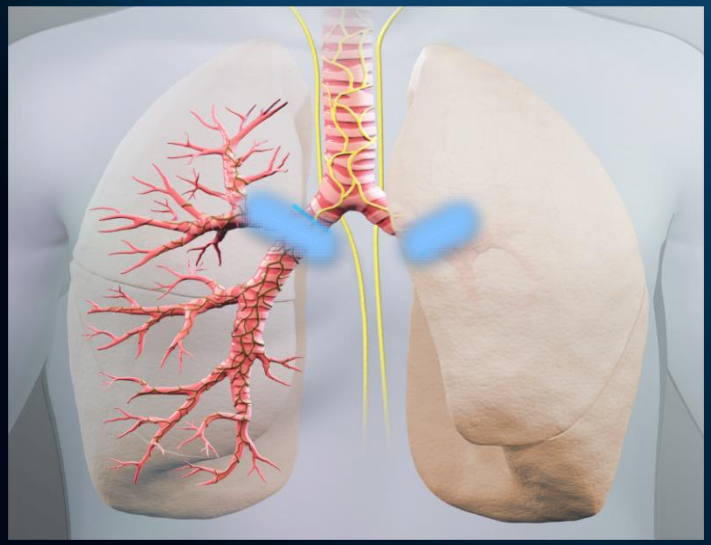
Criner G et al. AJRCCM. 2018. Published on 22-May-2018 as 10.1164/rccm.201803-0580OC

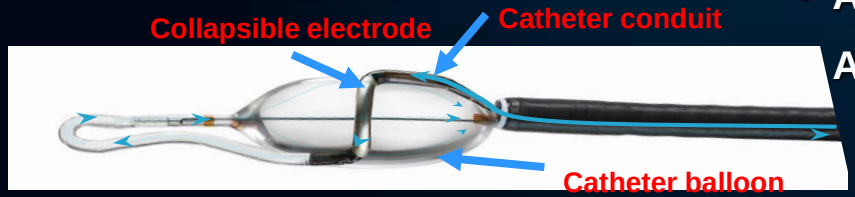
Criner et. al. AJRCCM 2018

Current UPMC Clinical Trials in COPD Exacerbator Phenotypes

- **The Unmet Need**
- **Precision Biologicals - Clinical Trials**
  - IL-5 monoclonal
  - IL-4/IL-13 monoclonal (Dupilimab) (BOREAS Trial)
  - TSLP Modulation (Tezepelumab) (COURSE trial)
  - IL-33 monoclonal
- **Bronchoscopic Device Intervention**
  - Targeted Lung Denervation (vagal RFA ablation)
  - Bronchial Rheoplasty (Electroporation)

Targeted Lung Denervation (TLD)





Denervation

- **Interrupts vagus nerve signaling to and from the lung (sensory disruption and decreased acetylcholine release)**

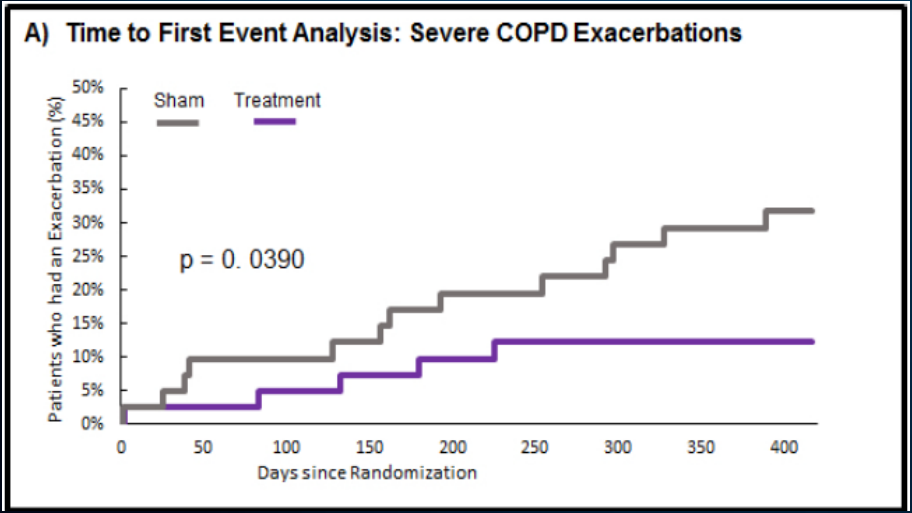
Lung

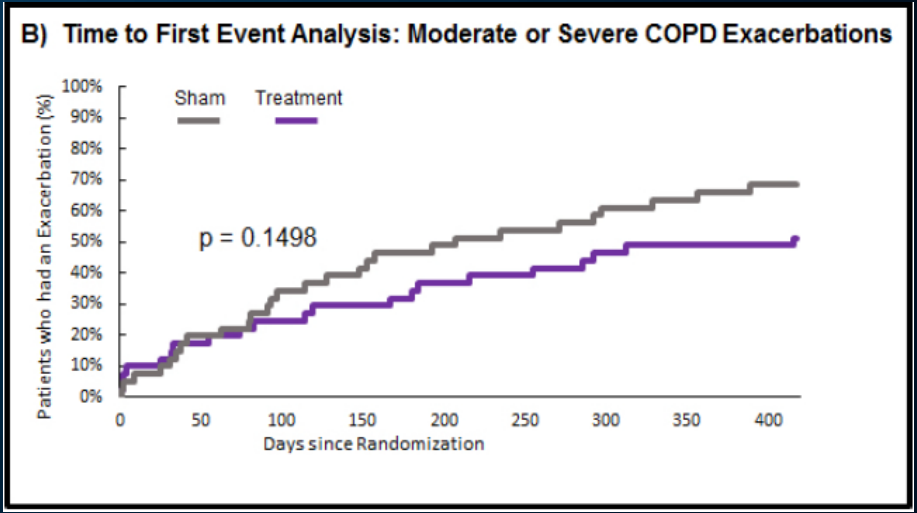
- Attenuates basal parasympathetic tone
  - decrease airway smooth muscle tone
  - decrease mucous secretion
- Blunts pulmonary nerve reflexes
  - decrease airway hyper-responsiveness and decreases exacerbations

Targeted

- **Anatomically to only the lung**
- **At the depth of the pulmonary nerves**

Targeted Lung Denervation
AIRFLOW-2 Study





Slebos et. al. AJRCCM '20

Conclusions

- COPD burden includes: Mortality, Exacerbations, Hospitalizations and readmissions, Symptoms and Costs
- Existing and emerging treatments are increasingly effective in altering the burden of COPD
- Attention to maintenance Inhaler Device Selection and and Adherence is as important as the specific drug
- Precision therapy is emerging ranging from biologicals targeting specific molecular pathways and devices targeting specific physiologic attributes

For Clinical trials email: ecrc@upmc.edu