COPD 2016

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Definition of COPD

- COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.
- Exacerbations and comorbidities contribute to the overall severity in individual patients.

Burden of COPD

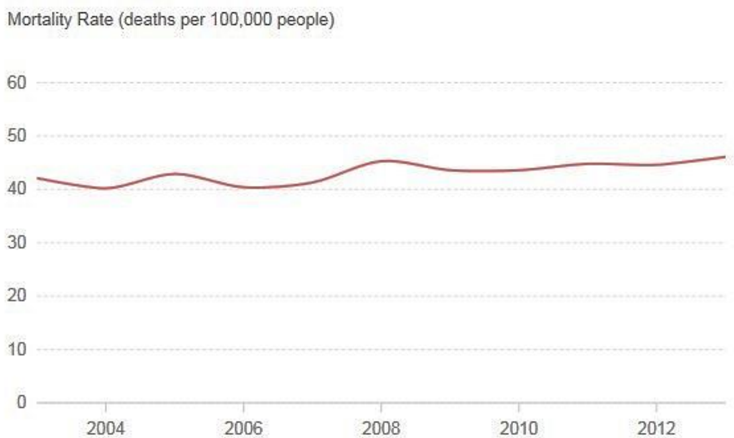
- Prevalence: Approximately 24 million people in the US. Only 12 million diagnosed
- 3rd leading cause of death since 2008 141,000 deaths (passed stroke)
- Approximately 3 million deaths/year worldwide
- Most Tobacco related (400,000 biomass related)

The Most Underfunded Disease per Death in US

#1. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease Research Funding and Mortality Over Time in the United States

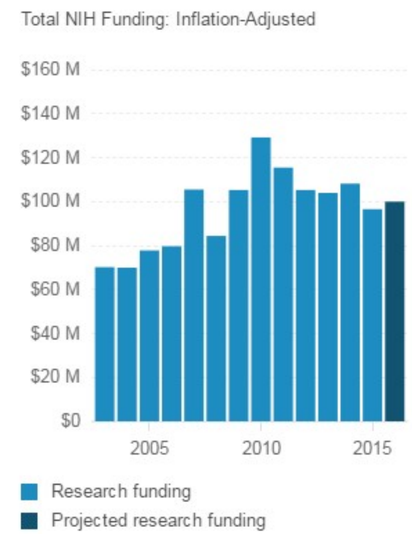
Research Funding | Mortality



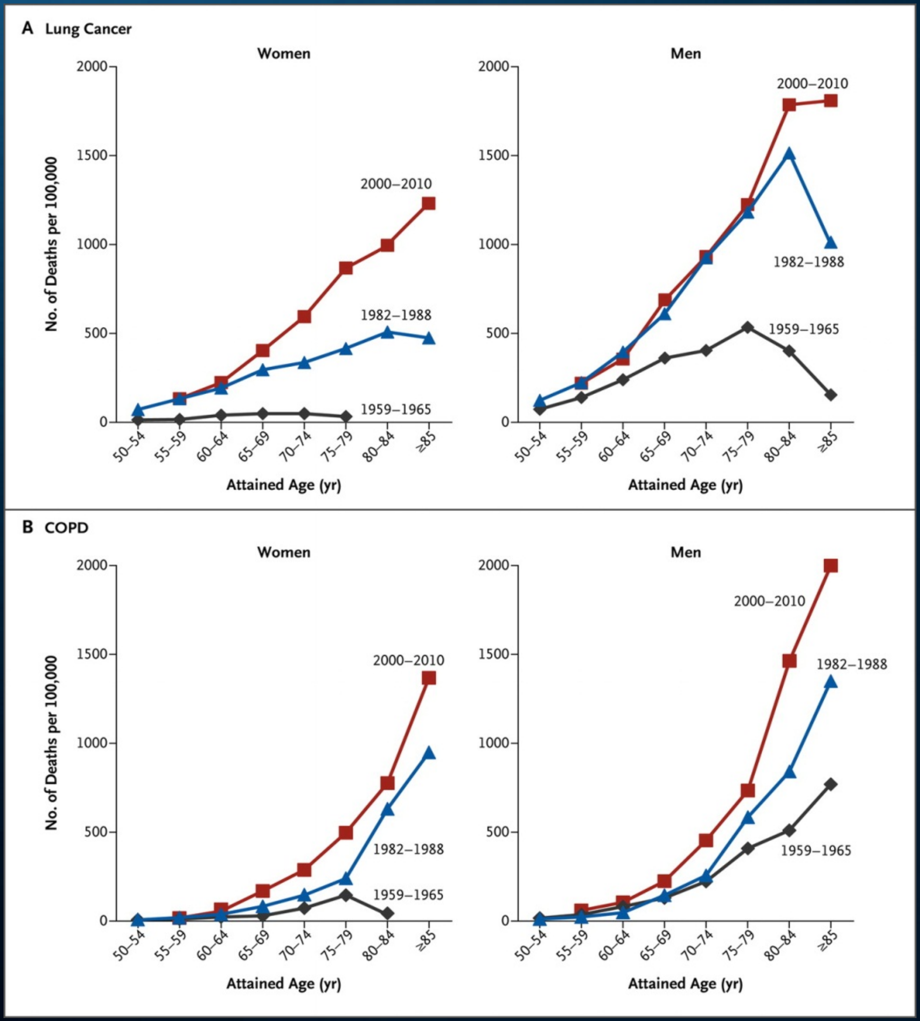
Chronic Obstructive Pulmonary Disease #1

Funding per Death: $663
Deaths in 2013: 145,575
Total Funding in 2015: $96,584,162
Average Funding Per Death for All Diseases (in the U.S.): $11,691

Chronic Obstructive Pulmonary Disease Research Funding and Mortality Over Time in the United States



Changes in Rates of Death from Lung Cancer and Chronic Obstructive Pulmonary Disease (COPD) over Time among Current Female and Male Smokers in the Three Time Periods.

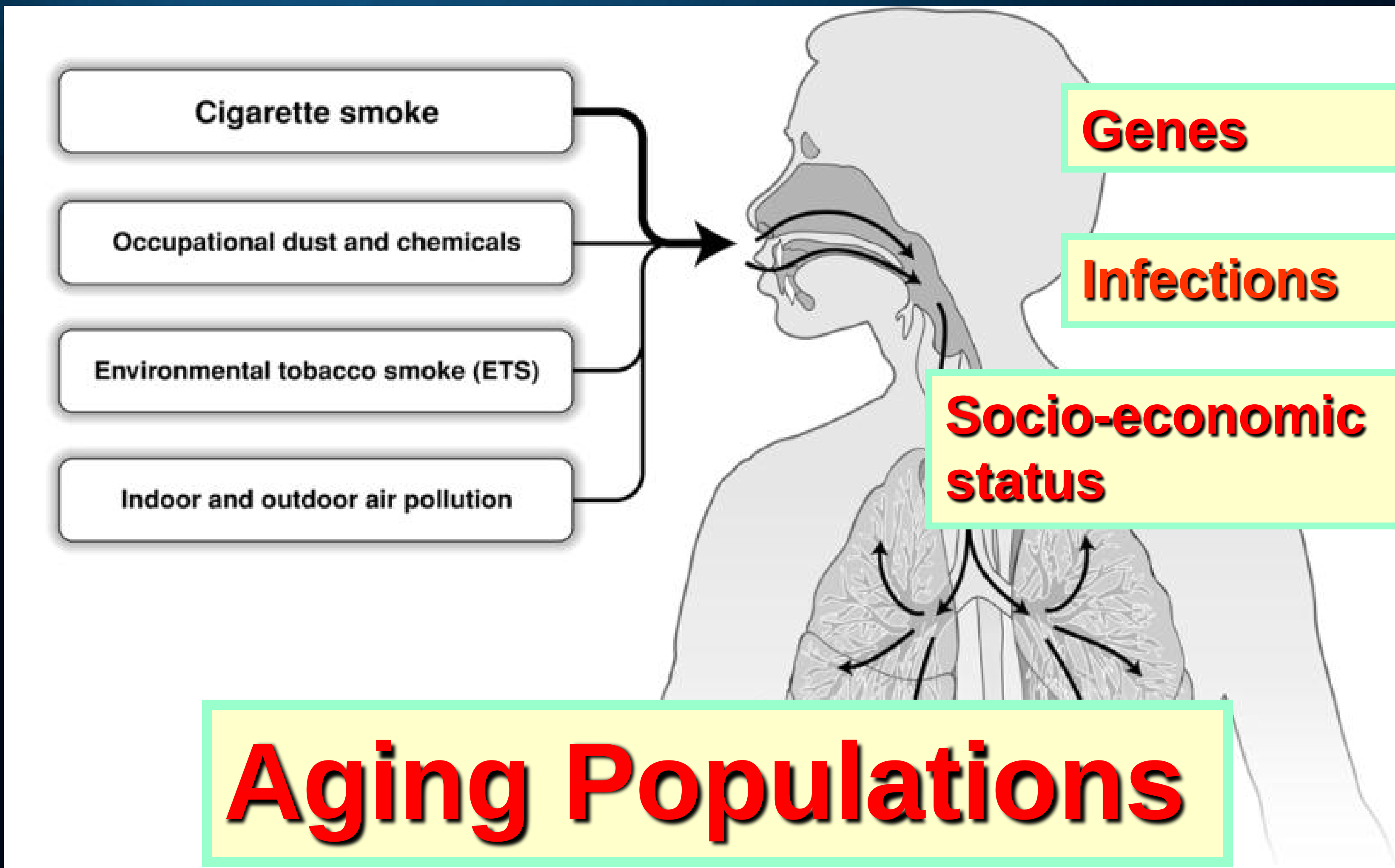


Thun MJ et al. N Engl J Med 2013;368:351-364.

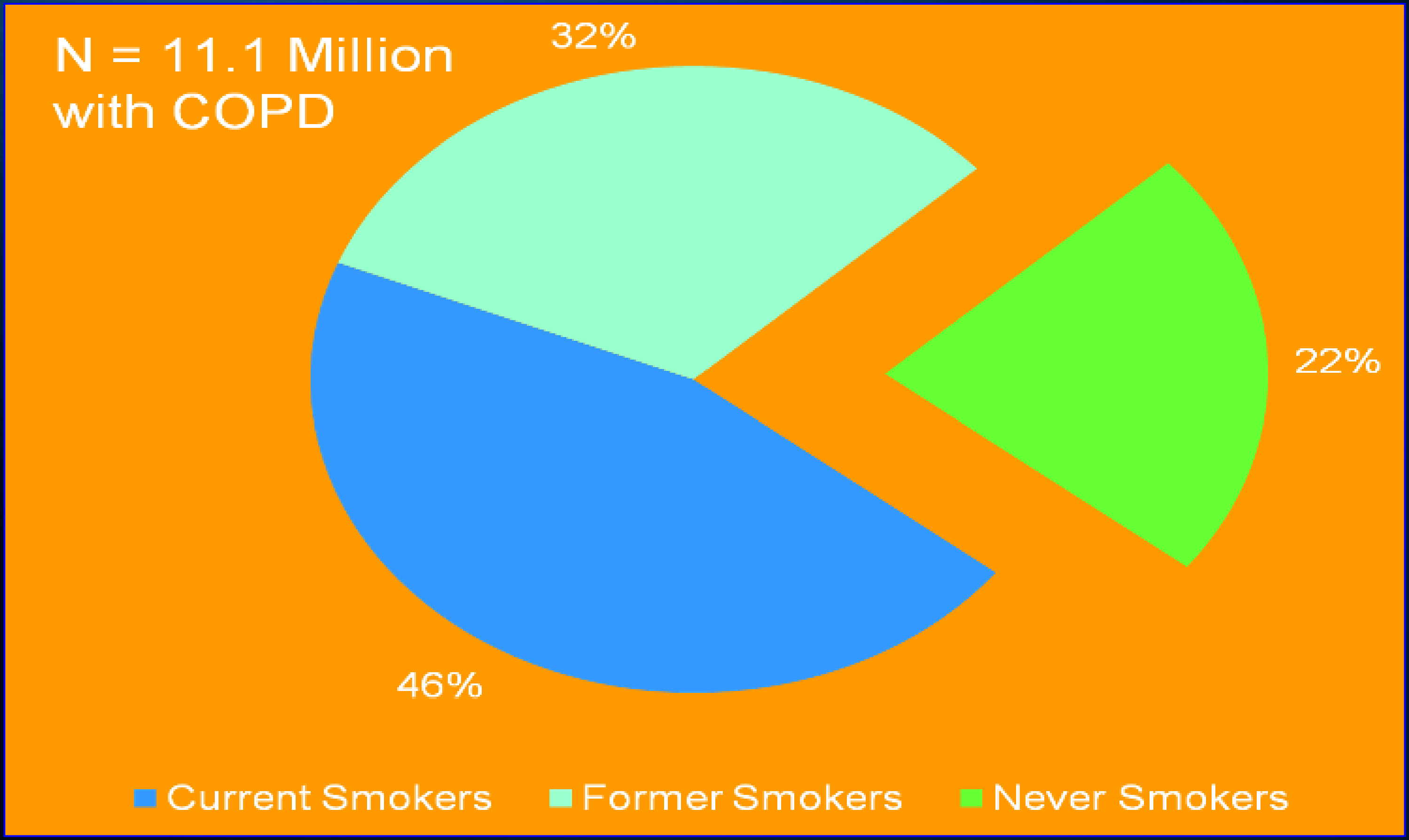
The Cigarette Burns Out But the Inflammation Rages On

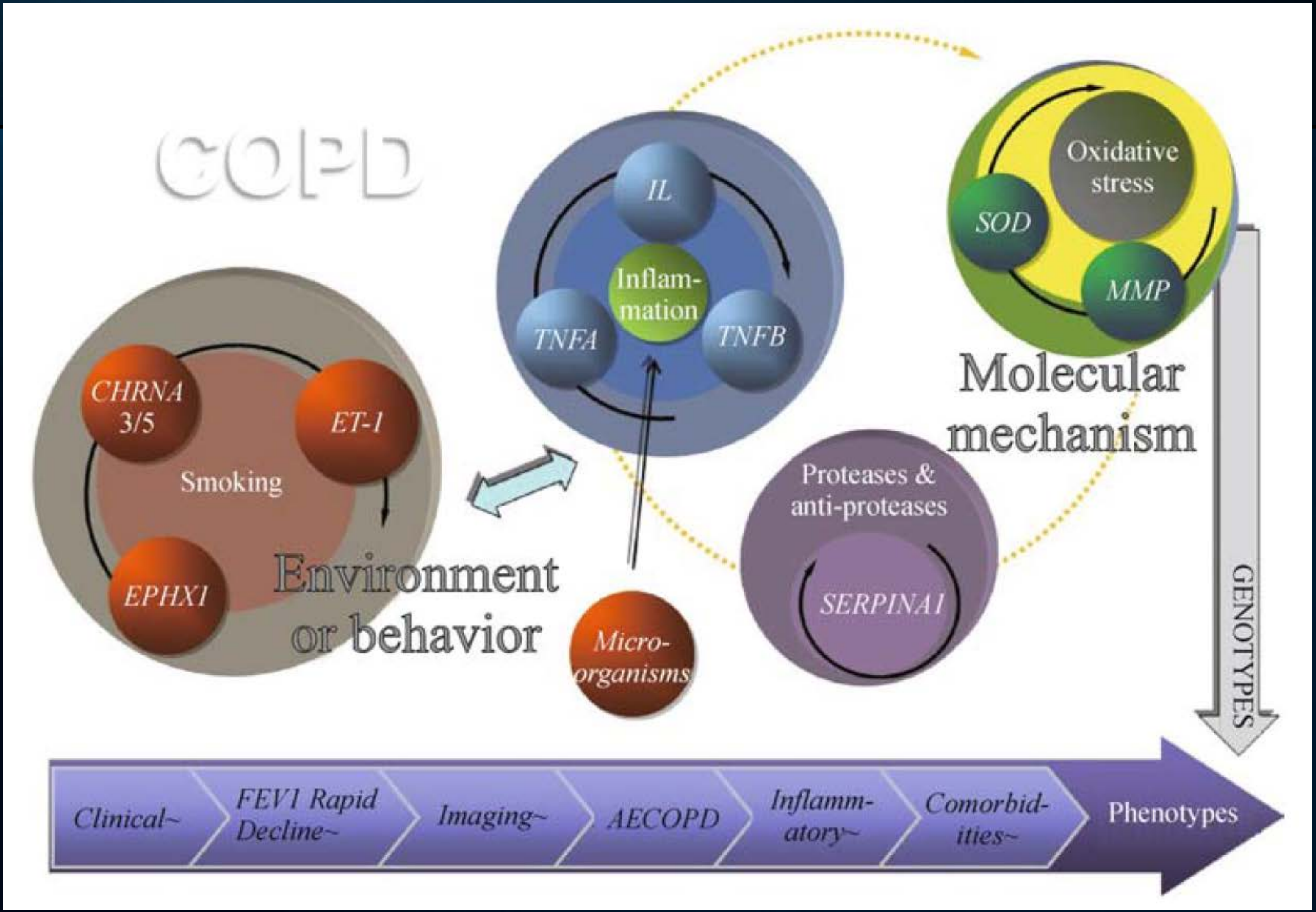
S. Shapiro

Risk Factors for COPD



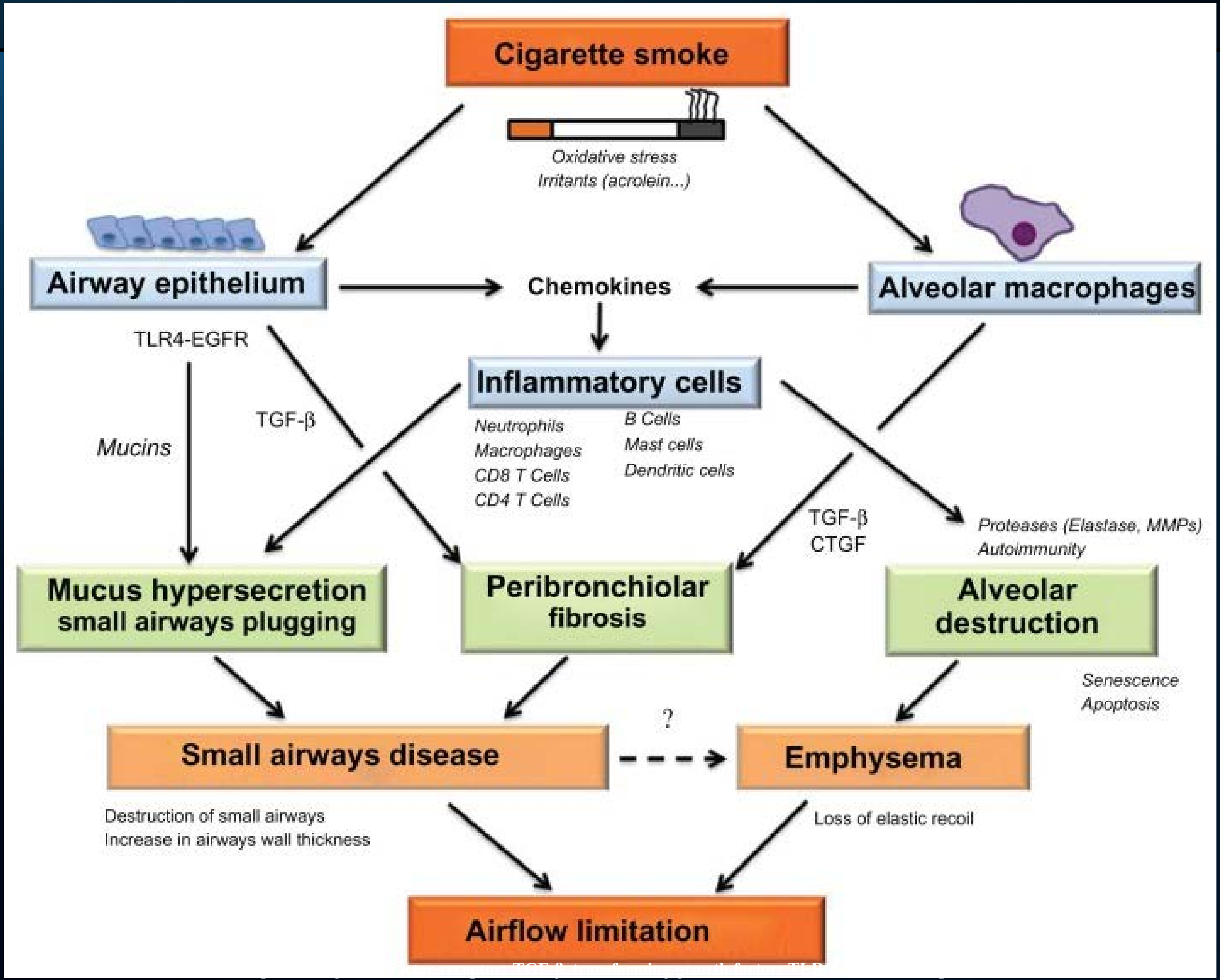
Smoking and GOLD 2+ COPD in NHANES 3





Chen et. al. Front. Med. 2013,

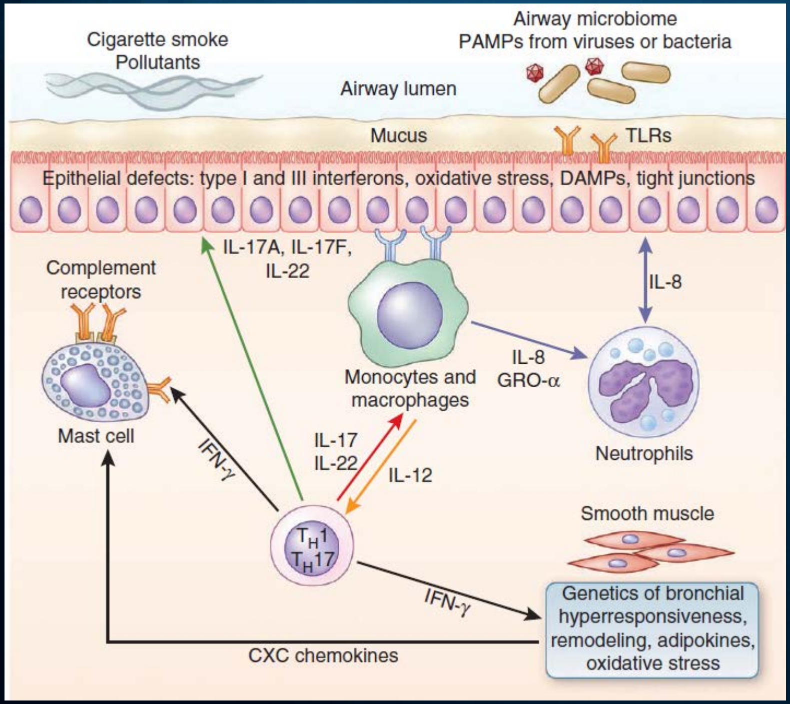
Mechanisms Leading to Airflow Limitation (Classic)



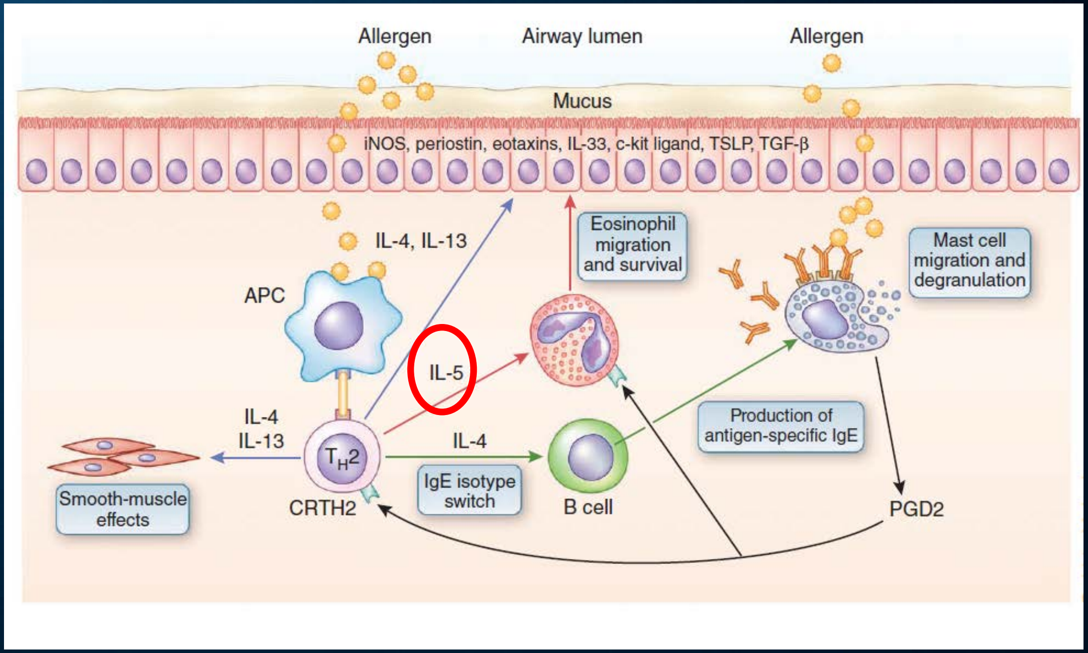
CTGF, connective tissue growth factor; MMPs, matrix metalloproteinases

Martin C et al. *Int J Chron Obstruct Pulmon Dis*. 2013;8:7-13. Reproduced with permission of Dove Medical Press.

Inflammatory Pathways in Obstructive Lung Disease: Opportunities for Individualized Therapy



TH1 (Traditional COPD pathways)

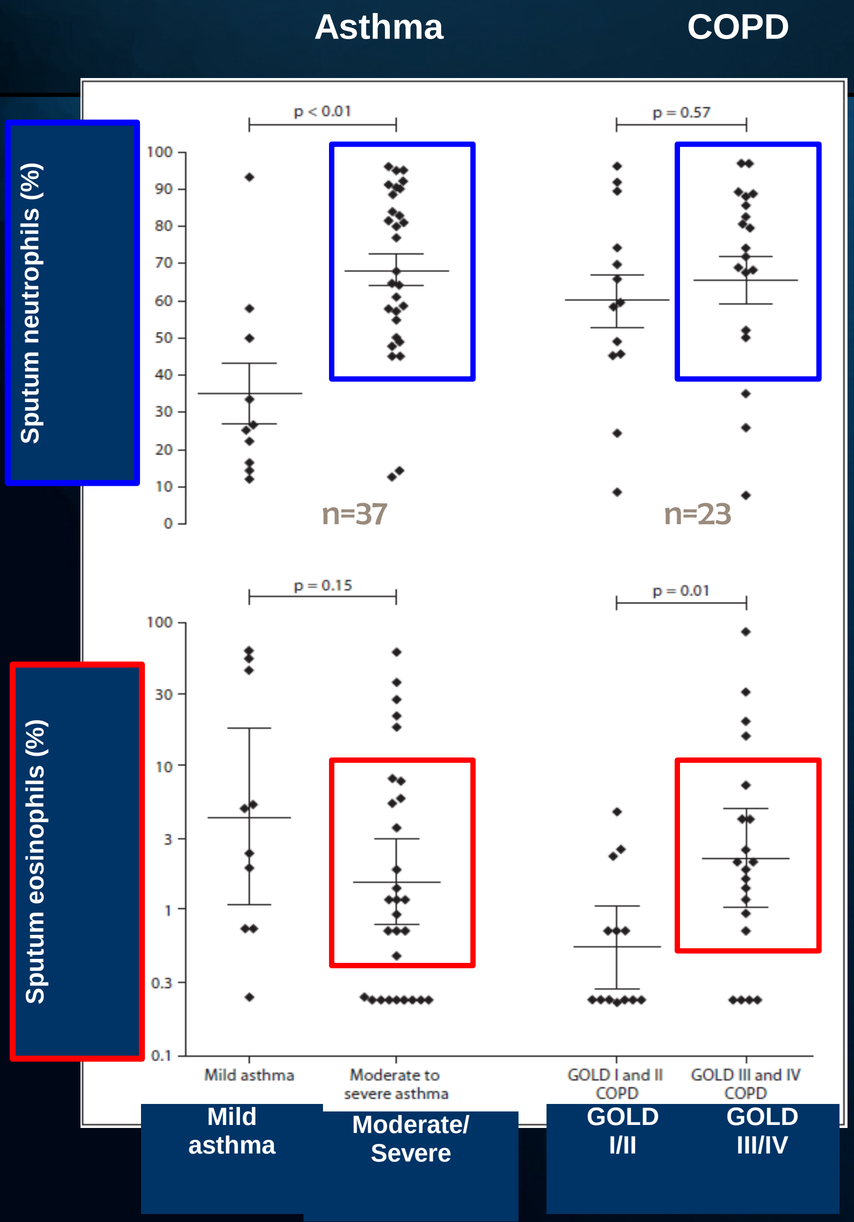


TH2 (Traditional Asthma pathways)

?COPD Overlap

Wenzel. Nature Med 2012

Asthma and COPD Overlap (ACOS) in Biology



Airway neutrophilic and eosinophilic inflammation:

Little differences in airway inflammatory phenotypes between moderate/severe asthma and severe/very severe COPD (GOLD III/IV)

Expression of IL-5 is similar in both asthma and COPD (not shown)

Eosinophilic phenotype is associated with over-expression of IL-5 in both asthma and COPD (not shown)

Bafadhel et al. *Respiration* 2012;83:36–44

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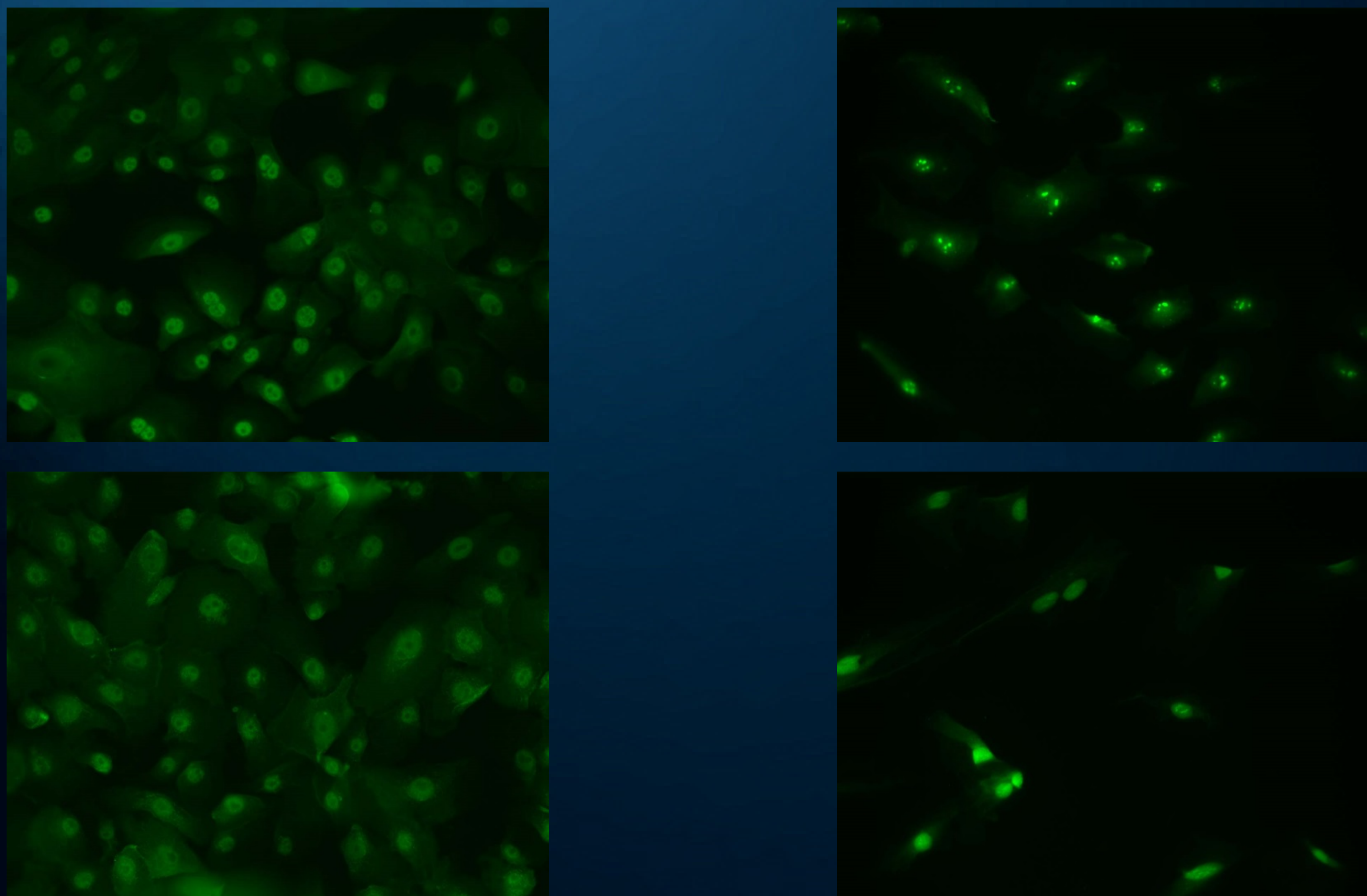
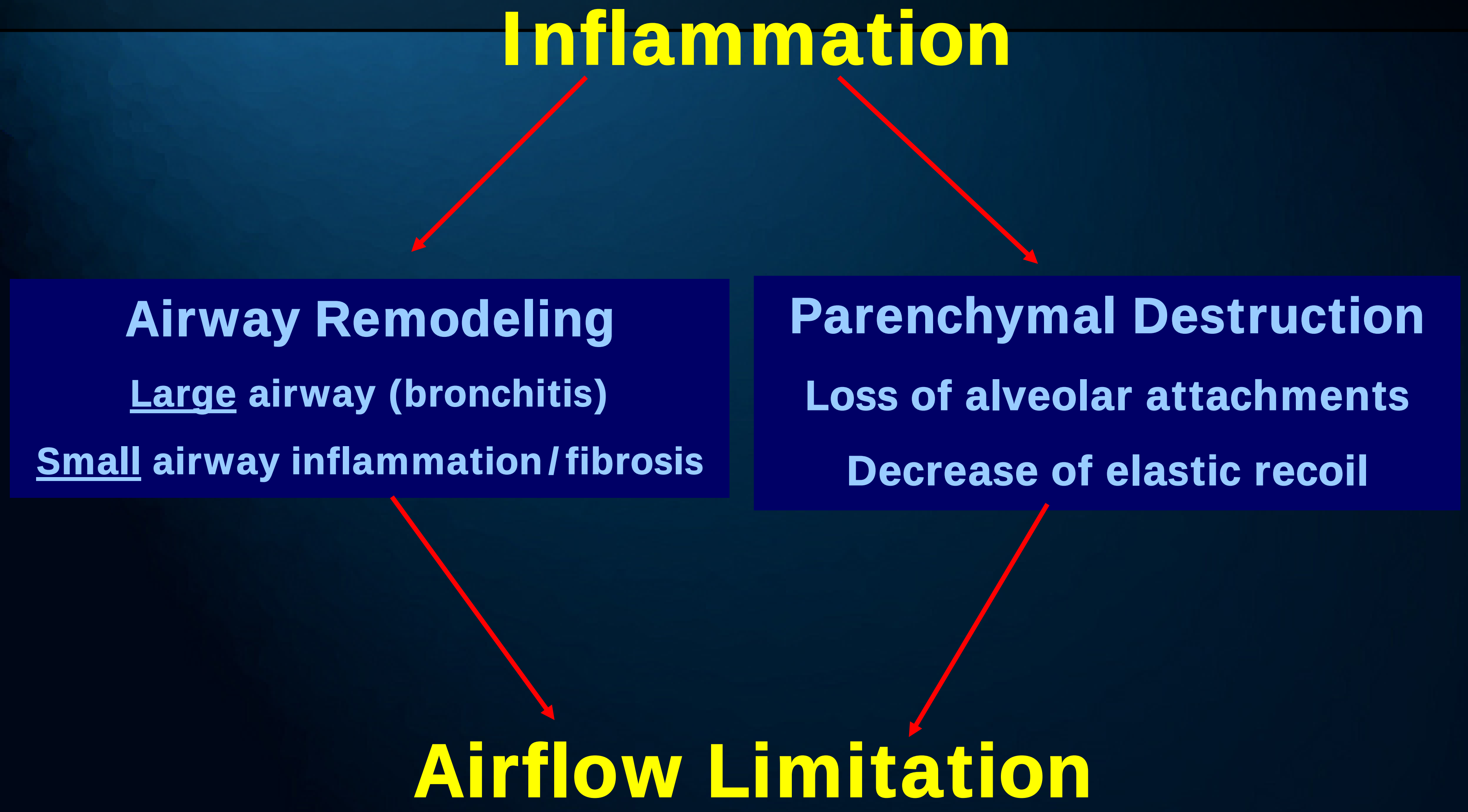
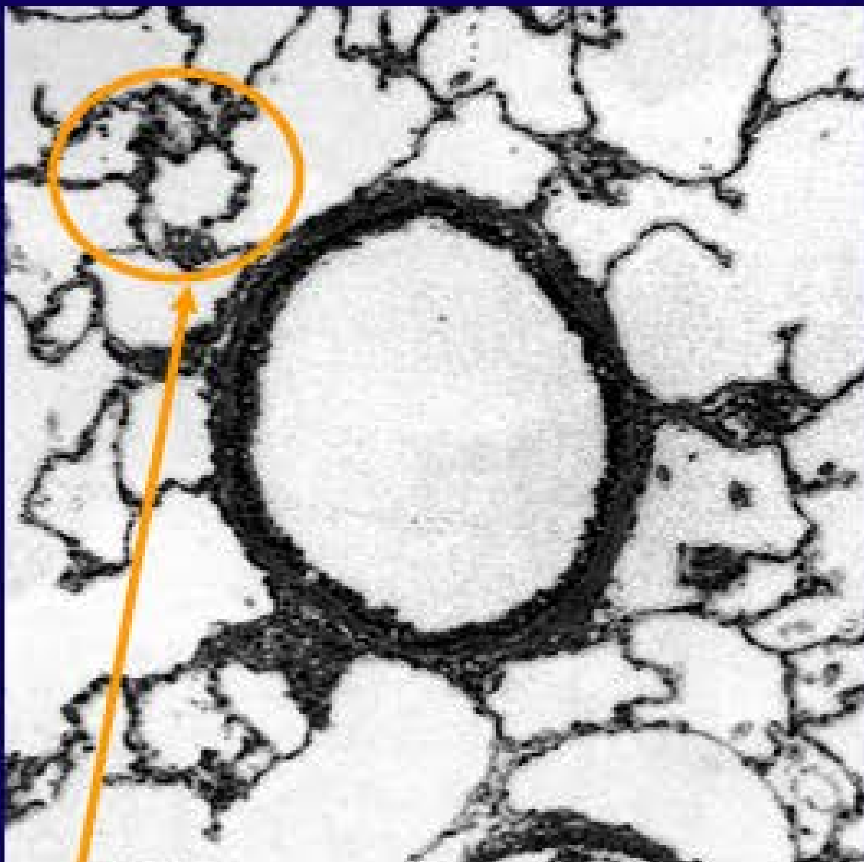
Autoimmunity in COPD:
Plasma with avidities against human airway epithelium (L) and endothelium (R)

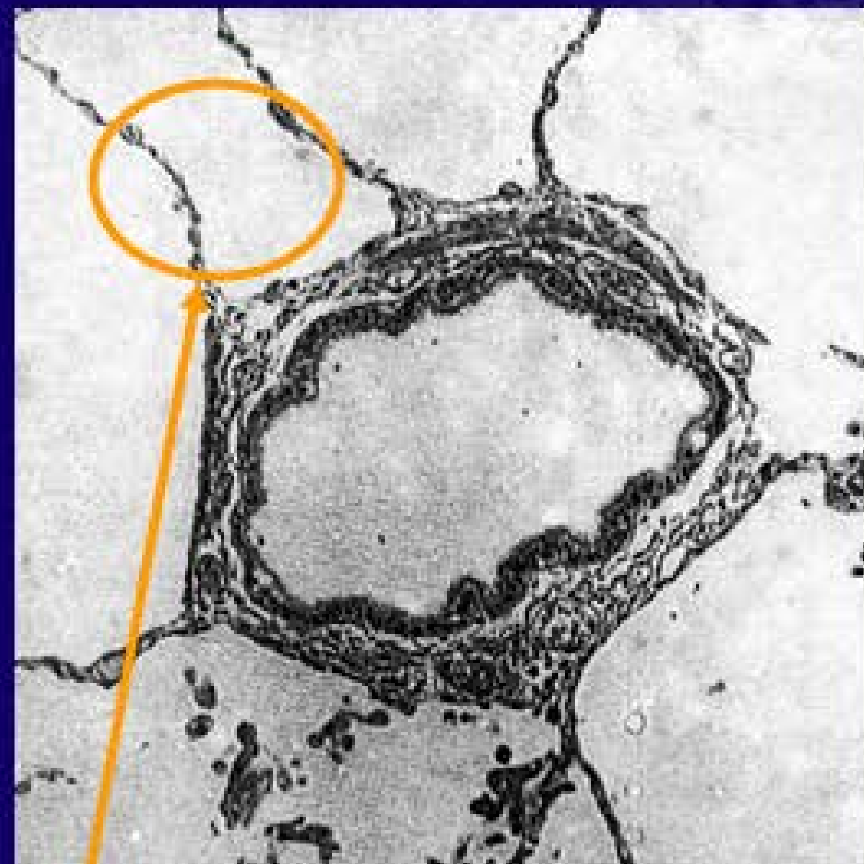



Inflammation
Airway Remodeling
Large airway (bronchitis)
Small airway inflammation / fibrosis
Parenchymal Destruction
Loss of alveolar attachments
Decrease of elastic recoil
Airflow Limitation

Normal **COPD**

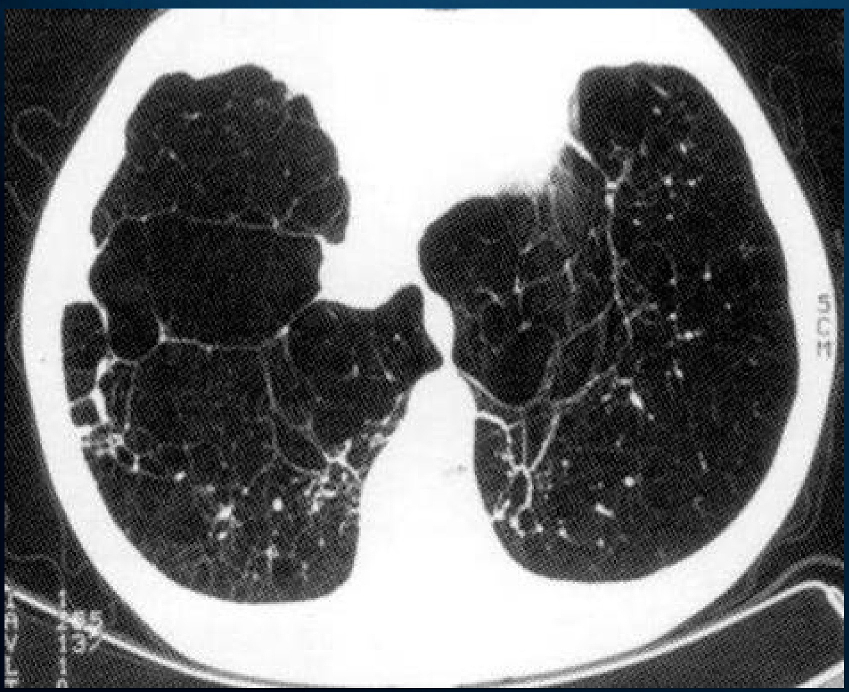


Parenchymal tethering

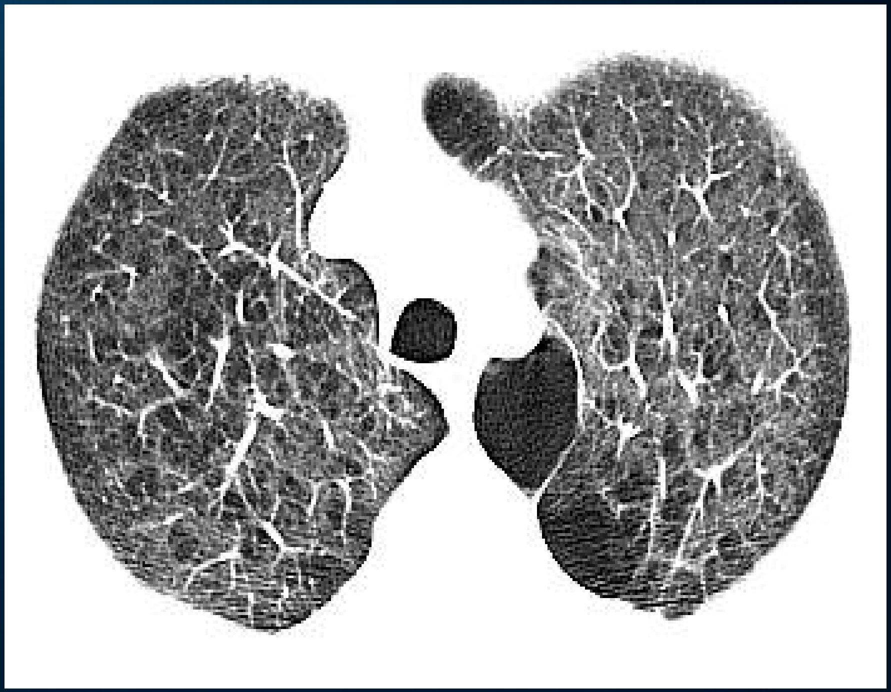


Loss of tethering

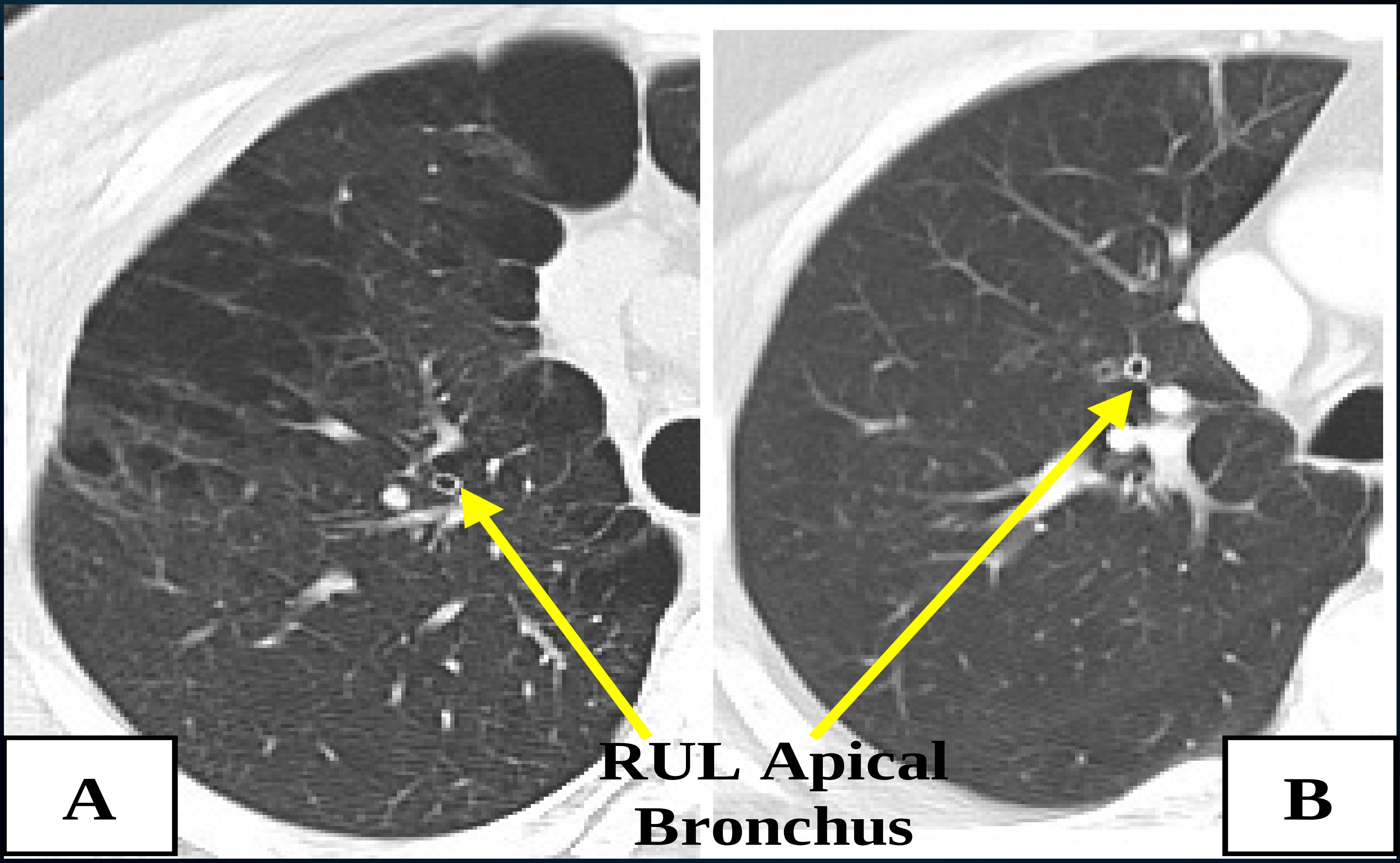
Emphysema vs. Peripheral Airway Dominant COPD



FEV_1 0.8 L



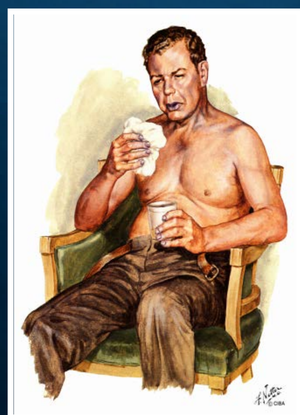
FEV_1 0.65 L



FEV1 124% pred

FEV1 34% pred

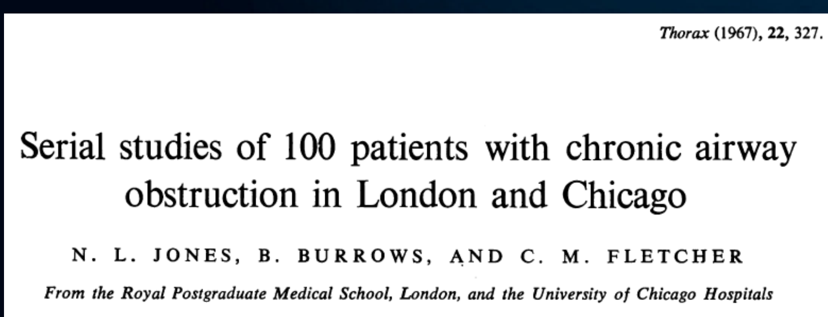
Subphenotypes of COPD: 1967



Chronic Bronchitis

Asthma

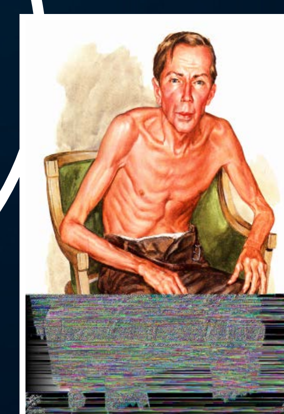
Emphysema


Thorax (1967), **22**, 327.

Serial studies of 100 patients with chronic airway obstruction in London and Chicago

N. L. JONES, B. BURROWS, AND C. M. FLETCHER

From the Royal Postgraduate Medical School, London, and the University of Chicago Hospitals



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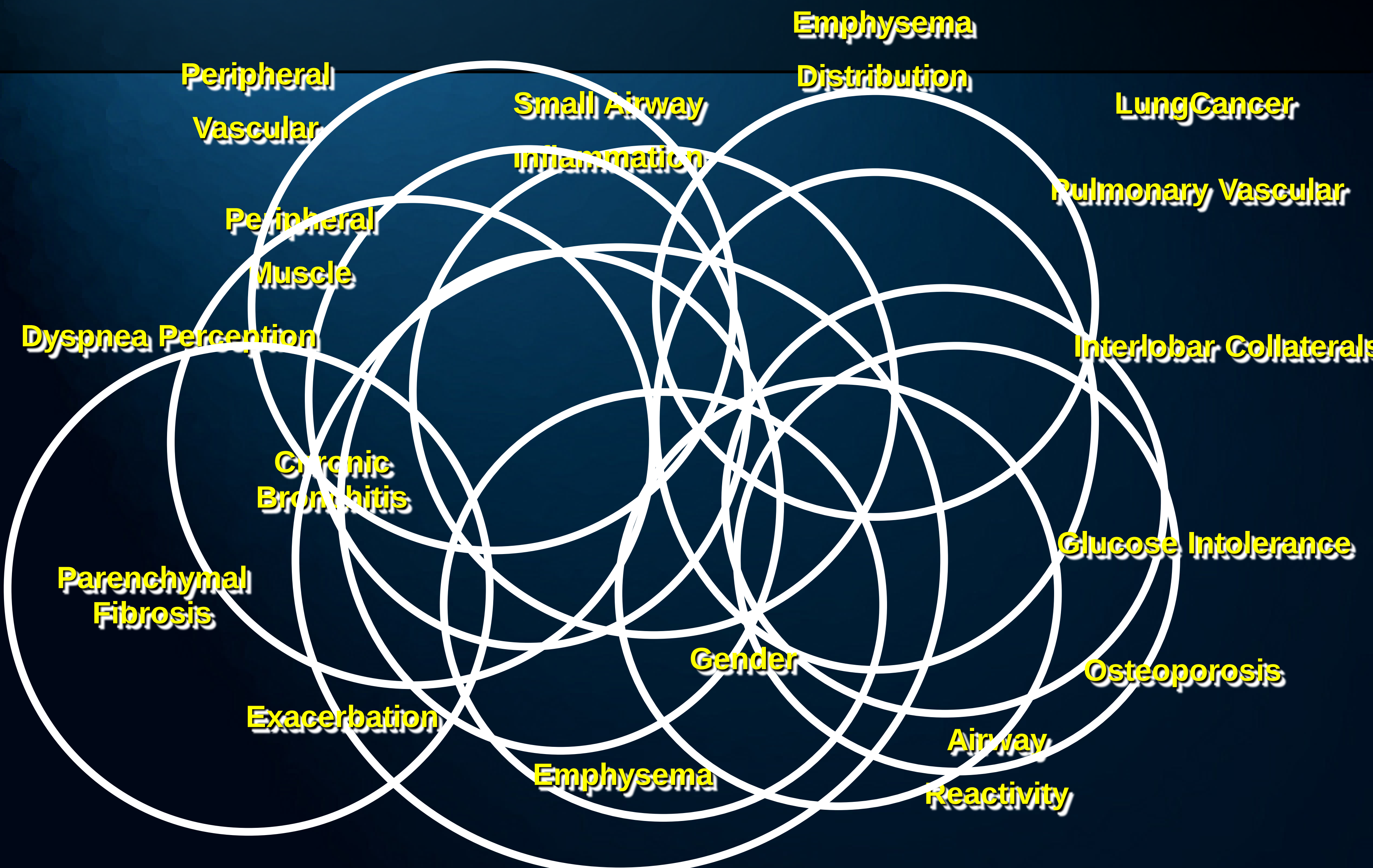
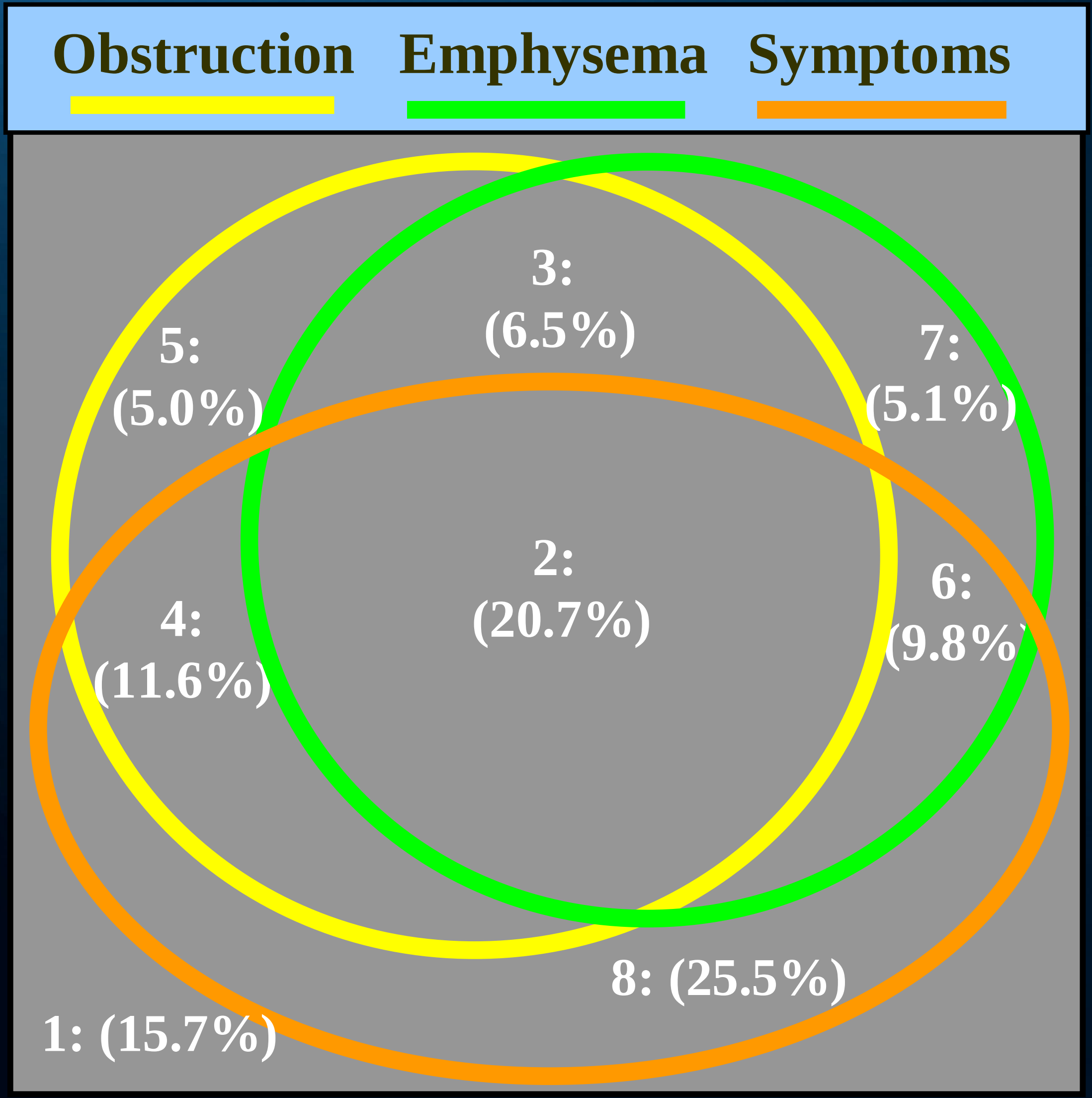
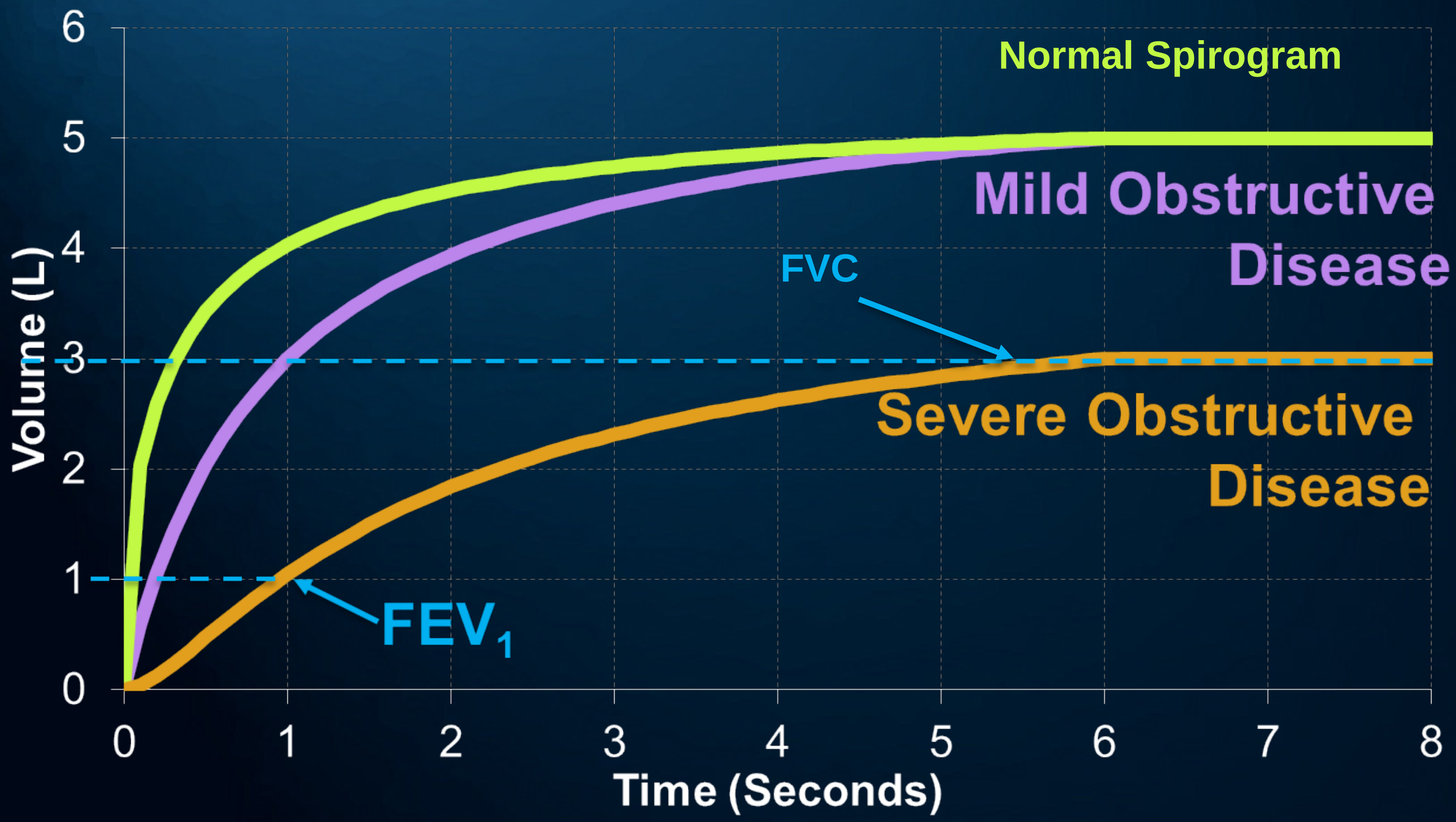
The Many Phenotypic Traits which Combine to form Multiple Phenotypes of COPD



Relationship Between Emphysema, Airway Obstruction and Symptoms (PLuSS Screening cohort n=3297)



Spirometry: Range of Severity



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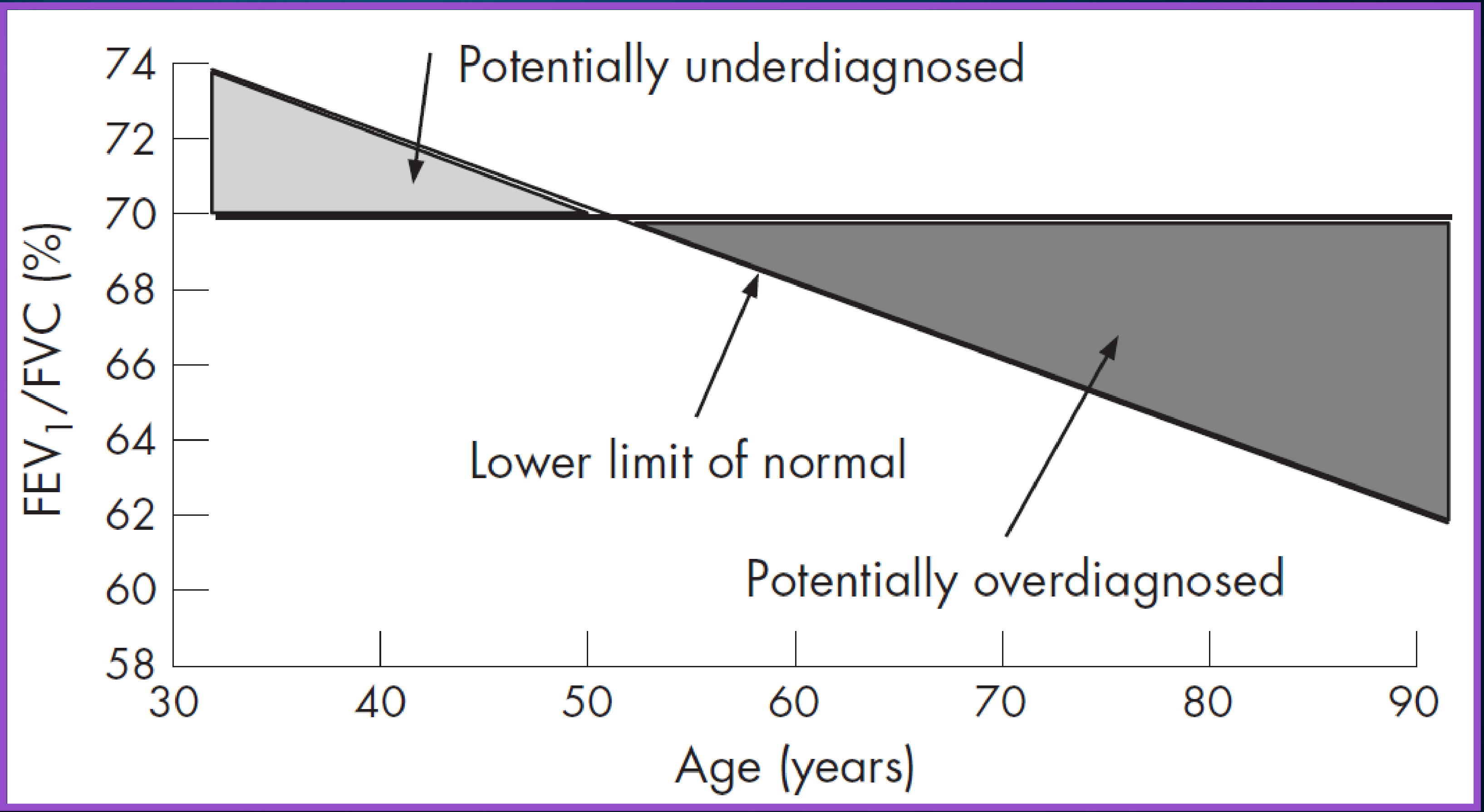
Classification of COPD Based on Severity of Airflow Limitations (GOLD 2011)

Category	Characteristics
I: Mild COPD	• FEV_1/FVC <70% (for stages I-IV) • FEV_1 ≥80% predicted
II: Moderate COPD	≥50% FEV_1 <80% predicted
III: Severe COPD	≥30% FEV_1 <50% predicted
IV: Very severe COPD	<30% FEV_1

FVC=forced vital capacity; GOLD=Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease

http://www.goldcopd.org/uploads/users/files/GOLD2011_Summary.pdf.

Age related Overdiagnosis of COPD Using Absolute FEV1/FVC < 0.7

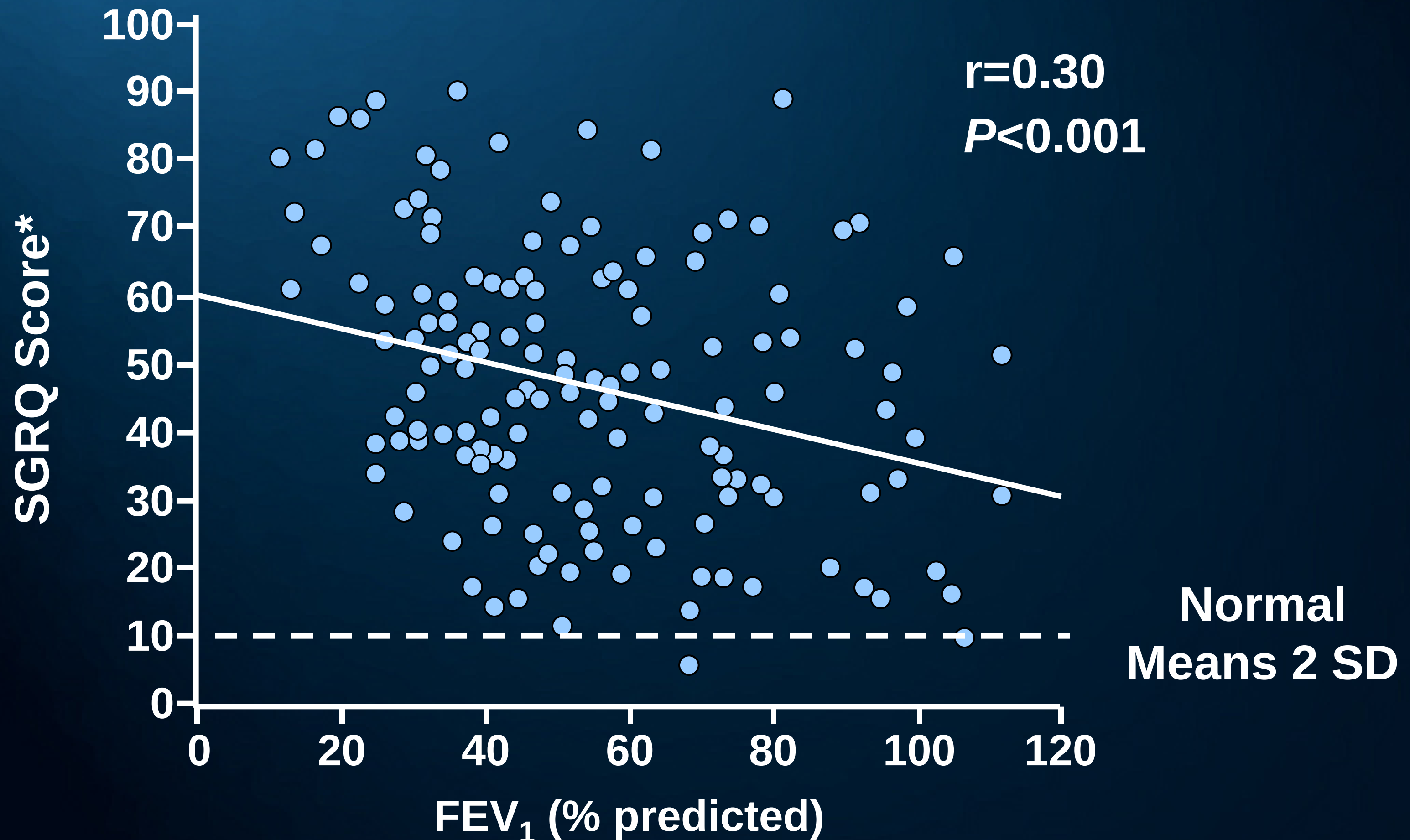


Mannino Thorax '07

No single parameter in patients with COPD is sufficient to be considered the gold standard to assess outcome.

— A. Fishman, 1994

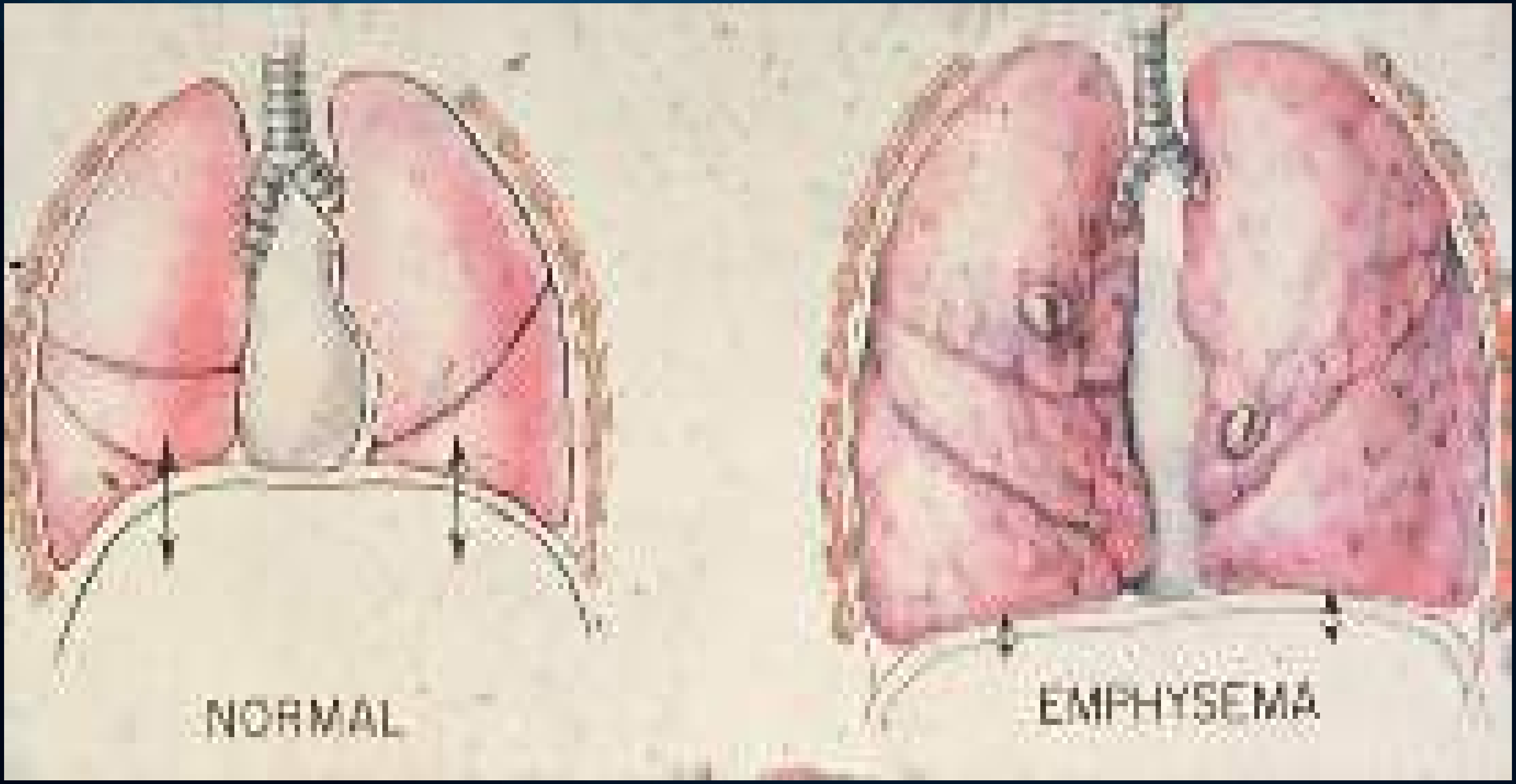
Correlation of Quality of Life Scores (SGRQ) With FEV_1 in Patients With COPD

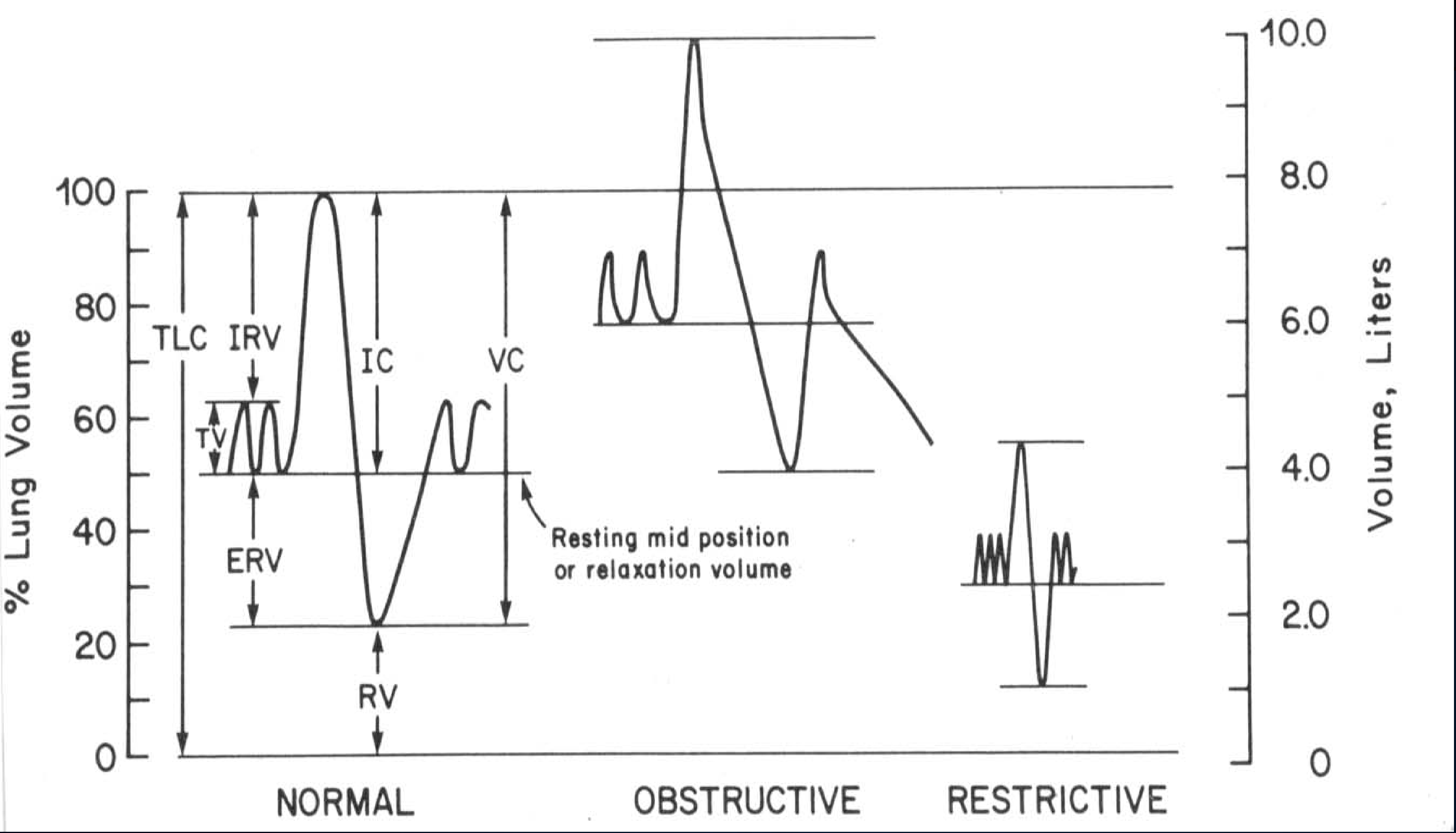


*Higher scores = worse quality of life.
SGRQ = St. George's Respiratory Questionnaire.

Jones PW. *Chest*. 1995;107(suppl):187S-193S.

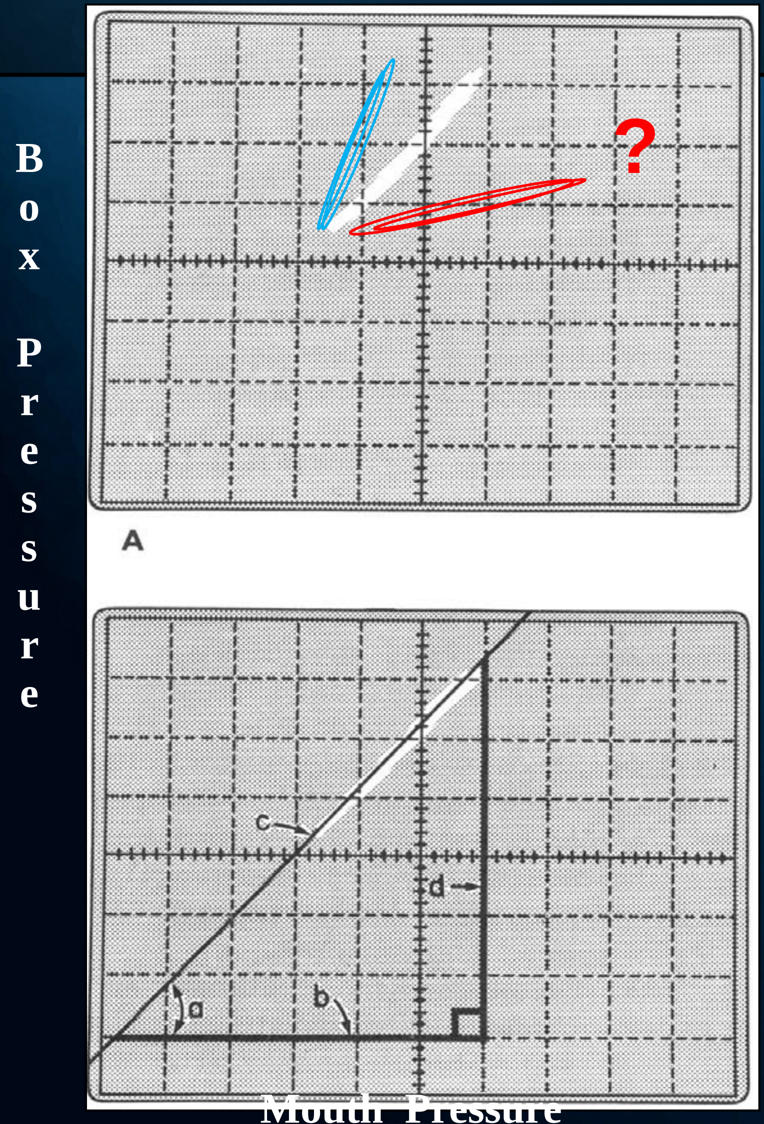
Hyperinflation in Emphysema

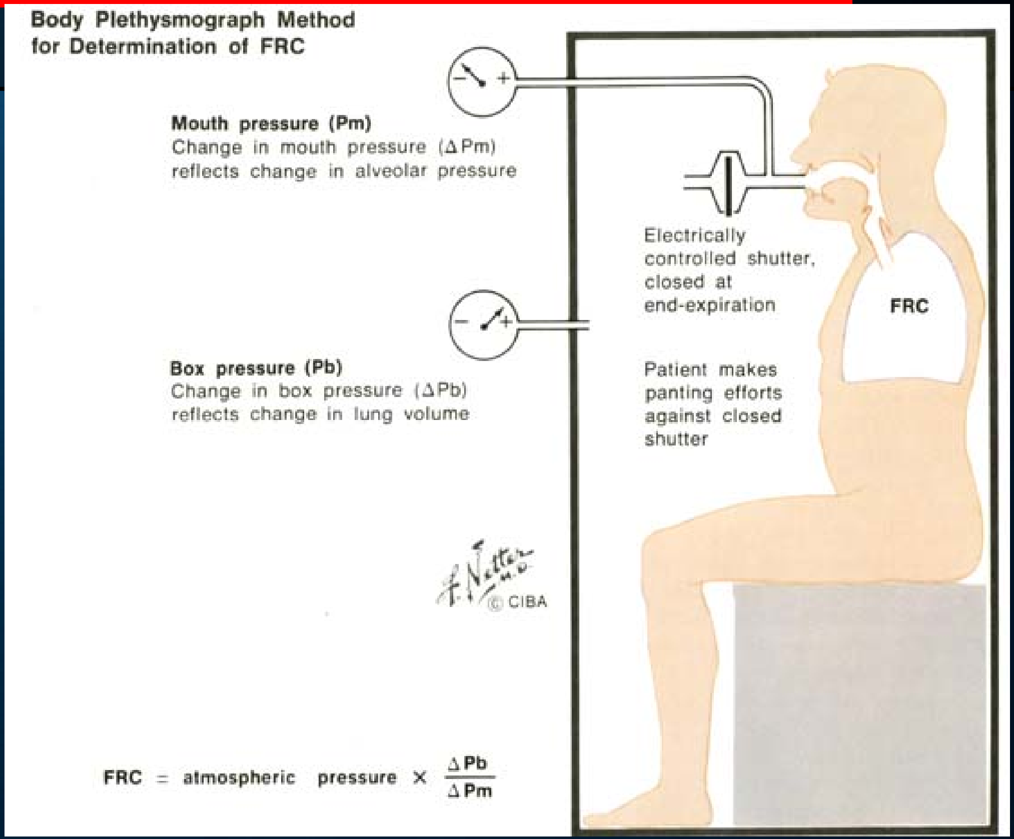


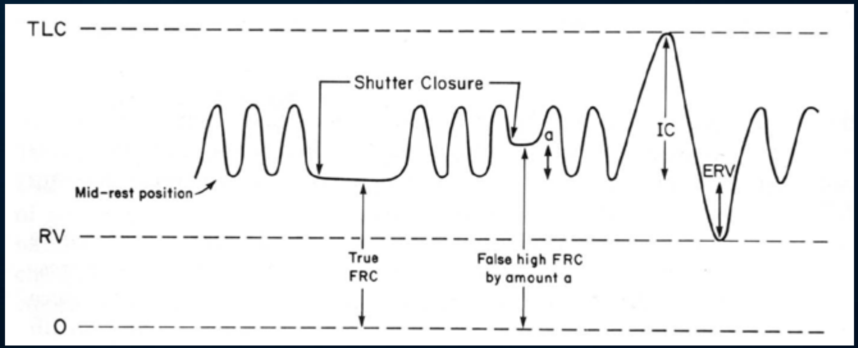


100
80
60
40
20
0
% Lung Volume
TLC
IRV
TV
ERV
IC
VC
RV
Resting mid position
or relaxation volume
10.0
8.0
6.0
4.0
2.0
0
Volume, Liters
NORMAL
OBSTRUCTIVE
RESTRICTIVE

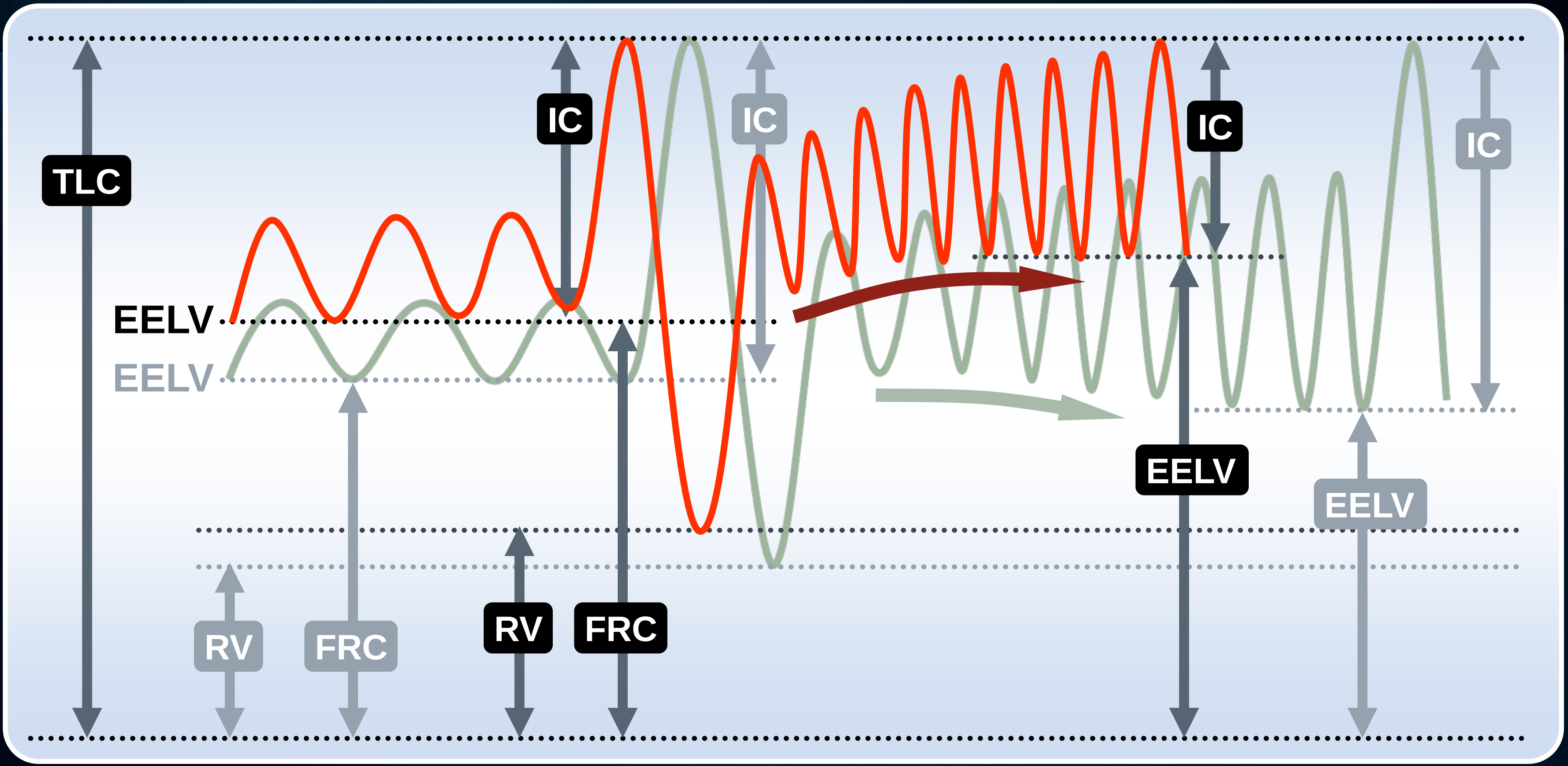
Plethysmographic Determination of FRC







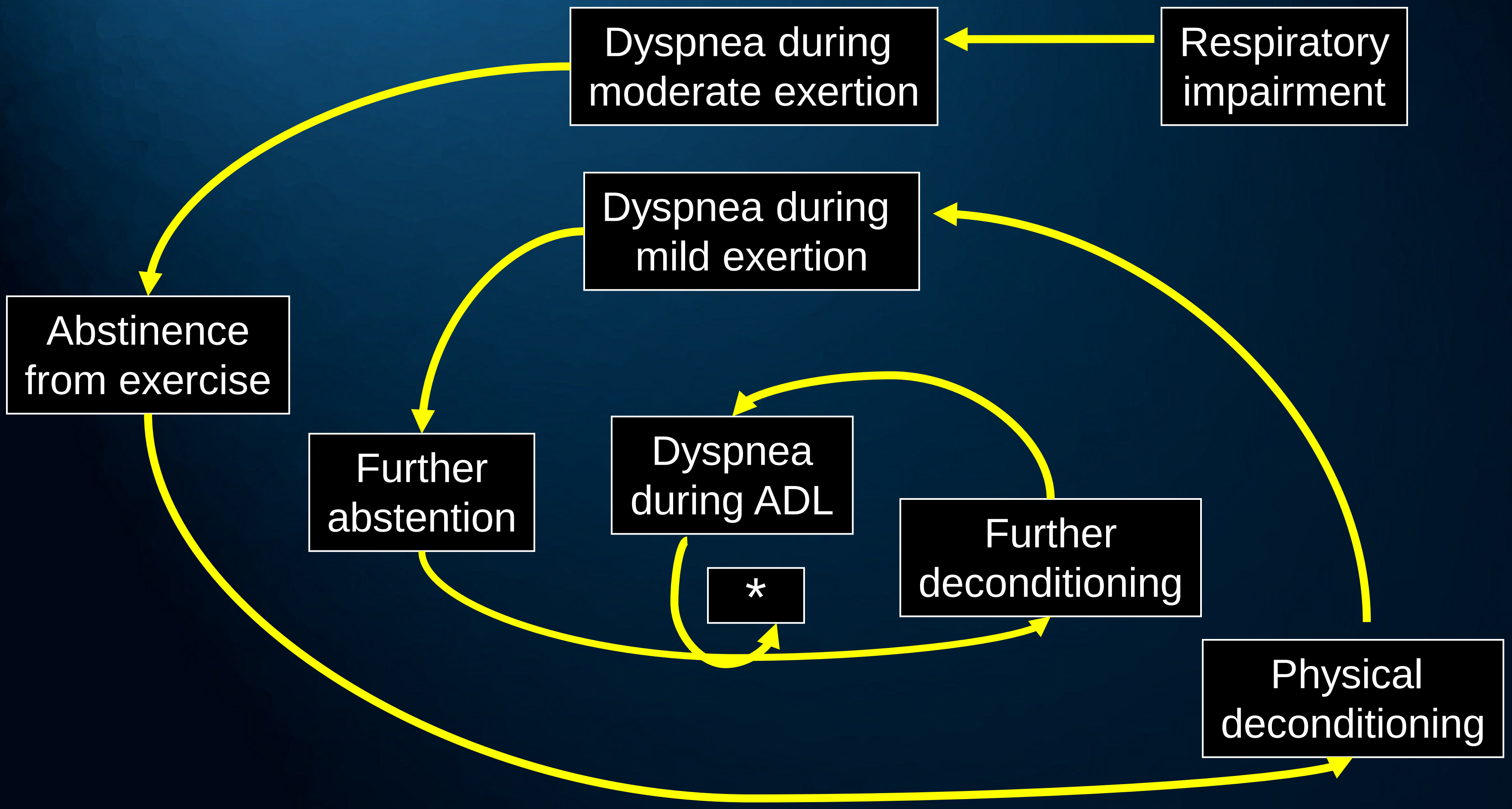
COPD
Exercise



TLC=total lung capacity; IC=inspiratory capacity;
EELV=end expiratory lung volume; RV=residual volume;
FRC=functional residual capacity

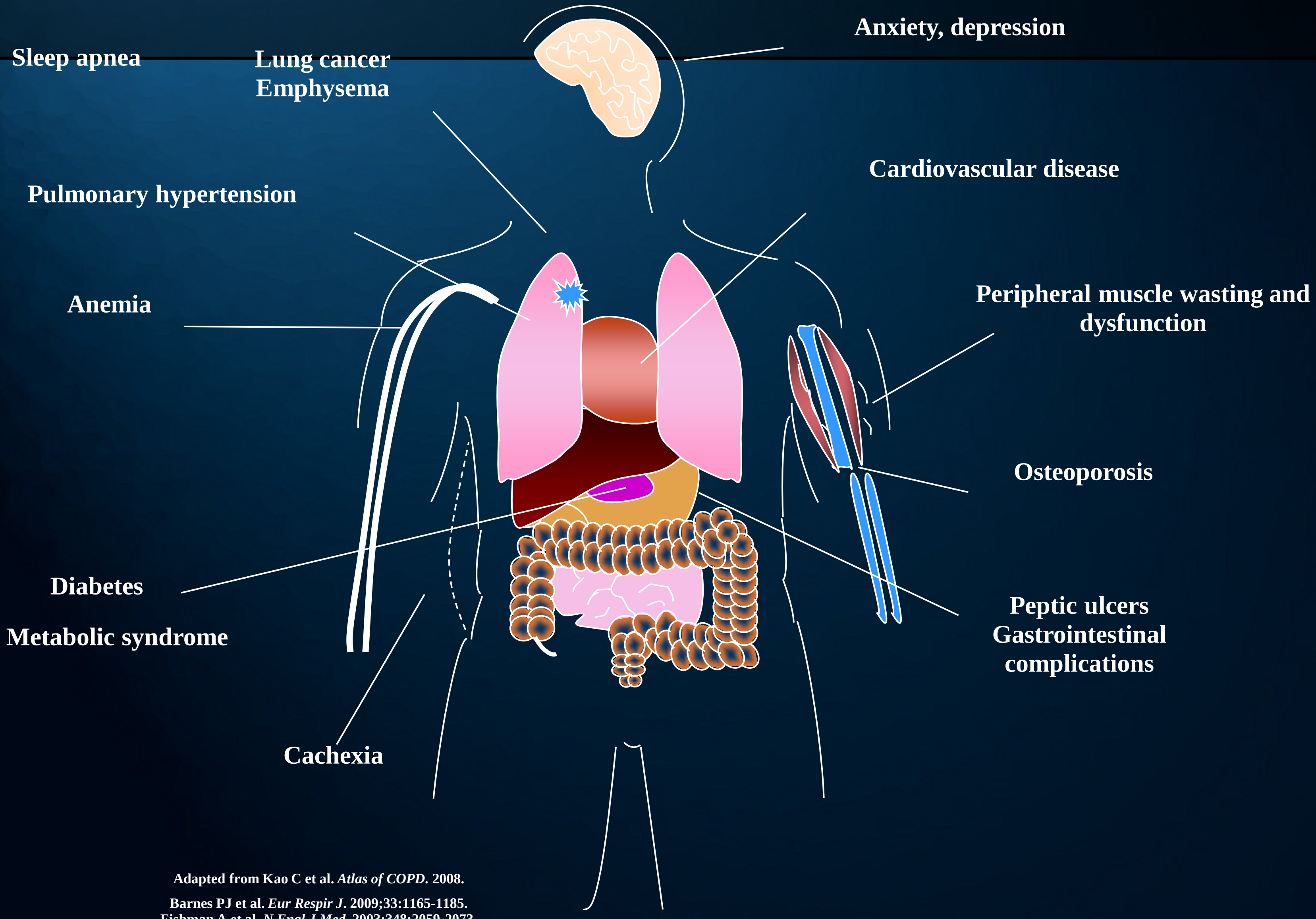
Adapted from: O'Donnell D, et al. Am J Respir Crit Care Med. 2001;164:770-777.

The Inactivity-Dyspnea Spiral



*Stay at home, depression, oxygen therapy, etc.
Adapted from Denis O´Donnell, MD.

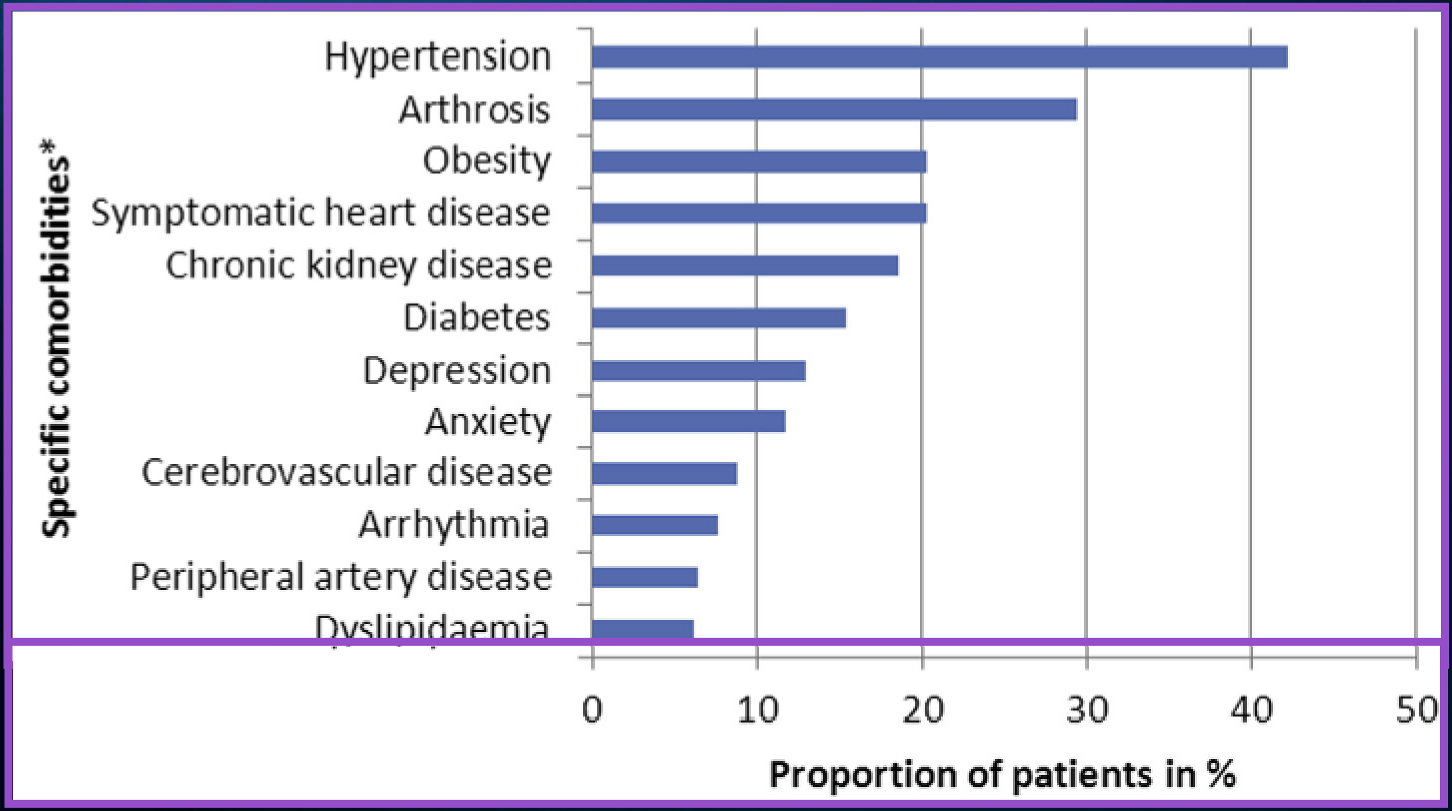
Comorbidities Are Common in COPD



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 Dysproportionate to Age Adjusted Population

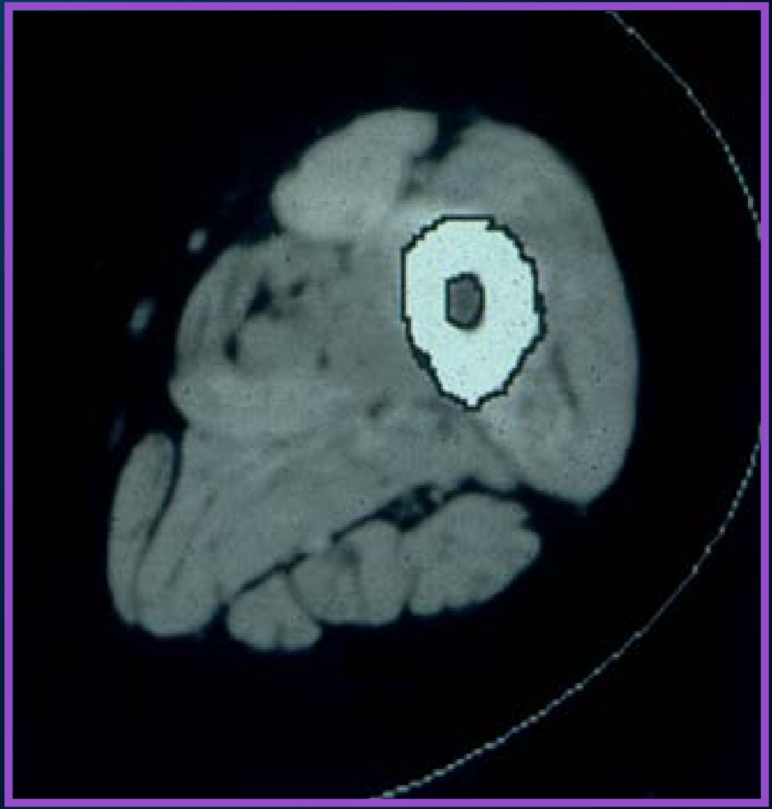


Frei *J Clin Epi* '14

Variation in Peripheral Muscle Structure May Contribute to Variation in Function

54-year-old, 5’ 9”, 6MW -1,230 ft

FEV_1 - 1.35 L



71-year-old, 5’ 11”, 6MW - 420 ft

FEV_1 - 0.71 L

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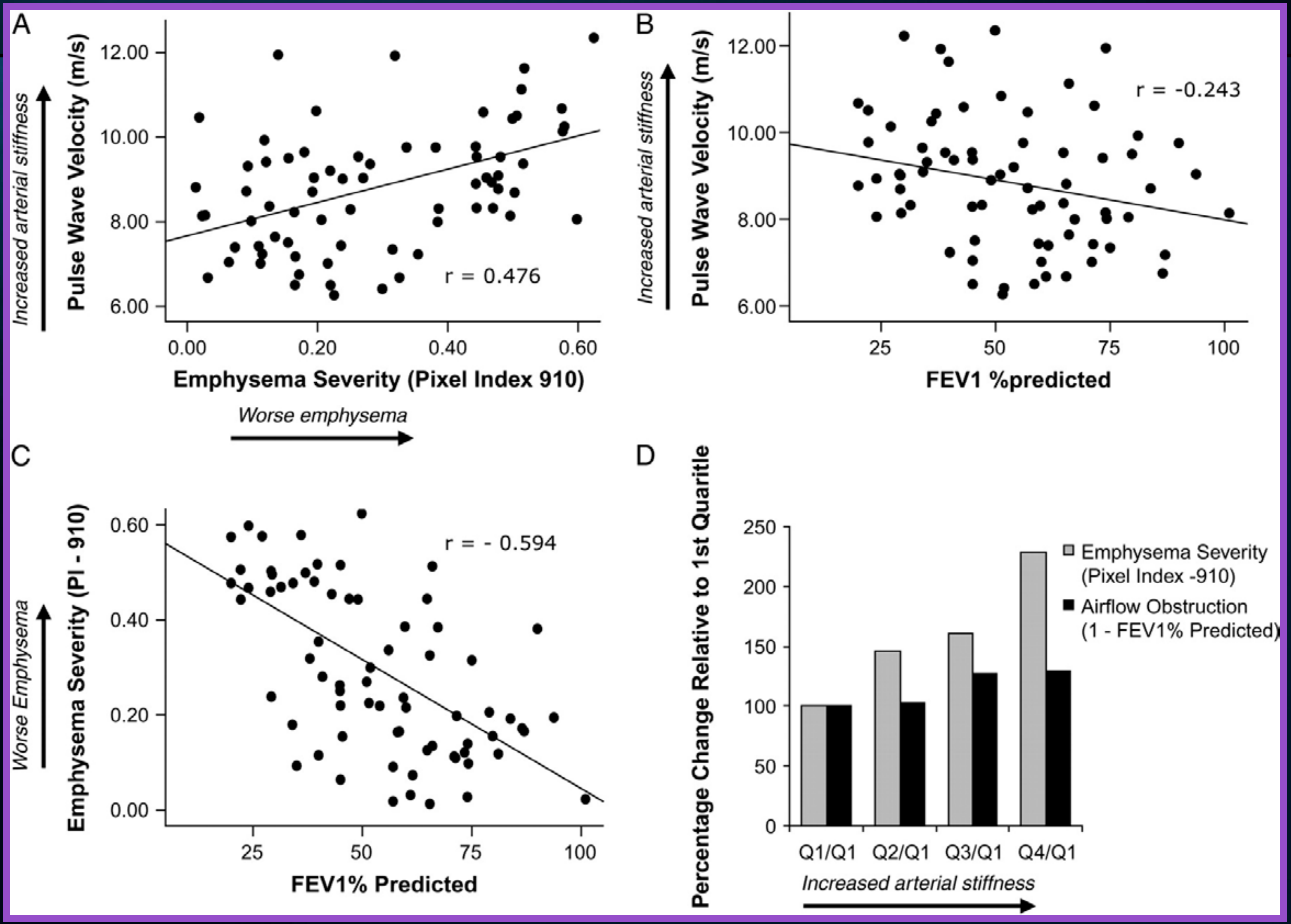
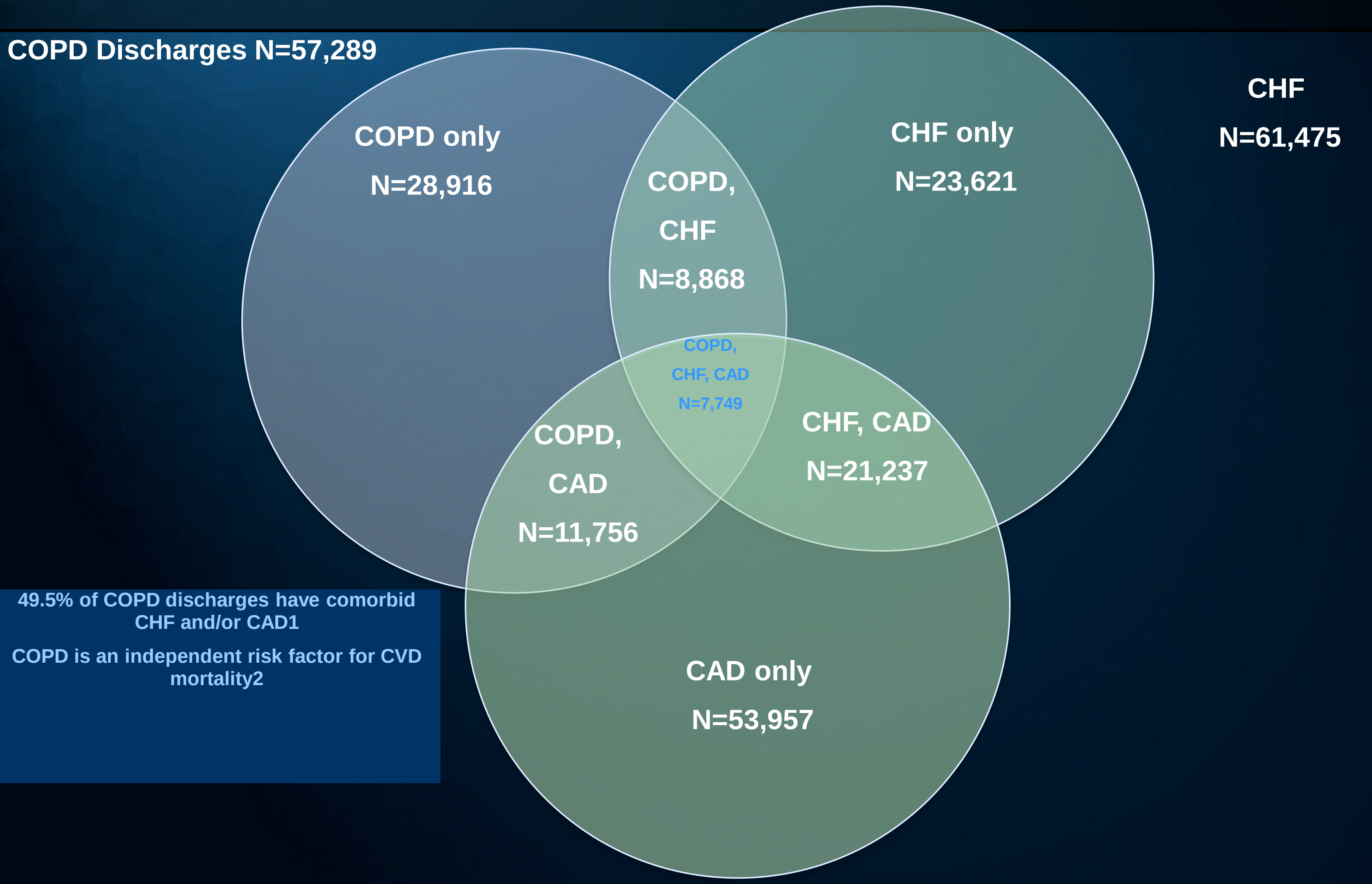
Association of Arterial Wall Stiffness with Phenotype
Emphysema Severity vs. Airflow Obstruction



McAllister et al *AJRCCM 2007 ;* 176: 1208-1214

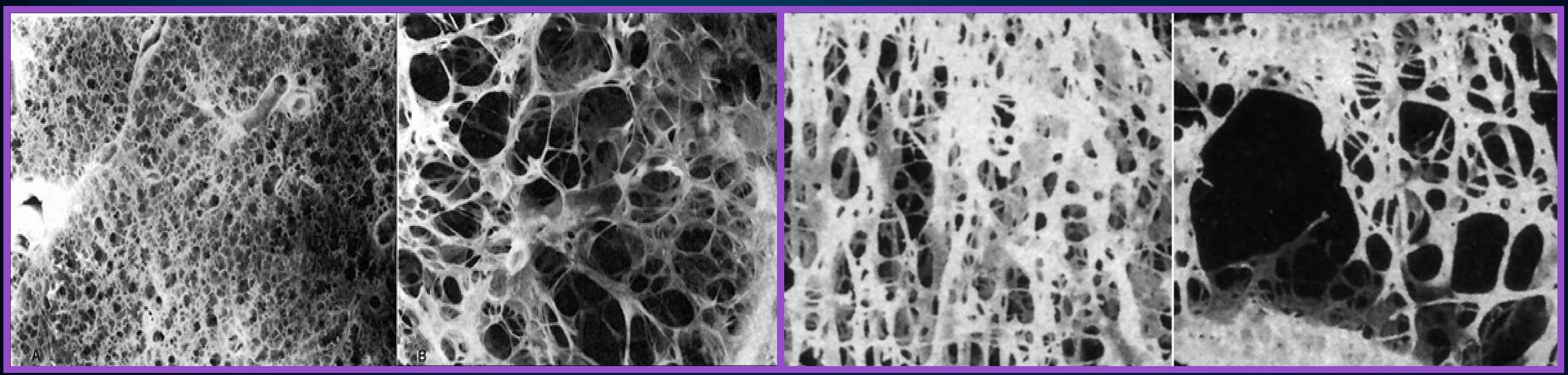
A Common Combination: COPD and Cardiac Disease



- 49.5% of COPD discharges have comorbid CHF and/or CAD1
- COPD is an independent risk factor for CVD mortality2

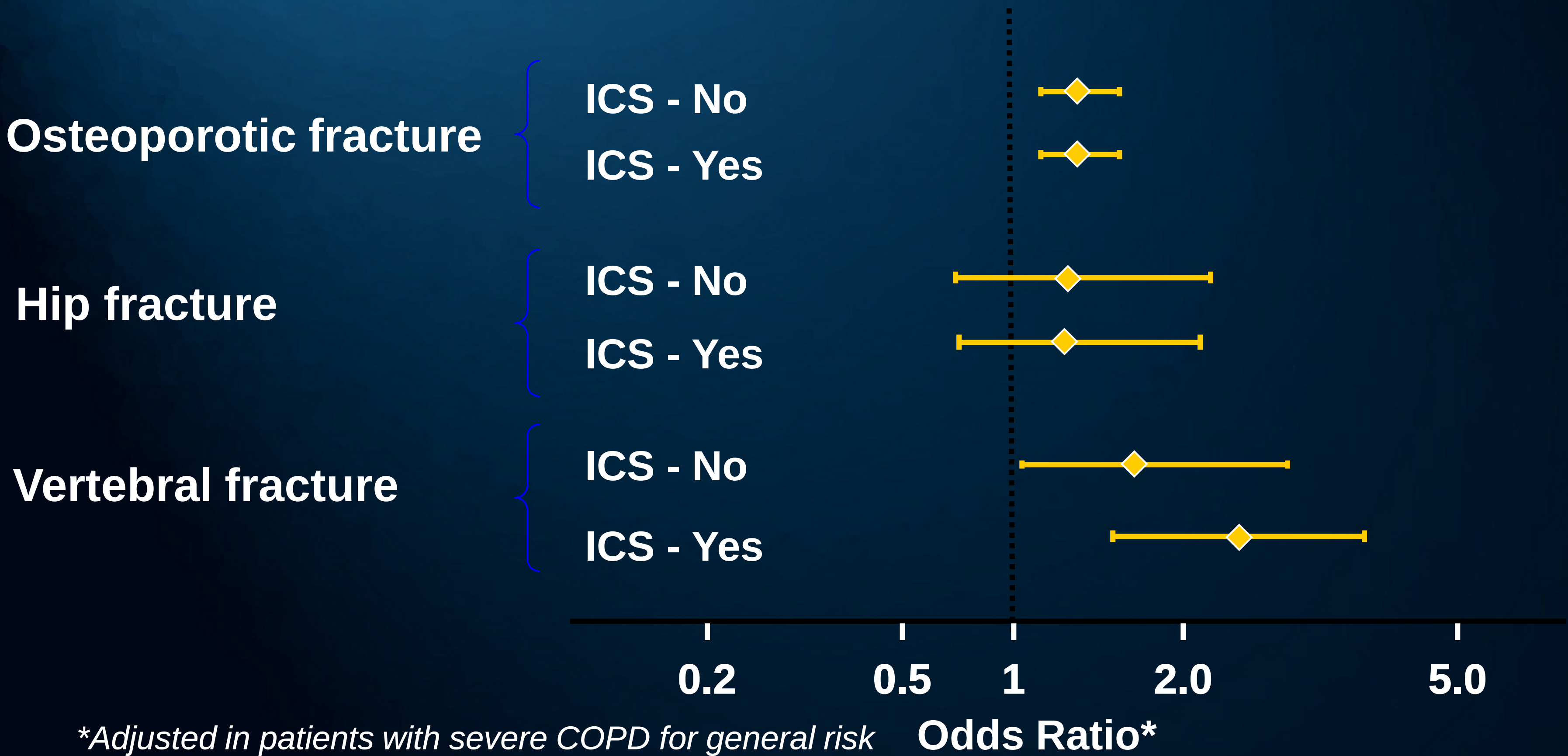
1. © Pittsburgh Regional Health Initiative 2010. Courtesy of Brian W. Carlin, MD. 2. Finkelstein J et al. *Int J COPD*. 2009;4:337–349.

Lung and Bone



Normal **Emphysema** **Normal** **Osteoporosis**

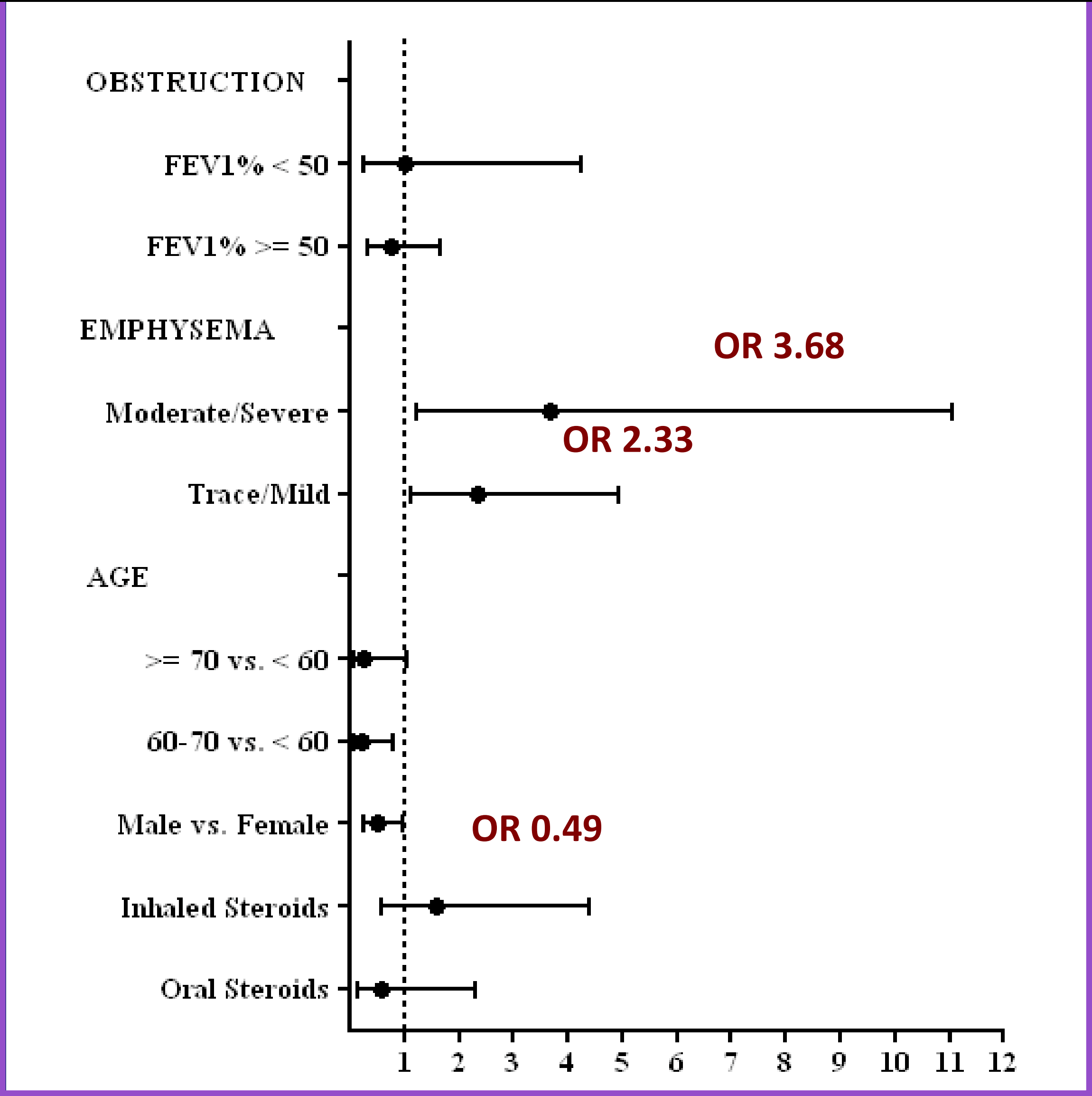
Severe Obstructive Airway Disease Is Associated With Greater Risk of Fracture



**Adjusted in patients with severe COPD for general risk factors, smoking status, duration of enrollment, and exposure to bronchodilators*

de Vries F, et al. *Eur Respir J.* 2005;25:879-884.

Radiographic Emphysema but NOT Air Flow Obstruction Associated with Risk of Of Low Bone Mineral Density on DEXA

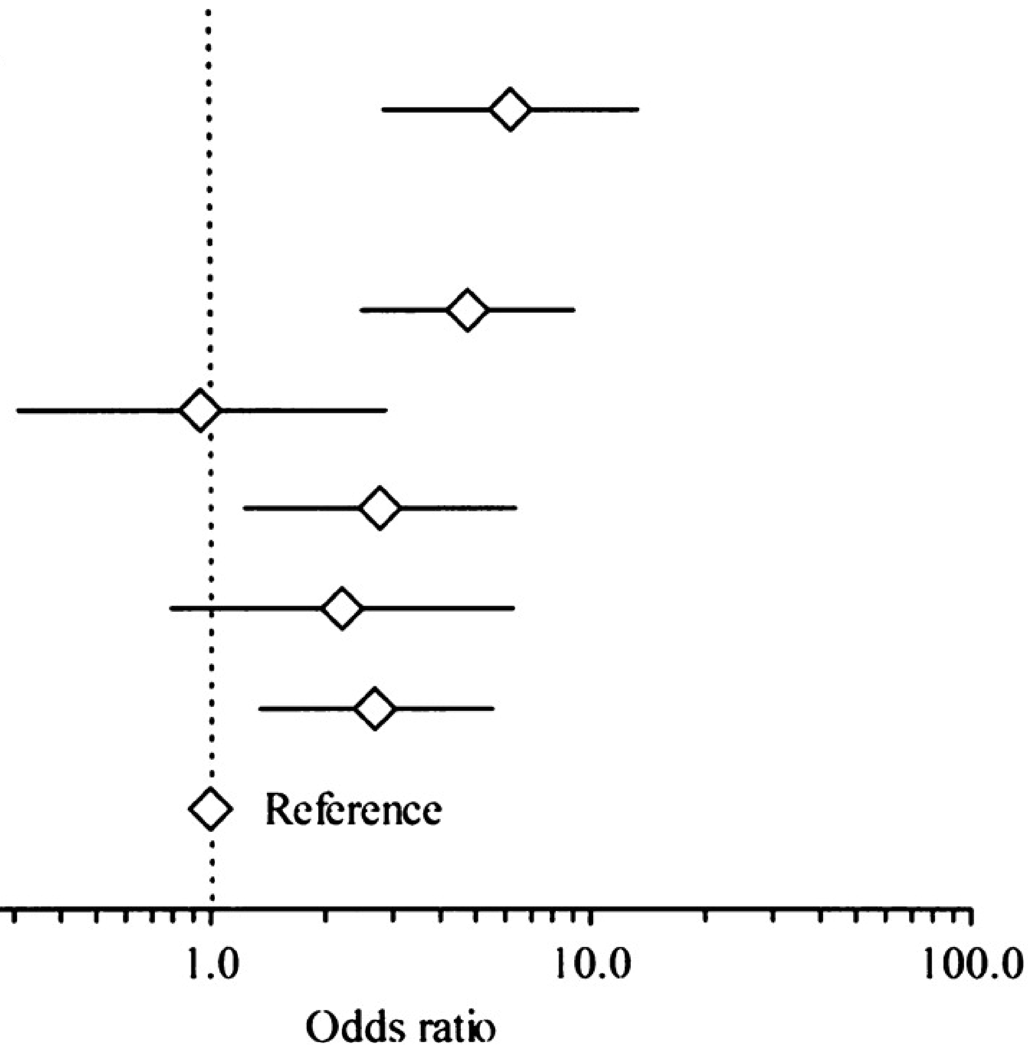


Bon *AJRCCM* '12

National Heart Lung and Blood Institute
People Science Health

Stronger association of Lung Cancer with CT Emphysema Compared to Airflow Obstruction

Airflow obstruction	Radiographic emphysema	Lung cancer Yes	Lung cancer No
III-IV	Yes	15	154
III-IV	No	0	63
II	Yes	32	472
II	No	4	320
I	Yes	11	287
I	No	5	190
None	Yes	17	558
None	No	15	1,495



Wilson et. al. *Am J Respir Crit Care Med 2008 ;178:738–744*

Predictors of Depression: Pittsburgh SCCOR cohort

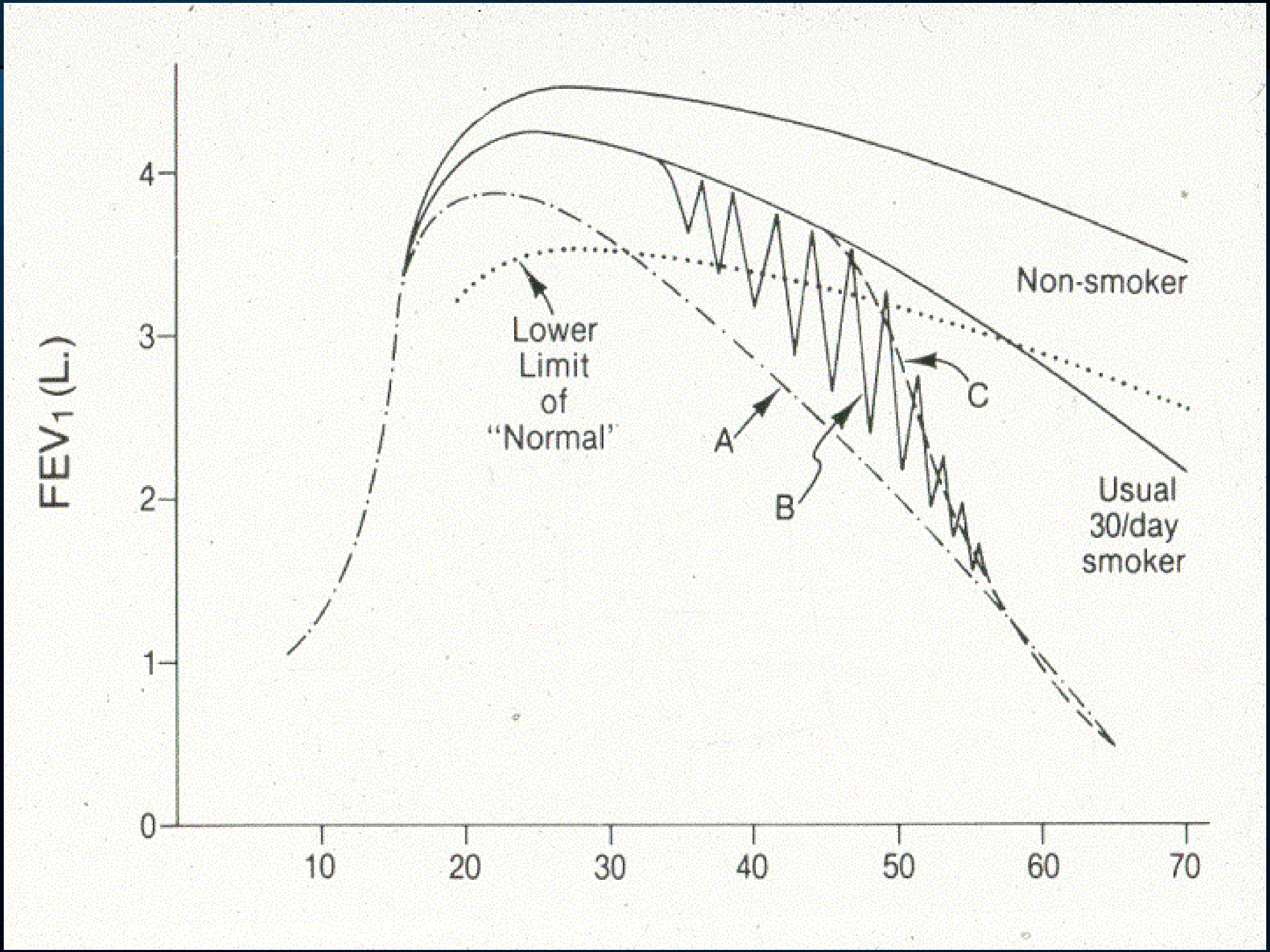
Increased depressive symptoms predicted by:

1. Decreased FEV1 % pred. ($p=0.0031$)
2. Female gender (0.0133)
3. Current smoking status ($p=0.0204$)
4. Increased plasma IL-6 concentration ($p=0.0227$)

N=450 Multivariate analysis

Natural History of Chronic Airflow Obstruction

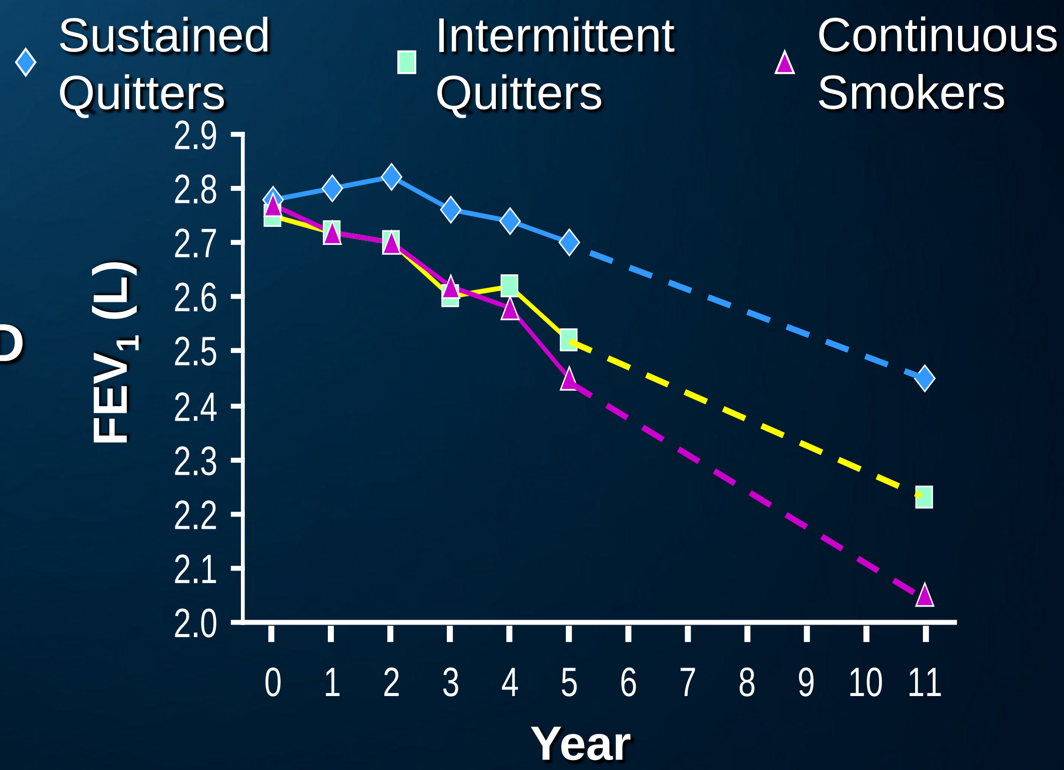
X



Adapted from Fletcher and Peto, Burrows

Does early Dx 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?**



Smoking Cessation Slows Lung Function Decline in Mild COPD: ***Lung Health Study at 11 Years***

Reproduced with permission from:

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

The Argument for Selective Screening

1. During the past 4 weeks, how much of the time did you feel short of breath?

None of the time	A little of the time	Some of the time	Most of the time	All of the time
☐ 0	☐ 0	☐ 1	☐ 2	☐ 2

2. Do you ever cough up any "stuff," such as mucus or phlegm?

No, never	Only with occasional colds or chest infections	Yes, a few days a month	Yes, most days a week	Yes, every day
☐ 0	☐ 0	☐ 1	☐ 1	☐ 2

3. Please select the answer that best describes you in the past 12 months.
I do less than I used to because of my breathing problems.

Strongly disagree	Disagree	Unsure	Agree	Strongly agree
☐ 0	☐ 0	☐ 0	☐ 1	☐ 2

4. Have you smoked at least 100 cigarettes in your ENTIRE LIFE?

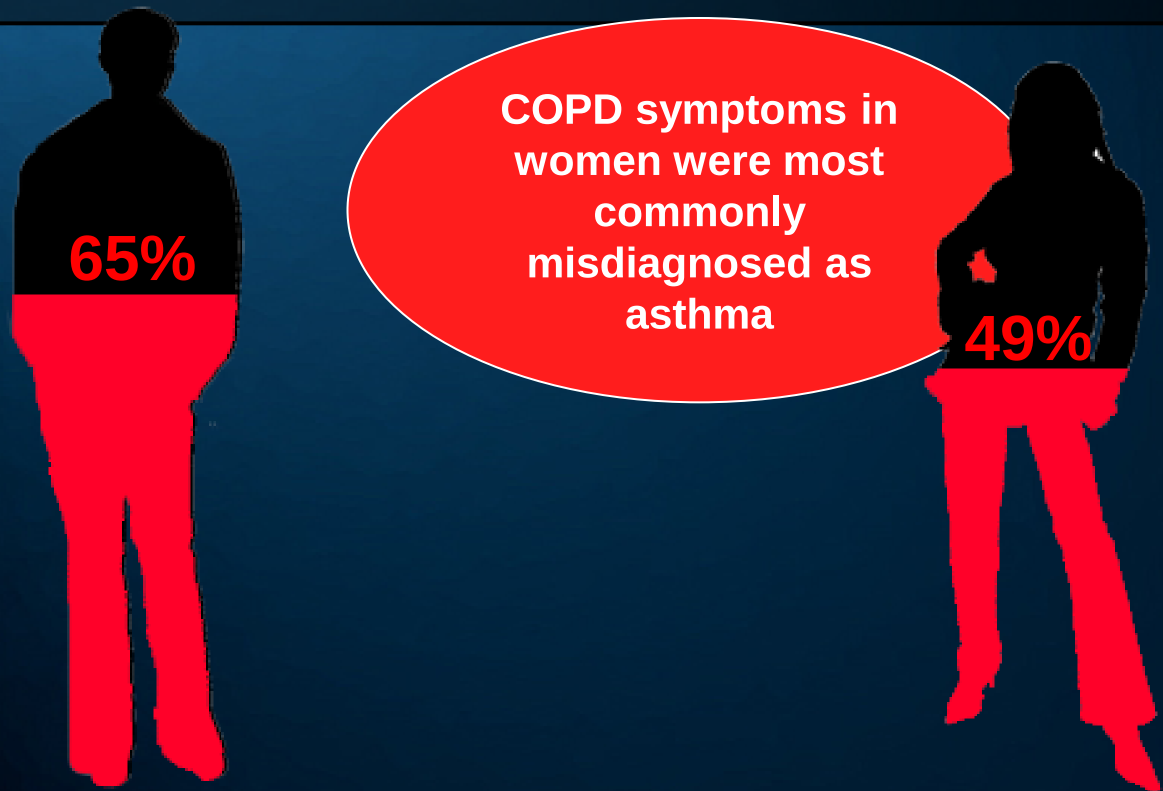
No	Yes	Don't know
☐ 0	☐ 2	☐ 0

5. How old are you?

Age 35 to 49	Age 50 to 59	Age 60 to 69	Age 70+
☐ 0	☐ 1	☐ 2	☐ 2

Martinez, et al., *COPD*, 2008;5:85. "COPD Screener"

Gender Bias: COPD Diagnosis Less Likely in Women with Identical Symptoms



Hypothetical Male Patient With COPD Symptoms
Diagnosed as COPD by
65% of physicians

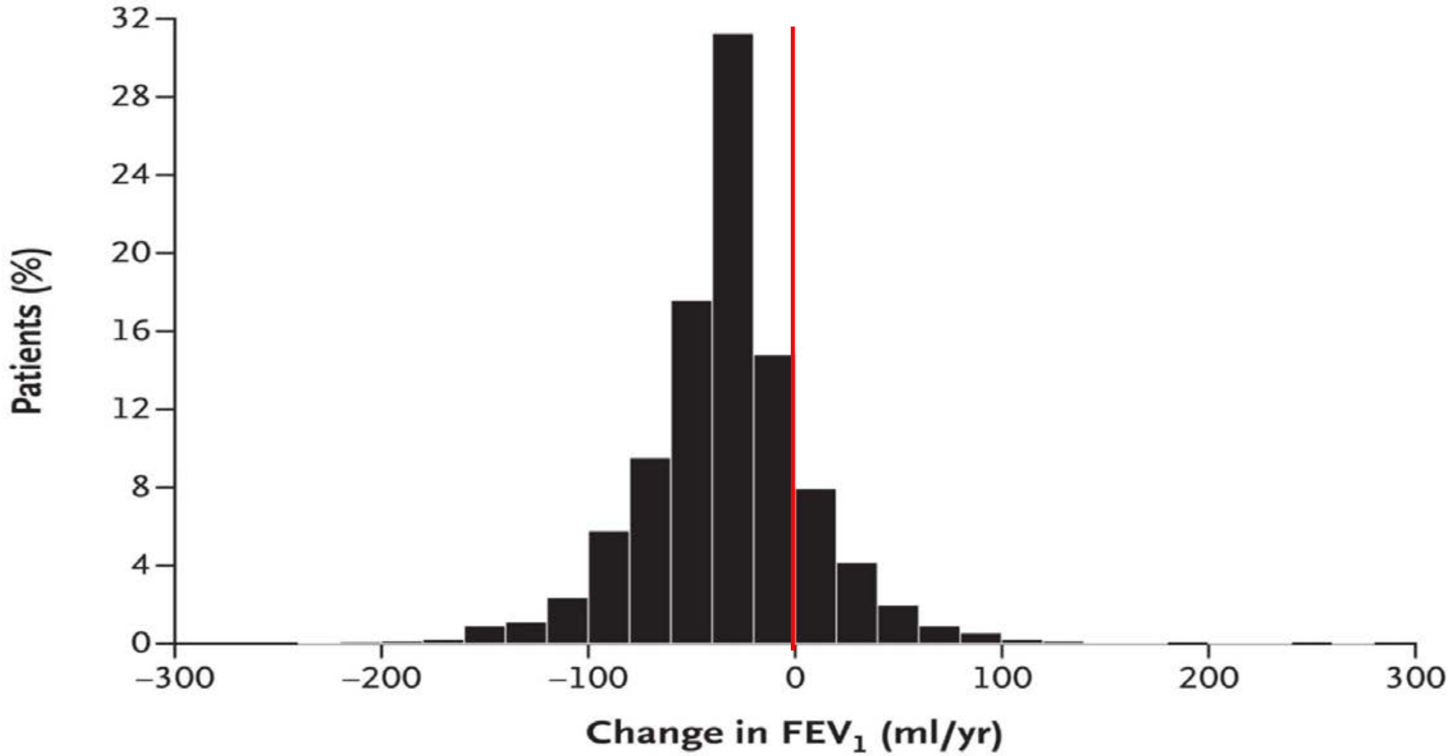
Hypothetical Female Patient With Identical COPD Symptoms
Diagnosed as COPD by
49% of physicians

Chapman KR, et al. *Chest*. 2001; 119:1691-1695.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

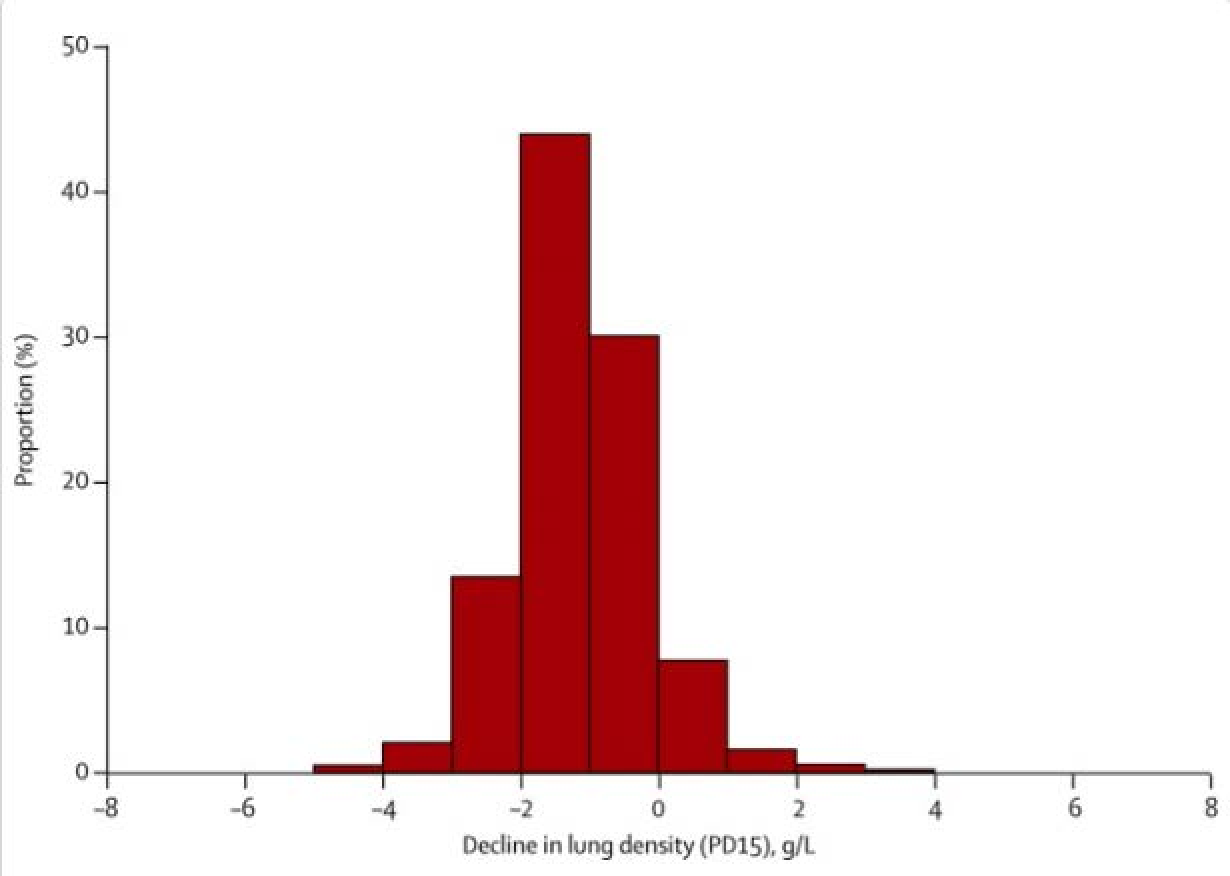
Changes in Forced Expiratory Volume in 1 Second over Time in COPD



Vestbo J et al. N Engl J Med 2011;365:1184-1192

Variation In Emphysema Progression

(ECLIPSE)



Coxson et al. *Lancet Respir Med*.**2013**;1:129-36.

Effects of Biomarkers on Baseline FEV1 and Annual Rate of Change in FEV1: Eclipse

Biomarker	Effect on Baseline FEV_1	P Value	Effect on Annual Rate of Change in FEV_1	P Value
	ml		*ml / yr*	
Fibrinogen	-93 ± 10.6	<0.001	-1 ± 2.1	0.63
Interleukin-6	0 ± 10.0	>0.99	1 ± 2.3	0.52
Interleukin-8	20 ± 9.9	0.04	-2 ± 2.0	0.36
TNF-α	1 ± 9.9	0.89	0 ± 1.8	0.84
C-reactive protein	-23 ± 10.3	0.037	4 ± 2.1	0.07
CC-16	33 ± 10.8	0.002	4 ± 2.2	0.04
Surfactant protein D	0 ± 10.3	0.96	-3 ± 2.1	0.18

Vestbo J et al. N Engl J Med 2011;365:1184-1192

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Association of Plasma Biomarkers with Severity and Progression of Emphysema

	Effect on baseline 15th percentile (g/L)		Effect on annual change (g/L per year)	
	Coefficient (SE)	p	Coefficient (SE)	p
SP- D	2·18 (0·47)	<0·0001	−0·23 (0·08)	0·004
sRAGE	3·87 (0·47)	<0·0001	0·24 (0·07)	0·001
Fibrinogen	−0·33 (0·49)	0·51	0·18 (0·08)	0·019
IL-6	−0·29 (0·48)	0·55	0·31 (0·09)	0·0009
IL-8	0·68 (0·44)	0·12	0·14 (0·08)	0·07
TNFα	0·23 (0·44)	0·60	0·03 (0·06)	0·61
CRP	0·13 (0·51)	0·80	−0·21 (0·08)	0·012
CC-16	−0·84 (0·49)	0·09	−0·11 (0·08)	0·15
CCL-18	−1·56 (0·48)	0·001	0·12 (0·08)	0·13

Cross sectional association not the same as longitudinal predictor

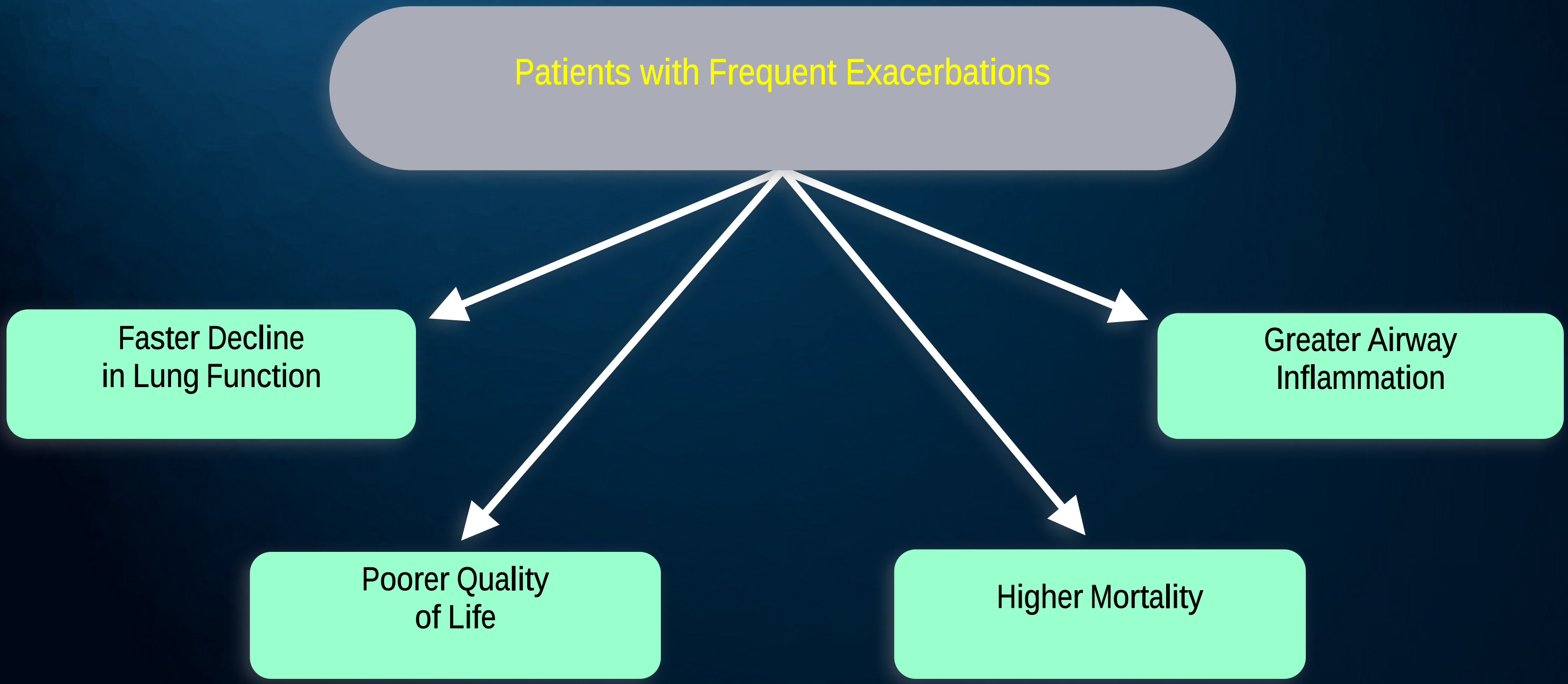
Coxson et al. *Lancet Respir Med.* **2013**;1:129-36.

An exacerbation of COPD is:

"an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication."

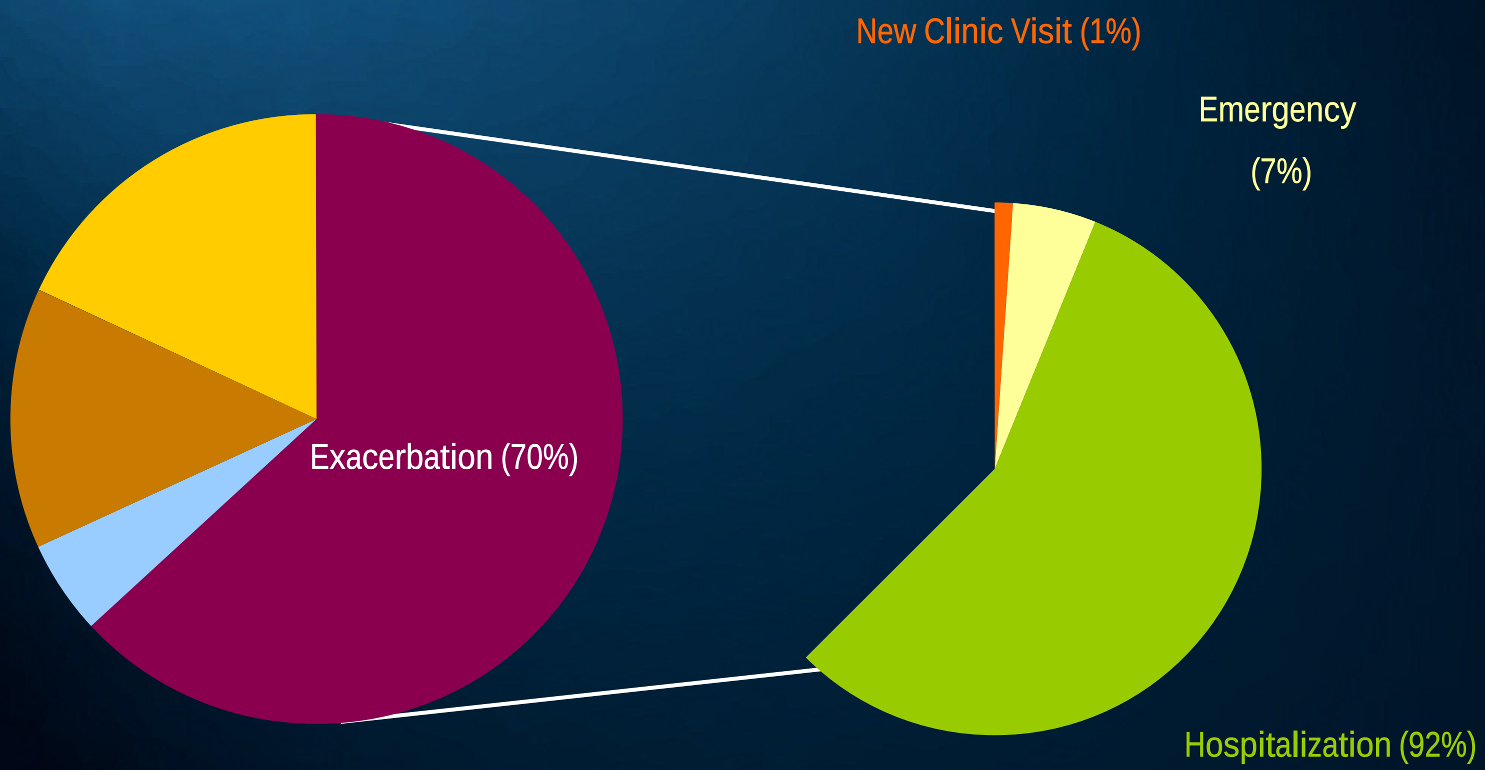
Global Strategy for Diagnosis, Management, and Prevention of COPD 2015. Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://www.goldcopd.org.

Impact of Exacerbations in COPD



Adapted from Wedzicha JA, Seemungal TA. *Lancet*. 2007;370:786-796.

Most COPD Costs are Hospital-related



30-day readmission rates for COPD are ~25%

Miravitlles M et al. *Chest.* 2002;121:1449-1455.

Jencks SF et al. *N Engl J Med.* 2009; 360:1418-1428.

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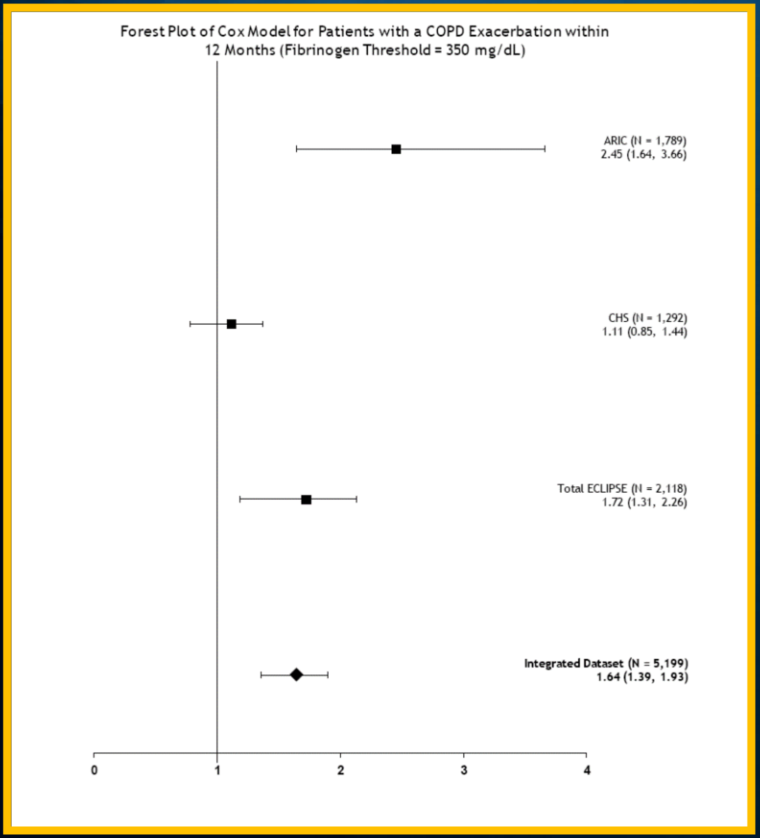
Attributes Associated With Exacerbation Risk

Patients with Moderate (GOLD Stage 2) COPD

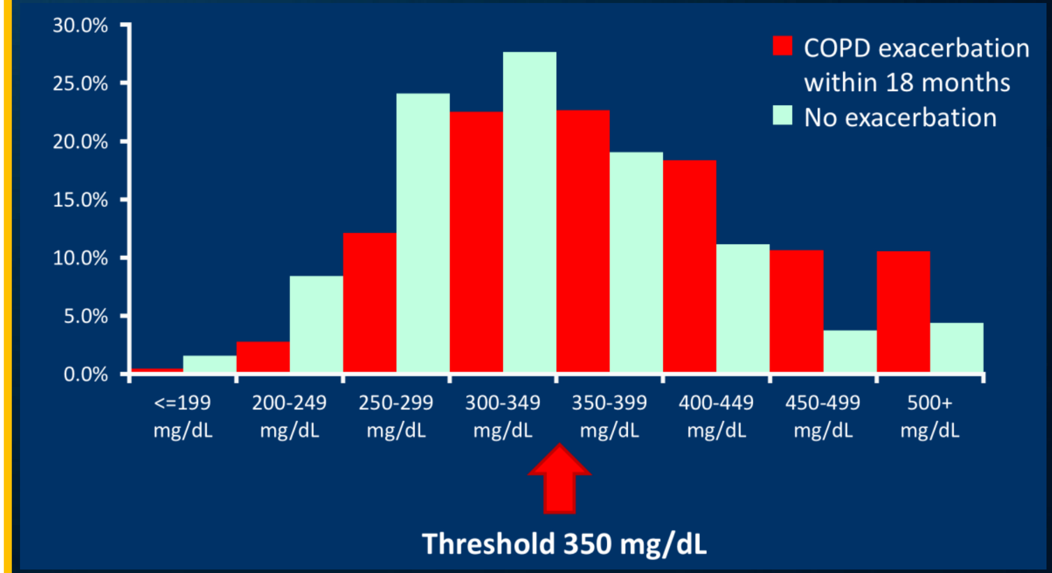
Factor	Number of Exacerbations						Overall P Value
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Women (N = 376)							
Exacerbation during previous year — yes vs. no	8.89 (4.32–18.29)	<0.001	2.28 (1.26–4.11)	<0.006	3.90 (1.82–8.34)	<0.001	<0.001
History of asthma — yes vs. no	3.38 (1.62–7.05)	<0.001	3.00 (1.59–5.66)	<0.001	1.12 (0.53–2.38)	0.76	<0.001
Fibrinogen — per increase of 1 SD on log scale	1.95 (1.28–2.97)	<0.002	1.22 (0.85–1.74)	0.28	1.60 (1.03–2.49)	<0.04	0.008
Men (N = 569)							
Exacerbation during previous yr — yes vs. no	7.38 (4.44–12.27)	<0.001	3.28 (2.09–5.13)	<0.001	2.25 (1.30–3.90)	0.004	<0.001
FEV_1 — per 100-ml decrease*	1.20 (1.11–1.31)	<0.001	1.07 (1.00–1.14)	<0.05	1.13 (1.04–1.23)	<0.006	<0.001
Chronic wheezing — yes vs. no	2.56 (1.55–4.23)	<0.001	1.40 (0.89–2.18)	0.14	1.83 (1.06–3.16)	<0.03	0.001

Hurst JR et al N Engl J Med 2010

Plasma Fibrinogen Stratification Tool for Exacerbations



COPD BIOMARKER QUALIFICATION CONSORTIUM
A COPD FOUNDATION INITIATIVE



Adapted from BE Miller, Tal-Singer R, Rennard SI, Furtwaengler A, Leidy N, Lowings M, Martin UJ, Martin TR, Merrill DD, Snyder J, Walsh J, Mannino DM. Plasma Fibrinogen Qualification as a Drug Development Tool in COPD: Perspective of the COPD Biomarker Qualification Consortium.(2016) *Am J Respir Crit Care Med*. Online Jan 8

Mission of the COPD Biomarkers Qualification Consortium (CBQC)

- Qualify biomarkers and patient-centered outcomes with regulatory agencies (FDA, EMA) to facilitate development of new treatments for COPD
- Identify drug development tools for which sufficient data exist to warrant consideration for qualification
  - Sources: pharma industry, academic and government databases
- Fill required gaps by facilitating collaborations among global consortia or investigators

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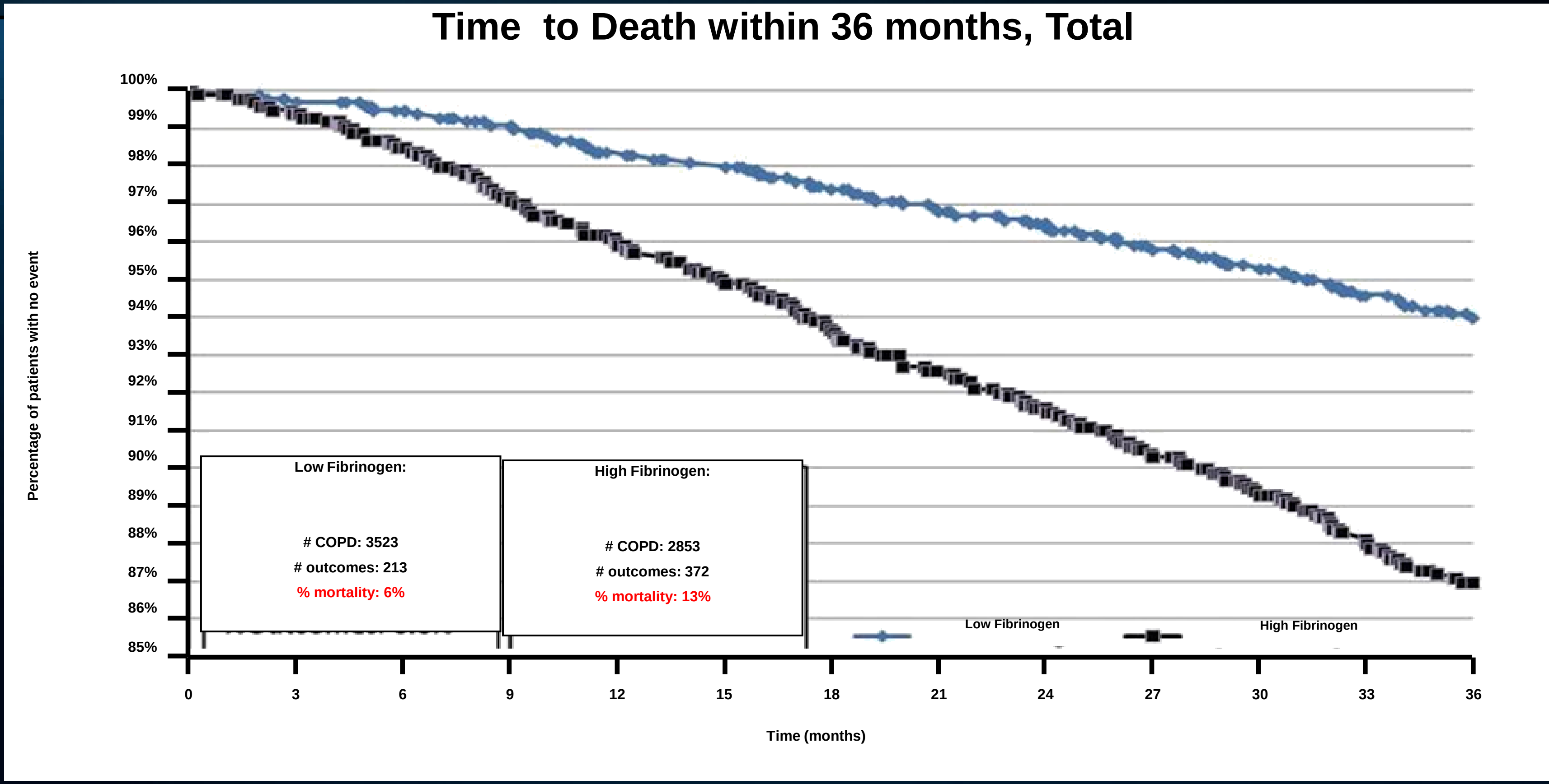
Plasma Fibrinogen & All Cause Mortality



Fibrinogen and COPD in the Biomarkers Qualification Consortium Database ATS 2013 poster

D.M. Mannino, B.E. Miller, A. Martin, R. Engle, J. Simeone, D.A. Lomas, J. Vestbo, R.G. Barr, M. Goldman, A. Maeser, S. Lanes, U. Martin, R. Tal-Singer, S.I. Rennard, D. Merrill

Highest Decline in FEV_1 Was Seen in Patients With Frequent Exacerbations Who Smoked

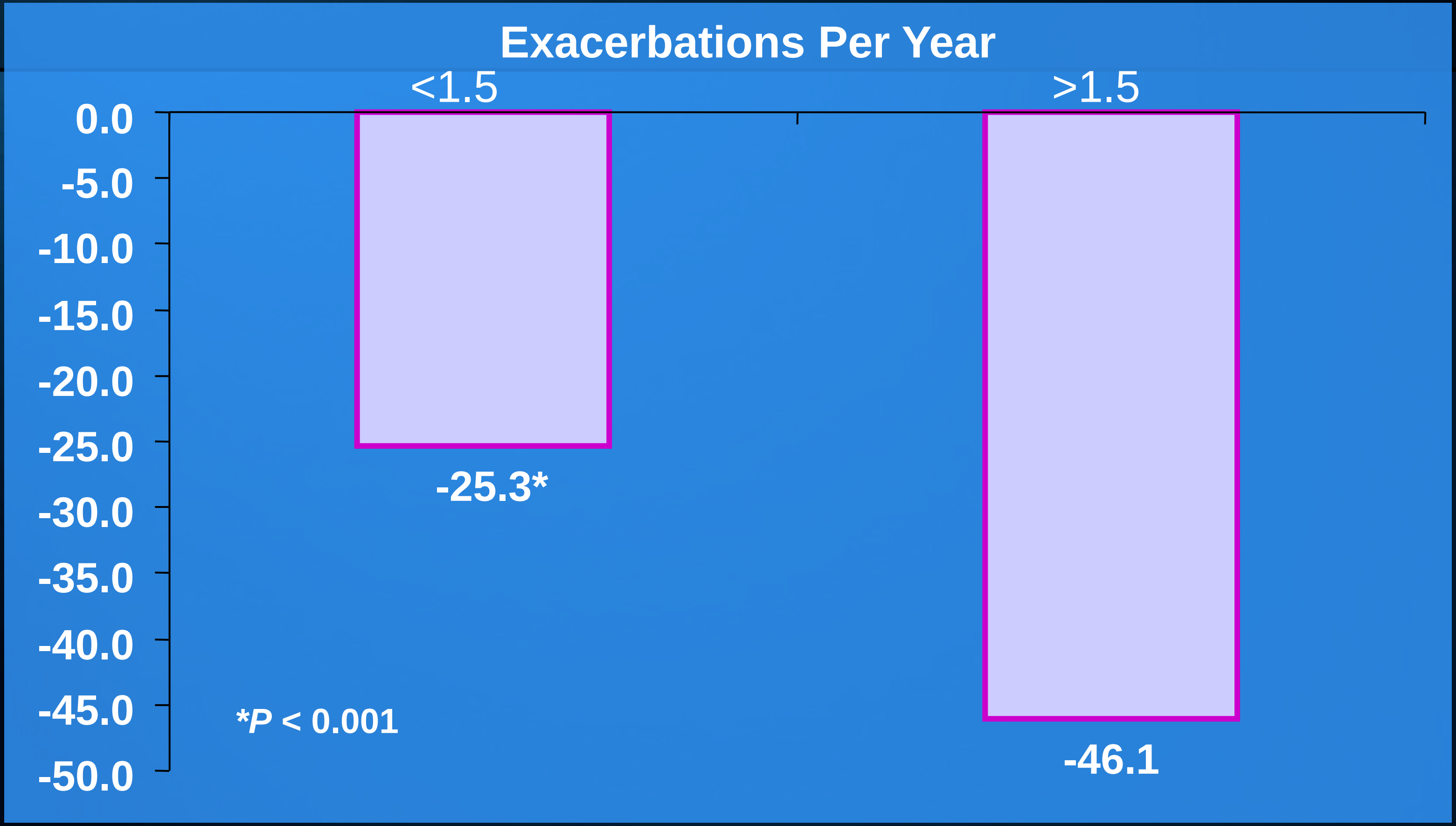
Average Decline in FEV_1 % Predicted Per Year Over 3 Years*

	Smokers			Ex-Smokers		
	N	Mean	95% CI P-Value	N	Mean	95% CI P-Value
Frequent exacerbations	22	-4.10	(-4.40, -3.80) <0.0001	29	-2.80	(-3.1, -2.5) <0.0001
Infrequent exacerbations	19	-3.15	(-3.55, -2.75) 0.002	27	-0.85	(-1.1, -0.5) 0.3

* Random effects modeling for COPD patients, smokers and ex-smokers separately, by exacerbation status. Adjusted for sex, age, smoking status, baseline FEV_1 (% predicted).

Makris D, et al. Resp Med. 2007;101:1305-1312. Reproduced with permission from Elsevier.

Frequency of Exacerbations Contributes to Decline in Lung Function



Results based on a secondary analysis of 32 patients who recorded daily FEV_1.
The median rate of exacerbations seen at clinic was 1.5 per patient per year.

Donaldson GC, et al. Thorax. 2002;57:847-852.

The BODE Index

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% predicted)	**≥ 65**	**50-64**	**36-49**	**≤ 35**
Distance walked in 6 min. (M)	**≥ 350**	**250-349**	**150-249**	**≤ 149**
MMRC dyspnea scale	**0-1**	**2**	**3**	**4**
BMI	**> 21**	**≤ 21**		

BODE = body mass index, obstruction, dyspnea, and exercise capacity;
MMRC = Modified Medical Research Council

Celli BR, et al. N Engl J Med. 2004;350:1005-1012.

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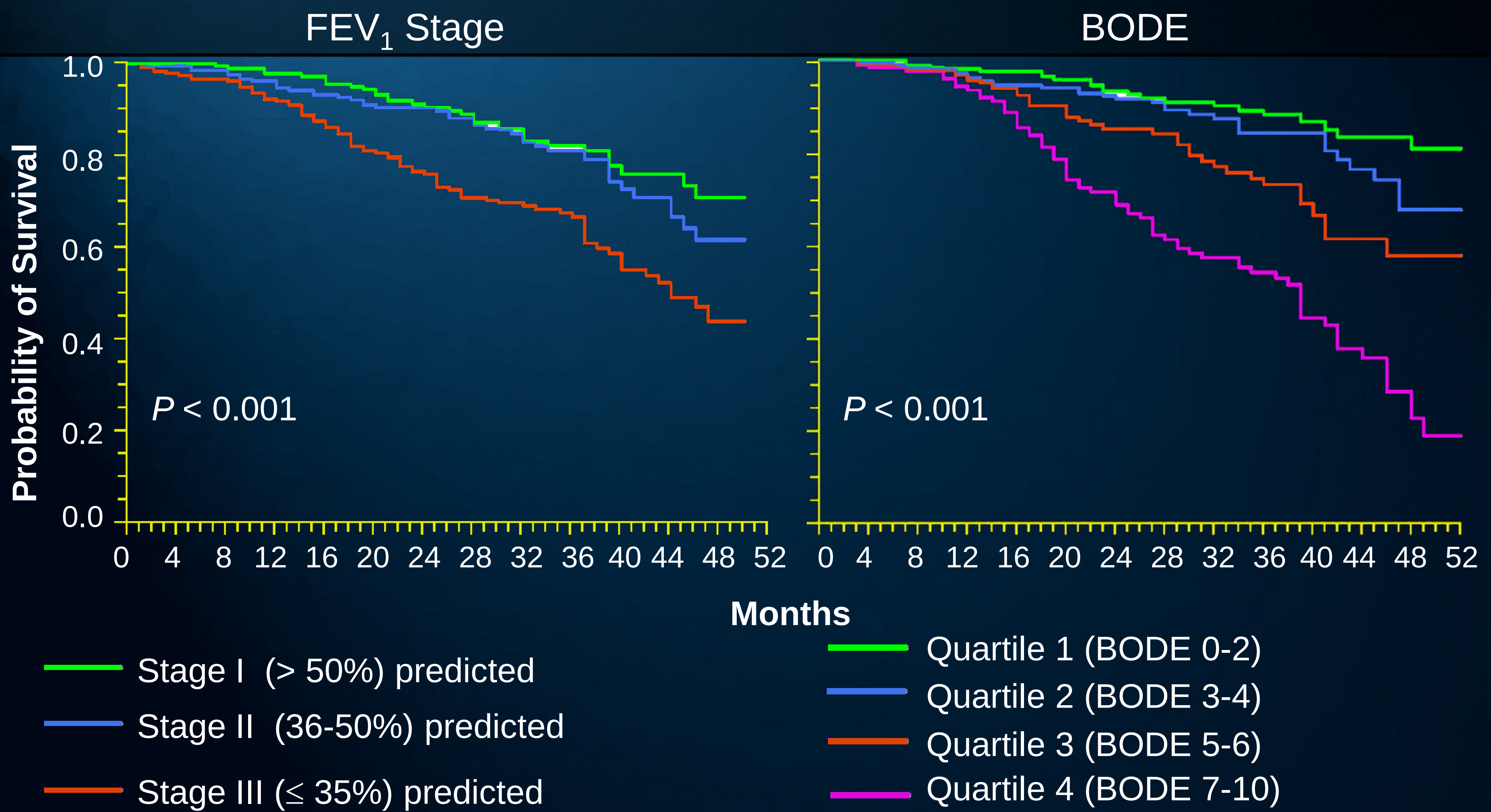
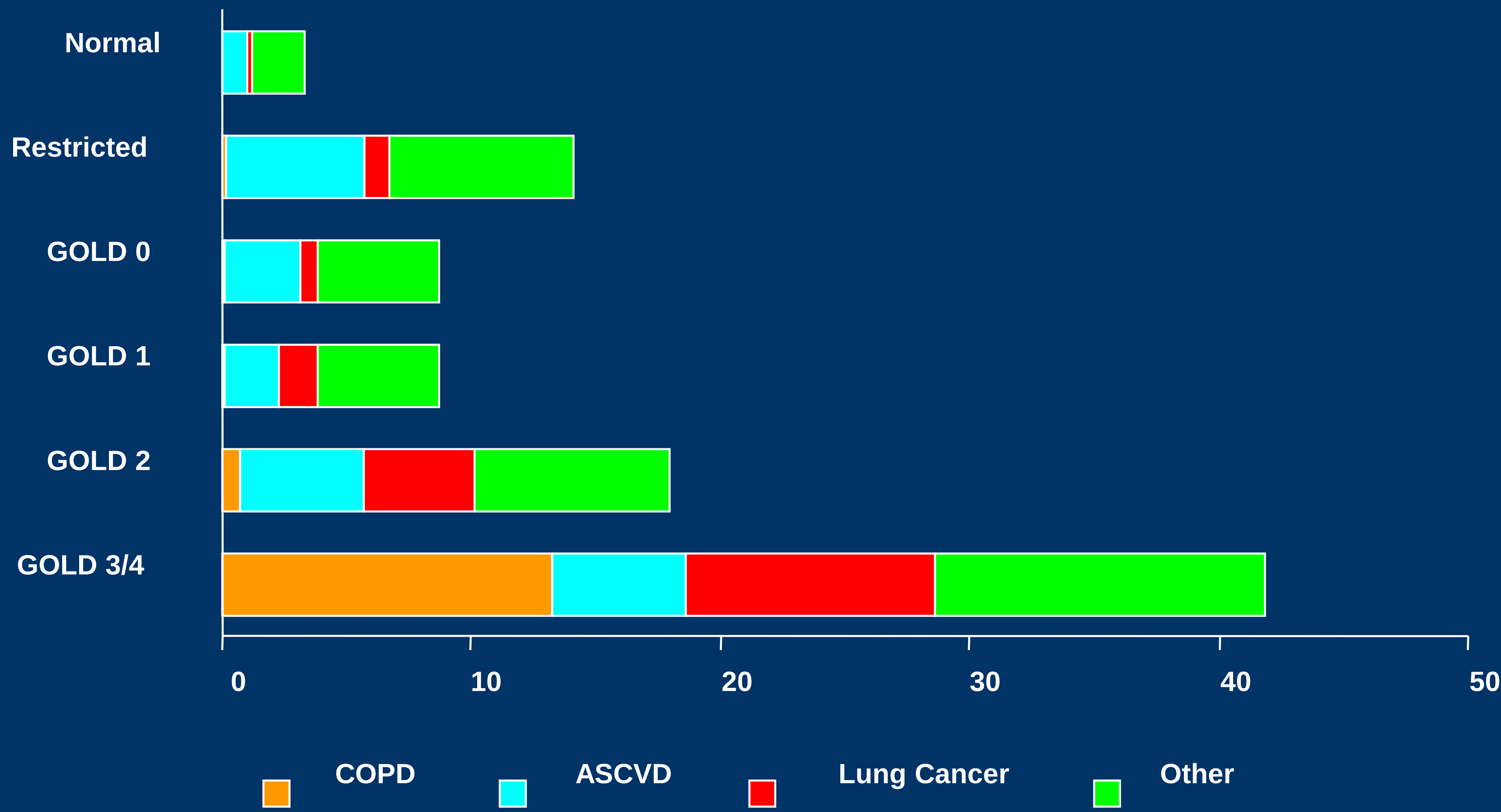
Survival in COPD



Celli BR, et al. N Engl J Med. 2004;350:1005-1012.

What do COPD Patients Die From? (rate per 1,000 person-years)



Mannino et al, *Resp Med*, Jan 2006

TREATMENT

Goals for Treatment of Stable COPD

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

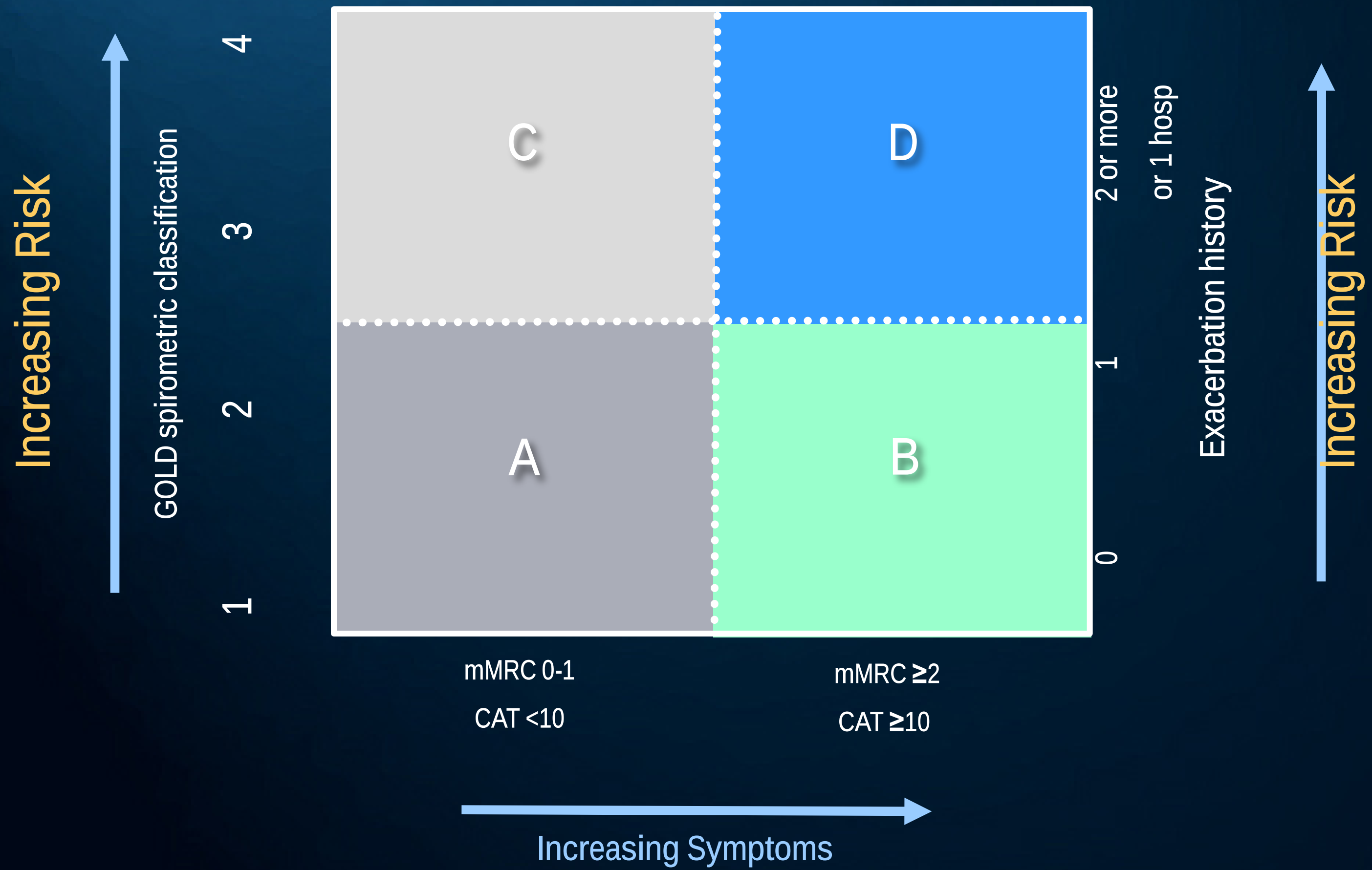
REDUCE SYMPTOMS

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

REDUCE RISK

Global Strategies for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2011.

Pharmacological Therapy of Stable COPD: GOLD 2011



http://www.goldcopd.org.

Functional Dyspnea Scale – Medical Research Council (mMRC)

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.

Celli BR et al. *Eur Resp J* 2004;23:932-946.

Pharmacologic Options

Bronchodilators

Short-acting

Anticholinergic (SAMA):
Ipratropium

β-agonists (SABA):
Albuterol
Levalbuterol
Metaproterenol
Pirbuterol

SAMA + SABA:
Ipratropium + albuterol

Long-acting

Anticholinergic (LAMA):
Tiotropium
Aclidinium
Umeclidinium

β-agonists (LABA):
Salmeterol
Formoterol
Arformoterol
Indacaterol (ultra)

LAMA + LABA:
Umeclidinium + vilanterol
Tiotropium + olodaterol

Theophylline

Anti-inflammatory

ICS + LABA

Fluticasone + Salmeterol
Budesonide + Formoterol
Fluticasone + Vilanterol

PDE-4 inhibitors

Roflumilast

Oral steroids

Prednisone
Methylprednisolone

Slide courtesy of Sanjay Sethi, MD.

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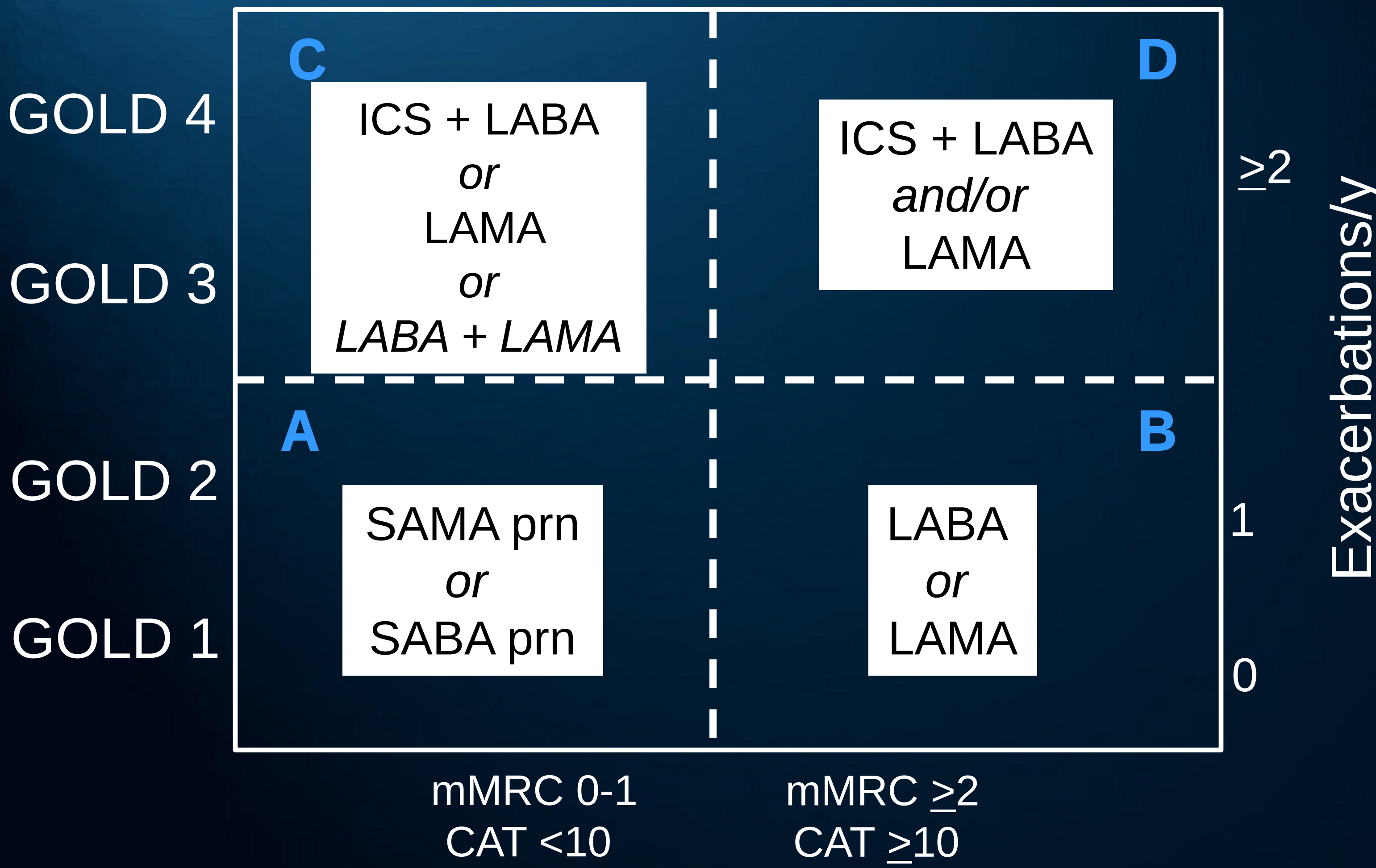
GOLD – Clinical Based (Symptom/Risk) Classification of COPD



www.goldcopd.org. Accessed 3/10/14.

COPD Foundation Clinical Phenotype Based Reclassification of COPD

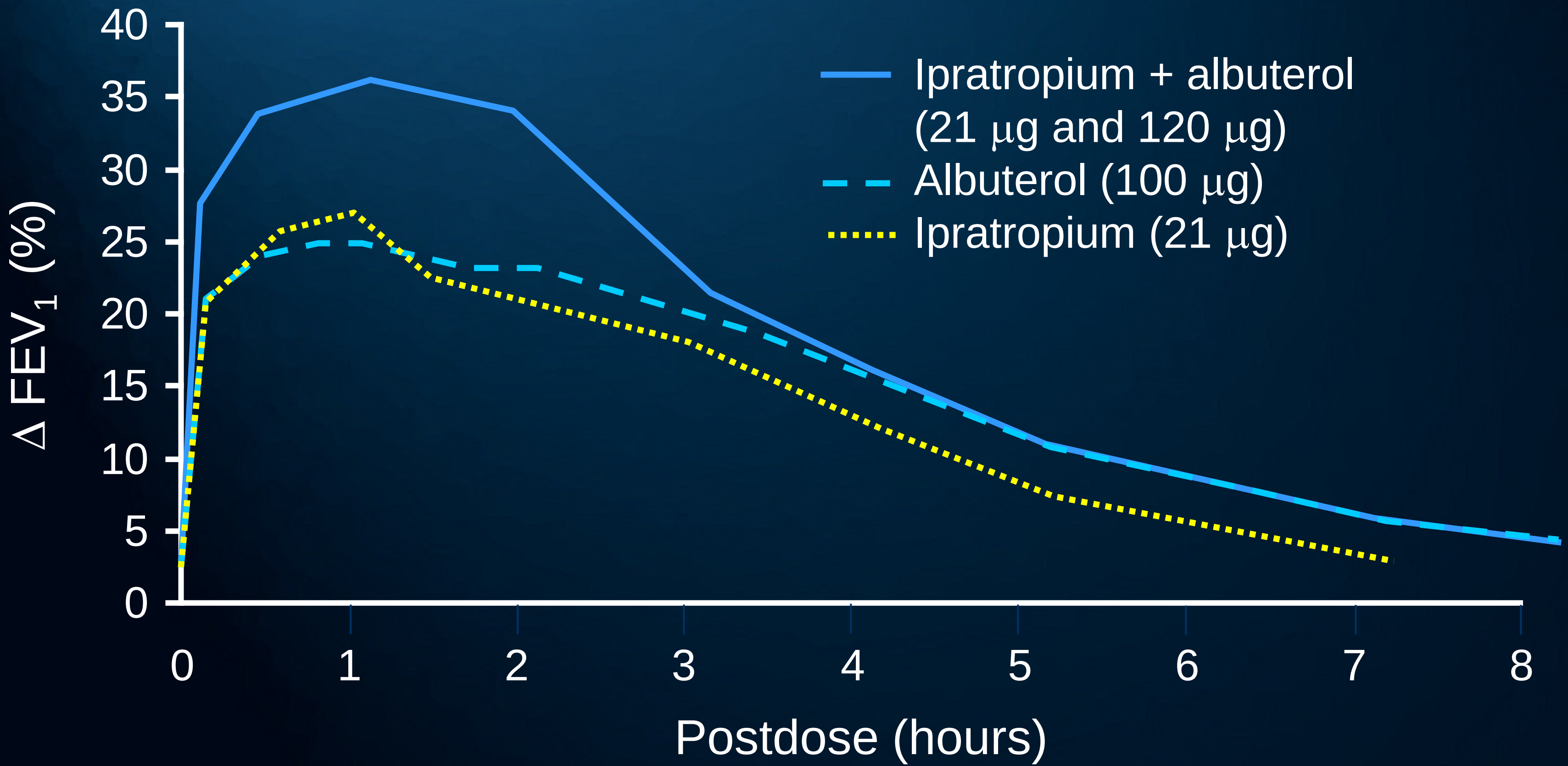
All patients should receive: Smoking cessation; vaccination for influenza, pneumococcus, pertussis, alpha-1 testing

	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

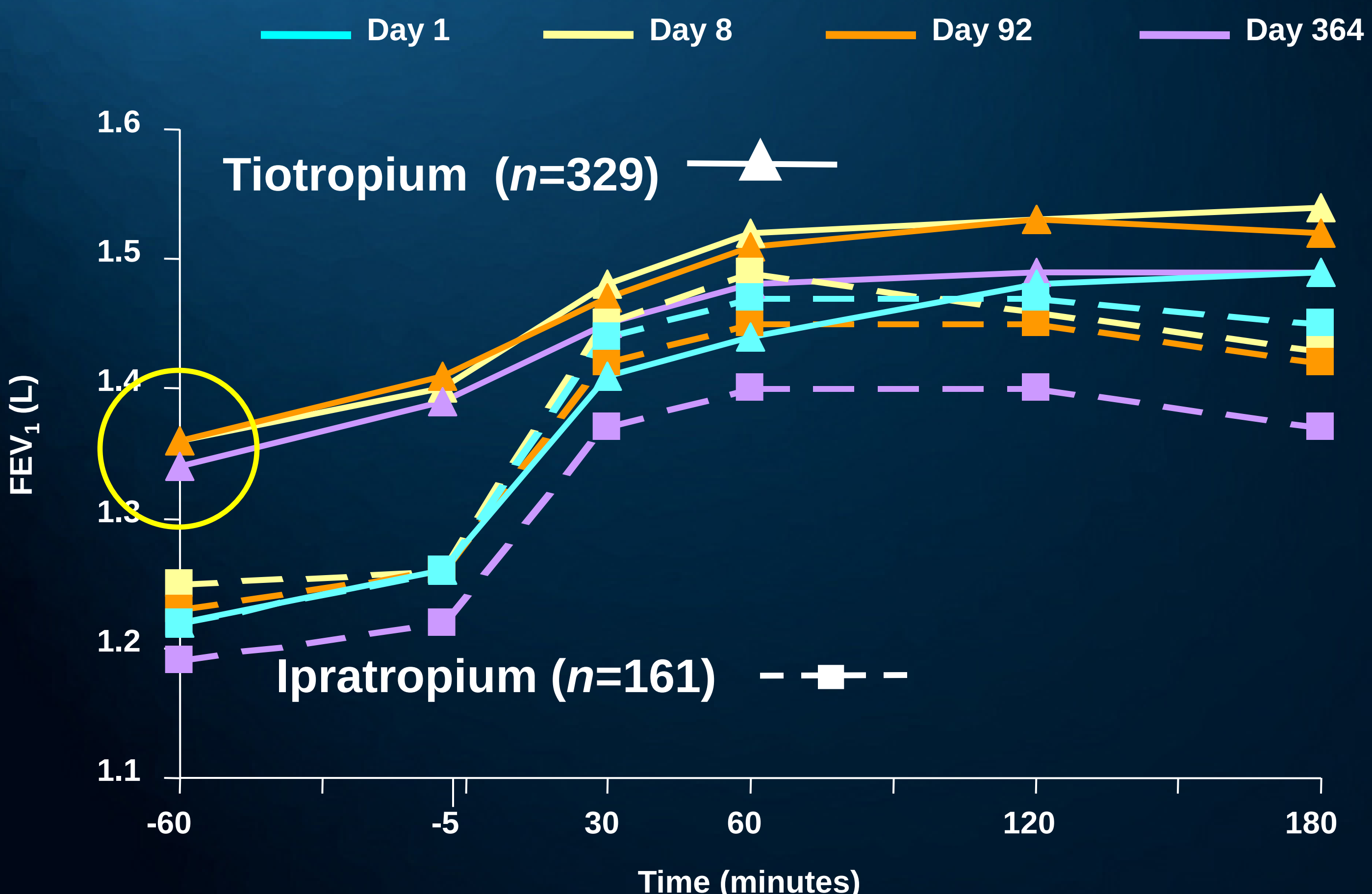
COPD Foundation. COPD Treatment. www.copdfoundation.org/Learn-More/For-Medical-Professionals/Treatment.aspx. Accessed 2/8/14.

Short-acting Bronchodilators: Ipratropium Bromide Plus Albuterol Sulfate



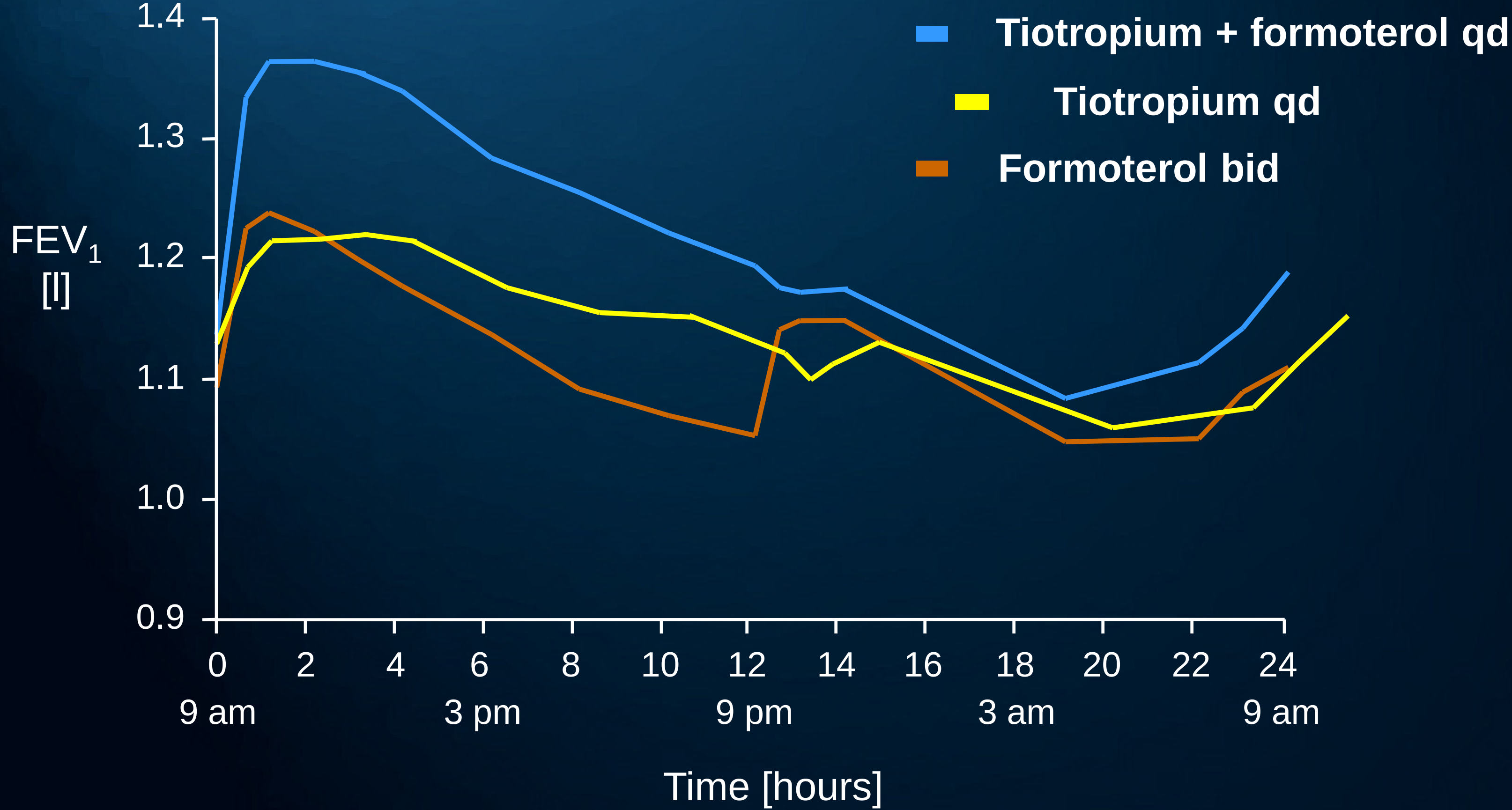
Combivent Inhalation Aerosol Study Group. *Chest.* 1994;105:1411-1419.

Impact of long vs. short acting anti-cholinergic on pre-dose FEV1.



Reproduced with permission. Vincken W et al. *Eur Respir J.* 2002;19(2):209-216.

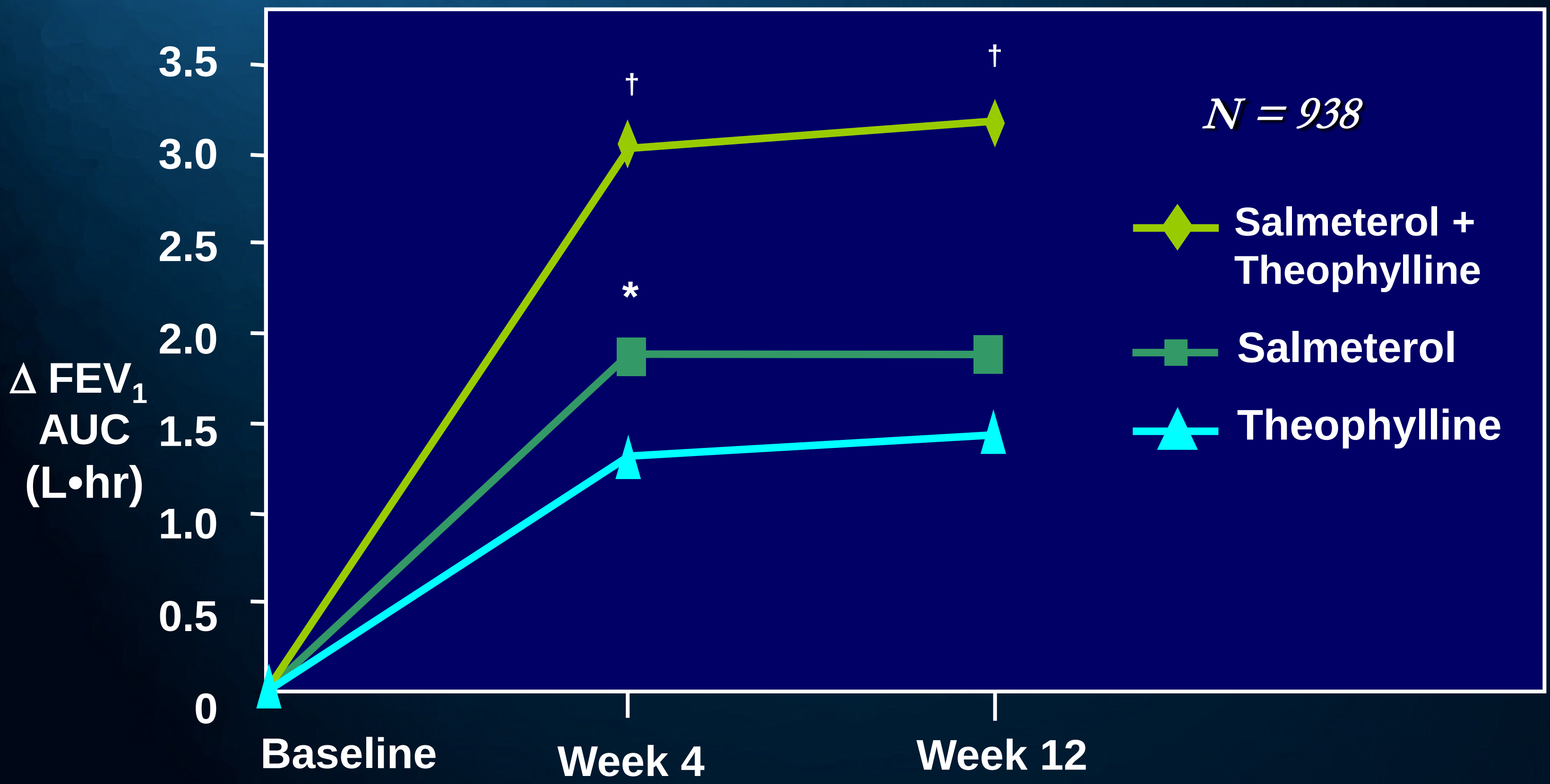
Combination Long Acting Beta and Anticholinergic impact on Mean FEV_1 over 24 h after 6 weeks Tx



van Noord JA et al. ERJ 2005;26:214-22

Trial 1184.3

Salmeterol in Combination With Theophylline: *ZuWallack*

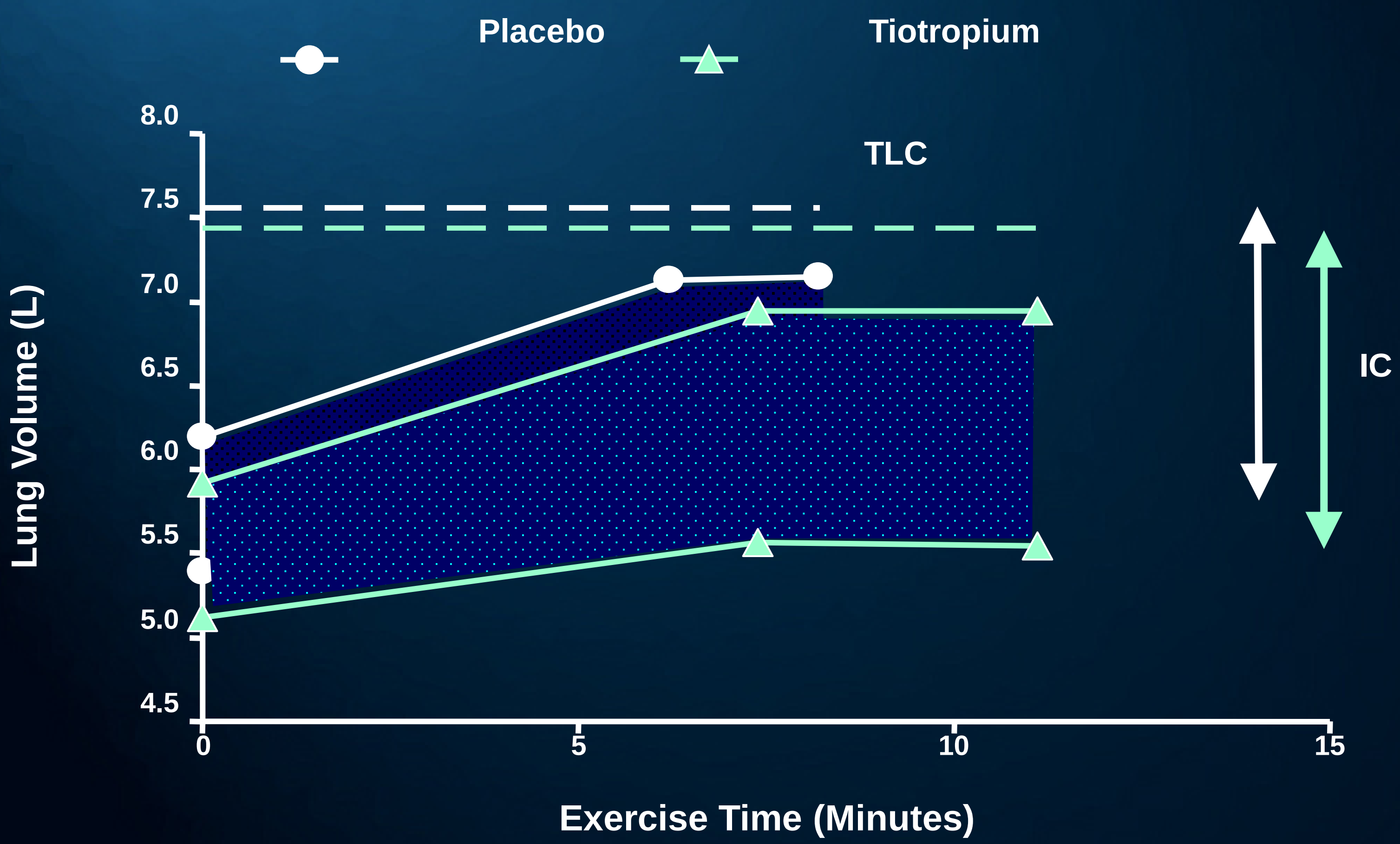


***P = .01 vs theophylline.**

†P < .001 vs salmeterol or theophylline

ZuWallack R et al. *Chest*. 2001.

Effect Tiotropium on Dynamic Hyperinflation



TLC, total lung capacity; IC, inspiratory capacity

O' Donnell DE, et al. *Eur Respir J*. 2004;23(6):832-840.

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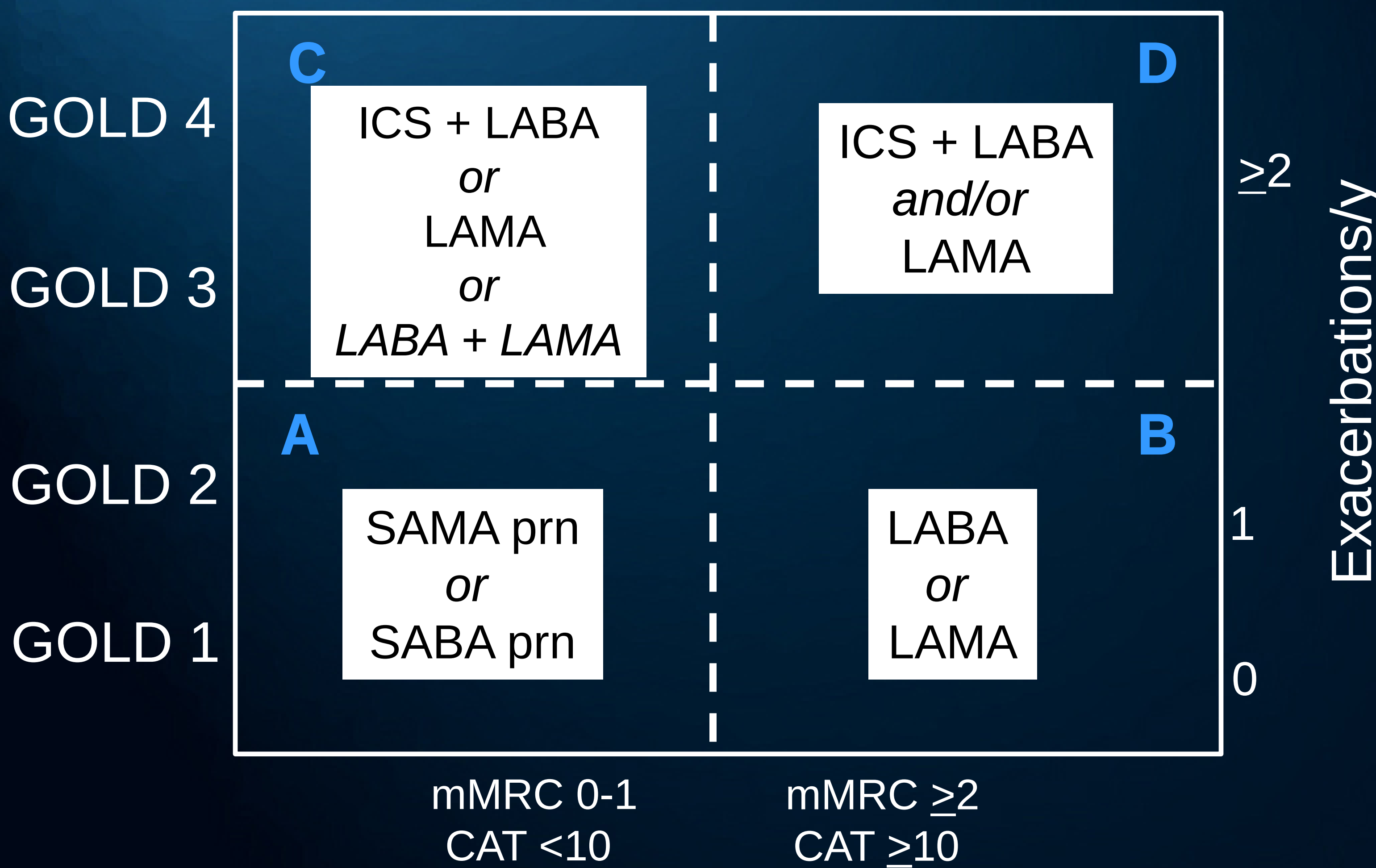
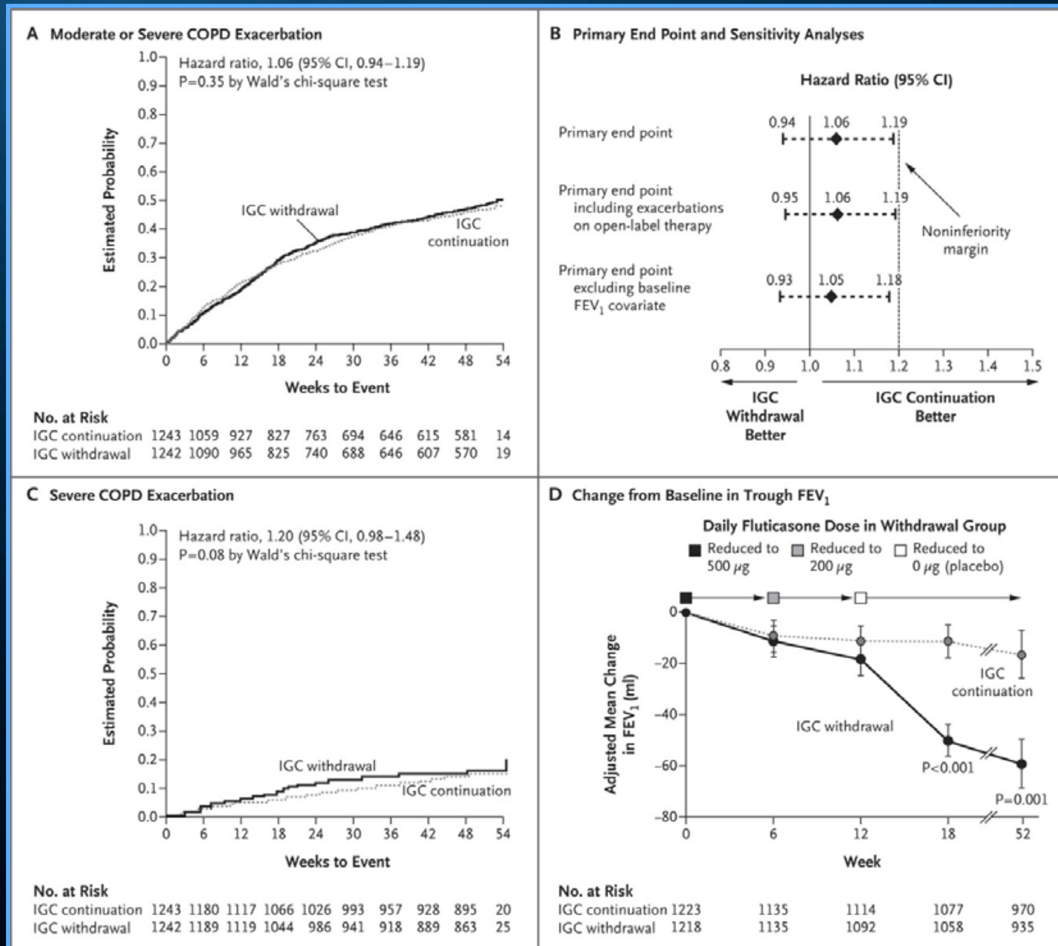
Preventing Exacerbations

GOLD – Clinical Based (Symptom/Risk) Classification of COPD



www.goldcopd.org. Accessed 3/10/14.

Wisdom Trial: Withdrawal of ICS in Patients on 2 Long-acting Bronchodilators**



*Patients with severe COPD; ** tiotropium + salmeterol; ICS, inhaled corticosteroids

Magnussen H et al; WISDOM Investigators. *N Engl J Med*. 2014;371:1285-1294.

Asthma COPD Overlap Syndrome
Proposed Diagnostic Criteria

Major Criteria	Minor Criteria
•Marked reversibility with bronchodilators (>15% and >400 mL in FEV1)	•Reversibility on 2 separate occasions (>12% and >200 mL in FEV1)
•History of asthma (<40 years of age)	•History of atopy
•Sputum eosinophilia	•Increased Total serum IgE

Overlap syndrome: 2 major criteria or 1 major + 2 minor criteria

Soler-Cataluña JJ et al. *Arch Bronconeumol.* 2012;48:331-337.

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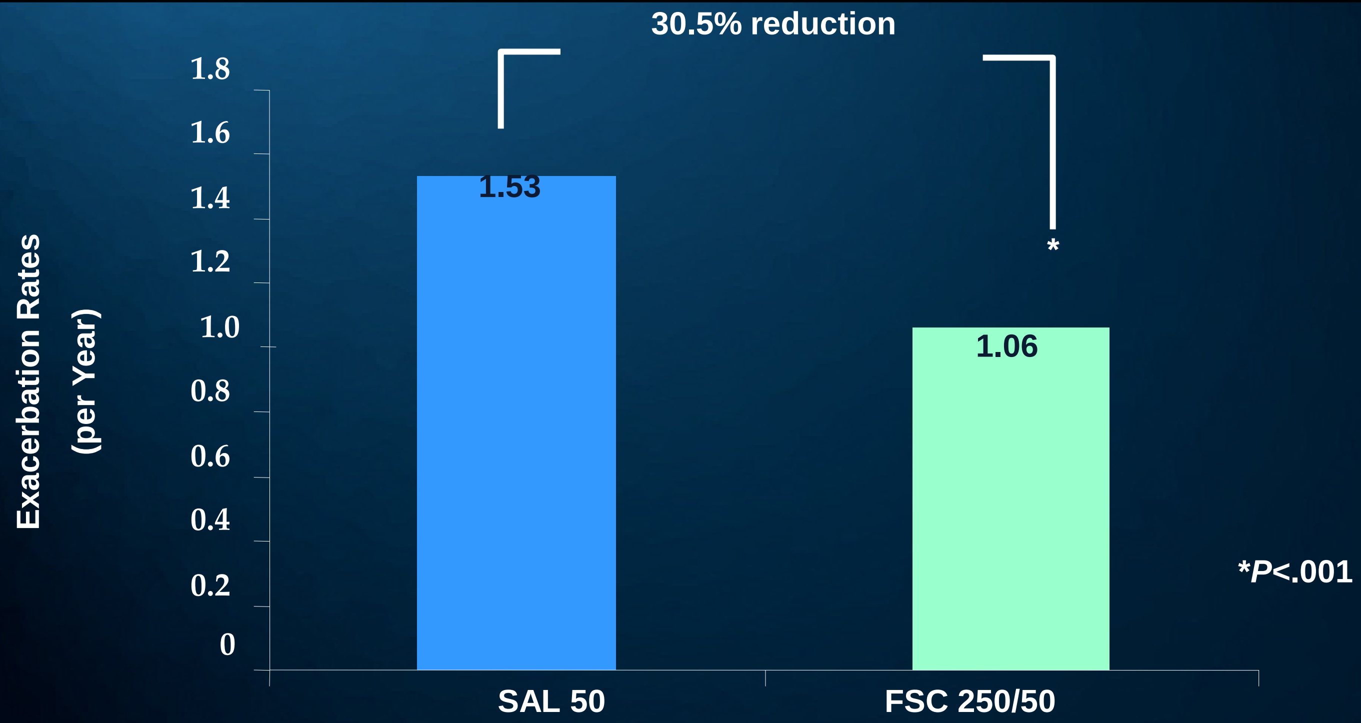
Fluticasone Propionate/Salmeterol 250/50 Decreases Moderate to Severe COPD Exacerbations in 1-Year Comparative Study



SAL 50=salmeterol 50 mcg; FSC 250/50=fluticasone 250 mcg+salmeterol 50 mcg

Moderate exacerbation: worsening of COPD symptoms requiring both a change in normal treatment (increased dose of prescribed medication or addition of new drugs [eg, oral steroids, antibiotics]) AND medical assistance

Severe exacerbation: worsening of COPD symptoms requiring hospital or emergency room treatment

Ferguson GT, et al. *Respir Med*. 2008;102(8):1099-1108.

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UPLIFT: Frequency of Exacerbations Compared With Control

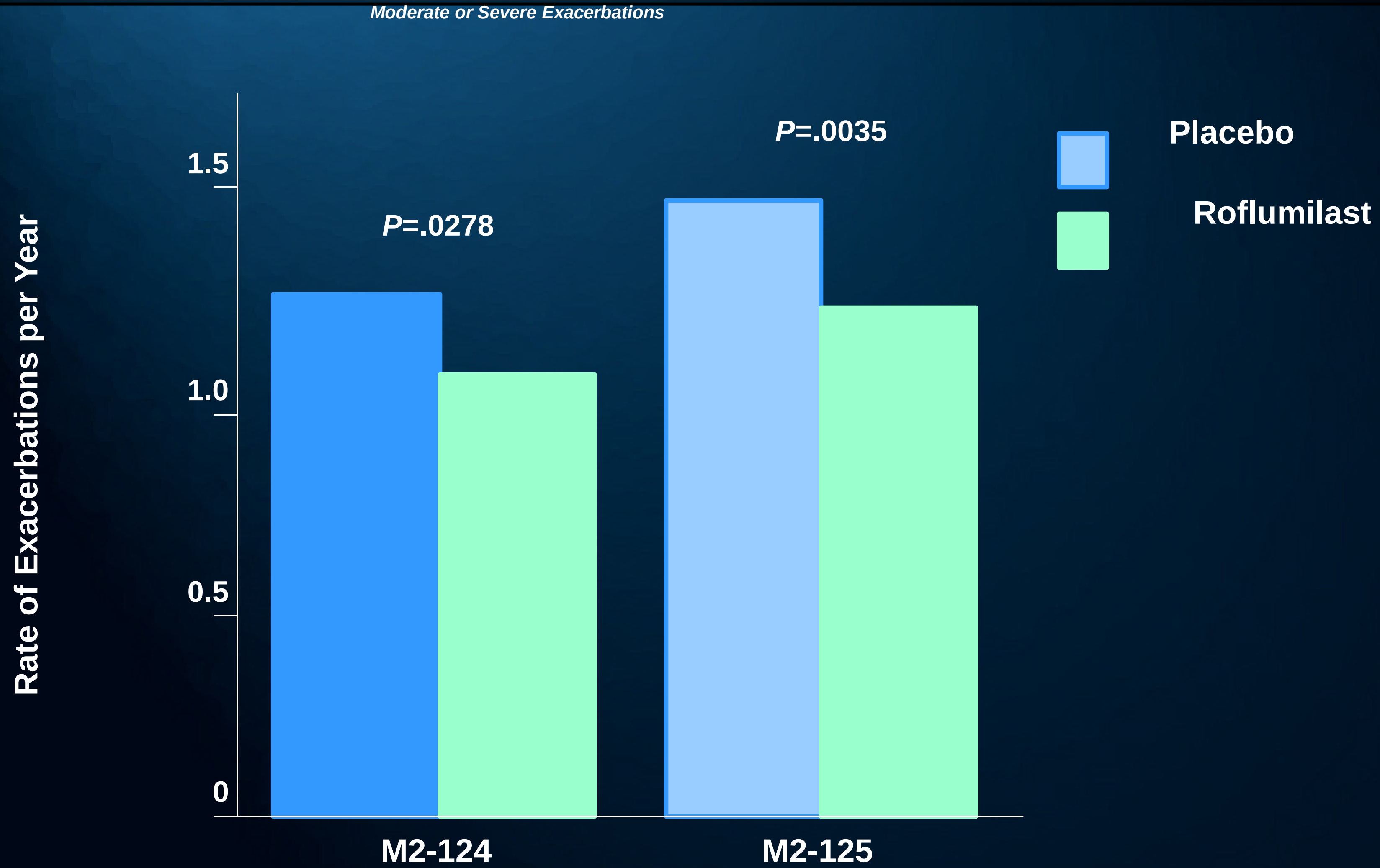
	Tiotropium Mean (SE)	Control Mean (SE)	Rate Ratio	95% CI	*P* Value
Number of exacerbations per patient-year	0.73 (0.02)	0.84 (0.02)	0.86	0.81-0.91	<.001

14% reduction in number of exacerbations

CI=confidence interval; SE=standard error

Tashkin DP, et al. *N Engl J Med.* 2008;359(15):1543-1554.

Effect of PDE4 Inhibitor (Roflumilast) in COPD: 1-Year Trials



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

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Adverse Effects of Roflumilast in Clinical Studies

Adverse Effects Reported by ≥2% of Patients Taking Roflumilast	Roflumilast	Placebo
	N=4438	N=4192
	n (%)	n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

- Adverse effects typically mild to moderate
- Occurred mainly within first weeks of therapy
- Mostly resolved on continued treatment
- Rare neuro-psychiatric events
  – Insomnia
  – Anxiety
  – Depressed mood
  – Suicidal ideation

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022522s000lbl.pdf.

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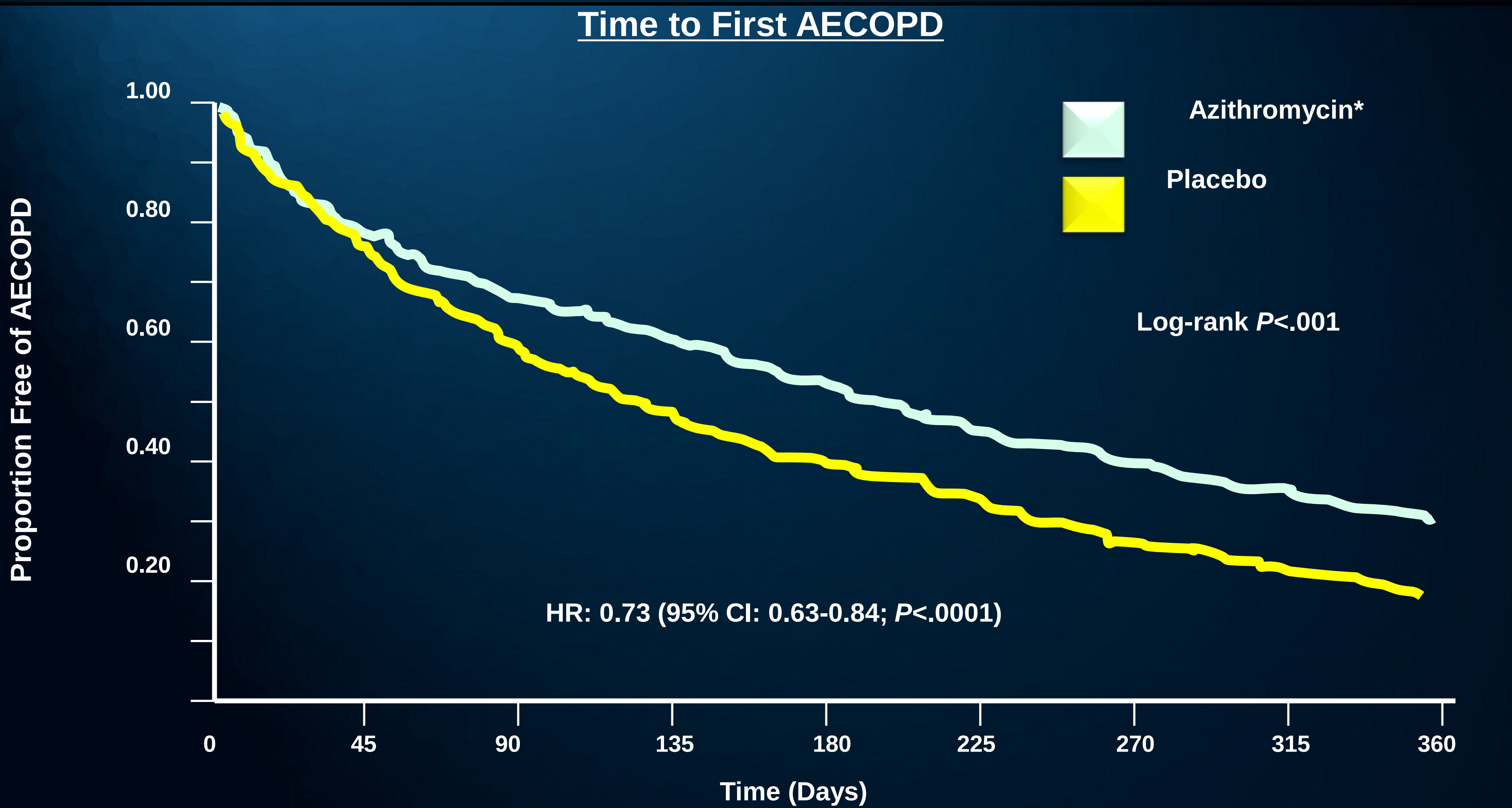
Daily Azithromycin Decreases Acute Exacerbation (AECOPD)



*Azithromycin 250 mg daily for 1 year.

AECOPD, acute exacerbation of COPD

Albert RK, et al. *N Engl J Med*. 2011;365:689-698.

Azithromycin is not indicated for prevention of AECOPD

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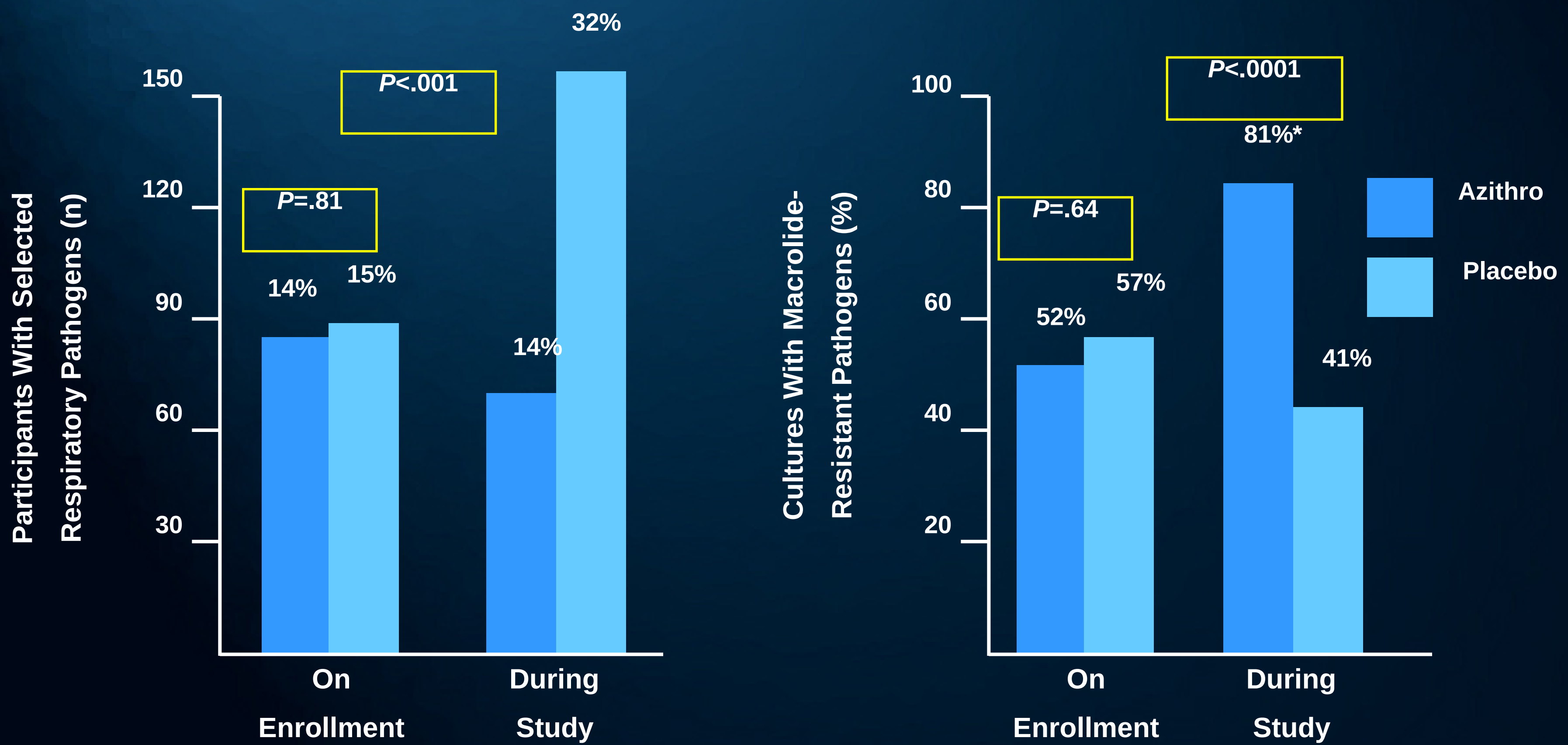
Azithromycin Study Microbiology



Azithro=azithromycin

Albert RK, et al. *N Engl J Med*. 2011;365(8):689-698.

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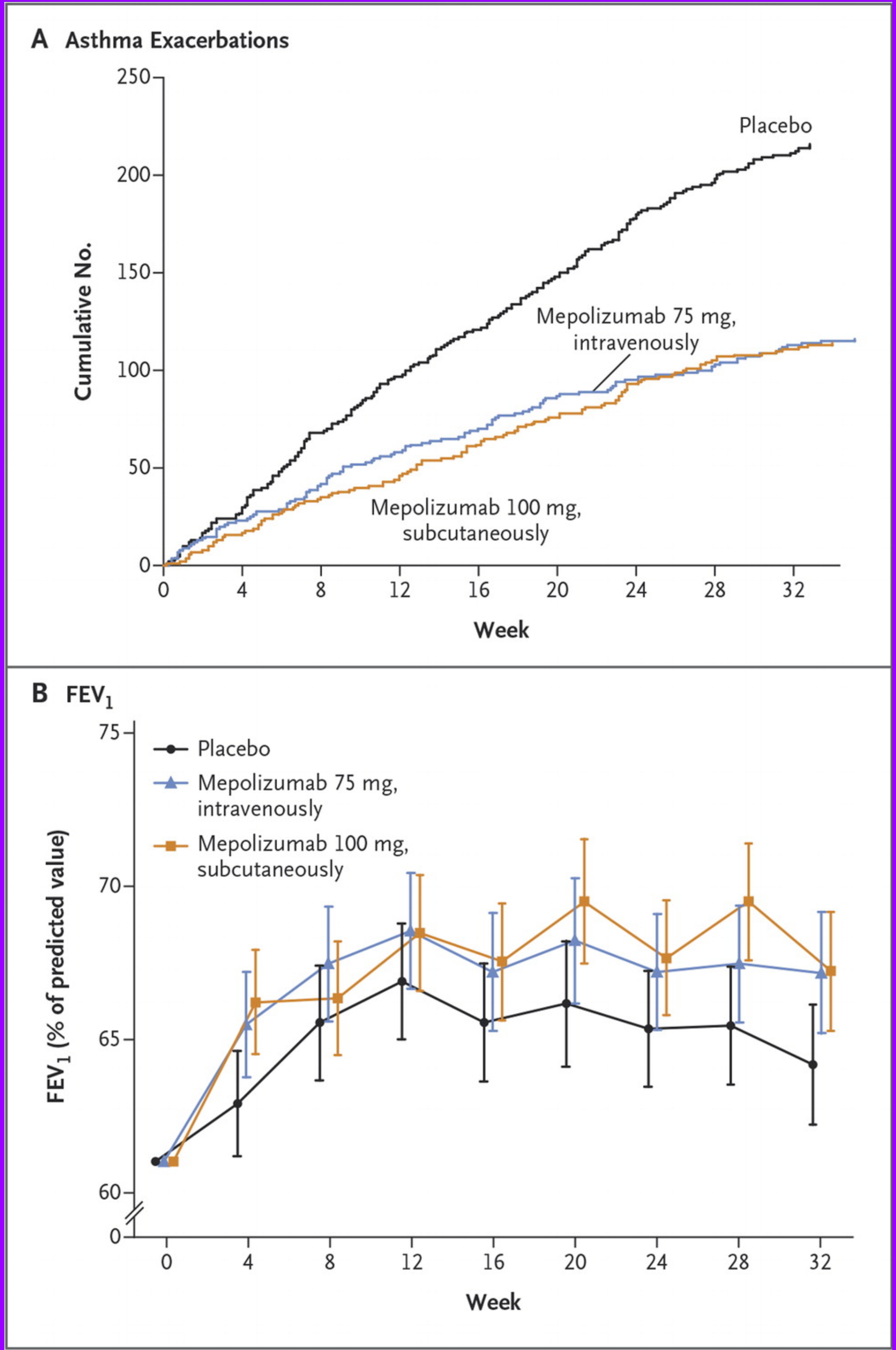
Azithromycin Adverse Reaction Considerations Hearing Changes and QT Prolongation

Audiogram Changes	Azithro (dB)		Placebo (db)		*P* Value
	Mean	95% CI	Mean	95% CI	
Start to 3rd month	-0.7	-1.0 to -0.3	-0	-0.4 to 0.4	.01
Start to 12th month	-1.2	-1.6 to -0.8	-0.9	-1.3 to -0.5	.25

- **Recent study of short-term (5 day) azithromycin risk of cardiovascular death 1:4,100 in high-risk patients**
- **Drug labels updated to strengthen with respect to the risk of QT interval prolongation and torsades de pointes**

Albert RK, et al. *N Engl J Med*. 2011;365(8):689-698.

PHASE III RESULTS



Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez, M.D., Ph.D. for the MENSA Investigators

N Engl J Med 2014; 371:1198-1207

Manage Exacerbations
Treatment Options

Oxygen: titrate to improve the patient's hypoxemia with a target saturation of 88%-92%.

Bronchodilators: Short-acting inhaled beta$_2$-agonists with or without short-acting anticholinergics are preferred.

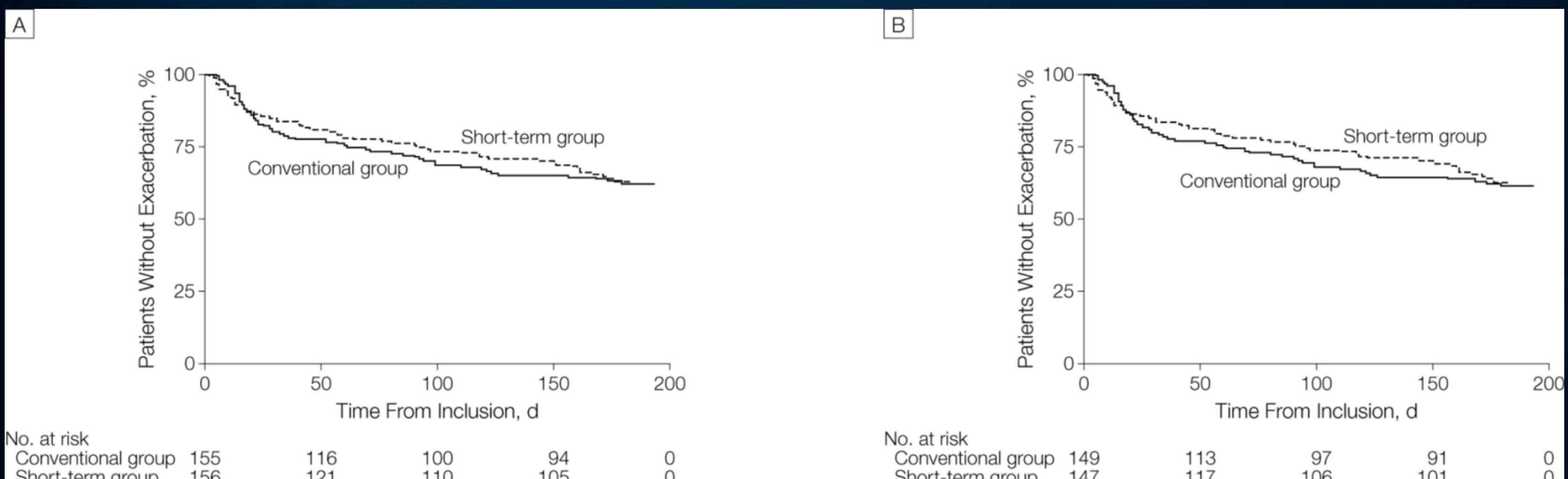
Systemic Corticosteroids: Shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), and reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 40 mg prednisone per day for 5 days is recommended.

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.

Functional Dyspnea Scale – Medical Research Council (mMRC)

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.
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4	I am too breathless to leave the house or I am breathless when dressing.

Celli BR et al. *Eur Resp J* 2004;23:932-946.

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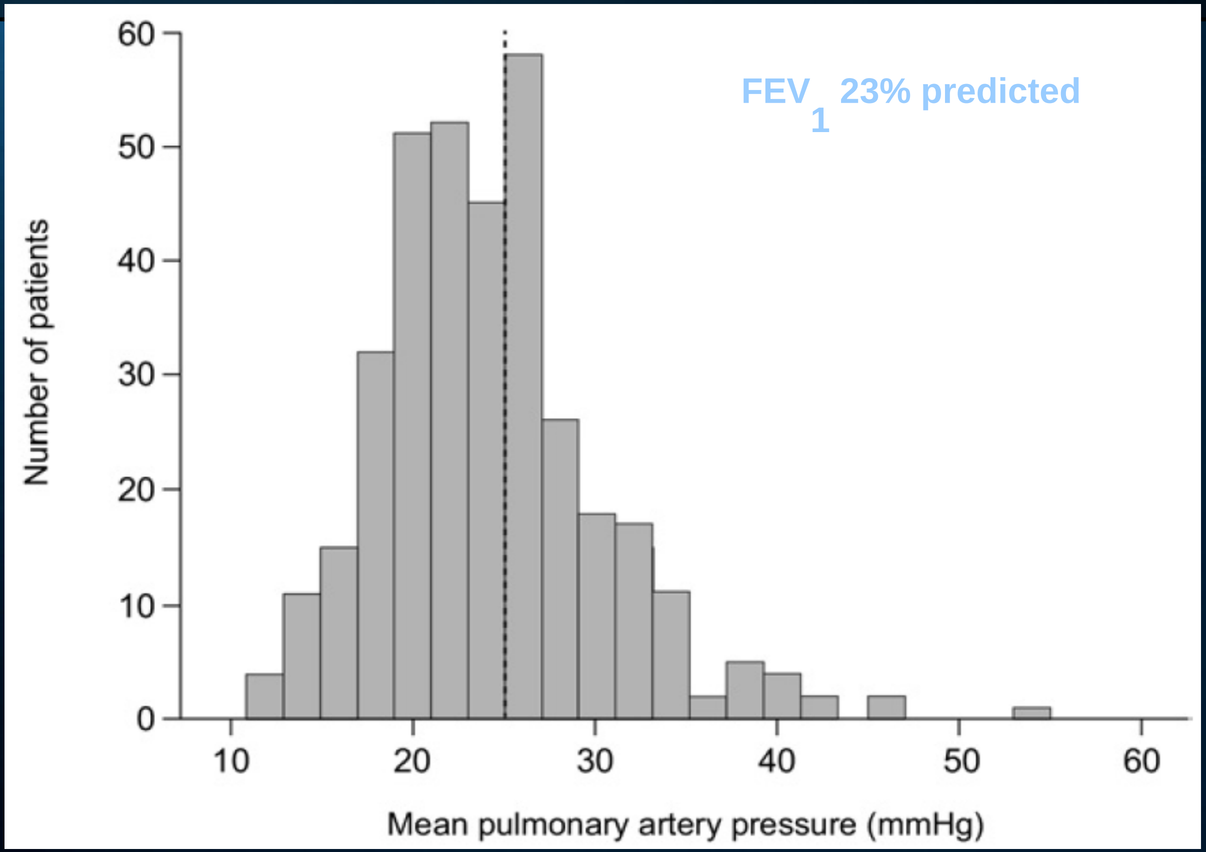
Pulmonary Hypertension in COPD

Pulmonary Hypertension in advanced COPD



PAP >35 mmHg, 3.9%

PAP >40 mmHg, 1.5%

Andersen et al. JHLT 2012;31:373

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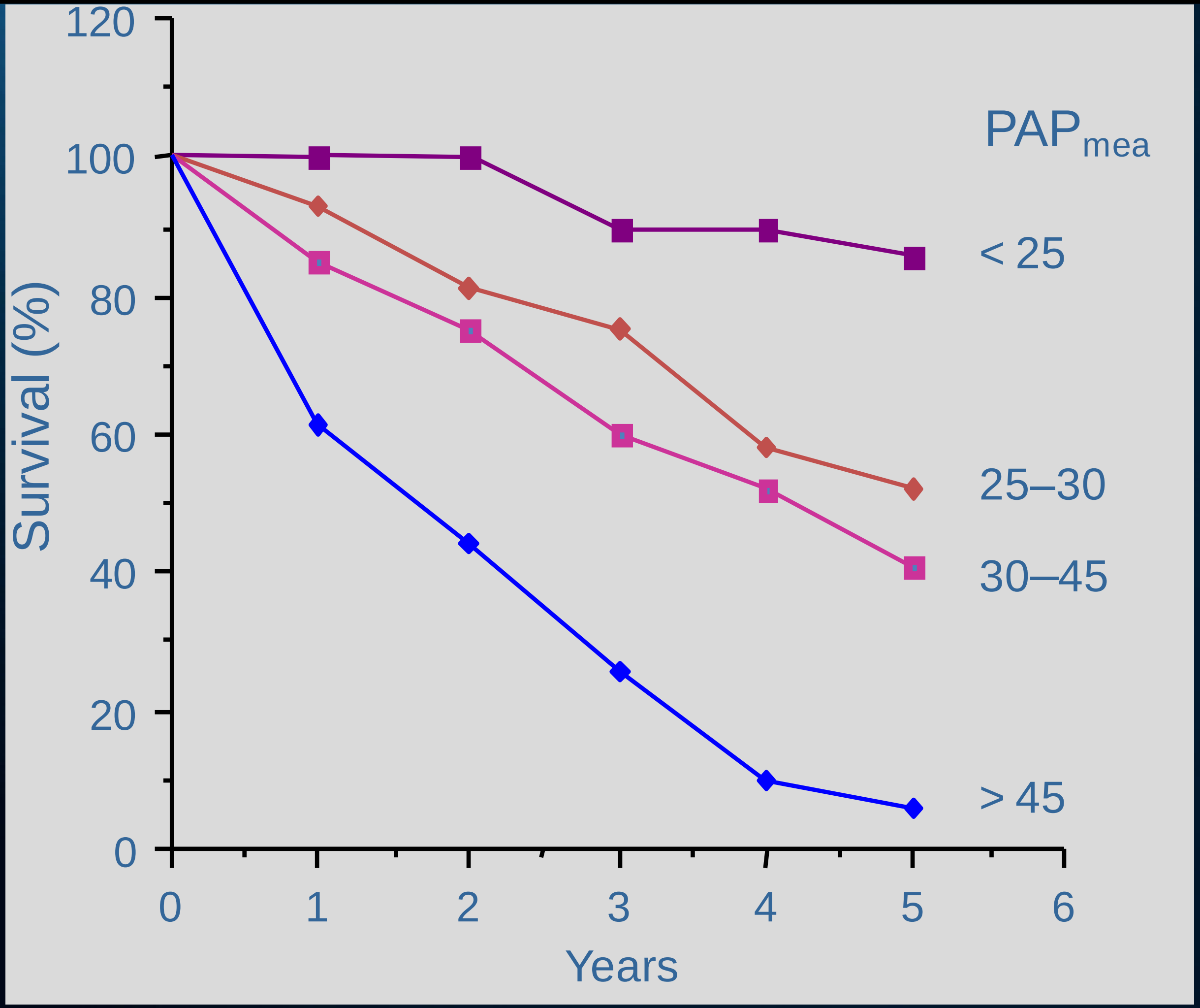
Clinical relevance of PH in COPD – Survival



Chaouat, AJRCCM 2005 / Nat Rev Cardiol 2011

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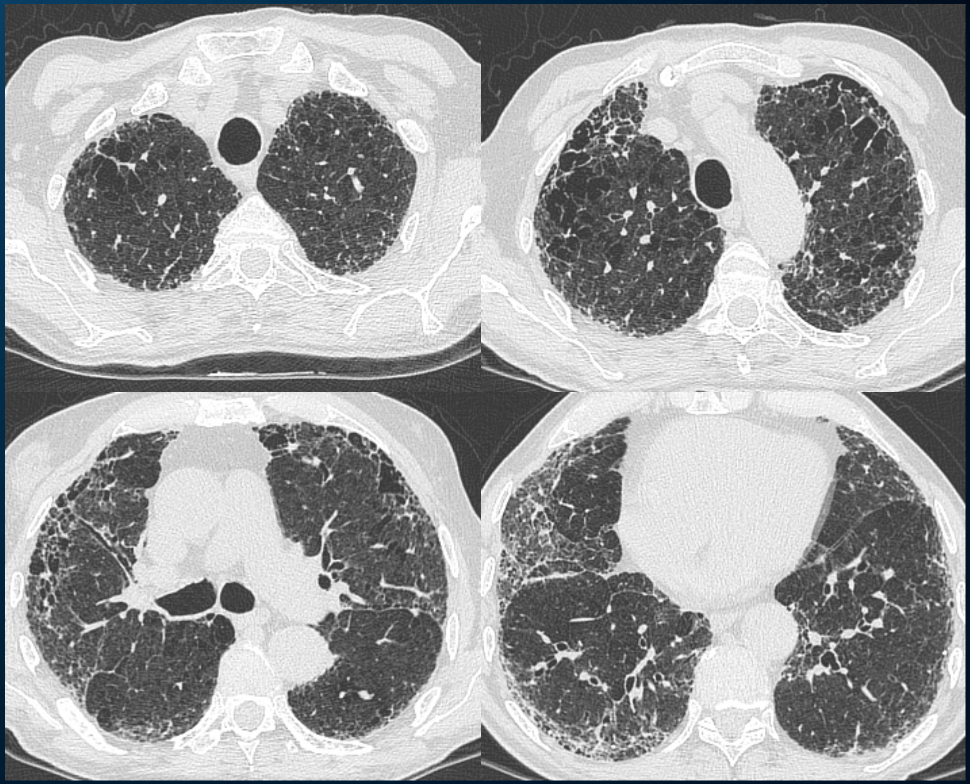
Combined pulmonary fibrosis and emphysema (CPFE)

- Patients with the syndrome of combined pulmonary fibrosis and emphysema (CPFE) particularly prone to develop PH

- In one series [1], 47% with CPFE had sPAP ≥ 45 mmHg at echocardiography



1. Cottin V *et al*, *Eur Respir J* 2005;26:586
2. Mejia et al, Chest 2009;13:10
3. Grubstein A et al, Respir Med 2005;99:948
4. Portillo K et al, Pulm Med 2012

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PDE5 inhibitors in COPD

Author	N	Drug (Design)	Dose	Follow-up	6MWD (m)		PAP (mmHg)	
					Pre	Post	Pre	Post
Alp	6	SIL (OL)	50mg/12h	3 m	351	433*	30	25*
Madden	7	SIL (OL)	50mg/8h	2 m	80	120*	39	34
Rietema	14	SIL (OL)	20mg/8h	3 m	389	394	20	---
Lederer[a]	10	SIL (RCT)	20mg/8h	1 m	458	458	---	---
Rao	33	SIL (RCT)	---	3 m	---	+190*[b]	53	41
Park	23	UDE (OL)	50mg/24h	2 m	315	348*	36 (sPAP)	30* (sPAP)
Blanco	60	SIL (RCT)	20mg/8h[c]	3 m	386	+0[d]	---	---

a Patients with PH excluded

b Compared with placebo

c Added to pulmonary rehabilitation

d Difference from gain in placebo

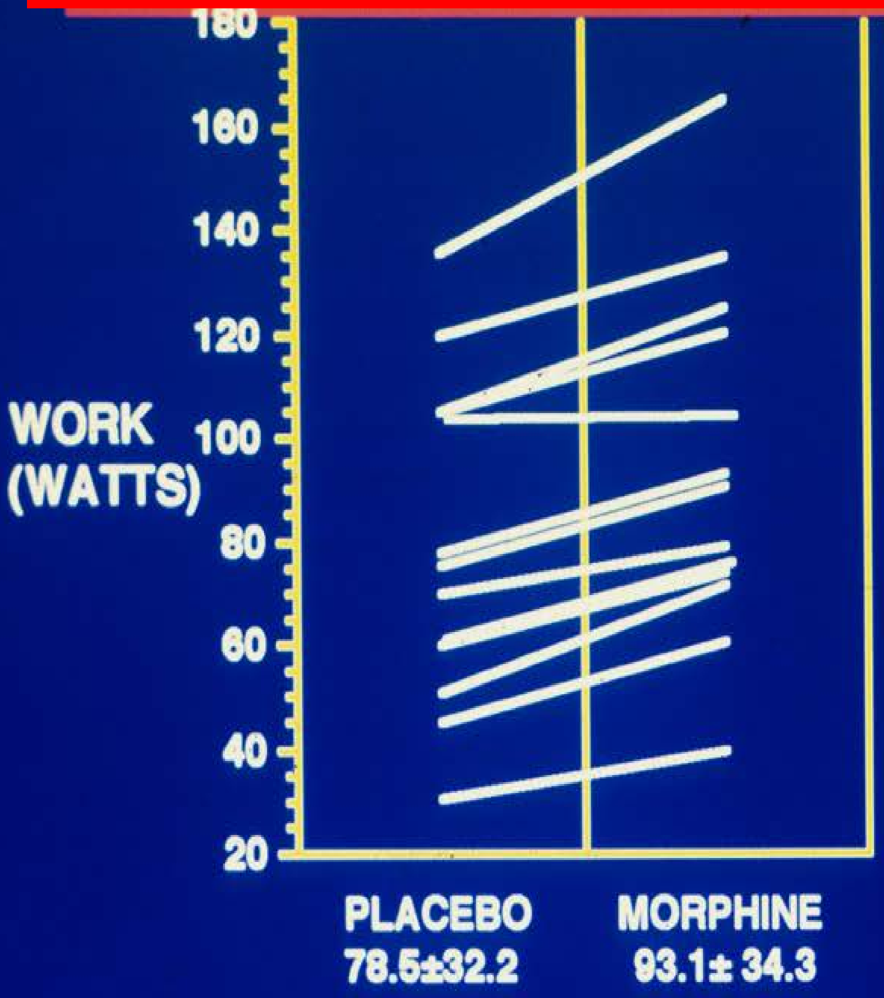
PDE5 inhibitors and COPD

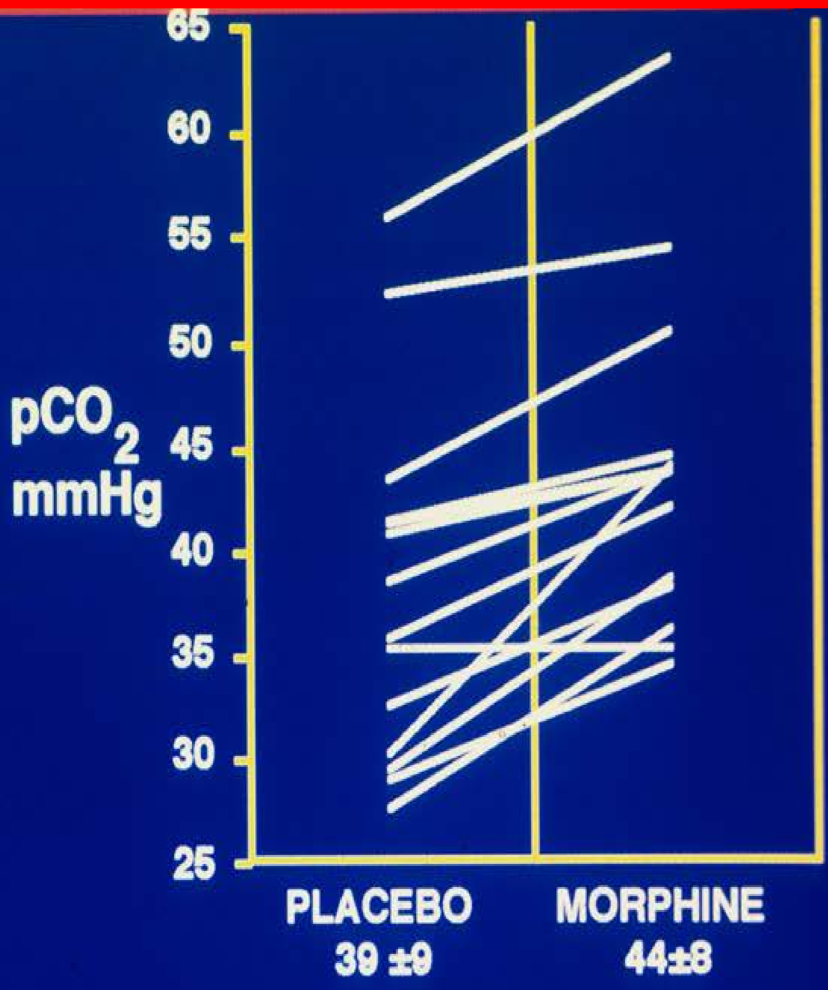
- Reduction of mPAP and PVR and increase in CI, may be accompanied by some deterioration of gas exchange
- Lack of long term beneficial effect in COPD patients in the absence of severe PH
- Small trial evidence for improved exercise tolerance in COPD linked with severe PH
- Large RCT focusing on severe PH-COPD missing

Disabling Dyspnea in COPD

Effect of Oral Morphine (0.8 mg/Kg solution) on Exercise Parameters in Patients With Disabling Dyspnea and COPD

Light et. al. Am Rev Respir Dis'89





NONPHARMACOLOGIC TREATMENT

Pulmonary Rehabilitation

An efficacious cost-effective intervention for improving functional performance, quality of life and decreasing healthcare utilization in patients with COPD

Programs are underused

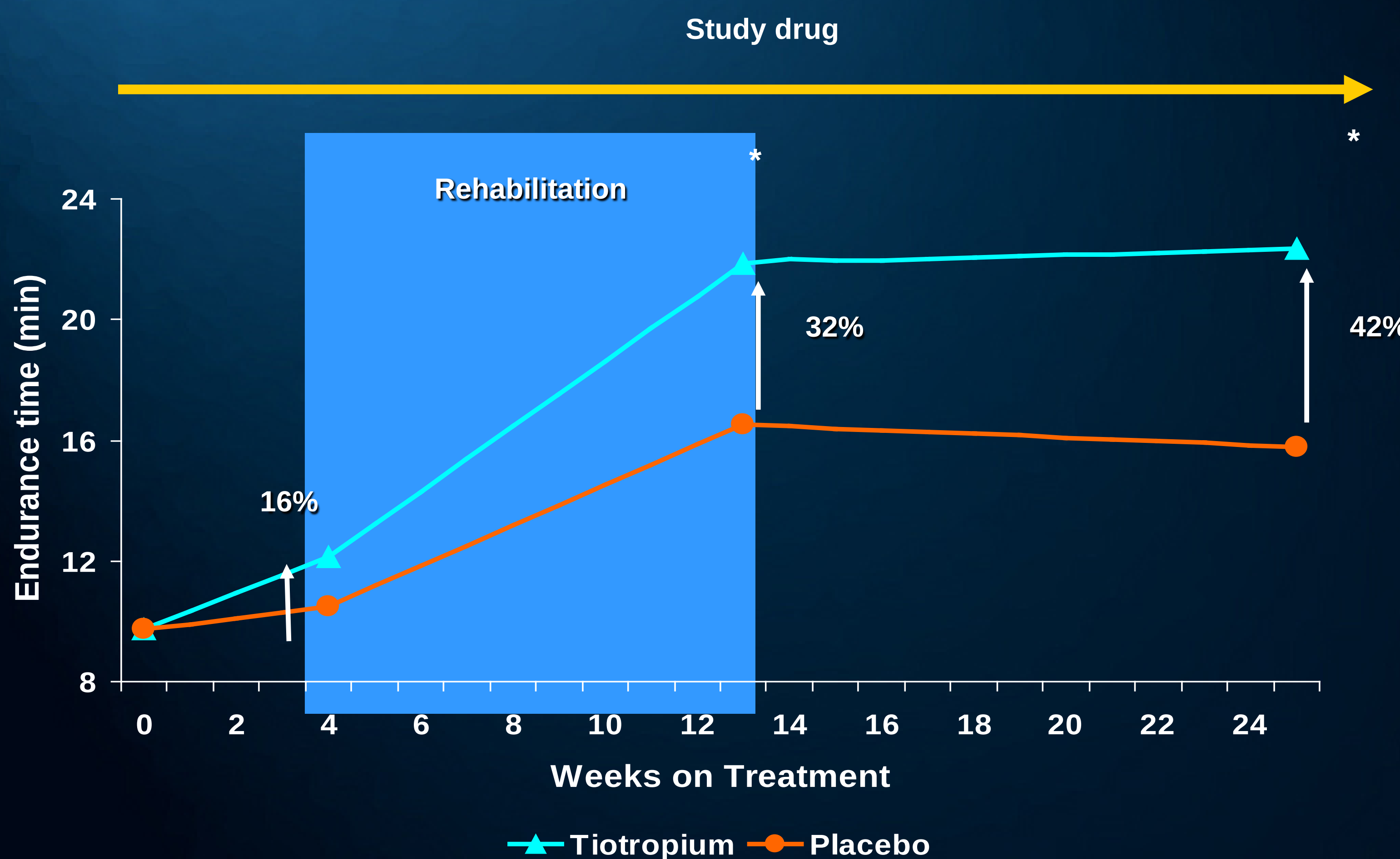
- Less than 2% of patients with COPD have participated in pulmonary rehabilitation
- Many factors, including health system, physician, and patient related, contribute to underuse

Components of pulmonary rehabilitation

- Exercise/physical activity training
- Education/Psychosocial support

Coultas D, et al. *Clin Pulmonary Med.* 2009;16(4):183-188.

Effect of Tiotropium on the Improvement in Exercise Tolerance Resulting from Rehabilitation



*P<0.05

Casaburi et al. ATS ‘04

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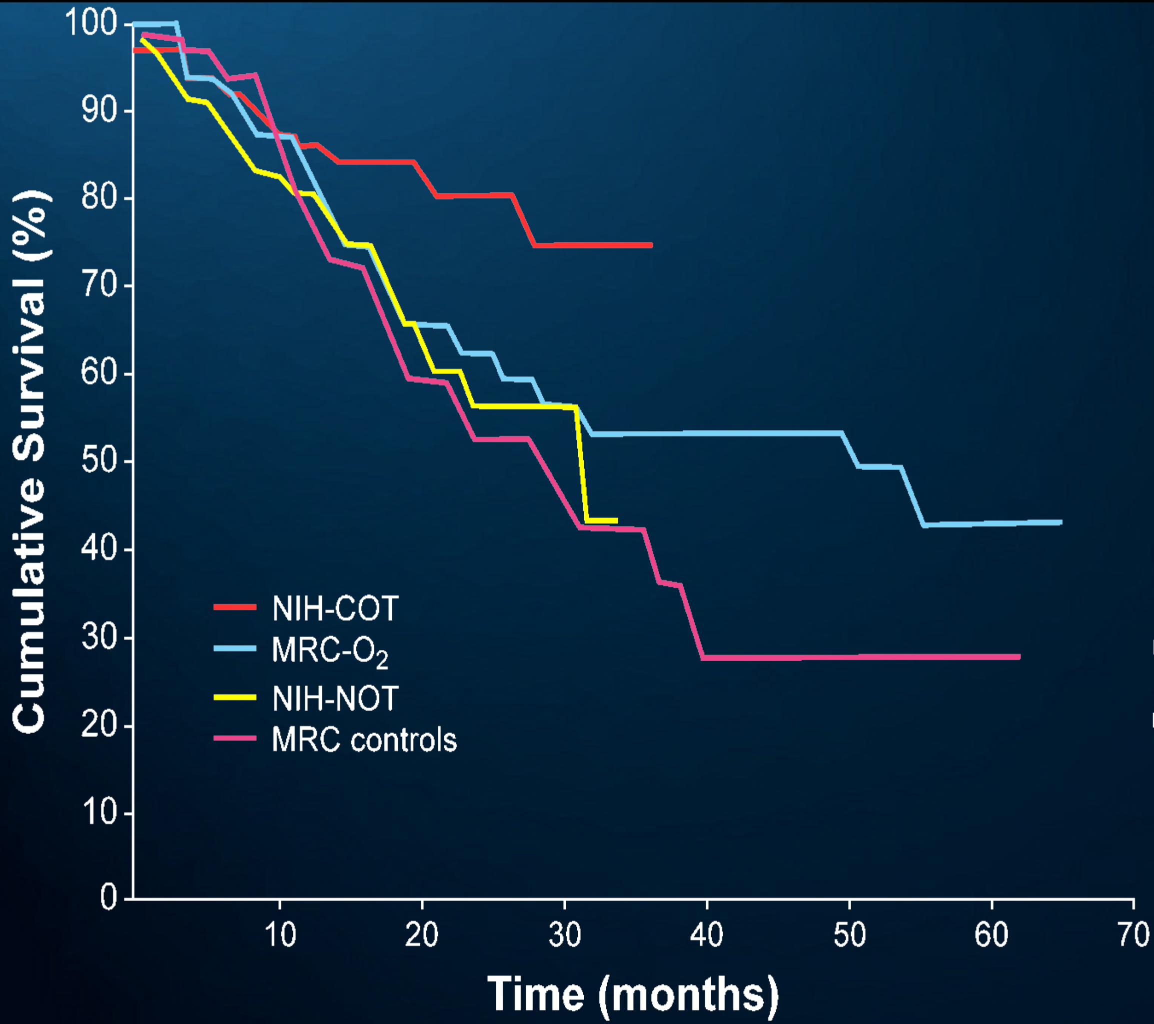
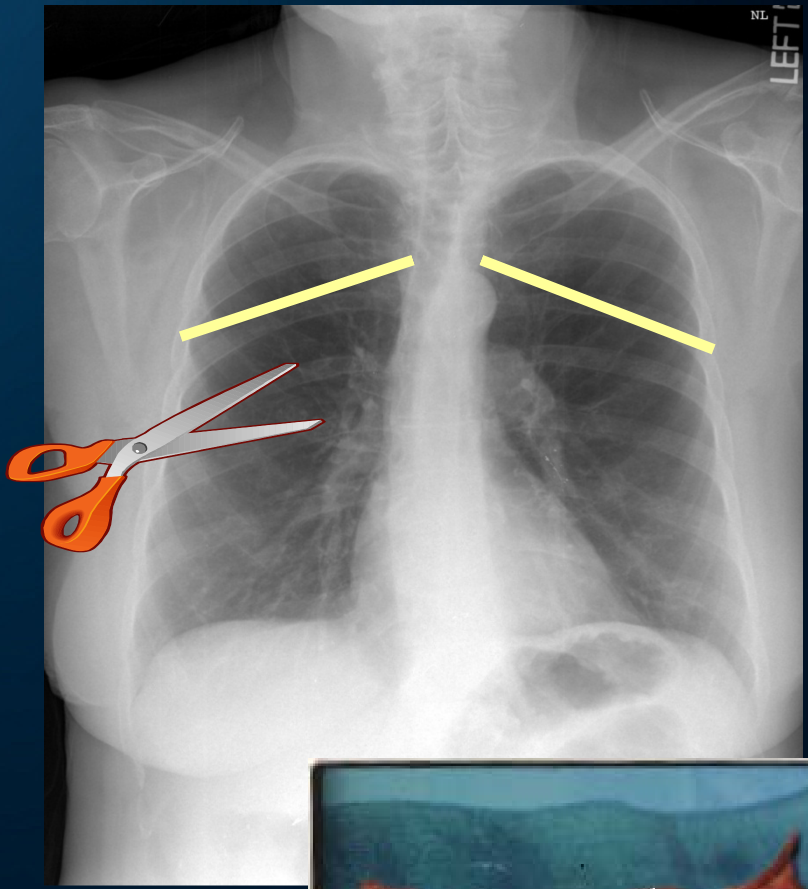
Improved COPD Survival on Long-term Oxygen Treatment

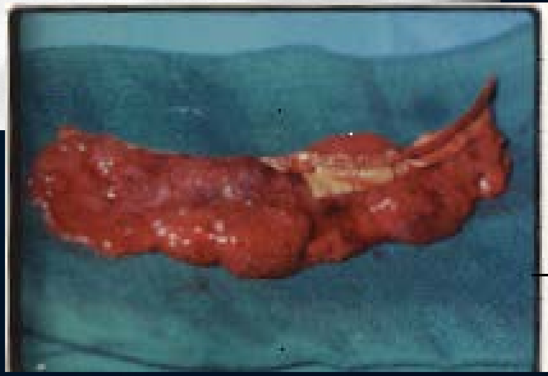


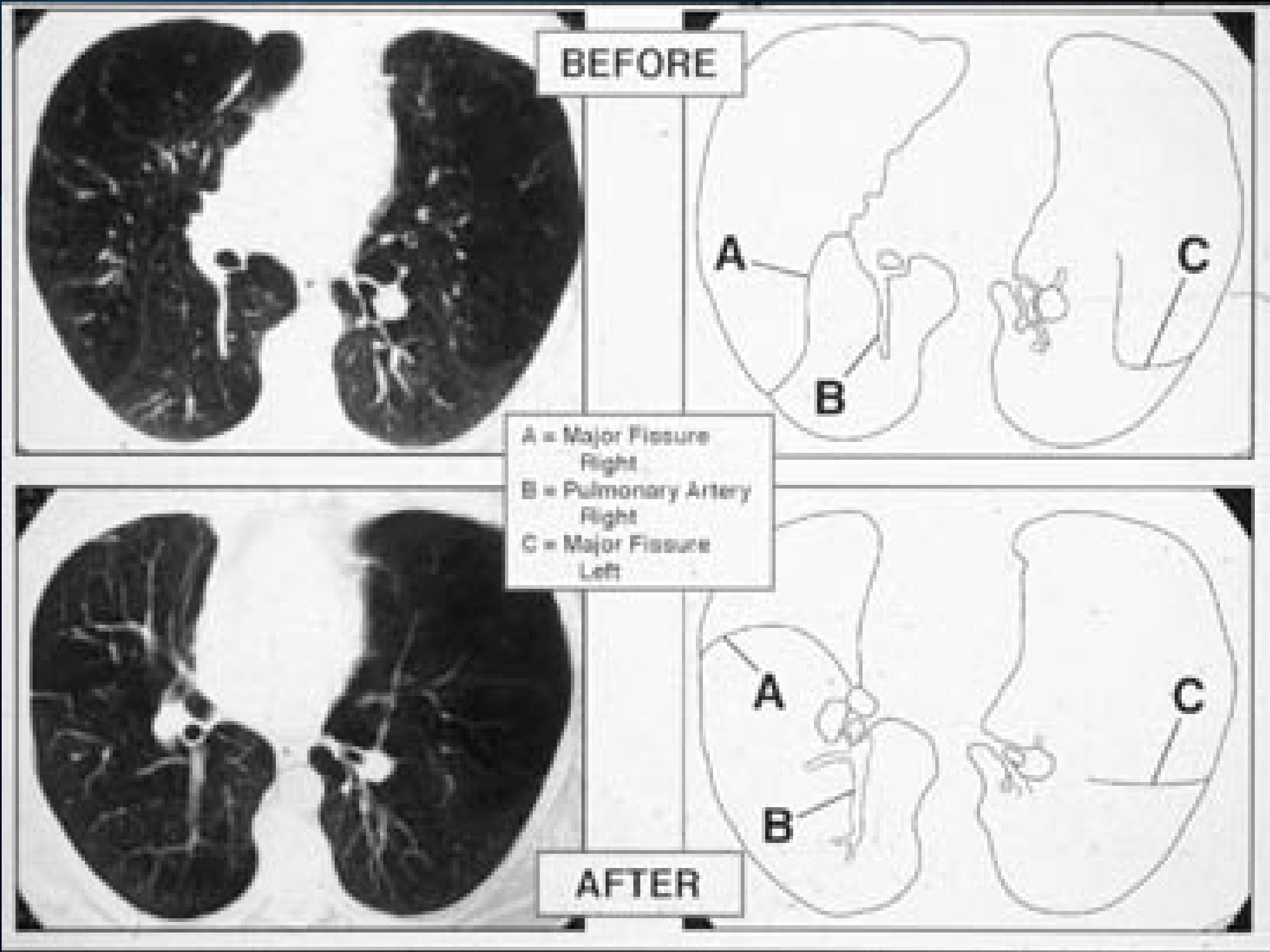
NIH-COT, National Institute of Health-Continuous Oxygen Therapy; MRC, Medical Research Council; NIH-NOT, National Institute of Health-Nocturnal Oxygen Therapy

Güell Rous R. *Int J Chron Obstruct Pulmon Dis*. 2008;3(2):231-237. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med*. 1980;93(3):391-398. Medical Research Council Working Party. *Lancet*. 1981;1(8222):681-686.

Lung Volume Reduction Surgery: A Surgical Treatment of Hyperinflation






BEFORE
A
B
C
A = Major Fissure Right
B = Pulmonary Artery Right
C = Major Fissure Left
A
B
C
AFTER

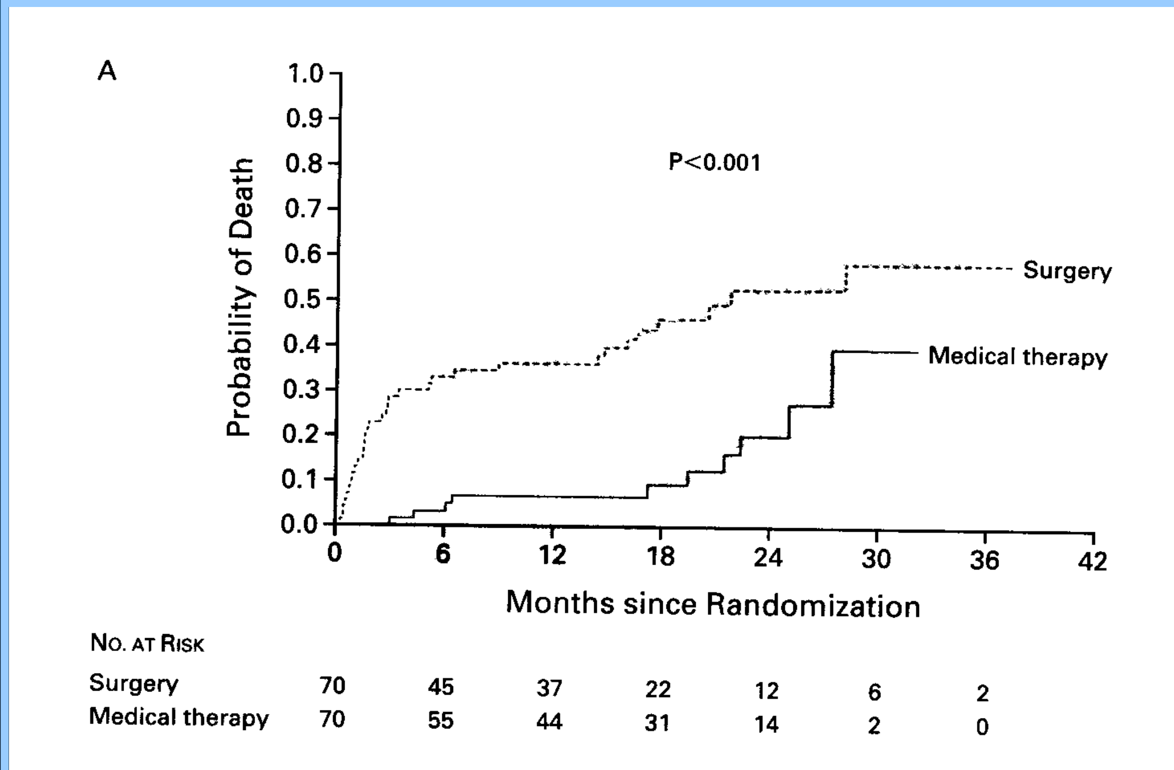
ORIGINAL ARTICLE

Patients at High Risk of Death after Lung-Volume–Reduction Surgery

National Emphysema Treatment Trial Research Group

N Engl J Med 2001;345:1075-83

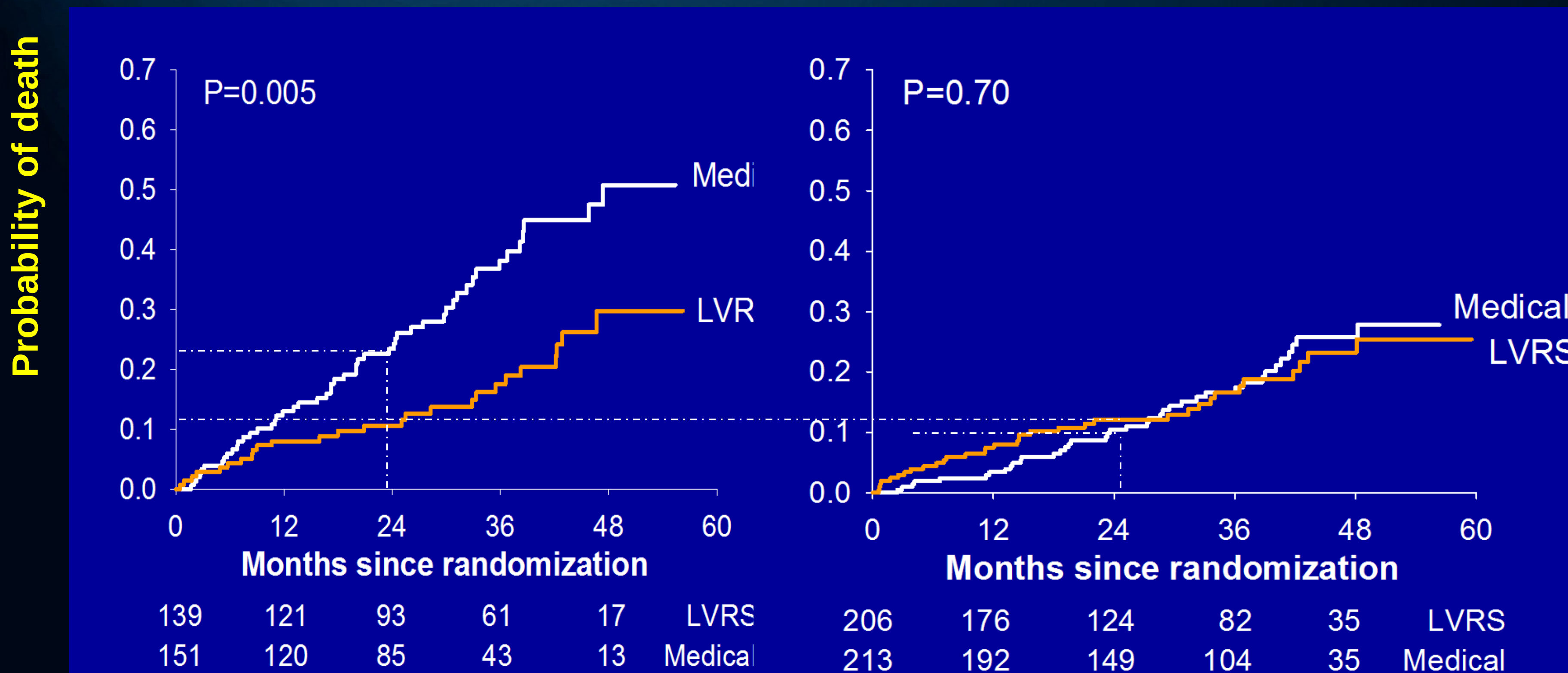
- **High Risk Subgroup (16%) enrolled in NETT**
- **$FEV_1 \leq 20\%$ pred. & either <u>homogeneous</u> CT scan or $DL_{CO} \leq 20\%$ pred.**



NETT Results: Improved Survival in Subgroup Upper-lobe disease and low exercise capacity

Upper-lobe disease/ low exercise capacity

Upper-lobe disease/ high exercise capacity



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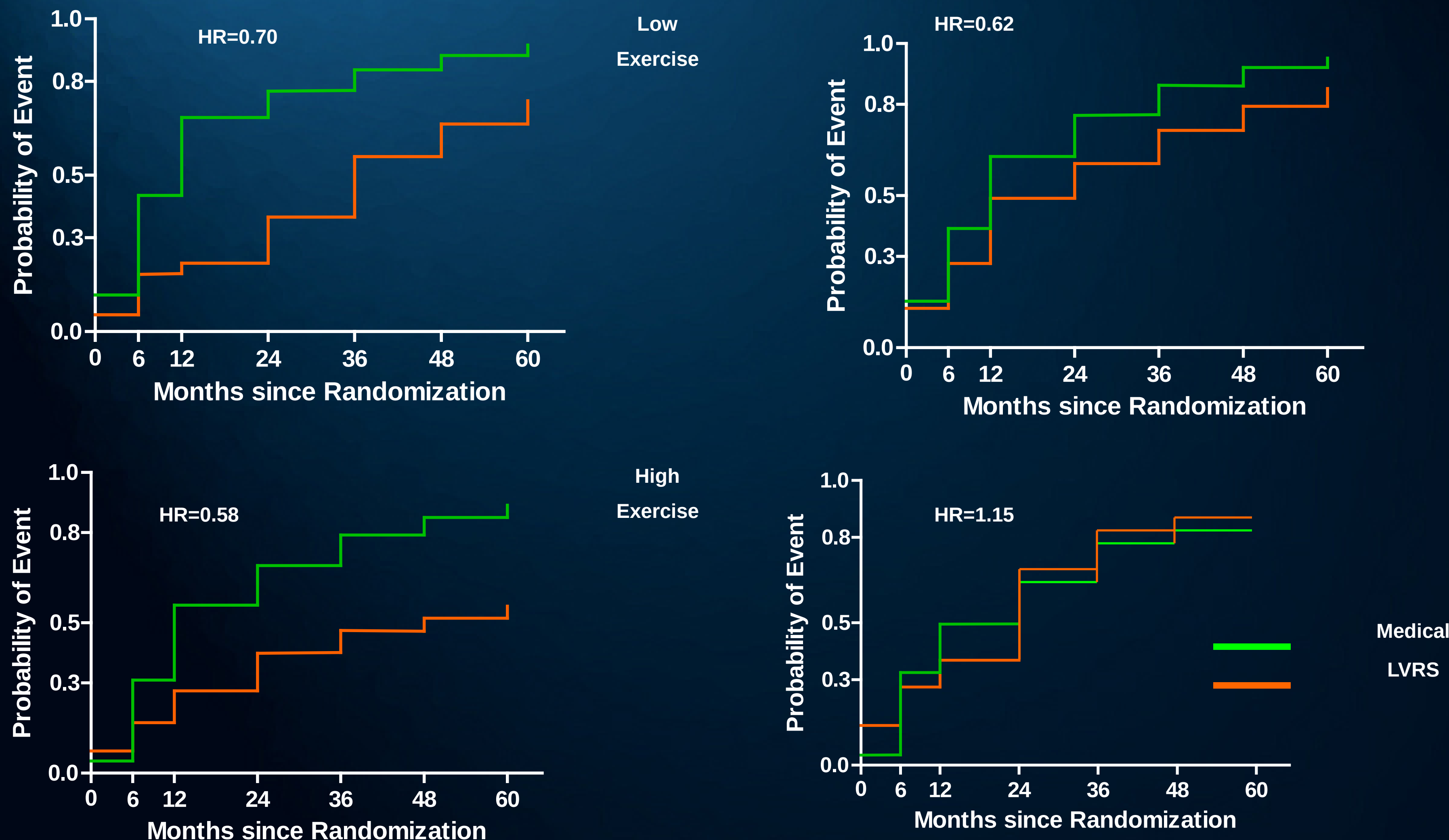
NETT: Impact of Phenotype (Heterogeneity and Exercise capacity) on Composite Endpoint (Mortality or QOL Decline)

Upper-Lobe Emphysema

Non-Upper-Lobe Emphysema

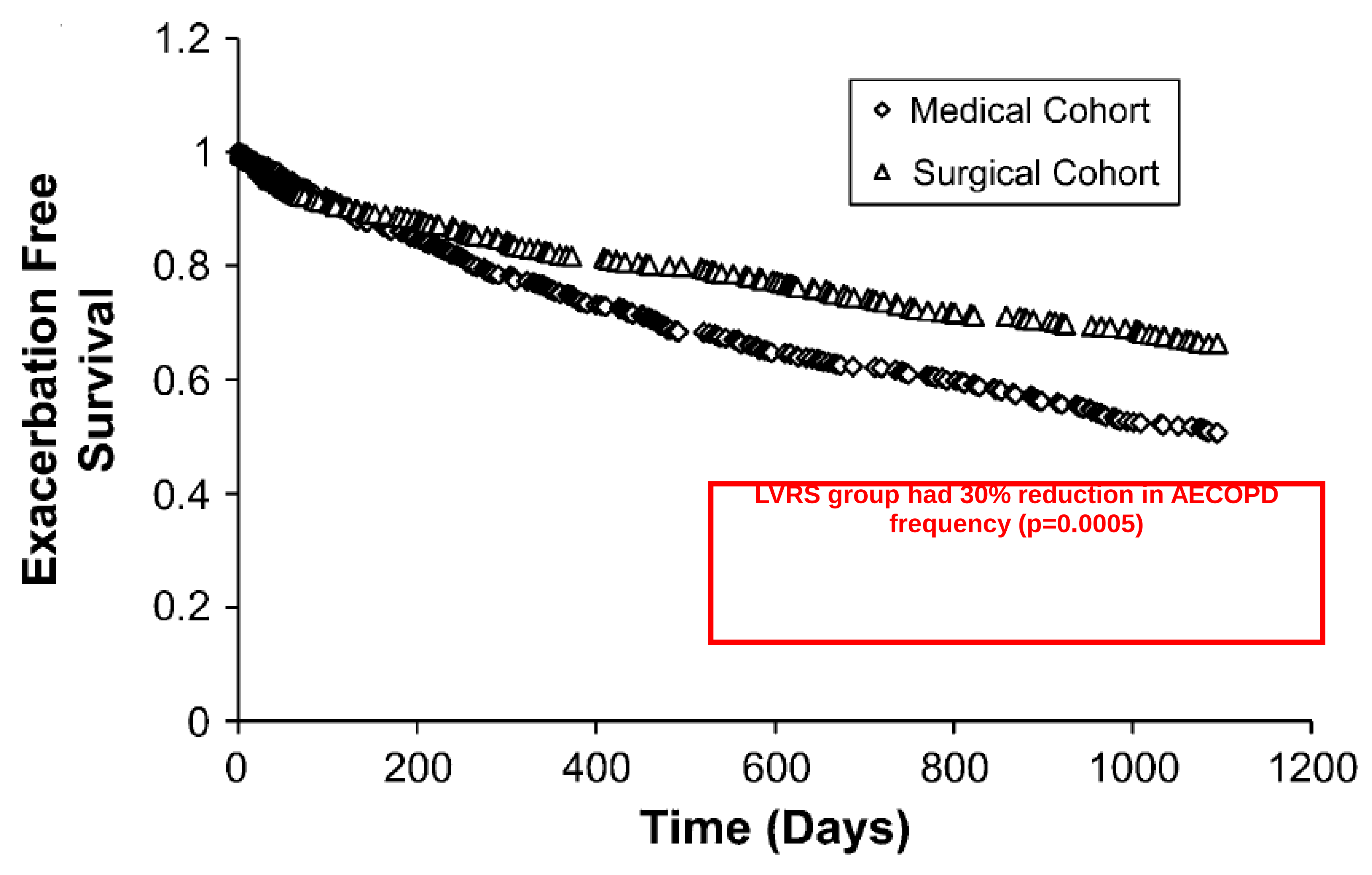


(HR at 3 yrs)

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

Effect of LVRS on AECOPD

Washko et al AJRCCM 2008



Rationale for Comparison of BVRS to LVRS

- **LVRS still the only intervention passing large RCT and with mortality benefit**
- **Strict Comparison not appropriate:**
  - Patients risk adverse: (median pneumothorax 7 days, 18% pneumonia, 22% re- reintubation, 8% tracheotomy, 4.3% mortality rate)
  - Selection criteria often different (e.g. homogeneous disease)

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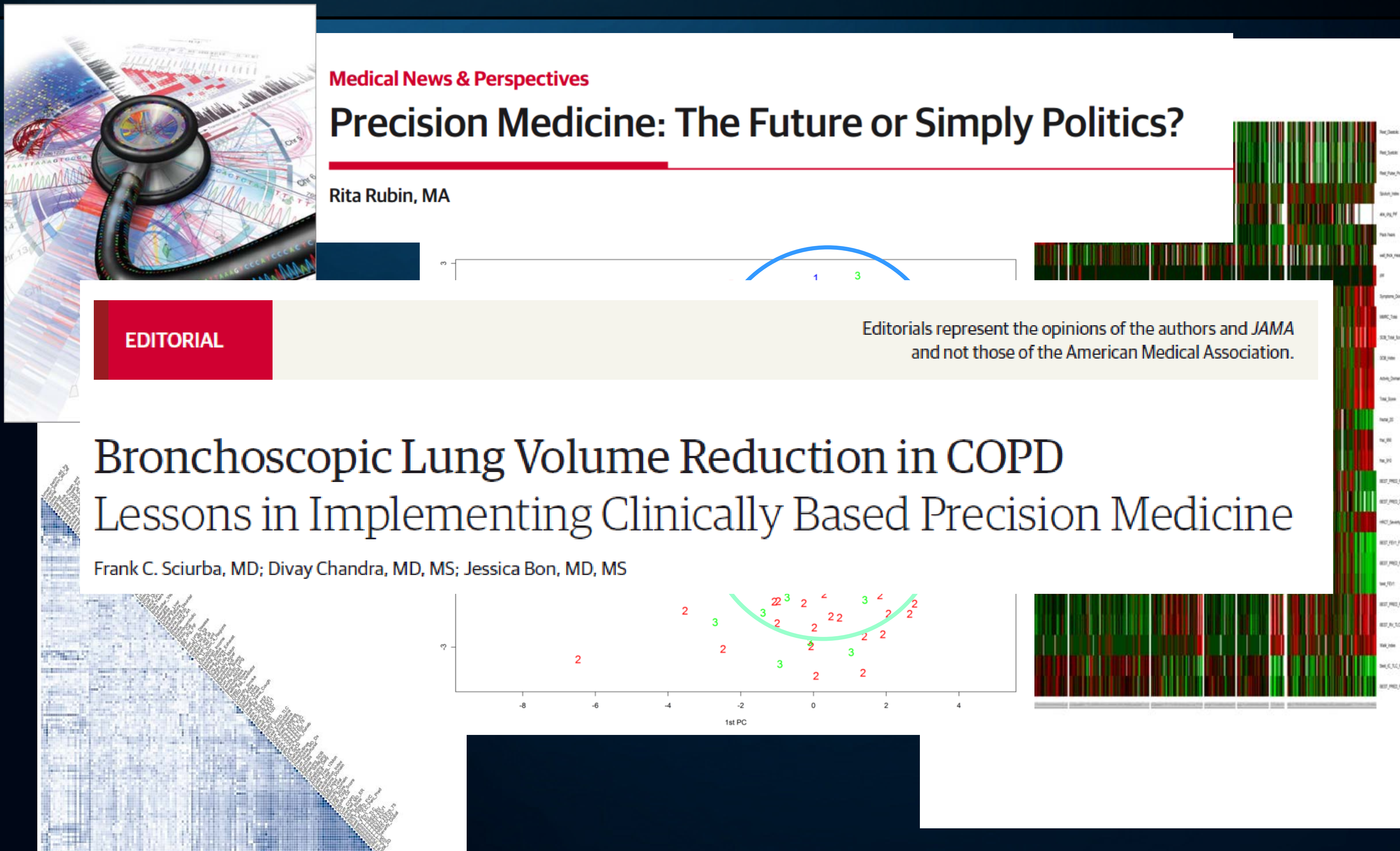
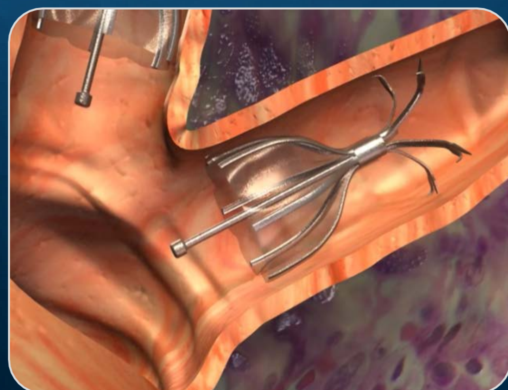
The "Promise" of Precision Medicine



Bronchoscopic Minimally Invasive Approaches to Volume Reduction

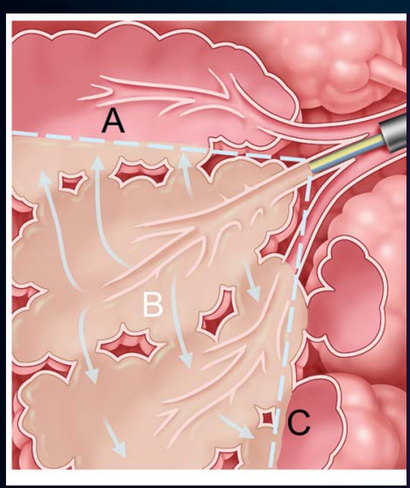
Valves

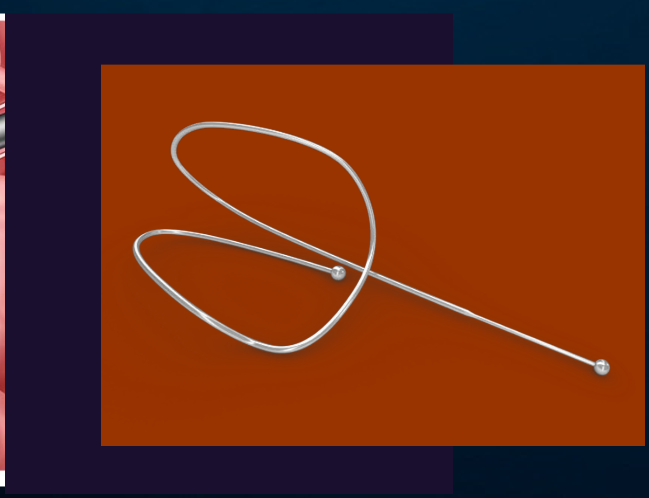


Foam

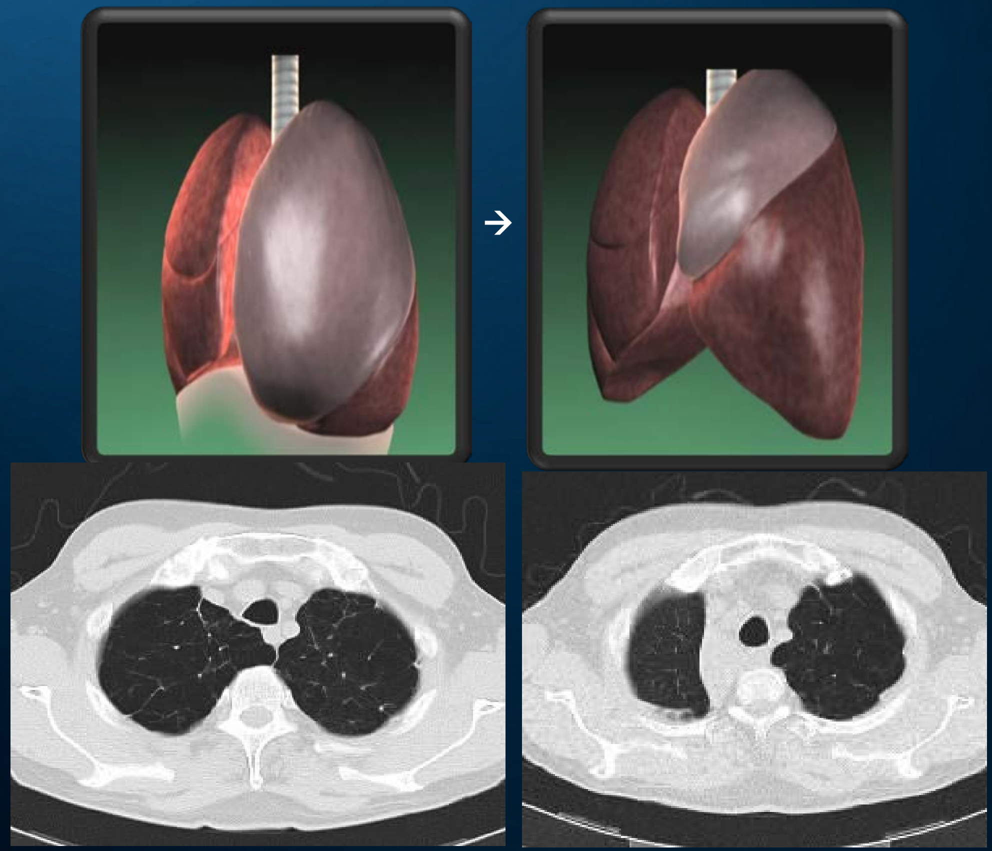
Coils

Steam





Bronchial Valves



- Target Lobe Volume Reduction
- Improved Respiratory Mechanics
- Improved Exercise & QOL

PneumRx Endobronchial Valve Deployment

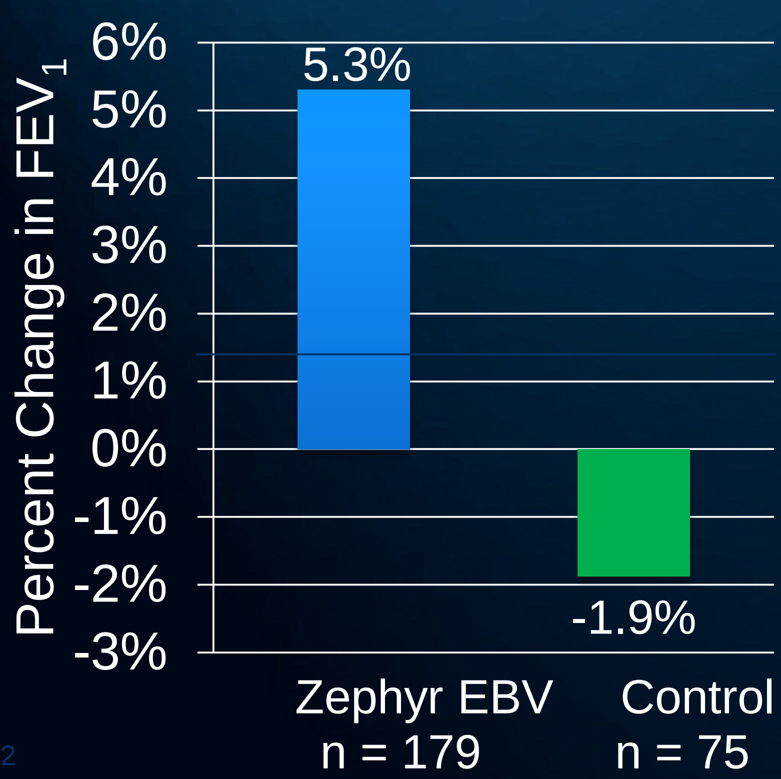
ORIGINAL ARTICLE

A Randomized Study of Endobronchial Valves for Advanced Emphysema

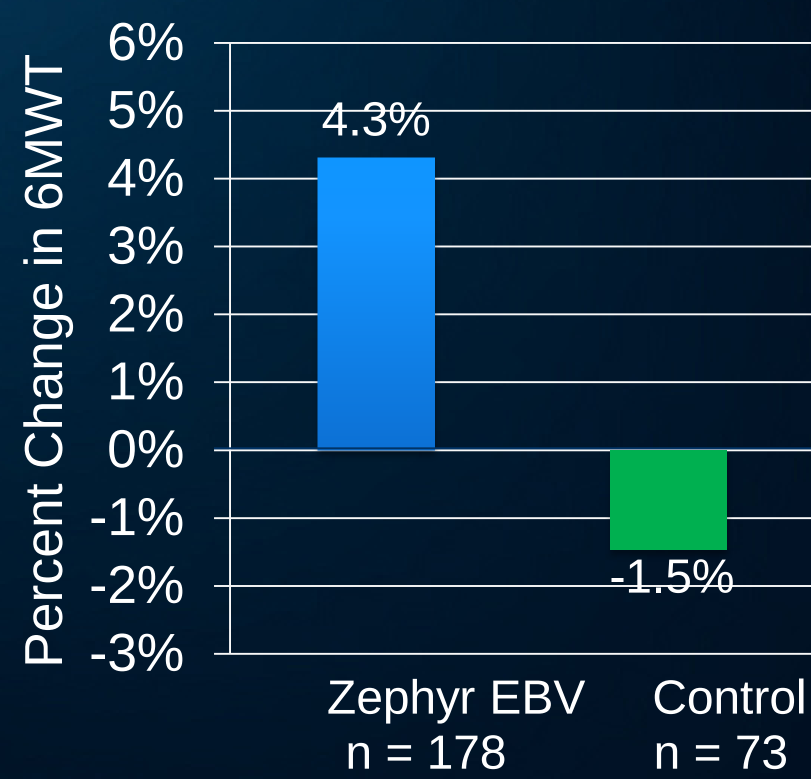
Frank C. Sciurba, M.D., Armin Ernst, M.D., Felix J.F. Herth, M.D., Charlie Strange, M.D., Gerard J. Criner, M.D., Charles H. Marquette, M.D., Ph.D., Kevin L. Kovitz, M.D., M.B.A., Richard P. Chiacchierini, Ph.D., Jonathan Goldin, M.D., Ph.D., and Geoffrey McLennan, M.D., Ph.D. for the VENT Study Research Group

N Engl J Med 2010; 363:1233-1244

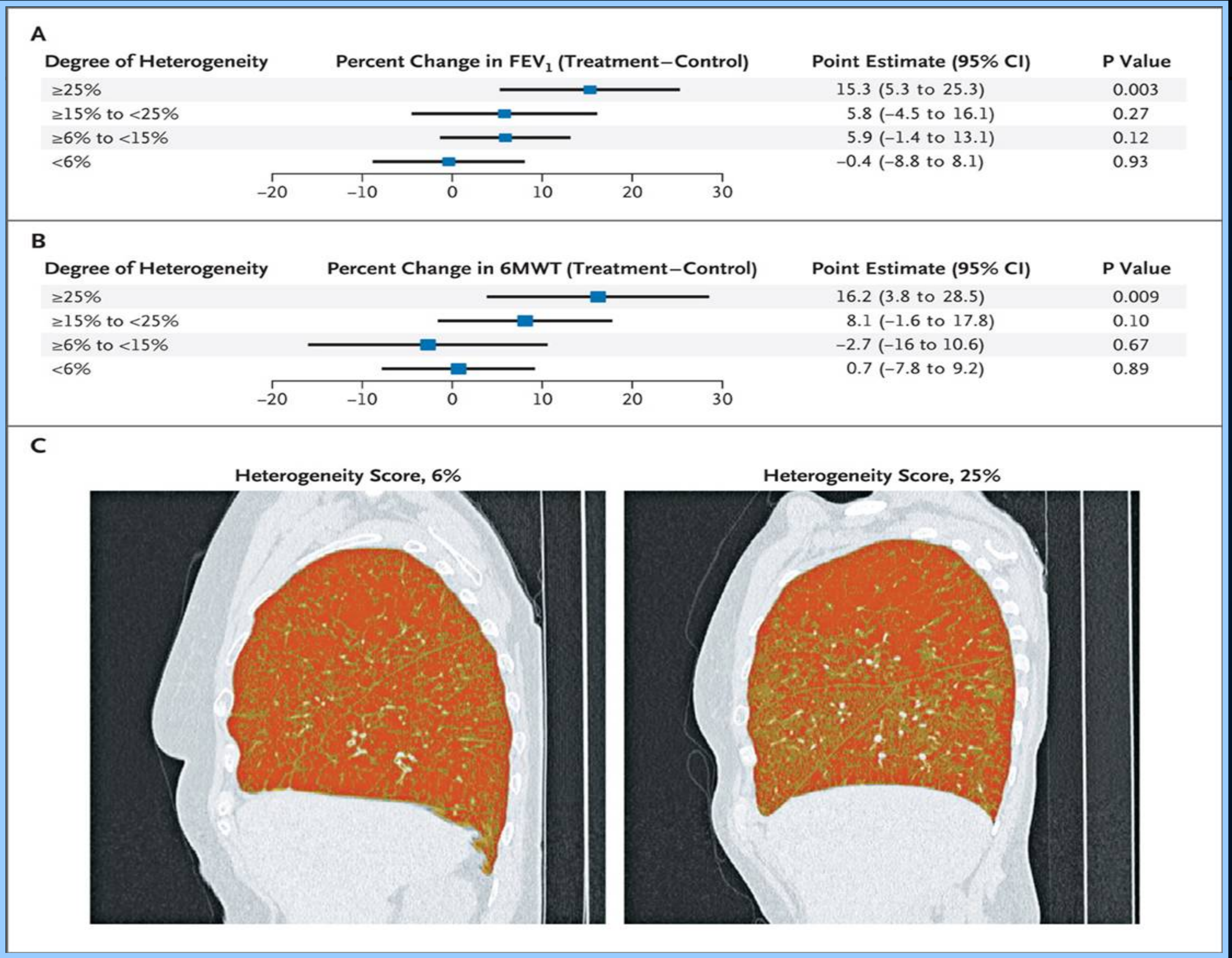
FEV_1 Change
Δ = 7.2%, p < 0.001
Abs. Δ = 64.2 ml , p < 0.001



6MWT Change
Δ = 5.8%, p = 0.008
Abs. Δ = 23.5 m, p = 0.009



Endobronchial Valves: Impact of Heterogeneity on Outcome (VENT)



(Sciurba, NEJM, 2010)

Impact of Fissure Integrity

Complete Incomplete

Incomplete fissures

- Proxy for inter-lobar Collaterals
- Attenuates volume reduction

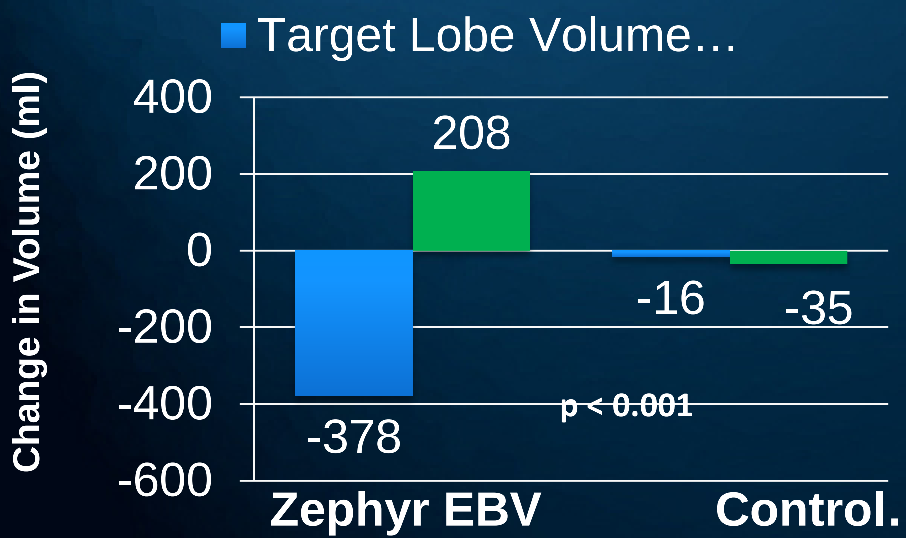
Rates of Incomplete Fissure:

- 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.

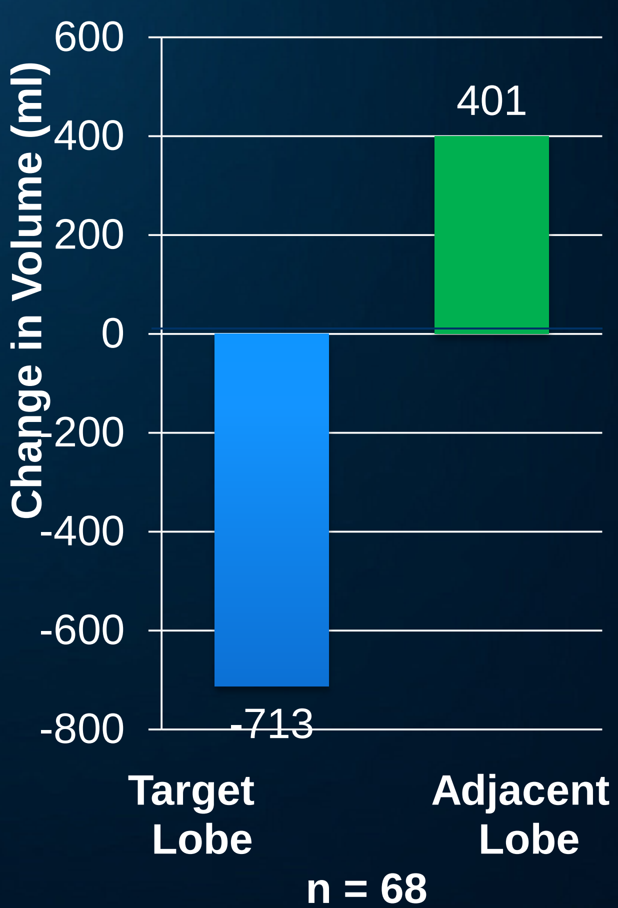
Impact of Fissure Integrity (Collateral Tracts) on Target and Adjacent Lobe Volume Changes Following Valve Placement (VENT)

All Patients



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

Treated Group with Complete Fissures



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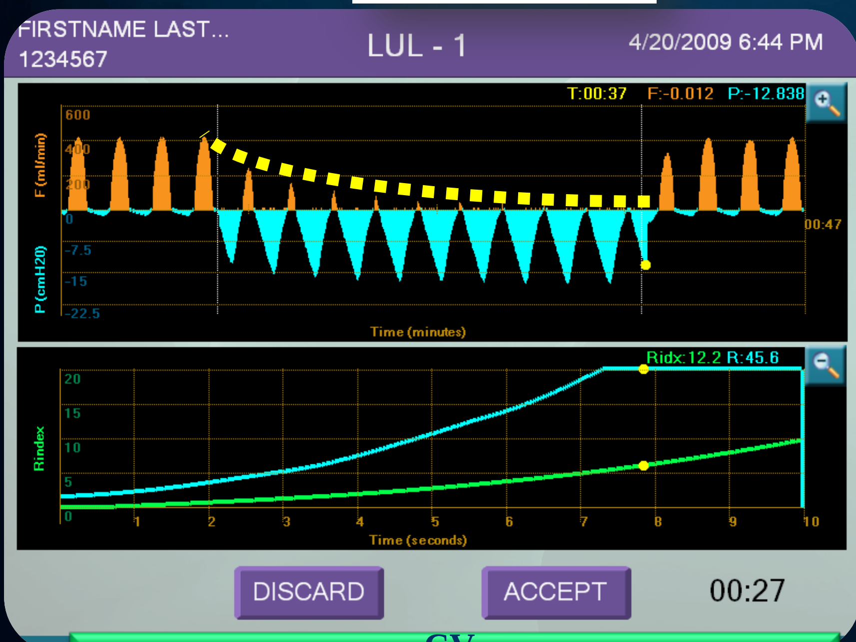
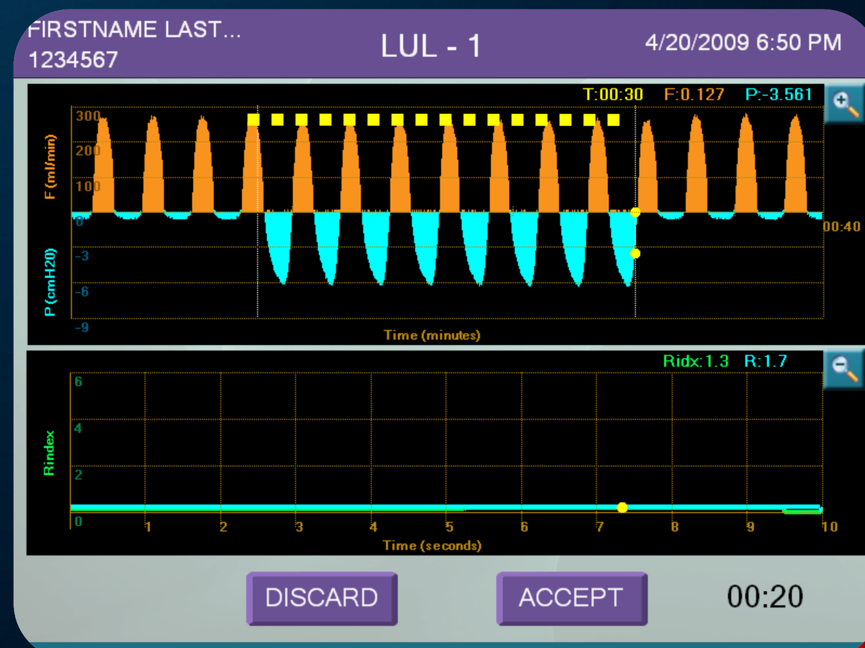
Measurement of Collateral Flow in the Lung with a Dedicated Endobronchial Catheter System

(Mantri J Bron Inter Pulm 2009)

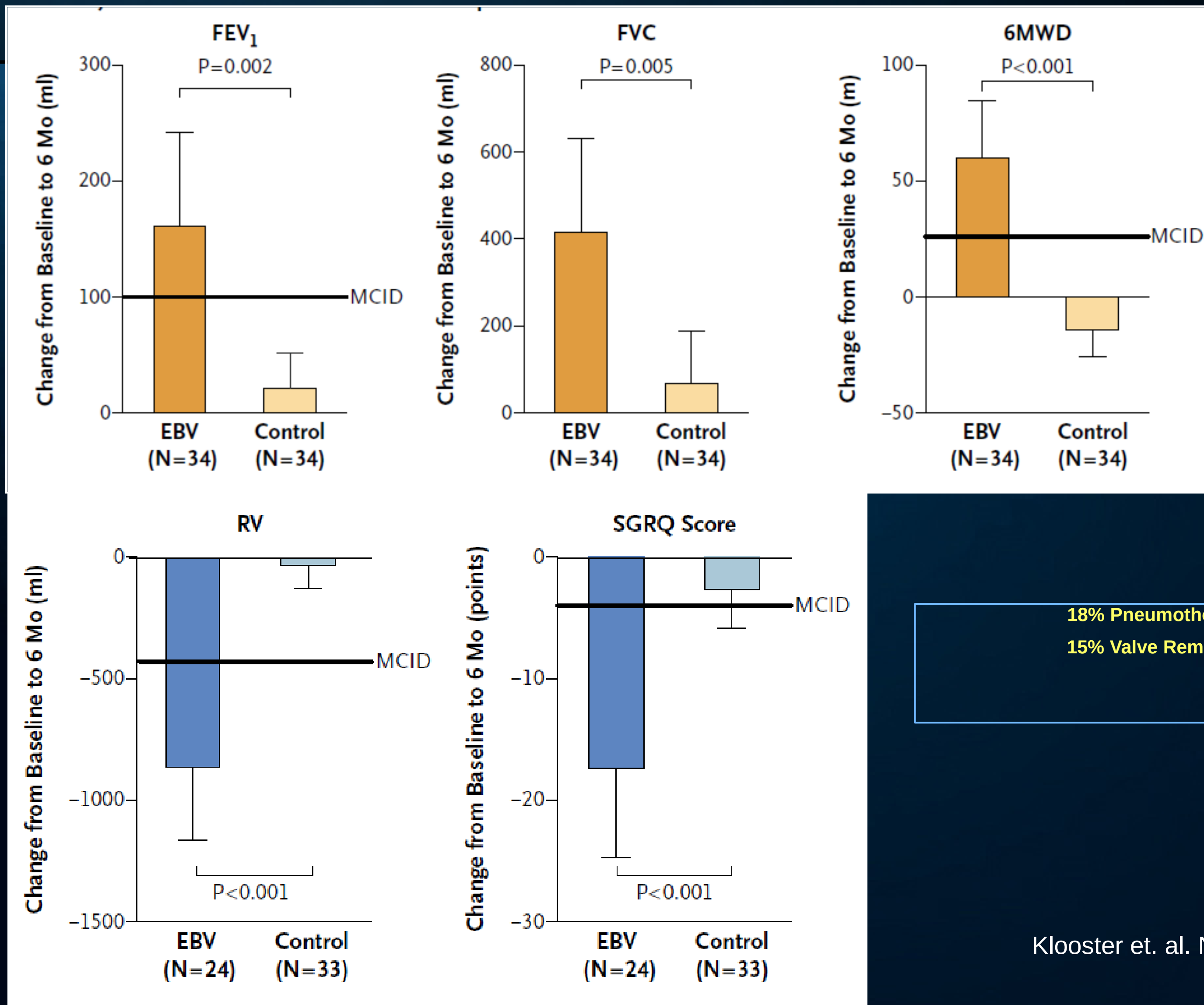


CV-
Little or No Collateral Ventilation



Significant Collateral Ventilation

EBV in Collateral flow Negative Heterogeneous Patients



18% Pneumothorax

15% Valve Removal

Klooster et. al. NEJM ‘16

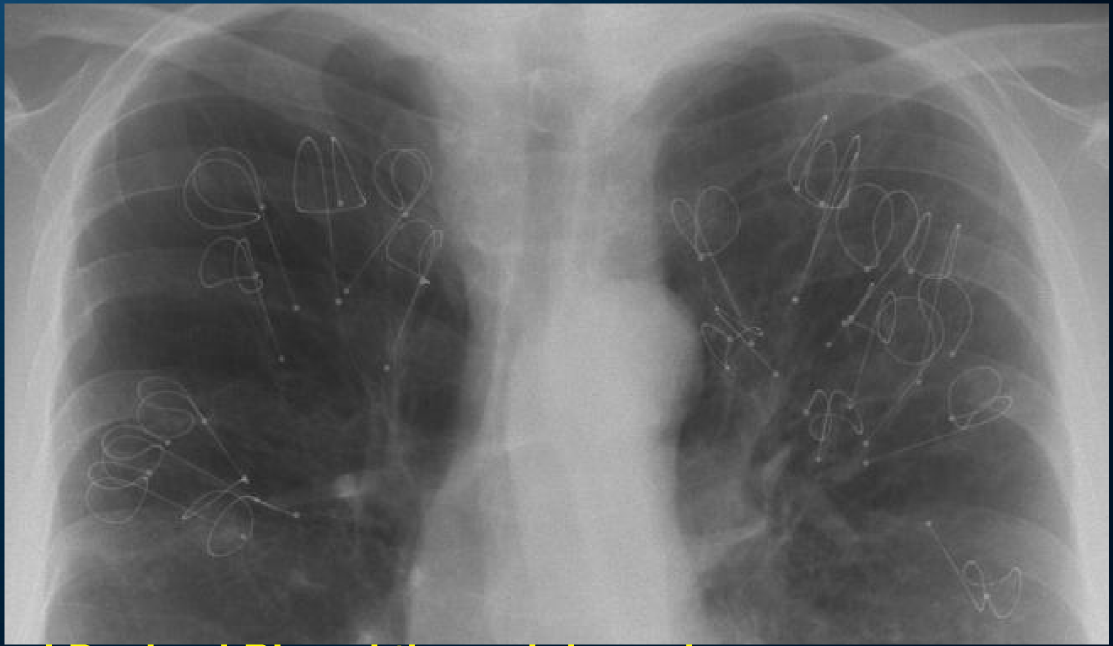
Pulmonx (Emphasys EBV): Status

- FDA non-approval: Panel recommended repeat trial in high heterogeneity subgroup '09
- EMA granted regulatory approvals in Europe

  (National access varies)
- More Precisely designed pivotal study currently enrolling (LIBERATE)
  - Heterogeneity > 15%
  - Uses Chartis Bronchoscopic flow assessment of collaterals
  - Repositioning of misplaced or migrated valves at 90 days.
  - More vigilant monitoring for pneumothorax (5 day admission)

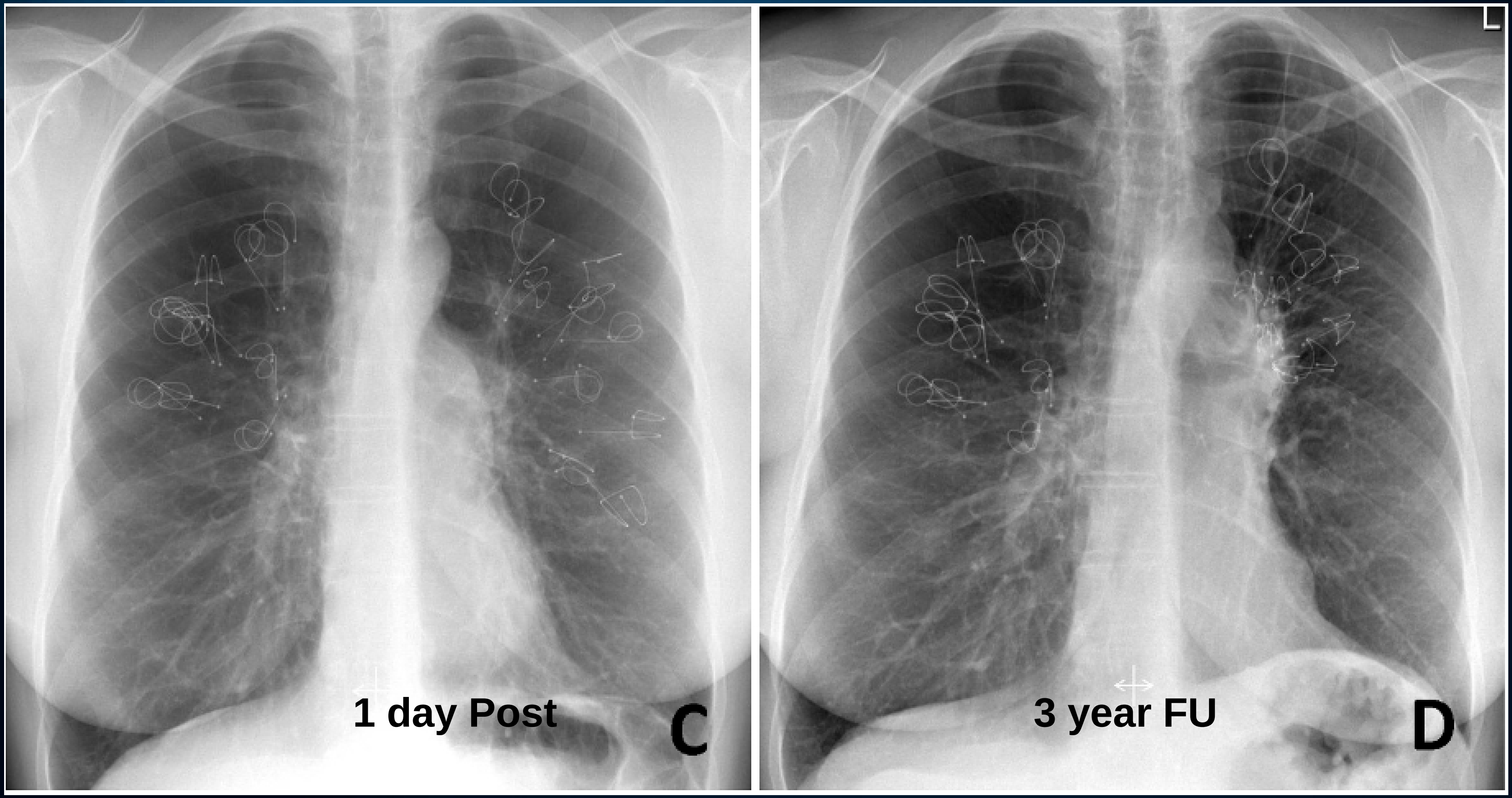
LUNG VOLUME REDUCTION (LVR) COILS

PneumRx



- Straight Nitinol Deviced Placed through bronchoscope
- Device Recoils to <u>Regionally</u> Compress Lung
- Unaffected by Collaterals
- 3 sizes 100, 125, 150mm
- 10-14 coils each side, sequentially 2-4 months apart

Radiographic Remodeling



Hartman, Klooster et al. Respirology 2014 EPub

Aggregate COIL results

	RESET[1] 3m	META ANALYSIS 6m[1-4]	META ANALYSIS 12m[1-4]	REVOLENS[5] 6m	REVOLENS[5] 12m	RENEW[6] 12m
n	T23:C22	125	96	T47:C49	T44:C47	315 T1:C1
FEV_1 % relative change	+10.6	+10%	+10%	+11%	+11%	+7%
RV Liters	-0.31	-0.51	-0.43	-0.37	-0.36	-0.31
6MWD meters	+64 (+51 vs -12)	+44	+38	+21 (+19 vs -2)	+21 (-2 vs -23)	+14.6m
SGRQ points	-8.4	-9.5	-7.7	-13.4	-10.6	-8.9

1) Shah, *Lancet Resp Med 2013;* 2) Slebos, *Chest 2012;* 3) Klooster, *Respiration 2014;* 4) Deslee, *Thorax 2014; 5) Deslee, JAMA 2016 6) Sciurba JAMA 2016*

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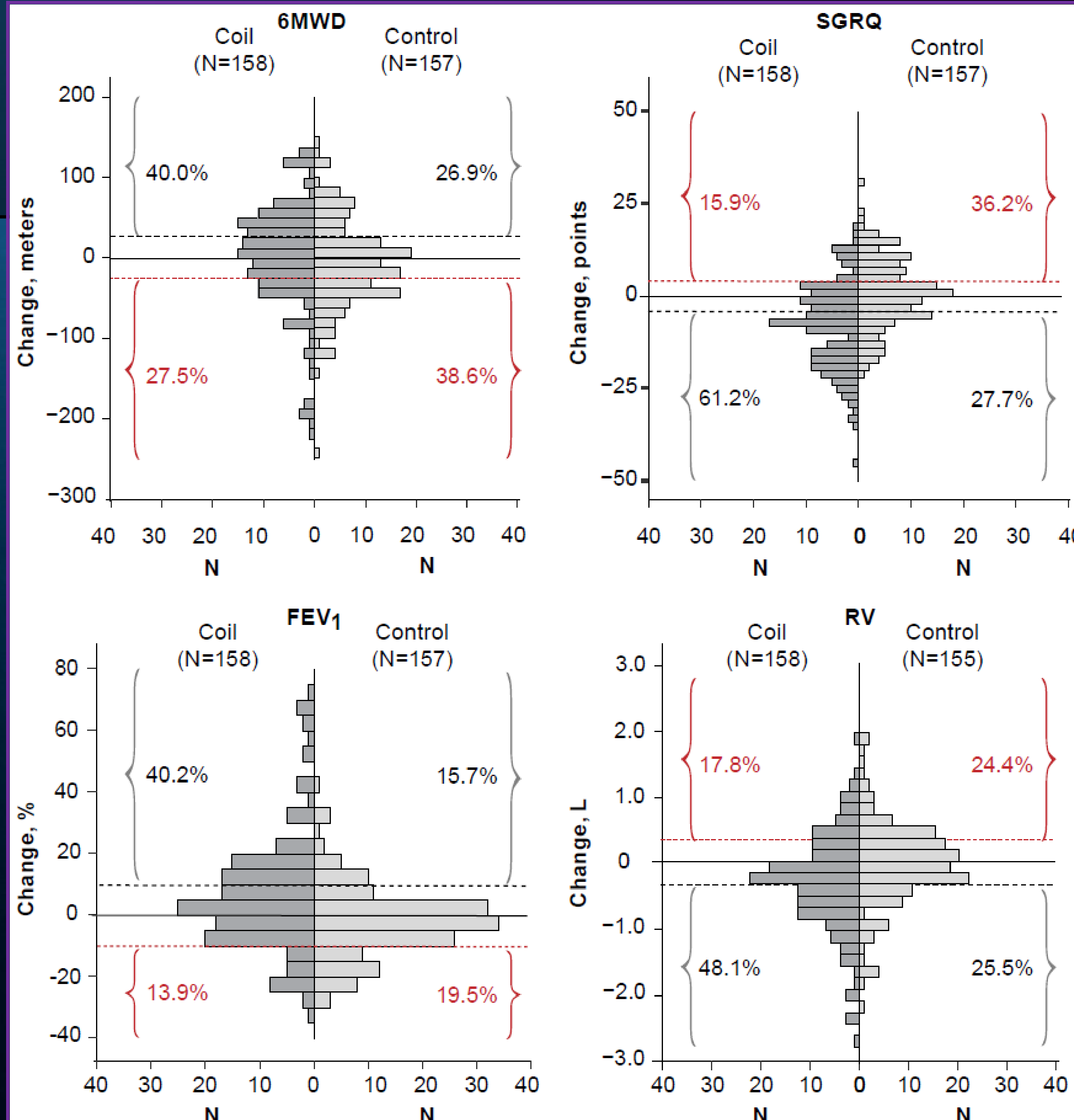
Results



<u>MCID</u>

6MWD 25 m

SGRQ -4 pts

FEV_1 10%

RV -0.35 L

Sciurba JAMA 2016

Results: Pre-specified Subgroup analyses
Impact of Hyperinflation and Emphysema Distribution

Between-group Differences*: Coil vs. Control

6MWD 14.6 m (0.4, ∞)
SGRQ -8.9 pts (-∞, -6.3)
FEV_1 7.0% (3.4, ∞)
RV -0.31 L (-∞, -0.11)

RV ≥ 225%

Heterogenous (N = 58)

6MWD 29.1 m (-8.8, 66.7)
SGRQ -10.1 pts (-16.3, -3.9)
FEV_1 12.3% (1.6, 22.1)
RV -0.37 L (-0.83, 0.08)

Homogenous (N = 177)

6MWD 20.7 m (2.5, 38.9)
SGRQ -10.0 pts (-13.3, -6.7)
FEV_1 8.3% (3.5, 12.9)
RV -0.25 L (-0.50, 0.00)

RV < 225%

Heterogenous (N = 14)

6MWD 16.2 m (-102.5, 84.1)
SGRQ -9.9 pts (-26.8, 7.1)
FEV_1 2.8% (-19.0, 16.6)
RV -0.43 L (-1.29, 0.44)

Homogenous (N = 66)

6MWD -16.7 m (-48.1, 16.1)
SGRQ -3.3 pts (-8.9, 2.4)
FEV_1 3.5% (-4.0, 11.1)
RV -0.35 L (-0.64, -0.06)

* Between treatment differences, mean (CI) based on ANCOVA for SGRQ and RV, median (CI) based on Hodges Lehmann estimator for 6MWD and FEV_1, from full ITT analysis set with multiple imputation. Confidence intervals are 1-sided 97.5% for full study, and 2-sided 95% for subgroups.

MCID: 6MWD 25 m; SGRQ -4 pts; FEV_1 10%; RV -0.35 L

Sciurba JAMA 2016

Coil Associated Opacities: Associated with Long Term Impovement

Can be harmless

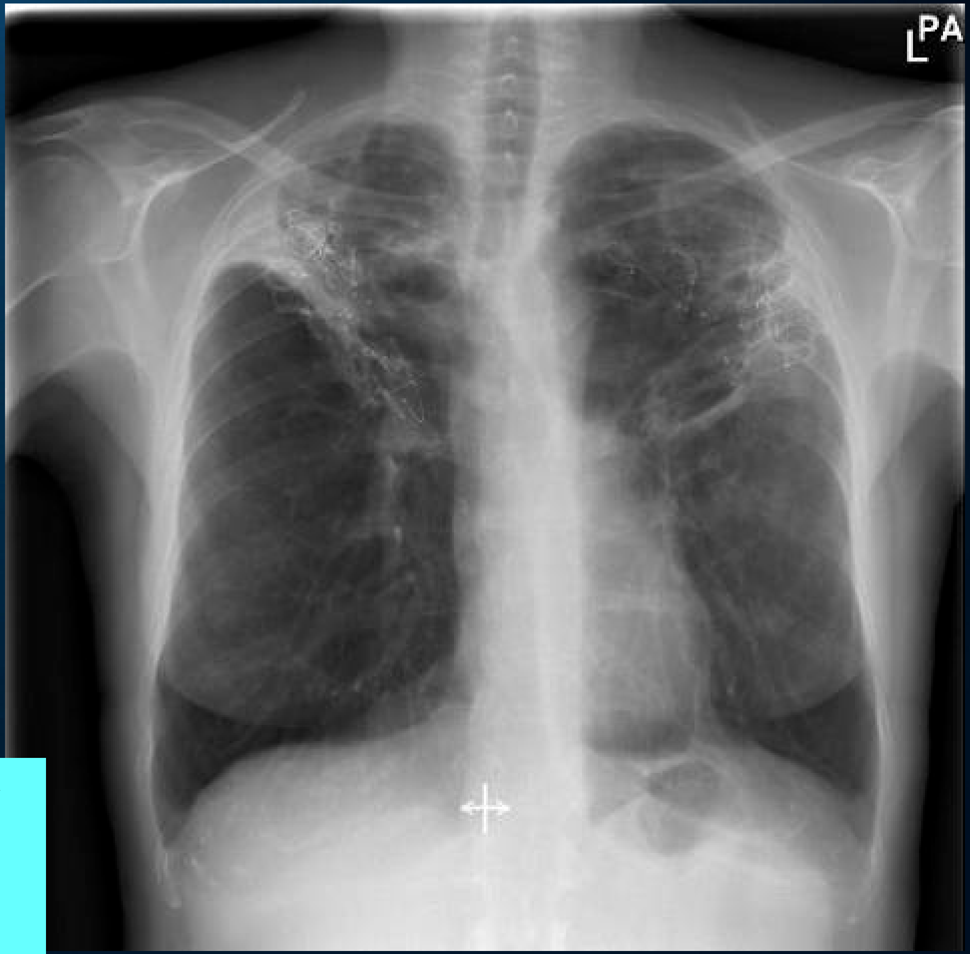
Can be symptomatic

Treat like pneumonia

- Be agressive
- Broad spectrum AB
- High dose steroids
- Suppotive care

Outcome can be very good

	Pre Tx	Post 2nd Tx
FEV_1, %pred	31	49
RV, L	3.65	2.43
6MWD, m	430	508
mMRC, points	3	1



LUNG TRANSPLANTATION

ISHLT

2012

J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

Lung Transplantation

End-stage lung disease

- COPD/ Alpha-1-Antitrypsin Deficiency
- Cystic Fibrosis
- Idiopathic Pulmonary Fibrosis
- Primary Pulmonary Hypertension

Guidelines for Selection

Clinically and physiologically severe lung disease

Limited life expectancy (12-24 mos)

All other treatment options utilized

Ambulatory with rehab potential

Satisfactory nutritional status

Appropriate mental status

Well motivated and compliant

Adequate financial/Insurance resources

Minimal to modest use of Prednisone

Age (most centers under 65 years of age)

Guidelines for Selection (COPD)

- **Progressive dysfunction despite smoking cessation**
- **Optimization of medications, pulmonary rehabilitation, and supplemental oxygen**
- **BODE index of 5 to 6**
- **$PaCO_2$ >50 mmHg and/or PaO_2 <60 mmHg**
- **FEV_1 <25 %predicted.**

Variable Points on BODE Index

Variable	0	1	2	3
FEV_1 (% pred.)	≥65	50-64	36-49	≤35
Six Minute Walk (m)	≥350	250-349	150-249	≤149
MMRC dyspnea scale	0-1	2	3	4
Body-mass index Kg/m2	> 21	≤ 21		

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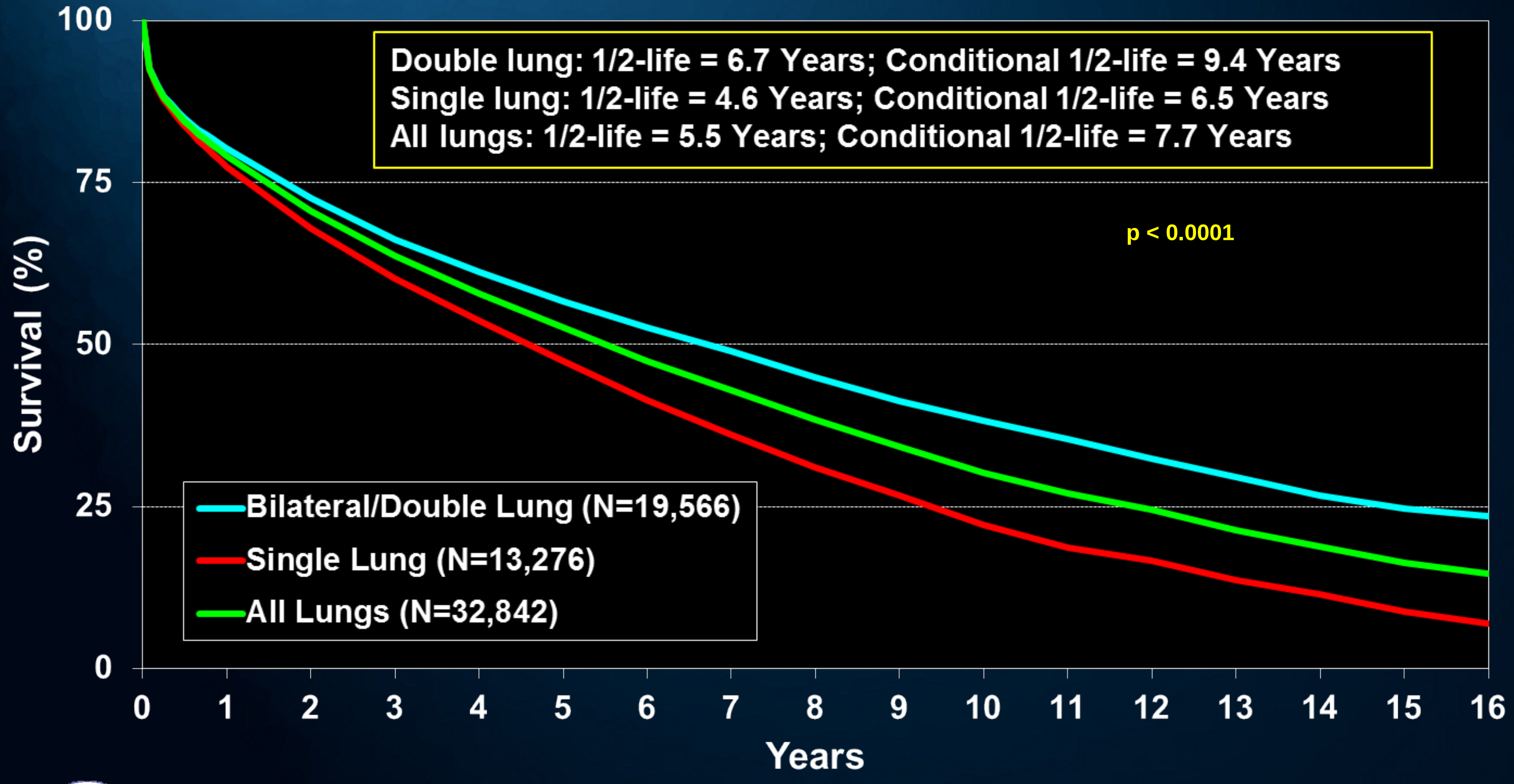
Lung Allocation Scoring (LAS)

- **Implemented in 2005**
- **LAS Score 0 to 100**
- **Designed to optomize survival benefit from transplant**
- **Balances risk of dying on waiting list (disease type and severity, etc.) with post-transplant prognosis (age, comorbidity, functional status etc.)**
- **Has shifted proportion of transplants toward IPF**

ADULT LUNG TRANSPLANTS
Kaplan-Meier Survival
(Transplants: January 1994 - June 2010)

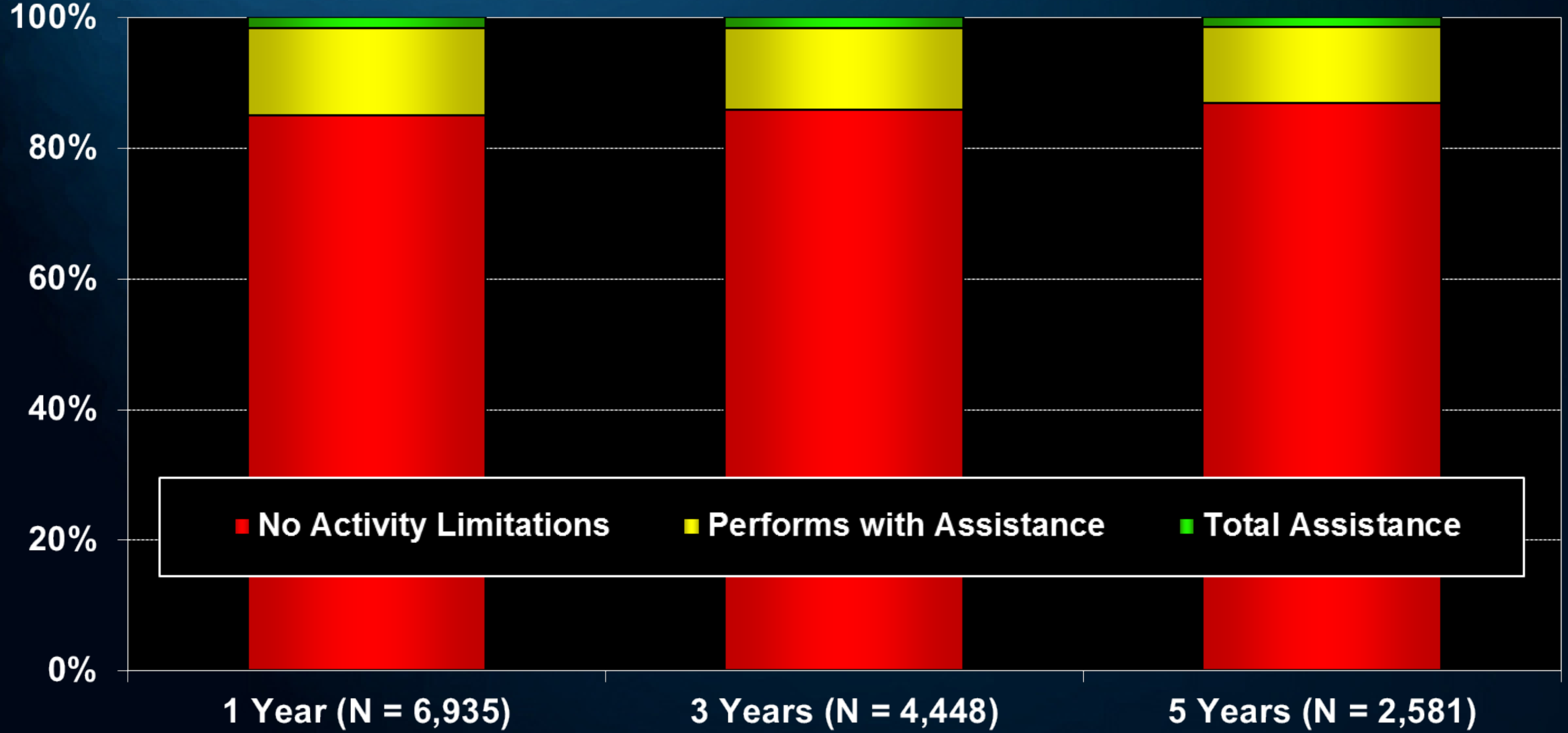


ISHLT

2012

J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

ADULT LUNG RECIPIENTS
Cross-Sectional Analysis
Functional Status of Surviving Recipients
(Follow-ups: April 1994 – June 2011)



ISHLT

2012

J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095

Noninvasive Ventilation in COPD

Noninvasive Positive Pressure Ventilation in COPD

Acute Respiratory Failure

- Decrease need for intubation and invasive ventilation
- Expedite weaning from invasive ventilation
- Postoperative support for thoracic surgery in patients with underlying COPD

Chronic Respiratory Failure?

- Standard Dose vs. High dose may yield different outcomes.
- Decrease hospitalization for AECOPD?
- Improve survival?
- Improve sleep?
- Improve QOL?
- Improve lung function and respiratory muscle strength?

Randomized Controlled trials of NIPPV in Chronic Stable COPD

Source	Complete/ enrolled	FEV_1 (L)	$PaCO_2$ (mmHg)	Length (mo)	IPAP/ EPAP
Gay	4/7	0.68	55	3	10/2
Strumpf	7/19	0.54	49	3	15/2
Meecham-Jones	14/18	0.86	56	3	18/2
Casanova	17/26	0.85	51	12	12-14/4

Wijkstra et al Chest; 2003:124 : 337

Meta-analysis NIPPV

Outcome	NIPPV/UC	Mean	95% CI
FEV_1	33/33	0.02	-0.04,0.09
FVC	33/33	-0.01	-0.14,0.13
PImax	24/24	6.2	0.2,12.2
PEmax	24/24	18.4	-11.8,48.6
PaO_2	33/33	0.0	-3.8,3.9
$PaCO_{2,}$	34/33	-1.5	-4.5,1.5
6 MWT	12/11	27.5	-26.8,81.8
Sleep efficiency	13/11	-4.0	-14.7,6.7

Wijkstra et al Chest; 2003:124 : 337

High Intensity Non-Invasive Positive Pressure Ventilation for Stable Hypercapnic COPD

Table 1. Ventilator settings for 69 patients receiving pressure-limited NPPV

	Mean ± SD	Min	Max
IPAP (cmH_2O)	28.0 ± 5.4	17	42
EPAP (cmH_2O)	4.6 ± 1.3	2	9
b_f (/min)	21.0 ± 2.8	10	26
Supplemental oxygen (l/min)	1.6 ± 1.5	0	6

IPAP = inspiratory positive airway pressure, EPAP = expiratory airway pressure, b_f = breathing frequency; SD = standard deviation.

(Windisch, Int Jour of Med Sci, 2009)

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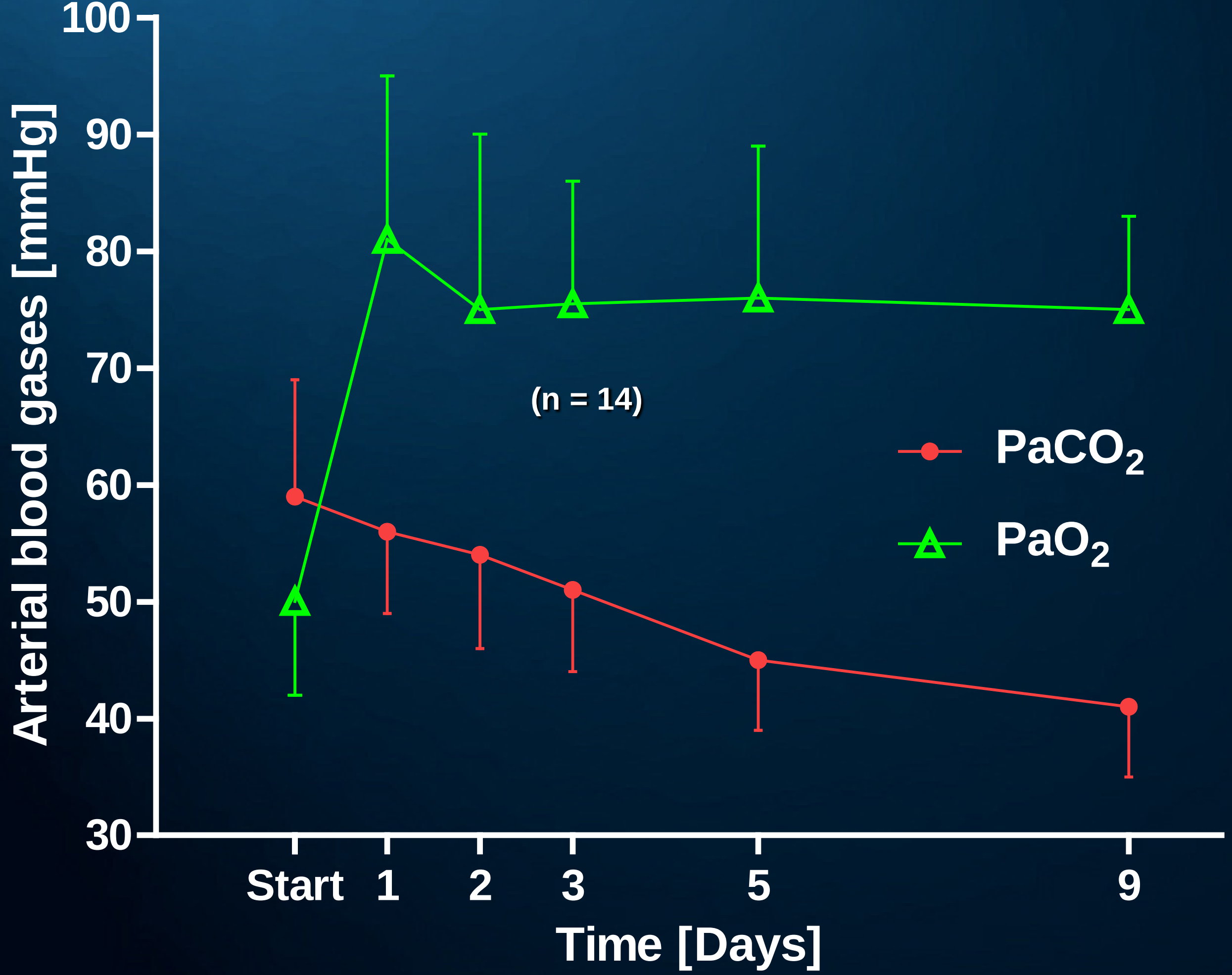
High Intensity Non-Invasive Positive Pressure Ventilation for Stable Hypercapnic COPD

(Windisch, Int Jour of Med Sci, 2009)

Table 2. Blood gas levels, lung function parameters, mouth occlusion pressures, hemoglobin and hematocrit prior to NPPV and 2 months after establishment of NPPV.

Variables	prior to NPPV	After 2 months of NPPV	95 % CI for the difference	p-value
pH	7.40 ± 0.04	7.40 ± 0.03	-0.01 / 0.02	0.598
$PaCO_2$ (mmHg)	51.2 ± 6.5	46.8 ± 5.8	-6.2 / -2.0	<0.001
PaO_2 (mmHg)	53.0 ± 8.1	58.0 ± 8.3	2.1 / 7.9	0.001
HCO_3^- (mmol/L)	31.3 ± 5.7	28.7 ± 5.4	-4.0 / -1.2	<0.001
TLC (%pred.)	109.2 ± 22	109.3 ± 21.6	n.f.	0.419
FVC (%pred.)	49.3 ± 13.3	54.6 ± 13.7	2.2 / 8.2	<0.001
FEV_1 (%pred.)	30.1 ± 12.2	34.6 ± 13.6	2.4 / 6.6	<0.001
FEV_1/FVC (%)	43.6 ± 10.1	45.6 ± 10.7	n.f.	0.68
P0.1 (kPa)	0.60 ± 0.57	0.46 ± 0.26	n.f.	0.056
PImax (kPa)	4.7 ± 2.3	5.6 ± 2.5	n.f.	0.501
Hb (g/dl)	14.6 ± 2.0	14.2 ± 1.7	-0.9 / -0.1	0.093
Hkt (%)	45.1 ± 6,5	43.7 ± 5.9	n.f.	0.005

Normalization of PaO2 and PaCO2 During nIPPV With Supplemental Oxygen



Windisch et. al. *Int J Med Sci* 2009;6:72-76.

Unanswered Questions Regarding NIPPV in Chronic Stable COPD

Does it work or not?

- Candidate selection
- Settings
- Duration of use
- Interface
- Cost effectiveness
- Insurance coverage

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The Hospital-Dependent Patient

David B. Reuben, M.D., and Mary E. Tinetti, M.D.

Characteristics of Patients Who Are Readmitted to Hospitals.*

Characteristic	Hospital-Dependent Patients	Patients with Failed Transitions	Patients with Chronic Critical Illness
Continuous need for life-sustaining equipment	–	–	+
Precipitous flares	+	+/–	+/–
Multiple chronic conditions	+	+/–	+
Decreased physiological reserve	+	+/–	+/–
Need for close monitoring by nursing staff	+	–	+/–
Need for immediate medical response	+	–	+/–

* A plus sign denotes usually present, a plus–minus sign sometimes present, and a minus sign usually absent.

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Reuben DB, Tinetti ME. et al. N Engl J Med 2014;370:694-697.

Advanced Illness Care – Kaiser Permanente's Model

TABLE 1
Results of Kaiser Permanente's in-home palliative care program

	Palliative care	Usual care
Higher satisfaction with care		
Very satisfied 30 days after enrollment[8]	93%	80%
Very satisfied 90 days after enrollment[8]	93%	81%
More likely to die at home		
Patients who died at home in accordance with their wishes[8]	71%	51%
Patients with COPD who died at home[9]	92%	37%
Patients with HF who died at home[9]	87%	47%
Patients with cancer who died at home[9]	87%	71%
Reduced utilization and costs		
Patients requiring hospitalization[8]	36%	59%
Patients visiting the emergency department[8]	20%	33%
Mean cost of care[8]	$12,670	$20,222
Reduction in cost for patients with COPD[9]	67% less	
Reduction in cost for patients with HF[9]	52% less	
Reduction in cost for patients with cancer[9]	35% less	

HF = heart failure; COPD = chronic obstructive pulmonary disease

Labson MC, et al. Innovative Models of home-based palliative care. The Cleveland Clinic of Journal of Medicine 2013: e-S30-eS35.

Conclusions

- **New paradigms for the treatment of COPD account for reduction of risk such as exacerbation and survival as well as improvement in symptoms.**
- **Secondary Pulmonary Hypertension in COPD may contribute to functional impairment and mortality risk…. Evidence for reduced risk associated with treatment particularly in more severe patients is evolving.**
- **Minimally Invasive bronchosocopic approaches to lung volume reduction which are independent of collateral flow show promise and are currently under investigation.**

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Well, this isn't a cheerful sign.