Primary Care Trends

Individualizing Therapy for the COPD Patient: Strategies for Delivering Guideline-Concordant Care

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The leading cause of death in the US is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents

COVID-19
600,000 deaths

Learning Objectives

1. Describe current guideline classification of patients with COPD
2. Apply guideline recommendations to devise maintenance therapies for patients with COPD
3. Outline currently available classes of medications and delivery systems
4. Select COPD medication and device taking into consideration patient characteristics and disease presentation

Patient Case #1

A 60 y/o man complains of dyspnea while loading his fishing boat the past year. He stopped smoking 6 months ago after 40 pack years. You suspect COPD.

Case #1 Related Question

What is the appropriate initial diagnostic test?

A. Chest CT

B. EKG

C. Metabolic Panel

D. Spirometry

Definition of COPD

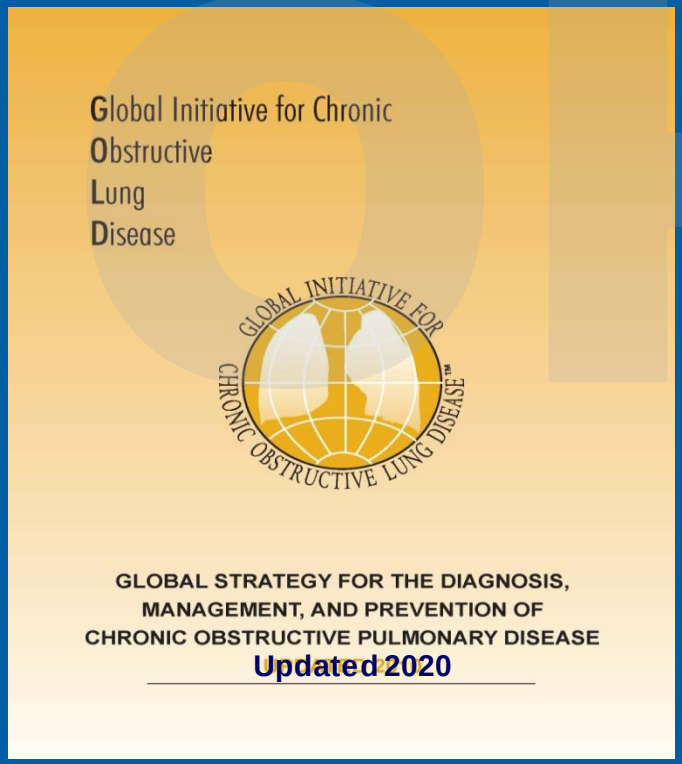
- COPD is a preventable and treatable disease
- Exacerbations and comorbidities contribute to the overall severity in individual patients
- The pulmonary component is characterized by airflow limitation that is not fully reversible.
- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

http://www.goldcopd.org

Global Initiative for Chronic Obstructive Lung Disease

http://www.goldcopd.org

Four Components of COPD Management

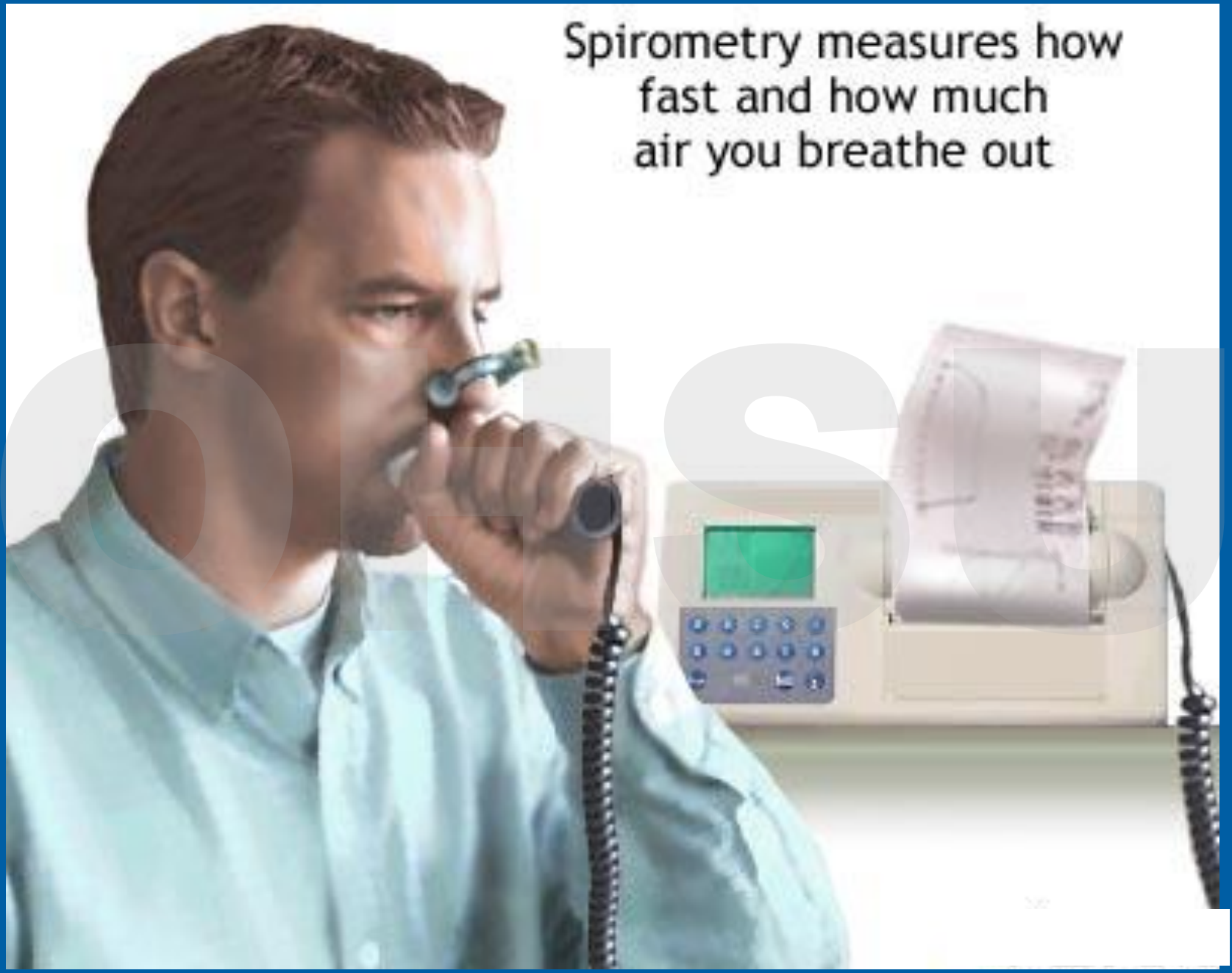


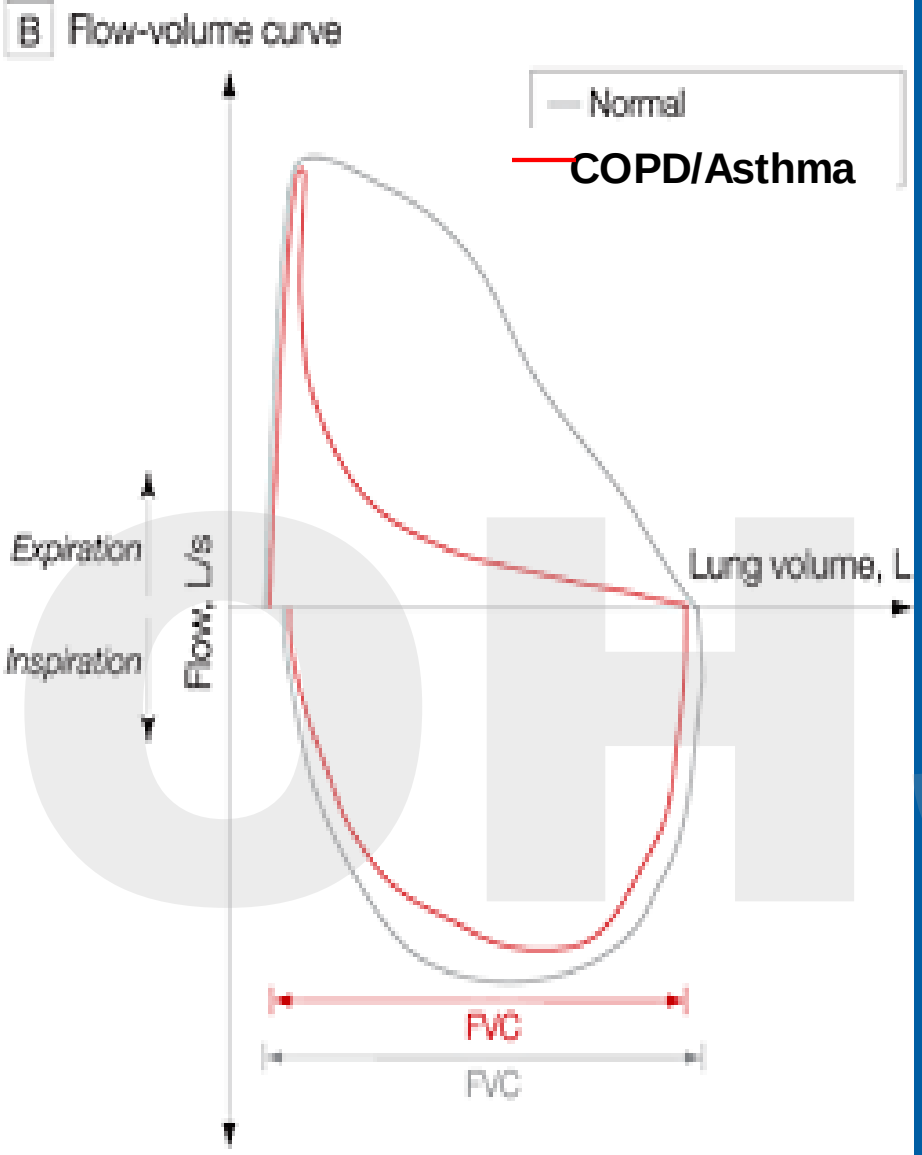
- Assess and monitor disease
- Reduce risk factors
- Manage stable COPD
- Manage exacerbations

www.goldcopd.com

Useful Diagnostic Tests

- Spirometry
- CBC with diff; eos
- Electrolyte panel- hypercapnia
- 6 MW
- Chest CT (low density)


Spirometry measures how
fast and how much
air you breathe out



COPD/Asthma Pulmonary Function

Case #1 Related Question

What is the appropriate initial diagnostic test?

A. Chest CT

B. EKG

C. Metabolic Panel

D. Spirometry

Patient Case #2

In this man on next visit, dyspnea is now noted climbing stairs or up inclines on walks with wife.
Spirometry shows

FVC-95% of predicted

FEV1-72%

FEV1/FVC-62%.

Case #2 Related Question

You confirm the diagnosis of COPD. What medication would be appropriate initial therapy?

A. Inhaled long-acting anti-muscarinic agent alone

B. Inhaled corticosteroid alone

C. Trial of short term prednisone

D. Oral Macrolide

COPD Treatment (old)

- Stop smoking
- Not much else

COPD Management

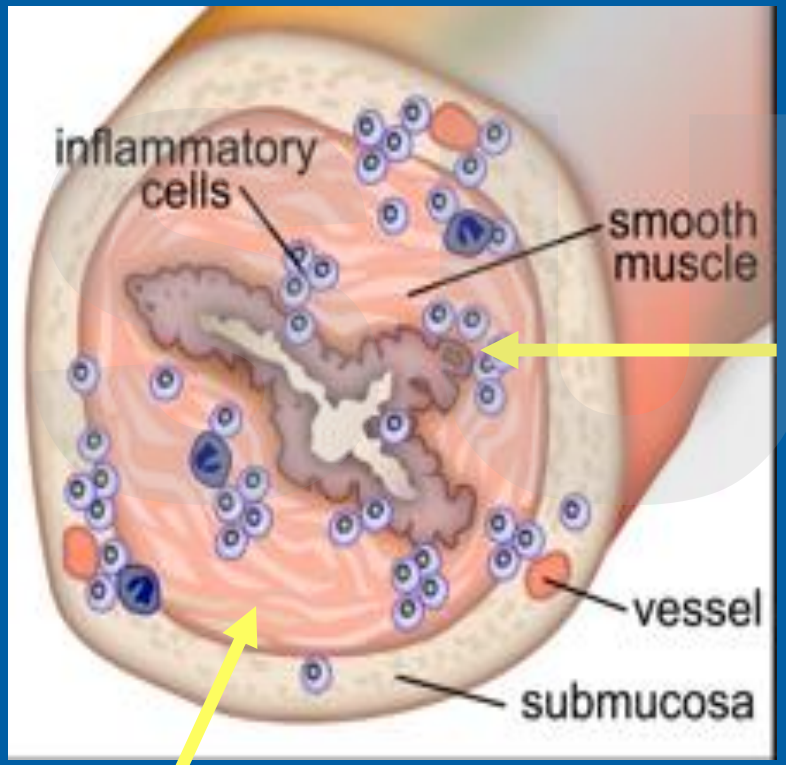
- Reduce smoking exposure: A*
- Medication: BD's, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Reduce exacerbations: A
- Health Care Directive
- Immunizations: Flu shot, Pneumococcal: A
- Low dose CT scan: A

*Level of evidence

Inhaler Actions

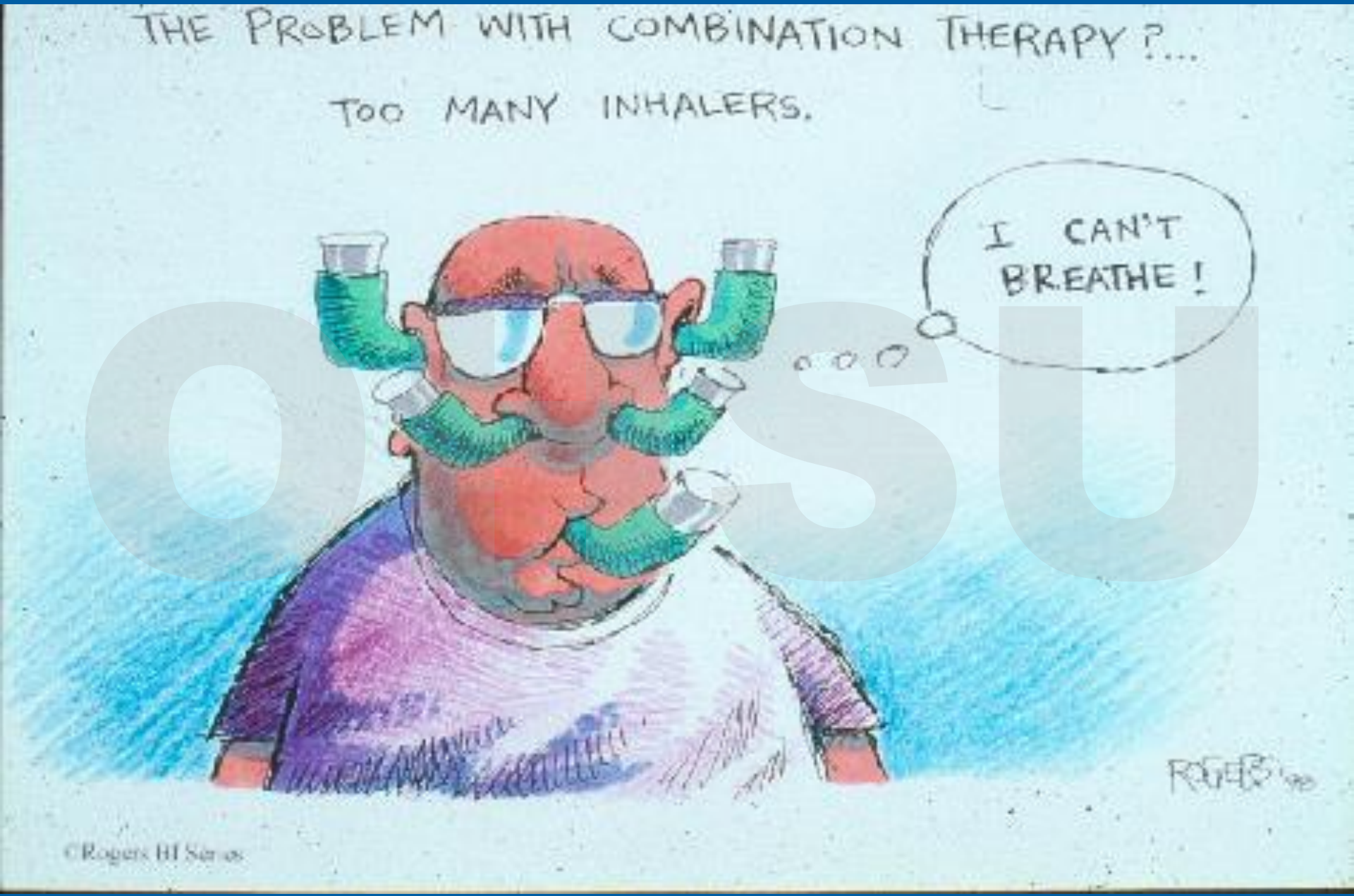
Normal Airway

COPD/Chronic bronchitis

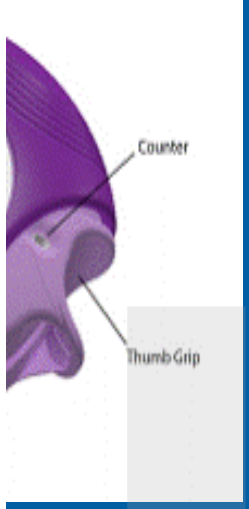


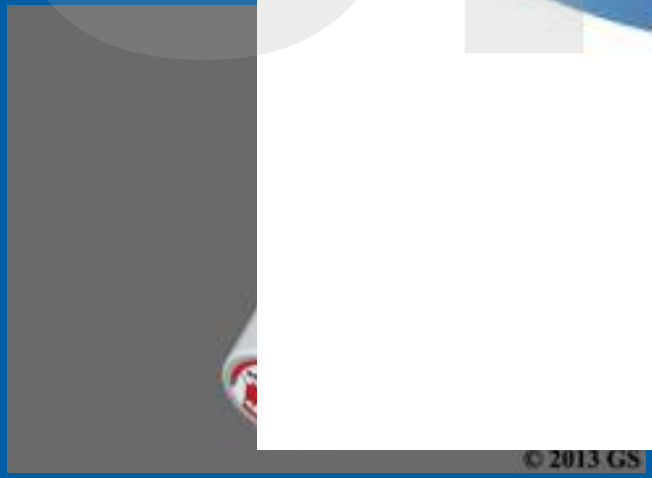
ICS

Long-Acting Muscarinic Agent
or
Long Acting Bronchodilator Agent


THE PROBLEM WITH COMBINATION THERAPY?...
TOO MANY INHALERS.
I CAN'T BREATHE!
ROGERS '98
© Rogers H Series

Inhaler devices





First Line Therapy

LAMA

or

LAMA plus LABA

If eos: ICS

or

ICS plus LABA

Or

ICS plus LABA plus LAMA

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD IMPACT

- R,DB, 1 year
- LABA+LAMA, ICS+LABA, ICS+LAMA+LABA
- 10, 355 subjects
- Primary endpoint: Rate moderate/severe exacerbations
- Adverse events: Pneumonia

DA Lipson: N Engl J Med 2018;378:1671

IMPACT Primary Results
Annual Rate of exacerbations

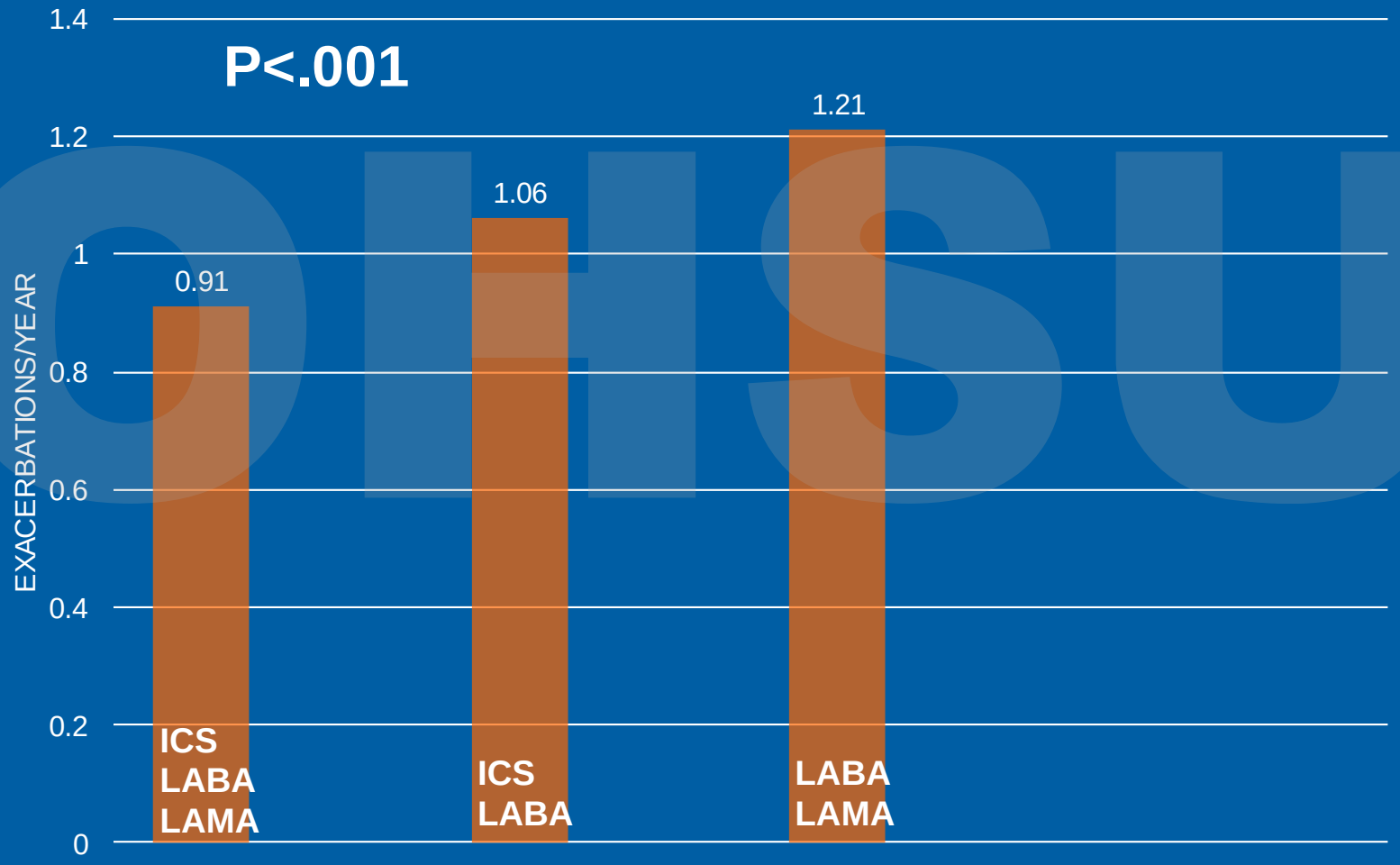
ICS+LABA+LAMA: 0.91/year

ICS+LABA: 1.06*

LABA+LAMA: 1.21*

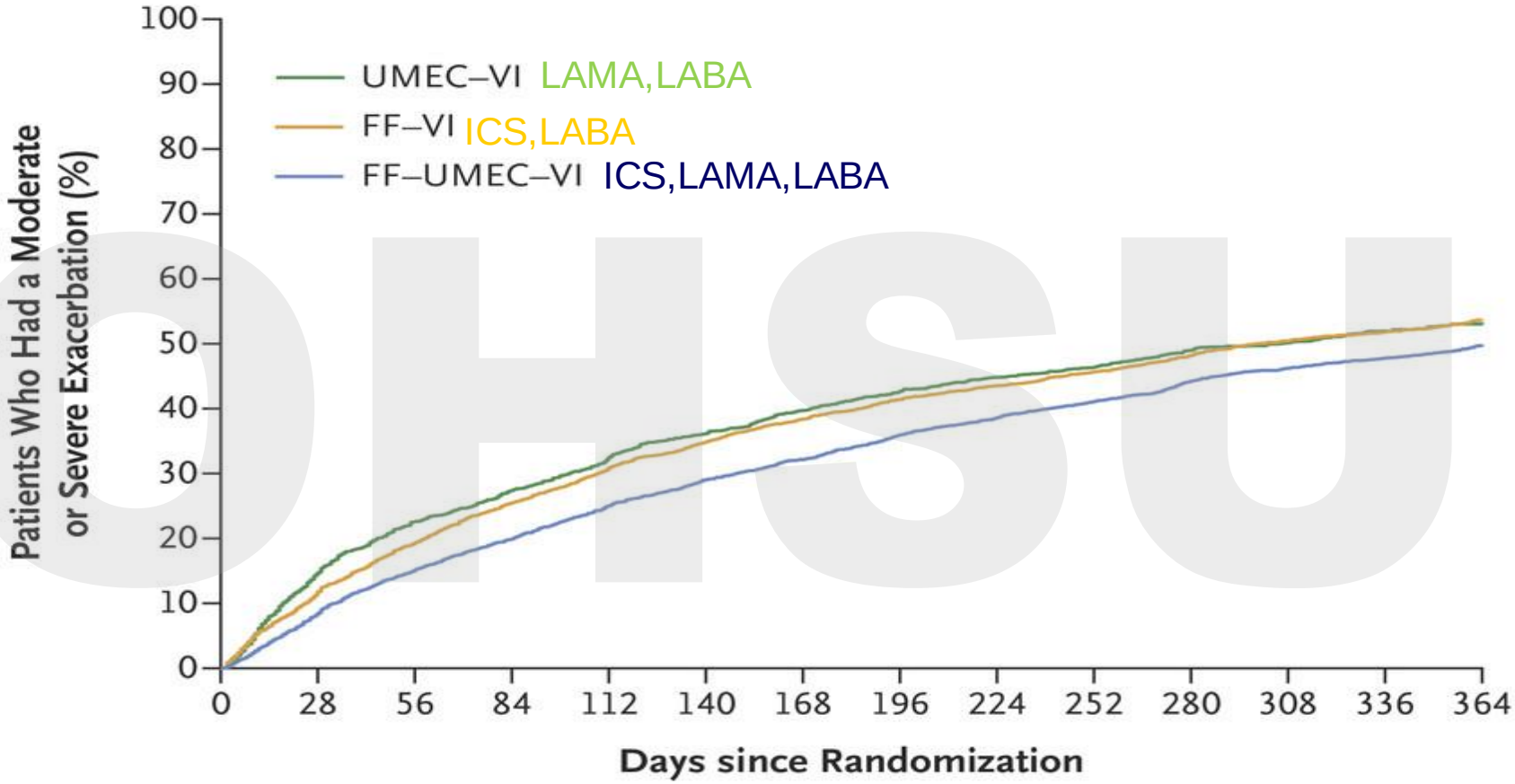
*P<.001

IMPACT Primary Results
Annual Rate of exacerbations



Patients(%) with moderate/severe exacerbations

B Time-to-First-Event Analysis

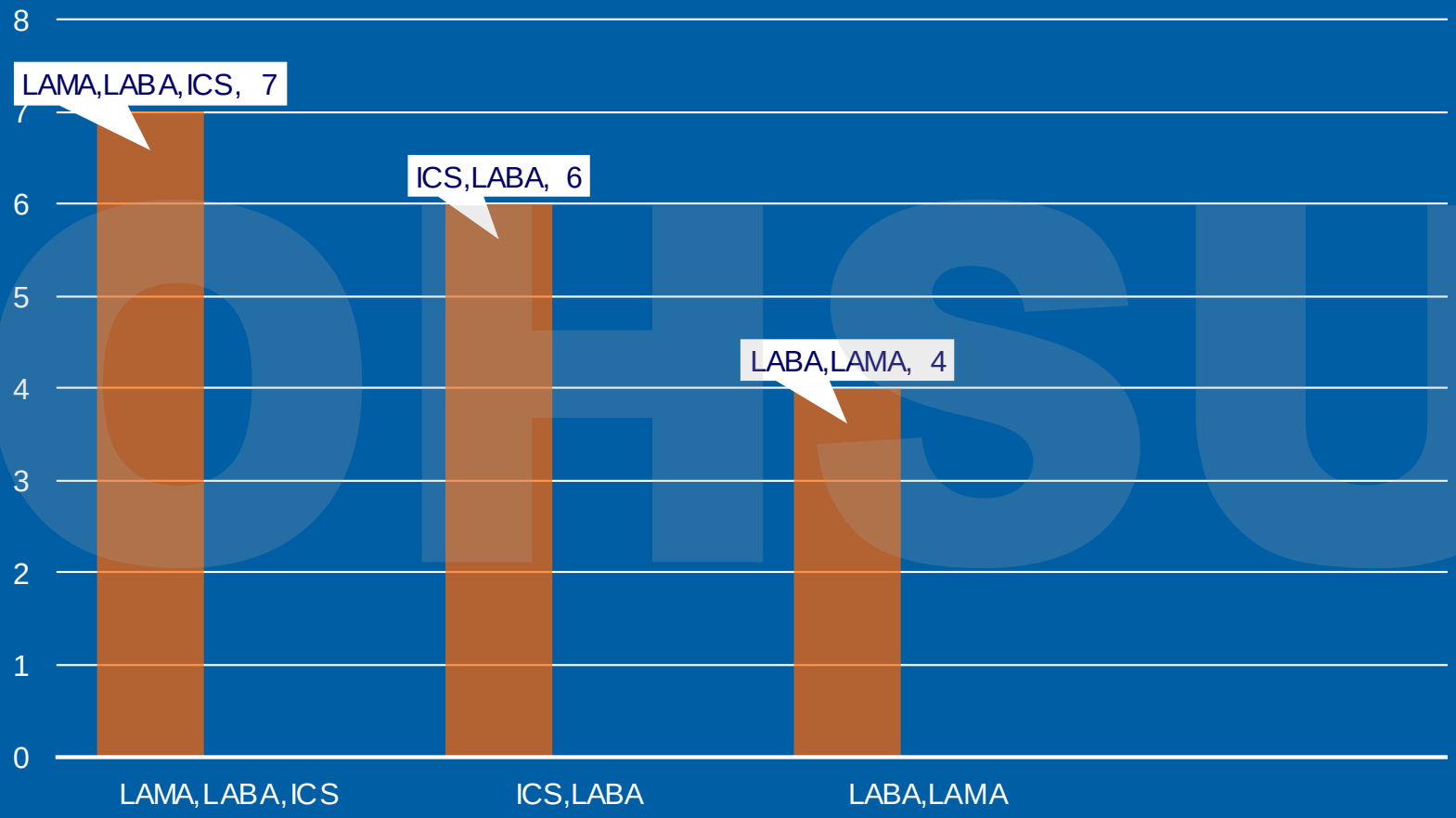


No. at Risk

UMEC–VI	2070	1721	1516	1406	1301	1201	1123	1059	1001	971	917	884	851	642
FF–VI	4134	3554	3133	2838	2620	2410	2250	2120	2004	1823	1823	1729	1671	1228
FF–UMEC–VI	4151	3758	3408	3186	2954	2752	2614	2457	2324	2216	2085	1988	1919	1419

DA Lipson: N Engl J Med 2018;378:1671

Pneumonia, %Subjects



Case #2 Related Question

You confirm the diagnosis of COPD. What medication would be appropriate initial therapy?

A. **Inhaled long-acting anti-muscarinic agent alone**

B. **Inhaled corticosteroid alone**

C. **Trial of short term prednisone**

D. **Oral Macrolide**

Helpful aids

- COPD Assessment Tool*
- BODE-prognosis; 4 years*
- GOLD Guidelines*

*Google

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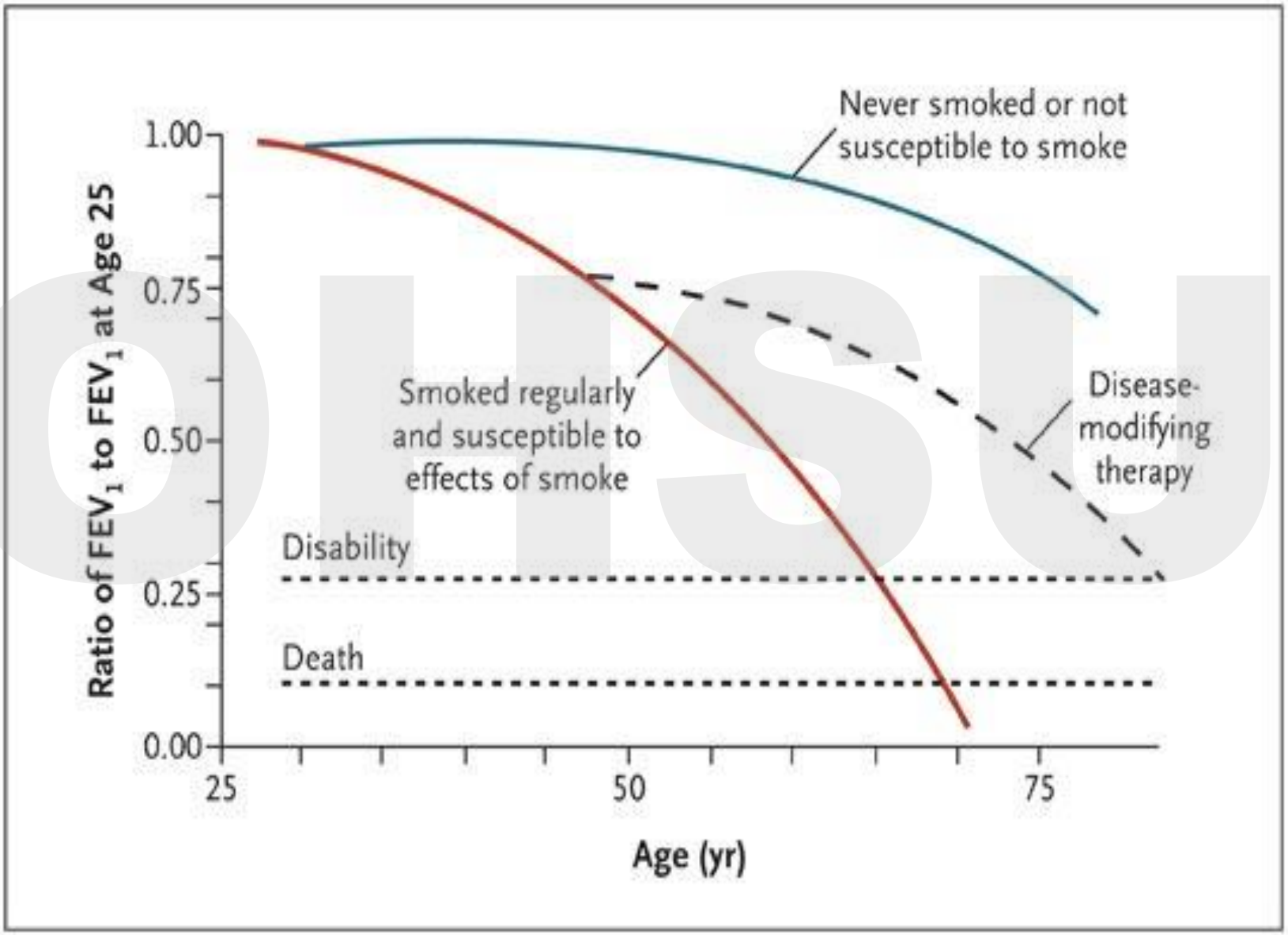
Association between the Ratio of FEV1 to FEV1 at the Age of 25 Years and Disability or Death



COPD Management

- General
- Medications
- ACOS
- Exacerbations

COPD Management

Alan F. Barker, MD

Pulmonary and Critical Care

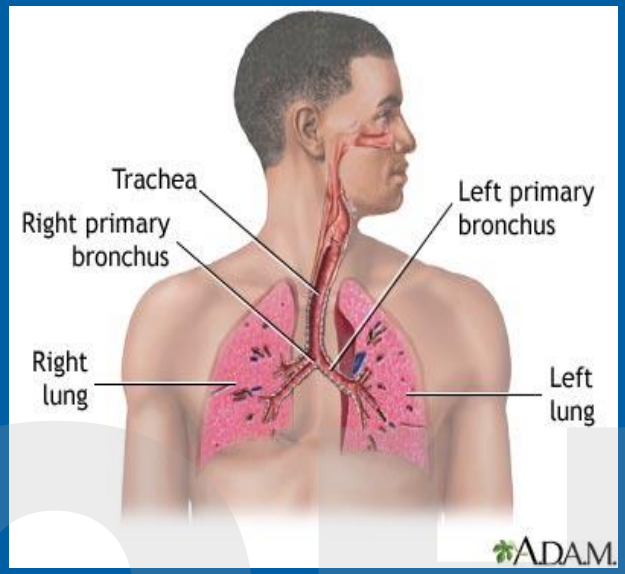
OHSU

IMPACT
% subjects with pneumonia

ICS+LABA+LAMA: 7%

ICS+LABA: 6%

LABA+LAMA: 4%



Aeroallergen

Normal bronchi

Who authored the following quote: "Ninety percent of the game is half mental.":

1. Winston Churchill
2. Pope Francis
3. Babe Ruth
4. **Yogi Berra**
5. Franklin Roosevelt

The leading cause of death in the US is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents

Who authored the following quote: "Ninety percent of the game is half mental.":

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Among leading causes of death in US, the one with a rising death rate is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents

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Quality Measure
COPD
Hospitals 2014

Number of hospital readmissions within 30 days to any hospital*

* Readmissions reduction project/CMS

Holy Grail
COPD Pharmacotherapy

- Mortality benefit

- Reduced decline in FEV1

Holy Grail
Cigarette smoking cessation

- Mortality benefit *
- Reduced decline in FEV1 #

* Anthonisen: Annals Int Med 142:233, 2005

Anthonisen: JAMA 272: 1497, 1994

Combination LA Beta agonist and aerosol steroids

- Do they prolong life?

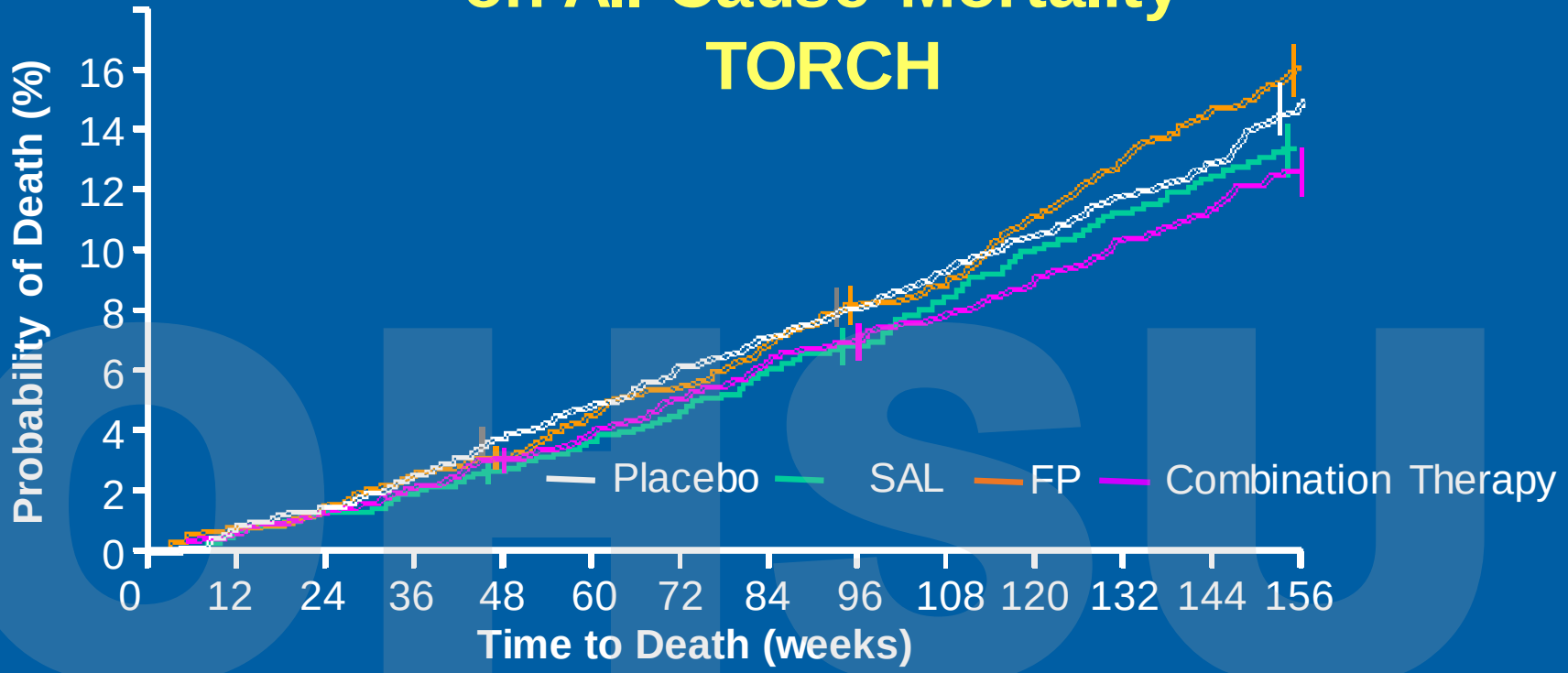
COPD

- Are they safe?

Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007

- R, DB, placebo, 3 year trial
- Objective: Effect on survival
- Salmeterol 50ug/Fluticasone 500ug, Salmeterol , Fluticasone, placebo; all BID
- 6112 patients, 40 % dropout rate

Effect of Combination Therapy on All-Cause Mortality TORCH



	Hazard Ratio	*P*-value
Combination Therapy vs Pbo (adjusted)	0.825	**0.052**
Combination Therapy vs SAL	0.932	0.48
Combination Therapy vs FP	0.774	0.007
SAL vs Pbo	0.879	0.18
FP vs Pbo	1.060	0.53

Primary End Point

Calverley PM. *N Engl J Med.* 2007;356:775

TORCH
Pneumonia

- Fluticasone/salmeterol: 19.6%*
- Fluticasone: 18.3 %*
- Salmeterol: 13.3%
- Placebo: 12.3 %

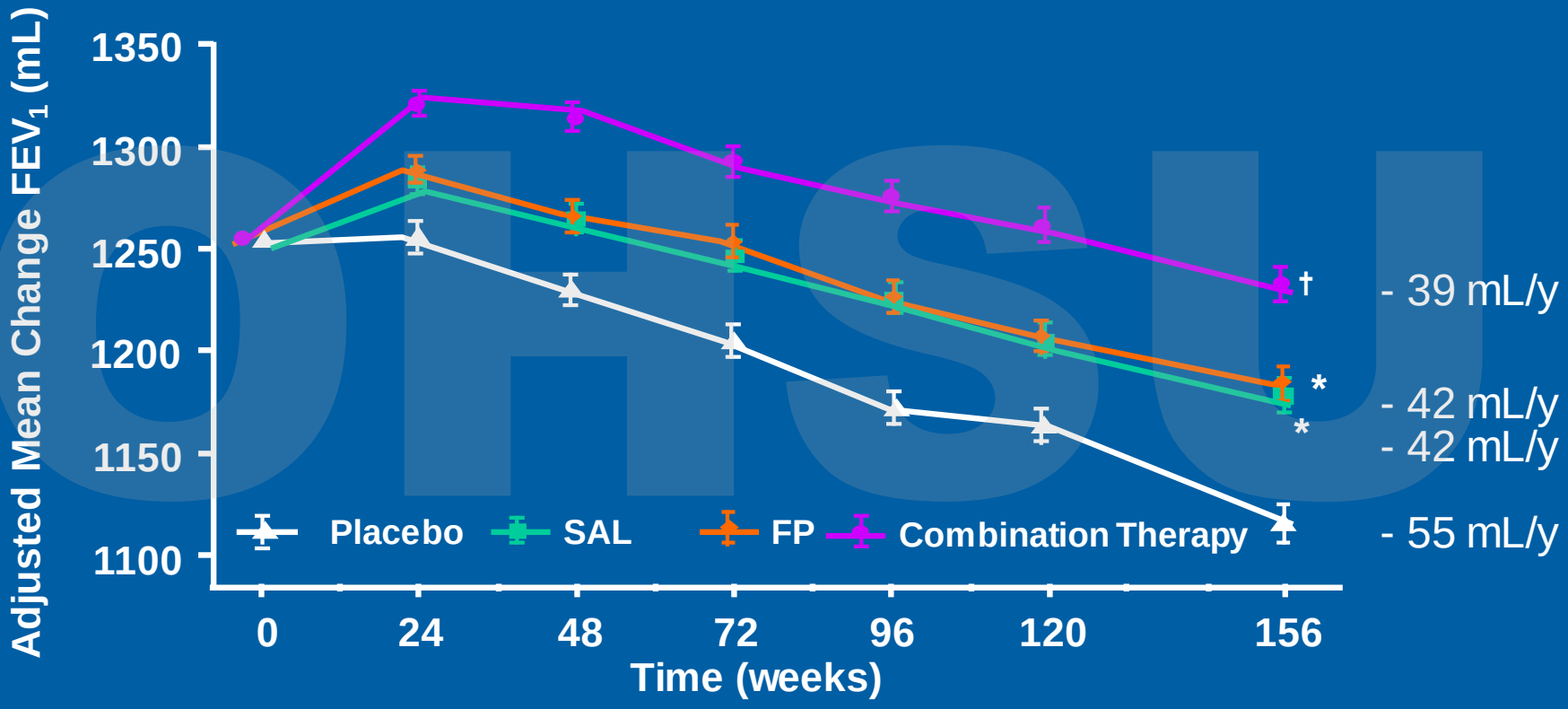
*P< 0.001

Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)

- Post-hoc analysis TORCH

- Examine rate decline FEV1 (Prognosis)

Therapy Reduces the Rate of Decline of Post-bronchodilator FEV_1 (TORCH)



*P = 0.003 vs placebo

† P < 0.001 vs placebo

Celli BR, et al. *Am J Respir Crit Care Med*. 2008;178:332-338.

Summary
LA BA/ICS

- Do not prolong survival… by .002
- May retard decline in pulmonary function
- ICS probably contribute to pneumonia

Anticholinergic aerosols

COPD

Are they effective?

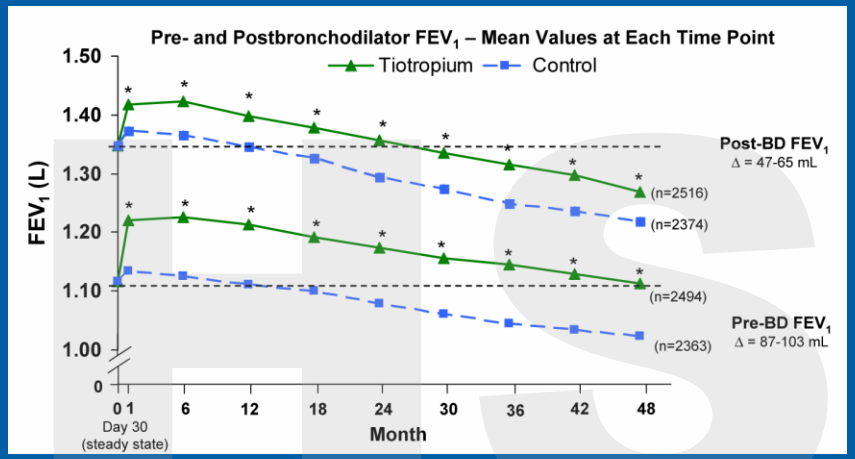
Tiotropium

- M1 and M3 selective LA muscarinic antagonist
- Most widely prescribed agent in COPD
- Side effects: dry mouth, urinary retention

Tashkin: A 4-year trial of tiotropium in chronic obstructive pulmonary disease. NEJM 359:1543, 2008

- R, DB, 4 years
- Tiotropium vs placebo
- Endpoints: 1-Rate decline FEV1; 2-SGRQ, exacerbations/COPD, mortality
- 5993 COPD patients; 40% dropout rate

UPLIFT: Lung Function (FEV_1) Over 4 Years



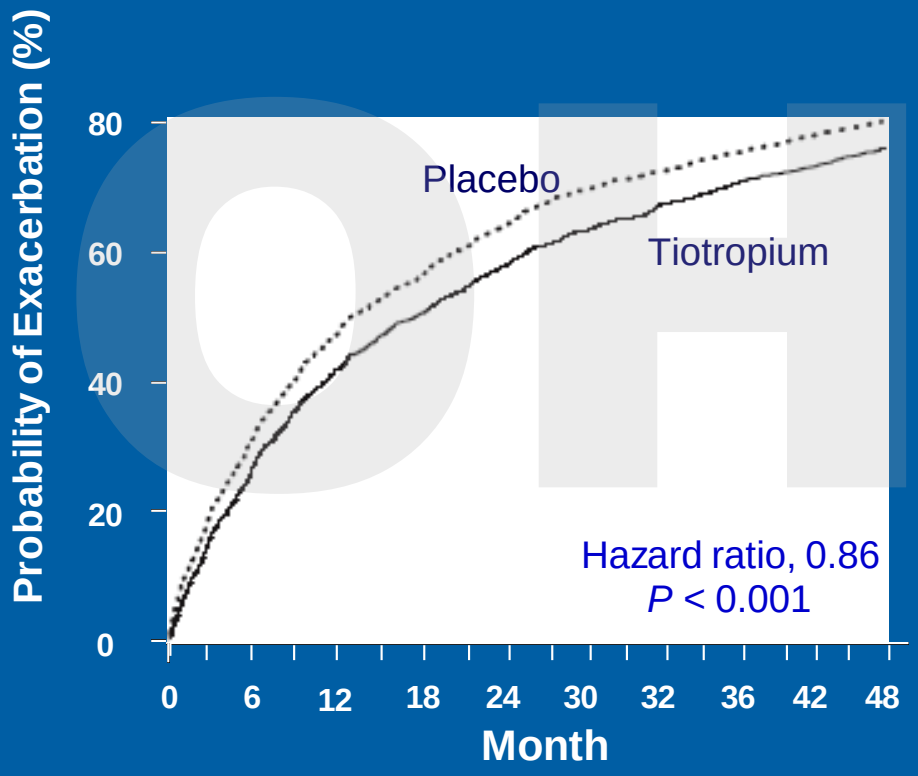
*$P < 0.0001$ vs. control

Rates of decline of FEV_1 after day 30 (Primary EP) were not significantly reduced by tiotropium

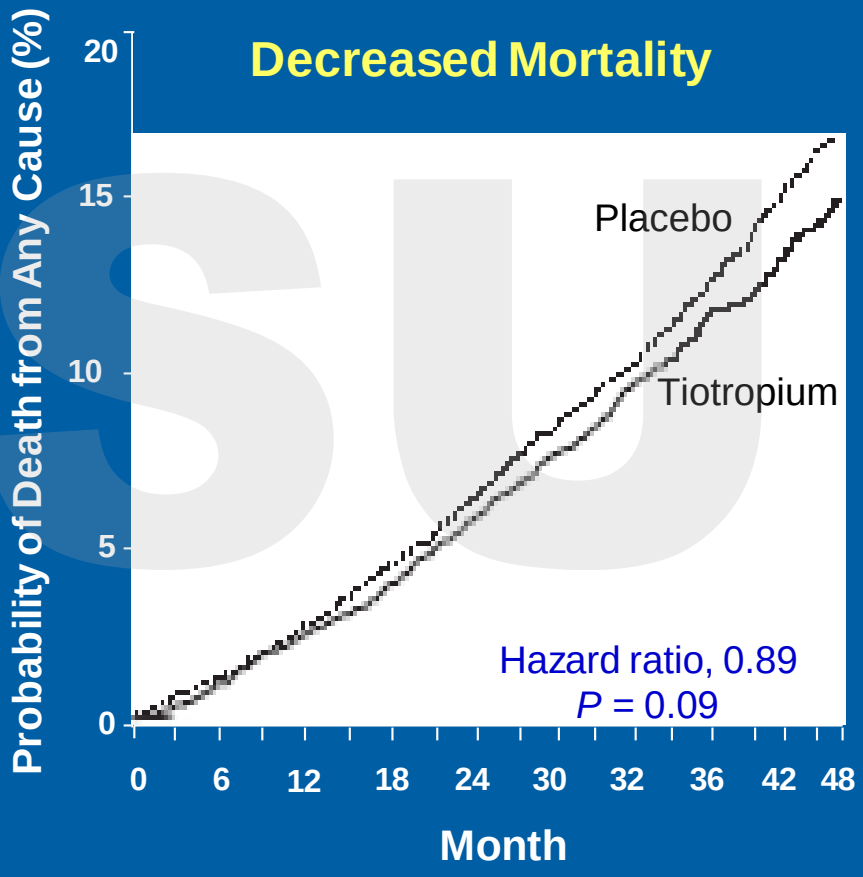
Tashkin DP, et al. *N Engl J Med*. 2008;359:1543-1554.

UPLIFT: Tiotropium Effects

Decreased COPD Exacerbations



Decreased Mortality



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

Summary
LA AC

- Improve symptoms, improve QOL, reduce hospitalizations
- Do not retard decline in pulmonary function

Asthma-COPD Overlap Syndrome

- Persistent airflow limitation
- Features shared by both asthma-COPD

Symptoms-Dyspnea, wheeze
Exacerbations
FEV1/FVC<70%
Prior inhaled meds

Why ACOS?

- Prognosis worse than either
- May require specialty consult
- Asthma- Controller meds needed; not LABA alone
- COPD-Controller meds best; not LACS alone

Factors Associated with Increased Exacerbation Frequency (ECLIPSE)

Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.*

Factor	Number of Exacerbations						P Value for Overall Model
	≥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*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007

* FEV_1 denotes forced expiratory volume in 1 second, and SGRQ St. George's Respiratory Questionnaire.

Hurst JR et al. N Engl J Med 2010;363:1128

The following is not effective in reducing exacerbations in COPD:

1. Macrolides
2. Acetyl cysteine
3. LABA/LACS combinations
4. LAMA
5. Statins

The following is not effective in reducing exacerbations in COPD:

1. Macrolides
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Criner: Simvastatin for prevention exacerbations in COPD. NEJM: 370:2201, 20

Exacerbation Prevention
Medications

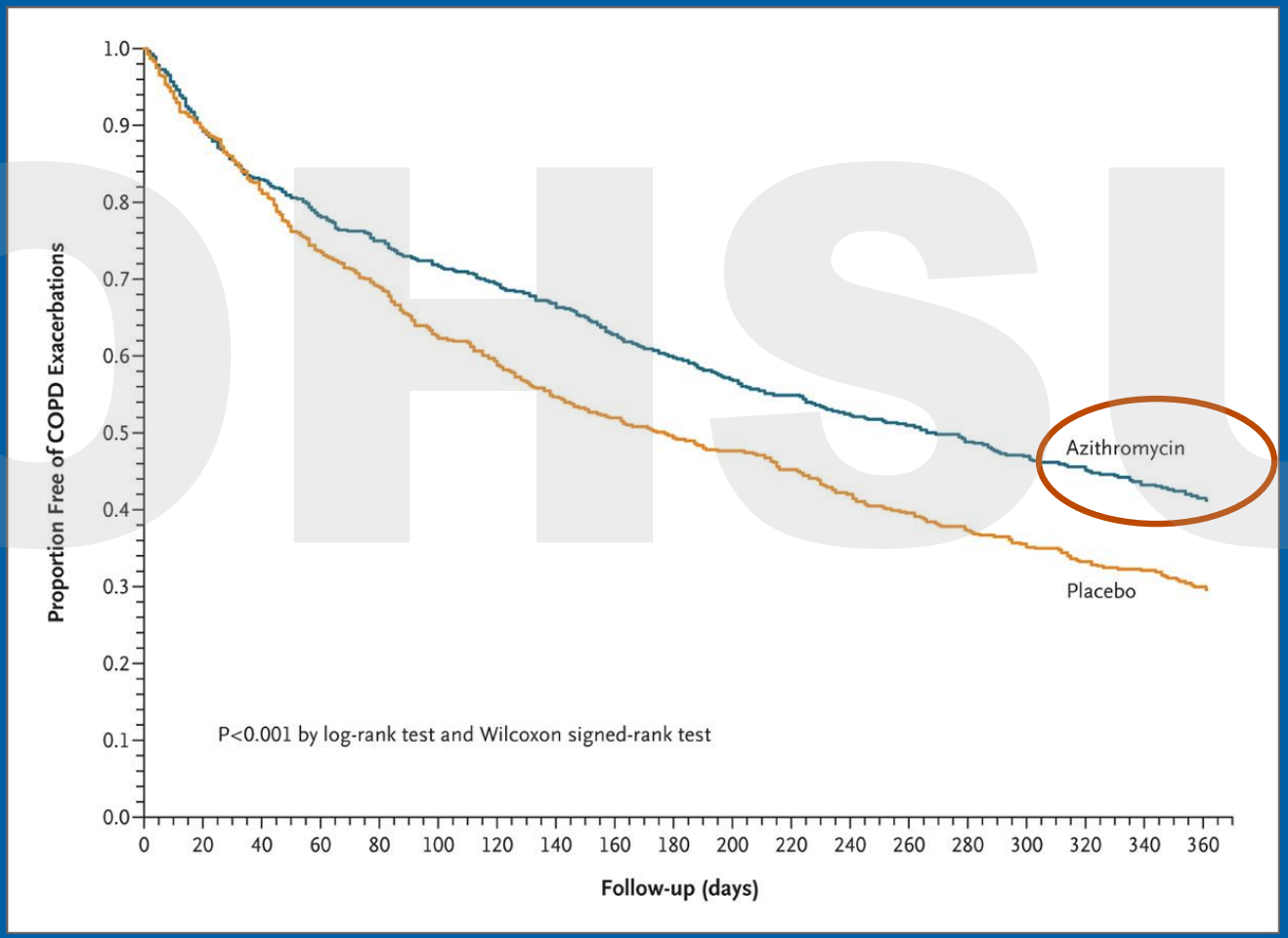
- LAMA, LACS/LABA
- Macrolides
- Phosphodiesterase inhibitors-roflumilast
- Acetyl cysteine (oral)
- Statins- NO!

Criner, Chest (ACCP, CTS) 14:883, 894, 2015

Albert: Azithromycin for prevention of exacerbations of COPD; NEJM 365:689, 2011

- RB, DB, 1 year
- Objective: Reduce exacerbation frequency
- Azithromycin 250 mg daily vs placebo
- 1142 subjects; 90% F/U

Proportion of Participants Free from Acute Exacerbations of COPD



Albert RK . N Engl J Med 2011;365:689

Downside(s) Azithromycin

- Arrhythmias (heart disease)

- Resistance to macrolides:

  Azithro: 81%

  Placebo: 41%

EKG for QT interval

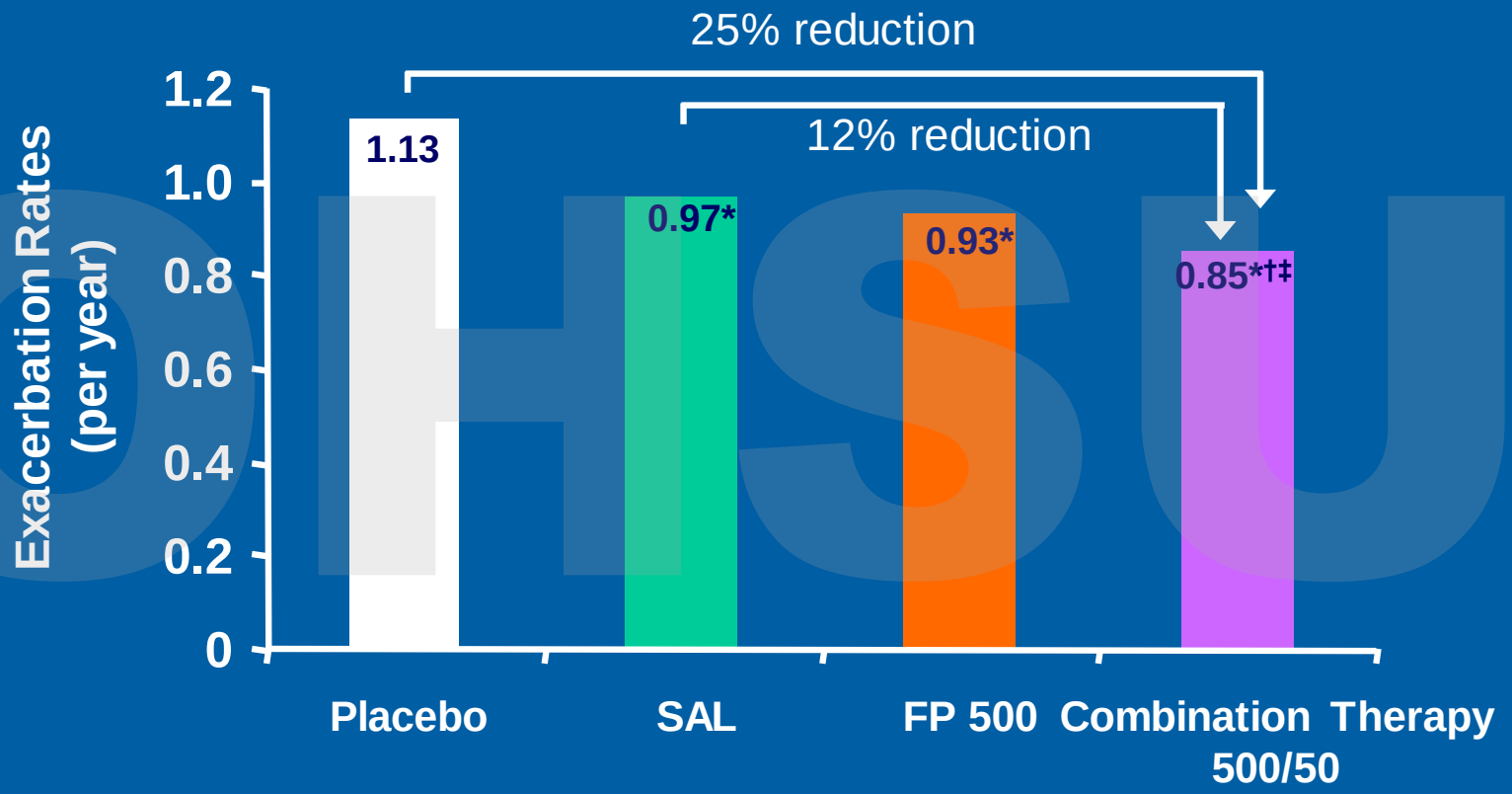
Conclusions

- Holy Grail has not been achieved
- LA BA/ICS are effective
- FDA, All LA BA have black box warning
- LA AC are effective
- ACOS-stay tuned
- Pay attention to exacerbations

Conclusions

- Holy Grail has not been achieved
- LA BA/ICS are effective
- FDA, All LA BA have black box warning
- LA AC are effective
- Concerns raised: Pneumonia

Combination Therapy 500/50 and Moderate-to-Severe COPD Exacerbations (Three-Year Data)

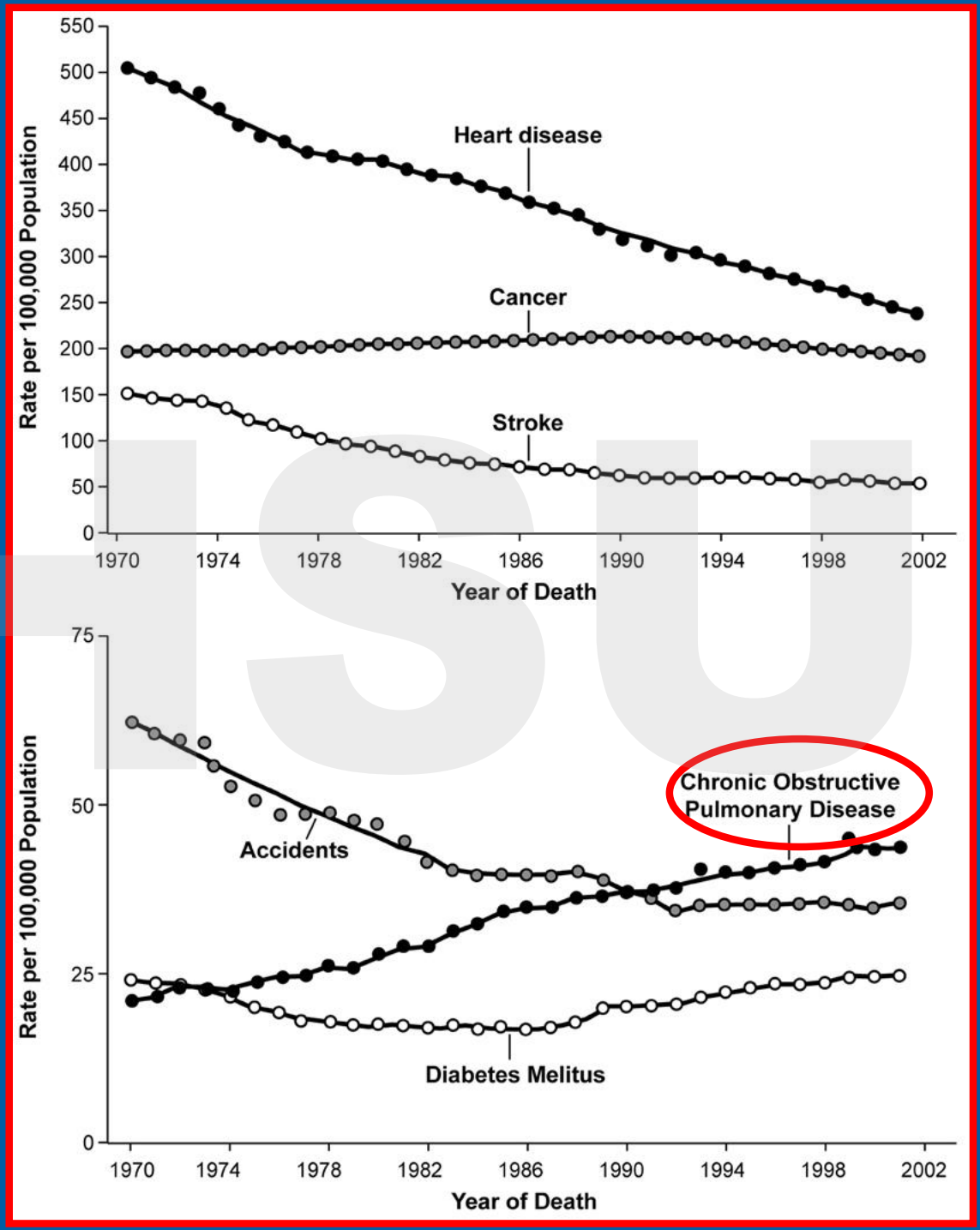


Exacerbations were defined as symptomatic deterioration requiring treatment with antibiotics or systemic corticosteroids (moderate), or hospitalization (severe)

* $P < 0.001$ vs placebo; † $P = 0.002$ vs SAL; ‡ $P = 0.024$ vs FP

Calverley PMA, et al. *N Engl J Med*. 2007;356:775-789.

Of the six leading causes of death in the United States, only COPD has been increasing steadily since 1970



Source: Jemal A. et al. *JAMA* 2005

Medications to reduce exacerbations

- Azithromycin
- Tiotropium
- Aerosol steroids
- Roflumilast
- Acetyl cysteine

Incidence Rate of Serious Adverse Events per 100 Patient-Years

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† P<0.05.

GOLD

Pharmacotherapy: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A).
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).

Management of Stable COPD

GOLD

Pharmacotherapy: Glucocorticosteroid

- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted (*Stage III: Severe COPD and Stage IV: Very Severe COPD*) and repeated exacerbations (Evidence A).

- An inhaled glucocorticosteroid combined with a long-acting $ß_2$-agonist is more effective than the individual components (Evidence A).

Exacerbations With Triple Combination Therapy

	Tiotropium (n = 156)	Tiotropium + Salmeterol (n = 148)	Tiotropium + Salmeterol + Fluticasone (n = 145)
% Pts with ≥ 1 exacerbations	62.8 %	64.8%	60.0%
Total Exacerbations	222	226	188
Exacerbations with Hospitalization	49	38	26
Incidence rate ratio compared with tiotropium + placebo (95% CI)		0.83 (0.54 to 1.27)	0.53 (0.33 to 0.86)

Aaron SD, et al. *Ann Int Med*. 2007;146(8):545-555.

Differential Diagnosis: COPD and Asthma

COPD

- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
- Largely irreversible airflow limitation

ASTHMA

- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

Proportion of Participants Free from Acute Exacerbations of COPD for 1 Year

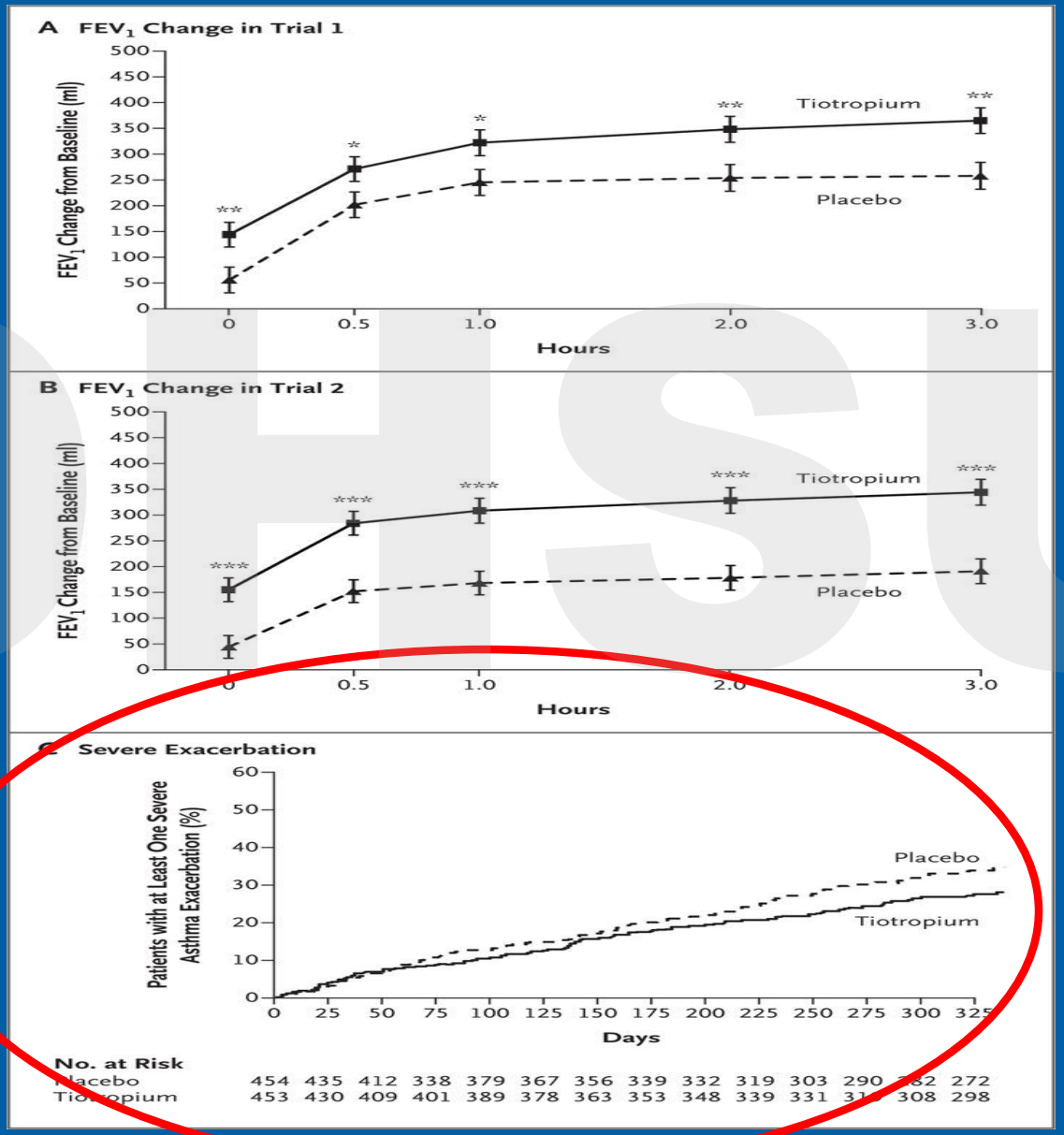
Table 2. Effect of Treatment for Chronic Obstructive Pulmonary Disease (COPD) on Hospitalization Rates, Emergency Department or Urgent Care Visits, and Unscheduled Office Visits.

Event	Azithromycin		Placebo		P Value*	Hazard Ratio (95% CI)†	P Value†
	no. of events	*mean events/ patient-yr (95% CI)*	*no. of events*	*mean events/ patient-yr (95% CI)*			
Hospitalization for any cause	323	0.74 (0.60–0.89)	329	0.95 (0.76–1.18)	0.13	0.94 (0.76–1.15)	0.52
Hospitalization related to COPD	156	0.34 (0.26–0.43)	200	0.49 (0.31–0.67)	0.14	0.82 (0.64–1.07)	0.15
Emergency department or urgent care visit	199	0.43 (0.34–0.53)	257	0.48 (0.39–0.57)	0.47	0.81 (0.63–1.04)	0.09
Unscheduled office visit	1202	2.46 (2.08–2.48)	1345	2.57 (2.21–2.60)	0.048	0.85 (0.74–0.98)	0.02
Intubations	11	0.02 (0.01–0.04)	16	0.04 (0.01–0.06)	0.23	0.79 (0.04–1.75)	0.56

* The P value is for the rate of events per patient-year.
† The hazard ratio and P value are for the time to the first event in the azithromycin group as compared with the placebo group.

Albert RK . N Engl J Med 2011;365:689

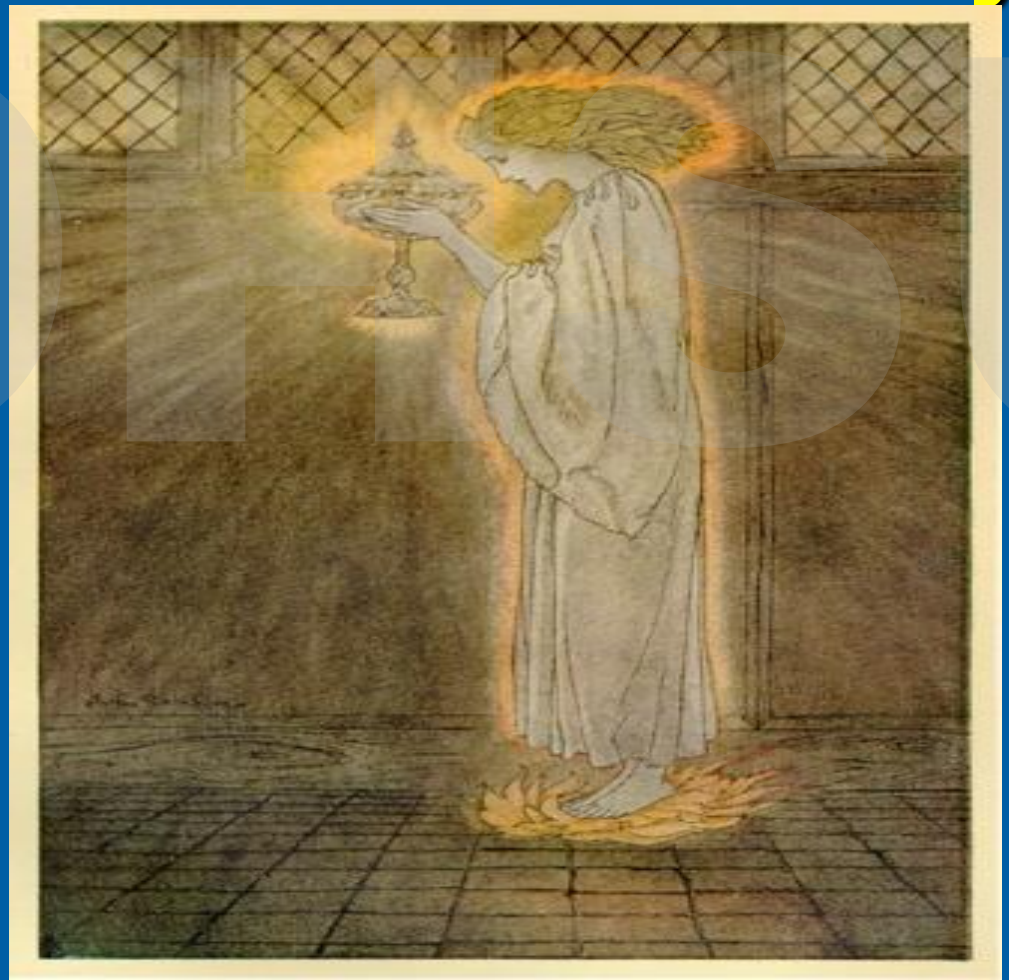
Lung Function and exacerbations



Kerstjens.NEJM; 2012;367:1198

with bronchoactive medications:

In search of the Holy



LA beta agonists and aerosol steroids in COPD

- Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007 (TORCH)

- Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)

Conclusion

- Holy Grail has not been achieved
- LA BA/ICS are effective
- LA AC are effective
- Concerns raised: Pneumonia, CV events
- FDA has not acted to remove or change

Ernst: Inhaled corticosteroid use in COPD and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med 176: 162, 2007

- Nested case control study/COPD
- Admin database/pneumonia/hospital
- COPD-176K; Hospital-24K
- Link any ICS

Meta Analysis
Anticholinergics

Outcome	#RCTs	Inhaled AC	Controls	RR	P-value
CV death	12	57/6156	31/6220	1.80	.008
MI	11	68/5430	43/5168	1.53	.03
Stroke	7	25/4548	18/4703	1.46	.20
All-cause Mortality	17	149/7472	115/7311	1.26	.06

COPD Management

- Reduce smoking exposure: A*
- Medication: BD's, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Reduce exacerbations: A
- Health Care Directive
- Immunizations: Flu shot, Pneumovax: A, B

*Level of evidence

Kerstjens:Tiotropium in asthma poorly controlled with standard combination therapy. NEJM, 367: 1198: 2012

- RB, DB, 48 weeks
- Objective: lung function, exacerbations
- Tiotropium vs placebo; all on LABA plus ICS
- 907 patients

GOLD Website Address

http://www.goldcopd.org

Managing exacerbations of COPD and asthma

Alan F. Barker
Pulmonary and Critical Care
Oregon Health and Science University
November 6, 2012

COPD Management

- Reduce smoking exposure: A
- Medication: BD's, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Surgery for emphysema: C
- Health Care Directive
- Immunizations: Flu shot, Pneumovax: A, B

LA beta agonists and aerosol steroids in COPD

- Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007 (TORCH)
- Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)
- Ernst: Inhaled corticosteroid use in COPD and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med 176: 162, 2007 (Admin data base)

COPD Management

- Reduce smoking exposure: A
- Medication: BD's, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Reduce exacerbation frequency: A
- Immunizations: Flu shot, Pneumovax: A, B

Conclusion

- Holy Grail has not been achieved
- LA BA/ICS are effective
- LA AC are effective
- Concerns raised: Pneumonia, CV events
- FDA has not acted to remove or change

Inhaled steroids/COPD Pneumonia

- Adjusted rate ratio/pneumonia/ICS: 1.70 (1.63-1.77)
- ARR/pneumonia/Death/ 30 days: 1.53 (1.30-1.80)
- Death/pneumonia highest for highest dose ICS or fluticasone 1000 ug/day
- No difference whether recent ICS

Cardiovascular Risks Anticholinergics Why?

- Arrhythmias (Lung Health Study, ipratropium)
- Elderly, much CV co morbidity
- COPD a systemic disease

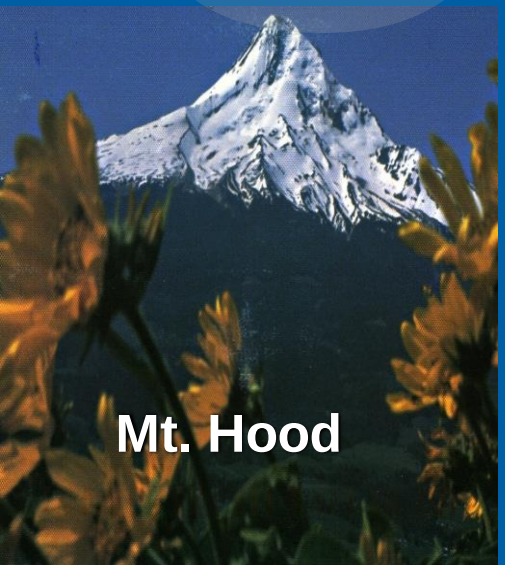
UPLIFT Trial Design

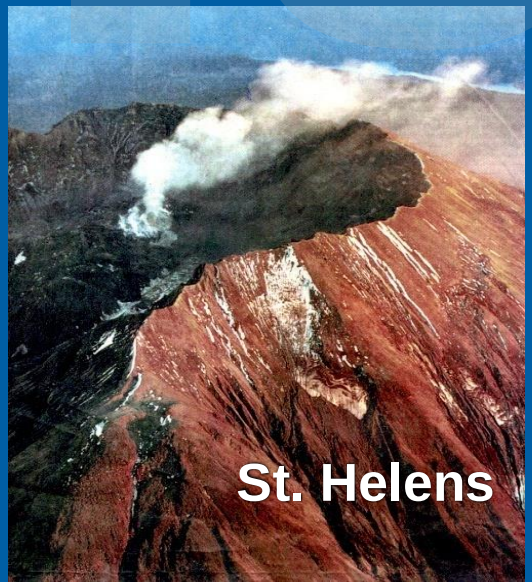
- Double-blind, randomized, placebo-controlled
- Prospective 4-year trial
- Tiotropium (18 mcg) or placebo once daily plus usual care, except for inhaled anticholinergics
- Coprimary endpoints (beginning on day 30)
  - Rate of decline in predose FEV_1
  - Rate of decline in postbronchodilator FEV_1

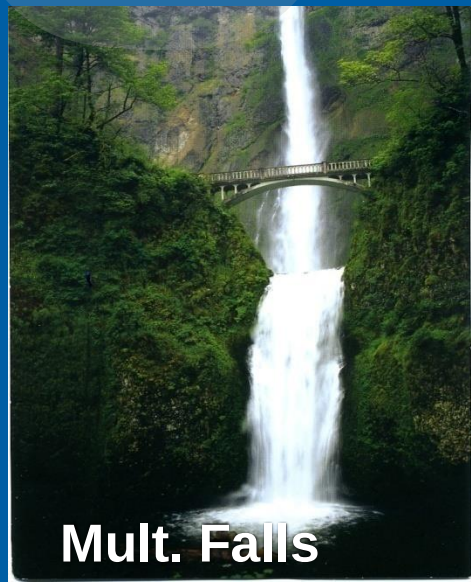
Tashkin DP, et al. *N Engl J Med*. 2008;359:1543-1554.

Managing exacerbations of COPD and asthma

Alan F. Barker
Pulmonary and Critical Care
November 6, 2012

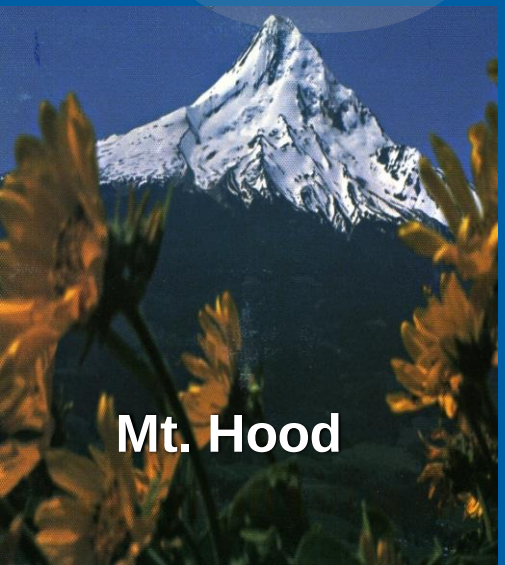


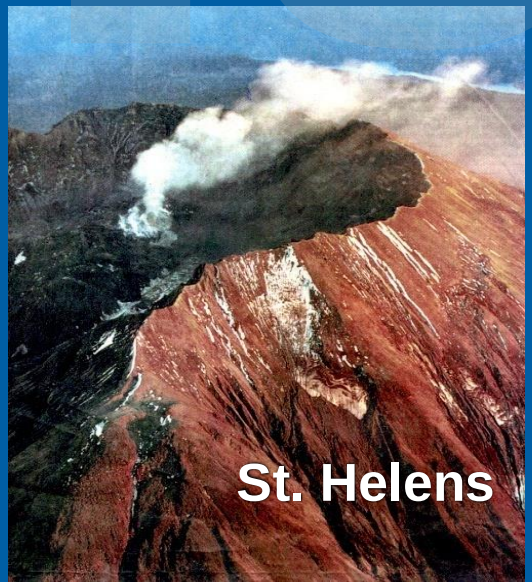


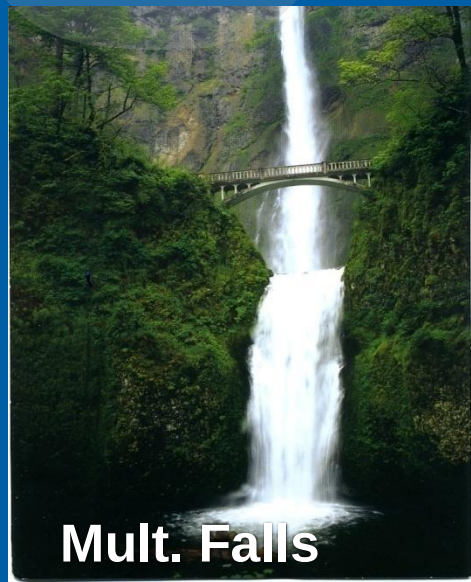


Current evidence for the treatment of chronic obstructive pulmonary disease

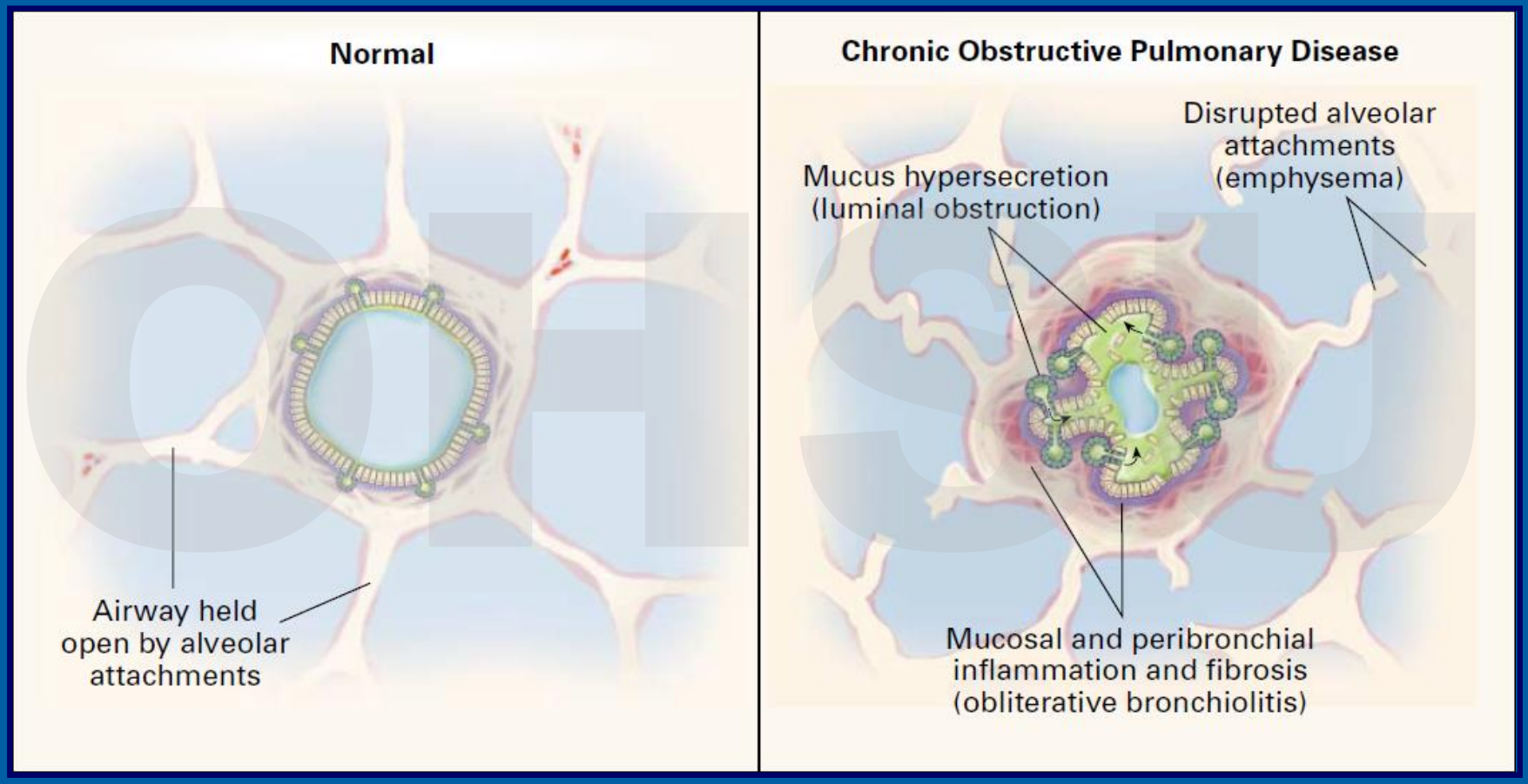
Alan F. Barker
Pulmonary and Critical Care
August 9, 2012


Mt. Hood


St. Helens


Mult. Falls

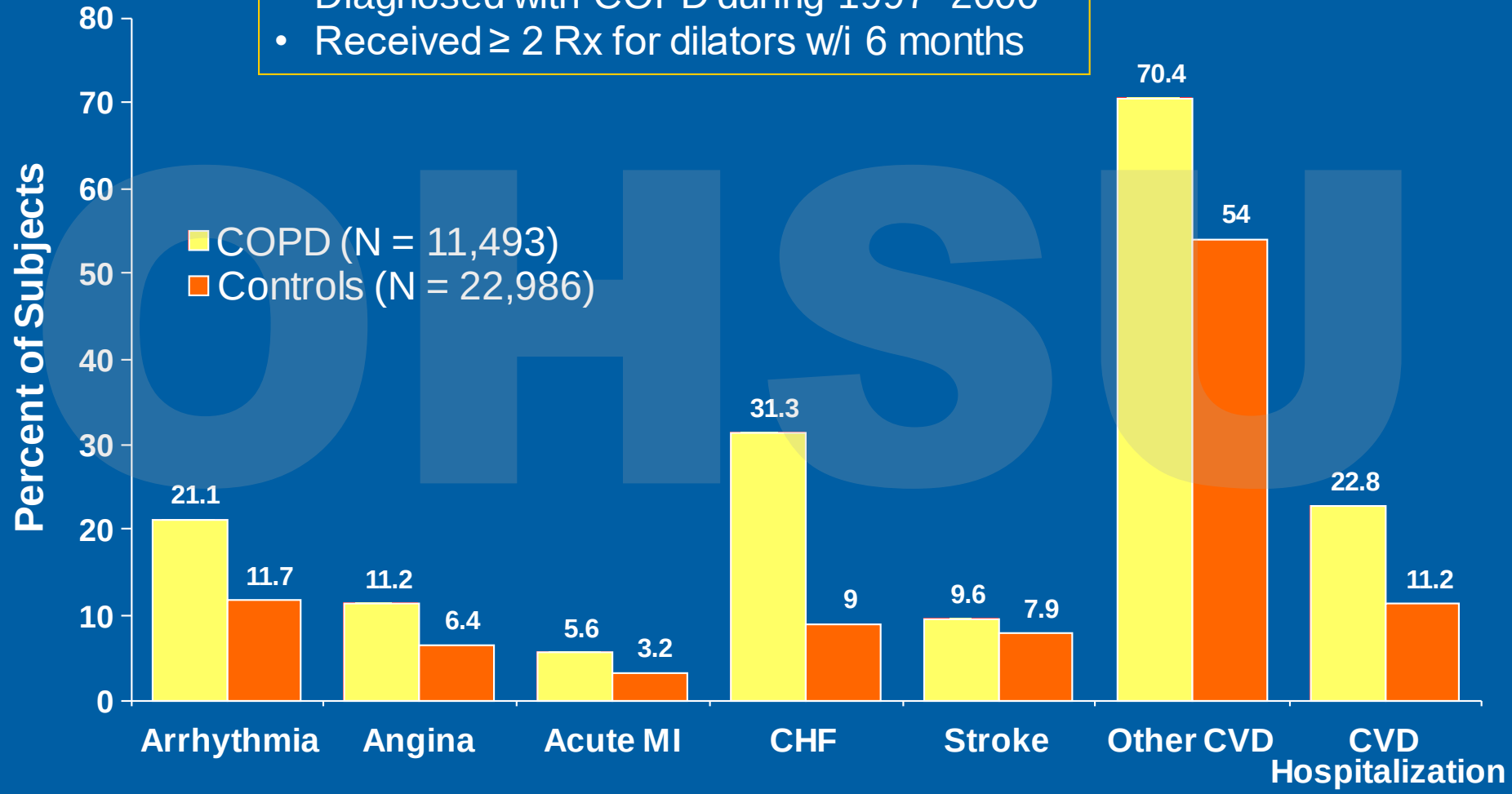
Mechanisms of Airflow Limitation in COPD



Barnes PJ. *N Engl J Med.* 2000;343:269-280.

Increased Risk for Cardiovascular Disease in COPD

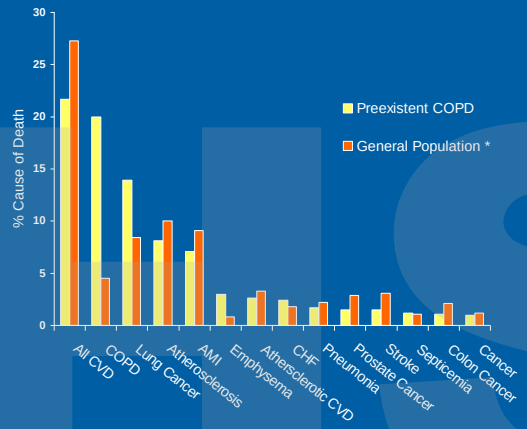
- Retrospective study of Canadian databases
- Subjects age ≥ 40 years
- Diagnosed with COPD during 1997–2000
- Received ≥ 2 Rx for dilators w/i 6 months



MI = myocardial infarction, CHF = congestive heart failure, CVD = cardiovascular disease;
All between-group differences P < 0.05 – adjusted for CV risk

Curkendall SM, et al. *Ann Epidemiol.* 2006;16:63-70.

What Do COPD Patients Die From?

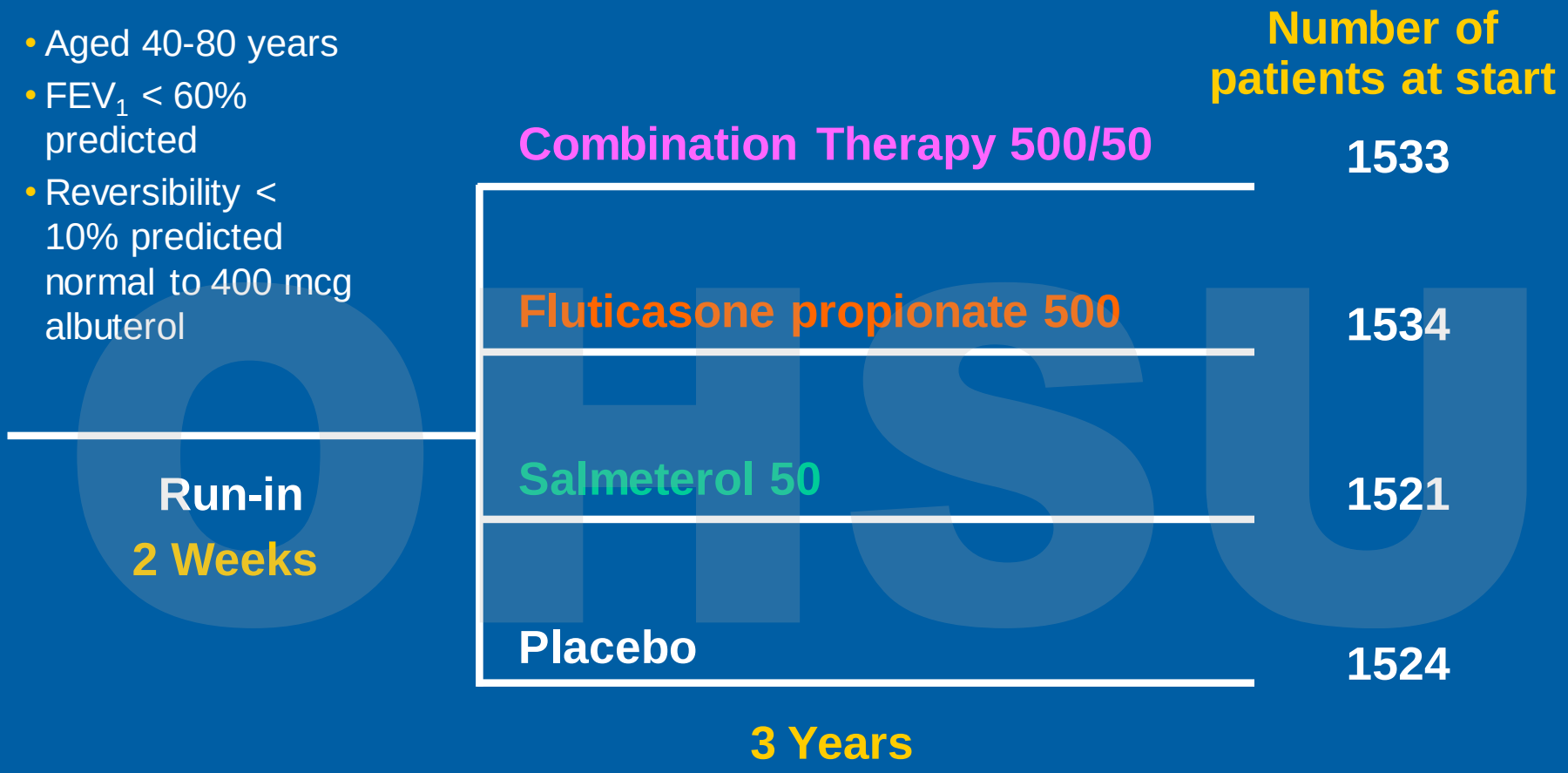


Pickard AS, et al. *COPD.* 2009;6:41-47.

* General Population data from CDC for males ≥ 45y

TORCH: Study Design

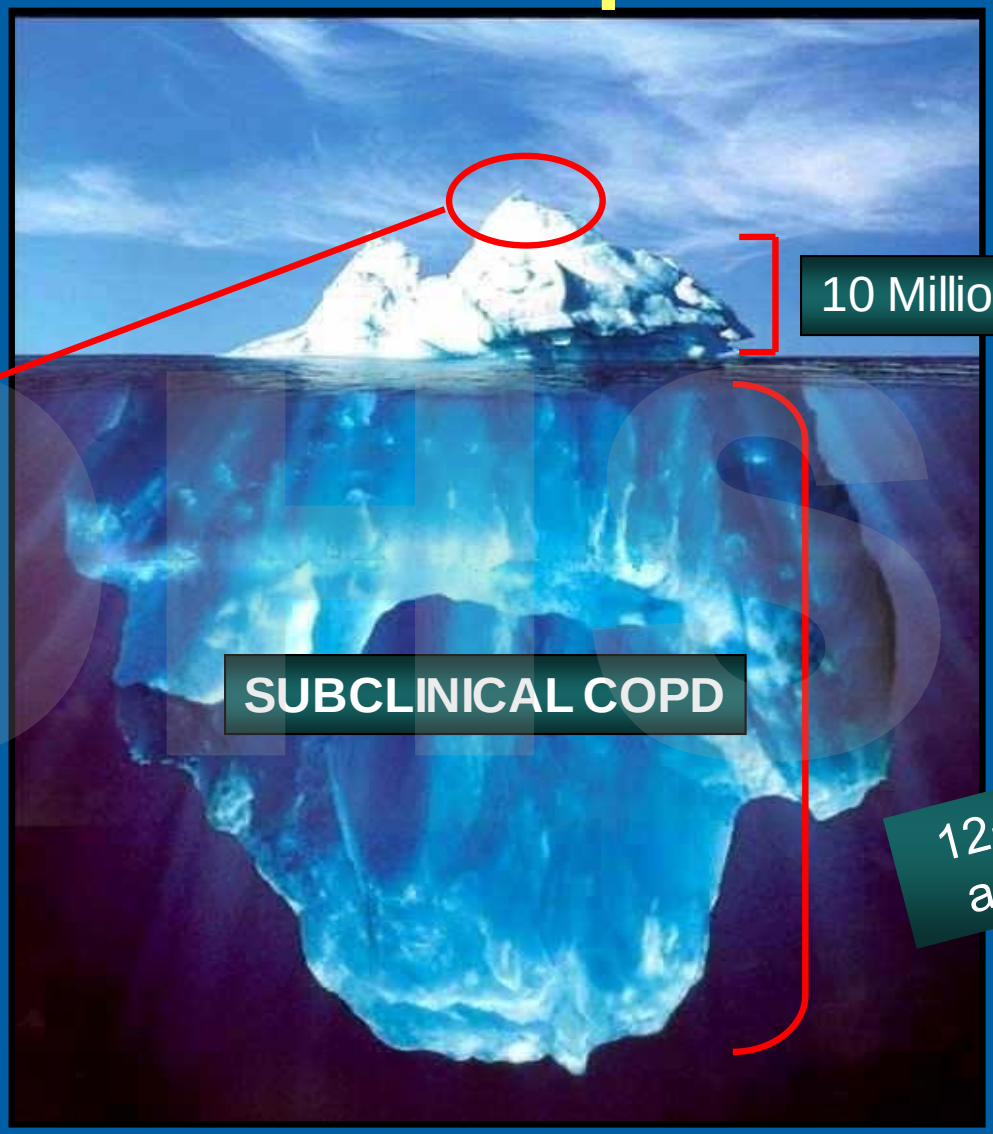
- Aged 40-80 years
- FEV_1 < 60% predicted
- Reversibility < 10% predicted normal to 400 mcg albuterol



TORCH: Towards a Revolution in COPD Health
COMBINATION THERAPY: salmeterol fluticasone combination
FP: fluticasone propionate
SAL: salmeterol

Vestbo J; TORCH Study Group. *Eur Respir J*. 2004;24(2):206-10.

Clinical COPD - Tip of the Iceberg



Adapted from Mannino DM: *MMWR Morb Mortal Wkly Rep*. 2002;51(SS06):1-16.

Therapy for COPD: Overview

Cigarette smoking cessation

GOLD Stage	I Mild	II Moderate	III Severe	IV Very Severe
	Active reduction of risk factors: influenza vaccine ***Add*** short-acting bronchodilators when needed			
		Add regular Rx with ≥1 long-acting bronchodilator when needed. ***Add*** rehabilitation		
			Add inhaled corticosteroids (ICS) if repeated exacerbations	
				Add O_2* ***Consider*** surgery

* If chronic respiratory failure.

GOLD , Updated 2008. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003.

Management of Stable COPD

Pharmacotherapy: Glucocorticosteroids

- The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known.
- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).

GOLD

Anticholinergics
Efficacy vs Risks

Benefits	Risks
Increased exercise capacity	Increased CV events
Decreased exacerbations	Increased MIs
Decreased hospitalizations/exacerbations	
Improvements Dyspnea index	
Improvements QOL	

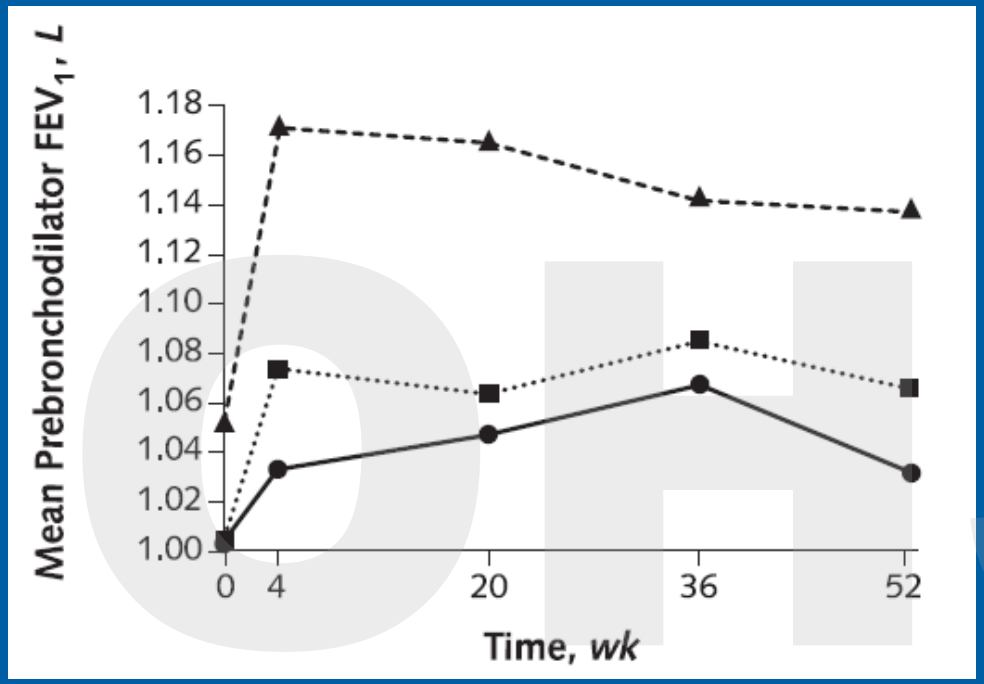
NNT COPD related hospitalizations: 20
NNH for CV events/MI: 40

GOLD Website Address

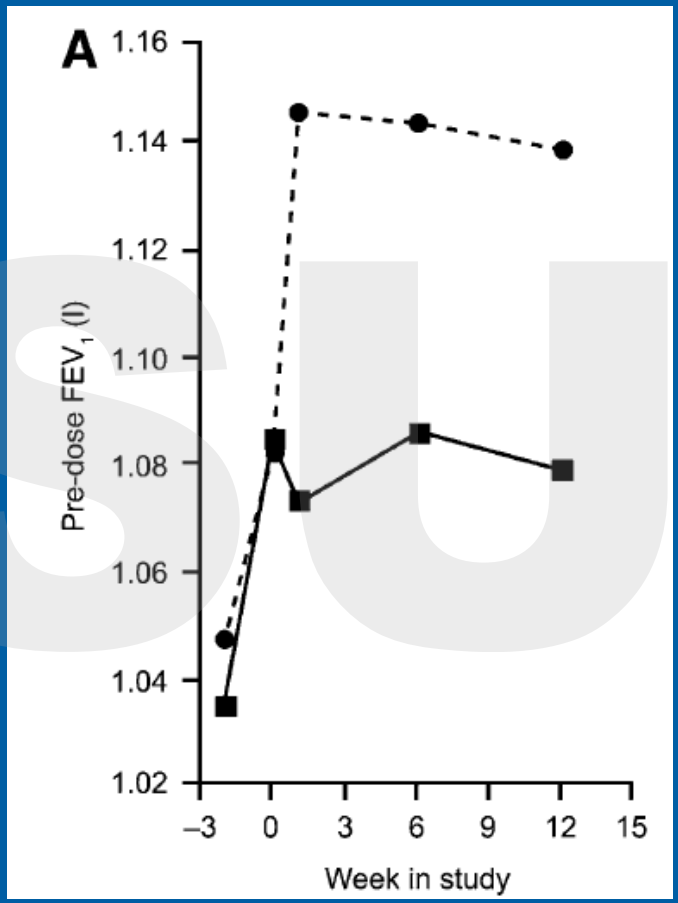
http://www.goldcopd.org

FEV_1 With Triple Combination Therapy

Tio +/- Fluc/Sal[1]



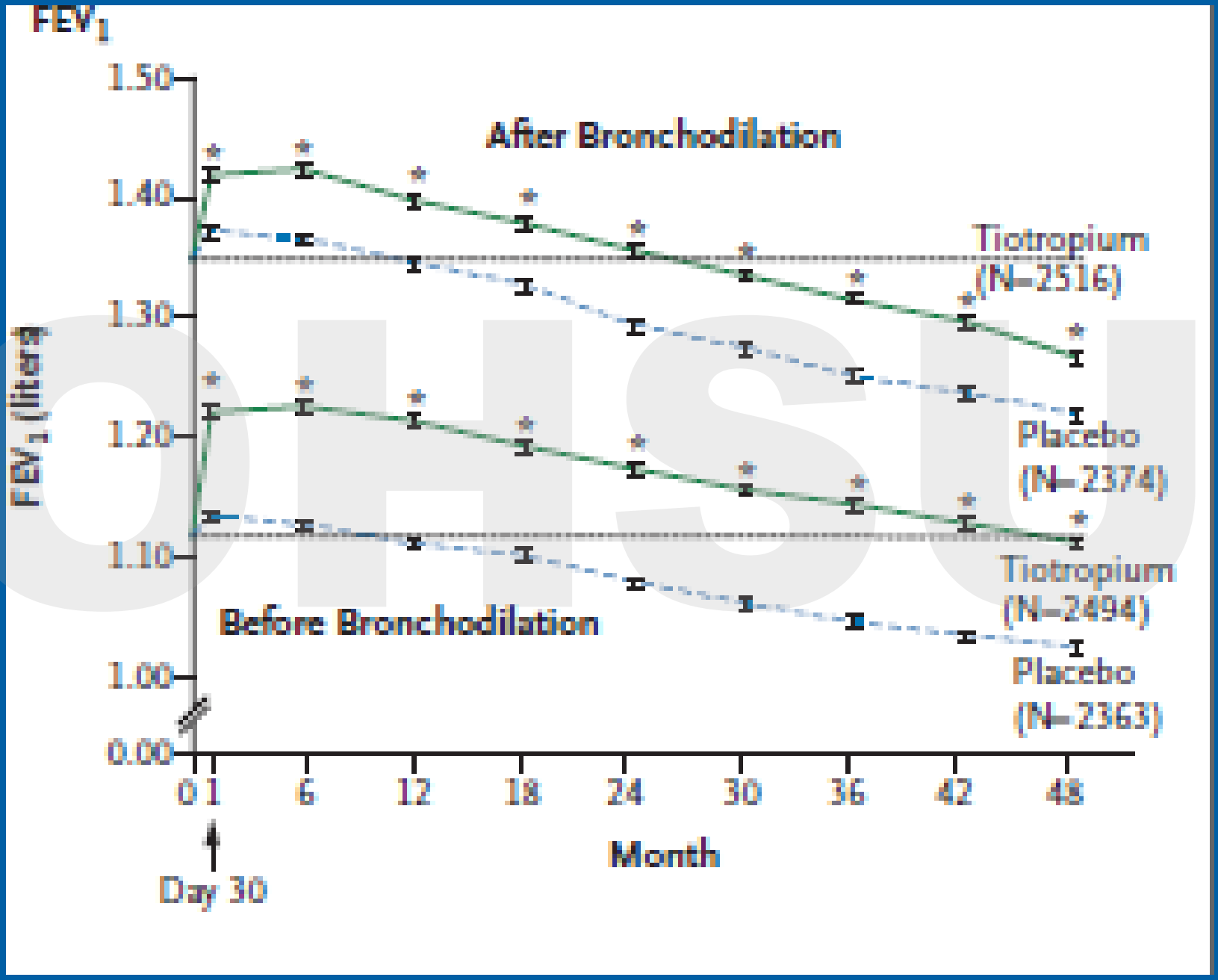
Tio +/- Bud/Form[2]



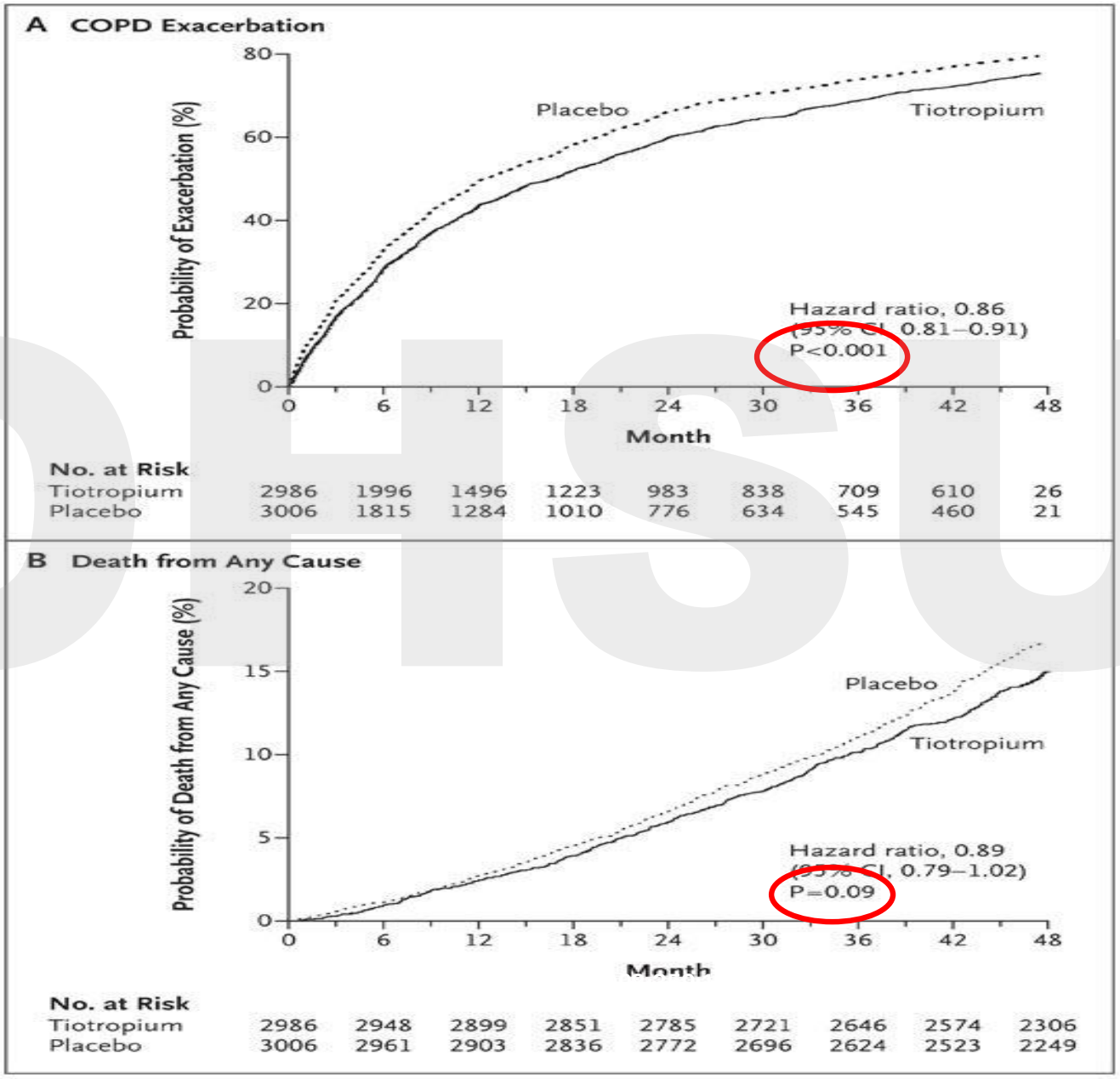
- BUD/FORM + TIO
- PBO + TIO

1. Aaron SD, et al. *Ann Intern Med.* 2007;146(8):545-555.
2. Welte T, et al. *Am J Respir Crit Care Med*. 2009;180(8):741-750.

Mean FEV1 and FVC before and after Bronchodilation



Kaplan-Meier Estimates of the Probability of COPD Exacerbation and Death from Any Cause



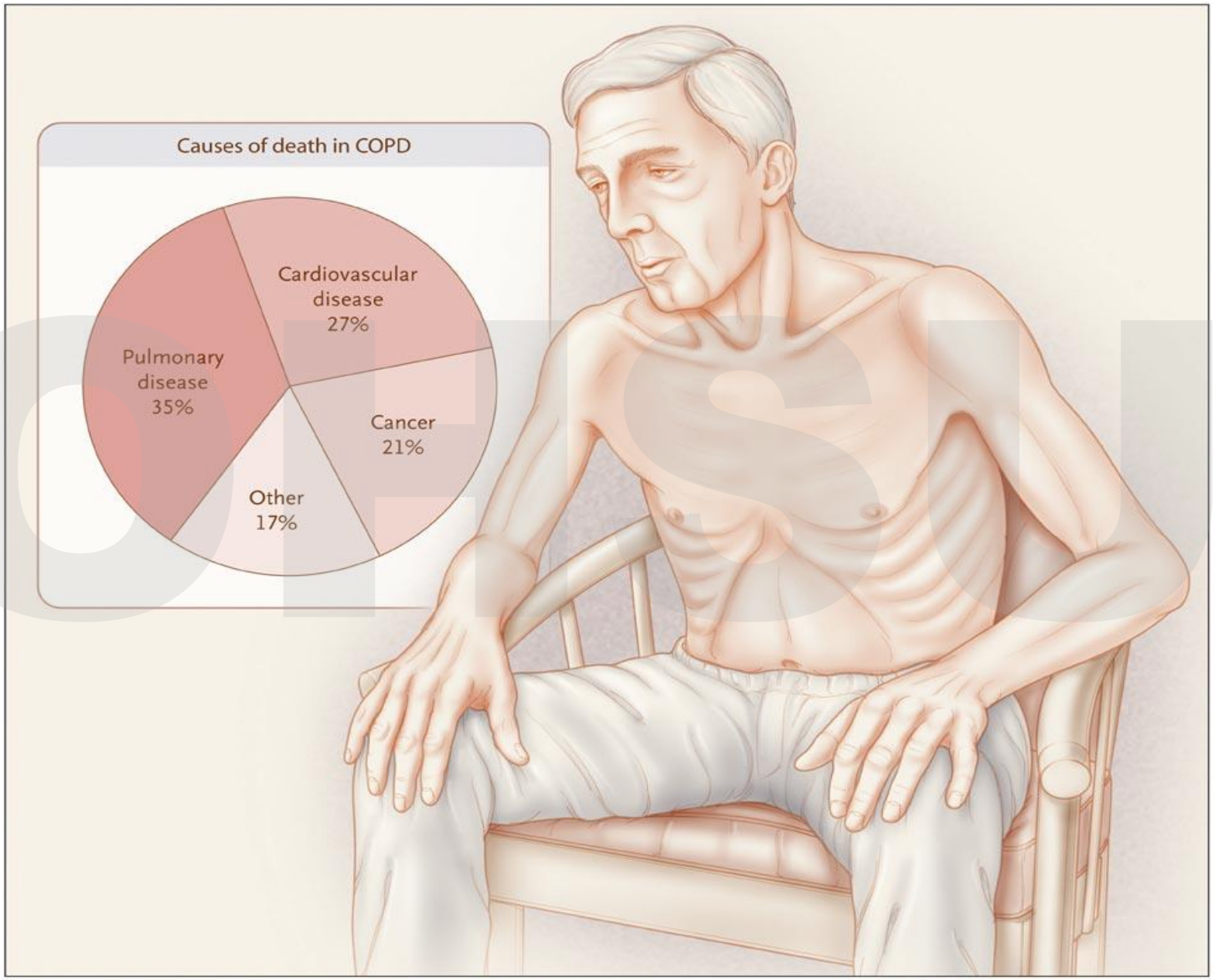
The BODE Index

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

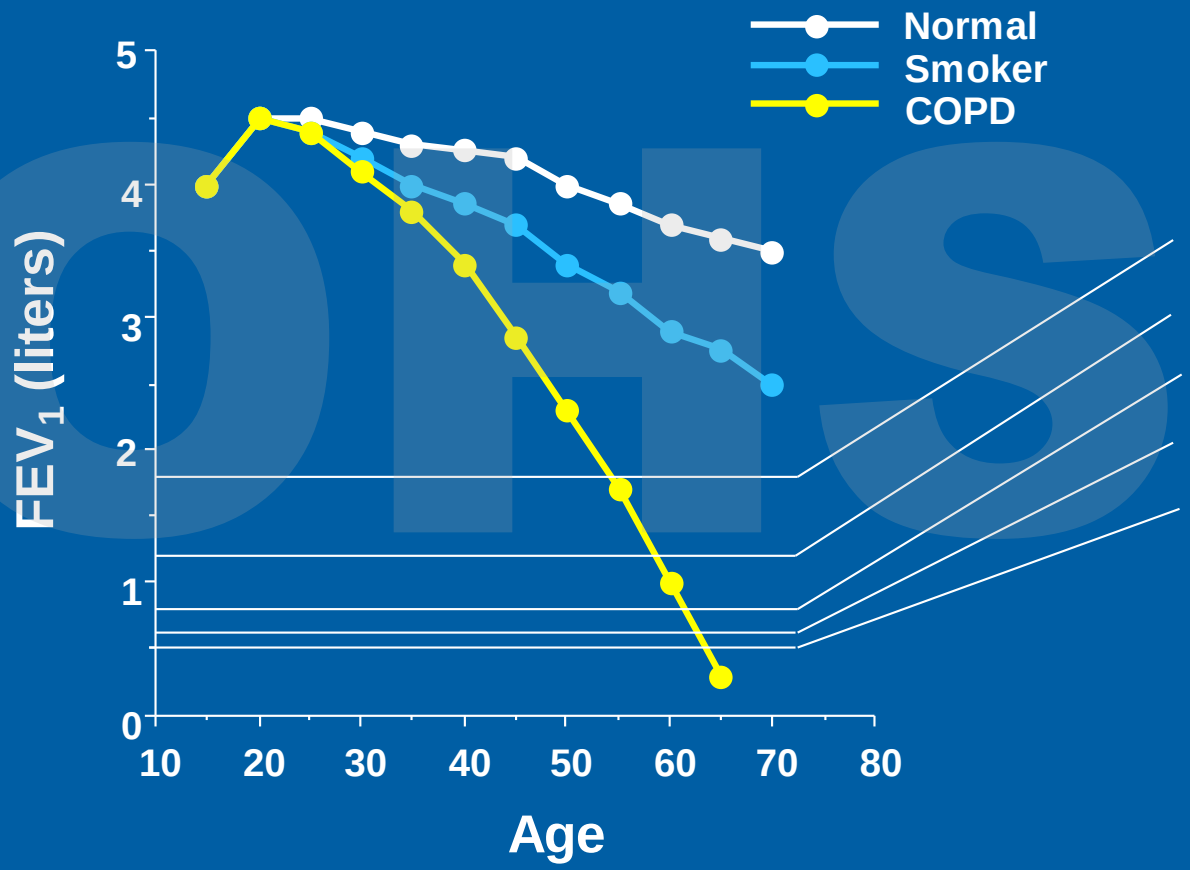
Celli BR, et al. *N Engl J Med.* 2004;350:1005-1012.

Causes of Death in Patients with COPD



Rabe K. N Engl J Med 2007;356:851-854

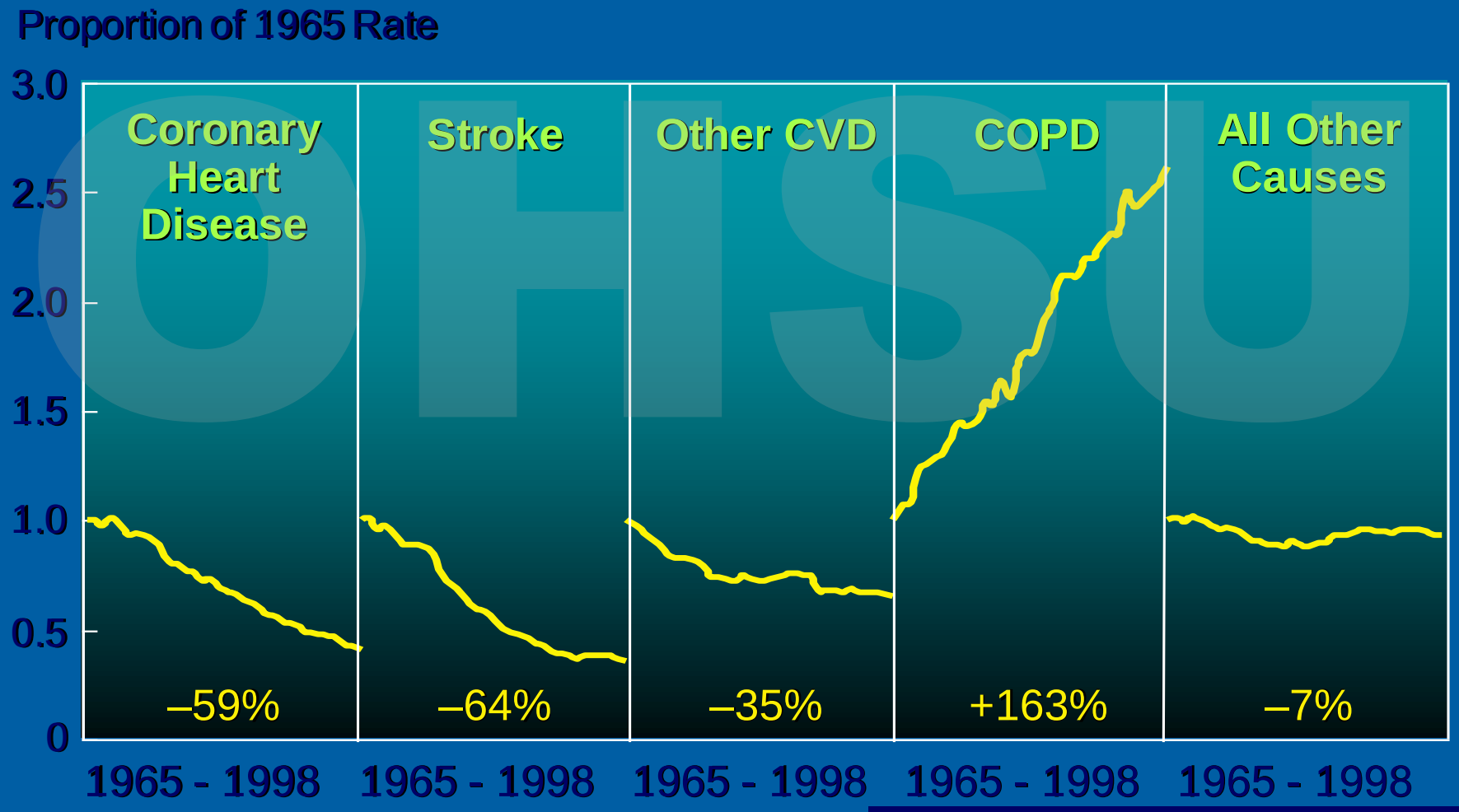
Natural History of COPD



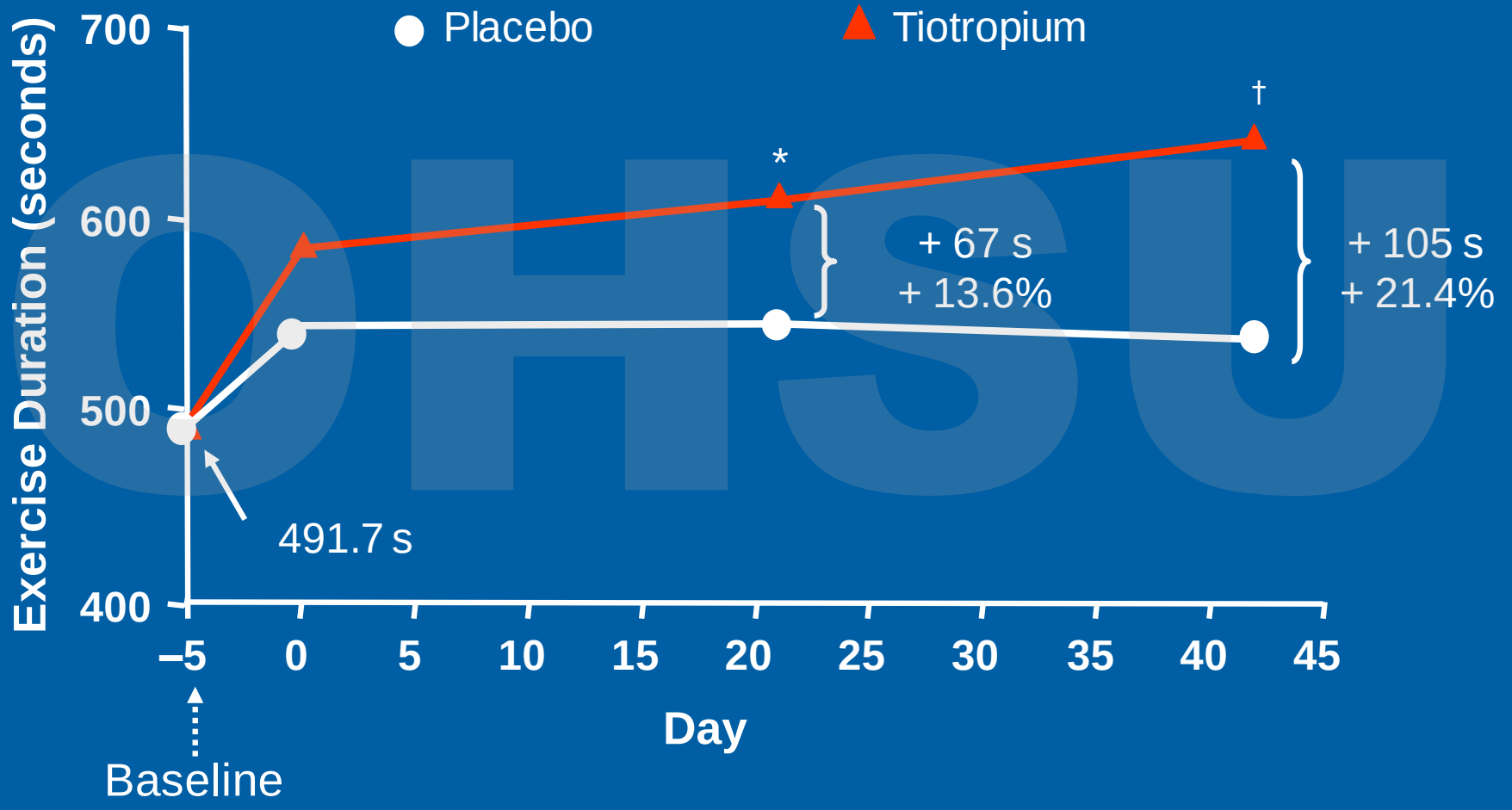
Dyspnea
Oxygen
Home bound
Bed bound
Death

Modified from Fletcher C, Peto R. *Br Med J*. 1977;1(6077):1645-1648.

Percent Change in Age-Adjusted Death Rates, U.S., 1965-1998



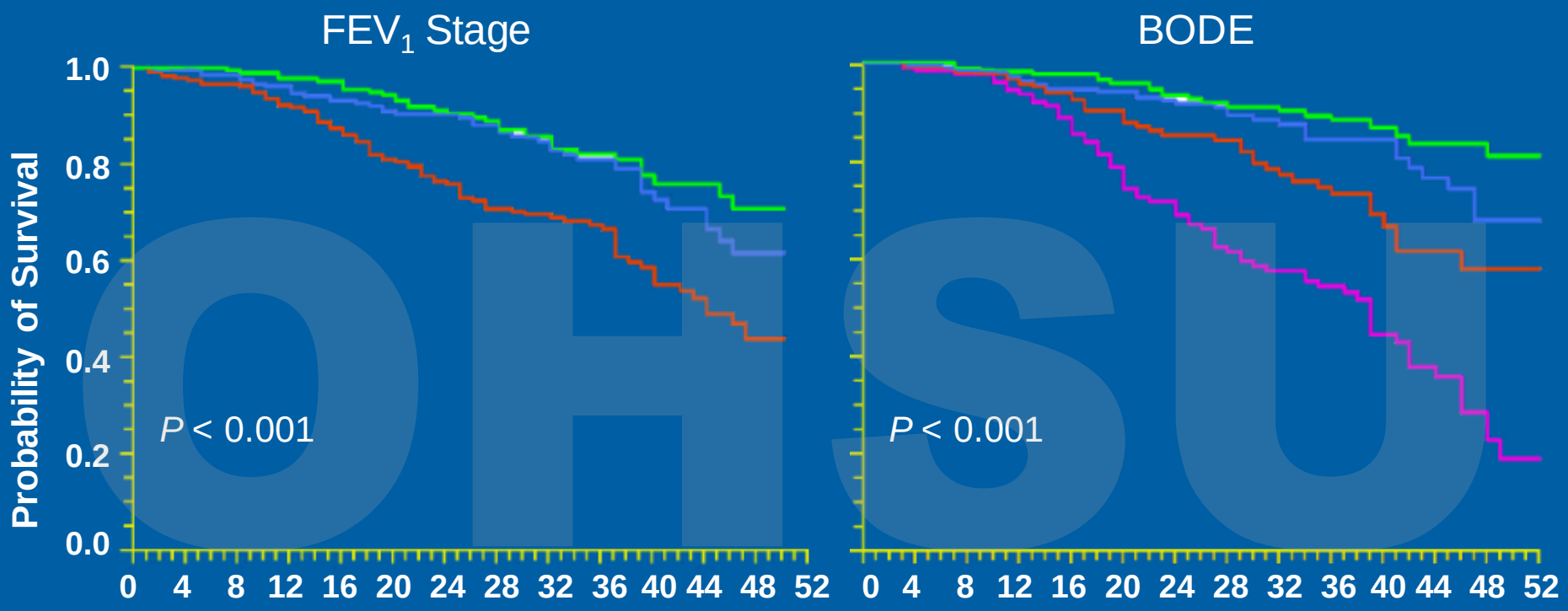
Exercise Duration with Tiotropium



*$P < 0.05$. †$P < 0.01$

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

Survival in COPD



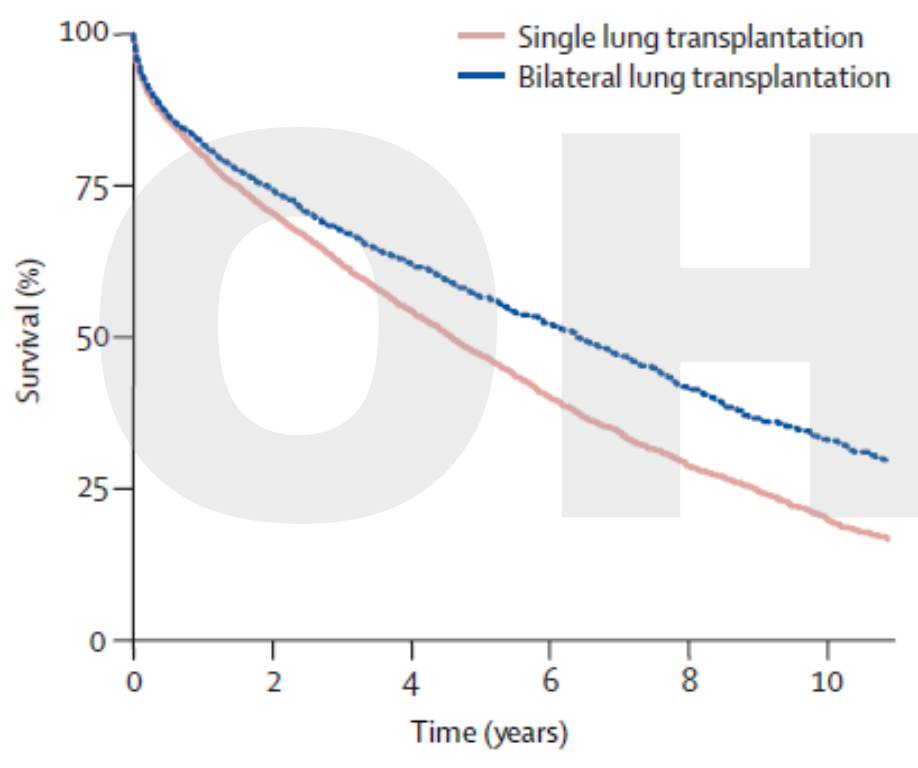
Celli BR, et al. *N Engl J Med.* 2004;350:1005-1012.

Manage COPD Exacerbations

Key Points

- Inhaled bronchodilators (particularly inhaled β_2-agonists with or without anticholinergics) and oral glucocortico-steroids are effective treatments for exacerbations of COPD (Evidence A).

Lung Transplantation and COPD



- Retrospective analysis of ISHLT database[1]
  - Bilateral LT N = 3525
  - Single LT N = 6358
- Median survival = 5 years
  - BLT 6.4 y
  - SLT 4.6 y $P < 0.0001$
- No survival difference if recipient > 60 y
- Questionable survival advantage compared to standard of care[2]
- LT may improve QOL

1. Thabut G, et al. *Lancet.* 2008;371(9614):744-751.
2. Stavem K, et al. *J Heart Lung Transplant.* 2006;25:75-84.

Management of Stable COPD

Pharmacotherapy: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.
- The principal bronchodilator treatments are β_2- agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A).
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).

Management of Stable COPD

Pharmacotherapy: Glucocorticosteroids

- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted (*Stage III: Severe COPD and Stage IV: Very Severe COPD*) and repeated exacerbations (Evidence A).

- An inhaled glucocorticosteroid combined with a long-acting $ß_2$-agonist is more effective than the individual components (Evidence A).

GOLD Guidelines for Diagnosing COPD: Risk Factors and Symptoms[1]

Risk Factors

- History of smoking or exposure to other risk factors
  - 80% to 90% of all COPD occurrences are attributable to smoking[2]
- Male or female > 40 years of age

Other

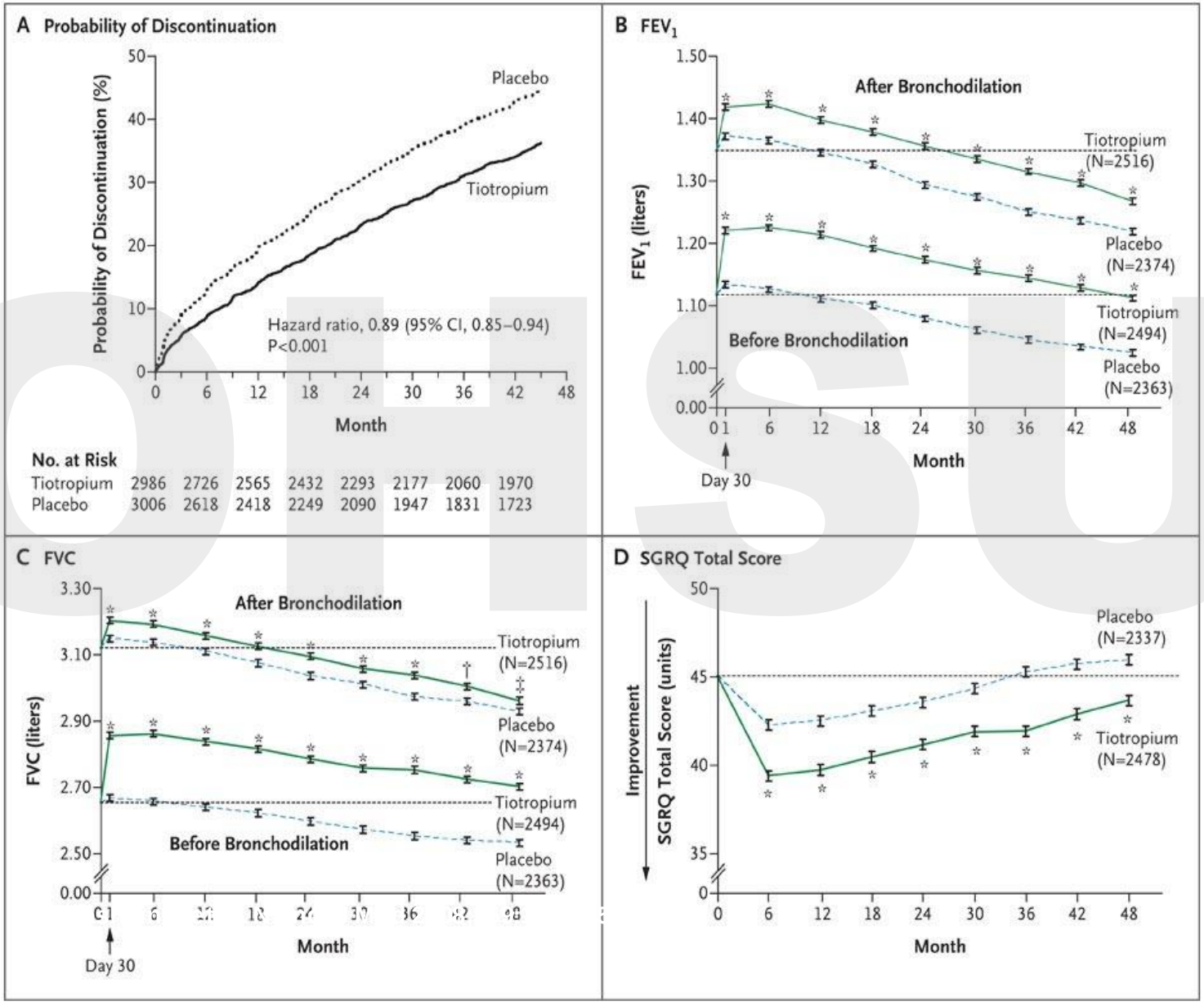
- Exposure to occupational dusts and chemicals, indoor and outdoor air pollutants, and infections
- Socioeconomic status

Symptoms

- Dyspnea/exercise intolerance/fatigue
- Chronic cough with or without sputum
- Reduction in activities of daily living

GOLD Guidelines 2008. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed September 2010.
CDC. Respiratory diseases. http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/00_pdfs/chapter4.pdf. Accessed September 2010.

Probability of Treatment Discontinuation, Mean FEV1 and FVC before and after Bronchodilation, and Scores for Health-Related Quality of Life



Spirometry

		Ref	Pre	% Ref	Post	% Ref	%Chg
FVC	Liters	3.69	3.21	87	3.48	94	9
FEV1	Liters	2.81	1.64	58	1.93	69	18
FEV1/FVC	%	76	51		55		
FEF25-75%	L/sec	2.29	0.60	26	0.77	33	26
PEF	L/sec	6.57	6.17	94	6.65	101	8
FIF50%	L/sec		3.42		3.87		13

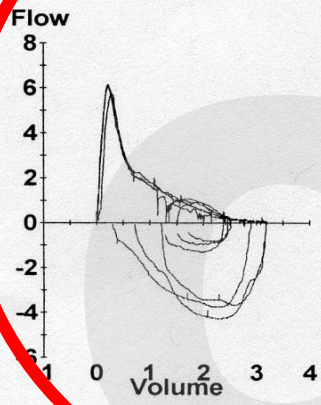
FVC>80

FEV1<80%

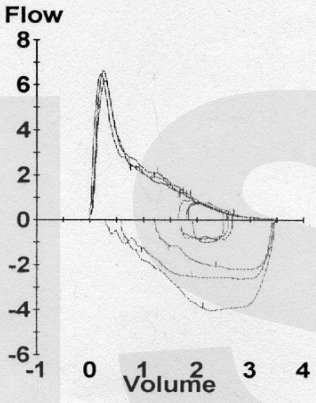
FEV1/FVC<70%

Obstruction

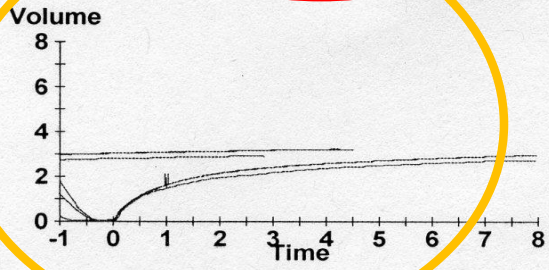
Pre Test Flow Volume Loop



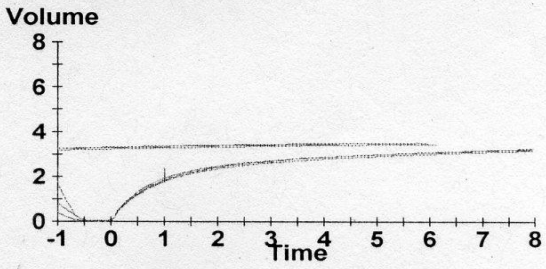
Post Test flow Volume Loop



Pre Test Volume / Time



Post Test Volume / Time



Pre Test DLCO

Patient History

Medication: Spiriva Advair Flonase

Are you short of breath at Rest: No

Are you short of breath on exercise: No

Four Components of COPD Management

- Assess severity and monitor disease
- Reduce risk factors
- Manage stable COPD through
  - Patient education
  - Pharmacologic management
  - Nonpharmacologic treatment
- Manage exacerbations

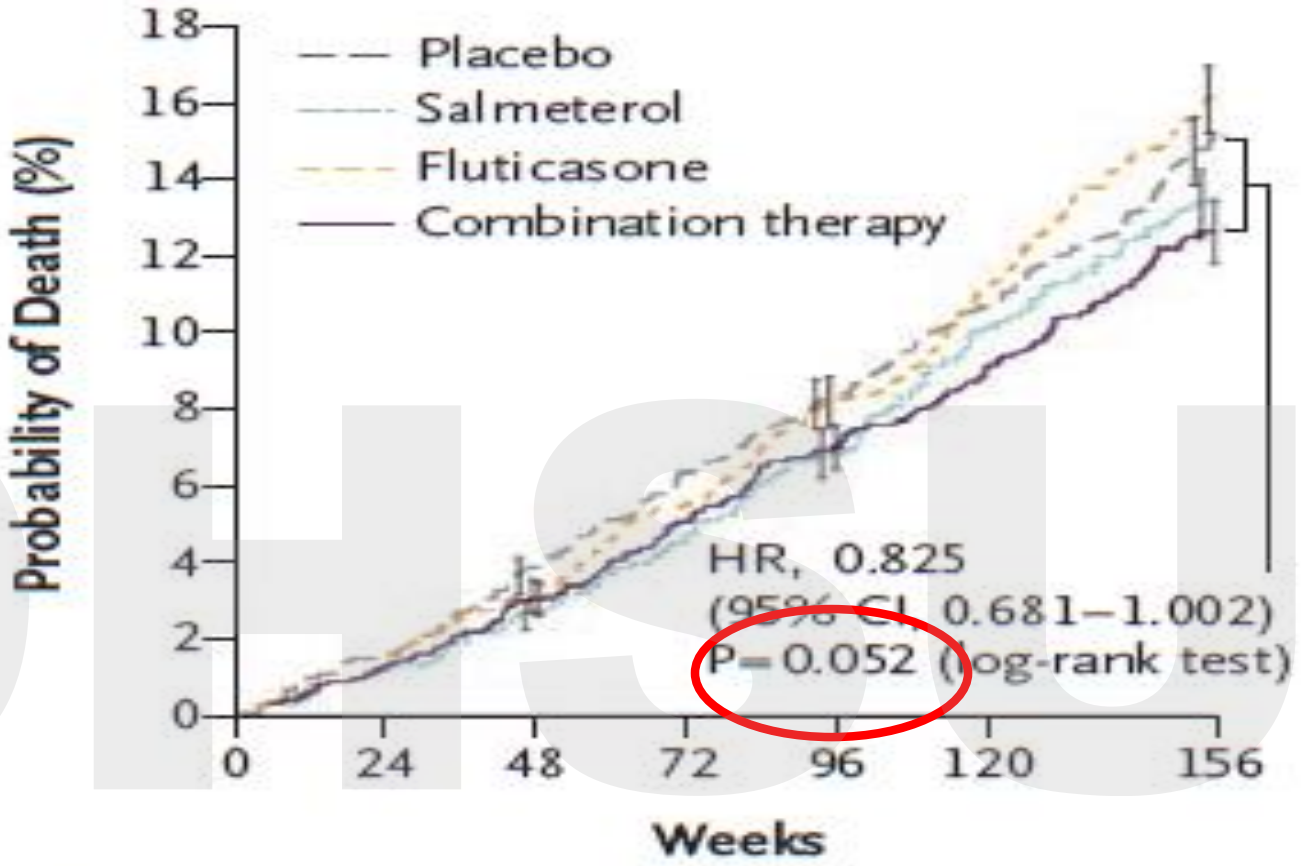
GOLD Recommendations. Updated 2008.
http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed September 2010.

Management of Exacerbations

	Objective	Strategy
Acute	Relieve dyspnea	SABA +/- short acting anticholinergic
	Reduce airway inflammation	Systemic corticosteroids
	Improve lung function	Systemic corticosteroids
	Eradicate infections	Antibiotics
Maintenance	Reduce risk of new exacerbation	Smoking cessation
		Pharmacotherapy •Salmeterol +/- fluticasone •Formoterol +/- budesonide •Tiotropium
		Immunizations •Influenza •Pneumonia
		Pulmonary rehab
		Self-management support

Anzueto A. *Am J Med Sci*. 2010 Jul 9. [Epub ahead of print]

Death from Any Cause



No. of Patients							
Placebo	1524	1500	1464	1428	1399	1361	1293
Salmeterol	1521	1502	1481	1451	1417	1368	1316
Fluticasone	1534	1512	1487	1450	1409	1363	1288
Combination therapy	1533	1514	1487	1456	1426	1393	1339

Incidence Rate of Serious Adverse Events per 100 Patient-Years

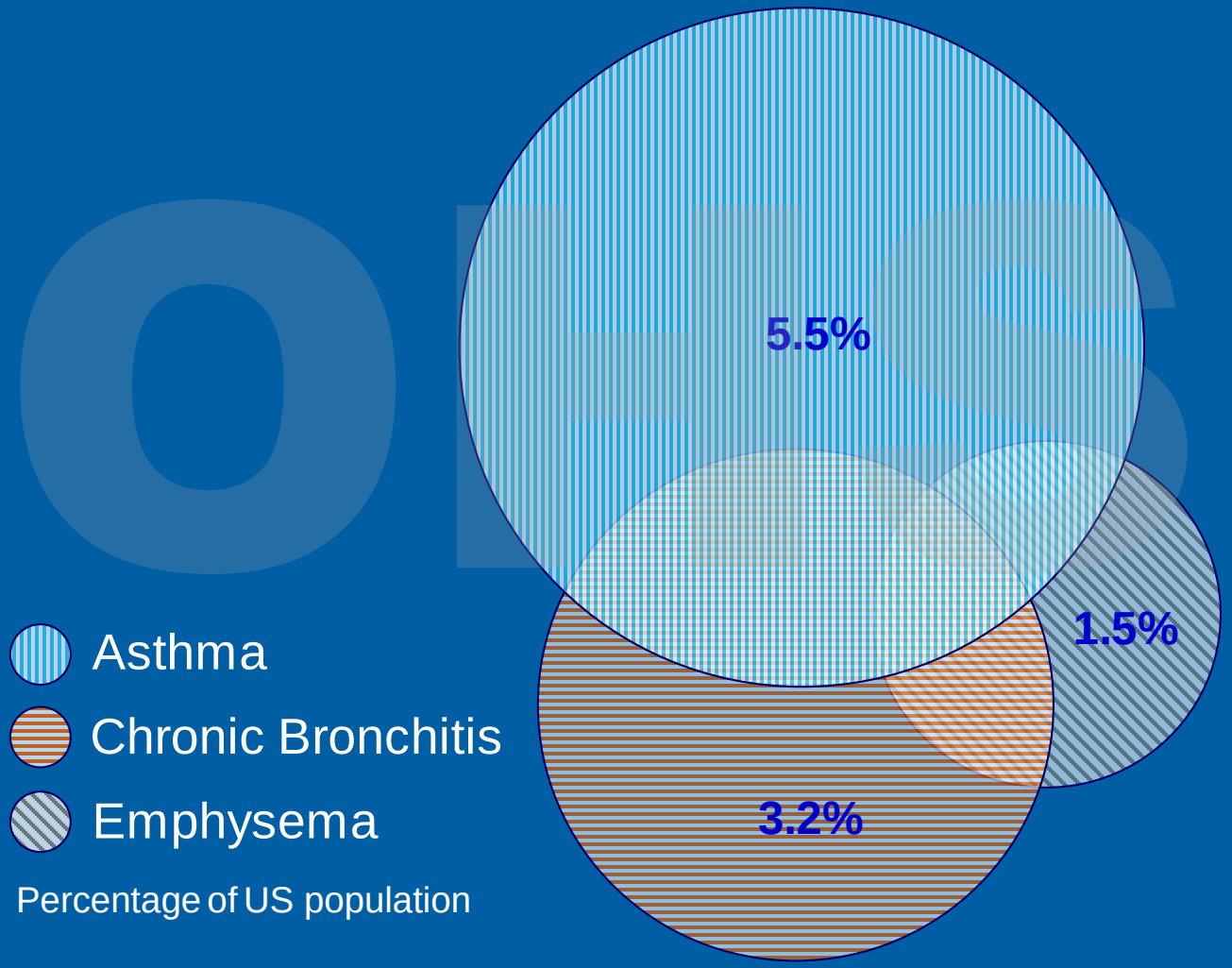
Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† $P<0.05$.

Obstructive Lung Disease Groups (NHANES III)

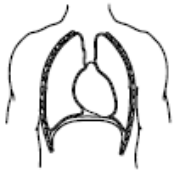


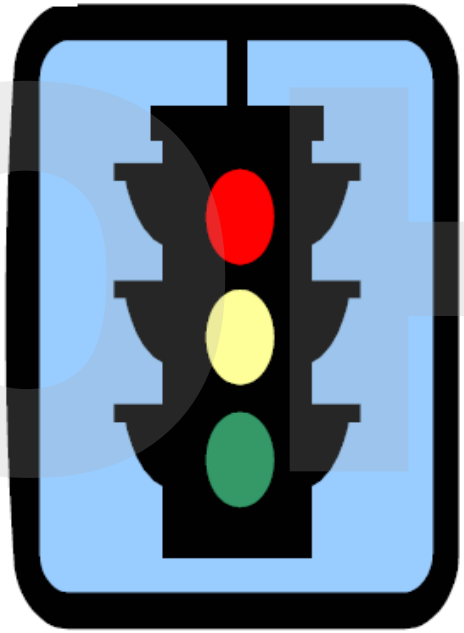
Soriano JB, et al. *CHEST*. 2003;124(2):474-481.

Patient Action Plan

PATIENT ACTION PLAN FOR COPD SIGNS & SYMPTOMS

Purpose: To promote patient identification and self-directed action for onset of symptoms related to COPD.





COPD --- Your Plan for ACTION

Use this guide to help you report changes in your symptoms to your doctor or nurse. When you report symptoms *early*, you are less likely to have to go to the hospital for treatment.

You are doing well when:

- You can do your normal activities
- You have no changes in your symptoms
- Your usual medicines are controlling your symptoms

Call your home care nurse or doctor in the next 24 hours when:

- You have increased shortness of breath with usual activity
- You are coughing more than usual
- You have increased wheezing
- You have increased sputum or it has changed in color
- You have to use short acting medicines more often
- You feel more tired or restless

Call 911 RIGHT AWAY when:

- You have severe shortness of breath or shortness of breath at rest
- You have chest pain that doesn't go away
- You lips or fingernails turn gray or blue
- You feel unusually sleepy or confused

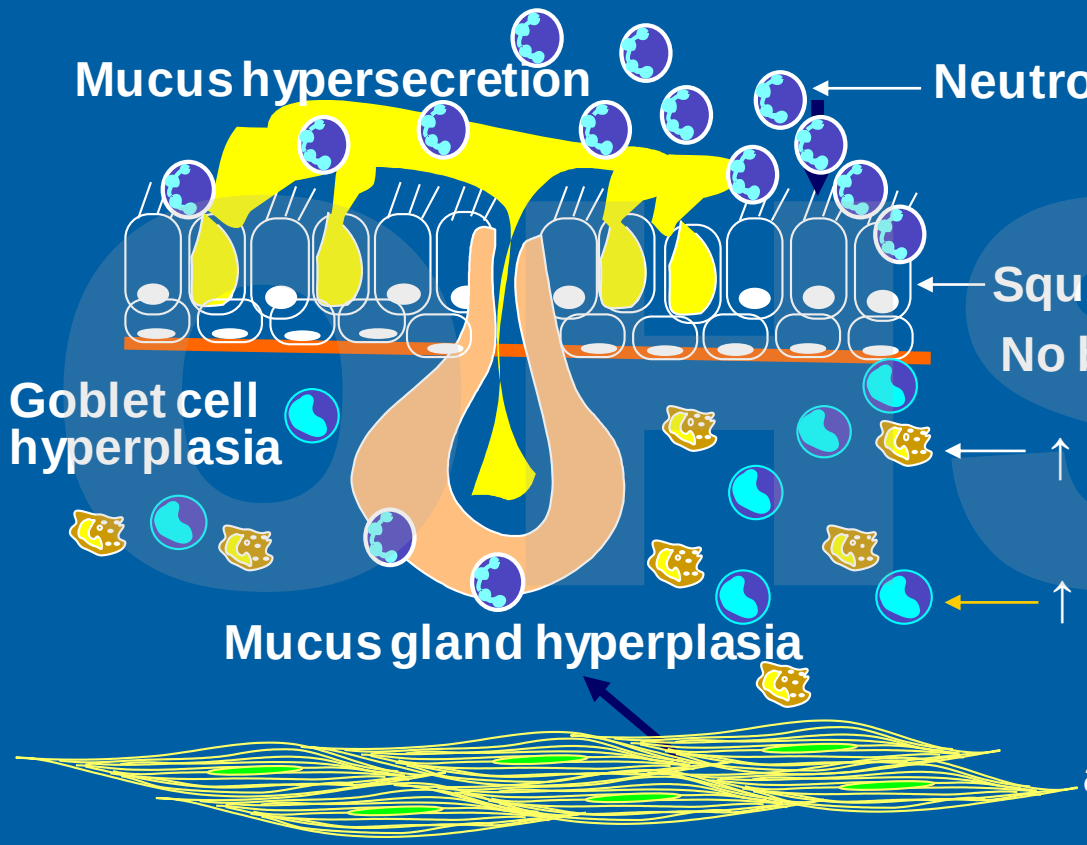
MD Name & Phone Number:_____

Tool developed by: Lisa Gorski, MS, APRN, BC, CRNI
Reference: National Heart, Lung, and Blood Institute (NHLBI) World Health Organization Workshop (2004) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: Executive summary: Available online: www.goldcopd.org

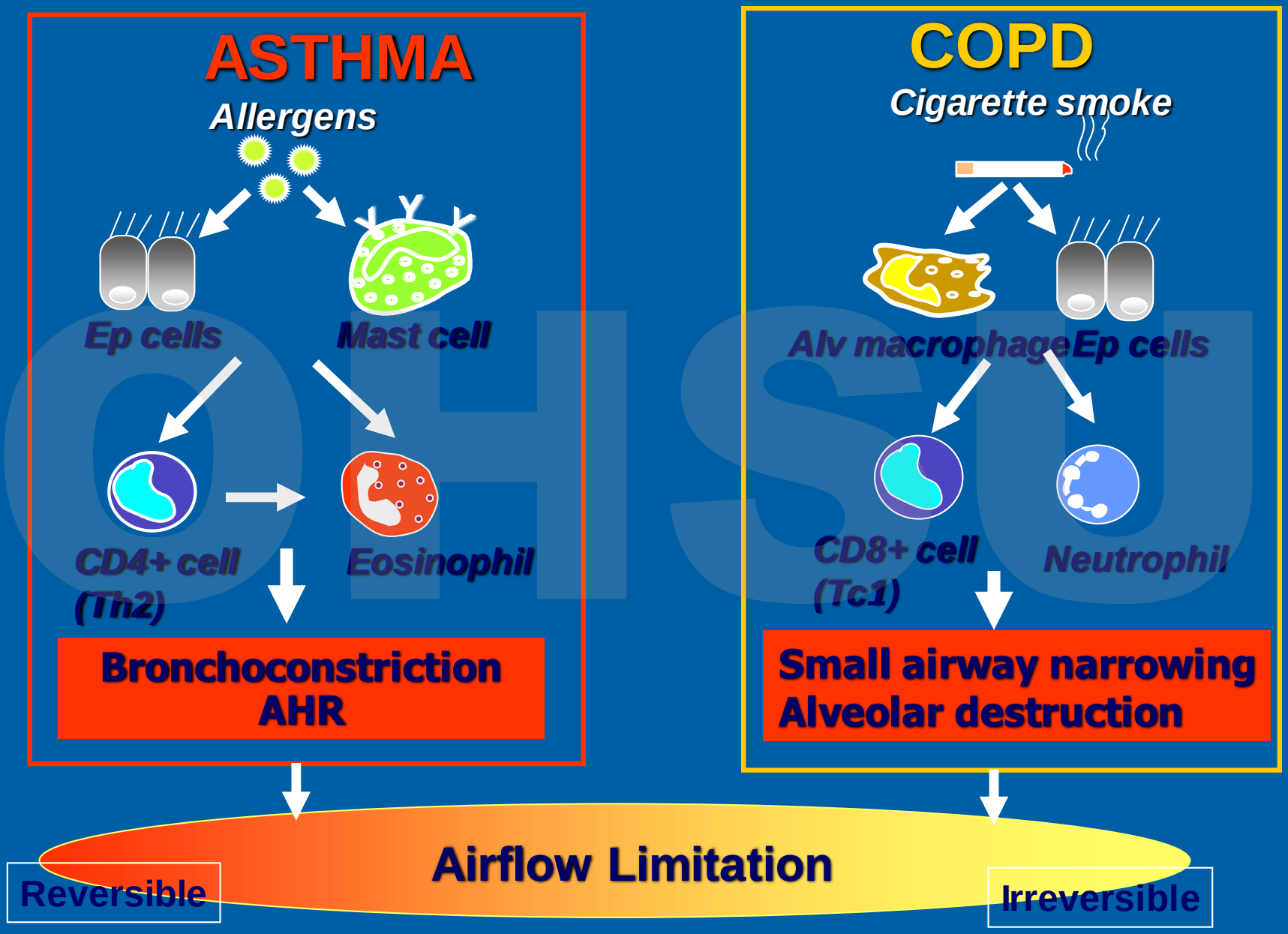
Patient Action Plan for COPD Signs & Symptoms
"Best Practices"

http://www.sdfmc.org/ClassLibrary/Page/Information/DataInstances/293/Files/1948/ASHHC_Patient_Action_Plan_fpr_COPD_signs_and_symptoms.pdf. Accessed September 2010.

Changes in Large Airways of COPD Patients

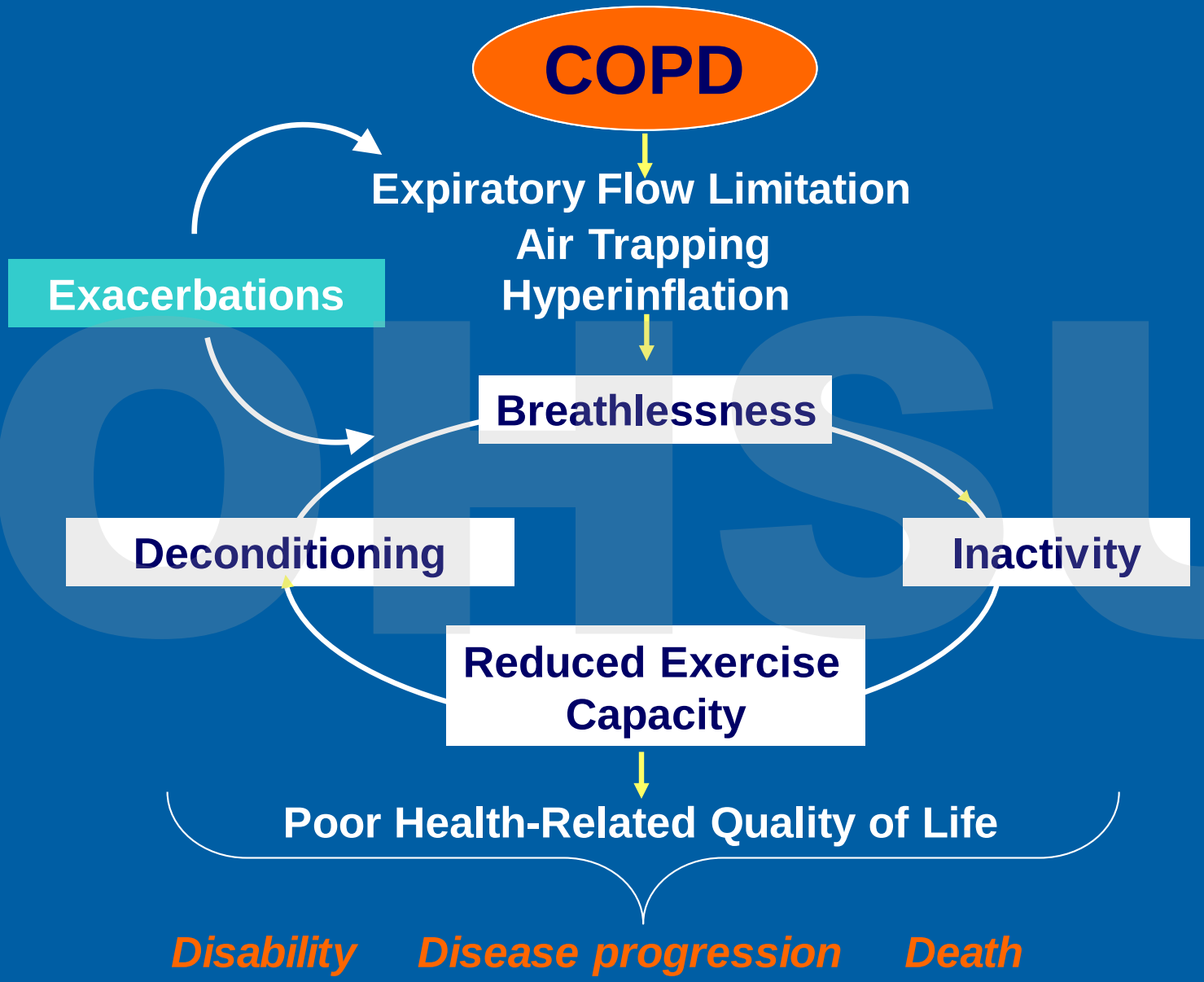


Source: Peter J. Barnes, MD

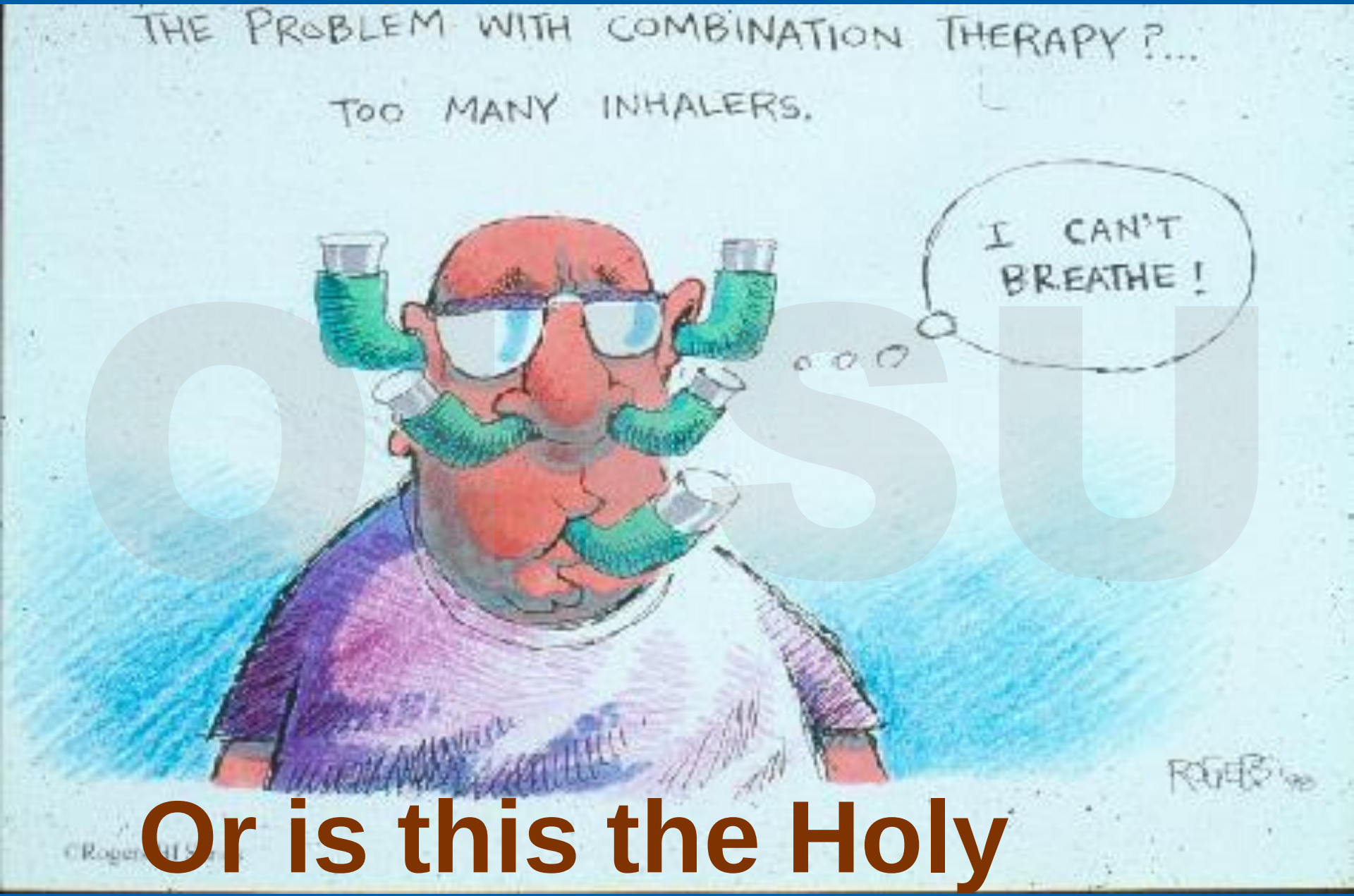


Source: Peter J. Barnes, MD

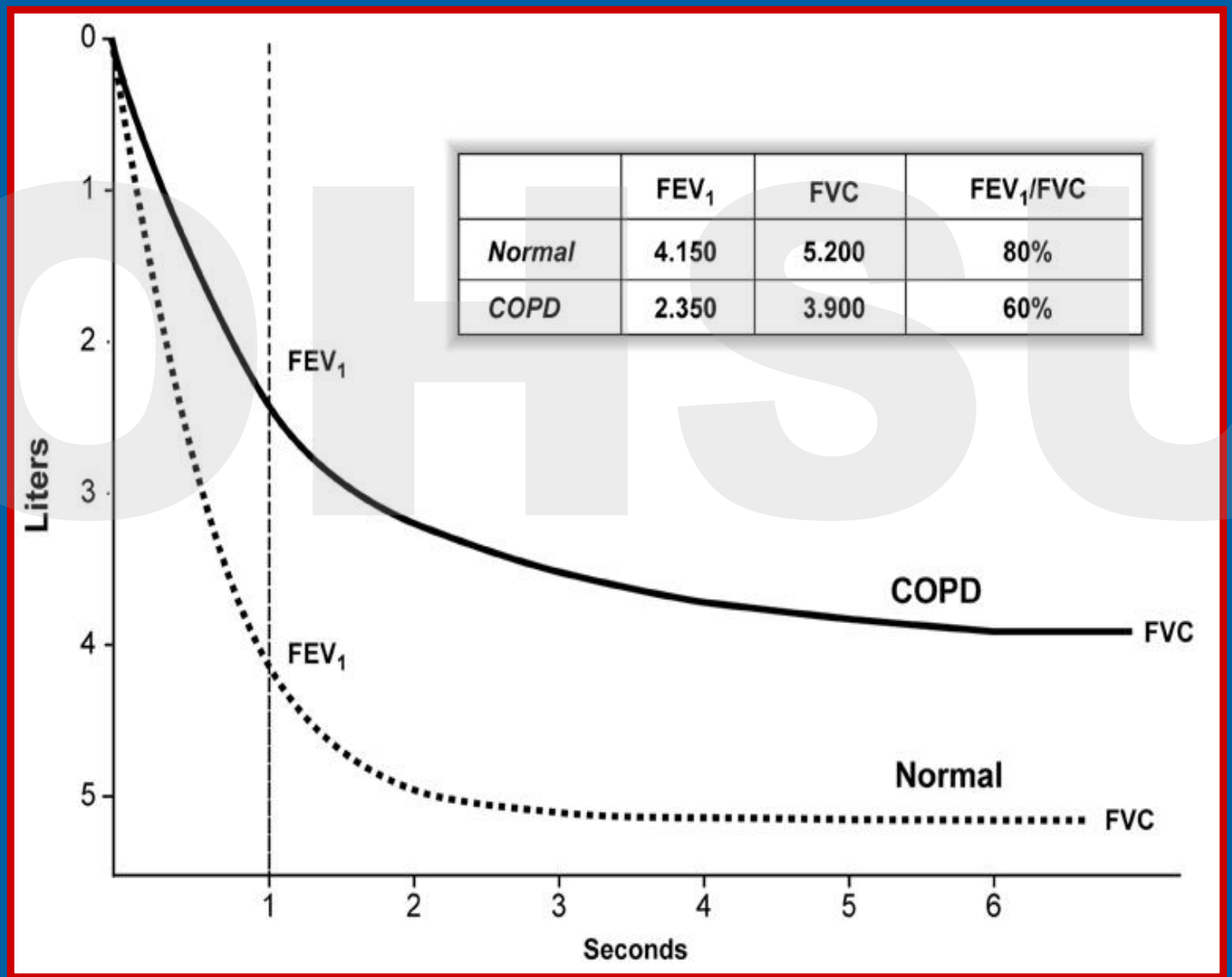
Clinical Course of COPD



Adapted from Decramer M. *Eur Respir Rev.* 2006;15:51-57.



Or is this the Holy Grail??



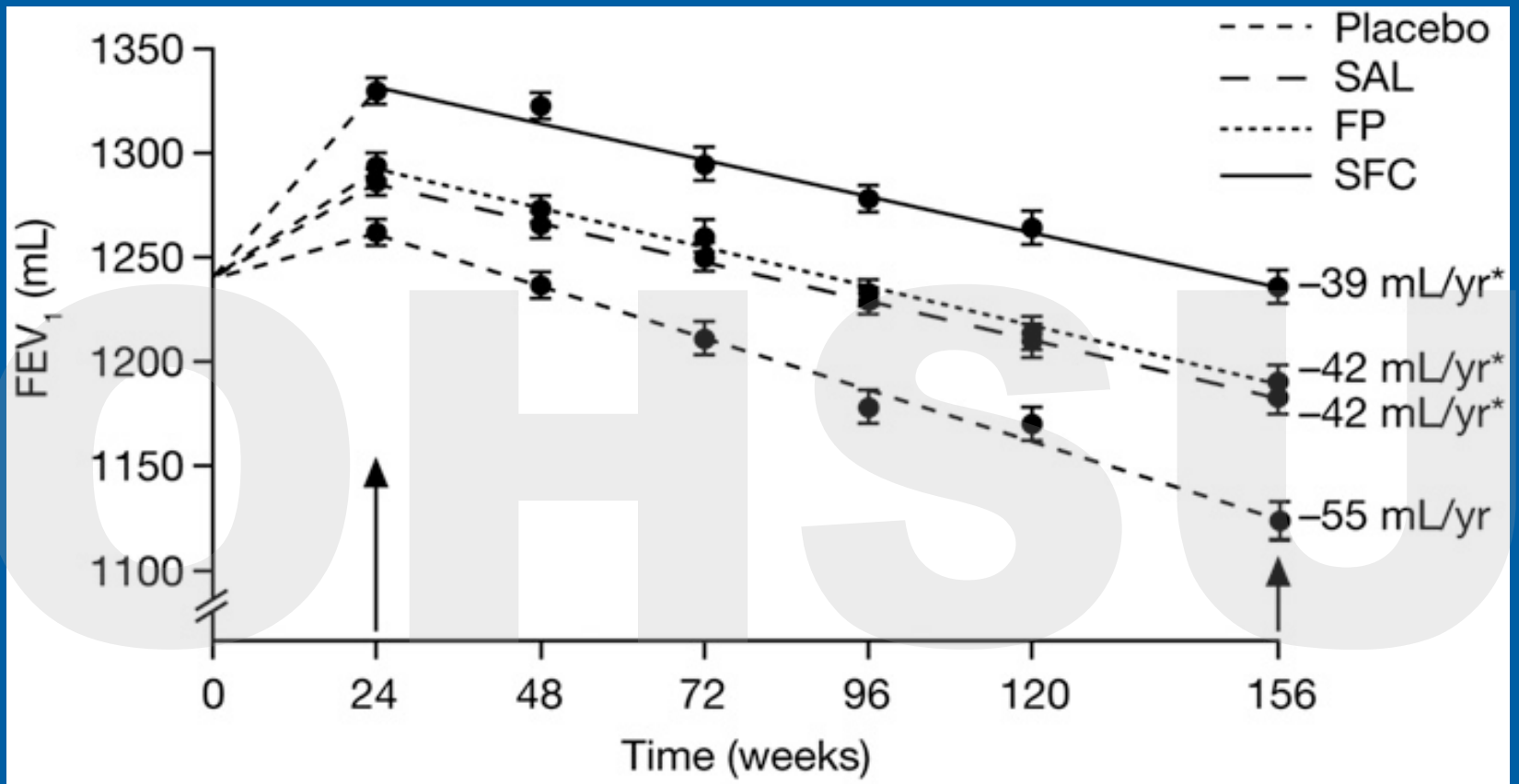
	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
COPD	2.350	3.900	60%

TORCH/Mortality

- Fluticasone/salmeterol: 12.6%*
- Placebo: 15.2%
- Salmeterol: 13.5%
- Fluticasone: 16.0%

*P=0.052

Rate of decline in FEV1 in TORCH



No. of patients

Placebo	1261	1248	1128	1049	979	906	819
SAL	1334	1317	1218	1127	1054	1012	934
FP	1356	1346	1230	1157	1078	1006	908
SFC	1392	1375	1281	1180	1139	1073	975

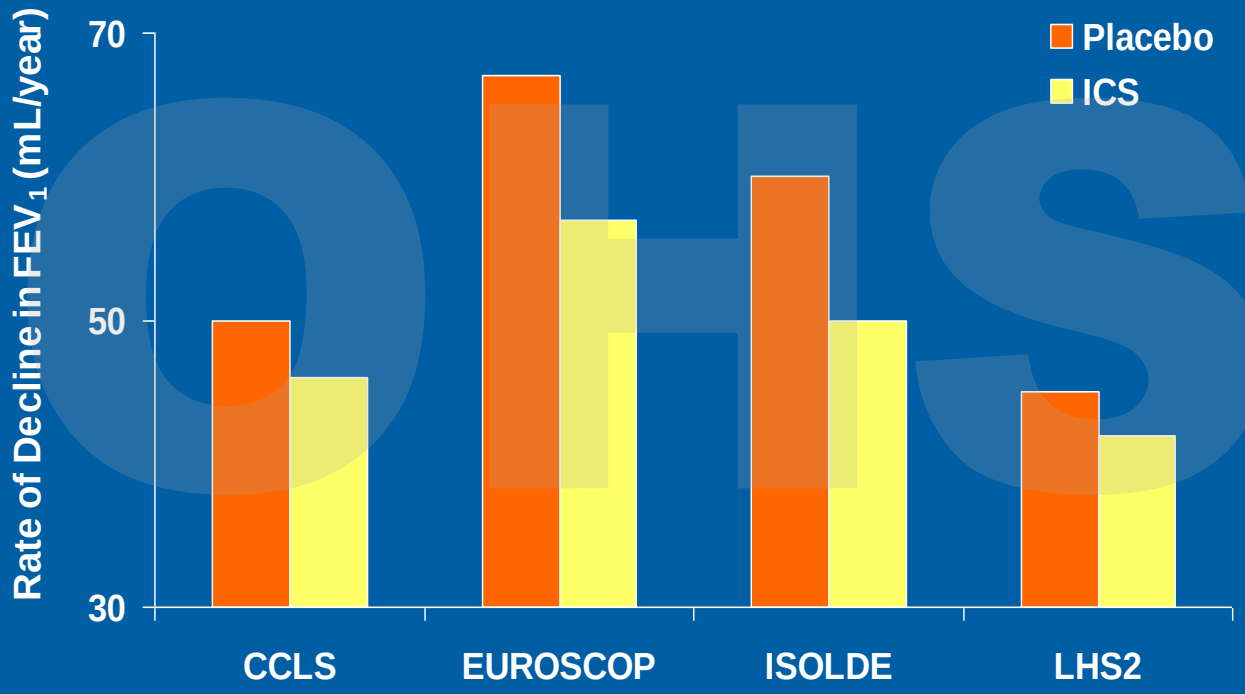
*P<.003

Celli: Am J Respir Crit Care Med 178: 332, 2008

Clinical Features Differentiating COPD and Asthma

Clinical Features	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time wakening with breathlessness and/or wheezing	Uncommon	Common
Association with atopic symptoms and seasonal allergies	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Favorable response to inhaled glucocorticoids	Inconsistent	Consistent

Inhaled Corticosteroids Alone Do Not Modify COPD Natural History



† No differences were statistically significant

Values represent mean annual declines in FEV_1, ml

CCLS = Copenhagen City Lung Study; *Lancet.* 1999;353:1819-1823.
EUROSCOPE = European Respiratory Society Study of COPD; *N Engl J Med.* 1999;340:1948-1953.
ISOLDE = Inhaled Steroids in Obstructive Lung Disease; *BMJ.* 2000;320:1297-1303.
LHS2 = Lung Health Study 2; *N Engl J Med.* 2000;343:1902-1909.
As summarized by MacNee and Calverley; *Thorax.* 2003;58:261-265.

Singh:Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 300:1439, 2008

- Systemic review/meta-analysis
- Cardiovascular risks of ACs: CV death, MI, stroke
- Randomized trials, 30 days
- 17/103 trials acceptable; 14,783 patients
- F/U 6 weeks to 5 years

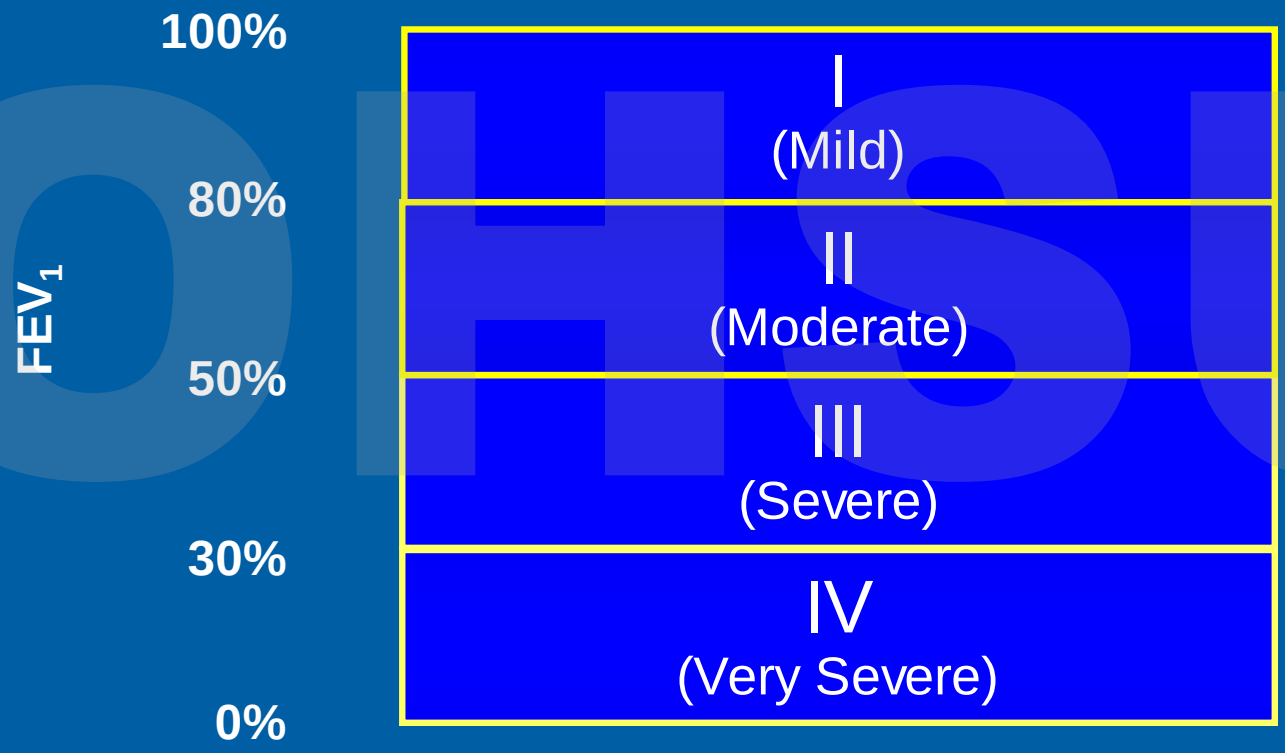
Inhaled Anticholinergics COPD

Tashkin: A 4-year trial of tiotropium in COPD. NEJM 359:1543, 2008

Singh:Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with COPD. JAMA 300:1439, 2008

ATS/ERS and GOLD Guidelines: Severity of COPD

COPD is defined as $FEV_1/FVC < 70\%$



ATS/ERS: American Thoracic Society/European Respiratory Society
GOLD: Global initiative for chronic Obstructive Lung Disease

GOLD Guidelines.http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed September 2010.