Current Evidence for the Treatment of Chronic Obstructive Pulmonary Disease

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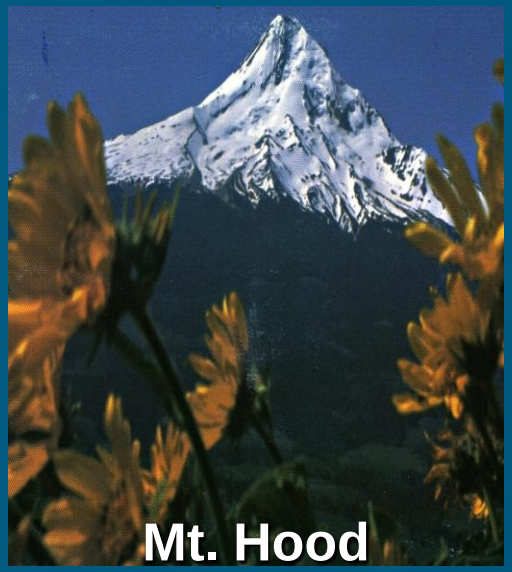
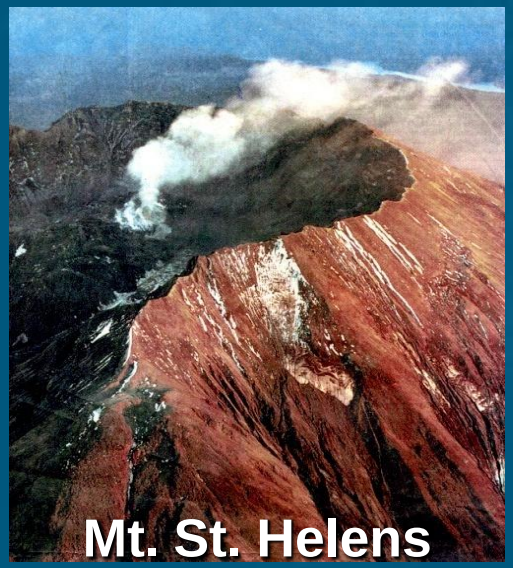
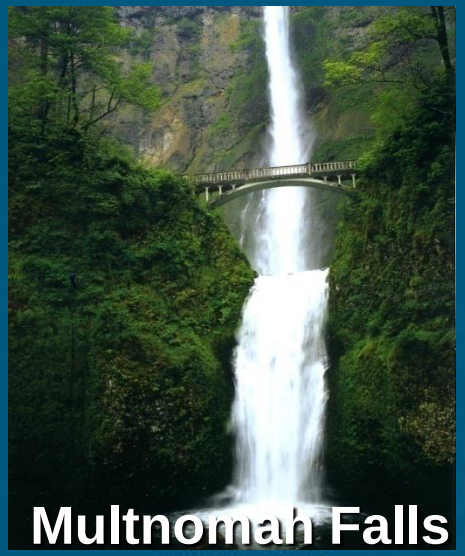

Mt. Hood


Mt. St. Helens


Multnomah Falls

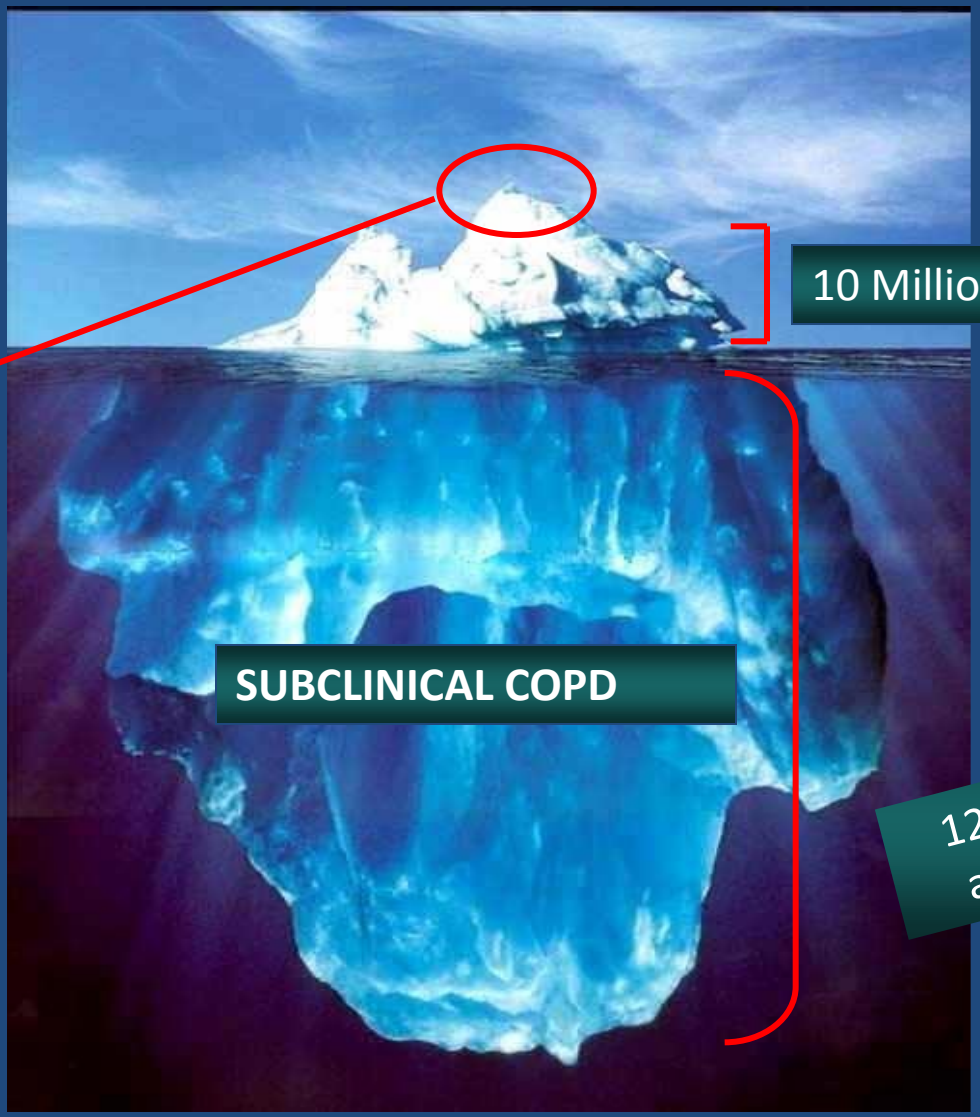
Faculty Disclosure

- No financial conflicts to disclose.

Objectives

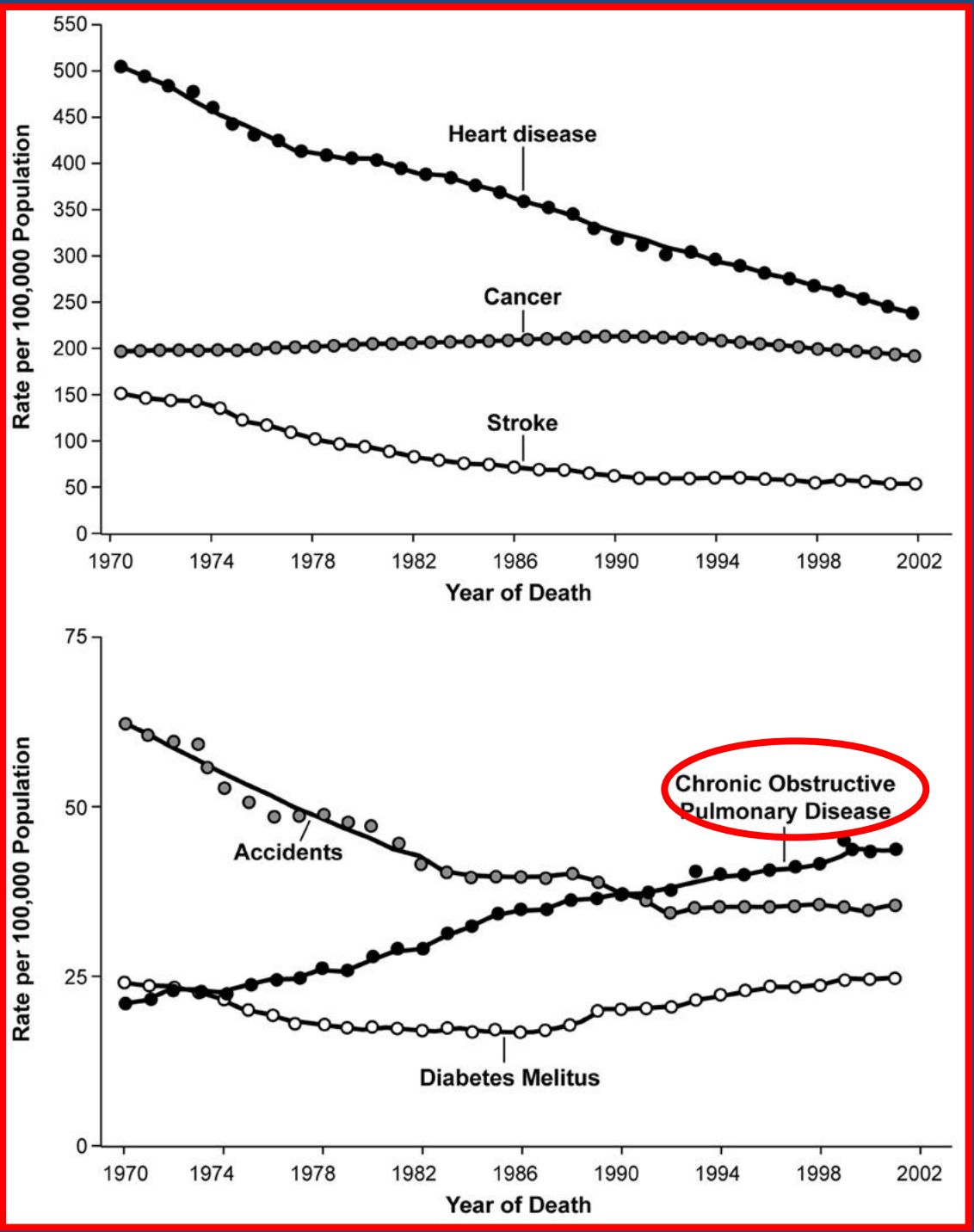
- Discuss the epidemiology and pathophysiology of COPD.
- Describe the role of the cholinergic system in the pathology of COPD.
- Recognizes the stages of COPD and be able to identify the differences between COPD and asthma.
- Discuss current guideline recommendations for the treatment of COPD
- Outline the role of inhaled bronchodilators and corticosteroids the treatment of COPD exacerbations in light of recent FDA proposed labeling changes for long-acting beta-agonists (LABAs)

Clinical COPD - Tip of the Iceberg



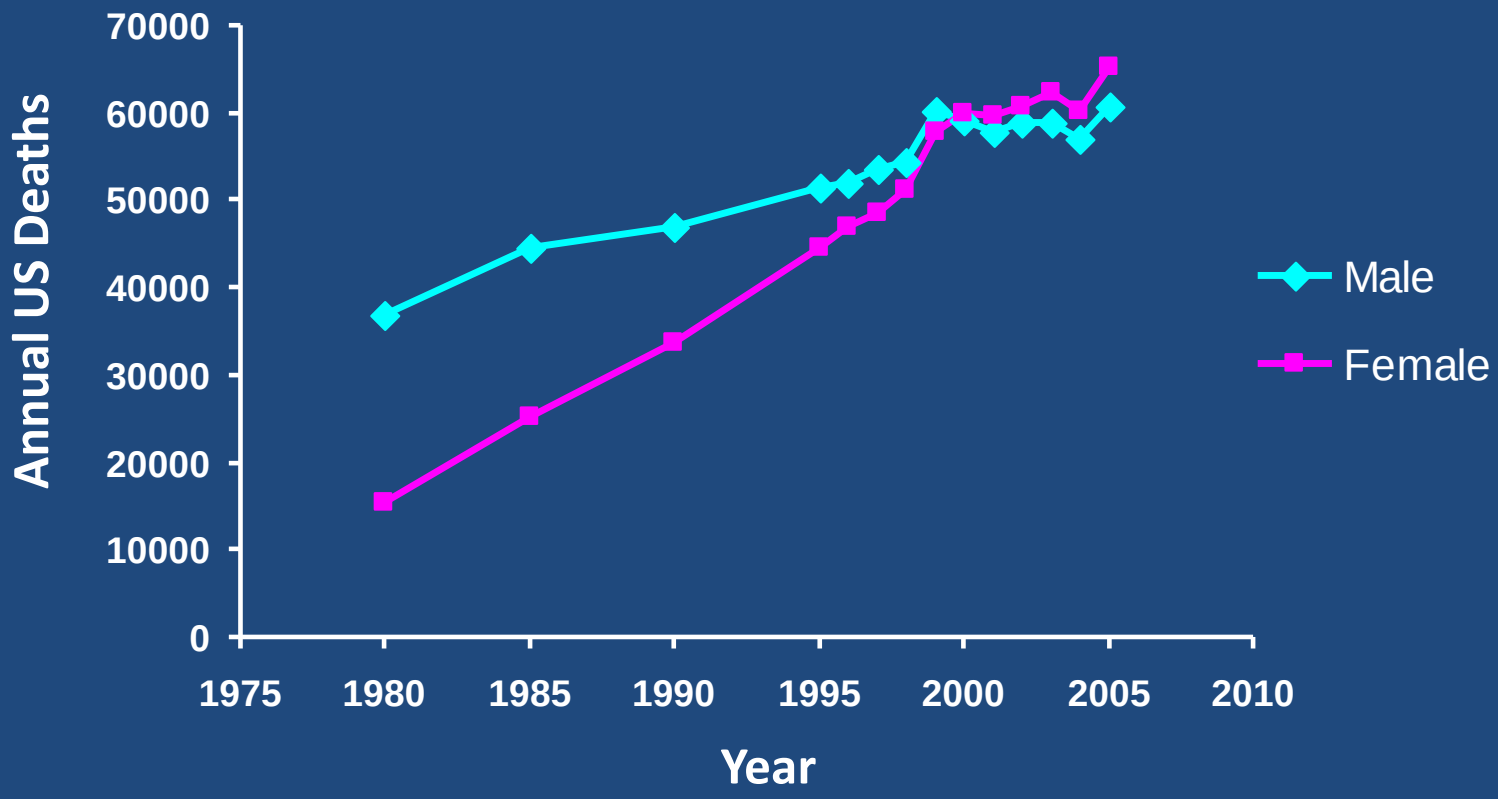
Adapted from Mannino DM: *MMWR Morb Mortal Wkly Rep*. 2002;51(SS06):1-16.

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

COPD Mortality



* Years after 2000 include adults aged ≥ 25y only

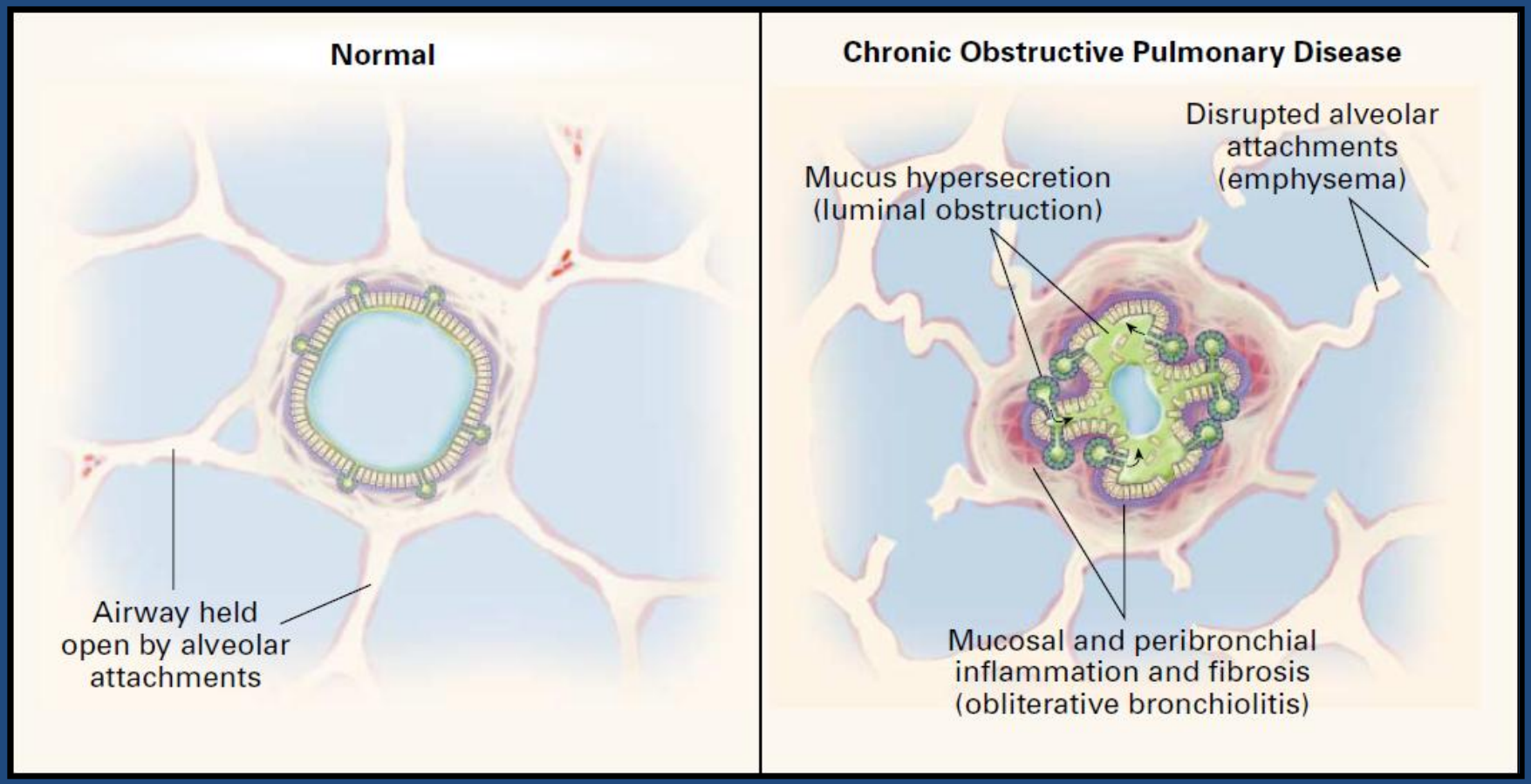
Mannino DM, et al. *MMWR Morb Mortal Wkly Rep*. 2002;51(SS-6):1-16.
Brown DW, et al. *MMWR Weekly*. 2008;57(45):1229-1232

Definition of COPD

- COPD is a preventable and treatable disease with extrapulmonary effects that may contribute to the severity in individual patients.
- Its 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

Mechanisms of Airflow Limitation in COPD



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

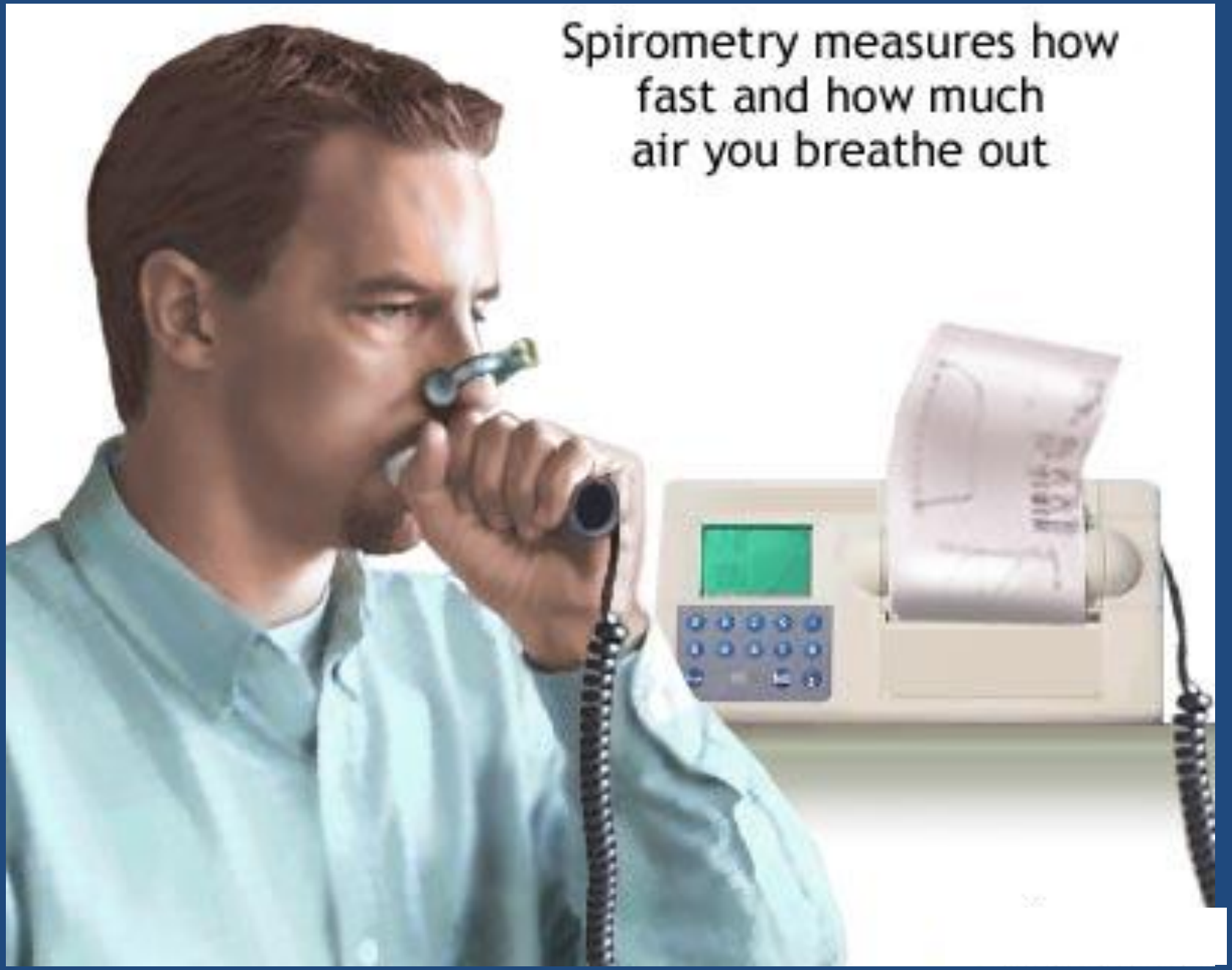
Differential Diagnosis: COPD and Asthma

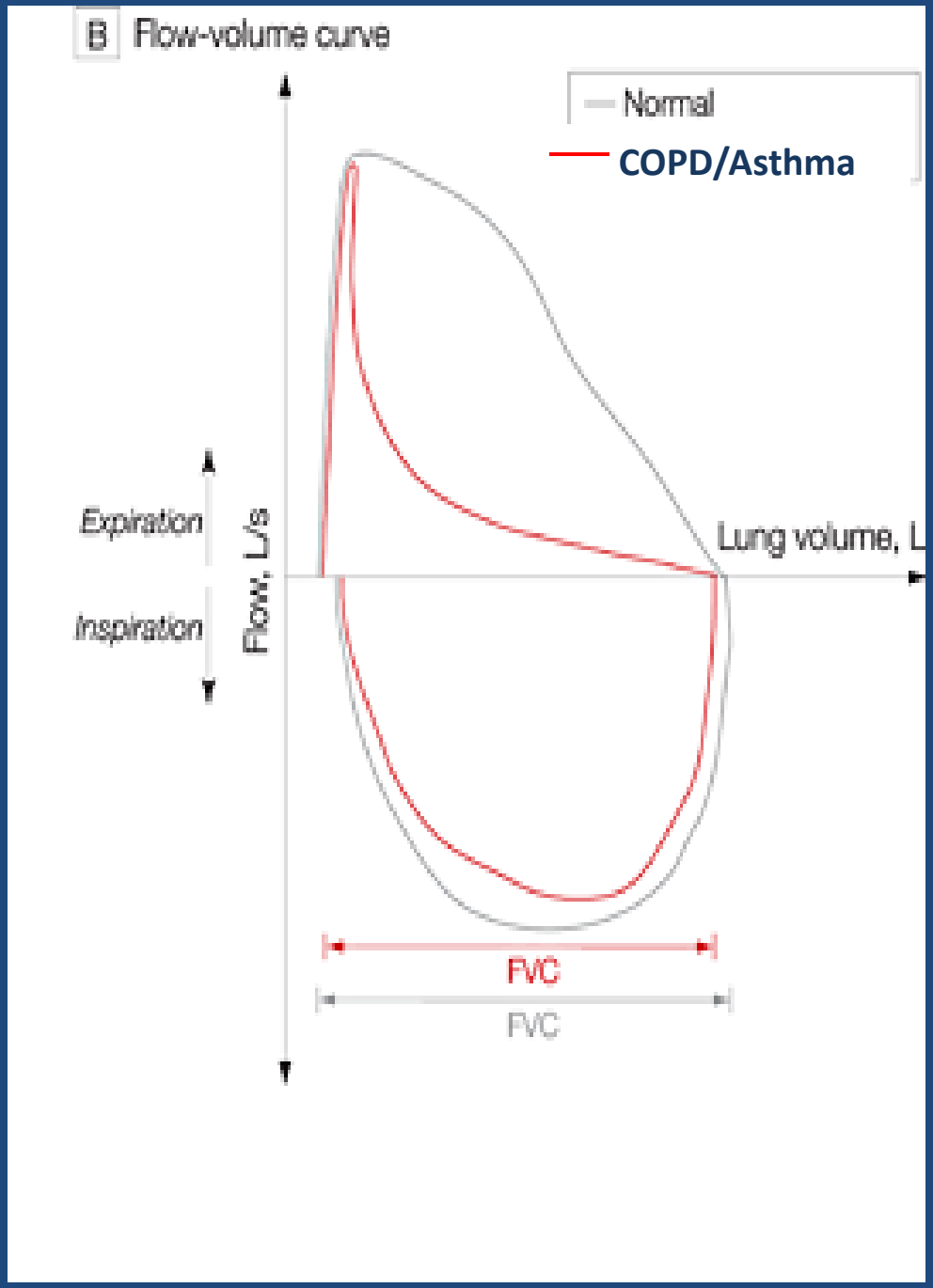
COPD

- 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

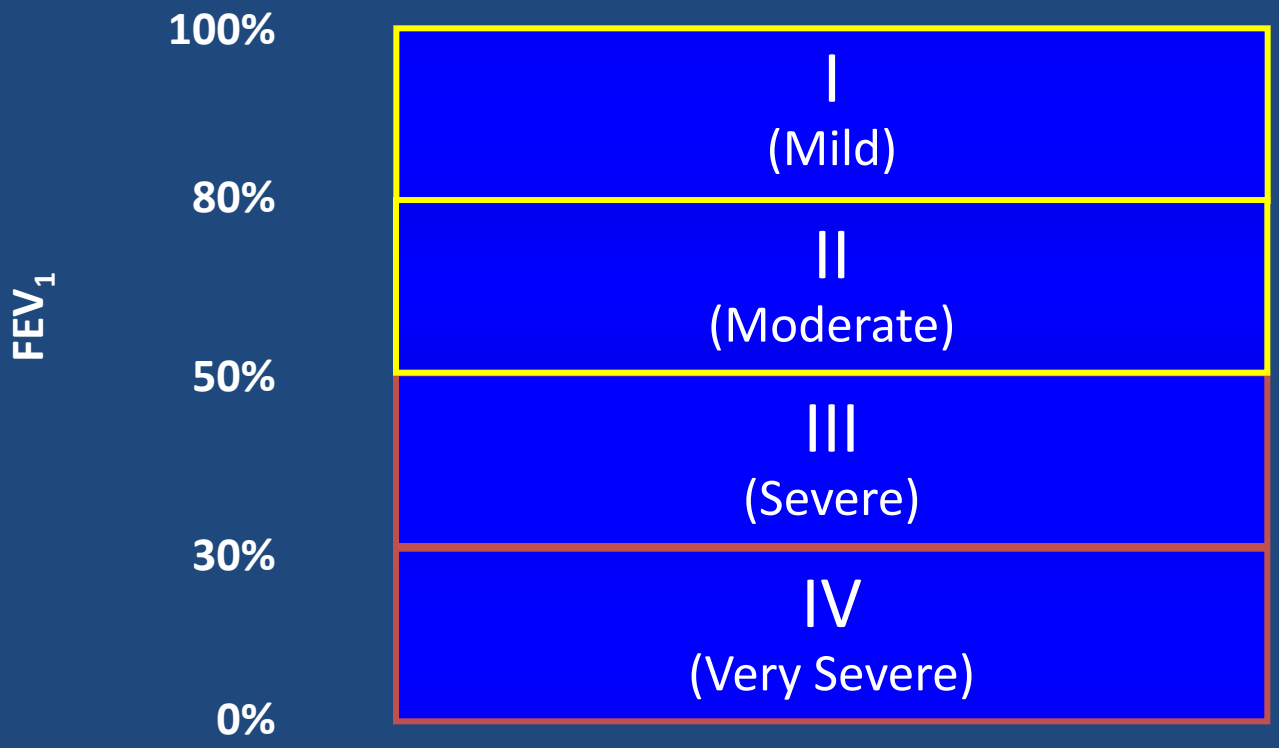

Spirometry measures how
fast and how much
air you breathe out



COPD/Asthma Pulmonary Function

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.

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.


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

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

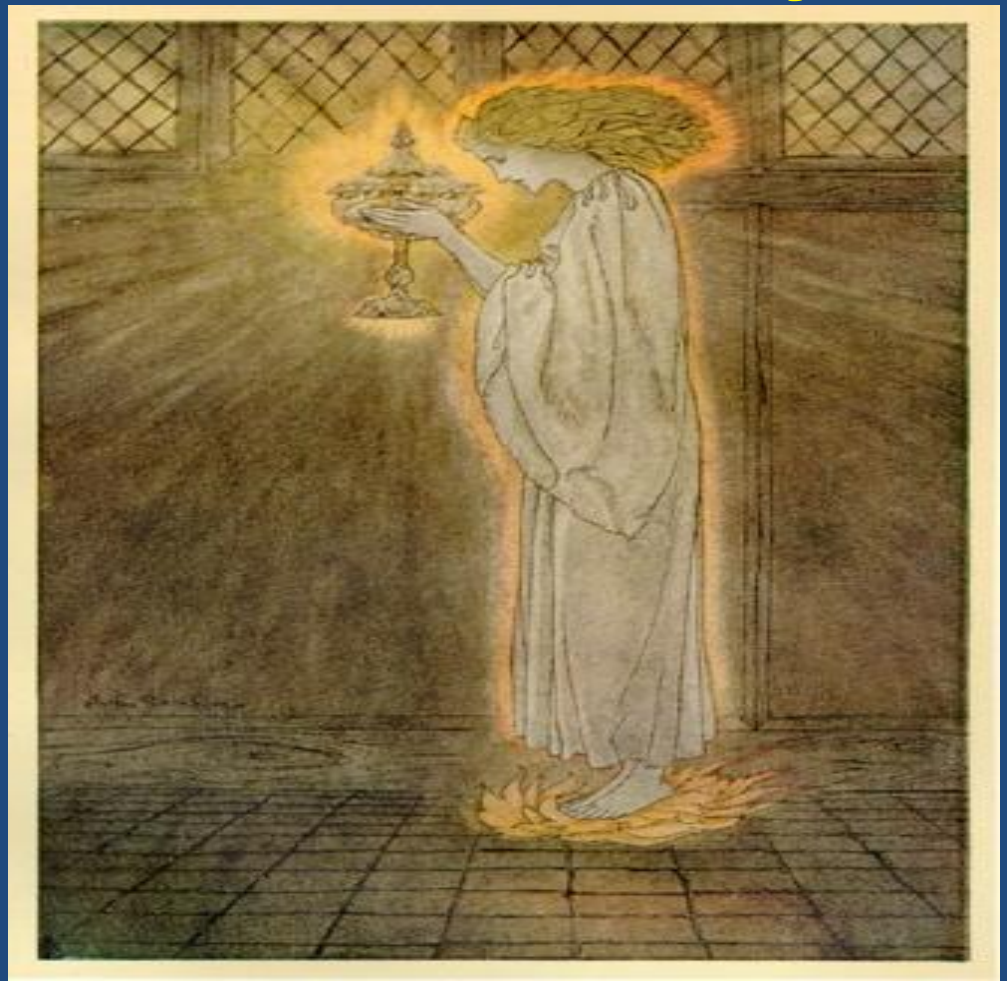
Pharmacotherapy: Glucocorticosteroid

- 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).

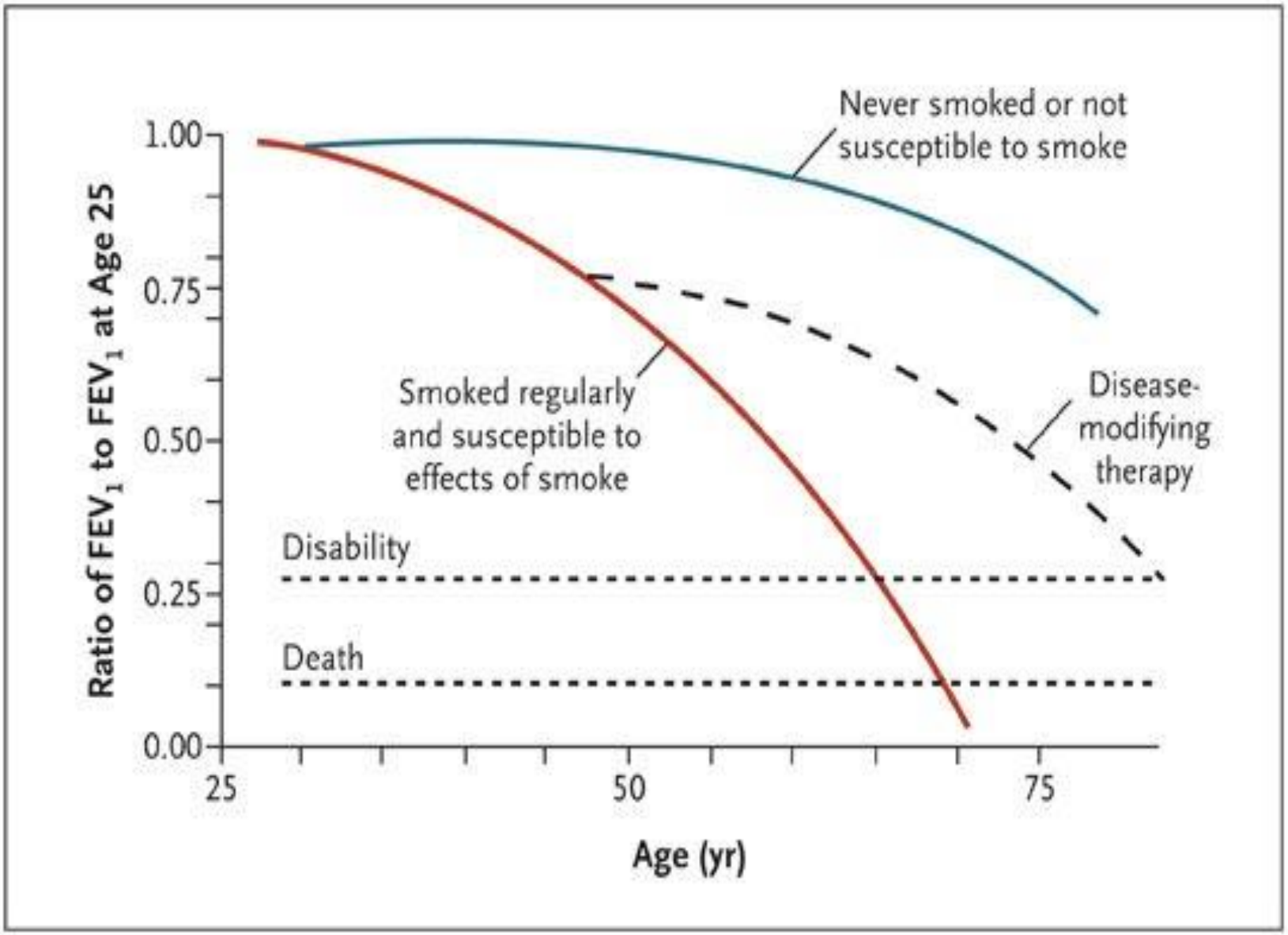
- An inhaled glucocorticosteroid combined with a long-acting ß$_2$-agonist is more effective than the individual components (Evidence A).

Management of COPD with bronchoactive medications:

In search of the Holy Grail



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



Holy Grail
COPD Pharmacotherapy

- **Mortality benefit**

- **Reduced decline in FEV1**

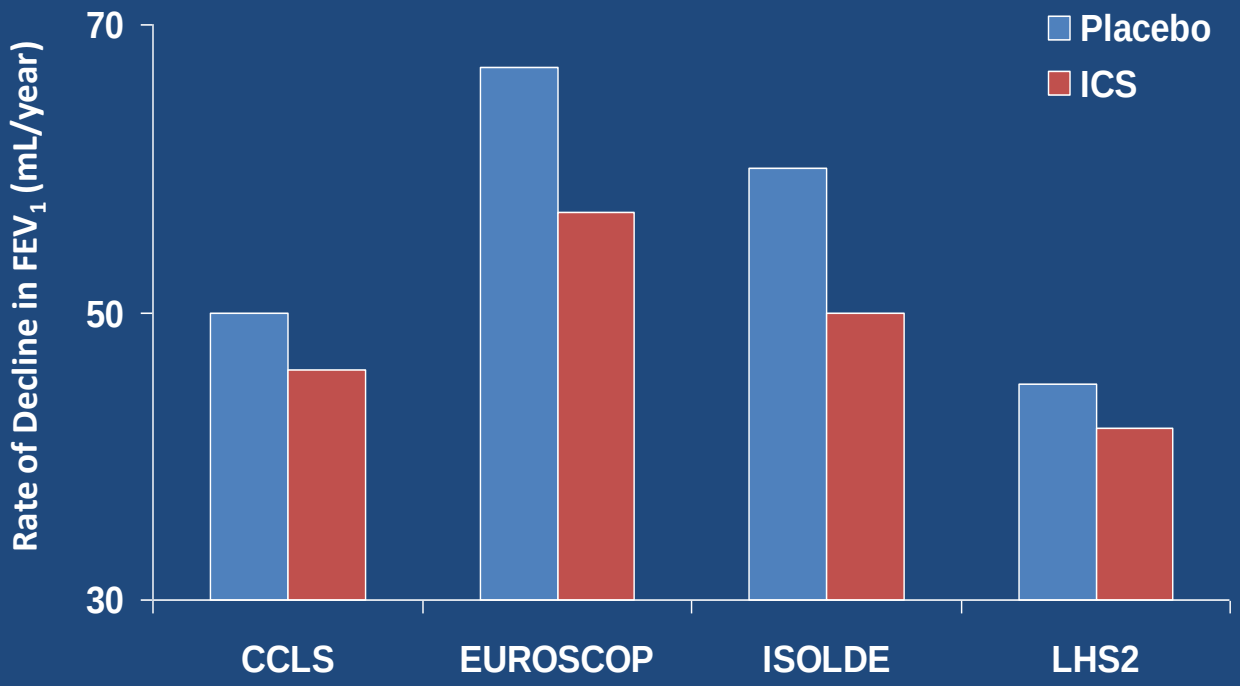
Holy Grail
Cigarette smoking cessation

- **Mortality benefit ***
- **Reduced decline in FEV1 #**

* Anthonisen: Annals Int Med 142:233, 2005

Anthonisen: JAMA 272: 1497, 1994

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.

Combination LA Beta agonist and aerosol steroids COPD

- Do they prolong life?

- Are they safe?

LA beta agonists and aerosol steroids in COPD

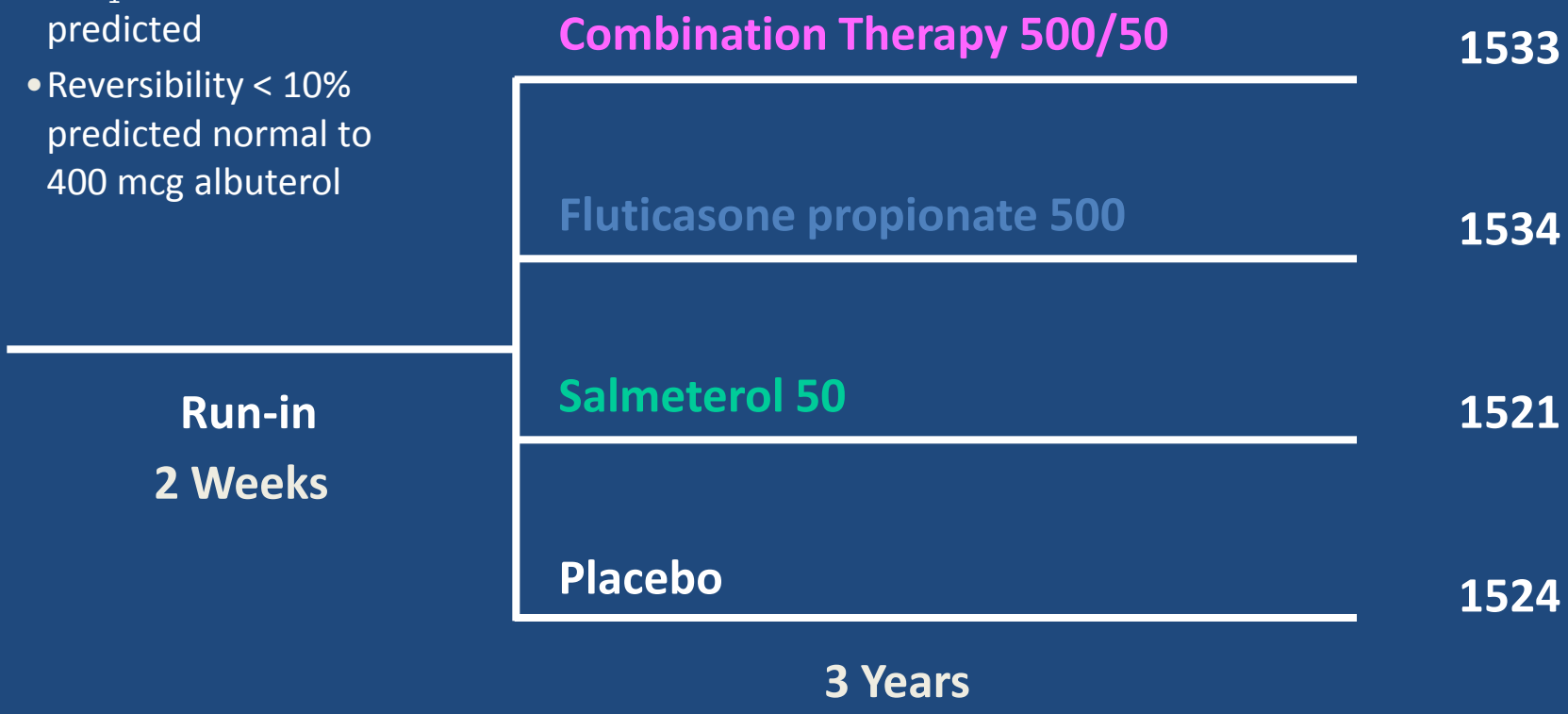
- **Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007 (TORCH)**
- **Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)**
- **Ernst: Inhaled corticosteroid use in COPD and the risk of hospitalization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

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

TORCH: Study Design

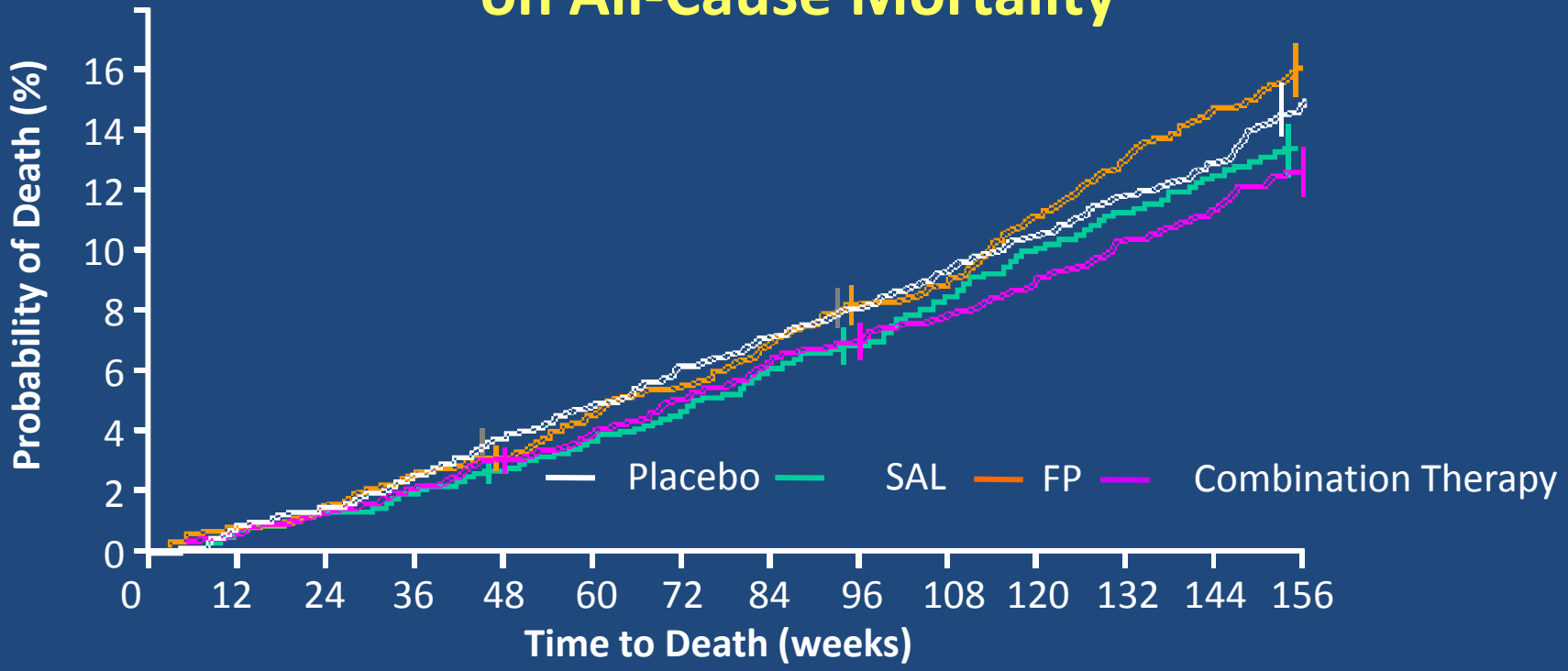
- Aged 40-80 years
- FEV_1 < 60% predicted
- Reversibility < 10% predicted normal to 400 mcg albuterol



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.

Effect of Combination Therapy on All-Cause Mortality



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

TORCH
Pneumonia

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

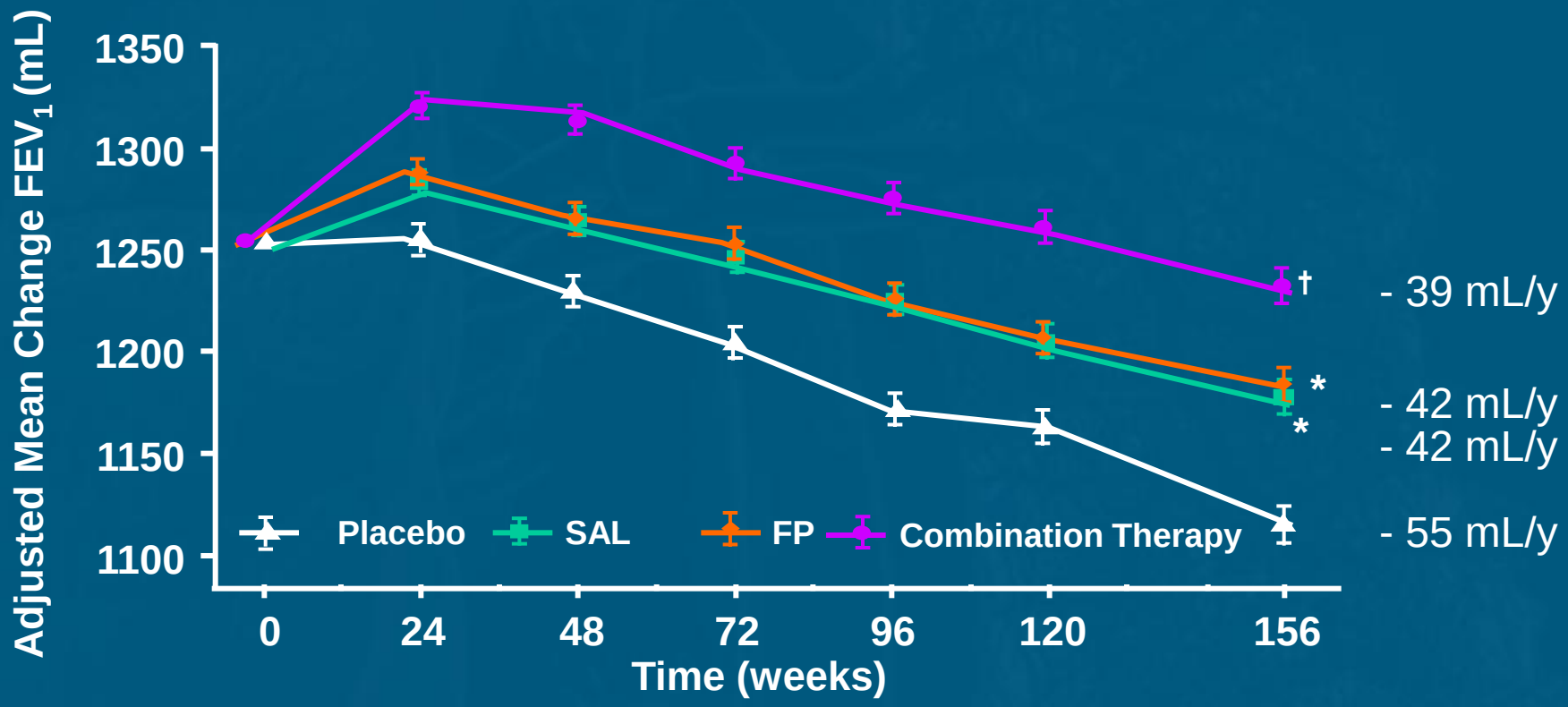
***P< 0.001**

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.

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

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

Summary
LA ICS/BA

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

Anticholinergic aerosols

COPD

Are they effective?

Are they safe?

Tiotropium

- M1 and M3 selective LA muscarinic antagonist
- Most widely prescribed agent in COPD
- Sales of $2.4 billion in 2007
- Side effects: dry mouth, urinary retention

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

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

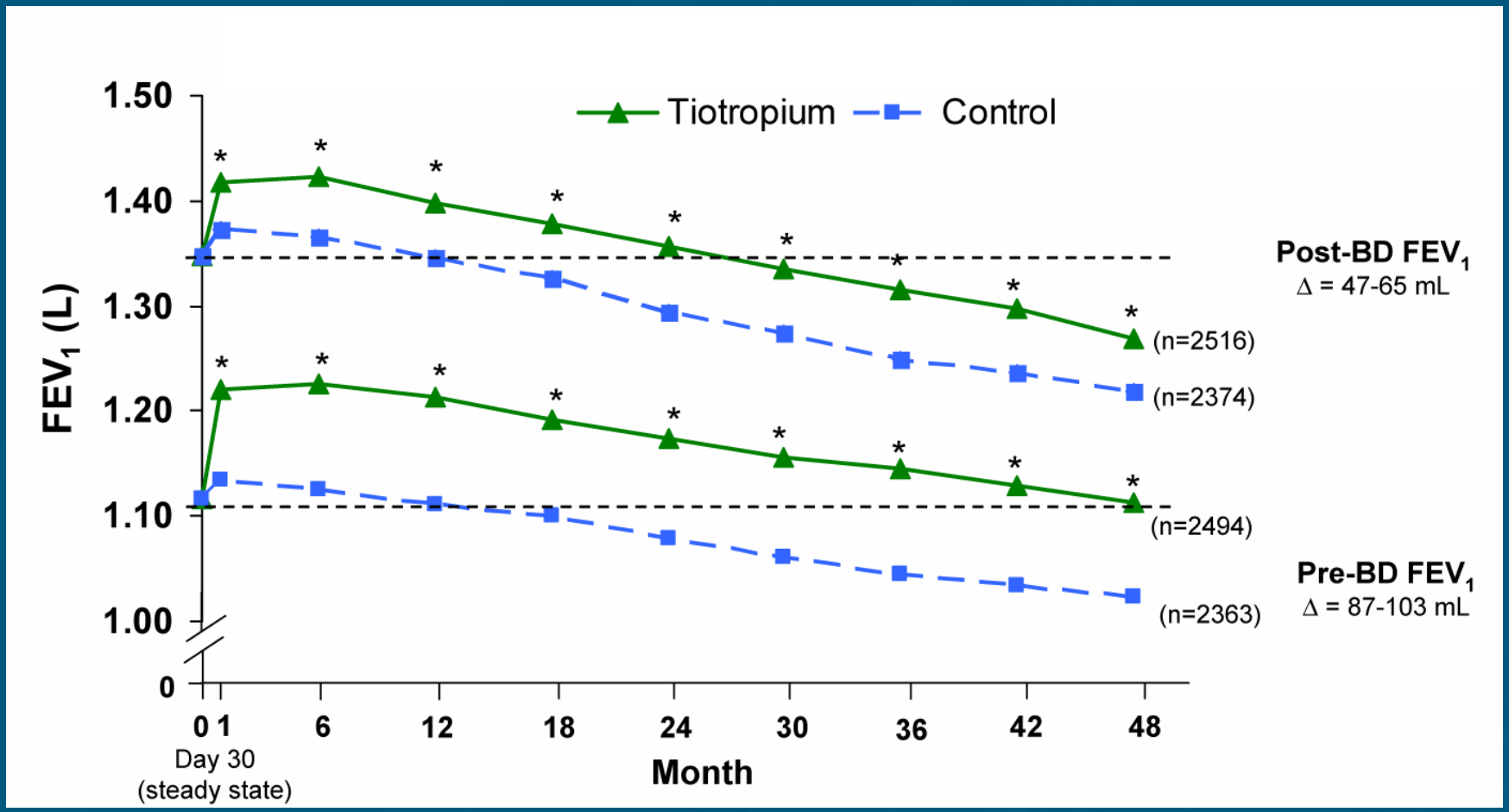
- R, DB, 4 years
- Tiotropium vs placebo
- Endpoints: 1-Rate decline FEV1; 2-SGRQ, exacerbations/COPD, mortality
- 5993 COPD patients; 40% dropout rate

UPLIFT 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.

UPLIFT: Lung Function (FEV_1) Over 4 Years

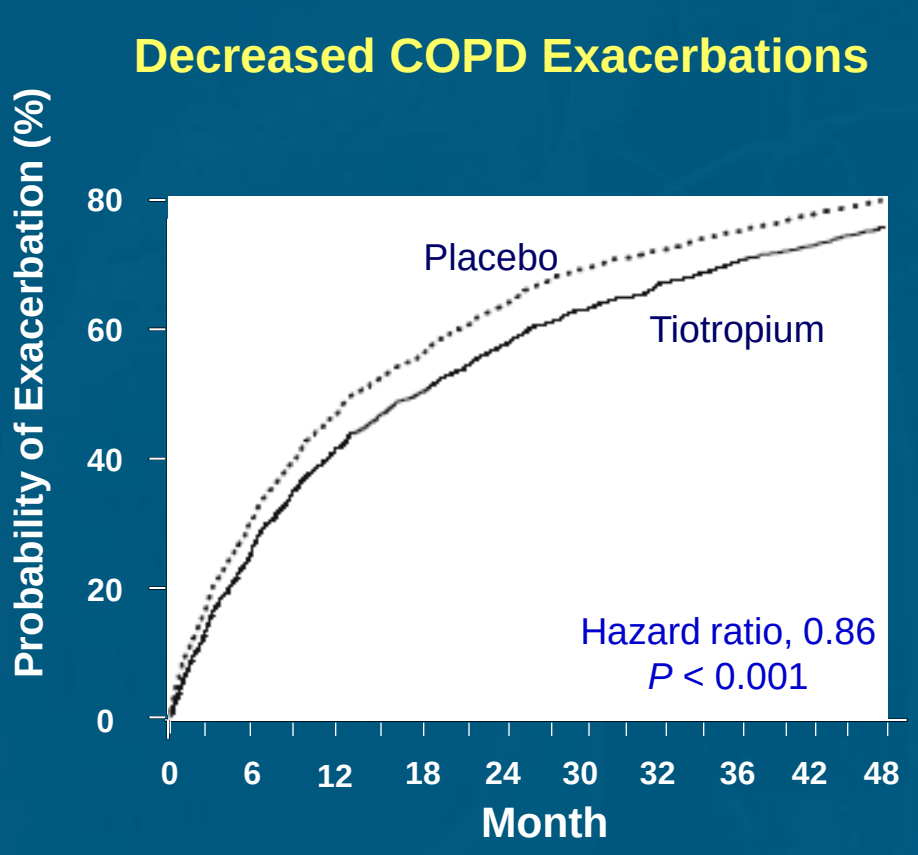


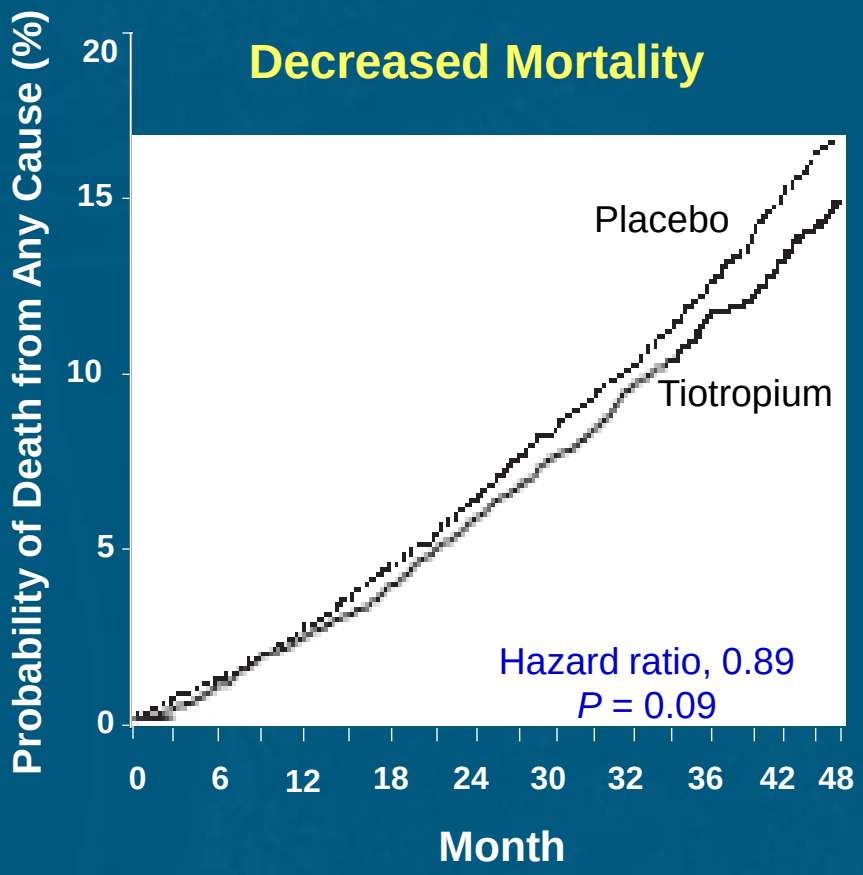
*$P < 0.0001$ vs. control

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





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

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.

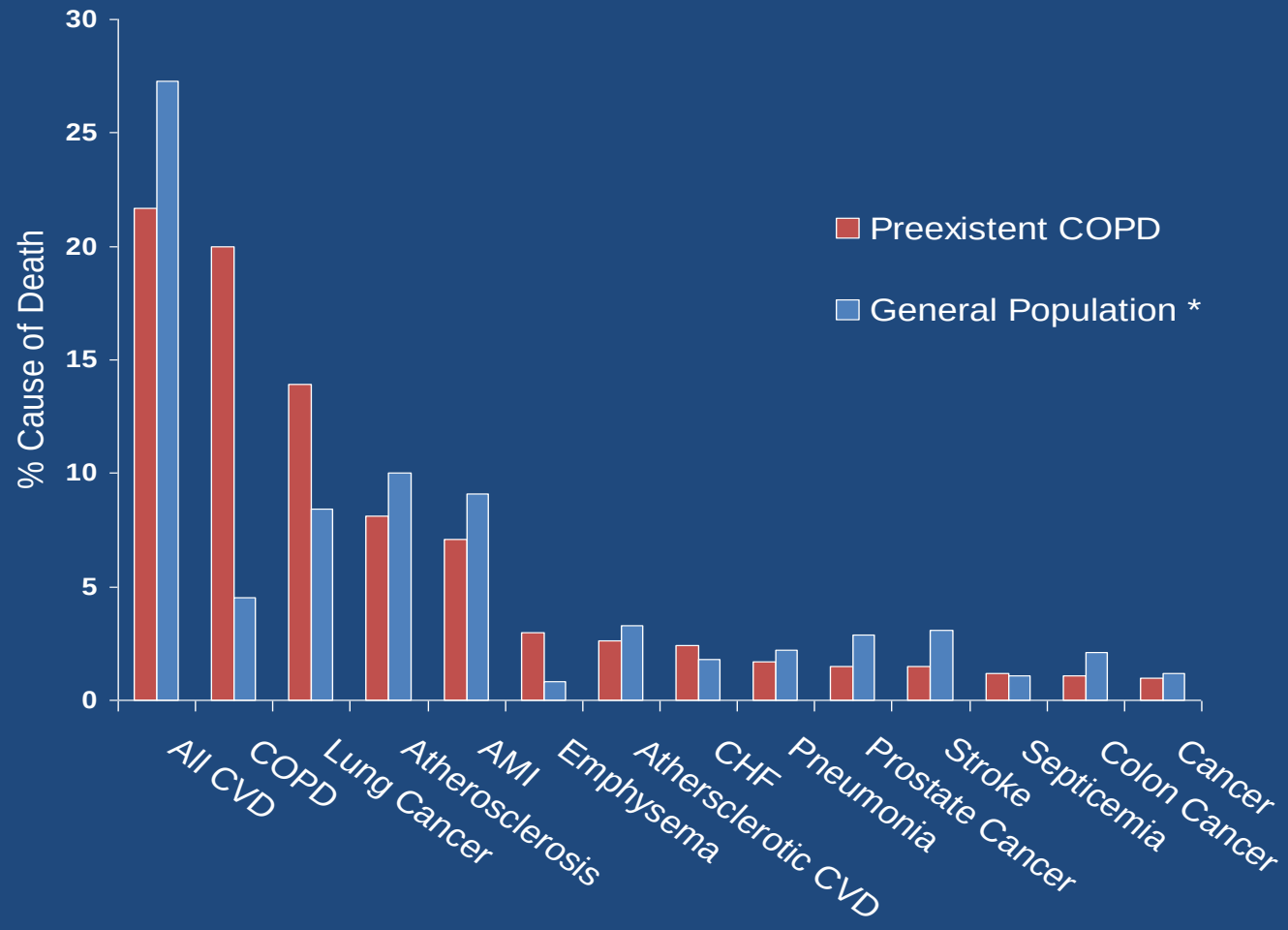
Singh:Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 300:1439, 2008

- 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

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

What Do COPD Patients Die From?

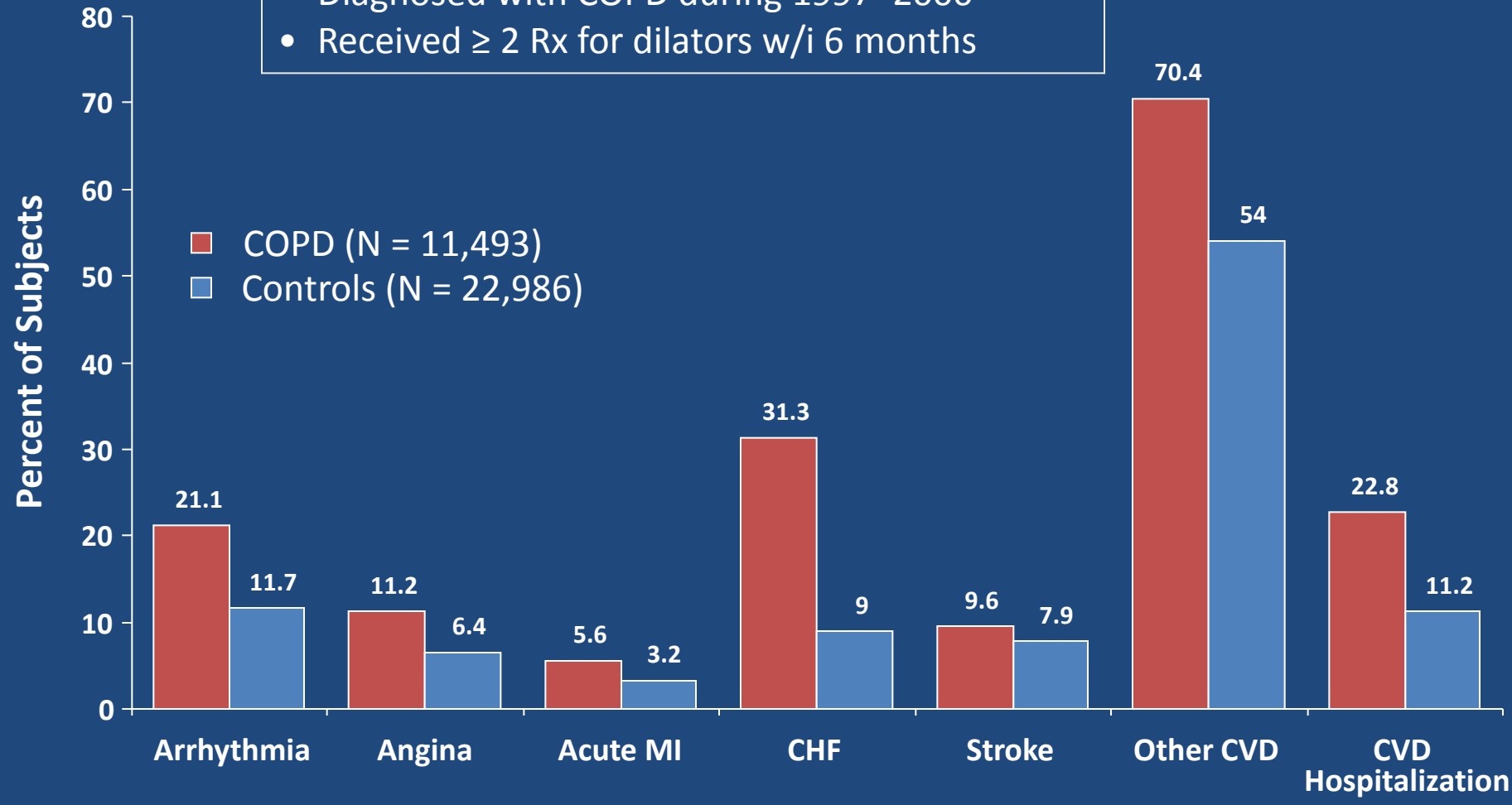


* General Population data from CDC for males ≥ 45y

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

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.

Cardiovascular Risks Anticholinergics Why?

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

Summary
LA AC

- Improve symptoms, improve QOL, reduce hospitalizations
- Do not retard decline in pulmonary function
- Open question whether contribute to CV events

Management of Exacerbations

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.

- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (Evidence B).

- Inhaled bronchodilators (beta$_2$-agonists and/or anticholinergics), theophylline, and systemic, preferably oral, glucocortico-steroids are effective for the treatment of COPD exacerbations (Evidence A).

Management of Exacerbations Cont'd

- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and/or fever) may benefit from antibiotic treatment (Evidence B**).**

- Noninvasive intermittent positive pressure ventilation (NIPPV) in exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (Evidence A).

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, CV events
- LA AC, FDA has not acted to remove or change product labeling, Nov, 2009