



# **Asthma and COPD: 2012**

**Jay Peters, M. D.**

**Pulmonary / Critical Care Medicine**

**University of Texas Health Science Center - San Antonio**

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[ps4h@uthscsa.edu](mailto:ps4h@uthscsa.edu)

# Trends of Asthma Morbidity/ Mortality

## ASTHMA

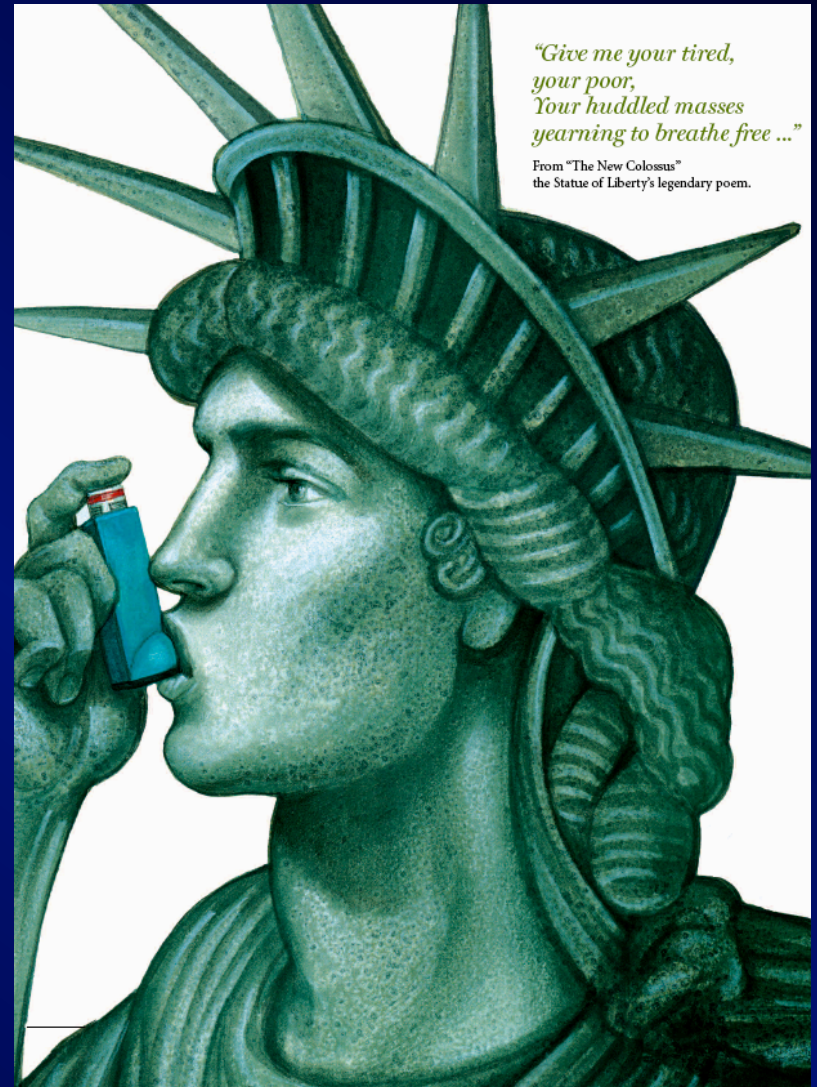
- 20 million asthma sufferers in US ~14 million are adult
- Lack of control is an enormous problem: healthcare costs = \$14 billion/yr
- 10.4 million unscheduled physician office visits
- 1.8 million ER visits
- 0.5 million hospitalizations
- **Asthma-related deaths > 10/day**

## Emphysema

- Prevalence > 2 million patients in the US Annual estimated health care costs \$1-5 billion
- Fourth leading cause of death (120,000 deaths in year 2000); expected to be third leading cause by year 2020.
- By 2020, number of women dying > men
- **Only disease among top 5 in which mortality is increasing**

# Why Are We Here?

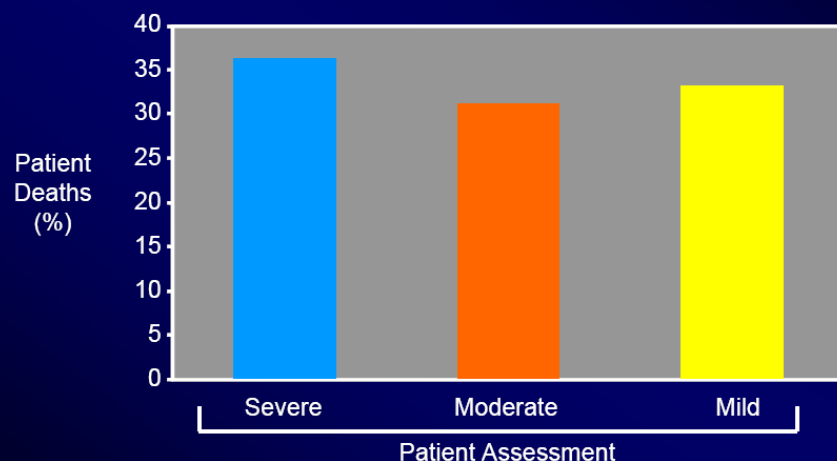
- JB 16 y.o. senior honors student
  - Captain high school soccer team
  - “Well controlled” asthma
  - 6 days with nocturnal cough/used MDI 3-4 times/night
- School bus traveling to regional playoffs
- Severe asthma attack while traveling on farm-market road
- Died prior to arrival at local hospital



# Why did this 16 year old girl die?

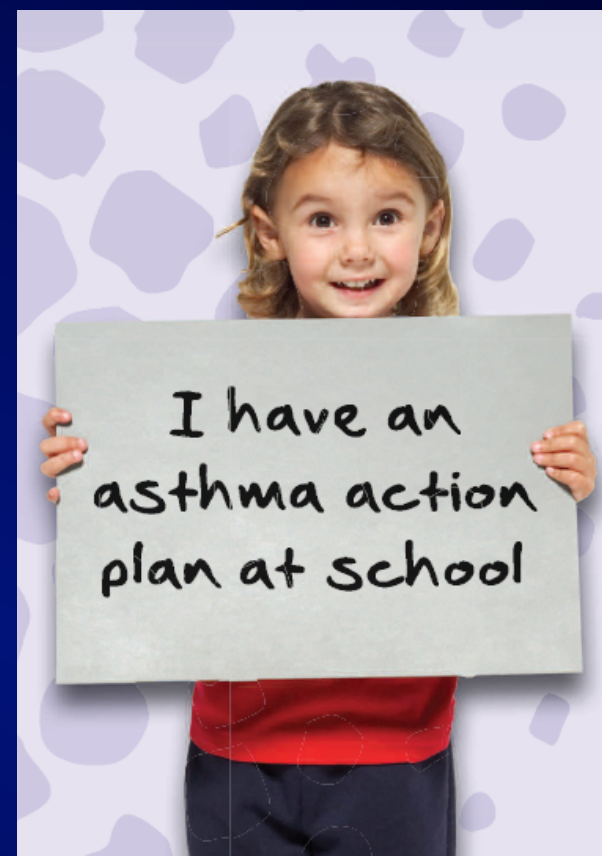
- She was on the “wrong side of the information gap”: just like 7/10 asthmatics

## Pediatric Asthma Deaths: Mild Patients Are Also at Risk



Findings from a cohort study reviewing all pediatric asthma-related deaths (n=51) in the Australian state of Victoria from 1986 to 1989.

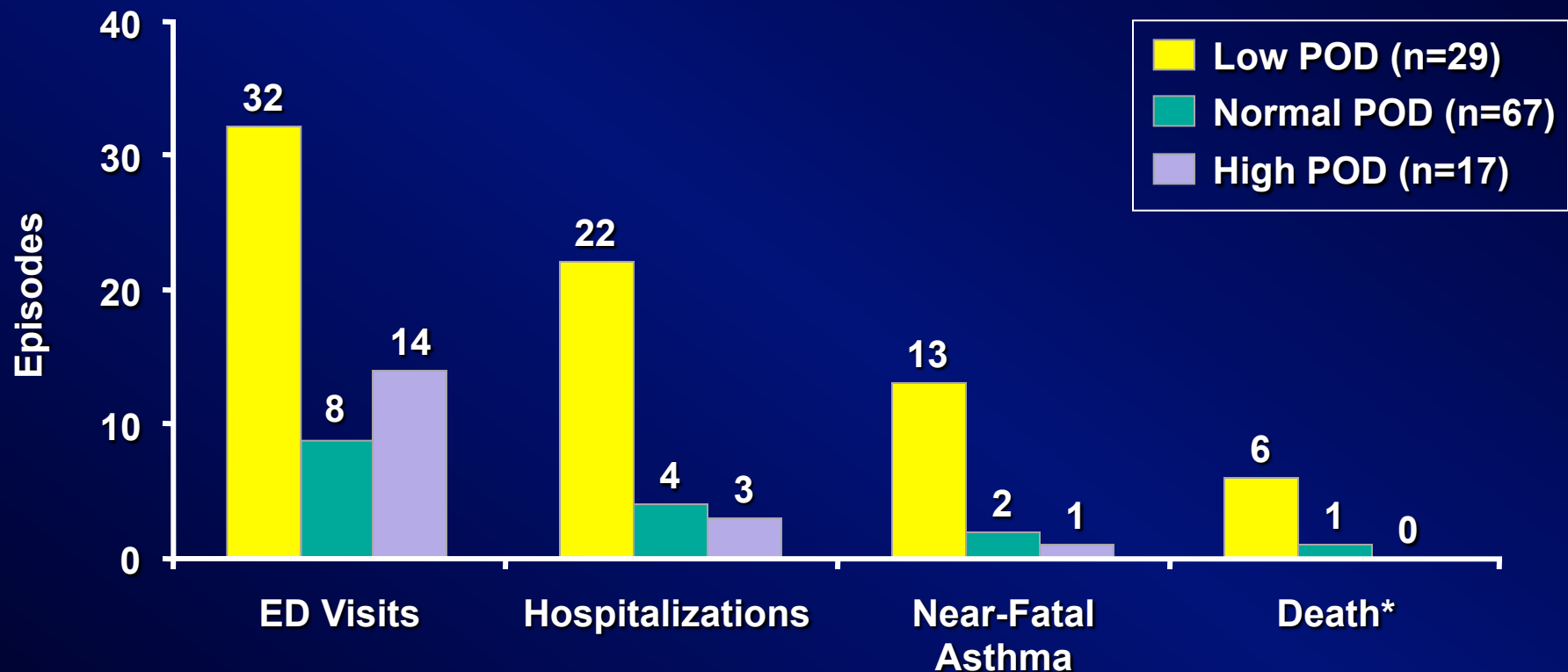
Robertson et al. *Pediatr Pulmonol.* 1992;13:95-100.





She was probably an "underperciever"

# Poor Perception of Dyspnea (POD)



\*Of deaths in the low POD group, 4 were asthma related, 2 were unknown.

Multiple studies now that show underpercievers with life-threatening asthma may have a 20% mortality from asthma

# ASTHMA 2012

- What have we learned ?
- What are the controversies ?

# Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school, or at home?

Score

All of the time **1**

Most of the time **2**

Some of the time **3**

A little of the time **4**

None of the time **5**

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day **1**

Once a day **2**

3 to 6 times a week **3**

Once or twice a week **4**

Not at all **5**

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?

4 or more nights a week **1**

2 or 3 nights a week **2**

Once a week **3**

Once or twice **4**

Not at all **5**

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day **1**

1 or 2 times per day **2**

2 or 3 times per week **3**

Once a week or less **4**

Not at all **5**

5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all **1**

Poorly controlled **2**

Somewhat controlled **3**

Well controlled **4**

Completely controlled **5**

Well controlled  $\geq 20$ ; 16-19 not well controlled,  $\leq 15$  very poorly controlled  
Available at: <http://www.asthmacontrol.com>.

Patient Total Score

- **ACT < 20 best predictor of asthma exacerbation**



# ***ENO* Measurement: ATS Guidelines**

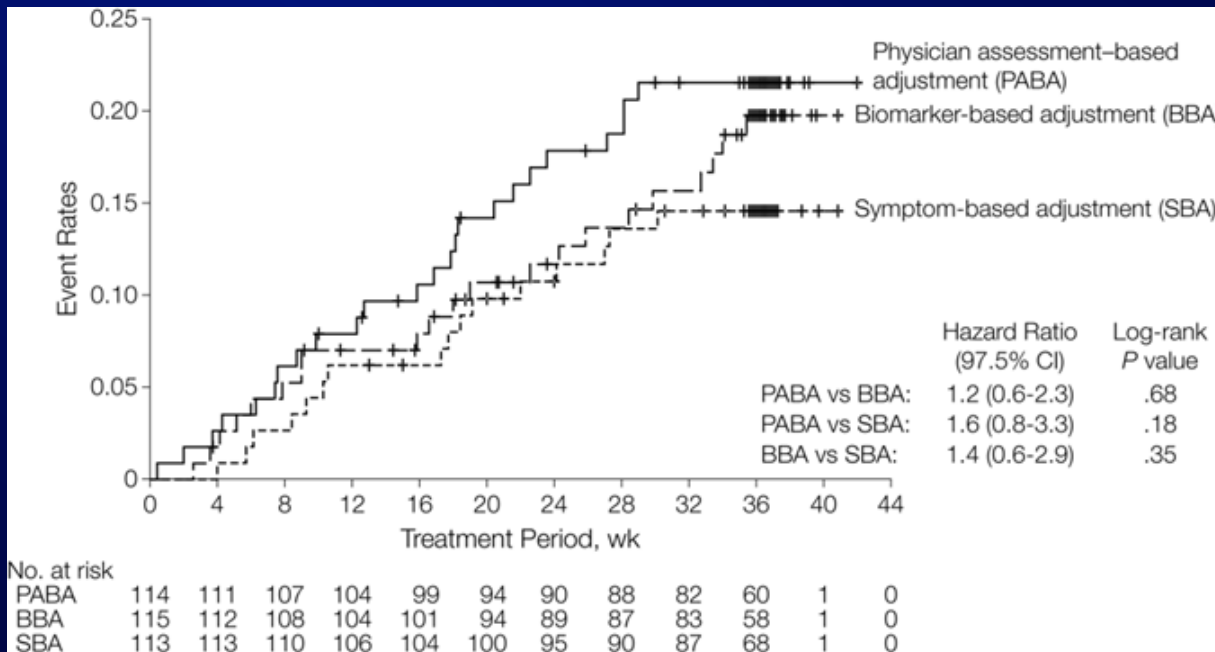
- **< 25 ppb ( 20 ppb in children) - eosinophilic inflammation and responsiveness to corticosteroids are less likely**
- **> 50 ppb (> 35 ppb in children) eosinophilic inflammation and responsiveness to corticosteroids is more likely**
- **25-50 ppb (20–35 ppb in children) gray zone and must use clinical judgment**

**Q: Does it help us clinically?**

# ASTHMA 2012

- **Who needs daily therapy ?**
- **How do we maximize therapy in severe asthma ?**

# Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma: The BASALT Randomized Controlled Trial



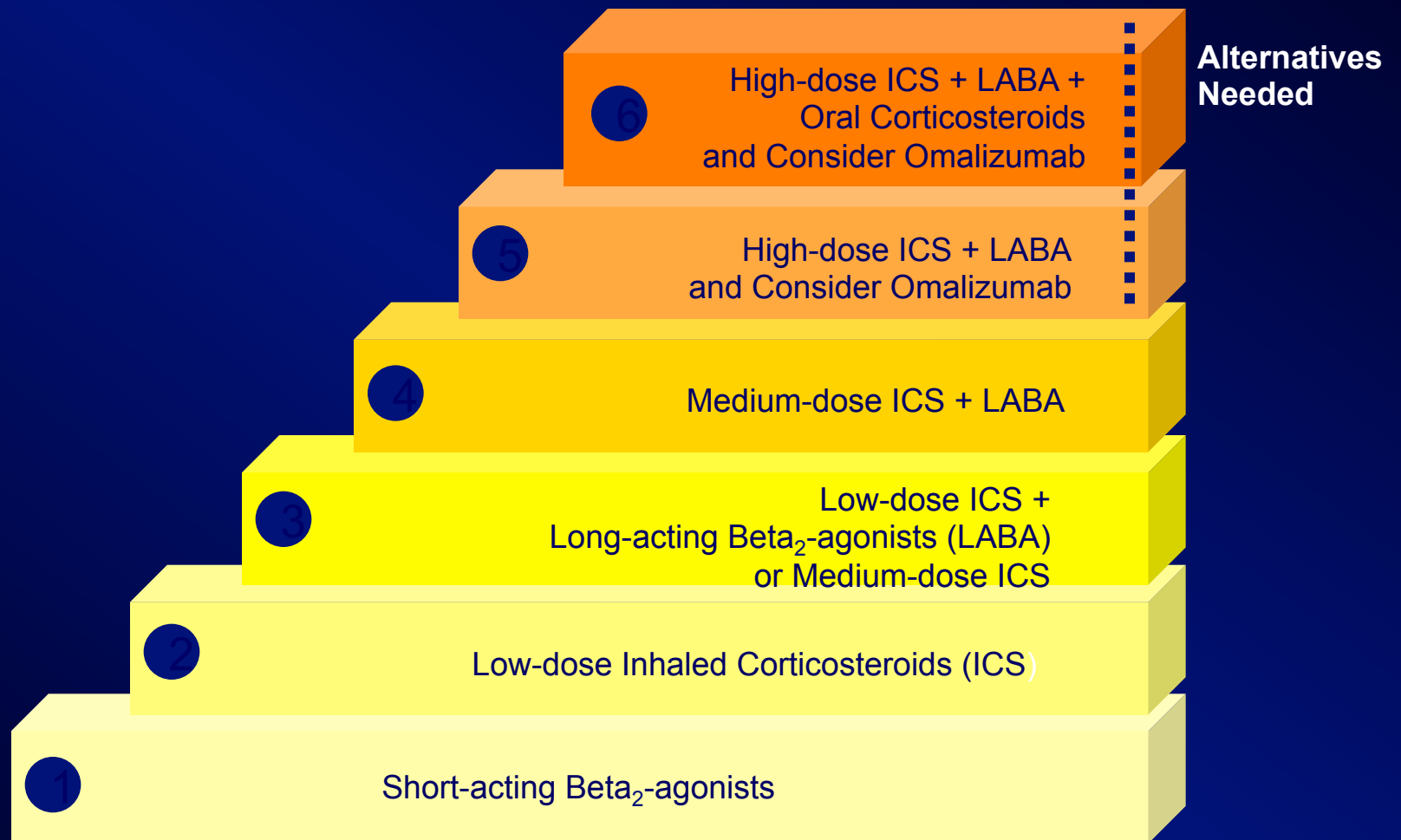
Mild to moderate asthma:  
 Duration – 36 weeks  
 N = 115/group  
 All on low dose ICS

- End point – time to asthma worsening
  - Continuous steroids vs. intermittent ICS/SABA: no difference
  - Physician based adjustment vs. exhaled nitric oxide: no difference
- Failure rate: 15% symptom based adjustment (patient decision)  
 22% physician based; 20% biomarker based

# Critique of BASALT Study

- Study design
  - To determine superiority; not equivalence
  - Primary endpoint: AM peak expiratory flow rate
  - Not powered to assess differences in exacerbations
  - Drop out rate 21% (patients failing to comply with q6 wk. evaluation)
- Conclusions:
  - ICS/SABA may be effective in subgroups of asthmatics
  - Frequent assessment of biomarkers (FeNO) not supported
  - Ethnic differences noted (Hispanics – better with MD adjustments)
  - Strategy not appropriate for underperceivers

# A Treatment Option for Severe Asthmatics



Adapted from National Asthma Education and Prevention Program (NAEPP) Guidelines. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, NIH Publication No. 07-4051, Revised August 2007.

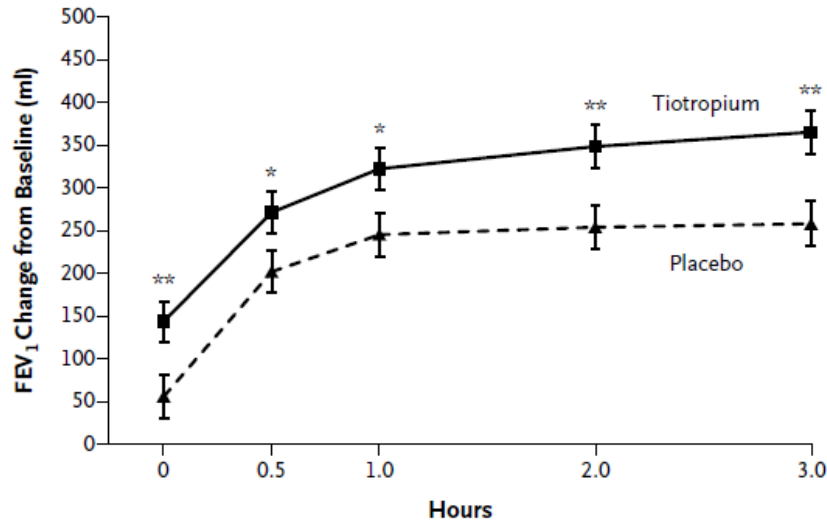


# Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

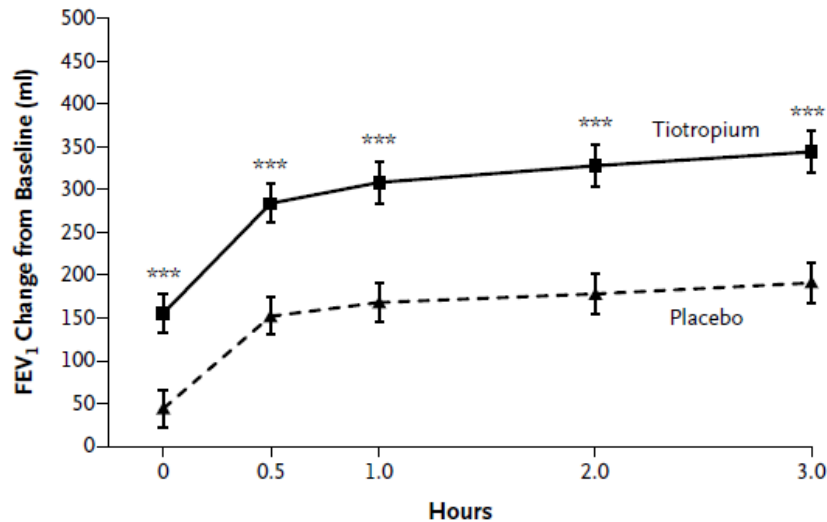
- 2 RCTs with 912 subjects
  - All on ICS/LABA combination
  - $FEV_1 < 80\%$
  - At least 1 "severe exacerbation" in prior year
- Clinical question: Would they benefit from LAMA?
- Study design:
  - Randomized to Tiotropium 5  $\mu\text{g}$  "soft-mist inhaler"
  - Endpoints:
    - Time to first exacerbation
    - Peak/trough  $FEV_1$

# Results: ICS/LABA +/- Tiotropium

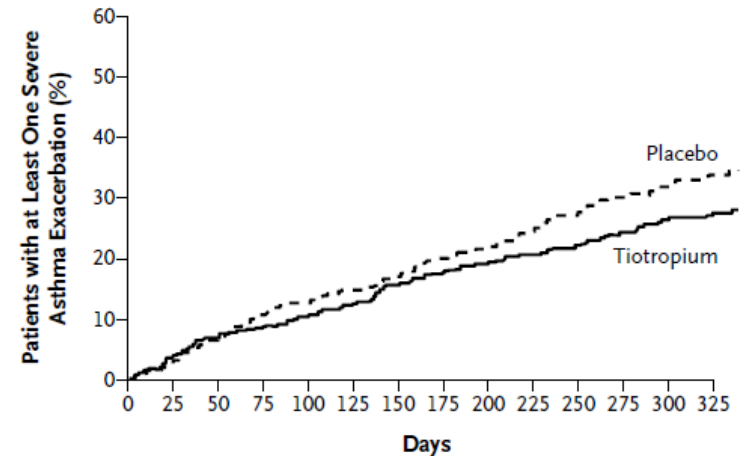
**A** FEV<sub>1</sub> Change in Trial 1



**B** FEV<sub>1</sub> Change in Trial 2



**C** Severe Exacerbation



No. at Risk

Placebo	454	435	412	338	379	367	356	339	332	319	303	290	282	272
Tiotropium	453	430	409	401	389	378	363	353	348	339	331	319	308	298

- Increased time to "severe" exacerbation from 226 to 282 days
- Overall 21% reduction in risk of "severe" exacerbation
- Mean change in FEV<sub>1</sub> = 86 ml in trial 1; 154 ml in trial 2

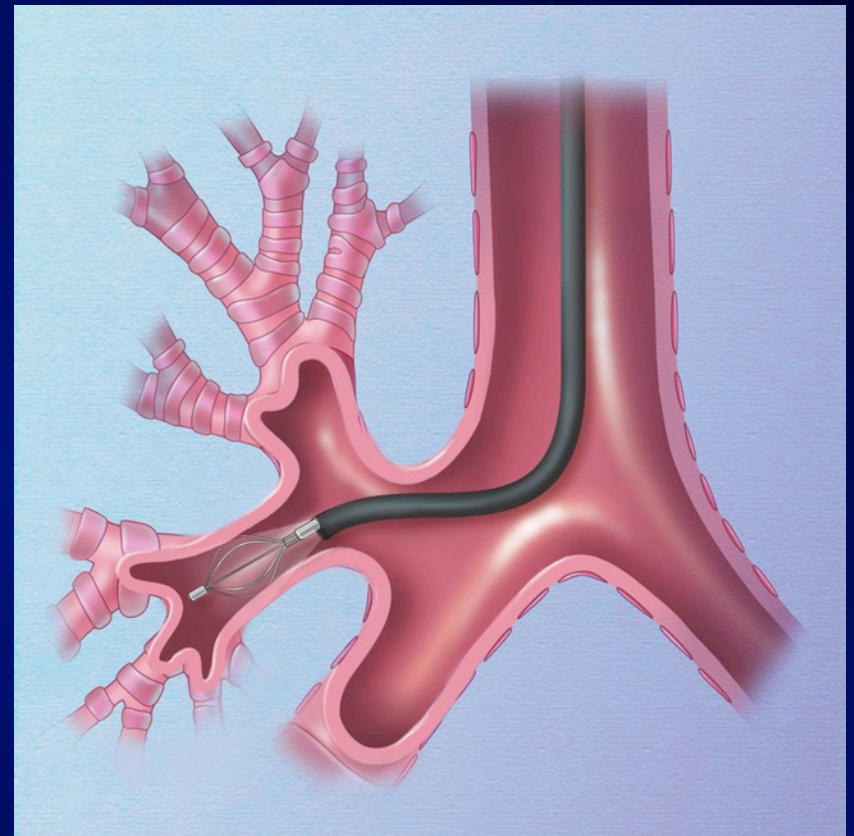
**Seems like a very positive study !**

# Critique of Study

- Generalizability: subjects moderately severe (FEV<sub>1</sub> 55-61% at baseline) but very responsive to SABA (over 200 ml)
- Definition of "severe exacerbation" = need to double ICS for at least 3 days
- Secondary endpoints
  - No difference in symptom free days
  - No difference in Asthma QoL score
  - NNT to prevent one episode = 34
- **Conclusion: may be of benefit to some asthmatics with frequent exacerbations if cost not an issue**

# Bronchial Thermoplasty: Treatment Method

- Shown to be "effective" in mild-moderate asthma
  - All visible and accessible airways (3-10mm) distal to mainstem bronchi are treated
  - Series of contiguous activations
  - 3 treatment sessions
- AIR 2: RCT/sham controlled study in subjects with severe asthma (n= 288)



Treatment = radiofrequency ablation of smooth muscle in the airway

# **Bronchial Thermoplasty: AIR 2 study Clinical Outcomes Summary at 1-Year\***

- **Improved asthma-related quality of life compared to control (AQLQ score)**
- **Improved clinical outcomes compared to control:**
  - **32% decrease in severe exacerbations**
  - **84% reduction in ER visits for respiratory symptoms**
  - **73% reduction in hospitalization for respiratory symptoms**
  - **66% less days lost from work, school and other daily activities due to asthma**
- **No unanticipated device-related adverse events**



# AIR 2: Data at 12 months

	Baseline		12 Month		Posterior Probability of Superiority
	BT (n = 190)	Sham (n = 98)	BT (n = 190)	Sham (n = 98)	
Primary effectiveness endpoint					
AQLQ	4.30 ± 1.17	4.32 ± 1.21	5.66 ± 1.06*	5.48 ± 1.15*	
Change from baseline	—	—	1.35 ± 1.10	1.16 ± 1.23	0.960
AQLQ responder analysis					
Percent of subjects with AQLQ change ≥0.5	—	—	78.9%	64.3%	0.996
Secondary effectiveness endpoints					
AQLQ symptoms domain	4.38 ± 1.20	4.39 ± 1.29	5.64 ± 1.04*	5.49 ± 1.11*	0.863
AQLQ activity limitations domain	4.54 ± 1.18	4.53 ± 1.21	5.79 ± 1.08*	5.60 ± 1.21*	0.900
AQLQ emotional functions domain	3.89 ± 1.51	3.99 ± 1.71	5.59 ± 1.28*	5.38 ± 1.48*	0.950
AQLQ environmental stimuli domain	3.94 ± 1.52	3.95 ± 1.64	5.41 ± 1.33*	5.24 ± 1.42*	0.856
ACQ	2.13 ± 0.87	2.09 ± 0.90	1.31 ± 0.94	1.32 ± 0.91	
Change from baseline	—	—	-0.82 ± 0.95	-0.77 ± 1.08	0.638
FEV <sub>1</sub> Pre-BD, % predicted	77.8 ± 15.65	79.7 ± 15.14	76.6 ± 17.74	79.1 ± 15.98	0.241
FEV <sub>1</sub> Post-BD, % predicted	86.1 ± 15.76	87.4 ± 13.18	83.4 ± 16.36	85.2 ± 14.13	0.371
amPEF (L/min)	383.8 ± 104.32	386.3 ± 112.59	411.6 ± 110.45	408.7 ± 117.56	0.806
Total symptom score <sup>†</sup>	3.8 ± 2.34	3.9 ± 2.53	2.1 ± 2.22	2.3 ± 2.17	0.637
Percent symptom-free days <sup>‡</sup>	16.4 ± 24.04	16.8 ± 23.10	40.8 ± 38.22	37.9 ± 36.95	0.776
Rescue medication use (puffs/7 days)	13.4 ± 19.17	11.8 ± 11.24	7.4 ± 15.01	7.5 ± 12.60	0.813
% Days rescue medication used	52.1 ± 36.48	51.8 ± 35.41	28.0 ± 36.09	29.8 ± 34.96	0.680
Severe exacerbations <sup>§</sup> (exacerbations/subject/year)			0.48 ± 0.067	0.70 ± 0.122	0.955
Days lost from work/school/other activities due to asthma			1.315 ± 0.361	3.915 ± 1.553	0.993

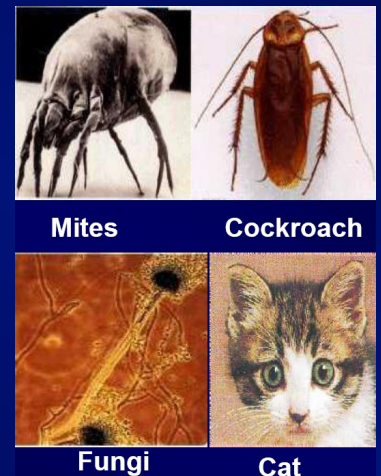
- Difference in AQLQ: Rx vs. Sham = 0.19 (N.S.)
- No difference in:
  - FEV<sub>1</sub> or PEF<sub>R</sub>
  - Rescue medication; symptom free days

# Conclusions: AIR 2 study

- Compared to sham control, thermoplasty reduced:
  - "Severe" exacerbations & E.D. visits
  - Missed days of school/work
- Bronchial thermoplasty is costly and resulted in hospitalization rate of 8.4% during protocol
- Hospitalizations were usually 1-2 days
- Bronchial thermoplasty
  - Approved by the FDA for severe asthma (age  $\geq$  18 yrs old)
  - May improve outcomes in subject failing optimal Rx
  - Unclear which asthma phenotype will benefit

# Update in Asthma 2012

- **What reduces exacerbations of asthma**
- Environmental tobacco smoke (ETS) = strongest predictor of respiratory illness in children
  - **Ban on ETS** in Scotland decreased asthma hospitalization by 18.2%
- Exercise can reduce bronchospasm
  - 3 months of **aerobic exercise training** significantly improved asthma QOL and asthma free days (p=0.001)
- Medication compliance: Is QD really better than BID ?
  - Indacaterol – once a day LABA
  - Ciclesonide – once a day high potency ICS
- **MOST IMPORTANT: Allergen Avoidance**  
**Most forgotten component in asthma education by MD**



# COPD 2012

- What have we learned about COPD?

# Basics of Treating COPD: 2012

- **Initiation of long-acting bronchodilator**
  - Canadian guidelines suggest cost-effective to start with either LABA (salmeterol/formoterol) or LAMA (tiotropium/acclidinium)
    - Less exacerbations & better quality of life
    - Much better compliance
- **Inhaled Corticosteroids: Risk vs. Benefit**
  - Risk: Increase risk of pneumonia with RR= 1.6
  - Benefit: FEV<sub>1</sub> < 50 % or "asthma/atopic" features with eosinophils, frequent exacerbations, or positive BD test
- **Home oxygen**
  - Saturation ≤ 88% ( or ≤ 89% with Cor Pulmonale)
  - Must wear oxygen 16 hours/day for survival benefit



# GOLD Guidelines 2012: Assess Symptoms

## Global Strategy for Diagnosis, Management and Prevention of COPD Modified MRC (mMRC) Questionnaire

- MRC: easy;  $\geq$  grade 2**
- **More aggressive Rx**
  - **Problem: only assesses dyspnea**

PLEASE TICK IN THE BOX THAT APPLIES TO YOU  
(ONE BOX ONLY)

mMRC Grade 0. I only get breathless with strenuous exercise.	<input type="checkbox"/>
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	<input type="checkbox"/>
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	<input type="checkbox"/>
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	<input type="checkbox"/>
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	<input type="checkbox"/>

- COPD Assessment Test (CAT):** 8-item measure of health status impairment in COPD
- Assesses dyspnea, cough, sputum production
  - Correlates well with SGRQ (St. George Respiratory Questionnaire)

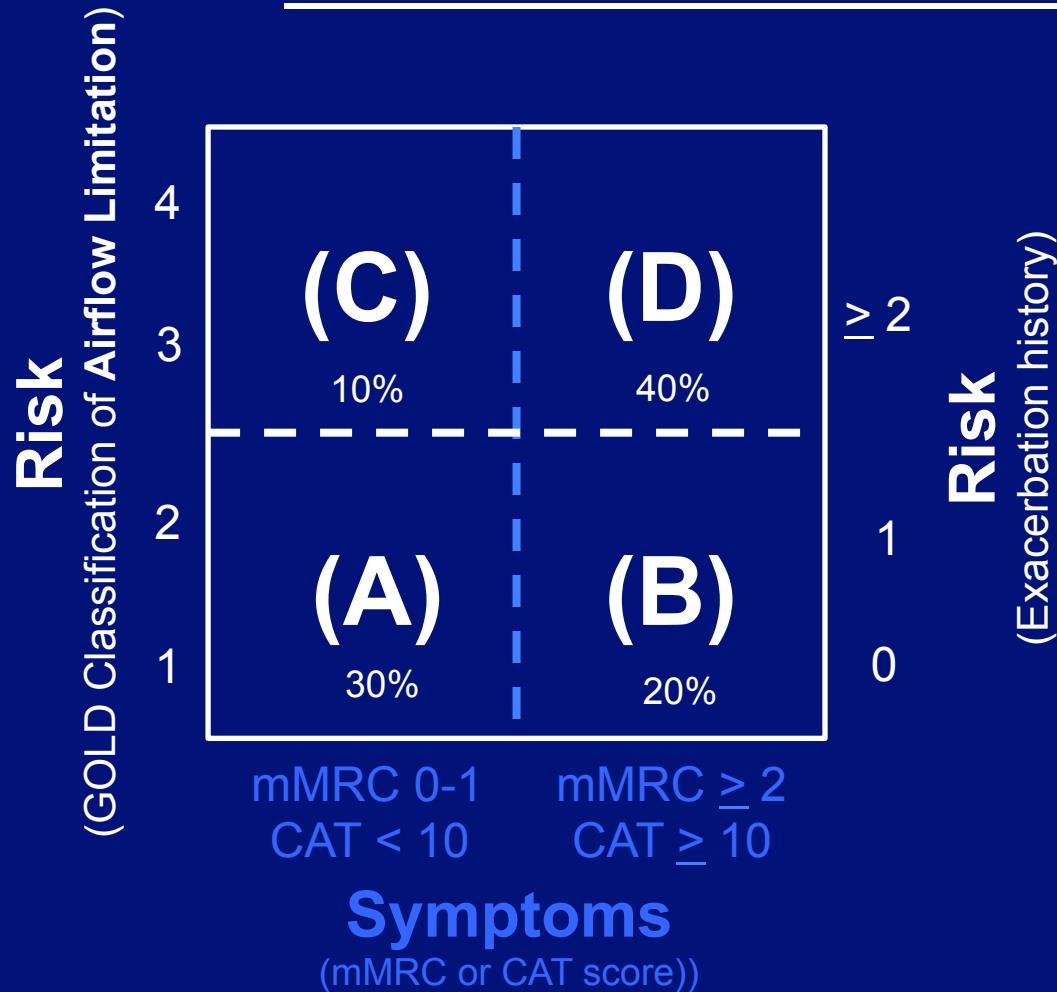
<http://catestonline.org>



# Global Strategy for Diagnosis, Management and Prevention of COPD

## Combined Assessment of COPD

### Assess risk of exacerbations next



$FEV_1 \geq 50\%$  and only  
0 or 1 exacerbations per year:  
Low Risk (A or B)

$FEV_1 < 50\%$  or two or  
more exacerbations per year:  
High Risk (C or D)



# Global Strategy for Diagnosis, Management and Prevention of COPD

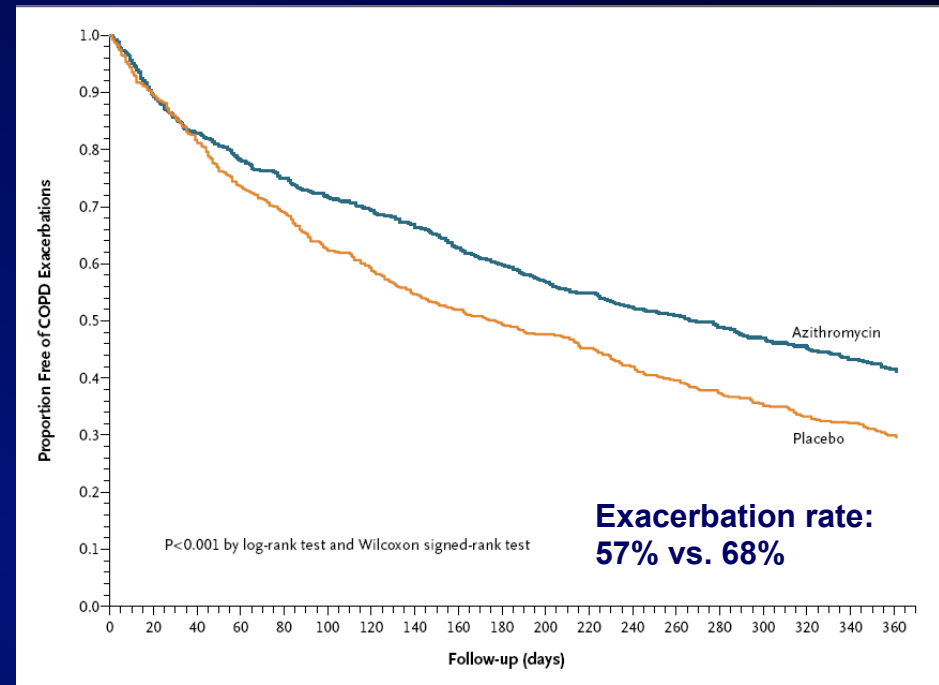
## Manage Stable COPD: Pharmacologic Therapy

*(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)*

Patient	First choice	Second choice	Alternative Choices
A	SAMA prn <i>or</i> SABA prn	LAMA <i>or</i> LABA <i>or</i> SABA and SAMA	Theophylline
B	LAMA <i>or</i> LABA	LAMA and LABA	SABA <i>and/or</i> SAMA Theophylline
C	ICS + LABA <i>or</i> LAMA	LAMA and LABA	PDE4-inh. SABA <i>and/or</i> SAMA Theophylline
D	ICS + LABA <i>or</i> LAMA	ICS and LAMA <i>or</i> ICS + LABA and LAMA <i>or</i> ICS+LABA and PDE4-inh. <i>or</i> LAMA and LABA <i>or</i> LAMA and PDE4-inh.	Carbocysteine SABA <i>and/or</i> SAMA Theophylline

# Controversy: Role of Azithromycin in COPD

- **Azithromycin for Prevention of Exacerbations of COPD**
  - RCT for 1 year (n = 1142)
  - Moderate-severe COPD
  - Azithro 250 mg QD
- **Results**
  - Time to exacerbation: 266 vs 174 days\*
  - SGRQ reduced 2.8 vs. 0.6
  - Exacerbations 1.48 vs 1.83/pt .yr.\* (\*p < 0.01)
- **Follow-up NEJM: Recommended *all* COPD patients with > 1 exacerbation be placed on Azithro**
- **Today: Azithro 250mg 3x/week very common “add-on” therapy**



N Engl J Med 2011;365:689-98

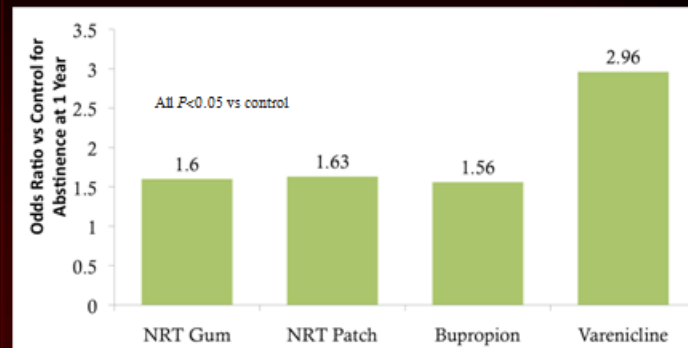
## Critique of Article:

- All patients – nl QT, nl hearing
- Greater hearing deficit
- Increase bacterial resistance noted
- Stage 4 COPD (LABA/ACS/LAMA) no benefit

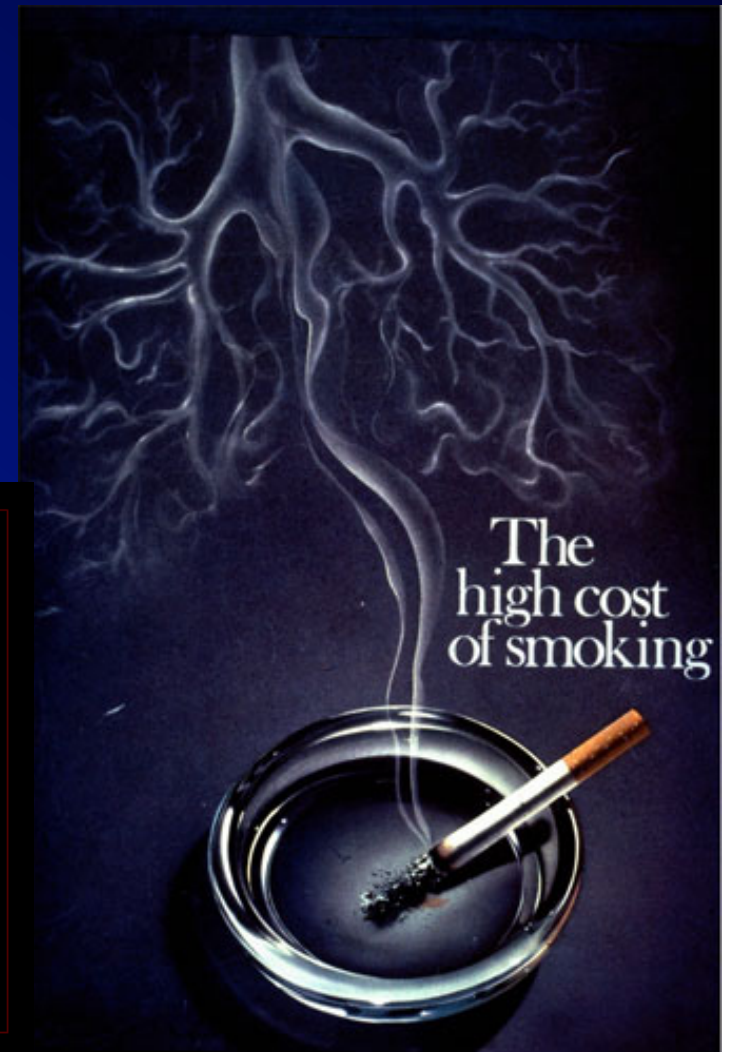
# The Key to Treating COPD: Smoking Cessation

- **Smoking cessation (Lung Health Study)**
  - Reduced all cause mortality (MI/  
Cancer)
  - Only therapy proven to prevent ↓  
FEV<sub>1</sub>
  - Average smoker quits 5 times prior  
to success

Pharmacotherapy for Smoking Cessation



NRT = Nicotine Replacement Therapy, Wu F, et al. *BMC Public Health*. 2006; 6:300-315.

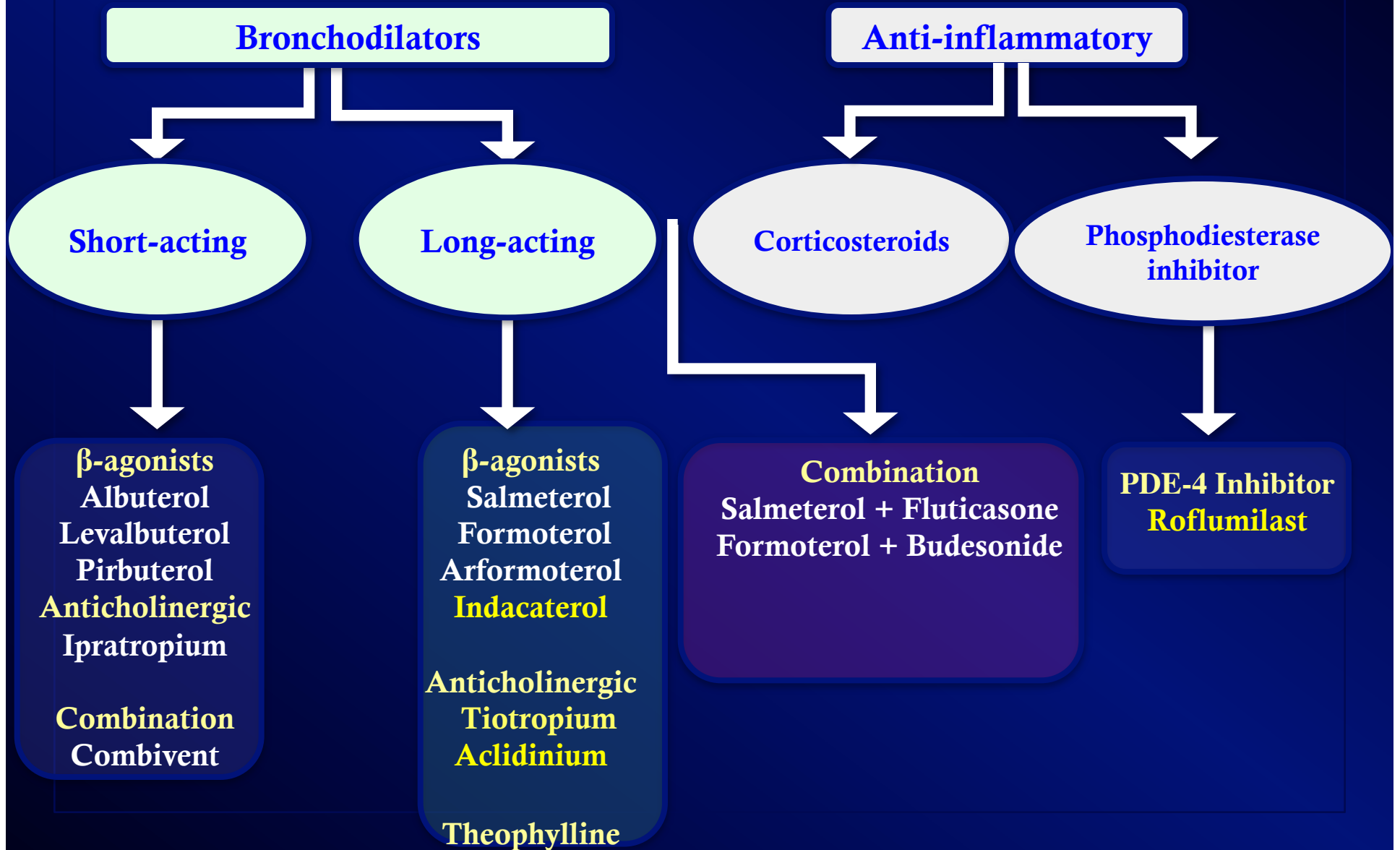




# Questions?

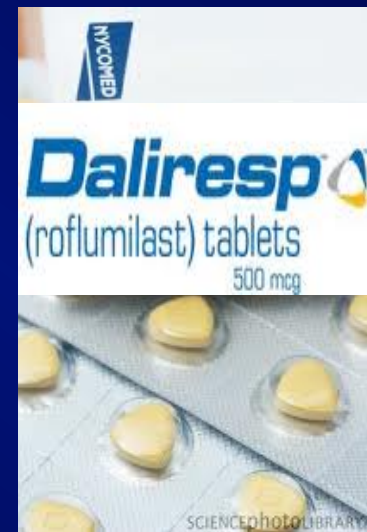


# GOLD Pharmacologic Treatment Options



# Roflumilast: PDE4- inhibitor

- Selection of patients who will benefit:
  - Severe COPD with chronic bronchitis
  - On LABA/ICS and LAMA
  - Exacerbation requiring steroids/hospitalization
- Mechanism of action: anti-inflammatory medication
- Benefits: reduced exacerbations
- Side effects:
  - Nausea/diarrhea (10 – 20%)
  - Weight loss (7.5%)
  - Anxiety/depression (6%)



500 mg 1x/day