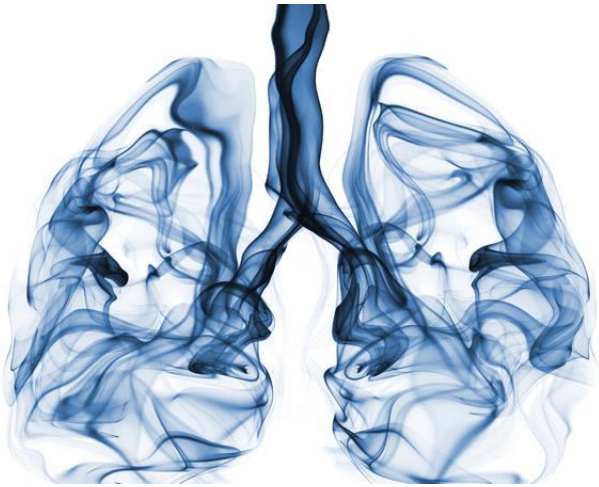
4 "Practice Changers" in Pulmonary Medicine for 2016



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Faculty Disclosures

- ***Grant Support:***
  - Roche
  - Actelion
  - Ikaria
  - United Therapeutics
  - Gilead
  - Bayer
  - GeNO
  - Novartis
  - Chesi

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  - Actelion
  - United Therapeutics
  - Gilead
  - Bayer
  - GeNO
  - Novartis

- ***DSMB:***
  - Gilead

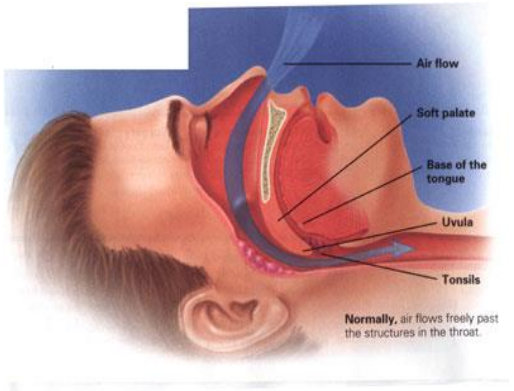
The 4 “Practice Changers”

- Suggest a novel treatment for patients with sleep apnea intolerant to PAP therapy
- Order lung cancer screening CT for appropriate patients
- Re-evaluate COPD documentation and treatment
- Consider PCV13 immunization for pneumococcal disease

Suggest a novel treatment for patients with sleep apnea intolerant to PAP therapy.

Obstructive Sleep Apnea Hypopnea Syndrome Pathophysiology

- Repetitive airway obstruction or collapse occurring during SLEEP
- To break an apnea the brain briefly "wakes up" causing sleep fragmentation
- During the apnea there is hypoxia, hypercapnia, and a rise in blood pressure:
  - *Severity of derangement depends on length of apnea and oxygen stores in lung at onset of apnea*
- By convention defined by apnea hypopnea index (AHI)≥5 with symptoms



Source: Atlanta Institute for ENT

Classification of Obstructive Sleep Apnea Based on Severity of Apnea-Hypopnea Index

- Apnea-Hypopnea Index (AHI) events/hour
  - Mild 5-15 events per hour
  - Moderate 15-30 events per hour
  - Severe > 30 events per hour

American Academy of Sleep Medicine, Sleep 22:667, 1999

Epidemiology

- Prevalence estimates from studies of mainly white men and women with BMI=25-28 demonstrate:
  - 1 in 5 adults has at least mild sleep apnea
  - 1 in 15 has at least moderate sleep apnea
  - 18 million people in US
- AHI≥5 and daytime hypersomnolence in 2% women and 4% men (Young et al. NEJM, 1993)
- Prevalence of non-sleepy patients with OSA likely higher

Sleep Apnea Risk Factors at Presentation

Non-Modifiable

- Age
- Sex
- Race/Ethnicity
- Genetics
- Marfan's, Down's and Pierre Robin syndromes

Modifiable

- Obesity (BMI$\geq$30 kg/m^2)
- Neuromuscular Disorders
- Craniofacial Abnormalities
- Endocrine Disorders
- Hormonal

Epworth Sleepiness Scale

Situation	Score
Sitting and Reading	
Watching TV	
Sitting inactive in a public place	
Passenger in a car	
Lying down to rest in afternoon	
Sitting, talking to someone	
Sitting after lunch without alcohol	
In a car, topped for minutes in traffic	
Total	Normal < 10

Likeliness of Dozing: 0 – Never, 1 – Slight Chance, 2- Moderate Chance
3 – High Chance

Johns M, *Sleep* 41(6): 540-545, 1991.

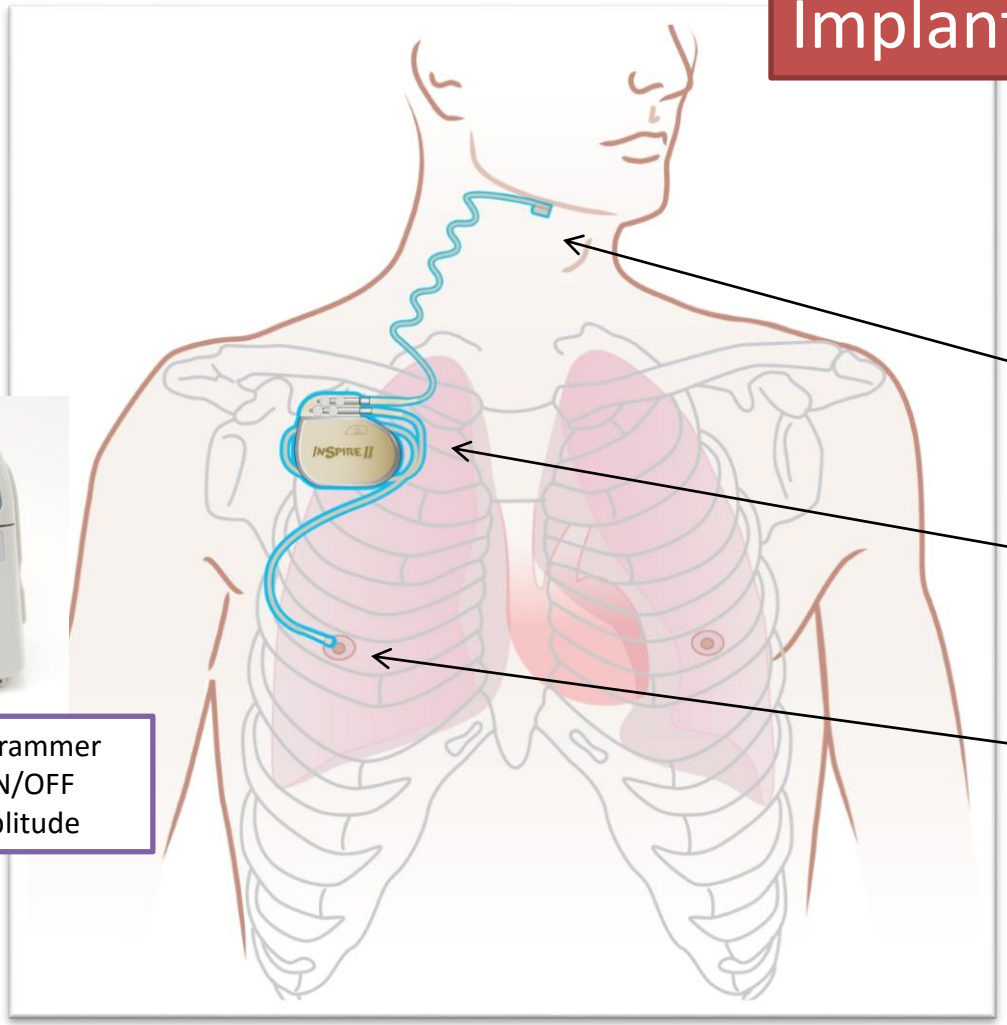
Consequences of Untreated Sleep Apnea

- Hypersomnolence
  - Decreased job performance
  - Inattentiveness and Accidents
- Memory Problems
- Personality Changes
- Systemic Manifestations
  - Metabolic
    - Weight Gain
    - Insulin Resistance
  - Cardiovascular
  - Increased Inflammation

Typically 20% of patients will be unable to tolerate PAP therapy

INSPIRE System for Hypoglossal Muscle Stimulation in OSA

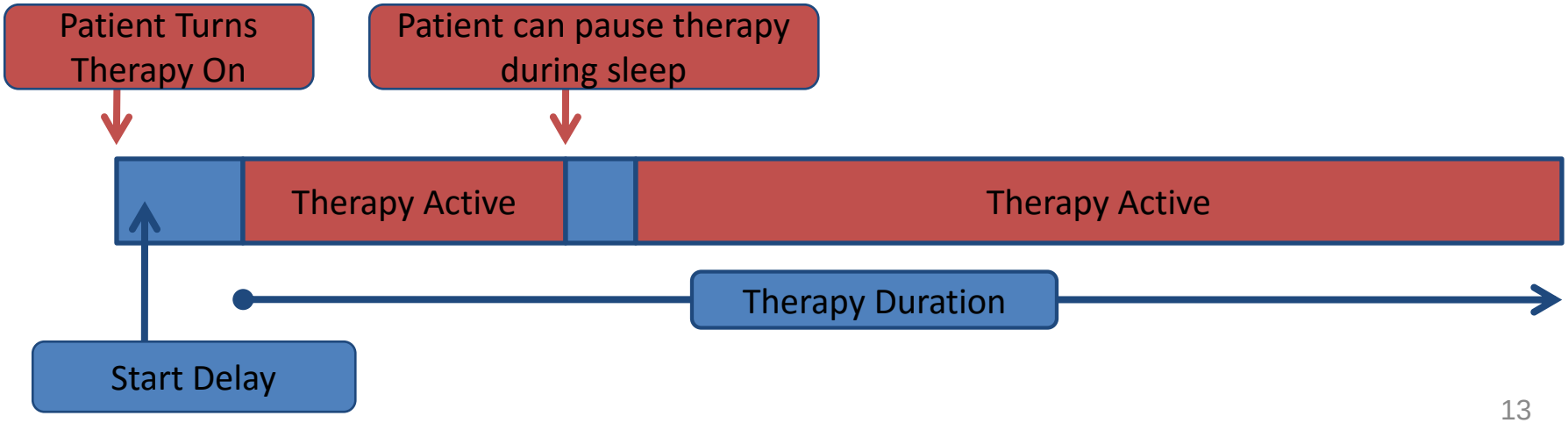
Patient Programmer
- Therapy ON/OFF
- Adjust amplitude



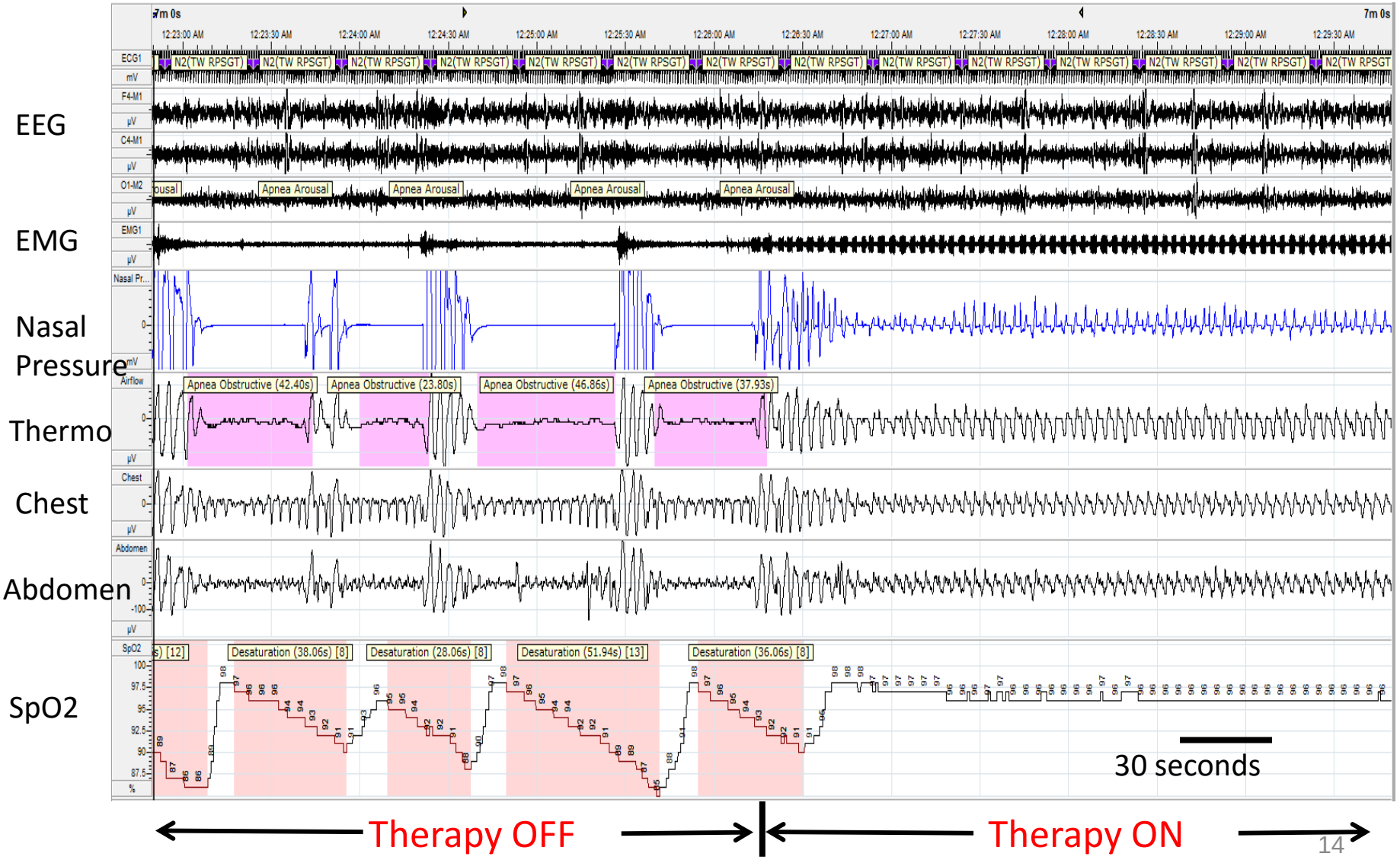
Implanted Components

- Stimulation Lead
- Implanted Pulse Generator (IPG)
- Sense Lead

Patient Activates Therapy before Sleep



Effect of Stimulation

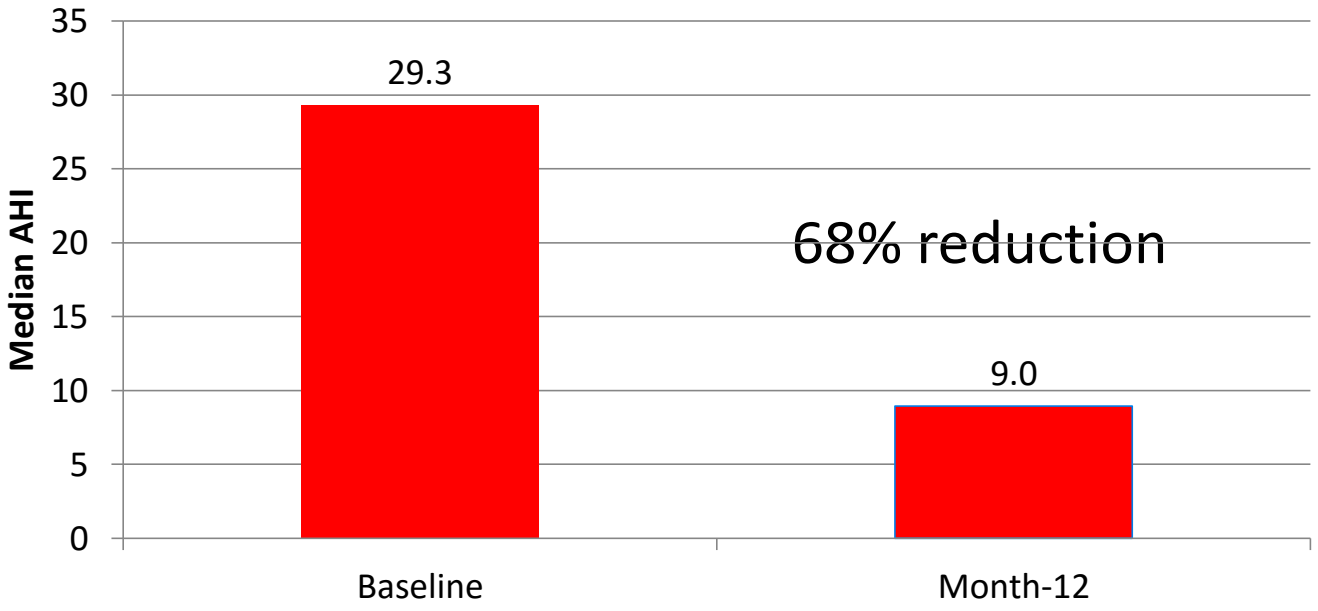


Important Selection Criteria

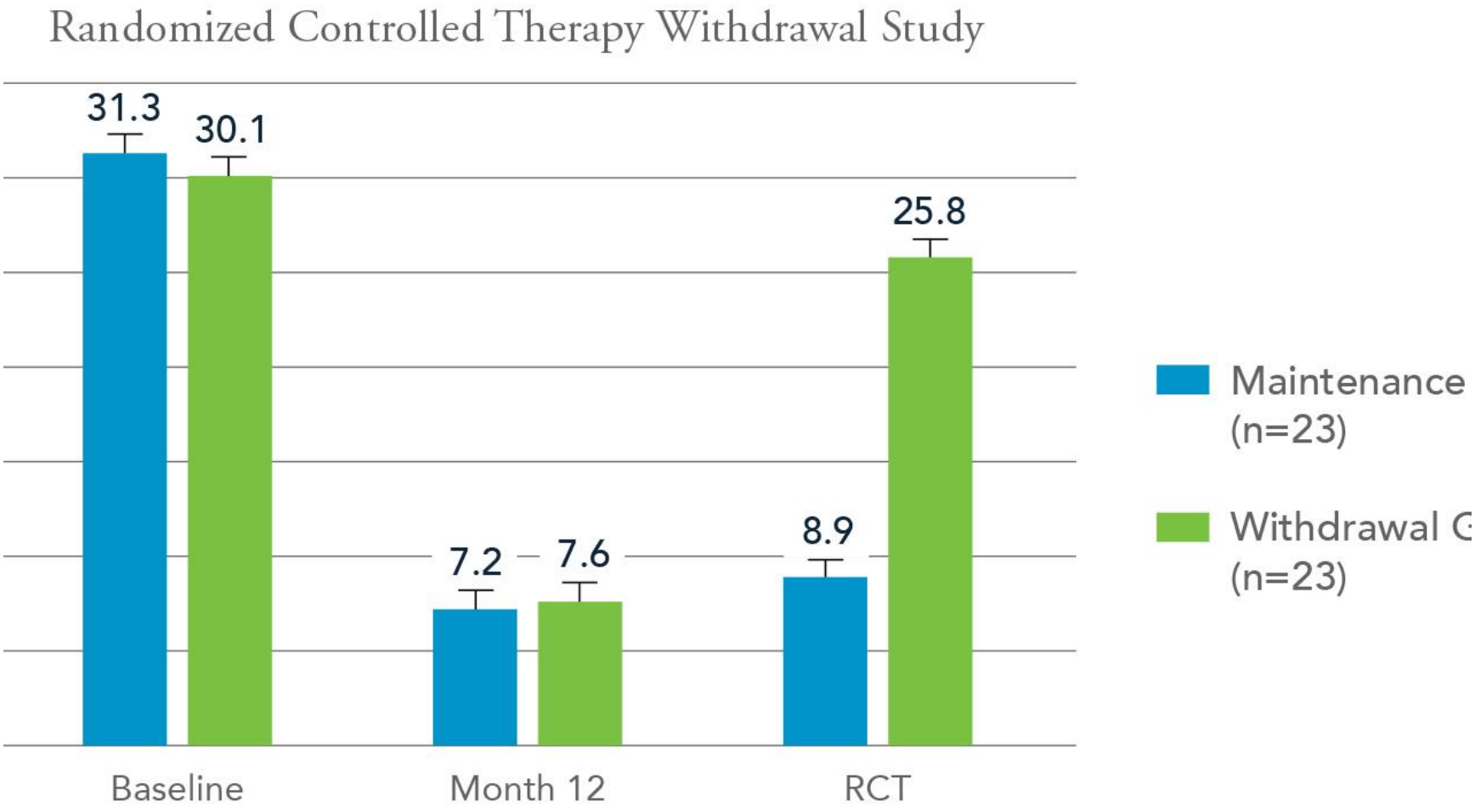
- *Inability to use CPAP as therapy for >4 hours a night for >70% of nights*
- AHI 20-65
- BMI <32, warning to BMI up to 35
- Age not specified but generally need to be in good health
- No lumps in nose or throat
- On Drug Induced Sedated Endoscopy (DISE): no concentric (camera shutter-like) closure of the back of the nose

STAR Efficacy Outcomes: Phase III Pivotal FDA Trial

- Apnea Hypopnea Index Endpoint
  - Endpoint: at least 50% responder rate (≥ 50% AHI reduction and AHI < 20 at 12 months – Sher criteria[1])
  - Outcome: 66% responder rate at 12 months



Strollo et al NEJM 2014



Strollo et al. *Otolaryngology -- Head and Neck Surgery* November 2014 151: 880-887

Order lung cancer screening CT for appropriate patients

Current Recommendations for Lung Cancer Screening*

- WHO?
  - Current or former smokers ages 55-74 in good health
  - ≥ 30 pack-year history
  - Quit less than 15 years

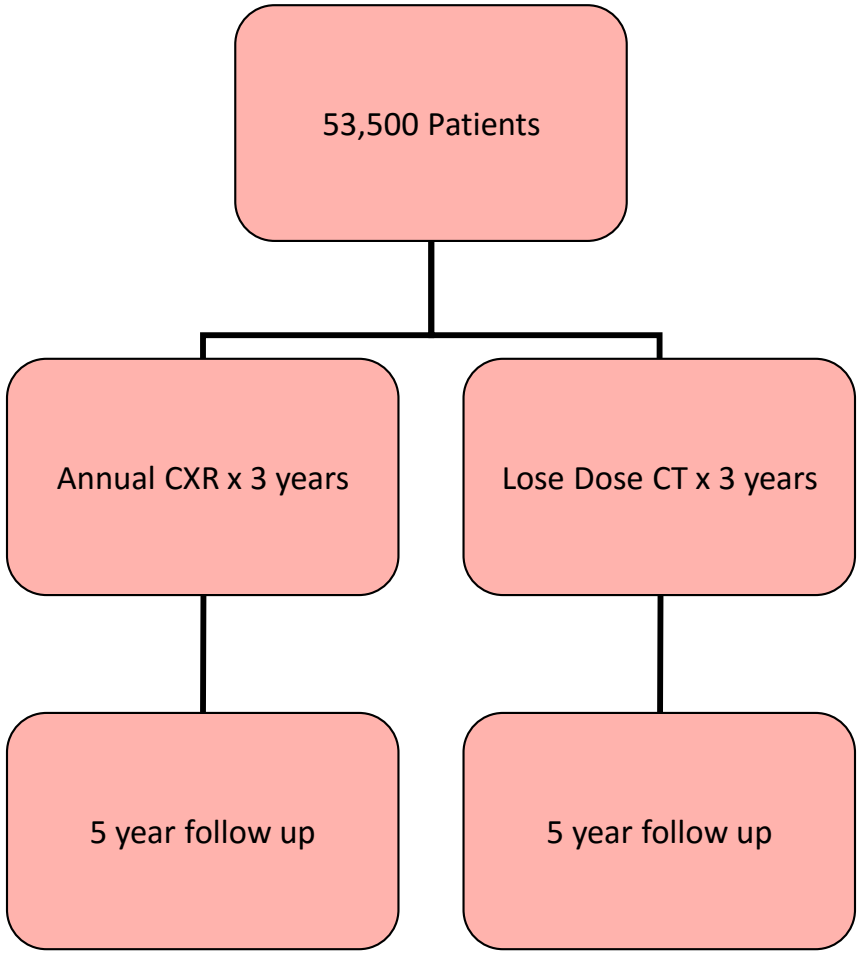
- WHAT?
  - Low dose helical CT (LDCT)
  - Organized screening program that has experience in LDCT

- Screening should not be viewed as an alternative to smoking cessation

*(American College of Chest Physicians, American Society of Clinical Oncology, the American Thoracic Society, the National Comprehensive Cancer Network (NCCN) and the American Lung Association)

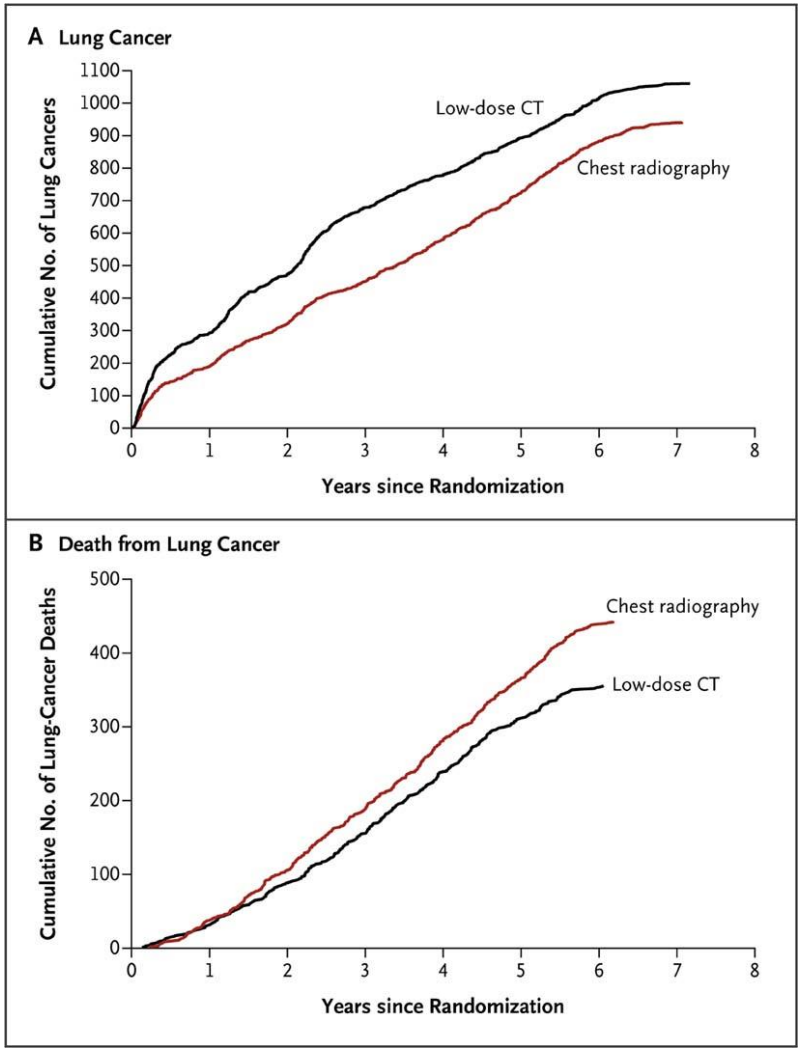
National Lung Screening Trial (NCI 2010)

- Utility of low dose CT screening for detection of lung cancer
- High risk patients for lung cancer
  - Current or previous smoker
  - >30 pack/year history
- Results
  - 354 vs 442 deaths from lung cancer
  - 20% reduction in lung cancer deaths in CT
- Caveats
  - **Cost**
  - **False (+) consequences**
  - **Radiation effects**



The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer in the National Lung Screening Trial



The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

Additional Findings in National Lung Screening Trial

Additional Findings

- 39.1% of the LDCT group had at least 1 positive finding
- 24% of surgical procedures yielded a benign result
- 367/1060 cancers in the LDCT group were diagnosed either after the screening period or in patients missing screening.
- Number needed to screen to prevent 1 death was 320

Potential Implications

- Huge burden of workup and liability
- Non-trivial “unnecessary” procedures
- Do additional years of screening need to be done?
- Are we detecting non-lethal cancers?
- Can this change/cost

The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

APPROVAL OF PAYMENT FOR LOW DOSE CT SCANNING FOR LUNG CANCER SCREENING IN HIGH RISK PATIENTS (2.5.2015)

Re-evaluate COPD documentation and treatment

Recently Approved COPD Treatments

- Oldaterol
  - Olodaterol (Striverdi Respimat)
  - Olodaterol and Tiotropium bromide (Stiloto™ Respimat®)
- Vilanterol + Fluticasone furoate + (Breo Ellipta)
- Umeclidinium
  - Umeclidinium (Incruse Ellipta)
  - Umeclidinium and Vilanterol inhalation powder (Anoro Ellipta)
- Aclidinium (Tudorza Pressair)
- Roflumilast (Daliresp®)

Recently Approved COPD Treatments

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- Aclidinium (Tudorza Pressair)
- Roflumilast (Daliresp®)

Roflumilast (Daliresp)

- Phosphodiesterase E4 inhibitor
- Approval: 2011
- Indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
- Dose 500 ug once daily

Recommendations for Use of Roflumilast in Primary Care

- Clear identification of patients eligible for roflumilast
- Phenotyping of patients in primary care
  - lung function measurement (FEV1<50%)
  - accurate health status classification
    - At least 1 exacerbation last year
    - Smoking > 20 pk/years
  - recording of chronic cough and regular sputum production

Price, D et al. Prim Care Respir J. 2011 Mar;20(1):45.

Additional Concerns with Roflumilast

- Roflumilast and suicidal thoughts or depression
- 20% of patients in trial had 5-10% weight loss
- GI Side effects

Q: Does the recent proliferation of new therapeutic agents for really change our treatment of COPD?
A: Quite Possibly

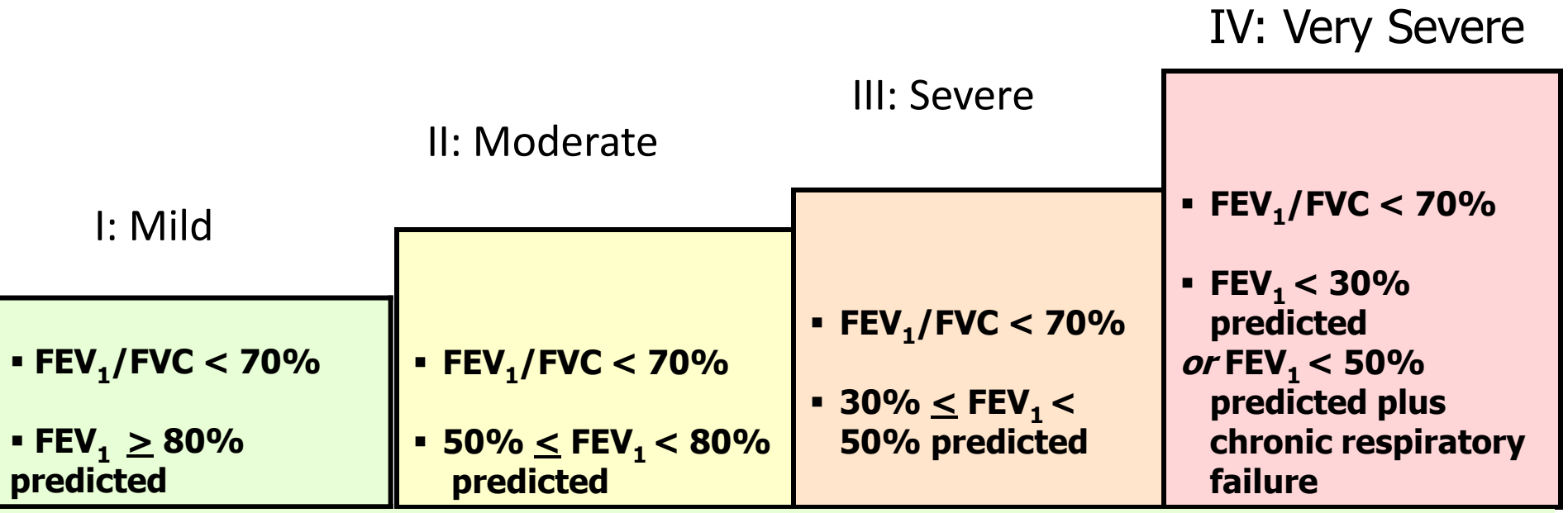
Q: Should I think about COPD Patients Differently?
A: Almost Certainly

2011+ Paradigm Shift in Global Recommendations for COPD Management

FEV1 Based Management Strategy with Some Escalation Based on Symptom Control

1) Reduce Symptoms
   - Relieve symptoms
   - Improve exercise tolerance
   - Improve health status
2) Reduce Risk
   - Prevent disease progression
   - Prevent and treat exacerbations
   - Reduce mortality

Therapy at Each Stage of COPD*



Active reduction of risk factor(s); influenza vaccination

Add short-acting bronchodilator (when needed)

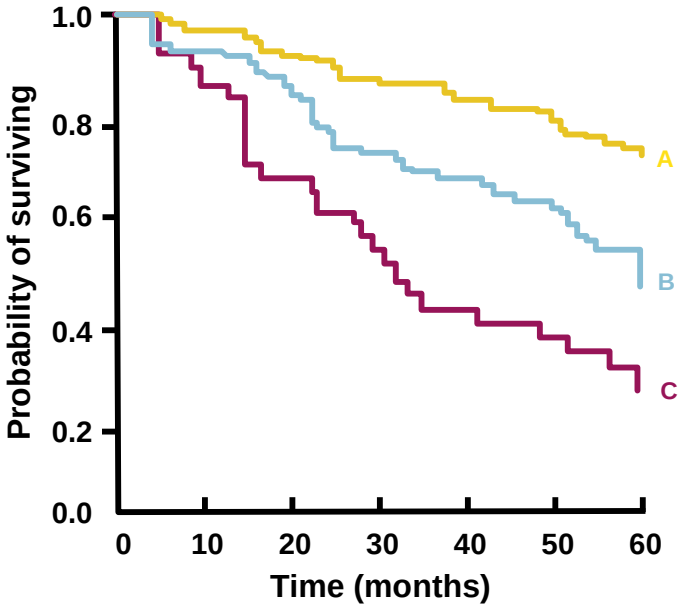
Add regular treatment with one or more long-acting bronchodilators (when needed); ***Add*** rehabilitation

Add inhaled glucocorticosteroids if repeated exacerbations

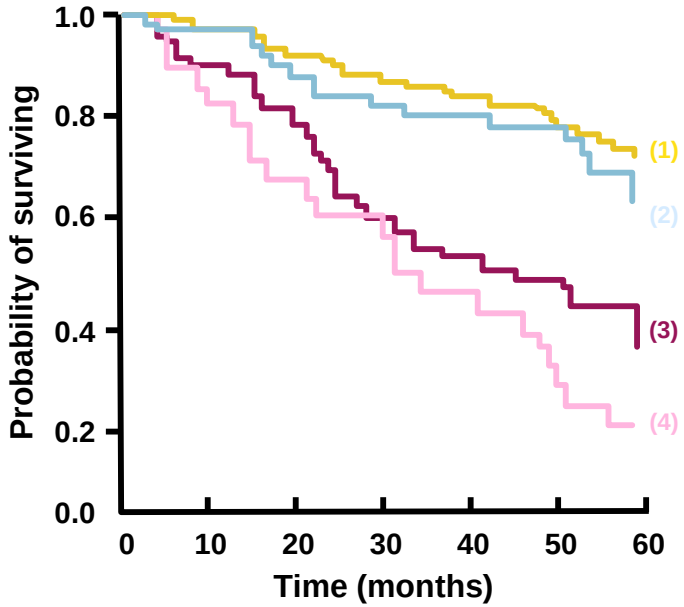
Add long term oxygen if chronic respiratory failure. ***Consider*** surgical treatments

***Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD**

Exacerbation Frequency and Severity Both Increase Mortality Risk

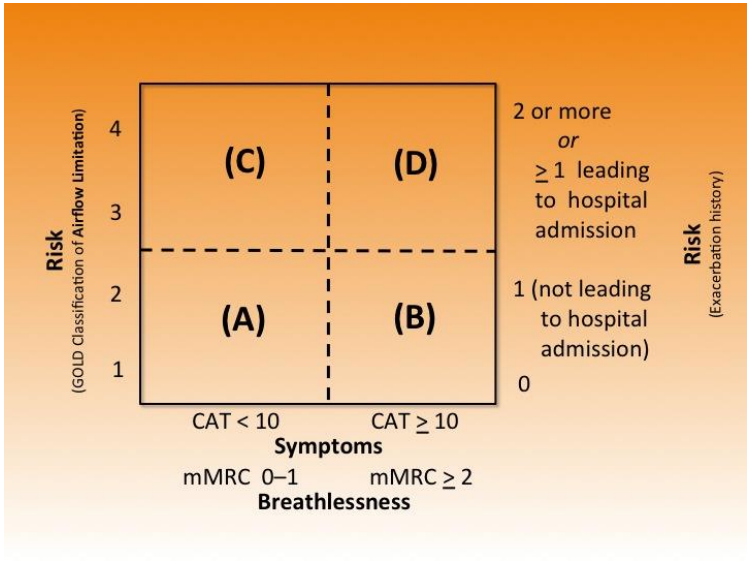


Group A patients with no acute exacerbations
Group B patients with 1–2 acute exacerbations requiring hospital management
Group C patients with ≥3 acute exacerbations



Group (1) no acute exacerbations
Group (2) acute exacerbations requiring emergency service visits without admission
Group (3) patients with acute exacerbations requiring one hospital admission
Group (4) patients with acute exacerbations requiring readmissions

Soler-Cataluña JJ, et al. *Thorax*. 2005;60:925-931.



Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk.)*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	< 10	0-1
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 10	≥ 2
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Tools Involved in Risk Assessment in Current GOLD Treatment Paradigm

- Simple spirometry
- COPD Assessment Test (CAT)
- Modified Medical Research Council Dyspnea Scale (mMRC)

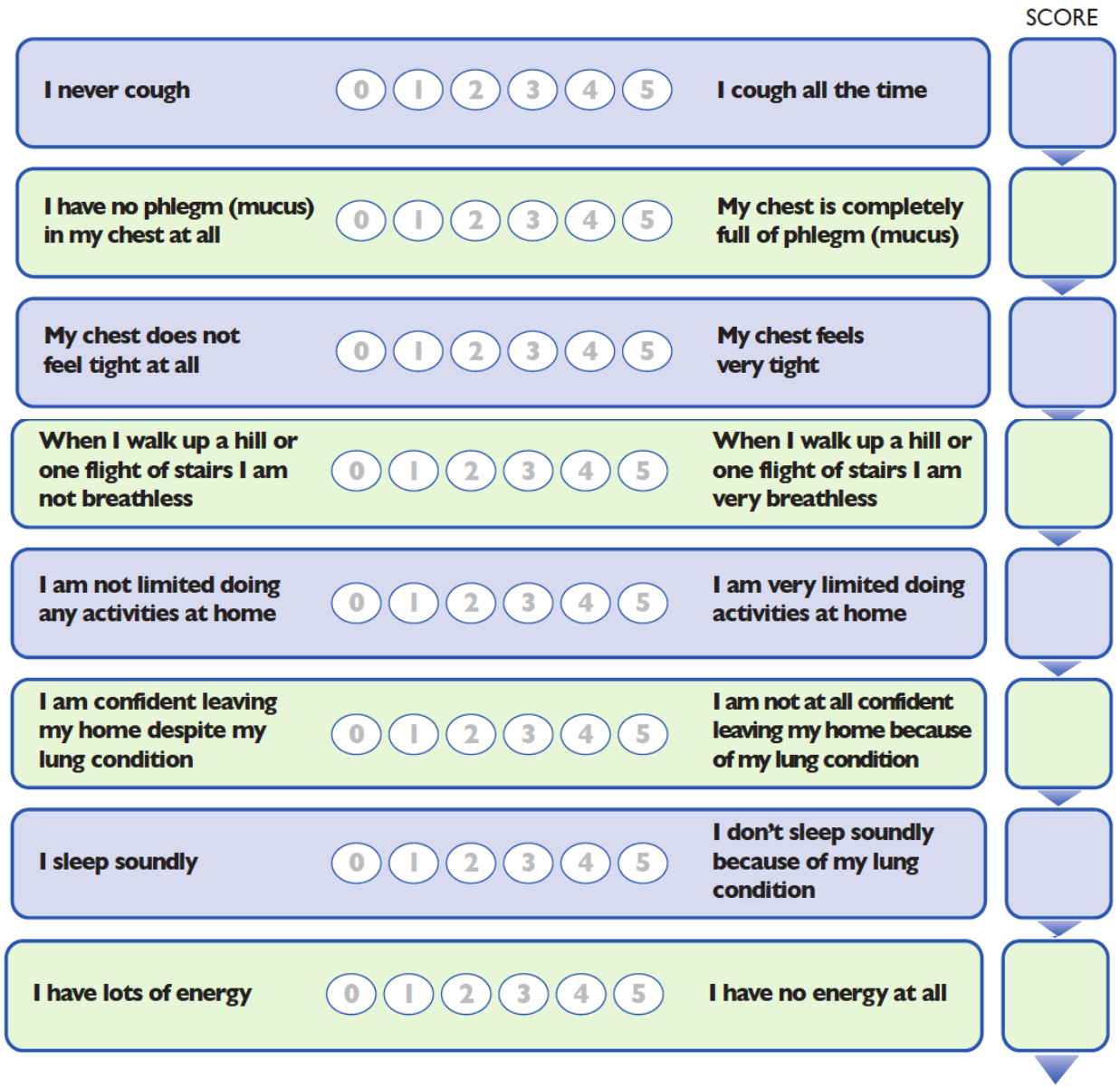
Global Strategy for Diagnosis, Management and Prevention of COPD

Classification of Severity of Airflow Limitation in COPD*

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

**Based on Post-Bronchodilator FEV_1*

COPD Assessment Test (CAT)



The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients

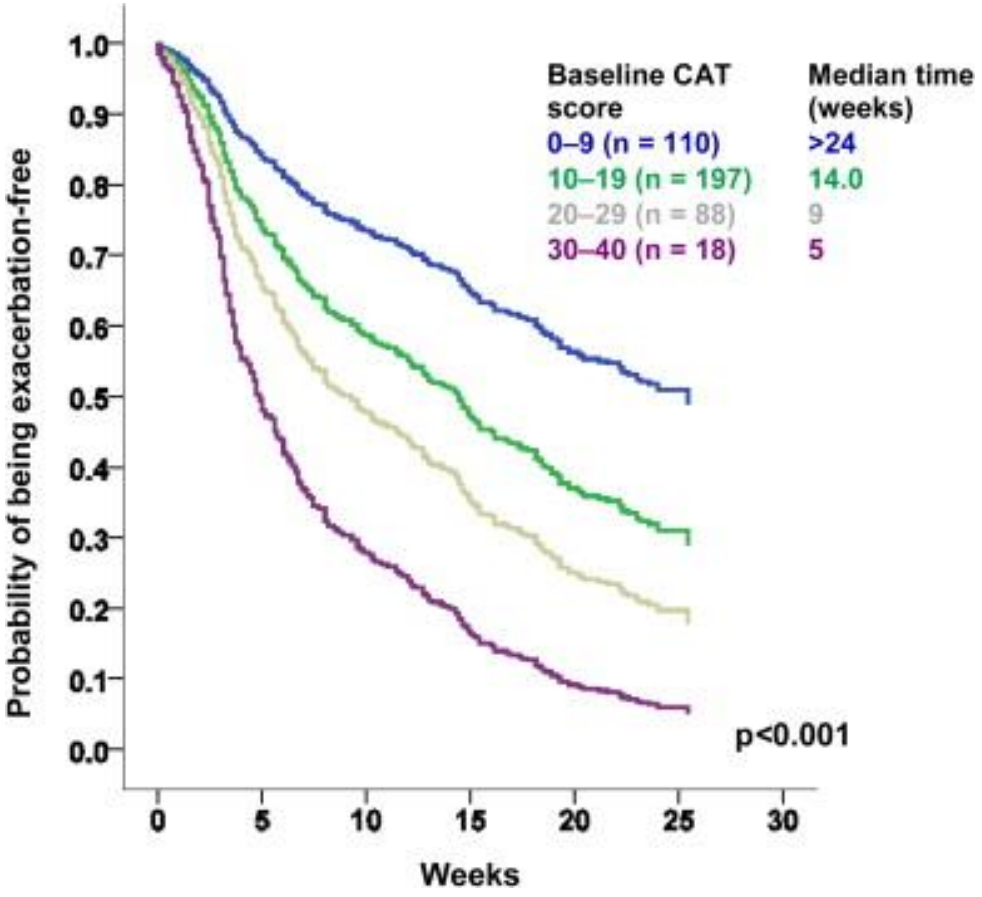


Figure 1. Adjusted time to first exacerbation by categorised baseline COPD assessment test (CAT) score.

Sang-Do Lee et al. Respiratory Medicine, Volume 108, Issue 4, 2014, 600–608

Modified Medical Research Council Dyspnea Scale (mMRC)

- Grade 0: breathless with strenuous exercise
- Grade I: short of breath when hurrying on the level or walking up a slight hill
- Grade II: walking slower than people of the same age on the level because of breathlessness or having to stop for breath when walking at own pace on the level
- Grade III: stopping for breath after walking about 100 yards or after a few minutes on the level
- Grade IV: too breathless to leave the house or breathless when dressing or undressing

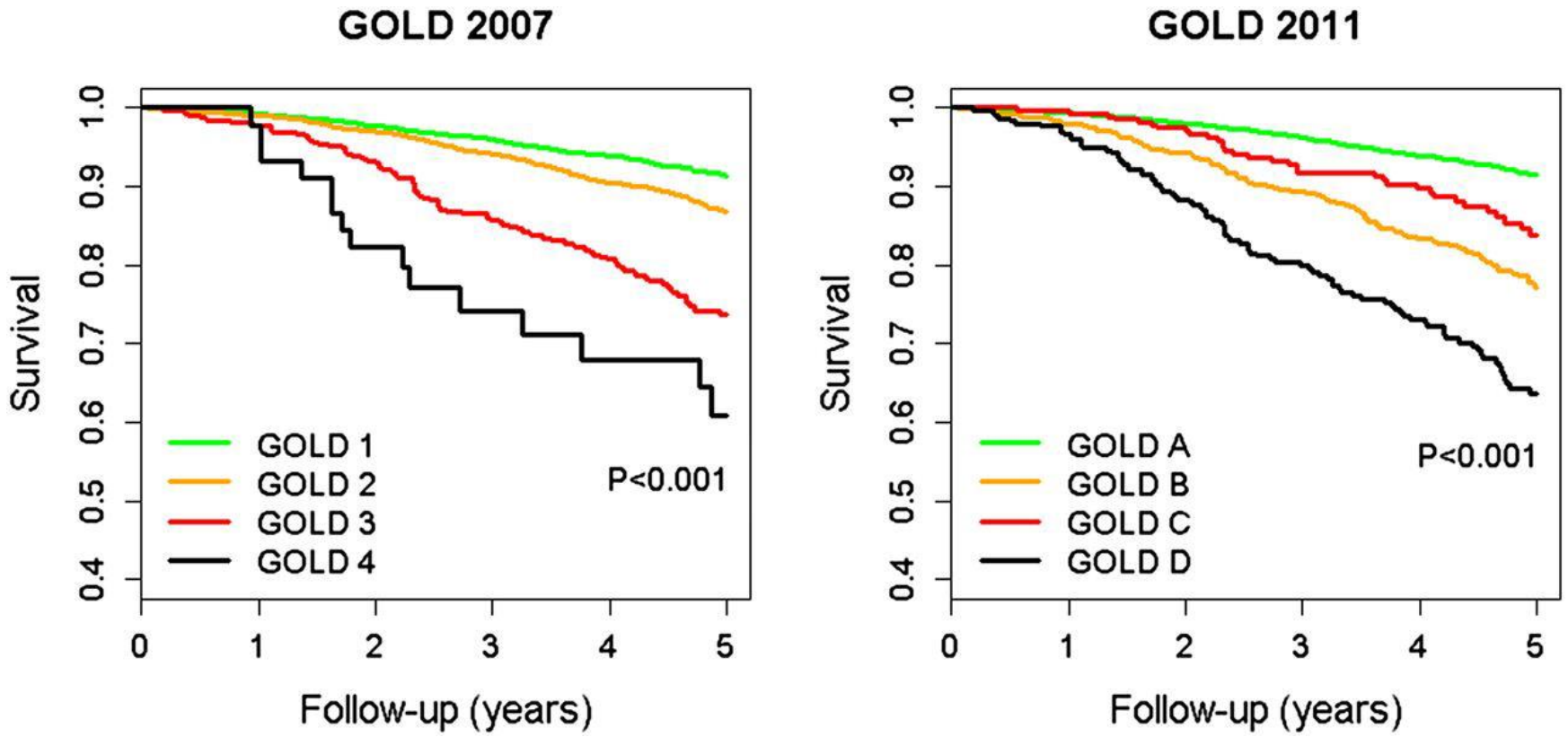
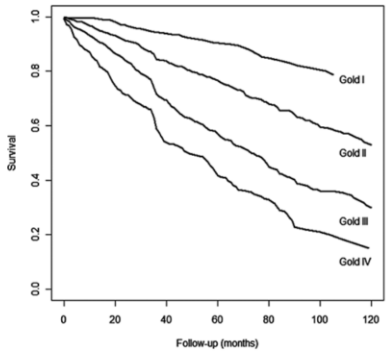


Figure 2. Survival shown as Kaplan-Meier curves according to the GOLD 2007 classification (*left*) and GOLD 2011 classification (*right*).

Lange et al. ; *Am J Respir Crit Care Med* **2012,** 186, 975-981.

Distribution and Prognostic Validity of the New Global Initiative for Chronic Obstructive Lung Disease Grading Classification New GOLD COPD Grading

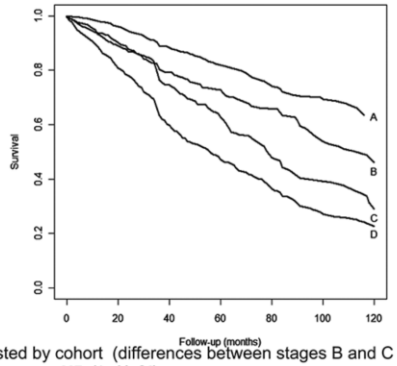
A Old GOLD



Cox model adjusted by cohort

	HR (95% CI)
COPD old GOLD II	1.78 (1.29-2.46)
COPD old GOLD III	2.84 (2.06-3.92)
COPD old GOLD IV	4.05 (2.87-5.72)

B New GOLD 2011



Cox model adjusted by cohort (differences between stages B and C disappears).

	HR (95% CI)
COPD new GOLD B	1.70 (1.38-2.10)
COPD new GOLD C	1.69 (1.39-2.08)
COPD new GOLD D	2.79 (2.35-3.32)

Chest. 2013;143(3):694-702. doi:10.1378/chest.12-1053

BODE Index for COPD Survival

Use this calculator to calculate prognosis in COPD (Chronic Obstructive Pulmonary Disease) using the BODE Index.

FEV_1 (% predicted)	≥65
6-minute walk distance (m)	≥350
Modified MRC Dyspnea Scale	0-1

0: Dyspneic on strenuous exercise
1: Dyspneic on walking a slight hill
2: Dyspneic on walking level ground; must stop occasionally due to breathlessness
3: Must stop for breathlessness after walking 100 yards or after a few minutes
4: Cannot leave house; breathless on dressing/undressing

Body Mass Index (kg/m^2)	>21

Submit

http:www.qxmd.com

Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of 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
Body-mass index§	>21	≤21		

* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.

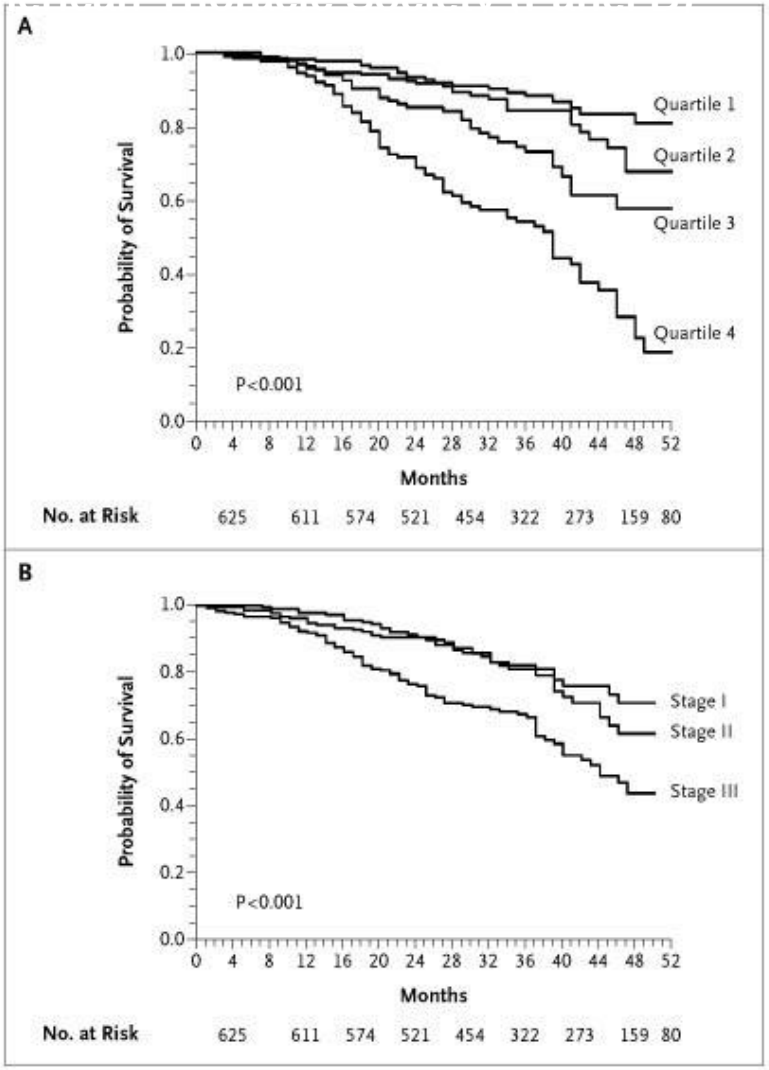
† The FEV_1 categories are based on stages identified by the American Thoracic Society.

‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

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

Kaplan-Meier Survival Curves for the Four Quartiles of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity Index (Panel A) and the Three Stages of Severity of Chronic Obstructive Pulmonary Disease as Defined by the American Thoracic Society (Panel B)



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

Practical Office Implementation

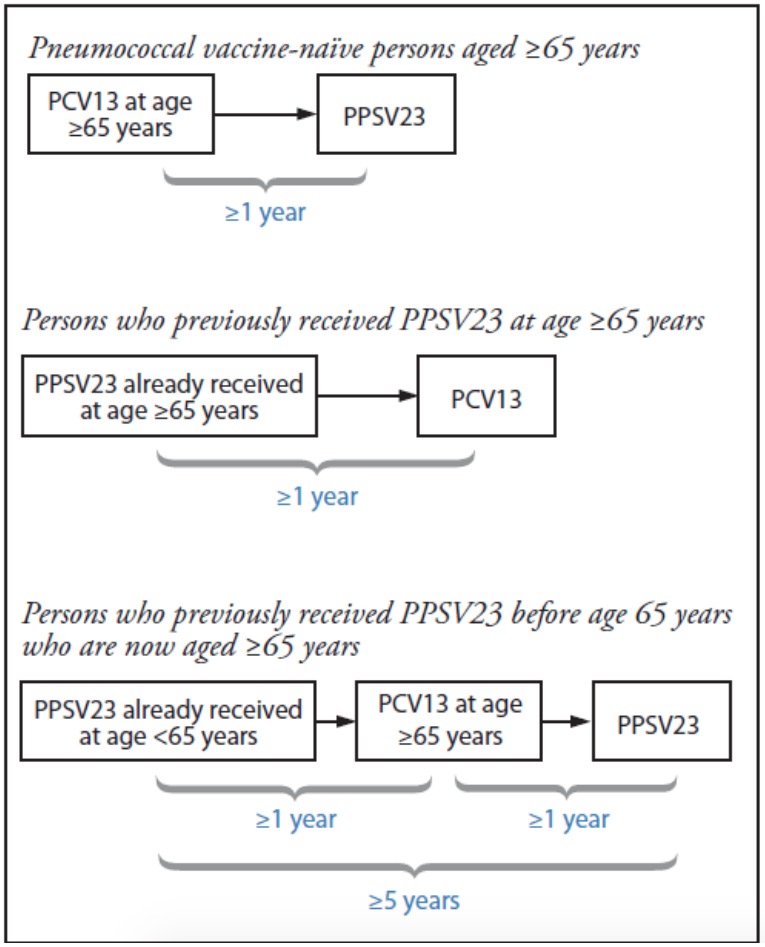
1) COPD – FEV1 = 40% predicted, GOLD Class 3, CAT Score = 8, Type C, BODE 5 (0+2+2+1). Currently on LABA and LAMA. Completed pulmonary rehab, not LVRS candidate. Currently with adequate oxygenation.

Consider Vaccination with Pneumococcal Polysaccharide Conjugated Vaccine (PCV 13)

What is the difference between PCV13 and PPSV23 pnuemococcal vaccines?

- PCV13 is a conjugated vaccine
- Difference in covered serotypes
  - Serotypes covered by PPSV23
    - 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F
  - Serotypes covered by PCV13
    - 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

New Recommendations ACIP PCV13 Age > 65*



*To be re-evaluaated in 2018

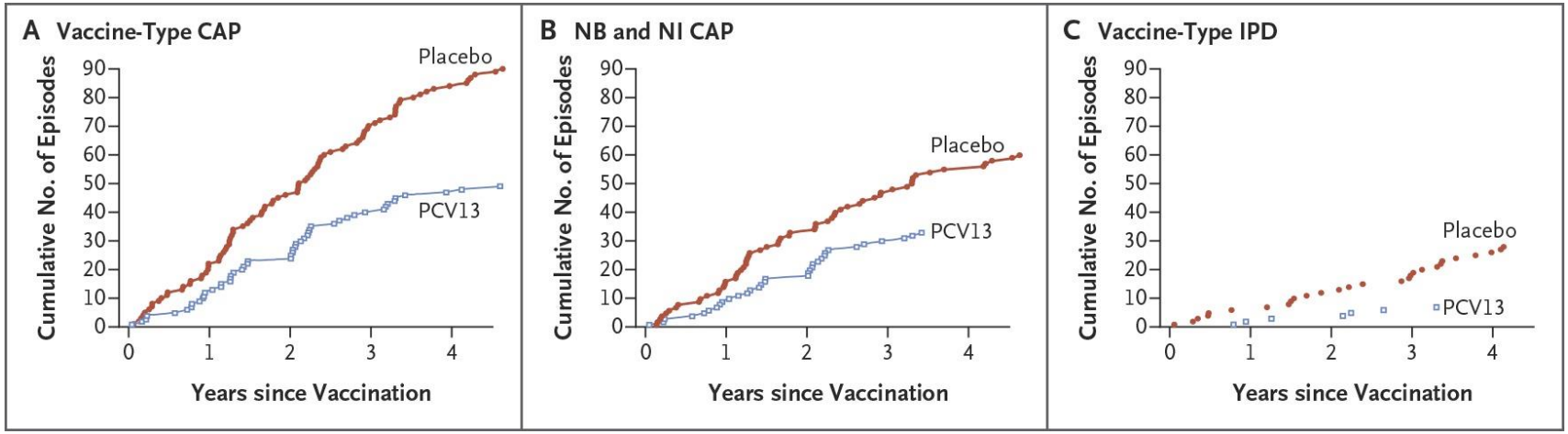
Original Article

Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

Marc J.M. Bonten, M.D., Ph.D., Susanne M. Huijts, M.D., Marieke Bolkenbaas, M.D., Chris Webber, M.D., Scott Patterson, Ph.D., Samantha Gault, M.B.A., Cornelis H. van Werkhoven, M.D., Anna M.M. van Deursen, M.D., Elisabeth A.M. Sanders, M.D., Ph.D., Theo J.M. Verheij, M.D., Ph.D., Michael Patton, B.Sc., Anne McDonough, M.P.H., Anita Moradoghli-Haftvani, B.Sc., Helen Smith, B.Sc., Tracey Mellelieu, B.Sc., Michael W. Pride, Ph.D., Graham Crowther, Ph.D., Beate Schmoele-Thoma, M.D., Daniel A. Scott, M.D., Kathrin U. Jansen, Ph.D., Rita Lobatto, M.D., Bas Oosterman, Ph.D., Nils Visser, M.Sc., Esther Caspers, M.Sc., Andre Smorenburg, M.Sc., Emilio A. Emini, Ph.D., William C. Gruber, M.D., and Diederick E. Grobbee, M.D., Ph.D.

N Engl J Med
Volume 372(12):1114-1125
March 19, 2015

Post Hoc Analysis of the Cumulative Episodes of the Primary and Secondary Efficacy End Points in the Per-Protocol Population.



Bonten MJM et al. N Engl J Med 2015;372:1114-1125

Table 1. Baseline Characteristics of the Participants.*

Characteristic	PCV13 Group (N=42,237)†	Placebo Group (N=42,255)†	All Participants (N=84,492)†
Sex — no. (%)			
Male	23,447 (55.5)	23,801 (56.3)	47,248 (55.9)
Female	18,790 (44.5)	18,454 (43.7)	37,244 (44.1)
Race — no. (%)‡			
White	41,600 (98.5)	41,614 (98.5)	83,214 (98.5)
Black	146 (0.3)	140 (0.3)	286 (0.3)
Asian	277 (0.7)	292 (0.7)	569 (0.7)
Other	205 (0.5)	199 (0.5)	404 (0.5)
Unknown	9 (<0.1)	10 (<0.1)	19 (<0.1)
Age at vaccination — yr			
Mean	72.8±5.7	72.8±5.6	72.8±5.7
Median (range)§	71.6 (61.9–101.1)	71.5 (63.3–99.5)	71.6 (61.9–101.1)
Age group — no. (%)			
<75 yr	29,006 (68.7)	29,064 (68.8)	58,070 (68.7)
≥75 and <85 yr	11,727 (27.8)	11,753 (27.8)	23,480 (27.8)
≥85 yr	1504 (3.6)	1438 (3.4)	2942 (3.5)

* Plus–minus values are means ±SD. Additional characteristics are listed in Table S2 in the Supplementary Appendix. PCV13 denotes 13-valent pneumococcal conjugate vaccine.

† The numbers of participants who received the study vaccine and for whom any safety data were available are shown. Four participants (three in the PCV13 group and one in the placebo group) were excluded because no safety data were available.

‡ Race was self-reported.

§ A total of 18 participants who were enrolled in the PCV13 group and 16 who were enrolled in the placebo group were younger than 65 years of age.

Table 3. Safety Outcomes.*

Event	Safety Subgroup		P Value†	All Participants		P Value†
	PCV13 (N=1006)	Placebo (N=1005)		PCV13 (N=42,237)	Placebo (N=42,255)	
	no. (%)			*no. (%)*		
Adverse event within 1 mo after vaccination	188 (18.7)	144 (14.3)	0.01			
Chronic medical condition diagnosed 1–6 mo after vaccination‡	17 (1.7)	12 (1.2)	0.46			
Serious adverse event						
Within 6 mo after vaccination	70 (7.0)	60 (6.0)	0.41			
Within 1 mo after vaccination				327 (0.8)	314 (0.7)	0.61
Death				3006 (7.1)	3005 (7.1)	0.98

* The numbers of participants who received study vaccine and for whom any safety data were available are shown. Four participants (three in the PCV13 group and one in the placebo group) were excluded because they had no safety data. Listed are events that occurred at least once in any participant.

† A two-sided Fisher's exact test was used to calculate the P value for the difference between percentages of participants who reported an event in each of the study groups.

‡ Newly diagnosed chronic medical conditions (including autoimmune or neuroinflammatory disease) were identified in subgroup participants by site staff members who conducted home visits; chronic medical conditions included conditions such as asthma, emphysema, hypertension, and cardiac failure.

- Among older adults, PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause.

Indications for PPSV23 Pneumococcal Vaccination in Patients 19-64 years old

- Cigarette smoking
- Chronic heart disease, including congestive heart failure and cardiomyopathy, but excluding hypertension
- Chronic lung disease, including asthma and chronic obstructive pulmonary disease
- Diabetes mellitus
- Alcoholism
- Chronic liver disease

Indication for PPSV23 +PCV13 age

- CSF Leak
- Cochlear Implant
- Asplenia
- Jmmunocompromised Patients
  - Immunodeficiency
  - HIV
  - ESRD
  - Leukemia, Lymphoma, Hodgkins Disease, Myeloma
  - Generalized Mailignancy
  - Solid Organ Transplant

MMWR 2014, 63:822

The 4 “Practice Changers”

- Suggest a novel treatment for patients with sleep apnea intolerant to PAP therapy
- Order lung cancer screening CT for appropriate patients
- Re-evaluate COPD documentation and treatment
- Consider PCV13 immunization for pneumococcal disease

QUESTIONS?

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	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		Theophylline
B	LAMA *or* LABA	LAMA and LABA		SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.		Carbocysteine N-acetylcysteine *SABA and/or* SAMA Theophylline

Group A COPD Patients

- Patients have few symptoms and low risk of exacerbations
- A short-acting bronchodilator is recommended as first choice
  - Based on effect on lung function and breathlessness
- Combination of short-acting bronchodilators or introduction of a long-acting bronchodilator is recommended as second choice

A	Short-acting anticholinergic prn *or* Short-acting $beta_2$-agonist prn	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist *or* Short-acting $beta_2$-agonist and Short-acting anticholinergic	Theophylline

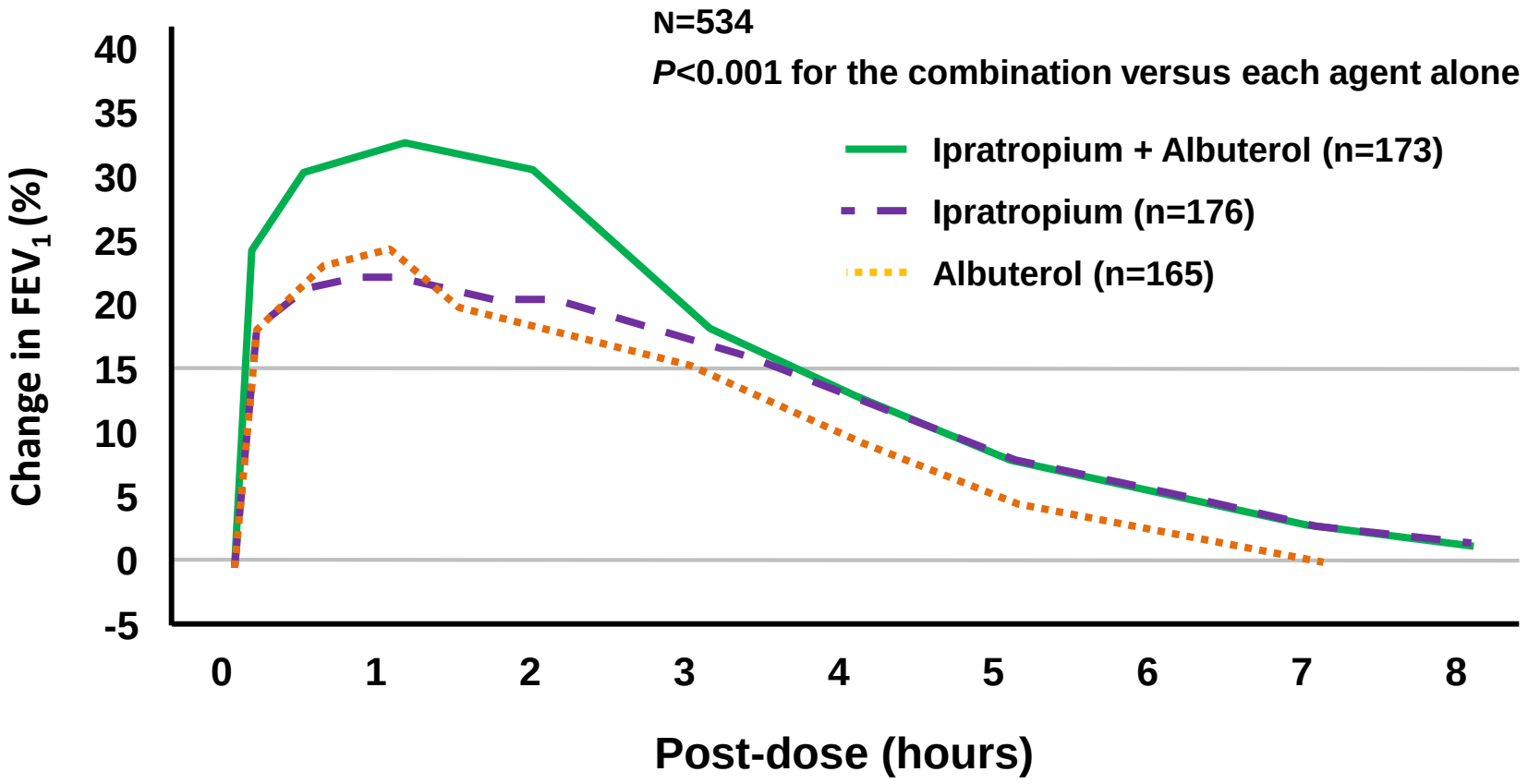
Short Acting Bronchodilators

DRUG	TRADE NAME	Mechanism of Action	DOSING INTERVAL	MISC
Albuterol	Proventil® Proair®	Short Acting Beta 2 Agonist (SABA)	Q 4-6 hours	Also available as nebulized agent
Pirbuterol	Maxair®	Short Acting Beta 2 Agonist (SABA)	Q 4-6 hours	
Ipratropium Bromide	Atrovent®	Short Acting Antimuscarinic (SAMA)	Q 4-6 hours	Also available as nebulized agent
Albuterol + Ipratropium Bromide	Combivent®	SABA + SAMA	Q 6 hours	Also available as nebulized agent

Ipratropium Bromide and Albuterol (Combivent®)

- Inhaled short acting anti-cholinergic/short acting beta adrenergic combination
- FDA Approved: October 1996, May 27, 1999
- Indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator
- 2 inhalations four times daily (18ug/103 ug per inhalation)

Short-acting Bronchodilators: Onset and Duration of Action



Adapted from COMBIVENT Inhalation Aerosol Study Group. *Chest*. 1994;105:1411-1419.

Group B COPD Patients

- Patients have more significant symptoms but still a low risk of exacerbations
- Long-acting bronchodilators are recommended as first choice
  - Choice is dependent on individual patient's perception of symptom relief
- In patients with severe breathlessness, a combination of long-acting bronchodilators is recommended as second choice
- Alternative choices include short-acting bronchodilators and theophylline

B	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist	Long-acting anticholinergic and long-acting $beta_2$-agonist	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic *and/or* Theophylline

Long Acting Antimuscarinics (LAMA)

Aclidinium (Tudorza Pressair)

- Inhaled long acting M3 blocker
- FDA Approval Date: July 23, 2012.
- Indicated for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- Twice daily inhalation (400 ug)

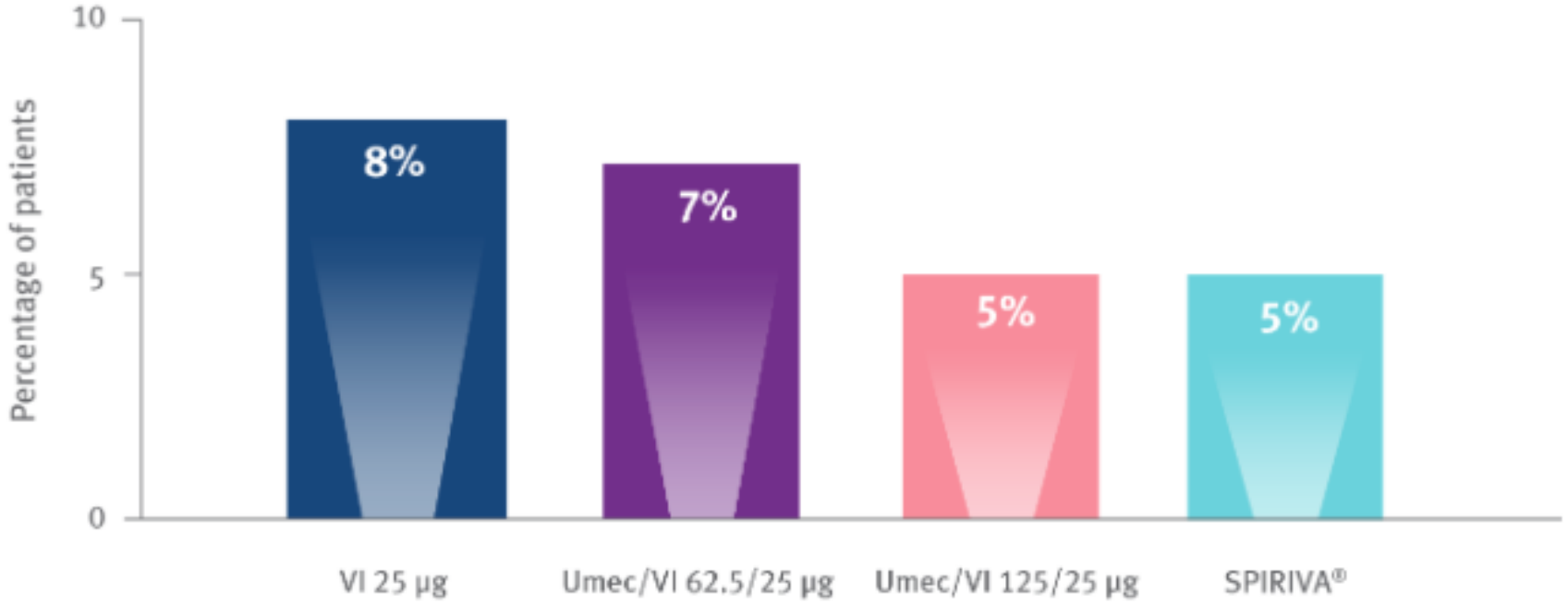
Umeclidinium (Incruse Ellipta)

- Inhaled long acting M3 blocker
- FDA Approval Date: April 30, 2014.
- Indicated for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- Once daily inhalation (62.5 ug)

Tiotropium Bromide (Spiriva)

- Inhaled long acting M3 blocker
- FDA Approval Date: Jan 30, 2004 for COPD, Dec 18, 2009.
- Indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.
- Handihaler: Once daily inhalation (18 ug)
- Respimat: Once daily inhalation of 2 puffs (2x 2.5 ug)

Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicenter, blinded, randomised controlled trials –Frequency of Exacerbation



Decramer M, Anzueto A, Kerwin E, et al. *Lancet Respir Med*. 2014;2(6):472-486

Long Acting Antimuscarinics (LAMA)

DRUG	TRADE NAME	INDICATION	DOSING INTERVAL	MISC
Tiotropium Bromide	Spiriva®	Broncho-dilation	qd	Decreased exacerbations
Umeclidinium	Incruse® Ellipta®	Broncho-dilation	qd	Decreased exacerbations
Aclidinium	Tudorza® Pressair®	Broncho-dilation	BID	Decreased exacerbations

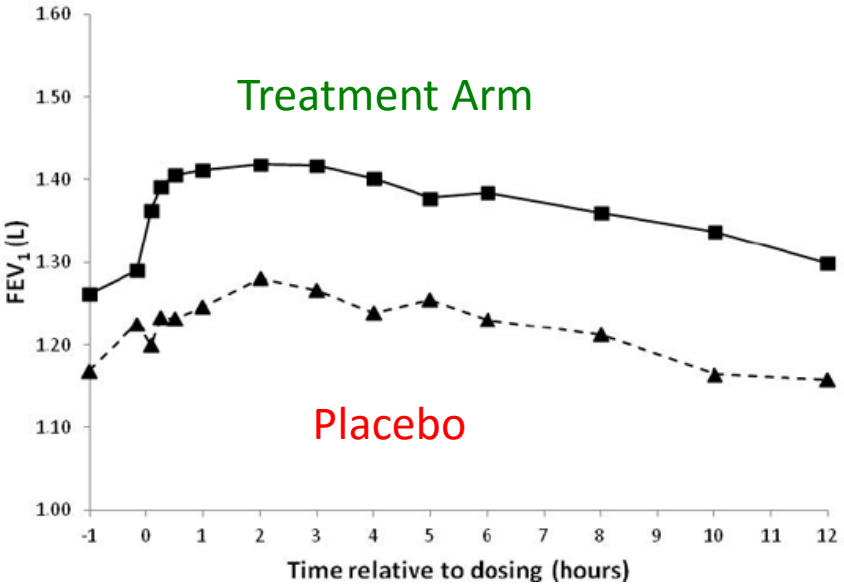
Long Acting Beta- Agonist (LABA)

Olodaterol (Striverdi Respimat)

- Inhaled long acting β2-agonist
- Jul 31, 2014
- Indicated to control symptoms in adults with chronic obstructive pulmonary disease (COPD)
- Once daily inhalation (5 ug)

Clinical Data for Olodaterol

- Typically enrolled patients with moderate to severe COPD
- > 40 years old
- > 10 pack year smoking history



GSK Package Insert

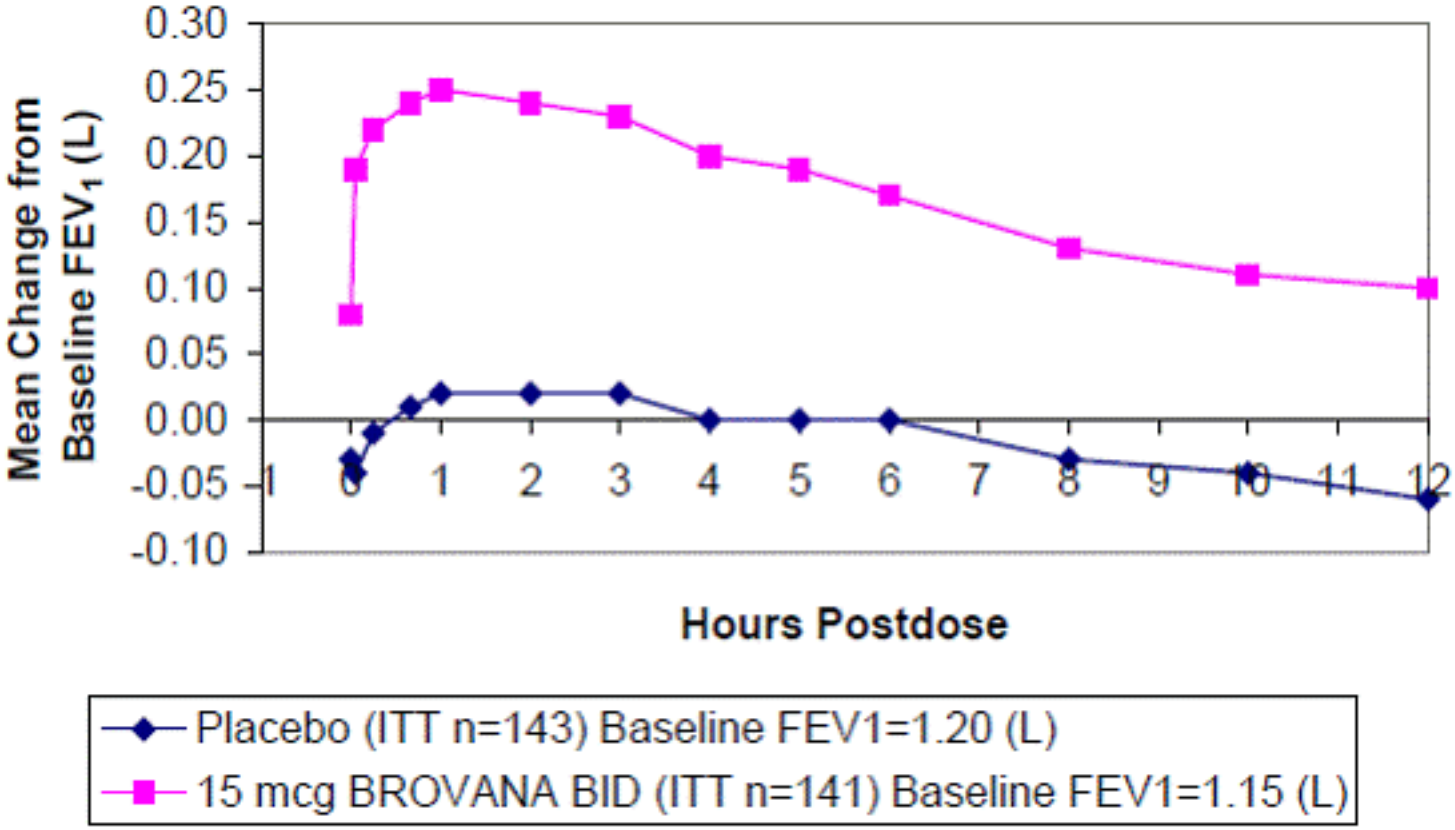
Formoterol Fumarate (Foradil Aerolizer or Performist)

- Inhaled long acting anti-cholinergic/LABA combination
- Approved: September 2001, May 11, 2007
- Indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.
- 1 inhalation twice daily (12 ug per inhalation)
- 1 vial 20ug/2ml nebulized twice daily

Aformoterol (Brovana®)

- Inhaled long acting beta-agonist (LABA)
- Approved: Oct 6, 2006
- Indicated as a long-term, twice-daily (morning and evening), maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- 15 ug nebulized twice daily

Bronchodilation of Brovana®



Indacaterol (Arcapta®)

- Inhaled long acting β2-agonist
- FDA Approval Date: Jul 1, 2011
- Indicated to control symptoms in adults with chronic obstructive pulmonary disease (COPD)
- Once daily inhalation (75 ug)

Salmeterol Xinafoate (Serevent®)

- Inhaled long acting β2-agonist
- FDA Approval Date: Sep 10, 2001
- Indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD)
- Twice daily inhalation (50 ug)

Long Acting Beta- Agonist (LABA)

DRUG	TRADE NAME	INDICATION	DOSING INTERVAL	MISC
Formoterol	Foradil® Performist®	Broncho-dilation	BID	Decreased exacerbations, nebulized
Olodaterol	Incruse® Ellipta®	Broncho-dilation	qD	Decreased exacerbations
Indacaterol	Arcapta®	Broncho-dilation	qD	
Salmeterol	Serevent®	Broncho-dilation	BID	
Aformoterol	Brovana®	Broncho-dilation	BID	Neubulized only
Villaterol			qD	Only in combination

Combination Agents

- Inhaled LAMA/LABA
  - Tiotropium Bromide and Olodaterol (Stiloto™ Respimat®)
  - Umeclidinium and Vilanterol inhalation powder (Anoro Ellipta)
  - Aclidinium bromide/Formoterol fumarate*
  - Glycopyrronium bromide and Indacaterol maleate****

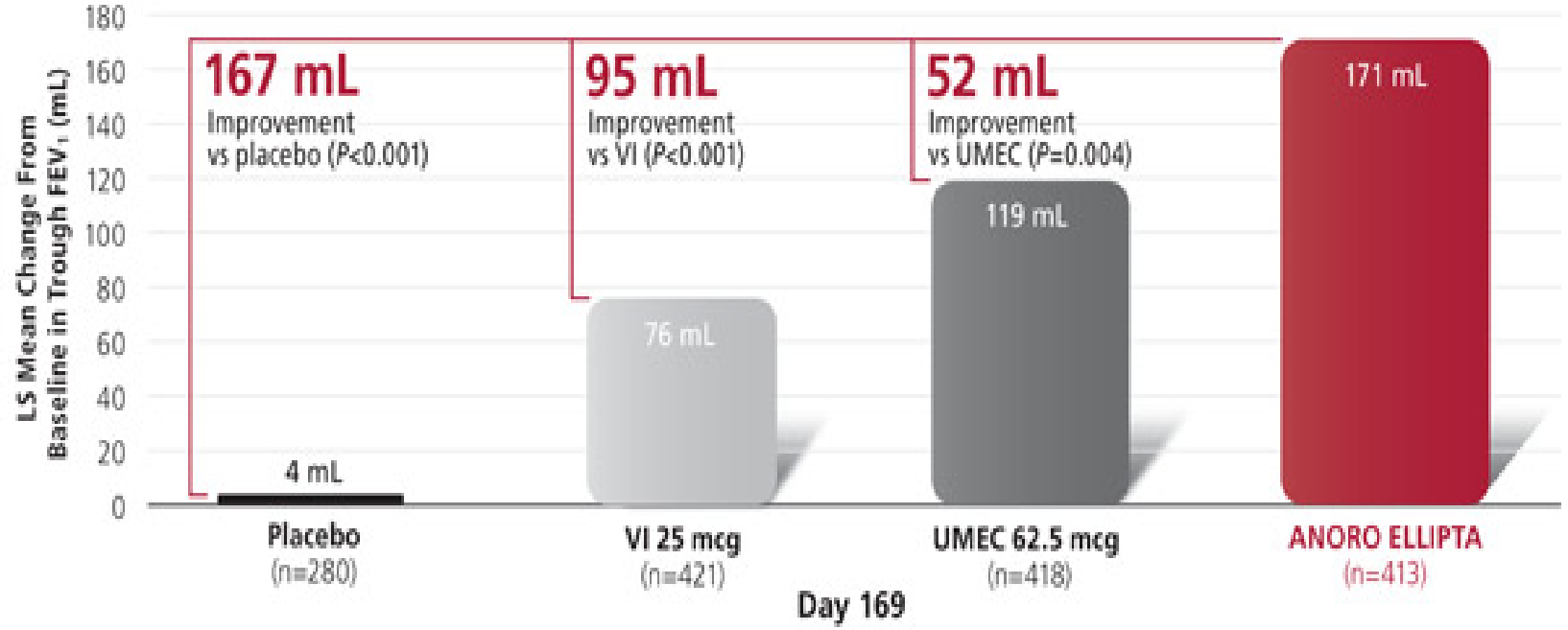
* Approved for use in EU

** Submitted for FDA approval by Novartis Early 2015

Umeclidinium and vilanterol inhalation powder (Anoro Ellipta)

- Inhaled long acting anti-cholinergic/LABA combination
- FDA Approval Date: December 18, 2013
- Indicated for maintenance of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema to improve patient symptoms.
- 1 inhalation daily (62.5ug/25 ug)

Clinical Studies



Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. . *Respir Med.* 2013;107(10):1538-1546

Tiotropium Bromide and Olodaterol (Stiloto™ Respimat®)

- Inhaled long acting anti-cholinergic/LABA combination
- Approved May 15, 2015
- Indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
- 2 inhalations once daily (2.5ug/2.5 ug per inhalation)

Group C COPD Patients

C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting $beta_2$-agonist or Long-acting anticholinergic and phosphodiesterase 4 inhibitor or Long-acting beta2-agonist and phosphodiesterase inhibitor	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline

Combination Agents

- Inhaled LAMA/LABA
  - Tiotropium Bromide and Olodaterol (Stiloto™ Respimat®)
  - Umeclidinium and Vilanterol inhalation powder (Anoro Ellipta)
  - Glycopyrronium bromide and Indacaterol maleate****

- Inhaled Steroid/LABA
  - Fluticasone Propionate + Salmeterol (Advair® 250ug/50ug)
  - Budesonide + Formoterol (Symbicort ® 160ug/4.5ug)
  - Fluticasone furoate + Vilanterol (Breo™ Ellipta™)

- Inhaled SABA/SAMA
  - Ipratropium Bromide + Albuterol
    - Combivent ®
    - Duoneb ®

***** Submitted for FDA approval by Novartis Early 2015

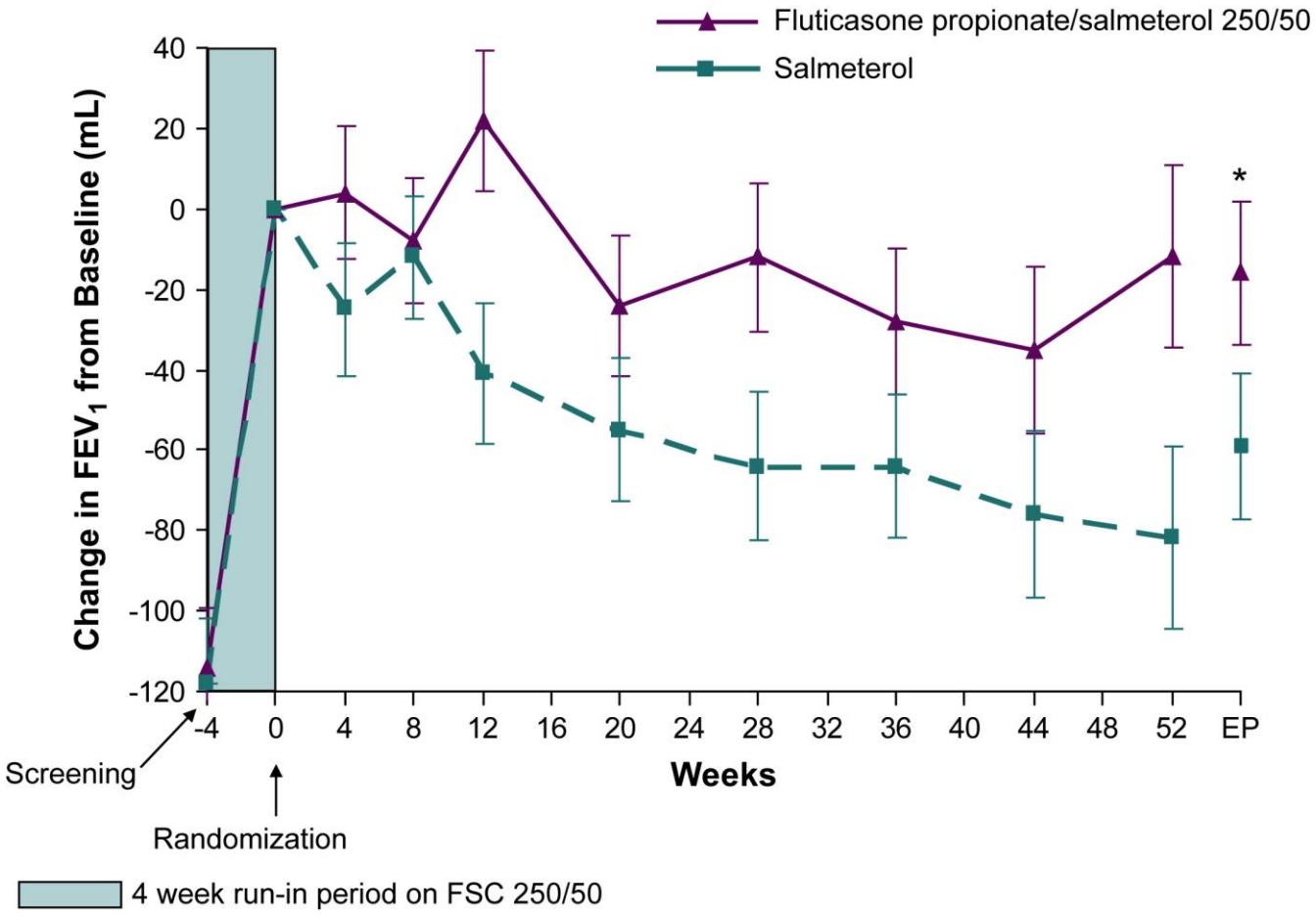
Fluticasone+Salmeterol (Advair Discus)

- Advair Discus 250ug/50ug is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease(COPD), including chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

- FDA Approval Date: Feb 27, 2009

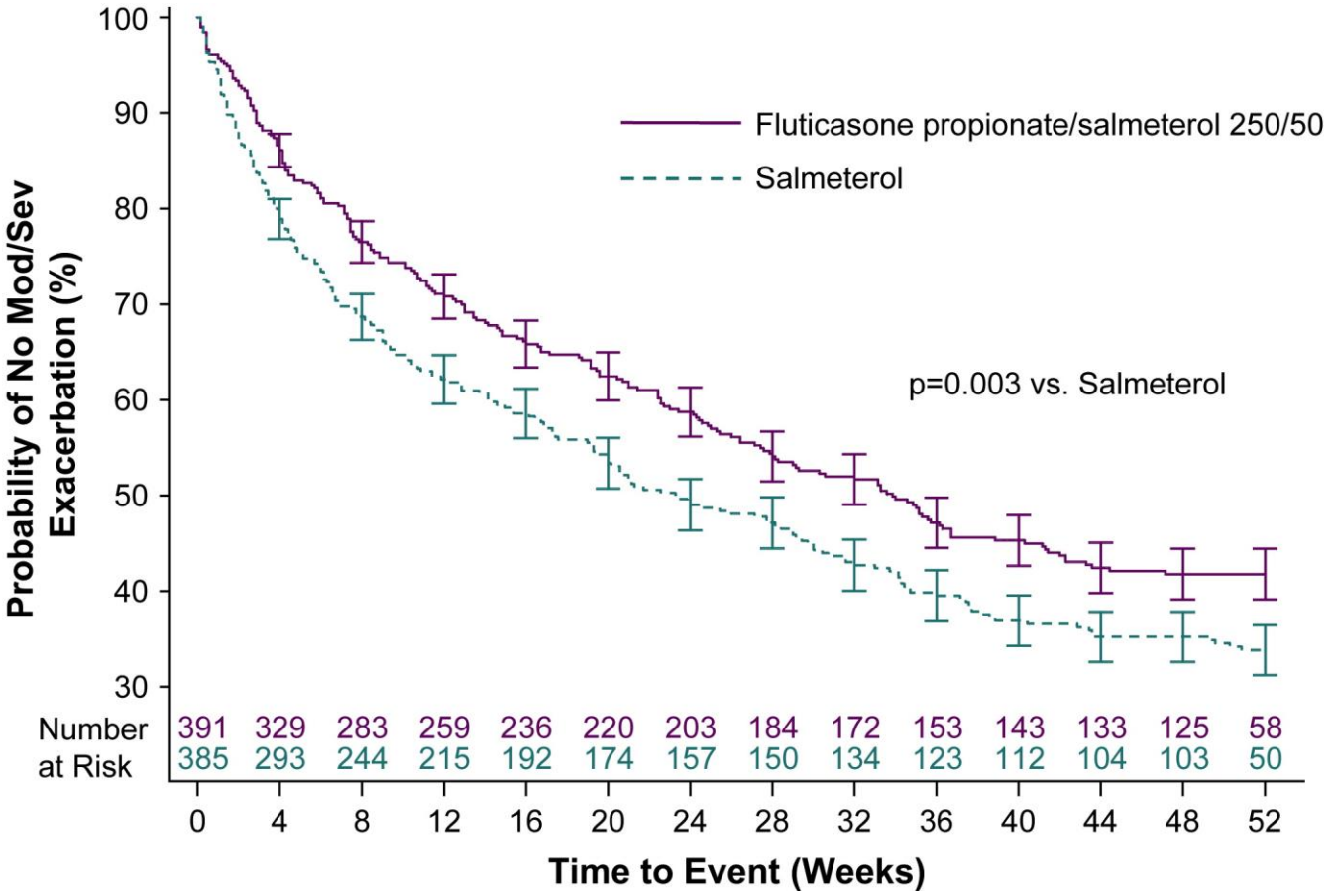
- 1 puff inhaled twice daily
- 250 ug/50 ug per puff

Improvement in FEV1 by Fluticasone Propionate/ Salmeterol vs Salmeterol



Respiratory Medicine 2008 102, 1099-1108DOI: (10.1016/j.rmed.2008.04.019)

Reduction of Moderate to Severe COPD Exacerbations by Fluticasone Propionate/ Salmeterol vs Salmeterol



Respiratory Medicine 2008 102, 1099-1108DOI: (10.1016/j.rmed.2008.04.019)

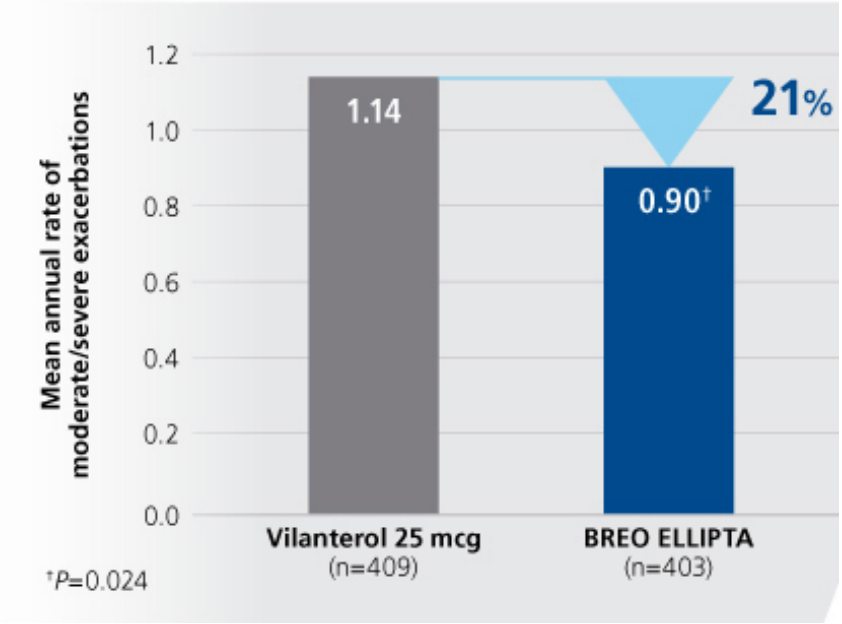
Budesonide+Formoterol (Symbicort)

- SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- FDA Approval Date: Feb 27, 2009
- 2 puffs inhaled twice daily
- 160 ug/4.5 ug per puff

Fluticasone furoate + vilanterol (Breo™ Ellipta™)

- Inhaled long acting corticosteroid/LABA combination
- FDA Approval date: May 10, 2013
- Indicated for maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- BREO ™ ELLIPTA ™ is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations
- 1 inhalation daily (100 ug/25 ug)

Decrease in Clinical Exacerbations with Fluticasone furoate + vilanterol



- N= 1633 patients
- Moderate to Severe COPD
- Moderate Exacerbations = steroid and/or antibiotic
- Severe = hospitalization

Package Insert

Long Acting Combination LABA + Inhaled Corticosteroids (ICS)

DRUG	TRADE NAME	INDICATION	DOSING INTERVAL
Fluticasone Propionate + Salmeterol	Advair®	Maintenance + Decrease Exacerbations	1 puff BID
Budesonide + Formoterol	Symbicort®	Maintenance	2 puffs BID
Fluticasone furoate + vilanterol	Breo™ Ellipta™	Maintenance	1 puff qD

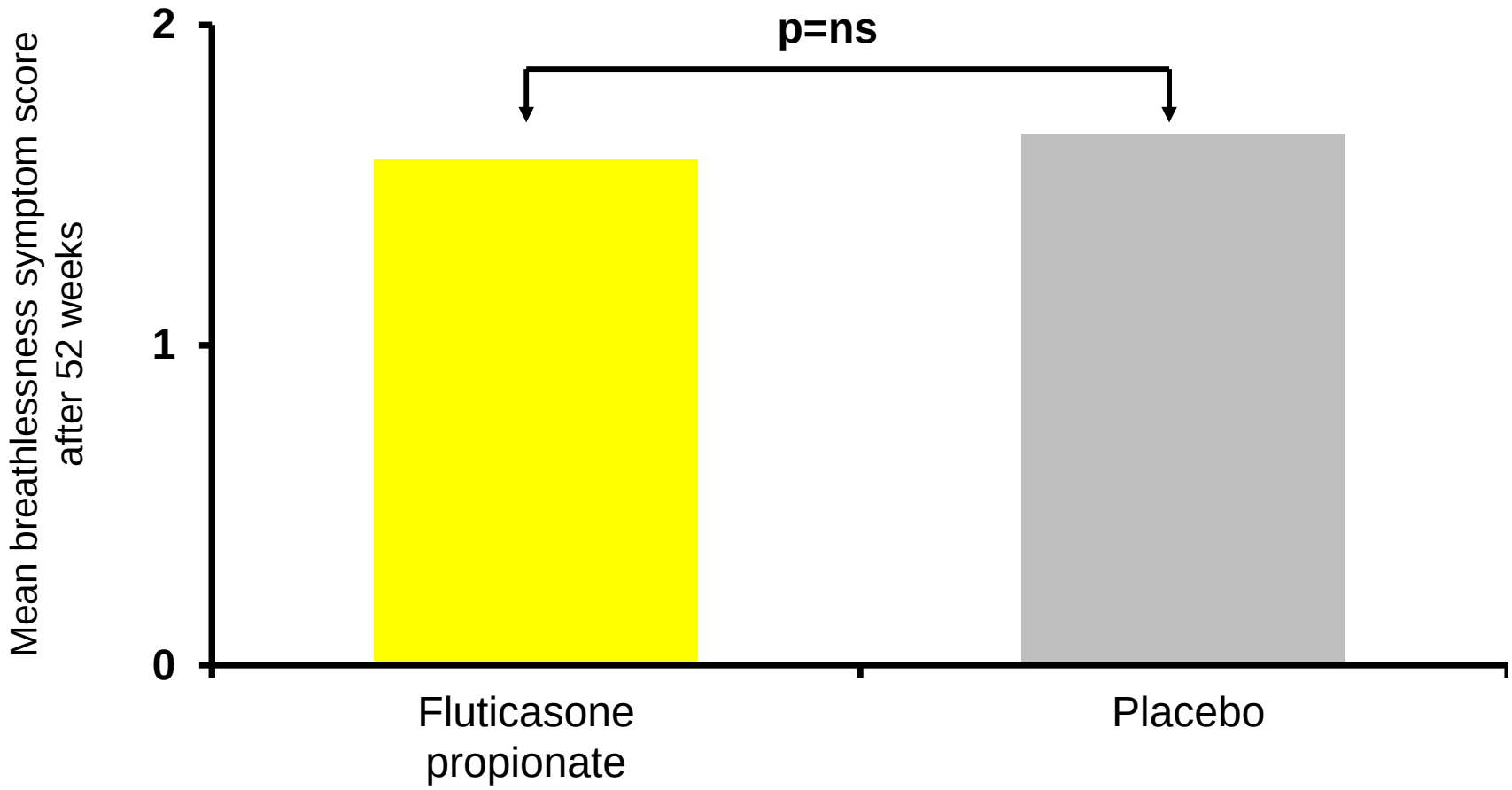
Increased risk of pneumonia with ICS use in patients with COPD: meta-analysis

- Significantly increased risk of serious pneumonia for
  - ICS vs placebo: risk ratio 1.51 (95%CI 1.08–2.10)
    285 events/3,881 patients vs 180 events/3,633 patients
  - ICS + LABA vs LABA: risk ratio 1.72 (95%CI 1.28–2.30)
    356 events/4,754 patients vs 217 events/4,728 patients
  - Total: ICS vs no ICS: risk ratio 1.60 (95%CI 1.33–1.92)
    641 events/8,635 patients vs 397 events/8,361 patients

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.

Singh S, et al. Arch Intern Med 2009;169:219–29

Inhaled corticosteroids do not improve symptoms of breathlessness



ns = not significant

Calverley PMA et al. Lancet 2003;361:449–56

Roflumilast (Daliresp)

- Phosphodiesterase E4 inhibitor
- Approval: 2011
- Indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
- Dose 500 ug once daily

Recommendations for Use of Roflumilast in Primary Care

- Clear identification of patients eligible for roflumilast
- Phenotyping of patients in primary care
  - lung function measurement (FEV1<50%)
  - accurate health status classification
    - At least 1 exacerbation last year
    - Smoking > 20 pk/years
  - recording of chronic cough and regular sputum production

Price, D et al. Prim Care Respir J. 2011 Mar;20(1):45.

Additional Concerns with Roflumilast

- Roflumilast and suicidal thoughts or depression
- 20% of patients in trial had 5-10% weight loss
- GI Side effects

Group D COPD Patients

D	Inhaled corticosteroid + long-acting $beta_2$-agonist and/*or* Long-acting anticholinergic	Inhaled corticosteroid plus long-acting anticholinergic and long-acting $beta_2$-agonist *or* Inhaled corticosteroid plus long-acting $beta_2$ agonist and phosphodiesterase 4 inhibitor *or* Long-acting $beta_2$ agonist and long-acting anticholinergic *or* Long-acting anticholinergic and phosphodiesterase 4 inhibitor	Carbocysteine Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline

Non-Pharmacologic Treatments for COPD

- Smoking Cessation
- Pulmonary Rehabilitation
- Oxygen Therapy
- Ventilatory Support
- Lung Volume Reduction Surgery
- Lung Transplantation
- Vaccination

From: Global Strategy for Diagnosis, Management and Prevention of COPD. GOLD Slideset 2015

Global Strategy for Diagnosis, Management and Prevention of COPD

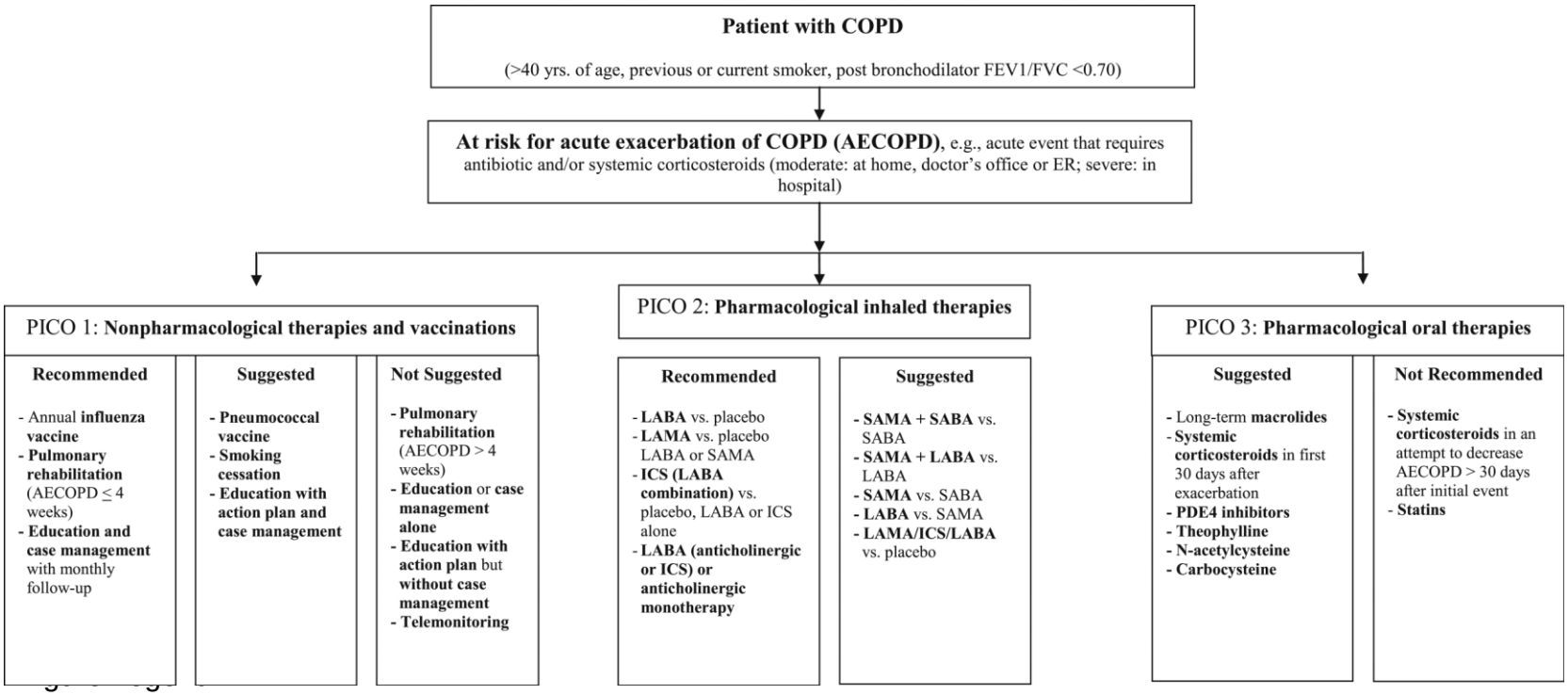
Manage Stable COPD: Non-pharmacologic

Patient Group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B, C, D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

CHEST™

From: Prevention of Acute Exacerbations of COPDCHEST and CTS AECOPD Guideline: American College of Chest Physicians and Canadian Thoracic Society Guideline

Chest. 2015;147(4):894-942. doi:10.1378/chest.14-1676



Decision tree for prevention of AECOPD according to three key clinical questions using the PICO format: nonpharmacologic therapies, inhaled therapies, and oral therapies. Note that the wording used is "recommended or not recommended" when the evidence was strong (level 1) or "suggested or not suggested" when the evidence was weak (level 2). AECOPD = acute exacerbation of COPD; ER = emergency room; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; PICO = population, intervention, comparator, outcome; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist.

Selected Topics

Benefits of Pulmonary Rehab In Patients with COPD

- Improve exercise capacity
- Enhance quality of life (QOL)
- Decrease exacerbations within 30 days of discharge
- Impact on Hospitalization and Mortality*

*Inconsistently shown

Mortality Benefits of Pulmonary Rehabilitation (N=246)

Endpoint	(-) Rehab	(+) Rehab
Hospitial LOS for Respiratory Related Illness	↑25%	↓20%
Mortality for Respiratory Related Illness	39%	7%
BODE Score	↑4% (worsened)	↓19% (improved

Cote CG, Celli BR Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J. 2005;26(4):630

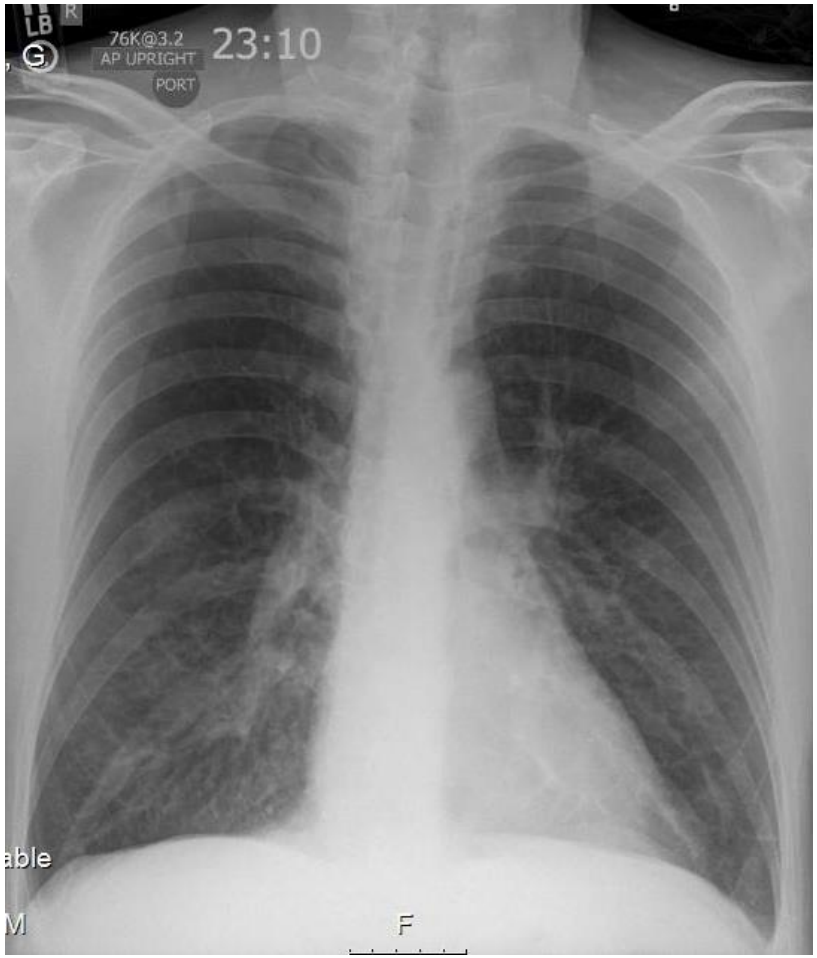
Surgical Options for Advanced COPD

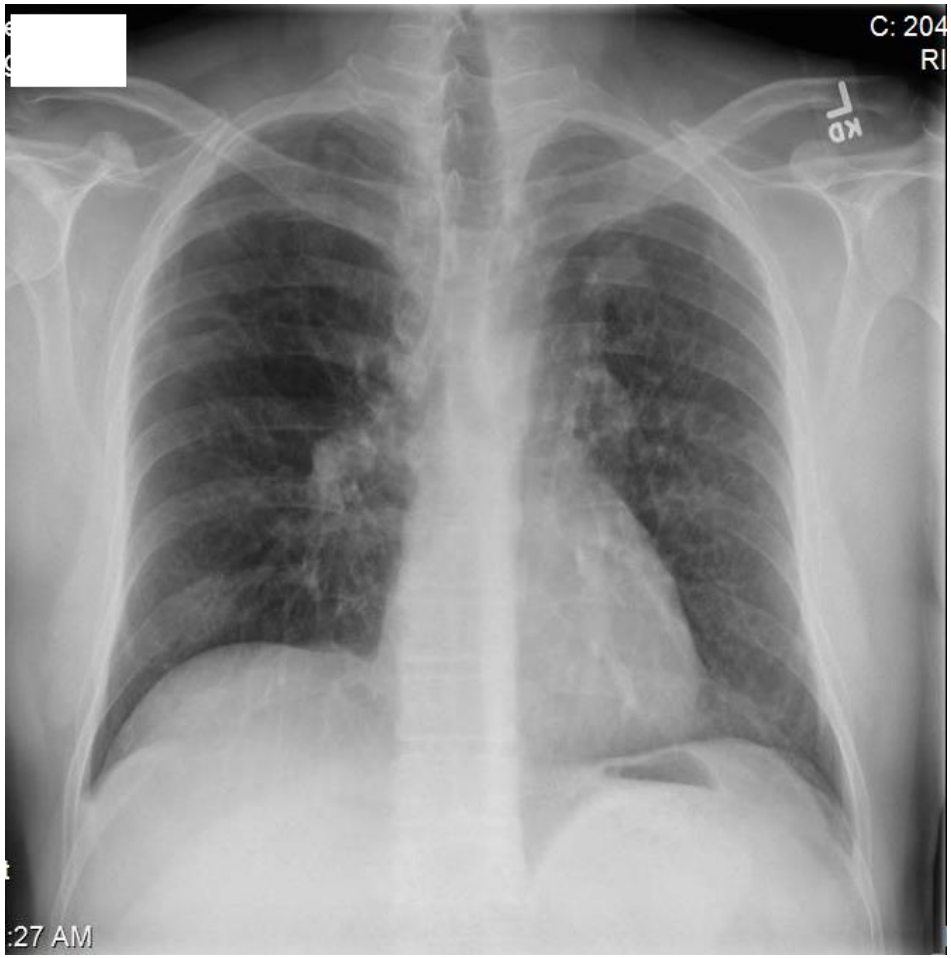
- Lung Volume Reduction Surgery
- Lung Transplantation

Lung Volume Reduction Surgery

- Only for Select Emphysema Patients
- Selection Criteria
  - 45% < FEV1 < 25%
  - TLC >100%
  - RV > 150%
  - Post Rehab Exercise Capacity
    - 6MW > 140m
    - CPET with < 40 watts(men), <25 watts(women)

LVRS Results





FEV_1 = 1.60 L (37%)

FEV_1 = 2.23 L (52%)

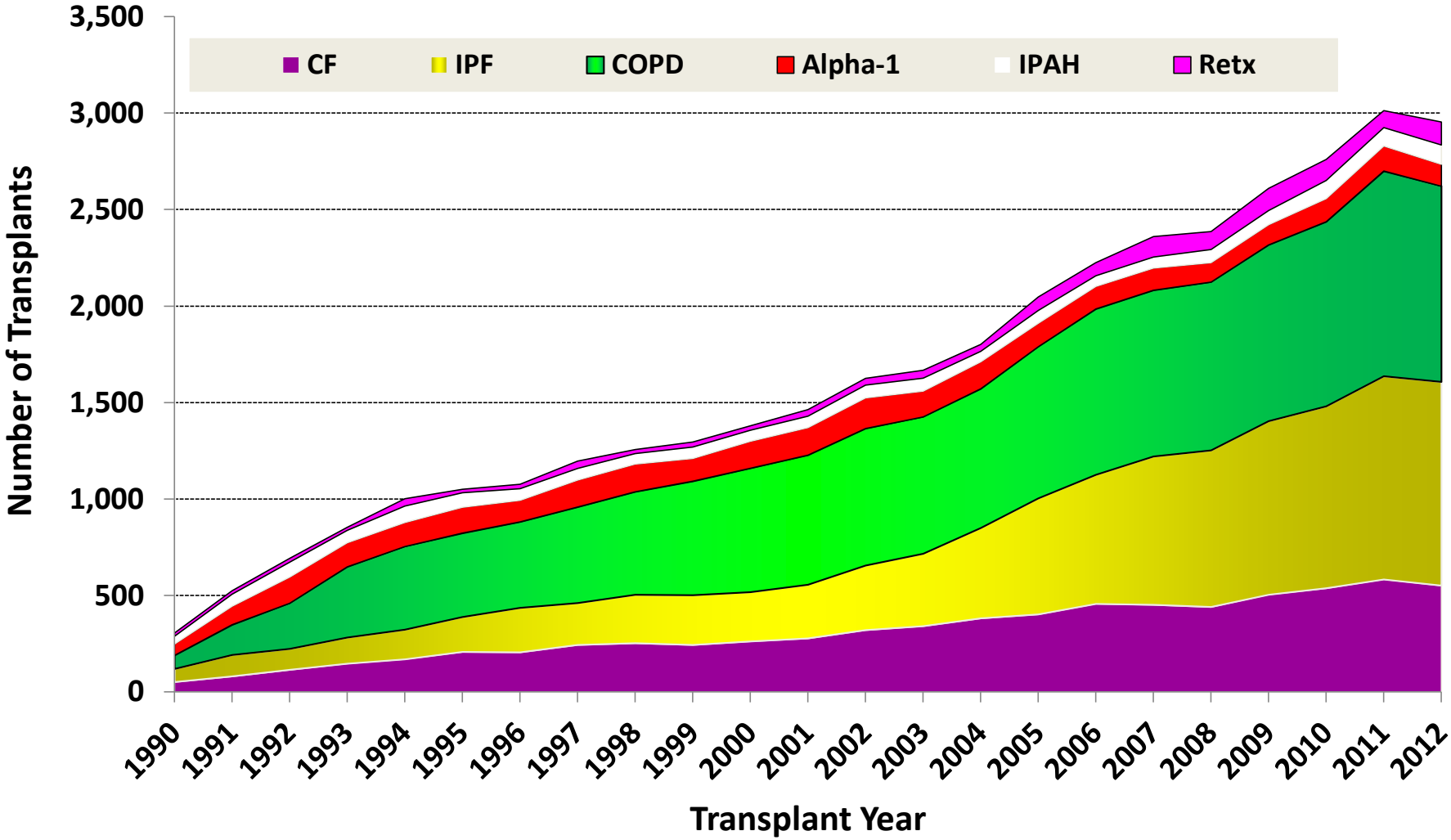
LVRS Results

Pulmonary Testing	Pre-LVRS	Post-LVRS
FEV_1(L/min	1.60 (37%)	2.23 (52%)
FVC (L)	4.29 (76%)	4.70 (84%)
TLC (L)	9.21 (113%)	7.73 (94%)
RV(L)	4.77 (186%)	2.97 (116%)

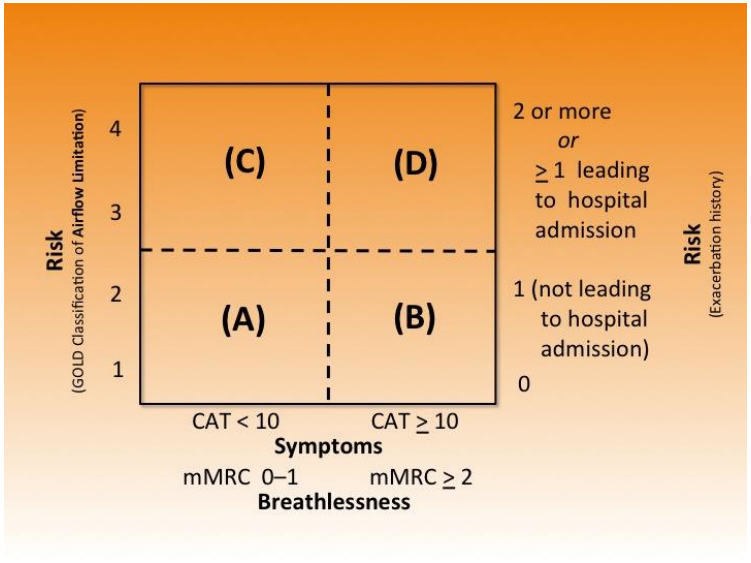
Lung Volume Reduction Surgery

- Exclusions
  - BMI, > 31.1 kg/m^2 (men) or > 32.3 kg/m^2 (women)
  - PCO_2, > 60 mm Hg
  - PO_2, < 45 mm Hg on room air
  - Active Smoking or quit < 4 months
  - Alpha 1 Antitrypsin Disease
  - Non-Apical Distribution of Emphysema

Adult Lung Transplants
Major Indications by Year (Number)



Summary



Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk.)*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	< 10	0-1
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 10	≥ 2
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce symptoms

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

Reduce risk

Manage Stable COPD: All COPD Patients

- Avoidance of risk factors
  - smoking cessation
  - reduction of indoor pollution
  - reduction of occupational exposure
- Influenza vaccination

Manage Stable COPD: Key Points

- Identification and reduction of exposure to risk factors are important steps in prevention and treatment.
- Individualized assessment of symptoms, airflow limitation, and future risk of exacerbations should be incorporated into the management strategy.
- All COPD patients benefit from rehabilitation and maintenance of physical activity.
- Pharmacologic therapy is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance.

Manage Stable COPD: Key Points

- Long-acting formulations of beta$_2$-agonists and anticholinergics are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.
- Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients with high risk of exacerbations.

Manage Stable COPD: Key Points

- Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.
- The phospodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with $FEV_1 < 50\%$ of predicted, chronic bronchitis, and frequent exacerbations.

Q: Does the recent proliferation of new therapeutic agents for really change our treatment of COPD?
A: Quite Possibly

Q: Should I think about COPD Patients Differently?
A: Almost Certainly

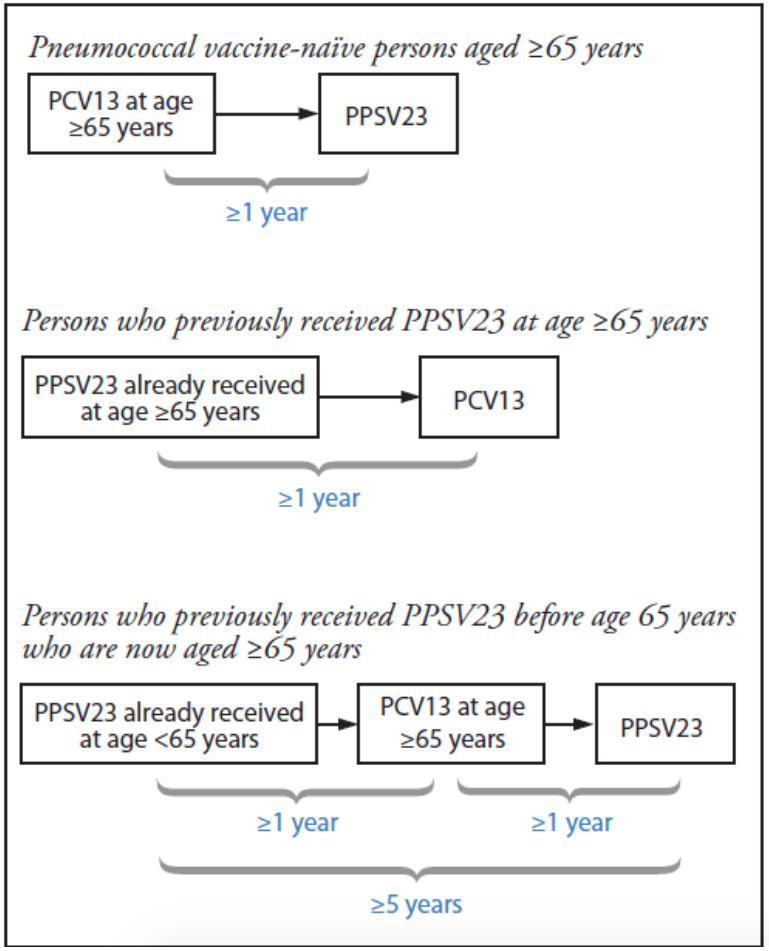
Appendix and Supplementary Slides

Carbocysteine

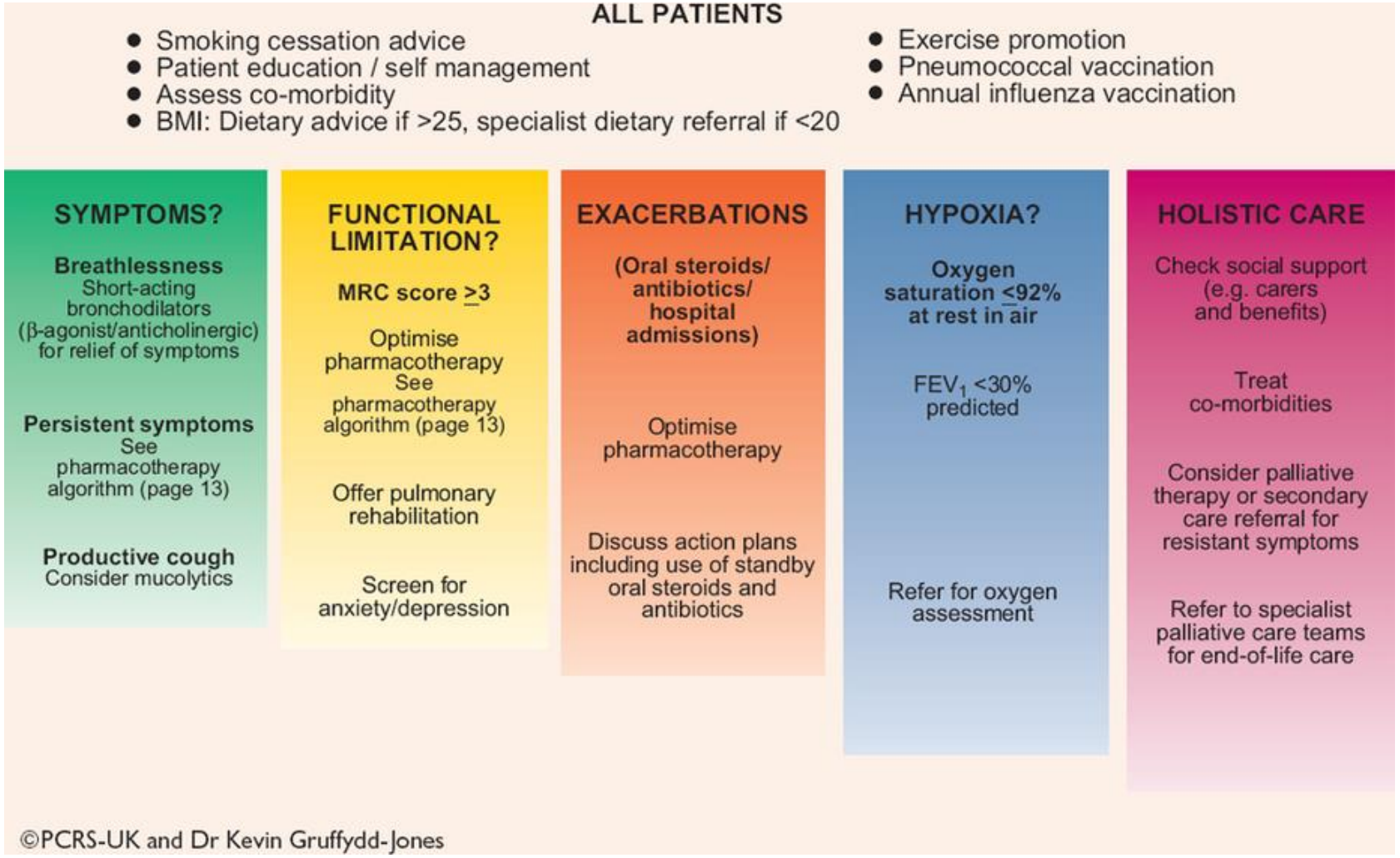
(R)-2-Amino-3-(carboxymethylsulfanyl)propanoic acid

- Not available in the United States
- Multiple Actions
  - muco-active drug
  - free radical scavenging
  - anti-inflammatory properties

ACIP Guidelines for Pneumococcal Vaccination



Multifactorial Approach to the COPD Patient

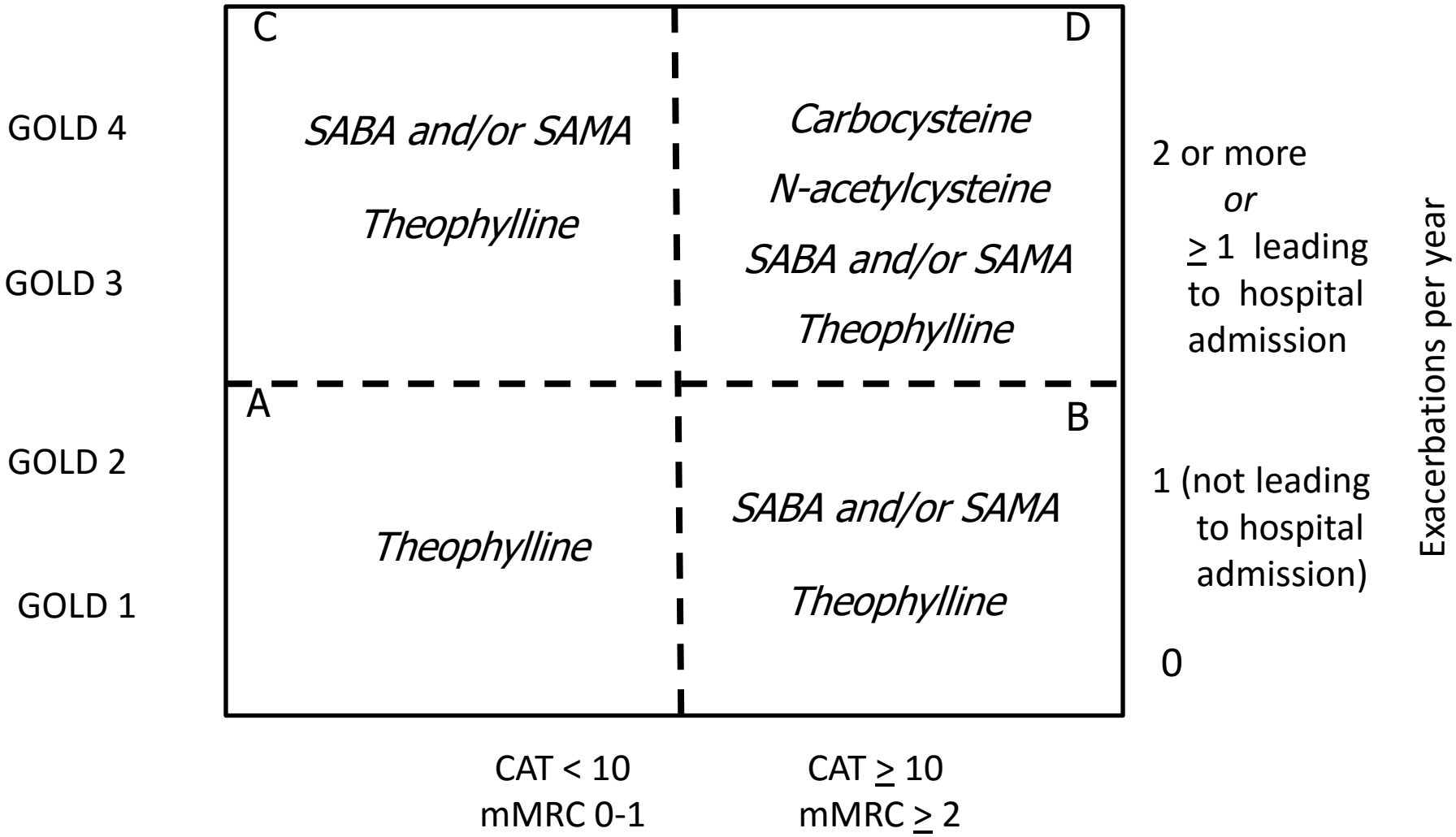


Kevin Gruffydd-Jones *Primary Care Respiratory Journal* (2012) **21**, 437–441

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

OTHER POSSIBLE TREATMENTS



Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: COPD Medications

Beta$_2$-agonists
Short-acting beta$_2$-agonists
Long-acting beta$_2$-agonists
Anticholinergics
Short-acting anticholinergics
Long-acting anticholinergics
Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler Combination long-acting beta$_2$-agonist + anticholinergic in one inhaler
Methylxanthines
Inhaled corticosteroids
Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler
Systemic corticosteroids
Phosphodiesterase-4 inhibitors