### Breathing New Air Into the Treatment of COPD & Asthma

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### **Disclosures Information**

2016 Annual Convention and Scientific Sessions

- I have no relevant or non relevant financial relationship with a commercial interest in this subject or other subject matter.
- I have no financial relationships to disclose.
- I will not discuss off label use or investigational use in my presentation.
- I will discuss the following off label use and/or investigational use in my presentation:

### **Lecture Objectives**

- Introduce new and interesting issues related to the diagnosis, assessment and management of obstructive pulmonary disease (COPD), Asthma and Overlaps.
- Discuss how to individualize pharmacological therapy in airflow obstruction.
- Examine contemporary strategies to assess, manage, and reduce exacerbations (multisystems).

# We Know Airflow Disease Is Important

# Respiration: The essence of life



"The Lord formed a man from the dust and breathed into his nostrils the breath of life, and the man became a living being" (Genesis)



Absence of a breathing is tested with a CO2 challenge Determining brain death in adults: American Academy of Neurology. Neurology 2010;74;1911

# Obstructive Pulmonary Diseases are <u>not</u> glamorous





# The Diseases are NOT Sexy



# Why It Matters Major Health Problem

- 30% increase in deaths worldwide in the past 10 years.
- The 3<sup>rd</sup> leading cause of death.
- Adults with COPD (compared to general population)
  - Unable to work (24 % vs. 5%)
  - Activity limitations (50% vs. 17%)
  - Difficulty walking, climbing stairs (38% vs. 11%)
  - Require specialized equipment (22% vs. 7%)

MMWR 2015; 64(11): 289 – 295. WHO. October, 2015. www.who.int/respiratory/copd.burden/en/

# **The Longitudinal History**



Years of Death

# What Went Wrong In Obstructive Pulmonary Disease



"In 14 years of modeling, this is my favorite shot of myself."

my favorite shot of myself."

Christy Turlington considers quitting smoking her biggest success. One of her biggest regrets is that she ever started.

CENTERS FOR DISEASE CONTROL AND PREVENTION



# **Airflow Heterogeneity**

Cote & Celli

	<u>PT # 1</u>	<u>PT # 2</u>	<u>PT # 3</u>	<u>PT #4</u>
	58 y	62 y	69 y	72 y
	FEV1: 28 %	FEV1: 33%	FEV1: 35%	FEV1: 34%
	MRC: 2/4	MRC: 2/4	MRC: 3/4	MRC: 4/4
	PaO2: 70 mmHg	PaO2: 57 mmHg	PaO2: 66 mmHg	PaO2: 60 mmHg
	6MWD: 540 mt	6MWD: 400 m	6MWD: 230 m	6MWD: 154 m
>	BMI: 30	BMIE 21	BMII: 34	BMIE 24
>	SCORE: 3	SCORE: 6	SCORE: 7	SCORE: 9
	STREE STREE	CH & Canton	120	
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		E		

FEV<sub>1</sub> 88% predicted FEV<sub>1</sub> % 72% Interpretation: Normal

FEV1102% predictedFEV1 %73%Interpretation: Normal

FEV181% PredictedFEV1 %74%Interpretation: Normal



# The Proportional Venn Diagram of Obstructive Lung Disease\*

<u>Non-proportional</u> Venn diagram of COPD showing subsets of patients with chronic bronchitis, emphysema, and asthma. The subsets comprising COPD are shaded.



Joan B. Soriano. Chest, Volume 124, Issue 2, 2003, 474–481 http://dx.doi.org/10.1378/chest.124.2.474

# The Proportional Venn Diagram of Obstructive Lung Disease\*

<u>Proportional</u> Venn diagram of COPD showing subsets of patients with chronic bronchitis, emphysema, and asthma. The subsets comprising COPD are shaded.



Proportional Venn diagram of OLD and airflow obstruction in the United States (NHANES III surveys from 1988 to 1994) in participants aged  $\geq$  50 years. Open circles within each area represent the proportion of OLD patients with objective airflow obstruction according to spirometry measurements. Note that there are eight open circles, one for each of the seven mutually exclusive conditions plus one on the right that represents participants with airflow obstruction who did not receive an OLD diagnosis.

Joan B. Soriano. Chest, Volume 124, Issue 2, 2003, 474–481 http://dx.doi.org/10.1378/chest.124.2.474

#### Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome:



### **Percentage of Patient with Overlap**



Soriano et al. Chest, Volume 124, Issue 2, 2003, 474–481 http://dx.doi.org/10.1378/chest.124.2.474

# Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome



#### Gerhardsson de Verdier M Value Health 2015; 18: 759

# Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome



Menezes AM et al PLANTINO Team. Chest 2014; 145(2): 297-304

# Frequency of exacerbations among patients with ACOS, COPD & Asthma



Miravitles M, Sorian JB, Ancochea J et al. Respir Med 2013; 107 (7) 1053 – 1060. Hardin M et al . Eur Respir J 2014; 44(4): 341-350. Menezes AM et al PLANTINO Team. Chest 2014; 145(2): 297-304.

## **Overlap Syndrome**

- Why is the Overlap between Asthma and COPD important?
- Patients are rarely included in clinical trails.
- ~ 50% develop fixed airflow limitations over the course of their lifetime.
  - ? corticosteroid resistance.
- May not be related to smoking.
- Diagnostic & prognostic purposes are unclear at present time.

# Obstructive Pulmonary Disease Risk & Smoking Cessation

Study of 749 men followed for 8 years. 1977



Adapted from Fletcher et al. Brit Med J. 1977;1:1645-1648

## **Course of Lung Function**



Adapted from Martinez, F et al. NEJM. 2016; 375: 871 – 8.

# Airway Function in early infancy & by age 22 years: a non-selective longitudinal cohort study

123 babies born Tucson Lung function at 2 m and 11, 16, & 22 Years



participants at ages 11, 16, and 22 years. We included an interaction term between survey (age 11, 16, and 22) and quartiles of infant VmaxFRC in the random-eff ects models. P values were estimated at each survey from the models.

#### Adapted from Stern D et al. Lancet 2007; 370: 758-64

### The Natural History Analysis of the Framingham Offspring Cohort



**Figure**. Mean FEV1 values (expressed as percent of its value at the age of 25) by age, for healthy never-smokers (NS), and continuous smokers (CS). (*A*) Data for males and (*B*) for females. The mean FEV1 decline value (and 95% confidence intervals) for males was 38.2 ml (33.9–42.6) and for females 23.9 ml (20.9–27.0), with a *P* value < 0.001. \**P* < 0.05 versus healthy never-smokers.

Adapted from Kohasnsal R, et al. Am J Respir Crit Care Med. 2009; 180: 3 – 10 Kalhan R et al. AJM 2010 123, 468. e1 – 468.e7

# **Birth - Course of Lung Function**



Determinants of loss

Adapted from Lange P et al. NEJM. 2015; 372: 2

## What Can Be Done?



Time

### **Biomarkers in COPD Patients**



Man et al. Thorax 2016; 61: 349

# Biomarkers CRP - Sensitive, but lacks Specificity



Relative Risk of Mortality for 1 SD increase in CRP

0.5

## Management / Treatment Goals

- Improve dyspnea
- Improved functional capacity
- Improve quality of life
- Reduce mortality
- Reduce infections & exacerbations
- Improve FEV<sub>1</sub> (lung function)

# **The Gift That Keep Giving**

#### Tobacco, a gift of the Americas to the Old World

Tobacco smoking was used in the Americas for thousands of years before the arrival of Europeans





Rodrigo de Jerez returned with Cristobal Colon and was jailed by the inquisition for 7 years because "only a possessed person could blow smoke from the mouth"

1492

### Barto

and having lighted one part of it, by the other they suck, absorb, receive that smoke inside with the breath, by which they become benumbed and almost drunk, and so it is said they do not feel fatigue. These musket they call tobacos. I knew Spaniards who were accustomed to take it, and being reprimanded for it, by telling them it was a vice, they replied they were unable to ceases using it. I do not know what relish or benefit they found in it

# LUNG HEALTH STUDY: Benefits of Smoking Cessation



Anthonisen et al. Am J Resp Crit Care Med. 2002; 166:675.

# **Combination Therapies**

- Combination Therapies
  - LAMA / LABA combinations
    - Aclidinium/indacaterol [Bretaris Genuair]
    - Umeclidinium/vilanterol [Anoro Ellipta]
    - Tiotropium/olodaterol [Stiolto Respimat]
    - Glycopyrronium/indacaterol [Ultibro Breezhaler]



#### Global Strategy for Diagnosis, Management and Prevention of COPD Pharmacologic Therapy = First Choice



Adaptive from © 2015 Global Initiative for Chronic Obstructive Lung Disease



Prevention of exacerbation is key treatment goal for patients with airflow obstruction

**COPD** exacerbations

Impaired quality of life

Accelerated lung function decline

**Frequent hospitalizations** 

**Increased mortality** 



### Exacerbations are Associated with a Decline in Health Status



**Exacerbation Frequency** 

SGRQ= St. George's Respiratory Questionnaire

Seemungal et al. Am J Resp Crit Care Med 2000;161: 1608 – 1613.

# Frequent exacerbation are associated with increased mortality



Soler-Cataluna et al. Thorax 2005; 60 : 925 - 931

#### In the POET Study, Treatment with tiotropium or salmeterol



Probability of a first exacerbation of chronic obstructive pulmonary disease (COPD) in the tiotropium and salmeterol groups

Exacerbations delayed 42 days 17% reduction in risk Hazard Ratio 0.83 p<0.001 log-rank test

Probability of a first severe exacerbation of COPD leading to hospitalization (Panel C) in the tiotropium and salmeterol groups

Hazard Ratio 0.72 p<0.001 log-rank test



Kaplan–Meier Curves for the Primary and Selected Secondary Outcomes.

Vogelmeier C et al. N Engl J Med 2011;364:1093-1103

# Experience of frequent exacerbations despite treatment



In the POET Study, a proportion of patient still experience >2 exacerbations during the study period while receiving treatment with tiotropium or salmeterol

Vogelmeier C, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011;364(12). Donaldson GC,, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847–52.

Soler-Cataluña JJ, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease.

Thorax 2005:60:925-31.

Celli B, Decramer M, Leimer I, et al. Cardiovascular safety of tiotropium in patients with COPD. Chest 2010;137:20-30.

# Subgroup Analysis from POET-COPD Study

Subgroup	Tiotropium	Salmeterol	Hazard Ratio (95% CI)	P value for Interaction
	no. of patier	nts/total no.		
Age (yr)				0.76
<55	237/655	258/665	0.88 (0.74–1.05)	
≥55 to <65	484/1462	522/1426	0.87 (0.77–0.98)	
≥65	556/1590	634/1578	0.83 (0.74–0.93)	
Sex				0.83
Male	913/2759	1016/2747	0.86 (0.78–0.94)	
Female	364/948	398/922	0.84 (0.73–0.97)	
COPD severity stage (GOLD)				0.05
Stage II	561/1781	635/1833		
Stage III	589/1597	627/1545	0.86 (0.77–0.97)	
Stage IV	127/329	152/291		
Smoking status				0.64
Noncurrent smoker	678/1929	746/1896	—— <b>—</b> 0.84 (0.75–0.93)	
Current smoker	599/1778	668/1773	0.87 (0.78–0.97)	
BMI				0.17
<20	105/286	134/271		
≥20 to <25	455/1230	501/1254	0.89 (0.79–1.02)	
≥25 to <30	424/1276	468/1284	0.87 (0.76–0.99)	
≥30	293/915	311/860		
Use of inhaled glucocorticoids at baseline				0.41
Yes	785/1986	839/1955		
No	492/1721	575/1714	0.82 (0.73–0.92)	
			0.4 0.6 0.8 1.0 1.2 1.4	
			Tiotropium Better Salmeterol Better	

#### Vogelmeier C et al. N Engl J Med 2011;364:1093-1103

#### FLAME is the first study to demonstrate superiority of Ultibro<sup>®</sup> Breezhaler<sup>®</sup> in exacerbations

1680 pts indacaterol– salmeterol–fluticasone glycopyrronium group LABA–LAMA

The indacaterol–glycopyrronium group had a delay to first and 11% lower exacerbation rate salmeterol– fluticasone group

(3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003)



FLAME Investigators N Engl J Med 2016; 374:2222-2234

## **Inhaled Corticosteroids**

- Limited efficacy vs. Placebo in monotherapy
  - Inconsistent prevention of FEV<sub>1</sub> decline
  - Reduced exacerbations (decline 0.19 per patient per year)
  - Slowed rate of QoL decline
  - Large role with asthma overlap patients
  - Increase risk of dysphonia & oral candidiasis
  - Debatable increase risk of pneumonia
    - Recent date does not support his risk?

# Inhaled Corticosteroids in DUAL Therapy

- TORCH : salmeterol + fluticasone vs. Individual components or placebo
  - Reduced exacerbation, improved health status and FEV<sub>1</sub>
  - Almost reduced mortality (vs. placebo) p=0.054
- **INSPIRE:** Salmeterol + fluticasone vs Tiotropium (Spiriva)
  - No difference in exacerbation rate
  - Reduced overall mortality in combination (HR 0.48)
  - Improved health scores

N Engl J Med 2007, 356: 775 Am J Respir Crit Care med 2008; 177: 19

# Withdrawal of Inhaled Steroids and Exacerbations of COPD





Magnussem Helgo et al. WISDOM Investigators N Engl J Med 2014; 371: 1285 – 94.

# **Roflumilast (Daliresp)**

- Reduced exacerbation by 13%
- Higher rate of adverse events & withdrawal
- Side effect may limit tolerability
  - Psychiatric symptoms
  - Weight loss
  - Diarrhea, nausea, headaches
  - Contraindicated in advanced liver disease

Martinez F et al. REACT Study Group. Lancet 2015; 385: 857 – 66.

# Azithromycin

- Macrolide antibiotic (1 year)
- Decreased frequency of exacerbations (HR 0.73)
  - Median time to first exacerbation was 266 days among patients receiving azithromycin compared with 174 days in the placebo group (P < 0.001).</li>
- More patient with improved QoL
  - The frequency of exacerbations also was significantly decreased in the azithromycin group.
- Concerns
  - Cardiovascular disease debated (prolonged QT)
  - Hearing loss (25% vs. 20 %)
  - Drug Resistance (did develop)

N Engl J Med 2011, 365: 689 Am J Respir Crit Care med 2014; 189: 1173

# Management of pulmonary disease beyond the lungs



Osteoporosis



Muscle Wasting



Depression/Anxiety

Morbidity & Mortality



Metabolism Disorders



Cognitive dysfunction

Obesity /Underweight

# A Prospective Study of COPD & Risk for Cognitive Impairment



5 year study / 4 different neuropsychological tests

Figure Legend:

Adjusted Kaplan-Meier Plots of Chronic Obstructive Pulmonary Disease (COPD) and Risk for Mild Cognitive Impairment (MCI)A, Relationship between COPD (present or absent) and the percentage of participants free of MCI. B, Relationship between COPD duration (>5 vs ≤5 years) or no COPD and the percentage of participants free of MCI, with age as the time scale.

#### JAMA Neurol. 2014;71(5):581-588. doi:10.1001/jamaneurol.2014.94

# Obstructive Pulmonary Disease A Closer Look at the Muscle

Majority of morbidity & mortality in COPD is related to extrapulmonary manifestations.



Adapted from :Sin DD and Man SFP. Thorax 2006; 61: 1-3



Normal = Dark Cell are Type II Fibers



Destruction of connective tissue, loss of type II fibers, disorganized tissue Body Mass, Fat-Free Mass, and Prognosis in Patients with Chronic Obstructive Pulmonary Disease from a Random Population Sample: Finding from the Copenhagen City Heart Study

- 1898 pts with COPD
- Bioelectric impedance measurement
- 7 year follow-up
  - ♂ FFMI 16kg/m<sup>2</sup>
  - ♀ FFMI 18.7 kg/m<sup>2</sup>





Vestbo J et al. AJRCCM 2006;173:79-83 Ferreira IM et al. Cochrane Database Sys Rev 2012 12: CD000998 Body Mass, Fat-Free Mass, and Prognosis in Patients with Chronic Obstructive Pulmonary Disease from a Random Population Sample: Finding form the Copenhagen City Heart Study

	Low FFMI	Low BMI	Normal BMI
Overall Mortality	1.5	1.8	1.3
COPD Mortality	2.4	3.2	2.0

Vestbo J et al. AJRCCM 2006; 173: 79-83

# Nutritional Supplementation has uncertain effects on patient important outcomes

NUTRITIONAL SUPPLEMENTATION VS. PLACEBO OR USUAL DIET (CONTROL) IN STABLE COPD

Outcomes	# of trails (n)	At end of Intervention		
		Supplement	Control	Mean diff. (95% CI)
Mean weight, kg	14 (512)	57	56	0.69 ( - 0.86 to 2.24)
Mean 6-min walk distance, m	5 (142)	411	397	14 (- 25 to 53)
Health Related QoL Score, total	4 (130)	NR	NR	- 0.36 (-0.77 to 0.06)
		Change fror	n baseline	to end of Intervention
Mean weight, kg	14 (511)	1.49	- 0.13	1.62 (1.27 to 1.96) kg
Mean 6-min walk distance, m	5 (140)	26	-14	40 (23 to 57) meters

I.M. Ferreira, D. Brooks, J. White, R. Goldstein. Nutritional supplementation for stable chronic obstructive pulmonary disease Cochrane Database Syst Rev, 12 (2012) CD000998.

# Management of pulmonary disease beyond the lungs

60-yr-old pts with echocardiographically confirmed CHF (n=5201) 60-yr-old pts with clinically & spirometry confirmed COPD (n=5218)

100



# Management of pulmonary disease beyond the lungs

Baseline Echocardiogram	CHF Group	COPD Group
Ejection Fraction %	32± 8	Pt <40% = 30
LVEDP	59.7 ± 9	47.4 ± 5
PA Systolic Pressure (mmHg)	39.8	Pt = 7 (diastolic dysfunction)
		Totals = 17% with HF
Baseline Lung Function	CHF Group	COPD Group
GOLD I (FEV <sub>1</sub> %<70, FEV <sub>1</sub> $\ge$ 80%)	13 (6.5%)	55 (25.2%)
GOLD I (FEV <sub>1</sub> %<70, FEV <sub>1</sub> $\ge$ 80%) GOLD II (50% $\le$ FEV <sub>1</sub> $\ge$ 80%)	13 (6.5%) 36 (17.9%)	55 (25.2%) 112 (51.4%)
GOLD I $(FEV_1 \% < 70, FEV_1 \ge 80\%)$ GOLD II( 50% $\le FEV_1 \ge 80\%)$ GOLD III( 30% $\le FEV_1 \le 50\%)$	13 (6.5%) 36 (17.9%) 25 (12.9)	55 (25.2%) 112 (51.4%) 35 (16%)

Totals = 37.3% w/ COPD

Macchia A. et al. Eur Respir J 2012; 39: 51 – 58.

### **Kaplan–Meier estimates of Survival**



Kaplan–Meier estimates of survival of patients with chronic obstructive pulmonary disease with left ventricular dysfunction (-----) and <u>without</u> left ventricular dysfunction (-----). Hazard ratio 2.34 (95% CI 0.99–5.54); p=0.053.

Kaplan–Meier estimates of survival of patients with chronic heart failure with airway obstruction (------) and without airway obstruction (------). Hazard ratio 0.77 (95% CI 0.37–1.58); p=0.474.

# Obstructive Pulmonary Disease Summary

- Remains a major cause of morbidity and mortality.
- There have been new insights into its pathophysiology & the role of inflammation.
- Management required a multisystem approach.
- We must look beyond the lungs to care for these patients.