

# Burden of COPD Exacerbations and Implications in Patients with COPD

Friday, June 17, 2011  
Madrid I ~ 3:25pm - 4:10pm

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## Objectives

- Discuss the burden of COPD
- Review incidence and implications of COPD exacerbations
- Consider the current guidelines for COPD management
- Review current and future treatment options

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**Burden of Chronic Obstructive  
Pulmonary Disease (COPD)  
Exacerbations and Implications  
in Patients With COPD**

Dennis M. Parker, M.D., F.C.C.P.

June 17, 2011

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**Disclosures**

- I am a paid consultant for:
  - GSK
  - Merck
  - Pfizer
- I have not received any financial consideration for this presentation from the above companies

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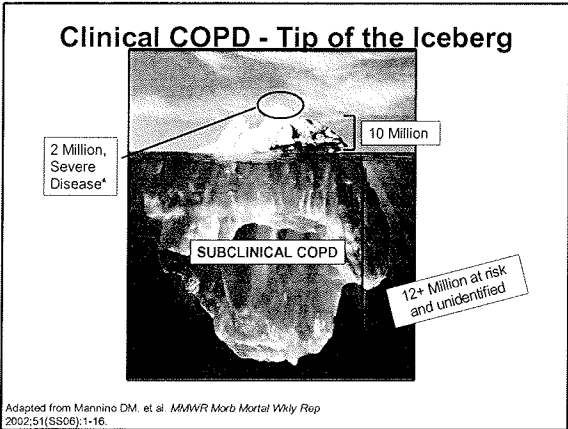
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### The Majority of Healthcare Costs for Managing COPD Are Associated With Exacerbations

- Total costs for COPD were estimated to be \$49.9 billion in 2007<sup>1</sup>
  - \$29.5 billion in direct costs
- 50%-75% of all COPD costs are for services associated with exacerbations<sup>2</sup>

1. American Lung Association. *Trends in chronic bronchitis and emphysema: morbidity and mortality*. February 2010. [www.lungusa.org](http://www.lungusa.org). Accessed June 2, 2010. [www.nhlbi.nih.gov/resources/docs/cht-book.htm](http://www.nhlbi.nih.gov/resources/docs/cht-book.htm). Accessed April 1, 2010.  
2. American Thoracic Society/European Respiratory Society. *Standards for the diagnosis and management of patients with COPD* [Internet]. Version 1.2. [www.thoracic.org/go/copd](http://www.thoracic.org/go/copd). Accessed June 2, 2010.

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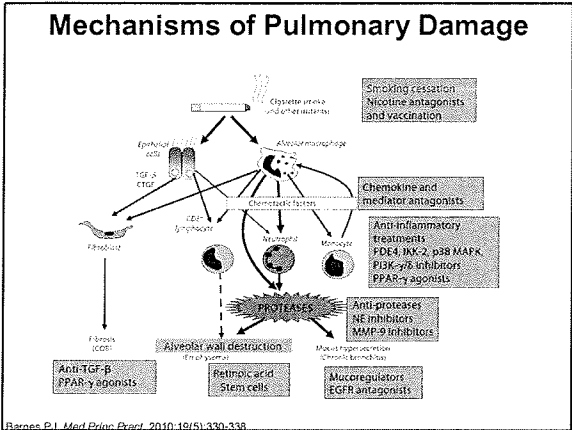
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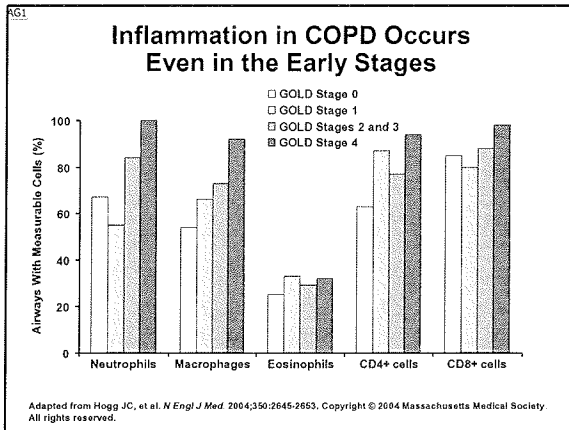
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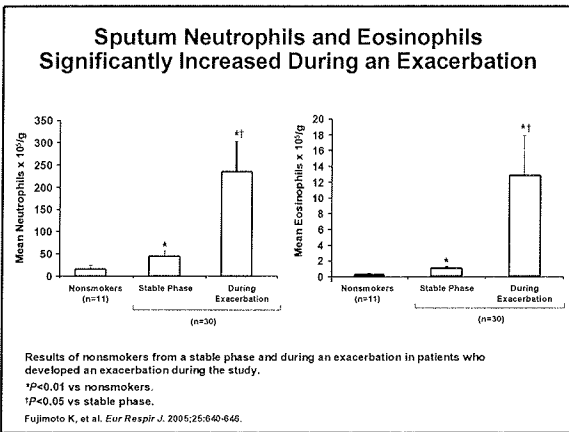
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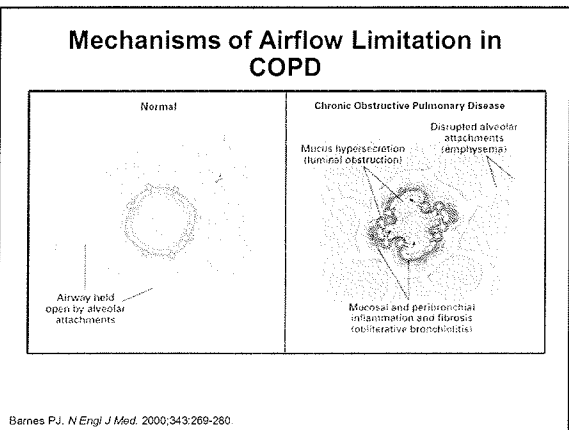
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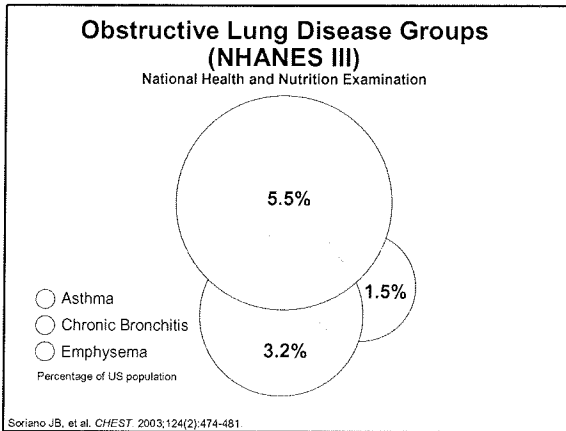
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**Slide 10**

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**AG1** Please include the notes in the "Notes" as speaker notes  
Anne Grimm, 6/3/2010




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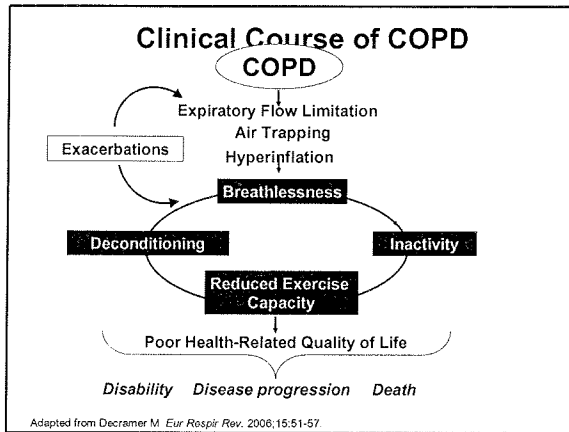
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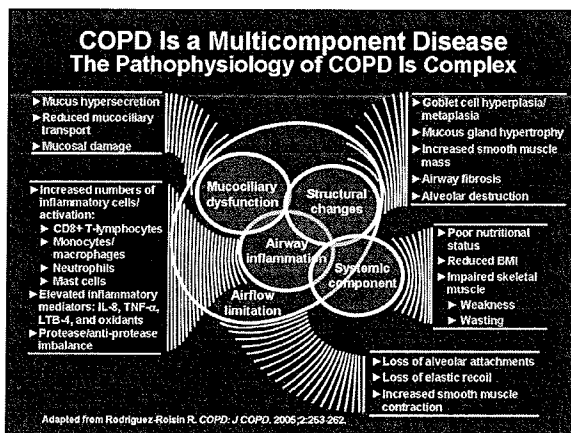
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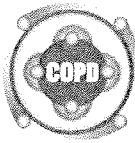
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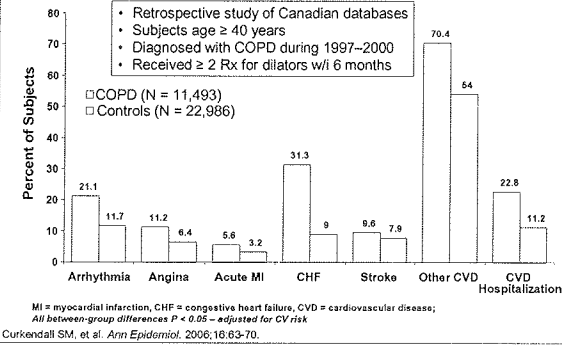
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# Respiratory Speakers Forum

## Increased Risk for Cardiovascular Disease in COPD




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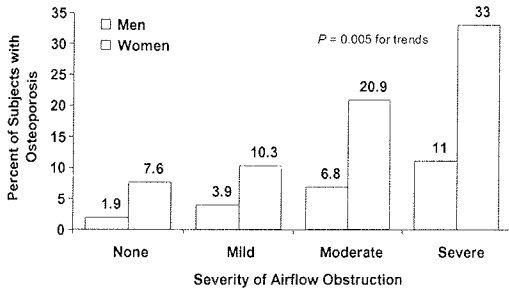
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## The Risk of Osteoporosis in Caucasians With Obstructive Airways Disease



Sin DD, et al. *Am J Med.* 2003;114:10-14.

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## Skeletal Muscle Dysfunction in COPD

- Low muscle mass
- Poor capillarity
- Low muscle oxidative enzyme activity
- Low fraction of type I fibers
- Muscle inflammation
- Corticosteroid myopathy
- Low levels of anabolic hormones
- Vasoregulatory abnormalities

Lactate Increase During Exercise



Mattainis F, et al. *Am J Respir Crit Care Med.* 1996;153:288-293

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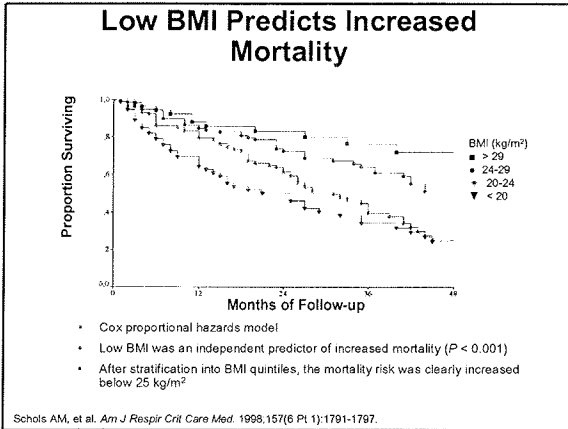
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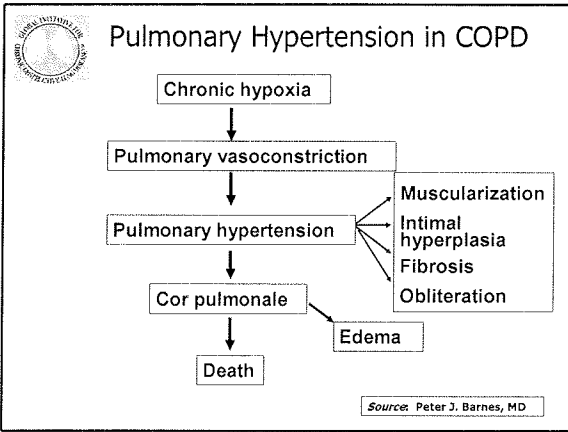
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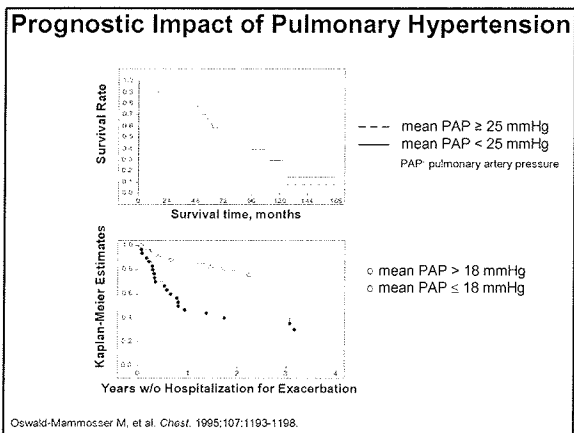
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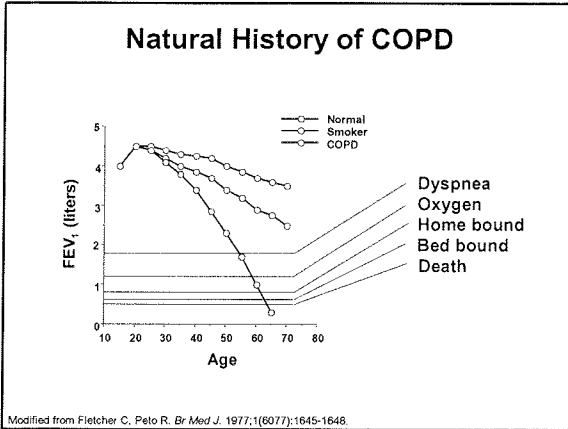
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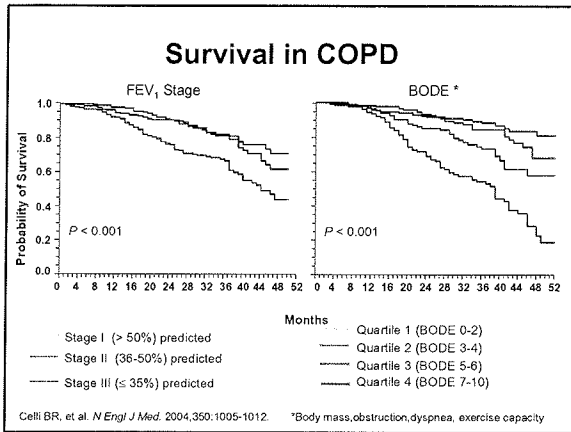
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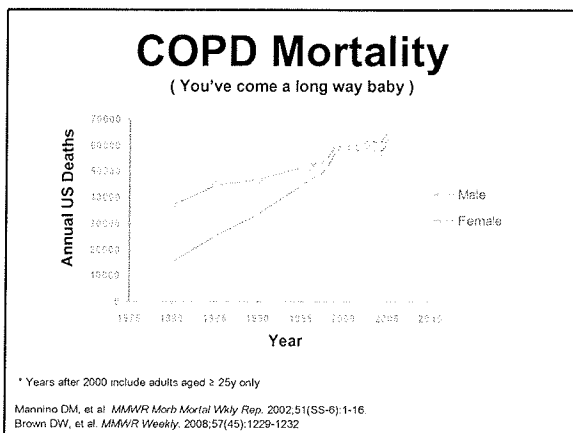
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### Four Components of COPD Management

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

GOLD Recommendations. Updated 2008.  
<http://www.goldcopd.com/Guidelineitem.asp?1=2&2=1&intid=2003>. Accessed September 2010.

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### Exacerbation Definition

- The definition of a COPD exacerbation is an acute change in a patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in therapy

American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. [www.thoracic.org/guidelines/copd](http://www.thoracic.org/guidelines/copd). Accessed June 2, 2010.

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### What Is the Incidence of COPD Exacerbations?

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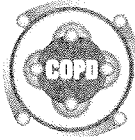
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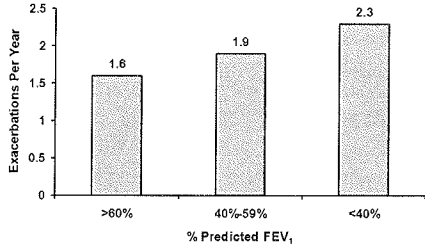
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### Exacerbation Frequency Increases With Disease Severity



Results based on a cross-sectional observational study of ambulatory COPD patients in Spain. General practitioners (N=201) between October 1994 and May 1995 completed a questionnaire on COPD characteristics of 1001 patients.  
Exacerbation was defined as an increase in dyspnea, sputum volume, and/or sputum purulence.  
Miravilles M, et al. *Respir Med*. 1999;93:173-178.

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### What Are the Implications of Exacerbations in Patients With COPD?

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### Evaluation of Link Between Exacerbations and Decline in Lung Function

**Objective:**

- Evaluate the relationship between the frequency of exacerbations and the decline in lung function

**Study Design:**

- Included patients with COPD attending outpatient clinics (FEV<sub>1</sub> <70% of predicted)
- In diaries, 109 patients recorded daily PEF, increase in symptoms (above normal)
  - Daily FEV<sub>1</sub> was recorded in subset of patients (n=32)
- Exacerbations were diagnosed based on diary cards or patients contacting the investigator
  - Exacerbations were defined as the presence for 22 consecutive days of increase in any 2 "major" symptoms (increase in dyspnea, sputum purulence, or sputum volume) or an increase in 1 "major" and 1 "minor" symptom (increase in nasal discharge, wheeze, sore throat, cough, or fever)
- Data were collected over 4 years

Donaldson GC, et al. *Thorax*. 2002;57:847-852.

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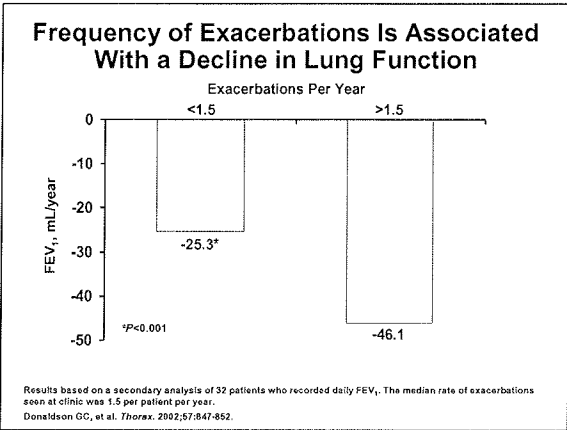
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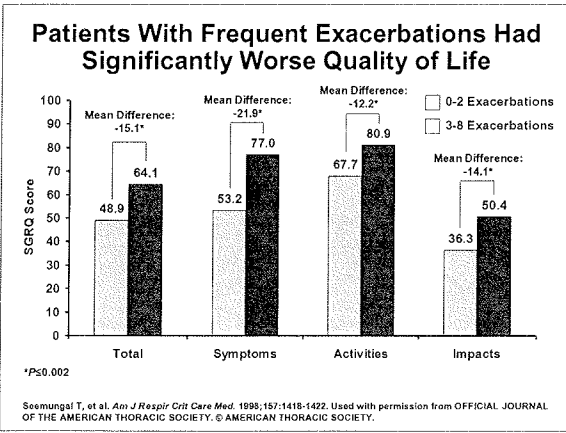
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### Recovery of Lung Function and Symptoms Following an Exacerbation Is Often Prolonged and Sometimes Incomplete

|   | PEF      | Symptoms |
|---|----------|----------|
| Time to recovery,* median days (IQR)              | 6 (1-14) | 7 (4-14) |
| Exacerbations recovering within 35 days           | 75.2%    | 86.1%    |
| Exacerbations recovering within 91 days           | 80.2%    | 90.9%    |
| Exacerbations that did not recover within 91 days | 7.1%     | 4.6%     |

\*Recovery time was defined as the time for the parameter (PEF or symptoms) to return to baseline from the onset of the exacerbation. Baseline was defined as the 8- to 14-day period preceding the exacerbation.  
 Data are not shown for the percentage of exacerbations where recovery time could not be determined and where the next exacerbation occurred before complete recovery.  
 IQR=interquartile range.  
 Seemungal T, et al. *Am J Respir Crit Care Med*. 2000;161:1608-1613.

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**What Are the Guideline  
Recommendations Regarding  
Exacerbations?**

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**Recommendations From COPD  
Management Guidelines**

- ATS guidelines recommend clinicians educate patients on the signs/symptoms of an exacerbation<sup>1</sup>
- GOLD guidelines state preventing exacerbations is key goal in disease management<sup>2</sup>

1. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. www.thoracic.org/goldcopd. Accessed June 2, 2010.  
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2009. www.goldcopd.org. Accessed June 2, 2010.

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**Recommendations From COPD Guidelines**

- ATS guidelines recommend clinicians educate patients on the signs/symptoms of an exacerbation<sup>1</sup>
- GOLD guidelines state preventing exacerbations is key goal in disease management<sup>2</sup>
- ATS guidelines recommend considering an ICS + LABD if patient has  $\geq 1$  exacerbation per year requiring antibiotics or oral corticosteroids (OCS), and FEV<sub>1</sub> <50% predicted<sup>1</sup>

ICS=inhaled corticosteroid; LABD=long-acting bronchodilator

1. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. www.thoracic.org/goldcopd. Accessed June 2, 2010.  
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – Updated 2009. www.goldcopd.org. Accessed June 2, 2010.

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### TORCH: Study Design

|                   | Number of patients at start |      |
|-------------------|-----------------------------|------|
| Run-in<br>2 Weeks | Combination Therapy 500/50  | 1533 |
|                   | Fluticasone propionate 500  | 1534 |
|                   | Salmeterol 50               | 1521 |
|                   | Placebo                     | 1524 |
| 3 Years           |                             |      |

• Aged 40-80 years  
 • FEV<sub>1</sub> < 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.

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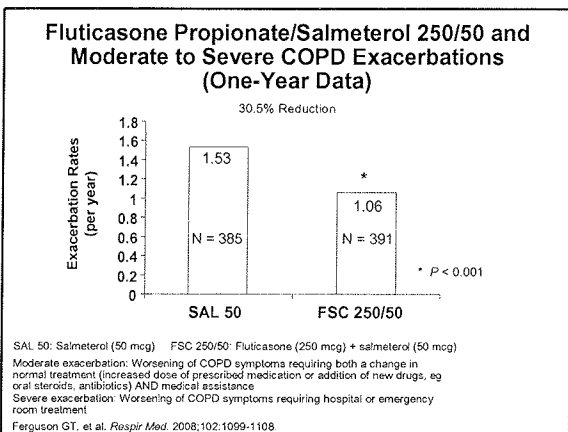
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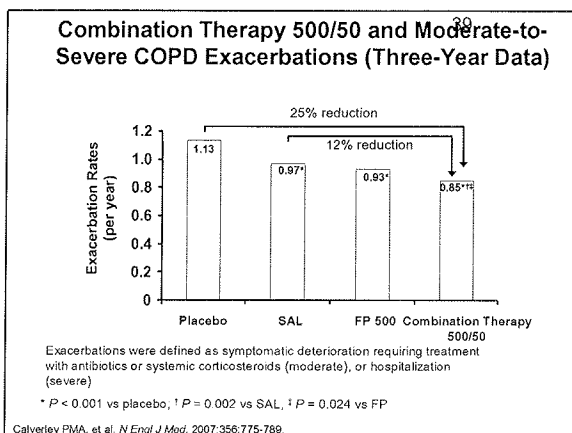
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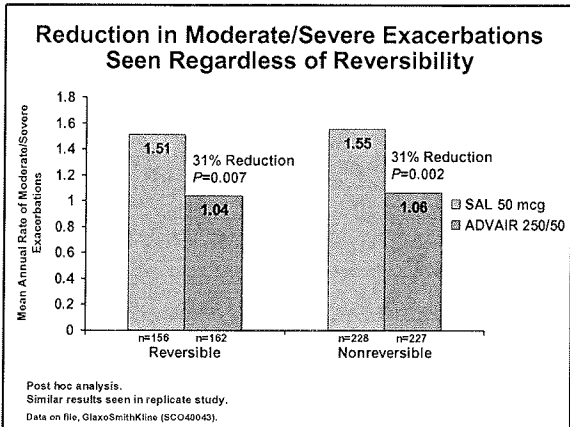
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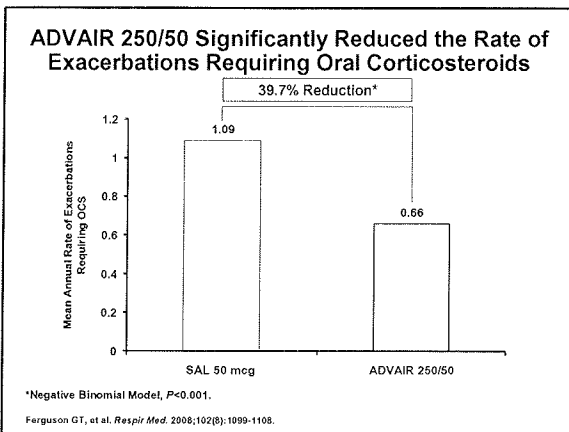
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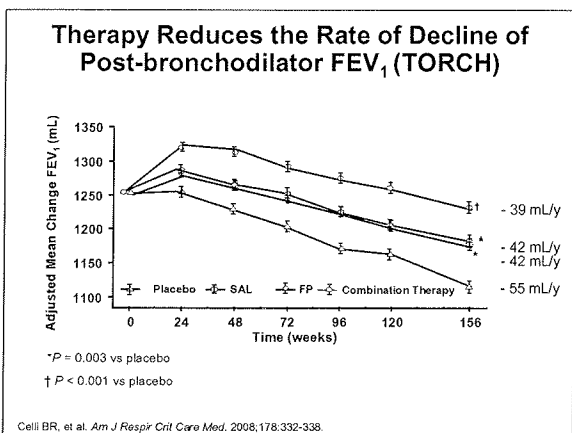
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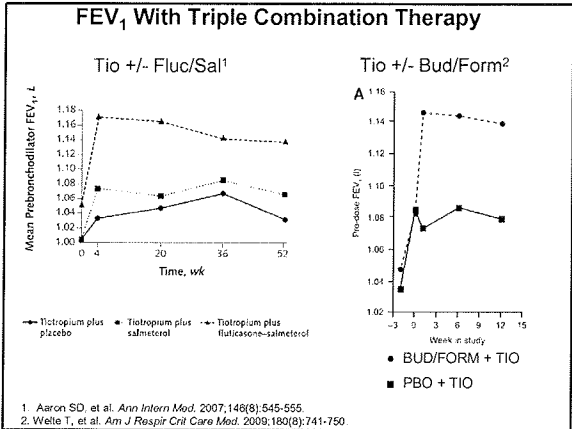
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### Exacerbations With Triple Combination Therapy

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

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

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**What's New?**

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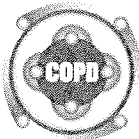
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**Role of High-Resolution Computed Tomography (HRCT) in  
 Diagnosis and Research**

- Characterization of emphysema
  - Identification
  - Regional distribution
  - Quantitation
  - Presence of large bullae
  - Pre-operative assessment tool for lung volume reduction surgery
- Phenotyping of emphysema vs airways disease (research application)
- Monitoring of structural integrity
- Potential assessment of lung cancer (more common in patients with COPD). Application for lung cancer screening has not yet been established

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**Biomarkers for COPD**

- Sputum
  - Neutrophil count
  - Inflammatory mediators (IL-8, Gro $\alpha$ , LT-B4, neutrophil elastase, MCP-1, neutrophil lipocalin)
  - Myeloperoxidase (MPO)
  - Matrix metalloproteinases 8, 9, 12
  - Exacerbation markers TNF $\alpha$ , IL-8, IL-6, MPO
  - Chemokines CXCR3 and CCR5
- BAL
  - Polymorphonuclear cells
  - Percent CD8 $^+$  T cells higher, CD4 $^+$  lower
  - Inflammation markers elevated (IL-8, IL-6, TNF $\alpha$ , MPO, eotaxin-1, ECP)
- Blood
  - CRP (prognostic but not specific)
  - Fibrinogen
  - Leukocytes
  - TNF $\alpha$
  - Endothelin-1 (also in exhaled breath condensate)

Snell N, Newbold P. *Curr Opin Pharmacol*. 2008;8:222-235.

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**INVOLVE Study Design**

Indacaterol, Formoterol, and Placebo

- Patients with moderate-severe COPD
- 1 $^{\circ}$  endpoint: trough FEV $_1$  (24 hours after dosing) at 12 weeks
- Treatment groups:

| Drug        | Dose       | n   |
|-------------|------------|-----|
| Indacaterol | 300 mcg qd | 437 |
|             | 600 mcg qd | 428 |
| Formoterol  | 12 mcg bid | 435 |
| Placebo     | qd or bid  | 432 |

Dahl R, et al. *Thorax*. 2010;65(6):473-479.

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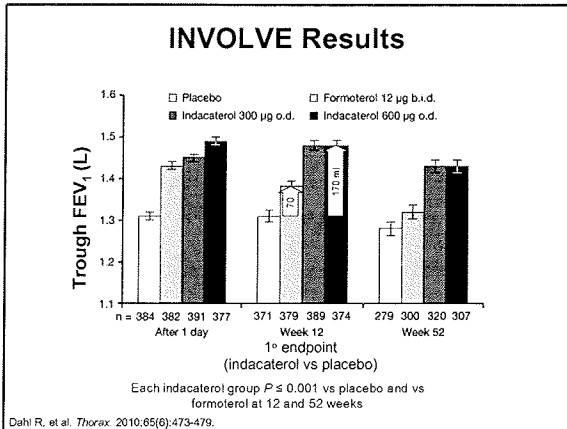
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### PDE4 Inhibitor Roflumilast Study Design

- Anti-inflammatory action
- Previously shown to improve lung function but not exacerbations
- Assess exacerbations in carefully selected patients
- Patients: confirmed COPD
  - Severe airflow limitation ( $FEV_1/FVC \leq 70\%$ )
  - Bronchitic symptoms
  - History of exacerbations
  - Current or former smokers ( $\geq 20$  pack-year history)
  - $> 40$  years old
- 2 parallel identical studies

Calverley PM, et al. *Lancet*. 2009;374(9691):685-694.

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### PDE4 Inhibitor Roflumilast Results

|                                   | M2-124 |      |          |        | M2-125 |      |          |            | Pooled |      |          |            |
|-----------------------------------|--------|------|----------|--------|--------|------|----------|------------|--------|------|----------|------------|
|                                   | Ref    | Pbo  | $\Delta$ | P      | Ref    | Pbo  | $\Delta$ | P          | Ref    | Pbo  | $\Delta$ | P          |
| $\Delta$ pre-dilator $FEV_1$ (mL) | 46     | 8    | 38       | 0.0003 | 33     | -25  | 58       | $< 0.0001$ | 40     | -9   | 48       | $< 0.0001$ |
|                                   |        |      | RR       |        |        |      | RR       |            |        |      | RR       |            |
| Mean exac rate (per pTyr)         | 1.08   | 1.27 | 0.85     | 0.028  | 1.21   | 1.49 | 0.82     | 0.004      | 1.14   | 1.37 | 1.37     | 0.0003     |

- Study confirms efficacy in selected patients with COPD
- No roflumilast effect on mortality or CRP levels
- Diarrhea, nausea, weight loss more common with roflumilast

Calverley PM, et al. *Lancet*. 2009;374(9691):685-694.

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### Lung Volume Reduction Therapies

- Lung Volume Reduction Surgery
- Bronchoscopic Emphysema Treatment
  - Endobronchial unidirectional Valves
  - BioLVR

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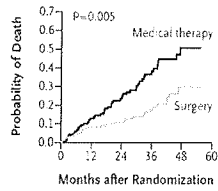
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### Volume Reduction Surgery in Chronic Obstructive Pulmonary Disease: NETT Trial

- 1218 severe COPD patients
- Rehabilitation
- Assess
  - CT distribution
  - Exercise performance
- Randomize
  - Surgery
  - Medical management
- Re-evaluate: 6 months, yearly
- Assess
  - Survival
  - Exercise

Upper lobe disease and poor exercise function



Fishman A, et al. *N Engl J Med*. 2003;348:2059-2073.

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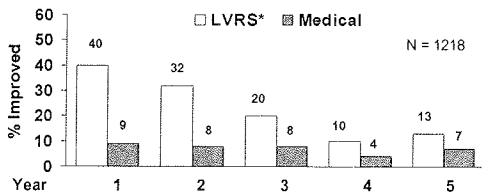
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### Health-related Quality of Life Improvement St. George's Respiratory Questionnaire



|          |         |     |         |     |         |     |       |     |      |     |
|----------|---------|-----|---------|-----|---------|-----|-------|-----|------|-----|
| No. pts. | 608     | 610 | 565     | 568 | 462     | 466 | 305   | 305 | 114  | 122 |
| P        | < 0.001 |     | < 0.001 |     | < 0.001 |     | 0.005 |     | 0.12 |     |

\*LVRs: lung volume reduction surgery

"Improvement": total SGRQ score > 8 units below postrehab baseline

Naunheim KS, et al. *Ann Thorac Surg*. 2006;82:431-443

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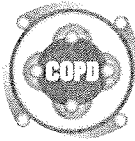
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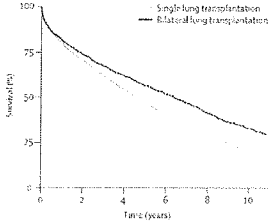
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### Lung Transplantation and COPD



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

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

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### Bronchoscopic Emphysema Treatment

- Unidirectional Valves
  - Results not as good as LVRS
  - Morbidity and Mortality much less
  - Valves not currently available for use in USA
- BioLVR
  - Biodegradable gel inserted into airway
  - Sclerosis of airway collapses segments
  - Not available yet

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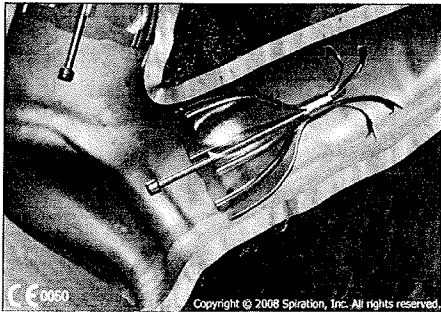
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### Endobronchial Valve



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**Respiratory  
Speakers  
Forum**

Thank You

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