Primary Care Trends

Individualizing Therapy for the COPD Patient: Strategies for Delivering Guideline-Concordant Care

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The leading cause of death in the US is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents

COVID-19
600,000 deaths
Learning Objectives

1. Describe current guideline classification of patients with COPD
2. Apply guideline recommendations to devise maintenance therapies for patients with COPD
3. Outline currently available classes of medications and delivery systems
4. Select COPD medication and device taking into consideration patient characteristics and disease presentation
Patient Case #1

A 60 y/o man complains of dyspnea while loading his fishing boat the past year. He stopped smoking 6 months ago after 40 pack years. You suspect COPD.
Case #1 Related Question

What is the appropriate initial diagnostic test?

A. Chest CT
B. EKG
C. Metabolic Panel
D. Spirometry
Definition of COPD

- COPD is a preventable and treatable disease.

- Exacerbations and comorbidities contribute to the overall severity in individual patients.

- The pulmonary component is characterized by airflow limitation that is not fully reversible.

- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

http://www.goldcopd.org
Global Initiative for Chronic Obstructive Lung Disease

http://www.goldcopd.org
Four Components of COPD Management

- Assess and monitor disease
- Reduce risk factors
- Manage stable COPD
- Manage exacerbations

www.goldcopd.com
Useful Diagnostic Tests

- Spirometry
- CBC with diff; eos
- Electrolyte panel- hypercapnia
- 6 MW
- Chest CT (low density)
Spirometry measures how fast and how much air you breathe out.
COPD/Asthma Pulmonary Function
Case #1 Related Question

What is the appropriate initial diagnostic test?

A. Chest CT
B. EKG
C. Metabolic Panel
D. Spirometry
Patient Case #2

In this man on next visit, dyspnea is now noted climbing stairs or up inclines on walks with wife. Spirometry shows FVC-95% of predicted FEV1-72% FEV1/FVC-62%.
Case #2 Related Question

You confirm the diagnosis of COPD. What medication would be appropriate initial therapy?

A. Inhaled long-acting anti-muscarinic agent alone
B. Inhaled corticosteroid alone
C. Trial of short term prednisolone
D. Oral Macrolide
COPD Treatment (old)

- Stop smoking
- Not much else
COPD Management

• Reduce smoking exposure: A*
• Medication: BD’s, aerosol steroids: A
• Pulmonary rehabilitation: A
• Treat infections: A
• Oxygen supplementation: A
• Reduce exacerbations: A

• Health Care Directive
• Immunizations: Flu shot, Pneumococcal: A
• Low dose CT scan: A

*Level of evidence
Inhaler Actions

Normal Airway

COPD/Chronic bronchitis

Long-Acting Muscarinic Agent or Long Acting Bronchodilator Agent
THE PROBLEM WITH COMBINATION THERAPY?

TOO MANY INHALERS.

I CAN'T BREATHE!
Inhaler devices
First Line Therapy

LAMA

or

LAMA plus LABA

If eos: ICS

or

ICS plus LABA

Or

ICS plus LABA plus LAMA
Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD IMPACT

- R, DB, 1 year
- LABA+LAMA, ICS+LABA, ICS+LAMA+LABA
- 10,355 subjects
- Primary endpoint: Rate moderate/severe exacerbations
- Adverse events: Pneumonia

IMPACT Primary Results
Annual Rate of exacerbations

ICS+LABA+LAMA: 0.91/year
ICS+LABA: 1.06*
LABA+LAMA: 1.21*

*P<.001
IMPACT Primary Results

Annual Rate of exacerbations

EXACERBATIONS/YEAR

P<.001

ICS
LABA
LAMA

ICS
LABA
LAMA
Patients(%) with moderate/severe exacerbations

**B** Time-to-First-Event Analysis

![Graph showing time-to-first-event analysis for different treatment groups.](chart)

- **ICS, LABA**
- **ICS, LAMA, LABA**
- **UMEC–VI, LAMA, LABA**
- **FF–VI, ICS, LABA**
- **FF–UMEC–VI, ICS, LAMA, LABA**

**Patients Who Had a Moderate or Severe Exacerbation (%)**

**Days since Randomization**

**No. at Risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>28</th>
<th>56</th>
<th>84</th>
<th>112</th>
<th>140</th>
<th>168</th>
<th>196</th>
<th>224</th>
<th>252</th>
<th>280</th>
<th>308</th>
<th>336</th>
<th>364</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMEC–VI</td>
<td>2070</td>
<td>1721</td>
<td>1516</td>
<td>1406</td>
<td>1301</td>
<td>1201</td>
<td>1123</td>
<td>1059</td>
<td>1001</td>
<td>971</td>
<td>917</td>
<td>884</td>
<td>851</td>
<td>642</td>
</tr>
<tr>
<td>FF–VI</td>
<td>4134</td>
<td>3554</td>
<td>3133</td>
<td>2838</td>
<td>2620</td>
<td>2410</td>
<td>2250</td>
<td>2120</td>
<td>2004</td>
<td>1823</td>
<td>1823</td>
<td>1729</td>
<td>1671</td>
<td>1228</td>
</tr>
<tr>
<td>FF–UMEC–VI</td>
<td>4151</td>
<td>3758</td>
<td>3408</td>
<td>3186</td>
<td>2954</td>
<td>2752</td>
<td>2614</td>
<td>2457</td>
<td>2324</td>
<td>2216</td>
<td>2085</td>
<td>1988</td>
<td>1919</td>
<td>1419</td>
</tr>
</tbody>
</table>

Pneumonia, \%Subjects

- LAMA, LABA, ICS, 7
- ICS, LABA, 6
- LABA, LAMA, 4
Case #2 Related Question

You confirm the diagnosis of COPD. What medication would be appropriate initial therapy?

A. Inhaled long-acting anti-muscarinic agent alone
B. Inhaled corticosteroid alone
C. Trial of short term prednisone
D. Oral Macrolide
Helpful aids

- COPD Assessment Tool*
- BODE-prognosis; 4 years*
- GOLD Guidelines*

*Google
Learning Objectives

1. Describe current guideline classification of patients with COPD
2. Apply guideline recommendations to devise maintenance therapies for patients with COPD
3. Outline currently available classes of medications and delivery systems
4. Select COPD medication and device taking into consideration patient characteristics and disease presentation
Association between the Ratio of FEV1 to FEV1 at the Age of 25 Years and Disability or Death
COPD Management

- General
- Medications
- ACOS
- Exacerbations
IMPACT

% subjects with pneumonia

ICS+LABA+LAMA: 7%
ICS+LABA: 6%
LABA+LAMA: 4%
Aeroallergen
Who authored the following quote: “Ninety percent of the game is half mental.”:

1. Winston Churchill
2. Pope Francis
3. Babe Ruth
4. Yogi Berra
5. Franklin Roosevelt
The leading cause of death in the US is:

1. **Cardiac/MI**
2. Cancer
3. Stroke
4. COPD
5. Accidents
Who authored the following quote: “Ninety percent of the game is half mental.”:

1. Winston Churchill
2. Pope Francis
3. Babe Ruth
4. Yogi Berra
5. Franklin Roosevelt
Among leading causes of death in US, the one with a rising death rate is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents
Among leading causes of death in US, the one with a rising death rate is:

1. Cardiac/MI
2. Cancer
3. Stroke
4. COPD
5. Accidents
Quality Measure
COPD
Hospitals 2014

Number of hospital readmissions within 30 days to any hospital*

* Readmissions reduction project/CMS
Holy Grail
COPD Pharmacotherapy

- Mortality benefit
- Reduced Decline in FEV1
Holy Grail
Cigarette smoking cessation

• Mortality benefit *

• Reduced decline in FEV1 #

* Anthonisen: Annals Int Med 142:233, 2005
# Anthonisen: JAMA 272: 1497, 1994
Combination LA Beta agonist and aerosol steroids

• Do they prolong life?

• Are they safe?
Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007

- R, DB, placebo, 3 year trial

- **Objective**: Effect on survival

- Salmeterol 50ug/Fluticasone 500ug, Salmeterol, Fluticasone, placebo; all BID

- 6112 patients, 40 % dropout rate
Effect of Combination Therapy on All-Cause Mortality

TORCH

Time to Death (weeks)

Probability of Death (%)

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination Therapy vs Pbo (adjusted)</td>
<td>0.825</td>
<td>0.052</td>
</tr>
<tr>
<td>Combination Therapy vs SAL</td>
<td>0.932</td>
<td>0.48</td>
</tr>
<tr>
<td>Combination Therapy vs FP</td>
<td>0.774</td>
<td>0.007</td>
</tr>
<tr>
<td>SAL vs Pbo</td>
<td>0.879</td>
<td>0.18</td>
</tr>
<tr>
<td>FP vs Pbo</td>
<td>1.060</td>
<td>0.53</td>
</tr>
</tbody>
</table>

TORCH
Pneumonia

• Fluticasone/salmeterol: 19.6% *

• Fluticasone: 18.3 % *

• Salmeterol: 13.3%

• Placebo: 12.3 %

* P < 0.001
Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)

- Post-hoc analysis TORCH

- Examine rate decline FEV1 (Prognosis)
Therapy Reduces the Rate of Decline of Post-bronchodilator FEV$_1$ (TORCH)

- 39 mL/y
- 42 mL/y
- 42 mL/y
- 55 mL/y

* $P = 0.003$ vs placebo
† $P < 0.001$ vs placebo

Summary
LA BA/ICS

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

COPD

Are they effective?
Tiotropium

- M1 and M3 selective LA muscarinic antagonist
- Most widely prescribed agent in COPD
- Side effects: dry mouth, urinary retention

- R, DB, 4 years
- Tiotropium vs placebo
- Endpoints: 1-Rate decline FEV1; 2-SGRQ, exacerbations/COPD, mortality
- 5993 COPD patients; 40% dropout rate
UPLIFT: Lung Function (FEV$_1$) Over 4 Years

* $P < 0.0001$ vs. control

Rates of decline of FEV$_1$ after day 30 (Primary EP) were not significantly reduced by tiotropium

UPLIFT: Tiotropium Effects

Decreased COPD Exacerbations

- Placebo
- Tiotropium

Hazard ratio, 0.86
$P < 0.001$

Decreased Mortality

- Placebo
- Tiotropium

Hazard ratio, 0.89
$P = 0.09$

Summary

LA AC

- Improve symptoms, improve QOL, reduce hospitalizations
- Do not retard decline in pulmonary function
Asthma-COPD Overlap Syndrome

- Persistent airflow limitation
- Features shared by both asthma-COPD

Symptoms - Dyspnea, wheeze
Exacerbations
FEV1/FVC < 70%
Prior inhaled meds
Why ACOS?

- Prognosis worse than either
- May require specialty consult
- Asthma- Controller meds needed; not LABA alone
- COPD-Controller meds best; not LACS alone
Factors Associated with Increased Exacerbation Frequency (ECLIPSE)

### Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of Exacerbations</th>
<th>P Value</th>
<th>Number of Exacerbations</th>
<th>P Value</th>
<th>Number of Exacerbations</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥2 vs. 0</td>
<td></td>
<td>1 vs. 0</td>
<td></td>
<td>≥2 vs. 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>odds ratio (95% CI)</td>
<td>P value</td>
<td>odds ratio (95% CI)</td>
<td>P value</td>
<td>odds ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Exacerbation during previous yr — any vs. none</td>
<td>5.72 (4.47–7.31)</td>
<td>&lt;0.001</td>
<td>2.24 (1.77–2.84)</td>
<td>&lt;0.001</td>
<td>2.55 (1.96–3.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁ — per 100-ml decrease</td>
<td>1.11 (1.08–1.14)</td>
<td>&lt;0.001</td>
<td>1.06 (1.03–1.08)</td>
<td>&lt;0.001</td>
<td>1.05 (1.02–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ score for COPD — per increase of 4 points</td>
<td>1.07 (1.04–1.10)</td>
<td>&lt;0.001</td>
<td>1.01 (0.99–1.04)</td>
<td>0.38</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of reflux or heartburn — yes vs. no</td>
<td>2.07 (1.58–2.72)</td>
<td>&lt;0.001</td>
<td>1.61 (1.23–2.10)</td>
<td>&lt;0.001</td>
<td>1.29 (0.97–1.70)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>White-cell count — per increase of 1×10³/mm³</td>
<td>1.08 (1.03–1.14)</td>
<td>0.002</td>
<td>1.02 (0.97–1.08)</td>
<td>0.45</td>
<td>1.06 (1.01–1.12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* FEV₁ denotes forced expiratory volume in 1 second, and SGRQ St. George’s Respiratory Questionnaire.
The following is not effective in reducing exacerbations in COPD:

1. Macrolides
2. Acetyl cysteine
3. LABA/LACS combinations
4. LAMA
5. Statins
The following is not effective in reducing exacerbations in COPD:

1. Macrolides
2. Acetyl cysteine
3. LABA/LACS combinations
4. LAMA
5. Statins

Criner: Simvastatin for prevention exacerbations in COPD. NEJM: 370:2201, 2014
Exacerbation Prevention
Medications

- LAMA, LACS/LABA
- Macrolides
- Phosphodiesterase inhibitors- roflumilast
- Acetyl cysteine (oral)
- Statins- NO!

Criner, Chest (ACCP, CTS) 14:883, 894, 2015
Albert: Azithromycin for prevention of exacerbations of COPD; NEJM 365:689, 2011

- RB, DB, 1 year
- **Objective:** Reduce exacerbation frequency
- Azithromycin 250 mg daily vs placebo
- 1142 subjects; 90% F/U
Proportion of Participants Free from Acute Exacerbations of COPD

Downside(s) Azithromycin

- Arrhythmias (heart disease)
- Resistance to macrolides:
  - Azithro: 81%
  - Placebo: 41%

EKG for QT interval
Conclusions

• Holy Grail has not been achieved

• LA BA/ICS are effective

• FDA, All LA BA have black box warning

• LA AC are effective

• ACOS - stay tuned

• Pay attention to exacerbations
Conclusions

• Holy Grail has not been achieved

• LA BA/ICS are effective

• FDA, All LA BA have black box warning

• LA AC are effective

• Concerns raised: Pneumonia
Exacerbations were defined as symptomatic deterioration requiring treatment with antibiotics or systemic corticosteroids (moderate), or hospitalization (severe).

* $P < 0.001$ vs placebo; † $P = 0.002$ vs SAL; ‡ $P = 0.024$ vs FP

Of the six leading causes of death in the United States, only COPD has been increasing steadily since 1970.

Source: Jemal A. et al. *JAMA* 2005
Medications to reduce exacerbations

- Azithromycin
- Tiotropium
- Aerosol steroids
- Roflumilast
- Acetyl cysteine
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tiotropium (N = 2986)</th>
<th>Placebo (N = 3006)</th>
<th>Relative Risk for Tiotropium vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>3.56</td>
<td>4.21</td>
<td>0.84 (0.73–0.98)†</td>
</tr>
<tr>
<td>Angina</td>
<td>0.51</td>
<td>0.36</td>
<td>1.44 (0.91–2.26)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.74</td>
<td>0.77</td>
<td>0.95 (0.68–1.33)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0.61</td>
<td>0.48</td>
<td>1.25 (0.84–1.87)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.29</td>
<td>0.48</td>
<td>0.59 (0.37–0.96)†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.21</td>
<td>0.37</td>
<td>0.58 (0.33–1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.69</td>
<td>0.97</td>
<td>0.71 (0.52–0.99)†</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>11.32</td>
<td>13.47</td>
<td>0.84 (0.77–0.92)†</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.37</td>
<td>0.31</td>
<td>1.20 (0.73–1.98)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>8.19</td>
<td>9.70</td>
<td>0.84 (0.76–0.94)†</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.38</td>
<td>0.62</td>
<td>0.61 (0.40–0.94)†</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.28</td>
<td>3.46</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0.90</td>
<td>1.31</td>
<td>0.69 (0.52–0.92)†</td>
</tr>
</tbody>
</table>

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† P<0.05.
Management of Stable COPD

Pharmacotherapy: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.

- The principal bronchodilator treatments are β₂-agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A).

- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).
The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted \((Stage \text{ III: Severe COPD and Stage IV: Very Severe COPD)}\) and repeated exacerbations \((\text{Evidence A})\).

An inhaled glucocorticosteroid combined with a long-acting \(\beta_2\)-agonist is more effective than the individual components \((\text{Evidence A})\).
## Exacerbations With Triple Combination Therapy

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium (n = 156)</th>
<th>Tiotropium + Salmeterol (n = 148)</th>
<th>Tiotropium + Salmeterol + Fluticasone (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Pts with ≥ 1 exacerbations</td>
<td>62.8%</td>
<td>64.8%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Total Exacerbations</td>
<td>222</td>
<td>226</td>
<td>188</td>
</tr>
<tr>
<td>Exacerbations with Hospitalization</td>
<td>49</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>Incidence rate ratio</td>
<td></td>
<td>0.83 (0.54 to 1.27)</td>
<td>0.53 (0.33 to 0.86)</td>
</tr>
</tbody>
</table>

## Differential Diagnosis: COPD and Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>ASTHMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset in mid-life</td>
<td>Onset early in life (often childhood)</td>
</tr>
<tr>
<td>Symptoms slowly progressive</td>
<td>Symptoms vary from day to day</td>
</tr>
<tr>
<td>Long smoking history</td>
<td>Symptoms at night/early morning</td>
</tr>
<tr>
<td>Dyspnea during exercise</td>
<td>Allergy, rhinitis, and/or eczema also present</td>
</tr>
<tr>
<td>Largely irreversible airflow limitation</td>
<td>Family history of asthma</td>
</tr>
<tr>
<td></td>
<td>Largely reversible airflow limitation</td>
</tr>
</tbody>
</table>
Proportion of Participants Free from Acute Exacerbations of COPD for 1 Year

Table 2. Effect of Treatment for Chronic Obstructive Pulmonary Disease (COPD) on Hospitalization Rates, Emergency Department or Urgent Care Visits, and Unscheduled Office Visits.

<table>
<thead>
<tr>
<th>Event</th>
<th>Azithromycin</th>
<th>Placebo</th>
<th>P Value*</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>mean events/patient-yr (95% CI)</td>
<td>no. of events</td>
<td>mean events/patient-yr (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>323</td>
<td>0.74 (0.60–0.89)</td>
<td>329</td>
<td>0.95 (0.76–1.18)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalization related to COPD</td>
<td>156</td>
<td>0.34 (0.26–0.43)</td>
<td>200</td>
<td>0.49 (0.31–0.67)</td>
<td>0.14</td>
</tr>
<tr>
<td>Emergency department or urgent care visit</td>
<td>199</td>
<td>0.43 (0.34–0.53)</td>
<td>257</td>
<td>0.48 (0.39–0.57)</td>
<td>0.47</td>
</tr>
<tr>
<td>Unscheduled office visit</td>
<td>1202</td>
<td>2.46 (2.08–2.48)</td>
<td>1345</td>
<td>2.57 (2.21–2.60)</td>
<td>0.048</td>
</tr>
<tr>
<td>Intubations</td>
<td>11</td>
<td>0.02 (0.01–0.04)</td>
<td>16</td>
<td>0.04 (0.01–0.06)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* The P value is for the rate of events per patient-year.
† The hazard ratio and P value are for the time to the first event in the azithromycin group as compared with the placebo group.
Lung Function and exacerbations

A FEV₁ Change in Trial 1

B FEV₁ Change in Trial 2

C Severe Exacerbation

Kerstjens.NEJM; 2012;367:1198
Management of COPD with bronchoactive medications: In search of the Holy Grail
LA beta agonists and aerosol steroids in COPD

- Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007 (TORCH)

- Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)
Conclusion

- Holy Grail has not been achieved
- LA BA/ICS are effective
- LA AC are effective
- Concerns raised: Pneumonia, CV events
- FDA has not acted to remove or change product labeling

- Nested case control study/COPD
- Admin database/pneumonia/hospital
- COPD-176K; Hospital-24K
- Link any ICS
### Meta Analysis
**Anticholinergics**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>#RCTs</th>
<th>Inhaled AC</th>
<th>Controls</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>12</td>
<td>57/6156</td>
<td>31/6220</td>
<td>1.80</td>
<td>.008</td>
</tr>
<tr>
<td>MI</td>
<td>11</td>
<td>68/5430</td>
<td>43/5168</td>
<td>1.53</td>
<td>.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>25/4548</td>
<td>18/4703</td>
<td>1.46</td>
<td>.20</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>17</td>
<td>149/7472</td>
<td>115/7311</td>
<td>1.26</td>
<td>.06</td>
</tr>
</tbody>
</table>
COPD Management

- Reduce smoking exposure: A*
- Medication: BD’s, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Reduce exacerbations: A
- Health Care Directive
- Immunizations: Flu shot, Pneumovax: A, B

*Level of evidence
Kerstjens: Tiotropium in asthma poorly controlled with standard combination therapy. NEJM, 367: 1198: 2012

- RB, DB, 48 weeks
- Objective: lung function, exacerbations
- Tiotropium vs placebo; all on LABA plus ICS
- 907 patients
GOLD Website Address

http://www.goldcopd.org
Managing exacerbations of COPD and asthma

Alan F. Barker
Pulmonary and Critical Care
Oregon Health and Science University
November 6, 2012
COPD Management

- Reduce smoking exposure: A
- Medication: BD’s, aerosol steroids: A
- Pulmonary rehabilitation: A
- Treat infections: A
- Oxygen supplementation: A
- Surgery for emphysema: C
- Health Care Directive
- Immunizations: Flu shot, Pneumovax: A, B
LA beta agonists and aerosol steroids in COPD

- Calverley: Salmeterol and fluticasone propionate and survival in COPD. NEJM 356: 775, 2007 (TORCH)

- Celli: Effect of pharmacotherapy on rate of decline of lung function in COPD. Am J Respir Crit Care Med 178:332, 2008 (TORCH)

COPD Management

• Reduce smoking exposure: A
• Medication: BD’s, aerosol steroids: A
• Pulmonary rehabilitation: A
• Treat infections: A
• Oxygen supplementation: A
• Reduce exacerbation frequency: A
• Immunizations: Flu shot, Pneumovax: A, B
Conclusion

• Holy Grail has not been achieved

• LA BA/ICS are effective

• LA AC are effective

• Concerns raised: Pneumonia, CV events

• FDA has not acted to remove or change
Inhaled steroids/COPD

Pneumonia

- Adjusted rate ratio/pneumonia/ICS: 1.70 (1.63-1.77)
- ARR/pneumonia/Death/ 30 days: 1.53 (1.30-1.80)
- Death/pneumonia highest for highest dose ICS or fluticasone 1000 ug/day
- No difference whether recent ICS
Cardiovascular Risks

Anticholinergics

Why?

• Arrhythmias (Lung Health Study, ipratropium)

• Elderly, much CV co morbidity

• COPD a systemic disease
UPLIFT Trial Design

- Double-blind, randomized, placebo-controlled
- Prospective 4-year trial
- Tiotropium (18 mcg) or placebo once daily plus usual care, except for inhaled anticholinergics
- Coprimary endpoints (beginning on day 30)
  - Rate of decline in predose FEV\(_1\)
  - Rate of decline in postbronchodilator FEV\(_1\)

Managing exacerbations of COPD and asthma

Alan F. Barker
Pulmonary and Critical Care
November 6, 2012
Current evidence for the treatment of chronic obstructive pulmonary disease

Alan F. Barker
Pulmonary and Critical Care
August 9, 2012
Mechanisms of Airflow Limitation in COPD

Normal

Chronic Obstructive Pulmonary Disease

- Disrupted alveolar attachments (emphysema)
- Mucus hypersecretion (luminal obstruction)
- Mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis)

Increased Risk for Cardiovascular Disease in COPD

- Retrospective study of Canadian databases
- Subjects age ≥ 40 years
- Diagnosed with COPD during 1997–2000
- Received ≥ 2 Rx for dilators w/i 6 months

MI = myocardial infarction, CHF = congestive heart failure, CVD = cardiovascular disease;

All between-group differences P < 0.05 – adjusted for CV risk

What Do COPD Patients Die From?


* General Population data from CDC for males ≥ 45y
### TORCH: Study Design

- Aged 40-80 years
- FEV$_1$ < 60% predicted
- Reversibility < 10% predicted normal to 400 mcg albuterol

#### Run-in 2 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients at start</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination Therapy 500/50</strong></td>
<td>1533</td>
</tr>
<tr>
<td>Fluticasone propionate 500</td>
<td>1534</td>
</tr>
<tr>
<td>Salmeterol 50</td>
<td>1521</td>
</tr>
<tr>
<td>Placebo</td>
<td>1524</td>
</tr>
</tbody>
</table>

#### 3 Years

**TORCH:** Towards a Revolution in COPD Health

**COMBINATION THERAPY:** salmeterol fluticasone combination

**FP:** fluticasone propionate

**SAL:** salmeterol

Clinical COPD - Tip of the Iceberg

Therapy for COPD: Overview

Cigarette smoking cessation

GOLD Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>I Mild</th>
<th>II Moderate</th>
<th>III Severe</th>
<th>IV Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active reduction of risk factors: influenza vaccine</td>
<td>Add short-acting bronchodilators when needed</td>
<td>Add regular Rx with ≥1 long-acting bronchodilator when needed. Add rehabilitation</td>
<td>Add inhaled corticosteroids (ICS) if repeated exacerbations</td>
<td>Add O₂* Consider surgery</td>
</tr>
<tr>
<td>* If chronic respiratory failure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management of Stable COPD

Pharmacotherapy: Glucocorticosteroids

- The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known.

- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).

GOLD
# Anticholinergics

## Efficacy vs Risks

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased exercise capacity</td>
<td>Increased CV events</td>
</tr>
<tr>
<td>Decreased exacerbations</td>
<td>Increased MIs</td>
</tr>
<tr>
<td>Decreased hospitalizations/exacerbations</td>
<td></td>
</tr>
<tr>
<td>Improvements Dyspnea index</td>
<td></td>
</tr>
<tr>
<td>Improvements QOL</td>
<td></td>
</tr>
</tbody>
</table>

NNT COPD related hospitalizations: 20  
NNH for CV events/MI: 40
http://www.goldcopd.org
FEV$_1$ With Triple Combination Therapy

Mean FEV1 and FVC before and after Bronchodilation
Kaplan-Meier Estimates of the Probability of COPD Exacerbation and Death from Any Cause

A. COPD Exacerbation

- Placebo
- Tiotropium

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>3006</td>
</tr>
<tr>
<td>6</td>
<td>2915</td>
</tr>
<tr>
<td>12</td>
<td>2824</td>
</tr>
<tr>
<td>18</td>
<td>2734</td>
</tr>
<tr>
<td>24</td>
<td>2544</td>
</tr>
<tr>
<td>30</td>
<td>2354</td>
</tr>
<tr>
<td>36</td>
<td>2164</td>
</tr>
<tr>
<td>42</td>
<td>1974</td>
</tr>
<tr>
<td>48</td>
<td>1784</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.86 (95% CI: 0.81–0.91), P<0.001

B. Death from Any Cause

- Placebo
- Tiotropium

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>3006</td>
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<tr>
<td>6</td>
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<tr>
<td>24</td>
<td>2544</td>
</tr>
<tr>
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<td>2354</td>
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<tr>
<td>36</td>
<td>2164</td>
</tr>
<tr>
<td>42</td>
<td>1974</td>
</tr>
<tr>
<td>48</td>
<td>1784</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.89 (95% CI: 0.79–1.02), P=0.09
# The BODE Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>FEV(_1)</strong> (% predicted)</td>
<td>(\geq 65)</td>
</tr>
<tr>
<td><strong>Distance walked in 6 min. (M)</strong></td>
<td>(\geq 350)</td>
</tr>
<tr>
<td><strong>MMRC dyspnea scale</strong></td>
<td>0-1</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>&gt; 21</td>
</tr>
</tbody>
</table>

BODE = body mass index, obstruction, dyspnea, and exercise capacity; MMRC = Modified Medical Research Council

Natural History of COPD


<table>
<thead>
<tr>
<th>Cause</th>
<th>Proportion of 1965 Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>-59%</td>
</tr>
<tr>
<td>Stroke</td>
<td>-64%</td>
</tr>
<tr>
<td>Other CVD</td>
<td>-35%</td>
</tr>
<tr>
<td>COPD</td>
<td>+163%</td>
</tr>
<tr>
<td>All Other Causes</td>
<td>-7%</td>
</tr>
</tbody>
</table>

Source: NHLBI/NIH/DHHS
Exercise Duration with Tiotropium

Exercise Duration (seconds)

Baseline: 491.7 s

Placebo:
- Day 0: 500 s
- Day 45: 500 s

Tiotropium:
- Day 0: 500 s
- Day 45: 607 s

+ 67 s, +13.6%

+ 105 s, +21.4%

*P < 0.05. †P < 0.01

Survival in COPD

FEV$_1$ Stage

BODE

Probability of Survival

Months

Stage I (> 50%) predicted
Stage II (36-50%) predicted
Stage III (≤ 35%) predicted
Quartile 1 (BODE 0-2)
Quartile 2 (BODE 3-4)
Quartile 3 (BODE 5-6)
Quartile 4 (BODE 7-10)

Manage COPD Exacerbations

Key Points

- Inhaled bronchodilators (particularly inhaled $\beta_2$-agonists with or without anticholinergics) and oral glucocorticoid-steroids are effective treatments for exacerbations of COPD (Evidence A).
Lung Transplantation and COPD

• Retrospective analysis of ISHLT database\(^1\)
  – Bilateral LT \(N = 3525\)
  – Single LT \(N = 6358\)

• Median survival = 5 years
  – BLT \(6.4 \text{ y}\)
  – SLT \(4.6 \text{ y}\) \(P < 0.0001\)

• No survival difference if recipient > 60 y

• Questionable survival advantage compared to standard of care\(^2\)

• LT may improve QOL

Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.

The principal bronchodilator treatments are β₂-agonists, anticholinergics, and methylxanthines used singly or in combination (Evidence A).

Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (Evidence A).
Management of Stable COPD

Pharmacotherapy: Glucocorticosteroids

- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations (Evidence A).

- An inhaled glucocorticosteroid combined with a long-acting β₂-agonist is more effective than the individual components (Evidence A).
GOLD Guidelines for Diagnosing COPD: Risk Factors and Symptoms

Risk Factors
• History of smoking or exposure to other risk factors
  – 80% to 90% of all COPD occurrences are attributable to smoking
• Male or female > 40 years of age

Other
• Exposure to occupational dusts and chemicals, indoor and outdoor air pollutants, and infections
• Socioeconomic status

Symptoms
• Dyspnea/exercise intolerance/fatigue
• Chronic cough with or without sputum
• Reduction in activities of daily living

Probability of Treatment Discontinuation, Mean FEV1 and FVC before and after Bronchodilation, and Scores for Health-Related Quality of Life
Spirometry

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref</th>
<th>Pre</th>
<th>% Ref</th>
<th>Post</th>
<th>% Ref</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (Liters)</td>
<td>3.69</td>
<td>3.21</td>
<td>87</td>
<td>3.48</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>FEV1 (Liters)</td>
<td>2.81</td>
<td>1.64</td>
<td>58</td>
<td>1.93</td>
<td>69</td>
<td>18</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>76</td>
<td>51</td>
<td></td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (L/sec)</td>
<td>2.29</td>
<td>0.60</td>
<td>26</td>
<td>0.77</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>PEF25-75% (L/sec)</td>
<td>6.57</td>
<td>6.17</td>
<td>94</td>
<td>6.65</td>
<td>101</td>
<td>8</td>
</tr>
<tr>
<td>FIF50% (L/sec)</td>
<td>3.42</td>
<td>3.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient History

Medication: Spiriva Advair Flonase
Are you short of breath at Rest: No
Are you short of breath on exercise: No

Obstruction
Four Components of COPD Management

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

# Management of Exacerbations

<table>
<thead>
<tr>
<th>Objective</th>
<th>Strategy</th>
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<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Relieve dyspnea</td>
<td>SABA +/- short acting anticholinergic</td>
</tr>
<tr>
<td>Reduce airway inflammation</td>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Improve lung function</td>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Eradicate infections</td>
<td>Antibiotics</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>Reduce risk of new exacerbation</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>• Salmeterol +/- fluticasone</td>
<td></td>
</tr>
<tr>
<td>• Formoterol +/- budesonide</td>
<td></td>
</tr>
<tr>
<td>• Tiotropium</td>
<td></td>
</tr>
<tr>
<td>Immunizations</td>
<td></td>
</tr>
<tr>
<td>• Influenza</td>
<td></td>
</tr>
<tr>
<td>• Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary rehab</td>
<td></td>
</tr>
<tr>
<td>Self-management support</td>
<td></td>
</tr>
</tbody>
</table>

Death from Any Cause

No. of Patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1524</th>
<th>1500</th>
<th>1464</th>
<th>1428</th>
<th>1399</th>
<th>1361</th>
<th>1293</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>1521</td>
<td>1502</td>
<td>1481</td>
<td>1451</td>
<td>1417</td>
<td>1368</td>
<td>1316</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1534</td>
<td>1512</td>
<td>1487</td>
<td>1450</td>
<td>1409</td>
<td>1363</td>
<td>1288</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>1533</td>
<td>1514</td>
<td>1487</td>
<td>1456</td>
<td>1426</td>
<td>1393</td>
<td>1339</td>
</tr>
</tbody>
</table>

HR, 0.825
(95% CI: 0.681–1.002)

P = 0.052 (Log-rank test)
### Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years. *

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tiotropium (N = 2986)</th>
<th>Placebo (N = 3006)</th>
<th>Relative Risk for Tiotropium vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>3.56</td>
<td>4.21</td>
<td>0.84 (0.73–0.98)†</td>
</tr>
<tr>
<td>Angina</td>
<td>0.51</td>
<td>0.36</td>
<td>1.44 (0.91–2.26)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.74</td>
<td>0.77</td>
<td>0.95 (0.68–1.33)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0.61</td>
<td>0.48</td>
<td>1.25 (0.84–1.87)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.29</td>
<td>0.48</td>
<td>0.59 (0.37–0.96)†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.21</td>
<td>0.37</td>
<td>0.58 (0.33–1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.69</td>
<td>0.97</td>
<td>0.71 (0.52–0.99)†</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>11.32</td>
<td>13.47</td>
<td>0.84 (0.77–0.92)†</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.37</td>
<td>0.31</td>
<td>1.20 (0.73–1.98)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>8.19</td>
<td>9.70</td>
<td>0.84 (0.76–0.94)†</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.38</td>
<td>0.62</td>
<td>0.61 (0.40–0.94)†</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.28</td>
<td>3.46</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0.90</td>
<td>1.31</td>
<td>0.69 (0.52–0.92)†</td>
</tr>
</tbody>
</table>

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† P<0.05.
Obstructive Lung Disease Groups (NHANES III)

- **Asthma**: 5.5%
- **Chronic Bronchitis**: 3.2%
- **Emphysema**: 1.5%

Percentage of US population

Patient Action Plan

PATIENT ACTION PLAN FOR COPD SIGNS & SYMPTOMS

Purpose: To promote patient identification and self-directed action for onset of symptoms related to COPD.

COPD --- Your Plan for ACTION

Use this guide to help you report changes in your symptoms to your doctor or nurse. When you report symptoms early, you are less likely to have to go to the hospital for treatment.

You are doing well when:
- You can do your normal activities
- You have no changes in your symptoms
- Your usual medicines are controlling your symptoms

Call your home care nurse or doctor in the next 24 hours when:
- You have increased shortness of breath with usual activity
- You are coughing more than usual
- You have increased wheezing
- You have increased sputum or it has changed in color
- You have to use short acting medicines more often
- You feel more tired or restless

Call 911 RIGHT AWAY when:
- You have severe shortness of breath or shortness of breath at rest
- You have chest pain that doesn’t go away
- Your lips or fingernails turn gray or blue
- You feel unusually sleepy or confused

MD Name & Phone Number: ________________________________

Tool developed by: Lisa Gorski, MS, APRN, BC, CRNI
Reference: National Heart, Lung, and Blood Institute (NHLBI)

Patient Action Plan for COPD Signs & Symptoms
“Best Practice”© OASIS ANSWERS, Inc. 2006

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Changes in Large Airways of COPD Patients

- Mucus hypersecretion
- Goblet cell hyperplasia
- Neutrophils in sputum
- Squamous metaplasia of epithelium
- No basement membrane thickening
- ↑ Macrophages
- ↑ CD8+ lymphocytes
- Little increase in airway smooth muscle

Source: Peter J. Barnes, MD
**ASTHMA**

- Allergens

  - Ep cells
  - Mast cell
  - CD4+ cell (Th2)
  - Eosinophil

  **Bronchoconstriction**
  **AHR**

**COPD**

- Cigarette smoke

  - Alv macrophage
  - Ep cells
  - CD8+ cell (Tc1)
  - Neutrophil

  **Small airway narrowing**
  **Alveolar destruction**

**Airflow Limitation**

- Reversible
- Irreversible

**Source:** Peter J. Barnes, MD
Clinical Course of COPD

COPD

Expiratory Flow Limitation
Air Trapping
Hyperinflation

Breathlessness

Deconditioning

Inactivity

Reduced Exercise Capacity

Poor Health-Related Quality of Life

Disability Disease progression Death

Adapted from Decramer M. Eur Respir Rev. 2006;15:51-57.
THE PROBLEM WITH COMBINATION THERAPY?...
TOO MANY INHALERS.

I CAN'T BREATHE!

Or is this the Holy Grail??
TORCH/Mortality

- Fluticasone/salmeterol: 12.6%
- Placebo: 15.2%
- Salmeterol: 13.5%
- Fluticasone: 16.0%

*P=0.052
Rate of decline in FEV1 in TORCH

*P<.003

# Clinical Features Differentiating COPD and Asthma

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker or ex-smoker</td>
<td>Nearly all</td>
<td>Possibly</td>
</tr>
<tr>
<td>Symptoms under age 35</td>
<td>Rare</td>
<td>Often</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent and progressive</td>
<td>Variable</td>
</tr>
<tr>
<td>Night time wakening with breathlessness and/or wheezing</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Association with atopic symptoms and seasonal allergies</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Significant diurnal or day-to-day variability of symptoms</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Favorable response to inhaled glucocorticoids</td>
<td>Inconsistent</td>
<td>Consistent</td>
</tr>
</tbody>
</table>
Inhaled Corticosteroids Alone Do **Not** Modify COPD Natural History

Values represent mean annual declines in \( \text{FEV}_1 \), ml

† No differences were statistically significant

CCLS = Copenhagen City Lung Study; *Lancet*. 1999;353:1819-1823.
ISOLDE = Inhaled Steroids in Obstructive Lung Disease; *BMJ*. 2000;320:1297-1303.
As summarized by MacNee and Calverley; *Thorax*. 2003;58:261-265.

• Systemic review/meta-analysis
• Cardiovascular risks of ACs: CV death, MI, stroke
• Randomized trials, 30 days
• 17/103 trials acceptable; 14,783 patients
• F/U 6 weeks to 5 years
Inhaled Anticholinergics
COPD

Tashkin: A 4-year trial of tiotropium in COPD. NEJM 359:1543, 2008

Singh: Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with COPD. JAMA 300:1439, 2008
ATS/ERS and GOLD Guidelines: Severity of COPD

COPD is defined as $\text{FEV}_1/\text{FVC} < 70\%$

- **I** (Mild)
- **II** (Moderate)
- **III** (Severe)
- **IV** (Very Severe)

ATS/ERS: American Thoracic Society/European Respiratory Society
GOLD: Global initiative for chronic Obstructive Lung Disease