**Effect of β-Blockers in Treatment of Chronic Obstructive Pulmonary Disease**

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**Objectives**

- Review β-adrenergic blockers
- Discuss the risks and benefits of β-blocker usage in COPD patients
- Discuss new studies that suggest addition of β-blockers can be beneficial in patients with COPD
- Discuss pharmacist’s role

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**Conundrum**

Should patients with a diagnosis of chronic obstructive pulmonary disease (COPD), which is a relative contraindication to β-blocker therapy, receive a β-blocker when a strong indication exists?

- Risks vs. Benefits
- Review literature available

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**COPD**

- Fourth leading cause of death worldwide
- Characterized by airflow limitation that is not fully reversible and usually progressive
- Diagnosis: Post-bronchodilator FEV1/FVC < 0.70 confirms the presence of airflow limitation in:
  - Consider COPD and perform spirometry if an individual is older than 40 years and:
    - Dyspnea
    - Chronic cough
    - Chronic sputum production
    - History of exposure to risk factors

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**Management of COPD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Mild</td>
<td>FEV1 &gt; 80% predicted</td>
<td>Regimen A: Reduction of risk factors; influenza vaccination + SABA as needed</td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>50% ≤ FEV1 &lt; 80% predicted</td>
<td>Regimen B = Regimen A + Regular treatment with one or more long-acting bronchodilators</td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>30% ≤ FEV1 &lt; 50% predicted</td>
<td>Regimen C = Regimen B + ICS if repeated exacerbations and rehabilitation</td>
</tr>
<tr>
<td>Stage IV: Very severe</td>
<td>FEV1 &lt; 30% predicted</td>
<td>Regimen D = Regimen C + Long-term oxygen therapy and consider surgical procedures</td>
</tr>
</tbody>
</table>

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**β-blockers**

- Block the action of endogenous catecholamines on:
  - β1-adrenergic receptors: Heart and in the kidneys.
  - β2-adrenergic receptors: Mainly in the lungs, gastrointestinal tract liver, uterus, vascular smooth muscle, and skeletal muscle.
  - β3-adrenergic receptors: are located in fat cells

**Cardiac Effects**

- Decrease contractility = (negative inotropy)
- Decrease relaxation rate = (negative lusitropy)
- Decrease heart rate = (negative chronotropy)
- Decrease conduction velocity = (negative dromotropy)
### β-blockers

- **Vascular Effects**
  - Smooth muscle contraction = (mild vasoconstriction)
- **Kidneys**
  - Inhibit renin by the kidneys
  - Tone down the Renin Angiotensin Aldosterone System (RAAS)
- **Nervous system**
  - Blockade of adrenaline and noradrenaline
  - Decrease anxiety, tremor and migraines

### Types of β-blockers

- Non-Cardioselective
  - propranolol
  - nadolol
  - timolol
  - pindolol
- Mixed beta and alpha-1 activity
  - carvedilol
  - labetalol
- Cardioselective
  - acebutolol
  - atenolol
  - bisoprolol
  - esmolol
  - metoprolol
  - nebivolol

### Risks of β-blockers in COPD

- Historically β-blockers have been avoided in asthma and COPD
- β-blockers ➔ potential bronchoconstriction
- Reduction in forced expiratory volume in one second (FEV)
- Increased airway hyperresponsiveness
- Inhibition of bronchodilator response to β agonists
- Exacerbation of COPD and complications

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### GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)

- “Cardiovascular disease (including ischemic heart disease, heart failure, atrial fibrillation, and hypertension) is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD”
- “Cardioselective β-blockers are NOT contraindicated in COPD”


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### What does ACC/AHA say?

- 2009 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction Suggest that β-blocker therapy after acute MI IS APPROPRIATE for many patients with COPD or other relative contraindications
- 2009 ACC/AHA Focused Update Guidelines for the Diagnosis and Management of Heart Failure in Adults
  - “MOST patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain REASONABLE candidates for β-blockade”

*J Am Coll Cardiol, 2009; 54:2205-2241*
Package Inserts

- **Warnings and Precautions**
  - *Chronic obstructive pulmonary disease…*
    - “metoprolol should be used with caution, in …COPD with a bronchoospastic component…”
    - “Use only if the potential benefit outweighs the potential risk”

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**Study Design**

- **Objective**: To examine the effect of β blockers in all-cause death and COPD exacerbation associated with the use of β blockers in COPD patients
- **Design**: Retrospective cohort study using Cox proportional (CP) hazards regression analyses
- **Setting**: 23 general practices in Netherlands
- **Population**:
  - Total 2230 patients, β-blocker use N=665, non β-blocker use N=1565
  - Subjects > 45 yr with an incident or prevalent diagnosis of COPD between 1996 – 2006
  - Study length: ~7.2y

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**Results**

- All cause mortality adjusted HR in patients on β-blocker was 0.68 (95% CI, 0.56-0.83)
- Adjusted HR for COPD exacerbation in patients on β-blocker was 0.68 (95% CI, 0.46-1.02)

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**CRITIQUE**

- Retrospective and observational study
- Misclassification and misdiagnosis of patients
- Cannot completely correct for cofounders
  - Severity of COPD illness
  - Benefits of concomitant drug use (ACE –I, ARB’s and statins)
Study Design

- **Objective:** To examine the effect of β blockers in the management of COPD assessing effect on mortality, hospital admissions, and exacerbations of COPD
- **Design:** Retrospective cohort study
- **Setting:** Tayside, Scotland (2001–2010)
- **Population:** 5977 patients aged ≥50 years with a diagnosis of COPD

Results

- B-blocker use was associated with an overall 22% reduction in mortality HR = 0.78 (95% CI of 0.67 to 0.92)
- 2005 patients died equating to an annual mortality of 34%.

Adjusted hazard ratios for inhaled corticosteroids with and without β blocker were 0.24 (0.20 to 0.49) and 0.69 (0.54 to 0.87)

Critique

- Author’s conclusions: β blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD
- However, it’s retrospective study. Results should be interpreted cautiously
- Many cofounding variables (severity of CV disease COPD among groups)
- Prospective randomized double blinded controlled trial needed to confirm these findings

Role of Pharmacist

- It is necessary:
  - To properly understand management of COPD
  - Evaluate literature in this controversial topic
  - No definite clinical trial exists to safely recommend β-blockers for all COPD patients.
  - Monitor initiation and up-titration of dose of β-blockers closely
  - Reduce dose/hold β-blocker if bronchospasm or complication occurs

Keep in Mind

- Smoking cessation
- Influenza vaccine annually
- Pneumococcal vaccine
- Not recommended
  - Antibiotics, other than for treating infectious exacerbations of COPD
  - Mucolytic agents
  - Antioxidant agents such as N-acetylcysteine
  - Regular use of antitussives
Patient Case

- B.P. is a 55 yo male who comes to the ER with CC of SOB due to COPD exacerbation and constant productive cough. This is the 3rd time in this year B.P is admitted to the hospital due to SOB
- PMH: CAD with a MI 8 years ago with stent X 1, HTN, COPD (1 pack of cigarettes X 50 years, CHF.
- Vitals: BP 145/85, HR: 88 bpm, RR: 24, Temp: 98.4F
- Allergic to PCN
- Home Rx: crestor 20mg daily, lisinopril 40mg daily, plavix 75 daily, aspirin 81mg, carvedilol 6.25 mg q12h, advair diskus 250/50 mg 1 puff BID, tiotropium 1 puff daily and albuterol MDI q4h PRN for SOB.
- Last spirometry test shows: FEV1 = 45% and FEV1/FVC = 55%. In the hospital he was started on oxygen therapy, prednisolone 40mg IV q8h, furosemide 20mg IV q12h, Duoneb q4h ATC as well as continuing his home medications in the hospital.
- CXR rules out pneumonia, Echocardiogram shows mild mitral regurgitation with LVEF of ~50%.

Besides anticoagulation therapy the physician asks for your recommendation on the β-blocker

True or False Questions

- β-blockers are indeed contraindicated in asthmatic and COPD patients
- β-blockers may actually be beneficial for those with mild and moderate COPD and CV disease
- β blockers (predominantly cardioselective) reduced mortality and COPD exacerbations when added to stepwise inhaled therapy for COPD in one of the studies.

Summary

- β-Blocker therapy for cardiovascular indications is underutilized in patients with COPD
- Mortality benefits are seen in patients with mild to moderate COPD who receive cardioselective β-blockers
- In conclusion patients with MILD TO MODERATE COPD should receive cardioselective β-blocker therapy when a strong indication exists
- A reliable prospective randomized controlled trial needed to answer this conundrum

References


THANK YOU

Questions?