ΑΡΤΗΡΙΑΚΗ ΥΠΕΡΤΑΣΗ ΚΑΙ ΠΝΕΥΜΟΝΟΠΑΘΕΙΕΣ

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Καρδιολόγος FESC
Clinical Hypertension Specialist ESH
Top 10 causes of death globally 2015

1. Ischaemic heart disease
2. Stroke
3. Lower respiratory infections
4. Chronic obstructive pulmonary disease
5. Trachea, bronchus, and lung cancer
6. Diabetes mellitus
7. Alzheimer disease
8. Diarrhoeal diseases
9. Tuberculosis
10. Road injury

Top 10 causes of death globally 2000

1. Ischaemic heart disease
2. Stroke
3. Lower respiratory infections
4. Chronic obstructive pulmonary disease
5. Diarrhoeal diseases
6. Tuberculosis
7. HIV/AIDS
8. Preterm birth
9. Trachea, bronchus, and lung cancer
10. Birth asphyxia
Deaths attributed to 19 leading risk factors by country income level 2004

WHO Global health risks: mortality and burden of disease attributable to selected major risks 2009
Worldwide, 3 in 10 deaths are caused by CVD and half of all CVD deaths are caused by hypertension:

- 56m deaths worldwide
- 17.5m deaths due to CVD
- 9.4m deaths due to hypertension

\[ \Rightarrow \frac{1}{2} \text{ of all CVD deaths caused by hypertension} \]

IFPMA 2016

IFPMA – International Federation of Pharmaceutical Manufacturers
Risk Factors for COPD

- Genes
  - Alpha 1 antitrypsin deficiency
  - MMP12
  - a-nicotinic acetylcholine receptor

- Infections
  - (Alpha 1 antitrypsin deficiency, MMP12, a-nicotinic acetylcholine receptor)

- Socio-economic status
  - Male

- Exposure to particles
  - Cigarette smoke
  - Occupational dust and chemicals
  - Environmental tobacco smoke (ETS)
  - Indoor and outdoor air pollution

- Aging Populations
  - Lung growth and development
    - Asthma/Bronchial hyperreactivity
    - Chronic Bronchitis

© 2014 Global Initiative for Chronic Obstructive Lung Disease
smoking
Effects of cigarette smoking on the cardiovascular system

Cigarette Smoking → Nicotine → Carbon Monoxide

- Decreased O2 Supply
- Increased Lactic Acidosis
- Myocardial ischemia
- Decreased VO2 max

Vascular dysfunction
- Increased Arterial stiffness
- Increased PWV
- Increased BP

Autonomic function dysregulation
- Increased Sympathetic activity
- Decreased Parasympathetic activity
- Increased Heart rate

Lipids metabolism
- Increased FFA
- Increased LDL cholesterol
- Decreased HDL cholesterol

Insulin resistance
- Decreased Insulin production
- Increased Free Radical
- Increased Oxidative stress

Endothelial dysfunction
- Increased Platelet aggregation
- Increased Thrombosis
- Increased Blood viscosity

Platelet function
Effects of acrolein on the CV system
Wide ranges of CV effects of acrolein inhalation from smoking and ambient air pollution are reported in animal studies

- Increase blood pressure
- Increase the risk of thrombosis
- Induce myocardial dysfunction and cardiomyopathy
- Impair vascular repair capacity and induce vascular injury
- Reduce cardiac contractility
- Increase the risk of cardiac ventricular arrhythmia

Hanan Qasim et al. J Am Heart Assoc 2017;6:e006353
Schematic representation of how smoking might add to several mechanisms linking obesity to CVD

e-cigarette
Sales (Millions of Dollars) of E-cigarettes in the U.S., 2008-2013
(Source: UBS)
PARTICULATE MATTER IS Dangerous to Lungs & Hearts

- About 9 – 18% of e-cig PM reaches alveoli and blood circulation
- Exposure to PM associated with:
  - Breathing problems
  - Worsened asthma
  - Less lung growth in kids
  - Lung cancer
  - Coronary artery disease
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Detected Concentration Range</th>
<th>Biological System Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>ND to 38.8 mg/mL (10, 62, 63)</td>
<td>Lung tumor promoter67, Addiction67, Gastrointestinal carcinogen67, Raises blood pressure and heart rate68, Reduce brain development in adolescents37</td>
</tr>
<tr>
<td>Cotine</td>
<td>NDa</td>
<td>Reduce fertility and reproduction69</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>0.11 to 2.94 µg/15 puffs53, 64, 65</td>
<td>Carcinogen70, Aggravation of alcohol-induced liver damage71</td>
</tr>
<tr>
<td>Chromium</td>
<td>ND to 0.0105 µg/15 puffs7, 66</td>
<td>Pulmonary irritation and inflammation, nasal mucosa atrophy and ulcerations81, Nasal mucosa atrophy, reduce fertility and reproduction82</td>
</tr>
<tr>
<td>Cadmium</td>
<td>ND to 0.022 µg/15 puffs64, 66</td>
<td>Increase risk of lung cancer83, Pulmonary and nasal irritation83</td>
</tr>
<tr>
<td>Lead</td>
<td>0.025 to 0.57 µg/15 puffs64, 66</td>
<td>Hypertension induction83, 84, 88, Renal damage88, CNS damage84, 88</td>
</tr>
<tr>
<td>Nickel</td>
<td>0.0075 to 0.29 µg/15 puffs64, 66</td>
<td>Carcinogen43, CNS and pulmonary damage85, Renal and hepatic toxicity85</td>
</tr>
</tbody>
</table>

Hanan Qasim et al. J Am Heart Assoc 2017;6:e006353
Current laws

- Prohibits selling e-cigs to minors (same as WA law RCW 26.28.080)
- Prohibits offering free/nominal-cost e-cigs
- Prohibits e-cig use in same areas where smoking prohibited by law
air pollution
Biological pathways linking PM exposure with CVDs
The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating CV events are shown.

A microRNA (abbreviated miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, that functions in RNA silencing and post-transcriptional regulation of gene expression.
Effects of air pollution on BP and HR variability: a panel study of vehicular traffic controllers in the city of São Paulo, Brazil
Average SBP and DBP in the population by level of personal exposure to PM$_{2.5}$ and age

- **SBP (mm Hg)**
  - 25–50 years: $\Delta$SBP = 4.1 (1.5 to 6.6) mmHg; $p = 0.002$
  - > 50 years: $\Delta$SBP = 0.7 (−0.8 to 2.1) mmHg; $p = 0.35$

- **DBP (mm Hg)**
  - $\Delta$DBP = 1.8 (0.4 to 3.2) mmHg; $p = 0.01$
  - $\Delta$DBP = −0.6 (−1.7 to 0.5) mmHg; $p = 0.25$

Jill Baumgartner et al
Environ Health Perspect 2011
Cohort-specific and meta-analysis estimates of association of PM$_{2.5}$ (A), absorbance PM$_{2.5}$ (B), PM$_{coarse}$ (C), and PM$_{10}$ (D) with SBP and HTN

European Study of Cohorts for Air Pollution Effects (ESCAPE)

Kateryna B. Fuks et al
Environ Health Perspect. 2014
Pathogenesis of COPD includes:

- Cigarette smoke
- Biomass particles
- Particulates

Host factors Amplifying mechanisms

- Anti-proteinases hypothesis
- Repair mechanisms apoptosis

Anti-oxidants balance

Oxidative stress systemic inflammation

Oxidative stress COPD PATHOLOGY

in subjects with severe alpha1-antitrypsin deficiency who smoke because of a deficient antiprotease protection against neutrophil elastase release in the lung.

V.K. Vijayan
Indian J Med Res 2013
Barnes JP
COPD
Chronic Obstructive Pulmonary Disease

The COPD spectrum

CHRONIC BRONCHITIS

EMPHYSEMA

Asthma
The overlap syndrome is the synergistic relationship between coexisting chronic pulmonary disease and obstructive sleep apnea.

Mieczkowski B et al
Int J Chron Obstruct Pulmon Dis 2014
Pathways to the diagnosis of COPD

GOLD Guidelines 2017

SYMPTOMS
- Shortness of breath
- Chronic cough
- Sputum

RISK FACTORS
- Host factors
- Tobacco
- Occupation
- Indoor/outdoor pollution

SPIROMETRY: Required to establish diagnosis
### Classification of Severity of Airflow Limitation in COPD*

<table>
<thead>
<tr>
<th>Classification</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOLD 1: Mild</strong></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; ≥ 80% predicted</td>
</tr>
<tr>
<td><strong>GOLD 2: Moderate</strong></td>
<td>50% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% predicted</td>
</tr>
<tr>
<td><strong>GOLD 3: Severe</strong></td>
<td>30% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% predicted</td>
</tr>
<tr>
<td><strong>GOLD 4: Very Severe</strong></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% predicted</td>
</tr>
</tbody>
</table>

*Based on Post-Bronchodilator FEV<sub>1</sub>*

**Global initiative for chronic Obstructive Lung Disease**
comorbidities
Patients with COPD have peripheral lung inflammation that may spill over into the systemic circulation, leading to skeletal muscle weakness and cachexia and increasing propensity to CV, metabolic and bone diseases and depression.

Barnes PJ  PLOS Medicine 2010
COPD Comorbidities

49.5% of COPD discharges have co-morbid CHF and/or CAD.
Forest plot showing the significantly higher prevalence of CV and cerebrovascular comorbidities in COPD patients in comparison with non-COPD patients

Yin, Hong-lei et al Medicine 2017
Higher Rates of Hospitalisation Due to Comorbidities in COPD

IHD = ischaemic heart disease
CHF = congestive heart failure
RF = respiratory failure
PVD = pulmonary vascular disease
TM = thoracic malignancy

Percent of Subjects

- Hypertension
- IHD
- Diabetes
- Pneumonia
- CHF
- RF
- PVD
- TM

Overall causes of death were in the TORCH study.

TORCH: Causes of death as adjudicated by the Endpoint Committee

- N=4951 with COPD
- Age: 65y
- follow-up 3 y

- Respiratory: 35%
- Cardiac: 27%
- Cancer: 21%
- Other: 10%
- Unknown: 7%

Wise et al PATS 2006
Metaanalysis of studies that reported RR of CV mortality based on FEV1 quintiles

Marcus\textsuperscript{19} 1.93 (1.46, 2.54), men

Hole\textsuperscript{16} 1.56 (1.26, 1.92), men

Hole\textsuperscript{16} 1.88 (1.44, 2.47), women

Schunemann\textsuperscript{20} 2.11 (1.20, 3.71), men

Schunemann\textsuperscript{20} 1.96 (0.93, 3.88), women

Pooled Estimate 1.75 (1.54, 2.01)

Relative Risk of Cardiovascular Mortality (Worst FEV\textsubscript{1} Quintile vs. Best FEV\textsubscript{1} Quintile)

Chest 2005;127;1952-1959
Results from Cox proportional HR that predict death within 5 yrs by modified GOLD category and the presence of no (■), one (□), two (▓) or three (▪) comorbid diseases (diabetes, HTN or CVD).
HYPERTENSION
The COPD comorbidities network (left-hand side) is compared with the non-COPD controls (right-hand side) in a lung-shaped layout.
### CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THE PREVALENCE OF COMORBIDITIES (%)

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Arthritis</th>
<th>Cardiac</th>
<th>HTN</th>
<th>Diabetes</th>
<th>Lipids</th>
<th>Psych</th>
<th>GI</th>
<th>Cancer</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Manen and colleagues (1)</td>
<td>1,145</td>
<td>36</td>
<td>13</td>
<td>23</td>
<td>5</td>
<td>9</td>
<td>15</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mapel and colleagues (2)</td>
<td>200</td>
<td>22</td>
<td>65</td>
<td>45</td>
<td>12</td>
<td>17</td>
<td>32</td>
<td>18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Soriano and colleagues (114)</td>
<td>2,699</td>
<td>28</td>
<td>22</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>26</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sidney and colleagues (9)</td>
<td>45,966</td>
<td>—</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Walsh and Thomashow (115)</td>
<td>3,000</td>
<td>70</td>
<td>50</td>
<td>52</td>
<td>16</td>
<td>38</td>
<td>62</td>
<td>4</td>
<td>32</td>
<td>—</td>
</tr>
</tbody>
</table>

*Definition of abbreviations:* — = no available data; GI = gastrointestinal disturbances; HTN = hypertension.
Multivariate regression predicting DM, HTN and CVD

Atherosclerosis Risk in Communities Study during 1986–1989
Cardiovascular Health Study during 1989–1990

<table>
<thead>
<tr>
<th>GOLD category</th>
<th>Diabetes mellitus</th>
<th>Hypertension</th>
<th>Cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or 4</td>
<td>1.5 (1.1–1.9)</td>
<td>1.6 (1.3–1.9)</td>
<td>2.4 (1.9–3.0)</td>
</tr>
<tr>
<td>2</td>
<td>1.4 (1.2–1.6)</td>
<td>1.4 (1.3–1.6)</td>
<td>2.2 (1.9–2.5)</td>
</tr>
<tr>
<td>1</td>
<td>0.9 (0.8–1.1)</td>
<td>1.1 (0.9–1.2)</td>
<td>1.7 (1.5–1.9)</td>
</tr>
<tr>
<td>0</td>
<td>1.4 (1.3–1.6)</td>
<td>1.2 (1.1–1.3)</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Restricted</td>
<td>2.1 (1.9–2.5)</td>
<td>1.5 (1.4–1.7)</td>
<td>2.4 (2.1–2.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Forest plot showing the significantly higher prevalence of HTN and DM in COPD

Yin, Hong-lei et al Medicine 2017
In relation to sleep dip, significant differences were observed both for S/DBP measurements, with attenuated dip in the COPD group and physiological dip in the control group.

BP parameters in COPD patients with sleep desaturation not caused by apnea

Graph 1 – Distribution of blood pressure dip during sleep.
Minimum saturation values achieved during sleep were not significantly different between the two groups.

BP parameters in COPD patients with sleep desaturation not caused by apnea.
More than 22 million Americans have OSA

80% of them are undiagnosed
Potential Etiological Risk Factors for Sleep Apnea and the Downstream Consequences

- Respiratory control instability
- Obesity
- Upper airway dysfunction

- Sleep apnea
  - Increased sympathetic nerve activity
  - Metabolic dysregulation
  - Inflammation
  - Oxidative stress
  - Vascular endothelial dysfunction
  - Intermittent hypoxia

- Heart disease
- Hypertension
- Atrial fibrillation

End-stage cardiovascular disease

Diseases Associated with OSA

- Hypertension: 35%
- Atrial Fibrillation: 49%
- Pacemakers: 59%
- Diabetes: 72%
- Congestive Heart Failure: 76%
- Obesity: 77%
- Drug Resistant Hypertension: 83%
- Night Time Heart Attacks: 91%
Sleep Apnea Prevalence in Cardiovascular Disease Patients

- Drug Resistant Htn
- Stroke or TIA
- CHF
- All Htn
- CAD

- Logan J Htn 2001
- Basetti Sleep, 1999
- Javaheri Circ 1999
- Nieto JAMA 2001
- Shafer Card 1999

80% 60% 50% 45% 30%
ABPm in a patient with newly diagnosed OSA

24h BP: 158/81 mmHg
Daytime BP: 158/82 mmHg
Nighttime BP: 162/80 mmHg
Pathogenic mechanism linking between the risks factors of COPD and Mets

**Risk Factors**
- Genetics
- Altered Nutrition and Lifestyle

**Metabolic Syndrome**
- Abdominal obesity, Insulin resistance, Diabetes
- Atherogenic dyslipidemia, Hypertension

**COPD**
- Airways obstruction
- Local inflammation
- Hypoxia
- Sedentary lifestyle
- Physical deconditioning

**Physical Inactivity**

**Local adipose tissue hypoxia**

**Systemic hypoxia**

**Increased systemic inflammation**

Dukhabandhu Naik, et al Indian J Endocrinol Metab 2014
Genes associated with Bronchial asthma, COPD, Tuberculosis, or E-HTN

Yoshiko Kaneko et al Int J Chron Obstruct Pulmon Dis 2013
Risk of co-morbidity in 1259 COPD patients by ACE genotype

<table>
<thead>
<tr>
<th>ACE genotype</th>
<th>IHD (n = 284)</th>
<th>Hypertension (n = 522)</th>
<th>Low physical activity (n = 505)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>ID</td>
<td>DD</td>
</tr>
<tr>
<td>Crude</td>
<td>1.00</td>
<td>1.1 (0.8–1.6)</td>
<td>1.2 (0.8–1.7)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.00</td>
<td>1.0 (0.4–2.4)</td>
<td>1.3 (0.5–3.4)</td>
</tr>
</tbody>
</table>

Lee J et al *Respiratory Medicine* 2009
Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (Evidence A).

- Regular and as-needed use of SABA or SAMA improves FEV₁ and symptoms (Evidence A).
- Combinations of SABA and SAMA are superior to either medication alone in improving FEV₁ and symptoms (Evidence A).

- LABAs and LAMAs significantly improve lung function, dyspnea, and health status and reduce exacerbation rates (Evidence A).
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations (Evidence B).

- Combination treatment with LABA and LAMA increases FEV₁ and reduces symptoms compared with monotherapy (Evidence A).

- Combination treatment with LABA and LAMA reduces exacerbations compared with monotherapy (Evidence B) or ICS/LABA (Evidence B).
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Evidence B).
- Theophylline exerts a small bronchodilator effect in stable COPD (Evidence A) that is associated with modest symptomatic benefits (Evidence B).

**Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist.**
Antiinflammatory Therapy in Stable COPD

ICSs
- An ICS combined with an LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (Evidence A).
- Regular treatment with ICSs increases the risk of pneumonia, especially in those with severe disease (Evidence A).
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status (Evidence A) and reduces exacerbations (Evidence B) compared with ICS/LABA or LAMA monotherapy.

Oral glucocorticoids
- Long-term use of oral glucocorticoids has numerous side effects (Evidence A) with no evidence of benefits (Evidence C).

PDE4 inhibitors
- In patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations:
  - A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations (Evidence A).
  - A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations (Evidence B).

Antibiotics
- Long-term azithromycin and erythromycin therapy reduces exacerbations over 1 year (Evidence A).
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance (Evidence A) and hearing test impairment (Evidence B).

Mucolytics/antioxidants
- Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations (Evidence B).

Other antiinflammatory agents
- Simvastatin does not prevent exacerbations in patients with COPD at increased risk of exacerbations and without indications for statin therapy (Evidence A). However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (Evidence C).
- Leukotriene modifiers have not been tested adequately in patients with COPD.

Oxygen Therapy and Ventilatory Support
- Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy (Evidence B).

ICS = inhaled corticosteroid; 
LABA = long-acting beta-agonist; 
LAMA = long-acting muscarinic antagonist; 
NAC = N-acetylcysteine; 
PDE4 = phosphodiesterase 4.
Pharmacologic treatment algorithms by GOLD for COPD grade

ICS = inhaled corticosteroid;
LABA = long-acting b-agonist;
LAMA = long-acting muscarinic antagonist.

Green boxes and arrows indicate preferred treatment pathways.

GOLD Guidelines 2017
Bubble plot showing percentage of participants in each comorbidity category taking ≥3 concomitant medications associated with specific adverse drug reactions (ADRs)

Peter Hanlon et al. BMJ Open 2018;8:e018404
Effect of acute and chronic β-adrenergic activation on endothelial nitric oxide synthase activity, expression and uncoupling

Toblli JE et al Vasc Health Risk Manag 2012
Use of Sympathomimetic Drugs Leads to Increased Risk of Hospitalization for Arrhythmias in Patients With Congestive Heart Failure

### Association Between Use of Sympathomimetic Agents and Risk of Hospitalization for Arrhythmia

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 149)</th>
<th>Controls (n = 149)</th>
<th>Odds Ratio (95% CI)*</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of any sympathomimetics</td>
<td>33 (22.1)</td>
<td>17 (11.4)</td>
<td>2.2 (1.2-4.3)</td>
<td>4.0 (2.0-15.1)</td>
</tr>
<tr>
<td>Systemic sympathomimetics</td>
<td>6 (4.0)</td>
<td>1 (0.7)</td>
<td>6.0 (0.7-49.8)</td>
<td>15.7 (1.1-228)</td>
</tr>
<tr>
<td>Inhalation sympathomimetics</td>
<td>21 (14.1)</td>
<td>12 (8.1)</td>
<td>1.8 (0.9-3.8)</td>
<td>2.4 (0.5-13.1)</td>
</tr>
<tr>
<td>Nasal sympathomimetics</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td>2.0 (0.2-22.1)</td>
<td>3.5 (0.2-70.5)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>14 (9.4)</td>
<td>12 (8.1)</td>
<td>1.2 (0.5-2.6)</td>
<td>1.4 (0.3-5.7)</td>
</tr>
</tbody>
</table>

*Significant effects are in boldface.
†Adjusted for age, sex, prior hospital admissions (for arrhythmia, chronic obstructive pulmonary disease, asthma, emphysema, myocardial infarction, or angina pectoris) in the preceding year, and concomitant use of corticosteroids, digoxin, oral anticoagulants, calcium antagonists, angiotensin-converting enzyme-inhibitors, β-blockers, ibopamine, laxatives, antiarrhythmics, (potassium-sparing) diuretics, nitrates, any proarrhythmic drugs (antipsychotic, antidepressant, antihistaminic, macrolide, or cisapride), and antidiabetics.

Arch Intern Med. 2000
### Use of β2 agonist and risk of AMI stratified by history of IHD

**N=2476 HTNcives Mage:67y**

<table>
<thead>
<tr>
<th>Use of β2 agonists</th>
<th>No history of ischaemic heart disease</th>
<th>History of ischaemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n = 1616 Controls n = 20 295</td>
<td>Adjusted OR+ (95% CI)</td>
</tr>
<tr>
<td>Current use (100 days before)</td>
<td>88</td>
<td>0.88 (0.67, 1.17)</td>
</tr>
<tr>
<td>First time use</td>
<td>9</td>
<td>1.13 (0.56, 2.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Average daily dose, inhaled salbutamol eq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤400 μg</td>
<td>19</td>
<td>0.66 (0.41, 1.08)</td>
</tr>
<tr>
<td>400–800 μg</td>
<td>27</td>
<td>0.92 (0.59, 1.43)</td>
</tr>
<tr>
<td>800–1600 μg</td>
<td>30</td>
<td>1.10 (0.71, 1.71)</td>
</tr>
<tr>
<td>&gt;1600 μg</td>
<td>3</td>
<td>0.49 (0.15, 1.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Cumulative dose, inhaled salbutamol eq.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.25 g</td>
<td>28</td>
<td>0.83 (0.55, 1.25)</td>
</tr>
<tr>
<td>0.25–1.00 g</td>
<td>23</td>
<td>0.72 (0.45, 1.15)</td>
</tr>
<tr>
<td>&gt;1.00 g</td>
<td>37</td>
<td>1.14 (0.76, 1.72)</td>
</tr>
</tbody>
</table>

**Adjusted OR+ (95% CI)**

- Current use: 1.93 (1.41, 2.65)
- First time use: 1.69 (0.67, 4.27)
- ≤400 μg: 2.38 (1.50, 3.76)
- 400–800 μg: 2.11 (1.24, 3.59)
- 800–1600 μg: 1.33 (0.73, 2.43)
- >1600 μg: 1.84 (0.66, 5.11)
- ≤0.25 g: 2.47 (1.60, 3.82)
- 0.25–1.00 g: 1.91 (1.19, 3.05)
- >1.00 g: 1.29 (0.72, 2.29)

**De Vries F et al British Journal of Clinical Pharmacology 2008**
Effect of β2-agonists compared with placebo on COPD withdrawals, hospitalizations and respiratory deaths (RR)

Shelley R Salpeter et al J Gen Intern Med. 2006
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% predicted) categories:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80%</td>
<td>Reference</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70-79%</td>
<td>2.19</td>
<td>1.35-3.53</td>
<td>0.001</td>
</tr>
<tr>
<td>60-69%</td>
<td>3.62</td>
<td>2.00-6.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≤60%</td>
<td>1.79</td>
<td>0.93-3.46</td>
<td>0.08</td>
</tr>
<tr>
<td>History of OSA</td>
<td>4.74</td>
<td>2.82-7.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of OSA or high OSA risk on SA-SDQ*</td>
<td>5.18</td>
<td>3.66-7.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.10</td>
<td>1.08-1.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.92</td>
<td>0.65-1.30</td>
<td>0.63</td>
</tr>
<tr>
<td>BMI</td>
<td>1.09</td>
<td>1.06-1.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.62</td>
<td>0.25-1.50</td>
<td>0.29</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0.66</td>
<td>0.40-1.10</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>1.65</td>
<td>1.18-2.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>1.96</td>
<td>1.29-2.98</td>
<td>0.002</td>
</tr>
<tr>
<td>ICS dose:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>0.86</td>
<td>0.50-1.45</td>
<td>0.56</td>
</tr>
<tr>
<td>Medium dose</td>
<td>1.21</td>
<td>0.75-1.95</td>
<td>0.44</td>
</tr>
<tr>
<td>High dose</td>
<td>2.18</td>
<td>1.37-3.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>2.07</td>
<td>1.24-3.46</td>
<td>0.006</td>
</tr>
<tr>
<td>LABA</td>
<td>1.60</td>
<td>1.14-2.26</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Univariate associations of systemic HTN

n=812 with asthma

*defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females

Susan Ferguson et al Lung 2015
Cardiovascular Safety of Tiotropium in Patients With COPD

19,545 patients randomized: 10,846 (tiotropium) and 8,699 (placebo) from 30 trials.

Rate ratio = 0.77; 95% CI = (0.60-0.98)
The results of randomised, controlled clinical trials for diuretics in COPD are not available
1) diuretics may be beneficial for the elimination of fluid retention developing in HF that frequently complicates COPD and also HTN
2) inhibit pulmonary vascular remodelling
3) Acetazolamide has been found to increase ventilation in COPD
4) may decrease the plasma level of K+ and this effect may be added to the hypokalaemic effects of steroids and b-2 adrenoceptor agonists, drugs that are frequently used in COPD
5) may also worsen CO2 retention, metabolic alkalosis-related hypoxia in hypoventilation patients and patients with chronic hypercapnia
6) increase haematocrit
7) deteriorate mucus secretion in bronchi

Therefore DIU are not recommended for universal use in hypertensive patients with COPD

Indapamide might be an exception to this rule, as in a 28 week study of hypertensive patients with COPD on standardised bronchodilator therapy, BP decreased by 48/30 mm Hg (mean value) and respiratory function improved over the same period
Diuretics

b2 receptors agonists drive K+ into the cells
corticosteroids: increase urinary potassium excretion
Less common problems

- **HYPERSENSITIVITY** - may manifest as interstitial nephritis, pancreatitis, rashes, blood dyscrasias (all very rare)

- **METABOLIC ALKALOSIS** due to increased sodium load at the distal convoluted tubule which stimulates the sodium/hydrogen exchanger to reabsorb sodium and excrete hydrogen

- **HYPERCALCEMIA**
Among patients with normal renal function, loop diuretics have a lesser antihypertensive effect than the thiazide diuretics. This may be related to the shorter duration of action of most loop diuretics when compared to the thiazides.

Loop diuretics may be useful in patients with COPD who have:
1) resistant hypertension
2) are volume overloaded
3) have an estimated glomerular filtration rate of 30 mL/min/m²
4) In addition, inhaled furosemide has shown some early promise as a dyspnea-relieving intervention in COPD.

Patients with COPD who have chronic respiratory acidosis or are receiving corticosteroids or β-agonists and do get treated with K⁺ wasting loop diuretics should undergo close monitoring of electrolyte levels and be considered for therapy with K⁺ supplements.

In addition, these drugs can increase hematocrit as well as lead to hemodynamic compromise in patients who are preload dependent in the setting of right HF.

Dipak Chandy Integrated Blood Pressure Control 2013
Annual use of ACE-I during 1981-91 in Sweden and concomitant reported cases of adverse respiratory reactions possibly related to use of these drugs.

H Lunde et al. BMJ 1994
TABLE

Mean values for bronchial reactivity and cough index before and after rechallenge with angiotensin converting enzyme inhibitors and after one year

<table>
<thead>
<tr>
<th>Case No</th>
<th>Airways conductance (/kPa/s)</th>
<th>PC_{35}SG_{sw} * (g/l)</th>
<th>Cough index (No of coughs/latency)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>1†</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.6</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5†</td>
<td>0.3</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>0.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*PC_{35}SG_{sw} = Concentration of histamine causing a 35% fall in baseline values of airways conductance.
†Patient had bronchial asthma.
### Univariate Correlates of ACE Inhibitor-Induced Cough in the Derivation Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cough (N=130)</th>
<th>No Cough (N=995)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>120 (92)</td>
<td>840 (84)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>39 (30)</td>
<td>368 (37)</td>
<td>.1</td>
</tr>
<tr>
<td>Coronary artery disease, n(%)</td>
<td>30 (23)</td>
<td>194 (20)</td>
<td>.3</td>
</tr>
<tr>
<td>Congestive heart failure, n(%)</td>
<td>10 (8)</td>
<td>76 (8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n(%)</td>
<td>6 (5)</td>
<td>33 (3)</td>
<td>.4</td>
</tr>
<tr>
<td>Asthma, n(%)</td>
<td>16 (12)</td>
<td>103 (10)</td>
<td>.5</td>
</tr>
<tr>
<td>Other respiratory diseases, n(%)</td>
<td>1 (0.8)</td>
<td>14 (1.4)</td>
<td>.6</td>
</tr>
<tr>
<td>Depression/anxiety, n(%)</td>
<td>44 (34)</td>
<td>270 (27)</td>
<td>.1</td>
</tr>
<tr>
<td>Other psychiatric diseases, n(%)</td>
<td>4 (3)</td>
<td>38 (4)</td>
<td>.7</td>
</tr>
<tr>
<td>Hemodialysis, n(%)</td>
<td>1 (0.8)</td>
<td>13 (1.3)</td>
<td>.6</td>
</tr>
<tr>
<td>Creatinine ≥1.6 mg/dL, n(%)</td>
<td>3 (2)</td>
<td>63 (6)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Concurrent Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics, n(%)</td>
<td>44 (34)</td>
<td>392 (39)</td>
<td>.2</td>
</tr>
<tr>
<td>Beta-blockers, n(%)</td>
<td>53 (41)</td>
<td>355 (36)</td>
<td>.3</td>
</tr>
<tr>
<td>Calcium antagonists, n(%)</td>
<td>19 (15)</td>
<td>155 (16)</td>
<td>.8</td>
</tr>
<tr>
<td>Low dose (≤325 mg/day) aspirin, n(%)</td>
<td>46 (35)</td>
<td>327 (33)</td>
<td>.6</td>
</tr>
<tr>
<td>High dose (&gt;325 mg/day) aspirin, n(%)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>.7</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs, n(%)</td>
<td>22 (17)</td>
<td>156 (16)</td>
<td>.7</td>
</tr>
<tr>
<td>Cyclo-oxygenase-2 inhibitors, n(%)</td>
<td>7 (5)</td>
<td>57 (6)</td>
<td>.9</td>
</tr>
</tbody>
</table>

Morimoto T et al J Gen Intern Med. 2004
Proportion of surviving patients hospitalized with COPD exacerbation by use of ACE inhibitor versus non-use

N=11,212
m age 74.0 y
98% male
hospitalized with acute COPD exacerbations
12.4% died within 90-days of hospital presentation

Use of statins and ACE- i prior to admission

(p < 0.001).

Mortensen EM et al Respir Res 2009
REDUCTION OF MORBIDITY AND MORTALITY BY STATINS, ACE-I AND ARBs IN PATIENTS WITH COPD

Mancini GB et al. JACC 2006
It has been known for years that ACEIs may cause coughs (5-20%) and exacerbate, or even induce, asthma. 10% of the reported adverse effect of ACEIs is bronchospasm. However, these anti-hypertensive agents have been proven to decrease CV morbidity and mortality of hypertensive patients as well as those with CAD and HF. They also decrease COPD-induced hospitalisation of patients. ACEIs may reduce the RAAS stimulation-related hypokalaemic effects of b-2 receptor agonists agents that are frequently used in COPD. It is important to note that the incidence of ACEI-related cough was not more frequent in patients with chronic bronchitis than in other populations. However, ACEIs may worsen the clinical stage in patients with asthma. The increased availability of bradykinin (which increases cough) and substance P (which causes bronchoconstriction) probably contribute to this unwanted effect. Unfortunately, studies including hypertensive patients with COPD are scarce.
Treatment of COPD and its comorbidities

1. Inhaled corticosteroids
2. Inhaled corticosteroids overspill
3. Statins, ACE inhibitors, PPAR agonists
4. PDE4 inhibitors, NF-KB inhibitors, P38 MAPK inhibitors
5. Skeletal muscle dysfunction
6. Cardiovascular disease
7. Systemic inflammation
8. Osteoporosis

Nicola J. Sinden
Ther Adv Chronic Dis. 2010
# Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial

**N=60 with COPD**

**Irbesartan**

## Lung function test results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Irbesartan</th>
<th></th>
<th>p-value[^4]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 months</td>
<td>Baseline</td>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>$P_{lmax}$ kPa</td>
<td>5.5±2.0</td>
<td>5.8±2.2</td>
<td>4.8±1.9</td>
<td>4.5±2.0</td>
<td>0.16</td>
</tr>
<tr>
<td>$P_{0.1lmax}$ kPa</td>
<td>3.3±1.0</td>
<td>3.4±1.7</td>
<td>2.9±1.0</td>
<td>2.7±1.3</td>
<td>0.47</td>
</tr>
<tr>
<td>FEV$_1$/vital capacity</td>
<td>42±12</td>
<td>38±11</td>
<td>40±7</td>
<td>43±13</td>
<td>0.07</td>
</tr>
<tr>
<td>Vital capacity L</td>
<td>2.3±0.7</td>
<td>2.5±1.0</td>
<td>2.3±0.7</td>
<td>2.1±0.7</td>
<td>0.18</td>
</tr>
<tr>
<td>FEV$_1$ L·s$^{-1}$</td>
<td>0.95±0.3</td>
<td>0.95±0.6</td>
<td>0.91±0.3</td>
<td>0.87±0.3</td>
<td>0.67</td>
</tr>
<tr>
<td>$R_{aw,tot}$ kPa·L$^{-1}$·s$^{-1}$</td>
<td>0.79±0.59</td>
<td>0.64±0.4</td>
<td>0.67±0.4</td>
<td>0.69±0.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Total lung capacity % pred</td>
<td>110.4±23</td>
<td>121.7±26.8$^*$</td>
<td>119.7±16</td>
<td>113.7±19.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Residual volume/total lung capacity %</td>
<td>66.2±11.0</td>
<td>70.4±10.3$^*$</td>
<td>68.9±7.2</td>
<td>68.8±7.3</td>
<td>0.08</td>
</tr>
<tr>
<td>$P_aO_2$ mmHg</td>
<td>64.4±10.4</td>
<td>62.5±11.8</td>
<td>65.7±10.4</td>
<td>66.7±12</td>
<td>0.31</td>
</tr>
<tr>
<td>$P_aCO_2$ mmHg</td>
<td>43.3±3.4</td>
<td>44.3±3.7</td>
<td>42.9±3.6</td>
<td>42.8±3.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Quadriceps maximal muscle strength N</td>
<td>22.1±9.1</td>
<td>22.3±9.8</td>
<td>19.6±8.6</td>
<td>21.6±9.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight kg</td>
<td>76.0±15.1</td>
<td>76.1±16.8</td>
<td>71.3±14.9</td>
<td>72.2±14.8</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Respiratory muscle strength in COPD patients was not influenced by ARBs

---

[^4]: Significance level for the test results.
Effects of placebo and irbesartan on haematocrit at baseline (□) and at follow-up at 4 months (■)

- **Placebo**: No significant difference (NS)
- **Irbesartan**: Significantly lower than placebo (p<0.001)
- **Drug**: Significantly lower than placebo (p=0.003)

S. Andreas et al. Eur Respir J 2006
Changes in cough frequency by VAS before and after 6-month antihypertensive treatment

Incidence, frequency and severity of persistent cough, pulmonary functions and bronchial hyperresponsiveness did not change in either the candesartan or CCB group

One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study

Logistic regression analysis of variables predictive of in-hospital mortality in patients admitted with COPD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.05</td>
<td>1.03–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCI, per point</td>
<td>1.08</td>
<td>1.01–1.15</td>
<td>0.016</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.34</td>
<td>0.94–1.92</td>
<td>0.104</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.82</td>
<td>0.52–1.30</td>
<td>0.397</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.39</td>
<td>0.89–2.19</td>
<td>0.153</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.19</td>
<td>0.85–1.66</td>
<td>0.320</td>
</tr>
<tr>
<td>Use of ARB</td>
<td>0.61</td>
<td>0.38–0.98</td>
<td>0.040</td>
</tr>
<tr>
<td>Use of β blocker</td>
<td>0.63</td>
<td>0.41–0.95</td>
<td>0.028</td>
</tr>
<tr>
<td>Use of statin</td>
<td>0.40</td>
<td>0.14–1.14</td>
<td>0.087</td>
</tr>
</tbody>
</table>

ARL, angiotensin II receptor blocker; CCI, Charlson comorbidity index; CI, confidence interval.

doi:10.1371/journal.pone.0114866.t003
RAAS-modifying therapies are associated with improved pulmonary health

*Kaplan Meier curves for the survival function for incidence of infection, inflammatory and structural outcomes in the lung. Figures were generated using STATA*

HTNcives  \((N = 3,496,488)\) 52% female  
Mage: 62y

Soto M, et al  
Clin Diabetes Endocrinol. 2017
RAS including Angiotensin receptors 1 and 2

ARBs attenuates cigarette smoke–induced lung injury and rescues lung architecture in mice

Podowski M et al Journal of Clinical Investigation  2012
ARBS

An important advantage of this anti-hypertensive class against ACEIs is that they practically do not cause cough, and ARB-related angioneurotic oedema is very rare. Patients with a history of ACEI-induced cough tolerate ARB as well as they do a placebo. However, in one study, losartan increased cough, a side-effect thought to be related to the inhibition of the endogenous release of NO. Contrary to this finding, in another study, losartan inhibited the metacholine induced bronchospasm and consequently decreased the reduction of FEV1. ARB is useful because the hypoxia stimulates the SNS and consequently the RAAS.
Efficacy of CCBs as maintenance therapy for asthma

peak expiratory flow

in the morning before the dose of study medication in the evening, before the bedtime dose
Calcium channel blockers (CCB)

CCBs induce smooth muscle relaxation in bronchi and inhibit the decrease in FEV1, either induced by physical activity or metacholine. They may slightly potentiate the β-2 receptor mediated bronchodilation and decrease non-specific bronchial reactivity. Therefore, use of CCBs may be beneficial in hypertensive patients with COPD. Clinical experience has shown that these drugs usually do not exert severe side effects on the airways. However, it is important to note that CCBs may worsen the normal ratio of perfusion/ventilation and consequently increase hypoxia; therefore, oxygen saturation monitoring is recommended. Hard end-point data on the use of CCBs in hypertensive patients with COPD has yet to be published.
Patients hospitalised with acute exacerbations of COPD with underlying IHD, HF or HTN

Outcomes of patients treated with a β-blocker on day 1 or 2 compared with late treated or untreated patients

- In-hospital mortality
  - Unadjusted—full cohort: $0.79$ (0.67 to 0.93)
  - Covariate and PS adjusted—full cohort: $0.84$ (0.70 to 1.00)
  - Adjusted—PS matched cohort: $0.88$ (0.71 to 1.09)

Late ventilation
- Unadjusted—full cohort: $0.86$ (0.73 to 1.02)
- Covariate and PS adjusted—full cohort: $0.92$ (0.76 to 1.10)
- Adjusted—PS matched cohort: $0.98$ (0.77 to 1.24)

30-day all-cause readmission
- Unadjusted—full cohort: $1.00$ (0.94 to 1.06)
- Covariate and PS adjusted—full cohort: $0.95$ (0.89 to 1.01)
- Adjusted—PS matched cohort: $0.96$ (0.89 to 1.03)

N=35082
≥40 years
29% BBs

22% β1-selective
7% non-selective

Stefan MS et al. Thorax 2012

THORAX
Outcomes of non-selective versus cardioselective β-blocker therapy

Patients hospitalised with acute exacerbations of COPD with underlying IHD, HF or HTN

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Non-selective β blocker versus cardioselective β blocker*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted—full cohort†</td>
<td>0.97 (0.70 to 1.35)</td>
</tr>
<tr>
<td>Covariate adjusted—full cohort‡</td>
<td>0.89 (0.63 to 1.25)</td>
</tr>
<tr>
<td>Covariate and propensity score adjusted—full cohort‡</td>
<td>0.86 (0.60 to 1.24)</td>
</tr>
<tr>
<td>Matched cohort adjusted for unbalanced covariates§ ¶</td>
<td>0.75 (0.47 to 1.19)</td>
</tr>
</tbody>
</table>

Late ventilation

| Unadjusted—full cohort†           | 1.28 (0.93 to 1.76)                                      |
| Covariate adjusted—full cohort‡   | 1.29 (0.93 to 1.79)                                      |
| Covariate and propensity score adjusted—full cohort‡ | 1.24 (0.88 to 1.74)                                      |
| Matched cohort adjusted for unbalanced covariates§ ¶ | 1.06 (0.68 to 1.65)                                      |

30-Day all-cause readmission**

| Unadjusted—full cohort†           | 1.35 (1.21 to 1.50)                                      |
| Covariate adjusted—full cohort‡   | 1.21 (1.08 to 1.36)                                      |
| Covariate and propensity score adjusted—full cohort‡ | 1.20 (1.06 to 1.35)                                      |
| Matched cohort adjusted for unbalanced covariates§ ¶ | 1.25 (1.08 to 1.44)                                      |

N=35082 ≥40 years

22% β1-selective 7% non-selective
The comparison of adjusted incidence risk ratios (IRRs) for total and severe exacerbations occurring during long-term follow-up in patients with COPD who are on or not on β-blocker therapy.
COPD is an independent predictor of death but not atherosclerotic events in patients with MI: analysis of the VALIANT

Valsartan in Acute Myocardial Infarction Trial (VALIANT)
Effect of β-blockers in treatment of COPD: a retrospective cohort study

Kaplan-Meier estimate of probability of survival among patients with COPD by use of β blockers.

There was a 22% overall reduction in all-cause mortality with β-blocker use.

Philip M Short et al. BMJ 2011;342:bmj.d2549
Adjusted HRs for **all cause mortality** among patients with COPD in reference to the control group (who received only inhaled therapy with short acting β agonists or antimuscarinics)

Philip M Short et al. BMJ 2011

ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV$_1$=forced expiratory volume in one second, SaO$_2$=arterial oxygen saturation
Improvement in pulmonary function in patients with CHF and COPD on switching from a nonselective to a cardioselective b-blocker. FEV1 returns to baseline levels on resumption of carvedilol.

*P=.02 vs carvedilol at baseline; † P=1.0 compared with carvedilol at baseline.

C = carvedilol

Jabbour A et al
JACC 2010
The actual data (mean ± SD) of FEV1 before administration and at different times after the administration of oral placebo, nebivolol, 5 mg, or celiprolol, 200 mg.

N=12

Nebivolol: b1-selectivity influence on FEV1 in patients with asthma

Beta-blocker under-use in COPD patients

CONSORT diagram

572 admissions retrieved

206 excluded: 156 repeat presentations, 26 incorrect diagnostic coding, 24 insufficient information

366 patients included for analysis (n=366)

156 patients (43%) had ≥1 indication for BBs

53 on BBs (34%)

61 not on BBs and no contraindications (39%)

210 patients (57%) had no indications for BBs

42 not on BBs but had ≥1 contraindications (27%)

Figure 1 CONSORT diagram.
Note: Text/data shown in bold are the important points.
Abbreviation: BB, beta-blocker.
b-blockers

The worsening or precipitation of asthma by non-selective b-blockers is well recognised but the cardio-selective b-1-adrenoceptor blockers and those exerting mild b-2-agonist activity (e.g. celiprolol), or those which, in addition to their high b-1 selectivity, increase the endogenous production of NO (nebivolol) affect airway function to either a much lesser extent or not at all.

Therapy with selective b-1 blockers is not contraindicated in cases of COPD and has also been proved to decrease total as well as CV mortality. In addition to these beneficial effects, they may also decrease the incidence of acute exacerbations of airways obstruction. Therefore, if needed in patients with COPD for HTN or CAD, highly selective b-1 blockers can be recommended.

The meta-analysis by Salpeter et al. indicated that non-selective b-blockers decreases, while cardio-selective b-blockers improves the bronchodilatatory effects of b-2 mimetics due to b-2 receptor up-regulation.
In a recent trial acute decompensated HF patients with COPD the mortality rate was higher in patients without b-blockers compared with those taking b-blockers. The use of b-blockers was the only factor significantly correlated with the mortality rate.

These findings support the recommendations to use b1-selective blockers in HF patients with COPD. Other studies showed that carvedilol, a non-selective b and a adrenoceptor blocker was well tolerated in patients with COPD with no reversible airway obstruction. Therefore, if needed in patients with COPD for HTN or CAD, CHF highly selective b-1 blockers can be recommended.

The meta-analysis by Salpeter et al. indicated that non-selective b-blockers decreases, while cardio-selective b-blockers improve the bronchodilatatory effects of b-2 mimetics due to b-2 receptor up-regulation.
Compelling and possible contra-indications to the use of antihypertensive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compelling</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (thiazides)</td>
<td>Gout</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Asthma</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>A-V block (grade 2 or 3)</td>
<td>Glucose intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Athletes and physically active patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)</td>
</tr>
<tr>
<td>Calcium antagonists (dihydropyridines)</td>
<td>A-V block (grade 2 or 3, trifascicular block)</td>
<td>Tachyarrhythmia</td>
</tr>
<tr>
<td></td>
<td>Severe LV dysfunction</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Calcium antagonists (verapamil, diltiazem)</td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Pregnancy</td>
<td>Women with child bearing potential</td>
</tr>
<tr>
<td></td>
<td>Angioneurotic oedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperkalaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral renal artery stenosis</td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Pregnancy</td>
<td>Women with child bearing potential</td>
</tr>
<tr>
<td></td>
<td>Hyperkalaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral renal artery stenosis</td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>Acute or severe renal failure (eGFR &lt;30 mL/min)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperkalaemia</td>
<td></td>
</tr>
</tbody>
</table>

ESH 2013
**a-1 adrenoceptor antagonists**
In general, these drugs do not affect airway resistance. Prazosin was found to partially inhibit cold air-induced bronchoconstriction.

The deteriorated airway function in COPD was not changed by these drugs; therefore they may be used in hypertensive patients with COPD.

**a- + b-adrenoceptor antagonists**
Increase bronchial spasm.

**a-2 adrenoceptor agonists**
May potentiate the histamine-induced bronchial spasm; therefore, they cannot be suggested for use on hypertensive patients with COPD.
There are no data for the use of the imidazoline I-1 receptor agonists (moxonidine).
However by the decrease in central sympathetic tone and reduction of the activity of RAAS, these drugs might be beneficial.
Effect of CPAP Therapy on BP in Patients With Resistant Hypertension

Javaheri S et al
JACC 2017
Comparison of a) survival and b) exacerbation-free survival in three populations: COPD alone; COPD with OSAS treated with continuous positive airway pressure (CPAP); and COPD with OSAS not treated with CPAP

Arnaud Cavaillès et al. Eur Respir Rev 2013
Forest plot showing effect of statins on all-cause mortality in COPD

Effect of pulmonary rehabilitation in patients with COPD

<table>
<thead>
<tr>
<th></th>
<th>Start of rehabilitation</th>
<th>End of rehabilitation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic PWV (m/s)</td>
<td>9.8 (3.0)</td>
<td>9.3 (2.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Brachial PWV (m/s)</td>
<td>9.0 (1.7)</td>
<td>8.9 (1.6)</td>
<td>0.535</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>33.9 (5.3)</td>
<td>33.6 (8.8)</td>
<td>0.833</td>
</tr>
<tr>
<td>Peripheral SBP (mmHg)</td>
<td>138 (20)</td>
<td>128 (24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peripheral DBP (mmHg)</td>
<td>83 (9)</td>
<td>78 (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peripheral PP (mmHg)</td>
<td>55 (15)</td>
<td>49 (19)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peripheral MAP (mmHg)</td>
<td>101 (12)</td>
<td>95 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>126 (21)</td>
<td>120 (23)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Central DBP (mmHg)</td>
<td>83 (12)</td>
<td>79 (12)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Central PP (mmHg)</td>
<td>43 (14)</td>
<td>41 (18)</td>
<td>0.471</td>
</tr>
<tr>
<td>Central MAP (mmHg)</td>
<td>103 (14)</td>
<td>95 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>76 (12)</td>
<td>76 (14)</td>
<td>0.933</td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>5.0 (0.7)</td>
<td>4.8 (0.8)</td>
<td>0.079</td>
</tr>
<tr>
<td>Total Fasting Cholesterol (mmol/L)</td>
<td>5.6 (1.2)</td>
<td>5.4 (1.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.4 (1.1)</td>
<td>3.3 (1.2)</td>
<td>0.389</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.7 (0.5)</td>
<td>1.6 (0.4)</td>
<td>0.050</td>
</tr>
<tr>
<td>ISWT (m)</td>
<td>190 (70)</td>
<td>274 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ Total Score</td>
<td>56.5 (13.9)</td>
<td>44.9 (16.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
A holistic approach to medical intervention

- Pharmacotherapy
- Pulmonary rehabilitation vaccinations
- Guideline based management for specific comorbidities

COPD

Modification of risk factors
- Smoking cessation (counseling/pharmacotherapy)
- Diet modification
- Physical activity

Comorbidities

Georgios Hillas et al Int J Chron Obstruct Pulmon Dis 2015
Potential targets for anti-inflammatory therapy

(A) Factors driving inflammation
  - Autoimmunity
  - Embedded particles
  - Bacteria

(B) Intracellular signaling
  - NFκB
  - STAT3

(C) Cytokines
  - TNF-α
  - IL-1
  - IL-6

(D) ROS

(E) Proteases
  - NE
  - MMPs

Cell surface receptor

Immune cell
  - Macrophage
  - T cell
  - Neutrophil

Paul T King
Clin Transl Med. 2015
Canakinumab is a human monoclonal antibody targeted at interleukin-1 b
Canakinumab, as Compared with Placebo, on Plasma Levels of High-Sensitivity CRP, LDL

CANTOS Trial

A High-Sensitivity C-Reactive Protein Level

B LDL Cholesterol Level

NEJM 2017
Cumulative Incidence of the Primary End Point and the Key Secondary CV End Point.

**A** Primary End Point with Canakinumab, 50 mg, vs. Placebo

- **Hazard ratio:** 0.93 (95% CI, 0.80–1.07)
- **P-value:** 0.30

**B** Primary End Point with Canakinumab, 150 mg, vs. Placebo

- **Hazard ratio:** 0.85 (95% CI, 0.74–0.98)
- **P-value:** 0.021

**C** Primary End Point with Canakinumab, 300 mg, vs. Placebo

- **Hazard ratio:** 0.86 (95% CI, 0.75–0.99)
- **P-value:** 0.031

**D** Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo

- **Hazard ratio:** 0.83 (95% CI, 0.73–0.95)
- **P-value:** 0.005

**No. at Risk**

- **Placebo:**
  - 3344, 3141, 2973, 2632, 1266, 210
- **Canakinumab:**
  - 2263, 2149, 2038, 1819, 938, 199

**No. at Risk**

- **Placebo:**
  - 3344, 3107, 2921, 2578, 1238, 206
- **Canakinumab:**
  - 2284, 2135, 2039, 1824, 892, 201

*NEJM 2017*
Incidence Rates and Numbers of Serious Adverse Events and Selected Safety Laboratory Data During Treatment, Stratified According to Trial Group.

### CANTOS Trial

<table>
<thead>
<tr>
<th>Adverse Event or Laboratory Variable</th>
<th>Placebo Group (N = 3344)</th>
<th>Canakinumab</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event — incidence rate per 100 person-yr (no. of patients with event)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>11.96 (1202)</td>
<td>11.41 (741)</td>
<td>11.71 (812)</td>
</tr>
<tr>
<td>Any serious adverse event of infection</td>
<td>2.86 (342)</td>
<td>3.03 (230)</td>
<td>3.13 (258)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0.24 (30)</td>
<td>0.24 (19)</td>
<td>0.37 (32)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.90 (112)</td>
<td>0.94 (74)</td>
<td>0.94 (80)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.22 (27)</td>
<td>0.18 (14)</td>
<td>0.24 (21)</td>
</tr>
<tr>
<td>Opportunistic infection†</td>
<td>0.18 (23)</td>
<td>0.16 (13)</td>
<td>0.15 (13)</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>0.03 (4)</td>
<td>0.13 (10)</td>
<td>0.05 (4)</td>
</tr>
<tr>
<td>Fatal infection or sepsis</td>
<td>0.18 (23)</td>
<td>0.31 (25)</td>
<td>0.28 (24)</td>
</tr>
<tr>
<td>Any cancer‡</td>
<td>1.88 (231)</td>
<td>1.85 (144)</td>
<td>1.69 (143)</td>
</tr>
<tr>
<td>Fatal cancer‡</td>
<td>0.64 (81)</td>
<td>0.55 (44)</td>
<td>0.50 (44)</td>
</tr>
<tr>
<td>Other adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction†</td>
<td>0.23 (29)</td>
<td>0.27 (21)</td>
<td>0.28 (24)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32 (385)</td>
<td>2.15 (164)</td>
<td>2.17 (180)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67 (202)</td>
<td>1.21 (94)</td>
<td>1.12 (95)</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80 (99)</td>
<td>0.43 (34)</td>
<td>0.35 (30)</td>
</tr>
<tr>
<td>Drug-induced liver injury†</td>
<td>0.18 (23)</td>
<td>0.15 (12)</td>
<td>0.13 (11)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24 (30)</td>
<td>0.30 (24)</td>
<td>0.37 (32)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.06 (7)</td>
<td>0.05 (4)</td>
<td>0.07 (6)</td>
</tr>
<tr>
<td>Any hemorrhage</td>
<td>4.01 (462)</td>
<td>3.33 (249)</td>
<td>4.15 (327)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.43 (53)</td>
<td>0.56 (44)</td>
<td>0.54 (46)</td>
</tr>
<tr>
<td>Hepatic variable — percent of patients with condition (no.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;3x normal value</td>
<td>1.4 (46)</td>
<td>1.9 (42)</td>
<td>1.9 (44)</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;3x normal value</td>
<td>1.1 (36)</td>
<td>1.5 (32)</td>
<td>1.5 (35)</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt;3x normal value</td>
<td>0.4 (15)</td>
<td>0.5 (11)</td>
<td>0.4 (10)</td>
</tr>
<tr>
<td>Bilirubin &gt;2x normal value</td>
<td>0.8 (26)</td>
<td>1.0 (21)</td>
<td>0.7 (15)</td>
</tr>
</tbody>
</table>

* Data are shown as incidence rates per 100 person-years (with numbers of patients with event) for adverse events and as percentages of patients with the condition (with numbers of patients) for hepatic variables to facilitate the comparison of rates between groups. All adverse-event categories are based on standardized queries or classification levels in the Medical Dictionary for Regulatory Activities, version 20.0, except those otherwise indicated.
† These adverse events, including drug-induced liver injury as a serious adverse event, were considered by the sponsor to be adverse events of special interest.
‡ Included here are cancers that were adjudicated by the cancer end-point adjudication committee.
Long-acting muscarinic antagonists (LAMAs)
The combination of LABA and LAMA drugs in a single inhaler is superior to either treatment alone. The LABA/LAMA combination is superior to a LABA/inhaled corticosteroid (ICS) combination in the prevention of exacerbations

Short-acting muscarinic antagonists (SAMA)
<table>
<thead>
<tr>
<th>ΑΔΡΕΝΕΡΓΙΚΟΙ ΔΙΕΓΕΡΤΕΣ</th>
<th>Έναρξη δράσης [λεπτά]</th>
<th>Διάρκεια δράσης [ώρες]</th>
</tr>
</thead>
</table>

**ΕΙΣΠΝΕΟΜΕΝΟΙ, ΒΡΑΧΕΙΑΣ ΔΡΑΣΗΣ ΕΚΛΕΚΤΙΚΟΙ (β2) ΔΙΕΓΕΡΤΕΣ (SABA)**

<table>
<thead>
<tr>
<th>Κλενβουτερόλη SPIROPENT</th>
<th>30</th>
<th>8-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ορσιπρεναλίνη+ ALUPENT</td>
<td>15-30</td>
<td>4</td>
</tr>
<tr>
<td>Σαλβουταμόλη AEROLIN</td>
<td>15</td>
<td>3-4</td>
</tr>
<tr>
<td>Τερβουταλίνη DRACANYL</td>
<td>6-15</td>
<td>2-4</td>
</tr>
</tbody>
</table>

**ΕΙΣΠΝΕΟΜΕΝΟΙ, ΜΑΚΡΑΣ ΔΡΑΣΗΣ ΕΚΛΕΚΤΙΚΟΙ (β2) ΔΙΕΓΕΡΤΕΣ (LABA)**

<table>
<thead>
<tr>
<th>Σαλμετερόλη SEREVENT</th>
<th>10-20</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Φορμοτερόλη FORADIL</td>
<td>10-20</td>
<td>12</td>
</tr>
</tbody>
</table>

**SERETIDE: Salmeterol + Fluticasone**

Rolenium: προπιονικής φλουτικαζόνης / σαλμετερόλης
Αντιχολινεργικά

SAMA

ATROVENT : Ipratropium

BEROVENT : ιπρατρόπιο / σαλβουταμόλη

LAMA

SPIRIVA : Τιοτροπίο: μακρας δρασης

Κορτικοστεροειδή

PULMICORT
BECOTIDE
FLIXOTIDE

SYMBICORT: Budesonide+Formoterol

Montelukast Sodium* SINGULAIR