Are Heart Rate Increases a Meaningful CV Safety Issue Associated with COPD Drugs?

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Introduction and Background

• Many COPD drugs on market and in DD have an effect on HR
  o SABAs, LABAs, LAMAs, ICS
  o ICS+LABAs+LAMAs, LABAs+LAMAs, ICS+LABAs

• The magnitude of drugs effect on HR varies between the drugs, their doses, and their classes

• In clinical R&D (unlike LQTS or SQTS), there is no clear numerical “thresholds” for the safety concern of DI-HR increment, particularly in COPD population

• At present, the link between DI-increase in HR and clinical outcomes in COPD is intuitive and suggestive rather than conclusive
Why Is There a Concern About an Increase in HR in COPD?

• **COPD population**
  - Resting HR is already elevated and HR “reserve” - diminished
  - Impaired ANS balance and adjustment of HR
  - Tends to be older with an increased prevalence of:
    - Co-morbidities (often HF and CAD) and abnormal conditions (eg. fever, hypoxemia, hypercapnia)
    - Associated concomitant medications (some – QT prolongers)
  - Ventricular and supraventricular arrhythmias (PACs, MAT, AF) - not uncommon

• **Drugs for COPD**
  - Some agents (chiefly SABAs, LABAs) further increase HR yet the Impact of drug-induced HR increase on M/M – less investigated
  - Tachyarrhythmia is a well-recognized side effect of beta-mimetic and anticholinergic agents
  - DDI becomes important due to polypharmacy

• **In general:**
  - Faster HR may promote systemic inflammation, atherosclerosis, reduces coronary artery reserves, increased mechanical stress to the heart and arterial wall, and aggravate cardiac dysfunctions
  - Might be associated with increased mortality

• **Although the association of HR and outcome** is suggestive, it does not, by itself, prove causality. High HR is often associated with:
  - Poor cardiorespiratory fitness (powerful predictor of mortality)
  - HTN, DM, obesity, atherogenic lipid profile
  - Impaired cardiac function
HR and Life Expectancy

There is a strong correlation between HR and life span in homeothermic mammals, including in humans. General rules:

- Lower HR - longer life, higher HR - shorter life
- If humans are predetermined to have ~3 billion heart beats/lifetime; reduction in mean HR from 70 to 60 beats/min throughout life would increase life span from 80 to 93.3 years

Inverse semilogarithmic relation between HR and life expectancy; excluding humans, spans a 35-fold difference in HR and a 20-fold difference in the life span of these mammals.

Galapagos tortoise with a life expectancy of 177 years and a HR of 6 bpm

From HJ Levine: JACC, 1997: Vol. 30, No. 4
Heart Rate and Mortality: (BEAUTIFUL1 Trial)

In Healthy Men (n=5,713)
(Age: 42-53; FU: 23 y)

In CAD (n=24,913)
(Both genders, FU: 14.7 y)

Fox et al. J Am Coll Cardiol 2007;50:823-830
Increased HR in COPD: Regulation and Possible Mechanisms

• **Regulation of HR** (regular and irregular):
  – Intrinsic (determining) cardiac factors:
    • Spontaneous rate of depolarization of pacemaker structures
    • Ventricular response (e.g. AV conduction in AF)
  – Extracardiac (modifying) factors:
    • ANS
    • Pre-existing diseases (e.g. CAD, hypertension, thyroid gland dysfunctions) and abnormal conditions (e.g. hypoxemia, hypercapnia, acid-base disturbances)
    • Medications

• **Possible Mechanisms:**
  – **Direct** (side) effect of (inhaled) beta-mimetic and anticholinergic agents on cardiac automaticity
    • B2-adrenoceptor stimulation Increases the slope of the slow diastolic depolarization and maximum diastolic potential
  – **Indirect**: via lung hyperinflation
    • Hyperinflation in COPD may lead to decrease of the ventricular size and function, with decreased stroke volume and cardiac output leading to an increase in HR
Drug-Induced Arrhythmias in COPD: Possible Mechanisms

• Most common: increased supraventricular (and ventricular) ectopic activities
• Drug-induced increase in HR in COPD might further diminish CA reserve in CAD pts, and likely deteriorate contractility and relaxation functions in HF pts resulting in deterioration of electrical stability
• The initiation of beta (2)-agonist treatment increases HR and might reduce K⁺ concentrations compared to placebo
• Although COPD patients are prone to cardiac arrhythmias, this seems not necessary to be related to QTc prolongation
  – Beta (2) agonists (in addition to increase HR) accelerate cardiac repolarizaion, as result – no change in QTc
  – QTc might be increased due to increased HR + concomitant QT-prolonging medications (eg. antibiotics) due to impaired adjustment of QT duration to the increase in HR (eg. LVH)
  – In patients with LQT1 and LQT2 (but not LQT3), beta-adrenergic stimulation might produce QT interval prolongation, induce TdP by increasing transmural dispersion of repolarization
Questions and Dilemmas

• HR: is it about EP, HD or both?
  – How to measure HR?
  – How to assess EP and HD aspects of HR?
• What else can be measured and assessed to characterize drug-induced changes in HR?
• **How relevant is of our knowledge about an increase in HR in clinical practice and DI-HR, particularly in COPD patients?**
• What could be acceptable (safety) threshold for the changes in HR?
Assessment of Drug-induced HR Changes in R&D: Clinical Aspects

• Drug effect:
  • Primary vs secondary
  • Acute (SABAs) vs chronic (LABAs)
  • At rest vs exercise
  • Oral vs inhaled vs i/v
  • Symptomatic vs asymptomatic
  • Early (SAD, MAD) vs later stages of R&D

• Additional indexes:
  • Rate of change and rate of recovery
  • Maximum HR at (a) (respiratory) exercise performance or (b) ETT
    • Heart rate reserve
  • Compensation/adjustment by BP, body temperature
  • HR ranges:
    • Magnitude of changes (mean HR over period of time)
    • Outliers
  • P waves morphology/polymorphism, ST-T changes, QT/QTc prolongation
Instead of Conclusions

1. HR is a simple and accessible clinical variable yet it is a complex index of cardiac safety
2. HR is an integral part of vital sign assessment in clinical practice and R&D, and its drug-induced changes should be interpreted in conjunction with other vital signs (BP, temperature)
3. HR changes should be evaluated from EP, HD, and clinical outcomes perspectives
4. There are no clear evidences that drug-induced HR increase is a clear-cut independent CV risk factor in COPD; the clinical data are suggestive rather than conclusive
5. The magnitude of HR increase should be consider as an important variable, particularly in COPD patients with CAD and HF
6. There is no acceptable (safety) threshold for the drug-induced changes in HR in COPD. Risk assessment should be done on the case-by-case basis
THANK YOU!
**Autonomic NS Dysfunction in COPD**

- Sympathetic and parasympathetic regulation of HR in patients with asthma differs from that in normal individuals, even in normal conditions in which the patient is free of an asthma attack.
- Patients with COPD characterized by impaired sympathetic-vagal balance; increased sympathetic activity at rest:
  - Elevated resting HR
  - Reduced baroreflex sensitivity
  - Reduced HRV: index of lower variability is often an indicator of abnormal and insufficient adaptability of the autonomous nervous system
  - Reduced respiratory sinus arrhythmia
  - Abnormal HR recovery after exercise
- Initiation of beta (2)-adrenoceptor agonist treatment increases HR, decreases HRV and potassium concentrations.
- In addition, cardiac autonomic control of HR is associated with inspiratory muscle weakness*

* - Reis MS. Clinics. 2010;65(4):369
## Summary

| What Was The CV Safety Issue | • Increase in HR without apparent improvement in mortality  
• Improvement in morbidity -?  
• Improvement in QoL – likely “yes” |
| Weight of Evidence | • Link between LABA and LAMA and HR - **demonstrated**  
• HR increase with LABA - **clear**  
• *What is the signal for LAMA ?* - **not so clear**  
• Signal for combination LABA+LAMA ? - **not so clear** |
| Presence of a Likely MOA for Risk | Need to be established with better certainty |
| Benefit / Risk Relationship for Drug? | Drug-induced increase in HR shouldn’t be the only drug effect in COPD |
| Is perceived risk: Generalizable to ALL Drugs in Class or with Same Efficacy MOA? | Short and long acting beta (2) agonists as a class  
Magnitude and duration of HR increment likely is important |
| Reasonable standard approach | ? |
COPD Drugs: HR and Mortality

- Resting HR is an independent predictor of CV and all-cause mortality in men and women with and without diagnosed CV disease (Fox K. JACC 2007:50;823)
  - Beta(2)-agonist use in COPD patients has been associated with an increased risk for MI, CHF, cardiac arrest, and acute cardiac death based on 13 single-dose trials and 20 longer duration trials (Salper SR. Chest, 2004;125(6):2309)
  - UPLIFT trial (n=5,993 COPD pts, 2005): no significant increase in the risk of stroke [0.95 (95% CI 0.70, 1.29)], heart attack [0.73 (95% CI 0.53, 1.00)], or CV death [0.73 (95% CI 0.56, 0.96)] between Spiriva HandiHaler and placebo. Furthermore, there was a statistically significant 16% decrease in the risk of death (p=0.016)
  - TIOSPIR trial (n=17,135 COPD pts; 2014): This meta-analysis explains safety concerns by regulatory agencies and indicates a 52% increased risk of mortality associated with tiotropium mist inhaler in patients with COPD
  - SABA: no differences between Tx groups for all-cause mortality (5-y Lung Health Study; Anthonisen, 2002)
  - SABA (ipratropium+alburerol or metaproterenol) + anticholine monotherapies: no mortality improvement
  - LABA: no improvement in all-cause mortality (meta-analysis; n=4198 pts (Sin, 2003)

- Of note, >50% are under-treated (based on US managed care and Medicare [Make B. 2012])
Heart Rate Reduction in Hypertension

Beta Blocker Reduction in Heart Rate Increased CV Risk
Systematic Review of 9 Trials of 34,906 Pts Rx with Beta Blockers

“In contrast to patients with myocardial infarction and heart failure, beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients.”

Bangalore et al. J Am Coll Cardiol 2008;52:1482
BEAUTIFUL Trial
Ivabradine in Pts with CAD and LV Dysfunction
HR Reduction by Inhibition of Sinus Node Activity

<table>
<thead>
<tr>
<th>Total study population (n = 10,917)</th>
<th>Subgroup - HR &gt;70 bpm (n = 5392)</th>
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<tbody>
<tr>
<td><strong>% of Pts</strong></td>
<td><strong>Ivab</strong></td>
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<tr>
<td>Composite</td>
<td>15.4</td>
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<td>CV Death</td>
<td>8.6</td>
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<tr>
<td>MI</td>
<td>3.6</td>
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<tr>
<td>Heart Failure</td>
<td>7.8</td>
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Fox K et al. Lancet 2008;372:807
Epidemiology of “COPD + CAD” population

• airflow limitation is an independent risk factor for cardiovascular diseases
• Chronic low-grade systemic inflammation, oxidative stress and increased platelet activation have been widely reported to be pathophysiological links between COPD and atherosclerosis
• Alveolar macrophages, bronchial epithelial cells and lymphocytes implicated in bronchial and alveolar inflammation, produce various inflammatory mediators such as interleukin (IL)-6 and IL-1β and tumor necrosis factor (TNF)-α. These cytokines may “spill-over” from the lung into the systemic circulation and stimulate hepatocytes to synthesize C-reactive protein (CRP) and fibrinogen, promoting a generalized inflammatory reaction
• COPD is a more complex disease process that does not only affect airways and lungs, but also the blood vessels, with a strong association between COPD and CAD
• COPD and CAD share common risk factors such as cigarette smoking, sedentary behavior
• Large-scale studies have estimated that cardiovascular deaths account for 20–50% of the mortality in COPD patients
• COPD is not significantly associated with an increased risk of early mortality in patients with CAD, it is an independent predictor of long-term mortality after PCI or CABG
• Warnier (2013): Abnormal ECGs more prevalent in COPD patients (50%) than in patients without COPD
  – Conduction abnormalities
  – The mean heart rate was higher in COPD patients (72 bpm) compared to controls (65 bpm), and bradycardia significantly less frequent in patients with COPD (1%) than in patients without COPD.
  – QTc prolongation less frequent in COPD patients (9% versus 14%, p = 0.01).
• **β₂** agonists: stimulates adenylyl cyclase activity; closing of calcium channel (smooth muscle relaxants; used to treat asthma and COPD). Selected examples are:

  • **salbutamol** (albuterol in USA)
  • **Levosalbutamol** (Levalbuterol in USA)
  • **Fenoterol**
  • **Formoterol**
  • **Isoproterenol** (β₁ and β₂)
  • **Metaproterenol**
  • **Salmeterol**
  • **Terbutaline**
  • **Clenbuterol**
  • **Isoetarine**
  • **pirbuterol**
  • **procaterol**
  • **ritodrine**
  • **epinephrine**

Undetermined/unsorted agonists:
- arbutamine
- befunolol
- bromoacetylprenololinentiane
- broxaterol
- cimaterol
- cirazoline
- denopamine
- dopexamine
- etilefrine
- hexoprenaline
- higenamine
- isoxsuprine
- mabuterol
- methoxyphenamine
- nylidrin
- oxyfedrine
- prenalterol
- ractopamine
- reprotoerol
- rimiterol
- tretoquinol
- tulobuterol
- zilpaterol
- zinterol
The first key question is
MOA and weight of evidence for a link between HR and COPD drugs
Yes there is a pathway between LABA and LAMA and heart rate, widely demonstrated
HR increase with LABA is clear
What is the signal for LAMA? not so clear
What is the signal for combination LABA and LAMA? not so clear
We can provide you articles

Now +++ is that HR increase a good surrogate for cardiac safety?
Is a few beats HR increase “enough” to trigger cardiac arrhythmias (Jay talk) and ischemic events (my talk)
Background and Introduction (2)

• An increasing body of scientific research and observational evidence indicates that resting heart rate (HR) is inversely related to the lifespan among homeothermic mammals and within individual species. In numerous human studies with patients stratified by resting HR, increased HR is universally associated with greater risk of death.

• Among mammals, there is an inverse semilogarithmic relation between heart rate and life expectancy:

• Plots of the calculated number of heart beats/lifetime among mammals against life expectancy and body weight (allometric scale of 0.5 x10^6) are, within an order of magnitude, remarkably constant and average 7.3 ± 5.6 x 10^8 heart beats/lifetime.

• These data yield a mean value of 10 x 10^8 heart beats/lifetime and suggest that life span is predetermined by basic energetics of living cells and that the apparent inverse relation between life span and heart rate reflects an epiphenomenon in which heart rate is a marker of metabolic rate.

• Smaller mammals have higher heart rates and shorter life spans than larger members of their class.

• The explanation of the former is a biophysical imperative in which the ratio of heat loss (a function of body surface area) to heat production (a function of body mass) increases as body size is reduced.
• The natural history of chronic obstructive pulmonary disease (COPD) includes gradually worsening shortness of breath and functional limitation, caused by a progressive decline in lung function and the development of co-morbid illnesses [1]. Multifocal atrial tachycardia, atrial fibrillation, and ventricular arrhythmias are common co-morbidities among patients with COPD.
• ICS inhaled corticosteroids
• LABA long acting beta2agonist
• SAMA short acting anti-muscarinic agent
• LAMA long acting anti-muscarinic agent
• I was talk that this meeting is though-provoking rather that “conclusive”
  – Our current status, thinking, and future directions
• Audience – pulmonologists with expertise in experts in COPD + cardiologists
• I am cardiologist with a special interest in cardiac safety in early development
• Recording, measuring, comparing, and interpretation the data – next session
• What do we know?
• What we do not know?
• What we think?
• In my 10-min presentation, I will try to highlight some aspects of HR in R&D from mostly from cardiology perspective
• Details will be discuss thereafter
• Time-dependent $\beta_2$-agonist therapy for asthma was associated with an increased risk for cardiac events (hazard ratio [HR] = 2.00, 95% confidence interval 1.26 to 3.15, $p = 0.003$) after adjustment for relevant covariates including time-dependent $\beta$-blocker use, gender, QTc, and history of asthma. This risk was augmented within the first year after the initiation of $\beta_2$-agonist therapy (HR = 3.53, $p = 0.006$). The combined use of $\beta_2$-agonist therapy and anti-inflammatory steroids was associated with an elevated risk for cardiac events (HR = 3.66, $p < 0.01$);
Beta (2) Agonists and CV Safety


- **BACKGROUND:** beta-Adrenergic agonists exert physiologic effects that are the opposite of those of beta-blockers. beta-Blockers are known to reduce morbidity and mortality in patients with cardiac disease. beta(2)-Agonist use in patients with obstructive airway disease has been associated with an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death.

- **OBJECTIVES:** To assess the cardiovascular safety of beta(2)-agonist use in patients with obstructive airway disease, defined as asthma or COPD.

- **METHODS:** A meta-analysis of randomized placebo-controlled trials of beta(2)-agonist treatment in patients with obstructive airway disease was performed, to evaluate the short-term effect on heart rate and potassium concentrations, and the long-term effect on adverse cardiovascular events. Longer duration trials were included in the analysis if they reported at least one adverse event. Adverse events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, or sudden death.

- **RESULTS:** Thirteen single-dose trials and 20 longer duration trials were included in the study. A single dose of beta(2)-agonist increased the heart rate by 9.12 beats/min (95% confidence interval [CI], 5.32 to 12.92) and reduced the potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54), compared to placebo. For trials lasting from 3 days to 1 year, beta(2)-agonist treatment significantly increased the risk for a cardiovascular event (relative risk [RR], 2.54; 95% CI, 1.59 to 4.05) compared to placebo. The RR for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50), and for all other events it was 1.66 (95% CI, 0.76 to 3.6).

- **CONCLUSION:** beta(2)-Agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events. The initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo. It could be through these mechanisms, and other effects of beta-adrenergic stimulation, that beta(2)-agonists may precipitate ischemia, congestive heart failure, arrhythmias, and sudden death.
EP effect of B2 Agonists

• Increase HR, accelerate repolarization (? balance), reduce K⁺
• We underline that B2-agonists increase repolarizing current
  – In fact, in sinus node, B2-adrenoceptor stimulation not only increases the slope of the slow diastolic depolarization and maximum diastolic potential, but also accelerates repolarization
  – Furthermore, B2-adrenoceptor stimulation also accelerates repolarization in Purkinje cells and papillary muscle.
• B-Agonists can decrease plasma potassium levels by stimulation of B2-adrenoceptors in the liver and skeletal muscle.
  – This reduction is produced by an increase in the transport of potassium ions into cells through the activation of Na+-K+ adenosine triphosphatase, which increases the uptake of potassium
in those at high risk. Epidemiologic studies have linked the use of inhaled $\beta_2$-agonists with excess mortality among asthmatic patients, but no clear cardiac mechanism to explain the excess deaths has emerged. In contrast, basic research has suggested that the cardiac $\beta_2$-receptor is cardioprotective.
• Sympathetic and parasympathetic regulation of HR in patients with asthma differs from that in normal individuals, even in normal conditions in which the patient is free of an asthma attack
• The parasympathetic system dominates, and the HR variability (HRV) is significantly lower in asthmatic patients compared with healthy control subjects
• Investigation of the autonomic nervous system in asthmatic patients is important, because the cholinergic nerves are the most important part of the bronchoconstrictory pathway
• A high variability in HR is a sign of good adaptability reflecting well-functioning autonomic control mechanisms. Conversely, lower variability is often an indicator of abnormal and insufficient adaptability of the autonomous nervous system
• Long-acting 2-adrenergic agonists (LABAs) are widely used as an add-on therapy to inhaled corticosteroids (ICS) for patients with moderate to severe asthma
• Initiation of 2-adrenoceptor agonist treatment increases HR and decreases HRV and potassium concentrations
• In particular, patients with hypoxemic COPD may have a subclinical autonomic neuropathy that has been associated with a prolonged ECG QTc interval and risk of ventricular arrhythmias and death.

• Besides, the chronotropic and electrophysiologic effects of beta2-agonists are enhanced by conditions of hypoxemia;
  – in fact, mild hypoxemia (90% O₂ saturation) has been demonstrated to add to prolongation of the QTc caused by fenoterol.

• However, Beta-agonists may decrease PaO₂ by increasing blood flow through poorly ventilated areas of the lung thereby increasing ventilation/perfusion mismatch.

• When the initial PaO₂ is <60 mm Hg, if a decrease in PaO₂ is produced by a (Beta 2-agonist, it may become clinically significant.
  – Consequently, B2-agonist therapy cannot be considered completely safe in patients with severe COPD.
• In patients with CVD, HR is a key indicator for the risk of heart attack
  – Ben Freedman (Sidney, Australia): “Those patients whose HR was above 70 bpm had significantly higher incidence of heart attacks, 46% increase in hospitalizations for non-fatal or fatal heart attack, and the need for surgery...” (11,000 people, across 33 countries)*

* - The Lancet, September 2008
Heart Rate Reduction and Mortality

Pharmacologic Interventions

Beta Blockers After MI

Beta Blockers After MI

In Heart Failure

Fox et al. J Am Coll Cardiol 2007;50:823-830