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
  - SABAs, LABAs, LAMAs, ICS
  - 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

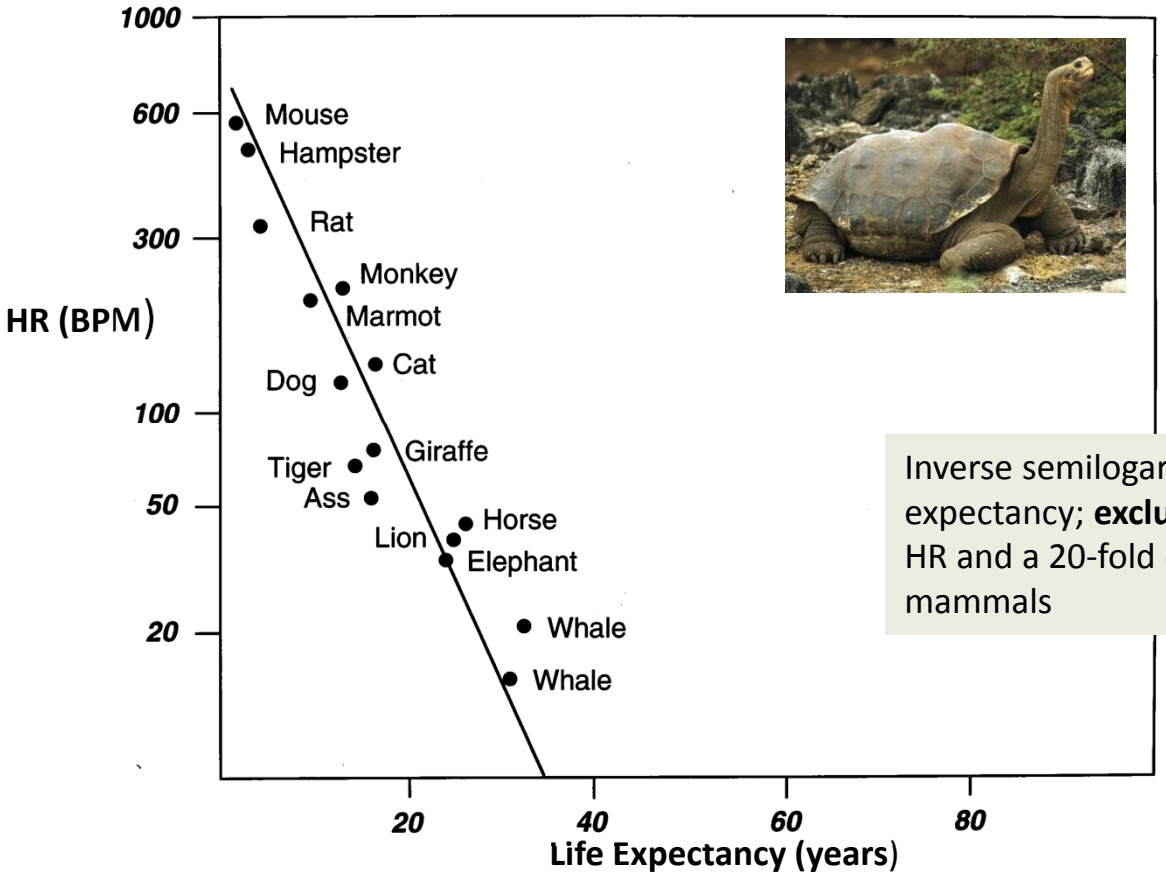
Why Is There a Concern About an Increase in HR in COPD?

- **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**



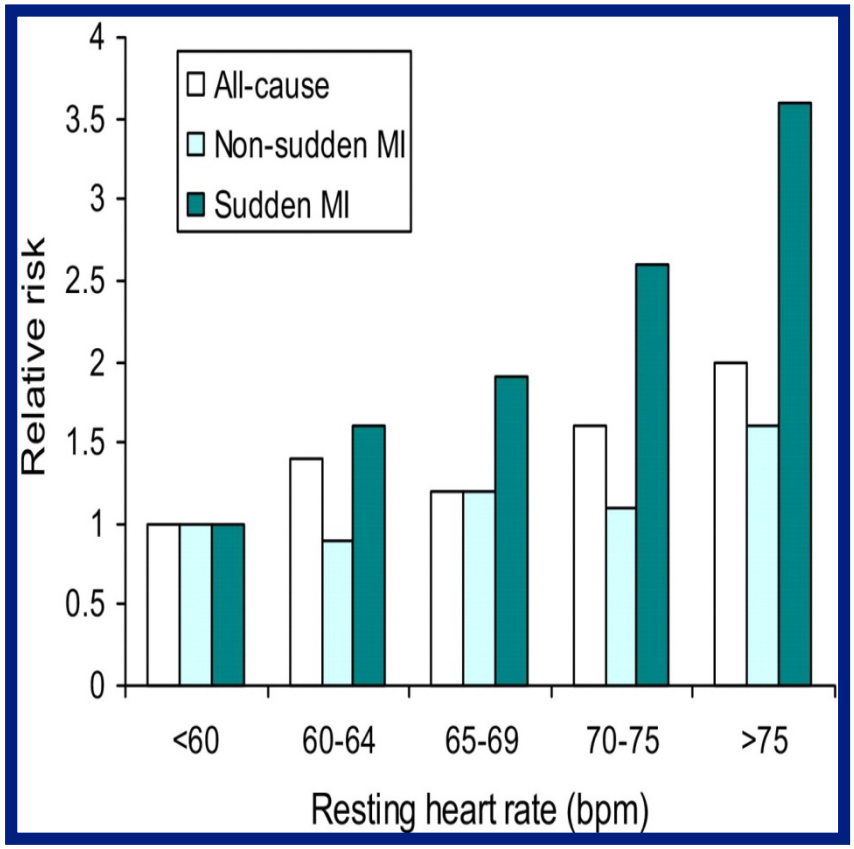
Galapagos tortoise with a life expectancy of 177 years and a HR of 6 bpm

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

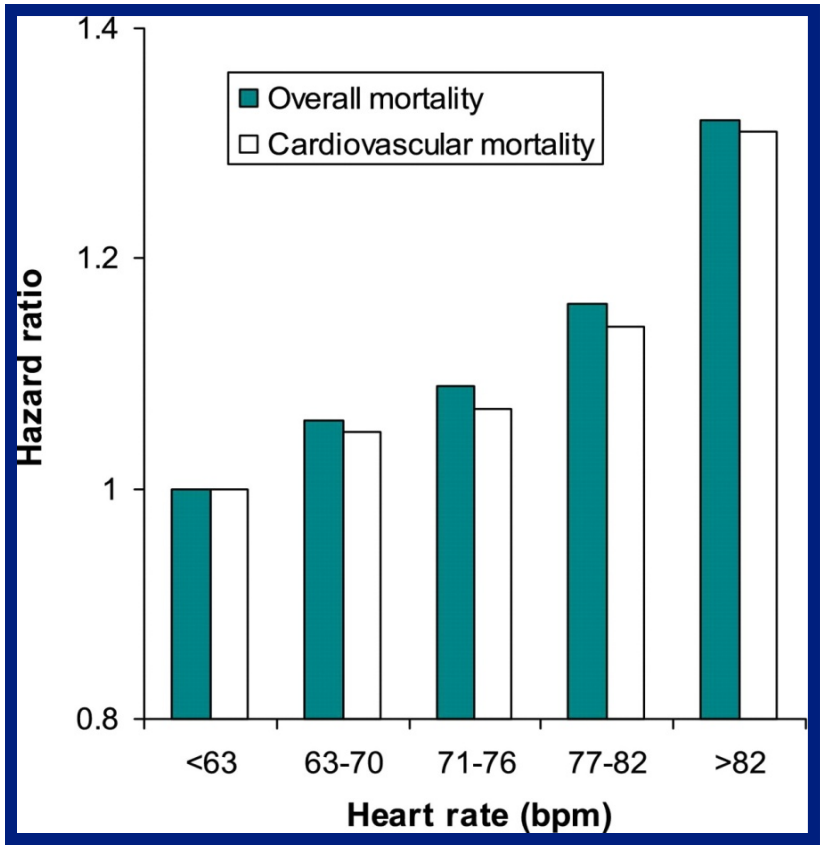
From HJ LEVINE: JACC , 1997:Vol. 30, No. 4

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 (eg. 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

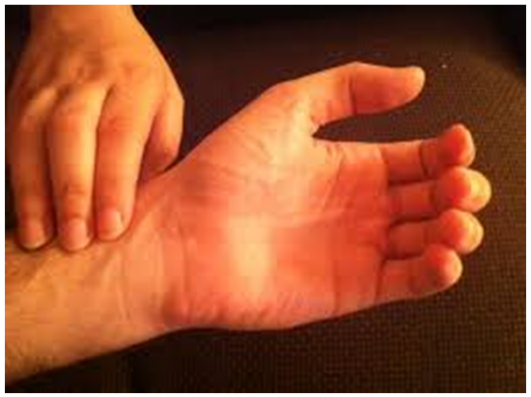
- **Possible Mechanisms:**
  - **Direct** (side) effect of (inhaled) beta-mimetic and anticholinergic agents on cardiac automaticity
    - B2-adrenoceptor stimulation Increases the slope of the slow diastolic depolarization and maximum diastolic potential
  - **Indirect**: via lung hyperinflation
    - 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

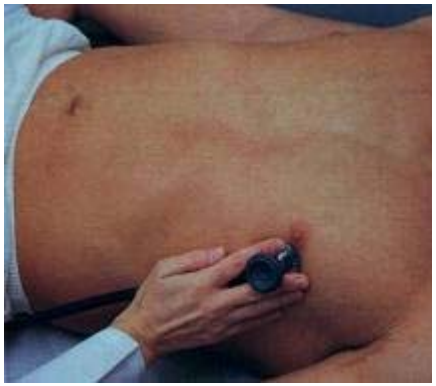
Drug-Induced Arrhythmias in COPD: Possible Mechanisms

- 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!