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- Bayer
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- Roche
- Servier

# Heart rate: a new risk factor for CAD and HF

**Roberto Ferrari** 



# *'Life begins with the first heart beat and ends with the last one'*

Aristotele

# HR : A story from afar

- Egyptians linked HR to the weight of the heart (cardiac hypertrophy)
- Believing that the heart represents the soul, weighed by the Gods for final judgement

### beats = weight = soul = judgement

Weighing the heart in front of Maat - Pa Nentwy tomb, VII Century

### The heart is the only organ left in situ!



# HR: A story from afar

- Egyptians were amazed by the "mysterious" beating of the heart
- A vital principle associated with life and its longevity

### HR in the general population



### HR: the timepiece of life



### Heart rate: the "timepiece" of mammalian life



Hummingbird





Rat

Bear









### What do they have in common ?

# The number of heart beats in a lifetime

- Hummingbird:
   lives 5 months
   HR 600 b/m
- Turtle:

lives 177 yearsHR 6 b/m

but ..... same number of heart beats in life: 7.3x10<sup>8</sup> beats!

# Heart rate: the "timepiece" of mammalian life



# Mammalians might have a predetermined number of heart beats

HJ Levin, JACC 1997

- HR controls endothelial "shear stress", NO release and vessel stiffness
- High HR causes dilation, more organ perfusion and energy consumption
- HR reflects/determins? body energy needs

- Living entities in the universe have a fixed amount of energy
   HR is the body language
- It communicates with 100 trillion cells!

# What about in man?

HR: independent predictor of allcause and CV mortality in:

- The general population
- Patients with CAD, LV dysfunction or hypertension
- Evidence from both prospective or retrospective studies

### **BEAUT JUL Heart rate as a predictor of**







Fox K .... Ferrari R The Lancet , Volume 372 , Issue 9641 , 807 - 816

### New data on HR and prognosis published after BEAUTIFUL study

#### About 205 000 patients included, >20 years of follow-up

Study	Population n		Follow-up	HR and prognosis
Shigetoh et al.	GP	614	20 y	HR>80 bpm as NOD
Jouven et al.	GP	5139	>20 y	HR/HR change= RF
Jouven et al. The three city stud	ly, GP	5855	4.9 y	HR= RF of CVM in elderly
The Copenhagen city heart stud	ly GP	6752	16 y	HR = RF of mortality
Danchin et al. The IPC cohort	GP	62 014	6 y	HR> 75 bpm/ HR increase = RF of NOD
Nauman et al,	GP	50 000	18 y	HR=CAD death
Brouwers et al.	GP	7366	7 y	HR= increased MA
Graham et al. FINRISK Study	GP	30 000	21 y	HR = RF of CVD
Zachariah et al, CV Health Stud	dy GP	5795	9.8 y	RHR= RF in elderly
Gitt et al. STAR Registry	SA	2002	1 y	HR>60 bpm = 2-fold higher 1-year mortality
Analysis from TNT	CAD	10 000	4.9 y	HR>70 bpm = RF
Antonio et al.	ACS	1367	1	Admission HR=RF
Meta-analysis, McAlister et al	HF/B	B 18 000		HRR ach =prognosis
Henkens et al	PAH	140	2 y	HR=predictor of prognosis
Anand et al.	НТХ	78	8.5 y	HR=predictor of mortality
Kaafarani et al.	Nonca	ardiac sur	jery	Controlling heart rate is vital

GP – general population; SA – stable angina; ACS – acute coronary syndrom, HF – heart failure; BB – beta-blockers; PAH- pulmonary arterial hypertension; HTX – heart transplantation; HR – heart rate; NOD – new onset of diabetes, RF- risk factor, y - years

# Heart rate in cardiology

# A marker?

A risk factor?

# Demonstration of a risk factor

# It is linked to prognosis Its modification improves prognosis

# Reduction of heart rate and outcomes in beta-blockers trials

### **Reduction in mortality (%)**





### Effect of change in HR and achieved HR on clinical outcomes in HF





Correlation of change in HR with relative risk reduction (RRR) in all-cause mortality

Correlation of final achieved HR with annualized mortality in 9 beta-blocker trials in 19 537 patients

Flannery et al. Am J Cardiol. 2008;101:865-869.

Beta-blockers exert other effects than HR reduction

- Reduce blood pressure
- Reduce contractility and O<sub>2</sub> consumption
- Counteract the negative effects of cathecolamines on the heart

- The newly developed if- inhibitor Ivabradine – selectively reduces HR without other known haemodynamic or biological effects
- It is therefore a usefull tool to test if HR is a risk factor

### The I<sub>f</sub> current of the sinus node



Robinson RB, DiFrancesco D. Fundamental and Clinical Cardiology; NY; Marcel Decker; 2001:151-170.

### Super selectivity of ivabradine: the sinus node and the *I<sub>f</sub>* channel



# Ivabradine programme

- Symptoms release in angina (12.000 P)
- Prognostic improvement in CAD with or without LV dysfunction (BEAUTifUL and SIGNifY 30.000 P)
- Prognostic improvement in HF (SHifT, 6.500 P)

### Effect of ivabradine on the primary endpoint (overall population)



### Effect of ivabradine on the primary composite endpoint ( $HR \ge 70$ bpm)



### Effect of ivabradine on hospitalisation for MI (*HR* ≥ 70 *bpm*)



### Effect of ivabradine on coronary revascularisation (*HR* ≥ 70 *bpm*)



# **BEAUT FUL Effect of ivabradine on primary composite end point**

### **All angina patients**

### HR <u>></u>70 bpm



\* Composite of cardiovascular mortality or hospitalization for fatal and nonfatal myocardial infarction or heart failure

Fox et al. Eur Heart J. In press.

## FROM









Addition of ivabradine to recommended therapy is beneficial in HF patients with elevated HR (> 70 bpm)





- To evaluate whether ivabradine improves outcomes in patients with:
  - **1** Moderate to severe chronic HF
  - **2** LV ejection fraction  $\leq 35\%$
  - **3** Sinus rhythm,  $HR \ge 70$  bpm and
  - **4** Recommended therapy



Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

#### **Cumulative frequency (%)**





# Is the HF outcome related to HR?

Is the benefit of ivabradine related to the achieved HR reduction?

### SHIT HR predicts HF outcome



#### Risk of CV death or hospitalisation for HF increases by 3% per 1bpm increase

# SHATPrimary composite endpointaccording to HR achieved at day 28\*

Patients with primary composite endpoint (%)



\*Data exclude patients reaching primary composite endpoint in the first 28 days

# Conclusion

### Heart Rate is a risk factor for:

- CAD patients with angina
- HF patients of any cause
- Consequently, the HR of these patients should be reduced to below 70 beats / min