Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the company/companies listed below that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Grant/Research Support</td>
<td>Bayer</td>
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<td>Boehringer Ingelheim</td>
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</table>
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
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

Meta-analysis: $n \geq 200,000$

HR: the timepiece of life
Heart rate: the “timepiece” of mammalian life

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 years  
  - HR 6 b/m

but …… same number of heart beats in life: $7.3 \times 10^8$ 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/determines 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 all-cause and CV mortality in:

- The general population
- Patients with CAD, LV dysfunction or hypertension
- Evidence from both prospective or retrospective studies
Heart rate as a predictor of:

**CARDIOVASCULAR DEATH**
- Hazard ratio = 1.34 (1.10 – 1.63)
- \( P = 0.0041 \)
- Heart rate \( \geq 70 \text{ bpm} \)

**HOSPITALISATION FOR HF**
- Hazard ratio = 1.53 (1.25 – 1.88)
- \( P < 0.0001 \)

**HOSPITALISATION FOR MI**
- Hazard ratio = 1.46 (1.11 – 1.91)
- \( P = 0.0066 \)

**REVASCULARISATION**
- Hazard ratio = 1.38 (1.02 – 1.86)
- \( P = 0.037 \)
New data on HR and prognosis published after BEAUTIFUL study

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

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

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

Meta-regression of beta-blocker trials n=19 537

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

$r^2=0.41$

Change in heart rate (bpm)

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

$r^2=0.53$

Heart rate achieved (bpm)

Beta-blockers exert other effects than HR reduction

- Reduce blood pressure
- Reduce contractility and $O_2$ consumption
- Counteract the negative effects of catecholamines 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 \( I_f \) current of the sinus node

Sinus node channels

Ca channel
T-type

Ca channel
L-type

K channel

Sinus node action potential and currents

Robinson RB, DiFrancesco D. Fundamental and Clinical Cardiology; NY; Marcel Decker; 2001:151-170.
Super selectivity of ivabradine: the sinus node and the $I_f$ channel

Ivabradine programme

• Symptoms release in angina (12,000 P)

• Prognostic improvement in CAD with or without LV dysfunction (BEAUTifulUL 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 ≥ 70 bpm)

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

Effect of ivabradine on coronary revascularisation (HR ≥ 70 bpm)
Effect of ivabradine on primary composite end point

All angina patients

HR (95% CI), 0.76 (0.58–1.00), P=0.05

HR (95% CI), 0.69 (0.47–1.01), P=0.06

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

Fox et al. Eur Heart J. In press.
FROM
BEAUTIFUL
TO
SIGNIFY
Addition of ivabradine to recommended therapy is beneficial in HF patients with elevated HR (> 70 bpm)
Objectives

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 \( \geq 70 \) bpm and
4. Recommended therapy
Primary composite endpoint

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

Cumulative frequency (%)

HR = 0.82 [95% CI 0.75-0.90]  
$p<0.0001$

- 18%
Further questions

• Is the HF outcome related to HR?

• Is the benefit of ivabradine related to the achieved HR reduction?
HR predicts HF outcome

Risk of CV death or hospitalisation for HF increases by 3% per 1bpm increase
Primary composite endpoint according to HR achieved at day 28* 

*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