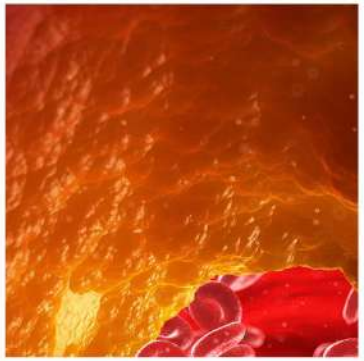
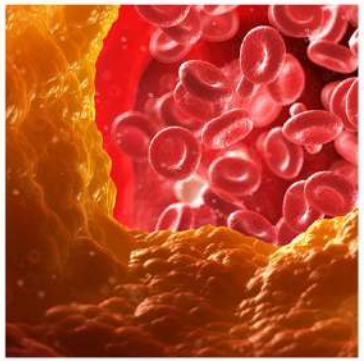
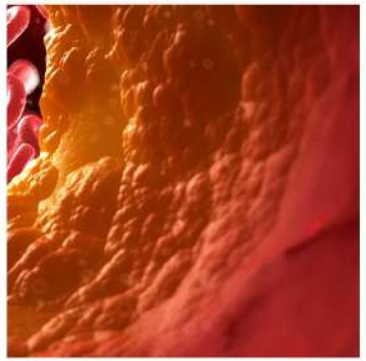
# The 2019 EMEA Cardiometabolic Workshop







Saturday,
16 November 2019

Baku, Azerbaijan

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INTERNATIONAL FOUNDATION

# Should increase in heart rate be considered a target in cardiovascular treatment?

H.A.J. Struijker-Boudier

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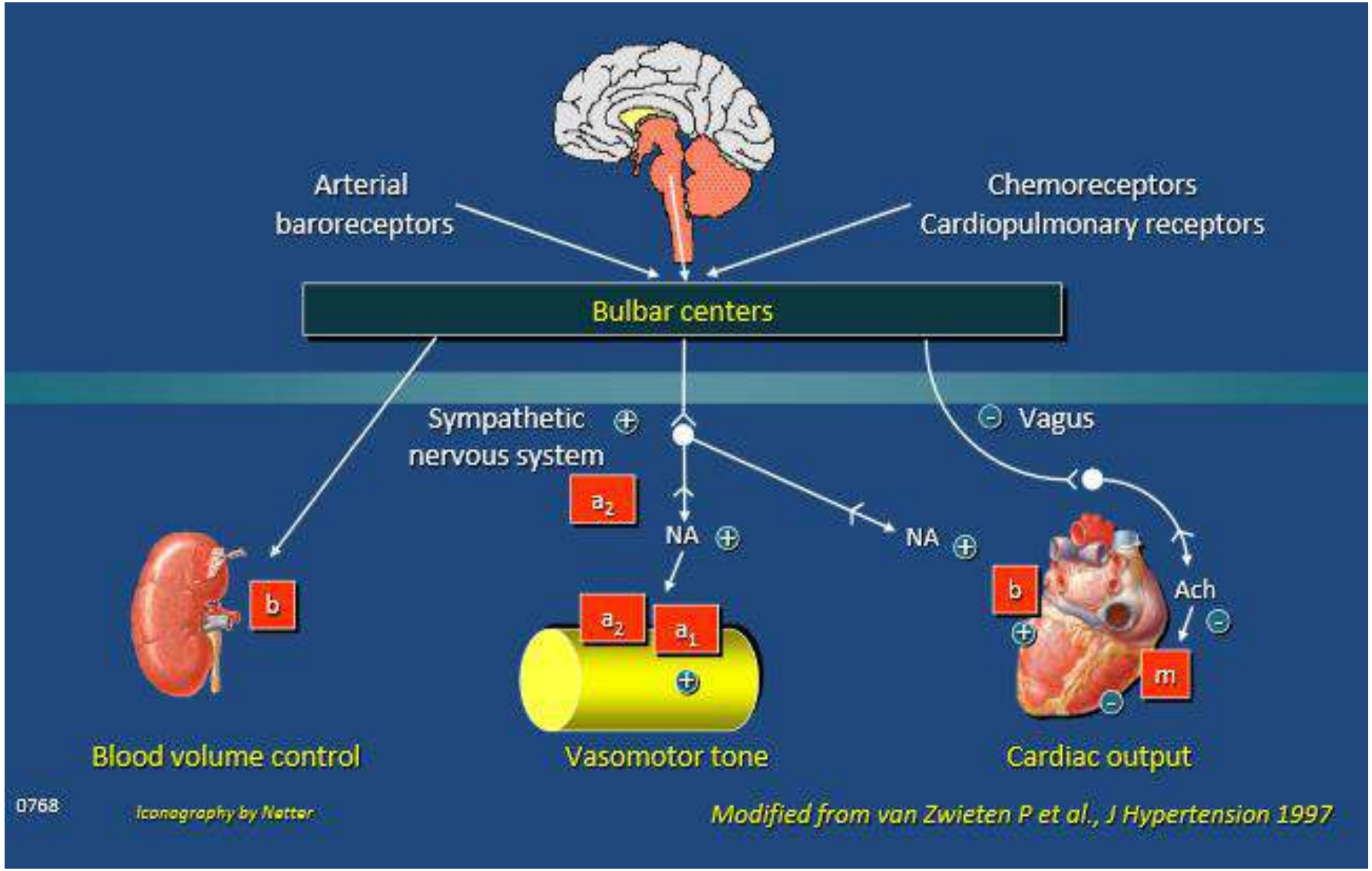
## Disclosures

H. Struijker-Boudier has received grants or consultation fees from Durect, Merck and Servier

# Learning objectives

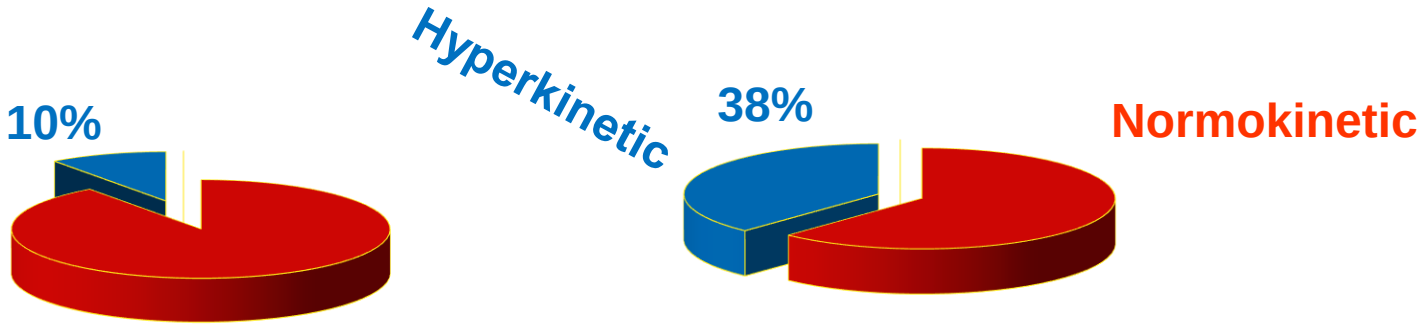
- Describe HR targets in hypertensive patients
- Discuss which type of investigation should be performed
- Illustrate possible therapeutic strategies

# Autonomic control of the cardiovascular system



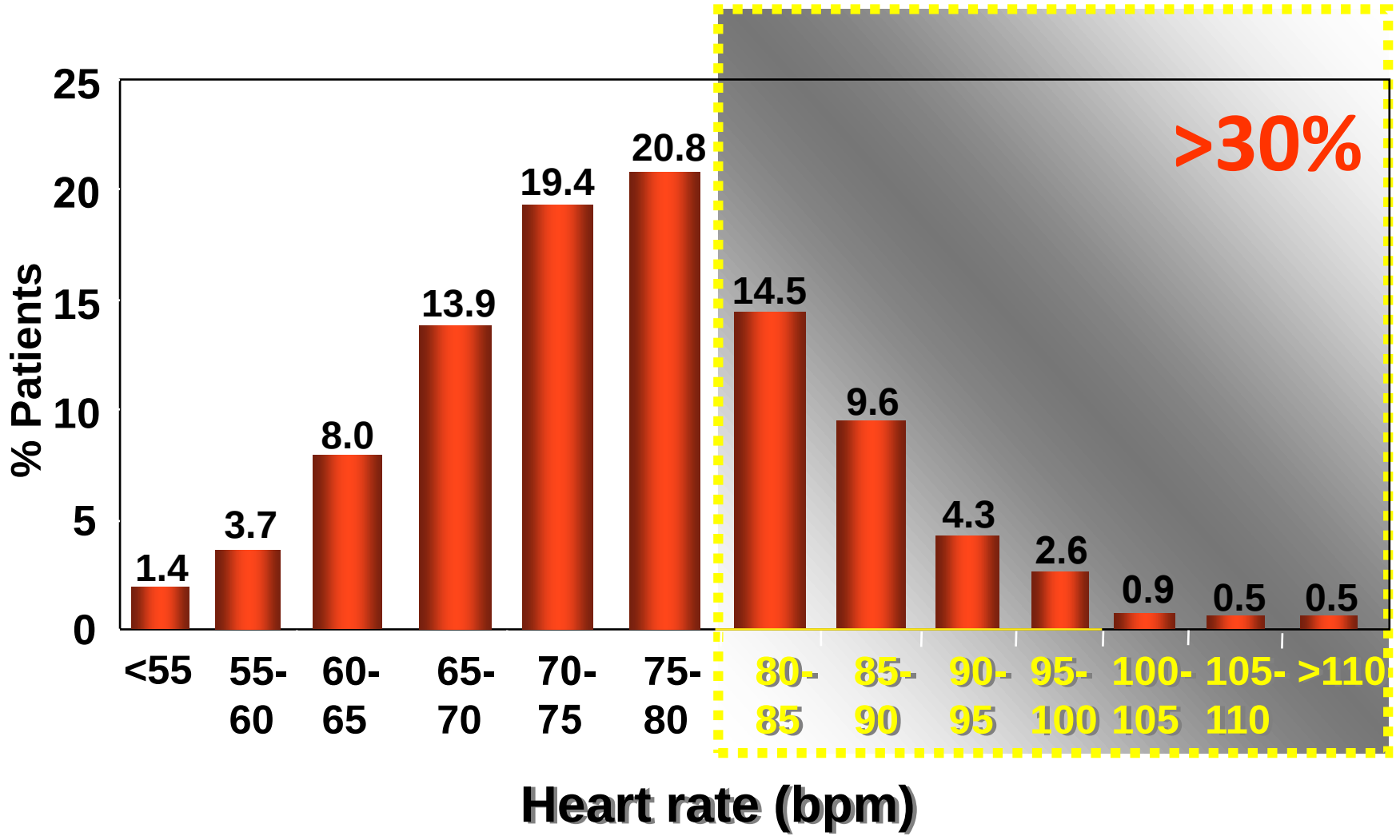
# Heart rate obtained by noninvasive (echo- Doppler) measurement in the Tecumseh population study

**A. Tachycardia is frequent**



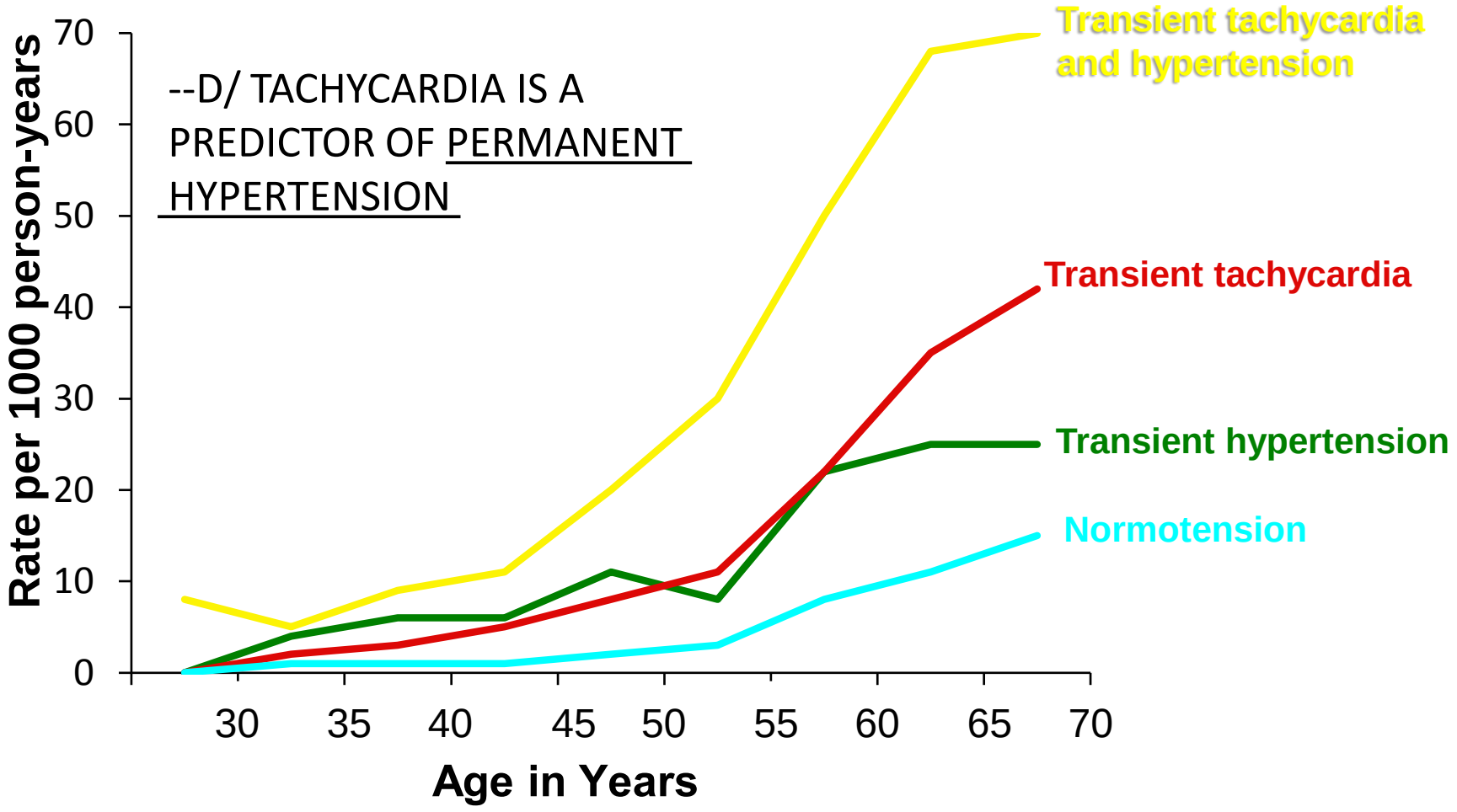

Julius et al J of Hypertension 1991, v 9

# Tachycardia is frequent also in established hypertension (n=38,145)



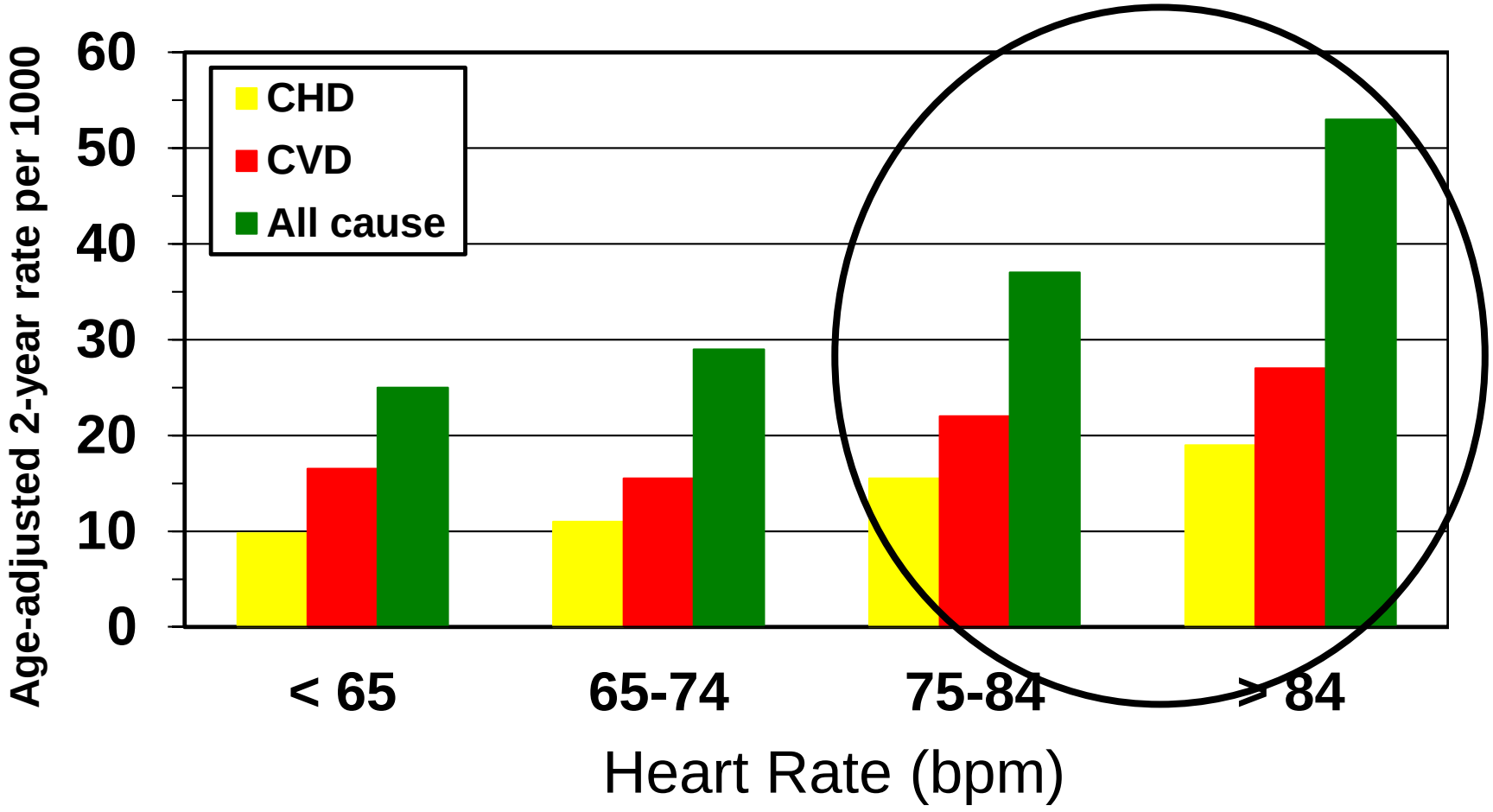

Farinaro E et al, Nutr Metab Cardiovasc Dis 1999:9;196

# Development of established hypertension in a study of 22,741 USA Army officers



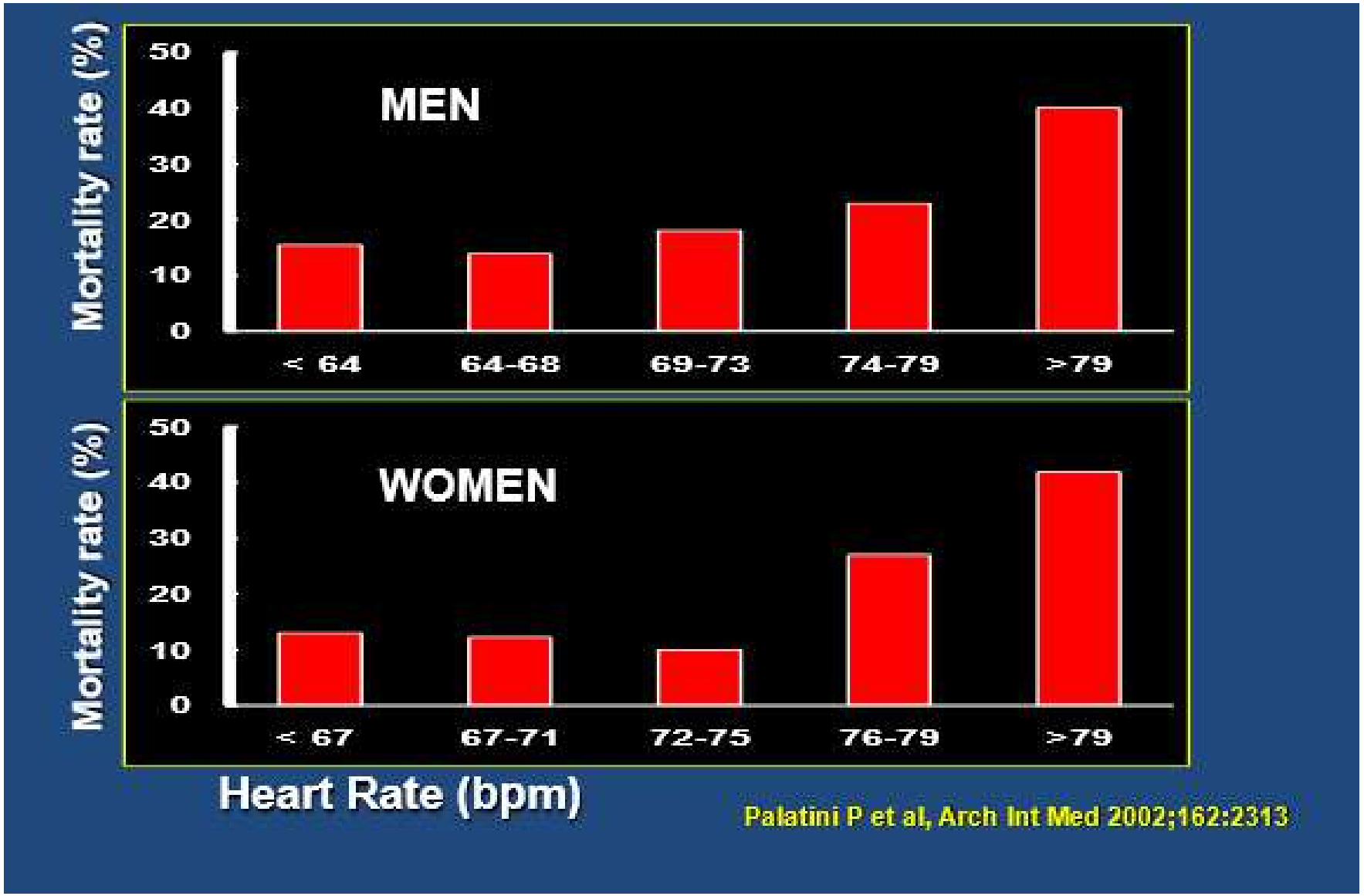

From Levy et al, JAMA

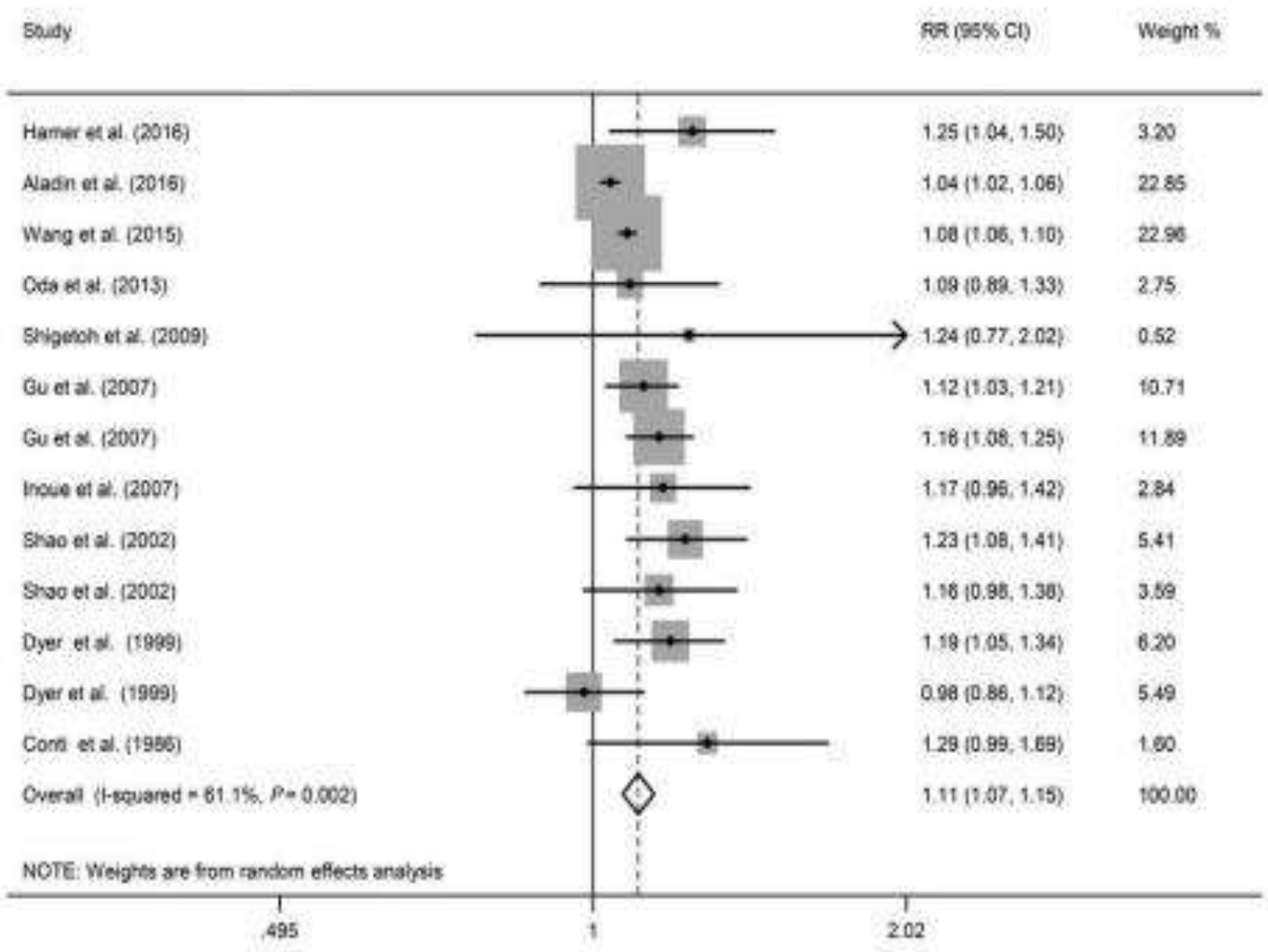
# ASSOCIATION OF HEART RATE WITH MORTALITY RATE AMONG MEN WITH HYPERTENSION (The Framingham Study)




Gillman et al., Am Heart J 1993; 125: 1148

# Mortality Rate by Quintile of Clinic Heart Rate In the ISH Patients from Syst-Eur Study






Yuanyuan Shi et al, Journal of Hypertension 2018, 36:995-1004

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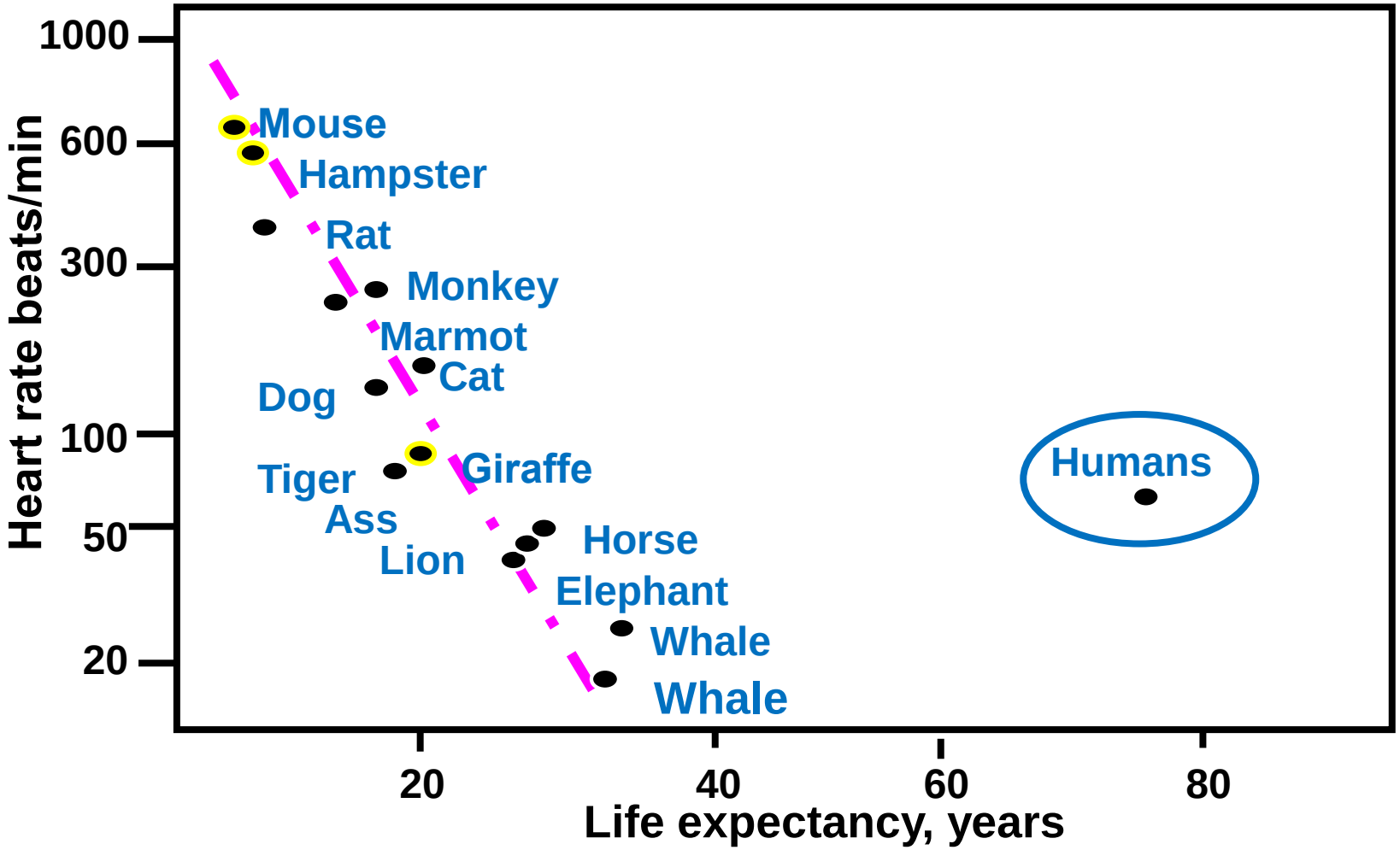
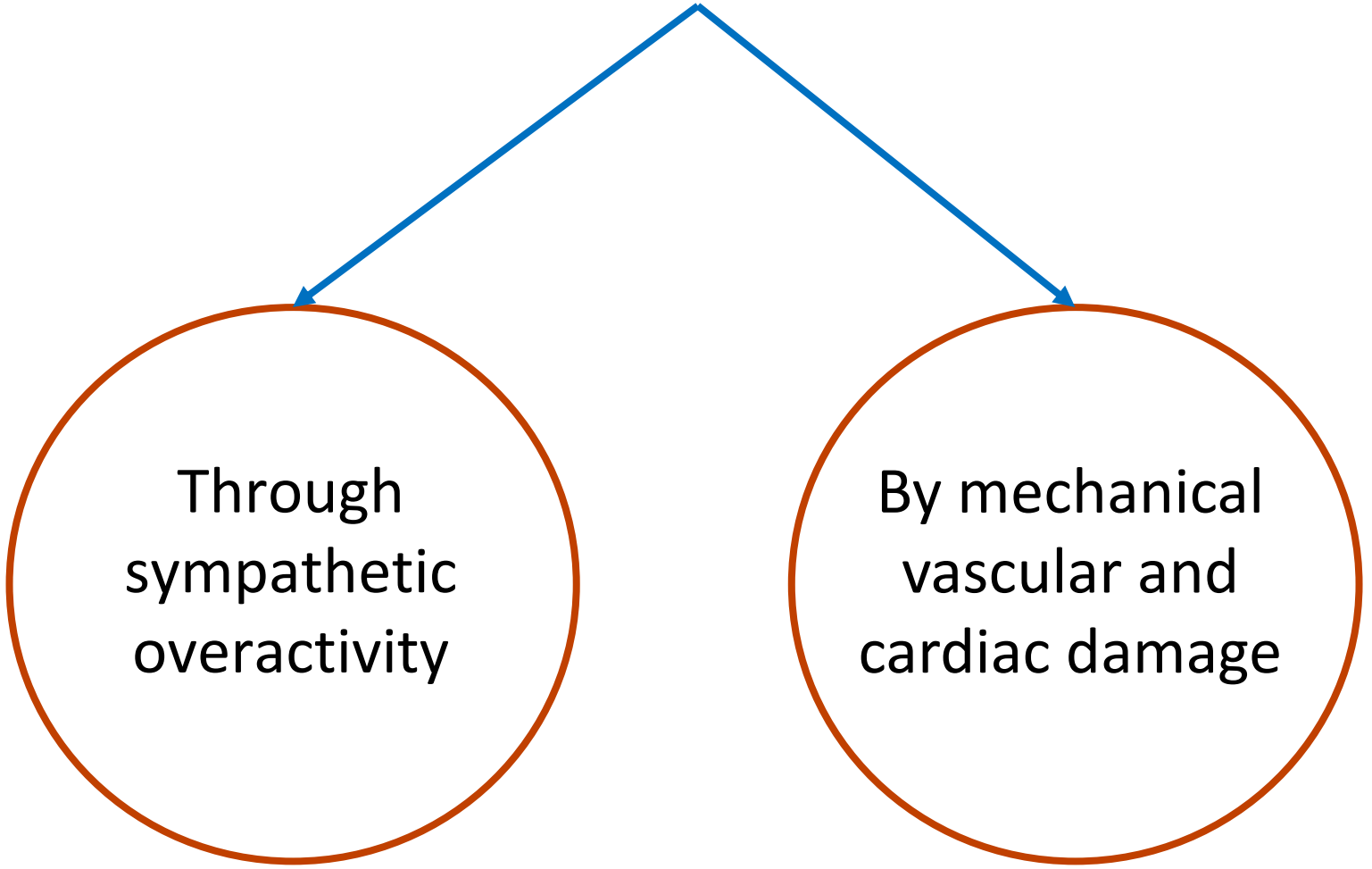
# -- E/ TACHYCARDIA IS A POTENT PREDICTOR OF MORTALITY

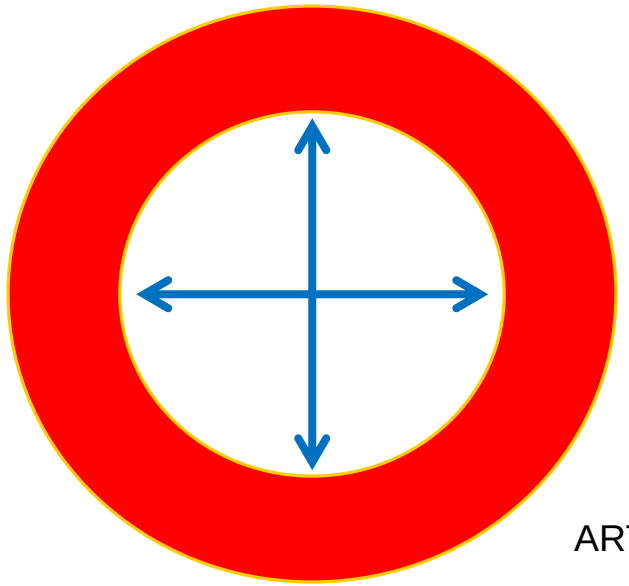



From Levin HJ, J Am Coll Cardiol 1997;30:1104-6

# How does Tachycardia increase the cardiovascular risk?



# Tachycardia amplifies the tensile stress in arteries



AORTA → Increased aortic pressure

Increased **pulse wave velocity**

Reflected pulse wave

ARTERIOLES → Thicker vessel wall smaller lumen

Blood pressure amplification

Can antihypertensive drugs with heart rate reducing properties improve prognosis in hypertensive patients with tachycardia?

# Pharmacological possibilities to reduce Sympathetic overdrive

- Centrally acting antihypertensives
- Alpha-blockers
- Non-dihydropyridine CCB’s
- Beta-blockers
- Ivabradine

The NEW ENGLAND JOURNAL of MEDICINE

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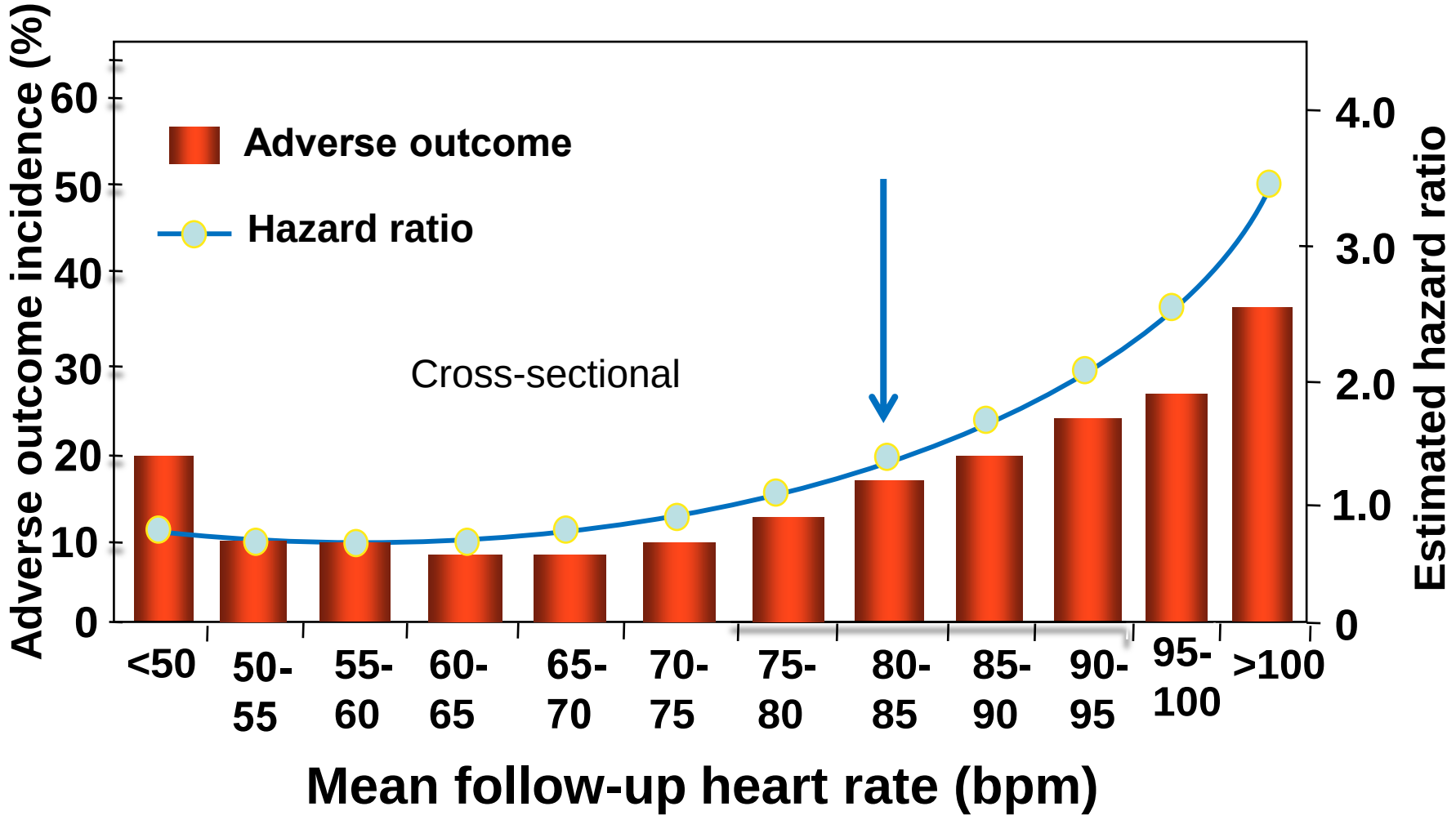
# Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

Kim Fox, M.D., Ian Ford, Ph.D., Philippe Gabriel Steg, M.D., Jean-Claude Tardif, M.D., Michal Tendera, M.D., and Roberto Ferrari, M.D., for the SIGNIFY Investigators*

ABSTRACT

# Relationship Between Follow-up Heart Rate And Outcome In The INVEST Study



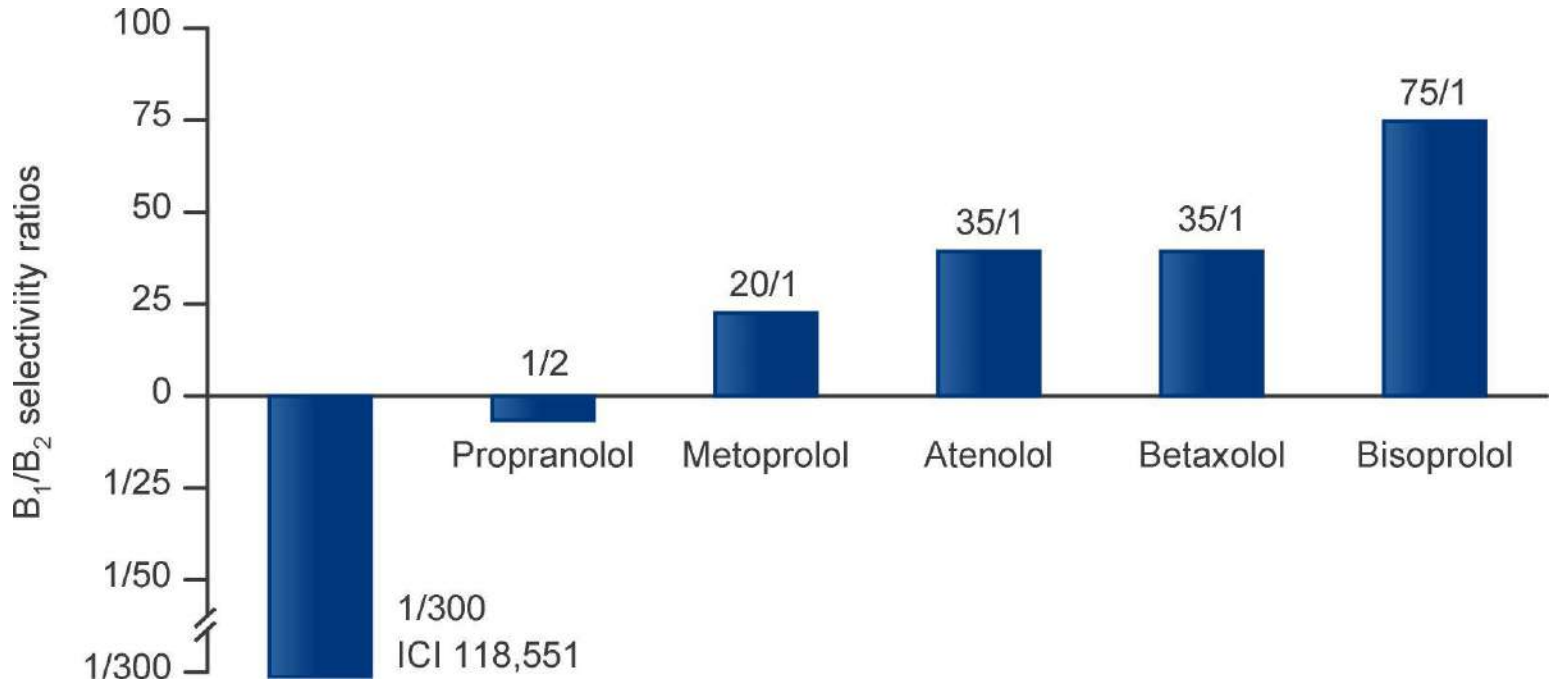

Kolloch R et al, Eur Heart J 2008;29:1327

# Most commonly used beta-blockers

| | Beta-1 selectivity | Bioavailability (%) | half-life (h) | Route of clearance | adverse effect on lipids/glucose |
|---|---|---|---|---|---|
| Bisoprolol | + + + + | 90 | 11-17 | renal/hepatic | none |
| Carvedilol | + | 60 | 7-10 | hepatic | + + |
| Nebivolol | + + + + | 90 | 10-20 | renal/hepatic | none |
| Metoprolol | + + + | 50 | 3-6 | hepatic | + + |
| Atenolol | + + | 40 | 5-7 | renal | + + + |
| Propranolol | - | 30 | 4-6 | hepatic | + + + + |

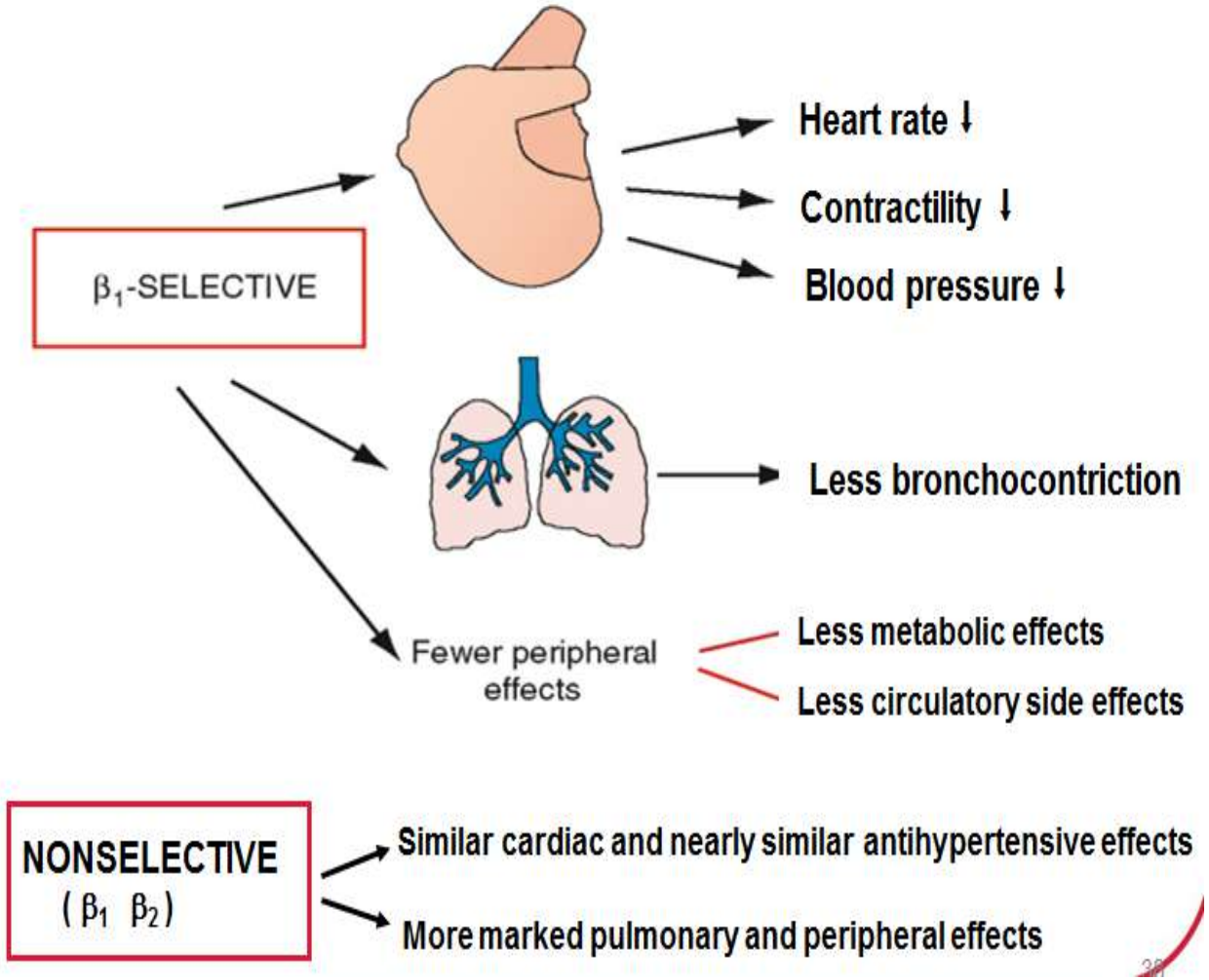
Source: Goodman and Gilman 11th edition 2006

# Bisoprolol blocks noradrenaline stimulation of beta1-receptors




Adapted from Wellstein A *et al*. J *Cardiovasc Pharmacol* 1986;**8**(Suppl):S36-40.)

# Advantages of selective β1-receptor blockade



# Drugs to be preferred in subjects with Clinical CV events

## 2018 ESH/ESC Guidelines

- Previous stroke: Any agent effectively lowering BP
- Previous myocardial infarction: BB, ACE inhibitor, ARB
- Angina pectoris: BB, calcium antagonist
- Heart failure: Diuretic, BB, ACE inhibitor, ARB, MRA
- Atrial fibrillation, prevention: ARB, ACE inhibitor, BB or MRA
- Atrial fibrillation, ventricular rate control: BB, non-dihydrop CA
- ESRD/proteinuria: ACE inhibitor, ARB
- Peripheral artery disease: ACE inhibitor, CA

BB, beta-blockers
CA, calcium antagonists
MRA, mineralcort recept antagonists

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Consensus Document

# Management of the hypertensive patient with elevated heart rate: Statement of the Second Consensus Conference endorsed by the European Society of Hypertension

Paolo Palatini[a], Enrico Agabiti Rosei[b], Edoardo Casiglia[a], John Chalmers[c], Roberto Ferrari[d], Guido Grassi[e], Teruo Inoue[f], Bojan Jelakovic[g], Magnus T. Jensen[h], Stevo Julius[i], Sverre E. Kjeldsen[j], Giuseppe Mancia[k], Gianfranco Parati[k], Paolo Pauletto[l], Andrea Stella[o], and Alberto Zanchetti[p]

Journal of Hypertension 2016, 34:813–821

# Management of the hypertensive patient with elevated heart rate Statement of the Second Consensus Conference endorsed by the European Society of Hypertension.

Conclusions

- **High HR is an important risk factor for cardiovascular disease**
- **HR measurement should be included in the overall assessment of the hypertensive patient**
- **HR might be included in future risk charts of international guidelines**
- **In most studies HR was considered to be elevated when it was higher than**

Lack of evidence makes it difficult to make practical therapeutic suggestions for the hypertensive patient with high HR. However, some degree of flexibility with management is expected and in symptomatic tachycardia HR reduction by available drugs (mostly β-1 selective β-blockers) should be considered.

- **The panelists unanimously made a plea for the implementation of a randomized clinical trial aiming at evaluating the effects of HR reduction in hypertensive patients with high HR**

**Palatini P et al, J Hypertens 2016;34:813**

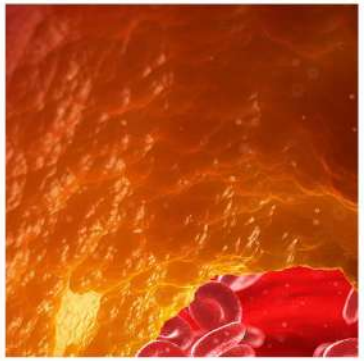
# Take home messages

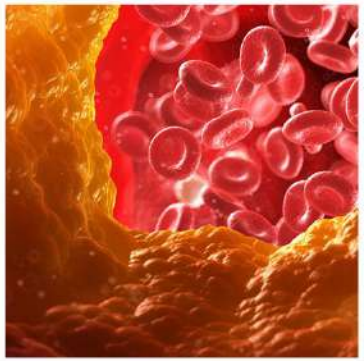
1. Heart rate is a partly blood pressure independent cardiovascular risk factor

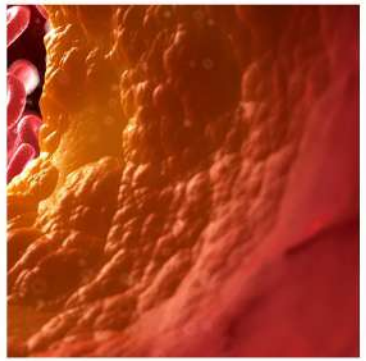
2. Reducing heart rate is a therapeutic target in hypertensive patients with an elevated heart rate

3. Beta-1 selective beta-blockers should be considered in these cases

# The 2019 EMEA Cardiometabolic Workshop







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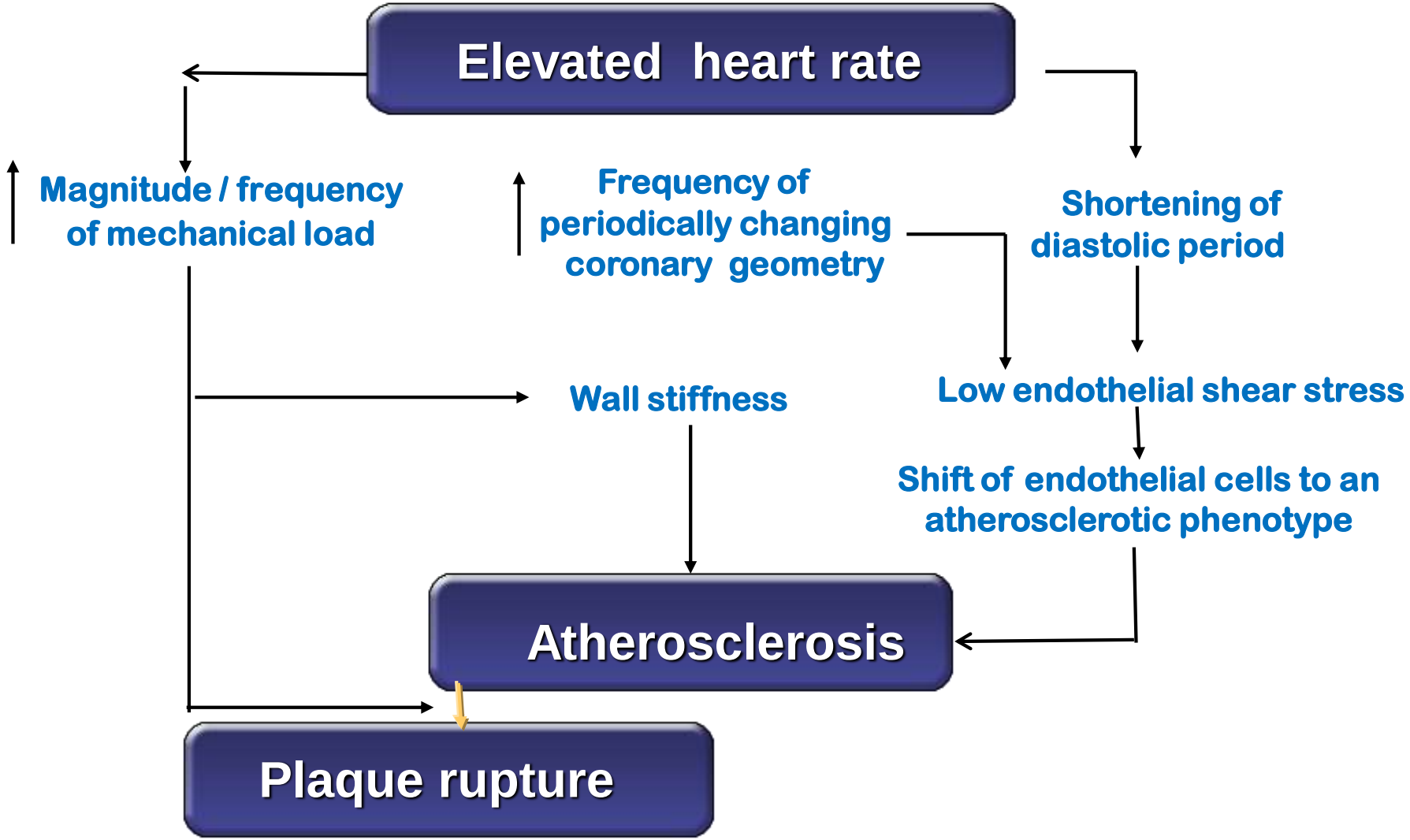
# F. Mechanisms of tachycardia's harmful effects are well understood

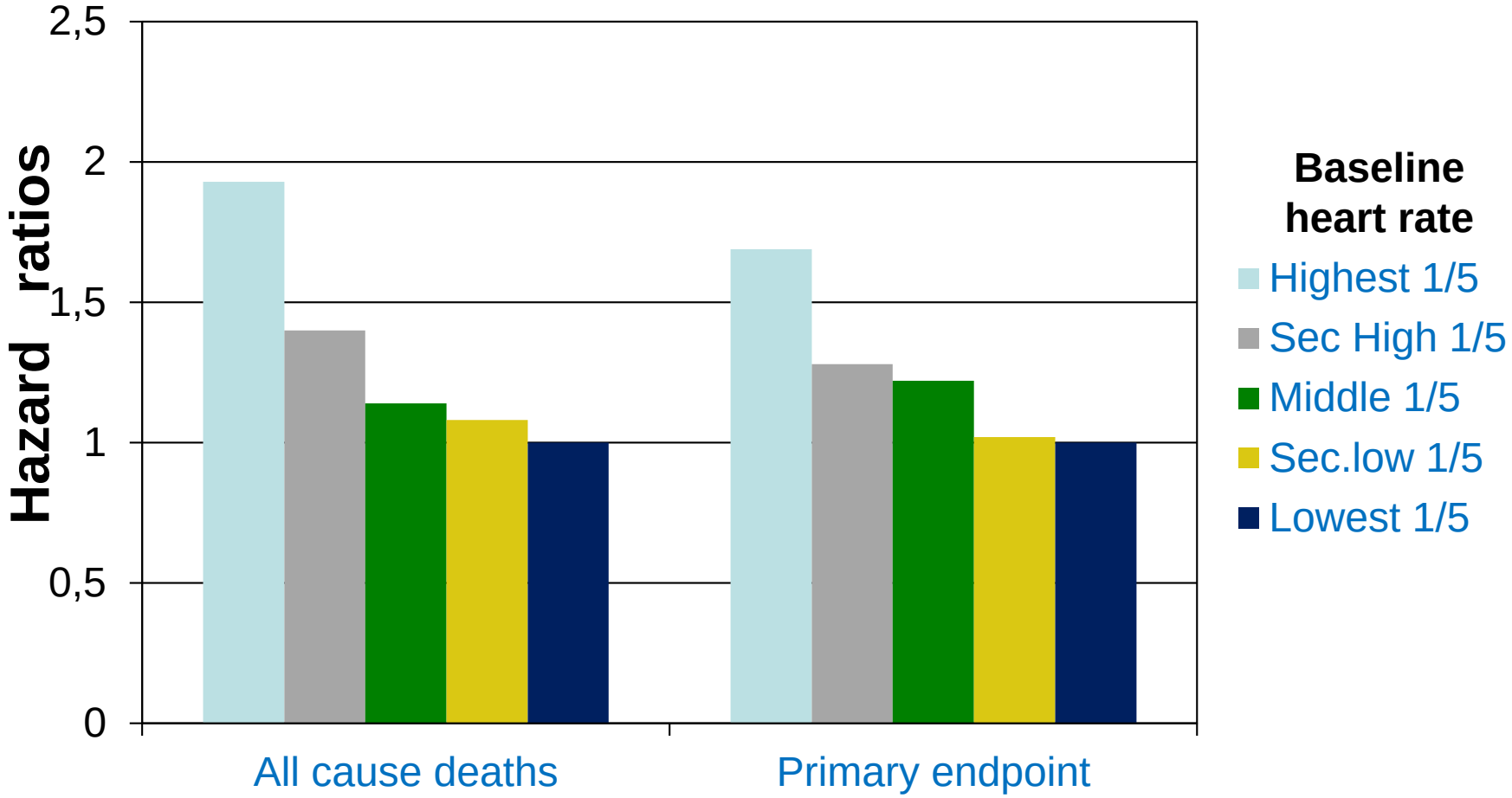



Adapted from Giannoglou G et al. *Int J Cardiol*. 2008;126:302-312

# Heart Rate as Independent Risk Factor

- Increased cardiac work and oxygen consumption
- Increased arterial wall stress
- Higher mean blood pressure
- Decreased arterial compliance
- Kidney damage (microalbuminuria)
- Facilitation to coronary plaque disruption

# VALUE study of 15,193 patients.
# Hazard ratios by quintiles of baseline heart rate.
# Cox regression models adjusted for baseline BP and risk factors.




Adapted from S. Julius, P. Palatini et al Am J Cardiol 2012 109

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# BETA—BLOCKERS
## History

- Beta-blockers were first developed by Sir James Black at the imperial chemical industries in the UK in 1962
- They are considered one of the most important contributions to clinical medicine and pharmacology in the 20$^{th}$ century
- Sir James Black was awarded the Nobel prize in 1988 for advances in medicine