

Heart Rate Reduction in Hypertension

Beneficial



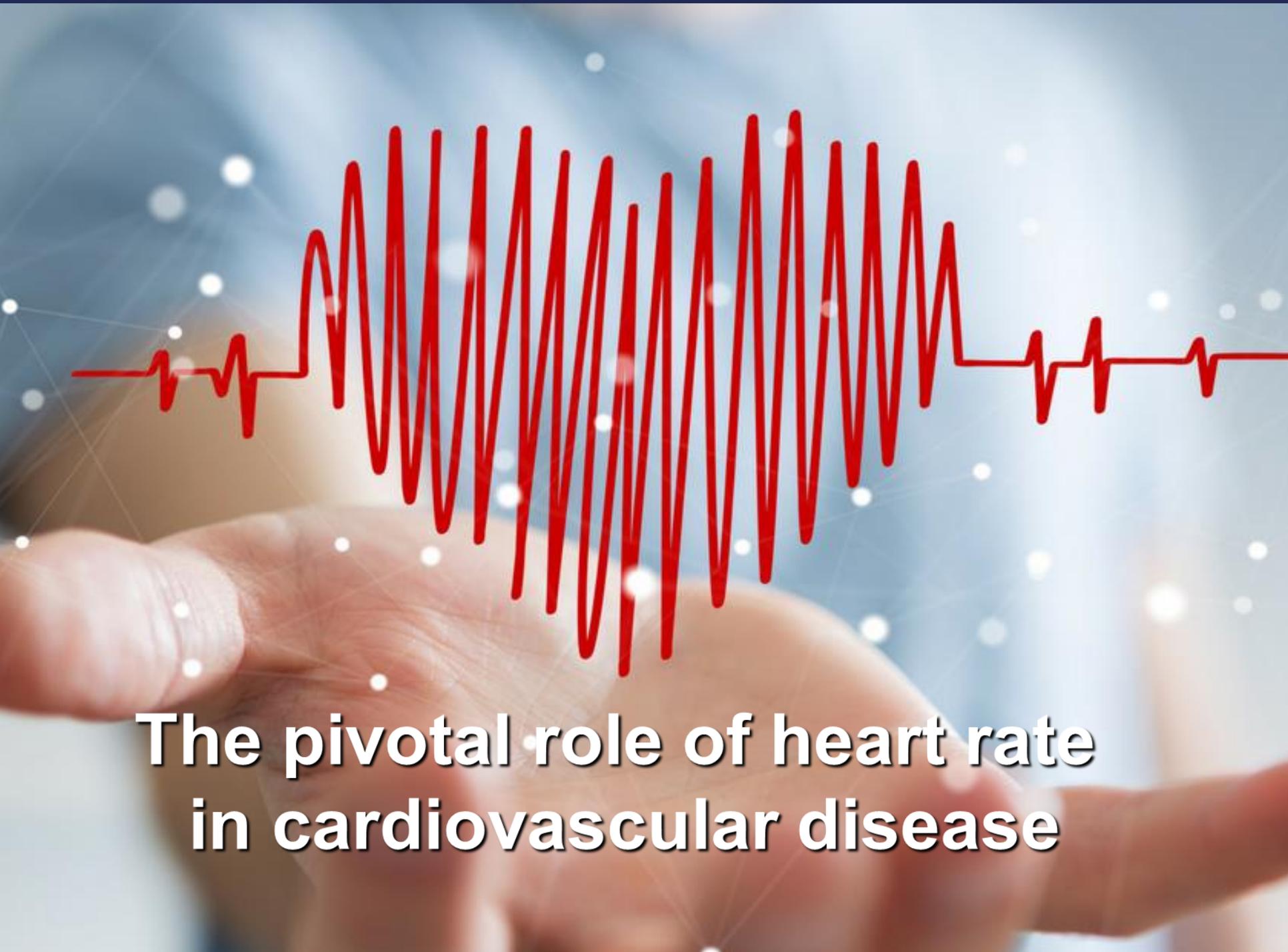
Neutral



Harmful

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**The pivotal role of heart rate
in cardiovascular disease**

The role of heart rate in cardiovascular disease

Elevated heart rate

Atherosclerosis

Endothelial dysfunction↑
Oxidative stress↑
Plaque stability↓
Arterial stiffness↑

Ischemia

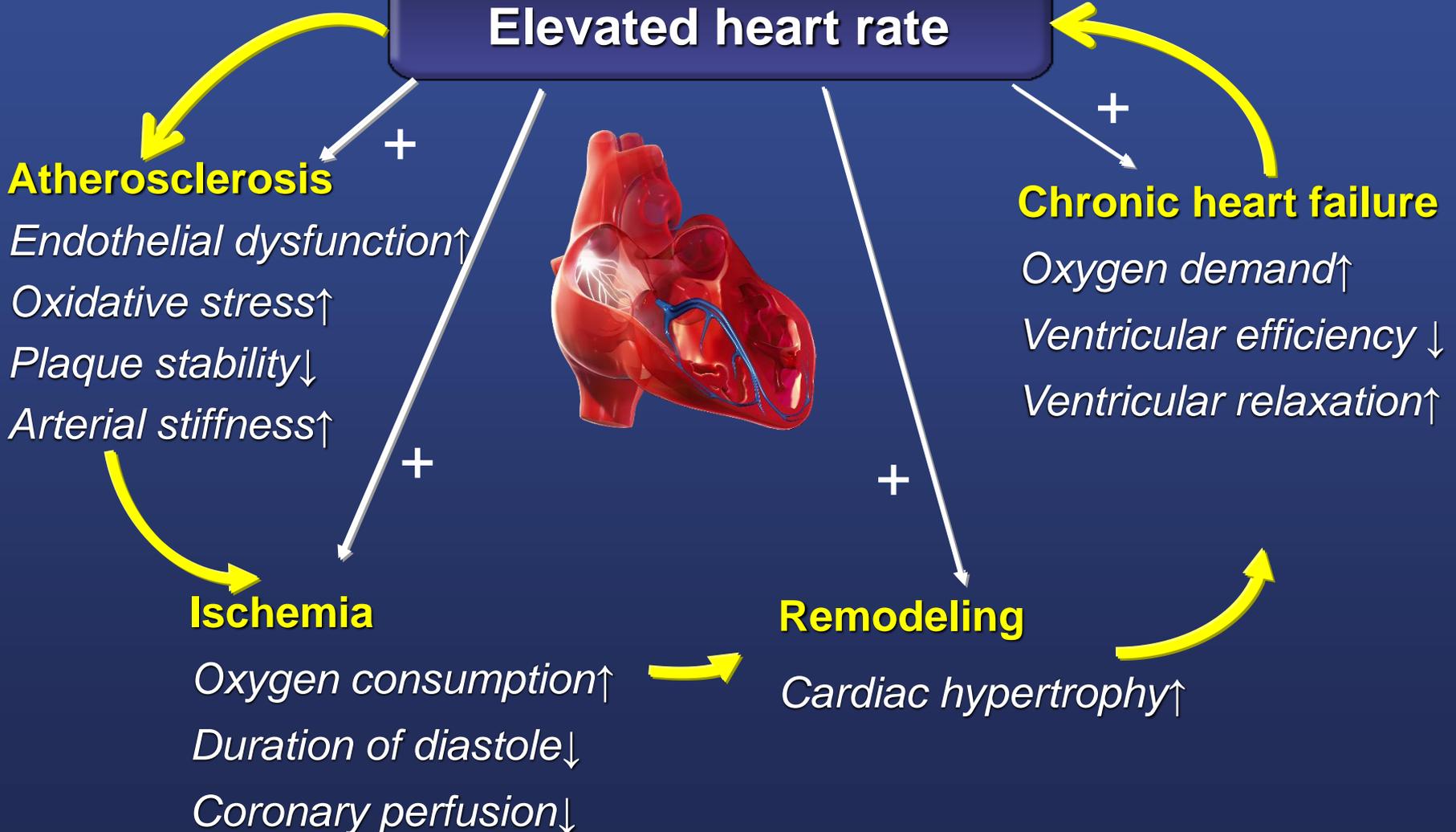
Oxygen consumption↑
Duration of diastole↓
Coronary perfusion↓

Remodeling

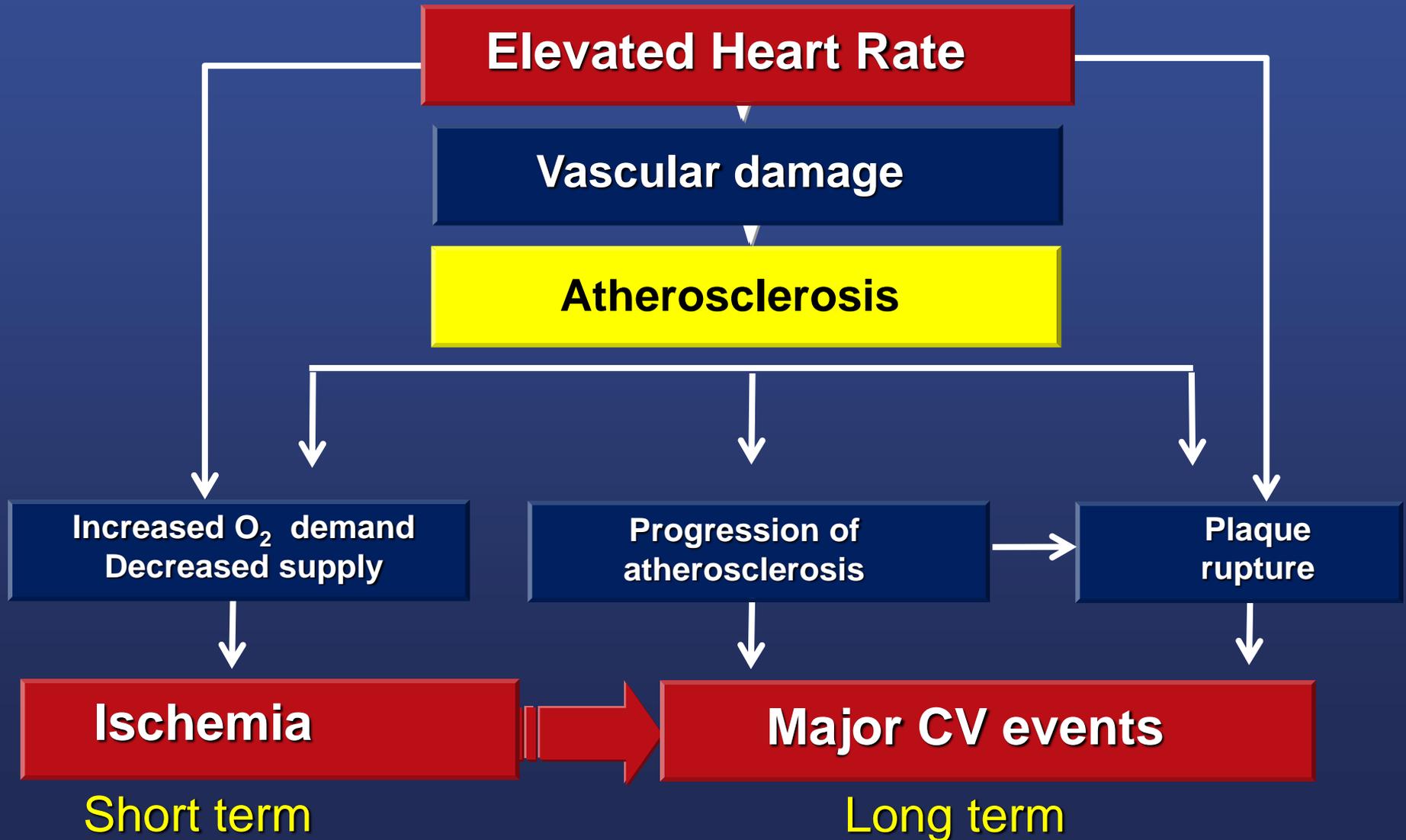
Cardiac hypertrophy↑

Chronic heart failure

Oxygen demand↑
Ventricular efficiency↓
Ventricular relaxation↑

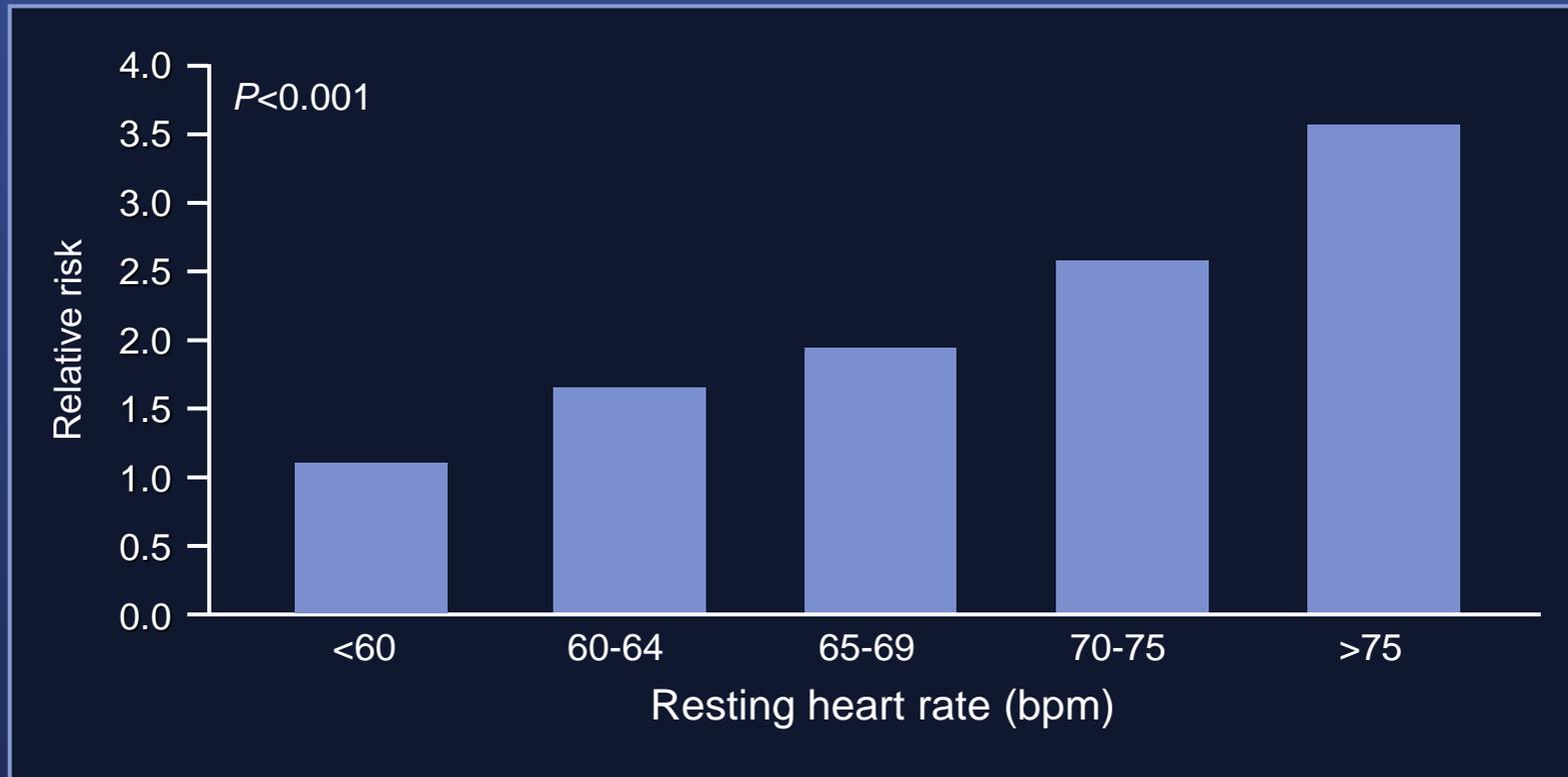


Role of elevated HR in the pathophysiology of CAD



Sudden death risk increases progressively with resting HR in the general population

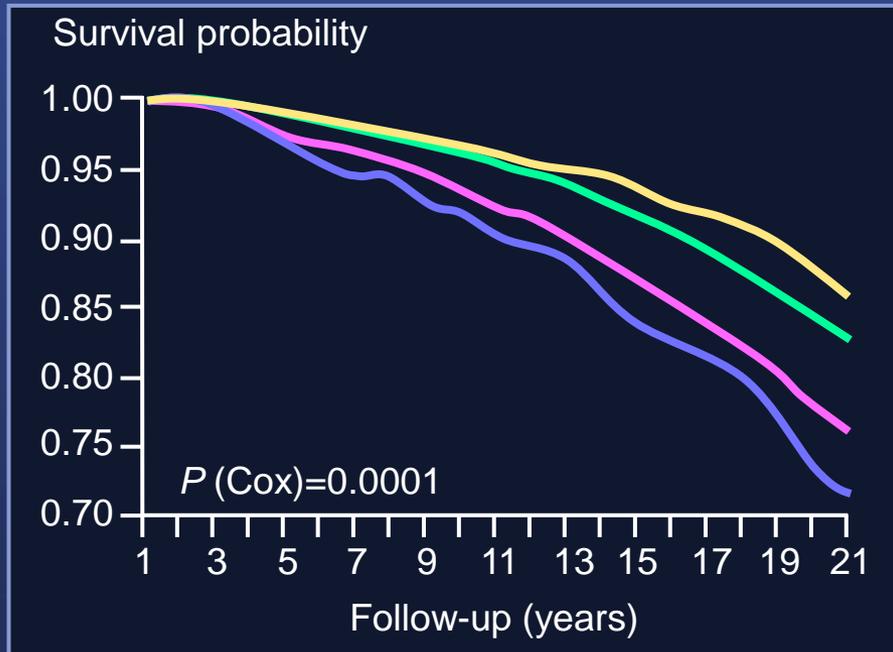
The Paris Prospective Study I , general population, 5713 men; 23-year follow-up



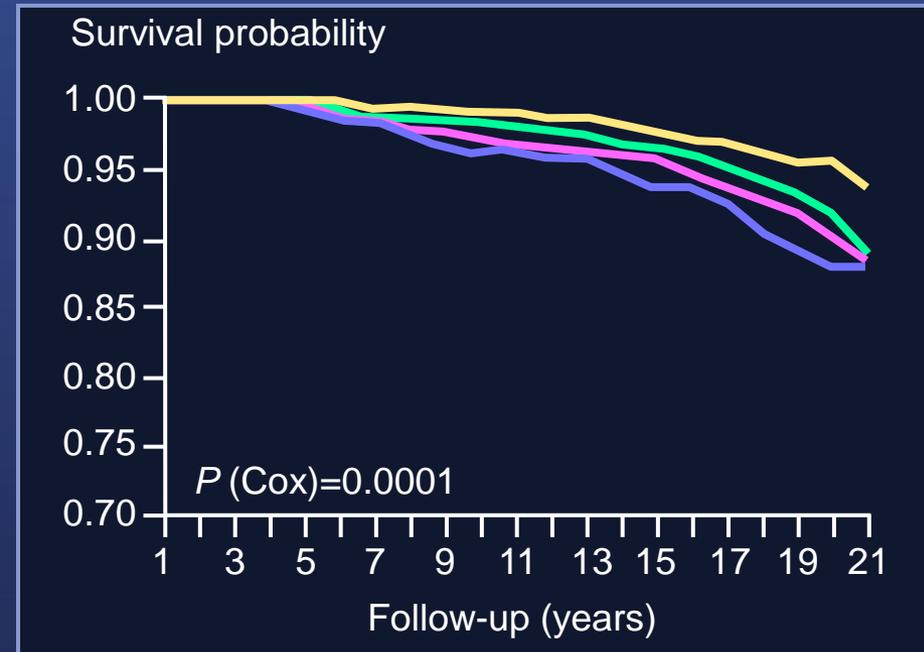
Resting heart rate independently predicts total and CV mortality in men and women

French cohort study, n=19 386 (12 123 men, 7263 women), 18-year follow-up

Men: all-cause mortality



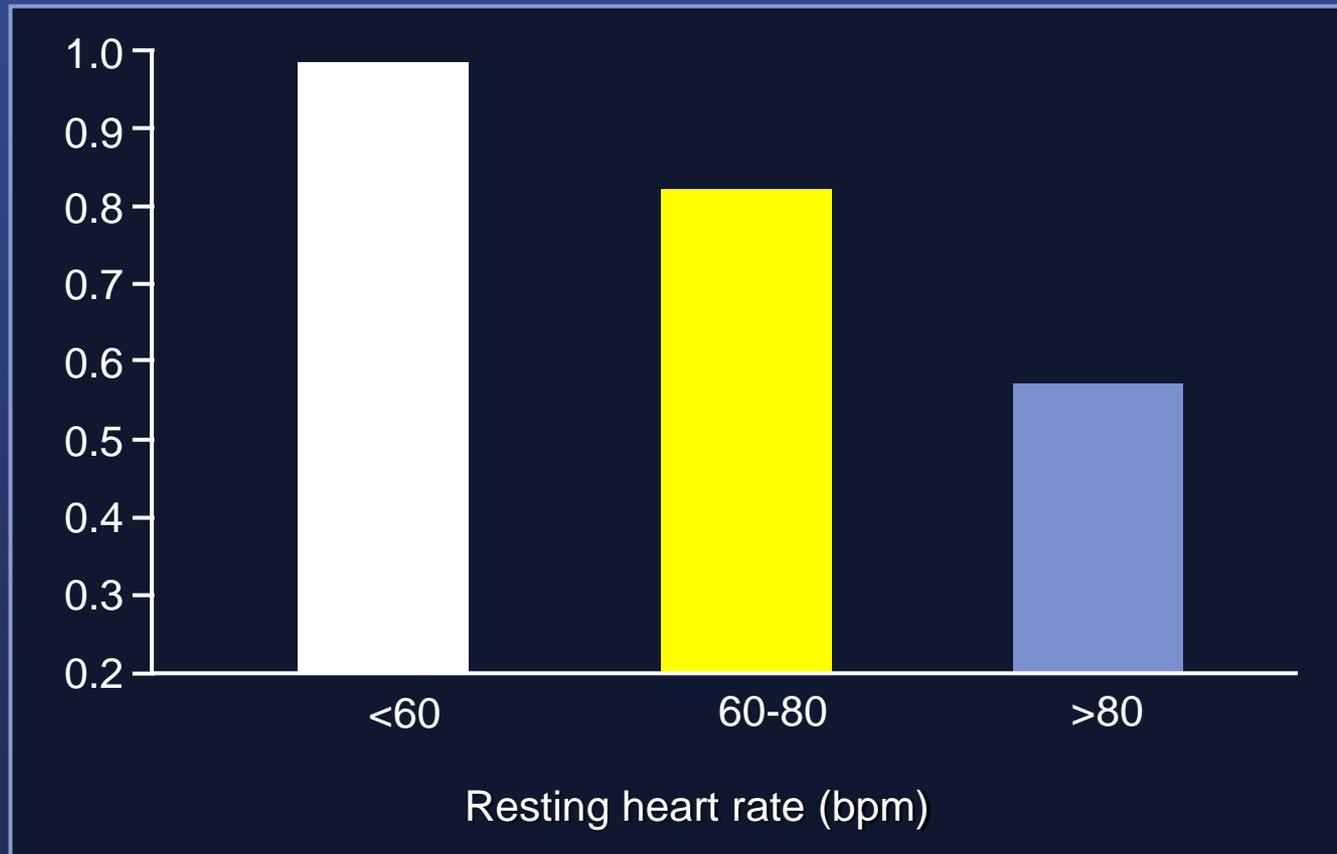
Women: all-cause mortality



— HR < 60 — 60 ≤ HR ≤ 80 — 80 < HR ≤ 100 — HR > 100 bpm

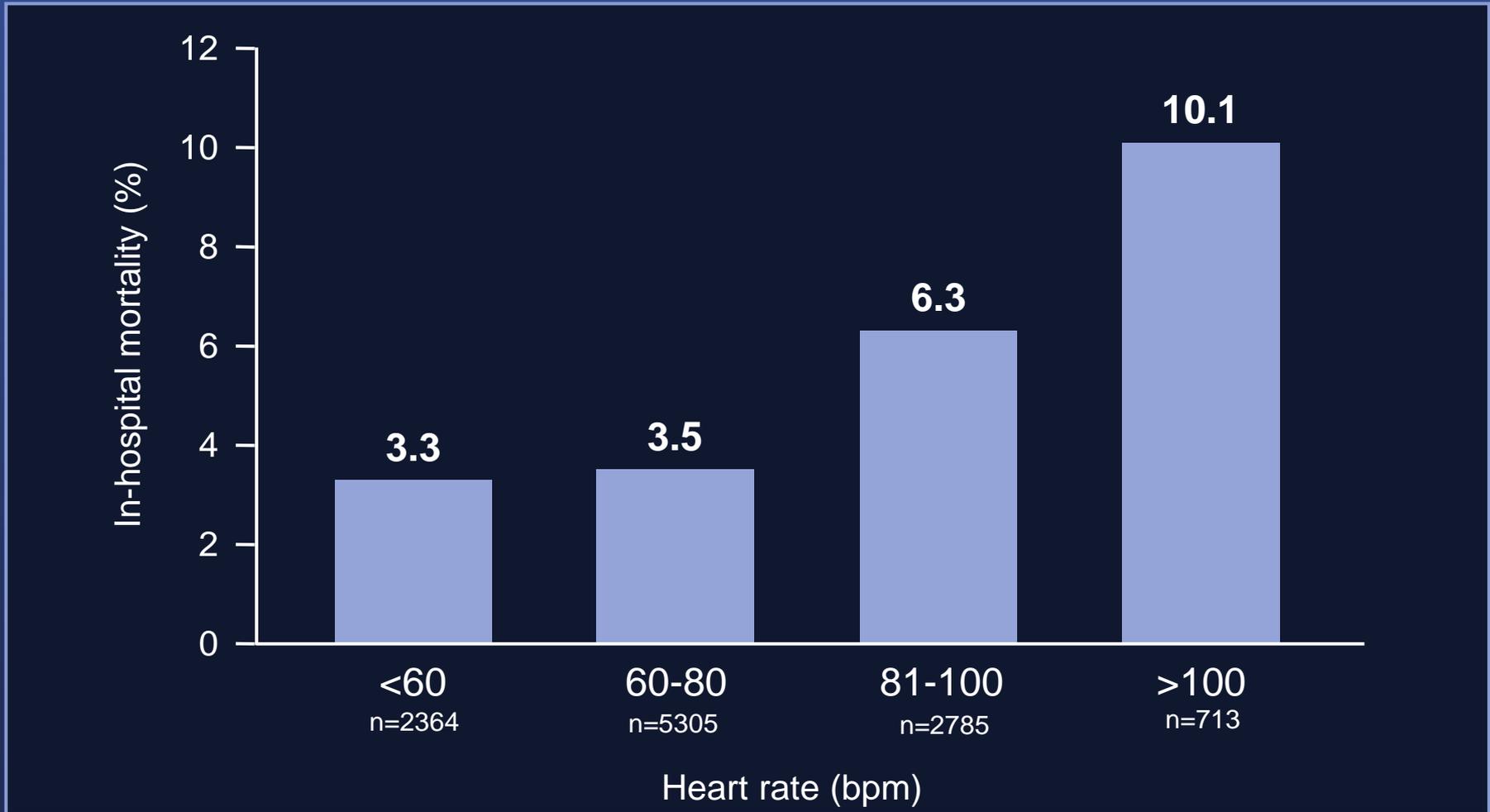
Resting heart rate: predicts survival in people aged >65 years

Cohort study in 1407 men aged from 65 to 70 years, follow-up 18 years

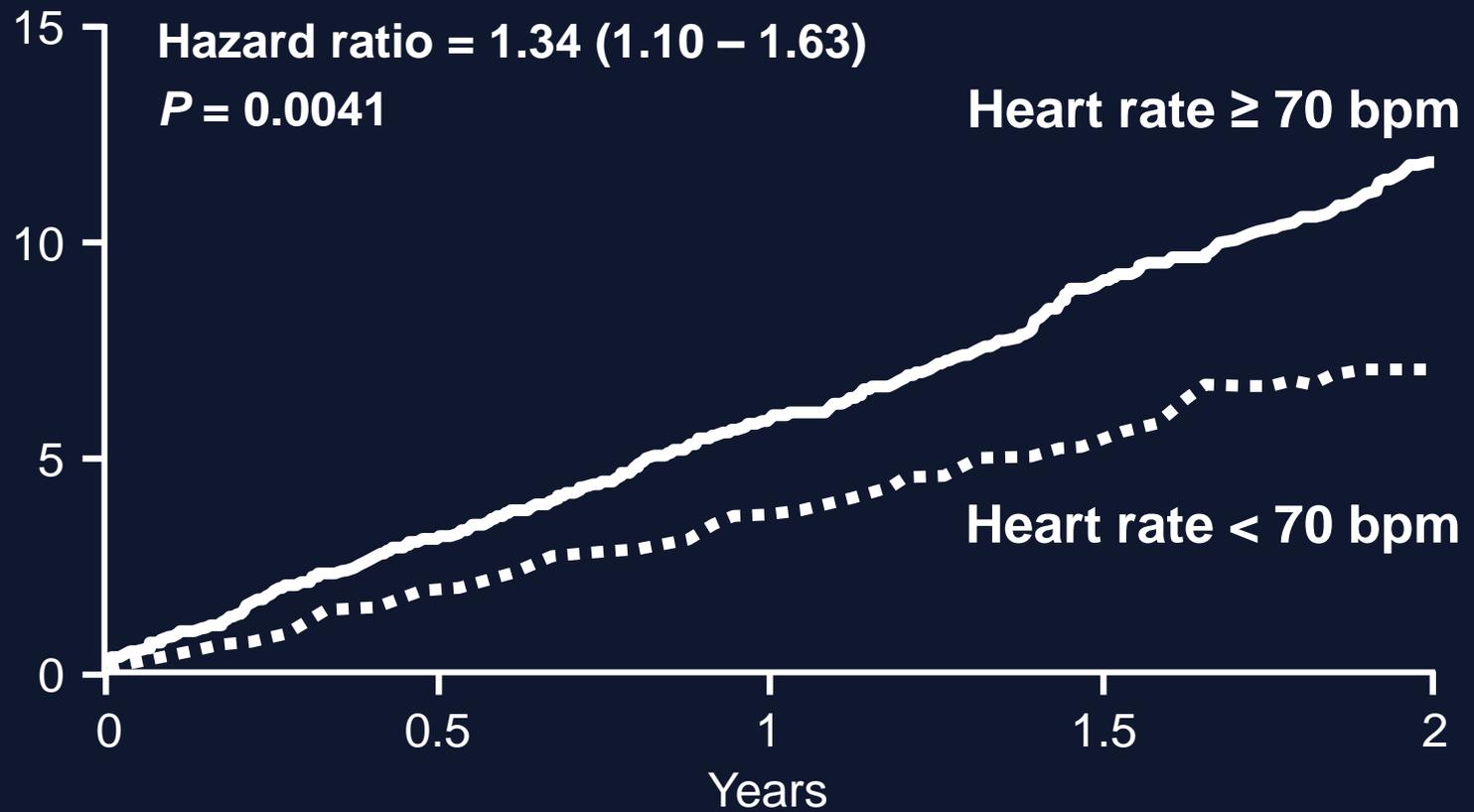


Heart rate at admission and in-hospital mortality in MI survivors

GISSI-3 study, 6-month follow-up; ECG



Prospective data from the BEAUTIFUL placebo arm; 5438 patients with stable CAD and LVSD
% with cardiovascular death





Hypertension & Heart rate

- Hypertension (HTN) is a widely prevalent major cardiovascular (CV) risk factor.
- The risk factors for development of HTN include age, smoking, alcohol, obesity, diabetes, renal damage and others.
- The other risk factors that might contribute to pathogenesis of HTN are often neglected and one such risk factor is heart rate (HR).
- Increase in HR is associated with increase in blood pressure (BP).
- A 3 – 4 times higher risk of HTN has been reported with increase HR even after controlling the traditional risk factors.
- Increasing HR in patients with HTN is associated with adverse CV outcomes.

Table 4 Factors influencing cardiovascular risk in patients with hypertension

Demographic characteristics and laboratory parameters
Sex ^a (men >women)
Age ^a
Smoking (current or past history) ^a
Total cholesterol ^a and HDL-C
Uric acid
Diabetes ^a
Overweight or obesity
Family history of premature CVD (men aged <55 years and women aged <65 years)
Family or parental history of early-onset hypertension
Early-onset menopause
Sedentary lifestyle
Psychosocial and socioeconomic factors
Heart rate (resting values >80 beats/min)

HR and Relation to Peripheral and Central Blood Pressure



- Changes in both peripheral and central pressures are strongly associated with HR and this relationship is quite complex.
- The difference between central pressure and peripheral blood pressure can be up to 20mmHg.
- With regard to CV outcomes, the strong heart study demonstrated that the central pulse pressure is more strongly associated with vascular hypertrophy, extent of atherosclerosis, and CV events than peripheral pulse pressure.

- Increase in HR is known to increase the peripheral pressure whereas it reduces the central pressure.
- These antagonistic effects of the HR on the two pressures raise concern with respect to selection of the antihypertensive medications.
- The **CAFÈ study** observed significant reduction in the central aortic pressure with amlodipine-based but not with the atenolol-based treatment despite similar reduction in the brachial pressures.
- Therefore, differences in central pressure with two treatments could possibly explain the differences in outcomes reported in the study.

- A further analysis from this CAFÈ data observed that HR has no effect on brachial pressure, but a significant inverse relationship exists between HR and central pressure.
- Multivariate analysis showed that HR was the major determinant of the central pressure.
- Thus, atenolol-based treatment was associated with less effective central pressure reduction relative to decrease in the peripheral pressure.

- This inverse association with the central aortic pressure has been found to be associated with increased risk of CV events with the use of BB in HTN.
- A metaanalysis of randomized controlled trials assessing HR changes with the use of BB in HTN reported increased risk of all-cause deaths ($r = -0.51$; $p < 0.0001$), CV deaths ($r = -0.61$; $p < 0.0001$), myocardial infarction ($r = -0.85$; $p < 0.0001$), stroke ($r = -0.20$; $p = 0.06$), or heart failure ($r = -0.64$; $p < 0.0001$) with lower HR in patients of HTN.

Resting HR and Risk of Incident HTN



➤ The question arises whether increase in HR increases the risk of incident HTN.?



- The **BEAT survey (2015)** performed in 3743 young (18 to 55 years) hypertensive reported average resting heart rate of 82.79 ± 10.41 bpm and BP of $146.82 \pm 15.46 / 89.08 \pm 8.8$ mmHg.
- HR had significant positive correlation with both SBP ($r = 0.247$, $p < 0.01$) and DBP ($r = 0.219$, $p < 0.01$).

- In the Kailuan cohort study (2014), Wang et al. from China studied 31507 participants with mean age of 46.3 ± 11.5 years having no known HTN.
- During the mean follow-up of 3.5 years, 39.88% developed HTN.
- In multivariate analysis, significant increase in new onset HTN with increase in the resting HR ($p < 0.0001$) was observed.
- Further, with increase in the resting HR by 10 bpm, a rise of 8% in HTN was reported.



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- **An increase in the resting HR is associated with increased risk of incident HTN.**
- **A linear association may be observed in individuals with HR >80 bpm.**

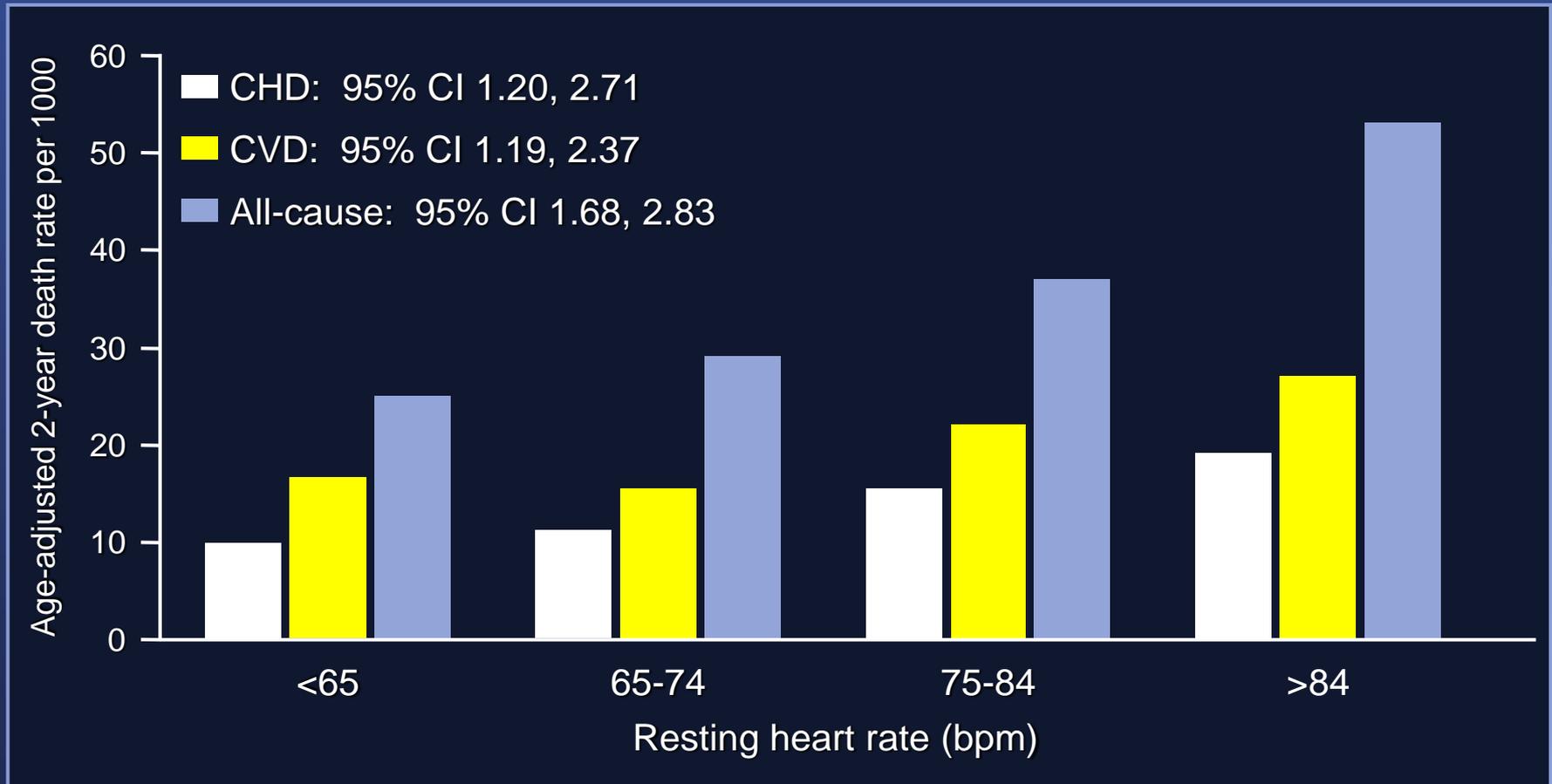
HR as a Prognostic Marker



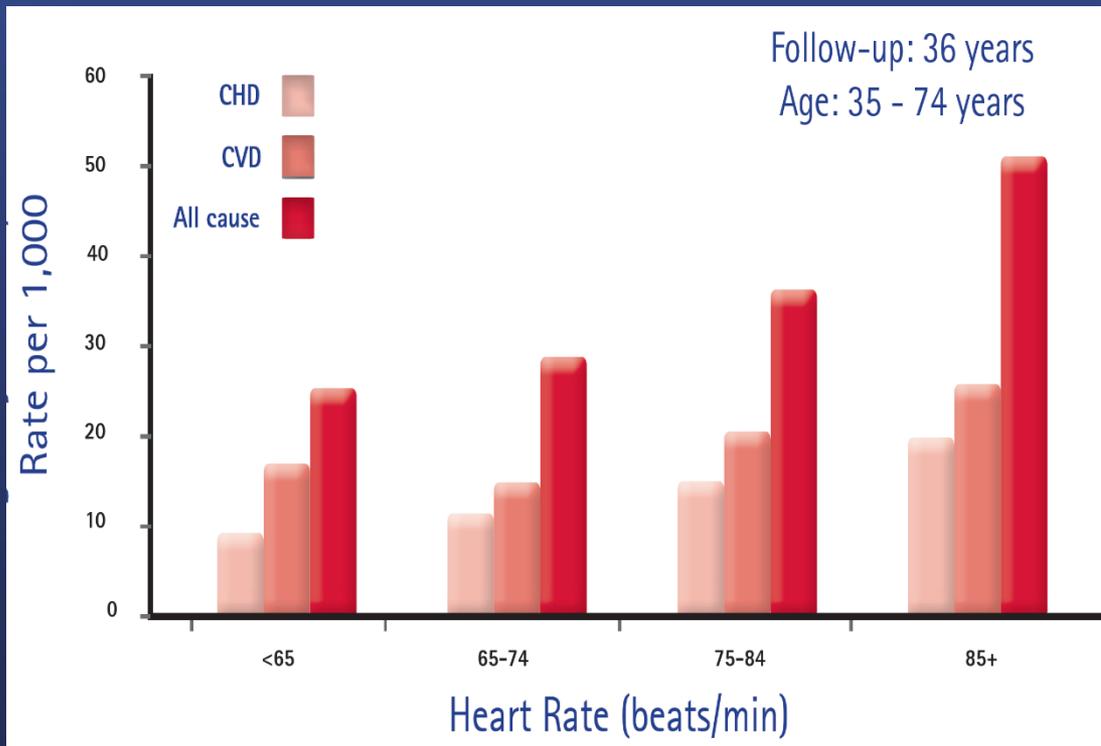
- Evaluation of **Framingham study** data by Gilman et al. 1993 suggested association of HR with mortality in patients of HTN not treated with antihypertensives.
- Each increase in HR of 40 bpm was associated with nearly two-times higher risk of all-cause mortality and 1.5-times higher risk of CV mortality suggesting HR as independent predictor of mortality in HTN.

All-cause mortality increases progressively with resting heart rate in men with hypertension

The Framingham Study, 2037 men with untreated hypertension, 36-year follow-up



Heart Rate & Mortality in Hypertensives: (4,530; 2037 M/2493 F)



Framingham Study

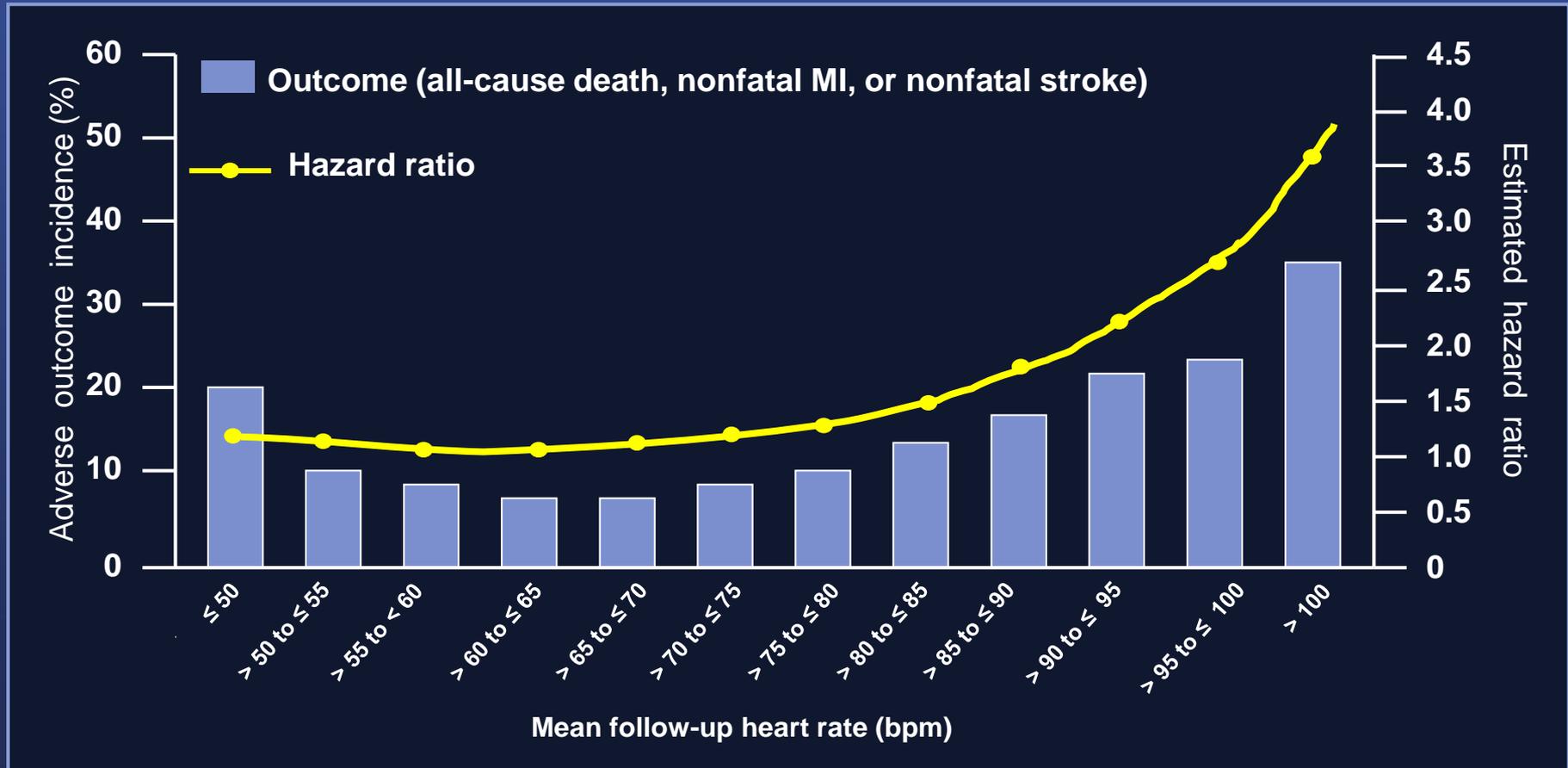
➤ HR measurement: ECG

- The **VALUE trial** suggested incremental risk of cardiac events with rise of HR.
- In patients with high-risk HTN, every supplemental increment of 10 bpm from baseline was associated with hazard ratio (HR) of 1.16 for composite cardiac outcome.
- Another evaluation of data from **LIFE study** reported 25% increase in risk of CV deaths and 27% higher risk of all-cause deaths with each increment in HR by 10 bpm.
- HR of 84 bpm or more was associated with increased risk of CV deaths (89%) and all-cause deaths (97%).

- Similar investigation done in **INVEST data** showed that baseline resting HR had linear association with adverse outcomes in patients of coronary artery disease (CAD) treated for HTN.
- Treatment with atenolol-strategy reduced HR more than verapamil-strategy with mean HR of 69.2 vs 72.8 bpm, respectively, by 24 months.
- Study concluded that on-treatment HR is better predictor of outcomes than resting HR.
- These analyses highlight the important fact that on treatment rise in HR is predictive of adverse outcomes and should be considered in all patients under treatment for HTN.

Impact of heart rate in patients with hypertension and coronary artery disease

INVEST study, 22 192 CAD patients; 2.7-year follow-up





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- **Resting HR has linear association with adverse outcomes.**
- **Each 10 bpm increase in resting HR can substantially increase the risk of adverse CV and mortality outcomes, and on-treatment HR can provide a better prognostic guide.**

Management of Elevated HR in HTN

Target HR in Patients with or without Comorbidities.

- The evidence from either observational or randomized trials suggesting a specific target at which there can be optimal benefits of HR lowering in patients of HTN is lacking.
- This restricts identifying specific target HR. For using BB in an Asian population, experts have suggested a target HR of <70 beats per min (bpm) in all HTN patients.
- In achieving this, higher propensity for various adverse effects including bradycardia with older BB deters their use.

- Newer BBs like nebivolol must be preferred as they reduce HR as well as both central and peripheral pressures.
- Further, target HR can be lowered to <65 bpm in patients with coexisting coronary artery disease.
- In an analysis from **SHIFT trial** in patients with systolic heart failure, sinus rhythm, and $HR \geq 70$ bpm on background of BB treatment, ivabradine addition was associated with significant reduction of composite primary endpoint (CV death or HF hospitalization) and HF hospitalization was reduced significantly in subgroups of no BB ($p=0.012$) and in all patients <50% of target BB dose.
- HTN was accompaniment in nearly 2/3rd of the patient population in each subgroup.

Possible Benefits with HR Reduction in HTN.

- A metanalysis by Xie et al. 2017, reported atenolol to be more beneficial than angiotensin converting enzyme inhibitors (ACEIs) in terms of reducing peripheral diastolic pressure and HR in patients of HTN within first 3-months of treatment.
- Another metanalysis by Nogueira-Silva et al. reported BP reduction by 10/8mmHg, pulse pressure by 2mmHg, and HR by 11 bpm with use of BB in HTN.

- in an interesting analysis from **SIMPLICITY registry**, Bohm et al. 2016, observed that renal denervation in uncontrolled HTN was associated with reduction HR at 12 months of follow-up.
- They suggested that HR reduction can be a target for renal denervation especially for higher HR at baseline.

Take Home Message



- Resting HR is one of the factors found to be associated with incident HTN.
- Elevated HR is a risk factor and not just a risk indicator.
- Heart rate in HTN tends to be elevated which has been identified as an independent predictor for adverse cardiovascular and mortality outcomes.
- It can aid in determining the prognosis of patients with HTN.
- Use of selective beta-1 blockers is advised in symptomatic cases with elevated HR.



Thank
you