

Merck Serono Satellite Symposium

“Dual control of blood pressure and heart rate for cardioprotection”

Hotel Excelsior, Dubrovnik, Croatia

28 September 2013



Dual Control of Blood Pressure and Heart Rate for Cardioprotection

Paolo Palatini

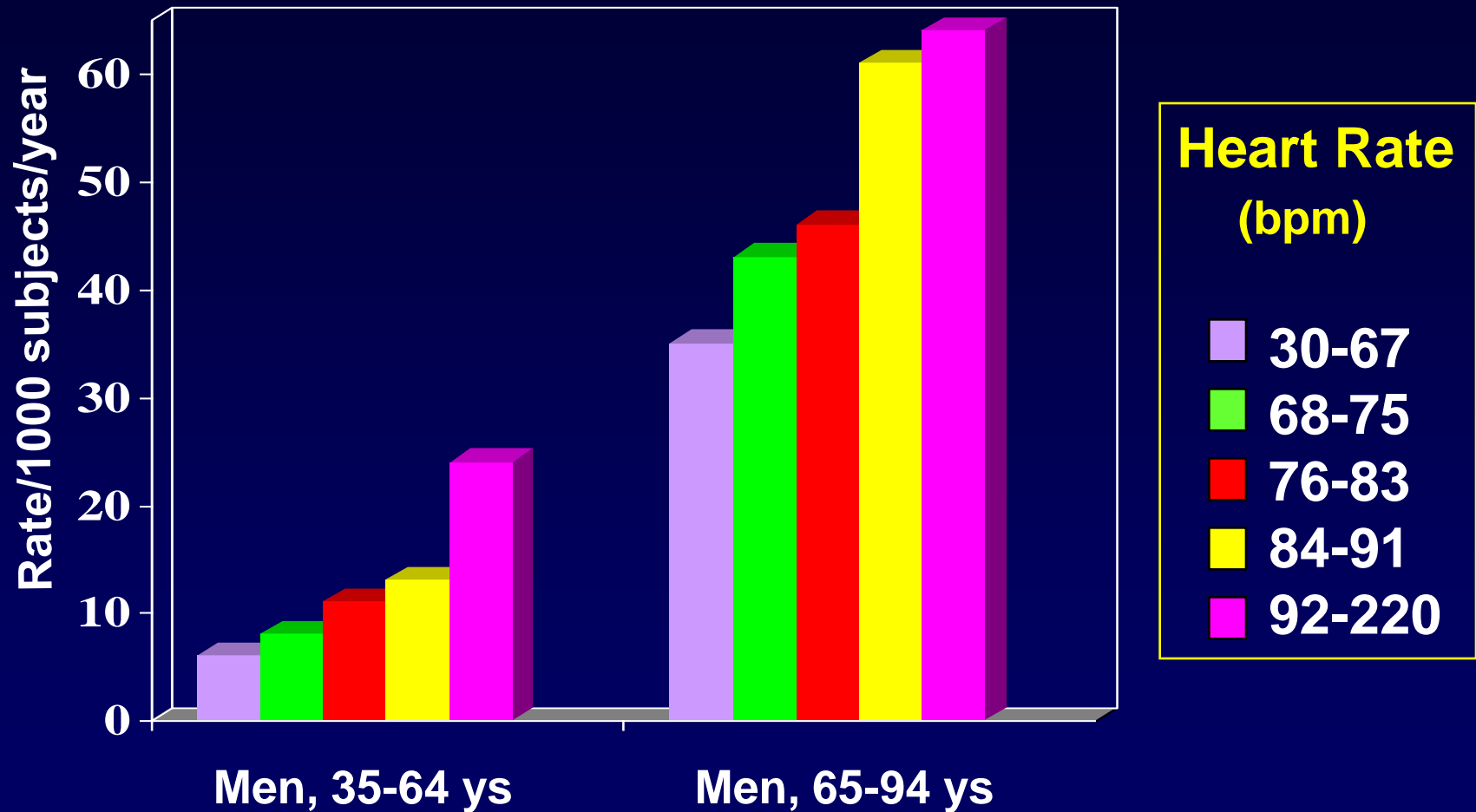
University of Padova, Padua, Italy



Jan Steen, 1626 - 1679

Heart Rate and All-Cause Mortality

The Framingham Study



Heart rate and the cardiovascular risk

Paolo Palatini and Stevo Julius*

Journal of Hypertension 1997, 15: 3-17

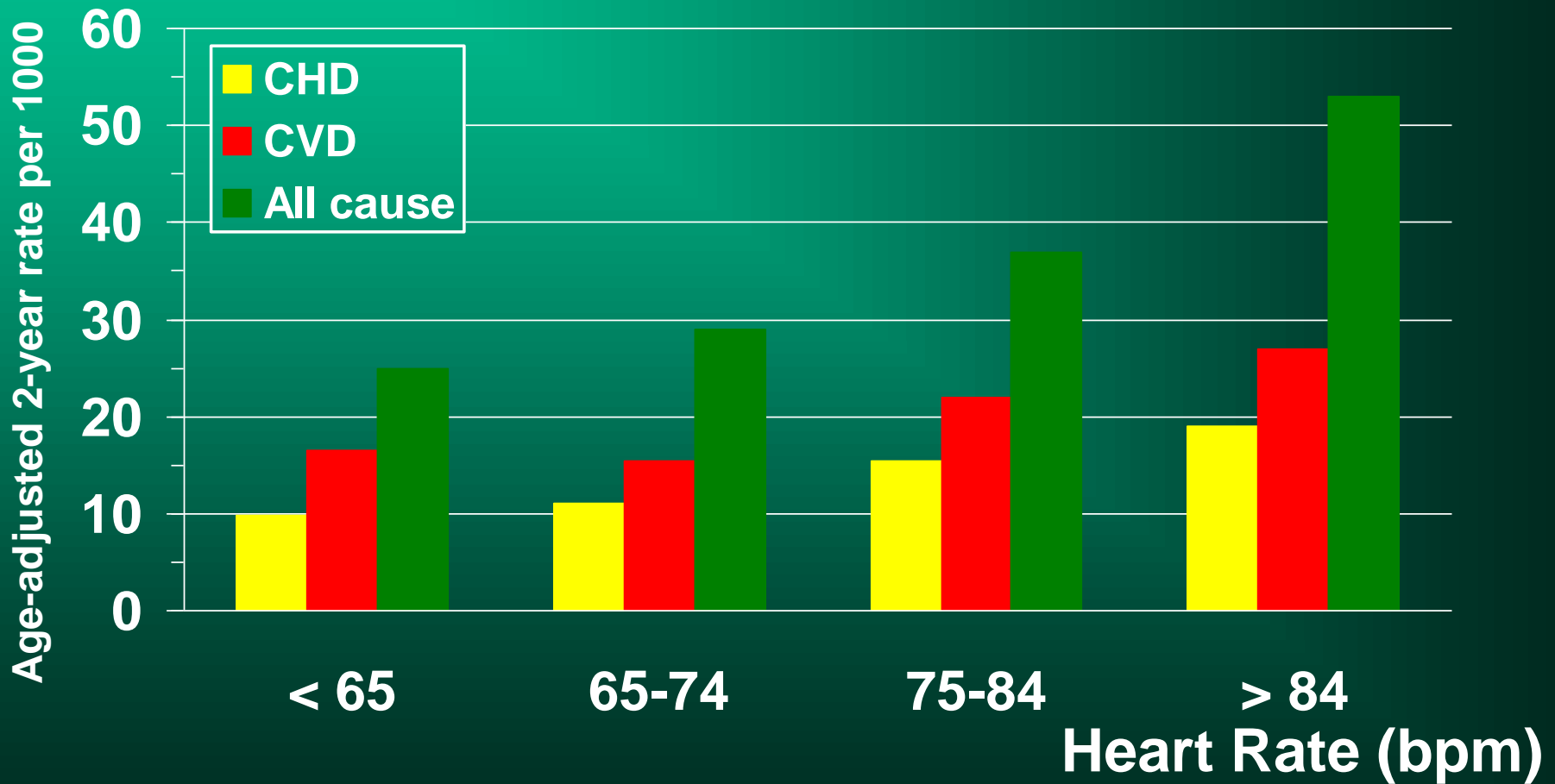
Association Between Resting Heart Rate and Mortality or CV Events

- Positive association with total and/or cardiovascular mortality in over 70 Studies
- Association independent of other risk factors
- Consistency similar to that for smoking
- Association present in different clinical settings
- Association still present after exclusion of first years after baseline evaluation
- Association with mortality less consistent for women

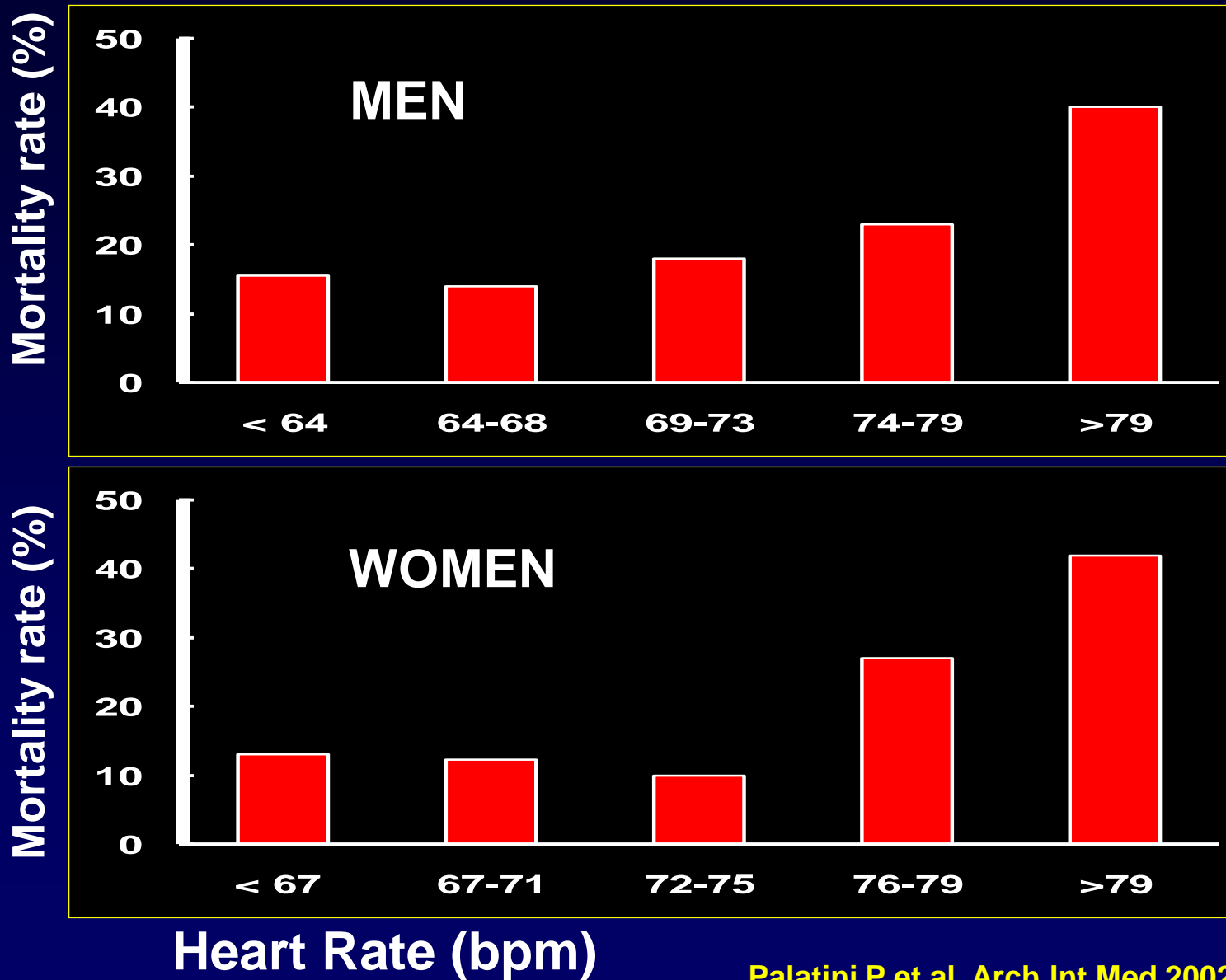
Role of elevated heart rate in the development of cardiovascular disease in Hypertension

(A review of 11 studies)

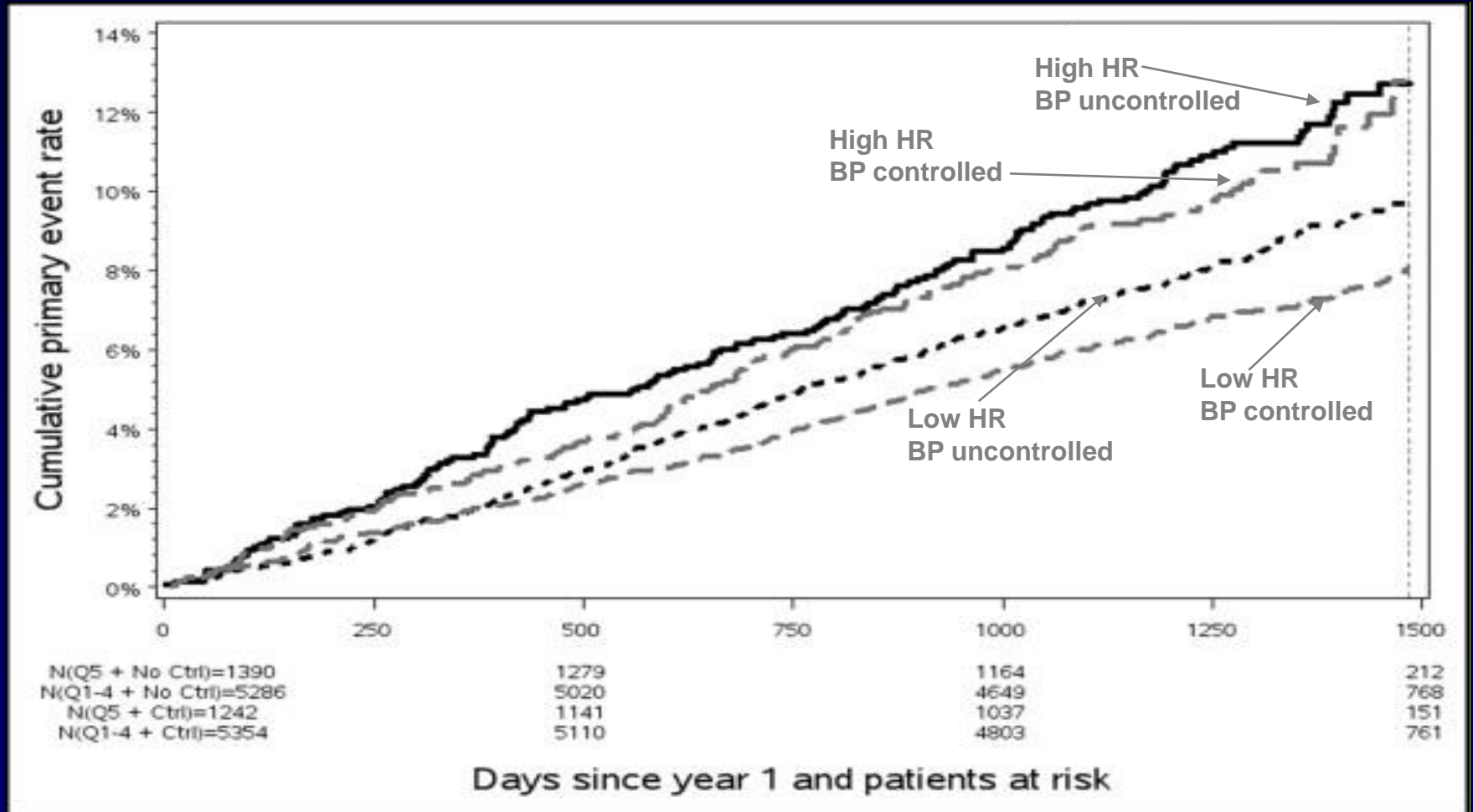
ASSOCIATION OF HEART RATE WITH MORTALITY RATE AMONG MEN WITH HYPERTENSION (The Framingham Study)



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

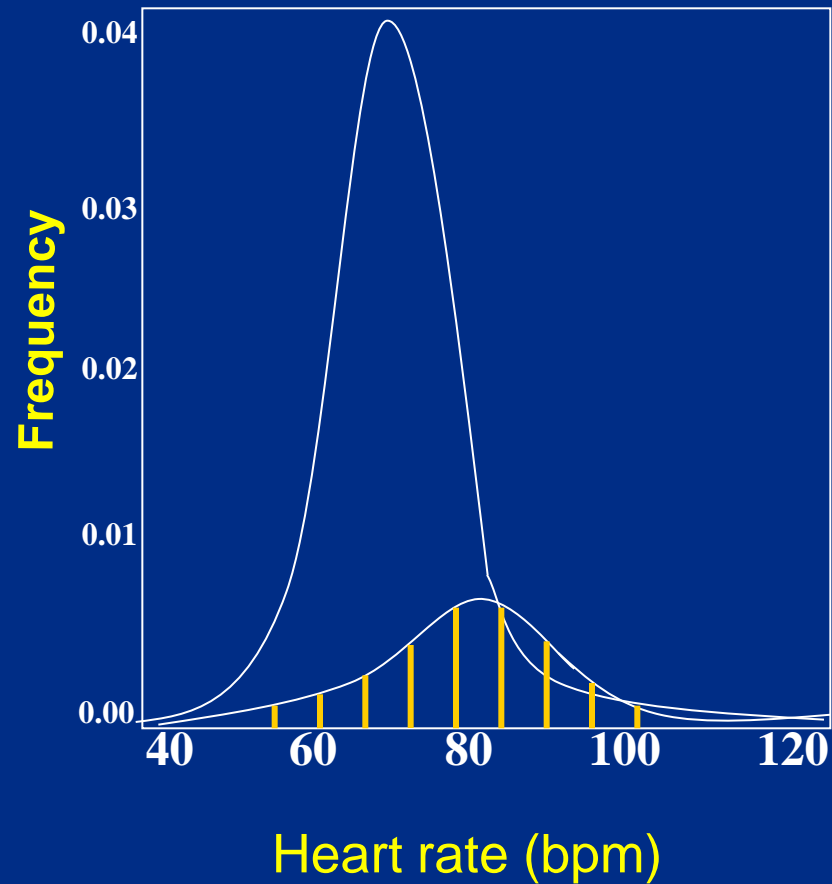
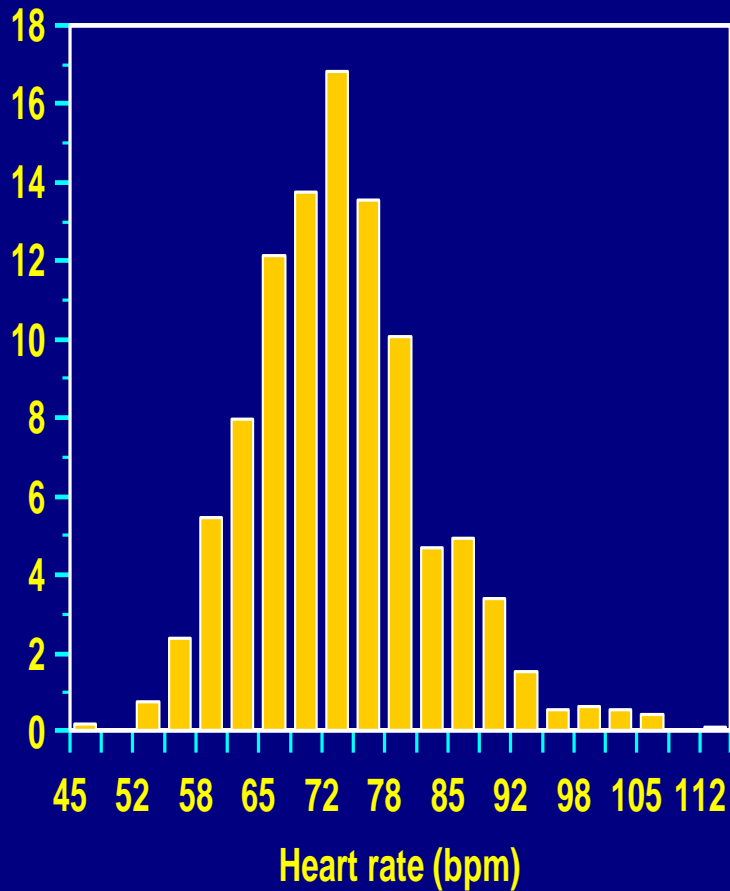


Kaplan-Meier plots of primary composite end point for high risk hypertensive patients stratified by HR quintile and BP control. The VALUE Study



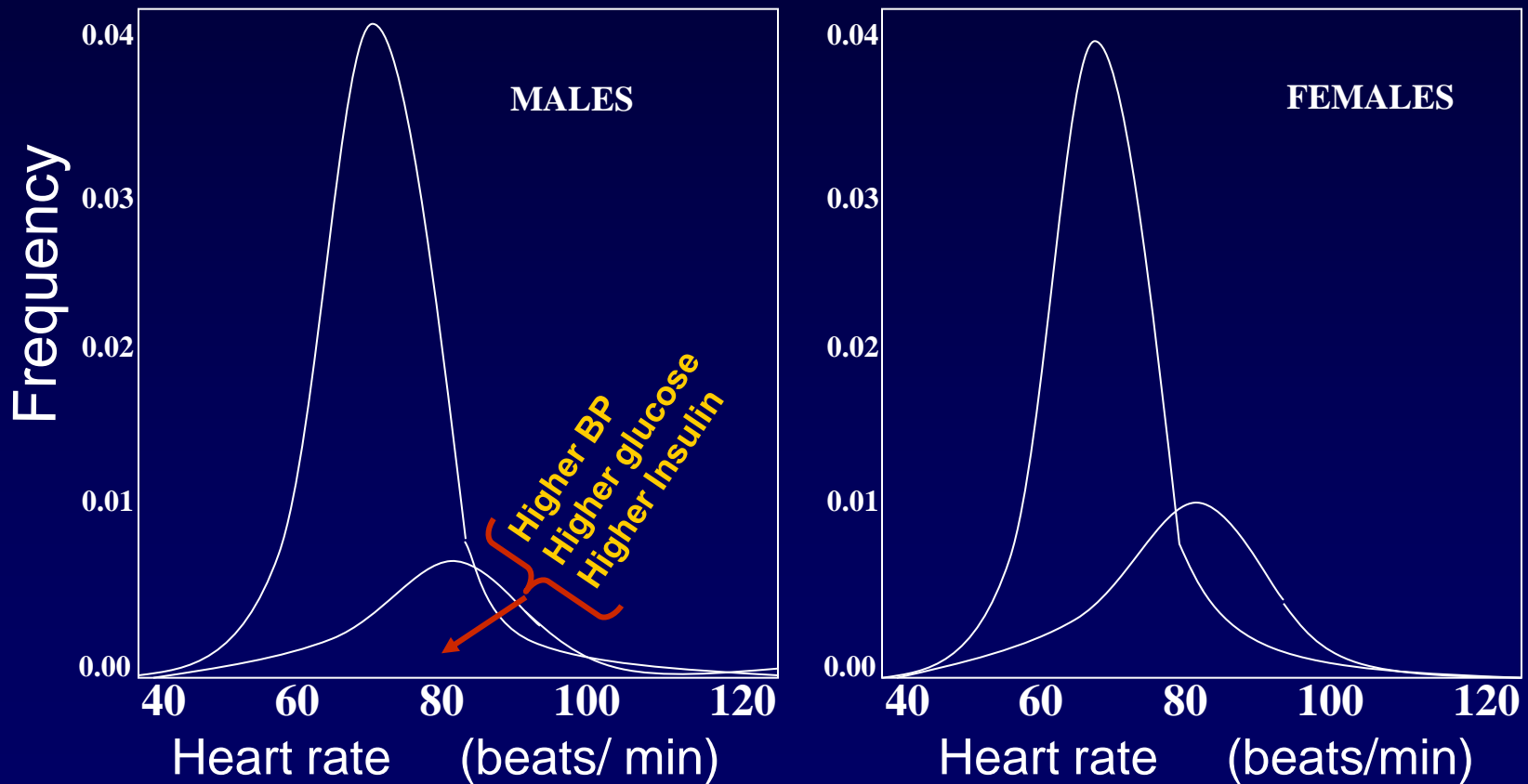
Pathogenetic Mechanisms For The Relationship Between Heart Rate And CV Risk

Heart Rate Distribution for the HARVEST Men before and after application of “Mixture Analysis”

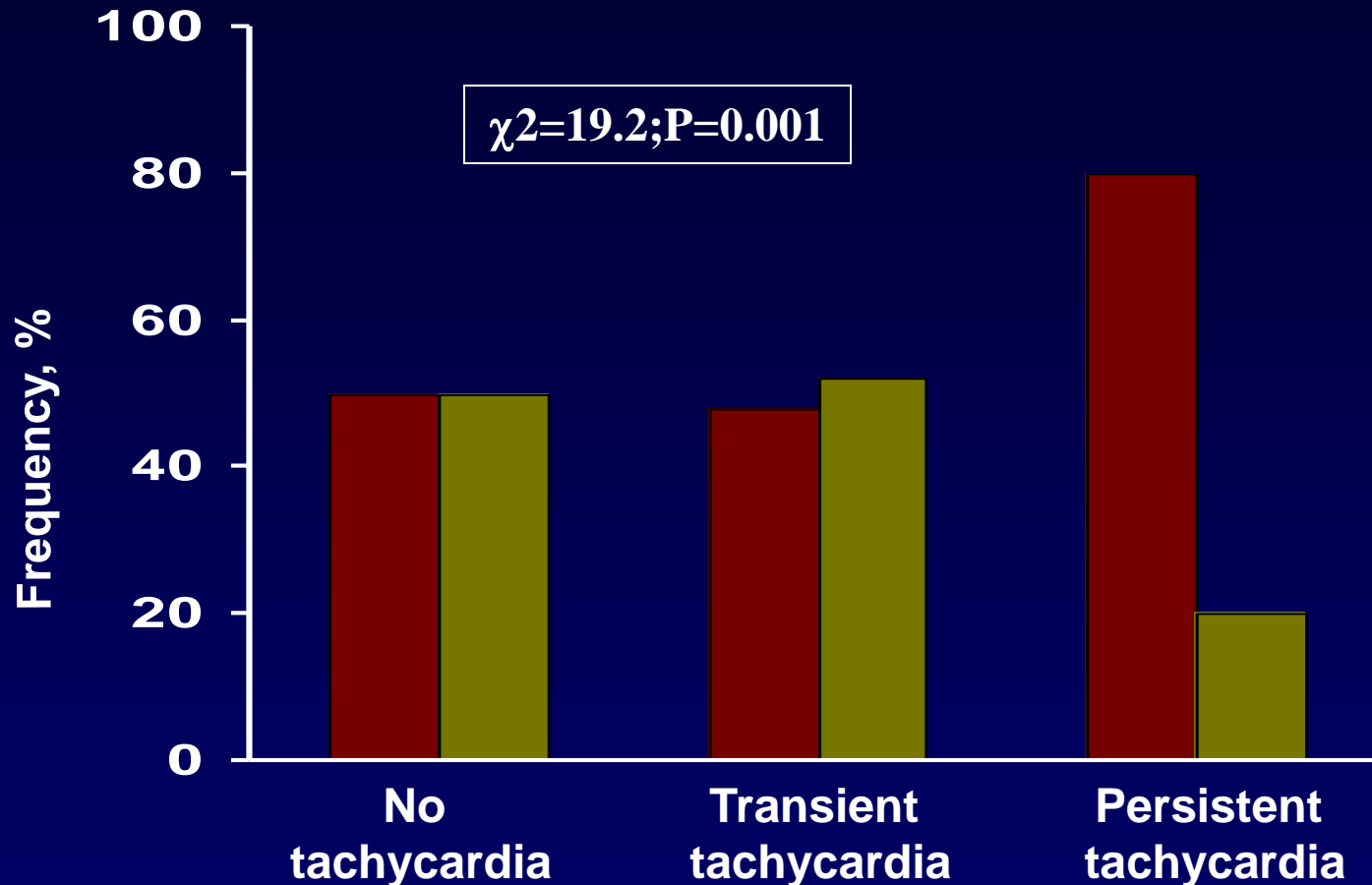


Coeff of Skewness, 0.58 ($P < 0.0001$). Coeff of Kurtosis, 0.8213 ($P = 0.0001$)
Kolmogorov-Smirnov test for Normal distribution: reject Normality ($P = 0.0027$)

Heart Rate Distribution for Two Subpopulations With "High" and "Normal" Heart Rate Identified by Mixture Analysis in Three Populations

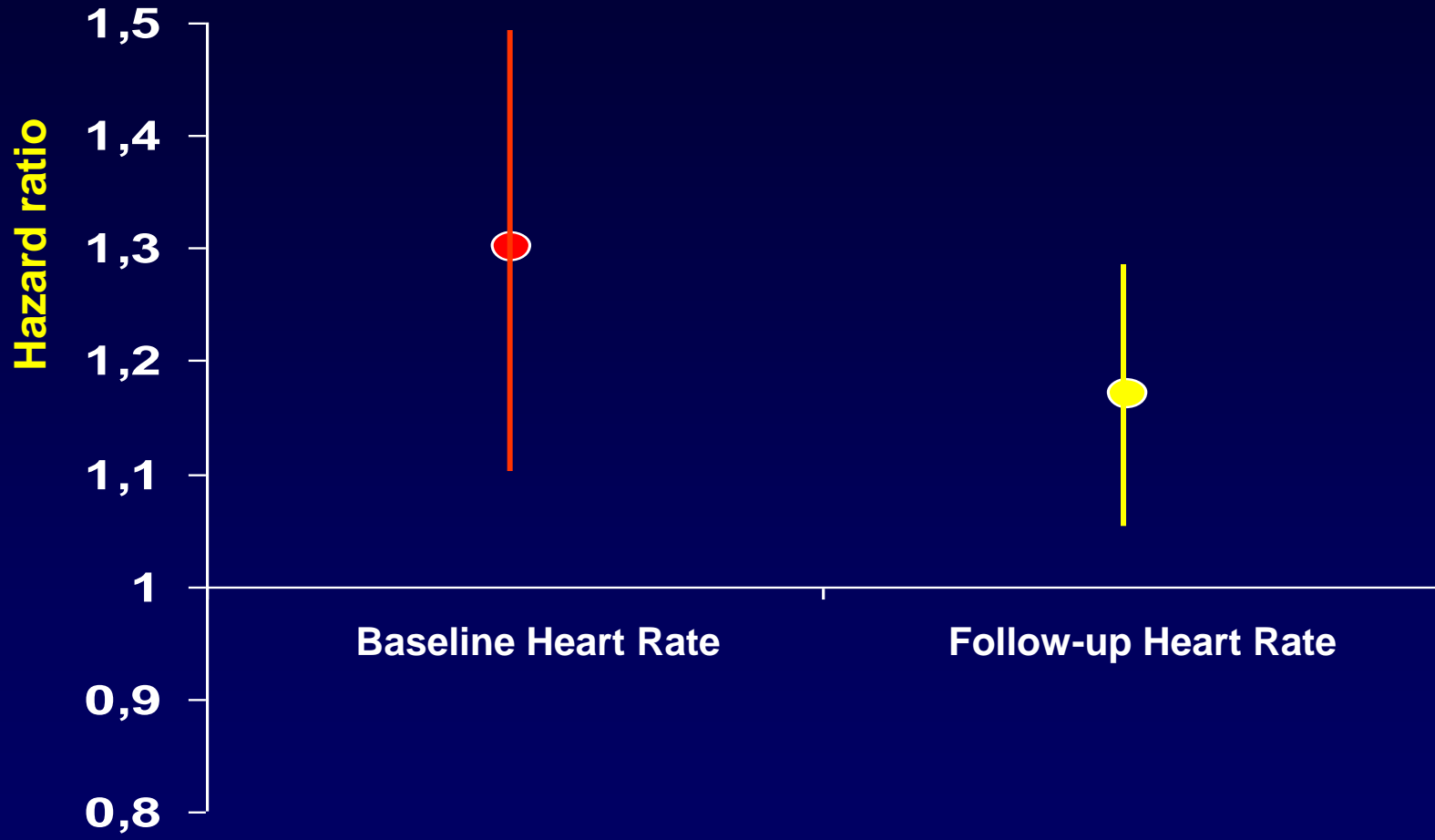


Frequency of Hypertension During a 6-year Follow-up in 1050 Stage 1 Hypertensives Divided by Heart Rate Status



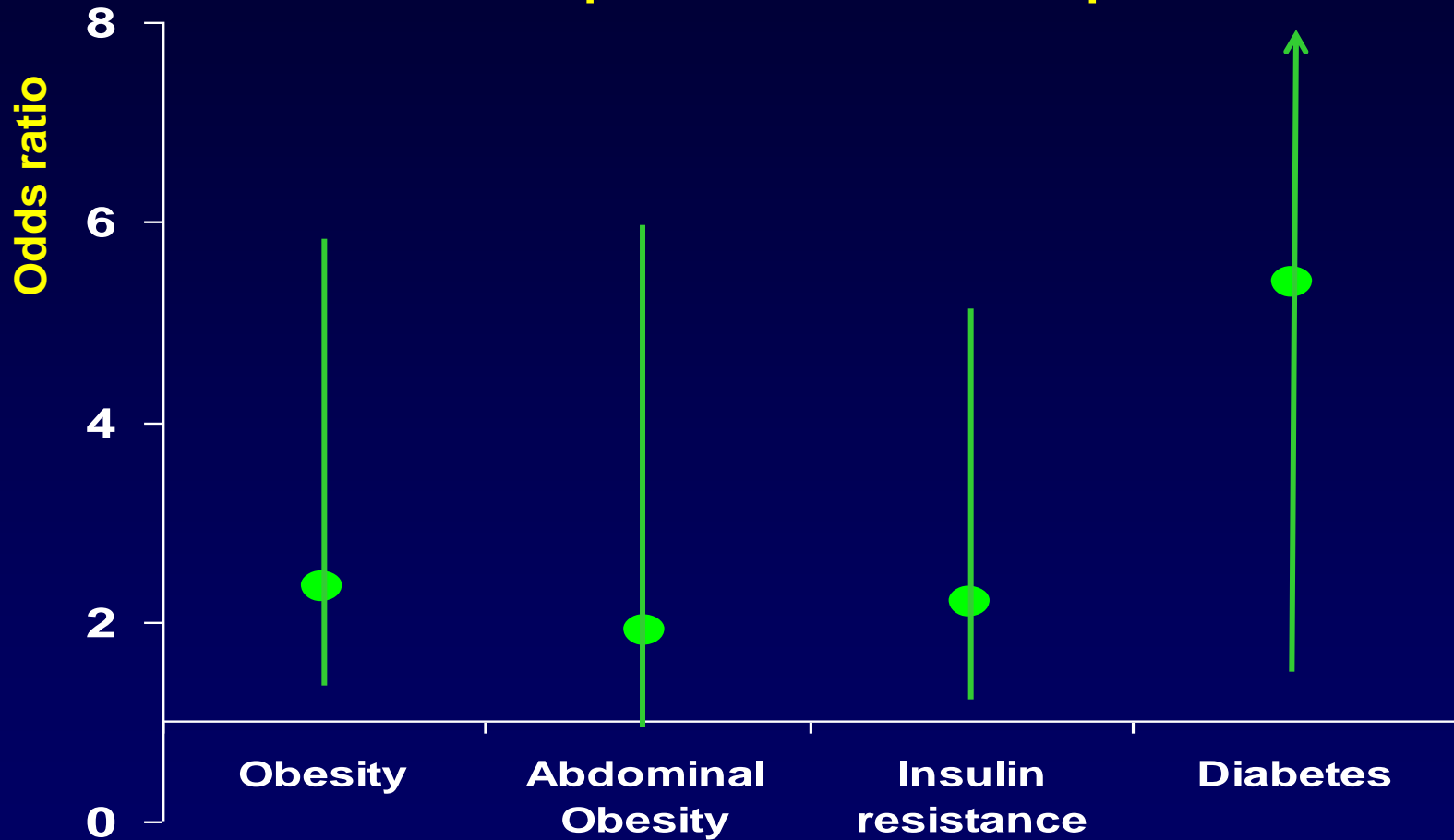
 Hypertension
 Normotension

7-year Risk Of Overweight Or Obesity Related To Heart Rate In 1008 Participants From The HARVEST*

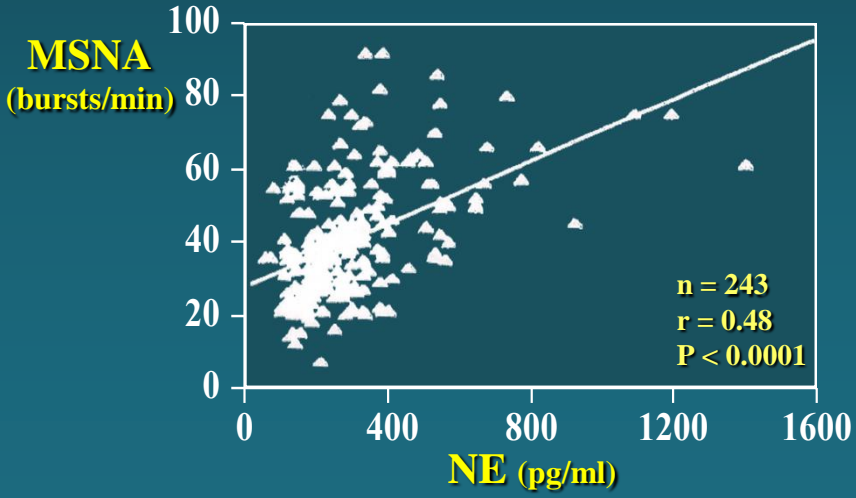
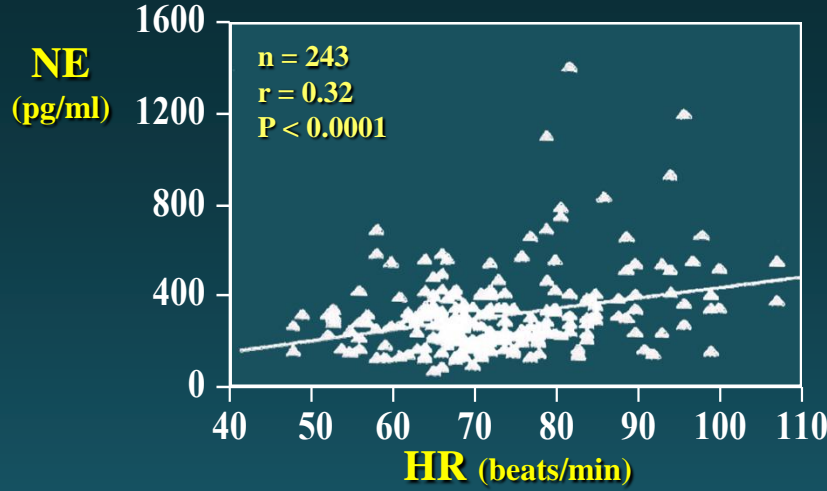
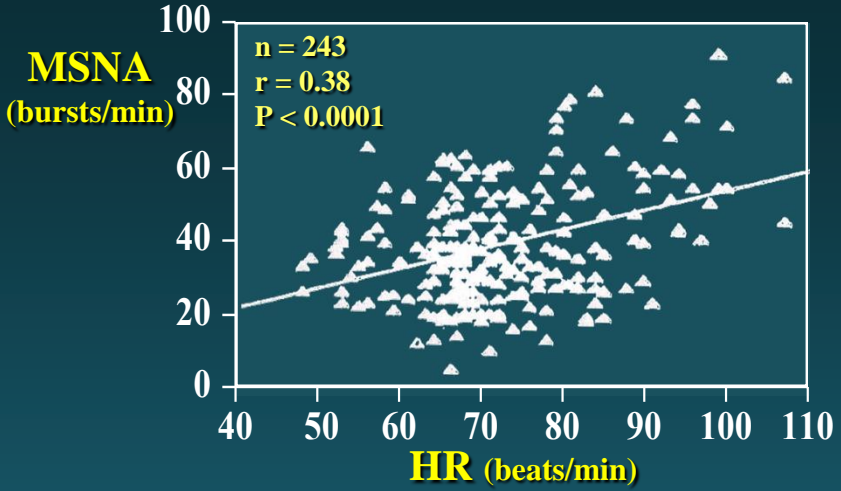


*Results of a multivariable Cox regression

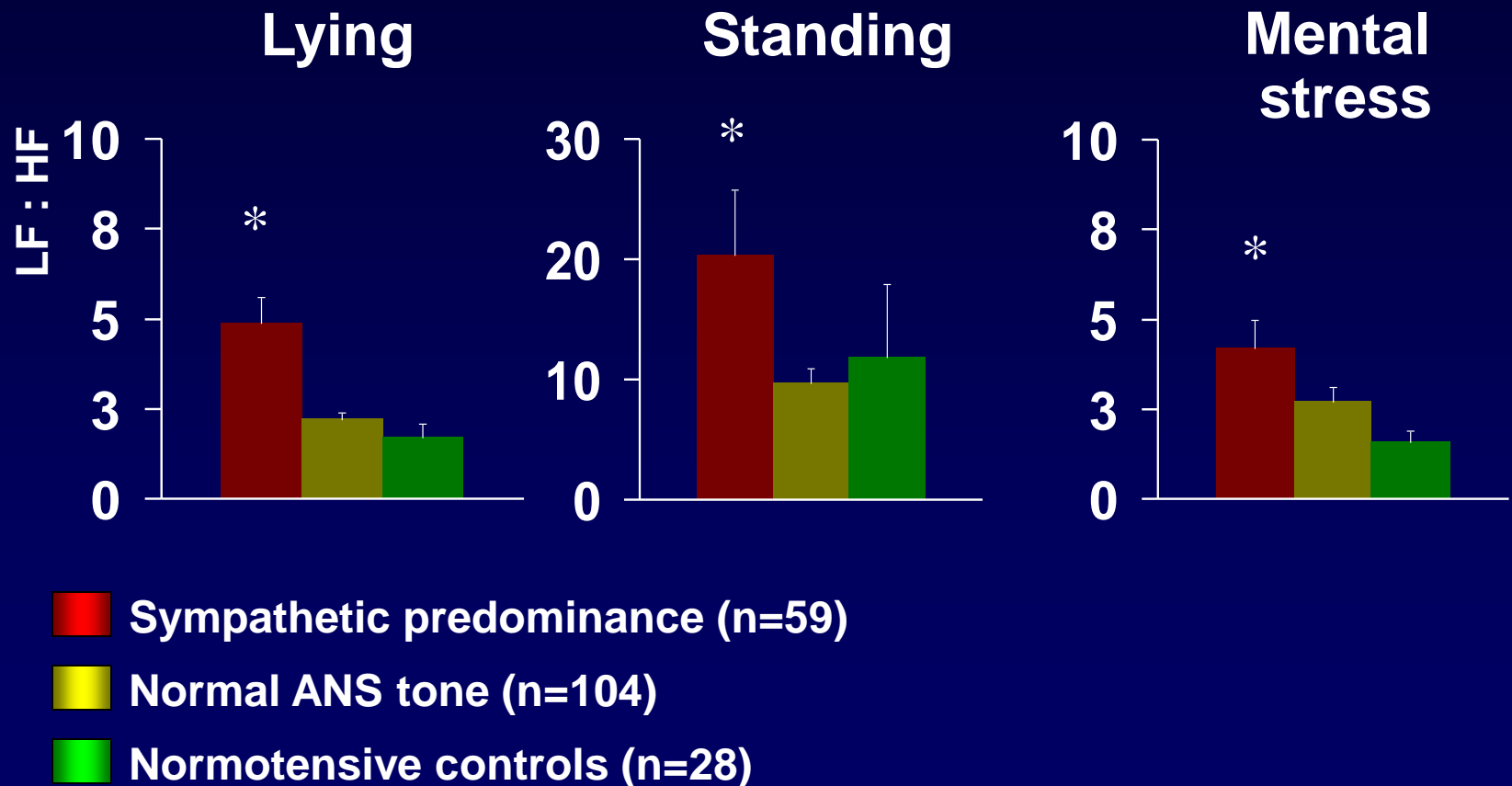
20-year Risk Of Metabolic Abnormalities For A Baseline Heart Rate ≥ 80 bpm In 637 Healthy Participants From Japan



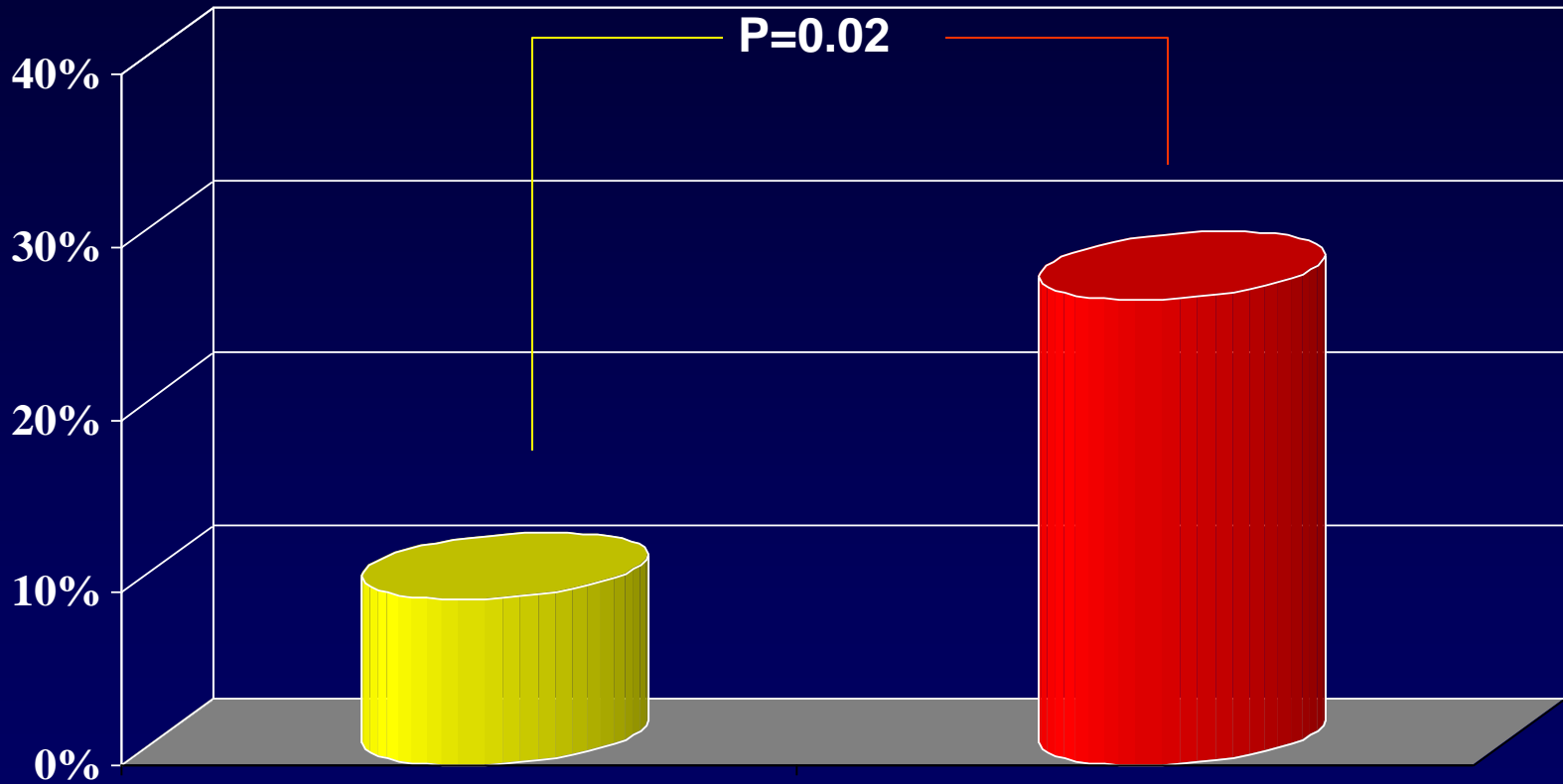
Relationships between HR, MSNA and Venous NE Values in NT, HT and CHF Patients



LF:HF Ratio in 163 Young Hypertensive Subjects from the HARVEST and 28 Normotensive Controls



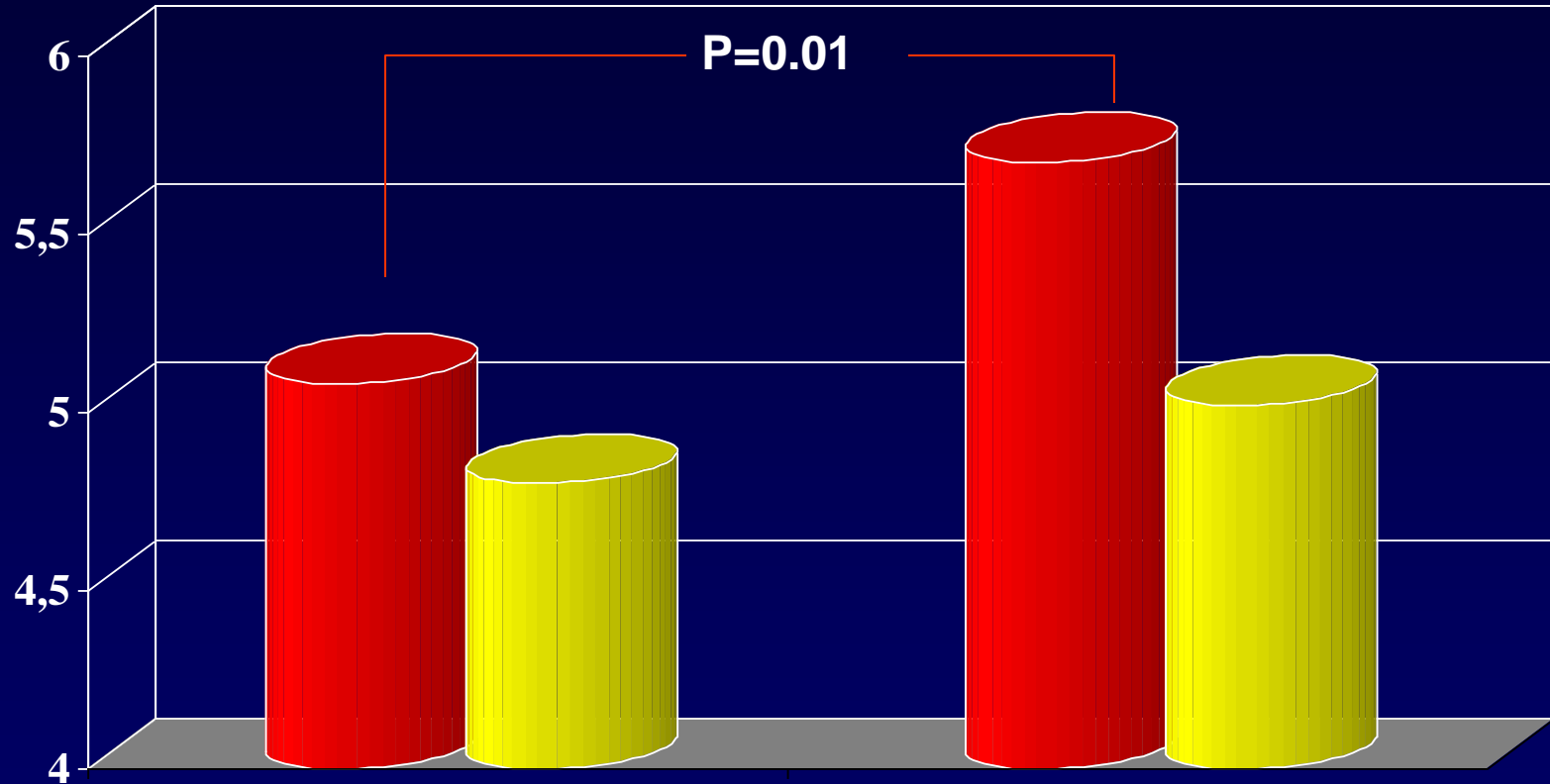
Frequency of Hypertension According to Autonomic Nervous System Activity in the HARVEST 6-year Follow-up in 163 Subjects



 Subjects with normal ANS activity

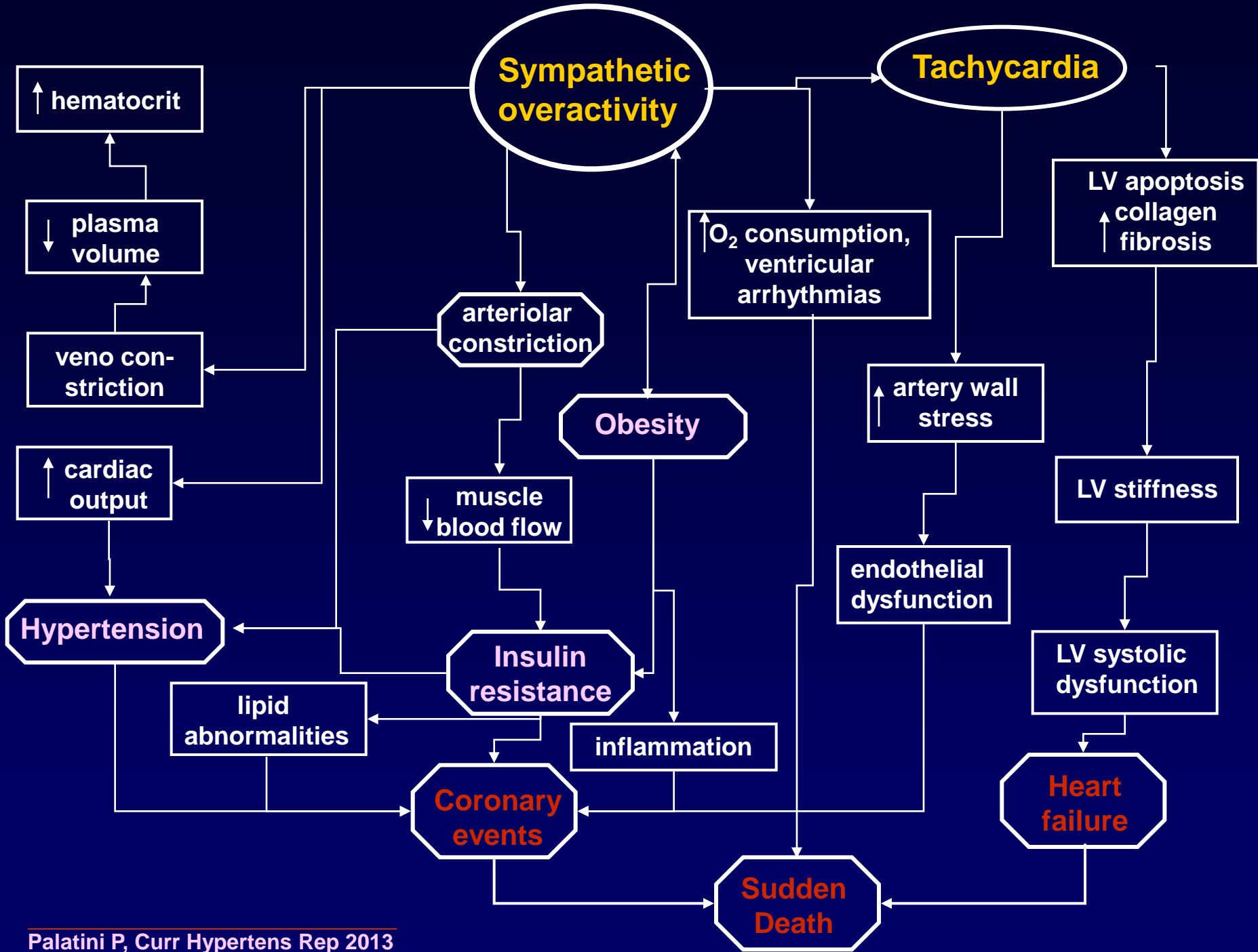
 Subjects with sympathetic predominance

Evolution of Cholesterol According to Autonomic Nervous System Activity in the HARVEST 6-year Follow-up in 163 Subjects

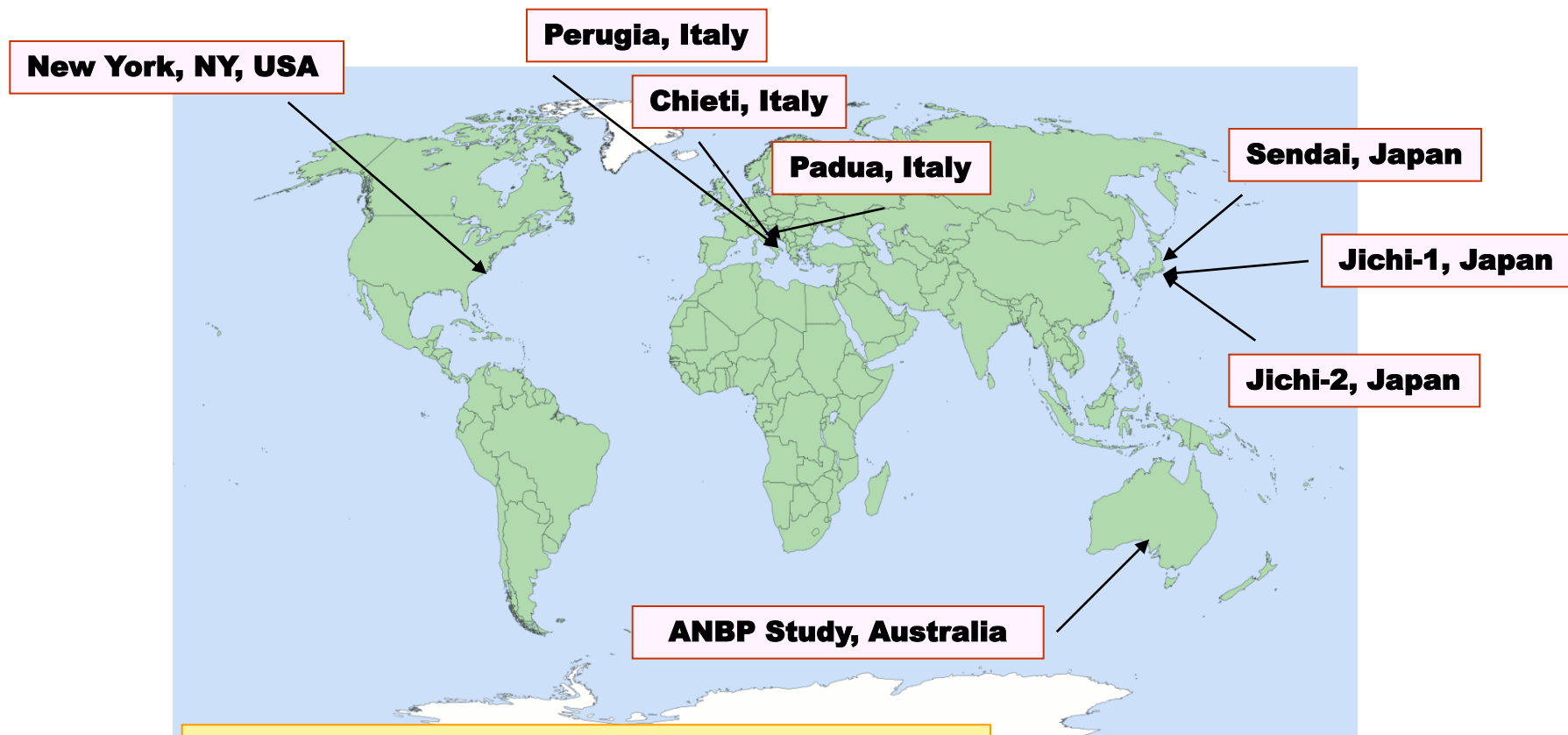


 Subjects with normal ANS activity

 Subjects with sympathetic predominance



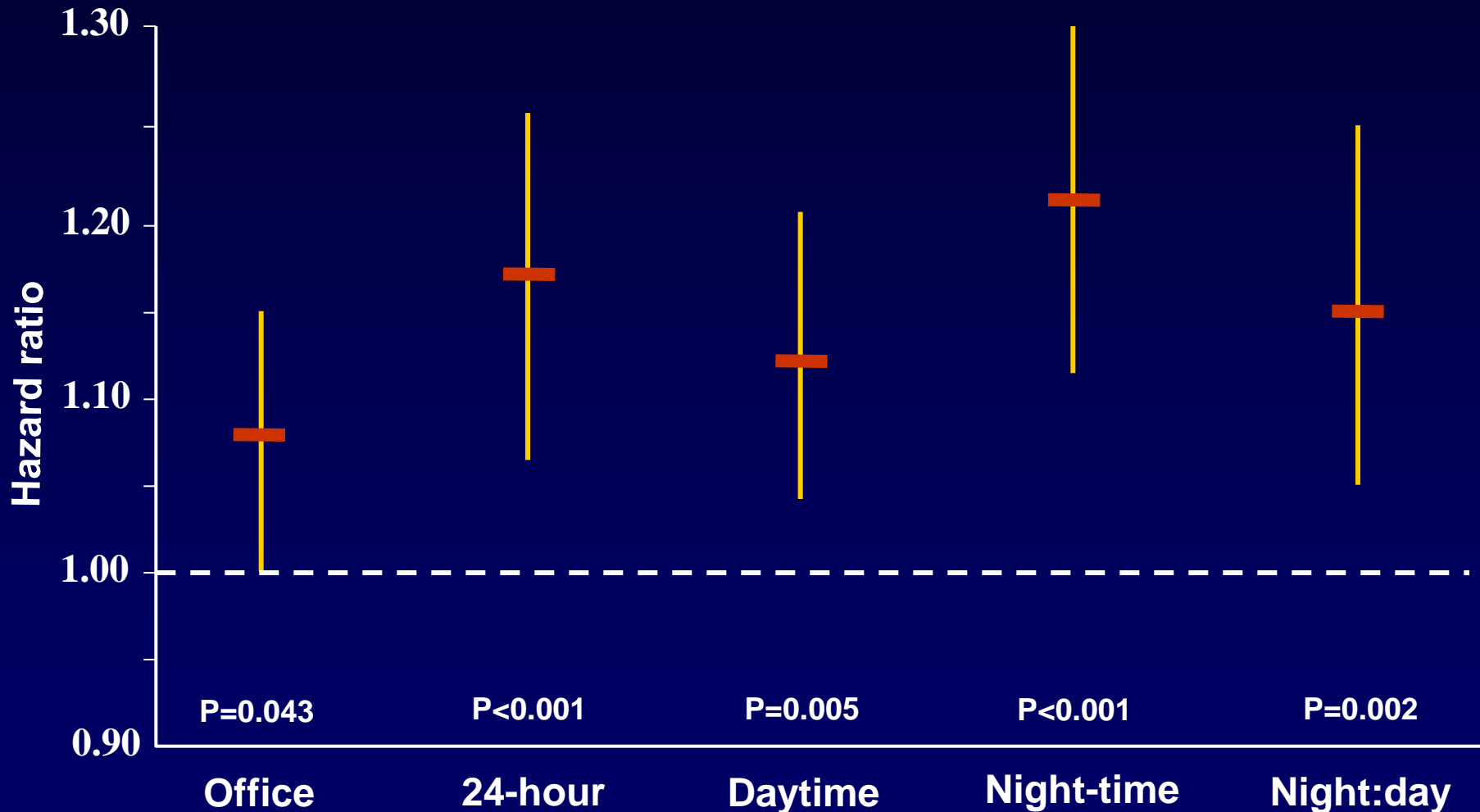
Ambulatory Blood Pressure in referred hypertensive patients: an INTERNATIONAL database (ABP- INTERNATIONAL, N = 11,235)



| | |
|-------------------------------------|--------|
| Ohasama Study, Sendai | n=1277 |
| Jichi Medical School - 1 | n=762 |
| Jichi Medical School - 2 | n=379 |
| New York Prognostic Effects of ABPM | n=1296 |
| Perugia, PIUMA study | n=3345 |
| Chieti | n=2254 |
| Padua, HARVEST Study | n=1209 |
| Australian National BP Study | n=713 |

Palatini P et al, Int J Cardiol 2103,
Feb 7 [Epub ahead of print]

HRs And 95% CIs of CVE for a 10 bpm Increment In age-and-sex adjusted Heart Rates Or a 10% Increment in the Night:Day Ratio*



*Adjusted also for average 24h heart rate

Palatini P et al, Int J Cardiol 2103, Feb 7 [Epub ahead of print]

The Cooper Clinic Mortality Risk Index

Clinical Score Sheet for Men

- Age (years)**

| | | | | | | |
|-------|-------|-------|-------|-------|-------|--------|
| 20-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | |
| 0 | 3 | 6 | 8 | 9 | 10 | points |
- Heart rate (bpm)**

| | | |
|-----|-----|--------|
| <80 | ≥80 | |
| 0 | 2 | points |
- Blood pressure (mmHg)**

| | | |
|---------|---------|--------|
| <140/90 | ≥140/90 | |
| 0 | 2 | points |
- Diabetes**

| | | |
|-----|----|--------|
| yes | no | |
| 0 | 4 | points |
- Smoking**

| | | | |
|-------|--------|---------|--------|
| never | former | current | |
| 0 | 1 | 4 | points |
- Body mass index (Kg/m²)**

| | | |
|-----|-----|--------|
| <35 | ≥35 | |
| 0 | 3 | points |
- Cardiorespiratory fitness (VO² Max)**

| | | | |
|-----|----------|------|--------|
| low | moderate | high | |
| 2 | 0 | 0 | points |

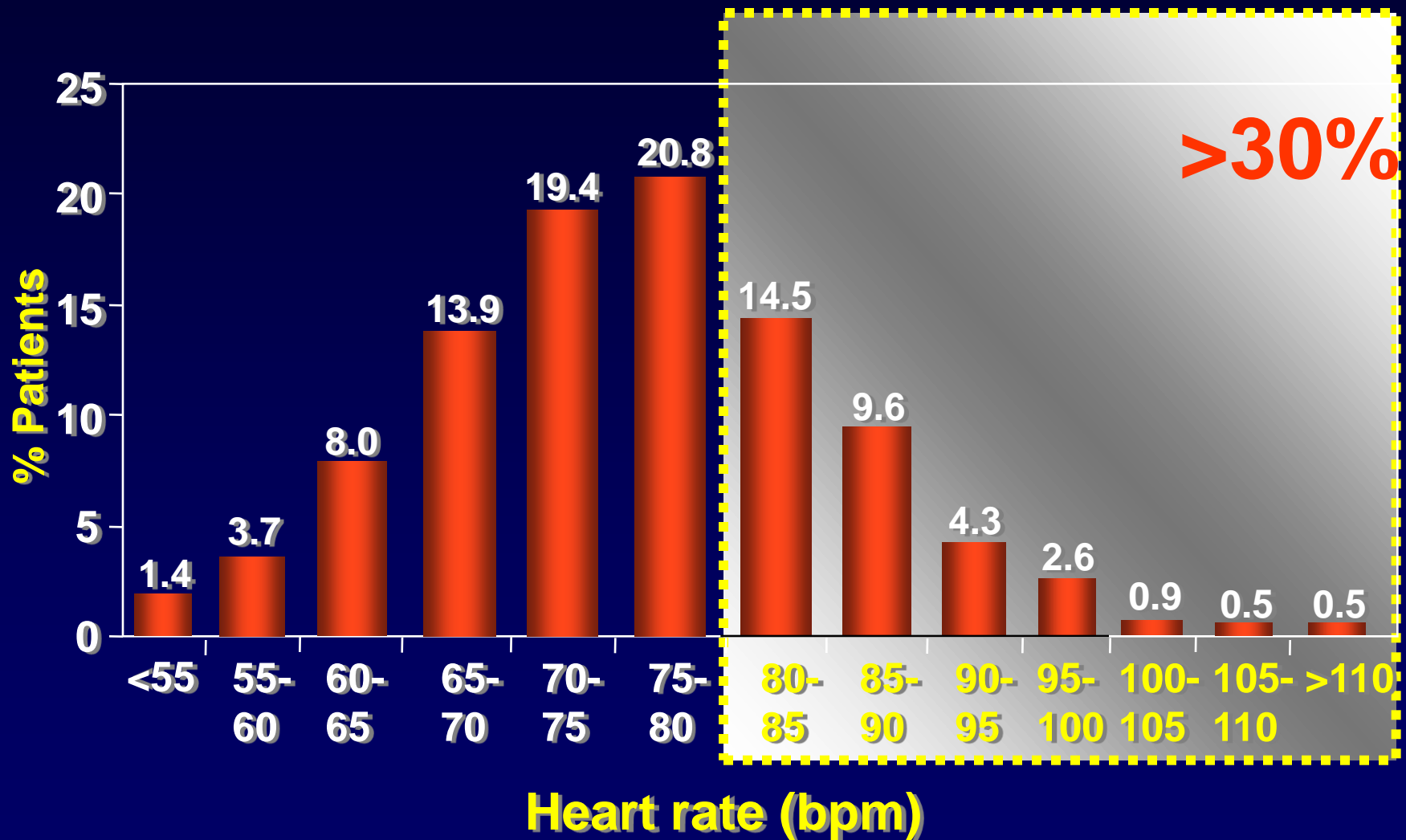
2013 ESH/ESC Guidelines for the management of arterial hypertension

BP measurements should **always be associated with measurement of heart rate**, because resting heart rate values independently predict CV morbid or fatal events in several conditions, including hypertension [62,63]

*Heart Rate reduction in
Hypertension.*

*An additional goal in
antihypertensive treatment?*

Heart Rate Distribution in Subjects With Hypertension (n=38,145)



Action of Antihypertensive Agents on Heart Rate

Diuretics

=↑

Beta-blockers

↓↓

Vasodilators

↑↑

Ca-A { **Dihydropyridines**
Phenylalkylamines
Benzothiazepines

↑=↓

↓

↓

ACE inhibitors

=

All receptor blockers

=

Centrally acting drugs

↓

Imidazoline receptor agonists

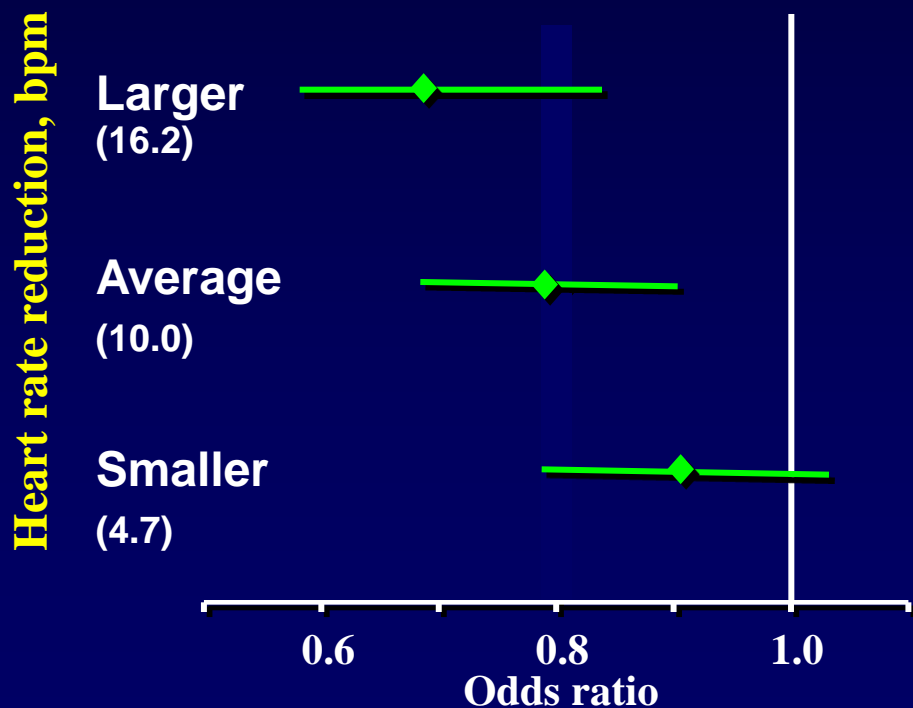
=↓

Relationship between tertile of Heart rate reduction and effect of treatment on mortality in AMI.

A meta-regression of randomized clinical trials

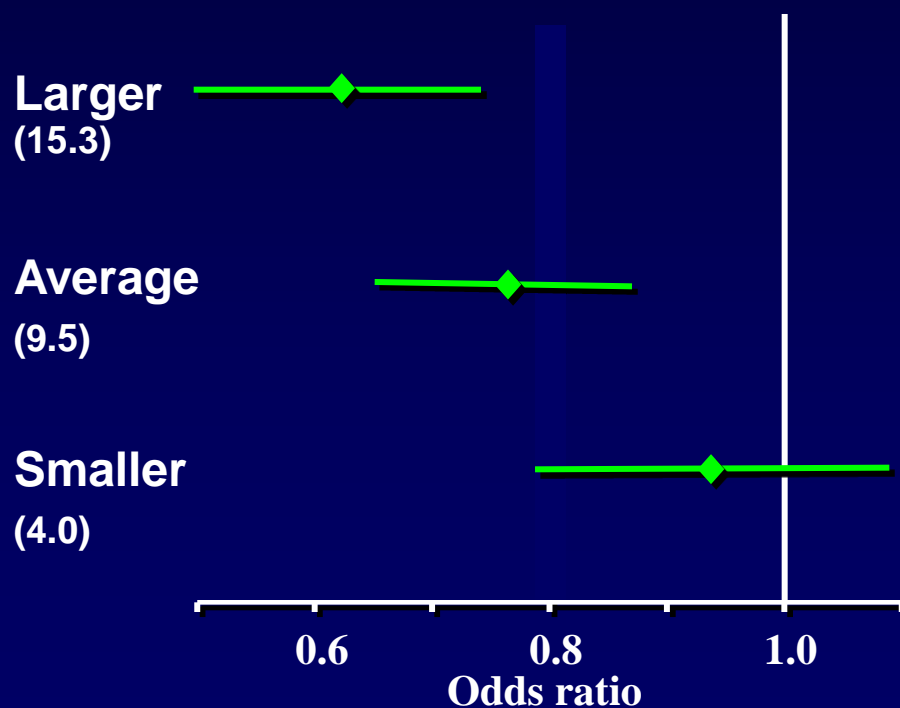
All-cause death

P for trend = 0.017

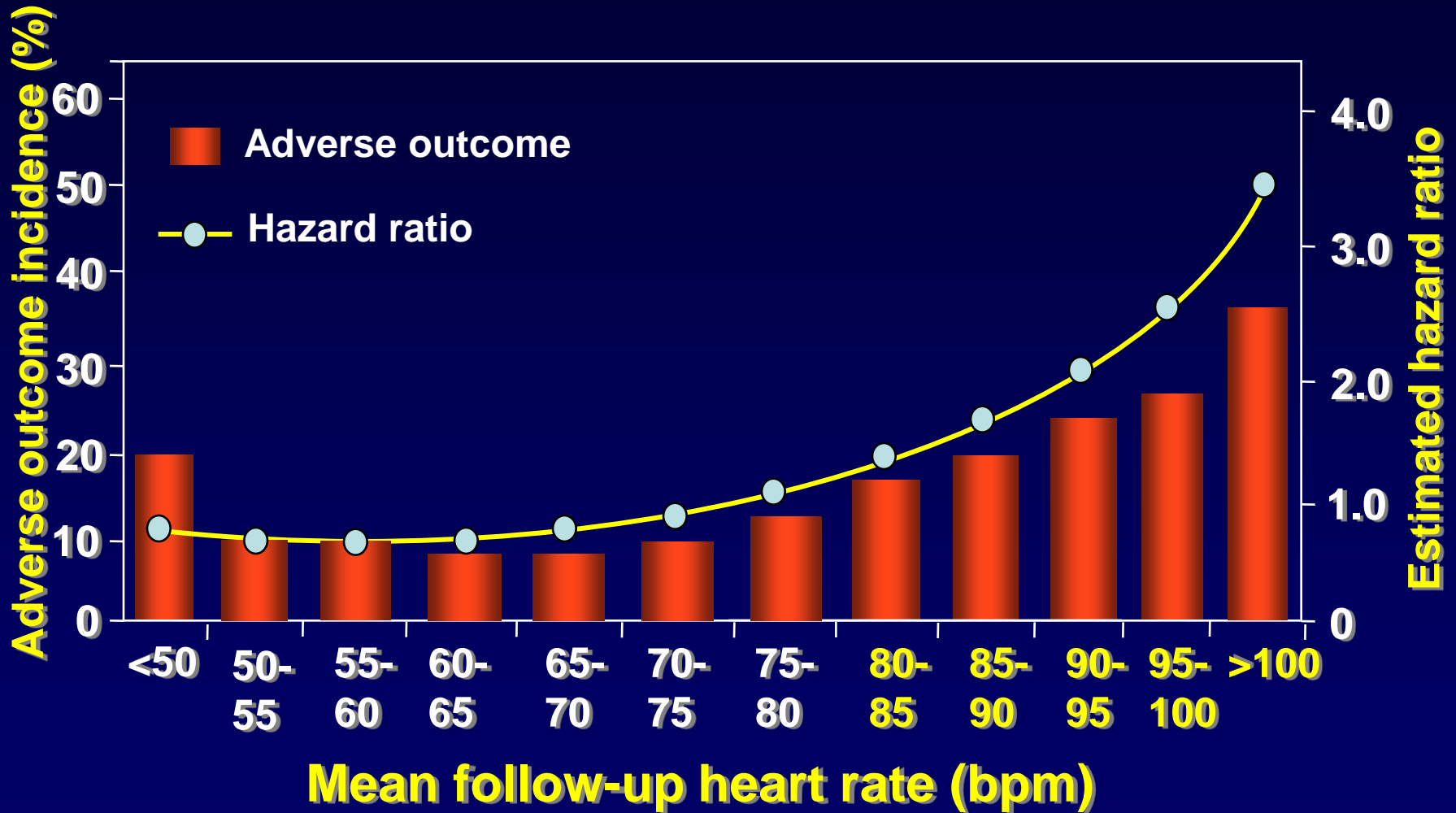


Cardiac death

P for trend = 0.0015

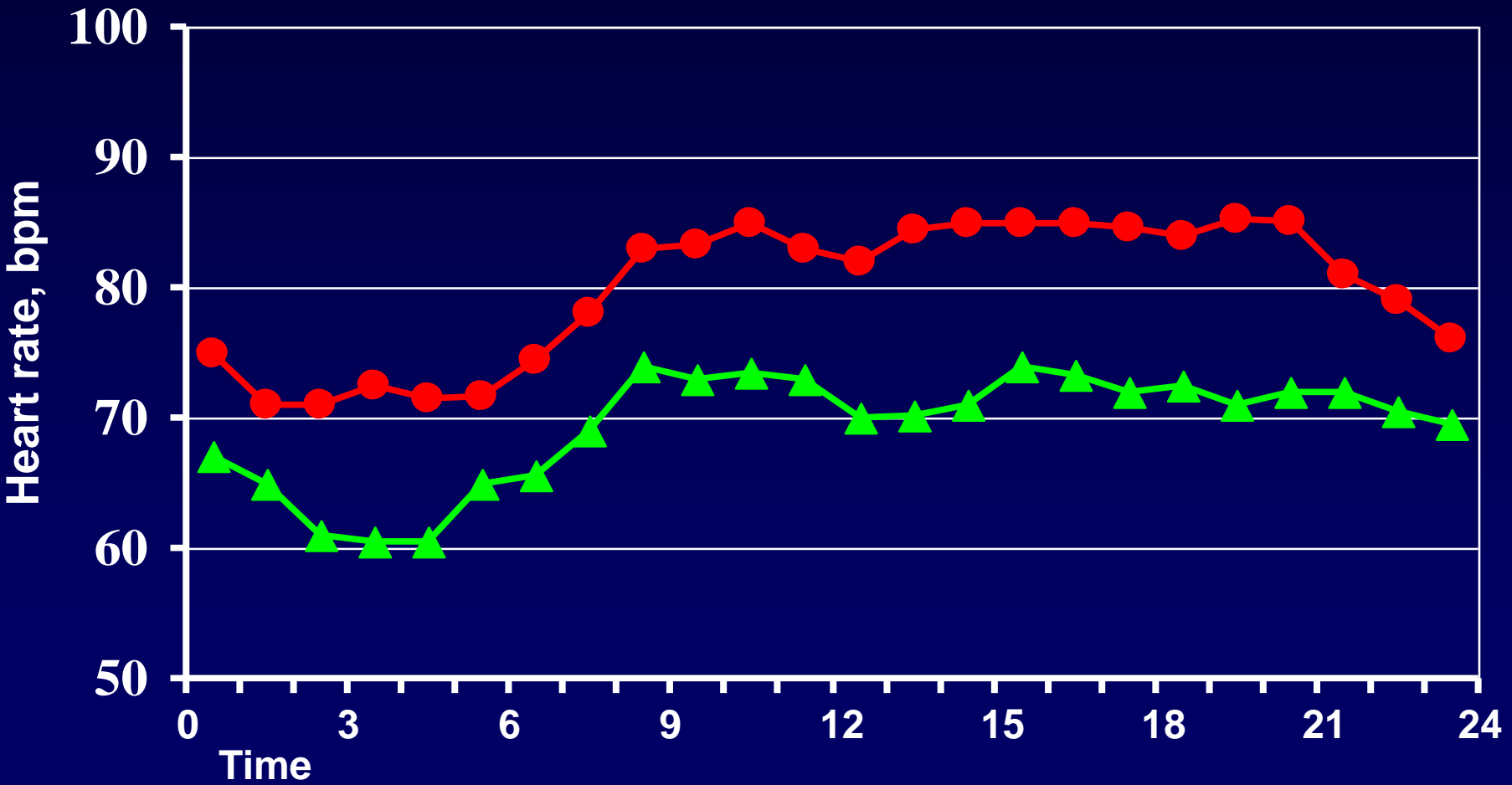


Relationship Between Follow-up Heart Rate And Outcome In The INVEST Study



Effect of Low-Dose Bisoprolol on 24-Hour Heart Rate in Patients with Dilated Cardiomyopathy

● Baseline ▲ Bisoprolol



Adapted from Anthonio RL et al, Am J Cardiol 1999;83:1286

The role of fixed-dose combination therapy in the management of hypertension

Prof. Davor Miličić

Department of Cardiovascular Diseases

University of Zagreb

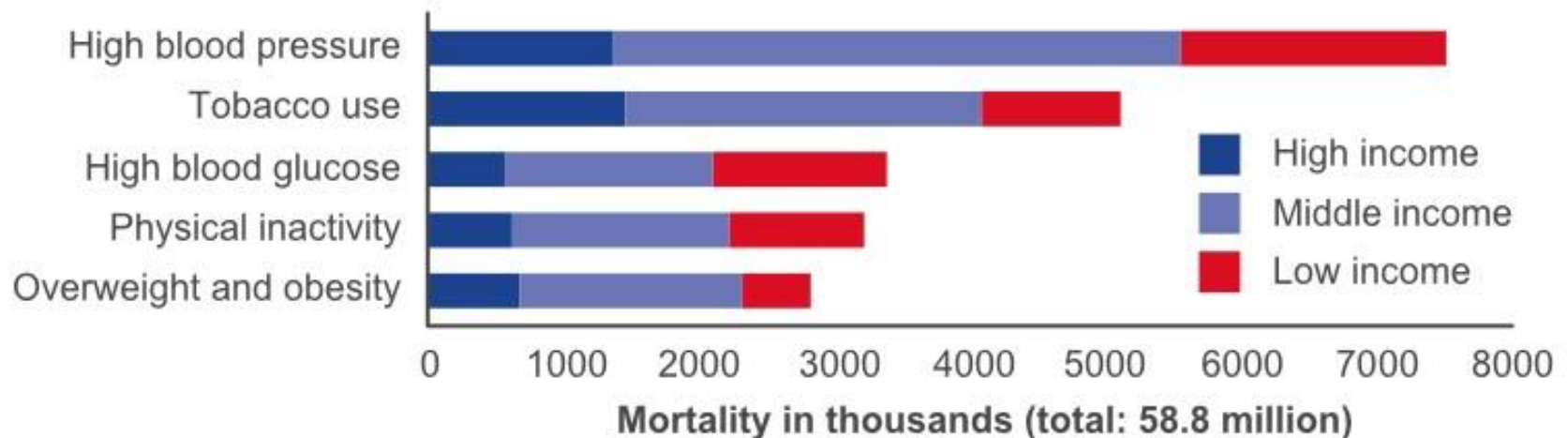
Croatia

Global burden of hypertension

- Hypertension is the primary major cause of premature death
- 972 million with hypertension estimated in 2000 predicted to rise to 1.56 billion by 2025
- 80% increase in hypertension expected in economically developing regions

WHO findings on hypertension

- The #1 global risk factor for premature mortality causing 7.5 million deaths per annum
- Responsible for 51% of stroke and 45% of ischaemic heart disease deaths



Management of hypertension today

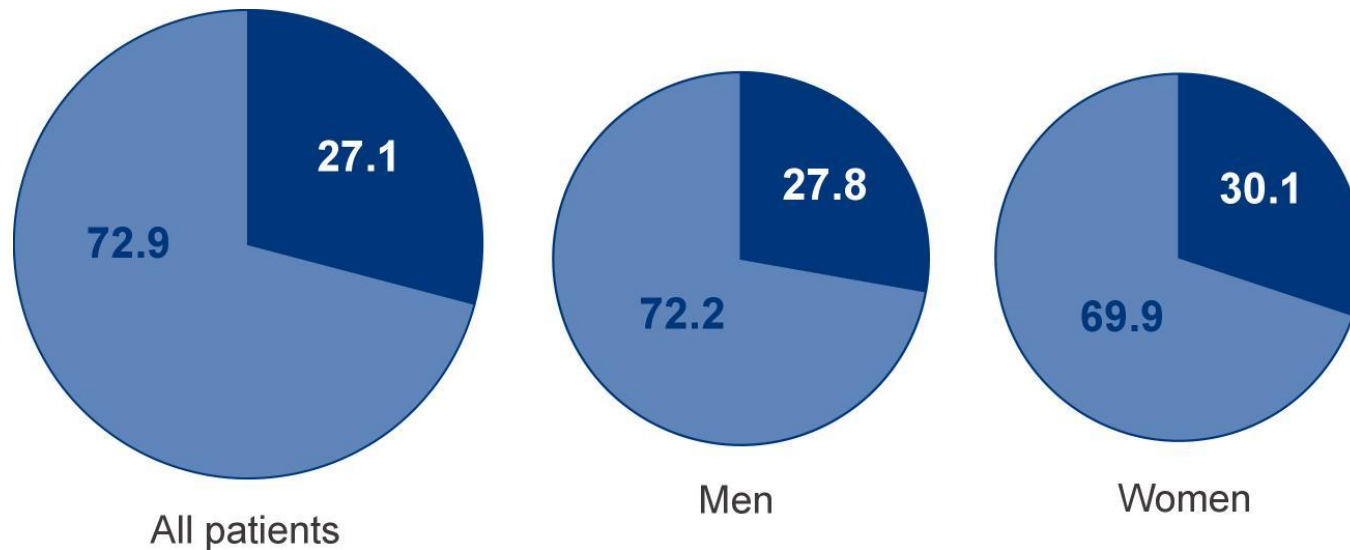
- The most common CV disorder affecting 27-55% of adults¹
- A major risk factor for CV and renal disease^{1,2}
- Level of protection achieved against CV diseases is related to the degree of BP reduction²
- However, only 20-55% of treated patients achieve and maintain internationally recognised targets^{1,2}

1. Wolf-Maier K *et al.* *Hypertension* 2004;**43**:10-17.

2. Struijker-Boudier H *et al.* *Int J Clin Pract* 2007;**61**:1592-602.

Poor BP control in practice populations¹

Cross-sectional survey of 5413 hypertensive patients in Denmark¹



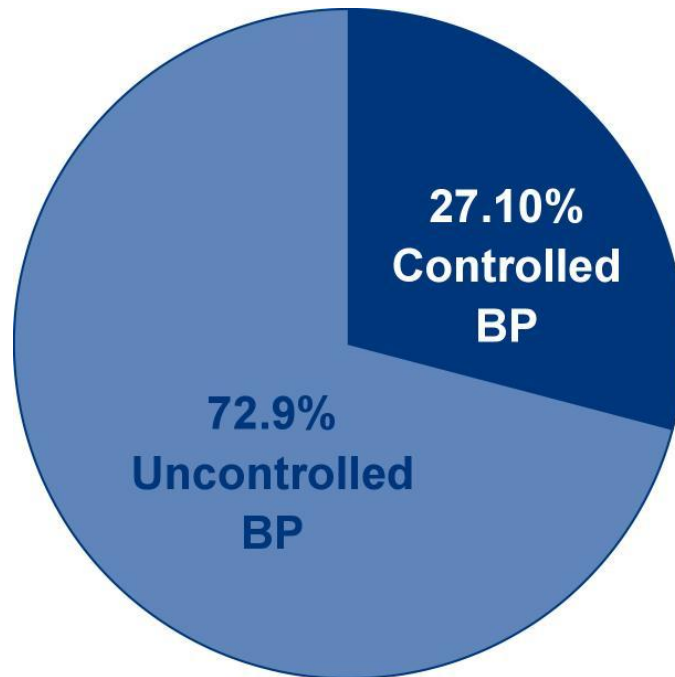
“Approximately 7 out of 10 hypertensive patients in Europe do not achieve target BP”²

■ Controlled BP
■ Uncontrolled BP

1. Paulsen M *et al.* *Family Practice* 2011; published online, May 19, 2011
2. Burnier M *et al.* *Int J Clin Pract* 2009;**63**:790-8.

Most treated patients in Eastern Europe do not achieve target BP

7,860 treated patients in the BP-CARE survey in Central and Eastern Europe (9 countries)



% of patients displaying office BP controlled (<140/90 mmHg) or uncontrolled \geq 140/90 mmHg)

Causes of inadequate BP control

| Patient/society | Misdiagnosis | Doctor |
|--|---------------------------------|--|
| Poverty, lack of health insurance | Improper BP recording technique | Physician inertia, poor motivation to deliver patient education |
| Lack of education, health beliefs | White coat syndrome | Multiple guidelines |
| Difficulty in implementing lifestyle change | Masked hypertension | Insufficient use of multiple agents or insufficient dosing |
| Compliance issues relating to cost, side-effects, inconvenience, pill burden | | Failure to identify secondary hypertension Authentic resistant hypertension |
| | | Interactions with other prescribed medication |

Adapted from Elijevich F *et al. Ther Adv Cardiovasc Dis* 2009;**3**:231-40.

Inadequate BP control is associated with increased risk of fatal events

| n=5128 Fully adjusted models § | Hazard ratio (95% CI) | |
|-----------------------------------|-----------------------|-----------------------|
| | Hypertension category | Hazard ratio (95% CI) |
| | All-cause mortality | CVD mortality |
| Treated controlled | 1.00 | 1.00 |
| Treated uncontrolled | 1.57 (1.28-1.91)* | 1.74 (1.36-2.22)* |
| Untreated | 1.34 (1.12-1.62)* | 1.37 (1.04-1.81)** |

Risk of CVD mortality increased by 74% in uncontrolled hypertensives ¹

Data from NHANES III in US hypertensive adults (1988-2006)

§ adjusted for age, race/ethnicity, smoking, hypercholesterolaemia, obesity, diabetes, CKD, HF, stroke

* p<0.01; ** p<0.05

1. Gu Q *et al. Am J Hypertens* 2010;**23**:38-45.

Multiple therapies are required to achieve target BP¹

| | Number of drugs needed to achieve BP 140/90 mmHg | | | | |
|--------------------|--|-------|-------|-------|-------|
| Patients | 1 | 2 | 3 | 4 | 5 + |
| Men (all ages) n | 333 | 400 | 408 | 248 | 104 |
| Men (all ages) % | 22.3% | 26.8% | 27.3% | 16.6% | 7.0% |
| Women (all ages) n | 154 | 263 | 387 | 317 | 219 |
| Women (all ages) % | 11.5% | 19.6% | 28.9% | 23.7% | 16.3% |

Evidence has continued to grow that in the vast majority of hypertensive patients, effective BP control can only be achieved by combination of at least two antihypertensive drugs ³

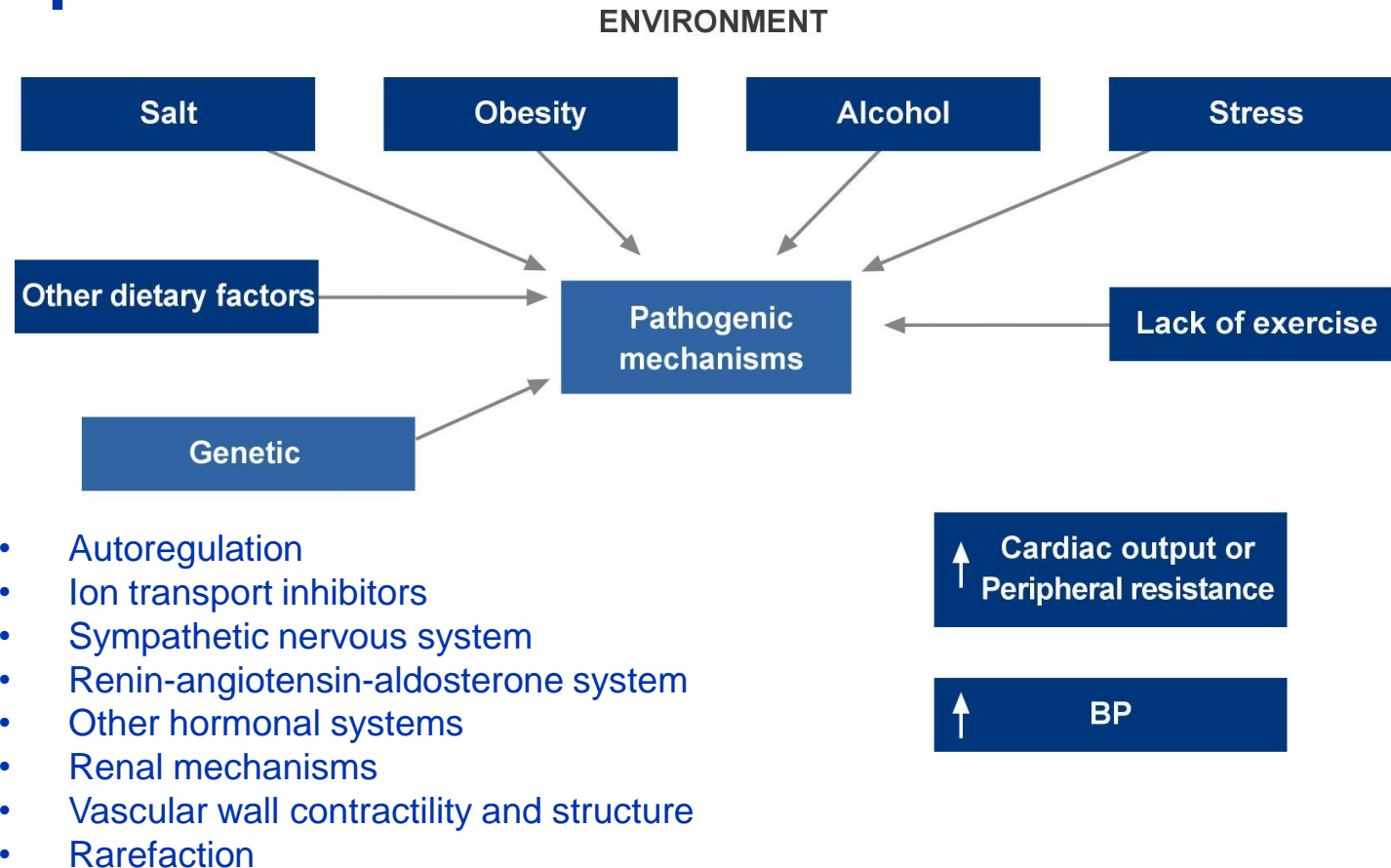
≥75% of patients require multiple therapies to achieve target ²

1. Adapted from Marshall T. *J Hum Hypertens* 2005;**19**:317-9.

2. Gradman A *et al. J Am Soc Hypertens* 2010;**4**:42-50.

3. Mancia *et al. J Hypertens* 2009; **27**:2121-58

Pathophysiology of essential hypertension: multiple causes



Rationale for combination therapy:¹

- Combines drugs acting in different physiological systems¹
- Blocks counter-regulatory responses¹
- Treats moderate/severe hypertension¹
- Reduces BP variability vs monotherapy^{1,3}

**>75% of patients require combination therapy
to achieve BP target²**

1. Sever P, Messerli FH. *Eur Heart J* 2011;**32**:2499-506.
2. Gradman A *et al.* *J Am Soc Hypertens* 2010;**4**:42-50.
3. Rothwell P *et al.* *Lancet* 2010;**375**:895-905.

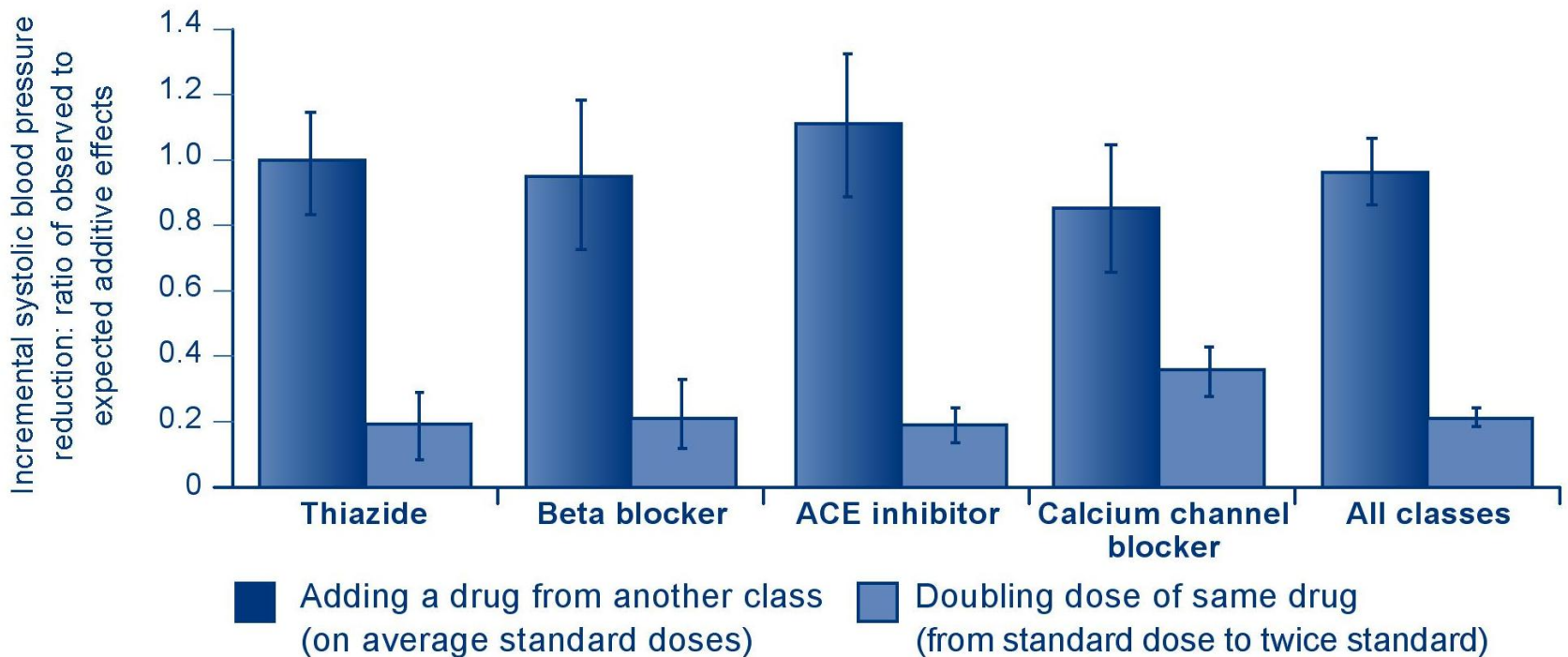
Criteria for an optimal fixed dose combination¹

- Component drugs should act via different and complementary mechanisms
- BP-decreasing effect of combination is greater than that of components alone
- Incidence of side-effects should be reduced or at least not increased
- Combination should be efficacious in once-daily treatment
- Combination should provide protection against target organ damage

Combination therapy is recommended in ESH/ESC guidelines²

1. Struijker-Boudier H *et al. Int J Clin Pract* 2007;**61**:1592-602.
2. Mancia G *et al. J Hypertens* 2009;**27**:2121-58. DOI:10.1097/HJH.0b013e328333146d.

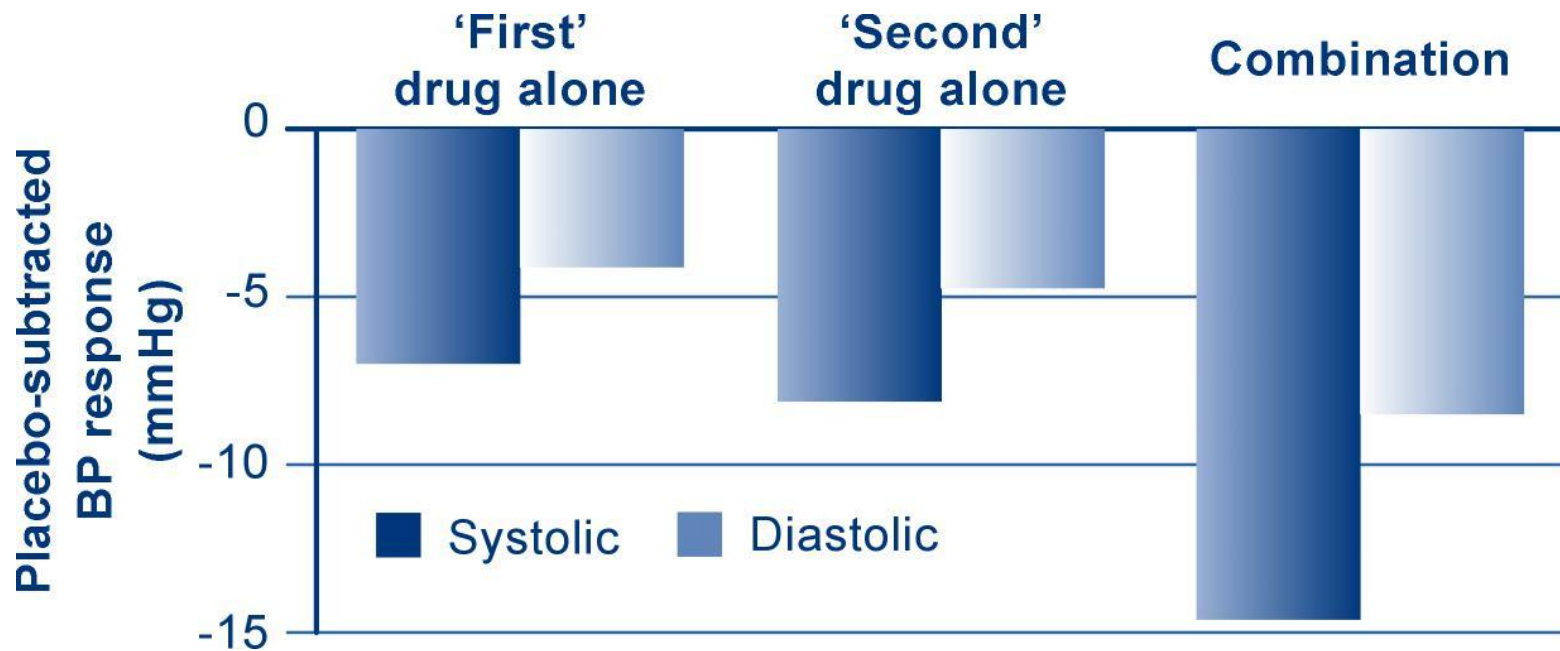
Combination therapy is more effective than increasing the dose of monotherapy



A meta-analysis of 42 trials and 10968 patients shows that combining two different antihypertensive classes gives approximately 5 times greater additional fall in BP than doubling the dose of a single drug.

Adapted from Wald D *et al. Am J Med* 2009;**122**:290-300.

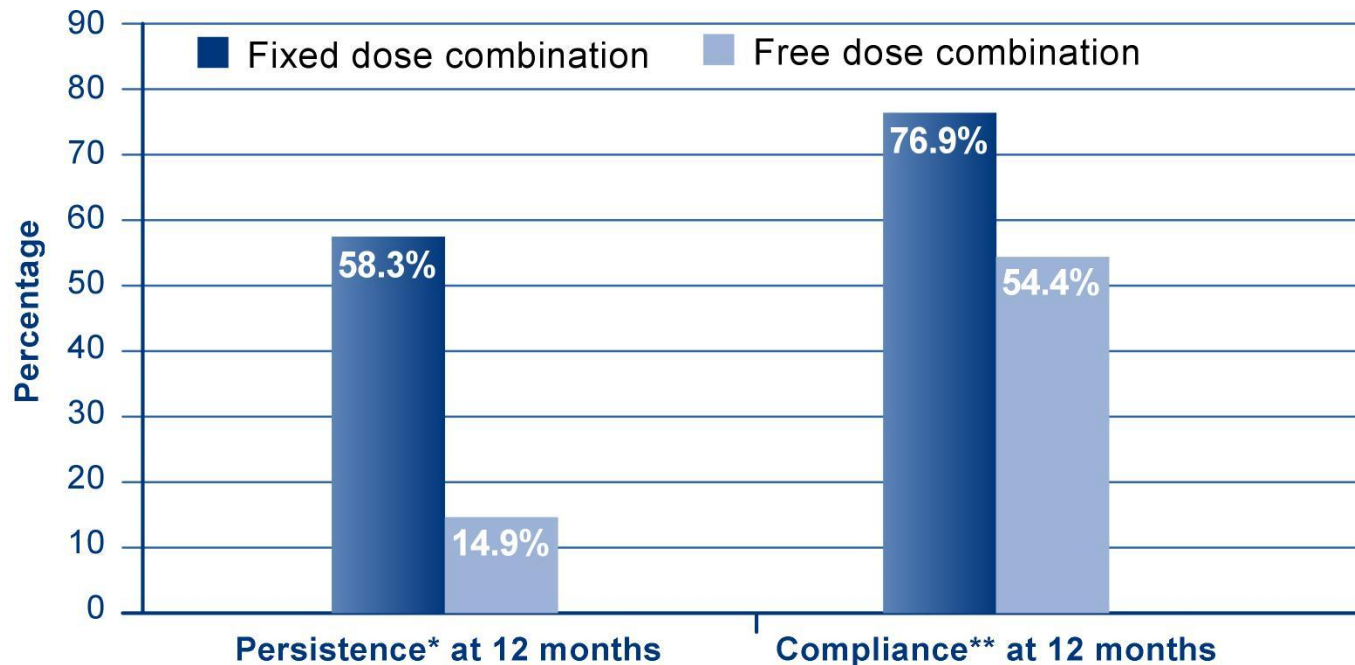
Combination of complementary therapies may improve drug efficacy



Effects of 2 different drugs on BP separately and in combination
(summary results from 119 randomised placebo-controlled comparisons from 50 trials)

Adapted from Law M *et al.* *BMJ* 2003;**326**:1427-31.

Fixed dose combinations improve compliance and persistence



Retrospective cohort of 14449 hypertensive patients receiving fixed dose combination and switched to free combination

*Patients regarded as persistent if remaining on therapy during the last month

** Compliance measured by Medication Possession Ratio (MPR)

Adapted from Hess G. *Pharmacy & Therapeutics* 2008;**33**:652-66.

Guidelines recommend use of combination therapy

| | |
|------------------------------|---|
| JNC 7 2003 ¹ | “More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes.” |
| ESH/ESC 2007 ² | “Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients. Use of more than one agent is necessary to achieve target BP in the majority of patients.” |
| ESH 2009 ³ | “Evidence has continued to grow that in the vast majority of hypertensive patients, effective BP control can only be achieved by combination of at least two antihypertensive drugs.” |

1. Chobanian A *et al.* JNC 7 guidelines. *Hypertension* 2003;**42**:1206-52.
2. Mancia G *et al.* ESH/ESC guidelines. *J Hypertens* 2007;**25**:1751-62.
3. Mancia G *et al.* Reappraisal of European guidelines. *Blood Press* 2009;**18**:308-347.



2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

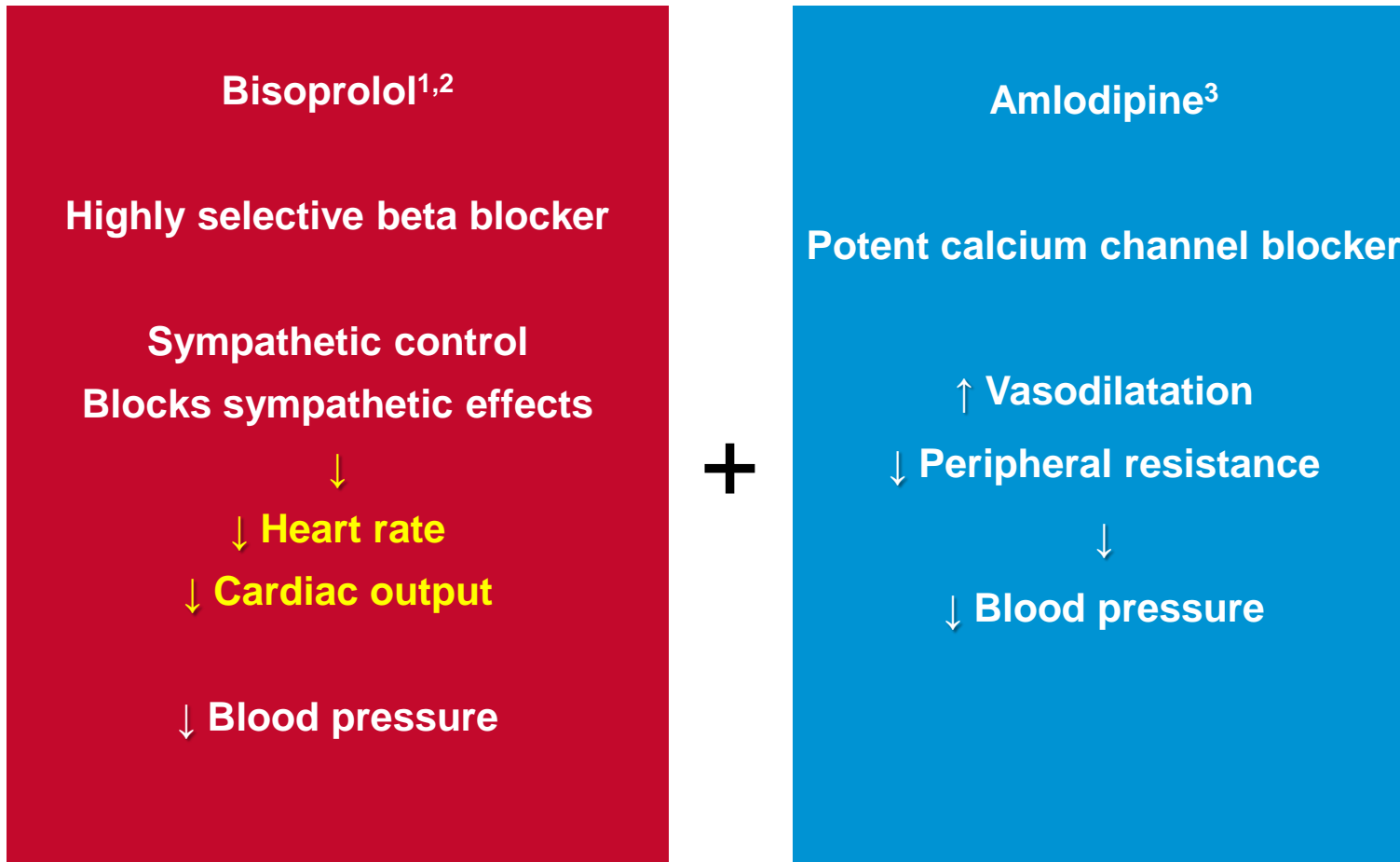
Authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redon (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), Faiez Zannad (France)

ESH Scientific Council: Josep Redon (President) (Spain), Anna Dominiczak (UK), Krzysztof Narkiewicz (Poland), Peter M. Nilsson (Sweden), Michel Burnier (Switzerland), Margus Viigimaa (Estonia), Ettore Ambrosioni (Italy), Mark Caulfield (UK), Antonio Coca (Spain), Michael Hecht Olsen (Denmark), Roland E. Schmieder (Germany), Costas Tsioufis (Greece), Philippe van de Borne (Belgium).

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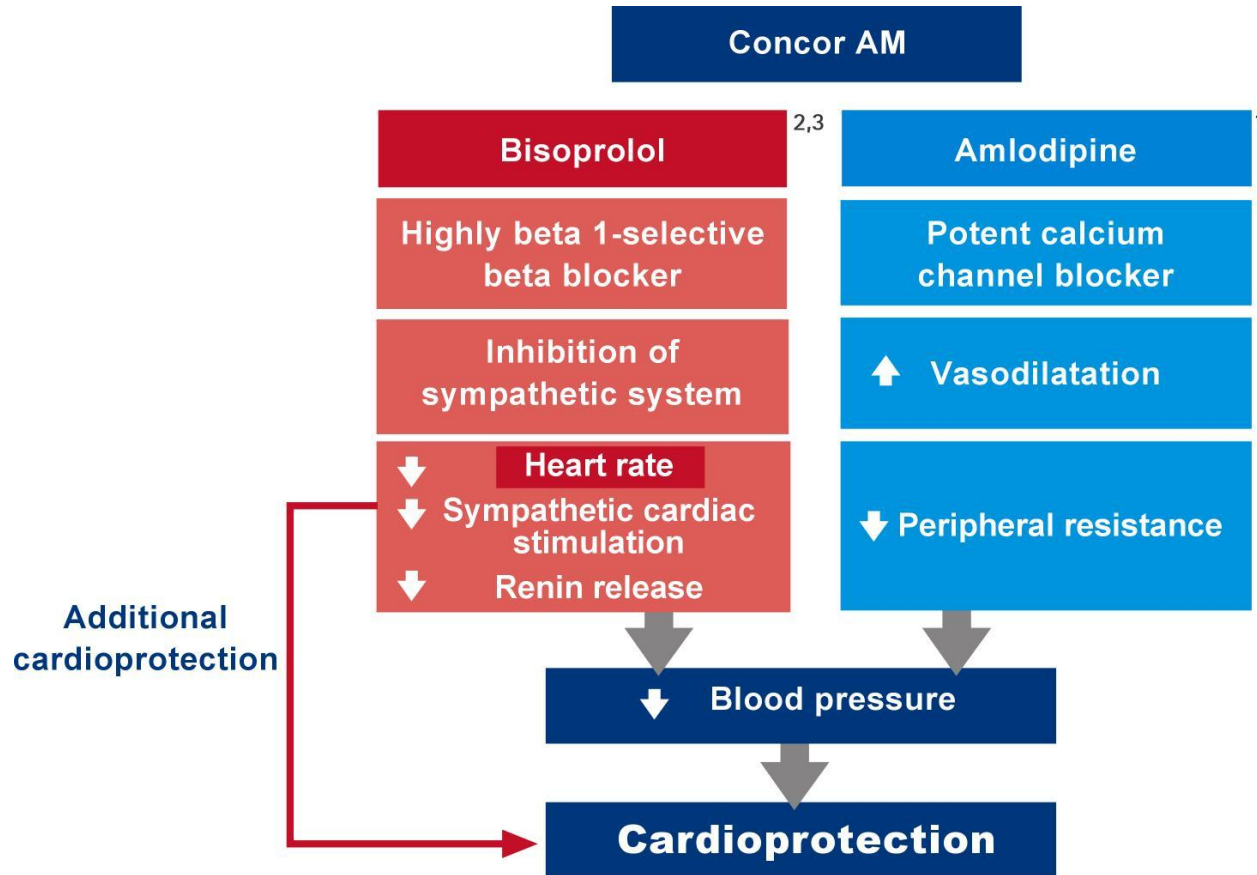
Complementary modes of action

Bisoprolol and amlodipine short product characteristics



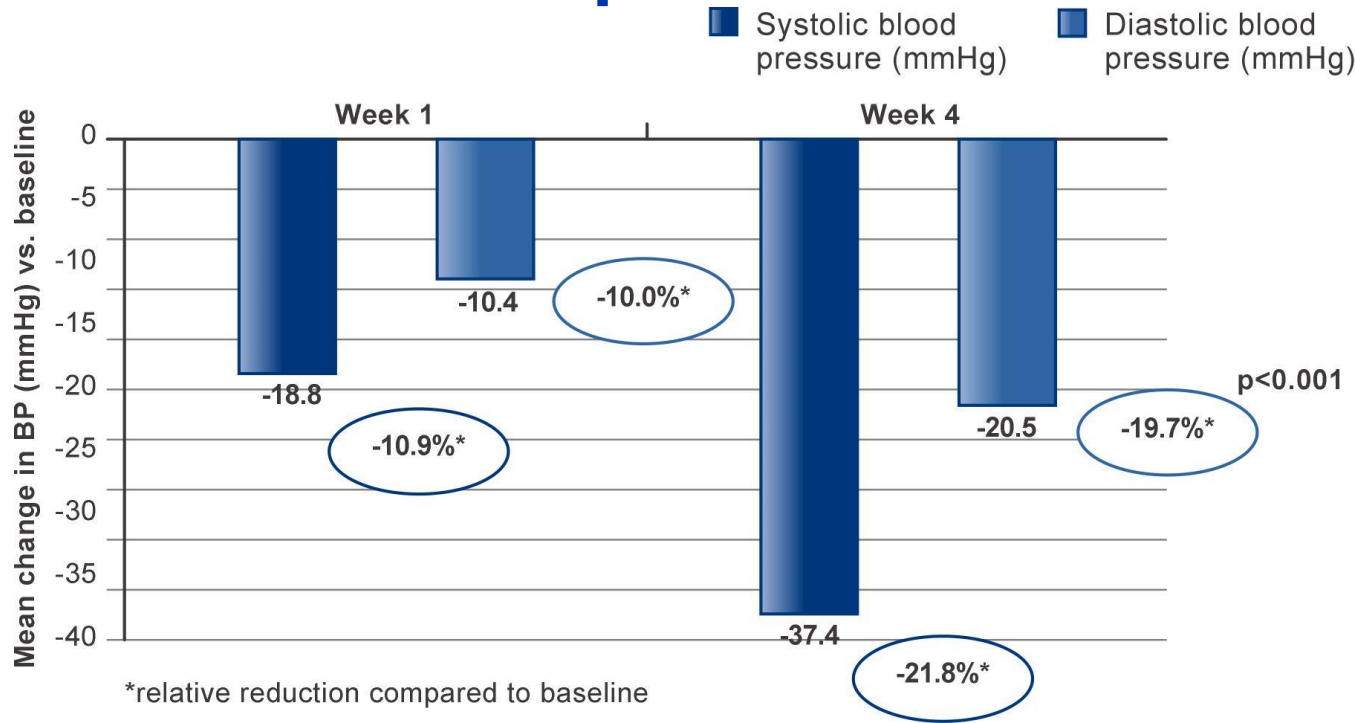
1. Cruickshank JM. *Int J Cardiol* 2007;**120**:10-27;
2. Palatini P *et al.* *Drugs* 2006;**66**:133-144.
3. Murdoch D and Heel RC. *Drugs* 1991;**41**:478-505.

Complementary cardioprotection beyond blood pressure control



1. Murdoch D and Heel RC. *Drugs* 1991;**41**:478-505;
2. Cruickshank JM. *Int J Cardiol* 2007;**120**:10-27;
3. Palatini P *et al.* *Drugs* 2006;**66**:133-144.

Concor AM provides a significant relative reduction in blood pressure within 4 weeks

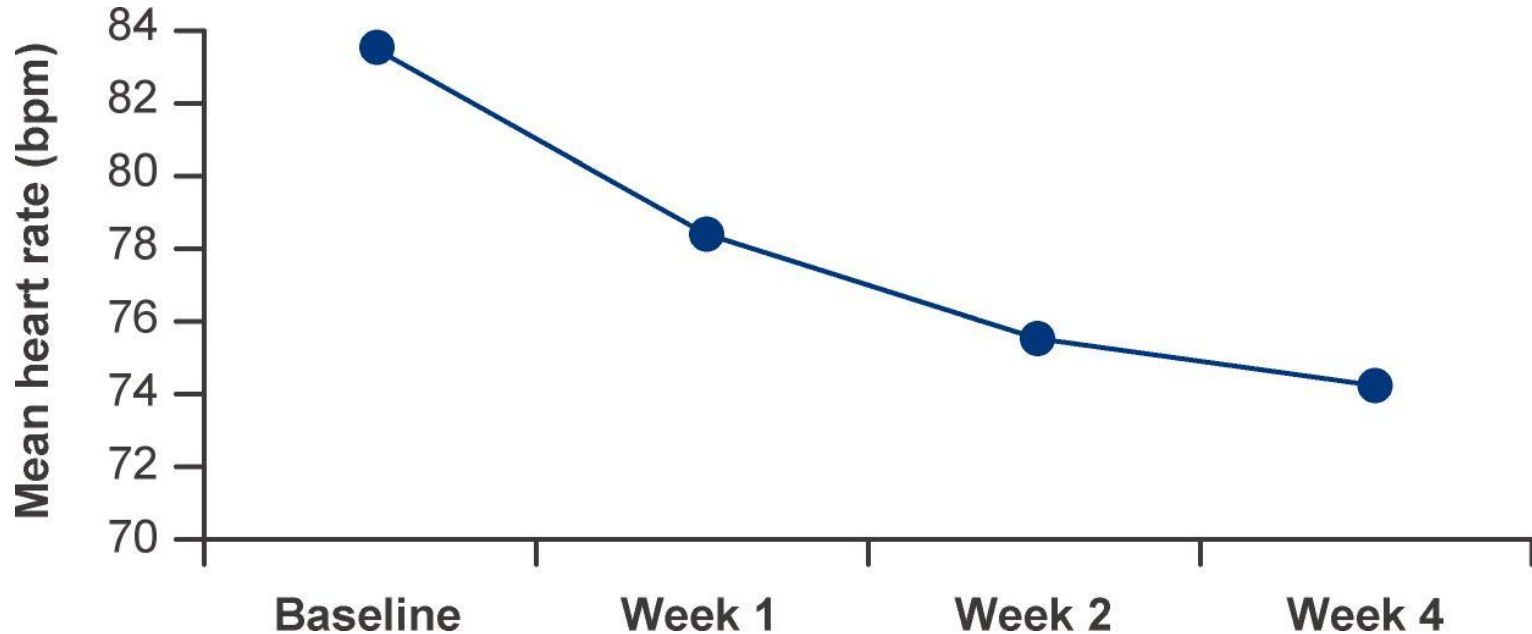


82.5% of patients achieved BP goal (<140/90 mmHg)

Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;61:225-34.

Concor AM significantly reduces heart rate

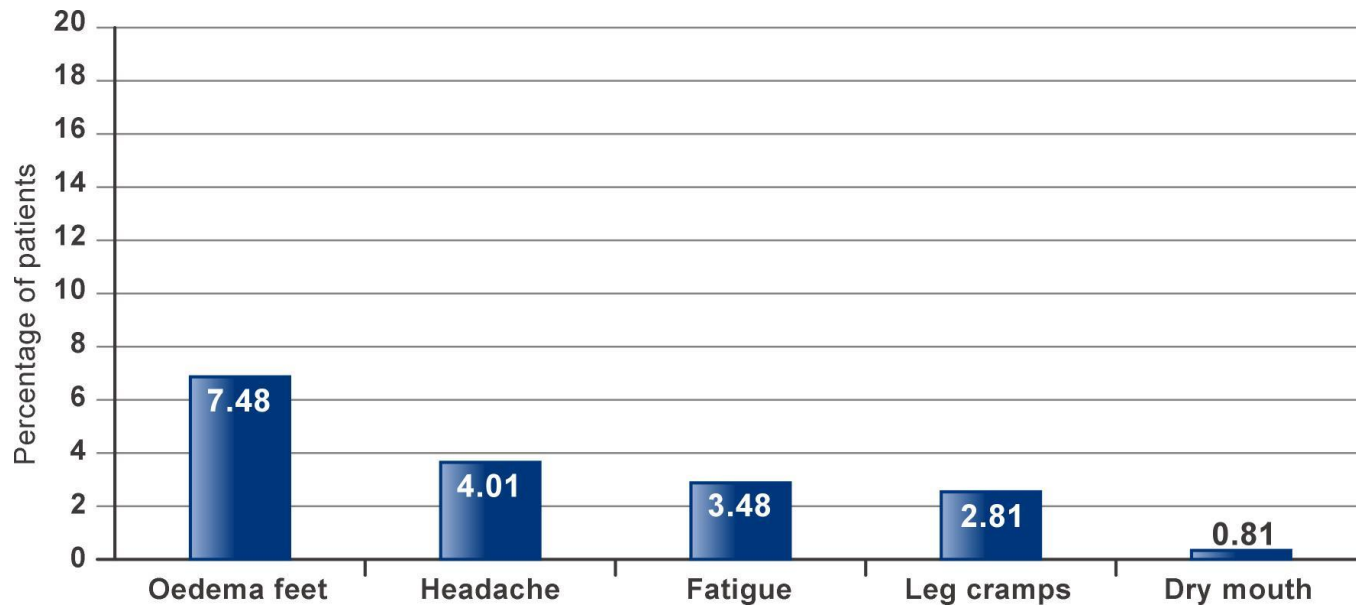


Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;**61**:225-34.

Good tolerability profile: adverse events

Adverse events reported during the study



After 4 weeks of treatment with Concor AM (5 mg + 5 mg) once daily, 90% of patients report good to excellent tolerability

Observational open-labelled, non-comparative survey of 801 patients with stage 2 hypertension in 169 Indian centres.

Adapted from Rana R & Patil A. *Indian Pract* 2008;61:225-34.

Conclusion

- Hypertension is the number one global risk factor for premature mortality
- Approximately 7 out of 10 hypertensive patients do not achieve target BP
- Causes for inadequate BP control involve many factors, one of the most important being poor patient compliance
- More than 75% of patients require combination therapy to achieve target BP
- Fixed dose combinations significantly improve patient compliance and number of controlled hypertensive patients