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
Heart Rate and All-Cause Mortality

The Framingham Study

Kannel WB et al 1987;113:1489
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

Modified from J Hypertens 2006;24:603
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)

Gillman et al., Am Heart J 1993; 125: 1148
Mortality Rate by Quintile of Clinic Heart Rate in the ISH Patients from the Syst-Eur Study

MEN

WOMEN

Heart Rate (bpm)

Mortality rate (%)
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

Palatini P et al, Hypertension 1997; 30: 1267
Frequency of Hypertension During a 6-year Follow-up in 1050 Stage 1 Hypertensives Divided by Heart Rate Status

\[ \chi^2 = 19.2; P = 0.001 \]

Palatini P et al, J Hypertens 2006,24:1873
7-year Risk Of Overweight Or Obesity Related To Heart Rate In 1008 Participants From The HARVEST*

*Results of a multivariable Cox regression

Adapted from Palatini P et al, Obesity 2011,19:618
20-year Risk Of Metabolic Abnormalities For A Baseline Heart Rate \( \geq 80 \text{ bpm} \) In 637 Healthy Participants From Japan

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

Grassi G. et al., J Hypertens 1998

MSNA (bursts/min) vs HR (beats/min)
- n = 243
- r = 0.38
- P < 0.0001

NE (pg/ml) vs HR (beats/min)
- n = 243
- r = 0.32
- P < 0.0001

MSNA (bursts/min) vs NE (pg/ml)
- n = 243
- r = 0.48
- P < 0.0001
LF:HF Ratio in 163 Young Hypertensive Subjects from the HARVEST and 28 Normotensive Controls

Lying

Standing

Mental stress

Sympathetic predominance (n=59)
Normal ANS tone (n=104)
Normotensive controls (n=28)

Palatini P et al, J Hypertens 2006, 24:1375
Frequency of Hypertension According to Autonomic Nervous System Activity in the HARVEST
6-year Follow-up in 163 Subjects

P = 0.02

Subjects with normal ANS activity

Subjects with sympathetic predominance

Palatini P et al, J Hypertens 2006, 24:1375
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

P=0.01

Palatini P et al, J Hypertens 2006, 24:1375
Sympathetic overactivity

- ↑ hematocrit
- ↓ plasma volume
- ↓ veno constriction
- ↑ cardiac output

Tachycardia

- ↑ O₂ consumption, ventricular arrhythmias
- ↓ artery wall stress
- ↓ LV stiffness

Hypertension

- ↓ arteriolar constriction
- ↓ muscle blood flow
- ↓ lipid abnormalities
- ↓ inflammation

Insulin resistance

Coronary events

- LV apoptosis, collagen fibrosis
- LV systolic dysfunction
- Heart failure

Sudden Death

Obesity

LV stiffness

Palatini P, Curr Hypertens Rep 2013
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 2013, Feb 7 [Epub ahead of print]
## The Cooper Clinic Mortality Risk Index

### Clinical Score Sheet for Men

<table>
<thead>
<tr>
<th>Factor</th>
<th>20-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>&lt;80</td>
<td>≥80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>&lt;140/90</td>
<td>≥140/90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>never</td>
<td>former</td>
<td>current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>&lt;35</td>
<td>≥35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory fitness (VO² Max)</td>
<td>low</td>
<td>moderate</td>
<td>high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

Farinaro E et al, Nutr Metab Cardiovasc Dis. 1999;9:196
<table>
<thead>
<tr>
<th>Category</th>
<th>Heart Rate Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>=↑</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>↑↑</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>↑=↓</td>
</tr>
<tr>
<td>Ca-A</td>
<td></td>
</tr>
<tr>
<td>Phenylalkylamines</td>
<td>↓</td>
</tr>
<tr>
<td>Benzothiazepines</td>
<td>↓</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>=</td>
</tr>
<tr>
<td>All receptor blockers</td>
<td>=</td>
</tr>
<tr>
<td>Centrally acting drugs</td>
<td>↓</td>
</tr>
<tr>
<td>Imidazolines receptor agonists</td>
<td>=↓</td>
</tr>
</tbody>
</table>
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**
- Larger (16.2)
- Average (10.0)
- Smaller (4.7)

**Cardiac death**
- Larger (15.3)
- Average (9.5)
- Smaller (4.0)

P for trend = 0.017

P for trend = 0.0015

Modified from Cucherat M, Eur Heart J, 2007;28:3012
Relationship Between Follow-up Heart Rate And Outcome In The INVEST Study

Mean follow-up heart rate (bpm)

Adverse outcome incidence (%)

- <50
- 50-55
- 55-60
- 60-65
- 65-70
- 70-75
- 75-80
- 80-85
- 85-90
- 90-95
- 95-100
- >100

Estimated hazard ratio

Kollock R et al, Eur Heart J 2008;29:1327
Effect of Low-Dose Bisoprolol on 24-Hour Heart Rate in Patients with Dilated Cardiomyopathy

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

Global health risks. WHO 2009
The most common CV disorder affecting 27-55% of adults\(^1\)

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 reduction\(^2\)

However, only 20-55% of treated patients achieve and maintain internationally recognised targets \(^1,2\)

Poor BP control in practice populations

Cross-sectional survey of 5413 hypertensive patients in Denmark

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

1. Paulsen M et al. Family Practice 2011; published online, May 19, 2011
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 ≥140/90 mmHg

# Causes of inadequate BP control

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

Inadequate BP control is associated with increased risk of fatal events

<table>
<thead>
<tr>
<th>Hypertension category</th>
<th>All-cause mortality</th>
<th>CVD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated controlled</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Treated uncontrolled</td>
<td>1.57 (1.28-1.91)*</td>
<td>1.74 (1.36-2.22)*</td>
</tr>
<tr>
<td>Untreated</td>
<td>1.34 (1.12-1.62)*</td>
<td>1.37 (1.04-1.81)**</td>
</tr>
</tbody>
</table>

Risk of CVD mortality increased by 74% in uncontrolled hypertensives

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

### Multiple therapies are required to achieve target BP\(^1\)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of drugs needed to achieve BP 140/90 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Men (all ages) n</td>
<td>333</td>
</tr>
<tr>
<td>Men (all ages) %</td>
<td>22.3%</td>
</tr>
<tr>
<td>Women (all ages) n</td>
<td>154</td>
</tr>
<tr>
<td>Women (all ages) %</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

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\(^2\)

Pathophysiology of essential hypertension: multiple causes

- Autoregulation
- Ion transport inhibitors
- Sympathetic nervous system
- Renin-angiotensin-aldosterone system
- Other hormonal systems
- Renal mechanisms
- Vascular wall contractility and structure
- Rarefaction

Adapted from Sever P, Messerli FH. *Eur Heart J* 2011;32:2499-506.
Rationale for combination therapy:¹

- Combines drugs acting in different physiological systems¹
- Blocks counter-regulatory responses¹
- Treats moderate/severe hypertension¹
- Reduces BP variability vs monotherapy¹,³

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

Criteria for an optimal fixed dose combination

- 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 guidelines

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.

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)

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

<table>
<thead>
<tr>
<th>JNC 7 2003 (^1)</th>
<th>“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.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESH/ESC 2007 (^2)</td>
<td>“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.”</td>
</tr>
<tr>
<td>ESH 2009 (^3)</td>
<td>“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.”</td>
</tr>
</tbody>
</table>

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 Waebber (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 Caufield (UK), Antonio Coca (Spain), Michael Hecht Olsen (Denmark), Roland E. Schmieder (Germany), Costas Tsiofis (Greece), Philippe van de Borne (Belgium).

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Cetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno W. Hoes (Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Per Anton Sirnes (Norway), Juan Luis Tamargo (Spain), Michal Tendera (Poland), Adam Torbicki (Poland), William Wiins (Belgium), Stephan Windcker (Switzerland).
Complementary modes of action
Bisoprolol and amlodipine short product characteristics

Bisoprolol$^{1,2}$
Highly selective beta blocker
Sympathetic control
Blocks sympathetic effects
\[\downarrow\] Heart rate
\[\downarrow\] Cardiac output
\[\downarrow\] Blood pressure

Amlodipine$^3$
Potent calcium channel blocker
\[\uparrow\] Vasodilatation
\[\downarrow\] Peripheral resistance
\[\downarrow\] Blood pressure

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;
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

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