# 1st International Meeting on Nitric Oxide: from basic science to clinical evidence

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## Smoothness index to assess antihypertensive therapy

In treated hypertensive patients cardiovascular protection arises from:

- The *magnitude* of BP reduction
- The *manner* in which the reduction is achieved (drug-induced increase in BP variability must be avoided)

# Antihypertensive treatment and prognostic outcome

As indicated by WHO/ISH and JNC-VI Guidelines:

The ideal antihypertensive therapy should induce a smooth and sustained reduction in BP throughout the 24h dosing interval

# Evaluation of antihypertensive drug efficacy by ABPM

ABPM is superior to office BP:

- Better evaluation of individual BP level (no alerting reaction to doctor's visit, no placebo effect, better reproducibility)
- Estimation of BP variability
- Greater prognostic value (mean BP and variability)
- Evaluation of magnitude, duration and homogeneity of the antihypertensive effect of the drug

# How to assess duration and homogeneity of antihypertensive treatment with ABPM?

Presently, two indices have been proposed and validated:

- Trough-to-peak ratio
- Smoothness index

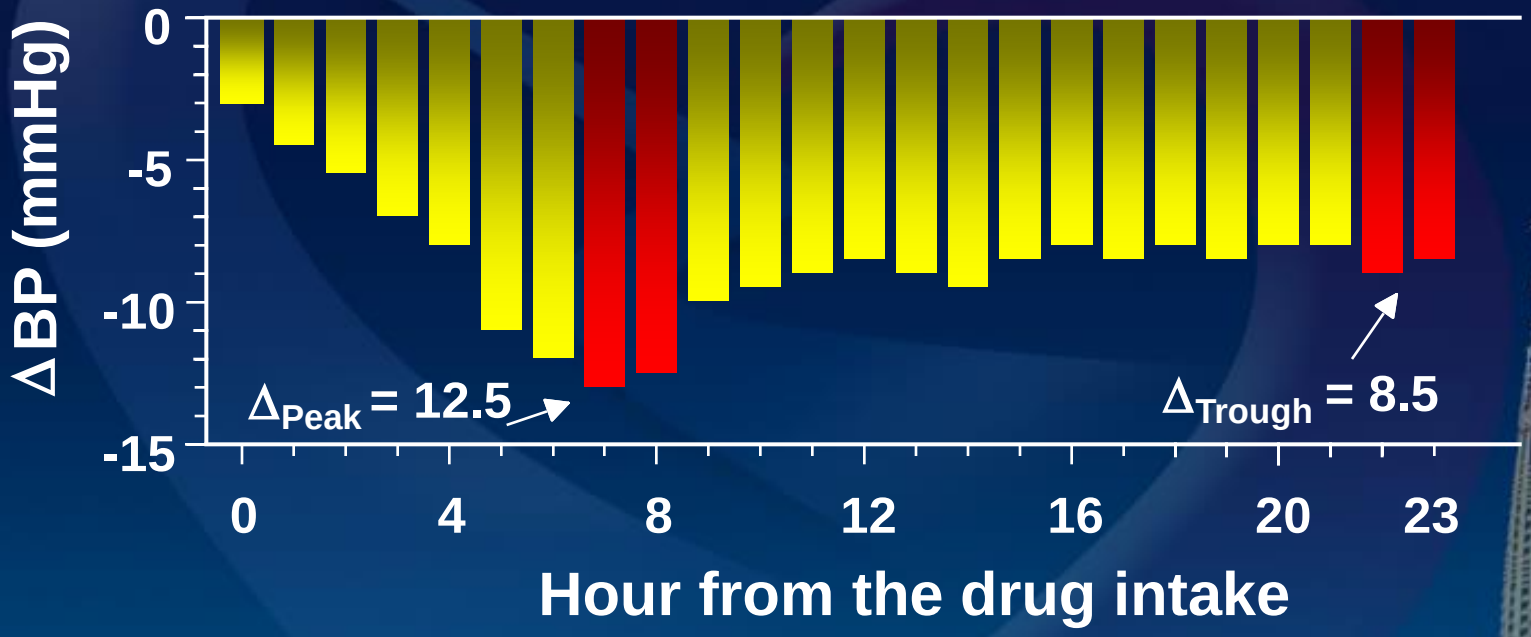
# Trough-to-peak ratio

"...based on the presumption that an antihypertensive drug should retain most of its peak effects at trough… the drug effect at trough… should be no less than one-half to

two-thirds of the peak effect…"

Food and Drug Administration 1988

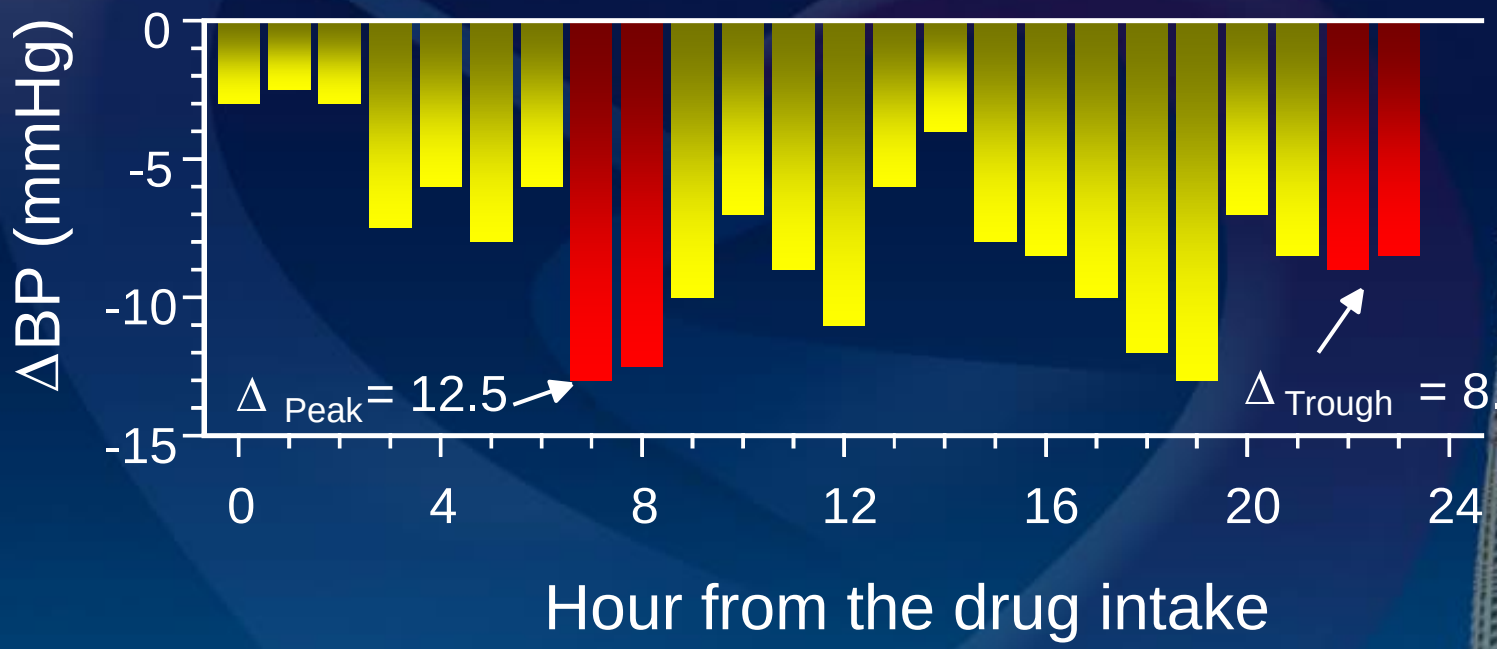
# Trough-to-peak ratio from ABPM




$$T/P\ ratio = \frac{\Delta_{Trough}}{\Delta_{Peak}} = 0.68$$

Omboni S. et al., J Hypertens 1995;13:1105-1112

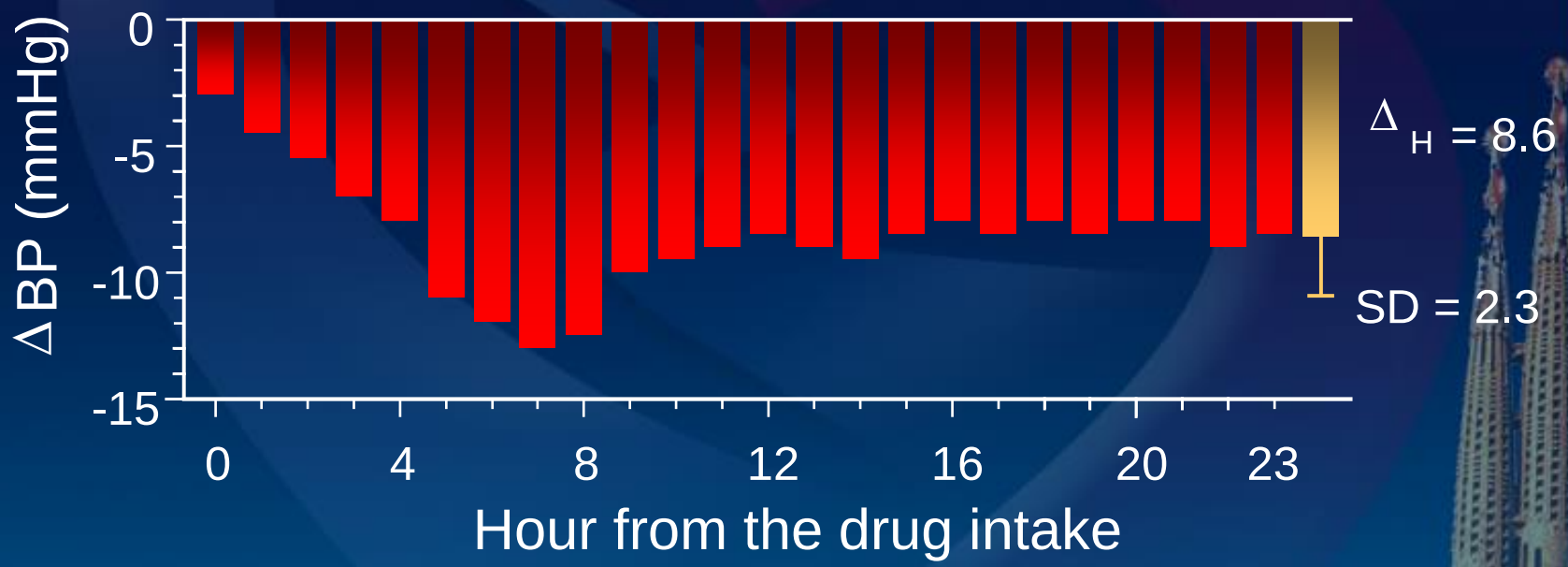
# Trough-to-peak ratio from ABPM




$$T/P\ ratio = \frac{\Delta_{Trough}}{\Delta_{Peak}} = 0.68$$

Omboni S. et al., J Hypertens 1995;13:1105-1112

# Smoothness index



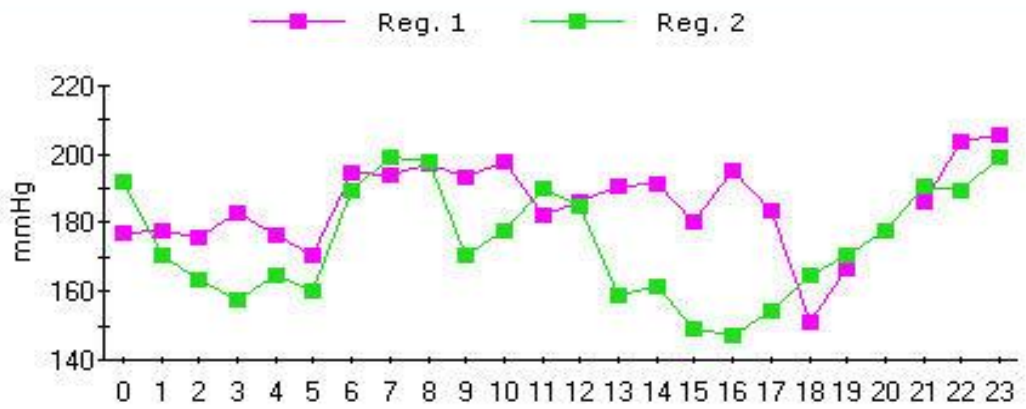

$$SI = \frac{\text{Average } \Delta_{H}}{SD} = 3.7$$

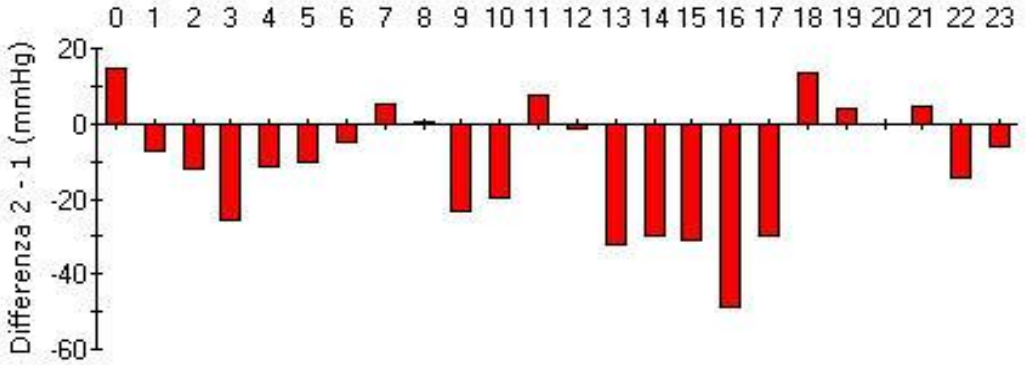
Parati G. et al., J Hypertens 1998;16:1685-1691

# Better evaluation of individual 24h BP control

Smoothness index

PAS | PAD



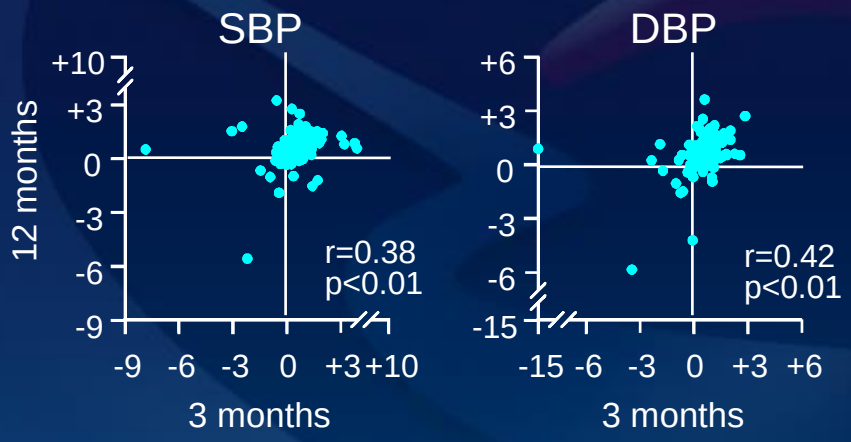

| t | Reg. 1 | Reg. 2 | Diff. 2-1 |
|---|---|---|---|
| 0 | 177,2 | 192,0 | 14,8 |
| 1 | 178,0 | 170,8 | -7,2 |
| 2 | 175,8 | 163,5 | -12,2 |
| 3 | 183,2 | 157,8 | -25,5 |
| 4 | 176,5 | 165,0 | -11,5 |
| 5 | 170,2 | 160,0 | -10,2 |
| 6 | 194,8 | 189,8 | -5,0 |
| 7 | 194,2 | 199,3 | 5,1 |
| 8 | 197,5 | 197,8 | 0,2 |
| 9 | 193,5 | 170,5 | -23,0 |
| 10 | 197,8 | 178,0 | -19,8 |
| 11 | 182,5 | 190,0 | 7,5 |
| 12 | 186,5 | 185,0 | -1,5 |
| 13 | 191,0 | 159,0 | -32,0 |
| 14 | 191,5 | 161,5 | -30,0 |
| 15 | 180,0 | 149,0 | -31,0 |
| 16 | 195,5 | 147,0 | -48,5 |
| 17 | 183,5 | 154,0 | -29,5 |
| 18 | 151,0 | 164,5 | 13,5 |
| 19 | 166,5 | 170,5 | 4,0 |
| 20 | | 177,5 | |
| 21 | 186,2 | 191,0 | 4,8 |
| 22 | 204,0 | 189,5 | -14,5 |
| 23 | 205,8 | 199,5 | -6,2 |

| | | |
|---|---|---|
| Ora Inizio | 10 | 9 |
| Media | -11,2 | |
| DS | 16,5 | |
| **SI** | **0,7** | |

# SI is highly reproducible

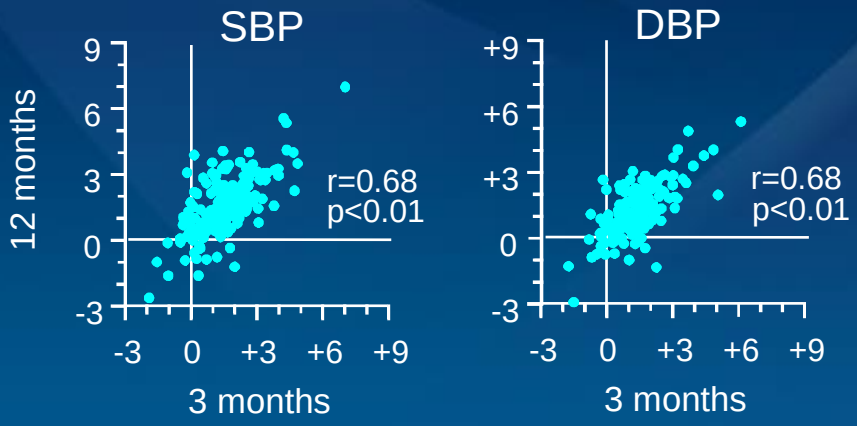
T/P ratio (n=174)

RC = 140 / 167 %



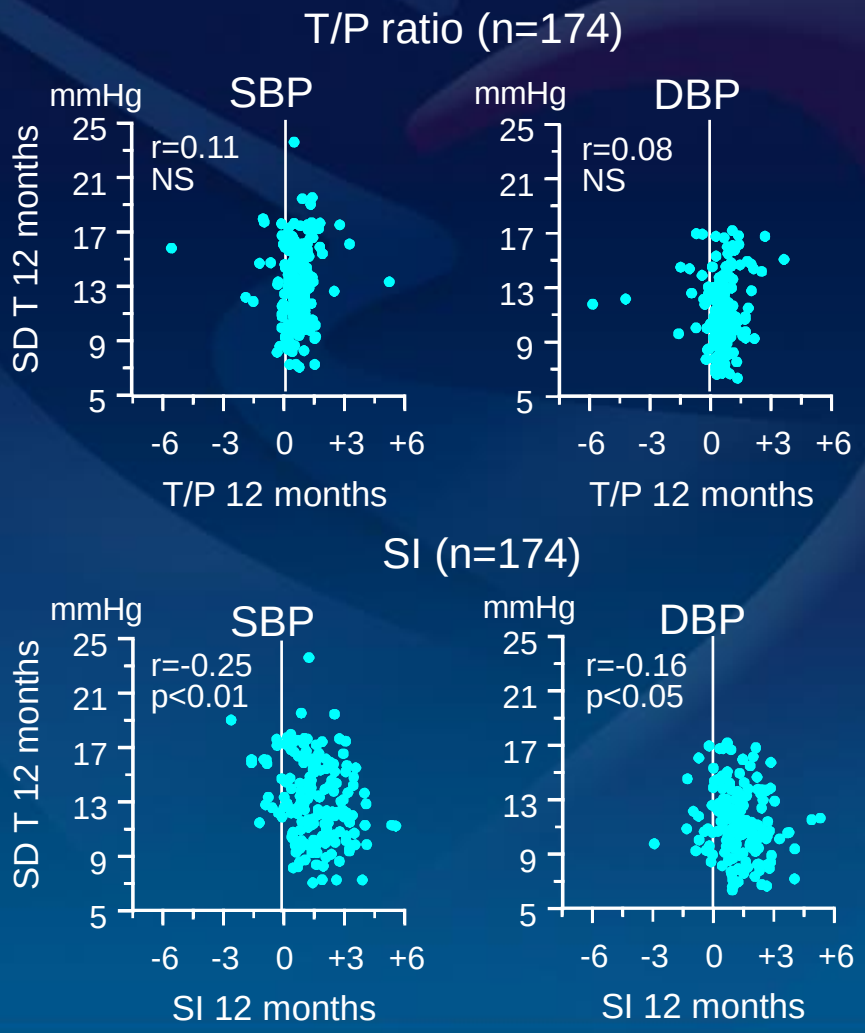

SI (n=174)

RC = 41 / 40 %



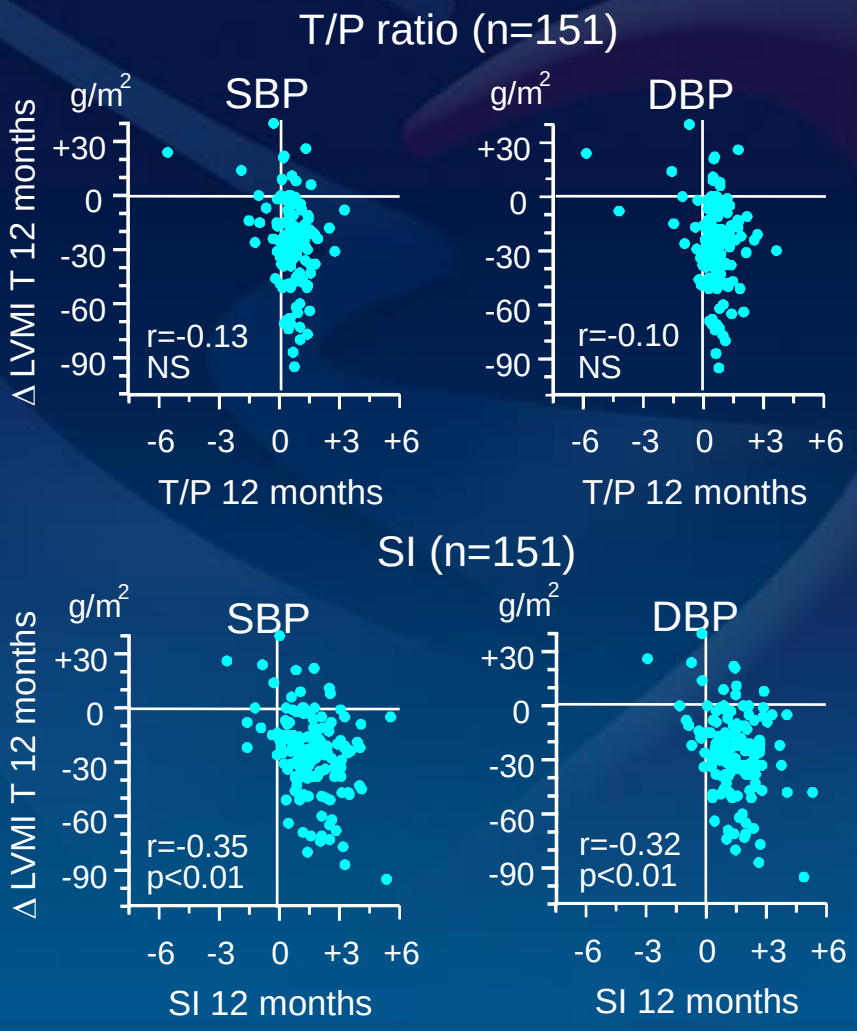

Parati G. et al., J Hypertens 1998;16:1685-1691

# SI correlates with BP variability




Parati G. et al., J Hypertens 1998;16:1685-1691

# SI is clinically relevant




Parati G. et al., J Hypertens 1998;16:1685-1691

# SI is clinically relevant

Smoothness index and changes in carotid artery IMT after 1 year of antihypertensive treatment

| | Smoothness index | | Trough-to-peak ratio | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Common carotid | -0.20* | -0.19* | 0.13 | 0.15 |
| Carotid bifurcation | -0.36** | -0.32** | 0.07 | -0.02 |
| Common carotid + carotid bifurcation | -0.31** | -0.29** | 0.09 | 0.05 |

n=100 correlation coefficients *p<0.05 **p<0.01

Rizzoni D. et al., J Hypertens 2001;19:703-711

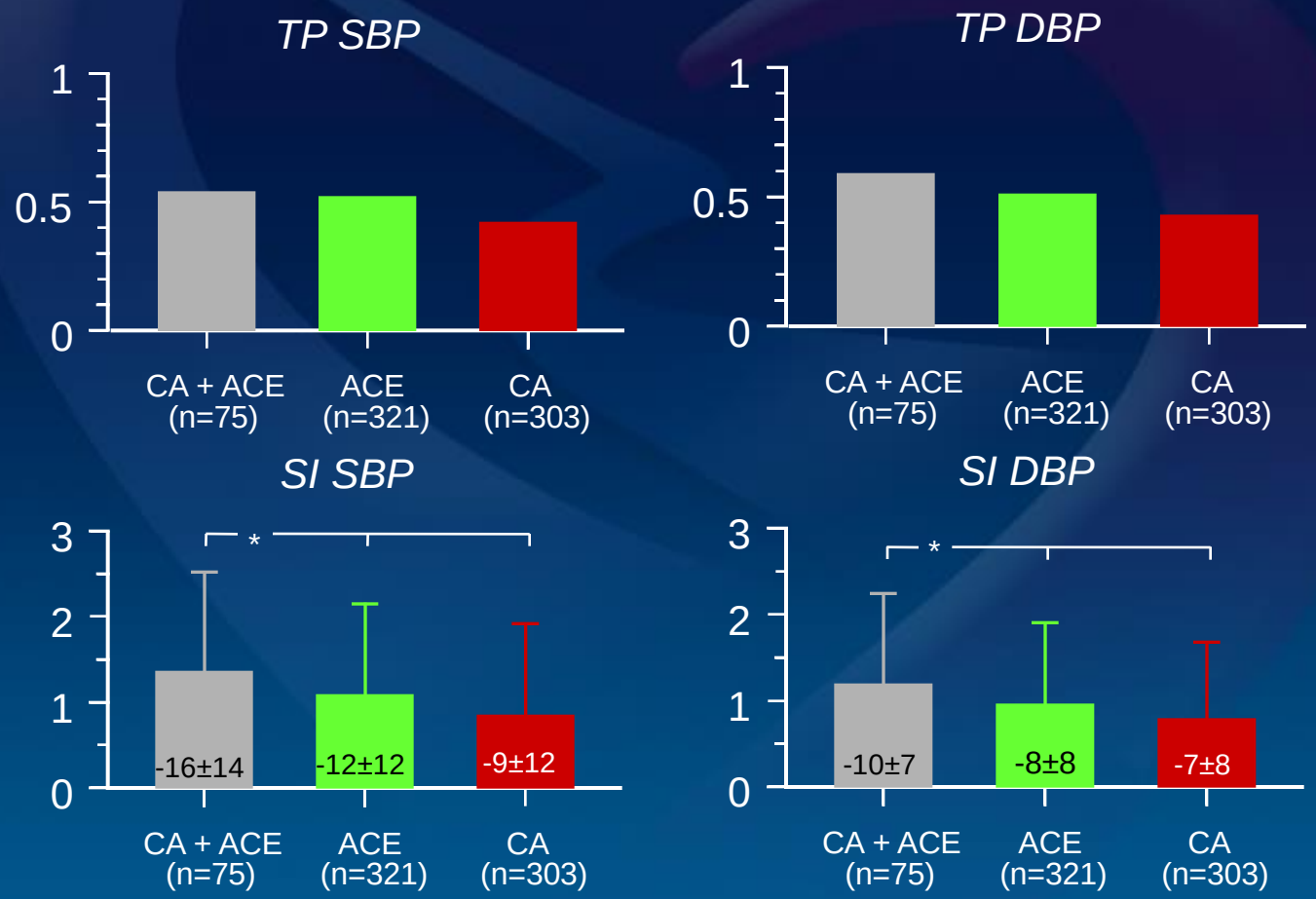
# SI has a negligible placebo effect

| | SBP | | DBP | |
|---|---|---|---|---|
| | Drug (n=894) | Placebo (n=112) | Drug (n=894) | Placebo (n=112) |
| Smoothness Index | 1.1±1.1 | 0.1±0.6 | 0.9±1.0 | 0.04±0.6 |
| Trough-to-peak ratio | 0.51 (0.40 / 1.36) | 0.11 (-0.90 / 0.60) | 0.53 (0.47 / 0.83) | 0.12 (-0.19 / 1.89) |

SI: mean±SD; T/P ratio: median and 5$^{th}$ and 95$^{th}$ percentile

Omboni et al. Blood Pressure Monitoring 1998;3:201-204

# Possibility to compare different drug treatments

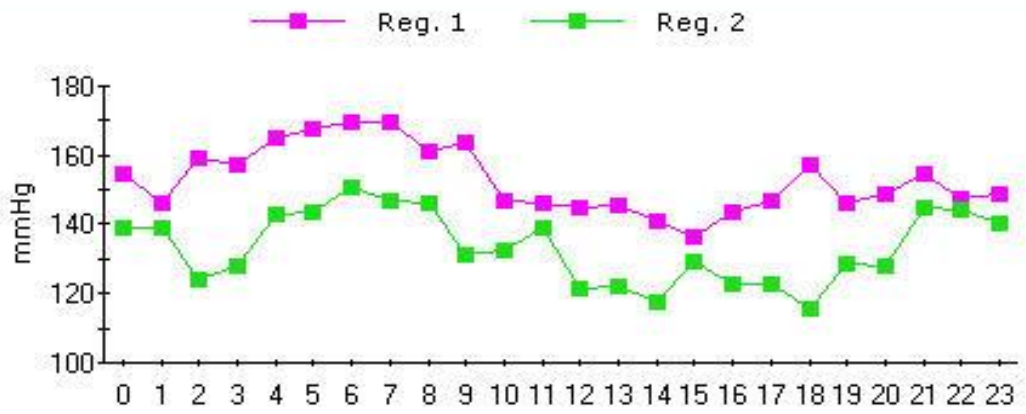


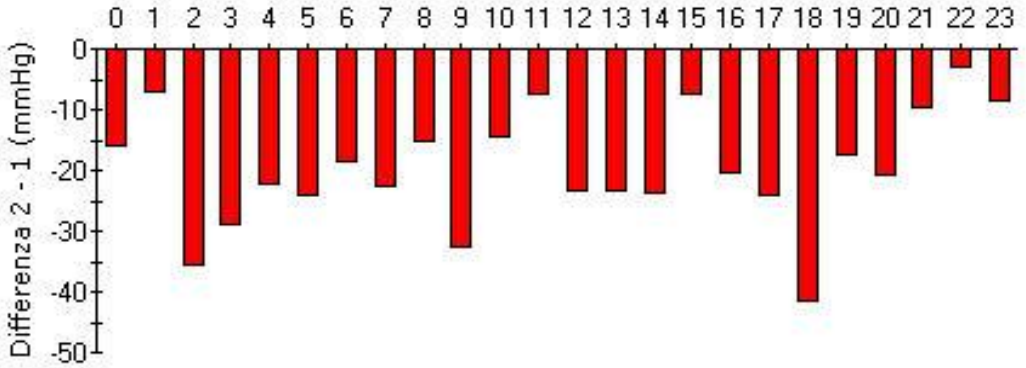

Omboni et al., J Hypertens 1998;16 (Suppl 2):S202

# SI after 8 weeks of single drug treatment

Smoothness index

PAS | PAD

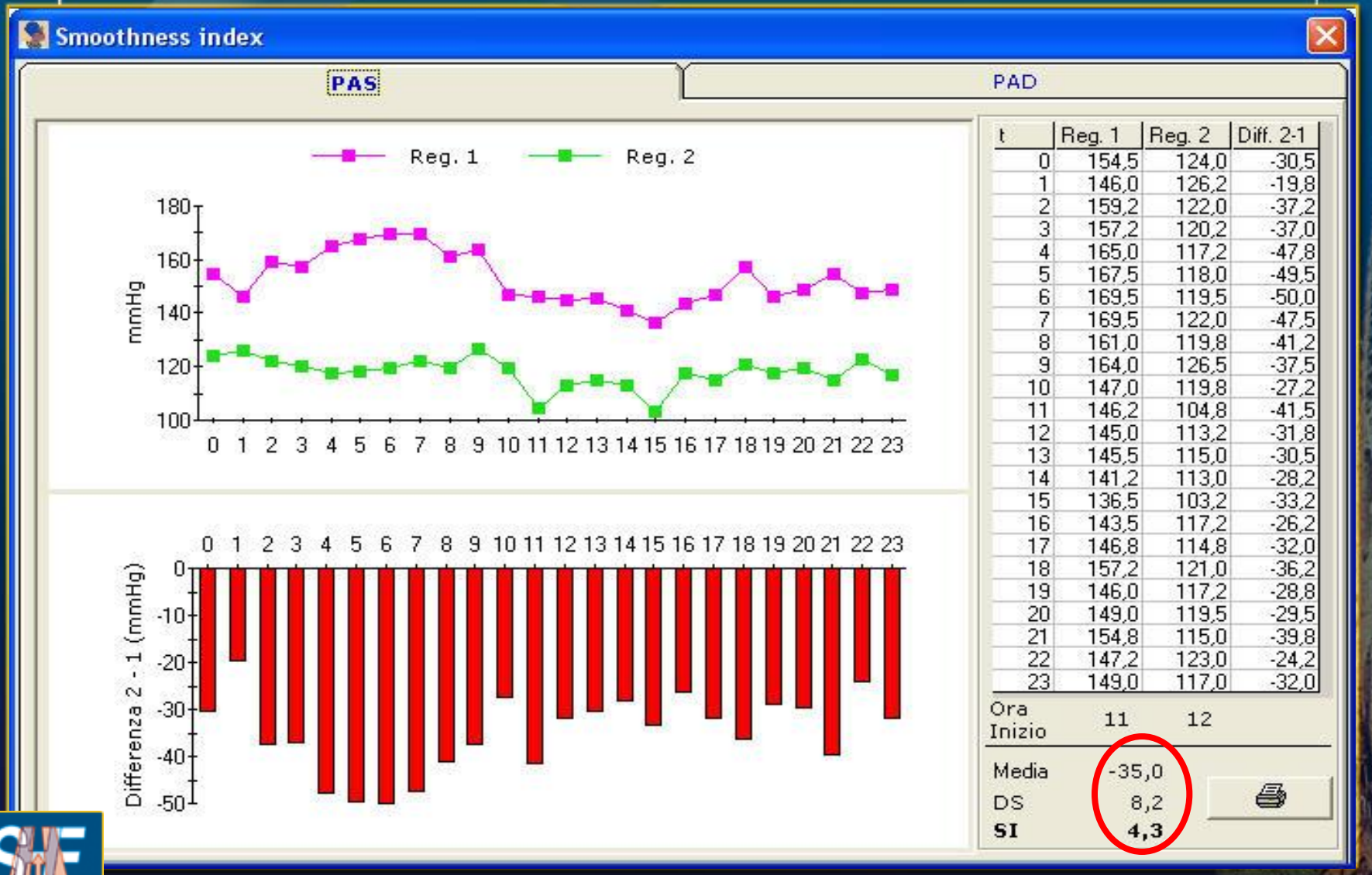



| t | Reg. 1 | Reg. 2 | Diff. 2-1 |
|---|---|---|---|
| 0 | 154,5 | 138,8 | -15,8 |
| 1 | 146,0 | 139,0 | -7,0 |
| 2 | 159,2 | 123,8 | -35,5 |
| 3 | 157,2 | 128,2 | -29,0 |
| 4 | 165,0 | 142,8 | -22,2 |
| 5 | 167,5 | 143,5 | -24,0 |
| 6 | 169,5 | 151,0 | -18,5 |
| 7 | 169,5 | 147,0 | -22,5 |
| 8 | 161,0 | 146,0 | -15,0 |
| 9 | 164,0 | 131,5 | -32,5 |
| 10 | 147,0 | 132,5 | -14,5 |
| 11 | 146,2 | 138,8 | -7,5 |
| 12 | 145,0 | 121,8 | -23,2 |
| 13 | 145,5 | 122,0 | -23,5 |
| 14 | 141,2 | 117,5 | -23,8 |
| 15 | 136,5 | 129,0 | -7,5 |
| 16 | 143,5 | 123,0 | -20,5 |
| 17 | 146,8 | 122,5 | -24,2 |
| 18 | 157,2 | 115,8 | -41,5 |
| 19 | 146,0 | 128,5 | -17,5 |
| 20 | 149,0 | 128,2 | -20,8 |
| 21 | 154,8 | 145,0 | -9,8 |
| 22 | 147,2 | 144,2 | -3,0 |
| 23 | 149,0 | 140,3 | -8,7 |

| | | |
|---|---|---|
| Ora Inizio | 11 | 11 |
| Media | -19,5 | |
| DS | 9,6 | |
| **SI** | **2,0** | |

# SI after 16 weeks of combination treatment

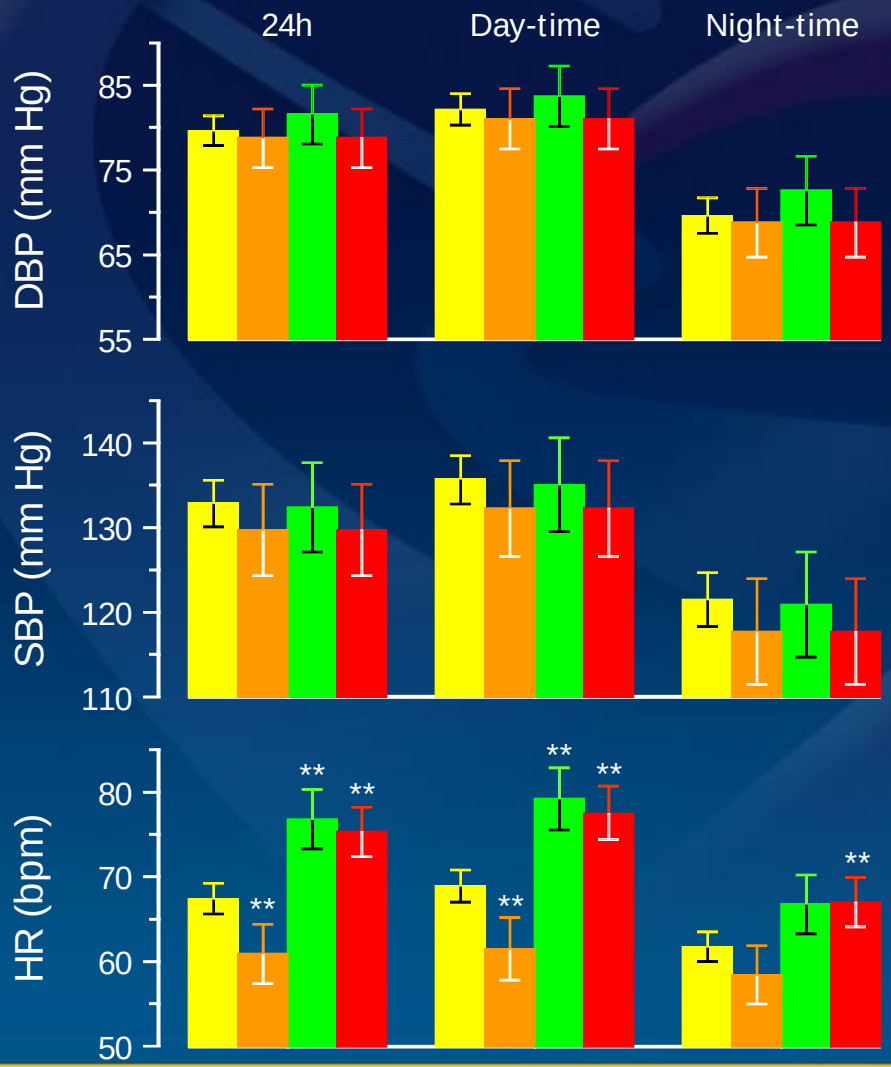



| t | Reg. 1 | Reg. 2 | Diff. 2-1 |
|---|---|---|---|
| 0 | 154,5 | 124,0 | -30,5 |
| 1 | 146,0 | 126,2 | -19,8 |
| 2 | 159,2 | 122,0 | -37,2 |
| 3 | 157,2 | 120,2 | -37,0 |
| 4 | 165,0 | 117,2 | -47,8 |
| 5 | 167,5 | 118,0 | -49,5 |
| 6 | 169,5 | 119,5 | -50,0 |
| 7 | 169,5 | 122,0 | -47,5 |
| 8 | 161,0 | 119,8 | -41,2 |
| 9 | 164,0 | 126,5 | -37,5 |
| 10 | 147,0 | 119,8 | -27,2 |
| 11 | 146,2 | 104,8 | -41,5 |
| 12 | 145,0 | 113,2 | -31,8 |
| 13 | 145,5 | 115,0 | -30,5 |
| 14 | 141,2 | 113,0 | -28,2 |
| 15 | 136,5 | 103,2 | -33,2 |
| 16 | 143,5 | 117,2 | -26,2 |
| 17 | 146,8 | 114,8 | -32,0 |
| 18 | 157,2 | 121,0 | -36,2 |
| 19 | 146,0 | 117,2 | -28,8 |
| 20 | 149,0 | 119,5 | -29,5 |
| 21 | 154,8 | 115,0 | -39,8 |
| 22 | 147,2 | 123,0 | -24,2 |
| 23 | 149,0 | 117,0 | -32,0 |

# Smoothness index: which reference value?

| Author | Year | n | T duration | | SI SBP | SI DBP |
|---|---|---|---|---|---|---|
| Parati et al. | 1998 | 136 | 1 year | Regression of LVH | 1.78±1.30 | 1.47±1.07 |
| Rizzoni et al. | 2001 | 37 | 1 year | Regression of carotid artery structural alterations | 1.42±1.39 | 1.23±1.34 |
| Parati et al. | 1998 | 15 | 1 year | No regression in LVH | 0.59±1.41 | 0.61±1.50 |
| Rizzoni et al. | 2001 | 63 | 1 year | Progression of carotid artery structural alterations | 0.45±0.90 | 0.38±0.85 |
| Omboni et al. | Unpub. | 777 | 4-8 wks | Short term-treatment | 1.02±1.11 | 0.88±0.92 |
| Mancia et al. | 2001 | 168 | 2 yrs | Long-term treatment (HOT) | 1.31±1.14 | 1.19±0.91 |
| Mancia et al. | 2002 | 78 | 3 yrs | Long-term treatment (INSIGHT) | 1.40±1.00 | 1.20±0.80 |

# Cardio-selective beta-blocker with vasodilating properties vs. classical beta-blocker, ACE-inhibitor and calcium-antagonist




Nebivolol 5 mg (n=56)

Atenolol 100 mg (n=15)

Lisinopril 20 mg (n=15)

Amlodipine 10 mg (n=21)

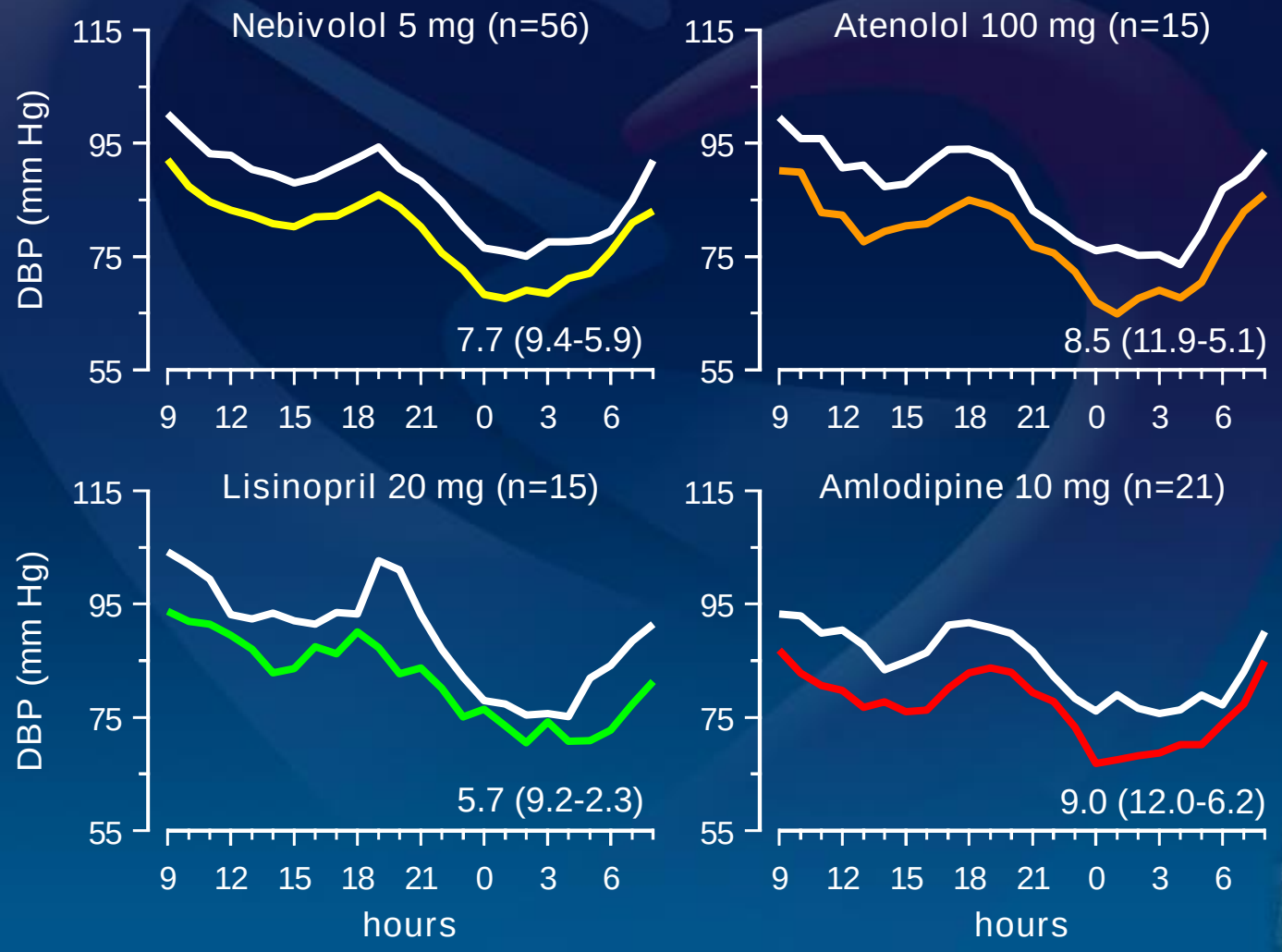
Mean (95% C.I.)

**p<0.01 vs. nebivolol

Baseline corrected means and 95% C.I. after 12 weeks of treatment

Parati G. et al., unpublished data

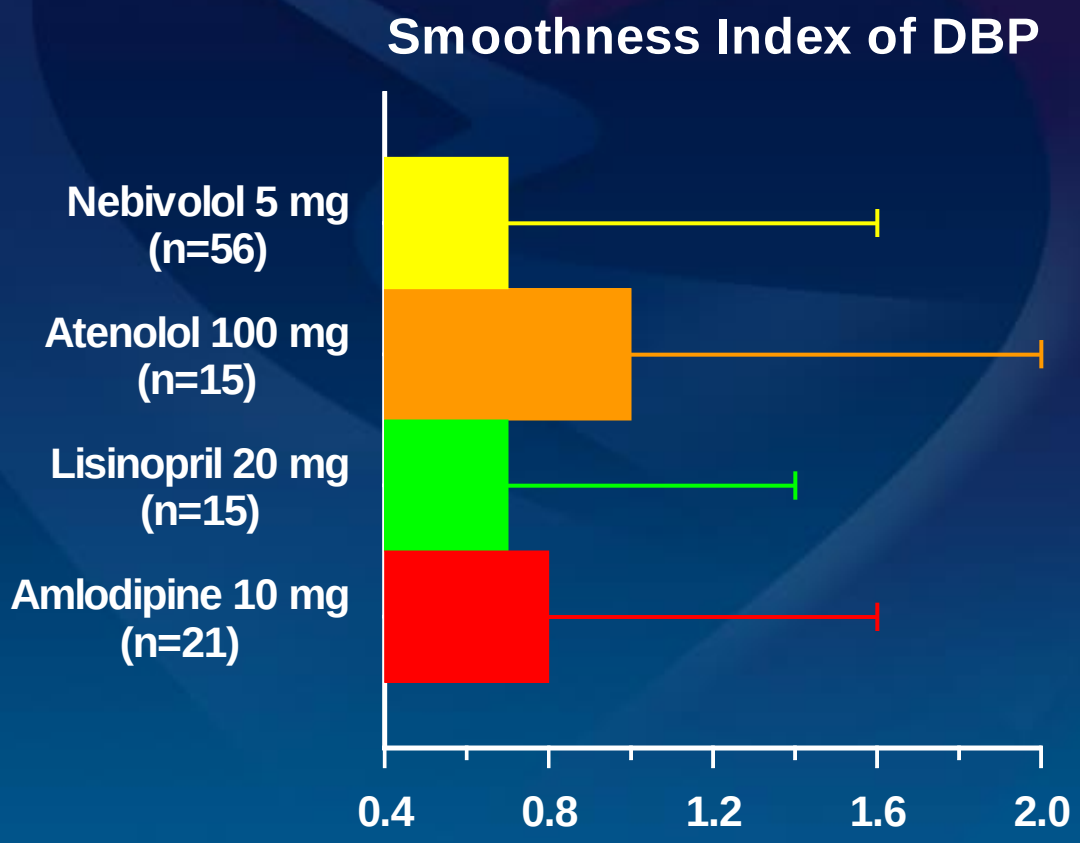
# Cardio-selective beta-blocker with vasodilating properties vs. classical beta-blocker, ACE-inhibitor and calcium-antagonist




Number at the bottom of graphs: baseline corrected mean 24h DBP changes and 95% C.I.

Parati G. et al., unpublished data

# Cardio-selective beta-blocker with vasodilating properties vs. classical beta-blocker, ACE-inhibitor and calcium-antagonist




Parati G. et al., unpublished data

# Cardio-selective beta-blocker with vasodilating properties vs. classical beta-blocker, ACE-inhibitor and calcium-antagonist

- Long-term treatment with nebivolol, a cardioselective beta-blocker with vasodilating properties, induces a consistent and sustained antihypertensive effect throughout the 24 hours
- This effect is similar to that observed with atenolol, a classical beta-blocker, lisinopril (an ACE-inhibitor) and amlodipine (a calcium-antagonist)
- Differently from lisinopril and amlodipine nebivolol has a potentially beneficial bradycardic effect, which is less consistent, an thus less dangerous in patients at risk, than that observed with atenolol

Parati G. et al., unpublished data