SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

60° CONGRESSO NAZIONALE

NAPOLI *25-28 Novembre 2015*

Simposio SIGG-SIIA

INNOVAZIONI TERAPEUTICHE NEL MANAGEMENT DELL'IPERTENSIONE ARTERIOSA NEL PAZIENTE ANZIANO

Moderatori: Claudio Borghi (Bologna), Nicola Ferrara (Napoli)

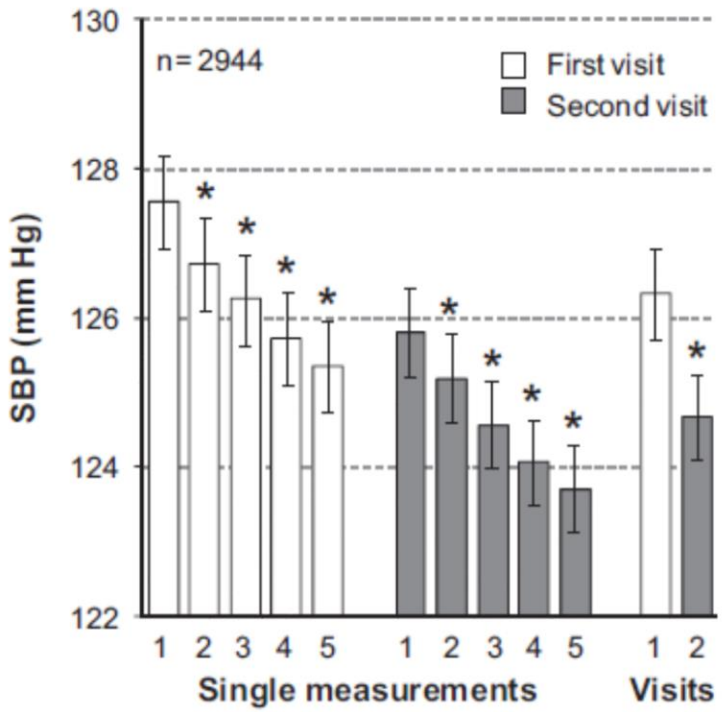
- **Variabilità pressoria e mortalità**
  Mario Bo (Torino)

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

–Sir William Osler

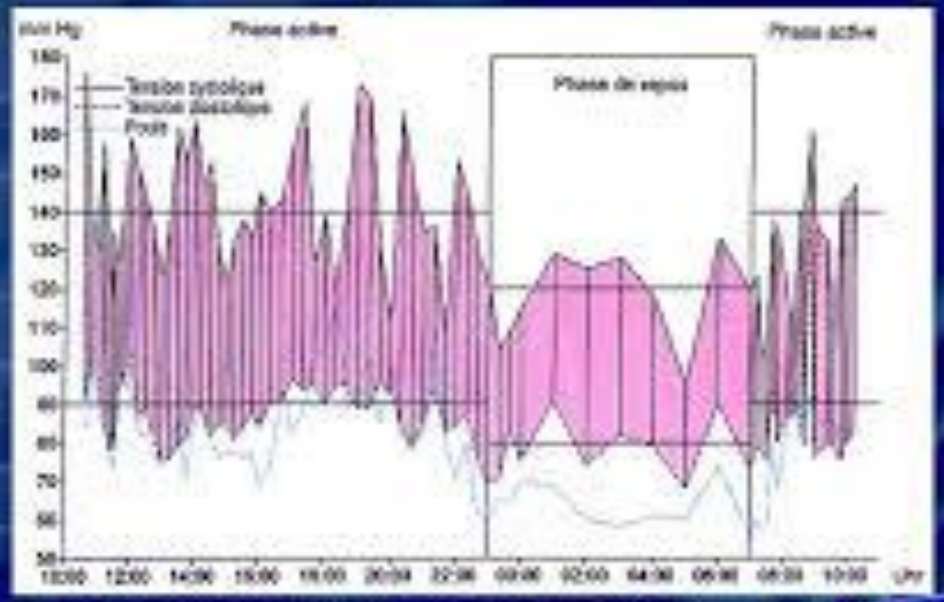
(*Hypertension*. 2012;60:1138-1147.)

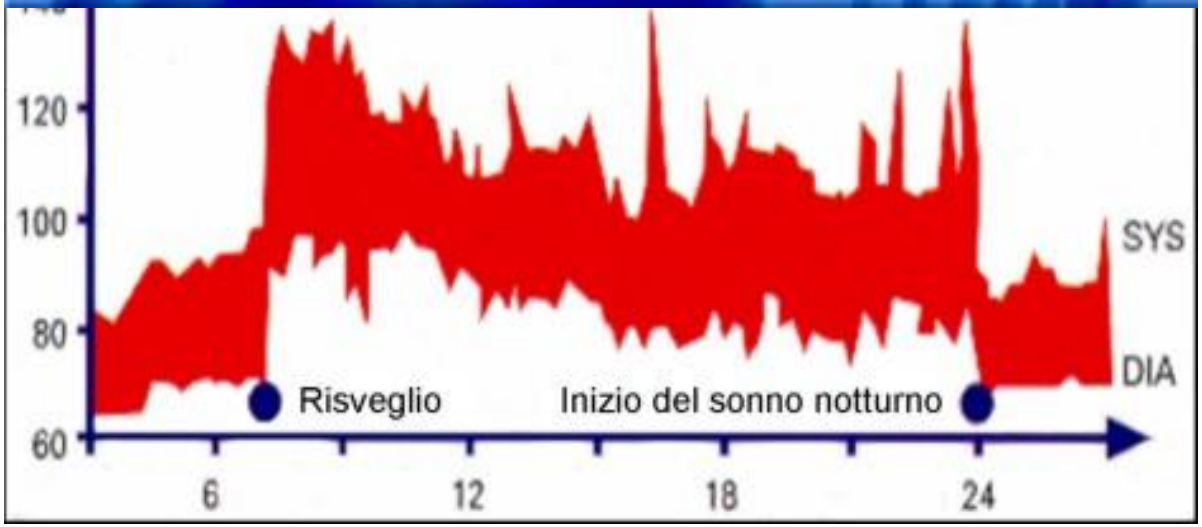
Within-Subject Blood Pressure Level—Not Variability—Predicts Fatal and Nonfatal Outcomes in a General Population



Nurses measured BP 5 times consecutively at each of two home visits 2 to 4 weeks apart.

Holter pressorio

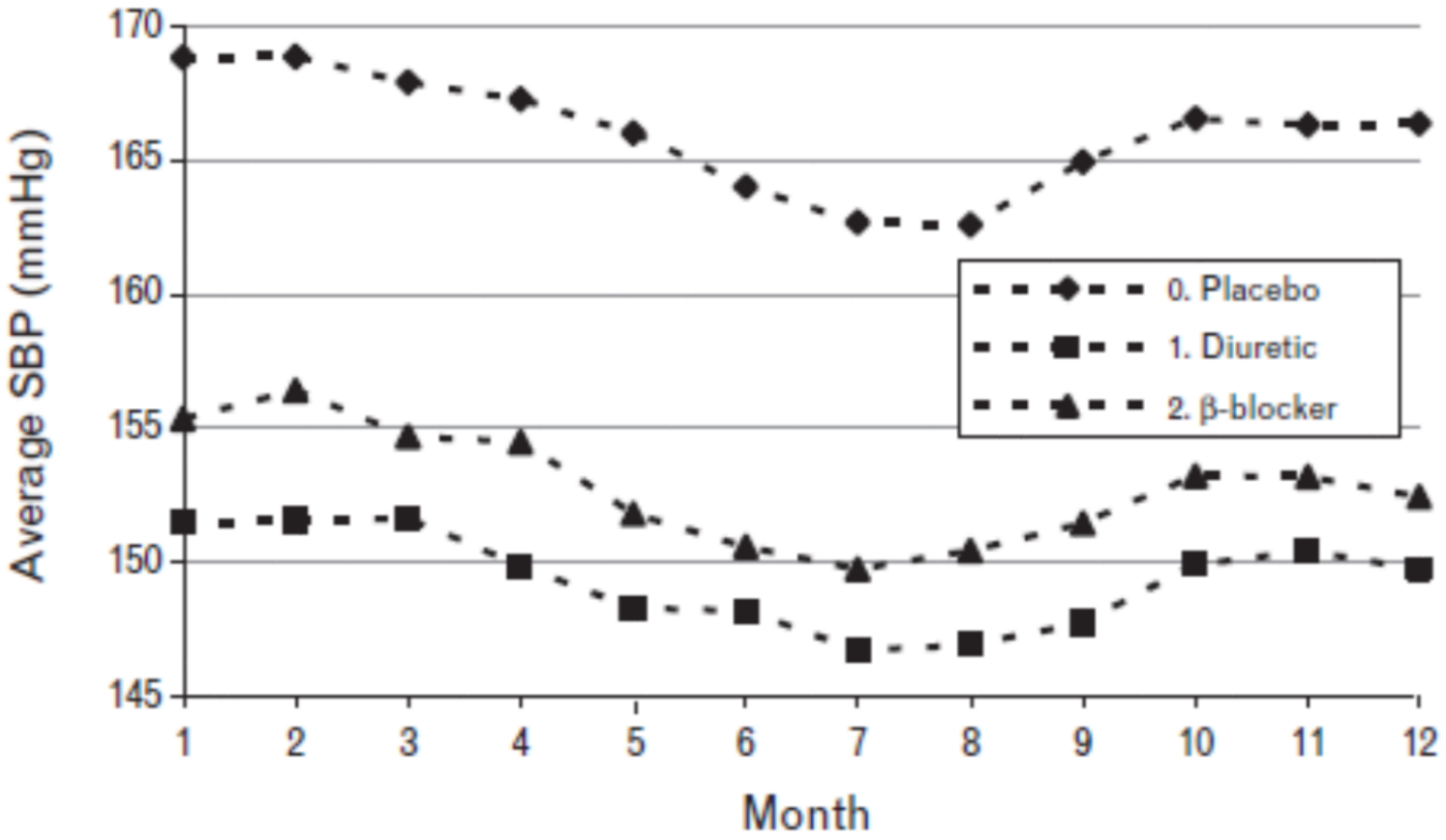




The predictive ability of blood pressure in elderly trial patients

Journal of Hypertension 2012, 30:1725–1733

4396 pazienti 65-74 anni del MRC trial (HCT-amiloride vs atenololo vs placebo)



Variazioni stagionali della PAS media

Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension

Lancet 2010; 375: 938–48

Peter M Rothwell

Measures of Variability

- SD=square root [sum of (individual reading–sample mean)^2/number of readings].
- CV=SD/mean.
- VIM=SD/mean^x; which is essentially similar to CV except that the mean BP denominator is raised to a certain power, x, that removes any correlation with mean BP. The derivation of x is explained in the text.
- ASV=average absolute difference between successive values.

140 150 160 130 120 mmHg $\bar{x} = \frac{1}{N}\sum_{i=1}^{N} x_i$ 700/5= **140 mmHg**

$$\sigma_X = \sqrt{\frac{0+100+400+100+400=1000}{5}},$$

SD=14,14 mmHg

$$\sigma_X^* = \frac{\sigma_X}{|\bar{x}|}.$$

CV=14,14/140= **10%**

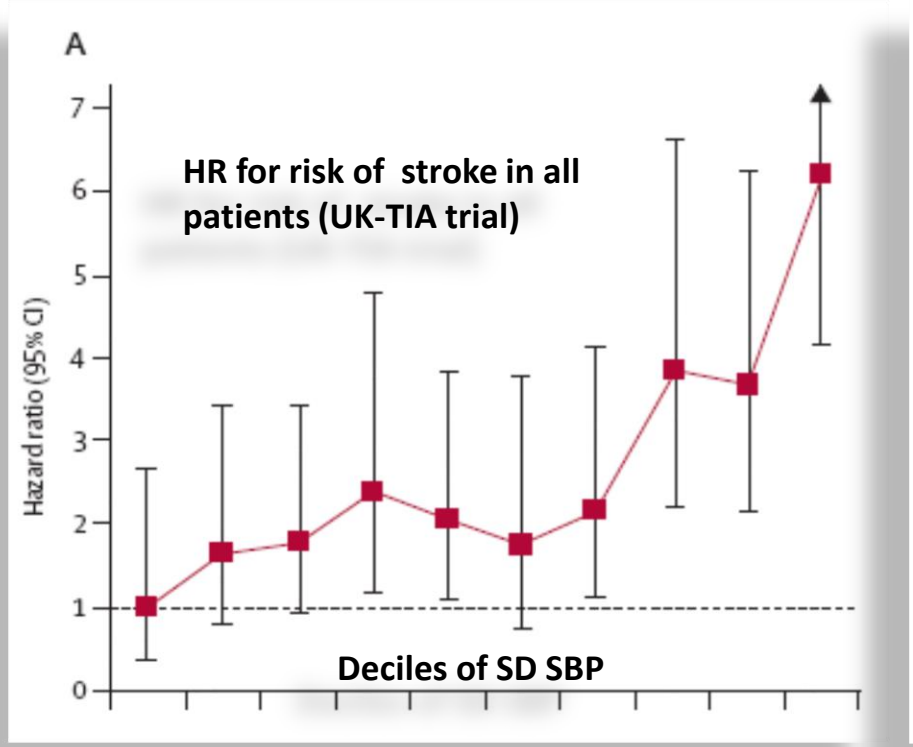
MMD=40-10=30 mmHg **ARV**=10+10+30+10=60/4=15 mmHg

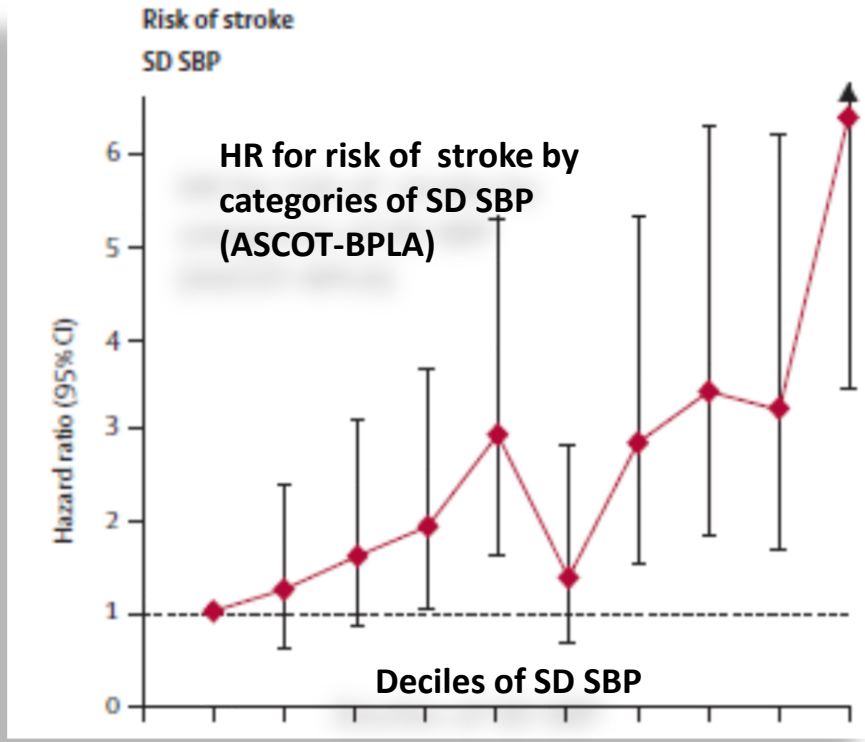
Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

Lancet 2010; 375: 895–905

Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlöf, Peter S Sever, Neil R Poulter

Risk of **stroke** in relation to **visit-to-visit variability (SD** and parameters independent of mean BP) in patients with previous TIA (**UK-TIA trial**) and in patients in **ASCOT-BPLA**

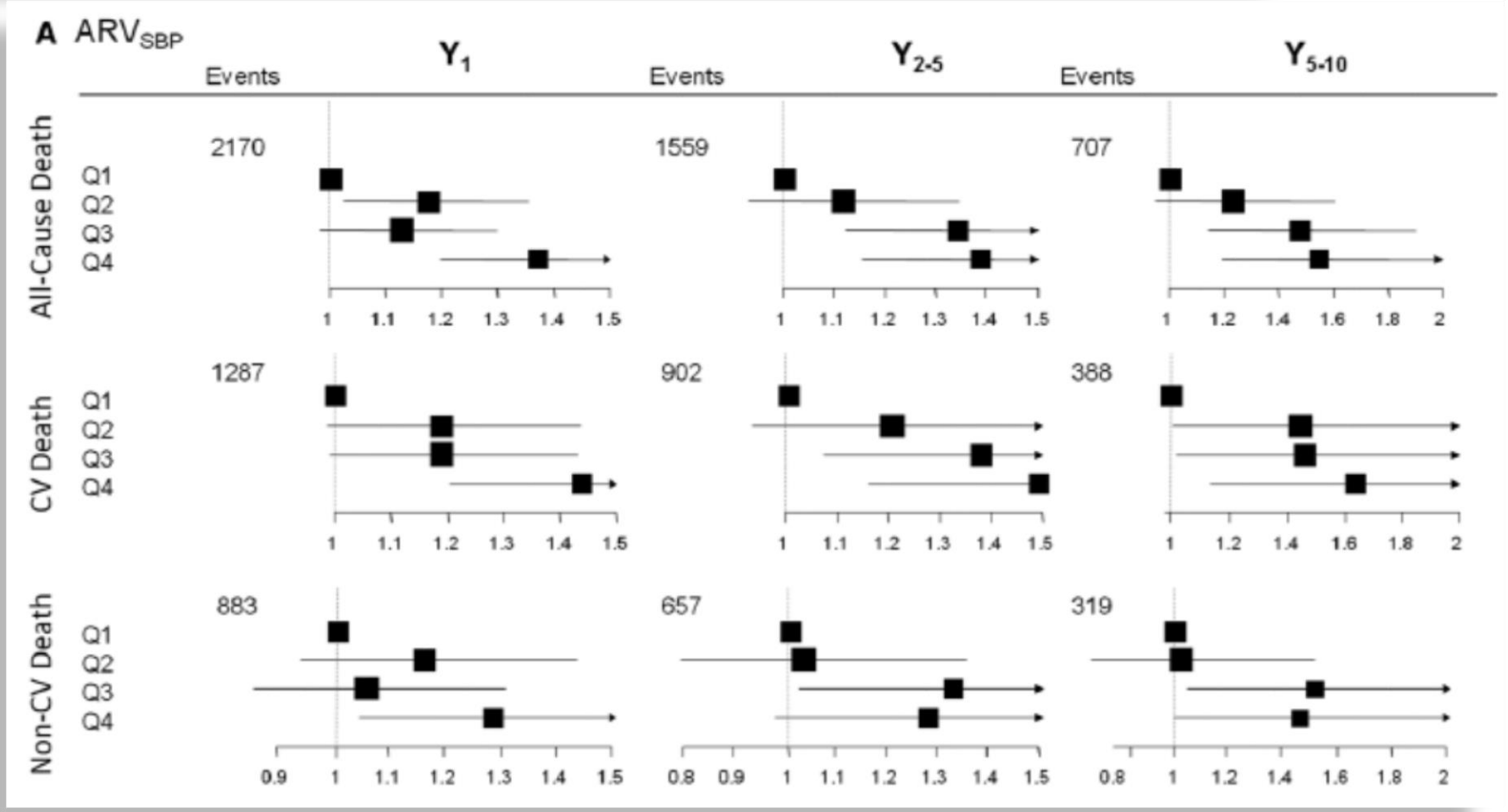




(*Hypertension*. 2013;62:698-705.)

Long-Term and Ultra Long–Term Blood Pressure Variability During Follow-Up and Mortality in 14 522 Patients With Hypertension

14522 pazienti ipertesi (**50 anni**); BPV valutata come ARV in 4 time-frame: 1 anno, 2-5 anni, 5-10 anni, >10 anni



Annals of Internal Medicine

ORIGINAL RESEARCH

Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality

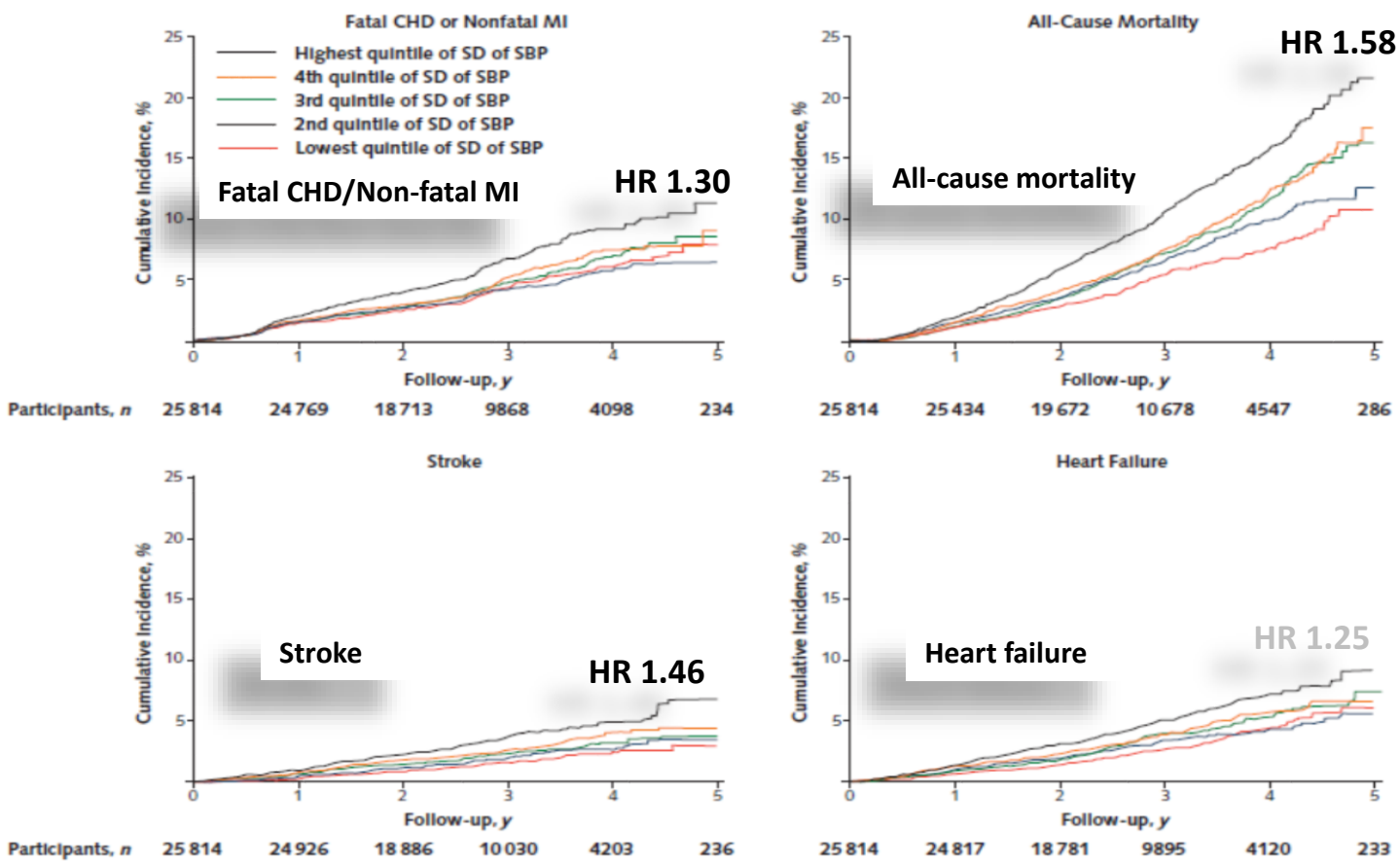
A Cohort Study

Ann Intern Med. 2015;163:329-338.

Paul Muntner, PhD; Jeff Whittle, MD; Amy I. Lynch, PhD; Lisandro D. Colantonio, MD; Lara M. Simpson, PhD; Paula T. Einhorn, MD; Emily B. Levitan, PhD; Paul K. Whelton, MD; William C. Cushman, MD; Gail T. Louis, RN; Barry R. Davis, MD; and Suzanne Oparil, MD

Post-hoc analysis of 25814 **ALLHAT** participants (mean **age 66**); follow-up 28 months; visit-to-visit variability defined as the **SD** across SBP measurements obtained at 7 visits

Figure 2. Cumulative incidence of the 4 outcomes, by quintile of intraindividual SD of SBP.



CHD = coronary heart disease; MI = myocardial infarction; SBP = systolic blood pressure.

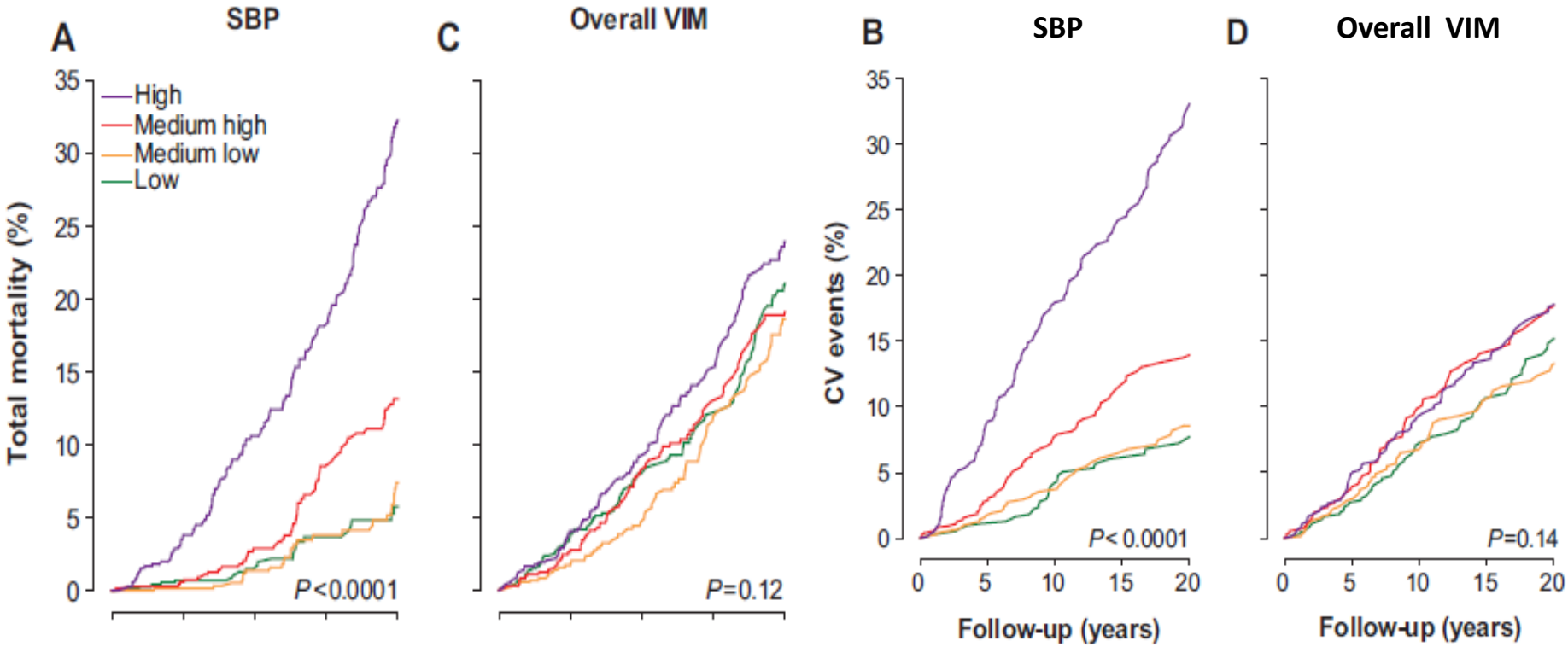
Diverse evidenze suggeriscono che la **variabilità dei valori pressori** sia un **fattore prognostico sfavorevole.** Tuttavia

- I dati al riguardo **non** sono del tutto **concordanti**
- Non è chiaramente definito se e quanto **la variabilità pressoria migliori** o aggiunga alla **stratificazione prognostica** attuale nel paziente iperteso
- Non vi è una chiara concordanza tra i diversi metodi di valutazione, tra **variabilità intra-individuale 24 ore** e **visit-to-visit,** e tra variabilità a **breve, medio e lungo termine**
- La variabilità è ovviamente dipendente dalla metodica utilizzata, dai parametri considerati e dalla «**frequenza**» delle osservazioni

(*Hypertension*. 2012;60:1138-1147.)

Within-Subject Blood Pressure Level—Not Variability—Predicts Fatal and Nonfatal Outcomes in a General Population

2944 general population subjects (mean age **44.9 years**, 50,7% women); within subject overall, within- and between-visit SBP variability calculated from VIM, MM-BP-D and ARV; 401 deaths and 311 fatal and non-fatal CV events during a median follow-up of 12 years

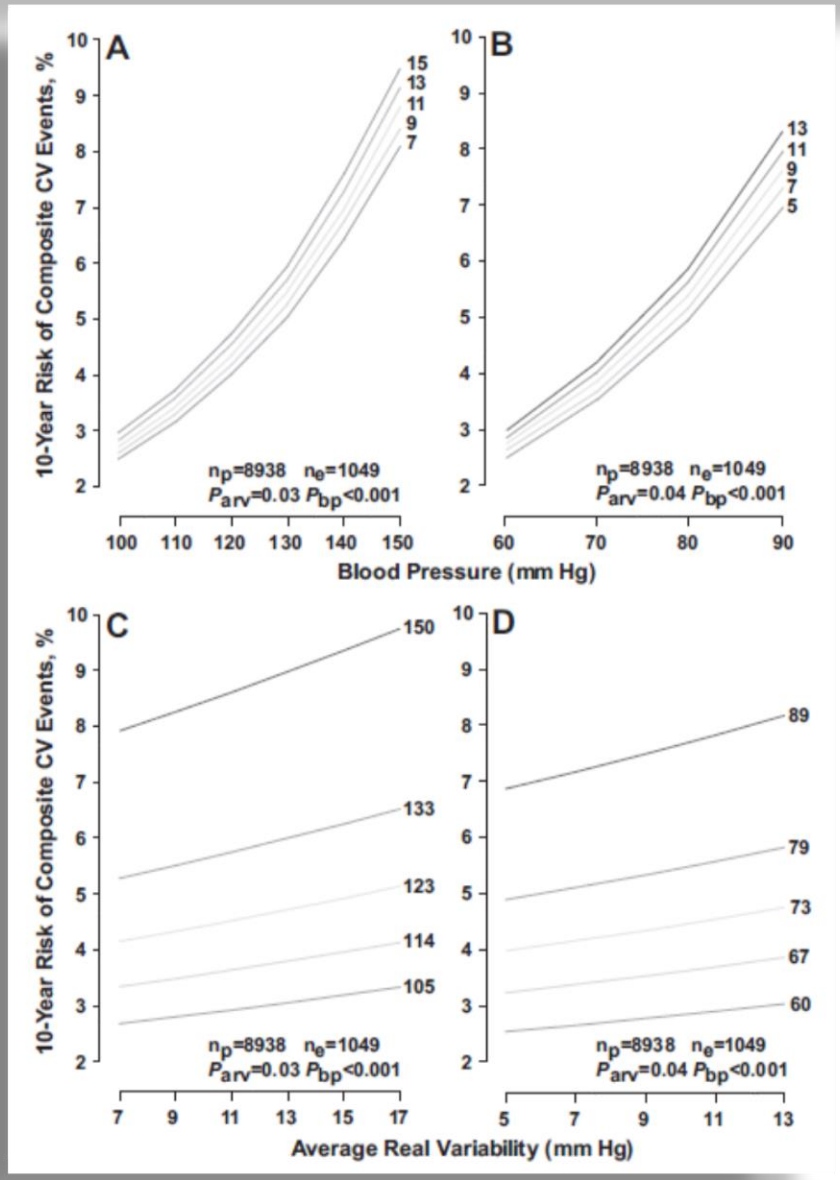


In conclusion, in an unbiased population sample, BP variability did not contribute to risk stratification over and beyond mean systolic BP

Prognostic Value of Reading-to-Reading Blood Pressure Variability Over 24 Hours in 8938 Subjects From 11 Populations

(*Hypertension*. 2010;55:1049-1057.)

8938 soggetti (**53 anni**, 46.8% femmine); BPV valutata mediante SD e ARV in ABPM. Follow-up 11,3 anni



In a large population cohort, which provided sufficient statistical power, **BP variability** assessed from 24-hour ambulatory recordings **did not contribute much to risk stratification over and beyond 24-hour BP**

IMPROVING PATIENT CARE | ORIGINAL RESEARCH

Measuring Blood Pressure for Decision Making and Quality Reporting: Where and How Many Measures?

Ann Intern Med. 2011;154:781-788.

Benjamin J. Powers, MD, MHS; Maren K. Olsen, PhD; Valerie A. Smith, MS; Robert F. Woolson, PhD; Hayden B. Bosworth, PhD; and Eugene Z. Oddone, MD, MHSc

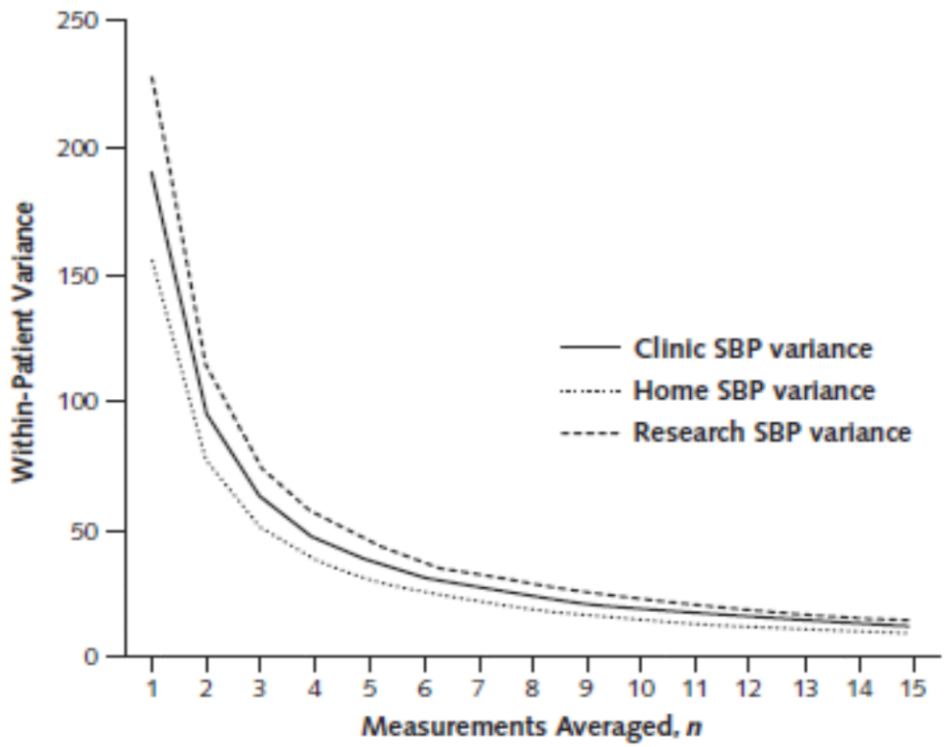
444 **veterans** with hypertension followed for 18 months

BP measured using a) standardized research BP measurements; b) clinic BP outpatient measurements; c) home BP monitor-based measurements

Patients classified as **in control** according to different methods of measurement:
28% by clinic measurement
47% by home measurement
68% by research measurement

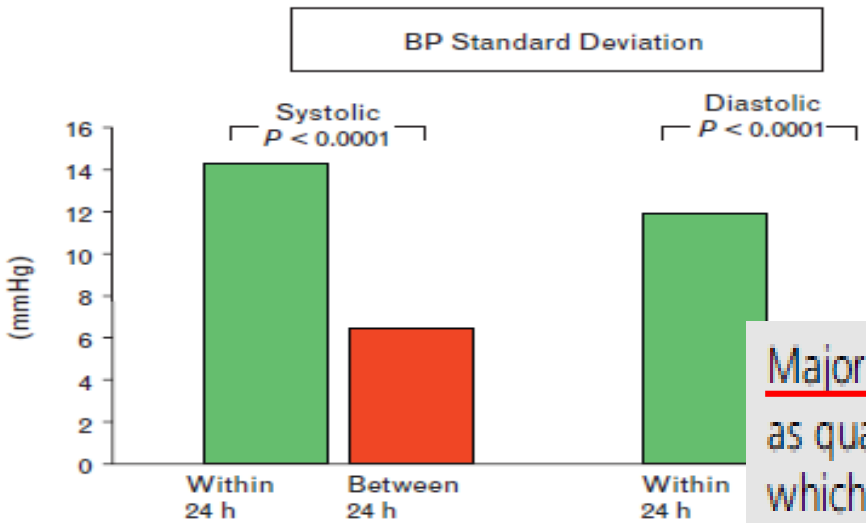
Conclusion: Physicians who want to have 80% or more certainty that they are correctly classifying patients' BP control should use the average of several measurements. Hypertension quality metrics based on a single measurement potentially misclassify a large proportion of patients.

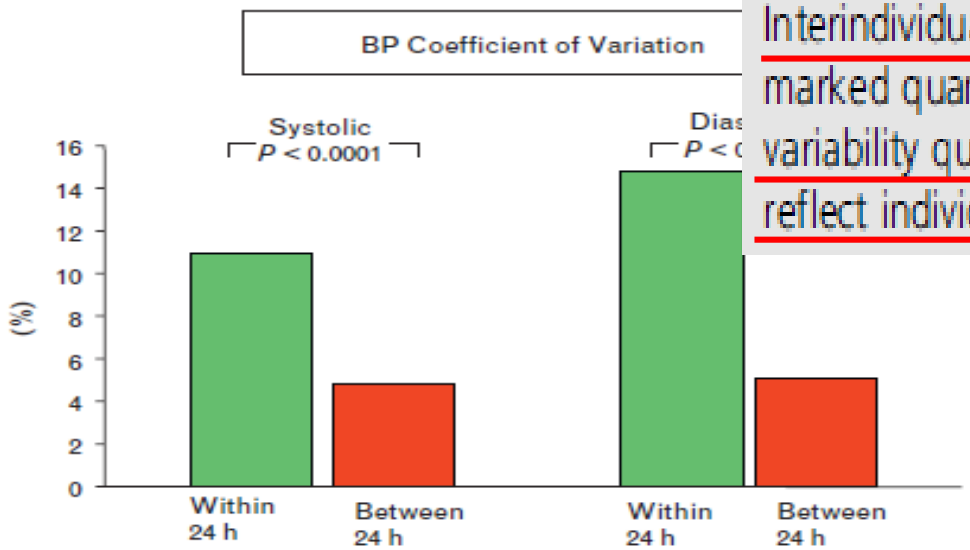
Figure 1. **Within-patient SBP variance and number of measurements.**

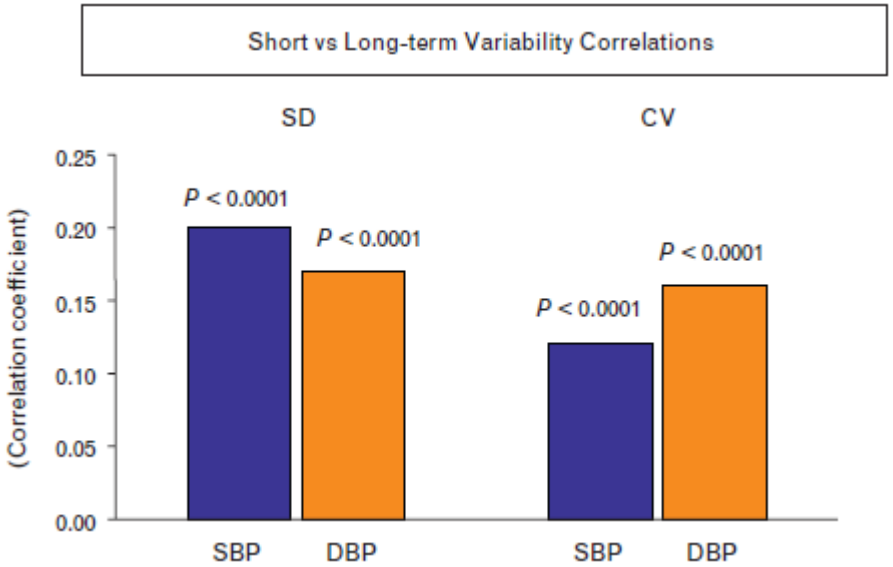


Journal of Hypertension 2012, 30:1241–1251

Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment







Major discrepancies exist between visit-to-visit BP variability as quantified by 24-h vs. clinic BP, making investigation of which of these indices is clinically more relevant important. Interindividual BP variability during treatment shows marked quantitative differences with intraindividual BP variability questioning whether its use can accurately reflect individual BP variations from one visit to another.

Sebbene alcune evidenze suggeriscano che la **variabilità dei valori pressori** sia un **fattore prognostico sfavorevole**

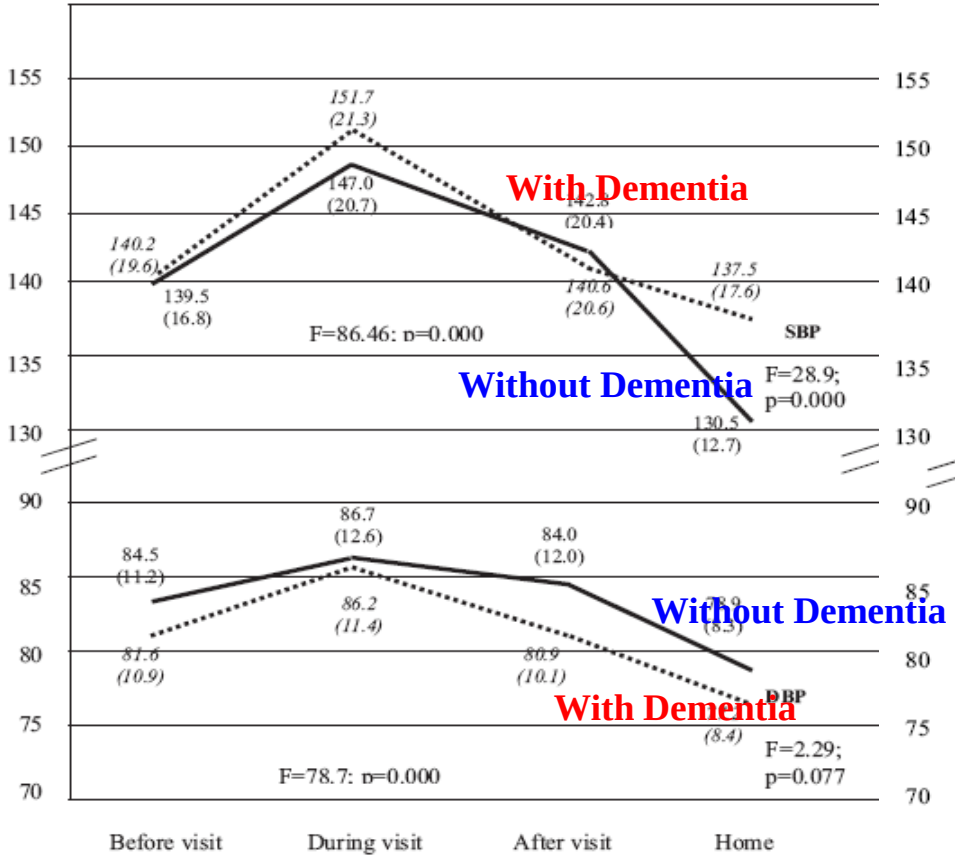
- I dati al riguardo **non** sono del tutto **concordanti**
- Non è chiaramente definito se e quanto **la variabilità pressoria migliori** o aggiunga alla **stratificazione prognostica** attuale nel paziente iperteso
- Non vi è una chiara concordanza tra **variabilità intra-individuale** e **variabilità inter-individuale**, e tra variabilità a **breve, medio e lungo termine**
- La variabilità è ovviamente dipendente dalla metodica utilizzata, dai parametri considerati e dalla «**frequenza**» delle osservazioni
- Non è chiaro quali siano i **meccanismi fisiopatologici** che sottendono questo fenomeno, in particolare se afferiscono direttamente al controllo pressorio o ad altri sistemi

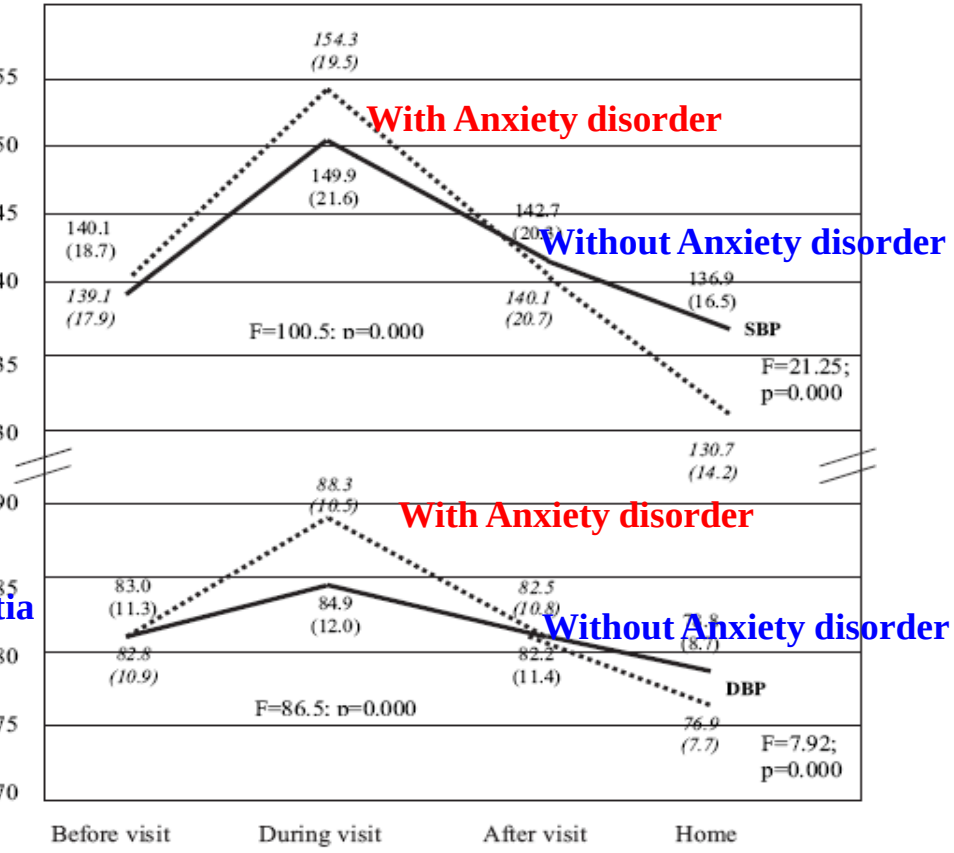
INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry (2008)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/gps.2145

White-coat effect among older patients with suspected cognitive impairment: prevalence and clinical implications

Bo Mario*, Massaia Massimiliano, Merlo Chiara, Sona Alessandro, Canadè Antonella and Fonte Gianfranco

273 patients (**72.6 years**, 61.1% females) evaluated at a first visit for suspected CI, evaulated using Clinical Insight Rating scale (CIR), Generalized Anxiety Disorder, (GAD) Guidelines for the Rating for Awareness Deficits (GRAD)





(*Hypertension*. 2007;49:1265-1270.)

Long-Term Prognostic Value of Blood Pressure Variability in the General Population

Results of the Pressioni Arteriose Monitorate e Loro Associazioni Study

Giuseppe Mancia, Michele Bombelli, Rita Facchetti, Fabiana Madotto, Giovanni Corrao, Fosca Quarti Trevano, Guido Grassi, Roberto Sega

ABPM in 2012 abitanti adulti di Monza; BPV valutata mediante 1) DS media 24 ore, giorno e notte; 2) differenza BP giorno-notte; erratic BP variability mediante analisi spettrale di Fourier. Follow-up 148 mesi

No relationship between the risk of death and 24-hour, day, and night BP SDs.

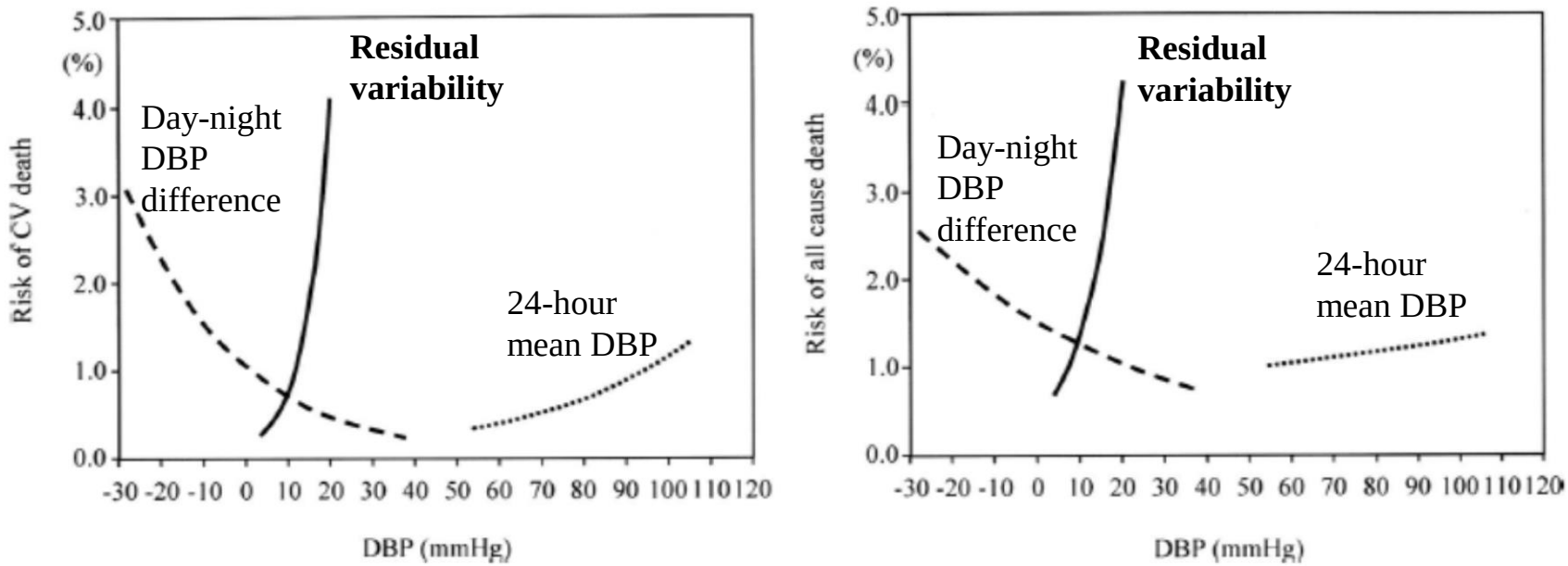


Figure 2. Risk of CV and all-cause death in relation to changes in day–night DBP difference (dashed line), residual variability (continuous line), and 24-hour mean DBP (dotted line). Negative numbers refer to greater night vs day DBP values. Curves have been drawn to cover the ranges of values displayed in the population. Symbols as in Figure 1.

….the relationship of BP to prognosis is complex and phenomena other than the 24-hous mean values are involved.... the first evidence that short-term erratic components of BP variability play a prognostic role

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- Non è chiaro infine **se e quali farmaci** esplichino un effetto favorevole sulla variabilità pressoria, ed in che misura questo incida dal punto di vista clinico.

Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke

Lancet Neurol 2010; 9: 469–80

19257 patients of the ASCOT-BPLA study and 4396 patients of the MRC trial. Visit-to-visit variability expressed as SD and as transformation uncorrelated with mean BP

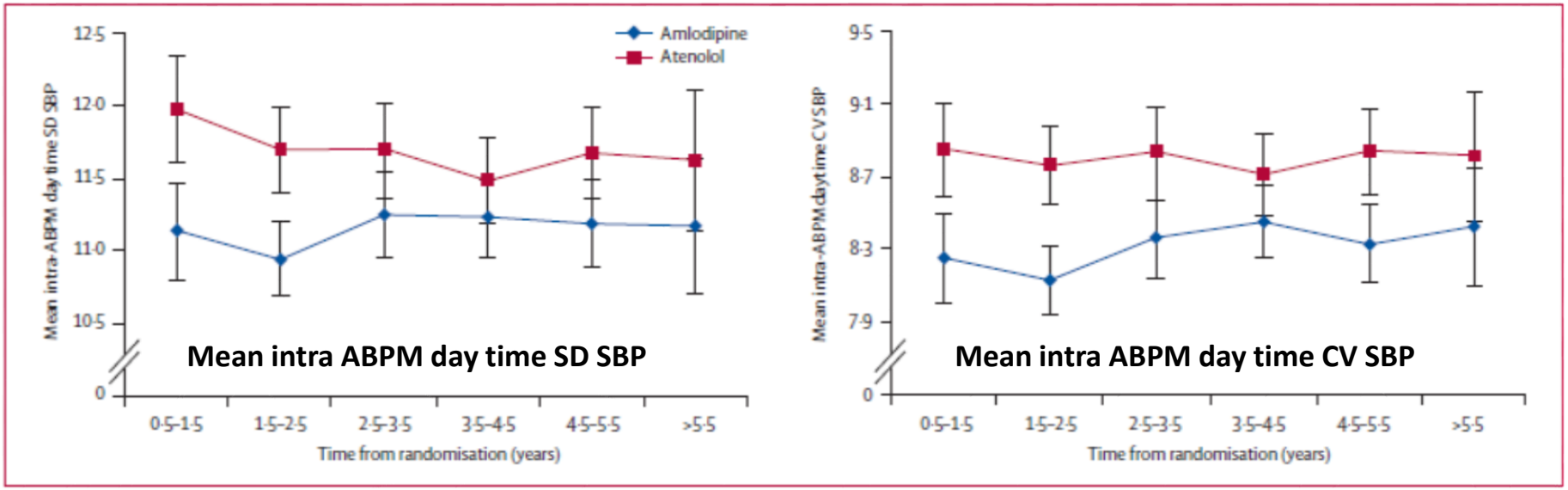

Figure 4: **Variability in daytime systolic blood pressure on ambulatory blood-pressure monitoring by randomised treatment allocation in ASCOT-BPLA**
Daytime SD SBP and CV SBP from yearly ABPM recordings during follow-up in ASCOT-BPLA. ABPM=ambulatory blood-pressure monitoring. SBP=systolic blood pressure. CV=coefficient of variation. Bars are 95% CI.

Interpretation The opposite effects of calcium-channel blockers and β blockers on variability of blood pressure account for the disparity in observed effects on risk of stroke and expected effects based on mean blood pressure. To prevent stroke most effectively, blood-pressure-lowering drugs should reduce mean blood pressure without increasing variability; ideally they should reduce both.

Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis

Alastair J S Webb, Urs Fischer, Ziyah Mehta, Peter M Rothwell

Lancet 2010; 375: 906–15

Effect of treatment on interindividual variance (SD^2) in BP (a surrogate for within-individual variability), expressed as the ratio of the variances (VR) was related to effects on clinical outcomes by use of random-effects meta-analysis of RCTs with different classes of antihypertensive drugs

	Patients	Trials	VR (95%CI)	p value: Pooled	Heterogeneity	Drug A	Drug B	Sign test
Drug class vs all other drug classes								
CCB	344	13	0·72 (0·58–0·90)	<0·0001	0·99	12	0	<0·0001
CCBND	141	9	0·72 (0·47–1·10)	0·1297	0·18	5	4	1·000
DD	302	14	0·83 (0·66–1·04)	0·1124	0·88	11	3	0·019
ARB	114	2	1·59 (0·84–3·01)	0·1450	0·67	0	2	0·500
ACEI	440	18	1·13 (0·93–1·37)	0·1834	0·96	6	11	0·383
BB	411	24	1·40 (1·15–1·71)	0·0018	0·80	5	18	0·011
Drug class vs placebo								
CCB	271	8	0·56 (0·39–0·80)	0·0016	0·97	7	0	0·0160
DD	303	6	0·86 (0·62–1·20)	0·3900	0·73	4	1	0·375
ARB	34	1	1·40 (0·51–3·87)	0·5100	--	0	1	--
ACEI	154	4	0·94 (0·59–1·52)	0·8100	0·82	2	2	1·000
BB	443	11	1·03 (0·78–1·36)	0·8400	0·87	4	6	0·754
Drug class vs drug class								
CCB vs BB	157	5	0·54 (0·33–0·87)	0·0110	0·99	5	0	0·063
CCB vs ACE	375	5	0·78 (0·58–1·05)	0·1000	0·91	4	0	0·125
CCB vs DD	118	2	0·84 (0·50–1·43)	0·5200	0·81	2	0	0·500
DD vs BB	217	5	0·68 (0·46–1·02)	0·0610	0·71	5	0	0·0630
DD vs ACE	205	4	0·80 (0·54–1·20)	0·2900	0·61	3	1	0·625
ARB vs ACE	80	2	1·59 (0·83–3·06)	0·1600	0·68	0	2	0·500
ACE vs BB	216	7	1·02 (0·68–1·53)	0·9200	0·99	3	4	1·000

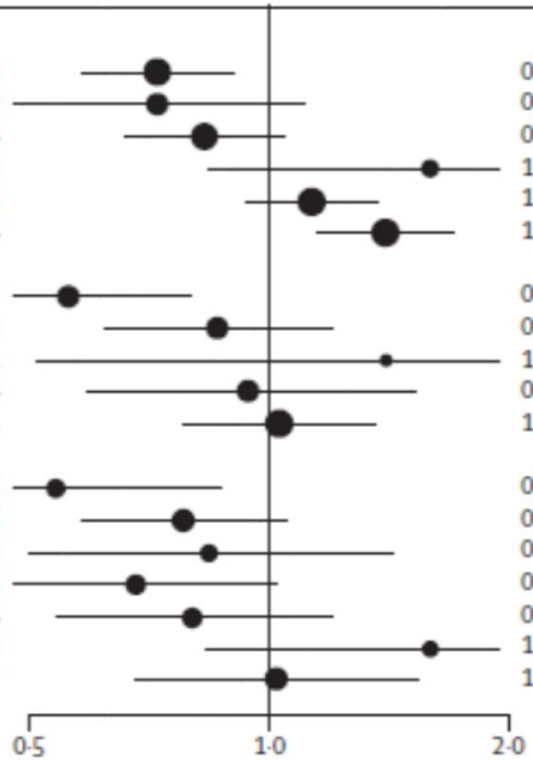

Figure 3: **Pooled estimates of variance ratio (VR) in systolic blood pressure at follow-up for within-trial comparisons between drug classes for 61 crossover trials**
Drug A=first drug class. Drug B=second drug class. CCB=calcium-channel blocker. CCBND=non-dihydropyridine calcium-channel blocker. DD=non-loop diuretic drug. ARB=angiotensin-receptor blocker. ACEI=angiotensin-converting enzyme inhibitor. BB=β blocker.

Journal of Hypertension 2012, 30:1241–1251

Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment

Giuseppe Mancia[a], Rita Facchetti[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

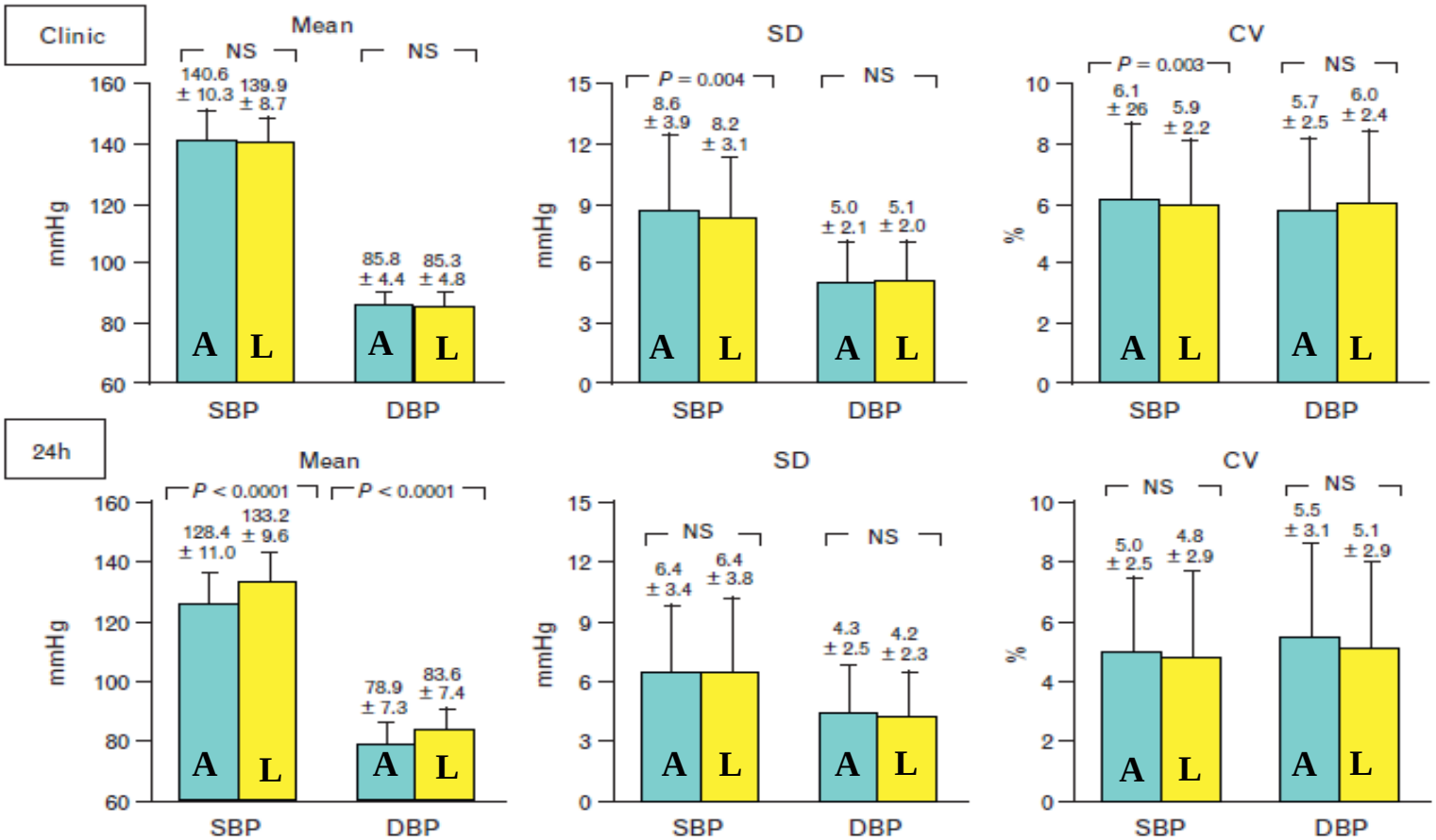

FIGURE 1 On-treatment clinic and 24-h BP mean and intraindividual visit-to-visit SDs and coefficient of variations (CVs) in patients randomized to atenolol (clinic, $n = 289$; 24-h, $n = 242$) or lacidipine (clinic, $n = 291$; 24-h, $n = 253$) who remained on monotherapy throughout the 4 years of the trial. The number of clinic BP values from which SD and CV were calculated was 8.0 ± 0.2 both for the atenolol and for the lacidipine group. The corresponding numbers of 24-h mean values were 3.7 ± 0.5 and 3.7 ± 0.5. Data are shown as means ± SD or percentage. Symbols as in Tables 1–4.

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- Non è chiaro infine **se e quali farmaci** esplichino un effetto favorevole sulla variabilità pressoria, ed in che misura questo incida dal punto di vista clinico.

- La variabilità pressoria è particolarmente **comune negli anziani**, donne in particolare, mentre la maggior parte dei dati disponibili sull'argomento derivano da studi condotti su adulti e vi sono poche evidenze negli ultrasettantacinquenni. Inoltre, valori di riferimento, strategie di approccio farmacologico e target terapeutici nell'anziano differiscono sostanzialmente rispetto alla popolazione più giovane

(*Hypertension*. 2012;60:1138-1147.)

Within-Subject Blood Pressure Level—Not Variability—Predicts Fatal and Nonfatal Outcomes in a General Population

Female sex, **older age**, higher mean systolic BP, lower BMI, a history og PAD and use of beta-blockers were the main correlates of SBP varibility

(*Hypertension*. 2013;62:698-705.)

Long-Term and Ultra Long–Term Blood Pressure Variability During Follow-Up and Mortality in 14 522 Patients With Hypertension

ARV-SBP was higher in **women** ($p<0.01$) and in **older age** ($p<0.001$), CKD ($p<0.01$) and prevalent CV disease ($P<0.01$).

(*Hypertension*. 2011;57:160-166.)

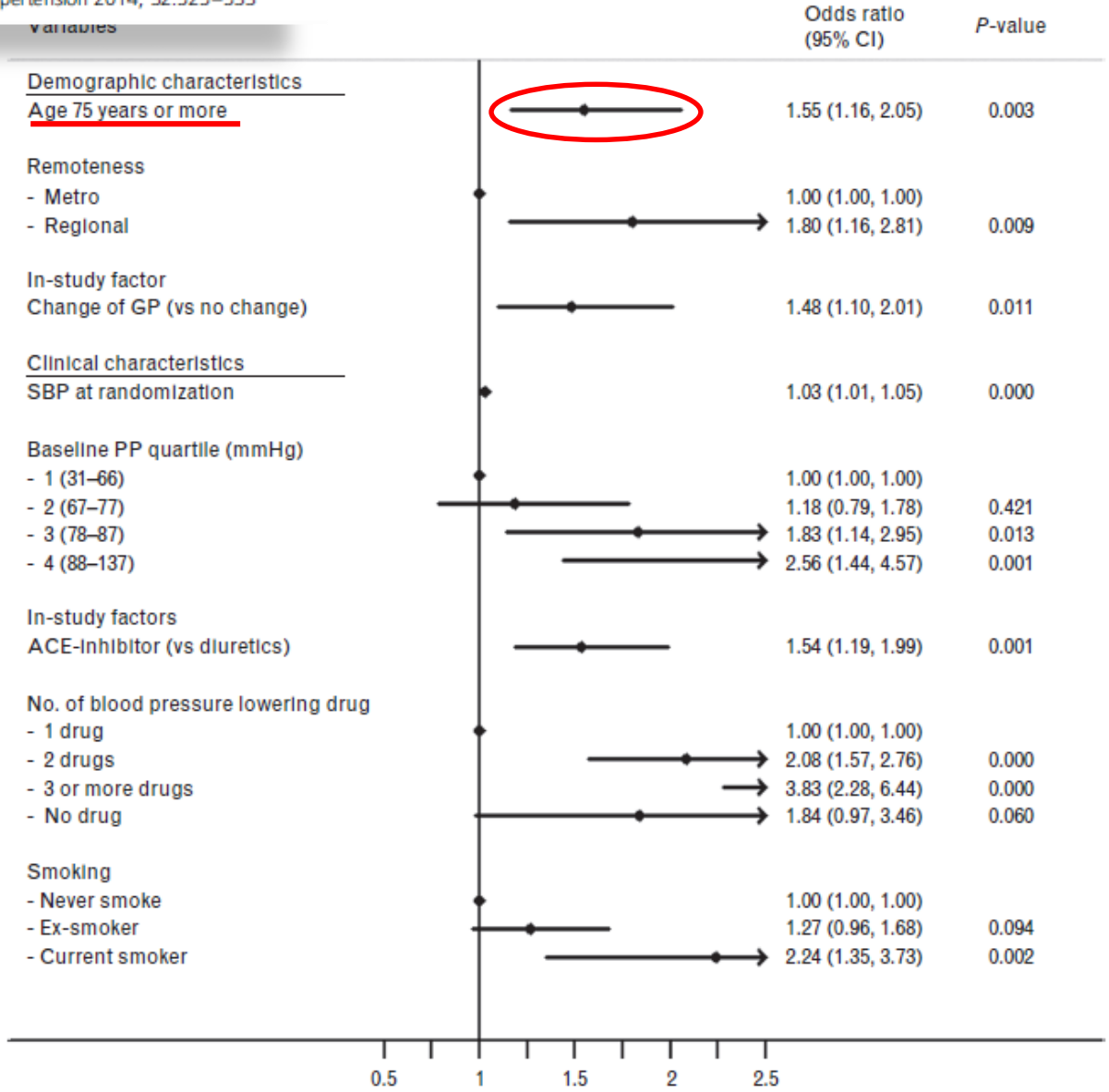
The Relationship Between Visit-to-Visit Variability in Systolic Blood Pressure and All-Cause Mortality in the General Population

Findings From NHANES III, 1988 to 1994

Older age, **female gender,** history of MI, higher mean SBP and PP, and use of ACE-Is were associated with higher SD in SBP

Systolic blood pressure variability is an important predictor of cardiovascular outcomes in elderly hypertensive patients

Journal of Hypertension 2014, 32:525–533



Factors associated with increased visit-to-visit variability

672 ABPM (57.6% F, **50.4% >75 anni**)

Età	**75,4±6,84**
PAS media	131,8±13,9
PAS DS	**18,7±3,7**
PAS CV	0,14±0.03
PAS varianza	362,2±144,4
PAD media	73,6±7,8
PAD DS	**14,0±3,3**
PAD CV	0,19±0.05
PAD varianza	204,6±95,0

PAS DS	65-74 (333)	18,3±3,5	**P<0.01**
	75-84 (265)	18,9±3,7	
	>=85 (74)	19,7±4,2	
	Tutti (672)	18,7±3,7	
PAS CV	65-74 (333)	0,14±0.03	
	75-84 (265)	0,14±0,03	
	>=85 (74)	0,15±0,04	
	Tutti (672)	0,14±0,03	
PAD DS	65-74 (333)	13,6±3,3	**P<0.01**
	75-84 (265)	14,3±3,3	
	>=85 (74)	14,7±3,3	
	Tutti (672)	14,0±3,3	
PAD CV	65-74 (333)	0,18±0,05	**P=0.00**
	75-84 (265)	0,20±0,05	
	>=85 (74)	0,21±0,05	
	Tutti (672)	0,19±0,05	

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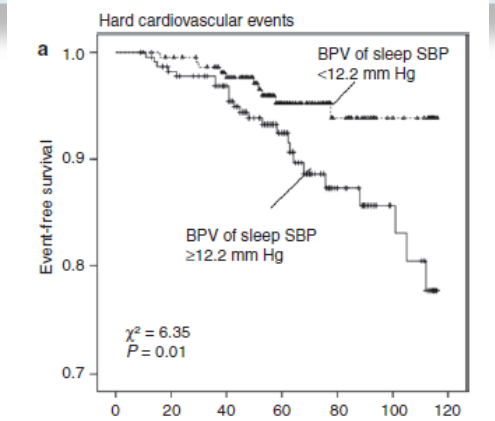
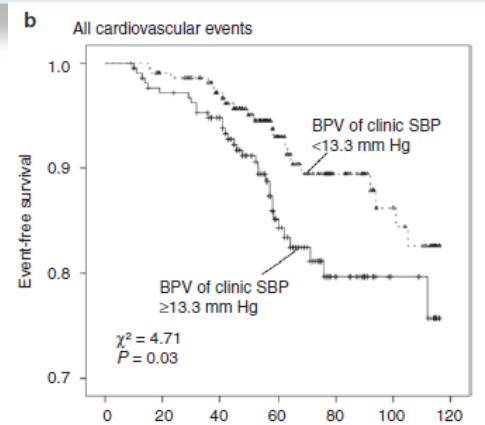
Visit-to-Visit and Ambulatory Blood Pressure Variability as Predictors of Incident Cardiovascular Events in Patients With Hypertension

ABPM in 457 HT patients (**mean age 67 years**, females 63.4%); VV BPV and ambulatory BPV calculated as the SDs of clinic BP, awake BP, and sleep BP; mean follow-up 67 months

Table 3 | Multivariable Cox regression analyses of SBP variability for cardiovascular events

	Hard CVD			All CVD		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age, mean per 10 years	2.27	1.37–3.76	<0.01	1.63	1.16–2.31	<0.01
Diabetes (yes or no)	2.99	1.35–6.63	<0.01	2.97	1.61–5.45	<0.01
Creatinine level per 0.1 mg/dl	1.24	1.05–1.46	0.01	1.12	0.98–1.28	0.09
Current smoking (yes or no)	—	—	—	1.61	0.88–2.94	0.12
Clinic SBP, mean per 10 mm Hg	—	—	—	1.18	1.0311.35	0.02
BPV (s.d.) of clinic SBP, per 5 mm Hg (per 1 s.d.)	0.75 (0.76)	0.48–1.17	0.20	1.48 (1.44)	1.12–1.97	<0.01
BPV (s.d.) of sleep SBP, per 5 mm Hg (per 1 s.d.)	1.49 (1.43)	1.04–2.13	0.03	1.03 (1.02)	0.74–11.43	0.88





*Hard CV events: stroke, MI, SCD

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Blood Pressure Variability and Cardiovascular Risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

5804 soggetti (**70-82 anni**); follow-up a 3 anni (4819 soggetti) e a 7 anni (1808 soggetti)

	Long-term follow-up (n = 1808)				
	Quartile of SD of systolic blood pressure, range in mmHg				
	Group 1 (n = 412) ≤10.5	Group 2 (n = 428) >10.5–≤13	Group 3 (n = 471) >13–≤16.5	Group 4 (n = 497) >16.5	P for heterogeneity
Vascular mortality (n = 315)	1 (ref)	1.1 (0.7–1.5)	1.5 (1.0–2.1)	1.6 (1.1–2.2)	0.016
Total mortality (n = 735)	1 (ref)	1.2 (1.0–1.5)	1.4 (1.1–1.7)	1.5 (1.2–1.8)	0.006

	Long-term follow-up (n = 1808)				
	Quartile of SD of diastolic blood pressure, range in mmHg				
	Group 1 (n = 431) ≤5.5	Group 2 (n = 452) >5.5–≤7	Group 3 (n = 460) >7–≤8.8	Group 4 (n = 465) >8.8	P for heterogeneity
Vascular mortality (n = 315)	1 (ref)	1.3 (0.9–1.8)	1.1 (0.8–1.5)	1.6 (1.2–2.2)	0.020
Total mortality (n = 735)	1 (ref)	1.2 (0.9–1.5)	1.1 (0.9–1.3)	1.4 (1.1–1.7)	0.012

Blood Pressure Variability: Assessment, Predictive Value, and Potential as a Therapeutic Target

Gianfranco Parati · Juan Eugenio Ochoa · Carolina Lombardi · Grzegorz Bilo

Curr Hypertens Rep (2015) 17: 23

Quali sono i meccanismi fisiopatologici sottesi alla BPV?

↑Central Sympathetic drive
↓Arterial/ cardiopulmonary reflex
Humoral, rheological, environmental, behavioral and emotional factors
Activity/ Sleep, Age

Improper dosing or titration of AHT
↓ Arterial compliance
Age

↓adherence and compliance to AHT
BP measurement errors
Age

Ventilation

Seasonal change

Aging

Quali indici di BPV adottare? Su quale intervallo di tempo valutare la BPV?

↑Very short term BPV (beat to beat)	↑Short term BPV (over 24h)	↑Mid term BPV (day-to-day)	↑Long term BPV (visit-to-visit <5years)*	↑Very long term BPV (visit-to-visit≥5 years)*
↑ SOD †	↑SOD †	↑SOD †	↑SOD †	↑ CV mortality
↑CV events ? ‡	↑CV events (stroke, MI)	↑CV events (stroke, MI)	↑CV events (stroke, MI)	↑ Non-CV mortality
↑ mortality? ‡	↑CV mortality	↑CV mortality	↑CV mortality	↑ All-cause mortality
↑Renal outcomes? ‡	↑All cause mortality	↑All cause mortality	↑ Non-CV mortality	↑ IHD mortality
	↑MA and proteinuria	↑MA	↑All cause mortality	
	↓ eGFR, progression to ESRD	↓ eGFR	↑MA and proteinuria	
			↓ eGFR	

Quanto aggiunge la BPV alla stratificazione prognostica abituale?

Blood Pressure Variability
Clarity for Clinical Practice

Clinical Messages From BPV Analyses

- Lowering mean BP remains the therapeutic goal of BP management.
- Further prospective work is needed to elucidate whether altering BPV will improve outcome.

(*Hypertension*. 2010;56:179-181.)

2013 ESH/ESC Guidelines for the management of arterial hypertension

3.1.2.1.3 Additional analyses A number of additional indices may be derived from ABPM recordings.[75–81] They include: BP variability,[75] morning BP surge,[76,77,81] blood pressure load,[78] and the ambulatory arterial stiffness index.[79,80] However, their added predictive value is not yet clear and they should thus be regarded as experimental, with no routine clinical use.