Effect of Fimasartan on BPV

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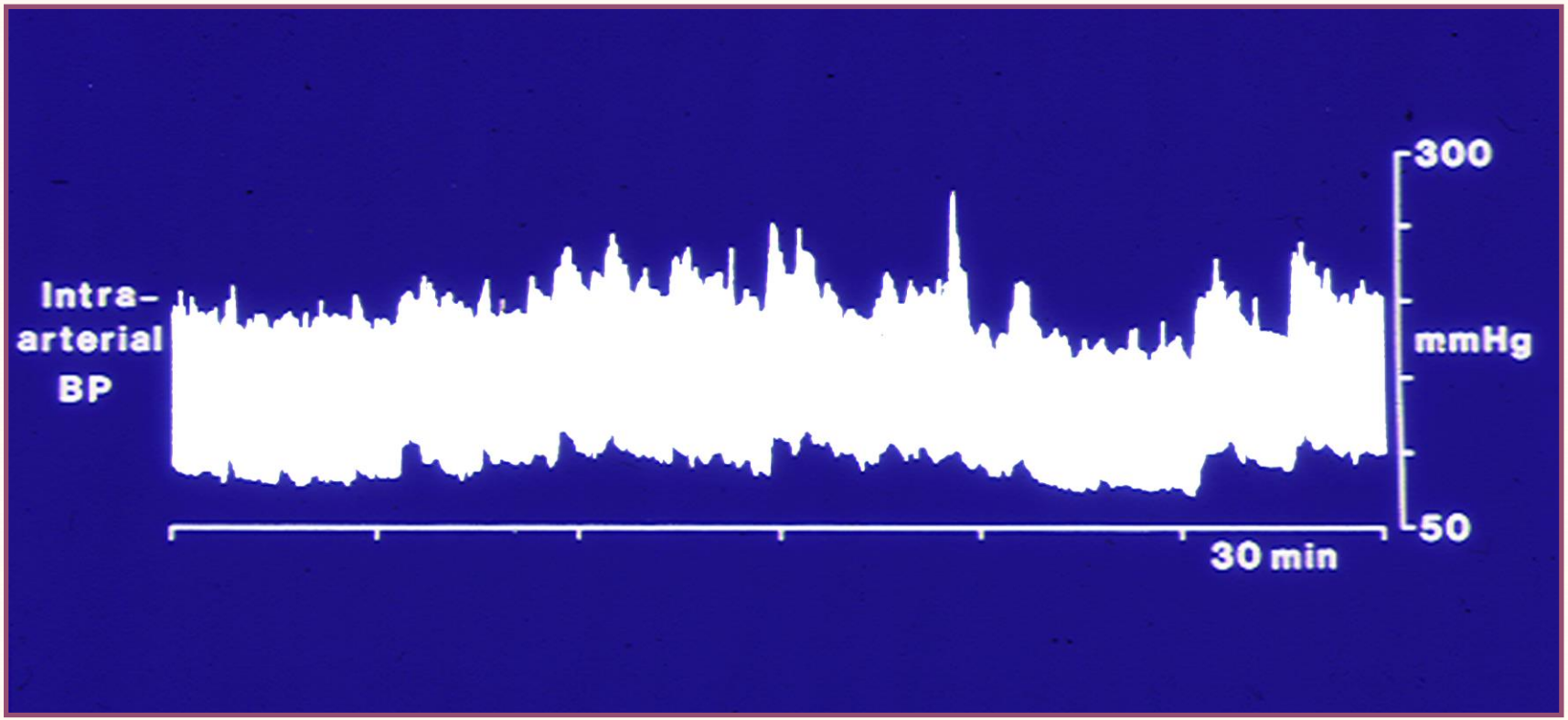
BP is a highly variable parameter

- Intra-arterial BP recording in a subject lying supine, at rest



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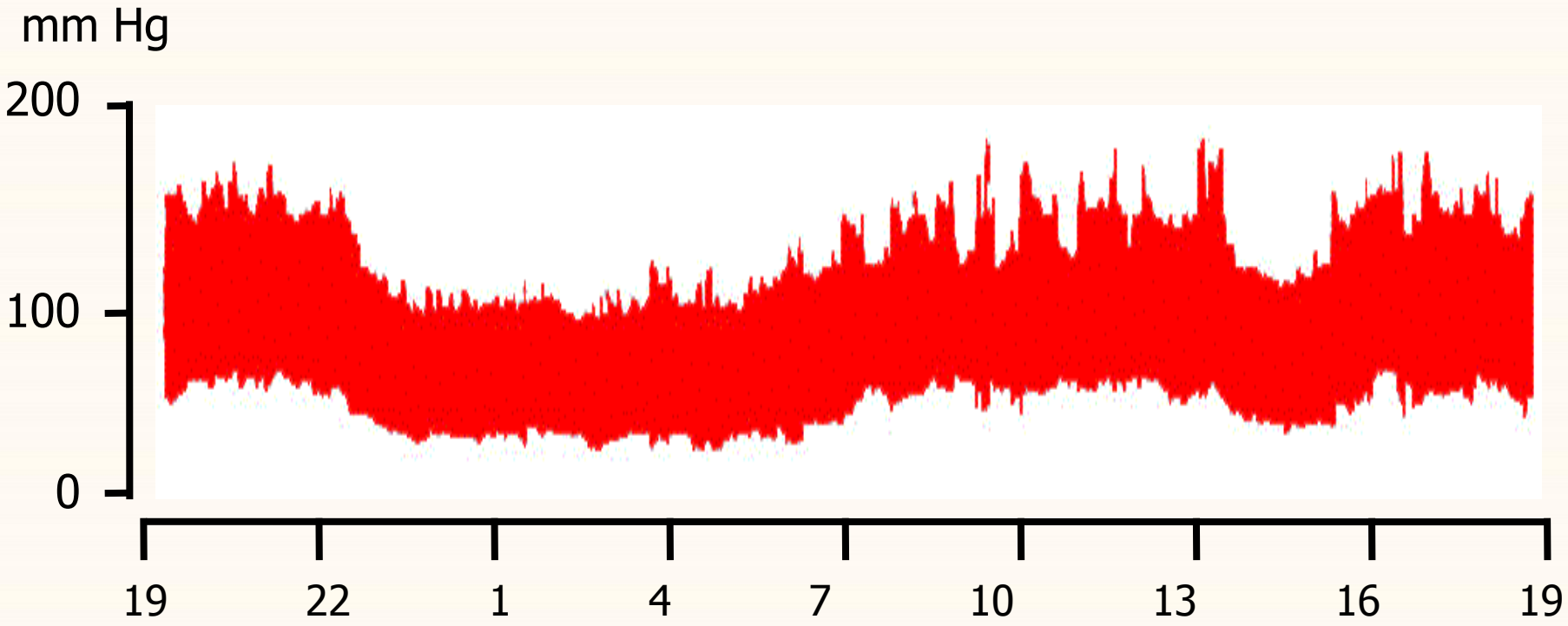
Time Variability of Arterial BP



Ref. Mancia G, Parati G, J Hypertens 1990;8(suppl. 7):S1-S13

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BP Variability (BPV)

Rather than representing a “background noise” or a phenomenon occurring at random, these variations are known to be the result of complex interactions between extrinsic environmental and behavioral factors and intrinsic cardiovascular regulatory mechanisms (neural central, neural reflex, and humoral influences) that are not yet completely understood.

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Parati G. et al, Nat. Rev. Cardiol. 2013; 10:143

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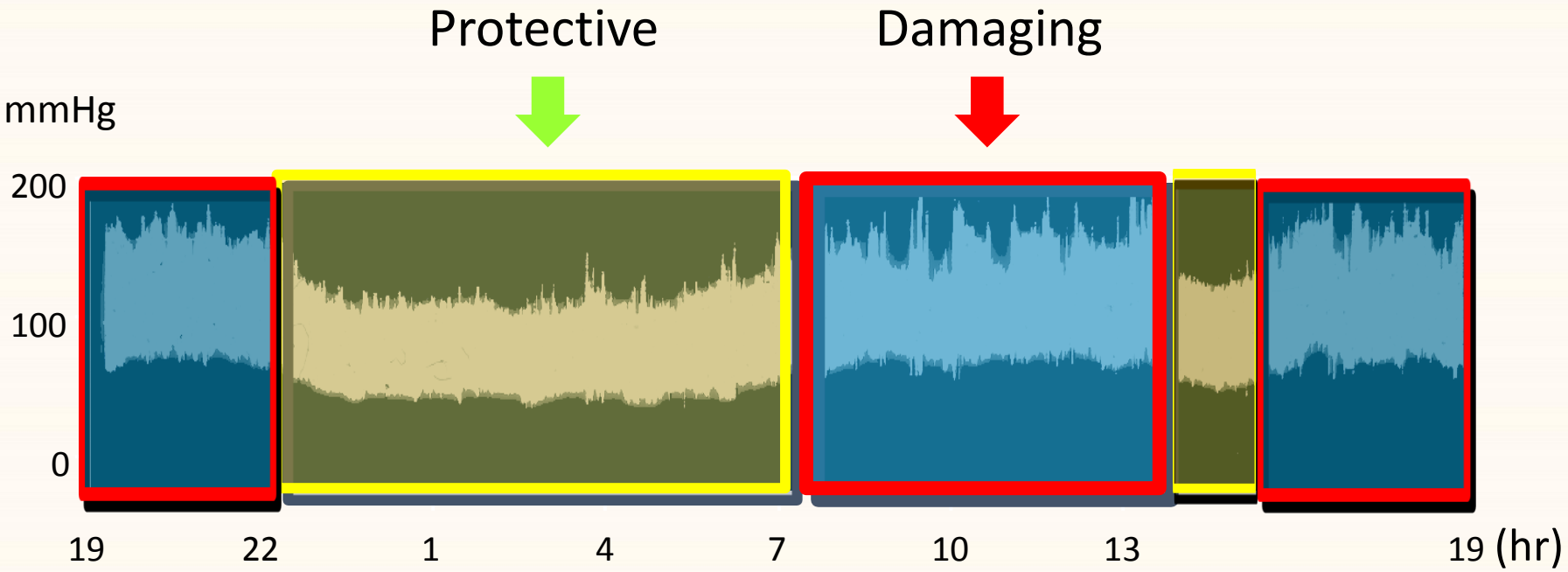
Different Prognostic Impact of Nocturnal BP Fall and Short Term BPV

24h Intra-Arterial BP



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Ref. Mancia G, Parati G 1983

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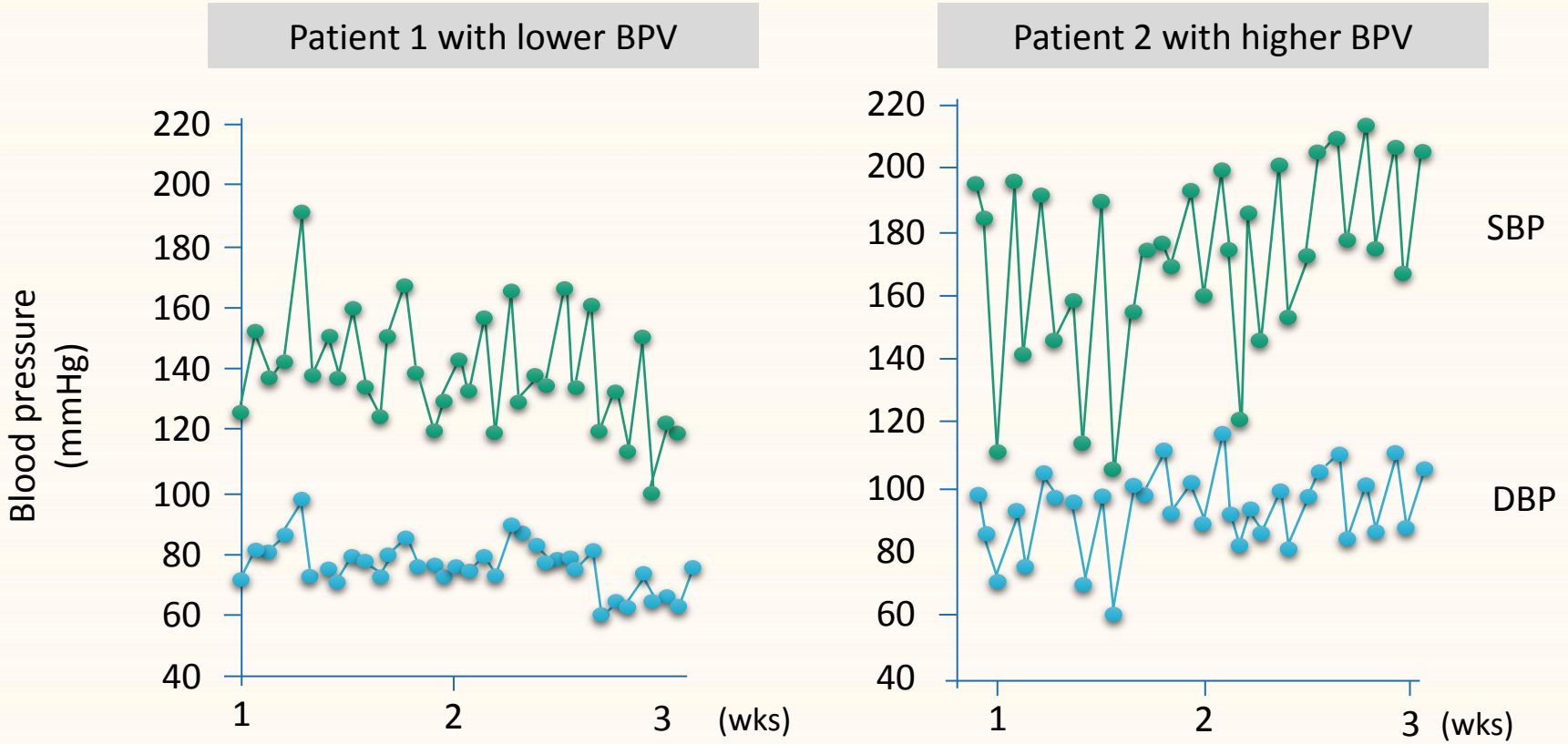
Within-individual BPV over time varies from one patient to another



Ref. Rothwell PM. *Lancet*. 2010;375:938-948.

BP Variability Subtypes

- *<u>Short-term BPV (within 24hrs):</u>*
  - ✓ Very short: beat-to-beat
  - ✓ Short: within a 24-h period

    minute-to-minute, hour-to-hour, and day-to-night
- *<u>Long-term BPV:</u>*
  - ✓ Day-to-day
  - ✓ Visit-to-visit
  - ✓ Seasonal

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BP Variability: Mechanism

Short-time Variability:

- ✓ Beat-to-beat
- ✓ Baroreceptors
- ✓ Respiration
- ✓ Sleep
- ✓ Chemoreceptors

Mechanisms: central and reflex autonomic modulation, reduced arterial compliance, humoral effects, rheological factors, emotional factors, behavioral influences/physical activity, sleep, postural changes.

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BP Variability: Mechanism

Long-term Variability:

- ✓ Day-to-day
- ✓ Visit-to-visit
- ✓ Seasonal: SBP and DBP have been reported to be lower during summer and higher during winter.

Mechanisms: less well studied.

Behavioral factors, increased arterial stiffness, poor BP control, or inconsistent office readings.

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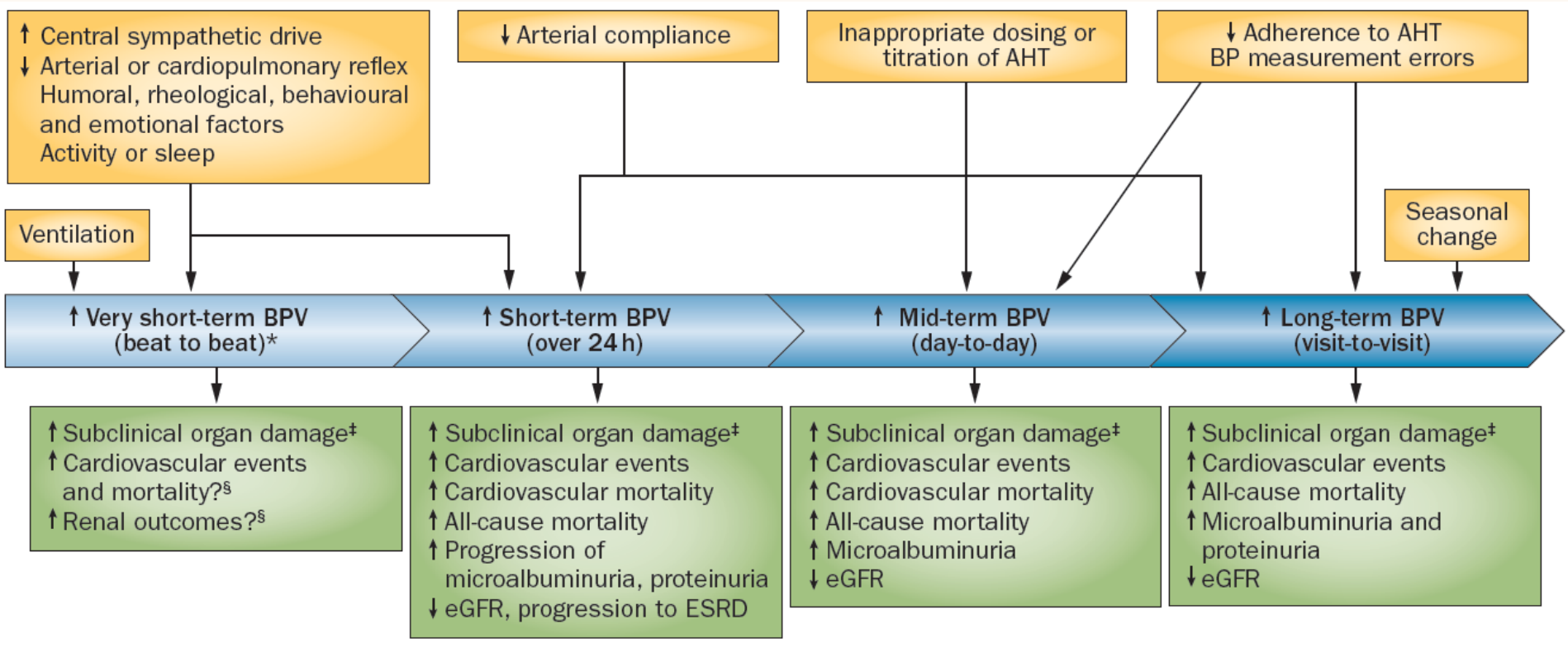
BP Variability:
Types, Determinants, and Prognostic Significance



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Ref. Parati G et al. Nature Reviews Cardiology. 2013.10:143-155 Kanarb®

Assessment of BPV

- Indices: SD, CV, day-to-night BP changes, average real variability (ARV), variability independent of mean (VIM), residual BPV, trough-to-peak ratio, night-to-day BP difference
- Smoothness Index: used to assess the amplitude and distribution over time of BP reduction by treatment.
  24-hourly BP changes/SD
- *Setting:*
  - ✓ Continuous beat-to-beat BP recordings: *SD*
  - ✓ Repeated OBPM: *SD, CV, ARV*
  - ✓ 24h ABPM: *SD, CV, residual BPV, ARV, VIM, day-to-night, trough-to-peak, night-to-day*
  - ✓ HBPM: *SD, CV, VIM*
  - ✓ Visit-to-visit: *SD, CV*

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Assessment of BPV

- *SD:* standard deviation of BP
- *CV:* SD/mean BP
- *Residual BPV:* fast fluctuations that remain after exclusion of the slower components of the 24 h profile through spectral analysis
- *ARV:* (BP2-BP1) + (BP3-BP2) + (BP4-BP3) + etc. /N
- *VIM:* SD/mean BP^X; the mean BP denominator is raised to a certain power, X, that removes any correlation with mean BP.
- *Day-to-night BP:* Dipping status
- *Night-to-day BP:* Morning surge

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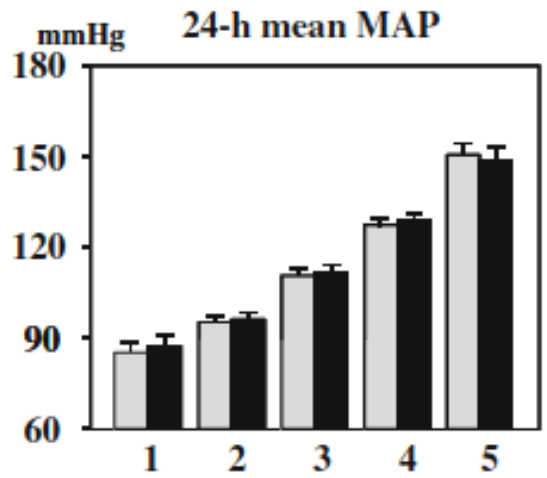
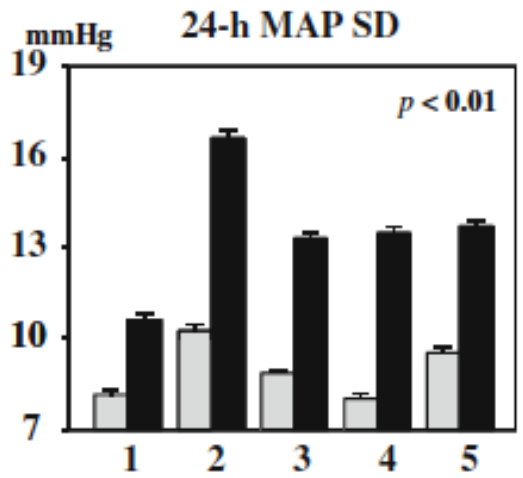
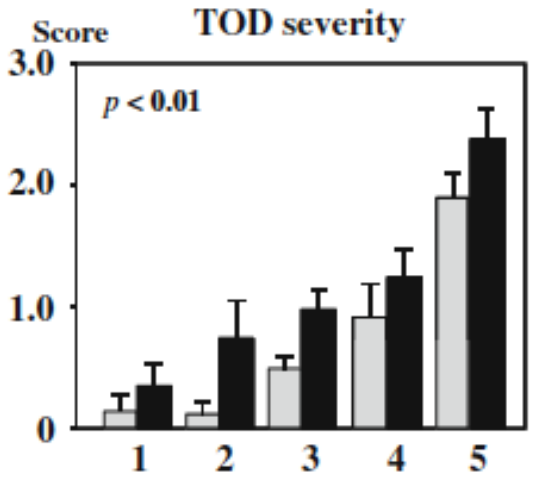
Prognostic Significance of Short-term, 24 hr BPV

Study	Design	Endpoint
Parati, 1987	Cross-sectional	TOD score
Palatini, 1992	Cross-sectional	TOD score
Mancia, Parati, 2001	Cross-sectional	Carotid IMT
Liu, 2003	Longitudinal (rats)	Cardiac /renal damage
Frattola, Parati, 1993	Longitudinal	LV mass (echo)
Sander, 2000	Longitudinal	Carotid IMT / CV events
Dawson, 2000	Longitudinal	Dead / dependency (after acute stroke)
Kikuya, 2000	Longitudinal	CV mortality
Pringle, Parati, 2003	Longitudinal	Stroke
Mena, 2005	Longitudinal	CV events
Mancia, 2007	Longitudinal	CV mortality
Tatasciore, Parati, 2007	Cross-sectional	Carotid IMT, LVMI
Parati, 2009	Longitudinal	CV events
Hansen, 2010	Longitudinal	Only DBP for CV events / stroke

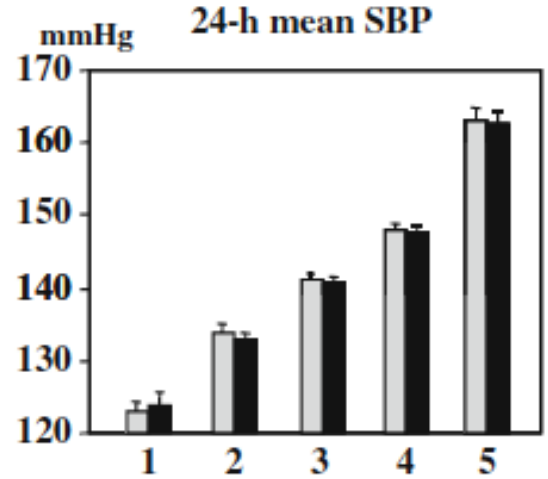
Relationship between 24 hr BPV and OD in HT

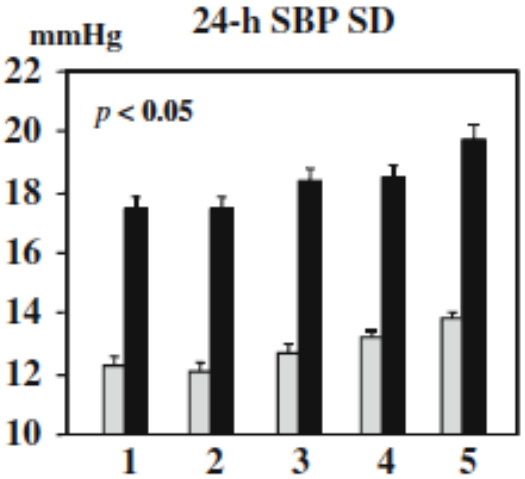


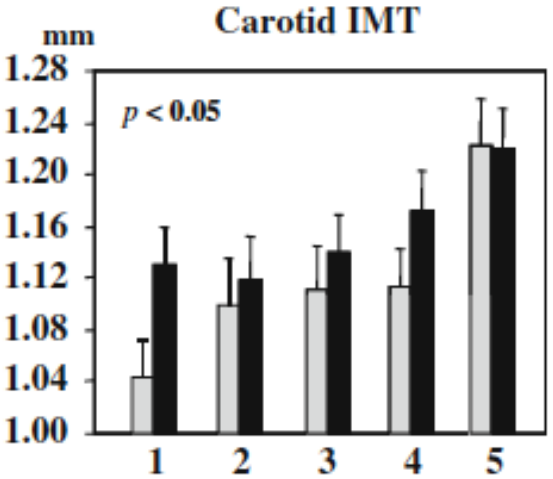




Quintiles of Intra-arterial BP







Quintiles of 24-hr mean SBP

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Mean BPV > group average

Mean BPV < group average

J Hypertens 1987;5:93-8.

J Hypertens 1993;11:1133-7.

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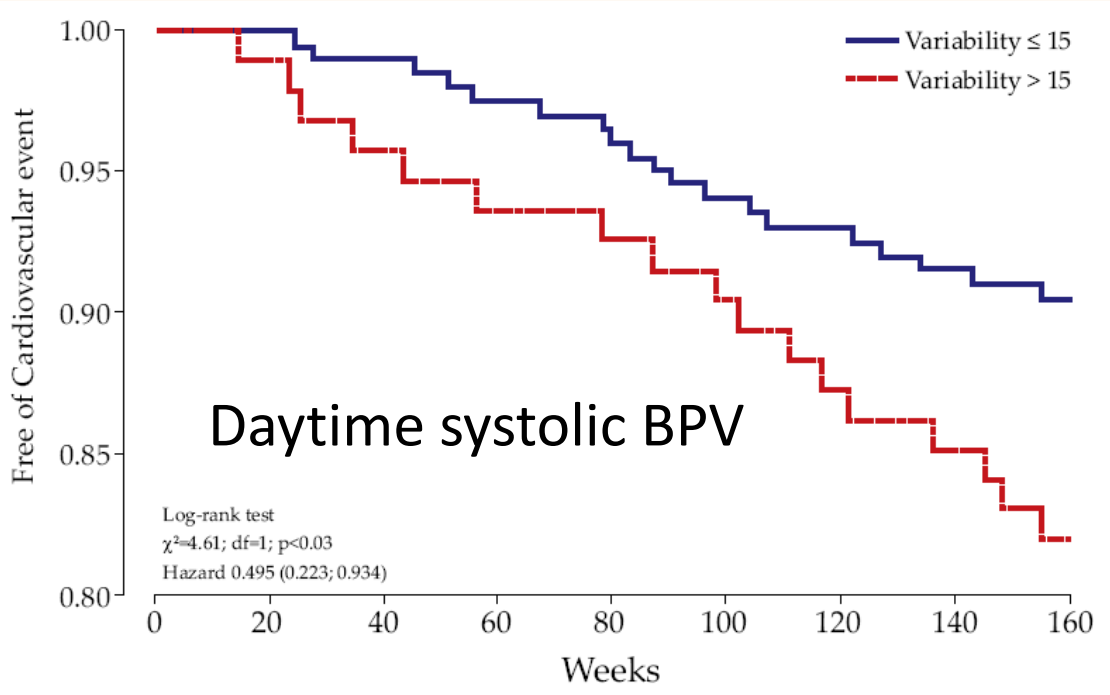
Relationship Between Circadian BP Patterns and Progression of Early Carotid Atherosclerosis

	Odds Ratio (95% CI)	*P*
Variability (>15 vs ≤15 mm Hg)	3.9 (1.4–11.1)	<0.01
Variation (nighttime blood pressure increase vs decrease)	1.27 (0.38–4.3)	NS
Blood pressure (hypertensive vs normotensive)	1.17 (0.55–2.07)	NS

Fatal and nonfatal CV events (TIA, MI, stroke)



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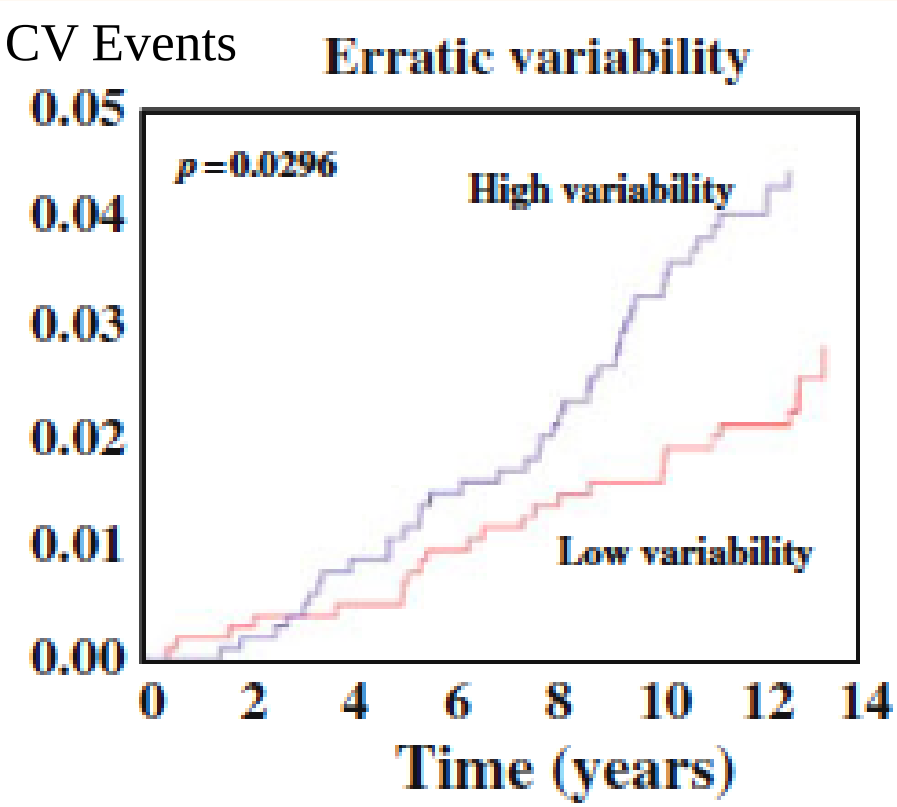
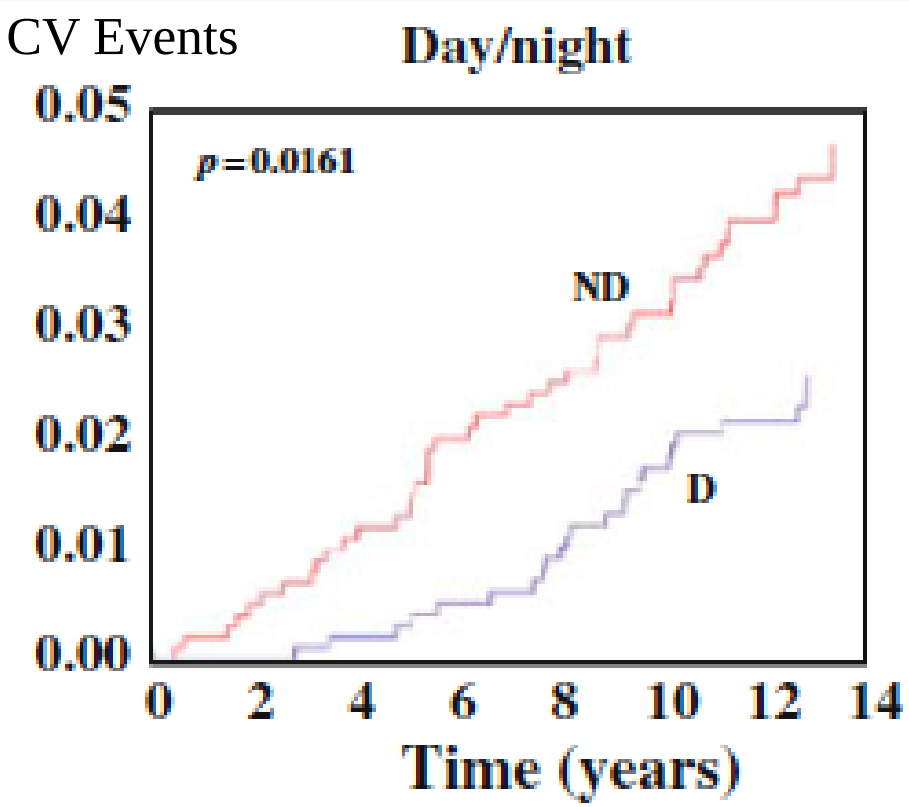
Sander D et al. Circulation. 2000;102:1536-1541

PAMELA Study;

CV Fatal Events in Relation with DBP Variability





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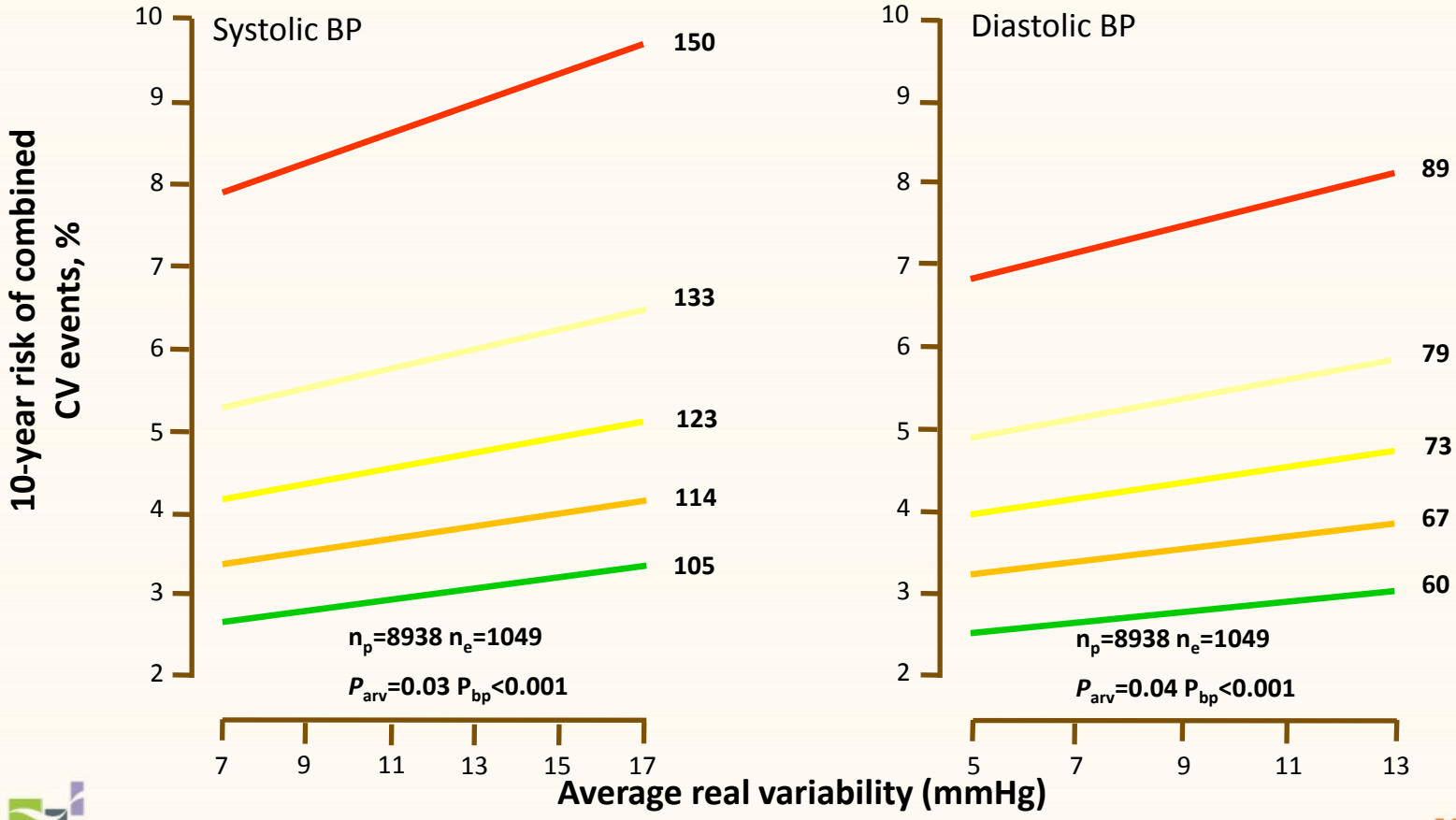
PAMELA study: Hypertension 2007;49:1265-70 Kanarb®

Prognostic Value of Reading-to-Reading BPV over 24 Hours in 8938 Subjects From 11 Population

10-year risk associated with ARV24 at different levels of BP



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Ref. Hansen TW et al, Hypertension 2010; 55: 1049-57

Prognostic Value of Reading-to-Reading BPV over 24 Hours in 8938 Subjects From 11 Population

Risk of a Composite CV Event Explained by Cox Regression

	Systolic Blood Pressure			Diastolic Blood Pressure		
Models	Likelihood Ratio	*P*	R^2 (%)	Likelihood Ratio	*P*	R^2 (%)
Basic model*	10 307.0	…	9.95	10 307.0	…	9.95
+24-hour blood pressure	10 213.4	< 0.001	11.1	10 258.2	< 0.001	10.6
+24-hour blood pressure and ARV	10 209.4	0.046	11.2	10 250.6	0.006	10.7

P values are for the improvement of the fit across nested models.

*The basic Cox model included as covariables, sex, age, 24-hour HR, BMI, smoking and drinking, serum cholesterol, history of CV disease, DM, and treatment with antihypertensive drugs.

BPV assessed from 24-hour ambulatory recordings did not contribute much to risk stratification over and beyond 24-hour BP.

Ref. Hansen TW et al, Hypertension 2010; 55: 1049-57

Prognostic Significance of Day-by-Day BPV

Studies assessing the prognostic value of home BPV

Study	Population (n)	Follow-up (years)	HBP (time/n/days)	HBPV measure	End points	Main findings
Kikuya *et al.* (Ohasama)[6]	General 2455	11.9	m/1/26	SD, CV	Mortality total, CVD, stroke, non-CVD, cardiac	Day/day S/D BPV independently associated with ↑Total, CVD, stroke mortality (not cardiac)
Hashimoto *et al.* (Ohasama)[10]	Men without stroke 902	13.1	m/1/26	SD	stroke according to smoking status	S-BPV associated with cerebral infarction in ever, not in never smokers
Asayama *et al.* (Ohasama)[11]	General 2421	12	m&e/1/26	VIM, MMD, ARV	CVD, total mortality	m SBP: VIM, ARV predicted total and CVD mortality in all. VIM predicted CVD mortality in treated and total mortality in untreated; m MMD not predictive. e SBP: only VIM predicted CVD mortality in all and in untreated. None of the new indices predicted stroke. VIM, MMD and ARV not incrementally predictive of outcome over and beyond mean SBP (minimal impact)
Johansson *et al.* (Finn-Home)[12]	General 1866	7.8	m&e/2/7	SD m–e, day/day (m&e), 1st–2nd	CVD, total mortality	BPV m–e, m day/day independent predictors of CVD events. SBPV m–e, m day/day, 1st–2nd predicted total mortality
Schutte *et al.*[13]	General 2944	12	≠/5/2 visits (2–4 weeks; nurses)	VIM, MMD, ARV	CVD mortality, morbidity	Not predictive of total and CVD mortality, or CVD events

Abbreviations: ARV, average real variability; BP, blood pressure; BPV, BP variability; CV, coefficient of variation; CVD, cardiovascular disease; day/day, day-by-day; e, evening; HBP, home BP; HBPV, home BPV; m, morning; MMD, difference between maximum and minimum BP; n, number; S, systolic; SD, standard deviation; VIM, variability independent of mean; ≠, differing.

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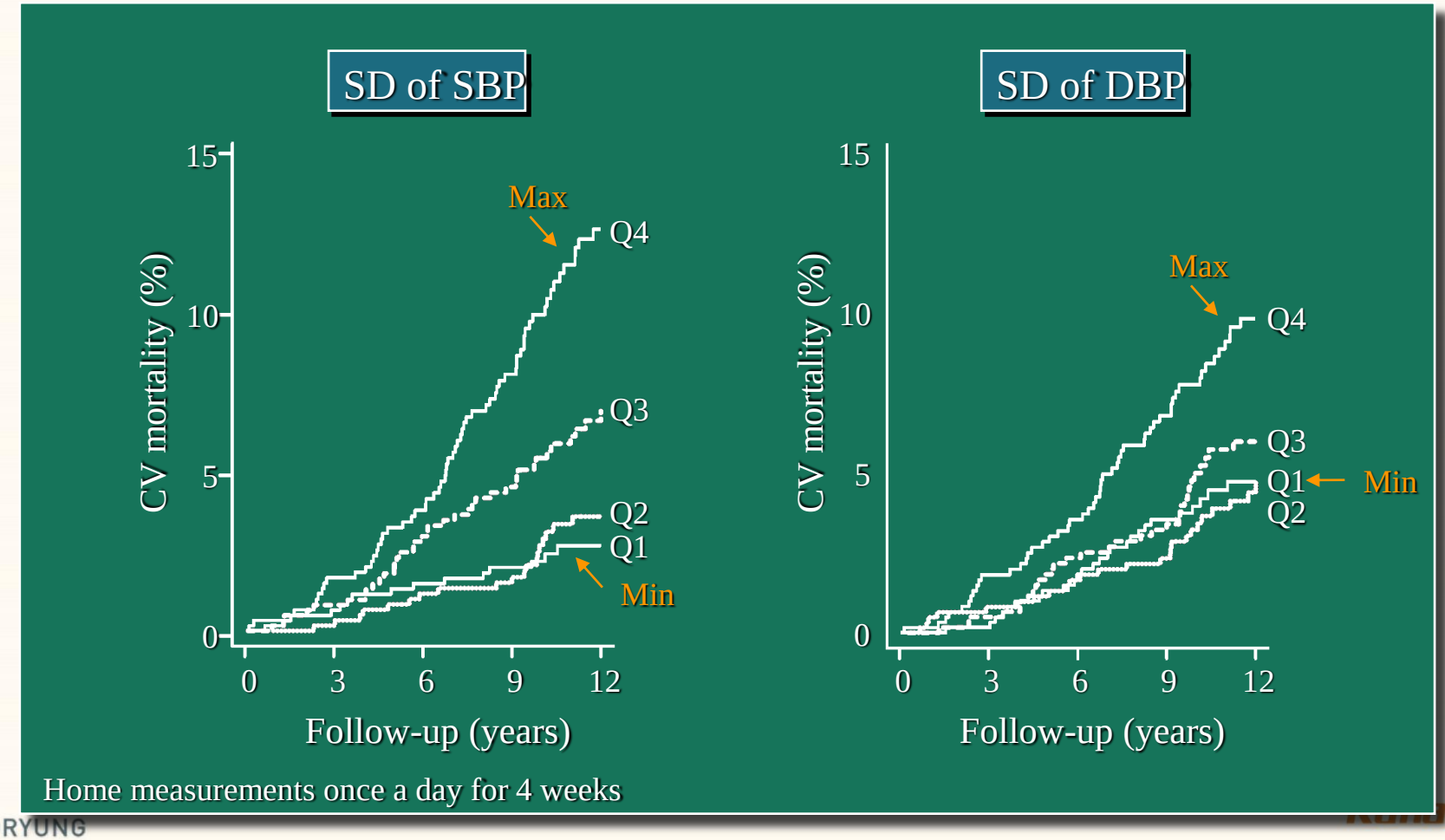
Stergiou GS et al. Hypertension Research 2014;37:565–572

OHASAMA STUDY

- *Kaplan-Meier Survival Estimates for CV Mortality across Quartiles of Day-by-Day BP Variability (HBPM) (n= 2455)*

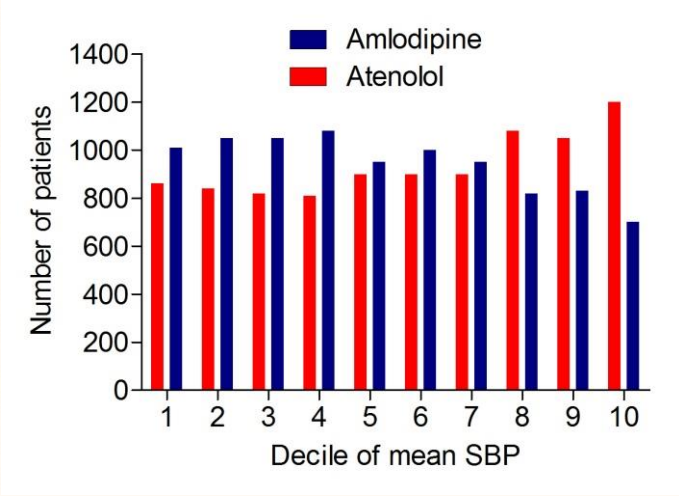


Ref. Kikuya et al. Hypertension. 2008

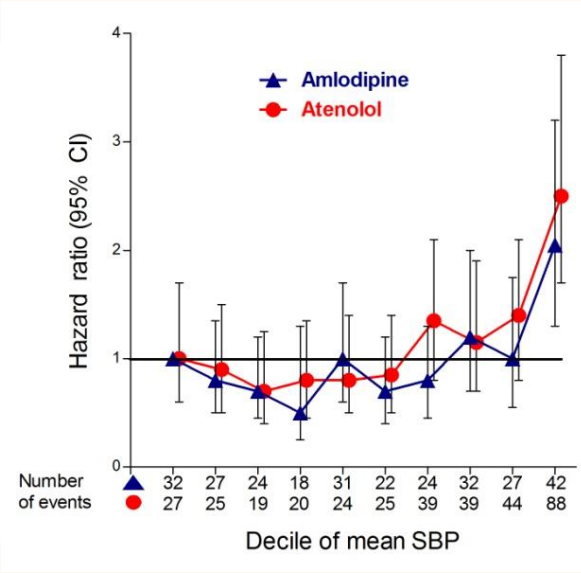
Prognostic Significance of Visit-to-Visit BPV

ASCOT-BPLA; Visit-to-visit mean SBP expressed in deciles

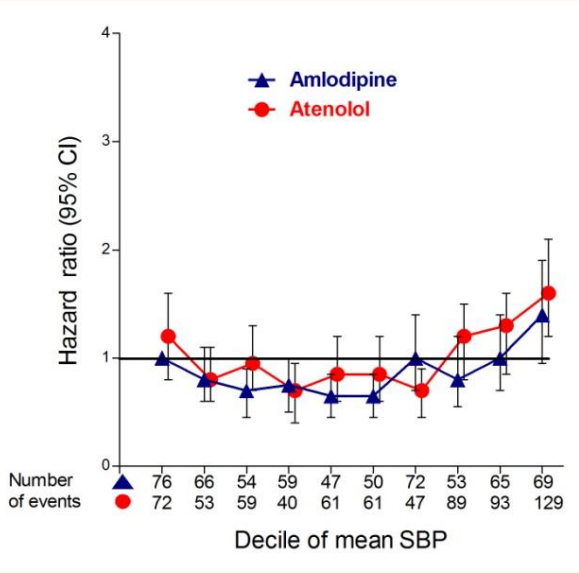
Mean SBP



Stroke risk



Coronary risk



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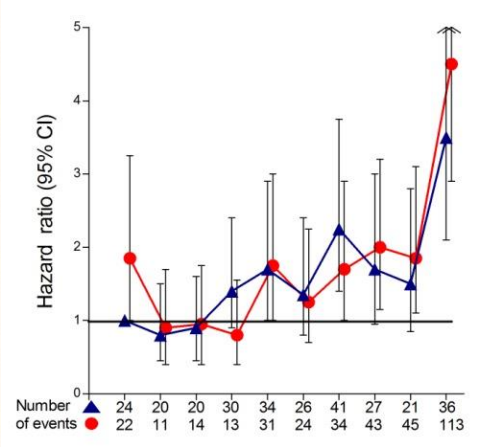
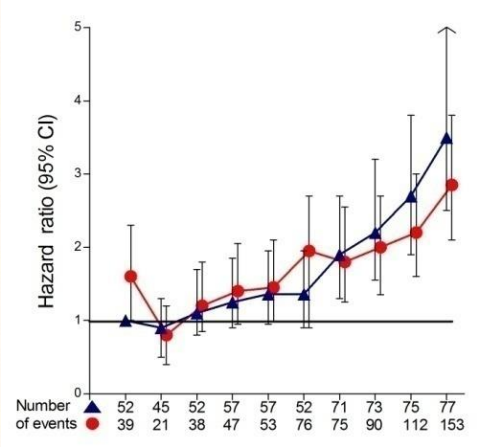
Prognostic Significance of Visit-to-Visit BPV

ASCOT-BPLA; Stroke and coronary risk expressed by decile of measure of visit-to-visit SBP variability

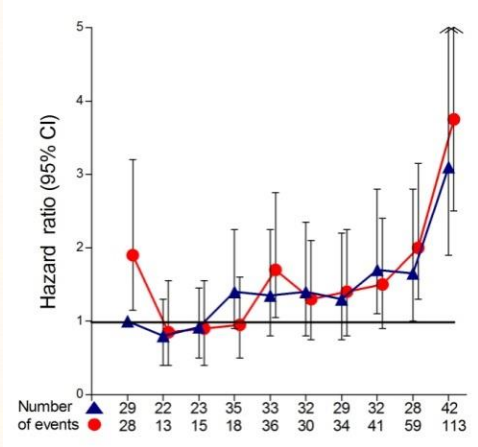
Stroke Risk **Coronary Risk**

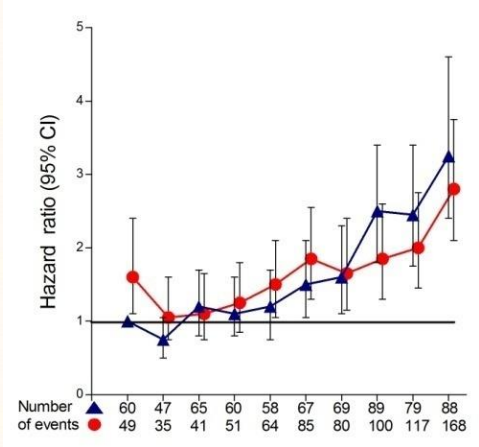
SD of SBP





CV of SBP





Amlodipine

Atenolol

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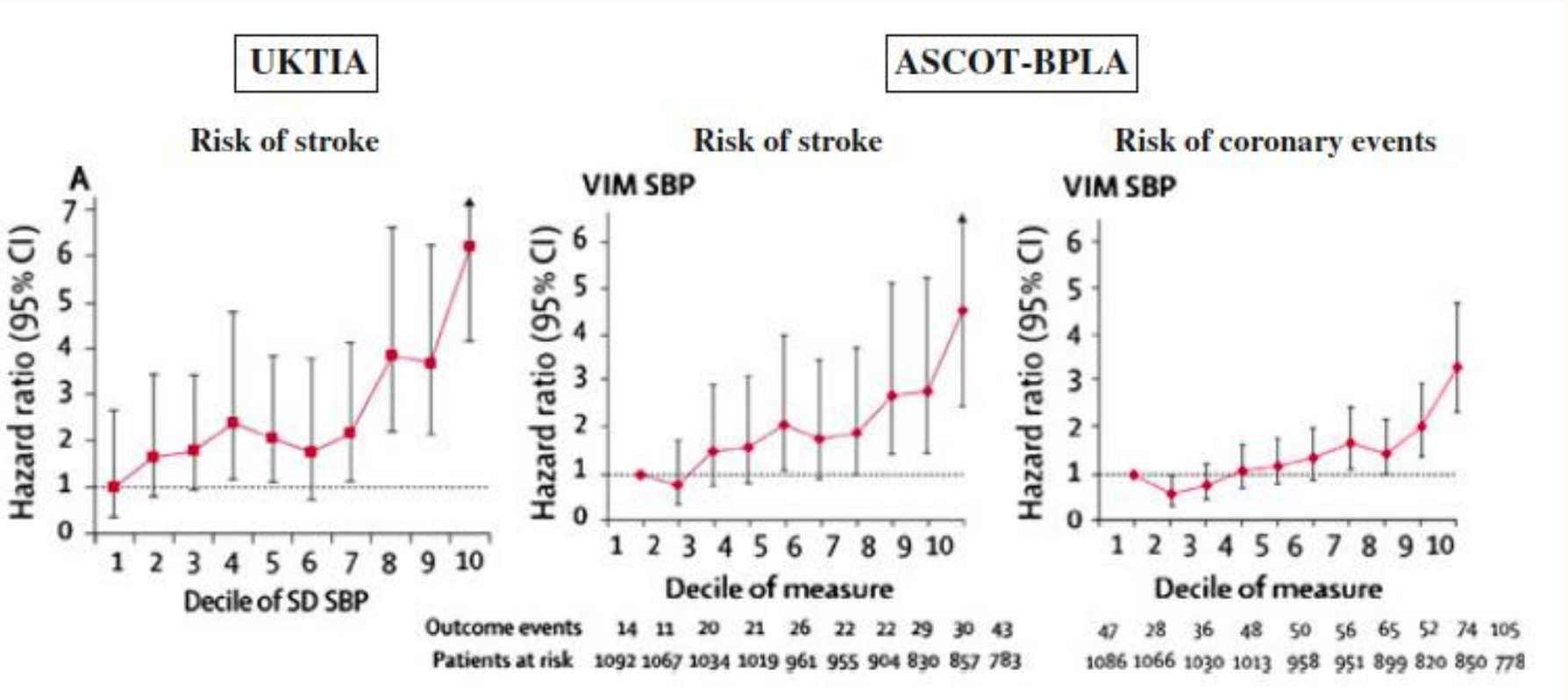
Visit-to-visit Variability and Risk of Stroke and Coronary Events in UK-TIA & ASCOT-BPLA

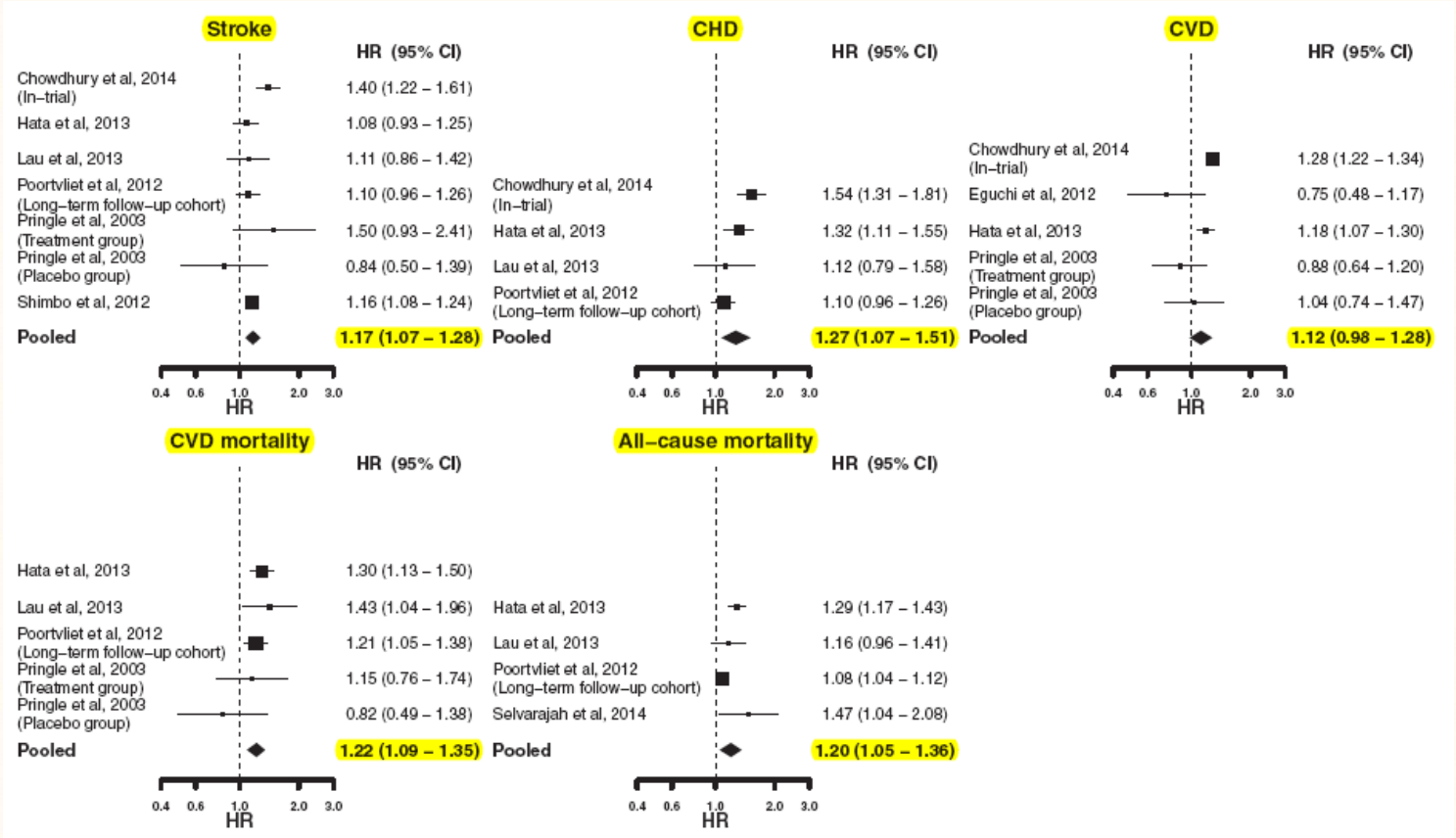


Ref. Rothwell PM et al., Lancet 2010; 375: 895-905

Prognostic Significance of Visit-to-Visit BPV

A Systematic Review and Meta-Analysis

Association of the SD of systolic blood pressure with outcomes

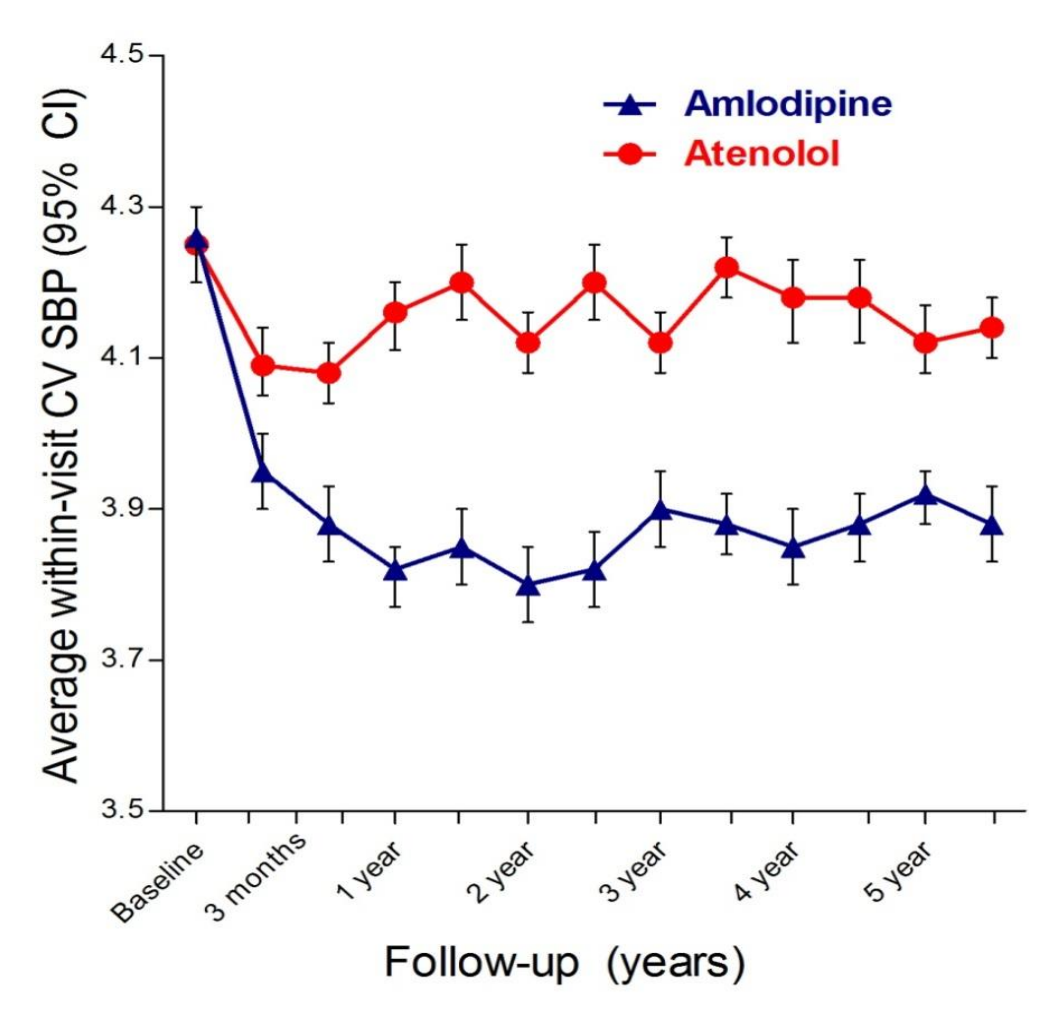


In summary, modest associations between visit-to-visit variability of BP and CVD and all-cause mortality are present in published studies.

Diaz KM et al. Hypertension. 2014;64:965-982

Which Class of Anti-hypertensives to Reduce BPV?

Within-visit variability of SBP in ASCOT-BPLA



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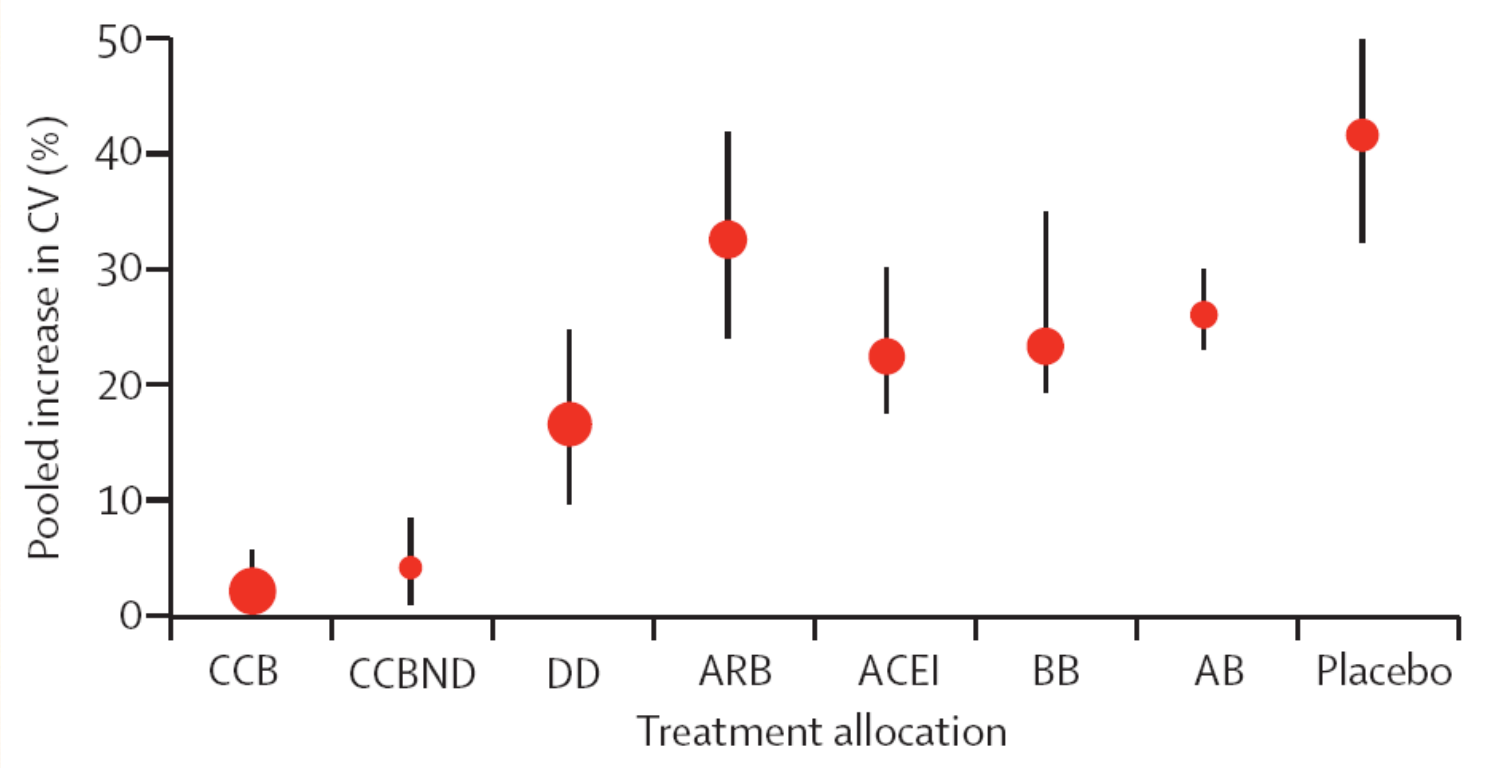
Which Class of Anti-hypertensives to Reduce BPV?

Effects of antihypertensive-drug class on visit-to-visit BPV in randomized controlled trials



CCBND=non-dihydropyridine CCB. DD=non-loop diuretic drug. BB=β-blocker. AB=α-1 blocker

Webb AJS et al. Lancet 2010; 375: 906–15

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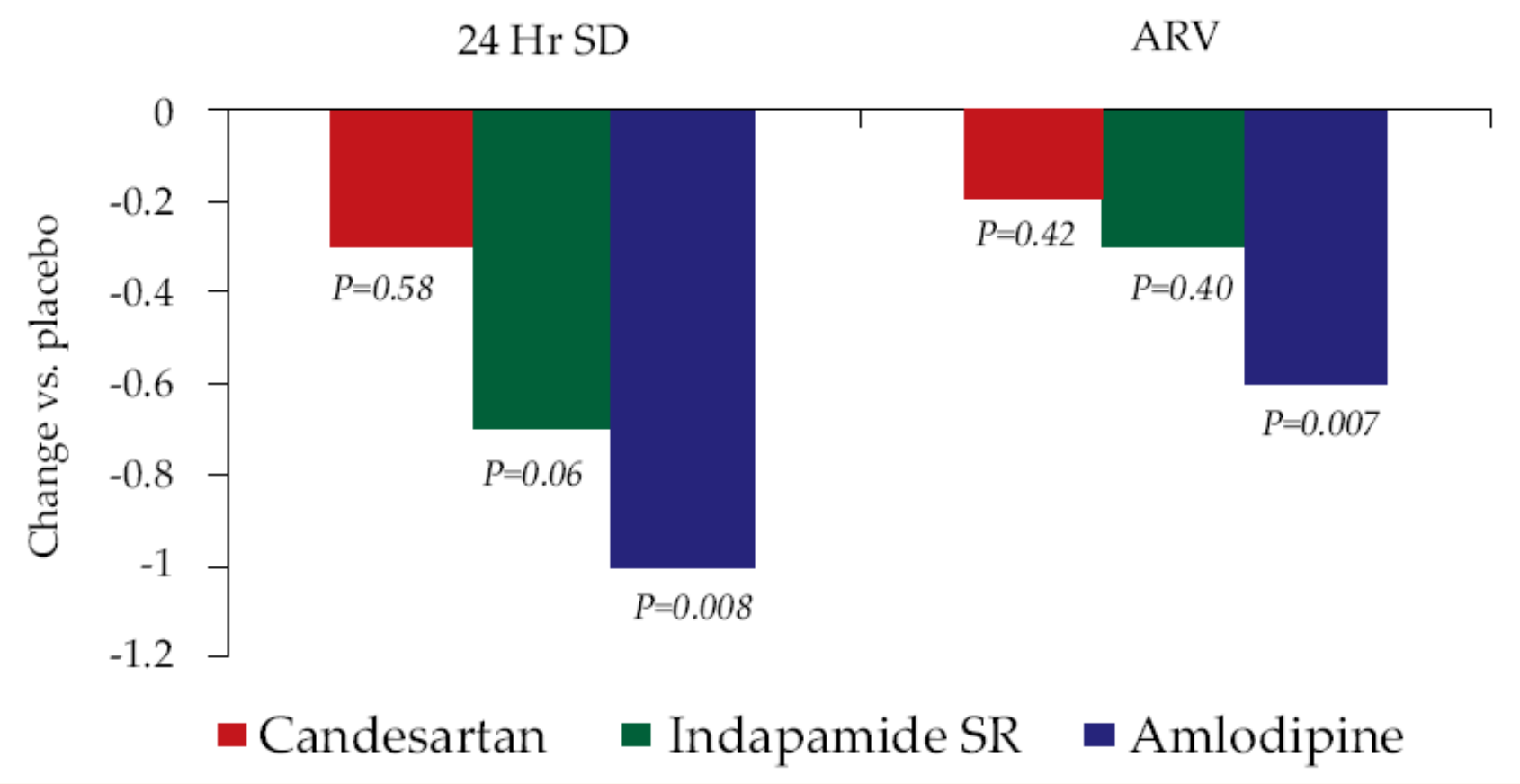
Which Class of Anti-hypertensives to Reduce BPV?

X-CELLENT Study



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Zhang Y et al. Hypertension. 2011;58:155-160
Chenniappan M. J Assoc Physicians India. 2015;63:47-53

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Perspectives

- BPV; Cause vs. Surrogate marker ?
- Is a drug-induced reduction in BPV accompanied by a reduction in event rate?
- Do different drug classes have a different effect on BPV and on outcome?
- Is there enough evidence to consider BPV as a new target for treatment?

Drug Design, Development and Therapy 2016: 10 1573-1580

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Fimasartan for independent reduction of blood pressure variability in mild-to-moderate hypertension

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5 May 2016
Number of times this article has been viewed

Mi-Seung Shin,[1] Dae Ryong Kang,[2] Changsoo Kim,[3] Eun Joo Cho,[4] Ki-Chul Sung,[5] Seok-Min Kang,[6] Dong-Soo Kim,[7] Seung Jae Joo,[8] Seung Hwan Lee,[9] Kyung-Kuk Hwang,[10] Jeong Bae Park[11]

[1]Division of Cardiology, Department of Internal Medicine, Gachon University

Background: The angiotensin receptor antagonist fimasartan lowered blood pressure (BP) in a previous large population study. The purpose of this study was to evaluate whether fimasartan treatment for 3 months affects clinical and home BP variability in addition to reducing BP.

Methods: The study enrolled 1,396 patients (mean age 56.2±10.0 years; males 53.6%) with mild-to-moderate hypertension who had a complete set of home BP measurements (morning and evening) and metabolic risk evaluation. During the 3 months of study, fimasartan alone was used to control BP at a daily dose of 30–120 mg. Clinical and home BP measurements were performed before and after the 3-month treatment. BP variability included beat-to-beat variability (clinical) and day-to-day variability (home)

Methods

1 Study Population

❖ Facility: 11 Hospitals / 582 Primary clinics (N=1,396)

2 Inclusion Criteria

❖ Diagnosed with hypertension, and intend to use fimasartan (age ≥20 yrs)
❖ Agree to participate in the study and sign the informed consent form
❖ Maintain a fasting state at each visit

3 Exclusion Criteria

❖ Patients who were treated with fimasartan at baseline

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Shin MS et al. Drug Des Devel Ther 2016;10:1573

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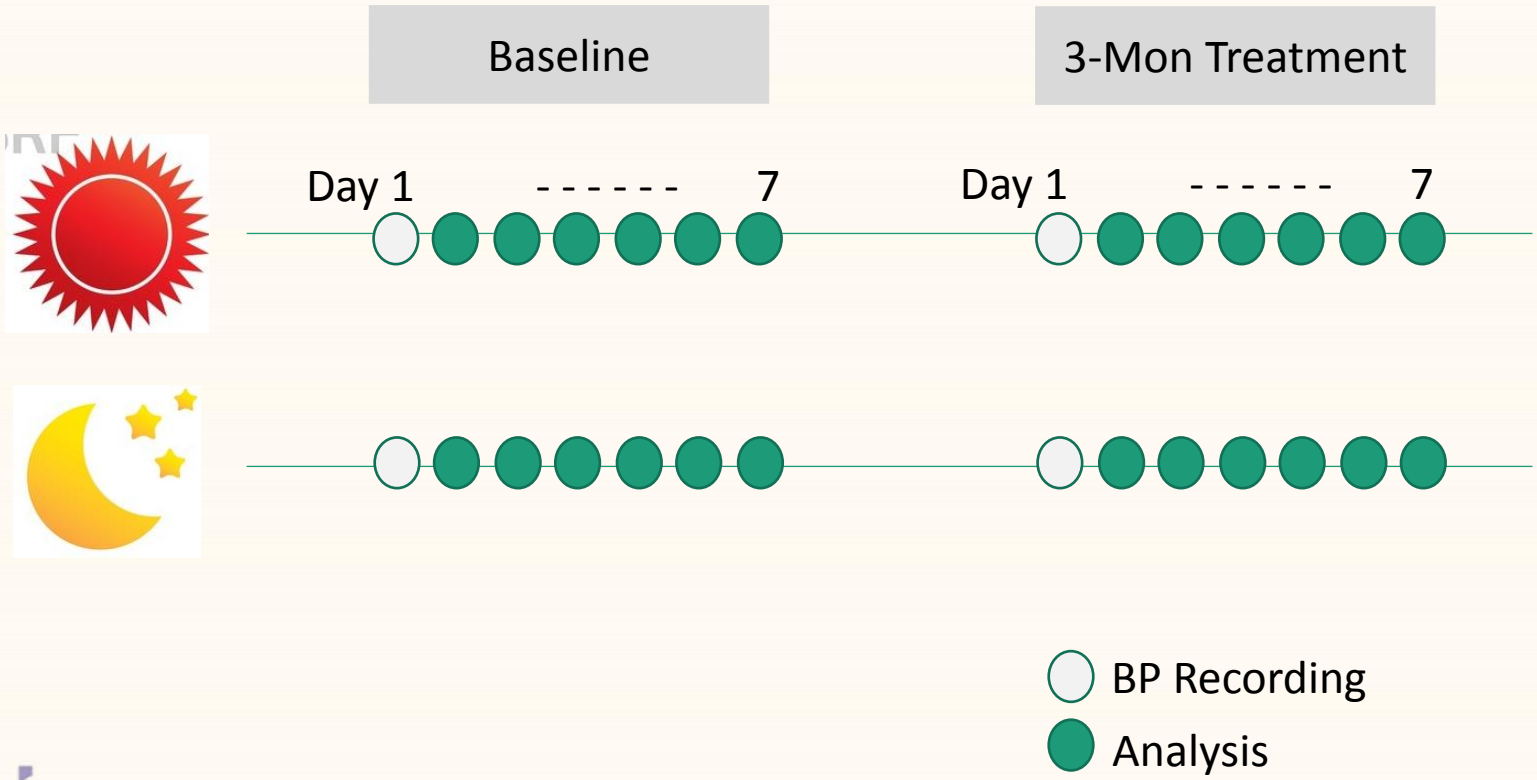
Methods

4 BP Measurement



BORYUNG 보령제약

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Methods

4 BP Measurement

- Morning BP
  - An average of 2 or more BP reading
  - 2-minute interval
  - same arm
  - within 1 hr of waking, after urination, sitting position
  - before taking medication or eating

- Evening BP
  - Before going to bed
  - After resting for 5 mins
  - Sitting position

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Results

1 Baseline Characteristics

	All (N=1,396)	Male (N=748)	Female (N=648)	P-value*
Age, mean ± SD (years)	56.17±10.00	55.47	56.98	0.0042
Body weight (kg), mean ± SD and mean	67.41±11.11	72.52	61.52	<0.0001
Height (cm)	162.91	168.80	156.11	<0.0001
Body mass index (kg/m^2)	25.32	25.42	25.21	0.2291
Current smoking, n (%)	249 (17.84)	231 (30.88)	18 (2.78)	<0.0001
Family history of CVD, n (%)	261 (18.70)	137 (18.32)	124 (19.14)	0.9239
History of hypertension (years)	4.13	4.23	4.02	0.4515
Duration of antihypertensive drug use (years)	3.87	3.92	3.80	0.6227
Current antihypertensive drug use, n (%)	946 (67.77)	516 (68.98)	430 (66.36)	0.2951
Diabetes, n (%)	245 (17.55)	150 (20.05)	95 (14.66)	0.0082
Ischemic heart disease, n (%)	96 (6.88)	54 (7.22)	42 (6.48)	0.5870
Stroke, n (%)	13 (0.93)	9 (1.20)	4 (0.62)	0.2807
Treatment type				
Naïve,[a] n (%)	450 (32.23)	232 (31.02)	218 (33.64)	0.0035
Switch,[b] n (%)	597 (42.77)	302 (40.37)	295 (45.52)	–
Add-on,[c] n (%)	349 (25.00)	214 (28.61)	135 (20.83)	–

Notes: *P-value between male and female. [a]Patients without previous antihypertensive medication who received fimasartan. [b]Patients who were switched from other antihypertensive drug to fimasartan. [c]Patients who received fimasartan as an add-on antihypertensive therapy.
Abbreviation: CVD, cardiovascular disease.

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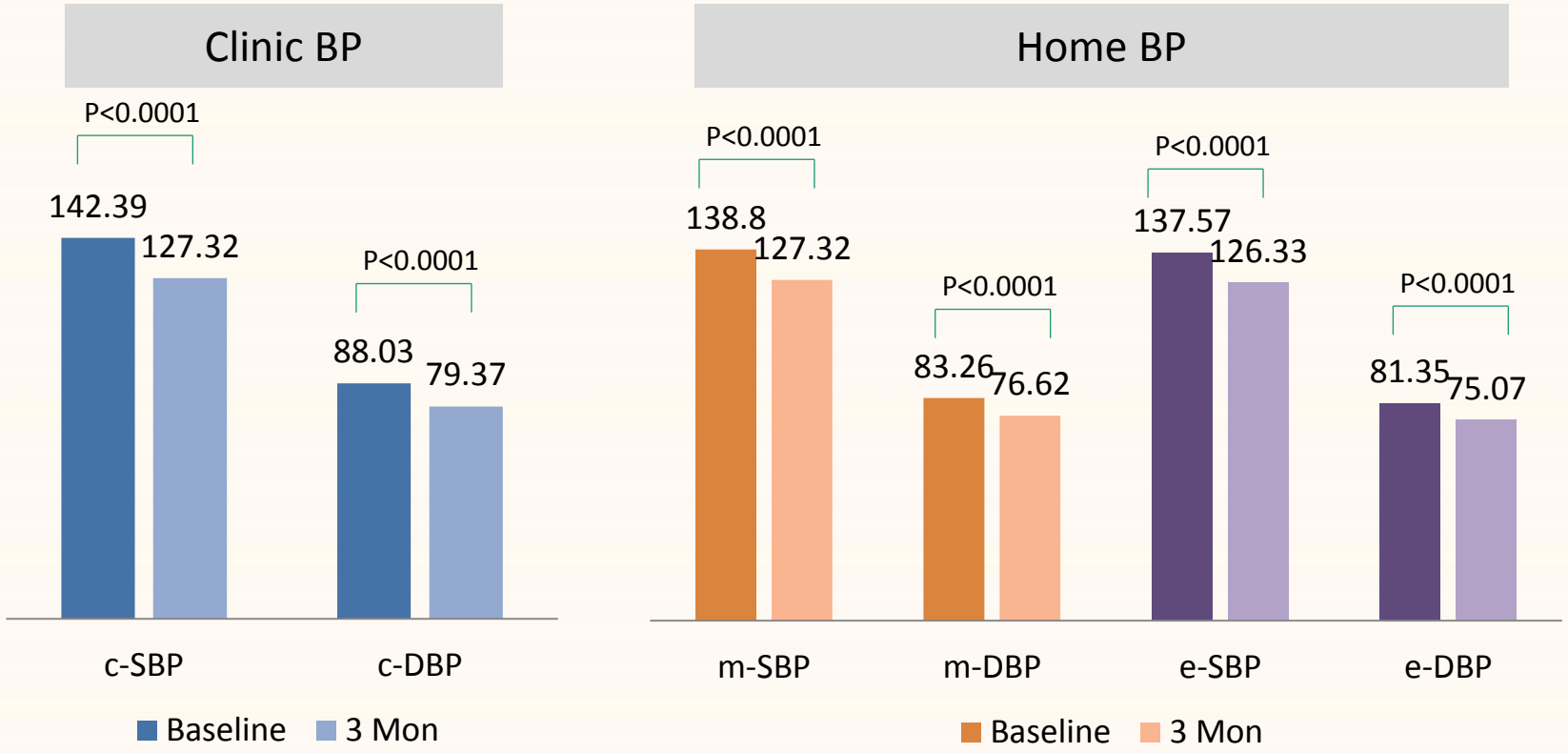
Results

2 Change in Blood Pressure



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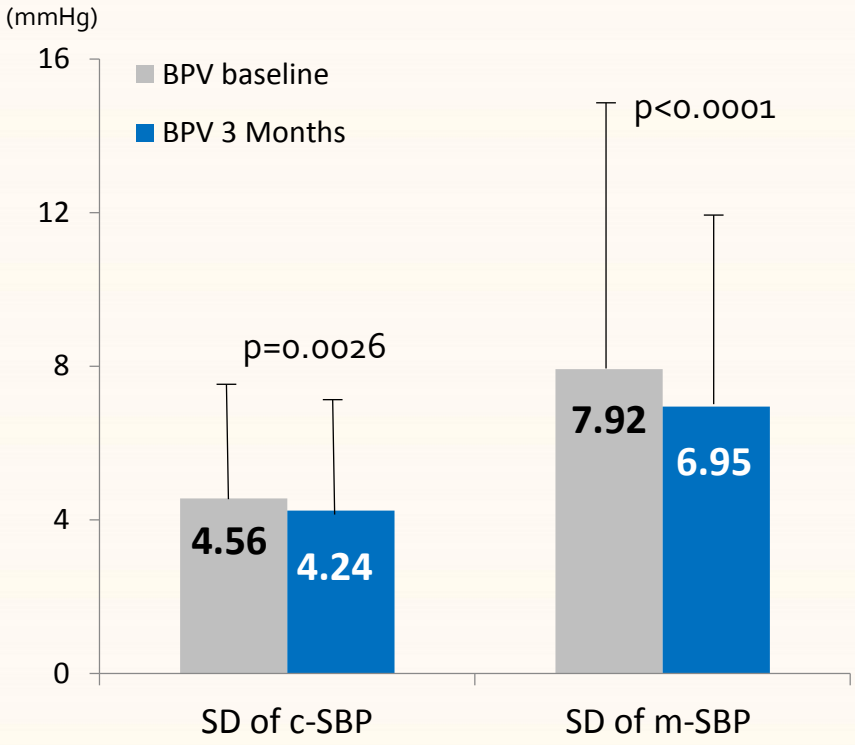
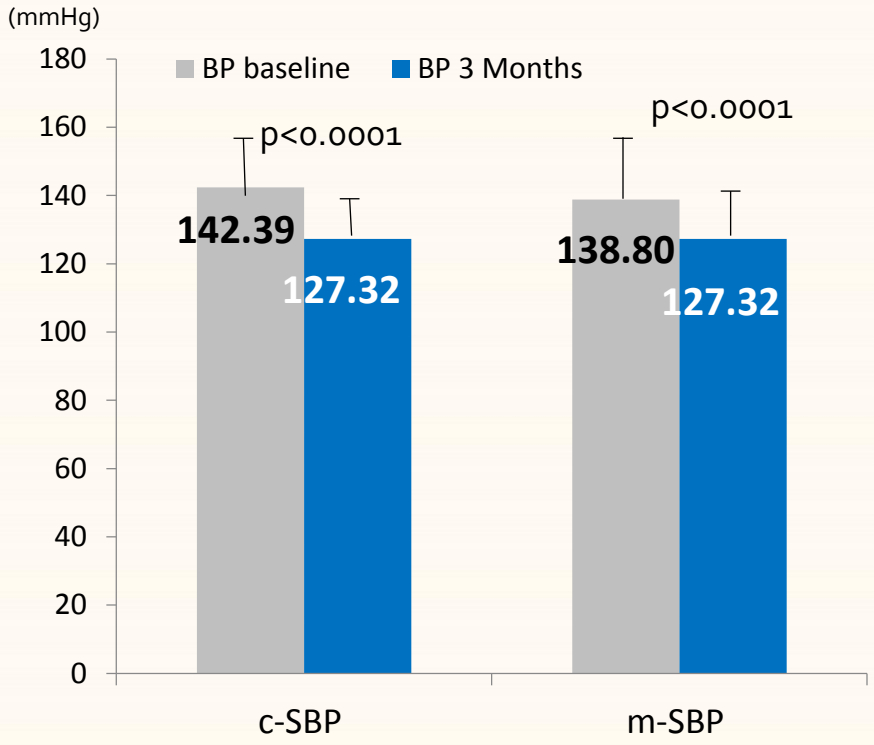
Results

3 Change in BP Variability





Changes in SD of beat-to-beat BP (BP variability) in clinic and Changes in SD of day-to-day morning BP (BP variability) in home settings after 3 months of fimasartan treatment

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Results

4 Factors Associated with BP Variability

	SD of clinical SBP				SD of morning home SBP			
	Simple regression		Multiple regression		Simple regression		Multiple regression	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Age (years)	0.02 (0.01)	0.0061	0.02 (0.01)	0.0065	0.05 (0.02)	0.0067	0.06 (0.02)	0.0005
Sex (females vs males [Ref])	0.14 (0.17)	0.4133	0.16 (0.22)	0.4737	1.07 (0.36)	0.0032	1.76 (0.44)	<0.0001
BMI (kg/m^2)	0.02 (0.03)	0.5668	0.01 (0.03)	0.6156	0.13 (0.06)	0.0246	0.10 (0.05)	0.0553
Smoking (current vs nonsmoker)	−0.26 (0.23)	0.2609	−0.20 (0.26)	0.4359	−0.06 (0.48)	0.9012	0.33 (0.51)	0.5172
Smoking (ex-smoker vs nonsmoker)	−0.17 (0.28)	0.5479	−0.20 (0.31)	0.5102	−0.52 (0.58)	0.3732	0.21 (0.61)	0.7287
Alcohol intake (vs no alcohol intake)	−0.05 (0.17)	0.7578	0.19 (0.21)	0.3635	−0.53 (0.36)	0.1421	0.30 (0.41)	0.4631
Diabetes	0.01 (0.23)	0.9616	−0.05 (0.23)	0.8124	0.78 (0.47)	0.0983	0.69 (0.46)	0.132
Clinic								
Clinical SBP (mmHg)	0.02 (0.01)	<0.0001	0.02 (0.01)	<0.0001				
Clinical HR (bpm)	−0.00 (0.01)	0.9686	0.00 (0.01)	0.7924				
Home								
Morning SBP (mmHg)					0.11 (0.01)	<0.0001	0.09 (0.01)	<0.0001
Morning HR (bpm)					0.13 (0.02)	<0.0001	0.09 (0.02)	<0.0001
	R^2=0.0191				R^2=0.1397			

Abbreviations: BMI, body mass index; bpm, beats per minute; HR, heart rate; R^2, multiple regression coefficient of determination; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

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5 Factors Associated with Changes of BP Variability after Fimasartan Treatment

	Simple regression		Multiple regression*		
	β (SE)	*P*-value	β (SE)	*P*-value	R^2
Changes in SD of clinical SBP					
Change in clinical SBP (mmHg)	0.03 (0.01)	<0.0001	0.04 (0.02)	0.0268	0.0213
Change in clinical HR (bpm)	–0.00 (0.01)	0.7058	–0.00 (0.01)	0.7055	0.0179
Changes in SD of morning home SBP					
Change in morning SBP (mmHg)	0.09 (0.01)	<0.0001	0.08 (0.03)	0.0258	0.0672
Change in morning HR (bpm)	0.15 (0.02)	<0.0001	0.08 (0.02)	0.0006	0.0762

Note: *These models are adjusted for age, sex, body mass index, and change in mean arterial pressure (DBP + [SBP–DBP]/3), where DBP is diastolic blood pressure.
Abbreviations: bpm, beats per minute; HR, heart rate; R^2, multiple regression coefficient of determination; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

*These models are adjusted for age, sex, body mass index, and change in mean arterial pressure (DBP + [SBP–DBP]/3).

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Medicine® Medicine 2016;95:e3764

OBSERVATIONAL STUDY

OPEN

Clinic and Home Blood Pressure Lowering Effect of an Angiotensin Receptor Blocker, Fimasartan, in Postmenopausal Women with Hypertension

Song-Yi Kim, MD, Seung-Jae Joo, MD, Mi-Seung Shin, MD, Changsoo Kim, PhD, Eun Joo Cho, MD, Ki-Chul Sung, MD, Seok-Min Kang, MD, Dong-Soo Kim, MD, Seung Hwan Lee, MD, Kyung-Kuk Hwang, MD, and Jeong Bae Park, MD

TABLE 4. Changes of Day-to-Day Blood Pressure (BP) and Heart Rate Variability After 3-Month Treatment With Fimasartan

	Premenopause		Postmenopause	
	Baseline	**After 3 Months**	**Baseline**	**After 3 Months**
Morning	N = 128		N = 297	
SD of systolic BP, mm Hg	8.96 ± 7.74	6.76 ± 5.03*	9.26 ± 7.31	7.63 ± 5.48*
Δ SD of systolic BP	−2.20 ± 8.93		−1.63 ± 8.46	
SD of diastolic BP, mm Hg	5.81 ± 4.97	4.89 ± 3.03	5.64 ± 4.36	4.90 ± 3.33*
Δ SD of diastolic BP	−0.91 ± 5.44		−0.74 ± 4.92	
SD of heart rate (/min)	5.41 ± 4.08	4.85 ± 3.07	5.05 ± 3.61	4.85 ± 3.41
Δ SD of heart rate	−0.63 ± 4.76		−0.19 ± 4.73	
Evening	N = 120		N = 269	
SD of systolic BP, mm Hg	9.66 ± 8.18	7.31 ± 5.69*	9.03 ± 5.44	7.83 ± 5.24*
Δ SD of systolic BP	−2.35 ± 8.25		−1.20 ± 6.25	
SD of diastolic BP, mm Hg	6.25 ± 4.93	5.33 ± 3.48*	5.41 ± 3.10	5.17 ± 3.11
Δ SD of diastolic BP	−0.92 ± 5.01		−0.23 ± 3.95	
SD of heart rate (/min)	5.94 ± 4.30	5.54 ± 4.90	5.43 ± 3.50	5.08 ± 3.22
Δ SD of heart rate	−0.47 ± 5.46		−0.36 ± 4.10	

Data are expressed as mean ± standard deviation (SD).
*$P < 0.05$ versus baseline.

Conclusions

- This study evaluated whether fimasartan treatment affected clinic and home BP variability in addition to reducing BP.
- Three months of fimasartan treatment reduced day-to-day BP variability independent of BP reduction in patients with mild-to-moderate hypertension.
- The results suggest that fimasartan attenuates BP fluctuations and provides better control of hypertension, which may provide an additional benefit for prevention of cardiovascular events.

경청해 주셔서 감사합니다.

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