**BLOOD PRESSURE VARIABILITY:**

 **methodological aspects, clinical relevance and practical indications\***

**ONLINE SUPPLEMENT**

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**Figure S1.** Limitation of spot BP measurements in reflecting average 24h BP levels. From Mancia et al. (1) by permission

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**Table S1. Threshold values for BPV considered in outcome studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Population characteristics** | **Systolic BPV** | **Diastolic BPV** | **Outcomes** | **Criteria for threshold determination**  | **Definition of BPV** |
| **Threshold values for short-term BPV** |
| Sander et al. (2) | N=286 mean age: 68 yrsfollow-up: 3.3 yrs | SD of daytime systolic ABP of 15mmHg |  | Progression of early carotid atherosclerosis (intima-media wall thickness, IMT) and cardiovascular events | upper 95% CI (14.9 mm Hg) of the average daytime systolic BPV of all 286 patients | within-subject SD of all systolic and diastolic readings during daytime measurement period |
| Ohasama Study (3) | N=1542 Japanese subjects from the general population Mean age: 61.7 yrsMean follow-up: 8.5 years | SD of daytime and night-time systolic ABP of 15.8 mmHg and 14.4 mmHg respectively | ns | Cardiovascular mortality | SD larger than third quintile | SD measured every 30 min by ABPM |
| ABP-International database(4)  | N=7112 untreated participants with BP ≥140 mmHg systolic or ≥90 mmHg diastolic | SD of night-time systolic ABP ≥12.2 mmHg | SD of night-time diastolic ABP ≥7.9 mm Hg | cardiovascular events, cardiovascular death, all-cause mortality | SD night-time systolic SD that best separated patients at low and high risk of cardiovascular event | SD of night-time BP |
| IDACO (5) | N=8938 subjects from 11 populations.Median follow-up: 11.3 yrs | ARV ≥16.2 mmHg | ARV ≥ 12.4 mmHg | Total and cardiovascular mortality | Quintiles of ARV | BP variability from the SD and ARV in 24-hour ambulatory BP recordings |
| Eguchi et al. (6) | N=457 hypertensive patients. Age: 67.0 yrsFollow-up: 67 months  | sleepsystolic BPV ≥12.2 mm Hg |  | Incident Cardiovascular Events | Median of BPV distribution. | SDs of awake and sleep BP. |
| IDACO Study(7) |  | a sleep-trough or pre-awakening morning surge in systolic BP below20 mm Hg |  |  | morning surge, > 90th percentile cut-off points ranging from the 5th to 95th percentile for the sleep-trough and pre-awakening morning surge in SBP |  |
| Palatini et al. (8) | N=1206 young patients screened for stage 1 hypertension.Age: 33.1 ± 8.5 yrsFollow-up: 15.4 ± 7.4 years | low (<12.8 mmHg) or high (≥12.8 mmHg) weighted SD of 24-h systolic ABP |  | cardiovascular events | Threshold value identifiedby receiver operating curve analysis (outcome driven cut-point). | weighted SD of 24-h systolic ABP |
| **Threshold values for midterm BPV** |
| IDHOCO (9) | N=6238Follow up: 9.3±3.6 yrs mean age: 60.0±12.9yrs from Japan,Greece, and Finland. | CV of systolic HBP >11.0%  | CV of diastolic HBP >12.8% | Cardiovascular morbidity and mortality | Highest decile of CV | CV of the first morning BPs on 3 to 7 days |
| The Finn-Home Study(10) | N=1866 Finnish adults.Age: Follow-up: 7.8 years |  |  | Incident CVD and all-causemortality |  | SDs of morning minus evening, day-by-day, and first minus second measurements |
| **Threshold values for long-term BPV** |  |
| Mehlum et al.(11) | N= 13803 hypertensive patients at different levels of cardiovascular riskfollow up: 4.2 yearsMean age:67.1 yrs | SD of SBP ≥17.9 mmHg  |  | cardiovascular events and stroke | Highest quintile of SD | SD of mean SBP from visits from 6 months onward in patients with ≥3 visits |
| Gosmanova (12) | N=2.865.157 US veteransMean age: 60 ± 13 yrsFollow up= | SD ≥15.6 mmHg |  | all-cause mortality, CHD, stroke and ESRD | Highest SD quartile | SD of the longitudinal intraindividual SBP measurementsin each patient |
| Rothwell, et al. (13) | N= 2006 patients presenting with TIA only from the UK-TIA trial and three validation cohorts(UK-TIA aspirin trial, ESPS-1, Dutch TIA trial, andASCOT-BPLA trial) | Top-decile of SBP SDTop-decile of max SBP  |  | Incident stroke | Top-decile of SBP SDTop-decile of max SBP  | SD SBP over 7 and 10 visits in and max SBP over 7 visits |
| Rothwell, et al. (13) | N= 2011 patients with previous TIA or stroke with treated hypertension (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm [ASCOT-BPLA]). | Top decile of residual variability |  | stroke and coronary events | Top decile of residual variavility | residual visit-to-visit variability in SBP on treatment |
| Eguchi et al. (6) | N=457 hypertensive patients. Age: 67.0 yrsFollow-up: 67 months | clinic systolic BPV ≥13.3mm Hg |  | Incident Cardiovascular Events | Median of BPV distribution. | SDs of clinic BP |

**Table S2.** Indices to assess consistency of BP control by treatment. Adapted from Parati et al. (14) by permission.

|  |  |  |  |
| --- | --- | --- | --- |
| **Index** | **Meaning** | **Calculation** | **formula** |
| **Smoothness Index (SI)** | reflects the size and homogeneity of BP reduction over the entire 24-hour period | Ratio between the mean of hourly BP reductions (∆H) and its standard deviation (SDΔH) (15).  | Immagine che contiene testo  Descrizione generata automaticamente |
| **Trough:peak ratio (T/P)** | reflects the pharmacological effect of a drug at the end of dosing interval (trough) relative to its peak effect; higher for long-acting drugs | Ratio between the BP reduction at the end of the between-dose interval (trough) and the BP reduction at the time of the maximal drug effect (peak). (16)  |  |
|  **Treatement On Variability Index ( TOVI)** | reflects the impact of a given treatment both on 24h mean BP levels and on absolute estimates of 24h BPV, thus accounting for circadian BP fluctuations, as well as for the dependence of 24-h SD on 24-h mean BP levels | ratio between the mean of 24-hourly BP reductions and the weighted 24-h SD (wSD) assessed under treatment. (17) | Immagine che contiene testo  Descrizione generata automaticamente |
| **morning to evening Home BP ratio** |  | Stergiou et al. (18) |  |

**Table S3 : Main clinical trials evaluating BP lowering drug effects on BPV**. From Nardin et al. (19) by permission

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of the study** | **Type of BPV** | **Treatment regimen** | **Main findings** |
| MAPEC StudyHermida et al. (20) | Short term BPV | Bedtime chronotherapy | The administration of ≥ 1 antihypertensive drug at bedtime was associated with a lower mean nocturnal BP and a lower cardiovascular risk after a median follow up of 5.6 years compared with all drugs ingestion in the morning |
| Hermida et al. (21) | Short term BPV | Bedtime administration of telmisartan | Bedtime administration of telmisartan was associated with a greater sleep-time relative BP decline without loss in 24-h efficacy |
| Hermida et al. (22) | Short term BPV | Bedtime administration of olmesartan | Bedtime intake of olmesartan was significantly more efficient than morning dosing in reducing the nocturnal BP mean and improving the awake/asleep BP ratio |
| Hoshino et al. (23) | Short term BPV | Bedtime administration of amlodipine-olmesartan combination | Bedtime administration of amlodipine–olmesartan combination reduced morning BP surge without an excessive nocturnal BP decline |
| Acelajado et al. (24) | Short term BPV | Bedtime administration of nebivolol | Nocturnal ingestion of nebivolol decreased pre-waking systolic BP from baseline |
| X-CELLENT StudyZhang et al. (25) | Short term BPV | 4 parallel treatment groups (placebo, candesartan, indapamide sustained release and amlodipine) | Indapamide sustained release and amlodipine were the only agents associated with a significantly reduction in BPV after 3-month treatment |
| Parati et al. (26) | Short term BPV | Telmisartan-amlodipine combination | Telmisartan–amlodipine combination exhibited a lower daytime BPV compared with various monotherapies |
| Omboni et al. (17) | Short term BPV | ACE inhibitors, dihydropyridine CCBs, thiazide diuretics in monotherapy or combination | The triple (olmesartan/dihydropyridine/thiazide diuretic) and the dual (olmesartan/dihydropyridine CCB or olmesartan/thiazide diuretic) combinations were associated with a greater decrease in BPV compared with monotherapies |
| ASCOT-BPLA trialRotwell et al. (27) | Short term BPVLong term BPV | Amlodipine versus atenolol based regimen | Visit-to-visit, ABPM and within-visit systolic BPV were lower in the amlodipine treatment group |
| Nishioka et al. (28) | Short term BPV | ARBs, BBs, CCBs and ACE inhibitors | BBs were associated with higher BPV rather than CCBs and ARBs in patients affected by cerebrovascular disease |
| Levi-Marpillat et al. (29) | Short term BPV | ARBs, BBs, CCBs, diuretics and ACE inhibitors | CCBs and diuretics showed a greater decrease in BPV |
| Liu-Deryke et al. (30) | Short term BPV | Nicardipine versus labetalol | In acutely hypertensive stroke patients the nicardipine treatment group exhibited a lower BPV than the labetalol treatment group |
| HOMED-BP StudyAsayama et al. (31) | Mid-term BPV | CCBs, ARBs, or ACE inhibitors | Day-to-day variability of self-measured home BP did not differ among the three treatment arms |
| Matsui et al. (32) | Mid-term BPV | Olmesartan/hydrochlorothiazide versus olmesartan/azelnidipine combination | Olmesartan/azelnidipine combination regimen based was associated with a lower day-to-day BPV than the olmesartan/hydrochlorothiazide based regimen |
| MRC TrialRotwell et al. (27) | Long term BPV | Atenolol versus diuretic based regimens | Thiazide like diuretics were more effective than BBs on long-term BPV |
| ALLHAT Study(33) | Long term BPV | 3 parallel treatment groups (chlorthalidone, amlodipine and lisinopril) | The amlodipine and lisinopril treatment arms were associated with a lower and higher systolic BPV, respectively, compared with chlorthalidone treatment group after 6 months following randomization |
| COLM TrialRakugi et al. (34) | Long term BPV | Olmesartan/CCBs versus olmesartan/diuretic combination | Olmesartan/CCB combination was more efficient in reducing systolic BPV compared with olmesartan/diuretic combination in very elderly hypertensives |
| COPE TrialUmemoto et al. (35) | Long term BPV | 3 parallel treatment groups (benidipine/diuretic,benidipine/ARBs and benidipine/BBs) | The benidipine/diuretic combination was more effective on long-term BPV than benidipine/ARBs and benidipine/BBs combinations |
| ELSA TrialMancia et al. (36) | Long term BPV | Atenolol versus lacidipine | Visit-to-visit BPV did not differ between atenolol and lacidipine |
| Shiga et al. (37) | Long term BPV | Single-pill fixed-dose combination of ARB/CCB versus ARB/diuretic | Seasonal BPV was similar between ARB/CCB and ARB/diuretic combinations |

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