**BLOOD PRESSURE VARIABILITY:**

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

**ONLINE SUPPLEMENT**

**Authors (writing task force)**

Parati Gianfranco1,2, Bilo Grzegorz1,2, Kollias Anastasios3, Pengo Martino1,2, Ochoa Juan Eugenio1, Castiglioni Paolo4, Stergiou George S3, Mancia Giuseppe5

**Document Reviewers**

Asayama Kei6.7,8, Asmar Roland9, Avolio Alberto10, Caiani Enrico G.1,11, De La Sierra Alejandro12, Dolan Eamon13, Grillo Andrea14, Guzik Przemysław15, Hoshide Satoshi16, Head Geoffrey A.17, Imai Yutaka8, Juhanoja Eeva18,19, Kahan Thomas20, Kario Kazuomi16, Kotsis Vasilios21, Kreutz Reinhold22, Kyriakoulis Konstantinos G.3, Li Yan23,24, Manios Efstathios25, Mihailidou Anastasia S.26, Modesti Pietro Amedeo27, Omboni Stefano28,29, Palatini Paolo30, Persu Alexandre31, Protogerou Athanasios D.32, Saladini Francesca30,33, Salvi Paolo1, Sarafidis Pantelis34, Torlasco Camilla1, Veglio Franco35, Vlachopoulos Charalambos36, Zhang Yuqing37

**\*A scientific statement of the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability.**

1-Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular Neural and Metabolic Sciences, Milan, Italy

2-Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

3-Hypertension Center STRIDE-7, National and Kapodistrian University of Athens, School of Medicine, Third Department of Medicine, Sotiria Hospital, Athens, Greece

4-IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

5- University Milano-Bicocca, Milano, Italy

6-Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan.  
7-Department of Cardiovascular Sciences, University of Leuven, and Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Belgium.  
8-Tohoku Institute for the Management of Blood Pressure, Sendai, Japan.

9-Foundation-Medical Research Institutes, Geneva, Switzerland

10-Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

11-Department of Electronics, Information, and Bioengineering, Politecnico di Milano, Italy

12-Hypertension Unit, Department of Internal Medicine, Hospital Mútua Terrassa, University of Barcelona, Barcelona, Spain.

13-Connolly Hospital, Dublin, Ireland

14- Department of Medicine, Surgery and Health Sciences, University of Trieste, Italy

15-Department of Cardiology–Intensive Therapy, University School of Medicine in Poznan, 49 Przybyszewskiego Str. 60-355 Poznan, Poland

16-Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

17-Baker Heart and Diabetes Institute, Melbourne Victoria Australia

18-Chronic Disease Prevention Unit, National Institute for Health and Welfare, Turku, Finland; Department of Medicine &

19-Department of Oncology; Division of Medicine, Turku University Hospital, University of Turku, Turku, Finland.

20-Karolinska Institute, Department of Clinical Sciences; , Division of Cardiovascular Medicine, Department of Cardiology, Danderyd University Hospital Corporation, SE-182 88 Stockholm, Sweden

21-Aristotle University of Thessaloniki, Thessaloníki, Greece

22-Charité – Universitätsmedizin Berlin, Germany

23-Department of Cardiovascular Medicine, Shanghai Key Laboratory of Hypertension and Medical Genomics, National Research Centre for Translational Medicine,

24-Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

25-Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra Hospital Athens, Greece

26-Department of Cardiology and Kolling Institute, Royal North Shore Hospital, St Leonards; Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia 2065.

27-Dept. Experimental and Clinical Medicine, University of Florence, Italy

28-Clinical Research Unit, Italian Institute of Telemedicine, Varese, Italy.

29-Department of Cardiology, Sechenov First Moscow State Medical University, Moscow, Russian Federation

30-Department of Medicine. University of Padova, Padua, Italy

31-Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium.

32-Cardiovascular Prevention and Research Unit, Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

33-Cardiology Unit, Cittadella Town Hospital, Padova

34-Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece

35-Internal Medicine Division and Hypertension Unit, Department of Medical Sciences, University of Turin Italy

36-Hypertension and Cardiometabolic Syndrome Unit, 1 Department of Cardiology, Medical School, National & Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

37- Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Corresponding Author**

Gianfranco Parati MD, FESC

Dept of Cardiovascular, Neural and Metabolic Sciences, S.Luca Hospital, IRCCS Istituto Auxologico Italiano, piazza Brescia, 20 - 20149 Milano, Italy. Tel. +39 02 619112890; Fax + 39 02 619112956; Cell +39 335 6043581 e-mail: gianfranco.parati@unimib.it . Orcid 0000-0001-9402-7439

**\*A scientific statement of the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability.**

1-Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular Neural and Metabolic Sciences, Milan, Italy

2-Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

3-Hypertension Center STRIDE-7, National and Kapodistrian University of Athens, School of Medicine, Third Department of Medicine, Sotiria Hospital, Athens, Greece

4- University Milano-Bicocca, Milano, Italy

5-IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

6-Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan.  
7-Department of Cardiovascular Sciences, University of Leuven, and Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Belgium.  
8-Tohoku Institute for the Management of Blood Pressure, Sendai, Japan.

9-Foundation-Medical Research Institutes, Geneva, Switzerland

10-Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

11-Department of Electronics, Information, and Bioengineering, Politecnico di Milano, Italy; Istituto Auxologico Italiano, IRCCS, Milan, Italy.

12-Hypertension Unit, Department of Internal Medicine, Hospital Mútua Terrassa, University of Barcelona, Barcelona, Spain.

13-Connolly Hospital, Dublin, Ireland

14-SC Medicina Clinica, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

15-Department of Cardiology–Intensive Therapy, University School of Medicine in Poznan, 49 Przybyszewskiego Str. 60-355 Poznan, Poland

16-Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

17-Baker Heart and Diabetes Institute, Melbourne Victoria Australia

18-Chronic Disease Prevention Unit, National Institute for Health and Welfare, Turku, Finland; Department of Medicine &

19-Department of Oncology; Division of Medicine, Turku University Hospital, University of Turku, Turku, Finland.

20-Karolinska Institute, Department of Clinical Sciences; , Division of Cardiovascular Medicine, Department of Cardiology, Danderyd University Hospital Corporation, SE-182 88 Stockholm, Sweden

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29-Department of Cardiology, Sechenov First Moscow State Medical University, Moscow, Russian Federation

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32-Cardiovascular Prevention and Research Unit, Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

33-Cardiology Unit, Cittadella Town Hospital, Padova

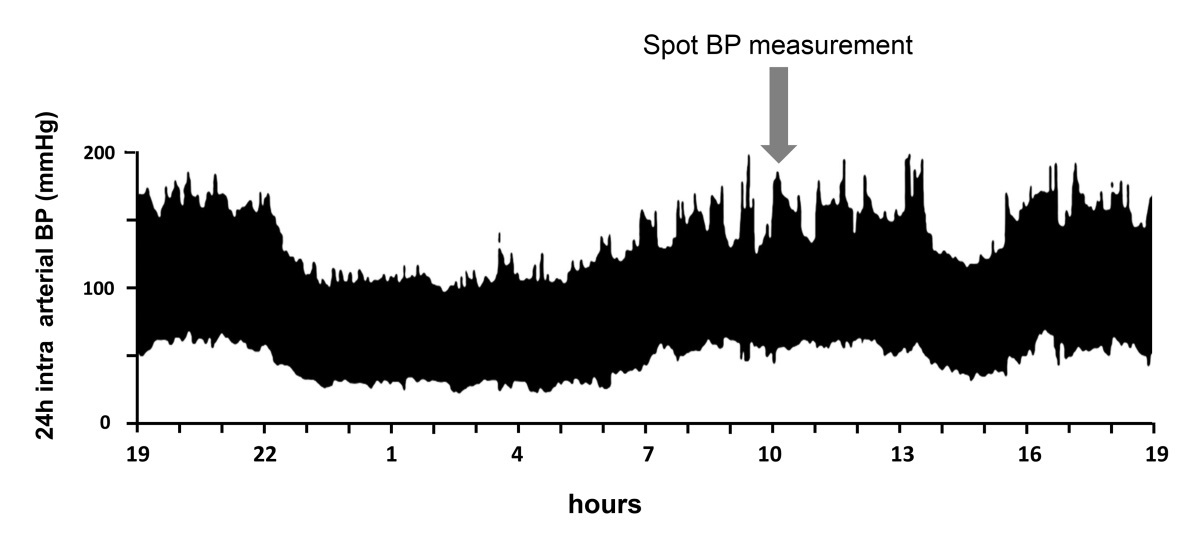
34-Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece

35-Internal Medicine Division and Hypertension Unit, Department of Medical Sciences, University of Turin Italy

36-Hypertension and Cardiometabolic Syndrome Unit, 1 Department of Cardiology, Medical School, National & Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

37- Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**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**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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 yrs  follow-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 yrs  Mean 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 yrs  Follow-up: 67 months | | sleep  systolic 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 below  20 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 yrs  Follow-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 identified  by receiver operating curve analysis (outcome driven cut-point). | weighted SD of 24-h systolic ABP |
| **Threshold values for midterm BPV** | | | | | | | | |
| IDHOCO (9) | | N=6238  Follow 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-cause  mortality |  | | 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 risk  follow up: 4.2 years  Mean 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 veterans  Mean age: 60 ± 13 yrs  Follow up= | SD ≥15.6 mmHg |  | all-cause mortality, CHD, stroke and ESRD | Highest SD quartile | | SD of the longitudinal intraindividual SBP measurements  in 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, and  ASCOT-BPLA trial) | Top-decile of SBP SD  Top-decile of max SBP |  | Incident stroke | Top-decile of SBP SD  Top-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 yrs  Follow-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 Study  Hermida 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 Study  Zhang 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 trial  Rotwell et al. (27) | Short term BPV  Long 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 Study  Asayama 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 Trial  Rotwell 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 Trial  Rakugi 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 Trial  Umemoto 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 Trial  Mancia 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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