Role and Relevance of Blood Pressure Variability in Hypertension Related Co-morbidities

Ashok Kumar¹, BC Kalmath², Georgi Abraham³, Johann Christopher⁴, PLN Kaparthi⁵, Louie Fischer⁶, Neeta Deshpande⁷, NK Mishra⁸, Praveen Raj⁹, Rajesh Javerani¹⁰, Ramesh Goyal¹¹, Reefa Dsouza⁹, Shashank R Joshi¹²

Abstract
Despite maintaining mean blood pressure at optimal levels, cardiovascular complications still occur in hypertensive patients. Blood pressure variability (BPV) has been implicated as a prominent factor responsible for incurring this additional risk.

In this review we attempted to generate a consensus on the importance of BPV in the hypertension management and to evaluate different therapeutic options available to reduce BPV.

Panel comprising of 11 leading experts from India in different areas of clinical practice (including nephrology, diabetes and endocrinology, cardiology, and critical care medicine) was convened. The board reviewed up to date literature on BPV, shared personal experiences from their clinical practice, and debated their opinions on the significance of BPV in hypertension management and also on various therapeutic options available to control it.

The reviewers agreed that BPV is frequently observed in hypertensive individuals and it is a critical factor in hypertension management. Blood pressure variability can be measured by ambulatory blood pressure monitoring, home blood pressure monitoring, and office blood pressure monitoring. Members concurred that variations in blood pressure that are 10 standard deviations above the mean blood pressure should be considered as pathologically significant and such variations should be reduced using pharmacological therapies. The board opined that Angiotensin II Receptor Blockers, Calcium Channel Blockers etc such as Olmesartan, Nifedipine can be used to reduce BPV. As a way forward, the panel recommends to bridge the evidence gap that establishes a possible direct relationship between BPV and cardiovascular complications.

Blood pressure variability has paramount role in the current hypertension management scenario. To reduce disease burden and increase quality of life of hypertensive individuals, physicians should consider lowering BPV along with physiological BP levels.

Introduction
Hypertension is one of the key risk factors for cardiovascular disease (CVD) and contributes to the burden of heart disease, stroke, kidney failure, and premature mortality and disability.¹ It is defined as systolic BP (SBP) and diastolic BP (DBP) equal to or above 140 mm Hg and 90 mm Hg respectively.¹ According to the 2014 global status report on non-communicable diseases, global prevalence of high BP in adults aged ≥ 18 years was around 22% and prevalence in India was 23%.² Global population is aging rapidly and there exists a linear relationship between hypertension and age.¹ In a systematic analysis of population-based studies from 90 countries, hypertension prevalence in world’s adult population was estimated to be around 31.1% (1.39 billion).³ Furthermore, the age-standardized prevalence of hypertension increased by 7.7% between 2000 and 2010 in low- and middle-income countries.³ In addition to this, hypertension is responsible for 9.4 million deaths globally due to CVD, 45% of mortality due to ischemic heart disease and 51% of deaths due to stroke.¹⁴ On the other hand, renal impairment and diabetes could lead to hypertension; it increases the risk of both microvascular and macrovascular complications in patients with diabetes.⁵ Therefore, to improve quality of life and prolong life expectancy of the global

¹Mahavir Heart Institute, Patna, Bihar; ²Bombay Hospital Mumbai, Maharashtra; ³The Madras Medical Mission Coimbatore, Tamil Nadu; ⁴Care Hospital, Hyderabad, Telangana; ⁵Apollo Hospital, Hyderabad, Telangana; ⁶MOSC Medical Hospital, Kerala; ⁷Belgaum Diabetes Centre, Belgaum, Karnataka; ⁸Urbashi Clinic, Bhubaneshwar, Orissa; ⁹Abbott Healthcare Pvt Ltd., Mumbai, Maharashtra; ¹⁰Chellaram Diabetes Hospital Pune, Maharashtra; ¹¹Gujarat Super Speciality Clinic, Ahmedabad, Gujarat; ¹²Lilavati Hospital, Mumbai, Maharashtra

Received: 02.10.2017; Accepted: 15.10.2017
population, control of hypertension is the need of the hour.

Despite the significance of elevated BP in developing vascular events, several aspects indicate the existence of other risk factors for the complications raised due to hypertension: 7

i) Predictive value of usual BP estimates falls with age whereas the incidence of stroke increase 100 fold from age 40 – 80 and the elderly people continue to benefit from antihypertensive drugs relatively. 7

ii) Even though the increased surge in morning BP is poorly associated with mean BP, it is highly predictive of stroke. 7

iii) Threshold of baseline SBP below which vascular risk ceases to fall has not been established and the reduction in risk occurs with antihypertensive drugs even when the baseline SBP is normal. 7

Blood pressure is a dynamic variable which shows marked fluctuations over short-term and/or long-term durations. 8 Several lines of evidence demonstrated that excessive BP fluctuations could develop target organ damage. 8

These variations in normal BP over a period of time are called as blood pressure variability (BPV). 9 The current review discusses briefly about biological clock dependent BP variations followed with an in depth review on various aspects of BPV, such as its definition and classification, its role in the morbidity and mortality of different diseases such as CVD, diabetes and renal complications, its impact on target organ damage and essential measures to control it.

**Circadian Variation of BP**

Blood pressure may be viewed as dynamic entity that follows a circadian rhythm and fluctuates throughout the day and night. 10

A complex interplay of multiple physiological mechanisms maintain the arterial pressure at a relatively constant level. Few decades ago, in a seminal study, Millar-Craig et al has established the biological clock dependent variations in BP using continuous intra-arterial BP monitoring. 11 This study showed that the BP was highest during mid-morning which fell progressively though out the day. Lowest BP was observed at night (nocturnal dip) but rose abruptly before awakening (morning surge). In normal population, a reduction in night time BP of 10% - 20% is observed when compared to day time mean. 12 Several intrinsic factors (haemodynamic and neurohormonal regulation), extrinsic factors (physical activity, sleep deprivation sleep quality and dietary sodium), behavioural factors (mental activity and emotional status) and lifestyle factors (smoking and alcohol consumption) influence the timing and amplitude of the natural rhythm of BP. 12

Physiological BP variations occur regularly in all individuals. However, they attain pathological significance only when the variations exceed beyond the acceptable limits. Normal circadian rhythm of BP is preserved during the initial stages of hypertension development, however, as the target organ damage alters the regulation of systemic BP, variability tend to increase. 13 In 25% - 35% of hypertensive patients, night BP reduction is less than 10% of the day time BP, this is termed as ‘non-dipper’ pattern. 12

On the contrary, in some patients there is a substantial increase in nocturnal BP, and these patients are considered as ‘reverse dippers’ or ‘risers’. 12 Even though morning BP surge is a regular phenomenon, abnormal early morning BP surge is associated with enhanced risk of cerebrovascular and cardiovascular events. 14 Conditions associated with non-dipper or riser pattern are diabetes, post-stroke, congestive heart failure, sleep apnoea syndrome, and orthostatic hypotension. 13 Furthermore, smoking, alcohol consumption, age > 60 years, cold weather, increased arterial stiffness and orthostatic hypertension are some of the factors associated with morning BP surge pattern. 15

**Blood Pressure Variability**

Blood pressure variability in simplistic terms can be defined as the variations in BP over time. These blood pressure fluctuations are generated by a complex interplay between several cardiovascular control mechanisms or during shift between daily life behavior and triggered by environmental situations. 15 Extent of these variations differ from person to person and are high in patients with defunct cardiovascular control mechanisms. 16 Typical examples of these routine fluctuations are rise in BP after physical activity or psychological stress and drop in BP levels during relaxation or sleep. 15

Studies on high CV risk populations have shown high BPV values in individual subjects as strong predictors of CV mortality and morbidity, even to a greater extent than average BP values. 17

Depending on the temporal measurements assessed, BPV can be classified into 5 different types: very short term, short term, mid-term, long term and very long term. 17 Very short term BPV can be defined as beat to beat variability whereas variability over 24 hours is called as short term BPV. Day to day variability is identified as mid-term BPV. Long term and very long term BPV are visit to visit variabilities (VVV) in BP measurements that are less than and greater than five years respectively. Various types of BPV are depicted in Figure 1. A strong relationship exists between BPV and BP levels; higher the BP levels, higher the BPV. 18

Different indices have been in practice to measure various types of BPV; they are reviewed extensively by Parati et al. 17 BPV is usually expressed as standard deviation (SD) of 24 h mean BP. 9 The SD and coefficient of variation are used
Methods and indices used to evaluate them.

Several different intrinsic and extrinsic factors are known to influence different types of BPV. In a population-based study on adult Chinese subjects with different ethnicities, Wei Li et al has demonstrated that BPV is influenced by various demographic, clinical and biochemical factors. Furthermore, the authors have also identified that average of night time systolic BP, average of day time diastolic BP, triglycerides, fasting blood glucose, and apolipoprotein A were significantly and independently associated with BPV. Moreover, individual types of BPV are distinctly influenced by different parameters which are listed in Table 1.

**Tools to Measure BPV**

Various tools enable to measure BPV. Twenty-four hour ambulatory blood pressure monitoring (ABPM) is one of them which helps to determine the BPV precisely. In principle, ABPM allows 24 hour (or even longer) recording of BP and evaluates various parameters such as mean BP, variations between daytime and night time, pressure loads, area under the curve, and pulse pressure variability. Furthermore, a 24 hour ABPM measurement renders the possibility to evaluate short-term BP variability between measurement intervals not longer than 15 minutes. These various assessments facilitated by ABPM are valuable for the clinical management of hypertension as they increase the accuracy for diagnosis and prediction of CV risk. Absolute indications for ABPM include identifying white-coat or masked hypertension and 24 hour abnormal BP patterns and assessing the efficacy of antihypertensive treatment. Some of the limitations of ABPM include discomfort during night time, occasional inability to detect genuine artefactual measurements,
limited availability of the devices, and high cost. Apart from this repeated measurements with well calibrated automated blood pressure monitoring device can be acquired at home (HBPM) or office (OBPM). From these values, BPV can be determined by calculating the SD or coefficient of variation.

**Why BPV is Significant in Clinical Practice?**

Hypertension incurs significant damage to vital organs of the body such as heart, kidney and brain. In addition, it also affects other key elements of the circulatory system including central and peripheral arteries. Major clinically relevant effect of BPV on an individual is target organ damage (TOD). Several clinical and experimental studies have established by now that BPV increases TOD. First evidence in support of this concept was dated back to 1987 when Parati G et al has assessed TOD in 108 hospitalized subjects with mild to severe hypertension. The authors found that subjects with lower 24 hour mean BP and 24 hour BP variability had lesser TOD. The prognostic significance of BPV was established later by Frattola A et al by examining 73 patients for a mean of 7.4 years. Determinants of end-organ damage identified in the study were long term BPV, clinic BP at the follow-up and the initial level of end-organ damage (P<0.05, for all 3 factors). In a cross-sectional study on 169 untreated primary hypertension patients, one of the factors significantly associated with differentiating patients with multiple organ damage from those with single organ damage was increased SBP variability.

Similarly, in a cross-sectional, multicentre study evaluating relationship between BPV and TOD in 1,173 CKD patients, BPV displayed a positive relationship with left ventricular hypertrophy in univariate analysis and also in multivariate analysis (OR per 1 mmHg increase in BPV: 1.053, P=0.006). To summarize, BPV increases TOD which in turn elicits the pathological complications of hypertension.

**Relevance of BPV in Various Diseases**

Considerable evidence have established the effect of BPV in various diseases such as CVD, diabetes, chronic kidney disease, stroke, etc. In a longitudinal observational study on 2455 residents of Ohasama in Japan (OHASAMA study), an increase in 1 SBP between-subject SD was associated with increased hazard ratios for CV (1.27, P=0.002) and stroke (1.41, P=0.0009) mortality. In another study which investigated the association of increased VVV and all-cause mortality, cardiovascular events, and end-stage renal disease (ESRD) in a cohort of 32,85,684 United States veterans, higher SBP variability in individuals with and without hypertension was associated with increased risks of all-cause mortality, coronary heart disease (CHD), stroke, and ESRD.

**Evidence from CV Risk Population**

Systematic review and meta-analysis of 41 publications (36 studies) by Stevens et al showed that the increased long term BPV in SBP was associated with risk of all-cause mortality (1.15, 95% CI:1.09 to 1.22), CVD mortality (1.18, 95% CI: 1.09 to 1.28), CVD events (1.18, 95% CI: 1.07 to 1.30), CHD (1.10, 95% CI: 1.04 to 1.16), and stroke (1.15, 95% CI: 1.04 to 1.27). Furthermore, higher mid-term and short term variability in daytime SBP were also associated with all-cause mortality (1.15, 95% CI: 1.06 to 1.26 and 1.10, 95% CI: 1.04 to 1.16, respectively). A post-hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) including 25, 814 participants determined hazard ratio (HR) for various CVD by comparing participants in the highest versus lowest quintile of SD of SBP (≥14.4 mmHg versus <6.5 mmHg). The results showed consistently high HR ratio for fatal CHD or non-fatal myocardial infarction (1.30 (1.06–1.59), for all-cause mortality 1.58 (1.32–1.90), for stroke 1.46 (1.06–2.01), and for heart failure 1.25 (0.97–1.61).

**Evidence from Diabetes Patients**

In an analysis of 8811 patients with type 2 diabetes (T2D) randomized to blood pressure and glucose lowering agents in the The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, VVV of SBP was significantly associated with the incidence of major micro- and macro-vascular events and all-cause mortality. Hazard ratios (highest tenth of SBP variability vs lowest tenth) were 1.54 (95% CI: 0.99–2.39) for macrovascular events and 1.84 (95% CI: 1.19–2.84) for microvascular events. A retrospective cohort study which evaluated VVV of SBP on CVD and mortality among 124,105 primary Chinese patients with T2DM identified a positive linear relationship between the VVV of SBP and the first incidence of CVD and all-cause mortality over a median follow-up time of 39.5 months. Furthermore, patients with SD of SBP ≤5 mmHg had the lowest risks of CVD and all-cause mortality, and those with SD of SBP of ≥10 mmHg had significantly higher risks.

**Key point:**

Every 1 SD increase in the SD of SBP was associated with increase in the risks of CVD, all-cause mortality and the composite of both events by 2.9% (95% CI: 2.4–3.4%), 4.0% (95% CI: 3.5–4.6%), and 3.4% (95% CI: 3.0–3.8%), respectively.

**Evidence from patients with renal complications**

Observational analysis of 2,739 participants with T2D and nephropathy in IDNT (Irbesartan Diabetic Nephropathy Trial) and the RENAAL (Reduction of End
Table 2: Evidence indicating the effect of BPV on various parameters in different types of population

<table>
<thead>
<tr>
<th>Study</th>
<th>Population characteristics (n)</th>
<th>BPV index</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sega R. et al. 2002**</td>
<td>General population (3200)</td>
<td>24 h BPV</td>
<td>Increased LVMI</td>
</tr>
<tr>
<td>Kikuya M. et al. 2008**</td>
<td>General population (2455)</td>
<td>Day to day SBPV</td>
<td>Increased risk of CV and stroke mortality</td>
</tr>
<tr>
<td>Muntner P. et al. 2011**</td>
<td>General population (956)</td>
<td>Visit to visit SBPV</td>
<td>Enhanced all-cause mortality</td>
</tr>
<tr>
<td>Schutte A. E. et al. 2011**</td>
<td>General population (409)</td>
<td>24 h SBPV</td>
<td>Increased risk of CV complications</td>
</tr>
<tr>
<td>Johansson J. et al. 2012**</td>
<td>General population (1866)</td>
<td>Day to day morning SBPV and DBPV</td>
<td>Increased rate of cardiovascular events</td>
</tr>
<tr>
<td>Iwata S. et al. 2012**</td>
<td>General population (≥ 50 years) with no history of stroke (795)</td>
<td>SBPV</td>
<td>Increased risk of atherosclerotic plaque formation at aortic arch</td>
</tr>
<tr>
<td>Sakakura K. et al. 2007**</td>
<td>Elderly population (&gt; 61 years) (202)</td>
<td>Ambulatory BPV</td>
<td>Increased cognitive dysfunction in people ≥ 80 years of age and reduced QOL in people with 61 to 79 years of age</td>
</tr>
<tr>
<td><strong>Hypertensive population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palatini P. et al. 1992**</td>
<td>Both normotensive and hypertensive patients (728)</td>
<td>Day time SBPV</td>
<td>Higher degree of retinal abnormalities</td>
</tr>
<tr>
<td>Sander D. et al. 2000**</td>
<td>Hypertensive patients with &gt; 55 years of age (286)</td>
<td>Day time SBPV</td>
<td>Increased early carotid atherosclerosis progression</td>
</tr>
<tr>
<td>Mancia G. et al. 2001**</td>
<td>Hypertensive patients (1663)</td>
<td>24 h SBPV</td>
<td>Increased intima media thickness</td>
</tr>
<tr>
<td>Schillaci G. et al. 2012**</td>
<td>Hypertensive patients (3000)</td>
<td>Short term SBPV</td>
<td>Increased aortic stiffness</td>
</tr>
<tr>
<td>Kawai T. et al. 2013**</td>
<td>Hypertensive patients (120)</td>
<td>SBPV</td>
<td>Enhanced renal vascular resistance, intima media thickness and plaque score.</td>
</tr>
<tr>
<td><strong>Patients with CV risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cay S. et al. 2011**</td>
<td>Normotensive, stable CHD patients planned for PCI (100)</td>
<td>24 h, daytime and night time SBPV and DBPV</td>
<td>High risk of restenosis</td>
</tr>
<tr>
<td>Vidal-Petiot E. et al. 2017**</td>
<td>Patients with stable CHD (15,828)</td>
<td>Visit to visit BPV</td>
<td>Increased risk of CV events</td>
</tr>
<tr>
<td>Bangalore S. et al. 2017**</td>
<td>Patients with history of MI (8,658)</td>
<td>SBPV</td>
<td>Increased risk of any coronary event, CV event, MI, stroke, death and CV death</td>
</tr>
<tr>
<td>de Havenon A. et al. 2017**</td>
<td>Patients with acute anterior circulation ischaemic stroke (110)</td>
<td>SBPV between 0 to 120 h after hospital admission</td>
<td>Worse neurological outcome after stroke</td>
</tr>
<tr>
<td><strong>Patients with diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kilpatrick E. S. et al. 2010**</td>
<td>T1DM patients (1441)</td>
<td>Visit to visit BPV</td>
<td>High risk of nephropathy</td>
</tr>
<tr>
<td>Ozawa M. et al. 2009**</td>
<td>Hypertensive diabetic patients (72)</td>
<td>Night time SBPV</td>
<td>Increased risk of CHD</td>
</tr>
<tr>
<td>Ushigome E. et al. 2011**</td>
<td>Patients with T2D (858)</td>
<td>Day to day BPV</td>
<td>Increased risk of macroalbuminuria</td>
</tr>
<tr>
<td>Hsieh Y. et al. 2012**</td>
<td>Patients with T2DM (2161)</td>
<td>Visit to visit SBPV and DBPV</td>
<td>High risk of all-cause mortality</td>
</tr>
<tr>
<td><strong>Patients with renal complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Iorio B. et al. 2012**</td>
<td>CKD patients not requiring dialysis (374)</td>
<td>Visit to visit SBPV</td>
<td>High risk of death</td>
</tr>
<tr>
<td>Yokota K. et al. 2013**</td>
<td>Patients with non-diabetic CKD (stage 3 or 4) (56)</td>
<td>Visit to visit SBPV</td>
<td>Enhanced renal function deterioration</td>
</tr>
<tr>
<td>McMullan C. J. 2013**</td>
<td>Hypertensive patients with reduced renal function (908)</td>
<td>Visit to visit SBPV</td>
<td>Enhanced overall and CV mortality</td>
</tr>
<tr>
<td>Mezue K. et al. 2017**</td>
<td>Patients with CKD (2,488)</td>
<td>Visit to visit DBPV</td>
<td>Worse CV outcomes and hypoperfusion related events</td>
</tr>
</tbody>
</table>

BPV, blood pressure variability; CHD, coronary heart disease; CKD, chronic kidney patients; CV, cardiovascular; DBPV, diastolic blood pressure variability; h hour; LVMI, left ventricular mass index; MI, myocardial infarction; n, number of participants in the study; PCI, percutaneous coronary intervention; SBPV, systolic blood pressure variability; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus;

Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) studies revealed that VVV of SBP was associated independently with increased risk of the composite kidney disease end point (HR per 1-SD increment, 1.08 [95% CI, 1.01-1.16]; \( P = 0.02 \)) and end-stage renal disease. Whittle J et al has assessed the association of VVV of BP with renal outcomes among 21, 245 participants in the ALLHAT study and found that higher VVV of BP was associated with higher risk of renal outcomes. Significant association between SD of SBP with incidence of ESRD was identified in the study (HR for second through fifth quintiles of SD of SBP versus first quintile were: 1.29 (95% CI, 0.75 to 2.22), 1.76 (95% CI, 1.06 to 2.91), 1.46 (95%CI, 0.88 to 2.43), and 2.05 (95%CI, 1.25 to 3.36); \( P_{\text{trend}} = 0.004 \). Ryu et al evaluated a relationship between BPV and TOD (defined as left ventricular hypertrophy
(LVH) and kidney injury) in a cross-sectional, multicenter study on 1, 173 hypertensive CKD patients using 24-hr ambulatory blood pressure monitoring. They identified a positive relationship between BPV and LVH (OR per 1 mmHg increase in BPV: 1.053, \( P = 0.006 \)).

When the prognostic value of BPV in 2839 adult participants in Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) was assessed, SD of SBP had a significant linear association with the primary outcome (death or major disability at 90 days (modified Rankin Scale score ≥2)) for both the hyper-acute phase (first 24 h spontaneous intracerebral haemorrhage (ICH)) (highest quintile adjusted OR 1.41, 95% CI 1.05–1.90; \( P = 0.0167 \)) and the acute phase (2–7 days after ICH) (highest quintile adjusted OR 1.57, 95% CI 1.14–2.17; \( P = 0.0024 \)). Furthermore, in a cohort of 6,506 elderly individuals, it was identified that dementia risk increased 10% for every 1 SD increase in CV of BP measured on 3 visits. More evidence on the effect of BPV on different parameters is available in Table 2.

### Guideline Recommendations on BPV

The European Society of Hypertension and European Society of Cardiology (ESH/ESC) 2013 guidelines for the management of arterial hypertension have recommended the diagnosis and management of hypertension in adults and the 2016 National Heart foundation of Australia (NHFA) guidelines for the diagnosis and management of hypertension in adults have mentioned about BPV. Both the guidelines advocate the importance of high quality trials to establish the direct effect of BPV reduction in lowering the CV risk. However, NHFA guidelines strongly recommend life style modification and consistent treatment adherence in patients at high risk with suspected SBP variability between visits.

### Therapeutic Management of BPV

Ultimate goal of therapeutic interventions should not only aim to reduce elevated BP but also decrease BPV. Furthermore, objective of any antihypertensive therapy is to prevent the fatal or non-fatal complications of hypertension, which could primarily be achieved by preventing the damage to target organs. Different classes of antihypertensive agents such as angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta blockers (BBs) and diuretics are available currently. Several studies showed that ARBs could reduce BPV significantly in a variety of patients. Olmesartan, one of the ARBs routinely used for hypertension management, has been shown to reduce BPV both in monotherapy and as well as in combination. A randomized double-blind, double-mimic controlled trial on 48 patients with mild to moderate essential hypertension showed that olmesartan reduced eight weeks of treatment with both systolic and diastolic 24 h BPV. Combination of olmesartan along with CCBs was highly effective in reducing BPV as compared to the combination of olmesartan and diuretics. In T2DM patients, olmesartan along with azelnidipine significantly lowered morning SBP as compared to olmesartan plus trichlormethiazide combination (6.4 ± 1.9 vs. 7.5 ± 2.6, \( P = 0.004 \)). In the Combination of Olmesartan and a calcium channel blocker (CCB) or a diuretic in Japanese elderly hypertensive patients (COLM) trial, VVV of SBP was significantly less in olmesartan plus CCB group as compared with olmesartan plus diuretics group (10.02 ± 5.31 vs. 10.46 ± 5.69; \( P = 0.006 \)). Similarly, in another study on 207 Japanese subjects, combination of olmesartan and azelnidipine decreased BPV more than the combination of olmesartan and hydrochlorothiazide (follow-up mean: 6.3 vs. 7.1 mm Hg). This reduction in BPV with ARB plus CCB combination is independently associated with reduction in arterial stiffness. Moreover, bedtime administration of olmesartan and amlodipine was able to reduce BPV and urinary albumin excretion in hypertensive patients.

Similarly, other agents have also been shown to reduce BPV either as monotherapy or in combination. A cohort study on 2780 patients treated with different antihypertensive agents revealed that short term BPV was significantly reduced by treatment with CCBs (mean differences in SD −0.50±0.50 mm Hg, \( P = 0.001 \)) or diuretics (mean difference in SD −0.17±0.15 mm Hg, \( P = 0.05 \)) either in monotherapy or in combination. In the same study, combination of CCBs with diuretics or ARBs reduced short term BPV significantly when compared to other combinations. In a prospective population-based cohort study on 6,537 participants, association between discrete antihypertensive drug classes and incident dementia controlling for blood pressure variability (BPV) in the preceding 4 years were assessed by Tully et al. After adjusting for coefficient of variation of BPV, lower dementia risk was associated with non-dihydropyridine calcium channel blocker (HR 0.56; 95% CI: 0.31–1.00, \( P = 0.05 \)) and loop diuretics (HR 0.45; 95% CI: 0.22–0.93, \( P = 0.03 \)) in the study. In the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) trial, visit to visit BPV of SBP was significantly lower in the amlodipine group when compared to (\( P < 0.0001 \)) atenolol group. Furthermore, variability decreased over time in amlodipine group as compared to atenolol group. Similarly in the Natrilix SR Versus...
Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) study, amlodipine and indapamide sustained release were associated with significant (P<0.007, P<0.04 respectively) reductions in BPV when compared to placebo or candesartan.79 Likewise, when the VVV of SBP among 24,004 patients randomized to either chlorthalidone or amlodipine or lisinopril was assessed in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial, it was lower in chlorthalidone (10.6 (SD=5.0)) and amlodipine (10.5 (SD=4.9)) groups than lisinopril (12.2 (SD=5.8)) group.80 To summarize, different therapeutic options are available to control BPV, therefore treatment should be tailor made on the basis of patients’ requirement. Combination of ARBs and CCBs has been shown to provide beneficial effects in reducing BPV in various settings.

Expert Opinion

Consensus Statement on the Role and Relevance of Blood Pressure Variability in the Current Hypertension Management Scenario in India

Objectives

Hypertension is highly prevalent in India and it is considered as one of the most important non-communicable diseases. In India hypertension prevalence was projected to reach 22.9% for men and 23.6% for women by 2025.65 Several hypertensive patients are at risk of developing CVD and stroke despite maintaining normal BP with the help of antihypertensive agents. BPV has been implicated as independent risk factor for various diseases and increase target organ damage. Therefore, it is imperative to discuss whether it is important to incorporate BPV in the holistic hypertension management in India. Appropriate information has to be percolated into the general clinical practice.

Methodology

An expert panel consisting of 11 leading medical experts from various regions of India in different areas of clinical practice including nephrology, diabetes and endocrinology, cardiology, and critical care medicine were convened to understand the prevalence of, the challenges associated with, and methods to treat BPV and determine the position of BPV in hypertension control in India. The panel has extensively reviewed the relevant literature and shared their opinions on the role and relevance of BPV in hypertension management. A final consensus statement is derived from the key opinions of all members of the panel.

General consensus

• BPV is critical factor in the management of hypertension.
• Take two back to back readings from a well calibrated automatic machine have to be taken. Average of these two readings has to be considered further.
• SD is the easiest way to calculate BPV. Mobile app can be provided to the doctors to calculate SD immediately. Ideal target is SD <10 mm Hg of SBP from the mean.
• Treatment of any patient should be individualized. It is better to adhere to night dose regimen with antihypertensive agents.
• Even after giving a medication when the BP is high during the next visit two possibilities are there: a. BP control is not occurring as expected. b. BPV might be high.
• In any case, under such circumstances, dose of the medication has to be increased or new medication could be added or could be switched to new medication.
• ARB plus amlodipine combination is good with different mechanisms of action.

Consensus on the Role and Relevance of BPV in Hypertension Management

• Board agrees that BPV has importance in the hypertension management scenario.
• Prevention/control of hypertension should not only focus on BP reduction but should also aim at lowering BPV.
• Board agrees that SD < 10mm Hg of SBP from mean should be set as target goal. Beyond that patients should be considered as high risk for developing CVDs.
• BPV is frequently high in patients with diabetes, renal and CV complications, and in elderly people.
• Various tools such as ABPM, HBPM, and OBPM can all be used to measure BPV depending on the context and feasibility.
• Studies aimed at determining the impact of BPV on cardiovascular complications and target organ damage has to be carried out.
• In order to fast track the evidence development process, retrospective, nested case-control studies can be initiated in future from the data available from the experts which could be used as a basis to initiate the prospective studies.
• Plans to use HBPM in a large scale to collect patient data shall be rolled out and mobile apps to facilitate the data entry and analysis shall be developed.

Conclusion

To summarize, BPV have been identified as a risk factor in the development of various hypertension related complications. Despite the availability of clinical evidence demonstrating that BPV could cause target organ damage, it
did not attain desired significance in routine clinical practice. Reasons for this could be due to the lack of high quality trials that evaluated a direct relationship between BPV reduction and lowering of the CV risk and the difficulty in measuring BPV in a busy outpatient setting. However, based on several evidences which demonstrated the association between BPV and various complications such as CV mortality, all-cause mortality, diabetes and renal complications etc., it is reasonable to include BPV in the diagnostic armamentarium of hypertension management.

References

34. Chan EY, Fung CS, Yu EY, Fong DY, Chen JY, Lam CL. Association of Visit-to-Visit Variability of Systolic Blood Pressure With Cardiovascular Disease and Mortality in Primary Care Chinese Patients With Type


42. Schutte AE, Schutte R, Huismann HW, van Rooyen JM, Fourie CM, Malan NT, Malan L. Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans: the SABPA Study. Hypertension Research 2011; 34:1127-34.


