Human Phenomena: Blood Pressure and Hypertension, Clinical Challenges and Dilemmas beyond Current Guidelines

Magdy A. Darwish

Family & Community Medicine Department, College of Medicine, University of Dammam, Saudi Arabia
magdar9123@yahoo.com

Abstract: Many guidelines adopt static numeric thresholds as a basis for identification, classification and management of hypertension. In real life and clinical practice blood pressure may be elevated in many situations in absence of hypertension. On the other hand, other situations in which the patient may be hypertensive meanwhile having normal or merely high normal static blood pressure measurement. Challenges with numeric diagnosis include – phenomena of false negative e.g. masked hypertension and phenomena of false positive e.g. white coat hypertension. False positive and false negative labeling of patients may have grave consequences. Many challenges exist with current guidelines and tools: Normal biologic variations and responses of blood pressure, inaccurate measurement which may occur due to variety of causes: patient, observer or technique factors in addition to labile, masked and paroxysmal hypertension. Abnormal patterns of blood pressure which are not considered in current guidelines e.g. Loss of nocturnal Blood Pressure dipping, Visit to visit variability of blood pressure, Exaggerated response to exercise and mental stress, Widened pulse pressure, Salt sensitivity and Postural hypertension may all have great diagnostic and/or prognostic significance with or without elevated static blood pressure measurements. All these call to look at hypertension as a syndrome – not just numerical definition and make effort to develop strategies for earlier diagnosis of this syndrome considering blood pressure value as only one of several cardiovascular markers of this syndrome.
[Magdy A. Darwish Human Phenomena: Blood Pressure and Hypertension, Clinical Challenges and Dilemmas beyond Guidelines Life Science Journal 2013;10(2):1072-1082]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 150

Keywords: blood pressure, hypertension, accuracy, labile, paroxysmal, masked, white coat, abnormal patterns, hypertension syndrome

1. Introduction

Worldwide, raised blood pressure (BP) is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This account for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS.[1] Blood pressure (BP) levels have been shown to be positively and continuously related to the risk for stroke and coronary heart disease. In some age groups, the risk of cardiovascular disease doubles for each increment of 20/10 mmHg of blood pressure, starting as low as 115/75 mmHg.[2] Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008. The proportion of the world's population with high blood pressure, or uncontrolled hypertension, fell modestly between 1980 and 2008. However, because of population growth and ageing, the number of people with uncontrolled hypertension rose from 600 million in 1980 to nearly 1 billion in 2008 [1].

Many guidelines and recommendations of different bodies and authorities depend on numerical values of blood pressure (static discrete BP thresholds) for diagnosis, classification, management and follow up of hypertension. Canadian Hypertension Education Program (CHEP) [3], European Society of Hypertension [4], The International Society of Hypertension (ISH), World Health Organization [5], National Institute for Health and Clinical Excellence (NICE) [6], Australian Heart Foundation [7] in addition to National Heart, Lung, and Blood Institute (NHLBI) [2] are widely accepted international guidelines adopting this approach

Keeping in mind that blood pressure (BP) serves as a biomarker for the disease hypertension and, as such, elevated BP is not synonymous with hypertension. Some individuals may exhibit elevated BP in the absence of hypertension, whereas other individuals with the same levels of BP might be classified into different stages of hypertension [8]

Two clinical challenges exist: accuracy of static discrete BP thresholds and its relevance when assessing CV risk in an individual patient and the other challenge is dynamic nature of BP, (variability of blood pressure): how to assess, patterns, prognostic significance and relevance when assessing CV risk in an individual patients

Physicians who want to have 80% or more certainty that they are correctly classifying patients' BP control should use the average of several measurements. Hypertension quality metrics based on a single clinic measurement potentially misclassify a large proportion of patients.[9]

BP has physiologically dynamic nature, in which tissue perfusion is matched with metabolic demands in a complex, ever-changing manner that depends on the coordinated activity of numerous mechanisms involved in homeostasis, including the sympathetic nervous system, the renin-angiotensin system, and the vasodilatory system (e.g. prostaglandins and nitric oxide).[10] According to this perspective, optimal BP can vary among individuals and within the same person, depending on hemodynamic circumstances. Sporadic BP elevations may occur in individuals who have no evidence of early cardiovascular disease (CVD).[11]

Today, blood pressure measurement is the most common vital sign taken in ambulatory care settings, and out-of-office blood pressure measurement, including self-monitoring, has gained popularity, making it easy to identify patients with different subtypes of blood pressure status[12].

Challenge (1): Accuracy of Office BP Measurement:

It is normal for BP to fluctuate from moment to moment, from day to night and from day to day. BP fluctuations may be related to many factors such as physical activity, emotion, position, respiratory cycle, diet, salt intake, alcohol ingestion, sleep deprivation and others. Even in otherwise normotensive individuals, BP fluctuation can be substantial during moments of physical or emotional stress or even without overt provocation. In physicians' offices, readings can be very stable in some patients, while varying markedly in others. Biologic variation of blood pressure is common, and many studies show that blood pressure measurements vary with physical activity, smoking, caffeine ingestion, emotional state, temperature of the room, and season. [13-15] In addition, the blood pressure measurement may be inaccurate because of inappropriate technique, improper equipment, or other biases related to the observer.[13, 16-17] Wrong Cuff Size e.g. Using a standard blood pressure arm cuff on an obese patient falsely raises systolic blood pressure by approximately 10 mm Hg. "Miscuffing" should be strongly discouraged.[15,16] Inappropriate Level of the Arm [5] and Terminal Digit Preference are common sources of error [16] Up to 20% of elderly patients with hypertension have an auscultatory gap, Excessive pressure with the stethoscope artificially lowers the diastolic reading, sometimes by 10 mm Hg or more, although the systolic reading is usually unaffected. [18]. The average difference in systolic blood pressure between the two arms is 6 to 10 mm Hg.[19-20.] Differences of 20 mm Hg or more are uncommon and usually indicate obstructed flow in the subclavian artery As normovolemic persons stand up from the supine position, the pulse increases on average by 10.9 beats/min, systolic blood pressure decreases by 3.5 mm Hg, and diastolic blood pressure increases by 5.2 mm Hg.[21] Postural hypotension, defined as a decrement in systolic blood pressure of 20 mm Hg or more, occurs in 10% of normovolemic individuals younger than 65 years and in 11% to 30% older than 65 years.[21] As persons age, the postural pulse increment diminishes ; this phenomenon and the observation that older persons have more postural hypotension suggest that autonomic reflexes decline as persons age[16]

Challenge (2): Impact of Inaccuracy of Office BP Measurement:

Although the most important commonly performed office test is blood pressure measurement, yet it is considerably undervalued.[22]However, population wide, small inaccuracies in blood pressure measurement can have considerable consequences. Underestimating true blood pressure by 5 mm Hg would mislabel more than 20 million Americans with Pre-hypertension when true hypertension is present. It has been predicted that the consequences of an untreated 5 mm Hg of excessive systolic blood pressure would be a 25% increase over current levels of fatal strokes and fatal myocardial infarctions for these individuals.[23] Conversely, overestimating true blood pressure by 5 mm Hg would lead to inappropriate treatment with anti- hypertension medications in almost 30 million Americans, with attendant exposure to adverse drug effects, the psychological effects of misdiagnosis, and unnecessary cost.[24]

The trap is that in acknowledging the consequences of small measurement inaccuracies, errors of 5 to 10 mm Hg commonly occur as a result of improper blood pressure technique[22]. For example, active listening by the patient, when the medical assistant is talking during blood pressure measurement, can increase systolic blood pressure by 10 mm Hg.[25] Obtaining a measurement from an unsupported arm can increase the systolic pressure by 10 mm Hg. Lack of back support and crossed legs increase blood pressure [26]. If a patient needs to urinate, a blood pressure measurement taken before bladder emptying can increase the systolic pressure by >10 mm Hg. Measurements taken over clothing or with tight clothing pushed up on the arm, causing a tourniquet effect, also produce significant artifacts[22,26]**.** If an initial blood pressure reading obtained by medical assistant is elevated and a physician then obtains a follow-up reading, that second reading may be lower because the alerting reaction has subsided, or it may be higher because of doctor-related white-coat effect [22].

Challenge (3): Dynamic Blood Pressure Nature:

Epidemiological studies of hypertension were initially based on blood pressure (BP) measurement in

a medical environment, using the auscultatory method with a mercury or aneroid sphygmomanometer. High BP variability led to the development of complementary measurement methods, such as self-BP measurement at home (SBPM or HBPM) and ambulatory BP measurement (ABPM) [28]. Over the past decade, ABPM and HBPM have been shown to be better correlated with target organ damage than conventional measurement in a medical environment [29] Moreover; several studies have shown that BP measurements by ABPM [30-33] or HBPM [34-35] predict cardiovascular mortality and morbidity more accurately than office BP (OBP) measurements. This is probably due to the lower variability of BP measurements by these methods owing to multiple measurements and standardization of the circumstances in which BP is measured. The definition of normal BP and its control under treatment is arbitrary and differ for OBP (<140/90mmHg) and diurnal-ABPM or HBPM (<135/85 mmHg) [2-7.] The combined use of two different measurements (OBP and ABPM or OBP and HBPM) has led to the identification of four groups of patients: Patients with normal OBP and normal HBPM (or ABPM) who are 'normotensive' (or 'controlled' if on antihypertensive treatment) ; Those with high OBP and high HBPM (or ABPM), described as 'hypertensive' (or 'uncontrolled') ; Patients with an OBP higher than the normal threshold but normal HBPM (or ABPM), described as 'white-coat hypertensive' and Finally, patients with normal OBP but high HBPM (or ABPM), described as 'masked hypertensive'. Pickering was the first to describe this group and to propose the term 'masked hypertension' [37] now generally used. Nevertheless, other terms have been or are still used: 'reverse white-coat effect', 'inverse white-coat hypertension', 'white-coat normotension', 'isolated clinic normotension', 'isolated home hypertension', 'isolated ambulatory hypertension', and 'masked uncontrolled hypertension'[28].

Challenge (4): Undiagnosed Masked Hypertension:

In spite of high prevalence of this condition and its impact on prognosis in treated hypertensives or untreated patients, most guidelines including 2007 ESC-ESH guidelines[4] provide no specific advice for treating this type of elevated blood pressure. Hypertension is under diagnosed and under treated in general but obviously, more so in this class of patients. Ambulatory Home recordings of blood pressure are the only tools that can help us to come to the diagnosis of masked hypertension. Should we make such recordings in all patients with "high normal values"? In all hypertensive? To check whether management is successful, do we need to re-check ambulatory or home values at regular intervals? [38]. Up Till now: no clear guidelines exist. Depending on the study population, setting, the prevalence of masked hypertension lies between 8% and 20% among untreated adults, and up to 61% among treated adults [39- 40]. Factors implicated to raise the ambulatory blood pressure relative to office blood pressure include smoking, increased physical activity, alcohol consumption, obesity, and psychosocial factors such as anxiety, interpersonal conflict, and job stress [41-45] Other factors such as a younger age and male gender are possible characteristics of patients with masked hypertension [41] patients with masked hypertension exhibit lower levels of anxiety in the office than those with white-coat hypertension.[44] Poor medication adherence and intake of medication just before clinic consultation (so that the peak effect is observed) have also been suggested as possible factors to explain in treated patients [42]

Unlike patients with white-coat hypertension, who are easy to identify given their elevated office blood pressure, the objective of making a diagnosis of masked hypertension is to identify patients who have persistently elevated out-of-office blood pressure and thus are not receiving treatment or are treated inadequately Thus, the increased popularity of self-monitoring of blood pressure and the availability of valid and accurate monitoring devices make it relatively easier to identify patients with masked hypertension[46]. Studies with untreated individuals have generally confirmed that masked hypertensives have more target organ damage than true normotensives; they have levels of target organ damage comparable to those of sustained hypertensives or have intermediate levels between true normotensives and sustained hypertensives [47-50]. Masked hypertension in treated patients suggests inadequate treatment and poor blood pressure control and several studies demonstrate more target organ damage in treated patients with masked hypertension than in those whose blood pressure is controlled [51-54].

Two important caveats should be noted first issue in masked hypertension is the reproducibility of measurements and how patients with masked hypertension can best be identified in the office setting, given that they all have normal office blood pressure. Proper identification of patients requires adequate risk stratification, because screening all patients with normal office blood pressure would be prohibitively expensive and unsustainable in any healthcare system. One approach proposed is to screen only those patients whose office blood pressure is just under the upper limit of normal, given that the office blood pressure of most patients with masked hypertension (especially smokers and the young) is in the high normal range [46, 55]

Challenge (5): Visit To Visit Variability and Its Prognostic Significance:

It has been shown that visit-to-visit variability in systolic blood pressure (SBP) is a powerful predictor of stroke and coronary events. Independent of mean SBP, that maximum SBP is more predictive than is mean SBP (on clinic readings or on ABPM), that residual variability in SBP on treatment has a poor prognosis, and that stable hypertension has a better prognosis than does episodic hypertension. These findings challenge the usual blood pressure hypothesis and have implications for diagnosis, treatment, and monitoring of patients with hypertension [56-58]

Visit-to-visit variability in SBP was related to factors that correlate with arterial stiffness, including age, female sex, smoking, diabetes, and peripheral vascular disease, but only age and mean blood pressure affected the prognostic value of variability. Variability increased with age, but its effect on stroke risk was greatest at young ages, perhaps because of fewer competing causes of stroke or death or because of greater susceptibility to target organ damage.[56] Schillaci, G (2010) highlighted importance of Variability of systolic blood pressure (BP) from visit to visit as an important predictor of future cardiovascular disease in people with previous cerebrovascular disease and in hypertensive subjects.[59]

The prognostic value of visit-to-visit BP variability is independent from, and additional to, that of average BP. An amlodipine-based regimen might reduce visit-to-visit BP variability more effectively than an atenonol-based regimen, and this might partly explain its stronger protective effect against stroke [59].

Challenge (6) Labile Hypertension:

Although all physicians are familiar with the term labile hypertension which is a commonplace clinical dilemma, there are no quantitative criteria to define or diagnose it. Its effects on cardiovascular (CV) outcome are unclear, and there are no guidelines for its treatment. The effect of treating the labile component of hypertension on CV outcome is also unknown.

In describing the tendency of blood pressure (BP) to fluctuate, the terms variability, reactivity, and lability have been widely used. BP variability is usually defined as the average variation of BP throughout the day, quantitated as the standard deviation of ambulatory BP readings. It is increased in hypertensive individuals and increases with aging[60-62]. Reduced baroreceptor sensitivity might be a contributing factor [63]. Antihypertensive drug therapy does not appear to affect it.[64]

Studies differ as to whether BP variability is associated with CV risk.[62,64,65] even if such an association exists, it is unclear whether BP variability is a cause or merely a marker for CV risk, perhaps simply reflecting arterial stiffness. However, Normal Labiality in Patients with Vulnerable Underlying Conditions For example, in patients with chronic aortic dissection, Marfan syndrome, angina, or cerebral aneurysm may be detrimental since transient BP elevation might be deleterious and reduction of even normal lability could be proposed to be protective in these cases [66]. BP reactivity is defined as the response to environmental stressors; individuals with increased reactivity are sometimes referred to as "hot reactors."BP reactivity is difficult to quantitate because an individual's reactivity differs from stressor to stressor, and even upon retesting with the same stressor.[67] Further obscuring its meaningfulness, reactivity in the laboratory is not strongly predictive of reactivity to real-life stressors[67-68]. Although many have suspected that BP reactivity is predictive of future development of hypertension and of CV risk, studies have not found this to be true.[69-71]BP lability is characteristic of human BP, and there is no clear definition that differentiates normal from abnormal lability [66].

Challenge (7): Alerting Phenomena and White Coat Hypertension:

The alerting phenomenon is the tendency of BP to rise at the time of measurement, usually, but not always, due to consciously perceived anxiety over the measurement. Although typically described as occurring during measurement by a physician, it can also occur during measurement at home. When limited to physician's offices, it is regarded as white coat hypertension. Surprisingly, studies show that patients with white coat hypertension do not have abnormal lability outside of physicians' offices.[72] if limited to home it may contribute falsely to diagnosis of masked hypertension. White coat hypertension is associated with a lower risk of CV events than is sustained hypertension, but the risk of events and of target organ damage is greater than that in normotensive individuals[73-75].The risk of ultimately developing sustained hypertension is also greater.[76] Therefore, it is essential that ambulatory or home BP be monitored for future development of sustained hypertension. Many patients who are anxious about their BP enter a vicious cycle in which elevated readings trigger anxiety, which results in yet higher readings, possibly including home readings, and more anxiety. Some patients end up incessantly checking their BP, further aggravating this problem. Ultimately, in some patients, it can become difficult to obtain a meaningful measure of BP, whether in the office or at home, that is not contaminated by this alerting phenomenon[66]. In addition to the alerting phenomenon, measurement inaccuracies can also misleadingly contribute to the impression of excessive lability. In addition, readings

at times of suspected BP elevation, e.g., during perceived agitation, can be misconstrued as excessive lability rather than appropriate physiologic reactivity[66].

Challenge (8) Paroxysmal Hypertension:

Patients with labile hypertension experience transient but substantial increases in BP. The increases usually occur in the setting of emotional distress, particularly anxiety. Labile hypertension can be asymptomatic or can be accompanied by symptoms such as headache, palpitations, or flushing. The BP usually falls spontaneously without intervention. BP elevation is usually readily attributed to emotional stress, by both physician and patient. A particular problem arises in patients who experience marked elevations prior to medical or surgical procedures, preprocedural BP elevation[66]. This is In contrast Paroxysmal Hypertension (Pseudo-pheochromocytoma) where BP elevation generally occurs in the absence of overt emotional distress, with most patients describing the paroxysms as having occurred "out of the blue" [77, 78]. They can last minutes, hours, or even days.[78]. Abrupt BP elevation is accompanied by prominent and very distressing physical symptoms, such as headache, palpitations, flushing, weakness, or dyspnea.[78] The paroxysms often provoke a marked fear of imminent death or stroke; the fear follows rather than precedes the onset of physical symptoms. Fear of recurrent symptomatic paroxysms can lead to restriction of lifestyle and functioning.[78] Patient usually insists that the blood pressure elevation is not related to emotional factors. Pheochromocytoma is found in <2% of patients with paroxysmal hypertension.[79] Catecholamine studies are usually normal but can be mildly abnormal either during or even between paroxysms, reflecting activation of the sympathetic nervous system.[78, 80]

Paroxysms typically present with one of two hemodynamic/hormonal patterns. One is characterized by an increase in heart rate and epinephrine level and the other by an increase instead in nor-epinephrine level without an increase in heart rate.[18] This suggests that stimulation of the adrenergic limb of the sympatho-adrenal system is dominant in some and of the neural limb in others.[80]. A specific personality profile associated with this disorder suggests a psychological basis, attributable to repressed emotion related to prior emotional trauma or a repressive (non-emotional) coping style [81]

Challenge (9): Abnormal Blood Pressure Patterns and Their Prognostic Impact:

Orthostatic Hypertension, Visit To Visit Variability, Loss Of Nocturnal Dip, Increased Pulse Pressure And Increased Salt Sensitivity Are some Abnormal Blood Pressure Patterns Which May Have Diagnostic And Prognostic Implications

Orthostatic hypertension, a measure of blood pressure variability, is a clinically important pathologic condition associated with the progression of target organ damage and subsequent cardiovascular risk. Orthostatic hypertension precedes hypertension and could be considered as Prehypertension if a patient has seated clinic BP <140/90 mmHg. The simple examination of orthostatic BP changes using a self-measured home BP monitoring, through which abnormal pathological conditions can be detected with high reproducibility without the white-coat effect. Orthostatic hypertension is associated with morning hypertension and increased neurohumoral activation [82]. Orthostatic hypertension is associated with increased occurrence of silent cerebrovascular ischemia[83]. It has been found to be positively associated with peripheral arterial disease[84]

Some individuals manifest large blood pressure changes in response to acute or chronic salt depletion or repletion, and are termed "salt sensitive". Salt sensitivity and resistance have a large variety of determinants, including genetic factors, race/ethnicity, age, body mass and diet (overall diet quality, macro- and micronutrient content), as well as associated disease states, e.g. hypertension, diabetes and renal dysfunction. Salt sensitivity can be modulated by improving the quality of the diet, e.g. the dietary approach to stop hypertension (DASH diet) can reduce salt sensitivity by increasing the slope of the pressure-natriuresis curve. Salt sensitivity in both normotensive and hypertensive persons has been associated with increased cardiovascular disease events and reduced survival. Increased attention to strategies that reduce salt sensitivity, i.e. improvement in diet quality and weight loss, particularly in high risk persons, is an urgent need.[85]

The circadian blood pressure (BP) rhythm is associated with worsened cardiovascular outcomes in patients who have an excessive morning BP surge and in those who lack the normal nocturnal BP fall (non-dippers). There are multiple pathophysiologic mechanisms underlying abnormalities in circadian BP, most importantly abnormalities in sympathetic nervous system activity, salt and volume balance, and activation of the renin-angiotensin system. Several of these factors can be modified by clinical interventions, either related to lifestyle changes and/or antihypertensive drug therapy. The timing of drug administration or specific drug delivery systems that lead to a greater effect at night and/or mitigate the early morning BP surge can correct abnormal circadian rhythms[86]. Thus, in practice, ambulatory blood pressure predicts mortality significantly better than clinic blood pressure. The availability of blood

pressure measures during sleep and, in particular, the pattern of dipping adds clinically predictive information and provides further justification for the use of ambulatory monitoring in patient management.[87]

Recent work suggests that a high pulse pressure is an important risk factor for heart disease. A meta-analysis in 2000, which combined the results of several studies of 8,000 elderly patients in all, found that a 10 mm Hg increase in pulse pressure increased the risk of major cardiovascular complications and mortality by nearly 20%.[88] The authors of the meta-analysis suggest that this helps to explain the apparent increase in risk sometimes associated with low diastolic pressure, and warn that some medications for high blood pressure may actually increase the pulse pressure and the risk of heart disease. Widened pulse pressure has also been found to be a risk factor for the development of atrial fibrillation.[89]

Challenge (10): Room For clinical definition Of Hypertension:

Perhaps the most convincing evidence against using BP thresholds to define hypertension is that there is no threshold of BP above 115/70 mm Hg that identifies CV risk -that is, risk is linear and doubles for each 20/10 mm Hg increase in BP [2] As a consequence of the dynamic nature of BP, it may be more clinically relevant to use BP patterns, rather than discrete BP thresholds as measured in the clinic, when assessing CV risk in an individual patient. Thus, the Hypertension Writing Group, a group of hypertension specialists convened by a president of the American Society of Hypertension (HWG) places particular attention on ambulatory BP and the contribution of systolic BP (SBP) and pulse pressure (the difference between SBP and diastolic BP [DBP]) to risk, because these are widely considered to be more accurate markers of CV risk than is office DBP, particularly in older patients.[10-11, 90]

Cardiovascular (CV) risk has been found to be elevated at BP levels previously considered normal; in some cases, sporadic elevations in BP levels may be physiologically benign and not associated with additional CVD risk[10-11, 91-92.] As a consequence, many hypertension experts consider elevated BP at its core a disease marker, rather than a cause of hypertension. Moreover, elevated BP, as 1 marker of CVD, frequently coexists with other equally compelling disease markers.[11] Elevated BP should not, therefore, be viewed or treated in isolation, but considered in the context of whole patient care.

A number of strategies have been proposed to help bridge the gap between guideline recommendations and clinical practice. For example, the HWG, proposed replacing the BP-threshold-based JNC 7 classification system [2] with a risk-based approach, which categorizes the stages of hypertension according to BP patterns and the presence or absence of other CV risk factors, early disease markers (classified as BP, cardiac, vascular, renal, and retinal changes), and target-organ damage (classified as cardiac, vascular, renal, and cerebrovascular damage).[10,91] The Writing Group defined hypertension as a progressive CV syndrome, the early markers of which may be present even before BP elevations are observed. To simplify risk stratification and align it more closely with clinical practice, the Writing Group proposed classifying all patients as either normal or hypertensive, with hypertension classified as stages 1, 2, or 3 (early, progressive, or advanced) [10] These guidelines propose that initiation of treatment should be individualized and guided by CV risk, not solely by BP thresholds[91]

The goal of the new definition was to identify individuals at risk for CVD at an earlier point in the disease process, as well as to avoid labeling persons as hypertensive who are at low risk for CVD.[10] Viewed from this perspective, the HWG believed that threshold-based classification systems of hypertension, such as that endorsed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[2] while serving as tools to identify patients across a broad range of CVD risk, may lead to underestimation or overestimation of clinical risk within individual patients. To simplify risk stratification and align it more closely with clinical practice, the HWG proposed Beyond the goal of providing a more clinically relevant assessment of global CV risk in clinical practice, this paradigm shift served to focus attention on the enormous unmet need regarding prevention and optimal treatment of hypertension across a spectrum of fields, from basic research and drug development to patient education and clinical management[10] Recently, the HWG further refined and updated the definition and classification of hypertension. Revised Definition of Hypertension From Hypertension Writing Group 2009 states that: Hypertension is a progressive CV syndrome arising from complex and interrelated etiologies, early markers of the syndrome are often present before BP elevation is sustained; therefore, hypertension cannot be classified solely by discreet BP thresholds, Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs, and lead to premature morbidity and death, Reduction of elevated BP generally confers a reduction in the risk for CV events.HWG separates elevated BP (one manifestation of the disease) from hypertension (the disease) [11]

The concept of elevated BP as a disease marker for hypertension, rather than its cause, is supported by evidence suggesting that the risk for renovascular and CV sequelae may be higher than expected in the presence of normal or near-normal BP in some patients, or, conversely, lower than expected in the presence of above-normal BP in others. Conversely, because adverse CV and renal outcomes increase across all BP values, hypertension-related morbidity and mortality can occur even at BP levels considered normal by conventional standards. The significant proportions of myocardial infarctions and strokes that occur in patients who have only slight BP elevation, or even normal BP, adds weight to this argument.[93] As a consequence of the dynamic nature of BP, it may be more clinically relevant to use BP patterns, rather than discrete BP thresholds as measured in the clinic, when assessing CV risk in an individual patient. Thus, the HWG places particular attention on ambulatory BP and the contribution of systolic BP (SBP) and pulse pressure (the difference between SBP and diastolic BP [DBP]) to risk, because these are widely considered to be more accurate markers of CV risk than is office DBP, particularly in older patients.[2, 90] Physiologic alteration in different systems may represent early markers of hypertensive cardiovascular disease. Blood pressure may show loss of nocturnal BP dipping, exaggerated BP responses to exercise or mental stress, salt sensitivity or widened pulse pressure. Early cardiac markers may include left ventricular hypertrophy (mild), increased atrial filling pressure, decreased diastolic relaxation or increased natriuretic peptide. Early renal markers include microalbuminuria and/or reduced estimated GFR (60-90 mL/min). Cerebrovascular markers may include stroke, transient ischemic attack, decreased cognitive function or dementia. Early retinal markers include hypertensive retinal changes or loss of vision

The earliest identifiable stage of hypertensive disease, stage 1 hypertension, is characterized by the presence of early CVD markers. Although BP levels are higher than 115/75 mm Hg and may be frankly elevated in patients at this stage, abnormal BP patterns - including loss of nocturnal dipping, exaggerated responses to exercise or mental stress, and widened pulse pressure - may provide clearer evidence of the presence of early hypertensive disease [10] Although patients should have more than one CV risk factor to be included in this category, they should not have any evidence of target-organ damage.

The paradigm shift in viewing elevated BP as a marker for hypertension and hypertension as a progressive CVD syndrome has important implications for treating patients in the clinical setting. In terms of treatment, lowering BP remains an important goal of antihypertensive therapy, yet ultimately the overarching objective is to prevent CV complications.[94] Treatment of other CV risk factors is therefore equally important. Moreover, CV risk factors, including elevated BP, are not only precipitators, but also continuous pathogenic components at every stage of progression of CVD.[94] Clinical strategies, therefore, need to focus on detecting and treating patients at risk at every stage along the continuum, from preventing target-organ damage and interrupting CVD progression in patients with early-stage hypertension, to making aggressive efforts to slow further disease progression and avoid CV events in patients with late-stage Whether all individuals with early-stage hypertension, as defined by the HWG, should be treated with antihypertensive therapy requires further study[94]

Conclusion and recommendations:

Elevated blood pressure although is one of biomarkers of hypertension but it should not be considered the only marker. Other markers of hypertension may exist even before blood pressure elevation.Current guidelines and strategies depend mainly on threshold blood pressure values to diagnose, classify, manage and follow up of hypertensive patients. These strategies are contaminated by lot of shortages, some of which have been discussed earlier. Not considering other forms of hypertension in which office blood pressure may be normal in presence of hypertensive syndrome - falsely negative e.g. masked hypertension or inaccurate measurement, other forms in which blood pressure may be high in absence of true hypertension syndrome – false positive e.g. alerting phenomena, white coat hypertension, other labile forms, normal biologic responses of blood pressure and inaccurate measurements which may occur due to variety of causes : patient, observer or technique factors are some sources of error. Abnormal blood pressure patterns have diagnostic and prognostic value and need to be considered in evaluating treated or untreated hypertensive.They may provide clearer evidence of the presence of early hypertensive disease. Although lowering blood pressure remains an important goal of antihypertensive therapy, yet the ultimate objective is to prevent cardiovascular complications. Clinical strategies, therefore, need to focus on detecting and treating patients at risk at every stage along the continuum, from interrupting Cardiovascular Disease and preventing target-organ damage.

It is a clinical challenge to develop better practical tools and strategies to assess early hypertensive disease and to consider other variables in assessment of hypertension. Development of ambulatory blood pressure devices was good progress in this challenge but again they need guidelines for

their use in daily clinical practice because screening all patients with normal office blood pressure and follow up of all hypertensive would be prohibitively expensive and unsustainable in any healthcare system.

Correspondence:
Dr. Magdy A. Darwish, Assistant Professor,
Family & Community Medicine Department,
College of Medicine, University of Dammam,
P. O. Box 2114, Dammam 31451, Saudi Arabia.
E-mail: magdar9123@yahoo.com

References

1. World health organization (WHO). Global Health Observatory (GHO). [Cited 2013 may 1]. Available from: http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en.
2. National Heart, Lung, and Blood Institute (NHLBI). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [Cited 2013 may 1]. Available from: http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm.
3. Canadian Hypertension Education Program (CHEP) [Cited 2013 may 1]. Available from: http://www.hypertension.ca/chep-dp2
4. European Society of Hypertension Guidelines for the Management of Arterial Hypertension [Cited 2013 may 1]. Available from: http://www.eshonline.org/Guidelines/ArterialHypertension.aspx.
5. The International Society of Hypertension (ISH) and World Health Organization. WHO/ISH Hypertension guidelines [Cited 2013 may 1]. Available from: http://www.who.int/cardiovascular_diseases/guidelines/hypertension/en/
6. National Institute for Health and Clinical Excellence (NICE) the clinical management of primary hypertension in adults [Cited 2013 may 1]. Available from : http://guidance.nice.org.uk/CG127/Guidance/pdf/English
7. Australian Heart Foundation Guide to management of hypertension 2008[Cited 2013 may 1]. Available from: http://www.heartfoundation.org.au/SiteCollectionDocuments/HypertensionGuidelines2008to2010Update.pdf
8. Giles TD; Materson BJ, Cohn JN; Kostis JB. Definition and classification of hypertension: an update. J Clin Hypertens (Greenwich). 2009; 11:611–614.
9. Powers BJ, Olsen MK, Smith VA, Woolson RF, Bosworth HB, Oddone EZ Measuring blood pressure for decision making and quality reporting: where and how many measures? Ann Intern Med. 2011 Jun 21;154(12):781-8,
10. Giles TD, Berk BC, Black HR, Cohn JN, Kostis JB, Izzo JL Jr, Weber MA. Expanding the definition and classification of hypertension. J Clin Hypertens (Greenwich). 2005;7:505-512
11. Giles TD. Assessment of global risk: a foundation for a new, better definition of hypertension. J Clin Hypertens (Greenwich). 2006; 8:5-14.
12. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D.: Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension 2008, 52:1–9.
13. Bailey R.H., Bauer J.H.: A review of common errors in the indirect measurement of blood pressure (sphygmomanometry). Arch Intern Med. 1993; 153: 2741-2748
14. Reeves R.A.: Does this patient have hypertension? How to measure blood pressure. JAMA. 1995; 273: 1211-1218
15. O'Brien E.: Review: a century of confusion; which bladder for accurate blood pressure measurement? J Human Hypertension. 1996; 10: 565-572
16. Steven McGee. Evidence-Based Physical Diagnosis, 2012 Third Edition Chapter 16, 119-134 by Saunders, an imprint of Elsevier Inc
17. Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZHuman blood pressure determination by sphygmomanometery. Circulation. 1993; 88: 2460-2470.
18. Londe S., Klitzner T.S.: Auscultatory blood pressure measurement: effect of pressure on the head of the stethoscope. West J Med. 1984; 141: 193-195
19. Lane D, Beevers M, Barnes N, Bourne J, John A, Malins S, Beevers DG.: Inter-arm differences in blood pressure: when are they clinically significant?. J Hypertens. 2002; 20: 1089-1095
20. Singer A.J., Hollander J.E.: Blood pressure: assessment of interarm differences. Arch Intern Med. 1996; 156: 2005-2008
21. McGee S., Abernethy W.B., Simel D.L.: Is this patient hypovolemic? JAMA. 1999; 281: 1022-1029
22. Handler J. The importance of accurate blood pressure measurement. Perm J. 2009 Summer; 13(3):51-4
23. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002 Dec 14; 360(9349):1903–13. Erratum in: Lancet 2003 Mar 22; 361 (9362):1060. [PubMed]
24. Jones DW, Appel LJ, Sheps SG, Roccella EJ, Lenfant C. Measuring blood pressure accurately:

new and persistent challenges. JAMA. 2003 Feb 26; 289(8):1027–30. [PubMed]
25. Le Pailleur C, Helft G, Landais P, Montgermont P, Feder JM, Metzger JP, Vacheron A. The effects of talking, reading, and silence on the “white coat” phenomenon in hypertensive patients. Am J Hypertens. 1998 Feb; 11(2):203–7.
26. Cushman WC, Cooper KM, Horne RA, Meydrech EF. Effect of back support and stethoscope head on seated blood pressure determinations. Am J Hypertens. 1990 Mar; 3(3):240–1.
27. Reeves RA. The rational clinical examination. Does this patient have hypertension? How to measure blood pressure. JAMA. 1995;273(15):1211–8.
28. Masked hypertension: a systematic review Guillaume Bobriea, Pierre Clersonb, Joe¨l Me´nardc, Nicolas Postel-Vinaya, Gilles Chatellierc and Pierre-Franc¸ois Plouina, Journal of Hypertension 2008, 26:1715–1725
29. O'BrienE, AsmarR, BeilinL, ImaiY, MallionJM, ManciaG, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; EuropeanSociety of HypertensionWorkingGroup on BloodPressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003; 21:821–848.
30. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E; Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 2003; 348:2407–2415.
31. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality. The Dublin outcome study. Hypertension 2005; 46:15–161.
32. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality. A population-based study. Hypertension 2005; 45:499–504.
33. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens 2005; 19:801–807.
34. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens 1998; 16:971–975.
35. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of ‘masked hypertension’ detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004; 291:1342–1349.
36. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. Kidney Int 2006; 69:406–411.
37. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension 2002;40:795–796.
38. Clement D. Masked Hypertension. ESC Councils. Council for Cardiology Practice.E-journal of Cardiology Practice. E-Journal Volume 7 N°34. 27 May 2009:
39. Bobrie G, Clerson P, Ménard J, Postel-Vinay N, Chatellier G, Plouin PF.: Masked hypertension: a systematic review. J Hypertens 2008, 26:1715–1725.
40. Verberk WJ, Kessels AG, de Leeuw PW: Prevalence, causes, and consequences of masked hypertension: a meta-analysis. Am J Hypertens 2008, 21:969–975.
41. Ogedegbe G: Causal mechanisms of masked hypertension: socio-psychological aspects. Blood Press Monit 2010, 15:90–92. This paper gives a thorough review of the literature in terms of the psychosocial and causal mechanisms of masked hypertension, based largely on the work of Dr. Thomas Pickering.
42. Aksoy I, Deinum J, Lenders JW, Thien T: Does masked hypertension exist in healthy volunteers and apparently well-controlled hypertensive patients? Neth J Med 2006, 64:72–77.
43. Obara T, Ohkubo T, Kikuya M, Asayama K, Metoki H, Inoue R, Oikawa T, Komai R, Murai K, Horikawa T, Hashimoto J, Totsune K, Imai Y; J-HOME Study GroupPrevalence of masked uncontrolled and treated white-coat hypertension defined according to the average of morning and evening home blood pressure value: from the Japan Home Versus Office Measurement Evaluation Study. Blood Press Monit 2005, 10:311–316.
44. Ogedegbe G, Pickering TG, Clemow L, Chaplin W, Spruill TM, Albanese GM, Eguchi K, Burg M, Gerin W.: The misdiagnosis of hypertension: the role of patient anxiety. Arch Intern Med 2008, 168:2459–2465.
45. Wang GL, Li Y, Staessen JA, Lu L, Wang JG.Anthropometric and lifestyle factors associated with white-coat, masked and sustained hypertension in a Chinese population. J Hypertens 2007, 25:2398–2405.
46. Ogedegbe G, Agyemang C, Ravenell JE Masked Hypertension: Evidence of the Need to Treat Curr Hypertens Rep (2010) 12:349–355
47. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB : Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. Ann Intern Med 1999, 131:564–572.

48. Kotsis V, Stabouli S, Toumanidis S, Papamichael C, Lekakis J, Germanidis G, Hatzitolios A, Rizos Z, Sion M, Zakopoulos N.: Target organ damage in "white coat hypertension" and "masked hypertension". Am J Hypertens 2008, 21:393–399.
49. Matsui Y, Eguchi K, Ishikawa J, Hoshide S, Shimada K, Kario K.: Subclinical arterial damage in untreated masked hypertensive subjects detected by home blood pressure measurement. Am J Hypertens 2007, 20:385–391
50. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G.: Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation 2001, 104:1385–1392.
51. Cuspidi C, Meani S, Fusi V, Valerio C, Catini E, Magrini F, Zanchetti A.: Isolated ambulatory hypertension and changes in target organ damage in treated hypertensive patients. J Hum Hypertens 2005, 19:471–477.
52. Kuriyama S, Otsuka Y, Iida R, Matsumoto K, Tokudome G, Hosoya T.: Morning blood pressure predicts hypertensive organ damage in patients with renal diseases: effect of intensive antihypertensive therapy in patients with diabetic nephropathy. Intern Med 2005, 44:1239–1246.
53. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, Caldarella MP, Neri M, Cuccurullo F, Mezzetti A.: Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 2005, 18:1422–1428.
54. Tomiyama M, Horio T, Yoshii M, Takiuchi S, Kamide K, Nakamura S, Yoshihara F, Nakahama H, Inenaga T, Kawano Y.: Masked hypertension and target organ damage in treated hypertensive patients. Am J Hypertens 2006, 19:880–886.
55. Pickering TG: The natural history of hypertension: prehypertension or masked hypertension? J Clin Hypertens (Greenwich) 2007, 9:807–810.
56. Rothwell, P. M., Howard, S. C., Dolan, E., O'Brien, E., Dobson, J. E., Dahlöf, B., Poulter, N. R. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lance* (2010). *t, 375*(9718), 895-905. Retrieved from http://search.proquest.com/docview/199059157?accountid=136546
57. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension.Lancet 2010; 375: 938.48.
58. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS; ASCOT-BPLA and MRC Trial Investigators. Effects of À blockers and calcium channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol. 2010 May; 9(5):469-80. doi: 10.1016/S1474-4422(10)70066-1. Epub 2010 Mar 11.
59. Schillaci G, Pucci G.The importance of instability and visit-to-visit variability of blood pressure.Expert Rev Cardiovasc Ther. 2010 Aug;8(8):1095-7. doi: 10.1586/erc.10.84.
60. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, di Rienzo M, Pedotti A, Zanchetti A.Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circ Res.1983*;* 3:96–104.
61. Mancia G. Blood pressure variability at normal and high blood pressure. Chest.1984*;*83*:*317–319.
62. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y.Prognostic significance of blood pressure and heart rate variabilities. The Ohasama study. Hypertension. 2000*;* 36:901–906.
63. Conway J, Boon N, Vann Jones J, Sleight P.Mechanisms concerned with blood pressure variability throughout the day. Clin Exp Hypertens.1985*;* 7:153–157.
64. Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, Jaaskivi M, Nachev C, Parati G, O'Brien ET, Tuomilehto J, Webster J, Bulpitt CJ, Fagard RH; Syst-Eur investigators.variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens. 2003*;* 21:2251–2257.
65. Khattar RS, Swales JD, Banfield A, Dore C, Senior R, Lahiri A. Prediction of coronary and cerebrovascular morbidity and mortality by direct continuous ambulatory blood pressure monitoring. Circulation. 1999*;* 100:1071–1076.
66. Mann SG. The Clinical Spectrum of Labile Hypertension: A Management Dilemma J Clin Hypertens (Greenwich). 2009; 11:491–497.
67. Grassi G. Evaluating sympathetic and haemodynamic responses to mental stressors: hankering or achievement? J Hypertens. 1996*;* 14:1155–1157.
68. Parati G, Pomidossi G, Casadei R, Ravogli A, Groppelli A, Cesana B, Mancia G.Comparison of the cardiovascular effects of different laboratory stressors and their relationship to blood pressure variability. J Hypertens.1988*;* 6:481–488.
69. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull. 1984*;* 96*(3):*435–464*, November.*
70. Light KC. Cardiovascular responses to effortful coping: implications for the role of stress in hypertension development. Psychophysiology. 1981*;* 18:216–225.

71. Fauvel JP, M'Pio I, Quelin P, Rigaud JP, Laville M, Ducher M.Neither perceived job stress nor individual cardiovascular reactivity predict high blood pressure. Hypertension.2003; 42(6):1112–1116.
72. Munakata M, Hiraizumi T, Tomiie T, Saito Y, Ichii S, Nunokawa T, Ito N, Taguchi F, Yamauchi Y, Yoshinaga K.Psychobehavioral factors involved in the isolated office hypertension: comparison with stress-induced hypertension. J Hypertens.1998; 16:419–4122.
73. Verdecchia P, Reboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, Imai Y, Ohkubo T, Kario K.Short- and long-term incidence of stroke in white-coat hypertension. Hypertension. 2005; 45:203–208.
74. Verdecchia P, Angeli F, Gattobigio R, Borgioni C, Castellani C, Sardone M, Reboldi G.The clinical significance of white-coat and masked hypertension. Blood Press Monit.2007; 12:387–389.
75. Palatini P, Mormino P, Santonastaso M, Mos L, Dal Follo M, Zanata G, Pessina AC.Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension: results from the HARVEST study. Hypertension.1998; 32:377–378.
76. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension. The OHASAMA study. Arch Intern Med. 2005; 165:1541–1546.
77. Mann SJ. Severe paroxysmal hypertension. An autonomic syndrome and its relationship to repressed emotions. Psychosomatics. 1996;37:444–450.
78. Mann SJ. Severe paroxysmal hypertension (pseudopheochromocytoma): understanding its cause and treatment. Arch Intern Med.1999; 159:670–674.
79. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS.Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med.2001; 134:315–329.
80. Sharabi Y, Goldstein DS, Bentho O, Saleem A, Pechnik S, Geraci MF, Holmes C, Pacak K, Eisenhofer G. Sympathoadrenal function in patients with paroxysmal hypertension: pseudopheochromocytoma. J Hypertens. 2007; 25:2286–2295.
81. Mann SJ. Severe paroxysmal hypertension (pseudopheochromocytoma). Curr Hypertens Rep. 2008 Feb;10 (1):12-8. Abstract.
82. Kario, K. (2009). "Orthostatic hypertension: A measure of blood pressure variation for predicting cardiovascular risk". Circ J. 2009 Jun; 73(6):1002-7. Epub 2009 May 9.
83. Kario, K.; Eguchi, K.; Hoshide, S.; Hoshide, Y.; Umeda, Y.; Mitsuhashi, T.; Shimada, K. (2002). "U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: Orthostatic hypertension as a new cardiovascular risk factor". Journal of the American College of Cardiology 40 (1): 133–141
84. Fan, X. H.; Sun, K.; Zhou, X. L.; Zhang, H. M.; Wu, H. Y.; Hui, R. T. (2011). "Association of orthostatic hypertension and hypotension with target organ damage in middle and old-aged hypertensive patients". Zhonghua yi xue za zhi 91 (4): 220–224. PMID: 21418863 [PubMed - indexed for MEDLINE] (abstract)
85. Franco V, Oparil S. Salt sensitivity, a determinant of blood pressure, cardiovascular disease and survival. J Am Coll Nutr. 2006 Jun; 25(3 Suppl):247S-255S.
86. Peixoto AJ, White WB.Circadian blood pressure: clinical implications based on the pathophysiology of its variability. Kidney Int. 2007;71(9):855-60.
87. Ben-Dov, Iddo Z.; Jeremy D. Kark, Drori Ben-Ishay, Judith Mekler, Liora Ben-Arie, Michael Bursztyn (March 26, 2007). "Blood Pressure Measurement and Cardiovascular Risk Predictors of All-Cause Mortality in Clinical Ambulatory Monitoring Unique Aspects of Blood Pressure during Sleep". Hypertension 49: 1235–1241.
88. Blacher J, Staessen JA, Girerd X, Gasowski J, Thijs L, Liu L, Wang JG, Fagard RH, Safar ME. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. Arch Intern Med 2000 Apr 24;160(8):1085-9
89. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D'Agostino RB Sr, Kannel WB, Levy D, Benjamin EJPulse pressure and risk of new-onset atrial fibrillation. JAMA. 2007 Feb 21;297(7):709-15
90. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation. 1999; 100:354-360.
91. Weir MR. Risk-based classification of hypertension and the role of combination therapy. J Clin Hypertens (Greenwich). 2008; 10:4-12.
92. Khosia N, Black HR. Expanding the definition of hypertension to incorporate global cardiovascular risk. Curr Hypertens Rep. 2006; 8:384-390.
93. Sierra C, de la Sierra A. Early detection and management of the high-risk patient with elevated blood pressure. Vasc Health Risk Manag. 2008:4; 289-296.
94. Basile J. Management of global risk across the continuum of hypertensive heart disease. J Clin Hypertens (Greenwich). 2006; 8:21-30.