

## Treatment of hypertension-should we be more aggressive?

MurtazaMustafa<sup>1</sup>, Jayaram Menon<sup>2</sup>, EM. Illzam<sup>3</sup>, AM. Sharifa<sup>4</sup>, MK. Nang<sup>5</sup>

<sup>1,5</sup> Faculty of Medicine and Health Sciences, University Malaysia, Sabah, Kota Kinabalu, Sabah, Malaysia.

<sup>2</sup>. Department of Gastroenterology, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia.

<sup>3</sup>. Poly Clinic Sihat, Likas, Kota Kinabalu, Sabah, Malaysia.

<sup>4</sup>. Quality Unit Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia.

Corresponding Author: MurtazaMustafa

**Abstract:** In 2014 approximately one billion adults or 22 % of the world population have hypertension (HTN), with 9.4 million deaths in 2010. The rates of HTN in children and adolescents have increased in the last 20 years in the United States. Lowest rates of HTN in the rural India and highest in Poland. HTN results from a complex interaction of genes and environments factors. HTN is classified as primary or essential, is due to lifestyle and genetic factors, and secondary HTN is due to identifiable cause e.g. chronic kidney disease, narrowing of the kidney arteries and endocrine disorder. Several environmental factors influence HTN. High salt intake, lack of exercise, obesity, and depression. Role of caffeine and vitamin D deficiency are less clear. Frequent symptoms include headaches, lightheadedness, vertigo, tinnitus, and altered vision. Severely elevated blood pressure equal or greater than a systolic 180 or diastolic 110 is considered as HTN emergency. HTN in gestation occurs in approximately 8-10% of pregnancies. Ambulatory blood pressure monitoring over 12 to 24 hours is the most accurate method to confirm diagnosis. Goal of blood pressure control a target below the range of 140-160/90-100 mmHg, and change in lifestyle. First line of medications for HTN include thiazide-diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Prevention of HTN include maintain normal body weight, reduce dietary salt intake, regular exercise, effective lifestyle change, limit alcohol consumption, and diet rich in fruit and vegetables.

**Keywords:** Primary hypertension, Emergencies in hypertension, Management, Prevention.

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### I. Introduction

Hypertension (HTN or HPT), also known as high blood pressure (HBP), is a long term medical condition in which blood pressure in the arteries is persistently elevated [1]. High blood pressure affects between 16 to 37% of the population globally [2]. In 2010, hypertension was believed to have been a factor in 18% (9.4 million) deaths [3]. Rates also vary markedly within WHO regions with rates as low as 3.4% (men) and 6.8% (women) in rural India, and as high as 69.9% (men) and 72.5% (women) in Poland [4]. High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure [2]. About 90-95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors [2]. The remaining 5-10% of cases are categorized as secondary blood pressure, that is due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, and endocrine disorder, or the use of birth control pills [2]. Lifestyle factors that increase the risk include excess salt, excess body weight, smoking and alcohol [5]. Normal blood pressure at rest is within the range of 100-140 millimeters mercury (mmHg) systolic and 60-90 mmHg diastolic [6]. High blood pressure is present if the resting blood pressure is persistently above 140/90 mmHg for most adults [2]. Different numbers apply to children [2]. Ambulatory blood pressure monitoring over 24 hours period appears more accurate than office best blood pressure [1]. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease [7]. Lifestyle changes and medications can lower blood pressure and decrease the risk of health complication [8]. The paper reviews the literature on clinical manifestation, treatment and prevention of hypertension.

### II. Historical perspectives

The English clergyman Stephen Hales made the first published measurement of blood pressure in 1773 [9]. However, hypertension as a clinical entity came into its own in 1896 with the invention of cuff-based sphygmomanometer by Scipione Riva-Rocci in 1896 [10]. This allowed easy measurement of systolic pressure in the clinic. In 1905, Nikolai Korotkoff improved the technique by describing the korotkoff sounds that are heard when artery is auscultated with a stethoscope while sphygmomanometer cuff is deflated. This permitted systolic

and diastolic pressure to be measured[10].The symptoms similar to symptoms of patients with hypertensive crisis are discussed in medieval Persian medical texts in the chapter of “fullness disease”[11].

The description of hypertension as a disease came among others from Thomas Young in 1808 and especially Richard Bright in 1836[9].The First report of elevated blood pressure in a person without evidence of kidney disease was made by Frederick Akbar Mahomed(1849-1884)[12].Historically the treatment for what was called the “hard pulse disease” consisted in reducing the quantity of blood by bloodletting or application of leeches[9].This was advocated by the Yellow Emperor of China, Cornelius Celsius, Galen, and Hippocrates The therapeutic approach for treatment of hard pulse disease included changes in lifestyle(staying away from anger and sexual intercourse),and dietary program( avoiding consumption of wine, meat, and pastries, reducing the volume of food in a meat, maintaining a low energy diet and dietary usage of spinach and vinegar)[12].In the 19<sup>th</sup> and 20<sup>th</sup> centuries, before effective pharmacological treatment for hypertension became possible, three treatment modalities were used, all with numerous side-effects: strict sodium restriction( for example rice diet)[9],sympathectomy-surgical ablation of parts of sympathetic nervous system, and pyrogen therapy-injection of substances that cause fever, directly reducing blood pressure[13].

First chemical for hypertension, sodium thiocyanate, was used in 1900 but had many side-effects and was unpopular[9].Several other agents were developed after the second World War, the most popular and reasonably effective of which were tetramethylammoniumchloride,hexamethonium hydralazine and reserpine(derived from the medicinal plant Rauwolfa serpentina).None of these were well tolerated[14].A major breakthrough was achieved with the discovery of the first well –tolerated orally available agents. The first was a chlorothiazide,the first thiazide diuretic and developed from the antibiotic sulfanilamide, which became available in 1958[15].Subsequently beta blockers,calcium channel blockers, angiotensin converting enzyme{ACE} inhibitors, angiotensin receptor blockers and renin inhibitors were developed as antihypertensive agents [13].

### **III. Worldwide prevalence**

As of 2014,approximately one billion adults or 22% of the population of the world have hypertension[16].It is more frequent in men[16],in those of low socioeconomic status[[17],and prevalence increases with age[17].It is more common in high, medium and low income countries[16].The prevalence raised blood pressure in highest in Africa(30% of both sexes)and lowest in WHO Region of Americas(18% for both sexes).Rates also vary markedly within WHO regions with rates as low as 3.4%(men) and 6.8%(women) in rural India and as high as 68.9%(men) and 72.5%(women) in Poland[4].In Europe hypertension occurs in about 30-45% of people as of 2013[6].In 1995 it was estimated that 43 million people(24% of the populations)in the United States had hypertension or were taking hypertensive medication[18].By 2004 this had increased to 29 % [19],and further to 34%(76 million US adults)by 2006 African adults in the United States have among the highest rates of hypertension in the world at 44%[20].It is also more common in Filipino Americans and less common in US whites and Mexican Americans[17].More than a third adults in China suffer from high blood pressure, but only one in 20 are able effectively to manage their condition, according to new research[21].

**High blood pressure in children:** Rates of high blood pressure in children and adolescents have increased in the last 20 years in the United States [22].Childhood hypertension, particularly in pre-adolescents, is more often secondary to an underlying disorder than in adults. Kidney disease is most common secondary cause of hypertension in children and adolescents. Nevertheless, primary or essential hypertension accounts for most cases [23].

### **IV. Contributory factors**

**Essential or primary hypertension:**Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified [24],as well as some rare genetic variants with large effects on blood pressure[25].Also,GWAS have identified 35 genetic loci related to blood pressure;12 of these genetic loci influencing blood pressure were newly found[26].Senetial SNP for each new genetic loci identified has shown an association with DNA methylation at multiple nearby Cpgsites. These sentinel SNP are located within genes related to vascular smooth muscle and renal function. DNA methylation might not effect in some way linking common genetic variation to multiple phenotypes even though mechanism underlying this association is nor understood. Single variant test performed in this study for 35 sentinelSNP(known and new)showed that genetic variants singly or in aggregate continue to risk of clinical phenotypes related to high blood pressure[26].

Blood pressure rises with aging and risk of becoming hypertensive in later life is considerable [27].Several environmental factors influence blood pressure. High salt intake raises the blood pressure in salt sensitive individuals, lack of exercise, obesity, and depression can play a role in individual cases[28].The possible role of other factors such as caffeine consumption, and vitamin D deficiency are less clear[29,30].Insulin resistance, which is common in obesity and is a component of syndrome X(or the metabolic

syndrome), is also thought to contribute to hypertension[31]. Events in early life like, such as low birth weight, maternal smoking, and lack of breast feeding may risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult life remain unclear[32]. An increased rate of high blood urea has been found in untreated people with hypertensive in comparison with people with normal blood pressure, although it is uncertain whether the former plays a casual role or is subsidiary to poor kidney function[33]. Blood pressure on average may be higher in the winter than in summer[34].

**Secondary hypertension:** Non-essential or secondary hypertension results from an identifiable cause. Kidney disease is the most common secondary cause of hypertension[35]. Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, acromegaly, Conn's syndrome or hyperaldosteronism, hyperthyroidism and pheochromocytoma[35]. Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive eating of liquorice, excessive drinking of alcohol and certain medicine, herbal remedies and illegal drugs[35]. Arsenic exposure through drinking water has been shown with to correlate with elevated blood pressure[36].

### **V. Pathognomonic**

In most people with established essential hypertension, increased resistance to blood flow (total peripheral resistance) accounts for high pressure while cardiac output remains normal[37]. There is evidence that some younger people with prehypertension or borderline hypertension have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension[38]. These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age[38]. Whether this pattern is typical of all people who ultimately develop hypertension is disputed[39]. The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and arterioles[40], although a reduction in the number or density of capillaries may also contribute[41]. Whether increased active arteriolar vasoconstriction plays a role in established essential hypertension is unclear[42]. Hypertension is also associated with decreased venous compliance, which may increase venous return increase cardiac preload and ultimately, cause diastolic dysfunction[43].

Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low a condition termed isolated systolic hypertension [44]. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure [45].

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either disturbances in the kidneys' salt and water handling (particularly abnormalities in the intrarenal renin-angiotensin system)[46], or abnormalities of the sympathetic nervous system[47]. These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension[48]. Interleukin 17 has garnered interest for its role in increasing the production of necrosis factor alpha, interleukin 1, interleukin 6, and interleukin 8[49].

### **VI. Clinical Manifestations**

Hypertension is rarely accompanied by symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with hypertension report headaches (particularly at back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears) altered vision or fainting episodes[50]. These symptoms, however might be related to associated anxiety rather than the high blood pressure[51]. On physical examination, hypertension may be associated with presence of changes in the optic fundus seen by ophthalmoscopy[52]. The severity of changes typical of hypertensive retinopathy is graded from I-IV, grades I and II may be difficult to differentiate[52]. The severity of retinopathy correlates roughly with the duration or severity of the hypertension[50].

**6.1. Non-essential or secondary hypertension:** Hypertension with certain additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause. For example, Cushing's syndrome frequently causes truncal obesity, glucose intolerance, moon face, a hump of fat behind the neck or shoulder, and purple abdominal stretch marks [35]. Hyperthyroidism frequently causes weight loss with increased appetite, fast rate, bulging eyes, and tremor. Renal artery stenosis (RAS) may be associated with localized abdominal bruit to the left or right of the midline (unilateral RAS), or in both locations (bilateral RAS). Coarctation of the aorta frequently causes a decreased blood pressure in lower extremities relative to

arms, or delayed or absent femoral arterial pulses. Pheochromocytoma may cause abrupt (“paroxysmal”) episodes of hypertension accompanied by headache, palpitations, pale appearance and excessive sweating [35].

**6.2. Emergencies in hypertensive:** Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic 110) is referred to as hypertensive emergency or crisis. Hypertensive urgency or hypertensive emergency, according to the absence or presence of end organ damage respectively [53]. In hypertensive urgency, there is no evidence of end organ damage resulting from elevated blood pressure. In these cases, oral medication are used to lower the BP gradually over 24 hours to 48 hours[54]. In hypertensive emergency, there is direct damage to one or more organs[55]. The most affected organs include the brain, kidney, heart and lungs, producing symptoms which may include confusion, drowsiness, chest pain and breathlessness[54]. In hypertensive emergency, the blood pressure must be reduced more rapidly to stop ongoing organ damage[54], however, there is a lack of randomized controlled trial evidence for this approach[56].

**6.3. Hypertension in gestation:** Hypertension occurs in approximately 8-10% of pregnancies [35]. Two blood pressure measurements six hours apart of greater than 140/90 mmHg is considered diagnostic of hypertension in pregnancy[57]. High blood pressure in pregnancy can be classified as pre-existing hypertension, gestational hypertension, or pre-eclampsia[58]. Pre-eclampsia is a serious condition of second half of pregnancy and following delivery characterized by increased blood pressure and the presence of protein in the urine[35]. It occurs in 5% of pregnancies and is responsible for approximately 16% of all maternal deaths globally[35]. Pre-eclampsia also doubles the risk of death of the baby around the time of birth[35]. Usually there are no symptoms in pre-eclampsia and it is detected by routine screening. When symptoms of pre-eclampsia occur the most common are headache, visual disturbance (often “flashing lights”), vomiting, pain over the stomach, and swelling. Pre-eclampsia can occasionally progress to life threatening condition eclampsia, which is a hypertensive emergency and has several serious complications including vision loss, brain swelling, seizure, kidney failure, pulmonary edema, and disseminated intravascular coagulation[a blood clotting disorder][35]. In contrast, gestational hypertension is defined as new-onset hypertension during pregnancy without protein in the urine[58].

**6.4. Hypertension in children:** Failure to thrive, seizure, irritability, lack of energy, and difficulty in breathing [59], can be associated with hypertension in neonates and young infants. In older infants and children, hypertension can cause headache, unexplained irritability fatigue, failure to thrive, blurred vision, nosebleeds, and facial paralysis [59].

## **VII. Diagnosis**

Hypertension is diagnosed on the basis of a persistently high resting blood pressure. Traditionally National Institute of Clinical Excellence recommends three separate resting sphygmomanometer measurements at monthly interval[60]. The American Heart Association recommends at least three resting measurements on at least two separate health care visits[61]. Ambulatory blood pressure monitoring over 12 to 24 hours is the most accurate method to confirm the diagnosis[62].

Once the diagnosis of hypertension has been made, healthcare providers should identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused by kidney disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and family history of hypertension [63]. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and require treatment [17]. Serum creatinine is measured to assess for the presence of kidney disease, which can be either the cause or the result of hypertension. Serum creatinine alone may overestimate glomerular filtration rate and recent guidelines advocate the use of predictive equation such as the modification of the diet in Renal Disease (MDRD) formula to estimate glomerular filtration rate (eGFR)[64]. eGFR can also provide a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Electrocardiogram (ECG) testing is done to check for evidence that heart is under strain from high blood pressure. It may also show whether there is evidence of that heart is under strain from high blood pressure. It may also show whether there is thickening of the heart muscle (left ventricular hypertrophy) or whether the heart has experienced a prior minor disturbance such as silent heart attack. A chest X-ray or an echocardiogram may also be performed for signs of heart enlargement or damage to the heart [35].

## **VIII. Management**

According to one review published in 2003, reduction of the blood pressure by 5mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease[65].

**8.1. Goal of blood pressure control:** Various groups have produced guidelines how low the blood pressure goal(target) should be when a person is treated for hypertension. These recommend a target below the range 140-160/90-100 mmHg for the general population [66].Controversy exists regarding the appropriate targets for certain subgroups, including the elderly, people with diabetes and people with kidney disease[67].Many expert groups recommend a slightly higher target of 150/90 mmHg for those over somewhere between 60-80 years of age[68].One expert group,JNC-8, recommend the target of 150/90 mmHg for those over 60 years of age[66],but some experts within this group disagree with this recommendations[69].Some expert groups have also recommended slightly lower targets in those with diabetes[68] or chronic kidney disease with proteinuria[70], but others recommend the same target as for general population[68].The issue of what is the best target and whether targets should differ for high risk individuals is unresolved [71],but current best evidence supports more intensive blood pressure lowering than advocated in some guidelines[72].

**8.2. Lifestyle change:** First line of treatment for hypertension is lifestyle changes, including dietary changes, physical exercise and weight loss. Though these have all been recommended in scientific advisories [73],a Cochrane systematic review found no evidence of weight loss diets on death or long term complications and adverse events with hypertension[74].The review did not find a decrease in blood pressure[74].Their potential effectiveness is similar to and at times exceeds a single medication. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication.[6].Dietary changes shown to reduce blood pressure include diets with low sodium[75],the DASH(dietary approaches to stop hypertension) diet[76],and vegetarian diets[77],While potassium supplementation is useful it is unclear if a high dietary potassium intake is beneficial [78].Physical exercise regimens which are shown to reduce blood pressure [79].Stress reduction techniques such as biofeedback or transcendental meditation may be considered as an add-on to other treatments to reduce hypertension, but do not have evidence for preventing cardiovascular disease on their own[79].

**8.3. Treatment:** Several classes of medications, collectively referred to as antihypertensive medications, are available for treating hypertension. First line medications for hypertension include thiazide-diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers[66].These medication may be used alone or in combination, the latter option may serve to minimize counter-regulatory mechanism that act to revert blood pressure values to pre-treatment levels[66].Most people require more than one medication to control hypertension[73].

**8.4. Non-responding hypertension:** Non-responding or resistant hypertension is defined as hypertension that remains above goal blood pressure level in spite of using at once, three antihypertensive belonging to different drug classes. Low adherence to treatment is an important cause of resistant hypertension [80].Resistant hypertension may also represent the result of chronic high activity of autonomic nervous system; this concept is known as” neurogenic hypertension”[81].

## **XI. Prevention**

Much of the disease burden of high blood pressure is experienced by people who are not labeled as hypertensive [82].Consequently, population strategies are required to reduce the consequences of high blood pressure and reduce the need for antihypertensive drug therapy. Lifestyle changes are recommended to lower blood pressure, before starting drug therapy. The 2004 British Hypertension Society guidelines [82],proposed lifestyle changes consistent with those outlined by the US National High BP Education Program [83], for the primary prevention of hypertension that include:

Maintain normal body weight for adults(e.g. body mass index 20-25 kg/m<sup>2</sup>).b.Reduce dietary sodium intake to<100mmol/day (< 6g of sodium chloride or<2.4 of sodium per day). c) Engage in regular aerobic physical activity such as brisk walking ≥ 30 min per day, most of the days of the week).d). Limit alcohol consumption to no more than 3 units/ day in men and no more than 2 units/ day in women).e). Consume a diet rich in fruit and vegetables (e.g. at least 5 portions per day).

Effective lifestyle modification may lower blood pressure as much as an individual antihypertensive drug. Combination of two or more lifestyle modification can achieve even better results[83].There is considerable evidence that reducing dietary salt intake lowers blood pressure, but whether this translates into a reduction in mortality and cardiovascular disease remains uncertain[84].Estimated sodium intake ≥6g/day and <3g/day are both associated with high risk of death or major cardiovascular disease, but the association between high sodium intake and adverse outcomes is only observed in people with hypertension[85].Consequently, in the absence results from randomized controlled trials, the wisdom of reducing levels of dietary salt below 3g/day has been questioned[85].

## **X. Conclusions**

The high blood pressure or hypertension (HTN) has high rates and mortality globally. High blood pressure rises with aging and risk of becoming hypertensive in later life is considerable. Primary or essential

HTN is due to genetic and environmental factors. Compliance with medication and lifestyle changes can lower blood pressure and decrease the risk of health complications.

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