

Review Article

Hypertension: A Brief ReviewRAKHI NEGI¹, LAXMI GOSWAMI¹, PREETI KOTHIYAL²¹Department of Pharmaceutics, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Patelnagar Dehradun, 248001²Department of Pharmacology, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Patelnagar Dehradun, 248001**ARTICLE DETAILS***Article history:*

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Hypertension is emerging as one of the severe epidemic disease. Hypertension occurs when blood pressure in the arteries is elevated which makes the heart to work harder than the normal heart. Blood pressure involves two measurements- systole and diastole which depend upon whether the heart is contracting (systole) or relaxing (diastole) between the beats. The purpose of this review is to study about various causes, signs and symptoms and treatment approaches of hypertension. This article includes pharmaceutical and non-pharmaceutical approaches to treat hypertension. Awareness about the disease could be the major approach to the treatment of the disease.

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INTRODUCTION

When the blood pressure is increased chronically in the arteries, the condition is called high blood pressure or hypertension. The blood flow through the arteries to the rest of the body with every heart beat by the heart. Blood pressure is defined as the force of blood that is pushing up against the walls of the blood vessels. The normal value for blood pressure is below 120/80. The value 120 represents the peak pressure in the arteries which is also called systolic blood pressure whereas 80 represents the minimum pressure in the arteries also called diastolic blood pressure.

Blood pressure between 120/80 and 139/89 is called prehypertension (to denote increased risk of hypertension), and a blood pressure of 140/90 or above is considered hypertension [1].

Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Untreated hypertension is usually associated with a progressive rise in blood pressure. The vascular and renal damage that this may cause can culminate in a treatment-resistant state.

Blood pressure is normally distributed in the population and there is no natural cut-off point above which 'hypertension' definitively exists and below which it does not. The risk associated with increasing blood pressure is continuous, with each 2 mmHg rise in systolic blood pressure associated with a 7% increased risk of mortality from ischaemic heart disease and a 10% increased risk of mortality from stroke. Hypertension is remarkably common in the UK and the prevalence is strongly influenced by age. In any individual person, systolic and/or diastolic blood pressures may be elevated. Diastolic pressure is more commonly elevated in people younger than 50. With ageing, systolic hypertension becomes a more significant problem, as a result of progressive stiffening and loss of compliance of larger arteries. At least one quarter of adults (and more than half of those older than 60) have high blood pressure [2].

Over the next 50 years, considerable research efforts contributed to a more refined understanding of the benefits of autonomic renal nerve modification. The kidneys are richly innervated with post-ganglionic sympathetic efferent fibers that associate with efferent and afferent renal arterioles, the juxtaglomerular apparatus, and the renal tubular system. Acute increase in efferent sympathetic nerve activity from the brain to the kidney results in renal

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vasoconstriction, renin release, and sodium retention (Fig.1) [3].

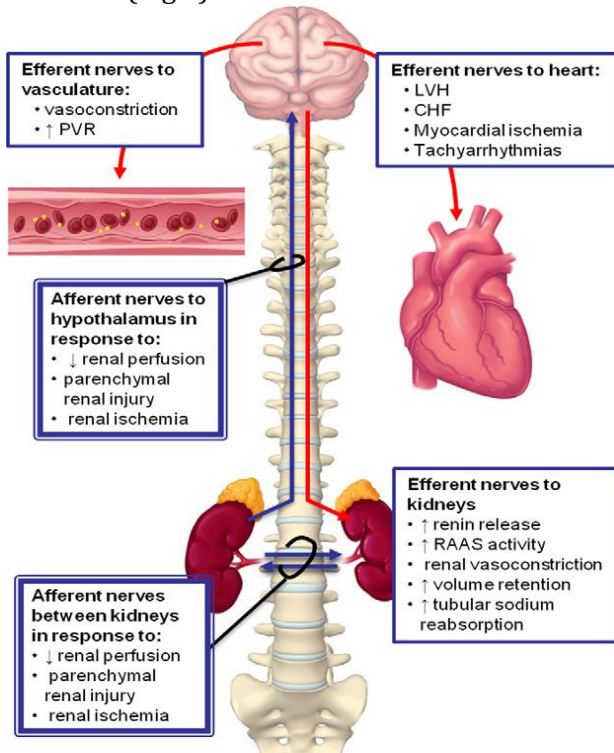


Figure 1: Pathways of Sympathetic Activity Leading to Hypertension↑= increased; ↓= decreased; CHF = chronic heart failure; LVH = left ventricular hypertrophy; PVR = peripheral vascular resistance; RAAS =renin-angiotensin-aldosterone system.

1.1 Classification

Hypertension

Primary (essential) hypertension Secondary hypertension

About 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause [4].The remaining 5–10% of cases (secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. The classification is based on the mean of two or more properly measured seated blood pressure readings on two or more office visits. Normal blood pressure is defined as levels <120/80 mmHg. Systolic blood pressure of 120–139 mmHg or diastolic blood pressure 80–89 mmHg is classified as pre hypertension. These patients are at increased risk for progression to hypertension. Hypertension is defined as systolic

blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Hypertension is divided into two stages:

- **Stage 1** includes patients with systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg.
- **Stage 2** includes patients with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg.

Isolated systolic hypertension is defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure <90 mmHg. Accelerated hypertension is characterized by markedly elevated blood pressure (diastolic blood pressure usually >120 mmHg) associated with retinal haemorrhage and exudates (grade 3 Kimmelstiel-Wilson retinopathy). If untreated, it commonly progresses to malignant hypertension, which is characterized by papilloedema (grade 4 Kimmelstiel-Wilson retinopathy). Both accelerated and malignant hypertensions are associated with widespread degenerative changes in the walls of resistance vessels including hypertensive encephalopathy, haematuria and renal dysfunction [5].

Table 1: Classification of blood pressure for adults aged ≥18 years

BP classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100

BP: blood pressure

Table 2: Classification of blood pressure for adults

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

BP: Blood Pressure

1.2 Signs and Symptoms

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. A proportion of people with high blood pressure report headaches (particularly at the 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 [6]. These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.

On physical examination, hypertension may be suspected on the basis of the presence of hypertensive retinopathy detected by examination of the optic fundus found in the back of the eye using ophthalmoscopy. Classically, the severity of the hypertensive retinopathy changes is graded from grade I-IV, although the milder types may be difficult to distinguish from each other [7].

- Tinnitus, lightheadedness, dizziness and/or vertigo
- Recurrent or worsening distended headache or head heaviness
- Chest oppression, palpitations
- Nose bleeding
- Shortness of breath
- Irritated, and getting anger easily
- Face or eye turns red
- Visual problems or variations
- Trembling, weakness or fatigue
- Disturbed sleep (Insomnia)
- Sore back and/or knees

If you are having higher blood pressure risk factors and having, two or more of high blood pressure symptoms, then get your blood pressure tested.

1.3 Cause of Hypertension

The exact causes of hypertension are usually unknown; there are several factors that have been highly associated with the condition (Figure 2). These include:

1. Smoking
2. Obesity or being overweight
3. Diabetes
4. Sedentary lifestyle
5. Lack of physical activity
6. High levels of salt intake (sodium sensitivity)
7. Insufficient calcium, potassium, and magnesium consumption
8. Vitamin D deficiency

9. High levels of alcohol consumption
10. Stress
11. Aging
12. Medicines such as birth control pills
13. Genetics and a family history of hypertension
14. Chronic kidney disease
15. Adrenal and thyroid problems or tumors^[1]

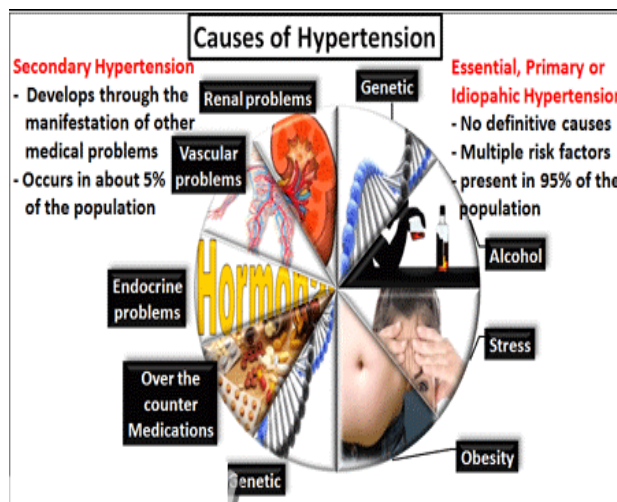


Figure 2: Figure showing causes of hypertension

2. Pathophysiology

Most of the mechanisms associated with secondary HTN are generally fully understood. However, those associated with essential (primary) HTN are far less understood. What is known is that cardiac output is raised early in the disease course, with normal total peripheral resistance (TPR). Overtime, cardiac output drops to normal levels, but TPR is increased. The following three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as atrial natriuretic factor being secreted to promote salt excretion with the side effect of raising TPR.
- An overactive renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to HTN [8].
- An overactive sympathetic nervous system, leading to increased stress responses [9].
- It is also known that HTN is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition (Fig. 3) [10].

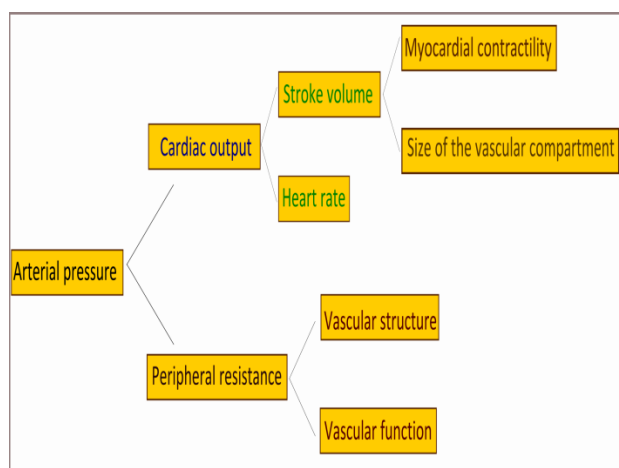


Figure 3: Pathophysiology of Hypertension

3. Role of Genes in Essential Hypertension

An estimated 30–60% of the variation in blood pressure between individuals, after adjustment for age and sex, is attributed to the effect of genetic factors. A child with a history of hypertension in both parents, and who has a sibling with hypertension, has a 40–60% chance of developing hypertension as an adult. If the sibling is a monozygotic twin, the risk of the same will increase to 80%. The genetic susceptibility to develop primary hypertension results from the effects of multiple genes and is modulated by multiple environmental determinants [11].

4. Treatment

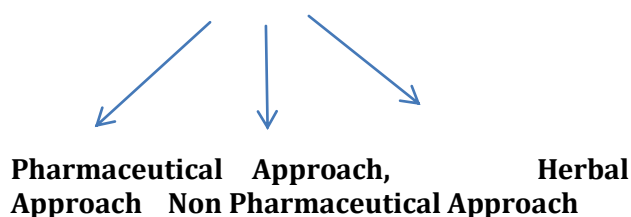
When to Initiate Treatment:

For patients with blood pressure readings goal:

- Systolic blood pressure 140–160 mm Hg or diastolic blood pressure 90–100 mm Hg: Consider a 6-month trial of lifestyle modification prior to initiating medications.
- Systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 100 mm Hg: Initiate medications.

Initiate medications.

Treatment approaches



4.1 Pharmaceutical approach

Overall, in hypertension, intervention trials that compared beta-blockers with non-slowing

antihypertensive drugs (thiazides, diuretics, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers and calcium channel blockers) (Table 3) failed to demonstrate the superiority of the former. Besides, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that the group given beta-blockers as first-line treatment had a worse cardiovascular outcome, even those patients with a high baseline HR. Moreover, in patients with hypertension, Bangalore et al. showed in a meta regression analysis that the lower the HR obtained with beta-blockers, the worse the prognosis (i.e. the higher the risks of cardiovascular events and death). The disappointing effects of beta-blockers in hypertension have been attributed to their unfavourable effects on lipid profile and insulin resistance. As far as the calcium antagonists are concerned, although they reduce HR to a lesser degree compared with beta blockers, they are free of the adverse metabolic effects, which are common to the latter. The recent French guidelines have gone a step further by removing beta-blockers as the cornerstone of resistant hypertension, with the result that, in principle, HR can no longer be lowered in most hypertensive subjects. Nevertheless, in hypertensive patients with a resting HR > 85 bpm, HR could be lowered with a programme of regular aerobic exercise. However, we know about the poor compliance of subjects with non-pharmacological measures (Fig. 4) [12].

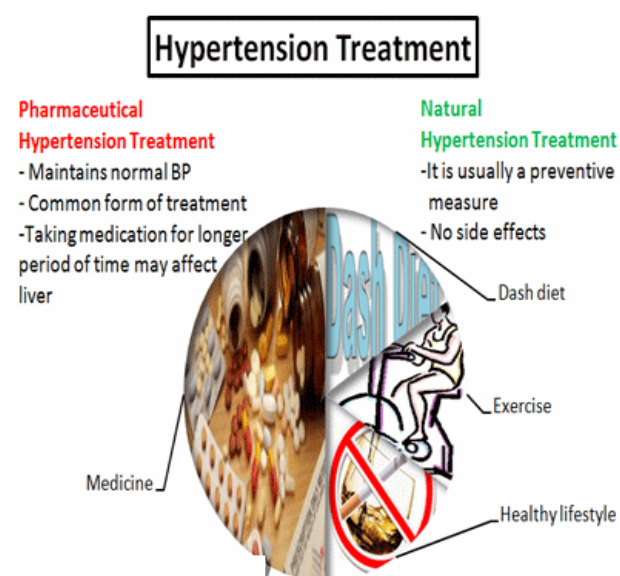


Figure 4: Different treatment approaches of Hypertension

Table 3: Conventional Anti-Hypertensive Drug Categories

Diuretics	decreasing blood volume
ACE inhibitors	reduce the production of angiotensin (a substance which causes arteries to constrict)
Beta-blockers	block the effects of epinephrine, resulting in vasodilation
Calcium-channel blockers	decrease the contractions of the heart and enhance vasodilation

4.1.1 Diuretics

Diuretics are now the most frequently prescribed antihypertensive drugs, following a period when their use declined in the early 1990s. This reflects recognition of their ability in lower doses to provide excellent protection against heart attacks, heart failure and stroke; a protection level equal to that seen with ACE inhibitors and CCBs.^[13] Diuretics induce natriuresis and reduce blood volume, and hence the cardiac output. Hormonal and intra renal counter-regulatory mechanisms, however, rapidly re-establish a steady state with sodium intake and excretion balanced within 3–9 days. With chronic use, plasma volume partially returns toward normal but at the same time peripheral vascular resistance decreases. The fall in peripheral vascular resistance may reflect the vasorelaxant effect seen in vitro ^[14].

4.1.2 Beta Blockers

For many years, β -adrenergic blockers were the second most popular antihypertensive drugs after diuretics. In view of their proven ability to provide secondary cardio protection after acute myocardial infarction, it was hoped that they would provide primary protection against initial coronary events as well. This hope, however, remains unfulfilled ^[15]. When compared with a diuretic in middle-aged patients, no significant difference between the two drugs in protecting against coronary mortality was noted in two large trials. Nevertheless, the benefits of β -adrenergic blockers in patients with either coronary artery disease or heart failure ensure that these drugs will continue to be widely used. β -Blockers decrease the cardiac output acutely by 15%–20% and this remains lowered chronically. On the other hand, the peripheral resistance usually rises acutely but falls toward (if not to) normal with time. Renin level falls promptly due to reduction in the processing of prorenin and active renin. β -Blockers have been proposed as initial monotherapy for most

hypertensives particularly those with coexisting coronary artery disease, heart failure, migraine, tremor and stress-induced arrhythmias ^[16].

4.1.3 Calcium channel blockers

Three types of CCB are dihydropyridines, phenylalkylamines and benzothiazepines. Only the voltage sensitive L- type channels are blocked by the CCBs. The three groups of CCBs bind to their own specific binding sites on the α_1 subunit; all restricting Ca^{2+} entry, though characteristics of channel blockade differ. Furthermore, different drugs may have differing affinities for various site specific iso forms of the L-channels. This may account for the differences in action exhibited by various CCBs ^[17]. They also restore nitric oxide availability, most probably by an antioxidant effect on endothelial cells. Additionally they relatively inhibit aldosterone production resulting in natriuresis. The increased excretion of sodium and water also probably reflects the unique ability of CCBs to maintain or increase effective renal blood flow and GFR, which has been attributed to their selective vasodilative action on renal afferent arterioles. Therefore, CCBs should only be added to ACE inhibitors if needed to control hypertension in patients with renal insufficiency ^[18]. The currently available preparations seem comparable in their antihypertensive effect, but the short-acting dihydropyridines have been noted to increase the frequency of angina and mortality after acute myocardial infarction. They have also been shown to increase coronary events when used to treat hypertension, due to the induced abrupt fall in blood pressure and consequent sympathetic activation. Long-acting CCBs do not share these dangers. The slow onset and long duration of action of amlodipine provide continued effect even if daily doses are missed. Because calcium entry is involved in so many cellular functions, concerns have been voiced about other potential adverse effects of CCBs. However, calcium metabolism seems to be little altered by these agents and initial reports of increased risks of cancer, bleeding and suicide have not been supported by subsequent data ^[19].

4.1.4 Angiotensin-converting enzyme inhibitors

Three different classes of ACE inhibitors have been developed. They are classified by the ligand of the zinc ion of ACE: sulfhydryl, phosphoryl and carboxyl. The most obvious manner by which ACE inhibitors lower the blood pressure is by reducing the circulating level of angiotensin II, thereby removing the direct vasoconstriction

induced by this peptide. At the same time, the activity of ACE within vessel walls and multiple tissues, including brain and heart, is inhibited to apparently variable degrees by different ACE inhibitors. However the role of tissue renin-angiotensin system remains uncertain. Some of the effects of ACE inhibitors may be mediated via inhibition of the breakdown of bradykinin, with an additional contribution from kinin stimulation of nitric oxide production. ACE inhibitors also blunt the expected increase in sympathetic activity seen after vasodilation. As a result, heart rate and cardiac output do not increase. Additionally, ACE inhibitors improve endothelial dysfunction and suppress endogenous endothelin secretion. As a consequence of these multiple effects, ACE inhibition results in a damping of arterial wave reflection and increased aortic distensibility [20].

Regardless of how ACE inhibitors lower the blood pressure, they do so in a manner that tends to protect the function of two organs: the heart and the kidneys. Renal protection may not be provided, however, for patients with the DD-ACE genotype that is associated with higher plasma ACE levels [21].

4.1.5 Angiotensin II receptor blockers

ARBs displace angiotensin II from its specific AT1 receptor, antagonizing all its effects and resulting in a fall in peripheral vascular resistance with little change in heart rate and cardiac output. No obvious good or bad effects of increased levels of angiotensin II have been noted [22]. ARBs are remarkably free of side effects. Because they do not increase kinin levels, the ACE inhibitor related cough is not countered. Angioedema, urticaria and taste disturbance are also rare [17].

4.2 Herbal approach

4.2.1 Ephedra or Ma Huang

This is one of the most commonly taken supplements and is called by a variety of names including ma huang, ephedra extract, ephedra sinica, ephedra equisetina, ephedra intermedia, ephedra geradiana, ephedra herb powder, ephedron, or ephedrine. All these names indicate the presence of ephedrine. Ephedra is sold as treatment for asthma, cold and flu symptoms, and weight loss. Combinations of other herbals and ephedra are also sold. For example, herbal phen-fen is marketed as a weight loss supplement and contains St. John's wort along with ma huang. It is very common for caffeine to

also be present in these supplements along with ephedra. Ephedrine stimulates adrenergic receptors and can increase heart rate and peripheral vascular resistance. It can also act on the central nervous system giving the individual a feeling of tremendous well-being [23].

4.2.2 Garlic (*Allium sativum*)

Garlic is commonly used among hypertensive patients because of its reputed benefit in reducing cardiovascular disease and lowering BP. Other claims for the benefits of garlic have included cancer prevention and anti-inflammation. Studies have suggested a multitude of physiologic effects including inhibition of platelet activity and increased levels of antioxidant enzymes. There are probably several active ingredients in garlic preparations. In the treatment of high BP, 27 small randomized placebo controlled trials of short duration were reviewed. Various doses of garlic were used providing about 3 to 6 mg of allicin per day. The majority of these studies found that garlic did not reduce BP compared to placebo, but the studies were small (Fig. 5) [23].



Figure 5: Garlic (*Allium sativum*)

4.2.3 Hibiscus sabdariffa

Hibiscus sabdariffa is one potential non pharmacological treatment. In folk medicine, the calyces' infusion is used for the treatment of several conditions including high BP. Anthocyanin's and proanthocyanidins compounds, detected in abundance in the aqueous infusion of the Hibiscus calyces, could be the bioactive compounds responsible for lowering the blood pressure based on earlier studies which proved the antihypertensive effects of anthocyanin's through the inhibition of angiotensin II converting enzyme and hence a vasodilatation effect in addition to its diuretic effect and the increased concentration of urinary sodium while maintaining normal potassium levels [24].

4.2.4 Ginkgo (Ginkgo biloba)

Ginkgo biloba, also known as Maidenhair Tree, is the oldest living tree species, dating back approximately 200 million years. Ginkgo seeds and leaves have been used in traditional Chinese medicine for over 5,000 years. In modern botanical medicine, extracts are made from the distinctive, fan-shaped leaves. These extracts contain approximately 24-percent flavone glycosides (primarily composed of quercetin, kaempferol, and isorhamnetin) and 6-percent terpene lactones (2.8- 3.4% ginkgolides A, B, and C, and 2.6-3.2% bilobalide). Other constituents include proanthocyanadins, glucose, rhamnose, organic acids (hydroxykinurenic, kynurenic, protocatechic, vanillic, shikimic), D -glucaric acid and ginkgolic acid and related alkylphenols. It is also used to treat hypertension (Fig. 6) [25].



Figure 6: Ginkgo biloba

4.3 Non Pharmaceutical approaches

4.3.1 Lifestyle modifications

Adoption of healthy lifestyles by all individuals is critical in the prevention of high blood pressure and an indispensable part of the management of those with hypertension. Lifestyle modifications decrease blood pressure; enhance antihypertensive drug efficacy and decrease cardiovascular risk. A diet low in saturated fat and high in complex carbohydrate is recommended. Such a diet includes whole grains, fruits, vegetables, nuts, seeds, legumes, fish, soya products, onions, garlic, foods rich in potassium, calcium, and magnesium (carrots, spinach, celery, alfalfa, mushrooms, lima beans, potatoes, avocados, broccoli, and most fruits), and restricts salt [26].

4.3.2 Cessation of smoking

Quitting smoking, a primary risk factor for cardiac disease, has immediate as well as long-

term benefits for patients with hypertension and the people with whom they live [27]. Smoking cessation markedly reduces overall cardiovascular risk, including the risk of coronary heart disease and stroke, compared with continued smoking. Although smoking is known to increase the risk of developing hypertension, there is currently no evidence that smoking cessation directly reduces blood pressure in people with hypertension [28].

4.3.3 Weight reduction and physical exercise

Weight reduction reduces blood pressure in overweight patients and has beneficial effects on associated risk factors such as insulin resistance, diabetes, hyperlipidaemia and LVH. Attainment of ideal body weight is by no means necessary to produce lower blood pressure. Blood pressure is lowered by 1.6/1.1 mmHg for every kilogram of weight loss. Many hypertensive patients have much more than 10 kg of excess adiposity and many of them would no longer be hypertensive if they lost even this amount of body fat. The blood pressure lowering effect of weight reduction may be enhanced by a simultaneous increase in physical exercise. Thus, sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis such as brisk walking for at least 30 minutes per day, most days of the week. However, isometric exercise such as heavyweight-lifting can have pressor effect and should be avoided. When hypertension is poorly controlled, and always for severe hypertension, heavy physical exercise should be discouraged or postponed until appropriate drug treatment has been instituted and found to be effective [29, 30].

4.3.4 Reduction of salt intake and other dietary changes

There is compelling evidence that dietary salt intake is the major cause of raised BP. The salt intake in most countries is between 9 and 12 g/day. When assessed in Latin America and the Caribbean after 2000, salt intake exceeds 9 g/day. This level of salt intake is about 40 times higher than the amount human ancestors ate during several million years of evolution. Such a large increase in salt intake is relatively recent in evolutionary terms. Excreting these large amounts of salt through the kidneys presents a major challenge to physiological systems. The consequence is a gradual rise in BP and an increase in the risk of CVD and renal disease [31]. On average, as dietary salt (sodium chloride) intake rises, so does BP. Evidence includes

results from animal studies, epidemiological studies, clinical trials, and meta-analyses of trials. To date, >50 randomized trials have been conducted. In one of the most recent meta-analyses [32] a median reduction in urinary sodium of ≈ 1.8 g/d (78 m mol /d) lowered systolic BP and diastolic BP by 2.0 and 1.0 mm Hg in non-hypertensive and by 5.0 and 2.7 mm Hg in hypertensive individuals. Patients should be advised to avoid added salt, to avoid obviously salted food (particularly processed foods) and to eat more meals cooked directly from natural ingredients containing more potassium. DASH (Dietary Approach to Stop Hypertension) diet, emphasized fruits, vegetables, and low-fat dairy products; included whole grains, poultry, fish and nuts; and was reduced in fats, red meat, sweets, and sugar-containing beverages. Accordingly, it was rich in potassium, magnesium, calcium, and fiber and was reduced in total fat, saturated fat, and cholesterol; it also was slightly increased in protein [33].

4.3.5 Cessation of alcohol consumption

In alcoholics, hypertension is common but settles after withdrawal from alcohol. This raises the possibility that alcohol may only exert a short-term effect on blood pressure [34]. Heavy drinkers may also experience a rise of blood pressure after acute alcohol withdrawal. Hypertensive patients who drink alcohol should be advised to stop drinking. If they insist on continuing to drink they should be advised, in any case, not to consume more than 30 ml of ethanol (the equivalent of two drinks per day) in men and no more than 15 ml of ethanol (one drink per day) in women and lighter-weight persons [5].

4.3.6 Acupuncture

Acupuncture is a Chinese method of treatment whose roots extend back 2,500 years or more. Acupuncture releases chemicals such as endorphins and enkephalins that can inhibit pain and generate a feeling of relaxation. Practitioners trained in Oriental medicine believe that a vital energy called "chi" circulates in the body through 12 main pathways called meridians. Each meridian is named after a particular organ or "official," but the term actually relates to the energetic function more than the structure or anatomy of the organ. There are both surface and internal projections for each meridian. The surface projections contain sites called acupuncture points. Oriental medicine practitioners insert needles into these points to influence the body's chi to restore health.

Published reports have indicated that acupuncture has a beneficial effect on blood pressure in studies of laboratory animals and humans [35].

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