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"Systemic Arterial Hypertension"

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Abstract-
Systemic arterial hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide and is associated with increased risk of cardiovascular disease (CVD). Fewer than half of those with hypertension are aware of their condition, and many others are aware but not treated or inadequately treated, although successful treatment of hypertension reduces the global burden of disease and mortality. The aetiology of hypertension involves the complex interplay of environmental and pathophysiological factors that affect multiple systems, as well as genetic predisposition. Evaluation of patients with hypertension includes accurate standardized blood pressure (BP) measurement, assessing patients' predicted risk of atherosclerotic CVD, evidence of target organ damage, detection of secondary causes of hypertension and presence of comorbidities, including CVD and kidney disease. Lifestyle changes, including dietary modifications and increased physical activity, are effective in lowering BP and preventing hypertension and its CVD sequelae. Pharmacological therapy is very effective in lowering BP and preventing CVD outcomes in most patients; first line antihypertensive medications include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, dihydropyridine calcium channel blockers and thiazide diuretics.

Keywords- Systemic arterial hypertension, diagnosis, disease prevention, management

INTRODUCTION-

Systemic arterial hypertension (hereafter referred to as hypertension) is characterized by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) and the diastolic BP (the pressure when the heart relaxes). The BP thresholds that define hypertension depend on the measurement method (Table 1). Several aetiologies can underlie hypertension. The majority (90–95%) of patients have a highly heterogeneous 'essential' or primary hypertension with a multifactorial gene-environment aetiology. A positive family history is a frequent occurrence in patients with hypertension, with the heritability (a measure of how much of the variation in a trait is due to variation in genetic factors) estimated between 35% and 50% in the majority of studies[1,2]. Genome-wide association studies (GWAS) have identified ~120 loci that are associated with BP regulation and together explain 3.5% of the trait variance[3,4,5]. These findings are becoming increasingly important as we search for new pathways and new biomarkers to develop more-modern 'omics'-driven diagnostic and therapeutic modalities for hypertension in the era of precision medicine[6].

Table 1 -. Definitions of hypertension based on the 2013 ESH/ESC guidelines

Category	Subtype	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office BP	NA	≥ 140	≥ 90
Ambulatory BP	Daytime (awake)	≥ 135	≥ 85
	Night time (asleep)	≥ 120	≥ 70
	24hr	≥ 130	≥ 80
Home BP	NA	≥ 135	≥ 85

For the diagnosis of hypertension, systolic BP, diastolic BP or both have to exceed the reported values.Several rare, monogenic forms of hypertension have been described (for example, the Liddle syndrome, glucocorticoid-remediable aldosteronism (a mineralocorticoid excess state) and mutations in *PDE3A* (which encodes cGMP-inhibited 3',5'-cyclic phosphodiesterase A)), in which a single gene mutation fully explains the pathogenesis of hypertension and indicates the best treatment modality[7,8,9]. If hypertension is caused by another condition (for example, primary aldosteronism, pheochromocytoma (a neuroendocrine tumour of the adrenal glands or other neuroendocrine tissues) or renal artery stenosis), it is referred to as secondary hypertension.Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), chronic kidney disease (CKD) and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide[10]. The

relationship between BP and the increased risk of CVD is graded and continuous, starting as low as 115/75 mmHg, well within what is considered to be the normotensive range. Successful prevention and treatment of hypertension are key in reducing disease burden and promoting longevity in the world's population. In treating hypertension, it is important to consider a person's predicted atherosclerotic CVD (ASCVD) risk more than the level of BP alone, as persons with high CVD risk derive the greatest benefit from BP lowering treatment[11].

This Primer will discuss the epidemiology and pathophysiology of primary hypertension, prevention strategies for slowing the progression of BP elevation, management strategies (including optimal BP targets) for lowering BP and preventing CVD outcomes in patients with established hypertension and the effects of antihypertensive treatment on quality of life; finally, we will explore knowledge gaps, future trends and the outlook for hypertension research and treatment over the next decade.

EPIDEMIOLOGY

In pre-industrial societies, BP levels had narrow distributions with mean values that changed little with age and averaged around 115/75 mmHg[12], a value that probably represents the normal (or ideal) BP for humans. However, in most contemporary societies, systolic BP levels rise steadily and continuously with age in both men and women. This ubiquitous finding could be explained because age is a proxy for the probability and duration of exposure to the numerous environmental factors that increase BP gradually over time, such as excessive sodium consumption, insufficient intake of dietary potassium, overweight and obesity, alcohol intake and physical inactivity. Other factors, such as genetic predisposition or adverse intrauterine environment (such as gestational hypertension or pre-eclampsia), have small but definite associations with high BP levels in adulthood[13]. Even modest rises in mean population BP lead to large increases in the absolute number of people with hypertension[14].As economic development progresses, hypertension initially affects those with a high socioeconomic status, but at later stages of economic development, the prevalence of hypertension and its consequences are greatest in those with lower socioeconomic status; this phenomenon is seen both within and between countries. Further, the speed of change prevalence of hypertension since 2000 to 2010 has been much more rapid than in previous epidemiological transitions[15].

Disease burden

Globally, 3.5 billion adults now have non-optimal systolic BP levels (that is, >110–115 mmHg) and 874 million adults have systolic BP ≥140 mmHg. Thus, approximately one in four adults has hypertension[16]. Between 1990 and 2015 there was a 43% increase in the total global number of healthy life years lost to non-optimal BP, driven by population increase, population aging and a 10% increase in the age-standardized prevalence of hypertension[16]. The Global Burden of Disease study has shown that non-optimal BP continues to be the biggest single risk factor contributing to the global burden of disease and to global all-cause mortality, leading to 9.4 million deaths and 212 million lost healthy life years (8.5% of the global total) each year[10].

CVD risk

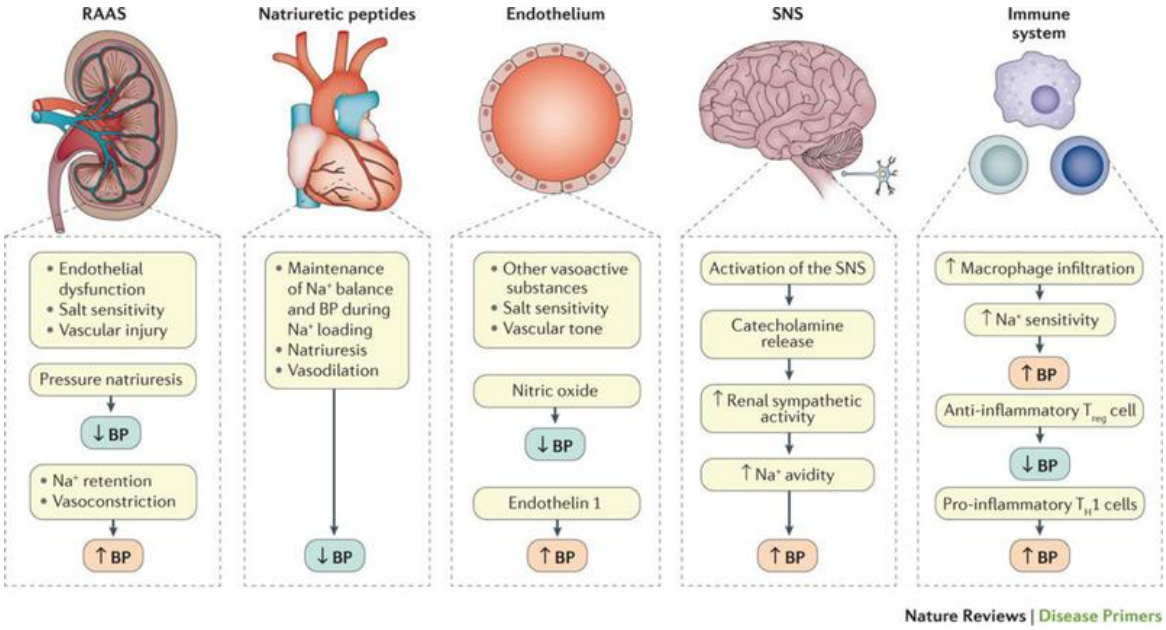
Prospective observational studies have repeatedly demonstrated a strong, continuous positive relationship between BP and CVD, with no evidence of a threshold for risk throughout the usual range of BP observed in clinical practice[17,18,19]. The relationship between BP and CVD applies to both systolic BP and diastolic BP, but is somewhat more robust for systolic BP in adults[19]. It is noted in both sexes, at all ages throughout adulthood and for all major manifestations of CVD, including stroke (ischaemic and haemorrhagic), coronary artery disease, heart failure, peripheral vascular disease and end stage renal disease (although there are variations in the strength of the associations and the slopes of the curves)[17,18,19,20] (Figure 1). The relationship is independent of other CVD risk factors, and level of BP has proven to be a major component of CVD risk in all prediction models[21]. Approximately two-thirds of all adults who have hypertension or receive treatment with BP lowering medication at 30 years of age have a ~40 % higher risk of experiencing a CVD event than their age-matched and sex-matched counterparts with a lower level of BP[18]. In addition, CVD events in individuals with hypertension tend to manifest about five years earlier than in individuals with a lower level of BP[18].

MECHANISMS/PATHOPHYSIOLOGY

BP regulation

BP is determined by several parameters of the cardiovascular system, including blood volume and cardiac output (the amount of blood pumped by the heart per minute) as well as the balance of arterial tone that is affected by both intravascular volume and neurohumoral systems (discussed in the following sections). The maintenance of physiological BP levels involves a complex interplay of various elements of an integrated neurohumoral system that includes the renin-angiotensin-aldosterone system (RAAS), the role of natriuretic peptides and the endothelium, the sympathetic nervous system (SNS) and the immune system (Figure 2). Malfunction or disruption of factors involved in BP control in any of these systems can directly or indirectly lead to increases in mean BP, BP variability or both, over time resulting in target organ damage (for example, left ventricular hypertrophy and CKD) and CVD outcomes[22].

Figure 2. The main neuroendocrine systems involved in the regulation of blood pressure.

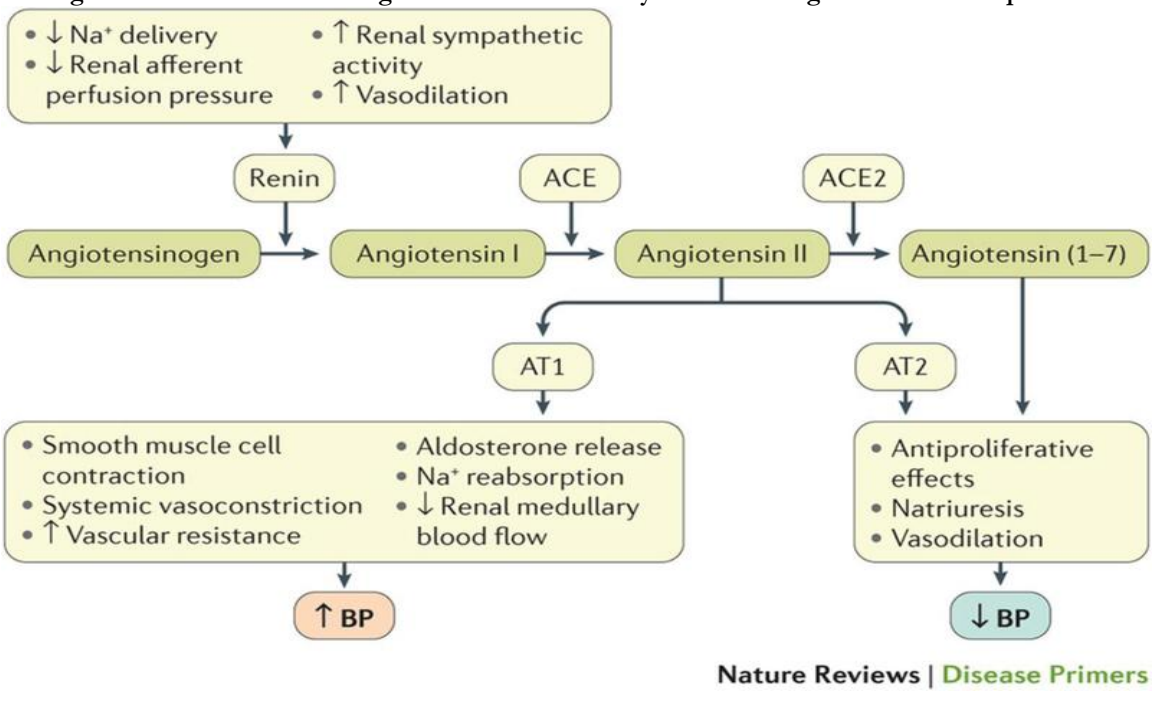


Neurohumoral, immune and organ systems involved in the maintenance of blood pressure. BP: Blood pressure, RAAS: renin-angiotensin-aldosterone system.

The pathophysiological mechanisms responsible for hypertension are complex and act on a genetic background. Primary hypertension involves multiple types of genes; some allelic variants of several genes are associated with an increased risk of developing primary hypertension and are linked in almost all cases to a positive family history (Box 1) This genetic predisposition, along with a host of environmental factors, such as high Na^+ intake, poor sleep quality or sleep apnoea, excess alcohol intake and high mental stress, contribute to the development of hypertension[22,23,24]. Finally, the probability of developing hypertension increases with aging, owing to progressive stiffening of the arterial vasculature caused by, among other factors, slowly developing changes in vascular collagen and increases in atherosclerosis[25,26,27]. Immunological factors can also play a major part, especially on the background of infectious or rheumatological diseases such as rheumatoid arthritis. The mosaic theory of hypertension describes its multifaceted pathophysiology[28,29].

Gene deletion studies in rodent models have evaluated cardiac ANP and BNP as paracrine regulators of vascular regeneration. Deletion of the genes encoding ANP and BNP exaggerates cardiac fibrosis and increase adverse left ventricular (LV) remodelling[38], and natriuretic peptide receptor A (NPRA) deficiency leads to increased BP, severe fibrosis and LV dysfunction. Further, deletion of the gene encoding the endothelial guanylyl cyclase-A (GC-A) receptor, a cell surface receptor for natriuretic peptides, leads to diminished vascular regeneration and angiogenesis in response to critical hind limb ischemia, as well as cardiac fibrosis and diastolic dysfunction.

Figure 3. Role of the renin-angiotensin-aldosterone system in the regulation of blood pressure.



DIAGNOSIS, SCREENING AND PREVENTION

Diagnosis and screening

Essential or primary hypertension is usually asymptomatic; thus, in clinical practice all adults should have their BP measured at regular office visits. Hypertension is most commonly diagnosed based on repeated BP measurements in a clinical office setting. Accurate measurement and recording of BP is essential to categorize the level of BP, ascertain BP-related CVD risk and guide management. Since 2010, methods to measure out-of-office BP have been increasingly introduced to guide diagnosis and treatment of hypertension. Table 1 These include home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM). HBPM refers to the measurement of BP at regular intervals by an individual at their home or elsewhere outside the clinic setting. ABPM consists of measuring and recording the BP at regular intervals (usually every 20–30 minutes), typically for the 24-hour period and while individuals go about their daily activities. The ability to measure out-of-office BP has enabled the identification of distinct BP phenotypes, including white coat or isolated clinic hypertension and masked or isolated ambulatory hypertension. White coat hypertension is characterised by elevated office BP but normal ABPM or HBPM readings. By contrast, masked hypertension is characterised by normal office readings but elevated out –of-office readings (ABPM and HBPM)

Diagnosis

The evaluation of a patient with hypertension requires more than the diagnosis of elevated BP. It should also include assessment of the CVD risk, target organ damage, and concomitant clinical conditions that may affect the BP or related target organ damage as well as recognition of features suggestive of secondary hypertension. Some of these investigations are routine tests necessary in all patients, but others only in specific patient groups identified by history, clinical examination, and routine tests. In rare inherited forms of hypertension, a single gene mutation explains the pathogenesis of hypertension[7,8,9]. (Figure 4) A small proportion of patients have a potentially reversible cause of hypertension, and a correct diagnosis might lead to a cure or a substantial improvement in BP control with a reduction of CVD risk. It is therefore appropriate to implement a simple screening for secondary hypertension in all patients. The screening is based on clinical history, physical examination and routine laboratory investigations . Secondary hypertension should also be considered in cases of a sudden worsening of hypertension, poor BP response to drug treatment or severe target organ damage, which is out of proportion to the duration and severity of hypertension. In these cases, specific diagnostic tests are indicated .

Prevention

The association between BP and risk of CVD highlights the importance of treating hypertension, especially when severe. Further, it also underscores the importance of strategies to reduce BP-related CVD risk in those who have a higher than normal level of BP (average systolic BP 120–129 mmHg) but below the hypertension threshold. Reducing BP in adults with a high normal BP (referred to as elevated BP in the 2017 US guidelines) provides the potential to directly reduce CVD risk and to prevent or at least slow the age-related tendency for individuals to develop hypertension.

In most countries there is a strong tendency for BP, especially systolic BP, and the prevalence of hypertension to increase progressively from childhood until late in life. However, studies in isolated societies that have limited contact with the outside world indicate that high BP is not an inevitable consequence of aging and that the rise in BP associated with local migration by members of isolated societies is related to changes in diet, decreased physical activity and consumption of alcohol. These reports underscore the logic of efforts to prevent high BP in settings where an age-related increase in BP is common.

Lifestyle changes-

A variety of nonpharmacological interventions have been shown to be effective in lowering BP and preventing hypertension. The most effective interventions are weight loss , reduced Na^+ intake , increased potassium intake , increased physical activity , reduced consumption of alcohol and diets like the Dietary Approaches to Stop Hypertension (DASH) diet that combine several elements which favorably affect BP. The DASH diet is especially successful when combined with other effective BP lowering interventions such as a reduced intake of dietary sodium. Lifestyle change is the best way for the individual to implement these interventions. Even small improvements in an individual's lifestyle can be valuable. Government agency and professional society websites provide helpful tips for lifestyle change and monitoring of BP. Careful monitoring of BP is essential because the beneficial effects of lifestyle change are predicated on maintenance of the intervention.

Dietary Approaches to Stop Hypertension (DASH) eating plan

Food group	Servings*	Examples of a serving
Whole grains	6–8 per day	1 slice whole grain bread
Vegetables	4–5 per day	1 cup of raw leafy vegetables
Fruits	4–5 per day	1 medium sized fruit
Dairy products (low-fat or fat-free)	2–3 per day	1 cup of milk or yogurt
Fats and oils	2–3 per day	1 teaspoon of margarine or vegetable oil or 1 tablespoon of mayonnaise or 2 tablespoons of salad dressing
Lean meat, poultry, fish	2–3 per day	2 ounces of cooked meats, chicken or fish
Nuts, seeds and legumes	4–5 per week	1/3 cup (1.5 ounces) of nuts or 2 tablespoons of peanut butter or 2 tablespoons (0.5 ounce) of seeds or ½ cup of cooked peas or beans
Candy and added sugars	5 or less per week	1 tablespoon of sugar, jelly or jam or 1 cup of lemonade

*Recommended frequency of servings for a 2,000 calorie per day diet.

Two complementary strategies aimed at achieving a small population-wide reduction in BP or a larger reduction in those who are at higher risk to develop hypertension can be employed to implement hypertension prevention interventions. Modelling studies suggest that a downward shift of as little as 2 mmHg in the population distribution of diastolic BP would result in a 17% reduction in the incidence of hypertension, a 14% reduction in the risk of stroke and transient ischemic attacks, and a 6% reduction in the risk of coronary heart disease. Public health interventions focused on dietary improvements and increases in physical activity that are known to lower BP provide the basis for the population-wide strategy. Diet in the general population can be favourably influenced by means of public health education campaigns, food product labelling, and collaborations with food manufacturers to reduce the calorie and sodium content of their products, as well as with fast food companies and restaurants to reduce portion size and to promote healthier food preparation and promotion practices. Physical activity can be enhanced by making it easier for members of the community to engage in exercise on a routine basis.

MANAGEMENT

BP treatment thresholds and targets

Until 2015, most guidelines recommended a target BP < 140/90 mmHg for most patients and < 150/90 mmHg for elderly patients over 60 or 80 years of age. However, after the publication of the Systolic blood Pressure Intervention Trial (SPRINT), target systolic BP values have been frequently debated. SPRINT was a randomized, open-label controlled trial that enrolled 9361 participants without diabetes mellitus but with increased CVD risk. Patients with a history of stroke were excluded. Participants were randomized to a standard systolic BP target < 140 mmHg or intensive systolic BP target < 120 mmHg. Intensive BP treatment in SPRINT resulted in a significantly greater (25%) reduction in the primary endpoint (first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure or death from cardiovascular causes), compared with standard treatment. Office BP measurement in SPRINT was performed with an automated device timed to start measurement after 5 minutes of rest in an effort to standardize measurements in the various clinics and minimize the white coat effect. Because large differences had been observed between automated office BP measurement and conventional auscultatory measurements (with the automated technique showing lower values), some groups have questioned the applicability of the SPRINT intensive systolic BP target of < 120 mmHg to ordinary office practice· Both the appropriate method(s) of measuring office BP (automated versus manual; unattended versus attended) and the appropriate BP targets for antihypertensive treatment are currently topics of vigorous debate. In summary, newer guidelines published after the SPRINT trial generally have more aggressive goals, at least for individuals < 65 years of age

Non-Pharmacological Management

Lifestyle advice is recommended for all patients with hypertension. The most effective interventions are the same as for prevention of hypertension. Targeted dietary approaches can reduce the systolic BP in individuals with hypertension. For example, reducing sodium intake (ideally to <2.3 g per day, or <1.5 g per day in those most susceptible to the effects of sodium on BP, but reduction by at least 1.0 g per day is desirable) can lower the systolic BP by 2–4 mmHg . A similar reduction can be expected with increases in potassium intake to 3.5– 5.0 g per day.

Reduced salt intake

For metabolic balance, the amount of salt consumed must be equal to that lost. Thus, under normal living conditions and physical activity levels, an intake of 5 g salt/day is considered sufficient, in line with the WHO recommendation (< 5 g per day). By contrast, the currently estimated dietary intake of salt is about 9–12 g per day in most countries. The current recommendations of the American Heart Association and American Society of Hypertension are stricter than the European guidelines, recommending lowering salt intake to 3.8 g per day, whereas the 2013 ESH/ESC guidelines recommend 5–6 g of salt per day

Randomized controlled trials carried out in persons with hypertension have consistently shown that reduced sodium intake is associated with reduction of BP. The most convincing evidence is provided by the Dietary Approaches to Stop Hypertension (DASH-sodium) trial, in which the effects of three different sodium intakes were tested separately in combination with two diets: the DASH diet, rich in fruit, vegetables, low-fat dairy products and reduced in saturated fat and cholesterol, and a control diet consisting of what many people in the United States typically eat. Reduction of sodium intake by ~0.9 g per day induced a greater BP reduction when the starting sodium intake was <2.3 g per day, which corresponds to about 6 g of salt per day; thus it is slightly more than the currently recommended < 1,500 mg/day of sodium by the 2017 US hypertension guidelines. Of note, sodium reduction reduced BP in non-hypertensive individuals on both diets. Reduced sodium intake can also prevent hypertension (relative risk reduction of about 20% with or without concomitant weight loss), improve hypertension control and thus, possibly, reduce need for antihypertensive medication. In the Intersalt study, lower sodium intake was associated with a blunted age-related rise in systolic BP.

There is strong evidence to support population-wide recommendations to lower salt intake. As more than 75% of dietary salt comes from processed foods (in western countries), any population strategy to reduce salt intake must involve food manufacturers and restaurants, in order to progressively reduce salt added to foods. So far, only three countries (Japan, Finland and the United Kingdom) have successfully reduced population salt intake.

Increased potassium intake

Healthy individuals with normal kidney function usually have a potassium intake of 4.7 g/day; a higher intake is not associated with increased risk because potassium is readily excreted in persons who do not have CKD. Increased potassium intake is associated with reduced BP in individuals with low as well as high baseline potassium intake. Of note, potassium reduces BP

to a greater extent in blacks than in whites. The effect of potassium on BP is dependent on salt intake. There is a greater BP reduction with increased potassium intake in the context of lower salt intake Thus, the best strategy is to increase potassium intake and reduce sodium intake at the same time. The preferred strategy to increase potassium intake is to increase consumption of fruits and vegetables that are rich in potassium rather than using supplements[115]. In individuals with impaired urinary potassium excretion, a potassium intake <4.7 g per day is recommended.
Moderate alcohol consumption
Keeping alcohol intake ≤2 standard drinks (~3.5 alcohol units) per day for men and ≤1 standard drink (~1.75 alcohol units) per day for women can also contribute to a 2–4 mmHg BP reduction.

Physical activity
Regular physical activity reduces BP in individuals with hypertension. Endurance training reduces BP more in persons with hypertension than in individuals with normal BP. A narrative review of 27 randomized clinical trials in individuals with hypertension showed that regular medium-intensity to high-intensity aerobic activity reduced BP by a mean of 11/5 mmHg. Sessions lasting 40–60 minutes performed at least three times a week had the greatest effect on BP. Three randomized controlled trials of isometric exercise (strength training) showed a BP reduction of similar magnitude to that induced by aerobic exercise in individuals with hypertension. A meta-analysis of 64 controlled studies of the efficacy of dynamic resistance training as stand-alone antihypertensive therapy showed BP reductions comparable with or greater than those with aerobic exercise training. Greater BP reductions occurred in individuals with higher resting BP (approx. 6/5 mmHg for individuals with hypertension and 3/3 mmHg for individuals with pre-hypertension) and in non-white individuals.

Weight Loss
Excess adiposity generally raises BP in susceptible individuals, and patients with hypertension who also have obesity require more antihypertensive medications to control their BP and are more likely to be treatment resistant. In a recent meta-analysis, any reduction in body weight lowered systolic BP by on average 2.69 mmHg and in diastolic BP by on average 1.34 mmHg . However, the response varies substantially between individuals. Lifestyle interventions, including hypocaloric diets and physical exercise, are commonly recommended for patients with obesity and hypertension, yet average weight loss is modest and most patients regain weight.

4. Hypertension and obesity.
Weight loss is recommended for individuals with obesity, and may be particularly important if these patients also have hypertension. Medications have been developed for the treatment of obesity, but their approval status differs between the United States and Europe: some drugs are only approved in the United States (for example, lorcaserin and topiramate/phentermine), whereas others are approved in Europe only. BP reductions in patients with hypertension have been reported for some weight loss medications, but their specific pharmacological actions may attenuate the positive influences of weight loss on BP and CVD outcomes. Bariatric surgery is very effective in reducing body weight, and the risk for arterial hypertension is substantially reduced up to five years following bariatric surgery. However, large and sustained body weight reductions are needed to substantially reduce BP following bariatric surgery and there are no large clinical trials specifically testing the effects of weight loss medications or bariatric surgery on hypertension control.
Antihypertensive Pharmacotherapy
Antihypertensive pharmacotherapy has evolved over several decades driven by development of various antihypertensive medication classes and large-scale outcomes trials proving their benefits on CVD morbidity and mortality. Clinicians are now faced with a plethora of antihypertensive medications of different drug classes and a variety of fixed dose combinations. Typically, antihypertensive pharmacotherapy begins with first-line antihypertensive medications either in monotherapy or in combination. Combination therapy may be preferable in patients with higher levels of pretreatment BP. First-line antihypertensive medications include ACE inhibitors, angiotensin II receptor blockers (also known as sartans), dihydropyridine calcium channel blockers, and thiazide diuretics. Beta-blockers are also indicated in patients with heart failure and reduced left ventricular ejection fraction or post myocardial infarction, and some guidelines recommend beta-blockers as first line antihypertensive medications . The choice should be based on individual efficacy and tolerability. Ethnicity affects the response to antihypertensive medications, and it has been suggested that calcium channel blockers and diuretics may be the first choice in blacks. Further, in specific clinical situations, for example hypertension in pregnant women, other medications such as alpha-methyldopa (an agonist of alpha adrenoreceptors in the central nervous system that inhibits the sympathetic nervous system) or labetalol (a beta adrenoreceptor blocker) are preferable, whereas some first line antihypertensives, for example ACE inhibitors and angiotensin II receptor blockers, are contraindicated because of increased risk for renal teratogenicity. Divided dosing of antihypertensive drugs tends to decrease adherence and should be avoided when possible.
BP cannot be controlled with monotherapy in many patients, particularly those with severe hypertension. When combining antihypertensive medications, it is important to consider whether the drugs have additive effects on BP or adverse effects, and whether the patient has comorbidities that mandate particular drug choices. ACE inhibitors or angiotensin II receptor blockers, thiazide diuretics and dihydropyridine calcium channel blockers are additive in lowering BP and can be combined as double or triple combination therapies. By contrast, combining ACE inhibitors and angiotensin II receptor blockers adds little BP lowering while increasing the risk for renal dysfunction and hyperkalaemia (high blood potassium levels, which can lead to cardiac arrhythmias). Similarly, combining RAAS inhibitors with beta-adrenoreceptor blockers adds little BP reduction, but this combination is indicated in patients following acute myocardial infarction or heart failure with reduced left ventricular ejection fraction for reasons beyond BP reduction

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