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Comprehensive Insights into Hypertension: Pathophysiology and Management

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Abstract

Hypertension is a significant risk factor for cardiovascular diseases, often coexisting with other metabolic abnormalities. Systolic blood pressure plays a critical role in determining cardiovascular risk, particularly in older populations. Essential hypertension, accounting for approximately 95% of cases, lacks a clearly identifiable cause despite extensive research. Globally, the incidence of hypertension continues to rise, with long-term treatment frequently falling short of achieving sustained blood pressure control. Epidemiological studies highlight the high prevalence of hypertension worldwide, with varying rates of awareness, treatment, and control across regions. Racial and ethnic disparities in hypertension prevalence have also been observed. The pathophysiology of essential hypertension involves complex interactions between genetic predispositions, sympathetic nervous system overactivity, renal mechanisms, vascular endothelial dysfunction, and hormonal factors such as the renin-angiotensin-aldosterone system. Obesity, obstructive sleep apnea, and insulin resistance are also significant contributors to hypertension development. Accurate blood pressure measurement is crucial for diagnosis, with out-of-office monitoring methods providing valuable information. Treatment primarily aims to prevent critical complications and should be tailored to individual needs. Lifestyle modifications, including weight reduction, physical activity, smoking cessation, and dietary changes, are recommended for all individuals with confirmed hypertension. When lifestyle

changes fail to achieve target blood pressure goals, pharmacological therapy becomes necessary. Various classes of antihypertensive drugs, such as diuretics, calcium channel blockers, ACE inhibitors, and ARBs, are available, each with unique mechanisms of action and side effect profiles. The selection of appropriate antihypertensive agents should consider factors such as age, comorbidities, and patient-specific characteristics to optimize treatment outcomes and minimize adverse effects.
Keywords: Hypertension, Pathophysiology, Management

Introduction

Hypertension is a significant and well-recognized risk factor for cardiovascular diseases (CVDs), contributing to a heightened likelihood of developing conditions such as coronary artery disease, congestive heart failure, stroke (both ischemic and hemorrhagic), renal failure, and peripheral arterial disease. This condition frequently coexists with other risk factors, such as diabetes, further compounding its detrimental effects on overall cardiovascular health. The coexistence of hypertension with other metabolic abnormalities amplifies its impact, making it a central concern in the prevention and management of CVDs.

Extensive epidemiological research highlights that systolic blood pressure (SBP) plays a more critical role than diastolic blood pressure (DBP) in determining cardiovascular risk, particularly in older populations. While diastolic blood pressure has traditionally received attention, contemporary data emphasize that systolic hypertension is the most prevalent form of hypertension across populations. Notably, in younger age groups, diastolic blood pressure may still contribute significantly to risk stratification. The focus on systolic hypertension reflects its predominance in clinical presentations and its stronger correlation with adverse cardiovascular outcomes.

Blood pressure (BP) is defined as the product of cardiac output and peripheral resistance, forming the physiological basis for understanding hypertension. The condition arises from increased cardiac output, heightened peripheral resistance, or both. Cardiac output, in turn, is influenced by stroke volume and heart rate, where stroke volume is a function of myocardial contractility and the size of the vascular compartment. Peripheral resistance is governed by both functional and structural changes in small arteries and arterioles, underscoring the complex interplay of vascular and cardiac factors in the pathogenesis of hypertension.

Hypertension represents a state of the vascular system in which the overall vasculature is set at an elevated pressure level unique to an individual. Essential hypertension, accounting for approximately 95% of all hypertension cases, lacks a clearly identifiable cause, despite extensive research into its underlying mechanisms. As defined by the Joint National Committee, hypertension is characterized by a blood pressure reading of ≥140/90 mmHg. This threshold serves as a clinical benchmark for diagnosis and intervention. Multiple risk factors have been implicated in the development of hypertension, including obesity, salt sensitivity, genetic predisposition, obstructive sleep apnea, insulin resistance, and heightened sympathetic nervous system activity. These risk factors interact in complex ways, contributing to the pathophysiological heterogeneity of the condition.

Despite considerable advances in understanding these risk factors, the precise pathophysiological mechanisms underlying hypertension remain incompletely elucidated. This ambiguity complicates efforts to curtail its prevalence and improve treatment outcomes. The incidence of hypertension continues to rise globally, posing a significant public health challenge. Furthermore, long-term treatment of hypertension frequently falls short of achieving sustained blood pressure control, emphasizing the need for a deeper exploration of its pathophysiology, innovative therapeutic strategies, and more effective public health interventions.

Epidemiology

Hypertension is widely regarded as one of the most critical modifiable risk factors for cardiovascular disease and is among the leading contributors to global morbidity and mortality. A systematic analysis conducted as part of the Global Burden of Disease Study 2017 identified high systolic blood pressure (SBP) as the foremost risk factor for mortality, accounting for 10.4 million deaths and 218 million disability-adjusted life-years (DALYs). In a study comprising 8.69 million participants from 154 countries, it was estimated that between 1990 and 2015, the proportion of individuals with an SBP of at least 110–115 mmHg increased from 73.1% to 81.3%, while those with an SBP of at least 140 mmHg rose from 17.3% to 20.5% (Forouzanfar et al., 2017). Additionally, the estimated annual death rate associated with SBP ≥110–115 mmHg increased by 7.1%, from 1356 per million, while deaths associated with SBP ≥140 mmHg increased by 8.6%, from 979 per million.

The 2019 May Measurement Month campaign, initiated by the International Society of Hypertension (ISH), screened more than 1.5 million individuals from 92 countries. Results revealed that 32.0% of participants had never had their blood pressure measured, and 34.0% were diagnosed with hypertension. Among those diagnosed, 58.7% were aware of their condition, and 54.7% were receiving antihypertensive medications (Beaney et al., 2020). Of hypertensive patients, 31.7% achieved blood pressure readings below 140/90 mmHg, and 23.3% reached readings below 130/80 mmHg. Among patients on at least one antihypertensive medication, 57.8% achieved control below 140/90 mmHg, and 28.9% achieved control below 130/80 mmHg. Approximately half of those receiving treatment were single-drug users. Since 2017, over 4.2 million individuals have had their blood pressure measured, with nearly one million adults identified as untreated or undertreated for hypertension.

Globally, awareness of hypertension varies significantly. In the Americas and Europe, at least 70% of individuals with hypertension are aware of their condition, compared to less than 40% in regions such as South Asia and sub-Saharan Africa. In a sample of 1.7 million adults in China, 44.7% were hypertensive, and only 44.7% of those with hypertension were aware of their condition (Lu et al., 2017). Furthermore, only 30.1% of these individuals were prescribed antihypertensive medications, and a mere 7.2% had controlled blood pressure. After standardizing for age and sex, rates of hypertension prevalence, awareness, treatment, and control were recorded as 37.2%, 36.0%, 22.9%, and 5.7%, respectively.

Among African populations, a systematic review and meta-analysis of 25 studies reported a pooled prevalence of elevated blood pressure (≥95th percentile) at 5.5% among children and adolescents and 12.7% for slightly elevated blood pressure (≥90th percentile and <95th percentile) (Noubiap et al., 2017). Increased body mass index (BMI) was strongly associated with elevated blood pressure, with children and adolescents (aged 2–19 years) with obesity experiencing a six-fold higher prevalence compared to non-obese counterparts. Public health strategies targeting obesity prevention are imperative to mitigate hypertension, as factors contributing to increased BMI span from childhood into adulthood. The meta-analysis further revealed that elevated blood pressure was more common in rural areas than urban settings, though no gender differences in prevalence were noted. Another study highlighted that individual of African origin exhibited higher hypertension prevalence compared to those of European origin (Ibrahim & Damasceno, 2012).

In the United States, a study identified a sharp increase in the progression from ideal blood pressure to pre-hypertension, beginning at age 8 for White boys and at age 25 for young African Americans. This finding underscores the early onset of heterogeneity in blood pressure trajectories across racial and ethnic groups. Prophylactic measures initiated in early adulthood may be crucial for preventing pre-hypertension, hypertension, and the subsequent development of disparities associated with race, ethnicity, and gender (Falkner & Lurbe, 2020). Analysis of

the original Framingham Heart Study cohort indicated that individuals generally maintained SBP below 120–125 mmHg. However, once SBP rose beyond this range, it progressed rapidly toward hypertension, a trend observed irrespective of the age of onset (Niiranen et al., 2018).
A comprehensive analysis of individual patient trajectories provided further insights, showing that lifetime SBP and diastolic blood pressure peaked at least 14 years before death and then declined steadily. Approximately 64.0% of patients in the study experienced an SBP reduction of at least 10 mmHg, which occurred across all groups, including those not receiving antihypertensive treatment. This decrease was most pronounced in older individuals and patients treated for conditions such as hypertension, dementia, heart failure, or late-life weight loss.

Pathophysiology

Hypertension can be categorized into essential and secondary types, with the majority of patients presenting with essential hypertension. The etiology of hypertension is multifactorial, involving contributions from environmental influences, genetic predispositions, and social determinants. An increasing understanding of the complex interplay between these factors continues to emerge, shedding light on the multifaceted nature of the condition (Taddei et al., 2018).
Advances in knowledge regarding the pathophysiology of hypertension have further illuminated its intricate mechanisms. In addition to traditional environmental risk factors such as obesity, physical inactivity, high sodium intake, and chronic stress, other contributors, including preterm birth or low birth weight (Haikerwal et al., 2020), and exposure to air and noise pollution, have been implicated in the development of hypertension. Immune system dysfunction and systemic inflammation have also been identified as significant components in the pathogenesis of hypertension. Notably, emerging evidence highlights the roles of gut microbiota and periodontitis in promoting systemic inflammation, which may contribute to elevated blood pressure.
The interactions between genetic predispositions and environmental factors underscore the importance of lifestyle modifications recommended in hypertension management guidelines. These recommendations emphasize weight reduction, adherence to a healthy diet, reduced dietary sodium intake, increased physical activity, and avoidance of smoking and excessive alcohol consumption.
In addition to environmental influences, the genetic underpinnings of hypertension represent a complex and expanding area of research. Findings from genome-wide association studies (GWAS) on blood pressure traits, including systolic, diastolic, and pulse pressure, have provided critical insights into key loci involved in blood pressure regulation. The identification of novel loci has facilitated the discovery of new mechanisms underlying blood pressure control and highlighted associations between blood pressure traits and lifestyle factors (Evangelou et al., 2018).

Pathophysiology of essential hypertension

1. Genetics

Hypertension often runs in families, with a parental history of hypertension significantly increasing the likelihood of its development in offspring, particularly when both parents are hypertensive. Studies suggest that approximately 60% of hypertension cases are attributable to familial associations, while 40% are linked to environmental factors.
Blood pressure (BP) regulation involves a complex network of interacting pathways, including renal, neural, endocrine, vascular, and other mechanisms, which influence the key determinants of BP—cardiac output and total peripheral resistance. Various genes within these systems contribute to BP regulation. According to a review by Padmanabhan et al., genome-wide association studies (GWAS) have identified over 100 single nucleotide polymorphisms

associated with BP traits, uncovering novel pathways of BP regulation and potential drug targets.

Genetic influences on BP regulation have been demonstrated through studies comparing monozygotic and dizygotic twins as well as genetically related versus adopted children. Several gene-related findings include:

1. **Corin Gene Mutations:** Two missense mutations in the corin gene, which encodes an enzyme that activates pro-ANP and pro-BNP into biologically active natriuretic peptides, may impair these peptides' defense against hypertension, contributing to the condition.
2. **Thiamine Transporter Variants:** Genetic variants affecting the thiamine transporter have been associated with increased cardiac output and reduced peripheral resistance.
3. **UMOD Gene Variants:** Variants in the UMOD gene, which encodes uromodulin, lead to overexpression of this protein and activation of the furosemide-sensitive renal sodium cotransporter NKCC2. Pharmacological inhibition of NKCC2 has been found effective in lowering BP in hypertensive patients.
4. **eNOS Activity Defects:** GWAS findings have linked defects in endothelial nitric oxide synthase (eNOS) activity to increased susceptibility to hypertension.
5. **Sodium Reabsorption Variants:** Single-gene mutations leading to altered net sodium reabsorption and variations in angiotensinogen and angiotensin receptor sequences have also been associated with hypertension.

Genes contributing to hypertension typically possess allelic variants that incrementally raise or lower BP levels. These effects are generally additive, with each genetic variant exerting a modest influence on BP (Padmanabhan et al., 2017).

2. Sympathetic Nervous System Overactivity

Increased sympathetic nervous system activity is associated with elevated heart rate, cardiac output, peripheral resistance, and levels of plasma and urinary norepinephrine (NE). This overactivity also results in regional NE spillover, peripheral postganglionic sympathetic nerve discharge, and alpha-adrenergic receptor-mediated vasoconstriction and vascular remodeling in the peripheral circulation. Sympathetic overactivity is an early feature of primary hypertension and is also observed in forms of hypertension linked to obesity, sleep apnea, early type 2 diabetes mellitus and prediabetes, chronic kidney disease, and heart failure.

Both central and peripheral mechanisms contribute to heightened sympathetic activity. Physical and emotional stress further activate sympatho-adrenal activity, leading to BP elevation.

3. Renal Mechanisms: Excess Sodium Intake and Pressure-Natriuresis

Hypertension has been associated with a fundamental defect in the kidneys' ability to excrete excess sodium, particularly in the context of high dietary salt intake. Evidence from populations with low sodium consumption demonstrates minimal or no incidence of hypertension. Studies have also shown that reducing salt intake correlates with BP reductions. Sodium contributes to BP elevation through:

1. **Volume-Dependent Mechanisms:** Increased sodium intake raises fluid volume and preload, thereby increasing cardiac output.
2. **Volume-Independent Mechanisms:** These include angiotensin-mediated central nervous system effects and heightened sympathetic activity.

In normotensive individuals, high salt intake triggers enhanced renal excretion of sodium and water, which normalizes fluid volume and BP. This is referred to as the pressure-natriuresis phenomenon, where elevated arterial pressure increases sodium and water excretion, restoring sodium balance. In primary hypertension, a resetting of the pressure-sodium excretion curve occurs, preventing BP normalization.

4. Vascular Mechanisms: Endothelial Dysfunction and the Nitric Oxide Pathway

The vascular endothelium plays a critical role in regulating BP through the production of nitric oxide (NO), a vasodilatory molecule, and endothelin (ET), a vasoconstrictor. Hypertension is characterized by endothelial dysfunction, including reduced production of endothelial-derived relaxing factors (NO and endothelial-derived hyperpolarizing factor) and increased production of pro-inflammatory, pro-thrombotic, and growth-promoting molecules such as endothelin, thromboxane, and transforming growth factor-beta.

The NO pathway is a key protective mechanism against hypertension. A deficiency in NO, often caused by its inactivation through reactive oxygen species (ROS), contributes to endothelial dysfunction in hypertensive individuals. Growth factors produced in the vascular endothelium, including platelet-derived growth factor, fibroblast growth factor, and insulin-like growth factor, are implicated in atherogenesis and organ damage. Chronic activation of endothelin-1 (ET-1) receptors in the kidneys is believed to play a significant role in hypertension pathogenesis (Flammer & Lüscher, 2010). Maintaining endothelial function is thus essential for vascular health and acts as a critical defense against atherosclerosis and hypertension.

5. Hormonal Mechanisms: The Renin-Angiotensin-Aldosterone System (RAAS)

Renin is a protease enzyme in circulation that plays a critical role in maintaining extracellular fluid balance and arterial vasoconstriction. It facilitates the conversion of angiotensinogen to angiotensin I, which is subsequently converted into angiotensin II (Ang II) by angiotensin-converting enzyme. Angiotensin II, a potent vasoactive peptide, induces vasoconstriction in arterial musculature, increasing peripheral resistance and elevating BP. It directly promotes sodium retention by enhancing the activity of Na^+/H^+ exchanger, Na^+/K^+ ATPase in the proximal tubule, $Na^+/K^+/2Cl^-$ transport in the loop of Henle, and various ion transporters in the distal nephron and collecting ducts. Angiotensin II also stimulates aldosterone release from the adrenal glands, which acts on renal epithelial cells to increase salt and water reabsorption, thereby raising blood volume and BP. Elevated renin levels, observed in hypertensive patients, are thought to contribute significantly to the development of hypertension.

6. Obesity-Related Hypertension

Several studies have proposed that weight gain enhances sympathetic nervous system activity, potentially as a mechanism to promote fat metabolism. However, this sympathetic overactivity often results in hypertension. Although the exact triggers for increased sympathetic output in obesity remain unclear, several proposed mechanisms include:

1. Sympathetic overactivity
2. Selective resistance to leptin
3. Adipokines produced by fat cells, such as leptin, fatty acids, and angiotensinogen, which have prohypertensive effects
4. Regulation of vascular smooth muscle by dipeptidyl peptidase 4
5. Overactivation of the RAAS.

7. Obstructive Sleep Apnea: Neurogenic Hypertension

Obstructive sleep apnea (OSA) is a significant contributor to neurogenic hypertension. Clinically, OSA is characterized by disturbed sleep, frequent awakenings, excessive nocturnal snoring, and daytime sleepiness. It involves episodes of apnea during sleep, resulting in recurrent hypoxia. Hypoxia activates carotid body chemoreceptors, reflexively increasing sympathetic activity, raising BP, and resetting the chemoreceptor reflex. EEG findings in OSA patients indicate desynchronized brain activity, while polysomnography (PSG) reveals varying levels of hypoxia. Continuous positive airway pressure (CPAP) therapy improves both nocturnal and daytime hypertension, with BP reductions often correlating with decreased sympathetic activity.

8. Insulin Resistance and Hypertension: Metabolic Syndrome

A study by Saxena et al. (2014) found a relationship between chronic stress or mental exhaustion, assessed using perceived stress scales and EEG, and diabetes. Chronic stress was linked to heightened basal sympathetic activity and diabetes. Increased sympathetic activity has been implicated in insulin resistance via stimulation of alpha-1 adrenergic receptors in the liver and muscle and inhibition of insulin secretion through alpha-2 adrenergic receptors in the pancreas. Insulin resistance (hyperinsulinemia), a hallmark of metabolic syndrome, elevates BP through mechanisms such as increased renal sodium reabsorption, activation of the sympathetic nervous system, alterations in transmembrane ion transport, and resistance vessel hypertrophy. Insulin resistance is also associated with obesity and dyslipidemia, both of which favor atherosclerosis and vascular stiffening, further exacerbating hypertension. Hypertension itself can contribute to insulin resistance by impairing insulin and glucose delivery to skeletal muscle, reducing glucose uptake. The common underlying mechanism for both insulin resistance and hypertension is thought to be central activation of the sympathetic nervous system.

9. Uric Acid and Hypertension

Numerous epidemiological and experimental studies have identified a strong correlation between hyperuricemia and conditions such as hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular events. A review by Borghi et al. (2017) confirmed that patients with gout or asymptomatic hyperuricemia have an elevated risk of cardiometabolic diseases, contributing to overall cardiovascular risk beyond traditional factors. Findings from the MRFIT (Multiple Risk Factor Intervention) and PAMELA (Pressure Arteriose Monitorate E Loro Associazion) trials, along with work by Kuwabara et al., suggest that elevated serum uric acid (UA) levels have a pathogenic role in cardiovascular disease.

Hyperuricemia may arise from overproduction or reduced renal clearance of UA. The development of hypertension is hypothesized to occur in two phases: an initial reversible phase caused by UA-mediated renal vasoconstriction and a subsequent irreversible phase characterized by impaired renal sodium excretion. Intracellular UA stimulates nicotinamide adenine dinucleotide phosphate oxidase, increasing oxidative stress in vascular smooth muscle and kidney tissues. This process initiates and sustains hypertension by altering mitochondrial responses, reducing endothelial nitric oxide levels, and activating the RAAS. Over time, hyperuricemia induces microvascular renal disease, which independently contributes to hypertension development (Borghi & Cicero, 2017).

10. Gender Differences

Hypertension is generally more prevalent in males than females, with androgens playing a role in vasoconstriction and hypertension through mechanisms such as upregulation of thromboxane A2, norepinephrine, angiotensin II expression, and endothelial activity. Prolonged testosterone administration in female-to-male transgender individuals has been shown to increase BP. Similarly, exogenous estrogen, whether used as contraceptive pills in premenopausal women or hormone replacement therapy in postmenopausal women, has been associated with elevated BP (Sandberg & Ji, 2012).

11. Racial and Ethnic Factors

Hypertension is more common, develops earlier, and is more severe in Black populations compared to other racial groups. It also results in greater target organ damage. The high prevalence of hypertension in this population is attributed to enhanced renal sodium absorption.

12. Vitamin D and Hypertension

Vitamin D insufficiency, defined by 25-hydroxyvitamin D (25[OH]D) levels below 30 ng/ml, has been linked to an increased risk of hypertension. Evidence suggests that vitamin D regulates vascular tone by influencing intracellular calcium concentrations in vascular smooth muscle

cells. Increased intracellular calcium inhibits renin secretion in juxtaglomerular cells, illustrating the interdependence of sodium-regulating hormones (e.g., RAAS) and calcium-regulating hormones (e.g., vitamin D) in hypertension development.

In vitro studies have demonstrated the vascular protective effects of 1,25(OH)2D, showing its ability to mitigate the harmful effects of advanced glycation end products on the endothelium and enhance nitric oxide system activity.

Secondary hypertension

1. Renal Causes of Secondary Hypertension

Renal causes of secondary hypertension are divided into renal parenchymal diseases and renovascular diseases. Renal parenchymal diseases encompass conditions such as polycystic kidney disease, typically inherited in an autosomal dominant manner, as well as glomerulonephritis, chronic tubulointerstitial disease, diabetic nephropathy, and obstructive uropathy. Chronic hypertension often coexists with chronic kidney disease (CKD), as hypertension can lead to CKD and vice versa. Establishing CKD as a cause of secondary hypertension can be challenging. Clinicians may find certain indicators helpful, such as abnormal findings on urinalysis, renal dysfunction preceding the onset of hypertension, or the presence of hypertension, proteinuria, or renal dysfunction early in pregnancy (e.g., superimposed pre-eclampsia). Furthermore, hypertension is more likely to result from CKD if it is mild relative to the severity of urinary abnormalities or kidney damage and is unaccompanied by cardiovascular complications. Baseline assessments for hypertension should include urinalysis, serum creatinine measurement, and kidney imaging. Significant abnormalities warrant referral to a nephrologist.

Not all patients undergo a full evaluation for secondary hypertension at the time of diagnosis. However, certain clinical findings, such as a creatinine increase exceeding 30% of baseline after initiating angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), recurrent flash pulmonary edema in patients with normal left ventricular ejection fraction, or kidney size discrepancies greater than 1.5 cm, necessitate investigation for renal artery stenosis. Renovascular disease includes fibromuscular dysplasia, which typically affects younger patients, and atherosclerotic renal artery stenosis, which is more prevalent among older patients. Hypertension related to renal artery stenosis arises from the overactivation of the renin-angiotensin (RA) system. Duplex Doppler ultrasonography is the initial imaging choice for renal arteries, though its accuracy can be limited in obese patients and depends on operator expertise. Magnetic resonance imaging (MRI) or computed tomographic (CT) angiography may be employed depending on renal function. If non-invasive imaging fails to provide a definitive diagnosis and clinical suspicion persists, renal artery angiography is considered the diagnostic gold standard.

Management of renal artery stenosis focuses on blood pressure control. ACE inhibitors and ARBs are effective in patients with both unilateral and bilateral stenosis. For atherosclerotic renal artery stenosis, evidence supporting angioplasty as a primary treatment is limited, and revascularization is typically reserved for cases where medical therapy fails. Renin-angiotensin blockade is generally well-tolerated, even in severe bilateral stenosis, and reduces mortality in patients with atherosclerotic renal artery stenosis unless absolute contraindications exist (Chrysochou et al., 2012). The CORAL study, which compared stenting with medical therapy for atherosclerotic renal artery stenosis, concluded that stenting does not significantly reduce the risk of clinical events beyond the benefits of multifactorial medical therapy. In contrast, for fibromuscular dysplasia, which tends to involve the mid and distal segments of the renal artery in younger patients, percutaneous angioplasty yields favorable outcomes and is recommended. Additional indications for percutaneous intervention include a short duration of hypertension before diagnosis, recurrent flash pulmonary edema, rapidly worsening hypertension, resistant hypertension, or progression of severe hypertension.

2. Primary Aldosteronism (PA)

Initially described by Jerome Conn in 1950, primary aldosteronism (PA) was once considered rare. However, its prevalence has increased due to advancements in laboratory assays, the use of the aldosterone-to-renin ratio (ARR) for screening, greater use of advanced imaging, and the incidental detection of adrenal abnormalities. While hypokalemia was previously considered a hallmark of PA, it is now recognized that most patients are normokalemic (Funder et al., 2016). PA is associated with higher cardiovascular morbidity and mortality compared to individuals with essential hypertension matched for age, sex, and blood pressure. Early diagnosis is crucial, as treatment can mitigate end-organ damage. PA may result from unilateral adenoma (Conn's syndrome), bilateral hyperplasia, or unilateral hyperplasia. Unilateral disease is typically treated with laparoscopic adrenalectomy, which improves blood pressure control in all cases and cures hypertension in approximately 50% of patients. Patients with bilateral hyperplasia are treated with mineralocorticoid receptor antagonists, such as spironolactone or eplerenone.

The onset of hypertension in PA typically occurs between 40 and 70 years of age. Most patients are asymptomatic, with hypokalemia observed in only a minority (~30%). In 2016, the Endocrine Society recommended screening for PA in patients with persistent blood pressure readings above 150/100 mmHg, resistant hypertension, controlled blood pressure (<140/90 mmHg) on four or more antihypertensive medications, or hypertension accompanied by hypokalemia (whether spontaneous or induced by diuretics). Recent expert opinions suggest screening for PA at least once upon diagnosing hypertension.

Before conducting PA screening, it is important to address hypokalemia, as it may falsely lower aldosterone levels and produce negative ARR results. Medications such as spironolactone, eplerenone, and amiloride should be discontinued for at least six weeks prior to testing. Other medications, including beta-blockers, ACE inhibitors, ARBs, and diuretics, should ideally be substituted with non-interfering drugs such as verapamil, hydralazine, or prazosin/doxazosin, as these minimally impact ARR. If substituting medications is unsafe or impractical, screening may proceed with results interpreted accordingly. Aldosterone, renin, and potassium levels should be measured between 8–10 a.m. with patients in a seated position. Elevated aldosterone concentration (typically >10 ng/dL) suppressed plasma renin activity (<1 ng/mL/h), and an ARR >20 indicate positive screening results, warranting referral to an endocrinologist.

3. Cushing's Syndrome (CS)

Cushing's syndrome (CS) is a relatively uncommon endocrine cause of secondary hypertension, affecting less than 0.1% of the general population. Key clinical features suggestive of CS include central obesity, facial plethora, skin atrophy, easy bruising, violaceous striae, hirsutism, and a buffalo hump. Hypertension is a common manifestation, affecting approximately 80% of patients with CS. Other notable clinical indicators include sudden worsening of metabolic control, unexplained osteoporosis and fractures, and psychiatric symptoms such as depression and psychosis. The most frequent cause of CS is exogenous CS, typically resulting from the use of potent steroids for coexisting conditions or over-the-counter medications. Therefore, exogenous CS must be excluded before considering screening for endogenous CS. Diagnostic tests for endogenous CS include 24-hour urinary cortisol, overnight dexamethasone suppression testing, salivary cortisol measurements, and cortisol day curves. If clinical suspicion remains high, referral to an endocrinologist for further evaluation is recommended.

4. Hyper-/Hypothyroidism

Both hyperthyroidism and hypothyroidism are associated with hypertension. Hypothyroidism often leads to diastolic hypertension, which results from low cardiac output compensated by peripheral vasoconstriction to ensure adequate tissue perfusion. Conversely, hyperthyroidism typically causes increased cardiac output, leading to elevated systolic hypertension. Clinical

symptoms indicative of thyroid dysfunction should be carefully assessed. Laboratory evaluation of thyroid function can be performed using measurements of free thyroid hormone (FT4) and thyroid-stimulating hormone (TSH).

5. Pheochromocytoma

Pheochromocytoma is a rare but significant cause of secondary hypertension, with an estimated prevalence of 0.2% among unselected hypertensive patients. It is, however, a frequent cause in patients presenting with hypertensive emergencies. The clinical course is often unpredictable, characterized by severe hypertension (e.g., 200/100 mmHg) that alternates with episodes of hypotension (Meifen et al., 2016), potentially resulting in multiorgan failure. Timely recognition is critical to prevent catastrophic outcomes. The condition arises from paroxysmal elevations in plasma catecholamines and is characterized by the "5 Ps": paroxysmal hypertension, palpitations, perspiration, pallor, and pounding headache.

Screening for pheochromocytoma involves measuring 24-hour urinary fractionated metanephrines or plasma metanephrines. Screening is indicated in symptomatic individuals, those with resistant hypertension, a family history of pheochromocytoma (e.g., MEN 2, von Hippel-Lindau syndrome, SDH mutations, neurofibromatosis), or an adrenal mass suggestive of pheochromocytoma. Positive screening results necessitate further imaging and referral to an endocrinologist.

6. Coarctation of the Aorta

Coarctation of the aorta is the second most common cause of hypertension in children and young adults. It typically involves constriction of the aortic lumen near the ligamentum arteriosum. Common symptoms include headaches, cold feet, and leg pain during physical activity. Clinical findings include hypertension with weak femoral pulses and a systolic murmur, which may be auscultated at the front or back of the chest. Posterior rib notching visible on chest radiographs is indicative of collateral circulation. Transthoracic echocardiography is the preferred initial screening method, but additional imaging techniques, such as CT or MRI, may also be employed. Early management options include surgical repair or percutaneous balloon angioplasty, both of which are equally effective.

7. Obstructive Sleep Apnea (OSA)

Obstructive sleep apnea (OSA) is one of the most prevalent causes of secondary hypertension. It is increasingly recognized as a contributing factor to resistant hypertension. Studies have demonstrated a high prevalence of OSA in patients with resistant hypertension, with rates of 65% in women and 95% in men (Hou et al., n.d.).

In Singapore, a study estimated the prevalence of moderate to severe OSA to be 30.5%. OSA is characterized by repeated episodes of partial or complete obstruction of the upper airway during sleep, leading to oxygen desaturation and arousals. The diagnosis of OSA is based on an apnea-hypopnea index (AHI) of ≥5. The AHI is defined as the number of apnea and hypopnea events per hour of sleep. OSA is classified into mild (AHI: 5–15), moderate (AHI: 16–30), and severe (AHI: >30) categories. Risk factors for OSA include male sex, obesity, and middle age. Common symptoms include fatigue, daytime sleepiness, snoring, morning headaches, difficulty concentrating, and irritability. Physical examination often reveals obesity, increased neck circumference due to soft tissue accumulation, or a large tongue.

Several tools are available for OSA screening, including the STOP, STOP-BANG, Epworth Sleepiness Scale (ESS), and the 4-Variable screening tool (4-V). Each tool varies in ease of use, sensitivity, and specificity. The STOP-BANG questionnaire is widely regarded as the simplest and most sensitive screening tool, with eight binary (yes/no) items assessing sleep apnea-related features. A STOP-BANG score of ≥3 demonstrates a sensitivity of 93% and 100% for detecting moderate-to-severe (AHI >15) and severe (AHI >30) OSA, respectively.

Polysomnography remains the gold standard diagnostic test for OSA. In recent years, home sleep tests have become increasingly utilized, particularly for uncomplicated cases with a high

pre-test probability of OSA. Patients with typical symptoms, relevant physical findings, or positive screening questionnaire results should be referred to a sleep specialist.

The primary treatment for OSA is continuous positive airway pressure (CPAP), which improves daytime symptoms and overall quality of life. CPAP or mandibular advancement devices (MAD) are typically combined with antihypertensive medications, as well as dietary and lifestyle interventions. Given the high rate of undiagnosed cases, clinicians should maintain a high index of suspicion and actively screen for OSA, particularly in patients with resistant hypertension.

Diagnosis

Blood Pressure Measurements

Accurate and reliable blood pressure measurement is fundamental for diagnosing hypertension. Blood pressure fluctuates continuously in response to endogenous and exogenous factors, necessitating standardized procedures for precise measurement. Despite educational efforts and simplification of the measurement process, non-standardized measurements have remained a persistent issue over decades. The widespread availability of non-validated blood pressure devices can result in incorrect diagnoses and improper management. The Lancet Commission on Hypertension identified critical actions to enhance global blood pressure management at both individual and population levels (Padwal et al., 2019).

Obtaining accurate blood pressure readings requires trained observers employing standardized methodologies. Multiple readings over time are necessary to account for regression to the mean and minimize the impact of elevated readings caused by white-coat hypertension. Common methods for measuring blood pressure in clinical practice include direct (intra-arterial) and indirect (cuff-based) approaches. Indirect measurements are typically performed via auscultation or automated devices, with the latter most often utilizing the oscillometric technique. Automated measurements can mitigate observer bias but may produce errors in certain scenarios, such as increased arterial stiffness or arrhythmias. While office blood pressure measurement remains the gold standard for diagnosing hypertension, current guidelines recommend confirming the diagnosis with out-of-office measurements, such as ambulatory or home blood pressure monitoring (Unger et al., 2020).

Both 24-hour ambulatory blood pressure monitoring and home monitoring are superior to office measurements for predicting cardiovascular events and are ideal for long-term follow-up. Unattended blood pressure measurements, which reduce patient–observer interaction and associated anxiety while minimizing observer errors, were first implemented in the SPRINT trial (SPRINT Research Group et al., 2015). On average, unattended systolic blood pressure readings are 10 mm Hg lower than office sphygmomanometer or oscillometric values, depending on baseline blood pressure, and should not be used interchangeably with other office measurements. However, large randomized controlled trials are still required to establish the utility of unattended measurements in predicting hypertension-mediated organ damage and their association with cardiovascular morbidity and mortality.

Blood pressure variability (BPV) is emerging as a novel potential risk factor for cardiovascular disease. Blood pressure is not constant but exhibits significant spontaneous oscillations over short-term periods (minutes to days) and long-term intervals (day-to-day, visit-to-visit, or seasonal). Studies in animal models suggest that increased BPV is associated with the development of target organ damage. In both the general population and hypertensive patients, increased short-term and long-term BPV has been independently associated with target organ damage and a higher risk of cardiovascular events. However, there remains a need to establish consensus on definitions, thresholds, and targets for BPV, as well as evidence that interventions to reduce BPV improve clinical outcomes.

Classification

The definition of arterial hypertension in all major guidelines is based on office blood pressure measurements. Although there are differences in definitions among the 2018 European Society of Cardiology (ESC)–European Society of Hypertension (ESH) guidelines, the 2017 American College of Cardiology (ACC)–American Heart Association (AHA) guidelines, and the 2020 International Society of Hypertension (ISH) guidelines, the criteria for initiating antihypertensive therapy are similar. Specifically, antihypertensive treatment is recommended for patients with blood pressure levels of at least 140/90 mm Hg who have a high cardiovascular risk or evidence of target organ damage. For patients with grade 1 hypertension (definitions vary by guideline), low-to-moderate cardiovascular risk, and no evidence of hypertension-mediated organ damage, pharmacological treatment to lower blood pressure is suggested only if the patient remains hypertensive after a period of lifestyle modification (Lonn et al., 2016).

All guidelines concur that multiple blood pressure measurements are required for an accurate diagnosis of arterial hypertension. For patients with elevated office blood pressure, the diagnosis should be confirmed using out-of-office measurements, such as home or ambulatory blood pressure monitoring. These out-of-office methods are also crucial for identifying white-coat hypertension or masked hypertension. It is important to note that the classification of normal blood pressure values differs between office and out-of-office measurements.

The classification of blood pressure differs across various guidelines. Below is a comparative summary:

- **According to ACC–AHA** (Whelton et al., 2018)**:**
  - **Normal:** Systolic BP < 120 mm Hg and Diastolic BP < 80 mm Hg.
  - **Elevated:** Systolic BP 120–129 mm Hg and Diastolic BP < 80 mm Hg.
  - **Stage 1 Hypertension:** Systolic BP 130–139 mm Hg or Diastolic BP 80–89 mm Hg.
  - **Stage 2 Hypertension:** Systolic BP ≥ 140 mm Hg or Diastolic BP ≥ 90 mm Hg.
- **According to ESC–ESH** (Williams et al., 2018)**:**
  - **Optimal:** Systolic BP < 120 mm Hg and Diastolic BP < 80 mm Hg.
  - **Normal:** Systolic BP 120–129 mm Hg or Diastolic BP 80–84 mm Hg.
  - **High-Normal:** Systolic BP 130–139 mm Hg or Diastolic BP 85–89 mm Hg.
  - **Stage 1 Hypertension:** Systolic BP 140–159 mm Hg or Diastolic BP 90–99 mm Hg.
  - **Stage 2 Hypertension:** Systolic BP 160–179 mm Hg or Diastolic BP 100–109 mm Hg.
  - **Stage 3 Hypertension:** Systolic BP ≥ 180 mm Hg or Diastolic BP ≥ 110 mm Hg.
  - **Isolated Systolic Hypertension:** Systolic BP ≥ 140 mm Hg and Diastolic BP < 90 mm Hg.

Treatment

LIFESTYLE MODIFICATION: This is recommended for all individuals with confirmed hypertension and comprises the following:

i. **Weight Reduction:** Weight loss is advised for individuals with a body mass index (BMI) greater than 25 kg/m². Waist circumference is recognized as a superior predictor of cardiovascular risk compared to other parameters. It is recommended to maintain a waist circumference below 102 cm in men and below 88 cm in women. A reduction of up to 5–20 mmHg in systolic blood pressure has been observed for every 10 kg of weight lost.

ii. **Physical Activity:** Physical inactivity is an independent cardiovascular risk factor, apart from its contribution to increased body weight. Regular aerobic physical activity, such as brisk walking for at least 30 minutes on a minimum of three days per week, has been associated with a reduction in blood pressure ranging from 4–9 mmHg.

iii. **Smoking or Tobacco Use:** Smoking is a significant independent risk factor for cardiovascular disease. Individuals who smoke typically exhibit higher ambulatory blood pressure levels compared to non-smokers. Quitting smoking is considered one of the most effective lifestyle interventions for reducing cardiovascular disease risk.
iv. **Excessive Alcohol Consumption:** Limiting daily alcohol intake to two drinks or less for men (equivalent to fewer than two bottles of beer) and less than one drink for women has been shown to lower blood pressure by 2–4 mmHg.
v. **Excessive Salt Intake:** There is a well-documented direct relationship between excessive salt consumption and elevated blood pressure. Reducing dietary salt intake to less than 6 g of sodium chloride per day (equivalent to 100 mmol of sodium) can result in a blood pressure reduction of 2–8 mmHg.
vi. **Dietary Approaches to Stop Hypertension (DASH):** This approach emphasizes consuming foods rich in whole grains, fish, poultry, and nuts while being abundant in potassium, calcium, magnesium, and fiber. It also limits the intake of red meat, sweets, sugar-sweetened beverages, saturated fats, and total fats. Adherence to this dietary pattern has been associated with a blood pressure reduction of 8–14 mmHg.
If the aforementioned lifestyle modifications fail to achieve the target blood pressure goals (<140/90 mmHg for most individuals and <130/80 mmHg for those with diabetes or chronic renal failure), drug therapy becomes necessary. Evidence demonstrates that lowering blood pressure by 5–6 mmHg can reduce the risk of stroke by 40%, coronary artery disease by 15–20%, and also diminish the likelihood of developing dementia, heart failure, and mortality from cardiovascular diseases.
The primary aim of treatment is to prevent critical complications of hypertension, including heart attack, stroke, and heart failure. Drug therapy should be tailored to individual needs, taking into account various factors, particularly in economically constrained settings. Age should also be carefully considered when managing hypertension with pharmacological interventions.

Classes Of Antihypertensive Drugs

Diuretics

Diuretics function by acting on different sections of the nephron to facilitate the excretion of salt and water. This leads to a decrease in blood volume, stroke volume, cardiac output, and, with prolonged use, a reduction in peripheral resistance. There are three main classes of diuretics clinically relevant for hypertension management: thiazide/thiazide-like diuretics, loop diuretics, and potassium-sparing diuretics. Among these, thiazides are the most frequently used in hypertension treatment.

Calcium Channel Blockers

Calcium channel blockers exert their effects by binding to L-type calcium channels located on vascular smooth muscle, cardiac muscle, and conduction cells, thereby inhibiting calcium influx. This results in vascular smooth muscle relaxation, decreased cardiac inotropy, and reduced chronotropy, depending on the cell type. These drugs also possess natriuretic and diuretic properties and are particularly effective in managing hypertension in black populations and elderly individuals. There are three classes of calcium channel blockers: dihydropyridines, phenylalkylamines, and benzothiazepines. Dihydropyridines (e.g., nifedipine, amlodipine) have the highest vascular selectivity and, consequently, the most significant blood pressure-lowering effects. Common side effects of dihydropyridines include headaches, flushing, tachycardia, and peripheral edema.

Angiotensin-Converting Enzyme Inhibitors (Aceis)

ACE inhibitors function by inhibiting the formation of angiotensin II, a potent vasoconstrictor, and by blocking kininase activity, leading to the accumulation of bradykinin, a vasorelaxant.

The overall effect is vascular relaxation. By preventing aldosterone release, these drugs reduce sodium and water retention. ACE inhibitors are more effective in high-renin states and less effective as monotherapy in individuals with low-renin hypertension, such as many black and elderly patients. Common side effects include dry cough, angioedema, hypotension, and hyperkalemia. These drugs are contraindicated in pregnancy and bilateral renal artery stenosis. Frequently used ACE inhibitors include captopril, lisinopril, enalapril, and ramipril.

Angiotensin Receptor Blockers (Arbs)

ARBs target the renin-angiotensin system, producing effects similar to ACE inhibitors by blocking type I angiotensin II receptors. However, ARBs do not inhibit kininase, so bradykinin accumulation does not occur, reducing the likelihood of side effects such as cough and angioedema. Examples of ARBs include losartan, valsartan, olmesartan, and candesartan.

Renin Inhibitors

Renin inhibitors act by preventing the conversion of angiotensinogen to angiotensin I, yielding blood pressure-lowering effects similar to ACE inhibitors and ARBs. The side effects are generally comparable to those of ACE inhibitors but tend to be less severe. Aliskiren is an approved renin inhibitor.

Alpha-Blockers

Alpha-blockers, particularly α1-blockers, act on vascular smooth muscle by blocking the post-synaptic actions of noradrenaline, thereby inducing vascular relaxation. They are more effective in conditions of heightened sympathetic tone. Side effects include dizziness, nasal congestion, headaches, reflex tachycardia, orthostatic hypotension, and fluid retention. Examples of commonly used alpha-blockers are prazosin and doxazosin.

Beta-Blockers

Beta-blockers work by competitively binding to beta-receptors in the heart's nodal, conductive, and muscle cells. This action decreases heart rate, contractility, conduction velocity, and ultimately cardiac output. Common beta-blockers include propranolol, atenolol, metoprolol, carvedilol, and bisoprolol. These drugs are particularly useful in managing tachyarrhythmias, thyrotoxicosis, and migraines but should be avoided in patients with bronchial asthma or second- or third-degree heart block. Their use in heart failure should be restricted to specialists and referral centers where cardiac function can be closely monitored.

Centrally Acting Drugs

These drugs act on α2-adrenoceptors in the medulla, reducing sympathetic stimulation to the heart and leading to decreased heart rate, contractility, cardiac output, and blood pressure. Alpha-methyldopa and reserpine are commonly used in low-income settings. Side effects include dizziness, dry mouth, sexual dysfunction, depression, and orthostatic hypotension.

Direct Vasodilators

Direct vasodilators act on the vascular wall, though the exact mechanism may involve potassium channel activation and calcium inhibition. These drugs are associated with reflex tachycardia, headaches, and flushing. Hydralazine is commonly used, while minoxidil, despite being one of the most effective antihypertensive drugs, can cause severe fluid retention and excessive hair growth.

Conclusion

Hypertension remains a significant global health burden and a leading contributor to cardiovascular morbidity and mortality. Its complex etiology, encompassing genetic, environmental, and lifestyle factors, underscores the necessity for a multifaceted approach to its management. While lifestyle modifications such as weight loss, dietary changes, and increased physical activity serve as fundamental preventive and therapeutic measures, pharmacological interventions tailored to individual needs remain crucial for achieving optimal blood pressure control. Emerging insights into the underlying mechanisms of hypertension,

including the roles of gut microbiota, immune dysfunction, and genetic predispositions, present opportunities for innovative therapies.

Despite advancements in treatment, hypertension control rates remain suboptimal, highlighting gaps in awareness, diagnosis, and adherence to therapy, especially in low-resource settings. Public health interventions focusing on early detection, education, and improved access to care are imperative to mitigate the global impact of this condition. Ultimately, an integrated strategy involving lifestyle changes, personalized medical care, and systemic policy-level interventions is essential for addressing the challenges of hypertension and reducing its associated health burdens.

References

Beaney, T., Schutte, A. E., Stergiou, G. S., Borghi, C., Burger, D., Charchar, F., Cro, S., Diaz, A., Damasceno, A., Espeche, W., Jose, A. P., Khan, N., Kokubo, Y., Maheshwari, A., Marin, M. J., More, A., Neupane, D., Nilsson, P., Patil, M., … MMM Investigators*. (2020). May Measurement Month 2019: The Global Blood Pressure Screening Campaign of the International Society of Hypertension. *Hypertension (Dallas, Tex.: 1979)*, *76*(2), 333–341. https://doi.org/10.1161/HYPERTENSIONAHA.120.14874

Borghi, C., & Cicero, A. F. G. (2017). Serum Uric Acid and Cardiometabolic Disease: Another Brick in the Wall? *Hypertension (Dallas, Tex.: 1979)*, *69*(6), 1011–1013. https://doi.org/10.1161/HYPERTENSIONAHA.117.09081

Chrysochou, C., Foley, R. N., Young, J. F., Khavandi, K., Cheung, C. M., & Kalra, P. A. (2012). Dispelling the myth: The use of renin–angiotensin blockade in atheromatous renovascular disease. *Nephrology Dialysis Transplantation*, *27*(4), 1403–1409. https://doi.org/10.1093/ndt/gfr496

Evangelou, E., Warren, H. R., Mosen-Ansorena, D., Mifsud, B., Pazoki, R., Gao, H., Ntritsos, G., Dimou, N., Cabrera, C. P., Karaman, I., Ng, F. L., Evangelou, M., Witkowska, K., Tzanis, E., Hellwege, J. N., Giri, A., Velez Edwards, D. R., Sun, Y. V., Cho, K., … Million Veteran Program. (2018). Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nature Genetics*, *50*(10), 1412–1425. https://doi.org/10.1038/s41588-018-0205-x

Falkner, B., & Lurbe, E. (2020). Primordial Prevention of High Blood Pressure in Childhood: An Opportunity Not to be Missed. *Hypertension (Dallas, Tex.: 1979)*, *75*(5), 1142–1150. https://doi.org/10.1161/HYPERTENSIONAHA.119.14059

Flammer, A. J., & Lüscher, T. F. (2010). Human endothelial dysfunction: EDRFs. *Pflugers Archiv: European Journal of Physiology*, *459*(6), 1005–1013. https://doi.org/10.1007/s00424-010-0822-4

Forouzanfar, M. H., Liu, P., Roth, G. A., Ng, M., Biryukov, S., Marczak, L., Alexander, L., Estep, K., Hassen Abate, K., Akinyemiju, T. F., Ali, R., Alvis-Guzman, N., Azzopardi, P., Banerjee, A., Bärnighausen, T., Basu, A., Bekele, T., Bennett, D. A., Biadgilign, S., … Murray, C. J. L. (2017). Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *JAMA*, *317*(2), 165–182. https://doi.org/10.1001/jama.2016.19043

Funder, J. W., Carey, R. M., Mantero, F., Murad, M. H., Reincke, M., Shibata, H., Stowasser, M., & Young, W. F., Jr. (2016). The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, *101*(5), 1889–1916. https://doi.org/10.1210/jc.2015-4061

Haikerwal, A., Doyle, L. W., Cheung, M. M., Wark, J. D., Opie, G., Roberts, G., Patton, G., & Cheong, J. L. Y. (2020). High Blood Pressure in Young Adult Survivors Born Extremely

Preterm or Extremely Low Birthweight in the Post Surfactant Era. *Hypertension (Dallas, Tex.: 1979)*, *75*(1), 211–217. https://doi.org/10.1161/HYPERTENSIONAHA.119.13780

Hou, H., Zhao, Y., Yu, W., Dong, H., Xue, X., Ding, J., Xing, W., & Wang, W. (n.d.). Association of obstructive sleep apnea with hypertension: A systematic review and meta-analysis. *Journal of Global Health*, *8*(1), 010405. https://doi.org/10.7189/jogh.08.010405

Ibrahim, M. M., & Damasceno, A. (2012). Hypertension in developing countries. *Lancet (London, England)*, *380*(9841), 611–619. https://doi.org/10.1016/S0140-6736(12)60861-7

Lonn, E. M., Bosch, J., López-Jaramillo, P., Zhu, J., Liu, L., Pais, P., Diaz, R., Xavier, D., Sliwa, K., Dans, A., Avezum, A., Piegas, L. S., Keltai, K., Keltai, M., Chazova, I., Peters, R. J. G., Held, C., Yusoff, K., Lewis, B. S., … HOPE-3 Investigators. (2016). Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *The New England Journal of Medicine*, *374*(21), 2009–2020. https://doi.org/10.1056/NEJMoa1600175

Lu, J., Lu, Y., Wang, X., Li, X., Linderman, G. C., Wu, C., Cheng, X., Mu, L., Zhang, H., Liu, J., Su, M., Zhao, H., Spatz, E. S., Spertus, J. A., Masoudi, F. A., Krumholz, H. M., & Jiang, L. (2017). Prevalence, awareness, treatment, and control of hypertension in China: Data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet (London, England)*, *390*(10112), 2549–2558. https://doi.org/10.1016/S0140-6736(17)32478-9

Meifen, Z., Zainudin, S. B., & Ling, C. C. (2016). Pheochromocytoma Crisis Triggered by Extra-Corporal Membrane Oxygenation Explantation. *Journal of Advances in Medicine and Medical Research*, 1–5. https://doi.org/10.9734/BJMMR/2016/21709

Niiranen, T. J., Henglin, M., Claggett, B., Muggeo, V. M. R., McCabe, E., Jain, M., Vasan, R. S., Larson, M. G., & Cheng, S. (2018). Trajectories of Blood Pressure Elevation Preceding Hypertension Onset. *JAMA Cardiology*, *3*(5), 427–431. https://doi.org/10.1001/jamacardio.2018.0250

Noubiap, J. J., Essouma, M., Bigna, J. J., Jingi, A. M., Aminde, L. N., & Nansseu, J. R. (2017). Prevalence of elevated blood pressure in children and adolescents in Africa: A systematic review and meta-analysis. *The Lancet. Public Health*, *2*(8), e375–e386. https://doi.org/10.1016/S2468-2667(17)30123-8

Padmanabhan, S., Aman, A., & Dominiczak, A. F. (2017). Genomics of hypertension. *Pharmacological Research*, *121*, 219–229. https://doi.org/10.1016/j.phrs.2017.04.031

Padwal, R., Campbell, N. R. C., Schutte, A. E., Olsen, M. H., Delles, C., Etyang, A., Cruickshank, J. K., Stergiou, G., Rakotz, M. K., Wozniak, G., Jaffe, M. G., Benjamin, I., Parati, G., & Sharman, J. E. (2019). Optimizing observer performance of clinic blood pressure measurement: A position statement from the Lancet Commission on Hypertension Group. *Journal of Hypertension*, *37*(9), 1737–1745. https://doi.org/10.1097/HJH.0000000000002112

Sandberg, K., & Ji, H. (2012). Sex differences in primary hypertension. *Biology of Sex Differences*, *3*(1), 7. https://doi.org/10.1186/2042-6410-3-7

SPRINT Research Group, Wright, J. T., Williamson, J. D., Whelton, P. K., Snyder, J. K., Sink, K. M., Rocco, M. V., Reboussin, D. M., Rahman, M., Oparil, S., Lewis, C. E., Kimmel, P. L., Johnson, K. C., Goff, D. C., Fine, L. J., Cutler, J. A., Cushman, W. C., Cheung, A. K., & Ambrosius, W. T. (2015). A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England Journal of Medicine*, *373*(22), 2103–2116. https://doi.org/10.1056/NEJMoa1511939

Taddei, S., Bruno, R. M., Masi, S., Solini, A., Taddei, S., Bruno, R. M., Masi, S., & Solini, A. (2018). *Epidemiology and pathophysiology of hypertension*. 2377–2388. https://doi.org/10.1093/med/9780198784906.003.0563_update_001

Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B., & Schutte, A. E. (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension (Dallas, Tex.: 1979)*, *75*(6), 1334–1357. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C., DePalma, S. M., Gidding, S., Jamerson, K. A., Jones, D. W., MacLaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A., … Wright, J. T. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*, *71*(6), 1269–1324. https://doi.org/10.1161/HYP.0000000000000066

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D., Coca, A., De Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S., Kreutz, R., Laurent, S., … Desormais, I. (2018). 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Blood Pressure*, *27*(6), 314–340. https://doi.org/10.1080/08037051.2018.1527177