Sleep quality assessment in patients with arterial hypertension

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SLEEP QUALITY ASSESSMENT IN PATIENTS WITH ARTERIAL HYPERTENSION

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List of abbreviations

ABPM: ambulatory blood pressure monitoring

ACE: Angiotensin-converting enzyme

AHI: Apnea-Hypopnea Index (AHI)

ANP: Atrial natriuretic peptide

BB: Beta-blockers

BMI: Body mass index

BNP: Brain natriuretic peptide

BP: Blood pressure

CCB: Calcium channel blocker

CHF: Congestive heart failure

CKD: Chronic kidney disease

CV: Cardiovascular

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

DM: Diabetes mellitus

ESS: Epworth sleepiness scale

HBPM: Home blood pressure monitoring

HFrEF: Heart failure with reduced ejection fraction

HMOD: Hypertensive end organ damage

MAP: Mean arterial pressure

NO: Nitric oxide

OBPM: Office blood pressure measurement

OSA: Obstructive sleep apnea

PSQI: Pittsburgh sleep quality index

SBP: Systolic blood pressure

WCH: White coat hypertension

WHO: World Health Organization

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1. INTRODUCTION

1.1 Definition and classification

Hypertension is a chronic health condition characterized by consistently elevated blood pressure (BP) levels in the arteries. BP is typically measured in two ways: systolic blood pressure (SBP), which indicates the pressure in the arteries when the heart contracts and pumps blood out, and diastolic blood pressure (DBP), which measures the pressure in the arteries when the heart is resting between beats (1)

The latest version of the European guidelines for the BP classification remains consistent with previous editions (2). Hypertension is still defined as SBP exceeding 140 mmHg and/or DBP exceeding 90 mmHg, with hypertensive individuals categorized into three grades based on the degree of BP elevation. Normotensive individuals are also categorized as optimal (< 120/80 mmHg), normal (120–129/80–85 mmHg), or high-normal (130–139/85–89 mmHg). Hypertension is divided into three grades based on severity, as depicted in Table 1 (3-6).

Table 1. Classification of office blood pressures and definitions of hypertensive grades.

Category	**Systolic (mmHg)**		**Diastolic (mmHg)**
Optimal	<120	and	<80
Normal	120-129	and	80-84
High-normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90
Isolated diastolic hypertension	<140	and	≥ 90

Source: Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension. Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). 2024:1;42(1):194.

1.2 Epidemiology

Hypertension is the most common cardiovascular disease (CVD) worldwide, and according to the World Health Organization (WHO), it affects 1.28 billion adults aged between 30 and 79 years, with two-thirds found in low-income and middle-income countries (7). In 2019, the average prevalence of hypertension in the mentioned age group was 34% among men and 32% among women (7). In Europe, this prevalence pattern is similar, with variations

between countries, and some Western countries reporting values below the average, while some Eastern European countries exhibit higher-than-average prevalence (7).

Among people below the age of 50, men tend to have a higher prevalence of hypertension, whereas women experience a more pronounced increase in SBP from their third decade, especially after menopause, which leads to a greater prevalence of hypertension in women in the older age groups (above 65 years) (8).

SBP generally increases with age, while DBP increases until age 50-60, followed by a brief period of stagnation and then a mild decrease (9). This increases the pulse pressure (the difference between SBP and DBP) with advancing age on a global scale, reflecting increased stiffening of the aorta (8).

In pre-industrial countries, the average BP levels were consistently around 115/75 mmHg, which indicates the typical or ideal BP for humans, with minimal changes across different age groups (10). In modern societies, systolic BP levels tend to increase steadily with age in both men and women. This trend can be attributed to age serving as a proxy for the probability and duration of exposure to various environmental factors that elevate BP gradually over time. These factors include insufficient dietary potassium, excessive sodium intake, obesity, lack of physical activity, and alcohol consumption. Additionally, genetic predisposition and adverse intrauterine environments, such as pre-eclampsia or gestational hypertension, have a minor association with elevated BP levels in adulthood (11).

As societies become more economically developed, hypertension initially affects individuals with higher socioeconomic status. Still, in the later stages of economic development, the prevalence and impact of hypertension are more pronounced among those with lower socioeconomic status. This phenomenon is observed both between and within countries. Furthermore, the rate of change in hypertension prevalence from 2000 to 2010 has been notably faster than in earlier epidemiological transitions (12).

1.3 Classification and etiology

1.3.1 Primary hypertension

The most common type of hypertension is classified as primary or essential, which accounts for about 90-95% of cases of hypertension. Primary hypertension has no detectable cause and has multifactorial etiology, including genetic, epigenetic, and environmental factors (13).

Hypertension is influenced by many genes or gene combinations. Identifying variant genes contributing to hypertension development is complex due to the intermediary phenotypes

controlling BP, including kidney function, cardiovascular (CV) hemodynamics, the endocrine system, and neural activity. These phenotypes are also controlled by different mechanisms, including BP itself. There are, therefore, many genes that could participate in the development of hypertension (14). Nonetheless, it must be noted that identified genes (more than 100 of them) contribute to a relatively low increase in BP and cannot completely explain the genetic component of hypertension. The cause of this "missing heritability" paradox is still a matter of debate (15).

Environmental risk factors are evidently associated with the development of primary hypertension, including physical activity, diet, and alcohol consumption. Overweight and obesity in multiple epidemiological studies, like the Framingham Heart Study and Nurses Health Study, have shown a direct relationship between body mass index (BMI) and an increase in BP (16, 17). Sodium intake is associated with BP in cross-sectional, prospective, and migrant cohort studies and accounts for much of age-related hypertension (17). Potassium intake is inversely related in cross-sectional, prospective, and migrant cohort studies (17). Increased potassium intake amplifies sodium's effect on BP, and a lower sodium-to-potassium ratio is associated with lower BP (17). Studies have demonstrated an inverse relationship between high BP and physical fitness, where even small amounts of physical activity have been associated with a lower risk of hypertension. The presence of a direct relationship between alcohol consumption and increased BP has repeatedly been demonstrated in prospective and cross-sectional cohort studies (17).

1.3.2 Secondary hypertension

Secondary hypertension is defined as elevated BP secondary to an identifiable cause (18). The prevalence is low and conducting routine evaluations in every case of hypertension is neither cost-effective nor time-efficient. However, it's crucial to identify the cause and mechanism of secondary hypertension in selected patient groups. This not only guides toward appropriate treatment but can also lead to the complete resolution of hypertension and discontinuation of antihypertensive medications (19).

Up to 10% of adults with hypertension are found to have secondary hypertension, with prevalence varying by age. Prevalence is highest in children under 12, accounting for 70 to 85 percent, and adults over 65, accounting for around 17% (20). Secondary hypertension is less prevalent in patients aged 19-39, accounting for 10 to 15% percent (21).

Renal parenchymal disease is the leading cause of secondary hypertension overall. Including various renal disorders such as glomerulonephritis, interstitial renal parenchymal

disease, polycystic kidney disease, and diabetic nephropathy (22). Over half of patients with renal parenchymal disease have hypertension, and its occurrence rises as renal parenchymal disorders worsen (23). Hypertension exacerbates renal parenchymal disease progression, accelerating renal function decline and increasing the risk of end-stage renal diseases (24).

Hypertension due to renovascular disease is caused by stenosis of renal arteries, which can be both unilateral and bilateral (25). Fibromuscular hyperplasia is the cause of renal artery stenosis in the younger population, especially females, while the older population is found to have renal artery stenosis due to atherosclerosis (26). Other vascular disorders that can lead to hypertension are coarctation of the aorta, arteriovenous fistula, and vasculitis of medium or large-sized arteries (27).

Endocrine disorders with increased hormone secretion can also cause secondary hypertension. The common endocrine disorders responsible for secondary hypertension include Cushing's syndrome, pheochromocytoma and primary aldosteronism, which account for most endocrine hypertension cases (28). Thyroid disorders, primary hyperparathyroidism, congenital adrenal hyperplasia, and acromegaly are infrequent causes of secondary hypertension (29).

Drug-induced hypertension represents a substantial cause of secondary hypertension. Therefore, it is crucial to review patients' medication history. Non-steroidal anti-inflammatory drugs are the most common drugs associated with worsening of BP, because of their extensive use. Other drugs associated with drug-induced hypertension are sodium-containing antacids, cocaine, amphetamine, antidepressants (like TCA and SNRI), appetite suppressants, oral contraceptives, mineralocorticoids, nicotine alcohol and immunosuppressants like cyclosporine (30).

1.3.3 White coat hypertension

White coat hypertension (WCH), also known as isolated clinic hypertension, describes elevated BP measurements in a clinic or office and normal out-of-office BP in individuals who are not receiving antihypertensive treatment (31). WCH describes the difference between elevated office BP and lower home BP, which primarily reflects the heightened response to stress during clinical visits with healthcare professionals (32,33). However, additional factors are also probably involved, as indicated by the inconsistent correlation between office and out-of-office BP differences and the white-coat effect measured directly through beat-to-beat BP recording (34,35).

The prevalence varies between studies, but WCH affects approximately 30% of individuals attending hypertension clinics. It is more prevalent in older patients (>50% in very

old individuals), women, and nonsmokers (6). Prevalence decreases when office BP is based on repeated measurements, or when healthcare professionals are not involved in the measurement (36). The white-coat effect can be seen across all hypertension grades, but the prevalence is highest in grade 1 hypertension.

The academic discourse debates whether WCH should be recognized as a benign condition. Studies indicate that in comparison to persistent hypertension, WCH is associated with lower rates of hypertensive target organ damage (HMOD) and CV events (37). However, patients with WCH show enhanced adrenergic activity, a higher risk of asymptomatic HMOD, and an increased frequency of metabolic risk factors compared to true normotensives (38,39).

To confirm the diagnosis of WCH, repeated BP measurements both in and out of the office should be performed. Lifestyle changes to reduce CV risk and close monitoring are recommended. The impact of treatment with antihypertensive medication in lowering out-of-office BP remains variable (40,41). The decision to initiate drug treatment in WCH patients remains unresolved, although they constitute a significant portion of trials demonstrating the benefits of antihypertensive therapy (42).

1.3.4 Masked hypertension

Masked hypertension (MH) refers to untreated patients with normal office BP readings and elevated out-of-office BP (43). Out of all the hypertensive patients attending hypertension clinics, around 10-20% have MH, with significant prevalence in population-based studies, especially among African American and Asian individuals (43-45).

The optimal approach for MH detection does not exist since it is impractical to screen all individuals with normal office BP. Individuals with a high-normal office BP measurement have a higher probability of MH. MH is more common in men, younger people, alcoholics, physically active individuals, and smokers (46,47). Chronic kidney disease (CKD), diabetes, low levels of HDL cholesterol, obesity, and a family history of hypertension are also associated with increased MH prevalence (46).

MH is associated with an increased risk of HMOD, including left ventricular hypertrophy, reduced kidney function, stiffness of large arteries, and thickness of carotid intima-media (48-51). Recent studies indicate that MH carries a substantially greater risk of CV events compared to normotension, like or slightly lower than sustained hypertension (43,52-54).

Confirmation of an MH diagnosis requires at least a second set of BP measurements both in and out of the office. The efficacy of antihypertensive therapy on MH remains unknown

due to the absence of RCT. Lifestyle modifications and follow-up controls are recommended for patients with confirmed MH. In patients with increased CV risk antihypertensive medication should be considered.

1.4 Pathophysiology of hypertension

1.4.2 Intravascular volume

Kidneys are both the cause and target of hypertension; they can cause hypertension by decreased excretion of sodium, SNS overactivity, and excessive renin secretion (55). Sodium is predominantly found in extracellular space and is the main determinant of extracellular fluid regulation (56). The effect of sodium on BP is achieved in combination with chloride, while non-chloride sodium salts have little or no effect on BP. When kidney excretion of sodium can't match up with NaCl intake, the sodium concentration promotes water retention, increasing vascular volume and BP (57).

Sodium can activate several endocrine/paracrine, neural, and vascular mechanisms that can increase arterial pressure, leading to higher urinary sodium excretion to maintain sodium balance. This process, known as "pressure-natriuresis," involves a reduced tubular absorption capacity, increased glomerular filtration rate, and hormonal influences like atrial natriuretic factor (58). Individuals with impaired sodium excretion need a more significant increase in arterial pressure to achieve natriuresis (56).

Hypertension dependent on NaCl may be the outcome of poor renal excretion capacity, either caused by increased mineralocorticoids resulting in higher sodium reabsorption in renal tubules or intrinsic renal disease (59). End-stage renal disease (ESRD) is a severe example of volume-dependent hypertension. Approximately 80% of these individuals can effectively manage vascular volume and hypertension through adequate dialysis. For the remaining 20%, hypertension results from heightened renin-angiotensin-aldosterone system (RAAS) activity, potentially alleviated by pharmacological inhibition of RAAS (56).

1.4.1 Autonomic nervous system

Adrenergic reflexes control short-term BP, while adrenergic function, hormones, and volume regulate long-term arterial pressure. Epinephrine, norepinephrine, and dopamine are essential in CV regulation (56).

Adrenergic receptors are mediated by guanosine nucleotide-binding receptor proteins and intracellular second messengers, affecting their responsiveness to catecholamines (60). Adrenergic receptors are divided into α and β types based on their pharmacology and

physiology and further differentiated into α1, α2, β1, and β2 receptors. α1 receptors induce vasoconstriction and are located in postsynaptic cells in smooth muscles (61). α1 receptor activation in the kidney increases tubular sodium reabsorption. α2 receptors are located on the presynaptic side of postganglionic nerve endings. The catecholamines activate α2 receptors, acting as negative feedback controllers by inhibiting norepinephrine release. β1 receptors are localized in the myocardial wall, and activating these receptors stimulates strength and rate of myocardial contraction. The activation of these receptors also stimulates renin release. β2 receptors are responsible for smooth muscle relaxation and vasodilatation (56).

Circulating catecholamine levels can impact the amount of tissue adrenoreceptors. Downregulation can be due to sustained catecholamine levels, which explains reduced responsiveness, such as orthostatic hypotension in pheochromocytoma patients (62). On the other hand, chronic reduction in neurotransmitter levels can increase adrenoreceptor numbers, enhancing responsiveness. Adrenergic receptor blockers may cause upregulation, resulting in temporary hypersensitivity upon withdrawal (56). Abrupt withdrawal of antihypertensive drugs, like clonidine, can lead to rebound hypertension due to α1 receptor upregulation (63).

Arterial baroreceptors, which are located in the aortic arch and the carotid sinus, are stimulated by stretch in the arterial wall, and the firing of these receptors increases with an elevation of arterial BP (64). The baroreceptors then stimulate a decrease in sympathetic outflow, which then decreases HR and arterial pressure. Over time, these baroreflexes adapt to the higher arterial pressure and get a new standard of normal pressure. The baroreflex control of arterial pressure declines with sustained hypertension over time, advanced age, and atherosclerosis (56).

Based on postganglionic nerve activity recordings with microelectrodes inserted into the peroneal nerve in the leg, sympathetic outflow seems to be generally higher in hypertensive individuals than in normotensive individuals (65). Sympathetic nervous system blockers are potent antihypertensive agents, suggesting their role in maintaining elevated arterial pressure (56).

Pheochromocytoma is a clear example of excessive catecholamine production from a tumor, which causes hypertension. Surgical tumor removal or medications like α1 receptor antagonists can lower BP (56).

1.4.3 Renin-angiotensin-aldosterone system

The RAAS affects BP regulation, with several effects, including pressure natriuresis, sodium retention, salt sensitivity, endothelial dysfunction, and vasoconstriction, contributing

significantly to the pathogenesis of hypertension (66). The RAAS is found in many organs, but the primary role is maintaining pressure-volume balance in the kidney, where it suppresses perfusion in volume-expanded conditions and sustains perfusion in volume-depleted states.

Renin, an aspartyl protease, and its precursor, prorenin, are enzymatically synthesized and stored in renal juxtaglomerular cells. Most circulatory renin is primarily synthesized in the afferent renal arteriole (67). Prorenin can be directly released into the bloodstream or activated within secretory cells before being secreted as active renin. Three primary factors influence renin secretion: decreased NaCl transport in the distal thick ascending limb of the loop of Henle, reduced stretch or pressure in the renal afferent arteriole, and SNS stimulation via β1 adrenoreceptors (68).

When released into the circulation, active renin cleaves angiotensinogen into an inactive decapeptide, angiotensin I. The inactive decapeptide is then cleaved into the active octapeptide, angiotensin II, by the angiotensin-converting enzyme (ACE), which is primarily located in the pulmonary circulation but not exclusively (69). ACE also cleaves other peptides, including the vasodilator bradykinin, which it inactivates. Angiotensin II primarily acts through angiotensin II type 1 receptors (AT1R) to act as a potent vasopressor, stimulate aldosterone secretion from the adrenal zona glomerulosa, and promote CV remodeling by utilizing various signal transduction cascades. The angiotensin II type 2 receptor (AT2R) conversely instigates vasodilation, enhances sodium excretion, and inhibits matrix formation and cell growth. AT1R blockade leads to increased AT2R activity (56).

Clear examples of renin-dependent hypertension are renin-secreting tumors. In the kidney, these tumors include Wilms tumor and, more commonly, benign hemangiopericytomas of the juxtaglomerular apparatus (70). Renin-producing carcinomas have also been observed in the adrenal glands, lung, pancreas, liver, and colon. Renovascular hypertension is another form of hypertension mediated by renin. Another renin-mediated form of hypertension is when there is obstruction of the renal artery, which reduces renal perfusion pressure, thereby increasing renin secretion. Over time, this hypertension may become less dependent on renin, possibly a consequence of secondary renal damage (56).

Not all cases of increased RAAS activity are associated with hypertension. The body may maintain arterial pressure and volume balance through heightened activity in this axis when faced with a low-sodium diet or volume contraction (56).

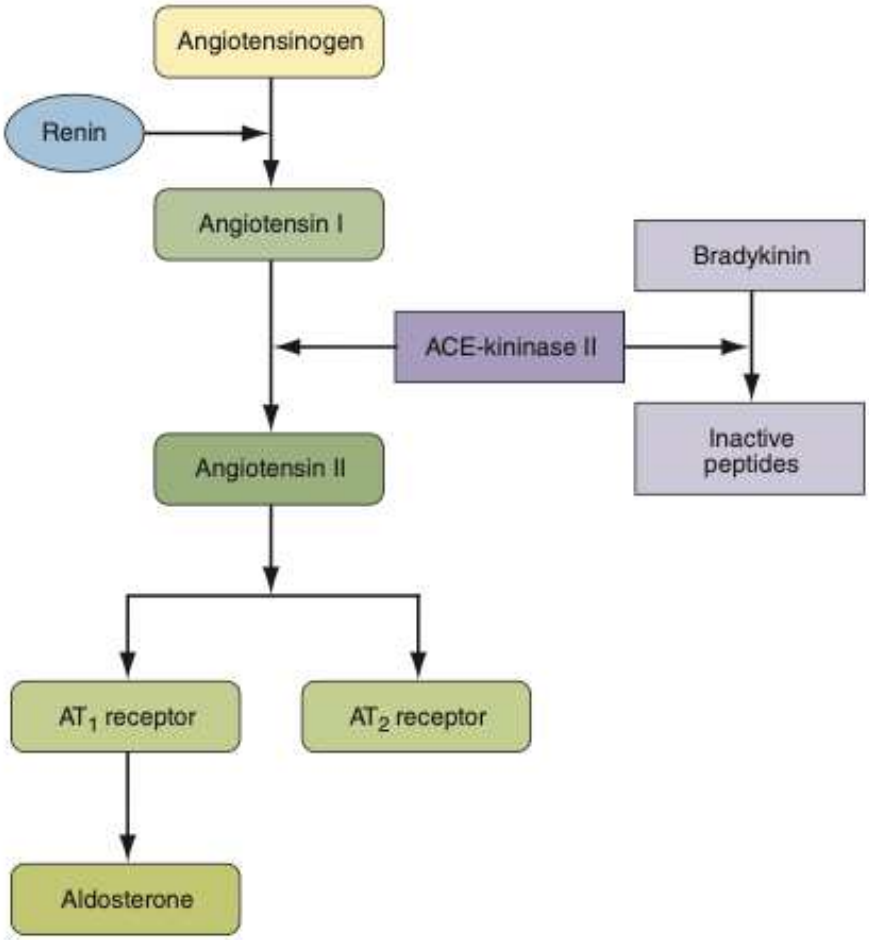

Figure 1 Renin-angiotensin-aldosterone axis. AT1 receptor: angiotensin 1 receptor. AT2 receptor: angiotensin 2 receptor. ACE kininase 2: angiotensin converting enzyme kininase 2. Source: Harrison TR, Resnick WR, Wintrobe MM. Harrison's principles of Internal Medicine. 21. edition. London: McGraw-Hill; 2022.

1.4.4 Natriuretic peptides

Brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) play crucial roles in salt sensitivity and hypertension. These peptides exhibit potent vasodilatory and natriuretic effects that are crucial for maintaining sodium balance and BP regulation during sodium loading (71,72). Stretching of ventricular and atrial walls triggers the release of BNP and ANP, resulting in systemic vasodilation and reduced plasma volume, which lowers the BP (73). Natriuretic peptides increase GFR by vasoconstriction of efferent arterioles in volume-expanded states and inhibit renal sodium reabsorption with both indirect and direct effects. Indirectly by inhibition of aldosterone release, and directly by decreasing the activity of Na+/K+-ATPase and the sodium-glucose cotransporter in the proximal tubule (72).

Natriuretic peptide deficiency contributes to hypertension. The atrial natriuretic peptide-converting enzyme, known as Corin, is mainly found in the heart, and it converts the ANP and BNP precursors into their active forms. Deficiency of Corin is associated with salt-sensitive hypertension, CHF, diabetes mellitus (DM), and volume overload (74). Natriuretic peptides possess therapeutic potential for various conditions that collectively increase the risk of DM and CVD (75).

1.4.5 Endothelium of blood vessels

The endothelium is crucial in the regulation of vascular tone and salt sensitivity through nitric oxide (NO) signal transduction pathways (76). Endothelial cells continuously release NO in response to flow-induced shear stress, which activates guanylate cyclase and intracellular cyclic GMP, leading to vascular relaxation (77). The inhibition of endothelial NO synthase interrupts NO synthesis, leading to elevated BP in humans and animals (78).

Endothelin 1 (ET1) is a potent vasoconstrictor that acts primarily on ETA receptors in vascular smooth muscle cells (79). Endothelial cells secrete other vaso-regulatory substances, including vasoconstrictors, such as prostaglandin A2, angiotensin 2, thromboxane A2, and vasodilators, such as prostacyclin. Other substances have vasodilating properties, such as Glucagon-like peptide 1 (GLP1), substance P, adrenomedullin, and calcitonin gene-related substances (80-82). Together with ET1 and NO, all these substances establish the endothelial effect on vascular tone and BP (79, 82-84).

Endothelial dysfunction is an essential component in the pathogenesis of hypertension. The children of parents with hypertension often exhibit compromised endothelium-dependent vasodilation, suggesting a genetic influence on endothelial dysfunction (85). In persistent hypertension, endothelial dysfunction is associated with both heightened oxidative stress and direct pressure-induced damage. Various enzyme systems generate reactive oxygen species, such as xanthine oxidase, NADPH oxidase, cyclooxygenase, and superoxide dismutase (85,86). NO bioavailability is reduced by the binding of superoxide anions, and this is a crucial factor that connects oxidative stress to hypertension and endothelial dysfunction (85). NADPH oxidase plays an essential role in the creation of oxidative stress, and several factors increase NADPH oxidase activity, such as ET1, angiotensin 2, noradrenaline, uric acid, tobacco smoking, and free fatty acids (83).

1.5 Hypertension-mediated organ damage (HMOD)

1.5.1 HMOD in the CV system

The most common cause of death in patients with hypertension is CVD (56). The heart is directly exposed to increased load in hypertension, leading to functional and structural modifications that in the initial phase are asymptomatic, but in the later phases are strong risk factors for subsequent CV events, such as atherosclerotic coronary artery disease, left ventricular hypertrophy, congestive heart failure (CHF), increased atrial size, different cardiac arrhythmias, and sudden death (6). In clinical settings, a comprehensive evaluation utilizing electrocardiography (ECG) and available imaging modalities is essential to assess all parameters indicative of hypertensive heart disease (6). Therapeutic management of hypertension, both pharmacological and non-pharmacological, can significantly decrease the risk of CV events (56).

In hypertensive patients, diastolic dysfunction is common, and about one-third of patients with CHF have an abnormal diastolic function but normal systolic function. Diastolic dysfunction is exacerbated by left ventricular hypertrophy and is most accurately assessed by cardiac catheterization (87). There are several noninvasive alternatives, such as transthoracic echocardiography and transesophageal echocardiography (56).

1.5.2 HMOD in the kidneys

After diabetes, hypertension is the most significant cause of CKD (6). The risk of kidney damage appears to have a stronger correlation with systolic than diastolic BP. Additionally, black men have a higher risk of developing ESRD at any degree of hypertension than white men (56).

Atherosclerotic vascular lesions associated with hypertension predominantly alter preglomerular arterioles, leading to ischemic changes in glomerular and postglomerular structures (56). Glomerular hyperperfusion can also result in direct damage to the glomerular capillaries. Progression in renal injury reduces autoregulation of blood flow, which means that the defense mechanism against renal damage gets weaker, and renal damage progresses faster (88). This can create a harmful cycle of renal damage, increased glomerular filtration, worsening hypertension, loss of nephrons, and further renal injury (56).

Renal function deterioration can be discovered through routine laboratory assessments, which estimate the glomerular filtration rate (GFR) according to serum creatinine levels (89). Serum creatinine is not sensitive enough to estimate renal impairment, as a substantial decrease in renal function may manifest before the elevation of serum creatinine levels. The classification

of CKD is based on eGFR, determined by the 2009 CKD-Epidemiology Collaboration formula, and the level of albuminuria (89,90,91). Preferably early in the morning, spot urine samples are used to measure the albumin: creatinine ratio (ACR). Based on albuminuria and reduced renal function, HMOD in the kidney can be diagnosed. Albuminuria may not be detectable in hypertension-induced kidney disease until GFR reduction has occurred (89).

1.5.3 HMOD in the brain

Elevated BP is a significant contributing factor to acute cerebrovascular events, including intracranial hemorrhage, transient ischemic attack (TIA), and ischemic stroke. Persistent arterial hypertension exerts an accumulative impact on cerebrovascular damage, such as white matter lesions, microbleeds, microinfarcts, atherosclerosis, silent cerebral infarcts, and cerebral atrophy (92).

Hypertension induces pathological changes in cerebral microvessels that impair their structure, function, and network architecture, leading to cerebral microbleeds and lacunar infarctions in the deep white matter, pons, and basal ganglia. It is presumed that they originate from the occlusion of the single small arteries that supply blood to subcortical regions of the brain. Hypertension is also associated with white matter lesions characterized by abnormal myelination, related to an elevated risk of cerebral stroke and cognitive impairment, including dementia (93,94).

Cerebral blood flow remains constant across a broad spectrum of arterial pressures (the mean arterial pressure ranges from 50 to 150 mmHg) due to the process known as autoregulation of blood flow. In individuals with malignant hypertension, the failure of autoregulation at the upper-pressure limit leads to vasodilation and excessive blood flow, resulting in encephalopathy (56). Typical symptoms are nausea and vomiting (often forceful), intense headaches, changes in mental status, and focal neurological signs. Untreated, hypertensive encephalopathy can rapidly progress to seizures, coma, and death within a few hours. It's crucial to differentiate hypertensive encephalopathy from other neurological conditions associated with hypertension, such as hemorrhagic or thrombotic stroke, cerebral ischemia, seizure disorders, pseudotumor cerebri, mass lesions, meningitis, delirium tremens, acute intermittent porphyria, uremic encephalopathy, and traumatic or chemical brain injury (56).

1.5.4 HMOD in the eye

Hypertensive retinopathy is classified according to fundoscopy, which detects moderate to severe retinal lesions such as microaneurysms, hemorrhages, papilledema, macula edema, and cotton wool spots (95). Milder retinal damage, such as general or focal arteriolar narrowing and arteriovenous nicking, has less predictive value and is less specific compared to the more severe retinal lesions (96). Hypertension is also a significant risk factor for ischemic optic neuropathy and occlusion of retinal arteries and veins (97).

1.6 BP measurement and monitoring

1.6.1 Standard office BP measurement

Standard or conventional office BP measurement (OBPM) is the most researched method for evaluating BP and is the most used method for the establishment of diagnosis, BP thresholds, BP classifications, CV risk factors, therapeutic interventions, and management (2,98,99). Despite its prevalent usage, the use of OBPM occasionally leads to overestimation of BP, overdiagnosis, and unnecessary treatment (2,98,100).

The BP monitor's cuff should be placed on a bare arm. Suitable cuff size is crucial for precise BP measurement, and needs to be chosen according to the circumference of the individual’s arm. A cuff that is bigger than necessary often underestimates BP, whereas a smaller cuff overestimates it (101). A validated electronic wrist-cuff device may be used if BP cannot be measured using an upper arm cuff device, but as it yields less accurate results, its use is not advocated (98).

Hypertension diagnosis should not be based on one single office visit but at least two separate visits with a minimum of two positive readings each time, except for patients at high risk based on the existence of CVD or HMOD and patients with BP that suggests grade 3 hypertension (180/110 mmHg) (98,102). In elderly patients (>65 years of age), patients with diabetes, treated hypertensive patients, patients with signs that point to postural hypotension, or patients with neurodegenerative disorders, BP should be monitored 1 and 3 minutes after reaching an upright position for detection of orthostatic hypotension (98). During the initial office visit, BP measurement should be measured in both arms, preferably with electronic devices capable of simultaneous measurement. An SBP difference between the arms of >10 mmHg must be confirmed by repeated measurements, and if the difference is confirmed, the following measurements should be taken on the arm with the higher BP, as it more accurately reflects arterial BP (103). Furthermore, a persistent SBP difference between arms exceeding 15 to 20 mmHg may indicate atherosclerosis and should be further investigated (104).

Unattended office BP measurement is performed automatically when the patient is alone in the examination room without any healthcare personnel present (105). Available data show that this quiet environment and the absence of variable response to medical personnel or the white coat effect, lead to reduced BP compared to standard OBPM (104,106,107). However, this method of monitoring is not so well researched compared to standard OBPM, and this method is more time-consuming, which can be difficult to accommodate due to the large number of patients (104). Considering these factors, the most practical and reasonable recommendation for BP measurement in clinical practice seems to be standard attended OBPM (6).

1.6.2 Home blood pressure monitoring (HBPM)

HBPM allows patients to measure their BP in their usual environment, away from the office. HBPM has a fairly low cost, which is most often covered by patients themselves and is well accepted for long-term use (108). Compared to office measurements, HBPM data are more reproducible and offer better predictions for various health outcomes, such as CV events, HMOD, and mortality (109-112).

HBPM should be performed following an established protocol using automated upper arm cuff devices (108). Preferably, devices equipped with automated storage that calculates the average and have the possibility to connect with PCs, mobile phones, or some other way of data transfer so it easily can be evaluated by the physician (108). It is important that the patients are informed about correct measurement conditions and posture, which are like those outlined for OBPM (108). The white-coat effect is absent or almost absent in HBPM on most individuals, so the readings are generally lower than in OBPM, so the diagnosis threshold for hypertension in HBPM is defined as ≥135/85 mmHg, corresponding to an office BP of ≥140/90 mmHg. (113,114, Figure 2).

BP values measured at home should be collected ahead of planned office visits or when substantial changes in BP are assumed. BP should be optimally measured for 7 days, and never less than 3 days. Two measurements about 1 minute apart in the morning (before taking medication, if applicable) and two measurements in the evening (108,115,116). HBPM enhances the persistence of BP control over extended periods of treatment (117).

HBPM has its limitations, such as the need for patient training, the frequent use of inaccurate devices, and the potential to induce anxiety, leading to excessive measurements and subsequent patient-initiated treatment adjustments (108). The lack of studies on HBPM-guided treatment and outcomes is one of the most important limitations of this monitoring technique.

1.6.3 Ambulatory blood pressure monitoring (ABPM)

ABPM is a BP monitoring method that includes multiple readings taken using a fully automated device on a continuous basis for 24 hours in conditions reflecting daily activities and sleep. During ABPM, patients are instructed to write down their symptoms, activities, medication intake times, meals, and sleep times (98).

In similarity to HBPM, it has an advantage over OBPM with a better prediction for various health outcomes, such as CV events, HMOD, and mortality, and the ability to identify MH and WCH (118-120). Additionally, an important advantage of ABPM is the measurement of the dipping status, which is the magnitude of nocturnal changes in BP, that has significant clinical relevance because night BP values have been found to predict events more accurately than daytime BP values (121,122). However, ABPM is not widely available in general practice settings, it is relatively expensive, unsuitable for frequent use, and may cause discomfort for patients (98).

As in HBPM, the white coat effect is absent, and the ambulatory BP values are generally lower compared to the office BP values. The diagnostic threshold for hypertension diagnosis is defined as ≥130/80 mmHg over 24 hours, with an awake mean of ≥130/80 mmHg and a mean during sleep time of ≥120/70 mmHg (6, figure 2).

Table 2. Definitions of hypertension according to the correspondence of home and ambulatory BP values with office BP.

Method	**Systolic(mmHg)**		**Diastolic(mmHg)**
Office BP	≥ 140	and/or	≥ 90
Ambulatory BP			
Awake mean	≥ 135	and/or	≥ 85
Asleep mean	≥ 120	and/or	≥ 70
24h mean	≥ 130	and/or	≥ 80
Home BP mean	≥ 135	and/or	≥ 85

BP: blood pressure. Source: Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension. Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). 2024:1;42(1):194.

1.7 Management of hypertension

1.7.1 Nonpharmacological treatment

Lifestyle modifications are advised for all individuals with hypertension. The most efficient interventions include physical exercise, weight loss, and dietary changes. These modifications are proven to lower systolic BP and are especially recommended for patients with hypertension and obesity (123).

1.7.1.1 Physical activity

Clinical trials conducted with hypertensive patients revealed that consistent endurance training, ranging from moderate to high intensity, led to an average reduction in BP of 11/5 mmHg (124). Workouts that were completed at least thrice weekly, lasting 40-60 minutes, had the best effects on BP (124). Studies with isometric exercise demonstrated reduced BP comparable to that of aerobic exercise. Additionally, a meta-analysis of 64 controlled studies has shown a reduction of BP with dynamic resistance training that is more significant or similar to aerobic exercise (125).

1.7.1.2 Weight loss

Excess body fat typically increases BP in individuals predisposed to hypertension. Obese hypertensive patients require higher amounts of antihypertensive medications to regulate their BP effectively and are at an increased risk of developing resistance to such treatments (126). A meta-analysis revealed that any form of weight loss results in an average reduction of 2.7 mmHg in SBP and 1.3 mmHg in DBP (127). Physical exercise and hypocaloric diets are recommended for all patients with hypertension and obesity. Although weight reduction is typically observed, the extent of weight loss tends to be minimal, and many patients subsequently experience weight regain. (128).

1.7.1.3 Reduced salt intake

To maintain metabolic balance, salt intake should match the amount lost, with 5g per day being sufficient under normal conditions, as recommended by the WHO (129). However, most countries have a daily dietary salt intake of about 9-12g. The American Heart Association suggests an even lower intake of 2.3g daily, while the European Society of Cardiology and the European Society of Hypertension recommend 5-6g daily (130, 6). Research, including randomized controlled trials, has shown that reducing sodium intake lowers BP, especially in those with hypertension (131). The DASH-sodium trial demonstrated significant BP reductions

with lower sodium intake, mainly when initial intake was below 2.3g daily (132). Sodium reduction benefits individuals with and without hypertension and can prevent the development of hypertension, improve the control of existing hypertension, and potentially reduce the need for medication (133, 134). Evidence strongly supports recommendations to reduce salt intake (135,136). Since over 75% of dietary salt comes from processed foods, successful reduction strategies must involve collaboration with food manufacturers and restaurants. Japan, Finland, and the United Kingdom have significantly reduced population salt intake (137).

1.7.1.4 Increased potassium intake

A daily potassium intake of 4.7 grams is average for healthy individuals with normal kidney function, and higher levels generally are not associated with a greater risk since individuals with healthy kidneys can efficiently excrete excess potassium. Increased levels of potassium intake have been shown to decrease BP in individuals with both high and low baseline potassium intake (138, 139).

The impact of potassium on BP is influenced by salt intake, with more significant reductions observed when potassium intake is increased alongside lower salt consumption (140). Therefore, the optimal approach is increasing potassium and decreasing sodium intake (141).

The best way to boost potassium levels is by eating more potassium-rich vegetables and fruits rather than relying on supplements. Keeping potassium intake below 4.7 grams daily is recommended for those with impaired kidney function (142).

1.7.2 Pharmacological treatment

Over the past several decades, antihypertensive pharmacotherapy has advanced significantly due to the creation of various classes of antihypertensive drugs and extensive outcome trials demonstrating their positive effects on CVD (143). Medical practitioners now have access to a wide range of antihypertensive medications from multiple drug categories, as well as numerous fixed-dose combinations.

1.7.2.1 Blockers of the renin-angiotensin-aldosterone system

Among RAAS inhibitors, angiotensin II receptor blockers (ARBs) and ACE inhibitors are considered first-line treatments for hypertension. Other RAAS-targeting drugs, like antagonists of mineralocorticoid receptors and direct renin inhibitors, are typically reserved for secondary use due to limited clinical evidence substantiating their efficacy as primary

treatments (123). ARBs and ACE inhibitors have been comprehensively studied in extensive hypertension trials (144).

Both classes have shown improved outcomes in patients with diabetic nephropathy or heart failure with reduced ejection fraction (HFrEF), making them excellent choices for these conditions. ARBs and ACE inhibitors are similarly effective in reducing CVD risk (145). They may improve glucose metabolism, making them suitable for younger patients and those at risk for type 2 DM, including those with metabolic syndrome (146).

ACE inhibitors are usually tolerated well and only need to be taken once daily, but they can cause reduced renal function, cough, hyperkalemia, and angioedema. The risk of angioedema is significantly higher in Black individuals and in patients using both DPP-4 inhibitors and ACE inhibitors (147, 148). ARBs can also cause kidney function deterioration and hyperkalemia but usually do not cause angioedema or cough.

1.7.2.2 Calcium-channel blockers

Calcium channel blockers (CCBs) are a class of drugs widely used for hypertension management, with two main categories: vascular-selective dihydropyridine (DHP) and non-dihydropyridine (non-DHP) calcium channel blockers.

CCBs exert their effect by binding and blocking L-channels in cardiac and vascular smooth muscle cells. DHP-CCBs, like amlodipine, primarily cause vasodilation, decreasing peripheral resistance and reducing BP (123).

There are differences between non-DHP- and DHP-CCBs regarding side effects and tolerability. While DHP-CCBs are used to control elevated BP in patients with HFrEF, caution is warranted due to their negative inotropic effect (6). Peripheral edema is a frequent side effect observed in patients taking DHP-CCBs, caused by peripheral vasodilation rather than reduced renal function or CHF. One advantage of DHP-CCBs is their compatibility with all first-line hypertension medications, and they exhibit a low potential for drug interactions (123).

Non-DHP-CCBs such as diltiazem and verapamil primarily target the heart but also contribute to lowering BP (6). Their inhibition of cardiac calcium channels reduces heart rate and cardiac contractility (149). Consequently, due to this negative inotropic effect, non-DHP-CCBs are not recommended for use in patients with HFrEF (6).

Meta-analysis comparing DHP-CCBs and non-DHP-CCBs with other medications has shown no significant differences in effectiveness (150). It is important to note that all CCBs can potentially cause or exacerbate constipation, particularly in older individuals (151). Additionally, both DHP-CCBs and non-DHP-CCBs inhibit the metabolizing enzyme

cytochrome P450 3A4, raising the possibility of drug-drug interaction that may compromise the safety and tolerability of other medications (152).

1.7.2.3 Diuretics

Thiazide and thiazide-like diuretics are the most used diuretics in hypertension management, and the difference lies in their chemical structure. Thiazide-type agent, such as hydrochlorothiazide, contains a benzothiadiazine ring whereas thiazide-like diuretics, such as chlorthalidone, indapamide, do not possess this ring (123). Regardless of the chemical structure, both function by inhibiting the sodium-chloride co-transporter in renal tubules. Both subclasses have been critical components of pharmacological antihypertensive treatment since the initial trials demonstrated the morbidity benefits of antihypertensive therapeutics (153).

Randomized controlled trials (RCTs) and meta-analyses (154-157) have consistently demonstrated the effectiveness of thiazide and thiazide-like diuretics in reducing CV morbidity and mortality. Thiazide-like diuretics, such as chlorthalidone and indapamide, are more potent drugs and have a longer duration of action than thiazide-type diuretic hydrochlorothiazide. However, some studies have indicated that chlortalidone may have a broader side-effect profile (6).

The diuretic doses have been significantly reduced over the years to achieve an improved risk-benefit profile for diuretics. Thiazide and thiazide-like diuretics can worsen glucose metabolism and, by that, increase the risk of DM. The impact of this metabolic action on long-term CVD risk remains uncertain (158). Thiazide and thiazide-like diuretics also promote natriuresis, and drug-related electrolyte disturbances are consequential adverse effects. Hyponatremia may result in confusion, seizures, and coma, posing life-threatening risks for older patients. Meanwhile, hypokalemia can induce muscle weakness and cardiac arrhythmias (123).

Thiazide and thiazide-like diuretics are considered less effective for hypertension in patients with reduced kidney function. Therefore, while loop diuretics, such as furosemide and bumetanide, are typically not recommended for uncomplicated hypertension, they are the option of choice for patients with CKD stages 4 and 5, and for those with severe fluid overload or retention, such as in CHF or nephrotic syndrome (6).

Potassium-sparing diuretics, such as amiloride, directly inhibit epithelial sodium channels on the luminal side of the late distal tubule and collecting duct. Potassium-sparing diuretic are used in edematous states and combined with loop diuretics or thiazide and thiazide-like diuretics to treat hypertension or CHF (6).

1.7.2.4 Beta-blockers

Beta-blockers (BBs) can lead to a reduction in BP by affecting various physiological pathways, including slowing heart rate, decreasing cardiac output, reducing sympathetic nervous system activity, and inhibiting renin release (159). BBs show several pharmacological differences across generations. Randomized controlled trials and meta-analyses have consistently demonstrated the efficacy of both first- and second-generation BBs, such as propranolol, atenolol, and metoprolol, in mitigating the risk of stroke, CHF, and significant CV outcomes in patients with hypertension (6).

Second-generation BBs are characterized by their beta1-selectivity and exhibit direct vasodilating properties. Third-generation BBs, exemplified by carvedilol and nebivolol, also demonstrate a direct vasodilating effect. Despite their vasodilating effect, BBs are primarily recommended in the treatment of specific indications such as CHF, atrial fibrillation, for young hypertensive women of childbearing age, as well as in hypertensive emergencies (160,161).

However, compared to other first-line antihypertensive medications, BBs are considered less effective (162). They are not typically initiated as initial therapy for uncomplicated essential hypertension due to the absence of evidence indicating a reduction in hypertension-related mortality (163).

Beta-blockers may induce bronchial obstruction in asthmatics. Additionally, BBs should not be administered concomitantly with non-DHP CCBs, which similarly reduce sinus node rate (123). Furthermore, BBs have been associated with an increased risk of new-onset DM, particularly in those with metabolic syndrome (6).

1.8 Sleep quality and hypertension

Healthcare research on sleep quality has become a substantial point of interest (164). Sleep disturbance can be a significant symptom of multiple causes, such as obstructive sleep apnea (OSA), and unhealthy sleep behaviors, such as short sleep duration. Among adults in the US, more than one-third sleep less than 7 hours per night, which is the minimum recommendation (165,166). Over 62% of shift workers, who make up 25% of workers in the US, sleep less than 7 hours per day (167,168). The prevalence of OSA is approximately 26% in adults aged 30 to 70 years, and the incidence rates vary according to sex, age, and BMI (169,170).

OSA, shift work, and short sleep duration are all associated with an increased risk of hypertension (171,172). Although evidence connects short sleep and shift work to hypertension,

they are not included as risk factors in hypertension guidelines, and their underlying mechanisms remain unclear, while OSA is considered a secondary cause of hypertension (173).

Strong epidemiological evidence from a 2016 American Heart Association scientific statement concluded that short sleep duration (≤5, ≤6, or ≤7 hours) increases the risk of hypertension (174). Intervention studies assessing repeated sleep restriction and sleep deprivation demonstrate that prolonged mild sleep restriction leads to higher BP over time, independent of psychological stressors (175).

Shift work has been linked with CVD mortality and morbidity (176). Multiple studies have provided evidence supporting the hypothesis that shift work raises the risk of hypertension (177-180). A meta-analysis conducted in 2017 revealed a 31% higher likelihood of hypertension in cohort studies and a 10% greater probability of hypertension in cross-sectional studies among shift workers (181). A cohort study from 2019 involving workers in manufacturing facilities assessed the occurrence of hypertension in people working shifts and revealed that workers who worked mostly night shifts and frequent rotations faced a four-fold higher risk of hypertension compared to those not working night shifts (180)

Sex and ethnic differences are also essential to consider in risk evaluation. Women may be more susceptible, especially in young adulthood. A meta-analysis showed that women who sleep ≤5 or ≤6 hours have a 36% higher risk of hypertension (182). Another meta-analysis showed a 68% increased risk of hypertension in women sleeping ≤5 hours compared to women sleeping ≤7 hours, and no results for men were observed (182). However, the Spanish Vitoria sleep cohort, including over 1000 individuals between 30 and 70 years, showed that there were no differences in risk based on gender (183).

Studies such as the National Health Interview Survey indicate that white adults are 41% less likely than black adults to report inadequate sleep (184). Objective data from the Chicago Area Sleep Study shows that white adults sleep approximately 48 minutes more than black adults (185). Shift work also poses a greater hypertension risk for Black adults, with rotating night shifts associated with an 81% higher risk in studies like the Nurses' Health Study (186). Additionally, Black women working night shifts are more prone to exhibit abnormal BP patterns while sleeping compared to women of other racial backgrounds (182). Furthermore, racial and ethnic disparities exist in the association between hypertension and OSA as well, demonstrated in the 2007-2008 National Health and Nutrition Examination Survey, in which OSA was associated with increased likelihood of hypertension among Whites and Hispanics, but not Blacks (187).

1.8.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) represents the most prevalent sleep-related breathing disorder, characterized by upper airway obstruction due to pharyngeal muscle collapse during sleep, resulting in hypopnea or apnea events (188). OSA is associated with reduced oxygen saturation during sleep, sleep disruption, and sleepiness during daytime, and significantly impacts overall quality of life (189-191). OSA is not only a sleep disorder, but it is also associated with multiple serious conditions such as hypertension, diabetes, stroke, coronary artery disease and overall increased mortality rate (192).

OSA and inadequate sleep duration exerts pathophysiological effects on the CV system and may increase the risk of hypertension through various physiological mechanisms, such as hormonal imbalance, disturbed autonomic balance, chronic intermittent hypoxia, inflammation, and oxidative stress collectively leading to vascular endothelial dysfunction followed by hypertension (193-195).

A meta-analysis from 2018 comprising 26 studies indicated that OSA correlates with an approximately threefold increase in the likelihood of resistant hypertension. Moreover, mild, moderate, and severe OSA were linked to an 18%, 32%, and 56% higher risk of hypertension, respectively (196). Additionally, hypertensive patients with OSA are at increased risk of progressing into resistant hypertension, characterized by hypertension, despite concurrent use of three different antihypertensive classes (195).

The severity of obstructive sleep apnea is typically classified by the number of sleep-related obstructive breathing events, and the most used is Apnea-Hypopnea Index (AHI) (197). Higher AHI indicates greater OSA severity and correlates with higher morning and evening BP (182).

In a 2019 meta-analysis involving 1562 patients with obstructive sleep apnea, 59.1% were found to have had non-dripping BP (198). Comparatively, patients with OSA had a 47% higher odds of non-dipping BP than controls, while moderate to severe OSA was associated with 67% increased odds of experiencing non-dipping BP (199).

In a clinical study of 100 patients with hypertension revealed that 10.5% of dippers and 43.5% of non-dippers had an AHI ≥15, indicating moderate to severe OSA (200). AHI was found to predict the presence of OSA among patients with non-dipping BP (201).

In the management of OSA, treatments such as continuous positive airway pressure (CPAP) and mandibular advancement devices (MAD) have been linked to decreased BP, potentially reducing the risk of CVD (202,203).

2. OBJECTIVES

The study's main aim was to analyze if there is a difference in daytime sleepiness and sleep quality between patients with primary hypertension and healthy controls.

In addition, we aimed to evaluate if there is a potential correlation between poorer sleep quality and higher mean arterial pressure (MAP) among hypertensive patients.

Hypotheses

1. Epworth sleepiness scale (ESS) will be slightly higher among patients with primary hypertension than healthy controls.
2. Pittsburgh Sleep Quality Index (PSQI) will also be slightly higher in patients with primary hypertension than in healthy controls.
3. Patients with primary hypertension and at the highest tertile of PSQI will have a higher 24h MAP compared to patients with primary hypertension and with lower tertile of PSQI.

3. SUBJECTS AND METHODS

3.1 Study design

The present research was conducted as a cross-sectional study at the Department of Pathophysiology, University of Split School of Medicine, Split, Croatia. The Ethical Committee of the University of Split School of Medicine approved the study in alignment with the principles outlined in the Declaration of Helsinki. The included participants were informed about the procedures before enrollment, and all participants provided informed consent before enrollment.

3.2 Subjects

Of a total of 98 participants, 48 were diagnosed with primary hypertension, and the remaining 50 served as healthy controls.

Inclusion criteria included: (1) age between 40 and 70 years; (2) Grade 1 or Grade 2 hypertension, as defined by the European Society of Cardiology guidelines); (3) BMI ranging from 18.5 to 35 kg/m^2 (204).

Exclusion criteria included: (1) presence of any form of secondary hypertension; (2) Use of any antihypertensive treatment other than ACE inhibitors, CCBs, or diuretics; (3) smoking; (4) consumption of cannabidiol-containing supplements; (5) presence of chronic conditions, including HF, malignancy, liver cirrhosis, DM, CKD, and epilepsy (6) presence of significant psychiatric disorders.

3.3 Study protocol

The visit included a comprehensive set of evaluations, such as blood sampling, bioimpedance analysis, anthropometric measurements, office BP, ambulatory BP measurement, and completing various surveys.

Participants were equipped with the Schiller BR-102 plus PWA 24-hour ambulatory BP measurement system (Schiller AG, Baar, Switzerland) to continuously monitor BP outside the laboratory. The device was programmed to record BP readings every 30 minutes during the day (08:00 – 23:00) and every hour during the night (23:00 – 08:00). Casadei method was used to interpret the results.

Venous blood samples were collected from each participant's antecubital vein, after a 12-hour fasting period. Blood analyses were conducted in a certified institutional biochemical laboratory following standard operating procedures. The laboratory analysts performing the analyses were blinded to the group allocation of the study participants.

3.4 Surveys

The extent of daytime sleepiness was evaluated using the ESS, which consists of eight questions that measure the probability of falling asleep in various daily settings. For each situation, the respondent rates their probability of falling asleep on a scale from 0 to 3, where 0 indicates no sleepiness, and 3 indicates a high chance of sleepiness (205). The responses to each of the 8 questions are then summed to produce a total score ranging from 0 to 24, and the interpretation of this score will indicate the level of daytime sleepiness. A score exceeding 10 is indicative of excessive sleepiness. ESS was initially used in patients with OSA and is now the most used survey to assess daytime sleepiness in various sleep-related problems (206).

The PSQI is a validated questionnaire to assess sleep quality and disturbances over one month in adults. The PSQI score is based on seven components (subjective sleep quality, sleep duration, sleep latency, sleep disturbances, habitual sleep efficiency, daytime dysfunction, and use of sleep medication), with each component rated on a scale from 0 (no difficulty) to 3 (severe difficulty). The PSQI provides a score ranging from 0 to 21, with higher scores indicating poorer sleep quality. The PSQI is widely used in clinical and research settings and aids in diagnosing sleep disorders and monitoring treatment efficacy (207).

3.5 Statistical analysis

The statistical analysis and graphical representation were conducted using SigmaPlot (Systat Software Inc., San Jose, CA, USA) and MedCalc Statistical Software version 20.113 (MedCalc Software Ltd., Ostend, Belgium). Quantitative variables were expressed as mean ± standard deviation (SD), whereas categorical variables were reported as a whole number (n) and percentage (%). For the estimation of the normality of data distribution, we used the Shapiro-Wilk test. Chi-squared ($\chi 2$) test was used to compare categorical variables, whereas the Student's t-test for independent samples and one-way ANOVA with *post hoc* Tukey test was employed for comparing quantitative variables. Statistical significance was set at 0.05 for all analyses.

4. RESULTS

Baseline characteristics of patients are delineated in detail in Table 3. Average 24h mean arterial pressure was higher in a population of patients with primary hypertension ($P < 0.001$). In the rest of the participants' baseline characteristics no significant differences were found between patients with primary hypertension and healthy controls.

Table 3. Baseline characteristics of the study population.

Parameter	**Primary hypertension (n = 48)**	**Healthy controls (n = 50)**	***P****
Age, years	57.6 ± 9.4	56.6 ± 9.8	0.552
Male sex, n (%)	25 (52.1)	27 (54)	0.578
Body mass index, kg/m^2	27.4 ± 3.1	27.1 ± 3.4	0.662
24h MAP, mmHg	105.3 ± 11.8	92.6 ± 10.9	<0.001
Socioeconomic status, n (%)			
Low	4 (8.3)	5 (10)	
Average	35 (72.9)	36 (72)	0.762
Above average	9 (18.8)	9 (18)	
Employment status, n (%)			
Employed	32 (66.7)	35 (70)	
Unemployed	8 (16.7)	8 (16)	0.645
Retired	8 (16.7)	7 (14)	
Education, n (%)			
Elementary school	1 (2.1)	0 (0)	
High school	25 (52.1)	26 (52)	0.787
Higher education	22 (45.8)	24 (48)	
FPG, mmol/L	5.2 ± 1.1	5.3 ± 0.9	0.107
LDL-C, mmol/L	3.4 ± 1.1	3.5 ± 1.2	0.423

FPG: Fasting plasma glucose; MAP: mean arterial pressure; LDL-C: low-density lipoprotein cholesterol. * Student's t-test or chi squared test

No differences were found in ESS score between patients with primary hypertension and healthy controls (6.1 ± 2.5 vs. 5.8 ± 2.6, $P = 0.624$) (Figure 2).

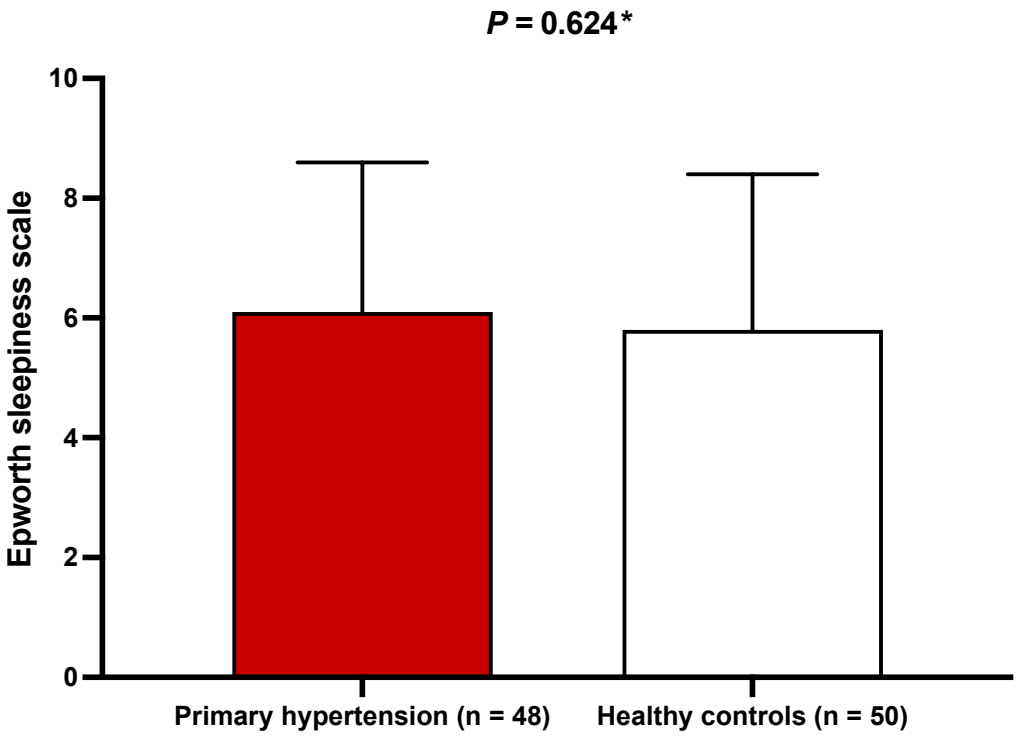

Figure 2. Comparison in ESS score between patients with primary hypertension and healthy controls. ESS: Epworth Sleepiness Scale. Data presented as mean ± SD. * Student's t-test

Similarly, PSQI score did not differ between patients with primary hypertension and healthy controls (6.2 ± 2.1 vs. 6.0 ± 2.4, $P = 0.767$) (Figure 3).

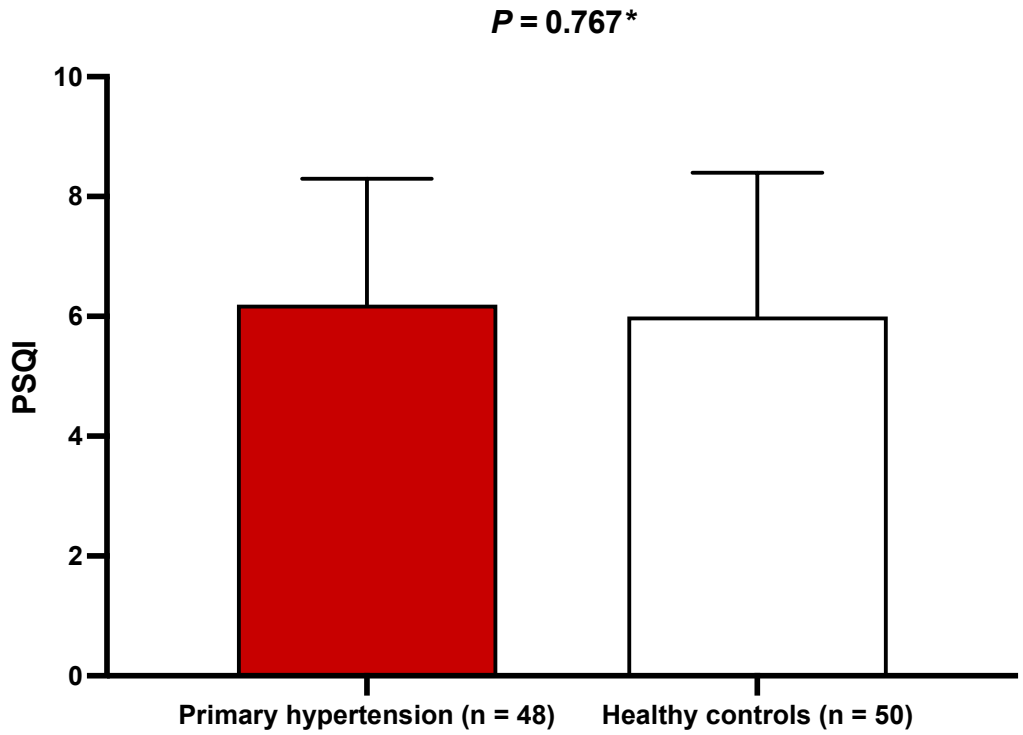

Figure 3. Comparison in PSQI score between patients with primary hypertension and healthy controls. PSQI: Pittsburgh Sleep Quality Index. Data presented as mean ± SD. * Student's t-test

In a population of patients with primary hypertension, patients at the highest quartile of PSQI had significantly higher average 24h mean arterial pressure in comparison to patients with lower tertile of PSQI (106.5 ± 11.2 vs. 102.3 ± 11.4 vs. 100.4 ± 11.2 mmHg, $P < 0.001$) (Figure 4).

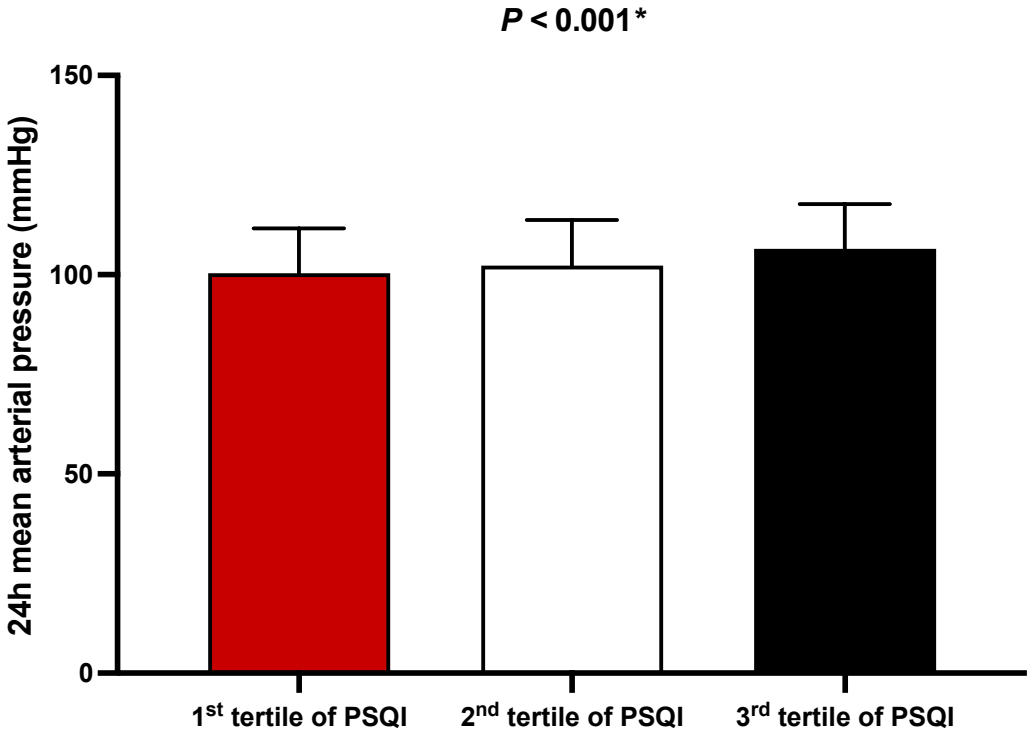

Figure 4. Comparison in average 24h mean arterial pressures with respect to PSQI score tertiles in patients with primary hypertension. PSQI: Pittsburgh Sleep Quality Index. Data presented as mean ± SD.*one-way ANOVA with *post hoc* Tukey test

5. DISCUSSION

In the present study, we tried to elaborate on whether increased daytime sleepiness and reduced sleep quality are more prevalent in the population with primary hypertension. The study included a total of 98 participants, 48 of which were diagnosed with primary hypertension, and the remaining 50 were healthy controls. Comparing the baseline parameters, such as age, sex, BMI, socioeconomic status, employment status, education level, fasting plasma glucose, and low-density lipoprotein cholesterol, no differences were found between the two groups. The only exception was the 24h MAP, which was significantly higher in the primary hypertension group compared to the healthy controls. The study analysis revealed no significant differences in ESS scores between the two groups, suggesting that daytime sleepiness did not differ markedly between hypertensive patients and healthy controls. Similarly, the PSQI scores were not significantly different, indicating comparable sleep quality in both study groups. In the second part of the study, we analyzed the hypertensive group alone, and the findings showed that patients in the highest tertile of PSQI scores had significantly higher 24h MAP compared to those in the lower tertiles. The study results suggest a potential correlation between poorer sleep quality and higher MAP among hypertensive patients.

Our results align with those reported by Gonzaga et al., who found no significant difference in sleep quality between hypertensive patients and normotensive controls using the PSQI (208). This implies that while hypertension is correlated to poor CV outcomes, it may not directly impact sleep quality measures in a general hypertensive population.

The significant association between higher PSQI scores and elevated MAP within the hypertensive group is supported by research from Pepin et al., who observed that poor sleep quality correlates with increased nocturnal BP and overall cardiovascular risk (209). The similarity in results emphasizes the potential impact of sleep disturbances on BP regulation in hypertensive individuals.

Fernandez-Mendoza et al., demonstrated that objective short sleep duration modifies the relationship between hypertension and mortality, indicating broader implications for overall mortality in hypertensive individuals (210). The study demonstrates our studies focus on the importance of sleep quality in managing hypertension and reducing the associated risks.

Moreover, Haack et al., demonstrated that increasing sleep duration significantly lowers BP, reinforcing the correlation between sleep quality and hypertension management (211). Their study results indicate that improvement of sleep duration and sleep quality could lead to better BP control, which also, to some extent, resonates with our study findings of a correlation between rescripted sleep quality and higher MAP.

Similarly, a study conducted in Southern Nigeria by Saeidi et al., showed that hypertensive patients with poor sleep quality had reduced BP control compared to the patients with better sleep quality (212). Standardized sleep questionnaires were used in their study, and the results demonstrated that sufficient sleep was associated with better BP management.

Other intervention studies, such as those reported by Makarem et al., have demonstrated that mild and severe sleep disturbance is associated with increased BP (213). Similarly, a systematic review by Yadav et al. indicated that insufficient sleep duration could be a significant risk factor for hypertension (214). These studies suggest that interventions to improve sleep quality could benefit BP control in hypertensive patients, highlighting an area for future research and clinical focus. Accordingly, it is worth mentioning that abundant data indicates that modifications of lifestyle, including sleep hygiene, might significantly improve CV outcomes in hypertensive individuals (215-216).

Several limitations to this study should be acknowledged. The sample size was relatively small (48 hypertensive patients and 50 healthy controls), which may limit the generalizability of the findings. More extensive studies are needed to confirm these results and provide more solid data. Another limitation is that the patients were recruited from only one medical center. Survey limitations are also present, as the study relied on self-reported sleep quality and daytime sleepiness, which raises concerns about potential recall bias and may not accurately reflect objective sleep parameters. Future studies should incorporate objective sleep assessments such as polysomnography or actigraphy to evaluate sleep disturbances comprehensively. The study employed a cross-sectional design, which limits the ability to infer causality. Longitudinal studies are needed to determine whether poor sleep quality contributes to the development of hypertension or if hypertension itself leads to sleep disturbances. Potential confounding factors such as lifestyle factors, medication use, and comorbid conditions were not fully accounted for in the analysis. Properly controlling for these variables in future research would enhance the validity of the findings.

Overall, the study highlights that are no significant differences in sleep quality or daytime sleepiness between hypertensive patients and healthy controls. However, hypertensive patients with poorer sleep quality exhibit higher 24h MAP. These findings underscore the importance of considering sleep quality in managing hypertension, as it may influence BP regulation. Further research with larger sample size, objective sleep measures, and longitudinal design is warranted to understand the complex relationship between sleep and hypertension. Addressing these factors may improve clinical outcomes and quality of life for patients with hypertension.

6. CONCLUSIONS

1. ESS was not higher among patients with primary hypertension than healthy controls.
2. PSQI was also not higher in patients with primary hypertension than in healthy controls.
3. Patients with primary hypertension and at the highest tertile of PSQI had a significantly higher 24h MAP compared to patients with primary hypertension and with lower tertile of PSQI.

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8. SUMMARY

Objectives: The aim of the study was to analyze if there is a difference in daytime sleepiness and sleep quality between patients with primary hypertension and healthy controls and to evaluate if there was a potential correlation between poorer sleep quality and higher MAP among hypertensive patients.

Materials and methods: The study employed a cross-sectional design conducted at the Department of Pathophysiology, University of Split School of Medicine, Croatia. Informed consent was obtained from all 98 participants, including 48 with primary hypertension and 50 healthy controls. The protocol included blood sampling, bioimpedance analysis, anthropometric measurements, OBPM, ABPM, and surveys. For ABPM used Schiller BR-102 plus PWA devices for 24-hour monitoring. Venous blood samples were taken after 12 hours of fasting and analyzed unthinkingly. Daytime sleepiness was measured using the ESS and sleep quality was assessed with PSQI.

Results: No significant differences were found in ESS scores (P = 0.624) or PSQI scores (P = 0.767) between the groups. Within the hypertensive group, higher PSQI scores were associated with significantly higher MAP (106.5 ± 11.2 vs. 102.3 ± 11.4 vs. 100.4 ± 11.2 mmHg, $P < 0.001$), indicating poorer sleep quality may be linked to higher BP.

Conclusion: The study results indicate that there is no significant difference in ESS and PSQI in patients with primary hypertension compared to the healthy controls. However, the study results suggest a potential correlation between poorer sleep quality and higher MAP among hypertensive patients.

9. CROATIAN SUMMARY

Naslov: Procjena kvalitete spavanja u bolesnika s arterijskom hipertenzijom

Ciljevi: Cilj studije bio je analizirati postoji li razlika u dnevnoj pospanosti i kvaliteti spavanja između bolesnika s primarnom hipertenzijom i zdravih kontrola te procijeniti postoji li potencijalna korelacija između lošije kvalitete spavanja i višeg srednjeg arterijskog tlaka među hipertenzivnim pacijentima.

Ispitanici i metode: Studija je provedena kao presječna studija na Katedri za patofiziologiju Medicinskog fakulteta Sveučilišta u Splitu, Hrvatska. Informiran pristanak je dobiven od svih 98 sudionika, uključujući 48 s primarnom hipertenzijom i 50 zdravih kontrola. Protokol je uključivao uzimanje uzoraka krvi, bioimpedancijsku analizu, antropometrijska mjerenja, mjerenje arterijskog tlaka (u ordinaciji, ali i uređajem za kontinuirano mjerenje arterijskog tlaka (KMAT)). Uređaji Schiller BR-102 plus PWA su korišteni za 24-satno praćenje arterijskog tlaka. Venski uzorci krvi uzimani su nakon 12-satnog posta i analizirani bez pristranosti. Dnevna pospanost mjerena je pomoću Epworthove skale pospanosti (engl. *Epworth Sleepiness Scale*, ESS), a kvaliteta sna procijenjena je pomoću Pittsburgh indeksa kvalitete spavanja (engl. *Pittsburgh Sleep Quality Index*, PSQI).

Rezultati: Nisu pronađene značajne razlike u rezultatima ESS (P = 0,624) niti PSQI (P = 0,767) između skupina od interesa. Unutar hipertenzivne skupine, viši PSQI rezultati bili su pristuni u bolesnika sa značajno višim prosječnim arterijskim tlakom (106,5 ± 11,2 vs. 102,3 ± 11,4 vs. 100,4 ± 11,2 mmHg, $P < 0,001$), što ukazuje na to da lošija kvaliteta sna može biti povezana s višim krvnim tlakom.

Zaključak: Rezultati studije ukazuju na to da nema značajnih razlika u ESS i PSQI između bolesnika s primarnom hipertenzijom i zdravih kontrola. Međutim, rezultati studije sugeriraju potencijalnu korelaciju između lošije kvalitete spavanja i višeg MAP-a među hipertenzivnim bolesnicima.

10. CURRICULUM VITAE

Personal information

Education

2019-2024 University of Split, school of medicine

2018-2019 ONH – Oslo nye høyskole, Medicine 1+5

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Work experience

July 2022-today. Medical assistant, Cardiology Department, Akershus University Hospital, Lørenskog, Norway

2021-2024, Assistant, Omsorgspartner (institution) *Son, Norway*

2018-2023, Assistant Hvam bolig (institution)| *Skjetten, Norway*

2016-2019, Sales associate Brilleland (optical store) *Strømmen, Norway*

Internship

2023, Nephrology Department, Akershus University Hospital, Lørenskog, Norway

Language skills

Norwegian (mother tongue)

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