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**UNIVERSITY OF SPLIT
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**PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) IN PATIENTS WITH
PRIMARY HYPERTENSION**

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1.1 HYPERTENSION

1. INTRODUCTION

1.1.1 Definition

The American College of Cardiology (ACC) and the American Heart Association (AHA) classifies a normal blood pressure as a systolic one below 120 mmHg and a diastolic one below 80 mmHg (1). They classify Stage 1 hypertension as > 130 mmHg/80 mmHg. The 2023 European Society of Hypertension (ESH) has set a threshold of >140 mmHg/90 mmHg for the diagnosis of hypertension (2). This means that a person classified with Grade 1 hypertension according to the ACC/AHA guidelines, can be considered a normal or high-normal blood pressure by the ESH guidelines. The high-normal blood pressure category is meant to identify individuals who could benefit from lifestyle interventions before they get hypertension and thereby avoid pharmacological treatment.

International Society of Hypertension (2020) (ISH) also operates with systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg (3) in repeated examinations in the Doctor's office. However, they have a higher threshold of >180 mmHg/80 mmHg when using Ambulatory blood pressure measurement (ABPM).

Children below 13 years are diagnosed with hypertension if they measure blood pressure above the 95th percentile of their age and sex. For kids older than 13 years the threshold is 130/80 mmHg.

Resistant Hypertension is defined as uncontrolled hypertension, that remains above 130/80 mm Hg despite treatment with 3 or more antihypertensives or requires 4 or more antihypertensives to be controlled. The antihypertensive medications need to be maximally dosed and have different mechanisms of action for this diagnosis to be valid.

Severe Hypertension, also known as stage 3 hypertension, is a condition characterized by extremely high blood pressure, typically with systolic readings of 180 mmHg or higher and/or diastolic readings of 120 mmHg or higher. This condition is a medical emergency and requires immediate attention to prevent potentially life-threatening complications (4).

A hypertensive crisis is a severe increase in blood pressure that can lead to a stroke or other critical health issues. It is categorized into two types; hypertensive urgency and hypertensive emergency. Hypertensive Urgency involves blood pressure readings of 180 mmHg systolic and 120 mmHg diastolic pressure or higher without immediate evidence of organ damage. Hypertensive Emergency involves the same values as in an urgency, but also includes evidence of organ damage, for example of the heart, brain, kidneys or eyes. The latter one is more urgent than the former one, but they both require immediate attention (5).

1.1.2 Prevalence

The World Health Organization estimates that 1.28 billion adults between 30-79 years have hypertension, but less than half of these are diagnosed and treated. Only around 21% of these have it controlled, which makes it a major cause of death worldwide (6). As many as 10.4 million people die from hypertension each year (7). The prevalence of hypertension is higher the older the population gets. 65-75 % of adults suffer from hypertension in the age group 65-74 years (8). Men is diagnosed with this condition more often than women when we are looking at the population below 65 years. This changes after menopause and from 75 years and above, the prevalence is higher in women than in men (1).

African American individuals have the highest prevalence of hypertension with about 56% of the adult population affected. Asian (46 %) and White (48 %) adults have a significantly lower prevalence, while Hispanic adults have the lowest occurrence with around 39% of the adult population affected (9-11).

1.1.3 Types of hypertension

The most common type of arterial hypertension is primary, accounting for around 90 percent of the cases (1), meaning that there is no known cause for the condition. However, there are several risk factors associated with this condition. Genetics is thought to play a significant role, as positive family history is associated with a higher risk. Poor dietary habits with a high sodium and low potassium intake is another risk factor, together with obesity, excessive alcohol consumption and smoking. As people get older, their blood vessels become less elastic, making advanced age associated with hypertension. Chronic stress is also considered to contribute to the development and exacerbation of primary hypertension (1).

The remaining five to ten percent is categorized as secondary hypertension, where there is a specific, identifiable cause. This condition can be suspected if there is an abrupt onset or if there is an exacerbation of previously controlled hypertension. Also, if the patient with hypertension is below 30 years of age or if the patient is above 65 years old and has an elevated diastolic blood pressure, one should consider secondary hypertension as an explanation. Resistant hypertension, hypertensive emergencies or in cases where the target organ damage is disproportionate to the degree of hypertension are also signs of a secondary etiology. Hypokalemia can also be a sign for secondary hypertension (12).

There are numerous causes for secondary hypertension. Renal hypertension can trigger systemic hypertension. Renal artery stenosis is one possible cause, where a narrowing of one

or both renal arteries leads to decreased blood flow to the kidneys. This decrease in blood pressure locally is detected by baroreceptors within the blood vessels, triggering the juxtaglomerular cells to release the enzyme renin. Renin then works to convert angiotensinogen to angiotensin I, which is cleaved into angiotensin II, primarily in the lungs. Angiotensin II itself is a powerful vasoconstrictor, which increases the peripheral vascular resistance and an elevation of the blood pressure. It also activates the sympathetic nervous system, leading to increased heart rate, cardiac output and vasoconstriction, all of which can raise the blood pressure. Further on, angiotensin II stimulates the adrenal gland to release aldosterone and the pituitary gland to release antidiuretic hormone. Aldosterone is a hormone that works on the distal tubules and the collecting ducts, increasing reabsorption of sodium ions from the urine. The increase in sodium concentration will raise the osmotic pressure and water will follow, thereby increasing blood volume and blood pressure (13).

Similarly, various renal parenchymal diseases, like chronic kidney disease, glomerulonephritis and polycystic kidney disease, can impair renal blood flow and increase blood pressure through RAAS as described earlier. When the parenchyma is damaged, volume regulation can be disturbed, possibly leading to water and sodium retention. Also, the physiological stress caused by the damaged kidney tissue can lead to activation of the sympathetic nervous system, increasing blood pressure by vasoconstriction and an increase in heart rate (14).

Different endocrine disorders can also cause secondary hypertension. In Conn's syndrome or hyperaldosteronism there's an overproduction of aldosterone by the zona glomerulosa of the adrenal glands, which will raise the blood pressure by the mechanisms described earlier (15).

In Cushing's syndrome or hypercortisolism, the overproduction of cortisol by the zona fasciculata of the adrenal cortex can cause hypertension by various mechanisms. It can increase heart rate by triggering the sympathetic nervous system to release norepinephrine, acting on beta-1-adrenergic receptors in the cardiac muscle cells, increasing force and rate of contractions. Cortisol also increases the sensitivity of the heart to these catecholamines. Norepinephrine, especially, also works on α_1 -receptors in the smooth muscle cells in blood vessels, causing vasoconstriction (16). Hypercortisolism will additionally impair vasodilation by causing endothelial dysfunction, inhibiting nitric oxide production, a vasodilator (17). In addition, it contributes to fluid retention by facilitating sodium reabsorption in the kidneys. Cortisol also acts on mineralocorticoid receptors in the renal tubules (although less potent than aldosterone), increasing the expression of sodium channels, leading to reabsorption of sodium from the urine and water with it (18). From here the sodium is transported into the interstitial

fluid by sodium-potassium ATPases, that are also stimulated by cortisol. It also activates RAAS by stimulating the release of renin (19). Further on, cortisol is associated with obesity, insulin resistance and dyslipidemia, which can contribute to hypertension (20).

An overactive thyroid gland, as seen in hyperthyroidism, can lead to secondary hypertension through the excessive production of thyroid hormones. Abnormally high amounts of thyroxine (T4) are produced and secreted by the thyroid gland and subsequently converted into triiodothyronine (T3), the active hormone (21, 22). T3 has different mechanisms through which it can raise the blood pressure. For example, it binds thyroid hormone receptors within cardiac myocytes and stimulates the production of contractile proteins like myosin and actin (22). This enhances cardiac contractility, stroke volume, and cardiac output, ultimately increasing the blood pressure (23). Thyroid hormones also work directly on the sinoatrial node and its pacemaker cells, leading to tachycardia and further increases in cardiac output (21). This hormone can also increase the activity of the renin-angiotensin-aldosterone system and sympathetic nervous system activity (24).

The sympathetic nervous system can also be excessively stimulated in adrenal hyperplasia or when there is an adrenal tumor, like pheochromocytoma, leading to production of catecholamines in higher quantities than normal (25, 26).

Patients suffering from hyperparathyroidism will have high levels of parathyroid hormone. It stimulates the osteoclasts to perform more bone resorption, releasing calcium and phosphate into the bloodstream. Additionally, it stimulates vitamin D production in the kidney, increasing the absorption of calcium from the intestines. It also binds specific receptors in the distal convoluted tubules that through a cascade trigger insertion of calcium channels, facilitating reabsorption of calcium into the tubular cells and further into the interstitial space. The thick ascending loop of Henle will also increase the calcium reabsorption to some degree. By enhanced sodium and chloride reabsorption, a favorable electrochemical gradient is created, leading to passive reabsorption of calcium ions through paracellular pathways. The hypercalcemia created by hyperparathyroidism through multiple mechanisms, can lead to secondary hypertension. First of all, it will contribute to vasoconstriction, because calcium will directly influence smooth muscle contractility in the vessel walls. Persistent hypercalcemia can also lead to calcification in blood vessel walls, reducing elasticity and causing elevated blood pressure. The increased reabsorption of calcium and sodium in the kidneys will lead to increased water reabsorption as well, increasing body fluid levels and the blood pressure.

Higher levels of calcium can also cause cardiac dysfunction, ultimately contributing to the secondary hypertension (27).

Obstructive sleep apnea is a sleep disorder, where patients experience apneic episodes while sleeping, due to collapse of the pharyngeal muscles. These apneic episodes cause hypoxia and hypercapnia, triggering the sympathetic nervous system into eliciting a “fight or flight” response with catecholamines. Epinephrine and norepinephrine released in such a response will lead to an increase in blood pressure, as described earlier (28).

Hypertension can also be induced by various medications or substances, like nonsteroidal anti-inflammatory drugs, oral contraceptives, decongestants, corticosteroids and cocaine. Pregnancy can be another cause, in conditions like gestational hypertension and preeclampsia (29).

1.1.4 Classifications

Hypertension is classified into different categories, according to severity. The categories differ slightly depending on which guidelines considered, which is summarized in Figure 1.

The elevated blood pressure bracket is meant to identify individuals who could benefit from lifestyle intervention and change of diet, in order to avoid developing hypertension (1).


Classification of hypertension in adults			
	2017 ACC/AHA guideline ^[1]	2014 JNC 8 guideline  ^{[2][7]}	2020 ISH guideline ^[3]
Normal blood pressure	<ul style="list-style-type: none"> • <u>SBP</u> < 120 mm Hg • AND <u>DBP</u> < 80 mm Hg 		<ul style="list-style-type: none"> • <u>SBP</u> < 130 mm Hg • AND <u>DBP</u> < 85 mm Hg
Elevated blood pressure	<ul style="list-style-type: none"> • <u>SBP</u> 120–129 mm Hg • AND <u>DBP</u> < 80 mm Hg 	<ul style="list-style-type: none"> • <u>SBP</u> 120–139 mm Hg • OR <u>DBP</u> 80–89 mm Hg 	<ul style="list-style-type: none"> • <u>SBP</u> 130–139 mm Hg • OR <u>DBP</u> 85–89 mm Hg
Stage 1 hypertension	<ul style="list-style-type: none"> • <u>SBP</u> 130–139 mm Hg • OR <u>DBP</u> 80–89 mm Hg 	<ul style="list-style-type: none"> • <u>SBP</u> 140–159 mm Hg • OR <u>DBP</u> 90–99 mm Hg 	
Stage 2 hypertension	<ul style="list-style-type: none"> • <u>SBP</u> ≥ 140 mm Hg • OR <u>DBP</u> ≥ 90 mm Hg 	<ul style="list-style-type: none"> • <u>SBP</u> ≥ 160 mm Hg • OR <u>DBP</u> ≥ 100 mm Hg 	

Figure 1: Classifications of Hypertension. ACC: American College of Cardiology, AHA: American Heart Association, JNC: Joint National Committee, ISH: International Society of Hypertension, SBP: Systolic Blood pressure, DBP: Diastolic Blood Pressure. Source: (1), (30-32).

Hypertension can also be classified as isolated systolic hypertension, isolated diastolic hypertension or combined systolic and diastolic hypertension. Isolated systolic hypertension is more common in young and old individuals. Particularly in older individuals, this can be due to stiffening of the blood vessels, resulting in an increased pulse pressure (1).

1.1.5 Risk Factors

As mentioned earlier, there are not many cases in which there is a clear cause for the hypertension. However, there are numerous risk factors that are associated with elevated blood pressure, that increase the risk for developing hypertension. These are especially important to identify in patients with a normal-high blood pressure, where we can induce lifestyle

modifications as a preventative measure to avoid the patient being diagnosed with hypertension (31).

A positive family history is an example of a non-modifiable risk factor. Black populations have higher rates of hypertension, earlier onset and more often suffer from the resistant type of hypertension. The Hispanic and Asian populations have the lowest risk (33). Gender can also be a non-modifiable risk factor; up until 65 years of age the prevalence is higher in men than in women. However, after menopause, the prevalence increases in women.

Modifiable risk factors are something the patient can control themselves and includes overweight and diabetes. Dietary choices like a high sodium diet, alcohol and smoking is also associated. Physical inactivity and psychological stress are also risk factors that should be dealt with (34).

Over 50% of patients diagnosed with hypertension has some sort of cardiovascular risk factor as well (35), for example history of atrial fibrillation, coronary artery disease, heart failure or peripheral vascular disease.

1.1.6 Signs and symptoms

The condition is rarely followed by any symptoms, which is why it is often referred to as “the silent killer”. Early symptoms may include dizziness, headache, tinnitus and chest discomfort. There are also some nonspecific symptoms that can be experienced with elevated blood pressure, like epistaxis, nervousness and sleep disturbances (36).

The absence of clear symptoms makes screening important. Screening for hypertension is a crucial public health strategy aimed at early detection and management of high blood pressure to prevent complications such as heart disease, stroke and kidney failure. This is especially true because of the serious complications caused by long standing elevated blood pressure, especially end-organ damage. This is also called hypertension-mediated-organ-damage, shortened HMOD. Regular blood pressure checks are recommended for all adults, starting at age 18, with more frequent screenings for those at higher risk, such as individuals with a family history of hypertension, obesity or other risk factors. Adults aged 40 and older, as well as those at increased risk, should have their blood pressures measured annually. Screening is usually done by using a sphygmomanometer at a doctor’s visit, but home blood pressure monitoring and ambulatory blood pressure measuring are alternatives (37, 38).

The cardiovascular system takes a lot of damage when working “against” hypertensive blood vessels. Arteries that are put under strain by high blood pressure over time becomes

thicker, less elastic and more prone to damage. The risk of atherosclerosis, narrowing of the blood vessels and blockages increases drastically. The heart is forced to work harder to pump blood against the damaged vessels, putting more strain on it. This can lead to enlargement of the heart chambers, like in left ventricular hypertrophy, weakening of the heart muscle and heart failure as well as myocardial infarction and other coronary artery diseases. This HMOD can be detected by a 12-lead ECG or more specifically by a transthoracic echocardiogram (39).

The blood vessels in the limbs can also be damaged, leading to peripheral artery disease (40). Narrowing of these vessels will reduce blood flow to arms and legs, producing symptoms such as claudication, where the patient experiences pain when walking (41). Blood flow to the distal vessels is important for wound healing, which will be impaired in this condition. The initial inflammatory phase, where damaged blood vessels are supposed to release inflammatory mediators like cytokines and chemokines to attract immune cells like neutrophils and macrophages, is inhibited in these patients (42). The proceeding proliferative phase is also impaired, as reduced oxygen and nutrient delivery will slow down fibroblast activity and collagen synthesis, essential in the production of granulation tissue and wound closure (43). The reduced blood flow to the wound also makes angiogenesis and epithelialization during the final stages of wound healing difficult, ultimately hindering new blood vessels from growing and the closure of the lesion (44). If debridement, topical therapy, and vascular interventions are not successful, it might be necessary to perform amputation in these individuals (45).

The kidneys have an essential role in controlling blood pressure as discussed earlier, but they also commonly suffer from hypertensive nephropathy if the condition is not well controlled (46). The delicate blood vessels of the glomeruli can be affected by a condition called glomerulosclerosis, inhibiting their ability to filter the blood effectively and ultimately leading to chronic kidney disease (47). Another complication is renal artery stenosis, which is compensated by the renin-angiotensin-aldosterone system (RAAS), retaining more salt and water, further worsening hypertension (48). The renal interstitium surrounding the kidney tubules is also at risk of inflammation, fibrotic scar formation, and atrophy of the tubules (49). This accumulation of scar tissue can alter kidney architecture and impair its function. Kidney function can be monitored by lab parameters like creatinine and urea serum concentrations. Urine dipstick tests to check for albuminuria and hematuria might also be indicative (50).

Similarly, to other arterial damage, the blood vessels in the retina can narrow and lead to hypertensive retinopathy, possibly causing vision changes. Occlusions in these vessels will cause more sudden symptoms as vision loss, only on the affected eye. The optic nerve can also be damaged, causing visual field defects and possibly permanent vision loss (51).

1.1.7 Measurements

There are different ways to measure blood pressure, giving different results. Both the ESH and the ACC/AHA guidelines recommend using cuffed devices for measurement. Several cuffless devices have been introduced to the market, but the measurements have not yet been proven to be accurate enough for them to be used in diagnosis of hypertension (52-54). If proven to be accurate, they would offer great improvements in terms of comfortability for the user, improving compliance, tolerability and avoiding technical issues.

The blood pressure should be measured in both arms, preferably at the same time. If there is a difference > 10 mmHg, use the higher value of the two. If the gap is even higher, > 20 mmHg, consider further investigations (55).

Conditions	<ul style="list-style-type: none"> • Quiet room with comfortable temperature. • Before measurements: Avoid smoking, caffeine and exercise for 30 min; empty bladder; remain seated and relaxed for 3–5 min. • Neither patient nor staff should talk before, during and between measurements.
Positions	<ul style="list-style-type: none"> • Sitting: Arm resting on table with mid-arm at heart level; back supported on chair; legs uncrossed and feet flat on floor (Figure 1).
Device	<ul style="list-style-type: none"> • Validated electronic (oscillometric) upper-arm cuff device. Lists of accurate electronic devices for office, home and ambulatory BP measurement in adults, children and pregnant women are available at www.stridebp.org.²² (see also Section 11: Resources) • Alternatively use a calibrated auscultatory device, (aneroid, or hybrid as mercury sphygmomanometers are banned in most countries) with 1st Korotkoff sound for systolic blood pressure and 5th for diastolic with a low deflation rate.²²
Cuff	<ul style="list-style-type: none"> • Size according to the individual's arm circumference (smaller cuff overestimates and larger cuff underestimates blood pressure). • For manual auscultatory devices the inflatable bladder of the cuff must cover 75%–100% of the individual's arm circumference. For electronic devices use cuffs according to device instructions.
Protocol	<ul style="list-style-type: none"> • At each visit take 3 measurements with 1 min between them. Calculate the average of the last 2 measurements. If BP of first reading is <130/85 mm Hg no further measurement is required.
Interpretation	<ul style="list-style-type: none"> • Blood pressure of 2–3 office visits ≥140/90 mm Hg indicates hypertension.

Figure 2. Recommendations for blood pressure measurement in office.

Source: International Society of Hypertension. ISH guidelines [Internet]. London, UK: ISH; 2020 [cited 2024 Jun 27]. Available from: https://ish-world.com/wp-content/uploads/2021/02/ISH_Guideline_Presentation_Slide_Deck_06.05.2020.pdf (55)

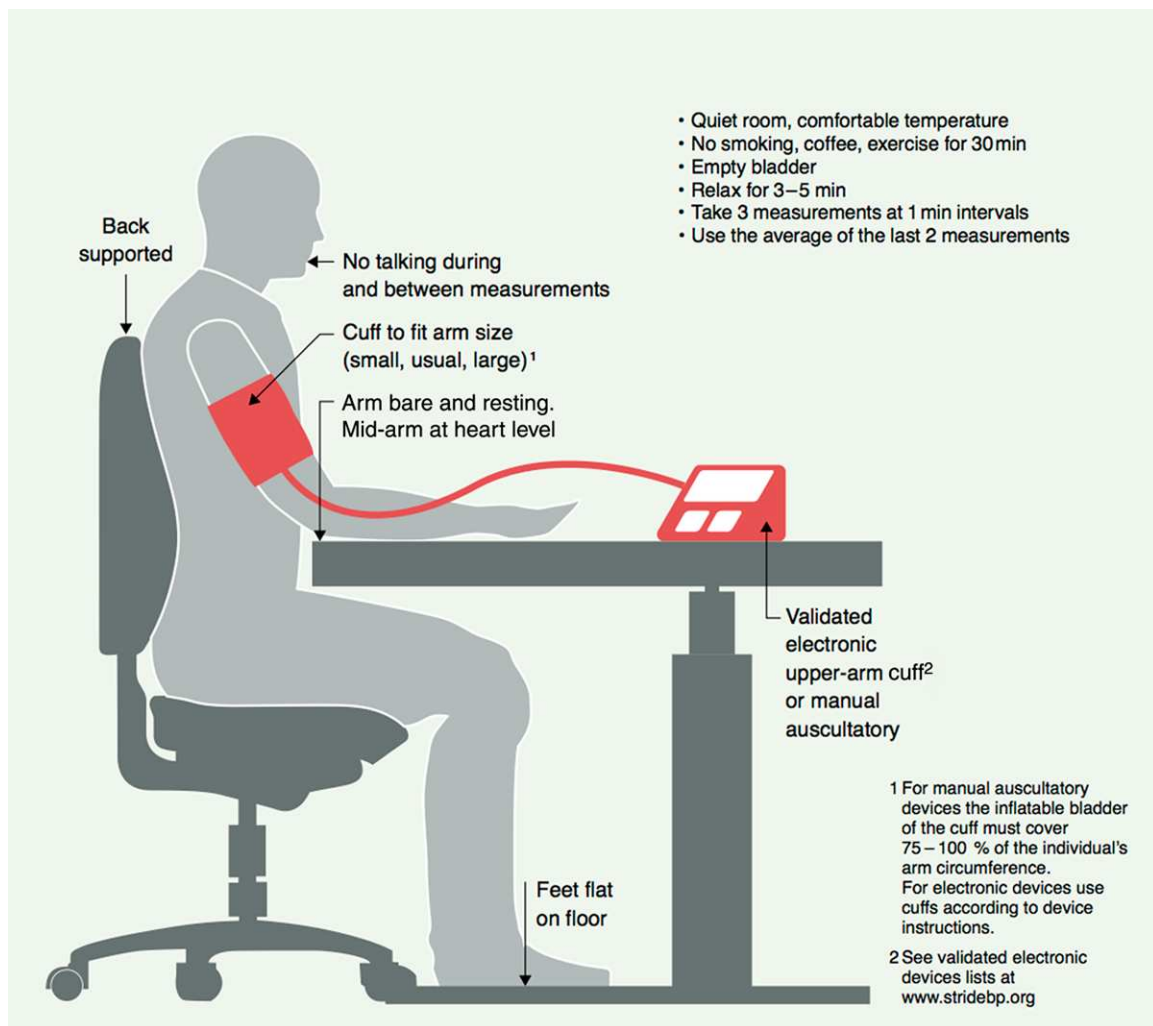


Figure 3. Visualization of how to measure blood pressure.

Source: International Society of Hypertension. ISH guidelines [Internet]. London, UK: ISH; 2020 [cited 2024 Jun 27]. Available from: https://ish-world.com/wp-content/uploads/2021/02/ISH_Guideline_Presentation_Slide_Deck_06.05.2020.pdf (55)

The phenomenon “white coat hypertension” describes the situation where in-office blood pressure measurement is elevated, while out-of-office measurement is normal. This is most likely to be caused by anxiety associated with the clinical setting. There is an alternative variant of this, called “white coat effect”, when a patient currently on antihypertensive medication records high in-office values, but normal out-of-office values (56).

The way to diagnose this is firstly by confirming the elevated in-office measurement, by taking new measurements several minutes apart. There is a possibility the patient will calm down after some time to relax. Secondly, repeat measurements on several visits. If the measurements are still elevated, consider doing an ambulatory blood pressure measurement, where the patient is wearing a measuring device with a cuff for 24 hours that does measurements in a set interval (for example every 15 or 30 minutes) (1). The diagnosis can be confirmed if

the in-office measurements are between 130-160/89-100 mmHg and the out-of-office measurements are below 130/80 mmHg.

Conversely, the phenomenon of “masked hypertension” describes a patient in which in-office measurements are normal, while out-of-office measurements are consistently elevated. If this patient is currently on antihypertensive medication, it is termed “masked uncontrolled hypertension”. It can be wise to screen for masked hypertension in patients with consistent in-office measurements of 120-129/75-79 mmHg (57).

The ISH guidelines states that the blood pressure should be measured above the threshold during 2-3 different office visits with 1-4 weeks intervals between them. The intervals depend on the measurement. If the measurement is as high as >160/110 mmHg you should remeasure within a few days or weeks, but if the measurement is 130/85 mmHg it is enough to schedule the next measurement within 3 years. However, the diagnosis can be made after one single visit if the blood pressure is above 180/110 mmHg and there is evidence of cardiovascular disease (9). If possible, confirm the diagnosis with out-of-office measurement.

1.1.8 Management

There are different ways to approach the management of hypertension. The 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension (58) and the 2017 American College of Cardiology/American Heart Association (ACC/AHA) (1) are two of the most used guidelines.

It is important to set a target blood pressure value that is the goal of the treatment of the hypertension. This value can vary in different patient groups. The ACC/AHA guideline recommends a target blood pressure of 130/80 mmHg for all age groups, while the ESH guideline has set higher values for elderly people. For patients from 65 to 79 years, the recommendation is a target blood pressure of 140/80 mmHg, while it is 140-150 mmHg for systolic blood pressure in patients 80 years or older. There are several reasons for keeping the systolic blood pressure a bit higher in geriatric patients, for example the risk of hypotension, especially orthostatic hypotension. If the blood pressure is too low, the patient can experience symptoms like dizziness and the risk of falls increases. They also have a lower tolerance to certain medications due to changes in metabolism and kidney function (58).

1.1.8.1 Non-Pharmacological Treatment

Non-pharmacological treatment of hypertension, often referred to as lifestyle modifications, plays a crucial role in managing and reducing high blood pressure. These approaches are typically recommended as the first line of defense, either alone for those with mildly elevated blood pressure or in conjunction with medication for those with more severe hypertension. One of the most effective dietary strategies is the DASH (Dietary Approaches to Stop Hypertension) diet, which emphasizes the consumptions of fruits, vegetables, whole grains and low-fat dairy products while reducing sodium intake. Lowering sodium intake to less than 2,300 mg per day and ideally to 1,500 mg per day, along with increasing potassium, calcium and magnesium can significantly help in reducing blood pressure levels (59).

Regular physical activity is another cornerstone of non-pharmacological treatment. Engaging in aerobic exercises such as brisk walking, jogging, swimming or cycling for at least 150 minutes per week has been shown to lower blood pressure effectively. Additionally, incorporating strength training exercises twice a week can further benefit cardiovascular health. Alongside physical activity, achieving and maintaining a healthy weight is vital, as excess weight can elevate blood pressure. Even modest weight loss, around 5-10 % of body weight, can have a substantial positive impact on blood pressure (60).

Limiting alcohol consumption is also essential for blood pressure management is also essential for blood pressure management. Men should restrict their intake to two drinks per day and women to one drink per day to help lower blood pressure (61). Smoking cessation is equally important, as quitting smoking improves overall cardiovascular health and can reduce blood pressure. Support programs and medications can aid in successfully quitting smoking (62).

Stress management techniques such as mindfulness, meditation, deep breathing exercises, yoga and progressive muscle relaxation can be beneficial in reducing blood pressure by managing chronic stress (63). Lastly, ensuring adequate and quality sleep is crucial, as poor sleep can negatively impact blood pressure. Prioritizing sleep health through good sleep hygiene practices can support overall blood pressure management efforts (64).

1.1.8.2 Pharmacological Treatment

Both the ESH and the ACC/AHA guidelines recommends initiation of antihypertensive treatment in patients with cardiovascular disease and a blood pressure above 130/80 mmHg. They are also both consistent on initiating pharmacotherapy in patients with a blood pressure above 140/90 mmHg, regardless of their cardiovascular risk status. The ACC/AHA guideline additionally recommends that patients with more than a ten percent risk of developing atherosclerotic cardiovascular disease over the next ten years should initiate drug treatment. The ESH guidelines has increased the limit for initiation of treatment to a systolic blood

pressure above 160 in elderly patients above 80 years old. Once treatment is initiated, there needs to be set a target blood pressure level (1, 58).

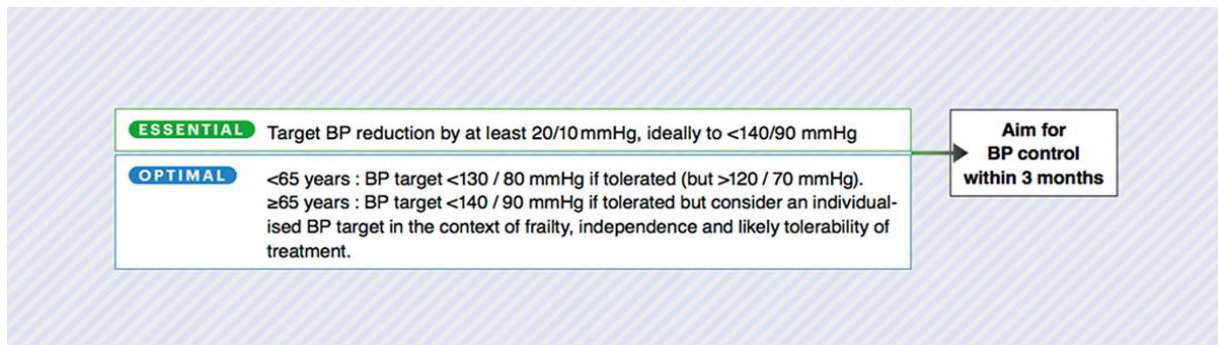


Figure 4. Office blood pressure targets for treated hypertension. BP: Blood Pressure.

Source: Jordan J, Kurschat C, Reuter H. Arterial Hypertension. *Hypertension*. 2021;77:299-310. (65)

There are four main classes of anti-hypertensive drugs; Angiotensin-converting-enzyme-inhibitors (ACEi), angiotensin receptor blockers (ARBs), thiazide diuretics and calcium channel blockers (CCBs). Additionally, beta-blockers (BBs) can be used in specific patient groups for lowering blood pressure (1).

Both ACE inhibitors (such as ramipril, lisinopril, captopril, enalapril) and ARBs (such as valsartan, losartan, candesartan) work by inhibiting the renin-angiotensin-aldosterone system (RAAS), though at different points in the pathway. ACE inhibitors block the enzyme responsible for converting angiotensin I to angiotensin II, primarily in the lungs, while ARBs prevent angiotensin II from binding to its receptors. This inhibition reduces vasoconstriction, sympathetic nervous system activation, and water and sodium reabsorption in the kidneys, and it also prevents cardiac hypertrophy and remodeling. Additionally, both drug classes inhibit the release of antidiuretic hormone and aldosterone, which are key in blood pressure regulation (66, 67). Both ACE inhibitors and ARBs are considered nephroprotective due to their ability to lower intraglomerular pressure, thus reducing the risk of serious kidney damage. They are commonly used to manage conditions such as hypertension, heart failure, and chronic kidney disease (66, 68). ACE inhibitors, however, are often associated with a dry cough in approximately 10% of patients, a side effect much less common with ARBs. In cases where the cough is problematic, switching to an ARB is recommended (66, 69). Both drug classes can cause hyperkalemia and angioedema, necessitating routine monitoring of potassium levels. They are contraindicated during breastfeeding and from the second trimester of pregnancy due

to the risk of fetal harm. It is crucial not to prescribe both ACE inhibitors and ARBs together because this combination increases the risk of hyperkalemia and renal dysfunction without additional therapeutic benefit (66, 70).

Thiazide diuretics (*chlorothiazide*, *hydrochlorothiazide*) increases the excretion of water, sodium and chloride by inhibiting sodium and chloride reabsorption in the proximal part of the distal convoluted tubules. This is done by blocking the Na⁺/Cl⁻ symporter and reduced the blood volume, resulting in a lowering of the blood pressure. Additionally, excretion of potassium and magnesium is increased, while calcium and uric acid is reabsorbed in a higher amount. This medication also has a direct vasodilative effect, lowering the blood pressure. Side effects include hypokalemia and subsequently metabolic acidosis, which can be avoided by potassium supplements. The risk of hypokalemia is also reduced if a thiazide is combined with an ARB, ACEi, amiloride or an aldosterone antagonist. Hypovolemia is another side effect, seen especially in elderly. In low doses, thiazides are safe to use during pregnancy and breastfeeding. There is also a chance of hyperglycemia, as well as retention of uric acid. Because of the side effects mentioned, this medication is contraindicated in patients with gout, anuria, severe hypokalemia and prediabetes or diabetes mellitus (71). Thiazides should be taken in the morning, so that the small increase in urine production does not wake the patient up during nighttime.

CCBs are classified into two main groups; nonhydropyridines and dihydropyridines (*nifedipine* – short-acting, *amlodipine* – long-acting), where the latter group is the one used in the treatment of hypertension. It works by blocking L-type calcium channels in blood vessels, causing vasodilating and a drop of blood pressure. Typical side effects include headache, peripheral edema and reflex tachycardia. This treatment is contraindicated in patients with acute coronary syndrome (72).

There are three different kinds of beta-blockers; combined alpha- and beta-adrenergic receptor antagonist (*carvedilol*, *labetalol*), noncardioselective beta-blockers (*nadolol*, *propranolol*) and cardioselective beta-blockers (*atenolol*, *bisoprolol*, *metoprolol*). Alpha-1 receptors are primarily found in the smooth muscle cells in the walls of blood vessels, leading to contraction, vasoconstriction, increase in peripheral resistance and blood pressure upon activation. Beta-1 receptors are primarily found in the heart, specifically in the sinoatrial node, atria and ventricles. Upon activation, it leads to positive chronotropic and ionotropic effects on the heart. *Carvedilol* works on both alpha- and beta-receptors, thus leading to vasodilation and a decrease in oxygen demand and workload of the heart by decreasing heart rate and contractility. The cardioselective beta-blockers have higher affinity for beta-1 receptors than

for beta-2 receptors and works primarily on the heart. The non-cardioselective beta-blockers have the same affinity for both beta-1 and beta-2 receptors (73).

Additionally, treating hypertension with cannabinoids is an emerging area of research. There is some promising data, but the field is still in its early stages. Cannabidiol is a non-psychoactive substance which have showed promising effect on blood pressure levels in several studies (74-77), although further research needs to be done on the area.

An important concept in both guidelines is the recommendation of a single-pill therapy. This will make it easier for the patient to comply, thereby improving adherence to the drug regiment prescribed by the doctor, which is essential for successful therapy and reaching the target blood pressure (78). There are several combination pills available on the market, combining calcium channel blockers, ACE-inhibitors, angiotension-receptor blockers and thiazides in various combinations. Limiting the treatment to one dose a day also improves adherence and thereby the results. Both the ESH and the ACC/AHA guidelines recommend that initial pharmacotherapy includes one of the following types of drugs; ACEIs, ARBs, CCBs or thiazide diuretics (1).

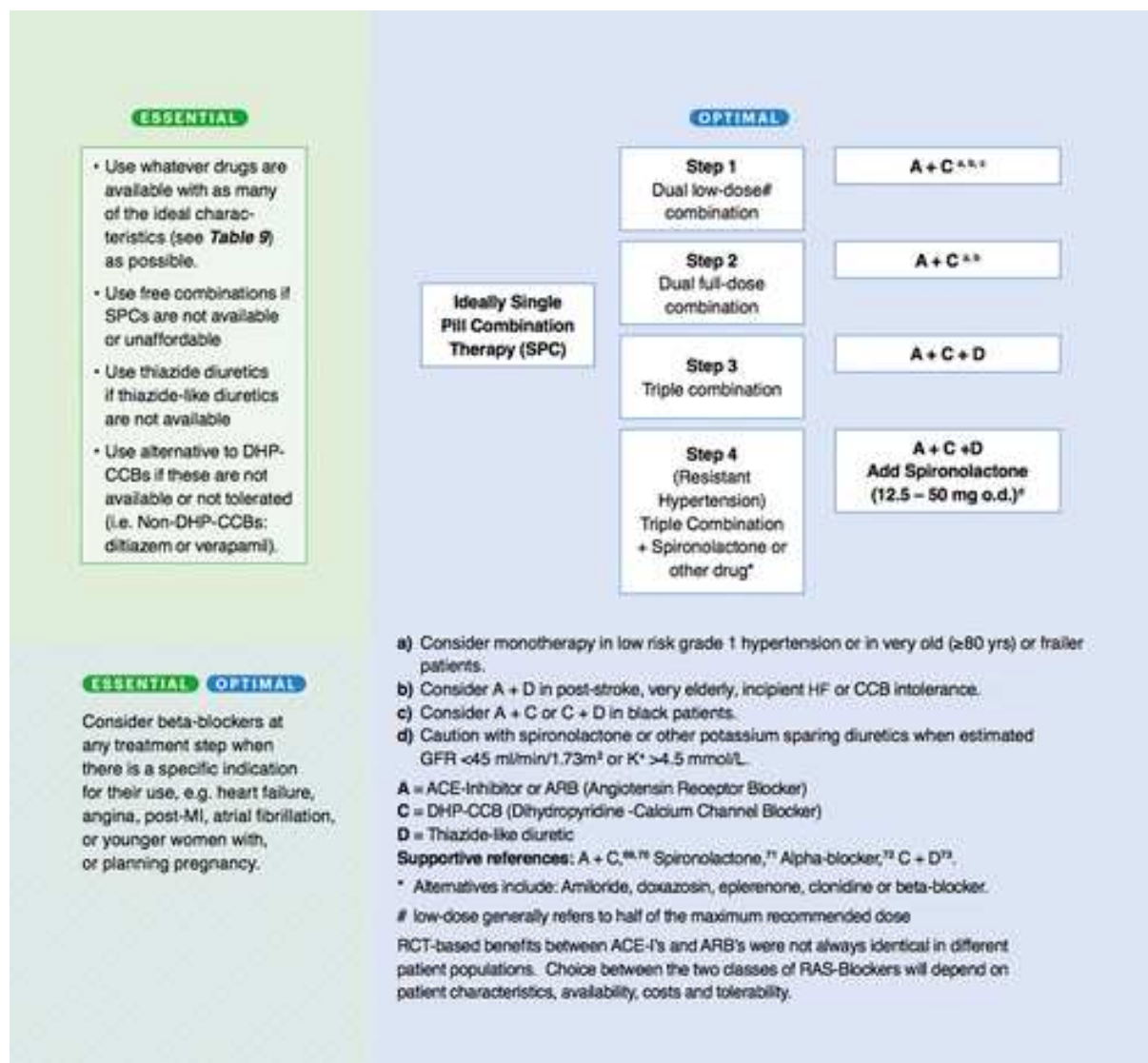


Figure 5. Treatment in Hypertension.

Source: Jordan J, Kurschat C, Reuter H. Arterial hypertension. Hypertension. 2021;77(2):299-310 (65).

Treatment guidelines can somewhat vary among different patient groups. In patients with diabetes mellitus, albuminuria or renal disease, ARBs or ACEIs are preferred, due to their nephroprotective effect (79). Black patients should include thiazide diuretics or CCBs in their initial treatment (80). This is also the case for patients with isolated systolic hypertension (81).

Both the ESH and the ACC/AHA guidelines recommend beta-blockers to be used in patients with hypertension combined with a history of ischemic heart disease or heart failure with reduced ejection fraction(carvedilol). The ESH guidelines also have this medication as an optional first-line therapy in all patients. The ESH guidelines also recommends beta-blockers in patients with atrial fibrillation, tachycardia, hypertension in pregnancy (labetalol) and hyperthyroidism (82). In patients with heart failure with preserved ejection fraction and a volume overload initial treatment should be a diuretic. If ejection fraction is preserved and there is no current volume overload, a diuretic, which kind depends on the kidney function, should be combined with an ARB or ACEi.

Beta blockers should be avoided as hypertensive treatment in patients with asthma, due to the bronchoconstrictive effect it has. Cardioselective beta-blockers can be used in this patient group if there is a particular indication (83).

The antihypertensive effect of taking thiazide diuretics is reduced in patients with reduced kidney function (creatinine clearance of 30-50ml/min). In advanced kidney failure where GFR is less than 30 milliliters per minute, loop diuretics (*furosemide*) can be used instead. Thiazides should also be avoided in gout patients, as uric acid levels can be increased by this medication (84). These patients should instead use ARBs, ACEIs and CCBs.

1.2 PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)

Plasminogen Activator Inhibitor-1 (PAI-1) is a protein that is critical in the regulation of fibrinolysis, a process that prevents blood clots from growing extensively. It is a member of the serine protease inhibitor (serpin) family and functions primarily by inhibiting tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) activity. These are enzymes involved in the conversion of plasminogen to plasmin, an essential enzyme for clot degradation (85).

1.2.1 Structure and function

PAI-1 is a protein that weighs 45 kilodalton and is encoded by the SERPINE1 gene on chromosome 7 (7q21.3-q22). It is composed of 379 amino acids. Various cell types, including endothelial cells, adipocytes, hepatocytes and platelets produce PAI-1. Structurally, PAI-1 is

characterized by a reactive center loop that is responsible for binding tPA and uPA. It also has a shutter region that undergoes conformational changes crucial for its inhibitory activity. In its active form, PAI-1 rapidly inhibits tPA and uPA by forming stable complexes with these enzymes, thereby preventing the conversion of plasminogen to plasmin. Plasmin is a potent proteolytic enzyme that breaks down fibrin clots, and by inhibiting its formation, PAI-1 plays a vital role in controlling clot stability and dissolution. However, PAI-1 is inherently unstable and can convert to a latent form that has no inhibitory activity, a process regulated by various molecular chaperones and binding partners (85).

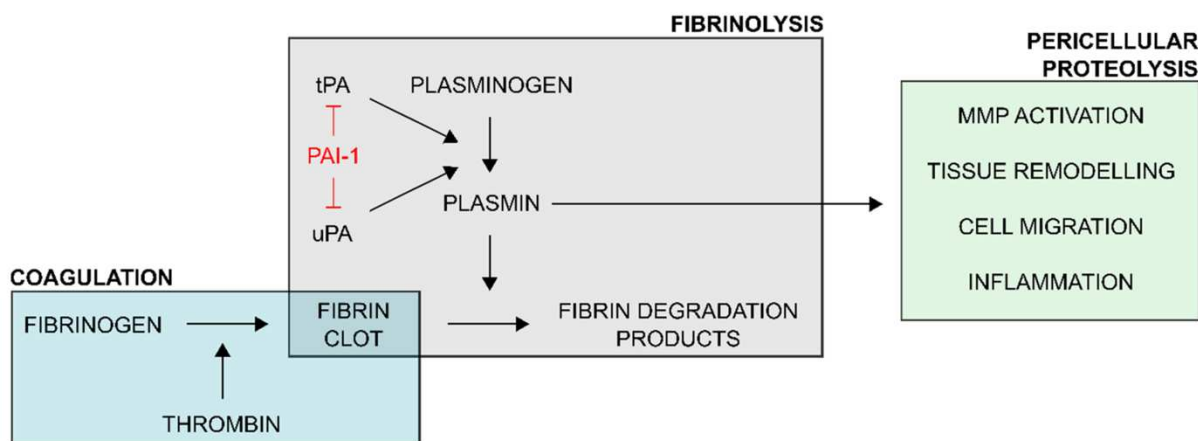


Figure 6. Function of PAI-1. tPA: Tissue Plasminogen Activator, PAI-1: Plasminogen Activator Inhibitor, uPA: Urokinase Plasminogen Activator, MMP: Matrix Metalloproteinase Activation.

Source: Sillen M, Declerck PJ. A narrative review on plasminogen activator inhibitor-1 and its (patho)physiological role: to target or not to target? *Int J Mol Sci.* 2021;22(5):2721 (85).

1.2.2 Regulation of PAI-1

The expression and activity of PAI-1 are tightly regulated at multiple levels, including transcriptional, post-transcriptional, and post-translational modifications. Several factors influence PAI-1 levels, for example cytokines, hormones, metabolic states, genetic variants and lifestyle. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) can upregulate PAI-1 expression (86). Additionally, hormones like insulin and glucocorticoids are known to increase PAI-1 levels, linking it to metabolic and stress responses (87). Insulin resistance and hyperglycemia, common in conditions like obesity and type 2 diabetes, are associated with elevated PAI-1 levels (88). Adipose tissue, particularly visceral fat, is a significant source of PAI-1, which partly explains the increased risk of thrombotic events in obese individuals (86). Polymorphisms in the SERPINE1 gene, such as

the 4G/5G promoter polymorphism, influence PAI-1 expression. Individuals with the 4G allele tend to have higher PAI-1 levels, which can contribute to a prothrombotic state (89). Factors such as diet, physical activity, and stress can also impact PAI-1 levels. For example, high-fat diets and sedentary lifestyles are linked to increased PAI-1, whereas regular physical activity can help reduce its levels (90).

1.2.3 PAI-1 and diseases

Elevated PAI-1 levels have been implicated in various pathological conditions, particularly those related to cardiovascular health and metabolic syndrome. High PAI-1 levels can reduce fibrinolysis, leading to an increased risk of thrombotic events such as myocardial infarction, stroke, and deep vein thrombosis. Additionally, PAI-1 is involved in the development and progression of several other diseases, for example cardiovascular diseases, metabolic syndromes, diabetes, cancer and in fibrotic diseases like pulmonary fibrosis, liver cirrhosis and chronic kidney disease. Elevated PAI-1 is a significant risk factor for cardiovascular diseases. By inhibiting fibrinolysis, high PAI-1 levels contribute to atherothrombosis, where atherosclerotic plaques can rupture and form occlusive thrombi. Patients with coronary artery disease often exhibit high plasma PAI-1 levels, which correlate with the severity of the disease (91). PAI-1 is closely linked to insulin resistance and type 2 diabetes. Adipose tissue, particularly visceral fat, secretes PAI-1, and its levels are often elevated in obese individuals. This elevation is associated with increased risk of thrombotic events and the development of cardiovascular complications in diabetic patients (50). PAI-1 is involved in cancer progression and metastasis. While it inhibits fibrinolysis, it also interacts with cell surface receptors and extracellular matrix components, influencing tumor cell adhesion, migration, and invasion. High PAI-1 levels are associated with poor prognosis in various cancers, including breast, ovarian, and gastric cancers (92). PAI-1 plays a role in tissue fibrosis by modulating extracellular matrix turnover. Elevated PAI-1 levels are observed in fibrotic conditions such as pulmonary fibrosis, liver cirrhosis, and chronic kidney disease, where it contributes to excessive deposition of extracellular matrix components (93).

1.2.4 Therapeutic target

Given its central role in regulating fibrinolysis and its involvement in various diseases, PAI-1 is a potential therapeutic target. Several approaches are being explored to modulate PAI-1 levels or activity, for example PAI-1 inhibitors, gene therapy, lifestyle interventions like weight loss and exercise and various pharmacological agents. Small molecule inhibitors and

monoclonal antibodies targeting PAI-1 are under development to enhance fibrinolysis and reduce thrombotic risk. These inhibitors aim to neutralize PAI-1 activity, thereby promoting clot breakdown (92). Approaches to downregulate SERPINE1 gene expression using RNA interference (RNAi) or CRISPR-Cas9 mediated gene editing are being investigated. RNAi involves small molecules binding to mRNA transcripts in the process of making these PAI-1 proteins, thereby inhibiting expression of the SERPINE1 gene. This reduction in protein synthesis can decrease the levels of PAI-1. The CRISPR-Cas9 strategy involves a Cas9-protein attached to a Guide RNA (gRNA). The gRNA guides the Cas9-protein to the SERPINE1 gene, where it makes a cut in the gene. The cell tries to repair this interruption in the genetic code, but often not successfully enough to produce functional PAI-1. These strategies aim to reduce PAI-1 production and alleviate its pathological effects (90). Given the influence of metabolic and lifestyle factors on PAI-1 levels, interventions such as weight loss, increased physical activity, and dietary modifications are effective in lowering PAI-1 levels and reducing associated disease risks (92). Certain medications, such as angiotensin-converting enzyme (ACE) inhibitors, statins, and thiazolidinediones, have been shown to reduce PAI-1 levels as part of their therapeutic effects in managing hypertension, dyslipidemia, and diabetes (92).

1.2.1.5 Role in Hypertension

Hypertension is often accompanied by vascular remodeling. Elevated PAI-1 levels can contribute to this by interfering with the balance between extracellular matrix deposition and degradation. Accumulation of extracellular matrix can contribute to vessel stiffening and narrowing (87). Elevated PAI-1 levels are also associated with endothelial dysfunction, which can be a key factor in the development of hypertension. PAI-1 can induce inflammation and reduce nitric oxide availability, a molecule that produces vessel dilation (87). Metabolic syndrome is a condition including hypertension, insulin resistance, dyslipidemia and obesity. Insulin resistance can impair vasodilation, thereby contributing to hypertension. Elevated PAI-1 levels are associated with this syndrome. This is another example of how PAI-1 can cause hypertension (88). High levels of PAI-1 contribute to a prothrombotic state, meaning an increased tendency for clot formation. Hypertension is a major risk factor for cardiovascular diseases, including stroke and myocardial infarction, where thrombosis plays a critical role. By inhibiting fibrinolysis, elevated PAI-1 levels can increase the risk of thrombotic events in hypertensive individuals (93).

In summary, PAI-1 is a critical regulator of fibrinolysis and plays a significant role in maintaining hemostatic balance. Dysregulation of PAI-1 is associated with a wide range of diseases, particularly those involving thrombotic and fibrotic processes. Understanding the

mechanisms governing PAI-1 expression and activity has important implications for developing targeted therapies to treat conditions associated with abnormal fibrinolysis.

2. OBJECTIVES

The principal aim of the present study was to explore differences in PAI-1 serum concentrations between patients with arterial hypertension compared to healthy age- and sex-matched controls. Additionally, we aimed to evaluate the correlation between PAI-1 serum concentrations and various anthropometric, clinical, and laboratory parameters in patients with arterial hypertension.

Hypotheses:

1. PAI-1 serum concentrations are significantly higher in patients with arterial hypertension compared to healthy age- and sex-matched controls.
2. PAI-1 serum concentrations are significantly higher in obese hypertensive patients compared to non-obese hypertensive patients.
3. There is a significant positive correlation between PAI-1 serum concentrations and diastolic blood pressure in patients with arterial hypertension.

3. SUBJECTS AND METHODS

3.1 Study design

The current research was carried out as a cross-sectional study at the Department of Pathophysiology, University of Split School of Medicine, Split, Croatia. Ethical approval was obtained from the Ethical Committee of the University of Split School of Medicine, adhering to the principles of the Declaration of Helsinki. All participants received detailed information about the study procedures before enrollment, and informed consent was obtained from each participant prior to their inclusion in the study.

3.2 Subjects

Of the total 80 participants enrolled, 40 were diagnosed with primary hypertension, while the remaining 40 were selected as healthy controls. Inclusion criteria required participants to be between 40 and 70 years of age, have Grade 1 or Grade 2 hypertension according to European Society of Cardiology guidelines, and have a BMI ranging from 18.5 to 35 kg/m² (94). Exclusion criteria included the presence of secondary hypertension, use of antihypertensive medications other than ACE inhibitors, calcium channel blockers, or diuretics, smoking, consumption of CBD-containing supplements, presence of chronic conditions such as heart failure, malignancy, liver cirrhosis, diabetes mellitus, chronic kidney disease, and epilepsy, as well as significant psychiatric disorders. Patients with hypertension were subclassified into obese (≥ 30 kg/m²) and non-obese (< 30 kg/m²).

3.3 Study protocol

The assessment included a comprehensive battery of evaluations, comprising blood sampling, bioimpedance analysis, anthropometric measurements, office blood pressure (BP), ambulatory BP monitoring, and completion of various surveys. Participants were outfitted with the Schiller BR-102 plus PWA 24-hour ambulatory BP monitoring system (Schiller AG, Baar, Switzerland) for continuous BP monitoring outside the laboratory. The device recorded BP readings every 30 minutes during the day (08:00 – 23:00) and hourly during the night (23:00 – 08:00), employing the Casadei method for interpretation.

Venous blood samples were collected from the participants' antecubital veins following a 12-hour fasting period. Biochemical analyses were conducted in a certified institutional laboratory following standard protocols. Laboratory personnel conducting the analyses were blinded to the participants' group allocations. Serum PAI-1 levels were assessed using ProcartaPlex multiplex immunoassays (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA). This technology utilizes Luminex xMAP (multi-analyte profiling) technology, enabling simultaneous detection and quantification of up to 80 protein targets in a

single 25–50 μ L sample of body fluids. Luminex technology utilizes uniquely dyed capture beads for each target in a multiplex ELISA-like assay, which are individually read using an xMAP instrument.

3.4 Statistical analysis

Data analysis and graphical representation were conducted using MedCalc Statistical Software version 20.113 (MedCalc Software Ltd., Ostend, Belgium) and SigmaPlot (Systat Software Inc., San Jose, CA, USA). Quantitative data were presented as mean \pm standard deviation (SD), while categorical data were reported as counts (n) and percentages (%). The normality of data distribution was assessed using the Shapiro-Wilk test. For comparisons involving categorical variables, the Chi-squared (χ^2) test was utilized. Student's t-test for independent samples or Mann Whitney test were employed for comparing quantitative variables. Correlation analysis between PAI-1 serum concentrations and selected anthropometric, clinical and laboratory parameters was performed using Pearson's correlation analysis. Statistical significance was defined as $P < 0.05$ for all analyses.

4. RESULTS

A total of 80 participants was included in the present study. Out of 80 participants, 40 patients were diagnosed with primary hypertension, whereas the other 40 were healthy age- and sex-matched controls. Patients with hypertension had significantly higher BP levels ($P < 0.001$), triglyceride serum concentrations ($P = 0.008$) and total cholesterol levels ($P = 0.028$). Baseline characteristics of the studied population were described in detail in the **Table 1**.

Table 1. Baseline characteristics of the study population.

Parameter	Hypertension group (n = 40)	Control group (n = 40)	<i>P</i> *
Age, years	55. ± 8.1	55.4 ± 7.3	0.861
Male sex, n (%)	22 (55%)	21 (52.5%)	0.822
Body mass index, kg/m ²	26.9 ± 2.9	26.2 ± 2.5	0.251
Disease duration, years	-	4 (2 – 6)	-
Systolic blood pressure, mmHg	139.7 ± 12.2	122.4 ± 8.2	<0.001
Diastolic blood pressure, mmHg	89.8 ± 6.1	79.9 ± 9.1	<0.001
Total cholesterol, mmol/L	5.7 ± 1.1	5.2 ± 0.9	0.028
LDL, mmol/L	3.5 ± 1.1	3.1 ± 1.0	0.092
HDL, mmol/L	1.5 ± 0.3	1.5 ± 0.2	0.998
Triglycerides, mmol/L	1.6 ± 0.8	1.2 ± 0.5	0.008

Abbreviations: LDL: low-density lipoprotein; HDL: high density lipoprotein.

* Student's t-test or chi squared test, as appropriate

Data are shown as mean ± standard deviations, median and interquartile range, or number and percentage, as appropriate

PAI-1 serum concentrations were significantly higher in patients with arterial hypertension in comparison to healthy age- and sex-matched controls ($4327,52 \pm 1100,26$ pg/mL vs. $2278,35 \pm 1046,43$ pg/mL, $P < 0.001$) (**Figure 7**).

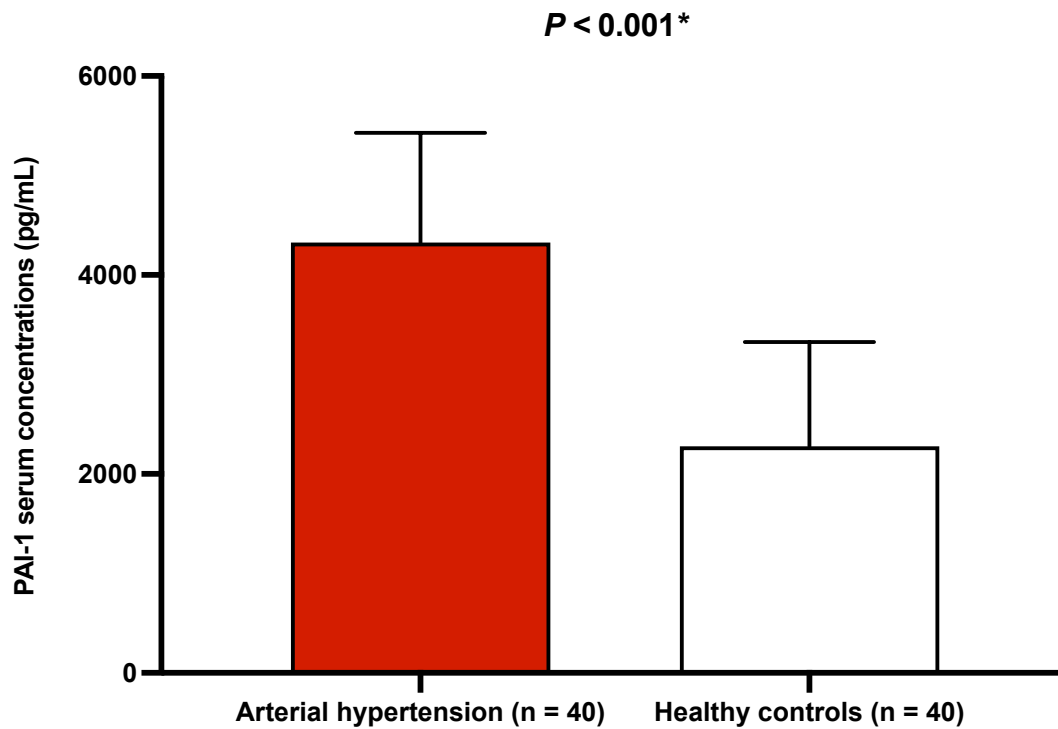


Figure 7 Comparison of PAI-1 concentrations between patients with arterial hypertension and healthy age and sex-matched controls. PAI-1: Plasminogen activator inhibitor-1. Data is shown as mean \pm standard deviation.

*Student's t-test

PAI-1 serum concentrations were significantly higher in obese hypertensive patients when compared to non-obese hypertensive patients (4445.32 ± 1146.36 pg/mL vs. 4173.88 ± 1211.33 pg/mL, $P = 0.031$) (**Figure 8**).

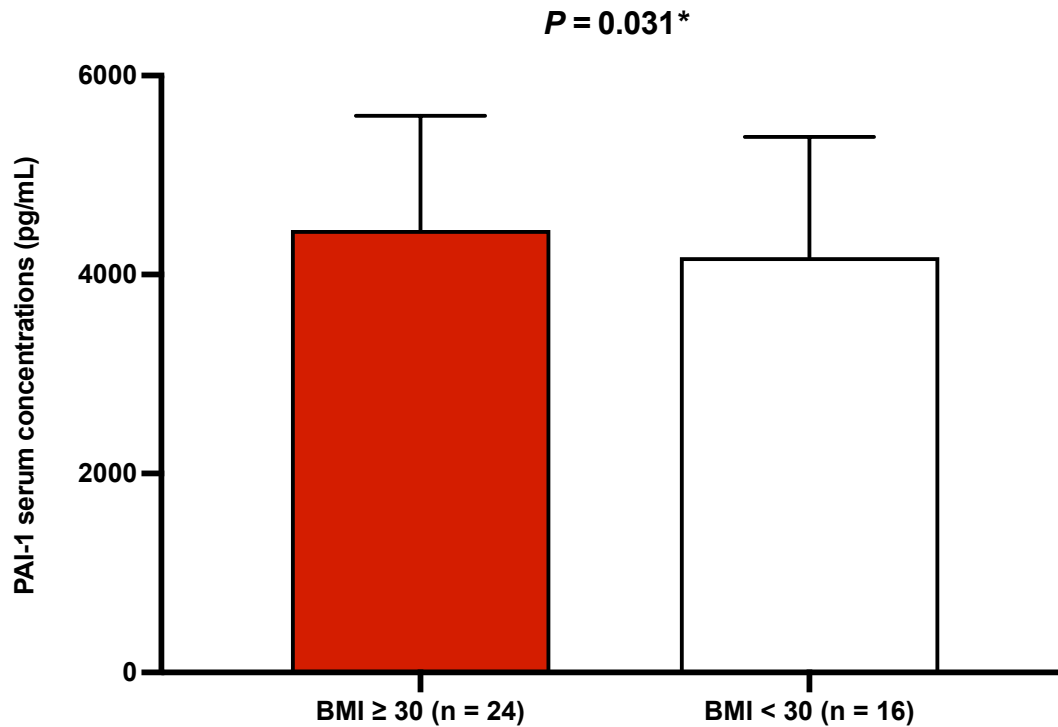


Figure 8. Comparison of PAI-1 concentrations between obese and non-obese patients with arterial hypertension. PAI-1: Plasminogen activator inhibitor-1. Data is shown as mean \pm standard deviation.

*Student's t-test

Correlation analysis between PAI-1 serum concentrations and various anthropometric, clinical, and laboratory parameters was presented in **Table 2**. There were no significant correlations between PAI-1 concentrations and age ($P = 0.358$), BMI ($P = 0.164$), total cholesterol ($P = 0.367$), LDL-C ($P = 0.305$), HDL-C ($P = 0.281$), or triglycerides ($P = 0.265$). However, a significant positive correlation was found between PAI-1 concentrations and diastolic blood pressure ($r = 0.314$, $P = 0.004$), indicating that higher PAI-1 levels are associated with increased diastolic blood pressure. The correlation with systolic blood pressure was marginally not significant ($P = 0.059$).

Table 2. Correlation analysis between PAI-1 serum concentrations and selected anthropometric, clinical and laboratory parameters.

Parameter	r–correlation coefficient	P*
Age	-0.104	0.358
BMI	0.157	0.164
Total cholesterol	-0.102	0.367
LDL-C	-0.116	0.305
HDL-C	0.122	0.281
Triglycerides	-0.126	0.265
Systolic blood pressure	0.212	0.059
Diastolic blood pressure	0.314	0.004

Abbreviations: BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol *Pearson’s correlation coefficient

5. DISCUSSION

The present study provides evidence that serum concentrations of plasminogen activator inhibitor-1 (PAI-1) are significantly elevated in patients with arterial hypertension compared to healthy controls. This finding aligns with the established understanding of PAI-1 as a key player in the pathophysiology of hypertension, where elevated levels are often indicative of impaired fibrinolysis and increased thrombotic risk (95). This finding is consistent with previous research demonstrating a link between increased PAI-1 levels and hypertension (96, 97). Moreover, this elevation in PAI-1 levels could be a marker for endothelial dysfunction, which is a known contributor to the development and progression of hypertension (95). The study also shows that obese hypertensive patients have higher PAI-1 concentrations than non-obese hypertensive patients, suggesting that obesity may exacerbate the impairment of fibrinolysis in hypertension. This observation highlights the synergistic effect of obesity on hypertension, potentially through mechanisms involving chronic inflammation and endothelial dysfunction (98).

Further adding to the complexity, PAI-1 is known to be upregulated in adipose tissue, which could partly explain the elevated levels seen in obese individuals with hypertension (98). Correlation analysis revealed a significant positive association between PAI-1 levels and diastolic blood pressure (99), indicating that higher PAI-1 is related to increased diastolic BP. This relationship underscores the potential of PAI-1 as a marker for vascular health, where higher levels may reflect ongoing vascular damage and remodeling processes that contribute to sustained elevated blood pressure (95). This supports the notion that PAI-1 may play a role in the pathogenesis of hypertension by promoting vascular remodeling and fibrosis (96). The positive association also suggests that targeting PAI-1 could help in managing diastolic hypertension, which is often more challenging to treat (95, 98). However, the lack of significant correlations between PAI-1 and other factors such as age, BMI, and lipid profile suggests that the relationship between PAI-1 and hypertension is complex and likely involves multiple mechanisms (99).

Moreover, the interaction between PAI-1 and the renin-angiotensin-aldosterone system (RAAS) could further complicate this relationship, as both pathways are crucial in blood pressure regulation and may influence each other (98).

The study's limitations include its single-center design, cross-sectional nature, and lack of inclusion of grade 3 hypertension. A multi-center approach could provide more generalized results, enhancing the validity and applicability of the findings across diverse populations. The cross-sectional design precludes establishing causality, as it is unclear whether elevated PAI-1 is a cause or consequence of hypertension. Additionally, the single-center design may limit the

generalizability of the findings to broader populations. Future longitudinal studies are needed to clarify the temporal relationship between PAI-1 and the development of hypertension. Such studies would be instrumental in understanding the progression of PAI-1 elevation in relation to hypertension onset and progression.

Despite these limitations, the study's findings have important clinical implications. Elevated PAI-1 levels may contribute to the increased cardiovascular risk associated with hypertension, particularly in obese individuals. Given that cardiovascular events remain a leading cause of morbidity and mortality in hypertensive patients, understanding the role of PAI-1 could aid in risk stratification and personalized treatment approaches (98). Targeting PAI-1 could potentially represent a novel therapeutic approach for reducing cardiovascular complications in hypertensive patients. Developing PAI-1 inhibitors or therapies that modulate its activity might offer new avenues for treatment, particularly for those who do not respond well to conventional therapies (95). However, further research is needed to determine the clinical utility of PAI-1 as a biomarker and to explore the efficacy of PAI-1-targeted interventions. Such research could pave the way for innovative treatments that specifically address the underlying fibrinolytic defects associated with hypertension (95).

In conclusion, this study demonstrates that serum PAI-1 concentrations are significantly higher in patients with arterial hypertension compared to healthy controls, with obesity exacerbating this effect. These findings add to the growing body of literature that positions PAI-1 as a critical biomarker and potential therapeutic target in hypertension management (95). The positive correlation between PAI-1 and diastolic blood pressure suggests that PAI-1 may play a role in the pathogenesis of hypertension. The identification of PAI-1 as a contributing factor to diastolic hypertension highlights the need for targeted therapeutic strategies (95). Future longitudinal studies are needed to clarify the causal relationship between PAI-1 and hypertension and to investigate the potential of PAI-1 as a therapeutic target for reducing cardiovascular risk in this population. By elucidating these relationships, future research could significantly enhance our ability to combat the cardiovascular risks associated with hypertension, ultimately improving patient outcomes.

6. CONCLUSION

1. PAI-1 serum concentrations are significantly higher in patients with arterial hypertension compared to healthy age- and sex-matched controls.
2. Within hypertensive patients, those who are obese exhibit significantly higher PAI-1 serum concentrations compared to non-obese hypertensive patients.
3. A significant positive correlation exists between PAI-1 serum concentrations and diastolic blood pressure, indicating that higher PAI-1 levels are associated with increased diastolic blood pressure.
4. PAI-1 serum concentrations do not show significant correlations with age, BMI, total cholesterol, LDL-C, HDL-C, or triglycerides, indicating that these factors may not directly influence PAI-1 levels in hypertensive patients.

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8. SUMMARY

Objectives: The primary objective of this study was to evaluate the differences in plasminogen activator inhibitor-1 (PAI-1) serum concentrations between hypertensive patients and healthy controls and to assess the potential impact of obesity on PAI-levels within the hypertensive population.

Subjects and methods: This cross-sectional study enrolled two groups, each consisting of 40 participants. One group consisted of patients diagnosed with hypertension, while the other one consisted of age- and sex-matched healthy controls. Serum PAI-1 concentrations were measured in a cohort of patients with arterial hypertension and age- and sex-matched healthy controls. Participants were categorized into obese and non-obese groups based on body mass index, with 30 kg/m² set as the threshold. Clinical parameters including blood pressure, lipid profile, and anthropometric data were collected. Correlation analysis between PAI-1 levels and various clinical and laboratory parameters was performed using Pearson's correlation coefficient.

Results: PAI-1 serum concentrations were significantly higher in patients with arterial hypertension in comparison to healthy age- and sex-matched controls (4327.52 ± 1100.26 pg/mL vs. 2278.35 ± 1046.43 pg/mL, $P < 0.001$). Furthermore, PAI-1 serum concentrations were significantly higher in obese hypertensive patients when compared to non-obese hypertensive patients (4445.32 ± 1146.36 pg/mL vs. 4173.88 ± 1211.33 pg/mL, $P = 0.031$). A significant positive correlation was found between PAI-1 levels and diastolic blood pressure ($r = 0.314$, $P = 0.004$). No significant correlations were found between PAI-1 and age, BMI, total cholesterol, LDL-C, HDL-C, or triglycerides, indicating that these factors may not directly influence PAI-1 levels in hypertensive patients.

Conclusion: Overall, these findings suggest that PAI-1 may be a useful biomarker for cardiovascular risk stratification in hypertensive patients. In addition, observations concerning difference in PAI-1 depending on body mass index highlight the impact of obesity on hypertensive pathology.

9. CROATIAN SUMMARY

Naslov: Inhibitor aktivatora plazminogena-1 (PAI-1) u pacijenata s primarnom hipertenzijom

Ciljevi: Primarni cilj ove studije bio je procijeniti razlike u koncentracijama PAI-1 u serumu između hipertenzivnih bolesnika i zdravih ispitanika te procijeniti potencijalni utjecaj pretilosti na razine PAI-1 unutar hipertenzivne populacije.

Ispitanici i metode: Studija je uključivala dvije skupine, svaka od 40 sudionika. Jedna skupina sastojala se od bolesnika s dijagnozom hipertenzije, dok je druga skupina uključivala dobno i spolno usklađene zdrave ispitanike. Koncentracije PAI-1 u serumu mjerene su u kohorti bolesnika s arterijskom hipertenzijom i dobno i spolno usklađenim zdravim ispitanicima. Sudionici su kategorizirani u pretile i nepretile skupine prema indeksu tjelesne mase, s pragom postavljenim na 30 kg/m². Prikupljeni su klinički parametri, uključujući krvni tlak, lipidni profil i antropometrijske podatke. Korelacijska analiza između razina PAI-1 i različitih kliničkih i laboratorijskih parametara provedena je korištenjem Pearsonovog korelacijskog koeficijenta.

Rezultati: Koncentracije PAI-1 u serumu bile su značajno više u bolesnika s arterijskom hipertenzijom u usporedbi sa zdravim dobno i spolno usklađenim ispitanicima ($4327,52 \pm 1100,26$ pg/mL naspram $2278,35 \pm 1046,43$ pg/mL, $P < 0,001$). Nadalje, koncentracije PAI-1 u serumu bile su značajno više u pretilih hipertenzivnih bolesnika u usporedbi s nepretilim hipertenzivnim bolesnicima ($4445,32 \pm 1146,36$ pg/mL naspram $4173,88 \pm 1211,33$ pg/mL, $P = 0,031$). Pronađena je značajna pozitivna korelacija između razina PAI-1 i dijastoličkog krvnog tlaka ($r = 0,314$, $P = 0,004$). Nisu pronađene značajne korelacije između PAI-1 i dobi, BMI-a, ukupnog kolesterola, LDL-C-a, HDL-C-a ili triglicerida, što ukazuje na to da ovi faktori možda ne utječu izravno na razine PAI-1 u hipertenzivnih bolesnika.

Zaključak: Ovi rezultati sugeriraju da PAI-1 može biti koristan biomarker za stratifikaciju kardiovaskularnog rizika u hipertenzivnih bolesnika. Osim toga, zapažanja o razlikama u razinama PAI-1 ovisno o indeksu tjelesne mase naglašavaju utjecaj pretilosti na patologiju hipertenzije.