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Comparative Evaluation of Guideline-Recommended Pharmacologic Management of Hypertension

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Abstract

Hypertension is a ubiquitous condition and poses one of the biggest preventable causes of cardiovascular mortality and morbidity worldwide. Despite the availability of effective diagnostic and therapeutic strategies, significant uncertainty persists regarding optimal treatment targets, pharmacological approaches and the interpretation of major clinical guidelines. This thesis aimed to provide a comprehensive overview of contemporary hypertension management, with focus on differences between international current guideline recommendations and their implication for clinical decision making. A structured review and comparative analysis of major hypertension guidelines and relevant clinical evidence was performed, with emphasis on basic underlying principles of hypertension development, screening strategies, non- pharmacological and pharmacological treatment pathways. Special attention was given to the positioning of major antihypertensive drug classes and treatment initiation strategies in newly diagnosed hypertensive patients.

These findings highlight the importance of early detection of subclinical organ damage, the expanded use of ambulatory and home blood pressure monitoring and the growing emphasis on individualized treatment selection based on comorbidities and tolerability and patient characteristics. While first line drug classes demonstrate comparable efficacy in blood pressure reduction, important differences in guideline interpretation and therapeutic prioritization remain. Additionally, uncertainty regarding optimal blood pressure target and long term outcome benefits of specific treatment strategies continues to influence clinical practice. In conclusion, contemporary hypertension management is increasingly shifting toward personalized, outcome driven approaches that integrate early risk stratification and tailored pharmacological therapy. Further research is required to refine treatment targets and optimize therapeutic algorithms to improve long term cardiovascular outcomes.

Zusammenfassung

Bluthochdruck ist eine weit verbreitete Erkrankung und stellt weltweit eine der größten vermeidbaren Ursachen für kardiovaskuläre Mortalität und Morbidität dar. Trotz der Verfügbarkeit wirksamer Diagnose- und Therapiestrategien bestehen weiterhin erhebliche Unsicherheiten hinsichtlich der optimalen Behandlungsziele, der pharmakologischen Ansätze und der Auslegung wichtiger klinischer Leitlinien. Ziel dieser Arbeit war es, einen umfassenden Überblick über das aktuelle Management von Bluthochdruck zu geben, wobei der Schwerpunkt auf den Unterschieden zwischen den aktuellen internationalen Leitlinienempfehlungen und deren Auswirkungen auf die klinische Entscheidungsfindung lag. Es wurde eine strukturierte Überprüfung und vergleichende Analyse der wichtigsten Leitlinien zur Hypertonie sowie der relevanten klinischen Evidenz durchgeführt, wobei der Schwerpunkt auf den grundlegenden Prinzipien der Hypertonieentstehung, Screening-Strategien sowie nicht-pharmakologischen und pharmakologischen Behandlungswegen lag. Besondere Aufmerksamkeit wurde der Positionierung der wichtigsten Klassen von Antihypertensiva und den Strategien zur Einleitung der Behandlung bei neu diagnostizierter Hypertonie gewidmet.

Diese Ergebnisse unterstreichen die Bedeutung der Früherkennung subklinischer Organschäden, des erweiterten Einsatzes von ambulanten und häuslichen Blutdruckmessungen sowie der zunehmenden Gewichtung einer individualisierten Behandlungsauswahl auf der Grundlage von Komorbiditäten, Verträglichkeit und Patientenmerkmalen. Während die Wirkstoffklassen der ersten Wahl eine vergleichbare Wirksamkeit bei der Blutdrucksenkung aufweisen, bestehen weiterhin wichtige Unterschiede in der Interpretation der Leitlinien und der therapeutischen Priorisierung. Darüber hinaus beeinflusst die Unsicherheit hinsichtlich des optimalen Blutdruckziels und der langfristigen Outcome-Vorteile spezifischer Behandlungsstrategien weiterhin die klinische Praxis. Zusammenfassend lässt sich sagen, dass sich das moderne Bluthochdruckmanagement zunehmend in Richtung personalisierter, ergebnisorientierter Ansätze verschiebt, die eine frühzeitige Risikostratifizierung und eine maßgeschneiderte medikamentöse Therapie integrieren. Weitere Forschung ist erforderlich, um die Behandlungsziele zu verfeinern und die therapeutischen Algorithmen zu optimieren, um die langfristigen kardiovaskulären Ergebnisse zu verbessern.

Contents

List of Abbreviations

ABBREVIATION	MEANING
ABPM	Ambulatory blood pressure monitoring
ACC	American college of cardiology
ACEi	Angiotensin converting enzyme inhibitor
AHA	American hypertension association
ALLHAT	Antihypertensive and lipid-lowering treatment to prevent heart attack trial
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
ATP	Adenosine triphosphate
BB	Beta-blocker
BMI	Body mass index
BNP	Brain natriuretic peptide
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CNS	Central nervous system
CV	Cardiovascular
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
DBP	Diastolic blood pressure
DHP-CCB	Dihydropyridine calcium channel blocker
eGFR	Estimated glomerular filtration rate
ENaC	Epithelial sodium channel
ESC	European society of cardiology
ESH	European society of hypertension
FTP	First line therapeutic
GFR	Glomerular filtration rate
HBPM	Home blood pressure monitoring
HCT	Hydrochlorothiazide
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HMOD	Hypertension mediated organ damage
HOPE	Heart outcomes prevention evaluation

HT	Hypertension
ISDN	Isosorbide dinitrate
LV	Left ventricle
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NO	Nitric oxide
NON-DHP-CCB	Non – dihydropyridine calcium channel blocker
PREVENT	Predicting risk of cardiovascular disease EVENTs
RAAS	Renin angiotensin aldosterone system
RCT	Randomized controlled trial
ROMK	Renal outer medullary potassium channel
RP	Reporting proportion
SCORE2	Systematic coronary risk evaluation 2
SCORE2-OP	Systematic coronary risk evaluation 2-older persons
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus

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1. Introduction

Hypertension (HT) is a globally ubiquitous condition and a primary determinant of cardiovascular disease (CVD). Hypertension is defined as increased and/or sustained systolic blood pressure levels above 140 mmHg and/or diastolic pressure above 90 mmHg. Approximately 33% of the global population of 8 billion live with hypertension. Hypertension is one of the leading causes of death from cardiovascular diseases and affects approximately 1 billion people worldwide. Systemic arterial hypertension is a multifactorial disease and can be triggered by factors such as physical inactivity, the intake of sodium-rich foods, obesity, alcohol, and tobacco consumption (Ferreira et al., 2017; León-Latre et al., 2014). Epidemiological data indicate that the mortality risk from cerebrovascular accidents and ischemic heart disease doubles for every 20-mmHg increment in systolic blood pressure (SBP) above 115 mmHg, and for every 10 mmHg rise in diastolic blood pressure (DBP) above 75 mmHg. The economic burden is substantial, with costs in the United States alone estimated at $76.6 billion in 2010. Consequently, optimizing the awareness, therapeutic management, and stringent control of hypertension remains a critical public health imperative to mitigate associated morbidity and mortality(Lewington S. et.al, 2002; Lloyd-Jones et al., 2010). Clear definitions of hypertension and its control are crucial to guide diagnosis, treatment, and surveillance to monitor progress towards HP objective. Indeed, hypertension is one of the most common causes of cardiovascular disease and cardiovascular mortality (Cutler et al., 2008; Egan, 2010; Institute of Medicine (U.S.), 2010).

The prevalence of hypertension increases steeply with age, which is important when considering the growing life expectancy in different countries (Zuin et al., 2025).In 2024 Austria´s life expectancy at birth was 82.3 years on average, despite gender gaps, putting them 6 months above the EU average. Notably, this value was achieved through reduced CVD mortality; nevertheless, cardiovascular disease remains the leading cause of death in Austria. On average 122 000 new CVD cases are registered per annum with approximately 1.2 million people living with a CVD leading to an incidence rate of 1340 per 100 000 of the population and a prevalence rate of 13 222 per 100 000 of the population (estimated in 2021). Incidence rates are 16%higher, and prevalence rates are 2% higher than the EU average. These figures are perhaps unsurprising considered alongside Austria´s average alcohol and tobacco consumption, and obesity rates which are well above the EU average (OECD / European Observatory on Health Systems and Policies, 2025). More recent findings by the WHO show that Austria´s hypertension prevalence is 38% (World Health Organization, 2025). CVD is not only the leading cause of morbidity and mortality in the European region but also in America, where the age-standardized prevalence was estimated at 34.5% (Wadhera et al., 2026).

Hypertension epidemiology is a complex topic with many factors affecting it ranging from traditional lifestyle determinants such as sodium intake and lack of exercise to social factors and physiological

occurrences (Satoh et al., 2026). Equally complex are its aetiology and pathophysiology, which is why the prevention and management of hypertension remains problematic for many countries, as well as being one of the top priorities for healthcare institutions (Wadhera et al., 2026).

Lifestyle modifications are the cornerstone of hypertension prevention and treatment. Beyond reducing blood pressure (BP) and enhancing hypertension control, these changes significantly improve cardiovascular and overall health. Patients frequently identify lifestyle adjustments as their highest priority in managing their condition. Consequently, major hypertension guidelines universally endorse lifestyle modifications as the first-line strategy to mitigate the risk of cardiovascular disease. When pharmacological treatment is necessary, lifestyle changes can synergistically amplify its efficacy. Notably, traditional interventions—such as dietary adjustments, alcohol moderation, smoking cessation, and aerobic exercise—have recently been expanded to include novel strategies like stress reduction, isometric training, and minimizing exposure to environmental pollution. Despite their proven efficacy, sustaining these lifestyle changes long-term remains challenging. Many individuals live in environments that hinder the adoption of healthy habits, and clinicians often lack the specific training required to effectively support behavioural changes. This issue is exacerbated by a lack of tailored information regarding the health literacy, cultural beliefs, and specific needs of diverse ethnic groups in hypertension management (Hanssen et al., 2022; Kaess et al., 2012; Tam et al., 2020).

Furthermore, to improve hypertension control, it is therefore necessary to identify and overcome the associated barriers and find solutions. Some of these barriers are more prevalent in high-income countries, while others are more relevant for low- and middle-income countries. Nevertheless, problems in hypertension management can be attributed to three levels within a healthcare system: the individual patient level, the healthcare system itself and the clinician level. At the patient level the biggest and most crucial barrier to achieving blood pressure control is medication non-adherence. This can be attributed some people not believing in the urgency of hypertension and its treatment, which is linked to a lack of medical literacy. At the healthcare system level, limited access to specialised healthcare facilities or missing primary care can lead to poor hypertension management(Bilo et al., 2025; Smolen et al., 2019). Conversely, physicians often fail to initiate or intensify pharmacological treatment for patients with elevated blood pressure, a phenomenon known as “clinical inertia”. This may be because the clinician trying to accommodate to the patient´s excuses and is not communicating the urgency of hypertension treatment, or because of a lack of training in how to achieve blood pressure control. The latter issue could be addressed by creating proper guidance that is easy to follow and applicable to most of the population. Due to the vast number of guidelines, it is inevitable that clinicians will be confused and uncertain about which to follow, which makes it harder for them to administer proper therapy, achieve long-lasting blood pressure control and ultimately lower the global

health burden. Nevertheless the lack of inpatient protocols creates variability in clinical practice, resulting in overtreatment or delayed intervention (Ogedegbe, 2008; Vempati et al., 2025).

Guidelines aim to create living documents that evolve alongside current knowledge and ultimately helping clinicians apply the latest randomized controlled trials (RCT) evidence (D. W. Jones et al., 2025). Despite often citing similar evidence, guidelines differ in their definitions and classifications of hypertension and treatment to some extent. Not to mention regional differences, social factors (e.g. smoking) and drug availability. This thesis therefore aims to compare and analyse the differences – with particular focus on difference in recommended blood pressure targets, treatment thresholds, pharmacological interventions and treatment algorithms, between the two leading guidelines, namely the latest American Heart Association (2025) (AHA) and European Society of Cardiology (2024) (ESC) guidelines. By systematically comparing these guidelines, this thesis aims to highlight how distinct methodological approaches can lead to variation in clinical recommendations despite addressing the same condition.

1.1. Definition and classification of hypertension

Hypertension, at its base can be defined as an elevation in systolic or diastolic blood pressure or both. Systolic blood pressure can be measured during the systole, the time during the contraction of the heart where blood is ejected into the arteries which causes a surge in arterial blood pressure. On the other hand, one can measure diastolic blood pressure, which is when the heart muscle relaxes after contraction and blood returns from the venous system to the heart. At that time blood pressure hits a trough level which is registered as the SBP (systolic blood pressure). Blood pressure values do not stay the same throughout the day; they follow a predictable diurnal rhythm, and values are lowest during nighttime, rise in the early morning hours and peak at noon (Zeind et al., 2024). This physiologic feature of the cardiovascular system is called blood pressure variability and is influenced by environmental factors (e.g. altitude or stress), emotions and physiologic factors like posture or blood volume (Parati et al., 2018). Since blood pressure is influenced by a plethora of factors, it can be complicated to measure true blood pressure in some individuals, which is why it is better to assess mean arterial pressure if possible, since it is less affected by fluctuations and gives more constant values that are more reliable (Stevens et al., 2016; Zeind et al., 2024).

There are many ways to classify hypertension, but the two major ways are by blood pressure values or by cause. The European Society of Cardiology (ESC) defines hypertension as a confirmed office systolic BP (blood pressure) of >140mmHg and a diastolic BP of >90mmHg. This definition is backed up by evidence from meta-analysis and randomized clinical trials which show that blood pressure lowering treatment is beneficial in patients with a BP above this threshold. Furthermore, patients above this range are at increased risk for fatal and non-fatal CVD (cardiovascular disease) outcomes and therefore BP lowering therapy is beneficial to them. Lastly, since the existing cutoff for high BP is standard, keeping it prevents many people from being classified as sick. Because of that the ESC proposes a new category to classify hypertension into (McEvoy et al., 2024) :

- Non elevated BP (<120/70 mmHg)
- Elevated BP (120-139 / 70-89 mmHg)
- Hypertension (> 140/90 mmHg)

The rationale behind this classification is, that the efficacy of BP-lowering treatment in the elevated BP range has been established in RCTs, but most people are not at high enough CVD risk to justify pharmacological treatment. In the non-elevated BP category, fewer people are at risk of CVD, and evidence for the benefit of BP-lowering treatment in this group is lacking. These categories are supposed to function as treatment categories and not prognostic categories (Giles et al., 2005; Kannel, 1996; Kikuya et al., 2007; Lewington S. et.al, 2002; McEvoy et al., 2024).

Another way to categorize hypertension is by cause, which distinguishes between primary and secondary hypertension. Primary hypertension is defined as hypertension without an underlying identifiable cause for their chronically elevated BP. It is also known as essential hypertension and the majority of hypertensive patients are diagnosed with this type.(McEvoy et al., 2024; Zeind et al., 2024) In contrast, secondary hypertension defined as hypertension that is caused by a disease or by clearly identifiable factors like primary aldosteronism, obstructive sleep apnoea, renovascular hypertension, Cushing syndrome or pheochromocytoma. Its distinction is important because treating the underlying cause may in BP normalization and discontinuation of antihypertensive treatment (Giles et al., 2005; Kannel, 1996; Kikuya et al., 2007; McEvoy et al., 2024; Rossi et al., 2020; Vasan et al., 2001).

If blood pressure control is not feasible through 3 blood pressure lowering drugs, then one might have "resistant hypertension". It is a severe form of hypertension, that is difficult to control and has a bad prognosis and increases the likeliness of an underlying secondary cause (Dybiec et al., 2023; Kannel, 1996; Lamirault et al., 2020; McEvoy et al., 2024; Vasan et al., 2001).

Even more dangerous are hypertensive crises, which are defined as situations in which BP values spike drastically above >180/110 mmHg. They are further distinguished into emergencies and urgencies, although the term "urgency" is seen as ambiguous by the European Society of Cardiology. Hypertensive emergencies are situations with acute or progressive target organ damage and require immediate hospitalization and immediate BP lowering treatment. Hypertensive urgencies come without acute or progressive organ damage and do not require hospitalization, but BP should be lowered slowly over the course of 24h but should not be forced all the way down to achieve target BP. (Khan et al., 2024; Miller et al., 2024; Zeind et al., 2024).

BP serves as a biomarker for the disease hypertension. However, individuals with the same levels of BP might have different stages of hypertension (Table 1). Furthermore, some individuals may exhibit elevated BP in the absence of hypertension. For purposes of calculating total CV risk, BP should be evaluated in the context of other CV risk factors and disease markers (Giles et al., 2005; Kannel, 1996).

1.2. Physiologic mechanisms of blood pressure regulation

Since hypertension represents a significant factor cardiovascular and cerebrovascular diseases and is the primary cause of premature mortality and mortality on a global scale, thus the prevention and control of hypertension represents a crucial global health strategy in the effort to reduce premature mortality from CVDs (Mills et al., 2020; Sudharsanan et al., 2021). Two primary factors dictate blood pressure: intravascular fluid volume and vasodilation capacity. While fluid volume depends on daily intake and output, vasodilation capacity relies on vascular elasticity, caliber and reactivity. The poorer the vasodilation capacity, the higher the blood pressure. Dysregulation in vascular contraction and relaxation is therefore a major driver in the pathogenesis of hypertension. At the cellular level, this dysfunction is largely triggered by aberrant signalling pathways within vascular endothelial cells and vascular smooth muscle cells (Augustin & Koh, 2017; Wenceslau et al., 2021).

In essence, the human body can regulate blood pressure over a short and long period of time via many different mechanisms. Short term regulation mechanisms are characterised by achieving strong reduction of current BP values, a fast onset but short – lived efficacy. Responsible for short term BP regulation are baroreceptors (pressure receptors), arterial chemoreceptors, and the central nervous system (CNS). Long term BP regulation is mostly achieved by controlling changes in blood volume mainly via the renin-angiotensin-aldosterone system (RAAS) (Brandes et al., 2020; Kajikawa & Higashi, 2024; Mogi & Kukida, 2025).

Baroreflex is known to be the most important nervous regulatory mechanism for maintaining balanced blood pressure. Baroreceptors are mechanosensory neurons and are located, among other places, in the epithelium of the carotid sinus and aortic arch. Their main purpose is to serve as real time blood pressure sensors by reacting to changes in blood vessel wall distension and maintaining mean arterial BP by regulating cardiac output and total peripheral resistance (Brandes et al., 2020; Halbach et al., 2020; Min et al., 2019).

Atrial stretch receptors have been demonstrated to regulate both arterial BP and blood volume. In order to comprehend the functionality of stretch receptors, it is imperative to differentiate between to distinct types: Type A and Type B. Type A receptors are located in the atria of the heart. Activation of these receptors leads to stimulation of the sympathetic nervous system but without the usually occurring downregulation of the parasympathetic nervous system. This effect can be seen if large volumes of fluids are administered or if atrial pressure spikes and causes and an increase in heart rate and stroke volume. On the other hand, if B Type stretch receptors are activated it leads to similar effects as if Baroreceptors were activated. Their influence, however, is mostly limited to renal function where they cause strong vasodilation which causes an increase in renal perfusion and ultimately leads to fluid

excretion. Furthermore, B Type receptor activation causes inhibition of renal sympathetic activity thus reducing the activity of the RAAS, which is an important factor in long term BP regulation (Brandes et al., 2020).

Cardiac chemoreceptors react to metabolites and hormones like potassium, bradykinin and adenosine, which are mostly secreted by ischemic myocytes and cause activation of the sympathetic nervous system and an increase in BP (Brandes et al., 2020; Kaufmann et al., 2020; Moore et al., 2022; Salah et al., 2025; Volpe, 1992; Wallbach et al., 2016).

Arterial chemoreceptors are located in the carotid and aortic body and respond to changes in oxygen partial pressure, usually if partial pressure declines. If that is the case, then the respiratory system and sympathetic neurons in the medulla oblongata are activated and cause vasoconstriction and an increase in blood vessel tone. By stimulating the respiratory system, pulmonary stretch receptors become stimulated which inhibit the parasympathetic nervous system and thus heart rate and cardiac output are increased (Brandes et al., 2020; Moore et al., 2022; Volpe, 1992).

Longterm BP regulation via renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin -aldosterone system is a critical hormone cascade primarily driven by angiotensin 2- derived from the proteolytic cleavage of angiotensinogen- and aldosterone. Although research in recent decades has revealed novel, multifaceted dimension of the RAAS, its paramount function continues to be the strict regulation of arterial blood pressure (Triebel & Castrop, 2024). Long-term regulation of arterial blood pressure is mainly carried out by the kidneys through the RAAS, as well as by the filling status and vascular capacity. For example, an increase in arterial blood pressure causes increased excretion of salt and fluid from the kidneys, which lowers cardiac output and thus leads to a reduction in blood pressure. Conversely, a decrease in arterial BP causes the opposite reaction. In contrast to short-term regulation, the long-term system is responsible for bringing blood pressure back to normal over several days. The renin-angiotensin-aldosterone system plays a key role in this process. In the kidneys, there is an increase in renin release as soon as there is a systemic drop in blood pressure or local renal vasoconstriction. In addition to indirect mechanisms such as a decrease in intravascular volume, there may also be a direct increase in renin release, either through beta 1 receptors in the juxtaglomerular apparatus or alpha receptor-mediated vasoconstriction of the afferent arteriole. Renin then leads to increased production of angiotensin 2, which causes sympathetic adrenergic-mediated vasoconstriction. Angiotensin2 has a direct vasoconstrictive effect only on the kidneys and is also the greatest stimulus for the release of aldosterone, which promotes salt and water retention increases blood volume (Bie & Damkjaer, 2010; Brandes et al., 2020; Briet & Schiffrin, 2010; Triebel & Castrop, 2024).

1.3. Pathophysiology of hypertension

As already discussed in the previous chapters, hypertension is a chronic elevation of blood pressure that, over the long term, leads to end organ damage and increased morbidity and mortality. Physiologically, blood pressure is the product of cardiac output and systemic vascular resistance. Consequently, patients with arterial hypertension may exhibit an increase in cardiac output, systemic vascular resistance or both. In younger individuals, cardiac output is frequently elevated, whereas in older patients, heightened systemic vascular resistance and increased vascular stiffness predominate. Vascular tone can be elevated due to enhanced alpha adrenoceptor stimulation or the increased release of vasoactive peptides like angiotensin and endothelin. The final common pathway for these mechanisms is an increase in cytosolic calcium within vascular smooth muscle cells, triggering vasoconstriction. Furthermore, several growth factors -including angiotensin and endothelin- promote an increase in vascular smooth muscle mass, a process known as vascular remodelling. Ultimately, the combined increase in systemic vascular resistance and arterial stiffness significantly augments the hemodynamic load on the left ventricle, inducing left ventricular hypertrophy and subsequent diastolic dysfunction (Cain & Khalil, 2002; Foëx & Sear, 2004).

The elusive aetiology of primary hypertension, alongside the precise mechanisms driving elevated blood pressure in both secondary and experimental models, has remained a central focus of scientific debate and research for over a century (Harrison et al., 2021). Although hypertension presents as a relatively simple phenotype- characterized by an increase in systemic blood pressure above an arbitrarily defined threshold- the underlying mechanisms are highly complex, involving a diverse array of neurohormonal, renal, metabolic and vascular factors. The aetiology of hypertension varies substantially across age groups. In children, it frequently manifests secondary to a renal or endocrine disorder. Conversely, most hypertensive adults present with essential hypertension. This term reflects that the exact mechanisms remain incompletely understood, despite the identification of well-defined pathogenic factors in cases associated with diabetes mellitus, obesity, hyperaldosteronism, renovascular disease or chronic kidney disease. In the elderly, hypertension is predominantly driven by factor related to vascular aging and diminished arterial elasticity(Beevers et al., 2001; Harrison et al., 2021)

A plethora of factors of neural and hormonal origin have been identified as contributors to the regulation of blood pressure. The adrenergic nervous system (alpha and beta adrenoceptors), the renin-angiotensin-aldosterone system (which comprises renin, angiotensin, and aldosterone), renal function and perfusion, hormonal factors (e.g. thyroid) and the vascular system (which regulates the release of nitric oxide) are but a few of the factors to be considered. In the event of dysregulation of blood pressure, specific compensatory mechanisms are typically initiated in response to the altered

cardiac demand. It has been demonstrated that an increase in cardiac output is accompanied by a reduction in total peripheral resistance, and vice versa. Cardiac output and total peripheral resistance primarily influence mean arterial pressure. In the event of a failure of these mechanisms, there will be an increase in peripheral resistance that will be permanent in order to maintain a normal level of cardiac output (Cain & Khalil, 2002; Harrison et al., 2021; Zeind et al., 2024).

The kidneys have been identified as a key component of blood pressure regulation. The primary function of the kidneys is the regulation of natriuresis, blood volume and blood pressure by means of the renin-angiotensin-aldosterone system. Several factors have been identified as potential triggers for renin secretion from the juxtaglomerular apparatus of the kidney. These include a decline in blood pressure or sodium levels, as well as reduced renal perfusion and volume depletion. Renin ultimately leads to the production of angiotensin 2, a highly potent vasoconstrictor and stimulant for the release of aldosterone. In summary, the aforementioned factors result in an elevation of blood pressure, an increase in sodium levels, and an increase in both water retention and potassium excretion. The rise in blood pressure consequently results in the suppression of renin secretion via a negative feedback loop (Harrison et al., 2021; McEvoy et al., 2024; Weinberger, 1996; Zeind et al., 2024). Conversely, elevated sodium intake has been demonstrated to induce the suppression of RAAS, resulting in natriuresis. In the event of systemic RAAS activation, the body requires elevated BP levels to facilitate sodium excretion and maintain adequate volume and BP. A further significant factor to be considered is renal vasoconstriction, which has been demonstrated to result in inflammation, the generation of reactive oxygen species, renal remodelling, and ineffective sodium excretion. This, in turn, can lead to hypertension (Harrison et al., 2021; McEvoy et al., 2024; Weinberger, 1996).

The endothelium plays a pivotal role in regulating vascular tone through the action of nitric oxide (NO), a highly effective vasodilator of smooth muscle tissue. However, in the event of endothelial dysfunction, there is a substantial decrease in the availability of NO (Zeind et al., 2024). Another crucial factor to consider is vascular stiffening in larger arteries, which results in a diminished capacity to buffer the pulsatile flow induced by the contraction of the heart. This phenomenon contributes to an increase in systolic blood pressure (Harrison et al., 2021; Mayet & Hughes, 2003; McEvoy et al., 2024; Weinberger, 1996).

The family of natriuretic peptides, including atrial and brain natriuretic peptides (ANP and BNP), play a key role on blood pressure regulation through the natriuretic, diuretic and vasorelaxant effects. Many A large number of experimental and human studies , ranging from pathophysiological to genetic investigations, supported ANP as the most relevant component of the family able to modulate blood pressure and to contribute to hypertension development (Mayet & Hughes, 2003; Rubattu & Gallo, 2022). Hormones such as natriuretic peptides are vital in regulating BP due to their natriuretic, diuretic

and vasorelaxant properties. Endothelin-1 is a highly potent vasoconstrictive peptide that is synthesised in virtually all cells, with vascular endothelium being the predominant source. Oestrogens have a plethora of effects, but of note is their sodium-retaining ability, which can be negated by progesterone, which is essentially a mineralocorticoid receptor antagonist. Testosterone, depending on the age of the individual, has been shown to either increase or decrease blood pressure. This, in turn, can be a contributing factor to the increased risk of cardiovascular disease observed in elderly male patients, as well as post-menopausal women(McEvoy et al., 2024). Finally, the potential association between insulin resistance and hyperinsulinemia with hypertension is a salient consideration. The authors posit that the underlying mechanism responsible for the coexistence of the four principal factors of the metabolic syndrome (hyperglycaemia, dyslipidaemia, hypertension and obesity) is insulin resistance (Demerath et al., 2014; McEvoy et al., 2024; Zeind et al., 2024).

Alpha adrenergic receptors and beta-adrenergic receptors have also been demonstrated to regulate blood pressure. The stimulation of central alpha adrenoceptors has been demonstrated to result in a reduction of sympathetic outflow, consequently leading to a decrease in blood pressure. The stimulation of peripheral alpha adrenoceptors by endogenous transmitters such as norepinephrine instigates the contraction of smooth muscle tissue, a process that is subject to the regulation of a negative feedback mechanism. The stimulation of peripheral beta adrenoceptors results in vasodilation, while the activation of cardiac beta adrenoceptors leads to an increase in heart rate and contractility. The sympathetic nervous system plays a pivotal role in blood pressure regulation and is observed to be upregulated in hypertensive patients compared to normotensive individuals. Upregulation commences in the early hypertensive stages and increases with age and hypertension severity. The phenomenon under investigation has been shown to increase blood pressure via several mechanisms, including peripheral vasoconstriction, stronger cardiac contraction, decreased venous capacitance and regulation of renal sodium and water excretion. The sympathetic nervous system has also been implicated in obesity-related hypertension, chronic kidney disease (CKD) and obstructive sleep apnoea syndrome. A divergence in autonomic regulation is evident between the sexes, with women exhibiting augmented sympathetic activity with advancing age and obesity, concomitant with diminished baroreceptor reflex sensitivity and reduced heart rate variability (McEvoy et al., 2024; Rubattu & Gallo, 2022; Zeind et al., 2024).

1.4. Clinical consequences of hypertension.

Systemic hypertension represents one of the most important modifiable determinants of premature morbidity and mortality, primarily through its strong contribution to cardiovascular disease. Although effective, pharmacological and non-pharmacological treatments are available, a substantial proportion of affected individuals remain undiagnosed or insufficiently treated. The development of hypertension is influenced by multiple interacting factors, including genetic susceptibility, environmental exposures and functional alterations in several organ systems involved in blood pressure regulation. Clinical management therefore requires reliable and standardized blood pressure measurement as well as an estimation of overall cardiovascular risk. In addition, patients should be evaluated for evidence of target organ damage, potentially reversible secondary causes of hypertension and relevant comorbidities such as chronic kidney disease. Non- pharmacological strategies. particularly improvements in diet and physical activity, play a crucial role in both the prevention and treatment of elevated blood pressure and may substantially reduce long-term cardiovascular complications. Persistently elevated BP can lead to hypertension mediated organ damage (HMOD), which is characterized by functional and structural changes in arteries or the organs they supply. The authors acknowledge that there are scenarios where other factors like diabetes can cause the same structural and functional alterations.(Chunyu et al., 2016; McEvoy et al., 2024; Surendran et al., 2016)

The brain poses an early target for hypertension mediated organ damage (HMOD). Some possible outcomes, if untreated, include stroke and transient ischaemic attack and cognitive decline. More importantly silent infarcts, micro bleeds and white matter lesions predict future stroke and cognitive impairment independently of other vascular risk factors, which means that damage can occur before the symptoms appear. Hypertension causes structural changes in cerebral blood vessels and disrupts the autoregulation of brain perfusion and increases the risk of cerebral aneurysms forming and rupturing as well as brain atrophy. Cognitive decline is most likely linked to hypoperfusion, dysfunctional autoregulation and cerebral vessel remodelling, all caused by sustained high BP over a long period of time. Neuroimaging also shows increased amounts of amyloid plaques, neurofibrillary tangles and brain atrophy suggesting possible contribution of hypertension to neurodegenerative processes. In summary, chronical hypertension damages cerebral vessels early, leading to silent brain injury, stroke risk and accelerated cognitive decline.(McEvoy et al., 2024; Surendran et al., 2016)

HMOD in the heart mainly affects the left ventricle (LV). Hypertension causes an increase in left ventricular wall stress and higher afterload leading to hypertrophy and remodelling of the LV and thus impairing systolic and diastolic function. Left ventricle hypertrophy is a strong prognostic marker in hypertension and is independently associated with myocardial infarction, heart failure, atrial fibrillation, stroke and cardiovascular death. This risk exists regardless of the BP levels achieved, which

means that the damage predicts outcome beyond measured pressure. Elevated left ventricular (LV) pressure affects the left atrium, causing dilation and dysfunction of the left atrium and increases risk of atrial fibrillation and if pressure remains high than pulmonary hypertension can form which is followed by right ventricular dysfunction. Ultimately, this leads to the development of heart failure which is proven by the fact that many patients with heart failure show a prior history of hypertension. It remains the main cause and driver for heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) (McEvoy et al., 2024; Surendran et al., 2016).

Other systems affected by hypertension are the kidneys. High BP can lead to acute and chronic kidney damage and the formation of chronic kidney disease, but on the other hand impaired renal function can cause hypertension, which makes hypertension both cause and consequence of chronic kidney disease. Hypertension is the second most common cause for kidney disease after Diabetes Mellitus. Kidney damage results in reduced estimated glomerular filtration rate (eGFR), which is associated with higher CVD risk, cerebrovascular events and mortality. It is also connected to non-traditional CVD risk factors like vascular calcification, inflammation, myocardial changes, and the development of CKD-associated cardiomyopathy (Gangwisch, 2014; Klag et al., 1996; McEvoy et al., 2024; Rapsomaniki et al., 2014).

As already mentioned, hypertension can induce systemic organ complication, collectively known as hypertension mediated organ damage. A prominent example is hypertensive retinopathy, where chronically elevated blood pressure damages retinal microcirculation and the retinal nerve fibre layer, potentially leading to progressive, painless visual impairment. Uniquely within the human body, the retinal microvasculature allows for direct, in vivo observation, enabling close monitoring of disease progression. Furthermore, the detrimental ocular effect of elevated blood pressure extends beyond hypertensive retinopathy; they can exacerbate pre-existing diabetic retinopathy, elevate intraocular pressure and precipitate the formation of thromboembolic lesions. Retinopathy can be caused by hypertension and is characterized by vascular changes, haemorrhage and microaneurysms and sometimes optic disc and macular oedema. It is also associated with other ocular diseases such as retinal vascular occlusion, age related macular degeneration and glaucoma. It is also a major cause factor for the progression of diabetic retinopathy. Data shows that around 10% of patients have mild retinopathy (without diabetes) and close to 70% in patients with uncontrolled hypertension. It often coexists with other HMOD markers and is an indicator for the effectiveness of blood pressure control (Dziedziak et al., 2022; Muiesan & Grassi, 2006; Wolffsohn & Hurcomb, 2002).

Hypertension and diabetes frequently coexist, representing two highly prevalent conditions with profound systemic implications. Their concurrence synergistically increases the risk of cardiovascular disease, renal dysfunction and other sever complications. Given that CVD is the primary cause of

morbidity and mortality in individuals with diabetes, superimposed hypertension significantly exacerbates this clinical burden. Notably, both conditions share overlapping pathophysiological mechanisms- including insulin resistance, vascular inflammation, endothelial dysfunction obesity, and oxidative stress. This suggests a complex mechanistic cross talk that potentially drives the development of further systemic diseases. Consequently, the effective management of diabetes mandates a comprehensive, multifaceted approach that addresses not only strict glycaemic control but also aggressive blood pressure and lipid management. Hypertension or elevated blood pressure is a common feature of Type 1 and 2 diabetes and increases the patients risk suffering from CVD events. Hypertensive patients often have insulin resistance and an increased risk of developing diabetes versus those without elevated BP. Diabetes is a major contributor to retinopathy and nephropathy, which can be managed by administering BP-lowering treatment. Although the risk for CVD outcomes varies in diabetes patients due to other potential risk factors, it is safe to say that they are at >10% 10-year risk estimation. A study published by the American Diabetes Association shows that the burden of concurrent hypertension and diabetes went up by 6% over the span of 19 years and showed that patients with hypertension and Type 2 Diabetes Mellitus (T2DM) have a 2,46 fold risk for all cause and 2,97 fold risk for cardiovascular mortality in comparison to the no-hypertension and no- diabetes cohort (Blaton, 2007; Cornier et al., 2008; De Boer et al., 2017).

1.5. Diagnosis of hypertension

Screening for HT

Often hypertension is discovered by chance for example during a routine checkup or emergency room situation, which is referred to as “opportunistic screening”. The other way in which hypertension can be diagnosed is by “systematic screening” in a healthcare setting. Opportunistic and systematic screening are defined as follows:

Systematic screening is defined as any process whereby individuals are identified and invited to attend a healthcare setting with the sole purpose of measuring their blood pressure and cardiovascular disease risk profile. In contrast, opportunistic screening involves the measurement of BP when patients attend a healthcare setting for any reason, including a routine check-up or the treatment of an acute or chronic condition (Alex H. Krist et al., 2021; Jin, 2021; Siu, 2015).

Moreover, screening for HT is very important since it increases the chances of hypertension being detected and therefore the benefits outweigh the harm. It is generally recommended to measure BP once all 3 years in case of normotensive people and people at low CVD risk. Because of the ageing population and progress of HT in Europe it is recommended to check BP values more often past a certain age (40 years) or if BP is elevated but criteria for treatment are not being met (McEvoy et al., 2024).

How to measure correctly:

Because hypertension is generally asymptomatic, thus it is mainly identified through routine clinical screening. Once diagnosed, blood pressure can be effectively modified through targeted lifestyle intervention. Furthermore, high quality randomized controlled trials have consistently demonstrated the efficacy of pharmacological antihypertensive treatments in significantly reducing both cardiovascular disease incidence and all-cause mortality. Accurate measurement of blood pressure is essential in the diagnosis of hypertension. Variables such as the patient's physical condition, ambient temperature, device accuracy, measuring technique and position can all influence the result. Furthermore, phenomena such as masked hypertension and white-coat hypertension have been observed, which underscores the necessity for multiple measurements to ensure a confirmed diagnosis. In the field of blood pressure measurement, three key definitions are of particular relevance (Harris et al., 2011; Patnode et al., 2017; Rees et al., 2013).

The first term that needs to be defined is office blood pressure, which is often referred to as clinical blood pressure. The measurement of office blood pressure can be achieved through the utilisation of either an automated device or a manual reading device. Consequently, either a healthcare professional

is required for the initial setup and ongoing maintenance, or the device can be configured for unattended measurements. In the absence of a standardised method of assessing blood pressure, the resultant readings may vary. Home blood pressure measurement (HBPM) is defined as the process whereby patients assess their blood pressure in the comfort of their own homes using a validated monitor. Ambulatory blood pressure measurement (ABPM) is a method by which blood pressure is measured in set intervals over a 24-hour period using an automated device. Given the multitude of factors that may influence blood pressure, the ESC has provided a standardised method for measuring BP accurately in each of the three settings previously mentioned (Harris et al., 2011; McEvoy et al., 2024; Nadar et al., 2006; Patnode et al., 2017; Rees et al., 2013).

Confirming hypertension diagnosis:

Office-based blood pressure measurement remains the standard of care for initial hypertension screening. Diagnostic techniques encompass the manual auscultatory method, which utilizes a stethoscope to detect Korotkoff sounds, and the automated oscillometric method, wherein a pressure transducer registers cuff pressure oscillations during gradual inflation or deflation. Ultimately establishing a formal diagnosis of hypertension typically requires confirmatory readings following an initially elevated office blood pressure measurement. However, a solitary office blood pressure measurement is inadequate for the reliable confirmation of a hypertension diagnosis. As Office blood pressure has been shown to have lower specificity for diagnosing hypertension than ambulatory blood pressure monitoring, the ESC recommends that out-of-office confirmation of elevated blood pressure be conducted using ABPM. To confirm a diagnosis of hypertension, numerous health systems recommend conducting office-based blood pressure measurements on separate days for patients presenting with initially elevated readings. Although repeat office readings tend to be lower than the initial values, they remain susceptible to the same patient-, device-, protocol-, and observer- related limitations. Furthermore, relying solely on office-based confirmation fail to capture diurnal blood pressure fluctuations or variations that occur during a patient's routine daily activities (Kallioinen et al., 2017; Muntner et al., 2019; Omboni et al., 2016).

In case that the initial screening blood pressure falls within the range of 120–139/70–89 mmHg, then the recommendation is for out-of-office confirmation to be conducted either via ambulatory blood pressure monitoring or home blood pressure monitoring. This principle pertains to all other BP categories; however, if BP lies between 140–159/90–99 mmHg, the diagnosis should be based on out-of-office readings. In instances where the performance of ambulatory blood pressure monitoring or home blood pressure monitoring is not feasible, confirmation may be obtained through the repeated undertaking of in-office measurements on multiple occasions (Musini et al., 2017; Nadar et al., 2006; Omboni et al., 2016; Patnode et al., 2017; Rees et al., 2013).

2. Methods

This thesis provides a comparative analysis of two major contemporary guidelines on hypertension management, offering insight into how hypertension develops, why guidance is necessary, and how it is treated. This was achieved through systematic literature research. Textbooks were used to explain basic physiological concepts and the mechanisms of action of common drugs, in order to facilitate an understanding of further claims and correlations between the guidance. PubMed were used to find studies and papers on this topic and gather information. The two main guidelines referenced in this paper were retrieved from their official websites.

To ensure the selection of relevant material and data, the following keywords and combinations of keywords were used:

- Hypertension
- Arterial hypertension
- Physiology
- Pathophysiology
- Epidemiology
- Hypertension management guideline

After reading the abstracts, the most relevant papers were selected and read in full. Their references were then used to find more literature.

3. Results- Comparison of hypertension treatment: American college of cardiology/American hypertension association and European society of cardiology/European society of hypertension guidelines

3.1.1. Goals of BP-lowering therapy

It is well known that hypertension is a prominent preventable cause of premature morbidity and mortality. People with hypertension and established cardiovascular disease are at particular high risk, so reducing blood pressure to below standard targets may be beneficial. This strategy could reduce cardiovascular mortality and morbidity but could also increase adverse events. The optimal blood pressure target in people with hypertension and established cardiovascular disease remains unknown. Observational studies consistently demonstrate a linear relationship between blood pressure and the risk of cardiovascular events. Furthermore, randomized controlled trials indicate that reducing blood pressure by as little as 10 mmHg in hypertensive patients can lower an individual's lifetime risk of cardiovascular and stroke related mortality by 25% to 40%. Despite hypertension being such a prevalent and treatable condition, the optimal therapeutic target remains subject of ongoing debate- both in the general population and across specific age groups. Notably, while older hypertensive patients face a significantly higher baseline risk for cardiovascular and cerebrovascular events compared to younger individuals, they are simultaneously more susceptible to the adverse complications with pharmacological antihypertensive therapy. The overall goal of managing BP in patients with hypertension is to reduce associated morbidity and mortality which present themselves in the form of hypertension associated complication like renovascular disease for instance. Blood pressure reduction or prevention of elevated BP can be achieved through both pharmacological and non-pharmacological interventions. Non-pharmacological strategies primarily encompass lifestyle modifications, including the regulation of sodium and potassium intake, regular physical activity, weight management and abstinence from smoking and excessive alcohol consumption. As these measures are widely recognized and well established, they will not be discussed in detail within this thesis, instead, the following section focuses on pharmacological treatment approaches. Substantial evidence demonstrates a consistent association between BP reduction and decreases in both absolute and relative CVD risk across age groups. This has led to the widely accepted therapeutic principle that lower BP levels are generally associated with improved cardiovascular outcomes, provided that treatment remains safe and well tolerated (Kronish et al., 2017; Law et al., 2009; Levy et al., 2016; McEvoy et al., 2024; Woolsey et al., 2017; Zeind et al., 2024).

3.2. Difference in blood pressure classification and hypertension definition

The availability of multiple clinical guidelines on a single topic present both distinct advantages and notable challenges. On the downside, conflicting recommendations can lead to confusion and clinical decision paralysis. Furthermore, navigating multiple guidelines imposes additional time constraints on clinicians, potentially resulting in unrealistic expectations, heightened stress and diminished job satisfaction. Conversely, this multiplicity offers substantial benefits. A competitive landscape can drive improvements in guideline quality, while a diverse array of options allows clinicians to select the framework that best aligns with their specific needs. For instance, practitioners might base their choice on geographic relevance, the absence of industry influence, rigorous development policies or overall usability. Additionally, the coexistence of varying guidelines serves as a crucial reminder that these documents are advisory recommendations rather than legally binding directives. Ultimately, discrepancies between guidelines often highlight areas of clinical uncertainty, thereby stimulating target future research (Mancia et al., 2023; McCarthy et al., 2025; Qumseya et al., 2021; Williams et al., 2018a).

While the 2024 ESC and 2025 ACC (American College of Cardiology) /AHA hypertension guidelines share foundational principles—such as prioritizing patient-cantered care and lifestyle interventions—they present distinct approaches to blood pressure management. Notably, they diverge significantly regarding blood pressure categorization, specific therapeutic targets, and the utilization of risk stratification tools. A nuanced understanding of these distinctions is imperative for clinicians; it enables the application of tailored diagnostic and therapeutic strategies that align with regional standards and individual patient profiles, ultimately optimizing cardiovascular outcomes. Both the ACC/AHA and ESH (European Society of Hypertension) /ESC guidelines comprehensively address a wide array of clinical topics. In a notable departure from previous iterations, both documents strongly emphasize the critical importance of accurate blood pressure measurement, with the ACC/AHA offering particularly explicit protocols on the subject. Furthermore, they strongly advocate for routine home BP monitoring by patients. Therapeutically, there is a shared consensus on initiating treatment with single-pill combination therapies. Compelling evidence demonstrates that this approach significantly improves patient adherence and increases the likelihood of achieving target BP goals—a paradigm that is heavily championed in the ESH/ESC guidelines research (Bakris et al., 2019; Mancia et al., 2023; McCarthy et al., 2025; Qumseya et al., 2021; Williams et al., 2018a).

There are notable differences between the AHA and ESC guidelines when it comes to BP categories and BP thresholds for initiating pharmacologic treatment. While the ESC describes only three BP categories (non- elevated, elevated and hypertension as mentioned in chapter 1.1), the AHA suggests defining four stages as follows:(D. W. Jones et al., 2025)

- Normal: <120/80mmHg
- Elevated: 120-129 /<80 mmHg
- Hypertension stage 1: 130 -139 / 80-89mmHg
- Hypertension stage 2: >140/90 mmHg

The AHA and ESC both determine BP values of <120/80 mmHg as “normal blood pressure”. What the American guidance classifies as hypertension stage 1 is still only considered as elevated BP by the European guidance.(Grassi, 2025) The ESC reasoning for keeping the hypertension cutoff at >140/90 mmHg is that it is the BP value above which blood pressure lowering treatment leads to a net benefit in close to all patients. Furthermore the “elevated” group was added with the reason that patients in that group and patients with higher CVD risk are proven to benefit from BP lowering treatment in terms of risk reduction of cardiovascular events. (Liu et al., 2024; McCarthy et al., 2025; Zhang et al., 2021) The AHA/ACC explain their choice by arguing that their decision behind naming these categories was based on pragmatic interpretation of BP related CVD risk and benefit of BP reduction in clinical trials. They also emphasize that this classification is most useful for undiagnosed adults to make decisions about strategies to prevent or manage high blood pressure or to monitor treatment efficacy and success.(D. W. Jones et al., 2025) Unlike the US guidelines, the ESC also refrains from terms like “ normal BP “ or “normotensive” or “optimal” because CVD risk still increases per unit of BP even in people with BP <120/70 which might demotivate patients from taking lifestyle changes seriously and adapting them. They have also decided to keep the classification of hypertension values rather simple by not implementing different stages based on consideration of many other factors that might affect blood pressure like renal function (Liu et al., 2024; McCarthy et al., 2025; Zhang et al., 2021).

BP value	*AHA/ACC*	*ESC*
<120/<80mmHg	Normal	Non elevated
120-129/<80mmHg	Elevated	Elevated
130-139/80-89 mmHg	Hypertension Stage 1	Elevated
>140/90 mmHg	Hypertension Stage 2	Hypertension

Table 1:Overview of different blood pressure categories

While both the 2024 ESC and 2025 AHA/ACC guidelines share a foundational commitment to patients centred care and underscore the critical role of hypertension management in cardiovascular health, they diverge significantly in their diagnostic and therapeutic frameworks. Regarding blood pressure categorization, the ESC introduces the concept of “elevated BP” (120-139/70.89 mmHg) while maintaining the traditional threshold of hypertension (>140/90mmHg), utilizing distinct out of office metrics. Conversely, the ACC/AHA explicitly defines “elevated BP” as 120-129/<80 mmHg, “Stage 1 Hypertension” as 130-139/80-89mmHg and “Stage 2 Hypertension” as >140/>90 mmHg, relying on primarily on office thresholds. Therapeutic targets also differ: the ESC recommends a general target range of 120-129/70-79mmHg with allowanced for individualized flexibility, whereas the ACC/AHA advocates for a stricter target of <130/80mmHg, pushing for <120/80mmHg in high-risk populations. Finally for risk stratification, the ESC employs SCORE2 (Systematic Coronary Risk Evaluation 2)/SCORE2-OP (Systematic Coronary Risk Evaluation 2-Older Persons) systems, setting >10% 10-year CVD risk threshold for treatment consideration. In contrast to the ESC, the AHA/ACC utilizes the PREVENT (Predicting risk of cardiovascular disease events) calculator, establishing a lower threshold of >7.5% 10-year CVD risk for initiating therapy at lower BP levels (Azizi & Juraschek, 2025; Grassi, 2025; Khan et al., 2024; Mancia et al., 2023; McEvoy et al., 2024).

3.2.1. Cardiovascular risk estimation

Identifying individuals who benefit the most from pharmacological treatment is a new aspect of the ESC guidelines. It is done by estimating CVD risk for each patient especially in cases were BP values stay above 130/80mmHg despite 3 months of active lifestyle changes. Since outcomes of many clinical trials show a net benefit of BP reduction when enrolling high risk individuals (defined as people with BP over 130/80mmHg) in their studies; the ESC has put more emphasis on CVD risk assessment and identifying high risk individuals when screening for patients who should receive pharmacological treatment. Based on these facts, the ESC devised a 4 step plan to identify people eligible for treatment initiation: (Azizi & Juraschek, 2025; Grassi, 2025; Khan et al., 2024; Mancia et al., 2023; McCarthy et al., 2025)

1) Individuals with elevated blood pressure and established CVD, CKD, HMOD, diabetes, or familial hypercholesterolemia should be considered at high enough risk to consider pharmacological intervention.
2) Second, if high risk factors (mentioned in the first point) are absent, then SCORE2 or SCORE2-OP should be used instead to assess 10-year CVD risk. If the estimated 10-year CVD risk is greater than 10%, then the patient is at high enough risk to warrant pharmacological treatment.
3) If individuals present with borderline 10-year CVD risk (defined as a 10 Year risk between 5%-10%), then the ESC guidelines recommend up classification based on nontraditional risk markers. This recommendation is based on the insight that CVD risk is often underestimated among these people.
4) Finally, if patients show borderline CVD risk with elevated blood pressure but are free from nontraditional risk modifiers then it is recommended to consider specific risk assessment via measurement of coronary artery calcium score, pulse wave velocity, cardiac biomarkers or carotid or femoral plaques to up classify these patients if any result should be abnormal.

The AHA recommend that treatment should already be initiated at BP >140/90 mmHg for all adults and at >130/80 for groups that receive special benefit through early intervention (D. W. Jones et al., 2025). The rationale for this recommendation is the calculation of CVD risk using the PREVENT (Predicting risk of cardiovascular disease events) calculator as opposed to SCORE2 /SCORE2-OP which is used by the ESC. PREVENT includes factors like body mass index, a broader age range and kidney function, which puts more emphasis on renal and metabolic factors and leads to the decision that treatment thresholds should be lower than <140/90 mmHg, as it is the case with the ESC. Although both guidelines agree on the fact that risk estimation is crucial to select the right treatment path, it is not common practice to do so and remains a big problem and barrier when it comes to implementing guideline recommendation in daily clinical practice (Grassi, 2025).

3.3. Non-pharmacological interventions

Both guidelines AHA and ESC mention the same interventions that can be applied to achieve a reduction in blood pressure. Nevertheless, there are differences in their guidance, most notably that the AHA does not mention smoking cessation. Life style changes are also handled differently in the ESC guidance in terms of evidence, since the authors disclaim that there is no need for life style interventions to be supported by RCTs and therefore acknowledge that these intervention are less likely to be subjected to clinical outcome trials and that the risk of adverse or toxic effects through lifestyle interventions is low. Both guidelines recommend a regulation of sodium and potassium intake, regular physical activity and exercise, alcohol restriction, weight reduction and dietary strategies (McCarthy et al., 2025).

Smoking:

The ESC recommends quitting smoking and tobacco consumption since it independently causes CVD events and all-cause mortality to increase. By stopping to smoke vascular health will improve and lower the risk in CVD events, cancer and all-cause mortality (Critchley & Capewell, 2003; Thomson et al., 2022). They do state that effects on chronic BP increase appear to be small, but smoking does raise daily BP and affects the risk of CVD (Gupta et al., 2023; D. W. Jones et al., 2025; McCarthy et al., 2025; McEvoy et al., 2024).

Sodium and Potassium

Regulation of dietary sodium intake is emphasized by both guidelines, but recommendation differ slightly from each other. The ESC recommends limiting daily sodium intake to roughly 2g sodium / day, if possible, in all adults with hypertension or elevated blood pressure which is equivalent to 5g sodium chloride. The AHA, however suggests starting with <2300 mg sodium/per day and moving down to <1500mg/day which is claimed to the ideal limit to prevent and treat hypertension. Even bigger emphasis is put on potassium intake by both guidance's, which also differentiate between patients with and without CKD. It is therefore recommended by the ESC that patients without moderate to severe CKD and with high daily sodium intake should increase their potassium intake by 0,5-1g/day either by diets rich in fruit or by substituting sodium salts with potassium salts(Marklund et al., 2020), where 75% should be taken up by sodium chloride and 25% potassium chloride. In this regard it is suggested to monitor potassium levels in patients with CKD or patients under potassium sparing drugs (diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers). In contrast, the AHA suggest potassium-based salt substitutes in individuals with and without hypertension. They do recommend the potassium supplementation in patients with hypertension, but do not provide a specific number

unlike the ESC (Aburto et al., 2013; He et al., 2020; D. W. Jones et al., 2025; McCarthy et al., 2025; McEvoy et al., 2024).

Alcohol

Both guidelines agree upon the fact that optimal health outcome is achieved by alcohol abstinence.(Griswold et al., 2018) Nevertheless, the ESC suggests limiting alcohol intake to <100g/week(Tasnim et al., 2020). Since the amount of alcohol contained in a singular drink differs depending on the country, they do not give an exact number of how many drinks can be consumed but rather say that the average drink contains 8-15g of pure alcohol(Tasnim et al., 2020), while the AHA recommends a limit of 1 or less drinks/day for women and 2 or less drinks/day for men, while the recommendation made by the ESC is equal for both men and women(D. W. Jones et al., 2025; McCarthy et al., 2025; McEvoy et al., 2024).

Weight, diet and exercise

European guidance suggests aiming for a healthy BMI (Body Mass Index) as well as waist circumference values to reduce BP while also adapting to DASH diet (dietary approaches to stop hypertension). They further recommend more than 150 minutes of moderate intensity aerobic exercise per week or alternatively very intense aerobic exercise for 75 minutes per week over the course of 3 days which should be complemented with twice a week low- moderate intensity dynamic(Hanssen et al., 2022; MacDonald et al., 2016) or isometric training to reduce CVD and blood pressure. On the contrary, American guidelines suggest weight reduction of at least 5% for obese/ overweight people alongside the suggestion of adapting the DASH (Dietary approaches to stop hypertension) diet. They do suggest exercise as well but keep it rather vague by only mentioning aerobic exercise or resistance training without giving any ranges like the ESC (Hanssen et al., 2022; D. W. Jones et al., 2025; McCarthy et al., 2025; McEvoy et al., 2024).

3.4. Pharmacological interventions

3.4.1. Drug classes available for treatment

Diuretics

Current hypertension guidelines universally endorse diuretics as one of three equally weighted first-line treatment options. Nevertheless, extensive discourse comparing the side effect profiles of various antihypertensive classes has arguably engendered a disproportionate fear regarding the metabolic effects associated with diuretics. It is evident from the clinical data that the likelihood of encountering laboratory abnormalities of clinical significance is remarkably low. Conversely, the therapeutic benefits, specifically effective volume control, natriuresis, and significant reductions in cardiovascular morbidity and mortality, are profound. Furthermore, acknowledging the clinically significant differences in safety and efficacy among these agents, several international guidelines now explicitly distinguish between traditional thiazides (e.g., hydrochlorothiazide) and thiazide-like diuretics (e.g., chlorthalidone, indapamide), with many increasingly recommending the longer-acting thiazide-like agents. As further evidence comes to light, it may eventually become necessary to further subdivide chlorthalidone and indapamide into distinct pharmacological classifications (Anisman et al., 2026; Burnier et al., 2019; Duarte & Cooper-DeHoff, 2010).

Thiazide- type

Their primary mechanism of action is by inhibiting the Sodium-chloride cotransporter system of the distal tubule. Thiazides are also inhibitors of the carbonic anhydrase which causes a reduction in glomerular filtration rate (GFR) and thus weakens their overall efficacy. When compared to loop diuretics a few differences become apparent. For instance, the efficacy of thiazides amounts to roughly 5-8% of the filtered sodium. They do have a longer half lifetime and cause no post diuretic sodium retention unlike loop diuretics. More importantly, thiazides do not interfere with the kidneys ability to concentrate urine but affect its ability to dilute urine because of an increase in luminar sodium. Furthermore, they cause reabsorption of calcium. When therapy is initiated blood pressure will decline to fluid excretion and connected reduction of blood volume, after some time blood pressure reduction is caused by the reduction in vascular resistance mediated through stimulation of calcium activated potassium channels (Aktories et al., 2022; Burnier et al., 2019; Duarte & Cooper-DeHoff, 2010; F. H. Messerli et al., 2011).

Thiazides diuretics have been demonstrated to induce adverse effects, including hypokalaemia, which can lead to arrythmias such as torsade de pointes and ventricular fibrillation. As demonstrated by Bangalore et al. (2007) and Elliott & Meyer (2007), there is a reduction in glucose tolerance, which

consequently results in a higher incidence of new-onset diabetes, particularly when concomitantly administered with beta-blockers(Bangalore et al., 2007; Elliott & Meyer, 2007). It is imperative to comprehend that the occurrence of adverse effects of these agents is proportionate to their dosage. On the other hand, the efficacy of these agents in reducing blood pressure exhibits very little correlation with increasing dosages. This indicates that higher dosages do not result in a more pronounced reduction in blood pressure (Ellison & Loffing, 2009). The rationale behind their preferential use in low dose monotherapy, is to mitigate the risk of adverse effects is low, or in combination with other diuretics, where the addition of Hydrochlorothiazide serves to enhance the diuretic effect of loop diuretics, in cases where loop diuretics alone prove ineffective (Blebea et al., 2025; F. H. Messerli et al., 2011).

Thiazide diuretics such as Hydrochlorothiazide (HCT), Chlorthalidone, Indapamide or Xipamide are utilised in the management of hypertension and oedema. Among these HCT stands out as the most prevalent (Blebea et al., 2025). They are the only group of diuretics that is regarded as First-line therapy drugs in hypertension by the ESC and AHA guidelines(Blebea et al., 2025; D. W. Jones et al., 2025; McEvoy et al., 2024). Research conducted using randomised controlled trials demonstrate that there is no difference in the occurrence of major cardiovascular outcome events between Chlorthalidone and HCT, which suggests that they are both equally effective (Burnier et al., 2019; Ishani et al., 2022). Indapamide has been demonstrated to exhibit a reduced degree of interaction with glucose metabolism and is therefore a safer choice in patients with diabetes. In general they can be also used in patients with hypercalciuria, given their capacity to promote calcium reabsorption (Blebea et al., 2025). In terms of the reduction of blood pressure, thiazides appear to as efficacious as ACEi, ARBs, BB, and CCB and have achieved similar reduction in blood pressure (Burnier et al., 2019; Law et al., 2003; F. H. Messerli et al., 2011).

Loop diuretics

Loop diuretics are indicated as pharmacological agents for the management of hypertension. They are the most potent of all known diuretics, capable of inducing the excretion of 15% to 25% of filtered sodium. This class includes furosemide, bumetanide, torsemide, piretanide, azosemide, ethacrynic acid, indacrinone, muzolimine, ozolinone, xipamide and tienilic acid. While the first loop diuretics were mercurial agents now of historical interest only. The synthesis of orally active furosemide in 1959 established it as the loop diuretic of choice, since then, additional agents have been developed, the primary differences among them lie in their pharmacokinetics. Because loop diuretics act from the luminal side of the nephron, urinary rather than serum concentrations are the major determinant of their therapeutic response. Extensively bound to serum albumin, they cannot enter the tubular lumen via glomerular filtration. Instead, they reach their active site through active secretion by the organic

acid transport pump in the straight segment of the loop of Henle. These drugs are rapidly absorbed, reaching peak serum concentration within 0.5hours to 2 hours. However, the onset of action for oral furosemide is slower compared to other loop diuretics, as its rate of absorption is slower than its rate of elimination (Aktories et al., 2022; Musini et al., 2015a; Perola,P et al., 1985; Vadász & Chadha, 1982; Wertheimer, 1971).

Loop diuretics inhibit the sodium potassium chloride co transporter system in the ascending part of the loop of Henle and cause an increase in fluid excretion to up to 45 litres per day. They mostly affect the kidney's ability to concentrate urine. By blocking the cotransporter system in the macula densa, tubuloglomerular feedback loops are interrupted which helps in sustaining GFR and prohibits downregulation of fluid excretion (Aktories et al., 2022; Campbell et al., 1998; Musini et al., 2015a).

It is evident that loop diuretics have clinical advantages over other diuretics. Loop diuretics induce the most potent diuresis of all, with efficacy observed in patients exhibiting a GFR of < 30ml/min, which Thiazides do not do. The effects of these substances are known to occur rapidly. The combination of these factors result in a highly efficacious treatment for situations where fast and strong diuresis is needed, such as in cases of ascites or pulmonary oedema (Blebea et al., 2025; Campbell et al., 1998; Ferrari et al., 2025; Musini et al., 2015a). Despite their advantages they come with drawbacks like causing post diuretic sodium retention, which is a compensatory mechanism of the body and is also sometimes referred to as diuretic resistance. This phenomenon can be attributed to the drug´s brief half-life of 3-6h. Following the initial administration, the effects of the medication begin to dissipate after approximately sixteen hours. During this subsequent period, the diuretic effects of the medication are absent, yet sufficient for the kidneys to compensate for the water and electrolyte loss. This state persists until another dose is administered. This effect has not been observed in thiazide diuretics. As posited by Ferrari et al. (2025), a further consequence of the condition under discussion is hypokalaemia (Campbell et al., 1998; Ferrari et al., 2025; Musini et al., 2015a).

While loop diuretics are not the primary treatment option in isolated hypertension, they are used as add-on agents or in cases of congestive heart failure, ascites, pulmonary oedema or advanced CKD. In cases of heart failure the combination of these agents with aldosterone antagonists may be considered if efficacy is not sufficient enough, otherwise furosemide poses the most common agent among the three (Malha & Mann, 2016). Neither the AHA nor the ESC have Furosemide, Torasemide or Bumetanide listed as First-line therapeutics for hypertension (D. W. Jones et al., 2025; McEvoy et al., 2024). In fact a Cochrane review shows that furosemide compared to four other diuretics, has rather low antihypertensive properties and are much more often used for their great diuretic effect (Campbell et al., 1998; Díez et al., 2009; Musini et al., 2015b). However, a gap in literature exists since there are few trials available that compare the effects of Furosemide vs Torasemide/Bumetanide, and even if,

then groups and dosages are mostly not comparable (Campbell et al., 1998; Díez et al., 2009; Malha & Mann, 2016; Musini et al., 2015a).

Potassium sparing diuretics

Potassium sparing diuretics that inhibit the epithelial sodium channel (ENaC), such as amiloride and triamterene, are most commonly used in combination with thiazide or loop diuretics to reduce urinary potassium wasting. In addition to their potassium conserving effect, these agents may contribute modestly to blood pressure control by promoting sodium excretion and reducing intravascular volume. However, available evidence suggests that their antihypertensive efficacy as monotherapy is limited and overall and the overall magnitude of blood pressure reduction remains uncertain, particularly at low doses. Existing systematic reviews indicate that low dose ENaC blockers do not produce a clinically significant reduction in blood pressure, while evidence for higher doses is still insufficient. Comparative evaluation of their role against other antihypertensive classes, specifically in combination regimes, remains important for guiding optimal dosing strategies and future head to head studies (Aktories et al., 2022; Heran et al., 2012; Martins et al., 2023).

Sodium is absorbed in the late distal tubule via epithelial sodium channels, causing depolarisation of the tubule cell, which leads to the formation of an electrical gradient and thus the outflow of potassium through selective potassium channels (ROMK) on the luminal side of the cell and, on the other hand, from the interstitium through the intercellular spaces. This effect is seen as a functional Na/K exchange, which is stimulated by aldosterone and inhibited by the diuretics amiloride and triamterene. Both substances reversibly block ENaC in the luminal cell membrane. Since there is only a small amount of sodium in the later part of the distal tubule, their natriuretic effect is weak but can increase to 3-5% of glomerular filtered sodium under certain circumstances. It is mainly administered in combination with thiazides or loop diuretics due to its potassium-retaining effect. Furthermore it does not affect GFR (Aktories et al., 2022; Heran et al., 2012; Martins et al., 2023).The most notable adverse effect is hyperkalaemia when paired with other potassium sparing agents like ARBs or ACEi(D. W. Jones et al., 2025). Amiloride and triamterene have been demonstrated to be minimally effective as blood pressure lowering agents when not combined with other antihypertensive drugs. They should also not be used in patients with a GFR of <45ml/min. In contrast to thiazide which can be used in cases of a GFR of >30ml/min and loop diuretics which can be used in cases where GFR is even lower. Generally Amiloride and Triamteren are used in combination with thiazides in patients with hypokalaemia on thiazide monotherapy or as a substitute for spironolactone in cases of intolerance(D. W. Jones et al., 2025; McEvoy et al., 2024). The ESC and the AHA both recommend them as alternative or addons in therapy of resistant hypertension, but it seems that they are not commonly used in isolated hypertension patients (D. W. Jones et al., 2025; McEvoy et al., 2024).

Aldosterone antagonists

Primary aldosteronism is increasingly recognized as a prevalent underlying cause of hypertension. In a comprehensive evaluation of over 600 hypertensive patients, Mosso et al. (2003) demonstrated that the prevalence of aldosteronism correlates directly with the severity of hypertension. Utilizing the staging criteria from the sixth report of the Joint National Committee (JNC 6) in untreated individuals, primary aldosteronism was identified in 2% of patients with Stage 1 hypertension, 8% with Stage 2 and 13% with Stage 3 (>180/110 mmHg) This study aligns with numerous contemporary reports indicating an overall hyperaldosteronism prevalence of 15% to 30% across general and specific hypertensive populations (Calhoun et al., 2002; Mosso et al., 2003; Nishizaka et al., 2004; Pratt-Ubunama et al., 2005).

Many clinical studies demonstrated the aldosterone antagonists effectively manage resistant hypertension, even when standard multidrug therapies – such as those combining a diuretic with an ACE inhibitor or ARB- fail. Notably, blood pressure decreased even in patients without diagnosed hyperaldosteronism. This improvement might stem from the drugs added diuretic properties, however, it is hypothesized that it points to a broader role of aldosterone driving resistant hypertension, independent of elevated systemic levels (Calhoun et al., 2002; Mosso et al., 2003; Nishizaka et al., 2004; Pratt-Ubunama et al., 2005).

Spironolactone is a synthetic aldosterone analogue. The active metabolite Canrenone, in conjunction with Spironolactone and Eplerenon, has been demonstrated to inhibit the the binding of aldosterone to cytosolic mineralocorticoid receptor. Consequently, the effects of aldosterone (sodium retention and potassium secretion) are negated. Moreover, the effects of aldosterone antagonists are delayed, since the effects of previously bound aldosterone first have to subside (Aktories et al., 2022; Calhoun et al., 2002; Mosso et al., 2003).

The adverse effects of spironolactone encompass sexual dysfunction, gynecomastia and hyperkalaemia. The effects are dose and duration dependent. In comparison to spironolactone, eplerenone has been demonstrated to show a reduced incidence rate for adverse effects. The issue lies in the fact that a significant proportion of individuals are unable to tolerate such effects which consequently results in discontinuation and non-compliance (Struthers et al., 2008).In the treatment of primary aldosteronism, spironolactone and eplerenone are considered the preferred medications. Similarly, in cases of resistant hypertension and heart failure, these medications are often used as a fourth add-on (Calhoun et al., 2002; McEvoy et al., 2024; Mosso et al., 2003).

ACEI:

Angiotensin converting enzyme inhibitors inhibit the conversion of Angiotensin 1 into Angiotensin 2 and thus reduce the vasoconstrictive effect of Angiotensin 2 and reduce aldosterone secretion. ACEi lower BP even in patients with low Angiotensin 2 concentrations or without renin production. ACE is also responsible for the cleavage of bradykinin, substance P and kallidin, whose concentration consequently increases if ACE is inhibited. These 3 substances can cause NO release in the endothelium as well as stimulate PGE2 and prostacyclin release. Part of ACEi efficacy is attributed to that effect. Whether ACEi have an effect on catecholamines remains subject of current research (Aktories et al., 2022; Chen et al., 2021; Reboussin et al., 2018; Whelton et al., 2018).

ACE inhibitors and angiotensin receptor blockers (ARB) effectively lower blood pressure through inhibition of the renin- angiotensin system and are equally recommended as first line medications in the treatment of hypertension. In the 2017 ACC/AHA and the 2018 ESC/ESH guidelines on hypertension, ACE inhibitors and ARBs both carry the strongest recommendation, class 1, as first line agents for initiation of antihypertensive therapy on the highest level of evidence, A. There is extensive evidence showing that blood pressure lowering by renin- angiotensin- system inhibition using these drug classes improves cardiovascular outcomes, as shown in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and HOPE (Heart Outcomes Prevention Evaluation) trials as well as in meta-analyses and systematic reviews (Lithell et al., 2003; Reboussin et al., 2018; Whelton et al., 2018; Williams et al., 2018b).

ACEi pose one of the most prescribed antihypertensive agents and are recommended as first line therapy in hypertension. Metanalysis show that adverse effects like dry cough (most common), hyperkalaemia and angioedema can occur. The occurrence of dry cough is not connected to dosage or duration of ACEi. Evidence investigating the rate of angioedema in patients under ACEi therapy is divided(Na Takuathung et al., 2022). Some suggest that there is no increased risk of angioedema(Na Takuathung et al., 2022) while others suggest that it depends on the ethnicity of the patient and that certain ethnic groups are more prone towards developing angioedema(Brown et al., 2017; Gibbs et al., 1999). Another Metanalysis compared the efficacy and safety among Lisinopril, Captopril, Ramipril, Enalapril and Trandolapril, in patients with heart failure. Enalapril was the most effective in reducing mean arterial pressure, but it has the highest incidence for dry cough and renal function deterioration. Lisinopril was found to be the worst choice due to an increase in all-cause mortality and limited effects on reducing blood pressure. Out of the named ACEi, trandolapril has achieved the highest rank in regards to reducing blood pressure, while Ramipril was associated with the lowest rate of all-cause mortality (Reboussin et al., 2018; Sun et al., 2016; Williams et al., 2018b).

ACE inhibitors are recommended by the ESC and AHA as first line therapy in hypertension, either alone or in combination. When compared to other first line choices such as dihydropyridine CCB, ARBs and diuretics; no significant difference in blood pressure reduction can be found(Law et al., 2003), however, when looking at beta -blocker, who are also recommended as first line therapeutics by the ESC, though not by the AHA, ACEi have been shown to be more effective at preventing strokes than BBs(McEvoy et al., 2024). ACEi have been found to further reduce all-cause mortality significantly in patients with hypertension(Van Vark et al., 2012). Furthermore, ACE inhibitors are more effective at reducing albuminuria than other agents and should therefore be considered in the therapy of patients with hypertension and chronic kidney disease. In regard to heart failure ACEi are also recommended as part of the treatment (D. W. Jones et al., 2025; Lithell et al., 2003; McEvoy et al., 2024; Reboussin et al., 2018; Williams et al., 2018b).

ARBs

Angiotensin receptor blockers block angiotensin 2 receptor subtype 1 and therefore inhibit the effects of Angiotensin 2 (vasoconstriction and aldosterone secretion) (Aktories et al., 2022; Psaty et al., 2003; Sanders et al., 2011).

ARBS affects various organ systems like the cardiovascular system, electrolyte balance or the kidney, and therefore cause some adverse effects of which hyperkalaemia, renal dysfunction and angioedema are of high clinical relevance. Studies that compare the safety of different ARBs namely Losartan, Irbesartan, Valsartan, Telmisartan, Olmesartan, Azilsartan showed following results: Losartan had the highest reporting proportion (RP) for angioedema (Ogura & Shiraishi, 2025; Psaty et al., 2003; The ONTARGET investigators, 2008). Irbesartan showed higher risk of electrolyte disorders. All ARBs show low incidence rates for respiratory disorders which is why they are used in cases of ACEi intolerance due to dry cough. Valsartan showed higher RP for cardiovascular disorders which is most likely caused due to its widespread use in high risk patients with heart failure or post MI patients (Ogura & Shiraishi, 2025). All in all ARBS demonstrate excellent safety profiles, whether in monotherapy or in combination with others and seem to be superior to ACEi (Abraham et al., 2015; Barnett et al., 2004; Psaty et al., 2003).

Comparison of the efficacy in blood pressure reduction of selected ARBs like Candesartan, Valsartan, Telmisartan, Irbesartan and Losartan have shown following results(Abraham et al., 2015): The CLAIM studies have shown that candesartan achieved stronger reduction in blood pressure than respective doses of losartan(Andersson & Neldam, 1998; Lacourcière & Asmar, 1999). Olmesartan was able to lower blood pressure to a greater extent than Valsartan and Losartan. Telmisartan has been found to show stronger effects on blood pressure reduction than Valsartan in large controlled trials (Littlejohn et al., 2000).Furthermore Irbesartan was shown to be more efficacious than losartan and valsartan in respective dosages(Kassler-Taub et al., 1998).

The AHA and ESC both regard ARBs as first line therapy in hypertension and say that ARBs are to be used in cases of ACEi intolerance. ARBs are recommended in patients with CKD, although the AHA warns about the use of ARBs in patients with bilateral renal artery stenosis because of the risk of acute renal failure. Furthermore, they are recommended in patients with heart failure. It is generally advised to not use ARBs in combination with ACEi, due to increased risk of renal damage (Barnett et al., 2004; D. W. Jones et al., 2025; McEvoy et al., 2024; Špinar et al., 2010).

Dihydropyridine CCB

Current guideline recommends initiating pharmacological treatment when blood pressure reaches >150/90 mmHg in adults over 60 years old, or >140/90 mmHg in adults under 60 and in patients with diabetes, regardless of age. For the general non- Black population, initiating therapy should include a thiazide diuretic, CCB and ACEi, or an ARB. For Black patients, including those with diabetes, initial treatment should specifically feature a thiazide type diuretic or a CCB. Because of these recommendations, CCBs have emerged as a cornerstone for initial antihypertensive monotherapy. Evidence demonstrated that CCBs do not increase the risk of coronary artery events or strokes, making them a highly favourable option for both monotherapy and combination regimens. They may also provide specific protective benefits beyond standard blood pressure reduction. Today, dihydropyridine CCBs are among the most frequently prescribed antihypertensive medications in China and other East Asian nation (Armstrong, 2014; Jarari et al., 2015; Kjeldsen et al., 2014; Mancia G et al., 2013; Verdecchia et al., 2005).

CCB, which include both dihydropyridines such as nifedipine and amlodipine and non-dihydropyridines (verapamil and diltiazem), are among the most widely prescribed agents for the management of essential hypertension. Several large outcome risk trials and comprehensive meta-analyses have found that CCBs reduce the cardiovascular morbidity and mortality associated with uncontrolled hypertension, including stroke. CCBs, however, appear less effective than ACEi and diuretics for preventing heart failure and myocardial infarction. CCBs are among the agents listed as potential first line therapy, either alone or in combination with other agents in hypertension management guidelines. Furthermore, CCBs are suitable for add-on therapy in combination with diuretics, ACEi and ARBs. Calcium channel blockers inhibit one specific type of calcium channels in our body. T-type calcium channels are an integral part of neurons and heart where they play a role in the transient influx of calcium and the induction of action potential. N and P type channels are crucial for the release of neurotransmitters. Regarding blood pressure, L type calcium channels are of utmost importance. They are important for the influx of calcium in the heart and in smooth muscle tissue in blood vessels where they, under physiological circumstances, induce vasoconstriction. L type calcium channels pose the main target for drugs like nifedipine or amlodipine and cause relaxation in smooth muscle tissue mainly in arteries and arterioles including coronary arteries. If compared to Verapamil and Diltiazem, calcium channel blockers of a different type, a major advantage comes up which is that dihydropyridine CCBs have close to no effect on the heart. Which distinguishes them from Verapamil and Diltiazem whose effects on vasculature and heart are not selective for either one but always appear together (Aktories et al., 2022; Armstrong, 2014; Mancia G et al., 2013; Verdecchia et al., 2005).

This group of drugs has a minimal side effect profile with mainly peripheral oedema as their most relevant side effect (K. E. Jones et al., 2024; Lee, 2023; Makarounas-Kirchmann et al., 2009). Peripheral oedema are more likely to occur in women and their occurrence is also connected to dosage and drug choice (Sica, 2006). Peripheral oedemas are formed when precapillary hydrostatic pressure increases due to disproportionate changes in vascular wall resistance. With Nifedipine having the strongest vasodilatory effect it is also the one to where risk of oedema is highest. Although this side-effect can be countered by pairing CCBs with ACEi or ARB, which balances capillary pressure(K. E. Jones et al., 2024).

Advantages of CCBs are their stronger reduction in BP over 24 hours in comparison to other first line therapeutics and its protective factor due to reducing hypertension mediated organ damage. In people with left ventricular hypertrophy (LVH) CCB were able to reduce LVH by 11% with only ARBs surpassing them. Which makes them good choices in hypertensive patients with LVH. In spite of these findings, dihydropyridine CCB were not found to be protecting against heart failure in comparison to other first line therapeutics(Lee, 2023). Although according to the ESC they can be used as add-ons if all other first line drugs are not enough to control heart failure in a patient (Lee, 2023; McEvoy et al., 2024).

Non-dihydropyridines CCB-Verapamil and Diltiazem

Diltiazem and Verapamil are both non- dihydropyridine calcium channel blockers (non-DHP-CCB) frequently prescribed for specific cardiovascular conditions. Despite belonging to the same medication class, their distinct pharmacological profiles significantly influence how they are used in clinical practice. This post explores the key differences between verapamil and diltiazem, highlighting essential characteristics to consider when optimizing patients' cardiovascular therapy. Verapamil and diltiazem are commonly used non-DHP CCBs. This class of CCB works centrally within the heart, slowing contractility and lowering heart rate. Given their ability to affect the hearts electrical system, they are commonly used in managing cardiac arrhythmias, like atrial fibrillation, as well as hypertension and angina. Furthermore, key differences arise when comparing the safety profiles of verapamil versus diltiazem. Despite being in the same therapeutic class, verapamil and diltiazem have slightly different pharmacological effects. Both medications reduce the heart rate, decrease cardiac output through negative inotropic effects, and increase vasodilation; however, verapamil is a much stronger negative inotrope. Verapamil and Diltiazem have the same action of mechanism as Nifedipine and Amlodipine but in addition to their antihypertensive properties they also affect the heart where they have negative inotropic, dromotropic and chronotropic effects, which can be of disadvantage in regard to treating essential hypertension. Adverse effects include bradycardia and reduction of cardiac output (Aktories et al., 2022; Armstrong, 2014; Jarari et al., 2015; K. E. Jones et al., 2024).

Renin inhibitor- Aliskiren

The renin-angiotensin-aldosterone system is a critical regulator of blood pressure and fluid homeostasis in both normotensive and hypertensive individuals, furthermore, its dysregulation is a primary driver of hypertension mediated organ damage. Inhibiting renin to control hypertension presents a valid therapeutic strategy, as it blocks the RAAS cascade at its point of activation. Specifically, the cleavage of angiotensinogen by renin constitutes the initial and rate. Limiting step in the synthesis of angiotensin 2. Aliskiren, the inaugural member of a novel class of orally direct renin inhibitors, is currently approved for the management of hypertension. Clinical evidence demonstrates its efficacy in lowering blood pressure across the general hypertensive population, as well as withing specific cohorts such as patients with obesity, while maintaining a safety and tolerability profile comparable to that of a placebo. Preclinical models indicate that Aliskiren confers renoprotective, cardioprotective and anti-atherosclerotic benefits that appear to operate independently of its primary antihypertensive effects. In clinicals settings, it has been shown to reduce proteinuria in diabetic patients and induce favourable neurohormonal modulations in those with symptomatic heart failure. Nevertheless, further long-term cardiovascular outcome trials are warranted to fully delineate the definitive role of direct renin inhibitors withing the contemporary antihypertensive armamentarium (Aktories et al., 2022; Gradman & Kad, 2008; Oparil, 2009).

Alpha 1 blocker- Doxazosin

Alpha blockers are alpha adrenoceptor antagonists and inhibit the effects of catecholamines like adrenaline and norepinephrine. They do not possess intrinsic activity and only have an effect when they can inhibit catecholamines, which makes alpha blockers dependent on sympathetic tone and the plasma concentration of adrenaline and noradrenaline. This is the reason why alpha blockers have stronger blood pressure lowering effects, while the patient is standing as opposed to them laying, since sympathetic tone is higher while standing upright. Alpha 1 adrenergic receptor antagonists, including prazosin, terazosin and doxazosin, are established antihypertensive agents that are generally well tolerated. Despite this, their long-term use as first line therapy for hypertension has remained limited because their blood pressure lowering effect as single agents is modest. In addition, these drugs are associated with notable adverse effects such as pronounced hypotension after the initial dose and persistent orthostatic blood pressure drops, particularly in patients with reduced salt intake or those receiving concomitant diuretics and other antihypertensive therapies. Nevertheless, they still retain clinical value in selected patients with essential hypertension, especially when hypertension coexists with hypercholesterolemia or lower urinary tract symptoms related to benign prostatic enlargement. Additional therapeutic applications have also been explored in conditions such as Raynaud phenomenon and heart failure, particularly as adjuncts to other cardiovascular medications. Several

characteristics make alpha 1 blockers attractive in certain hypertensive populations. One important benefit is their ability to counteract excessive sympathetic nervous system activity, which contributes to the pathophysiology of elevated blood pressure. Moreover, these agents may provide favorable metabolic effects, including modest improvements in glucose metabolism and lipid profiles through enhanced insulin sensitivity and better glucose tolerance. Because of these potential advantages, doxazosin at doses 2-8 mg daily was evaluated in the 1990s ALLHAT trial alongside an angiotensin converting enzyme inhibitor and a calcium channel blocker, with the aim of determining whether this regimen could outperform thiazide diuretics in blood pressure control and cardiovascular risk reduction.(Chung et al., 2011; Davis, 1996; Rossitto et al., 2010; Williams et al., 2018b).

Doxazosin preferably inhibits alpha 1 receptor, which causes relaxation of smooth muscle tissue in blood vessels, vasodilation and a reduction in peripheral resistance. These effects trigger compensation mechanism like reflex tachycardia and increased renin release, which increases the activity of RAAS and all in all counteracts the antihypertensive effect of Doxazosin (Aktories et al., 2022; Grimm, 1989; Li et al., 2022).

Beta blockers

For a period of 50 years Beta-Blockers (BB) have constituted a fundamental component of antihypertensive treatment. BB were initially recommended as one of the first line treatment options for primary hypertension by the Joint National Committee on Detection, Evaluation and Treatment of high blood pressure form the first report in 1977 and was upheld in subsequent reports up until its seventh report in 2003. However, Messerli et al (1998;2003) raised concerns about this preference due to paucity of the evidence for BB to reduce morbidity or mortality in patients with uncomplicated hypertension. Many meta-analyses investigated the roles of BB in hypertension, and they clearly demonstrated that efficacy of BB in hypertension is inferior compared with other classes of antihypertensive drugs: ACEi, ARBs,CCB and thiazide type diuretics. Accordingly, the AHA/ACC and Japanese Society of Hypertension guidelines no longer recommend BB as first line therapy for hypertensive patients without compelling indication (Bradley HA et al., 2006; Carlberg et al., 2004; Lindholm et al., 2005; F. Messerli, 2003; F. H. Messerli et al., 1998).

In general Beta-Blockers have negative chronotropic, dromotropic, inotropic, lusitropic and bathmotropic effects on the heart. They reduce beta 2 adrenoceptor mediated vasodilation in peripheral blood vessels but in total cause a reduction in blood pressure by reducing heart rate and cardiac output, by increasing sensitivity of Baroreceptors, by reducing beta 1 mediated renin release, reduced secretion of norepinephrine and by reducing the activity of the sympathetic nervous system (Aktories et al., 2022; Bradley HA et al., 2006; Carlberg et al., 2004; Chobanian et al., 2003; Lindholm et al., 2005; F. H. Messerli et al., 1998). There are many BB with different properties, which can be categorized into:

1) Beta 1 receptor selectivity: Metoprolol, Atenolol and Bisoprolol are all examples for beta 1 adrenoceptor selective drugs. Of note, beta 1 selectivity is only ensured in low dosages since saturation of beta 1 receptors can lead to the binding of beta 2 receptors if drug concentration is high enough. This carries an advantage since they reduce possibility of side effects like vasoconstriction, bronchoconstriction and hypoglycemia (Aktories et al., 2022; Carlberg et al., 2004; Chobanian et al., 2003; Lindholm et al., 2005; F. H. Messerli et al., 1998).
2) Intrinsic activity: Most Beta-Blockers do not cause agonism of beta-1-adrenoceptors and are pure antagonists and block the effects of adrenaline and norepinephrine. Pindolol and Labetalol, however, possess intrinsic activity and are partial agonists of beta-1 and beta-2 adrenoceptors, which contradicts their main purpose. It is for their intrinsic activity that their efficacy might be reduced in some cases and that desired cardiac or blood pressure lowering effects might not be achieved. In contrast, Metoprolol, Bisoprolol, Carvedilol and Nebivolol do not possess intrinsic activity and might be better suited to treat hypertension (Aktories et al.,

2022; Carlberg et al., 2004; Chobanian et al., 2003; Lindholm et al., 2005; F. H. Messerli et al., 1998).

3) Additional vasodilating effect: Carvedilol and Nebivolol are BB with additional vasodilating activity, in contrast to the other BB which rather cause a certain degree of vasoconstriction. Carvedilol has the ability to also bind an inhibit alpha receptors and cause vasodilation that way, while Nebivolol increases the synthesis of nitric oxide in vascular endothelium (Aktories et al., 2022; Carlberg et al., 2004; Chobanian et al., 2003; Lindholm et al., 2005; F. H. Messerli et al., 1998).

Central acting drugs – Clonidine

The antihypertensive efficacy of central alpha 2 receptor agonists is well established in the relevant literature. Clonidine, the prototypical agent within this class, demonstrated significant antihypertensive efficacy in the Veterans Affair Cooperative Study, with notable benefits observed in White and older Black populations. While the blood pressure- lowering capacity of centrally acting agents is comparable to that of first-line antihypertensive classes, including diuretics, ACEi and CCB – their primary clinical utility lies in their roles as adjunctive therapy. Specifically, these agents are highly effective in attenuating the reflex sympathetic activation frequently induced by direct vasodilators, such as hydralazine and minoxidil. Furthermore, centrally acting sympatholytic offer distinct advantages in specific patient subpopulations. It has been demonstrated that, they are particularly beneficial in the management of labile hypertension associated with prominent anxiety. From a metabolic standpoint Metabolically, these agents are deemed safe for patients with diabetes mellitus, as they do not adversely affect glycaemic control. Additionally, they are well tolerated by patients with comorbid reactive airway disease, including asthma. In the perioperative setting, clonidine is frequently utilized not to only manage sympathetically driven hypertensive episodes but also for its well-documented anaesthetic- and analgesic- sparing properties. Clonidine is a lipophilic agent that can pass through the blood brain barrier and bind alpha 2 receptors in the medulla oblongata, which adrenaline and noradrenaline cannot. It reduces the activation rate of sympathetic neurons and increases the activation rate of parasympathetic neurons. It also regulates the release of adrenaline and noradrenaline by activating alpha-2 -adrenoceptors which causes antihypertensive effects (Aktories et al., 2022; Dollery, 1988; Fenton et al., 2006; Frohlich, 1980; Goldberg & Gehr, 1985; Rahn et al., 1999; Sica, 2007; van Zwieten, 1999).

Direct vasodilators - Hydralazine and Minoxidil

During the preceding century, direct vasodilators and sympatholytic agents represented some of the earliest antihypertensive medications to be discovered and utilized. However, they have many side effects which have reduced the use of these agents in recent decades. The available data do not provide sufficient evidence to support the utilisation of these medications. Furthermore, the number of randomised controlled trials that provide substantial evidence of the efficacy of these medications is limited. However, it has been demonstrated that blood pressure lowering effects of these agents is comparable to other more contemporary drug classes. In contemporary practice, direct vasodilators and sympatholytic agents, particularly hydralazine and clonidine, are often utilized in refractory hypertension. Hydralazine and minoxidil may also be useful alternatives for patients with renal dysfunction and both hydralazine and methyldopa are considered first line for the treatment of hypertension in pregnancy. Hydralazine has also found widespread use for the treatment of systolic

heart failure in combination with isosorbide dinitrate (ISDN). The data to support use of this combination in African Americans with heart failure are particularly robust. Hydralazine with ISDN may also serve as an alternative for patients with an intolerance to angiotensin antagonists. Given these niche indications, vasodilators and sympatholytics are still useful in clinical practice; therefore, it is prudent to understand the existing data regarding efficacy and the safe use of these medications. Minoxidil is a potassium channel opener and increases the probability of ATP-gated potassium channels opening and causing hyperpolarization. This then leads to a reduction in intracellular calcium which leads to vasodilation on arterial blood vessels. Minoxidil can cause many other effects like bronchodilation, shortening of action potential and inhibition of insulin secretion, because ATP-gated potassium channels are also present in the heart, bronchi, and beta cells of the pancreas. For these effects to happen it needs to be metabolized into its active form “minoxidilsulfate”. Nowadays it is only used as a last resort in hypertension management (Aktories et al., 2022; Hariri & Patel, 2026; McComb et al., 2016; Tarkin & Kaski, 2016; Zsotér, 1983).

The exact mechanism of action of Hydralazine remains unclear, however, it causes a decrease in total peripheral resistance via vasodilation of arteries and arterioles. Hydralazine is not able to decrease mean arterial pressure if administered on its own, due to strong compensation mechanisms of the RAAS (Aktories et al., 2022; Hariri & Patel, 2026; McComb et al., 2016; Tarkin & Kaski, 2016; Zsotér, 1983).

3.4.2. Differences in First Line-Therapeutics

Both the AHA and the ESC recognize four major antihypertensive drug classes with strong evidence for blood pressure lowering effects as “first-line therapeutics” (FTP) and pose the preferred agents for therapy initiation since they demonstrate equally strong reductions in blood pressure. These include angiotensin-converting- enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, thiazide and thiazide type diuretics. These are drug classes supported by a large body of evidence demonstrating their effectiveness in blood pressure reduction, cardiovascular disease prevention and overall tolerability. Consequently, both guidelines emphasize the fact that treatment initiation should be individualized based on patient characteristics, comorbid conditions (e.g heart failure) and anticipated drug tolerability. Despite their general agreement on FTP, notable differences exist in the clinical interpretation of FTP. The AHA postulates a more restrictive definition of first-line therapy and explicitly distinguish the four classes from other antihypertensive agents, namely Beta-blockers. BB are not considered as FTP in uncomplicated hypertensive situations. BB ought to be used in special cases such as angina, heart failure, post myocardial infarction (post MI) or when heart rate control is required, since large cohort studies found that the initial use of BB in newly diagnosed people leads to an increased risk for MI, stroke or acute coronary syndrome. In contrast the ESC acknowledges BB as one of the major antihypertensive drug classes with proven cardiovascular outcome benefits. Although they are not commonly recommended as first- line therapy in the general population, their role is described in a more integrated and flexible manner. They recommend this class in specific scenarios, namely angina, heart failure, post-MI and when heart rate control is necessary. Furthermore, greater attention is given to pharmacological subclass selection, in which they state that if BB are to be used then cardio selective and vasodilatory BB are preferred due to their advantageous metabolic and hemodynamic profile. Nevertheless, reasons why they are not regarded as FTP in uncomplicated hypertension are high discontinuation rates due to adverse effects, lesser protection against stroke and when combined with diuretics, they may increase the chance of new-onset diabetes in predisposed individuals. In addition, ACEi, ARB, and CCB seem superior in preventing HMOD progression. The Table provided below shows a summary of the most common drugs used in hypertension therapy, their primary use cases, special indications and notable properties that are important to know when prescribing these drugs (Abuhasira et al., 2025; D. W. Jones et al., 2025; McEvoy et al., 2024; Thomopoulos et al., 2015; Wright et al., 2018; Xie et al., 2018).

In instances where BP targets are not met through optimised therapy and adherence, the administration of additional drugs (ADD ONS) may be considered as an adjunct to the pre-existing therapy. The following add-ons are to be considered: mineral corticoid receptor antagonists (MRA), of which spironolactone is a particularly potent agent in cases of resistant hypertension. However, trials demonstrating the risk reduction of CVD in primary hypertension remain limited. Consequently, the

ESC decided to assign it a Class 2b recommendation, thereby slightly weakening their recommendation in comparison to their 2018 guidance. The evidence supporting the use of other antihypertensive agents, such as alpha-blockers, hydralazine, minoxidil, other potassium-sparing diuretics and centrally acting agents, is less robust. Consequently, their use should generally be reserved for cases where first-lline therapy is not sufficient, given their greater propensity to cause side effects (Abuhasira et al., 2025; D. W. Jones et al., 2025; McEvoy et al., 2024; Thomopoulos et al., 2015; Wright et al., 2018).

Table 2:Indication, notable features and examples of important antihypertensive drugs

	ACEi	ARB	Dihydropyridine CCB	Thiazide/ Thiazide like Diuretics	BB	MRA	ADD ONS
Primary use	First line treatment in hypertension reduce CV events	First line alternative to ACEi due to similar CV protection	First-Line hypertension therapy due to effective BP reduction	First-line treatment	Not Firstline in hypertension	Resistant Hypertension	If standard therapy fails
Special indication	HF,Post MI, prevetnion of HMOD	ACEi intolerance	Organ damage prevention	Often in combination therapy resistant hypertension	Angina HF Post MI Heart rate control	HF	
Special properties	preferred in high risk CV patients and superior to BB for stroke prevention	Comperable benefits to ACEi	Superior to BB in stroke prevention and useful in patients in need of poten BP reduction	Risk of diabetes if paired with BB in predisposed patients	Low compliance due to side effects Less effective in stroke prevention than the first 4 drugs	Lack of evidence in primary hypertension therefore slightly weaker recommendation	Weak CV outcome data Greater adverse effects
Example drugs	Enalapril Lisinopril Ramipril	Losartan Valsartan Candesartan	Amlodipin Nifedipin	Hydrochlorthiazide Chlorthalidone Indapamide	Bisoprolol Metoprolol Carvedilol Nebivolol	Spironolactone	Alpha-blockers Hydralazine Minoxidil

3.4.3. Combination therapy

Combination therapy is frequently required for effective hypertension management, as using agents from different drug classes can have additive or synergistic BP lowering effects that surpasses those accomplished by dose escalation of a single medication. This enhanced efficacy is partly attributable to the targeting of multiple pathophysiological mechanisms underlying hypertension. Lower doses of individual agents may also reduce adverse effects and improve treatment adherence, although evidence for these benefits remains debated (McEvoy et al., 2024).

Current ESC guidance recommends upfront low-dose combination of two first-line therapeutics, ideally administered as a single pill combination, for adults with confirmed hypertension to facilitate faster BP control and support long term adherence. The rationale behind this is that evidence demonstrates that combination therapy can achieve more rapid and consistent blood pressure reduction, facilitate the use of lower doses of drugs and improve long term adherence. In contrast, patients with slightly elevated BP, lower CVD risk or patients with special conditions that warrant a more individualized approach should initially receive monotherapy. In comparison to the ESC guidance, the AHA prefer an alternative strategy to the well-known “stepped care approach”. In adults with Stage 1 hypertension, commencing treatment with a single first line agent is deemed reasonable. Treatment should be further intensified through dose titration or addition of further first line drugs if blood pressure control does not suffice. For patients with stage 2 hypertension, it is recommended by the AHA to commence treatment with two first line agents from different pharmacological classes, preferably combined in a singular pill, for the same reasons as stated in the ESC guidance. As mentioned before referred first line agents include ACEi, ARB, dihydropyridine CCB, thiazide and thiazide like diuretics used either alone or in combination. However, both guidelines agree that combining two RAAS inhibitors is not advantageous and should therefore not be done. Most patients should begin with a low does single pill combination containing two of these agents (Guerrero-García & Rubio-Guerra, 2018; D. W. Jones et al., 2025; King et al., 2026; McEvoy et al., 2024; Rosas-Peralta et al., 2025).

Despite these recommendations, response to BP lowering drugs varies among individuals, highlighting the importance of personalized treatment approaches, including consideration of racial and ethnic differences. If BP remains uncontrolled despite maximally tolerated triple therapy consisting of a RAAS blocker, CCB, and diuretic, resistant hypertension should be suspected and specialist evaluation considered. Spironolactone is recommended as the preferred fourth line agent, while eplerenone, other MRA or BBs (like labetalol, carvedilol or nebivolol) may be used when spironolactone is not tolerated, despite BB appearing less effective in this context. Additional therapies including, hydralazine, amiloride. Triamterene, centrally acting agents and alpha blockers, should be reserved for refractory cases due to a lack of evidence and a higher risk for adverse effects. Minoxidil should be

considered only as a last line therapy. Polypills that combine BP-lowering drugs, lipid-lowering and antiplatelet therapies have demonstrated effectiveness in broader CVD prevention, although their availability remains limited in some regions (Guerrero-García & Rubio-Guerra, 2018; King et al., 2026; McEvoy et al., 2024; Rosas-Peralta et al., 2025).

4. Discussion

Hypertension remains one of the most significant modifiable risk factors for cardiovascular morbidity and mortality worldwide, and optimal pharmacological management continues to evolve in response to emerging clinical evidence and changing guideline recommendations. This thesis aimed to examine clinically relevant aspects of pharmacological treatment strategies of uncomplicated hypertension, with particular emphasis the selection of drug classes and highlight existing advantages and disadvantages of specific substances within their respective groups, the role of combination treatment and implications of cardiovascular risk reduction. The findings highlight the importance of individualized treatment approaches that balance rapid blood pressure control with tolerability and long – term adherence, reflecting ongoing differences in international guidelines strategies. In particular, contemporary recommendations increasingly emphasize earlier use of combination therapy and fixed-dose formulations to improve blood pressure target achievement in routine clinical practice. The following discussion synthesizes these findings in the context of current evidence and explore their implications for clinical decision-making in hypertension.

The findings of this thesis should be interpreted within the broader context of the substantial global burden imposed by hypertension and the persistent challenges in achieving adequate blood pressure control in clinical practice. Despite well-established evidence linking blood pressure reduction to significant decreases in cardiovascular morbidity and mortality, management remains suboptimal due to factors such as poor long-term adherence to lifestyle measures, clinical inertia in treatment intensification, and variability in healthcare system structures. In this setting, clinical practice guidelines paly a crucial role in translating randomized controlled trial evidence into practical treatment algorithms. However, differences in methodological interpretation and therapeutic philosophy between major international guidelines may contribute to variability in treatment initiation strategies, particularly regarding the timing and role of combination pharmacotherapy.

The interpretation of blood pressure values is inherently complex due to physiological variability and the influence of environmental and behavioural factors, which may contribute to differences in diagnostic thresholds and treatment initiation strategies across guidelines. Importantly, contemporary classification of hypertensions is increasingly treatment oriented rather than purely prognostic, as blood pressure categories directly inform therapeutic escalation pathways and the use of combination pharmacotherapy. Furthermore, the recognition of resistant and severe hypertension as high-risk clinical states underscores the need for structured treatment algorithms and early intensification strategies aimed at achieving timely blood pressure control.

Antihypertensive treatment is inherently complex and often non-linear, largely reflecting the multifactorial physiological mechanisms that regulate blood pressure under normal conditions. Blood pressure control is mediated by the interaction of neural reflexes, vascular tone, renal sodium handling, and hormonal systems like the RAAS, making it unlikely that dysregulation of a singular pathway leads to the development and persistency of hypertension. This provide a strong rationale for combinational pharmacotherapy, as monotherapy may be insufficient to achieve stable blood pressure reduction in many patients. Moreover, the distinction between short term and long-term volume dependent mechanism highlights the value of drug combinations that target multiple pathways. Within this framework drugs that target the RAAS, such as ACEi and ARBs, play a crucial role in treatment strategies and current guidance. Overall, the biological complexity of blood pressure regulation supports the use of individualized treatment approaches and simplifies therapeutic algorithms that facilitate timely treatment intensification and improved blood pressure control.

Because of the complex and often clinically silent pathophysiology of hypertension, early diagnosis remains challenging and HMOD may already be present at the time that HT is first detected. In fact, HMOD can manifest before HT is formally diagnosed and may therefore serve as an early indicator of sustained blood pressure elevation. The brain represents an early target for HMOD, where micro bleeds and white matter lesions predict future risk of stroke and cognitive decline, further supporting the concept that clinically relevant organ damage can occur prior to the development of overt symptoms. Cardiac involvement is characterized by LVH and is a strong indicator for MI, atrial fibrillation heart failure and cardiovascular death. Renal impairment is both cause and driver of hypertension; declining eGFR is associated in increased CV events and mortality. The clinical burden of HT is enhanced by its often coexistence with diabetes mellitus which substantially increases CV and all-cause mortality risk. Together, these observations highlight that early detection of organ injury is a critical component of hypertension management.

A major clinical challenge is that a substantial proportion of affected individuals remain unaware of their condition. This underscores the importance of screening strategies, standardized blood pressure assessment, comprehensive global cardiovascular risk. Systematic screening strategies can improve early detection rates, thereby increasing opportunities for timely intervention and reducing long -term burden of hypertension- related complications. In this context, standardization of blood pressure measurement is particularly relevant. Greater emphasis in HBPM and ABPM can reduce patient misclassification, improve diagnostic accuracy and support more appropriate treatment allocation. This approach facilitates the identification of individuals who would benefit from pharmacological therapy while avoiding unnecessary treatment in patients at lower cardiovascular risk, ultimately representing a simple yet effective strategy that reduces the global burden of hypertension.

Building on the importance of early detection and accurate risk stratification, the subsequent clinical challenge lies in defining optimal blood pressure treatment targets. While more intensive blood pressure reduction may further decrease cardiovascular morbidity and mortality, it may also increase the risk of treatment- related adverse events, highlighting the need to balance therapeutic benefit with safety. A large body of evidence supports the claim that a reduction in BP by as little as 10mmHg, however, can lower an individual's lifetime risk of cardiovascular and stroke related mortality. Nevertheless, the optimal therapeutic target remains a subject of ongoing debate, both in general hypertensive population and across different age groups. This is especially relevant in older patients, who exhibit higher baseline CVD risk but are simultaneously more susceptible toto complications from antihypertensive treatment. Overall, the primary goal of blood pressure management is the reduction of hypertension associated morbidity and mortality through both pharmacological and non-pharmacological interventions. Evidence consistently supports the principle that lower blood pressure levels are associated with improved cardiovascular outcomes, provided that treatment remains safe, individualized and well tolerated.

Following up on the fact that no clear blood pressure target has been agreed upon, clinicians must also navigate differences between major hypertensive guidelines that shape diagnostic and therapeutic decision making. The existence of multiple guidelines certainly poses challenges but also creates opportunities for healthy optimization and improvement of hypertension guidelines. The availably of multiple clinical guidelines lays ground for confusion and decision paralysis amongst clinicians, however, this diversity can enhance quality through competition and enable clinicians to adapt guidelines that best suit their approach and best reflect individual patient characteristics and regional as well as ethnical differences. Notably, European and American guidance share basic principles when discussing lifestyle modification, BP measurement for example. Differences appear when it comes to their definition and classification and treatment thresholds of elevated blood pressure. The AHA adopts lower diagnostic cut-offs and emphasize earlier intervention based on cardiovascular risk reduction observed in clinical trials, while the ESC/ESH recommend higher thresholds, reflecting a stronger focus on net benefit and pragmatic risk-benefit considerations. These discrepancies underscore persistent areas of uncertainty in hypertension management and highlight the need for individualized clinical decision making.

Hypertension is largely preventable, with lifestyle modifications representing the most accessible and cost-effective strategy for both prevention and early management. Both the ESC and AHA guidelines consistently emphasize the importance of non- pharmacological interventions supported by robust evidence. Key recommendations include dietary sodium reduction and increased potassium intake where appropriate, both of which have demonstrated beneficial effects on blood pressure control.

Although the two guidelines differ slightly in their specific intake thresholds, the overall therapeutic rationale remains consistent. Both also highlight the importance of moderating alcohol consumption, ideally advocating abstinence to optimize cardiovascular health, while providing pragmatic upper limits when complete avoidance is not feasible. Additional shared recommendations include adherence to dietary patterns such as the DASH diet, regular physical activity, weight reduction and the achievement of healthy body mass index, all of which contribute to lowering hypertension risk and improving cardiovascular outcomes. A notable distinction of the stronger emphasis placed by the ESC on smoking cessation as a core component of cardiovascular risk reduction, reflecting broader preventive priorities that extend beyond blood pressure control alone. Collectively, these measures underline the central role of lifestyle optimization as a foundational pillar in hypertension prevention strategies.

The second way to prevent and treat hypertension is by commencing antihypertensive drug treatment. A plethora of drug classes and individual drugs are at humanities disposal and each of them come with their own set of benefits and adverse effects. As discussed earlier, combination of multiple antihypertensive agents in a single pill is what current guidance advocates for in order to achieve sustained blood pressure control and maximizes tolerability and efficacy of the agents used. First line agents recommended for treatment initiation are ACEi, ARB, diuretics, DHP-CCB.

Diuretics remain a fundamental component of contemporary antihypertensive therapy, although their clinical roles differ substantially across subclasses. Thiazide and thiazide like diuretics are consistently recommended as first- line agents in both the ESC and AHA guidelines due to their robust evidence for reducing cardiovascular morbidity and mortality and their strong synergistic potential in combination therapy. Increasingly, longer acting thiazide-like diuretics are preferred because of more sustained blood pressure control and favourable outcome data. While concerns regarding metabolic adverse effects such a hypokalaemia or impaired glucose tolerance persists, these findings are largely dose-dependent and can be mitigated through low dose administration and drug combinations. In contrast, loop diuretics play a more specialized role, being particularly valuable in patients with advanced CKD, heart failure or volume overload, but are generally not recommended as FTP due to their shorter duration of action and weaker long-term blood pressure lowering effects. Potassium sparing diuretics, are primarily used as adjunctive therapies to counteract electrolyte disbalance or in resistant hypertension, where aldosterone antagonists have demonstrated substantial blood pressure reductions. However, the risk of hyperkalaemia and endocrine- related adverse events may limit their tolerability in some patients. Overall, the diuretic class illustrates the importance of individualized treatment selection in hypertension management, with drug choice guided by comorbidities, renal function, volume status and treatment resistance rather than a uniform class effect.

Inhibition of the RAAS system represents a central pillar of contemporary antihypertensive therapy. ACEi and ARB are among the most widely prescribed antihypertensive agents, supported by robust evidence demonstrating reductions in cardiovascular morbidity, stroke incidence and all- cause mortality, as highlighted in major trials such as ALLHAT and HOPE. Consequently, both drug classes carry the highest level of recommendation in current ESC and AHA guidelines and are frequently used as FTP in uncomplicated hypertension as well as in patients with comorbid conditions including CKD, and heart failure. Beyond their blood pressure- lowering effects, RAAS inhibitors confer important organ- protective benefits as well as their impact on albuminuria, which contribute to their prominent role in multidrug regimens. However dual RAAS inhibition is generally avoided due to limited efficacy and an increased potential for renal damage and hyperkalaemia. While ACE inhibitors are often associated with adverse effects like dry cough and more rarely angioedema, ARBs are often better tolerated and therefore represent a suitable alternative in patients with intolerance. Overall, RAAS targeting therapies exemplify a shift towards outcome – oriented and comorbidity driven antihypertensive management, highlighting the importance of individualized drug selection based on patient risk and treatment tolerability.

DHP-CCB are the last of the 4 major antihypertensive drug classes regarded as FTP by the AHA and ESC. Their strong and sustained blood pressure lowering efficacy and favourable outcome data demonstrates reductions ins stroke and overall CV morbidity. DHP-CBB are used in monotherapy and combination regimens, and are used in isolated hypertension, uncomplicated hypertension and individuals with LVH, where meaningful regression of hypertensive cardiac remodelling has been observed. In contrast non-DHP-CCB exert additional negative inotropic and chronotropic effects, which may be advantageous in patients with concomitant arrhythmias or angina but can limit their use in uncomplicated hypertension due to their cardiac effects. CCBs are generally well tolerated, peripheral oedema remains the most clinically relevant adverse effect, potentially mitigated when paired with RAAS inhibitors. Despite their benefits, CCBs appear to be less effective in preventing heart failure events.

Aliskiren is the first orally available agent from the class of direct renin- inhibitors and has demonstrated effective blood pressure reduction across hypertensive populations with a safety profile comparable to established therapies. In addition, clinical data suggests renoprotective and cardioprotective effects, including reduction in proteinuria. However, despite these promising findings, robust long term cardiovascular outcome data remain limited and Aliskiren occupies a relatively modest position in guideline directed hypertensive management. Their future clinical role will most likely depend on further evidence clarifying outcome benefits and optimal positioning within combination treatment strategies.

Beta blockers have been involved in the treatment of blood pressure for the longest times; however, their role has evolved substantially in contemporary hypertension management. While effective in lowering blood pressure, multiple meta-analyses have demonstrated that traditional BB are generally less effective than other FTP in preventing stroke and major cardiovascular events in patients with uncomplicated hypertension. Recent international guidelines no longer recommend BB as universal first- line agents in the absence of specific comorbidities such as coronary artery disease, post-MI or tachycardia. The emergence of newer vasodilating BB with more favourable haemodynamic and metabolic profiles has further refined their clinical positioning.

Alpha-2 blockers play in contrast to all other agents a very limited, but clinically relevant role in hypertension management. Although they effectively reduce peripheral blood pressure their use in monotherapy has declined due to comparatively weaker outcome evidence and the risk of first- dose hypotension. Nowadays, their preferred use lies in adjunctive therapy, particularly in patients with resistant hypertension or specific comorbidities such as hypercholesterolemia.

Lastly, centrally acting agents and direct vasodilators occupy a niche role in hypertension management. Although their BP lowering efficacy is comparable to that of FTP, their use is generally reserved for adjunctive therapy in resistant hypertension due to tolerability concerns and the need to counteract reflex sympathetic activation. Clonidine may be useful in patients with labile – anxiety related hypertension and in perioperative settings, while hydralazine and minoxidil are typically considered last- line options in resistant hypertension.

The main differences between the AHA and ESC in regard to first line therapeutics is the use of BB. The ESC generally acknowledges them as a major antihypertensive compound while the AHA does not, which is why the ESC also recommends different subgroups of BB if they happen to be administered. Both guidelines agree that BB should be used in special comorbid constellations like heart-failure or post MI patients. Otherwise, there is little difference between which FTP is chosen. Nevertheless, their opinions differ when it comes to combination therapy, particularly when to initiate combination therapy. The ESC is a strong advocate for early initiation of low dose combination therapy of two FTP preferably in a single pill. This is due to evidence demonstrating that early low dose combination therapy leads to rapid BP control and facilitates treatment adherence. The AHA on the other hand, emphasizes their adapted stepped care approach, where depending on the stage of hypertension, monotherapy still may suffice.

In summary, hypertension remains a major and largely preventable driver of global cardiovascular morbidity and mortality, requiring a comprehensive and individualized management approach. Early detection of organ damage, accurate cardiovascular risk stratification and timely initiation of effective

pharmacological and lifestyle interventions are central to improving long-term outcomes. While contemporary guidelines provide robust frameworks for treatment, important differences in therapeutic thresholds, drug positioning and escalation strategies reflect ongoing uncertainties in optimal hypertension management. The increasing emphasis on combination therapy, comorbidity-driven drug selection and treatment tolerability highlights a broader shift towards personalized care rather than uniform blood pressure-centred approaches. Future research should aim to further clarify optimal treatment targets, improve risk prediction models and identify strategies to enhance long-term adherence and implementation of guideline directed therapy. Ultimately, advancing hypertension management will depend not only on pharmacological innovation but also on earlier diagnosis, integrated prevention strategies and sustained patient engagement.

5. Conclusion

This thesis provides a comprehensive overview of contemporary hypertension management, with particular emphasis on key differences between major internation guidelines and their implications in clinical practice. By synthesizing current evidence and highlighting areas of divergence, this work contributes to a clearer understanding of therapeutic decision-making and may help clinicians navigate guideline variability more effectively.

The findings underscore the importance of early detection of HMOD, improved screening strategies and the expanded use of ABPM and HBPM to enhance diagnostic accuracy. In addition, the central role of lifestyle modification and individualized pharmacological treatment- guided by patient characteristics, comorbidities and tolerability- emerges as a fundamental principle for optimizing long-term cardiovascular outcomes and reducing the global burden of hypertension.

Despite significant advances in treatment strategies, important uncertainties remain. In particular, the identification of optimal blood pressure targets across diverse patient population continues to represent major research priority. Furthermore, more direct comparative studies within antihypertensive drug classes are needed to refine therapeutic selection and support truly personalized treatment approaches. Continued progress in these areas will be essential to further improve hypertension control and cardiovascular risk reduction in clinical practice.

Overall, this thesis highlights that successful hypertension management increasingly depends on early risk identification and individualized therapeutic strategies rather than uniform treatment algorithms.

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