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REVIEW ARTICLE

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Antihypertensive treatment – achievements and perspectives in Europe by 2026 Italian, Swiss and Norwegian patient care

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ABSTRACT

Purpose: The aim of this perspective review paper is to provide a concise overview of selected aspects of contemporary hypertension care in Norway, Switzerland, and Italy; European countries with populations of approximately 5.5, 9, and 61 million inhabitants, respectively. These countries show remarkably similar prevalences of hypertension, as well as comparable proportions of hypertensive patients who are diagnosed, treated, and controlled.

Methods: Each country has contributed to the development of hypertension management in distinctive ways. This is illustrated by the evolution of hypertension care in the three countries—which advanced hypertension management through different but complementary contributions.

Results: Italy has provided extensive clinical and research expertise, together with sustained engagement in the European Society of Hypertension and in the development of European guidelines. Norway has been strongly involved in the design and conduct of many large clinical trials that helped define the clinical evidence base in the field, and with general practitioners as investigators. Also, the government financed major surveys and epidemiological studies with blood pressure (BP) as a key variable including collecting data for modern risk assessment in old people (SCORE2-Old People). Switzerland, for its part, made important contributions to the development of new antihypertensive drugs, particularly blockers of the renin–angiotensin system and calcium antagonists. Switzerland was also among the first European countries to accept, promote, and reimburse ambulatory blood pressure monitoring performed by general practitioners, already by the late 1980s.

Conclusion: We summarise novelties in text boxes besides basic principles, recent clarifications, and important unresolved issues, supported by selected key references.

PLAIN LANGUAGE SUMMARY

We aimed to provide a concise overview of selected aspects of contemporary hypertension care in Norway, Switzerland, and Italy. Each country has advanced hypertension management through different but complementary contributions. Italy has provided extensive clinical and research expertise and organising the European Society. Norway has been strongly involved in the design and conduct of many large clinical trials that helped define the clinical evidence base in the field. Switzerland has made important contributions to the development of new antihypertensive drugs. These countries show remarkably similar prevalences of hypertension, as well as comparable proportions of hypertensive patients who are diagnosed, treated, and controlled.

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Antihypertensive treatment; blood pressure; blood pressure control; cardiovascular disease; guidelines; hypertension; systolic treatment target

Introduction

The first professional initiatives aimed at improving hypertension care in Europe emerged in the first half of the 1970s, beginning with the establishment of national hypertension societies in Belgium in 1972, Greece in 1973; Italy and Germany in 1974; Spain, France, and the Netherlands in 1975; and

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Switzerland in 1976—approximately 50 years ago. The Nordic countries followed some few years later including Norway in 1986. This growing interest in the clinical management of hypertension, as well as in hypertension research and education, led to the foundation of the European Society of Hypertension (ESH) in 1989 through the enthusiasm and perseverance of several experts who are now recognised as leading figures in the field, including professors Alberto Zanchetti, Wilhelm Birkenhäger, Hans Brunner, Lennart Hansson, Per Lund-Johansen, Giuseppe Mancia, John Reid, and others [1]. Each country has contributed to the development of hypertension management in distinctive ways. In this review, this is illustrated by the evolution of hypertension care in three countries—Italy, Norway, and Switzerland – which advanced hypertension management through different but complementary contributions. Italy has provided extensive clinical and research expertise, together with sustained engagement in the ESH and in the development of European guidelines. Norway has been strongly involved in the design and conduct of many large clinical trials that helped define the clinical evidence base in the field, and with general practitioners as investigators. Also, the government financed major surveys and epidemiological studies with blood pressure (BP) as a key variable including collecting the data for modern risk assessment in old people (see below). Switzerland, for its part, made important contributions to the development of new antihypertensive drugs, particularly blockers of the renin–angiotensin system and calcium antagonists. Switzerland was also among the first European countries to accept, promote, and reimburse ambulatory blood pressure monitoring performed by general practitioners, already by the late 1980s.

Norway, Switzerland, and Italy have populations of approximately 5.5, 9, and 61 million inhabitants, respectively. They may therefore be regarded as small, medium-sized, and large European countries, all with relatively high-income levels per capita in 2026. Despite these demographic differences, the countries show remarkably similar prevalences of hypertension, as well as comparable proportions of hypertensive patients who are diagnosed, treated, and controlled [2] (Table 1). Recent surveys and reports on hypertension care have been published or commented upon for Norway [3], Switzerland [4], and Italy [5]. In practice, the diagnosis, treatment, and overall care of patients with hypertension are largely similar across these countries. This similarity may be also explained, at least in part, by many years of collaborative research and joint work on European hypertension guidelines.

The aim of this review is to provide a concise overview of selected aspects of contemporary hypertension care in Italy, Switzerland and Norway. We first address features common to all people with hypertension, then briefly consider secondary hypertension due to specific diseases, before discussing in greater detail the major clinical challenges of essential hypertension. We summarise novelties in text boxes besides basic principles, recent clarifications, and important unresolved issues, supported by selected key references.

Hypertension: Definition, severity and grading

Hypertension (blood pressure (BP) ≥140 mmHg and/or ≥90 mmHg) is defined as the BP level at which antihypertensive drugs can lower the risk of future cardiovascular and kidney disease. This was shown in prospective, randomised and controlled studies performed in the 1960s, 70s and 80s. Later studies have demonstrated similar effects for lowering isolated systolic hypertension and in older patients. According to the Global Burden of Disease Study, hypertension has been the most prevalent modifiable cause of disease and death worldwide since 2003 [6].

As opposed to hypertension, some societies now use the concept of *elevated BP* (120-139/70-89 mmHg) as a new term, intended to highlight BP levels that increase the risk of future cardiovascular, brain and kidney diseases, as well as premature death, but without evidence for reduced risk from

Table 1. The status for hypertension in Norway, Switzerland and Italy – adults 30–79 yrs (2024).

		Percent of hypertensives in countries and millions of patients		
Country	Prevalence	Diagnosed	Treated	Controlled
Norway	35% (1.2 mill)	70% (0.8 mill)	53% (0.6 mill)	33% (0.4 mill)
Switzerland	26% (1.5 mill)	78% (1.1 mill)	63% (0.9 mill)	41% (0.6 mill)
Italy	42% (16.4 mill)	70% (11 mill)	64% (10 mill)	33% (5.5 mill)

Selected data [2] from Global report on hypertension 2025: high stakes – turning evidence into action. Geneva: World Health Organisation; 2025. Cataloguing-in-Publication (CIP) data are available at https://iris.who.int/.

prevention in outcome trials. In the literature, such BP has previously been called pre-hypertension, labile hypertension, or borderline hypertension and 'high normal BP' by the European Society of Hypertension [7]. The European Society of Cardiology (ESC) [8] now recommends drug treatment for 'elevated BP' if the 10-year risk from traditional risk factors assessed with Systematic Coronary Risk Evaluation-2 (SCORE-2) or SCORE2-OP (old people) exceeds ≥10% [9,10]. There is major scepticism among authors of ESH guidelines whether drug treatment of hypertension, especially among older patients, should be based on global risk and not on 'evidence' from randomised outcome trials [11,12].

NOVELTY TEXT BOX:
'Elevated BP' (120-139/70-89 mmHg) is a new term introduced by the European Society of Cardiology (ESC). ESC recommends non-pharma and pharma treatment if global cardiovascular risk is 10% or higher in people above 18 years of age assessed by SCORE2 and SCORE2-OP. However, there is no evidence from trials to support drug treatment of 'elevated BP' ('high normal BP' in ESH guidelines). Indeed, the HOPE-3 study showed people in the high-risk category with 'elevated BP' did not benefit from BP lowering drug treatment. ESH have therefore maintained the recommendation that drug treatment is only initiated when BP is >140/90 mmHg.

Table 2 shows – modified from the European Guidelines [7,8] – the classification of high BP by disease stage (vertically) and the grading of BP levels (horizontally). The classification is based on office BP measurements and applies to patients above the age of 18 years who neither take antihypertensive drugs nor have any acute illness. If systolic and diastolic BP are staged or graded differently, the condition should be classified at the highest level. Additional risk factors for heart and vascular diseases, brain disease, kidney disease, and premature death, should be specified according to the stage. For example, a patient may have hypertension in Stage I with concurrent hypertension-mediated organ damage (HMOD), typically left ventricular hypertrophy (LVH), and another serious risk factor such as type 2 diabetes.

Isolated systolic hypertension is defined as a systolic BP ≥140 mmHg, with a simultaneous diastolic BP <90 mmHg. This is typically a form of hypertension encountered in older people, although not exclusively, and is caused by widespread fibrosis and stiffness in the aorta or large arteries. The preventive effect of antihypertensive treatment is especially effective in such cases [7]. In younger people, isolated systolic hypertension can be a sign of an acute stress reaction but isn't necessarily

Table 2. Cardiovascular risk assessment of blood pressure and hypertension related to grading and disease stages by ESH.

Disease Stage	Other Concomitant Risk Factors	High normal (ESH) Elevated (ESC)	Mild Hypertension Grade 1	Moderate Hypertension Grade 2	Severe Hypertension Grade 3	Additional Assessment
	<120/70 mmHg = normal BP	120–139 mmHg 70–89 mmHg	140–159 mmHg 90–99 mmHg	160–179 mmHg 100–109 mmHg	≥180 mmHg and/or ≥110 mmHg	<50 years / 60–69 years / ≥70 years <2.5% / <5% / <7.5% 2.5 to <7.5% / 5 to <10% / 7.5 to <15% ≥7.5% / ≥10% / ≥15%
1	No other CV risk factors	Low risk*	Low risk*	Moderate risk**	High risk	
1	1–2 risk factors (family, cholesterol, smoking)	Low risk*	Moderate risk**	Moderate to high risk	High risk	
1	≥3 risk factors (family, cholesterol, smoking)	Moderate risk**	Moderate to high risk	High risk	High risk	
2	HMOD, CKD grade 3, type-2 DM	Moderate to high risk	High risk	Very high risk	Very high risk	
3	Established CV disease, grade 4–5 CKD	Very high risk	Very high risk	Very high risk	Very high risk	

The blood pressure level of 120-139/70-89 mmHg, high normal blood pressure by ESH, is characterised as 'elevated' blood pressure by ESC.
CV = Cardiovascular, HMOD = hypertension mediated organ damage, CKD = chronic kidney disease, DM = diabetes mellitus, ESH = European Society of Hypertension, ESC = European Society of Cardiology, SCORE2 = Systematic Coronary Risk Estimation 2 and Systematic Coronary Risk Estimation 2-Older Persons.
The table on the top in the right column under the heading 'Additional Assessment' shows a complementary assessment of low risk in disease stage 1 with SCORE2/SCORE2-OP ≥70 years. With a 10-year risk ≥10%, treatment (both non-drug and drug) is recommended by ESC. ESH recommends BP >140/90 mmHg for drug treatment.
The table is based on office measurements. For low risk*, standardised measurements are repeated on 3 independent occasions to assess grading, and for moderate risk**, on 2 independent occasions. 24-hour blood pressure monitoring and home blood pressure measurements are used more freely to diagnose office hypertension ('white coat hypertension') or masked hypertension ('masked hypertension').

Table 3. High blood pressure – stage classification of severity, grading, and follow-up [7,8].

Stage	Blood Pressure	Intervention and follow-up
Normal blood pressure	Systolic <120 and diastolic <70 mmHg	No special but occasional check measurement is recommended.
ESH: Normal blood pressure ESC: Elevated blood pressure	Systolic 120-129 mmHg and/or diastolic 70-79 mmHg	Non-drug measures like exercise, weight control, a 'healthy diet' with low sodium, low sugar, and limited alcohol are recommended. Using nicotine (smoking, snus) is not advised.
ESH: High normal blood pressure ESC: Elevated blood pressure	Systolic 130–139 mmHg and/or diastolic 80–89 mmHg	Non-pharmacological measures. Medication is given if there is already established heart-brain-vascular disease, CKD grade 3, HMOD, diabetes (ESH), and at a 10-year 10% risk (SCORE2, SCORE2-OP) (ESC).
ESH and ESC: Hypertension	Systolic ≥140 and/or diastolic ≥90 mmHg	Both ESH and ESC recommend confirming the diagnosis as well as non-pharmacological measures and medication treatment.
ESH: Hypertension grade I – mild hypertension	Systolic 140–159 mmHg and/or diastolic 90–99 mmHg	Establish the diagnosis with several blood pressure measurements. Non-pharmacological treatment. Drug treatment is usually recommended.
ESH: Hypertension grade II – moderate hypertension	Systolic 160–179 mmHg and/or diastolic 100–109 mmHg	Establish the diagnosis. Non-drug measures. Combination drug treatment is recommended.
ESH: Hypertension grade III – severe hypertension	Systolic ≥ 180 mmHg and/or diastolic ≥ 110 mmHg	Establish the diagnosis, non-pharmacological measures. Medication combination or triple therapy is always recommended.

HMOD = hypertension mediated organ damage, CKD = chronic kidney disease, DM = diabetes mellitus, ESH = European Society of Hypertension, ESC = European Society of Cardiology, SCORE2 = Systematic Coronary Risk Estimation 2 and Systematic Coronary Risk Estimation 2-Older Persons.

The table is based on office measurements. For low risk, standardised measurements are repeated on 3 separate occasions to assess grading, and for moderate risk, on 2 separate occasions. 24-hour blood pressure monitoring and home blood pressure measurements are used more freely to diagnose office hypertension ('white coat hypertension') or out-of-office hypertension ('masked hypertension').

harmless [13]. *Isolated diastolic hypertension* is most common in younger people [14], is linked to significant excess mortality, but the effects of prevention in these people have not been studied in randomised controlled trials.

Table 3 shows a simplified summary of the staging of severity level, grading, and follow-up as presented by the European societies in their guidelines [7,8]. About one third of the adult population has hypertension that requires medical treatment. Successful treatment will greatly lower the risk of cardiac, brain, vascular and kidney disease, as well as premature death. Stroke, heart failure, arterial aneurysms, dementia, and nephrosclerosis (arteriolosclerosis) are examples of complications that can largely be prevented. Hypertension is the most common cause of stroke, the risk of which is halved by antihypertenisve treatment in randomised studies when assessed as 'intention to treat' and reduced by about two thirds if assessed as 'on treatment'. Importantly, the risk of stroke increases with age, which is why preventive treatment should not have an upper age limit. However, treatment evidence above 85 years of age is scarse and evidence in frail patients ('frailty') is scarce at any age.

NOVELTY TEXT BOX:
The risk of stroke increases with age, but is reduced by about two thirds if assessed as 'on treatment'. Therefore, preventive drug treatment should not have an upper age limit. However, evidence for treatment in people above the age of 85 years is scarse. Evidence in frail patients ('frailty') is scarce at any age.

Blood pressure regulation and pathophysiology of high blood pressure

Blood pressure is influenced by numerous environmental, lifestyle and genetic factors which may induce acute as well as sustained elevations of BP as summarised by ESH (Figure 1). As shown in the centre of the figure, quite specific cardiovascular and kidney mechanism cause hypertension, or cause the BP to rise acutely or over the long run. These mechanisms apply to all patients, although an additional cause of the high BP is detected in certain organs in about 10% (secondary hypertension, see below).

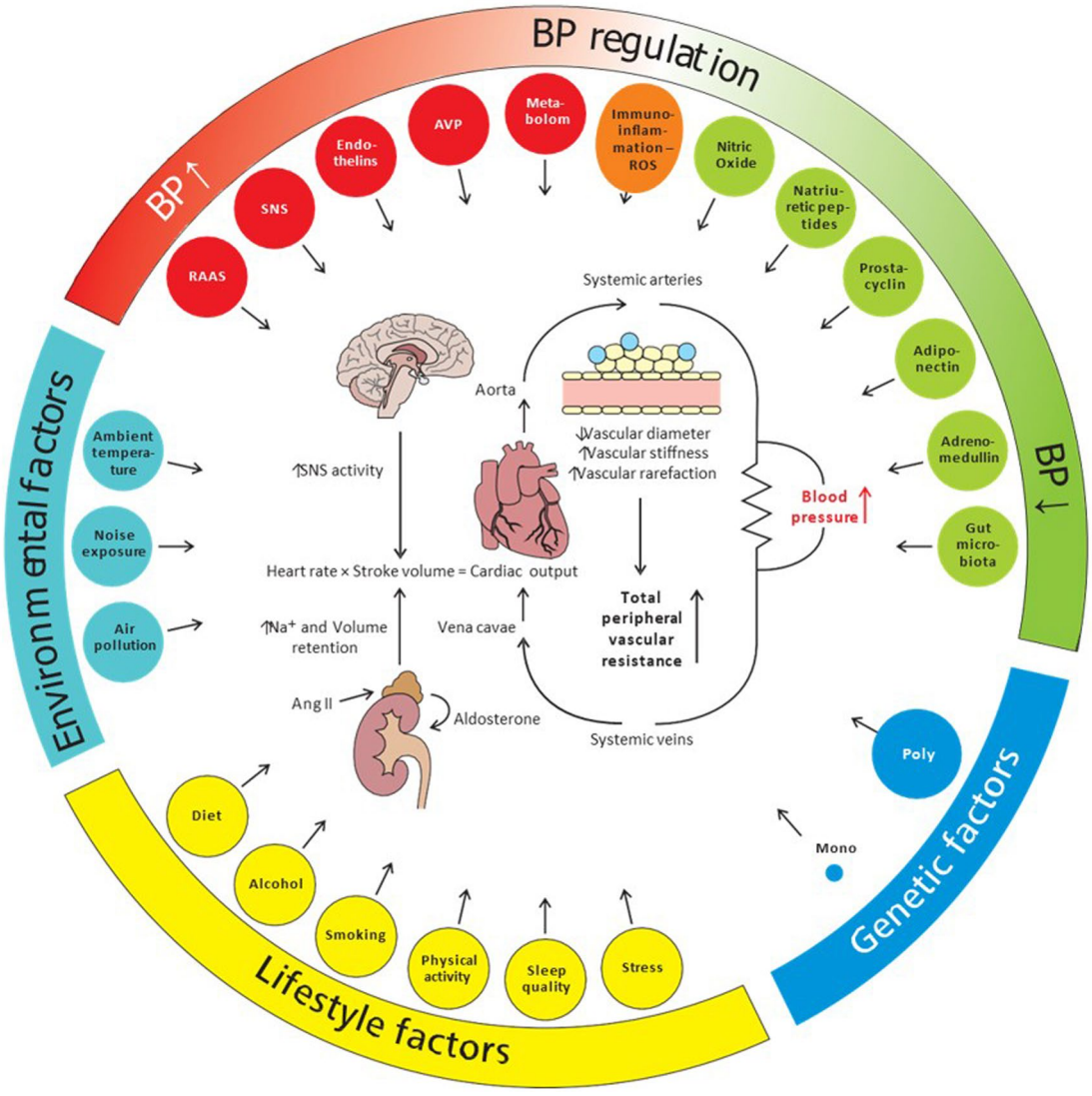


Figure 1. Pathophysiology and regulation of blood pressure as summarised by the European Society of Hypertension Guidelines for the Management of Arterial Hypertension in 2023 [7].

BP is determined by the heart's contractile property (inotropism) and the total peripheral vascular resistance which is mostly set by small arteries and arterioles [15]. High BP is caused by a disease process in the arterial bed, from arterioles to large arteries and the aorta. At an early stage, consolidation of smooth muscle cells and the extracellular matrix in small arteries and precapillary arterioles occurs. As a result, the wall of these vessels is slightly hypertrophic in patients with hypertension while the lumen is reduced. As a consequence, the rise in vascular resistance and blood pressure follows a steeper curve during any form of physical or mental activity ('stress') [16].

With increasing age, the large arteries also show a loss of elastin and therefore elasticity, with stiffening of the tunica media and increase of pulse wave velocity. This is a different mechanism than *atherosclerosis,* where lipids and inflammatory cells as well as calcium deposits accumulates in tunica intima. Of note, atherosclerosis is also worsened by high BP. As a result of the arterial stiffening, there is a greater traumatic effect of blood pressure pulsatility on the endothelium, i.e. the first barrier against damage to the integrity of the vessel wall. Pulse pressure and central BP – measured at the peak of a high pulse curve (augmentation index) – increases because the reflection of the pulse wave from the peripheral vascular beds increases. High BP is therefore caused by a disease process in the arteries of the body's organs – from arterioles to large arteries and the aorta.

The root cause for most cases of high BP and hypertension is still unresolved. Although a strong familial predisposition has been shown, extensive genetic studies have not been conclusive. Increased

activity in the renin-angiotensin-aldosterone system, sympathetic activation, and reduced parasympathetic control are the main drivers of high BP and associated arterial disease. The kidneys play an important role by producing renin, activating the sympathetic nervous system, but also by retaining salt (NaCl) and water in the tubules. This was already recognised in the 1950s; diuretics and sympathetic-inhibiting drugs were therefore first developed to treat hypertension.

Secondary hypertension

In secondary hypertension, high BP is a result of diseases in specific organs.

Kidney diseases such as acute and chronic glomerulonephritis, chronic pyelonephritis, and polycystic kidney disease are usually accompanied by high BP. The mechanisms are complex.

In *renal artery stenosis*, high BP is related to increased activity in the renin-angiotensin-aldosterone system. This is not an uncommon cause of hypertension, particularly in younger patients, where fibromuscular dysplasia may be the underlying pathology [17]. Of note, in fibromuscular dysplasia other vessels than renal arteries may be affected and be a source of complications [17]. In older people, atherosclerosis may be the cause of renal artery stenosis.

Coarctation of the aorta is a congenital narrowing (stenosis) in the aortic arch, after the branch arteries to the arms and head. The stenosis leads to high BP in the arms and low BP in the legs.

Diseases of the endocrine organs, such as *hyperthyroidism*, *Cushing's syndrome*, *Conn's syndrome*, and *pheochromocytoma*, often cause high BP. Pheochromocytoma is a tumour in the adrenal medulla that produces excessive amounts of adrenal medulla hormones – catecholamines. This can lead to acute BP crises. Hyperaldosteronism and Conn's syndrome are caused by an unregulated renin-independent excessive production of aldosterone. They are found in up to 20% of patients with treatment for resistant hypertension [18] who do not respond upon regular BP-lowering medications, despite documented intake. This is probably the most common cause of secondary hypertension. There is a change in concept occurring these days with a continuum between modest inappropriate increases in aldosterone levels as observed in resistant hypertension and very high aldosterone levels observed in true primary aldosteronism. Patients with hyperaldosteronism have a higher cardiovascular risk than patients with essential hypertension at comparable BP levels.

These patients respond particularly well to mineralocorticoid receptor antagonists (MRA, aldosterone antagonists, the most important being spironolactone). In patients with a unilateral overproduction of aldosterone surgical removal of the tumour is the recommended therapeutic approach, unless contra-indications. Aldosterone synthase inhibitors have been developed and are investigated in clinical studies.

NOVELTY TEXT BOX:
There is a continuum from the modest increase in aldosterone levels observed in resistant hypertension to the very high aldosterone levels observed in true primary aldosteronism. Both are targets for treatment, and important new drug principles have been developed for antihypertensive treatment and cardiovascular protecion in this context:
- Non-steroidal aldosterone receptor blocker (e.g. finerenone)
- Aldosterone synthase inhibitors (e.g. baxtrostat, lorundrostat, vicadrostat)

There can also be other causes of secondary hypertension, for example *high intracranial pressure* (brain tumour). In that case, the hypertension is due to a reflex reaction to ensure blood supply to the brain (Cushing reflex).

Hypertension is also a key element in *preeclampsia* in pregnant women. Any form of hypertension during pregnancy must be monitored closely and treated (α-methyldopa, metoprolol, labetalol, possibly with the addition of nifedipine OROS). No inhibitors of the renin-angiotensin-aldosterone system can be used during pregnancy due to the risk of teratogenic effects. Diuretics should also be avoided.

Sleep apnoea syndrome is also commonly associated with the development of hypertension particularly among overweight and obese patients.

Symptoms and signs will be reflected both from the underlying disease and from symptoms caused by the high BP itself, and successively from symptoms or signs related to organ complications.

The *treatment* basically follows the same guidelines as for essential hypertension (*see below*), in addition to specific treatment of the underlying disease. In some patients, high BP can be corrected by surgery for the primary condition. This applies to pheochromocytoma, Conn's syndrome, and coarctation of the aorta. Some cases of renal artery stenosis (70-80% stenosis) can be corrected with percutaneous transluminal angioplasty (PTA), although study results have varied regarding BP control and preserving kidney function. Complications and prognosis usually depend on the underlying disease, but if left untreated, high BP can cause the same complications as in essential hypertension.

Essential hypertension

In essential (or primary) hypertension, no explanatory conditions in other organ systems are found. This applies to approximately 90% of all cases. Still, a lot is known about the deranged function of a number of systems controlling BP (Figure 1): In many studies, increased activity in the sympathetic nervous system has been detected [19–23], especially in younger people. A prevailing hypothesis is that young, predisposed individuals (prehypertensive) react with a particularly strong increase in cardiac output, and thus also increased BP, in connection with sympathetic activation during stress. Over time, this puts strain on the peripheral small arteries and arterioles (resistance vessels), which develop thickened walls (vascular hypertrophy characterised by fibrosis and collagen) and eventually provide permanent increased resistance (see above). BP will then remain elevated with normal, or even reduced, cardiac output (heart failure).

Similarly, many studies have shown that people with high BP tend to have a relatively fast heart rate. Observational data from large treatment studies have shown that reducing heart rate to <80 beats/min is strongly associated with less atrial fibrillation, heart failure, and death [24,25].

The prevalence of hypertension in a population increases with the average salt (NaCl) intake, which should be reduced to about 3–5 g/day at an individual level.

Family disposition is a definite cause of hypertension. However, extensive attempts [26] to map predisposing genes have not yielded convincing results. It is assumed that hundreds, if not thousands, of candidate genes are relevant. BP tends to follow a significant 'tracking' pattern, meaning that if it's high in childhood and adolescence, it tends to stay high in adulthood.

Overweight and especially obesity (BMI >30 kg/m^2) are clearly linked to hypertension. A rule of thumb is that a 1 kg change in body weight results in a 1 mmHg change in systolic BP. Bariatric surgery or taking a GLP-1 receptor agonist (semaglutide, tirzepatide, liraglutide) can lead to significant weight loss and a substantial drop in BP, but may also cause nutritional problems.

Excessive alcohol consumption often causes hypertension, partly because alcohol itself has effects on the sympathetic nervous system, but also due an increased risk of poor medication adherence.

Glucose intolerance and insulin resistance are common in people with hypertension. This may be due to poor microcirculation in skeletal muscle and fat tissue, leading to compensatory hyperinsulinemia. There is a close link between type 2 diabetes and hypertension; treating hypertension has been the most effective way to prevent cardiovascular disease, kidney disease, and premature death in people with diabetes, followed by statin treatment.

It is also well known that many BP control systems interact with each other in a sort of positive feedback fashion, for which activation of one system reinforces the activation of the others and vice versa.Typical examples are the reciprocal activation influences of sympathetic nervous system [27] and insulin levels or of the renin-angiotensin levels in the body [28]. This favours the multifactorial nature of essential hypertension in most patient. It collateraly provides an explanation for the greater anti-hypertensive effect of combinations of drugs with different mechanisms of action in most patients [29].

Symptoms and signs

Essential hypertension usually occurs without symptoms for many years. High BP is often discovered during a routine check-up, or if the high BP causes symptoms like headaches, fatigue, dizziness, a

feeling of warmth, and heart palpitations. With long-term untreated hypertension, the first symptoms typically appear as a result of complications in the heart, brain, kidneys, and worst-case, as sudden unexpected death due to such complications ('the silent killer').

NOVELTY TEXT BOX:
Cuffless BP measuring devices are under development. These are better tolerated and accepted by patients, but the clinical validation remains limited. Therefore, untill further evidence, cufless BP measurements are not recommended to establish the diagnosis of hypertension, even after the expected validation by the Food and Drug Agency in the USA.

Diagnosis and work-up

The diagnosis of hypertension is made through repeated BP measurements under standardised conditions at the office using a standard arm cuff measuring device (sitting for five min in a quiet room with the cuff at heart level) [30]. Three measurements at one-minute intervals should be taken, with the average of the second and third readings used (Figure 2). High home or 24 h or even only night-time BP elevation carries a significantly higher risk than 'office hypertension' only ('white coat' hypertension). Therefore, out of office 24h ambulatory BP monitoring is recommended to confirm the diagnosis of hypertension whenever available. Today, one challenge is the development of cuffless BP measuring devices; some of them having been validated by the Food and Drug Agency. Cuffless

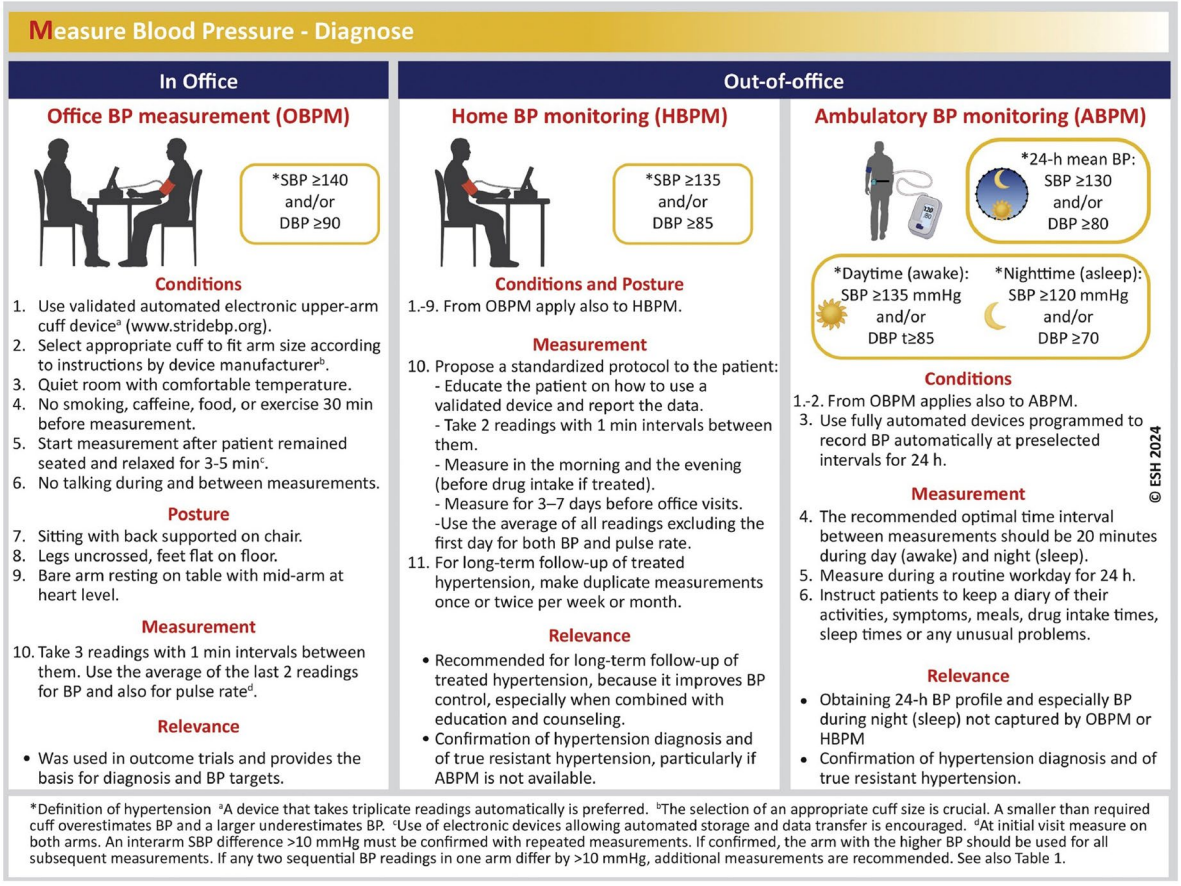


Figure 2. Summary of diagnostic work-up of hypertension as illustrated by the European Society of Hypertension Clinical Practice Guidelines in 2023 [30].

devices [31–34] are better tolerated and accepted by patients but the clinical validation remains limited. So far they are not recommended to establish the diagnosis of hypertension.

Patients with '*elevated BP*' (high normal BP) or *white coat hypertension* can more frequently develop hypertension, diabetes and left ventricular hypertrophy [35] making follow-up important, and 24-hour recordings recommended. The same applies to people with high systolic BP during physical activity [36,37] and to people in whom elevation is limited to home or ambulatory BP with normal office BP values [38].

NOVELTY TEXT BOX:
People with 'elevated BP' (high normal BP), white coat hypertension, high systolic BP during physical activity and masked hypertension (high home or ambulatory BP) more frequently develop hypertension, diabetes and left ventricular hypertrophy. Therefore, follow-up of people in these categories is important, and 24-hour recordings are recommended.

Once hypertension is suspected or diagnosed, searching for hypertension-mediated organ damages (HMOD) is important for assessing the severity. Presence of HMOD is strongly increasing the risk for the various complications of hypertension. The presence of HMOD is supporting selected treatments choices, the intensity of treatment and urgency to get started, but also structure important follow-up plans including methods to imply. In principe HMOD may affect various organs but in practice the focus is on the brain, the heart and the kidneys. Silent brain damage such as white matter legions, microbleeds and lacunar infarctions may cause early cognitive impairment as described in a book which the Working Group of Hypertension and the Brain of the ESH recently published [39]. Both echocardiography and electrocardiography (ECG), even thoracic X-ray, may reveal left ventricular hypertrophy (Figure 3) and/or increased left atrial size. Hypertensive kidney disease may be detected by urinalyses and blood tests.

Figure 3 shows concentric *left ventricular hypertrophy (LVH)* with increased wall thickness and mass (photo taken at Oslo University Hospital in 1984). The left ventricle develops a thicker wall, leading to reduced wall compliance and lower pumping ability. Reduced wall compliance causes diastolic dysfunction, high end-diastolic pressure, and a risk of acute pulmonary edoema during rapid heart rates (for example, newly-onset atrial fibrillation) or volume overload (for example, a salty meal causing fluid retention in the kidneys). A heart with concentric LVH also develops systolic dysfunction, with low cardiac output and poor contractility seen especially along the longitudinal axis. Heart failure with preserved ejection fraction (HFpEF) has almost always been preceded by hypertension and concentric LVH, whereas hypertension with eccentric hypertrophy may precede heart failure with reduced ejection fraction (HFrEF) [40].



Figure 3. Cross-section of the ventricles of the heart from a patient who had suffered long-lasting hypertension. The left ventricle suffered from concentric left ventricle hypertrophy. (Photo taken at Oslo University Hospital in 1984).

Treatment target for BP in patients with heart failure has been discussed through many years but recently individual patient data (IPD) merged from four major RCTs in HFpEF suggest that the lowest mortality during treatment is observed for the target range of 120–140 mmHg in systolic BP [41,42]. Otherwise drug treatment for hypertension in patients with heart failure is the same whether patients have reduced (HFrEF) or preserved ejection fraction (HFpEF) [43].

NOVELTY TEXT BOX:
A heart with concentric LVH can also develop systolic dysfunction, with low cardiac output and poor contractility along the longitudinal axis. Heart failure with preserved ejection fraction (HFpEF) therefore involves combined systolic and diastolic dysfunction. Drug treatment for hypertension in patients with manifest heart failure is the same whether patients have reduced (HFrEF) or preserved ejection fraction (HFpEF). Target systolic BP in patients with HFpEF is in the range of 120–140 mmHg to achieve the lowest mortality.

Reduced *kidney function* is examined with a urine test (dipstick and microscopy) and measurement of serum creatinine or estimated glomerular filtration rate (eGFR). eGFR calculator are available online. One open questions is whether eGFR should be calculated based on creatinine or cystatin C as differences in association with the cardiovascular risk have been observed [44]. Protein excretion in the urine is most often measured as an albumin:creatinine ratio.

During *ophthalmoscopy* or preferably *fundus photography*, the severity of hypertension is assessed according to fundus hypertonicus grade I–IV (Keith-Wegener grading), where grade I involves changes in the calibre of small arteries, grade II involves arterio-venous crossing phenomena, grade III includes haemorrhages and exudates, and grade IV includes papilledema (swollen optic disc) as a sign of increased intracranial pressure.

When early HMOD occurs, high BP must be treated with close monitoring. Normalisation of LVH or left ventricular dysfunction can be monitored by both echocardiography and electrocardiography [45–47], and can often be observed after a few months of BP control. These effects are associated with a significant improvement in long-term prognosis. Close follow-up also applies to patients with other important risk factors for heart and vascular diseases, kidney disease, and early death (genetic predisposition, diabetes, high cholesterol, or smoking).

If *secondary hypertension* is suspected (*see above*), the patient should undergo further assessment with a range of special tests. The younger the patient is, and the higher the BP, the more likely such an evaluation will reveal secondary hypertension.

Treatment of hypertension

High BP and hypertension are often accompanied by other risk factors that also contribute to the development of heart and vascular disease, kidney disease, and premature death, including obesity, diabetes and hyperlipidaemia with which BP levels show a quantitative relationship [48]. This is often collectively referred to as *metabolic cardiovascular* or *atherothrombotic syndrome* ('thrombotic' refers to increased blood platelet activity) [49]. For long-term risk reduction, antihypertensive drug treatment should always be supported by non-pharmacological measures, including physical exercise, weight control, healthy diet including less added sugar (fructose) and sodium restriction (<5-6 g NaCl/day), low alcohol intake, and non-smoking.

Statins prevent myocardial infarction and strokes in people treated for hypertension [50]. Recently it was pointed out that proprotein convertase subtilisin–Kexin type 9 (PCSK9) inhibition with evolocumab led to a lower risk of first cardiovascular events than placebo among patients with atherosclerosis or diabetes who were without a previous myocardial infarction or stroke but with mostly uncontrolled hypertension [51,52]. Acetylsalicylic acid (ASA) has some preventive effects in hypertensive patients [53,54] but the benefits are limited due to increased risk of bleeding complications. Hence, ASA is only recommended in secondary prevention [7,8].

NOVELTY TEXT BOX:
In primary prevention, lowering of LDL cholesterol with proprotein convertase subtilisin–Kexin type 9 (PCSK9) inhibitors such as evolocumab on top of statin may be effective add-on treatment to prevent cardiovascular disease in patients with known atherosclerosis or diabetes and hypertension who have not achieved adequate blood pressure control.

According to ESH guidelines, the treatment target in hypertension is <140/90 mmHg for most patients, and <130/80 mmHg for high-risk patients [7]. These BP levels should be reached within a few weeks [55], and BP should later be kept under such control if the treatment is well tolerated [7,8]. Poor control and large fluctuations in BP (BP variability both within the 24 h and over a longer term (i.e. between visits) are associated with a higher risk of complications [56,57]. Poor drug adherence [58] or doctor inertia [59] are two major causes of uncontrolled BP in hypertension. According to WHO [2], 33% of Norwegian patients, 33% of Italian patients and 41% of Swiss patients had BP control <140/90 mmHg in 2024 (Table 1), indicating a large potential in all countries for further improved prevention.

Up to 50% of all patients with hypertension show signs of cardiac remodelling on echocardiography, either as eccentric or concentric LVH [60], while up to 20% show signs of LVH in the ECG. LVH usually regresses with BP-lowering drug treatment, associated with improved prognosis [45–47] but interstitial and perivascular fibrosis may cause permanent myocardial injury. Large observational sub-studies of clinical trials [61–64] have shown increased mortality in patients with ECG-LVH and systolic BP lowered below 130 mmHg, possibly because of ischaemia in the degenerated microcirculation [61]. A target BP of 130–140 mmHg is therefore recommended for many patients with LVH, especially older patients.

Patients with all stages of chronic kidney disease show a significant preventive effect on death and cardiovascular complications when treated for high BP [65–67]. Large, randomised studies conducted in USA and China have shown that a systolic BP target of <120 mmHg results in fewer cardiovascular complications compared to target <140 mmHg, but a target of <130 mmHg is supported by two large Chinese outcome trials. However, all trials with target <120 mmHg have made use of an open design, which make the results open to alternative explanations. Furthermore, they have shown worsened kidney function [68] as compared with aiming at the target <130 mmHg [69–71].

Most BP-lowering medications available today have a 24-hour effect and therefore the same preventive benefit regardless of the time of intake. However, taking the medications at breakfast is strongly recommended for improved adherence [72,73].

Drug treatment for hypertension

For 'elevated BP' (120-139/70-89 mmHg) and mild hypertension grade I with low risk (Table 2), without sign of heart, kidney, or blood test abnormalities, lifestyle changes should be tried before treatment with antihypertensive drugs. Lifestyle changes have the added benefit, even in resistant cases, to act in synergy with medical treatment.

Drug selection depends on the degree of hypertension, tolerance (side effects), and the effect of the treatment. Emphasis should be placed on ensuring that office BP is lowered to the level that has been shown to maximise cardiovascular protection. The same applies to ambulatory and home BP, although their treatment-related control levels are ill known due to the absence of their use in clinical trials. The same applies to white coat and masked hypertension, conditions associated with selective elevation of office and out-of-office BP, respectively, in which cardiovascular risk is elevated but no trial has addressed whether and to what extent antihypertensive drug treatment is beneficial.

For achieving optimal BP-control, a combination of drugs is usually needed. However, for several reasons monotherapy remains the most common treatment in most countries. To overcome this problem, guidelines recommend to start treeatment with a drug combination of two drugs moving to three drugs if BP control is not achieved. They also recommend to use single pill combination whenever possible because reducing the number of daily pills improves adherence to treatment [58]. With a double drug combination in a single pill approximately 50-60% of the patients can achieve

BP control while with a triple single pill combination BP control can be achieved in 80–90% of the patients: The only triple combination registered in Norway is thiazide, valsartan, and amlodipine in various dosages (Exforge®). In Switzerland and Italy several similar triple combinations are commercially available. Double and triple combinations have the benefits not only that the components potentiate the BP lowering effects of each other but also that they counteract potential adverse effects.

NOVELTY TEXT BOX:
Patients with chronic kidney disease (CKD) at any stage have preventive effects on death and cardiovascular complications when treated for high BP with any major group of antihypertensive drugs (diuretics, beta-blockers, ACE-inhibitors, ARBs and calcium-antagonists), irrespective of the level of systolic BP.

However, large, randomised outcome trials of hypertensive patients with preserved kidney function performed in the USA and in China have shown significant deterioration of kidney function when aiming at target systolic BP below 120 mmHg.

Drug-based BP treatment can cause side effects that necessitates a drug switch. Motivation is a key, but controlled studies show that most people feel better once high BP is brought under control [7,8]. Low adherence to treatment [58], low persistence on treatment and therapeutic inertia of the treating physician (failure to upgrade treatment to achieve BP control) remain a major obstacle to optimised treatment worldwide [59].

NOVELTY TEXT BOX:
Low adherence to treatment, low treatment persistence and therapeutic inertia of the treating physician (failure to adjust treatment to achieve BP control) remain major obstacles to optimised treatment worldwide.

With a double drug combination in a single pill, approximately 50-60% of the patients can achieve BP control, while with a triple single pill combination 80–90 % of patients achieve control, reducing the incidence of cardiovascular events.

Diuretics

Usually, a slow-acting diuretic of the thiazide type (Esidrex®) is used. The main effect of thiazides is that they reduce vascular resistance in the arterioles and cause a mild reduction in blood volume. BP reduction could be about 5–10 mmHg. Thiazides 12.5 or 25 mg are therefore mostly used in combination with an ACE inhibitor or ARB to boost their effect. Thiazides have metabolic side effects if given in larger doses (50 mg or more): diabetes, increased serum triglycerides, hypokalaemia, hypomagnesemia, and gout (podagra).

Amiloride is a mild potassium- and magnesium-sparing diuretic that is used in combination with a thiazide (Moduretic mite®).

Aldosterone antagonists (mineralocorticoid receptor antagonists (MRA), spironolactone, eplerenone) are recommended as a fourth medication for patients with severe hypertension, but they lack preventive documentation ('evidence') in hypertension. Spironolactone can cause hyperkalemia in reduced kidney function, and men can develop bothersome gynaecomastia. Aldosterone synthase inhibitors (baxdrostat, lorundrostat, vicadrostat) are better tolerated than aldosterone antagonists and may soon be available for clinical use. Also non-steroidal finerenone is available in particular for patients with diabetes.

'Loop diuretics' (furosemide, bumetanide) are more potent and need to be used in patients with severly reduced kidney function and in heart failure with fluid retention.

Calcium channel blockers

Calcium channel blockers (calcium antagonists) like dihydropyridine derivatives (nifedipine, amlodipine), as well as diltiazem and verapamil, block the transport of calcium ions (Ca^{2+}) through the membrane in smooth muscle cells, causing small arteries and arterioles to widen (relax) and lowering BP through peripheral vasodilation. Among dihydropyridines, only forms that release the

drug slowly in the gastrointestinal tract should be used (oros, gits, uno, retard). The non-dihydropyridine derivatives diltiazem and verapamil increase conduction time through the atrio-ventricular (AV) node, which makes them suitable for rapid atrial fibrillation with concurrent hypertension, but they usually shouldn't be combined with beta-blockers due to the risk of AV block. In that case, the ECG must be checked regularly. Diltiazem significantly increases cyclosporine blood levels through CYP3A4 enzyme inhibition, potentially leading to cyclosporine toxicity. This major drug interaction requires careful monitoring and possible dose adjustments when these medications are used together.

Other treatment options for rapid atrial fibrillation with concurrent hypertension are ineffective or can have serious side effects with long-term use (digoxin, amiodarone). Swelling at the front of the calves (due to vasodilation), constipation, flushing, and headache are the most common side effects of calcium channel blockers. Calcium channel blockers are anti-ischemic, and are therefore widely used by patients who also have coronary artery disease and/or angina pectoris.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) include, among others, captopril, enalapril, lisinopril, and ramipril. These are used to treat both high BP and heart failure. For patients with diabetic or non-diabetic chronic kidney disease with high BP and protein in the urine, ACE inhibitors are a preferred treatment because they help maintain kidney function better than other treatments lowering both BP and albuminuria. These drugs work by blocking the ACE enzyme, which converts angiotensin I into angiotensin II. The antihypertensive effect is therefore enhanced by diuretics, which are typically given in combination preparations. Combining it with the calcium antagonist amlodipine is also particularly effective. The most common side effect (10% of the treated patients) is annoying dry cough caused by the lack of breakdown of bradykinin. Angioedema is an infrequent side effect of ACE inhibitors. In kidney disease, one needs to watch out for hyperkalemia and an increase in serum creatinine. The latter is especially relevant in renal artery stenosis. Captopril is used rarely due to its short half-life but it may be useful in patients with dysautonomia and hypotension during the day but hypertension during the night. Direct renin inhibitors (aliskiren) are very long-acting and effective in lowering BP but they lack preventive evidence because of lack of adequate clinical studies.

Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) include, among others, losartan, valsartan, irbesartan, candesartan, and telmisartan. ARBs counteract the effect of angiotensin II by specifically and selectively blocking angiotensin II receptors (AT-1 receptors) on target organs, including smooth muscle cells in the heart and blood vessels. This drug group has been exceptionally well tolerated in large registration studies, with less headache than placebo [74], and better persistence than other antihypertensive drug classes. The treatment principle counteracts harmful proliferation and hypertrophy in the heart and blood vessels. This is documented in large studies of patients with hypertension, diabetes, post myocardial infarction, and heart failure. The BP-lowering effect is, as with ACE inhibitors, especially good in combination preparations with a small dose of thiazide. Both groups of medications are contraindicated during pregnancy due to the risk of teratogenic effects. That is also the case for valsartan-sacubitril (Entresto®), a single molecule that works both as an ARB and a neprilysin inhibitor with strong BP-lowering effects. It's used for heart failure, but it was originally developed to treat hypertension [75] and is now registered for hypertension in many countries.

Beta-blockers

Beta blockers, such as propranolol, which is non-selective, and atenolol, metoprolol, bisoprolol, and nebivolol, all β-1 selective, attenuate the effects of adrenaline and noradrenaline on the heart as well

as the release of renin from the kidneys. This leads to a slower heart rate and lower BP, but also a slight reduction in peripheral vascular resistance. In susceptible individuals, non-selective beta blockers can trigger asthma. The use of cardio (β-1) selective beta-blockers may be prefered in people with asthma, as they are rarely causing contractions in the smooth muscles of the bronchii. Chronic obstructive pulmonary disease (COPD) patients often have concommitant coronary artery disease or heart failure, and most can safely use β-1 selective blockers. The most common side effects are sleep disturbances, fatigue, impotence, and reduced ability to exercise. The treatment can also increase triglyceride levels and lower HDL in the blood. Treatment with beta-blockers is preferred [76] if the patient with high BP has coronary artery disease, heart failure, rapid atrial fibrillation, and pronounced sinus tachycardia. There are multiple concomitant diseases that favour beta-blocker treatment [77], but overall beta-blocker is used less in uncomplicated hypertension due to limited tolerance.

Other sympathetic inhibitors

Doxazosin is an α-1 selective blocker and will therefore inhibit the sympathetic nervous system's effect on peripheral blood vessels. The result is that the vessels widen, reducing resistance. Older patients can experience orthostatic hypotension. Other side effects are rare. Unlike thiazides and beta-blockers, α-1 blockers have a beneficial effect on blood lipids by lowering LDL cholesterol and triglycerides, and improving insulin sensitivity. Doxazosin and other α-1 blockers are also used for prostate issues (in older men), and caution is needed in patients with established heart disease due to some reflex tachycardia and fluid retention (which also limits their use in hypertension).

Labetalol and carvedilol have both beta- and alpha-blocking properties. These medications reduce cardiac output and the peripheral resistance in the arterioles. Carvedilol, like bisoprolol, metoprolol, and nebivolol, improve survival in patients with heart failure with reduced ejection fraction (HFrEF).

The major medication groups mentioned above have been shown to prevent hypertension-related complications [7]. The randomised trials have included patients with well-documented hypertension (BP >140/90 mmHg with or without previous treatment) in placebo-run in or roll-over design including all randomised trials of head-to-head comparisons of medication groups discussed above [78–86]. However, no randomised outcome trial have shown that drug treatment of high normal BP ('elevated BP') prevent cardiovascular complications. On the contrary, in the HOPE-3 study participants with systolic BP in the high normal BP range ('elevated BP', 120-139/70-89 mmHg) did not benefit from active BP lowering treatment [87]. Central α-2 agonists (moxonidine, α-methyldopa, clonidine) are rarely used or have been deregistered. Vasodilators (hydralazine) have been deregistered, but are available upon request. Minoxidil is known to promote hair growth.

Development of new antihypertensive drugs

Drugs that reduce cardiovascular complications but with a modest reduction in BP like finerenone [88] or GLP1 receptor agonists [89] are available. This is an unusual situation for diabetic and non-diabetic patients with chronic kidney disease with and without hypertension.

One endothelin antagonist like bosentan has for many years been available for treatment of pulonary hypertension [90]. Endothelin receptor antagonists may now be introduced as a new therapeutic concepts for treatment of arterial hypertension [91].

Aldosterone synthase inhibtors have demonstrated marked reduction in BP in resistant hypertension [92,93].

Angiotensinogen has a key role in the pathogenesis of hypertension. Zilebesiran is an investigational RNA interference therapeutic agent which inhibits hepatic angiotensinogen synthesis. Zilebesiran has dose-dependent decreases in serum angiotensinogen levels and decreased 24-hour ambulatory BP lasted for up to 24 weeks after a single subcutaneous dose of zilebesiran of 200 mg or more [94].

NOVELTY TEXT BOX:
Finerenone and GLP1 receptor agonists reduce cardiovascular complications, but show modest reduction of BP.

Endothelin receptor antagonists may be introduced as a new therapeutic concepts for treatment of arterial hypertension.

Aldosterone synthase inhibtors have demonstrated marked reduction in BP in resistant hypertension.

Zilebesiran is an investigational RNA interference therapeutic agent which inhibits hepatic angiotensinogen synthesis.

Complications due to high BP and phenotypes of severe hypertension

Complications from hypertension may manifest only after few years, especially in the heart, blood vessels, brain, and kidneys. Kidney complications (arteriolosclerosis, nephrosclerosis, the most common cause of kidney failure next to diabetic kidney disease) can worsen hypertension in a vicious cycle. The complications depend on the severity of the patient's hypertension, the duration, and the treatment effect. Most of these complications are related to high BP and can be significantly countered by BP treatment. Medication to lower BP also reduces mortality from heart and vascular diseases by 20% and overall mortality by 10%. Medication to lower BP therefore has a very high cost-benefit ratio.

Treatment-resistant hypertension is defined as high BP despite being prescribed at least three medications at the highest tolerated dose, including a diuretic. True resistant hypertension may affect 10% of patients treated for hypertension and is diagnosed after excluding white-coat hypertension, medication nonadherence, and secondary hypertension such as primary aldosteronism [95,96]. Frequently, the condition is caused by poor adherence to the prescribed medication ('apparent' treatment-resistant) [58]. If suspected, drug levels can be measured in blood [97,98] or in urine [99] though such chemical adherence testing (CAT) and therapeutic drug monitoring (TDM) does not improve drug adherence in randomised controlled clinical studies [99,100].

NOVELTY TEXT BOX:
'Apparent' resistant hypertension is frequently caused by poor drug adherence. If suspected, drug levels can be measured in blood or in urine though such chemical adherence testing (CAT) and therapeutic drug monitoring (TDM) does not by itself improve blood pressure in randomised controlled clinical studies.

Refractory hypertension is rare and involves persistent high BP despite confirmed adherence to medication but with more than 4 prescribed drugs and a controlled or uncontrolled BP. Experimental treatments like renal sympathetic denervation [101–105], baroreceptor-activating therapy, or other ways to stimulate the parasympathetic and inhibit the sympathetic nervous system are ongoing for patients who continue to have high BP despite documented medication use and no signs of secondary hypertension.

Malignant hypertension can develop in some patients. In this case, the diastolic BP stays constantly high (often above 140 mmHg), and the patient has papilledema (swelling of the optic disc). If untreated, the prognosis is poor.

In a *hypertensive crisis*, BP rises suddenly, and the patient develops cerebral reactions like headaches, neurological symptoms, and severe vascular changes in the retina. The patient can become confused and may even lose consciousness (hypertensive encephalopathy). There is an acute risk of brain haemorrhage and heart failure. Treatment with an intravenous infusion of a vasodilating drug such as sodium nitroprusside (Nipride) or glyceryl nitrate should therefore be started as soon as possible. There are several other treatment options, but to avoid hypoperfusion, meaning that the tissues get too little blood supply, it's especially important to lower BP gradually. In this critical phase, the patient needs close monitoring, and BP must be measured continuously.

Conclusion

As discussed in this paper numerous issues in clinical hypertension research have been resolved through the past years. However, as pointed out there are remaining problems with BP targets especially in patients with heart enlargement and chronic kidney disease – should systolic BP be lowered below 140, 130 or 120 mmHg (?) especially in older patients. Another major issue has appeared namely the need for trial evidence in 'elevated BP' (120-139/70-89 mmHg) – a term introduced by ESC [8] with guideline suggestion of drug treatment in patients with global cardiovacular risk above 10%.

Otherwise diagnosis, treatment and control of hypertension has been improving in parallell in Norway, Switzerland and Italy through many years. Remaining main problems are of more practical character namely the need to convince patients to take their antihypertensive medication (improve adherence) – especially through many years (improve persistence). The other main problem is physician inertia – namely convince all practicing physians that they must prescribe enough antihypertensive medication to control individual high BP. It is worthwhile to mention at the end that high BP in up to 80–90% of patients may be controlled with 1 antihypertensive pill taken daily – a pill containing suited doses of RAAS-blocker (ARB or ACE-inhibitor, calcium-antagonist usually amlodipine and hydrochlorothiazide). However, one issue that has been resolved in the 3 countries, is the accessibility to and the reimbursement of single pill combinations, a context which is not yet generalised within European countries, despite the fact that the use of single pill combinations is cost-saving as reported recently in Italy [106]. An additional problem is that in Italy healthcare autorities support treatment strategies based on initial monotherapy, which is in part responsible for low use of drug combinations and greater improvement of BP control.

Digital health technologies, such as telemonitoring, wearables, and other mobile health platforms, are becoming frequently adopted tools in hypertension management, particularly those that have undergone regulatory approval [107]. The concept of Hybrid Health Care partly in presence and partly at distance might develop due to the lack of doctors but there are clear limitations.

Author contributions

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SEK reports lecture honoraria during past 3 years from Amgen, Boehringer-Ingelheim, Cadilla, Emcure, Getz, Hikma, J.B. Pharma, Merck, and Vector-Intas. MB reports lecture honoraria from Bayer, Menarini, Sanofi, and Servier. GM is chair of the writing committee of the 2023 European Society of Hypertension Guidelines and SEK and MB are committee members. GM reports lecture honoraria from Astra Zeneca, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Menarini Group, Merck, Novartis, Recordati, Sandoz, Sanofi, and Servier. JG and MKS report no conflicts.

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Data availability statement

No datasets were generated or analysed during the current study.

References

[1] Grassi G. Thirty-five years of the European Society of Hypertension: from past to future. J Hypertens. 2024;42(9):1516–1520. doi: 10.1097/HJH.0000000000003778.
[2] Global report on hypertension 2025: high stakes – turning evidence into action. Geneva: World Health Organization; 2025.
[3] Kjeldsen SE, Gjelsvik B, Klemsdal TO. Treatment of hypertension in Norway in relation to new European hypertension guidelines. Explor Med. 2026;7:1001390. doi: 10.37349/emed.2026.1001390.
[4] Di Gangi S, Brenner R, Grischott T, et al. Blood pressure control and antihypertensive treatment in Swiss general practice: a cross-sectional study using routine data. Swiss Med Wkly. 2024;154:3898. doi: 10.57187/s.3898.
[5] Volpe M, Muiesan ML, Tocci G, et al. Management of patients with arterial hypertension in Italy: a consensus document of the Italian Society of Hypertension (SIIA) and the Italian Society for Cardiovascular Prevention (SIPREC) about the recommended care pathway and areas for improvement. High Blood Press Cardiovasc Prev. 2026;33(1):1–11. doi: 10.1007/s40292-025-00756-3.
[6] GBD 2023 Causes of Death Collaborators. Global burden of 292 causes of death in 204 countries and territories and 660 subnational locations, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025;406(10513):1811–1872. doi: 10.1016/S0140-6736(25)01917-8.
[7] Mancia G, Kreutz R, Brunström M, et al. ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071. doi: 10.1097/HJH.0000000000003480.
[8] McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45(38):3912–4018. doi: 10.1093/eurheartj/ehae178.
[9] SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439–2454. doi: 10.1093/eurheartj/ehab309.
[10] SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455–2467. doi: 10.1093/eurheartj/ehab312.
[11] Kjeldsen SE, Brunström M, Burnier M, et al. Should treatment of 'elevated' blood pressure, especially in older people, be based on global risk estimation? Blood Press. 2024;33(1):2430228. doi: 10.1080/08037051.2024.2430228.
[12] Kjeldsen SE, Brunström M, Burnier M, et al. Management of 'Elevated' blood pressure according to the 2024 European Society of Cardiology Guidelines: lack of supportive evidence and high risk of excessive treatment. Blood Press. 2025;34(1):2480608. doi: 10.1080/08037051.2025.2480608.
[13] Rietz H, Pennlert J, Nordström P, et al. Prevalence, time-trends and clinical characteristics of hypertension in young adults: nationwide cross-sectional study of 1.7 million Swedish 18-year-olds, 1969-2010. J Hypertens. 2022;40(6):1231–1238. doi: 10.1097/HJH.0000000000003141.
[14] Sundström J, Neovius M, Tynelius P, et al. Association of blood pressure in late adolescence with subsequent mortality: cohort study of Swedish male conscripts. BMJ. 2011;342:d643. doi: 10.1136/bmj.d643.
[15] Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003;139(9):761–776. doi: 10.7326/0003-4819-139-9-200311040-00011.
[16] Folkow B. Physiological aspects of primary hypertension. Physiol Rev. 1982;62(2):347–504. doi: 10.1152/physrev.1982.62.2.347.
[17] Piotte J, Stoenoiu MS, Jamison C, et al. Ten tips for the diagnosis and management of fibromuscular dysplasia. Clin Kidney J. 2026;19(8):sfag234. doi: 10.1093/ckj/sfag234.
[18] Eide IK, Torjesen PA, Drolsum A, et al. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. J Hypertens. 2004;22(11):2217–2226. doi: 10.1097/00004872-200411000-00026.
[19] Julius S, Majahalme S. The changing face of sympathetic overactivity in hypertension. Ann Med. 2000;32(5):365–370. doi: 10.3109/07853890008995939.
[20] Esler M, Leonard P, Jackman G, et al. Study of noradrenaline uptake and spillover to plasma in normal subjects and patients with essential hypertension. Prog Biochem Pharmacol. 1980;17:75–83.
[21] Mancia G, Grassi G. The autonomic nervous system and hypertension. Circ Res. 2014;114(11):1804–1814. doi: 10.1161/CIRCRESAHA.114.302524.

[22] Kjeldsen SE, Flaaten B, Eide I, et al. Increased peripheral release of noradrenaline and uptake of adrenaline in essential hypertension? Clin Sci (Lond). 1981;61(Suppl 7):215s–217s. doi: 10.1042/cs061215s.
[23] Flaa A, Eide IK, Kjeldsen SE, et al. Sympathoadrenal stress reactivity is a predictor of future blood pressure: an 18-year follow-up study. Hypertension. 2008;52(2):336–341. doi: 10.1161/HYPERTENSIONAHA.108.111625.
[24] Julius S, Palatini P, Kjeldsen SE, et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. Am J Cardiol. 2012;109(5):685–692. doi: 10.1016/j.amjcard.2011.10.025.
[25] Okin PM, Kjeldsen SE, Julius S, et al. Effect of changing heart rate during treatment of hypertension on incidence of heart failure. Am J Cardiol. 2012;109(5):699–704. doi: 10.1016/j.amjcard.2011.10.026.
[26] Padmanabhan S, Melander O, Johnson T, et al. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. PLoS Genet. 2010;6(10):e1001177. doi: 10.1371/journal.pgen.1001177.
[27] Grassi G, Dell'Oro R, Quarti-Trevano F, et al. Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia. 2005;48(7):1359–1365. doi: 10.1007/s00125-005-1798-z.
[28] Borghi C, Rossi F, SIF Task Force. SIIA Task Force. Role of the renin-angiotensin-aldosterone system and its pharmacological inhibitors in cardiovascular diseases: complex and critical issues. High Blood Press Cardiovasc Prev. 2015;22(4):429–444. doi: 10.1007/s40292-015-0120-5.
[29] Mancia G, Failla M, Grappiolo A, et al. Present and future role of combination treatment in hypertension. J Cardiovasc Pharmacol. 1998;31(Suppl 2):S41–S44. doi: 10.1097/00005344-199800002-00007.
[30] Kreutz R, Brunström M, Burnier M, et al. 2024 European Society of Hypertension clinical practice guidelines for the management of arterial hypertension. Eur J Intern Med. 2024;126:1–15. doi: 10.1016/j.ejim.2024.05.033.
[31] Thompson B, Rigon PA, Ponte B, et al. Mesure de la pression artérielle sans brassard: une perspective romande du « cuffless» [Cuffless blood pressure monitoring: perspective from Romandy]. Rev Med Suisse. 2025;21(930):1615–1618. French. doi: 10.53738/REVMED.2025.21.930.47789.
[32] Heimark S, Bøtker-Rasmussen KG, Stepanov A, et al. Accuracy of non-invasive cuffless blood pressure in the intensive care unit: promises and challenges. Front Med (Lausanne). 2023;10:1154041. doi: 10.3389/fmed.2023.1154041.
[33] Hove C, Sæter FW, Stepanov A, et al. A prototype photoplethysmography-based cuffless device shows promising results in tracking changes in blood pressure. Front Med Technol. 2024;6:1464473. doi: 10.3389/fmedt.2024.1464473.
[34] Parati G, Pengo MF, Avolio A, et al. for the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability. Nocturnal blood pressure: pathophysiology, measurement and clinical implications. Position paper of the European Society of Hypertension. J Hypertens. 2025;43(8):1296–1318. doi: 10.1097/HJH.0000000000004053.
[35] Mancia G, Facchetti R, Vanoli J, et al. White-coat hypertension without organ damage: impact on long-term mortality, new hypertension, and new organ damage. Hypertension. 2022;79(5):1057–1066. doi: 10.1161/HYPERTENSIONAHA.121.18792.
[36] Mariampillai JE, Liestøl K, Kjeldsen SE, et al. Exercise systolic blood pressure at moderate workload is linearly associated with coronary disease risk in healthy men. Hypertension. 2020;75(1):44–50. doi: 10.1161/HYPERTENSIONAHA.119.13528.
[37] Mariampillai JE, Prestgaard EE, Kjeldsen SE, et al. Novel insights into stroke risk beyond resting and maximal bicycle exercise systolic blood pressure. J Hypertens. 2021;39(10):2022–2029. doi: 10.1097/HJH.0000000000002894.
[38] Cuspidi C, Facchetti R, Quarti-Trevano F, et al. Incident left ventricular hypertrophy in masked hypertension. Hypertension. 2019;74(1):56–62. doi: 10.1161/HYPERTENSIONAHA.119.12887.
[39] Hypertension and Brain Damage 2nd edition. A. Coca Editor. Springer Nature Switzerland AG.; 2024. p. 1–310.
[40] Chinali M, Aurigemma GP, Gerdts E, et al. Development of systolic dysfunction unrelated to myocardial infarction in treated hypertensive patients with left ventricular hypertrophy. The LIFE Study. Explor Med. 2022;3:160–172. doi: 10.37349/emed.2022.00082.
[41] Kjeldsen SE, Wachtell K, Devereux RB. Blood pressure control and outcomes in heart failure patients with preserved ejection fraction: an individual participant data meta-analysis of four major trials. Eur J Heart Fail. 2026;00:1–4. doi: 10.1093/ejhf/xuag269.
[42] Lu H, Claggett BL, Ostrominski JW, et al. Time in blood pressure range and cardiovascular outcomes in HFmrEF/HFpEF: a pooled participant-level analysis of four large-scale trials. Eur J Heart Fail. 2026:xuag245. doi: 10.1093/ejhf/xuag245.
[43] Rist A, Sevre K, Wachtell K, et al. The current best drug treatment for hypertensive heart failure with preserved ejection fraction. Eur J Intern Med. 2024;120:3–10. doi: 10.1016/j.ejim.2023.10.008.
[44] Estrella MM, Ballew SH, Sang Y, Chronic Kidney Disease Prognosis Consortium Investigators and Collaborators., et al. Discordance in creatinine- and cystatin C-based eGFR and clinical outcomes: a meta-analysis. JAMA. 2025;334(21):1915–1926. doi: 10.1001/jama.2025.17578.
[45] Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004;292(19):2350–2356. doi: 10.1001/jama.292.19.2350.

[46] Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA. 2004;292(19):2343–2349. doi: 10.1001/jama.292.19.2343.
[47] Okin PM, Wachtell K, Devereux RB, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA. 2006;296(10):1242–1248. doi: 10.1001/jama.296.10.1242.
[48] Mancia G, Bombelli M, Lanzarotti A, et al. Systolic vs diastolic blood pressure control in the hypertensive patients of the PAMELA population. Pressioni Arteriose Monitorate E Loro Associazioni. Arch Intern Med. 2002;162(5):582–586. doi: 10.1001/archinte.162.5.582.
[49] Kjeldsen SE, Gjesdal K, Eide I, et al. Increased B-thromboglobulin in essential hypertension: interactions between arterial plasma adrenaline, platelet function and blood lipids. Acta Med Scand. 1983;213(5):369–373. doi: 10.1111/j.0954-6820.1983.tb03753.x.
[50] Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149–1158. doi: 10.1016/S0140-6736(03)12948-0.
[51] Kjeldsen SE, Kreutz R, Mancia G. Evolocumab for primary prevention of cardiovascular disease. N Engl J Med. 2026;394(16):1657–1658. doi: 10.1056/NEJMc2602103.
[52] Bohula EA, Marston NA, Bhatia AK, for the VESALIUS-CV Investigators., et al. Evolocumab in patients without a previous myocardial infarction or stroke. N Engl J Med. 2026;394(2):117–127.,. doi: 10.1056/NEJMoa2514428.
[53] Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT). randomised trial. HOT Study Group. Lancet. 1998;351(9118):1755–1762. doi: 10.1016/s0140-6736(98)04311-6.
[54] Kjeldsen SE, Kolloch RE, Leonetti G, et al. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. Hypertension Optimal Treatment. J Hypertens. 2000;18(5):629–642. doi: 10.1097/00004872-200018050-00017.
[55] Mariampillai JE, Eskås PA, Heimark S, et al. A case for less intensive blood pressure control: it matters to achieve target blood pressure early and sustained below 140/90 mmHg. Prog Cardiovasc Dis. 2016;59(3):209–218. doi: 10.1016/j.pcad.2016.09.002.
[56] Mehlum MH, Liestøl K, Kjeldsen SE, et al. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. Eur Heart J. 2018;39(24):2243–2251. doi: 10.1093/eurheartj/ehx760.
[57] Mancia G, Bombelli M, Facchetti R, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. Hypertension. 2007;49(6):1265–1270. doi: 10.1161/HYPERTENSIONAHA.107.088708.
[58] Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124(7):1124–1140. doi: 10.1161/CIRCRESAHA.118.313220.
[59] Burnier M. Poor Physician adherence to clinical guidelines in hypertension-time for physicians to face clinical inertia. JAMA Netw Open. 2024;7(8):e2426830. doi: 10.1001/jamanetworkopen.2024.26830.
[60] Palmieri V, Okin PM, Bella JN, et al. Losartan intervention for end-point reduction in hypertension. Echocardiographic wall motion abnormalities in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE Study. Hypertension. 2003;41(1):75–82. doi: 10.1161/01.HYP.0000045081.54784.36.
[61] Kjeldsen SE, Egan B, Mancia G, et al. Target systolic blood pressure in patients with left ventricular hypertrophy. Eur J Intern Med. 2026;146:106760. doi: 10.1016/j.ejim.2026.106760.
[62] Okin PM, Kjeldsen SE, Devereux RB. The relationship of all-cause mortality to average on-treatment systolic blood pressure is significantly related to baseline systolic blood pressure: implications for interpretation of the Systolic Blood Pressure Intervention Trial study. J Hypertens. 2018;36(4):916–923. doi: 10.1097/HJH.0000000000001620.
[63] Heimark S, Mehlum MH, Mancia G, et al. middle-aged and older patients with left ventricular hypertrophy: higher mortality with drug treated systolic blood pressure below 130 mm Hg. Hypertension. 2023;80(8):1739–1748. doi: 10.1161/HYPERTENSIONAHA.123.21454.
[64] Burnier M, Mariampillai JE, Kjeldsen SE. The paradox of blood pressure control in patients with hypertension and left ventricular hypertrophy. Future Cardiol. 2026;
[65] Burnier M, Damianaki A. Hypertension as cardiovascular risk factor in chronic kidney disease. Circ Res. 2023;132(8):1050–1063. doi: 10.1161/CIRCRESAHA.122.321762.
[66] Zeng G, Bidel Z, Yang Q, Blood Pressure Lowering Treatment Trialists' Collaboration., et al. Pharmacological blood-pressure lowering for the prevention of cardiovascular disease and death across the full spectrum of chronic kidney disease severity: an individual-participant data meta-analysis. Lancet. 2026;407(10539):1626–1638. doi: 10.1016/S0140-6736(26)00367-3.

[67] Kjeldsen SE, Halvorsen LV, Burnier M. Blood pressure and cardiovascular protection in chronic kidney disease: things are moving in nephrology! Blood. Press. 2026;35(1):2728279. doi: 10.1080/08037051.2026.2728279.
[68] Guo X, Sun G, Xu Y, et al. Benefit-harm trade-offs of intensive blood pressure control versus standard blood pressure control on cardiovascular and renal outcomes: an individual participant data analysis of randomised controlled trials. Lancet. 2025;406(10507):1009–1019. doi: 10.1016/S0140-6736(25)01391-1.
[69] Olsen E, Jamerson K, Schmieder RE, et al. Effects of valsartan vs amlodipine and achieved lower blood pressure on the incidence of end-stage kidney disease: the VALUE Trial. Eur J Intern Med. 2025;133:55–63. doi: 10.1016/j.ejim.2024.12.021.
[70] Kjeldsen SE, Burnier M, Zoccali C, et al. Optimal kidney protection by moderate aggressive treatment of hypertension. Curr Hypertens Rep. 2026;28:1–14. doi: 10.1007/s11906-026-01395-2.
[71] Olsen E, Søraas CL, Schmieder RE, et al. Low achieved systolic blood pressure related to kidney protection in diabetic and non-diabetic high-risk hypertensive patients. Am J Hypertens. 2025;38(12):1106–1119. doi: 10.1093/ajh/hpaf093.
[72] Burnier M, Kreutz R, Narkiewicz K, et al. Circadian variations in blood pressure and their implications for the administration of antihypertensive drugs: is dosing in the evening better than in the morning? J Hypertens. 2020;38(8):1396–1406. doi: 10.1097/HJH.0000000000002532.
[73] Mackenzie IS, Rogers A, Poulter NR, for the TIME Study Group., et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet. 2022;400(10361):1417–1425. doi: 10.1016/S0140-6736(22)01786-X.
[74] Laurell K, Gustafsson S, Lampa E, et al. Persistence to antihypertensive drug classes in uncomplicated hypertension: a nationwide Swedish cohort study. EClinicalMedicine. 2026;91:103696. doi: 10.1016/j.eclinm.2025.103696.
[75] Ruilope LM, Dukat A, Böhm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375(9722):1255–1266. doi: 10.1016/S0140-6736(09)61966-8.
[76] Mancia G, Brunström M, Burnier M, et al. Rationale for the inclusion of β-blockers among major antihypertensive drugs in the 2023 European Society of Hypertension Guidelines. Hypertension. 2024;81(5):1021–1030.) doi: 10.1161/HYPERTENSIONAHA.124.22821.
[77] Mancia G, Kjeldsen SE, Kreutz R, et al. Individualized beta-blocker treatment for high blood pressure dictated by medical comorbidities: indications beyond the 2018 European Society of Cardiology/European Society of Hypertension Guidelines. Hypertension. 2022;79(6):1153–1166. doi: 10.1161/HYPERTENSIONAHA.122.19020.
[78] Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet. 2000;356(9227):359–365. doi: 10.1016/s0140-6736(00)02526-5.
[79] Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000;356(9227):366–372., doi: 10.1016/S0140-6736(00)02527-7.
[80] Dahlöf B, Devereux RB, Kjeldsen SE, et al. for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995–1003. doi: 10.1016/S0140-6736(02)08089-3.
[81] Julius S, Kjeldsen SE, Weber M, VALUE trial group., et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022–2031. doi: 10.1016/S0140-6736(04)16451-9.
[82] Dahlöf B, Sever PS, Poulter NR, et al. for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906. doi: 10.1016/S0140-6736(05)67185-1.
[83] Jamerson K, Weber MA, Bakris GL, ACCOMPLISH Trial Investigators., et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–2428. doi: 10.1056/NEJMoa0806182.
[84] Kjeldsen SE, Dahlöf B, Devereux RB, et al. for the LIFE Study Group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA, 12. 2002;288:1491–1498. doi: 10.1001/jama.288.12.1491.
[85] Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet. 2004;363(9426):2049–2051. doi: 10.1016/S0140-6736(04)16456-8.

[86] Weber MA, Bakris GL, Jamerson K, for the ACCOMPLISH Investigators., et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol. 2010;56(1):77–85. doi: 10.1016/j.jacc.2010.02.046.
[87] Lonn EM, Bosch J, López-Jaramillo P, for HOPE-3 Investigators., et al. Blood-Pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2009–2020. doi: 10.1056/NEJMoa1600175.
[88] Agarwal R, Ruilope LM, Ruiz-Hurtado G, et al. Effect of finerenone on ambulatory blood pressure in chronic kidney disease in type 2 diabetes. J Hypertens. 2023;41(2):295–302. doi: 10.1097/HJH.0000000000003330.
[89] Katsi V, Manta E, Fragoulis C, et al. Weight loss therapies and hypertension benefits. Biomedicines. 2024;12(10):2293. doi: 10.3390/biomedicines12102293.
[90] Krum H, Viskoper RJ, Lacourciere Y, et al. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan hypertension investigators. N Engl J Med. 1998;338(12):784–790. doi: 10.1056/NEJM199803193381202.
[91] Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022;400(10367):1927–1937. doi: 10.1016/S0140-6736(22)02034-7.
[92] Flack JM, Azizi M, Brown JM, et al. Efficacy and safety of baxdrostat in uncontrolled and resistant hypertension. N Engl J Med. 2025;393(14):1363–1374.). doi: 10.1056/NEJMoa2507109.
[93] Laffin LJ, Kopjar B, Melgaard C, for the Advance-HTN Investigators., et al. Lorundrostat efficacy and safety in patients with uncontrolled hypertension. N Engl J Med. 2025;392(18):1813–1823. doi: 10.1056/NEJMoa2501440.
[94] Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Engl J Med. 2023;389(3):228–238. doi: 10.1056/NEJMoa2208391.
[95] Fadl Elmula FEM, Mariampillai JE, Heimark S, et al. Medical measures in hypertensives considered resistant. Am J Hypertens. 2024;37(5):307–317. Erratum in: am J Hypertens. 2024; 37:448. doi: 10.1093/ajh/hpad118.
[96] Azizi M, Vongpatanasin W, Fisher NDL, et al. Diagnosis and management of resistant hypertension: a review. JAMA. 2026;335(16):1428–1439. doi: 10.1001/jama.2026.1221.
[97] Bergland OU, Halvorsen LV, Søraas CL, et al. Detection of nonadherence to antihypertensive treatment by measurements of serum drug concentrations. Hypertension. 2021;78(3):617–628. doi: 10.1161/HYPERTENSIONAHA.121.17514.
[98] Olsen E, Halvorsen LV, Rognstad S, et al. Characteristics of adherent and non-adherent patients with hypertension in a Norwegian cross-sectional study. Explor Med. 2025;6:1001279. doi: 10.37349/emed.2025.1001279.
[99] Tomaszewski M, Gupta P, Chowienczyk P, et al. Chemical adherence testing-guided intervention versus standard of care in patients with hypertension who are non-adherent to antihypertensive treatment in the UK (OUTREACH): a multicentre, randomised controlled trial. Lancet Prim Care. 2026;2(5):100154. doi: 10.1016/j.lanprc.2026.100154.
[100] Halvorsen LV, Søraas CL, Larstorp ACK, et al. Effect of therapeutic drug monitoring on adherence and blood pressure: a multicenter randomized clinical trial. Am J Hypertens. 2024;37(10):826–836. doi: 10.1093/ajh/hpae059.
[101] Esler M. Renal denervation for treatment of drug-resistant hypertension. Trends Cardiovasc Med. 2015;25(2):107–115. doi: 10.1016/j.tcm.2014.09.014.
[102] Kjeldsen SE, Esler MD. Take a blood pressure pill or undergo renal denervation? Lancet. 2018;391(10137):2298–2300. doi: 10.1016/S0140-6736(18)31126-7.
[103] Kjeldsen SE, Fadl Elmula FEM, Persu A. Future of renal sympathetic denervation in the treatment of hypertension. J Am Coll Cardiol. 2019;73(13):1643–1645. doi: 10.1016/j.jacc.2019.02.008.
[104] Persu A, Stoenoiu MS, Maes F, et al. Late outcomes of renal denervation are more favourable than early ones: facts or fancies? Clin Kidney J. 2023;16(12):2357–2364. doi: 10.1093/ckj/sfad231.
[105] Messerli FH, Bavishi C, Brguljan J, et al. Renal denervation in the antihypertensive arsenal - knowns and known unknowns. J Hypertens. 2022;40(10):1859–1875., doi: 10.1097/HJH.0000000000003171).
[106] Morabito G, Gregorio C, Ieva F, et al. Cost-effectiveness of single-pill and separate-pill administration of antihypertensive triple combination therapy: a population-based microsimulation study. BMC Public Health. 2024;24(1):1808. doi: 10.1186/s12889-024-19346-4.
[107] Parati G, Goncalves A, Soergel D, et al. New perspectives for hypertension management: progress in methodological and technological developments. Eur J Prev Cardiol. 2023;30(1):48–60. doi: 10.1093/eurjpc/zwac203.