WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

The Evolving of Hypertension: Pathophysiology, Risk Determinants, Target Organ Damage, Precision Management, and Future Therapies

Emmanuel Amos Mhandisha[1a], Prince Mathew Dabo[1b], Prabhjot Singh[1c*]

[1]School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, India, 147301
[a]emamos689@gmail.com
[b]princematthew1010@gmail.com
[c]prabhjotsingh0304@gmail.com
***Corresponding Author**: Prabhjot Singh,
Assistant Professor,
School of Pharmacy,
Desh Bhagat University,
Mandi Gobindgarh, Punjab, India, PIN: 147301.
Email- prabhjotsingh0304@gmail.com
ORCID id: https://orcid.org/0009-0008-4224-0754

ABSTRACT :

Hypertension is a multifactorial, heterogeneous cardiovascular condition one of the most important modifiable risk factors for premature cardiovascular, cerebrovascular and renal disease. It is the result of complex interactions between the genetic susceptibility, renal sodium handling, activation of neurohormones, vascular dysfunction, metabolic abnormalities, inflammation, environmental exposures and lifestyle. Patients with Continued Stable Hypertension (ST) have hypertension-mediated organ damage (HMO) namely Left Ventricular Hypertrophy, Heart Failure, Cerebrovascular Disease, Chronic Kidney Disease, Vascular Remodelling and Retinal Injury. Even though the burden is still high – approximately 1.4 billion adults (ages 30-79 years) are affected worldwide. Modern management is now moving away from (blood pressure) BP reduction to cardiovascular-risk assessment, early detection of organ damage, out of office BP monitoring and personalised management and long-term adherence to treatment. New 'elevated blood pressure (BP) category added to 2024 European Society of Cardiology (ESC) guideline and emphasis on the importance of out-of-office (blood pressure) BP assessment. The American Heart Association/American College of Cardiology (AHA/ACC) guideline also added details on strategies for prevention, diagnosis, evaluation and treatment. The new strategies are precision medicine, artificial intelligence, wearable devices, renal denervation and mechanism targeted pharmacotherapies. The positive results of the latest phase 3 trial indicate baxdrostat, an aldosterone synthase inhibitor, has shown efficacy.

Keywords: Hypertension, Pathophysiology, Precision Management, Risk Determinants, Target Organ Damage.

1. INTRODUCTION

Hypertension is a primary preventable risk factor for cardiovascular disease, stroke, chronic kidney disease, heart failure and premature mortality, and a major public-health problem in the world. While hypertension often is not manifested by any symptoms, progressive increase of blood pressure leads to progressive changes in the structure and function of the blood vessels and to cumulative damage to the heart, brain, kidneys, retina and peripheral vascular system[1].

This burden is still significant in the rest of the world. In 2024, the World Health Organization estimated that there are about 1.4 billion adults (age 30-79) with hypertension. There is a significant proportion who are undiagnosed, untreated and/or poorly controlled, highlighting the fact that hypertension continues to be a clinical and health system problem[2].

Rather hypertension is a disease and should not be considered as mere a number. It is a multifaceted biological phenotype resulting from the interaction of genetic, renal, neurohormonal, vascular, metabolic and inflammatory factors, environmental exposures and behavioural factors. They are all present to varying extents in different people, resulting in significant variation in disease presentation and response to treatment[3].

The hypertension-phenotype has therefore broadened from merely an elevated blood pressure to cover cardiovascular risk, organ damage caused by hypertension, comorbidities, reaction to treatment and individual characteristics[4]. Repeat measurements and home or ambulatory blood pressure monitoring are increasingly used in the diagnosis to obtain an accurate diagnosis.

The dynamic structure opens possibilities for precision hypertension management. New and emerging phenotyping, biomarker, digital blood pressure,

artificial intelligence and mechanism-specific therapy could enable future treatment to shift away from the treatment algorithm and towards more personalized prevention and treatment strategies[5].

2. PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

2.1 Renal, Neurohormonal, and Vascular Mechanisms

Cardiac output, vascular resistance, blood volume, arterial compliance and neurohormonal regulation are the primary factors that influence blood pressure[6]. These regulatory mechanisms are permanently altered such that the blood vessels have higher resistance, they retain sodium or their extracellular fluid content expands, or inappropriate neurohormones are turned on[7].

This is because the kidneys are very important in the control of long-term blood pressure and are the primary controllers of sodium and water excretion. Abnormal pressure-natriuresis can lead to sodium retention and increase of the extracellular fluid volume[8]. Over-activation of the renin–angiotensin–aldosterone system (RAAS) also helps retain sodium, trigger vasoconstriction, stimulate sympathetic nervous system, induce vascular remodelling, cause oxidative stress and inflammation[9].

Angiotensin II acts as a vasoconstrictor by stimulating angiotensin (AT1 receptors) and causes a release of aldosterone. Aldosterone increases the reabsorption of sodium and may play a role in fibrosis of the blood vessels and of the blood vessels of the heart. Hyperaldosteronism might thus be a pathophysiological mechanism in resistant hypertension and cardiovascular remodelling[10].

An important role also is played by the sympathetic nervous system (SNS). Hyperactivity of sympathetic nerves leads to the stimulation of the heart, myocardial contractility, peripheral vascular resistance and renal renin release. Renal sodium handling may also be influenced by the chronic activation of the sympathetic system, as may also be the autonomic system[11].

Another fundamental mechanism is that of vascular dysfunction[13]. In endothelial dysfunction, the availability of nitric oxide is diminished, which leads to increased oxidative stress, increased vasoconstriction and inflammation of the vascular system. Continued vascular damage leads to smooth muscle growth, deposition of extracellular matrix, stiffness of the artery and remodelling of structure[14].

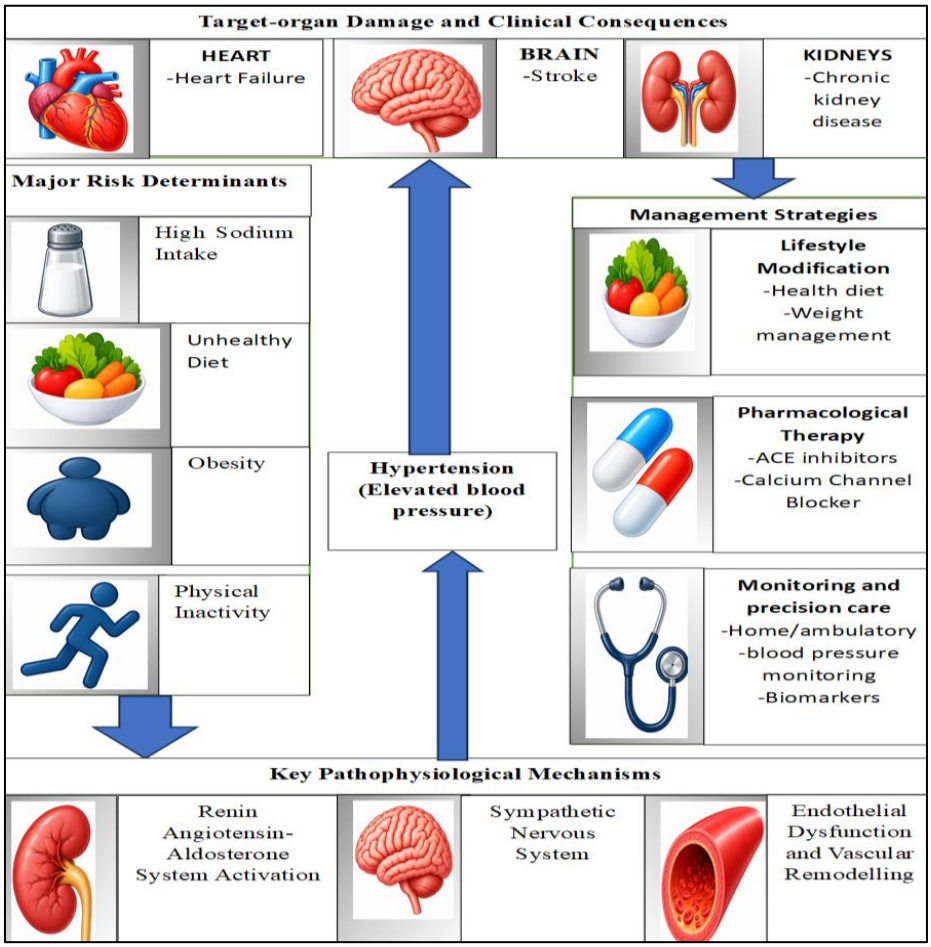


Figure 1. Integrated Overview of Risk Factors, Pathophysiological Mechanisms, Target-Organ Damage and Management Strategies in Hypertension

2.2 Genetic, Metabolic, Inflammatory, and Environmental Interaction

There is no single molecular pathway that is responsible for the development of hypertension. There is a dynamic relationship between genetic susceptibility and environmental exposures and behaviour throughout life[15]. Genetic variations may impact renal sodium handling, vascular tone, sympathetic drive, endocrine function and metabolism. Environmental and lifestyle factors greatly impact on genetic predisposition, however[16].

Obesity is especially significant in that excess adiposity could lead to increased sympathetic activity, activation of the renin–angiotensin–aldosterone system, renal sodium handling and cause inflammation. The adipose tissue has biologically active mediators, like leptin and adiponectin, that may affect vascular and metabolic pathways[17].

Insulin resistance can affect blood pressure by changing sodium regulation, the function of the blood vessels, increasing the power of the sympathetic system, and inducing metabolic inflammation. These mechanisms are important for the common occurrence of hypertension, obesity, dyslipidaemia and type 2 diabetes mellitus[18].

The involvement of inflammatory mechanisms in hypertension is gaining increasing acceptance. Oxidative stress and immune activation can affect the endothelial function and lead to vascular remodelling[19]. The gut microbiome is also of interest due to the possibility of interactions between microbial metabolites and intestinal ecology with other systems, such as immune, metabolic, vascular and blood pressure regulation. Currently, though, while the microbiome research has been translated into clinical practice, the process is still too early[20].

Table 1. Integrated mechanisms, determinants, target organ effects and therapeutic approach in hypertension

Domain	Major mechanisms/determinants	Important consequences	Clinical/therapeutic implications
Renal	Sodium retention, impaired pressure-natriuresis, altered renal hemodynamic	Volume expansion and sustained blood pressure elevation	Sodium reduction, diuretics, renal protection
Renin–angiotensin–aldosterone system	Renin, angiotensin II, aldosterone activation	Vasoconstriction, sodium retention, fibrosis, inflammation	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, aldosterone synthase inhibitors
Sympathetic nervous system	Increased sympathetic activity, impaired autonomic regulation	Vasoconstriction, increased heart rate and renin release	Pharmacological treatment and selected device-based strategies
Vascular	Endothelial dysfunction, oxidative stress, arterial stiffness	Increased vascular resistance and pulse pressure	Blood pressure control, exercise, dietary intervention
Metabolic	Obesity, insulin resistance, adipokine imbalance	Sodium retention, sympathetic activation, inflammation	Weight management and metabolic-risk reduction
Inflammatory	Cytokine signalling, immune-cell activation, oxidative stress	Vascular dysfunction and tissue remodelling	Investigation of inflammatory pathways
Genetic/epigenetic	Heritable susceptibility and gene–environment interaction	Individual variation in blood pressure and treatment response	Precision medicine and pharmacogenomic research
Lifestyle	Excess sodium, low potassium intake, inactivity, alcohol, tobacco, poor diet	Increased blood pressure and cardiovascular risk	Lifestyle modification and prevention
Sleep/stress	Sleep deprivation, obstructive sleep apnoea, psychosocial stress	Sympathetic and neuroendocrine activation	Sleep assessment, obstructive sleep apnoea treatment, stress management
Cardiac hypertension-mediated organ damage	Left ventricular hypertrophy, fibrosis, diastolic dysfunction	Heart failure, atrial fibrillation, ischemic disease	Early detection and intensive risk-factor management
Cerebrovascular hypertension-mediated organ damage	Small-vessel disease and arterial remodelling	Stroke and cognitive impairment	Blood pressure control and vascular-risk prevention
Renal hypertension-mediated organ damage	Albuminuria, nephrosclerosis, declining estimated glomerular filtration rate	Chronic kidney disease and progressive renal dysfunction	Renal protection and individualized treatment
Emerging targets	Aldosterone synthase, renal sympathetic nerves, endothelin and other pathways	Persistent/uncontrolled hypertension	Novel pharmacological and device-based therapies

3. RISK DETERMINANTS AND LIFESTYLE RELATED DRIVERS

3.1 Dietary, Adiposity, and Physical Activity Determinants

One of the more well-known modifiable factors affecting blood pressure (BP) is dietary sodium. High sodium consumption leads to higher extracellular fluid volume and can also lead to higher vascular stiffness and neurohormonal activity especially in salt-sensitive people. On the other hand, dietary potassium can cause natriuresis, and thus aid in lowering blood pressure[21].

Eating is also a factor. Fruits and vegetables, whole grains, legumes and other minimally processed foods are rich in potassium, Fiber and micronutrients, and typically minimize intake of high sodium and energy-dense foods. Dietary patterns, like the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean dietary patterns, are important dietary components of cardiovascular prevention programs, therefore[22].

Exercise enhances vascular function, autonomic control, metabolic status and body composition. Exercise (either aerobic or resistance) can help lower blood pressure. The combination of various modes of physical activity may have more comprehensive cardiovascular benefits than single mode activity[24].

3.2 Alcohol, Tobacco, Sleep, Psychosocial Stress, and Social Determinants

Drinking alcohol can raise blood pressure, especially when the amount of alcohol consumed is higher. Therefore, lowering the amount of alcohol consumed can help lower blood pressure[25].

Tobacco exposure leads to endothelial dysfunction, oxidative stress, vascular inflammation, arterial stiffness and atherosclerosis. Therefore, quitting smoking is an integral part of a cardiovascular-risk-reduction strategy[26].

The sleep characteristics also impact on blood pressure regulation. Short sleep duration, fragmented sleep, irregular sleep timing, and obstructive sleep apnoea (OSA) all can lead to increase of sympathetic activity and disrupt metabolic and endocrine regulation. Resistant hypertension involves this relevance of obstructive sleep apnoea (OSA)[27].

Social determinants are also a factor of importance. Diagnosis, treatment and blood pressure control may be affected by access to healthcare, the cost of medications, literacy, socioeconomic determinants, healthy food availability, and organization of healthcare services[29].

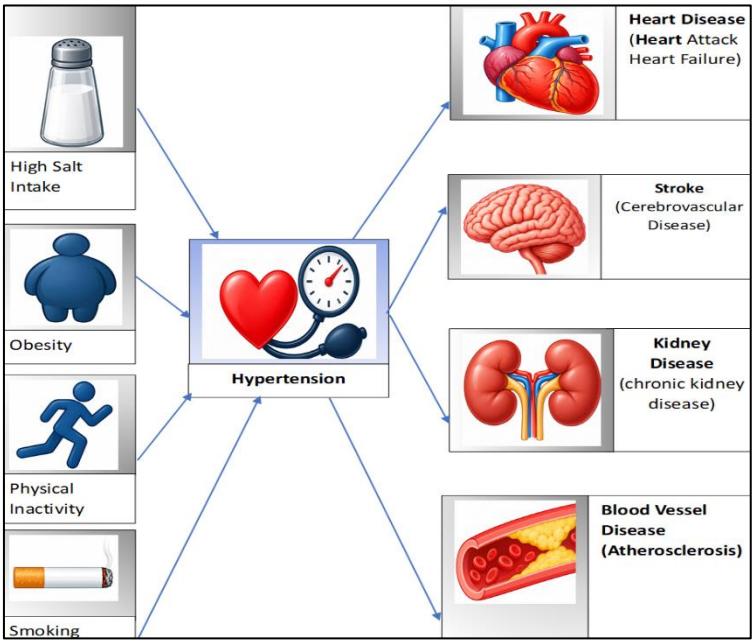


Figure 2. Major Modification Risk Factors and Cardiovascular and Renal Consequences of Hypertension

4. TARGET ORGAN DAMAGE AND CARDIOVASCULAR CONSEQUENCES

4.1 Cardiac and Vascular Consequences

Chronic hypertension is one of the main organs that is affected by the heart. Maintained stress causes a rise in wall stress of the left ventricle and may trigger compensatory hypertrophy. At first, left ventricular hypertrophy (LVH) can maintain wall stress, but with time, LVH can cause the myocardium to become stiffer, to not relax well, to develop fibrosis in the interstitial, and to become dysfunctional in the diastolic phase[30].

With the passage of time, the remodelling process of the heart muscle from hypertension may lead to an atrial enlargement, atrial fibrillation, coronary artery disease, heart failure with preserved ejection fraction, and ultimately to a systolic dysfunction[31].

Arterial remodelling is also caused by hypertension. Arterial stiffness is caused by an increase in vascular smooth muscle activity, collagen deposition, endothelial dysfunction and calcification. The resulting increase in arterial stiffness will further increase after load of the heart muscle and could further trigger cardiovascular remodelling[32].

4.2 Cerebral, Renal, Retinal, and Multiorgan Damage

Chronic elevation of blood pressure is very harmful to the brain. High blood pressure is linked with ischemic and haemorrhagic stroke, white-matter changes, abnormalities of the white matter, and vascular cognitive impairment[33].

Renal injury is a sequela and a risk factor of hypertension. Ongoing pressure damage to the glomeruli can lead to albuminuria, nephrosclerosis and reduced estimated glomerular filtration rate (eGFR). As kidney function declines, sodium retention and activation of neurohormones can further contribute to increased blood pressure[34].

The retinal vascular changes can be useful in providing clinically accessible evidence of chronic microvascular injury. Evaluation of hypertension-related organ damage thus helps to determine whether the high blood pressure has already caused structural or functional changes and therefore helps to identify patients at risk for such changes[35].

The notion of organ damage due to hypertension is gaining importance since organ damage can give information beyond that of blood pressure. Thus, cardiac, renal, vascular and cerebral evaluations can potentially add to the overall cardiovascular-risk profile[36]**.**

5. CONTEMPORARY DIAGNOSIS AND BLOOD PRESSURE ASSESSMENT

5.1 Office, Home and Ambulatory Blood Pressure Measurement

Correct taking of blood pressure is critical to diagnosis. Clinically important misclassification can occur due to errors in cuff size, patient posture, insufficient rest, talking while taking the blood pressure reading, or using the wrong equipment[37].

The European Society of Cardiology guideline on hypertension was revised in 2024 by introducing a new category of elevated blood pressure between normal blood pressure and hypertension and adding the recommendations to measure blood pressure outside of the clinic, if possible[38].

Home blood pressure monitoring (HBPM) can facilitate multiple blood pressure readings under standardised conditions and enhance the detection of persistent hypertension. Ambulatory blood pressure monitoring (ABPM): Measures blood pressure throughout the day and night and are useful in detecting circadian abnormalities[39].

Diagnosis should extend beyond blood pressure measurement. Clinical evaluation should consider age, family history, smoking, obesity, diabetes mellitus, dyslipidaemia, kidney disease, established cardiovascular disease, medication use, and secondary causes[40].

Assessment for hypertension-mediated organ damage may include electrocardiography (ECG), echocardiography when indicated, renal function and albuminuria testing, retinal assessment, and vascular evaluation[41].

Secondary hypertension should be considered when hypertension occurs at an unusually young age, is severe or resistant, has abrupt onset or deterioration, or is accompanied by suggestive clinical or biochemical findings. Important causes include primary aldosteronism, renal disease, renovascular disease, obstructive sleep apnoea, endocrine disorders, and medication or substance effects[42].

6. CONTEMPORARY PREVENTION AND MANAGEMENT

6.1 Lifestyle and Non-Pharmacological Management

The basic tenet of prevention and treatment for hypertension is lifestyle modification. Key interventions include: reducing dietary sodium, upping potassium containing foods, as clinically appropriate, following a healthy eating pattern, maintaining a healthy weight, balanced body weight, exercising regularly (aerobic and resistance), eating the right number of fluids and avoiding tobacco, improving sleep quality. If it does exist, then treating obstructive sleep apnoea, socializing in a safe environment and coping with social and environmental issues[43].

It is important to not consider lifestyle interventions as stand-alone interventions as they often work synergistically. For instance, a lot of people experience better sleep apnoea, better insulin sensitivity, a better physical capacity and better dietary quality at the same time when they lose weight[44].

Population-level measures also are relevant. Other interventions that can be implemented beyond the individual include blood pressure screening, public education, access to healthy foods, and food reformulation, improved food labelling[45].

6.2 Pharmacological Treatment and Resistant Hypertension

The main classes of first line antihypertensive drugs are the thiazide or thiazide-like diuretics, angiotensin-converting enzyme (ACE) inhibitors,

angiotensin receptor blockers (ARBs) and calcium-channel blockers (CCBs). When appropriate, mineralocorticoid receptor antagonists (MRAs) play a special role in resistant hypertension[46].

Hypertension is a disease with a complex pathogenesis, which often necessitates multitarget therapy. Single-pill combinations may help to decrease the number of pills required and may help with adherence[47].

Individual treatment should be used depending on the blood pressure level, cardiovascular risk, kidney function, age, comorbidities, side effects and patients' preferences[48].

Systematic evaluation of Resistant Hypertension is needed. Apparent resistance can be caused by the measurement of blood pressure, lack of compliance, the white coat phenomenon, inadequate treatment, excessive sodium intake, obesity, obstructive sleep apnoea (OSA), secondary hypertension, or inappropriate drug combinations[49].

Therefore, true resistant hypertension must be ruled out first, before switching to advanced therapies.

7. PRECISION HYPERTENSION AND HEALTH

7.1 Precision Phenotyping and Biomarker Guided Treatment

Most of the treatments of hypertension are based on population level algorithms. However, there are a lot of differences in the mechanisms and treatment response of patients. Precision hypertension is the use of biological phenotype, comorbidities, genetic factors, hypertension-induced organ damage, treatment responsiveness and environmental exposures for patient classification[50].

In the future pharmacogenomic studies could lead to the identification of people that are more likely to respond to certain classes of drugs or develop certain side effects. Most of the candidate biomarkers are still awaiting validation in large and diverse populations, however[51].

Any precision tool that is clinically useful must be reproducible, clinically meaningful (in terms of outcome or conventional clinical measurements), cost effective and have the capability of altering patient management[52]**.**

7.2 Artificial Intelligence, Wearables, and Remote Monitoring

Health technologies are driving change in blood pressure monitoring. Blood pressure devices in the home can wirelessly send multiple readings to health-care providers, and a variety of wearable devices can give health-care providers data on physical activity, sleep, heart rate, and other behavioural metrics[53].

Machine learning can be used to assist in automated blood pressure analysis, risk prediction, identification of abnormal patterns, and clinical decision support. But algorithmic systems need to be robustly validated and evaluated with respect to calibration, bias, data quality, privacy, cyber security and interoperability requirements from the outside[54].

Digital solutions should be used in addition to clinical judgment. They have the greatest promise for combining longitudinal data with clinical and behavioural information to detect changes in risk and to promote adherence[55].

8. EMERGING THERAPIES AND FUTURE THERAPEUTIC STRATEGIES

8.1 Aldosterone Synthase Inhibition and Device Based Therapy

Aldosterone dysregulation is one of the major mechanisms in hypertension that is difficult to control. Aldosterone synthase inhibitors are designed to have a more selective effect on the production of aldosterone than traditional means[56].

Baxdrostat is a very clinically advanced agent in this therapeutic class. The BaxHTN phase 3 trial included patients with uncontrolled or resistant hypertension who were taking multiple antihypertensive drugs who were randomly assigned to baxdrostat or placebo. The study showed impressive decreases in systolic blood pressure (BP) and showed clinical proof of aldosterone synthase inhibition as a treatment option for refractory hypertension[57].

Another mechanism-based treatment is renal denervation. The intervention will be directed towards an attenuation of renal sympathetic signalling and could be used in specific patients with poorly controlled hypertension despite best pharmacological treatment[58].

The uses of renal denervation in clinical practice are still evolving in terms of patient selection, efficacy, durability, long term safety and cost effectiveness[59].

8.2 Future Molecular and Systems Based Therapies

Potential future treatments involve intervention of endothelin signalling pathways, inflammatory pathways, renal sodium transport, sympathetic activity, genetic regulation, and ribonucleic acid mediated mechanisms, as well as altering gut microflora[60].

Lowering the dose frequency might improve adherence with the use of long-acting drug delivery systems. Specific pathophysiological phenotypes may also be the basis for combination therapy that will be more important in the future[61].

Thus, the future of the therapy of hypertension is likely to be a combination of the various drug classes that have been developed, drugs that target specific mechanisms, and devices; digital monitoring and individualized risk assessment[62].

9. KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

There is significant research progress in the understanding of hypertension; however there remain several basic areas of uncertainty. The first is that there is no biological heterogeneity characterisation. At present, treatment for hypertension is primarily dependent on the level of blood pressure, and the clinical risk level, while individuals with the same blood pressure level can have completely different mechanisms. Vascular stiffness, inflammatory state, metabolic dysfunction and genetic susceptibility can vary widely among patients, as can the ability to cope with sodium and the activity of the RAAS system and the activation of the sympathetic nervous system. It will then be necessary for future studies to identify the reproducible mechanistic phenotypes that will be translatable into clinically relevant treatment pathways[63].

The need for the few clinical validations of precision hypertension biomarkers is another important one that's yet to be addressed. A myriad of blood-borne, genetic, metabolic, inflammatory and imaging markers have been associated with hypertension, and/or treatment responsiveness. But it's not enough to take to the clinic. The development of biomarkers provides the potential for providing more information than current clinical parameters and the use of treatment based on the biomarker may be associated with improved cardiovascular and renal outcomes further research is needed to determine this[64].

One of the resistant hypertension gaps is the fourth gap. While several mechanisms and secondary causes have been described, resistant hypertension is not easily differentiated from apparent resistant hypertension that occurs because of poor adherence, inaccurate measurement, white-coat hypertension or suboptimal treatment. New home/ambulatory-blood pressure diagnostic algorithms are needed, as are home-adherence assessment, biochemical phenotyping, renal assessment and secondary cause screening[66].

A fifth gap is when new therapies are converted to long-term clinical outcomes. Many new interventions have been found to lower blood pressure, but it's not known if this decrease in blood pressure helps to lower the risk for stroke, heart failure, heart-related death, kidney disease progression or death. This means that future trials need to be more oriented towards clinically relevant aspects and have a sufficient follow-up period in future, the focus should be Patient-centred outcomes[67].

The sixth gap has to do with the long-term safety and appropriate location of mechanism-specific therapies. The efficacy and safety of aldosterone synthase inhibitors, renal denervation, endothelin-pathway therapies and other emerging treatments should continue to be studied in real-world patients for durability of response, drug interactions, renal effects, electrolyte abnormalities, procedural issues, and efficacy[68].

Table 2. Contemporary and Emerging Hypertension Management Strategies

Strategy	Principal objective	Examples	Key research/clinical considerations
Dietary modification	Reduce blood pressure and cardiovascular risk	Sodium reduction, Dietary Approaches to Stop Hypertension diet, Mediterranean-style diet, potassium-rich foods	Adherence, cultural adaptation, food environment
Weight management	Reduce metabolic and hemodynamic burden	Caloric optimization, exercise, structured weight-management programs	Long-term sustainability and individualized intervention
Physical activity	Improve vascular and autonomic function	Aerobic and resistance exercise	Exercise capacity, comorbidities, adherence
Conventional pharmacotherapy	Lower blood pressure and prevent complications	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, thiazide/thiazide-like diuretics	Drug selection, adverse effects, adherence
Resistant-hypertension therapy	Address persistent uncontrolled blood pressure	Mineralocorticoid receptor antagonists and optimized multidrug regimens	Confirm true resistance and exclude secondary causes
Out-of-office monitoring	Improve diagnostic accuracy	Home blood pressure monitoring and ambulatory blood pressure monitoring	Device validation, patient training, data quality
Precision medicine	Match treatment to biological phenotype	Biomarkers, renin/aldosterone profiling, pharmacogenomics	Prospective clinical validation required
Digital health	Improve longitudinal blood pressure monitoring	Connected blood pressure devices and telemonitoring	Privacy, cybersecurity, interoperability, accessibility
Artificial intelligence	Support diagnosis and risk prediction	Prediction models and clinical decision support	External validation, bias, calibration, explainability
Renal denervation	Reduce renal sympathetic activity	Catheter-based renal denervation	Patient selection, durability, long-term outcomes

Aldosterone synthase inhibition	Reduce aldosterone production	Baxdrostat and related agents	Safety, electrolyte effects, long-term outcomes
Future molecular therapies	Target specific biological pathways	Endothelin, inflammatory, ribonucleic acid-based, microbiome approaches	Mechanistic validation and safety
Population prevention	Reduce incidence and treatment burden	Screening, salt-reduction policies, healthier food environments	Cost-effectiveness and health-system implementation

10. CONCLUSION

Hypertension is a multifactorial, complex systemic disorder brought about by involvement of several different factors, including renal, vascular, neurohormonal, metabolic, inflammatory, genetic, behavioural and environmental factors. It has several effects other than hypertension, that can contribute to the gradual progression of hypertension related organ damage, such as to the heart, brain, kidneys, retina and vasculature. Knowing what the problem is and then taking the necessary steps to conduct the appropriate assessment of blood pressure in the office, appropriate cardiovascular risk assessments, early detection of organ damage, lifestyle modification, evidence-based pharmacotherapy, and helping to support long-term adherence to therapy are important aspects of effective management. While there has been major progress in the prevention, diagnosis and management of hypertension, there is still a great deal to be done to control blood pressure and to provide high-quality health care. Heterogeneity of the organism and individualized treatment based on the characteristics and mechanisms of the disease should be considered more in detail in future treatment. Precision phenotyping, biomarkers, pharmacogenomics, artificial intelligence, remote monitoring, renal denervation and mechanism-specific drugs are all new technologies that could increase the effectiveness of treatment and personalization. Validated studies with a wide range of patients in well-conducted clinical trials are necessary to demonstrate potential for clinically relevant cardiovascular and renal benefit, safety, cost-effectiveness and generalizability to different patient populations for clinical application. An evidence-based and effective approach to healthcare coupled with innovative technology can help optimize hypertension management and reduce preventable morbidity and mortality. Continuous multidisciplinary research and equitable translation into real life and sustainable improvements in global cardiovascular and renal health will be needed to realize the advances in hypertension biology in the real world**.**

CONFLICT OF INTEREST:
The authors have no conflicts of interest regarding this investigation**.**

FUNDING:

The authors received no financial support for the research, authorship, or publication of this article.

COMPETING INTERESTS:

The authors declare that they have no competing interests, financial or non-financial, relevant to the content of this article.

ACKNOWLEDGEMENTS

Not applicable.

11. REFERENCE

1. Burnier, M. and A. Damianaki, *Hypertension as Cardiovascular Risk Factor in Chronic Kidney Disease.* Circ Res, 2023. **132**(8): p. 1050-1063.
2. Liu, F. and X. Lu, *Hypertension and human health: Evidence and prospects.* Chronic Dis Transl Med, 2024. **10**(2): p. 89-91.
3. Wang, X., et al., *The immune system in cardiovascular diseases: from basic mechanisms to therapeutic implications.* Signal Transduction and Targeted Therapy, 2025. **10**(1): p. 166.
4. Randjelovic, M., et al., *Blood pressure phenotypes and hypertension-associated cardiac damage.* J Hypertens, 2026. **44**(10): p. 1822-1829.
5. Liu, Y. and B. Wang, *Advanced applications in chronic disease monitoring using IoT mobile sensing device data, machine learning algorithms and frame theory: a systematic review.* Frontiers in Public Health, 2025. **Volume 13 - 2025**.
6. Wolff, C.B., et al., *New understanding of circulatory blood flow and arterial blood pressure mechanisms.* Cardiovasc Res, 2022. **118**(4): p. e29-e31.
7. Manolis, A.A., T.A. Manolis, and A.S. Manolis, *Neurohumoral Activation in Heart Failure.* Int J Mol Sci, 2023. **24**(20).
8. Lew, S.Q., et al., *The role of intra- and interdialytic sodium balance and restriction in dialysis therapies.* Front Med (Lausanne), 2023. **10**: p. 1268319.
9. Hengel, F.E., J.-P. Benitah, and U.O. Wenzel, *Mosaic theory revised: inflammation and salt play central roles in arterial hypertension.* Cellular & Molecular Immunology, 2022. **19**(5): p. 561-576.
10. Koumallos, N., et al., *Angiotensin Regulation of Vascular Homeostasis: Exploring the Role of ROS and RAS Blockers.* Int J Mol Sci, 2023. **24**(15).
11. Varzideh, F., et al., *Autonomic neurotransmission in cardiovascular regulation and pathophysiology.* Front Neurosci, 2025. **19**: p. 1739330.

12. P, S. and C. Vellapandian, *Hypothalamic-Pituitary-Adrenal (HPA) Axis: Unveiling the Potential Mechanisms Involved in Stress-Induced Alzheimer's Disease and Depression.* Cureus, 2024. **16**(8): p. e67595.
13. Hatamova, M., et al., *Chronic Stress, Diabetes, and Cardiovascular Disease: Epidemiologic Evidence, Pathogenetic Insights, and Therapeutic Strategies.* Cureus, 2026. **18**(1): p. e102108.
14. Wang, X. and B. He, *Endothelial dysfunction: molecular mechanisms and clinical implications.* MedComm (2020), 2024. **5**(8): p. e651.
15. Karabaeva, R.Z., et al., *Epigenetics of hypertension as a risk factor for the development of coronary artery disease in type 2 diabetes mellitus.* Front Endocrinol (Lausanne), 2024. **15**: p. 1365738.
16. Liu, M., D.S. Kim, and S. Park, *Gene-Lifestyle Interactions in Renal Dysfunction: Polygenic Risk Modulation via Plant-Based Diets, Coffee Intake, and Bioactive Compound Interactions.* Nutrients, 2025. **17**(5).
17. Ahmed, N., et al., *From fat to filter: the effect of adipose tissue-derived signals on kidney function.* Nat Rev Nephrol, 2025. **21**(6): p. 417-434.
18. Sakr, H.F., et al., *Insulin Resistance and Hypertension: Mechanisms Involved and Modifying Factors for Effective Glucose Control.* Biomedicines, 2023. **11**(8).
19. Krzemińska, J., et al., *Arterial Hypertension-Oxidative Stress and Inflammation.* Antioxidants (Basel), 2022. **11**(1).
20. Ayivi-Tosuh, S.M., et al., *Gut-Microbiome Interactions: Characterization, Therapeutic Implications and Machine Learning.* Sage Open Pathol, 2026. **19**: p. 30502098251415109.
21. Kazi, R.N.A., *Silent Effects of High Salt: Risks Beyond Hypertension and Body's Adaptation to High Salt.* Biomedicines, 2025. **13**(3).
22. Baroutis, D., et al., *DASH Diet and Preeclampsia Prevention: A Literature Review.* Nutrients, 2025. **17**(12).
23. Stasi, A., et al., *Obesity-Related Chronic Kidney Disease: Principal Mechanisms and New Approaches in Nutritional Management.* Front Nutr, 2022. **9**: p. 925619.
24. Da Costa-Santos, N., et al., *Combined Exercise Training Promotes More Benefits on Cardiovascular Autonomic Modulation in Ovariectomized Rats Than Isolated Aerobic or Resistance Training.* Diabetes Metab Syndr Obes, 2023. **16**: p. 1903-1913.
25. Fuchs, F.D. and S.C. Fuchs, *The Effect of Alcohol on Blood Pressure and Hypertension.* Curr Hypertens Rep, 2021. **23**(10): p. 42.
26. Higashi, Y., *Smoking cessation and vascular endothelial function.* Hypertens Res, 2023. **46**(12): p. 2670-2678.
27. Brown, J., et al., *Obstructive Sleep Apnea and Hypertension: Updates to a Critical Relationship.* Curr Hypertens Rep, 2022. **24**(6): p. 173-184.
28. Lei, A.A., et al., *Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus-A Mini Review.* Int J Mol Sci, 2025. **26**(7).
29. Metlock, F.E., et al., *Impact of Social Determinants of Health on Hypertension Outcomes: A Systematic Review.* Hypertension, 2024. **81**(8): p. 1675-1700.
30. Mutai, S.M., et al., *Hypertension and left ventricular geometry: Diagnosis, prognosis, and management.* Excli j, 2026. **25**: p. 756-775.
31. Kockskämper, J. and F. Pluteanu, *Left Atrial Myocardium in Arterial Hypertension.* Cells, 2022. **11**(19).
32. Herzog, M.J., et al., *Arterial stiffness and vascular aging: mechanisms, prevention, and therapy.* Signal Transduct Target Ther, 2025. **10**(1): p. 282.
33. Huang, H., et al., *Association between Blood Pressure and Post-Stroke Cognitive Impairment: A Meta-Analysis.* Rev Cardiovasc Med, 2024. **25**(5): p. 174.
34. De Bhailis Á, M. and P.A. Kalra, *Hypertension and the kidneys.* Br J Hosp Med (Lond), 2022. **83**(5): p. 1-11.
35. Dziedziak, J., et al., *Impact of Arterial Hypertension on the Eye: A Review of the Pathogenesis, Diagnostic Methods, and Treatment of Hypertensive Retinopathy.* Med Sci Monit, 2022. **28**: p. e935135.
36. Kim, H.L., *Arterial stiffness and hypertension.* Clin Hypertens, 2023. **29**(1): p. 31.
37. Ishigami, J., et al., *Effects of Cuff Size on the Accuracy of Blood Pressure Readings: The Cuff(SZ) Randomized Crossover Trial.* JAMA Intern Med, 2023. **183**(10): p. 1061-1068.
38. Tocci, G., et al., *Reclassification of patients with normal blood pressure levels after 2024 European society of cardiology guidelines on hypertension.* J Hypertens, 2025. **43**(12): p. 2008-2015.
39. Şirin, H., et al., *Comparison of Home Blood Pressure Monitoring with and without Training: Does Adherence to the Recommended Instructions Overlook Hypertension?* Anatol J Cardiol, 2024. **28**(10): p. 499-506.
40. Avasia, A., M. Medipally, and M. Parasnis, *White Coat Hypertension in Primary Care: A Narrative Review.* Cureus, 2025. **17**(10): p. e95256.
41. Bui, T.D., et al., *Diagnostic Testing Patterns Influence the Detected Burden of Hypertension-Mediated Organ Damage in Hospitalized Hypertensive Patients.* J Clin Hypertens (Greenwich), 2026. **28**(4): p. e70241.
42. Sarathy, H., et al., *Evaluation and Management of Secondary Hypertension.* Med Clin North Am, 2022. **106**(2): p. 269-283.
43. Kozioł-Kozakowska, A., et al., *Dietary Strategies in the Prevention and Treatment of Hypertension in Children and Adolescents: A Narrative Review.* Nutrients, 2024. **16**(16).
44. Mou, J., et al., *The impact of comprehensive healthy lifestyles on obstructive sleep apnea and the mediating role of BMI: insights from NHANES 2005-2008 and 2015-2018.* BMC Pulm Med, 2024. **24**(1): p. 601.

45. Samakosky, M.J. and S.A. Norris, *Alleviating the public health burden of hypertension: debating precision prevention as a possible solution.* Glob Health Action, 2024. **17**(1): p. 2422169.

46. Reinhart, M., et al., *First-line diuretics versus other classes of antihypertensive drugs for hypertension.* Cochrane Database Syst Rev, 2023. **7**(7): p. Cd008161.

47. Espinoza, A., C. Lynn, and S. Neal, *Are Single-Pill Antihypertensive Combinations Superior to Multi-Pill Regimens at Reducing All-Cause Mortality and Cardiovascular Events?* J Am Board Fam Med, 2025. **38**(6): p. 1117-1119.

48. Huang, Z., et al., *Effects of post-treatment systolic blood pressure on adverse outcomes in hypertensive population with comorbidity.* Scientific Reports, 2026. **16**(1): p. 14594.

49. Flack, J.M., M.G. Buhnerkempe, and K.T. Moore, *Resistant Hypertension: Disease Burden and Emerging Treatment Options.* Curr Hypertens Rep, 2024. **26**(5): p. 183-199.

50. Nitzan, M. and I. Nitzan, *Feasibility of Precision Medicine in Hypertension Management-Scope and Technological Aspects.* J Pers Med, 2022. **12**(11).

51. Alobaidi, S., *Emerging Biomarkers and Advanced Diagnostics in Chronic Kidney Disease: Early Detection Through Multi-Omics and AI.* Diagnostics (Basel), 2025. **15**(10).

52. Schäfer, H., et al., *The Value of Clinical Decision Support in Healthcare: A Focus on Screening and Early Detection.* Diagnostics (Basel), 2025. **15**(5).

53. Sinou, N., et al., *The Role of Wearable Devices in Blood Pressure Monitoring and Hypertension Management: A Systematic Review.* Cureus, 2024. **16**(12): p. e75050.

54. Skalidis, I., et al., *Artificial Intelligence and Advanced Digital Health for Hypertension: Evolving Tools for Precision Cardiovascular Care.* Medicina (Kaunas), 2025. **61**(9).

55. Figueiredo, T., et al., *Understanding Adherence to Digital Health Technologies: Systematic Review of Predictive Factors.* J Med Internet Res, 2025. **27**: p. e77362.

56. Laffin, L.J. and S.E. Nissen, *Aldosterone synthase inhibitors for hypertension: A breakthrough facing barriers to adoption.* PLoS Med, 2026. **23**(2): p. e1004900.

57. Flack, J.M., et al., *Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension.* N Engl J Med, 2025. **393**(14): p. 1363-1374.

58. Stephan, D., et al., *Renal denervation in 2025: long-term evidence supporting sympathetic modulation as a durable strategy for uncontrolled hypertension.* Int J Cardiol Cardiovasc Risk Prev, 2026. **29**: p. 200587.

59. Wang, T.D., *Renal Denervation: New Evidence Supporting Long-Term Efficacy, Alternative Access Routes, and Cost-Effectiveness.* J Clin Hypertens (Greenwich), 2024. **26**(12): p. 1528-1530.

60. Rakotoarison, A., et al., *Endothelin Inhibitors in Chronic Kidney Disease: New Treatment Prospects.* J Clin Med, 2024. **13**(20).

61. Nammas, M., *The Impact of Drug Delivery Systems on Pharmacokinetics and Drug-Drug Interactions in Neuropsychiatric Treatment.* Cureus, 2025. **17**(6): p. e85563.

62. Liu, L., et al., *The effect of digital therapeutics intervention on improving hypertension management in adults: a meta-analysis of randomized controlled trial.* Hypertension Research, 2025. **48**(2): p. 456-469.

63. Sundström, J., et al., *Heterogeneity in Blood Pressure Response to 4 Antihypertensive Drugs: A Randomized Clinical Trial.* Jama, 2023. **329**(14): p. 1160-1169.

64. Trillaud, E., et al., *Tracking Biomarker Responses to Exercise in Hypertension.* Curr Hypertens Rep, 2023. **25**(10): p. 299-311.

65. *ACNP 64th Annual Meeting: Poster Abstracts P1-P291.* Neuropsychopharmacology, 2026. **51**(1): p. 74-242.

66. Sharma, R., et al., *Resistant hypertension: Epidemiology, mechanisms and contemporary therapeutic strategies.* Heart Int, 2026. **20**(1): p. 40-53.

67. Yang, Q., et al., *A meta-analysis of the long-term effects of antihypertensive therapy on the risk of major cardiovascular disease across 51 randomized trials.* Nature Medicine, 2026. **32**(8): p. 3082-3092.

68. Gao, Y., X. Mu, and X. Pang, *Efficacy and safety of aldosterone synthase inhibitors for uncontrolled hypertension: a meta-analysis of randomized controlled trials and systematic review.* Front Pharmacol, 2025. **16**: p. 1664810.