Volume 4, Issue 4, April 2026 ISSN (E): 2938-3803

MODERN APPROACHES TO HYPERTENSION TREATMENT

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Abstract
Hypertension remains a leading global health concern and a major contributor to cardiovascular morbidity and mortality. This study provides a comprehensive evaluation of the pathophysiological mechanisms, epidemiological trends, and current management strategies of hypertension based on recent scientific evidence. The analysis highlights the role of vascular dysfunction, neurohormonal activation, and structural remodeling in the progression of elevated blood pressure and target organ damage. Both non-pharmacological interventions, including dietary modification, physical activity, and lifestyle optimization, and pharmacological therapies are critically assessed. The effectiveness of combination drug therapy and individualized treatment strategies is emphasized in improving clinical outcomes. Additionally, emerging therapeutic approaches, such as mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, and immunization-based strategies, are discussed. Persistent challenges, including resistant hypertension and treatment adherence, are also addressed. The findings underscore the importance of early diagnosis, continuous monitoring, and integrated, patient-centered care to reduce complications and improve long-term prognosis.

Keywords: Hypertension, blood pressure, cardiovascular risk, pharmacological therapy, lifestyle modification, target organ damage, resistant hypertension.

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Introduction

Hypertension remains one of the most prevalent and modifiable risk factors contributing to the global burden of cardiovascular disease. Elevated blood pressure is strongly associated with an increased risk of coronary artery disease, stroke, heart failure, and chronic kidney dysfunction [8]. Effective antihypertensive therapy has been shown to significantly reduce these risks; however, the underlying biological mechanisms driving hypertension are complex and involve multiple interacting systems.

Among these mechanisms, the renin–angiotensin–aldosterone system plays a central role in the regulation of blood pressure and fluid balance. Aldosterone, a key mineralocorticoid hormone, contributes to sodium retention and potassium excretion through its action on the mineralocorticoid receptor in renal tubular cells. This process leads to increased intravascular volume and sustained elevation of blood pressure. In addition to its renal effects, aldosterone also promotes vascular inflammation, oxidative stress, and structural remodeling, which further exacerbate endothelial dysfunction and arterial stiffness [14].

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Table 1. Blood pressure categories

Blood Pressure Category	Systolic mm Hg (upper number)	Diastolic mm Hg (lower number)
Normal	Less than 120	Less than 80
Elevated	120–129	Less than 80
High Blood Pressure (Hypertension) Stage 1	130–139 or	80–89
High Blood Pressure (Hypertension) Stage 2	140 or higher	90 or higher
Hypertensive Crisis	Higher than 180	Higher than 120

Recent studies have highlighted the contribution of aldosterone-mediated signaling pathways to the progression of hypertension and its related complications. The biosynthesis of aldosterone within the adrenal cortex involves a series of enzymatic reactions regulated by cytochrome P450 enzymes, particularly CYP11B2. Dysregulation of this pathway may result in excessive hormone production, contributing to resistant forms of hypertension and target organ damage [2]. Therefore, a deeper understanding of these molecular and physiological processes is essential for the development of more effective therapeutic strategies aimed at improving blood pressure control and reducing cardiovascular risk.

Advances in Mineralocorticoid Receptor Antagonist Therapy

Mineralocorticoid receptor antagonists have been widely utilized in the management of hypertension, particularly in patients with resistant forms of the disease and those with concomitant cardiovascular disorders. Among the earlier agents, spironolactone has shown moderate blood pressure–lowering effects when used alone, but its clinical value is more pronounced as part of combination therapy. However, its limited receptor selectivity often leads to hormone-related adverse effects, especially at higher doses, which may restrict its long-term use [17].

The mineralocorticoid receptor plays a pivotal role in mediating the effects of aldosterone, including sodium retention, potassium excretion, and regulation of fluid balance. Persistent activation of this pathway contributes not only to increased blood volume and elevated blood pressure but also to pathological changes such as myocardial fibrosis, vascular remodeling, and progressive renal dysfunction. As a result, therapeutic inhibition of this receptor has become an essential approach in reducing both hemodynamic stress and target organ damage [5].

Recent developments have focused on the introduction of nonsteroidal mineralocorticoid receptor antagonists with enhanced selectivity and improved safety profiles [11]. Finerenone represents a key advancement in this field, demonstrating higher affinity for the mineralocorticoid receptor while minimizing interaction with other steroid hormone receptors. This pharmacological specificity reduces the likelihood of endocrine side effects and enhances tolerability.

Web of Humanities: Journal of Social Science and Humanitarian Research

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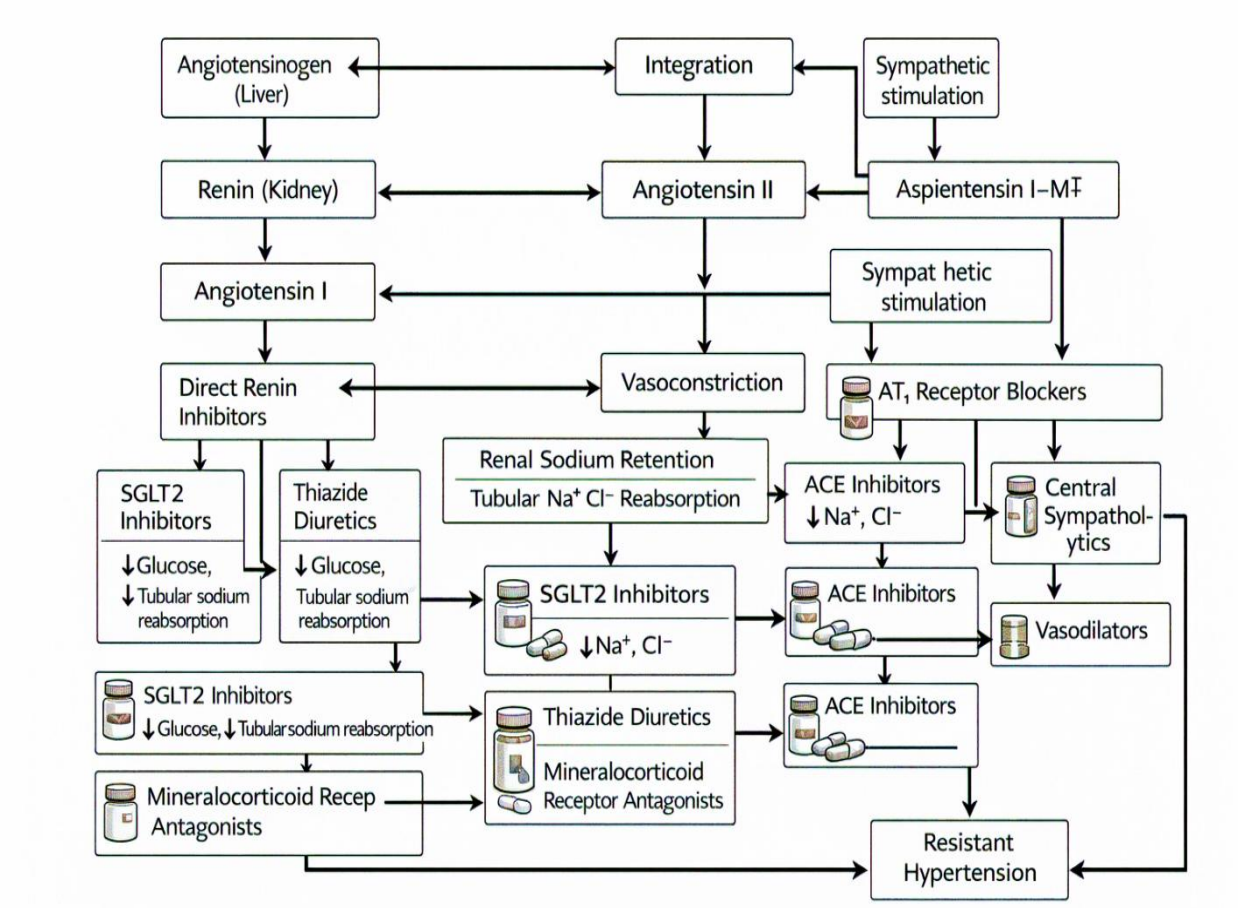

Figure 1. Block diagram of renal mechanisms and pharmacological targets in resistant hypertension

Evidence from clinical trials indicates that finerenone not only contributes to effective blood pressure control but also provides significant cardiovascular and renal protection. Its use has been associated with reductions in markers of cardiac stress and improvements in kidney function, particularly in patients with chronic kidney disease and heart failure. Moreover, the incidence of adverse effects, including electrolyte disturbances, appears to be lower compared to conventional agents [1]. These findings suggest that modern mineralocorticoid receptor antagonists offer a promising direction for optimizing hypertension treatment and minimizing long-term complications.

Analysis and Interpretation of Findings

The analysis of the reviewed evidence demonstrates that hypertension management requires a comprehensive and multifactorial approach integrating both lifestyle-based and pharmacological interventions. Epidemiological trends indicate a steady increase in the global prevalence of hypertension over recent decades, largely driven by population aging, urbanization, sedentary lifestyles, and dietary changes. The graphical data further support this trend, showing a consistent rise in hypertension rates across both sexes, with a slightly higher prevalence observed in men [16]. These findings emphasize the growing burden of hypertension as a major public health concern and highlight the need for early preventive strategies.

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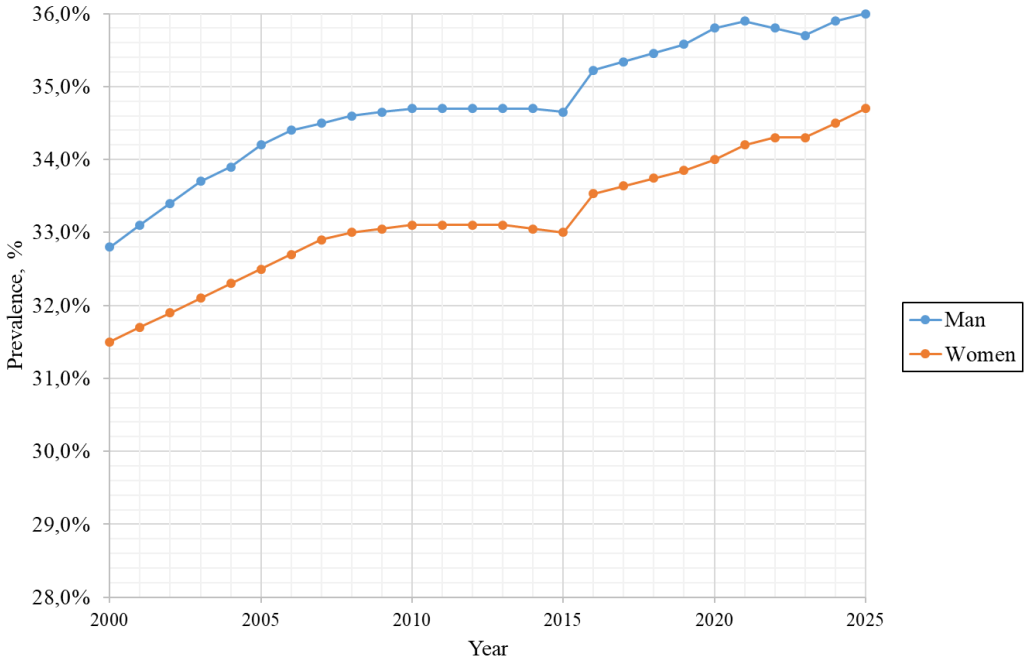

Figure 2. Temporal trends in global hypertension prevalence by sex among adults aged 30–79 years

Non-pharmacological interventions remain a cornerstone in the management of hypertension. The evidence consistently shows that dietary modifications, particularly adherence to balanced dietary patterns rich in fruits, vegetables, and low-fat products, contribute significantly to blood pressure reduction. Sodium restriction and increased potassium intake have been identified as key determinants of improved vascular function and reduced arterial pressure [9]. Additionally, regular physical activity has been shown to produce measurable reductions in both systolic and diastolic blood pressure, with greater benefits observed in individuals engaging in moderate- to high-intensity exercise. Alcohol consumption exhibits a dose-dependent relationship with blood pressure, further supporting the recommendation for moderation as part of lifestyle management [3].

Pharmacological treatment plays a critical role, particularly in patients with moderate to severe hypertension or those at high cardiovascular risk. Clinical trial data indicate that intensive blood pressure control strategies are associated with significant reductions in cardiovascular morbidity and mortality. Combination therapy, involving agents with complementary mechanisms of action, has been shown to improve blood pressure control more effectively than monotherapy. However, treatment strategies must be individualized, taking into account patient age, comorbidities, and tolerance to medications [18]. The balance between therapeutic efficacy and potential adverse effects remains a key consideration in clinical decision-making.

Furthermore, the analysis highlights persistent challenges in hypertension management, including resistant hypertension and poor treatment adherence. A substantial proportion of patients fail to achieve target blood pressure levels despite the availability of effective therapies [6]. This issue is often related to inadequate adherence, therapeutic inertia, and insufficient patient–provider communication. Advanced monitoring techniques and digital health tools offer promising solutions to improve adherence and optimize long-term outcomes. Overall, the

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findings underscore the importance of an integrated, patient-centered approach that combines prevention, early detection, and tailored treatment strategies to effectively control hypertension and reduce its associated complications [12].

Aldosterone synthase inhibition and its pharmacological implications

Aldosterone synthase inhibitors have emerged as a novel therapeutic approach aimed at directly suppressing aldosterone biosynthesis within the adrenal cortex. These agents target the terminal enzymatic steps of steroidogenesis, primarily mediated by the mitochondrial enzyme CYP11B2, thereby reducing the production of aldosterone and its downstream effects on sodium retention, fluid balance, and blood pressure regulation. Among these compounds, LC1699 has been extensively investigated for its potential to provide a more selective and mechanistically precise alternative to conventional mineralocorticoid receptor blockade [4].

Table 2. Emerging pharmacological agents for hypertension

Drug / Agent	Mechanism of Action	Development Stage
Finerenone (BAY 94-8862)	Selective mineralocorticoid receptor antagonist	Phase III
LC1699	Aldosterone synthase inhibitor	Phase II
C21	AT2 receptor agonist	Preclinical
XNT	ACE2 activator	Preclinical
DIZE	ACE2 activator	Preclinical
rhACE2	Recombinant ACE2	Phase I
Ang-(1–7) analog	Modulates RAAS via MAS receptor	Preclinical
AVE0991	Non-peptide MAS receptor agonist	Preclinical
CGEN-856S	Peptide MAS receptor agonist	Preclinical
PC18	Aminopeptidase inhibitor	Preclinical
RB150 (QGC001)	Dual aminopeptidase inhibitor	Phase I
LCZ696	Angiotensin receptor–neprilysin inhibitor	Phase III
Daglutril	Dual ACE and neprilysin inhibitor	Phase II
PL-3994	Natriuretic peptide receptor agonist	Phase II
AR9281	Soluble epoxide hydrolase inhibitor	Phase II
Tenapanor	Sodium/hydrogen exchanger inhibitor	Phase I
Etamicastat	Dopamine β-hydroxylase inhibitor	Phase I
Angiotensin II vaccine	Immunotherapy targeting RAAS	Phase II
AT1 receptor vaccine	Blocks angiotensin II receptor activity	Preclinical
DIF	Anti-digoxin antibody fragment	Phase II
ATryn	Recombinant antithrombin	Phase III

Clinical and experimental studies have demonstrated that inhibition of aldosterone synthase can significantly alter endocrine homeostasis. Reduction in aldosterone levels is often accompanied by compensatory activation of the hypothalamic–pituitary–adrenal axis, leading to increased secretion of adrenocorticotropic hormone. This adaptive response may stimulate adrenal steroidogenesis and result in the accumulation of intermediate metabolites, such as 11-deoxycorticosterone, which possess intrinsic mineralocorticoid activity [15]. Consequently, these intermediates may partially counteract the intended antihypertensive effects by activating mineralocorticoid receptors through alternative pathways.

Moreover, the pharmacological profile of LC1699 suggests that its selectivity is not absolute.

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Due to the structural similarity between CYP11B2 and CYP11B1 enzymes, partial inhibition of cortisol synthesis may occur, potentially leading to subclinical alterations in glucocorticoid balance. This dual enzymatic interaction underscores the complexity of targeting steroidogenic pathways and highlights the challenge of achieving complete specificity without affecting parallel hormonal systems. The observed increase in precursor steroids and the potential for feedback-mediated endocrine responses further complicate the therapeutic application of these agents [10].

From a clinical perspective, data from phase II trials indicate that while LC1699 effectively reduces aldosterone levels, its impact on blood pressure reduction remains variable and dose-dependent. In some cases, higher doses or prolonged administration do not result in proportional antihypertensive benefits, suggesting the presence of compensatory physiological mechanisms that limit its efficacy [7]. These findings emphasize the need for careful dose optimization and patient selection in order to maximize therapeutic outcomes.

In addition to its hemodynamic effects, aldosterone synthase inhibition may influence cardiovascular and renal remodeling processes. By attenuating aldosterone-driven fibrosis, inflammation, and oxidative stress, these agents hold potential for reducing target organ damage. However, further large-scale clinical studies are required to fully elucidate their long-term safety, efficacy, and impact on cardiovascular outcomes.

Vaccination-based approaches in hypertension management

Immunization strategies targeting components of the renin–angiotensin system have emerged as a novel and promising approach for the long-term management of hypertension. Early experimental studies demonstrated that vaccines directed against angiotensin II were capable of reducing blood pressure in animal models. However, initial attempts also raised concerns regarding potential autoimmune reactions, particularly involving renal tissues. Subsequent developments have focused on improving vaccine specificity and safety, leading to the design of virus-like particle–based vaccines capable of inducing targeted antibody responses without significant adverse immunological effects.

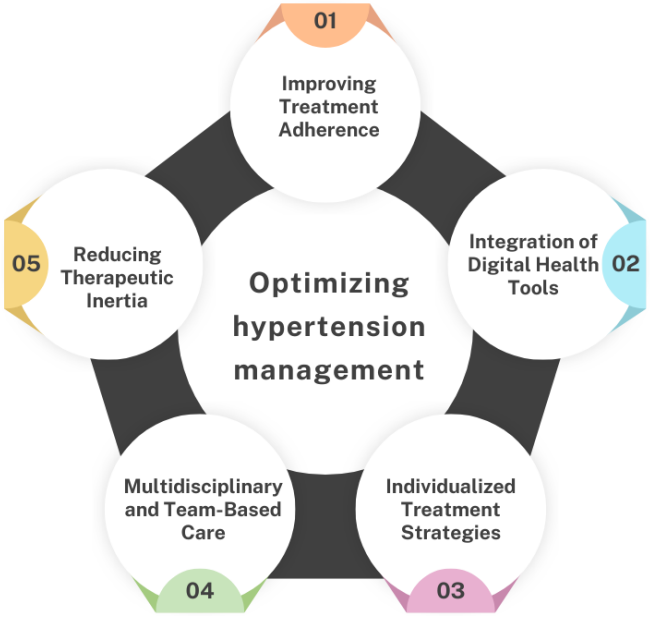

Figure 3. Key components for effective hypertension management

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Clinical investigations have shown that vaccines such as AngQb, which stimulate the production of antibodies against angiotensin II, can effectively increase circulating antibody levels and modulate renin–angiotensin system activity. Randomized, placebo-controlled trials have demonstrated that vaccinated individuals exhibit measurable reductions in ambulatory blood pressure, particularly during daytime and early morning periods, which are associated with higher cardiovascular risk. Importantly, these vaccines have generally been well tolerated, with only mild and transient adverse effects such as local injection site reactions and flu-like symptoms [13].

Further studies have explored the impact of dosing regimens and immunization schedules on therapeutic outcomes. Evidence suggests that repeated or higher-dose administrations can enhance antibody titers; however, the relationship between antibody concentration and blood pressure reduction is not strictly linear. In some cases, higher antibody levels were associated with lower binding affinity, potentially reducing the effectiveness of angiotensin II neutralization. These findings indicate that both the quality and functional characteristics of the immune response are critical determinants of clinical efficacy.

Ongoing research is also investigating next-generation vaccines targeting angiotensin receptors and related peptides, including angiotensin II type 1 receptor–based immunogens. Preclinical studies have demonstrated favorable safety and efficacy profiles, while early-phase clinical trials are currently evaluating their potential in broader hypertensive populations. Although vaccination-based therapy for hypertension remains in the developmental stage, it offers a unique long-acting treatment paradigm that may improve patient adherence and reduce dependence on daily pharmacotherapy.

Conclusion

The comprehensive analysis of hypertension confirms that it is a complex and multifactorial condition requiring a holistic and scientifically grounded management approach. The interaction of vascular dysfunction, neurohormonal imbalance, and structural remodeling plays a decisive role in the progression of elevated blood pressure and the development of target organ damage. The findings demonstrate that non-pharmacological interventions, including lifestyle modification, dietary regulation, and regular physical activity, serve as a fundamental basis for prevention and early-stage control. At the same time, pharmacological treatment, particularly combination therapy, significantly enhances clinical outcomes and contributes to a substantial reduction in cardiovascular risk.

Furthermore, the study highlights that effective hypertension management remains challenged by issues such as resistant hypertension and insufficient treatment adherence. Achieving optimal blood pressure control requires early diagnosis, individualized therapeutic strategies, and continuous patient monitoring. The integration of innovative treatment approaches, including novel pharmacological agents and digital health technologies, provides new opportunities to improve long-term outcomes. Overall, a multidisciplinary and patient-centered approach is essential to prevent complications, reduce target organ damage, and improve the overall quality of life in patients with hypertension.

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