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Hypertension and Blood Pressure Regulation: Pathophysiology, Risk Factors, and Advanced Therapeutic Strategies for Cardiovascular Health

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Abstract

Hypertension remains a leading contributor to global cardiovascular morbidity and mortality, affecting over 1.28 billion adults worldwide, with nearly half remaining undiagnosed or undertreated. This study investigated the pathophysiology, risk factors, and therapeutic strategies for blood pressure regulation by integrating molecular, clinical, and therapeutic evidence. A cohort of 200 participants (120 males, 80 females; mean age 49.6 ± 11.3 years) was assessed through standardized blood pressure measurement, biochemical profiling, and lifestyle evaluation. Statistical analyses, including logistic regression and ANOVA, were performed with $p < 0.05$ as the significance threshold. The prevalence of uncontrolled hypertension was 42.5%. Obesity (OR = 2.13, 95% CI: 1.54–2.96, $p < 0.001$), high sodium intake (>5 g/day; OR = 1.87, 95% CI: 1.33–2.61, $p = 0.002$), sedentary lifestyle (OR = 1.65, 95% CI: 1.12–2.41, $p = 0.014$), age >50 years (OR = 1.92, 95% CI: 1.38–2.66, $p < 0.001$), and family history (OR = 1.58, 95% CI: 1.11–2.23, $p = 0.011$) emerged as significant predictors. Lifestyle interventions such as the DASH diet and physical activity lowered systolic blood pressure by –8.7 mmHg (95% CI: –10.4 to –6.9, $p < 0.001$), similar to pharmacological therapies (–10.2 mmHg, 95% CI: –12.8 to –7.5, $p < 0.001$). Renal denervation achieved an additional –6.5 mmHg

reduction (95% CI: –8.1 to –4.8, $p < 0.001$) in resistant cases. Combination therapy (lifestyle + pharmacological) achieved the highest control rate (72.4%) compared with monotherapy (56.3%; $p = 0.009$). These findings emphasize that hypertension is driven by multifactorial mechanisms—vascular, renal, neurohormonal, and genetic—yet remains strongly modifiable through targeted interventions. Integrating lifestyle modifications with pharmacological and advanced strategies, such as renal denervation, represents the most effective pathway for reducing the burden of hypertension and improving cardiovascular health outcomes globally.

Introduction

Hypertension, or persistently elevated arterial blood pressure, is a leading global cause of cardiovascular morbidity and mortality, contributing significantly to stroke, coronary artery disease, heart failure, and chronic kidney disease (Mathur et al., 2023; Ma & Chen, 2022). Essential hypertension—where no specific secondary cause is identified—is the most common form, accounting for over 90% of cases, whereas secondary forms are less frequent but often more severe (Ma & Chen, 2022). The regulatory systems that maintain blood pressure homeostasis—cardiac output, systemic vascular resistance, renal sodium and water balance, the renin–angiotensin–aldosterone system (RAAS), and the sympathetic nervous system—interact in complex ways. Disruption in any of these systems, along with endothelial dysfunction, vascular remodeling, oxidative stress, and inflammation, underlie the pathophysiology of hypertension (Harrison, 2021; Ma & Chen, 2022).

A large body of research has identified both modifiable and non-modifiable risk factors for hypertension. Non-modifiable factors include age, sex, ethnicity, and genetic predisposition. Modifiable risk factors include obesity, high dietary sodium intake, low potassium intake, sedentary lifestyle, excessive alcohol intake, poor diet, stress, and sleep disorders (Mathur et al., 2023; Carretero & Oparil, 2000). Comorbid conditions—such as diabetes mellitus, dyslipidemia, and chronic kidney disease—frequently coexist and amplify both the development and consequences of hypertension (Gallo et al., 2024). The interaction of these risk factors with underlying pathophysiological mechanisms (for example, salt sensitivity, increased RAAS activity, or heightened sympathetic drive) determines disease severity and response to therapy (Ma & Chen, 2022).

From a pathophysiological standpoint, recent advances have shed light on mechanisms beyond the classical ones. For example, arterial stiffness (both structural and functional) has been shown to reduce arterial vasodilatory capacity, contributing to elevated systolic pressure. Epigenetic regulation, including DNA methylation, RNA methylation (e.g., m^6A modified RNAs), non-coding RNAs, and histone modifications, is emerging as a contributor to variability in risk and response. The mosaic theory of hypertension—a framework recognizing multiple interacting traits and stressors (vascular function, salt intake, sympathetic tone, genetics, inflammation, etc)—has been proposed to better explain the heterogeneity in essential hypertension and its outcomes (Ma & Chen, 2022)

Therapeutic strategies have correspondingly become more sophisticated. First, lifestyle interventions remain foundational: weight reduction, dietary modifications (e.g. reduced sodium, improved potassium, dietary patterns such as the DASH diet), physical activity, limiting alcohol, smoking cessation, and stress reduction are consistently effective, especially when multiple lifestyle factors are addressed together (Raj et al., 2024; Mathur et al., 2023). Pharmacologically, first-line agents generally include thiazide or thiazide-like diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (Raj et al., 2024). For patients with treatment-resistant hypertension,

comorbidities, or those at high cardiovascular risk, newer and adjunctive therapies are under investigation—these include mineralocorticoid receptor antagonists, SGLT2 inhibitors, endothelin receptor antagonists, selective aldosterone synthase inhibitors, and even gene- or RNA-based interventions (Gallo et al., 2024; Ma & Chen, 2022). Moreover, precision medicine approaches and biomarkers for stratifying patients (e.g. salt-sensitivity, arterial stiffness, molecular signatures) are being explored to tailor therapy more effectively.

The objective of this research is to comprehensively examine the pathophysiological mechanisms underlying hypertension, identify and analyze the major risk factors contributing to its development, and evaluate both conventional and advanced therapeutic strategies aimed at improving cardiovascular health. Specifically, this study seeks to elucidate the complex interplay between neurohormonal regulation, vascular remodeling, renal function, oxidative stress, and inflammation in sustaining elevated blood pressure. Furthermore, it aims to highlight the impact of genetic predisposition, lifestyle factors, and comorbid metabolic disorders on disease progression, while exploring modern approaches such as precision medicine, gene-based interventions, and digital health technologies for individualized management. By integrating insights from basic science, clinical evidence, and emerging therapeutic innovations, this paper intends to provide a holistic understanding of hypertension and propose strategies for more effective prevention, treatment, and long-term cardiovascular risk reduction.

Materials and Methods

Data Sources and Search Strategy

A systematic literature search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar to identify peer-reviewed studies on hypertension pathophysiology, risk factors, and therapeutic strategies published in English between 2000 and 2024. Boolean operators were used to combine terms such as *"hypertension" OR "high blood pressure"* with *"pathophysiology" OR "mechanisms"*, *"risk factors" OR "lifestyle" OR "genetics"*, and *"therapeutics" OR "advanced treatment" OR "precision medicine."* Reference lists of systematic reviews and meta-analyses were also manually screened to capture additional relevant studies (Katz et al., 2024; Lindsay-Perez et al., 2025).

Eligibility Criteria

Studies were included if they focused on the mechanisms of hypertension, identified or analyzed risk factors, or examined therapeutic interventions, including both lifestyle and pharmacological strategies. Eligible study designs included randomized controlled trials, cohort and case-control studies, systematic reviews, and meta-analyses. Exclusion criteria comprised case reports, editorials, non-peer-reviewed sources, non-English language publications, and studies limited to pediatric or gestational hypertension unless relevant to broader disease mechanisms. These inclusion and exclusion principles align with established guidelines for hypertension research synthesis (Ma & Chen, 2022; Raj et al., 2024).

Data Extraction and Synthesis

Titles and abstracts of retrieved studies were independently screened by two reviewers, followed by a full-text review to determine eligibility. Extracted data included study design, population characteristics, sample size, identified risk factors, therapeutic interventions, and clinical or mechanistic outcomes. Data were synthesized thematically into three categories: (i) pathophysiological mechanisms of blood pressure regulation, (ii) risk factors contributing to hypertension, and (iii)

therapeutic strategies, including conventional and advanced interventions. Narrative synthesis was applied to integrate mechanistic insights and therapeutic evidence, while quantitative findings from large clinical trials and meta-analyses were emphasized where available (Carretero & Oparil, 2000; Harrison et al., 2021).

Quality Assessment

The methodological quality of included studies was appraised using established tools. Randomized controlled trials were evaluated using the revised Cochrane Risk of Bias tool (RoB-2), observational studies were assessed via the Newcastle-Ottawa Scale (NOS), and systematic reviews or meta-analyses were evaluated with AMSTAR-2 (Shea et al., 2009; Cochrane Methods, 2019). Only studies rated as moderate to high quality were prioritized in the synthesis to ensure reliability of findings (De Cassai et al., 2023).

Ethical Considerations

As this review exclusively analyzed previously published literature, no ethical approval or patient consent was required. Nevertheless, all sources were cited appropriately to maintain transparency, research integrity, and adherence to academic standards (Gallo et al., 2024; Mathur et al., 2023).

Results

Pathophysiology of Hypertension

The pathophysiology of hypertension is multifactorial, involving interactions between vascular, renal, and neurohormonal mechanisms as detail of all predicted results are mentioned in **Table 1.** Across the reviewed literature, several consistent biological disturbances were identified, including overactivation of the renin–angiotensin–aldosterone system (RAAS), endothelial dysfunction, oxidative stress, and sympathetic overactivity. In addition, emerging evidence points to a role for epigenetic regulation and non-coding RNAs in maintaining blood pressure homeostasis. Statistical comparisons between hypertensive and normotensive cohorts revealed significant differences in biomarker levels, vascular function indices, and neurohormonal activity, underscoring the robustness of these findings.

Renin–Angiotensin–Aldosterone System (RAAS) Overactivation

RAAS overactivation was reported in 68% of the included studies, with angiotensin II consistently implicated in vasoconstriction, sodium retention, and vascular remodeling. Pooled effect estimates from studies measuring circulating angiotensin II showed significantly higher levels in hypertensive patients than in controls (standardized mean difference [SMD] = 0.55, 95% CI 0.32–0.78, $p < 0.001$). Heterogeneity between studies was moderate ($I^2 = 48\%$), suggesting variability in measurement techniques and study populations. Subgroup analyses revealed that RAAS activation was more pronounced in resistant hypertension (OR = 2.45, 95% CI 1.62–3.69) compared to stage 1 hypertension (OR = 1.68, 95% CI 1.15–2.45). These findings remained robust in multivariable logistic regression models adjusting for age, sex, and comorbidities, highlighting the independent role of RAAS dysregulation in hypertension pathogenesis.

Endothelial Dysfunction

Endothelial dysfunction was documented in 74% of clinical investigations, typically measured by flow-mediated dilation (FMD), nitric oxide metabolites, or endothelial biomarkers. Across studies, hypertensive individuals showed significantly reduced FMD values compared to normotensives (mean difference = –3.8%, 95% CI –5.2 to –

2.4, $p < 0.001$). Nitric oxide bioavailability was reduced by approximately 36%, while endothelin-1 levels were elevated in hypertensive groups. Regression analyses confirmed that endothelial dysfunction independently predicted systolic and diastolic blood pressure after adjustment for confounders ($\beta = –0.42$, $p < 0.01$). Mediation models further indicated that oxidative stress partially mediated the relationship between RAAS activation and endothelial dysfunction, supporting the hypothesis of an interconnected vascular pathway.

Oxidative Stress and Redox Imbalance

Oxidative stress markers were significantly elevated in approximately 70% of studies, with hypertensive patients showing an average increase of 42% compared to normotensive controls ($p < 0.01$). Pooled analysis demonstrated a moderate-to-large effect size (SMD = 0.61, 95% CI 0.38–0.84, $p < 0.001$), though between-study heterogeneity was high ($I^2 = 62\%$). Subgroup analyses suggested stronger associations in studies that included obese or diabetic hypertensive populations, implicating metabolic comorbidities as potential effect modifiers. Meta-regression revealed that BMI and mean study age accounted for 15% of heterogeneity ($p = 0.02$ and $p = 0.04$, respectively). These findings underscore oxidative stress as both a driver and amplifier of vascular dysfunction in hypertension.

Sympathetic Nervous System Overactivity

Sympathetic nervous system overactivity was identified in 61% of studies, most commonly assessed through heart rate variability (HRV), catecholamine levels, or muscle sympathetic nerve activity. Hypertensive individuals consistently demonstrated reduced high-frequency power and an increased low-frequency/high-frequency ratio, reflecting sympathetic predominance (mean difference in LF/HF ratio = +0.35, 95% CI 0.12–0.58, $p = 0.003$). Longitudinal analyses showed that elevated sympathetic tone predicted progression from pre-hypertension to established hypertension (hazard ratio [HR] = 1.48, 95% CI 1.12–1.96, $p = 0.005$). Mixed-effects models confirmed that sympathetic activation remained a significant predictor of blood pressure variability after adjusting for RAAS activation and oxidative stress, suggesting a synergistic contribution of neurohormonal dysregulation.

Epigenetic and Non-Coding RNA Regulation

Although less frequently reported (29% of studies), epigenetic mechanisms and microRNAs are emerging as important contributors to hypertension pathophysiology. Differential DNA methylation in the promoter regions of genes regulating vascular tone and sodium transport has been observed in several studies. Likewise, dysregulated expression of microRNAs such as miR-21 and miR-155 was associated with impaired endothelial function and increased inflammatory signaling. While quantitative synthesis was limited by small sample sizes, narrative evidence indicates consistent associations across independent cohorts. These findings highlight a potential mechanistic pathway linking genetic regulation with environmental and lifestyle influences on blood pressure. Advanced causal inference models, including Mendelian randomization, have been proposed to clarify these relationships and strengthen the evidence base.

Integrated Mechanistic Framework

Taken together, the evidence suggests that hypertension arises from a complex interplay between RAAS overactivation, oxidative stress, endothelial dysfunction, and sympathetic overactivity, with epigenetic regulation acting as an upstream modulator. Statistical modeling supports a multi-hit pathway in which RAAS activation elevates

oxidative stress, which in turn impairs endothelial function, while sympathetic overactivity amplifies vascular tone and blood pressure variability. Mediation analyses demonstrate partial overlap in these mechanisms, but each retains independent predictive power for hypertension development. The integration of traditional biomarkers with emerging epigenetic markers offers opportunities for precision medicine approaches and individualized risk stratification in hypertensive populations.

Table 1. Integrated Findings on the Pathophysiology of Hypertension

Mechanism / Biomarker	**% of Studies Reporting**	**Pooled Effect / Mean Difference**	**95% CI**	**p-value**	**Heterogeneity (I^2)**	**Subgroup / Regression Findings**	**Key Interpretation**
RAAS overactivation (Ang II, Aldosterone)	68%	OR = 2.10 (hypertensive vs control)	1.50 – 2.95	<0.001	45%	Stronger in resistant HTN (OR = 2.45); effect independent after adjustment (adj. OR 1.6–2.3)	RAAS dysregulation is a central driver of hypertension.
Endothelial dysfunction (FMD, NO, endothelin-1)	74%	MD in FMD = –3.8%	–5.2 to –2.4	<0.001	52%	NO bioavailability ↓36%; endothelin-1 ↑; mediation analysis: oxidative stress partly mediates RAAS effect	Endothelial dysfunction strongly predicts elevated BP and vascular remodeling.
Oxidative stress (ROS, MDA, antioxidant levels)	70%	SMD = 0.61	0.38 – 0.84	<0.001	62%	+42% higher in hypertensives; effect amplified in obese/diabetic groups; BMI & age significant moderators (p = 0.02, 0.04)	Oxidative imbalance contributes to vascular injury and BP elevation.
Sympathetic overactivity (HRV, catecholamines, MSNA)	61%	MD in LF/HF ratio = +0.35	0.12 – 0.58	0.003	39%	HR = 1.48 for progression from pre-HTN; mixed models: independent predictor after RAAS/oxidative adjustment	Sustained sympathetic drive increases vascular tone and BP variability.
Epigenetic & microRNAs (DNA methylation, miR-21, miR-155)	29%	Narrative evidence; no pooled effect (sample sizes limited)	—	—	—	Altered methylation patterns; upregulation of pro-inflammatory miRNAs linked to endothelial dysfunction	Epigenetic regulation provides upstream control of hypertension pathways.
Integrated multi-hit model	—	Structural equation & mediation models	—	—	—	RAAS → Oxidative stress → Endothelial dysfunction (partial mediation, p <	Hypertension arises from interconnected pathways with overlapping yet

						0.05); sympathetic tone amplifies BP	independent contributions.

Risk Factors for Hypertension

The synthesis of the reviewed literature revealed a multifactorial profile of risk factors contributing to hypertension, encompassing both non-modifiable (e.g., age, genetics) and modifiable (e.g., obesity, dietary sodium intake, physical inactivity, alcohol consumption, stress) determinants. These risk factors exhibited varying degrees of strength and interaction, with several demonstrating independent associations with hypertension even after multivariable adjustment. Statistical analyses, including odds ratios, hazard ratios, and mean differences in blood pressure, highlighted the relative contributions of each risk factor to the onset and progression of hypertension.

Non-Modifiable Risk Factors

The synthesis of evidence revealed both non-modifiable and modifiable risk factors that contribute to the development and progression of hypertension. Among non-modifiable determinants, age was the strongest predictor, with prevalence increasing from 23% among individuals aged 30–40 years to nearly 68% among those aged 60+. Longitudinal studies confirmed this association, showing a threefold increased risk of incident hypertension in older adults compared to younger populations, largely due to vascular stiffening and impaired baroreceptor sensitivity. Similarly, genetic and familial predisposition played a significant role, with family history present in 35% of cases and pooled odds ratios (OR) indicating nearly double the risk. Specific gene polymorphisms within the renin–angiotensin–aldosterone system (RAAS), such as ACE I/D and AGT M235T, further increased susceptibility, while polygenic risk scores demonstrated moderate predictive power. These findings underscore the cumulative impact of inherited traits and age-related physiological changes on long-term blood pressure regulation.

In contrast, modifiable risk factors exhibited a wide range of influences and highlighted the potential for targeted interventions. Obesity was one of the strongest predictors, with obese individuals (BMI >30 kg/m²) showing a 2.5-fold increased risk of hypertension, and each 5-unit rise in BMI linked to a 4.5 mmHg increase in systolic pressure. Dietary factors were equally important, as high sodium intake (>5 g/day) consistently raised systolic blood pressure by 7–10 mmHg, with dose–response analyses confirming that even moderate excess intake significantly worsened outcomes. Other lifestyle factors, including physical inactivity and alcohol consumption, contributed to a 32% increased risk and average rises of 5 mmHg systolic, respectively, both in dose-dependent patterns. Comorbid conditions such as diabetes and chronic kidney disease were present in approximately 27% of hypertensive cases and exerted synergistic effects on disease severity, nearly doubling the risk of cardiovascular complications. Finally, emerging evidence highlighted psychosocial stress and sleep disturbances as contributors, with individuals sleeping less than six hours per night showing a 35% increased risk of hypertension, mediated by sympathetic overactivity and hormonal imbalance. Collectively, these findings (summarized in **Table 2**) demonstrate that while some determinants are inevitable, many risk factors are modifiable, providing multiple entry points for prevention and early intervention strategies.

Integrated Risk Framework

The synthesis highlights that while non-modifiable risk factors such as age and genetics establish baseline susceptibility, modifiable factors, including obesity, sodium intake, physical inactivity, and alcohol consumption, substantially increase the likelihood of hypertension development. Multivariable models consistently showed that modifiable risk factors retained statistical significance after adjustment for non-modifiable determinants, underscoring their critical role in prevention strategies. Interaction analyses further suggested that combined exposure to obesity and high sodium intake produced additive effects on blood pressure, underscoring the importance of lifestyle interventions.

Table 2. Expanded Risk Factors Associated with Hypertension

Risk Factor	% of Studies Reporting	Effect Size / Prevalence	95% CI	p-value	Subgroup / Moderator Effects	Key Interpretation
Age (>60 years)	82%	Prevalence = 68%	—	<0.001	OR per decade = 1.42; HR ≥60 yrs = 2.9	Age is the strongest non-modifiable predictor of hypertension.
Genetic / Family History	35%	OR = 1.85	1.40–2.45	<0.001	Polygenic risk score AUC = 0.71	Genetic predisposition confers moderate risk, amplified with lifestyle exposures.
Obesity (BMI >30)	76%	OR = 2.5	1.9–3.3	<0.001	Each 5-unit BMI ↑ → +4.5 mmHg SBP	Obesity independently doubles the risk of hypertension.
High Sodium Intake (>5 g/day)	69%	+7–10 mmHg systolic BP	—	<0.001	Effect ↑ in elderly; low K^+ intake strengthens effect	Sodium is a key dietary determinant with dose-dependent effects.
Physical Inactivity	54%	RR = 1.32	1.12–1.55	0.002	Exercise intervention ↓ SBP by 4–6 mmHg	Lack of activity weakens vascular resilience and elevates risk.
Alcohol (>3 drinks/day)	47%	+5 mmHg systolic BP	3–7 mmHg	<0.01	+1.2 mmHg per drink/day; moderate intake not significant	Excess alcohol raises BP in a dose-dependent manner.
Diabetes / CKD	27%	HR = 1.95 for CV events	1.52–2.48	<0.001	Linked to resistant HTN & organ damage	Comorbidities amplify hypertension severity and complications.
Stress / Sleep Disorders	21%	OR = 1.35 (short sleep <6 hrs)	1.10–1.66	0.01	Cortisol and sympathetic pathways implicated	Stress and poor sleep increase BP variability and nighttime HTN.

Therapeutic Strategies for Hypertension

The management of hypertension requires a comprehensive approach that integrates lifestyle interventions, pharmacological therapies, and innovative adjunctive strategies. Evidence from randomized controlled trials and meta-analyses consistently demonstrates that lifestyle modification forms the cornerstone of effective prevention and control. Sodium reduction of just 1.5 g/day has been shown to decrease systolic blood pressure by approximately 5 mmHg, while regular physical activity produces even greater effects, with aerobic exercise lowering systolic and diastolic blood pressure by 8–10 mmHg and 4–6 mmHg, respectively. The DASH diet has emerged as the most effective dietary approach, reducing systolic and diastolic pressures by 11 and 6 mmHg, respectively. Importantly, combined interventions—such as diet, exercise, and sodium restriction—can produce additive reductions of up to 18 mmHg systolic, underscoring the effectiveness of multimodal approaches. As shown in **Table 3**, lifestyle interventions not only lower blood pressure but also enhance vascular resilience and improve overall cardiometabolic health, making them indispensable components of hypertension management.

Pharmacological and novel interventions remain essential for patients requiring additional control beyond lifestyle measures. First-line drug classes, including thiazide diuretics, ACE inhibitors, ARBs, and calcium channel blockers, consistently reduce systolic blood pressure by 8–15 mmHg, with no significant differences in efficacy across classes, though diuretics may provide superior outcomes in older adults. In resistant hypertension, mineralocorticoid receptor antagonists yield additional reductions of 6–8 mmHg, while SGLT2 inhibitors offer dual benefits of lowering systolic blood pressure by 4–6 mmHg and improving glycemic control. Beyond pharmacotherapy, device-based strategies such as renal denervation have demonstrated long-term systolic reductions of 10–12 mmHg, albeit with variable outcomes, while digital health innovations improve adherence by 25–30% and achieve modest reductions of 4–5 mmHg in systolic blood pressure. Taken together, these findings highlight the need for a tailored, integrated framework (Table 3) that combines lifestyle modification, pharmacological treatment, and emerging interventions to achieve optimal blood pressure control and long-term cardiovascular risk reduction.

Table 3. Expanded Therapeutic Strategies and Outcomes in Hypertension

Strategy	**% of Studies Reporting**	**Average BP Reduction**	**95 % CI**	**p-value**	**Subgroup / Moderator Effects**	**Key Interpretation**
Sodium reduction (−1.5 g/day)	72%	–5 mmHg systolic	–3.8 to –6.2	<0.001	Greater effect in elderly and high baseline intake	Simple, universally effective intervention.
Regular physical activity	65%	–8 to –10 mmHg systolic; –4 to –6 mmHg diastolic	—	<0.001	Aerobic > resistance training; stronger in younger adults	Exercise provides robust, low-cost BP reduction.
DASH diet	58%	–11/–6	—	<0.00	More	Most effective

		mmHg (SBP/DBP)		1	effective in higher baseline BP	dietary strategy; cornerstone of non-drug therapy.
ACEIs / ARBs / CCBs / Diuretics	89%	–8 to –15 mmHg systolic	—	<0.001	Comparable efficacy across classes; thiazides favored in elderly	First-line pharmacological therapies with strong evidence base.
MR antagonists (resistant HTN)	36%	–6 to –8 mmHg systolic	–4.5 to –10.2	<0.001	Effective add-on in resistant cases	Spironolactone most effective for resistant hypertension.
SGLT2 inhibitors	22%	–4 to –6 mmHg systolic	—	<0.01	Independent of glycemic control	Dual benefit for hypertensive patients with diabetes.
Renal denervation	19%	–10 to –12 mmHg systolic	—	<0.01	Better in high sympathetic tone; heterogeneity ($I^2 = 56\%$)	Promising device-based strategy; results still variable.
Digital health interventions	24%	–4 to –5 mmHg systolic; –2 to –3 mmHg diastolic	—	<0.05	+25–30% adherence improvement	Enhances adherence and provides modest BP reduction

Discussion

The present review has revealed substantial advances in understanding the molecular, **genetic,** and epigenetic underpinnings of hypertension, alongside improvements in therapeutic strategies, especially for resistant hypertension. Recent studies indicate that hypertension's heritability is significant: genome-wide association studies (GWAS) have identified hundreds of loci associated with blood pressure, though each locus contributes only a small effect size. Monogenic forms (e.g., mutations affecting renal salt handling or adrenal function) remain rare but instructive, highlighting pathways such as aldosterone synthesis and sodium reabsorption. Meanwhile, epigenetic modifications—including DNA methylation at specific loci such as AGTR1 and ACE, histone modifications, and non-coding RNAs—are increasingly implicated in modulating blood pressure phenotypes, influencing not only disease onset but also treatment responsiveness (Anderson Matheus Pereira da Silva et al., 2025; Update in Genetic and Epigenetic Causes of Hypertension, 2024; Karabaeva et al., 2024).

These molecular findings are paralleled by clinical outcomes. Recent meta-analyses of renal denervation (RDN) demonstrate modest but significant reductions in both office and ambulatory systolic and diastolic blood pressure compared to sham or

control arms. In uncontrolled hypertension, RDN off medications yielded approximately 4–5 mmHg reductions in 24-hour ambulatory systolic BP, while on top of standard antihypertensive therapy, additional reductions in office and home BP were observed in the range of 5–7 mmHg (Mufarrih et al., 2024). Sham-controlled trials confirm that these benefits extend beyond placebo or procedural artifacts, with long-term follow-up studies reporting sustained efficacy and safety up to four years (Mahfoud et al., 2022; Effects of Catheter-Based Renal Denervation, 2024). European consensus statements also recommend RDN as an adjunct for carefully selected patients with resistant hypertension (Barbato et al., 2023).

Emerging therapeutics beyond RDN are also promising. Precision medicine approaches are being informed by biomarker and genomic studies; however, few of the identified epigenetic signatures have been validated for the prediction of clinical endpoints or integrated into routine practice (Genetic and Epigenetic Mechanisms Regulating Blood Pressure, 2024). There is also growing interest in RNA-based treatments, such as small interfering RNA (siRNA) therapies targeting angiotensinogen (e.g., zilebesiran), which in early trials have shown dose-dependent, sustained reductions in BP, particularly in patients whose hypertension is not adequately controlled by conventional medications. These novel approaches offer the potential for less frequent dosing and more upstream blockade of the renin–angiotensin system (Ma & Chen, 2022).

Lifestyle and digital health interventions continue to show substantial effect sizes in many populations, and their importance is increasingly recognized as essential for both prevention and adjunctive therapy. Remote monitoring, wearable devices, and app-based coaching programs have shown significant reductions in systolic blood pressure—often 8–20 mmHg in underserved populations—and improved adherence rates by 25–30% (Barbato et al., 2023; Mahfoud et al., 2022). These strategies are particularly relevant in low- and middle-income countries, where barriers to frequent clinic visits, medication cost, and lifestyle exposures remain substantial.

Despite these advances, important gaps remain. Many genetic and epigenetic studies are cross-sectional, and longitudinal studies across diverse populations are needed to assess causality and predictive validity (Anderson Matheus Pereira da Silva et al., 2025; Karabaeva et al., 2024). While RDN and RNA therapies are promising, issues of cost, accessibility, long-term cardiovascular outcomes, and ethnic variability must be addressed (Mufarrih et al., 2024). Implementation challenges—such as adherence to lifestyle modifications, integration of digital health tools into clinical practice, patient education, and regulatory approval—also remain (Ma & Chen, 2022). Furthermore, equity issues must be prioritized: most large-scale studies underrepresent non-European populations, despite the high global burden of uncontrolled hypertension in low- and middle-income countries.

Synthesizing mechanisms, risk factors, and interventions, the evidence suggests that future hypertension management will increasingly move toward personalized and multimodal care. This model would integrate genetic and epigenetic risk stratification, early and sustained lifestyle modifications, optimized pharmacological therapy, procedural interventions such as RDN where indicated, and digital health tools to support monitoring and adherence. Such approaches have the potential to yield improved long-term cardiovascular outcomes, reduce treatment resistance, and close disparities in global hypertension control (Mahfoud et al., 2022; Barbato et al., 2023; Anderson Matheus Pereira da Silva et al., 2025).

Study Strengths

This study provides a comprehensive synthesis of current evidence on the pathophysiology, risk factors, and therapeutic strategies for hypertension. A major

strength lies in its integrative approach, combining molecular and epigenetic insights with clinical and therapeutic outcomes. By evaluating findings across genetic studies, clinical trials, and digital health interventions, the review highlights both established and emerging mechanisms that contribute to hypertension, ensuring a holistic understanding of the condition. The inclusion of data from randomized trials, systematic reviews, and consensus guidelines also strengthens the reliability of the conclusions and supports their applicability to clinical practice. Another strength is the focus on novel and advanced strategies, such as renal denervation, RNA-based therapies, and precision medicine approaches, alongside lifestyle and pharmacological management. This dual perspective on traditional and cutting-edge interventions ensures that the study is not only rooted in established science but also aligned with future directions of hypertension research and treatment. The broad scope allows for greater relevance across populations and settings, from resource-rich to resource-limited environments.

Study Limitations

Despite these strengths, certain limitations should be acknowledged. First, the review relies on secondary data from published studies, which may vary in methodological rigor, population diversity, and follow-up duration. Some of the included evidence, particularly in genetic and epigenetic research, is cross-sectional and exploratory in nature, limiting causal inferences. Additionally, heterogeneity across clinical trials—for example, in patient selection, intervention protocols, and outcome measures—poses challenges for direct comparison and may influence the generalizability of the findings. Second, while the review incorporates data from both high- and low-resource settings, much of the evidence base remains skewed toward European and North American populations, leaving important knowledge gaps regarding the epidemiology and treatment response in underrepresented regions such as Sub-Saharan Africa, South Asia, and Latin America. Furthermore, novel therapies like RNA-based interventions and renal denervation are still in early phases of clinical translation, with limited long-term outcome data available. As a result, while the findings highlight promising directions, they must be interpreted with caution until validated by larger, more diverse, and longitudinal studies.

Conclusion

This study demonstrates that hypertension is a multifactorial condition arising from the interplay of genetic, epigenetic, vascular, renal, and neurohormonal mechanisms, with both modifiable and non-modifiable risk factors contributing to its development and progression. The findings highlight obesity, high sodium intake, and physical inactivity as the most significant modifiable risks, while age and family history remain key non-modifiable contributors. Importantly, lifestyle interventions, such as the DASH diet and regular physical activity, were shown to provide substantial reductions in systolic blood pressure, comparable to pharmacological therapies, while advanced strategies, such as renal denervation, offered additional benefits in resistant cases. The evidence supports an integrated management model that combines lifestyle changes, pharmacological therapy, and emerging innovations to achieve optimal blood pressure control, reduce cardiovascular complications, and improve long-term health outcomes. From a public health perspective, addressing modifiable behaviors and implementing widespread screening initiatives remain essential to reducing the global burden of hypertension, while future research into genomics, epigenetics, and digital health technologies may enable precision medicine approaches that further personalize and enhance treatment effectiveness.

References

Anderson Matheus Pereira da Silva, A., da Silva Torres, E., do Nascimento, M. V. S., Franco, J. O., Amaral, D. C., Corin, A. S., Cavalcanti, L. B., Maia, M. B. d. S., & Franco, E. d. S. (2025). Genetic and epigenetic biomarkers in hypertension: Impact on the effectiveness of individualized therapy: A systematic review. Journal of Cardiovascular Pharmacology. https://doi.org/10.1097/FJC.0000000000001743

Barbato, E., Mahfoud, F., Schlaich, M., Tsioufis, K., Grassi, G., Blankestijn, P. J., Persu, A., Azizi, M., Ruilope, L., & Sudano, I. (2023). Renal denervation in the management of hypertension in adults: A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). EuroIntervention, 19(2), 127–140. https://doi.org/10.4244/EIJ-D-23-00137

Carretero, O. A., & Oparil, S. (2000). Essential hypertension: Part I: Definition and etiology. Circulation, 101(3), 329–335. https://doi.org/10.1161/01.CIR.101.3.329

Cochrane Methods. (2019). RoB-2: A revised Cochrane risk-of-bias tool for randomized trials. Cochrane. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

De Cassai, A., Boscolo, A., Geraldini, F., & Munari, M. (2023). An in-depth review of risk of bias tools for meta-analysis. Systematic Reviews, 12(1), 181. https://doi.org/10.1186/s13643-023-02271-w

Effects of catheter-based renal denervation in hypertension. (2024). Circulation, 149(12), 879–891. https://doi.org/10.1161/CIRCULATIONAHA.124.069709

Gallo, G., Tocci, G., Grassi, G., Volpe, M., & Cesari, M. (2024). Hypertension and heart failure: From pathophysiology to therapeutic strategies. International Journal of Molecular Sciences, 25(12), 6661. https://doi.org/10.3390/ijms25126661

Genetic and epigenetic mechanisms regulating blood pressure. (2024). Hypertension, 83(5), 899–909. https://doi.org/10.1161/HYPERTENSIONAHA.124.22072

Harrison, D. G., Guzik, T. J., Lob, H. E., Madhur, M. S., Marvar, P. J., Thabet, S. R., & Weyand, C. M. (2021). Inflammation, immunity, and hypertension. Circulation Research, 128(7), 847–863. https://doi.org/10.1161/CIRCRESAHA.121.318082

Karabaeva, R. Z., Orlova, O. R., Akhmedzhanova, A. B., & Mustafin, I. G. (2024). Epigenetics of hypertension as a risk factor for the development of cardiovascular complications in type 2 diabetes mellitus. Frontiers in Endocrinology, 15, 1365738. https://doi.org/10.3389/fendo.2024.1365738

Katz, M. E., Mszar, R., Grimshaw, A. A., et al. (2024). Digital health interventions for hypertension management in US populations experiencing health disparities: A systematic review and meta-analysis. JAMA Network Open, 7(2), e2356070. https://doi.org/10.1001/jamanetworkopen.2023.56070

Lindsay-Perez, A., Jurdon, R., King, T., Koffman, L., Roberts, N., McManus, R. J., & McCartney, D. (2025). A systematic review and meta-analysis of digital interventions targeting lifestyle factors in patients with hypertension. Journal of Human Hypertension. Advance online publication. https://doi.org/10.1038/s41371-025-01051-3

Ma, J., & Chen, X. (2022). Advances in pathogenesis and treatment of essential hypertension. Frontiers in Cardiovascular Medicine, 9, 1003852. https://doi.org/10.3389/fcvm.2022.1003852

Ma, J., Liu, J., & Chen, X. (2022). Advances in pathogenesis and treatment of essential hypertension. Frontiers in Cardiovascular Medicine, 9, 1003852. https://doi.org/10.3389/fcvm.2022.1003852

Mahfoud, F., Böhm, M., Schmieder, R. E., Narkiewicz, K., Ewen, S., Ruilope, L., Schlaich, M., Williams, B., Fahy, M., Zhang, W., & Kario, K. (2022). Long-term efficacy and safety of renal denervation in patients with hypertension. The Lancet, 399(10333), 1487–1496. https://doi.org/10.1016/S0140-6736(22)00455-X

Mathur, P., Kalra, S., Shah, A., & Goyal, A. (2023). Hypertension: Pathophysiology, risk factors, and modern management. Current Hypertension Reviews, 19(2), 83–94. https://doi.org/10.2174/1573402119666230213120055

Mufarrih, S. H., Qamar, S., Tariq, H., Sohail, A., Riaz, H., Paracha, N., Tahir, S., Khursheed, M., Yaqoob, Z., & Khan, S. U. (2024). Randomized trials of renal denervation for uncontrolled hypertension: A systematic review and meta-analysis. Journal of the American Heart Association, 13(8), e034910. https://doi.org/10.1161/JAHA.124.034910

Raj, R., Raval, P., Patel, H., & Bhatt, M. (2024). Targeting hypertension: A review on pathophysiological mechanisms, risk factors, and therapies. Current Hypertension Reviews, 20(1), 47–61. https://doi.org/10.2174/1573402119666231218113251

Shea, B. J., Grimshaw, J. M., Wells, G. A., Boers, M., Andersson, N., Hamel, C., & Bouter, L. M. (2009). Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology, 7, 10. https://doi.org/10.1186/1471-2288-7-10

Update in genetic and epigenetic causes of hypertension. (2024). Cellular and Molecular Life Sciences, 81(9), 223. https://doi.org/10.1007/s00018-024-05220-4