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Journal of Clinical Research and Reports

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Review Article

Hypertension Phenotypes and Target Organ Damage: A Modern Clinical Perspective

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Received date: October 06, 2025; Accepted date: November 28, 2025; Published date: December 17, 2025

Citation: Mehmet A. Şahin, Macit Kalçik, Muhammet C. Çelik, Mucahit Yetim, Lütfü Bekar, et al, (2025) Closed-Loop Small Bowel Obstruction Caused by Meckel's Diverticulum: A Rare Case with Radiologic–Surgical Correlation, J Clinical Research and Reports, 22(1); **DOI:10.31579/2690-1919/589**

Abstract

Hypertension is a multifactorial and heterogeneous disease that remains the leading cause of global morbidity and mortality. Traditional diagnostic approaches based on office blood pressure (BP) thresholds fail to capture the dynamic variability of BP and its clinical implications. This narrative review synthesizes current evidence on hypertension phenotypes, sustained, masked, white-coat, non-dipper, and resistant, and their associations with target organ damage (TOD) affecting the heart, kidneys, brain, vasculature, and retina. A phenotype-based understanding reveals that the temporal pattern and circadian behavior of BP, rather than its absolute level alone, determine the risk and distribution of organ injury. Sustained and masked hypertension are strongly linked to left ventricular hypertrophy, microalbuminuria, and cerebrovascular disease, whereas non-dipping and resistant forms contribute disproportionately to nocturnal organ damage and renal dysfunction. White-coat hypertension, although previously deemed benign, carries a modest but measurable long-term cardiovascular risk. Advances in diagnostic modalities, including ambulatory and home BP monitoring, cardiac and vascular imaging, and biomarker profiling, have enabled early identification of subclinical TOD. Treatment strategies are evolving toward phenotype-guided management, integrating chronotherapy, targeted pharmacologic combinations, and emerging device-based interventions such as renal denervation and baroreceptor activation therapy. Future directions emphasize precision medicine approaches, combining digital health technologies, multi-omic data, and artificial intelligence–driven analytics to personalize therapy and prevent irreversible organ injury. Recognition of hypertension as a spectrum of biological phenotypes rather than a uniform disease represents a paradigm shift toward individualized cardiovascular protection and optimized long-term outcomes.

Kew Words: hypertension phenotypes; target organ damage; ambulatory blood pressure monitoring; masked hypertension; resistant hypertension; precision medicine

1.Introduction

Hypertension is defined as a chronic elevation of systemic arterial blood pressure and represents one of the most prevalent and modifiable global health risks. Historically diagnosed using arbitrary blood pressure thresholds, hypertension is now recognized as a heterogeneous disorder with multiple pathophysiological and clinical phenotypes. The clinical relevance of this diversity lies in the differential risk of cardiovascular morbidity, mortality, and target organ damage (TOD) associated with specific hypertension phenotypes.

Globally, an estimated 1.28 billion adults aged 30–79 years are living with hypertension, with approximately two-thirds residing in low- and middle-income countries (1). Despite the high prevalence, awareness, treatment, and control rates remain unacceptably low (1). The Global Burden of Disease study identified elevated systolic blood pressure (SBP) as the leading risk factor for mortality and disability-adjusted life years (DALYs) worldwide (2). In the 2019 analysis, elevated SBP accounted for more than 10 million deaths annually, underscoring the enormous global burden associated with uncontrolled hypertension (3).

While population-level management strategies, such as salt reduction, pharmacologic therapy, and lifestyle interventions, remain essential, it has become increasingly evident that hypertensive individuals exhibit substantial heterogeneity in clinical presentation, circadian blood pressure patterns, and target organ involvement. Traditional binary classification systems fail to capture this variability. Accordingly, a phenotype-based approach to hypertension has emerged, integrating office, home, and ambulatory blood pressure measurements to define distinct entities such as white-coat hypertension, masked hypertension, and sustained hypertension.

Moreover, variations in nocturnal blood pressure behavior (dipping vs. non-dipping or reverse-dipping patterns), blood pressure variability, and treatment resistance contribute to differences in organ damage and cardiovascular outcomes. The identification of these phenotypes provides insight into the mechanisms linking blood pressure elevation with microvascular and macrovascular injury in organs such as the heart, kidneys, brain, and retina.

This review aims to provide a contemporary clinical perspective on the relationship between hypertension phenotypes and target organ damage. The article first summarizes current classifications of hypertension phenotypes, then explores the pathophysiological mechanisms underlying phenotype-specific TOD. Subsequent sections examine organ-specific effects, clinical assessment tools, and emerging therapeutic approaches aimed at phenotype-guided management. Finally, the review highlights current research gaps and future directions toward precision medicine in hypertension.

2. Classification and Clinical Characteristics of Hypertension Phenotypes

The traditional approach to hypertension classification, based solely on clinic blood pressure (BP) thresholds, fails to reflect the complexity and dynamic nature of blood pressure regulation. The integration of ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) has allowed clinicians to identify several phenotypic subtypes with distinct prognostic implications. These phenotypes differ not only in hemodynamic characteristics but also in their relationship with cardiovascular and renal outcomes.

2.1. Office and Ambulatory Blood Pressure–Based Phenotypes

Sustained Hypertension is defined by persistently elevated BP in both office and out-of-office settings. It represents the classic form of hypertension and carries the highest risk of cardiovascular morbidity and mortality (4). Sustained hypertension is commonly associated with structural changes in the heart and vasculature, including left ventricular hypertrophy (LVH), increased arterial stiffness, and microvascular remodeling (5).

White-coat hypertension (WCH) refers to elevated office BP in the presence of normal out-of-office BP values. It is observed in approximately 10–20% of individuals diagnosed with hypertension in clinical settings (6). Initially regarded as benign, recent meta-analyses indicate that untreated WCH is associated with a modest but significant increase in cardiovascular risk compared with normotension (7). However, when properly monitored and untreated, the risk of target organ damage remains substantially lower than that observed in sustained hypertension (8).

In contrast, masked hypertension (MH) is characterized by normal BP values in the clinic but elevated BP outside the medical setting. Its prevalence ranges between 10–15% in the general population and may be higher among those with high-normal office BP (9). MH is strongly linked to increased sympathetic activity, psychosocial stress, and lifestyle factors such as alcohol consumption and smoking (10). Importantly, MH carries a cardiovascular risk similar to that of sustained hypertension due to its frequent association with subclinical target organ damage, including LVH and microalbuminuria (11).

Sustained Normotension refers to normal BP readings in all environments and represents the true reference group. Long-term follow-up data show that individuals with sustained normotension exhibit the lowest incidence of target organ injury and cardiovascular events (12).

2.2. Circadian Blood Pressure Patterns (Dipping Status)

Physiologically, BP follows a circadian rhythm with a nocturnal decline of 10–20% in normotensive individuals, a phenomenon known as dipping. Deviations from this pattern define several clinically relevant phenotypes: non-dipper (<10% nocturnal fall), reverse dipper (nocturnal BP rise), and extreme dipper (>20% decline). Non-dipping and reverse-dipping patterns have been linked to endothelial dysfunction, sympathetic overactivity, and altered sodium excretion (13).

Multiple studies have demonstrated strong associations between abnormal nocturnal BP profiles and cardiovascular outcomes. Non-dippers show higher rates of LVH, carotid atherosclerosis, and renal impairment, while reverse dippers have markedly increased risk of stroke and overall mortality (14,15). In contrast, extreme dippers may experience an elevated risk of silent cerebral infarction due to excessive nocturnal hypotension (16). These findings underscore the importance of ABPM in evaluating nocturnal BP behavior and guiding therapy timing.

2.3. Blood Pressure Variability and Morning Surge Phenotypes

Beyond static BP levels, blood pressure variability (BPV) and morning BP surge are increasingly recognized as independent cardiovascular risk factors. Excessive short-term BPV has been linked to increased arterial stiffness and microvascular injury, contributing to stroke and cognitive impairment (17). The morning BP surge, a rapid rise in BP upon awakening, has been associated with increased incidence of myocardial infarction and hemorrhagic stroke, particularly in elderly hypertensives with vascular stiffness (18). The identification of these dynamic BP phenotypes is crucial for risk stratification and therapeutic individualization.

2.4. Resistant and Refractory Hypertension

Resistant Hypertension (RH) is defined as the failure to achieve target BP despite adherence to three or more antihypertensive agents of different classes, including a diuretic. It affects approximately 10–20% of treated hypertensive patients (19). RH is characterized by high aldosterone levels, increased sympathetic tone, and a high prevalence of obstructive sleep apnea (20). This phenotype is strongly associated with TOD, including LVH, chronic kidney disease (CKD), and atherosclerotic cardiovascular disease (21).

A smaller subset of patients exhibits refractory hypertension, defined as uncontrolled BP despite the use of five or more antihypertensive agents. Unlike RH, this condition is primarily driven by neurogenic mechanisms with extreme sympathetic activation (22). It carries a particularly poor prognosis with rapid progression of renal and cardiac damage.

2.5. Secondary Hypertension Phenotypes

Secondary forms of hypertension, arising from distinct etiologies such as primary aldosteronism, renovascular disease, chronic kidney disease, pheochromocytoma, Cushing's syndrome, and obstructive sleep apnea, constitute additional phenotypic categories. Primary aldosteronism, for instance, accounts for up to 10% of all hypertension cases and is disproportionately represented among those with resistant hypertension (23). Each secondary phenotype demonstrates unique clinical and biochemical features, distinct treatment pathways, and differing risks for TOD (Tbale 1).

3. Pathophysiological Mechanisms Of Target Organ Damage

The relationship between hypertension and target organ damage (TOD) is mediated by a complex interplay of hemodynamic, neurohormonal, inflammatory, and structural mechanisms. While sustained blood pressure elevation remains the principal driver of vascular and tissue injury, emerging evidence suggests that the pattern and variability of blood pressure, rather than mean values alone, play a crucial role in determining the severity and distribution of organ damage across different phenotypes (24).

3.1. Hemodynamic Load and Arterial Stress

Persistent or intermittent increases in systolic blood pressure lead to mechanical strain on the vascular endothelium, smooth muscle, and extracellular matrix. This hemodynamic load induces structural remodeling of large arteries, manifested by medial hypertrophy, elastin degradation, and collagen deposition. The resulting arterial stiffness amplifies systolic pressure and pulse pressure, perpetuating a feedback loop that enhances left ventricular afterload and microvascular damage (25).

Sustained and masked hypertension phenotypes exert continuous vascular stress both during daytime and nighttime, which accelerates this remodeling process. In contrast, white-coat hypertension tends to produce transient BP elevations without consistent exposure to high pressure, resulting in less pronounced vascular injury (26). Non-dipping and reverse-dipping phenotypes, however, expose vascular tissues to continuous or nocturnal hypertension, a pattern associated with increased shear stress, impaired autoregulation, and microvascular ischemia in the kidneys, brain, and myocardium (27).

3.2. Endothelial Dysfunction and Oxidative Stress

Endothelial dysfunction is a unifying mechanism linking hypertension to vascular and organ injury. Impaired nitric oxide (NO) synthesis and increased production of reactive oxygen species (ROS) reduce vasodilatory capacity and promote inflammation and thrombosis. Elevated angiotensin II levels stimulate NADPH oxidase–dependent ROS generation, further aggravating oxidative stress and reducing NO bioavailability (28).

These mechanisms vary among phenotypes. In masked and resistant hypertension, sustained sympathetic activation and oxidative imbalance are prominent, whereas in non-dippers, nocturnal catecholamine excess and altered baroreceptor sensitivity contribute to endothelial injury. The cumulative effect is capillary rarefaction and impaired microcirculation, predisposing to ischemic injury in high-demand organs such as the myocardium and kidneys.

3.3. Inflammation and Immune Activation

Chronic low-grade inflammation plays a central role in hypertension-related TOD. Both innate and adaptive immune responses are activated, with T cells, macrophages, and dendritic cells infiltrating the vascular wall and renal tissue. These immune cells secrete cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), that promote fibrosis, vascular remodeling, and myocardial hypertrophy (29).

Animal and clinical studies demonstrate elevated inflammatory markers in resistant and masked hypertension, suggesting a stronger inflammatory phenotype compared with white-coat hypertension. The degree of inflammatory activation correlates closely with the extent of organ damage, particularly in the kidney and left ventricle.

3.4. Neurohormonal Dysregulation

The renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS) are pivotal in both the initiation and perpetuation of hypertension. Angiotensin II induces vasoconstriction, enhances sodium reabsorption, and stimulates aldosterone secretion, which collectively elevate intravascular volume and blood pressure. Persistent activation of these pathways also promotes myocardial fibrosis, glomerulosclerosis, and vascular stiffness (30).

Sympathetic overactivity, especially in resistant and refractory hypertension, drives increased peripheral vascular resistance and sustained vasoconstriction. Meanwhile, RAAS hyperactivation, typical of non-dipper and volume-dependent phenotypes, contributes to salt retention and loss of nocturnal BP decline. These neurohormonal alterations provide a mechanistic bridge between BP phenotype and organ injury pattern.

3.5. Microvascular Remodeling and Rarefaction

Microvascular remodeling refers to structural and functional changes in small arteries and arterioles, including wall thickening and lumen narrowing. These changes impair tissue perfusion, leading to hypoxia and metabolic stress in downstream tissues. Chronic hypertension causes microvascular rarefaction, or a reduction in the number of perfused capillaries, which limits oxygen delivery to vital organs (31).

Masked and sustained hypertension phenotypes are most closely associated with early microvascular rarefaction, even before overt organ dysfunction develops. Conversely, the intermittent pressure surges of white-coat hypertension rarely induce irreversible microvascular damage. Persistent microcirculatory impairment contributes to progressive left ventricular hypertrophy, renal dysfunction, and cerebral small vessel disease, hallmarks of chronic hypertensive injury.

In summary, the development of target organ damage in hypertension is determined not only by the magnitude of blood pressure elevation but also by its temporal pattern, circadian variation, and associated neurohormonal and inflammatory milieu. Recognition of these mechanistic differences among phenotypes underscores the need for individualized therapeutic strategies aimed at both blood pressure control and protection of the microvasculature.

4. Target Organ Damage Across Hypertension Phenotypes

Target organ damage (TOD) represents the cumulative effect of sustained hemodynamic load, neurohormonal dysregulation, oxidative stress, and microvascular injury associated with hypertension. The pattern and severity of organ involvement differ substantially between hypertension phenotypes, highlighting the clinical relevance of individualized assessment. The heart, kidneys, brain, vasculature, and retina are the principal targets, and each exhibits phenotype-specific vulnerability (Table 2).

Phenotype	Definition (Based on BP Measurement)	Detection Method	Typical Circadian Pattern	Clinical Features	Risk of Target Organ Damage
Sustained Hypertension	Elevated office and out-of-office BP	Office + ABPM/HBPM	Variable	Long-standing hypertension, LVH, renal dysfunction	High
White-Coat Hypertension	Elevated office BP, normal out-of-office BP	ABPM/HBPM	Normal dipper	Often anxiety-related, low risk if untreated	Low–Moderate
Masked Hypertension	Normal office BP, elevated out-of-office BP	ABPM/HBPM	Often non-dipper	Frequently undiagnosed, metabolic risk factors common	High
Non-Dipper Hypertension	<10% fall in nocturnal BP	ABPM	Blunted or absent dipper	Sleep apnea, CKD, diabetes common	High (especially renal and cerebrovascular)

Resistant Hypertension	BP ≥140/90 mmHg despite ≥3 drugs (including diuretic)	Office + ABPM	Often reverse dipper	Volume overload, sympathetic activation	Very High

Table 1: Classification and Characteristics of Major Hypertension Phenotypes

Abbreviations: BP: blood pressure; ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; LVH: left ventricular hypertrophy; CKD: chronic kidney disease.

Target Organ	Sustained HT	Masked HT	White-Coat HT	Non-Dipper HT	Resistant HT	Predominant Mechanism
Heart	LVH, diastolic dysfunction	LVH	Minimal changes	LVH, fibrosis	Severe LVH, HFpEF	Pressure overload, RAAS activation
Brain	Stroke, cognitive decline	Small vessel disease	Rare	Silent infarction, white matter lesions	Stroke, vascular dementia	Endothelial injury, microangiopathy
Kidney	Microalbuminuria, CKD	Early nephropathy	Rare	Reduced nocturnal renal perfusion	Rapid GFR decline	Glomerular hyperfiltration, oxidative stress
Vasculature	Arterial stiffness, IMT ↑	Arterial stiffness ↑	Normal	Atherosclerosis	Severe arterial remodeling	Vascular inflammation, stiffness
Retina	Hypertensive retinopathy	Early arteriolar narrowing	Normal	Advanced retinopathy	Severe microvascular injury	Microvascular rarefaction

Table 2: Hypertension Phenotypes and Associated Target Organ Damage

Abbreviations: HT: hypertension; LVH: left ventricular hypertrophy; HFpEF: heart failure with preserved ejection fraction; GFR: glomerular filtration rate; IMT: intima–media thickness; RAAS: renin–angiotensin–aldosterone system.

4.1. Cardiac Target Organ Damage

The myocardium is among the earliest and most affected organs in chronic hypertension. The primary structural manifestation is left ventricular hypertrophy (LVH), resulting from pressure overload and neurohormonal activation. LVH increases myocardial oxygen demand, decreases coronary perfusion reserve, and predisposes to diastolic dysfunction and arrhythmias (5).

Among phenotypes, sustained hypertension and masked hypertension are most strongly associated with LVH and concentric remodeling, reflecting persistent exposure to elevated BP even outside clinical settings (32). Conversely, white-coat hypertension tends to exhibit minimal or reversible LVH, provided it remains untreated and closely monitored (6). Non-dipping and reverse-dipping phenotypes are associated with more pronounced nocturnal wall stress and higher left ventricular mass index (27).

Chronic pressure overload also promotes interstitial fibrosis via angiotensin II–mediated collagen deposition and inflammatory signaling, contributing to heart failure with preserved ejection fraction (HFpEF) (33). Moreover, increased arterial stiffness and pulse pressure accelerate the coupling between vascular and cardiac dysfunction, leading to ischemic heart disease even in the absence of obstructive coronary artery lesions.

4.2. Cerebrovascular Target Organ Damage

Hypertension is the leading modifiable risk factor for both ischemic and hemorrhagic stroke. The magnitude and pattern of BP elevation, particularly during nighttime, have major prognostic implications for cerebrovascular outcomes (34). Non-dipper and reverse-dipper phenotypes exhibit higher rates of silent brain infarction, white matter hyperintensities, and cognitive decline compared to dippers with similar mean BP levels (15).

Ambulatory BP monitoring studies have shown that each 10-mmHg increase in nighttime systolic BP correlates with a 20% increase in stroke risk (14). Morning BP surge has also been identified as a determinant of intracerebral hemorrhage, likely due to abrupt rises in vascular shear stress upon awakening (35).

Cerebral small vessel disease (SVD), a hallmark of hypertensive brain injury, manifests as microbleeds, lacunar infarctions, and leukoaraiosis on MRI. These lesions are particularly frequent in patients with sustained or masked hypertension, suggesting that continuous 24-hour BP elevation accelerates microvascular damage and impairs autoregulation (36).

4.3. Renal Target Organ Damage

The kidney is both a target and a mediator of hypertensive injury. Elevated systemic BP increases glomerular capillary pressure, leading to endothelial dysfunction, podocyte injury, and progressive nephron loss. The resulting decline in renal function contributes to sodium retention and further BP elevation, forming a self-perpetuating cycle (37).

Phenotype-specific data indicate that non-dippers and resistant hypertensives exhibit the most significant renal impairment, including reduced glomerular filtration rate (GFR) and higher prevalence of microalbuminuria (38). Ambulatory studies demonstrate a close association between nighttime BP and urinary albumin excretion, reinforcing the pathogenic role of nocturnal hypertension in renal injury (39).

In contrast, white-coat hypertension rarely leads to overt renal dysfunction, whereas masked hypertension, owing to unrecognized sustained pressure load, may cause early microalbuminuria and progressive nephrosclerosis (12). Primary aldosteronism–related hypertension, a secondary phenotype, accelerates glomerular sclerosis through aldosterone-induced oxidative stress and inflammation.

4.4. Vascular Target Organ Damage

Hypertension induces macrovascular remodeling, characterized by increased arterial stiffness, intima–media thickening, and endothelial dysfunction. The measurement of carotid–femoral pulse wave velocity (PWV) and carotid intima–media thickness (CIMT) provides a noninvasive means to quantify vascular injury.

Masked and sustained hypertension are consistently associated with greater PWV and CIMT compared with normotension or white-coat hypertension (40). In particular, high BP variability and morning surge phenotypes correlate with accelerated arterial aging and plaque instability (17). The underlying mechanisms include chronic exposure to pulsatile stress, inflammation, and impaired nitric oxide–mediated vasodilation.

Persistent arterial stiffness increases cardiac afterload and reduces coronary perfusion, establishing a vicious cycle that links vascular aging to cardiac and renal dysfunction. These observations position vascular damage as both a marker and mediator of hypertensive disease progression.

4.5. Retinal and Microvascular Damage

The retina provides a direct window into the microvasculature and mirrors systemic vascular injury. Chronic hypertension produces characteristic retinal changes, arteriolar narrowing, arteriovenous nicking, and microaneurysm formation, collectively termed hypertensive retinopathy (41).

Non-dipping and sustained hypertension are most strongly associated with retinopathy progression. Optical coherence tomography (OCT) and retinal imaging studies reveal early arteriolar remodeling and capillary rarefaction in masked hypertensives, even in the absence of overt fundoscopic abnormalities (42).

Because retinal vascular alterations closely parallel cerebral microangiopathy, retinal examination can serve as a surrogate marker for systemic microvascular health. The presence of hypertensive retinopathy has been independently linked to an increased risk of stroke and chronic kidney disease (43).

In summary, distinct hypertension phenotypes display characteristic patterns of target organ involvement. Sustained and masked hypertension are associated with widespread, continuous vascular injury and high TOD burden. Non-dipping and resistant hypertension contribute predominantly to nocturnal and renal damage, while white-coat hypertension typically presents with minimal or reversible organ injury. Recognition of these phenotype-specific patterns is critical for accurate risk stratification and early therapeutic intervention.

5. Clinical Assessment and Diagnostic Tools

Accurate identification of hypertension phenotypes and early detection of target organ damage (TOD) are fundamental to personalized management. Conventional office blood pressure (BP) measurements alone are insufficient to capture the full hemodynamic profile of hypertensive patients. The integration of ambulatory and home BP monitoring, imaging modalities, and biochemical markers allows clinicians to detect phenotypic variability and quantify organ involvement more precisely.

5.1. Blood Pressure Monitoring Techniques

Office BP measurement remains the cornerstone of hypertension diagnosis. However, it is susceptible to measurement error, observer bias, and situational factors such as anxiety (“white-coat effect”). Accurate measurement requires the use of validated automated devices, appropriate cuff size, and repeated readings after a rest period (44). Despite its limitations, office BP retains prognostic value when performed under standardized conditions.

Ambulatory Blood Pressure Monitoring (ABPM) provides 24-hour recordings of BP and is the gold standard for distinguishing between sustained, masked, and white-coat hypertension (45). It enables assessment of mean daytime and nighttime pressures, circadian patterns (dipping status), and morning surge. ABPM-derived nighttime BP has shown superior predictive value for cardiovascular morbidity and mortality compared with clinic BP (14). Phenotypes such as non-dipper and reverse-dipper hypertension can only be detected via ABPM, making it indispensable for comprehensive risk stratification.

Home Blood Pressure Monitoring (HBPM) offers a practical and cost-effective alternative for long-term BP evaluation. It correlates strongly with cardiovascular outcomes and allows detection of masked hypertension in patients with normal office readings (46). HBPM also enhances patient engagement and treatment adherence. However, it lacks nocturnal BP information and may underestimate BP variability compared with ABPM.

5.2. Imaging Modalities for Organ Damage Assessment

Echocardiography is the most widely used imaging tool for cardiac structural and functional assessment. It quantifies left ventricular mass, wall thickness, and diastolic function. The presence of left ventricular hypertrophy (LVH) or abnormal diastolic relaxation in hypertensive patients signifies established cardiac TOD (47). Tissue Doppler imaging and strain analysis further improve early detection of subclinical myocardial dysfunction.

Carotid ultrasound measures carotid intima–media thickness (CIMT) and plaque burden, both of which predict cardiovascular risk beyond BP levels alone. Carotid–femoral pulse wave velocity (PWV) assessment remains the gold standard for evaluating arterial stiffness, a key marker of vascular damage (40). Magnetic resonance imaging (MRI) and computed tomography (CT) angiography may be used in select cases to evaluate vascular remodeling or aortic aneurysm formation.

Cerebral MRI is the preferred modality for detecting hypertensive brain injury. It visualizes white matter hyperintensities (WMH), lacunar infarcts, and microbleeds associated with chronic hypertension (48). The burden of small vessel disease on MRI correlates strongly with ambulatory nighttime BP and non-dipping patterns.

Ultrasound and MRI allow assessment of renal size, cortical thickness, and resistive index, while Doppler studies detect renovascular hypertension. Early parenchymal changes, including reduced cortical perfusion, may precede overt renal failure, particularly in resistant or non-dipper hypertensive phenotypes (49).

Fundoscopic examination remains a simple yet powerful method to detect hypertensive retinopathy. Digital retinal photography and optical coherence tomography (OCT) can quantify microvascular changes objectively. Retinal arteriolar narrowing and arteriovenous nicking are associated with systemic microvascular disease, making retinal assessment a valuable surrogate for generalized vascular health (43) (Table 3).

Organ System	Primary Diagnostic Methods	Key Measurable Parameters	Clinical Significance
Cardiac	Echocardiography, ECG, Cardiac MRI	LV mass index, diastolic function (E/e’), strain imaging	Detects LVH and early myocardial dysfunction
Renal	Serum creatinine, cystatin C, urine albumin-to-creatinine ratio, renal Doppler ultrasound	eGFR, albuminuria, renal resistive index	Identifies early nephropathy and renovascular disease
Cerebral	Brain MRI, CT scan, cognitive testing	White matter hyperintensities, lacunar infarcts, microbleeds	Quantifies hypertensive small vessel disease
Vascular	Carotid ultrasound, pulse wave velocity, ankle–brachial index	Carotid IMT, arterial stiffness, atherosclerotic plaque	Reflects macrovascular remodeling and stiffness

Retinal	Fundoscopy, OCT, retinal photography	Arteriolar narrowing, AV nicking, microaneurysms	Serves as a non-invasive marker of systemic microvascular injury

Table 3: Diagnostic Tools in the Evaluation of Hypertensive Target Organ Damage

Abbreviations: ECG: electrocardiogram; LVH: left ventricular hypertrophy; MRI: magnetic resonance imaging; IMT: intima–media thickness; AV: arteriovenous; OCT: optical coherence tomography; eGFR: estimated glomerular filtration rate.

5.3. Laboratory and Biomarker Evaluation

Laboratory evaluation provides essential information that complements imaging and blood pressure (BP) monitoring in the assessment of hypertensive target organ damage (TOD) and secondary hypertension. Biochemical markers allow detection of subclinical injury at an early stage, often before structural abnormalities become apparent.

Renal biomarkers such as serum creatinine, cystatin C, and the estimated glomerular filtration rate (eGFR) remain the primary indicators of kidney function in hypertensive patients. Among these, microalbuminuria, quantified through the spot urine albumin-to-creatinine ratio, serves as a sensitive and early marker of hypertensive nephropathy. The presence of even minimal albuminuria signifies glomerular endothelial dysfunction and predicts progressive renal impairment as well as cardiovascular events (50).

Cardiac biomarkers provide complementary insight into myocardial involvement. Circulating natriuretic peptides, including B-type natriuretic peptide (BNP) and its N-terminal prohormone (NT-proBNP), reflect myocardial wall stress and help identify left ventricular dysfunction before overt heart failure develops. Elevated levels of these peptides in asymptomatic hypertensive individuals often indicate early diastolic dysfunction or subclinical left ventricular hypertrophy (51).

Metabolic and inflammatory markers further refine cardiovascular risk stratification. Measurements of fasting glucose, lipid profile, C-reactive protein (CRP), and uric acid are valuable in identifying coexisting metabolic derangements, systemic inflammation, and oxidative stress, pathways that are particularly relevant in resistant and metabolic hypertension (52).

The integration of biomarker data with imaging modalities and out-of-office BP monitoring enables a comprehensive evaluation of hypertensive disease burden. Such multidimensional profiling enhances the detection of subclinical organ involvement, supports individualized therapeutic decisions, and strengthens preventive strategies aimed at halting progression toward irreversible target organ damage.

5.4. Integrative Assessment and Emerging Tools

Recent advances in digital health and machine learning have enhanced the ability to detect hypertension phenotypes and predict TOD progression. Wearable continuous BP monitors, smartphone-based oscillometric devices, and AI-driven ABPM analytics offer real-time data acquisition and personalized feedback (53).

Moreover, multimodal diagnostic algorithms combining ABPM, echocardiography, and biomarker data allow clinicians to stratify patients into risk clusters with higher accuracy than BP readings alone. Future research aims to incorporate genomic, metabolomic, and proteomic markers to refine phenotype classification and improve early detection of TOD.

In summary**,** the assessment of hypertension phenotypes requires a multifaceted diagnostic approach that integrates BP monitoring, imaging, and laboratory evaluation. ABPM remains the cornerstone of phenotype classification, while echocardiography, vascular imaging, and biomarker analysis provide crucial insights into subclinical organ damage. These tools collectively enable clinicians to transition from a population-based to a personalized hypertension management paradigm.

6. Therapeutic Strategies

The management of hypertension has evolved from uniform blood pressure (BP) reduction toward phenotype-specific and organ-protective strategies. While pharmacologic and lifestyle interventions remain the foundation of treatment, growing evidence supports individualized approaches guided by BP phenotype, circadian rhythm, and associated target organ damage (TOD). This section outlines current therapeutic principles and emerging precision strategies designed to optimize long-term outcomes.

6.1. General Management Principles

The fundamental goal of antihypertensive therapy is to prevent cardiovascular and renal events by reducing BP and mitigating TOD. Major guidelines recommend a target BP of <130/80 mm Hg for most patients, provided that it is tolerated (54). Non-pharmacologic therapy forms the cornerstone of management across all phenotypes and includes:

- **Sodium restriction:** Reducing daily sodium intake below 2.3 g/day effectively lowers BP and enhances drug response.
- **Weight reduction:** Every 1 kg of weight loss lowers systolic BP by roughly 1 mm Hg.
- **Physical activity:** Moderate aerobic exercise (150 min/week) improves endothelial function and decreases sympathetic activity.
- **Alcohol moderation and smoking cessation:** Both improve vascular compliance and reduce overall cardiovascular risk.
- **Sleep optimization:** Adequate sleep and management of obstructive sleep apnea are particularly relevant in resistant and non-dipper hypertension (19).

These measures are universally applicable but have variable efficacy depending on the underlying phenotype.

6.2. Phenotype-Specific Pharmacological Strategies

Sustained Hypertension: Standard first-line pharmacologic classes, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide/thiazide-like diuretics, remain the foundation of treatment (55). Fixed-dose combination therapy is now recommended as initial treatment to improve adherence and BP control. Sustained hypertensives typically require dual or triple therapy due to persistent vascular remodeling and neurohormonal activation.

White-Coat Hypertension: Pharmacologic treatment is generally unnecessary unless additional cardiovascular risk factors or TOD are present. Instead, lifestyle modification and regular out-of-office monitoring are emphasized (56). Over-treatment may increase the risk of hypotension without measurable cardiovascular benefit.

Masked Hypertension: This phenotype demands active pharmacologic intervention despite normal office BP, as the associated risk of cardiovascular events and TOD parallels that of sustained hypertension (57). Morning dosing or 24-hour coverage with long-acting agents is preferred to control unrecognized daytime hypertension.

Non-Dipper and Reverse-Dipper Hypertension: Chronotherapy, timing medication to restore physiological nocturnal BP decline, has demonstrated superior outcomes in nocturnal hypertensives. Administering at least one antihypertensive agent at bedtime reduces nighttime BP and improves cardiovascular prognosis (58). Agents with prolonged half-lives (e.g., ACEIs, ARBs, and CCBs) are ideal for this approach.

Resistant Hypertension: Management begins with confirming true resistance and excluding secondary causes. Optimal triple therapy includes an ACEI/ARB, a CCB, and a thiazide-like diuretic. Mineralocorticoid receptor antagonists (MRAs), particularly spironolactone, are the most effective fourth-line agents and improve BP control and regression of LVH (59). If uncontrolled, additional options include beta-blockers, alpha-1 blockers, or loop diuretics (in CKD).

Refractory Hypertension: This rare phenotype often reflects extreme sympathetic activation. Centrally acting sympatholytic agents such as clonidine or moxonidine may provide benefit. Emerging interventional therapies, renal denervation and baroreceptor activation therapy, have demonstrated reductions in 24-hour ambulatory BP and may serve as adjuncts for this difficult group (60).

Secondary Hypertension: Etiology-specific therapy is essential. Examples include adrenalectomy or MRA therapy for primary aldosteronism, revascularization for renal artery stenosis, and continuous positive airway pressure (CPAP) for obstructive sleep apnea (Table 4).

Phenotype	Diagnostic Tools	Typical Biomarker Findings	Therapeutic Approach	Follow-Up Strategy
Sustained HT	Office BP + ABPM	↑ BNP/NT-proBNP, microalbuminuria	Combination antihypertensive therapy	Regular ABPM + organ damage monitoring
White-Coat HT	ABPM confirmation	Normal biomarkers	Lifestyle modification, observation	Annual ABPM or HBPM
Masked HT	ABPM/HBPM screening	Mild ↑ CRP, early microalbuminuria	Initiate pharmacologic therapy	3–6 monthly BP reassessment
Non-Dipper HT	Nighttime ABPM	↑ Urinary albumin, renal resistive index	Bedtime dosing, sleep apnea evaluation	Repeated ABPM for rhythm normalization
Resistant HT	Office + ABPM + lab screening	↑ Aldosterone, uric acid, NT-proBNP	Triple therapy + MRA ± renal denervation	Specialist follow-up every 3 months

Table 4. Diagnostic and Therapeutic Implications of Hypertension Phenotyping

Abbreviations: ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; BNP: B-type natriuretic peptide; CRP: C-reactive protein; MRA: mineralocorticoid receptor antagonist.

6.3. Blood Pressure Variability and Target Organ Protection

Beyond mean BP reduction, minimizing blood pressure variability (BPV) is increasingly recognized as crucial for TOD prevention. Long-acting antihypertensives, such as CCBs and ACEIs, achieve smoother 24-hour control and lower BPV, leading to reduced rates of stroke, myocardial infarction, and renal impairment (17). In addition, consistent adherence to medication and avoidance of abrupt therapy withdrawal are critical to maintain hemodynamic stability.

6.4. Novel and Emerging Therapies

Originally developed for diabetes, these agents exhibit mild BP-lowering effects and potent cardiovascular and renal protection. SGLT2 inhibitors improve endothelial function and reduce intraglomerular pressure, making them attractive adjuncts for hypertensive patients with metabolic syndrome or chronic kidney disease (61).

Catheter-based renal sympathetic denervation targets renal afferent and efferent nerves to reduce sympathetic outflow. Randomized trials have demonstrated sustained reductions in both office and ambulatory BP, particularly in resistant hypertension (62). Baroreceptor activation therapy, via carotid sinus stimulation, offers another option for patients with uncontrolled hypertension despite maximal medical therapy (63).

Experimental agents targeting oxidative stress, endothelin pathways, or vascular inflammation are under investigation. These include endothelin receptor antagonists and selective mineralocorticoid receptor modulators that reduce fibrosis and vascular stiffness.

6.5. Precision and Personalized Medicine

The emerging paradigm of precision hypertension management integrates clinical, hemodynamic, and molecular data to guide therapy. Phenotype-specific approaches may soon be enhanced by:

- **Genomic profiling:** identification of polymorphisms affecting salt sensitivity or drug metabolism (e.g., CYP11B2, ACE).
- **Biomarker-guided therapy:** using plasma renin activity or urinary aldosterone to tailor RAAS blockade.
- **Artificial intelligence (AI):** machine learning algorithms that predict therapeutic response and detect masked or nocturnal hypertension patterns from ABPM datasets (64).

These tools have the potential to transition clinical practice from reactive BP control to proactive prevention of organ injury, allowing true personalization of hypertension care.

In conclusion, the management of hypertension requires an integrated approach balancing pharmacologic precision with lifestyle modification. Recognition of hypertension phenotypes provides the framework for tailoring therapy, optimizing BP control, and preventing target organ damage. The future of hypertension treatment lies in precision medicine, where therapy is defined not solely by BP level but by phenotype, risk profile, and underlying pathophysiology.

7. Prognosis and Clinical Outcomes

The clinical outcomes of hypertension vary substantially among phenotypes, reflecting differences in hemodynamic exposure, neurohormonal activation, and cumulative target organ damage (TOD). Contemporary cohort studies and meta-analyses have clarified that the risk of cardiovascular morbidity and mortality is not determined solely by mean blood pressure (BP) levels but also by BP pattern, variability, and circadian rhythm (17).

7.1. Long-Term Cardiovascular Outcomes

Sustained Hypertension confers the highest long-term risk for cardiovascular (CV) morbidity and mortality. Large population studies have demonstrated that individuals with sustained hypertension exhibit a two- to threefold higher risk of myocardial infarction, stroke, and heart failure compared with normotensive controls (65). Persistent mechanical load and arterial stiffening contribute to progressive left ventricular

hypertrophy (LVH) and diastolic dysfunction, culminating in heart failure with preserved ejection fraction (HFpEF).

Masked hypertension (MH) carries a cardiovascular risk comparable to sustained hypertension despite normal office BP readings. In the Ohasama and Finn-Home studies, MH independently predicted higher rates of fatal and non-fatal cardiovascular events and all-cause mortality (9). The unrecognized nature of MH often delays treatment initiation, allowing early subclinical organ damage to progress unchecked.

White-coat hypertension (WCH) was once considered benign; however, longitudinal studies have shown that untreated WCH is associated with modestly increased risks of developing sustained hypertension and future CV events (7). The PAMELA study demonstrated that approximately one-third of untreated WCH patients transition to sustained hypertension over a decade, suggesting that WCH represents an intermediate risk state rather than a harmless entity (8).

Resistant hypertension (RH) has a poor prognosis, with markedly elevated risks of stroke, heart failure, chronic kidney disease (CKD), and cardiovascular death (66). Even after adjustment for office BP, RH independently predicts adverse outcomes, likely reflecting the contribution of sustained nocturnal hypertension, increased BP variability, and higher prevalence of comorbidities such as obesity and diabetes.

7.2. Target Organ Damage Regression and Reversibility

Effective BP reduction can lead to partial regression of TOD, although reversibility depends on both phenotype and duration of exposure. Sustained and masked hypertension often induce structural cardiac and renal changes that regress slowly, whereas white-coat hypertension–related alterations are largely functional and reversible (67). Pharmacologic control of nocturnal BP in non-dipper and resistant phenotypes has been associated with significant reductions in LV mass, microalbuminuria, and carotid intima–media thickness (68). However, persistent endothelial dysfunction and microvascular remodeling may limit full restoration of normal organ architecture in long-standing hypertension.

7.3. Phenotype Transition and Dynamic Risk

Hypertension phenotypes are not static. Longitudinal studies show frequent transitions among them, driven by aging, weight gain, lifestyle factors, and inadequate therapy (69). WCH and MH are particularly dynamic: up to 40% of WCH patients progress to sustained hypertension, while 20–30% of MH patients normalize their BP with lifestyle modification. Understanding these transitions is clinically important, as phenotype evolution often signals increased cardiovascular vulnerability. Regular ambulatory or home BP monitoring is therefore essential to detect such shifts early and adapt management accordingly.

In conclusion, sustained and masked hypertension carry the greatest long-term risk of cardiovascular and renal events, while white-coat hypertension represents a borderline but evolving condition. Non-dipping and resistant phenotypes confer disproportionate risk for stroke, heart failure, and renal failure due to continuous pressure load and neurohormonal activation. Timely identification and dynamic monitoring of hypertension phenotypes are essential to prevent irreversible target organ damage and improve prognosis.

8. Future Perspectives and Research Directions

Despite major advances in the understanding and treatment of hypertension, substantial knowledge gaps persist regarding phenotype-specific mechanisms, prognostic implications, and optimal management strategies. Future research must focus on integrating molecular, hemodynamic, and digital data to achieve precision medicine in hypertension.

8.1. Integrating Multi-Omic and Genetic Profiling

The application of genomics, transcriptomics, proteomics, and metabolomics offers the potential to redefine hypertension beyond conventional BP thresholds. Genome-wide association studies (GWAS) have identified more than 900 loci associated with BP regulation, implicating genes involved in renal sodium handling, vascular tone, and neurohormonal pathways (70). However, the translation of these findings into phenotype-based classification remains limited.

Emerging evidence suggests that certain genotypes, such as polymorphisms in ACE, ADD1, and CYP11B2, may influence salt sensitivity and treatment response (71). Integrating genetic markers into clinical phenotyping could improve prediction of therapy efficacy and progression toward target organ damage (TOD). Prospective studies combining multi-omic data with clinical and ambulatory BP phenotypes are essential to establish mechanistic links between genotype, phenotype, and organ injury.

8.2. Artificial Intelligence and Digital Hypertension Management

Artificial intelligence (AI) and digital health technologies have the potential to revolutionize hypertension care. Machine learning algorithms can analyze large-scale ABPM and wearable sensor data to identify hidden phenotypes such as masked, nocturnal, or highly variable BP patterns (72).
AI-assisted risk prediction models already outperform traditional statistical methods in forecasting cardiovascular events, particularly when combined with imaging and laboratory data.

Continuous BP monitoring via photoplethysmography-based wearables, cuffless devices, and smartphone-integrated sensors will soon enable real-time hypertension surveillance and personalized feedback loops. These technologies can facilitate earlier detection of phenotype transitions, such as from white-coat to sustained hypertension, and optimize therapy titration.

8.3. Longitudinal and Phenotype-Guided Clinical Trials

Most clinical trials in hypertension have traditionally focused on office blood pressure (BP) measurements as the primary endpoint. While this approach has shaped modern therapeutic guidelines, it neglects dynamic BP parameters such as nocturnal levels, circadian variation, and blood pressure variability, factors now recognized as powerful predictors of cardiovascular outcomes. As a result, conventional trial designs have limited ability to capture the full pathophysiological spectrum of hypertension and its diverse clinical phenotypes.

Future antihypertensive trials must transition toward phenotype-guided designs that stratify patients based on ambulatory blood pressure monitoring (ABPM)–defined profiles and objective markers of target organ damage (TOD). Such an approach would enable the identification of high-risk subgroups who might benefit from more aggressive or tailored interventions.

Several critical questions remain unanswered and require direct investigation. Can early pharmacologic treatment in masked hypertension prevent or delay cardiovascular events to the same extent as in sustained hypertension? Does the timing of antihypertensive therapy, specifically chronotherapy, provide a mortality benefit across all patient populations, or is its efficacy confined to those with non-dipping or reverse-dipping patterns? Furthermore, are device-based therapies such as renal denervation and baroreceptor activation superior to pharmacologic escalation in refractory hypertension characterized by sympathetic overactivity?

Addressing these unresolved questions through rigorously designed, phenotype-stratified clinical trials will be essential for refining hypertension management. Such evidence will enable the development of targeted treatment algorithms that align therapeutic intensity with the

biological risk inherent to each phenotype, ultimately advancing the field toward precision cardiovascular medicine.

8.4. Toward Precision and Preventive Hypertension Medicine

The convergence of molecular biology, digital monitoring, and AI-driven analytics is paving the way for precision hypertension medicine. This paradigm envisions real-time BP profiling combined with biomarker-guided drug selection and adaptive treatment algorithms. Early identification of high-risk phenotypes, before irreversible organ damage occurs, will enable preventive rather than reactive management.

Ultimately, success will depend on large-scale data integration, interdisciplinary collaboration, and equitable access to technology across healthcare systems. As phenotype-based understanding deepens, hypertension management will evolve from population-level thresholds toward individualized cardiovascular protection.

9. Conclusión

Hypertension is a multifaceted disease encompassing diverse hemodynamic and biological profiles. The recognition of distinct phenotypes, sustained, masked, white-coat, non-dipper, and resistant, has transformed clinical understanding from a uniform numerical model to a dynamic, individualized framework. Each phenotype carries a unique risk spectrum for cardiovascular and renal complications, largely determined by its temporal blood pressure pattern and the extent of target organ involvement.

Contemporary evidence demonstrates that nocturnal blood pressure, circadian rhythm disruption, and blood pressure variability are stronger predictors of adverse outcomes than office measurements alone. Therefore, the integration of ambulatory and home blood pressure monitoring into standard care is indispensable.

Phenotype-based management, incorporating both pharmacologic and lifestyle strategies, provides an opportunity to align treatment intensity with true biological risk. Emerging digital technologies, machine learning analytics, and molecular profiling are expected to further refine this approach, allowing early identification of high-risk individuals and prevention of irreversible organ injury.

The future of hypertension management lies in precision medicine , a model that transcends traditional diagnostic thresholds to deliver personalized therapy, minimize target organ damage, and ultimately reduce global cardiovascular burden.

Contributorship: All of the authors contributed planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: No financial funding was received for this study.

Competing interests: All of the authors have no conflict of interest.

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DOI:10.31579/2690-1919/589