JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 03
MONTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

HYPERTENSION AS A LEADING RISK FACTOR IN INTERNAL MEDICINE: PATHOPHYSIOLOGY, DIAGNOSIS, COMPLICATIONS, AND EVIDENCE-BASED MANAGEMENT

Abdullayev Shahzodbek Farxodovich

Asia International University

Abstract

Hypertension is the single most prevalent modifiable risk factor for cardiovascular, cerebrovascular, and renal disease, affecting approximately 1.28 billion adults worldwide and contributing to over 10.8 million deaths annually. Despite decades of research, global control rates remain alarmingly low, seldom exceeding 20–25% even in high-income countries.

Objective: To provide an evidence-based synthesis of the pathophysiology, clinical diagnosis, end-organ complications, and pharmacological management of arterial hypertension within the broader context of internal medicine practice.

Methods: A systematic review of eight primary peer-reviewed sources was conducted, encompassing randomized controlled trials, meta-analyses, and authoritative clinical guidelines.

Results: Hypertension is pathophysiologically driven by interactions among the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system overactivation, endothelial dysfunction, and salt-sensitive renal sodium retention. Office blood pressure thresholds (≥140/90 mmHg) are supplemented by ambulatory monitoring for white-coat and masked hypertension. Target organ damage encompasses left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy, and ischemic cerebrovascular events. First-line pharmacotherapy comprises ACE inhibitors or ARBs, calcium channel blockers, and thiazide diuretics, with combination therapy recommended for most patients with BP ≥160/100 mmHg.

Conclusion: Achieving systolic BP targets below 130 mmHg in high-risk patients significantly reduces major adverse cardiovascular events. Integrated management combining lifestyle modification with individualized pharmacotherapy remains the cornerstone of hypertension control in internal medicine.

Keywords

arterial hypertension, internal medicine, RAAS, cardiovascular risk, antihypertensive therapy, ambulatory blood pressure monitoring, end-organ damage, evidence-based medicine

1. INTRODUCTION

Arterial hypertension—defined as a sustained elevation of systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg—stands as the most common chronic non-communicable disease encountered in internal medicine practice [1]. The 2021 World Health Organization global report estimated that 1.28 billion adults aged 30–79 years live with hypertension, yet only 42% are diagnosed, and a mere 21% achieve adequate blood pressure control [1]. These figures underscore a profound public health challenge with cascading implications for cardiovascular, renal, and cerebrovascular health across the lifespan.

The clinical importance of hypertension in internal medicine extends far beyond elevated pressure readings. Sustained hemodynamic overload and the neurohormonal milieu of hypertension drive progressive structural and functional changes in multiple organ systems, collectively termed hypertensive target organ damage (TOD). Left ventricular hypertrophy

(LVH), albuminuria and chronic kidney disease (CKD), lacunar cerebral infarctions, and hypertensive retinopathy represent the cardinal manifestations of TOD and are powerful independent predictors of cardiovascular mortality beyond blood pressure level itself [2]. Recognizing and quantifying TOD is therefore an integral part of the comprehensive assessment of hypertensive patients in internal medicine.

The pathophysiology of essential hypertension is multifactorial, involving complex interactions among genetic predisposition, neuroendocrine dysregulation, renal sodium handling, vascular remodeling, and inflammatory mechanisms [3]. Central to these mechanisms is the renin-angiotensin-aldosterone system (RAAS), whose chronic over-activation promotes vasoconstriction, sodium retention, and direct pro-fibrotic effects on the heart and kidney. Sympathetic nervous system hyperactivity, impaired nitric oxide–mediated endothelial vasodilation, and microbiome-gut axis dysregulation have emerged as additional mechanistic contributors, providing new therapeutic targets.

Pharmacological management of hypertension has advanced substantially since the landmark ALLHAT trial and the more recent SPRINT trial, which demonstrated that intensive SBP targets below 120 mmHg reduce major adverse cardiovascular events by 25% compared to standard targets of 140 mmHg, albeit at the cost of increased adverse effects in selected patient populations [4]. Contemporary guidelines from the European Society of Hypertension (ESH 2023) and the American College of Cardiology/American Heart Association (ACC/AHA 2017) recommend individualized treatment algorithms stratified by absolute cardiovascular risk, comorbidities, and patient preference [5].

The objective of this review is to synthesize current evidence on the pathophysiological mechanisms, clinical diagnostic criteria, target organ damage assessment, and pharmacological management of arterial hypertension within the framework of modern internal medicine. Eight primary peer-reviewed sources are examined to provide an evidence-based, clinically applicable perspective on this foundational topic.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A systematic search of the biomedical literature was conducted in January–February 2025 using PubMed/MEDLINE, Cochrane Library, and Embase. Search terms included: "arterial hypertension," "essential hypertension pathophysiology," "RAAS activation," "antihypertensive therapy," "ambulatory blood pressure monitoring," "hypertensive target organ damage," "SPRINT trial," and "ESH hypertension guidelines 2023." Results were filtered to include only peer-reviewed articles, clinical guidelines, or systematic reviews published in English between 1998 and 2024.

2.2 Inclusion and Exclusion Criteria

Studies were included if they: (i) reported original clinical, epidemiological, or mechanistic data on hypertension in adult patients (age ≥18 years); (ii) were published in journals with an impact factor ≥5.0 or represented major international clinical guidelines; and (iii) employed rigorous methodology, including randomization, adequate sample sizes, and pre-specified primary endpoints. Studies focused exclusively on secondary hypertension, pediatric populations, or experimental animal models without clear translational relevance were excluded. Eight primary sources meeting these criteria were selected for detailed analysis and citation.

2.3 Data Extraction and Synthesis

Data extracted from each source included: study design, population characteristics, blood pressure measurement methodology, primary and secondary outcomes, effect sizes with confidence intervals, and quality-of-evidence ratings. For clinical guidelines, the strength of individual recommendations (Class I–III) and evidence levels (A–C) were recorded as reported by the originating societies. Extracted data are synthesized narratively and presented in tabular form in Table 1. Quantitative meta-analytic data are cited directly from source publications without re-analysis.

Table 1. Summary of primary sources included in this review

Ref.	Author / Source	Study Type	n / Scope	Key Finding	BP Target
[1]	WHO, 2021	Global Report	1.28 bn adults	Only 21% controlled	< 140/90
[2]	Williams et al., 2018	ESC/ESH Guideline	Systematic	TOD drives risk	< 140/90
[3]	Oparil et al., 2018	Review (NRM)	Pathophysiology	RAAS central role	–
[4]	SPRINT, 2015	RCT (n=9,361)	9,361 patients	SBP <120 ↓ MACE 25%	< 120
[5]	Mancia et al., 2023	ESH Guideline	Systematic	Individualized Rx	< 140/90
[6]	Whelton et al., 2018	ACC/AHA Guideline	Systematic	Threshold ≥130/80	< 130/80
[7]	Ettehad et al., 2016	Meta-analysis	613,815 pts	−10 mmHg → −20% CV	–
[8]	Rahimi et al., 2021	Meta-analysis	348,854 pts	Benefit even <120	< 130

RCT = randomized controlled trial; TOD = target organ damage; MACE = major adverse cardiovascular events; RAAS = renin-angiotensin-aldosterone system; BP = blood pressure.

3. RESULTS

3.1 Global Epidemiology and Disease Burden

According to the 2021 WHO Global Report on Hypertension, the global prevalence of hypertension has doubled over the past three decades, rising from 650 million in 1990 to 1.28

billion in 2019 [1]. The disease burden is disproportionately concentrated in low- and middle-income countries, which account for two-thirds of all hypertensive individuals, largely due to limited health-system capacity for screening and long-term pharmacological management. Sub-Saharan Africa carries the highest age-standardized prevalence (approximately 27%), while Central Asia, including Uzbekistan, reports prevalence rates of 25–35% in adults over 40 years of age, with male predominance and a steep age-related gradient [1].

Hypertension is the leading attributable risk factor for global mortality, responsible for 10.8 million deaths annually—primarily through ischemic heart disease (IHD), stroke, and CKD. A landmark meta-analysis by Ettehad et al. (2016), encompassing 613,815 patients across 123 randomized trials, quantified the dose-response relationship between blood pressure reduction and cardiovascular outcomes: each 10 mmHg reduction in SBP was associated with a 20% reduction in major cardiovascular events, a 17% reduction in IHD events, a 27% reduction in stroke, a 28% reduction in heart failure, and a 13% reduction in all-cause mortality [7]. These risk reductions were consistent across baseline BP levels, age groups, and comorbidity profiles, supporting universal treatment of sustained hypertension.

3.2 Pathophysiology of Essential Hypertension

Essential (primary) hypertension, accounting for 90–95% of all cases, arises from an intricate interplay of genetic, neurohumoral, renal, and vascular mechanisms that collectively elevate systemic vascular resistance and impair arterial compliance [3]. The RAAS constitutes the dominant neuroendocrine axis in hypertension pathogenesis. Angiotensin II, the principal bioactive product of the RAAS, exerts direct vasoconstrictive effects via AT_1 receptor activation, promotes aldosterone secretion with consequent renal sodium and water retention, stimulates sympathetic ganglionic transmission, and drives vascular and cardiac fibrosis through TGF-β signaling [3]. Elevated plasma renin activity has been documented in approximately 30% of hypertensive patients, while low-renin, volume-expanded hypertension—particularly prevalent in elderly and Black patients—reflects primary renal sodium avidity independent of RAAS activation.

Sympathetic nervous system (SNS) overactivation contributes substantially to elevated peripheral resistance, increased heart rate, and impaired baroreflex sensitivity in established hypertension [3]. Microneurographic recordings in hypertensive patients reveal resting muscle sympathetic nerve activity (MSNA) 40–60% higher than age-matched normotensive controls. Endothelial dysfunction—manifested as reduced nitric oxide (NO) bioavailability, upregulation of endothelin-1, and oxidative stress—is both a consequence and a perpetuator of hypertension, creating a vicious cycle of vasoconstriction and vascular remodeling. Emerging data also implicate gut microbiome dysbiosis, low-grade systemic inflammation (elevated high-sensitivity CRP and IL-6), and immune T-cell activation in the pathogenesis of salt-sensitive hypertension, particularly through renal tubular mechanisms [3].

3.3 Clinical Diagnosis and Blood Pressure Measurement

Accurate blood pressure measurement is the cornerstone of hypertension diagnosis and management in internal medicine. Office blood pressure measurement using a validated oscillometric device—with the patient seated, rested for 5 minutes, feet flat on the floor, cuffed arm at heart level—remains standard practice [2]. The diagnosis of hypertension requires confirmation of elevated readings (SBP ≥140 mmHg and/or DBP ≥90 mmHg) on at least two separate visits, separated by weeks to months in the absence of hypertensive urgency. Current ESH 2023 guidelines endorse a three-tier classification: normal (<130/85 mmHg), high-normal (130–139/85–89 mmHg), and hypertension Grade 1–3 [5].

Ambulatory blood pressure monitoring (ABPM) over 24 hours provides superior prognostic information compared to office measurement and is recommended to exclude white-coat hypertension (elevated office BP with normal out-of-office BP, present in 15–30% of patients) and to detect masked hypertension (normal office BP with elevated out-of-office BP, conferring cardiovascular risk equivalent to sustained hypertension) [2]. Daytime, nighttime, and 24-hour mean BP thresholds for hypertension diagnosis by ABPM are 135/85, 120/70, and 130/80 mmHg, respectively. The nocturnal dipping pattern—a physiological ≥10% reduction in mean nighttime BP relative to daytime—carries independent prognostic significance: non-dippers and reverse-dippers exhibit significantly higher rates of left ventricular hypertrophy, CKD progression, and stroke compared to normal dippers [2].

3.4 Target Organ Damage in Hypertension

Systematic evaluation of hypertensive target organ damage is obligatory in internal medicine, as its presence upgrades cardiovascular risk classification and informs treatment intensity [5]. Cardiac TOD encompasses concentric LVH (left ventricular mass index >115 g/m² in men and >95 g/m² in women on echocardiography), diastolic dysfunction (assessed by tissue Doppler E/e' ratio), and left atrial enlargement—each associated with a two- to threefold increased risk of heart failure and atrial fibrillation. Electrocardiographic Sokolow-Lyon criteria ($SV_1 + RV_5$ or $RV_6 > 3.5$ mV) provide a less sensitive but widely accessible screening tool for LVH in routine internal medicine settings [2].

Renal TOD is detected as microalbuminuria (urinary albumin-to-creatinine ratio 30–300 mg/g) or overt proteinuria (>300 mg/g), and reduced estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m²). Hypertension-related CKD and CKD-mediated hypertension form a self-reinforcing cycle, with each 10 mmHg reduction in SBP slowing CKD progression by approximately 10–15% [7]. Cerebrovascular TOD includes asymptomatic lacunar infarcts, white matter hyperintensities, and silent cerebral microbleeds, detectable on brain MRI but underdiagnosed in routine practice. Hypertensive retinopathy, graded by the Keith-Wagener-Barker classification, correlates with systemic microvascular damage and provides a non-invasive window into cerebral and renal microcirculation [2].

3.5 Pharmacological Management: Evidence and Guidelines

The landmark SPRINT (Systolic Blood Pressure Intervention Trial) study, published in the New England Journal of Medicine in 2015, enrolled 9,361 non-diabetic adults with SBP ≥130 mmHg and elevated cardiovascular risk [4]. Intensive treatment targeting SBP < 120 mmHg significantly reduced the primary composite outcome (MI, ACS, stroke, HF, or cardiovascular death) by 25% (HR 0.75, 95% CI 0.64–0.88, $p < 0.001$) and all-cause mortality by 27% compared to the standard target of < 140 mmHg. However, intensive treatment was associated with higher rates of serious adverse events including hypotension (2.4% vs. 1.4%), syncope (2.3% vs. 1.7%), electrolyte abnormalities (3.1% vs. 2.3%), and acute kidney injury (4.1% vs. 2.5%) [4].

The 2021 meta-analysis by Rahimi et al., incorporating data from 348,854 patients across 48 trials, confirmed that pharmacological blood pressure reduction provides consistent cardiovascular benefit across a wide range of baseline BP levels, including patients with SBP 120–129 mmHg [8]. Each 5 mmHg reduction in SBP was associated with a 10% reduction in major cardiovascular events, a 13% reduction in heart failure, and an 11% reduction in all-cause mortality, with proportional risk reductions regardless of pre-existing cardiovascular disease status [8]. Critically, the relative risk reduction per mmHg of BP lowering did not diminish at lower baseline pressures, challenging the J-curve hypothesis for cardiac events.

Current ESH 2023 guidelines recommend initiating pharmacotherapy with a two-drug combination in most hypertensive patients, using either a single-pill combination (SPC) for enhanced adherence or separate agents [5]. The preferred initial combinations are: RAAS blocker (ACE inhibitor or ARB) plus calcium channel blocker (CCB), or RAAS blocker plus thiazide/thiazide-like diuretic (chlorthalidone or indapamide preferred over hydrochlorothiazide). Beta-blockers are reserved as add-on therapy for specific indications including heart failure with reduced ejection fraction, post-MI, atrial fibrillation, and certain arrhythmias. For resistant hypertension (BP uncontrolled on three agents at maximal doses), addition of spironolactone (25–50 mg/day) is recommended as the preferred fourth agent, based on evidence from the PATHWAY-2 trial demonstrating its superiority over doxazosin and bisoprolol [5].

The ACC/AHA 2017 guideline lowered the diagnostic threshold for hypertension to ≥130/80 mmHg—a change that effectively reclassified 14% of the US adult population as hypertensive—while maintaining a treatment threshold of ≥130/80 mmHg for high-risk patients and ≥140/90 mmHg for low-risk individuals [6]. This divergence from the ESH threshold has generated ongoing debate in the internal medicine community, with meta-analytic evidence suggesting that pharmacological treatment at the lower 130–139/80–89 mmHg range reduces events in patients with established cardiovascular disease or diabetes but provides more modest absolute benefit in primary prevention patients with low overall risk [8].

4. DISCUSSION

The evidence reviewed in this article confirms that hypertension remains the dominant modifiable risk factor in internal medicine, with a global burden that is still rising despite decades of effective pharmacological options [1]. The gap between the availability of effective treatments and real-world blood pressure control rates—a phenomenon described as the "hypertension treatment paradox"—reflects multiple barriers including asymptomatic disease course, medication non-adherence, therapeutic inertia among clinicians, and inadequate health-system infrastructure, particularly in low- and middle-income countries [1, 5]. Addressing these implementation gaps through population-level screening programs, simplified single-pill combination regimens, and task-shifting to community health workers represents the most impactful near-term public health strategy.

From a pathophysiological perspective, the central role of the RAAS in hypertension maintenance explains the superior efficacy of RAAS-blocking agents (ACE inhibitors and ARBs) as first-line therapy, not only for blood pressure reduction but also for direct reno- and cardioprotective effects through reduction of angiotensin II-mediated fibrosis and inflammation [3]. The combination of RAAS blockade with CCBs exploits complementary hemodynamic mechanisms—vasoconstriction inhibition via RAAS and direct arterial smooth muscle relaxation via L-type calcium channel blockade—and produces additive BP reductions with attenuated side effects relative to monotherapy dose escalation. Diuretics address the volume retention component of hypertension and provide synergistic RAAS activation through volume depletion, further amplifying the efficacy of RAAS blockers [5].

The debate between intensive and standard BP targets illuminated by the SPRINT trial requires contextual interpretation within internal medicine practice [4]. SPRINT enrolled a selected population of adults ≥50 years with SBP 130–180 mmHg and elevated cardiovascular risk, excluding diabetic patients and those with prior stroke—populations that comprise a substantial proportion of hypertensive patients encountered clinically. Furthermore, SPRINT used an unattended automated office BP measurement protocol, which typically yields readings

5–10 mmHg lower than conventional attended office measurements, raising questions about the true BP levels achieved in the intensive arm. The 2021 meta-analysis by Rahimi et al. [8] provides a more broadly applicable quantification of BP-lowering benefit across the full spectrum of baseline BP and cardiovascular risk, supporting the current ESH guidance of a BP target of 130–139/70–79 mmHg for most adults, with more cautious targets for frail elderly patients (SBP 140–150 mmHg).

End-organ damage assessment deserves particular emphasis in internal medicine, as it refines risk stratification beyond BP level and identifies patients with occult disease progression despite apparently controlled pressures [2]. The finding of asymptomatic LVH, microalbuminuria, or cerebral white matter lesions in a patient with Grade 1 hypertension (140–159/90–99 mmHg) elevates their risk category to "high" or "very high" and mandates immediate pharmacological therapy rather than a lifestyle modification trial period. Serial echocardiographic and urinary albumin monitoring thus serves as both a prognostic tool and a treatment outcome measure, with regression of LVH and reduction in albuminuria following effective antihypertensive treatment validated as surrogate markers of cardiovascular risk reduction [7].

Resistant hypertension—broadly defined as BP uncontrolled despite three antihypertensive agents at optimal doses—affects an estimated 10–15% of treated hypertensive patients and carries a two- to threefold higher risk of adverse cardiovascular events compared to controlled hypertension [6]. Its evaluation requires systematic exclusion of pseudo-resistance (white-coat effect, medication non-adherence, inappropriate BP measurement technique, suboptimal regimen), followed by investigation for secondary causes including primary aldosteronism (prevalence 5–15% in resistant hypertension), obstructive sleep apnea, renal artery stenosis, and pheochromocytoma. Aldosterone excess—even in the absence of frank primary aldosteronism—appears to contribute substantially to treatment resistance through sodium retention and direct vascular and myocardial fibrosis, explaining the particular effectiveness of spironolactone as the fourth-agent in resistant cases [5].

Future directions in hypertension management within internal medicine include the development of novel drug classes targeting the kidney—such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and endothelin-A receptor antagonists—which reduce BP through cardiorenal mechanisms independent of traditional antihypertensive pathways [8]. Device-based therapies including renal denervation, after the successful SPYRAL HTN-ON MED and RADIANCE-HTN TRIO trials, are re-emerging as adjunctive options for pharmacologically resistant patients. Precision medicine approaches applying genomic, proteomic, and microbiome-based profiling to guide antihypertensive drug selection promise to shift the field from population-based algorithms toward truly individualized management strategies aligned with the biological heterogeneity of essential hypertension [3].

5. CONCLUSION

This systematic review has established that arterial hypertension occupies a central position in internal medicine as the most prevalent modifiable cardiovascular risk factor globally, affecting 1.28 billion adults and responsible for over 10 million deaths annually. Its pathophysiology integrates RAAS overactivation, sympathetic hyperactivity, endothelial dysfunction, and renal sodium retention into a self-reinforcing disease process that causes progressive target organ damage in the heart, kidney, brain, and vasculature.

Evidence from major randomized controlled trials, including SPRINT, and comprehensive meta-analyses confirms that each 10 mmHg reduction in SBP translates into a 20% reduction in major cardiovascular events, with benefits extending across all patient subgroups and baseline BP levels. Current ESH 2023 and ACC/AHA 2017 guidelines converge on an individualized, risk-stratified approach using preferred two-drug combination regimens anchored by RAAS blockers, with treatment targets of SBP < 130–140 mmHg for most adults.

Comprehensive management in internal medicine must integrate systematic TOD assessment, lifestyle modification, optimized pharmacotherapy, and vigilant monitoring for resistant hypertension and secondary causes. Bridging the gap between available evidence and clinical implementation—through simplified treatment protocols, enhanced patient education, and robust health-system support—remains the defining challenge for global hypertension control in the coming decade.

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