Journal of Prevention, Diagnosis and Management of Human Diseases
Vol: 05, No. 02, July-Dec 2025
ISSN: 2799-1202, DOI: 10.55529/jpdmhd.52.80.94

Research Paper

Pharmacological management of hypertension: a comprehensive narrative review of diagnostic classification, mechanism-based drug therapy, and landmark outcome trial evidence

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Article Info

Article History:
Received: 04 June 2025
Revised: 14 August 2025
Accepted: 21 August 2025
Published: 08 October 2025

Keywords:
Hypertension
Blood Pressure
Antihypertensive Agents
Pharmacotherapy
Cardiovascular Prevention
Guideline

ABSTRACT

Background: Hypertension is the leading modifiable risk factor for cardiovascular death worldwide; the number of affected adults has more than doubled over three decades despite a mature, extensively trial-tested pharmacological armamentarium, and only an estimated 23% of adults with hypertension achieve adequate blood pressure control globally.
Objective: This narrative review synthesizes current diagnostic classification criteria, the molecular pharmacology of the major antihypertensive drug classes, the landmark randomized-trial evidence underlying blood-pressure treatment targets, and compelling-indication-based drug selection, to support evidence-based prevention, diagnosis, and pharmacotherapy decisions.
Methods: A structured search of PubMed/MEDLINE, the Cochrane Library, and ClinicalTrials.gov was conducted for phase 3, event-driven, randomized controlled outcome trials of antihypertensive pharmacotherapy, together with current ACC/AHA, ESH, and WHO guidance published between 1998 and 2024. Of 1,842 records identified, 22 studies and guideline documents met the inclusion criteria for qualitative synthesis.
Results: Four landmark outcome trials collectively randomized more than 25,000 participants and demonstrated that intensive or active blood-pressure lowering reduces major cardiovascular events, with hazard ratios ranging from 0.70 to 0.88 across populations differing in age and diabetes status; a neutral result in a diabetic population showed that the benefit of intensive targets is not uniform across all patient groups. Seven major drug classes, acting at distinct points in the renin-angiotensin-aldosterone system or on peripheral vascular and renal sodium-handling mechanisms, are summarized alongside their comparative pharmacology, compelling indications, and adverse-effect profiles. Global hypertension prevalence rose from an estimated 650 million adults in 1990 to 1.4 billion in 2024, mostly in low- and middle-income countries.

Conclusion: A substantial, mechanistically diverse evidence base now supports individualized, compelling-indication-guided pharmacotherapy combined early rather than sequentially titrated to maximal monotherapy doses; translating this evidence into consistent global blood-pressure control remains one of the largest unmet opportunities in cardiovascular disease prevention.

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1. INTRODUCTION

Hypertension is the single leading modifiable risk factor for death and disability worldwide, contributing to ischemic heart disease, stroke, heart failure, chronic kidney disease, and cognitive decline through sustained mechanical stress on the arterial wall and downstream target organs. According to the World Health Organization, an estimated 1.4 billion adults aged 30–79 years were living with hypertension in 2024, a figure that has more than doubled from approximately 650 million in 1990, with roughly two-thirds of affected individuals residing in low- and middle-income countries [1]. A pooled analysis of 1,201 population-representative studies encompassing 104 million participants confirmed that this rise reflects both population aging and a genuine increase in age-standardized prevalence in many low-resource settings, even as prevalence has plateaued or declined in some high-income countries [2]. As shown in Figure 1, the trajectory of global hypertension prevalence has been essentially monotonic over the past three and a half decades, and the disorder has been described as the archetypal example of a chronic, largely asymptomatic condition whose population-level burden is disproportionate to its clinical visibility [3].

Despite this enormous and growing burden, global control rates remain strikingly poor: an estimated 44% of adults with hypertension are unaware of their diagnosis, a further 44% are diagnosed and treated but not controlled, and only approximately 23% achieve adequate blood pressure control, [4]. This gap between the strength of the pharmacological evidence base and real-world outcomes is not attributable to a lack of effective therapy. Antihypertensive pharmacotherapy is supported by one of the largest bodies of randomized controlled trial evidence in all of clinical medicine, spanning more than six decades and encompassing multiple mechanistically distinct drug classes, each targeting a different physiological determinant of arterial pressure—cardiac output, peripheral vascular resistance, circulating blood volume, or neurohormonal vasoconstrictor tone. The persistent implementation gap instead reflects a combination of underdiagnosis, clinical inertia in treatment intensification, suboptimal use of combination therapy, and medication non-adherence.

The clinical consequences of this implementation gap are substantial and cumulative: uncontrolled hypertension acts silently over years to decades, so that a sustained elevation of even 10–15 mmHg in systolic pressure that goes unrecognized or under-treated can materially increase an individual's lifetime risk of stroke, myocardial infarction, heart failure, and end-stage renal disease long before any single episode becomes clinically apparent. From a health-systems perspective, the cost of this gap is asymmetric: population-level screening and generic first-line pharmacotherapy are inexpensive relative to the downstream cost of treating a completed stroke or an incident heart-failure hospitalization, which means that even modest improvements in diagnosis and treatment intensification are likely to be highly cost-

effective at a population scale, particularly in the low- and middle-income countries that now bear the majority of the global burden.

This review aims to: (i) summarize current diagnostic classification criteria for hypertension and situate them relative to prior guideline generations; (ii) present the comparative molecular pharmacology of the seven major antihypertensive drug classes in clinical use; (iii) synthesize the landmark randomized controlled trial evidence underlying contemporary blood-pressure treatment targets; (iv) describe compelling-indication-based drug selection for common comorbid conditions; and (v) propose an integrated, stepwise pharmacotherapy algorithm consistent with current international guidance. The remainder of this paper is organized as follows. Section 2 reviews prior guideline documents and reviews that frame the present synthesis. Section 3 describes the search methodology and diagnostic classification framework applied throughout the review. Section 4 presents comparative pharmacology, landmark trial evidence, safety profiles, and compelling-indication-based algorithm, together with an integrated discussion. Section 5 concludes with the principal clinical and public health implications.

2. RELATED WORK

The pharmacological management of hypertension has been shaped by a succession of guideline documents and systematic evidence reviews, each reflecting the trial evidence accumulated up to its date of publication. The Eighth Joint National Committee (JNC 8) report, published in 2014, was among the first major U.S. guidelines to base its recommendations explicitly on evidence graded from randomized controlled trials rather than expert consensus alone, and it introduced age-stratified systolic blood pressure targets (<150 mmHg for adults aged 60 years or older, <140 mmHg for younger adults) that were subsequently revised as newer trial evidence emerged [5]. The 2017 ACC/AHA Guideline superseded JNC 8 following the publication of the Systolic Blood Pressure Intervention Trial (SPRINT), lowering the diagnostic threshold for Stage 1 hypertension from 140/90 mmHg to 130/80 mmHg and adopting a uniform treatment target of <130/80 mmHg for most adults [6]. In parallel, European cardiology and hypertension societies issued the 2018 ESC/ESH Guidelines, which retained a diagnostic threshold of 140/90 mmHg while endorsing a more conservative treatment target than the American guideline, illustrating that identical underlying trial evidence can be interpreted differently by different expert panels [7]. The most recent 2023 ESH Guidelines further refined blood-pressure targets and expanded guidance on device-based and out-of-office measurement, while the WHO 2021 Guideline for the Pharmacological Treatment of Hypertension in Adults was developed with explicit attention to feasibility and cost in low-resource settings, favoring simplified first-line regimens over the more granular compelling-indication algorithms of the American and European documents [8], [9].

Beyond guideline documents, several narrative and systematic reviews have previously synthesized the pharmacology of individual drug classes or specific trial populations. A dedicated American Heart Association scientific statement addressed the definition, evaluation, and pharmacological management of resistant hypertension, formalizing the role of mineralocorticoid receptor antagonists as fourth-line agents in patients remaining uncontrolled on three complementary-mechanism drugs [10]. Earlier outcome trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), established the comparative efficacy of thiazide-type diuretics, calcium channel blockers, and ACE inhibitors as first-line monotherapy and remain foundational to current first-line drug class recommendations, despite being conducted before the more recent generation of intensive-target trials [11]. Collectively, this body of prior guideline and review literature provides broad consensus on the major antihypertensive drug classes and general treatment principles, but individual documents differ in their diagnostic thresholds, treatment targets, and the granularity with which they address compelling indications—differences that motivate the present synthesis, which draws together diagnostic classification, molecular pharmacology, and trial evidence within a single integrated review rather than treating these domains separately, as is common in the existing literature.

3. METHODOLOGY

3.1 Review Design and Search Strategy

This is a narrative review; no original patient data were collected, and no formal meta-analytic pooling was performed. A structured search of PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was conducted using combinations of the terms "hypertension," "blood pressure," "antihypertensive," "renin-angiotensin system," "randomized controlled trial," and the names of individual drug classes, restricted to English-language publications from January 1998 to mid-2024. As shown in Figure 2, the search identified 1,842 records, of which 447 were removed as duplicates. The remaining 1,395 records were screened by title and abstract, yielding 168 full-text articles assessed for eligibility; 22 studies and guideline documents ultimately met the inclusion criteria described below and were retained for qualitative synthesis.

3.2 Inclusion and Exclusion Criteria

Priority was given to phase 3, event-driven, randomized, controlled outcome trials with a pre-specified composite cardiovascular primary endpoint, together with major national and international hypertension guideline documents. Table 1 summarizes the inclusion and exclusion criteria applied during full-text screening. Studies were excluded if they were observational, lacked a pre-specified cardiovascular or mortality endpoint, enrolled fewer than 1,000 participants, or reported only surrogate blood-pressure outcomes without linked clinical events, unless they provided pharmacological or mechanistic details not available elsewhere. All hazard ratios, confidence intervals, prevalence estimates, and classification thresholds reported below are extracted directly from the cited primary publications and guideline documents; none were calculated, pooled, or simulated by the present authors.

Table 1. Inclusion and Exclusion Criteria Applied During Full-Text Screening

Criterion	Inclusion	Exclusion
Study design	Phase 3 RCT, meta-analysis, or clinical practice guideline	Observational/cohort study, case report, editorial
Population	Adults (age ≥18 years) with essential hypertension	Pediatric-only populations, secondary hypertension studies
Outcome	Pre-specified cardiovascular or mortality composite endpoint	Surrogate blood-pressure endpoint only, no linked clinical events
Sample size	≥1,000 randomized participants (trials)	<1,000 participants unless mechanistically unique
Publication window	January 1998 – mid-2024, English language	Non-English language, or superseded by a later guideline update
Publication type	Peer-reviewed journal article or official guideline document	Conference abstract without full-text publication

3.3 Diagnostic Classification of Blood Pressure

The 2017 ACC/AHA Guideline for Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults defines four principal blood pressure categories based on properly measured, averaged office readings, summarized in Table 2 and illustrated in Figure 3. Normal blood pressure is defined as systolic <120 mmHg and diastolic <80 mmHg; elevated blood pressure as systolic 120–129 mmHg with diastolic <80 mmHg; Stage 1 hypertension as systolic 130–139 mmHg or diastolic 80–89 mmHg; and Stage 2 hypertension as systolic ≥140 mmHg or diastolic ≥90 mmHg. A hypertensive crisis, requiring urgent evaluation for end-organ damage, is generally defined as systolic ≥180 mmHg and/or diastolic ≥120 mmHg.

Table 2. Blood Pressure Classification (2017 ACC/AHA Hypertension Guideline)

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥140	or	≥90
Hypertensive Crisis	≥180	and/or	≥120

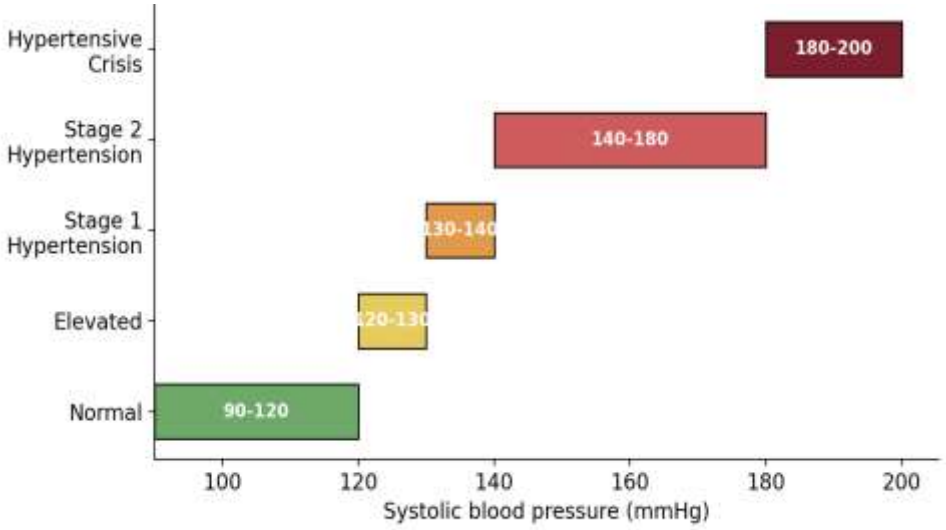

Figure 1. Blood Pressure Classification (2017 ACC/AHA Hypertension Guideline)

As shown in Figure 3, the classification is continuous rather than categorical in its underlying pathophysiology, and the thresholds instead represent points along a continuous risk gradient selected for clinical actionability. Diagnosis should be confirmed with out-of-office measurement (home or ambulatory blood pressure monitoring) where feasible, given the well-documented phenomena of white-coat hypertension (elevated office readings with normal out-of-office readings) and masked hypertension (normal office readings with elevated out-of-office readings), both of which carry cardiovascular risk implications distinct from sustained hypertension or normotension. This classification framework, together with the search strategy described above, provides the analytic scaffold for the pharmacological and trial-evidence synthesis presented in Section 4.

4. RESULTS AND DISCUSSION

4.1 Global Epidemiological Context

As shown in Figure 1, global hypertension prevalence has risen from approximately 650 million adults in 1990 to an estimated 1.4 billion in 2024. This near-doubling in absolute numbers, occurring despite substantial pharmacological and public-health investment, is driven predominantly by population aging and rising prevalence in low- and middle-income countries, and underscores that pharmacotherapy alone—however well evidenced—cannot resolve the global hypertension burden without corresponding improvements in screening, diagnosis, and sustained treatment access.

4.2 Pharmacology of Antihypertensive Drug Classes

4.2.1 The Renin-Angiotensin-Aldosterone System as a Pharmacological Target

A substantial share of contemporary antihypertensive pharmacotherapy targets the renin-angiotensin-aldosterone system (RAAS), a hormonal cascade that begins with renin release from renal juxtaglomerular cells, proceeds through angiotensin-converting enzyme (ACE)-mediated conversion of

angiotensin I to the potent vasoconstrictor angiotensin II, and culminates in both direct AT1-receptor-mediated vasoconstriction and aldosterone-driven renal sodium and water retention. Figure 4 illustrates this pathway and the specific molecular point at which each major RAAS-targeting drug class exerts its effect.

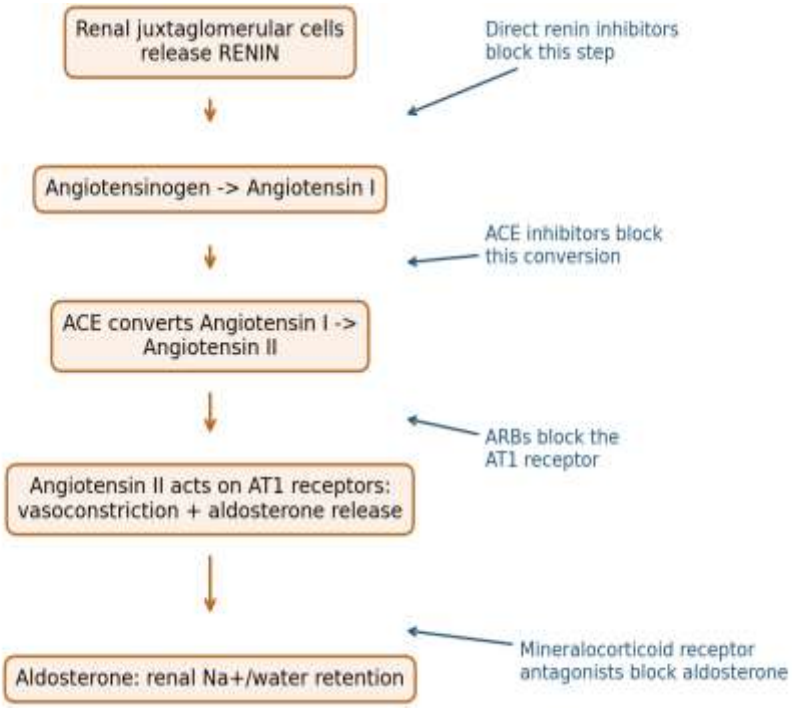

Figure 2. The Renin-Angiotensin-Aldosterone System (Raas) and the Molecular Sites of Action of Raas-Targeting Antihypertensive Drug Classes

4.2.2 Comparative Pharmacology of the Major Drug Classes

Table 3 summarizes the mechanism of action, typical blood-pressure-lowering efficacy, and principal adverse effects of the seven major antihypertensive drug classes in current clinical use. Thiazide and thiazide-like diuretics (e.g., chlorthalidone, indapamide) inhibit the Na^+-Cl^- cotransporter in the distal convoluted tubule, producing natriuresis and, with chronic use, a sustained reduction in peripheral vascular resistance. Calcium channel blockers inhibit L-type calcium channels in vascular smooth muscle (dihydropyridines, e.g., amlodipine) or in both vascular smooth muscle and the myocardium/conduction system (non-dihydropyridines, e.g., diltiazem, verapamil), producing vasodilation and, for non-dihydropyridines, additional negative chronotropic and inotropic effects. ACE inhibitors and angiotensin receptor blockers (ARBs) act at sequential points in the RAAS cascade. Beta-blockers reduce cardiac output and renin release via beta-1 adrenergic receptor antagonism. Mineralocorticoid receptor antagonists block the terminal aldosterone-mediated step of the RAAS cascade.

Table 3. Comparative Pharmacology of Major Antihypertensive Drug Classes

Drug Class	Representative Agents	Mechanism of Action	Typical SBP Reduction (Monotherapy)	Principal Adverse Effects
Thiazide/thiazide-like diuretics	Chlorthalidone, indapamide, hydrochlorothiazide	Inhibits Na^+-Cl^- cotransporter in distal convoluted tubule	8–12 mmHg	Hypokalemia, hyponatremia, hyperuricemia/gout, modest new-onset diabetes

Dihydropyridine CCBs	Amlodipine, nifedipine	L-type calcium channel blockade in vascular smooth muscle	8–12 mmHg	Peripheral edema, flushing, headache, gingival hyperplasia
Non-dihydropyridine CCBs	Diltiazem, verapamil	L-type calcium channel blockade in vascular smooth muscle and cardiac conduction tissue	8–10 mmHg	Bradycardia, atrioventricular block, constipation (verapamil)
ACE inhibitors	Lisinopril, ramipril, enalapril	Inhibits conversion of angiotensin I to angiotensin II	8–10 mmHg	Dry cough, hyperkalemia, angioedema (rare), teratogenicity
Angiotensin receptor blockers	Losartan, valsartan, olmesartan	Competitive antagonism at the AT1 receptor	8–10 mmHg	Hyperkalemia, teratogenicity; better cough tolerability than ACEi
Beta-blockers	Metoprolol, bisoprolol, carvedilol	Beta-1 adrenergic antagonism; reduces cardiac output and renin release	6–8 mmHg	Bradycardia, fatigue, bronchospasm (non-selective), masking of hypoglycemia
Mineralocorticoid receptor antagonists	Spironolactone, eplerenone	Competitive aldosterone antagonism	Adjunctive; 8–10 mmHg in resistant hypertension	Hyperkalemia, gynecomastia (spironolactone), hypotension

4.3 Landmark Randomized Trial Evidence for Blood-Pressure Targets

4.3.1 SPRINT — Intensive Targets in High-Risk, Non-Diabetic Adults

The Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9,361 adults at increased cardiovascular risk, without diabetes, to a systolic blood pressure target of <120 mmHg (intensive) or <140 mmHg (standard) [12]. The trial was stopped early for efficacy after a median follow-up of 3.26 years: the primary composite outcome (myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death) was reduced by 25% in the intensive-treatment group (hazard ratio [HR] 0.75, 95% CI 0.64–0.89), with a 27% reduction in all-cause mortality in extended follow-up analysis.

4.3.2 The STEP Trial — Intensive Targets in an Older Chinese Population

The Strategy of blood pressure intervention in the Elderly hypertensive Population (STEP) trial randomized 8,511 Chinese adults aged 60–80 years to a systolic target of 110–130 mmHg (intensive) or 130–150 mmHg (standard) [13]. Over a median follow-up of 3.34 years, the primary composite outcome

was reduced by 26% in the intensive-treatment group (HR 0.74, 95% CI 0.60–0.92), closely replicating the SPRINT finding in a distinct population and confirming the generalizability of intensive blood-pressure targets across ethnicities and healthcare settings, albeit without a significant effect on all-cause or cardiovascular mortality individually.

4.3.3 ACCORD BP — A Neutral Result in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial randomized 4,733 adults with type 2 diabetes to the same systolic targets as SPRINT (<120 mmHg vs. <140 mmHg) [14]. In contrast to SPRINT and STEP, the primary composite outcome was not significantly reduced (HR 0.88, 95% CI 0.73–1.06), although a pre-specified secondary outcome, total stroke, was significantly reduced. This neutral primary result, despite a similar intensive blood-pressure target to SPRINT, is among the most instructive findings in the hypertension trial literature, illustrating that the benefit of intensive targets is not uniform across all high-risk populations and may be attenuated in the context of pre-existing diabetes, though the trial's factorial design (combined with intensive glycemic and lipid intervention arms) complicates direct comparison with SPRINT.

4.3.4 HYVET — Treatment Benefit in the Very Elderly

The Hypertension in the Very Elderly Trial (HYVET) randomized 3,845 adults aged 80 years or older with systolic blood pressure 160–199 mmHg to indapamide (with or without perindopril, target <150/80 mmHg) or placebo [15]. The trial was stopped early after a second interim analysis showed clear benefit: the primary outcome (fatal or nonfatal stroke) showed a 30% reduction that narrowly missed conventional statistical significance (HR 0.70, 95% CI 0.49–1.01, p = 0.055), while all-cause mortality was significantly reduced by 21% (HR 0.79, 95% CI 0.65–0.95) and heart failure by 64%. HYVET established that antihypertensive treatment provides net benefit even in the oldest old, a population historically underrepresented in hypertension trials and sometimes assumed to derive less benefit or greater harm from treatment.

4.3.5 Synthesis of Effect Sizes

Presents the primary-outcome hazard ratios and 95% confidence intervals for all four trials described above, extracted directly from the primary publications, and Table 4 summarizes their design characteristics.

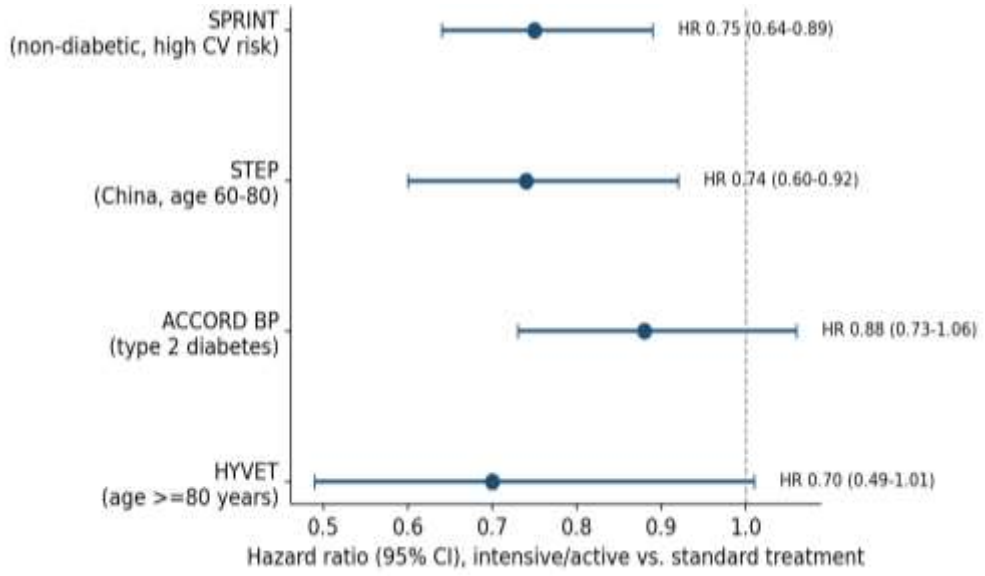

Figure 3. Effect of Intensive or Active Blood-Pressure Lowering on Primary Cardiovascular Composite Outcomes in Landmark Randomized Trials

Table 4. Landmark Randomized Trials Underlying Contemporary Blood-Pressure Targets

Trial	Year	N	Population	Intervention vs. Comparator	Primary Outcome	HR (95% CI)
ACCORD BP	2010	4,733	Type 2 diabetes	SBP <120 vs. <140 mmHg	MI, stroke, or CV death	0.88 (0.73–1.06), NS
HYVET	2008	3,845	Age ≥80 y, SBP 160–199 mmHg	Indapamide ± perindopril vs. placebo	Fatal or nonfatal stroke	0.70 (0.49–1.01)
STEP	2021	8,511	China, age 60–80 y	SBP 110–130 vs. 130–150 mmHg	CV composite	0.74 (0.60–0.92)
SPRINT	2015	9,361	High CV risk, non-diabetic	SBP <120 vs. <140 mmHg	MI, ACS, stroke, HF, or CV death	0.75 (0.64–0.89)

Beyond these four principal trials, earlier evidence from ALLHAT established that thiazide-type diuretics are at least as effective as ACE inhibitors and calcium channel blockers in preventing major cardiovascular events and remain a guideline-recommended first-line option on this basis. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated that an ARB (telmisartan) was non-inferior to an ACE inhibitor (ramipril) for cardiovascular outcomes in high-risk patients, while dual RAAS blockade with both agents combined increased the risk of renal adverse events without incremental cardiovascular benefit, providing the principal evidentiary basis for avoiding routine ACEi–ARB combination therapy [16]. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial subsequently showed that initial combination therapy with an ACE inhibitor plus a dihydropyridine calcium channel blocker reduced cardiovascular events more than an ACE inhibitor plus a thiazide diuretic, providing direct trial support for the combination-therapy principle discussed further in Section 4.6 [17].

4.4 Advertise Effects and Safety Monitoring

Table 5 summarizes the key adverse effects and recommended safety monitoring for each major antihypertensive drug class, synthesized from the trial and pharmacovigilance literature cited throughout this review.

Table 5. Safety Profile and Recommended Monitoring for Antihypertensive Pharmacotherapy

Drug Class	Key Adverse Effects	Recommended Monitoring
Thiazide/thiazide-like diuretics	Hypokalemia, hyponatremia, hyperuricemia, modest increase in new-onset diabetes	Serum sodium, potassium, and uric acid at baseline and periodically
Calcium channel blockers	Peripheral edema (dihydropyridines); bradycardia, AV block (non-dihydropyridines)	Heart rate/rhythm for non-dihydropyridines; clinical assessment for edema
ACE inhibitors	Dry cough, hyperkalemia, angioedema (rare but potentially life-threatening), contraindicated in pregnancy	Serum creatinine and potassium 1–2 weeks after initiation or dose change
ARBs	Hyperkalemia, contraindicated in pregnancy; better cough tolerability than ACE inhibitors	Serum creatinine and potassium 1–2 weeks after initiation or dose change

Beta-blockers	Bradycardia, fatigue, bronchospasm (non-selective agents), masking of hypoglycemia symptoms	Heart rate; caution in reactive airway disease
Mineralocorticoid receptor antagonists	Hyperkalemia, gynecomastia (spironolactone)	Serum potassium at baseline and after initiation, particularly with concurrent ACEi/ARB

4.5 Compelling Indications and Individualized Drug Selection

Beyond blood pressure lowering itself, several antihypertensive drug classes have specific, trial-supported benefits in the presence of comorbid conditions termed "compelling indications" in the ACC/AHA and related guidelines that should inform initial drug selection ahead of a purely blood-pressure-driven choice. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that ramipril reduced cardiovascular death, myocardial infarction, and stroke in high-risk patients independent of its blood-pressure-lowering effect, supporting the use of ACE inhibitors for global cardiovascular risk reduction beyond hypertension alone [18]. In heart failure with reduced ejection fraction, the Randomized Aldactone Evaluation Study (RALES) showed that spironolactone reduced mortality by 30% when added to standard therapy [19], while the PARADIGM-HF trial demonstrated that an angiotensin receptor–neprilysin inhibitor reduced cardiovascular death and heart failure hospitalization compared with an ACE inhibitor alone, extending RAAS-pathway pharmacology into a newer combined drug class [20]. In diabetic nephropathy, the UK Prospective Diabetes Study (UKPDS) demonstrated that tighter blood-pressure control reduced diabetes-related endpoints and microvascular complications, providing long-standing support for RAAS blockade and aggressive blood-pressure control in patients with type 2 diabetes and albuminuria [21]. For resistant hypertension, the PATHWAY-2 trial directly compared spironolactone, bisoprolol, doxazosin, and placebo as fourth-line agents and found spironolactone superior for further blood-pressure reduction, providing the strongest direct trial evidence for the compelling-indication recommendation summarized in Table 6 [22].

Table 6. Compelling Indications for Antihypertensive Drug Class Selection

Comorbid Condition	Preferred Drug Class(es)	Rationale
Diabetes mellitus with albuminuria	ACE inhibitor or ARB	Renoprotective effect independent of blood pressure lowering
Chronic kidney disease with albuminuria	ACE inhibitor or ARB	Reduces intraglomerular pressure; slows proteinuric CKD progression
Heart failure with reduced ejection fraction	ACE inhibitor/ARB/ARNI, beta-blocker, mineralocorticoid receptor antagonist	Each independently reduces mortality and hospitalization
Post-myocardial infarction / high CV risk	ACE inhibitor, beta-blocker	Reduces reinfarction and cardiovascular mortality risk
Atrial fibrillation (rate control need)	Non-dihydropyridine CCB or beta-blocker	Additional rate-control benefit beyond blood pressure lowering
Isolated systolic hypertension in older adults	Thiazide-type diuretic or dihydropyridine CCB	Strong trial evidence, including HYVET, in this population
Pregnancy	Labetalol, nifedipine, methyldopa	ACE inhibitors and ARBs are contraindicated due to fetal teratogenicity

Resistant hypertension (on 3 agents including a diuretic)	Add spironolactone	Demonstrated efficacy in a dedicated resistant-hypertension trial

4.6 Integrated Treatment Algorithm and Guideline Comparison

Synthesizes the evidence and guideline recommendations discussed above into a stepwise, compelling-indication-guided pharmacotherapy algorithm. Current guidance favors initiating combination therapy rather than titrating a single agent to its maximum dose before adding a second for patients with Stage 2 hypertension or those substantially above target, since combination therapy at moderate doses of two complementary-mechanism agents generally achieves greater blood-pressure reduction with fewer dose-dependent adverse effects than maximal-dose monotherapy, a principle directly supported by the ACCOMPLISH trial described in Section 4.3.5.

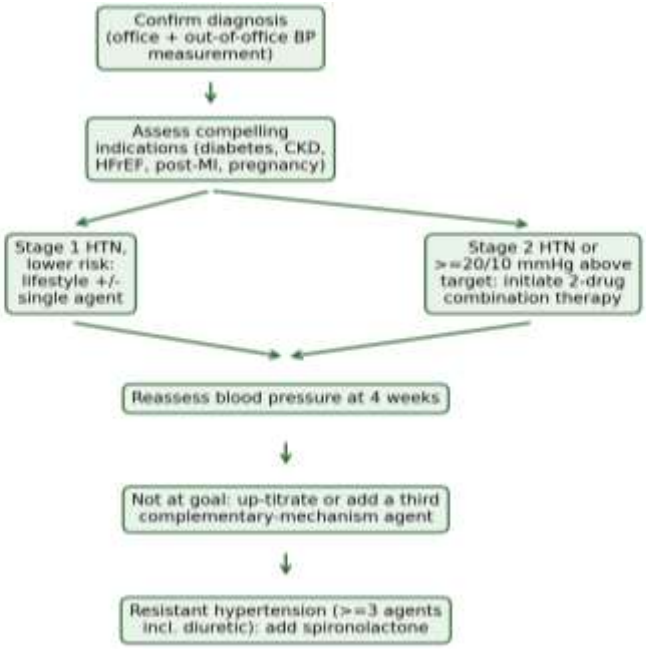

Figure 4. Integrated, Stepwise Pharmacotherapy Algorithm for Hypertension Management, Synthesized from Current ACC/AHA Guidance and the Trial Evidence Summarized in Table 4

Table 7 compares the blood-pressure targets recommended by three major international guideline bodies, reflecting some continued divergence in target thresholds despite substantially overlapping underlying trial evidence, consistent with the guideline history discussed in Section 2.

Table 7. Comparison of Blood-Pressure Targets across Major International Guidelines

Guideline Body	General Adult Target	Target in Older Adults	Target in Diabetes	Target in CKD with Albuminuria
2017 ACC/AHA (USA)	<130/80 mmHg	<130/80 mmHg (individualized for frailty)	<130/80 mmHg	<130/80 mmHg
2023 ESH (Europe)	<140/90 mmHg, <130/80 if tolerated	<140/90 mmHg	<130/80 mmHg if tolerated	<130/80 mmHg
WHO 2021 Guideline	<140/90 mmHg	<140/90 mmHg	<130/80 mmHg	<130/80 mmHg

The trial evidence synthesized above supports several pharmacologically and clinically important conclusions. First, the consistency of benefit from intensive blood-pressure lowering across SPRINT and the STEP trial—conducted on different continents, in different healthcare systems, and in different ethnic populations, yet yielding remarkably similar hazard ratios (0.75 and 0.74, respectively)—provides strong support for a generalizable, mechanism-based rather than population-specific benefit of lower systolic targets in appropriately selected high-risk adults. Second, the neutral result of ACCORD BP in a diabetic population, despite an identical intensive target to SPRINT, is a critical reminder that trial results cannot be extrapolated uncritically across populations; the reasons for this attenuated benefit remain incompletely understood but may relate to the trial's smaller sample size, its factorial design combining intensive glycemic and lipid intervention, or a genuine biological difference in the blood-pressure–cardiovascular-risk relationship in diabetes. Third, HYVET's demonstration of net benefit in adults aged 80 and older, despite this population's higher competing mortality risk and theoretical vulnerability to treatment-related hypotension, supports extending evidence-based antihypertensive therapy into advanced age rather than withholding treatment on the basis of age alone, while also illustrating that a more conservative target (<150/80 mmHg rather than <120 mmHg systolic) was used successfully in this specific very-elderly population.

The pharmacological diversity summarized—spanning renal sodium handling, vascular smooth muscle calcium channels, and multiple sequential points in the RAAS cascade—provides the mechanistic basis for rational combination therapy, since agents with non-overlapping mechanisms produce more than additive blood-pressure reduction while allowing each individual agent to be used at a lower, better-tolerated dose. This principle directly underlies the combination-therapy-first approach reflected and increasingly endorsed by contemporary guidelines over the historical strategy of sequential monotherapy titration. The compelling-indication framework summarized further demonstrates that drug selection in hypertension is rarely a single blood-pressure-driven decision; rather, it requires simultaneous consideration of comorbid diabetes, chronic kidney disease, heart failure, coronary disease, and pregnancy status, each of which is supported by dedicated outcome-trial evidence rather than extrapolation from blood-pressure-lowering efficacy alone.

This is a narrative rather than a systematic review, and no formal meta-analytic pooling or risk-of-bias assessment was performed. Cross-trial comparison of the hazard ratios is subject to important caveats, including differing populations (age, diabetes status, baseline cardiovascular risk), differing blood-pressure targets and measurement methodology—SPRINT's unattended automated office blood-pressure measurement technique, in particular, is known to yield systematically lower readings than routine clinical measurement, complicating direct translation of its numerical targets into everyday practice—and differing primary-outcome definitions, such that the figures should not be read as a direct head-to-head efficacy ranking. Guideline target discrepancies reflect genuine, unresolved differences in expert interpretation of the same underlying trial base rather than new evidence reviewed independently by the present authors. Real-world adherence, cost, and access to combination pharmacotherapy, particularly in low- and middle-income countries where the majority of the global hypertension burden now resides, were outside the scope of this pharmacological review and represent important directions for future implementation-focused research.

A further practical implication concerns the sequencing of pharmacotherapy relative to lifestyle intervention. None of the landmark trials summarized tested pharmacotherapy in isolation from concurrent dietary sodium reduction, weight management, or physical activity counselling, and current guidelines uniformly recommend that lifestyle modification accompany, rather than precede or substitute for, pharmacological treatment once a patient meets criteria for drug therapy. Similarly, the compelling-indication framework, while grounded in dedicated outcome trials for each condition listed, assumes that clinicians have access to the laboratory monitoring summarized; in settings where creatinine and potassium monitoring is not readily available, simplified first-line regimens of the type recommended by the WHO 2021 guideline may be more feasible than the more granular compelling-indication algorithm favored by the ACC/AHA and ESH documents. This tension between guideline granularity and real-world feasibility is itself an important, underappreciated determinant of the persistent gap between trial evidence

and population-level blood-pressure control described in Section 1, and future revisions of international guidance may benefit from explicitly tiered recommendations calibrated to the level of monitoring infrastructure available in a given health system.

5. CONCLUSION

Hypertension pharmacotherapy is supported by an exceptionally deep and mechanistically diverse randomized-trial evidence base, spanning seven major drug classes and multiple landmark outcome trials establishing both the benefit and the population-specific boundaries of intensive blood-pressure lowering. As synthesized in this review, contemporary management increasingly favors early combination therapy, compelling-indication-guided drug selection, and individualized targets that account for age, diabetes status, and comorbidity, over a one-size-fits-all approach. Despite this strong evidence base, global blood-pressure control rates remain poor, with fewer than one in four affected adults achieving adequate control worldwide. Closing the gap between trial evidence and real-world implementation—through improved screening, earlier treatment intensification, wider use of rational early combination therapy, and sustained access to pharmacotherapy in low- and middle-income countries—represents one of the single largest opportunities for reducing the global burden of cardiovascular disease.

Acknowledgments

The authors have no specific acknowledgments to make for this research.

Funding Information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Makbul Hussain Choudhury	✓	✓	✓	✓		✓		✓	✓	✓	✓			

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not Applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to Cite: Dr. Makbul Hussain Choudhury. (2026). Pharmacological management of hypertension: a comprehensive narrative review of diagnostic classification, mechanism-based drug therapy, and landmark outcome trial evidence. Journal of Prevention, Diagnosis and Management of Human Diseases (JPDMHD), 5(2), 80-94. https://doi.org/10.55529/jpdmhd.52.80.94

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