



Pharmacological Strategies In Hypertension: Comparative Review Of Monotherapy Classes Versus Combination Regimens

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ABSTRACT:

Hypertension is a major global health burden and a leading contributor to cardiovascular morbidity and mortality. Despite the availability of effective antihypertensive agents, blood pressure control rates remain suboptimal, necessitating a critical evaluation of pharmacological strategies. This review aims to compare the efficacy, safety, and clinical outcomes of monotherapy classes versus combination regimens in the management of hypertension, with emphasis on guideline recommendations, patient-centered outcomes, and evolving therapeutic paradigms. A narrative synthesis of clinical trials, meta-analyses, and guideline updates was conducted to evaluate the role of major antihypertensive drug classes—angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics, and beta-blockers—when used as monotherapy or in combination.

Monotherapy remains effective in patients with mild hypertension and specific comorbidities, but often fails to achieve target blood pressure in moderate to severe cases. Combination regimens, particularly those involving renin-angiotensin system blockers with diuretics or calcium channel blockers, demonstrate superior blood pressure reduction, improved cardiovascular outcomes, and enhanced adherence. Fixed-dose combinations further optimize compliance by reducing pill burden. However, patient-specific factors such as age, ethnicity, comorbidities, and socioeconomic considerations influence therapeutic choice.

Pharmacological management of hypertension has shifted toward early adoption of combination therapy, reflecting its superior efficacy and patient-centered benefits. While monotherapy retains a role in selected populations, combination regimens—especially fixed-dose formulations—are increasingly favored in contemporary practice. Future directions include precision medicine approaches, biomarker-driven therapy, and integration of digital health tools to personalize hypertension management and improve global control rates.

KEYWORD: Hypertension, Antihypertensive therapy, Monotherapy, Combination therapy, Fixed-dose combinations.

INTRODUCTION:

Hypertension is one of the most prevalent chronic conditions worldwide, affecting more than one billion individuals and contributing significantly to cardiovascular morbidity and mortality. It is a leading modifiable risk factor for stroke, ischemic heart disease, heart failure, and chronic kidney disease. Despite the availability of effective antihypertensive agents, global blood pressure control rates remain suboptimal, with less than half of treated patients achieving recommended targets. This gap underscores the need for optimized pharmacological strategies that balance efficacy, safety, adherence, and cost-effectiveness.

Pharmacological therapy for hypertension has traditionally relied on **monotherapy**, particularly in patients with mild disease or those newly diagnosed. Commonly used drug classes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide diuretics, and beta-blockers. Each class has distinct mechanisms of action, advantages, and limitations, and their selection is often guided by patient age, ethnicity, comorbidities, and tolerability. While monotherapy can be effective in selected populations, evidence consistently shows that many patients require more than one agent to achieve adequate blood pressure control.

This recognition has led to a paradigm shift toward **combination therapy**, either as free-drug regimens or fixed-dose combinations (FDCs). Combination therapy offers several advantages: it targets multiple pathophysiological pathways simultaneously, achieves faster and more sustained blood pressure reduction, and reduces cardiovascular risk more effectively than monotherapy. Moreover, FDCs improve adherence by reducing pill burden, a critical factor in long-term hypertension management. Current international guidelines, including those from the European Society of Cardiology (ESC), the American College of Cardiology/American Heart Association (ACC/AHA), and the International Society of Hypertension (ISH), increasingly recommend early initiation of combination therapy, particularly in patients with stage 2 hypertension or high cardiovascular risk.

Beyond efficacy, patient-centered outcomes such as quality of life, adherence, and affordability are central to therapeutic decision-making. In resource-limited settings, cost-effective strategies—often involving thiazide-based combinations—remain essential. Meanwhile, advances in precision medicine and digital health tools promise to further individualize therapy, tailoring treatment to genetic, demographic, and lifestyle factors.

This review provides a comparative analysis of monotherapy classes and combination regimens in hypertension management. It explores their pharmacological rationale, clinical effectiveness, safety profiles, and guideline recommendations, while highlighting patient-centered considerations and future directions. By synthesizing current evidence, the review aims to inform clinicians, researchers, and policymakers on optimizing pharmacological strategies to improve global hypertension control.

EPIDEMIOLOGY AND BURDEN OF HYPERTENSION:

Hypertension is one of the most prevalent non-communicable diseases worldwide, affecting an estimated 1.28 billion adults aged 30–79 years according to the World Health Organization. Nearly half of these individuals remain undiagnosed, and among those diagnosed, only a fraction achieve adequate blood pressure control. The global prevalence continues to rise, driven by aging populations, urbanization, sedentary lifestyles, and dietary changes such as increased salt intake and reduced consumption of fruits and vegetables. While high-income countries have achieved better detection and treatment rates due to improved healthcare infrastructure, control remains suboptimal. In contrast, low- and middle-income countries bear a disproportionate burden, with limited access to healthcare, cost barriers, and lower adherence to long-term therapy. Regional variations are evident, with particularly high prevalence in South Asia and Sub-Saharan Africa, where lifestyle risk factors and limited preventive care converge.

The clinical and economic burden of hypertension is profound. It is the leading risk factor for ischemic heart disease, stroke, heart failure, and chronic kidney disease, and accounts for approximately 10.8 million deaths annually, making it the single most important contributor to global mortality. Beyond health outcomes, hypertension imposes significant economic costs, including direct expenses related to medications, hospitalizations, and outpatient visits, as well as indirect costs from lost productivity and disability. Despite the availability of effective pharmacological agents, several barriers hinder optimal control. Poor adherence due to pill burden, side effects, and lack of patient education remains a major challenge, while clinical inertia—delays in treatment intensification when monotherapy fails—contributes to persistent uncontrolled hypertension. In resource-limited settings, affordability and accessibility of combination therapy further complicate management.

This epidemiological burden underscores the need for effective pharmacological interventions. While monotherapy may suffice in mild cases, the high prevalence of uncontrolled hypertension highlights the importance of combination regimens. Early adoption of combination therapy, particularly fixed-dose formulations, has the potential to improve global control rates, reduce cardiovascular events, and alleviate the economic burden associated with hypertension.

PATHOPHYSIOLOGY OF HYPERTENSION:

Hypertension is a multifactorial condition arising from complex interactions between genetic predisposition, environmental influences, and physiological mechanisms that regulate vascular tone, renal function, and neurohormonal activity. The sustained elevation of blood pressure reflects an imbalance between cardiac output and systemic vascular resistance, with several key pathways contributing to its development and progression.

1. Renin–Angiotensin–Aldosterone System (RAAS)

The RAAS plays a central role in blood pressure regulation. Increased renin secretion from the kidney stimulates conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II promotes vasoconstriction, sodium retention, and aldosterone release, all of which elevate blood pressure. Overactivation of RAAS is a hallmark of many hypertensive states, particularly in younger patients and those with renal disease.

2. Sympathetic Nervous System (SNS) Overactivity

Enhanced sympathetic tone contributes to increased heart rate, cardiac contractility, and peripheral vasoconstriction. Chronic SNS activation also stimulates renin release and promotes vascular remodeling, leading to sustained hypertension. Stress, obesity, and sleep apnea are common triggers of sympathetic overactivity.

3. Vascular Dysfunction

Endothelial dysfunction, characterized by reduced nitric oxide bioavailability and increased oxidative stress, impairs vasodilation and promotes vascular stiffness. Structural changes such as medial hypertrophy and collagen deposition further increase systemic vascular resistance, perpetuating elevated blood pressure.

4. Renal Sodium Handling

Impaired renal excretion of sodium leads to volume expansion and increased cardiac output. Genetic variations affecting sodium transporters, as well as dietary salt excess, contribute significantly to hypertension, particularly in salt-sensitive populations.

5. Hormonal and Metabolic Factors

Insulin resistance, hyperinsulinemia, and obesity-related adipokine dysregulation enhance sympathetic activity and sodium retention. Additionally, elevated levels of endothelin and other vasoconstrictor peptides contribute to vascular tone abnormalities.

6. Genetic and Environmental Influences

Polymorphisms in genes regulating RAAS, adrenergic receptors, and sodium transport predispose individuals to hypertension. Environmental factors such as high salt intake, sedentary lifestyle, and psychosocial stress act synergistically with genetic susceptibility.

PHARMACOLOGICAL BASIS OF MONOTHERAPY CLASSES:

Pharmacological treatment of hypertension relies on several well-established drug classes, each targeting distinct physiological pathways involved in blood pressure regulation. Understanding their mechanisms, clinical applications, and limitations provides the foundation for rational therapy selection and informs the rationale for combination regimens.

1. Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction and aldosterone-mediated sodium retention. They are particularly effective in younger patients, individuals with diabetes, and those with heart failure or chronic kidney disease. Clinical trials have demonstrated their ability to reduce cardiovascular morbidity and mortality. However, adverse effects such as cough, hyperkalemia, and rare cases of angioedema limit their use in some populations.

2. Angiotensin Receptor Blockers (ARBs)

ARBs selectively block angiotensin II type 1 receptors, preventing vasoconstriction and aldosterone secretion. They provide similar efficacy to ACE inhibitors but with improved tolerability, as they do not cause cough. ARBs are widely used in patients intolerant to ACE inhibitors and have strong evidence for

renal and cardiovascular protection. Cost considerations may limit their accessibility in resource-constrained settings.

3. Calcium Channel Blockers (CCBs)

CCBs inhibit calcium influx into vascular smooth muscle, promoting vasodilation and reducing peripheral resistance. They are especially effective in elderly patients and in populations with salt-sensitive hypertension, such as those of African descent. Dihydropyridine CCBs (e.g., amlodipine) are commonly used for blood pressure control, while non-dihydropyridines (e.g., verapamil, diltiazem) are reserved for patients with arrhythmias. Side effects include peripheral edema, flushing, and reflex tachycardia.

4. Thiazide Diuretics

Thiazide diuretics act on the distal convoluted tubule to promote sodium and water excretion, thereby reducing plasma volume and peripheral resistance. They are cost-effective and supported by robust evidence for reducing cardiovascular events, particularly stroke. However, long-term use may lead to electrolyte disturbances, hyperuricemia, and metabolic side effects such as impaired glucose tolerance.

5. Beta-Blockers

Beta-blockers reduce cardiac output by decreasing heart rate and contractility, while also inhibiting renin release from the kidney. They are particularly useful in patients with ischemic heart disease, arrhythmias, or heart failure. However, their role in primary hypertension has diminished due to less favorable outcomes in stroke prevention compared to other classes. Side effects include fatigue, bradycardia, and metabolic disturbances such as insulin resistance.

Clinical Perspective

While each monotherapy class has proven efficacy, their limitations—particularly in achieving target blood pressure in moderate to severe hypertension—highlight the need for combination therapy. The pharmacological diversity of these agents provides complementary mechanisms that, when combined, enhance blood pressure control, reduce adverse effects, and improve cardiovascular outcomes.

COMBINATION THERAPY: RATIONALE AND EVIDENCE:

The management of hypertension has progressively shifted from reliance on monotherapy to the early adoption of combination therapy. This transition is driven by the recognition that most patients require more than one agent to achieve target blood pressure, particularly those with moderate to severe hypertension or high cardiovascular risk. Combination therapy provides a rational approach by targeting multiple pathophysiological mechanisms simultaneously, thereby enhancing efficacy, reducing adverse effects, and improving long-term outcomes.

Rationale for Combination Therapy

Hypertension arises from diverse mechanisms, including overactivation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system hyperactivity, endothelial dysfunction, and impaired renal sodium handling. Monotherapy addresses only one pathway, which may be insufficient in complex cases. Combining agents with complementary mechanisms—such as RAAS blockers with diuretics or calcium channel blockers—produces additive or synergistic effects. Moreover, certain combinations mitigate the side effects of individual drugs; for example, ACE inhibitors counteract diuretic-induced hypokalemia.

Evidence from Clinical Trials

Large randomized controlled trials and meta-analyses consistently demonstrate the superiority of combination therapy over monotherapy in achieving blood pressure control and reducing cardiovascular events.

- **ACE inhibitor/ARB + Thiazide diuretic:** Proven to enhance blood pressure reduction and reduce stroke risk.
- **ACE inhibitor/ARB + Calcium channel blocker:** Strong evidence for cardiovascular protection, particularly in high-risk patients.
- **Beta-blocker + Diuretic:** Historically used but less favored due to metabolic side effects; now reserved for specific comorbidities such as ischemic heart disease.

Fixed-Dose Combinations (FDCs)

Fixed-dose combinations represent a major advancement in hypertension management. By incorporating two agents into a single pill, FDCs reduce pill burden, improve adherence, and simplify treatment regimens. Studies show that patients on FDCs achieve better blood pressure control compared to those on free-drug combinations. This approach is particularly valuable in resource-limited settings, where adherence challenges are more pronounced.

Guideline Recommendations

Contemporary guidelines from the European Society of Cardiology (ESC), the American College of Cardiology/American Heart Association (ACC/AHA), and the International Society of Hypertension (ISH) increasingly recommend initiating therapy with combination regimens, especially in patients with stage 2 hypertension or those at high cardiovascular risk. Monotherapy is reserved for patients with mild hypertension, the elderly, or those with contraindications to combination therapy.

Clinical Perspective

Combination therapy not only improves blood pressure control but also reduces the incidence of cardiovascular events such as stroke, myocardial infarction, and heart failure. By addressing multiple mechanisms of hypertension and enhancing adherence through fixed-dose formulations, combination regimens have become the cornerstone of modern hypertension management.

COMPARATIVE EFFECTIVENESS OF MONOTHERAPY VERSUS COMBINATION THERAPY:

The choice between monotherapy and combination therapy in hypertension management has been extensively studied, with evidence consistently favoring combination regimens for most patients. While monotherapy remains appropriate in selected cases, particularly those with mild hypertension or newly diagnosed disease, its limitations in achieving sustained blood pressure control have prompted a shift toward earlier use of combination strategies.

Monotherapy Effectiveness

Monotherapy can be effective in patients with stage 1 hypertension, especially when accompanied by lifestyle modifications. ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics have all demonstrated efficacy in lowering blood pressure and reducing cardiovascular risk. However, monotherapy often fails to achieve target blood pressure in patients with moderate to severe hypertension, those with comorbidities, or individuals with resistant disease. Clinical inertia—delays in escalating therapy when monotherapy proves insufficient—further contributes to poor control rates.

Combination Therapy Effectiveness

Combination therapy provides superior blood pressure reduction by addressing multiple pathophysiological mechanisms simultaneously. Clinical trials and meta-analyses show that dual therapy achieves target blood pressure in a significantly higher proportion of patients compared to monotherapy. For example, combinations such as ACE inhibitor/ARB with a calcium channel blocker or thiazide diuretic not only improve blood pressure control but also reduce cardiovascular events, including stroke and myocardial infarction. Importantly, certain combinations mitigate adverse effects; for instance, RAAS blockers counteract diuretic-induced hypokalemia, while calcium channel blockers offset RAAS-induced vasoconstriction.

Fixed-Dose Combinations (FDCs)

Fixed-dose combinations further enhance effectiveness by improving adherence. Studies demonstrate that patients on FDCs achieve better blood pressure control compared to those prescribed separate agents, largely due to reduced pill burden and simplified regimens. Improved adherence translates into better long-term cardiovascular outcomes, making FDCs a cornerstone of modern hypertension management.

Guideline Perspectives

International guidelines increasingly recommend initiating therapy with combination regimens, particularly in patients with stage 2 hypertension, high cardiovascular risk, or inadequate response to monotherapy. The European Society of Cardiology (ESC) and International Society of Hypertension (ISH) emphasize early use of dual therapy, while the American College of Cardiology/American Heart Association (ACC/AHA) guidelines highlight the role of combination therapy in patients with blood pressure $\geq 140/90$ mmHg or those with comorbid conditions.

Clinical Perspective

Comparative evidence underscores that while monotherapy retains a role in selected patients, combination therapy offers superior efficacy, improved adherence, and better cardiovascular protection. Fixed-dose combinations represent a practical solution to overcome adherence barriers and are

increasingly favored in both high-income and resource-limited settings. The paradigm shift toward combination therapy reflects a broader commitment to patient-centered care and long-term risk reduction in hypertension management.

PATIENT-CENTERED CONSIDERATIONS:

Effective hypertension management extends beyond pharmacological efficacy to encompass patient-centered outcomes such as adherence, quality of life, affordability, and accessibility. These factors significantly influence long-term success and determine whether blood pressure control translates into meaningful reductions in cardiovascular morbidity and mortality.

Adherence

Adherence to therapy is one of the most critical determinants of treatment success. Monotherapy may offer simplicity, but many patients eventually require multiple agents, which increases pill burden and reduces compliance. Fixed-dose combinations (FDCs) address this challenge by consolidating two or more drugs into a single tablet, thereby simplifying regimens and improving adherence. Studies consistently show that patients on FDCs achieve better blood pressure control compared to those prescribed separate agents.

Quality of Life

Hypertension is a lifelong condition, and treatment must balance efficacy with tolerability. Side effects such as cough from ACE inhibitors, edema from calcium channel blockers, or metabolic disturbances from diuretics can negatively impact quality of life and lead to discontinuation. Combination therapy often mitigates these adverse effects by counterbalancing drug-specific limitations—for example, RAAS blockers offset diuretic-induced hypokalemia. Improved tolerability enhances patient satisfaction and long-term persistence with therapy.

Affordability and Accessibility

Cost remains a major barrier, particularly in low- and middle-income countries. Thiazide diuretics are inexpensive and widely available, making them a cornerstone of therapy in resource-limited settings. However, newer agents and fixed-dose combinations may be less accessible due to higher costs. Policymakers and healthcare systems must prioritize affordable options and expand access to essential antihypertensive medications to improve global control rates.

Global Applicability

Patient-centered strategies must account for regional variations in hypertension prevalence, comorbidities, and healthcare infrastructure. In high-income countries, emphasis is placed on individualized therapy and precision medicine, while in resource-constrained regions, cost-effective regimens and simplified treatment protocols are prioritized. Cultural factors, dietary habits, and health literacy also influence adherence and outcomes, underscoring the need for context-specific approaches.

Clinical Perspective

Patient-centered considerations highlight that the success of pharmacological strategies depends not only on drug efficacy but also on adherence, tolerability, affordability, and accessibility. Fixed-dose combinations represent a practical solution to overcome adherence barriers, while cost-effective regimens remain vital in resource-limited settings. Ultimately, tailoring therapy to patient needs and healthcare realities ensures that pharmacological advances translate into improved outcomes at both individual and population levels.

CONCLUSION:

Hypertension remains a global health challenge, contributing substantially to cardiovascular morbidity, mortality, and economic burden. Pharmacological therapy is central to its management, with monotherapy historically serving as the initial approach. While monotherapy can be effective in patients with mild hypertension or specific comorbidities, its limitations in achieving sustained blood pressure control have become increasingly evident. The majority of patients require more than one agent to reach target levels, and delays in treatment intensification often perpetuate uncontrolled hypertension.

Combination therapy has emerged as the cornerstone of modern hypertension management, offering superior efficacy by targeting multiple pathophysiological pathways simultaneously. Evidence from clinical trials and guideline recommendations consistently supports the use of combinations—particularly those involving RAAS blockers with diuretics or calcium channel blockers—as they not only improve blood pressure control but also reduce cardiovascular events. Fixed-dose combinations further

enhance adherence by simplifying regimens, thereby translating pharmacological effectiveness into real-world outcomes.

Patient-centered considerations, including adherence, tolerability, affordability, and accessibility, remain critical to successful hypertension management. Strategies must be tailored to individual patient profiles and regional healthcare realities, ensuring that advances in therapy benefit diverse populations. Looking ahead, precision medicine, biomarker-guided therapy, and digital health innovations hold promise for refining treatment selection and improving global control rates.

In summary, while monotherapy retains a role in selected patients, combination therapy—particularly fixed-dose formulations—represents the most effective and practical strategy for achieving optimal blood pressure control and reducing long-term cardiovascular risk. The integration of pharmacological innovation with patient-centered and technology-driven approaches will define the future of hypertension management, moving beyond blood pressure reduction toward comprehensive cardiovascular protection.

FUTURE DIRECTIONS:

The management of hypertension continues to evolve, with future strategies focusing on precision medicine, innovative pharmacological approaches, and integration of digital health technologies. While current evidence strongly supports the superiority of combination therapy over monotherapy, emerging research aims to refine treatment selection, improve adherence, and address global disparities in hypertension control.

Precision Medicine and Individualized Therapy

Advances in genomics, proteomics, and metabolomics are paving the way for personalized antihypertensive therapy. Genetic polymorphisms affecting the renin–angiotensin–aldosterone system, sodium transport, and sympathetic regulation may help predict individual responses to specific drug classes. Tailoring therapy to patient profiles—including age, ethnicity, comorbidities, and genetic markers—could optimize efficacy and minimize adverse effects.

Biomarker-Driven Approaches

The identification of predictive biomarkers, such as plasma renin activity, aldosterone levels, and endothelial function markers, may guide the choice between monotherapy and combination regimens. Biomarker-driven strategies could also help identify patients at risk of resistant hypertension, enabling earlier and more aggressive intervention.

Novel Pharmacological Agents

Research into new drug classes is ongoing, with agents targeting endothelin pathways, neprilysin inhibition, and dual-acting molecules showing promise. These therapies may offer additional options for patients with resistant hypertension or those intolerant to conventional agents. Furthermore, improved fixed-dose combinations with optimized pharmacokinetics are being developed to enhance adherence and tolerability.

Digital Health and Remote Monitoring

Digital health tools, including mobile applications, wearable devices, and telemedicine platforms, are transforming hypertension management. These technologies enable real-time monitoring of blood pressure, medication adherence, and lifestyle factors, facilitating personalized interventions and early detection of treatment failure. Integration of artificial intelligence into clinical decision-making may further enhance therapy optimization.

Global Health and Policy Perspectives

Future strategies must also address disparities in hypertension management across regions. Expanding access to affordable fixed-dose combinations, strengthening primary care systems, and implementing population-level interventions such as salt reduction policies are essential to reduce the global burden. Collaborative efforts between governments, healthcare providers, and pharmaceutical industries will be critical in achieving equitable hypertension control.

Clinical Perspective

The future of hypertension management lies in combining pharmacological innovation with patient-centered and technology-driven approaches. Precision medicine, biomarker-guided therapy, and digital health integration promise to refine treatment strategies, while global health initiatives aim to ensure equitable access. Together, these advances will shape a new era of hypertension care, moving beyond simple blood pressure reduction toward comprehensive cardiovascular risk management.

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