WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 6, 320-342. Review Article ISSN 2277–7105

COMPARATIVE STUDY OF MONOTHERAPY VERSUS COMBINATION THERAPY IN HYPERTENSION MANAGEMENT

D. Jothieswari*[1], Are Jayasri[2], Ankem Gayathri[3], Billupati Pavan[4], Achukatla Afroze Ali[5], Bogguru Manoj Kumar[6]

[1]Professor and Principal, Dept of Pharmaceutical Analysis, Sri Venkateswara College of Pharmacy.

[2]Pharm.D, Assistant Professor, Department of Pharmacy Practice, Sri Venkateswara College of Pharmacy.

[3,4]Professor and Principal, Dept of Pharmaceutical Analysis, Sri Venkateswara College of Pharmacy (Autonomous) RVS Nagar Tirupati Main Road, Chittoor -517127, AP.

[5,6]Pharm.D, Assistant Professor, Department of Pharmacy Practise, Sri Venkateswara College of Pharmacy (Autonomous) RVS Nagar Tirupati Main Road, Chittoor -517127, AP.

Article Received on 11 Feb. 2026,
Article Revised on 03 March 2026,
Article Published on 16 March 2026,

https://doi.org/10.5281/zenodo.19044277

***Corresponding Author**
D. Jothieswari
Professor and Principal, Dept. of Pharmaceutical Analysis, Sri Venkateswara College of Pharmacy, (Autonomous) RVS Nagar Tirupati Main Road, Chittoor -517127, AP.

How to cite this Article: D. Jothieswari*[1], Are Jayasri[2], Ankem Gayathri[3], Billupati Pavan[4], Achukatla Afroze Ali[5], Bogguru Manoj Kumar[6]. (2026). Comparative Study of Monotherapy Versus Combination Therapy In Hypertension Management. World Journal of Pharmaceutical Research, 15(6), 320–342.

ABSTRACT

Background: Hypertension is a major global public health problem and a leading risk factor for cardiovascular morbidity and mortality. Patients do not achieve proper blood pressure control because they have access to effective antihypertensive medications. The treatment guidelines currently recommend healthcare providers to select between single-drug treatment and multiple-drug treatment based on three factors which include the patient's hypertension severity and their personal attributes and existing medical conditions. **Objective:** The study compares monotherapy and combination therapy to determine which treatment option provides better outcomes for hypertension treatment through blood pressure control and safety measures and treatment effectiveness. **Methods:** The researchers conducted this study to compare blood pressure control between two treatment methods which included monotherapy and combination antihypertensive therapy for their research. The researchers collected data about the patient population through assessment of their demographic

information and initial blood pressure readings and their treatment methods and both their blood pressure reduction results and their success in reaching target blood pressure levels and their experience with adverse drug reactions. The researchers used statistical methods to examine the treatment group differences between the two study groups. **Results:** Combination therapy provided better blood pressure control results than monotherapy because more patients reached their target blood pressure goals. The group that used combination therapy experienced more substantial reductions in both systolic and diastolic blood pressure measurements. The combination therapy produced more side effects than standard treatment but the resulting side effects were mostly minor and could be treated. The monotherapy treatment method achieved successful results for patients who had mild cases of hypertension. **Conclusion:** Combination therapy is more effective than monotherapy in achieving optimal blood pressure control, particularly in patients with moderate to severe hypertension. However, monotherapy remains a suitable initial approach for selected patients with mild hypertension. Individualized treatment selection based on patient profile and disease severity is essential for effective hypertension management.

KEYWORDS: Hypertension, monotherapy, combination therapy, blood pressure management, cardiovascular risk.

INTRODUCTION

Burden of Hypertension

The World Health Organization considers hypertension a critical public health issue that affects over one billion people because its rates keep rising with the dual effects of aging populations and changed lifestyle patterns.[1] Elevated blood pressure stands as a top global health risk because it generates cardiovascular diseases and stroke and chronic kidney disease. Global Burden of Disease studies have shown hypertension to be a primary reason for disability-adjusted life years (DALYs) because it causes long-term health problems and early death. The burden of hypertension exists at a higher level in low- and middle-income countries because they lack adequate healthcare facilities to manage the condition which affects approximately two-thirds of their hypertension cases.[2] The increasing rates of hypertension in developing areas result from several factors including rapid urban growth and unhealthy eating patterns and high salt consumption and lack of physical activity and obesity and tobacco and dangerous alcohol use. Hypertension rates remain high in high-income countries because people age and their lifestyle-related risk factors continue to exist, even

though treatment and awareness level have risen. The economic burden of hypertension on healthcare systems rises because of increased costs for both outpatient services and hospital stays and treatment of cardiovascular diseases.[3] Poor blood pressure control leads to increased risk for cardiovascular events, which include myocardial infarction, heart failure and stroke, that will happen to the patient. The asymptomatic nature of hypertension in its early stages causes doctors to miss detecting the condition which results in more severe health problems for patients. The world faces a major issue because people cannot control their blood pressure even though doctors have various effective blood pressure medications and scientific clinical guidelines at their disposal. The world suffers from ineffective hypertension treatment because patients fail to take their medications and healthcare systems lack proper delivery methods.[4,5] International and national guidelines emphasize early detection, lifestyle modification, and appropriate pharmacological intervention as essential strategies to reduce the burden of hypertension-related complications. The World Health Organization has identified hypertension control as a priority target for reducing the global burden of non-communicable diseases. Epidemiological studies that extend over long periods show that people who manage their blood pressure successfully experience fewer cardiovascular health problems and lower death rates.[6] The increasing problem of hypertension must receive urgent attention because it leads to more premature deaths while creating severe health problems worldwide.

Need for Effective Pharmacotherapy in Hypertension

Hypertension serves as a significant modifiable risk factor which increases the chances of both cardiovascular diseases and death, while ongoing high blood pressure conditions create an elevated stroke risk and myocardial infarction risk and heart failure risk and chronic kidney disease risk, which requires complete medication treatment to decrease these health risks. The need for blood pressure control through medical treatment becomes essential because patients with moderate to severe hypertension require treatment which helps them achieve and maintain their blood pressure goals.[6,7] Antihypertensive drug therapy combined with early treatment methods, which begin with actual medical procedures, has decreased cardiovascular events and total mortality rates. Hypertension treatment through effective medications protects against blood pressure-induced damage to vital organs by preventing conditions like left ventricular hypertrophy and nephropathy and retinopathy, which results in better clinical results. The complex nature of hypertension development requires blood pressure treatment through multiple pharmacological agents, which should include

medications that target different bodily systems such as renin–angiotensin–aldosterone system and sympathetic nervous system and vascular tone system. The requirement for evidence-based pharmacotherapy methods exists because poorly managed hypertension remains a widespread issue which affects global populations due to treatment deficiencies and medical staff failures to implement necessary actions.[8]

Rationale for comparing monotherapy vs combination therapy

The management of hypertension often begins with monotherapy, but many patients fail to achieve target blood pressure with a single agent, highlighting the potential benefit of combination therapy to improve efficacy. The side effects from individual drugs restrict monotherapy, but combination therapy enables users to take two or more drugs at lower doses, which decreases side effects while increasing blood pressure treatment success.[9] The research shows that combination therapy especially fixed-dose combinations lead to better patient compliance and medication persistence than using multiple distinct drugs, which is essential for treating chronic disorders like hypertension. The treatment of hypertension occurs through various pathways because the disease develops from multiple factors and combination therapy shows better cardiovascular benefits through its mechanism-based treatment than monotherapy.[10] The clinical trials show that combination therapy achieves blood pressure targets faster and in more patients compared to monotherapy, which decreases the chances of developing long-term health issues like stroke and myocardial infarction and kidney disease. The advantages of monotherapy still make it suitable for patients who present with low risk or fresh hypertension diagnoses, which requires a comparative study to discover the best treatment methods for each specific patient group.

Epidemiology of hypertension

The global prevalence of hypertension affects 31.1% of adults worldwide which equals 1.39 billion people and this condition stands as the main treatable element that increases cardiovascular disease risk and leads to early mortality. The COVID-19 pandemic has created an increasing demand for hypertension treatment especially in low and middle income countries because their people show higher hypertension rates than high income countries while their populations continue to age and shift their lifestyles.[11] The main factors that determine blood pressure levels in a population include both the age and sex distribution of that group and the specific geographical region of their residence. All over the world people fail to recognize their hypertension condition because they lack knowledge about it and do

not seek medical help which leads to their untreated high blood pressure condition and permanent danger of developing cardiovascular disease. People who have hypertension control their condition through major lifestyle changes but they need to stop eating salty foods and lose weight and start exercising and limit their alcohol intake while they maintain healthy eating habits. Epidemiological studies show that more than half of diagnosed patients worldwide have hypertension which remains uncontrolled and needs urgent treatment. Community surveys illustrate similar patterns at national and local levels for example in India where hypertension prevalence was 22.0% with low awareness (27%), treatment (25%), and control (9%) among adults over 30 in a rural district.[12] The rising obesity rates and the increase in sedentary behaviors during the last twenty years have led to a nearly twofold rise in high blood pressure cases among children and adolescents according to current research.

Pathophysiology of Hypertension

Mechanisms Involved in Blood Pressure Regulation

1. Increased Cardiac Output

The relationship between blood pressure and cardiac output together with systemic vascular resistance establishes that blood pressure becomes higher when cardiac output rises. The combination of higher heart rates and greater stroke volume results in a higher arterial blood pressure according to this principle which operates in essential hypertension's initial phase through sympathetic nervous system activity that increases both heart rate and myocardial contractility resulting in higher blood pressure.[13]

2. Increased Peripheral Vascular Resistance

The condition of sustained high blood pressure develops because small arteries and arterioles experience structural and functional changes which lead to higher peripheral vascular resistance. The changes that occur in blood vessels involve vascular smooth muscle hypertrophy together with endothelial dysfunction and reduced nitric oxide availability which results in people experiencing continuous vasoconstriction and heightened blood flow resistance.[14]

3. Sympathetic Nervous System Overactivity

The sympathetic nervous system becomes excessively active which causes hypertension through three primary mechanisms: it raises heart rate and increases myocardial contractility and induces vasoconstriction. The kidneys retain sodium because of chronic sympathetic

stimulation while simultaneously generating renin which causes blood pressure to rise even more.[13,14]

4. Renin–Angiotensin–Aldosterone System (RAAS) Activation

Overactivation of the RAAS functions as the primary mechanism which causes hypertension to develop. Angiotensin II causes strong blood vessel constriction while it also triggers aldosterone release which results in the body retaining both sodium and water. These effects lead to increases in both peripheral resistance and blood volume which results in higher blood pressure.[15]

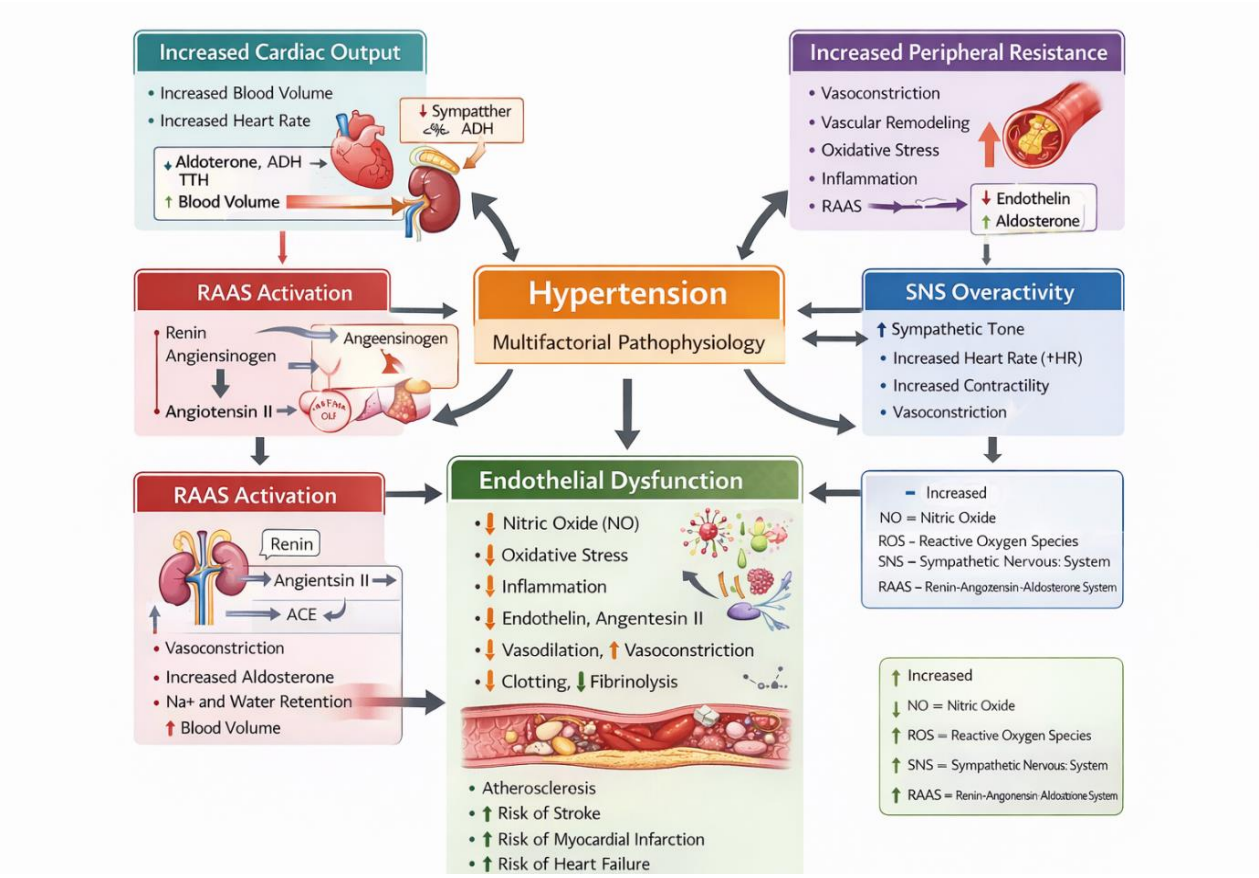

Figure 1: Multifactorial Pathophysiology of Hypertension.

5. Renal Sodium and Water Retention

The kidneys regulate long-term blood pressure through sodium and water balance. Impaired renal excretion of sodium leads to increased extracellular fluid volume and plasma volume, which raises cardiac output and blood pressure. Abnormal pressure–natriuresis mechanisms are commonly observed in essential hypertension.[15]

6. Endothelial Dysfunction

Endothelial cells help control vascular tone by releasing nitric oxide, which acts as a vasodilator, and endothelin, which functions as a vasoconstrictor. The combination of decreased nitric oxide availability and increased endothelin production in hypertension creates a situation where blood vessels cannot dilate properly, which leads to increased blood vessel resistance that maintains elevated blood pressure.[16]

7. Vascular Remodeling and Arterial Stiffness

Chronic hypertension causes blood vessels to undergo structural transformations which result in blood vessels developing more collagen and losing their ability to stretch. Arterial stiffness reduces the ability of arteries to buffer systolic pressure, leading to elevated systolic blood pressure and widened pulse pressure, particularly in elderly individuals.[15]

Classification of Antihypertensive Drugs

Antihypertensive drugs are classified into two main categories based on the specific blood pressure regulatory systems which they affect through their different pharmacological mechanisms. Hypertension treatment starts with diuretics which include thiazide, loop, and potassium-sparing diuretics that lower blood pressure through sodium and water excretion to decrease plasma volume and vascular resistance. Thiazide and thiazide-like diuretics receive the highest recommendation because they have shown effectiveness in diminishing cardiovascular-related health issues and deaths.[17] The antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors occurs through their ability to block the conversion process from angiotensin I into angiotensin II, which leads to blood vessel dilation and reduced aldosterone production. These agents provide significant advantages to diabetic patients who also suffer from chronic kidney disease and heart failure. Angiotensin II receptor blockers (ARBs) selectively block angiotensin II type 1 receptors, producing similar hemodynamic effects to ACE inhibitors while being better tolerated in patients who develop ACE inhibitor–induced cough or angioedema. Calcium channel blockers (CCBs) reduce blood pressure by inhibiting L-type calcium channels in vascular smooth muscle and cardiac tissue, leading to vasodilation and decreased myocardial contractility.[18] Dihydropyridine CCBs predominantly act on vascular smooth muscle, whereas non-dihydropyridine agents also affect cardiac conduction and heart rate. Beta-adrenergic blockers lower blood pressure by reducing cardiac output and inhibiting renin release from the kidneys through of β_1 adrenergic receptors. Although no longer preferred as first-line therapy in uncomplicated

hypertension, beta-blockers remain valuable in patients ischemic heart disease, arrhythmias, and heart failure. Other classes of antihypertensive agents include alpha-adrenergic blockers, which reduce peripheral vascular resistance through vasodilation, centrally acting sympatholytic that decrease sympathetic outflow from the central nervous system, direct vasodilators that relax arteriolar smooth muscle, and direct renin inhibitors, which suppress the renin–angiotensin–aldosterone system at its point of activation.[19] These agents are generally reserved for resistant hypertension or specific clinical indications due to their adverse effect profiles and limited outcome data.

Mono therapy in hypertension

Hypertension is a major global public health problem and a leading modifiable risk factor for cardiovascular morbidity and mortality, necessitating effective and evidence-based treatment strategies. Monotherapy, defined as the use of a single antihypertensive agent to achieve blood pressure control, remains an important initial approach in the management of patients with mild to moderate hypertension. International and national clinical guidelines recommend initiating treatment with monotherapy in patients with stage 1 hypertension or those with low to moderate cardiovascular risk profiles.[20] The rationale for monotherapy includes simplicity of treatment, improved patient adherence, reduced pill burden, and lower risk of adverse drug reactions compared with multi-drug regimens. Several classes of antihypertensive drugs, including diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and beta-blockers, are approved for use as monotherapy. Clinical trials have demonstrated that monotherapy can effectively reduce systolic and diastolic blood pressure in a substantial proportion of newly diagnosed hypertensive patients.[21] The selection of the correct monotherapy treatment depends on the individual patient characteristics which include their age and existing medical issues and their ethnic background and how well they can handle medications. The elderly population together with patients who have pure systolic hypertension benefits from monotherapy treatment which requires them to increase their medication dosage through gradual steps. Monotherapy provides benefits to patients but it does not always meet blood pressure targets for people who have either extremely high blood pressure or multiple cardiovascular health threats. Patients with blood pressure management problems require either higher medication doses or the use of multiple medications to attain their desired blood pressure targets. The use of monotherapy in certain patient groups becomes less effective because high medication doses produce dangerous effects that prevent successful treatment results. Monotherapy serves as

an essential treatment method for both early hypertension management and the treatment of patients who have simple medical conditions. The knowledge of monotherapy advantages and disadvantages enables medical professionals to develop personalized treatment plans which lead to better results in hypertension management.[22]

Rationale for Monotherapy

The treatment of stage 1 hypertension and low to moderate cardiovascular risk patients first requires doctors to use monotherapy because this method achieves effective blood pressure control while exposing patients to fewer medications which leads to fewer side effects. The use of one antihypertensive medication establishes a treatment baseline, which enables doctors to evaluate how patients react to the medicine and whether they can handle it, along with their ability to keep using it during the long-term treatment of hypertension.[23]

Monotherapy establishes a straightforward treatment plan which increases patient treatment adherence and sustained treatment execution needed to maintain constant blood pressure control. A single medication effectively treats most patients when the drug class selection matches their personal characteristics which include age and existing health conditions and their ethnic background. Monotherapy provides better safety than combination treatment because it minimizes the chances of drug interactions, making it the preferred first treatment choice for elderly patients and those taking multiple medications.[24] Monotherapy serves as a cost-effective treatment option because it reduces treatment expenses and healthcare resource needs, which proves especially beneficial in areas with limited healthcare resources.

Efficacy of Monotherapy

Monotherapy serves as an effective starting treatment for hypertension which works particularly well in patients who have stage 1 hypertension and only a low to moderate risk of developing cardiovascular disease because it helps most patients reach their blood pressure targets without requiring multiple medications. The evaluation of drug effectiveness and tolerability becomes clearer through the use of a single antihypertensive agent, which helps patients follow their treatment plan better while they adjust their medication dose before needing stronger treatment.[25] Clinical trials demonstrate that thiazide diuretics, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and beta-blockers as first-line medications can effectively decrease systolic and diastolic blood pressure when administered alone. Monotherapy is particularly beneficial in elderly patients and newly diagnosed individuals, where gradual blood pressure reduction is preferred to avoid

hypotension and related complications. Additionally, effective monotherapy has been associated with a reduction in hypertension-related cardiovascular outcomes when blood pressure targets are achieved and maintained. However, while monotherapy is efficacious in many patients, its effectiveness may be limited in those with severe hypertension or multiple comorbidities, necessitating close monitoring and timely intensification of treatment.[26]

Limitations of Monotherapy

Monotherapy often fails to achieve target blood pressure in a large proportion of hypertensive patients because the single drug used in treatment addresses only one of the multiple pathophysiological mechanisms that control blood pressure.[27] The process of dose escalation for monotherapy requires doctors to increase medication doses until they find the optimal level for successful blood pressure management. Patients with diabetes mellitus or chronic kidney disease or cardiovascular disease will find monotherapy less effective because their hypertension arises from multiple causes that necessitate treatment with multiple medications.[28] The main limitation of monotherapy occurs because patients respond differently to antihypertensive drugs which results from their unique genetic and ethnic backgrounds and environmental factors that determine their drug response. Patients who use monotherapy will experience blood pressure control that lasts less than 24 hours because the treatment does not maintain control during early morning hours which leads to an increased risk of cardiovascular events because their clinic blood pressure appears controlled.[29] Patients will experience extended periods of uncontrolled hypertension which results from monotherapy usage because it prevents their doctors from achieving effective blood pressure management.

Combination Therapy in hypertension

Combination therapy uses two or more drugs that work through different mechanisms to create better treatment results which single drug treatment. In hypertension management, combination therapy is often required because most patients do not achieve target blood pressure levels with a single antihypertensive agent.[30] The method enables treatment to use smaller quantities of each medication which increases treatment effectiveness while decreasing the chances of experiencing medication-related side effects. Researchers developed combination therapy to treat multiple biological systems that control blood pressure through various mechanisms which include the renin–angiotensin–aldosterone system and sympathetic nervous system and vascular smooth muscle tone. Physicians should

start combination therapy as the first treatment option for patients who already had stage 2 hypertension or who face high cardiovascular risks. The evidence indicates that combination therapy leads to higher blood pressure normalization rates when used against stepwise monotherapy escalation.[31] Healthcare professionals use rational drug combinations to decrease the tendency of doctors and patients to delay their treatment decisions when they manage hypertension. Patients can better follow their treatment plans because fixed-dose combinations make it easier to take their medications at scheduled times which boosts treatment results. Clinical trials have demonstrated that combination therapy lowers blood pressure fluctuations while delivering stable blood pressure control throughout the day. The synergistic action of combined agents contributes to better protection against target organ damage, including stroke, myocardial infarction, and renal impairment.[32] Combination therapy is particularly beneficial in patients with comorbid conditions such as diabetes mellitus, chronic kidney disease, and heart failure. International hypertension guidelines increasingly support the use of combination therapy as first-line treatment in appropriate patient populations. Safety and tolerability profiles of commonly used combinations have been well established through long-term clinical studies. The availability of evidence-based combinations allows clinicians to individualize therapy based on patient characteristics and risk profiles.[33] Overall, combination therapy represents a cornerstone in modern hypertension management aimed at achieving optimal blood pressure control and reducing cardiovascular morbidity and mortality.

Rationale for Combination Therapy

Combination therapy uses two or more drugs that work through different mechanisms to create better treatment results which single drug treatment. In hypertension management, combination therapy is often required because most patients do not achieve target blood pressure levels with a single antihypertensive agent.[34] The method enables treatment to use smaller quantities of each medication which increases treatment effectiveness while decreasing the chances of experiencing medication-related side effects. Researchers developed combination therapy to treat multiple biological systems that control blood pressure through various mechanisms which include the renin–angiotensin–aldosterone system and sympathetic nervous system and vascular smooth muscle tone. Physicians should start combination therapy as the first treatment option for patients who already had stage 2 hypertension or who face high cardiovascular risks. The evidence indicates that combination therapy leads to higher blood pressure normalization rates when used against stepwise

monotherapy escalation.[35] Healthcare professionals use rational drug combinations to decrease the tendency of doctors and patients to delay their treatment decisions when they manage hypertension. Patients can better follow their treatment plans because fixed-dose combinations make it easier to take their medications at scheduled times which boosts treatment results. Clinical trials have demonstrated that combination therapy lowers blood pressure fluctuations while delivering stable blood pressure control throughout the day.

Fixed dose combinations

Fixed-dose combinations (FDCs) in hypertension management refer to the formulation of two or more antihypertensive agents with complementary mechanisms of action into a single dosage form, aimed at improving therapeutic outcomes and patient convenience. The FDCs achieve their blood pressure reduction effects through their ability to treat multiple biological pathways which control blood pressure including the renin–angiotensin–aldosterone system and the regulation of vascular smooth muscle tone and sodium–water balance.[36] The primary benefit of FDCs lies in their ability to enhance patient adherence through their design which combines multiple medications into one pill that reduces pill consumption and makes it easier for patients who need to take medicines over long periods to manage their chronic hypertension. FDCs function as a treatment option which enables patients to take smaller amounts of each medication and experience fewer negative side effects while their blood pressure treatment results from the combined effects of the different drugs.[37] FDCs function as essential tools for doctors who treat stage 2 hypertensive patients and those whose blood pressure remains high despite monotherapy because early combination treatment delivers rapid and prolonged blood pressure control. The use of fixed-dose combinations brings about savings in healthcare expenditures because they decrease prescription amounts while enhancing blood pressure management and reducing the occurrence of hypertension-related medical issues which include stroke and myocardial infarction. However, the use of FDCs has limitations, including reduced flexibility in dose titration and the potential difficulty in identifying the causative agent if an adverse drug reaction occurs, which necessitates careful patient selection and monitoring.

Comparative Outcomes of Monotherapy and Combination Therapy

Blood pressure reduction

Combination therapy produces better blood pressure outcomes because it treats multiple hypertension-related physical processes which include fluid volume and blood vessel

resistance. Clinical evidence demonstrates that combining two antihypertensive agents from different classes results in additive or synergistic effects which lead to more pronounced blood pressure lowering than increasing the dose of a single drug.[38]

Rate of target blood pressure achievement

Patients treated with combination therapy achieve recommended target blood pressure levels at a higher rate than those receiving monotherapy, particularly in individuals with moderate to severe hypertension. The combination therapy leads to higher success rates for patients who need to achieve their blood pressure goals according to clinical practice guidelines while it decreases the number of patients who need to switch medications or increase their dosages.[39]

Time to blood pressure control

Combination therapy achieves blood pressure control more rapidly than monotherapy because two complementary agents touch off quicker medicinal effects than one drug. Studies indicate that early blood pressure normalization with combination therapy may reduce the duration of uncontrolled hypertension which lowers the short-term risk of cardiovascular complications associated with persistently elevated blood pressure.[40]

Safety and Tolerability Profile

The process of choosing antihypertensive medication requires evaluation of safety and treatment effectiveness because hypertension becomes a condition that needs permanent attention. The safety profiles of monotherapy and combination therapy show major differences because each treatment method exposes patients to different drug amounts and requires distinct dosage patterns and exhibits unique drug interaction effects. The use of one drug in monotherapy results in better treatment tolerance while combination therapy provides better blood pressure management yet brings new safety risks.[41] The evaluation of adverse drug reactions together with potential drug–drug interactions and overall risk–benefit assessment must take place to determine the suitable therapeutic path for each patient.

Adverse Drug Reactions

Adverse drug reactions represent the most significant factor which determines whether patients will tolerate antihypertensive treatment. Monotherapy leads to lower rates of adverse effects which occur at less severe levels because patients only take one class of medication, which helps to identify drug-related side effects with greater ease. The need to increase

monotherapy dosage arises when blood pressure fails to reach target levels, which causes a higher probability of experiencing dose-dependent side effects that include hypotension and electrolyte disturbances and bradycardia.[42] Combination therapy enables patients to take two or more drugs at reduced doses because different drugs work together to decrease side effects, but this approach creates more mild adverse effects because of combined drug effects.

Drug–Drug Interactions

Drug interactions between medications create significant safety problems for people who use multiple medications or who have multiple health conditions. The treatment of hypertension through monotherapy presents a safer choice because it generates fewer pharmacokinetic and pharmacodynamic interactions than other treatment methods. The use of combination therapy results in higher chances of drug interactions which occur between antihypertensive drugs and the diabetes and cardiovascular and renal disorder medications that patients take. The combination of renin–angiotensin system inhibitors with potassium-sparing diuretics creates an elevated hyperkalemia risk which requires labs to conduct tests for patient safety.[43]

Risk–Benefit Analysis

The selection of either monotherapy or combination therapy requires an extensive assessment of risks and advantages between these two treatment options. The safety of monotherapy remains high while it delivers better patient tolerability, but its limited effectiveness causes uncontrolled hypertension which raises the chance of long-term cardiovascular problems for patients. Combination therapy delivers faster and more effective blood pressure reduction, which results in better cardiovascular outcomes, but these advantages need assessment against the higher risk of negative reactions and drug interactions.[44] Fixed-dose combination medications improve patient adherence through decreased pill consumption, which leads to better overall treatment results in suitable patient groups.

Medication adherence and patient compliance

Medication adherence and patient compliance are key determinants of effective hypertension management. Adherence refers to the extent to which a patient follows the prescribed medication regimen, while compliance emphasizes the patient-provider agreement on treatment. Poor adherence is a major obstacle in hypertension care, as studies show that nearly half of patients discontinue therapy within the first year, leading to uncontrolled blood pressure and increased cardiovascular risk.[45] Adherence to antihypertensive therapy strongly

influences clinical outcomes. Patients with high adherence are more likely to achieve blood pressure targets and reduce cardiovascular complications. Conversely, poor adherence contributes to suboptimal blood pressure control and higher hospitalization rates.

Pill Burden

Pill burden, defined as the number of tablets a patient must take daily, is a major factor affecting adherence. High pill burden is linked to lower adherence rates, as patients often feel overwhelmed by complex regimens. Simplifying the regimen by reducing the number of daily pills improves adherence and persistence in antihypertensive therapy.[46]

Role of Single Pill Combinations (SPCs)

Single pill combinations (SPCs) integrate two or more antihypertensive agents into one tablet, reducing regimen complexity. Evidence shows that SPCs significantly improve adherence compared to multiple separate pills (free-equivalent combinations). By lowering pill burden and simplifying dosing schedules, SPCs help patients maintain long-term adherence and achieve better blood pressure control.[47]

Impact on Cardiovascular Outcomes

Stroke

Initial combination antihypertensive therapy reduces early stroke risk. In a large cohort study, patients who started treatment with dual antihypertensive therapy had significantly lower incidence of first stroke within the first 6 months compared with monotherapy, likely due to faster and greater blood pressure reduction. Antihypertensive therapy, especially with combinations, decreases stroke recurrence.[48] Meta-analysis evidence shows that antihypertensive drugs particularly ACE inhibitors in combination significantly reduce the risk of recurrent stroke compared with no treatment, indicating benefit of combination strategies in secondary prevention.

Myocardial Infarction

Combination therapy is associated with reduced composite cardiovascular events, including myocardial infarction, in observational cohorts. In a large matched cohort study, initial combination therapy led to significantly lower risk of cardiovascular events, such as MI, compared with delayed or monotherapy, mainly through earlier attainment of target blood pressure. Patients requiring combination therapy may still have high risk unless well controlled. Retrospective data from the VALUE trial showed that hypertensive patients

needing combination therapy had similar or somewhat worse MI event rates compared with those controlled by monotherapy, underscoring the importance of baseline risk and BP control rather than the number of drugs alone.[49]

Heart Failure

Combination therapy reduces hospitalization for heart failure compared with monotherapy. In the Systolic Hypertension in Europe trial analysis, adding enalapril to nitrendipine significantly reduced heart failure events compared with monotherapy, suggesting enhanced cardiac protection from combination therapy. Observational evidence suggests early combination therapy is linked with lower risk of heart failure and other cardiovascular events.[50] In a real-world Italian cohort, fixed-dose combination therapy was associated with reduced hospitalization for cerebrovascular disease and heart failure compared with monotherapy.

Mortality

Combination therapy may reduce all-cause and cardiovascular mortality. In the Systolic Hypertension in Europe trial follow-up, combination therapy was linked with lower total mortality compared with monotherapy, though the findings were from a posthoc analysis and require confirmation in larger trial. Multiple cardiovascular medications, including antihypertensives in combination with other classes, are associated with lower long-term all-cause mortality after stroke. In a large population cohort of stroke survivors, patients on multiple cardiovascular drugs including antihypertensive combinations — had significantly lower mortality compared with those on monotherapy.[51]

Guideline Recommendations

Recent updates from the World Health Organization further emphasize the use of standardized treatment protocols and fixed-dose single-pill combinations to improve global hypertension control rates, particularly in low- and middle-income countries. The American College of Cardiology and American Heart Association continue to advocate early intensification of therapy if target blood pressure is not achieved within one month of initiation, highlighting the importance of timely follow-up and dose titration. Similarly, the European Society of Cardiology and European Society of Hypertension recommend rapid escalation to triple-drug therapy when dual therapy fails, typically combining a renin–angiotensin system blocker, calcium channel blocker, and thiazide-like diuretic. Collectively, these recommendations reflect a shift from stepwise monotherapy toward early, evidence-

based combination strategies aimed at achieving faster and sustained blood pressure control while improving long-term cardiovascular outcomes.

International Guidelines

Initiation of Combination Therapy in International Guidelines: Most major international guidelines, including the World Health Organization (WHO), recommend initial combination therapy preferably as a single-pill combination of two first-line classes (ACE inhibitor/ARB plus calcium channel blocker or thiazide/thiazide-like diuretic) especially when baseline blood pressure is ≥20/10 mm Hg above target to enhance blood pressure control and adherence. ACC/AHA Guideline on Monotherapy vs Combination: The American College of Cardiology/American Heart Association (ACC/AHA) guideline suggests beginning with monotherapy in stage 1 hypertension (BP >130/80 mm Hg) but recommends upfront combination therapy for stage 2 hypertension or when blood pressure is >20/10 mm Hg above goal, reflecting evidence that most patients require two or more drugs to achieve targets.[52] ESC/ESH Recommendation for Combination First-Line: The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines strongly emphasize initiating treatment with two-drug combinations for most patients with hypertension, with monotherapy reserved for those close to target BP or frail elderly patients, indicating a broader role for combination therapy. Single-Pill Combinations to Improve Adherence: Both ACC/AHA and ESC/ESH international guidelines endorse the use of single-pill combinations to reduce pill burden, improve adherence, and simplify treatment regimens, which is especially important given the frequent need for multiple agents in hypertension management.[53]

National (Indian) Guidelines

Indian Recommendation for Combination Initiation in Higher BP: Indian hypertension guidelines recommend starting with combination therapy in patients with blood pressure significantly above target (e.g., SBP ≥160 mm Hg or DBP ≥100 mm Hg), acknowledging that monotherapy is often insufficient for rapid and effective control in moderate-to-severe presentations. Selection of Drug Classes in Indian Practice: Indian recommendations align with international practice by prioritizing ACE inhibitors/ARBs, calcium channel blockers, or thiazide-like diuretics as first-line agents and recommend combination therapy particularly ACEI/ARB plus CCB to achieve more effective blood pressure reduction than monotherapy. Indian Guideline Endorsement of Dual Therapy in High-Risk Groups: National expert

guidance from India emphasizes dual combination antihypertensive therapy — especially ACEI or ARB with a dihydropyridine CCB — in high-risk groups such as patients with diabetes, to enhance cardiovascular protection and improve adherence.[54]

Special populations

Elderly patients: Efficacy of combination therapy in the elderly: In elderly hypertensive patients, combination antihypertensive therapy has been shown to achieve better blood pressure reduction and similar or improved cardiovascular protection compared with monotherapy, and some evidence indicates specific combinations (e.g., ARB + CCB) may be preferable in very elderly patients due to favorable safety and outcomes.[55]

Diabetes and Chronic Kidney Disease (CKD)

Need for multiple agents in diabetes with hypertension: Patients with diabetes often require two or more antihypertensive medications typically an ACE inhibitor or ARB plus another class such as a calcium channel blocker or diuretic to achieve lower blood pressure targets that significantly reduce diabetic nephropathy progression and cardiovascular risk compared with monotherapy alone. Combination therapy in CKD: In individuals with chronic kidney disease, combination therapy often includes a renin–angiotensin system inhibitor with a calcium channel blocker or diuretic to optimize blood pressure control and reduce microalbuminuria, because monotherapy alone is frequently insufficient in achieving guideline-recommended targets.[56]

Resistant Hypertension

Definition and complexity of resistant hypertension: Resistant hypertension is defined as blood pressure that remains above goal despite the concurrent use of three different classes of antihypertensive medications including a diuretic at maximally tolerated doses, which intrinsically necessitates combination therapy beyond simple monotherapy to achieve control. Stepwise combination approach in resistant cases: In resistant hypertension, a stepwise approach to pharmacologic management involves maximizing therapy with combinations that include an RAS blocker, long-acting calcium channel blocker, and a diuretic, and often adding further agents, because monotherapy or suboptimal combination regimens fail to achieve target blood pressure.[57]

Figure 2: Conceptual framework comparing monotherapy and combination therapy in hypertension management and their impact on cardiovascular outcomes.

CONCLUSION

Hypertension remains a major global health challenge and a leading contributor to cardiovascular morbidity and mortality. The management of hypertension needs doctors to learn its detailed pathophysiological mechanisms which include elevated cardiac output base vascular resistance and excessive sympathetic activity and activation of renin-angiotensin-aldosterone system and endothelial impairment and sodium retention in kidneys. Monotherapy which uses only one antihypertensive drug proves effective for patients who have both mild hypertension and cardiovascular risk factors. The treatment provides two benefits because it generates fewer side effects while offering easy dosing which helps patients follow their treatment. Patients need multiple treatments because their blood pressure target cannot be reached through monotherapy. The use of combination therapy which employs two or more antihypertensive drugs that work through different methods delivers better blood pressure management because it treats multiple underlying medical conditions. The method produces a quick and lasting decrease in both systolic and diastolic blood pressure which increases the chances of achieving guideline blood pressure goals and decreases the chances of developing long-term medical problems which include stroke and myocardial infarction and chronic kidney disease. The combination therapy treatment increases the chance of experiencing mild side effects but healthcare providers can decrease

this danger through proper medication selection and patient supervision. The study proves that doctors need to create personalized treatment plans for their patients. The correct combination therapy should start early when doctors base their decision on the patient needs which include disease severity and existing health conditions and individual characteristics of the patient. Clinicians should adopt a patient-centered approach to ensure the safe and effective management of hypertension, balancing efficacy with tolerability to achieve the best long-term cardiovascular outcomes.

REFERENCES

1. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control. Circulation. 2016; 134(6): 441–450.
2. GBD 2017 Risk Factor Collaborators. Global risk assessment of behavioral, environmental, and metabolic risks. Lancet. 2018; 392(10159): 1923–1994.
3. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension. Lancet. 2017; 389(10064): 37–55.
4. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension. Lancet. 2005; 365(9455): 217–223.
5. Ibrahim MM, Damasceno A. Hypertension in developing countries. Lancet. 2012; 380(9841): 611–619.
6. Egan BM, Li J, Hutchison FN, Ferdinand KC. Hypertension in the United States. Circulation. 2014; 130(19): 1692–1699.
7. Gaziano TA, Bitton A, Anand S, et al. The global cost of nonoptimal blood pressure. J Hypertens. 2009; 27(7): 1472–1477.
8. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting cardiovascular disease burden. Circulation. 2011; 123(8): 933–944.
9. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet. 2007; 370(9587): 591–603.
10. Zhou B, Carrillo-Larco RM, Danaei G, et al. Worldwide trends in hypertension. Lancet. 2021; 398(10304): 957–980.
11. Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019; 124(7): 1124–1140.
12. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA guideline. Hypertension. 2018; 71(6): e13–e115.
13. World Health Organization. Global status report on noncommunicable diseases. WHO; 2014.

14. Law MR, Morris JK, Wald NJ. Blood pressure lowering and cardiovascular risk. BMJ. 2009; 338: b1665.
15. Mancia G, Grassi G. The global burden of hypertension. J Hypertens. 2014; 32(1): 3–5.
16. Lawes CMM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease. Lancet. 2008; 371(9623): 1513–1518.
17. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death. Lancet. 2016; 387(10022): 957–967.
18. Carretero OA, Oparil S. Essential hypertension: definition and etiology. Circulation. 2000; 101(3): 329–335.
19. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension. N Engl J Med. 2008; 359: 2417–2428.
20. Gupta AK, Arshad S, Poulter NR. Fixed-dose combinations of antihypertensive agents: meta-analysis. Hypertension. 2010; 55(2): 399–407.
21. Gradman AH, Basile J, Carter B, Bakris GL. Combination therapy in hypertension. J Clin Hypertens. 2010; 12: 532–540.
22. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for high blood pressure in adults. JAMA. 2014; 311(5): 507–520.
23. Mills KT, Stefanescu A, He J. Global epidemiology of hypertension. Nat Rev Nephrol. 2020; 16(4): 223–237.
24. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology and effective interventions. Nat Rev Cardiol. 2021; 18(11): 785–802.
25. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors. Lancet. 2020; 396(10258): 1223–1249.
26. Gupta R, Gaur K, Ram CVS. Emerging trends in hypertension epidemiology in India. J Hum Hypertens. 2019; 33(8): 575–587.
27. Schiffrin EL. Vascular remodeling in hypertension. Hypertension. 2012; 59(2): 367–374.
28. Esler M. The sympathetic nervous system in hypertension. J Hypertens. 2000; 18(7): S3–S6.
29. Atlas SA. The renin-angiotensin aldosterone system. J Manag Care Pharm. 2007; 13(8): 9–20.
30. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension. Circ Res. 2015; 116(6): 991–1006.
31. Vanhoutte PM, Shimokawa H, Feletou M, Tang EH. Endothelial dysfunction and vascular disease. Acta Physiol. 2009; 196(2): 193–222.

32. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines. Eur Heart J. 2018; 39(33): 3021–3104.
33. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee. Hypertension. 2003; 42(6): 1206–1252.
34. Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and control of hypertension. J Am Coll Cardiol. 2018; 72(11): 1278–1293.
35. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin receptor blockers in hypertension. J Am Coll Cardiol. 2018; 71(13): 1474–1482.
36. Oparil S, Acelajado MC, Bakris GL, et al. Hypertension. Nat Rev Dis Primers. 2018; 4: 18014.
37. Aronow WS. Treatment of hypertension in older persons. Curr Hypertens Rep. 2018; 20(7): 56.
38. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment. BMJ. 2003; 326(7404): 1427.
39. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. N Engl J Med. 1993; 328(13): 914–921.
40. White WB. Importance of blood pressure control over 24 hours. J Manag Care Pharm. 2007; 13(8): 34–39.
41. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy vs monotherapy. Am J Med. 2009; 122(3): 290–300.
42. Turnbull F, Neal B, Algert C, et al. Effects of different BP-lowering regimens. Lancet. 2003; 362(9395): 1527–1535.
43. Unger T, Borghi C, Charchar F, et al. 2020 ISH Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334–1357.
44. Mancia G, Rea F, Corrao G, Grassi G. Two-drug combinations as first-step treatment. Circ Res. 2019; 124(7): 1113–1123.
45. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve compliance. Am J Med. 2007; 120(8): 713–719.
46. Kawalec P, Holko P, Gawin M, Pilc A. Effectiveness of fixed-dose combination therapy. Arch Med Sci. 2018; 14(5): 1125–1136.
47. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments. BMJ., 2008; 336(7653): 1114–1117.
48. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003.

49. Thomopoulos C, Parati G, Zanchetti A. Effects of antihypertensive treatment on adherence. Hypertension. 2015; 65(2): 270–281.
50. Volpe M, Tocci G, Borghi C, et al. Single-pill combination therapy in hypertension. High Blood Press Cardiovasc Prev. 2016; 23(4): 341–351.
51. Noubiap JJN, et al. Initial antihypertensive combination therapy and stroke prevention. J Thorac Dis. 2019; 11(7): 3066–3074.
52. Rea F, Corrao G, et al. Initial combination therapy reduces cardiovascular events. J Clin Hypertens. 2012; 14(3): 133–140.
53. Palmer BF. Managing hyperkalemia caused by RAAS inhibitors. N Engl J Med. 2004; 351(6): 585–592.
54. Bangalore S, Messerli FH, Whelton PK, et al. Adverse effects and tolerability of antihypertensive therapy. J Am Coll Cardiol. 2019; 73(14): 1762–1773.
55. Ministry of Health & Family Welfare (India). Standard Treatment Guidelines: Hypertension. Government of India; 2016.
56. World Health Organization. Guideline for the Pharmacological Treatment of Hypertension in Adults. WHO; 2024.
57. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association. Hypertension [Internet]. 2018; 72(5): Available from: http://dx.doi.org/10.1161/hyp.0000000000000084