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Review Article

A contemporary review on combination therapy for hypertension management in India

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ABSTRACT

Hypertension affects nearly one-third of Indian adults, yet only one in six patients achieve adequate blood pressure control. This narrative, evidence-informed review synthesizes data from PubMed, Scopus and Google Scholar (2000–2025) on antihypertensive combination therapy, with additional focus on Indian epidemiology and prescribing patterns. Evidence suggests that early initiation of combination therapy—particularly as single-pill combinations (SPCs)—may offer more rapid and sustained blood pressure reduction by targeting multiple pathophysiological pathways simultaneously. Indian patients have a unique cardiometabolic phenotype characterized by increased abdominal obesity, diabetes, dyslipidemia, heightened sympathetic tone, elevated resting heart rate, and enhanced renin-angiotensin-aldosterone system (RAAS) activation, resulting in higher cardiovascular risk at younger ages. This review evaluates clinical evidence from dual, triple, and quadruple combination trials, summarizes current global and regional guideline recommendations, and highlights gaps in Indian practice, including persistent underutilization of combination regimens in moderate- to high-risk patients. The objective is to review global evidence for Indian clinical practice and discuss strategies for optimizing risk-stratified hypertension management.

Keywords: Hypertension management, Single-pill combination, Low-dose combination, Indian phenotype, Resting heart rate

INTRODUCTION

Hypertension is a prevalent chronic condition characterized by sustained elevation of arterial blood pressure. Hypertension remains a leading modifiable risk factor for cardiovascular disease, affecting approximately one-third of adults worldwide. In India, the prevalence of hypertension among adults aged 30–79 years is around 30%, Despite this high prevalence, only 39% of hypertensive individuals are diagnosed, 33% receive treatment, and a mere 17% achieve adequate blood pressure control.[1] This difference between prevalence and control highlights a substantial gap in the effective management of hypertension.

Current clinical guidelines recommend a comprehensive approach to managing hypertension. This includes early detection through screening, accurate diagnosis, regular blood pressure monitoring and tailored therapeutic strategies to prevent high blood pressure (BP)-mediated target organ damage and minimize the risks of uncontrolled hypertension.

Recent hypertension guidelines strongly recommend early initiation of combination therapy rather than monotherapy, particularly for patients with blood pressure ≥140/90 mmHg or those with elevated cardiovascular risk. Combination therapy-preferably as a single-pill combination (SPC), has been shown to achieve better blood pressure control and improved clinical outcomes.

This review emphasizes the potential of combination antihypertensive therapy as a practical and evidence-based approach to improve blood pressure control in the Indian population. By highlighting its advantages—such as enhanced efficacy, improved patient adherence, faster achievement of target BP, and reduced risk of adverse events—this article aims to support the shift from conventional monotherapy to Low- to standard-dose fixed combinations as the new standard in hypertension management. This review also explores clinical evidence and guideline recommendations advocating for broader adoption of this strategy to address the growing burden of uncontrolled hypertension.

RATIONALE FOR COMBINATION THERAPY VERSUS MONOTHERAPY

When patients with high blood pressure are not able to reach target levels using a single medication, physicians have two choices: either increase the dose of that one drug—which may lead to more side effect or use a combination of different medications that work well together and have fewer side effects. To prevent complications, it's important to begin treatment early, bring the blood pressure under control quickly, and make sure the patient continues taking the prescribed medications regularly.

High blood pressure is caused by multiple underlying mechanisms in the body. A single drug (monotherapy) usually targets only one or two of these pathways, which may not be enough for effective blood pressure control. In contrast, using a combination of medications that work through different mechanisms can address several pathophysiological pathways of hypertension at the same time. This approach has been shown to be two to five times more effective than monotherapy in lowering blood pressure.[2,3] While increasing the dose of a single drug can reduce the risk of coronary heart disease events by 29% and strokes by 40%, combining two drugs with different actions can reduce coronary heart disease events by 40% and strokes by 54%.[3] Therefore, combination therapy not only improves blood pressure control but also offers stronger protection for vital organs.

Overall, combining medications appears to be a more effective and safer than increasing the dose of a single drug. The benefits of fixed-dose combination therapy in hypertension management are shown in Figure 1.

Fixed-dose combinations, where ≥2 antihypertensive agents are combined into a single pill, offer several benefits. They can improve patient adherence, simplify the treatment regimen, and lower overall treatment costs. However, one drawback is that the individual doses of each drug cannot be adjusted separately, which can limit flexibility in tailoring the therapy to the patient's needs.[2,4]

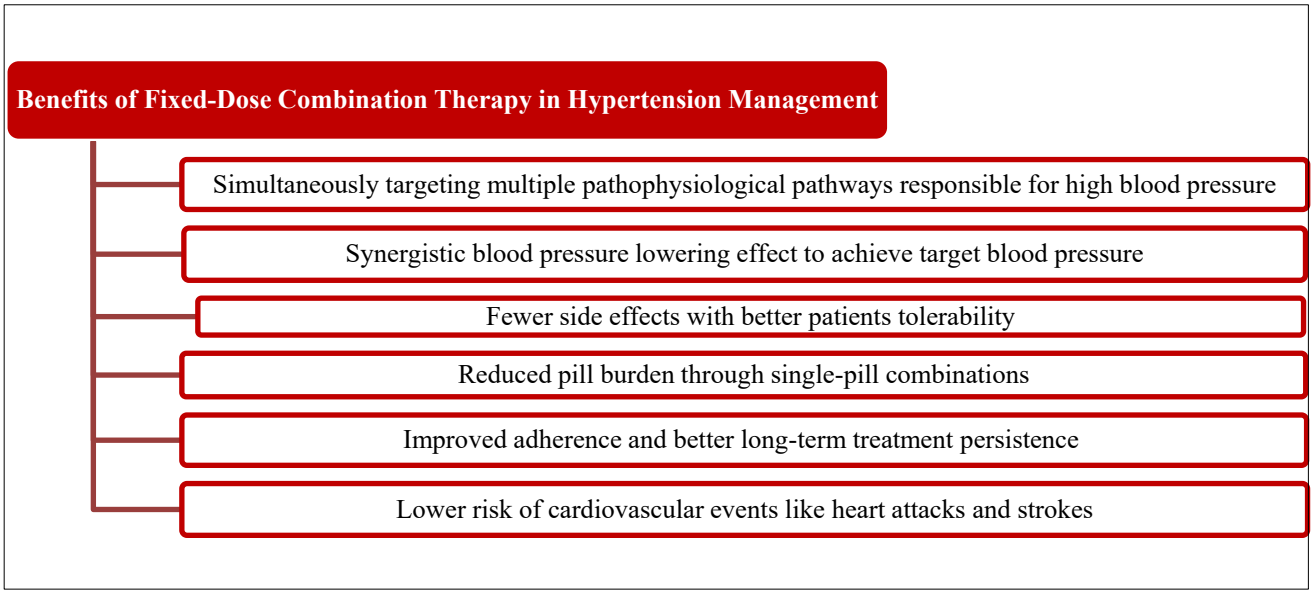

Figure 1: Benefits of fixed-dose combination therapy in hypertension management.

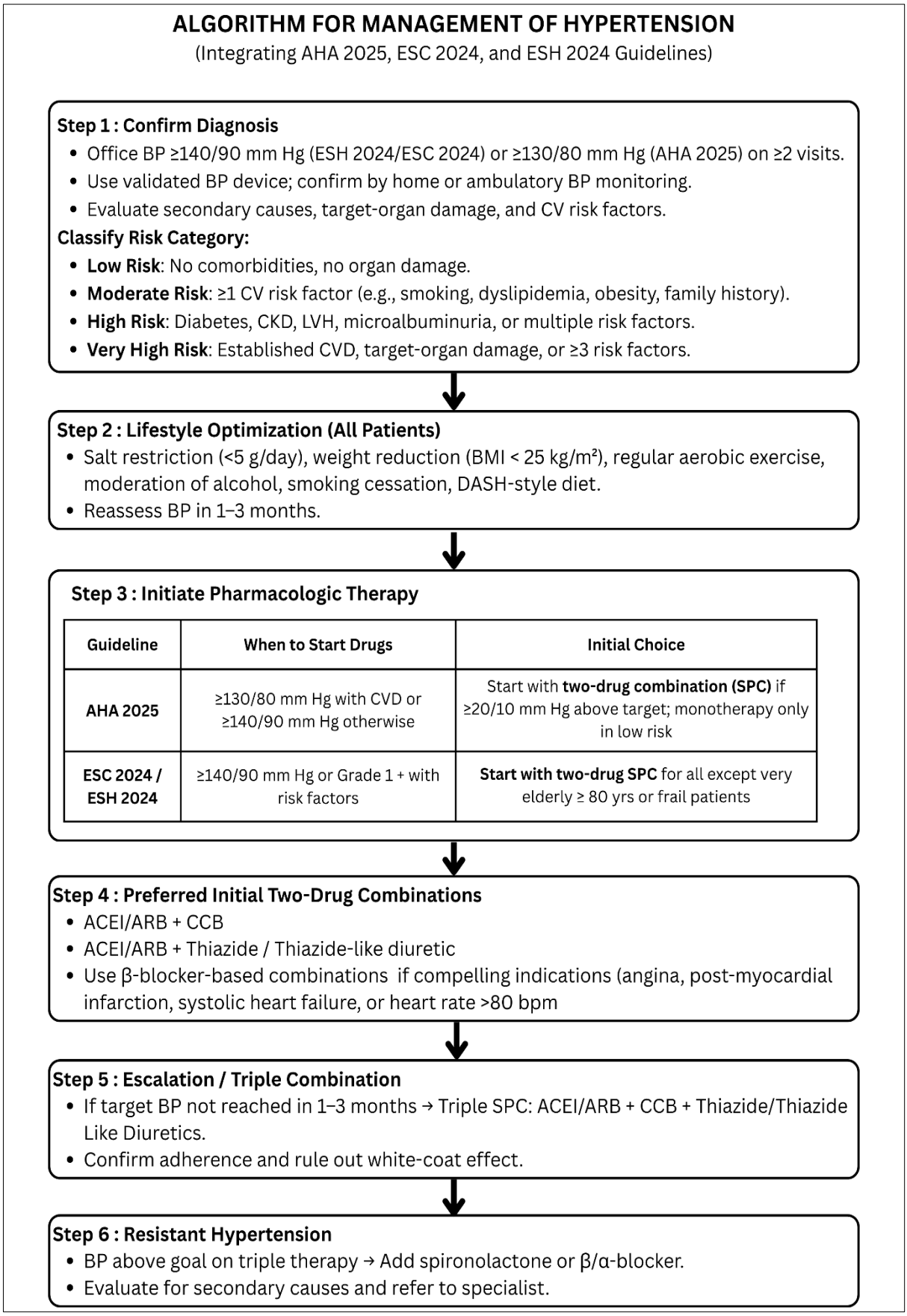

Figure 2: Stepwise evidence-based algorithm for hypertension management integrating recommendations from the 2025 AHA and 2024 ESC/ESH guidelines.

GUIDELINES RECOMMENDATION ON COMBINATION ANTIHYPERTENSIVE THERAPY

Recent hypertension guidelines consistently emphasize early initiation of combination therapy for more effective blood pressure control. The 2025 American Heart Association/American College of Cardiology hypertension guideline recommends initiating dual therapy with two first-line agents for adults with blood pressure ≥140/90 mmHg, preferably as an SPC.[5] This dual-agent strategy enhances early blood pressure control, reduces therapeutic inertia, and improves long-term adherence. The guideline highlights use of complementary drug classes (e.g., an ACE inhibitor or ARB with a calcium-channel blocker or thiazide diuretic) to rapidly achieve target blood pressure and reduce cardiovascular risk.[6] By endorsing SPC at the outset, the guideline aims to streamline therapy, minimize pill burden and side-effects, and optimize outcomes in patients with higher-level hypertension.[7]

The 2024 European Society of Hypertension (ESH) Guidelines recommend initiating pharmacological treatment with a two-drug combination in most patients with grade 1 or higher hypertension, preferably as SPC. The rationale is to achieve better blood pressure control more rapidly, reduce therapeutic inertia, and improve medication adherence. This approach is especially recommended for patients with blood pressure ≥140/90 mmHg or those at high cardiovascular risk. The ESH also stresses the importance of using agents from complementary classes—typically combining a renin–angiotensin system inhibitor (ACEI or ARB) with a calcium channel blocker (CCB) or diuretic. Furthermore, the ESH 2024 guidelines emphasize the use of initial low-dose combinations to optimize the balance between efficacy and tolerability, minimizing adverse effects while achieving prompt BP reduction. Monotherapy is recommended only in selected patients, including those with grade 1 hypertension and low cardiovascular risk, individuals who are elderly or frail, or patients whose baseline BP is only slightly above target.[8]

A stepwise, evidence-based algorithm integrating the 2025 AHA and 2024 ESC/ESH guidelines was used to guide hypertension management, as shown in Figure 2.

CLINICAL EVIDENCE ON COMBINATION THERAPY

Dual combination therapy

A comprehensive systematic review by Salam et al evaluated 33 trials examining the efficacy of initial dual combination therapy. The findings revealed that low-dose dual combinations (each drug below standard dose) achieved greater reductions in systolic blood pressure compared to standard-dose monotherapy with no significant differences for diastolic pressure. Importantly, adverse event rates and treatment withdrawals were not increased relative to monotherapy.[9] Similarly, Bennett et al reported that combining two antihypertensive agents at quarter doses achieved blood pressure reductions equivalent to those obtained with a standard dose of monotherapy, but with significantly fewer side effects. These results underscore the value of low-dose combinations as an effective and safer initial strategy.[10] A recent randomized trial (TOPSPIN) conducted in India further supports the efficacy of dual combination therapy, demonstrating that three different dual combinations—amlodipine–perindopril, perindopril–indapamide, and amlodipine–indapamide—produced similar and substantial reductions in both 24-hour ambulatory and office blood pressure, with approximately 70% of participants achieving BP control (<140/90 mmHg) at 6 months. All regimens were well-tolerated, reinforcing the utility of dual therapy as an effective initial strategy.[11] A recent analysis provided key trends in prescribing practices for newly diagnosed hypertension patients in India. Among 4,723 patients, 65% were initiated on combination therapy, and nearly 98% of those received single-pill combinations (SPCs). The most frequent combinations were ARB + CCB (26%) and ARB + diuretic (12%), reflecting growing physician alignment with guideline-based combination therapy. However, a considerable proportion (28.9%) of moderate-to-high-risk patients still received monotherapy, underscoring the need for earlier and broader adoption of fixed-dose combinations to achieve optimal BP control.[12]

Triple combination therapy

Evidence supporting early triple therapy has been strengthened by the TRIUMPH trial, conducted in Sri Lanka, which randomized 700 adults (mean age 56 years; baseline BP 154/90 mmHg; 29% with diabetes) to either a fixed-dose triple combination or usual care. After six months, blood pressure control was significantly higher in the triple-pill group (70% versus 55%; RR 1.25, 95% CI 1.08–1.44).[13] These findings demonstrate that triple low-dose combinations can provide superior outcomes compared with standard stepwise care.

The recent USFDA approval of a low-dose triple combination therapy (telmisartan/amlodipine/indapamide: 10/1.25/0.625 mg, 20/2.5/1.25 mg, and 40/5/2.5 mg) underscores a global paradigm shift toward very-low-dose, multi-mechanistic antihypertensive regimens.[14,15] This advancement further strengthens the evidence that combination strategies can deliver superior blood pressure control with a reduced risk of adverse effects—a principle of particular importance in the Indian context, where medication adherence, pill burden, and therapeutic inertia remain significant barriers to achieving optimal hypertension management. Recent published data indicate that, out of a total of 4,723 newly diagnosed hypertension patients, only 14% were started on regimens containing three or more antihypertensive agents. Notably, the ARB + CCB + diuretic fixed-dose combination accounted for 8% of all prescriptions.[12] This emerging trend underscores

a meaningful shift toward early intensification of therapy in real-world Indian practice, suggesting that clinicians increasingly consider multi-mechanistic treatment strategies for more aggressive blood pressure control.

Quadruple combination therapy

The QUADRO trial, presented at ESC Congress 2024, demonstrated that a single-pill quadruple combination of perindopril, indapamide, amlodipine, and bisoprolol (10/2.5/5/5 mg or 10/2.5/10/5 mg) was significantly more effective than the same triple therapy (perindopril, indapamide and amlodipine 10/2.5/5 mg or 10/2.5/10 mg) taken as separate pills in patients with resistant hypertension. After eight weeks, mean office systolic BP reduction was −20.7 mmHg in the quadruple group versus −11.3 mmHg with triple therapy ($p<0.0001$), with superior control also seen in 24-hour ambulatory and home BP measurements. Overall BP control (<140/90 mmHg) was achieved in 66.3% of patients receiving the quadruple single pill compared to 42.7% on triple therapy. Importantly, the combination was well tolerated, with no major adverse events reported.[16] These findings highlight that single-pill quadruple combinations can effectively enhance blood pressure control and adherence, particularly in patients with resistant hypertension.

INDIAN HYPERTENSIVE PHENOTYPE AND PRACTICE GAP

The Indian hypertensive population exhibits a distinct clinical and metabolic phenotype characterized by higher prevalence of abdominal obesity, diabetes, and dyslipidemia, factors that substantially elevate cardiovascular risk.[17,18] In India, the age-adjusted prevalence of metabolic syndrome is around 25% in urban adults, with a markedly higher burden in women (~31%) than men (~18.5%).[19] Indians also exhibit a unique autonomic and hormonal pattern, with consistently higher resting heart rates (often ≥80 beats/min)[20] and enhanced activation of the renin–angiotensin–aldosterone system (RAAS).[19] Elevated heart rate not only reflects increased sympathetic tone but is also an independent predictor of cardiovascular morbidity and mortality, even among patients with controlled blood pressure.[21] This phenotype underscores the need for therapeutic strategies that address both blood pressure and heart rate modulation**.** Incorporating treatments within combination regimens that effectively modulate sympathetic activity and lower resting heart rate may offer additional cardiovascular protection.[16] Given the high burden of metabolic disease and early vascular aging among Indian patients, targeting heart rate as a co-primary therapeutic goal may enhance cardiovascular protection and improve long-term outcomes.

Even with growing awareness and availability of evidence-based treatment guidelines, many newly diagnosed hypertensive patients in India are still not receiving the right level of therapy—especially those at higher cardiovascular (CV) risk. A recent large Indian study involving over 4700 patients found that about 35% were started on monotherapy, even though guidelines recommend a combination treatment for patients at moderate to very high CV risk. Moreover, 38% of high-risk patients on dual therapy which according to risk categorisation were eligible for triple combination therapy. Additionally, 29% patients of it actually belonged to the higher risk category but still received just one antihypertensive drug. In fact, 10% patients had more severe grade 2 or 3 hypertension, where combination therapy is clearly needed to prevent complications.[12] Another study showing that nearly 75% of hypertensive patients fail to achieve adequate blood pressure control with monotherapy, highlighting its limited effectiveness in most cases.[22] This points to a major gap between guideline recommendations and actual practice. Reasons for this may include doctors being cautious about prescribing multiple drugs, concerns about side effects, or lack of tools to properly assess patient risk during consultations.

These findings emphasize the need to shift clinical practice toward initiating treatment with combination therapy, especially among hypertensive patients stratified into moderate to high cardiovascular risk categories using standardized risk assessment tools. By starting with a two-drug regimen in a single-pill combination, physicians can achieve better and faster blood pressure control while also improving medication adherence. This approach not only aligns with global and Indian guideline recommendations but also addresses the current gap of under-treatment seen in real-world settings. Adopting such a strategy early in treatment could significantly reduce long-term cardiovascular complications and improve outcomes for patients across India.

CARDIOVASCULAR RISK STRATIFICATION BASED APPROACH FOR HYPERTENSION MANAGEMENT

Cardiovascular risk stratification remains a cornerstone of hypertension management, guiding treatment thresholds, drug selection, and the intensity of combination therapy. Patients with high-normal BP and no or minimal risk factors are generally managed without pharmacological therapy, whereas those with grade 1 hypertension and low cardiovascular risk may begin with monotherapy or low-dose dual therapy depending on their risk profile.[23,24] As the number of risk factors increases—such as ≥3 risk factors or early evidence of organ damage—dual therapy becomes the recommended first-line approach even at lower BP grades to prevent progression.[24] In grade 2 hypertension, most patients require dual or triple combinations, especially when accompanied by CKD, diabetes, or HMOD.[24] For grade 3 hypertension or established CVD, guidelines uniformly support triple-drug therapy from the outset to achieve rapid and sustained BP control.[24] This structured risk-based approach reinforces that combination therapy—preferably as fixed-dose

formulations—remains central to effective and timely BP management across increasing risk strata.

CONCLUSION

Contemporary global and Indian data consistently demonstrate that early initiation of combination therapy preferably as a single-pill combination targeting multiple pathophysiological pathways of high blood pressure helps to achieve faster, more sustained blood pressure control, improves adherence, minimize adverse effects of antihypertensive drugs and reduces cardiovascular risk. Indian hypertensive patients should be categorized based on India specific risk calculator and manage high blood pressure through combination therapy for prevention of future cardiorenal complications.

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REFERENCES

1. World Health Organization. Global report on hypertension 2025: high stakes: turning evidence into action. Available at: https://www.who.int/publications/i/item/9789240115569. Accessed on 12 January 2026.
2. Burnier M. Antihypertensive Combination Treatment: State of the Art. Curr Hypertens Rep. 2015;17:51.
3. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290-300.
4. Bakris GL. Combined Therapy With a Calcium Channel Blocker and an Angiotensin II Type 1 Receptor Blocker. J Clin Hypertens. 2008;10:27-32.
5. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension. 2025;82(10):e212-e316.
6. Azizi M, Juraschek SP. A trans-Atlantic perspective on the 2025 AHA/ACC Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Circulation. 2025;152:743-7.
7. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension. 2025;82.
8. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45(38):3912-4018.
9. Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, et al. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2019;37:1768-74.
10. Bennett A, Chow CK, Chou M, Dehbi HM, Webster R, Salam A, et al. Efficacy and Safety of Quarter-Dose Blood Pressure-Lowering Agents: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hypertens Dallas Tex 1979. 2017;70:85-93.
11. Prabhakaran D, Roy A, Chandrasekaran AM, Kondal D, Mukherjee S, Kiru G, et al. Comparison of dual therapies for hypertension treatment in India: a randomized clinical trial. Nat Med. 2025;31:3169-75.
12. Alexander T, Hiremath JS, Swahney JPS, Chandra S, Jain P, Chandra P, et al. Identifying Drug Prescription in Newly Diagnosed Hypertension Patients in India. J Clin Hypertens Greenwich Conn. 2025;27:e14963.
13. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed Low-Dose Triple Combination Antihypertensive Medication vs Usual Care for Blood Pressure Control in Patients With Mild to Moderate Hypertension in Sri Lanka: A Randomized Clinical Trial. JAMA. 2018;320:566-79.
14. Rodgers A, Salam A, Schutte AE, Cushman WC, de Silva HA, Di Tanna GL, et al. Efficacy and Safety of a Novel Low-Dose Triple Single-Pill Combination Compared With Placebo for Initial Treatment of Hypertension. JACC. 2024;84:2393-403.
15. Rodgers A, Salam A, Schutte AE, Cushman WC, Silva HA de, Tanna GLD, et al. Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial. The Lancet. 2024;404:1536-46.
16. European Society of Cardiology. A single tablet with 4 blood pressure-lowering drugs can be more effective than taking 3 drugs in separate pills. Available at: https://www.escardio.org/The-ESC/Press-Office/Press-releases/A-single-tablet-with-4-blood-pressure-lowering-drugs-can-be-more-effective-than-taking-3-drugs-in-separate-pills. Accessed on 12 January 2026.
17. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, et al. Metabolic non-

communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11:474-89.
18. Hiremath JS, Wander GS, Dasbiswas A, Mantri RR, Khan A, Bardoloi N, et al. Bridging the Gap: Managing Hypertension in Indian Patients with Metabolic Syndrome. J Assoc Physicians India. 2025;73(5):e34-e40.
19. Zhao G, Wang T, Luan Y, Xu Y, Qin N, Chen W, et al. Research progress on the correlation between renin-angiotensin-aldosterone system (RAAS) and cardiovascular and cerebrovascular diseases. J Renin Angiotensin Aldosterone Syst. 2025;26:14703203251351194.
20. Chopra HK, Nanda NC, Das AK, Kripalani A, Jadhav U, Wander GS, et al. BEAT-HTN India: Burden, Epidemiology, and Trends of Hypertension - A Nationwide Survey. Cardiol Res. 2025;16:403-12.
21. Ho JE, Larson MG, Ghorbani A, Cheng S, Coglianese EE, Vasan RS, et al. Long-term Cardiovascular Risks Associated With an Elevated Heart Rate: The Framingham Heart Study. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2014;3:e000668.
22. Gorostidi M, De La Sierra A. Combination Therapy in Hypertension. Adv Ther. 2013;30:320-36.
23. Verma N, Rastogi S, Chia Y, Siddique S, Turana Y, Cheng H, et al. Non-pharmacological management of hypertension. J Clin Hypertens. 2021;23:1275-83.
24. Rosas-Peralta M, Mancia G, Camafort M, Galván-Oseguera H, Ferrario CM, Alcocer L, et al. Single pill combination therapy for hypertension: New evidence and new challenges: Combination Therapy for Hypertension. Trends Cardiovasc Med. 2025;35(8):497-503.

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