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Review Article

Combination therapy for hypertension management: insights from the Indian experts

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ABSTRACT

Cardiovascular diseases (CVDs) pose a significant global health challenge, with India bearing a disproportionate burden of CVD-related morbidity and mortality. Hypertension (HTN) is a major risk factor for CVDs, affecting nearly 30% of the Indian population. Achieving target blood pressure (BP) levels is crucial for reducing cardiovascular risk, necessitating aggressive antihypertensive therapy. Combination therapy has emerged as a cornerstone in HTN management, especially in high-risk patients. This review delves into the literature and perspectives of Indian cardiologists on combination therapy for HTN management. Despite the efficacy of contemporary antihypertensive medications, a substantial proportion of patients fail to reach target BP levels with monotherapy. Combination therapy offers synergistic effects, addressing multiple pathways involved in HTN pathogenesis. Recent guidelines recommend initiating treatment with two-drug combinations, transitioning to three-drug combinations in resistant cases. Combination therapy not only enhances BP control but also reduces the risk of cardiovascular events and mortality compared to monotherapy. Optimal management of HTN requires personalized approaches, considering individual patient profiles and comorbidities such as coronary artery disease (CAD), diabetes mellitus (DM), dyslipidemia, and heart failure (HF). In such cases, combination therapy plays a pivotal role in mitigating cardiovascular risks. ARB/CCB combination therapy, particularly telmisartan/amlodipine, demonstrates significant efficacy and tolerability across various patient populations, including those with metabolic risk factors and renal impairment. Expert recommendations highlight the importance of individualized therapy, patient education, early diagnosis, and initiation with dual therapy in India. Strategies to improve medication adherence and compliance, such as single-pill double or triple combinations, are emphasized. Moreover, awareness of newer treatment options and contactless diagnostic instruments is crucial for optimizing HTN management. In conclusion, combination therapy stands as a cornerstone in HTN management, offering enhanced efficacy, tolerability, and cardiovascular protection. Tailored approaches guided by expert recommendations are essential to address the growing burden of HTN and reduce the socioeconomic impact of CVDs in India.

Keywords: HTN, Combination therapy, CVDs, Cardiovascular risk, Personalized medicine, Telmisartan, Amlodipine

INTRODUCTION

Cardiovascular diseases (CVDs) continue to be a leading cause of death globally, posing a serious public health risk.[1] According to the global burden of disease (GBD) report, CVDs have risen to the top of the mortality list, putting significant strain on healthcare systems worldwide. Notably, the burden of CVDs is particularly obvious in India, where the country has a higher incidence of CVD-related mortality than the world average. According to statistics from the GBD research, India has a CVD death rate of 272 per 100,000 people,

which is higher than the global average of 235 per 100,000 population.[1] In barely over two decades, the incidence of CVD cases has risen dramatically, from 25.7 million in 1990 to a shocking 54.5 million by 2016. This more than two-fold rise highlights the critical need for comprehensive policies to combat India's increasing cardiovascular disease epidemic. Furthermore, in 2014, the World Economic Forum and the Harvard School of Public Health collaborated on research that shed light on the enormous economic implications of CVDs in India. The report's estimates foresee significant economic losses due to CVDs, with a startling number of about $2.17 trillion between 2012 and 2030.[2] Such staggering economic burdens highlight the importance of concerted efforts to deploy preventative interventions and optimize healthcare resources to reduce socioeconomic effect of CVDs in India.

Hypertension (HTN), a significant risk factor for CVDs, is alarmingly common among the Indian population, complicating disease treatment and preventative efforts. According to recent estimates, HTN affects nearly 30% of Indian people, worsening the country's cardiovascular morbidity and mortality.[1] Furthermore, the findings of the Great India BP study highlight the prevalence of HTN in the Indian population, with approximately one in every three persons suffering from this quiet but formidable precursor to cardiovascular issues.[3]

Identifying and attaining appropriate target blood pressure (BP) levels is critical in reducing the increased cardiovascular risk associated with HTN, especially in high-risk group patients. Aggressive antihypertensive medication is critical in achieving these goals, providing considerable cardiovascular risk reduction advantages.[4]

An advisory board meeting including eminent cardiologists from India was conducted to understand their perspectives on combination therapy for HTN management. This review provides an overview of relevant literature and summarizes the perspectives of Indian specialists on the combination therapy for hypertension.

HYPERTENSION MANAGEMENT WITH DUAL AND TRIPLE COMBINATION THERAPY

Despite the efficacy of contemporary antihypertensive medications, a substantial proportion-approximately 70%-of hypertensive individuals fail to attain the therapeutic target of BP below 140/90 mmHg when treated with monotherapy. The majority of hypertensive patients typically require a combination of antihypertensive medications to effectively reach therapeutic goals. Recent guidelines advocate for the initiation of treatment with two drugs in individuals exhibiting a systolic BP >20 mmHg and/or a diastolic BP >10 mmHg above the specified targets, as well as in those with heightened cardiovascular risk. Furthermore, a notable proportion of patients-approximately 25%-may necessitate the addition of a third antihypertensive agent to attain desired therapeutic outcomes.[5]

In scenarios where hypertensive patients exhibit inadequate BP control, therapeutic strategies typically entail either escalating the dosage of monotherapy, thereby increasing the potential for adverse effects, or transitioning to combination drug therapies with a reduced propensity for side effects. Timely initiation of treatment, expedited achievement of therapeutic goals, and vigilant adherence to medication regimens are essential to minimize the likelihood of complications and optimize clinical outcomes.[6,7]

The etiological routes that contribute to high BP in individuals are diverse, and monotherapy often targets one or two of these mechanisms. In contrast, using combination pharmacotherapy allows for contemporaneous management across multiple separate HTN pathways. Antihypertensive effectiveness can be increased by two to fivefold when two medicines with different mechanisms work together. Clinical evidence suggests that while increasing the dosage of monotherapy reduces coronary events by 29% and cerebrovascular events by 40%, combining two antihypertensive agents with different mechanisms results in even greater risk reductions, with coronary events decreasing by 40% and cerebrovascular events decreasing by 54%. Thus, combination treatment appears as a more effective technique for protecting target organs than merely raising the dosage of monotherapy.[5]

Recent ESH 2023 guidelines advocate starting therapy with a two-drug combination, then increasing the dosage of the combination components or switching to a three-drug combination as the next therapeutic step. Furthermore, the recommendations urge for the use of single tablet combinations whenever possible. Initial monotherapy may be recommended in some patient populations, such as the elderly, fragile patients, those with minor BP elevations, or those with high normal BP and a considerably raised cardiovascular risk.[8]

HTN is the leading risk factor for the development of CAD and HF.[9,10] When combined with comorbid disorders like diabetes and dyslipidaemia, HTN increases the risk of cardiovascular disease.[11] As a result, the need for accurate and effective management is critical. Achieving and maintaining a BP target of <130/80 mm of Hg is crucial for patients at high risk of cardiovascular complications, including HF, CAD, DM, and dyslipidaemia. For individuals with HF, a combination of diuretics, angiotensin converting enzyme inhibitors/ Angiotensin II receptor blockers (ACE inhibitors/ARBs), and beta blockers is recommended to alleviate symptoms and enhance prognosis. In patients with CAD or DM, early initiation of antihypertensive therapy, coupled with personalized combination regimens, is pivotal for mitigating cardiovascular risks and improving long-term outcomes. Adhering closely to European Society of

Cardiology (ESC) and American College of Cardiology (ACC) guidelines ensures a comprehensive approach to HTN management, aiming to reduce the burden of cardiovascular disease in vulnerable patient populations.[1]

OPTIMAL MANAGEMENT OF HTN TO MITIGATE RISK OF CAD

HTN constitutes 25% of CAD risk, while abnormal lipids contribute 75%. Treatment of HTN decreases CAD risk by 17%. The BP target for individuals with prior CAD or ischemic heart disease (IHD) is <130/80 mmHg, with caution advised against lowering levels below <120/70 mmHg. RAAS inhibitors and beta-blockers are frontline agents for those with prior CAD, alongside consideration of calcium channel blockers (CCBs) in anginal symptom presence. Recent studies preferentially recommend ARBs over ACE inhibitors in stable CAD patients for HTN management, yielding comparable cardiovascular outcomes. Thiazide-like diuretics, especially chlorthalidone, are advocated for additional BP control in CAD patients. Regular BP and cardiac function monitoring, ideally every three months, are crucial for this high-risk population. High adherence to antihypertensive treatment significantly reduces cardiovascular event risk, underscoring its importance in secondary prevention of major adverse cardiovascular events (MACE) in patients with HTN and CAD. A target BP of less than 130/80 mmHg is recommended for adults with stable IHD and HTN. Initial therapy involves dual combinations of ACE inhibitors or ARBs plus beta-blockers or CCBs, followed by triple combinations and eventually augmented with spironolactone or other diuretics, alpha-blockers, or beta-blockers.[1,12]

OPTIMAL MANAGEMENT OF HTN WITH DYSLIPIDAEMIA

HTN and dyslipidaemia are major CV risk factors often coexisting; around two-thirds of hypertensive patients have dyslipidaemia, and half of dyslipidemic patients are hypertensive. Elevated cholesterol levels double CV risk in hypertensive individuals. Despite preventable nature of CVD through risk factor management, there's tendency to prioritize treating individual diseases like HTN/ hypercholesterolemia over managing overall CV risk.[13]

Combination therapy, exemplified by a single-pill formulation containing an angiotensin-converting enzyme inhibitor, a calcium channel blocker, and a statin, has demonstrated enhanced adherence and reduced cardiovascular risk. Triple therapy, comprising an angiotensin-converting enzyme inhibitor, a calcium channel blocker, and a statin, shows a marked decrease in major cardiovascular events, attributed to synergistic effects at the vascular level translating to clinical efficacy. Fixed-dose combinations of antihypertensive agents and a statin offer improved management for hypertensive patients with concurrent hypercholesterolemia, enhancing adherence, expediting therapeutic attainment, and lowering adverse cardiovascular outcomes. Clinicians should recognize factors linked to poor adherence, such as duration of therapy, youth, female gender, and absence of prior cardiovascular events, to target and mitigate risk, ultimately reducing cardiovascular events.[13]

OPTIMAL MANAGEMENT OF HTN WITH DIABETES

HTN and DM represent prominent lifestyle diseases in Indian and South Asian populations, frequently co-occurring due to shared pathophysiological mechanisms. Common pathways include obesity, insulin resistance, inflammation, and oxidative stress. In India, up to 50% of HTN cases are concomitantly diagnosed with DM.[14]

Research society for the study of diabetes in India (RSSDI) recommends non-pharmacological interventions as the initial approach, emphasizing nutrition education to decrease salt, sodium, and trans-fat intake while promoting consumption of nuts, fresh fruits, vegetables, and potassium-rich foods. For HTN control, RSSDI advises engaging in 50 to 60 minutes of physical activity three to four times weekly. ARBs are the preferred first-line therapy for pharmacological management due to their superiority over other antihypertensive agents like ACE inhibitors. Combination therapy with CCBs alongside ARBs is encouraged to enhance BP control and mitigate adverse events. Additionally, RSSDI recommends considering novel molecules such as cilnidipine in combination with ARBs to provide superior cardiovascular and renal protection for diabetic hypertensive patients.[14]

OPTIMAL MANAGEMENT OF HTN TO MITIGATE RISK OF HF

Individuals with DM face a doubled risk of incident HF compared to those without diabetes, attributable to the presence of major HF risk factors such as obesity, advanced age, sleep apnoea, dyslipidaemia, HTN, chronic kidney disease (CKD), and CAD. For adults with HF with reduced ejection fraction (HFpEF) exhibiting volume overload symptoms, the ACC recommends initiating diuretics for HTN control, followed by ACE inhibitors or ARBs and beta blockers to achieve a systolic BP of <130 mmHg. According to the 2018 ESC guidelines, initial therapy should comprise ACE inhibitor or ARB plus diuretic plus beta blocker, with second-line treatment involving ACE inhibitor or ARB plus diuretic plus beta-blocker plus mineralocorticoid receptor antagonist (MRA). ESC HF consensus 2019 advocates for effective combinations for HFrEF, including sacubitril/valsartan + beta-blocker + MRA, and ACE inhibitor + beta-blocker + MRA + ivabradine, resulting in reduced all-cause mortality and hospitalizations. Additionally, the 2016 ESC HF guidelines underscore the role of ivabradine in reducing HF hospitalization and cardiovascular death in symptomatic patients with reduced left ventricular ejection fraction (LVEF) and elevated sinus rhythm.[1]

Considering the significance of combination therapy, the panel deliberated on role of combining ARBs with CCBs.

THERAPEUTIC BENEFIT OF COMBINATION THERAPY IN MANAGEMENT

Combination therapy for HTN typically involves four main classes of medications: thiazide diuretics, CCBs, ACEIs, and ARBs. It's important to note that ACEIs and ARBs should not be used concurrently. Initial therapy for patients with HF with reduced ejection fraction typically consists of a beta blocker and either an ACEI, ARB, or angiotensin receptor-neprilysin inhibitor, followed by additional therapy with a mineralocorticoid receptor antagonist and a diuretic based on volume status. Patients with chronic kidney disease and proteinuria should receive treatment with an ACEI or ARB in combination with a thiazide diuretic or calcium channel blocker. For patients with DM, treatment is similar to those without diabetes unless proteinuria is present, in which case combination therapy should include an ACEI or ARB.[15]

Combining a CCB with an ARB offers significant clinical benefits. This approach aligns with recommendations from the Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high BP (JNC 7) guidelines, leveraging the complementary mechanisms of action of both agents to achieve enhanced efficacy in lowering BP. Studies indicate that this combination results in additive BP-lowering effects across various patient populations with a lower incidence of adverse events (AEs). Additionally, ARBs mitigate CCB-induced peripheral oedema by reducing fluid volume and dilating both arterial and venous capillary beds, thereby enhancing tolerability. Unlike diuretics and β-blockers, neither CCBs nor ARBs increase the risk of new-onset diabetes, with ARBs potentially improving insulin sensitivity and exerting beneficial effects on metabolic pathways. Each agent also offers specific benefits within its drug class, such as stroke protection and renal protection with ARBs, and stroke reduction and treatment of angina and cardiac ischemia with CCBs.[16]

While primary aim of antihypertensive therapy is BP control and improved cardiovascular and renal outcomes, evidence suggests compelling indications for specific drug classes as initial therapy. For instance, ARBs are indicated for conditions like HF and CKD, while CCBs are preferred for left ventricular hypertrophy and angina. Combinations of agents can offer additional benefits based on these indications. Major HTN guidelines outline these compelling indications.[16]

In this context, the combination of telmisartan and amlodipine is a preferred choice in patients with hypertension due to its substantial and sustained 24-hour BP-lowering effect, as well as its ability to reduce the risk of cardiovascular events and death.[17] This combination is particularly effective in patients with metabolic risk factors, allowing a high proportion of them to achieve BP targets.[18] In diabetic hypertensive patients, the telmisartan/amlodipine combination has been shown to provide prompt and greater BP decreases compared to amlodipine monotherapy, with the majority of patients achieving the BP goal.[19]

Furthermore, in hypertensive patients with diabetic and non-diabetic renal impairment, the use of an angiotensin II receptor blocker-based combination therapy, such as telmisartan/amlodipine, is recommended due to its superior Reno protective and cardiovascular benefits.[20]

A recent observational prospective study conducted across five centres in India by Rajadhyaksha et al assessed current clinical practices for HTN management. Findings revealed that diabetes (31.6%) was the most prevalent comorbidity. Combination therapy of amlodipine + telmisartan was most prescribed regimen overall (27.1%), with preference for this combination (16%) observed particularly in patients with the diabetes.[21]

EXPERT SUGGESTIONS FOR HTN MANAGEMENT

HTN with different comorbidities or age group

Recent trends indicate a rise in HTN among younger individuals, particularly in rural areas, due to lifestyle factors like stress and obesity. Over the past decade, patient profiles have shifted, with an increase in younger, obese, and prediabetic/diabetic individuals presenting with HTN.

Personalized treatment approach

While guidelines provide valuable insights, HTN treatment should be personalized to suit individual patient conditions and needs.

Preferred medications

Telmisartan is favoured in HTN management, especially for newly diagnosed patients, those with diabetes, CKD, or IHD. Additional medications may be considered based on specific patient profiles and comorbidities.

Treatment strategies

The consensus leans towards increasing the dose of current medication rather than switching drugs for HTN management. Combination therapy is preferred to achieve target BP, reducing the long-term economic burden on patients.

Recommended therapies

Monotherapy is recommended for isolated high BP, with diuretic combinations preferably administered in the morning. Beta blockers may be suitable for managing nocturnal BP variations. Dual therapy is recommended

for higher BP levels or in the presence of risk factors like HF or DM with low HTN goals.

Switching medications and combination therapy

Medication switching is favoured when BP remains uncontrolled, with angiotensin receptor blockers (ARBs) and CCBs being preferred combinations. Telmisartan with Cilnidipine or β blockers may be considered for patients with sympathetic overactivity.

Specific scenarios

β blockers are not recommended for uncomplicated HTN but may be suitable for managing conditions such as angina, HF/in specific patient demographics. Combination therapy with telmisartan and CCBs is favoured for HTN with CAD, while β blockers are preferred for IHD.

Management of comorbidities

Management strategies for HTN with dyslipidaemia typically involve combining telmisartan with atorvastatin. In hypertensive patients with CKD, Telmisartan is preferred followed by amlodipine and then β blockers.

Treatment considerations

Single-pill triple combinations should be approached cautiously, and fixed-dose combinations FDCs should only be considered after BP control with individual drugs. Patient education and compliance remain significant challenges in HTN management. Awareness of newer treatment options, personalized approaches, and early diagnosis are emphasized for effective management.

CONCLUSION

In conclusion, combination therapy represents a cornerstone in HTN management, offering enhanced efficacy, tolerability, and cardiovascular protection. Tailored approaches guided by expert recommendations are essential to address the growing burden of HTN and reduce the socioeconomic impact of CVDs in India

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