Potential Role of Triple Combination of Amlodipine + Telmisartan + Hydrochlorothiazide in Hypertension Management

Content

Background and Objective of the Survey

Hypertension is one of the leading causes of the increasing global deaths due to cardiovascular diseases (CVDs) and chronic kidney diseases (CKDs) 230 million adults are suffering from hypertension in India. Study reports suggest that more than half of hypertension patients have uncontrolled blood pressure (BP) in India. Although monotherapy may be effective for some patients, most patients usually require a multifactorial approach involving 2 or more antihypertensive agents addressing different pathophysiologic mechanisms to achieve BP control. Dual combinations do not achieve BP control in 15-20% of patients, and it is estimated that 3 antihypertensive agents are needed to achieve BP control in approximately 25% of patients.

Many studies show that individuals with more CV risk factors generally need more anti-hypertension agents to successfully manage their BP. Combination therapy using different mechanisms can lead to more effective BP lowering. In addition, combination therapies block counter-regulatory mechanisms that often limit the efficacy of monotherapy.

The combination of Telmisartan 40 or 80 mg/day and HCTZ 12.5 mg/day (as a fixed-dose combination in some trials) is more effective than each agent alone in patients with mild to moderate hypertension. Patients with severe hypertension, Telmisartan 80 to 160 mg/day plus HCTZ and Amlodipine reduced BP as effectively as enalapril 20 to 40 mg/day in combination with the same agents. The triple drug fixed dose combination of Telmisartan, Amlodipine and HCTZ is found to be effective and safe option for the optimal management of hypertension.

The objective of the survey is:

To evaluate the potential role of triple combination of Amlodipine + Telmisartan + Hydrochlorothiazide in hypertension management.

Methodology of the Survey

A survey was conducted the potential role of triple combination of Amlodipine + Telmisartan + Hydrochlorothiazide in hypertension management. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Mechanisms of action in combination therapy
- Triple-combination therapy in hypertension and its benefits
- Telmisartan – pharmacodynamic and pharmacokinetic properties, therapeutic efficacy, tolerability, dosage and administration
- Amlodipine – clinical indications, pharmacodynamics and pharmacokinetics, monotherapy and combination therapy
- Hydrochlorothiazide – antihypertensive efficacy and clinical implications
- Abstract

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction

Hypertension is one of the leading causes of the increasing global deaths due to CVDs and CKDs 230 million adults are suffering from hypertension in India. Study reports suggest that more than half of hypertension patients have uncontrolled BP in India. An increased prevalence of high BP in young Indian adults has become a serious health concern. Indian patients should be educated about the benefits of lifestyle modification, treatment, and compliances, which may help in achieving the targeted BP control in the population. Dual-drug combination treatment initiation, preferably in a single pill for stage II hypertension is also recommended. ARBs as anti-hypertensive agents are the most common component of dual and triple therapies in India.[1]

Although monotherapy may be effective for some patients, most patients usually require a multifactorial approach involving 2 or more antihypertensive agents addressing different pathophysiologic mechanisms to achieve BP control. Dual combinations do not achieve BP control in 15-20% of patients, and it is estimated that 3 antihypertensive agents are needed to achieve BP control in approximately 25% of patients. This estimate is consistent with data from the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), where after 5 years, 23% of study participants required 3 or more antihypertensive drugs to achieve a BP goal of <140/90 mmHg. Other clinical trials have reported even greater proportions of participants requiring 3 or more agents.[2]

In the International Verapamil-Trandolapril Study (INVEST), all participants had coronary artery disease and approximately half required 3 or more antihypertensive drugs to achieve BP control at 2 years. Additional studies, including the Study on Cognition and Prognosis in the Elderly (SCOPE) and the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, have reported the proportion of participants requiring 3 or more anti-hypertensive agents to be 49% and 32%, respectively. In the African American Study of Kidney Disease and Hypertension (AASK), participants received, on average, agents from 3 drug classes to achieve lower BP goals. Given this collective data, the need for 3-drug combinations in hypertension management is well documented. The strategy of triple-combination therapy was first investigated over 40 years ago with a randomized, controlled trial evaluating the combination of reserpine, hydralazine,

and hydrochlorothiazide (HCTZ); although results were favorable, this approach gave way to an era of sequential monotherapy. Over the past several decades, as the multifactorial nature of hypertension became well accepted and better understood, a number of antihypertensive agents with improved efficacy and tolerability became available as fixed-dose combination products. Current guidelines support the use of combination therapy with agents with complementary mechanisms of action to achieve BP control. Therefore, in clinical practice, the focus is less on identification of the best single agent and more on the identification and use of preferred combinations for hypertension treatment. Several Food and Drug Administration (FDA)-approved triple-combination treatments for hypertension are available, including valsartan (VAL)/Amlodipine (AML)/HCTZ, olmesartan (OM)/AML/HCTZ, and aliskiren (ALI)/AML/HCTZ. This review will dis-cuss the rationale for combining antihypertensive agents with complementary mechanisms of action with a particular focus on approved triple-combination treatments.[2]

Complementary antihypertensive mechanisms of action in combination therapy

The multiple physiologic pathways contributing to BP elevation underscore the limitations of single-agent therapy. Not only is it challenging to normalize BP by addressing only a single pressor mechanism, but targeting a single mechanism often results in compensatory responses that undermine efficacy or lead to unwanted adverse events (AEs) related to the antihypertensive agent .Thus, combining agents that address different aspects of the pathophysiology underlying hypertension (i.e., targeting both renin-dependent and renin-independent pathways) may result in greater BP lowering and potentially improve tolerability. For example, the combination of an angiotensin receptor blocker (ARB) or direct renin inhibitor (DRI) with a calcium channel blocker (CCB) and a diuretic is based on the complementary mechanisms of action of these drug classes.[2]

Triple-combination therapy in hypertension

While each of the drug classes has clear efficacy in the management of hypertension, overwhelming evidence supports those combinations of different drug classes, particularly those with complementary mechanisms of action, produce greater BP reductions compared with monotherapy. Based on a meta-analysis of over 40 hypertension trials, combining antihypertensive agents from 2 different classes was estimated to result in a 5-fold greater BP

reduction compared with doubling the dose of a single agent. Beyond BP reduction the combination of 3 antihypertensive agents, each at half the standard dose, has been estimated to produce greater reductions in coronary heart disease and stroke risk compared with standard doses of monotherapy. A variety of FDA-approved, fixed-dose, dual-combination drugs and, more recently, triple-combination treatments for hypertension are available. Initiating antihypertensive treatment with a com-bination regimen (including single-pill combinations) has been associated with greater and more rapid BP control as well as lower risk of developing a major cardiovascular event compared with initiating treatment with monotherapy and then switching to combination therapy. When triple-combination therapy is needed, the European Society of Cardiology/European Society of Hypertension guidelines recommend the use of an RAAS blocker with a CCB and a diuretic as rational and effective.[2]

Benefits of triple-combination treatment

Approximately 50% of adults with hypertension in the US do not have adequate BP control despite treatment. Factors that contribute to this inadequate control may include under-treatment relative to current guideline recommendations and poor adherence to medications. Poor adherence can lead to negative outcomes; in a recent study of patients with hypertension, worse adherence to medications was associated with a higher incidence of stroke symptoms. Fixed-dose, single-pill combination treatments simplify antihypertensive regimens and result in improved patient adherence to therapy compared with multiple-pill/free-combination regimens. Meta-analyses have reported that fixed-dose combinations resulted in significant improvements (29% increase) in adherence and persistence and a significant reduction (24%) in the risk of noncompliance compared with free-drug combinations in patients with hypertension. Clinical inertia, or the failure of a physician to initiate or intensify therapy when indicated, results in under-treatment and is another important contributor to inadequate BP control. The availability of fixed-dose combinations that lead to more rapid achievement of BP goals can help address clinical inertia and ultimately improve BP control.[2]

Telmisartan

Telmisartan, also referred to as BIBR 277, is a non-peptide amphiphilic molecule with a benzimidazole structure with heteroaromatic substituents which possesses one acidic and two basic centers. Telmisartan is a highly selective (Ki = 3.7 nM), competitive AT1 receptor

antagonist lacking intrinsic activity at the AT1 receptor. Moreover, Telmisartan exhibits no relevant affinity (Ki >10,000 nmol/L) for the AT2 receptor and does not directly modify renin or ACE enzymatic activity. By antagonizing AT1 receptor-mediated signaling, Telmisartan inhibits vasoconstriction and aldosterone secretion induced by angiotensin II, the main effector peptide of the RAS, and consequently lowers systemic BP.[3]

Pharmacodynamic properties

Telmisartan is an angiotensin II (AII) receptor antagonist that is highly selective for type 1 AII (AT1) receptors. In normotensive male volunteers enrolled in a randomized, double-blind, placebo-controlled study, Telmisartan 20 to 80 mg dose-dependently attenuated AII induced increases in diastolic BP (DBP), systolic BP (SBP) and heart rate (HR). Single doses of Telmisartan 20 to 80 mg inhibited AII-induced increase in DBP by >25% within 0.3 to 1.1 hours when administered 30 minutes after intravenous administration of AII (the dose of AII was that which produced maximal increases in SBP). During repeated challenges, AII-induced increases in BP were inhibited by >25% for 26.9, 35.4 and 40.5 hours among those randomized to Telmisartan 20, 40 and 80 mg, respectively. Plasma levels of AII and active renin increased to maxima within 4 hours of treatment.[4]

In concert with these neurohormonal changes, urinary flow and sodium and potassium excretion were significantly and dose-dependently increased in the first 3 hours after administration of Telmisartan 20 to 80 mg. In untreated patients with hypertension Telmisartan had a significant natriuretic effect during the first 3 days of treatment. Urinary sodium excretion was significantly greater in recipients of Telmisartan 80 mg/day than in those randomized to Telmisartan 40 mg/day or placebo. The differences between groups were no longer significant after 15 days of treatment, although a trend toward greater total daily sodium excretion was apparent in recipients of the higher Telmisartan dosage. Significant increases in plasma renin activity and AII levels occurred in patients treated with Telmisartan 40 to 120 mg/day in a randomized, placebo controlled 4-week study.[4]

Telmisartan has a potassium-sparing effect in patients with hypertension that attenuated the kaliuretic effect of HCTZ when the 2 drugs were co-administered. Systemic vascular resistance was reduced and systemic vascular and brachial artery compliance increased in patients with

hypertension during treatment with Telmisartan 40 mg/day. Telmisartan 40 mg/day reduced arterial stiffness in patients with type 2 diabetes mellitus and hypertension in a randomized, double-blind, placebo-controlled, 3-week, crossover study. During 9 months of treatment with Telmisartan 40 or 80 mg/day, BP and left ventricular (LV) mass index were significantly reduced compared with baseline in patients with hypertension and mild to moderate LV hypertrophy. When introduced 7 days after the withdrawal of ACE inhibitors, single doses of Telmisartan 10 to 80 mg improved hemodynamic variables in patients with stable mild to moderate congestive heart failure enrolled in a multicenter, randomized, double-blind, placebo-controlled study. In patients with mild to moderate congestive heart failure, no significant change in exercise capacity, ejection fraction, New York Heart Association class or health-related quality of life score occurred when enalapril 10 mg twice daily was replaced with Telmisartan 10 to 40 mg/day in a 12 week, randomized, double-blind, multicenter trial.[4]

Pharmacokinetic properties

There is a high degree of interindividual variability in the plasma concentration profile of Telmisartan. As a result of saturable first-pass metabolism, the oral bioavailability of Telmisartan is dose dependent (42.4% after a single 40 mg oral dose) and maximum plasma concentrations (Cmax) increase disproportionately after oral administration. Administration with food reduced the bioavailability of a 40 mg dose by 6%, thus Telmisartan may be taken with or without food. Steady state plasma concentrations were achieved after approximately 5 to 7 days. The area under the plasma concentration-time curve (AUC) of Telmisartan was 1.2-fold greater in elderly females than males after administration of 120 mg/day for 7 days.[4]

Telmisartan is extensively distributed to tissues (mean apparent volume of distribution at steady state was 460 to 510L in healthy male volunteers) and is highly bound (99.5%) to plasma proteins, including albumin, α-1-acid glycoprotein, γ-globulin and lipoproteins. A pharmacologically inactive acyl glucuronide conjugate, which comprised 16% of the drug in circulation after a single 40 mg dose, is the only metabolite of Telmisartan. Biliary-fecal excretion is the primary route of elimination of Telmisartan and its metabolite. The mean terminal elimination half-life of the drug was ≈24 hours in healthy volunteers and patients with hypertension. Cmax, AUC0-24 and AUC0-∞ of Telmisartan were markedly reduced and the

mean free fraction of the drug in plasma was approximately doubled in patients undergoing dialysis compared with healthy volunteers.[4]

The absolute bioavailability of Telmisartan was increased in patients with hepatic impairment (to 97.2%) and the Cmax and AUC0-∞ of Telmisartan were approximately 3-fold greater in hepatically-impaired patients compared with healthy controls. In healthy male volunteers, Telmisartan had a small effect on plasma warfarin concentrations, but there was no change in the international normalized ratio. AUC, Cmax and minimum plasma concentrations of digoxin increased during coadministration with Telmisartan in healthy male volunteers. The increase in Cmin did not exceed the predefined range for a lack of interaction, but serum digoxin concentrations should be monitored during concomitant therapy with Telmisartan. Telmisartan had no effect on the pharmacokinetics of Amlodipine, glibenclamide (glyburide), HCTZ, ibuprofen, paracetamol (acetaminophen) or simvastatin.[4]

Therapeutic efficacy

Placebo-controlled and dose-finding studies

Oral Telmisartan 20 to 160 mg once daily consistently reduced supine SBP and DBP (primary end-point) to a significantly ($p \leq 0.05$) greater extent than placebo at trough or throughout the 24-hour dosage interval in randomized, double-blind, multicenter studies in patients with mild to moderate hypertension or isolated systolic hypertension. Generally, Telmisartan 20 to 160 mg/day did not show a significant dose-response relationship with the exception of 1 study, where a statistically significant linear dose-response relationship for SBP was observed. Dosages above 80 mg once daily did not result in further BP reduction in patients with mild to moderate hypertension. The drug was generally more effective in White than in Black patients, although Black patients still experienced clinically meaningful reductions in BP with Telmisartan.[4]

Comparisons with other antihypertensive agents

Telmisartan 40 mg titrated to 80 or 120 mg once daily produced similar antihypertensive effects, as assessed by primary end-points, to Amlodipine 5 mg titrated to 10 mg once daily or atenolol 50 mg titrated to 100 mg once daily (with or without the addition of HCTZ if patients remained hypertensive) in 232 to 533 patients with mild to moderate hypertension in

randomized, double-blind, multicenter, titration-to-response trials. Ambulatory BP monitoring (ABPM) has shown that Telmisartan 40 mg titrated to 120 mg provides better BP control during night-time and in the last 4 hours of the dosage interval than Amlodipine 5 mg titrated to 10 mg. In randomized, double-blind studies of 4 to 52 weeks 'duration in patients with mild to moderate hypertension, Telmisartan 20 mg once daily titrated to 80 or 160 mg (when patients remained hypertensive) was similar in efficacy to enalapril 5 mg once daily titrated to 20 mg or lisinopril 10 mg once daily titrated to 40 mg (HCTZ was also added when patients remained hypertensive in these studies) and Telmisartan 40 to 160 mg once daily was at least as effective at reducing BP as enalapril 20 mg once daily and similar in efficacy to lisinopril 20 mg once daily.[4]

Telmisartan 40 mg/day titrated to 80 mg and enalapril 10 mg/day titrated to 20 mg [with furosemide (frusemide) if patients remained hypertensive] appeared to reduce BP to a similar extent in patients with mild to moderate hypertension and moderate renal failure. Telmisartan 80 mg once daily was more effective at reducing BP measured by ABPM over the 18- to 24-hour post dose interval or the whole 24- hour post dose interval than submaximal dosages of losartan (50 mg once daily) or valsartan (80 mg once daily) and was as effective as the fixed-dose combination of losartan 50 mg plus HCTZ 12.5 mg once daily. These randomized trials were conducted in patients with mild to moderate hypertension; 2 trials were nonblind, 1 was double-blind. In patients with severe hypertension, Telmisartan 80 mg/day titrated to 160 mg/day reduced BP as effectively as enalapril 20 mg/day titrated to 40 mg/day (in patients who remained hypertensive on monotherapy, HCTZ 25 mg/day and Amlodipine 5 mg/day were added sequentially) in a randomized, nonblind, multicenter study.[4]

In combination and in comparison, with HCTZ

In randomized, double-blind trials, the combination of Telmisartan 40 or 80 mg/day and HCTZ 12.5 mg/day (as a fixed-dose combination in some trials) is more effective than each agent alone in patients with mild to moderate hypertension. Telmisartan monotherapy was generally more effective than hydrochlorothiazide monotherapy at lowering BP in a similar patient group, but these agents were similar in efficacy in patients with isolated systolic hypertension. Telmisartan 40 or 80 mg once daily administered alone or in combination with other

antihypertensive agents produced a sustained antihypertensive effect for up to 1 (≈64% of patients) or >3 years (≈84% of patients) in 2 noncomparative extension studies.[4]

Tolerability

According to pooled tolerability data, adverse events reported by >5300 patients who received Telmisartan (including 1758 patients in placebo-controlled studies) were generally mild and transient and occurred at a similar incidence as those reported by placebo recipients. The only adverse events occurring at a markedly higher incidence with Telmisartan than placebo was back pain (2.6 vs 0.9%), diarrhea (2.8 vs 1.1%) and upper respiratory tract infection (6.7 vs 5.1%), although headache was much more common with placebo than Telmisartan (7.1 vs 15.1%). 2.8% of patients who received Telmisartan and 6.1% of placebo recipients discontinued treatment because of adverse events. In randomized, double-blind or nonblind, comparative trials, Telmisartan had a similar tolerability profile to Amlodipine or atenolol (with or without HCTZ), other AII receptor antagonists (valsartan and losartan) and HCTZ alone or Telmisartan in combination with HCTZ (including Telmisartan 40 or 80 mg with HCTZ as a fixed-dose combination), although oedema was more common with Amlodipine than Telmisartan.[4]

Telmisartan was also at least as well tolerated as the ACE inhibitors lisinopril and enalapril. Furthermore, Telmisartan produced a significantly lower incidence of dry cough than lisinopril in patients with a history of ACE inhibitor-related cough in a study for which this parameter was the primary end-point (15.6 vs 60%; $p = 0.001$). Telmisartan and enalapril, both in combination with HCTZ and Amlodipine, were similarly tolerated in patients with severe hypertension.[4]

Dosage and administration

Telmisartan, alone and in combination with other antihypertensive agents, is indicated for the treatment of hypertension. The usual recommended dosage is 40 mg once daily. Some patients may experience benefit at a dosage of 20 mg/day. In patients in whom a satisfactory BP response is not achieved, the dosage may be increased to a maximum of 80 mg once daily. The maximum antihypertensive effect is generally attained 4 to 8 weeks after the start of treatment. As HCTZ complements the BP-lowering effect of Telmisartan, the combination of Telmisartan

and a thiazide diuretic may be appropriate in some patients. Telmisartan may be given with or without food. Dosage adjustments are not required on the basis of age, gender or renal dysfunction. The manufacturer recommends that Telmisartan be used with caution in patients with hepatic impairment, in whom the dosage should not exceed 40 mg/day, and those with depleted intravascular volume.[4]

Place of Telmisartan in the management of hypertension

There are many therapeutic options for the management of patients with hypertension, including 6 main classes of antihypertensive drugs which provide broadly similar, clinically significant reductions in BP. The main classes of antihypertensive drugs include AII receptor antagonists, diuretics, β-adrenoceptor antagonists, calcium channel antagonists, ACE inhibitors and αadrenoceptor antagonists. The classes mainly differ with regard to adverse event profiles and the amount of evidence supporting long term improvements in morbidity and mortality. Recent guidelines for the management of hypertension from the third working party of the British Hypertension Society (1999) and the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High BP (1997) recommend thiazide diuretics or β-adrenoceptor antagonists as first-line drug therapy in otherwise healthy patients with hypertension.[4]

The most extensive direct evidence for a reduction in cardiovascular mortality and morbidity is with diuretics and β-adrenoceptor antagonists. Another drug class should be administered if there are contraindications for diuretics or β-adrenoceptor antagonists or compelling indications for the other drugs; for example, prescribing AII receptor antagonists for patients who do not tolerate ACE inhibitors (usually because of cough). If monotherapy does not adequately lower BP, it is recommended that another agent is substituted or added. In contrast, recent guidelines issued jointly by the WHO and the International Society of Hypertension (1999) indicate that all 6 major drug classes, including AII receptor antagonists, are suitable as initial therapy for the pharmacological management of hypertension, but advise that preference be given to agents with proven mortality/ morbidity benefits. As with the other 2 sets of guidelines, it is recommended that each patient's comorbidities and individual needs are considered when deciding on treatment. The guidelines also recommend the use of low-dose

combination therapy, such as the combination of AII receptor antagonists and diuretics, before the up titration of monotherapy in order to achieve BP control.[4]

Generally, drugs that are intrinsically long acting are preferred for the treatment of hypertension because hypertension requires persistent, rather than intermittent, control. Compliance is thought to improve with once daily administration; a long-acting effect minimizes variation in BP lowering during a 24-hour dosage interval and, if doses are missed, beyond the dosage interval. Telmisartan is a selective AII receptor antagonist which is highly selective for the AT1 receptor, and has a long duration of action and a long mean terminal elimination t1⁄2 of about 24 hours. At a wide range of dosages, including the recommended dosages of 40 and 80 mg once daily, this drug has demonstrated good antihypertensive efficacy in double-blind, randomized, placebo-controlled clinical trials in both men and women with mild to moderate hypertension. Telmisartan was generally more effective at reducing BP in White than in Black patients, although this latter patient group still experienced clinically meaningful reductions in BP with Telmisartan.[4]

Telmisartan 40 mg titrated to 120 mg/day demonstrated similar antihypertensive efficacy, as assessed by primary endpoints, to titrated dosages of Amlodipine 5 to 10 mg/day and atenolol 50 to 100 mg/day in comparative trials. ABPM has shown that Telmisartan 40 mg titrated to 120 mg provides better BP control during night-time and in the last 4 hours of the dosage interval than Amlodipine 5 mg titrated to 10 mg. Telmisartan 40 to 160 mg once daily is also at least as capable of reducing BP as enalapril 20 mg once daily and has similar efficacy to lisinopril 10 to 40 mg once daily (with or without HCTZ). In patients with severe hypertension, Telmisartan 80 to 160 mg/day plus HCTZ and Amlodipine reduced BP as effectively as enalapril 20 to 40 mg/day in combination with the same agents. The combination of Telmisartan 40 or 80 mg/day and HCTZ 12.5 mg/day was more effective than each agent alone and Telmisartan monotherapy was generally more effective than HCTZ monotherapy at lowering BP in patients with mild to moderate hypertension.[4]

Amlodipine

Calcium channel blockers (CCBs) were first introduced over 35 years ago initially for coronary heart disease (CHD), but they soon gained wide recognition for their efficacy in hypertension.

The initial indication, besides hypertension, also included angina, peripheral vascular disease and some arrhythmic conditions. Amlodipine has many unique qualities that set it apart from other agents in this class.[5]

Clinical indications, pharmacodynamics and pharmacokinetics

Amlodipine is a long-acting, lipophilic, third generation dihydropyridine (DHP) CCBs that exerts its action through inhibition of calcium influx into vascular smooth muscle cells and myocardial cells, which results in decreased peripheral vascular resistance (PVR). Amlodipine is indicated for the treatment of high BP (BP)/hypertension and angina. In addition, a number of randomized trials have ascertained its utility in angina pectoris. Amlodipine is usually dosed on a once daily basis because of its long half-life, which is favorable for patient compliance. A starting dose of 5 mg is usually recommended with a maximum daily dose of 10 mg. In the elderly population and those with hepatic failure, a starting dose of 2.5 mg is recommended. Amlodipine has a gradual onset of action and hence no significant reflex neuroendocrine activation. Activating reflex mechanisms, such as increased PVR and elevated heart rate, can cause negative effects on lipid and carbohydrate metabolism. These notable adverse effects are commonly seen with other agents including the first generation β-blockers (BBs; such as atenolol and metoprolol) and earlier generation of DHPs. Amlodipine has a high bioavailability, ranging from 60% to 80%; it undergoes hepatic metabolism and shows some impaired elimination in the setting of liver cirrhosis but no accumulation with renal failure. Amlodipine also has a slow rate of elimination over 40–60 hours. If Amlodipine is discontinued, BP generally returns to baseline over 1 week without any dangerous rebound elevations in BP (unlike clonidine).[5]

Side effect profile

The most commonly reported adverse effect hindering compliance with Amlodipine is peripheral oedema. However, this adverse effect can be minimized if the agent is given at bedtime, and lower doses (2.5 or 5 mg/day) are used. Indeed, the bedtime administration of nifedipine gastrointestinal therapeutic system was associated with a 93% reduction in oedema compared with morning dosing (1% vs 13%, $p < 0.001$, respectively). Other reported side effects include dizziness, fatigue, headache, palpitations and nausea, although these are generally not bothersome enough to cause discontinuation of the drug. Amlodipine is

contraindicated in breastfeeding women, cardiogenic shock and unstable angina. Also, its vasodilatory effect can lead to decreased cardiac output in the setting of aortic stenosis.[5]

Role as monotherapy in hypertension

Several hypertension trials have investigated the efficacy of Amlodipine monotherapy versus other agents, including diuretics, ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). The outcomes of these trials suggest that Amlodipine has a neutral effect on several preexisting comorbid states, which will be discussed below. The Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis (CAMELOT) trial, enrolled 1991 patients with angiographically documented coronary artery disease (CAD) and randomized them to Amlodipine 10 mg, enalapril 20 mg, or placebo and followed them over 24 months. Atherosclerotic progression was also assessed in a sub study of 274 patients as well using intravascular ultrasound. Although the baseline BP was low to begin with, 129/78, both groups showed similar BP lowering, 4.8/2.5 and 4.9/2.4 for Amlodipine and enalapril, respectively. Amlodipine significantly reduced non-fatal myocardial infarction (MI) by 26% and stroke or transient ischemic attack by 50% (number needed to treat = 16), whereas enalapril had no significant benefit compared with placebo. Moreover, there was a statistically significant reduction in hospitalization rate for angina ($p = 0.003$) with Amlodipine versus enalapril. This study suggests that normotensive patients treated with Amlodipine show reduced rates of CV events and hospitalizations compared with enalapril and evidence of slowing of atherosclerotic progression.[5]

Studies have shown that nitric oxide (NO) production is diminished in patients with hypertension. A small study carried out by Masayoshi and colleagues measured exhaled NO in seven previously untreated participants to assess whether Amlodipine has an effect on NO. Their study found that NO production in the pulmonary circulation was increased as evidenced by increased NO measurements in exhaled air after 2 months of Amlodipine therapy. Another small study by Zhang and colleagues evaluated NO production in explanted hearts, which were harvested during transplant. Previous studies suggest that NO release from endothelial cells is a kinin mediated mechanism. Kinins are usually degraded by ACE. ACEIs facilitate the accumulation of these compounds, which was the rational for enlisting ramiprilat for comparison. While Amlodipine was found to increase NO production in these failing hearts, it

was similar to the NO production noted with ramiprilat. The authors postulated that this may be one of the mechanisms of Amlodipine's beneficial effects in heart failure (HF), which is not a feature shared by other members of the CCB class. Thus, the enhancement of NO production may account for the beneficial effects of this drug on the CV system. Additionally, Amlodipine has anti-inflammatory and antioxidative effects giving it vasoprotective effects beyond its BP-lowering benefits. Interestingly, these benefits were noted by the authors to be caused by an increase in endothelial NO synthase expression and inhibition of ACE. Thus, Amlodipine may even be beneficial for patients with high renin hypertension.[5]

Role in combination therapy for hypertension

While thus far Amlodipine has shown to be non-inferior to many other anti-hypertension therapies, the focus on hypertension treatment seems to be shifting more towards combination therapy. Less than 50% of patients with stage I or II hypertension are adequately controlled with monotherapy, and thus initial treatment for hypertension in the majority of patients will require two agents. The classical approach to treating hypertension where one first-line agent is maximized before another is added may be flawed since this is a multifactorial disease often occurring with a number of comorbidities. Many studies show that individuals with more CV risk factors generally need more anti-hypertension agents to successfully manage their BP. Combination therapy using different mechanisms can lead to more effective BP lowering. In addition, combination therapies block counter-regulatory mechanisms that often limit the efficacy of monotherapy. Furthermore, using multiple agents to lower doses may reduce side effects, and thus improve patient compliance.[5]

The issue arises as to which fixed combinations provide the most benefits. Thiazides in combination with ACEIs or ARBs have synergistic BP-lowering activity, whereas thiazides and BBs have deleterious effects on the metabolic profile. CCBs are powerful vasodilators but can result in renin-angiotensin-aldosterone system (RAAS) activation, thus an ACEI or ARB counteracts this mechanism and leads to enhanced antihypertensive effect. Growing evidence from trial data also shows that CCBs with ACEIs or ARBs may provide the best long-term outcomes. The ACCOMPLISH trial was a randomized, controlled trial in which 11,506 patients with hypertension with high risk for adverse CV events were assigned Amlodipine + benazepril versus HCTZ + benazepril. The primary end point was the composite of CV death

or major adverse CV events. The Amlodipine + benazepril combination was superior to the HCTZ + benazepril for lowering CV death and adverse events. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) included a total of 19 257 patients with hypertension (baseline BP, 164/95 mmHg) and at least three other cardiac risk factors. This trial, which was stopped for benefit after 5.5 years, showed that the Amlodipine + perindopril versus atenolol + thiazide diuretic significantly reduced all-cause mortality (RRR, 11%; p = 0.0247;). Additionally, Amlodipine + perindopril reduced CV mortality by 24% (p = 0.001), coronary events by 13% (p = 0.007) and strokes by 23% (p = 0.0003). At the point where rates of CV death diverged (red arrow) most of the patients (78%) were treated with the combination of perindopril + Amlodipine rather than Amlodipine monotherapy.[5]

The Assessment of combination Therapy of Amlodipine/Ramipril (ATAR) study was an 18-week randomized prospective double-blinded Brazilian study which compared the combination of Amlodipine and ramipril versus Amlodipine monotherapy. The mean changes in ambulatory BP measurements were statistically significant between the combination versus the Amlodipine monotherapy group, 18.7% vs 7.6%, p = 0.011, respectively. In addition, the reported incidence of peripheral oedema was lower in the combination group. The Candesartan and Diuretic versus Amlodipine in hypertensive patients (CANDIA) trial evaluated candesartan + HCTZ combination versus Amlodipine monotherapy. This multicenter, double-blinded, randomized trial assessed patients with mild-to-moderate hypertension not adequately controlled with monotherapy. After 8 weeks of therapy, there was no significant difference between the two groups. Systolic BP decreased by about 15 mmHg; however, there was a higher discontinuation rate with Amlodipine versus the combination drug due to peripheral oedema, 18% vs 6%, respectively. These findings suggest that while both agents are effective in lowering BP, the candesartan + HCTZ combination was better tolerated and hence may lead to better patient compliance.[5]

The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High BP (COACH) study was a study evaluating an ARB + Amlodipine combination versus placebo. The 1940 patients in this 8-week treatment study showed achievement of BP goals (<140/90) with the combination therapy and again, a lower incidence of peripheral oedema. These findings were echoed in the Telmisartan plus Amlodipine Study in Amlodipine 5 mg

(TEAMSTA-5), which tested another ARB + Amlodipine combination. The study showed that the combination of Telmisartan 40/80 mg plus Amlodipine 5 mg was superior to Amlodipine 10 mg monotherapy. CCBs are potent vasodilators and hence reduce BP effectively but can result in RAAS activation. Therefore, the rational for a CCB/RAAS inhibitor combination drug would theoretically provide vasodilation while buffering RAAS activation. Another combination with RAAS blocker and HCTZ has been shown to be effective. Triple therapy with valsartan + Amlodipine + HCTZ was compared with dual combination with valsartan + HCTZ, Amlodipine + valsartan or Amlodipine + HCTZ. This was a randomized, double-blinded study in 2271 patients with moderate-to-severe hypertension. The goal was to attain a BP goal of <140/90. The outcomes showed that this triple therapy combination was superior to any of the dual combination drugs at reducing sitting systolic and diastolic BP ($p < 0.0001$). The more pronounced findings were in those with higher baseline BP and the results were consistent over all ages, genders and ethnicities. The adverse events reported were similar across all treatment groups and included peripheral oedema as the most common, along with headache and dizziness.[5]

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) has been available for half a century and remains the most commonly prescribed antihypertensive drug worldwide. In the U.S. alone, >134.1million prescriptions of HCTZ were written in the year2008. For comparison, the second most commonly prescribed drug was atenolol, with 44 million prescriptions. More than a third of the HCTZ prescriptions (47.5 million) were written for monotherapy and the remainder in fixed combination, mostly with blockers of the renin-angiotensin system. The dose of HCTZ prescribed was almost exclusively (>97%) 12.5 to 25 mg/day, and hypertension remains, by far, the most common indication. Over the past 30 years, this persistent prescription pattern of HCTZ has been heavily influenced by reports of the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High BP, all 7 of which recommended “thiazides” or “thiazide-like drugs” or “thiazide-type diuretics” as first-line or as preferred therapy for hypertension. In an attempt to promote the use of thiazide-type diuretics, the National Heart, Lung, and Blood Institute sponsored the ALLHAT/JNC7 (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial/Joint National Committee Seventh Report) dissemination project, which reached 18,524 physicians in 1,698 venues through 147 physician

educators. This effort resulted in a small increase in thiazide-type diuretics use that almost exclusively consisted of HCTZ. However, despite the extensive use, little evidence is available regarding the efficacy and safety of HCTZ for the treatment of essential hypertension, particularly at the dose of 12.5 to 25 mg.[6]

Antihypertensive efficacy

The antihypertensive efficacy of HCTZ in the dose of 12.5 to 25 mg was assessed from 14 randomized controlled trials. The mean baseline BP in these studies was 148 $\pm$ 7.5/92 $\pm$ 5.6 mmHg. After treatment with HCTZ for a mean duration of 17 weeks, systolic ABP decreased by 6.5 mmHg (95% CI: 5.3 to 7.7 mmHg) and diastolic ABP by 4.5 mmHg (95% CI: 3.1 to 6.0 mmHg). Other antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and calcium antagonists were significantly more efficacious than HCTZ in the dose of 12.5 to 25 mg.[6]

At a daily dose of 50 mg and above, HCTZ's antihypertensive efficacy seems to be similar to most other drug classes. However, all biochemical adverse effects such as hypokalemia, hyponatremia, hyperuricemia, insulin resistance, and visceral fat accumulation are dose dependent and become clinically more significant with daily doses exceeding 25 mg. Thus, biochemical adverse effects of HCTZ may prohibit the prescription of higher doses in many patients. An additional concern is the risk of sudden cardiac death that has been shown to increase in a dose dependent fashion with HCTZ doses exceeding 25 mg daily.[6]

Clinical implications

HCTZ still remains the most commonly prescribed antihypertensive drug in the U.S. and worldwide. The National Heart, Lung and Blood Institute continues to advocate the use of "thiazide-type diuretics," which, for practicing physicians, simply means HCTZ in a daily dose of 12.5 to 25 mg. However, because the BP-lowering effect of HCTZ is inferior to that of every other drug class and outcome data at commonly used doses are nonexistent, its use as a first-line antihypertensive agent is ill advised. On a milligram-per-milligram basis using pooled data, chlorthalidone, for which solid outcome data are available, produced greater reductions in systolic BP than HCTZ did, while mean changes in potassium were found to be equivalent.[6]

Abstracts

The efficacy and long-term safety of a triple combination of 80 mg Telmisartan, 5 mg Amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension[8]

Aim: The aim of this study was to compare 80 mg Telmisartan/5 mg Amlodipine/12.5 mg HCTZ (T80/A5/H12.5) with 80 mg Telmisartan/12.5 mg HCTZ (T80/H12.5) to determine their relative BP-lowering effects in essential hypertensive patients with inadequate control and to evaluate the long-term safety of T80/A5/H12.5 in a 52-week extension period.

Methodology: Patients (n = 132) were randomly assigned to receive double-blind treatment with T80/A5/H12.5 or T80/H12.5 for 8 weeks after a 6-week run-in-period of T80/H12.5. All 126 patients who completed the double-blind period entered the 52-week open-label extension and received T80/A5/H12.5. The adjusted mean changes from the reference baseline of the trough-seated systolic and diastolic BP (SBP/DBP) at week 8 were significantly larger in the T80/A5/H12.5 group (-10.6/-8.8 mmHg) than in the T80/H12.5 group (-2.3/-1.3 mmHg) ($p < 0.0001$). The BP-lowering effect of T80/A5/H12.5 was maintained over the 52-week extension period.

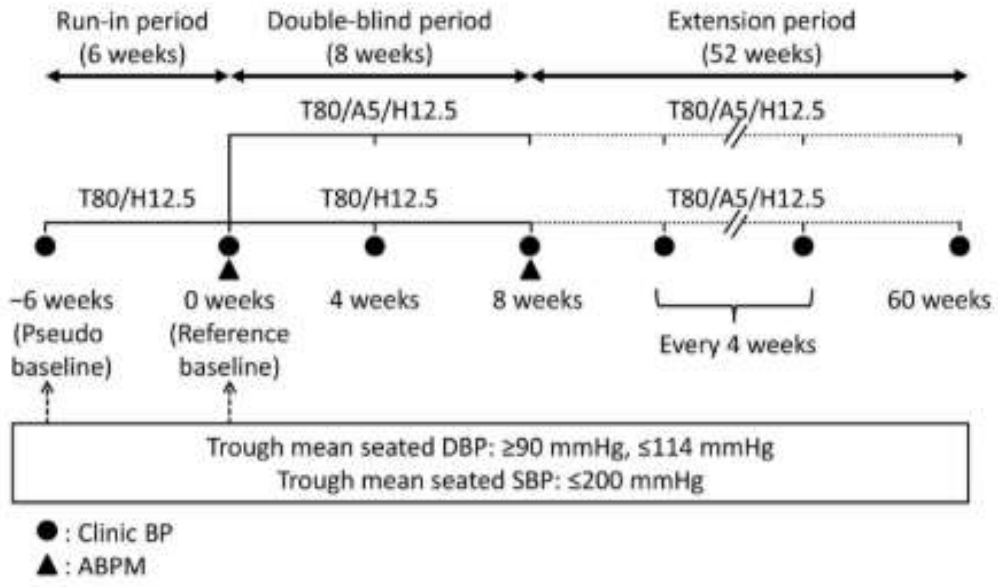


Figure 1. Trial design

Abbreviations: A: Amlodipine; ABPM: Ambulatory blood pressure monitoring; DBP: Diastolic blood pressure; H: Hydrochlorothiazide; SBP: Systolic blood pressure; T: Telmisartan

Results: The adverse events (AEs) during both treatment periods were generally mild. Drug-related AEs were reported in one patient in each group in the double-blind period and in five patients exposed to T80/A5/H12.5 in the double-blind and/or open-label extension period. T80/A5/H12.5 therapy was clinically and statistically superior to T80/H12.5 therapy for the reduction of BP in patients with essential hypertension uncontrolled with T80/H12.5, and its BP-lowering effect was maintained in the long term. T80/A5/H12.5 was generally well-tolerated.

Effect of hydrochlorothiazide in addition to Telmisartan/Amlodipine combination for treating hypertensive patients uncontrolled with Telmisartan/Amlodipine: a randomized, double-blind study[8]

The efficacy and safety of Telmisartan 80 mg/Amlodipine 5 mg plus HCTZ 12.5 mg (T80/A5/H12.5) was examined for its ability to treat hypertension in Japanese patients whose hypertension is uncontrolled with Telmisartan 80 mg/Amlodipine 5 mg (T80/A5). Patients aged ⩾ 20 years who had essential hypertension despite taking two or three antihypertensive drugs entered a 6-week run-in period on T80/A5. Patients whose hypertension remained uncontrolled were randomly assigned to either the T80/A5/H12.5 group (n = 149) or the T80/A5 group (n = 160), once daily for 8 weeks. After 8 weeks, patients in the T80/A5/H12.5 group showed a significantly greater adjusted mean reduction in both seated diastolic BP and seated systolic BP than those in the T80/A5 group. Furthermore, more patients achieved a diastolic/systolic BP of <90/140 mmHg in the T80/A5/H12.5 group compared with the T80/A5 group. The most common adverse events were nasopharyngitis, elevated blood uric acid levels and hyperuricemia, and the latter two events were more frequent in the T80/A5/ H12.5 group than in the T80/A5 group. Overall, T80/A5/H12.5 administered for 8 weeks significantly reduced systolic and diastolic BP and was well tolerated by patients with hypertension uncontrolled with T80/A5.

Efficacy and safety of triple drug fixed-dose combination of Telmisartan, Amlodipine and hydrochlorothiazide in the management of hypertension[9]

Background: High BP (BP) is the most prevalent chronic disease in India and its prevalence is rapidly increasing among urban and rural populations. This study was conducted to assess

the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and HCTZ 12.5 mg.

Methods: 30 hypertensive patients having systolic BP ≥160 mmHg and diastolic BP ≥100 mmHg who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan HCTZ combinations were enrolled in this study. The treatment period was of 120 days and patients were administered once daily fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and HCTZ 12.5 mg. Patients were evaluated on 30th, 60th and 120th days of treatment.

Results: There was statistically significant ($p < 0.0001$) decrease in systolic BP from baseline to 30^{th}, 60^{th} and 120^{th} day of treatment mean ± SD (157.0 ± 8.68 mmHg vs 148.7 ± 8.19, 137.3 ± 7.84, and 127.0 ± 7.02 mmHg) respectively. Similarly, the diastolic BP (DBP) was significantly ($p < 0.0001$) reduced from the baseline to the 30^{th}, 60^{th} and 120^{th} day of treatment (100.0 ± 6.43 mmHg vs. 96.0 ± 6.21, 86.6 ± 6.06 and 80.6 ± 2.53 mmHg respectively).

Conclusion: Thus, triple drug fixed dose combination of Telmisartan, Amlodipine and HCTZ was found to be effective and safe option for the optimal management of hypertension.

References:

1. Prem Kumar A, Ghorai A, Kriplani V, *et al*. Clinical data analysis of Telmisartan for hypertension management in Indian population. *Bioinformation*. 2021;17(6):652-9.
2. Neutel JM, Smith DHG. Hypertension Management: Rationale for Triple Therapy Based on Mechanisms of Action. *Cardiovascular Therapeutics*. 2013;31(5):251-8.
3. Deppe S, Böger RH, Weiss J, *et al*. Telmisartan: a review of its pharmacodynamic and pharmacokinetic properties. *Expert Opinion on Drug Metabolism & Toxicology*. 2010;6(7):863-71.
4. Sharpe M, Jarvis B, Goa KL. Telmisartan. *Drugs*. 2001;61(10):1501-29.
5. Fares H, DiNicolantonio JJ, O'Keefe JH, *et al*. Amlodipine in hypertension: a first-line agent with efficacy for improving BP and patient outcomes. *Open Heart*. 2016;3(2):e000473.

6. Messerli FH, Makani H, Benjo A, *et al*. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory BP monitoring: a meta-analysis of randomized trials. *Journal of the American College of Cardiology*. 2011;57(5):590-600.
7. Higaki J, Komuro I, Shiki K, *et al*. The efficacy and long-term safety of a triple combination of 80 mg Telmisartan, 5 mg Amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension. *Hypertension Research*. 2016;40(1):51-60.
8. Higaki J, Komuro I, Shiki K, *et al*. Effect of hydrochlorothiazide in addition to Telmisartan/Amlodipine combination for treating hypertensive patients uncontrolled with Telmisartan/Amlodipine: a randomized, double-blind study. *Hypertension Research*. 2017;40(3):251-58.
9. Balraj M, Faruqui A. Efficacy and safety of triple drug fixed-dose combination of Telmisartan, Amlodipine and hydrochlorothiazide in the management of hypertension. *International Journal of Research in Medical Sciences*. 2015:1858-62.

Survey Form

1) As per your opinion which is the unmet medical need in current Hypertension management?

A. Aggressive blood pressure control

B. Combinations addressing different pathophysiological mechanisms responsible for increase in blood pressure

C. Decreasing risk of cardiovascular disease and end organ damage

2) In your clinical practice, which is the preferred calcium channel blocker in patients with uncontrolled hypertension?

A. Amlodipine

B. Azelnidipine

C. Cilnidipine

D. Benidipine

3) In your clinical practice, which is your preferred dual combination of antihypertensive drug in newly diagnosed hypertension patients?

A. Angiotensin II receptor blockers (ARBs) plus calcium channel blocker (CCB)

B. ACE inhibitors plus CCB

C. ARBs plus Thiazide diuretics

D. ACE inhibitors plus Thiazide diuretics

4) In your clinical practise when do you consider adding a Thiazide Diuretic to a patient already on dual combination therapy?

A. Inadequate blood pressure control

B. Reducing risk for heart failure

C. Resistant hypertension

5) In your clinical practice, which is your preferred Thiazide diuretic?

A. Hydrochlorothiazide

B. Chlorthalidone

6) As per your opinion, what percentage of patients with hypertension may require triple combination therapy to achieve target BP effectively?

A. <25%
B. 26-50%
C. 51-75%
D. >75%

7) In your opinion, what would be ideal patient profile for a triple drug combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. Uncontrolled hypertension
B. Resistant hypertension
C. Newly diagnosed patients with SBP >160 mmHg and associated comorbidities

8) As per your opinion, what is/are the clinical advantage(s) associated with the usage of fixed dose combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. Faster reduction of BP
B. Beneficial impact on patient compliance
C. Improved tolerability
D. Beneficial in patients with higher CV risk

9) As per your opinion, what percentage of patients will achieve blood pressure goal after treatment with a combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. 26-50%
B. 51-75%
C. 75-90%
D. >90%

10) As per your opinion, what can be the average duration of Amlodipine + Telmisartan + Hydrochlorothiazide therapy in hypertension?

A. Less than 6 months

B. 6 months to 1 year

C. >1 year to 5 years

D. Life-long

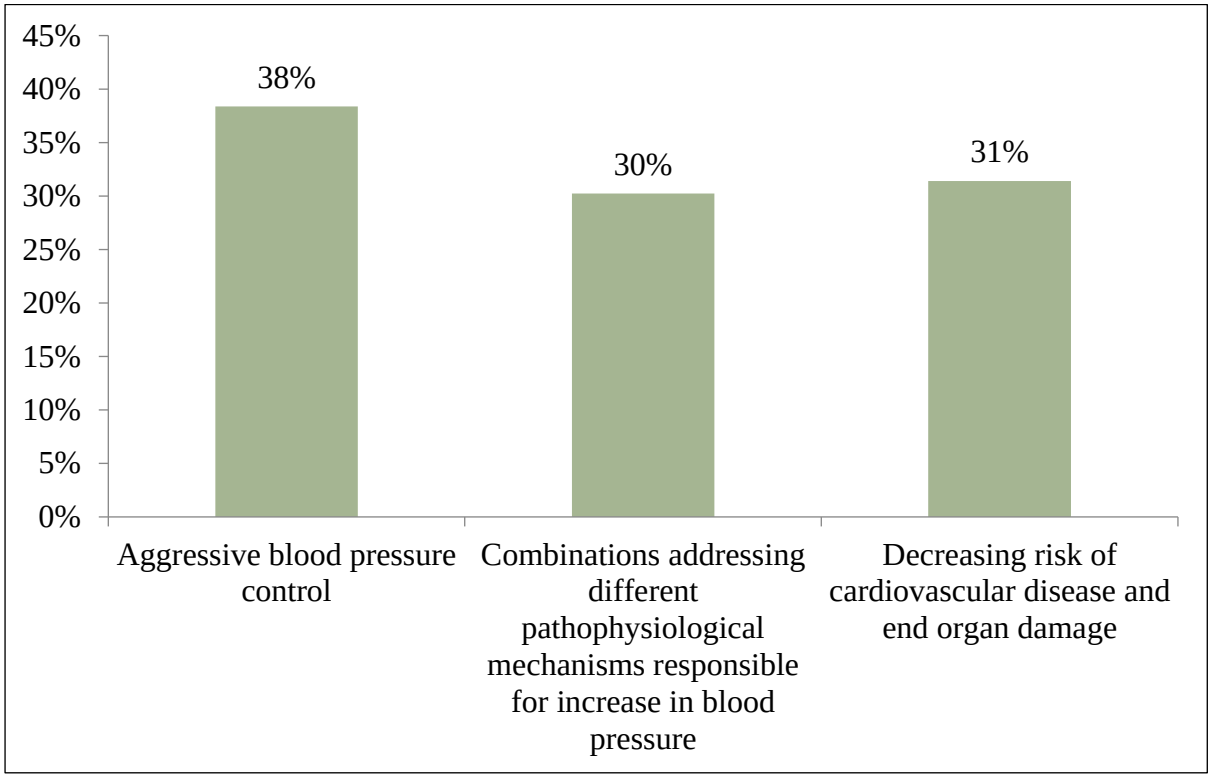
Survey Findings

1) As per your opinion which is the unmet medical need in current hypertension management?

A. Aggressive blood pressure control

B. Combinations addressing different pathophysiological mechanisms responsible for increase in blood pressure

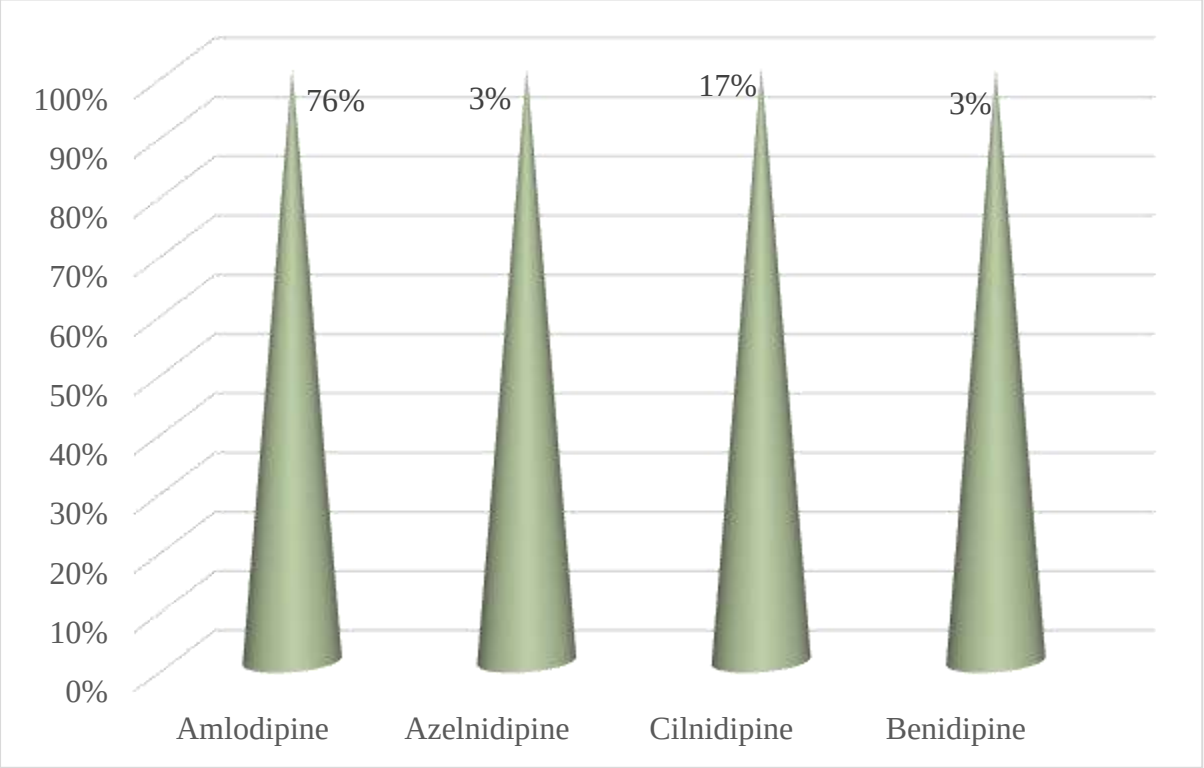
C. Decreasing risk of cardiovascular disease and end organ damage



As per 38% of doctors, aggressive blood pressure control is the unmet medical need in current hypertension management.

2) In your clinical practice, which is the preferred calcium channel blocker in patients with uncontrolled hypertension?

A. Amlodipine
B. Azelnidipine
C. Cilnidipine
D. Benidipine



According to majority of 76% doctors, Amlodipine is the preferred calcium channel blocker in patients with uncontrolled hypertension.

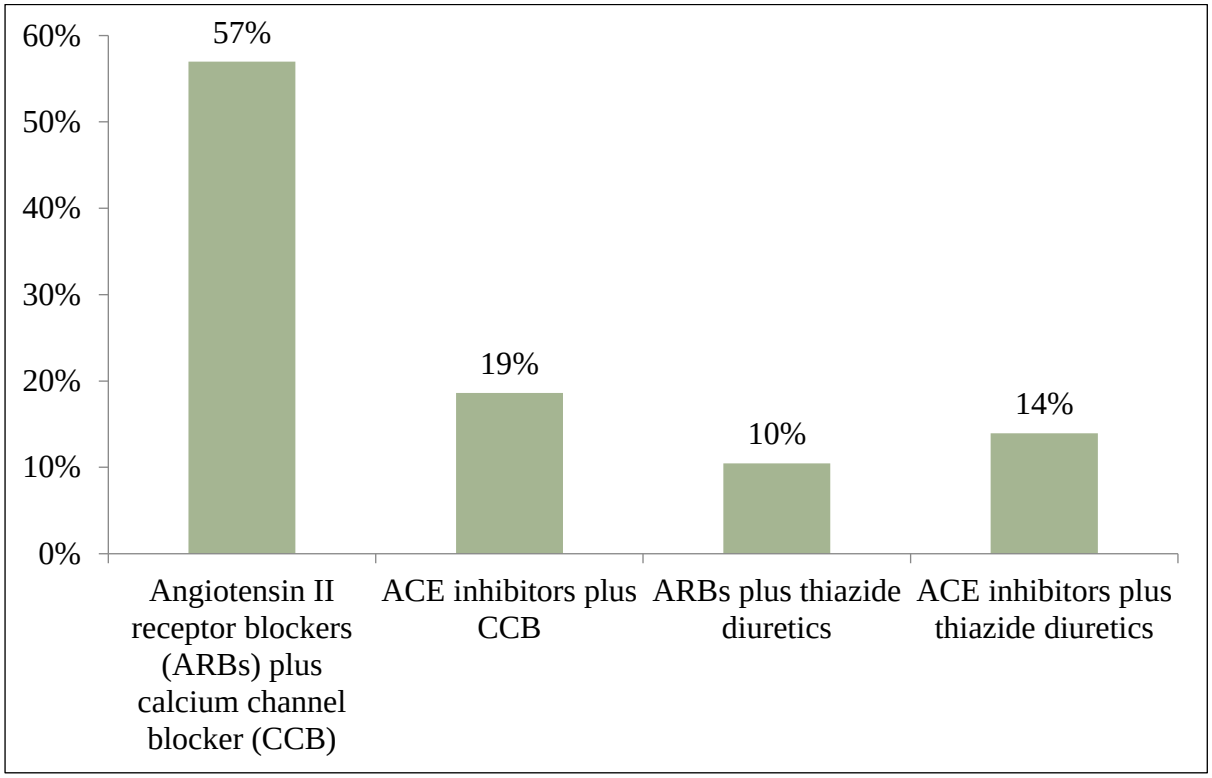
3) In your clinical practice, which is your preferred dual combination of antihypertensive drug in newly diagnosed hypertension patients?

A. Angiotensin II receptor blockers (ARBs) plus calcium channel blocker (CCB)

B. ACE inhibitors plus CCB

C. ARBs plus thiazide diuretics

D. ACE inhibitors plus thiazide diuretics



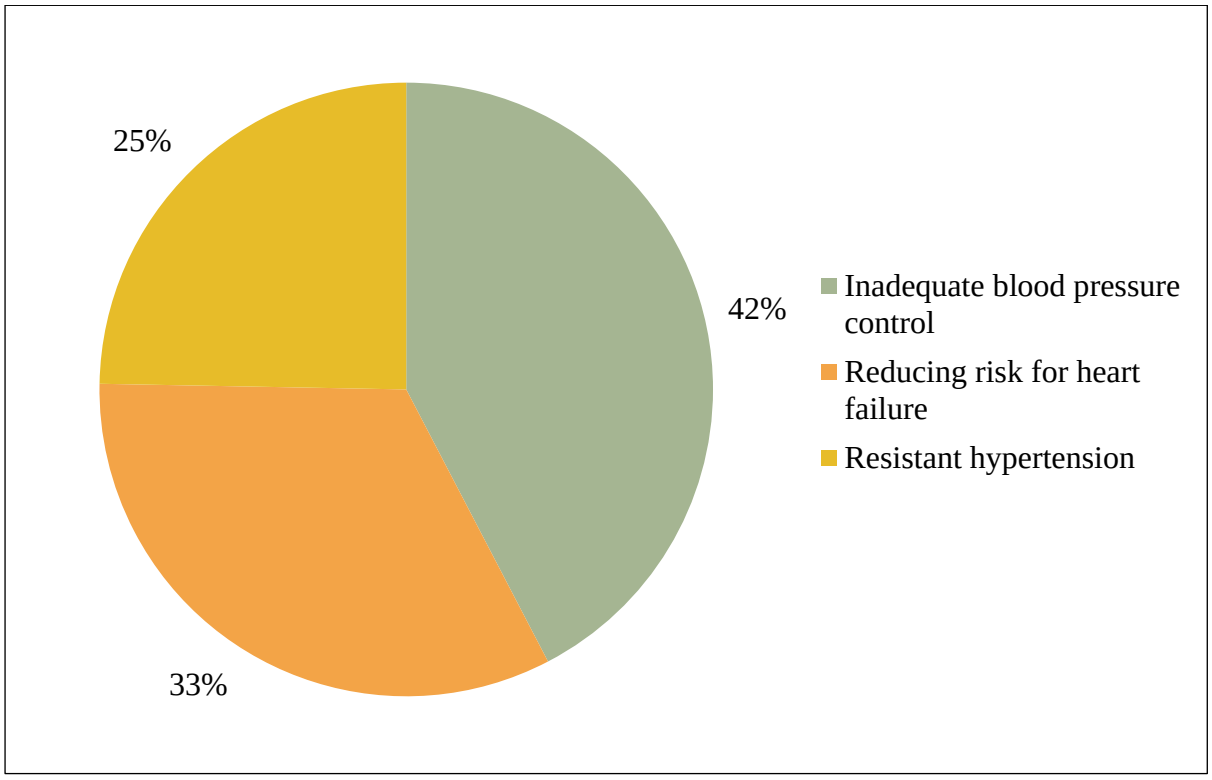
According to 57% of doctors, ARBs plus CCB is their preferred dual combination of antihypertensive drug in newly diagnosed hypertension patients.

4) In your clinical practise when do you consider adding a thiazide diuretic to a patient already on dual combination therapy?

A. Inadequate blood pressure control

B. Reducing risk for heart failure

C. Resistant hypertension

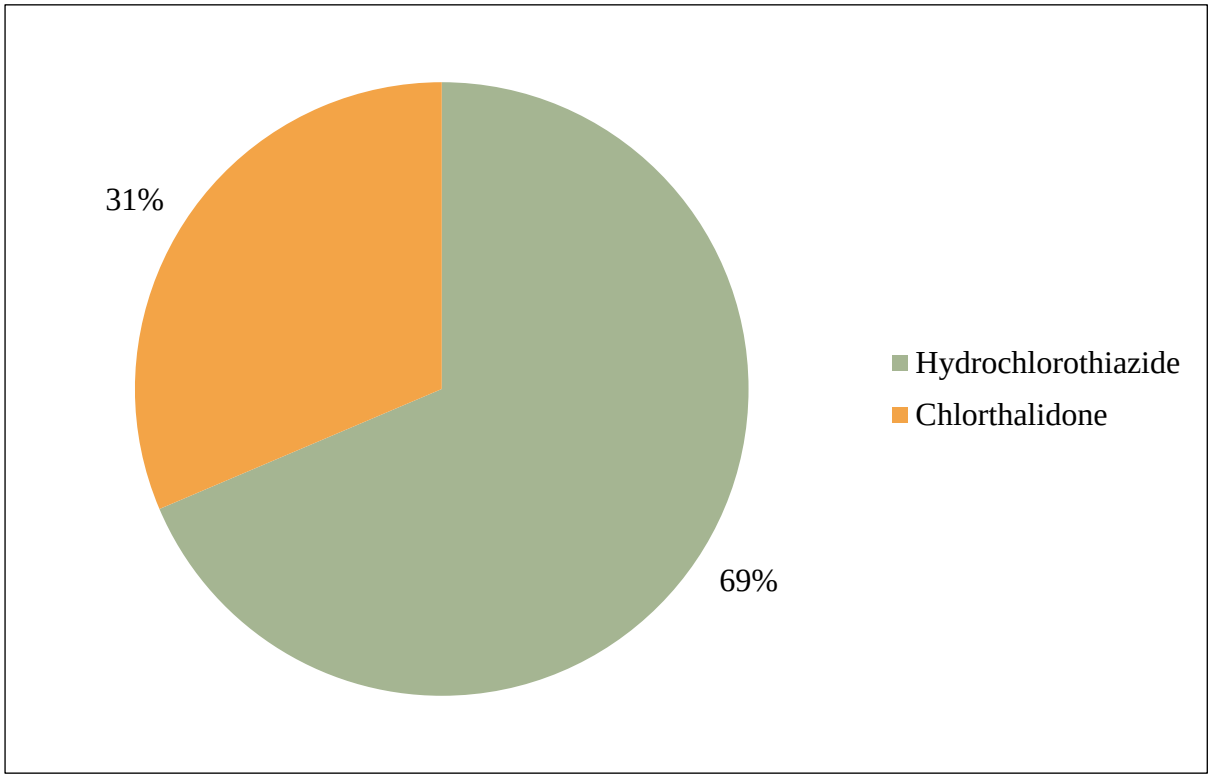


Around 42% of doctors consider adding a thiazide diuretic to a patient already on dual combination therapy when there is inadequate blood pressure control.

5) In your clinical practice, which is your preferred Thiazide diuretic?

A. Hydrochlorothiazide

B. Chlorthalidone



A majority of doctors, 69%, in their clinical practice prefer hydrochlorothiazide as the thiazide diuretic of choice.

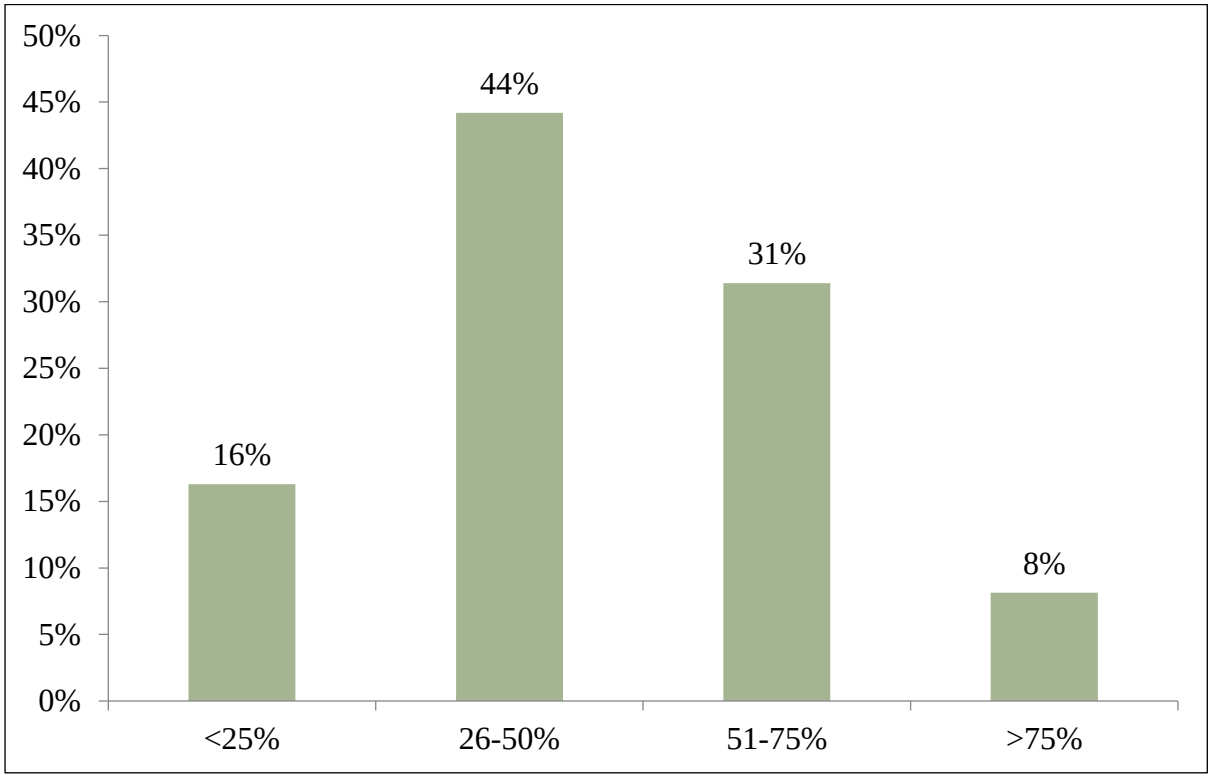
6) As per your opinion, what percentage of patients with hypertension may require triple combination therapy to achieve target BP effectively?

A. <25%

B. 26-50%

C. 51-75%

D. >75%



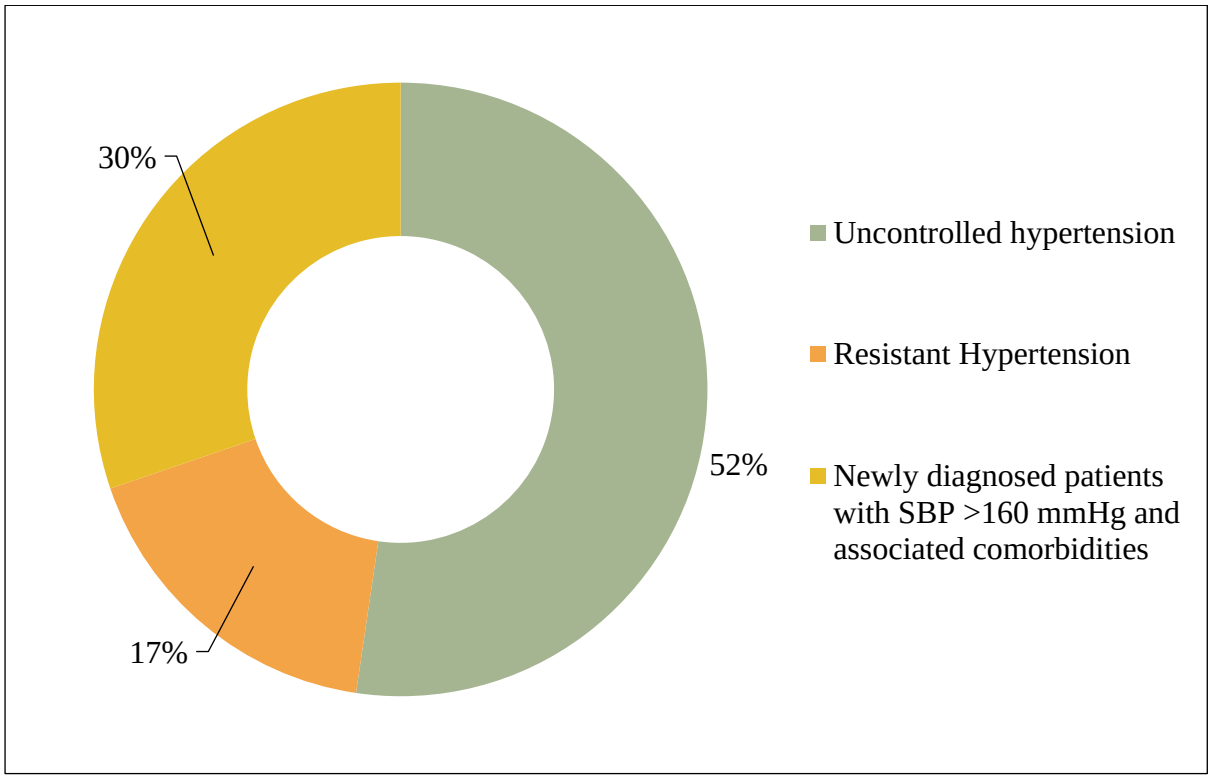
As per 44% of doctors, 26-50% of patients with hypertension may require triple combination therapy to achieve target BP effectively.

7) In your opinion, what would be ideal patient profile for a triple drug combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. Uncontrolled hypertension

B. Resistant hypertension

C. Newly diagnosed patients with SBP >160 mmHg and associated comorbidities



According to 52% of doctors, newly diagnosed patients with SBP >160 mmHg and associated comorbidities would be ideal patient profile for a triple drug combination of Amlodipine + Telmisartan + Hydrochlorothiazide.

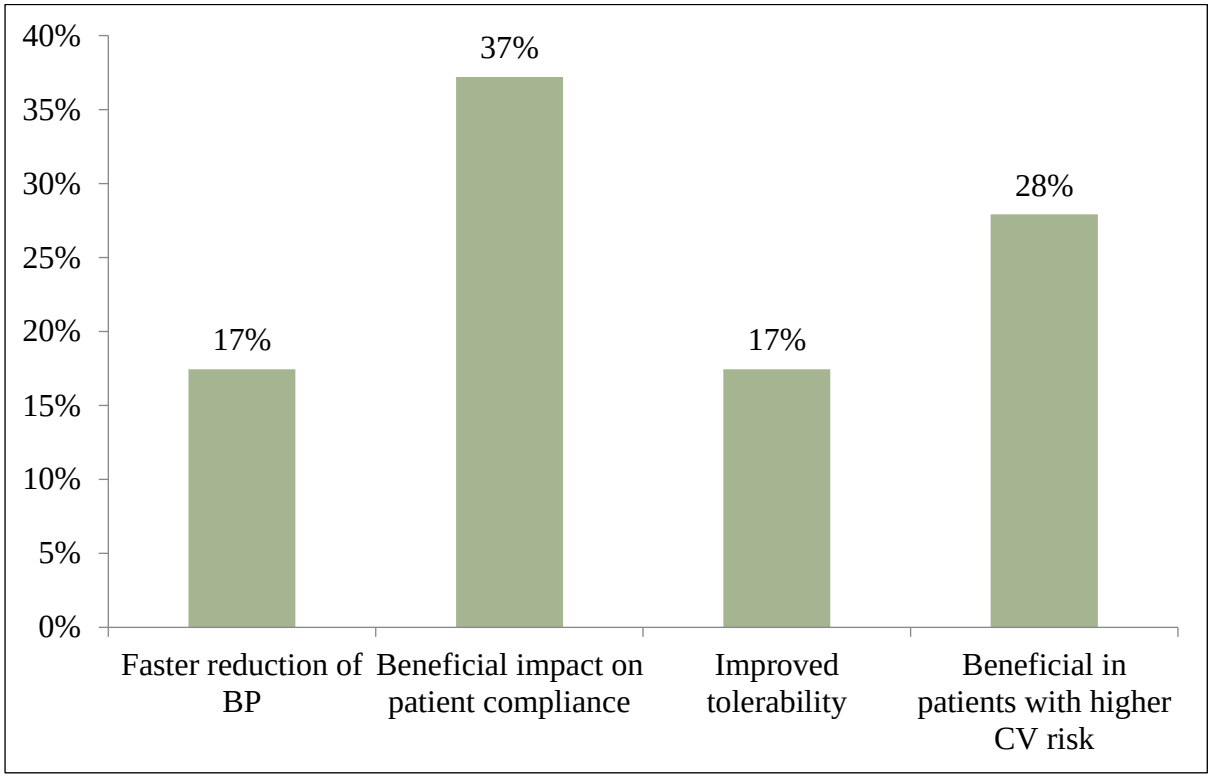
8) As per your opinion, what is/are the clinical advantage(s) associated with the usage of fixed dose combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. Faster reduction of BP

B. Beneficial impact on patient compliance

C. Improved tolerability

D. Beneficial in patients with higher CV risk



Around 37% of doctors, the clinical advantage associated with the usage of fixed dose combination of Amlodipine + Telmisartan + Hydrochlorothiazide is beneficial impact on patient compliance.

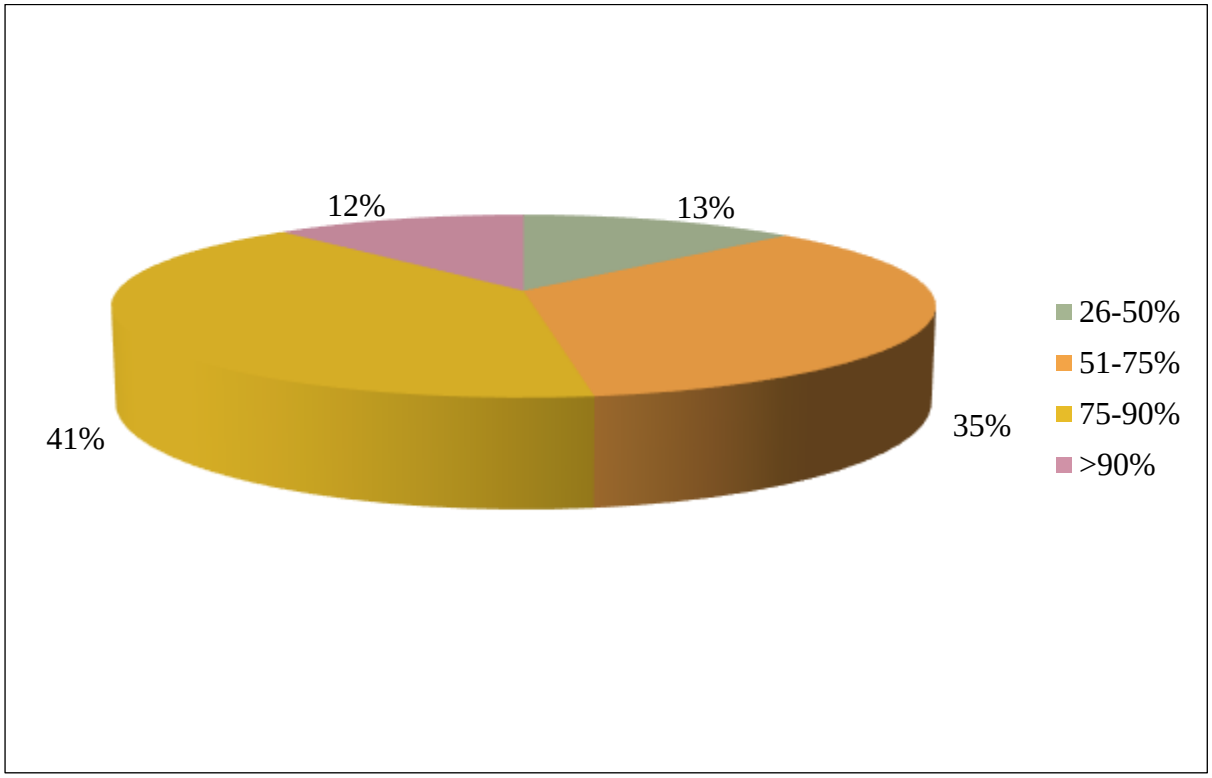
9) As per your opinion, what percentage of patients will achieve blood pressure goal after treatment with a combination of Amlodipine + Telmisartan + Hydrochlorothiazide?

A. 26-50%

B. 51-75%

C. 75-90%

D. >90%



According to 41% of doctors, 75-90% of their patients will achieve blood pressure goal after treatment with a combination of Amlodipine + Telmisartan + Hydrochlorothiazide.

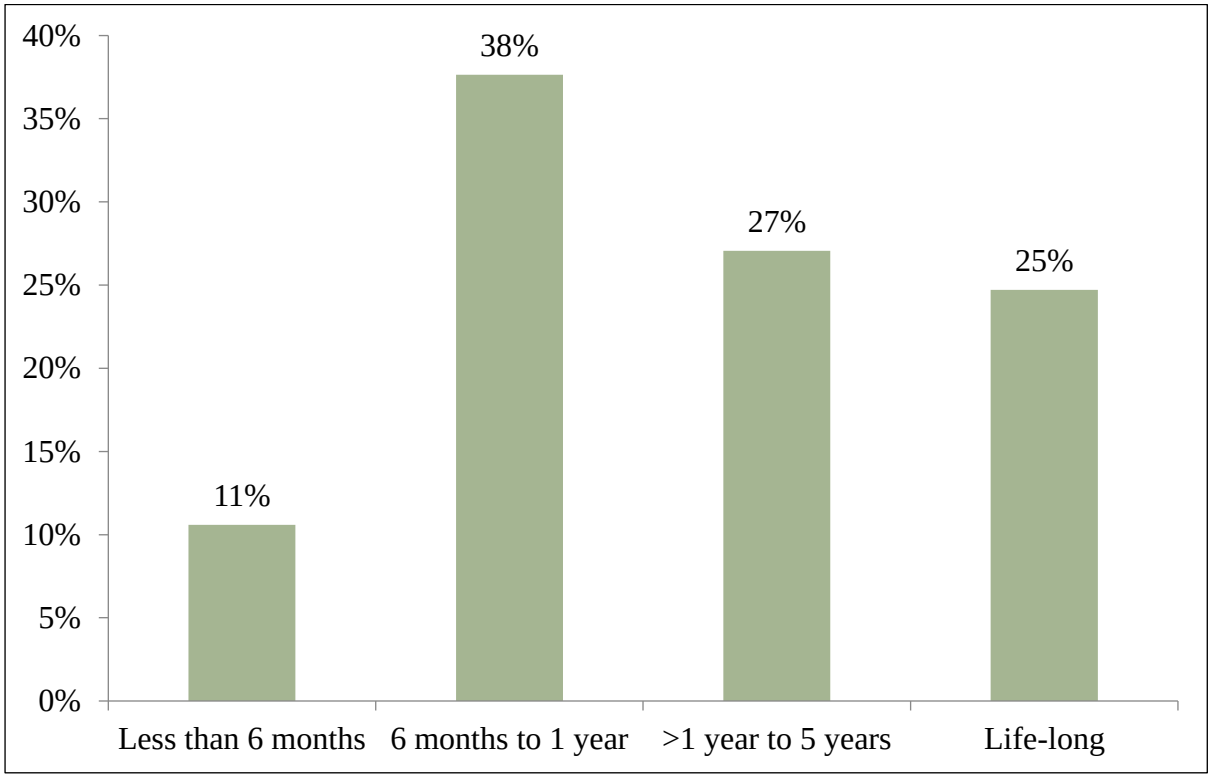
10) As per your opinion, what can be the average duration of Amlodipine + Telmisartan + Hydrochlorothiazide therapy in hypertension?

A. Less than 6 months

B. 6 months to 1 year

C. >1 year to 5 years

D. Life-long



As per 38% of doctors, 6 months to 1 year can be the average duration of Amlodipine + Telmisartan + Hydrochlorothiazide therapy in hypertension.

Summary

- As per 38% of doctors, aggressive blood pressure control is the unmet medical need in current hypertension management.
- According to majority of 76% doctors, Amlodipine is the preferred calcium channel blocker in patients with uncontrolled hypertension.
- According to 57% of doctors, ARBs plus CCB is their preferred dual combination of antihypertensive drug in newly diagnosed hypertension patients.
- Around 42% of doctors consider adding a thiazide diuretic to a patient already on dual combination therapy when there is inadequate blood pressure control.
- A majority of doctors, 69%, in their clinical practice prefer hydrochlorothiazide as the thiazide diuretic of choice.
- As per 44% of doctors, 26-50% of patients with hypertension may require triple combination therapy to achieve target BP effectively.
- According to 52% of doctors, newly diagnosed patients with SBP >160 mmHg and associated comorbidities would be ideal patient profile for a triple drug combination of Amlodipine + Telmisartan + Hydrochlorothiazide.
- Around 37% of doctors, the clinical advantage associated with the usage of fixed dose combination of Amlodipine + Telmisartan + Hydrochlorothiazide is beneficial impact on patient compliance.
- According to 41% of doctors, 75-90% of their patients will achieve blood pressure goal after treatment with a combination of Amlodipine + Telmisartan + Hydrochlorothiazide.
- As per 38% of doctors, 6 months to 1 year can be the average duration of Amlodipine + Telmisartan + Hydrochlorothiazide therapy in hypertension.

Consultant Opinion

Based on the analysis of the survey regarding the management of hypertension, here are recommendations and potential opportunities for improvement in patient care and strategies for pharmaceutical companies.

Market opportunities

Identify the growing prevalence of hypertension as an opportunity for pharmaceutical companies to develop and market effective triple combination therapies like Amlodipine, Telmisartan, and Hydrochlorothiazide.

Value for healthcare professionals

Provide continued education and training for healthcare professionals on the optimal management of hypertension, including the use of triple combination therapies, to enhance patient care and outcomes.

Adverse effect management

Conduct further research and development to minimize the side effects associated with triple combination therapies for hypertension, ensuring better tolerability and adherence to treatment.

Withdrawal management

Develop guidelines and protocols for the safe withdrawal of medications used in hypertension management, especially in patients experiencing adverse effects or those requiring a change in therapy.

Market positioning

Position the triple combination of Amlodipine, Telmisartan, and Hydrochlorothiazide as an effective first-line treatment option for hypertension, emphasizing its ability to provide comprehensive blood pressure control with fewer adverse effects compared to monotherapy or dual therapy.

Personalized treatment decisions

Encourage healthcare providers to consider individual patient characteristics when making treatment decisions for hypertension, thereby optimizing patient outcomes and minimizing treatment-related complications.

Improving patient outcomes

Collaborate with healthcare providers to develop comprehensive treatment plans that address not only blood pressure control but also comorbidities and lifestyle modifications, thereby improving overall patient outcomes and quality of life.

Innovation and research

Invest in ongoing research and development to explore novel treatment options and therapeutic approaches for hypertension, including the development of targeted therapies based on patient-specific characteristics and underlying etiologies.

By addressing these aspects, both healthcare professionals and pharmaceutical companies can work together to optimize hypertension management, improve treatment outcomes, and enhance patient care.

Notes

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