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REVIEW ON NEW ASPECTS OF COMBINATION TREATMENT OF HYPERTENSION

Gandharv Singh Lodhi, Divya Vishwakarma, Gulsaba Khan and Rupesh Kumar Jain*

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

***Corresponding Author: Rupesh Kumar Jain**
Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

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ABSTRACT
Pharmacological treatment of hypertension has been shown to reduce the risk of stroke, coronary events, heart failure and progression of renal disease. However, rates of successful blood pressure control remain low among treated patients while antihypertensive medication represents a large and increasing proportion of healthcare expenditure in many countries. Several influential pharmacoeconomic analyses have confirmed the cost effectiveness of conventional antihypertensive treatments, usually involving monotherapy with diuretics or beta-blockers, compared with alternative strategies. With the evolution of pharmacological treatment of hypertension, various classes of agent (diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium antagonists and alpha 1-blockers) have become available for the initiation of antihypertensive therapy. As monotherapy, each type of agent will normalize blood pressure in about half of all hypertensive patients. Replacing one drug with another that acts through a different mechanism improves the probability of controlling blood pressure. Another way to increase the number of responders is to increase the dose; however, this often results in more side effects. A preferable way of improving efficacy is to combine low doses of drugs that have different impacts on the cardiovascular system, thus opposing the compensatory responses that tend to limit the blood pressure drop. Recent review has shown that a considerable proportion of the total cost of antihypertensive treatment in general practice is due to factors such as inadequate blood pressure control, poor compliance with therapy, discontinuation and switching between therapies. These factors operate to a much lesser extent in well-conducted clinical trials, and have not been fully incorporated into most economic studies. Some novel strategies, particularly low dose combinations of antihypertensive agents, may offer advantages in terms of efficacy, reduced adverse effects and improved compliance with treatment. There is therefore a need for comprehensive pharmacoeconomic analyses of novel strategies, taking these additional factors into account. Until such studies are available, the wider use of low dose combination therapy and other novel strategies should not be held back on the basis of earlier economic studies that have not included all relevant considerations.

KEYWORDS: Antihypertensive drugs, Hypertension, Cardiovascular disease, Combination therapy.

INTRODUCTION
More than 70% of adults treated for primary hypertension will eventually require at least two antihypertensive agents, either initially as combination therapy or as add-on therapy if monotherapy and lifestyle modifications do not achieve adequate blood pressure control. Four main classes of medications are used in combination therapy for the treatment of hypertension: thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). ACEIs and ARBs should not be used simultaneously. In black patients, at least one agent should be a thiazide diuretic or a calcium channel blocker. Patients with heart failure with reduced ejection fraction should be treated initially with a beta blocker and an ACEI or ARB (or an angiotensin receptor–neprilysin inhibitor), followed by add-on therapy with a mineralocorticoid receptor antagonist and a diuretic based on volume status. Treatment for patients with chronic kidney disease and proteinuria should include an ACEI or ARB plus a thiazide diuretic or a calcium channel blocker. Patients with diabetes mellitus should be treated similarly to those without diabetes unless proteinuria is present, in which case combination therapy should include an ACEI or ARB.[1] Cardiovascular disease is the leading cause of death worldwide, and hypertension is a modifiable risk factor for cardiovascular disease. Risk increases with incremental increases in blood pressure, even within the normal range. More than 70% of adults treated for primary hypertension will eventually require at least two antihypertensive agents. Hypertension is a serious global health issue, affecting millions of patients. Despite having various antihypertensive agents that have shown their efficacy and safety, the percentage of patients achieving the recommended therapeutic goals is

unacceptably low.[1] Hypertension is a risk factor for cardiovascular disease – uncontrolled hypertension increases the relative risk from two to four times for coronary disease, stroke, heart failure, peripheral arterial disease, renal insufficiency, atrial fibrillation and dementia/cognitive impairment. Undoubtedly, poorly controlled hypertensive patients have an increased risk for cardiovascular complications.[2] Cardiovascular disease is the most common cause of death in the population, and hypertension is one of the most important treatable risk factors. Lowering blood pressure (BP) is associated with considerable benefits including a reduced risk of stroke, myocardial infarction, and cardiovascular mortality. However, treating hypertension to targets is often challenging. Data from clinical studies and registries suggest that more than two-thirds of patients with hypertension require treatment with two or more antihypertensive drugs to achieve their target BP goals. It was shown that using a combination therapy lead to a better BP control than increasing the dose of monotherapy. Moreover, the concomitant use of drugs with different mechanisms of action can offset potential side effects of each drug. Taking these data into consideration, various single-pill combinations have been developed and used to improve BP goals attainment and patient adherence. To review the various pharmacological approaches currently proposed for the treatment of hypertension. Low-dose drug combinations are generally well tolerated and the treatment of hypertension can be simplified by using fixed-dose combinations. These combinations have the potential to become a valuable alternative in the initiation of antihypertensive therapy. The combination of an angiotensin receptor blocker (ARB) and hydrochlorothiazide (HCTZ) is well-tolerated and able to effectively reduce BP, particularly when used as a single-pill combination. Initial treatment with the ARB irbesartan in combination with HCTZ has been proven to be as safe as monotherapy and more effective in patients with moderate and severe hypertension, in obese patients with mild-to-moderate hypertension, and in patients with type 2 diabetes and hypertension.[3] Swiss hypertension guidelines valid at the time when the present study was conducted recommended the use of combination therapies in all patients presenting with systolic/diastolic BP above 160/100 mmHg, even if no treatment was administered previously. Nonetheless, hypertension remains undertreated and there is a need to implement consensus guideline recommendations in clinical practice. Many physicians are reluctant to treat hypertension aggressively and still prescribe low dose monotherapy for initial treatment. One reason for this cautious approach is the fear of possible adverse events, including hypotension. Hypertension has a prevalence of 30.5% in Mexico, which is almost the same reported by other Latin-American countries, except for Colombia and Peru.[2] Its prevalence continues to increase with age. Consequently, in subjects over 70 years, the prevalence of hypertension reaches 60–70%.[3] Despite the effectiveness of modern antihypertensive drugs, approximately 70% of hypertensive patients fail to achieve the therapeutic goal of blood pressure <140/90 mmHg with monotherapy; and even less patients will reach the new therapeutic goals <130/80 mmHg recommended in the 2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults,[4] using only one antihypertensive drug. In fact, long-term prospective studies have shown that hypertensive patients were not effectively treated with monotherapy and needed an average of three drugs for adequate control.[5]

Hypertension therapy

A meta-analysis showed that angiotensin-converting enzyme inhibitors but not angiotensin receptor blockers reduced the incidence of doubling of the serum creatinine level in patients with diabetes mellitus, but it did not affect progression to end-stage renal disease. Another meta-analysis showed that angiotensin-converting enzyme inhibitors were superior to angiotensin receptor blockers for reducing all-cause and cardiovascular mortality. Compared with monotherapy, initial combination therapy achieves blood pressure control more quickly with similar tolerability. However, in a randomized controlled trial, patients who started on monotherapy eventually achieved blood pressure control similar to that of patients who started on combination therapy. Although improved adherence to antihypertensive medications is expected to decrease morbidity and mortality, a large systematic review found that the effects of fixed-dose combination therapy on all-cause mortality or atherosclerotic cardiovascular disease events are uncertain.[6]

Combination therapy

When hypertensive patients do not achieve adequate control of their blood pressure, the options to try and achieve required treatment goals are to increase the dose of monotherapy (which increases the risk of side effects) or to use drug combinations with minimum side effects. In order to avoid complications, it is important to start treatment as soon as possible, achieve the goals in the shortest time possible and ensure treatment adherence.[1,6] The mechanisms that lead to a blood pressure increase in a patient are diverse – monotherapy acts on one or at best two of these mechanisms, while the use of combinations of drugs allows for action on several different hypertensive mechanisms.[7] By combining two drugs with different mechanisms of action, an antihypertensive effect of two to five times greater than that obtained by monotherapy is possible.[7,8] Increasing the dose of monotherapy reduces coronary events by 29% and cerebrovascular events by 40%, while combining two antihypertensive agents with a different mechanism of action reduces coronary events by 40% and cerebrovascular events by 54%.[9] Thus, the use of combination therapy provides greater protection to a target organ than increasing the dose of monotherapy.

Advantages of the combination of antihypertensive drugs are RASIs prevent pretibial edema induced by calcium channel blockers, counteract the release of renin caused by natriuretics and RASIs block the release of aldosterone induced by natriuretics and the resulting hypokalemia. Most combinations of antihypertensive agents, whether at fixed doses or free combinations, include a diuretic. These combinations have been shown to produce greater blood pressure reductions than those seen with monotherapies.[8] Combinations of a calcium antagonist with a renin–angiotensin system inhibitor (RASI), whether an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), have also been shown to be effective and safe in the management of the hypertensive patient.[7,9] The available evidence on these drug combinations is now presented. The only study that directly compares two combinations of antihypertensive drugs is the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH). In this study, 11,462 high-risk cardiovascular patients over 55 years of age (60.4% with diabetes mellitus) were included. They were divided into two groups – one group received the combination benazepril plus amlodipine, and the other group received the combination benazepril plus hydrochlorothiazide. Trial duration was designed for 5 years; however, the study was suspended at month 39 because the calcium antagonist plus ACEI combination was found to be superior to the ACEI plus hydrochlorothiazide combination in reducing cardiovascular, cerebrovascular and renal events, despite a similar reduction in systolic and diastolic values in both groups (the mean difference in blood pressure between the two groups at the end of the study was 0.9 mmHg systolic and 1.1 mmHg diastolic).[10] The renal outcomes of the Ongoing Telmisartan Alone or in combination with Ramipril Global Endpoint Trial (ONTARGET) study included 25,620 participants, who were randomly assigned to ramipril, telmisartan or to a combination of both drugs.[11] After 56 weeks follow-up, the combination of telmisartan plus ramipril significantly increased the risk of dialysis, doubling serum creatinine, and caused a greater fall in the glomerular filtration rate than the ramipril or telmisartan groups, which has called into question the benefits of this combination.

In the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), 8561 patients were randomly assigned to aliskiren or placebo as an adjunct to another RAS inhibitor; however, the trial was stopped prematurely after a median follow-up of 32.9 months.[12] In the Aliskiren Study in Post-MI patients to Reduce remodelling (ASPIRE) trial, the addition of aliskiren to the standard therapy, including an inhibitor of the RAAS in 820 high-risk post-MI patients, was associated with more adverse effects, and did not result in further attenuation of left ventricular remodeling after a follow-up of 26–36 weeks.[13] These two studies provided sufficient evidence that the combination of a direct inhibitor of renin (aliskiren) with ACEI or ARB should be avoided.[12] In 2012, the Food and Drug Administration advised that combinations of two agents that act on the renin–angiotensin axis should not be used, particularly if one of the agents is aliskiren. In summary, combinations of two agents that act on the renin–angiotensin axis should not be used.[9] Hypertension is a serious public health concern with inadequate control of blood pressure (BP) worldwide. Contributing factors include low efficacy of drugs, underuse of combination therapies, irrational combinations, physicians' therapeutic inertia and poor adherence to treatment. Current guidelines recommend the use of initial (dual) combination therapy in high-risk patients for immediate BP response, better short- and long-term BP control, and continued/improved patient adherence. This article aims to review the existing evidence of triple-combination therapies with respect to efficacy, safety and adherence to treatment. It is estimated that three drugs are required to achieve BP control in approximately one-fourth to one-third of patients. Randomized controlled trials (RCTs) have shown that triple combinations of amlodipine/valsartan/hydrochlorothiazide, amlodipine/ olmesartan/ hydrochlorothiazide and amlodipine/ telmisartan/ hydrochlorothiazide produce greater BP reductions, with greater proportions of patients achieving BP control compared with dual therapies. Further evidence also demonstrates that triple-combination therapy is efficacious for moderate to severe hypertension, with substantial additional BP reduction over dual regimens. Both RCTs and post-marketing observational studies have shown consistent and comparable efficacy in both the general population and high-risk hypertensive subgroups. Triple therapies are generally well tolerated with adverse event profiles similar to dual regimens. In addition, fixed-dose combinations used as single pill improve patient adherence leading to better long-term BP control. Depending on regional circumstances, they may also be cost effective. Thus, single-pill triple combinations of different classes of drugs with complementary mechanisms of action help to treat patients to goal with improved efficacy and better adherence to treatment.

Combinations of antihypertensive drugs have actions unrelated to their effect on blood pressure that can have an impact on the prognosis of patients.

Metabolic effects

Antihypertensive drugs have distinct metabolic effects. Both beta blockers and diuretics are associated with insulin resistance and a higher risk of type 2 diabetes, whereas ACEIs and ARBs improve insulin resistance.[14] Beta blockers and thiazides increase triglyceride levels, whereas calcium channel blockers increase high density lipoprotein levels.[13] In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT BPLA study), 19,257 patients with hypertension who had at least three other cardiovascular risk factors and aged 40–79 years were assigned to receive either amlodipine (adding perindopril as required) or atenolol (adding

bendroflumethiazide and potassium as required). In this study, the amlodipine-based regimen was more effective in reducing cardiovascular events than the atenolol-based regimen.[14] At the end of the study, several metabolic variables differed significantly from baseline to final visit between treatment regimens; triglycerides and glucose had a significant reduction ($p<0.0001$) in the amlodipine-based group, whereas high density lipoprotein levels significantly ($p<0.0001$) increased in the amlodipine-based group.[15] In the Study of Trandolapril-Verapamil SR and Insulin Resistance (STAR) trial, there were 240 hypertensive patients with glucose intolerance who were followed for 1 year. The combination of trandolapril plus verapamil was more effective than the combination of losartan plus hydrochlorothiazide in reducing the risk of new-onset diabetes mellitus. Our group reported that the same combination of trandolapril plus verapamil increased adiponectin levels and reduced resistin levels more than ACEI monotherapy – both desirable effects in hypertensive patients at high cardiovascular risk.

Nephroprotective effect

Two studies with combined therapy showed that the progression of normoalbuminuria to microalbuminuria in hypertensive type 2 diabetic subjects can be stopped. In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), 1204 subjects were randomly assigned to receive treatment with trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo over 3 years.[16] At the end of the study, the use of trandolapril plus verapamil decreased the progression from normoalbuminuria to microalbuminuria. In the Action in Diabetes and Vascular Disease (ADVANCE) trial, there were 11,140 patients with type 2 diabetes who were randomised to treatment with a fixed combination of perindopril plus indapamide or matching placebo, in addition to current therapy.[17] After a mean follow-up of 4.3 years, the combination therapy reduced the progression from normoalbuminuria to microalbuminuria. In both studies, the nephroprotective effect was independent of its effect on blood pressure. Interestingly, this progression was not prevented with monotherapy. No studies have shown that the progression of microalbuminuria to normoalbuminuria in subjects with diabetes mellitus type 1 can be stopped.

Hemodynamic aspects

Two studies evaluated the effect of combining an ARB plus calcium antagonist compared with an ARB plus hydrochlorothiazide on the central pressure in hypertensive patients.[18] In both studies, the combination of the ARB plus the calcium antagonist achieved greater reductions of central aortic pressure than the combinations with the natriuretic agent. The Conduit Artery Functional Endpoint (CAFE) study recruited 2199 patients from five centres where the ASCOT trial was conducted, in whom central aortic pressures were measured at repeat visits for up to 4 years.[20] At the end of the study, and despite similar brachial systolic blood pressures between treatment groups, there were substantial reductions in central aortic pressures with the amlodipine regimen (95% CI: 3.3–5.4; $p<0.0001$). The authors concluded that the differences in central aortic pressures may explain the different clinical outcomes between the two treatment arms in ASCOT.

Elderly patients

The only study that has evaluated the effect of two combinations of antihypertensive drugs in the elderly is the Combinations of OL Mesartan (COLM) study, which included 5141 patients followed for an average of 3.3 years.[21] The study initially found no difference between the combinations of olmesartan with diuretic or amlodipine on outcomes in elderly patients. However, there were fewer adverse reactions in the group with calcium antagonist. In a subanalysis of the COLM study in 2223 subjects older than 75 years, it was found that the combination with the calcium antagonist achieved a greater reduction of cases of cerebrovascular disease and generated fewer side effects than the combination with natriuretic in this age group.[22] A *post hoc* analysis of the Systolic Hypertension in Europe (Syst-Eur) study, which included 1074 subjects older than 60 years with a 6 years follow-up, found that the combination of nitrendipine plus enalapril was more effective than nitrendipine monotherapy in decreasing the incidence of heart failure, cardiovascular and cerebrovascular events, and total mortality.[21]

Vascular function

Two studies have shown that the combination of perindopril plus indapamide or trandolapril plus verapamil, further improved endothelium-dependent vasodilation and endothelial function compared with monotherapy. The combination of trandolapril plus verapamil also showed protection against structural alterations and reduced neointima formation. The combination of benazepril plus amlodipine was more effective than high doses of both monotherapies in improving arterial compliance, reducing arterial stiffness and decreasing left ventricular mass. Combined therapy of irbesartan plus diltiazem ameliorated endothelial dysfunction to a greater extent than both monotherapies in 150 hypertensive patients.

Inflammation

There are studies that show that the combination of an ACEI with a calcium antagonist is more effective than monotherapy in reducing various mediators of inflammation (such as interleukins, tumour necrosis factor and adhesion molecules). This anti-inflammatory effect has not been seen with diuretics. In the OLAS study, the combination of olmesartan plus amlodipine significantly reduced the tumour necrosis factor-α, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and interleukins-1b, 6 and 8 when compared with olmesartan plus hydrochlorothiazide, whereas c-reactive protein showed a similar reduction in both groups.[22,23]

Patients with heart disease

The available evidence suggests that better results are obtained in patients with ischemic heart disease with combinations that include an RASI plus a calcium antagonist.[37] On the other hand, patients with heart failure benefit more from the combination of a diuretic plus an inhibitor of the renin–angiotensin axis.[24]

Other effects

The combination of losartan plus a calcium antagonist produces greater reductions in uric acid levels than the combination of losartan plus hydrochlorothiazide.[25] This could provide additional benefits in hypertensive patients with obesity and/or hyperuricemia, whether asymptomatic or with gout.

CONCLUSION

About 70% of hypertensive patients require the combination of at least two antihypertensive agents to reduce blood pressure levels below the recommended goals. Combination therapy should be initiated in patients with systolic pressure 20 mmHg above the target or diastolic pressure 10 mmHg above the recommended goal. Dual therapy should also be started in patients with high cardiovascular risk. Combination therapy provides greater antihypertensive power than the use of high doses of monotherapy, adding several mechanisms of action that block various pathways of increased blood pressure, in addition to providing greater protection to target organs than monotherapy, and reduced potential for side effects. The combinations recommended by the most commonly used guidelines include a RASI associated with a calcium antagonist or a natriuretic. Amongst these combinations, those that include a calcium antagonist have been shown to be more effective in reducing mortality, cardiovascular events, cerebrovascular events and kidney damage than those using hydrochlorothiazide. Combinations that include a calcium antagonist have been shown to have beneficial effects unrelated to their antihypertensive effect. These actions are metabolic, anti-inflammatory, renal protective, and improve vascular structure and function. Combinations that include a diuretic have given better results in patients with heart failure.

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