

# **Hypertension: the use of combination therapy (peer-reviewed review article)**

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## **Abstract**

Control of hypertension and treatment of concomitant pathophysiologic conditions require use of multiple drugs. Unfortunately, most studies regarding hypertensive disease have focused on monotherapy. Thus, our knowledge of combination therapy in the treatment of hypertension is to a great extent extrapolation from monotherapy. Angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists combinations should be particularly efficacious in reducing hypertensive target organ disease. Both of these drug classes have been shown to reduce hypertensive heart disease, diminish microproteinuria, and the decline in renal function. With regard to hypertensive vascular disease, both ACE inhibitors and calcium antagonists have documented benefits. However, their use together in left ventricular hypertrophy and in patients with coronary heart disease, while promising, must be proven through carefully designed, prospective, randomized trials.

Key Words: ACE inhibitors, calcium antagonists, left ventricular hypertrophy, hypertension, congestive heart failure

## **Introduction**

Monotherapy in hypertension control has been the traditional route for many years. Yet the use of only one drug to control arterial pressure is successful in 50 to 60 percent of all patients. [Chalmers] One reason for the low success rate is the ritual increase in the dose of the sole drug prescribed, leading to prolonged treatment with high doses and, thus, an increase in side effects. Patients, in turn, become non-compliant. Another reason for the failure to control blood pressure is that one drug addresses only one physiological pathway of many that leads to hypertension. Multiple mechanisms are involved in the pathogenesis of hypertension. [Messerli, 1993] Monotherapy in general will only interfere with one of these mechanisms, thereby potentially allowing the other mechanisms to compensate. Therefore, given that hypertension is a multifactorial condition, combination therapy makes more therapeutic sense. By choosing two drugs from appropriate classes of agents, the primary actions of drugs acting through different mechanisms are put into play, while they oppose the homeostatic compensations that limit the fall in blood pressure. [See Table 1] Combination therapy may have an advantage in that it synergistically interferes with pathogenetic mechanisms. Thus, lower doses can be used and the problem of dose-dependent side effects is minimized. Another rationale for combination therapy is that sustained hypertension often leads to target organ disease in the heart, the kidneys and the brain. Certain antihypertensive drugs, such as angiotensin converting enzyme inhibitors (ACE inhibitors), affect target organ disease independent of their antihypertensive efficacy. Unfortunately, most studies regarding hypertensive disease have focused on monotherapy. Thus, our knowledge of combination therapy in the treatment of hypertension is, to a great extent, extrapolation from monotherapy. This paper will explore the benefits of the ACE inhibitors in combination with calcium antagonists in terms of their efficacy in left ventricular hypertrophy (LVH) and coronary heart disease (CHD).

## **Combination therapy: general principles**

Antihypertensive efficacy of a single drug is often lowered due to the potential stimulation of

compensatory mechanisms serving to restore blood pressure to its preset levels. Combination therapy allows the use of lower doses of each antihypertensive agent; therefore, compensatory stimulation may be diminished, and, conceivably, the second component of combination may counteract this stimulation. For example, Jakobsen et al demonstrated that, in normotensive volunteers, the renin-angiotensin system contributes to mask the hypotensive effect of a single oral dose of the dihydropyridine, nifedipine. However, the concomitant administration of the ACE inhibitor, benazepril, discloses the hypotensive effect and limits the baroreflex-mediated increase in heart rate secondary to vasodilation. [Jakobsen] Adding a second drug may also unmask an antihypertensive effect of the first component as in the case of racial differences that were seen in black patients in response to low-dose captopril that were abolished by the addition of hydrochlorothiazide. [VA Coop Study] Whether the combination of two different antihypertensive agents results in an additive, subadditive, or supradditive effect on arterial pressure is unclear. Holland et al showed a synergistic effect of captopril and hydrochlorothiazide in the treatment of low-renin hypertension in black patients. [Holland] However, Nicholson et al found that hydrochlorothiazide is not additive when given with verapamil. [Nicholson] Our most recent analysis shows that, at most, an additive effect on blood pressure can be obtained. [See Table 2]

As mentioned, using monotherapy often means raising the dose of the antihypertensive agent to levels that can produce toxic effects. Postural hypotension, bradycardia, myocardial ischemia with subsequent myocardial infarction, cardiac arrhythmias, and profound shock are all symptoms that can result from high doses of some older antihypertensive agents. Fagan elegantly documents that to avoid side effects, refrain from increasing the dose of monotherapy drug above one that controls blood pressure in about half of the patients. [Fagan] Thus, a low-dose combination of two different agents reduces the risk of dose-related adverse reactions while still allowing sufficient blood pressure reduction.

Apart from increased efficacy, several other reasons exist that can lead the clinician to consider combination therapy. For example, the addition of one agent may counteract some deleterious effects of the other. Weinberger reported that adjunctive ACE inhibitor therapy attenuated diuretic-associated hypokalemia, hyperglycemia, hyperuricemia, and hypercholesterolemia. [Weinberger] Vasodilatory edema that occasionally occurs with dihydropyridine calcium antagonists has been reported to diminish when ACE inhibitors were added. In a study conducted by Frishman et al, the edema seen with amlodipine monotherapy was minimized when benazepril was added to the regimen. [Frishman, Ram] The drugs, in combination, produced a more favorable blood pressure control profile with a better tolerance record than either drug alone.

The combination of an ACE inhibitor and a calcium antagonist is conceptually attractive because the calcium antagonist provides primarily arterial vasodilation, whereas the ACE inhibitor adds balance with some venous dilation, a characteristic that applies particularly to the dihydropyridine calcium antagonists, and which produces an almost exclusive arteriolar dilation. [Frishman, Landau] The natriuretic effect of calcium antagonists complements ACE inhibitor therapy much as diuretic therapy does, but it makes it possible to control blood pressure without using a diuretic when that is desirable. [Kaplan]

Each agent provides theoretical or actual benefits when certain concomitant conditions are present: ACE inhibitors for left ventricular dysfunction/heart failure, diabetic nephropathy, and postmyocardial infarction, and calcium antagonists for angina, certain arrhythmias, and various vasospastic conditions. [Kaplan] Both agents have, theoretically, beneficial hemodynamic and nonhemodynamic effects on the kidney, the heart, and the vasculature that are pressure-independent. Therefore, such combinations may

be particularly appropriate in patients with diabetic nephropathy, nondiabetic renal disease, and either hypertensive or atherosclerotic heart disease. In the common situation in which a hypertensive diabetic patient has angina and nephropathy, this combination—with or without the addition of a diuretic—would seem to be ideal.

Recent data suggest that the combination of calcium antagonists and ACE inhibitors has a favorable effect on hypertensive target organ disease, possibly exceeding the effect of the reduction of blood pressure per se. Bakris found that, in hypertensive type 2 diabetics, the combination of reduced doses of an ACE inhibitor and calcium antagonist attenuate both albuminuria and the rate of decline in glomerular filtration rate. Also, high doses of ACE inhibition alone may be detrimental to renal function in late stage diabetics with renal insufficiency. [Bakris; Lash] ACE inhibitors in combination with calcium antagonists are particularly efficacious in reducing left ventricular hypertrophy and may be useful in patients with coronary heart disease (CHD).

### **Left ventricular hypertrophy**

The results of basic and clinical research over the last 30 years have shown that hypertension cannot be treated merely by inducing vasodilation and a fall in blood pressure. The development of hypertension is linked with changes in carbohydrate and lipid metabolism and with the development of organ damage, mainly of the heart and kidneys. We now know that different elements of blood pressure control mechanisms can lead to hypertension, emphasizing the need to select the appropriate type of hypertensive drug in treating different patients. Osswald noted that calcium antagonists and ACE inhibitors have synergistic effects on sodium and fluid balance and on the renin-angiotensin-aldosterone system. [Osswald] Thus a combination of these two antihypertensive drug classes is likely to be beneficial in certain subgroups of patients with hypertension. While large trials are needed to truly prove this hypothesis, we recognize that, of all antihypertensive drugs, ACE inhibitors are probably the most effective in reducing LVH. [Dahlof, Pennert; Bohlen; Cruickshank] Dahlof performed a meta-analysis of 109 studies comprising 2357 patients which showed that ACE inhibitors, beta-blockers, and calcium antagonists all reduce left ventricular mass by reversing wall hypertrophy, and that the effect is most pronounced with ACE inhibitors. [Dahlof, Pennert] Recently, Schmieder et al performed a meta-analysis that only considered randomized studies comparing the effects of two or more therapies by assessing LVH and structure with blindly read echocardiograms. [Schmieder, Martus; Schmieder, Schlaich] Similar to previous meta-analyses, the decrease in left ventricular mass was greater with active drug treatment than with placebo and was directly related to the pretreatment left ventricular mass, control of pressure and duration of treatment. When the analysis was adjusted for the study duration, ACE inhibitors were most efficient in reducing LVH, followed by calcium channel blockers, the diuretics and the beta-blockers. [Schmieder, Martus; Schmieder, Schlaich] Indeed, some reports suggest that ACE inhibitors may lower blood pressure more than one would expect from their unloading properties alone. The ability of ACE inhibitors at a dose that does not lower blood pressure to produce regression in LVH supports the hypothesis that the local cardiac renin-angiotensin system is a significant determinant of heart structure and function. [Pfeffer; Dzau] Pfeffer showed that in patients with asymptomatic left ventricular dysfunction after myocardial infarction, long-term administration of the ACE inhibitor, captopril, was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events. [Pfeffer] These benefits were observed in patients who received thrombolytic therapy, aspirin, or beta-blockers, as well as those who did not, suggesting that treatment with captopril leads to additional improvement in outcome among selected survivors of myocardial infarction. In comparison, the calcium antagonists seem slightly less potent in reducing LVH than the ACE inhibitors.

No conclusive data exist to show that a reduction in LVH would confer a benefit that exceeded the one

conferred by the reduction in arterial pressure per se. These drawbacks notwithstanding, one can extrapolate that the combination of an ACE inhibitor with a calcium blocker ought to be particularly efficacious with regard to a reduction of LVH [See Table 3]. Because both these drug classes have the potential to interfere with pathogenesis of LVH at a similar level, one can argue that this combination will reduce LVH more than one would expect from its blood pressure lowering effects alone. Whether angiotensin II receptor inhibitors, either in monotherapy or in combination, are as efficient as ACE inhibitors in reducing LVH remains undocumented at the present time. Most of the other commonly used combinations, such as diuretics plus beta-blockers, ACE inhibitors plus beta-blockers, as well as beta-blockers plus dihydropyridine calcium antagonists, are prone to reduce LVH in parallel with the fall in arterial pressure.

Is there any drug combination that should be avoided in patients with LVH? Drug classes that either stimulate the renin angiotensin system or the sympathetic nervous system, or both, are less likely to reduce LVH than drug classes that do not stimulate these systems. The combination of an arteriolar vasodilator, such as hydralazine or minoxidil, with a diuretic should, therefore, probably not be used in an asymptomatic patient with LVH. Such a combination may also synergistically elicit hypokalemia, which could aggravate or trigger ventricular arrhythmias.

### **Coronary artery disease**

Myocardial ischemia has been shown to be common among hypertensive patients. [Kannel; Strauer] This may be due to the development of coronary atherosclerosis, exaggerated reactivity of cardiac arterioles, increased hemodynamic burden of the heart and increase in left ventricular mass. The two drug classes most commonly used to treat coronary artery disease are the calcium antagonists and the beta-blockers. But should they be used in combination? Short-acting dihydropyridines may have a detrimental effect on myocardial oxygenation, [Boden; Schanzenbacher, Deeg; Schanzenbacher, Liebau; Sia; Wilson; Opie; Psaty] and there is at present an agreement that they should not be used for treatment of coronary disease and hypertension. [NHLBI; Laragh] On the other hand, many studies attest to the safety and efficacy of longer acting calcium antagonists [O'Connor; Cohn; DEFIANT-II; Rehnqvist; Gong; Braun; Jick; Aursnes]. Braun et al did a cohort study of 11,575 patients with coronary artery disease and determined that calcium antagonist therapy in such patients did not harbor an increased risk of mortality. [Braun] In fact, calcium antagonists are particularly useful in vasospastic angina pectoris. Logic, therefore, dictates the use of a combination of these two drug classes in hypertensive patients who are suffering from coronary artery disease and who require two or more drugs to lower arterial pressure. Indeed, fixed combinations of some dihydropyridine calcium antagonists and beta-blockers have been marketed outside the United States [Messerli, 1992; Dahlof, Jonsson] but only for hypertension and not for coronary artery disease. By and large, the combination of a heart rate lowering calcium antagonist, such as verapamil or diltiazem, with a beta-blocker should be avoided because the two molecules could exert synergistic negative chronotropic and negative inotropic effects.

Whether the combination of an ACE inhibitor and a calcium antagonist is therapeutically justifiable in patients with CHD remains to be seen. Angiotensin, a vasoconstrictive peptide, is now known to be an agent of vascular oxidative stress, vascular growth, and inflammation, and can directly influence the pathophysiology of CHD. [Dzau, 1998] Angiotensin-converting enzyme inhibition has been shown to improve endothelium-dependent vasodilator responsiveness in patients with CHD. Koh et al showed that ACE inhibitor therapy selectively improves endothelium-dependent vasodilator responsiveness by increased nitric oxide (NO) bioactivity in relation to vascular smooth muscle in such patients, an effect achieved at a lower rate of NO release from the endothelium. [Koh] These research findings suggest that ACE inhibitors may reduce angiotensin II-induced oxidant stress within the vessel wall and protect

NO from oxidative inactivation, an effect that may reduce endothelial NO synthesis required for vasomotor regulation.

New insights from basic laboratory studies and clinical trials have raised the intriguing possibility that the renin-angiotensin-kinin system may play a critical part in the pathophysiology of atherosclerosis. [Flack] These studies suggest the possibility of an important new therapeutic role for ACE inhibitors: reduction in the risk of atherosclerosis and the complications of coronary artery disease. Ongoing large-scale trials will establish whether the findings from basic laboratory studies and clinical heart failure trials will apply to patients with ischemic heart disease irrespective of the presence or absence of left ventricular dysfunction.

### **Conclusion**

Using multiple drug therapy in hypertension to achieve maximal therapeutic benefits seems logical based on clinical evidence. Unfortunately, most studies regarding target organ damage in hypertension were carried out by focusing on the effects of monotherapy. Extrapolating from these studies, however provocative and suggestive they are, may not always prove to be beneficial in terms of hard end points, i.e. morbidity and mortality. Therefore, the exact benefits of any particular combination therapy will have to be defined by prospective, carefully designed, randomized trials.

The role of ACE inhibitor-calcium antagonist combinations in reducing hypertensive end-organ damage, especially renal and cardiac, is promising but is yet to be fully clarified. In the meantime, for patients in whom a multidrug antihypertensive regimen is desirable, these fixed-dose combinations of ACE inhibitors and calcium antagonists offer a convenient, once-daily, effective and well-tolerated addition to our therapeutic options. Hopefully, the cost to the patient will also be less than the two agents prescribed separately. Because many hypertensive patients are already taking a regimen that includes both of these classes of drugs, we should carefully assess whether a fixed-dose preparation would benefit many of our patients.

### **Tables**

Table 1: Pharmacologically rational antihypertensive combinations [Frishman, Landau; Reid; Sica; Kaplan]

- COMBINATION > RATIONALE
- Thiazide diuretic + potassium-sparing diuretic > Provides diuresis with a lower risk of hypokalemia
- Thiazide diuretic + adrenergic inhibitor > Diuretic reduces volume retention associated with adrenergic inhibitors
- Beta-blocker + diuretic > Beta-blocker can blunt the tachycardia and rise in plasma renin activity associated with thiazide diuretics; the diuretic opposes any sodium retention caused by the beta-blocker
- Beta-blocker + dihydropyridine > Beta-blocker can attenuate the tachycardia and sympathetic nervous system stimulation calcium antagonists that occurs with dihydropyridine; calcium antagonist can inhibit adrenergic vasoconstriction associated with beta-blockade

- Beta-blocker + alpha-blocker > Beta-blocker prevents tachycardia and renin stimulation associated with alpha-blocker; alpha-blocker can inhibit vasoconstriction associated with beta-blockade
- ACE inhibitor + diuretic > Diuretic can enhance the efficacy of the ACE inhibitor, even in patients with low-renin hypertension; ACE inhibitor can enhance the efficacy of a diuretic in normal-to-high renin hypertension and ameliorate many of the metabolic adverse effects of diuretics, including hypokalemia
- ACE inhibitor + calcium antagonist > Calcium antagonist-associated natriuresis complements ACE inhibitor effect; angiotensin-II independent additional vasodilation; ACE inhibitor primarily dilates efferent arterioles, and calcium antagonist primarily dilates afferent arterioles in the kidney
- Diuretic + sympatholytic or alpha-blocker > Diuretic reduces volume retention associated with adrenergic inhibitors

Table 2: Effects of combination therapy observed versus predicted blood pressure reduction. Taken from: Messerli FH, Michalewicz L. Cardiac effects of combination therapy. *Amer J Hypertens.* 1997;10:146S-152S. Table 1.

Table 3: Possible synergism resulting from a combination of a calcium antagonist and an ACE inhibitor. Taken from: Messerli FH, Michalewicz L. Cardiac effects of combination therapy. *Amer J Hypertens.* 1997;10:146S-152S. Table 2.

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