Low-Dose Combination Therapy: The Rationalization for an ACE Inhibitor and a Calcium Channel Blocker in Higher Risk Patients

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As more high-risk hypertensives are treated and the need for more intensive antihypertensive therapy is recognized, combination therapies are increasingly used. For initial therapy, particularly for relatively low-risk patients, low-dose combinations are often appropriate. For those who require additional therapy, higher doses of combinations may provide further efficacy while minimizing dose-dependent side effects of monotherapy, thereby improving adherence to therapy. Those combination agents should provide 24-h control with one daily dose, thereby ensuring protection in the early morning hours. Combining an angiotensin converting enzyme inhibitor and a calcium channel blocker is a rational approach to treating hypertension. Not only does it provide significantly better blood pressure control than individual components used as monotherapy, it also minimizes dose-dependent side effects. Also, combining agents from different classes results in complementary mechanisms of action that provide other cardiovascular protective benefits.

Key Words: Angiotensin converting enzyme inhibitors, calcium channel blockers, antihypertension therapy.

For multiple reasons, major shifts in the therapy of hypertension are in process. First, more and more patients are at higher and higher risk than previously. Those higher risks reflect the increasing age of the population at large, the tremendous increase in the number of type 2 diabetics reflects the marked increase in obesity in all industrially advanced societies, and the survival of patients with heart attacks, stroke, heart failure, or renal insufficiency who used to die earlier.

Second, multiple randomized, controlled trials have provided conclusive evidence that in such high-risk patients, the appropriate goal of antihypertensive therapy must be considerably lower than previously thought. Perhaps first recognized in hypertensive patients with renal insufficiency, then in hypertensive diabetics, and more recently, in patients who have active coronary heart disease or cerebrovascular disease, the evidence is now clear: to provide maximal protection, therapy must be started at blood pressure (BP) levels of 130/85 mm Hg and should reach a goal as low as 120/75 mm Hg or, if well tolerated, even lower.

Third, to achieve these goals, multiple drugs are almost always necessary. Perhaps most clearly shown in the recent consensus report on therapy of hypertension in patients with renal insufficiency, three or four drugs have usually been needed to lower BP to the predetermined lower goals of therapy in the high-risk patients enrolled in 5 recent trials.

The Rationale for Low-Dose Combination Therapy

The rationale was nicely described in the Sixth Report of the Joint National Committee (JNC-VI): Newly developed formulations provide additional medication choices. For example, combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent adverse effects. Very low doses of a diuretic (eg, 6.25 mg of hydrochlorothiazide) can potentiate the effect of the other agent without producing adverse metabolic effects. Low-dose combinations with an angiotensin converting enzyme (ACE) inhibitor and a nondihydropyridine calcium antagonist may reduce proteinuria more than either drug alone.
nations of a dihydropyridine calcium antagonist and an ACE inhibitor induce less pedal edema than does the calcium antagonist alone.\textsuperscript{10}

Obviously, the most logical combinations are those that include agents that lower BP by different mechanisms (eg, a diuretic plus a \( \beta \)-blocker or an ACE inhibitor plus a calcium channel blocker (CCB). As noted in the quote from JNC-VI, the latter combination has been shown to reduce the incidence of the most common side effect of CCB, dependent edema.\textsuperscript{10} This combination has also shown more promise in reducing cardiovascular events than either monotherapy, as demonstrated in the Fosinopril Versus Amlodipine Cardiovascular Events Trial.

The Need for Long-Acting Drugs

Whatever drugs are used, singly or in combination, they should provide sustained effect over the entire 24 h with one dose a day. In the words of JNC-VI: The optimal formulation should provide 24-h efficacy with a once-daily dose, with at least 50\% of the peak effect remaining at the end of the 24 h. Long-acting formulations that provide 24-h efficacy are preferred over short-acting agents for many reasons: 1) adherence is better with once-daily dosing; 2) for some agents, fewer tablets incur lower cost; 3) control of hypertension is persistent and smooth rather than intermittent; and 4) protection is provided against whatever risk for sudden death, heart attack, and stroke that is due to the abrupt increase of BP after arising from overnight sleep. Agents with a duration of action beyond 24 h are attractive because many patients inadvertently miss at least one dose of medication each week.

The Rationale for and Benefits of Combining an ACE Inhibitor and a CCB

The combination of an ACE inhibitor and a CCB provides multiple advantages over monotherapy, such as significantly greater BP control and minimized CCB-induced pedal edema. These two classes of drugs work in entirely different ways, both providing peripheral vasodilation with little direct effects on cardiac output. Of course, in the presence of an activated renin-angiotensin system as with systolic dysfunction leading to heart failure, an ACE inhibitor provides impressive reduction of the afterload on the left ventricle, therefore, these drugs have become standard therapy for congestive failure. Perhaps by more direct effects on ventricular remodeling, ACE inhibitors also reduce recurrences of myocardial infarction.\textsuperscript{3} On the other hand, dihydropyridine CCB have been found to reduce the occurrence of various complications in patients with angiographically documented coronary artery disease.\textsuperscript{11}

Perhaps the most beneficial effects of the ACE inhibitor–CCB combination have been found in patients with renal insufficiency, in particular related to diabetic nephropathy. By themselves, ACE inhibitors protect against progressive renal damage and reduce proteinuria by their preferential effect on efferent anteriolar resistance, reduc-
ing intraglomerular pressure more specifically than any other agents. The CCB, reducing afferent arteriolar resistance, may not reduce proteinuria because of the increase in intraglomerular flow but will preserve renal perfusion and glomerular filtration. As seen in the African American Study of Kidney Disease and Hypertension trial, CCB by themselves are not as renoprotective as are ACE inhibitors. However, in combination with an ACE inhibitor, CCB have been shown to provide additional long-term renal protection. This combination is recognized as an effective therapy for reducing both systemic and intrarenal hypertension, thereby protecting the kidneys.

**Conclusion**

In view of the widening recognition that more intensive antihypertensive therapy is needed to protect the increasing population of high-risk patients, the added values of combinations of drugs will be increasingly recognized. A particularly vivid demonstration of the importance of multiple drug therapy was shown by Gaede et al. in their study of 160 diabetic hypertensives with microalbuminuria. Half were randomly assigned to more intensive therapy including tighter control of hypertension, hyperglycemia, and dyslipidemia, as well as routine use of ACE inhibitors and aspirin along with more physical activity and dietary changes. At the end of 3.8 years, those who were more intensively treated had almost 70% lesser rates of progression of nephropathy, retinopathy, and autonomic neuropathy compared to those given “standard” therapy (Fig. 2).

Because of the need for more aggressive BP control in high-risk patients who are unlikely to reach target BP goals with monotherapy, it may be necessary to use combination therapy. Low-dose combinations of antihypertensive agents, such as an ACE inhibitor and a CCB, can provide additional control of hypertension, while minimizing the likelihood of dose-dependant adverse effects.

Obviously, such added protection requires more intensive follow-up, more drugs, more expense, and more motivation. But the payoffs are far greater than the costs. The use of appropriate combinations of antihypertensive drugs surely will help in providing protection to our expanding high-risk hypertensive population.

**References**


