

The following abstracts, from medical journals containing literature on hypertension, were selected for their relevance to this Special Report supplement.

Amlodipine/Benazepril Combination in Essential Hypertension

A multicenter, double-blind, randomized, parallel-group study involving 308 patients with essential hypertension has found that once-daily combination therapy with amlodipine 5 mg/benazepril 20 mg was statistically and clinically superior to amlodipine 5 mg alone, benazepril 20 mg alone, and placebo in lowering blood pressure. After a placebo run-in period, patients were randomized to treatment groups and took medication once a day for 8 weeks. Blood pressure was measured after 4 and 8 weeks of treatment and evaluated by 24-hour monitoring before randomization and before the final visit. The response rates were 87% for patients receiving the amlodipine/benazepril combination, 67.5% for those receiving amlodipine alone, 53.3% for those receiving benazepril alone, and 15.8% for those on placebo. Ambulatory monitoring demonstrated that the combination maintained the hourly mean diastolic blood pressure at 90 mm Hg or less, whereas monotherapy did not. The combination was also well tolerated, with an adverse event rate of 15.6% versus 24.7%, 6.5%, and 11.7% in patients receiving amlodipine alone, benazepril alone, and placebo, respectively. Moreover, the combination was associated with less edema (7.8%) than amlodipine monotherapy (16.7%).

Kuschnir E, Acuña E, Sevilla D, et al Treatment of patients with essential hypertension: Amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo *Clin Ther* 1996;18:1213-1223.

Choosing Antihypertensive Drugs in Clinical Practice

Physicians who treat patients with hypertension are faced with a dilemma. Should they choose drugs from older classes that provide less-than-optimal antihypertensive effects? Or should they choose newer agents that appear to be very promising but whose endpoint benefits in hypertension have not yet been proved? Regarding the newer drug classes, the author of this report notes that angiotensin-converting enzyme inhibitors (and potentially angiotensin receptor blockers) have been shown to protect the heart and kidney in a number of cardiovascular conditions, but not in formal hypertension trials as yet. Similarly, calcium channel blockers have been shown to protect against stroke and cardiovascular events in patients with isolated systolic hypertension, but definitive coronary data are still not available. Combination therapy, whereby 2 drugs given together provide a stronger antihypertensive effect than either drug given alone, is an efficacious and convenient approach to treatment, but there are no clinical endpoint data on this approach available at this time. Until ongoing prospective trials evaluating antihypertensive agents are completed, the author suggests that physicians be guided by their clinical judgement and their own interpretations of available data.

Weber MA. Translating data on antihypertensive drugs into clinical practice. *Am J Hypertens* 1998;11:89S-94S

Two Fixed-Dose Combinations Versus Their Monotherapies

In a randomized, multicenter, double-blind, placebo-controlled, parallel-group trial, 2 fixed-dose combinations of enalapril and extended-release diltiazem were found to be more effective than their monotherapies in reducing trough (24 hours, 2 hours postdose) sitting diastolic blood pressure levels. Both fixed-dose combinations were also more effective than both diltiazem monotherapies in reducing trough sitting systolic blood pressure levels. The study, which involved 891 patients with sitting diastolic blood pressure levels between 95 mm Hg and 115 mm Hg, consisted of a 12-week treatment phase followed by a 36-week open-label phase. Patients were randomly assigned to enalapril 5 mg, extended-release diltiazem 120 mg, extended-release diltiazem 180 mg, a fixed-dose combination of enalapril 5 mg/extended-release diltiazem 120 mg, a fixed-dose combination of enalapril 5 mg/extended-release diltiazem 180 mg, or placebo. In the open-label phase, 562 patients received the fixed combination, which was titrated as needed to keep the diastolic blood pressure at 90 mm Hg or below. Efficacy was determined by trough sitting blood pressure measurements at week 12 and again at the end of the open-label phase of the study. All active treatments significantly reduced sitting diastolic and systolic blood pressure versus placebo. In addition, the fixed combination effectively lowered sitting diastolic and systolic blood pressure during the open-label extension. Safety of the fixed-dose combinations, as determined by patient symptoms, clinical laboratory tests, and electrocardiograms, was also demonstrated in the study.

Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK, for the Enalapril/Diltiazem ER Comparison to Monotherapies Group. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. *Am J Hypertens* 1998;11:23-30.

Combination Therapy With Diuretics

Multiple studies have demonstrated that the response rate to any single class of antihypertensive agent, when given as monotherapy, is roughly 45% to 55%. Consequently, approximately half of the hypertensive population will require a second drug for adequate blood pressure control. In this regard, combination therapy with low-dose diuretics (< 25 mg hydrochlorothiazide or its equivalent) has become an attractive alternative to first-line therapy in patients with essential hypertension. Data from numerous clinical trials have shown that the addition of 6.25 mg or 12.5 mg hydrochlorothiazide to most antihypertensive drugs has an additive or synergistic effect on blood pressure reduction. The side-effect profile of low doses of diuretics is similar to that of placebo, and the metabolic side effects of diuretics are significantly reduced when these agents are used in low doses.

Neutel JM, Black HR, Weber MA. Combination therapy with diuretics: An evolution of understanding. *Am J Med* 1996;101(suppl 3A):61S-70S.

Managing Hypertensive Renal Disease

The authors of this review article note that it is necessary to control systolic and diastolic hypertension in order to reduce the incidence of hypertensive end-stage renal disease, which continues to increase annually. In addition, they say, reversible causes should be sought in any patient with hypertension who develops renal insufficiency. They recommend that blood pressure be reduced to 130/85 mm Hg to slow the progression of renal failure, and to 120/75 mm Hg in African-Americans with renal insufficiency and in patients with renal disease and proteinuria in excess of 1 g/day. Although any antihypertensive regimen that effectively lowers blood pressure will help slow progressive renal failure, use of angiotensin-converting enzyme inhibitors is especially beneficial because these agents have been shown to reduce blood pressure and provide renoprotection in patients with renal insufficiency secondary to hypertension, glomerulonephritis, and diabetic nephropathy.

Moore MA, Epstein M, Agodoa L, Dworkin LD. Current strategies for management of hypertensive renal disease. *Arch Intern Med* 1999;159:23-38.

Hypertension Optimal Treatment (HOT) Trial

In this large, multinational study, intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events. The aim of the Hypertension Optimal Treatment (HOT) trial was to assess the optimum target diastolic blood pressure and the potential benefits of low-dose aspirin in treating hypertension. The trial involved 18,790 patients from 26 countries who had hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg. They were randomized to a target diastolic blood pressure: 6264 to ≤ 90 mm Hg, 6264 to ≤ 85 mm Hg, and 6262 to ≤ 80 mm Hg. Felodipine (5 mg once a day) was given as baseline therapy, and additional therapy and dose increments were prescribed in 4 steps to reach the randomized target blood pressure. Angiotensin-converting enzyme (ACE) inhibitors or beta blockers were added at step 2, the felodipine dose was doubled at step 3, and the dose of either the ACE inhibitor or the beta blocker was doubled at step 4. If necessary, a diuretic was added at step 5. In addition, 9399 patients were randomly assigned to receive aspirin (75 mg/day) and 9391 to placebo. In the ≤ 90 mm Hg, ≤ 85 mm Hg, and ≤ 80 mm Hg groups, diastolic blood pressure was reduced by 20.3 mm Hg, 22.3 mm Hg, and 24.3 mm Hg, respectively. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg, and the lowest risk for cardiovascular mortality occurred at 86.5 mm Hg. There was a 51% reduction in major cardiovascular events in patients with diabetes in the ≤ 80 mm Hg target group compared with diabetics in the ≤ 90 mm Hg target group. Aspirin reduced major cardiovascular events by 15% and all myocardial infarction by 36%. While aspirin had no effect on the incidence of stroke or fatal bleeds, it doubled the incidence of nonfatal major bleeds.

Hansson L, Zanchetti A, Carruthers SG, et al for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-1762.

Fixed-Dose Combination Therapy

The authors of this review article relate the rationale for fixed-dose combination therapy to the concept that antihypertensive efficacy may be improved when 2 classes of antihypertensive agents are combined. Tolerability is also enhanced because 1 drug of a fixed combination can counterbalance some of the adverse effects of the second drug. Another novel concept is that fixed-dose combination therapy may enhance salutary effects on target organs above and beyond the expected antihypertensive effects. Among the salutary effects on target organs are regression of left ventricular hypertrophy and slowing the progression of renal disease. The authors also discuss several fixed-dose combinations, particularly angiotensin-converting enzyme inhibitor/calcium channel blocker combinations.

Epstein M, Bakris G. Newer approaches to antihypertensive therapy: Use of fixed-dose combination therapy. *Arch Intern Med* 1996;156:1969-1978

Combination Therapy and Renal Disease Progression

African-Americans, persons with diabetic nephropathy, and persons with renal insufficiency or ≥ 1 g of proteinuria require blood pressure control of $<130/85$ mm Hg to preserve renal function. Since single-agent therapy will never achieve this level of blood pressure control, multiple antihypertensive agents are necessary. However, compliance with therapy decreases as the number of medications increases. Fixed-dose combinations thus emerge as important alternatives to multiple-agent therapy because they achieve adequate reductions in blood pressure while maintaining compliance. Certain types of angiotensin-converting enzyme inhibitors and calcium channel blocker combinations seem to have better overall effects than do others in achieving adequate blood pressure control and preserving renal function. The author reviews these combinations with respect to blood pressure reduction and renal protection.

Bakris GL. The role of combination antihypertensive therapy and the progression of renal disease hypertension: Looking toward the next millennium. *Am J Hypertens* 1998;11:158S-162S

Effects of Amlodipine on Chronic Heart Failure

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study has found that amlodipine does not increase cardiovascular morbidity or mortality in patients with severe chronic heart failure. This is in contrast to previous studies that have found that calcium channel blockers increase mortality and morbidity in this population. In the PRAISE trial, 1153 patients with severe chronic heart failure and ejection fractions below 30% were randomly assigned to double-blind treatment with amlodipine (571 patients) or placebo (582 patients) for 6 to 33 months; their usual therapy was continued during this time. In addition, the randomization was stratified according to whether the patients had ischemic or nonischemic causes of heart failure. The primary endpoint of the study was death from any cause and hospitalization for major cardiovascular events. Primary endpoints were reached in 39% of the amlodipine group and in 42% of the placebo group, representing a 9% reduction in the combined risk of fatal and nonfatal events with amlodipine. Mortality was 33% in the amlodipine group and 38% in the placebo group, representing a 16% reduction in the risk of death with amlodipine. While there was no difference between the 2 groups in the occurrence of either endpoint in patients with ischemic heart disease, amlodipine reduced the combined risk of fatal and nonfatal events by 31% in patients with nonischemic dilated cardiomyopathy. The study investigators note that the possibility that amlodipine prolongs survival in patients with nonischemic dilated cardiomyopathy requires further study.

Packer M, O'Connor CM, Ghali JK, et al for the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-1114.

The Pharmacist's View of Combination Therapy

The author of this article describes a review of the literature on the use of combination therapy versus monotherapy in hypertension and on the pharmacologic actions and appropriateness of 7 major antihypertensive combinations. The literature review focused on clinical studies dealing with the efficacy of combination therapy in reducing blood pressure and included major hypertension texts addressing combination therapy. Data from these sources were evaluated with respect to study design, clinical outcomes, and the use of antihypertensive classes commonly seen in practice. Available data show that angiotensin-converting enzyme (ACE) inhibitors plus diuretics or calcium channel blockers produce synergistic effects on blood pressure, and beta blockers plus diuretics or calcium channel blockers produce additive effects. Combinations that are ineffective include beta blockers plus ACE inhibitors and dihydropyridine calcium blockers plus diuretics, although there are specific circumstances where these combinations may be used clinically. The author points out that the pharmacist who understands and applies the pharmacology of these antihypertensive agents can help physicians make rational decisions when they select combination therapy.

Rodgers PT. Combination drug therapy in hypertension: A rational approach for the pharmacist. *J Am Pharm Assoc* 1998;38:469-479.