sive patients. However, substantially better response rates may be achieved in Stage 1 hypertensive patients using the age by race construct. In fact, achieving recommended BP goals may require 2, 3 or even more agents, particularly in high-risk hypertensive patients. Major clinical outcome trials, including the HOT (Hypertension Optimal Treatment) study, UKPDS (United Kingdom Prospective Diabetes Study), and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), have shown that 40% to 50% of patients require multiple agents to achieve BP control.

Because of the complexity of medication regimens and the need for more intensive goals for CV risk reduction, it is important to consider therapeutic strategies to simplify the approach to BP control and enhance long-term compliance. The JNC 7 guidelines now recommend initiating antihypertensive therapy with 2 agents, either as separate prescriptions or in fixed-dose combinations, when BP is more than 20 mm Hg above systolic goal or 10 mm Hg above diastolic goal. Combination antihypertensive therapy has been shown to provide greater efficacy and tolerability, compared with high-dose monotherapy. An ideal combination regimen will provide additive or even synergistic BP control, 24-hour BP control, and target-organ protection. An emerging body of evidence in diverse populations suggests that the combination of an angiotensin-converting enzyme inhibitor and a calcium channel blocker is more effective than commonly used monotherapies.

The SOLACE (Safety of Lotrel vs Amlodipine in a Comparative Efficacy Trial) trial evaluated the efficacy and safety of initial combination therapy versus monotherapy in patients with Stage 2 hypertension. The major objective of SOLACE was to compare the percentage of subjects treated with combination amlodipine besylate/benazepril HCl and subjects treated with amlodipine besylate monotherapy who achieved reductions in SBP of greater than or equal to 25 mm Hg (if baseline SBP was <180 mm Hg), or a reduction in SBP of greater than or equal to 32 mm Hg (if baseline SBP was greater than or equal to 180 mm Hg). At Week 12, 74% of patients randomized to combination therapy achieved treatment success compared with 54% of those randomized to amlodipine besylate (P<0.0001). Notably, the incidence of peripheral edema was significantly higher in the monotherapy group compared with that in the combination group (23.0% vs 12.6%, respectively; P=0.01).

The results from clinical trials support the JNC 7 recommendation for use of initial combination therapy in patients with Stage 2 hypertension or diabetes. Use of a combination agent may be appropriate as initial therapy in patients at high CV risk, such as those with diabetes, CV disease, renal insufficiency, or any combination of these risk factors. Furthermore, because multiple antihypertensive agents are necessary to achieve BP goals in so many patients, the use of combination therapy in addition to, or in replacement of, a failed monotherapy also is a rational option.

Key Words: Combination antihypertensive therapy, systolic hypertension, isolated systolic hypertension, Lotrel, amlodipine, benazepril, SOLACE.

EXTENDING THE BENEFITS OF COMBINATION ANTIHYPERTENSIVE THERAPY TO MORBIDITY AND MORTALITY REDUCTION

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The ultimate reason for lowering blood pressure (BP) is to reduce the morbidity and mortality associated with hypertension. In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35%-40%; reductions in myocardial infarction of 20%-25%; and reductions in heart failure >50%. Combination therapy in hypertension, using low doses of 2 or more agents, increase BP-lowering efficacy and improves tolerability, compared with monotherapy. The possibility exists that specific combination therapies could improve cardiovascular (CV) outcomes, not only through controlling BP but also through mechanism-specific CV and renal-protective benefits beyond BP reduction. While the use of combination antihypertensive therapy is needed to achieve BP in the majority of patients, sparse clinical trial data are available for determination of the optimal selection of agents for combination therapy.

Recent large, clinical hypertension trials such as ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and ANBP-2 (the second Australian National Blood Pressure Study) have reached different conclusions regarding the optimal agent to use when initiating antihypertensive therapy. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has followed the findings of ALLHAT in recommending the use of thiazide diuretics for initiating therapy in patients with uncomplicated hypertension. However, few patients with hypertension are actually uncomplicated. Perhaps the most important question to be answered is not which antihypertensive class should be utilized for initiation of therapy, but which combination of agents will produce the best clinical outcomes in hypertensive patients?

An exciting possibility is that specific drug combinations may confer target-organ protection in addition to and independent of their BP-
lowering effects. However, the merits of various combinations of anti-hypertensive agents have not previously been studied in prospective, randomized, controlled clinical trials. A new clinical trial, ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), is the first large clinical trial to directly compare CV mortality and morbidity rates for 2 fixed-dose combination therapies. The ACCOMPLISH trial will evaluate whether an angiotensin-converting enzyme (ACE) inhibitor/calcium channel blocker combination or an ACE inhibitor/diuretic combination provides greater benefits in reducing morbidity and mortality from CV events in a high-risk hypertensive population. The trial will randomize subjects to either amlodipine besylate/benazepril HCl (Lotrel) or benazepril HCl/diuretic, and is currently recruiting patients from the United States and Northern European countries. There is substantial study evidence supporting the use of ACE inhibitors in hypertensive patients with diabetes, renal insufficiency and/or proteinuria. Thus, the use of the ACE inhibitor benazepril in both treatment groups allows for the inclusion of these important high-risk patient subgroups in the ACCOMPLISH trial. Results from ACCOMPLISH should provide much-needed guidance for selecting optimal combination therapy for high-risk hypertensive patients.

Key Words: Combination antihypertensive therapy, systolic hypertension, Lotrel, amlodipine, benazepril, ALLHAT, ACCOMPLISH.

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