Achieving Goal Blood Pressure in Patients With Type 2 Diabetes: Conventional Versus Fixed-Dose Combination Approaches

George L. Bakris, MD;[1] Matthew R. Weir, MD;[2] on behalf of the Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators

Data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrate that only 11% of people with diabetes who are treated for high blood pressure achieve the blood pressure goal of <130/85 mm Hg recommended in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). The current study tests the hypothesis that initial therapy with a fixed-dose combination will achieve the recommended blood pressure goal in patients with type 2 diabetes faster than conventional monotherapy. This randomized, double-blind, placebo-controlled study had as a primary end point achievement of blood pressure <130/85 mm Hg. Participants (N=214) with hypertension and type 2 diabetes received either amlodipine/benazepril 5/10 mg (combination) or enalapril 10 mg (conventional) once daily for 4 weeks, titrated to 5/20 mg/day or 20 mg/day, respectively at this time, if target blood pressure was not achieved. Hydrochlorothiazide (HCTZ) 12.5 mg/day was added for the final 4 weeks, if target blood pressure was still not reached. Time from baseline to achieve blood pressure <130/85 mm Hg was shorter in the combination group (5.3±3.1 weeks combination vs. 6.4±3.8 weeks conventional; p=*0.001). At 3 months, more participants in the combination group achieved treatment goal (63% combination vs. 37% conventional;* p=*0.002). Data analysis at 3 months comparing blood pressure control rates between the fixed-dose combination group (without HCTZ) to the conventional group (receiving HCTZ) showed an even greater disparity in blood pressure goal achievement (87% combination without HCTZ vs. 37% conventional group with HCTZ;* p=*0.0001). We conclude that initial therapy with a fixed-dose combination may be more efficacious than conventional monotherapy approaches for achieving blood pressure goals in the diabetic patient. A fixed-dose combination approach appears as safe as the current conventional approaches. (J Clin Hypertens. 2003;5: 202–209)* ©2003 Le Jacq Communications, Inc.

From the Departments of Preventive and Internal Medicine, Rush-Presbyterian–St. Luke's Medical Center, Chicago, IL;[1] Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD[2]
Address for correspondence:
George L. Bakris, MD, Vice-Chairman, Department of Preventive Medicine, Rush-Presbyterian–St. Luke's Medical Center; Director, Rush Hypertension Research Center, 1700 West Van Buren Street, Suite 470, Chicago, IL 60612
E-mail: gbakris@rush.edu
Manuscript received November 10, 2002;
revised December 5, 2002;
accepted January 20, 2003

Elevated blood pressure (BP) increases the risk of cardiovascular and renal disease in the already-at-risk diabetic patient. Therefore, the antihypertensive armamentarium must be strategically deployed early and intensively to meet the challenge of protecting hypertensive patients with type 2 diabetes against the serious risk of cardiovascular complications. High BP is prevalent in diabetic patients; more than one half of the patients with

type 2 diabetes also have high BP.[1,2] Compared with patients who have only one of these conditions, patients who have both conditions are almost twice as likely to experience a cardiovascular event and are five to six times as likely to develop end-stage renal disease.[3–5] Furthermore, an estimated 35%–75% of cardiovascular and renal complications of diabetes can be attributed to high BP.[2]

The benefits of reducing BP to the recommended goal of <130/85 mm Hg in diabetic patients are clear. Results of United Kingdom Prospective Diabetes Study 38 (UKPDS 38)[6] showed that each decrease of 10 mm Hg in mean systolic BP (SBP) was associated with a 15% reduction in risk for death related to diabetes, an 11% reduction in risk for myocardial infarction, a 13% reduction in risk for microvascular complications, and a 12% reduction in risk for any diabetes-related complication. In the Hypertension Optimal Treatment (HOT) study,[7] a 51% reduction in cardiovascular events was seen in diabetic patients randomized to a group with a target diastolic BP (DBP) of ≤80 mm Hg compared with those randomized to a target DBP of ≤90 mm Hg. These statistics underscore the critical need for intensive BP control in hypertensive patients with type 2 diabetes.[8]

There is increasing emphasis on integrating BP treatment into overall morbidity and mortality risk management strategies for patients with concomitant high BP and diabetes.[9–11] Apart from achieving BP control, the use of specific antihypertensive drugs—specifically, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—also reduces the risk for cardiovascular and renal disease in such patients.[5,9] Moreover, diuretics or calcium channel blocker (CCB)-based treatment regimens are documented to reduce cardiovascular risk in hypertensive patients *without* macroalbuminuria or preexisting kidney disease.[12–14]

Recent analyses of clinical trials demonstrate that most diabetic and nondiabetic hypertensive patients require multidrug therapy to reach their target BP.[5] In UKPDS,[6] more than one half of the participants required two or more drugs to reach their goal BP, and 29% needed three or more antihypertensive medications to reach and maintain the target BP after 9 years of follow-up. An emerging body of evidence in mixed populations over the past two decades suggests that fixed-dose combination therapy is more effective than commonly used monotherapies in achieving target BP goals.[15–22] All these studies demonstrate that fixed-dose combination therapies are more efficacious for BP lowering and better tolerated than either of the monotherapy components. It should also be noted, that most of the studies included the use of a diuretic with a β blocker or an ACE inhibitor; an ACE inhibitor/CCB combination has also been found effective.

Since only 11% of those with type 2 diabetes treated for hypertension achieve the recommended BP goal of <130/85 mm Hg,[23] it is important to develop strategies that increase the percentage of people who achieve control. Given the aforementioned data coupled with the high cardiovascular and renal risk in diabetic patients, we considered this group an ideal cohort in which to test the hypothesis that initial fixed-dose combination therapy will result in a higher percentage of diabetic participants achieving goal BP in a more timely manner compared with monotherapy approaches.

METHODS

The Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) was a 12-week, randomized, multicenter, double-blind, parallel-group trial. Following a maximum 3-week placebo run-in period, 214 participants recruited from 22 centers around the United States with diagnoses of type 2 diabetes and high BP were randomized in a 1:1 fashion to receive either amlodipine/benazepril (Lotrel) 5/10 mg/day (n=106) or enalapril (Vasotec) 10 mg/day (n=108) for 4 weeks (treatment period 1) (Figure 1).

Participants who reached the target BP of <130/85 mm Hg during treatment period 1, continued treatment at the initial dose level. For those who did not achieve the target BP, medication was titrated to the next highest dose—amlodipine/benazepril 5/20 mg/day or enalapril 20 mg/day—for another 4 weeks (treatment period 2). If participants failed to achieve the target BP by the end of treatment period 2, hydrochlorothiazide (HCTZ) 12.5 mg/day was added to their treatment regimen for the final 4 weeks of the study (treatment period 3).

The study was completed by 89% of the participants. Table I shows the baseline demographics of the two treatment groups.

Inclusion and Exclusion Criteria

Patients were considered eligible to enroll in SHIELD if they had a confirmed diagnosis of hypertension and a documented history of type 2 diabetes. The diagnosis of diabetes was based on a fasting glucose of >126 mg/dL or a history of diabetes requiring medications. Hypertension was based on history and requirement of medications to lower BP at the initial visit as well as a blood

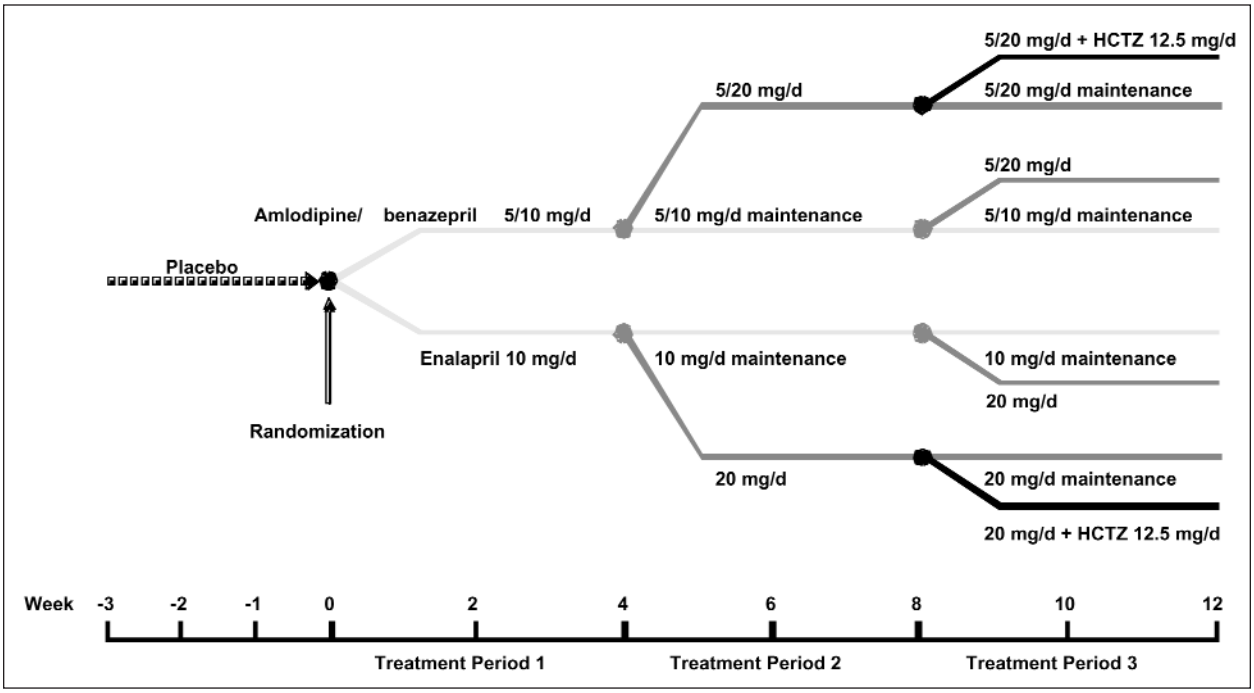

Figure 1. Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) study design. Participants who achieved the target blood pressure (BP) (<130/85 mm Hg) during treatment period 1 (weeks 0–4) continued treatment at the initial dose. Those who did not achieve the target BP were dose-titrated to the next level during treatment period 2 (weeks 4–8). For participants who did not achieve target BP by the end of treatment period 2, hydrochlorothiazide (HCTZ) 12.5 mg/d was added to the regimen during treatment period 3 (weeks 8–12).

pressure of >140/90 mm Hg during the washout period. Additional inclusion criteria included age ≥18 and ≤80 years; mean seated DBP (SeDBP) of ≥90 and ≤109 mm Hg; and serum creatinine ≤3.0 mg/dL. Women had to be postmenopausal for 1 year before enrollment or use an effective form of contraception and have a negative serum pregnancy test. All eligible candidates had to provide signed informed consent before enrolling in the study or participating in any study-related activities. Exclusion criteria included proteinuria of >1 g/day; abnormal physical or laboratory findings that would put the patient at risk or interfere with his or her participation in the study; any disease of the gastrointestinal system or liver; any condition that would result in impaired absorption, metabolism, or excretion of study medications or their metabolites; impaired renal function; history of malignancy (not including basal cell carcinoma) within the previous 5 years; autoimmune disorders; cardiac dysrhythmias; history of coronary artery disease, congestive heart failure, or clinically relevant cardiac valvular disease; failure to discontinue all antihypertensive medications at visit 1; a recent history of illicit drug use or excessive alcohol consumption; allergy or hypersensitivity to amlodipine, benazepril, HCTZ, or any ACE inhibitors, CCBs, or ARBs or any of their components; participation in any investigational clinical study within 30 days of enrollment; and the inability to give informed consent.

Study Drug Administration

Participants were provided with the study medication in the form of kits and were instructed to take the medication once daily in the morning. The following medications were prohibited for the duration of the study: any other antihypertensive agents or potassium-sparing diuretics; antianginal medications

Table I. Demographic Summary by Treatment Group: Safety Population

Subject characteristics	Amlodipine/ benazepril (N=106)	Enalapril (N=108)
Age (years; mean±SD)	58±10	57±11
Sex (N [%])		
Male	63 (59)	64 (59)
Female	43 (41)	44 (41)
Race (N [%])		
Caucasian	56 (53)	62 (57)
African American	40 (38)	36 (33)
Asian	2 (2)	3 (3)
Other	8 (8)	7 (7)

of any kind; lithium; antiarrhythmic drugs, including digitalis glycosides; and monoamine oxidase inhibitors. Participants were asked to notify investigators before starting any new medications, including over-the-counter medications.

Efficacy Measures

The primary study end point was the time from randomization to the first treatment success. Treatment success was defined as achievement of the target BP of <130/85 mm Hg. Blood pressure was measured at all centers by trained personnel in the seated position and with a mercury sphygmomanometer. An average of three blood pressures taken 5 minutes apart was used to determine a mean value for each visit. The primary end point was assessed in an intent-to-treat model, defined as all randomized participants who took at least one dose of study medication and from whom at least one post-baseline BP measurement was obtained. Seated systolic blood pressure (SeSBP) and SeDBP were measured using a dedicated calibrated standard sphygmomanometer or a validated digital device and an appropriately sized cuff. Mean SeSBP/SeDBP was based on three readings.

Secondary efficacy variables included change from baseline to week 12 in the following: SeSBP and SeDBP, glycosylated hemoglobin (HbA_{1c}), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

Statistics

Adjusted means and corresponding 95% confidence intervals were computed using the least squared means. Analysis of covariance of all secondary efficacy variables was carried out using baseline assessment as a covariable and treatment as a factor. If the assumptions of the parametric test were not satisfied, then a nonparametric test (i.e., the Wilcoxon rank sum test) was used to compare the two groups. Where appropriate, multiple regression analyses were performed to identify prognostic factors.

Safety Assessments

The safety population included all participants who took at least one dose of study medication. All adverse effects (AEs), including serious AEs, were monitored and their severity and relationship to study medication were noted. Hematology, blood chemistry, and urine tests performed at a central laboratory were documented, vital signs were measured, and physical examinations were performed.

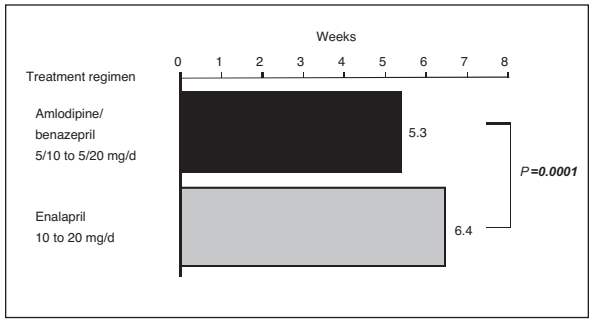

Figure 2. Mean time (weeks) to achieve blood pressure goal <130/85 mm Hg (intent-to-treat population). Treatment success was defined as the first achievement of the target blood pressure of <130/85 mm Hg.

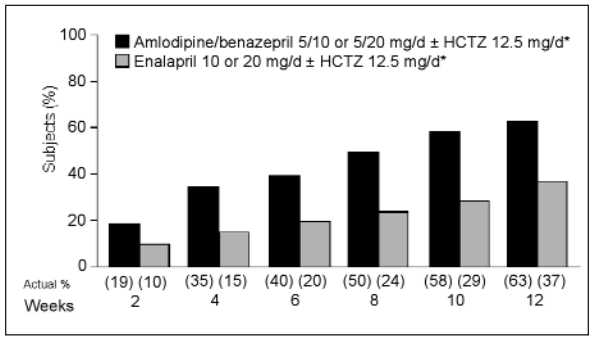

Figure 3. Percentage of all participants achieving target blood pressure (BP) (<130/85 mm Hg) by week and treatment group (intent-to-treat population). Only the first recorded treatment success for each subject was included. The denominator in the calculation of the percentage of participants was the total number of participants in each treatment group at each visit.
**If the maximum dosage regimens did not reduce BP to target level, hydrochlorothiazide (HCTZ) 12.5 mg/d was added at week 8 (so weeks 10 and 12 reflect diuretic add-on therapy).*

RESULTS

Primary End Point

The mean time from randomization to achievement of treatment goal (defined as the first incidence of a BP <130/85 mm Hg) was significantly shorter among participants who received fixed-dose combination therapy with amlodipine/benazepril compared with those who received the conventional approach (enalapril monotherapy): 5.3±3.1 weeks vs. 6.4±3.8 weeks, respectively; p=0.0001 (Figure 2). The median time to target BP was 4 weeks in the amlodipine/benazepril group and 6 weeks in the enalapril group.

The percentage of amlodipine/benazepril-treated participants who achieved goal BP exceeded that of enalapril-treated participants at every assessment (Figure 3). Only the first achievement of treatment goal for each subject was included in this analysis. By week 12, the percentage of participants achieving treatment goal was 63% (n=64/106) among those

Table II. Change in Secondary Efficacy Variables From Baseline to Week 12: ITT Population (Observed Case Analysis)

	Baseline (Week 0)		Week 12		Change From Baseline		
	Amlodipine/ benazepril	Enalapril	Amlodipine/ benazepril	Enalapril	Amlodipine/ benazepril	Enalapril	*P* Value
SeSBP (mm Hg)							
N	102	106	99	105	99	105	0.002
Mean±SD	155.7±13.2	156.2±15.3	135.6±15.9	141.9±18.2	–20.5±16.0	–14.5±13.6	
SeDBP (mm Hg)							
N	102	106	99	105	99	105	0.001
Mean±SD	97.0±6.5	96.5±5.8	83.2±9.2	86.9±11.0	–13.9±8.7	–9.6±9.1	
HbA_{1c} (%)							
N	84	88	94	100	77	84	0.497
Mean±SD	7.7±1.6	7.6±1.7	7.9±1.7	7.8±1.8	0.2±1.0	0.1±0.9	
TC (mg/dL)							
N	102	104	95	102	95	100	0.460
Mean±SD	201.6±37.1	197.1±37.6	202.3±38.4	201.8±44.6	0.0±25.4	3.8±30.0	
LDL-C (mg/dL)							
N	93	99	90	94	84	90	0.716
Mean±SD	117.7±34.2	113.4±32.6	119.4±33.2	113.5±32.1	0.9±22.4	0.9±22.4	
HDL-C (mg/dL)							
N	101	104	95	102	94	100	0.244
Mean±SD	45.9±10.5	45.4±11.5	46.1±10.7	46.7±12.3	0.6±5.8	1.6±5.4	
TG (mg/dL)							
N	102	104	95	102	95	100	0.039
Mean±SD	208.2±160.5	207.2±170.0	191.3±113.5	222.7±235.8	–21.7±109.9	14.8±133.3	

ITT=intent-to-treat; SeSBP=seated systolic blood pressure; SD=standard deviation; SeDBP=seated diastolic blood pressure; HbA_{1c}=glycosylated hemoglobin; TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides

receiving amlodipine/benazepril combination therapy, compared with 37% (n=35/108) among participants receiving enalapril monotherapy (p=0.0002). To reach their target BP at week 12, 61% (n=65/108) of the participants treated with enalapril required adjunctive therapy with HCTZ, compared with 44% (n=48/106) of those treated with amlodipine/benazepril.

Given the newer National Kidney Foundation and American Diabetes Association guidelines for a goal BP of <130/80 mm Hg in type 2 diabetes, a separate analysis was performed. However, the separation in control rate differences between the two groups persisted. In this analysis, the percentage of participants who achieved a BP of 130/80 mm Hg at week 4 was 36% in the amlodipine/benazepril group, compared with 8% in the enalapril group, rising to 59% and 19%, respectively, at week 8, and 70% and 31% at week 12.

Secondary End Points

Participants who received the combination therapy regimen experienced greater reductions in SeSBP and SeDBP than did participants who received the enalapril regimen. At week 12, participants randomized to amlodipine/benazepril experienced a significantly greater reduction in SeSBP (20.5±16.0 mm Hg vs. 14.5±13.6 mm Hg; p=0.002) and SeDBP (13.9±8.7 mm Hg vs. 9.6±9.1 mm Hg; p=0.001) than did participants randomized to enalapril (Table II).

At week 12, triglyceride levels had decreased in the amlodipine/benazepril group (mean decrease 21.7 mg/dL) but had increased in the enalapril group (mean increase 14.8 mg/dL); the difference was significant (p=0.039) (Figure 4). Changes from baseline for all other lipid parameters were comparable between the treatment groups. No significant differences were detected between the two treatment groups in HbA_{1c} change from baseline, suggesting that glycemic control was similar in both groups.

Safety Results

Eighty-nine percent of participants completed the study. The most common reason for discontinuation was withdrawal of consent. The number of participants reporting AEs was similar in both treatment groups—65 (61.3%) in the amlodipine/benazepril group vs. 70 (64.8%) in the enalapril group. The majority of AEs reported were mild to moderate in severity. The AEs reported most frequently in both

groups were headache, upper respiratory tract infection, dizziness, edema of the lower limbs, and cough. With the exception of edema, which was less commonly seen in the enalapril group, the incidence of AEs was similar in both groups. Insomnia, nausea, fatigue, and exacerbation of diabetes were less common in the amlodipine/benazepril group than in the enalapril group.

Laboratory results were similar for both groups. Hematocrit and hemoglobin declined in a few participants in both treatment groups. However, there were no trends or important differences between treatment groups for any of the hematology parameters.

There were no deaths during the study. Two serious AEs were reported for each group. In the amlodipine/benazepril group, one subject reported right-sided chest pain but completed the study; the other subject discontinued the study after reporting a diabetic foot ulcer with cellulitis. In the enalapril group, one subject reported a recent diagnosis of bronchoalveolar carcinoma, which caused her to withdraw consent for the study; another subject had a hypertensive crisis and was lost to follow-up. We determined that these AEs were unrelated to study medications.

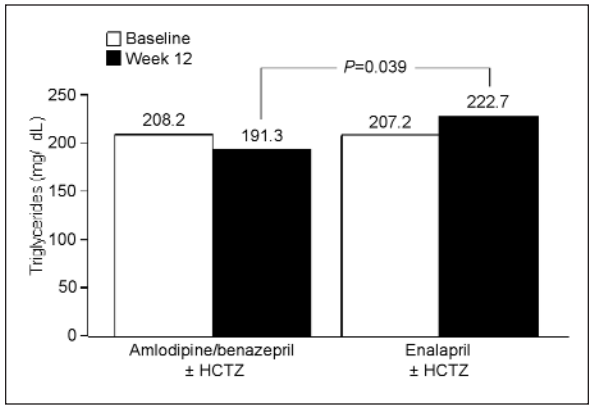

Figure 4. Change in serum triglyceride levels from baseline to week 12 (intent-to-treat population; includes participants in both treatment groups who received hydrochlorothiazide [HCTZ] at week 8). Participants in the amlodipine/benazepril group had a mean decrease of 21.7 mg/dL, compared with a mean increase of 14.8 mg/dL among participants in the enalapril group, a statistically significant difference.

DISCUSSION

In SHIELD, initial treatment of hypertension in participants with type 2 diabetes using a fixed-dose combination of an ACE inhibitor/CCB was associated with greater efficacy for achieving BP goals with fewer AEs, compared with treatment starting with ACE inhibitor monotherapy and adding a thiazide diuretic. Moreover, a higher cumulative percentage of participants who initially received combination therapy maintained BP treatment goal compared with the conventional treatment group. This disparity in achievement of BP goals between groups was maintained regardless of whether target BP was <130/85 mm Hg or <130/80 mm Hg. It is noteworthy that even after HCTZ was given at week 8 to those who failed to achieve target BP, only an additional 12% of the 75% previously not at goal BP in the conventional group achieved their BP goal. This contrasts to an additional 6% of the 19% not at BP goal achieving their BP goal in the combination group.

The results of this study are consistent with all previous studies that examine combination agents on BP lowering. It supports the concept that initial therapy with one pill that contains two different BP lowering agents achieves BP goal in a larger percent of patients vs. one pill containing a single agent.[15–22] Our study further extends these observations by demonstrating that a significantly higher percentage of patients starting with fixed-dose combination therapy achieved BP goal when compared with the monotherapy group who later received a second antihypertensive agent. Thus, these data, taken together with previous studies, support a strategy of fixed-dose combination therapy as first-line treatment in high-risk patients in whom lower BP goals are indicated.

Debate continues regarding the level of BP reduction that optimizes cardiovascular risk reduction. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[9] recommends a target BP of <130/85 mm Hg for persons with concomitant hypertension and diabetes. The National Kidney Foundation 2000 guidelines[5] and the 2002 American Diabetes Association guidelines for the treatment of hypertensive patients with diabetes[8] recommend an even lower target BP (<130/80 mm Hg), based on data that correlate an increased risk for cardiovascular events with mortality risk in diabetic patients with systolic BP >120 mm Hg.[24]

Type 2 diabetes and hypertension are interrelated and often occur as concomitant diseases. When they coexist, the risk of atherosclerotic cardiovascular disease and nephropathy are greatly increased. The primary objectives of hypertension management in patients with diabetes are to reduce BP to the recommended target BP and thus reduce the risk of renal and cardiovascular complications without adversely affecting glycemic and lipid control. As noted by Sowers and colleagues,[1] lifestyle modifications are important for all patients with diabetes; however, in those with BP in the high-normal range (130–139/85–89 mm Hg) and above, antihypertensive pharmacotherapy is particularly important.

Several studies and analyses have demonstrated the need for multiple medications to achieve target BP in hypertensive patients with diabetes.[5–7,16,18,25]

The rationale for using fixed-dose combination therapy to manage hypertension in diabetic patients is based not only on the effects on BP and target organ disease but the different mechanisms of action of the components that help reduce cardiovascular risk as seen in combinations of β blockers with diuretics, ACE inhibitors or ARBs with diuretics, or ACE inhibitors and CCBs. Combination therapy is also beneficial because lower doses of each component drug are often used, reducing the risk of AEs and improving patient adherence with therapy.[21,25,26] This is exemplified by the use of ACE inhibitors and dihydropyridine (DHP) CCBs to decrease the likelihood of pedal edema, due in part, to the venodilating effects of the ACE inhibitor.[27] This is also seen with ACE inhibitor/diuretic use where the ACE inhibitor helps reduce any abnormities of potassium.[28]

The component classes of antihypertensive agents in the combination used in this trial were examined in the HOT[7] and Systolic Hypertension in Europe (Syst-Eur)[29] trials, where both showed that intensive BP reduction using a CCB as the first-line agent significantly decreased cardiovascular morbidity and mortality in patients with hypertension and diabetes. Results of the Swedish Trial in Old Patients With Hypertension 2 (STOP-Hypertension 2)[30] showed that CCBs were as effective as diuretics, β blockers, and ACE inhibitors in reducing morbidity and mortality in hypertensive patients with diabetes. A comparison of overall results however, indicated that the use of a DHP CCB was less effective in reducing the incidence of myocardial infarction or heart failure than an ACE inhibitor-based regimen.

The cardiovascular benefits of CCBs appear to be derived almost exclusively from their BP-lowering effect. CCBs are somewhat more efficacious for lowering BP than ACE inhibitors in some population groups, i.e., elderly, and in those who consume large amounts of sodium, i.e., more than 6 g/day.[31] While it is clear that use of short-acting CCBs increase risk of cardiovascular events,[32] long-acting CCBs have been shown to be safe and effective for reducing cardiovascular outcomes, especially strokes, in patients who have hypertension with or without diabetes.[11,12,33,34]

However, DHP CCB use of any kind, regardless of duration of action, should be avoided in people with any form of kidney disease with macroalbuminuria (albumin:creatinine ratio ≥300 mg albumin/g creatinine) unless such individuals are also being treated with an ACE inhibitor or ARB.[5,8,34] The American Diabetes Association recommends the use of DHP CCBs only in combination with—*but not instead of*—ACE inhibitors or ARBs for patients with diabetes and elevated BP.[8]

Apart from BP goals, another finding in this study was a significant increase in triglyceride levels at study end in the conventional group compared with the combination group. It is difficult to account for this finding since both groups received diuretics; however, one explanation is the significantly greater use of diuretics in the conventional group. Increases in triglycerides have been observed in other short-term studies with diuretics.[35,36] However, a caveat should be issued: this is a short-term study; all long-term studies with low-dose diuretics have not been shown to affect lipid profiles in a negative way.[37–39] Thus, while statistically significant in this study, these changes do not affect cardiovascular outcome, since in studies of a year or more diuretics have been shown to reduce cardiovascular risk in every trial to date.[9,12,14,17]

The interpretation of our findings comes with some limitations. First, almost 40% of the participants were African American, a group well known to respond to CCBs more than ACE inhibitors. This would certainly explain some of the differences in BP achievement by week 8, where no diuretic was used in the ACE inhibitor arm. However, even after diuretics were added to this arm they did not approach the BP control rates seen when starting with an ACE inhibitor/CCB combination 1 month later. Second, the duration of follow-up was shorter after a diuretic was added than before its use and the dose of HCTZ was not titrated to 25 mg, as is commonly done in clinical practice. Lastly, there is some selection bias in the secondary analysis where the small number of participants in the fixed-dose combination group, who required diuretics, was excluded and only those on the ACE inhibitor/CCB combination were compared with those on an ACE inhibitor/diuretic. We excluded those with the most difficult to control BP in the ACE inhibitor/CCB group but included them in the ACE inhibitor arm, thus favoring the ACE inhibitor/CCB group. It should be noted that no difference between the primary comparison (intention-to-treat) vs. the secondary comparison was detected.

In conclusion, hypertensive patients with type 2 diabetes need more rigorous control of BP in an easier, simpler fashion, given the remarkable complexity of the multiple drug regimens needed to control their comorbid medical problems (e.g., diabetes, obesity, high cholesterol). Given the very poor BP control rate, i.e., 11% in this cohort, the use of fixed-dose combination therapy is an important therapeutic consideration, as it facilitates quicker and easier attainment of goal BP and should lead to a greater proportion of people with diabetes who achieve BP goal.

Acknowledgment: This study was funded by Novartis Pharmaceuticals.

REFERENCES

1 Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension.* 2001;37: 1053–1059.

2 Hillier TA, Pedula KL. Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. *Diabetes Care.* 2001;24(9):1522–1527.

3 Deedwania PC. Hypertension and diabetes: new therapeutic options. *Arch Intern Med.* 2000;160:1585–1594.

4 Grossman E, Messerli FH, Goldbourt U. High blood pressure and diabetes mellitus: are all antihypertensive drugs created equal? *Arch Intern Med.* 2000;160:2447–2452.

5 Bakris GL, Williams M, Dworkin L, et al., for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2000;36:646–661.

6 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703–713.

7 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) randomised trial. *Lancet.* 1998;351:1755–1762.

8 American Diabetes Association. American Diabetes Association: clinical practice recommendations 2002. *Diabetes Care.* 2002; 25(suppl 1):S1–147.

9 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1997; 157:2413–2446.

10 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.

11 Chowdhury TA, Kumar S, Barnett AH, et al. Treatment of hypertension in patients with type 2 diabetes: a review of the recent evidence. *J Hum Hypertens.* 1999;13:803–811.

12 Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet.* 2001;358: 1305–1315.

13 Neal B, MacMahon S, Chapman N, for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet.* 2000;356:1955–1964.

14 Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. *Arch Intern Med.* 1998;158(7):741–751.

15 Gradman AH, Acevedo C. Evolving strategies for the use of combination therapy in hypertension. *Curr Hypertens Rep.* 2002;4(5):343–349.

16 Elliott WJ. Is fixed combination therapy appropriate for initial hypertension treatment? *Curr Hypertens Rep.* 2002;4(4):278–285.

17 Freis ED. Controlling high blood pressure: a simple and effective approach. *Compr Ther.* 2001;27(3):209–212.

18 Hilleman DE, Ryschon KL, Mohiuddin SM, et al. Fixed-dose combination vs. monotherapy in hypertension: a meta-analysis evaluation. *J Hum Hypertens.* 1999;13(7):477–483.

19 Moser M, Black HR. The role of combination therapy in the treatment of hypertension. *Am J Hypertens.* 1998;11(6 pt 2):73S–78S.

20 Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med.* 1996;156(17):1969–1978.

21 Muiesan G, Magnani B, Agabiti-Rosei E, et al. Evaluation of the effect of timolol alone and in combination with hydrochlorothiazide and amiloride in the treatment of mild to moderate arterial hypertension: a double-blind, controlled study. *Clin Sci Mol Med Suppl.* 1976;3:529s–531s.

22 Kaplan NM. Low-dose combination therapy: the rationalization for an ACE inhibitor and a calcium channel blocker in higher risk patients. *Am J Hypertens.* 2001;14:8S–11S.

23 Coresh J, Wei GL, McQuillan G, et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med.* 2001;161:1207–1216.

24 Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993; 16(2):434–444.

25 Bakris GL. A practical approach to achieving recommended blood pressure goals in diabetic patients. *Arch Intern Med.* 2001;161:2661–2667.

26 Ambrosioni E. Pharmacoeconomics of hypertension management: the place of combination therapy. *Pharmacoeconomics.* 2001;19(4):337–347.

27 Weir MR, Rosenberger C, Fink JC. Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. *Am J Hypertens.* 2001;14(9 pt 1):963–968.

28 Middeke M, Richter WO, Schwandt P, et al. The effects of antihypertensive combination therapy on lipid and glucose metabolism: hydrochlorothiazide plus sotalol vs. hydrochlorothiazide plus captopril. *Int J Clin Pharmacol Ther.* 1997;35(6):231–234.

29 Tuomilehto J, Rastenyte D, Birkenhager WH, et al., for the Systolic Hypertension in Europe Trial Investigators. Effects of calcium channel blockade in older patients with diabetes and systolic high BP. *N Engl J Med.* 1999;340:677–684.

30 Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs on cardiovascular mortality and morbidity in elderly patients with hypertension: the Swedish Trial in Old Patients with Hypertension-2. *Lancet.* 1999;354:1751–1756.

31 Weir MR, Chrysant SG, McCarron DA, et al. Influence of race and dietary salt on the antihypertensive efficacy of an angiotensin-converting enzyme inhibitor or a calcium channel antagonist in salt-sensitive hypertensives. *Hypertension.* 1998; 31:1088–1096.

32 Psaty BM, Furberg CD, Kuller LH, et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. *Arch Intern Med.* 2001;161:1183–1192.

33 Kizer JR, Kimmel SE. Epidemiologic review of the calcium channel blocker drugs: an up-to-date perspective on the proposed hazards. *Arch Intern Med.* 2001;161:1145–1158.

34 Koshy S, Bakris GL. Therapeutic approaches to achieve desired blood pressure goals: focus on calcium channel blockers. *Cardiovasc Drugs Ther.* 2000;14:295–301.

35 Bagatin J, Sardelic S, Pivac N, et al. Comparison of chlorthalidone, propranolol and bopindolol in six-month treatment of arterial hypertension. *Int J Clin Pharmacol Res.* 1998;18(2):73–78.

36 Samuelsson O, Pennert K, Andersson O, et al. Diabetes mellitus and raised serum triglyceride concentration in treated hypertension—are they of prognostic importance? Observational study. *BMJ.* 1996;313(7058):660–663.

37 Lakshman MR, Reda DJ, Materson BJ, et al. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med.* 1999;159(6): 551–558.

38 Weir MR, Moser M. Diuretics and beta-blockers: is there a risk for dyslipidemia? *Am Heart J.* 2000;139:174–183.

39 Moser M. Lipid abnormalities and diuretics. *Am Fam Physician.* 1989;40:213–220.