Low-Dose Combination Therapy as First-Line Hypertension Treatment for Blacks and Nonblacks

L. Michael Prisant, MD, Joel M. Neutel, MD, Keith Ferdinand, MD, Vasilios Papademetriou, MD, Vincent DeQuattro, MD, W. Dallas Hall, MD, and Matthew R. Weir, MD

Augusta and Atlanta, Georgia; Irvine, Orange, and Los Angeles, California; New Orleans, Louisiana; Washington, DC; and Baltimore, Maryland

To assess the efficacy and safety of bisoprolol/6.25-mg hydrochlorothiazide (HCTZ), amlodipine, and enalapril in black and nonblack patients, data from two comparative studies were pooled and subgroup analyses performed. Both studies had similar designs and included all three active treatments. The second study also included a placebo group. Subjects (n=541) with a sitting diastolic blood pressure of 95-114 mmHg were titrated to achieve a diastolic blood pressure ≤90 mmHg. The studies included 114 blacks and 427 nonblacks.

Results of an intention-to-treat analysis of mean change from baseline after 12 weeks of treatment showed the following: 1) blood pressure was significantly lowered by all three active drugs compared with baseline or placebo; 2) in blacks, bisoprolol/6.25-mg HCTZ resulted in significantly greater reductions of systolic and diastolic blood pressure than enalapril or placebo, but was not significantly different from amlodipine; 3) in nonblacks, bisoprolol/6.25-mg HCTZ resulted in significantly greater reduction of diastolic blood pressure than amlodipine, enalapril, or placebo. The placebo-corrected change in blood pressure was greater for blacks than whites on the bisoprolol/6.25-mg HCTZ combination, but this was not statistically significant. Bisoprolol/6.25-mg HCTZ controlled diastolic blood pressure to ≤90 mmHg in significantly more patients than enalapril or placebo in blacks and nonblacks. The difference in control rates was not significant versus amlodipine. The incidence of drug-related adverse events was similar between treatments; however, bisoprolol/6.25-mg HCTZ had a lower discontinuation rate due to lack of blood pressure control or adverse experiences in both blacks and nonblacks. (*J Natl Med Assoc.* 1999;91:40-48.)

From the Section of Cardiology, Medical College of Georgia, Augusta and Emory University, Atlanta, Georgia; the University of California, Irvine, the Orange County Heart Institute and Research Center, Orange, and the Division of Cardiology, University of Southern California Medical Center, Los Angeles, California; the Heartbeats Life Center, New Orleans, Louisiana; the Hypertension Research Department of Veterans Affairs Medical Center, Georgetown University, Washington, DC; and the Division of Nephrology and Clinical Research Unit, University of Maryland Medical Center, Baltimore, Maryland. Requests for reprints should be addressed to Dr L. Michael Prisant, BBR 6515A, Section of Cardiology, Medical College of Georgia, Augusta, GA 30912-3105.

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The treatment of hypertension in blacks is especially important because of the disproportionately greater rate of cardiovascular disease. Furthermore, the mean blood pressure and overall prevalence of hypertension are greater at every age compared with whites.[1] However, blood pressure control remains as low in blacks as in whites.[1] New approaches to improve control of blood pressure have been well-received. Low-dose combination antihypertensive

therapy is an approach that may enhance compliance and control rates and yet be cost effective.[2-7] However, data are scant whether low-dose combination therapy is equally as effective in blacks compared with nonblacks.[8-11]

The combination of bisoprolol, a cardioselective long-acting beta-blocker, 2.5 mg to 10 mg with 6.25 mg of hydrochlorothiazide (bisoprolol/HCTZ) has an antihypertensive effect that has been shown to be additive in a 12-cell multifactorial study (n=512).[8] In a second study (n=547), bisoprolol 5 mg/6.25-mg HCTZ demonstrated a response rate of 73%; bisoprolol 5 mg, 61%; HCTZ 25 mg, 47%; and placebo, 27% in patients with mild to moderate hypertension.[10] This study also demonstrated that the combination of bisoprolol 2.5 mg and HCTZ 6.25 mg once daily was as effective or more effective than four times the dose of the individual components in reducing diastolic blood pressure.[10] It was approved by the Food and Drug Administration as a first-line therapy in the treatment of mild to moderate hypertension.[12] Analysis of these two trials suggested that bisoprolol as monotherapy or in combination with a small dose of diuretic would be effective in treating hypertension in blacks.[13,14]

The use of angiotensin-converting enzyme (ACE) inhibitors in the treatment of hypertension is well-established. Enalapril maleate has a half-life of approximately 11 hours after multiple dosing. Its onset of antihypertensive activity occurs within 1 hour, peaking in 4 to 6 hours. In a multicenter study of 265 hypertensives treated with 5-40 mg of enalapril, it was concluded that a single daily dose of 10-20 mg was effective and well-tolerated.[15] It also has been suggested that higher doses of ACE inhibitors are effective in blacks.[16,17]

Amlodipine is a third-generation calcium channel antagonist. It is a long-acting dihydropyridine compound with pharmacokinetic properties of slow oral absorption (peak of 6-12 hours) and a terminal elimination half-life of 30-50 hours. This makes it suitable for once-daily dosing. Studies have described its safety and efficacy in controlling hypertension.[18] The uniform effectiveness of calcium channel antagonists in blacks and whites is generally recognized.[16,19]

Two clinical studies were conducted to compare the efficacy and safety of bisoprolol/HCTZ, enalapril, and amlodipine. The first study (n=218) was a randomized, double-blind, parallel dose-escalation trial comparing bisoprolol/HCTZ (2.5/6.25, 5/6.25, and 10/6.25 mg once daily) to enalapril (5, 10, and 20 mg once daily) and amlodipine (2.5, 5, and 10 mg once daily) in the treatment of patients with mild to moderate essential hypertension.[20] Results demonstrated that bisoprolol/HCTZ was as efficacious as amlodipine and better than enalapril at the doses studied. There was a lower adverse event rate and fewer dropouts due to adverse events on bisoprolol/HCTZ compared with enalapril and amlodipine.

The second study (n=323) was also a randomized, double-blind, parallel dose-escalation trial comparing bisoprolol/HCTZ (2.5/6.25, 5/6.25, and 10/6.25 mg once daily) to enalapril (5 mg once daily, 10 mg once daily, 10 mg twice daily, and 20 mg twice daily), amlodipine (2.5, 5, and 10 mg once daily), and placebo in treatment of patients with mild to moderate essential hypertension.[21] This study demonstrated that bisoprolol/HCTZ was more effective in reducing sitting diastolic blood pressure (DBP) than amlodipine and enalapril, bisoprolol/HCTZ was more effective in reducing sitting systolic blood pressure (SBP) than enalapril, and bisoprolol/HCTZ controlled more patients than amlodipine and enalapril (where control is defined as sitting DBP $\leq$90 mmHg). There were fewer overall dropouts on bisoprolol/HCTZ compared with amlodipine or enalapril and a comparable number of dropouts due to adverse events. The overall adverse event rate did not differ significantly by treatment.

In each of the comparative studies, results were summarized for several subgroups, but no definitive conclusions could be drawn due to small sample size. A further detailed subgroup analysis that combined data from both comparative studies was needed to study the treatment effectiveness between racial groups (black versus nonblack).

This combined analyses assessed the efficacy and safety in black and nonblack patients. The primary endpoint was change in sitting DBP from baseline to the end of treatment for 12 weeks. Secondary endpoints include change in sitting SBP and heart rate from baseline to week 12. Adverse events also were summarized by treatment group for blacks and nonblacks.

MATERIALS AND METHODS

Study Design

First Comparative Study. This study was a 17-week multicenter, randomized, double-blind, three-arm parallel dose-escalation trial comparing bisoprolol/

HCTZ, amlodipine, and enalapril in the treatment of patients with stage 1 and 2 hypertension.[20] Patients satisfying the inclusion/exclusion criteria were randomized to one of three treatment groups within each center. Randomization was stratified by race.

After a 4- to 5-week single-blinded placebo washout period in which patient eligibility for the randomization was determined, a 4-week double blind dose titration period began. Medication could be increased one dose level at a time in 2-week intervals until the sitting DBP was ≤90 mmHg. Patients whose sitting DBP was ≤90 mmHg remained on the same dose. The doses for titration were 2.5/6.25, 5/6.25, and 10/6.25 mg once daily for patients on bisoprolol/HCTZ; 2.5, 5, and 10 mg once daily for patients on amlodipine; and 5, 10, and 20 mg once daily for patients on enalapril. Patients were maintained on their final dose until the study was completed.

Second Comparative Study. The second comparative study was a 23-week multicenter, randomized, double-blind, four-arm parallel dose-escalation trial comparing bisoprolol/HCTZ, amlodipine, enalapril, and placebo in the treatment of patients with stage 1 and 2 hypertension.[21] Patients satisfying the inclusion/exclusion criteria were randomized to one of four treatment groups within each center. Randomization was stratified by race.

After a 4 to 5 week single-blinded placebo washout period in which patient eligibility for the randomization was determined, a 6-week double-blind dose titration period followed. The medication could be increased one dose level at a time in 2-week intervals after randomization until patient sitting DBP was ≤90 mmHg. Patients whose sitting DBP was ≤90 mmHg remained on the same dose. The doses for titration were 2.5/6.25, 5/6.25, 10/6.25, and 10/6.25 mg once daily for patients on bisoprolol/HCTZ; 2.5, 5, 10, and 10 mg once daily for patients on amlodipine; and 5 mg once daily, 10 mg once daily, 10 mg twice daily, and 20 mg twice daily for enalapril. A 12-week, two-stage dose maintenance phase followed titration. During the first stage of maintenance phase, patients remained on the same dose of their last titration dose for 6 weeks. At 6 weeks, patients with sitting DBP >95 mmHg were dropped from the study. The remaining patients were treated for an additional 6-week dose maintenance phase until the study was completed.

Comparison of the Study Designs. The two trials included the same patient population with an almost identical study design except for the following differences in the second comparative study: 1) an extra treatment group (placebo), 2) an extra dose level for enalapril (20 mg twice daily), 3) a 20-mg daily dose of enalapril (rather than 10 mg twice daily), 4) a titration phase of 6 weeks rather than 4 weeks, and 5) a dose-maintenance phase of 12 weeks rather than 8 weeks. Patients were withdrawn from the second study after 6 weeks if sitting DBP >95 mmHg.

Statistical Methods and Definitions

Data from the two comparative studies were pooled for the integrated safety and efficacy analysis. Because the second comparative study had an extra 4 weeks in the dose-maintenance phase, data from the second comparative study after the 12th week were ignored. Therefore, only data from the beginning of the studies to the time point when patients were on treatment for 12 weeks were used for safety and efficacy analysis.

The average of the sitting DBP, sitting SBP, and sitting heart rate from the last three visits of the single-blinded placebo washout period was defined as the baseline measurement. For each sitting parameter at week 12, the change from baseline was computed as the difference between the measurement at week 12 and the baseline measurement. If patients did not have data at week 12, the last available measurement prior to week 12 was used to calculate the change from baseline. The primary endpoint in the efficacy analysis was the change in sitting DBP from baseline to week 12. Secondary efficacy endpoints, change in sitting SBP and sitting heart rate from baseline to week 12, also were analyzed. All randomized patients were included in the safety summaries.

As outlined previously, there were several subtle yet important differences between the first and second comparative studies. Therefore, a treatment/study variable (TRTSTUDY) was constructed to reflect the inherent study blocking variable (ie, study drug versus first or second study).

Treatment group comparisons of demographic characteristics and baseline vital signs used all randomized patients from both comparative studies. Pearson's χ^2 test was used to test for the independence between treatment group and race (black and nonblack). Continuous baseline characteristics (age, height, weight, and sitting vital signs) were analyzed using one-way analysis of variance with the factor TRTSTUDY.

For the comparison of race (black versus non-

Table 1. Baseline Characteristics: Gender, Age, and Weight by Race in the Combined Studies

	No.	% Female	Age (Years)	Weight (lbs)
Black				
Placebo	13	23.1	48	212
Bisoprolol/6.25 HCTZ	40	57.5	54	182
Amlodipine	27	29.3	52	195
Enalapril	34	47.1	55	204
Nonblack				
Placebo	66	40.9	56	199
Bisoprolol/6.25 HCTZ	113	32.7	55	196
Amlodipine	127	33.9	54	197
Enalapril	121	30.6	56	198

HCTZ=hydrochlorothiazide.

black), change from baseline for vital signs was compared using ANOVA. The model included terms for baseline vital sign measurement, TRT-STUDY, subgroup parameter, and TRTSTUDY subgroup interaction. The treatment by study interaction was estimated and tested, and the least-squares mean for each active treatment within the black and nonblack subgroups was estimated. The Holm's adjustment for multiple comparisons was used in assessing *P* values.

A patient was defined as controlled if sitting DBP at week 12 (or last measurement of sitting DBP, if prior to week 12) was ≤90 mmHg. A patient was defined as a responder if sitting DBP at week 12 was ≤90 mmHg or change from baseline to week 12 was ≥10 mmHg. The overall control and response rates for treatment groups were compared across and within subgroups using Fisher's Exact Test at α=.05. Comparisons between bisoprolol/HCTZ and each of the other treatments (amlodipine, enalapril, and placebo) were made only if the hypothesis of equal control rates (or response rates) was rejected. The Holm's procedure was used to adjust for multiple comparisons.

Adverse events were summarized by treatment group and by COSTART (Coding Symbols for Thesaurus of Adverse Reaction Term). Severity of adverse events and assessment of the relationship between drug and adverse events also were summarized by treatment group and COSTART (eg, headache, dizziness, and cough). Treatment groups (regardless of dose level) were compared overall using Fisher's Exact Test for the percentage of patients experiencing at least one adverse event. Additionally, treatment groups were compared overall for any COSTART experienced by more than 4% of the total patient population. When significant overall differences in adverse event rates were detected ($P \leq .05$), the adverse event rate for bisoprolol/HCTZ was compared with the adverse event rates for placebo, amlodipine, and enalapril. Fisher's Exact Test (α=.05) also was used for the pairwise comparisons.

RESULTS

Seven hundred thirty-six patients were screened for enrollment in the two studies, 541 (74%) of whom were randomized into the double-blind phase (218/266 or 82% in the first study and 323/470 or 69% in the second study). One hundred fifty-three patients were assigned to bisoprolol/HCTZ (75 in the first and 78 in the second study), 154 to amlodipine (72 in the first and 82 in the second study), 155 to enalapril (71 in the first and 84 in the second study), and 79 to placebo (all in the second study).

Demographic characteristics were similar across treatment groups (Table 1) as were baseline blood pressure and heart rate (Table 2). The distribution of sex, age, and weight did not differ significantly with respect to treatment blocked by study. The distribution of race (black versus nonblack) differed significantly in that there was a higher percentage of black patients in the first study (29% blacks) than in the second study (16% blacks).

Efficacy Analyses at Week 12

Blacks. Table 3 summarizes the 12-week changes in blood pressure and heart rate by treatment group

Table 2. Baseline Sitting Blood Pressure and Heart Rate by Race

	Blood Pressure (mmHg)		Heart Rate (Beats/Minute)	
Treatment & Race	**Study 1**	**Study 2**	**Study 1**	**Study 2**
Placebo				
Black	—	156/103	—	73
Nonblack	—	154/99	—	73
Bisoprolol/6.25 HCTZ				
Black	158/99	155/99	71	71
Nonblack	152/100	152/100	74	76
Amlodipine				
Black	148/99	149/102	75	69
Nonblack	149/99	153/101	74	74
Enalapril				
Black	152/99	157/103	73	75
Nonblack	153/100	153/100	75	73

HCTZ=hydrochlorothiazide.

and race. Among blacks, bisoprolol/HCTZ (−12.7/−10 mmHg) was significantly better than placebo (+3.4/-0.8 mmHg) and enalapril (−4.3/−6 mmHg) at lowering sitting DBP and sitting SBP. There was no significant difference in change from baseline to week 12 between bisoprolol/HCTZ (−12.7/−10 mmHg) and amlodipine (−13.7/−10.3 mmHg) for sitting DBP or sitting SBP. The decrease in sitting heart rate from baseline to week 12 was significantly more for bisoprolol/HCTZ (−4.6 beats/minute) when compared with amlodipine (0.7 beats/minute) or enalapril (1.6 beats/minute), but the decrease for bisoprolol/HCTZ was not significantly different from placebo (−0.8 beats/minute).

Nonblacks. Among nonblacks, bisoprolol/HCTZ (−12.9 mmHg) was significantly better than placebo (−2.8 mmHg), amlodipine (−10.3 mmHg), and enalapril (−8.7 mmHg) at lowering sitting DBP. Bisoprolol/HCTZ (−14.5 mmHg) was significantly better than placebo (−0.8 mmHg) and enalapril (−10.6 mmHg) at lowering sitting SBP, but not significantly better than amlodipine (−12.1 mmHg). The placebo-corrected change in blood pressure was somewhat greater for blacks than whites (−16.1/−10.7 versus −13.7/−10.1 mmHg) on the bisoprolol/6.25 mg HCTZ combination, but this was not statistically significant (P=.56 for systolic and P=.70 for diastolic blood pressure). The decrease in sitting heart rate from baseline to week 12 was significantly more for bisoprolol/HCTZ (−6.6 beats/minute) compared with placebo (0.23 beats/minute), amlodipine (1.4 beats/minute), and enalapril (0.23 beats/minute).

Response and Control Rates

Blacks. Table 4 and Figure 1 display the control and response rates by race. In black patients, the overall control rate for bisoprolol/HCTZ was significantly better than the rates for placebo (P<.01) and enalapril (P <.05) but not significantly different from amlodipine. The respective control rates were 63% for bisoprolol/HCTZ, 59% for amlodipine, 32% for enalapril, and 0% for placebo, with response rates being 63%, 74%, 38%, and 8%, respectively.

Nonblacks. Among nonblacks, the control and response rates for bisoprolol/HCTZ were significantly better than the rates for placebo and enalapril but not significantly different from amlodipine. The respective overall control rates were 68% for bisoprolol/HCTZ, 58% for amlodipine, 51% for enalapril, and 26% for placebo, with response rates of 77%, 68%, 59%, and 28%, respectively.

Adverse Events

Blacks. Potential drug-related adverse events are summarized in Table 5. Among blacks, 65 (57%) of the 114 randomized patients volunteered adverse events between randomization and week 12 of treatment. Thirty-three (29%) of the 114 randomized black patients experienced an adverse event that was considered potentially drug-related. By treat-

Table 3. Change in Blood Pressure and Heart Rate by Treatment Group and Race, Week 12*

Parameter	Estimate of Change from Baseline† & *P* Value for Change from Baseline				Estimated Difference‡ & *P* Value for Pairwise Comparison		
	Placebo (n=78) (13, 65)	Bisoprolol/HCTZ (n=152) (40, 112)	Amlodipine (n=154) (27, 127)	Enalapril (n=155) (34, 121)	Bisoprolol/HCTZ *v* Placebo	Bisoprolol/HCTZ *v* Amlodipine	Bisoprolol/HCTZ *v* Enalapril
Diastolic Blood Pressure							
Black (n=114)	0.76	−9.95	−10.32	−6.02	−10.71	0.37	−3.93
P value	.7008	<.0001	<.0001	<.0001	<.0001§	.8394	.0210§
Nonblack (n=425)	−2.84	−12.89	−10.27	−8.66	−10.05	−2.62	−4.23
P value	.0013	<.0001	<.0001	<.0001	<.0001§	.0049§	<.0001§
Systolic Blood Pressure							
Black (n=114)	3.39	−12.67	−13.67	−4.29	−16.06	1.00	−8.39
P value	.3649	<.0001	<.0001	.0716	<.0002§	.7772	.0094§
Nonblack (n=425)	−0.83	−14.50	−12.11	−10.63	−13.66	−2.39	−3.87
P value	.6165	<.0001	<.0001	<.0001	<.0001§	.1741	.0303
Heart Rate							
Black (n=114)	−0.80	−4.63	0.74	1.62	−3.83	−5.37	−6.25
P value	.6980	<.0001	.6248	.2169	.1083	.0056§	<.0005§
Nonblack (n=425)	0.23	−6.64	1.44	0.23	−6.87	−8.08	−6.86
P value	.8031	<.0001	.0309	.7387	<.0001§	<.0001§	<.0001§

*Intention-to-treat analysis.
†Change from baseline based on two-sided *t*-test of least-squares means.
‡Pairwise comparisons based on two-sided *t*-test on difference of least-squares means.
§Significant result using Holm's procedure to control type I error.
HCTZ=hydrochlorothiazide.

ment group, the breakdown of these 33 patients was 3/13 (23%) in the placebo group, 13/40 (33%) in the bisoprolol/HCTZ group, 7/27 (26%) in the amlodipine group, and 10/34 (29%) in the enalapril group. There was no statistically significant difference among groups (P=.87).

The most frequently reported potential drug-related adverse events were asthenia (8%) and headache (8%) in the bisoprolol/HCTZ group; nonspecific edema (7%) and headache (7%) in the amlodipine group; and headache (18%) and cough (6%) in the enalapril group. In the placebo group, asthenia, headache, and diarrhea were the most common and occurred at a rate of 7.7% each.

Nonblacks. Among nonblacks, 280 (65%) of the 427 randomized patients reported adverse events between randomization and week 12 of treatment. One hundred six (25%) of the 427 experienced an adverse event that was considered potentially drug-related. By treatment group, the breakdown of these 106 patients was 18/66 (27%) in the placebo group, 23/113 (20%) in the bisoprolol/HCTZ group, 36/127 (28%) in the amlodipine group, and 29/121 (24%) in the enalapril group. There was no statistically significant difference among groups (P=.53).

The most frequently reported potential drug-related adverse events were asthenia (5%), headache (4%), and dizziness (4%) in the bisoprolol/HCTZ group; peripheral edema (9%), nonspecific edema (7%), and asthenia (5%) in the amlodipine group; and headache (7%), cough (4%), and asthenia (4%) in the enalapril group. In the placebo group, cough, peripheral edema, and headache were the most common and occurred at a rate of 4.5% each.

DISCUSSION

Hypertension remains a potent risk factor for renal failure, stroke, and heart disease in black individuals.[22] Low-dose combination antihypertensive therapy may be an approach to enhance medication adherence, visit compliance, and control rates, yet be cost effective.[2,3,5,23] No previous studies have

Table 4. Control and Response Rates at Week 12 by Race*†

Treatment Group & Dose at Last Visit	Black			Nonblack		
	No.	Control Rate (%)	Response Rate (%)	No.	Control Rate (%)	Response Rate (%)
Placebo	**13**	**0.0‡**	**7.7§**	**65**	**26.2**	**27.7‡**
Bisoprolol/6.25 HCTZ						
2.5/6.25 mg once daily	10	20.0	20.0	34	29.5	29.5
5/6.25 mg once daily	14	25.0	25.0	38	21.4	23.2
10/6.25 mg once daily	16	17.5	17.5	40	17.0	24.1
Overall	**40**	**62.5**	**62.5**	**112**	**67.9**	**76.8**
Amlodipine						
2.5 mg once daily	6	18.5	18.5	17	11.8	11.8
5 mg once daily	5	7.4	7.4	37	18.9	18.9
10 mg once daily	16	33.3	48.1	73	27.6	37.0
Overall	**27**	**59.3**	**74.1**	**127**	**58.3**	**67.7**
Enalapril						
5 mg once daily	5	5.9	8.8	23	13.2	13.2
10 mg once daily	8	17.6	17.6	29	14.0	14.0
20 mg once daily	12	2.9	2.9	23	4.1	5.0
10 mg twice daily	3	2.9	5.9	22	12.4	15.7
20 mg twice daily	6	2.9	2.9	24	7.4	10.7
Overall	**34**	**32.4‖**	**38.2**	**121**	**51.2‖**	**58.7¶**

*Intention-to-treat analysis.
†Tests of treatment comparison are based on Fisher's Exact Test. Significant result using Holm's procedure to control type I error.
‡$P<.0001$ for bisoprolol/HCTZ versus placebo.
§$P<.0009$ for bisoprolol/HCTZ versus placebo.
‖$P<.05$ for bisoprolol/HCTZ versus enalapril.
¶$P<.0034$ for bisoprolol/HCTZ versus enalapril.
HCTZ=hydrochlorothiazide.

examined combination versus traditional therapy in hypertensive blacks.

In combining the data from the above two comparative studies, several conclusions can be reached for black participants. Bisoprolol/HCTZ was significantly better than placebo or enalapril monotherapy at lowering sitting DBP and sitting SBP. In fact the placebo-corrected change in blood pressure was somewhat greater for blacks than nonblacks (−16.1/−10.7 versus −13.7/−10.1 mmHg) on the bisoprolol/HCTZ combination. However, there was no significant difference between blacks and nonblacks in the amount of change in systolic or diastolic blood pressure. There was no difference in change from baseline to week 12 between bisoprolol/HCTZ and amlodipine for sitting DBP or sitting SBP. Decrease in sitting heart rate from baseline to week 12 was significantly more for bisoprolol/HCTZ compared with amlodipine or enalapril, but the decrease for bisoprolol/HCTZ was not significantly different from placebo.

The overall control rate for bisoprolol/HCTZ was significantly better than the rates for placebo or enalapril, but not significantly different from amlodipine (Figure 1). The overall response rate for bisoprolol/HCTZ was significantly better than the rate for placebo but not significantly different from amlodipine or enalapril. There did not appear to be any difference in adverse events with respect to treatment in black patients.

For nonblack patients, bisoprolol/HCTZ was significantly better than placebo, amlodipine, or

Table 5. Drug-Related Adverse Events by Race

	No. (%) Black (n=114)				No. (%) Nonblack (n=427)			
	Placebo (n=13)	Bisoprolol/ HCTZ (n=40)	Amlodipine (n=27)	Enalapril (n=34)	Placebo (n=66)	Bisoprolol/ HCTZ (n=113)	Amlodipine (n=127)	Enalapril (n=121)
Any adverse event	3 (23.1)	13 (33)	7 (26)	10 (29)	18 (27.2)	23 (20)	36 (28)	29 (24)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asthenia	1 (7.7)	3 (8)	0 (0)	1 (3)	0 (0)	6 (5)	6 (5)	5 (4)
Cough	0 (0)	0 (0)	0 (0)	2 (6)	3 (4.5)	0 (0)	3 (2)	5 (4)
Headache	1 (7.7)	3 (8)	2 (7)	6 (18)	3 (4.5)	5 (4)	3 (2)	8 (7)
Dizziness	0 (0)	1 (3)	1 (4)	1 (3)	1 (1.5)	4 (4)	3 (2)	4 (3)
Dyspnea/wheezes	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	1 (0.9)	1 (0.8)	1 (0.8)
Impotence	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	2 (1.8)	2 (1.6)	1 (1.6)
Nonspecific edema	0 (0)	1 (3)	2 (7)	1 (3)	0 (0)	0 (0)	9 (7)	1 (1)
Peripheral edema	0 (0)	1 (3)	1 (4)	0 (0)	3(4.5)	1 (1)	12 (9)	0 (0)

Abbreviations: HCTZ=hydrochlorothiazide.

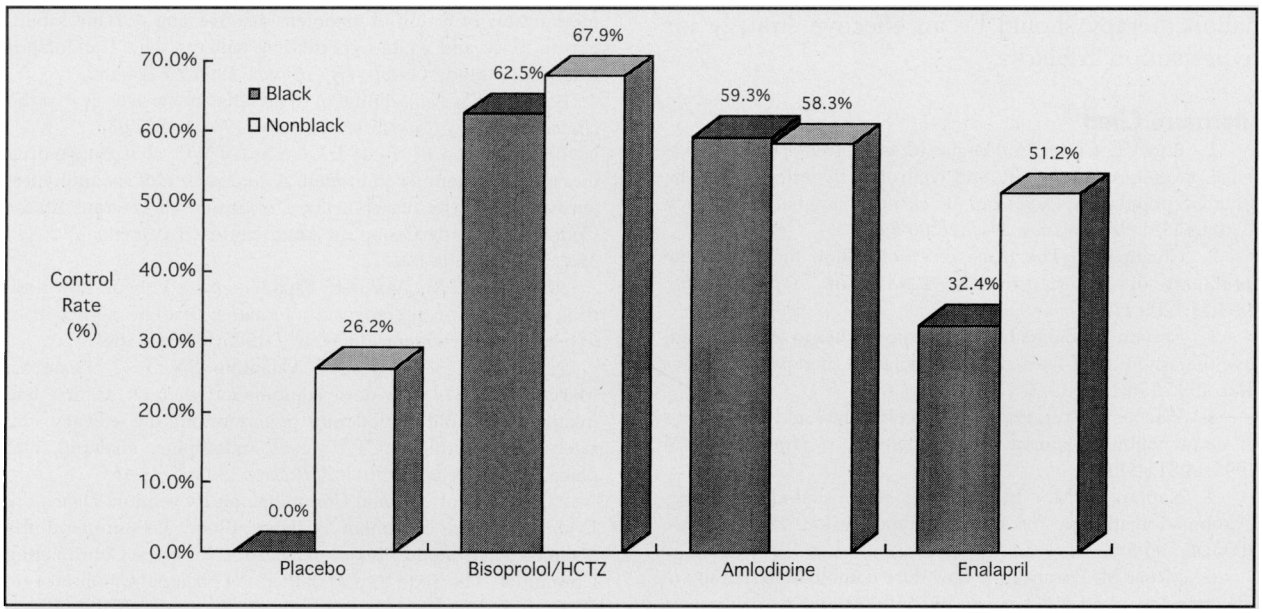

Figure 1.
Overall control rates (diastolic blood pressure ≤90 mmHg) for blacks and nonblacks treated with placebo, bisoprolol/6.25-mg hydrochlorothiazide (HCTZ), amlodipine, and enalapril.

enalapril at lowering sitting DBP. Bisoprolol/HCTZ was significantly better than placebo at lowering sitting SBP but not significantly better than amlodipine or enalapril. Decrease in sitting heart rate from baseline to week 12 was significantly more for bisoprolol/HCTZ compared with placebo, amlodipine, or enalapril. The control (Figure 1) and response rates for bisoprolol/HCTZ were significantly better than the rates for placebo and enalapril, but no different from amlodipine. Adverse event rates were comparable across treatment for nonblack patients, with the exception of what appeared to be a higher rate of edema for amlodipine patients relative to the other treatments.

In this study, a flat response and control rate for enalapril was observed with black patients (Table 4). For example, among blacks, the response rate for 5 to 10 mg once daily of enalapril was 9% to 18% ver-

sus 3% to 6% for 10 to 20 mg twice daily. A higher response rate at higher doses of the ACE inhibitor was not observed as seen in other studies,[16,17] but the overall number of blacks allocated to the ACE inhibitor group was too small. The overall placebo-corrected control rates (32% versus 25%) and response rates (31% versus 31%) were equivalent in blacks and nonblacks, primarily because of the relatively higher response to placebo in nonblacks. In contrast, higher amlodipine dosing was required in improved control and response rates in blacks and nonblacks. The effectiveness of low-dose combination therapy in blacks is supported by the fact that the placebo-corrected change in blood pressure was greater for blacks than nonblacks (−16.1/−10.7 versus −13.7/−10.1 mmHg) on the bisoprolol/H combination. Likewise, the placebo-corrected response rate was greater for blacks compared with nonblacks (54.8% versus 49.1%). Therefore, low-dose combination therapy should be an effective strategy for hypertension in blacks.

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