

MEET THE EXPERTS:
EFFECTIVE USE OF
COMBINATION DRUG THERAPY
IN THE TREATMENT OF
MINORITY HYPERTENSIVE
POPULATIONS

L. MICHAEL PRISANT, MD
W. DALLAS HALL, MD
JACKSON T. WRIGHT, JR., MD



A MONOGRAPH PUBLICATION
OF THE INTERNATIONAL SOCIETY ON HYPERTENSION IN BLACKS
JULY 1997

This program was made possible by an unrestricted educational grant from Procter & Gamble Health Care and Wyeth-Ayerst Laboratories.

Copyright © 1997
International Society on Hypertension in Blacks
2045 Manchester Street, NE
Atlanta, Georgia 30324

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means—electronic, mechanical, photocopying, recording, or otherwise—without prior written permission of the publisher.

**Meet the Experts:
Effective Use of
Combination Drug Therapy
in the Treatment of
Minority Hypertensive
Populations**

Table of Contents

Contributor Profiles 2

Combination Therapy: Rediscovered 3
L. Michael Prisant, M.D.

Combination Therapy: Advantages and
Disadvantages of First-Line Fixed Dose Therapy 7
W. Dallas Hall, M.D.

Use of Combination Antihypertensive
Therapy in the Black Hypertensive 10
Jackson T. Wright, Jr., M.D.

Contributor Profiles



L. Michael Prisant, MD, FACC, FACP is a professor of medicine at the Medical College of Georgia. He completed his undergraduate training at Emory University. He has been a faculty member of the Medical College of Georgia since 1982. He is involved with research, patient care, and teaching, and is the author of more than 190 articles, book chapters, monographs and abstracts. He is board-certified in internal medicine, cardiology, and clinical pharmacology and has added qualifications in geriatric medicine. His appointment is with the Section of Cardiology. He is director of the Fellowship Training

Program. His interests include hypertension and hypertensive heart disease, lipids, racial differences in cardiovascular disease, heart failure, ambulatory blood pressure monitoring and echocardiography.

W. Dallas Hall, MD, FACP, a native of Calhoun, Georgia, completed college, medical school, internal medicine/chief residency and a nephrology fellowship at Emory University and Grady Memorial Hospital in Atlanta. His interest in hypertension in minority populations grew out of his 20-year service at Grady, a hospital that serves 700,000 medically indigent inner-city patients. In 1976, he established a Division of Hypertension in the Department of Medicine at Emory University and has since been professor of medicine and director of the Division of Hypertension. Dr. Hall has published three books (including *Hypertension in Blacks*), 68 book chapters and 87 original articles. He is or has been the principal investigator of several NIH clinical trials including Oral Contraceptive Hypertension, Systolic Hypertension in the Elderly Program (SHEP), the African American Study of Kidney Disease (AASK) and the Women's Health Initiative (WHI).



Jackson T. Wright, Jr., MD, PhD, FACP is a professor of medicine, Division of Hypertension at Case Western Reserve University (CWRU), Cleveland, Ohio, and director of the Clinical Hypertension Program at CWRU/University Hospitals of Cleveland. In addition, he is chief of the Hypertension Section and the Hypertension/Lipid Clinic at the Cleveland V.A. Center. A native of Pittsburgh, Pennsylvania, Dr. Wright received his B.A. from Ohio Wesleyan University and his M.D. and Ph.D (Pharmacology) from the University of Pittsburgh School of Medicine. He is board-certified in internal medicine and was one of

the first in the country to receive subspecialty board certification in clinical pharmacology. An experienced clinical investigator, Dr. Wright has published extensively and served on many national and international advisory panels. He currently chairs the executive committee for the largest study ever-attempted for the treatment of high blood pressure and cholesterol, "The Antihypertensive and Lipid Lowering Heart Attack Prevention Trial."

Combination Therapy: Rediscovered

L. Michael Prisant, MD, FACC, FACP, Professor of Medicine
Director of Cardiology Fellowship Training Program
Section of Cardiology, Medical College of Georgia
Augusta, Georgia

There has been increasing public awareness of the health hazards of hypertension since the early '70s. Physicians have enhanced their understanding of the earliest manifestations of hypertensive target organ damage involving the heart, kidneys and arteries. The pharmacological treatment of hypertension has become more complex and diverse. Despite all of this progress, our treatment goals are not being achieved at the expected level. Using a definition of hypertension as a systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, the 1976-1980 National Health and Nutrition Examination Survey (NHANES II) observed that blacks had a higher prevalence of hypertension than whites (38% versus 29%).¹ In this survey, 66% of blacks were aware of their hypertension and 39% were treated with medication; however, only 13% of hypertensives achieved a blood pressure

level below 140/90 mmHg (Figure 1).

Ten years since this original report, there has been some improvement. The prevalence of hypertension has declined in blacks (32.4%) and whites (23.3%).² Figure 2 displays the results of the Third NHANES, 1988-1991. In this recent survey, 74% of blacks were informed of their hypertension and 57% were dosed with medication. The number of hypertensive patients achieving a blood pressure level below 140/90 mmHg increased to 25%. (Figure 2). Some may view this improvement as a success and others may believe that our attempts at blood pressure control are halfhearted.

The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) emphasized the importance of reducing morbidity and mortality associated with hy-

Hypertension Awareness, Treatment and Control Status
1976-1980

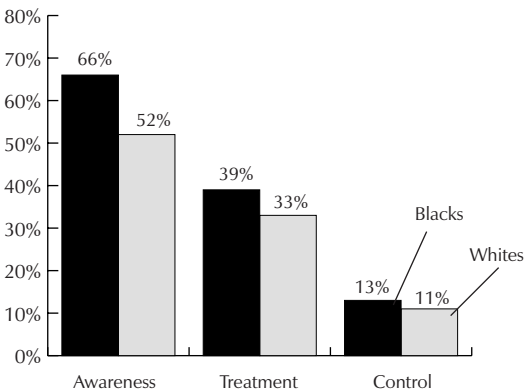


Fig. 1—Results of 1976-1980 National Health and Nutrition Examination Survey using definition of hypertension as blood pressure, 140/90 mmHg
Data derived from *Hypertension* 1985;7:457-468.

Hypertension Awareness, Treatment and Control Status
1988-1991

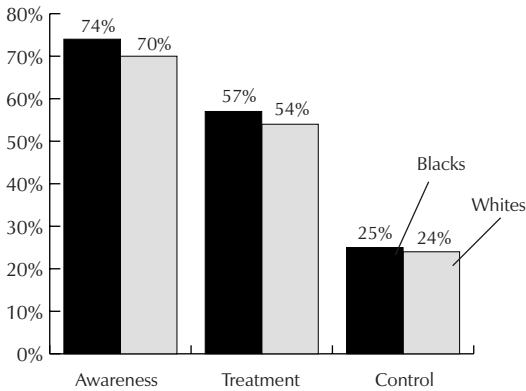


Fig. 2—Results of 1988-1991 National Health and Nutrition Examination Survey using definition of hypertension as blood pressure, 140/90 mmHg

Data derived from *Hypertension* 1995;25:305-313.

perception.³ Once the diagnosis of hypertension is confirmed by accurate blood pressure measurements based on the mean of two or more readings taken at two or more visits following an initial set of measurements, then therapy is initiated (Figure 3).

Nonpharmacological treatment is reasonable as the initial therapy for individuals with Stage 1 hypertension (140-159/90-99 mmHg) and patients without target organ damage. It is also concomitant therapy to any antihypertensive drug prescription. Weight reduction, lower sodium intake, restriction of ethanol consumption, and regular physical activity are the recommended lifestyle modifications that may favorably impact on blood pressure in highly motivated patients. Recently, the Dietary Approaches to Stop Hypertension (DASH) trial documented a diet rich in fruits, vegetables, and low-fat dairy foods and other foods with reduced saturated and total fats also significantly lowers blood pressure.⁴ This study tested the combined effects of nutrients that occurred together in food and controlled for the effects of salt, body weight and alcohol.

Typically, the effectiveness of nonpharmacological remedies are tried for three to six months. For patients failing the trial period, a strategy of antihypertensive drug therapy is executed.

Diuretics and beta-blockers are recommended as the initial treatment of hypertension since this therapy has been proven to reduce morbidity and mortality. However, coexisting diseases may be reasons to choose alternative drugs. Unless the blood pressure is very high, it is reasonable to wait one to three months to assess the efficacy of the initial drug therapy. However, if blood pressure is not controlled, then one is left with three options (Figure 3): 1) upward drug titration; 2) combination of drugs; and 3) substitution of another drug. *Upward drug titration* has the merit of maintaining a single therapy and the disadvantage of diminishing increments of blood pressure reduction and increasing side effects with higher doses. *Substitution therapy* (sequential monotherapy) has the potential of the discovery of an agent that is synchronized with the underlying pathophysiology of the patient and the draw-

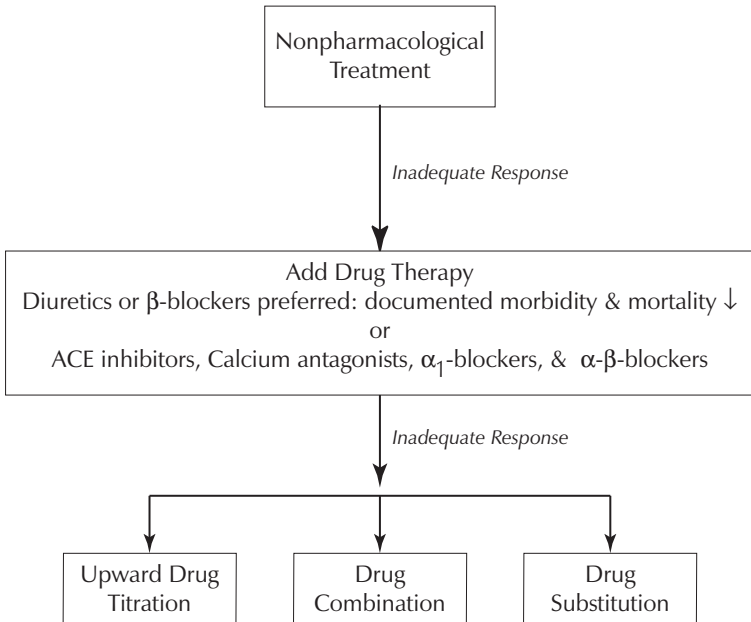
back of a lengthy testing period and the loss of confidence in the physician. *Combination drug therapy* has the benefit of a higher control rate. In addition, combining unlike drugs with distinct modes of action will often allow lower doses of drugs to be used to attain goal blood pressure, thereby lessening the possibility for dose-dependent side effects. One should be cognizant of the individual components of the combination to avoid untoward dose-independent side effects.

There has been a renewed interest in combination drug therapy for the treatment of hypertension because of the failure to achieve blood pressure control in the majority of the hypertensive population. The Food and Drug Administration recognizes two currently marketed fixed combinations,

bisoprolol/6.25mg hydrochlorothiazide (HCTZ) (Ziac) and captopril/HCTZ (Capozide) for *initial* treatment of hypertension. Other combinations that have been recently approved include benazepril/amlodipine (Lotrel), enalapril/felodipine (Lexxel), and verapamil/trandolapril (Tarka); these combinations should not be used as first-line therapy.

Prospective trials have shown the effectiveness of combination therapy compared to upward drug titration. These randomized, double-blind trials involved 541 patients with mild-to-moderate essential hypertension (seated DBP 95-144 mmHg). All patients received a 4-5 week placebo washout period, followed by 12 weeks of therapy, which involved dose titration and maintenance at the therapeutic dose. Blood pres-

Fig. 3—Joint National Committee Algorithm



sure readings were taken 24 hours after the dose.

In both studies, the agents were the same, however, the dosing was varied slightly. In the first study, all agents were dosed once daily, amlodipine (2.5 mg, 5 mg, 10 mg), bisoprolol/5.25 mg HCTZ (2.5 mg, 5 mg, 10 mg), and enalapril (5 mg, 10 mg, 20 mg).⁵ In the second study, amlodipine (A) and bisoprolol/6.25 mg HCTZ (Z) were taken qd at the above-mentioned doses while enalapril (E) was administered 5 mg qd, 10 mg qd, 10 mg bid and 20 mg bid. A placebo (P) was also included in this study.⁶(Table 1)

References

1. Subcommittee on Definition and Prevalence of the 1984 Joint National Committee. Hypertension prevalence and the status of awareness, treatment, and control in the United States. *Hypertension*.

1985;7:457-468.
 2. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in US adult population. Results from the Third National Health and Examination Survey, 1988-1991. *Hypertension*. 1995;25:305-313.
 3. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V). *Arch Intern Med*. 1993; 153:154-183.
 4. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997; 336:1117-1124.
 5. Prisant LM, Weir MR, Papademetriou V, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J*. 1995; 130:359-366.
 6. Neutel JM, Rolf CN, Valentine SN, Li J, Lucas C, Marmorstein BL. Low-Dose Combination Therapy as First Line Treatment of Mild-to-Moderate Hypertension: The Efficacy and Safety of Bisoprolol/HCTZ Versus Amlodipine, Enalapril and Placebo. *Cardiovascular Rev & Rep*. 1996;17(11):33-44.

TABLE 1

	First Comparative Study			Second Comparative Study			
	Amlodipine (A)	Enalapril (E)	Bisoprolol /HCTZ (Z)	Amlodipine (A)	Enalapril (E)	Bisoprolol /HCTZ (Z)	Placebo (P)
N	72	71	75	82	84	78	79
Mean Reductions from Baseline							
sDBP* (mm Hg)	-10.2 ^E	-6.6	-10.7 ^E	-9.9 ^P	-9.0 ^P	-12.7 ^{AEP}	-1.9
sSBP* (mm Hg)	-12.8	7.3	-13.4 ^E	-11.8 ^P	-9.8 ^P	-14.5 ^{EP}	-1.1
sHR* (beats/min)	2.1	1.3	-6.2 ^E	0.3	0.5	-6.5 ^{AEP}	0.9
Control rate (%)	61 ^E	42	64 ^E	56 ^P	44 ^P	77 ^{AEP}	21
Response rate (%)	69 ^E	45	71 ^E	70 ^P	52 ^P	84 ^{AEP}	24
Control Rate: % patients with sDBP ≤ 90 mm Hg Response Rate: % patients with sDBP ≤ 90 mm Hg or mean reduction in sDBP ≥ 10 mm Hg from baseline ^{A,E,P} significant at p<0.05 compared to amlodipine (A), enalapril (E) or placebo (P) *sDBP=seated diastolic BP; sSBP=seated systolic BP; sHR=seated heart rate							

Combination Therapy: Advantages and Disadvantages of First-Line Fixed Dose Therapy

W. Dallas Hall, MD, FACC, Professor of Medicine

Director, Division of Hypertension, Emory University School of Medicine
Atlanta, Georgia

Introduction

In past decades, combination type drugs such as Ser-Ap-Es or Aldoril were often the leading choices for antihypertensive therapy. There was major concern, however, about adverse effects, especially common with the relatively high doses available. Moreover, in responsive patients, the physician never knew that monotherapy with only one of the components might have been adequate and less expensive. Initial or sequential monotherapy with a single drug thus became the standard over the next 20 years.

Rationale for Combination Therapy

In 1993, JNC-V acknowledged that combining antihypertensive drugs with different mechanisms of action will often allow use of lower doses of drugs, reducing dose-dependent adverse effects.¹ This option differed from earlier recommendations to uptitrate monotherapy to maximum tolerated doses before considering additional or alternate therapy.

Despite marked improvement in the awareness and treatment rates for hypertension, the most recent NHANES III data indicated that only 27% of hypertensive patients were controlled.² Poor medication adherence, missed appointments, and adverse effects were identified as major reasons for the lack of blood pressure control.^{3,4} Cramer et al⁵ placed microprocessors in the cap to record every bottle opening and reported that patients receiving therapy one, two,

three or four times daily had average adherence rates of 87%, 81%, 77% and 39%, respectively. In a similar study of 105 patients who were prescribed antihypertensive drugs once, twice or thrice daily, Eisen et al⁶ reported that the prescribed number of doses were removed from the bottle on 84%, 75% and 59% of days, respectively.

These and other data encouraged the use of initial once daily combination therapy to achieve control of blood pressure more efficiently with a reduced number of office visits for uptitration or sequential trials of monotherapy.^{7,8} Formulations with lower doses of individual components became available to reduce adverse effects. Several of the combinations made good pharmacological sense, such as the addition of a beta blocker or ACE inhibitor to a low dose diuretic, thereby inhibiting the sympathetic nervous system stimulation and renin-angiotensin-aldosterone activation induced by the diuretic.⁹

Available Combination Therapies

Table 1 is a list of currently available fixed combination antihypertensive drugs. Most have relatively low dose ingredients with additive effects on lowering blood pressure. The categories include diuretic plus potassium-sparing diuretic, diuretic plus beta blocker, diuretic plus ACE inhibitor, diuretic plus angiotensin receptor blocker, and ACE inhibitor plus calcium channel antagonist (CCA). Another combination not listed

but recently reported effective is a dihydropyridine CCA (nifedipine) plus a phenylalkylamine CCA (sustained release diltiazem or verapamil).¹⁰

Most of the listed combination drugs are approved for the treatment of hypertension, but not for *initial* therapy. Two fixed combination formulations, however, have received FDA approval for initial therapy: Capozide and Ziac. Approval of a low-dose combination drug for initial therapy requires

that each component contributes to the blood pressure lowering effect, plus evidence that any dose dependent adverse effects are offset by the benefits.¹¹

Many of the fixed dose combinations feature very low doses of a diuretic. Specifically, a 12.5 mg dose of HCTZ is available with Prinzide, Zesteretic, or Hyzaar; and a 6.25 mg dose of HCTZ is available with Ziac or Lotensin HCT. Low doses of diuretic therapy are now preferred because the ma-

TABLE 1—Examples of combination antihypertensive drugs

1. DIURETIC + POTASSIUM-SPARING DIURETIC

Aldactazide-25	(25 spironolactone + 25 HCTZ)
Aldactazide-50	(50 spironolactone + 50 HCTZ)
Dyazide	(50 triamterene + 25 HCTZ)
Maxzide	(75 triamterene + 50 HCTZ)
Maxzide-25	(37.5 triamterene + 25 HCTZ)
Moduretic	(5 amiloride + 50 HCTZ)

2. BETA BLOCKER + DIURETIC

Inderide	(40 or 80 propranolol + 25 HCTZ)
Corzide	(40 or 80 nadolol + 5 bendroflumethazide)
Lopressor HCT	(50 or 100 metoprolol + 25 HCTZ) (100 metoprolol + 50 HCTZ)
Tenoretic	(50 or 100 atenolol + 25 chlorthalidone)
Ziac*	(2.5, 5 or 10 bisoprolol + 6.25 HCTZ)

3. ANGIOTENSIN CONVERTING ENZYME INHIBITOR + DIURETIC

Vaseretic	(10 enalapril + 25 HCTZ)
Capozide*	(25 or 50 captopril + 15 or 25 HCTZ)
Prinzide	(20 lisinopril + 12.5 or 25 HCTZ)
Zestoretic	(20 lisinopril + 12.5 or 25 HCTZ)
Lotensin HCT	(5, 10 or 20 benazepril + 6.25, 12.5 or 25 HCTZ)

4. ANGIOTENSIN RECEPTOR BLOCKER + DIURETIC

Hyzaar	(50 losartan + 12.5 HCTZ)
--------	---------------------------

5. ACE-I + CALCIUM CHANNEL ANTAGONIST

Lotrel	(10 or 20 benazepril + 2.5 or 5 amlodipine)
Lexxel	(5 enalapril + 5 felodipine)
Tarka	(1 trandolapril + 240 verapamil) (2 trandolapril + 180 or 240 verapamil) (4 trandolapril + 240 verapamil)

6. MISCELLANEOUS

Ser-Ap-Es	(0.1 reserpine + 15 HCTZ + 25 hydralazine)
Aldoril	(250 or 500 methyl dopa + 15, 25, 30 or 50 HCTZ)
Combipres	(0.1, 0.2 or 0.3 clonidine + 15 chlorthalidone)

* FDA - approved fixed combination for initial treatment of hypertension

majority of the blood pressure lowering effect occurs with the low doses, whereas most of the clinical and metabolic adverse effects are dose dependent.¹² For example, in Ziach, neither the 6.25 mg HCTZ nor the 2.5 mg bisoprolol produce effective reduction in blood pressure, but the combination (2.5-10 mg bisoprolol plus 6.25 mg HCTZ) is just as or more effective than amlodipine (2.5-10 mg) or enalapril (5-20 mg), and without the adverse diuretic effects of hypokalemia or dyslipidemia.¹³⁻¹⁵

Low dose monotherapy with diuretics (e.g., 12.5 mg HCTZ,¹² 12.5 mg chlorthalidone^{16, 17} 1.25 mg indapamide¹⁸) has definite efficacy for lowering blood pressure. Moreover, in the SHEP trial, low dose diuretic-based therapy (i.e., 12.5 mg chlorthalidone) was not associated with any increase in ventricular ectopy.¹⁹ Some amount of diuretic therapy is needed in most patients with resistant hypertension because the underlying mechanism (in compliant patients) is typically volume expansion.²⁰

Selected References

1. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The fifth report of the joint national committee on detection, evaluation, and treatment of high blood pressure (JNC-V). *Arch Intern Med.* 1993;153:154-183.
2. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension.* 1995;25:305-313.
3. Sanson-Fisher RW, Clover K. Compliance in the treatment of hypertension. A need for action. *Am J Hypertens.* 1995;8:82S-88S.
4. Miller NH, Hill M, Kottke T, et al. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation.* 1997;95:1085-1090.
5. Cramer JA, Mattson RH, Prevey ML, et al. How often is medication taken as prescribed? A novel assessment technique. *JAMA.* 1989;261:3273-3277.
6. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med.* 1990;150:1881-1884.
7. Kaplan NM, Gifford RW Jr. Choice of initial therapy for hypertension. *JAMA.* 1996;275:1577-1580.
8. Materson BJ, Reda DJ, Williams D. Lessons from combination therapy in Veterans Affairs studies. *Am J Hypertens.* 1996;9:187S-191S.
9. Abernethy DR. Pharmacological properties of combination therapies for hypertension. *Am J Hypertens.* 1997;10:13S-16S.
10. Saseen JJ, Carter BL, Brown TER, et al. Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. *Hypertension.* 1996;28:109-114.
11. Fenichel RR, Lipicky RJ. Combination products as first-line pharmacotherapy. *Arch Intern Med.* 1994;154:1429-1430.
12. Kaplan NM. The case for low dose diuretic therapy. *Am J Hypertens.* 1991;4:970-971.
13. Prisant LM, Weir MR, Papademetriou V, et al. Low-dose combination therapy: an alternative first-line approach to hypertension therapy. *Am Heart J.* 1995;130:359-366.
14. Saunders E, Neutel J. A new antihypertensive strategy for black patients: low-dose multimechanism therapy. *J Natl Med Assoc.* 1996; 88:171-175.
15. Neutel JM, Rolf CN, Valentine SN, et al. Low-dose combination therapy as first line treatment of mild-to-moderate hypertension: the efficacy and safety of bisoprolol/ HCTZ versus amlodipine, enalapril and placebo. *Cardiovasc Rev Rpt.* 1996;17:1-9.
16. Morledge JH, Ettinger B, Aranda J, et al. Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am Geriatr Soc.* 1986;34:199-206.
17. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program. *JAMA.* 1991;265:3255-3264.
18. Hall WD, Weber MA, Ferdinand K, et al. Lower dose diuretic therapy in the treatment of patients with mild to moderate hypertension. *J Human Hypertens.* 1994;8:571-575.
19. Kostis JB, Lacy CR, Hall WD, et al. The effect of chlorthalidone on ventricular ectopic activity in patients with isolated systolic hypertension. *Am J Cardiol.* 1994;74:464-467.
20. Graves JW, Bloomfield RL, Buckalew VM Jr. Plasma volume in resistant hypertension: guide to pathophysiology and therapy. *Am J Med Sci.* 1989;298:361-365.

Use of Combination Antihypertensive Therapy in the Black Hypertensive

Jackson T. Wright, Jr., MD, PhD, Professor of Medicine
Case Western Reserve University

Director, Clinical Hypertension Program, University Hospitals of Cleveland
Chief, Hypertension Section and the Hypertension/Lipid Clinic
Cleveland VAMC, Ohio

Hypertension is a major risk factor for cardiovascular disease, particularly cardiac morbid or mortal events, especially in black populations.^{1,2} It is clear that treatment of hypertension will prevent total cardiovascular morbidity and mortality, as well as nearly all of the individual cardiovascular complications, e.g., progression to accelerated and malignant hypertension, stroke, congestive heart failure, and coronary heart disease (CHD).^{3,4} The major controversy is whether one or more classes of antihypertensive agents have greater efficacy in preventing CHD and renal events.⁵⁻⁷ In the past 25 years, numerous new antihypertensive agents have become available, allowing wide flexibility in choice of mechanisms, dose schedules, side effects, and cost. In response to the variety of therapeutic options available, the Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension (JNC) and other advisory bodies have recommended angiotensin-converting-enzyme (ACE) inhibitors and calcium channel blockers (CCB), α_1 -blockers, and α_1 - β blockers as well as diuretics and beta-blockers as initial treatment for uncomplicated essential hypertension.^{3,4} However, diuretics and beta blockers were preferred because of the availability of clinical trial data documenting their ability to reduce the complications of hypertension.

While combination antihypertensive preparations have been available for many

years, a number of factors have resulted in the resurgence of their popularity. First, monotherapy is effective in achieving blood pressure control in only about half of the hypertensives studied (and these studies generally preselected participants to exclude patients unlikely to achieve control with monotherapy). There are now increasing data documenting the greater efficacy and/or tolerability of the currently available combination agents compared to the components prescribed separately.⁸⁻¹³ Additionally, more flexible dosing alternatives are now available with the combination agents. Whereas in the past, the prescription of agents in a combination product resulted in a substantial increase in cost, the cost of combination agents now more closely approximates the cost of the separate components. (Table 1) When these features are added to the obvious advantages of simplification of the regimen, combination antihypertensive preparations have become increasingly popular. Because of the severity of hypertension in black hypertensives, this population is less likely to be controlled on monotherapy with any agent. Additionally, in the black hypertensive, the resistance to the blood pressure lowering efficacy of beta blockers, angiotensin, converting enzyme inhibitors, and angiotensin II antagonists has been a consistent finding. However, when these agents are used in combination with diuretic therapy, this racial difference in efficacy disappears. Thus, the consideration of a

combination preparation is very often a reasonable option in this challenging hypertensive population.

An increasing number of combination products are now available. (Table 1) Most preparations contain a thiazide diuretic, although combination products are now available consisting of ACE inhibitors and CCBs. While the combinations are effective in low-

ering blood pressure, only the components of diuretics and beta blockers have been shown to decrease mortality and morbidity. Since the black hypertensive is at highest risk for the clinical sequelae of hypertension, this must be a consideration in the choice of product until the results of the clinical outcome trial now in progress are available documenting the clinical benefit of the ACE

TABLE 1— Once-daily combination drugs for hypertension

Drug	Trade Name	Cost Per Month
Beta-Adrenergic Blockers and Diuretics		
Atenolol 50 or 100 mg/chlorothalidone 25 mg	Tenormin vs Tenoretic	\$27.81-42.22 \$32.10-45.10
Bisoprolol 2.5, 5 or 10 mg/hydrochlorothiazide 6.25 mg	Ziac*	\$27.89
Nadolol 40 or 80 mg/bendroflumethiazide 5 mg	Corgard vs Corzide	\$34.20-43.45 \$39.53-52.16
Propranolol extended-release 80, 120 or 160 mg/hydrochlorothiazide 50 mg	Inderal LA vs Inderide LA	\$28.30-45.83 \$42.13-56.13
Ace Inhibitors and Diuretics		
Benazepril 5, 10, 20 mg/hydrochlorothiazide 6.25, 12.5 or 25 mg	Lotensin HCT	\$20.04
Captopril 25 or 50 mg/hydrochlorothiazide 15 or 25 mg	Capoten vs Capozide*	\$18.94-32.24 \$22.13-38.00
Enalapril 5 or 10 mg/hydrochlorothiazide 12.5 or 25 mg	Vasotec vs Vaseretic	\$28.50-29.93 \$29.93-33.32
Lisinopril 10 or 20 mg/hydrochlorothiazide 12.5 or 25 mg	Prinivil; Zestril vs Prinzide; Zestoretic	\$24.39-26.10 \$27.22-29.82
Angiotensin II Receptor Antagonists and Diuretics		
Losartan 50 mg/hydrochlorothiazide 12.5 mg	Cozaar and Hyzaar	\$33.00
Calcium-Channel Antagonist and ACE Inhibitors		
Amlodipine 2.5 or 5 mg/benazepril 10 or 20 mg	Separately vs Lotrel	\$56.64 \$38.90-40.85
Diltiazem 180 mg/enalapril 5 mg	Tezcem	N/A
Verapamil/trandolapril 2/180, 1/240, 2/240, 4/240 mg	Tarka	N/A
Felodipine 5 mg/enalapril 5 mg	Lexxel	N/A
Other Combinations		
Guanethidine 10 mg/hydrochlorothiazide 25mg	Esimil	\$20.74
Reserpine 0.125 mg/hydrochlorothiazide 25 or 50 mg	Hydropres	\$1.44
*Approved for initial therapy		
1996 Redbook average wholesale price		

inhibitors and CCBs.

Thus, in selecting combination therapy, the same considerations apply as in the selection of the individual agents. For the black hypertensive who has no specific indication or contraindication for a given agent and who is unlikely to be controlled on or tolerate low-to-moderate doses of a single agent, combination therapy with a diuretic/beta blocker combination is a reasonable choice. This exploits the abundant clinical outcomes data documenting the effectiveness of these individual agents in preventing the complications of hypertension. In other hypertensives, the choice of a combination preparation will be based upon the indications for the individual agents. Thus, in the hypertensive who has diabetic nephropathy, congestive heart failure, or has experienced a large myocardial infarction, a combination product containing an ACE inhibitor is a rational selection. Data on blood pressure reduction using combination preparations have thus far included too few blacks to clearly document the synergism/additivity of the combination of these agents compared to the individual components in this population. However, in the hypertensive who requires a CCB for blood pressure control but who experiences edema with this product, the combination of the CCB with an ACE inhibitor may lessen the edema.

References

1. Wright, JT Jr. and Douglas, JG. Drug therapy in the black hypertensive. In: *Pathophysiology of Hypertension in Blacks*. John Fray and Janice G. Douglas ed. Oxford Press; 1993.
2. Rahman R, Douglas JG, and Wright JT Jr.: Pathophysiology and treatment implications of hypertension in the African-American population. *Endocrinol Metab Clin NA*. 1997;26:3-1-20.
3. Joint National Committee on the Detection, Evaluation and Treatment of Hypertension. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of high blood pressure. *Arch Intern Med*. 1993; 153:154-181.
4. Report of the British Hypertension Society Working Party. Treating mild hypertension: Agreement from the large trials. *Brit Med J*. 1989; 298:694-698.
5. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman W, Grimm RH, LaRosa J, Whelton PK, Perry HM, Alderman MH, Ford CE, Oparil S, Francis C, Prochan M, Pressel S, Black HR, Hawkins CM. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens*. 1996;9:342-360.
6. Wright JT Jr., Kirk KA, Kusek JW, Toto R, Lee JY, Agodoa LY, Randall OS, Glassock R, for the AASK Pilot Study Investigators. Design and baseline characteristics of participants in the African-American study of kidney disease and hypertension (AASK) pilot study. *Cont Clin Trials*. 1996;16:3S-16S.
7. World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood pressure lowering treatments. *J Hypertens*. 1997; (Submitted).
8. Frishman WH, Bryzinski BS, Coulson LR, et al. A multifactorial trial design to assess combination therapy in hypertension: treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med*. 1994;154:1461-68.
9. Soffer BA, Wright JT Jr, Pratt JH, Weins B, Goldberg AI, Sweet, CS: Antihypertensive effects of the angiotensin II receptor antagonist losartan potassium on a background of hydrochlorothiazide in patients with essential hypertension. *Hypertension*. 1995; 26: 112-117.
10. Prisant LM, Weir MR, Papademetriou V, et al. Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J*. 1995;130:359-366.
11. Frishman WH, Ram VS, McMahon FG, et al. Comparison of amlodipine and benazepril monotherapy t amlodipine plus benazepril in patients with systemic hypertension. A randomized, double-blind, placebo-controlled, parallel-group study. *J Clin Pharm*. 1995;35:1060-1066.
12. Sica DA. Fixed-dose combination antihypertensive drugs. Do they have a role in rational therapy? *Drugs*. 1994;48:16-24.
13. Gradman AH, Cutler NR, Davis PJ, et al. Enalapril-felodipine ER in essential hypertension: a factorial design study of combination therapy. *Am J Cardiol*. 1997;79:431-435.

About ISHIB

The International Society on Hypertension in Blacks (ISHIB) is a unique nonprofit professional membership organization devoted to improving morbidity and mortality among ethnic populations. ISHIB was founded in Atlanta, Georgia in 1986 to respond to the problem of high blood pressure among ethnic groups and to bridge the black-white disease gap. Expansion of the organizational scope has been implemented to include renal disease, diabetes, stroke, lipid disorders, and other cardiovascular risk factors. The objectives of the Society are:

- to promote public awareness of the harmful effects of hypertension, especially among minorities
- to develop health-related programs to improve the quality of life in ethnic populations worldwide
- to educate the public on ways to prevent the complications of hypertension
- to stimulate research and clinical investigation
- to disseminate scientific findings to aid in the understanding of differences in hypertension among ethnic groups.

ISHIB Programs

Ethnicity & Disease. The Society's medical journal is a highly respected source of information on disease patterns in ethnic populations throughout the world.

The International Interdisciplinary Conference on Hypertension in Blacks. Now in its 12th year, this conference brings together medical researchers, practitioners and other healthcare professionals to learn about the most recent prevention and treatment options for hypertension and its related cardiovascular risk factors, especially within minority populations. This year's conference is scheduled for July 20-24, 1997 in London, England. Plenary sessions and workshops will address topics surrounding the theme, *Hypertension and Target Organ Damage: Prevention and Management in the African Diaspora.*

Church High Blood Pressure Sunday. On the first Sunday in May, ISHIB provides speakers to churches to discuss hypertension and other cardiovascular diseases, and conducts on-site blood pressure screening.

13th International Interdisciplinary Conference on Hypertension in Blacks July 12-15, 1998, Charleston, South Carolina

For many years, South Carolina has had the unfortunate distinction to be the state with the highest stroke mortality in our nation. In South Carolina, stroke mortality occurs with twice the frequency in African Americans compared to Caucasians. The Charleston Heart Study found that hypertension was a contributing factor in the death of 42% of African-American patients compared to only 18% of white patients.

Meeting Scientific Co-Chairs

James Sowers, M.D.

Wayne State University

Eddie Green, M.D.

Medical University of South Carolina

Local Meeting Planning Committee

Brent M. Egan, M.D.

Medical University of South Carolina

DeAnna Cheek, M.D.

Medical University of South Carolina



International Society on Hypertension in Blacks
2045 Manchester Street, NE
Atlanta, Georgia 30324
404-875-6263

NON-PROFIT ORG.
U.S. POSTAGE
PAID
PERMIT NO. 3805
ATLANTA, GA