

THE EFFECTIVE USE OF CALCIUM ANTAGONISTS

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## Objectives

The purpose of this monograph is to provide practicing physicians with current, practical information on the treatment of African-American hypertensive patients, especially as it relates to pharmacological therapies using calcium antagonists. After reading this material, the physician should be able to:

- Understand the therapeutic implications of the use of calcium antagonists in African-American patients;
- Have a working knowledge of the physiologic rationale for using calcium antagonists in the treatment of hypertension;
- Recognize the difference in delivery systems used by calcium channel blockers.
- Understand the research and scientific studies that support the therapeutic use of calcium antagonists for patients being treated for hypertension.

*This program was made possible by an educational grant from Bayer Corporation.*

See accompanying Prescribing Information for Adalat CC (nifedipine) Extended Release Tablet.

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## Preface

Dear Colleague:

This monograph, *The Effective Use of Calcium Antagonists*, has been compiled pursuant to the 11th International Interdisciplinary Conference on Hypertension in Blacks held in July 1996. It offers healthcare providers and medical researchers an analysis of the effect of calcium antagonists in hypertension management, especially among minority populations.

The information presented herein provides specific details about the use of calcium antagonists that fall into these classes: phenylalkylamine, benzothiazepine and dihydropyridine. Readers will find information on the current trends in prescribing these drugs, a discussion on the physiologic rationale for calcium antagonist therapy and considerations for using calcium antagonists in all patient populations.

As a product of the International Society on Hypertension in Blacks (ISHIB), this monograph reaches two goals of the society: (1) to stimulate research and clinical investigation; and (2) to disseminate scientific findings to aid in the understanding of differences in hypertension among ethnic groups. Much effort has been made to ensure the accuracy of the scientific information presented and is believed to be correct at the time of publication.

I hope you will find this monograph useful in the treatment and management of hypertension in your patients, or as you continue research on the efficacy of drug therapies to control hypertension within different ethnic populations.

Sincerely,

James W. Reed, MD, FACP, FACE  
President, International Society on Hypertension in Blacks  
Professor of Medicine  
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## Contributor Profiles



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**James W. Reed, MD, FACP, FACE** serves as director of the Internal Medicine Residency Program, and since 1985, has been a professor of medicine at Morehouse School of Medicine in Atlanta, Georgia. In June 1992, he was elected president of the International Society of Hypertension in Blacks, after serving as the Society's vice president and founding member since 1987. Dr. Reed earned his medical degree from Howard University College of Medicine and completed a residency program in internal medicine at Madigan Army Medical Center, Tacoma, Washington. He completed a post-doctoral research fellowship in endocrinology and metabolism from the University of California Medical Center. Dr. Reed has earned many awards and has authored and presented more than 40 articles, papers and book chapters relating to internal medicine, endocrinology and metabolism.

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**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.



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**Vincent DeQuattro, MD, FACC, FACP** serves as chief, Hypertension Diagnostic Laboratory, USC School of Medicine and director, Hypertension, Division of Cardiology, at LAC-USC Medical Center. He attended UCLA, UC at San Francisco (B.S. in Pharmacy). He received his medical degree and Distinguished Alumni Achievement Award from George Washington University. He completed his internship and internal medicine residency at LAC-USC Medical Center, and fellowships in cardiovascular disease, LAC-USC Medical Center and White Memorial Medical Center. He is a fellow of the American College of Physicians and American College of Cardiology. He was a member of the Fourth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. He has contributed more than 160 journal and chapter publications in the diagnosis, etiology and therapy of primary and secondary hypertension, and the pathophysiology of hypertensive heart disease and specific interactions with the sympathetic nervous system.

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**Lawrence M. Resnick, MD** serves as professor of medicine and director of hypertension at Wayne State University Medical Center in Detroit, Michigan. He completed his medical degree at Northwestern University and internship and residency programs in medicine at the University of Chicago Hospital and Clinics. He was a fellow in endocrinology at Columbia-Presbyterian Medical Center and a research fellow in endocrinology at the Walter Reed Army Institute of Research. Dr. Resnick is the author of more than 200 abstracts and articles. He holds editorial positions for publications including the *American Journal of Hypertension*, *National Kidney Foundation Nutrition and Blood Pressure Reviews*, *Magnesium and Trace Elements*, and *Cardiovascular Risk Factors—An International Journal*.



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**Kenneth A. Jamerson, MD** received his undergraduate and medical degrees from the University of Michigan in Ann Arbor, where he also completed his residency in internal medicine and a fellowship in hypertension. Currently, he is assistant professor of internal medicine at the University of Michigan, where he also serves as the medical director of the Minority Health Care Institute. Dr. Jamerson has presented his research both nationally and internationally. He is actively involved in research under NHLBI grants and serves as a peer-reviewer for several prominent journals including *Archives of Internal Medicine*, *Hypertension*, *Journal of Hypertension*, *Blood Pressure*, and *American Journal of Physiology*. Dr. Jamerson has authored a number of scientific articles, several of which resulted from the study of a cohort of patients in a rural Michigan community (The Tecumseh Blood Pressure Study).

## Introduction

L. Michael Prisant, M.D.  
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Calcium antagonists work by blocking the entrance of calcium from the outside of the cell to the inside of the cell through the voltage-dependent calcium channels. Calcium blockade prevents the interaction of calcium and calmodulin, ultimately preventing the actin-myosin interaction, which is responsible for vasoconstriction; therefore, calcium channel blockers ultimately result in vasodilation.

There are three major calcium channel blocker sites: a dihydropyridine site for nifedipine, a phenylalkylamine for verapamil, and a benzothiazepine site for diltiazem. These sites interact with each other to a certain degree. For instance, if you block the dihydropyridine site, the benzothiazepine site may be facilitated. Alternately, if you block the phenylalkylamine site, the dihydropyridine or the benzothiazepine sites may be inhibited.

There also may be differences in tissue affinity and vasoselectivity, the importance of which continues to be very controversial. In addition, there may be some inhibition of the baroreceptor reflex, as well as inhibition of aldosterone release. Many of the calcium antagonists also have a natriuretic and a diuretic effect that can be seen acutely and, in some cases, repetitively.

The various calcium channel blockers, listed according to class, compound and brand, can be found in Table 1. Since the introduction of the short-acting dihydropyridines and the phenylalkylamines in the early '80s and the benzothiazepines in the late '80s, many additions have been made to the class of calcium channel blockers. Each one of these calcium antagonists, with the exception of amlodipine, have a relatively short half-life; therefore, various drug delivery systems have been developed to prolong the therapeutic effect of these drugs.

TABLE 1.—Calcium channel blockers, according to class, compound and brand

Class	Compound	Brand
Phenylalkylamine	Verapamil	Calan SR (1986)
		Covera-HS (1996)
		Isoptin SR (1986)
		Verelan (1990)
Benzothiazepine	Diltiazem	Cardizem SR (1988)
		Cardizem CD (1991)
		Dilacor XR (1992)
		Tiazac (1995)
Dihydropyridine	Amlodipine	Norvasc (1992)
		Plendil (1991)
		Dynacirc (1991)
		DynaCirc CD (1994)
	Nicardipine	Cardene (1989)
		Cardene-SR (1992)
	Nifedipine	Adalat CC (1993)
		Procardia XL (1989)
Nisoldipine	Sular (1996)	

For example, with verapamil, the Spheroidal Oral Delivery Absorption System (SODAS) uses little beads that have a rate control coating, which allow gradual delivery of verapamil throughout the gut and the proximal portion of the colon, resulting in a drop in blood pressure over a period of 24 hours.

The Geomatrix delivery system is used for diltiazem in tablets that expand as water is absorbed into a rate-control delivery device. The outside portions do not expand; however, the inside portion expands so that diltiazem gradually empties through the side walls as more fluid enters. This reservoir is delivered over a 24-hour period.

The GITS (Gastrointestinal Therapeutic System) is a delivery system, which consists of a polymeric push layer with an osmotic drug core encased by a hard semi-permeable membrane. This polymeric push layer expands as water goes through a semi-permeable membrane. During this expansion, nifedipine is delivered through a precision-drilled laser hole over a period of 24 hours. Nifedipine GITS is very effective in lowering blood pressure with increasing doses.

A different kind of delivery system, the Coat Core delivery system, is used for Adalat CC (nifedipine) Extended Release Tablet. It has a light protective film coat that surrounds a slow-release hydrophilic gel and an inner coat that is fast-released. As the tablet surface erodes, nifedipine from the outer matrix coat is dissolved and absorbed. As this occurs, nifedipine is released from the inner core, compensating for the decreasing release of nifedipine from the outer coat. With this delivery system, it is important to instruct the patient not to bite the tablet. Chewing on the tablet can result in dose dumping—a very rapid release of nifedipine into the system. The patient should take the tablet on an empty stomach. The Coat Core delivery system has also been tested in a randomized, double-blind placebo controlled study, comparing nifedipine doses of 30 mgs, 60 mgs, and 90 mgs, during a 10-week study period. This study showed that the delivery system is very effective in lowering blood pressure as shown in Figure 1.

*...[C]alcium antagonists... have a relatively short half-life; therefore, there have been many attempts using novel drug delivery systems to prolong the therapeutic effect of these drugs.*

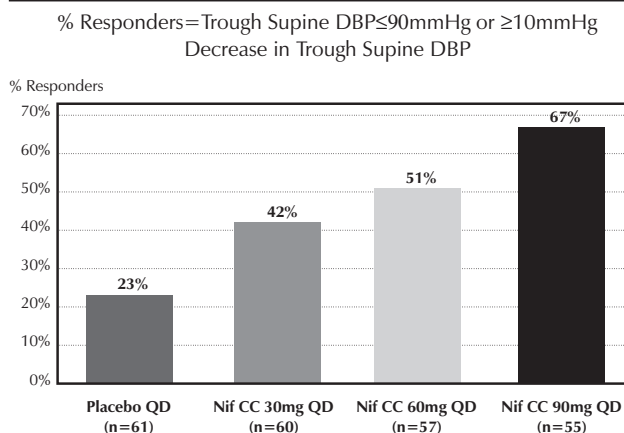


FIG 1. — Nifedipine coat-core responses. Reprinted with permission of the publisher from author: *Clin Ther* 15:963-973, Copyright 1993 by Excerpta Medica, Inc.

It is reasonable to question whether or not there may be similarities between the nifedipine GITS delivery system and the nifedipine Coat Core delivery system. Since there are differences in nifedipine blood levels between Adalat CC and Procardia XL, it would be reasonable to assume that there may be differences in how patients respond to the drugs over a 24-hour period. Double-blind studies that compare both delivery systems have found very similar reduction in systolic blood pressures and in diastolic blood pressures as shown in Figure 2. A similar reduction also occurs at the 60 mg dose of both nifedipine Coat Core and nifedipine GITS delivery systems.

FIG 2.—Mean change in systolic and diastolic 24-hour ambulatory blood pressure measurement for all patients valid for efficacy analysis; a comparison of 30 mg and 60 mg for both NIF CC and NIF GITS. All data are smoothed and baseline subtracted. SBP=systolic blood pressure; NIF CC=nifedipine coat-core; DBP=diastolic blood pressure; NIF GITS=nifedipine gastrointestinal therapeutic system. Reprinted with permission of the publisher from author: *ClinTher* 17(2):304, Copyright 1995 by Excerpta Medica, Inc.

It is important to remember that with any delivery system, there are certain features that must be considered. For instance, because the GITS delivery system is so hard, patients must be warned to swallow

the tablets whole, without chewing. Exercise caution when using any drugs with patients who have derangements in their gastrointestinal system. If they have rapid transit (chronic diarrhea), all drugs with a drug delivery system may be less effective.

**...[For patients with] rapid transit (chronic diarrhea), all drugs with a drug delivery system may be less effective.**

With an understanding of calcium antagonists and their delivery systems, the controversy surrounding the use of calcium antagonists needs to be addressed. Early in

1989, the *British Medical Journal* published a manuscript from Held, Yusuf, and Furberg which was a meta-analysis of 19,000 patients in 28 randomized trials of myocardial infarction and unstable angina. The conclusion of these trials was that, at least for the short-acting dihydropyridines, there was greater hazard in using these drugs with acute myocardial infarction or unstable angina. Dr. Vincent DeQuattro will present issues relating to this controversy.

Dr. Lawrence Resnick will explore the relationship of insulin sensitivity and hypertensive target organ damage. It has been suggested that derangements in intracellular calcium, magnesium and

sodium status may alter insulin resistance. Insulin resistance may affect various target organ tissues: the fat and skeletal muscle, the kidney, the central nervous system, the heart and vascular smooth muscle, which ultimately may manifest itself with left ventricular hypertrophy, progressive kidney disease, diabetes and atherosclerosis. Dr. Resnick discusses appropriate optimal utilization of calcium antagonists.

And finally, we have been told that younger patients and whites respond better to beta-blockers and angiotensin converting enzyme inhibitors than blacks and elderly patients. (Joint National Committee. Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med.* 1993; 153:154-183.) Alternately, calcium antagonists and diuretics are more effective in older patients and blacks and less effective in younger patients. In this monograph, Dr. Kenneth Jamerson discusses the wisdom of this approach in African Americans.

## Toward Improved Antihypertensive Therapy with Calcium Channel Blockers

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Outcome trials are the scientific method of determining if an antihypertensive agent really works; and for a therapy to work well, it should reduce mortality. The FDA requires only that blood pressure be controlled safely, but current evidence-based medicine demands answers to the mortality/morbidity question. We need this outcome trial information on **all** the classes of antihypertensives, including calcium channel blockers. For example, we often rely on surrogate endpoints such as control of blood pressure or control of PVCs. If we treat hypertensives with PVCs using beta-blockers or calcium channel blockers, we may see both control of blood pressure and suppression of PVCs. However, as we learned from the CAST trial with flecainide and encainide, PVCs can be controlled, but mortality may increase.<sup>1</sup> On the other hand, the Lewis trial demonstrated that captopril, an ACE inhibitor, reduced proteinuria, which is another surrogate endpoint in diabetic hypertensives with nephropathy, although blood pressure was controlled with diuretic and conventional therapy.<sup>2</sup> Importantly, captopril also reduced morbidity and mortality without influencing blood pressure. Unfortunately, there are no outcome trials measuring mortality endpoints for most of the antihypertensive agents in use today, especially in patients with uncomplicated hypertension.

The SHEP Trial,<sup>3</sup> an outcome trial cited and relied upon by the Fifth Joint National Committee (JNC-V),<sup>4</sup> was a study of systolic hypertensives with an average age of 72 and an average blood pressure of 170/77 mmHg at baseline. Five thousand patients were treated in the trial, half with placebo and half with a diuretic or diuretic/beta-blocker combination. The investigators reported significant reductions in nonfatal heart attacks and strokes, 27% and 36%, respectively. A meta-analysis of the results of this outcome trial, combined with those of four or five similar trials in the elderly, revealed significant reductions in mortality as well as morbidity. These combined data persuaded the JNC-V to recommend diuretic and beta-blocker therapy for the uncomplicated patient with hypertension. JNC-V also recommended use of calcium channel blockers, ACE inhibitors, and alpha blockers for patients with complications and contraindications for diuretic therapy.

In March of 1995, headlines in newspapers around the nation warned readers, “Hazards seen in blood pressure drugs!” and “Patients taking calcium channel blockers may be increasing their risk of heart attack by 60%!” Over the years, there have been similar news reports in regard to other antihypertensives and cardiovascular drugs. Reserpine reportedly caused breast cancer, but this was never proven in outcome trials. Digitalis therapy was indicted as “a potentially lethal drug” and it had been known to cause a propensity for cardiac arrhythmias. However, a recent outcome trial with digitalis therapy in patients with chronic congestive heart failure, found no influence on mortality, but importantly a reduction of morbidity and hospitalizations.<sup>5</sup> Diuretics were blamed as “problematic” in the past.

In 1989, media releases urged patients to ask their doctors about the dangers of diuretic therapy, since they raise blood fats, potentially increasing the risk for coronary atherosclerosis and ischemic heart disease.

Two case control studies, published in 1994 and 1995 respectively, reported that antihypertensive therapy increased primary cardiac arrest when diuretics were used without potassium or potassium supplementation.<sup>6,7</sup> It is noteworthy that the cardiovascular mortality reductions in SHEP were obtained with frequent attention to serum potassium. The investigators had the option of adding potassium supplementation or potassium sparing agents when potassium levels were 4.0 meq/L or less. However, the additions were mandated when the serum potassium was 3.5 meq/L or less. Thus, the SHEP investigators may have had the benefit of normokalemia to offset the sudden death risk.

In March 1995, the media released the preliminary results of the Seattle Health Cooperative Study - A Case Control Analysis, warning the public that calcium channel blocker therapy was associated with a 60% increased risk of myocardial infarction.<sup>8</sup> The report was a belated retrospective analysis of heart attack frequency of their “cases,” i.e., hypertensives taking calcium channel blockers compared to that of patients on beta-blocker therapy “controls.” Ten out of 1,000 “controls” had a myocardial infarction when taking beta-blockers; 16 out of 1,000 “cases” sustained a myocardial infarction when taking calcium channel blockers. Thus the difference,  $16 - 10 = 6$  then divided by 10, equals 60%. A 60% relative increase of myocardial infarction means an absolute increase of 0.6%. If true, this would be a staggering statistic in terms of additional heart attacks in the United States related to calcium channel blocker therapy.

Of course, there are major differences between case control studies and outcome-based trials. In outcome trials, therapy is assigned in a randomized, placebo-controlled, double-blind fashion. In case control studies, caregivers or physicians may select antihypertensive therapy peculiar to the patient’s underlying condition, therefore, confounding the drug’s effect with that of the patient’s cardiovascular disease. In the Cooperative Health Study, patients chosen for calcium channel blocker therapy initially had twice as many coronary risk factors as patients who were selected to receive diuretic and beta-blocker therapy.<sup>8</sup> Further, in the Seattle Study only immediate-release calcium channel blockers were used, and although nifedipine and verapamil have been cleared by the FDA for stable and vasospastic angina, these agents are not indicated for hypertension.

In September 1995, immediate-release nifedipine was disparaged further by the publication of a meta-analysis of 16 outcome trials of nifedipine in patients after an acute myocardial infarction or unstable angina. The Seattle Cooperative investigators reported that nifedipine caused a dose-related increase in mortality, warning that short-acting nifedipine in doses above 60 mg per day caused a two- to three-fold increase in mortality.<sup>9</sup> However, therapy

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*We need this outcome trial information on ALL the classes of antihypertensives, including calcium channel blockers.*

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with 60 mg of nifedipine or less per day did not change mortality. The authors speculated that the untoward mortality effects were due to increased sympathetic activity reflexively related to the rapid release formulation. Sympathetic nerve activation by nifedipine is associated with the rate of rise of nifedipine levels in blood as shown in a 1987 report.<sup>10</sup> Nifedipine was infused intravenously to normal volunteers at a rate of 13 mg/hour. Heart rate was increased 20 beats per minute without change in blood pressure. There was no increase in heart rate (see Figure 1) and there was a significant reduction of blood pressure when the rate of infusion was initiated at one-tenth the rate or 1.3 mg/hour and was gradually increased to achieve plasma nifedipine levels equivalent to that of the high rate of infusion.<sup>10</sup>

FIG 1.—A 13 mg/hour nifedipine infusion was initiated in normal volunteers and the heart rate increased rapidly and remained elevated at 20 beats/minute or more above baseline for several hours. A week later, nifedipine was infused at a rate of 1.3 mg per hour, and the infusion rate was increased gradually to achieve the same blood levels of nifedipine as the initial rapid infusion with no changes in heart rate. The slowly rising nifedipine levels reduced blood pressure without changing heart rate. Reprinted with permission of the publisher of *Clinical Pharmacology and Therapeutics*. 1987; 41:26-30.

formulation versus the sustained-release preparation of nifedipine. The increases of plasma catecholamines were 50%<sup>13</sup> and 20%,<sup>12</sup> respectively.

The term “bungee phenomena” applies to the fall and subsequent rise in blood pressure concomitant with the rise and fall of nifedipine levels after immediate-release nifedipine. In contrast to this phenomenon, Figures 2A and 2B demonstrate the sustained blood levels and the smooth, controlled blood pressures after administration of the Coat Core delivery system of nifedipine, known as Adalat CC (nifedipine) Extended Release Tablet, and the system known as nifedipine GITS (Procardia XL) to normal volunteers. We also compared the lowering of ambulatory blood pressure in patients taking the GITS system with that of patients taking the ACE inhibitor enalapril on a once-daily basis. The control of blood pressure after the ACE inhibitor wanes dramatically after midnight if the medication is given in the morning. On the other hand, nifedipine GITS controlled blood pressure throughout the 24-hour cycle (Figure 3).<sup>13</sup>

FIG 2A.—Plasma nifedipine levels with Adalat CC 60 mg vs. Procardia XL 60 mg in healthy volunteers.

FIG 2B.—Systolic and diastolic BP responses: Adalat CC 60 mg vs. Procardia XL 60 mg in healthy volunteers.

*The term “bungee phenomena” applies to the fall and subsequent rise in blood pressure concomitant with the rise and fall of nifedipine levels after immediate-release nifedipine.*

Earlier, we found that the beta-receptor antagonist, metoprolol, reduced the frequency and duration of ischemic episodes and controlled ambulatory blood pressure in hypertensives with stable angina.<sup>11</sup> However, we observed different results in a similar cohort of patients when immediate-release nifedipine was used instead of metoprolol.<sup>12</sup> Immediate-release nifedipine reduced ischemic episodes in a minority of the hypertensives, those with controlled ambulatory blood pressure, but not for those with uncontrolled ambulatory blood pressure. We measured plasma catecholamine responses to both immediate-release and sustained-release nifedipine in hypertensives both with and without angina. Sympathetic neural activation as assessed by the rise in plasma norepinephrine appeared greater with the immediate-release

FIG 3.—Nifedipine GITS blood pressure control throughout 24-hour cycle.

Recent outcome trial results have broadened our knowledge base regarding calcium channel blockers and cardiovascular disease. The STONE Trial, conducted in China, utilized a slow-release formulation of nifedipine in patients with hypertension and demonstrated reduction in morbidity.<sup>14</sup> The DEFIANT trial investigators found a reduction of blood pressure with nisoldipine and a reduction in morbidity.<sup>15</sup> The slow-acting dihydropyridine, amlodipine, was studied in patients with ischemic and dilated cardiomyopathy in the PRAISE trial.<sup>16</sup> All patients were treated with ACE inhibitors as well as diuretic and digitalis therapy. While there was no overall improvement in mortality, there were reductions of both morbidity and mortality in patients with non-ischemic cardiomyopathy. Thus, preliminary reports regarding slow-release and slow-onset calcium channel blockers from outcome trials are positive and comforting, and appear to contradict the earlier dire warnings related to immediate-release formulations. Slow-release formulations of nifedipine appear to be neutral on morbidity and mortality events in a variety of patients with hypertension and cardiovascular disease.

A recent cohort study found no excess mortality with calcium channel blockers in hypertensives. The study of Israeli patients compared morbidity/mortality of those treated with calcium channel blockers, mostly diltiazem and nifedipine, with that of patients on other therapies. Mortality rates with these drugs were similar whether patients received calcium channel blockers or other antihypertensives. There were no differences in mortality in any subgroup: men, women, age less than 55, or more than 65, etc.<sup>17</sup>

Pahor and colleagues<sup>18</sup> reported different results from Braun et al<sup>17</sup> regarding the relative survival rates of patients treated with calcium channel blockers or treated without calcium channel blockers. They followed a cohort of hypertensives prospectively and examined results by case-control analyses. There was a hierarchy of survival rates in which the highest were patients treated with ACE inhibitors (89%) and beta blockers (87%), and the lowest rate occurred for patients treated with immediate-release nifedipine (60%). The rate limiting immediate-release verapamil (85%) and diltiazem (70%) were immediate in their effects on survival.<sup>18</sup>

Generally, the blood pressure responses of Caucasian patients to the various agents are of equal magnitude. On the other hand, there is a hierarchy of blood pressure responsiveness of African-American patients to calcium channel blockers, diuretics, ACE inhibitors and beta-blockers.<sup>19</sup> Calcium channel blockers or diuretics usually provide excellent blood pressure control in African Americans,<sup>20</sup> and salt-sensitive patients,<sup>21</sup> and in those receiving non-steroidal medications in comparison to the often less effective latter two agents.<sup>22</sup> Sustained-release calcium channel blockers reduce left ventricular mass.<sup>23</sup> Calcium channel blockers also improve the poorly compliant myocardium of hypertensives, a frequent finding in hypertensive heart disease, often antedating the left ventricular hypertrophy.<sup>24</sup>

Systolic failure may eventually intervene in patients with hypertension. Preferred treatments for systolic failure in hypertensive patients at the present time are ACE inhibitors and diuretics. ACE inhibitors appear to reduce ischemic events in patients with congestive heart failure, perhaps by enhancing the release of bradykinin, nitric oxide, and prostacycline from coronary vascular endothelium. However, other therapeutic agents are being considered to offset the harmful effects of angiotensin II and endothelin on coronary vascular endothelial function. While ACE inhibitors block the formation of angiotensin II, both endothelin receptor antagonists and calcium channel blockers have been found to antagonize the deleterious effects of endothelin.<sup>25</sup> There are at least two ongoing trials to test the hypothesis that calcium channel blockers may be beneficial in both patients with hypertension as well as those with congestive heart failure—PRAISE II with amlodipine in dilated cardiomyopathy and MACH-I with mibefradil in ischemic and dilated cardiomyopathy. Mibefradil is a rate-limiting non-dihydropyridine calcium channel blocker that blocks “T” channels selectively.<sup>26</sup>

There are additional ongoing outcome trials in hypertensives testing the efficacy of calcium channel blockers in reduction of morbidity/mortality. INSIGHT is enrolling high-risk hypertensives with blood pressure of 150/95 mmHg or greater, or if only systolic blood pressure is elevated, it must be greater than 160 mmHg. This study of 6,600 patients compares long-acting nifedipine with diuretic/potassium sparing diuretics. If the patient has an inadequate response to nifedipine or to the diuretic, beta-blocker therapy is added. Substudies are evaluating 24-hour blood pressure, left ventricular hypertrophy regression, renal function, and tissue calcification.<sup>27</sup> Work by O'Rourke and others has demonstrated that the calcium channel blockers improve the reduced compliance of the conduit blood vessels in patients with hypertension.<sup>28</sup> Patients with reduced compliance have raised pulse and systolic pressures and lowered diastolic pressures as seen generally in the elderly hypertensive. In the HOT Trial, felodipine is being studied in a large cohort of hypertensives to determine which level of achieved diastolic blood pressure lowers mortality/morbidity more: less than 90, less than 85, and less than 80 mmHg diastolic blood pressure.<sup>29</sup> Alderman et al performed a case-control study, nested within a systematic

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*Calcium channel blockers  
or diuretics usually  
provide excellent blood  
pressure control in African  
Americans...*

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hypertension control program for a prospective cohort of 4,350 people (first seen 1981-1984). Cases were hypertensives having either death or hospitalization; controls were matched for age, gender and demographic characteristics. Compared with those on beta-blockers, those on long-acting calcium antagonists were not at greater risk for cardiovascular events. However, among 38 matched pairs who were both on calcium antagonists, the adjusted risk ratio for short-acting (immediate-release) versus long-acting was 8.6 (1.9-39.0),  $p < 0.1$ .<sup>30</sup>

**Compared with those on beta-blockers, those on long-acting calcium antagonists were not at greater risk for cardiovascular events.**

Presently, we are awaiting the results of the ongoing outcome trials for the morbidity data to confirm the favorable results with long-acting calcium channel blockers found by Alderman and reported in the PRAISE and STONE Trials. Ongoing trials, such as ALLHAT with amlodipine, CONVINCe with verapamil, INSIGHT with nifedipine, PRE-DICT with diltiazem, are all randomized, double-blind, placebo-controlled trials investigating the effects of these important classes of calcium channel blockers in comparison to ACE inhibitor, diuretic, or alpha blocker therapies on mortality, morbidity, and heart attack endpoints.<sup>31</sup> Hypertensives under study include those with excess risk for coronary artery events.<sup>15</sup> These data are crucial to further expand the role for informed selection of antihypertensive therapy, including the calcium channel blockers, for patients with hypertension to prevent the sequelae of their cardiovascular disease.

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# Physiologic Rationale for Calcium Antagonist Therapy in Essential Hypertension

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## Introduction

Two basic concepts that are relevant to hypertensive cardiovascular disease are often ignored despite being central to a proper understanding of and clinical approach to our patients. First, high blood pressure is a “vital” sign, as is temperature, pulse, and respiration. The underlying cause(s) of this sign are unknown, and thus the condition itself is named according to its sign, as essential hypertension. Unfortunately, the cumulative experience of more than two decades of world-wide clinical trials indicates that getting rid of only one aspect of hypertensive disease, the elevated blood pressure, gets rid of only part of the excess cardiovascular risk associated with hypertension.

What we call hypertension carries with it other peripheral manifestations present in other body systems, such as left ventricular hypertrophy and insulin resistance, reflecting the same underlying pathophysiology in skeletal muscle, fat, and other tissues. As such, a reasonable goal, not yet attained, would be to identify common factors underlying not only the elevations of blood pressure, but the other multisystemic aspects of hypertensive cardiovascular disease as well. Focusing on such underlying factors would allow treatment of the disease process itself, rather than just the level of blood pressure.

A second concept is the pathophysiologic and clinical heterogeneity of hypertension. The same elevation of blood pressure that leads to the diagnosis of “essential” hypertension may result from many different “primary” causes, which just happen to have hypertension as one shared clinical manifestation. This immediately implies that when we ask, “Is this drug good or ‘preferred’ for hypertension?” the answer should be, “It depends.” For example, the salt-sensitive hypertensive responds to dietary salt recommendations and to different drug classes differently from an individual who is not salt-sensitive.

## Altered Cellular Calcium as a Fundamental Lesion in Hypertension

### Calcium as a Common Unifying Factor in the Pathophysiology of Hypertension

Our approach to the understanding, clinical evaluation, and treatment of hypertensive disorders is based on an analysis of mineral ion metabolism. Defects in cellular ion levels, characterized by elevations of cytosolic free calcium and reciprocal suppression of free intracellular magnesium levels, predict the extent of many different aspects of hypertensive disease.<sup>1</sup> In 1984, Erne and Bolli observed a direct correlation between cytosolic free calcium levels in platelets and the level of the blood pressure.<sup>2</sup> The higher the free calcium, the higher the pressure. An opposite, inverse relation has been observed

in some subjects between extracellular, serum ionized calcium and blood pressure—the lower the ionized calcium, the higher the blood pressure.<sup>3</sup> Excess intracellular free cytosolic calcium in hypertension may, in some situations, be of extracellular origin. Thus, when such a maldistribution of calcium between inside and outside the cell occurs, blood pressure rises in proportion to the cellular accumulation of calcium from the extracellular space. In these situations, calcium channel blockade represents the treatment modality of choice.

Excess steady-state levels of cytosolic free calcium is also an underlying feature of other aspects of hypertensive vascular disease, including myocardial hypertrophy and insulin resistance. The higher the free cytosolic calcium, the greater the left ventricular mass. Conversely, the lower the serum ionized calcium, the greater the LV mass.<sup>4</sup> Similarly, when ion levels before and after an oral glucose tolerance test in normotensive and hypertensive subjects were studied, fasting cytosolic free calcium levels were not only higher in hypertensives in the basal fasting state, but they also predicted the subsequent hyperinsulinemic response to glucose loading. The higher the free calcium, the more hyperinsulinemic was the subject’s response, consistent with a role for excess cytosolic free calcium in mediating peripheral insulin resistance. Thus, cytosolic accumulation of calcium is at least one underlying feature consistently present in and linking different pathophysiologic aspects of what we call hypertension, expressed differently in different organ systems as elevated blood pressure, cardiac hypertrophy, and insulin resistance (Figure 1).<sup>5</sup>

*Defects in cellular ion levels, characterized by elevations of cytosolic free calcium and reciprocal suppression of free intracellular magnesium levels, predict the extent of many different aspects of hypertensive disease.*

FIG 1.—Ionic hypothesis of cardiovascular and metabolic disease, in which altered distributions of intracellular free ions such as cytosolic free calcium (Cai-f), intracellular free magnesium (Mgi-f), pH (pHi), and sodium (Nai), present as a lesion common to many, if not all tissues, result in the different multisystemic manifestations characteristic of hypertension, aging, and “Syndrome X” in Western societies.

### Calcium, Renin and the Heterogeneity of Hypertension

How can this apparently uniform calcium-related intracellular lesion help us to evaluate and treat individuals with hypertension, especially in view of the heterogeneity of clinical hypertension? One drug may lower pressure significantly in a given subject, and a second drug in that same subject may have little or no effect. This

heterogeneity of clinical responses to drugs and to other kinds of environmental factors can also be understood in terms of calcium-related cellular defects.

For example, renin-sodium profiling and the volume-vasoconstriction model of hypertension described by Laragh and Sealey,<sup>6</sup> focuses on hormone systems normally functioning to regulate ion movements into and out of cells, both the monovalent ions, sodium and potassium metabolism via the renin-aldosterone system, as well as the divalent cations, via calcium regulating hormones such as PTH and 1,25 dihydroxyvitamin D (1,25 D). There is an inverse linkage between these systems in subjects with hypertension, the low renin state having higher PTH and 1,25 D levels, and vice versa in

inappropriately high renin subjects.<sup>7</sup> In turn, these hormone systems regulate cytosolic free calcium levels by opposite mechanisms. Hormones such as 1,25 D directly open calcium channels and thus facilitate cellular calcium uptake from the extracellular space.<sup>8</sup> Conversely, angiotensin II also increases cytosolic free calcium, but by initial release of calcium from intracellular stores.<sup>9</sup> Importantly, since the metabolic set-point of these hormone systems differ from individual to individual, the varied clinical responses to different diets and

drug therapies can be explained on the basis of differing hormone-dependent cellular calcium responses to any particular therapeutic maneuver. The hypertensive subject with suppressed or "low" renin activity, having reciprocally higher 1,25 D levels, is more prone to experiencing a pressor response to dietary salt loading, since the higher 1,25 D levels found in the low renin subject potentiates extracellular calcium movement into the cytosol. A high salt diet excessively stimulates these same calcium hormones and causes a fall in circulating serum ionized calcium,<sup>10</sup> and a reciprocal rise in cytosolic free calcium, and thus in blood pressure. Thus, the heterogeneity of clinical hypertensive disease can be assessed by evaluating plasma renin activity, which tests differing proportions of steady-state cytosolic free calcium levels derived from extracellular vs. intracellular sources (Figure 2).

FIG 2.—Divalent cation levels in different forms of hypertension. Extracellular vs. intracellular sources of excess cytosolic free calcium levels and suppressed intracellular free magnesium levels in different renin forms of essential hypertension.

## The Mechanism of Salt-Sensitive Hypertension and the Role of Calcium Channel Antagonists

### How Does Salt Raise Blood Pressure in Salt-Sensitive Subjects?

We studied essential hypertensive individuals who were randomly allocated to low salt (UNaV<50 mEq/d) and high salt (UNaV>200 mEq/d) diets, each for one month. Cytosolic free calcium levels were higher and intracellular free magnesium levels were reciprocally lower on the high salt diet. In salt-insensitive subjects, only modest changes in free calcium, and no changes in intracellular free magnesium were observed (Figure 3).<sup>11</sup>

Thus, there is an apparent correlation between the ability of dietary salt to raise blood pressure and its ability to raise levels of cytosolic free calcium. Salt-induced shifts in calcium from the

FIG 3.—Intracellular ionic consequences of high and low dietary salt intakes in salt-sensitive and salt-insensitive essential hypertensive subjects.

extracellular to the intracellular compartment have been associated with a parallel rise in blood pressure.<sup>10</sup>

To test the possibility of preventing calcium from entering the cell, and preventing dietary salt from raising blood pressure, we utilized calcium channel blocking agents, which interfere with extracellular calcium uptake. According to the above (see Figure 2), blocking extracellular calcium transport intracellularly with calcium channel blockers should be selectively and especially beneficial to the low renin, salt-sensitive individual. Could calcium channel blockers stop or at least blunt the ability of salt to raise blood pressure? Patients

received either placebo or nifedipine tablets on high or low dietary salt intake. Cytosolic free calcium and blood pressure rose significantly with salt loading on placebo tablets. However, on nifedipine therapy, the rise in pressure on high vs. low salt was blunted and no longer significant, in parallel with a significant blunting of the salt-induced elevation in cytosolic free calcium levels as well (Figure 4).<sup>11</sup>

FIG 4.—Intracellular free calcium (Cai) and magnesium (Mgi) ion content, and diastolic blood pressure (DBP) in essential hypertensive subjects on low vs. high salt diets, treated with either placebo (P) or calcium channel antagonist (nifedipine, N) regimens. In Panel A, subjects are compared on high vs. low salt diets for each treatment modality. In Panel B, each treatment is compared on each salt diet.

This data not only supports the mechanism of salt-sensitive hypertension as being dependent on cellular calcium uptake from the extracellular space. It also directly demonstrates that calcium channel blockers interfere with the mechanism by which salt raises pressure in salt-sensitive individuals.

### How Should We Treat Salt-Sensitive Hypertension?

Clinically, then, we have at least two drug therapies for the salt-sensitive hypertensive patient: diuretic therapy and calcium channel blockade. Diuretics lower blood pressure by a reduction of volume; however, this has little to do with the underlying problem. By contrast, calcium channel antagonists appear to be mechanism-specific for the pathophysiology underlying the clinical problem of salt-sensitive hypertension. Indeed, salt-sensitive subjects given either nitrendipine or verapamil exhibit a markedly enhanced fall in pressure compared to salt-insensitive subjects receiving the same dose of drug (Figures 5,6).<sup>12, 13</sup>

FIG 5.—Differential effects of calcium channel antagonist therapy with verapamil on diastolic blood pressure (% DBP) in salt-sensitive vs. salt-insensitive subjects. PRA = plasma renin activity;  $Ca^{++},io$  = serum ionized calcium; 1,25D = 1,25 dihydroxyvitamin D.

FIG 6.—Differential effects of calcium channel antagonist therapy with nitrendipine on diastolic blood pressure (% DBP), serum ionized calcium ( $Ca^{++},io$ ), and 1,25 dihydroxyvitamin D (% 1,25D). PRA = plasma renin activity.

An excess cytosolic free calcium level of extracellular origin is the fundamental lesion accounting for the enhanced sensitivity to calcium channel blockade in salt sensitive hypertension, the suppressed plasma renin values, and lower serum ionized calcium levels observed in salt-dependent forms of hypertension. In these subjects, reversing this extracellular vis a vis intracellular maldistribution of calcium thus lowers blood pressure while restoring serum ionized calcium levels and renin values back toward normal. Therefore, for low renin, salt-sensitive hypertensive patients, calcium channel blocking agents should be the drug of first choice.

Identifying the salt-sensitive subject may require a 3-6 month trial of low salt intake. If the patient experiences a significant fall in pressure, then one may presume him to be salt-sensitive. If a further lowering of pressure is required, consider calcium channel antagonist

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*...[C]alcium channel blockers interfere with the mechanism by which salt raises pressure in salt-sensitive individuals.*

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therapy. A low plasma renin activity value can also identify the salt sensitive subject for whom calcium channel blockade is the most appropriate drug choice (see Figures 5,6). Lastly, elderly and black hypertensive populations are also characterized by a higher prevalence of salt-sensitive hypertensive disease, and exhibit a commensurately greater antihypertensive response to calcium channel blockade compared to beta blocking agents or converting enzyme inhibitors. Based on all of the above, therefore, clinical criteria that distinguish subjects for whom calcium channel antagonist therapy will be most beneficial include: i) lower serum ionized calcium levels, albeit still within the normal range, ii) lower plasma renin activity, and iii) dietary salt sensitivity. Each of these criteria, in turn, reflects the same underlying lesion-increased cytosolic free calcium of extracellular origin.

### The Relation of Dietary Calcium to Calcium Channel Antagonist Therapy

Since oral calcium supplementation is used as an adjunct to the prevention and therapy of osteoporosis and since calcium could antagonize the effects of calcium channel blocking drugs, is the use of calcium channel blockers compatible with consuming extra amounts of calcium? We investigated this issue by adding either calcium carbonate (500 mg q.i.d.) or placebo tablets to ongoing therapy with

the calcium channel blocking drug, isradipine. We observed that isradipine in the presence of oral calcium supplementation lowered blood pressure, especially diastolic pressure, to a greater extent than isradipine together with a placebo tablet. In parallel with the further fall in blood pressure, we observed a further lowering of cytosolic free calcium with the calcium-calcium blocker combination compared with the placebo-calcium blocker treatment.<sup>14</sup> This

is understandable in view of the normal physiological suppression of PTH and 1,25 D levels in response to increased oral calcium intake.

### Summary

In summary, alterations of cellular calcium metabolism, characterized in part by excess steady-state cytosolic free calcium levels, represent at least one necessary component of the pathophysiology underlying elevations of blood pressure and many, if not all of the other tissue abnormalities contributing to cardiovascular risk in subjects with 'essential' hypertension, such as cardiac hypertrophy and insulin resistance. Furthermore, the extracellular origin of this excess cytosolic free calcium is a characteristic feature of salt-sensitive forms of hypertensive disease, and helps to explain the suppressed plasma renin activity and lower serum ionized calcium levels observed in sodium-dependent hypertension. Therefore, calcium channel blockade, by interfering with the calcium-based mechanism by which dietary salt elevates pressure, is the drug class of choice in the treatment of salt-sensitive hypertension in low renin, black, and elderly populations. By reversing the pathophysiologic process underlying cardiovascular risk in many organ systems, rather than just by lowering the blood pressure, it also holds out the promise,

when used in appropriately sensitive subjects, of improving long-term clinical outcomes to a greater extent than has been obtained with older, more non-specific forms of antihypertensive therapy.

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## Calcium Antagonists in African-American Patients

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When initiating monotherapy for the treatment of essential hypertension, multiple determinants factor into the decision. The goal of treatment is to lower blood pressure and lessen the likelihood of progression to target organ failure.

Physicians frequently prioritize these determinants and make decisions to initiate monotherapy utilizing the race of an individual. All too often, however, the black/white issue is overstated and given too much consideration. The overall goal of this review is to suggest the appropriate "role" for racial profiling in the initial selection of an anti-hypertensive agent.

### Epidemiologic Considerations

Figure 1 demonstrates that blood pressure levels can predict the likelihood of a patient developing a cardiovascular event. The data

FIG 1.—Relative risk of stroke and CHD, estimated from the combined results of prospective observational studies for five categories of DBP. (Estimates of the usual DBP in each baseline DBP category are from mean DBP values in the Framingham study recorded 4 years after baseline measurement.) The *solid squares* represent disease risk in each category relative to risk in the whole study population (square size is proportional to the number of events in each DBP category). *Vertical lines* represent 95% confidence intervals for the estimates of relative risk. (Reproduced with permission from MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-773.) Reprinted with permission by *The Lancet Ltd* ©1990.

represent a meta-analysis of multiple studies demonstrating a direct relationship between diastolic blood pressure and both stroke and ischemic heart disease.

The rationale for treating elevated blood pressure is clear and carries particular potential benefits for African Americans who are at a greater risk of developing hypertension and its sequelae. As shown in Figure 2, as the age of a population increases, the risk of hypertension rises. This risk is particularly strong for African Americans.

### Renal Disease

African Americans also distinguish themselves from other ethnic and minority groups with higher death rates from strokes, when compared to Hispanics, Asians, Pacific Islanders and Native Americans.<sup>1-2</sup> African Americans have near-epidemic rates of End Stage Renal Disease (ESRD). While there are multiple etiologies for ESRD, hypertension is the most common cause in African Americans, diabetes in Native Americans, and glomerular nephropathy in Asian Americans.<sup>3</sup> A curious observation concerning the control of blood pressure in African Americans is that treatment of elevated blood pressure may not provide similar benefits in renal function in black versus non-black subjects. The Multiple Risk Factor and Intervention Trial provides information on the effect of BP control on renal function in both black and white subjects. Non-blacks had a lower creatinine than did the black subjects.<sup>4-6</sup> Over the six-year follow-up, non-blacks had decreased creatinine levels, while receiving the exact same therapy as blacks; at the end of the six years of follow-up, the levels were back up to baseline. To the contrary, African Americans began with higher creatinine and over the course of the study, creatinine became even higher. Thus renal disease is of special concern in African Americans.<sup>7</sup>

FIG 2.—Mean systolic and diastolic blood pressures for white and black men and women in various age groups in the 1976-1980 National Health and Nutrition Examination Survey (NHANES II). (Reproduced with permission from Rowland M, Roberts J. Blood pressure levels and hypertension in persons ages 6-74 years. United States, 1976-80. *NCHS Advance Data, No. 84, Vital and Health Statistics of the National Center for Health Statistics*. US Department of Health and Human Services. Washington, DC, Oct 8, 1982.)

## Lifestyle Modification

When it comes to treatment, the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure advocates for lifestyle modification as initial therapy.<sup>8</sup> The value of this intervention cannot be over-emphasized. Aerobic exercise can help patients maximally vasodilate blood vessels to skeletal muscle and thereby change glucose and insulin metabolism in skeletal muscle.<sup>9</sup> Lifestyle modifications are particularly useful in African Americans as this ethnic group has excess rates of hypertension and diabetes. Prescription for lifestyle modifications should be given by culturally competent individuals whenever possible. Metabolic problems, such as insulin resistance, occur in the skeletal muscle. Therefore, benefits for blood pressure and metabolic aberrations that impart cardiovascular risk are achieved with lifestyle modification.

*Lifestyle modifications are particularly useful in African Americans as this ethnic group has excess rates of hypertension and diabetes.*

## Pharmacologic Intervention

When the health-care provider elects adding antihypertensive drugs to the regimen, the long-term clinical trial data demonstrating the impact of diuretics and beta blockers on morbidity and mortality must be given priority. In the fall of 1997, there will be data available on morbidity and mortality from a calcium channel blocker based regime, the Hypertension Optimal Treatment Study (HOT). With morbidity and mortality data on calcium blockers and ACEI's the prioritization of antihypertensive medication may be modified in the near future.

Many physicians and researchers believe that unique and special recommendations for African Americans are needed. Most would suggest that blacks should receive diuretics first and avoid potent vasodilators. Much of that theory lies in misconceptions about race and its impact on the clinical management of patients. Race is a biological construct that refers to the sub-categorization of a population. Characteristics of a race include the physically distinguishable features that differ from other subspecies and the specific geographic region that the race inhabits. In America, however, we tend to use one phenotypic characteristic that typifies a group and label it a "race." For example, with skin tone, "black" is considered a racial description whether you are from Australia or Africa, despite the fact that these two geographical regions have totally different genetic lineages. Perhaps the most incorrect race categorization is within the white race. In America, anyone who speaks Spanish may be considered Hispanic. It would be difficult to define genetic markers to describe some of the attributes that we, in America, consider race-related.

A second misconception that leads us to different treatment recommendations for blacks is that blacks are thought to have expanded plasma volume. When plasma volume is expanded, there is a compensatory low plasma renin activity. This observation is used to substantiate recommendations for preferring the usage of diuretics while deferring the usage of ACEIs. Further, agents that cause potent vasodilation will result in expanded plasma volume and will not be advantageous in blacks. Very few studies in the literature confirm that

FIG 3.—Average mean reduction in blood pressure from prospective trials during 1988-1993 involving African Americans.

blacks have expanded plasma volume. In fact, the majority of black and white hypertensives are euolemic or plasma volume contracted. Less than a third of blacks are plasma volume expanded.<sup>10</sup> Therefore, there is little physiological data to support this drug treatment strategy.

Using the Medline database, 13 trials were identified between 1988 and 1992 that examined the response rates from different antihypertensive drugs in African Americans (Figure 3). It could be anticipated that approximately two-thirds of subjects respond to any agent. In blacks, the response rate was between 60 and 70 percent whether the agent was a calcium channel blocker, ACE inhibitor or diuretic.<sup>11</sup> The magnitude of BP reduction is greatest with calcium channel blockers and diuretics.

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## Conclusion

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Despite the recent controversy, calcium antagonists are one of the most commonly prescribed antihypertensive agents. A review of the possible uses for calcium antagonists indicates many opportunities for conservatively treating more than one problem. For instance, a drug from the phenylalkylamine group would be very useful for a patient with recurrent supraventricular tachycardia and hypertension.

Although there continues to be multiple uses for calcium antagonists, like all other classes of drugs, there are associated side effects. These side effects include: constipation with the phenylalkylamines, asthenia with the benzothiazepines, flushing and tachycardia with the short-acting dihydropyridine group, and headaches and edema with the long-acting dihydropyridines. Verapamil has the potential for complete heart block, especially in patients who have renal insufficiency. It is metabolized to norverapamil, which is renally excreted and is pharmacologically active. Diltiazem may cause heart failure, contrary to popular belief, and the short-acting dihydropyridines may precipitate angina. Physicians must also be aware of drug-drug interactions with verapamil and diltiazem. These drugs increase digoxin, quinidine, theophylline, and carbamazepine levels. Verapamil and diltiazem interact with lithium causing loss of control in bipolar syndrome from decreasing levels of lithium. There is also a risk of myocardial depression or frank heart failure when combining the non-dihydropyridines with antiarrhythmics and beta-blockers and the potentiation of sinoatrial and atrioventricular block in combination with digitalis or beta-blockers.

It is also true that calcium antagonists are myocardial depressants since calcium is necessary for myocardial contraction. In one study, an electrically isolated heart muscle was made to be independent of preload and afterload. In this case, nifedipine was a more potent myocardial depressant than verapamil, diltiazem or isradipine. However, because of afterload reduction, nifedipine appears to be less of a myocardial depressant. A current study, the PRAISE trial, suggests no adverse effect of amlodipine in the setting of congestive heart failure—especially for patients with non-ischemic cardiomyopathy.

Avoidance of using the short-acting dihydropyridines for hypertensive urgencies is also prudent because of an uncontrolled drop in systolic and diastolic blood pressure. Short-acting dihydropyridines should not be used for hypertensive emergencies or hypertension treatment. Patients may not have the appropriate organ flow reserve to allow them to survive such an event. Therefore, the nifedipine-induced ischemia is a potential problem. Also, there is no FDA indication for such a use.

Fortunately, there are studies in progress to answer the question as to whether or not it is dangerous to lower blood pressure with calcium antagonists. The International Nifedipine Study Intervention as Goal in Hypertension Treatment (INSIGHT) randomized nearly 6,600 patients. One objective of this double-blind comparison of a diuretic and an extended-release nifedipine with or without atenolol

is to assess the rate of morbidity (stroke, myocardial infarct, heart failure or vascular death). A secondary objective is to assess total mortality, vascular mortality and events. Studies of this type will help answer the question as to whether or not it makes a difference as to how we lower blood pressure. The ongoing Calcium Antagonist in Blacks study, sponsored by ISHIB and funded by Bayer Corporation, is a double-blind, randomized, multi-comparison of three dihydropyridines. It will look at socio-economic factors as well as the drugs' efficacy for lowering blood pressure.

And, finally as it has been mentioned, cost is an issue for our patients. Because of the competition that exists among multiple pharmaceutical companies, we are offered cost options for treating patients. For example, only one choice of a benzothiazepine existed at premium retail prices a few years ago. Now, however, we have diltiazem alternatives. In addition there are alternatives to the more expensive dihydropyridines of Norvasc and Procardia XL: Sular (nisoldipine), DynaCirc (isradipine), a BID drug, Plendil, (felodipine), and Adalat CC (nifedipine) (*Med. Lett. Drugs. Ther.* 1996; 38:13-14).

In conclusion, calcium antagonists should be considered for blacks and whites as well as young and old patients. They should be considered for patients who have lipid disorders, diabetes, stable angina, asthma and peripheral vascular disease. They may be used for patients who have depression and impotence.

We have a group of drugs that continue to be useful and we know will continue to be investigated. When we treat our patients, we have to control blood pressure. We also have to look at other risk factors so that we lower blood pressure without negatively impacting the quality of life. We must consider all these issues while remembering that the most important thing is what happens to the blood vessels and what it takes to help patients survive.

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*In conclusion, calcium antagonists should be considered for blacks and whites as well as young and old patients.*

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## Self-Assessment Quiz

- Which of the following compounds is not associated with its proper class?
  - Verapamil is in the class of phenylalkylamines.
  - Nicardipine is in the class of benzothiazepines.
  - Nifedipine is in the dihydropyridine class.
- The coat-core drug delivery system has a light protective film coat that surrounds a slow-release hydrophilic gel and an inner coat that is fast-released.
  - True
  - False
- Which of these drug delivery systems utilizes little beads that have a rate control coating to allow for a gradual delivery through the gut and colon?
  - The Geomatrix delivery system
  - The Spheroidal Oral Delivery Absorption System
  - The Gastrointestinal Therapeutic System
- Which study trial found that PVCs could be controlled with flecainide and encainide, but that mortality may increase?
  - The SHEP Trial
  - The CAST Trial
  - The HOT Trial
- The fall and subsequent rise in blood pressure concomitant with the rise and fall of nifedipine levels after immediate-release nifedipine is referred to as:
  - Cyclical response rate
  - The bungee phenomena
  - The boomerang effect
- Metoprolol has been found to reduce the frequency and duration of ischemic episodes and controlled ambulatory blood pressure in hypertensives with angina.
  - True
  - False
- Which study has offered preliminary reports regarding slow-release and slow-onset calcium channel blockers as beneficial, or at least of neutral impact to morbidity and mortality events?
  - The DEFIANT trial
  - The Stone trial
  - The PRAISE trial
  - All of the above
- Sustained-release calcium channel blockers reduce right ventricular mass.
  - True
  - False
- Defects in cellular ion levels, which predict the extent of many different aspects of hypertensive disease are characterized by:
  - Elevations of cytosolic free calcium and the subsequent suppression of free intracellular magnesium levels
  - Decreased levels of cytosolic free calcium and the resulting increase of free intracellular magnesium levels.
  - Elevations of cytosolic free calcium and elevations of free intracellular magnesium levels.
- Salt-induced calcium that was shifted from the extracellular to the intracellular compartment has been associated with a parallel rise in blood pressure.
  - True
  - False
- In regard to salt-sensitive hypertensives, which of the following drug therapies have been found to be the most effective in the treatment of hypertension, especially within low renin, black, and elderly populations?
  - ACE inhibitors
  - Diuretics
  - Calcium channel blockers
- Which ethnic group is known for having the highest death rate from strokes?
  - Hispanics
  - Native Americans
  - African Americans
- The Fifth Report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure recommends which of the following as the initial treatment regimen?
  - Diuretic monotherapy
  - Lifestyle modification
  - Use of ACE Inhibitors
- What percentage of the African-American population is considered to have plasma volume expanded?
  - More than 50%
  - Less than 33%
- One side effect from the use of calcium antagonists in the phenylalkylamine class is:
  - Asthenia
  - Tachycardia
  - Constipation
- Which current study is a double-blind, randomized, multi-comparison of three dihydropyridines assessing the socio-economic factors as well as the efficacy of the drug therapy for lowering blood pressure?
  - The Calcium Antagonists in Blacks Trial
  - The INSIGHT study
  - The PRAISE Trial
- For patients taking a once-daily ACE inhibitor, blood pressure control wanes after midnight.
  - True
  - False
- One preferred therapy for systolic failure in hypertensive patients at the present time is:
  - ACE inhibitors
  - Calcium channel blockers
  - Diet control
- Hypertension carries other peripheral manifestations, such as:
  - Acne and other skin disease
  - Left ventricular hypertrophy
  - Glaucoma
- Race is a biological construct that refers to the sub-categorization of a population.
  - True
  - False

**13th International Interdisciplinary  
Conference on  
Hypertension in Blacks  
July 11-16, 1998  
Charleston, South Carolina**

For many years, South Carolina has had the unfortunate distinction as 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

## About ISHIB

The International Society on Hypertension in Blacks (ISHIB) is a unique nonprofit professional membership organization devoted to ethnicity and disease. 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 and lipid disorders. 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 concomitant diseases, 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.



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