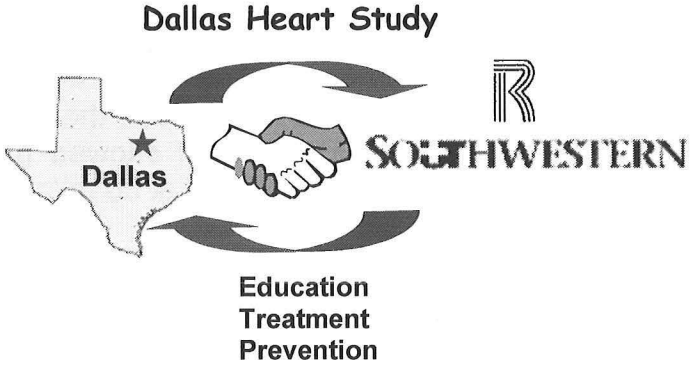
ETHNICITY, HYPERTENSION, AND THE DALLAS HEART STUDY



INTERNAL MEDICINE GRAND ROUNDS
UT Southwestern Medical Center

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Interests: Hypertension in Special Populations (African Americans, Diabetics, Chronic Renal Failure), Neural Mechanisms of Hypertension

This is to acknowledge that Ron Victor, MD has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Victor will not be discussing off-label uses in his presentation.

CASE PRESENTATION

The patient is a 42 year-old African American man with hypertension first diagnosed incidentally in 1999. At that time, his BP was 180/100 mm Hg and he was obese with a BMI of 30 kg/m2. The eye grounds showed arteriolar narrowing and arteriovenous crossing-defects and the remainder of the physical examination was unremarkable. The serum creatinine was 1.5 mg/dl, serum potassium 4.2, and fasting glucose 90.

He was treated with a multi-drug regimen of HCTZ 25 mg per day (thiazide diuretic), amlodipine 10 mg per day (dihydropyridine CCB), and clonidine 0.3 mg three times daily (central sympatholytic). His blood pressure at first improved but then became increasinglydifficult to treatment with office pressures in the160s/90s. He was referred in 2002 for evaluation and treatment of refractory hypertension. On examination, his blood pressure was 165/95 mmHg, EKG showed LVH, the serum creatinine was 2.6, serum K 4.6, glucose 95. A 24h urine specimen showed protein excretion of 550 mg/day and the creatinine clearance was calculated at 30 ml/min/1.73m2.

Two key questions are: (1) why such aggressive hypertension by age 40, and (2) what changes can we make in his medical regimen to improve his blood pressure and impact his prognosis by delaying the onset of end-stage renal disease and preventing stroke and myocardial infarction?

To address these questions, I will review hypertension in African Americans from four perspectives: epidemiology, gene-environment interactions, selection of antihypertensive medications, and community-based interventions. This review is not encyclopedic but rather provides an overview of several on-going areas of clinical research at our medical school, in particular the Dallas Heart Study. Several more comprehensive reviews are recommended[1-7].

I. EPIDEMIOLOGY OF HYPERTENSION IN AFRICAN AMERICANS.

Hypertension in African Americans constitutes an enormous public health problem. Compared with whites, Hispanics, and all other ethnic groups, hypertension is not only more prevalent in blacks, but it also starts at a younger age, is more severe, and causes far greater target organ disease leading to excessive death and disability from coronary artery disease, heart failure, stroke, and renal failure[1-7].

As early as 1932, James M. Adams, an industrial physician in New Orleans, noted the excessive burden of hypertension in African Americans[8]. He found that blood pressures were higher in African American compared with Caucasian workmen and that the African American workmen missed twice as many days from work due to heart and kidney disease. In the Bogalusa Heart Study of school-age children, blood pressures of African American boys and girls were a few mm Hg higher at every age group than of white boys and girls[2]. However, as shown by the latest NHANES data, the major ethnic differences in hypertension prevalence become apparent in young adulthood[6].

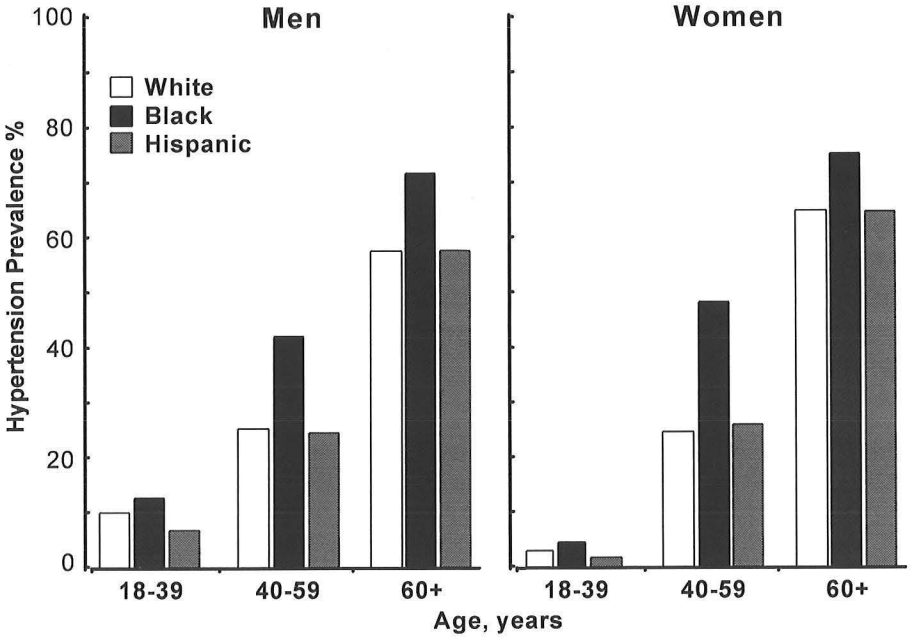


Figure 1. Hypertension prevalence in U.S. adults by age, gender, and ethnicity. From NHANES 1999-2000 (IH Hajjar and TA Kotchen, *JAMA*, 2003)[6].

In both men and women of all three major ethnic groups in the U.S., hypertension prevalence rises sharply with age. African Americans have more hypertension at all ages but the greatest differential is at 40-59 year old age group. As hypertension is present in almost 40% of African American men in the 4th decade of life (compared with 20% in White or Hispanic men), our patient is by no means atypical.

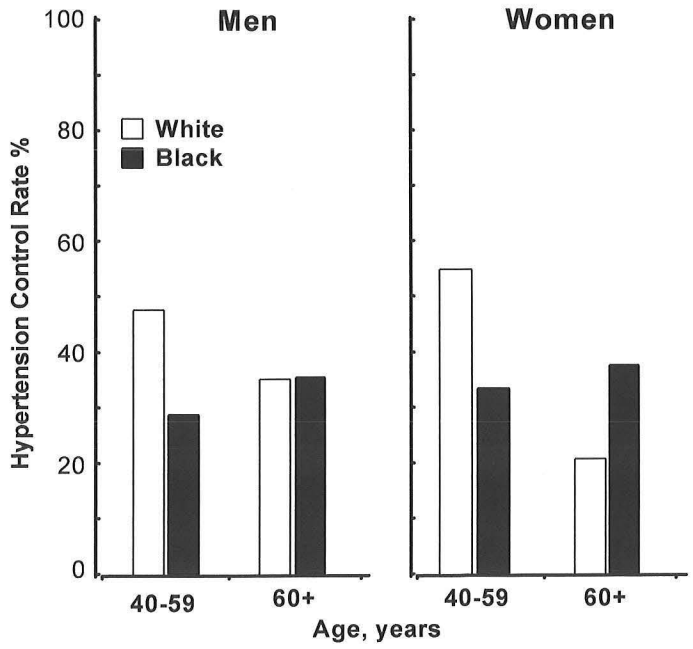


Figure 2. Hypertension control rates by age, gender, and ethnicity. It is at the younger age group that hypertension control rates (% of all hypertensives with BP < 140/90) are worse in African Americans than Caucasians. From NHANES 1999-2000 (IH Hajjar and TA Kotchen, *JAMA*, 2003)[6].

Again, our patient is illustrative.

The greater prevalence of hypertension and lower control rates in younger African American adults explain much of the dramatic ethnic disparity in hypertensive target organ damage. The discrepancy is particularly evident in the "expanded stroke belt, which includes the Southeastern United States and Texas[9-11]. As many as 30% of all deaths in hypertensive black men and 20% of all deaths in hypertensive black women have been attributed to uncontrolled hypertension[12]. In 1998, hypertension caused 3.3 times more deaths in black than white women and 3.7 times more deaths in black than white men[12]. The overall death rates from hypertensive stroke and hypertensive heart disease are 1.8 and 1.5 times greater respectively in blacks than whites and the occurrence of hypertensive nephrosclerosis is 4.2 times greater[12]. In the 18-45 year old age range, the incidence of nephrosclerosis requiring hemodialysis is 20 times greater in blacks than whites[13, 14].

Whether in African Americans the excessive nephrosclerosis is related to susceptibility genes or simply higher blood pressures is an open question. Environmental and societal issues must be involved because in the past two decades the incidence of end stage renal disease from hypertension has leveled off in whites but continued to increase dramatically in African Americans, causing the ethnic gap to widen.

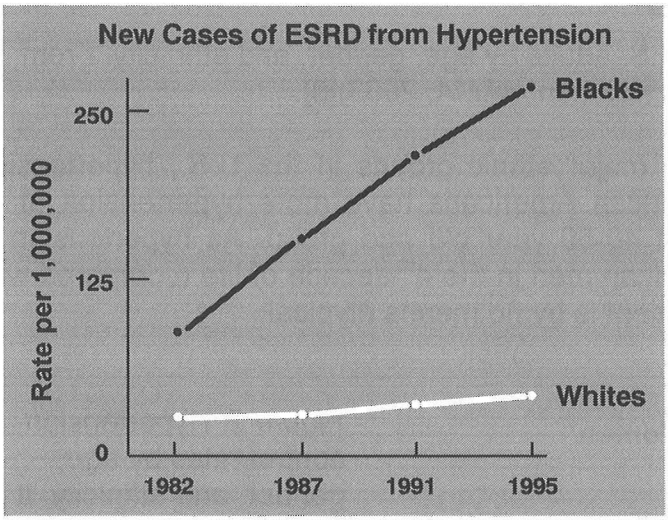


Figure 3. Secular trends in non-diabetic end-stage renal disease from hypertension (i.e., hypertensive nephrosclerosis) by ethnicity. Source: US Renal Database System, 1999.

Despite a dramatic decline in U.S. death rates from cardiovascular disease over the past three decades, cardiovascular mortality remains higher among African Americans than whites or other demographic groups and the ethnic gap in cardiovascular deaths is widening, especially among individuals less than 65 years of age[12]. The ethnic differential, measured as years of productive life lost, is two times greater for African American women than white women and four times greater for African American men than white men[12]. Within each ethnic and gender group, cardiovascular mortality has been shown to vary markedly by regions, states, and counties[15, 16]. This remarkable geographic variation suggests the importance of environmental exposures. In Texas, the widening ethnic gap in cardiovascular mortality is particularly evident here in Dallas County (Figure 4).

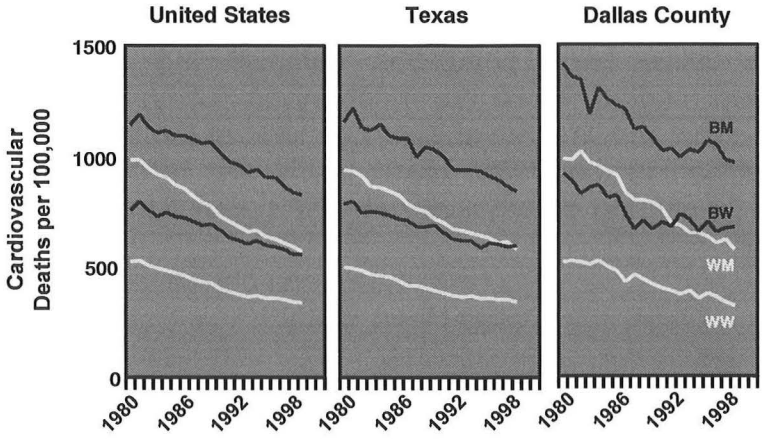


Figure 4. Secular trends in total cardiovascular mortality for NH Black men (BM) and women (BW) and white men (WM) and women (WW) for the U.S., Texas, and Dallas County. Ages 35-84 Y, age-adjusted to Census 2000. ICD 9: 390-448.9 Source: CDC Wonder, 2002.

In Dallas cardiovascular death rates have declined progressively in white men and women throughout the last two decades but stopped declining in African American men in women by1990. For the first time, cardiovascular mortality in African American women now exceeds that in white men, possibly foreshadowing an adverse secular trend across the U.S.

Because the major cardiovascular diseases are such complex phenotypes, pinpointing the key sources of ethnic inequalities in cardiovascular health is going to require extensive knowledge not only of risk factor profiles and the genetics of individuals and populations but also of the contemporary social context in which these differences exist. Such a multidisciplinary approach is expensive and it requires a team of investigators who can focus a wide range of scientific expertise on this one large clinical problem. With generous funding from the Donald W. Reynolds Foundation, my colleagues and I have the opportunity to study this problem from many different angles by establishing a Cardiovascular Clinical Research Center at UT Southwestern.

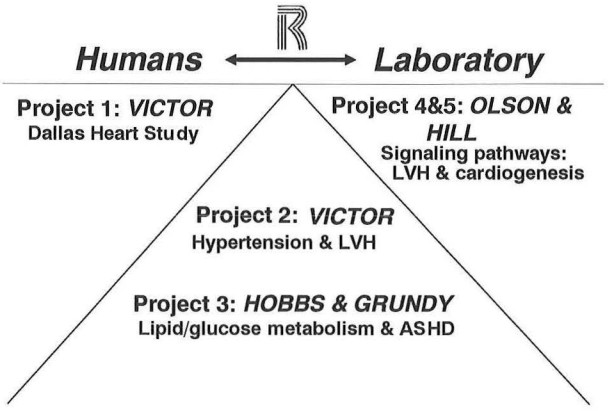


Figure 5. Spectrum and integration of clinic and basic research in the Donald W. Reynolds Cardiovascular Clinical Research Center at UT Southwestern.

Project 1, the Dallas Heart Study, is the epidemiological platform for all clinical research in the center (see below). In particular, it supports mechanistic substudies in the General Clinical Research Center (GCRC). Project 2 studies the mechanistic underpinnings of excessive hypertension and hypertensive heart disease in African Americans. Project 3, led by Dr. Helen Hobbs (the center director) and Dr. Scott Grundy, explores ethnic differences in the insulin-resistance metabolic syndrome. The fourth project, led by Drs. Eric Olson and Joe Hill, is integrated bench and *in vivo* mouse research that is rapidly elucidating new candidate genes for ventricular hypertrophy and novel therapeutic targets and approaches for interrupting the hypertrophic process in the heart and using stem cells for cardiac repair.

The Dallas Heart Study. In general, there a two types of clinical research: epidemiological studies, which utilize large population samples but are largely descriptive, and laboratory -based studies, which are mechanistic but typically utilize small non-representative samples that the limit the ability to generalize the findings to a diverse population. The concept behind the Dallas Heart Study was to combine the advantages of both approaches by utilizing an ethnically diverse population sample for the study of disease mechanisms.

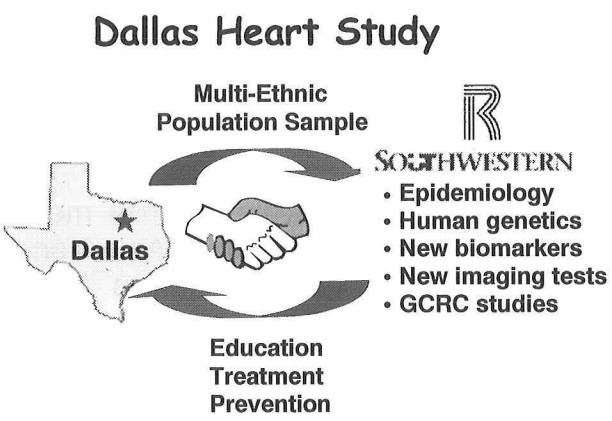


Figure 6: Goals and objectives of the Dallas Heart Study.

In the first phase of the research, we sought to utilize a multi-ethnic population sample: (a) to carefully estimate ethnic differences in cardiac risk factors in Dallas, (b) for genetic epidemiology, (c) to discover new biomarkers of early disease, (d) to evaluate new imaging tests for early detection of subclinical heart disease, and (e) to support mechanistic studies in our GCRC. In the second phase, our goals are to use this new information to enhance the education, prevention, and treatment of heart disease in the community we serve. The long-term objective is to reduce cardiovascular death rates in Dallas County and begin to close the gap in the burden of heart disease between the different ethnic groups in this community.

As a first step in achieving these goals, we assembled a population sample of Dallas County residents to collect three sets of data:

1. Household Survey: a 90 minute in-home health interview in adults, conducted by trained field staff.

2. Biospecimen Collection: an in-home collection of blood and urine specimens after an overnight fast, conducted by trained phlebotomists.

3. Non-Invasive Imaging Tests: a battery of imaging tests, conducted by trained medical personnel at our UT Southwestern research clinic (Roger's Imaging Center).

Community Partnership/Informed Consent. During the nine months prior to initiation of subject recruitment, a partnership between our research team and Dallas County community leaders was established by creating a Community Advisory Board for the Dallas Heart Study. The Community Advisory Board was co-chaired by a prominent African American minister, a Hispanic civic leader, and a Caucasian businessman and included over 250 civic leaders and local government officials. The community advisory board included an ethics committee that developed the subject consent forms, which then were approved by the institutional review boards at both UT Southwestern and

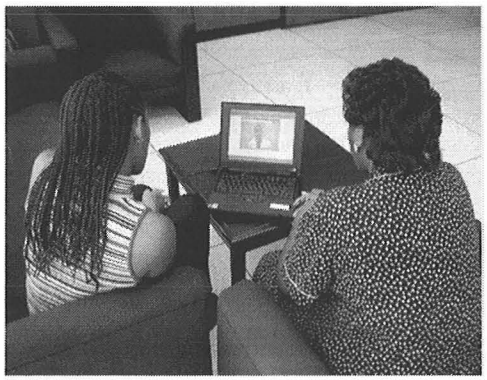
Research Triangle Institute, who were responsible for developing the sampling frame and managing the field staff.

To augment the informed consent process, ethnic-specific videos were developed and loaded on the laptop computers carried by each of the field staff recruiters.

Figure 7. Recruitment videos.

We also hired a fulltime director of community relations, Ms. Myra Hollins, who developed and implemented a broad-based program of community outreach.

Sampling Methodology. To support our mechanistic studies in the GCRC, we decided on a final sample of 3000 adults to complete all three parts of data collection. We wanted 50% of the sample to be African American (Non-Hispanic Black) and 50% to be women. To fulfill these requirements would have required that we begin with a random sample of 45,000 addresses. Because the cost was prohibitive, a more economically efficient approach was to over-sample in predominately African American neighborhoods, which reduced the sample size requirements to 15,000 addresses. We began by purchasing a complete list of postal addresses in Dallas County (over 800,00 addresses) and used the U.S. Census data to develop a random sample of 15,000 addresses that would meet our study requirements. Trained went to as many of these households as they could locate and gain access to (over 12,000) in order to make a complete list of people living in each house. From this list, we developed a random sample of 7,823 individuals 18 to 65 years of age who were eligible to participate.



Visit 1: Home Interview *(Figure 8).*
Of these, 6101 individuals ages 18-65Y completed the home interview, which was conducted with the aid of laptop computers. The interview included a detailed medical, social, and family history about heart disease and cardiac risk factors as well as detailed questions about health beliefs. In addition. we assessed height and weight and measured blood pressure five times with automated sphygmomanometers to reduce subjectivity in the measurement. We achieved our recruitment goals in that 55% of these subjects were African American and 53% were women.

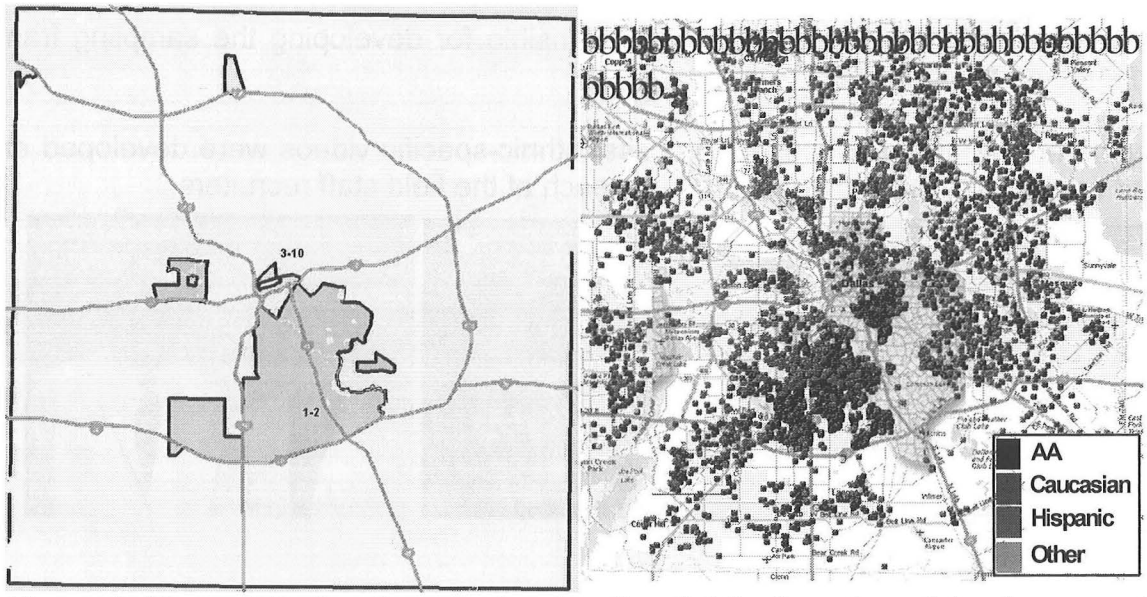
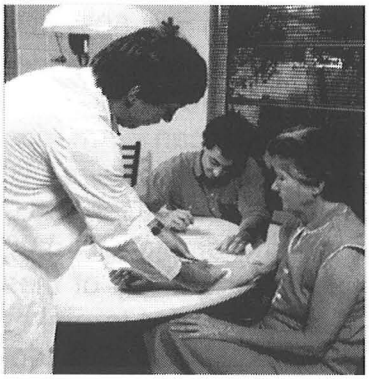


Figure 9. Maps of Dallas County showing the distribution of our interview sample. The left panel shows the areas with the highest concentration of African American households (dark areas) in which we oversampled and the right panel is a plots our participants' houses on geographic coordinates.



Visit 2: Home Phlebotomy *(Figure 10).* After the home interview, subjects ages 30-65 were invited to participate in phlebotomy and clinic tests. Of those eligible (n=4,525), 3,398 subjects went on to complete the phlebotomy visit on a separate day. This consisted of collection of fasting blood and urine specimens. DNA was isolated from all of these individuals and stored for subsequent analysis. Blood pressure was measured five more times with the same automated device.

Visit 3: Clinic Tests

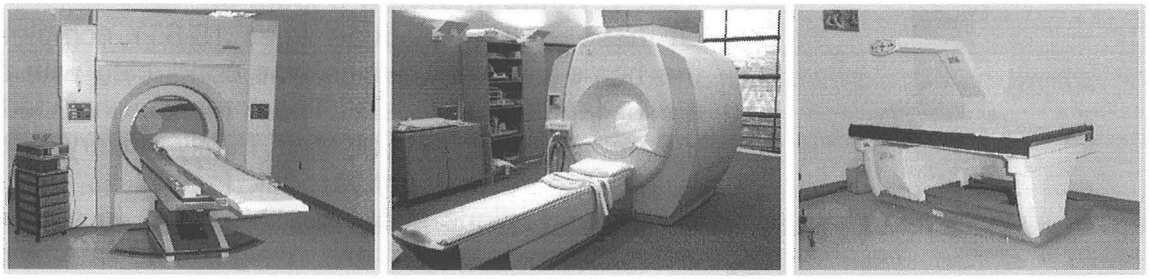


Figure 11. Non-Invasive Imaging Tests. Of the phlebotomy subjects, 2,971 individuals went on to complete the clinic tests. These included measurement of coronary calcification with electron beam computerized tomography (EBCT, left panel); of left ventricular mass and function, aortic distensibility, and subcutaneous and omental fat

with magnetic resonance imaging (MRI, middle panel), and body fat distribution with dual X-ray absorptometry (DXA, right panel). In addition, we obtained EKGs and five more blood pressure measurements.

Our overall participation rates compare favorably with those of other cardiovascular studies in communities[17-22]. Although much has been written about barriers to recruitment of minority research subjects, we achieved very good participation rates (>75%) from all ethnic groups at each step of the process.

II. SUSCEPTIBILITY GENES

Dazzling genetic research has revealed eight forms of severe hypertension that are inherited as Mendelian traits[23]. In each case, the detailed molecular mechanism involves a final common pathway: the ability of the renin-angiotensin-aldosterone system to regulate renal sodium excretion. These Mendelian forms of hypertension are extremely rare and the question is whether defects in any of the same genes contribute to primary hypertension which afflicts 50 million Americans and 7 million African Americans.

The ever-growing list of plausible candidate genes and environmental risk factors thus far has thwarted the genetic dissection of primary hypertension and the susceptibility to hypertensive target organ damage either by the candidate gene approach, genome wide scans, sib pair analysis, or case-control studies[24-26]. The few positive leads have been plagued by lack of reproducibility, with small convenience samples leading to high rates of both false positive and false negative associations[27-29].

In searching for genes that individually impart a modest increase or decrease in the risk of hypertension and hypertensive cardiovascular disease, we have assembled a population-based cohort with much larger numbers of African American cases and controls than in previous genetic association studies which often rely on small groups of clinic patients. A critical feature of our approach is the generation of detailed, rigorously defined phenotypes such as the measurement of left ventricular mass with MRI, which has a much higher resolution than echocardiography.

Importance of Accurately Phenotyping Blood Pressure.
A key question is whether African Americans not only have more hypertension than other ethnic groups but also more rapid acceleration of target organ damage for any given level of blood pressure elevation. This is generally assumed to be the case and fueled the search for susceptibility genes that might accelerate the hypertrophic process to pressure overload. Alternatively, greater target organ damage in African Americans may be due to a greater time-integral blood pressure load, either a longer duration of hypertension prior to entry into the study or to more persistent blood pressure elevations throughout the day.

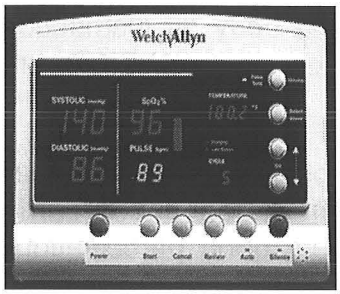


Figure 12. Automatic oscillometric sphygmomanometer. To improve the phenotyping of blood pressure in the Dallas Heart Study, a total of fifteen measurements were obtained, five measurements during each of two home visits and five more measurements in the research clinic. An extensively validated oscillometric sphygmanometer was utilized to enhance accuracy and minimize subjectivity in the measurement[30].

While office blood is clearly a major determinant of cardiovascular risk in epidemiological studies and lowering the blood pressure with drug treatment reduces this risk[3, 31], there is increasing evidence that out-of-office blood pressure is an even better predictor of target organ damage and cardiovascular outcomes[32, 33]. The reason is that the blood pressure in a person's daily life is a better reflection of the time-integral blood pressure load on the cardiovascular system than is the office readings, which can be transiently elevated due to the *white coat* effect, the adrenergic surge in blood pressure caused by the anxiety of having blood pressure measured in the doctor's office.

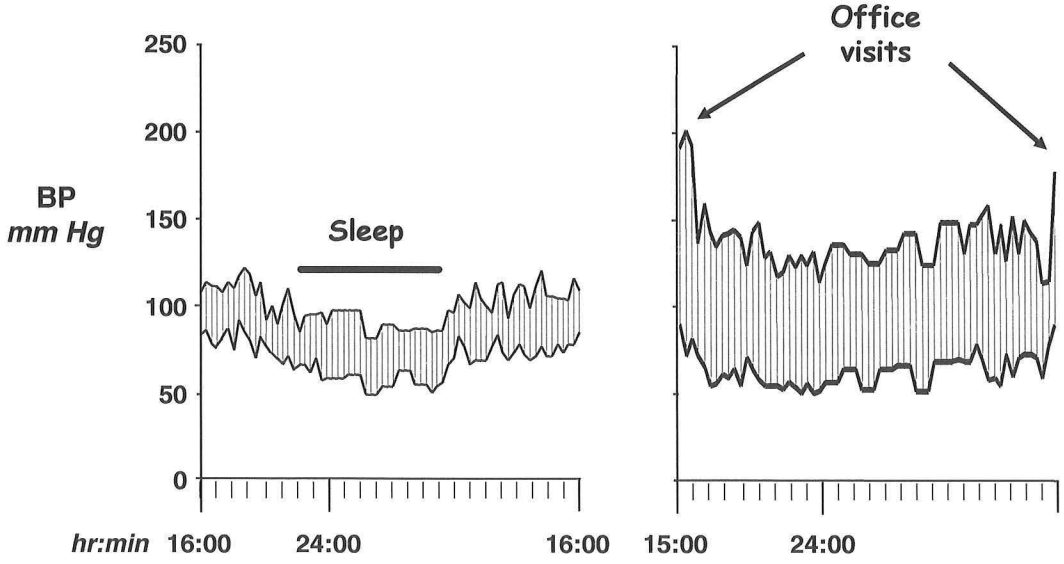


Figure 13. White coat hypertension by ambulatory blood pressure monitoring. The two tracing are from 24h ambulatory blood pressure monitoring which automatically records a person's blood pressure every 20 minutes throughout the day and night. The left panel is from a healthy normotensive Parkland medical house officer, showing the normal nocturnal dip in blood pressure, and the right panel is from an 80 year old woman with a dramatic white coat effect superimposed on mild isolated systolic hypertension (courtesy of Dr. Wanpen Vongpatanasin). Detection of the white coat reaction in the patient prevented over-treatment.

Clinic studies have estimated that up to 30% of patients being treated for hypertension have white coat hypertension and do not need to be treated[32]. However, this is a topic of considerable debate largely between epidemiologists (who emphasize the prognostic importance of office blood pressure) and clinicians (who deal with white coat hypertension in daily practice). The studies in the literature have largely involved Caucasian patients and the prevalence and consequences of white coat hypertension in African Americans is unknown. We are utilizing the Dallas Heart Study cohort to better define the prevalence of white coat hypertension in a multiethnic population and to determine whether such office-only hypertension is or is not accompanied by target organ damage (e.g., LVH).

Ambulatory blood pressure monitoring also has revealed that some patients actually have lower pressures in the office, the flip side of white coat hypertension[33]. Termed *reverse white coat hypertension*, *home-only hypertension*, *white coat normotension*, and *masked hypertension*, there are several highly individualized factors that can cause blood pressure to fall transiently when the patient comes to the physician's office. These include smokers who put out their cigarette before seeing the doctor, difficult patients who take their antihypertensive medications mainly on the day of their office visit, and possibly patients who have such stress in their daily lives that they find the office visit relaxing.

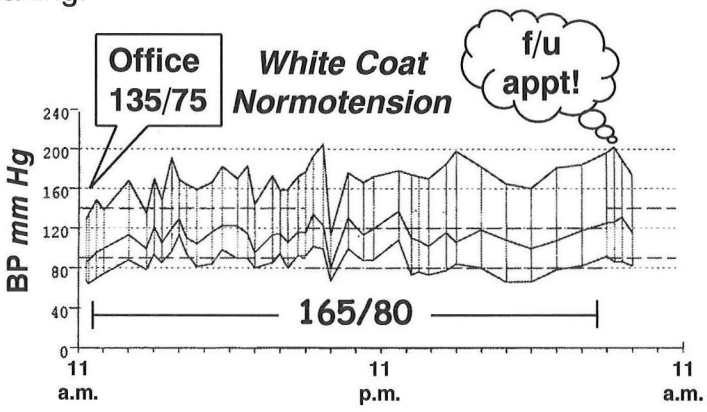


Figure 14. White coat normotension. The 24h ambulatory BP tracing is from a 58 year old African American man. His BP appeared to be well controlled in the office at 135/75 mm Hg but increased sharply as soon as he returned to work, with his out-of-the-office BP averaging 165/80 mm Hg.

Detection of white coat normotension together with echocardiographic evidence of marked LVH lead to an intensification of the antihypertensive regimen. We are investigating the prevalence of such masked hypertension our multiethnic population to determine if reliance on office measurements leads to under-treatment of hypertension and excessive progression of target organ damage in African Americans.

Salt-Induced Hypertension as a Gene-Environment Interaction

One theory holds that individuals living in salt-poor regions of African evolved mechanisms to minimize renal sodium excretion. While efficient sodium reabsorption should provide a survival advantage under salt-poor conditions, this is hypothesized to predispose to salt-dependent hypertension when such individuals are exposed to a high-sodium Western diet. Regardless of the veracity of this theory[34-36], plasma renins are generally lower in African American than Caucasian hypertensive clinic

patients[5]. Low renin hypertension generally is assumed to reflect an expanded blood volume, causing feedback suppression of plasma renin activity. As a cautionary note, elevated blood pressure per se also causes feedback suppression of renin and renin levels fall progressively with progressive loss of nephrons due to increasing age or duration of hypertension. So, lower renin values do not necessarily imply cause-and-effect.

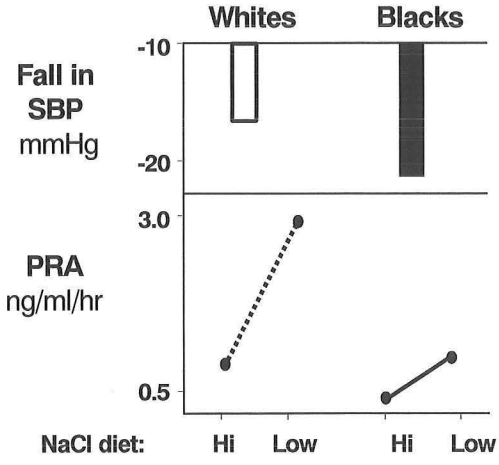


Figure 15. In this clinic study, a low-salt diet was found to cause a larger fall in systolic blood pressure (SBP) in Black than White hypertensives. The proposed explanation is that in the white patients the volume-dependent fall in blood pressure is partially offset by a reactive rise in plasma renin activity (PRA) and thus angiotensin II. By contrast, in the Black patients the reduction in blood pressure is greater because basal PRA is lower and the compensatory increase is blunted. From F. He et al., *Hypertension*, 1998.

At the cell and molecular level, low-renin hypertension could be caused by gain-in-function mutations in the *epithelial sodium channel* (*ENaC*), which is responsible for reabsorption of the final 2-3% of the filtered sodium from the distal nephron[23].

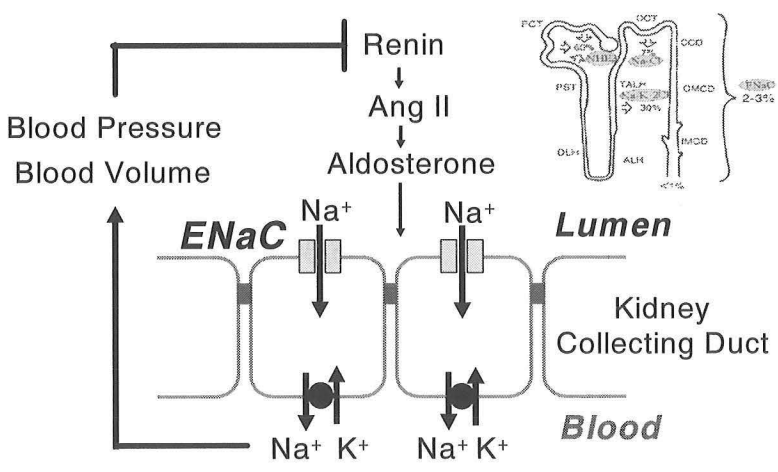


Figure16. Consequences of ENaC overactivity. Increased flux of Na+ from the luminal side of the epithelial cells drives the Na+/K+/ATPase on the basolateral side, increasing Na+ reabsorption and renal K+ excretion. The expanded blood volume causes hypertension and feedback suppression of renin. The serum potassium is reduced.

The number of ENaC channels on the cell surface is the result of a shifting balance between the production of new channels and the internalization and destruction of old channels by a process termed ubiquinization. With a low salt diet, aldosterone secretion causes Na+ reabsorption by preventing channel ubiquinization[37].

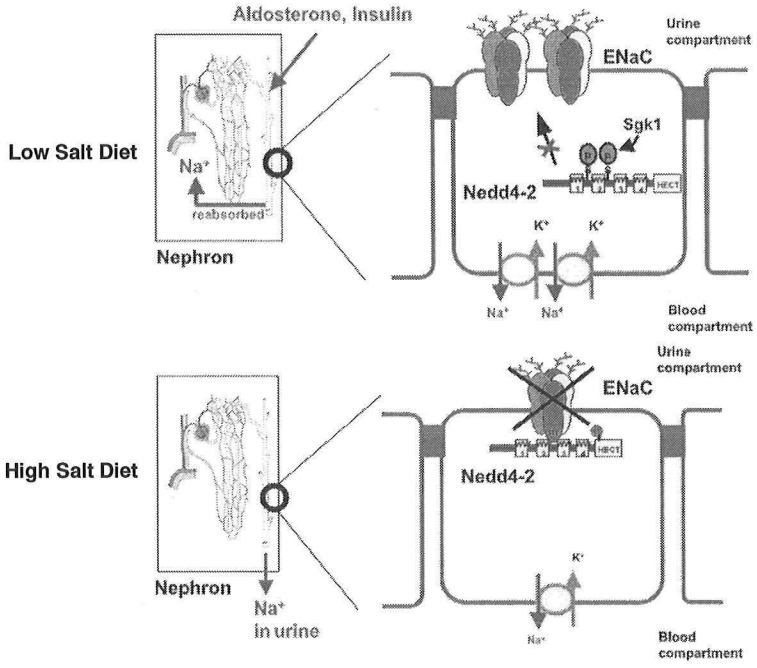


Figure 17. Aldosterone and regulation of ENaC endocytosis. From E Kamynina and O Staub, *Am J Physiol*, 2002.

Aldosterone causes transcription of a kinase that phosphorylates the ubiquitin ligase transcription factor Nedd4 so it cannot bind to ENaC. With a high salt diet, aldosterone is suppressed and Nedd4 is not phosphorylated, allowing ENaC to undergo endocytosis. As a result, more Na+ is excreted in the urine.

There are three ENaC subunits and mutations that truncate 30-50 amino acids of the cytoplasmic C-terminus of the beta or gamma subunit cause Liddle's Syndrome, a form of severe salt-dependent hypertension that is inherited as an autosomal dominant trait[23]. The hallmarks of the syndrome are early onset of familial hypertension, suppressed plasma renins, and hypokalemia.

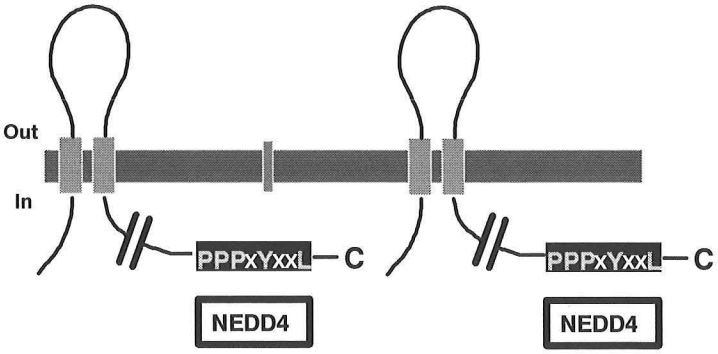


Figure 18. Molecular mechanism of hypertension in Liddle's Syndrome. The truncated C-terminus no longer contains the NEDD4 binding site, so the channels cannot undergo endocytosis, even in response to a high salt diet. This mechanism was worked about by a former Parkland house officer, Dr. Pete Snyder[38-40].

Liddle's Syndrome is very rare and the question is whether there are more subtle gain-in-function mutations that contribute to the high prevalence of hypertension in Blacks[41-45].

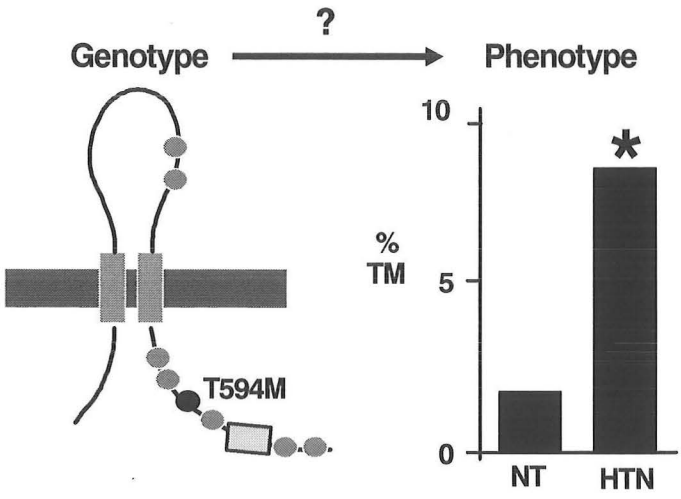


Figure 19. ENaC sequence variations and primary hypertension. Left panel, 8 single nucleotide polymorphisms (SNPs) have been discovered in the beta subunit of the human ENaC gene (Su and Menon, *Drug Met Disp*, 2001). One of these, a missense mutation (T594M), is found only in people of West African descent. Right panel, in a widely cited study, the polymorphism was detected in 2% of normotensive Blacks but in 8% of hypertensive Blacks. From EH Baker et al., *Lancet*, 1998.

A shortcoming of the above study [43]is the small sample size (348 subjects in all yielding a total of 20 TM heterozygotes) derived from a non-random clinic population. We are in the process of determining if we can confirm this association using our large population-based sample. Defective channel ubiquinization is not a plausible mechanism by which this SNP might predisponse to hypertension, because the Nedd4 binding site is left intact.

The same group recently has suggested that all Black hypertensive patients should be genotyped for the T594M polymorphism, reasoning that the ideal antihypertensive agent for such patients should be amiloride, a specific ENaC antagonist[44].

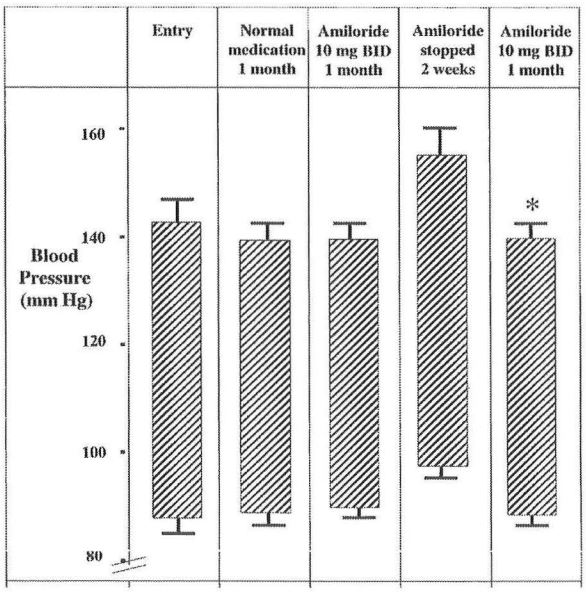


Figure 20. T594M polymorphism and BP response to amiloride. In 9 Black hypertensives with the TM genotype, amiloride alone—normally a weak diuretic--lowered pressure just as well as did a thiazide or loop diuretic in combination with one or two other conventional antihypertensive medications. From EH Baker et al., *Hypertension*, 2002.

These are really pilot data that have not been confirmed using appropriate controls, including patients with similar degrees of hypertension who do not carry this polymorphism.

The genetics of primary human hypertension in general and of pharmacogenetics in particular are areas of active investigation and other sequence variations, or combinations of multiple variations, may prove more promising than the example sited above. Ideally, precise genetic and phenotypic markers would allow each patient to be treated with the best combination of drugs. At the present, however, I am aware of no candidate genes for primary hypertension or for predicting the response to antihypertensive drug therapy that have been proven to withstand the acid test of reproducibility.

III. SELECTION OF ANTIHYPERTENSIVE THERAPY

The lower plasma renin levels common in African American hypertensives may suggest volume-dependent hypertension requiring diuretic therapy[46]. Alternatively, lower plasma renins may be caused by a longer duration and greater severity of hypertension or by concomitant nephrosclerosis, the latter being a compelling indication for ACE inhibitor-based therapy (see below).

As monotherapy, an ACE inhibitor or a β-blocker yield a smaller decrease in blood pressure in older hypertensive African American men than white men[3, 47].

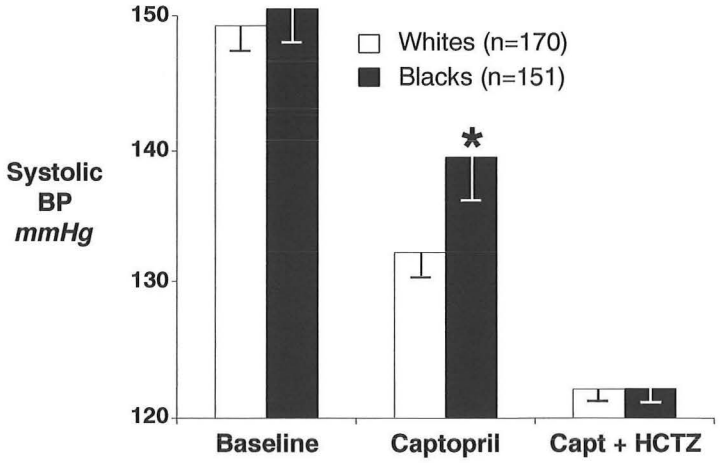


Figure 21. Importance of combination therapy. The key point is that, when higher doses of an ACE inhibitor(or ARB) are used in combination with a thiazide diuretic, antihypertensive efficacy is amplified, and ethnic differences disappear[48, 49]. From, the VA Cooperative Group, *Br. J. Clin. Pharm.*, 1982.

Because combination therapy is required to reach blood pressure goals in most hypertensive patients[3], especially those with more severe hypertension and additional cardiovascular risk factors, the results achieved with monotherapy have less and less practical relevance to modern clinical practice. It takes at least drugs of two different classes to lower blood pressure to < 140/90 mm Hg in most mild hypertensives[50] and three or four different drugs to reach more stringent blood pressure goals in high risk patients[14].

The renin-angiotensin system certainly is one of the most important targets for antihypertensive drug[51]. The interaction of Ang II with G-protein coupled AT_1 receptors accelerates numerous cellular processes that contribute not only to hypertension but also to its end-organ damage, including (1) aldosterone secretion,

which produces renal salt and water retention; (2) peripheral vasoconstriction; (3) growth of cardiac and vascular smooth muscle cells, leading to cardiac and vascular hypertrophy; (4) production of superoxide anions and other reactive oxygen species that inactivate nitric oxide, thereby inhibiting endothelial-dependent vasodilatation; and (5) augmentation of both central sympathetic outflow and prejunctional modulation of norepinephrine release from peripheral sympathetic nerve terminals, thereby leading to excessive stimulation of α adrenergic receptors. For these reasons, drugs that block the renin-angiotensin-aldosterone system are postulated to exert organo-protective effects above and beyond their ability to lower blood pressure.

In this regard, it is important to review the results of the recent Antihypertensive and Lipid Lowering to Prevent Heart Attacks Trial (ALLHAT) because African Americans comprised 35% of the 40,000 patients enrolled[52].

ALLHAT was a monotherapy-based trial in which the thiazide-type diuretic Chlorthalidone was compared against, among other drugs, an ACE inhibitor Lisinopril for the primary endpoint of fatal MI and non-fatal coronary heart disease. For the primary endpoint, the drugs were indistinguishable. But for the secondary endpoint of stroke, differences emerged.

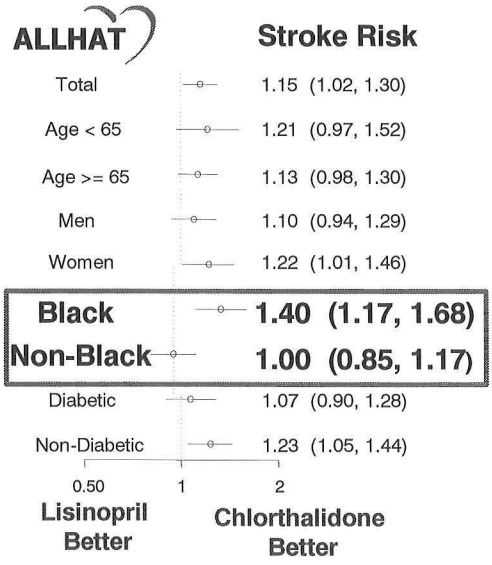


Figure 22. ALLHAT results for stroke. Overall, Chlorthalidone was slightly superior to Lisinopril in preventing stroke and this result was driven largely by the African American participants who experienced a 40% greater reduction in the risk of stroke with the diuretic-based than with the ACE inhibitor-based therapy. The key caveat is that over the 5-year study period, systolic blood pressure in the African American patients was 4-6 mm Hg lower with the diuretic than with the ACE inhibitor. The difference in blood pressure reductions achieved with these 2 different regimens is 50% of the overall systolic blood pressure reduction in ALLHAT, which averaged 10 mm Hg. From ALLHAT Officers, *JAMA*, 2002.

Thus, the ALLHAT data reinforce the importance of lowering blood pressure to prevent stroke in all patient subgroups, including African Americans.

Because of the unequal blood pressure lowering, these data do not speak to the issue of whether or not ACE inhibitors possess special cardioprotective benefits beyond blood pressure or whether such putative benefits vary by ethnicity.

In ALLHAT, overall hypertension control rates were worse for African Americans than for other groups (Black men: 63%, Other men: 70%; Black women: 59%, Other women: 65%)[50]. Because 35-40% of all these study participants were still on monotherapy at

the end of the trial, the ALLHAT data underscore the inadequacy of monotherapy to treat even mild hypertension and speak to a greater need for combination antihypertensive therapy, especially in high risk individuals (i.e., African Americans)[2].

For the majority of hypertensive patients, clinicians should place a far greater emphasis on the numbers of medications needed to lower the blood pressure to goal rather than on the selection of the initial agent. This is why the latest guidelines recommend starting with combination therapy when blood pressure is more than 20/10 mm Hg above goal[3].

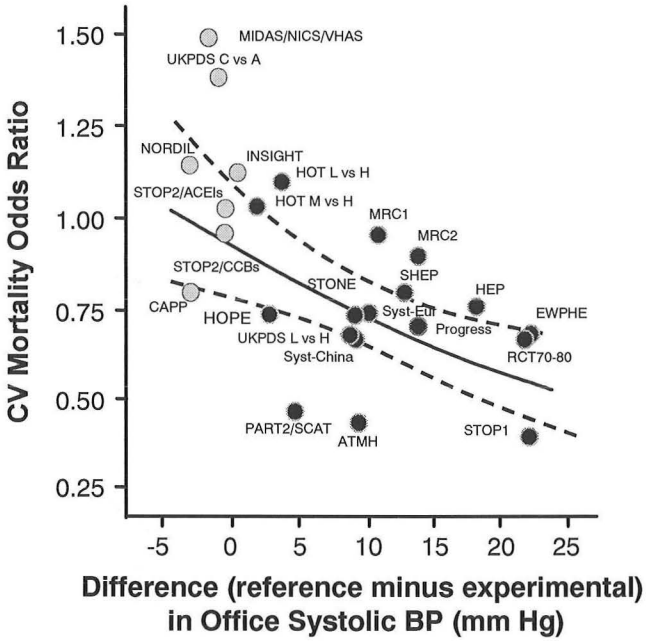


Figure 23. Meta-analysis of 31 hypertension treatment trials involving 182,764 patients. The odds ratio of total cardiovascular mortality is plotted against the difference in systolic blood pressure between reference treatment (placebo, standard therapy, or less intense therapy) vs. experimental treatment (active therapy, new therapy, or more intense therapy). Despite many different drug classes being tested, the greater the reduction in systolic blood pressure the greater the cardiovascular protection afforded[31]. From E Staessen, *J Hypertens*, 2003.

Because of such a powerful blood pressure effect, it has been very difficult to prove that any class of antihypertensive agents affords additional cardiac protection beyond blood pressure lowering.

In contrast, there is a solid evidence base for recommending ACE inhibitors as first line therapy to slow the progression of hypertensive nephrosclerosis in hypertensive patients, African Americans as well as Caucasians[13].

In rat models of chronic renal insufficiency, ACE inhibitors have been shown to cause balanced dilation of the afferent and efferent renal arterioles, causing a reduction in glomerular pressure that retards the progression to end-stage renal disease[13]. In contrast, pure arterial vasodilators such as dihydropryridine calcium channel blockers (CCBs) preferentially dilate the afferent renal arteriole, raising intraglomerular pressure and accelerating the loss of nephrons.

The African American Study of Kidney Disease (AASK) compared the effects of initial antihypertensive therapy with an ACE inhibitor (Ramipril), a dihydropyridine CCB (Amlodipine), or a β-blocker (Metoprolol) on the decline in GFR in African American

hypertensives with mild-to-moderate renal insufficiency. In the subgroup of patients with proteinuria at the time of randomization, baseline serum creatinine averaged 2.7 and baseline GFR averaged 38 ml/min/1.73m^2[53, 54].

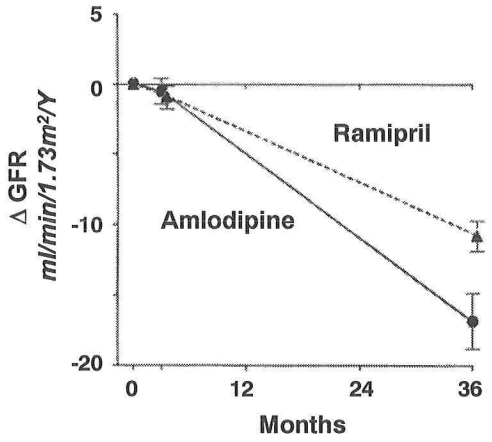


Figure 24. Main results of the AASK trial for patients with baseline proteinuria. For such patients, the decline in GFR over the 36 months of the study was 36% slower with the ACE inhibitor than with the CCB, even though excellent and comparable blood pressure reductions were achieved with both regimens (Ramipril: 151/96 to 135/82 mmHg; Amlodipine: 150/96 to 133/81 mm Hg). From Agadoa et al., *JAMA*, 2001.

The important results bear directly on the selection of antihypertensive therapy for the illustrative patient presented at the outset of this grand rounds, a 42 year old African American man with proteinuric renal insufficiency due to poorly controlled hypertension.

Two points should be emphasized by the data:

1. When part of a multi-drug regimen that includes an appropriate diuretic, ACE inhibitor-based therapy can result in excellent control of hypertension in African American patients even in the setting of moderately advanced renal insufficiency. Thiazide diuretics are ineffective when the GFR falls below 60 ml/min and the appropriate choice is a loop diuretic[5].

2. ACE inhibition provided renal protection despite African American ethnicity and renal insufficiency, two factors that are traditionally associated with low-renin hypertension. Proteinuric renal insufficiency from hypertension is an indication for ACE-inhibitor based therapy regardless of the patient's ethnicity[2, 13, 14].

Once the ACE inhibitor has been titrated, the AASK results suggest that a beta-blocker is a reasonable third line agent. If the blood pressure still is not at goal despite an ACE inhibitor, loop diuretic, and beta-blocker, most authorities believe it is safe to add a CCB for synergy. There are excellent animal data indicating that ACE inhibition rescues the deleterious effect of dihydropyridine CCBs on the renal microcirculation.

However, once hypertensive nephrosclerosis is advanced to the point of significant proteinuria and the need for a loop diuretic, it is no longer a matter of if the patient is going to require renal replacement therapy but rather when. If one extrapolates the AASK data for another three years, switching our patient to the appropriate ACE inhibitor-based antihypertensive regimen would delay the development of end-stage

renal disease by two-to-three years. Based on historical data, it is reasonable to estimate that reducing the patient's blood pressure from the160s/90s to 130s/80s would delay this by another two-to-three years regardless of the medications used[14]. Thus, a realistic estimate of our patient's prognosis is that, under even the best circumstances, chronic hemodialysis will be initiated before age 50. The incidence of MI and stroke are extraordinarily high in the hemodialysis population and the case-fatality rates are very high[13].

Figure 25. Barry White (1944-2003). A case in point is the R&B great Barry White who was born in Galveston, Texas in 1944, developed end-stage renal disease in the Fall of 2002 after years of uncontrolled hypertension, and died of a stroke at the age of 58 this July 4th, 2003.

The only way to prevent end-stage renal disease and premature cardiovascular death in such individuals is to detect, treat, and control the hypertension much earlier in life. That EKG-LVH and hypertensive retinopathy were present at the time of diagnosis (age 42) in our patient means that the hypertension likely went undetected and untreated for years.

IV. COMMUNITY-BASED INTERVENTION

The Dallas Heart Study provides detailed information about the gaps in awareness, treatment, and control of hypertension in Dallas County.

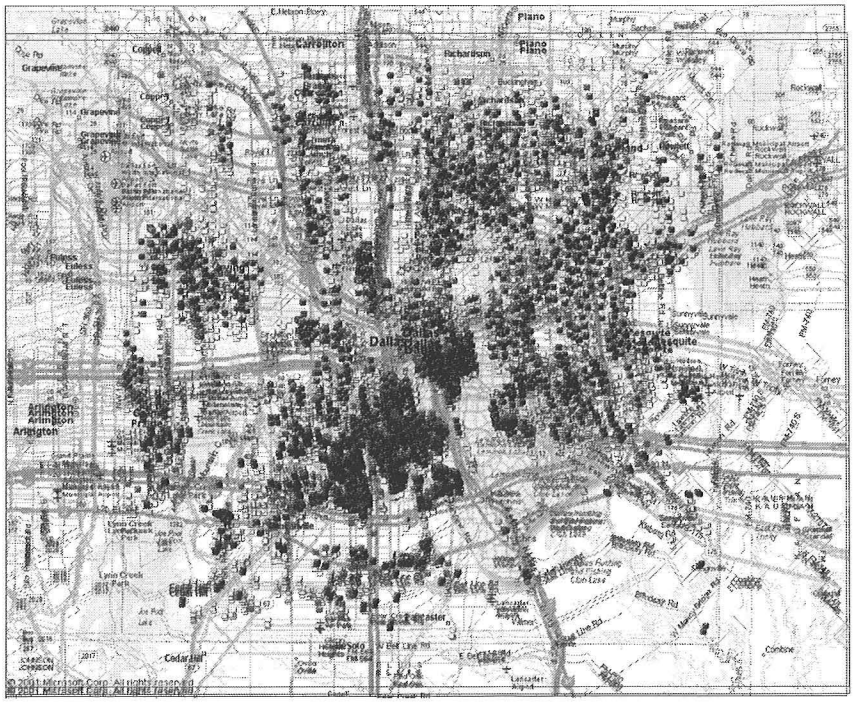


Figure 26. Geomap showing the large numbers of study participants whose blood pressures were elevated even though they were aware of their diagnosis (untreated, under-treated, or not adherent) and those who were unaware of their diagnosis until they took part in the study.

Before age 60, African American men are the demographic group with the greatest prevalence and severity of hypertension and the poorest control rates[6]. Across the

U.S. and in Dallas, over half of all hypertensive African American men go untreated and only about 20% have their hypertension controlled to a blood pressure of < 140/90 mmHg. As a consequence, in 1995, the age-adjusted heart disease death rate among African American men was 29% higher than the rate for white men, 90% higher than that for American Indian and Alaska Native men, 97% higher than that for Latino men, and 126% higher than the rate for Asian and Pacific Islander men[15]. These age-adjusted death rates underestimate the true magnitude of the disadvantage because of ethnic disparities in the age-distribution of heart disease deaths. Among African American men, 40% of all heart disease deaths occur in men under the age of 65;.by comparison, only 21% of heart disease deaths among white men occur before the age of 65[15]. Such premature deaths are of particular public health significance because they are considered preventable and represent unnecessary loss of many productive years of life. Our illustrative patient is a case in point.

The demographics of our primary care clinics (COPCs) document the necessity for a community-based approach to this problem.

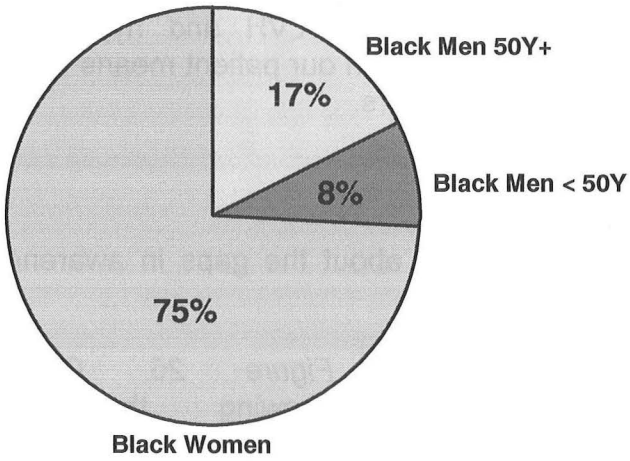


Figure 27. Clinic demographics. There are two COPCs in the southern sector that serve a largely African American clientele. In 2002, a total of 4,743 African American patients were seen for hypertension. Of these, 75% were women and only 8% were African American men less than 50 years of age.

Because hypertension is so prevalent in 30-49 y/o African American men, we need to go outside the traditional health care system to find the young men with undetected and untreated hypertension before they develop advanced target organ disease.

To address this issue, dozens of publications have enthusiastically endorsed *church-based outreach programs* in bringing cardiovascular disease prevention to the African American community [55]. Despite this enthusiasm, there exists a dearth of scientific data -- not a single randomized controlled trial -- proving that church-based hypertension education programs work[55]. Community-based interventions need to cast a broader net if they are going to reach the sizable numbers of men who are not regular church-goers. In a study in inner-city Milwaukee, only 27% of African American men had attended church at any time in the past year. In the lower socioeconomic strata, only 26% of the men had attended any community activity, religious or secular, in the past year[56]. These data underscore the challenge in even finding the large numbers of African American men with untreated hypertension.

Using the emergency department as the main avenue to identify African American men with untreated hypertension, Hill and colleagues recently evaluated a 12-month intervention consisting of a nurse-community health worker team in combination with usual health care[57, 58]. The results underscore the difficulty in making a real world impact in this demographic group. Despite providing access to a nurse case-worker, free prescription medications, and free-transportation to clinic, only 38% of potential participants came for the initial screening visit and only 39% of the participants entered care. The net result was a trivial effect on blood pressure.

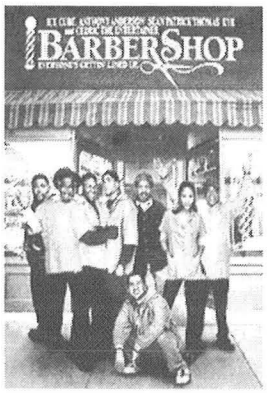


Figure 28. Barbershop: The Movie. As dramatized by the recent movie, lay authors have suggested that for African American men barbershops are often the nerve center of their communities[59, 60]. In his recent book Barbershop Talk: The Other Side of Black Men, Melvin Murphy argues that the barbershop is "one of the few places where black men gather and do not feel threatened ...the barbershop has provided an emotional safe haven for men who have endured exploitation for more than 200 years as African American males. Having gained authority and respect far beyond their education level, the black barbers have a long history of shaping tradition and molding public opinion[60]."

For this reason, barbers may be uniquely positioned to influence their clients' health behavior and thus their blood pressures. In addition to a long-standing and trusting barber-client relationship, there are other reasons to hypothesize that barbershops provide a uniquely effective setting to improve the early detection and treatment of hypertension in young African American men. These include a positive social environment, user-friendly hours, and a uniquely valued incentive: discounted haircuts. Furthermore, our initial data indicate that most of the barbershop clients are long-term patrons that come to the same shop and usually the same barber every week or every other week. Such long-term patronage and a high frequency of visits may make the barbershop an attractive setting for long-term treatment and follow-up of a chronic condition such as hypertension.

Dr. Keith Ferdinand, a cardiologist in New Orleans, was among the first to propose a barbershop-based intervention as a model for cardiovascular risk reduction in an African American community[61, 62]. His and similar demonstration proiects have been conducted in other cities but none have been evaluated[62-64].

We are in the process of conducting a pilot study to begin to rigorously test the efficacy of a barbershop-based intervention on the control of hypertension. The experimental design is shown in the figure below.

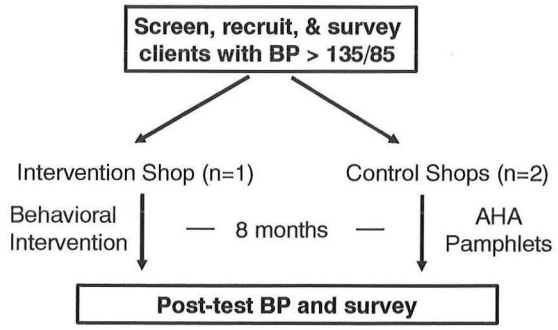


Figure 29. Experimental Design. At three barbershops, we screened and recruited long-term clients of three barbershops with uncontrolled hypertension (out-of-office BP > 135/85 mm Hg) and administered a pre-test survey questionnaire to assess their knowledge and attitudes about hypertension.

For six months, we conducted an intense behavioral intervention at one shop and only left AHA pamphlets on hypertension in African Americans in the control shops. We now are in the process of collecting post-test BPs and surveys at all three barbershops.

We modeled our intervention after that used in the AIDS Community Demonstration Project that succeeded in changing risky behaviors in low income underserved African American communities, including our own[65]. The theoretical basis is called Social Learning Theory[66], which holds that people need to have a model after which to pattern their new behavior and personal social reinforcement of any behavior change they attempt. In other words, education alone is rarely sufficient to change a person's behavior; rather we learn to change by example and when we are reinforced by our peers.

Here the behaviors we want to change are related to blood pressure measurement, referral to and adherence with medical treatment. Hypertensive clients who have taken successful steps in this direction become the role models for other men in the barbershop. Using the men's own words, role model stories are written with two main messages: (1) get the blood pressure numbers to goal (<135/85 mmHg for out-of-office blood pressure), (2) because the medical consequences of elevated blood are devastating to African American men and their families. The emphasis is on the numbers.

During peak business hours (Thursday morning through Saturday evening), lay field staff and students measure the participant's blood pressures in the barbershop and discuss the recorded pressures with the participant, using role model stories to suggest specific ways of getting the numbers closer to goal. Interval medication and lifestyle changes are charted and participants with uncontrolled hypertension are referred to our nurse who is in the barbershop every Friday. Our nurse refers untreated participants for medical care and educates treated patients about the importance of obtaining and maintaining goal blood pressure. Specific behavioral goals are set for each participant.

Post-test evaluation is underway and will be completed by the Fall.

V. CONCLUSIONS AND ACKNOWLEDGEMENTS

The gap in the burden of hypertension between African Americans and other ethnic groups has continued to widen over the past three decades. Any attempt to close this gap is going to require a multi-faceted approach. While it is important to try to provide a better mechanistic understanding of the gene-environment interactions involved in primary human hypertension and its attendant target organ damage, the progress to date has been slow and the eventual impact on clinical medicine is unknown. In the meantime, there already exists abundant evidence that, if appropriate antihypertensive treatment can be provided and utilized, most of the excessive morbidity and mortality in African Americans could be prevented. Innovative community-based approaches to this difficult problem need to be developed and rigorously evaluated.

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