THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER at DALLAS

INTERNAL MEDICINE GRAND ROUNDS

HEART FAILURE IN AFRICAN AMERICANS:

"A CARDIOVASCULAR ENIGMA NOW RESOLVED?"

July 21, 2005

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DISCLOSURES

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I currently have a financial interest/arrangement or affiliation with the following organizations that may represent a potential conflict of interest.

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The Washington Post

Heart Drug for Blacks Endorsed
Racial Tailoring Would Be a First; Idea Stirs Debate

By Rob Stein
Washington Post Staff Writer
Friday, June 17, 2005; A01

Federal health advisers yesterday endorsed the approval of a drug to treat heart failure in African Americans, which would make the controversial pill the first medicine targeted at a specific racial group.

The Food and Drug Administration advisory panel voted unanimously to recommend that the agency approve a request by NitroMed Inc. of Lexington, Mass., to sell the drug BiDil for patients with severe heart failure, and a majority agreed with the company that its label should say it is specifically intended for African Americans.

F.D.A. Panel Approves Heart Remedy for Blacks

By STEPHANIE SAUL – The NY Times
June 17, 2005

A Food and Drug Administration advisory panel recommended the approval of a heart-failure drug specifically for African-Americans yesterday, after a discussion about race, genetics and medicine.

The F.D.A. usually heeds the advice of its advisory panels, meaning that the drug, called BiDil, is

likely to become the first treatment ever designed and marketed for one racial group

WSJ.com THE WALL STREET JOURNAL. ONLINE

FDA Panel Backs Use of Heart Drug In Black Patients

By JENNIFER CORBETT DOOREN and ZACHARY A. GOLDFARB
Staff Reporters of THE WALL STREET JOURNAL
June 17, 2005 3:46 a.m.

A Food and Drug Administration advisory panel recommended that the agency approve a heart-failure drug for African-Americans, clearing the path toward the U.S.'s first race-specific medicine.

The panel unanimously endorsed approval of BiDil, a three-times-a-day pill made by NitroMed Inc., Lexington, Mass., though only seven of the nine members supported labeling requested by the company that would direct use of the drug toward people who identify themselves as African-American. The split reflects a heated debate over the role of race in medicine that has surrounded the drug's development.

Newsday.com

Panel recommends cardiac drug for blacks

BY DELTHIA RICKS
STAFF WRITER

June 17, 2005

A government advisory panel Thursday unanimously recommended a controversial heart-failure drug, which is targeted at African-Americans, marking the first time a medication has been aimed at a specific racial group.

"Of all the forms of inequality, injustice in health is the most shocking and inhumane."

Martin Luther King, Jr., Ph.D.

PREFACE

The foregoing headlines define a punctuation mark in a long journey that targets optimal management of a serious illness with a sharpened focus on a high risk population that bears a disproportionate disease burden. That this population is defined by race has galvanized a national debate, enabled a new paradigm in clinical research and engaged previously disenfranchised patients and their providers into mainstream American medicine.

An editorial published in 2000, "Heart Failure in African Americans: A Cardiovascular Enigma", framed the then state-of-the-art by positing that not all patients affected by heart failure have reaped a benefit from the salutary advances in medical therapy and raised the provocative concern that heart failure in African Americans indeed represents a different malady than heart failure in other patients. (1) Several comments from that editorial are worth excerpting…

"It is my assertion, however, that African American patients do respond to neurohormonal antagonism. The available data do… raise appropriate concerns that the most salient neurohormonal mechanisms have not yet been identified in the African American population…what is inescapable…is the discovery of yet another devastating consequence of uncontrolled hypertension…I believe a prospective randomized trial testing heart failure regimens in African Americans is warranted…but social and ethical issues challenge the design of such a trial."(1)

The focus of this presentation is to determine how these issues have been addressed and whether or not recent advances in medical therapy now support full or partial resolution of this cardiovascular enigma.

Clyde W. Yancy, M.D.

INTRODUCTION

The demographics of the US population are quite dynamic and are changing rapidly. Currently, white Americans constitute no more than 70% of the population. It is estimated that by 2050 there will no longer be a majority population in this country.(2) This burgeoning growth of ethnic populations in the United States necessitates a heightened awareness of the health care circumstances, demands and needs for our changing populace. Within the domain of cardiovascular disease and its responsiveness to medical, device and surgical therapies resides the most palpable examples of the growing health care concerns that involve these emerging special populations.

Before engaging in a thought process regarding "special populations", it is worth noting that exploration of cardiovascular disease in populations defined by a racial/ethnic stratification must be done with deliberate thought and a broad perspective. Guidelines for the incorporation of race in medicine have been suggested with the intent being to depoliticize the issue of race in medicine and to establish a consistent approach that limits bias and conjecture at the highest order. (3) The suggested Guidelines are as follows:

1. *When race/ethnicity is used as a study variable, the reason for its use should be specified.*
2. *In citing race/ethnicity data from any source, authors should describe the way in which individuals were assigned to racial/ethnic categories. If racial/ethnic identification was self-reported, authors should specify whether individuals answered an open-ended question or chose from a fixed set of categories*
3. *Race/ethnicity should not be used as a proxy for genetic variation. Statements about genetic differences should be supported by evidence from gene studies. Genetic hypotheses should be firmly grounded in existing evidence, clearly stated, and rigorously tested.*
4. *In stating hypotheses and describing study results, authors should distinguish between race/ethnicity as a risk factor and race/ethnicity as a risk marker*
5. *In the interpretation of racial/ethnic differences, all conceptually relevant factors should be considered, including racism and discrimination*, SES, *social class, personal or family wealth, environmental exposures, insurance status, age, diet and nutrition, health beliefs and practices, educational level, language spoken, religion, tribal affiliation, country of birth, parents' country of birth, length of time in the country of residence, and place of residence*
6. *Because lack of adjustment for SES or social class is the most important potential source of bias in studies of racial/ethnic differences, researchers should make every effort to adjust for conceptually relevant measures of SES or social class when comparing racial/ethnic groups. Unadjusted findings should be clearly labeled as such, and in general they should be reported in conjunction with adjusted findings for comparison purposes*
7. *In describing racial/ethnic groups, authors should use terminology that is not stigmatizing, does not reflect unscientific classification systems, and does not imply that race/ethnicity is an inherent, immutable attribute of an individual.*

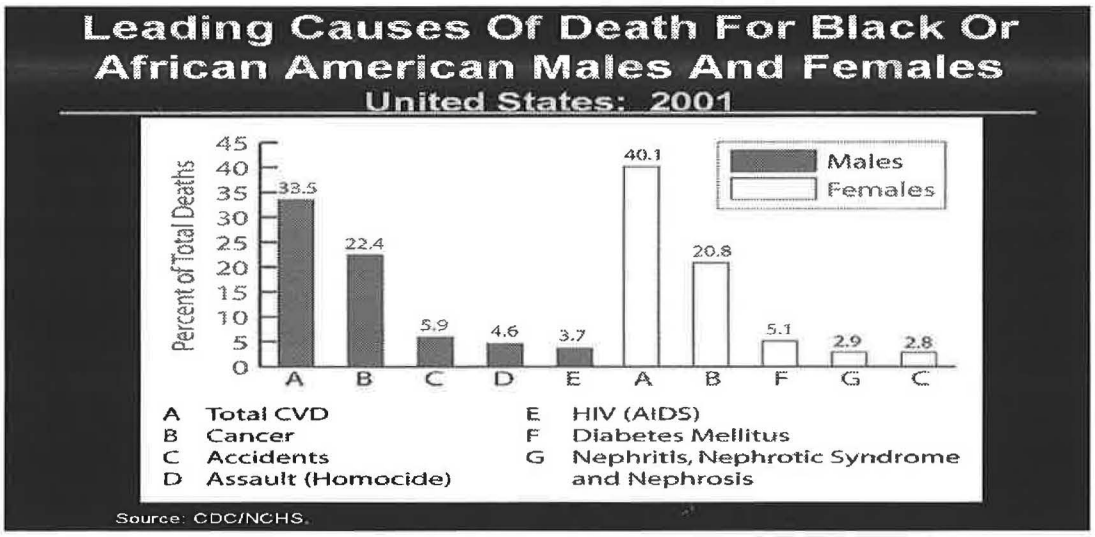
Further polarization of already disenfranchised groups should not be the end result of increased awareness of population group differences. Rather, the result should be an

enhanced capability of facilitating meaningful reductions in any disproportionate disease burden. To achieve this goal, there must be a full explanation of the peculiarities of cardiovascular disease that incorporates physiological, genetic, environmental, and social factors in special populations. Of the "special populations", it is the African American group that has garnered the most attention to date but issues pertinent to Hispanic Americans, Native American Indians, Asian Americans and Indians of Asian origin are not far from the horizon.

HEART DISEASE IN AFRICAN AMERICANS

Despite very real concerns that African Americans experience a disproportionate risk of death from human immunodeficiency virus (HIV) disease, trauma, cancer, and accidents, the available evidence from the American Heart Association 2005 Update on Cardiovascular Disease and Stroke suggests that, similar to the majority of the population, cardiovascular disease is the leading cause of death in African Americans (Figure 1).(4)

Figure 1



Cardiovascular disease represents the cause of death in 33.5% of African American men and 40.1% of African American women. These numbers compare to 36.6% for white men and 39.8% for white women. (4) Hypertension has traditionally been regarded as the most important cardiovascular disease process affecting African Americans. The Third National Health and Nutrition Examination Survey [NHANES III] provided data on the distribution of hypertension in African Americans. Six million African Americans are affected by hypertension with a crude prevalence rate of 29.9% for men and 27.3% for women. These values represent the highest penetration of hypertension for all populations surveyed. The prevalence of stage III hypertension [> 180/110 mmHg] is likewise disproportionate affecting 8.5% of African Americans vs. 1% of whites. The mean systolic BP of all African Americans is 3 mmHg higher than for all whites [125/75 vs. 122/74]. (5,6) Similar to the conundrum of hypertension in African Americans, heart

failure in African Americans appears to be growing and is quite prevalent in a similarly disproportionate way.

Whereas the incidence of heart failure in the general population is 2%, the incidence of heart failure in African Americans is at least 50% higher and in African American women it may be 100% higher. (7) When the disease occurs it does so at a younger age; leads to greater disease severity measured by the New York Heart Association classification scheme; and is associated with a higher morbidity, vis-à-vis hospitalizations; and a worrisome possibility that mortality due to heart failure may be similarly increased. See Table I. (1) For these reasons, there has been a recent focus on heart failure in African Americans.

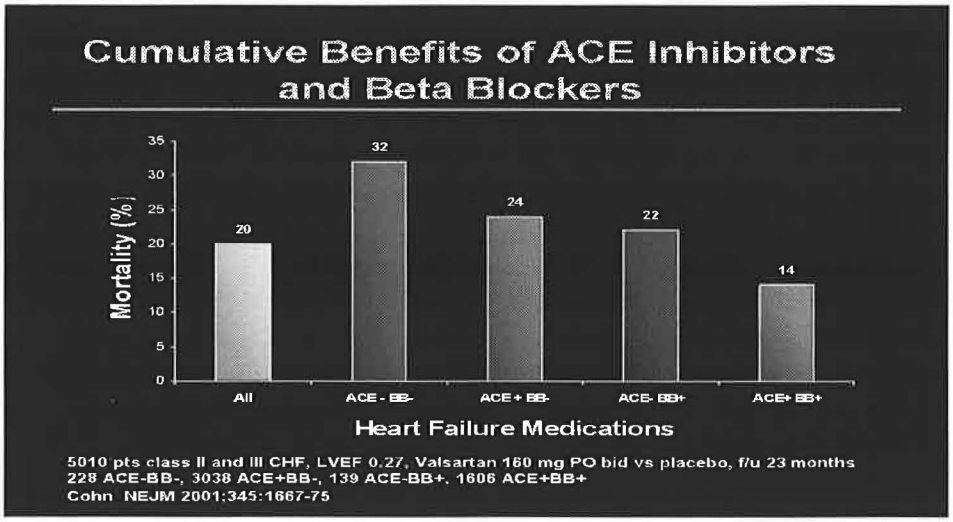
Table I

Characteristics of Heart Failure in African Americans
-occurs at an earlier age
-more likely to have a non-ischemic etiology
-associated with worse disease severity at time of diagnosis
-higher rate of hospitalizations
- possibility of excess mortality

HEART FAILURE IN AFRICAN AMERICANS

Chronic heart failure has evolved from a near fatalistic diagnosis to an imminently treatable disease entity with significant improvements in morbidity and mortality expected from the best application of evidence-based treatment strategies. Institution of the suite of neurohormonal antagonists, especially renin-angiotensin-aldosterone system antagonists and beta blockers, that target perturbations in the neurohormonal response to left ventricular dysfunction has led to substantial gains in mortality, reductions in frequency of hospitalization, and improvements in symptom status in those patients afflicted with heart failure.(8-12) The adjunctive benefit of device therapy has served to further reduce the risk of death in patients with ambulatory heart failure.(13, 14) The best available published data would now place the annual mortality rate due to heart failure in optimally treated patients at 5% to 7%. See Figure 2. (15) This is only fractionally higher than the anticipated annual mortality risk for similarly aged persons in the United States who are unaffected by heart failure. However, the pressing and clinically pertinent question is whether these positive treatment outcomes can be extrapolated to all patient groups afflicted with heart failure.

Figure 2

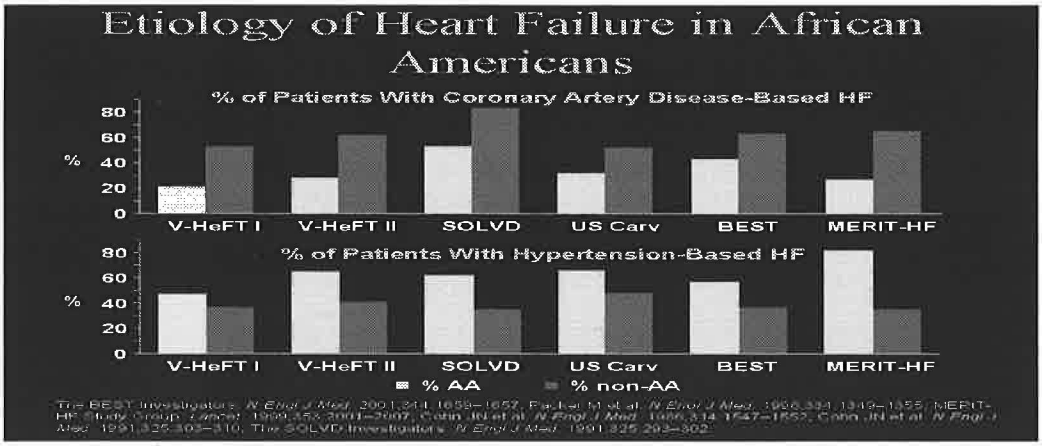


A review of clinical trials in heart failure, (which serve as our highest tier of data), unfortunately fails to deliver convincing evidence that these striking gains in outcomes can be expected in African Americans affected by heart failure. This concern is, in part, driven by the inconsistent representation of African Americans in cardiovascular clinical trials, which has varied from less than 3% to 100%. Moreover, few trials in heart failure, if any, have pre-specified a subgroup analysis of outcomes in the African American cohort. Thus, the data queries regarding African Americans in clinical heart failure trials are primarily retrospective and subject to the inherent inaccuracies associated with retrospective post hoc analyses of underrepresented subgroups. As a consequence, the data regarding African Americans derived from clinical trials in heart failure are, at best, "hypothesis-generating" and cannot be determined to be definitive. Despite these important provisos, signals, some of which are concerning, have been gleaned from the clinical trial experience.

THE EPIDEMIOLOGY OF HEART FAILURE IN AFRICAN AMERICANS

Perhaps the most important observation lies in the epidemiology of the disease. Usually, the leading cause of left ventricular dysfunction leading to heart failure is ischemic heart disease with subsequent myocardial injury. However, the imputed etiology of left ventricular dysfunction is different in African Americans compared with white Americans. A careful review of the recorded etiologies of left ventricular dysfunction from several of the major clinical trials in heart failure demonstrates a lower likelihood of documented ischemic heart disease as the putative cause of left ventricular dysfunction and a greater likelihood of nonischemic, principally hypertensive disease, as the sole potential explanation for left ventricular dysfunction. See figure 3. (16) This influence of hypertension as a sole contributor to left ventricular dysfunction in African Americans is seemingly unique to the African American population and varies from 30% to as high as 60% depending on the trial queried. In contradistinction, hypertension as a sole cause of heart failure in white Americans is less with published reports as low as 4%. (17)

Figure 3



Hypertension, as it affects African Americans, is a malignant disease process. The prevalence of hypertension in African Americans is at least 3 to 7 times higher than in white Americans. The rate of end-stage renal disease resulting from hypertension is 2000% higher, and the rate of stroke and associated fatality is considerably higher.(18-21) The incidence of left ventricular hypertrophy (LVH) is 3-fold higher, and the pattern of LVH (i.e., concentric hypertrophy) is one known to be more malignant. (22) Overall, these data would suggest that hypertension is indeed a *more malignant disease* process in African Americans, implying that the vascular response to hypertension is especially injurious. How hypertension begets heart failure however is an enigma itself. Mechanisms responsible for the conversion of hypertensive heart disease with intact systolic function to hypertensive heart disease with impaired systolic performance have not been fully elucidated [but have been previously discussed in these grand rounds- "The Natural History of Hypertensive Heart Disease: Does it lead to heart failure?" 10/26/2000- C. Yancy, M.D.]. It is therefore quite difficult to firmly embrace a definitive causative role for hypertension in the genesis of systolic dysfunction. Nevertheless, the relationship between hypertension and heart failure in African Americans cannot be ignored and the clinical imperative to effectively control hypertension in African Americans should reflect this concern.

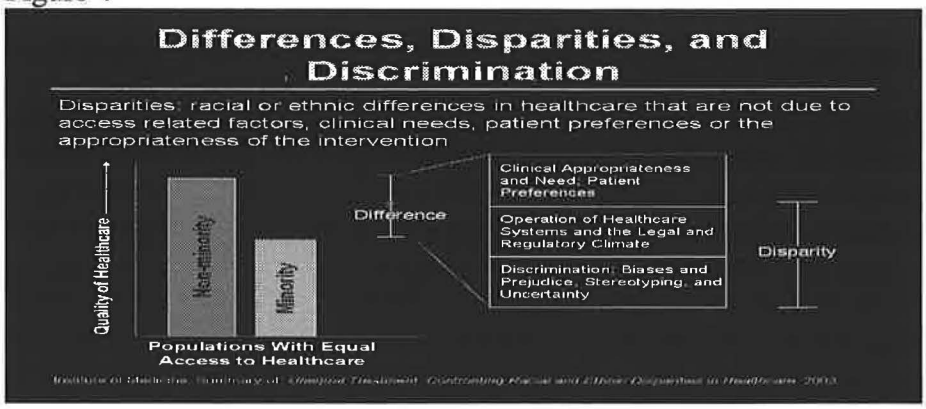
Hypotheses for Disproportionate Disease Burden

A number of plausible explanations for the apparent disease excess seen in African Americans with hypertensive heart disease and heart failure have been proposed with no single proven causative theory.

The psychosocial burdens of the African American culture are easily recognizable and are undoubtedly important. No discussion about cardiovascular health and outcomes in African Americans can be complete without acknowledging that healthcare disparities do exist and go far beyond simple issues of patient preference or indication/lack of indication for a given therapy. See figure 4. (23, 24) Ultimately, there are access to

health care concerns, health care delivery system impediments and issues of bias that exert a negative influence on cardiovascular disease management in African Americans. To have truly effective treatment strategies in place for all patients, these issues regarding healthcare disparities must be addressed and overcome.

Figure 4



It is tempting to impugn socioeconomic variations as a plausible explanation for differences in cardiovascular disease incidence and outcomes but data that control for objective measures of socioeconomic status still reveal cardiovascular disease excess in African Americans- an observation which strongly implicates *physiological differences.* In the SOLVD [Studies of Left Ventricular Dysfunction] trials completed in patients with minimally and moderately symptomatic heart failure, financial distress was not associated with adverse outcomes in the African American cohort. An educational level < 8^{th} grade was associated with lesser outcomes but in a multiracial analysis, all groups were similarly affected. (25)

The striking incidence of obesity in African Americans does appear to be linked to the presence of hypertension and likely contributes to the complex milieu responsible for excessive cardiovascular disease in African Americans. As populations of African origin have emigrated from West Africa, through the Caribbean and into North America, there is a near-linear relationship with the increase in mean body mass index and blood pressure.(26)

Clearly, the incidence of hypertension and obesity contribute to the observed burden of cardiovascular disease in African Americans, but the potential presence of important additional physiological differences must be considered. An emerging but still incipient database of single nucleotide polymorphisms (SNPs) raises the possibility that within those persons self-described as African American, a clustering of unfavorable gene expressions may contribute to the increased incidence of cardiovascular disease. Candidate genes for which unfavorable SNPs have been described in African Americans include transforming growth factor (TGF) β-1, endothelin, β-1 adrenergic receptors, aldosterone synthase, nitric oxide (NO) synthase, and the 825T allele of the GNB-3 G protein subunit (Table 2). (27-31)
There is considerable interest in TGF β-1. This primitive cytokine has been associated with mesangial hypertrophy and LVH. Polymorphism of the gene encoding for TGF β-1

has been described, and the highest levels of TGF β-1 have been seen in African Americans with hypertension.(28) It has been noted that TGF β-1 stimulates the production of endothelin, which is perhaps the most potent vasoconstrictor. Clearly, this may be associated with more malignant patterns of hypertension.

Several SNPs of the adrenergic system have also been described. Substitution of glycine for arginine at position 389 on the β-1 adrenergic receptor creates a loss-of-gain function that is consistent with a down-regulated sympathetic nervous system and perhaps a decreased response to β-blockers. (29, 30, 31) This SNP of the β-1 adrenergic receptor has been described in African Americans. However, an even more worrisome pattern has been described in the setting of the wild-type β-1 receptor in concert with a deletion polymorphism of the α-1 receptor. This combination, reportedly present almost exclusively in African Americans, leads to an especially malignant course of heart failure.(31) These SNPs and the several others listed may be operative in the progression of heart failure, but the distribution of these genetic variations is not homogeneous in the African American population. Nevertheless, genetic signals, which appear to serve as a plausible construct for the excess representation of heart failure in African Americans, do exist. See Table II. (28-31)

TABLE II

GENETIC POLYMORPHISM	CLINICAL IMPLICATIONS
Beta 1 adrenergic receptor; Gly – 389	Sub-sensitive beta-1- receptor; decreased affinity for agonist and less cAMP generation
Beta 1 adrenergic receptor; ARG- 389/alpha 2C Del322-325 receptor	Presence of both polymorphisms is associated with increased risk for heart failure in blacks; RR 10.11 when both are present
NOS3, polymorphism of G894T; Asp298 variant	Sub-sensitive Nitric Oxide system
Aldosterone Synthase	? Excessive fibrosis
TGF-Beta 1	40% higher TGF Beta 1 levels;? Higher endothelin levels;? More fibrosis
G Protein 825-T Allele	Marker of low renin HTN, LVH & stroke

Adapted from: Yancy CW. Does Race Matter in Heart Failure? American Heart Journal 2003.;146:203-206.

There are at least two even more provocative lines of evidence regarding the influence of single nucleotide polymorphisms in heart failure.

Perhaps the most studied of the polymorphisms is the ACE gene, with a focus on the dual deletion, dual insertion and the heterogeneous alleles. Within the Genetic Risk Assessment of Cardiac Events [GRACE] study done at the University of Pittsburgh, the impact of beta blocker therapy within genetic subsets has been evaluated, especially in African Americans with heart failure. Beta blockers were strikingly effective in the ACE DD cohort but minimally so in the ACE II cohort. (32,33). Even more intriguing is the role of the Nitric Oxide Synthase 3 [NOS3 or endothelial nitric oxide synthase] polymorphism, Asp298. This variant is a risk factor for coronary artery disease, hypertension, and stroke and is associated with a less good survival for patients affected with heart failure. (32, 34). However, ACE-inhibitor therapy may be more effective in patients with the Asp298 variant. Within GRACE, the frequency of the Asp298 variant

was 60% for white patients with heart failure vs. only 30% for African American patients with heart failure. (32, 34) The influence of this SNP on observed lesser responsiveness of ACE-inhibitors in African Americans is indeed intriguing but clearly far from definitive.

Although this is an exciting area of investigation, it is evident that any genetic influence is likely to be contextual and quite complex, and will reflect gene-gene interactions, gene-environment interactions, and gene-drug interactions. Databases to date have been small and quite arbitrary reflecting the inherent bias of clinical referral patterns and investigator selection bias. Larger initiatives are needed. Within the larger African American Heart Failure Trial [A-HeFT], a prospective genetic sub study is forthcoming. The Genetic Risk Assessment of Heart Failure in African Americans [GRAHF] will address the impact of several of the more compelling candidate genetic polymorphisms.

WHAT HAVE WE LEARNED FROM CLINICAL TRIALS IN HEART FAILURE THAT HAVE INCLUDED AFRICAN AMERICANS?

A number of published trials have reported data as a function of race. The Studies of Left Ventricular Dysfunction (SOLVD) were among the first to suggest differential outcomes as a function of race.(17, 25, 35) A post hoc analysis of the primary trial results demonstrated that mortality from heart failure was higher in African Americans, with a 1.8-fold increase for African American men and a striking 2.4-fold increase for African American women.(25) These data persisted even after adjusting for educational level and measures of financial stress, which are both crude but quantifiable measures of socioeconomic status. A subsequent reanalysis that adjusted for the degree of left ventricular dysfunction and for trial participation (i.e., SOLVD Prevention or SOLVD Treatment trial) yielded no differences in mortality, but showed a significantly higher risk (44%) for hospitalization in the African American patients compared with white patients (P=.005).(36) A suggested clinical explanation for this apparent lower responsiveness to the ACE- inhibitor enalapril was the lack of a blood pressure-lowering response at the doses used in the trial in African Americans compared with others.(36) These observations would in fact be consistent with a broad statement that ACE inhibitors are less effective in African Americans. These data do not, however, resolve the question of an excess mortality risk since the matched patient population in this reanalysis was overrepresented by lower-risk patients.

Conflicting data points have also emerged from the clinical trial experience with β-blockers. A recent RAND corporation meta-analysis incorporated data reported by race from the major published β-blocker trials in heart failure. (37) Whereas the aggregate benefit of β-blockers for the majority population was a 31% reduction in mortality, the apparent benefit of β-blockers in African Americans was only *3%* (Figures 5 & 6).

Figure 5

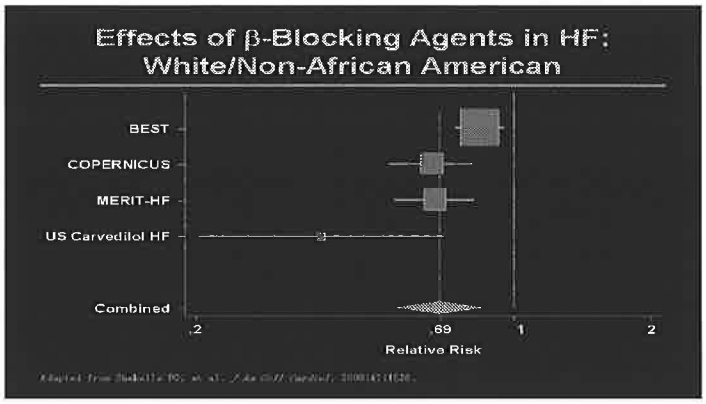
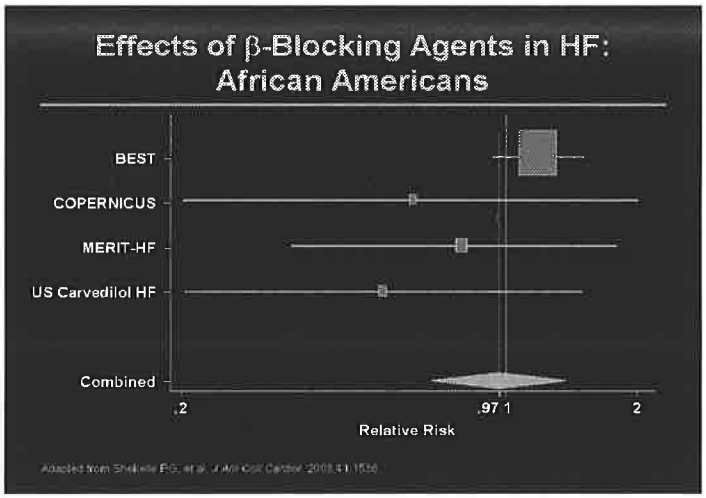


Figure 6



These unfavorable data are heavily influenced by the negative outcomes from the Beta-Blocker Evaluation of Survival Trial (BEST). (38) Within this trial that evaluated the effect of bucindolol on survival in patients with advanced heart failure, no apparent benefit was realized in the African American cohort, although a benefit was seen in the white American cohort. However, the magnitude of that benefit was approximately 50% less than that typically seen in prior trials with β-blockers. Subsequent data since have emerged to confirm that bucindolol has partial intrinsic sympathomimetic activity and, as such, represents an unfavorable β–blocking agent for heart failure. (39) Nevertheless, there was an apparent difference in the benefit of β-blocker therapy in African Americans versus white Americans, raising the concern that African Americans with heart failure exhibit lesser responsiveness to beta blockers.

The experience with carvedilol has been quite different and varies substantially from the observations seen with bucindolol. In both the United States Carvedilol Heart Failure Trials program and the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS), retrospective analyses by ethnicity showed statistically significant benefits with carvedilol. (40, 41) The US Carvedilol Heart Failure Trials program demonstrated that the combination of carvedilol and an ACE inhibitor yielded similar outcomes in both African Americans and non-African Americans. (40) For both groups, the reduction in the progression of heart failure, defined as death due to heart failure, hospitalization for heart failure, or worsening symptoms requiring augmented medical therapy, was greater than 50%. These benefits were supported by observations of similar improvements in measures of left ventricular function and similar hemodynamic effects on heart rate and blood pressure. (40) Thus, therapy with the combination of ACE inhibitors and carvedilol was demonstrated to be effective in African American patients. It remains unclear whether these benefits are limited to carvedilol. Data from the Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF) trial are inconclusive because too few African Americans were included in this trial of nearly 4000 people (42). A summary of major clinical trials in heart failure that reported data as a function of race can be found in Table III

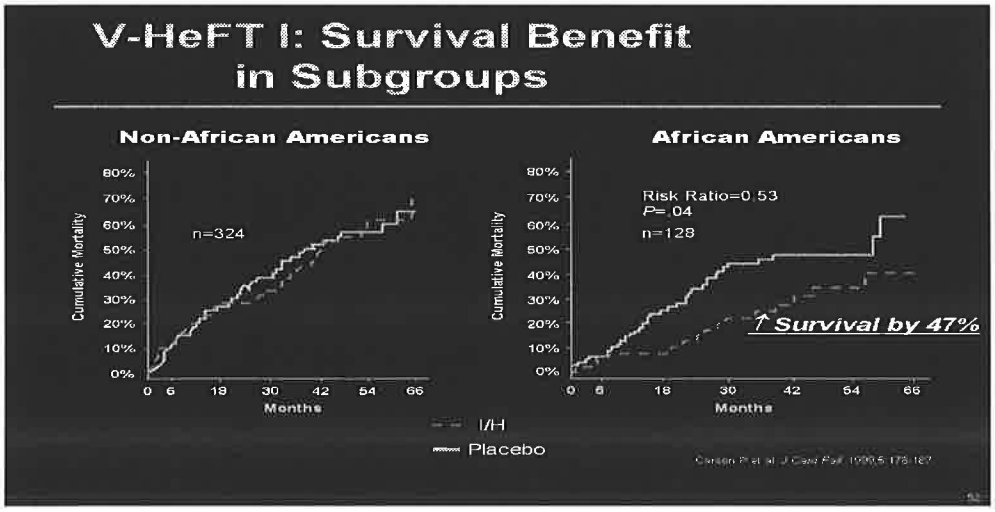
TABLE III

STUDY	% OF AA	DESIGN	INTERVENTION	RESULTS
V-HeFT I (43)	29%	Double-blind RCT; primary endpoint: mortality	Placebo vs. hydralazine/isosorbide nitrate Background: diuretics & digoxin	Annual mortality rate decreased from 17.9% to 9.7%; p=0.04
V-HeFT II (43)	27%	Double blind RCT; primary endpoint: mortality	Hydralazine/isosorbide dinitrate vs. enalapril Background: diuretics & digoxin	Annual mortality rate: 12.9% to 12.8%; p= NS
SOLVD-treatment (25)	12%	Double blind RCT; primary endpoint: mortality	Placebo vs. Enalapril in NYHA Class II/III HF	No mortality difference blacks vs. non-blacks in a matched population, RE: LVEF and clinical trial participation; RR 0.92 vs. 0.95; higher hospitalization rate for blacks; RR 0.95 vs. 0.54;p=0.005
SOLVD-prevention (35)	9.8%	Double blind RCT; primary endpoint: mortality	Placebo vs., Enalapril in NYHA class I/II HF	No difference in the prevention of heart failure using enalapril; statistically significant difference in the incidence of heart failure;RR 1.81; p<0.001
BEST (38, 39)	23%	Double blind RCT; primary endpoint: all cause mortality	Placebo vs. Bucindolol in NYHA Class III & IV; randomization stratified for women and blacks Background: diuretics, ACE-inhibitors; digoxin at investigator's discretion	Non-significant 17% increase in risk of death on bucindolol; p=0.27
MERIT-HF (42)	<5%	Double blind RCT; primary endpoint mortality	Placebo vs. Metoprolol Succinate in NYHA class II/IV; mostly II/III	Insufficient numbers to ascertain efficacy
U.S. Carvedilol Trials Program (40)	20%	4 concurrent trials; double blind RCT design; mortality was not a predetermined endpoint	Placebo vs. Carvedilol in NYHA class II-IV; mostly II/III with protocol participation determined by 6 minute walk time; background: diuretics, ACE-inhibitors and digoxin at investigator's discretion	Similar efficacy between black and non-black groups; reduction in death for any cause or hospitalization for any cause-48%; reduction in worsening of heart failure-54%
COPERNICUS (41)	5%	Double blind RCT design; primary endpoint: all cause mortality	Placebo vs. Carvedilol in NHYA class III/IV; LVEF <0.25 (mean 0.19)	Similar efficacy between black and non-black groups despite small number of blacks

Neither of the signature trials using aldosterone antagonists for left ventricular dysfunction, either chronic class III/IV heart failure or post-myocardial infarction left ventricular dysfunction had a sufficient number of African Americans to make any statement regarding subgroup responsiveness. (11, 12) The issue regarding responsiveness to angiotensin-receptor antagonists [ARB] is unclear as unpublished data from the Valsartan in Heart Failure Trial [Val-HeFT] suggested that African Americans randomized to the ARB did not demonstrate the same degree of efficacy as the overall patient population. [personal communication, J. Cohn, M.D.]. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, an investigation of high-risk hypertensive patients, recruited only 4% of subjects who were African American. A perusal of this subgroup would be completely unproductive. (44) There was even less representation of African Americans in the Heart Outcomes Prevention Evaluation (HOPE) study, thus there are no data from which a statement can be made about the value of ACE inhibitors in African American patients at high risk for vascular events. (45)

The clinical trial experience that has prompted the most intrigue in this arena is the original Vasodilator Heart Failure Trials (V-HeFT I and II). (43) V-HeFT I is considered a landmark trial because it established for the first time that the outcomes of heart failure could be slightly improved by medical therapy. Of the 480 patients in V-HeFT- I, 180 were African American. A post hoc retrospective analysis of this subgroup yielded the striking finding that a signal of significant survival benefit from the combination of isosorbide dinitrate and hydralazine (ISDN/HYD) was seen in the African American group. (43) The benefit of ISDN/HYD when added to diuretics and digoxin in African American patients resulted in a > 40% survival benefit. See figure 7. (43)

Figure 7



When V-HeFT II was re-queried to determine outcomes as a function of race for therapy on an ACE inhibitor versus the vasodilating regimen of ISDN/HYD, it was discovered

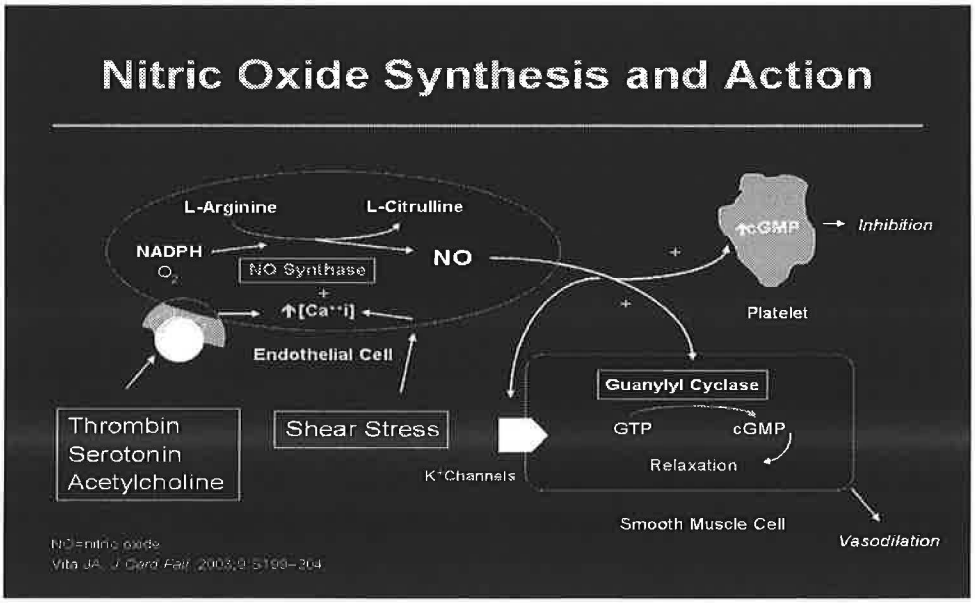
that the white patients responded better to an ACE inhibitor than to ISDN/HYD. The African American patients fared equally well on an ACE inhibitor or vasodilator therapy .(43) The correct interpretation of this revisit of V-HeFT I and II is not that African Americans failed to respond to ACE inhibitors but rather that they had a more robust response to ISDN/HYD. Is this apparent benefit from ISDN/HYD simply a blood pressure lowering effect from vasodilator therapy or might there be other factors involved?

NITRIC OXIDE BIOLOGY, HOMEOSTASIS AND CLINICAL RELEVANCE

Nitric oxide, originally named "endothelium derived relaxation factor" was only recently discovered and subsequently named in 1987. Its importance in human health and disease is notable. Furchgott, Ignarro and Murad were awarded the Nobel Prize in 1998 for identifying NO and elucidating its pleiomorphic effects. NO is fairly ubiquitous with functions that include vasodilation, neurotransmission and elimination of pathogens. It is produced by endothelial cells from a family of oxidoreductases that bear close homology to the cytochrome P_{450} system of enzymes. (46, 47)

Three "synthases" have been identified: NOS I (neuronal NOS or nNOS), NOS 2 (inducible NOS or iNOS) and NOS 3 (endothelial NOS or eNOS). NOS 3 or eNOS is activated by agonists acting on G protein coupled receptors and by shear forces and changes in O_2 delivery. (48) L-arginine and oxygen serve as substrates for NOS while nicotinamide adenine dinucleotide phosphate [NADPH], flavin adenine dinucleotide [FAD], heme, flavin adenine mononeucleotide [FMN], calmodulin and tetrahydrobiopterin serve as cofactors. The byproduct of NO synthesis is L-citrulline plus $NADP^+$. NO produces vasodilation by activating soluble guanylate cyclase (sGC) with subsequent production of cyclic guanosine monophosphate [cGMP]. (48) See figure 8

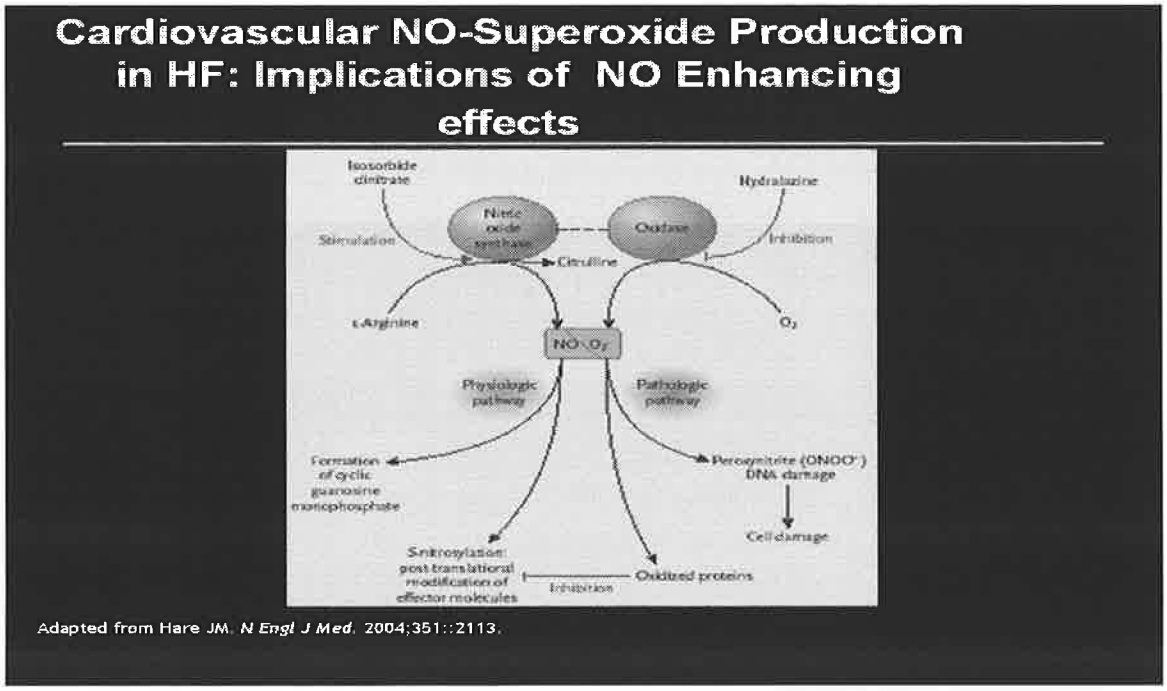
Figure 8



Nitric oxide influences organ function by its post-translational effects on effector molecules. This occurs most often at cysteine residues and is termed S-nitrosylation. (49) S-nitrosylation of ion channels within the heart maintains normal calcium flux important in systolic and diastolic function. S-nitrosylation of hemoglobin regulates blood flow. Within the myocardium, low doses of NO enhance contractility while higher doses [as derived from high output inducible NOS or NOS 2] may depress LV contraction. The release of NO in small quantities appears to incline vascular tone towards vasodilation through cGMP production. (49).

Superoxide [O_2-], facilitates S-nitrosylation at physiological levels but disrupts S-nitrosylation at pathological levels. It does so by targeting the same cysteine residues as NO and prevents S-nitrosylation from occurring. (49) Pathological levels of superoxide will also react with NO and lead to the production of peroxynitrite. (50). This process of excess superoxide production and disruption of S-nitrosylation is at least one characteristic of *oxidative stress.* The balance between the effects of NO and superoxide has been termed the "nitroso-redox" balance. (49) [See Figure 9] If this balance is inclined towards low NO and excess superoxide, cell injury may ensue. Additionally, a deficiency of nitric oxide synthase may increase the activity of oxidases and lead to increased production of superoxides. The activity of these oxidases are also increased by angiotensin II—a characteristic neurohormonal perturbation in heart failure.

Figure 9



Knockout murine models devoid of eNOS have been consistently associated with the development of hypertension supporting a role for eNOS derived NO as a variable in blood pressure homeostasis. Additional characteristics of the eNOS -/- phenotype include

decreased plasma renin, impaired angiogenesis, insulin resistance and left ventricular hypertrophy. (51) The parallelism with certain clinical phenotypes of hypertension is unavoidable.

Abnormalities in the regulation of NOS and the release of NO have been implicated in diabetes and atherosclerosis and reduced NO appears to be involved in thrombosis, platelet aggregation, immunodeficiency and impotence. Excessive production is pathologic as it invokes hypotension in the setting of sepsis and it reacts with superoxide [O_2^-] to form peroxynitrite which is known to be cytotoxic [this may be beneficial in the setting of iNOS activation in macrophages which targets microbial pathogens or tumor cells]. See Table IV for physiological functions of NO and associated pathological states with NO. (46, 49, 52)

Table IV

Physiological functions of NO in the cardiovascular system	Pathological states associated with NO
Maintains vascular smooth muscle relaxation	Hypertension
Regulates vascular tone	Ischemic heart disease
Regulates blood flow to tissues	Atherosclerosis
Regulates myocardial contractility	Heart failure
Inhibit platelet aggregation and adhesion	Ischemia-reperfusion
Exert an overall antiatherogenic effect	Hypercholesterolemia

Adapted from ref 46.

This discussion regarding NO is germane to the considerations of heart disease in African Americans. There are intriguing data to suggest that African Americans have diminished NO bioavailability and increased oxidant stress. (53) Nitric oxide has a half life of 2-5 seconds in vivo and is not easily assayed. The application of nanotechnology utilizing electrochemical sensors smaller than 200nm in diameter has been used to measure intracellular NO levels. Data acquired from single human umbilical vein endothelial cells [HUVEC] are quite enlightening. In young women, immediately post-partum and pre-screened for an absence of pre-existing cardiac disease, striking differences in nitric oxide homeostasis have been identified. Western blot analysis demonstrates that eNOS expression in African American women is twice that seen in whites, i.e., *higher*. Utilizing nanosensors, the measured bioactivity of NO is however markedly *lower*. After stimulation of eNOS with calcium, the pattern of NO production and peroxynitrite release is quite different. There is an early peak of NO followed by a peak of $ONOO^-$ in white women while African American women demonstrate an initial peak in $ONOO^-$ followed by a blunted and later peak in NO. The rate of release of NO is five times slower and the rate of release of peroxynitrite is two times faster. These data would suggest that despite having more eNOS, the production of NO is blunted, perhaps "uncoupled", in African Americans and provides direct evidence for reduced NO bioavailability in African Americans. (53, 54)

Indirect evidence comes from classical physiological experiments that demonstrate reduced forearm vasodilation in normal and hypertensive African Americans compared to whites. When LNMA, an inhibitor of eNOS, is given to normal African Americans and whites, a reduction in forearm blood flow in response to known vasodilating stimuli is seen in whites with no change noted in African Americans. (55) The conclusion that African Americans function as if eNOS is inhibited at baseline indirectly supports reduced NO bioavailability as well.

Nitrates stimulate NO signaling and may be metabolized to NO in a process known as biotransformation. Thus, nitrates serve as exogenous donors of nitric oxide. Nitrates demonstrate protean clinical effects in the setting of cardiovascular disease including relief of angina, lowering of blood pressure and vasodilation. These favorable effects are unfortunately attenuated after brief exposure to nitrates and the phenomenon of "nitrate tolerance" has been invoked as an explanation. Various mechanisms have been implicated but the more plausible theories include activity of mitochondrial aldehyde oxidase and the production of $ONOO^-$ and superoxide. [Ref] Inhibition of mitochondrial aldehyde oxidase and inhibition of the production of these reactive oxygen species [ROS] and or removal of the same might be deemed beneficial.

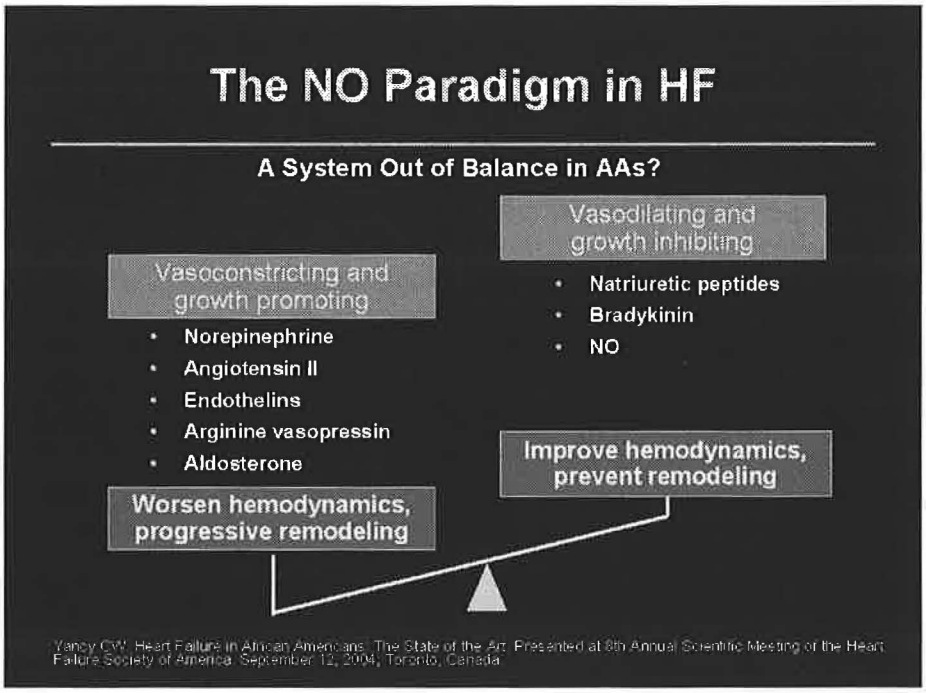
Hydralazine is an intriguing compound that indeed has vasodilatory properties but also represents a potent reactive oxygen species scavenger, especially with regards to $ONOO^-$, and an inhibitor of reactive oxygen species production- perhaps through its inhibition of NADH and NADPH oxidases. Hydralazine also blocks NOS 2 and COX-2 gene expression. (56) The most provocative data now demonstrate that nitrate tolerance occurs via inhibition of mitochondrial aldehyde dehydrogenase, ALDH, which bioactivates nitroglycerin. Hydralazine blunts nitrate tolerance by preventing the NTG induced increase in superoxide production. Hydralazine may also prevent the inhibition of ALDH by reactive oxygen species. (49, 56) In-vitro and clinical data are consistent with a reduction in nitrate tolerance. Vascular smooth muscle strips exposed to NTG yield high levels of ROS with that increase attenuated when NTG plus hydralazine are given. (57) In the clinical context, the administration of NTG to patients with heart failure is associated with a dramatic decline in left ventricular filling pressures but eventual restoration of elevated pressures-a phenomenon consistent with nitrate tolerance. When NTG is given with hydralazine, the reduction in left ventricular filling pressures is sustained. (58) The foregoing biological data and clinical correlates would suggest that the combination of nitrates plus hydralazine represents a candidate therapeutic regimen to enhance nitric oxide bioavailability.

To summarize this discussion, nitric oxide and superoxide exist in a balanced state that promotes normal circulatory and endothelial cell function when NO is adequate and superoxide is at physiological levels. In an environment where NO is replete, there is less platelet aggregation, reduced sheer forces, less leukocyte accumulation, a decreased stimulus for thrombosis and lower blood pressure. In an NO-depleted/O_2- excess environment, the endothelium is at risk for platelet aggregation, leukocyte adhesion and thrombosis, and presumably vascular events, especially hypertension and ventricular remodeling. The production of NO depends upon adequate stores of nicotinamide

adenine dinucleotide phosphate (NADPH) but the activity of NADH and NADPH oxidases inhibits the production of NO and yields instead superoxide and peroxynitrite - both markers of oxidative stress. Therefore, a plausible pathological consideration in cardiovascular disease might be diminished NO availability along with increased oxidative stress. Since nitrates represent an exogenous donor of NO and hydralazine inhibits oxidase activity, this combination has the potential to restore the balance between NO and superoxide.

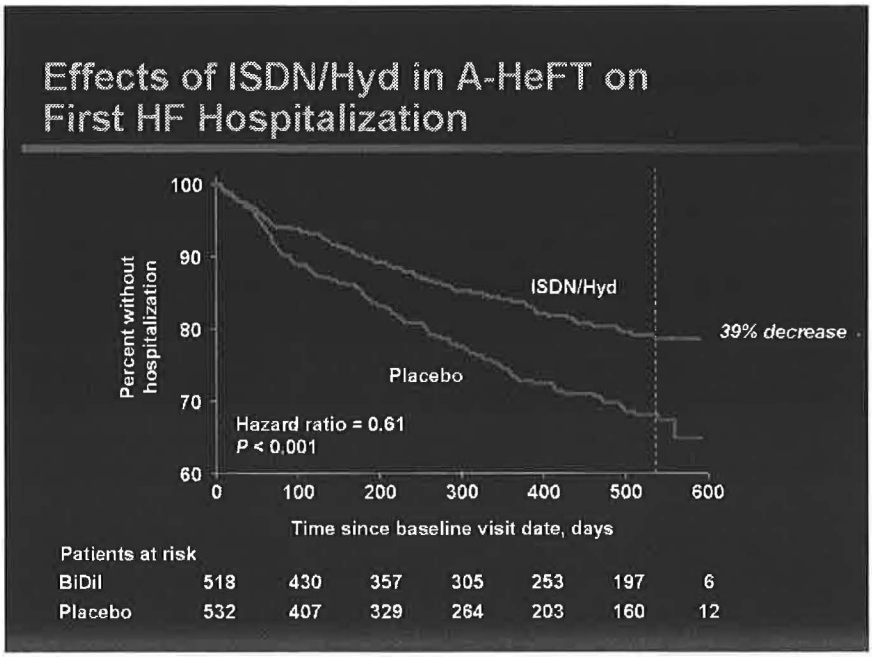
African Americans have demonstrable evidence of diminished nitric oxide bioavailability and enhanced production of peroxynitrite. It is plausible [but not yet proven] that the progression of cardiovascular disease, esp., heart failure, in African Americans might be a result not only of an activated neurohormonal system but also a deficient endogenous vasodilator/growth-inhibiting system. If this is a valid hypothesis, then an adjunctive approach in the management of heart failure in African Americans might be an increase in NO bioavailability along with a decrease in oxidant stress in a background consisting of traditional neurohormonal blockade. See figure 10.

Figure 10



These issues may have direct bearing on the results of the African American Heart Failure Trial (A-HeFT). (59)

Figure 12



The implications of these findings are noteworthy. The mortality rate in the placebo treated patients was ~10% consistent with what would have been expected for this disease severity on standard therapy for heart failure. To achieve a further 43% reduction in the risk of death accentuates the unique benefit of isosorbide dinitrate/hydralazine in combination with standard medical therapy in this patient cohort.

It is intriguing to reflect on the 47% mortality advantage seen in the V-HeFT I experience. The similarity of benefit irrespective of background therapy, i.e., 47% when background therapy is digoxin and diuretics vs. 43% when background therapy is diuretics, ACE-inhibitors and beta blockers, would implicate a novel mechanism of action that is not otherwise modulated by standard therapies. It is tempting to consider enhanced NO availability as the imputed mechanism of action that is operative but it is important to emphasize that A-HeFT is not a proof of concept trial for the efficacy of enhancing nitric oxide bioavailability. Much additional work will need to be done to establish cause and effect. This however represents an important new direction in cardiovascular research.

CONCLUSIONS

Heart failure in African Americans is likely to be a unique disease entity. Its natural history, epidemiology, morbidity, and perhaps even its mortality vary from heart failure in white patients. The influence of hypertension, and its more aggressive natural history in African Americans, is inescapable and carries with it important messages for disease prevention through effective treatment. The data regarding responsiveness to contemporary evidence-based medical therapy are inconsistent and reflect the inherent inaccuracy of post hoc retrospective analyses of underpowered subgroups. There are, however, no data to support avoidance of background therapy including evidence-based strategies, specifically, ACE inhibitors and β-blockers, and it is the judgment of this author that these evidence-based therapies for heart failure are indeed effective in African Americans and should not be omitted from any contemporary treatment regimen.

Ongoing efforts to explain the excess cardiovascular disease burden in African Americans have targeted mechanisms that lead to more malignant varieties of hypertension and genetic profiles that might predispose patients to more advanced left ventricular dysfunction and/or lower responsiveness to medical therapy. Any statements regarding the influence of genetic factors must be taken in the appropriate context because gene-gene interactions, gene-environment interactions, and gene-drug interactions are all likely to occur.

The newest theory regarding the progression of cardiovascular disease in African Americans embraces previous observations of unique benefits from vasodilator therapy in this group. The most relevant vasodilating regimen, isosorbide dinitrate and hydralazine, has now been identified as one that potentially increases NO bioavailability by donating NO while reducing oxidative stress through maintenance of appropriate levels of NADPH and inhibition of superoxide production Specific testing of the benefit of this unique vasodilatory combination has been performed in the setting of African Americans with moderately severe to severe heart failure who are receiving standard evidence-based medical therapy. The favorable outcomes seen in A-HeFT are likely to redefine the state of the art for heart failure in African Americans.

In summary, three points can be stated—1.) an important new treatment for heart failure has emerged; 2.) a patient cohort known to experience a disproportionate disease burden from heart failure can now realize clinically demonstrable benefits and an important cardiovascular disease inequity can be diminished; and 3.) a new mechanism of cardiovascular disease progression has been implicated and serves as a potential opportunity for additional therapeutic advances.

The data emanating from the A-HeFT experience are important, if not landmark. We should not fail to implement these treatment strategies in African Americans with heart failure. At least part of the enigma is resolved.

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