INTERNAL MEDICINE GRAND ROUNDS

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UT SOUTHWESTERN MEDICAL CENTER

THE NATURAL HISTORY OF HYPERTENSIVE HEART DISEASE:

DOES IT LEAD TO HEART FAILURE?

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Biographical Sketch

Clyde W. Yancy, M.D. is an associate professor of Internal Medicine in the Department of Internal Medicine, Division of Cardiology at UT Southwestern Medical Center. Currently he serves in several roles within the medical center and at its affiliated hospitals:

-Medical Director, Heart Failure/Transplant Service, UT Southwestern
-Medical Director, UT Southwestern/St. Paul Medical Center Heart Transplant Program
-Medical Director, Baylor University Medical Center/UT Southwestern Medical Center Heart Transplant Program on the campus of BUMC, Dallas TX
-Program Director, Cardiovascular Institute at St. Paul Medical Center which encompasses the Heart Failure Program/Clinic and the Pulmonary Hypertension Clinic

Dr. Yancy also serves on several State and National Entities focused on Cardiovascular Health:

-National Board of Directors, American Heart Association
-Past President, Texas Affiliate of the American Heart Association
-President, Texas Coalition on Cardiovascular Disease and Stroke-*a public advocacy organization that is aligned with both the Texas legislature and the newly created Cardiovascular Council within the Texas Department of Health*
-Texas Medical Association, subcommittee on Cardiovascular Disease
-National Transplant Cardiology Research Database, Executive Committee
-Chair-Elect, American Heart Association Subcommittee on Heart Failure and Transplantation, 2001

There are several ongoing initiatives with entities within the pharmaceutical industry including Astra-Zeneca, Merck & Co., Monarch, Sanofi-Synthelabo, SmithKline Beecham, and Roche

Professional Interests: Treatment of advanced heart failure including newer pharmaceutical agents and devices; Heart failure in special populations; Newer immunosuppressive therapy in heart transplantation; Exercise dysfunction s/p cardiac transplantation; and Cardiovascular Health as a public health initiative.

Hobbies include: golfing; cycling; fitness; music; travel

His passion in life is parenting Kristin, 11, and Nina, 9.

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HYPERTENSION AS A CAUSE OF HEART FAILURE

Introduction

Heart failure continues to be a leading cause of cardiovascular morbidity, mortality and health care expenditures with its highest prevalence in the elderly population. Heart failure affects ~10% of all individuals >79 years old. Two per cent of the adult population over the age of 65 is hospitalized for heart failure on an annual basis. (Ref 1) Of all patients affected with heart failure, 75% are > 65 years old. The costs of therapy are staggering and easily approach tens of *billions* of dollars annually. The individual cost of care for advanced heart failure management can approach $20,000 per year. (Ref 2) Newer medical therapies such as vasopeptidase inhibitors, endothelin antagonists, TNF receptor antagonists, and natriuretic peptides are likely to become available in the near future. As well, we are entering an era of device therapy for heart failure, e.g., implantable defibrillators, triple chamber pacing and infarct exclusion procedures. The standard of care for this condition will become even more complex and more costly-- to the extent perhaps that the optimal management of heart failure applied to the entire population at risk may become cost-prohibitive.

The consistent use of neurohormonal antagonists, especially angiotensin converting enzyme inhibitors and beta-blockers, has resulted in substantive decrements in death, the combined endpoint of death and hospitalizations, and hospitalizations for heart failure. (Ref 3, 4, 5, 6, 7) It is apparent however that any significant decline in cardiovascular morbidity, mortality and health care expenditures due to heart failure will need to result from earlier intervention. As such, this necessarily entails an evaluation of causative factors with a search for preventable and/or modifiable causes of heart failure.

The recent description of potentially unique characteristics of heart failure in African-Americans has yielded a possible target for preventing heart failure in a large number of individuals. (Ref 8) An emerging database (with significant contributions from researchers here at UT Southwestern; see appendix and Ref. 9, 10) has identified a higher mortality rate, unique epidemiology, different disease etiology, and in an as yet unresolved issue, a potentially important difference in response to medical therapy for heart failure—especially with regards to the use of neurohormonal antagonists. A recent review of the SOLVD (Studies of Left Ventricular Dysfunction) trials demonstrated that the mortality rate for African Americans with heart failure was 1.8 fold higher for men and 2.4 fold higher for women when compared to the non-African American population. (Ref 9) In all reported databases, heart failure occurs at an earlier age in African Americans, has a greater incidence of left ventricular hypertrophy, worse disease severity at the time of diagnosis and more advanced left ventricular dysfunction at the onset of clinical disease. A retrospective review of both Veterans Administration Heart Failure

Trials (V-HeFT I & II) has suggested that all of the survival advantage attributed to direct vasodilator therapy with nitrates and hydralazine in V-HeFT I occurred only in the African American population. Moreover, in V-HeFT II, which demonstrated a survival advantage of angiotensin converting enzyme inhibitor therapy when compared to direct vasodilator therapy, the only group to show this survival advantage was the non-African American population. (Ref 11) Perhaps the most disturbing data come from the BEST trial (Beta-Blocker Evaluation of Survival Trial) which is a randomized, controlled trial of beta-blocker therapy in heart failure that failed to reach its prespecified endpoint of a reduction in all cause mortality. Apart from drug-specific issues related to the use of bucindolol, this trial differed substantially from other studies due to a study population that included 23% African Americans (By contrast the recent COPERNICUS and MERIT-HF trials both had fewer than 5% non-white participants, Ref 4, 7). African American patients failed to show a survival advantage in response to bucindolol and had a disturbing but non-statistically significant trend towards increased mortality on bucindolol therapy. (Ref 9)

All of the foregoing observations are indeed disturbing and suggest a number of unresolved questions. A plausible explanation for these disparate outcomes may be found in a review of disease etiology. Consistently, every reported database regarding heart failure in African Americans has demonstrated the striking presence of hypertension as the presumed **primary** cause of heart failure. Aggregate data taken from the major heart failure trials have suggested that ~60% of cases of heart failure in African Americans can be attributed to hypertensive heart disease. It has been suggested that *"The majority of heart failure in African Americans is ostensibly preventable, and the mandate for effective antihypertensive strategies should be strengthened."* (Ref 8) Implicit in this statement is the premise that hypertensive heart disease leads to heart failure and that treatment of hypertension reduces the incidence of heart failure. Clearly, not all heart failure in African Americans is due to hypertension and not all heart failure in non-African Americans is due to ischemic heart disease. In fact, the entire population affected by hypertension is at risk for heart disease. As such several questions can be raised:

1. What are the data that indeed demonstrate that hypertension does lead to heart failure?
2. Does therapy of hypertension lead to a reduction in cardiovascular disease in general and specifically, does treatment of hypertension reduce the incidence of heart failure?
3. What mechanisms may be responsible for the development of left ventricular hypertrophy in the setting of hypertension?
4. Are there current or future strategies that may be uniquely beneficial in attenuating the progression of hypertensive heart disease to left ventricular failure?

QUESTION 1: DOES HYPERTENSION LEAD TO HEART FAILURE?

The best information that specifically addresses hypertension as a cause for heart failure comes from the Framingham data. (Ref 12, 13). A total of 5143 subjects were followed from January 1, 1970 with hypertension assessed at periodic clinical evaluations and heart failure identified by the presence of two major or one major and two minor criteria

(see Table I, Ref 14]. There were 72422 person-years of follow up with a mean follow-up of 14.1 years. There were 392 cases of heart failure identified. (See Figure 1,Ref 15) In ***91%,*** (357/392), hypertension predated the onset of heart failure. Among the hypertensive subjects, myocardial infarction, diabetes, left ventricular hypertrophy and valvular heart disease were predictive of increased risk for heart failure. Even after accounting for these risk factors, the hazard of developing heart failure in hypertensive subjects vs. normotensive subjects was 2-fold in men and 3-fold in women. (Ref 16) A population-attributable risk was identified for the relationship between hypertension and heart failure. The population-attributable risk represents the percentage of disease cases that can be attributed to a risk factor given its prevalence and hazard ratio and it assumes a causal relationship between the risk factor and the occurrence of disease. Relative risk describes risk to an individual whereas population-attributable risk reflects the public health impact of a specific risk factor. This calculation for hypertension and heart failure yielded a population-attributable risk of 39% for men and 59% for women. This means that 39% of heart failure was attributable to hypertension in men as compared to 34% for myocardial infarction and 7% for valvular heart disease. (Ref 16) The suggestion is that hypertension may be the most important precursor of heart failure. (See Table II, Ref 15) To emphasize the importance of hypertension in the development of heart failure, a group of elderly patients in the Framingham Heart Study were followed for over 40 years and the development of heart failure was evaluated. Only *11%* of men and *15%* of women had neither hypertension nor coronary artery disease. (See Figure 2, Ref 15, 17)

In hypertensive subjects, the presence of myocardial infarction was associated with a 5-6-fold increase in risk for heart failure. Left ventricular hypertrophy in these hypertensive subjects was associated with a 1.9 fold increase risk of heart failure for men and 2.8 fold increase risk for women. Diabetes and hypertension resulted in an increased risk of heart failure of 1.78 for men and 3.57 for women. Pre-existing valvular heart disease was seen in 30% of hypertensive heart failure cases and was associated with a 2 fold increased risk for heart failure. (Ref 16)

Data that are <u>not</u> available from the Framingham Heart Study pertain to the unanswered question of the incidence of hypertension-only cases of heart failure. A major limitation of the Framingham Heart Study is a patient population that is virtually 100% Caucasian. The recent experience of major heart failure trials has demonstrated that hypertension, as the sole cause of heart failure in a non-African American population is quite low. One of the foregoing risk factors (prior myocardial infarction, diabetes, left ventricular hypertrophy and valvular heart disease) appears to be necessary even in the presence of hypertension. This may not be the case in African Americans or other populations with a higher incidence of hypertension. A "Framingham-like" survey in a population with a higher prevalence of hypertension might yield a striking number of "hypertension only" cases of heart failure and an even higher relative risk and population-attributable risk of developing heart failure in the setting of hypertension. Two ongoing surveys may provide such data: The Jackson Heart Study (University of Mississippi-H. Taylor, M.D., principal investigator) and the Dallas Heart Disease Prevention Project as a part of the Reynolds Grant (UT Southwestern Medical Center, R.S. Williams M.D. et al)

TABLES I and II

TABLE I Clinical signs and symptoms as diagnostic criteria for heart failure [a]

Major criteria
Paroxysmal nocturnal dyspnea (PND)
Neck vein distention (JVD)
Acute pulmonary edema
Central venous pressure (CVP) >16 cm H_2O
Hepatojugular reflux (HJR)
Weight loss of more than 10 lb with therapy
Third heart sound (S3)
Minor criteria
Bilateral ankle edema
Nocturnal dyspnea
Hepatomegaly
Pleural effusion
Decreased vital capacity (FVC)
Heart rate (100 bpm)

[a] Two major or one major and two minor criteria to make diagnosis.

TABLE II Population-Attributable Risk Associated With Major Causes of Cardiac Failure in Framingham Heart Study Participants

	Prevalence		Relative Risk*		Population-Attributable Risk	
Risk Factor	Men	Women	Men	Women	Men	Women
Hypertension	60%	62%	2.07	3.35	39%	59%
Myocardial infarction	10%	3%	6.34	6.01	34%	13%
Valvular heart disease	5%	8%	2.47	2.13	7%	8%

*Adjusted for age and risk factors such as angina, diabetes, and left ventricular hypertrophy.
Adapted from *JAMA*.[13]

FIGURES 1 and 2

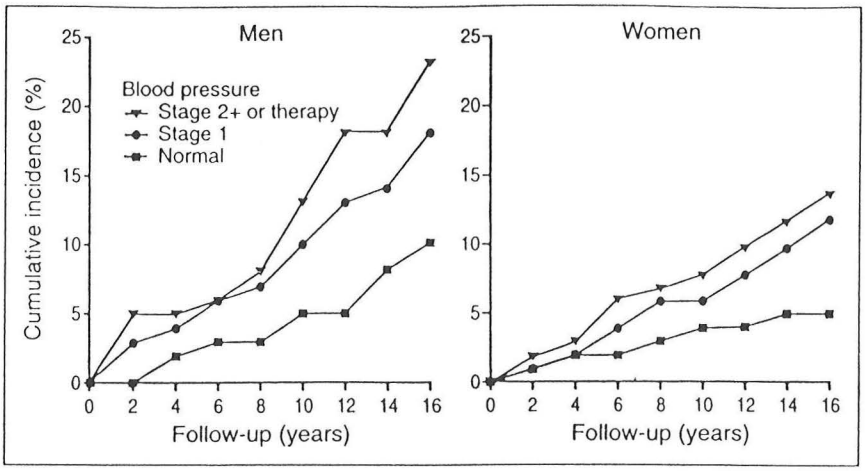


FIGURE 1. Cumulative incidence of cardiac failure during a mean follow-up of 14.1 years in Framingham Heart Study participants aged 60–69 years at baseline. Stage 1 hypertension = systolic blood pressure (SBP) 140–159 mm Hg or diastolic blood pressure (DBP) 90–99 mm Hg in subjects not receiving antihypertensive treatment; stage 2 or greater = SBP ≥160 mm Hg, DBP ≥100 mm Hg, or current treatment for hypertension. (Adapted with permission from *JAMA*.[13])

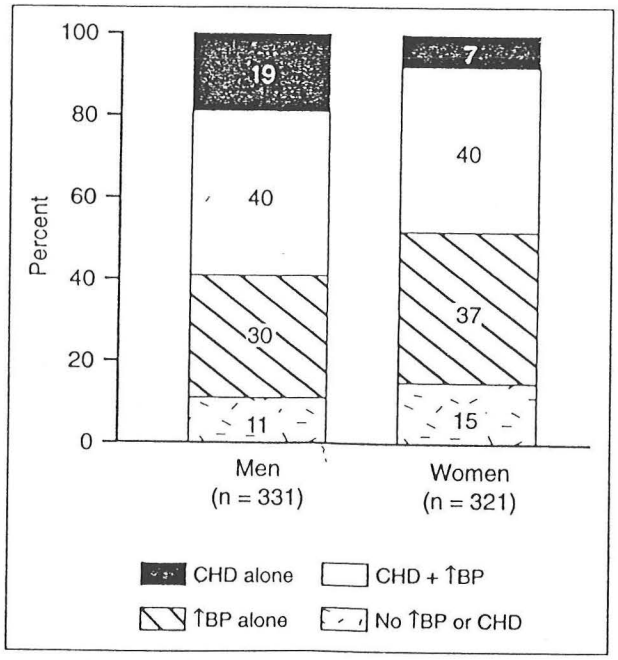


FIGURE 2. History of coronary heart disease (CHD) and hypertension (↑ BP) in middle-aged and elderly Framingham Heart Study participants in whom cardiac failure developed, mean age 70 years at time of cardiac failure. (Data from *J Am Coll Cardiol*.[15])

Clinical Correlation#1—The majority of heart failure is due to known and potentially modifiable risk factors, principally hypertension and atherosclerosis manifest as ischemic heart disease, that can at least in part be ameliorated by aggressive primary prevention strategies.

QUESTION 2: DOES THERAPY OF HYPERTENSION LEAD TO A REDUCTION IN CARDIOVASCULAR DISEASE IN GENERAL AND SPECIFICALLY, DOES TREATMENT OF HYPERTENSION REDUCE THE INCIDENCE OF HEART FAILURE?

Surprisingly, the answer to the foregoing question is not at first evaluation clear. In general the benefit of anti-hypertensive therapy has been greater regarding risk reduction for stroke but less so for heart disease. This concern was sharply underscored by the recent termination of the use of doxazosin, an alpha-adrenergic blocker, in the ALLHAT trial [The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial]. In this trial the risk of heart failure in patients treated with doxazosin was ***doubled***, 8.13% vs. 4.45% as compared to those patients on a thiazide diuretic only. (Ref 18)

The ALLHAT trial enrolled 42,448 patients from 625 centers, age >55, with hypertension and at least one other coronary heart disease risk factor. Additional risk factors considered included history of prior myocardial infarction, stroke, left ventricular hypertrophy, diabetes, tobacco abuse and low high-density lipoprotein. The patients were randomly assigned to one of four regimens: chlorthalidone, doxazosin, amlodipine and lisinopril. There were 15,268 patients assigned to chlorthalidone and 9,067 patients assigned to doxazosin. Planned follow-up was 4-8 years. Entry BP was 145/83 in the doxazosin group and 145/84 in the chlorthalidone group. The primary endpoint was coronary heart disease death or non-fatal myocardial infarction. Secondary endpoints were all-cause mortality, stroke, angina, coronary revascularization, heart failure and peripheral arterial disease. The doxazosin arm was stopped prematurely at a mean of 3.3 years of follow-up. There were 365 deaths in the doxazosin arm and 608 deaths in the diuretic arm (RR 1.03). Total mortality was not different. The doxazosin arm had a higher risk of stroke (RR 1.19; 95% CI, 1.01-1.40, p=0.04). When heart failure was considered separately, the risk was doubled (RR 2.04; 95% CI, 1.79-2.32; p<0.001). See figure 3, (Ref 18).

How is this peculiar observation to be reconciled? Alpha-blocker therapy is widely used, especially for prostate disease. The drug class is associated with lowered cholesterol levels and improved insulin sensitivity—both are factors which should *improve* cardiovascular outcomes. The data were evaluated by an intent to treat analysis whether subjects remained on active therapy or not. Whereas 86% of patients treated with diuretics remained on active therapy, only 75% of those treated with doxazosin remained on active therapy. This difference in compliance combined with an intent to treat analysis may have influenced the outcomes in an unfavorable way.

Importantly, there was a difference in the degree of BP reduction in the group on doxazosin vs. diuretics. The mean systolic BP in the doxazosin group was 3mmHg higher than in the diuretic group. The diastolic BP mean was similar in both groups. See figure 4, (Ref 18). This seemingly trivial difference in systolic blood pressure may have been quite important in the genesis of heart failure. In the Systolic Hypertension in the Elderly Program, (Ref 19), a 12 mmHg reduction in systolic BP using diuretics resulted in a 49% reduction in heart failure incidence. In the Systolic Hypertension in Europe Trial, a 10mmHg reduction in systolic BP (using nitrendipine) resulted in a 29% decrease in heart failure incidence. It is thus plausible that a 3 mmHg difference could account for a 10-20% difference in heart failure incidence.

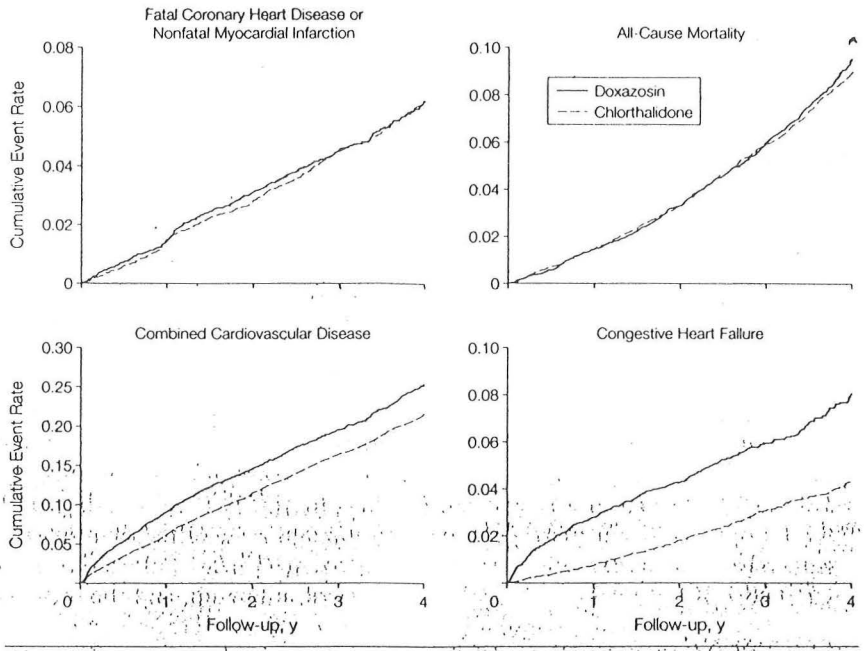
Another plausible explanation is the lack of reduction in left ventricular hypertrophy using doxazosin compared to diuretics which was demonstrated in the Treatment of Mild Hypertension Study. It is also known that alpha blockers are associated with an increase in plasma volume and appear to be associated with an increase in plasma norepinephrine levels—something we know to be harmful in the genesis and maintenance of heart failure.

The actual explanation for this finding may never be fully elucidated and may be a function of several, if not all, of the foregoing explanations.

Clinical Correlation #2: Based on this review of the ALLHAT data, it would seem inappropriate to use doxazosin as monotherapy in the setting of systolic hypertension associated with concomitant coronary heart disease risk factors. However diuretic therapy in this same setting appears to change the natural history of cardiovasacular disease due to hypertension.

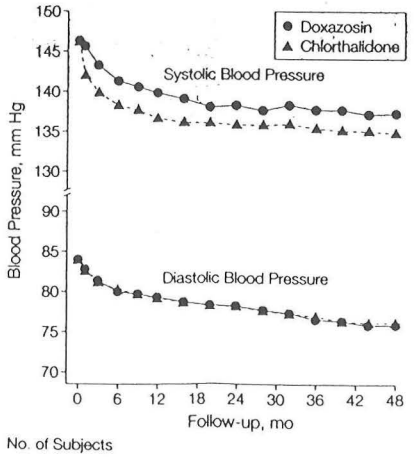
FIGURES 3 and 4

Figure 3. Kaplan-Meier Estimates for Outcomes in the Doxazosin and Chlorthalidone Groups



Kaplan-Meier estimates are shown for coronary heart disease (primary outcome; $P=.71$), all-cause mortality ($P=.56$), combined cardiovascular disease ($P<.001$), and congestive heart failure ($P<.001$).

Figure 4. Average Systolic and Diastolic Blood Pressure During ALLHAT Follow-up



No. of Subjects

Chlorthalidone				
15268	11902	9620	5380	2633
Doxazosin				
9067	6799	5530	3044	1487

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

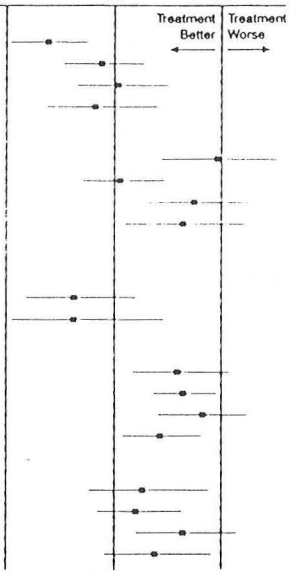
Fortunately, this peculiar experience with doxazosin therapy from the ALLHAT trial is buffeted by an increasing database that suggests that the natural history of cardiovascular disease due to hypertension can be altered by effective, and simple, antihypertensive therapy and that specific reductions in the incidence of heart failure can be realized, especially in patients with systolic hypertension.

In a major review article by Psaty et. al., published in 1997, 18 long-term randomized trials were reviewed and included in a meta-analysis to determine the efficacy of anti-hypertensive therapy on stroke and cardiovascular disease. (Ref 20) These trials included 48,220 patients in randomized trials followed for an average of 5 years. Three treatment regimens predominated: high dose diuretics (especially in the early studies); lower dose diuretics (especially in trials of systolic hypertension therapy); and beta blockers. All three therapies reduced the incidence of stroke: RR 0.49, 0.66, and 0.71 for high dose diuretics, low dose diuretics and beta-blockers respectively. High dose diuretic therapy and beta-blocker therapy were no better than placebo at reducing coronary heart disease, RR 0.99 and 0.93 respectively. Low dose diuretic therapy did reduce the incidence of coronary artery disease, RR 0.72.

All three strategies were effective in reducing the incidence of heart failure (however heart failure per se was not consistently followed in all of the trials). The RR with low dose diuretics was 0.58; for beta blocker therapy, the RR was also 0.58. The RR was strikingly low (RR 0.17!) for higher dose diuretics but there were only 41 recorded events among the 9 trials using high dose diuretics, thus this finding is a statistical aberration. See table III, (Ref 20).

TABLE III.

Outcome / Drug Regimen	Dose	No. of Trials	Events, Active Treatment/Control	RR (95% CI)
Stroke				
Diuretics	High	9	88/232	0.49 (0.39-0.62)
Diuretics	Low	4	191/347	0.66 (0.55-0.78)
β-Blockers		4	147/335	0.71 (0.59-0.86)
HDFP	High	1	102/158	0.64 (0.50-0.82)
Coronary Heart Disease				
Diuretics	High	11	211/331	0.99 (0.83-1.18)
Diuretics	Low	4	215/363	0.72 (0.61-0.85)
β-Blockers		4	243/459	0.93 (0.80-1.09)
HDFP	High	1	171/189	0.90 (0.73-1.10)
Congestive Heart Failure				
Diuretics	High	9	6/35	0.17 (0.07-0.41)
Diuretics	Low	3	81/134	0.58 (0.44-0.76)
β-Blockers		2	41/175	0.58 (0.40-0.84)
Total Mortality				
Diuretics	High	11	224/382	0.88 (0.75-1.03)
Diuretics	Low	4	514/713	0.90 (0.81-0.99)
β-Blockers		4	383/700	0.95 (0.84-1.07)
HDFP	High	1	349/419	0.83 (0.72-0.95)
Cardiovascular Mortality				
Diuretics	High	11	124/230	0.78 (0.62-0.97)
Diuretics	Low	4	237/390	0.76 (0.65-0.89)
β-Blockers		4	214/410	0.89 (0.76-1.05)
HDFP	High	1	195/240	0.81 (0.67-0.97)



Meta-analysis of randomized, placebo-controlled clinical trials in hypertension according to first-line treatment strategy. Trials indicate number of trials with at least 1 end point of interest. RR indicates relative risk; CI, confidence Interval; and HDFP, Hypertension Detection and Follow-up Program Study (5484 subjects in stepped care and 5455 in referred care). For these comparisons, the numbers of participants randomized to active therapy and placebo were 7768 and 12 075 for high-dose diuretic therapy; 4305 and 5116 for low-dose diuretic therapy; and 6736 and 12 147 for β-blocker therapy. Because the Medical Research Council trials[26] included 2 active arms, the placebo group is included twice in these totals, once for a diuretic comparison and again for a β-blocker comparison. The total number of participants randomized to active therapy and control therapy were 24 294 and 23 926, respectively.

The inescapable conclusion from this review and meta-analysis is that anti-hypertensive therapy has been shown to reduce the incidence of stroke and cardiovascular disease in general and that both diuretic therapy and beta blocker therapy for hypertension are associated with a reduction in the incidence of heart failure.

Of the trials reviewed for this meta-analysis, several merit separate comments.

The Systolic Hypertension in the Elderly Program evaluated 4736 patients, >60 years old with systolic BP between 160 and 219 but a diastolic BP < 90mmHg. The patients were entered into a placebo controlled randomized trial using stepped care with chlorthalidone, 12.5 to 25mg, (step 1) and atenolol 25-50mg, (step 2). Fatal and nonfatal heart failure was a primary outcome measurement. Follow-up was 4.5 years. Heart failure events occurred in 55 of 2365 patients on active therapy and 105 of 2371 patients on placebo. RR 0.51; 95% CI, 0.37-0.71; p<0.001—*the number needed to prevent one event, 48.* For those patients with a prior myocardial infarction, the RR was 0.19; 95% CI 0.06-0.53; p=0.002—*the number needed to prevent one event, 15.* See figure 5, (Ref. 19).

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) was a double blind randomized controlled trial in 1627 elderly patients with hypertension. Patients were assigned to either beta-blockers or a combination of hydrochlorothiazide and amiloride. Active treatment was compared to **placebo.** Fatal and non-fatal strokes were reduced by 47%, and major cardiovasacular events including myocardial infarctions were reduced by 40%. Total mortality was reduced by 43%, (Ref 21).

STOP-Hypertension-2 study was a second trial designed to compare conventional therapies, i.e., diuretics and beta blockers, with newer therapies, specifically angiotensin converting enzyme inhibitors (enalapril and lisinopril) and newer calcium channel blockers (isradipine and felodipine). The trial randomized 6614 patients with entry BP criteria of systolic BP >180 mmHg, or diastolic BP > 105 mmHg or both. Patients received either conventional therapy or newer therapy. ACE-inhibitors were given to 2205 patients and calcium antagonists were given to 2196 patients. Conventional therapy was given to 2213 patients. Overall, there was no difference in the outcomes of fatal stroke, fatal myocardial infarction or other fatal cardiovascular events, RR 0.99. However, the relative risk for developing heart failure trended lower with ACE-inhibitor therapy, RR 0.83, 95% CI, 0.67-1.03, p=0.09. There was a slight trend towards an increase in heart failure events in patients treated with calcium channel blockers, RR 1.06. See figure 6, (Ref 22).

An updated meta-analysis of therapy of isolated systolic hypertension in the elderly was recently reported. Heart failure incidence was not an evaluated data point, however several findings were noteworthy and are pertinent to this discussion. In this meta-analysis by Staessen et. al., the focus was only on trials in patients with systolic hypertension. (Ref 23) Eight trials were combined encompassing 15,693 patients, age > 60 and systolic BP > 160 mmHg with a diastolic BP < 95mmHg. The remarkable finding

FIGURES 5 and 6

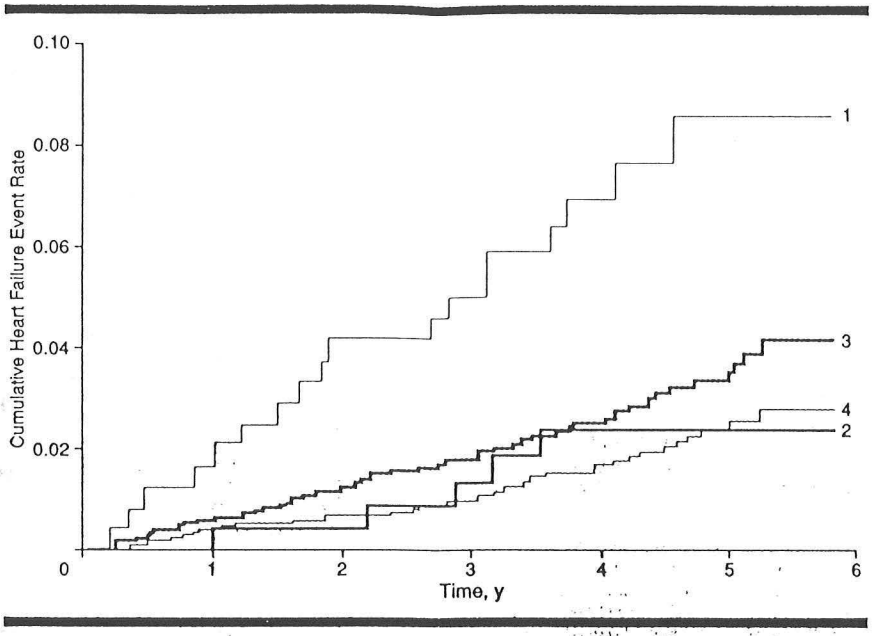
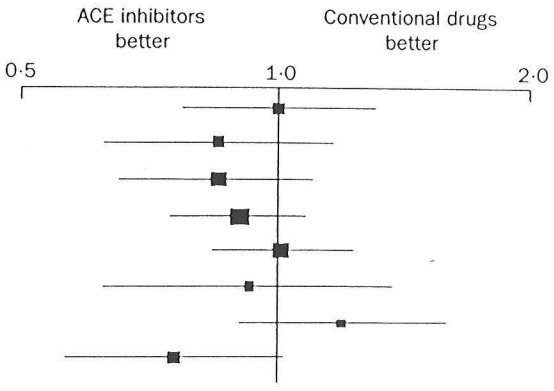


Figure 5.—Occurrence of fatal and hospitalized nonfatal heart failure in the active therapy and placebo groups of the Systolic Hypertension in the Elderly Program among participants who had a history or electrocardiographic evidence of myocardial infarction (MI) at baseline and among those who did not have a history or electrocardiographic evidence of MI at baseline. Line 1 indicates placebo group (patients with a history of MI at baseline); line 2, active therapy group (patients with a history of MI at baseline); line 3, placebo group (patients with no history of MI at baseline); and line 4, active therapy group (patients with no history of MI at baseline).

FIGURE 6.

	Relative risk (95% CI)*	p
Cardiovascular mortality	1·01 (0·84–1·22)	0·89
All myocardial infarction	0·90 (0·72–1·13)	0·38
All stroke	0·90 (0·74–1·08)	0·24
All major cardiovascular events	0·94 (0·82–1·07)	0·32
Total mortality	1·02 (0·89–1·18)	0·76
Frequency of diabetes mellitus	0·96 (0·72–1·27)	0·77
Frequency of atrial fibrillation	1·15 (0·94–1·41)	0·18
Frequency of congestive heart failure	0·83 (0·67–1·03)	0·095



Relative risk of cardiovascular mortality and morbidity for ACE inhibitors vs conventional drugs

*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.

from this trial was that diastolic blood pressure in this group was **inversely correlated with total mortality.** This would suggest that a widened pulse pressure is particularly problematic. (See figure 7). The number of patients needed to treat to prevent one cardiovascular death was 119 if the pulse pressure was < 90mmHg but this number decreased to **63** for a pulse pressure >90 mmHg. The authors correctly point out that if improving distensibility of the large arteries could be proven to change outcomes, the management of hypertension is this group of patients might change in a profound way.

The Captopril Prevention Project (CAPPP) was a randomized trial, recently reported, that evaluated 10985 patients with diastolic hypertension (DBP > 100mmHg) in a randomized trial conducted in 536 centers in Sweden and Finland. (Ref 24) Primary endpoints were a composite of fatal and non-fatal myocardial infarction, stroke and cardiovascular deaths. Patients were randomized to either captopril or conventional anti-hypertensive therapy with diuretics and beta-blockers. Cardiovascular mortality was lower with captopril but the rate of myocardial infarction was similar and more strokes were seen in the captopril group. Blood pressure was higher in the captopril group and the incidence of diabetes was likewise higher. The blood pressure difference was 2mmHg but once again, it is suggested that this seemingly minor difference in BP control may have accounted for a 15% difference in outcomes. Among the patients with diabetes, there was a 66% lower rate of fatal and non-fatal myocardial infarctions in the captopril group than in the conventional group. See figure 8. (Ref 24) The authors conclude that the use of ACE-inhibitors for hypertension control is as effective as conventional therapy with diuretics and beta-blockers for the prevention of cardiovascular morbidity and mortality but perhaps less effective for the prevention of stroke. In the setting of diabetes, ACE-inhibitor therapy appears most effective.

Clinical Correlation #3: The available data support the hypothesis that therapy of hypertension is associated with a reduction in the incidence of both stroke and cardiovascular events. The effect of anti-hypertensive therapy on heart failure appears to be greatest in the elderly patient with systolic hypertension. The width of the pulse pressure may represent a novel "risk factor" in this patient population. A pulse pressure > 90mmHg is associated with worse outcomes. The presence of a wide pulse pressure should prompt aggressive intervention with anti-hypertensive therapy. Curiously, minor reductions in blood pressure control may be associated with significant improvement in the natural history of hypertensive heart disease. Surprisingly, there does not appear to be a dramatic benefit of ACE-inhibitors over conventional therapy except in those hypertensive patients with established diabetes.

FIGURES 7 and 8

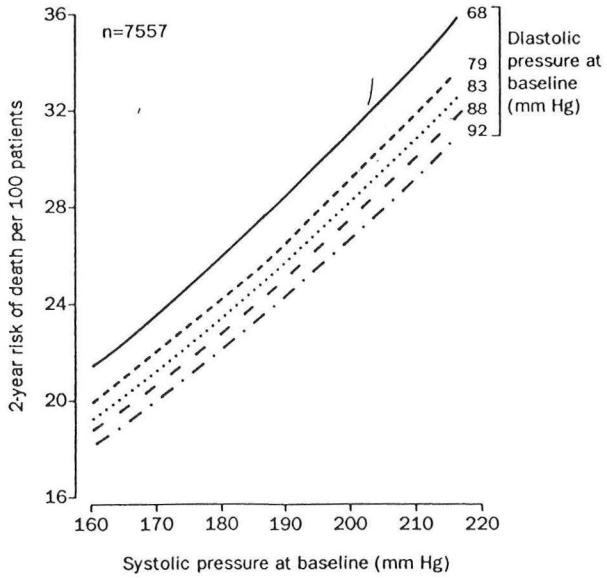
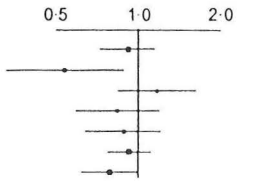


Figure 7. **Risk of death associated in control patients with systolic pressure at baseline at fixed levels of diastolic pressure**

The 2-year probability of death was standardised to female sex, mean age (70 years), no previous cardiovascular complications, and non-smoking.

FIGURE 8.

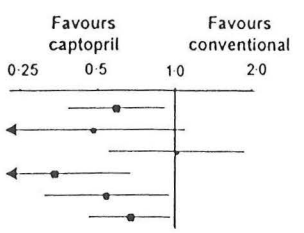
	Relative risk* (95% CI)	p
Primary endpoint	0·92 (0·72–1·16)	0·47
Fatal cardiovascular events	0·54 (0·33–0·89)	0·015
Stroke, fatal and non-fatal	1·18 (0·84–1·65)	0·34
Myocardial infarction, fatal and non-fatal	0·84 (0·59–1·21)	0·35
All fatal events	0·89 (0·64–1·23)	0·48
All cardiac events	0·93 (0·77–1·13)	0·48
Diabetes mellitus	0·78 (0·62–0·99)	0·041



Relative risk in previously untreated patients (n=5245)

*Adjusted for age, sex, diabetes, and systolic blood pressure.

	Relative risk* (95% CI)	p
Primary endpoint	0·59 (0·38–0·91)	0·019
Fatal cardiovascular events	0·48 (0·21–1·10)	0·085
Stroke, fatal and non-fatal	1·02 (0·55–1·88)	0·95
Myocardial infarction, fatal and non-fatal	0·34 (0·17–0·67)	0·002
All fatal events	0·54 (0·31–0·96)	0·034
All cardiac events	0·67 (0·46–0·96)	0·030



Relative risk in patients with diabetes mellitus at baseline (n=572)

*Adjusted for age, sex, systolic blood pressure, and previous treatment.

Although not a hypertension trial, the Heart Outcomes Prevention Evaluation Study [HOPE] is a major trial addressing the effects of ramipril on cardiovasacular outcomes in people at high risk for cardiovascular events. (Ref. 25) Over 9000 patients (9541) were randomized to ramipril or vitamin E vs. placebo. The patients were to be followed for 4-6 years in a study powered to detect a 12% relative risk reduction in cardiovascular death, myocardial infarction or primary stroke. The secondary outcomes were the need for revascularization, incidence of heart failure, and diabetic complications, especially microalbuminuria. Inclusion criteria were age >55 with any evidence of vascular disease (e.g., coronary artery disease, prior stroke, peripheral vascular disease) OR diabetes plus one other risk factor. Patients who already had heart failure were excluded.

The trial was stopped 6 months early because of a striking benefit of ramipril on the primary outcomes compared to placebo. There was a 25% reduction in the composite outcome of myocardial infarction, stroke and cardiovascular death. (P=0.0004). Myocardial infarction was reduced by 22%; stroke was decreased by 33% and CV death by 37%. Importantly, there was a 17% reduction in heart failure incidence.

Of the patients enrolled, 46.5% (4,355 patients) had a history of hypertension, and demonstrated a greater reduction in the composite endpoint, RR 0.78 compared to 0.82, when compared to those patients without a history of hypertension. Importantly, the placebo event rate for hypertensive patients was among the highest for all groups studied. The average blood pressure reduction in the HOPE trial was a change of only 2.4 mmHg, systolic, and 1.0 mmHg, diastolic.

From a public health perspective, if 25% of all patients with vascular disease similar to the HOPE study group were treated with ramipril, nearly one million fewer deaths would occur globally on an annual basis. Nearly one-half million fewer episodes of heart failure and diabetic complications would occur.

Clinical Correlation #4: In my opinion, the HOPE data represent a new standard of care for a large population of patients at risk for cardiovascular events. Patients over the age of 55 with known atherosclerotic disease should be started on low dose ACE-inhibitor therapy even in the absence of overt left ventricular dysfunction, with or without concomitant hypertension. Whether or not this is a class effect of ACE-inhibitors, a unique effect of "tissue ACE-inhibitors" or peculiar to ramipril is not known. Until additional data are available, ramipril would appear to be the most appropriate drug in this setting.

The foregoing trials demonstrate that treatment of hypertension in an at-risk population leads to a reduction in cardiovascular events and a reduction in episodes of heart failure. The reduction in episodes of heart failure is likely due to the reduction in cardiovascular events but clearly there is an as yet unidentified contribution from hypertensive heart disease. Neither the natural history of, nor the incidence of overt left ventricular dysfunction due solely to hypertension in the absence of coronary artery disease has been

described. The true incidence is also likely to vary among the population studied and almost assuredly will be influenced by ethnic and/or genetic factors.

If one presumes that this natural history exists, it is important to consider mechanisms that may be responsible for the conversion from intact ventricular function in the setting of hypertension to left ventricular failure.

QUESTION 3: WHAT MECHANISMS MAY BE RESPONSIBLE FOR THE DEVELOPMENT OF HEART FAILURE IN THE SETTING OF HYPERTENSION?

The presence of left ventricular hypertrophy demonstrates that hypertension, as a mechanical stimulus, leads to a biological signal which in a permissive environment contributes to abnormal cell growth. This response is not uniform since left ventricular hypertrophy occurs in only 30% of patients with hypertension (Ref 26). This would support the necessary presence of other factors in order for left ventricular hypertrophy to develop. In fact, it would appear that certain patients, perhaps the majority, are *protected* from LVH in the setting of hypertension while others experience *exaggerated hypertrophy.*

The process of ventricular hypertrophy, i.e., remodeling, is presumed to occur in response to hypertension as an adaptation to long-term exposure to an elevated blood pressure. Stimuli that may participate in this process are likely to be both mechanical and biological. Mechanoreceptors have been hypothesized to be present on myocardial cells. Mechanical stress has been shown to activate protein kinase C which in turns activates several MAP (mitogen activated protein) kinase pathways. This ultimately leads to increased protein synthesis. (Ref 27) Protein kinase C pathways also increase gene transcriptional programs for increased protein synthesis. Fetal gene programs may also become activated and when applied to terminally differentiated cells lead to cellular hypertrophy. Biological signals undoubtedly contribute to this process. Angiotensin II is a major stimulus for hypertrophy and increased adrenergic activity, i.e., increased plasma norepinephrine activity, similarly elicits a growth response. See figure 9, (Ref 28). Patterns of hypertrophy have been described and are of clinical importance. Concentric hypertrophy describes an increase in left ventricular wall thickness without an increase in chamber volume. Eccentric hypertrophy involves an increase in chamber dimensions with a lessor increase in wall thickness. Concentric hypertrophy is predominantly seen in middle aged patients while eccentric hypertrophy is rarely seen in patients less than 50 years of age. Eccentric hypertrophy is associated with obesity which is an important co-factor in the development of left ventricular hypertrophy and ultimately heart failure. Ref 28) A landmark publication by Devereaux established the natural history of the various patterns of hypertrophy seen in 253 hypertensive subjects. (Ref 29) See figure 10, (Ref 28). Both mortality and cardiovascular events occur most commonly in concentric hypertrophy.

FIGURES 9 and 10

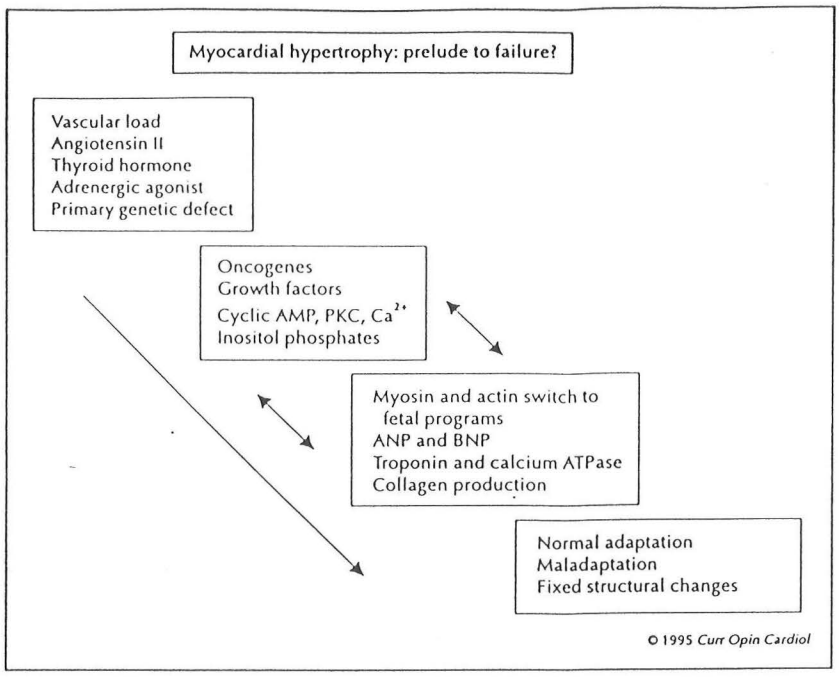


Fig. 9. The factors and pathways by which left ventricular hypertrophy (LVH) develops in response to the increase of LV mechanical stress, secondary to hypertension. Not all of the stimuli listed contribute to LVH in all cases. However, the increased vascular load of hypertension as a stimulus for hypertrophy is common to all patients. The process of hypertrophy develops in the direction indicated by the *large arrow*. *Double-headed* arrows indicate reversible or fluctuating steps in the process. ANP—atrial natriuretic peptide; BNP—brain natriuretic peptide; PKC—protein kinase C.

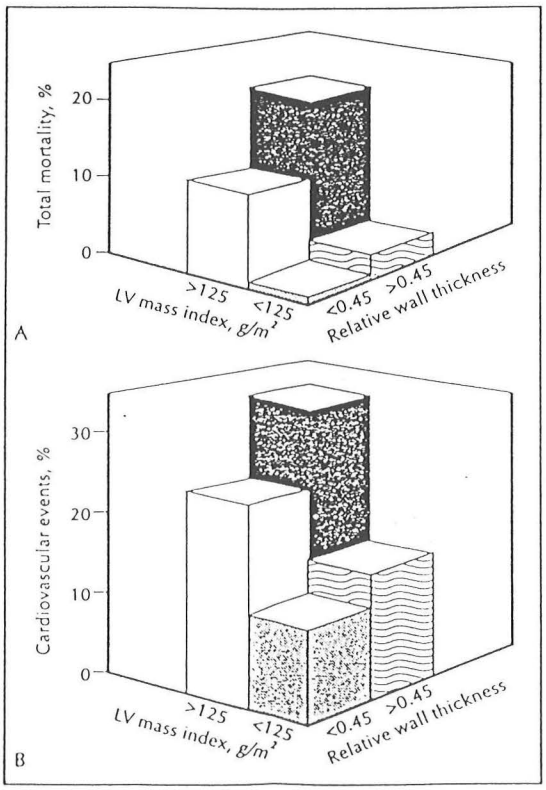
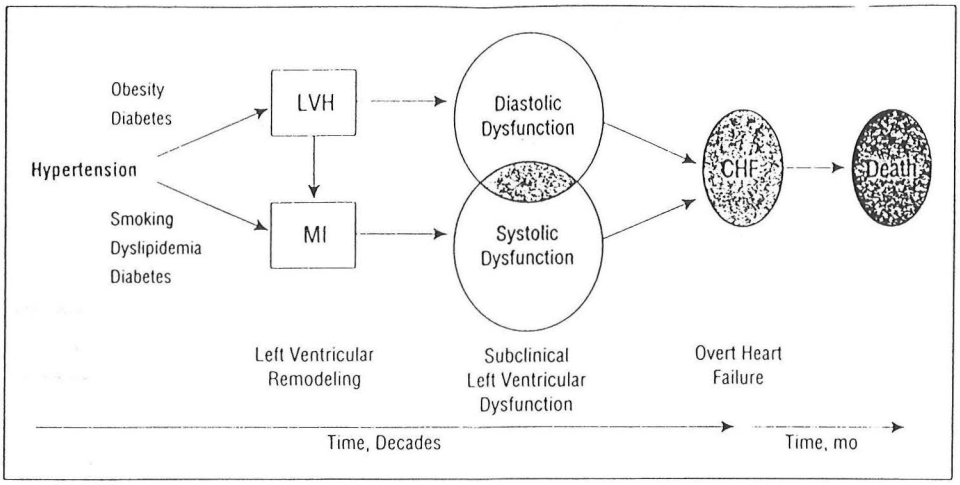


Fig. 10 Occurrence of varying patterns of left ventricular (LV) remodeling in hypertension, and their relationship to total mortality *(panel A)* and cardiovascular (CV) events *(panel B)* in 253 hypertensive patients. Mortality and CV events occurred most commonly among patients with concentric hypertrophy *(black bars)*, followed by eccentric hypertrophy *(open bars)*, and concentric remodeling *(striped bars)*; they were least common in patients with no evidence of LV remodeling *(gray bars)*. *(From* Devereaux *et al.* [3•]; with permission.)

FIGURE 11



Progression from hypertension to congestive heart failure. LVH indicates left ventricular hypertrophy; MI, myocardial infarction; and CHF, chronic heart failure.

It has been suggested that patients progress from hypertension to left ventricular hypertrophy to diastolic dysfunction and ultimately overt heart failure with systolic dysfunction. See figure 11 (Ref 30).

A description of diastolic dysfunction is beyond the focus of this work but several reviews are available in the literature and the reader is advised to peruse those references. Ref...

Recently, several candidate biological systems have been identified which may in fact promote the development of left ventricular hypertrophy and/or lead to over systolic heart failure.

Natriuretic Peptides

The natriuretic peptides, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide participate in cardiovascular homeostasis. They share properties of natriuresis, vasodilation, renin inhibition, antimitogenesis and improved lusitropic properties (i.e., improved left ventricular compliance). It is apparent that the absence of this influence results in substantial cardiovascular morbidity. (Ref 31) Animal studies in knockout models devoid of the natriuretic peptide receptor A (NPRA) have demonstrated the presence of elevated blood pressure and the development of marked hypertrophy with interstitial fibrosis in a pattern that is consistent with human hypertensive heart disease. Sudden death and heart failure occurred in virtually all animals. (Ref 32)

These observations are key because they suggest that genetic modification of the natriuretic peptide system is associated with hypertension and hypertensive heart disease. Importantly, preliminary data are available (Ref 33) that demonstrate that genetic polymorphism exists in the second intron of the human ANP gene and this may be a candidate gene to determine familial susceptibility to hypertension.

Beta receptor Polymorphism

The beta-1 adrenergic receptor is expressed on the heart and mediates the actions of cathecholamines of the sympathetic nervous system. A genetic polymorphism has been described at amino acid position 389. Either glycine or arginine can be found with an allele frequency of 0.26 and 0.74 respectively. The Gly-389 was formerly considered the human "wild-type" (i.e., normally expressed) but in fact, Arg-389 is likely to be the normal expression. When both types are overexpressed and exposed to isoproterenol, the resultant adenyl cyclase activity was markedly reduced in the Gly-389 variant. This would suggest the presence of a naturally occurring polymorphism that contributes to a suboptimal response to adrenergic stimuli and perhaps a less robust response to adrenergic blockade. This polymorphism may define a group at higher risk for progressive left ventricular dysfunction and with a reduced response to adrenergic blockade. It is intriguing that very preliminary data have demonstrated that the Gly-389 polymorphism may be overexpressed in African American patients. (Ref 34, 35) A

similar polymorphism at Il-163 in beta-2 receptors has not only been described but is also associated with a worsened prognosis in the setting of heart failure.

Transforming Growth Factor-Beta 1

Several cell lines, including endothelial cells and vascular smooth muscle cells, secrete transforming growth factor beta-1. It facilitates extracellular matrix assembly by stimulation of collagen synthesis and prevention and degradation of the extracellular matrix. Its overproduction has been associated with fibrosis. TGF-B1 has been implicated in hypertension and left ventricular hypertrophy. It is stimulated by angiotensin-II and may mediate the abnormal growth promoting effects of angiotensin-II. TGF-B1 stimulates the expression of mRNA encoding endothelin-1 and increases renin release from juxtaglomerular cells in the kidney.

It has recently been discovered that TGF-B1 is hyperexpressed in hypertensives compared to normotensives and that the highest levels have been seen in African Americans with hypertension. Additionally, a genetic polymorphism has been described at codon 10 for proline in the human TGF-B1 gene. Codon 10 polymorphisms have been shown to be associated with more vascular disease and generate higher mRNA activity for TGF-B1. The authors of this seminal work propose that TGF-B1 contributes to the pathogenesis of hypertension by directly causing blood pressure elevation and by subsequently causing vascular injury, fibrosis via an increase in the extracellular matrix and ventricular hypertrophy. They further propose that the mechanism of blood pressure elevation is via stimulation of endothelin-1 and through release of renin from the kidney. This contributes to additional angiotensin-II production which then stimulates TGF-B1 and an "autoamplification loop" ensues. This is an elaborate hypothesis which if correct, describes a very plausible mechanism for hypertensive heart disease and its overt expression in selected individuals. (Ref 36)

Endothelin-1 and Endothelin Receptors

Endothelin is a potent vasoconstrictor produced by vascular endothelial cells. Three isoforms have been described but only endothelin-1 has cardiovascular properties. [Endothelin-2 may function in the kidney and endothelin-3 may be active in the central nervous system and the gastrointestinal tract]. In addition to its role as a vasoconstrictor, endothelin-1 contributes to remodeling and appears to be present in heart failure, systemic hypertension, pulmonary hypertension and atherosclerosis. Endothelin-1 levels are thought to increase by *de novo* synthesis due to the effects of various stimuli on gene transcription. Factors promoting proendothelin-1 synthesis include angiotensin-II, catecholamines, inflammatory mediators, hypoxia and shear stress. See Figure 12, (Ref 37). Preproendothelin-1 is cleaved by an endoprotease to big endothelin-1 which is then acted on by endothelin converting enzymes to yield endothelin-1.

The effects of endothelin-1 are mediated by endothelin receptors of which there are two, ET-A and ET-B. ET-A is located on vascular smooth muscle cells, cardiomyocytes and fibroblasts. ET-B receptors are on vascular endothelium and mediate vasodilation via

stimulation of nitric oxide and prostacyclin release. Nitric oxide is an inhibitor of endothelin-1 synthesis. ET-A receptors appear to mediate the mitogenic effect of endothelin-1 and vasoconstriction predominantly through smooth muscle hypertrophy. Endothelin-1 also stimulates collagen type IV synthesis in fibroblasts and as such contributes to the extracellular matrix formation that is the hallmark of the remodeling process. (Ref 37)

Endothelin-1 does not appear to be causative in human hypertension but becomes more important with increasing severity of hypertension and in all forms of hypertension associated with salt sensitivity. African-Americans are believed to have salt-sensitive hypertension and have been demonstrated to have an activated endothelin-1 system based on elevated levels of ET-1 in hypertension. It is hypothesized that chronic over-expression of ET-1 may occur in this setting. Animal experiments with spontaneously hypertensive animals and salt-sensitive hypertensive animals demonstrated that the use of an ET-A receptor antagonist lowered blood pressure in the salt-sensitive animals but did not affect blood pressure in the spontaneously hypertensive animal. In separate experiments, salt-sensitive animals were given a high NaCl diet with dramatic increases in blood pressure and a 3-fold increase in endothelium dependent contraction in response to acetylcholine. The use of an ET-A receptor antagonist blunted this BP rise. The use of ET-A receptor antagonists has also been shown to increase the number of apoptotic cells in the aortic wall which perhaps acts to normalize hypertrophy and restore elasticity. (Ref 37)

A remarkable experiment done by Iwanaga and colleagues demonstrated a potential role for endothelin-1 in the transition from left ventricular hypertrophy to overt left ventricular dysfunction and failure. Salt-sensitive animals with hypertension and left ventricular hypertrophy had serial assessment of serum and tissue endothelin-1 levels. At the stage of LVH, the levels were not elevated but once overt heart failure ensued, serum and left ventricular endothelin levels increased by 3.8 and 5.4 fold respectively. The LV endothelin levels correlated inversely with a decrease in fractional shortening. The experiment was repeated but at the LVH stage, the animals were randomized to either an endothelin receptor antagonist (bosentan) or doxazosin. Both regimens lowered blood pressure but only the ET receptor antagonist ameliorated the progression to LV failure by attenuating the decrease in LV fractional shortening by 51%. (Ref 38) It is tantalizing to speculate on the potentially profound impact endothelin receptor blockade might have on the natural history of hypertensive heart disease in populations at highest risk.

FIGURE 12

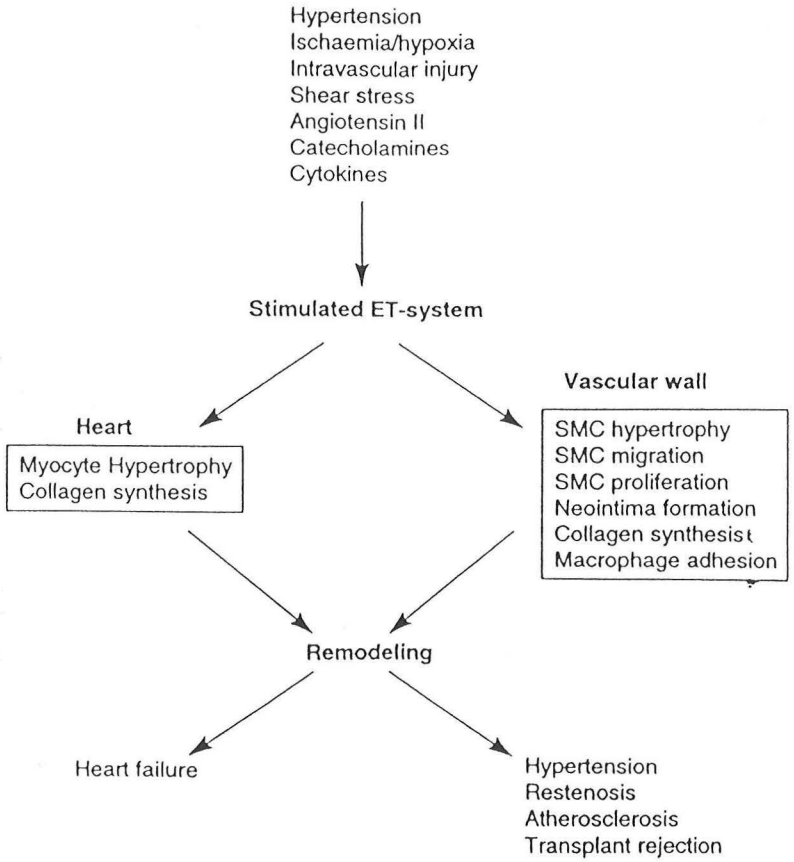


Figure 12. Involvement of a stimulated ET-1 system in cardiac and vascular remodeling.

Clinical Correlation #5: The foregoing mechanistic data do not immediately yield an option for improved management of hypertension, but the insight gained is compelling. It appears that a genetic basis may exist both in regards to susceptibility to hypertension and the development of left ventricular dysfunction in the setting of hypertension. Polymorphisms of the natriuretic peptide system, beta-adrenergic receptors, transforming growth factor beta-1 and endothelin systems may all be operative in the pathogenesis, morbidity and mortality due to hypertensive heart disease. In the near future, anti-hypertensive therapy may be "tailored" to pathophysiological markers that relate to the mechanisms of disease. It is intriguing that at least two of these described abnormalities, TGF-beta-1 and Endothelin-1 in salt-sensitive hypertension, may be uniquely expressed in African Americans who suffer a disproportionate burden of hypertensive heart disease.

QUESTION 4: ARE THERE CURRENT OR FUTURE TREATMENT STRATEGIES THAT MAY BE UNIQUELY BENEFICIAL IN ATTENUATING THE PROGRESSION OF HYPERTENSIVE HEART DISEASE TO LEFT VENTRICULAR FAILURE?

Dual Metallopretease Inhibitors/Vasopeptidase inhibitors

These agents inhibit both neutral endopeptidase enzymes and angiotensin converting enzymes. One of the neutral endopeptidase enzymes is atriopeptidase which breaks down atrial natriuretic peptide. Other neutral endopeptidase activity is directed towards kinins and endothelin (influenced by neutral endopeptidase E-24.11. Ref...). Elevated atrial natriuretic peptide concentrations have been found in human hypertension and appear to be especially present in low-renin rather than high renin essential hypertension. The exogenous administration of ANP lowers blood pressure but this is not a practical option for chronic administration due to problems associated with administering peptides. The use of NEP inhibitors with action on atriopeptidase inhibits the breakdown of ANP and increases circulating levels. The administration of NEP only inhibitors has not resulted in a reduction in blood pressure perhaps because the administration of NEP inhibitors appears to be associated with a delayed clearance of angiotensin-II. Concomitant administration with ACE-inhibitors or given in a formulation that includes an ACE-inhibitor appears to be much more promising. (Ref 39)

To test the efficacy of combined NEP/ACE inhibitors, Norton et al. evaluated black hypertensives in South Africa with sampatrilat, a combined NEP and ACE inhibitor, vs. lisinopril. (Ref 40) In this group of patients known to be resistant to ACE-inhibitor therapy, the use of sampatrilat resulted in improved blood pressure control. The favorable response on blood pressure occurred even though lisinopril lowered ACE activity more so than sampatrilat. Whether the improved BP control achieved with NEP/ACE inhibitors is solely due to the effects of increased ANP levels or an as yet unidentified other property of NEP/ACE inhibitors is not known.

Omapatrilat has been evaluated in over 500 patients with heart failure in the IMPRESS trial. (Ref 41) Patients were randomized to omapatrilat vs. lisinopril and followed for 24 weeks. Endpoints were exercise time, NYHA class and a combined endpoint of morbidity and mortality (death and hospitalization). There was no difference in exercise times but Omapatrilat improved NYHA functional class more than lisinopril. Omapatrilat also produced significant improvement in the combined endpoint of death and hospitalizations, RR 0.52, $p<0.04$. A larger survival trial, OVERTURE, is now ongoing to further test these potential advantages of combined NEP/ACE inhibition over ACE inhibitors only.

Carvedilol

Carvedilol is a third generation vasodilating beta-blocker with marked anti-oxidant properties. It has been associated with improved outcomes when given to patients with heart failure. A 65% reduction in mortality has been realized in short-term trials. (Ref 6) In advanced heart failure, the recently reported COPERNICUS trial demonstrated a 34% reduction in all-cause mortality in those patients treated with carvedilol plus an ACE-inhibitor. (Ref 7) The drug is the first beta blocker approved for heart failure. Carvedilol is also approved for hypertension. Several properties of carvedilol may be important in this setting. Carvedilol has anti-ischemic properties based on a reduction in heart rate and contractility. The alpha blockade of carvedilol in concert with its non-selective beta blockade lowers afterload and wall tension. In animal experiments, carvedilol significantly limits infarct size even when compared to a regimen of propranolol and doxazosin which should provide the same pharmacological profile. An ongoing trial, CAPRICORN, is evaluating the use of carvedilol post-myocardial infarction.

A potential advantage of carvedilol is its anti-oxidant properties. Cardiomyocytes are sensitive to oxygen-derived free radicals which can induce arrhythmias and apoptosis. Carvedilol inhibits free radical formation and is 10-fold more potent in its anti-oxidant activity than vitamin E. Carvedilol also inhibits ICAM-1 gene expression which prevents oxygen radical release by neutrophils and suppresses neutrophil migration. In animal models of ischemia, carvedilol produces nearly complete suppression of apoptosis. This may be an important property in the setting of cardiac hypertrophy. (Ref. 42)

The role of other compounds including angiotensin receptor antagonists (Ref 43), vasopressin antagonist, newer aldosterone antagonists, endothelin converting enzyme inhibitors and endothelin receptor blockers awaits further investigation.

SUMMARY

Hypertension is an important and perhaps leading cause of heart failure, either as a cofactor with other known risk factors such as myocardial infarction, left ventricular hypertrophy and diabetes or as a sole cause of left ventricular dysfunction. The actual incidence of hypertensive heart disease leading to left ventricular failure as a primary causative factor is not known but is suspected to vary according to ethnic and genetic variables.

Available data from large randomized controlled clinical trials now clearly demonstrate that cardiovascular outcomes are favorable influenced by anti-hypertensive therapy and that the incidence of heart failure can be reduced in certain populations with effective blood pressure control. Low dose diuretic therapy, beta blockers and ACE-inhibitors appear to be the best agents among those currently available.

The conversion from hypertensive heart disease with intact left ventricular function to overt LV failure likely progresses via left ventricular hypertrophy, the pattern of which can be predictive of clinical outcomes. An emerging database is beginning to identify mediators of hypertrophy, especially variances in the atrial natriuretic system, elevated transforming growth factor beta-1, beta-receptor polymorphisms and activated endothelin systems. Certainly other systems are involved but are not yet apparent.

Future treatment strategies may encompass more precise targeting of specific pathophysiological markers responsible for the progression of disease and thus more effectively ameliorate the development of left ventricular dysfunction.
By controlling hypertensive heart disease, the incidence of heart failure can be substantially decreased and the excessive human and economic costs attributable to heart failure can be profoundly reduced.

APPENDIX

Editorial

Heart Failure in African Americans: A Cardiovascular Enigma

The increasing fund of knowledge in heart failure has resulted in rapid and substantial contributions to both our understanding of this disease and our armamentarium targeted toward this disease. The result has been an improvement in the outcome of patients affected with heart failure. Recent clinical trials suggest that the natural history of this disease can be significantly improved, but the question is raised, do all patients derive similar benefit? In the absence of prospective trials, post hoc subgroup analysis (with all of the associated limitations) has been used to answer questions regarding heart failure in special populations. The observations regarding heart failure in African Americans have been both unique and alarming.

As a cardiovascular malady, heart failure affects 3% of the African American population in the United States (1). Recent attention has been drawn to this disease as it affects African Americans based on apparent differences in the natural history of heart failure and a more worrisome prognosis. Several epidemiological observations have been consistent in all available databases: heart failure occurs at an earlier age in African Americans compared with others; the incidence of documented epicardial coronary disease is lower; and there is a striking disproportionate incidence of hypertension as a plausible cause of heart failure (2,3,4). The incidence of hypertension as a likely cause of heart failure in African Americans is consistently 60% or greater in most databases compared with as low as 4% in other patients (2,5). Conversely, the incidence of documented myocardial infarctions is consistently lower. The data regarding prognosis are alarming. There is a greater incidence of left ventricular (LV) hypertrophy, which is predictive of future cardiac events. The hospitalization rate for heart failure is higher. Of greatest concern, the mortality rate is markedly increased: a 1.8-fold increase for affected African American men and a 2.4-fold increase for women compared with all other patients (2,6). These observations have generated appropriate concern and raise the question, what are the explanations for this cardiovascular enigma?

The explanation for these incongruous findings is not readily available, but several potential explanations are suspected. It is tempting to impugn socioeconomic status and limited access to preventive and/or maintenance health care. However, data from the Studies of Left Ventricular Dysfunction (SOLVD) trials do not support socioeconomic factors as important contributors to the excess mortality rate seen in African Americans affected with heart failure. An evaluation of the presence of financial distress was not associated with adverse outcomes in univariate analysis. An educational level less than eighth grade was a significant correlate of excess mortality rate, but in a multifactorial model it was not associated with outcomes (2). A second plausible explanation relates to the disproportionate incidence of hypertension and, thus, hypertensive heart disease. Hypertension is 3- to 7-fold more prevalent in African Americans. The incidence of end-stage renal disease is 15- to 18-fold higher and mortality from stroke is 3- to 6-fold higher. LV hypertrophy occurs in 31% of African Americans with hypertension as compared with 10% in other patients with hypertension (7). An interesting corollary,

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therefore, emerges when the end-organ damage caused by hypertension is surveyed in the African American population. There seems to be a more malignant vascular response to hypertension resulting in both an increased incidence of end-organ disease and a worse pathogenecity. The presence of more advanced LV dysfunction and a greater severity of heart failure class at the time of heart failure diagnosis in African Americans supports this observation. The question now becomes, are there true physiological differences that may in fact contribute to this pathology and may represent the basis for dissimilar responses to pharmacological interventions?

Both the renin-angiotensin and sympathetic nervous systems are suspected to play a much smaller role in the control of blood pressure in African American patients when compared with others. The experience in the hypertension literature has suggested that the response to both angiotensin-converting enzyme (ACE) inhibitors and β-blockers may be less robust in African American patients and that higher doses of both agents may be required to adequately control blood pressure (8). This is perhaps related to a greater proportion of salt-sensitive hypertension in African Americans and lower circulating plasma renin activity compared with other hypertensive patients (9). Regarding heart failure, African American patients have been shown to have either similar or lower norepinephrine levels despite more severe LV dysfunction (2,18). Recent data have described an overexpression of transforming growth factor (TGF)-β1 in both normotensive and hypertensive African Americans. TGF-β1 protein levels and TGF-β1 messenger RNA levels are highest in African Americans with hypertension (10). It is intriguing to postulate that a surfeit of growth factors may be responsible for accelerated vascular injury in hypertension that leads to increased end-stage renal disease, stroke, and LV hypertrophy. Yet another potential explanation has emerged. β-Receptor polymorphism may be present in African Americans. A substitution in adrenergic receptors at amino acid position 389 of glycine for arginine has been described. Adrenergic receptors with the 389 glycine substitution have been shown to result in reduced coupling to adenyl cyclase in the presence of increasing concentrations of isoproterenol (11). Affected adrenergic receptors would thus show a subsensitive response to agonist. If such a polymorphism is verified in African Americans, this would identify an important physiological difference that might have an impact on the natural history of cardiovascular disease. Other potential areas of concern can be hypothesized, including possible nuances in nitric oxide dependent arterial relaxation (12), endothelin production, and endothelin receptor efficacy (13). More work is clearly needed in all of these areas to establish a cause-and-effect relationship. It is increasingly likely, however, that real differences may exist, and this will have an impact on medical therapy for heart failure in African Americans. The question now becomes, what have we learned from clinical trials?

The results of several major clinical trials have suggested that African American patients may not respond as well as other patients to neurohormonal antagonism in the setting of heart failure.

It has been suggested that all of the survival advantage in the Vasodilator Heart Failure Trial (V-HeFT) I study of direct vasodilator therapy was seen in the African American patients, and no advantage was seen in other patients. The annual mortality rate in African American patients on placebo therapy was 17.3%, which decreased to 9.7% on direct vasodilator therapy ($P = .04$). For all other patients, the difference between placebo therapy and direct vasodilator therapy was 18.8% versus 16.9% (P = NS) (14). Importantly, the interactive P value was .11, thus the between group difference was not significant. Therefore, the findings relating to African American patients can only be interpreted in the context of a retrospective, post hoc analysis of a subgroup that was not prospectively defined and was not statistically different from the larger cohort in whom negative results were seen.

In V-HeFT II, it was reported that only non–African American patients showed a survival advantage with ACE-inhibition. Once again, the data are quite interesting. The reduction in annual mortality rate for other patients was impressive, 11.0% on enalapril therapy. In African American patients with heart failure, the reduction in annual mortality

rate was nearly identical for both direct vasodilator therapy (12.9%) and ACE-inhibitor therapy (12.8%). This would suggest that ACE-inhibition was not significantly better than direct vasodilator therapy in African American patients as was reported (14). When compared with historical controls from V-HeFT I, however, both strategies were equally beneficial in African Americans, ie, 17.3% reduced to either 12.8% or 12.9%. Again, the interaction *P* value was negative for between group differences. Thus, the data do not support a lack of benefit from neurohormonal antagonism but rather support a similar and favorable response for both direct vasodilatory therapy and ACE-inhibitor therapy in African American patients with heart failure.

To date, β-adrenergic blockade has been shown to be effective in all patients studied. Data are available for mild heart failure (Australia-New Zealand trial), mild to moderate heart failure (U.S. Carvedilol Heart Failure Trials, Cardiac Insufficiency Bisoprolol Study [CIBIS II], and Metoprolol CR/XL Randomized Intervention Trial in Heart Failure [MERIT-HF]), moderately severe heart failure (CIBIS II & MERIT-HF), and as of March 2000, severe heart failure (Carvedilol Prospective Randomized Cumulative Survival Trial [COPERNICUS]) (15–18). The survival advantage, reduction in hospitalization, and improvement in quality of life have all been profound, and thus β-adrenergic blockade should be applied widely in all appropriate patients with heart failure. What defines appropriate continues to be a clinical conundrum. Recently, it has been suggested that racial differences may exist in the pharmacological response to adrenergic blockade.

The β-Blocker Evaluation of Survival Trial (BEST) data have raised caution regarding the use of β-adrenergic blockade in African American patients with heart failure. This trial enrolled 627 African American patients, which represented 23% of the enrolled patients. Randomization in this trial was stratified based on race (African American *v* others). As noted in other major heart failure trials, African American patients had more advanced heart failure, more severe LV dysfunction, and a disproportionate incidence of hypertension as a potential cause for heart failure. Not only did the African American patients fail to realize a survival advantage from bucindolol, but there was also a worrisome but nonsignificant 17% increase in mortality rate versus placebo-treated patients, (P = NS). There was, however, a statistically significant qualitative interaction between race and treatment effect (19).

The BEST data are juxtaposed with the carvedilol experience. Of the 1,094 patients studied in the United States Heart Failure Trials program, 217 were African American. Their profile again reflected the expected finding of more advanced heart failure, worse LV function, and a higher incidence of hypertension. For the combined end point of mortality and all-cause hospitalization, there was a definite treatment advantage for African American patients who received carvedilol. The difference was similar in magnitude to that seen in other patients, and importantly, the interaction *P* value was not statistically significant. Carvedilol was effective in reducing mortality and decreasing hospitalizations in both African Americans and other patients. There was a similar and robust increase in LV ejection fraction for African Americans and other patients as well.

Taken together, how do we reconcile the results of these clinical trials? The first observation is that there is a paucity of substantive data ergo the need for additional data generation referable to heart failure in African Americans. It is my assertion, however, that African American patients do respond to neurohormonal antagonism. The available data do, however, raise appropriate concerns that the most salient neurohormonal mechanisms have not yet been identified in the African American population. I would consider the results of V-HeFT I and II and BEST as hypothesis generating but not of sufficient power to withhold the most effective therapy for heart failure from African Americans. An analysis of the SOLVD database showed "no evidence of interaction between race and random assignment to treatment with enalapril or placebo with respect to outcomes . . ." (2). This would suggest a benefit for African American patients treated with ACE-inhibitors. The clinical data from the carvedilol experience are convincing that in African American patients with mild to moderate heart failure β-blockade is effective and should not be withheld. For patients with more advanced disease, the BEST database remains

worrisome. It is imperative that data from MERIT-HF and the recently completed COPERNICUS trials are carefully evaluated for outcomes in African Americans, especially those with advanced heart failure.

It is important to note that no data within the African American population with heart failure have been collected in an a priori, prospective manner with the statistical power to truly determine the efficacy of drug therapy on clinical outcomes. I believe a prospective randomized trial testing heart failure treatment regimens in African Americans is warranted based on the foregoing information, but social and ethical issues challenge the design of such a trial. What is inescapable, however, is the discovery of yet another devastating consequence of uncontrolled hypertension. The majority of heart failure in African Americans is ostensibly preventable, and the mandate for effective antihypertensive strategies should be strengthened. Currently, therapy for heart failure in African American patients should continue to parallel that of all other patients according to evidence-based guidelines. Specifically, neurohormonal antagonism should represent the mainstay of therapy. As more data emerge, this issue will be revisited.

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