Heart Failure Therapy in Special Populations: The Same or Different?

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Traditional clinical trials of heart failure therapy have focused on fairly homogenous patient populations. Therefore, a pressing question is raised regarding whether it is appropriate to extrapolate findings from these trials to other groups, such as the elderly, women, and African Americans. Based on current knowledge, the differences among these groups should be acknowledged as subtle and represent a need for heightened clinical awareness and more vigorous investigation. These special populations, however, should receive medical therapy for heart failure that is consistent with the results from the major trials and is in accordance with published heart failure guidelines.

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Important discoveries in the management of patients with heart failure have led to significant improvements in quality of life and survival for patients affected with left ventricular dysfunction. Broad application of these initiatives is expected to dramatically reduce the morbidity, mortality, and financial expenditures for this condition. Yet, a pressing clinical question is raised regarding the appropriateness of extrapolating findings from traditional clinical trials done in

fairly homogeneous patient populations to a more diverse population mosaic that includes more elderly, women, and ethnic minorities. The moniker "special populations" has recently been ascribed to these groups of patients. Available data would suggest that the epidemiology and natural history of heart failure in these groups is sufficiently unique that a more focused perspective is warranted. A common theme repeated in any analysis of heart failure in these special populations is the prevalence of hypertension as perhaps the most significant risk factor for heart failure.

Data sources from which these questions can be addressed emanate from post hoc subgroup analyses of major published clinical trials and as such are compromised by the retrospective nature of the data source. With the exception of the African American Heart Failure Trial (A-HeFT),[1] prospective trials in these special populations have not been done. Nevertheless, sufficient consistency in the available databases exists to allow for important observations regarding the epidemiology, natural history, and treatment of heart failure in these special populations.

Heart Failure in Older Patients

The average age of patients affected with heart failure in traditional clinical trials is approximately 65 years, yet the median age of patients presenting with symptomatic heart failure in community hospitals is 75.[2] There are very few data sets that specifically focus on the patient with heart failure beyond the age of 70. Data taken from the Acute Decompensated Heart Failure Registry (ADHERE) document that the older patient with heart failure is more likely to have preserved systolic function and has a higher in-hospital mortality rate.[2] There are no specific treatment guidelines yet established for heart failure with preserved systolic function, and most treatment recommendations are targeted toward the underlying etiology of left ventricular dysfunction. Given the over-representation of hypertension in the elderly as a basis for heart failure, it seems reasonable to vigorously embrace the effective and appropriate treatment of hypertension in the elderly. Both the Systolic Hypertension in the Elderly Trial (SHEP)[3] and the Swedish Trial of Hypertension in Older Persons (STOP)[4] demonstrate that diuretics plus ß-blockers are especially effective regimens to improve cardiovascular mortality and to reduce the incidence of heart failure. The recent Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines further embrace this strategy and advise physicians to target goal blood pressure reductions in all patients, including the elderly, in order to achieve an expected 50% decrease in the incidence of heart failure.[5]

These data would suggest that it is unwarranted and medically inappropriate to withhold angiotensin-converting enzyme (ACE) inhibitor and ß-blocker therapy in older patients with heart failure.

Several of the major clinical trials in symptomatic heart failure with impaired systolic function have reported outcomes in patients older than 65 years. Most notably, the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) reported that patients older than 65 with advanced heart failure and systolic dysfunction fared as well as patients younger than 65.[6] Further support for this observation can be seen in the U.S. Carvedilol Heart Failure Trials Program and within the Metoprolol Extended Release Randomized Intervention Trial in Heart Failure (MERIT-HF).[7,8] Taken together, these data would suggest that the expected 48% reduction in event rates due to heart failure, including death, hospitalization, and worsening disease, and the 35% reduction in overall mortality should be seen in the elderly patient with mild to severe symptomatic heart failure and systolic dysfunction. A smaller, separate database of patients older than 70 years with heart failure has demonstrated a tolerability of 87%, whereas efficacy data reveal a mean improvement in left ventricular ejection fraction (LVEF) of 12 ejection fraction units.[9]

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Women With Heart Failure

Women with heart failure typically

represent no more than 20% of the patient populations studied in major clinical trials, but data from ADHERE suggest that nearly 50% of patients admitted to hospital with a diagnosis of heart failure are women.[2,10] Not only is hypertension a significant comorbidity for women, but obesity and diabetes play important roles as well. Documented coronary artery disease does occur, and a search for ischemic heart disease is always appropriate. Gender-specific concerns include peripartum cardiomyopathy and chemotherapy-induced left ventricular dysfunction.

Data regarding therapeutic responses to usual drug treatment strategies are limited to post hoc analyses. Data from the Southern California Evidence-Based Practice Center, RAND Health, are especially provocative.[11] Pooled data taken from a meta-analysis of the major published ACE inhibitor trials suggest an overall survival advantage of 18% (RR 0.82) for men but only 8% for women.[11] Remarkably, neither the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) nor Studies of Left Ventricular Dysfunction (SOLVD) databases showed a survival advantage with ACE inhibitor therapy in women.[12,13] Post hoc analysis of the Digitalis Investigation Group Trial demonstrated that women had a greater risk for digoxin toxicity occurring at a lower serum digoxin level.[14] In the recently reported Australian antihypertensive trial, a reduction in mortality with ACE inhibitor therapy was seen only in men.[15] These data would seemingly support a differential response in women to ACE inhibitors and digoxin when used in the treatment of heart failure. The retrospective nature of all of the foregoing observations greatly compromise the data points and, at best, yield only ideas or initiatives for further investigation.

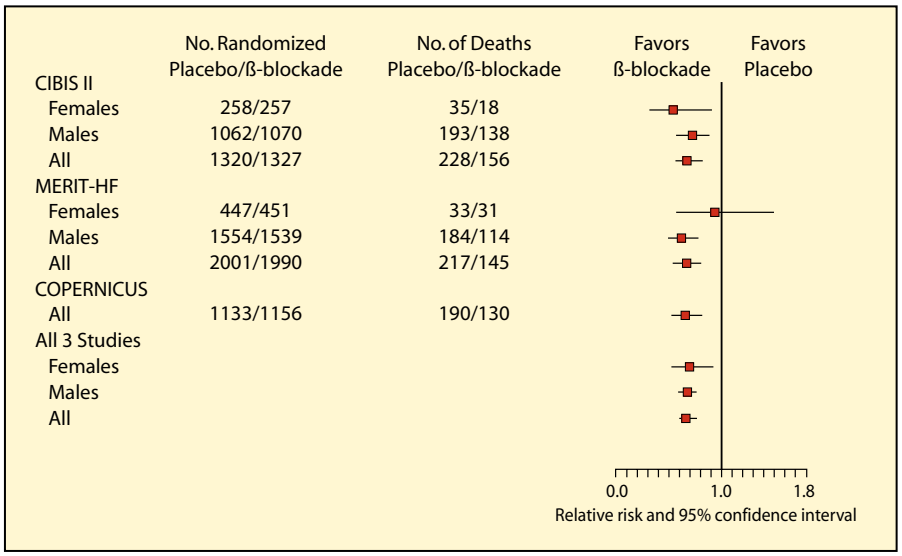

Figure 1. *Data points from recent clinical trials of the use of ß-blockers in men and women with heart failure due to systolic dysfunction. Adapted with permission from Ghali et al. Metoprolol CR/XL in female patients with heart failure: Analysis of the experience in metoprolol extended-release randomized intervention trial in heart failure (MERIT-HF).* Circulation. *2002;105:1585-1591.*

Thus, neither digoxin nor ACE inhibitors should be withheld from women on the basis of these retrospective analyses.

The use of ß-blockers for women affected with heart failure appears to be less worrisome, but subtleties in the response to ß-blockers do seem to be evident. The Beta Blocker Evaluation of Survival Trial (BEST) enrolled 593 women in an investigation of the benefit of bucindolol in chronic heart failure. Women (and African Americans) in this trial failed to demonstrate a beneficial response to bucindolol.[11,16] However, these data are less worrisome for gender or race-based differences in the responsiveness to ß-blockers and more consistent with potentially important differences within the ß-blocker drug class. Use of bisoprolol, a $ß_1$-selective ß-blocker, in the Cardiac Insufficiency Bisoprolol Study (CIBIS) trials was seemingly as effective in women as in men, with a similar and statistically significant endpoint noted.[17] Within the MERIT-HF trial, metoprolol succinate was given to 898 women with mild to moderate heart failure. A benefit on all-cause mortality was not seen, but the combined endpoint of mortality and all-cause hospitalization was reduced by 21%.[8] Within the U.S. Carvedilol Heart Failure Trials Program, 31% of the patients studied were women. The relative risk for mortality reduction was 0.32, $P = .028$. It is important to note that the U.S. Carvedilol Heart Failure Trials Program did not have mortality as a predetermined endpoint.[7] Within the COPERNICUS trial, 25% of patients studied were women. The point estimate for the reduction in mortality was identical for women and men, but because of a smaller cohort, the confidence limits for women were quite broad. For the combined endpoint of death plus hospitalization for any reason, a statistically significant benefit was indeed noted.[6] These important data points from recent clinical trials in heart failure support widespread use of ß-blockers plus ACE inhibitors in women affected with heart failure

due to systolic dysfunction (Figure 1).

African Americans With Heart Failure

Perhaps the greatest concern regarding heart failure in special populations is in the African American group. Sufficient data are available to raise important questions regarding the epidemiology, natural history, and prognosis of heart failure in African Americans. Moreover, important concerns have been raised regarding responsiveness to pharmacologic agents. The discussions regarding heart failure in African Americans are further confounded by the nonphysiologic nature of race. Unlike age and gender designations, race is a fairly arbitrary sociopolitical construct. Thus, any observations made regarding heart failure in any African American cannot be assumed to be universally applicable for all African Americans with heart failure.

When affected with heart failure, African American patients tend to be younger, with more advanced left ventricular systolic dysfunction on presentation. The clinical class is likewise more advanced, and the morbidity, measured as the need for hospitalizations, is increased.[18] Arguments are ongoing regarding the absence or presence of an excess mortality risk. Early evaluations from the SOLVD trials suggested that mortality risk was increased by as much as twofold—especially in the African American woman. A later reanalysis of the SOLVD trials, both Prevention and Treatment, matched for severity of left ventricular dysfunction and clinical trial participation, did not yield important differences in mortality, but the risk of hospitalization was 44% less in white patients taking enalapril compared with African Americans.[19,20] The SOLVD Prevention trial demonstrated that enalapril reduced the incidence of new onset heart failure in both African Americans and whites, but the rate of development of heart failure was significantly higher for African Americans.[21]

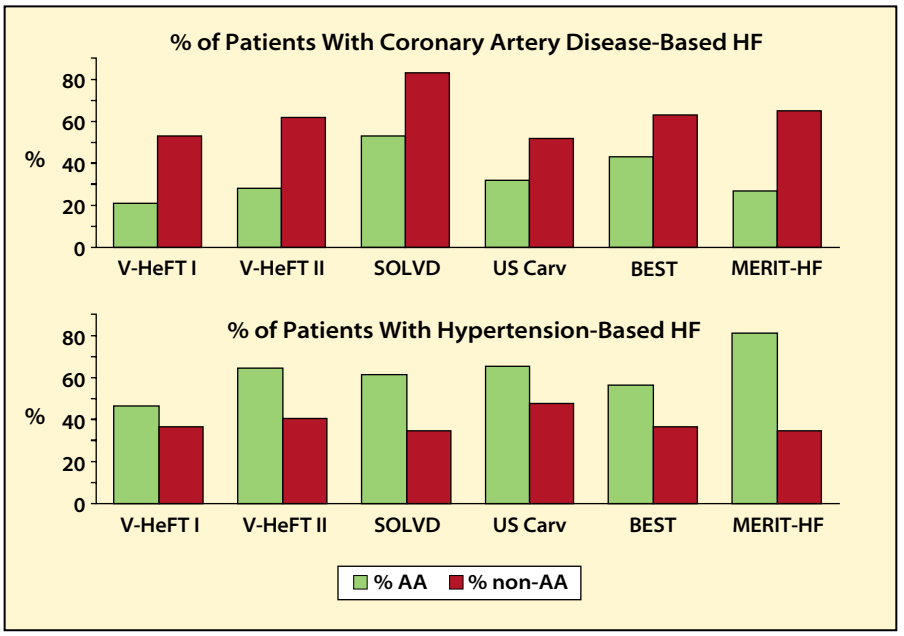

Figure 2. *Etiology of heart failure (HF) in African Americans (AA). Data from the BEST Investigators,[16] Packer et al,[7] the MERIT-HF Investigators,[8] Cohn et al,[32,33] and the SOLVD Investigators.[13]*

Important data points from recent clinical trials in heart failure support widespread use of ß-blockers plus ACE inhibitors in women affected with heart failure due to systolic dysfunction.

The imputed etiology of left ventricular dysfunction in African Americans is a core concern. A review of several large trials in heart failure with regard to the presumed etiology of left ventricular dysfunction demonstrates the consistent finding that African Americans are more likely to have a nonischemic etiology of left ventricular dysfunction (Figure 2).[18] It is presumed that most of the nonischemic burden is due to hypertension, but similar concerns can be raised regarding a higher incidence of dilated cardiomyopathy and the influence of alcohol within the African American cohort.

Hypertension is pervasive in African Americans and will likely affect 80% of all African Americans. Hypertensive heart disease appears to be especially malignant in the African American patient. The incidence of left ventricular hypertrophy is threefold higher, and the pattern of left ventricular hypertrophy is the more worrisome pattern of concentric hypertrophy, which is known to be associated with an increased event rate.[22,23] Given that stroke and renal disease are likewise seen at higher event rates in African Americans,[22,23] an argument can be made that hypertension elicits adverse vascular responses in African Americans.

Several plausible hypotheses represent tenable explanations for

hypertension-associated cardiovascular disease. Subtle differences in the renin-angiotensin-aldosterone system, sympathetic nervous system, and nitric oxide system have been described. The proinflammatory cytokine, transforming growth factor-ß1 (TGF-ß1), mediates cellular hypertrophy and interstitial growth. TGF-ß1 is known to be associated with glomerular hypertrophy, left ventricular hypertrophy, and stroke. TGF-ß1 mediates the release of endothelin—the most potent endogenous vasoconstrictor.[24] Early data points suggest that in some markedly hypertensive African American patients, TGF-ß1 circulates in excess.[24] This may be due to a single-nucleotide polymorphism that leads to overexpression of TGF-ß1. Genetic variations in the renin-angiotensin-aldosterone system and sympathetic nervous system have also been implicated. Single-nucleotide polymorphisms affecting the expression of adrenergic receptor-ß1, -ß2, and -α, have garnered the most interest.[25,26]

The work of Liggett and colleagues has demonstrated an overdistribution of an apparent loss of gain polymorphism of the ß1-receptor that might explain a reduced responsiveness to ß-blockers in African Americans.[25,26] That same group has also identified a particularly pathologic expression of a ß1-receptor polymorphism along with an α-receptor polymorphism that results in excessive release of the neuroeffector hormone norepinephrine. This pathobiologic combination has been described only in African Americans affected with heart failure.[26] There are additional polymorphisms in the regulatory G proteins that may be overexpressed in African Americans.[27] These discoveries from genomic medicine are tantalizing but still incipient. Much more investigation and clinical validation are required to firmly impute genetic variation as a platform to explain differences in the natural history of heart failure as it affects African Americans.

The treatment of heart failure in African Americans has generated significant debate, based largely on presumptions derived from the hypertension experience that African Americans do not respond well to ACE inhibitors or ß-blockers. Given the benefit of these agents in the management of heart failure, the avoidance of ACE inhibitors and ß-blockers in African Americans with heart failure would seem to be contrary to recommended treatment strategies.

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The Vasodilator in Heart Failure Trials (V-HeFT) I and II established the benefit of vasodilator therapy in the management of heart failure. A retrospective review of the data from V-HeFT I demonstrated that the benefit of isosorbide dinitrate and hydralazine was quite robust in the African American patient and much less so in white patients. V-HeFT II demonstrated the superiority of enalapril over isosorbide dinitrate plus hydralazine in white patients. In the African American patient, there was a similar benefit of isosorbide dinitrate and hydralazine versus enalapril. Given the placebo event rates in the V-HeFT populations, both treatment strategies were effective in African Americans.[28] The remaining question thus regards the unique responsiveness to vasodilator therapy seen in African Americans. Moreover, this peculiar response to the combination of nitric oxide donors (nitrates) and antioxidants (hydralazine) appears to implicate dysregulation of the nitric oxide system in African Americans. This is the basis for the A-HeFT, which is randomizing African American patients with heart failure to placebo versus a proprietary combination of long-acting nitrates and hydralazine with a background of otherwise appropriate medical therapy.[1] A composite endpoint that includes death, hospitalization, and quality of life represents the primary event.

Conventional medical therapy of heart failure in African Americans should otherwise be presumed to be similar to and not different from therapy of heart failure in non–African Americans. The totality of data regarding the use of ACE inhibitors as specific therapy for heart failure in African Americans would suggest an important clinical benefit. The disparity in the rate of hospitalization seen in the SOLVD trials is a concern and might have been related to the dose of the ACE inhibitor. As noted in V-HeFT II and SOLVD, the use of ACE inhibitors in African Americans yielded results that were consistent with the overall trial results.[20] The use of aldosterone antagonists in the setting of chronic heart failure and/or for post–myocardial infarction left ventricular dysfunction with heart failure represents a useful adjunctive strategy in the treatment algorithms of heart failure. A subgroup analysis done within the EPHESUS (Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) database demonstrates that nonwhites fared

as well as whites when treated with eplerenone.[29] Subgroup data from trials using angiotensin receptor antagonists referable to African Americans with heart failure are not readily available, but it is presumed that the responsiveness to angiotensin receptor antagonists would likewise be effective and of similar magnitude in African Americans with heart failure.

The use of ß-adrenergic receptor blockers has substantially improved outcomes in heart failure. These agents along with ACE inhibitors represent the cornerstone of any reasonable treatment strategy for heart failure. Within the African American patient population, data once again strongly support the use of these agents. As mentioned earlier, the BEST experience did not support the use of bucindolol in African Americans with heart failure, but this clearly appears to be a drug-specific response.[16] Subgroup data from the MERIT-HF trial were not quite robust enough to make a specific comment on the benefit of extended-release metoprolol succinate, but the direction of drug effect appeared to be consistent with a positive response to this agent in African Americans.[8] The database regarding the use of carvedilol in African Americans with heart failure is the most robust and perhaps the most clinically compelling database yet available to support appropriate evidence-based therapy of heart failure in African Americans. Within the U.S. Carvedilol Heart Failure Trials Program, 216 of the 1094 trial participants were African American. This group realized a 54% improvement in the progression of heart failure, defined as a reduction in death due to heart failure, hospitalization for heart failure, or the need to change medical therapy due to heart failure. Within the non–African American cohort (Figure 3), a 51% improvement was noted in the progression of heart failure.[30] The difference in the response of these two cohorts was statistically identical. To further support these data, a number of surrogates of drug efficacy were identified. The improvement in LVEF, decrease in heart rate, and effect on blood pressure were all consistent with the expected drug effect and again were statistically similar to those seen in the larger, non–African American cohort.[30] An analysis of the African American cohort from the COPERNICUS trial further confirmed the benefit of carvedilol in African Americans. Despite having a proportionally smaller representation of African Americans in COPERNICUS than in the U.S. Carvedilol Trials Program, the consistency of response was quite striking. African Americans realized a statistically important reduction in cardiovascular events that was in keeping with the overall trial results and was not dissimilar from that seen in the larger, non–African American cohort.[31] Thus, the totality of the carvedilol experience would suggest that the combination of ACE inhibitors and ß-blockers, especially carvedilol, is effective and appropriate therapy for African Americans with all stages of heart failure.

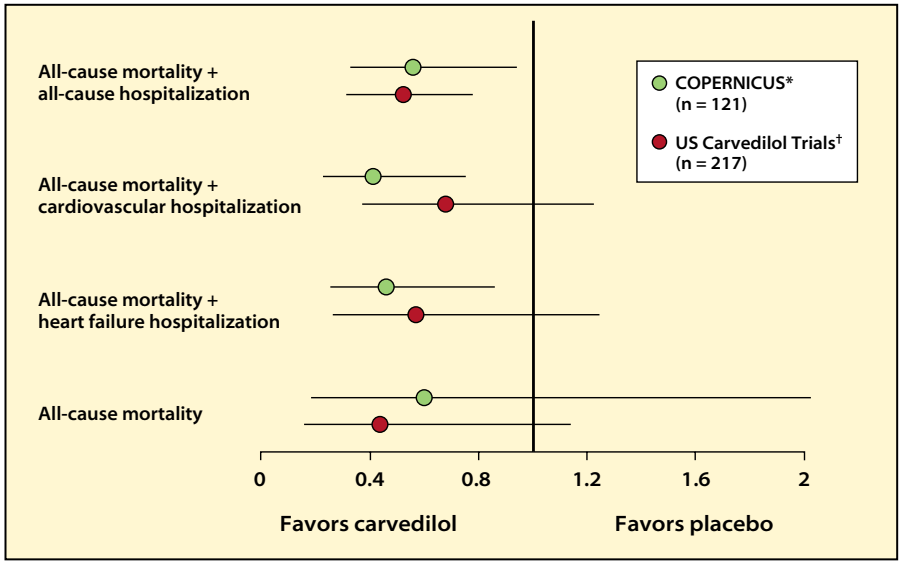

Figure 3. *Effect of carvedilol in African American patients with heart failure. *Data from Packer[34] (mean duration 10.5 months). †Data from Yancy et al.[30] (mean duration 6.5 months). COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study.*

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Summary

Heart failure affects all segments of the population and if left untreated or incompletely treated, imparts a dreadful burden of cardiovascular morbidity and mortality on those affected. The important clinical trial results demonstrating salutary bene-

fit of neurohormonal antagonists as therapy for heart failure should be extended to all patients affected with heart failure, not just those who are similar to the groups of patients studied within the major trials. The elderly, women, and ethnic minorities should all receive optimized medical therapy for heart failure that is consistent with the results seen in the major trials and is in line with recommendations from published heart failure guidelines. There are differences in the epidemiology, natural history, and perhaps even drug responsiveness within these groups when they are affected with heart failure. But based on current knowledge, these differences should be acknowledged to be subtle and to represent the basis for heightened clinical awareness and more vigorous investigation, but the medical therapy of heart failure should be considered similar and not different. ■

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Main Points

- The average age of patients affected with heart failure in traditional clinical trials is approximately 65 years, yet the median age of patients presenting with symptomatic heart failure in community hospitals is 75. There are very few data sets that specifically focus on the patient with heart failure beyond the age of 70.
- There are no specific treatment guidelines yet established for heart failure with preserved systolic function, and most treatment recommendations are targeted toward the underlying etiology of left ventricular dysfunction. Given the overrepresentation of hypertension in the elderly as a basis for heart failure, it seems reasonable to vigorously embrace the effective and appropriate treatment of hypertension in the elderly.
- Data from COPERNICUS, the U.S. Carvedilol Heart Failure Trials Program, and MERIT-HF suggest that it is unwarranted and medically inappropriate to withhold angiotensin-converting enzyme (ACE) inhibitor and ß-blocker therapy in older patients with heart failure. Given the higher event rates seen in the elderly, the potential for benefit from ACE inhibitor and ß-blocker therapy may be greatest within the elderly.
- Important data points from recent clinical trials in heart failure support widespread use of ß-blockers plus ACE inhibitors in women affected with heart failure due to systolic dysfunction.
- The imputed etiology of left ventricular dysfunction in African Americans is a core concern. A review of several large trials in heart failure with regard to the presumed etiology of left ventricular dysfunction demonstrates the consistent finding that African Americans are more likely to have a nonischemic etiology of left ventricular dysfunction.
- The database regarding the use of carvedilol in African Americans with heart failure is the most robust and perhaps the most clinically compelling database yet available to support appropriate evidence-based therapy of heart failure in African Americans.
- The totality of the carvedilol experience would suggest that the combination of ACE inhibitors and ß-blockers, especially carvedilol, is effective and appropriate therapy for African Americans with all stages of heart failure.

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