Special Clinical Considerations of Beta-Blocker Treatment

Clyde W. Yancy, MD

Departments of Medicine and Cardiology, Heart Failure/Transplantation Services, University of Texas Southwestern Medical Center, Dallas, TX

Outcomes for heart failure have improved considerably with the implementation of neurohormonal antagonism that includes angiotensin-converting enzyme inhibitors and ß-blockers. Despite the robust benefit of ß-blockers for heart failure, it is not clear that the benefit can be extended to all patient groups. Special clinical consideration thus needs to be given to the elderly, women, and African Americans. A retrospective review of available data suggests that despite differences in the natural history of heart failure for these groups, significant benefit can still be expected from the use of ß-blockers for heart failure. Future trials will address these groups in a prospective manner.
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The management of heart failure has experienced a revolution in treatment strategies and, importantly, in expectations of therapeutic interventions. The inhibition of deleterious neurohormonal pathways has yielded striking benefits regarding the morbidity and mortality of heart failure. Earlier estimates of survival in heart failure suggested a nearly 30% annual mortality rate, but more recent clinical trial data have demonstrated an annual mortality rate of <10% for patients with ambulatory heart failure.[1] Even for severe heart failure, the application of best-treatment strategies, especially with the use of β-blockers, has resulted in an annual mortality rate of approximately 15%.[2] It would be expedient to extrapolate the findings of clinical trials to the entire population affected with heart failure and to ignore issues of differing patient groups, existing comorbidities, or polypharmacy. However, the burden that each practicing

physician faces at the bedside of a given patient with heart failure to use the best available therapy raises the question of whether or not contemporary medical interventions, especially the addition of β-blockers, are broadly applicable to all patients or whether they vary among differing patient populations. This review will focus on special clinical considerations of β-blocker treatment as it applies to the elderly, women, and African Americans. It must be stated, however, that few, if any, clinical trials have prospectively recruited special populations and tested drug efficacy in these populations. Thus, the data reviewed represent post-hoc analyses from major trials, with all the attendant risks of such a review. Nevertheless, a surprising amount of data emerges from such an exercise.

Special Clinical Considerations of Beta-Blocker Treatment

Not only are there pertinent questions regarding different patient groups, but there are also important questions about comorbidities, polypharmacy, and clinical presentations. How do patients with concomitant obstructive lung disease or significant diabetes respond to β-blocker treatment? Can β-blockers be given safely with other agents that may have β-blocking properties, especially amiodarone and sotalol? How should β-blocker treatment be considered in the patient already on a post–myocardial infarction (MI) β-blocker who subsequently presents with heart failure? Are β-blockers for heart failure safe in patients with resting bradycardia? In patients who are very young and have heart failure, are β-blockers safe when administered over 20, 30, or more years? These important questions represent the dissociation between the clinical trial experience and the everyday management environment of practitioners who evaluate patients with heart failure. These issues, however, will not be covered in this article largely because data are simply not available for scholarly discourse on these subjects. Even within the confines of patient subgroups, data are lacking for important segments of the population, eg, heart failure in children, heart failure induced by chemotherapeutic agents, heart failure in the young adult, and heart failure in Hispanic Americans. Potential variances that may exist in these groups will eventually need to be addressed. Data that are currently available for a review of special clinical considerations as a function of patient subgroups include heart failure in the elderly, heart failure in women, and heart failure in African Americans. These subgroups will be the focus of the remainder of this article.

Heart Failure in the Elderly: The Effects of Beta-Blocker Therapy

Given the increasing number of elderly in the United States, heart failure in the elderly is a growing clinical and public health concern. Heart failure is most prevalent in the elderly, affecting 6%–10% of all persons over the age of 65. Moreover, of all patients hospitalized for heart failure, 80% are over 65. Heart failure as a diagnosis is the leading health care expenditure of Medicare.[3]

The elderly patient affected with heart failure has a different disease presentation from that of other patients. Specifically, the incidence of heart failure with preserved systolic function is higher in the elderly than in any other patient group, approaching a 50% incidence. The reasons for this are intriguing. There is a loss of left ventricular (LV) compliance with aging that is caused by senescence of the myocardium, with apoptosis leading to cell loss and fibrosis resulting in replacement of normal ventricular tissue. Although not sufficient to affect LV systolic performance, this process does lead to changes in LV compliance. When diastolic heart failure does develop, the prognosis is slightly better than that for systolic heart failure, with an annual mortality rate of ~10% in the setting of diastolic heart failure.[3] An important factor in the development of diastolic dysfunction leading to heart failure in the elderly is the associated presence of hypertension, especially systolic hypertension.

The association of hypertension and heart failure in the elderly is quite striking. The Framingham database demonstrated in an elderly cohort that hypertension is present as a cofactor or perhaps as the sole cause of LV failure in nearly 30% of all elderly patients affected with heart failure.[4] This is of particular importance because systolic hypertension in the elderly as a cause of heart failure may be modifiable by medical therapy.

Systolic Hypertension Studies

The Systolic Hypertension in the Elderly Project (SHEP). The Systolic Hypertension in the Elderly Project (SHEP)[5] is a landmark study that identified the risk of systolic hypertension and the benefit of intervention with a simple antihypertensive regimen of thiazide diuretics and β-blockers. Patients in the SHEP trial were all >60 years of age. The entry systolic blood pressure (BP) was 160–219 mmHg. Patients were randomized to placebo (given that the benefit of therapy of systolic hypertension had not yet been established), or to a regimen of thiazide diuretics with β-blockers added to effect better BP control. Even without achieving what would currently be accepted as goal BP

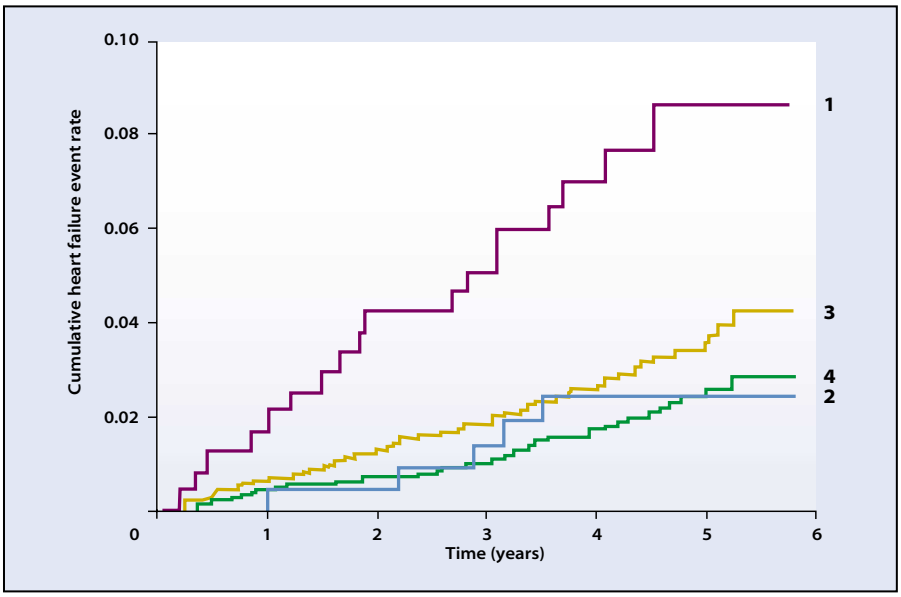


Figure 1. *Occurrence of fatal and hospitalized nonfatal heart failure in the active therapy and placebo groups of the Systolic Hypertension in the Elderly Program among participants who had a history or electrocardiographic evidence of myocardial infarction (MI) at baseline and among those who did not 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). Adapted, with permission, from Kostis et al.*[5]

reductions, the benefit of therapy was impressive. The reduction in the onset of heart failure was nearly 50%. Even greater was the reduction in the onset of heart failure in the group of elderly patients with both systolic hypertension and a history of a prior MI (Figure 1). Based on the number needed to treat, 48 patients with systolic hypertension would need to be treated to prevent one occurrence of heart failure, whereas only 15 patients with both systolic hypertension and a prior history of MI would need to be treated.[5]

The Swedish Trial in Older Patients with Hypertension (STOP-Hypertension). These findings were corroborated in the Swedish Trial in Older Patients with Hypertension (STOP-Hypertension),[6] which demonstrated a 43% reduction in mortality when a thiazide diuretic and β-blockers were given to men and women, aged 70 to 84 years, with systolic hypertension. These data further demonstrate a major opportunity to change the natural history of cardiovascular disease in the elderly. An important other finding has been the negative risk of a widened pulse pressure in the elderly. A meta-analysis of outcome trials showed that in patients with systolic hypertension, the wider the pulse pressure the higher the mortality risk.[7] Newer therapies—eg, advanced glycosylated end-product (AGE) cross-link breakers—carry the promise of being able to selectively lower pulse pressure by improving vascular compliance. Whether this approach will facilitate a reduction in cardiovascular events in the elderly will require intense investigation.[8]

Medical Therapy Studies

The Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). A review of published trials demonstrated the definite benefit of medical therapy when elderly patients are affected with symptomatic heart failure. The Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) study[9] evaluated the benefit of using controlled-release/extended-release metoprolol in 3991 patients with New York Heart Association (NYHA) class II to IV heart failure. The overall trial results demonstrated a 35% reduction in all-cause mortality with the addition of extended-release metoprolol to standard therapy for heart failure. These results were equally demonstrable in the population > 65 years of age and provide data that would support the use of β-blocker therapy in mild to moderate heart failure, age notwithstanding.[9]

The U.S. Carvedilol Heart Failure Study. In the U.S. Carvedilol Heart Failure Study,[10] 1094 patients with mild to moderate heart failure were entered into one of four concurrent protocols to test the benefit of adding carvedilol to standard therapy for heart failure. The study demonstrated a striking decrease in the combined endpoint of death or hospitalizations resulting from heart failure. Although mortality was not a predetermined endpoint for the trial, a 65% reduction in mortality was observed. This benefit was noted to extend both to patients < 65 years and those > 65 years. The event-free survival in the patients with mild heart failure in that trial revealed a 48% reduction in the primary endpoint of clinical progression defined as death, hospitalization resulting from heart failure, or a sustained increase in medical therapy (Figure 2).

The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) trial[2] evaluated the benefit of carvedilol added to a standard

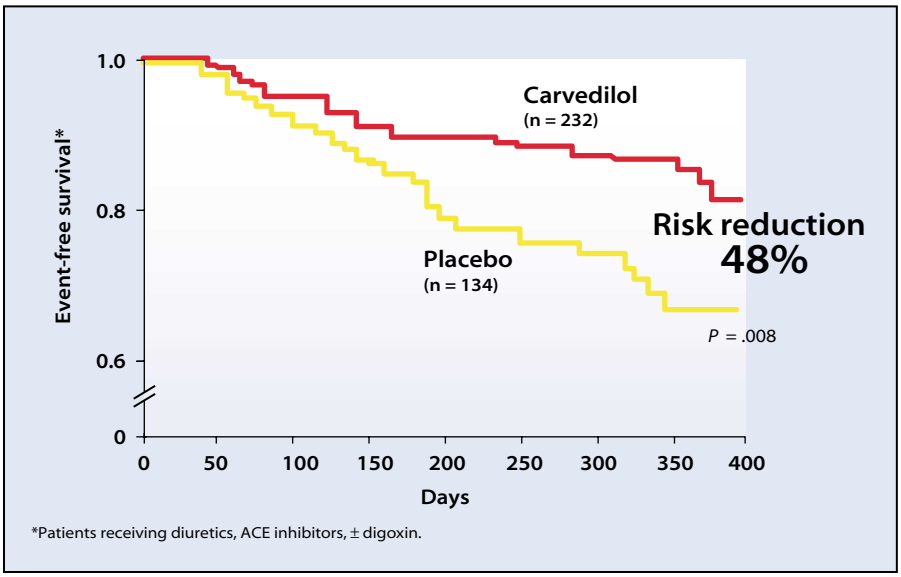


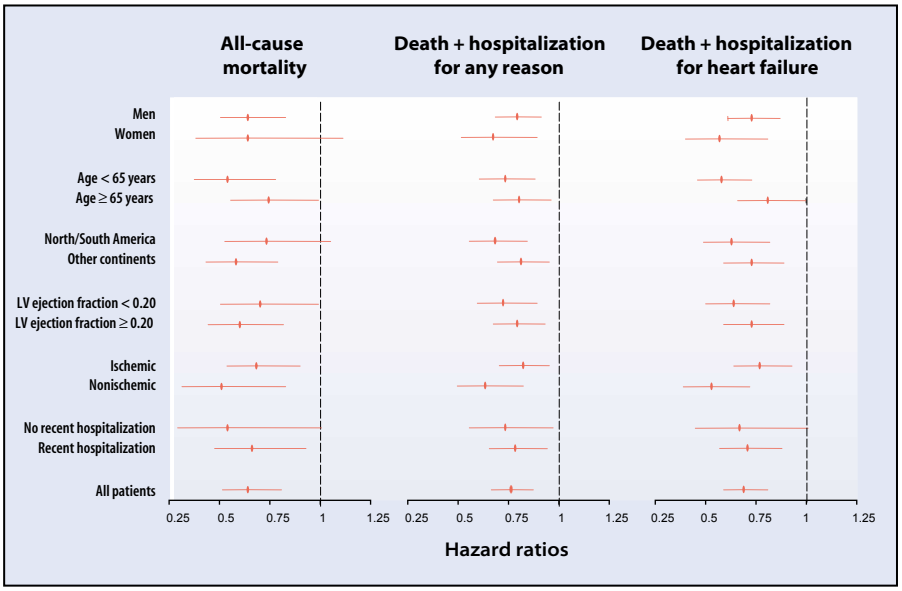
Figure 2. *The effect of carvedilol on clinical progression in mild heart failure. Adapted, with permission, from Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. U.S. Carvedilol Heart Failure Study Group.* Circulation. *1996;94:2800–2806.*

regimen of angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digoxin in patients with advanced heart failure. In this trial, advanced heart failure was identified as symptoms at rest on chronic stable medical therapy with diuretics and ACE inhibitors and a left ventricular ejection fraction (LVEF) < 0.25. The mean age of the patients enrolled was 63.2 years, and 65% had an antecedent hospitalization for heart failure within the previous year. The results demonstrated a 35% reduction in mortality when carvedilol was added to a regimen of ACE inhibitors, diuretics, and digoxin in patients with advanced heart failure. The subsequent subgroup analysis demonstrated that patients > 65 years of age derived a similar and statistically important benefit from carvedilol as did patients < 65 years of age (Figure 3). This benefit was seen both in a reduction in mortality reduction and in the combined endpoint of death or hospitalization for any reason.[2]

In order to assess the benefit of β-blocker therapy in an even older cohort, Cioffi and Stefanelli[11] evaluated a group of patients > 70 years of age with heart failure. The mean age was 76 ± 6. Carvedilol was added to a standard heart failure regimen, and the patients were compared to a control group not on carvedilol. Tolerability was 87% in the elderly patients. The functional class improved, and the LVEF increased from 30% to 42%. The mortality rate was high—25%—demonstrating that systolic dysfunction in the elderly patient with heart failure carries with it a prognosis of great concern.[11]

The available data currently suggest that heart failure in the elderly is a major public health concern, accounting for the bulk of hospitalizations. The contribution of diastolic dysfunction cannot be overlooked, and the importance of systolic hypertension in the elderly must be emphasized. Effective treatment of systolic hypertension in the elderly with thiazide diuretics and β-blockers changes the natural history of heart failure. When symptomatic heart failure is present, therapy with a regimen of ACE inhibitors, diuretics, digoxin, and β-blockers, especially carvedilol, yields substantial benefits with a reduction in hospitalizations and mortality, even in patients > 65 years of age.

Figure 3. *Results of the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). LV, left ventricular. Adapted, with permission, from Packer et al.[2]*



Heart Failure in Women: The Effects of Beta-Blocker Therapy

Heart failure has been affecting women, especially older women, at an alarming rate. Often the symptoms go unrecognized, and the complaints of exertional fatigue and loss of energy are attributed to aging. The original Framingham analysis suggested that the outcomes for women with heart failure were slightly better than those for men; but this difference is likely caused by the influence of hypertension leading to diastolic heart failure, and thus the better prognosis.[4] The more recent analysis from the Studies of Left Ventricular Dysfunction (SOLVD)[12] did not demonstrate an important gender difference in mortality resulting from heart failure due to systolic dysfunction.

When women are affected with heart failure, they are more likely to have hypertension and diabetes, to be African American, and to be obese. The incidence of coronary artery disease leading to LV dysfunction and subsequent heart failure is lower in women than in men and the incidence of concomitant tobacco abuse is similarly lower in women.[13]

Women's Issues

In response to hypertension, women are more likely to develop concentric ventricular hypertrophy from pressure loading, a pattern that is dissimilar from the pattern seen in men. Diabetes is also a much more prevalent risk factor for heart failure in women than in men and may be an issue in younger women, especially when obesity is a co-existent factor. Retrospective analyses of the natural history of ischemic heart disease from several older databases suggest that the pathology of ischemic heart disease is just as ominous for women as for men. Older studies revealed a strikingly high morbidity and mortality rate post-MI, but this may have been influenced by a high mortality rate in African American women in those trials. In the Coronary Artery Surgery Study (CASS), there was an excess of heart failure and pulmonary edema seen after bypass surgery in women compared with men; again, it is not clear if this is purely a gender difference or a difference related to the caliber of the coronary vasculature and technical limitations of surgery.[13]

Medical Therapy for Heart Failure in Women

Regarding medical therapy for heart failure affecting women, data from 30 randomized trials of the use of ACE inhibitors for heart failure from LV systolic dysfunction failed to demonstrate a benefit from ACE inhibition in women similar to that seen in men. In fact, women did not demonstrate a mortality benefit. Such a review, however, is terribly limited by selection bias and sample size.[14] The Vasodilator Heart Failure Trials (V-HeFT I and II) did not include a significant number of women because these were studies of a population of veterans. Thus, we have no data regarding the benefit, or risk, of vasodilator therapy for heart failure in women.

Effective treatment of systolic hypertension in the elderly with thiazide diuretics and ß-blockers changes the natural history of heart failure.

Other interesting issues regarding LV dysfunction are the incidence of resultant LV dysfunction seen after exposure to anthracyclines and in response to treatment with the antibody to the HER-2/neu oncogene (Herceptin)—both used in the treatment of breast cancer. Are the effects on LV function specific to gender? This is an unknown issue. Similarly, peripartum cardiomyopathy is limited to women and carries with it a variable prognosis dependent upon the incidence of spontaneous recovery. At a basic level, estrogen regulates genes responsible for prostacyclin, endothelin-1, E-selectin, vascular endothelial growth factor, and matrix metalloproteinase-2. Estrogen also has an effect on genes regulating fibrinogen, tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1), platelet-derived growth factor, transforming growth factor-β-1, and protein S. How the balance of these vascular, thrombogenic, and fibrogenic genes is expressed is likely to affect the clinical experience of cardiovascular disease expression in women.

The Beta-Blocker Evaluation of Survival Trial (BEST). The β-blocker experience has likewise been complicated. The β-Blocker Evaluation of Survival Trial (BEST)[15] tested the potential benefit of bucindolol in addition to standard medical therapy for advanced heart failure. The trial failed to demonstrate a survival advantage for the primary endpoint of an all-cause reduction in mortality.[15] This trial differed from many other clinical trials in its patient population. In an a priori manner, the intent of the investigators was to enroll a patient population that was ≥20% female and ≥20% minority, especially African American. It has been suggested that this population demographic is at least in part responsible for the failure to achieve the primary endpoint in the study. It must be recognized that even in the group that demonstrated a

response to bucindolol—ie, white males with class III heart failure—the magnitude of the benefit was only one half that seen with other β-blocking agents. Thus, drug differences may exist between bucindolol and the other β-blockers that have shown positive results. This may also suggest that the benefit of β-blocker therapy cannot yet be considered a class effect, and drug-specific outcomes need to be considered.

The BEST trial enrolled a female population of 593 women (28%) with advanced heart failure. Thirty percent of the women were black. Women were more likely to have a nonischemic etiology of LV failure. The mean plasma norepinephrine level was lower in women than in men. Atrial fibrillation imparted a two-fold increased risk of death in women in this trial. In response to the β-blocker bucindolol, no mortality benefit was seen in the female population.[15]

The Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). The original publication of the Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) study, which also had 898 women—a 29% female cohort—failed to show an all-cause mortality benefit in response to extended-release metoprolol given to women with NYHA class II and III heart failure.[9] A recently reported re-analysis of the female cohort of all 898 women demonstrated that there was a 21% reduction in events (P = .04) for the combined endpoint of mortality and all-cause hospitalization. In addition, the reduction in cardiovascular hospitalizations was 29%, and the reduction in hospitalizations for worsening heart failure was 42%. For the group of women with severe heart failure, (n = 183), the corresponding reductions in hospitalizations were 57% and 72%, respectively.[16] These data would suggest a significant benefit from β-blocker therapy for women with moderately severe and advanced heart failure.

The U.S. Carvedilol Heart Failure Study. The experience with carvedilol is quite encouraging and demonstrates that mortality from heart failure in women is statistically significantly improved with carvedilol plus ACE inhibitor therapy. A total of 256 women (31%) were enrolled in the U.S. Carvedilol Heart Failure Trials Program. The relative risk for a mortality benefit in women was 0.32 (P = .028) compared to men (RR, 0.43; P = .007), and the confidence limits did not cross the line of identity. Of note, mortality was not a predetermined endpoint for the U.S. Carvedilol Heart Failure Trials Program.

The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). The COPERNICUS trial evaluated the benefit of carvedilol added to a standard heart failure regimen in patients with advanced heart failure. A total of 465 women (25%) were enrolled in the COPERNICUS trial, which was summarized earlier. The results demonstrated that the point estimate of the reduction in mortality for men and women was identical, ie, a 35% reduction in mortality in the setting of advanced heart failure. The confidence intervals for this benefit in women were broad and did cross the line of identity. For the combined endpoints of death plus hospitalization for any reason and for death plus hospitalization for heart failure, the odds ratios were similar to those seen in men and were statistically significant (Figure 3).[2]

These data would support the use of β-blockers along with standard therapy for heart failure in women. It is of some concern that the efficacy of ACE inhibition is not known, but it is encouraging that women's response to β-blockers, especially for the combined endpoints of death plus hospitalization, is so robust. Women should represent yet another group in whom β-blocker therapy should be employed for the management of heart failure.

Heart Failure in African Americans: The Effects of Beta-Blocker Therapy

Perhaps the greatest concern regarding the efficacy of β-blocker therapy in patient subgroups is within the African American population. Heart failure in the African American patient has emerged as an important clinical consideration. Fortunately, a growing database is available to investigate this issue.

Overall, heart failure in African Americans carries with it special concern: the African American patient affected with heart failure has a more worrisome natural history, a unique epidemiolgy, a higher incidence of adverse outcomes, and may demonstrate potentially important clinical differences in the response to medical therapy, especially neurohormonal antagonists. The incidence of heart failure in the African American population is as much as two-fold higher than in all other groups. This is especially pertinent for the African American female.[17]

When affected with heart failure, African American patients tend to have the onset of disease at an earlier age, to have more advanced LV dysfunction at the time of diagnosis, and to be in a more advanced NYHA clinical class. In a striking manner, the etiology of LV dysfunction in the African American patient with heart failure is more likely to result from hypertensive heart disease, perhaps as the sole or putative cause

of heart failure.[17] This is not to say that it represents the only cause: nearly 40% of African Americans still have ischemic heart disease as the cause of LV dysfunction leading to heart failure. A search for all causes of LV dysfunction should occur irrespective of the race of the patient affected with heart failure.

Studies in Left Ventricular Dysfunction

The rate of hospitalization for heart failure is higher in African Americans and mortality rates may be higher than in others with heart failure, although these data remain a point of controversy. An earlier report from the Studies of Left Ventricular Dysfunction (SOLVD) database suggested that mortality was higher in the African American patient, but this observation did not adjust for a difference in disease severity at the time of enrollment in the trials.[18] A more recent re-analysis of the SOLVD database matched 800 black patients with 1196 white patients from the prevention and treatment trials for LV dysfunction and for trial participation. This group of patients, both black and white, was overpopulated with patients in the SOLVD Prevention Trial, thus this was a low-risk cohort. In this low-risk subset of patients, mortality trended higher in the black group than in the white, but did not reach statistical significance. Hospitalizations were, however, statistically different for the black versus white patient in the trial. There was an over 40% reduction in hospitalizations in the white patients in response to therapy with enalapril that was not seen in the black patients. In addition, there was an important difference in BP response between the two groups: the white patients experienced a 6/3 mmHg drop in BP in response to enalapril. For the same dose of enalapril, the black patients had a 0/0 mmHg response.[19] Thus, the difference in response to ACE inhibitor therapy may have been a function of the dose administered.

An important ancillary finding from the SOLVD studies was an assessment of the impact of socioeconomic status on disease outcomes. It is easy to assume that differing clinical outcomes in black patients are a function of a lower socioeconomic status. If that is the case, then controlling for this variable should reveal similar disease outcomes. Within the SOLVD experience, a univariate analysis of educational level and measures of financial distress did correlate with mortality, but after adjusting for these crude markers of socioeconomic status, a mortality difference was still evident.[18] This finding would suggest that potential physiological differences might exist that are responsible for different clinical outcomes.

Medical Therapy for Heart Failure in African Americans

The Beta-Blocker Evaluation of Survival Trial (BEST). The response to β-blocker therapy has similarly been an issue. In the BEST trial reviewed earlier, more than 600 black patients were studied—representing the largest population of black patients yet studied in a heart failure trial. Within the black group with advanced heart failure, the addition of bucindolol demonstrated an 18% increase in mortality—a statistically insignificant response, but nevertheless, a very disturbing trend.[15]

The U.S. Carvedilol Heart Failure Study. The experience with carvedilol has been much more positive and appears to provide outcomes that are clinically useful in the management of heart failure affecting the African American patient.

The U.S. Carvedilol Heart Failure Trials Program enrolled 217 African American patients with mild to moderate heart failure. As expected, the African American group had more advanced LV dysfunction and more symptomatic heart failure. The response of this group to carvedilol, a β-blocker with both nonselective β-blocking properties and β-blocking properties that also is an antioxidant, was looked at in a retrospective review. The African American patients were compared to the non–African American patients for all prespecified endpoints. The resulting analysis demonstrated a benefit of therapy in the African American group that was statistically significant compared to placebo and was of the same magnitude as that seen in the non–African American group (Figure 4).[20] The interactive *P* value for all endpoints tested was not significantly different for the two groups, suggesting that the response seen was statistically similar in both groups. Importantly, there was a 54% reduction in the progression of heart failure, defined as death resulting from heart failure, hospitalization for heart failure, and a sustained increase in medical therapy for heart failure. For the same parameter of progression of heart failure, the benefit of carvedilol plus standard therapy for heart failure in the non–African American group was 51%. Although it was not a predetermined endpoint, mortality reduction in the African American group was nearly 50%.[20]

These data are in contradistinction to the BEST data. Are the data from the U.S. Carvedilol Heart Failure Trials Program spurious? An evaluation of the hemodynamic response to carvedilol would suggest that the benefit seen is real and is consistent with the physiological response to therapy. An increase in LV function in response to β-blocker therapy has

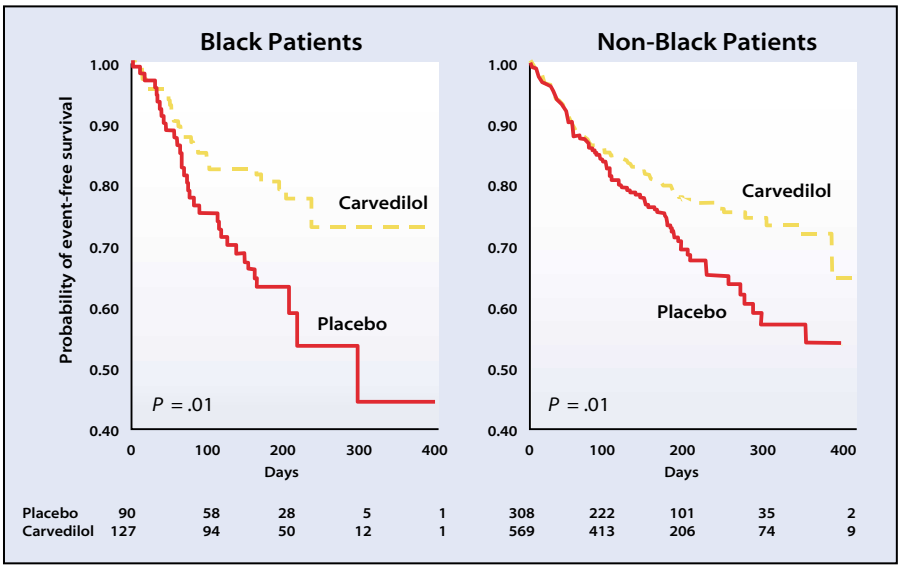


Figure 4. *U.S. Carvedilol Heart Failure Study trials: effect of race on death or hospitalization for any cause. Data from Yancy et al.*[20]

been suggested as a surrogate of improved survival in the setting of chronic heart failure. The improvement in LV function was 10 ejection fraction (EF) units in the African American group and 9 EF units in the non–African American group. The change in BP was less than 2 mmHg for both groups, and the reduction in the heart rate was ~13 beats per minute for both groups. Once again, the interactive *P* value was not different between the two groups.[20] These data would suggest that the clinical benefit seen in outcomes has a physiological basis and is a real benefit.

The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). The findings of the U.S. Carvedilol Heart Failure Trials Program are further buffeted by the results from the COPERNICUS trial. As noted above, the COPERNICUS trial enrolled patients with advanced heart failure. Within this patient population, 121 individuals were African American. Their response to carvedilol was quite favorable and was once again similar in magnitude to the benefit seen in the overall trial. Moreover, the results were significant for all predetermined endpoints when compared to placebo therapy. When the outcomes in African American patients in both carvedilol trials were compared, there was a strikingly similar benefit seen for all classes of heart failure. These data would suggest that a regimen of β-blocker therapy, especially carvedilol, plus ACE inhibitors and diuretics, is beneficial in African American patients.[2]

The African American Heart Failure Trial (A-HeFT). Of note, all of the foregoing data are from retrospective reviews of studies that were not prospectively powered to evaluate

Main Points

- Heart failure management and outcomes are significantly better with contemporary therapy that includes ACE inhibitors and β-blockers.
- Special clinical consideration needs to be given to whether or not these benefits are applicable to all patient groups.
- The elderly presenting with heart failure have a higher incidence of diastolic heart failure, presumably resulting from a higher incidence of hypertension, especially systolic hypertension. The progression to heart failure may be ameliorated by the use of diuretics plus β-blockers for systolic hypertension. When affected with heart failure, elderly patients fare just as well on β-blocker therapy, and the drugs should not be withheld.
- Women with heart failure differ, with a higher incidence of hypertension and diabetes, but a lower incidence of ischemic heart disease leading to LV dysfunction. Surprisingly, there are few data points to suggest meaningful benefit from ACE-inhibitor therapy, but the data with β-blockers demonstrate significant improvements in morbidity and mortality resulting from heart failure.
- African Americans with heart failure may have a unique clinical malady, given the higher incidence of hypertensive heart disease and the frequent presence of more advanced disease on presentation. Despite concerns regarding differential responses to neurohormonal antagonism, the data regarding the use of β-blockers, especially carvedilol, demonstrate significant benefit that is of the same magnitude as that seen in all patients studied, including mild to moderate and advanced heart failure.
- To date, all groups of patients appear to derive significant benefit from β-blocker therapy, and this should be a part of all management strategies for heart failure, unless there is an obvious contraindication to its use.

important subgroup questions. Thus, questions still remain for all of the groups discussed in this paper. An attempt is underway to evaluate outcomes in an African American patient population prospectively. The African American Heart Failure Trial (A-HeFT) is underway and is testing the hypothesis that adding a nitric oxide donor (Bidil combination therapy with isosorbide dinitrate and hydralazine [NitroMed, Bedford, MA]) to a regimen of ACE inhibitors and diuretics will be beneficial. Although not mandated per protocol, β-blocker use has been robust to date and is present in 75% of patients enrolled in this trial. The data forthcoming from the study will represent the first opportunity to evaluate outcomes in an African American population in a prospective manner and should provide valuable information.

Summary

Among the many special clinical considerations regarding the use of β-blockers for heart failure, available data strongly suggest that β-blockers are effective in all patients yet evaluated. In particular, substantial data demonstrate that the important patient subgroups of the elderly, women, and African Americans derive significant benefit from β-blocker therapy for heart failure. More data are required to confirm the unique physiological and therapeutic features of these populations. It is not entirely clear whether or not future trials should be prospectively designed to incorporate patient subgroups as predetermined populations or whether, as in the case of the A-HeFT trial, dedicated trials should be done in populations restricted to the subgroup in question. It would be unwieldy to proceed in the latter fashion, and it would be a clinical disservice to design multiple treatment strategies and algorithms that rely solely on age, gender, or race. In particular, race is much too heterogeneous to describe a consistent physiological response to LV dysfunction. Until incontrovertible data are available, *all* patients with LV systolic dysfunction should be treated with ACE inhibitors and β-blockers unless there is an overwhelming contraindication. ■

Until incontrovertible data are available, all patients with LV systolic dysfunction should be treated with ACE inhibitors and ß-blockers unless there is an overwhelming contraindication to doing so.

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