Controversies in the Use of Beta Blockers in Heart Failure

Recent evidence from randomized controlled trials has provided compelling evidence to support the use of β blockers in most patients with heart failure due to systolic dysfunction. There is little disagreement about the mortality benefit provided by adding β blockers to standard therapy, which may include angiotensin-converting enzyme inhibitors, diuretics, and sometimes digoxin. A few areas are still controversial. The authors review the available literature encompassing four of those controversial areas: 1) the comparability among β blockers; 2) the utility of β blockers among patients with New York Heart Association class I and class IV heart failure symptoms; 3) the impact of race on the effectiveness of β blockers; and 4) the safety and efficacy of β blockers among patients on concomitant therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or spironolactone. (CHF. 2003;9:255–262) ©2003 CHF, Inc.

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Recent trials have provided compelling evidence to support the use of β blockers in heart failure (HF) due to systolic dysfunction.[1–4] Current, major published guidelines support this concept and offer guidance on how to administer them in appropriate patients.[5–9] Still, there are controversies.

The majority of patients with HF may derive long-term benefit from the addition of β blockers to background therapy, which may include angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, and digoxin. Only one comparative trial between β blockers in heart failure has been completed. This trial did not resolve the issue of comparability. Little clinical data exists among patients with New York Heart Association (NYHA) class I symptoms and some controversy remains over the appropriateness of routine administration to patients with NYHA class IV symptoms. Additionally, retrospective analyses of prior HF trials[10] and one recently completed β-blocker trial[11] have raised the specter of racial differences in the response of HF patients to pharmacologic therapy. Finally, there also remains uncertainty about how β blockers may interact with other medications. Evidence for the efficacy of β blockers was being gathered at the same time that spironolactone was being evaluated for its use in HF in the Randomized Aldactone Evaluation Study (RALES).[12] As a result, none of the β-blocker trials were conducted with spironolactone as part of background therapy and only 10% of the RALES population was on β blockers. The recently released Valsartan Heart Failure Trial (Val-HeFT) uncovered a possible adverse interaction among patients on β blockers with concomitant ACE inhibitors and angiotensin receptor blockers (ARBs).[13]

In this paper, we will review the literature describing these controversies, including: 1) the comparability among β blockers; 2) the utility of β blockers among patients with NYHA class I and class IV symptoms; 3) the impact of race on the efficacy of β blockers; and 4) the safety and efficacy of β blockers among patients on concomitant therapy with ACE inhibitors, ARBs, or spironolactone.

Comparability Among β Blockers

Pharmacologic differences among β blockers suggest that perhaps one β blocker may be preferred to another in regard to efficacy, tolerability, and practicality. To evaluate the differences among β blockers, this section will focus on pharmacologic, theoretical, evidenced-based, and practical issues among β blockers. This section will deal primarily with bisoprolol, carvedilol, and metoprolol, which are three of the four β blockers tested in large mortality trials among HF patients and the only ones with a proven mortality benefit. Bucindolol is the fourth β blocker tested and has not demonstrated a mortality benefit in HF. Bucindolol is not available in this country. It will be discussed briefly in the section below on comparability of agents and will be discussed in more detail in the section on racial differences in the response to medications.

Pharmacologic Properties and Theoretical Considerations. Metoprolol and bisoprolol are considered second generation β blockers, meaning that they are cardioselective and have no ancillary properties.[14] Third generation β blockers may either be cardioselective or noncardioselective and may have potentially important ancillary properties. Carvedilol is a third generation β blocker that is noncardioselective with α-blocking properties.[14] Bucindolol is also noncardioselective, but without the α-blocking properties of carvedilol. The pharmacologic profiles are shown in Table I.

Metoprolol and Bisoprolol. As seen in Table I, metoprolol and bisoprolol are cardioselective for the β_1 receptor. A potential, theoretical advantage of selective β_1 blockade may include the safe administration to patients with asthma since the β_2 receptor is not blocked. Bisoprolol has even greater selectivity than metoprolol. In patients with low blood pressure, these β blockers may be better tolerated initially since they do not possess vasodilating properties. In regard to the pathophysiology of HF, recent animal data[15–17] have suggested that the β_1 receptor is primarily responsible for the development of dilated cardiomyopathy. In one study in mice, overexpression of the β_1 receptor five-fold resulted in development of dilated cardiomyopathy, whereas overexpression of the β_2 receptor 100-fold resulted in development of cardiomyopathy.[16,17] Other animal data[18,19] have suggested that apoptosis is mediated by the β_1 receptor and that stimulation of the β_2 receptor may have antiapoptotic effects. Overall, these data would favor the use of metoprolol or bisoprolol since, theoretically, antagonism of the β_1 receptor is most critical and nonantagonism of the β_2 receptor is beneficial.

Carvedilol. Carvedilol blocks β_1, β_2, and α_1 receptors (Table I). Debatably, the most important driving force in the development and maintenance of systolic dysfunction is the activation of the sympathetic nervous system (i.e., elevated norepinephrine concentrations). Theoretically, since the heart contains three different adrenergic receptors (β_1, β_2, and α_1 receptors) that may be activated by norepinephrine, blocking all three receptors (complete adrenergic blockade) vs. just one receptor could be more efficacious. Furthermore, carvedilol also decreases systemic and cardiac adrenergic drive and maintains downregulation of the β receptor.[20] These properties, along with blocking all three receptors, may provide the best protection against excess adrenergic drive that is present in patients with HF.

Table I. Pharmacologic Properties

PROPERTY	BISOPROLOL	BUCINDOLOL	CARVEDILOL	METOPROLOL
β_1 Blockade	+	+	+	+
β_2 Blockade	–	+	+	–
α_1 Blockade	–	–	+	–
Vasodilation	–	+ (Mild)	+ (Acute)	–
Antioxidant	–	–	+ (?)	–
Lowers cardiac NE	–	+	+	–
Lowers systemic NE	–	++	+	–

– =does not demonstrate this property; + =demonstrates this property; + (?)=demonstrates this property with a degree of uncertainty; ++= demonstrates this property to a greater extent; NE=norepinephrine

When a β blocker is initially started in HF patients in whom cardiac function is highly dependent upon adrenergic drive, there is a slight drop in cardiac output. The α-blocking properties of carvedilol mediate vasodilatation that may decrease afterload and negate this drop in cardiac output. This affect may allow for less chance of decompensation on initiation of therapy. For metoprolol and bisoprolol, their mechanism for maintaining cardiac output would be unopposed stimulation of β_2 receptors in the periphery.

Carvedilol may also possess antioxidant properties that could theoretically be beneficial in HF patients. Antioxidant effects may result in antiproliferative effects, improved endothelial function, decreased ischemic-induced damage, and apoptosis. Any of these effects would be beneficial in HF patients since each of these effects may contribute to the maintenance and progression of HF.

Evidence Base. From a theoretical perspective, it can be argued that each β blocker should be the "best" for treating HF patients. To determine whether or not these theoretical arguments actually translate into clinical benefit, evaluation of the available clinical data is required. For this purpose, studies evaluating end points such as mortality, hospitalizations, tolerability, and left ventricular ejection fraction will be discussed. For mortality, hospitalizations, and tolerability, the four largest placebo-controlled trials will be evaluated: Cardiac Insufficiency Bisoprolol Study II (CIBIS II),[1] Metoprolol Randomized Intervention Trial in Heart Failure (MERIT-HF),[2] Carvedilol Prospective Randomized Cumulative Survival Study Group (CORPERNICUS),[4] and Beta-Blocker Evaluation of Survival Trial (BEST).[11] Additional mention will be given to the US Carvedilol Heart Failure Trials.[3] Finally, the Carvedilol or Metroprolol European Trial (COMET)[21] will be reviewed.

Mortality. There are randomized, placebo-controlled mortality trials on four different agents that can be evaluated. As seen in Table II, the risk reduction among the trials appears to be similar with the exception of the BEST trial which is the only large mortality trial in which no mortality benefit was detected.[11] The largest mortality benefit was reported from the US Carvedilol Heart Failure Trial which demonstrated a 65% reduction in mortality.[3] Whether or not the risk reduction seen in this trial is actually that great is a matter of debate, since it was not specifically designed as a mortality trial like the other three trials and data from four separate trials were combined to achieve their end point. Furthermore, only one of the four trials demonstrated a mortality benefit. Additionally, deaths during the single blind run-in were not included in the analysis. It should also be noted that, among the positive trials, the placebo mortality rate was highest and left ventricular ejection fraction was lowest for the COPERNICUS trial, which makes head-to-head comparisons using these data difficult.[4] However, in post hoc analyses of patients with severe HF in the MERIT-HF and CIBIS II trials, the placebo mortality rate and the mortality risk reduction of metoprolol and bisoprolol are similar to that achieved by carvedilol in COPERNICUS.[22,23] For the CIBIS II trial, NYHA class IV patients had an approximate 25% placebo mortality rate and a 26% reduction in mortality based on 224 patients in the placebo group and 221 patients in the treatment group.[22] NYHA class III patients had an approximate 16%–17% placebo mortality rate and a 34% reduction in mortality based on 1096 patients in the placebo group and 1106 patients in the treatment group.[22] In the MERIT-HF subanalysis in NYHA class III and IV patients, the placebo mortality rate was 19.1% and the risk reduction in total mortality was 39% in 396 placebo patients and 399 treatment patients.[23]

Table II. Outcomes of Mortality Trials

OUTCOMES*	BEST	CIBIS II	CORPERNICUS	MERIT-HF
Mortality reduction	10% (NS)	34%	35%	34%
Duration of study	2 Years	16 Months	10.4 Months	12 Months
Placebo mortality rate	33%	13.2%	18.5%	11%
Hospitalizations reduction	8% (NS)	20%	N/A	18%
Withdrawal rates placebo vs. Tx	23% vs. 25%	15% vs. 15%	18.5% vs. 14.8%	15.3% vs. 13.9%

*As reported from each study; mortality reduction=total mortality risk reduction compared to placebo; hospitalization reduction=total hospitalization risk reduction compared to placebo; withdrawal rates=permanent discontinuation of treatment for each group; Tx=treatment group; NS=not statistically significant; trial acronyms expanded in the text

The only mortality trial not to show a benefit was BEST.[11] This trial is discussed in more detail in the section on the impact of race. Bucindolol is a unique agent and the patients in the BEST trial were different in terms of the severity of the disease and racial breakdown. It is unclear which of these factors is most responsible for the outcome.

A direct comparison of the effect of two different β blockers, carvedilol and metoprolol, on mortality was performed in the COMET trial.[21] In this trial, carvedilol reduced mortality by 17% compared with metoprolol over a 58-month follow-up period. However, the differences in the dose and formulation of metoprolol between the MERIT-HF and COMET trials may have contributed to the apparent superiority of carvedilol.

In the MERIT-HF trial, patients received a high dose of metoprolol (200 mg q.d. target/159 mg q.d. achieved) in an extended-release formulation. In the COMET trial, patients received a lower dose of metoprolol (50 mg b.i.d. target/85 mg q.d. achieved) in an immediate-release formulation. Arguably, these differences in dose and formulation may not have produced clinically significant differences in β blockade. However, that contention is based on the lower bioavailability of the extended-release formulation (approximately 65%) and on extrapolations from dose-response relationships in normal volunteers.[24,25]

Hospitalizations. Data for total hospitalizations are shown in Table II.[1,2,4,11,26] Once again, subgroup analysis was done for patients with severe HF for the CIBIS II and MERIT-HF trials.[1,2] For CIBIS II, the reduction in hospitalizations was 5% (95% confidence interval [CI], 0.78–1.17) for NYHA class IV patients and 17% (95% CI, 0.74–0.93) for class III patients. For MERIT-HF, hospitalizations were reduced by 27% ($p=0.0037$). The data available for the COPERNICUS trial show that 32.2% of the patients receiving carvedilol were hospitalized at least once vs. 38.1% for placebo ($p=0.0029$).[27] Overall, all three of these β blockers reduce hospitalizations and the reduction in hospitalizations appear to be similar among the trials.

Tolerability. It has been discussed that since carvedilol has vasodilating properties it should be the best tolerated. To examine this, evaluating the withdrawal rates among the trials is one approach. As seen in Table II, the withdrawal rates were similar in the treatment groups compared with placebo. Metoprolol XL and carvedilol even demonstrated a lower withdrawal rate than placebo. These data indicate that all three β blockers evaluated are well tolerated in the treatment of HF compared with placebo.

Left Ventricular Ejection Fraction. There has been no trial larger than 150 patients that has directly compared the effects of a third generation β blocker to a second generation β blocker.[28] However, there have been a number of smaller trials that have evaluated the impact of β blockers on improving ejection fraction either against placebo or active treatment. In a meta-analysis,[28] 2184 patients from 19 randomized controlled trials of carvedilol or metoprolol were evaluated. The average duration of therapy was approximately 8 months and the mean daily dose of carvedilol was 58±1 mg and the equivalent of 162±1 mg of metoprolol extended release. It is stated that in 15 placebo-controlled trials, the placebo-corrected increase in ejection fraction for carvedilol was 0.065 and 0.038 for metoprolol, both of which were significantly increased compared with their respective placebo controls ($p<0.0001$). From these trials, the increase in ejection fraction for carvedilol was significantly greater than with metoprolol ($p=0.002$; weighted mean of the treatment differences was 0.026±0.007). In four trials in which carvedilol and metoprolol were directly compared, carvedilol increased ejection fraction by 0.084 with metoprolol increasing ejection fraction by 0.057, $p=0.09$. Overall, these data indicate that both carvedilol and metoprolol significantly increase ejection fraction compared with placebo and that carvedilol may increase it to a greater extent.

Practical Issues. Practical issues to consider are ease of administration and cost. In this regard both bisoprolol and metoprolol XL have slight advantages since both

Table III. Cost Comparison

DRUG	TARGET DOSE	COST*
Bisoprolol (Zebeta)	10 mg q.d.	$40.81
Carvedilol (Coreg)	25 mg b.i.d.	$90.67
Metoprolol XL (Toprol XL)	200 mg q.d.	$55.71

*Cost for a 30-day supply to consumers based on prices from drugstore.com, July 7, 2002

may be dosed once a day vs. twice a day for carvedilol. In regard to cost, as seen in Table III, both bisoprolol and metoprolol XL are lower than carvedilol for a 30-day supply at target dose levels. This may have significant implications in those patients who are not covered with prescription insurance. Additionally, only carvedilol and metoprolol succinate are approved by the Food and Drug Administration (FDA) and dosed appropriately for initiation in HF.

The most significant practical conclusion is that β blockers (i.e., carvedilol, metoprolol XL, and bisoprolol) significantly reduce mortality and hospitalizations in patients with HF and that all appropriate HF patients need to be considered for treatment with any one of these β blockers.

The Utility of β Blockers Among Patients With NYHA Class I and NYHA Class IV Symptoms

NYHA Class I. None of the major clinical trials which have established the efficacy of bisoprolol, carvedilol, and metoprolol in HF have systematically enrolled NYHA class I patients.[1–4] The Carvedilol Post-Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) study did enroll some asymptomatic patients and detected a trend toward improved mortality.[29] It is hard to generalize these findings to all NYHA class I patients because all of the patients were postmyocardial infarction, no subgroup analysis was published isolating class I patients, and there were some statistical concerns.

The epidemiology of this class is poorly characterized, but some data are emerging. McDonagh[30] reviewed the available epidemiologic literature and described studies with different methodologies on different populations revealing a prevalence range from 1.4%–6.8%. In the North Glascow MONICA (monitoring cardiovascular disease) population study,[31] 71% of these asymptomatic patients had evidence of ischemic heart disease. Hypertension was predictive in the presence of heart disease but was not an independent predictor.[30] The prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD) also looked at asymptomatic patients, but recruitment was aimed at patients with known heart disease so this register may not be representative of the general population.[32]

The outcome of patients with asymptomatic HF is poor. The Framingham study[33] revealed that men with a decrease in fractional shortening of 4% had a relative risk of a cardiovascular event of 1.42 (95% CI, 1.12–1.81) within 4 years. In SOLVD,[31] placebo mortality was 15.8% at an average follow-up of 37.4 months.

In spite of the above data, there are no recommendations to perform routine screening of the general population or even of high-risk patients for asymptomatic HF. It is reasonable to assume that a large percentage of NYHA I patients will be identified as part of an evaluation for hypertension or heart disease. In both of these instances, β blockers are indicated. We are unaware of any ongoing trials with β blockers in NYHA class I patients. Data will not be forthcoming soon to clarify this issue. The only evidence to support treating asymptomatic patients with β blockers comes from the expectation that many of the asymptomatic patients identified will have comorbid conditions justifying their use.

NYHA Class IV. Two trials have been published that sought to evaluate the efficacy of β blockers among patients with advanced, chronic HF—COPERNICUS and BEST.[4,11] The other β blocker mortality trials had insufficient numbers of class IV patients.

COPERNICUS enrolled 2289 patients chosen because they had symptoms at rest or with minimal exertion for at least 2 months and an ejection fraction of less than 25%. All were on some combination of therapy that included ACE inhibitors, diuretics, digitalis, and spironolactone. Among those excluded were patients needing intravenous inotropes or vasodilators, those with marked congestive symptoms, and those requiring intensive care for their HF symptoms.

The COPERNICUS study was terminated early (average duration of therapy, 10.4 months) by the data safety monitoring board because of the significance of the beneficial impact of carvedilol on mortality. The risk of death at 1 year was 18.5% in the placebo group and 11.4% in the treatment group. This 35% relative reduction in the risk of death was extended to the subgroup of patients with the lowest ejection fraction. Though the magnitude of the benefit is impressive, the findings do not necessarily justify the use of carvedilol among the sickest HF patients. Significantly decompensated patients were excluded from this trial and the placebo mortality rate was lower than might be expected for a study of class IV patients. Therefore, this trial does not justify the use of carvedilol in patients who are hypotensive, significantly volume overloaded, requiring intravenous inotropic agents, or requiring care in an intensive care unit.

The BEST trial[11] is discussed in more detail in the section on racial differences in response to medication. Though the trial was designed to study the efficacy of bucindolol among patients with advanced HF, there are several factors limiting the applicability of this trial. Only 8% of the enrolled patients were NYHA class IV and the authors concede that conclusions cannot be made about the effect of bucindolol in

these patients. The overall trial was neutral with regard to the mortality impact of bucindolol. Bucindolol cannot be recommended in class IV patients.

Patients presenting with symptoms of decompensated HF may do so either on or off β blockers. A prudent approach for patients who have been previously compensated while on a stable dose of a β blocker would be to continue the β blockers unless the patient is hemodynamically unstable. In that setting, the β blocker should be discontinued but may be reconsidered when the patient is stable again. Among patients presenting with class IV symptoms and not on a β blocker, diuretics and ACE inhibitors should be started first. The initiation of β blockers can await the patient's stabilization.

The Impact of Race on the Efficacy of β Blockers

Racial differences in the epidemiology and mortality risk of HF have been described.[10,34,35] Analysis of hospitalization records reveals a pattern of black patients with HF being younger, having more hypertension, more diabetes, more renal disease, less ischemic disease, and higher readmission rates than white patients.[10,34]

Mortality patterns are less consistent. National mortality data in 1995 reveal an age-adjusted death rate due to HF among people older than 65 years as 1.08-times as high for black men as for white men and 1.06 times as high for black women as for white women.[36] In contrast, Alexander and colleagues[10] found a lower postdischarge mortality rate among blacks at 1 year and Philbin and DiSalvo[34] found a relative inhospital mortality rate for blacks of 0.832. If mortality differences exist between races it is unclear if they are due to differences in comorbidities, access to care, or other factors.

Recently, the focus has been on understanding a possible differential racial response to medications. Recent retrospective analyses of data gathered in the Vasodilator Heart Failure Trials (V-HeFT I and V-HeFT II)[37] and in SOLVD[38] illustrate this point. In V-HeFT I,[37] there was a significant decrease in mortality among black patients, but not white patients, who received hydralazine plus isosorbide dinitrate (H-I). The placebo mortality rate was similar between the races. In V-HeFT II,[37] treatment with enalapril vs. H-I demonstrated a mortality benefit only among white patients. Finally, a matched cohort analysis of data from SOLVD[38] revealed that enalapril was associated with a significant reduction in hospitalizations (44%; 95% CI, 27–57), systolic blood pressure (5.0±17.1 mm Hg), and diastolic blood pressure (3.6±10.6 mm Hg) among white patients but not among black patients. In the placebo group, the black patients had a higher mortality rate than that of the white matched controls. There was no statistically significant mortality benefit of enalapril in either group.

Racial differences may exist in β blocker responsiveness as well. Rutledge[39] compiled data from studies looking at racial responsiveness to β blockade and found that normotensive blacks and whites respond differently to β blockade, that hypertensive blacks are relatively hyporesponsive with whites when β blockers are given as monotherapy, and that β blockers with alpha properties may be equally efficacious among blacks and whites.

The BEST trial is the only β blocker mortality trial designed prospectively to examine the impact of race on the effectiveness of β blockers in HF.[19] Interpretation of this study is difficult. Overall, the trial was neutral, with annualized mortality rates in the placebo and treatment groups of 33% and 30%, respectively (p=0.13). However, the trial was terminated early because of the "totality of evidence regarding the usefulness of β blocker treatment derived from BEST and other studies." The BEST study revealed a significant improvement in mortality among nonblack patients (hazard ratio, 0.82; 95% CI, 0.70–0.96) but a trend toward harm among black patients (hazard ratio, 1.17; 95% CI, 0.89–1.53). Bucindolol has never been proved to have a mortality benefit in HF patients in any large randomized trial, so it is difficult to know which of the results from BEST are idiosyncratic and which are generalizable.

Twenty-three percent of the patients enrolled in BEST were black, CIBIS II and COPERNICUS did not report a racial breakdown, and MERIT-HF enrolled less than 5% blacks.[1,2,4] The investigators in the US Carvedilol Heart Failure Trials[37] conducted a post hoc analysis of the impact of carvedilol among black patients. They revealed a statistically significant improvement in mortality among nonblack patients (relative risk, 0.32; 95% CI, 0.17–0.62) but an insignificant difference among black patients (relative risk 0.44; 95% CI, 0.15–1.28). Composite end points of death plus hospitalization showed benefit among both groups. The limitations of this study have been described elsewhere in this paper.

It is difficult to form conclusions regarding these trends indicating racial differences. Race is difficult to define and is clearly not a pure distinction. Differences in epidemiology have been described based upon the geographic origin of the black population.[41] Racial differences may reflect the frequency of polymorphisms rather than their presence or absence in one group vs. another. There are insufficient data at this time to withhold β blockers based upon race.

Interactions With Other Medications Commonly Used in the Treatment of HF

ACE Inhibitors and Diuretics. Beta blockers clearly improve survival among patients with HF who are already receiving ACE inhibitors and diuretics. In the three pivotal β blocker trials—CIBIS II, MERIT-HF, and COPERNICUS—the vast majority of patients were taking an ACE inhibitor (89%–96%) and a diuretic (90%–99%) as part of background therapy.[1,2,4] Ironically, the beneficial effects of β blockers in the absence of these drugs has not been established in large mortality trials and must be inferred.

Aldosterone Antagonists. Beta blockers also appear to improve survival among patients with HF who are receiving spironolactone in addition to ACE inhibitors and diuretics. However, the number of patients supporting this conclusion is small. In COPERNICUS,[4] 20% of the patients were taking spironolactone without reported adverse effects during the addition of carvedilol. In RALES,[12] 10% of the patients were taking β blockers in addition to ACE inhibitors and diuretics. In this subgroup, spironolactone appeared to produce greater benefit than in patients who were not receiving β blockers. Another aldersterone antagonist, eplerenone, was tested in postinfarction patients with HF in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[42] In EPHESUS, 75% of patients were on β blockers. Overall mortality was reduced from 16.7% to 14.4% over 16 months with the addition of eplerenone. A subgroup analysis of patients on both angiotensin blockade and β blockade revealed a reduction in mortality of approximately 25%, which is greater than that of the overall trial. These data imply that adding aldersterone blockade to β blockade is beneficial.

Angiotensin Receptor Blockers. ARBs appear to increase mortality among patients with HF who are also receiving β blockers and ACE inhibitors. In Val-HeFT,[11] the largest mortality trial of an ARB in HF reported to date, valsartan increased the risk of mortality by more than 40% compared with placebo in patients receiving β blockers and ACE inhibitors. Whether ARBs interact negatively with β blockers, ACE inhibitors, or only the combination of the two, remains uncertain. In the 140 patient subgroup in Val-HeFT receiving only a β blocker without an ACE inhibitor, valsartan had a statistically uncertain effect on mortality.

The Evaluation of Losartan in the Elderly (ELITE-II) study[43] also suggested a potential negative interaction between β blockers and ARBs in patients with HF. Although there was no placebo arm in ELITE II, therapy with the ARB losartan increased mortality compared to therapy with the ACE inhibitor captopril among the 20% of patients who were receiving β blockers.

Despite these data, at least one other trial of ARBs in HF patients who may also be receiving β blockers has not reported a negative interaction. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, patients initially randomized to an ACE inhibitor, ARB, or combination of ACE inhibitor and ARB, were later further randomized to metoprolol or placebo without reported negative interaction between β blocker and ARB therapy.[44] Additional data may also be available describing the impact of candesartan and β blockers when results from the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) study are released. Therefore, conclusions about a negative impact of β blockers in patients also receiving ARBs should be tentative and subject to review of additional data when they are available.

Beta blockers should be administered in combination with ACE inhibitors and diuretics to patients with HF. Pending the results of the EPHESUS trial, β blockers can also be administered to patients receiving aldosterone antagonists. The currently available data do not support the addition of ARB therapy to patients with HF who are receiving ACE inhibitors and β blockers.

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