Implications of Heart Failure Drug Trials: COMET, CHARM, EPHESUS

Brian Hiestand, MD, FACEP,* William T. Abraham, MD, FACP, FACC, FAHA†

*Department of Emergency Medicine, †Division of Cardiovascular Medicine, Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH

Activation of the renin-angiotensin-aldosterone and adrenergic nervous systems plays a major role in the progression of heart failure, and inhibitors and antagonists of these neurohormonal systems improve outcomes. β-Blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists have been shown to improve parameters such as ventricular remodeling, ejection fraction, and renal function and to reduce rates of morbidity and mortality. This article reviews 3 recent clinical trials that have added to our knowledge of the use of these agents. Two of the studies—EPHESUS and COMET—demonstrated significant reduction in all-cause mortality, whereas the third—CHARM—showed a marginal reduction. These trials established that it is feasible to design and execute heart failure studies of sufficient scale to assess improvement in rates of mortality and morbidity.

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Heart failure continues to increase in incidence and prevalence worldwide. It remains a diagnosis with substantial associated morbidity and mortality. The underlying pathophysiology of heart failure involves a dynamic among dysfunctional myocardium, hemodynamic alterations, and the activation of a variety of neurohormonal systems. In this context, activation of the renin-angiotensin-aldosterone and adrenergic nervous systems plays a major role in heart failure disease progression, and inhibitors and antagonists of

these systems improve outcomes. For example, treating heart failure patients with agents such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone antagonists will improve physiologic parameters such as ventricular remodeling, ejection fraction, and renal function. Moreover, these agents have been shown to improve outcomes by reducing rates of morbidity and mortality. Recent randomized, controlled trials add to our fund of knowledge regarding the use of these agents as well as other neurohormonal antagonists (eg, angiotensin receptor blockers), in the treatment of heart failure. In this article, we review 3 recent pharmacologic trials that address these approaches to the management of heart failure. These studies—the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), the Carvedilol or Metoprolol European Trial (COMET), and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program—were all designed to enroll significant numbers of subjects to detect clinically significant changes in mortality and measures of morbidity, not just changes in physiologic parameters.

RALES studied a chronic advanced heart failure population whereas EPHESUS enrolled patients with impaired left ventricular systolic function immediately after myocardial infarction, a heterogeneous group to say the least.

EPHESUS: Aldosterone Blockade in Myocardial Infarction–Related Heart Failure

EPHESUS[1] evaluated the mortality benefit of selective aldosterone blockade in patients experiencing left ventricular systolic dysfunction following acute myocardial infarction. Eplerenone is a specific aldosterone antagonist that lacks the glucocorticoid, androgen, and progesterone receptor activity of spironolactone.[2] EPHESUS extended the work of the Randomized Aldactone Evaluation Study (RALES), wherein investigators demonstrated a mortality and rehospitalization benefit in patients randomized to spironolactone therapy added to standard management (loop diuretic plus ACE inhibition).[3] However, RALES studied a chronic advanced heart failure population whereas EPHESUS enrolled patients with impaired left ventricular systolic function within a short time following acute myocardial infarction, a heterogeneous group to say the least.

To be included in EPHESUS, subjects had to demonstrate signs consistent with heart failure (pulmonary congestion on chest radiograph, pulmonary congestion as demonstrated by rales on physical examination, or an S_3 gallop) within 3 to 14 days after myocardial infarction. The myocardial infarction criterion could be satisfied by either electrocardiogram or biomarker evidence. Left ventricular ejection fraction (LVEF) $\leq$ 40% was required for inclusion; ventricular angiography, echocardiography, or radionuclide angiography could be used to document impaired ventricular contractility after the index myocardial infarction. Subjects with diabetes mellitus did not have to demonstrate symptoms of heart failure, as the odds of mortality in diabetics with asymptomatic left ventricular dysfunction after myocardial infarction had been shown to be similar to that of nondiabetic patients with symptomatic left ventricular dysfunction.[4] Subjects already on potassium-sparing diuretics, those with serum creatinine $\geq$ 2.5 mg/dL (220 μmol/L), or those with a serum potassium $\geq$ 5.0 mmol/L were excluded. Other standard therapies for myocardial infarction and heart failure were allowed. Patients randomized to the eplerenone arm were started on 25 mg/d. At 4 weeks, the dose was increased to 50 mg/d. A stepwise planned dose reduction was available in case of hyperkalemia.

Study Design

EPHESUS was a multinational double-blind, randomized, placebo-controlled study. Two "co-primary" endpoints were identified: time to death from any cause and a combined endpoint of either time to cardiovascular mortality or time to cardiovascular morbidity requiring a hospitalization after randomization. Cardiovascular endpoints were broadly defined as relating to heart failure, arrhythmia, stroke, or acute coronary ischemia. Interestingly, the published methodology outline[5] for EPHESUS describes the collection and assessment of quality-of-life measures, as does an additional article from the coauthors[6]; as of the date of this review, these data on quality-of-life measures have not been published.

All data were analyzed on the intention-to-treat principle, provided that the subject received at least 1 dose of study medication or placebo. The investigators designed the study duration based on a specific event rate, not a specified length of time. By not terminating the study until 1012 deaths occurred, the investigators allowed for the preservation of the power of their analysis with the prespecified sample size, even in the setting of decreased mortality in both arms due

to improved "standard" medical care when compared with the earlier trials that formed the basis for their sample size calculations.

Results

The investigators reached their enrollment goals (3319 subjects in the eplerenone arm and 3313 in the placebo arm). The groups were well matched in baseline characteristics, including medical history and medication use. Eplerenone significantly decreased both all-cause mortality and the combined endpoint of cardiovascular mortality or hospitalization. The relative risk reduction for all-cause mortality was 15%. The secondary endpoint of cardiovascular mortality also favored eplerenone, with 407 subjects in the eplerenone group dying from a cardiovascular cause versus 483 subjects in the placebo group. All subtypes of cardiovascular death demonstrated a reduced relative hazard ratio with eplerenone; however, sudden cardiac death was the only subtype in which this reduction was statistically significant. Both the risk of hospitalization for heart failure and the number of hospitalizations for heart failure were significantly reduced in the eplerenone group as well.

From a safety endpoint, the eplerenone group experienced a statistically significant but clinically irrelevant increase in serum creatinine compared with the placebo group (0.02 mg/dL vs 0.06 mg/dL). Of more concern was the rate of serious hyperkalemia (serum potassium $\geq$ 6.0 mmol/L): 5.2% in the eplerenone group compared with 3.9% in the placebo group. In patients with a creatinine clearance $<$ 50 mL/min, the incidence of hyperkalemia was nearly doubled at 10.1% in the eplerenone group compared with 5.9% in the placebo group. Although hospitalizations for hyperkalemia were increased in the eplerenone group (12 vs 3 subjects), only 1 death was attributed to hyperkalemia, and this was in a subject in the placebo group. It should be noted that this is substantially higher than the incidence of hyperkalemia reported by the RALES study of 2% in the spironolactone group.[3]

In summary, EPHESUS was a well-designed study that demonstrated significant benefit in both all-cause and cardiovascular-specific mortality when eplerenone, for patients with left ventricular dysfunction following acute MI, was added to standard therapy. There is an increased risk of hyperkalemia with eplerenone use.

EPHESUS does not address whether eplerenone is a superior agent to spironolactone for aldosterone blockade. Given the specificity of eplerenone for mineralacorticoid receptors, there may be increased tolerability and therefore increased compliance when compared with spironolactone. However, the comparative efficacy and tolerability of nonspecific versus specific aldosterone blockers have not been addressed. Likewise, subjects in EPHESUS had a very high rate of usage of ACE inhibitors/angiotensin receptor blockers (87%), β-blockers (75%), and diuretics (60%), raising the bar for eplerenone to add incremental benefit. It is not known to what extent eplerenone would demonstrate a benefit in patients who are not currently on optimal standard therapy.

COMET: Broad-Spectrum Versus Receptor-Specific Adrenergic Blockade

COMET[7] sought to compare carvedilol, a broad-spectrum adrenergic antagonist with activity at the α_1-, β_1-, and β_2-receptors, against metoprolol tartrate, which has high specificity for the β_1-receptor. Before COMET, multiple studies had demonstrated a mortality benefit when β-blockade was compared with placebo in patients with symptomatic heart failure.[8-10] COMET provided a large-scale randomized, double-blind trial to evaluate comparative mortality benefits between the 2 agents.

Subjects included in COMET had to have symptomatic heart failure (New York Heart Association [NYHA] II-IV) with an LVEF $\leq$ 35% documented within 3 months prior to enrollment. Subjects were required to be on diuretics and ACE inhibitors (if tolerated), although recent changes in medication regimen would preclude enrollment in the trial. Likewise, current use of β- or α-blockers, amiodarone, class I antiarrhythmic drugs, or calcium channel blockers excluded subject enrollment. Other exclusion criteria were recent myocardial infarction or unstable angina, recent ventricular arrhythmia, significant valvular disease, and contraindication to β-blockade (eg, bradycardia, conduction block, hypotension, history of asthma/chronic obstructive pulmonary disease).

Subjects were randomized to an initial dose of 3.125 mg carvedilol twice per day or 5 mg metoprolol tartrate twice per day. Doses were increased every 2 weeks to a target dose of 25 mg carvedilol twice per day or 50 mg metoprolol tartrate twice per day, or until the subject could not tolerate a further dose increase.

Study Design

As mentioned previously, COMET was a multicenter double-blind, randomized trial. The initial primary endpoint was all-cause mortality. However, the decision was made by the investigators, while the trial was still enrolling subjects, to add an additional primary composite endpoint of all-cause mortality and all-cause

hospitalization. The investigators stated that they had no knowledge of interim results at the time of the study modification, and that this additional primary endpoint was added to ensure that COMET and the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[10] had identical primary endpoints.[11] Several secondary endpoints assessed cardiovascular death, rate of hospitalizations, worsening of heart failure, and the combined endpoint of cardiovascular death, nonfatal myocardial infarction, heart transplantation, or worsening of heart failure.

All subjects who received at least 1 dose of study medication were analyzed on the intention-to-treat principle. COMET was designed as an event-driven survival study, such that 1020 fatal events were required to provide 80% power to detect a 20% risk reduction in the primary endpoint.

Results

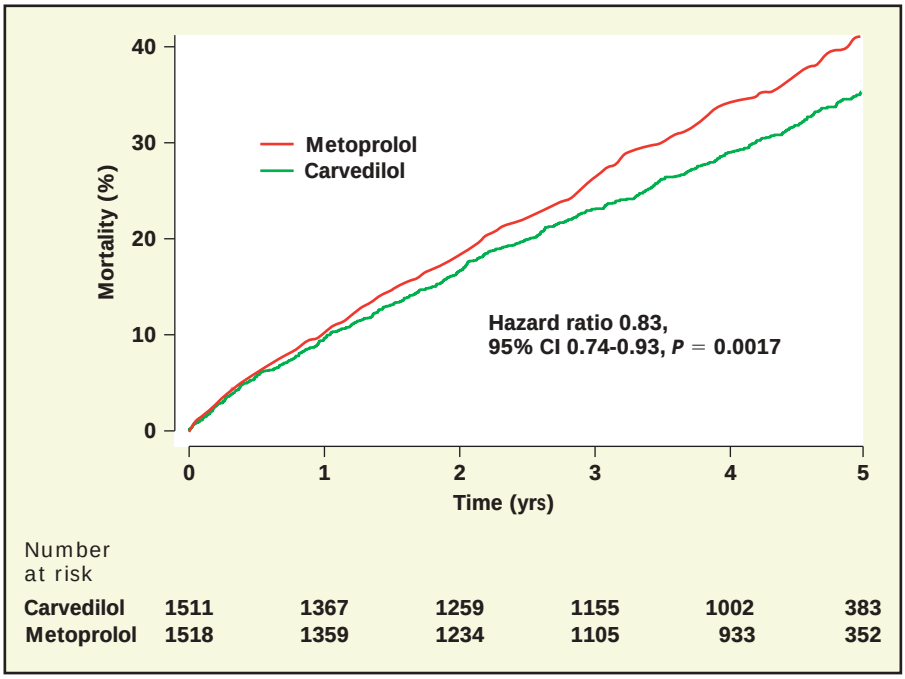
Between December 1, 1996, and January 15, 1999, 3029 subjects were enrolled. Follow-up was terminated on November 15, 2002, because of projections that the required event rate of 1020 deaths would be met by that time. In actuality, 1112 deaths occurred in the study. Subjects in the 2 groups were generally well matched in baseline characteristics. Carvedilol provided a significant decrease in the risk of both all-cause mortality and cardiovascular death. Compared with metoprolol tartrate, carvedilol produced a relative risk reduction in all-cause mortality of 17% (Figure 1). However, for the composite primary endpoint of all-cause mortality and all-cause hospitalization, the slight benefit seen in the carvedilol group was not statistically significant.

There was a statistically significantly greater drop in mean resting heart rate in the carvedilol group than in the metoprolol group. Likewise, the decrease in mean systolic blood pressure was greater in the carvedilol group than in the metoprolol group. These differences in physiologic parameters were relatively small, so that the clinical significance of these observations is unclear. However, as Dargie notes in his accompanying editorial,[12] this does raise the question as to whether the metoprolol target dose was adequate to compare against carvedilol.

Permanent discontinuation of the study drug occurred equally in both groups (32%). Bradycardia and serious hypotension were also similarly distributed between groups. In the carvedilol group, 75% of subjects maintained the target dose of 25 mg twice per day, with a mean daily maintenance dose of 41.8 mg per day. In the metoprolol group, 78% maintained the target dose of 50 mg twice per day, with a mean daily maintenance dose of 85 mg per day. The incidence of adverse events slightly favored the carvedilol group.

In summary, COMET demonstrated a survival advantage with carvedilol over metoprolol tartrate. No benefit in morbidity was noted, using the proxy measure of rehospitalization. Questions persist over whether the dosage of metoprolol tartrate was adequate. However, given that the percentage of subjects tolerating the target dose was quite similar and that the difference in physiologic parameters was small, it is likely that the target dose of metoprolol tartrate is of less importance than the formulation itself. These findings suggest an advantage of comprehensive adrenergic blockade over selective adrenergic receptor blockade in the treatment of heart failure.

Figure 1. *Kaplan-Meier survival analysis from the Carvedilol or Metoprolol European Trial (COMET). Reproduced with permission from Poole-Wilson et al.*[7]



CHARM: Candesartan Assessed in a Variety of Roles

The CHARM program evaluated candesartan, an angiotensin II receptor

blocker, in a variety of heart failure populations. CHARM was described in 4 papers: CHARM-Added[13] (candesartan or placebo plus ACE inhibitor), CHARM-Alternative[14] (candesartan or placebo in patients intolerant of an ACE inhibitor), CHARM-Preserved[15] (candesartan or placebo in patients with preserved systolic function), and CHARM-Overall,[16] which described the mortality effects on the summary population of the 3 substudies. Each substudy was powered to evaluate a composite primary outcome of cardiovascular death or hospital admission for heart failure, whereas CHARM-Overall evaluated the effect of candesartan use on all-cause mortality in a pooled analysis of all study arms. In each substudy, candesartan was started at either 4 mg or 8 mg per day and increased to a target dose of 32 mg daily as tolerated. All subjects had to have symptomatic (NYHA II-IV) heart failure at the time of enrollment. Patients with known renal insufficiency, hyperkalemia, critical aortic or mitral stenosis, recent myocardial infarction or open-heart surgery were excluded, as were patients already on angiotensin receptor blockers. A committee blinded to treatment assignment adjudicated cause of death, first myocardial infarction, and first hospital admission for heart failure.

CHARM-Preserved

CHARM-Preserved enrolled subjects with congestive heart failure and an LVEF > 40%. Initially, ACE inhibitors were disallowed in both the candesartan and placebo arms. However, after the publication of the HOPE (Heart Outcomes Prevention Evaluation) trial[17] demonstrated a reduction in cardiovascular death, myocardial infarction, and stroke in high-risk patients without heart failure with ramipril, ACE inhibitors were allowed as optional agents in both arms. Relative risk reduction and hazard ratios were adjusted for imbalances in prespecified baseline characteristics.

In CHARM-Preserved, 3023 patients were randomized, with 1514 assigned to the candesartan group and 1509 to placebo. Several comorbid illnesses were slightly more prevalent in the candesartan group, including diabetes, previous myocardial infarction, and continued smoking. Candesartan did not demonstrate a significant improvement in the unadjusted composite primary outcome of cardiovascular death or hospitalization for heart failure. Once the results were adjusted for imbalances between treatment arms, a marginally significant reduction in the primary outcome was seen. Cardiovascular and all-cause mortality were unaffected by candesartan. This indicates the reduction in the composite endpoint was primarily driven by a significant reduction in the number of patients having at least 1 hospital admission for heart failure in the candesartan group. In addition, the overall number of hospital admissions for heart failure was also decreased by candesartan use.

CHARM-Added

CHARM-Added evaluated the effects of adding candesartan to subjects already on ACE inhibitors. In contrast to CHARM-Preserved, the LVEF had to be < 40%. CHARM-Added had the additional requirement that patients with NYHA class II heart failure had been admitted to the hospital for a cardiovascular cause within the 6 months prior to enrollment. As in CHARM-Preserved, results were adjusted for imbalances between treatment arms.

In this substudy, 2548 subjects were randomized: 1276 to candesartan and 1272 to placebo. All subjects in the candesartan group were taking an ACE inhibitor, as were 1270 (99.8%) of placebo subjects. Enalapril, lisinopril, captopril, and ramipril were the most commonly used ACE inhibitors. Both unadjusted and adjusted analyses of the composite primary outcome of cardiovascular death or hospitalization for heart failure demonstrated significant improvement in the candesartan group. This improvement was noted across all predefined subgroups. Considered individually, cardiovascular death, the incidence of hospitalization for heart failure, the number of hospitalizations for heart failure, and the proportion of subjects with multiple admissions for heart failure were all improved in the candesartan group. All-cause mortality was not improved by candesartan treatment.

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CHARM-Alternative

The CHARM-Alternative trial required subjects to have had an ACE inhibitor discontinued by their physician for a documented reason at some point prior to enrollment. Subjects had to have symptomatic heart failure (NYHA II-IV) and an LVEF ≤ 40%. The primary endpoint was a composite of cardiovascular death or hospital admission for heart failure. Serious renal impairment and hyperkalemia precluded enrollment. As in the other study arms, hazard

Table 1
Hazard Ratios for the Composite Primary Outcomes of Each of the CHARM Substudies*

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
CHARM-Alternative		
Cardiovascular death or heart failure hospitalization	0.77 (0.67–0.89)	0.70 (0.60–0.81)
Cardiovascular death	0.85 (0.71–1.02)	0.80 (0.66–0.96)
Heart failure hospitalization	0.68 (0.57–0.81)	0.61 (0.51–0.73)
CHARM-Added		
Cardiovascular death or heart failure hospitalization	0.85 (0.75–0.96)	0.85 (0.75–0.96)
Cardiovascular death	0.84 (0.72–0.98)	0.83 (0.71–0.97)
Heart failure hospitalization	0.83 (0.71–0.96)	0.83 (0.71–0.97)
CHARM-Preserved		
Cardiovascular death or heart failure hospitalization	0.89 (0.77–1.03)	0.86 (0.74–1.00)
Cardiovascular death	0.99 (0.80–1.22)	0.95 (0.76–1.18)
Heart failure hospitalization	0.85 (0.72–1.01)	0.84 (0.70–1.00)

*The individual components of the composite outcome are also listed.

ratios and relative risk reductions were adjusted for imbalances in prespecified baseline characteristics between study arms.

Of 2028 subjects, 1013 were randomized to candesartan and 1015 to placebo. The most common reasons for ACE inhibitor discontinuation were cough (72%), symptomatic hypotension (13%), and renal dysfunction (12%). For the composite primary endpoint of cardiovascular death or heart failure hospitalization, candesartan provided a significant benefit in both the unadjusted and covariate-adjusted analyses. The hazard reduction in CHARM-Alternative was greater than in the other substudies (Table 1). The reduction in the cardiovascular mortality component was not significant in the unadjusted analysis but did reach significance when adjusted for baseline differences between groups. Likewise, the improvement in all-cause mortality in the candesartan group did not reach statistical significance until the hazard ratio was adjusted. Candesartan treatment significantly decreased the incidence and number of hospitalizations for heart failure.

Angioedema occurred in 3 subjects in the candesartan group, all of whom had angioedema or anaphylaxis documented as the reason for ACE intolerance. Candesartan was restarted in 2 of the 3 subjects without further angioedema.

CHARM-Overall

CHARM-Overall provided a pooled analysis of the 3 component substudies with the primary endpoint of all-cause mortality. Covariate analysis was used to adjust for imbalances in prespecified baseline characteristics between groups. All-cause mortality was not significantly reduced in the unadjusted analysis; however, after adjustment for between-group differences, candesartan did provide a 10% relative risk reduction in all-cause mortality. This was primarily driven by a reduction in cardiovascular death, especially in the groups with depressed LVEF. Table 2 summarizes the outcome measures for CHARM-Overall.

Adverse Events

Table 3 summarizes the rates of drug discontinuation, impaired renal function, and hyperkalemia across the 3 substudies. It should be noted that although monitoring of serum creatinine and potassium was recommended at all sites during active titration of study drug dosage, only the North American sites had mandated monitoring of laboratory parameters.

In summary, the CHARM program was a methodologically rigorous, well-designed, complementary cohort

Table 2
Hazard Ratios for Mortality Outcomes in CHARM-Overall

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
All-cause mortality	0.91 (0.83–1.00)	0.90 (0.82–0.99)
Cardiovascular mortality	0.88 (0.79–0.97)	0.87 (0.78–0.96)
Cardiovascular mortality or heart failure hospitalization	0.84 (0.77–0.91)	0.82 (0.75–0.88)

Table 3
Rates of Adverse Events in the CHARM Substudies*

	Doubling of Serum Creatinine (%)	Hyperkalemia (%)	Rate of Discontinuation Due to Adverse Event (%)
CHARM-Alternative			
Candesartan	5.5†	3	24
Placebo	1.6	1	22
CHARM-Added			
Candesartan	7	5	24‡
Placebo	6	1	18
CHARM-Preserved			
Candesartan	6§	2	18‖
Placebo	3	1	14

*All significant differences are within-study comparison only.
†$P = .015$
‡$P = .0003$
§$P = .007$
‖$P = .001$

of studies. Candesartan was shown to modestly improve survival and decrease hospitalization in a variety of heart failure types, with its strongest effects demonstrated in subjects who could not tolerate ACE inhibition and therefore had no protection against the deleterious effects of angiotensin II. However, candesartan also was beneficial in patients with left ventricular dysfunction already on an ACE inhibitor, indicating that such patients would likely benefit from further inhibition of the renin-angiotensin-aldosterone axis. Further clarification of the combined effects of ACE inhibition, candesartan use, and spironolactone use may have been interesting, but as only 17% of the CHARM-Added population was on spironolactone, the subgroup sample size would likely have proven too small for meaningful analysis.

The authors are to be commended for including CHARM-Preserved, as there exists a dearth of literature regarding the increasingly prevalent condition of heart failure with preserved systolic function. Although the impact of candesartan on the composite primary outcome of cardiovascular death or hospitalization for heart failure was small, there was a much greater impact on the endpoint of heart failure hospitalization. A formal cost analysis weighing the marginal increase of candesartan management versus standard therapy against hospitalization costs would be both appropriate and welcome.

Summary

We have examined 3 large, well-executed studies that have provided evidence for benefit in heart failure populations. EPHESUS and COMET both demonstrated substantial significant reductions in all-cause mortality. CHARM-Overall demonstrated a marginal reduction in all-cause

Main Points

- Recent studies of agents affecting the renin-angiotensin-aldosterone and adrenergic nervous systems have recruited large populations of heart failure patients, in order to measure these agents' effects on overall mortality and morbidity, not only changes in physiological parameters.
- The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) was a well-designed study that demonstrated significant benefit in both all-cause and cardiovascular-specific mortality when eplerenone was added to standard therapy.
- The Carvedilol or Metoprolol European Trial (COMET) demonstrated a survival advantage with carvedilol over metoprolol tartrate. No benefit in morbidity was noted, using the proxy measure of rehospitalization.
- The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program was a methodologically rigorous, well-designed, complementary cohort of studies. Candesartan was shown to modestly improve survival and decrease hospitalization in a variety of heart failure types, with its strongest effects demonstrated in subjects who could not tolerate angiotensin-converting enzyme inhibition and therefore had no protection against the deleterious effects of angiotensin II.

mortality; a later planned substudy demonstrated a significant reduction in all-cause mortality in a pooled analysis of the low ejection fraction substudies.[18] Morbidity was generally assessed using the proxy measure of hospitalization, although we may yet see quality-of-life assessment data published in the future.

These trials have established that it is feasible to design and execute heart failure studies of sufficient scale to assess improvement in mortality and morbidity outcomes. As multiple neuroendocrine components contribute to the pathophysiology of heart failure, particularly the renin-angiotensin-aldosterone and adrenergic nervous systems, it is becoming clearer that multiple agents are required for optimal patient treatment. For a new agent to join the ranks of polypharmacy, it will have to demonstrate at least equivalence, if not superiority, in truly relevant outcome measures. This requirement seems to have been met by the aldosterone antagonist eplerenone, adrenergic receptor blocking agent carvedilol, and angiotensin receptor blocker candesartan, as shown in EPHESUS, COMET, and CHARM, respectively. ■

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