# Mortality and Morbidity Reduction With Candesartan in Patients With Chronic Heart Failure and Left Ventricular Systolic Dysfunction

## Results of the CHARM Low–Left Ventricular Ejection Fraction Trials

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***Background***—Patients with symptomatic chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF) have a high risk of death and hospitalization for CHF deterioration despite therapies with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and even an aldosterone antagonist. To determine whether the angiotensin-receptor blocker (ARB) candesartan decreases cardiovascular mortality, morbidity, and all-cause mortality in patients with CHF and depressed LVEF, a prespecified analysis of the combined Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) low LVEF trials was performed. CHARM is a randomized, double-blind, placebo-controlled, multicenter, international trial program.

***Methods and Results***—New York Heart Association (NYHA) class II through IV CHF patients with an LVEF of ≤40% were randomized to candesartan or placebo in 2 complementary parallel trials (CHARM-Alternative, for patients who cannot tolerate ACE inhibitors, and CHARM-Added, for patients who were receiving ACE inhibitors). Mortality and morbidity were determined in 4576 low LVEF patients (2289 candesartan and 2287 placebo), titrated as tolerated to a target dose of 32 mg once daily, and observed for 2 to 4 years (median, 40 months). The primary outcome (time to first event by intention to treat) was cardiovascular death or CHF hospitalization for each trial, with all-cause mortality a secondary end point in the pooled analysis of the low LVEF trials. Of the patients in the candesartan group, 817 (35.7%) experienced cardiovascular death or a CHF hospitalization as compared with 944 (41.3%) in the placebo group (HR 0.82; 95% CI 0.74 to 0.90; $P<0.001$) with reduced risk for both cardiovascular deaths (521 [22.8%] versus 599 [26.2%]; HR 0.84 [95% CI 0.75 to 0.95]; $P=0.005$) and CHF hospitalizations (516 [22.5%] versus 642 [28.1%]; HR 0.76 [95% CI 0.68 to 0.85]; $P<0.001$). It is important to note that all-cause mortality also was significantly reduced by candesartan (642 [28.0%] versus 708 [31.0%]; HR 0.88 [95% CI 0.79 to 0.98]; $P=0.018$). No significant heterogeneity for the beneficial effects of candesartan was found across prespecified and subsequently identified subgroups including treatment with ACE inhibitors, β-blockers, an aldosterone antagonist, or their combinations. The study drug was discontinued because of adverse effects by 23.1% of patients in the candesartan group and 18.8% in the placebo group; the reasons included increased creatinine (7.1% versus 3.5%), hypotension (4.2% versus 2.1%), and hyperkalemia (2.8% versus 0.5%), respectively (all $P<0.001$).

***Conclusion***—Candesartan significantly reduces all-cause mortality, cardiovascular death, and heart failure hospitalizations in patients with CHF and LVEF ≤40% when added to standard therapies including ACE inhibitors, β-blockers, and an aldosterone antagonist. Routine monitoring of blood pressure, serum creatinine, and serum potassium is warranted. **(*Circulation*. 2004;110:2618-2626.)**

**Key Words:** heart failure ■ ventricles ■ angiotensin-converting enzyme inhibitors ■ adrenergic beta-antagonists ■ aldosterone antagonists

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**The online-only Data Supplement, which contains information about the CHARM Executive Committee, CHARM Data Safety and Monitoring Committee, CHARM Endpoint Committee, CHARM Steering Committee, and investigators participating in the CHARM trials, is available with this article at http://www.circulationaha.org.**

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Clinical trials have shown the lifesaving and symptomatic benefits of angiotensin-converting enzyme (ACE) inhibitors,[1–3] β-blockers,[4–7] and in selected patients, an aldosterone antagonist, for patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF).[8] These treatment strategies have been used worldwide with an accompanying reduction in age-adjusted mortality of CHF patients.[9–13] Still, the consequences of CHF are great, with its increasing prevalence and persistent high morbidity and mortality.[13–15] More patients are now at risk for CHF because of the high global prevalence of hypertension and ischemic heart disease.[14–18] Patients with CHF and left ventricular systolic dysfunction (patients with an ejection fraction that is in general ≤40%) are especially problematic, and these patients have been the focus of the vast majority of clinical trials studying interventions in CHF.[1–8,18]

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Angiotensin II type 1 receptor blockers (ARB) provide a therapy that can attenuate the deleterious effects of the renin-angiotensin-aldosterone system, including complications of hypertension,[19–21] diabetes,[22,23] and perhaps even heart failure.[19,24] In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot trial, the addition of the ARB candesartan to enalapril in CHF patients with depressed ejection fraction demonstrated favorable effects on hemodynamics, left ventricular remodeling, and neurohormonal activity, particularly when a β-blocker (metoprolol CR/XL) was used.[25] The Valsartan Heart Failure Trial (Val-HeFT) suggested that adding the ARB valsartan to conventional treatment (including ACE inhibitors in 93% of patients, β-blockers in 35%, and spironolactone in 5%) for patients with CHF and low ejection fraction (n=5010) decreased the risk of a composite co-primary outcome of death or cardiovascular morbidity by 13%.[24] However, no impact was found on total, or specifically on cardiovascular mortality in ValHeFT. Furthermore, the beneficial effect on the composite end point was attributable to a 24% reduction in first adjudicated hospitalization for heart failure. In a subset analysis of 1610 patients (32% of the trial population) who were given both ACE inhibitors and β-blockers at baseline, the addition of valsartan was unexpectedly associated with worse outcomes. Despite the weaknesses and problems associated with clinical trial subset analysis, these observations led the Val-HeFT investigators to caution clinicians about using the combination of an ACE inhibitor, a β-blocker, and valsartan in CHF patients, and heart failure treatment guidelines subsequently discouraged neurohumoral blockade with this so-called triple therapy approach.[26–30]

The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) was a program of clinical trials designed to address a broad spectrum of symptomatic CHF patients.[31–36] Three distinct yet integrated and complementary clinical trials running in parallel were randomized double-blind comparisons of candesartan to placebo.[31,33–35] Each trial in the CHARM program was independently designed to determine whether the addition of candesartan to other CHF therapies would reduce the risk of cardiovascular death or hospital admission for CHF. The first trial was patients with LVEF ≤40% already treated with ACE inhibitors (CHARM-Added, n=2548); the second was patients with LVEF ≤40% who could not tolerate ACE inhibitors (CHARM-Alternative, n=2028); and the third was patients with CHF but LVEF >40% (CHARM-Preserved, n=3025).[33,34,35] The overall CHARM program (n=7601) was a separately powered and analyzed cohort comprising the 3 CHARM clinical trials with the overarching end point of total mortality, irrespective of background therapy or baseline LVEF.[36] An additional important dimension of the CHARM program was a prespecified analysis of the combined CHARM low LVEF trials (the pooled CHARM-Added and CHARM-Alternative trials). This design feature was carefully considered and important because earlier studies with ACE inhibitors, β-blockers, aldosterone antagonists, and ARBs in CHF were conducted specifically in this problematic population.

This is, then, the first report from a unique data set and distinguishes itself from previous CHARM program reports by including only patients randomized with depressed LVEF (≤40%). This analysis also studied prespecified and some subsequently defined patient subsets to gain greater insight into the role of candesartan in the management of CHF cases. Indeed, in view of the sometimes equivocal and inconclusive data from previous ARB trials in patients with CHF and low LVEF,[24,26,37] it is timely and important to specifically focus on this population.

## Methods

### Patients and Methods

CHARM was performed at 618 sites in 26 countries. The general design of CHARM, including randomization procedures, monitoring, and follow-up, has been described elsewhere.[31,36] Clinical trial ethical review committees approved CHARM at all participating centers. Every patient provided informed consent before randomization. Adult patients (≥18 years) with symptomatic CHF (NYHA class II through IV) for at least 4 weeks were eligible for the CHARM-Alternative and CHARM-Added trials. The CHARM-Added trial required patients to take an ACE inhibitor. If investigators observed that an ACE inhibitor was not tolerated, then patients could be entered into the CHARM-Alternative trial. The ejection fraction must have been ≤40% and determined within 6 months of trial entry. Regarding patients treated with an ACE inhibitor, investigators were provided with recommended doses of various agents based on previous trial observations and asked to document that the dose of ACE inhibitor had been individually optimized and unchanged for ≥30 days before randomization. Patients in CHARM-Added who were in NYHA class II had the additional requirement of a hospitalization for a cardiac-related reason in the previous 6 months. Patients were enrolled between March 1999 and March 2001, with follow-up concluded in March 2003, when all patients had the opportunity to be observed for at least 2 years. Figure 1 summarizes the disposition of the 4576 patients who were randomized (2289 assigned to candesartan and 2287 assigned to matching placebo) into the clinical trials. Candesartan or placebo treatment group status was determined by computer-generated assignment and provided through a coordinating telephone center with the assignment code held at an independent site, as well as by the data safety monitoring committee. Two (0.1%) patients were lost to follow-up in the placebo group and 5 (0.2%) were lost in the candesartan group, with respect to vital status at the final visit. Median follow-up was 40 months. The initial dose of the study drug was either 4 or 8 mg once daily at the discretion of the study physician. Study drug dose was then doubled as tolerated every 2 weeks while aiming for a target

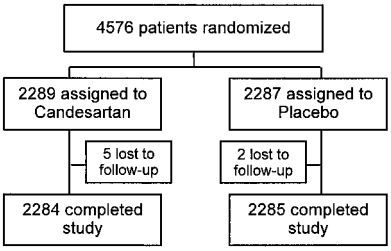


**Figure 1.** CHARM low LVEF trials analysis.

dose of 32 mg once daily. Monitoring of blood pressure, serum creatinine, and serum potassium was recommended during dose escalation. Patients were observed at 2, 4, and 6 weeks after randomization and then again at 6 months, after the maintenance dose was reached. Subsequently, patients were observed every 4 months until the end of the trial. Routine laboratory assessments were made of patients enrolled in CHARM from North America at baseline, at 6 weeks, and then yearly thereafter.

An independent data safety monitoring committee was established to oversee the safety of patients and to monitor trial progress. This team had access to all data through an independent statistical center. Predefined stopping rules for efficacy or safety were focused on mortality from the overall CHARM program. An independent blinded clinical event committee adjudicated study outcomes of cardiovascular deaths, CHF hospitalizations, and nonfatal myocardial infarctions (MIs).

The use of conventional heart failure treatments, including β-blockers, diuretics, digitalis, and spironolactone, when appropriate, was recommended. ACE inhibitors were required for patients in the CHARM-Added trial. Discontinuation of these agents and the study drug was left to the discretion of patients and physicians, with reasons for discontinuation documented and patients subsequently observed for outcomes.

Cardiovascular death or admission to the hospital for management of worsening CHF was the primary outcome for the individual CHARM trials and for the present analysis. Prespecified secondary outcomes included (1) the individual components of the composite primary end point (cardiovascular death and hospitalization for CHF); (2) cardiovascular death, admission to a hospital for CHF, or nonfatal MI; (3) cardiovascular death, admission to a hospital for CHF, nonfatal MI, or nonfatal stroke; (4) cardiovascular death, admission to a hospital for CHF, nonfatal MI, nonfatal stroke, or coronary revascularization; and (5) death (any cause) or admission to a hospital for CHF. More important, all-cause mortality also was a prespecified secondary outcome for the analysis of the pooled low LVEF trials.

All deaths were classified as cardiovascular unless an unequivocal noncardiovascular cause was established. A CHF hospital admission was defined as admission to the hospital necessitated by heart failure and primarily for its treatment, or when heart failure became a major component of the patient's hospital admission. A patient admitted to a hospital for CHF decompensation had to have documented signs and symptoms of worsening heart failure requiring treatment with at least intravenous diuretics, necessitating at minimum an overnight stay. Evidence of worsening heart failure had to include 1 commonly associated heart failure finding such as increasing dyspnea on exertion, orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, increasing fatigue or decreasing exercise tolerance, worsening renal function, increased jugular-venous pressure, and radiological signs of CHF. Criteria for the diagnosis of a MI included presence of standard myocardial necrosis biomarkers and typical electrocardiographic changes in a clinical setting compatible with MI.

## Statistical Methods

The CHARM-Added and CHARM-Alternative trial data were pooled with outcome analysis for the present study based on the intention-to-treat principle in all randomized patients. All major outcomes were analyzed by time to first event. For the primary analysis a log-rank test stratified by trial was employed to compare the time-to-event distributions. The present investigators estimated hazard ratios with 95% CIs using a Cox regression with treatment as a factor. A Cox regression also was used to analyze the time-to-event outcomes for the first 1 year and first 2 years of treatment, with data censored at these respective time points. The number of hospital admissions was compared with Wilcoxon's rank sum test. The present writing group used 2-sided probability values and considered $P<0.05$ to be statistically significant for treatment comparisons and $P<0.10$ for tests of interaction.

# Results

## Patient Characteristics and Treatment

Baseline characteristics of the study participants, including details of their background medical treatment, are listed in Table 1. Overall, about two thirds of patients were NYHA functional class III. The mean age of the patients was 65 years and the mean LVEF was 29%. Previous MI had been noted in ≤60% of the patients. Overall, 55.8% of candesartan-assigned and 55.6% of placebo-assigned patients were taking an ACE inhibitor, with the remainder unable to tolerate this drug class. Enalapril, lisinopril, captopril, and ramipril were the most commonly used ACE inhibitors, accounting for 74% of the ACE inhibitor group. Of the patients taking an ACE inhibitor, 96% in each group were receiving the optimum individualized doses of the agent at randomization. The mean daily ACE inhibitor dose at randomization for the candesartan group was 16.8 mg of enalapril, 17.7 mg of lisinopril, 82.7 of mg captopril, and 7.3 mg of ramipril without significant differences for the control group. In addition, 54.8% of candesartan patients and 55.3% of placebo patients were taking a β-blocker, and 20.6% of candesartan and 19.6% of placebo patients were being treated with spironolactone. The most commonly used β-blockers were metoprolol (47% of those taking a β-blocker), carvedilol (31%), atenolol (9%), and bisoprolol (6%). Doses of the β-blockers used were similar in the placebo and candesartan groups. By the end of the trials, 45.8% of surviving patients in the candesartan group and 48.7% in the placebo group were taking ACE inhibitors; 64.0% and 67.2%, respectively, taking β-blockers; and 22.2% and 26.8%, respectively, taking spironolactone. The initial dose of the study drug was 4 mg in 84% of patients and 8 mg in 16%. The mean daily doses for patients taking the study drug at 6 months were 24 mg in the candesartan group and 27 mg in the placebo group, and subsequent mean doses were similar to these thereafter. Reaching the target dose of 32 mg once daily were 60% of the candesartan group and 73% of the placebo group on study drug.

## Outcomes

Cardiovascular death or hospital admission for CHF management was observed in 817 (35.7%) patients in the candesartan group and 944 (41.3%) in the placebo group (HR 0.82, 95% CI 0.74 to 0.90, $P<0.001$; Table 2 and Figure 2). These figures translate into an average annual event rate of 14.0% in the candesartan group and 17.3% in the placebo group. The number of deaths from any cause in the candesartan group was 642 (28.0%) as compared with 708 (31.0%) in the placebo group (HR 0.88, 95% CI 0.79 to 0.98, $P=0.018$;

**TABLE 1. Baseline Patient Characteristics (n=4576)**

| | Candesartan (n=2289) | Placebo (n=2287) |
|---|---|---|
| Patient characteristics | | |
| Age, mean (SD), y | 65.1 (10.9) | 65.3 (11.1) |
| ≥75 y, n (%) | 445 (19.4) | 484 (21.2) |
| Men, n (%) | 1697 (74.1) | 1691 (73.9) |
| Women, n (%) | 592 (25.9) | 596 (26.1) |
| Ethnicity, n (%) | | |
| White | 2038 (89.0) | 2065 (90.3) |
| Black | 93 (4.1) | 107 (4.7) |
| Other | 158 (6.9) | 115 (5.0) |
| Heart disease risk factors | | |
| NYHA class, n (%) | | |
| II | 799 (34.9) | 781 (34.1) |
| III | 1421 (62.1) | 1424 (62.3) |
| IV | 69 (3.0) | 82 (3.6) |
| LVEF, mean (SD) | 0.29 (0.08) | 0.29 (0.07) |
| Heart rate, mean (SD), bpm | 74.1 (13.7) | 73.7 (12.9) |
| Blood pressure, mean (SD), mm Hg | | |
| Systolic | 127.0 (19.0) | 127.7 (18.7) |
| Diastolic | 75.7 (10.9) | 76.0 (10.6) |
| BMI, mean (SD), kg/m$^2$ | 27.7 (5.2) | 27.6 (5.0) |
| Medical history, n (%) | | |
| CHF hospitalization | 1687 (73.7) | 1663 (72.7) |
| MI | 1343 (58.7) | 1321 (57.8) |
| Current angina | 1259 (55.0) | 1276 (55.8) |
| Stroke | 198 (8.4) | 202 (8.8) |
| Diabetes mellitus | 654 (28.6) | 652 (28.5) |
| Hypertension | 1109 (48.4) | 1134 (49.6) |
| Atrial fibrillation | 600 (26.2) | 602 (26.3) |
| Pacemaker | 209 (9.1) | 207 (9.1) |
| Implantable cardioverter defibrillator | 87 (3.8) | 81 (3.5) |
| Current smoker | 343 (15.0) | 362 (15.8) |
| Percutaneous intervention | 340 (14.9) | 362 (15.8) |
| Coronary artery bypass grafting | 595 (26.0) | 542 (23.7) |
| Previous cancer | 140 (6.1) | 147 (6.4) |
| Medical therapies, n (%) | | |
| ACE inhibitor | 1277 (55.8) | 1272 (55.6) |
| β-Blocker | 1255 (54.8) | 1264 (55.3) |
| Diuretic | 2012 (87.9) | 2015 (88.1) |
| Spironolactone | 472 (20.6) | 448 (19.6) |
| Digoxin/digitalis | 1190 (52.0) | 1222 (53.4) |
| Calcium antagonists | 301 (13.1) | 297 (13.0) |
| Other vasodilators | 871 (38.1) | 933 (40.8) |
| Oral anticoagulants | 804 (35.1) | 786 (34.4) |
| Antiarrhythmic agents | 290 (12.7) | 303 (13.2) |
| Aspirin | 1230 (53.7) | 1254 (54.8) |
| Other antiplatelet agents | 100 (4.4) | 100 (4.4) |
| Lipid-lowering drug | 961 (42.0) | 930 (40.7) |

Table 2 and Figure 3A). This significant effect on outcomes was noted early (Figure 3), with the differences observed in the first 2 years and then maintained throughout the duration of the trial (Table 3). A 30% risk reduction in cardiovascular death or CHF hospitalization was observed in the first year and 23% risk reduction during the first 2 years in the candesartan group (both $P<0.001$). There was a 33% 1-year risk reduction ($P<0.001$) and 20% ($P=0.001$) 2-year risk reduction in all-cause mortality (Table 3). Figure 3B demonstrates that the impact on all-cause mortality was attributable to the significant 16% risk reduction in cardiovascular deaths ($P=0.005$) over the duration of the study period, with no effect on noncardiovascular deaths ($P=0.60$).

Additional outcomes are summarized in Table 2. Candesartan significantly reduced both the risk of cardiovascular mortality and of hospital admission for CHF decompensation individually, and it significantly decreased the risk of each of the secondary composite outcomes. The candesartan group experienced 521 (22.8%) cardiovascular deaths as compared with 599 (26.2%) in the placebo group (HR 0.84, 95% CI 0.75 to 0.95, $P=0.005$). Candesartan also significantly reduced the risk of patients' experiencing a first hospital admission for CHF after randomization (Table 2), the proportion of patients with multiple admissions for CHF, and the total number of hospital admissions for CHF (Table 4). The total number of hospital admissions for CHF was 1052 in the candesartan group as compared with 1444 in the placebo group, a 27.1% reduction ($P<0.001$, for difference in distribution). All-cause hospitalization also was reduced by candesartan, with the mean number of hospitalizations per patient per follow-up year at 1.25 for placebo (4633 events in 1501 patients) and 0.95 for the candesartan group (4180 events in 1462 patients; $P=0.003$). Candesartan exerted no significant effect on the relatively small number of other cardiovascular component outcomes including nonfatal MI, nonfatal stroke, and coronary revascularization, although each of the composite outcomes was reduced significantly (each $P<0.001$; Table 2).

More important, candesartan reduced the risk of cardiovascular death or admission to a hospital for CHF in all protocol prespecified or subsequently defined subgroups, with no evidence of heterogeneity of treatment effect based on subgroup assignment (Figure 4). Candesartan reduced this mortality and morbidity risk consistently whether patients were treated with β-blockers, ACE inhibitors, or spironolactone, each alone or in combination.

The benefits demonstrated in this intention-to-treat analysis were observed despite more patients permanently discontinuing candesartan than they did placebo. At the final study visit, 528 (23.1%) survivors in the candesartan group and 429 (18.8%) in the placebo group were no longer taking the study medication because of an adverse event or laboratory abnormality ($P<0.001$). Concerns regarding creatinine increase caused study drug discontinuation in 7.1% of candesartan versus 3.5% of placebo patients ($P<0.001$), hypotension in 4.2% versus 2.1% ($P<0.001$), and hyperkalemia in 2.8% versus 0.5% ($P<0.001$), respectively. We also noted that in the CHARM-Added cohort, at the last trial visit, 91.4% of placebo and 87.2% candesartan patients were taking ACE

**TABLE 2. CHARM Left Ventricular Systolic Dysfunction Trials: Primary and Secondary Composite and Component Outcomes**

| Outcomes | Candesartan, n (%) (n=2289) | Placebo, n (%) (n=2287) | Hazard Ratio (95% CI) | *P* |
|---|---|---|---|---|
| Cardiovascular death or CHF hospitalization | 817 (35.7) | 944 (41.3) | 0.82 (0.74–0.90) | <0.001 |
| Cardiovascular death | 521 (22.8) | 599 (26.2) | 0.84 (0.75–0.95) | 0.005 |
| CHF hospitalization | 516 (22.5) | 642 (28.1) | 0.76 (0.68–0.85) | <0.001 |
| Cardiovascular death, CHF hospitalization, or nonfatal MI | 848 (37.0) | 970 (42.4) | 0.82 (0.75–0.90) | <0.001 |
| Cardiovascular death, CHF hospitalization, nonfatal MI, or nonfatal stroke | 881 (38.5) | 991 (43.3) | 0.84 (0.76–0.92) | <0.001 |
| Cardiovascular death, CHF hospitalization, nonfatal MI, nonfatal stroke, or coronary revascularization | 944 (41.2) | 1052 (46.0) | 0.84 (0.77–0.92) | <0.001 |
| All-cause death or CHF hospitalization | 910 (40.0) | 1020(44.6) | 0.84 (0.77–0.92) | <0.001 |
| All-cause death | 642 (28.0) | 708 (31.0) | 0.88 (0.79–0.98) | 0.018 |



inhibitors (an 8.6 and 12.8% decrease from trial start, respectively), with 61.9% of placebo and 58.5% candesartan patients at the recommended ACE inhibitor dose. Because of the important question of the safety of multidrug therapy for heart failure, particularly the risk of hypotension, hyperkalemia, or renal insufficiency when spironolactone was used in addition to an ACE inhibitor, a β-blocker, and candesartan, a subgroup analysis of these patients was conducted. The study drug was stopped in 29 of 109 (26.6%) patients taking ACE inhibitor, spironolactone, β-blocker, and candesartan versus 23 of 128 (18%) taking ACE inhibitor, spironolactone, β-blocker, and placebo ($P=0.110$), suggesting only a modest increase in adverse events with this particular polypharmacy.

## Discussion

The CHARM low LVEF trials analysis demonstrates that adding candesartan to standard heart failure treatment, often including an ACE inhibitor, a β-blocker, or an aldosterone antagonist (or all 3) in CHF patients with LVEF ≤40%, decreases the risk of cardiovascular death and admission to the hospital for CHF decompensation, as well as all-cause mortality. These beneficial effects of candesartan were evident early after the initiation of therapy and the differences were sustained throughout the entire treatment period. A 33% risk reduction in all-cause mortality ($P<0.001$) occurred with candesartan at 1 year (Table 3), which compares favorably with the 34% total mortality reduction with metoprolol CR/XL in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart (MERIT-HF) trial at a mean follow-up of 1 year[6] and the 23% reduction in all-cause mortality at 1 year in the enalapril group of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial.[2] This reduction in mortality was evident irrespective of the presence

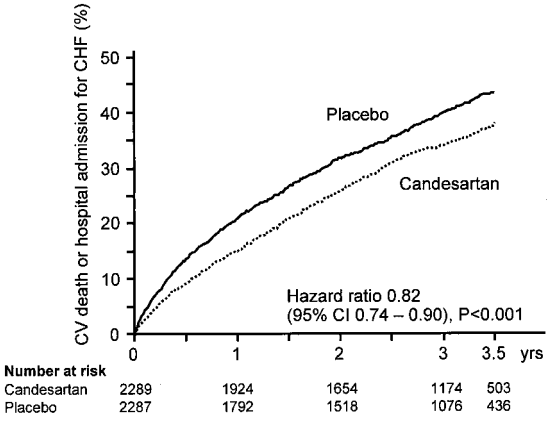


**Figure 2.** Cardiovascular death or chronic heart failure hospitalization.

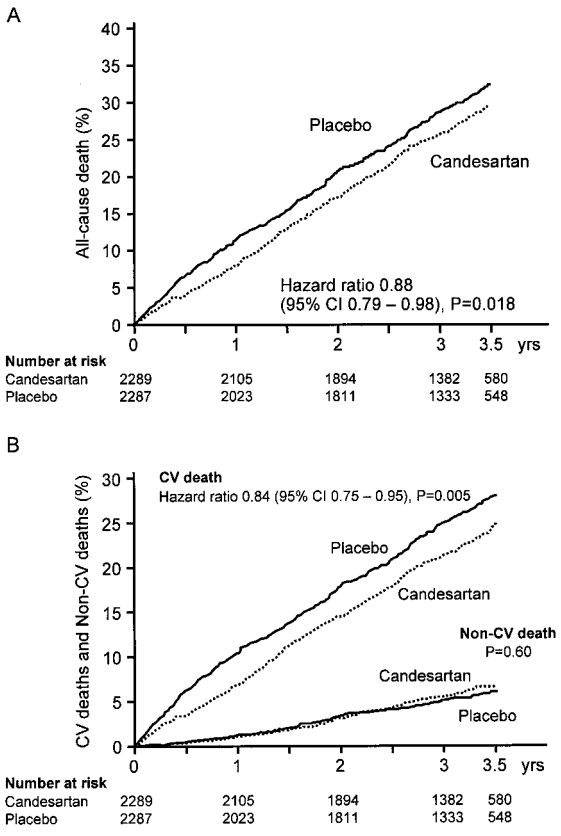


**Figure 3.** (A) All-cause death. (B) Cardiovascular and noncardiovascular death.

**TABLE 3. CHARM Left Ventricular Systolic Dysfunction Trials: 1- and 2-y Mortality and Morbidity Outcomes**

| | Cardiovascular Death or CHF Hospitalization | | | | All-Cause Mortality | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of Events, n (%) | | | | No. of Events, n (%) | | | |
| Time Point, y | Candesartan | Placebo | HR (95% CI) | *P* | Candesartan | Placebo | HR (95% CI) | *P* |
| 1 | 344 (15.0) | 474 (20.7) | 0.70 (0.61–0.80) | <0.001 | 181 (7.9) | 263 (11.5) | 0.67 (0.56–0.81) | <0.001 |
| 2 | 581 (25.4) | 718 (31.4) | 0.77 (0.69–0.86) | <0.001 | 391 (17.1) | 475 (20.8) | 0.80 (0.70–0.92) | 0.001 |

of ACE inhibitor therapy, as a test for ACE inhibitor interaction was not significant (CHARM-Alternative versus CHARM-Added subgroups HR 1.142, 95% CI 0.860 to 1.521, $P=0.37$).

Particularly important is that the benefits of reducing cardiovascular death or hospital admission for CHF morbidity were observed in all prespecified and subsequently identified subgroups of patients, with no evidence of treatment heterogeneity in any of the analyses. More specifically, these results provide evidence that the addition of candesartan to regimens including various combinations of an ACE inhibitor, a β-blocker, and an aldosterone antagonist was beneficial. In view of the significant reduction in total mortality, which was driven by a substantial decrement in cardiovascular death (Figure 3), the addition of candesartan in this population appears to have added value, which is incremental to the addition of other neurohormonal antagonists that might be prescribed. This observation reinforces the fact that polypharmacy is necessary in CHF patients with low LVEF, if the goal is to achieve the lowest possible morbidity and mortality. Taken in their entirety in a heterogeneous population of CHF patients with low LVEF, these data support earlier mechanistic studies (particularly the RESOLVD pilot trial) that suggested favorable neurohumoral, hemodynamic, and left ventricular remodeling effects with a combination of an ARB (candesartan) and an ACE inhibitor (enalapril); this was particularly true with the subsequent addition of a β-blocker (metoprolol CR/XL). Consistent with anticipated hemodynamic and neurohormonal modulating effects, the use of these drug combinations in the CHARM low LVEF trials was associated with a modest increase in hypotension, hyperkalemia, and increased serum creatinine leading to discontinuation of the drug.

These data in 4576 CHF patients with low LVEF can be compared with the findings reported in 5010 participants in the Val-HeFT trial.[26] In the Val-HeFT study, valsartan added to conventional treatment (ACE inhibitors in 93%, β-blockers in 35%, and spironolactone in 5% of patients) produced a significant reduction in cardiovascular morbidity that was primarily the result of a 24% reduction in first CHF hospital admissions. The CHARM low LVEF trials analysis reveals the same 24% reduction in first adjudicated CHF hospitalizations with candesartan. Candesartan also significantly reduced the total number of CHF hospitalizations by 27%. Most important, these CHARM data demonstrate a significant diminution in cardiovascular mortality and even total mortality with candesartan. Results of the CHARM low LVEF trials analysis provide additional findings that support a wider use of ARBs (specifically, candesartan) in heart failure. For example, in the Val-HeFT study, little evidence of additional benefit was found when valsartan was added to a recommended dose of an ACE inhibitor (particularly when a β-blocker was also used). However, in CHARM, the beneficial effects of candesartan were evident irrespective of whether patients were taking an ACE inhibitor and whether an ACE inhibitor, when used, was being prescribed at a recommended dose.[34]

**TABLE 4. Hospital Admissions for Worsening Heart Failure**

| | Candesartan | Placebo |
|---|---|---|
| No. of patients | 2289 | 2287 |
| Patients with | | |
| 0 Hospital admissions, n (%) | 1754 (76.6) | 1614 (70.6) |
| 1 Hospital admission, n (%) | 294 (12.8) | 339 (14.8) |
| 2 Hospital admissions, n (%) | 125 (5.5) | 165 (7.2) |
| ≥3 Hospital admissions, n (%) | 116 (5.1) | 169 (7.4) |
| No. of patients admitted to hospital, n (%) | 535 (23.4) | 673 (29.4) |
| Total CHF hospital admissions | 1052 | 1444 |

P<0.001 for difference in distribution of investigator-reported CHF hospital admissions, candesartan vs placebo.

Also intriguing is the suggestion that certain combinations of neurohumoral modulating agents in CHF patients might be harmful. The Losartan Heart Failure Survival Study (ELITE II) trial, which studied losartan, raised the possibility of a negative outcome in CHF patients when losartan was combined with a β-blocker.[37] A similar concern was again raised when a retrospective subgroup analysis of Val-HeFT data suggested an adverse interaction in the group that added valsartan to an ACE inhibitor and a β-blocker.[24] Their findings prompted the Val-HeFT investigators to express a "safety concern" about this combination and they hypothesized that "extensive blockade of multiple neurohormonal systems in patients with heart failure could be deleterious."[24] In the CHARM low LVEF trials analysis, the demonstration of a beneficial effect on cardiovascular mortality and morbidity with candesartan in combination with an ACE inhibitor and a β-blocker (or even an aldosterone antagonist) should mitigate the concerns raised by other studies. Indeed, 237 patients in this analysis were taking a combination of ACE inhibitor, β-blocker, and spironolactone at the start of the trial. As Figure 4 demonstrates, the point estimate for benefit was about the same for groups with or without spironolactone plus ACE inhibitor and β-blocker, but because of smaller numbers of patients taking this triple therapy at randomization, the confidence intervals are wide. More important, the test for the interaction of spironolactone use with outcomes was not significant ($P=0.26$).

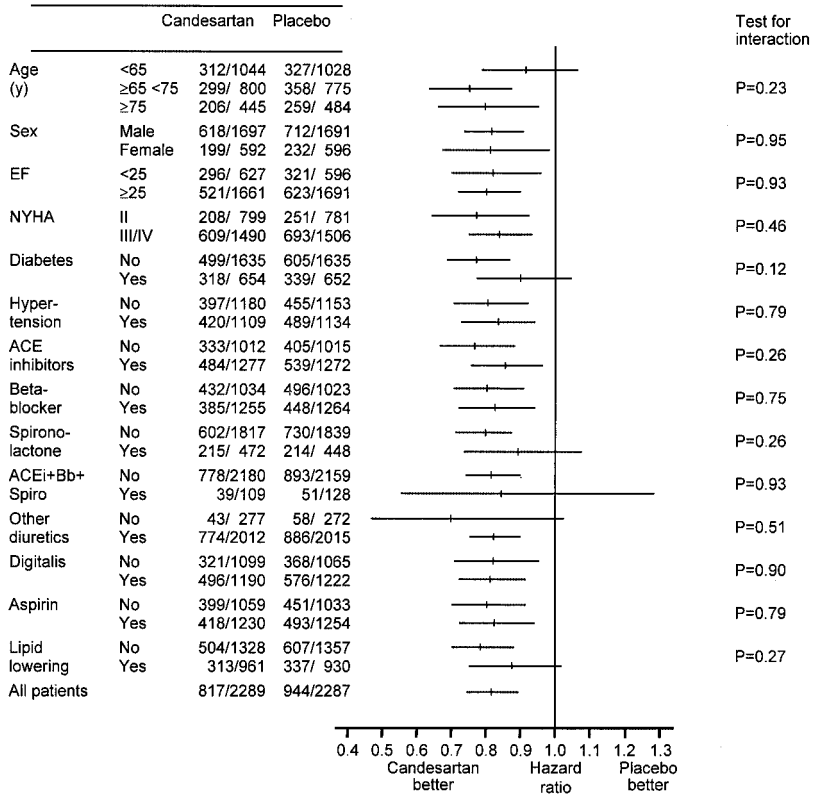


**Figure 4.** Effect of candesartan on cardiovascular death or heart failure hospital admission (point estimates of HRs with 95% CIs). Probability values are for testing of interaction (heterogeneity).

The reasons for the different observations in the clinical trials reviewed are unclear. Candesartan does have distinctive $AT_1$-receptor binding properties that are characterized by high affinity (tight binding) and slow dissociation,[38] but it is not known whether the disparate subgroup analyses can be ascribed to this fact, the drug doses studied, the play of chance, or other factors. One must be appropriately cautious, however, in drawing conclusions based on subgroup analyses, which have well-known limitations.[39]

The CHARM low LVEF trials analysis studied a population with a conventional heart failure definition, one that has been used in the majority of previous CHF clinical trials. Nonetheless, a potential limitation of the present study is that the proportion of patients not taking an ACE inhibitor in this analysis (44%) is large. This was the case because of the CHARM program design, which recruited patients who could not tolerate these drugs (specifically, the CHARM-Alternative trial). Furthermore, in general, the frequency of use of ACE inhibitors by patients with systolic left ventricular dysfunction is less than that desired. For example, in the Acute Decompensated Heart Failure National Registry (ADHERE), which included 40 952 patients admitted to a hospital in 2002 for decompensated congestive heart failure, only 41% of patients were taking an ACE inhibitor (with 11% taking an ARB) at presentation.[40] This cohort contained a large number of patients with new-onset CHF, many of whom had relatively normal left ventricular systolic function; these groups might not be expected to be taking an ACE inhibitor at hospital presentation. To balance this observation are data from the recent Medicare spending, the physician workforce, and beneficiaries' quality of care analysis, which demonstrate that from 2000 to 2001, ACE inhibitor use in patients discharged from the hospital with heart failure and LVEF <40% was 65.5%.[41] Furthermore, in the EuroHeart Failure Survey program, 79.9% of patients discharged from the hospital after being admitted for decompensated heart failure were taking an ACE inhibitor, and 60% of heart failure patients in the IMPROVEMENT of Heart Failure Programme showed an attempt was made at ACE inhibitor up titration.[42,43] It is interesting to note that only 20% of participants in the latter registry were taking the combination of an ACE inhibitor and $\beta$-blocker (data presented were not stratified for ejection fraction).[43] The present writing group believes that these observations support the applicability of our CHARM low LVEF trials analysis to CHF populations generally when left ventricular systolic dysfunction is present.

An analysis of the CHARM low LVEF trials demonstrates a further decrease in CHF morbidity and mortality when drug combination protocols with proven efficacious agents at appropriate doses are used. The use of these drug combinations is a challenge, but clinicians should not ignore that CHF treatments evolved from ACE inhibitors being added to digoxin and a diuretic to subsequent supplementation with a $\beta$-blocker and then prescription of an aldosterone antagonist in some patients. It has been demonstrated that adding an ARB (candesartan titrated to a target dose of 32 mg once daily) can even further decrease CHF morbidity and mortality in CHF patients with low LVEF.

In conclusion, these additional prespecified analyses from the CHARM program demonstrate that the ARB candesartan significantly reduces cardiovascular death, hospital admission for decompensated heart failure, and all-cause mortality in

patients with CHF and LVEF ≤40% when added to standard therapies including ACE inhibitors, β-blockers, and an aldosterone antagonist, or their combination. Routine monitoring of blood pressure, serum creatinine, and serum potassium is warranted. This approach offers the clinician an opportunity to make additional improvements in the poor prognosis of CHF patients when left ventricular systolic dysfunction is present by adding this ARB to other treatments that are proven to be efficacious in similar settings.

## Disclosure

AstraZeneca R&D Molndal (Molndal, Sweden) provided financial support for the CHARM trials program. In addition, representatives from AstraZeneca were involved in protocol design, data analysis, data interpretation, and manuscript preparation. All final data analysis for the primary and secondary outcomes was independently verified by the statistical center at the London (UK) School of Hygiene and Tropical Medicine, where data were also maintained. The AstraZeneca Clinical Development Leader was Birgitta Lindholm and the Study Team Leader was Lennart Janson. Drs Cohen-Solal, Dietz, Dunlap, Granger, Hradec, Kuch, McKelvie, McMurray, Pfeffer, Probstfield, Ostergren, Solomon, Swedberg, Young, and Yusuf receive research grant support from and act as consultants to AstraZeneca. Drs Michelson, Olofsson, and Held are employees of AstraZeneca.

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# Mortality and Morbidity Reduction With Candesartan in Patients With Chronic Heart Failure and Left Ventricular Systolic Dysfunction: Results of the CHARM Low-Left Ventricular Ejection Fraction Trials

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