Candesartan reduced mortality and hospital admissions in chronic heart failure


**Question**
In patients with chronic heart failure (CHF), does the angiotensin-receptor blocker (ARB) candesartan reduce death and hospital admissions?

**Design**
3-component, randomized (allocation concealed*), blinded (clinicians, patients, data collectors, outcome assessors, monitoring committee, manuscript writers, and data analysts),* placebo-controlled trial with median 37.7-month follow-up (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM] study).

**Setting**
618 centers in 26 countries.

**Patients**
7601 patients who were ≥ 18 years of age and had symptomatic CHF (New York Heart Association class II to IV) for ≥ 4 weeks. Major exclusion criteria included serum creatinine ≥ 265 μmol/L; serum potassium ≥ 5.5 mmol/L; bilateral renal artery stenosis; symptomatic hypotension; critical aortic or mitral stenosis; myocardial infarction, stroke, or open-heart surgery in the previous 4 weeks; use of an ARB in the previous 2 weeks; other serious disease likely to limit 2-year survival; and potential for pregnancy. 7599 patients (mean age 66 y, 68% men) were included in the analysis; 7589 patients completed the study.

Patients were enrolled in 1 of 3 component trials: CHARM-Added involved patients with left ventricular ejection fraction (LVEF) ≤ 40% who were being treated with an angiotensin-converting enzyme (ACE) inhibitor for ≥ 30 days (n = 2548); CHARM-Alternative involved patients with LVEF ≤ 40% who were intolerant of ACE inhibitors (n = 2028); and CHARM-Preserved involved patients with LVEF > 40% (n = 3023). CHARM-Overall involved all patients.

**Intervention**
Patients were stratified by site and component trial to candesartan, 4 or 8 mg once daily, doubled every 2 weeks to a target dose of 32 mg once daily from 6 weeks onward (n = 3803) or placebo (n = 3796).

**Main outcome measures**
All-cause mortality (CHARM-Overall) and a composite outcome of cardiovascular death or hospitalization for worsening CHF in the 3 component trials. Secondary outcomes included doubling of creatinine levels and potassium level ≥ 6.0 mmol/L.

**Main results**
Analysis was by intention to treat. Overall, all-cause mortality was reduced more with candesartan than with placebo (Table), mainly because of fewer cardiovascular deaths (18% vs 20%, adjusted hazard ratio 0.87, 95% CI 0.78 to 0.96). Fewer patients who received candesartan had the composite outcome of cardiovascular death or hospitalization for CHF than did patients who received placebo in the CHARM-Added and CHARM-Alternative component trials (Table). In CHARM-Preserved, the reduction in the composite outcome with candesartan reached borderline statistical significance (Table). The rates of doubling creatinine level for the candesartan and placebo groups were 6% vs 4% (P = 0.002) (CHARM-Overall), 7% vs 6% (P = 0.5) (CHARM-Added), 5.5% vs 1.6% (P = 0.015) (CHARM-Alternative), and 6% vs 3% (P = 0.007) (CHARM-Preserved). The rates for potassium level ≥ 6.0 mmol/L for the candesartan and placebo groups were 2% vs 1% (P = 0.017) (CHARM-Overall), 3% vs 1% (P = 0.089) (CHARM-Added), 3% vs 1.3% (P = 0.26) (CHARM-Alternative), and 2% vs 1% (P = 0.32) (CHARM-Preserved).

**Conclusions**
In patients with chronic heart failure (CHF), the angiotensin-receptor blocker candesartan reduced mortality (particularly cardiovascular) and hospital admissions for worsening CHF. Patients with reduced left ventricular ejection fraction with or without baseline angiotensin-converting enzyme inhibitor treatment showed the most benefit.
ValHeFT and CHARM on cardiovascular mortality. In ValHeFT, results in this particular subset were due to chance. The CHARM-Added results, however, suggest that the ValHeFT blocker, adding an ARB was associated with an increased risk for death.

Patient with CHF already treated with both an ACE inhibitor and a β-blocker. Direct comparative studies of an ARB and an aldosterone blocker rather than an ARB based on the results of the Randomized Aldactone Evaluation Study (RALES) (2). However, in RALES, only a relatively small proportion of patients were receiving both an ACE inhibitor and a β-blocker. Direct comparative studies of an ARB and an aldosterone blocker when added to an ACE inhibitor and a β-blocker in patients with CHF caused by systolic left ventricular dysfunction are needed.

In patients with CHF and preserved systolic function (CHARM-Preserved), candesartan was shown to be of only marginal benefit. Further studies are clearly required to determine the optimal strategy to reduce cardiovascular events in this important subset of patients whose incidence is increasing because of aging and increasing incidence of hypertension and diabetes mellitus.

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References