Candesartan reduced mortality and hospital admissions in chronic heart failure

Pfeffer MA, Swedberg K, Granger CB, *et al*. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–66.
Clinical impact ratings GP/FP/Primary care ★★★★★★☆ IM/Ambulatory care ★★★★★★☆ Cardiology ★★★★★★☆

McMurray JJ, Östergren J, Swedberg K, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–71.
Clinical impact ratings GP/FP/Primary care ★★★★★★☆ IM/Ambulatory care ★★★★★☆☆ Cardiology ★★★★★☆☆

Granger CB, McMurray JJ, Yusuf S, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–6.
Clinical impact ratings GP/FP/Primary care ★★★★★★☆ IM/Ambulatory care ★★★★★☆☆ Cardiology ★★★★★★☆

Yusuf S, Pfeffer MA, Swedberg K, *et al*. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–81.
Clinical impact ratings GP/FP/Primary care ★★★★☆☆☆ IM/Ambulatory care ★★★★★☆☆ Cardiology ★★★★★★★

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

METHODS

Design: 3-component randomised, placebo controlled trial (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM] study).

Allocation: concealed.*

Blinding: blinded (clinicians, patients, data collectors, outcome assessors, monitoring committee, manuscript writers, and data analysts).*

Follow up period: median 37.7 months.

Setting: 618 centres in 26 countries.

Patients: 7601 patients who were ⩾18 years of age and had symptomatic CHF (New York Heart Association class II–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. 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: stratified by site and component trial and allocated to candesartan, 4 or 8 mg once daily, doubled every 2 weeks to a target dose of 32 mg once daily from 6 weeks onwards (n = 3803) or placebo (n = 3796).

Outcomes: all cause mortality (CHARM-Overall) and a composite outcome of cardiovascular death or hospital admission for worsening CHF in the 3 component trials. Secondary outcomes included doubling of creatinine concentrations and potassium concentration ⩾6.0 mmol/l.

Patient follow up: 7599 patients (mean age 66 y, 68% men) were included in the analysis; 7589 patients completed the study.

*See glossary.

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% *v* 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 hospital admission 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 concentration for the candesartan and placebo groups were 6% *v* 4% (p = 0.002) (CHARM-Overall), 7% *v* 6% (p = 0.5) (CHARM-Added), 5.5% *v* 1.6% (p = 0.015) (CHARM-Alternative), and 6% *v* 3%, (p = 0.007) (CHARM-Preserved). The rates for potassium concentration ⩾6.0 mmol/l for the candesartan and placebo groups were 2% *v* 1% (p = 0.017) (CHARM-Overall), 3% *v* 1% (p = 0.089) (CHARM-Added), 3% *v* 1.3% (p = 0.26) (CHARM-Alternative), and 2% *v* 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.

Abstract and commentary also appear in ACP Journal Club.

For correspondence: Professor C H A R M-Overall: M A Pfeffer, Brigham and Women's Hospital, Boston, MA, USA. mpfeffer@rics.bwh.harvard.edu

For correspondence: Professor C H A R M-Added: J McMurray, Western Infirmary, Glasgow, UK. j.mcmurray@bio.gla.ac.uk

For correspondence: Dr C H A R M-Alternative: C B Granger, Duke University Medical Center, Durham, NC, USA. grang001@mc.duke.edu

For correspondence: Professor C H A R M-Preserved: S Yusuf, McMaster University, Hamilton, Ontario, Canada. yusufs@mcmaster.ca

Source of funding: AstraZeneca R&D.

Commentary

The CHARM study extends our knowledge of the role of ARBs in patients with CHF.

Least surprising but still important was the finding in the CHARM-Alternative study that candesartan resulted in a significant reduction in cardiovascular mortality and hospital admission for heart failure. The Valsartan Heart Failure Trial (ValHeFT) reached a similar conclusion,[1] and valsartan is indicated in patients with heart failure caused by systolic left ventricular dysfunction who are not taking an ACE inhibitor. However, the result of ValHeFT was determined in a retrospective analysis and included a relatively small number of patients and events. The CHARM-Alternative study, on the other hand, was prospective and adequately powered with a significant number of events.

It is likely that ARBs used at the appropriate dose, such as valsartan 160 mg twice daily or candesartan 32 mg daily, are equivalent to target doses of an ACE inhibitor, such as enalapril 10 mg twice daily. However, the therapy of choice in patients with CHF caused by systolic left ventricular dysfunction will probably remain an ACE inhibitor because of the relatively large number of patients in whom these agents have been studied and their reasonable cost.

The CHARM-Added trial is also important because it suggests that an ARB should be added to an ACE inhibitor and a β blocker in patients with mild to moderate CHF caused by systolic left ventricular dysfunction. Whereas the reduction in cardiovascular mortality in the CHARM-Added trial was moderate, the reduction in the combined endpoint of cardiovascular mortality and hospital admission for heart failure is both clinically and statistically significant. ValHeFT suggested that in a patient with CHF already treated with both an ACE inhibitor and a β blocker, adding an ARB was associated with an increased risk of death. The CHARM-Added results, however, suggest that the ValHeFT results in this particular subset were due to chance.

Somewhat less clear is the explanation for the discrepancy between ValHeFT and CHARM on cardiovascular mortality. In ValHeFT, valsartan had no effect on cardiovascular mortality and its significant benefit on the combined endpoint of cardiovascular mortality and hospital admission for heart failure was entirely the result of a reduction in hospital admissions for heart failure. In the CHARM-Added study, there was a reduction in both cardiovascular mortality and hospital admissions for heart failure. Whether this disparity reflects a difference in the effectiveness of valsartan and candesartan, their relative dosing strategy, or other factors remains to be determined. A further study of an ARB in this situation would therefore be ethical and useful.

In patients with severe heart failure, an aldosterone blocker might be the preferred agent to add to an ACE inhibitor and a β 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.

Bertram Pitt, MD
University of Michigan
Ann Arbor, Michigan, USA

1 Cohn JN, Tognoni G. A randomized trial of angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–75.
2 Pitt B, Zannad F, Remme WJ, *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–17.

Candesartan *v* placebo for chronic heart failure (CHF) at median 37.7 months*

Trial	Outcomes	Candesartan	Placebo	Unadjusted HR (95% CI)	Adjusted analysis†		
					HR (CI)	RRR (CI)	NNT (CI)
Overall	All cause mortality	23%	25%	0.91 (0.83 to 1.00)	0.90 (0.82 to 0.99)	8.8% (0.9 to 16)	46 (26 to 463)
CHARM-Added	Composite	38%	42%	0.85 (0.75 to 0.96)	0.85 (0.75 to 0.96)	12% (3 to 20)	21 (12 to 79)
CHARM-Alternative	Composite	33%	40%	0.77 (0.67 to 0.89)	0.70 (0.60 to 0.81)	25% (15 to 34)	11 (8 to 17)
CHARM-Preserved	Composite	22%	24%	0.89 (0.77 to 1.03)	0.86 (0.74 to 1.00)	12% (0 to 23)	Borderline significance

*Composite endpoint = cardiovascular death or hospital admission for worsening CHF; CHARM = Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity; HR = hazard ratio. Other abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article using Cox proportional hazards model.
†Adjusted for baseline covariates, including patients' characteristics, heart disease risk factors, medical history, and medical treatment.