

Optimising the use of Angiotensin Receptor Blockers in the Management of Chronic Heart Failure

John McMurray

Keywords:
Candesartan,
Angiotensin
receptor blocker,
Chronic heart
failure,
Safety,
Efficacy

Western Infirmary and
University of Glasgow,
Glasgow, UK

Correspondence to:
Professor John
McMurray,
Department of
Cardiology,
Western Infirmary,
Glasgow G11 6NT, UK
Tel: +44 141 211 1838
Fax: +44 141 211 2252
E-mail: j.mcmurray@
bio.gla.ac.uk

JRAAS 2005;6
(suppl 2):S2–S5

Abstract

The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) trial programme provided clear evidence of the efficacy of candesartan in the management of chronic heart failure (CHF) associated with reduced left ventricular (LV) systolic function. The morbidity and mortality benefits of candesartan were consistent irrespective of age, sex, ethnic origin or baseline heart failure therapy. Extensive safety analyses of the CHARM data have demonstrated that candesartan was well tolerated by patients receiving an angiotensin-converting enzyme (ACE) inhibitor (even at maximal doses) and beta-blocker, and by patients previously intolerant to an ACE inhibitor. They also demonstrated a low incidence of adverse effects, characteristic of drugs that inhibit the renin-angiotensin-aldosterone system.

CHARM provides conclusive evidence confirming the role of candesartan in the management of CHF patients with LV systolic dysfunction. Treatment should be initiated early to ensure optimum outcome, starting at a low dose (4 mg once daily) and increasing to a target dose of 32 mg once daily. Routine monitoring of blood pressure and of serum creatinine and potassium is warranted.

Introduction

The angiotensin receptor blockers (ARBs) are the most recent class of drug shown to be of benefit in patients with chronic heart failure (CHF), as recognised in the recent revision of the European Society of Cardiology (ESC) guidelines for the management of CHF.¹ The evidence base for these new recommendations mainly derives from the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) trial programme, the largest study to date in heart failure.

CHARM was designed as three, parallel, independent, integrated, randomised, double-blind, placebo-controlled clinical trials comparing candesartan with placebo in three distinct populations of CHF patients (Figure 1). Two of these studies included patients with low left ventricular

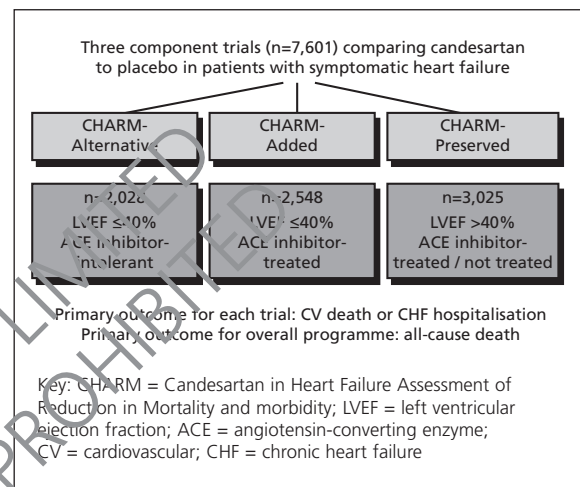


Figure 1
Design of the CHARM programme

ejection fraction (LVEF ≤ 40%). CHARM-Added² enrolled 2,548 patients with reduced LVEF who were symptomatic despite optimal therapy with an angiotensin-converting enzyme (ACE) inhibitor in addition to other heart failure treatment; CHARM-Alternative³ enrolled 2,028 symptomatic patients with reduced LVEF who were not receiving an ACE inhibitor due to previous intolerance. Key patient characteristics at baseline in CHARM-Added and CHARM-Alternative are summarised in Table 1.

Both CHARM-Added² and CHARM-Alternative³ demonstrated significant morbidity and mortality benefits with candesartan in patients with CHF, reducing the primary composite endpoint of cardiovascular death and CHF hospitalisation. A pre-planned pooled analysis of both studies reinforced this finding (hazard ratio [HR] 0.82, p<0.001) and also demonstrated a significant reduction in all-cause mortality in patients with low LVEF (HR 0.88, p=0.018).^{4,5}

Perceived safety concerns may lead to reluctance to prescribe an ARB in patients with low LVEF, especially in those already treated with an ACE inhibitor.¹ Discussion of the efficacy and safety of candesartan in specific patient groups, based on the CHARM data, should overcome such perceptions.

**Journal of
the Renin-
Angiotensin-
Aldosterone
System**

(Including other
Peptidergic Systems)

December 2005
Volume 6
Supplement 2

Table 1
Key patient characteristics at baseline for the CHARM-Alternative³ and CHARM Added² trials

	CHARM-Alternative		CHARM-Added	
	Candesartan (n=1,013)	Placebo (n=1,015)	Candesartan (n=1,276)	Placebo (n=1,272)
Mean age (SD), years	66.3 (11.0)	66.8 (10.5)	64.0 (10.7)	64.1 (11.3)
Proportion of patients, %				
• Male	68.2%	68.1%	78.8%	78.6%
• ≥75 years	23.0%	23.5%	16.6%	19.3%
• European origin	88.4%	88.8%	89.6%	91.5%
• Ischaemic heart failure	69.7%	66.9%	62.2%	62.6%
NYHA class III: III, %	48.1%: 48.4%	47.2%: 49.2%	24.5%: 73.0%	23.7%: 72.7%
Mean LVEF (SD), %	29.8 (7.6)	30.0 (7.2)	28.0 (7.5)	28.0 (7.5)
Medical treatment, %				
• ACE inhibitor	-	-	100%	99.8%
• Diuretic	85.3%	85.6%	90.0%	90.1%
• Beta-blocker	54.6%	54.5%	55.0%	55.9%
• Spironolactone	24.7%	23.0%	17.4%	16.9%

Key: SD = standard deviation; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; ACE = angiotensin-converting enzyme

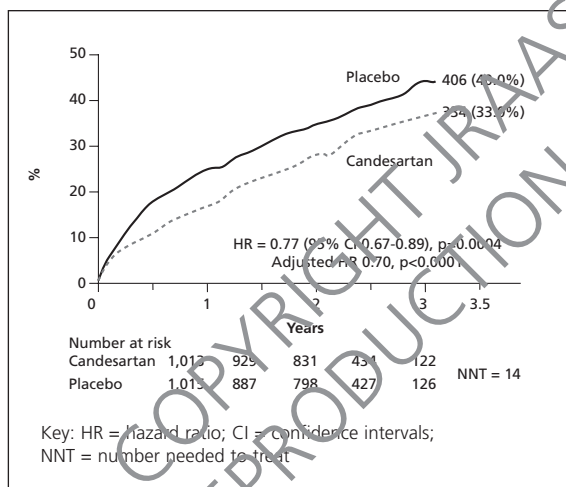


Figure 2
Cardiovascular death or chronic heart failure hospitalisation: results from the CHARM-Alternative trial. Reprinted from *The Lancet*, Granger et al.³ Copyright 2003 with permission from Elsevier

Who Should Receive an ARB?
Patients Intolerant to ACE Inhibitor Therapy

There is no doubt that treatment with an ARB is clearly indicated in patients with prior intolerance to ACE inhibitors, based on evidence from CHARM-Alternative. In that trial, treatment with candesartan led to a significant reduction in the primary outcome of cardiovascular death or CHF hospitalisation (by 23%, p=0.0004) (Figure 2).³ This effect was apparent early and was sustained throughout the study, emphasising the importance of early introduction of treatment in this patient group.

Baseline data indicated that the most common reasons for ACE inhibitor intolerance were cough

and, to a lesser extent, symptomatic hypotension and renal dysfunction.³ At the end of the study, the overall proportion of patients who permanently discontinued treatment due to adverse events or laboratory abnormalities was similar in the candesartan and placebo groups (21.5% vs. 19.3%, p=0.23).³ Not unexpectedly for an agent that acts on the renin-angiotensin-aldosterone system (RAAS), patients were more likely to have permanently discontinued treatment with candesartan due to hypotension (3.7% vs. 0.9% with placebo, p<0.0001), renal dysfunction (6.1% vs. 2.7%, p<0.0001) and hyperkalaemia (1.9% vs. 0.3%, p=0.0005).³ In particular, patients whose previous intolerance was due to renal dysfunction were more likely to have discontinued treatment (with either candesartan or placebo) due to increased creatinine (23.1% vs. 12.0% in the placebo group, p<0.0001) or increased potassium (13.6% vs. 1.0%),³ suggesting that these adverse effects are not caused by ARBs (Figure 3).

Thus, data from CHARM-Alternative support the efficacy and safety of candesartan in heart failure patients who are intolerant to an ACE inhibitor. The clearest indication for the use of candesartan is in those patients intolerant to an ACE inhibitor due to cough or angioedema. Careful monitoring is recommended in patients intolerant to an ACE inhibitor due to hypotension, hyperkalaemia or renal dysfunction.

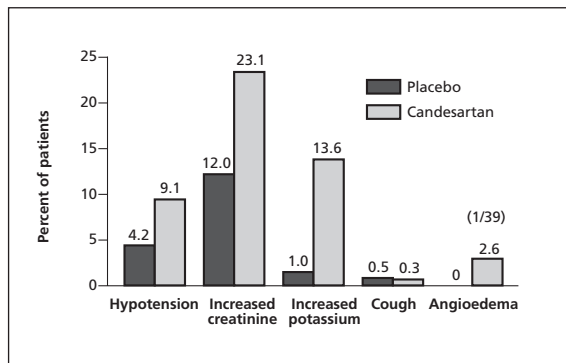


Figure 3 Permanent study drug discontinuation in the CHARM-Alternative trial,³ summarised by reason for previous ACE inhibitor intolerance

Patients who Remain Symptomatic Despite Optimal Therapy

There has previously been reluctance to add an ARB to the treatment regimen of symptomatic patients who are already receiving an ACE inhibitor and a beta-blocker, largely attributable to findings from the Valsartan Heart Failure Trial (Val-HeFT).⁶ In that trial, treatment with valsartan (160 mg twice daily) in addition to conventional CHF therapy significantly reduced the risk of the composite endpoint of death and cardiovascular morbidity (admission to hospital for CHF, ≥ four hours' intravenous treatment for CHF without admission, or cardiac arrest with resuscitation) by 13.2% compared with placebo, mainly driven by a 27.5% reduction in the risk of hospital admission for CHF.⁶ However, subsequent analyses suggested that patients treated with an ACE inhibitor and a beta-blocker at baseline actually fared worse when valsartan was introduced.⁶

Findings from CHARM-Added effectively counter these concerns. Treatment with candesartan in patients remaining symptomatic despite optimal therapy (all received an ACE inhibitor and 55% also received a beta-blocker) (Table 1), significantly reduced the primary composite endpoint of cardiovascular death or hospitalisation for worsening CHF by 15% (p=0.011) (Figure 4), and cardiovascular death alone by 16% (p=0.029).² As in CHARM-Alternative,³ these effects were rapid in onset and striking after one year follow-up. Additionally, a significantly higher proportion of patients showed improvement in New York Heart Association (NYHA) functional class on candesartan compared with placebo (p=0.003).⁷ These data from CHARM were largely responsible for recognition of the important role of ARBs in the management of CHF patients who remain symptomatic despite conventional therapy including an ACE inhibitor, as detailed in the updated guidelines.¹

CHARM-Added also showed that the efficacy of candesartan was not influenced by baseline use of a beta-blocker in addition to an ACE inhibitor.

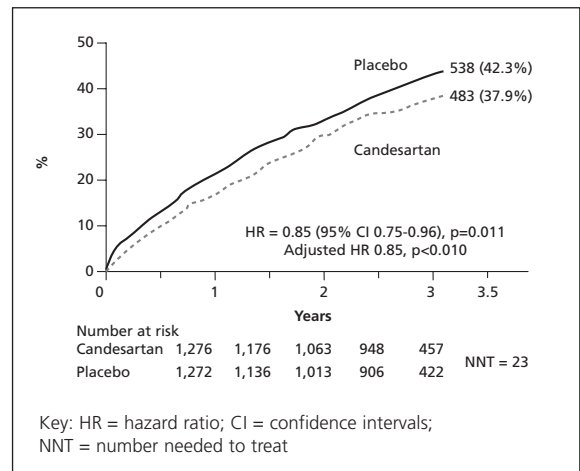


Figure 4 Cardiovascular death or chronic heart failure hospitalisation in the CHARM-Added trial. Reprinted from *The Lancet*, McMurray et al.² Copyright 2003 with permission from Elsevier

Patients on 'triple therapy' (i.e. ACE inhibitor, beta-blocker and candesartan) showed similar incremental reductions in cardiovascular death and CHF hospitalisation to patients who were not taking a beta-blocker at baseline.² Among patients who were taking both an ACE inhibitor and beta-blocker at baseline, cardiovascular death occurred in 25% of patients on candesartan compared with 27% in the placebo group (p=0.22); by comparison, in patients who were not taking a beta-blocker at baseline, cardiovascular death rates were 35% and 39%, respectively (p=0.20).²

Safety concerns have been raised about patients receiving a high dose of an ACE inhibitor in addition to an ARB. However, data from CHARM-Added showed that candesartan was as effective in patients taking a recommended dose of an ACE inhibitor as in those patients taking a lower dose.² Moreover, subsequent analysis of the CHARM-Added database showed that the benefits of candesartan were preserved even in patients on high doses of ACE inhibitor, with or without a beta-blocker.

Special Subgroups

Pooled analyses of data from CHARM in patients with reduced LVEF clearly demonstrated that the morbidity and mortality benefits of candesartan therapy were consistent across a wide range of patient subgroups.^{4,5} Candesartan was as effective in younger (< 65 years) as in older patients (≥ 75 years), was effective in male and female patients and there was no evidence that ethnic origin influenced response to treatment response.⁴ Moreover, the efficacy of candesartan was consistent irrespective of whether patients received beta-blockers, ACE inhibitors or an aldosterone antagonist.⁴

Currently, there are only limited data relating to the safety and efficacy of the combination of an ARB, ACE inhibitor, beta-blocker and spironolac-

