ELSEVIER

European Journal of Heart Failure 10 (2008) 157–163

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

Efficacy and tolerability of adding an angiotensin receptor blocker in patients with heart failure already receiving an angiotensin-converting inhibitor plus aldosterone antagonist, with or without a beta blocker. Findings from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial

R.A.P. Weir [a,b], John J.V. McMurray [a,b,*], Margareta Puu [c], Scott D. Solomon [d], Bertil Olofsson [c], Christopher B. Granger [e], Salim Yusuf [f], Eric L. Michelson [g], Karl Swedberg [h], Marc A. Pfeffer [d] for the CHARM Investigators

[a] *Department of Cardiology, Western Infirmary, Glasgow, G11 6NT, United Kingdom*
[b] *Faculty of Medicine, University of Glasgow, United Kingdom*
[c] *AstraZeneca R&D, Mölndal, Sweden*
[d] *Brigham & Women's Hospital, Boston, MA, USA*
[e] *Duke University Medical Center, Durham, NC, USA*
[f] *HGM-McMaster Clinic, Hamilton, Ontario, Canada*
[g] *AstraZeneca LP, Wilmington, DE, USA*
[h] *Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden*

Received 25 July 2007; received in revised form 1 November 2007; accepted 12 December 2007
Available online 31 January 2008

Abstract

Background: The efficacy and safety of adding an angiotensin receptor blocker (ARB) in heart failure (HF) patients already taking an angiotensin-converting enzyme-inhibitor (ACE-I) plus an aldosterone antagonist is uncertain (especially if taking a beta blocker as well). The CHARM-Added trial describes the largest experience of using multiple inhibitors of the renin–angiotensin–aldosterone system (RAAS) together.

Methods and results: 2548 HF patients, taking an ACE-I (936 no spironolactone/no beta blocker; 1175 no spironolactone/beta blocker; 199 spironolactone/no beta blocker; 238 sprionolactone/beta blocker), were randomized to placebo or candesartan and followed for 41 months (median). The primary outcome was cardiovascular death or HF hospitalization. In patients taking both a beta blocker and spironolactone (in addition to an ACE-I) at baseline, the candesartan:placebo hazard ratio was 0.85(95% CI 0.56, 1.29), compared to 0.85(95% CI 0.75, 0.96) in all randomized patients (interaction p value 0.49).

The relative risk of discontinuation of candesartan (compared to placebo) because of hypotension, increased serum creatinine or hyperkalemia was not increased in patients taking spironolactone at baseline.

Conclusions: An ARB may provide added benefit, at acceptable risk, in HF patients already taking spironolactone as well as an ACE-I and beta blocker. These findings must be confirmed in a prospective randomized trial before this approach can be recommended, routinely.

Keywords: Heart failure; Mortality; Angiotensin receptor blocker; Aldosterone antagonist; Beta blocker; Angiotensin-converting enzyme inhibitor

* Corresponding author. Department of Cardiology, Western Infirmary, Glasgow, G11 6NT, United Kingdom. Tel.: +44 141 330 3479; fax: +44 141 330 6955.
E-mail address: j.mcmurray@bio.gla.ac.uk (J.J.V. McMurray).

1388-9842/$ - see front matter
doi:10.1016/j.ejheart.2007.12.006

1. Introduction

Blockade of the renin–angiotensin–aldosterone system (RAAS) is a fundamental part of modern heart failure treatment. Initial observations of benefit with an angiotensin-converting enzyme (ACE) inhibitor [1,2] were followed by demonstrations of further value from the concomitant use of two inhibitors of the RAAS — first with an ACE inhibitor and an aldosterone antagonist in severe HF, [3] and subsequently with the combination of an ACE inhibitor and an angiotensin receptor blocker (ARB) [4–6].

Despite the fact that each of these classes of medication acts on the same neurohumoral pathway, there are differences in the degree of aldosterone suppression with the various agents and their combinations. In particular, the use of an ACE inhibitor and ARB together, fails to suppress aldosterone in the long-term, probably because aldosterone secretion is not controlled, exclusively, by angiotensin II. Consequently, the concomitant use of all three, an ACE inhibitor, ARB and aldosterone antagonist is theoretically attractive, although there are also concerns about the safety of using these agents together.

The clinical effects of using all three of these inhibitors of the RAAS together in HF have not, however, been described. Furthermore, the efficacy and safety of using these three inhibitors in addition to a beta blocker has not been reported and is particularly important, as beta blockade is now routinely indicated in patients with heart failure and a low ejection fraction [7–9]. Because beta blockers also suppress renin, angiotensin II and even aldosterone secretion, the potential risks of renal dysfunction, hyperkalemia and hypotension may be increased further when these three RAAS inhibitors are used in conjunction with a beta blocker [10–12].

To investigate these questions further, we analyzed the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) — Added trial [13] in which all patients were treated with an ACE inhibitor. These patients were randomized to the addition of placebo or the ARB candesartan, but neither beta blocker ($n=1413$) nor spironolactone ($n=437$; 238 both beta blocker and spironolactone) use was taken into consideration during randomization.

2. Methods

2.1. The CHARM Program

The design, baseline findings and primary results of the CHARM Program have been reported in detail [13–16]. Briefly, it consisted of three independent but related trials in which patients with NYHA class II–IV HF were randomized to placebo or candesartan (target dose 32 mg once daily). Patients were enrolled into the individual CHARM trials according to left ventricular ejection fraction (LVEF) and treatment with an ACE inhibitor. Patients with a LVEF ≤ 0.40 and taking an ACE inhibitor were enrolled in CHARM-Added. In this trial, patients in NYHA Class II had to have had a hospital admission for a cardiac reason in the previous 6 months (this had the effect of increasing the proportion of NYHA class III/IV patients in CHARM-Added). Patients with a serum creatinine ≥ 3 mg/dL (265 μmol/L) were excluded. Patients with a serum potassium ≥ 5.5 mmol/L (or history of marked ACE inhibitor induced hyperkalemia resulting in a serum potassium ≥ 6.0 mmol/L or a life-threatening adverse event) were also excluded. There was no specific lower blood pressure criterion for exclusion, although patients with current symptomatic hypotension could not be randomized. The CHARM Program was completed, as planned, two years after the last patient was randomized and the median follow-up in CHARM-Added was 41 months.

The primary outcome for each of the three component trials was the composite of death from a cardiovascular cause or unplanned admission to hospital for the management of worsening HF and in the overall program, death from any cause.

At each follow-up visit, investigators were asked whether study drug had been discontinued because of: symptomatic or severe hypotension, increased serum creatinine or hyperkalemia (and other reasons).

2.2. Statistical analysis

Summary statistics of an extensive list of baseline characteristics including demographics, history and etiology of HF, co-morbidity, body mass index, vital signs, clinical signs and symptoms of HF, ECG findings and HF medications, were analyzed according to use of beta blocker, spironolactone or their combination (in addition to an ACE inhibitor) at randomization. Cox's proportional-hazards modeling was used to estimate the hazard ratio for the effect of treatment on each clinical outcome. Data are presented as estimated hazard ratios with a corresponding 95% confidence interval for the hazard ratios. Interaction p values are derived from the likelihood-ratio test. These were prespecified as exploratory analyses, and additional *post hoc* and supportive analyses were done for the purpose of describing more completely the clinically relevant observations that emanated from the initial analyses related to efficacy and safety.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the four treatment groups are shown in Table 1. Compared to other patients, those taking spironolactone had a lower median LVEF and systolic blood pressure. Fewer had a presumed ischemic etiology (and history of myocardial infarction) and a greater proportion had a history of prior heart failure hospitalization. A greater proportion of patients taking spironolactone also received a diuretic and digoxin, and were more likely to be

Table 1
Patient characteristics according to baseline treatment with spironolactone, a beta blocker or both (in addition to an ACE inhibitor)

	No spironolactone No beta blocker (n=936)	No spironolactone beta blocker (n=1175)	Spironolactone No beta blocker (n=199)	Spironolactone and beta blocker (n=238)
Patients' characteristics				
Mean (SD) age (yr)	66 (10.9)	63 (11)	65 (11)	63 (11)
Age ≥ 75 years (%)	214 (23)	165 (14)	40 (20)	38 (16)
Male (%)	706 (75)	954 (81)	158 (79)	188 (79)
NYHA class [number (%)]				
II	214 (23)	288 (25)	51 (26)	61 (26)
III	693 (74)	862 (73)	132 (66)	169 (71)
IV	29 (3)	25 (2)	16 (8)	8 (3)
Median (IQR) LV ejection fraction (%)	29 (22,35)	30 (24,35)	28 (20,32)	26 (20,33)
Mean (SD) heart rate (bpm)	76 (13)	71 (13)	79 (13)	71 (13)
Mean (SD) blood pressure (mm Hg)				
Systolic	127 (19)	126 (19)	120 (17)	119 (18)
Diastolic	76 (11)	76 (11)	73 (11)	72 (11)
Heart failure cause [number (%)]				
Ischaemia	592 (63)	758 (65)	121 (61)	119 (50)
Hypertension	64 (6.8)	78 (6.6)	12 (6.0)	12 (5)
Idiopathic	232 (25)	292 (25)	54 (27)	90 (38)
Medical history [number (%)]				
Hospital admission for HF	699 (75)	886 (75)	166 (83)	214 (90)
Myocardial infarction	513 (55)	683 (58)	105 (53)	116 (49)
Current angina	173 (19)	272 (23)	29 (15)	42 (18)
Stroke	86 (9.2)	93 (8.0)	17 (8.5)	24 (10)
Diabetes mellitus	268 (29)	363 (31)	59 (30)	68 (29)
Hypertension	437 (47)	593 (51)	82 (41)	116 (49)
Atrial fibrillation	274 (29)	285 (24)	59 (30)	69 (29)
Pacemaker	96 (10.3)	89 (7.6)	27 (14)	19 (8.0)
Percutaneous coronary intervention	123 (13)	187 (16)	30 (15)	36 (15)
Coronary artery bypass grafting	235 (25)	288 (25)	55 (28)	46 (19)
Implantable cardioverter defibrillator	22 (2.4)	52 (4.4)	3 (1.5)	23 (10)
Medical treatment [number (%)]				
Spironolactone	0 (0)	0 (0)	199 (100)	238 (100)
Beta blocker	0 (0)	1175 (100)	0 (0)	238 (100)
Diuretic	840 (90)	1017 (87)	199 (100)	238 (100)
Digoxin	558 (60)	628 (53)	137 (69)	165 (69)
Aspirin	480 (51)	644 (55)	85 (43)	102 (43)
Oral anticoagulant	328 (35)	443 (38)	86 (43)	114 (48)
Antiarrhythmic agent	156 (17)	87 (7.4)	46 (23)	31 (13)
Lipid-lowering drug	343 (37)	553 (47)	71 (36)	82 (35)
Long acting nitrate	284 (30)	408 (35)	59 (30)	77 (32)

Number of patients shown in columns, with percent or standard deviation in brackets, as indicated.

receiving an oral anticoagulant and less likely to be receiving aspirin. These contrasts were most pronounced when patients taking both spironolactone and a beta blocker (in addition to an ACE inhibitor) were compared to those taking no additional neurohumoral blocker i.e. only an ACE inhibitor (Table 1).

3.2. Clinical outcomes

3.2.1. Primary composite outcome: cardiovascular death or heart failure hospitalization

Baseline spironolactone use, or spironolactone and beta blocker use, did not modify the effect of candesartan on reducing the risk of the composite outcome of cardiovascular death or hospitalization for heart failure: the candesartan: placebo hazard ratio was 0.85 (95% CI 0.56, 1.29) in the 238 patients taking both spironolactone and a beta blocker (in addition to an ACE inhibitor) at baseline, compared to 0.85 (0.75, 0.96) in all randomized patients (interaction p value 0.49) (Fig. 1 and Table 2).

We did additional supportive analyses looking at patients taking spironolactone during the study (rather than just at baseline) and in patients actually taking spironolactone at their study visit preceding an event. Both these analyses showed that treatment with spironolactone did not modify the effect of candesartan, in keeping with the primary analysis. The candesartan:placebo hazard ratio for the outcome of cardiovascular death or heart failure hospitalization in

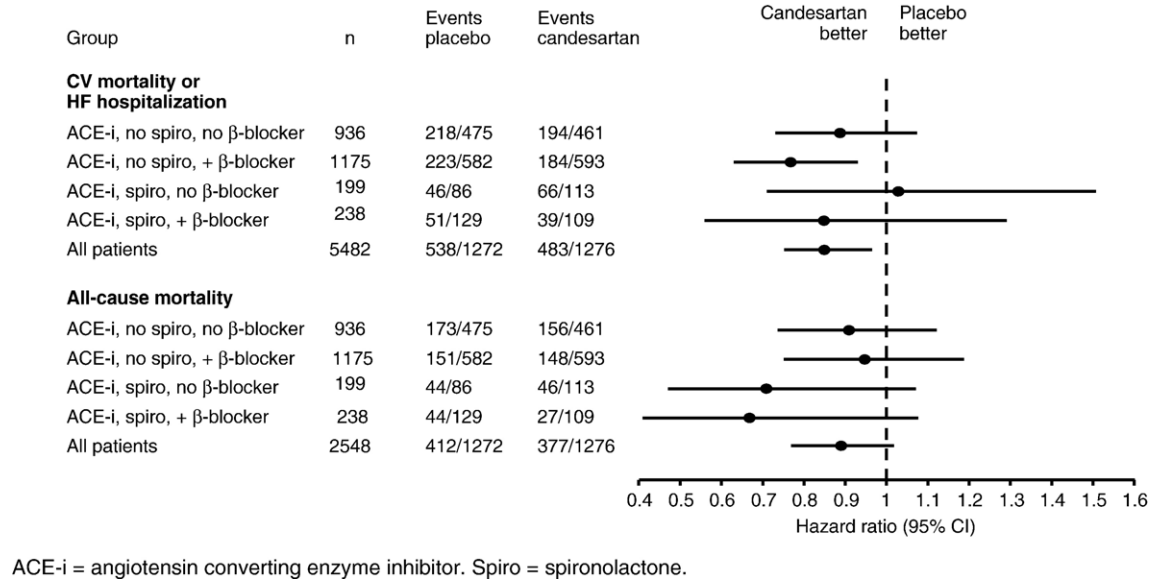

Fig. 1. Candesartan:placebo hazard ratios for cardiovascular death or heart failure hospitalization and all-cause mortality, according to baseline use of neurohumoral anatagonists. ACE-I = angiotensin-converting enzyme inhibitor. Spiro = spironolactone. HF = Heart failure.

patients taking an ACE inhibitor and spironolactone *during the study* (n=975) was 0.894 (0.747, 1.070) and for those taking an ACE inhibitor, beta blocker and spironolactone (n=712) it was 0.778 (0.625, 0.970).

3.2.2. Effect of candesartan on components of primary composite outcome

The effect of candesartan on the two components of the primary composite is also shown in Table 2.

3.2.2.1. Cardiovascular death. Candesartan reduced the risk of cardiovascular death, irrespective of background treatment with spironolactone (or spironolactone and beta blocker) in addition to an ACE inhibitor.

3.2.2.2. Heart failure hospitalization. On the other hand, candesartan did not appear to reduce the risk of heart failure hospitalization, when added to spironolactone (or a beta blocker and spironolactone), although the tests for interaction were not significant.

To investigate this further, we calculated the number of hospital admissions for heart failure (as opposed to patients admitted) in the candesartan and placebo groups, according to baseline spironolactone (or spironolactone and beta blocker) treatment. Again, candesartan treatment reduced hospitalizations for heart failure in patients not treated with spironolactone at baseline but did not appear to have an effect in those taking spironolactone at baseline. The numbers of hospitalizations in the candesartan/placebo groups, respectively, were: no spironolactone/no beta blocker 157/173; no spironolactone/beta blocker 142/195; spironolactone/no beta blocker 51/34 and spironolactone/beta blocker 31/35.

3.2.3. All-cause mortality

Baseline spironolactone or beta blocker and spironolactone use did not modify the effect of candesartan on all-cause mortality (Fig. 1 and Table 2).

Our supportive analyses were consistent with the primary analysis. The candesartan: placebo hazard ratio for the outcome of death from any cause in patients taking an ACE inhibitor and spironolactone *during the study* (n=975) was 0.871 (0.695, 1.093) and for those taking an ACE inhibitor, beta blocker and spironolactone (n=712) it was 0.795 (0.589, 1.072).

3.3. Tolerability and safety

The proportion of patients which had to discontinue study drug for hypotension, increased serum creatinine or hyperkalemia in each combination treatment group is shown in Table 3. The risk of discontinuation for each of the three adverse events was higher in patients treated with candesartan. The relative increase in risk of hypotension and increased serum creatinine with candesartan was similar in patients taking the various baseline combinations of ACE inhibitor, beta blocker and spironolactone examined. The only suggestion of heterogeneity was with the risk of hyperkalemia, the relative risk of which appeared to be greater in patients taking neither a beta blocker nor spironolactone at baseline.

4. Discussion

The principal finding of this analysis of the CHARM-Added trial was that treatment with spironolactone (or spironolactone and a beta blocker), in addition to an ACE

Table 2
Pre-specified outcomes in the CHARM-Added trial, according to baseline treatment with spironolactone, a beta blocker or both (in addition to an ACE inhibitor)

	Events per 1000 years follow-up				
	Candesartan	Placebo	HR (95% CI)	*p* for interaction	
				1*	2*
CV death or HF hospitalization					
No spironolactone/no beta blocker (n=936)	166	189	0.89 (0.73, 1.08)	0.491	0.290
No spironolactone/beta blocker (n=1175)	108	142	0.77 (0.63, 0.93)		0.494
Spironolactone/no beta blocker (n=199)	262	254	1.03 (0.71, 1.50)		
Sprionolactone/beta blocker (n=238)	128	153	0.85 (0.56, 1.29)		
All patients (n=2548)	141	166	0.85 (0.75, 0.96)		
CV death					
No spironolactone/no beta blocker	92	104	0.88 (0.69, 1.12)	0.652	0.842
No spironolactone/beta blocker	62	73	0.85 (0.66, 1.09)		0.436
Spironolactone/no beta blocker	135	167	0.81 (0.52, 1.28)		
Sprionolactone/beta blocker	65	106	0.62 (0.37, 1.04)		
All patients	73	93	0.84 (0.72, 0.98)		
HF hospitalization					
No spironolactone/no beta blocker	112	127	0.89 (0.70, 1.13)	0.082	0.074
No spironolactone/beta blocker	64	99	0.65 (0.51, 0.83)		0.551
Spironolactone/no beta blocker	170	171	1.00 (0.63, 1.59)		
Sprionolactone/beta blocker	85	69	1.26 (0.72, 2.21)		
All patients	90	110	0.83 (0.71, 0.96)		
All-cause death					
No spironolactone/no beta blocker	116	127	0.91 (0.74, 1.13)	0.383	0.828
No spironolactone/beta blocker	80	85	0.95 (0.75, 1.19)		0.874
Spironolactone/no beta blocker	148	210	0.71 (0.47, 1.07)		
Sprionolactone/beta blocker	80	120	0.67 (0.41, 1.08)		
All patients	98	111	0.89 (0.77, 1.02)		

1* Test of whether or not the treatment effect differs in the 4 different subgroups (No Spiro/No BB, No Spiro/BB, Spiro/No BB, Spiro/BB).
2* Test of whether or not the treatment effect differs for patients with BB compared to patients without BB, for patients with no spironolactone and for patients with spironolactone separately.

inhibitor, at the time of randomization, did not modify the therapeutic effect of candesartan in patients with symptomatic heart failure. Additional analyses examining treatment with spironolactone at any time during the trial and at the visit preceding an outcome event produced consistent findings. Our findings suggest that adding candesartan as a third inhibitor of the renin–angiotensin–aldosterone system may be more beneficial than just using dual therapy with an ACE inhibitor and aldosterone antagonist, though this hypothesis needs to be tested in a prospective clinical trial. In addition, this apparent incremental benefit was observed in patients taking a beta blocker as well i.e. even adding candesartan as a fourth neurohumoral antagonist appeared to improve outcome.

Closer inspection of the components of the primary composite outcome of cardiovascular death or heart failure hospitalization in CHARM-Added suggested that candesartan did not appear to reduce the risk of hospital admission for worsening heart failure in patients taking spironolactone in addition to an ACE inhibitor. The beneficial effect of candesartan on reducing the risk of cardiovascular mortality was, however, preserved. This limited observation on heart failure hospitalizations must be treated with caution as it is based on a *post hoc* observation in subgroups consisting of few patients who experienced a small number of events. We had no *a priori* hypothesis anticipating this observation and it is a finding that is difficult to explain. Nevertheless, that adding an ARB may provide an additional cardiovascular mortality benefit, even in the absence of an effect on heart failure hospitalization, is of considerable potential importance.

The apparent incremental benefit of adding candesartan to an ACE inhibitor and spironolactone (or ACE inhibitor, spironolactone and beta blocker) was obtained at the price of more hypotension, renal dysfunction and hyperkalemia. The absolute rate of discontinuation of placebo study drug for each of these adverse events was higher in patients treated with spironolactone at baseline and the rate was higher still in such patients given candesartan compared to placebo. Although the *relative* risk of discontinuation of candesartan (compared to placebo) was not increased more in patients treated with spironolactone at baseline (compared to those not taking spironolactone at baseline), the absolute risk clearly was.

Contrary to what might have been anticipated, we did not find greater intolerance of candesartan in patients treated

Table 3
Reasons for permanent study drug discontinuation according to baseline treatment with spironolactone, a beta blocker or both (in addition to an ACE inhibitor)

	Discontinuation of study drug								
	Hypotension			Increased serum creatinine			Hyperkalemia		
	Candesartan	Placebo	HR	Candesartan	Placebo	HR	Candesartan	Placebo	HR
No spironolactone/no beta blocker	12.9	13.5	0.96 (0.50, 1.87)	27.8	16.4	1.92 (0.68, 5.37)	13.7	0.7	18.67 (2.49. 139.8)
No spironolactone/beta blocker	14.5	7.9	1.83 (0.96, 3.50)	22.3	10.8	2.07 (1.20, 3.58)	9.3	2.8	3.33 (1.23, 9.03)
Spironolactone/no beta blocker	33.6	14.5	2.43 (0.67, 8.85)	45.1	24.3	1.92 (0.68, 5.37)	16.5	0	∞
Spironolactone/beta blocker	15.3	13.9	1.11 (0.32, 3.38)	35.1	16.6	2.11 (0.78, 5.69)	12.1	8.2	1.47 (0.33, 6.55)
All patients	15.5	10.9	1.43 (0.96, 2.14)	27.1	14.2	1.92 (1.37, 2.68)	11.7	2.4	4.84 (2.36, 9.91)

Rate per 1000 years of follow-up.
The rate (per 1000 patient years of follow-up) of permanent discontinuation of candesartan:placebo treatment for hypotension was 13.8/10.3 in those not taking spironolactone at baseline and 24.0/14.1 in those taking spironolactone at baseline — HR 1.34 (0.85,2.12) and 1.76 (0.75, 4.15), respectively. The same figures for increased serum creatinine were 24.6/13.2 in those not taking spironolactone at baseline and 39.9/19.4 in those taking spironolactone at baseline — HR 1.87 (1.28, 2.73) and 2.07 (1.01, 4.23), respectively. The figures for hyperkalemia were 11.2/1.9 in those not taking spironolactone at baseline and 14.2/5.2 in those taking spironolactone at baseline — HR 5.85 (2.46, 13.9) and 2.74 (0.74, 10.1), respectively. The discontinuation rates for each of these 3 reasons were not mutually exclusive.

with both spironolactone and a beta blocker, compared to spironolactone alone (in addition to an ACE inhibitor). This is likely to reflect selection bias related to the ability of patients to tolerate all three non-randomized neurohumoral blockers.

This report has a number of limitations. The analysis was in large part retrospective and the number of patients ($n=437$) treated with spironolactone at baseline was relatively small (and spironolactone treatment was not randomized). The confidence intervals around the efficacy and safety outcomes were wide. In the CHARM-Added trial, candesartan was add-on therapy in patients with symptomatic but stable chronic heart failure and LV systolic dysfunction, already receiving an ACE inhibitor with or without spironolactone and with or without a beta blocker, and therefore does not provide direct information on the efficacy or safety of adding these drugs in other sequences or clinical situations. Nevertheless, our study provides the only sizeable experience of using these three or four inhibitors of the RAAS together and, as such, provides the best available answers to frequently asked clinical questions about the potential efficacy and safety of their concomitant use in patients with chronic heart failure. For example, in the RALES trial, spironolactone was added to an ACE inhibitor in patients with advanced symptomatic heart failure with LV systolic function, but only a small minority of patients were receiving a beta blocker [3].

In summary, the clinical benefit of candesartan was not modified in patients treated with spironolactone (or the combination of spironolactone and a beta blocker) in addition to an ACE inhibitor at baseline in the CHARM-Added study, which translated into additive benefit when these drugs were used together. Hypotension, increased serum creatinine and hyperkalaemia leading to study drug discontinuation occurred more frequently in patients treated with spironolactone at baseline. The risk of discontinuation for these reasons was also higher in the candesartan than in the placebo group, though the placebo:candesartan hazard ratio was not modified by baseline spironolactone use. These findings suggest that angiotensin receptor blockade may provide added benefit, at acceptable risk, in patients taking spironolactone as well as an ACE inhibitor and beta blocker. This approach cannot, however, be recommended, routinely, unless our findings are confirmed in a prospective randomized trial.

5. Disclosures

The CHARM-Added trial was sponsored by AstraZeneca R&D and the primary analyses for this manuscript were done by Drs. Puu and Olofsson. Drs. Puu, Olofsson and Michelson are employees of AstraZeneca. Drs. McMurray, Solomon, Granger, Yusuf, Swedberg and Pfeffer have received research support from and have served as consultants to AstraZeneca and other companies with products related to the subject of this publication.

References

[1] [No authors listed]. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429–35.

[2] [No authors listed]. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293–302.

[3] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

[4] McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 1999;100:1056–64.

[5] Cohn JN, Anand IS, Latini R, Masson S, Chiang YT, Glazer R, et al. Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. Circulation 2003;108:1306–9.

[6] Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN. Augmented short— and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. Vasodilator Heart Failure Trial (V-HeFT) Study Group. Circulation 1999;99: 2658–64.

[7] [No authors listed]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.

[8] [No authors listed]. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.

[9] Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.

[10] Holmer SR, Hengstenberg C, Mayer B, Engel S, Lowel H, Riegger GA, et al. Marked suppression of renin levels by beta-receptor blocker in patients treated with standard heart failure therapy: a potential mechanism of benefit from beta-blockade. J Intern Med 2001;249: 167–72.

[11] Saito M, Nakayama D, Takada M, Hirooka K, Yasumura Y. Carvedilol accelerate elevation of serum potassium in chronic heart failure patients administered spironolactone plus furosemide and either enalapril maleate or candesartan cilexetil. J Clin Pharm Ther 2006;31: 535–40.

[12] Aggarwal A, Wong J, Campbell DJ. Carvedilol reduces aldosterone release in systolic heart failure. Heart Lung Circ 2006;15:306–9.

[13] McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, 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.

[14] Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.

[15] McMurray J, Ostergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S, et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur J Heart Fail 2003;5:261–70.

[16] Swedberg K, Pfeffer M, Granger C, Held P, McMurray J, Ohlin G, et al. Candesartan in heart failure—assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators. J Card Fail 1999;5:276–82.