Relationship of dose of background angiotensin-converting enzyme inhibitor to the benefits of candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)–Added trial

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Background Whether an angiotensin receptor blocker is of benefit when added to a full dose of angiotensin-converting enzyme (ACE) inhibitor in heart failure (HF) is uncertain.

Methods The effect of candesartan, compared with placebo, in 2548 patients randomized in the CHARM-Added trial was analyzed according to (i) ACE inhibitor dose at baseline, (ii) ACE inhibitor dose during follow-up, and (iii) combination treatment with ACE inhibitor and β-blocker at baseline. The main outcome was the composite of cardiovascular death or HF hospitalization.

Results The benefit of candesartan was not modified by the dose of ACE inhibitor. In all patients (n = 2548), the candesartan/placebo hazard ratio (HR) for the primary outcome was 0.85 (95% CI 0.75-0.96). In patients taking a guideline recommended dose of ACE inhibitor at baseline (n = 1291), this HR was 0.79 (95% CI 0.67-0.95; interaction *P* value .26). In patients taking a Food and Drug Administration–designated maximum dose of ACE inhibitor (n = 529), this HR was 0.75 (95% CI 0.57-0.98; interaction *P* value .29). The benefit of candesartan was preserved in patients taking β-blockers in addition to a higher dose of ACE inhibitor and in patients maintaining a high dose of ACE inhibitor throughout follow-up.

Conclusions These clinical findings support the pharmacologic evidence that ACE inhibitors and angiotensin receptor blockers have distinct mechanisms of action and show that their combined use improves outcomes in patients with HF more than an evidence-based dose of ACE inhibitor alone. (Am Heart J 2006;151:992-8.)

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The theoretical reasons for combining an angiotensin-converting enzyme (ACE) inhibitor and angiotensin II type 1 receptor blocker (ARB) in heart failure (HF) are well known.[1] However, for this strategy to be valuable, clinically, it must offer benefits incremental to those obtained with an optimal dose of an ACE inhibitor. We present evidence that this is so, based upon analyses of the CHARM-Added trial, which were carried out during the approval process for candesartan as a treatment of heart failure by the US Food and Drug Administration (FDA).

Methods

Patients and procedures

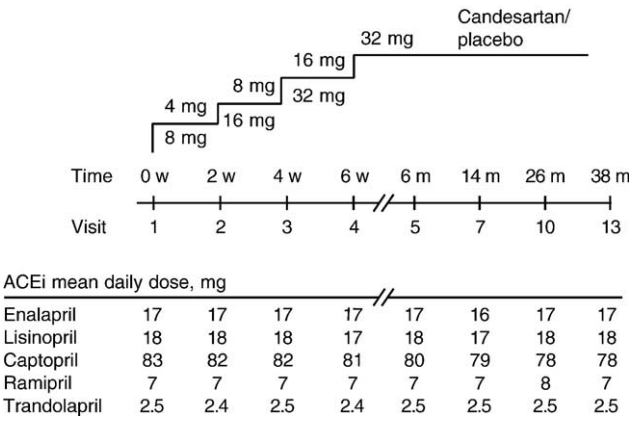
The inclusion criteria for CHARM-Added were New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction ≤40%, and a constant dose of ACE

Table I. Daily dose of ACE inhibitors used in CHARM-Added and subgroup analyses by dose

ACE inhibitor	% on Rx	Dose in CHARM-Added (mg/d)	≥Recommended (CHARM prespecified), * n = 1291		≥Maximum (FDA),† n = 721		≥Maximum (FDA revised),‡ n = 529	
			Dose (mg/d)	Patients (%)	Dose (mg/d)	Patients (%)	Dose (mg/d)	Patients (%)
Enalapril	27	17	20	52	20	52	40	10
Lisinopril	19	18	20	52	40	15	20	52
Captopril	17	83	150	21	150	21	300	2
Ramipril	11	7	10	39	10	39	10	39
Trandolapril	6	2.5	2	90	4	27	4	27
Perindopril§	6	4	4	83	16	1	16	1
Quinapril	5	25	20	60	80	7	80	7
Fosinopril	5	20	20	59	40	20	40	20
Benazepril§	3	26	20	62	80	5	80	5
Other§‖	1	–						
All	100			50.70		28.30		20.80

Rx, treatment.
* Based on the European Society of Cardiology guidelines [12].
† US FDA communication, December 2004.
‡ FDA communication, January, 2005.
§ Not approved by FDA for treatment of heart failure.
‖ Cilazapril and moexipril.

Figure 1



Dosing and visit schedule in the CHARM-Added trial. Mean daily dose (in milligrams) for the 5 most commonly used ACE inhibitors at baseline (visit 1) and during the trial. *ACEi*, ACE inhibitor.

inhibitor for ≥30 days.[2] Investigators were given the target and mean achieved doses ACE inhibitors shown to be of benefit in randomized trials in HF and after myocardial infarction and asked to individually optimize ACE inhibitor treatment accordingly, that is, to aim for an evidence-based target dose or, failing that, the maximum tolerated dose of ACE inhibitor. The study had ethical approval at all centers, and each patient gave written informed consent.

Randomization, follow-up, and outcomes

Randomized treatment with candesartan or matching placebo was usually started at a dose of 4 mg once daily, and the dose was doubled at 2 weekly intervals, as tolerated, according to a forced titration protocol with recommended monitoring of blood pressure, serum creatinine, and potassium. The target dose was 32 mg once daily from 6 to 8 weeks onward (Figure 1).

The primary outcome in CHARM-Added was cardiovascular (CV) death or HF hospitalization. Other prespecified outcomes included death or HF hospitalization and all-cause mortality.

Subgroups

The 2 prespecified subgroup analyses divided patients into those taking (1) the recommended dose or more, or less than the recommended dose, of ACE inhibitor (based on the European Society of Cardiology guidelines, Table I) and (2) β-blocker or no β-blocker at baseline.[2]

Post hoc subgroup analyses were carried out according to

1. Baseline treatment with an FDA-recommended maximum dose of ACE inhibitor (communications, December 2004 and January 2005; Table II).
2. Maintenance of maximum dose of ACE inhibitor during follow-up, until an outcome event or final visit.
3. Baseline treatment with maximum dose of ACE and β-blocker.

Statistical methods

Hazard ratios (HRs) and corresponding 95% CIs for candesartan versus placebo analyses within ACE inhibitor dose

groups were derived from Cox proportional hazard models with only treatment in the model. The analyses were repeated adjusting for 32 prospectively defined potential confounding variables, as previously reported, with the exclusion of ACE inhibitor use as a covariate.[2] Tests for heterogeneity across subgroups were also conducted.

Results

The baseline characteristics of patients taking or not taking a maximum dose of ACE inhibitor (FDA recommendation, January 2005) are shown in Table II. Overall, there was little difference between patients in these 2 groups, though patients taking a higher dose of ACE inhibitor were more likely to have a history of hypertension.

Enalapril, lisinopril, captopril, ramipril, and trandolapril accounted for 80% of all ACE inhibitors used (Table II). The mean daily doses were 16.8, 17.7, 82.2, 6.8, and 2.5 mg in the candesartan group and 17.2, 17.7, 82.7, 7.3, and 2.4 mg in the placebo group. In the opinion of the site investigators, 96% of the patients were on an optimum individualized dose of ACE inhibitor. The dose was maintained during follow-up (Figure 1). A recommended dose of ACE inhibitor or more was used in 51% of the patients at baseline and maintained in 47% of the candesartan group and 50% of the placebo group at the 6 months' visit (after completion of the study drug titration).

Other treatments used at baseline (end of study) included β-blocker 55% (64% candesartan and 68% placebo) and spironolactone 17% (20% candesartan and 25% placebo).

Primary outcome in overall study and prespecified subgroups

Four hundred eighty-three (37.9%) patients in the candesartan and 538 (42.3%) in the placebo group experienced CV death or HF hospitalization (HR 0.85; 95% CI 0.75-0.96, $P = .011$ unadjusted, $P = .010$ covariate adjusted) (Figure 2). Candesartan reduced this risk in the 2 predefined subgroups with no evidence of heterogeneity of treatment effect.

Post hoc subgroups

The results of the analyses, using the 2 higher ACE inhibitor dose thresholds suggested by the FDA, are shown in Figures 2 and 3. Baseline dose of ACE inhibitor did not modify the effect of candesartan on any clinical outcome.

Similarly, maintenance of a maximum ACE inhibitor dose during study follow-up (Figure 4) or baseline treatment with a combination of both a maximum dose of ACE inhibitor and β-blocker did not modify the effect of candesartan (Figure 5).

Table II. Baseline characteristics of patients taking and not taking a maximum dose of ACE inhibitor (as defined by the FDA January 2005)

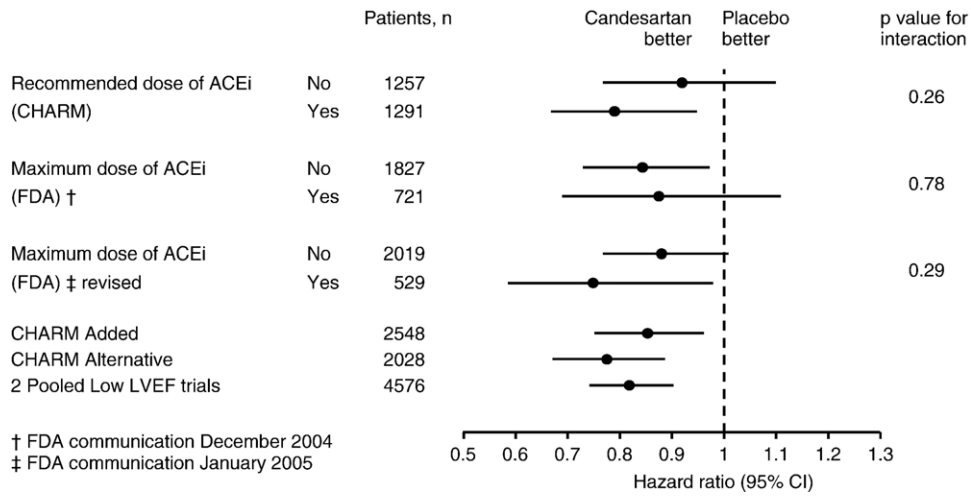
	Not maximum dose (n = 2019)	Maximum dose (n = 529)
Age (y)		
Mean (SD)	64 (11)	64 (11)
≥65 (%)	50	49
Sex		
Male (%)	78	81
Systolic BP (mm Hg)		
Mean (SD)	125 (18)	126 (20)
<100 (%)	4.9	6.2
100 to <140 (%)	69.3	66.5
≥140 (%)	25.8	27.2
Diastolic BP (mm Hg)		
Mean (SD)	75 (11)	75 (11)
<70 (%)	22.7	27.6
70 to <90 (%)	64.0	58.6
≥90 (%)	13.2	13.8
Etiology (%)		
Ischemic	64	56
Idiopathic	25	30
Hypertensive	5.8	9.1
NYHA class (%)		
II	25	22
III	72	76
IV	3.2	2.5
LVEF (%)		
Mean (SD)	30 (10)	30 (10)
Medical history (%)		
HF hospitalization	77	76
Myocardial infarction	57	50
Angina	53	52
Stroke	8.1	10.8
Hypertension	46	56
Diabetes mellitus	29	34
Atrial fibrillation	27	29
Concomitant medication (%)		
Diuretic	90	92
Digitalis glycoside	58	60
β-Blocker	55	59
Spironolactone	17	16
Baseline creatinine (mg/dL)		
≥2.0 (%)	5.4	3.9

BP, blood pressure.

Components of primary outcome

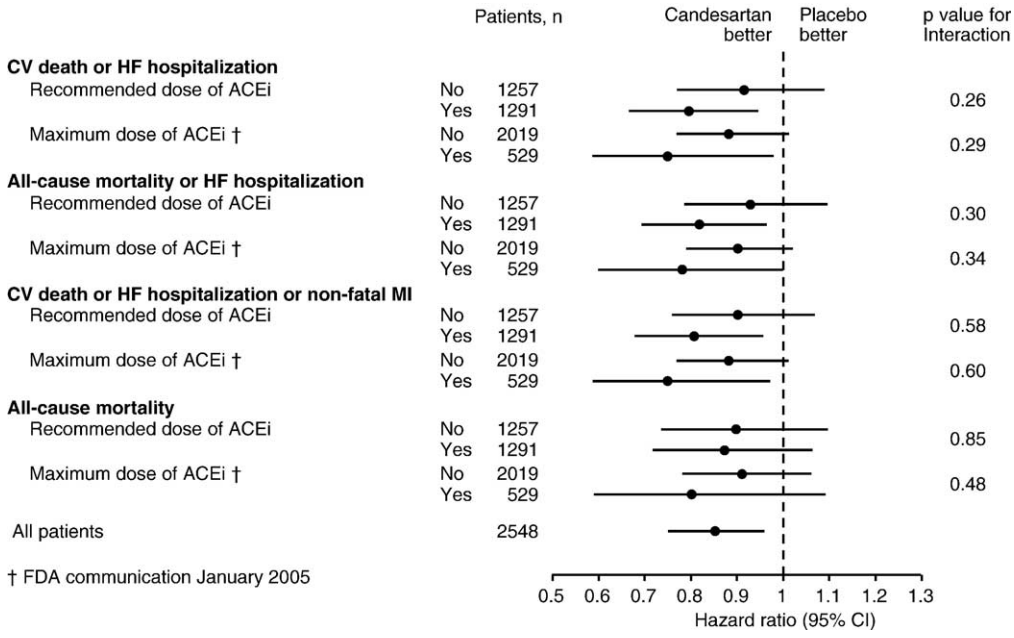
The HR for CV death was 0.864 (95% CI 0.727-1.027) in those not taking a maximum dose and 0.764 (95% CI 0.543-1.075) in those taking a maximum dose of ACE inhibitor. The HR for heart failure hospitalization was 0.865 (95% CI 0.728-1.029) in those not taking a maximum dose and 0.698 (95% CI 0.507-0.961) in those taking a maximum dose. In other words, the background ACE inhibitor dose did not modify the effect of candesartan on either component of the primary outcome.

Figure 2



Primary outcome of CV death or HF hospitalization for patients in CHARM-Added at recommended or higher dose of ACE inhibitor or maximum dose of ACE inhibitor as defined by the US FDA in the communication of December 2004 and as revised in January 2005. Also presented are the results for CHARM-Alternative (no ACEi) and the pooled results for these 2 trials in patients with low LVEF. *ACEi*, ACE inhibitor.

Figure 3

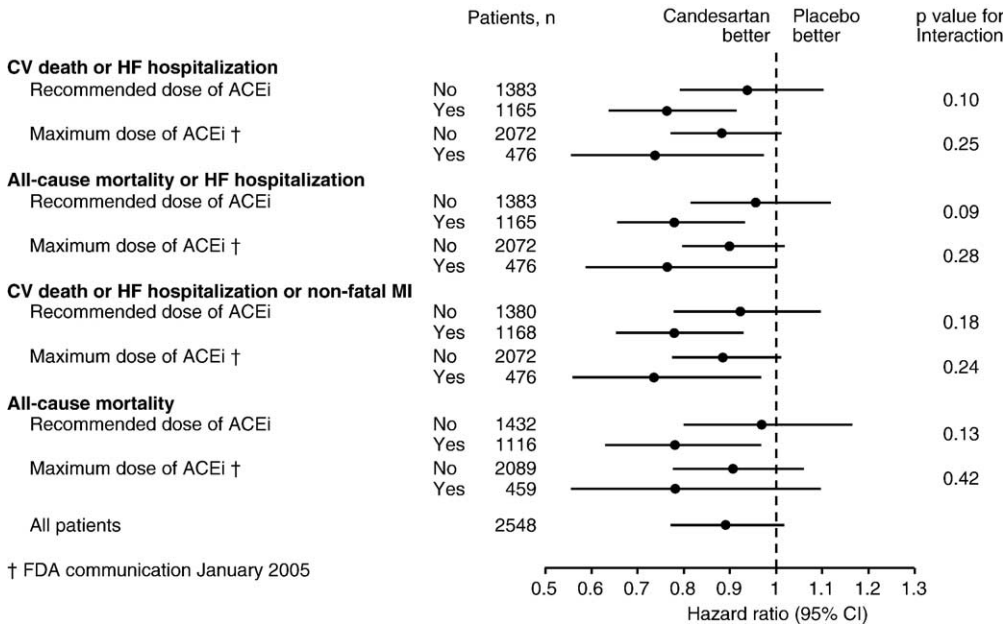


Outcome analyses based on recommended or higher ACE inhibitor dose at baseline, and maximum or higher (as defined by FDA in January 2005) ACE inhibitor dose at baseline.

Tolerability

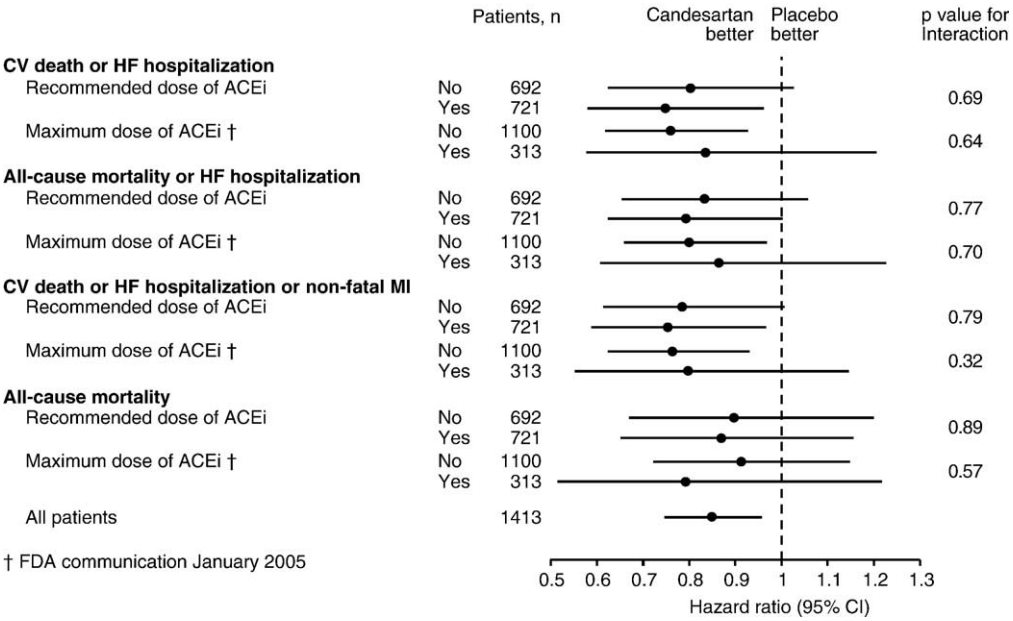
In CHARM-Added, the rates of study drug discontinuation in the candesartan and placebo groups were creatinine increase (7.8% vs 4.1%), hypotension (4.5% vs 3.1%), and hyperkalemia (3.4% vs 0.7%). These rates in the subgroup taking a maximum dose of ACE inhibitor (second definition) were 7.4% versus 8.1%, 4.5% versus 3.1%, and 4.1% versus 1.5%, respectively.

Figure 4



Outcome analyses in a subgroup of patients maintained at recommended or higher ACE inhibitor (ACEi) dose during the trial, and maximum or higher (as defined by FDA in January 2005) ACE inhibitor dose during the CHARM-Added trial.

Figure 5



Outcome analyses in the subgroup of patients taking a β-blocker at baseline (n = 1413) and either recommended or higher ACE inhibitor dose at baseline, or maximum or higher (as defined by FDA in January, 2005) ACE inhibitor dose at baseline.

Discussion

The CHARM investigators used evidence-based doses of ACE inhibitors, and there was a clinical benefit of adding candesartan irrespective of ACE inhibitor dose.

The most studied ACE inhibitor in HF (and most commonly used in CHARM-Added) is enalapril.[3-7] The target and mean achieved daily doses in the 5 large trials that used forced titration were CONSENSUS (target 20 mg BID, mean achieved daily dose 18.4 mg), SOLVD-Treatment (T) (10 mg BID, 16.6 mg), V-HeFT II (10 mg BID, 15.0 mg), OVERTURE (10 mg BID, 17.7 mg), and CARMEN (10 mg BID, 16.8 mg, and 14.9 mg in the group receiving active treatment with the β-blocker carvedilol).[3-7] In CHARM-Added, the mean daily dose was 17.0 mg. The doses of ACE inhibitor used in CHARM-Added exceed those in other recent add-on trials in HF (eg, daily enalapril dose of 15 mg in RALES and 14 mg in MERIT-HF) and greatly exceed those used in clinical practice (weighted mean daily dose of enalapril from 13,764 patients in 7 community and hospital studies 13.8 mg).[8-10] The dose of ACE inhibitor was maintained during follow-up in the candesartan group in CHARM-Added. Despite all of these, there was a benefit from adding candesartan.

Could the same benefit have been obtained by increasing the dose of ACE inhibitor, above those shown to be effective in prior trials? This hypothetical question has 2 parts. First, would patients tolerate higher doses? Other than the data from the large randomized trials such as SOLVD-T in which 51% of the patients could not be titrated up to 10 mg of enalapril twice daily (despite an active run-in period), there is very little other information on this subject.[4] The mean achieved daily dose of enalapril (18.4 mg) in CONSENSUS where the target dose was 20 mg BID was only slightly higher than in SOLVD-T (16.6 mg)[3], and only 22% of patients reached the target dose. Some patients can tolerate larger doses, but how representative these are of all patients with HF is unknown. Of greater importance is the second part of the question; that is, even if patients can be titrated to higher than evidence-based doses of ACE inhibitors, will this lead to greater clinical benefit? Only one trial compared an evidence-based dose to a higher dose, randomizing 248 patients with symptomatic HF and left ventricular ejection fraction (LVEF) ≤35% to enalapril 20 or 60 mg daily.[11] The mean doses achieved were 17.9 and 42.5 mg daily, respectively (72.5% and 32.5%, respectively, reached the target dose by 3 months). After 12 months, there was no difference in mortality or morbidity between the 2 treatment groups, although the number of events was small. There was also no statistically significant or clinically meaningful difference in blood pressure, heart rate, left ventricular ejection fraction, or NYHA functional class.

Overall, therefore, the effect of candesartan was similar in patients taking no ACE inhibitor (CHARM-Alternative), a moderate dose of ACE inhibitor (all patients in CHARM-Added), or a high dose of ACE inhibitor (maximum dose subgroup analysis of CHARM-Added). These findings support the pharmacologic evidence that ACE inhibitors and ARBs have distinct mechanisms of action and that, clinically, these 2 classes of drug can complement each other in a way that improves outcomes in patients with HF. A more stringent test of this hypothesis, however, would be a prospective randomized comparison of the effect of adding either additional ACE inhibitor or an ARB on clinical outcomes in patients with HF.

In summary, candesartan is beneficial in patients with HF receiving conventional treatment, including a β-blocker, irrespective of background dose of ACE inhibitor. Moreover, the addition of the ARB candesartan improves outcomes beyond those achievable with even an optimal or maximum dose of ACE inhibitor.

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