Acute and 3-month treatment effects of candesartan cilexetil on hemodynamics, neurohormones, and clinical symptoms in patients with congestive heart failure

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Background This study evaluated the short-term and long-term effects of the angiotensin II type 1 receptor antagonist candesartan cilexetil on hemodynamics, neurohormones, and clinical symptoms in patients with congestive heart failure (CHF).

Methods In this multicenter, double-blind, parallel-group study, 218 patients with CHF (New York Heart Association class II or III) with impaired left ventricular function (ejection fraction ≤40%) and pulmonary capillary wedge pressure ≥13 mm Hg were randomly assigned to 12 weeks of treatment with placebo (n = 44) or candesartan cilexetil (2 mg [n = 45], 4 mg [n = 46], 8 mg [n = 39], or 16 mg [n = 44]) once daily after a 2-week placebo run-in period. Hemodynamic measurements were performed by right heart catheterization over a 24-hour period after single (day 1) and repeated (3-month) treatment with the study drug.

Results On regression analysis of the time-response curves, single and multiple doses of candesartan cilexetil produced sustained, significant, and dose-dependent reductions in pulmonary capillary wedge pressure (short-term effect $P = .036$, long-term effect $P = .035$) and mean pulmonary arterial pressure (short-term effect $P = .031$, long-term effect $P = .042$). Systemic vascular resistance showed a trend toward decreasing with dose on short-term and long-term treatments. No consistent changes were seen in cardiac index. Compensatory increases in plasma renin activity and angiotensin II levels with decreases in aldosterone and atrial natriuretic peptide were dose-dependent and significant. Candesartan cilexetil improved clinical symptoms, stabilized patient New York Heart Association status compared with placebo, and was judged to be an efficacious treatment by the investigators. More patients receiving placebo stopped the trial prematurely because of an adverse event than in any candesartan cilexetil group, and there was no excess of deaths in any treatment group. Candesartan was safe and well tolerated at all dosages.

Conclusions Candesartan cilexetil demonstrated significant short-term and long-term improvements in hemodynamic, neurohormonal, and symptomatic status and was well tolerated in patients with CHF. (Am Heart J 2003;145:e14.)

Congestive heart failure (CHF) is associated with hemodynamic abnormalities and neurohormonal activation.[1,2] The renin-angiotensin-aldosterone system is activated[3,4] in CHF, and blockade has been proven to improve symptoms and survival.[5,6]

Recent hemodynamic and neurohumoral evaluation indicates that angiotensin II receptor antagonists can be beneficial in the treatment of CHF.[7,8] Candesartan cilexetil is a long-acting angiotensin II type 1 receptor antagonist[9] that has been shown to be safe and efficacious in the treatment of hypertension and to improve exercise tolerance and symptoms in CHF.[10]

This 3-month, placebo-controlled study investigated the effects of candesartan cilexetil on hemodynamic, neurohormonal, and symptomatic responses in patients with CHF with impaired left ventricular function.

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Methods

Study population

White patients of either sex (aged 18-75 years) with mild-to-moderate symptomatic CHF (New York Heart Association class II or III) and impaired left ventricular function (ejection fraction ≤40%) who provided written informed consent were enrolled. Patients had to have pulmonary capillary wedge pressure (PCWP) ≥13 mm Hg at baseline. The study was conducted according to the Declaration of Helsinki, the European guidelines of Good Clinical Practice, and the patient information leaflet. Relevant national and regional ethics committees approved the consent forms.

Study design

This was a phase II, double-blind, placebo-controlled, multicenter, parallel-group study. After a 2-week placebo run-in period, eligible patients were randomly assigned at baseline to 1 of 5 parallel treatment groups (2, 4, 8, or 16 mg candesartan cilexetil or placebo) for 12 weeks. In view of the placebo treatment group, the patients or their physicians could stop their medication any time during the study. To avoid the random assignment of unstable patients, they could be excluded at any time during the run-in phase and treated appropriately by their physician. To further safeguard patient safety, the whole study period was scrutinized by an expert independent safety committee comprising a cardiologist, a statistician, and an epidemiologist. After patients received their randomized first dose, the single-dose safety and efficacy assessments were performed. On the following day, all patients received 2 mg candesartan cilexetil (or placebo), and treatment was subsequently uptitrated by doubling the dose at weekly intervals over a 3-week period to reach the respective randomized dose in which patients were maintained for the rest of the study. Study medication was taken orally once daily.

Concomitant background heart failure therapy was to be kept constant from the screening visit throughout the study. The intake of digitalis, diuretics, and short-acting nitrates was withheld on days of catheterization; long-acting nitrates had to be stopped at least 1 day before catheterization.

Treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT_1) antagonists (other than the study medication), agents used for the treatment of angina (other than short-acting nitrates), psychotropics, potassium-sparing diuretics, anti-inflammatory drugs, antiarrhythmics (other than amiodarone), and renin inhibitors were not permitted.

Efficacy assessment

The primary efficacy parameters were PCWP, systemic vascular resistance (SVR), and cardiac index. Secondary parameters were mean pulmonary arterial pressure (PAP), mean right atrial pressure (RAP), mean arterial blood pressure, heart rate, neurohormones, symptom scores for breathlessness, fatigue and ankle swelling, physicians' overall efficacy score, NYHA classification, and quality of life using the validated measure of the subjective health status SF-36 questionnaire.[11] Safety parameters included adverse events, vital signs, 12-lead electrocardiogram, and laboratory parameters.

Hemodynamic parameters were measured by right heart catheterization at the baseline visit (visit 2) and after 12 weeks of treatment (visit 6), following a standardized procedure. A 7.5F thermodilution Swan-Ganz catheter was placed not <3 hours before medication, and 2 readings were obtained at 30 minutes before and immediately before administration of the study medication. Patients were randomly assigned, in case the variability of PCWP between these 2 readings was <10% or further readings verified hemodynamic stability. The last value before drug intake was to be used as the baseline value at visit 2. PCWP was read as an electronic mean over a 12-second period. PAP and PCWP measurements were taken at end-expiration with the catheter in the pulmonary artery, 1 minute after flushing. RAP was measured by use of electronic integration of the RAP waveform, 1 minute after flushing the catheter. Three separate readings were obtained for each parameter and averaged. Cardiac output was measured by thermodilution technique (in a few centers with the Fick principle),[11] taking the mean of 3 readings, or in the case of a >10% variability, 5 measurements. SVR and cardiac index were calculated by standard formulas.[12]

Mean systolic and diastolic blood pressures were determined by averaging 3 consecutive measurements obtained at intervals of at least 2 minutes (standard sphygmomanometer, standardized procedure).

Blood sampling for neurohormonal measurement, assessments of quality of life (SF-36 questionnaire), symptom scores for breathlessness, fatigue and ankle swelling (Visual Analogue Scale), NYHA classification, and heart rate measurement were performed at baseline and after 12 weeks. At the end of the study, the investigator rated the patient response to blinded treatment as "very good/good," "satisfactory," "poor," or "not assessable."

Neurohormones were sampled in a standardized procedure, stored under appropriate conditions (−70°C), and centrally analyzed. Plasma renin activity, angiotensin II, aldosterone, and atrial natriuretic peptide were measured by radioimmunoassay and adrenaline and noradrenaline by high-pressure liquid chromatography.

Tolerability

Adverse events were recorded at each visit, regardless of their relation to the study medication. Laboratory safety parameters were assessed at study enrollment, at baseline, and after 6 and 12 weeks of randomized treatment.

Statistical analysis

In this early phase II study, the sample size of 35 patients per group was based on clinical considerations. For all hemodynamic parameters and neurohormonal variables, mean time-response curves were generated, and area under the curve (AUC) from time 0 (immediately before administration of study drug) to 8 hours after administration of the drug ($AUC_{0\text{-}8h}$) was derived by use of the linear trapezoidal rule. Derived $AUC_{0\text{-}8h}$ values and the values obtained 4 hours after administration of the drug (estimated c_{max} of candesartan cilexetil) were submitted to linear regression analysis and to a 1-way analysis of covariance, with the last available predose value at visit 2 being the covariant.

Results obtained for the physicians' assessment of efficacy score were compared between each active treatment group

Table I. Baseline demographic and clinical characteristics, Safety population (n = 218)

Characteristic	Placebo (n = 44)	CC 2 mg (n = 45)	CC 4 mg (n = 46)	CC 8 mg (n = 39)	CC 16 mg (n = 44)
Sex (%)					
Male	35 (79.5)	32 (71.1)	43 (93.5)	36 (92.3)	40 (90.9)
Female	9 (20.5)	13 (28.9)	3 (6.5)	3 (7.7)	4 (9.1)
Age (y)	58.0 ± 11.8	55.7 ± 10.2	54.4 ± 11.6	45.0 ± 10.0	55.7 ± 11.8
<65 (%)	26 (59.1)	37 (82.2)	37 (80.4)	34 (87.2)	33 (75.0)
≥65 (%)	18 (40.9)	8 (17.8)	9 (19.6)	5 (12.8)	11 (25.0)
Ejection fraction* (%)	29.7 ± 5.8	22.8 ± 8.0	29.0 ± 6.8	30.0 ± 6.7	29.1 ± 6.1
CHF duration (y)	3.7 ± 3.6	2.9 ± 3.8	3.2 ± 4.6	3.5 ± 4.0	3.2 ± 4.0
PCWP (mm Hg)	19.4 ± 5.8	16.2 ± 4.6	19.9 ± 5.9	18.5 ± 4.5	19.0 ± 5.6
NYHA class (%)					
II	26 (59.1)	31 (68.9)	26 (56.5)	21 (53.8)	30 (68.2)
III	18 (40.9)	14 (31.1)	20 (43.5)	18 (46.2)	14 (31.8)

Values are presented as mean ± SD unless otherwise indicated.
*Investigator readings.

and placebo by means of the Wilcoxon-Mann-Whitney test. Results of the NYHA classification were analyzed with a transition table at baseline and at visit 6.

The safety population was defined as all patients with at least one intake of study medication; the intention-to-treat (ITT) population was defined as all patients in the safety population who had a baseline and at least one postbaseline efficacy assessment; and the per protocol (PP) population was defined as the ITT population but without major protocol violations.

Results

Two hundred sixty-two patients were enrolled. Two hundred eighteen evaluable patients were randomly assigned to treatment with placebo (n = 44) or candesartan cilexetil (CC) (2 mg [n = 45], 4 mg [n = 46], 8 mg [n = 39], or 16 mg [n = 44]). Twenty-nine patients discontinued prematurely, with the greatest proportion of withdrawals recorded for the placebo (n = 10) and the 2 mg candesartan cilexetil treatment groups (n = 7).

Twelve patients with major protocol violations were excluded from the PP population. There were no relevant group differences regarding number or pattern of major violations.

Overall, the main demographic and baseline characteristics of the safety population were generally similar across groups (Table I), although in the 2 mg candesartan cilexetil group, duration of CHF and PCWP was slightly lower. The proportion of female patients was highest in the placebo and the 2 mg groups, and the mean age was lowest in the 8 mg candesartan cilexetil group. There were more elderly patients in the placebo group. In all groups, the principal causes of CHF were coronary heart disease and/or cardiomyopathy. The most frequently prescribed previous treatments for CHF were diuretics, cardiac glycosides, antiarrhythmics, agents acting on the renin angiotensin system, and antithrombotics; no substantial differences between the groups were observed regarding concomitant disease or medication (Table II).

Analysis of efficacy: Results

Because the results for the ITT and the PP analysis were very similar, only results from the ITT population are presented.

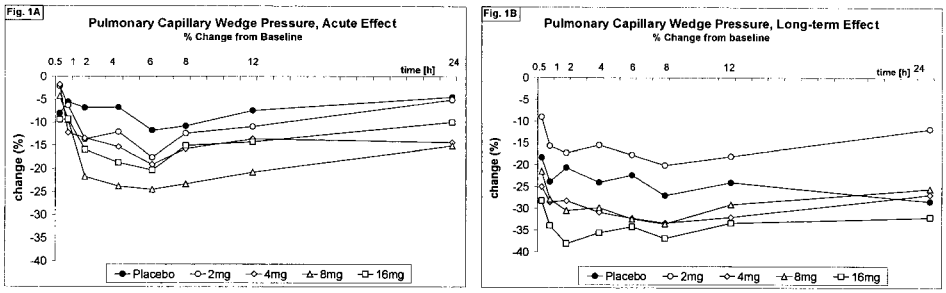
Hemodynamic parameters. After oral single-dose administration, an initial fall in mean PCWP in all treatment groups was observed that was greatest after ~6 hours (Figure 1, *A*). After 3 months of treatment, mean PCWP values in all treatment groups were considerably lower than those after first-dose administration. Decreases were largest in the 16-mg candesartan cilexetil group (Figure 1, *B*).

Regression analysis for the $AUC_{0\text{-}8h}$ values (Figure 2, *A*) and for the 4-hour postdose recordings after single-dose and multiple-dose administration showed a consistent, statistically significant dose-dependent effect on PCWP (Table III).

The pairwise comparison of PCWP $AUC_{0\text{-}8h}$ and 4-hour postdose (estimated c_{max} of candesartan cilexetil) values obtained after single dosing and after 3-month treatment showed statistically significant decreases for the 8 mg and 16 mg candesartan cilexetil groups after single-dose administration, and approached significance for 16 mg after 3 months of treatment (Table IV).

Mean PAP results were consistent with those observed for PCWP. The regression analysis revealed significant treatment effects in terms of a reduction of PAP on both assessment days (Figure 2, *B,* Table III). The pairwise comparison showed statistically significant reductions in $AUC_{0\text{-}8h}$ for all candesartan cilexetil groups except for the 2 mg group after single-dose administration (CC [cande-

Figure 1



PCWP, time-response curves, and change from baseline (baseline = 0 hour at visit 2) treatment effect after single-dose administration (**A,** short-term) and multiple-dose administration (**B,** long-term) in the ITT population.

Table II. Percentage of patients with relevant concomitant medications at baseline: Safety population (n = 218)

Therapeutic main group	Placebo (n = 44)	CC 2 mg (n = 45)	CC 4 mg (n = 46)	CC 8 mg (n = 39)	CC 16 mg (n = 44)
Cardiac therapy	90.9	97.8	84.8	87.2	95.5
Cardiac glycosides	81.8	77.8	65.2	79.5	77.3
Vasodilators	29.5	44.4	47.8	35.9	54.5
Antiarrhythmics	36.4	24.4	28.3	33.3	31.8
Other cardiac preparations	6.8	6.6	-	5.1	2.3
Diuretics	90.9	93.3	89.1	94.9	88.6
Antithrombotic agents	75.0	84.4	82.6	84.6	88.6
Mineral supplements	52.3	46.7	39.1	51.3	47.7
Drugs used in patients with diabetes	15.9	11.1	17.4	15.4	18.2
Plsma substitutes and perfusion solutions	18.2	11.1	4.3	12.8	9.1
Antihypertensives	2.3	13.3	8.7	12.8	6.8

CC, Candesartan citexetil.

sartan cilexetil]: 4 mg, $P = .021$; 8 mg, $P = .003$; 16 mg, $P = .010$) and for the 16 mg group after multiple-dose administration ($P = .047$). After single-dose administration, 8 mg and 16 mg candesartan cilexetil also produced significantly greater reductions than placebo in mean PA pressure 4 hours after dosing ($P = .006$ and $P = .018$, respectively).

SVR tended to decrease with dose on both single and multiple dosing (Figure 2, *C*). On single dosing, the pairwise comparison revealed statistically significant differences with respect to placebo for $AUC_{0\text{-}8h}$ ($P = .011$, 8 mg candesartan cilexetil), and for both 8 mg and 16 mg at the 4-hour value after dosing ($P = .015$, $P = .030$, respectively). The differences between candesartan cilexetil and placebo did not reach statistical significance at 3 months.

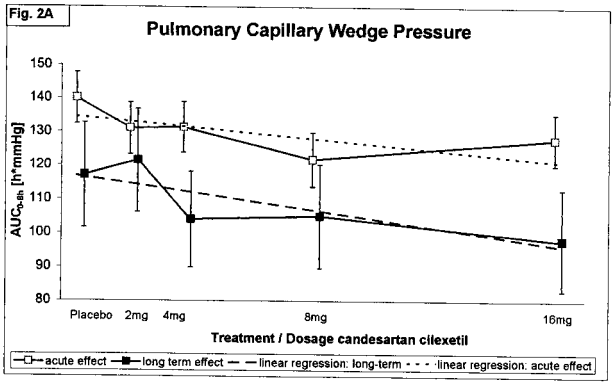
No statistically significant changes were observed in cardiac index or RAP.

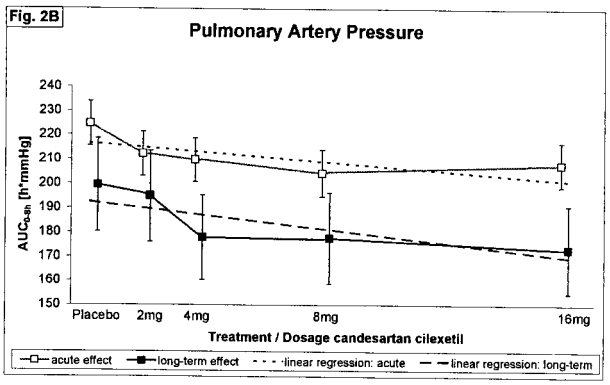
Neurohormonal variables. Consistent with the known pharmacologic action of angiotensin II receptor antagonists, increases in mean plasma renin activity and angiotensin II levels and a decrease of aldosterone plasma concentrations were observed (Figure 3, *A-D*), with statistically significant dose-dependent effects both acutely and after 3 months of treatment (ANF decreased at 3 months, only) (Table V). There was no significant effect on mean plasma noradrenaline or adrenaline.

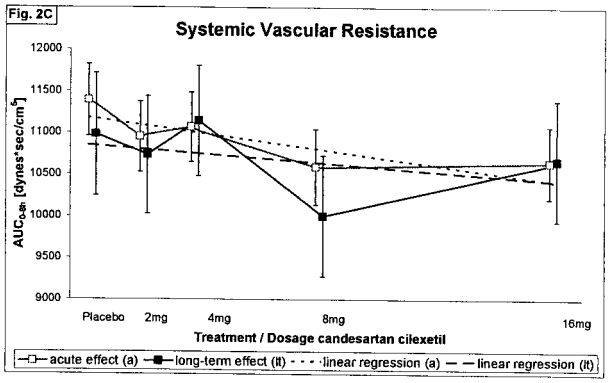
Clinical symptoms, symptom and efficacy scores. After 3 months of treatment, significant improvements of CHF symptoms "breathlessness" (16 mg CC, $P = .034$) and "tiredness/fatigue" (4 mg, $P = .025$; 8 mg, $P = .045$; 16 mg, $P = .051$), as assessed by patients using a visual analogue scale, were observed in comparison with placebo. There were no significant effects on the parameter "swollen ankle."

After 3 months of treatment, the change in patient clinical symptoms categorized by NYHA functional class was maintained or improved in more patients in all candesartan cilexetil treatment groups compared

Figure 2







PCWP **(A),** PAP **(B),** SVR **(C),** $AUC_{0\text{-}8h}$ (adjusted mean ± 95% CI), regression analysis, and short-term and long-term effects in the ITT population. Superimposed *hatched line* represents line of regression for both data sets.

with placebo (placebo, 92.5%; CC: 2 mg, 97.4%; 4 mg, 95.5%; 8 mg, 94.6%; 16 mg, 100%). The only patients deteriorating to NYHA class IV were observed in the placebo group, whereas the only treatment group without any deterioration of NYHA class was the 16 mg candesartan cilexetil group.

Table III. Hemodynamics—regression analysis: ITT-population (n = 218)

	$AUC_{0\text{-}8h}$ [h×dynes×sec/cm^5]	4 hours postdose [dynes×sec/cm^5]
PCWP		
Acute effect	.036	.009
Chronic effect	.035	.040
PAP		
Acute effect	.031	.037
Chronic effect	.042	.089
SVR		
Acute effect	.194	.036
Chronic effect	.324	.872

Values denote *P* values for the deviation from zero of the slope of the regression line.

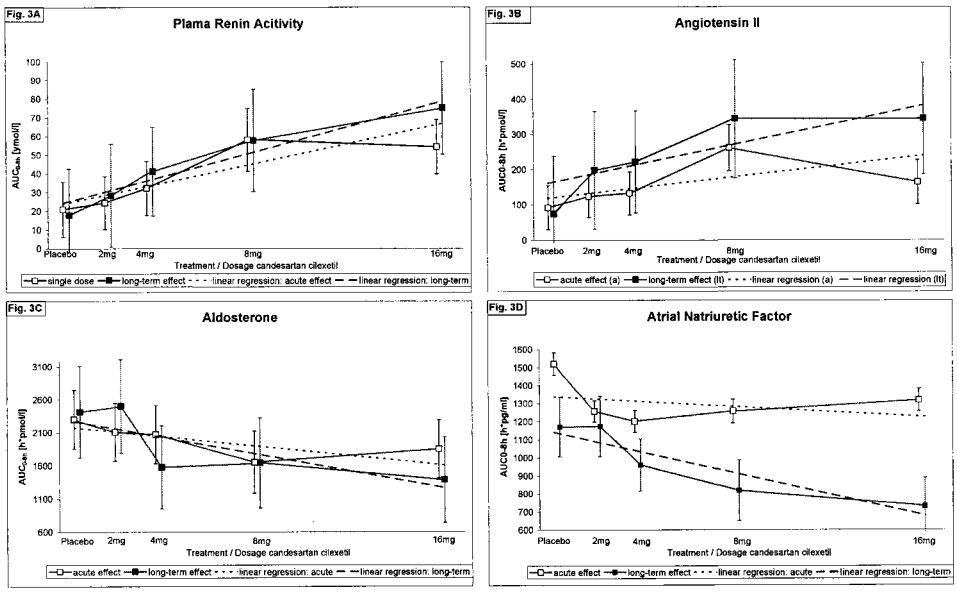
Quality of life assessment (SF-36 questionnaire) revealed a statistically significant improvement compared with placebo for the categories reflecting physical activity ("physical functioning": 4 mg, $P = .043$, and 16 mg, $P = .043$; "role-functioning–physical": 16 mg, $P = .036$). There were also improvements seen in the categories "social functioning," "vitality," and "change of health," which did not reach statistical significance. No changes could be observed in the categories "bodily pain," "mental health," "general health perception," and "role functioning–emotional."

Analysis of efficacy assessment by the investigating physicians after 3 months of treatment revealed a dose-dependent benefit of candesartan cilexetil compared with placebo. The proportion of patients rated as "very good/good" increased from 25% in the placebo group up to 48% in the 16 mg candesartan cilexetil group (2 mg, 31%; 4 mg, 39%; 8 mg, 44%). Conversely, ratings of "poor" were higher in the placebo group (21%) than in all candesartan cilexetil treatment groups (2 mg, 16%; 4 mg, 13%; 8 mg, 9%; 16 mg, 9%).

Safety evaluation. During the run-in period, 31 patients had 32 adverse events, 12 of which were considered serious. During the 12 weeks of randomized treatment, 111 patients reported a total of 264 adverse events. The majority of adverse events were classified as mild in all treatment groups. The proportion of patients reporting at least one adverse event was lower in all candesartan cilexetil groups (2 mg, 47%; 4 mg, 41%; 8 mg, 51%; 16 mg, 57%) than in the placebo group (59%). The most common adverse events are displayed in Table VI.

In total, 17 patients were withdrawn because of adverse events (placebo: n = 6; CC: 2 mg, n = 4; 4 mg, n = 1; 8 mg, n = 3; 16 mg, n = 3), and 31 patients had serious adverse events (SAE), of which 7 resulted in death (placebo: n = 2; CC: 2 mg, n = 2, 1 each in the other treatment groups). All deaths were cardiac in

Figure 3



Neurohormones: Plasma renin activity **(A),** angiotensin II **(B),** aldosterone **(C),** and atrial natriuretic factor **(D);** $AUC_{0\text{-}8h}$ (adjusted mean ± 95% CI), regression analysis, and short-term and long-term effects in the ITT population. Superimposed *hatched line* represents line of regression for both data sets.

Table IV. PCWP, pair wise group comparison, one-way ANCOVA: ITT-population (n = 218)

	$AUC_{0\text{-}8}$ (mm Hg × h)			4 hours postdose (mm Hg)		
Dosage/effect	**a.m.d.**	**95% CI**	***P***	**a.m.d.**	**95% CI**	***P***
2 mg						
Acute	−9.08	−19.93, 1.77	.100	−1.56	−3.29, 0.16	.076
Chronic	4.34	−17.31, 25.98	.693	0.26	−2.55, 3.08	.854
4 mg						
Acute	−8.74	−19.31, 1.83	.104	−1.56	−3.24, 0.12	.069
Chronic	−13.07	−33.77, 7.64	.215	−2.15	−4.84, 0.54	.117
8 mg						
Acute	−18.26	−29.29, −7.23	.001	−3.37	−5.12, −1.61	<.001
Chronic	−12.08	−33.66, 9.50	.271	−2.13	−4.94, 0.67	.136
16mg						
Acute	−12.24	−22.92, −1.55	.025	−2.35	−4.06, −0.65	.007
Chronic	−19.14	−40.42, 2.14	.078	−2.54	−5.30, 0.23	.072

Data represent the results of a pair wise comparison with the last available predosing value as covariate. *a.m.d,* Adjusted mean difference; *acute,* effect after single dose administration; *chronic,* effect after 3 months treatment.

origin, and one was considered to be probably related to the trial drug (2 mg candesartan cilexetil). There were more SAEs in the placebo group (n = 18) compared with the candesartan cilexetil groups (2 mg, n = 5; 4 mg, n = 3; 8 mg, n = 3; 16 mg, n = 2). Two SAEs in the 2 mg candesartan cilexetil group (atrial fibrillation and hypotension) and one event in the 8 mg candesartan cilexetil group (decompensation of left heart failure) were thought to be at least possibly related to the study medication. There were 10 adverse events leading to hospitalization in the placebo group compared with candesartan cilexetil (2 mg, n = 7; 4 mg, n = 3; 8 mg, n = 6; and 16 mg, n = 5).

No clinically relevant changes in laboratory safety parameters were observed. One patient (16 mg CC) had an electrocardiographic abnormality that was reported as an SAE and not related to study medication. However, one patient (16 mg CC) did have an electrocardiographic abnormality reported as an SAE that was judged to be related to the study medication.

Discussion

Until data are available from the outcome trials with angiotensin II receptor antagonists, which are planned or underway,[13,14] effects of angiotensin II receptor antagonists on hemodynamics, neurohormones, and signs and symptoms of CHF are the only clinical markers for evaluating this therapeutic approach in the treatment of CHF.

Hemodynamic effects

This double-blind, placebo-controlled study clearly demonstrates that treatment with candesartan cilexetil can improve the hemodynamic, neurohormonal, and symptomatic status in patients with chronic symptomatic CHF and left ventricular dysfunction.

Candesartan cilexetil significantly decreased PCWP and PAP in a dose-dependent manner after the first dose administration. This effect was sustained over the treatment period of 3 months and reflects an improvement in ventricular function. On regression analysis, there was a tendency for SVR to decrease with dose after single-dose administration. Differences in methods of calculation (Fick-principle, thermodilution) and types of equipment used may be responsible for the absence of detectable effects on cardiac output and subsequent calculation of cardiac index in this multicenter study.

Neurohumoral changes

Consistent with the known pharmacologic mode of action of a selective AT_1 receptor antagonist, treatment with candesartan cilexetil led to a compensatory increase of angiotensin II and plasma renin activity and a corresponding decrease of aldosterone plasma concentration, demonstrating sustained and effective blockade over the treatment period. Decreases of plasma aldosterone levels have been shown to be associated with beneficial effects on mortality and morbidity in patients with CHF.[15] In addition to the desired inhibition of the deleterious effect of angiotensin II on the cardiovascular system at the AT_1 receptor, stimulation of the AT_2 receptor is believed to be beneficial as the result of vasodilation caused by activation of the NO/cGMP system.[16]

The observed decrease of atrial natriuretic peptide, a prognostic marker in CHF, in all treatment groups except the placebo group is consistent with the significant reduction seen in PCWP reflecting improvement in left ventricular end-diastolic pressure and function.

Table V. Neurohormones—regression analysis: ITT-population (n = 218)

	Acute effect *P*	Chronic effect *P*
Plasma renin activity		
$AUC_{0\text{-}8}$	.0002	.0007
4 hours after dosing	.0019	.0312
Angiotensin II		
$AUC_{0\text{-}8}$	.0389	.0211
4 hours after dosing	.1522	.0325
Aldosterone		
$AUC_{0\text{-}8}$	.1640	.0206
4 hours after dosing	.0281	.0352
Atrial natriuretic factor		
$AUC_{0\text{-}8}$	.5578	.0018
4 hours after dosing	.5100	.0014

P values for the deviation from zero of the slope of the dose dependence. *Acute,* Effect after single dose administration; *chronic,* effect after 3 months treatment.

The beneficial effect of candesartan cilexetil on the hemodynamic and neurohumoral variables was associated with statistically significant improvements in CHF-specific symptoms (breathlessness and tiredness/fatigue) and with a stabilization and improvement of the clinical status in terms of NYHA classification compared with placebo. These findings were supported by the results of the physicians' efficacy assessment and by quality-of-life assessment, which revealed significantly higher scores for the active drug than placebo for categories reflecting physical capability.

Candesartan cilexetil was safe and well tolerated in this study, with an overall incidence and profile of adverse events comparable to placebo.

The data demonstrate that candesartan cilexetil provides an effective and long-lasting blockade of the renin-angiotensin-aldosterone system in CHF, which leads to beneficial changes in clinical symptoms and the hemodynamic status with an overall benefit in the treatment of such patients. The results of this study on symptoms are consistent with those of a previous 3-month trial in which candesartan cilexetil significantly improved exercise tolerance and clinical symptoms in patients with CHF.[10]

In summary, candesartan cilexetil produces sustained dose-dependent beneficial effects on hemodynamic and neurohormonal parameters and on clinical symptoms in patients with CHF.

Limitations

One of the major limitations of this study is the absence of a control patient collective receiving ACE inhibitors.

Table VI. Number (%) of patients with adverse events during randomized treatment in >5% patients in any treatment group and adverse events relevant to heart failure: Safety population (n = 218)

Adverse event	Placebo (n = 44)	CC 2 mg (n = 45)	CC 4 mg (n = 46)	CC 8 mg (n = 39)	CC 16 mg (n = 44)	Total (n = 218)
Dyspnoea	3 (6.8)	7 (15.6)	2 (4.3)	3 (7.7)	2 (4.5)	17 (7.8)
ECG Abnorm.*	4 (9.1)	7 (15.6)	2 (4.3)	1 (2.6)	3 (6.8)	17 (7.8)
Cardiac failure	5 (11.4)	1 (2.2)	–	1 (2.6)	2 (4.5)	9 (4.1)
Liver function†	4 (9.1)	1 (2.2)	1 (2.2)	1 (2.6)	1 (2.3)	8 (3.7)
URTI	3 (6.8)	1 (2.2)	1 (2.2)	2 (5.1)	–	7 (3.2)
Oedema, peripheral	2 (4.5)	1 (2.2)	1 (2.2)	1 (2.6)	1 (2.3)	6 (2.8)
Hyperuricaemia	1 (2.3)	–	–	–	3 (6.8)	4 (1.8)
Hypotension	–	2 (4.4)	–	1 (2.6)	1 (2.3)	4 (1.8)
Sinusitis	–	–	–	2 (5.1)	1 (2.3)	3 (1.4)
Angina pectoris	–	1 (2.2)	–	–	2 (4.5)	3 (1.4)

URTI, Upper respiratory tract infection.
*ECG abnormalities lumping of adverse events, atrial fibrillation, bradycardia, bigeminy, bundle branch block, and ventricular extrasystole.
†Abnormal result in liver function tests.

Preferentially, patients showing an intolerance toward ACE inhibitors or patients without ACE inhibitor therapy were included. By reason of a randomization ratio of 4:1, 20% of the patients under therapy with digitalis, diuretics, and vasodilators received a placebo for a period of 3 months. They all showed a clinically stable condition and underwent close clinical controls. Therefore, the inclusion of a placebo group was accepted by all ethic committees except for one. Clinical routine with reference to ACE inhibitor therapy in patients with CHF shows that one third of patients do not undergo therapy at all, and another third of patients receive ACE inhibitors in too-low doses, leaving only one third of patients optimally treated with ACE inhibitors.

The number of patients needed to treat in the SOLVD treatment trial examining patients in NYHA classes II to III with an ejection fraction of <35% (that is, a patient collective similar to that of the present study) was 22. This means 22 patients were treated with enalapril for a period of 3 years to save 1 life.[5]

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