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Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure☆

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Abstract

Background: Candesartan cilexetil is a new angiotensin II receptor blocker with a high affinity for the angiotensin II-subtype 1 receptor. *Aims:* This 6-month study examined the safety and efficacy of candesartan cilexetil, 8 mg once daily, to prevent the progression of congestive heart failure (CHF). *Methods:* This randomised, double-blind, placebo-controlled study enrolled 305 patients with CHF who were not receiving ACE inhibitor therapy. The composite primary efficacy endpoint was progression of CHF or addition or dose escalation of CHF medications. The secondary endpoints were incidence of cardiovascular events and changes in left ventricular function. *Results:* The study was prematurely terminated after the second interim safety analysis. The incidence of confirmed progression of CHF was significantly lower in the candesartan group (7.4%) than in the placebo group (22.2%), with a risk reduction of 66.7% and a risk difference of −14.8% (95% CI: −22.8 to −6.8%, $P<0.001$). Cardiovascular events were also significantly lower during treatment with candesartan than with placebo (10.8% vs. 22.9%) with a risk reduction of 52.8% and a risk difference of −12.1% (95% CI:−20.6 to −3.6%, $P<0.01$). The actively treated group had a significant improvement in hemodynamics. Candesartan was well tolerated. *Conclusion:* Candesartan cilexetil, 8 mg/day, significantly reduced the progression of CHF when compared with placebo.

Keywords: Candesartan cilexetil; Congestive heart failure; Randomised study; RAS inhibition

1. Introduction

Chronic congestive heart failure (CHF) is a growing health issue that remains associated with a high morbidity and mortality despite several important therapeutic advances [1–4]. In addition, the need to frequently rehospitalise patients for management of CHF represents a considerable socioeconomic burden [5]. Among the treatment options available, pharmacologic modulation of the renin-angiotensin system has been particularly successful [6–8]. Candesartan cilexetil is a new angiotensin II receptor blocker with a high affinity for the angiotensin II type 1 receptor subtype (AT_1), currently indicated for the treatment of hypertension. In a short-term dose-finding study, candesartan cilexetil improved exercise capacity and alleviated signs and symptoms in patients with CHF [9]. The present multicenter, double-blind, parallel-group, placebo-controlled study (assessment of response to candesartan in heart failure in Japan: ARCH-J) was designed to examine the long-term efficacy and safety of candesartan cilexetil in patients with CHF over a treatment period of up to 6 months.

2. Methods

2.1. Patient population

Patients eligible for enrolment in ARCH-J were ambulatory or hospitalised men and women, ≥20 years of age, with symptomatic CHF due to previous myocardial infarction, hypertensive heart disease, dilated cardiomyopathy or valvular disease. They were in New York Heart Association (NYHA) functional class II or III, with a

☆ All ARCH-J Study Investigators are listed in the Appendix.

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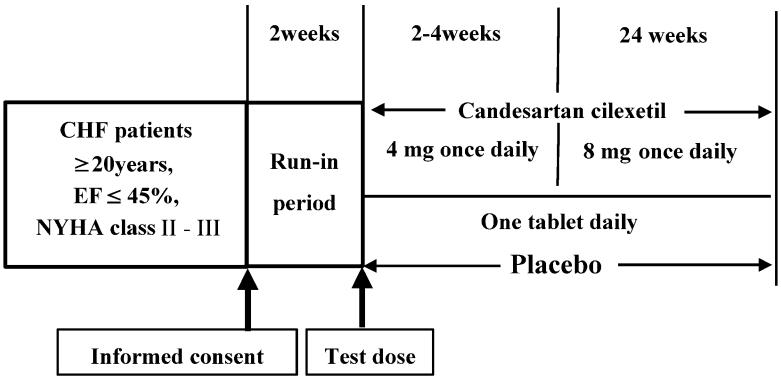

Fig. 1. Summary of the study design.

left ventricular ejection fraction ≤45% measured by two-dimensional echocardiography, radionuclide imaging or contrast ventriculography within 2 months prior to enrolment. Patients with unstable angina, life-threatening ventricular arrhythmias, severe valvular stenosis, hypertrophic obstructive cardiomyopathy, advanced respiratory disease, myocardial infarction within 1 month of enrolment, cardiogenic shock or severe hypotension, symptomatic cerebrovascular disease within 3 months, a serum creatinine >2.0 mg/dl, hyperkalemia, advanced hepatic dysfunction or a history of drug allergy or hypersensitivity, were excluded from participation in the study. Women who were pregnant, nursing or had childbearing potential, patients being treated with another investigational drug, and patients who were considered ineligible by the investigators for any other reason, were also excluded from enrolment. The study conformed to the principles of the declaration of Helsinki (WMA General Assembly, Somerset West, 1996, and Edinburgh, 2000). It was conducted at 91 medical institutions in Japan, after its review and approval by the ethics review boards of each institution. All patients granted their written informed consent to participate in the study before being enrolled. Patients who had been treated with an angiotensin-converting enzyme inhibitor (ACE-I) were enrolled in the study if: (a) their symptoms were not satisfactorily controlled; (b) they were intolerant of ACE-I; or (c) were willing to participate in a placebo-controlled study. Before obtaining their informed consent, patients were informed of the following:

- ACE inhibitors were one of the treatment alternatives, should they not wish to participate in the study. Treatment with ACE inhibitors was associated with a reduced mortality in several clinical trials conducted in Europe and in the USA. However, the use of ACE inhibitors was not allowed during this study.
- Manifestations of heart failure may worsen during the study. If that happened, however, the study drug would be promptly withdrawn and appropriate alternative treatments would be administered.

A population of 160 patients in each randomisation arm was the original enrolment target. This number was based on an estimated CHF progression rate of 15% in the placebo group vs. 5% in the candesartan group, from results of previous ACE inhibitor trials [6,8]. Including expected drop-outs, we planned for 200 patients in each randomisation arm.

2.2. Study protocol

Fig. 1 summarises the study protocol. After having been screened, eligible patients who gave their consent to participate in the study entered a run-in period of 2–4 weeks to confirm the stability of their symptoms, during which prior treatment with ACE inhibitors had to be discontinued. After receiving a 4-mg test dose of candesartan cilexetil to confirm tolerance of a single dose of the study drug, with special attention to hypotension-related symptoms, patients were randomly assigned in a double-blind fashion to treatment with placebo or candesartan cilexetil, 4 mg once daily, for 2–4 weeks. This was followed by a second double-blind treatment period using placebo or candesartan cilexetil, 8 mg once daily, for 6 months. Concomitant medications, including diuretics, inotropic agents, antiarrhythmics and β-adrenergic blockers, were continued throughout the study. Patients were followed up at intervals of 2–4 weeks to monitor their clinical progress, with a particular focus on: (1) compliance with the prescribed study drug regimen; (2) the severity of CHF according to the NYHA heart failure functional classification, based on a detailed history and physical examination; and (3) possible interim adverse cardiac events. In addition, a complete blood count and biochemistry tests (including liver enzymes), urinalysis, chest roentgenograms for measurement of the cardiothoracic ratio and standard 12-lead electrocardiograms and M-mode

echocardiograms were performed at study entry, and at 3 months, and 6 months of follow-up, or at the time of premature study termination. The echocardiographic left ventricular end-diastolic dimension (LVDd) and end-systolic dimension (LVDs), percentage fractional shortening (% FS), and left ventricular ejection fraction were also measured.

2.3. Study endpoints

The composite primary efficacy endpoint of the study, 'confirmed progression of CHF,' included the following: (1) patient hospitalisation for the management of CHF; or (2) addition of, or increase in, any medication(s) administered specifically for the management of CHF in response to an apparent aggravation of its manifestations, such as increase in dyspnea, or detection of marked pulmonary congestion or pleural effusion, mandating the continuation of the medication(s) beyond the next follow-up visit.

A secondary endpoint of the study was the occurrence of a cardiovascular event, including progression of CHF, cardiac death, life-threatening arrhythmias, myocardial infarction, coronary artery disease—defined as angina, coronary artery intervention or revascularization—stroke and transient ischaemic attack. The Clinical Event Evaluation Committee examined the case report forms collected at the completion of the study, to verify the accuracy of each investigator's assessment of all cases of progression of CHF. The committee examined all reported progressions of CHF with a view to standardise the assessment among investigators, and requested the investigators whose assessment was questioned to clarify the reason until a consensus was reached between the committee and the investigator.

Progression of CHF was not recorded as an adverse event because it was the primary study endpoint.

2.4. Statistical analysis

A primary analysis of all efficacy variables was performed using the full analysis set (FAS) on an intention-to-treat basis [10].

The baseline characteristics of each treatment group were compared by the contingency table χ^2 test, the 2-sample Wilcoxon test**,** and Student's *t*-test, as appropriate. The primary analysis examined inter-group differences in the proportion of patients who reached a primary endpoint by the 2×2 contingency table χ^2 test. Logistic and Cox models were used to adjust for the influence of known risk factors. Analysis of the secondary endpoints was performed by the 2-sample Wilcoxon test for ordered categorical data, 2×2 contingency table χ^2 test for binary data, and Student's *t*-test for comparison of continuous variables. The incidence of adverse events in each treatment group was compared by the 2×2 contingency table χ^2 test. Event-free survival was analysed by the Kaplan–Meier method. Differences in event-free survival were tested by the log-rank test. Data are presented as the mean $\pm$ S.D. An alpha level of 0.05 was considered statistically significant.

3. Results

Between June 1997 and August 2000, 313 patients were enrolled in ARCH-J. The number of patients enrolled at the 91 participating sites was in the range of 1–12 (median = 3). Because the recruitment of patients was slow, a large number of participating medical centres was necessary to complete the study in a timely fashion.

Of the 313 patients enrolled in the study, 8 were not randomised after a test dose of candesartan cilexetil, administered to confirm the tolerance of the study drug. Seven of the patients were not randomised due to adverse events caused by the test dose, such as marked hypotension, and one patient exited the study immediately after having received the test dose. Of the 305 patients whose tolerance of candesartan cilexetil had been confirmed with the test dose, 155 were randomised to active treatment and 150 to placebo (Fig. 2).

Seven patients assigned to candesartan cilexetil and 6 patients to placebo were excluded from the full analysis set (Table 1). Therefore, FAS were available for 148 patients randomised to candesartan cilexetil and 144 assigned to placebo. A total of 298 patients were included in the safety analyses, after exclusion of 3 patients in the candesartan group and 2 patients assigned to placebo, for whom good clinical practice (GCP) violations had been reported, and a single patient in each group who had not received any study drug.

The baseline characteristics of the two treatment groups were similar (Table 2). The mean follow-up of the 148 patients randomised to candesartan cilexetil was 153 ± 65 days vs. 158 ± 62 days for the 144 patients randomised to placebo (ns).

The safety and ethical aspects of the study were monitored by an independent Data and Safety Monitoring Board, which conducted interim analyses to determine whether continuation of the study may be detrimental to the patients. The first and second interim analyses were conducted after one third, and two thirds of the target number of patients had been enrolled, respectively. The study was to be terminated early if differences by the 2×2 contingency table χ^2 test between the candesartan and the placebo groups met predefined *P* values (0.0267 and 0.0205 for the first and second analysis, respectively) calculated by Pocock type alpha spending function, to control type I errors in either of the following endpoints: (1) progression of CHF; (2) adverse events; or (3) combination of (1) and (2). Enrolment was stopped in August 2000 when 313

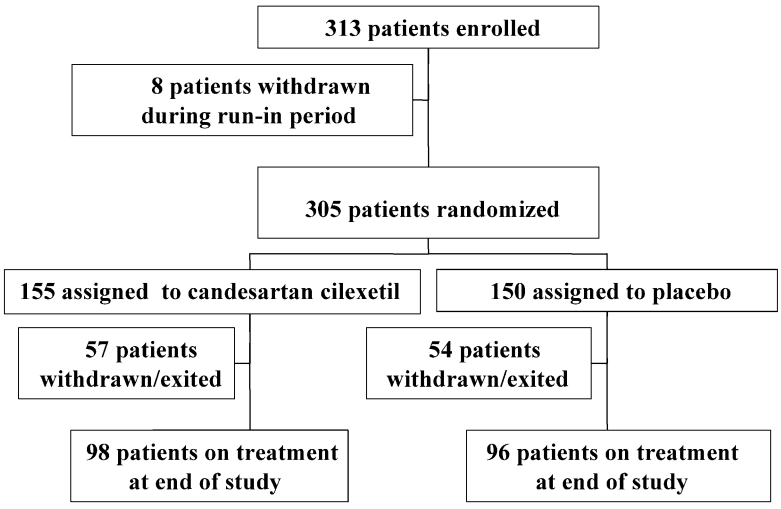

Fig. 2. Disposition of patients. Detail of withdrawal/exits from the active treatment group and placebo group, respectively: progression of CHF, 12, 31; inability to increase dosage because of hypotension, 5, 0; adverse events, 18, 6; premature completion of the study, 12, 13; other reasons, 3, 1; withdrawal of consent, 6, 2; non-compliance, 1, 1.

Table 1
Patients excluded from full analysis set in each study group

Reason for exclusion	Candesartan	Placebo
Violation of good clinical practice	3	2
Asymptomatic heart failure	2	1
Study medication not administered	2	1
Interim unstable angina pectoris	–	2

patients had been enrolled, and the independent monitoring board recommended that the study be closed after the second interim safety analysis.

3.1. Event rates

Progression of CHF was confirmed in 11 patients (7.4%) treated with candesartan cilexetil vs. 32 patients treated with placebo (22.2%), representing a risk reduction of 66.7% and a risk difference of −14.8% (95% CI, −22.8 to −6.8%, $P<0.001$), (Table 3). Hospitalisation for management of CHF was reported in eight and 17 patients, and addition or dose escalation of any CHF medication in three and 15 patients in the candesartan and placebo groups, respectively. All patients were ultimately discharged from the hospital or recov-

Table 2
Baseline characteristics of the 2 treatment groups (FAS)

Characteristic	Candesartan ($n=148$)	Placebo ($n=144$)
Age, years (mean ± S.D.)	63.1 ± 11.3	64.4 ± 10.9
Men/women	78/22	77/23
NYHA functional class II/III	76/24	72/28
LVEF,% (mean [median])	35.3 [34.6]	34.1 [33.9]
Underlying disease		
Previous myocardial infarction	23.0	27.8
Hypertension	7.4	5.6
Dilated cardiomyopathy	55.4	58.3
Valvular insufficiency	4.1	2.8
Others	10.1	5.6
Previous treatment with ACE-I	43.9	52.8
Ambient drug therapy		
Cardiac glycoside	51.4	52.8
Diuretic	84.5	81.9
Vasodilator	55.4	58.3
Beta-adrenergic blocker	18.9	21.5

Unless specified otherwise, numbers indicate percentage of patients.
FAS = full analysis set; NYHA = New York Heart Association; LVEF = left ventricular ejection .fraction; ACE-I = angiotensin-converting enzyme inhibitor.

Table 3
Number (%) of patients with confirmed progression of congestive heart failure (CHF) in each study group

Outcome	Candesartan ($n=148$)	Placebo ($n=144$)	Risk reduction	Risk difference (95% CI)	P value
Progression of CHF	11 (7.4%)	32 (22.2%)	66.7%	−14.8% (−22.8 to −6.8%)	0.0004
Hospitalisation for CHF	8	17			
Addition/increase in medication	3	15			

Table values are numbers of patients (%), unless otherwise indicated. CI = confidence interval.

ered, except two patients in the placebo group whose outcomes were fatal.

Fig. 3 illustrates the significant difference ($P<0.01$, log-rank) in cumulative rate of confirmed progression of CHF in the candesartan vs. the placebo group. The treatment advantage conferred by candesartan cilexetil was consistent in subgroup analyses based on age <65 vs. ≥ 65 years, NYHA functional class II vs. III, presence vs. absence of previous treatment with an ACE-I, and presence vs. absence of concomitant treatment with a beta-adrenergic blocker (Fig. 4). Cardiovascular events, a secondary endpoint, were also significantly lower in the candesartan group (10.8%) than in the placebo group (22.9%), with a risk reduction of 52.8% and a risk difference of −12.1% (95% CI, −20.6 to −3.6%, $P<0.01$). Fatal cardiovascular events occurred in two patients in each treatment group (ventricular fibrillation and stroke in one patient each in the candesartan group, and death due to progression of CHF in two patients in the placebo group). The only other death recorded during the study was a suicide in the placebo group.

3.2. Left ventricular function

Between baseline and the last observation, changes in roentgenographic cardiothoracic ratio and echocardio-

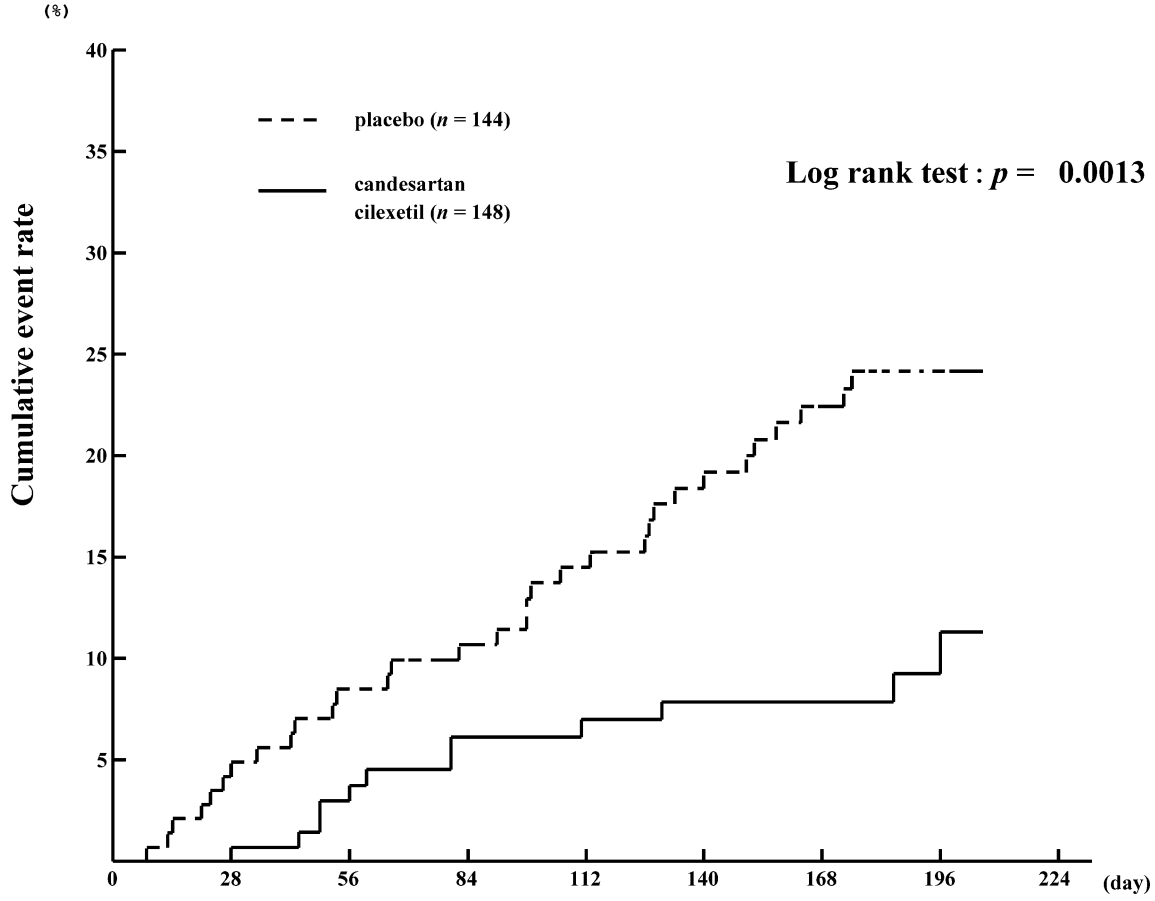

Fig. 3. Cumulative incidence of confirmed progression of congestive heart failure (CHF). By log-rank analysis, the difference in event rate in the candesartan group (unbroken line) vs. placebo group (broken line) was statistically significant ($P<0.01$).

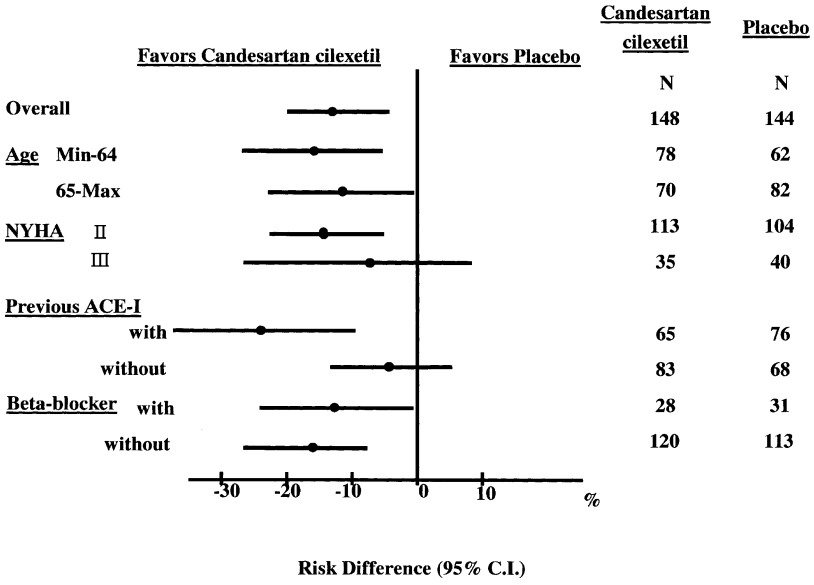

Fig. 4. Subgroup analyses of the efficacy of candesartan vs. placebo.

graphic measurements were consistent with an overall improvement of cardiac function in the candesartan group. Significant efficacy was observed between baseline and the last measurement in all the indices in the actively treated group compared to the placebo group (Table 4).

3.3. Safety of candesartan cilexetil

The safety analysis included 151 patients treated with candesartan cilexetil and 147 patients treated with placebo. Though active treatment was generally well tolerated, drug-related adverse signs and symptoms occurred more commonly during the administration of candesartan cilexetil (31.1%) than during placebo (21.1%, $P<0.05$). Adverse events in the candesartan group were mainly attributable to its known pharmacologic properties, including hypotension and postural light-headedness (Table 5). The incidence of laboratory abnormalities was 43.0% in the actively treated group, vs. 42.2% in the placebo group (ns). Overall, non-cardiovascular adverse effects that did or did not require discontinuation of treatment occurred in 58.9% of patients randomised to candesartan cilexetil vs. 51.0% of patients assigned to placebo ($P=0.17$).

4. Discussion

Among the important milestones in the fight against heart failure, the development of drugs that modify the

Table 4
Changes in cardiothoracic ratio and echocardiographic indices of left ventricular function between baseline and last measurement in each treatment group

Measurement	Treatment	Baseline	Last measurement	Δ	*P* value
CTR (%)	Candesartan	55.6±6.3	54.7±7.6	−1.7±7.4	0.0002
	Placebo	55.2±6.4	56.1±7.1	+1.8±8.1	
LVDd (mm)	Candesartan	61.9±12.1	60.1±11.2	−2.4±9.2	0.15
	Placebo	64.1±9.9	63.5±10.5	−0.8±9.0	
LVDs (mm)	Candesartan	50.9±8.9	47.6±9.6	−6.2±11.7	0.007
	Placebo	53.5±10.2	52.4±11.7	−2.0±12.2	
%FS	Candesartan	17.4±7.2	20.8±7.8	28.5±55.4	0.004
	Placebo	16.9±5.8	18.1±7.8	10.6±39.4	
LVEF (%)	Candesartan	35.1±11.9	40.9±13.0	23.8±46.0	0.004
	Placebo	34.2±10.4	36.0±13.2	8.4±34.4	

CTR = cardiothoracic ratio; %FS = percentage fractional shortening; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction. Δ = change between baseline and last measurement.

ΔLVEF is expressed as a percentage of the baseline value. *P* indicates significant level of Δ between candesartan and placebo group. All values are means ± S.D.

Table 5
Most frequent treatment-related adverse events in each study group of ARCH-J

Adverse event	Candesartan ($n=151$)	Placebo ($n=147$)
Postural light-headedness	13 (8.6)	3 (2.0)
Nonpostural light-headedness	14 (9.3)	5 (3.4)
Hypotension	10 (6.6)	2 (1.4)

Values indicate numbers (%) of patients.

renin–angiotensin–aldosterone system, beginning with ACE-Is, is most prominent [11,12]. More recently, angiotensin II AT_1 receptor blockers have been introduced clinically with a view to achieve a more complete and reliable suppression of angiotensin II activity [13], as well as mitigate the intolerable adverse effects sometimes observed during ACE-I therapy. By virtue of its tight binding to, and slow release from, the AT_1 receptor, candesartan has largely confirmed these hopes in the management of hypertension [14].

To date, the safety and efficacy of candesartan cilexetil, up to 16 mg daily, have been compared with placebo in two short-term studies in patients with CHF. In one study, active treatment was significantly more effective than placebo therapy in increasing exercise capacity, decreasing the roentgenographic cardiothoracic ratio, and in alleviating signs and symptoms of CHF [9]. In the other, which recruited patients unable to tolerate treatment with ACE-Is, candesartan cilexetil was well tolerated and associated with lower rates of progression of CHF, myocardial infarction, and all-cause hospitalisation than treatment with placebo, although the differences did not reach statistical significance [15]. In both studies, the safety of candesartan cilexetil was similar to that of placebo.

In the extended RESOLVD pilot study [16], the combination of candesartan cilexetil, 4–8 mg, and enalapril 20 mg, caused a greater improvement in left ventricular function and lowered aldosterone concentrations to a greater extent than either agent alone. There were no differences in cardiovascular morbidity and mortality between the treatment regimens.

The Val-HeFT trial was a large placebo-controlled study of high-dose valsartan in patients with chronic heart failure and a left ventricular ejection fraction $<0.40\%$. The majority of patients were also treated with a standard heart failure drug regimen, which included ACE-Is [17]. Though there was no survival benefit, there was a significant relative risk reduction of 13% by valsartan ($P=0.009$) in the second primary endpoint, most apparent with regard to hospitalisation for heart failure (27% risk reduction). Subgroup analyses revealed that much of this positive effect was confined to the 7% of patients who were not treated with ACE-Is. Furthermore, there was a trend towards a negative effect of valsartan in the subgroup treated with both an ACE inhibitor and a beta-adrenergic blocker. Thus, several unanswered questions remain regarding the position of AT_1-receptor blockers in the treatment resources available for patients with CHF [18]. To a great extent, this is due to a paucity of large outcome studies comparing AT_1-receptor blockers with placebo in patients untreated with ACE-I.

4.1. Contributions of ARCH-J

Safety and efficacy of candesartan cilexetil. The results of ARCH-J convincingly show the effectiveness of candesartan cilexetil compared with placebo in a population of patients with mild to moderate CHF treated for 6 months. The risk of progression of CHF as a single clinical endpoint, as well as the risk of progression of CHF combined with all other major adverse cardiovascular events, was decreased by over 50% by active treatment.

The subgroup analysis suggests that the preventive effect on the progression of CHF was greater in patients previously treated with an ACE-I. One cannot exclude the possibility that the progression of CHF was caused by the change in drug regimen from an ACE-I to placebo. However, at baseline, the patients untreated with an ACE-I had less severe ventricular dilatation than the pretreated patients. Furthermore, at study entry, 50% of pretreated patients were hospitalised, vs. 38% of non-treated patients, which suggests that, on average, the non-treated patients had less severe CHF than the pretreated patients (Table 6).

In addition, this stratification to evaluate the effect of ACE-I pretreatment was somewhat imprecise, because neither the duration of pretreatment with an ACE-I nor the interval between the discontinuation of treatment and the beginning of the study medication drug were considered. Therefore, the same subgroup analysis was performed by using an alternate definition of ACE-I pretreatment, whereby patients pretreated with an ACE-I for >1 month and/or up to 14 days before the start of study medication were counted as 'treated,' and the remainders as 'untreated.' This analysis confirmed a statistically significant effect of candesartan cilexetil vs. placebo in the 'treated' subgroup ($P<0.05$), as was found when applying the original definition of ACE-I pretreatment. In addition, the difference between candesartan and placebo in the 'untreated' subgroup based on this alternate definition of ACE-I pretreatment was also statistically significant ($P<0.05$). An important

Table 6
Baseline characteristics of patients previously treated vs. previously untreated with an ACE-I

Characteristic	Treated with ACE-I ($n=141$)	Untreated with ACE-I ($n=151$)
Age, years (mean ± S.D.)	62.3 ± 11.5	65.1 ± 10.5[a]
Men/women (% of patients)	78/22	77/23
Inpatients/outpatients (% of patients)	50/50	38/62[a]
NYHA II/III (% of patients)	72/28	76/24
LVEF, %	35.5 (35.5)	33.9 (33.4)
LVDd, mm	64.5 (63.0)	62.0 (61.0)[b]
LVDs, mm	52.9 (52.5)	51.8 (52.0)

Unless specified otherwise, values are means (median).
NYHA = New York Heart Association functional class; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; ACE-I = angiotensin-converting enzyme inhibitor.
[a] $P<0.05$.
[b] $P<0.1$, ACE-I-treated vs. ACE-I untreated group.

result of the post hoc subgroup analysis was the observation, in patients who had been unsuccessfully pretreated with an ACE-I, of a more effective prevention of CHF progression by substituting candesartan cilexetil than by the withdrawal of the ACE-I without substituting an alternate treatment.

Implementation of a new composite study endpoint. It is noteworthy that a significant treatment advantage was found in favour of candesartan cilexetil vs. placebo, despite the enrolment of a relatively small patient population with mild to moderate CHF, and a follow-up no longer than 6 months. These encouraging results are probably attributable to the power of the composite endpoint used in this study, which has not previously been described. In an era when the therapeutic value of ACE inhibitors for patients with CHF is no longer debatable, it was important to withdraw or withhold such therapy from the smallest number of patients for the shortest possible length of time. No clinical trial has confirmed the favourable effects of ACE-Is on mortality and morbidity in Japanese patient populations with CHF, in whom, in contrast to European or North American patients, non-ischaemic is apparently more prevalent than ischaemic heart disease. Because this was the first clinical trial planned to examine the effects of renin–angiotensin system inhibition in Japanese patients with CHF, a placebo-controlled design was required to show efficacy. However, it would not have been ethically acceptable to use mortality as an endpoint in such a trial. In this perspective, 'prevention of progression of CHF' was the most robust, as well as ethically acceptable, surrogate endpoint. In addition, safety was optimised by the protocol provision to withdraw the study medication and promptly replace it with alternate treatments as soon as progression of CHF was observed.

The composite endpoint used in this protocol allowed the safe conduct of a placebo-controlled trial, which seems even more pertinent after the recent concerns that have been expressed with regard to the effectiveness of angiotensin II blockers for the management of CHF [19].

4.2. Limitations of the study

Because the trial was placebo-controlled, the population of the ARCH-J study was highly selected, including patients who had remained clinically stable during the run-in period. Whether these results can be extrapolated to patients with more severe CHF is uncertain. In this relatively low-risk population, there were few deaths during the 6 months of observation. Consequently, whether candesartan cilexetil lowers mortality in patients with CHF could not be determined in this trial. However, one large-scale ongoing study scheduled to be completed in 2003 is enrolling patients with depressed left ventricular function who are intolerant of, or are being treated with, ACE inhibitors, as well as patients with relatively preserved left ventricular function, with the aim of measuring the effects of long-term therapy with candesartan cilexetil on both morbidity and mortality [20].

In conclusion, by using a new composite endpoint, the present ARCH-J study was able to show a clear treatment advantage of candesartan cilexetil in a small population of patients with mild to moderate CHF who were not receiving ACE inhibitor therapy.

Acknowledgments

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Appendix A: Committees and investigators of ARCH-J

Steering Committee

C. Kawai (Chair person), T. Sugimoto, S. Kimata, Y. Yazaki, S. Sasayama.

Clinical Event Evaluation Committee
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Data and Safety Monitoring Committee
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