Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors

Christopher B. Granger, MD,[a] Georg Ertl, MD,[b] Jerzy Kuch, MD,[c] Aldo P. Maggioni, MD,[d] John McMurray, MD,[e] Jean-Lucien Rouleau, MD,[f] Lynn Warner Stevenson, MD,[g] Karl Swedberg, MD,[h] James Young, MD,[i] Salim Yusuf, MB, BS,[j] Robert M. Califf, MD,[a] Bradley A. Bart, MD,[a] Peter Held, MD,[k] Eric L. Michelson, MD,[l] Mary Ann Sellers, RN,[a] Gunilla Ohlin, MSc,[k] Rodney Sparapani, MS,[a] and Marc A. Pfeffer, MD,[g] for the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Investigators* ***Durham, NC; Heidelberg, Germany; Warsaw, Poland; Milan, Italy; Glasgow, United Kingdom; Montreal, Quebec, Canada; Boston, Mass; Göteborg, Sweden; Cleveland, Ohio; Hamilton, Ontario, Canada; Mölndal, Sweden; and Wayne, Pa***

Background Many patients with congestive heart failure do not receive the benefits of angiotensin-converting enzyme (ACE) inhibitors because of intolerance. We sought to determine the tolerability of an angiotensin II receptor blocker, candesartan cilexetil, among patients considered intolerant of ACE inhibitors.

Methods Patients with CHF, left ventricular ejection fraction less than 35%, and history of discontinuing an ACE inhibitor because of intolerance underwent double-blind randomization in a 2:1 ratio to receive candesartan (n = 179) or a placebo (n = 91). The initial dosage of candesartan was 4 mg/d; the dosage was increased to 16 mg/d if the drug was tolerated. A history of intolerance of ACE inhibitor was attributed to cough (67% of patients), hypotension (15%), or renal dysfunction (11%).

Results The study drug was continued for 12 weeks by 82.7% of patients who received candesartan versus 86.8% of patients who received the placebo. This 4.1% greater discontinuation rate with active therapy was not significant; the 95% confidence interval ranged from 4.8% more discontinuation with placebo to 13% more with candesartan. Titration to the 16-mg target dose was possible for 69% of patients who received candesartan versus 84% of those who received the placebo. Frequencies of death and morbidity were not significantly different between the candesartan and placebo groups (death 3.4% and 3.3%, worsening heart failure 8.4% and 13.2%, myocardial infarction 2.8% and 5.5%, all-cause hospitalization 12.8% and 18.7%, and death or hospitalization for heart failure 11.7% and 14.3%).

Conclusions Candesartan was well tolerated by this population. The effect of candesartan on major clinical end points, including death, remains to be determined. (Am Heart J 2000;139:609-17.)

Although angiotensin-converting enzyme (ACE) inhibitors reduce mortality and morbidity rates among patients with congestive heart failure (CHF),[1] a substantial number of persons with heart failure are not receiving the benefits of ACE inhibitor therapy. Registries and databases show that at least 20% of patients with left ventricular systolic dysfunction have not been treated with ACE inhibitors.[2-7] In addition, approximately 10% of patients with CHF are intolerant of ACE inhibitors.[2] The most common reasons are coughing, symptomatic hypotension, and renal insufficiency.

The benefit of ACE inhibitors is believed to result primarily from inhibition of the production of angiotensin II, although the benefit also may derive from a decrease in the breakdown and resulting higher levels of bradykinin.[8,9] The increase in bradykinin with use of ACE inhibitors, which does not occur with angiotensin receptor blockers, also may contribute to the adverse effects of ACE inhibitors, such as coughing and angioedema. Angiotensin receptor blockers differ from ACE inhibitors in that they block the effect of

From the [a]Duke Clinical Research Institute, Durham; [b]Medical University Klinik Mannheim, Heidelberg; [c]University School of Medicine, Warsaw; [d]Mario Negri Institute, Milan; [e]University of Glasgow; [f]Montreal Heart Institute; [g]Brigham and Women's Hospital, Boston; [h]Göteborg University; [i]Cleveland Clinic Foundation; [j]McMaster University, Hamilton; [k]Astra Hässle AB, Mölndal; and [l]Astra-Merck Pharmaceuticals, Inc, Wayne.

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**The complete list of investigators is in the Appendix.*

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Reprint requests: Christopher B. Granger, MD, Box 3409, Duke University Medical Center, Durham, NC 27710.

E-mail: grang001@mc.duke.edu

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Table I. Baseline characteristics (randomization visit)

Characteristic	Placebo (n = 91)	Candesartan (n = 179)
Demographic features		
Age (y)	65 (58, 73)	66 (58, 74)
Female sex	25.3%	34.1%
Severity of heart failure (%)		
NYHA class II	47.3	57.0
NYHA class III	49.5	36.3
NYHA class IV	3.3%	6.7%
LV ejection fraction	29 (23, 32)	26 (22, 30)
Cause of heart failure (%)		
Ischemic	71.4	71.5
Idiopathic dilated	11.0	18.4
Hypertensive	6.6	3.4
Valvular	3.3	4.5
Other, unable to determine	7.7	2.3
Medical history (%)		
Myocardial infarction	61.5	62.6
Stroke	9.9	4.5
Hypertension	39.6	36.3
Diabetes	16.5	20.1
Atrial fibrillation or flutter	19.8	26.8
Sustained ventricular tachycardia or fibrillation	14.3	11.2
Implanted defibrillator	4.4	2.2
Physical examination		
Systolic blood pressure, supine (mm Hg)	130 (115, 144)	130 (118, 140)
Heart rate (beats/min)	72 (66, 82)	76 (65, 83)
Electrocardiographic findings (%)		
Atrial fibrillation or flutter	7.7	13.4
Medications (%)		
Digoxin	62.6	60.3
Diuretics	71.4	76.0
β-Blockers	19.8	21.8
Angiotensin receptor blocker*	9.9	10.6
Aspirin	57.1	55.3
Hydralazine	9.9	14.0
Lipid-lowering agents	24.2	25.1
Amiodarone	13.2	16.2

Data are median value or percentage. Numbers in parentheses are 25th and 75th percentiles.
LV, Left ventricular.
*More than 1 month before randomization.

angiotensin II at the AT_1 receptor, thus blocking the effects of angiotensin II produced through both ACE-dependent and ACE-independent pathways.

There is limited information about the effects of angiotensin receptor blockers on heart failure. The relatively small Evaluation of Losartan in the Elderly (ELITE) trial was designed to evaluate the effects of the angiotensin receptor blocker losartan on the renal function of elderly persons with CHF. Losartan therapy was associated with a lower mortality rate than was captopril therapy.[10] Excluding those who died, 12% of losartan-treated patients discontinued the study drug; 21% of captopril-treated patients did so. When results of small studies comparing the effects of losartan with those of enalapril were pooled, a lower mortality rate was suggested with losartan.[11]

Another dose-finding pilot study, Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD), found similar effects on neurohormones of the selective long-acting angiotensin receptor blocker candesartan cilexetil (candesartan) added to enalapril. There were favorable effects on remodeling with the combination of candesartan and enalapril.[12] The effects on functional status and clinical outcomes were neutral. Whether potent inhibition of angiotensin with any of the angiotensin receptor blockers reduces rates of mortality and morbidity, either alone or with ACE inhibitor therapy, has not been determined.

The Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) trial was designed as a randomized, double-blind, placebo-controlled pilot study to evaluate the use of candesartan for 12 weeks by a population of patients with CHF, left ventricular systolic dysfunction, and history of intolerance of ACE inhibitors. The inves-

tigators tested the feasibility of evaluating use of candesartan in a subsequent large mortality trial by determining whether patients who did not benefit from ACE inhibitors as a consequence of intolerance could undergo maintenance therapy with candesartan.

Methods

Patients

Eligible patients included those with left ventricular ejection fraction less than 35%, CHF (New York Heart Association [NYHA] class II through IV), and intolerance of ACE inhibitors. A patient was considered to be intolerant of ACE inhibitors if a physician caring for the patient discontinued ACE inhibitor therapy because of a perceived adverse effect, such as angioedema, anaphylaxis, neutropenia, cough, symptomatic hypotension, or azotemia. Investigators graded their degree of certainty that the adverse event was caused by the ACE inhibitor as high, medium, or low. Patients who were currently taking an ACE inhibitor were excluded, as were those with a creatinine level of 220 μmol/L (2.5 mg/dL) or more, a potassium level more than 5.5 mmol/L (5.5 mg/dL), or a history of serious hyperkalemia induced by use of an ACE inhibitor, use of potassium-sparing diuretics, known renal arterial stenosis, or renal transplantation. Other exclusion criteria were use of an angiotensin receptor blocker or any investigational drug within 30 days, pregnancy, poor compliance, uncontrolled hypertension, unstable angina, acute myocardial infarction, percutaneous coronary angioplasty or coronary artery bypass operation within 30 days, stroke or transient ischemic attack within 3 months, obstructive valvular heart disease, constrictive pericarditis, or any noncardiac illness that limited expected survival to less than 2 years.

Other than the randomized treatment assigned, all medical therapy and other management decisions were left to the discretion of the treating physician. All patients included in the study gave informed consent, and the ethics committee at each study site approved the protocol. To obtain a broad perspective and develop a registry of ACE inhibitor intolerance, the study was conducted at 90 sites in 7 countries: Canada, Germany, Poland, Sweden, Switzerland, the United Kingdom, and the United States. The large number of centers relative to the target number of patients to be enrolled was necessary because of the relatively small number of ACE inhibitor–intolerant patients available for enrollment.

Randomization and drug treatment

After a 1-week, single-blind, placebo run-in phase, patients were randomly assigned in a 2:1 ratio to receive candesartan or a placebo. The initial dose was 4 mg candesartan or matching placebo. After 2 weeks the dose was titrated to 8 mg and after 4 weeks to 16 mg. Total duration of drug treatment was 12 weeks. Patients were instructed to take their medication once a day, in the morning. At the investigator's discretion, patients were allowed to start taking 2 mg of medication but were required to increase the the dose to 4 mg within 1 week. A decrease was permitted from 16 to 8 mg or from 8 to 4 mg but not from 4 mg to 2 mg.

End points

Evaluations were conducted at the beginning of the run-in period, at randomization, and after 2, 4, 6, 8, and 12 weeks of use of the medication. The following were performed at entrance to the study, after 12 weeks of drug use, and selectively at interim visits: assessment of NYHA class, physical examination, laboratory tests, 6-minute walk test, quality-of-life assessment, compliance assessment, and evaluation for adverse events. Tolerability, the primary end point, was defined as the percentage of the randomized population completing the 12-week, double-blind, treatment period with the study drug at the 4-, 8-, or 16-mg level.

Data were collected on all adverse events. Serious adverse events included those that were fatal or life-threatening, caused permanent or serious disability, or caused new or prolonged hospitalization. Major cardiovascular clinical events that occurred during the study period were ascertained for all patients. Quality-of-life evaluation included use of the Minnesota Living with Heart Failure questionnaire[13] and the SF-36 Health Survey.[14] Functional status was assessed with a 6-minute walking test performed twice before randomization, to determine the baseline and a measure of reproducibility, and once during the 12th week of treatment.

Statistical analysis

There was no formal statistical hypothesis. The sample size was determined so that 95% confidence intervals (CIs) of the discontinuation rate of candesartan would not exceed 6%. Comparisons were made between the treatment and control arms for all randomly assigned patients according to the intent-to-treat principle. Tolerability of candesartan versus placebo was determined to be the difference in the proportion of patients completing the 12-week period taking at least 4 mg of study drug as well as the 95% CI of that difference. Distributions of continuous variables are reported as median values with 25th and 75th percentiles in parentheses. Discrete variables are reported as percentages. Incidences of adverse events in each group were compared by the χ^2 test. The Wilcoxon rank sum test was used to compare categoric variables such as NYHA class.

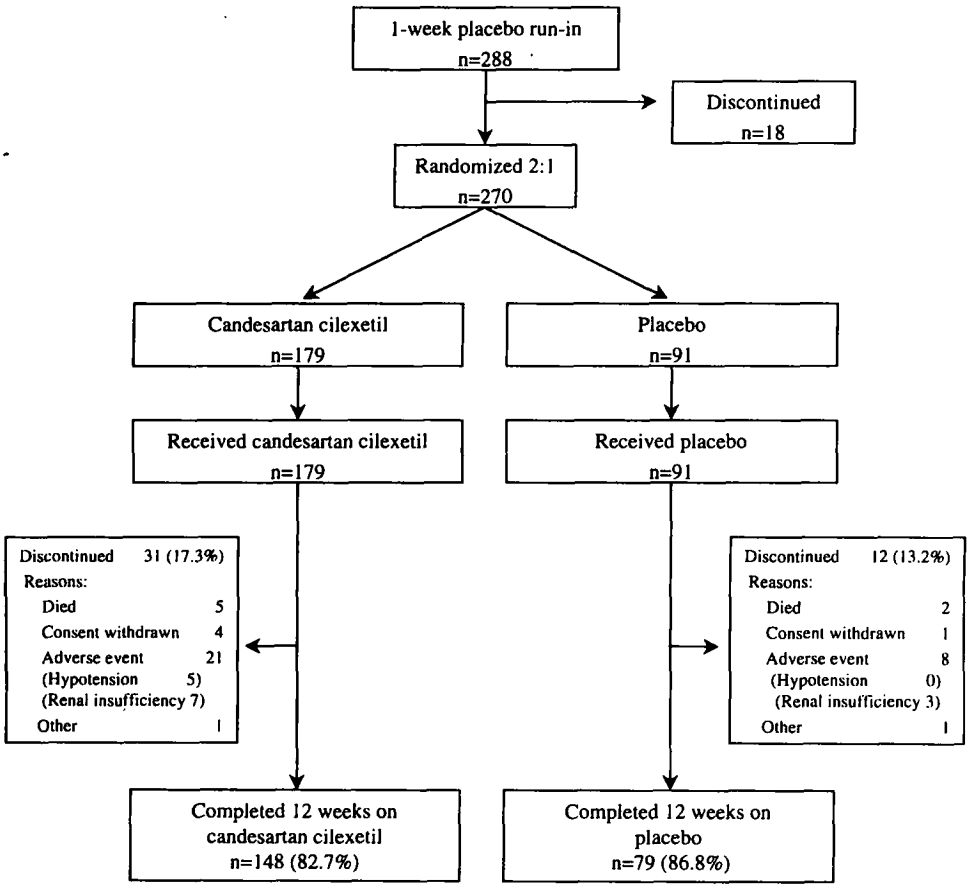
The proportion of discontinuations between the candesartan and placebo groups was further evaluated with respect to the presumed mechanism of ACE inhibitor intolerance that resulted in study eligibility. Adverse events specific to ACE inhibitors were defined as angioedema, anaphylaxis, neutropenia, cough, rash, taste disturbance, gastrointestinal symptoms, and hyperkalemia. Events related to general vasodilatory properties were symptomatic hypotension and azotemia.

Results

Patient recruitment began on October 31, 1996, and ended on June 11, 1997. Follow-up data collection was completed on October 3, 1997. The baseline characteristics are shown in Table I. Median left ventricular ejection fraction was 27%. Most of the patients had an ischemic cause of heart failure, and most cases of heart failure were NYHA class II or III. Ten percent of patients had taken angiotensin receptor blockers in the past.

The manifestations of prior ACE inhibitor intolerance ascribed by the treating physicians are shown in Table II. Of the 270 patients randomly assigned, 67% had a

Figure 1



Patient disposition during the placebo run-in and 12-week treatment period according to randomized treatment assignment. One additional patient in each group died after study drug had been discontinued.

cough, 15% had symptomatic hypotension, and 11% had renal dysfunction. Hypotension was a more common reason for discontinuation of ACE inhibitors for the candesartan group than it was for the placebo group. The investigators had a high degree of certainty that symptoms of cough, symptomatic hypotension, and renal dysfunction represented intolerance of ACE inhibitors. They had a low degree of certainty for rash, pruritus, or gastrointestinal upset.

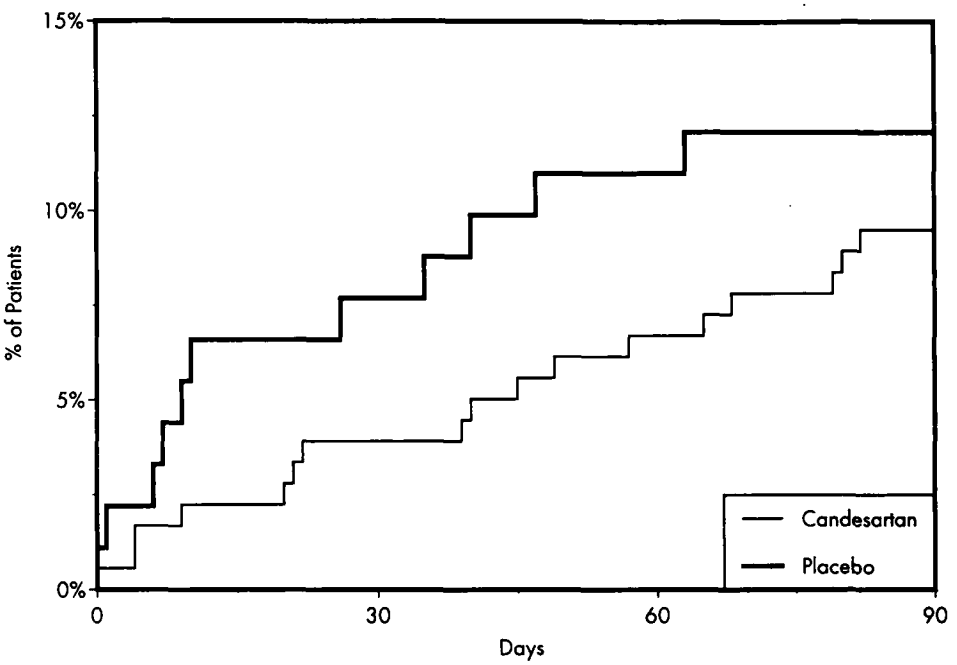
Ability to tolerate candesartan

Two hundred eighty-eight patients were enrolled in the 1-week placebo run-in phase; 270 (94%) of these patients were randomly assigned—91 to placebo and 179 to candesartan. Patient disposition according to treatment group is shown in Figure 1. Of patients randomly assigned to receive candesartan, 82.7% (95% CI, 77.1%-88.2%) completed the 12-week period of therapy with the study drug; 86.8% (95% CI, 79.9%-93.8%) of the placebo group did so. There was no significant difference in discontinuation rates between the treatments; 4.1% more candesartan-assigned patients had early discontinuation (95% CI, 4.8% fewer to 13% more).

The most common reasons for discontinuation of the study drug were worsened heart failure, elevated creatinine level, and hypotension. Discontinuation because of hypotension was more common among the candesartan-assigned patients (5 [3%] vs none in the placebo group). Discontinuation because of renal insufficiency was similar between the 2 groups (7 [4%] in the candesartan group vs 3 [3%] in the placebo group). While taking the study drug, 5 (3%) patients in the candesartan group and 2 (2%) in the placebo group died. One additional patient in each group died before the end of the 12-week follow-up period and after the study drug had been prematurely discontinued.

Of patients assigned to take candesartan, 64% completed 12 weeks with the highest dose (16 mg); 84% of placebo-assigned patients did so. Seventy-six percent of patients who received candesartan were treated at some

Figure 2



Worsening of congestive heart failure by follow-up week 12 among patients randomly assigned to receive candesartan (*thin line*) or placebo (*heavy line*).

time during the study with the highest dose; 85% of the placebo group were so treated. Among patients who discontinued the study drug, the median number of days taking the drug was 29 for the candesartan group and 26 for the placebo group.

Ability to tolerate candesartan according to type of ACE inhibitor intolerance

Reasons for previous intolerance of ACE inhibitors were divided into those believed to be specific to ACE inhibitors (cough, angioedema, hyperkalemia, taste disturbance) and those expected with any vasodilator (symptomatic hypotension, renal failure). Seventy-five percent of patients had ACE inhibitor-specific reasons only, 15% had general vasodilator reasons only, and 10% had both. Candesartan had higher tolerability when ACE inhibitors had been stopped for a reason believed to be specific to ACE inhibitors. Of these patients 87.2% completed 12 weeks of taking candesartan; the overall rate was 82.7%, $P = .02$.

Major cardiovascular events

Major cardiovascular events are summarized in Table III. Mortality rate for all randomized patients at the end of the 12-week follow-up period was similar for the 2 groups: 3.4% for candesartan and 3.3% for placebo. Worsening CHF (Figure 2), hospitalization for heart failure, unstable angina, and myocardial infarction tended to be less common among patients who received candesartan than among the placebo group. The point estimates showed 20% to 50% reductions, although the differences were not statistically significant. Symptomatic hypotension was more common with candesartan ($P = .03$).

Table II. Manifestations of ACE inhibitor intolerance

Mechanism*	Placebo (n = 91)	Candesartan (n = 179)
Cough (%)	64.8	68.2
Symptomatic hypotension (%)	8.8	18.4
Renal failure (%)	11.0	11.2
Hyperkalemia (%)	4.4	5.6
Gastrointestinal upset (%)	7.7	7.3
Taste disturbance (%)	8.8	2.8
Rash, pruritus (%)	3.3	6.7
Angioedema (%)	4.4	4.5
Anaphylaxis (%)	0	0.6
Other (%)	8.8	6.7

*Not mutually exclusive.

Functional class and quality of life

There was no overall difference between the candesartan and the group placebo in change in NYHA functional class (Table IV). Nor was there any measurable effect on quality of life as measured with the Min-

Table III. Cardiovascular clinical events

Event	Placebo (n = 91)	Candesartan (n = 179)	P value	Odds ratio (95% CI)
Death	3 (3.3)	6 (3.4)	1.0	1.0 (0.25-4.2)
Worsening of CHF	12 (13.2)	15 (8.4)	0.22	0.61 (0.27-1.4)
All hospitalizations	17 (18.7)	23 (12.8)	0.20	0.64 (0.32-1.3)
For worsening CHF	11 (12.1)	15 (8.4)	0.33	0.67 (0.29-1.5)
For unstable angina	5 (5.5)	5 (2.8)	0.31	0.49 (0.14-1.8)
Acute myocardial infarction	5 (5.5)	5 (2.8)	0.31	0.49 (0.14-1.8)
Sustained symptomatic hypotension	0	9 (5.0)	0.03	ND
Stroke	1 (1.1)	0	0.34	ND
Death or hospitalization for worsening CHF	13 (14.3)	21 (11.7)	0.55	0.80 (0.38-1.7)

Values are number with percentage in parentheses.
ND, Not determined because there were no events in one group.

Table IV. Functional status

NYHA class*	Placebo (n = 91)	Candesartan (n = 179)
Improvement (%)	8	4
Worsening (%)	17	12
No change (%)	75	84

*Change from baseline to final visit.

nesota Living with Heart Failure Questionnaire (overall median scores at baseline and final visit were 32 and 32 for candesartan, 42 and 38 for placebo) or SF-36 Health Survey (better and worse were 45% and 11% for candesartan, 54% and 9% for placebo). There was also no significant measurable difference in the effect on 6-minute walking test. The median increase from baseline to final testing was 20 meters for candesartan and 31 meters for placebo.

Changes in blood pressure, renal function, and electrolyte values

In the comparison between last visit and first visit, patients assigned to candesartan had a median 10 mm Hg drop in systolic and 6 mm Hg drop in diastolic blood pressure. The placebo group had no change in systolic and diastolic blood pressure. Heart rate did not change in either group. Creatinine level increased more than 100 μmol/L (1.1 mg/dL) in 2 (1.1%) candesartan-treated patients and did not increase in placebo-assigned patients. Potassium level increased to more than 5.5 mmol/L (5.5 mg/dL) in 2.2% of candesartan-treated and 2.2% of placebo-treated patients.

Discussion

This study showed that patients with CHF and previous intolerance of ACE inhibitors can tolerate candesartan. Nearly 83% of patients completed the 12-week treatment period with candesartan, which was not significantly less than the 87% who completed the period taking a placebo. As expected, tolerance of candesartan tended to be better among patients whose intolerance of ACE inhibitors seemed to be specific to ACE inhibitors, such as a cough, rather than a general vasodilator-related reason, such as hypotension.

ACE inhibitor intolerance

Although treatment with ACE inhibitors for patients with symptomatic CHF is known to reduce mortality rate,[1] at least 20% of patients with heart failure do not take ACE inhibitors,[2] in part because of intolerance. Estimates of the incidence of intolerance of ACE inhibitors among patients with heart failure range from 5% to 10%.[4-6] A registry compiled by the investigators in the SPICE trial found that 10% of all patients with left ventricular dysfunction who had been treated with ACE inhibitors had the drugs discontinued because of perceived intolerance.[2] Moreover, 6% of all patients with left ventricular systolic dysfunction were both intolerant of ACE inhibitors and were candidates for therapy with angiotensin receptor blockers, according to the criteria used in this trial. This is a small percentage; however, with an estimated 2 million persons in the United States alone with heart failure,[15] 120,000 such patients become candidates for angiotensin receptor blocker therapy. This study showed that patients intolerant of ACE inhibitors can tolerate another approach to inhibiting the renin-angiotensin system. The finding that direct inhibition of the effect of angiotensin is tolerated by patients with a history of intolerance of ACE inhibitors suggests that intolerance of ACE inhibitors is primarily mediated through effects other than those of angiotensin.

Ability to tolerate candesartan

Most patients tolerated candesartan, and more than 75% reached the target dose of 16 mg, a dose shown to

be effective for the control of hypertension.[16] By 12 weeks, the proportion of patients taking candesartan was similar to the proportion taking the placebo. Although 5% of patients in the candesartan group had sustained hypotension, only 3% discontinued candesartan because of hypotension, and 3% in both the candesartan group and the placebo group stopped the drug because of renal insufficiency. Candesartan was particularly well tolerated by patients who had a history of intolerance of ACE inhibitors because of a presumed ACE inhibitor-specific intolerance, predominantly cough.

Clinical outcomes and quality of life

The use of candesartan in this study resulted in a reduction in blood pressure similar to the 4 to 6 mm Hg reduction by standard doses of ACE inhibitors for patients with CHF in the Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) treatment trials.[17,18]

This tolerability study was not intended to examine the effect of candesartan on clinical events. If it is assumed that candesartan therapy caused a 35% relative reduction in the combined end point of death and worsening heart failure, as has been found with ACE inhibitors,[1] given the overall rate observed, there was only 9% power to detect such a difference. Nevertheless, the general tendency toward fewer heart failure and ischemic events with candesartan is consistent with the possibility of an important treatment effect.

The lack of a measurable effect on 6-minute walking distance and quality of life in a 12-week study was similar to previous findings with ACE inhibitors and other angiotensin receptor blockers in the management of heart failure. In those studies 8 to 12 weeks of treatment with enalapril and losartan was associated with no significant improvement.[19,20]

Limitations

A limitation of this study was the lack of objective documentation of previous intolerance of ACE inhibitors. Some patients with a history of discontinuation of ACE inhibitors because of intolerance may not have had true intolerance, especially those with a cough. Nevertheless, the definition used is a meaningful and relevant one because these patients were having ACE inhibitor therapy withheld.

Clinical implications

This study showed that a large population of patients with heart failure who are intolerant of ACE inhibitors can tolerate candesartan. Although several clinical outcome trials are underway, whether angiotensin receptor blockers improve survival in heart failure is not yet known. As part of the evaluation of angiotensin receptor blockers in large trials, studying the population of patients intolerant of ACE inhibitors is a feasible and important objective in the search for improving therapy for heart failure.

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Appendix

Steering committee

M. Pfeffer (study chair), United States; R. Califf (director, Duke Clinical Research Institute), United States; S. Yusuf, Canada; J. Rouleau, Canada; G. Ertl, Germany; A. Maggioni, Italy; J. Kuch, Poland; K. Swedberg, Sweden; J. McMurray, United Kingdom; L. Stevenson, United States; J. Young, United States; P. Held, Sweden*; E. Michelson, United States.* (*Nonvoting members.)

Coordinating center

Duke Clinical Research Institute, Durham, NC. Clinicians: R. Califf, C. Granger, B. Bart. Project leader: M. Sellers.

Institutions and participants by country (number of patients)

United States (76). Tower Cardiology, Los Angeles: R. Davidson; Veterans Affairs Medical Center, San Francisco: B. Massie, S. Ammon; Mount Sinai Medical Center, Miami Beach, Fla: G. Lamas, S. Rubin; University Cardiology Consultants, Tamarac, Fla: R. Schneider; Watson Clinic LLP, Lakeland, Fla: K. Browne; Heart Care Midwest, Peoria, Ill: A. Chu, M. Pierson; Alton Ochsner Medical Foundation, New Orleans: F. Smart; University of Maryland Medical System and Baltimore Veterans Affairs Medical Center, Baltimore: R. Freudenberger, M. Cines; Brigham and Women's Hospital, Boston: L. Stevenson, C. Smith; Mid-American Cardiology, Kansas City, Mo: C. Porter; University of Missouri Hospital & Clinic, Columbia: G. Flaker, K. Belew; Nebraska Heart Institute, Lincoln: C. Meckel, P. VerMass; Dartmouth-Hitchcock Cardiology Research, Lebanon, NH: B. Hettleman; Duke University Medical Center, Durham, NC: C. O'Connor, K. Hansley; Christ Hospital, Cincinnati, Ohio: D. Kereiakes; Cleveland Clinic Foundation, Cleveland, Ohio: J. Young; University Hospital and The Lindner Center for Cardiovascular Research, Cincinnati, Ohio: L. Wagoner; Cardiovascular Clinic, Oklahoma City, Okla: J. Anderson; Portland Cardiovascular Institute, Portland, Ore: S. Lewis, J. Mitchell; Geisinger Clinic, Danville, Pa: F. Menapace; HUP Cardiology, Philadelphia: E. Loh; Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston: M. Zile; Cardiology Group of Memphis, Memphis, Tenn: F. McGrew, S. Burgess; Trinity Cardiology, Tyler, Tex: J. Jackman, S. Crispin; Cardiovascular Associates Ltd., Norfolk, Va: W. Old, B. Bariciano; Appleton Heart Institute, Appleton, Wis: P. Ackell, M. Noble.

Canada (73). Hamilton General Hospital, Hamilton, Ont, Coordinating Center: S. Yusuf, J. McKay, E. Wieczek; London Health Sciences Center, London, Ont: M. Arnold; Clinique de Cardiology de Levis, Levis, Quebec: P. Auger; Niagara Medical Center, Niagara Falls, Ont: Y. Chan; Royal Victoria Hospital, Montreal, Quebec: E. Elstein; University of Calgary, Foothills Hospital Heritage Medical Research, Calgary, Alberta: D. Isaac; St. Joseph's Hospital, Hamilton, Ont: A. Kitching; Thunder Bay Regional Hospital, Port Arthur General Cardiology Research, Thunder Bay, Ont: C. Lai; Hamilton General Hospital, Hamilton, Ont: R. McKelvie, J McCay; Sunnybrook Health Science Center, Toronto, Ont: C. Morgan; Surrey Memorial Hospital, Surrey, BC: P. Polasek; Centenary Health Centre, Scarborough, Ont: A. Ricci; Hopital Laval, Quebec, Quebec: N. Robitaille; Hospital Notre Dame, Montreal, Quebec: F. Sestier; General Hospital Health Science Centre, St.John's, Newf: B. Sussex; Hopital Enfant Jesus, Quebec, Quebec: P. Talbot; Montreal Heart Institute, Montreal, Quebec: J. Rouleau; London Clinical Research, Sherbrooke, Quebec: J. Bedard; University of Alberta, Edmonton, Alberta: D. Humen; Royal Columbian Hospital, New Westminster, BC: R. Kuritzky; Grey Nuns Community Health Center, Edmonton, Alberta: M. Senaratne; University of Ottawa Heart Institute, Ottawa, Ont: R. Davies; Royal Alexandria Hospital, Edmonton, Alberta: W. Hui; Plains Health Centre, Regina, Sask: N. Habib; North Shore Cardiology, North Vancouver, BC: K. Woo; Misericordia Hospital, Edmonton, Alberta: P. Greenwood.

Poland (46). University School of Medicine, Warsaw: J. Kuch; University School of Medicine, Lodz: M. Krzeminska-Pakula; Central Hospital of Military University School of Medicine, Warsaw: J. Adamus; Voivodeship Hospital, Bialystok: A. Stogowski; Voivodeship Hospital, Wroclaw: K. Wrabec; Silesian University School of Medicine, Zabrze: J. Wodniecki; Pomeranian University School of Medicine, Szczecin: Z. Kornacewicz-Jach; Institute of Cardiology, Jagiellonian University, Krakow: W. Piwowarska; Voivodeship Hospital, Siedlce: P. Kolodziej; Voivodeship Hospital, Torun: K. Jaworska.

United Kingdom (31). Glasgow Royal Infirmary, Glasgow: M. Cobbe, H. Young; Queens Medical Centre, Nottingham: A. Cowleya, D. Blakey; Royal Victoria Hospital, Belfast: D. Nicholls; York District Hospital, York: M. Pye, B. Wiseman; Stobhill Hospital, Glasgow: F. Dunn, A. Wright; Royal Alexandria Hospital, Paisley: I. Findlay; Glasgow Clinical Research Initiative in Heart Failure, University of Glasgow, Glasgow: J. McMurray;

Wythenshawe Hospital, Manchester: S. Ray, T. Coppinger; North Manchester General Hospital, Manchester: J. Swan, M. MacAskill; Queens University of Belfast, Belfast: B. Silke, A. Fairweather.

Sweden (27). Hjärtmottagningen, Borås: C. Wettervik, L. Björklund; Med klin, Danderyd: T. Kahan, M. Rydell; Hjärt-ärlforskning, Göteborg: B. Karlsson, L. Winberg; Hjärtmottagningen, Malmö: P. Bhiladvala, A. Ivarsson; Kardiologkliniken, Lund: B. Kornhall; Hjärtmottagningen, Falun: H. Saetre, E. Pihl; Kranskäralsmottagningen, Karlstad: R. Carlsson, C. Wikström; Med klin, MIVA, Mölndal: L. Klintberg, L. Ortgren; Hjärtmottagningen, Västerås: G. Agert, M. Rolandson; Östra University Hospital, Göteborg: K. Swedberg, M. Schaufelberger.

Germany (16). Klinikum der Stadt Mannheim, Mannheim: G. Ertl, P. Gaudron, I. Kugler; Universität Klinik Mainz, Mainz: H. Darius; Kreiskrankenhaus Starnberg, Starnberg: P. Trenkwalder; Innere Abteilung, Offenbach: H.P. Nast; Universität Klinikum Rudolf Virchow FU Berlin, Berlin: K. Osterziel; Ruppiner Klinikum GmbH, Neuruppin: K. Schmailzl; Stadt Krankenstalten, Ludwigshafen: J. Senges; Dr. Horst-Schmidt-Kliniken, Wiesbaden: M. Sigmund; Universität Kliniken Koln, Koln: W. Bohm; Wilhelm-Pieck-Universität, Rostock: W. Urbaszek.

Switzerland (1). Ospedale Civico, Lugano: T. Moccetti.

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