

Meta-analysis: Effect of ACE-Inhibitors on Outcomes in Patients with Renal Insufficiency

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ABSTRACT To assess the relationship between baseline serum creatinine (Scr) levels and the protective effect of angiotensin-converting enzyme (ACE)-inhibitors on the development of end-stage renal failure in patients with renal disease, we conducted a meta-analysis of all randomized controlled trials that compared ACE-inhibitors with either placebo or other anti-hypertensive agents in patients with renal insufficiency. The pooled outcome was end-stage renal failure or a doubling of the baseline serum creatinine concentration (DScr). ACE-inhibitors

are effective in slowing the progression of renal insufficiency, not only in patients with a serum creatinine value of below 3.0 mg/dl but also in those with a serum creatinine value of 3.0 mg/dl or more.

KEY WORDS Angiotensin-converting enzyme-inhibitors, renal insufficiency, serum creatinine, meta-analysis, efficacy, end-stage renal failure

INTRODUCTION

According to a report of the Japanese Society for Dialysis Therapy published in 2001,¹ more than 209,000 patients in Japan were receiving long-term, chronic dialysis; this number has been increasing steadily at a rate of more than 10,000 patients per year since 1983. The main causes of chronic renal failure are diabetic nephropathy (36.2%), glomerulonephritis (33.6%), and hypertensive nephrosclerosis (7.0%).¹ Conse-

quently, although the incidence of cerebrovascular and cardiac events declined in recent years, the number of patients with end-stage renal failure (ESRF) has continued to grow, along with an increase in the number of cases of diabetes and glomerulonephritis.¹

Angiotensin-converting enzyme (ACE)-inhibitors slow the progression of renal disease in patients with diabetic nephropathy and with other nondiabetic nephropathies. In diabetic patients with microalbuminuria and normal renal function,

Table 1 Study Characteristics Included in the Meta-analysis

Study	Year	Country	Blinded	Intervention (mg/day)		Follow-up (Months)	Patients (No.)			Age
				ACE-I, Dose	Control, Dose		Total (Men %)	ACE-I	Control	
Stornello ²⁸	1989	Italy	Double	Enalapril, 5	Placebo	12	16 (43.8)	8	8	46.5
Captopril Trial ⁵	1993	USA	Double	Captopril, 75	Placebo	36 [‡]	409 (25.9)	207	202	34.5
Bauer ²⁷	1992	USA	Double	Enalapril, 5–40	Placebo	18	33 (72.7)	18	15	50.6
REIN Stratum ¹²¹	1999	Italy	Double*	Ramipril, 1.25–5.0	Placebo	31 [‡]	186 (74.7)	99	87	49.7
AIPRI Trial ²⁰	1996	Italy	Double	Benazepril, 10	Placebo	36	583 (72.2)	300	283	51
REIN Stratum ²²²	1997	Italy	Double*	Ramipril, 1.25–5.0	Placebo	16	166 (78.3)	78	88	49.3
Toto ⁸	1993	USA	Single	Enalapril, 5–40	Placebo	36	124 (63.7)	64	60	52
Brenner ⁸	1993	USA	Single	Enalapril, 5–40	Placebo	36	112 (64.3)	53	59	47
Ihle ^{25,26}	1996	Australia	Double	Enalapril, 5	Placebo	24	70 (51.4)	36	34	44.5
Cinotti ¹⁸	2001	Italy	No	Lisinopril, 5–10	Conventional [†]	22.5	131 (65.6)	66	65	50.9
Kamper ¹⁷	1992	Denmark	No	Enalapril, 2.5–	Conventional [†]	≤24	70 (52.9)	35	35	48.5
Himmelmann ²⁴	1995	Sweden	Double	Cilazapril, 2.5–5	Atenolol, 50–100	24	260 (48.1)	131	129	65
van Essen ²³	1994	Netherlands	Single	Enalapril, 10–40	Atenolol, 50–100	48	103 (66.0)	51	52	50
Hannedouche ¹⁶	1994	France	No	Enalapril, 5–10	Acebutolol, 400 Atenolol, 100	36	100 (53.0)	52	48	52
Zucchelli ¹⁹	1992	Italy	No	Captopril, 25–100	Nifedipine, 20–40	36	121 (57.9)	60	61	55.0

* The design changed from a double-blinded to an open-label study.

† Conventional treatment indicates medications with unspecified conventional antihypertensive remedies except for other ACE-inhibitors or angiotensin-receptor blockers (ARBs).

‡ Median.

§ Unpublished data provided by study investigators.^{30,31}

¶ Data from Jafar et al. *Ann Intern Med* 2001;135(2):73–87.²⁹

ACE-I = angiotensin-converting enzyme-inhibitor; AD = antidiabetic agent; B = beta-adrenergic blocker; C = calcium-channel blocker; CA = central alpha-adrenergic agonist; D = diuretic; I = insulin; PA = peripheral alpha-adrenergic blockers; V = vasodilator.

ACE-Inhibitors and Renal Insufficiency

ACE-inhibitors slow the progression of disease to overt proteinuria;^{2,3} in patients with proteinuria, these drugs also decrease the excretion of urinary protein, slow the decline in the glomerular filtration rate (GFR), slow the increase in serum creatinine (Scr) level, and delay the onset of renal failure.^{4,5} These changes occur in patients with or without pre-existing hypertension: the renoprotective effect of ACE-inhibitors is independent of antihypertensive effects.⁶ In some studies,^{2,5,7} ACE-inhibitors are more effective for the kidneys than for controlling blood pressure.

For these reasons, the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)*⁸ and the *Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2000)*⁹ have recommend the use of ACE-inhibitors in patients with high blood pressure and chronic renal disease to control hypertension and to slow progressive renal failure. As a result, ACE-inhibitors are now accepted as the first choice of treatment for patients with chronic renal failure in Japan.¹⁰

Despite these benefits, however, ACE-inhibitors and angiotensin-receptor blockers (ARBs) sometimes lead to acute renal

failure and to hyperkalemia in patients with moderate to severe renal insufficiency.¹¹ In Japan, the package inserts briefly mention precautions, particularly for patients whose SCr is 3.0 mg/dl or greater. However, borderline values are based not upon a specific reference but merely on the weak evidence from episodes encountered by specialists in nephrology.

This article reviews renal function in relation to Scr levels and describes the effects of ACE-inhibitors on the progression of renal failure and on the occurrence of acute renal failure.

METHODS

Using a meta-analysis to combine data from randomized controlled trials of ACE-inhibitors in patients with renal disease, we attempted to assess the efficacy of ACE-inhibitors in slowing the progression to end-stage renal disease (ESRD).

Literature Search

We searched MEDLINE (1966 to July 2001) and Igaku-Chuo-Zasshi (from 1987 to January 2002) online databases to identify English-language and Japanese-language publications of randomized controlled trials on the effects of ACE-inhibitors on patients with chronic renal disease. We evaluated abstracts, and those that were not excluded, according to the criteria listed later in this article, were reviewed in full. We scrutinized reference lists, relevant review articles, and *JSH 2000* for sources of additional published data.

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Table 1 Study Characteristics Included in the Meta-analysis (Continued)

Hyper-tension (%)	Causes of Renal Disease (No.)							Concomitant Medication	Dietary Advice?		
	Glomer-ular Disease	Polycystic Disease	Inter-stitial Disease	Nephro-sclerosis	Diabetic Nephrop-athy	Reflux Nephrop-athy	Hered-itary Nephritis			Others, Unknown	
36.9					16 409 (IDDM)				AD B, D, PA, CA, V	Yes	
81.7	85	14			33			87	B, D, PA, V, AD, I	Yes	
82.0	192	64	105	97	21			104	B, C, D, PA, CA, V	Yes	
	103	9						54	B, C, D, PA, CA, V [†]	Yes	
100	NA	NA	NA	NA	0	NA	NA	NA	B, D, PA, CA, V		
	NA	NA	NA	NA	0	NA	NA	NA	B, D, PA, CA		
	40	8		0		16		6	B, C, D, PA, CA	Yes	
	76	17	28					10	B, C, D, CA, PA	Yes	
84.3	17	11	17		13			14	B, C, D, V	Yes	
100	0	0	0	0	0	0	0	0	B, C, D	No	
	27	14	23	30				9	C, D, CA		
100	47	16	19	8				6	4	C, D, CA	No
100	35	12	23	36				15	B, D, CA, PA	Yes	

ACE-Inhibitors and Renal Insufficiency

Study Selection Criteria

We included 13 published and two unpublished reports of randomized controlled trials in patients with diabetic or non-diabetic renal disease that compared (1) the effect of anti-hypertensive regimens, including ACE-inhibitors, and (2) the effect of regimens without ACE-inhibitors or placebo. We included a trial if:

- a follow-up of at least one year was planned.
- the average Scr concentration or the GFR (when the Scr level was not available at baseline) was provided.
- the total number of patients who progressed to ESRF or whose renal function deteriorated more than 50% from baseline during follow-up was stated.

Hypertension or renal insufficiency at baseline levels was not necessarily required for our criteria. We gathered some data from review articles and examined unpublished data from those articles in which authors had requested data from the investigators. We also included the reported data, based on personal communications, if they met the criteria presented earlier.

Definitions

Our definition of chronic renal disease was intentionally broad to include all potential causes of renal disease *except* for renovascular hypertension and renal artery stenosis. ESRF was measured by the start of dialysis or transplantation, and a two-fold deterioration of renal function was defined as a doubling of the Scr concentration (DScr) of more than 50% from the baseline during follow-up.

Exclusion Criteria

The principal criteria for ineligibility were as follows:

- patients in nonrandomized controlled trials
- patients in nonparallel or crossover studies
- patients who were followed for less than one year
- patients with renovascular disease, including renovascular hypertension and renal artery stenosis
- patients with ESRD who were undergoing dialysis, post-kidney transplantation, or nephrectomy
- patients with chronic congestive heart failure
- pregnant women
- pediatric patients (younger than an average of 16 years of age)
- patients with a history of allergy to ACE-inhibitors

Outcomes and Data Extraction Criteria

In this study, we defined both ESRF and DScr as the primary endpoints. We listed the number of patients who reached these endpoints and extracted several specific types of data to be incorporated into the analysis from the articles. The extracted information included the number of patients at the start of the study, their sex, the average patient age, specific ACE-inhibitors and their doses, control regimens, duration of follow-up, causes of renal disease, average baseline Scr (or GFR, when the Scr value was not available), the average baseline albumin or protein excretion, pre-treatment mean systolic and

diastolic blood pressures, outcomes, mortality rates, and patient withdrawals from the study. For all studies, the Scr levels were standardized to milligrams per deciliter (mg/dl), and the excretion of urine albumin and protein was standardized to milligrams per 24 hours.

Statistical Analysis

We calculated the pooled estimate of effect by using the Mantel-Haenszel method,^{12,13} which assumes a fixed-effect model. Using this method, as previously described, we calculated the variance of individual effect assessments, the weight of each study, and, ultimately, the summary odds ratios (ORs) and 95% confidence intervals (CIs) for the endpoints of ESRF and DScr when studies were homogeneous.¹⁴ For any trial that had no (zero) events, we added a constant of 0.5 to each zero cell of the corresponding 2 × 2 table before calculating the statistics.¹⁵ We assessed the homogeneity of effect by calculating a Q statistic, in which the number of degrees of freedom was equal to the number of trials included in the analysis minus 1 if a P value of less than .05 was considered statistically significant.

We used intention-to-treat analysis and included all randomized patients in the statistical analysis, regardless of the reasons for withdrawal from the study during the follow-up intervention period and regardless of the patient's ability to satisfy the protocol criteria.

RESULTS

We identified 13 published^{5,16-28} and two unpublished (Brenner BM, et al.; Toto RD, et al.) randomized controlled trials that met inclusion and exclusion criteria and nine of the published studies from a MEDLINE search.^{16-23,25,26} We obtained four published studies^{5,24,27,28} by a manual search of the bibliographies in related articles (Table 1). Basically, we extracted data from the original article, but when further data were necessary,²³⁻²⁸ we used reliable review articles²⁹⁻³¹ in which the data met our criteria. We also extracted the data of two unpublished trials from these review articles, in which all the necessary data had been obtained by individual personal communication between the reviewer and the investigators.

Although both stratum 1²¹ and stratum 2²² are the subclasses of the Ramipril Efficacy in Nephropathy (REIN) trial, we treated these data as two distinct trials because the patient groups did not overlap with each other at randomization.

In one published trial,²⁴ all patients had normal Scr levels and none had glucosuria; however, their initial GFR was less than 100 mg/dl, and the loss of renal function with time was greater than the age-matched normotensive population. We therefore included this trial in the meta-analysis.

Tables 1 and 2 present the baseline characteristics of the 15 studies that met the inclusion criteria. Of those patients identified, the control groups received placebo in nine studies, conventional treatments in two studies, beta blockers in three studies, and calcium-channel blockers in one study.

Placebo-Controlled Trials

Nine placebo-controlled studies included a total of 1,699 patients, with 863 randomly assigned to receive ACE-inhibitor therapy and 836 patients assigned to receive placebo.

ACE-Inhibitors and Renal Insufficiency

The follow-up period ranged from approximately one to three years. Five studies evaluated enalapril; two studies, ramipril; and the remaining two, benazepril and captopril, respectively. Most of the patients (26% to 78%) were men, whose average age ranged from 35 to 52 (see Table 1). Mean baseline Scr levels were 1.3 to 4.8 mg/dl, and most patients had proteinuria, with a mean urinary protein excretion of 2.7 g/24 hours (Table 2).

Many researchers gave dietary advice to the patients, and, when necessary, they added various conventional medications other than ACE-inhibitors and ARBs (i.e., beta-adrenergic blockers, calcium-channel blockers, diuretics, peripheral alpha-adrenergic blockers, central alpha-adrenergic agonists, vasodilators, and antidiabetic agents, including insulin) to both groups. Table 3 lists the ORs of individuals and their outcomes.

End-Stage Renal Failure

Of the 863 patients randomly assigned to receive an ACE-inhibitor, 67 patients (7.8%) entered dialysis or transplantation (ESRF); in contrast, 104 of 836 patients (12.4%) randomly assigned to the placebo group progressed to ESRF. The pooled overall OR for ESRF was 0.59 (95% CI, 0.42–0.83), and the homogeneity among studies was significant ($P > .91$) (Figure 1). There was also homogeneity in ESRF between the two subgroups of trials of different baseline Scr levels: the summary OR in the subgroup of patients with Scr concentrations below 2.0 mg/dl was 0.65 (95% CI, 0.37–1.15, $P = 0.63$) and 0.55 (95% CI, 0.35–0.85, $P = .74$, homogeneity) in the subgroup with Scr levels ≥ 2.0 and below 3.0.

The same result was obtained for the other six active-controlled studies in the analysis. That is, the summary OR

in 15 trials was 0.59 (95% CI, 0.45–0.77, $P = .93$, homogeneity), and the pooled OR was 0.53 (95% CI, 0.45–0.82, $P = .81$) in the subgroup of patients with values of Scr ≥ 2.0 and below 3.0 but the pooled OR was 0.77 (95% CI, 0.46–1.31, $P = .55$, homogeneity) in the subgroup of those with Scr levels below 2.0.

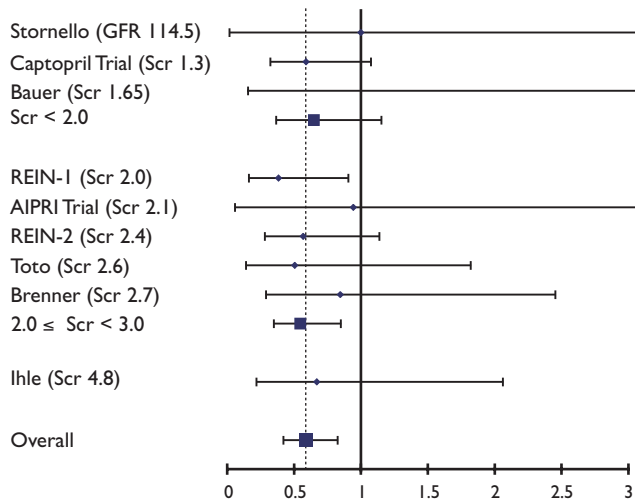


Figure 1 Odds ratios (ORs) and their 95% confidence intervals (CIs) for end-stage renal failure (ESRF) in each of nine placebo-controlled trials. The overall pooled OR was 0.59 (95% CI, 0.42–0.83, $P > .91$, homogeneity). AIPRI = ACE-Inhibition in Progressive Renal Insufficiency Trial; GFR = glomerular filtration rate; REIN = Ramipril Efficacy in Nephropathy Trial.

Table 2 Baseline Characteristics of Each Study Population at Randomization

Study	Serum Creatinine (mg/dl)	GFR (ml/min/1.73 m ²)	Creatinine Clearance (ml/min/1.73 m ²)	Urinary Protein Excretion (g/24 hr)	Urinary Albumin Excretion (mg/24 hr)	Urea Nitrogen Excretion (g/24 hr)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Stornello ²⁸		114.5			337.5			
Captopril Trial ⁵	1.3		81.5	2.8 (≥ 0.5)		10.5	138.5	85.5
Bauer ²⁷	1.65	62.1	77.4	2.7			143	82.5
REIN Stratum 1 ²¹	2.0	46.5	52.3	1.7		19.4	143.5	89.2
AIPRI Trial ²⁰	2.1	NA	42.6	1.8		15.2	143	87.5
REIN Stratum 2 ²²	2.4	38.8	45.5	5.4		20.6	148.9	91.9
Toto [†]	2.6	34	41	—			131	82.5
Brenner [†]	2.7	36	49	2.2			141	90
Ihle ^{25, 26}	4.8	15.2	15.4	2.1			150.5	87.5
Cinotti ¹⁸	2.3	35.8	36.3	0.5			141.6	85.8
Kamper ¹⁷	4.4*	15.9*			16.5* mmol/24 hr	12.1*	145.5*	91*
Himmelmann ²⁴	1.0	82.0	NA				169	100
van Essen ²³	1.8	71	NA				154	90.5
Hannedouche ¹⁶	3.0	25.7	NA	2.2		6.2	166.5	102
Zucchelli ¹⁹	3.0	NA	30.5	1.8			165	100

All data are shown as mean.

* Data are the mean of the reported median value of ACE-I group and control group in the original article.

† Unpublished data provided by the study investigators.^{30,31}

ACE-I = angiotensin-converting enzyme-inhibitor; BP = blood pressure; GFR = glomerular filtration rate.

ACE-Inhibitors and Renal Insufficiency

Table 3 Odds Ratio and 95% Confidence Interval from Each Study of Patients with Renal Insufficiency

Study	Sample Size		End-Stage Renal Failure				DSCr					
			ACE-I	Control	OR	95% CI		ACE-I	Control	OR	95% CI	
	ACE-I	Control				Lower	Upper				Lower	Upper
Stornello ²⁸	8	8	0	0	1.000	0.0176	56.86	0	0	1.000	0.0176	56.86
Captopril Trial ⁵	207	202	20	31	0.590	0.324	1.074	25	43*	0.508	0.297	0.869
Bauer ²⁷	18	15	2	0	3.750	0.000	90.00	2*	0	3.750	0.156	90.00
REIN Stratum 1 ²¹	99	87	9	18	0.383	0.162	0.905	NA	NA			
AIPRI Trial ²⁰	300	283	1	1	0.943	0.059	15.15	30	56	0.450	0.279	0.726
REIN Stratum 2 ²²	78	88	17	29	0.567	0.282	1.139	1	11	0.091	0.011	0.721
Toto [‡]	64	60	4	7	0.505	0.140	1.821	NA	NA			
Brenner [‡]	53	59	7	9	0.845	0.291	2.454	5	4	1.432	0.364	5.640
Ihle ^{25,26}	36	34	7	9	0.670	0.218	2.062	NA	NA			
Cinotti ¹⁸	66	65	2	5	0.375	0.070	2.007	3	7 [†]	0.395	0.095	1.598
Kamper ¹⁷	35	35	10	13	0.677	0.248	1.847	NA	NA			
Himmelmann ²⁴	131	129	0	0	0.985	0.019	50.01	NA	NA			
van Essen ²³	51	52	5	2	2.717	0.502	14.70	NA	NA			
Hannedouche ¹⁶	52	48	10	17	0.434	0.175	1.077	NA	NA			
Zucchelli ¹⁹	60	61	7	14	0.443	0.165	1.192	NA	NA			

* Including the number of patients whose renal insufficiency resulted in end-stage renal failure.

† Number of patients whose renal function (glomerular filtration rate) was halved by 50% from the baseline.

‡ Unpublished data provided by study investigators.^{30,31}

ACE-I = angiotensin-converting enzyme inhibitor—treated group; CI = confidence interval; Control = control group; DSCr = doubling of serum creatinine concentration; OR = random effects odds ratio.

As for the subgroup of patients with Scr levels greater than 3.0, only one trial²⁵ was conducted (OR = 0.67 [95% CI, 0.22–2.06]). We were unable to calculate summary ORs in the placebo-controlled trials, but three more active-controlled studies were performed in patients whose average baseline Scr levels were 3.0 mg/dl or greater.^{16,17,19}

Next, we combined the ORs in patients with ESRF from the four studies. Of the 183 patients randomly assigned to receive ACE-inhibitor treatment, 34 patients (18.6%) entered dialysis or transplantation (ESRF); in contrast, ESRF developed in 53 of 178 patients (30%) who had been randomly assigned to the control group. The pooled overall OR was 0.53 (95% CI,

0.32–0.87), and the homogeneity among four studies was significant ($P > .83$) (Figure 2). This estimate changed very little even when the placebo-control study was excluded (Table 4); in other words, after the exclusion of the study by Ihle et al.,²⁵ the overall OR did not change.

Doubling of Serum Creatinine Levels

Aside from two studies that yielded no data, homogeneity was present in secondary outcomes (DSCr) in six studies, for which the pooled OR for DSCr was 0.49 (95% CI, 0.35–0.68, $P = .84$, homogeneity) (Figure 3). The summary OR for the subgroup with levels of Scr below 2.0 mg/dl was 0.55 (95% CI, 0.33–0.93, homogeneity $P = .57$). However, no homogeneity existed in the subgroup of 2.0 of Scr concentrations at or below 3.0 mg/dl ($P < .05$, homogeneity), and there was no study of the subgroup of patients with Scr levels above 3.0 mg/dl. Because the number of SCr doublings could be obtained only from these six studies, we performed no further analyses.

Active-Controlled Trials

We identified six randomized, active-controlled studies in addition to the placebo-controlled trials. Three studies involved beta-blocker controls, two used conventional treatments, one included calcium-channel blockers, and none of the trials used ARBs. (“Conventional” treatment indicates the medications with unspecified conventional antihypertensive drugs except for ARBs.)

All of the studies reported the number of patients who progressed to ESRF, but no studies reported the number of patients in whom kidney function deteriorated more than two times from the baseline (DSCr); the only exception was one

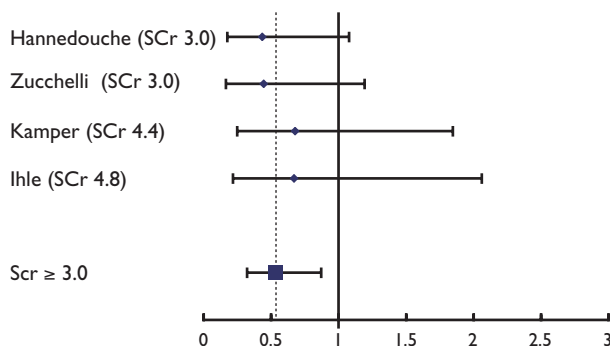


Figure 2 Odds ratios (ORs) and their 95% confidence intervals (CIs) for end-stage renal failure (ESRF) in each of four placebo-controlled or active-controlled trials in the subgroup of patients with a serum creatinine concentration (Scr) of 3.0 mg/dl or greater. The overall pooled OR was 0.53 (95% CI, 0.32–0.87, $P > .83$, homogeneity).

ACE-Inhibitors and Renal Insufficiency

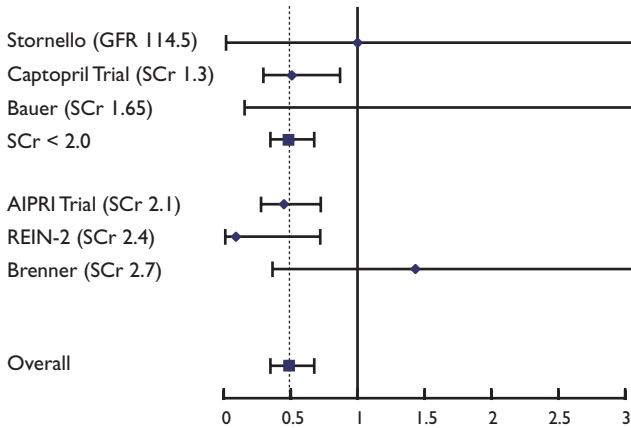


Figure 3 Odds ratios (ORs) and their 95% confidence intervals (CIs) for serum creatinine concentrations in each of six placebo-controlled trials. The pooled OR for the subgroup of patients with SCr levels below 2.0 mg/dl was 0.55 (95% CI, 0.33–0.93, $P = .57$, homogeneity) and the overall pooled OR was 0.49 (95% CI, 0.35–0.68, $P > .84$, homogeneity). AIPRI = ACE-Inhibition in Progressive renal Insufficiency trial; GFR = glomerular filtration rate; REIN = Ramipril Efficacy in Nephropathy Trial.

study¹⁸ that had reported the number of patients whose GFR was reduced more than 50% from baseline.

The pooled ORs for every control group are shown in Figure 4. A total of 201 patients were randomly assigned to receive either ACE-inhibitors (101 patients) or conventional treatment (100 patients); 12 and 18 patients in these groups, respectively, progressed to ESRF. However, there was no statistical difference in the pooled number of patients with ESRF between the ACE-inhibitor and conventional treatment groups (OR = 0.57 [95% CI, 0.24 to 1.35, homogeneity $P > 0.45$]).

From a total of 463 patients who were randomly assigned to receive ACE-inhibitors (234 patients) or beta blockers (229 patients), 15 and 19 patients in these groups, respectively, progressed to ESRF. However, there was no statistical difference in the pooled number of patients with ESRF between the treatment arms either (OR = 0.70 [95% CI, 0.33–1.47, $P > .19$, homogeneity]). For calcium-channel blockers, because only one trial fit our selection criteria¹⁹ (OR = 0.44 [95% CI, 0.17–1.19]), we did not calculate summary ORs.

Death and Adverse Reactions

Table 5 shows the reported mortality rates and major patient-withdrawal rates in each study after randomization. Most of these deaths were caused by nonrenal factors, and there was no difference in the number of deaths between the groups. In the patients receiving ACE-inhibitors, 19 patients experienced the side effect of cough and 14 had hyperkalemia; in the control groups, five patients had cough and five patients had hyperkalemia.

DISCUSSION

We conducted this study to demonstrate the relationship between baseline renal function and the effectiveness of ACE-inhibitors in patients with chronic renal failure. We performed subgroup analysis by using a meta-analysis based on Scr levels at baseline. Although death is most commonly used as the

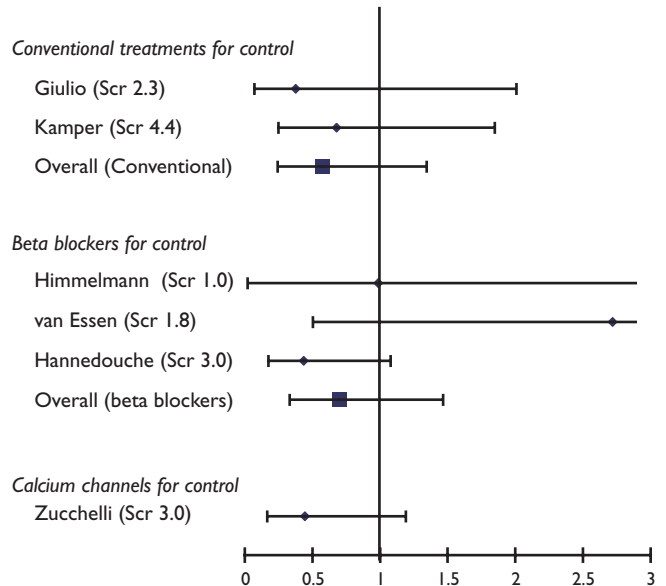


Figure 4 Odds ratios (ORs) and their 95% confidence intervals (CIs) for end-stage renal failure (ESRF). Summary ORs were estimated in every control group in each of six placebo-controlled trials. The pooled OR for angiotensin-converting enzyme-inhibitors versus conventional treatment was 0.57 (95% CI, 0.24–1.35, $P > .83$). The pooled OR, compared with beta blockers, was 0.70 (95% CI, 0.33–1.47, $P > .19$, homogeneity).

Table 4 Summary Odds Ratios in End-Stage Renal Failure in Studies of Subgroups of Patients with Serum Creatinine Levels of 3.0 mg/dl or Greater

Studies Included in Analysis	No. of Studies	Summary Odds Ratio	95% CI		P Value
			Lower	Upper	
All studies*	4	0.530	0.322	0.870	0.810
Active-controlled studies†	3	0.500	0.287	0.871	0.720

* All four studies included in subgroup of serum creatinine concentration of 3.0 mg/dl or greater.

† Three active-controlled trials except for the placebo-controlled studies of Ihle et al.^{25,26}

CI = confidence interval.

ACE-Inhibitors and Renal Insufficiency

Table 5 Potential Major Side Effects Caused by Treatment with Angiotensin-Converting Enzyme-Inhibitors

Study	Baseline Serum Creatinine (mg/dl)	Death*		Cough		Hyperkalemia		Total Withdrawal†	
		ACE-I	Control	ACE-I	Control	ACE-I	Control	ACE-I	Control
Stornello ²⁸		NA	NA	NA	NA	NA	NA	NA	NA
Captopril Trial ⁵		8 (5) ^{††}	14 (3) ^{††}	NS	NS	3 [‡]	0	NS	NS
Bauer ²⁷	Scr < 2.0	NS	NS	NS	NS	2 ^{**}	0	NA	NA
Himmelmann ²⁴		0	0	13	3 [‡]	NS	NS	25	14
van Essen ²³		2	1	1	0	0	0	11	6
REIN Stratum 1 ²¹		1	0	1	0	0	1	NS	NS
AIPRI Trial ²⁰		8	1	1	2	5	3	68	61
REIN Stratum 2 ²²	2 ≤ Scr < 3.0	2	1	NS	NS	1	1	NS	NS
Toto ^{††}		0	2	NA	NA	NA	NA	25	10
Brenner ^{††}		2	1	NA	NA	NA	NA	17	18
Cinotti ¹⁸		NS	NS	0	0	1	0	4	3
Ihle ^{25,26}		1	1	NS	NS	NS	NS	17	6
Kamper ¹⁷	Scr > 3.0	1	4	NS	NS	NS	NS	5	7
Hannedouche ¹⁶		1	2	1	0	2	0	12	14
Zucchelli ¹⁹		1	0	2	0	0	0	16	15

* Death includes the number of patients who died after randomization in each study.

† Total number of withdrawal includes deaths.

‡ Bronchospasm with beta blockers.

** Transient hyperkalemia spontaneously reversed to normal levels.

†† Numbers in parentheses represent the number of patients whose deaths were related to renal problems.

‡‡ Unpublished data provided by the study investigators.^{30,31}

ACE-I = angiotensin-converting enzyme-inhibitor; AIPRI = ACE Inhibition in Progressive Renal Insufficiency Study; NA = no data available; NS = not specified in corresponding literature; REIN = Ramipril Efficacy in Nephropathy Study.

primary endpoint for this kind of study, we adopted ESRF and DScr as endpoints in our study. The reported mortality rates included deaths mainly from nonrenal causes, such as myocardial infarction, asthma, postoperative complications, and diabetic coma. Thus, using death as an endpoint might not reveal accurate results.

As a whole, ACE-inhibitors were effective in preventing the progression of renal insufficiency, no matter which endpoints were used. There was no discrepancy between the summary ORs in nine placebo-controlled trials and in 15 trials, including six active-controlled trials.

These results also appear to support the findings from two other meta-analyses.^{30,31} In subgroup analyses, ACE-inhibitors were effective in the subgroup of patients with values of Scr ≥ 2.0 and below 3.0 mg/dl on ESRF; in contrast, there was no significance in the subgroup with Scr levels below 2.0 mg/dl. For DScr, however, there was significance in the subgroup with Scr concentrations of less than 2.0 mg/dl. This difference might be caused by the degree of the remaining renal function at baseline; that is, the course of ESRF development is relatively long in patients with low baseline Scr levels (who had a slight renal insufficiency), and patients would progress not to ESRF but to DScr during the follow-up period.

In contrast, the course of progression to ESRF is relatively short in patients with the greater baseline Scr levels (whose disease was more advanced), and ESRF developed in many patients. This may be reflected in the Captopril Study and in

the ACE-Inhibition in Progressive Renal Insufficiency (AIPRI) Study, which involved patients with slight kidney insufficiency, compared with the REIN-2 studies or those by Brenner and colleagues.^{30,31} As a result, although we could not estimate the summary ORs on the combined endpoint of ESRF and DScr, we ensured that these results supported the efficacy of ACE-inhibitors in patients with baseline Scr levels below 3.0 mg/dl. Interestingly, although the combined endpoints of ESRF and DScr must be better for this analysis, we could analyze these endpoints only separately, because the patients with a DScr could not be entirely distinct from those who progressed to ESRF.

For the subgroup of patients with SCr levels at 3.0 or greater, there were no randomized controlled studies of DScr, but there was only one placebo-controlled trial with the endpoint of ESRF. We combined a placebo-controlled study and three active-controlled studies in this subgroup analysis and performed a sensitivity analysis (Table 4). We found that ACE-inhibitors were efficacious against deterioration of renal function in patients with Scr levels at or below 3.0 mg/dl. We performed the sensitivity analysis to confirm the validity of combining a placebo-controlled study and the other multiple, controlled studies in this meta-analysis. There was no difference between the subgroup analysis and the sensitivity analysis. The ORs and their 95% CIs were nearly equal, thus lending support to our conclusion.

Although ACE-inhibitors were effective in this analysis, this treatment poses risk. ACE-inhibitor therapy in patients with se-

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rious renal insufficiency (with baseline Scr levels of 3.0 mg/dl or less) can lead to acute renal failure or hyperkalemia. However, for the reported mortality and number of patients with hyperkalemia, cough, and total withdrawals in the 15 adopted studies, there seemed to be no relation between their incidence and baseline Scr levels: the risks associated with ACE-inhibitor treatment in patients with Scr levels above 3.0 mg/dl are similar to the risks in patients with Scr levels of 3.0 mg/dl or below (Table 5). Therefore, we assume that the identical use of ACE-inhibitors can be practical with some dosage adjustment according to baseline renal function.

At this point, we have evaluated only the efficacy of the ACE-inhibitors. All studies that we identified aimed to evaluate the renoprotective effect of ACE-inhibitors, but the data on adverse reactions were insufficient to allow a thorough, careful analysis. Therefore, we plan to conduct an investigation in Japan to determine:

- the efficacy of ACE-inhibitors in patients with Scr levels of 3.0 mg/dl or greater.
- the risks associated with ACE-inhibitor treatment.
- the initial dose needed to treat renal insufficiency.
- the most effective type of ACE-inhibitor.

After this step, we plan to define the risks and benefits of treatment with ACE-inhibitors in patients with various renal dysfunctions.

CONCLUSION

ACE-inhibitors are effective in controlling the progression of renal disease to ESRF or DScr, not only in patients with Scr levels of 3.0 mg/dl and lower but also in patients with Scr levels above 3.0 mg/dl. It is expected that future research will clarify the risks and benefits of ACE-inhibitor therapy in patients with renal dysfunction.

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