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Effect of Angiotensin-Converting Enzyme Inhibitors on the Progression of Nondiabetic Renal Disease: A Meta-Analysis of Randomized Trials

Ioannis Giatras, MD; Joseph Lau, MD; and Andrew S. Levey, MD, for the Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group*

Background: The effect of angiotensin-converting enzyme (ACE) inhibitors in slowing the decline in renal function in nondiabetic renal disease varies among studies.

Purpose: To use meta-analysis to assess the effect of ACE inhibitors on the development of end-stage renal disease caused by factors other than diabetes.

Data Sources: The English-language medical literature, identified by a MEDLINE search, and unpublished studies.

Study Selection: All randomized studies that compared ACE inhibitors with other antihypertensive agents and had at least 1 year of planned follow-up were selected. Studies of diabetic renal disease and renal transplants were excluded. A total of 1594 patients in 10 studies was included.

Data Extraction: Data on end-stage renal disease, death, drop out, and blood pressure were extracted. Study investigators confirmed results and provided additional data.

Data Synthesis: Among 806 patients receiving ACE inhibitors, 52 (6.4%) developed end-stage renal disease and 17 (2.1%) died; in the 788 controls, the respective values were 72 (9.1%) and 12 (1.5%). The pooled relative risks were 0.70 (95% CI, 0.51 to 0.97) for end-stage renal disease and 1.24 (CI, 0.55 to 2.83) for death; the studies were not significantly heterogeneous. The decreases in weighted mean systolic and diastolic blood pressures during follow-up were 4.9 and 1.2 mm Hg greater, respectively, in the patients who received ACE inhibitors.

Conclusions: Angiotensin-converting enzyme inhibitors are more effective than other antihypertensive agents in reducing the development of end-stage nondiabetic renal disease, and they do not increase mortality. It could not be determined whether this beneficial effect is due to the greater decline in blood pressure or to other effects of ACE inhibition.

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From New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts. For current author addresses, see end of text.

*For members of the Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group, see Appendix.

Angiotensin-converting enzyme (ACE) inhibitors slow the progression of diabetic renal disease. In patients with microalbuminuria, these drugs slow progression to overt proteinuria (1, 2); in patients with proteinuria, they decrease urine protein excretion and slow the decline in glomerular filtration rate, the increase in serum creatinine level, and the onset of renal failure (3, 4). These effects occur in patients with or without preexisting hypertension, and in some studies (1, 4, 5), the beneficial effect on renal disease seems to have been greater than the effect on blood pressure.

Maschio and colleagues (6) reported a beneficial effect of ACE inhibition on the progression of nondiabetic renal diseases. Their multicenter clinical trial compared the ACE inhibitor benazepril with placebo for effect on the increase in serum creatinine level in 583 patients with various renal diseases. Although the incidence of the primary outcome measure (a twofold increase in baseline serum creatinine level) was significantly lower in the ACE inhibitor group, the difference between groups in follow-up mean serum creatinine level was small (0.1 to 0.2 mg/dL). Because renal disease progresses slowly, only two patients developed end-stage renal disease during this trial. Finally, the mortality rate was significantly ($P = 0.04$) higher in the ACE inhibitor group than in the placebo group (1 death per 93 patient-years compared with 1 death per 656 patient-years). In this study, therefore, neither the magnitude of the beneficial effect nor the safety of ACE inhibition was established conclusively.

Several smaller randomized trials of ACE inhibitors in patients with nondiabetic renal disease have

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also been reported (7–17). These studies, however, did not have uniform results. Possible sources of variability include different methods of measuring renal function, different causes and severity of renal disease, use of different ACE inhibitors, and small sample sizes. Thus, it remains uncertain whether ACE inhibitors are preferable to other antihypertensive agents in the treatment of nondiabetic renal diseases.

We used meta-analysis to combine information from randomized trials of ACE inhibitors in patients with nondiabetic renal disease. Our objectives were to assess 1) the effect of ACE inhibitors on the progression of renal disease, as judged by the onset of renal failure (the unequivocal and clinically relevant outcome measure); 2) the safety of ACE inhibitors, as judged by mortality rates; and 3) the effect of ACE inhibitors on blood pressure.

Methods

Literature Search

The meta-analysis was performed by using methods described elsewhere (18, 19). We searched the MEDLINE database for English-language studies on the effect of ACE inhibitors on renal disease in humans that were published between 1977 (the year in which the studies of ACE inhibitors in humans were first published) and May 1996. We also searched references, review articles, and abstracts from recent U.S. and international congresses. In addition, we sent letters to investigators who had experience in conducting trials that studied the effect of antihypertensive agents on the progression of renal disease to ask about other published or unpublished reports.

Selection Criteria

We included data from published or unpublished reports of randomized, controlled studies in which most patients had nondiabetic renal disease. The included studies had a planned length of follow-up of at least 1 year and reported the number of patients who developed end-stage renal disease (measured by initiation of dialysis or transplantation), died, and dropped out. If a series of papers was published by the same authors, all data were retrieved from the most recent report. Studies of patients who predominantly had diabetic renal disease or who had had renal transplantation were excluded. We did not require that patients have hypertension or renal insufficiency at baseline.

Data Extraction

Two authors extracted the data. We defined four outcome measures: end-stage renal disease, death, the combined outcome of end-stage renal disease or death, and drop out. The four outcome measures were summarized for each randomly assigned group in each study. This summary was sent to the principal investigator or co-investigator with a request to verify the data; provide any missing data; and, when applicable, update the results of ongoing studies. We also requested individual patient data for all studies.

The mean systolic and diastolic blood pressures during follow-up were computed as the weighted mean of the blood pressure results reported in published reports or from results provided to us by the investigators. Mean baseline and follow-up blood pressures of the ACE inhibitor and control groups were weighted by the number of patients in each group. We then computed the decline in weighted mean blood pressures from baseline to follow-up in both groups and the difference between groups in the weighted mean decreases in blood pressure.

Statistical Analysis

A two-sided P value less than 0.05 was used to indicate statistical significance. No adjustment was made for multiple comparisons.

Comparison of Randomly Assigned Groups

For each study, we computed the relative risk for each outcome in the ACE inhibitor group compared with the control group. The pooled relative risk for each outcome was computed by using the random-effects model described by DerSimonian and Laird (19). The random-effects model incorporates both between-study and within-study variability. Heterogeneity in relative risk among studies was assessed by use of the chi-square test. The data are presented as relative risks with 95% CIs.

We also compared the changes in weighted mean blood pressure during follow-up. Some studies did not provide data on the variability of follow-up blood pressures or individual patient data. Thus, we could not compute estimates of variance or CIs for the differences in the decline in blood pressure between groups.

Meta-Regression Analysis

Meta-regression analysis is a statistical method used to determine whether specific factors (covariates) influence the magnitude of the point estimate of the treatment effect across studies (20). The results are generally reported as slope coefficients and CIs. For the analyses reported here, characteristics of the sample in each study were related to the

Table 1. Characteristics of Studies of Nondiabetic Renal Disease Included in the Meta-Analysis*

Study (Reference)	Year†	Patients	Men	Mean Age	Planned Length of Follow-up	Mean Baseline Level of Renal Function		
						Plasma Creatinine Level	Creatinine Clearance	Glomerular Filtration Rate
		n	%	*y*	*mo*	*mg/dL*	*mL/min*	
Zucchelli et al. (7, 8)	1992	121	58	55	36	3.0	30	NA
Kamper et al. (9)	1992	70	53	48	24	4.4	NA	16
Brenner et al.‡	1993	112	64	47	36	2.7	49	36
Toto et al.‡	1993	124	64	52	36	2.6	41	34
van Essen et al.‡	1994	103	66	50	48	1.8	NA	71
Hannedouche et al. (10)	1994	100	53	51	36	3.0	NA	25
Bannister et al. (11)	1995	51	77	47	12	1.1	105	70
Himmelmann et al. (14)	1995	260	48	65	24	1.0	NA	82
Becker et al. (12) and Ihle et al. (13)	1996	70	51	44	24	4.2	15	15
Maschio et al. (6)	1996	583	72	51	36	2.1	43	NA

* NA = not available.
† The year of publication or approximate year of completion of unpublished studies is indicated.
‡ Unpublished data provided by the study investigators.

relative risk for end-stage renal disease in that study. We used univariate linear regression analysis to examine the effect of selected baseline variables and the difference in blood pressure between the randomly assigned groups on the relative risk expressed on a logarithmic scale. These analyses may be less sensitive for detecting associations than are multiple regression analysis of individual patient data in a pooled analysis.

Data Synthesis

Selection and Characteristics of the Studies

Ten published randomized trials with at least 1 year of follow-up were identified (6–17). Four unpublished studies that met these criteria were identified; three were completed and one was ongoing (Brenner BM, Toto R, van Essen GG, Aurell MA. Personal communications). No data on end-stage renal disease, death, or drop out were available for four studies (three published and one unpublished); thus, these studies were not included. After exclusions, seven published (6–14) and three unpublished studies were included, with a total of 1594 patients. Six studies—three published (6, 12–14) and the three unpublished—were blinded, and four studies were not blinded (7–11). Investigators from all 10 studies confirmed the number of randomly assigned patients and the number of patients who reached each defined outcome.

Characteristics of the studies and the patient samples are listed in **Tables 1** to **4**. The planned length of follow-up ranged from 12 to 48 months (**Table 1**). Most patients were men (range, 48% to 77%), and the mean age ranged from 44 to 66 years. Mean baseline impairment of renal function was mild in three studies (mean serum creatinine level, 1.0 to 1.8 mg/dL), moderate in five studies (mean serum creatinine level, 2.1 to 3.0 mg/dL), and severe in two studies (mean serum creatinine level, 4.2 to 4.4 mg/dL). In most studies, the proportion of patients with hypertensive nephrosclerosis, glomerular and interstitial diseases, and polycystic kidney disease was similar to that of patients with nondiabetic end-stage renal disease (**Table 2**) (21). One

Table 2. Causes of Renal Disease in Studies Included in the Meta-Analysis*

Study (Reference)	Hypertensive Nephrosclerosis	Glomerular Diseases	Insterstitial Diseases	Polycystic Kidney Disease	Other
	←		%		→
Zucchelli et al. (7, 8)	30	30	19	9	12
Kamper et al. (9)	0	43	24	16	17
Brenner et al.†	NA	NA	NA	NA	NA
Toto et al.†	NA	NA	NA	NA	NA
van Essen et al.†	29	26	22	14	9
Hannedouche et al. (10)	8	47	19	16	10
Bannister et al. (11)	0	100	0	0	0
Himmelmann et al. (14)	100	0	0	0	0
Becker et al. (12) and Ihle et al. (13)	0	57	26	11	6
Maschio et al. (6)	17	36	18	11	18

* NA = not available.
† Unpublished data provided by the study investigators.

Table 3. Target and Achieved Blood Pressures and Antihypertensive Medications in Studies Included in the Meta-Analysis*

Study	Study Design			ACE Inhibitor Group					Control Group				
	Target Blood Pressure		Concomitant Medication	Achieved Blood Pressure				Prescribed Medication and Dosage	Achieved Blood Pressure				Prescribed Medication and Dosage
				Baseline		Follow-up			Baseline		Follow-up		
	SBP	DBP		SBP	DBP	SBP	DBP		SBP	DBP	SBP	DBP	
	mm Hg			← mm Hg →				mg/d	← mm Hg →				mg/d
Zucchelli et al. (7, 8)	NS	<95	D, F	166	101	135	82	Captopril, 12.5–50	164	99	139	82	Nifedipine, 10–20
Kamper et al. (9)	120–140	80–90	B, C, D, G	152	91	136	82	Enalapril, ≥2.5	143	89	135	84	NS
Brenner et al.†	NS	65–80	B, D, E, F	141	90	124	79	Enalapril, 5–40	141	90	130	79	Placebo
Toto et al.†	NS	<95	B, D, E, F, G	134	82	133	84	Enalapril, 5–40	128	83	134	85	Placebo
van Essen et al.†	NS	<95 or change >10	C, D	153	90	136	79	Enalapril, 10–40	155	91	138	80	Atenolol, 50–100
Hannedouche et al. (10)	NS	<90	C, D, F	167	103	149	90	Enalapril, 5–10	166	101	150	89	Acebutolol, 400; Atenolol, 100
Bannister et al. (11)	NS	NS	NS	158	98	136	84	Enalapril, 5–20	151	95	138	86	Nifedipine, 20–60
Himmelmann et al. (14)	NS	<90	B, C, D	168	100	153	89	Cilazapril, 2.5–5	170	100	156	86	Atenolol, 50–100
Becker et al. (12) and Ihle et al. (13)	NS	NS	B, C, D, E, F	147	87	141	82	Enalapril, 5	154	88	154	88	Placebo
Maschio et al. (6)	NS	90 while supine	NS	142	87	135	84	Benazepril, 10	144	88	144	88	Placebo

* ACE = angiotensin-converting enzyme; B = β-adrenergic blockers; C = calcium-channel blockers; D = diuretics; DBP = diastolic blood pressure; E = peripheral α-adrenergic blockers; F = central α-adrenergic agonists; G = vasodilators; NS = not specified; SBP = systolic blood pressure.
† Unpublished data provided by the study investigators.

study (11), however, included only patients with IgA nephropathy, and another study (14) included only patients with essential hypertension. Two studies included patients with diabetic nephropathy: 13 of 70 patients (19%) in one study (9) and 21 of 583 patients (3.6%) in the other (6). These patients are included in our analysis.

Table 3 lists blood pressures and data on antihypertensive medications. Enalapril was used in seven studies, and captopril, cilazapril, and benazepril were used in one study each. The control groups received placebo in four studies, β-adrenergic blockers in three studies, calcium-channel blockers in two studies, and an unspecified combination of antihypertensive agents in one study. The same blood pressure target was defined for both ACE inhibitor and control groups in each study, and various medications other than ACE inhibitors, including β-adrenergic blockers, calcium-channel blockers, diuretics, peripheral α-adrenergic blockers, central α-adrenergic agonists, and vasodilators, were added to both groups as needed in an effort to reach the target. Variation in baseline blood pressure was due, in part, to the timing of blood pressure measurements dictated by study protocol (for example, measurement while patients received medications compared with measurement while patients did not receive medications). Weighted mean baseline systolic blood pressures were 150.1 mm Hg in the ACE inhibitor group and 151.0 mm Hg in the control group. Weighted mean baseline diastolic blood pressures were 91.7 mm Hg and 91.9 mm Hg, respectively. In most studies, blood pressure declined from baseline to follow-up. Weighted mean follow-up systolic blood pressures were 138.3 mm Hg in the ACE inhibitor group and 143.6 mm Hg in the control group. Weighted mean follow-up diastolic blood pressures were 84.2 mm Hg and 85.6 mm Hg, respectively. Therefore, the respective declines in weighted mean systolic and diastolic blood pressure were 4.9 and 1.2 mm Hg greater in the ACE inhibitor group than in the control group.

Decline in renal function was estimated from the serum creatinine level in seven studies, creatinine clearance in four studies, and glomerular filtration rate in nine studies (**Table 4**). The methods for measuring glomerular filtration rate included renal clearance of inulin in one study, plasma clearance of technetium-99m pentetate in two studies, plasma clearance of chromium 51 EDTA in three studies, and renal clearance of iodine ^{125}iothalamate in three studies. None of the studies was designed to detect a difference in end-stage renal disease or death. Five studies concluded that ACE inhibitors were more effective than other antihypertensive agents in slowing the decline in renal function. Five studies (including the three unpublished studies) did not find that ACE inhibitors were more effective.

Comparisons of Randomly Assigned Groups

The number of randomly assigned patients in each group who reached the defined outcomes is shown in **Table 5**. Because of the slow rate of progression of renal disease and the relatively short duration of follow-up, few patients in any study developed renal failure or died.

End-Stage Renal Disease

The relative risk for the onset of end-stage renal disease in the ACE inhibitor group compared with the control group is shown in the left side of the **Figure**.

Table 4. Main Outcome Measures and Conclusions in Studies Included in the Meta-Analysis*

Study (Reference)	Main Outcome Measures Related to Decline in Renal Function†	Conclusion
Zucchelli et al. (7, 8)	GFR, creatinine clearance, plasma creatinine level	No difference
Kamper et al. (9)	GFR	ACE inhibitors more effective
Brenner et al.‡	GFR, creatinine clearance, plasma creatinine level	No difference
Toto et al.‡	GFR, creatinine clearance, plasma creatinine level	No difference
van Essen et al.‡	GFR, plasma creatinine level	No difference
Hannedouche et al. (10)	GFR, plasma creatinine level	ACE inhibitors more effective
Bannister et al. (11)	GFR	No difference
Himmelmann et al. (14)	GFR	ACE inhibitors more effective
Becker et al. (12) and Ihle et al. (13)	GFR, creatinine clearance, plasma creatinine level	ACE inhibitors more effective
Maschio et al. (6)	Plasma creatinine level	ACE inhibitors more effective

* ACE = angiotensin-converting enzyme; GFR = glomerular filtration rate.
† GFR measured on a subset of patients.
‡ Unpublished data provided by the study investigators.

The reported relative risk for end-stage renal disease ranged from 0.51 to 3.36 and was not significant in any single study. However, the pooled relative risk was 0.70 (CI, 0.51 to 0.97), indicating a statistically significantly lower risk for development of end-stage renal disease in the ACE inhibitor group. The result of the test for heterogeneity of relative risk among studies was not significant ($P < 0.75$ and >0.5), indicating that treatment effect did not significantly differ among studies. Restricting the analysis to the seven published studies gave similar results (relative risk, 0.65 [CI, 0.45 to 0.94]). In the seven studies that used enalapril, the pooled relative risk for end-stage renal disease was 0.74 (CI, 0.52 to 1.05).

Death

The relative risk for death is shown in the right side of the **Figure**. The pooled relative risk was not significant (1.24 [CI, 0.55 to 2.83]), and the result of the test for heterogeneity among studies was not significant ($P > 0.2$). In Maschio and colleagues' study (6), a trend toward an increased risk for death was seen in the ACE inhibitor group (relative risk, 7.55 [CI, 0.95 to 60.0]). In the other studies, the pooled relative risk was 0.89 (CI, 0.36 to 2.17).

Combined Outcome (End-Stage Renal Disease or Death) and Drop Outs

No significant difference was seen in the risk for the combined outcome of end-stage renal disease or death (relative risk, 0.80 [CI, 0.55 to 1.17]). If Maschio and colleagues' study (6) is omitted from the analysis, the risk for end-stage renal disease or death is significantly lower in the ACE inhibitor group (relative risk, 0.70 [CI, 0.52 to 0.94]). The number of drop outs did not significantly differ among studies (relative risk, 1.16 [CI, 0.91 to 1.47]).

Meta-Regression Analysis

We used meta-regression analysis to examine the associations of baseline factors and blood pressure during follow-up with the effect of ACE inhibitors on end-stage renal disease.

Baseline Factors

We related the relative risk for end-stage renal disease (on a logarithmic scale) in each study to the

Table 5. Summary of Main Outcomes in the Randomly Assigned Groups*

Study (Reference)	ACE Inhibitor Group					Control Group				
	Randomly Assigned Patients	ESRD	Death	Death or ESRD	Drop Out	Randomly Assigned Patients	ESRD	Death	Death or ESRD	Drop Out
	← n →					← n →				
Zucchelli et al. (7, 8)	60	7	1	8	15	61	14	0	14	16
Kamper et al. (9)	35	10	1	11	4	35	13	4	17	3
Brenner et al.†	53	7	2	9	17	59	9	1	10	18
Toto et al.†	64	4	0	4	25	60	7	2	9	10
van Essen et al.†	51	5	3	8	13	52	2	1	3	15
Hannedouche et al. (10)	52	10	1	11	11	48	17	2	19	12
Bannister et al. (11)	24	1	0	1	1	27	0	0	0	6
Himmelmann et al. (14)	131	0	0	0	25	129	0	0	0	14
Becker et al. (12) and Ihle et al. (13)	36	7	1	8	16	34	9	1	10	12
Maschio et al. (6)	300	1	8	9	42	283	1	1	2	38
Total	806	52	17	69	169	788	72	12	84	144

* All values are the numbers of patients. ACE = angiotensin-converting enzyme; ESRD = end-stage renal disease.
† Unpublished data provided by the study investigators.

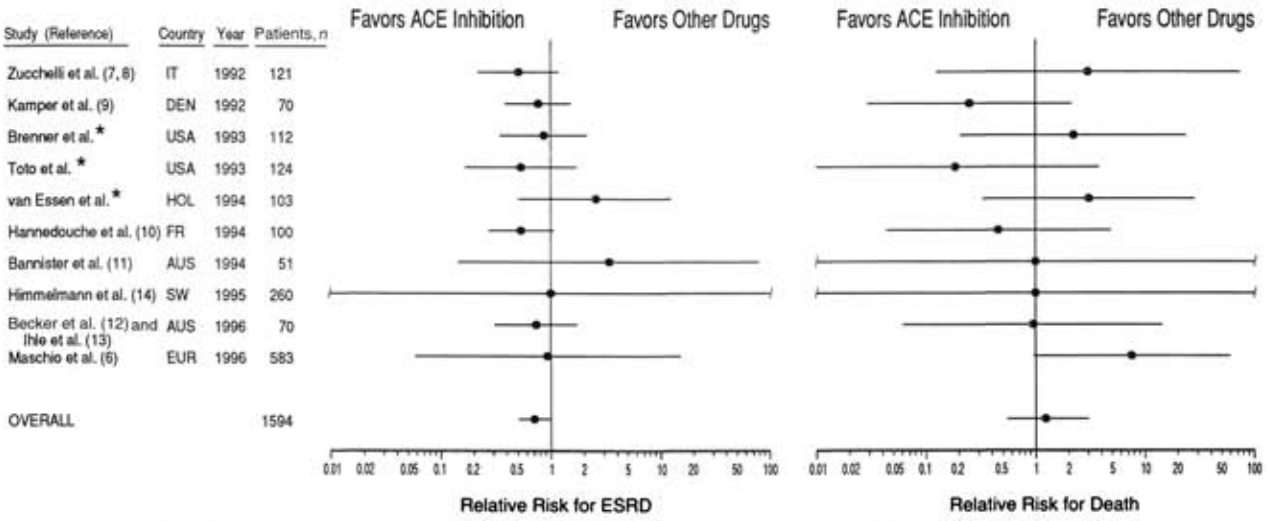

Figure. Effect of angiotensin-converting enzyme (*ACE*) inhibition on risk for end-stage renal disease (*ESRD*) and death in patients with nondiabetic renal disease. Data are the relative risk with 95% CIs on a logarithmic scale. The pooled relative risk for end-stage renal disease was 0.70 (95% CI, 0.51 to 0.97), indicating a significantly lower risk in the ACE inhibitor group. The result of the test for heterogeneity among studies was not significant ($P <$ 0.75 and >0.2), indicating that the relative risk did not significant differ among studies. The pooled relative risk for death was not significant (1.24 [CI, 0.55 to 2.83]), and the result of the test for heterogeneity among studies was not significant ($P > 0.2$). The year of publication or approximate year of completion of the unpublished studies is given. Interrupted lines indicate that the CIs extend to infinity because no events occurred in these studies. * = Unpublished data provided by study investigators. AUS = Australia; DEN = Denmark; EUR = Europe; FR = France; HOL = the Netherlands; IT = Italy; SW, Sweden; USA = United States.

following characteristics of that study: the percentage of male patients; mean patient age; percentage of patients with nephrosclerosis, glomerular diseases, interstitial diseases, polycystic kidney disease, and other or unknown conditions; mean serum creatinine level; mean glomerular filtration rate; mean systolic and diastolic blood pressures; and planned duration of follow-up. It is important to note, however, that with the exception of baseline renal function, these analyses had limited power because the variability in these factors across studies was not great (**Tables 1** to **3**).

Baseline glomerular filtration rate was reported in 8 of 10 studies (**Table 1**). Using the mean baseline creatinine clearance and serum creatinine level in the remaining two studies, we estimated that the mean baseline glomerular filtration rate was 26 mL/min in Zucchelli and colleagues' studies (7, 8) and 38 mL/min in Maschio and colleagues' study (6). The regression coefficient of baseline glomerular filtration rate on the logarithm of relative risk for end-stage renal disease was 0.017 (CI, −0.0063 to 0.041). Serum creatinine levels were measured in all 10 studies. The regression coefficient for the association between mean baseline serum creatinine level and the logarithm of relative risk was −0.096 (CI, −0.48 to 0.29). These results do not suggest a relation between the mean baseline level of renal function and the treatment effect.

Follow-up Blood Pressure

We next related the relative risk for end-stage renal disease in the ACE inhibitor group in each study (on a logarithmic scale) to the observed difference between groups in the decline in systolic and diastolic blood pressures in that study. For decrease in systolic blood pressure, the regression coefficient was −0.007 (CI, −0.13 to 0.11). For decrease in diastolic blood pressure, the regression coefficient was −0.004 (CI, −0.21 to 0.20). These analyses do not reveal a statistically significant association between mean blood pressure reduction and the beneficial effect of ACE inhibitors; however, the CIs are too wide to rule out a clinically significant association.

Discussion

Diabetes is the single largest cause of end-stage renal disease in the United States, accounting for approximately 30% of new cases (21). Over the past decade, many clinical trials have shown that ACE inhibitors are effective in slowing the progression of diabetic renal disease (1–4). Most patients with end-stage renal disease have other renal diseases; for several reasons, however, progress in identifying effective treatments for these other diseases has been slower. First, the prevalence of other individual renal diseases is lower than that of diabetic renal disease, and the inclusion of patients with various diseases in clinical trials creates a heterogeneous study sample that may not uniformly respond to treatment. Second, unlike diabetes, most renal diseases have no clearly defined stages other than the progressive decline in renal function, which is

often used as a surrogate end point in clinical trials. However, differences in methods of measuring renal function can lead to discrepancies in the interpretation of results of clinical trials (22–24). Third, in most diseases other than diabetes, the mean rate of decline in renal function is slow. Within the limited duration of most clinical trials (2 to 4 years), few patients reach a "hard" end point, such as the onset of end-stage renal disease or death. Thus, most clinical trials did not have sufficient statistical power to determine the effect of the intervention on end-stage renal disease or death.

The Modification of Diet in Renal Disease (MDRD) Study, the largest clinical trial to date in patients with nondiabetic renal disease, recently showed a beneficial effect of a lower-than-usual blood pressure goal in patients with renal insufficiency and proteinuria (25, 26). In that study, ACE inhibitors were the treatment of choice in both the usual and low blood pressure groups; thus, the effect of ACE inhibitors themselves was not studied. Many clinical trials comparing ACE inhibitors with other antihypertensive agents have now been completed, but the results are not uniform. In the largest clinical trial conducted thus far (6), neither the magnitude of the benefit nor the safety of ACE inhibitor therapy was established conclusively.

We therefore combined data from randomized trials in nondiabetic renal disease and found a significantly lower risk for end-stage renal disease in patients treated with ACE inhibitors. In animals, ACE inhibition slows rather than arrests the progression of renal disease (27). It is therefore likely that the lower risk that we observed reflects a delay in the onset of end-stage renal disease; this delay is consistent with a slowing of progression rather than full prevention of that outcome. Furthermore, other clinical trials suggest that changes in renal function predict the time to onset of end-stage renal disease (4, 28). Thus, we infer that the beneficial effect of ACE inhibitors on the development of end-stage renal disease we found in our analysis reflects a slowing in the decline in renal function. Unfortunately, the decline in renal function was not expressed in a similar way in all studies. A pooled analysis of individual patient data could provide an estimate for the magnitude of the slowing of the rate of progression.

We used meta-regression analysis to explore possible associations between the treatment effect and clinical or demographic characteristics. Maschio and colleagues (6) suggested that men and patients with proteinuria benefited most from ACE inhibition. We could not confirm or refute these findings because variability across studies in these characteristics was not great. Other studies have shown that lack of variability may limit the power of meta-regression analysis compared with analysis of individual patient data (20). Regression analysis that uses individual patient data rather than group data would allow more sensitive evaluation of the magnitude of benefit in subgroups. The mean level of baseline renal function varied widely among studies, but we did not observe a significant relation between mean baseline renal function and relative risk for end-stage renal disease with ACE inhibitor treatment. As in diabetic nephropathy, we suspect that treatment with ACE inhibitors is beneficial in patients who have nondiabetic renal diseases in which the degree of impaired renal function varies widely (1, 2, 4). In practice, ACE inhibitors could be prescribed early and their use continued throughout the course of chronic renal disease.

We found no significant difference in the risk for death between the ACE inhibitor and control groups. This finding is consistent with Maschio and colleagues' conclusion (6) that the higher mortality rate in their ACE inhibitor group was a chance event rather than a detrimental effect of the treatment. Nonetheless, several side effects and risks of ACE-inhibitor therapy are well described in patients with chronic renal disease. These risks include hyperkalemia, cough, mild reduction in glomerular filtration rate in patients with parenchymal renal disease, and acute renal failure in patients with bilateral renal artery stenosis or volume depletion (29–31). Patients receiving ACE inhibitors should have regular measurement of blood pressure, renal function, and serum electrolyte levels, especially during intercurrent illness.

We observed a greater decline in blood pressure in patients who received ACE inhibitors than in those receiving other antihypertensive agents, even though the target blood pressure was the same in both the ACE inhibitor and control groups. The magnitude of the difference in decline in systolic blood pressure (4.9 mm Hg) is large enough to have a clinically significant beneficial effect on the progression of renal disease (25, 26). In meta-regression analysis, no statistically significant relation was seen in the difference between randomly assigned groups in blood pressure decline and the beneficial effect of ACE inhibition. However, the CIs for the regression coefficients were too wide to exclude a clinically significant association. Thus, we could not conclusively determine whether the beneficial effect of ACE inhibition was due to the greater decline in blood pressure.

Angiotensin-converting enzyme inhibition slows the progression of renal disease in animals by numerous mechanisms. In addition to decreasing systemic blood pressure, ACE inhibition decreases glomerular capillary pressure, reduces proteinuria, and suppresses mediators of glomerular and tubular hy-

pertrophy and fibrosis (31, 32). These effects seem to be shared among ACE inhibitors and among angiotensin-II–receptor antagonists (33). No studies directly comparing different ACE inhibitors were available, and we found no apparent differences among clinical trials of different ACE inhibitors. However, the number of studies of agents other than enalapril was too small to allow meaningful comparisons. Reports of clinical trials of angiotensin-II–receptor antagonists on slowing the progression of renal disease have not yet been published.

Like all meta-analyses, our analysis is limited by differences among the clinical trials, particularly in patients' baseline characteristics. However, the result of the test for heterogeneity among studies was negative, indicating that ACE inhibition has a consistently beneficial effect despite these differences. The analysis is also limited by the lack of uniform data on other outcomes, such as rates of decline in renal function, and by lack of individual patient data. Hence, as discussed above, we could not determine the magnitude of the slowing of the decline in renal function or determine whether ACE inhibitor therapy was more or less beneficial in subgroups of patients defined by clinical or demographic characteristics. It is also possible that the patients who developed end-stage renal disease during the short follow-up were not representative of the majority of patients enrolled in these studies, but we believe that this is unlikely. If these patients were atypical, the beneficial effect of ACE inhibitors on the development of end-stage renal disease may not accurately reflect their effect on the decline in renal function. Finally, as discussed above, we could not determine whether the beneficial effect was due to the greater decline in blood pressure or to other effects of ACE inhibition.

In summary, the findings from our meta-analysis of randomized trials suggests that ACE inhibitors have a substantial beneficial effect in delaying the onset of end-stage renal disease and do not increase mortality. Together with the recent results of the largest study thus far to show a beneficial effect on the decline in renal function (6), our meta-analysis supports the conclusion that ACE inhibitors may be more effective than other antihypertensive agents in slowing the progression of chronic renal disease.

Note added in proof: Since submission of the manuscript, the unpublished report by van Essen and colleagues has been published in abstract form (J Am Soc Nephrol. 1996;7:1400), and a full-length article is in press (Kidney Int Suppl). In addition, a study by the GISEN group (16) has been published (Lancet. 1997;349:1857-63); this study showed a beneficial effect of ramipril in nondiabetic renal disease. Including the GISEN group results in our meta-analysis does not substantially change the results. The pooled relative risks in the 11 studies are 0.69 (CI, 0.53 to 0.91) for end-stage renal disease and 1.32 (CI, 0.61 to 2.88) for death.

Appendix

The members of the Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group who contributed data include Drs. Pietro C. Zucchelli, Anne-Lise Kamper, Svend Strandgaard, Paul P. Leyssac, Robert D. Toto, Barry M. Brenner, Nicolaos E. Madias, Barbara G. Delano, Shahnaz Shahinfar, Gabe G. van Essen, Alfred J. Apperloo, Dick de Zeeuw, Paul E. de Jong, Paul Landais, Jean-Pierre Grünfeld, Kym M. Bannister, Lennart Hansson, Anders Himmelmann, Gavin J. Becker, Benno U. Ihle, and Giuseppe Maschio.

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Requests for Reprints: Andrew S. Levey, MD, Division of Nephrology, Department of Medicine, New England Medical Center, 750 Washington Street, NEMC# 391, Boston, MA 02111.

Current Author Addresses: Drs. Levey and Giatras: Division of Nephrology, Department of Medicine, New England Medical Center, 750 Washington Street, NEMC# 391, Boston, MA 02111.
Dr. Lau: Division of Clinical Care Research, New England Medical Center, 750 Washington Street, Boston, MA 02111.

References

1. **Viberti G, Mogensen CE, Groop LC, Pauls JF.** Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA. 1994;271:275-9.
2. **Laffel LM, McGill JB, Gans DJ.** The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med. 1995;99:497-503.
3. **Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M.** Renal protective effect of enalapril in diabetic nephropathy. BMJ. 1992;304:339-43.
4. **Lewis JE, Hunsicker LG, Bain RP, Rohde RD.** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-62.
5. **Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF.** Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med. 1993;118:129-38.
6. **Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al.** Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996; 334:939-45.
7. **Zucchelli P, Zuccala A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, et al.** Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. Kidney Int. 1992;42:452-8.
8. **Zucchelli P, Zuccala A, Gaggi R.** Comparison of the effects of ACE inhibitors and calcium channel blockers on the progression of renal failure. Nephrol Dial Transplant. 1995;10:46-51.
9. **Kamper AL, Strandgaard S, Leyssac PP.** Effect of enalapril on the progression of chronic renal failure. A randomized controlled trial. Am J Hypertens. 1992;5:423-30.
10. **Hannedouche T, Landais P, Goldfarb B, el Esper N, Fournier A, Godin M, et al.** Randomized controlled trial of enalapril and β-blockers in non-

diabetic chronic renal failure. BMJ. 1994;309:833-7.
11. **Bannister KM, Weaver A, Clarkson AR, Woodroffe AJ.** Effect of angiotensin-converting enzyme and calcium channel inhibition on progression of IgA nephropathy. Contrib Nephrol. 1995;111:184-93.
12. **Becker GJ, Whitworth JA, Ihle BU, Shahinfar S, Kincaid-Smith PS.** Prevention of progression in non-diabetic chronic renal failure. Kidney Int Suppl. 1994;45:S167-70.
13. **Ihle BU, Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ.** Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: a controlled double-blind trial. Am J Kidney Dis. 1996; 27:489-95.
14. **Himmelmann A, Hansson L, Hannson BG, Hedstrand H, Skogstrom K, Ohrvik J, et al.** ACE inhibition preserves renal function better than beta-blockade in the treatment of essential hypertension. Blood Press. 1995;4:85-90.
15. **Bianchi S, Bigazzi R, Baldari G, Campese VM.** Long-term effects of enalapril and nicardipine on urinary albumin excretion in patients with chronic renal insufficiency: a 1-year follow-up. Am J Nephrol. 1991;11:131-7.
16. **Remuzzi G, Tognoni G, Ruggenenti P, Perna A.** A long term, randomized clinical trial to evaluate the effects of ramipril on the evolution of renal function in chronic nephropathies. Gruppo Italiano Studi Epidemiologici in Nefrologia (GISEN). Journal of Nephrology. 1991;3:193-202.
17. **Okamura M, Kanayama Y, Negoro N, Inoue T, Takeda T.** Long-term effects of calcium antagonists and angiotensin-converting enzyme inhibitors in patients with chronic renal failure of IgA nephropathy. Contrib Nephrol. 1991;90:161-5.
18. **Sacks HS, Berrier J, Restman D, Ancona-Berk VA, Chalmers T.** Meta-analysis of randomized controlled trials. N Engl J Med. 1987;316:450-5.
19. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.
20. **Berlin JA, Antman EM.** Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials. 1994; Jun 4: Doc No134.
21. U.S. Renal Data System. USRDS 1995 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:B1, 70, 154.
22. **Levey AS.** Measurment of renal function in chronic renal disease [Clinical Conference]. Kidney Int. 1990;38:167-84.
23. **Levey AS, Bosch JP, Coggins CH, Greene T, Mitch WE, Schluchter MD, et al.** Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996;7:556-66.
24. **Levey AS, Beck GJ, Bosch JP, Caggiula AW, Greene T, Hunsicker LG, et al.** Short-term effects of protein intake, blood pressure, and antihypertensive therapy on glomerular filtration rate in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996;7:2097-109.
25. **Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al.** The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330:877-84.
26. **Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, et al.** Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med. 1995;123:754-62.
27. **Anderson S, Rennke HG, Brenner BM.** Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest. 1986;77:1993-2000.
28. **Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, et al.** Predictors of progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int. 1997;51:1908-19.
29. **Israili ZH, Hall WD.** Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med. 1992;117:234-42.
30. **Keane FW, Anderson S, Aurell M, de Zeeuw D, Narins RG, Povar G.** Angiotensin converting enzyme inhibitors and progressive renal insufficiency. Current experience and future directions. Ann Intern Med. 1989;111:503-16.
31. **Brunner HR.** ACE inhibitors in renal disease [Clinical Conference]. Kidney Int. 1992;42:463-79.
32. **Hunsicker LG, Levey AS.** Progression of chronic renal disease. Mechanisms, risk factors, and testing of interventions. In: Jacobson HR, Striker GE, Klahr S, eds. The Principles and Practice of Nephrology. 2d ed. St. Louis: Mosby–Year Book; 1995:622-31.
33. **Ichikawa I.** Will angiotensin II receptor antagonists be renoprotective in humans? Kidney Int. 1996;50:684-92.

Without ascribing divine power to the physicians, personal contact with the patient is admittedly an important factor in physiologic rapport. Not only will a painstaking history afford invaluable information to the physician but the patient will ordinarily gain composure and ease. The complete physical examination remains the most essential ingredient in the comprehensive study of the patient. By the physician's "quietly efficient thoroughness he will convey the comforting assurance of his interest and competence."

William Shainline Middleton
Values in Modern Medicine
Madison, WI: Univ of Wisconsin Pr; 1973

Submitted by:
George E. Magnin, MD
Marshfield Clinic
Marshfield, WI 54449

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