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Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease

A Meta-Analysis of Patient-Level Data

Tazeen H. Jafar, MD, MPH; Christopher H. Schmid, PhD; Marcia Landa, MA; Ioannis Giatras, MD; Robert Toto, MD; Giuseppe Remuzzi, MD; Giuseppe Maschio, MD; Barry M. Brenner, MD; Annelise Kamper, MD; Pietro Zucchelli, MD; Gavin Becker, MD; Andres Himmelmann, MD; Kym Bannister, MD; Paul Landais, MD; Shahnaz Shahinfar, MD; Paul E. de Jong, MD, PhD; Dick de Zeeuw, MD; Joseph Lau, MD; and Andrew S. Levey, MD, for the ACE Inhibition in Progressive Renal Disease Study Group*

Purpose: **To examine the efficacy of ACE inhibitors for treatment of nondiabetic renal disease.**

Data Sources: **11 randomized, controlled trials comparing the efficacy of antihypertensive regimens including ACE inhibitors to the efficacy of regimens without ACE inhibitors in predominantly nondiabetic renal disease.**

Study Selection: **Studies were identified by searching the MEDLINE database for English-language studies evaluating the effects of ACE inhibitors on renal disease in humans between May 1977 (when ACE inhibitors were approved for trials in humans) and September 1997.**

Data Extraction: **Data on 1860 nondiabetic patients were analyzed.**

Data Synthesis: **Mean duration of follow-up was 2.2 years. Patients in the ACE inhibitor group had a greater mean decrease in systolic and diastolic blood pressure (4.5 mm Hg [95% CI, 3.0 to 6.1 mm Hg]) and 2.3 mm Hg [CI, 1.4 to 3.2 mm Hg], respectively) and urinary protein excretion (0.46 g/d [CI, 0.33 to 0.59 g/d]). After adjustment for patient and study characteristics at baseline and changes in systolic blood pressure and urinary protein excretion during follow-up, relative risks in the ACE inhibitor group were 0.69 (CI, 0.51 to 0.94) for end-stage renal disease and 0.70 (CI, 0.55 to 0.88) for the combined outcome of doubling of the baseline serum creatinine concentration or end-stage renal disease. Patients with greater urinary protein excretion at baseline benefited more from ACE inhibitor therapy ($P = 0.03$ and $P = 0.001$, respectively), but the data were inconclusive as to whether the benefit extended to patients with baseline urinary protein excretion less than 0.5 g/d.**

Conclusion: **Antihypertensive regimens that include ACE inhibitors are more effective than regimens without ACE inhibitors in slowing the progression of nondiabetic renal disease. The beneficial effect of ACE inhibitors is mediated by factors in addition to decreasing blood pressure and urinary protein excretion and is greater in patients with proteinuria. Angiotensin-converting inhibitors are indicated for treatment of nondiabetic patients with chronic renal disease and proteinuria and, possibly, those without proteinuria.**

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For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 138-139.

*For other members of the ACE Inhibition in Progressive Renal Disease Study Group, see Appendix 1.

Chronic renal disease is a major public health problem in the United States. According to the 1999 Annual Data Report of the U.S. Renal Data System, more than 357 000 people have end-stage renal disease (ESRD), and the annual cost of treatment with dialysis and renal transplantation exceeds $15.6 billion (1). Patients undergoing dialysis have reduced quality of life, a high morbidity rate, and an annual mortality rate of 20% to 25% (1). Identification of therapies to prevent ESRD is an important public health goal.

Angiotensin-converting enzyme (ACE) inhibitors are highly effective in slowing the progression of renal disease due to type 1 diabetes (2–6), and evidence of their efficacy in type 2 diabetes is growing (7–12). However, although 14 randomized, controlled trials have been completed (13–25; Brenner BM; Toto R. Personal communications), no consensus exists on the use of ACE inhibitors in nondiabetic renal disease (26–28). In a previous meta-analysis of 11 randomized, controlled trials, we found that therapy with ACE inhibitors slowed the progression of nondiabetic renal disease (29). Since our meta-analysis was performed on group data rather than individual-patient data, we could not fully assess the relationship between the effect of ACE inhibitors and blood pressure, urinary protein excretion, or other patient characteristics (30). Thus, we could not determine whether an equal reduction in blood pressure or urinary protein excretion by using other antihypertensive agents would be as effective in slowing the progression of renal disease. Nor could we determine whether

Table 1. **Study and Patient Characteristics in the Randomized, Controlled Trials Included in the Pooled Analysis***

Variable	Study (Reference)				
	1 (13)	2 (14)	3†	4‡	5 (15)
Year of publication	1992	1992	1993	1993	1994
Authors' conclusion§	NS	ACE inhibitor better	NS	NS	NS
Primary outcome	GFR, creatinine clearance, serum creatinine concentration	GFR	GFR, creatinine clearance, serum creatinine concentration	GFR, creatinine clearance, serum creatinine concentration	GFR, serum creatinine concentration
Study characteristics					
Sample size	121	55	106	122	103
Planned duration of follow-up, *y*	3	2	3	3	4
Study medication in ACE inhibitor group	Captopril	Enalapril	Enalapril	Enalapril	Enalapril
Dosage range of ACE inhibitor, *mg/d*	12.5–50	≥2.5	5–40	5–40	10–40
Study medication in control group	Nifedipine	Not specified	Placebo	Placebo	Atenolol or acebutolol
Concomitant antihypertensive medications in both groups	Diuretics, central α-adrenergic agonists	β-Adrenergic blockers, calcium-channel blockers, diuretics, vasodilators	β-Adrenergic blockers, diuretics, peripheral α-adrenergic blockers, central α-adrenergic agonists	β-Adrenergic blockers, diuretics, α-adrenergic blockers, central α-adrenergic agonists, vasodilators	Calcium-channel blockers, diuretics
Blinding	No	No	Yes	Yes	Yes
Dietary advice	Yes	Yes	Yes	Yes	Yes
Baseline patient characteristics					
Men, %	63	49	65	64	65
White, %	100	100	44	40	99
Cause of renal disease, %					
Glomerular disease	26	31	33	7	26
Polycystic kidney disease	10	20	14	0	14
Hypertensive nephrosclerosis	29	0	36	90	29
Tubulointerstitial disease	20	29	5	3	22
Other	15	20	12	0	9
Hypertension, %‖	100	93	98	100	100
Age, *y*	55	50	47	52	51
Serum creatinine concentration, *μmol/L (mg/dL)*	265 (3.0)	442 (5.0)	239 (2.7)	230 (2.6)	159 (1.8)
Systolic blood pressure, *mm Hg*	165	147	141	130	154
Diastolic blood pressure, *mm Hg*	100	90	91	82	91
Urinary protein excretion, *g/d*	1.7	1.9	2.3	0.7	1.6
Patient characteristics during follow-up					
Systolic blood pressure, *mm Hg*	142	136	131	134	138
Diastolic blood pressure, *mm Hg*	87	84	83	84	80
Urinary protein excretion, *g/d*	1.6	1.4	1.3	0.9	1.1
Outcomes, *n*¶					
Doubling of baseline serum creatinine concentration	22	9	13	14	10
ESRD	21	21	15	10	7
Death	1	2	3	2	4
Doubling of baseline serum creatinine concentration or ESRD or death	29	25	23	24	14
Withdrawal, *n***	30	4	33	30	24
Completed study, *n*	62	26	50	68	65
Relative risk (95% CI)††					
ESRD	0.50 (0.20–1.24)	0.80 (0.34–1.91)	0.97 (0.35–2.69)	0.47 (0.12–1.83)	2.30 (0.58–15.4)
Doubling of baseline serum creatinine concentration or ESRD	0.55 (0.25–1.18)	0.85 (0.37–1.91)	1.39 (0.58–3.36)	1.16 (0.50–2.69)	1.69 (0.48–6.02)

* Values are given as percentages or means, as appropriate. ACE = angiotensin-converting enzyme; ESRD = end-stage renal disease; GFR = glomerular filtration rate; NS = not significant.
† Brenner BM. Personal communication.
‡ Toto R. Personal communication.
§ Authors' conclusions based on the primary outcome for each study.
‖ Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, receipt of antihypertensive medications before enrollment, or classification as "hypertensive" by the investigators.
¶ Number of events.
** Discontinuation from study before doubling of baseline serum creatinine concentration, ESRD, death, or end of follow-up.
†† Relative risks for outcome in the ACE inhibitor group versus control group, computed by using unadjusted time-to-event analysis.

Table 1—**Continued**

Study (Reference)					
6 (16)	**7 (17)**	**8 (18)**	**9 (19)**	**10 (20)**	**11 (21, 22)**
1994	1994	1995	1996	1996	1997/1999
ACE inhibitor better	NS	ACE inhibitor better	ACE inhibitor better	ACE inhibitor better	ACE inhibitor better
GFR, serum creatinine concentration	GFR	GFR	GFR, creatinine clearance, serum creatinine concentration	Serum creatinine concentration	GFR, serum creatinine concentration
99	47	255	67	562	323
3	1	2	2	3	2.2
Enalapril	Enalapril	Cilazapril	Enalapril	Benazepril	Ramipril
5–10	5–20	2.5–5.0	5	10	1.25–5.0
Atenolol or acebutolol	Nifedipine	Atenolol or acebutolol	Placebo	Placebo	Placebo
Calcium-channel blockers, diuretics, central α-adrenergic agonists	β-Adrenergic blockers, diuretics, α-adrenergic blockers	β-Adrenergic blockers, calcium-channel blockers, diuretics	β-Adrenergic blockers, calcium-channel blockers, diuretics, α-adrenergic blockers, central α-adrenergic agonists	β-Adrenergic blockers, calcium-channel blockers, diuretics, α-adrenergic blockers, central α-adrenergic agonists, vasodilators	β-Adrenergic blockers, calcium channel blockers, diuretics, α-adrenergic blockers, central α-adrenergic agonists, vasodilators
No	Yes	No	Yes	Yes	Yes
No	Yes	No	Yes	Yes	Yes
50	80	49	48	72	77
100	100	100	100	100	99
50	100	0	60	34	51
15	0	0	15	11	1
7	0	100	0	17	13
19	0	0	2	19	7
9	0	0	23	19	28
100	100	100	100	92	84
51	48	63	46	51	49
265 (3.0)	124 (1.4)	88 (1.0)	371 (4.2)	186 (2.1)	194 (2.2)
167	152	161	150	142	144
102	95	94	88	88	89
2.2	1.7	0.1	2.1	1.8	3.4
154	136	157	144	140	140
91	85	90	85	86	87
1.7	1.8	0.1	1.8	1.6	3.1
26	1	0	11	77	40
27	0	0	15	2	58
3	0	1	2	9	4
40	1	1	24	88	73
19	5	40	19	120	63
40	41	214	24	354	187
0.48 (0.22–1.06)	–	–	0.97 (0.35–2.68)	0.89 (0.06–14.2)	0.51 (0.30–0.87)
0.46 (0.24–0.90)	–	–	1.10 (0.48–2.59)	0.44 (0.27–0.70)	0.47 (0.29–0.77)

the baseline blood pressure, urinary protein excretion, or other patient characteristics modified the response to treatment.

In the current report, we used pooled analysis of individual-patient data to answer these questions. We reasoned that the large number of patients in the pooled analysis would provide sufficient statistical power to detect relationships between patient characteristics and risk for progression of renal disease and interactions of patient characteristics with treatment effect. In principle,

strong and consistent results from analysis of this large database would clarify the effects of ACE inhibitors for treatment of nondiabetic renal disease.

METHODS

Study Design

We obtained individual-patient data from nine published (13–22) and two unpublished (Brenner BM; Toto R. Personal communications) randomized, controlled trials assessing the effects of ACE inhibitors on renal disease progression in predominantly nondiabetic patients. Search strategies used to identify clinical trials have been described elsewhere and are reviewed in Appendix 2.

We included 11 randomized trials on progression of renal disease that compared the effects of antihypertensive regimens including ACE inhibitors to the effects of regimens without ACE inhibitors, with a follow-up of at least 1 year. In these studies, the institutional review board at each participating center approved the study, and all patients gave informed consent. Patients underwent randomization between March 1986 and April 1996.

Hypertension or decreased renal function was required for entry into all studies. Exclusion criteria common to all studies were acute renal failure, treatment with immunosuppressive medications, clinically significant congestive heart failure, obstructive uropathy, renal artery stenosis, active systemic disease, insulin-dependent diabetes mellitus, history of transplantation, history of allergy to ACE inhibitors, and pregnancy. **Table 1** shows characteristics of the patients in each study.

Before randomization, patients already taking an ACE inhibitor were switched to alternative medications for at least 3 weeks. After randomization, the ACE inhibitor groups received enalapril in seven studies (14–19; Brenner BM; Toto R. Personal communications) and captopril (13), benazepril (20), cilazapril (18), and ramipril (21, 22) in one study each. The control groups received placebo in five studies (19–22; Brenner BM; Toto R. Personal communications), a specified medication in five studies (nifedipine in two studies [13, 17] and atenolol or acebutolol in three studies [15, 16, 18]), and no specified medication in one study (14). Other antihypertensive medications were used in both groups to reach the target blood pressure, which was less than 140/90 mm Hg in all studies. All patients were followed at least once every 6 months for the first year and at least once yearly thereafter. Blood pressure and laboratory variables were measured at each visit. **Table 1** shows outcomes of each study.

We pooled the 11 clinical trials on the basis of similarity of study designs and patient characteristics. In addition, the presence of preexisting hypertension and use of antihypertensive agents in most patients in the control groups in each clinical trial justified pooling data from placebo-controlled and active-controlled trials. Thus, the pooled analysis addresses the clinically relevant question of whether antihypertensive regimens including ACE inhibitors are more effective than antihypertensive regimens not including ACE inhibitors in slowing the progression of nondiabetic renal disease.

Outcomes

Two primary outcomes were defined: ESRD, defined as the initiation of long-term dialysis therapy, and a combined outcome of a twofold increase in serum creatinine concentration from baseline values or ESRD. Because ESRD is a clinically important outcome, we believed that definitive results of analyses using this outcome would be clinically relevant. However, because most chronic renal diseases progress slowly, few patients might reach this outcome during the relatively brief follow-up of these clinical trials, resulting in relatively low statistical power for these analyses. Doubling of baseline serum creatinine is a well-accepted surrogate outcome for progression of renal disease in studies of antihypertensive agents (2, 20) and would be expected to occur more frequently than ESRD, providing higher statistical power for analyses using this outcome. Doubling of baseline serum creatinine concentration was confirmed by repeated evaluation in only one study, which used this variable as the primary outcome. Therefore, we did not require confirmation of doubling for our analysis. Other outcomes included death and a composite outcome of ESRD and death.

"Withdrawal" was defined as discontinuation of follow-up before the occurrence of an outcome or study end. Reasons for withdrawal were 1) nonfatal side effects possibly due to ACE inhibitors, including hyperkalemia, cough, angioedema, acute renal failure, or hypotension; 2) nonfatal cardiovascular disease events, including myo-

cardial infarction, congestive heart failure, stroke, transient ischemic attack, or claudication; 3) other nonfatal events, such as malignant disease, pneumonia, cellulitis, headache, or gastrointestinal disturbance; and 4) other reasons, including loss to follow-up, protocol violation, or unknown.

Statistical Analysis

Five investigators participated in data cleaning. Summary tables were compiled from the individual-patient data from each study and checked against tables in published and unpublished reports. Discrepancies were resolved by contacting investigators at the clinical or data coordinating centers whenever possible. Because the studies followed different protocols, we had to standardize the variable definitions, follow-up intervals, and run-in periods; details of our approach are provided in Appendix 2.

S-Plus (MathSoft, Inc., Seattle, Washington) and SAS (SAS Institute, Inc., Cary, North Carolina) software programs were used for all statistical analyses (31, 32). Univariate analysis was performed to detect associations between the covariates and outcomes. Baseline patient characteristics were treatment assignment (ACE inhibitor vs. control), age (logarithmic transformation), sex, ethnicity, systolic blood pressure, diastolic blood pressure, mean arterial pressure, serum creatinine concentration (reciprocal transformation), and urinary protein excretion. Study characteristics were blinding, type of antihypertensive regimen in the control group, planned duration of follow-up, whether dietary protein or sodium was restricted, and year of publication. Baseline patient characteristics and study characteristics were introduced as fixed covariates. Since renal biopsy was not performed in most cases and since criteria for classification of cause of renal disease were not defined, the cause of renal disease was not included as a variable in the analysis. Follow-up patient characteristics (blood pressure and urinary protein excretion) were adjusted as time-dependent covariates; the value recorded at the beginning of each time segment was used for that segment. This convention was used so that each outcome would be determined only by previous exposure. The intention-to-treat principle was followed for comparison of randomized groups.

Cox proportional hazards regression models were used to determine the effect of assignment to ACE inhibitors (treatment effect) and other covariates on risk for ESRD and the combined outcome (33, 34). Multivariable models were built by using candidate predictors that were associated with the outcome ($P < 0.2$) in the univariate analysis. Each model was adjusted for study, but since some studies had no events, we could not include a dummy variable for each study. Rather, we adjusted models for studies that differed significantly from the rest (studies 2 [14], 5 [15], 10 [20], and 11 [21, 22]). We also performed tests for interactions between all covariates and treatment effect. All P values were based on two-sided tests, and significance was set at a P value less than 0.05. Results are expressed as relative risks with 95% CIs.

Residual diagnostics were performed on these final models (33, 34). The proportional hazards assumption was checked by computing the Schoenfeld residuals and verifying that they had no significant correlation with the ranked failure times. A graphical check was also made by plotting the residuals against time and fitting a smooth curve with 95% confidence bands. No variable showed nonproportional hazards across studies. Potential influence points were checked by looking at the score residuals. Linearity of covariates was assessed by modeling the binary outcome in a Poisson generalized additive regression as a function of all the terms in the survival model using a smooth spline representation of the continuous variables and an offset term that equaled the difference between the log of the predicted values and the linear predictor from the Cox model. To calculate this log, we added 0.01 to values predicted to equal zero.

Role of the Funding Sources

The funding sources had no role in the design, conduct, or reporting of the study.

RESULTS

Patient and Study Characteristics

In the 11 studies, a total of 1946 patients were enrolled. Of these patients, 983 were assigned to the ACE inhibitor group and 963 were assigned to the control group. We excluded 66 patients with non–insulin-dependent diabetes mellitus and 20 patients with missing baseline values for blood pressure, serum creatinine,

Table 2. **Comparison of Randomized Groups in the Pooled Analysis***

Variable	All Patients	ACE Inhibitor Group	Control Group	*P* Value†
Patients, *n*	1860	941	919	
Baseline characteristics				
Men, *n (%)*	1215 (65)	615 (65)	600 (65)	>0.2
Nonblack ethnicity, *n (%)*	1746 (94)	881 (94)	865 (94)	>0.2
Cause of renal disease, *n (%)*				>0.2
Glomerular disease	611 (33)	310 (33)	301 (33)	
Polycystic kidney disease	142 (8)	68 (7)	74 (8)	
Hypertensive nephrosclerosis	614 (33)	305 (32)	309 (34)	
Tubulointerstitial disease	219 (12)	113 (12)	106 (12)	
Other	274 (15)	145 (15)	129 (14)	
Hypertension, *n (%)*	1708 (92)	862 (92)	846 (92)	>0.2
Age, *y*	52 ± 13	52 ± 13	52 ± 13	>0.2
Serum creatinine concentration, *μmol/L (mg/dL)*	203 ± 106 (2.3 ± 1.2)	203 ± 106 (2.3 ± 1.2)	203 ± 106 (2.3 ± 1.2)	>0.2
Systolic blood pressure, *mm Hg*	148 ± 22	148 ± 21	149 ± 22	>0.2
Diastolic blood pressure, *mm Hg*	91 ± 11	90 ± 11	91 ± 11	>0.2
Urinary protein excretion, *g/d*	1.8 ± 2.3	1.8 ± 2.5	1.8 ± 2.1	>0.2
Follow-up characteristics				
Systolic blood pressure, *mm Hg*	142 ± 17	139 ± 16	144 ± 16	<0.001
Diastolic blood pressure, *mm Hg*	86 ± 8	85 ± 7	87 ± 8	<0.001
Urine protein excretion, *g/d*	1.6 ± 1.8	1.4 ± 1.8	1.7 ± 2.0	<0.001
Outcomes, *n (%)*				
ESRD	176 (9.5)	70 (7.4)	106 (11.6)	0.002
Doubling of baseline serum creatinine concentration	223 (12.1)	89 (9.5)	134 (14.7)	0.001
Doubling of baseline serum creatinine concentration or ESRD	311 (16.8)	124 (13.2)	187 (20.5)	0.001
Death	31 (1.6)	20 (2.1)	11 (1.2)	0.12
Death or ESRD	207 (11.1)	90 (9.6)	117 (12.8)	0.03
Withdrawals, *n (%)*	387 (20.8)	207 (22.0)	180 (19.6)	0.2
ACE inhibitor side effects‡	55 (3.0)	40 (4.3)	15 (1.6)	0.001
Nonfatal cardiovascular disease§	36 (1.9)	18 (1.9)	18 (2.0)	>0.2
Other nonfatal event‖	90 (4.8)	55 (5.8)	35 (3.8)	0.04
Lost to follow-up or unknown	206 (11.1)	94 (10.0)	112 (12.2)	0.13
Completed study, *n (%)*	1131 (60.8)	590 (62.7)	541 (58.9)	0.15
Duration of follow-up, *y*	2.2 ± 1.1	2.2 ± 1.1	2.2 ± 1.1	>0.2

* Values are given as the number (percentage) of patients or the mean ± SD. ACE = angiotension-converting enzyme inhibitor; ESRD = end-stage renal disease.
† Comparison of variables between randomized groups was done by using the *t*-test for continuous variables and chi-square test for discrete variables.
‡ Nonfatal angioedema, hyperkalemia, cough, acute renal failure, and hypotension.
§ Myocardial infarction, congestive heart failure, stroke, transient ischemic attacks, and claudication.
‖ Malignant disease, pneumonia, cellulitis, headache, gastrointestinal disturbances, and other events.

or urinary protein excretion. Thus, the final sample included 1860 patients. **Table 1** shows the end points, investigators' conclusions, study characteristics, patient characteristics, and outcomes for each study. We compared characteristics of the 1860 patients included in the analysis with those of the 20 nondiabetic patients who were excluded because of missing values; no significant differences were observed.

Comparison of Randomized Groups

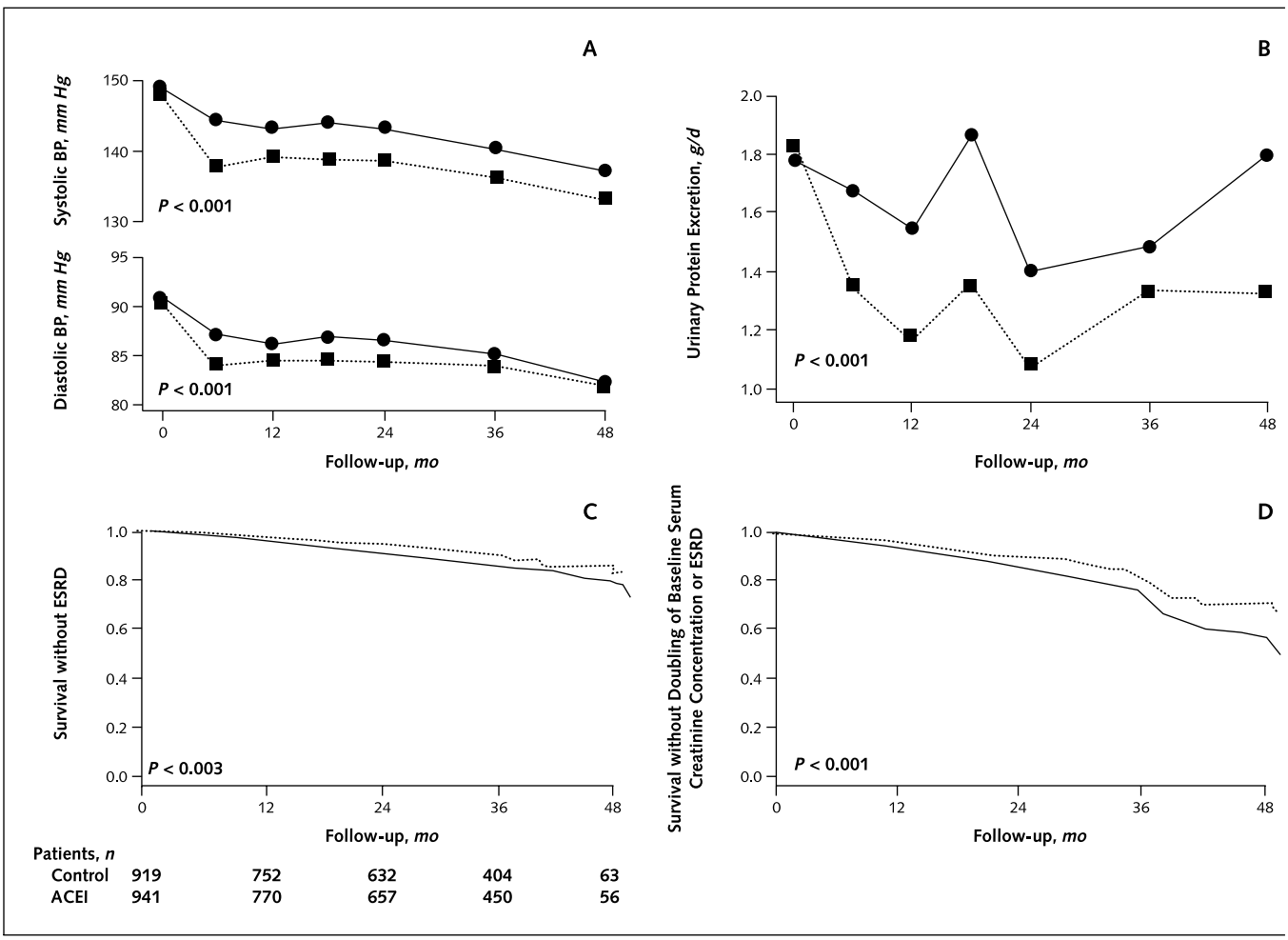
Of the 1860 patients included in our analysis, 941 were assigned to the ACE inhibitor group and 919 were assigned to the control group (**Table 2**). All patient characteristics were balanced between groups at baseline. Changes in blood pressure and urinary protein excretion during follow-up are shown in **Table 2** and **Figure 1A** and **1B**. Mean systolic and diastolic blood pressures decreased in both groups during follow-up, but these decreases were 4.5 mm Hg (95% CI, 3.0 to 6.1 mm Hg) and 2.3 mm Hg (CI, 1.4 to 3.2 mm Hg) greater, respectively, in the ACE inhibitor group. Mean urinary protein excretion decreased in the ACE inhibitor group but remained relatively stable in the control group. The mean decrease in urinary protein excretion was 0.46 g/d (CI, 0.33 to 0.59 g/d) greater in the ACE inhibitor group.

A total of 1131 patients (60.8%) completed the studies; 311 patients (16.8%) developed the combined outcome of doubling of baseline serum creatinine concentration or ESRD, 31 died (1.6%), and 387 (20.8%) withdrew before reaching a specified outcome (**Table 2**). Mean duration of follow-up was 2.2 years for both

groups. Significantly fewer patients in the ACE inhibitor group than the control group developed ESRD (7.4% vs. 11.6%; $P = 0.002$), the combined end point of doubling of baseline serum creatinine or ESRD (13.2% vs. 20.5%; $P = 0.001$), and the combined outcome of ESRD or death (9.6% vs. 12.8%; $P = 0.03$). The rate of withdrawal before reaching an outcome was relatively high (20.8%) but did not differ significantly between groups ($P = 0.2$). Withdrawal because of nonfatal side effects possibly due to ACE inhibitors and other nonfatal events was more common in the ACE inhibitor group than the control group (4.3% vs. 1.6% [$P = 0.001$] and 5.8% vs. 3.8% [$P = 0.04$]). The incidence of death or nonfatal episodes of cardiovascular disease did not differ significantly between groups.

Rates of survival without ESRD (**Figure 1C**) and survival without the combined outcome of doubling of serum creatinine or ESRD (**Figure 1D**) were greater in the ACE inhibitor group than the control group. Unadjusted relative risks for these outcomes in the ACE in-

Figure 1. **Blood pressure (*A*), urinary protein excretion (*B*), survival without end-stage renal disease (*ESRD*) (*C*), or the combined outcome of doubling of baseline serum creatinine concentration or ESRD (*D*) during follow-up among patients taking angiotensin-converting enzyme inhibitors (*ACEI*) (*dotted line*) and controls (*solid line*).**



Follow-up measurements were reported more often during the first 2 years and less often thereafter. Mean blood pressure and mean urinary protein excretion during follow-up were defined as the mean of all available follow-up values for each patient. Change during follow-up was defined as the baseline value minus the mean follow-up value for each patient. The number of patients with follow-up data available for analysis of survival without ESRD is shown below the x-axis of panel C. Slightly fewer patients had follow-up measurements of blood pressure and urinary protein excretion than for ascertainment of ESRD.

Table 3. **Unadjusted and Adjusted Treatment Effect***

Analysis	Relative Risk (95% CI)†	
	ESRD	Doubling of Baseline Serum Creatinine Concentration or ESRD
Unadjusted	0.63 (0.47–0.85)	0.64 (0.51–0.80)
Adjusted for baseline variables‡	0.62 (0.45–0.85)	0.59 (0.47–0.74)
Adjusted for baseline variables and decrease in systolic blood pressure	0.66 (0.48–0.89)	0.64 (0.50–0.80)
Adjusted for baseline variables and decrease in urinary protein excretion	0.66 (0.49–0.91)	0.66 (0.52–0.83)
Adjusted for baseline variables, decrease in systolic blood pressure, and decrease in urinary protein excretion	0.69 (0.51–0.94)	0.70 (0.55–0.88)

* ESRD = end-stage renal disease.
† Relative risk for outcome in angiotensin-converting enzyme inhibitor group versus control group.
‡ Baseline variables for both models were sex; logarithm of age; reciprocal of serum creatinine concentration; systolic blood pressure; urinary protein excretion; and terms for studies 2 (13), 5 (14), 10 (20), and 11 (21, 22). Other baseline variables considered for analysis ($P < 0.2$ in univariate analysis) were diastolic blood pressure, mean arterial pressure, type of antihypertensive regimen in the control group, planned duration of follow-up, whether or not the investigators were blinded, whether or not dietary advice was given, and year of publication.

hibitor group were 0.63 (CI, 0.47 to 0.85) and 0.64 (CI, 0.51 to 0.80), respectively (**Table 3**). Unadjusted relative risks were 1.77 (CI, 0.85 to 3.70) for death and 0.76 (CI, 0.54 to 1.07) for the combined outcome of ESRD or death.

Treatment Effect, Adjusted for Baseline and Follow-up Characteristics

Baseline patient characteristics found to be independently associated with increased risk for ESRD in the multivariable model were younger age, female sex, higher serum creatinine concentration, higher systolic blood pressure, and higher urinary protein excretion (data not shown). The only significant study characteristic was study itself (data not shown). After adjustment for these covariates, the treatment effect remained significant: The relative risks for ESRD or the combined outcome of doubling of baseline serum creatinine or ESRD in the ACE inhibitor group were 0.62 (CI, 0.45 to 0.85) and 0.59 (CI, 0.47 to 0.74), respectively (**Table 3**).

We next considered follow-up covariates. In multivariable analysis, smaller decreases in systolic blood pressure and urinary protein excretion were associated with greater risks for ESRD ($P < 0.001$ and $P = 0.002$, respectively) and doubling of baseline serum creatinine or ESRD ($P < 0.001$ and $P < 0.001$, respectively). After separate and combined adjustment for changes in blood pressure and proteinuria during follow-up, the treatment effect remained significant in multivariable models using each outcome (**Table 3**). These findings suggest that the beneficial effect of ACE inhibitors is mediated by mechanisms in addition to their effects of decreasing blood pressure and urinary protein excretion.

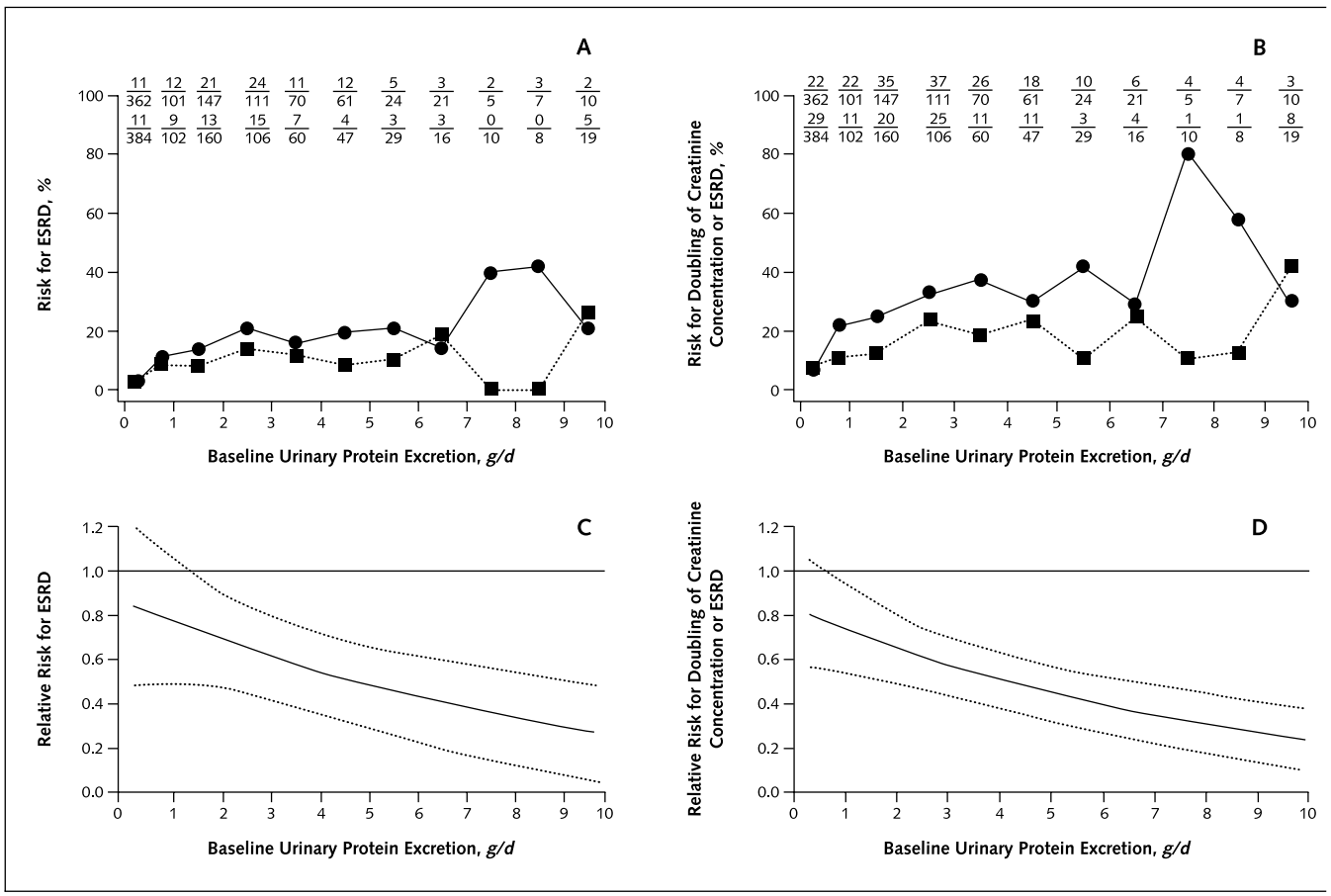
Impact of Baseline Factors on ACE Inhibitor Effect

To determine whether the effect of ACE inhibitors varied according to baseline patient or study characteristics, we searched for interactions between the ACE inhibitor effect and the significant baseline covariates in multivariable models using each outcome (ESRD and doubling of baseline serum creatinine or ESRD). In both models, baseline urinary protein excretion significantly modified the ACE inhibitor effect ($P = 0.03$ and $P = 0.001$, respectively). The relative risk was 0.09 (CI, 0.06 to 0.12) and 0.09 (CI, 0.07 to 0.11) lower, respectively, in patients with baseline urinary protein excretion of 2.0 g/d than in those with baseline urinary protein excretion of 1.0 g/d. No other baseline factors modified the ACE inhibitor effect in either model.

We explored this relationship further by performing stratified analyses on the risk for both outcomes according to baseline urinary protein excretion. The risk for both outcomes in the ACE inhibitor and control groups appeared to be greater at higher levels of baseline urinary protein excretion than at lower levels (**Figure 2A** and **2B**). The risk appeared to be lower in the ACE inhibitor group than the control group, and the difference between groups appeared to be greater at higher levels of baseline urinary protein excretion. The unadjusted relative risks for ESRD were 1.01 (CI, 0.44 to 2.32), 0.66 (CI, 0.28 to 1.56), 0.59 (CI, 0.37 to 0.94), and 0.54 (CI, 0.32 to 0.92), respectively, in patients with baseline urinary protein excretion less than 0.5, 0.5 to 1.0, 1.0 to 3.0, and greater than 3.0 g/d. The corresponding relative risks for the combined outcome of doubling of baseline serum creatinine or ESRD were 1.35 (CI, 0.78 to 2.35), 0.44 (CI, 0.21 to 0.90), 0.58 (CI, 0.40 to 0.84), and 0.51 (CI, 0.34 to 0.75).

Figure 2C and **2D** show the relationship between baseline urinary protein excretion as a continuous linear variable and the relative risk for both outcomes in mul-

Figure 2. **Risk for end-stage renal disease (*ESRD*) (*A*), combined outcome of doubling of serum creatinine or ESRD (*B*), or relative risk for these outcomes (*C* and *D*) in patients taking angiotensin-converting enzyme inhibitors (*squares*) and controls (*circles*), according to baseline urinary protein excretion.**



The values above the graphs in panels A and B are the fraction of patients with events in the control group (*upper row*) and angiotensin-converting enzyme inhibitor group (*lower row*). Relative risks were calculated from multivariable models controlling for significant baseline patient and study characteristics. The solid horizontal line at a relative risk of 1.0 in panels C and D indicates no difference between the ACE inhibitor and control groups; the solid and dotted curved lines represent point estimates and 95% CIs for the relative risks. *P* values for tests for interaction between baseline urinary protein excretion and treatment were 0.03 and 0.001, respectively.

tivariable models adjusting for baseline patient and study characteristics. In both panels, the point estimate of the relative risk is below 1.0, indicating a beneficial effect of ACE inhibitors, at all values of baseline urinary protein excretion. However, the upper bound of the 95% CI crosses the relative risk of 1.0 at urinary protein excretions of approximately 1.5 and 0.5 g/d, respectively. Regression coefficients for the multivariable model for the combined outcome are 0.83 (CI, 0.61 to 1.14) for treatment (ACE inhibitor vs. control), 0.76 (CI, 0.59 to 0.97) for male sex, 0.85 (CI, 0.79 to 0.91) for age (0.2 × baseline), 0.50 (CI, 0.45 to 0.55) for reciprocal of serum creatinine (0.1 dL/mg), 1.15 (CI, 1.09 to 1.22) for systolic blood pressure (10–mm Hg increments), 6.73 (CI, 3.76 to 12.0) for urine protein excretion (1.0-g/d increments), and 0.28 (CI, 0.13 to 0.60) for interaction between treatment and urine protein excretion. The model also included terms for studies 2 (14), 5 (15), 10 (20), and 11 (21, 22).

We also used alternative statistical models to explore the impact of baseline urinary protein excretion less than 1.0 g/d on the ACE inhibitor effect (Appendix 2). The results were similar: A greater beneficial effect was observed at higher baseline urinary protein excretion, and a benefit may exist at levels less than 0.5 g/d.

Overall, we interpret these findings as indicating a

stronger beneficial effect of ACE inhibitors in slowing the progression of renal disease in patients with higher baseline urinary protein excretion. The effect appears to be robust in patients with baseline urinary protein excretion greater than approximately 0.5 g/d but inconclusive at lesser values.

Sensitivity Analyses

To determine whether the treatment effect or interaction of the treatment effect with baseline urinary protein excretion was affected by inclusion of any of the clinical trials, we repeated the analyses, excluding each trial one at a time. The results did not differ substantially from those reported here.

We also assessed whether the treatment effect and interaction of the treatment effect with baseline urinary protein excretion differed between clinical trials that compared ACE inhibitors with placebo and those that compared ACE inhibitors with other antihypertensive regimens. The regression coefficients were similar but the confidence intervals were wider, reflecting the smaller sample size. In models that controlled for baseline characteristics and did not have interaction terms, the relative risks for ESRD were 0.70 (CI, 0.41 to 1.19) and 0.63 (CI, 0.33 to 1.21), respectively, and the relative risks for the combined outcome were 0.58 (CI, 0.44 to 0.77) and 0.57 (CI, 0.37 to 0.86).

Finally, to determine whether results of the analysis were affected by the choice of the date of the baseline measurements, we repeated the analyses three times, restricting the study sample to patients for whom baseline measurements were obtained within 30 days of the "begin date" ($n = 1698$), those for whom all baseline measurements were obtained on the same date within 4 months before the begin date ($n = 1095$), and those for whom all baseline measurements were obtained on the same date within 30 days of the begin date ($n = 1037$). In all three cases, all major results were similar to those reported here.

DISCUSSION

The effectiveness of ACE inhibitors in the treatment of diabetic renal disease is widely acknowledged (35, 36). However, most patients with chronic renal disease do not have diabetes. Our pooled analysis of individual-patient data from 11 randomized, controlled trials reveals strong and consistent effects of ACE inhibitors in slowing the progression of nondiabetic renal disease. As in diabetic renal disease, ACE inhibitors decrease blood pressure and urinary protein excretion, slow the increase in serum creatinine, and reduce the incidence of ESRD. In addition, the beneficial effect of ACE inhibitors is stronger in patients with greater proteinuria at the onset of therapy. As in diabetic renal disease, a greater decrease in blood pressure and urinary protein excretion are associated with lower risk for progression, but the beneficial effect of ACE inhibitors is mediated by factors in addition to their effects on blood pressure and urinary protein.

Others have speculated that the benefit of ACE inhibition in slowing the progression of renal disease may be related to inhibition of the effects of angiotensin II on intrarenal hemodynamics or on growth factors and fibrosis (37–41). Our analyses cannot test these hypotheses directly. However, our findings suggest that if these hypotheses are correct, these other beneficial effects of ACE inhibitors are not reflected entirely by their effects on systemic blood pressure and proteinuria.

Maschio (20) and Remuzzi (21) and their colleagues noted a greater beneficial effect of ACE inhibitors in patients with greater baseline proteinuria. We used multivariable analysis to search for interactions between the treatment effect and baseline clinical characteristics, including proteinuria. Testing for interactions in clinical trials is often limited, however, because statistical power for detection of interactions is lower than that for detection of the treatment effect, and the sample size for clinical trials is usually sufficient only to test for the treatment effect. We believed that the larger sample available in pooled analysis could overcome this limitation (30). The only significant interaction that we observed was that between treatment effect and baseline urinary protein excretion. These analyses showed a strong beneficial effect in patients with urinary protein excretion greater than approximately 0.5 g/d. We believe that this interaction is robust because it was significant in the model that used ESRD as the outcome ($P = 0.03$) and in the model that used the combined outcome of doubling of baseline serum creatinine or ESRD ($P = 0.001$) (**Figure 2C** and **2D**).

Our results cannot rule out the possibility of a threshold level of urinary protein excretion below which ACE inhibitors do not slow the progression of nondia-

betic renal disease. Urinary protein excretion in most normal persons is less than 0.5 g/d; however, the upper limit of normal can extend to 0.2 to 0.3 g/d, depending on the method of measurement (42, 43). The wide confidence interval, the imprecision of urinary protein measurements near the normal range, and the different methods used to measure urinary protein across studies preclude detection of a precise threshold level. Overall, our data provide conclusive evidence of a stronger beneficial effect of ACE inhibitors in patients with baseline urinary protein excretion of approximately 0.5 g/d or more (values just above the upper range of normal) but do not provide sufficient evidence to recommend for or against treatment with ACE inhibitors in patients with lower levels of proteinuria (values near the normal range).

The interactions with age, sex, ethnicity, baseline blood pressure, and baseline serum creatinine concentration were not significant. Testing for some of these interactions may have been limited, since few patients were black or had normal blood pressure. Nonetheless, we found no evidence to suggest that ACE inhibitors have less beneficial effect in these subgroups.

Our findings have important implications for the use of ACE inhibitors in clinical practice. Currently, few consensus recommendations or clinical practice guidelines exist for detection and treatment of chronic renal disease during chronic renal insufficiency (26). Consequently, chronic renal insufficiency is underdiagnosed and undertreated in the United States (44), and opportunities for prevention of ESRD are lost. We believe that our results provide a firm foundation for development of clinical practice guidelines on use of ACE inhibitors to slow the progression of chronic renal disease. Our results show that antihypertensive regimens including ACE inhibitors are more effective than regimens not including ACE inhibitors in slowing progression of nondiabetic renal disease. Therefore, we conclude that ACE inhibitors should be the antihypertensive agents of first choice in nondiabetic renal disease, as they are in diabetic renal disease.

Our results show that decreasing blood pressure and urinary protein excretion are additional therapeutic goals. If blood pressure or urinary protein excretion remains elevated despite administration of the maximal dose of an ACE inhibitor, other agents should be added to reach target values. Treatment with the ACE inhibitor should be continued, however, since it has an independent beneficial effect to slow progression of renal disease. Our results also show that patients with proteinuria are at higher risk for progression than are those without proteinuria and that ACE inhibitors are more effective in the former patients. Thus, the presence of proteinuria in chronic renal disease is a strong indication for treatment with ACE inhibitors.

Finally, our results raise important questions about screening for proteinuria in nondiabetic patients without hypertension or renal insufficiency. The absence of significant interactions of the treatment effect with the baseline level of blood pressure and serum creatinine concentration suggests that ACE inhibitors may be effective in patients with chronic renal disease who do not have hypertension or elevated serum creatinine concentrations.

The Heart Outcomes Prevention Evaluation (HOPE) study showed that the ACE inhibitor ramipril reduced the risk for cardiovascular disease events and mortality in patients 55 years of age or older who had preexisting cardiovascular disease or diabetes and at least one cardiovascular disease risk factor (45). However, the HOPE study did not establish an indication for ACE inhibitors in nondiabetic renal disease. First, the HOPE study did not include nondiabetic patients with renal disease. Second, it did not show a beneficial effect of ramipril on serum creatinine concentration or development of ESRD in nondiabetic persons. Third, it is likely that few patients included in our pooled analysis would have met the inclusion criteria for the HOPE Study. Although we cannot determine precisely what fraction of patients included in our analysis had cardiovascular disease or cardiovascular disease risk factors other than hypertension, the mean age of patients in our analysis was only 52 years and significant cardiovascular disease was an exclusion criterion in most trials. Thus, we conclude that our results substantially extend the indications for ACE inhibitors beyond their current scope.

Our analysis had limitations. First, we did not include three small randomized trials that did not provide data on outcomes (23–25). However, our database includes 1946 of 2122 (92%) patients who were included in clinical trials that we identified as eligible for our pooled analysis. Second, the appropriateness of combining data from different studies is questionable. However, analysis showed that the protocols and patients were

sufficiently similar to permit pooling (**Table 1**). In particular, measurements of blood pressure and renal function allowed uniform definition of exposure and outcomes. In addition, our previous meta-analysis of group data (29) and our current analyses of pooled individual-patient data revealed no significant difference among studies in the treatment effect. Third, some studies in our analysis had a high rate of patient withdrawal, which may create bias. We think that this is unlikely because the rate of withdrawal did not differ between the ACE inhibitor and control groups; we used Cox regression analysis, which accounts for differences in duration of follow-up; and the treatment effect did not change after removal of studies with high withdrawal rates (>20%) (data not shown). Fourth, detection of relationships with time-dependent covariates depends on the frequency and precision of measurements of the variables. Blood pressure and urinary protein excretion can vary over time because of true biological variability as well as measurement error. Substantial error in measurement of these variables, which were correlated with both treatment and outcome, could weaken their effect on the outcome, thereby apparently enhancing the treatment effect. The significant treatment effect that we observed after controlling for changes in blood pressure and urinary protein excretion during follow-up may be due in part to measurement error. Fifth, we used the results of short-term studies to infer the efficacy of therapy for a chronic disease. Although we did not observe deviation from the assumption of proportional hazards, long-term follow-up of patients in these clinical trials might reveal more differences in treatment efficacy than do short-term studies. We cannot answer this question because our study group was unable to resume contact with study participants.

Many other important questions remain unanswered; we plan to address these by using our database. For example, analysis of the rate of decrease in glomerular filtration rate would probably have greater statistical power to detect interactions of baseline and follow-up factors with the treatment effect. The effect of concomitant antihypertensive agents administered to patients in both the ACE inhibitor and control groups should also be considered. Our analyses do not reveal the mechanism of the greater beneficial effect of ACE inhibitors in patients with higher baseline urinary protein excretion. We plan to perform analyses to determine whether this reflects a greater antiproteinuric effect in patients with higher baseline proteinuria. Finally, our analyses do not define the optimal target blood pressure or urinary protein excretion with antihypertensive treatment. This will require analysis of the risks and benefits of ACE inhibitors at various blood pressures and degrees of urinary protein excretion during follow-up, as well as interactions of follow-up blood pressure and urinary protein excretion with baseline and other follow-up characteristics.

In summary, we conducted a pooled analysis of 11 randomized trials of the effect of ACE inhibitors on the progression of nondiabetic renal disease. The results provide strong and consistent evidence of the beneficial effects of ACE inhibitors in nondiabetic renal disease that are similar to their effects in diabetic renal disease. We believe that ACE inhibitor therapy is indicated in most patients with chronic renal disease.

Appendix 1: Additional Members of the ACE Inhibition in Progressive Renal Disease Study Group

Bergamo, Italy: P. Ruggenenti, A. Perna; Copenhagen, Denmark: S. Strandgaard; Melbourne, Australia: B.U. Ihle; Göteborg, Sweden: L. Hannson; Paris, France: J.P. Grunfeld; Groningen, the Netherlands: G.G. Van Essen, A.J. Apperloo; Verona, Italy: L. Oldrizzi, C. Marcantoni; Boston, Massachusetts: N.E. Madias, M. Reddy, P.C. Stark, T. Karim; Brooklyn, New York: B. Delano.

Appendix 2: Search Strategy and Results

Studies were identified by searching the MEDLINE database for English-language studies evaluating the effects of ACE inhibitors on renal disease in humans between May 1977 (when ACE inhibitors were approved for trials in humans) and September 1997. We also searched for abstracts in the proceedings of U.S. and international conferences, review articles, and references cited in published studies. We contacted investigators who had experience in conducting trials on this subject and inquired whether they knew of any other published or unpublished trials on this subject.

We originally found 10 published (13–20, 23–25) and 4 unpublished studies (Brenner BM; Toto R; Van Essen GG; Remuzzi G. Personal communications). Since then, 2 (15, 21, 22) of the 4 unpublished studies have been published. We contacted each principal investigator to obtain data on ESRD and death and included the study only if information on these outcomes was available. We were unable to obtain that information

from 3 studies (23–25) of a total of 176 patients. Thus, our analysis includes data from 9 published (13–22) and 2 unpublished (Brenner BM; Toto R. Personal communications) studies of 1946 patients.

Database Formulation

The "begin date" for each study was defined as the time at which treatment with study medications was begun. The "end date" was defined as the time at which the patient reached an outcome or completed the specified follow-up period.

Values assigned for baseline blood pressure and serum creatinine concentration were measured within 3 months before the study begin date. Baseline urinary protein excretion was measured within 4 months before the begin date. The value nearest the begin date was considered the baseline value. Follow-up values for systolic and diastolic blood pressure, serum creatinine concentration, and urinary protein excretion were also recorded. Supine systolic and diastolic blood pressure were measured after 5 to 10 minutes of rest in all studies except one (14), which provided only sitting blood pressure readings. Laboratory methods of measuring serum creatinine concentration and urinary protein excretion varied across studies. Two (18, 20) studies performed dipstick assessment of urinary protein and performed quantitative measurement only if the dipstick test result was positive. For these two studies, all "dipstick-negative" results were assigned a value of 0.1 g/d. In all other studies, urinary protein excretion of 0.1 g/d or less was assigned a value of 0.1 g/d. Values greater than 0.1 g/d were recorded as the exact values reported in the study.

Ethnicity was recorded for all patients but was not classified uniformly. For our analysis, ethnicity was classified as African American (black) or nonblack. Renal biopsy was not performed routinely. The cause of renal disease was determined by nephrologists at each clinical center on the basis of history, physical examination, urinalysis, and other laboratory tests and was classified as diabetic renal disease (type 2 diabetes mellitus), glomerular diseases, tubulointerstitial disease, polycystic kidney disease, hypertensive nephrosclerosis, and other causes of renal diseases.

Alternative Statistical Model To Assess the Impact of Baseline Urine Protein Excretion on the ACE Inhibitor Effect

We used a two-slope spline with a knot point below urinary protein excretion of 1.0 g/d to model the interaction between baseline urinary protein excretion and ACE inhibitor effect with ESRD and with the combined outcome of doubling of baseline serum creatinine or ESRD. The optimal fit for both models included a knot point at 0.6 g/d ($P = 0.61$ and $P = 0.02$, respectively, for the comparison of the spline model with the linear model). At baseline urinary protein excretion less than the knot point, the relative risk was not as low as in the linear models. For both models, the point estimate and the upper bound of the 95% confidence interval cross the relative risk of 1.0 at urinary protein excretion of approximately 0.4 g/d and 0.5 g/d, respectively. These data are consistent with the results of the models using baseline urinary protein as a linear variable. The effect appears to be robust in patients with baseline urinary protein greater than approximately 0.5 g/d. Thus, both the linear and spline models, which make assumptions about the shape of the curve relating baseline urinary protein excretion to the ACE inhibitor effect, predict that ACE inhibitors might also be beneficial in patients with lower levels of urinary protein excretion. However, both the stochastic uncertainty (shown in the confidence intervals) and the uncertainty about the appropriate model make the data inconclusive in patients with urinary protein excretion less than 0.5 g/d.

From New England Medical Center, Tufts University School of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts; University of Texas at Southwestern, Dallas, Texas; Institute di Recherche, Farmacologiche "Mario Negri," Bergamo, Ospedale Civile Maggiore, Verona, and Ospedale M. Malphigi, Bologna, Italy; Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; The Royal Melbourne Hospital, Melbourne, and Royal Adelaide Hospital, Adelaide, Australia; Sahlgrenska University Hospital, Göteborg, Sweden; Hôpital Necker, Paris, France; Merck Research Laboratories, West Point, Pennsylvania; and University of Groningen, Groningen, the Netherlands.

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

Current Author Addresses: Dr. Jafar: Department of Medicine, The Aga Khan University, Stadium Road, PO Box 3500, Karachi, Pakistan. Dr. Schmid: Division of Clinical Care Research, Biostatistics Research Center, New England Medical Center, Box 63, 750 Washington Street, Boston, MA 02111.

Ms. Landa: Division of Clinical Care Research, New England Medical Center, Box 63, 750 Washington Street, Boston, MA 02111.
Dr. Giatras: 50 G. Papandreou Street, Nea Erythrea, 14671 Athens, Greece.
Dr. Toto: Dallas Nephrology Associates, 6010 Forest Park Road, Suite 100, Dallas, TX 75235.
Dr. Remuzzi: Institute di Recherche, Farmacologiche "Mario Negri," Via Gavezzeni 11, 24125 Bergamo, Italy.
Dr. Maschio: Division Nefrologia, Ospedale Civile Maggiore, 37126 Verona, Italy.
Dr. Brenner: Renal Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02111.
Dr. Kamper: Department of Nephrology, Herlev Hospital, University of Copenhagen, DK 2730 Herlev, Denmark.
Dr. Zucchelli: Department of Nephrology, Ospedale M. Malphigi, Via P. Palagi 9, Bologna, Italy.
Dr. Becker: Department of Nephrology, The Royal Melbourne Hospital, Grattan Street, Melbourne, Victoria 3050, Australia.
Dr. Himmelmann: Department of Clinical Pharmacology, Sahlgrenska University Hospital, S41345 Göteborg, Sweden.
Dr. Bannister: Renal Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia.
Dr. Landais: Service d'Informatique et de Statistiques Médicales, Hôpital Necker, 161 rue de Sèvres, 75743 Paris Cedex 15, France.
Dr. Shahinfar: Merck Research Laboratories, 10 Sentry Parkway, Walton and Stenton Avenue, BL-1, Blue Bell, PA 19422.
Drs. de Jong and de Zeeuw: University of Groningen, Oostersingel 59, 9713 EZ Groningen, the Netherlands.
Dr. Lau: Division of Clinical Care Research, New England Medical Center, Box 827, 750 Washington Street, Boston, MA 02111.
Dr. Levey: Division of Nephrology, New England Medical Center, 750 Washington Street, Box 391, Boston, MA 02111.

Author Contributions: Conception and design: C.H. Schmid, I. Giatras, R. Toto, G. Remuzzi, G. Maschio, B.M. Brenner, A. Kamper, P. Zucchelli, G. Becker, A. Himmelmann, K. Bannister, P. Landais, S. Shahinfar, P.E. de Jong, D. de Zeeuw, J. Lau, A.S. Levey.
Analysis and interpretation of the data: T.H. Jafar, C.H. Schmid, M. Landa, J. Lau, A.S. Levey.
Drafting of the article: T.H. Jafar, C.H. Schmid, A.S. Levey.
Critical revision of the article for important intellectual content: T.H. Jafar, C.H. Schmid, M. Landa, R. Toto, P.E. de Jong, A.S. Levey.
Final approval of the article: T.H. Jafar, C.H. Schmid, M. Landa, I. Giatras, R. Toto, G. Remuzzi, G. Maschio, B.M. Brenner, A. Kamper, P. Zucchelli, G. Becker, A. Himmelmann, K. Bannister, P. Landais, S. Shahinfar, P.E. de Jong, D. de Zeeuw, J. Lau, A.S. Levey.
Provision of study materials or patients: R. Toto, G. Remuzzi, G. Maschio, B.M. Brenner, A. Kamper, P. Zucchelli, G. Becker, A. Himmelmann, K. Bannister, P. Landais, S. Shahinfar, P.E. de Jong, D. de Zeeuw, A.S. Levey.
Statistical expertise: C.H. Schmid, J. Lau.
Obtaining of funding: T.H. Jafar, C.H. Schmid, S. Shahinfar, J. Lau, A.S. Levey.
Administrative, technical, or logistic support: C.H. Schmid, M. Landa, A.S. Levey.
Collection and assembly of data: T.H. Jafar, M. Landa, I. Giatras, A.S. Levey.

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