Progression of Chronic Kidney Disease: The Role of Blood Pressure Control, Proteinuria, and Angiotensin-Converting Enzyme Inhibition

A Patient-Level Meta-Analysis

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Background: **Angiotensin-converting enzyme (ACE) inhibitors reduce blood pressure and urine protein excretion and slow the progression of chronic kidney disease.**

Purpose: **To determine the levels of blood pressure and urine protein excretion associated with the lowest risk for progression of chronic kidney disease during antihypertensive therapy with and without ACE inhibitors.**

Data Sources: **11 randomized, controlled trials comparing the efficacy of antihypertensive regimens with or without ACE inhibitors for patients with predominantly nondiabetic kidney disease.**

Study Selection: **MEDLINE database search for English-language studies published between 1977 and 1999.**

Data Extraction: **Data on 1860 nondiabetic patients were pooled in a patient-level meta-analysis. Progression of kidney disease was defined as a doubling of baseline serum creatinine level or onset of kidney failure. Multivariable regression analysis was performed to assess the association of systolic and diastolic blood pressure and urine protein excretion with kidney disease progression at 22 610 patient visits.**

Data Synthesis: **Mean duration of follow-up was 2.2 years. Kidney disease progression was documented in 311 patients. Systolic blood pressure of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression. Angiotensin-converting enzyme inhibitors remained beneficial after adjustment for blood pressure and urine protein excretion (relative risk, 0.67 [95% CI, 0.53 to 0.84]). The increased risk for kidney progression at higher systolic blood pressure levels was greater in patients with urine protein excretion greater than 1.0 g/d ($P < 0.006$).**

Conclusion: **Although reverse causation cannot be excluded with certainty, a systolic blood pressure goal between 110 and 129 mm Hg may be beneficial in patients with urine protein excretion greater than 1.0 g/d. Systolic blood pressure less than 110 mm Hg may be associated with a higher risk for kidney disease progression.**

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See editorial comment on pp 296-298.

Chronic kidney disease is a major public health problem in the United States. The prevalence of kidney failure (recorded as end-stage renal disease) has risen steadily since Medicare assumed funding for the condition in 1973. By 2010, it is estimated that the prevalence will be greater than 650 000 (1). The prevalence of earlier stages of chronic kidney disease is even higher. The Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, estimates that 5.6 million persons 17 years of age or older had decreased kidney function, as defined by an elevated serum creatinine concentration ($\geq$141 μmol/L [$\geq$1.6 mg/dL] in men and $\geq$124 μmol/L [$\geq$1.4 mg/dL] in women) (2).

Hypertension and proteinuria occur in most patients with chronic kidney disease and are risk factors for faster progression of kidney disease. Antihypertensive agents reduce blood pressure and urine protein excretion and slow the progression of kidney disease. The sixth report of the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommends a lower blood pressure goal for patients with decreased kidney function ($<$130/85 mm Hg if urine protein excretion is $<$1 g/d and $<$125/75 mm Hg if urine protein excretion is $>$1 g/d) than for patients without target organ damage ($<$140/90 mm Hg) (3). It is not known whether even lower blood pressure might provide additional benefit. On the other hand, there is concern about excessive lowering of blood pressure because it may be associated with a higher risk for cardiovascular disease (4, 5). Additional lowering of blood pressure might also have a detrimental effect on kidney disease.

The recommendations in JNC-VI are based principally on the results of the Modification of Diet in Renal Disease (MDRD) Study (6, 7), a study of nondiabetic kidney disease that did not evaluate the effect of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers. Since publication of the JNC-VI, other large studies and meta-analyses have shown that antihypertensive regimens containing ACE inhibitors or angiotensin-receptor blockers seem to be more effective than other regimens in slowing the progression of chronic kidney disease (8–17). In some studies, the beneficial effect of these agents seemed to be greater in patients with proteinuria (8–11, 13) and was mediated in part by their effects to lower blood pressure and urine protein excretion (13). Of these studies, only the African American Study of Kidney Disease and Hypertension (AASK) compared two levels of blood pressure in patients treated with an ACE inhibitor (11). In that study of patients with hypertensive nephrosclerosis, a type of kidney disease associated with low levels

of proteinuria, a lower blood pressure goal did not reduce the risk for progression of kidney disease when compared with a usual blood pressure goal. However, the AASK does not address the relationships of blood pressure and urine protein excretion with the progression of kidney disease in patients with higher levels of urine protein excretion. We performed a patient-level meta-analysis using data from the ACE Inhibition in Progressive Renal Disease (AIPRD) Study Group database (13) to assess these relationships among patients with nondiabetic kidney disease across a wide range of urine protein excretion values during antihypertensive therapy with and without ACE inhibitors.

Context

Guidelines recommend a blood pressure of less than 130/80 mm Hg for patients with chronic kidney disease.

Contribution

This meta-analysis showed that systolic blood pressure and urinary protein excretion were related to the risk for renal disease progression in patients with nondiabetic kidney disease. Systolic pressures of 110 to 129 mm Hg were associated with the lowest risks. Higher risks with higher pressures were marked in patients with protein excretion greater than 1.0 g/d and were not apparent in those with lower urinary protein excretion.

Implications

In patients with urinary protein excretion greater than 1.0 g/d, systolic blood pressure of 110 to 129 mm Hg is associated with the lowest risk for progression of renal disease.

–The Editors

METHODS

Study Design

The AIPRD Study Group database includes 1860 patients with nondiabetic kidney disease enrolled in 11 randomized, controlled trials of ACE inhibitors to slow the progression of kidney disease. The database contains information on blood pressure, urine protein excretion, serum creatinine concentration, and onset of kidney failure during 22 610 visits. Inclusion and exclusion criteria, search strategies for identifying clinical trials, and details of database formulation have been previously described (13, 18).

The AIPRD Study Group was formed in 1997. Briefly, we identified studies by searching the MEDLINE database for English-language reports evaluating the effect of ACE inhibitors or kidney disease in humans between 1977 (when ACE inhibitors were approved for trials in humans) and 1999 (when the database was closed). We included only randomized trials (with a minimum 1-year follow-up) that compared the effects of antihypertensive regimens that included ACE inhibitors with the effects of regimens that did not include ACE inhibitors. Hypertension or decreased kidney function was required for entry into all studies. Exclusion criteria common to all studies were acute kidney failure, treatment with immunosuppressive medications, clinically significant congestive heart failure, obstructive uropathy, renal artery stenosis, active systemic disease, type 1 diabetes mellitus, history of transplantation, history of allergy to ACE inhibitors, and pregnancy. The institutional review board at each participating center approved the study, and all patients gave informed consent. Patients were enrolled between March 1986 and April 1996.

All patients were randomly assigned to antihypertensive regimens either with or without ACE inhibitors. The ACE inhibitors included captopril, enalapril, cilazapril, benazepril, and ramipril. Concomitant antihypertensive medications were used in both groups to achieve a target blood pressure less than 140/90 mm Hg in all studies. All patients were followed at least once every 3 months for the first year and at least once every 6 months thereafter.

Justification for pooling the 11 clinical trials is based on the similarity of study designs and patient characteristics. Justification for pooling placebo-controlled and active-drug–controlled trials is based on the presence of preexisting hypertension and the use of antihypertensive agents in most patients in the control groups in each clinical trial. Thus, the pooled analysis addresses the clinically relevant question of the relationship of the level of blood pressure and urine protein excretion with the kidney disease progression during antihypertensive therapy, either with or without ACE inhibitors.

Definition and Ascertainment of Blood Pressure and Urine Protein Excretion

Clinical trial protocols stipulated measurement of blood pressure more frequently than urine protein excretion. In our database, "visit" was defined as any contact with patients during which study-related information was recorded or clinical variables were measured. Blood pressure was recorded on the same day as the visit in 94% of the visits and within 3 months before the visit in 99% of the visits. Urine protein excretion was recorded on the same day as the visit in 62% of the visits and within 6 months before the visit in 97% of the visits.

Blood pressure and urine protein excretion levels at follow-up visits are defined as the "current" levels. We used "current" as well as baseline levels as the variables of interest for these analyses because guidelines for blood pressure target current values (3) and our previous studies have demonstrated that the current level of urine protein excretion is a stronger predictor of kidney disease progression than is the baseline level (19).

Blood pressure was measured by using a mercury sphygmomanometer in nine studies (8–10, 20–24; Brenner BM. Personal communication) (93% of visits) and calibrated automatic device in two studies (25, 26). Systolic and diastolic blood pressure were measured after 5 to 10

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

Variable	Study (Reference)						
	Zucchelli et al. (20)	Kamper et al. (21)	Brenner et al.† (13)	Toto et al.‡ (13)	van Essen et al. (25)	Hannedouche et al. (22)	Bannister et al. (26)
Study characteristics							
Date of publication	1992	1992	1993	1993	1994	1994	1994
Patients, *n*	121	55	106	122	103	99	47
Mean duration of follow-up, *y*	2.3	2.2	2.1	2.3	3.2	2.1	0.9
Visits, *n*	1601	193	2333	3850	474	833	96
Visits when blood pressure was assessed, *n*	1592	191	1990	3449	461	824	95
Visits when proteinuria was assessed, *n*	1575	193	752	603	433	321	93
Patient characteristics							
Men, %	63	49	65	64	65	50	80
Nonblack ethnicity, %	100	100	44	40	99	100	100
Cause of kidney disease, %							
Glomerular disease	26	31	33	7	26	50	100
Polycystic kidney disease	10	20	14	0	14	15	0
Hypertensive nephrosclerosis	29	0	36	90	29	7	0
Tubulointerstitial disease	20	29	5	3	22	19	0
Other	15	20	12	0	9	9	0
Hypertension, %	100	93	98	100	100	100	100
Mean age, *y*	55	50	47	52	51	51	48
Mean baseline serum creatinine concentration, *μmol/L (mg/dL)*	265 (3.0)	442 (5.0)	239 (2.7)	230 (2.6)	159 (1.8)	265 (3.0)	124 (1.4)
Mean baseline SBP, *mm Hg*	165	147	141	130	154	167	152
Mean baseline DBP, *mm Hg*	100	90	91	82	91	102	95
Mean baseline urine protein excretion, *g/d*	1.7	1.9	2.3	0.7	1.6	2.2	1.7
Mean follow-up SBP, *mm Hg*§	142	136	131	134	138	154	136
Mean follow-up DBP, *mm Hg*§	87	84	83	84	80	91	85
Mean follow-up urine protein excretion, *g/d*§	1.6	1.4	1.3	0.9	1.1	1.7	1.8
Kidney disease outcomes, *n*							
Kidney disease progression‖	28	23	20	22	10	37	1
Doubling of baseline serum creatinine concentration	22	9	13	14	10	26	1
Kidney failure	21	21	15	10	7	27	0
Death, *n*	1	2	3	2	4	3	0
Withdrawal, *n*¶	30	4	33	30	24	19	5
Completed study, *n***	62	26	50	68	65	40	41

* DBP = diastolic blood pressure; SBP = systolic blood pressure.
† Personal communication.
‡ Personal communication.
§ Follow-up values are averaged over all mean values for each patient.
‖ Combined outcome of doubling of serum creatinine concentration or kidney failure.
¶ Withdrawals exclude patients who died, developed kidney failure, or had a doubling of serum creatinine concentration.
** Completed study excludes patients who died, developed kidney failure, had a doubling of serum creatinine concentration, or withdrew.

minutes of rest in the supine position in 10 studies (8–10, 20, 22–26; Brenner BM. Personal communication) and in the sitting position in 1 study (21). Urine protein excretion was reported as total urine protein excretion in a 24-hour urine sample in 10 studies (8–10, 20–22, 24–26; Brenner BM. Personal communication) (95% of visits). One study performed a dipstick assessment in an untimed urine sample and reported quantitative measurement only if the dipstick result was positive (23). For that study, all values of "dipstick negative" were assigned a value of 0.1 g/d. In all studies, results for urine protein excretion of 0.1 g/d or lower were also 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 and rounded to the nearest 0.1 g/d.

Outcomes

Serum creatinine concentration was recorded on the same day as the visit in 78% of visits and within 3 months after the visit in 96% of the visits. The primary outcome for the pooled analysis was "kidney disease progression," defined as a combined end point of a twofold increase (doubling) in serum creatinine concentration from baseline values or development of kidney failure, defined as the initiation of long-term dialysis therapy.

Statistical Analyses

We used S-Plus 2000 (Insightful Corp., Seattle, Washington) and SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina), software programs for statistical analyses. Cox proportional hazards regression analysis was performed to detect associations between the covariates and outcomes. Baseline patient characteristics were treatment assignment (ACE inhibitor vs. control, using the intention-to-treat principle), age (logarithmic transformation), sex, ethnicity, systolic blood pressure, diastolic blood pressure, serum creatinine concentration (reciprocal transformation), and urine protein excretion. Study characteristics included blinding, the type of antihypertensive regimen in

Table 1—**Continued**

Study (Reference)				
Himmelmann et al. (23)	Ihle et al. (24)	Maschio et al. (8)	Ruggenenti et al. (9, 10)	Total
1995	1996	1996	1997/99	1992–1999
255	67	562	323	1860
1.8	1.4	2.4	2.1	2.2
1895	588	7456	3292	22 610
1404	558	7417	3254	21 235
783	529	6913	1919	14 114
49	48	72	77	65
100	100	100	99	94
0	60	34	51	33
0	15	11	1	8
100	0	17	13	34
0	2	19	7	12
0	23	19	28	14
100	100	92	84	92
63	46	51	49	52
88 (1.0)	371 (4.2)	186 (2.1)	194 (2.2)	203 (2.3)
161	150	142	144	148
94	88	88	89	91
0.1	2.1	1.8	3.4	1.8
157	144	140	140	142
90	85	86	87	86
0.1	1.8	1.6	3.1	1.6
0	22	79	69	311
0	11	77	40	223
0	15	2	58	176
1	2	9	4	31
40	19	120	63	387
214	24	354	187	1131

the control group, the planned duration of follow-up, whether dietary advice was given, the year of publication, and a term for studies that differed substantially from the rest (studies 2, 5, 10, and 11), as previously described (13). Baseline patient characteristics and study characteristics were introduced as fixed covariates. Because kidney biopsy was not performed in most cases and criteria for classification of cause of kidney disease are based in part on urine protein excretion, the cause of kidney disease was not included as a variable in the analysis.

Patient characteristics (blood pressure and urine protein excretion) at follow-up visits were adjusted as time-dependent covariates, with each time segment corresponding to the interval between study visits. The value recorded at the beginning of each time segment was defined as the current level and was used for that segment. We used this convention so that each outcome would be determined only by previous exposure. If a blood pressure or urine protein measurement was not recorded for a particular visit, values from the previous visit were carried forward. Sensitivity analyses, omitting visits with imputed data over a long interval, demonstrated no substantial differences from the results presented here (data not shown).

Because blood pressure was the target of antihypertensive therapy in each trial, it is possible that the blood pressure during follow-up might reflect the severity of kidney disease in addition to the effect of antihypertensive therapy. Thus, the observed relationship between current blood pressure and kidney disease progression might reflect "reverse causation" (more severe kidney disease causing higher blood pressure). In principle, a stronger relationship of higher baseline blood pressure to kidney disease progression than current levels would be more consistent with the causal hypothesis rather than with reverse causation. Similarly, a stronger relationship of higher blood pressure earlier during follow-up (closer to baseline) to kidney disease progression than levels later in follow-up (closer to current) would also be more consistent with the causal hypothesis. As sensitivity analyses, we compared the relationship of baseline and follow-up systolic blood pressure with kidney disease progression by examining multivariable models containing only baseline levels, baseline and follow-up levels, and only follow-up levels (three models) using various definitions of follow-up levels: 1) as a fixed covariate either as the mean of all follow-up levels or the 6-month level or 2) as a time-dependent covariate either as the current level or the level 12 months before ascertainment of kidney disease progression.

In all models, current levels of blood pressure and urine protein excretion were expressed as categorical variables. Systolic and diastolic blood pressures were divided into categories according to stages defined by the JNC-VI. The reference ranges for systolic and diastolic blood pressure were 110 to 119 mm Hg and 74 mm Hg or lower, respectively. Urine protein excretion was divided into categories by 0.5-g/d increments below 2.0 g/d, 1.0 g-increments between 2.0 to 5.9 g/d, and 6.0 g/d or more because clinical decision making in nondiabetic kidney disease is not usually based on finer stratification. The reference range for urine protein was less than 0.5 g/d.

Multivariable models were built by using candidate predictors that were associated with outcomes ($P < 0.2$) in bivariate analysis (27, 28). Clinically significant variables were forced in the model. All P values were based on two-sided tests, and significance was set at a P value less than 0.05. Associations are expressed as relative risks with 95% CIs. The proportional hazards assumption was checked by computing the Schoenfeld residuals and determining that they exhibited 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. Potential influence points were checked by examining the score residuals.

To determine whether the relationships of current

Table 2. **Adjusted Relative Risk for Kidney Disease Progression by Systolic Blood Pressure during Follow-up***

Systolic Blood Pressure†	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)‖
mm Hg	←	*n*	→	
<110	253	947	10	2.48 (1.07–5.77)
110–119	548	1976	12	1.00
120–129 (JNC normal)	959	3746	32	1.23 (0.63–2.40)
130–139 (JNC high-normal)	1220	4506	59	1.83 (0.97–3.44)
140–159 (JNC stage 1 hypertension)	1501	7369	113	2.08 (1.13–3.86)
≥160 (JNC stage 2 and 3 hypertension)	1088	4066	85	3.14 (1.64–5.99)
Total	5569	22 610	311	

* Kidney disease progression is defined as doubling of baseline serum creatinine concentration or kidney failure. JNC = Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
† JNC stage refers to classification of systolic blood pressure by the JNC (3).
‡ Number of patients with even a single reading of systolic blood pressure in the corresponding range. Each patient may be assigned more than once in the group depending on the systolic blood pressure at each visit.
§ Number of patient visits with blood pressure in the corresponding range.
‖ Factors other than current systolic blood pressure and current urine protein excretion in the multivariable model included assignment to angiotensin-converting enzyme inhibitor group (relative risk, 0.67 [95% CI, 0.53 to 0.84]), female sex (relative risk, 1.35 [CI, 1.05 to 1.73]), younger age (relative risk, 0.84 [CI, 0.78 to 0.90] per 20% higher age), lower reciprocal serum creatinine concentration (relative risk, 0.51 [CI, 0.47 to 0.56] per 0.1 dL/mg higher), higher baseline systolic blood pressure (relative risk, 1.03 [CI, 1.00 to 1.07] per 5 mm Hg), higher baseline urine protein excretion (relative risk, 1.01 [CI, 0.96 to 1.07] per 0.1 g/d), and higher baseline diastolic blood pressure (relative risk, 1.03 [CI, 0.96 to 1.10] per 5 mm Hg higher). Current diastolic blood pressure is not included.

blood pressure and urine protein excretion with kidney disease progression were affected by patient characteristics, we tested for interactions of these variables with age, sex, reciprocal of the baseline serum creatinine concentration, baseline systolic blood pressure, baseline urine protein excretion, and antihypertensive drug regimen (with or without ACE inhibitors). On the basis of the MDRD Study (6, 7) and the AASK (11), which showed interactions between baseline urine protein and target blood pressure on the progression of nondiabetic kidney disease, we tested for interactions between current blood pressure and current urine protein excretion. On the basis of the results of the MDRD Study and recommendations in JNC-VI, we defined a "high" level of urine protein excretion as 1.0 g/d or more. We also tested other cutoff values for urine protein. The fit of models with and without interactions was compared by using likelihood ratio tests.

Role of the Funding Sources

The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Patient and Study Characteristics

We included 11 studies in our analysis, with a total of 1946 patients. We excluded 66 patients with type 2 diabetes and 20 patients with missing baseline values for blood pressure, urine protein excretion, or serum creatinine concentration. Thus, the final study sample included 1860 patients. **Table 1** shows the characteristics of each study and the characteristics of patients included in each study.

As previously reported (13), 311 patients (16.8%) experienced kidney disease progression (doubling of baseline

Table 3. **Adjusted Relative Risk for Kidney Disease Progression by Urine Protein Excretion during Follow-up***

Urine Protein Excretion†	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)‖
g/d	←	*n*	→	
<0.50	1022	9708	52	1.00
0.5–0.9	699	3340	35	0.96 (0.62–1.49)
1.0–1.4	616	2249	23	0.89 (0.54–1.47)
1.5–1.9	548	1712	26	1.21 (0.74–1.96)
2.0–2.9	629	2316	48	1.67 (1.09–2.54)
3.0–3.9	423	1280	38	2.25 (1.43–3.53)
4.0–4.9	320	737	29	3.43 (2.09–5.64)
5.0–5.9	194	476	20	3.41 (1.91–6.06)
≥6.0	234	792	40	4.77 (2.92–7.81)
Total	4685	22 610	311	

* Kidney disease progression is defined as doubling of baseline serum creatinine concentration or kidney failure.
† Urine protein is rounded to the nearest 100 mg/d.
‡ Number of patients with even a single reading of urine protein excretion in the corresponding range. Each patient may be assigned more than once in the group depending on the value of urine protein at each visit.
§ Number of patient visits with urine protein in the corresponding range.
‖ For factors other than current systolic blood pressure and current urine protein in the multivariable model, see Table 2.

serum creatinine concentration or kidney failure): 124 (13.2%) in the ACE inhibitor group and 187 (20.5%) in the control group ($P = 0.001$). A total of 176 (9.5%) developed kidney failure: 70 (7.4%) in the ACE inhibitor group and 106 (11.6%) in the control group ($P = 0.002$).

Kidney Disease Progression

Multivariable Model without Interactions

By themselves, the baseline and current levels of systolic blood pressure ($P < 0.001$ for both), diastolic blood pressure ($P = 0.006$ and $P = 0.007$, respectively), and urine protein excretion ($P < 0.001$ for both) were significantly related to kidney disease progression. In multivariable analysis, baseline and current levels of systolic blood pressure ($P < 0.001$ for both) and urine protein excretion ($P < 0.001$ for both), but not diastolic blood pressure ($P > 0.2$ for both), remained significantly related to kidney disease progression. **Tables 2** and **3** show the multivariable relative risks for kidney disease progression for current levels of systolic blood pressure and urine protein excretion.

The lowest risk for kidney disease progression was at current levels of systolic blood pressure of 110 to 129 mm Hg (**Table 2**). Compared with the reference range (systolic blood pressure of 110 to 119 mm Hg), current systolic blood pressures less than 110 mm Hg were associated with a relative risk of 2.48 (95% CI, 1.07 to 5.77). Current systolic blood pressures of 130 mm Hg or more were associated with a steep increase in relative risk from 1.83 (CI, 0.97 to 3.44) at 130 to 139 mm Hg to 3.14 (CI, 1.64 to 5.99) at 160 mm Hg or more.

The lowest relative risk for kidney disease progression was at current levels of urine protein less than 2.0 g/d (**Table 3**). Above this level, the relative risk increased from 1.67 (CI, 1.09 to 2.54) at current urine protein excretion between 2.0 and 2.9 g/d to 4.77 (CI, 2.92 to 7.81) at current urine protein excretion of 6.0 g/d or greater.

After adjustment for current levels of systolic blood pressure and urine protein excretion, the risk for kidney disease progression was lower in patients assigned to ACE inhibitor therapy (relative risk, 0.67 [CI, 0.53 to 0.84]). **Table 2** shows other covariates included in the model for kidney disease progression.

Sensitivity Analyses

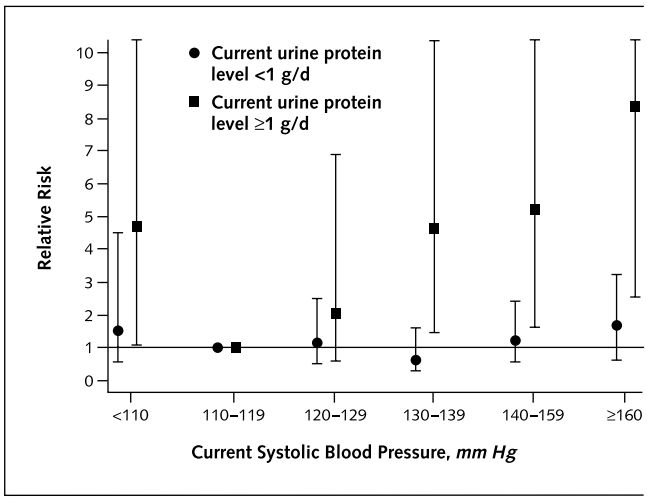
In all multivariable models (data not shown), baseline and follow-up systolic blood pressure between 110 and 129 mm Hg were associated with the lowest risk for kidney disease progression. In general, for a systolic blood pressure of 130 mm Hg or greater, risk ratios were higher for baseline levels than for follow-up levels.

Tests for Interactions

Among the hypothesized interactions, the interactions between baseline serum creatinine concentration and baseline urine protein excretion and between baseline serum creatinine concentration and current urine protein excretion were significant ($P < 0.001$). The relationship between current urine protein excretion and risk for kidney disease progression was stronger in patients with lower compared with higher baseline serum creatinine concentration (data not shown). Interactions between treatment (ACE inhibitor vs. control) and current systolic blood pressure and between treatment and current urine protein excretion were not significant ($P > 0.2$ for both).

Because the interaction of current systolic blood pressure with current urine protein excretion creates many categories, several of which have few events, we reduced the number of categories of urine protein excretion to two (<1.0 and ≥1.0 g/d) to display the effects of this interaction (**Figure**). Similar results were obtained with cutoff values for urine protein of 0.5, 1.5, and 2.0 g/d. The relationship between blood pressure and risk for kidney disease progression differed between patients with higher and those with lower current urine protein excretion (interaction, $P = 0.006$). In patients with higher levels of current urine protein excretion, the optimal current systolic blood pressure seemed to be 110 to 119 mm Hg. The point estimate for the relative risk for kidney disease progression

Figure. **Relative risk for kidney disease progression based on current level of systolic blood pressure and current urine protein excretion.**



The relative risk for patients with a current urine protein excretion of 1.0 g/d or greater represents 9336 patients (223 events), and the relative risk for patients with a current urine protein excretion less than 1.0 g/d represents 13 274 visits (88 events). The reference group for each is defined at a systolic blood pressure of 110 to 119 mm Hg. Confidence intervals are truncated, as shown. Results are from a single multivariable model including two levels for urine protein excretion, six levels for systolic blood pressure, and the interaction of current systolic blood pressure and current urine protein excretion. Covariates include assignment to angiotensin-converting enzyme inhibitor versus control group, sex, age, baseline systolic blood pressure, baseline diastolic blood pressure, baseline urine protein excretion, baseline serum creatinine concentration (<2.0 or ≥2.0 mg/dL [<177 or ≥177 μmol/L]), interaction of baseline serum creatinine and baseline urine protein excretion, interaction of baseline serum creatinine and current urine protein excretion, and study terms.

was approximately five times higher in patients with systolic blood pressure less than 110 mm Hg. At higher systolic blood pressures, the risk increased steeply: It was approximately twofold higher at a current systolic blood pressure of 120 to 129 mm Hg and more than fourfold higher at a current systolic blood pressure greater than 130 mm Hg. By contrast, in patients with lower levels of current urine protein excretion, the risk for kidney disease progression was relatively constant over a wide range of current systolic blood pressures, with an increase in the point estimate for the relative risk at a systolic blood pressure of less than 110 or 160 mm Hg or greater.

DISCUSSION

Our results show independent, strong, graded relationships between higher levels of current systolic blood pressure and urine protein excretion and the risk for kidney disease progression during antihypertensive therapy with or without ACE inhibitors in patients with nondiabetic kidney disease. After adjustment for systolic blood pressure, diastolic pressure was not a risk factor. The lowest risk for kidney disease progression seemed to be at levels of current systolic blood pressure of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d. However, the relationship of the level of current systolic blood pressure with the risk for kidney disease progression varied with the level of current urine protein excretion. At levels of current urine protein excretion greater than 1.0 g/d, the risk for kidney disease progression increased steeply at current systolic blood pressures greater than 120 to 130 mm Hg; however, at levels of current urine protein excretion less than 1.0 g/d, there was little relationship between risk for kidney disease progression and current systolic blood pressure from 110 to 159 mm Hg. At both levels of current urine protein excretion, a current systolic blood pressure less than 110 mm Hg was associated with a higher risk for kidney disease progression. The findings were similar in patients receiving antihypertensive regimens with or without ACE inhibitors.

Our results should be interpreted with caution. They are based on a patient-level meta-analysis of clinical trials that were not designed primarily to assess the effect of lowering blood pressure and urine protein excretion on kidney disease progression. Although patients were randomly assigned to antihypertensive regimens with or without ACE inhibitors, patients were not assigned at random to different targets for blood pressure or urine protein excretion during follow-up. Thus, the association between higher levels of current blood pressure or urine protein excretion and higher risk for kidney disease progression that we observed may be confounded by unmeasured variables or reflect reverse causation. In addition, CIs for the risk for kidney disease progression for discrete levels of blood pressure and urine protein excretion were wide. Nonetheless, we believe that the associations we observed are robust. The relationships for higher systolic blood pressure and urine protein excretion as independent risk factors ($P < 0.001$ for each) and for their interaction ($P < 0.006$) for kidney disease progression were highly statistically significant. Our statistical models were adjusted for all measured variables included in our database, including age, sex, treatment with ACE inhibitors, baseline blood pressure, urine protein excretion, and serum creatinine concentration. Sensitivity analyses were consistent with the causal hypothesis but do not refute the alternative hypothesis of reverse causation. In addition, our findings are consistent with results of other studies.

The finding that systolic blood pressure is more strongly associated with kidney disease progression than is diastolic blood pressure was also observed in a recent analysis of data from the Systolic Hypertension in the Elderly Program (29). The higher risk for kidney disease progression at current systolic blood pressures less than 110 mm Hg is consistent with animal studies and clinical experience that lower systemic blood pressure may reduce kidney perfusion and decrease kidney function (30, 31). Of note, this finding cannot be explained by reverse causation. However, it is based on a small number of events and requires confirmation in other studies. The finding of a stronger beneficial effect of lowering blood pressure in patients with proteinuria is consistent with animal studies showing a marked beneficial effect of lowering blood pressure on the progression of glomerular disease (diseases associated with proteinuria) (32, 33). It is also consistent with the results of the MDRD Study (6, 7) and the AASK (11), which showed that lowering blood pressure in patients with higher but not lower levels of urine protein excretion had a greater beneficial effect on kidney disease progression. These results provide additional support for the recommendation of the JNC-VI (3)—a lower blood pressure target for patients with urine protein excretion of 1 g/d or greater.

No clinical trials have specifically targeted lower versus higher levels of urine protein excretion in chronic kidney disease. Our analyses suggest that urine protein excretion less than 2.0 g/d is associated with the lowest risk for kidney disease progression. It is difficult to estimate the additional benefit, if any, of lower levels of urine protein excretion because of the small number of events in patients with low levels of proteinuria. It is worth noting that our analyses related the current level of urine protein excretion, rather than the "baseline" level, as described in clinical trials. The current level of urine protein may be the more appropriate measure for clinical decision making because it reflects the patient's current clinical status, including the antiproteinuric effect of antihypertensive agents (19).

Because of the high risk for cardiovascular disease in patients with chronic kidney disease (34, 35), the JNC-VI (3) and the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease (34) recommend an upper limit of systolic blood pressure of 130

mm Hg in patients with decreased kidney function. Our analysis suggests that this level of systolic blood pressure, and possibly an even lower level (for example, 110 to 119 mm Hg), may also be beneficial in slowing the progression of kidney disease in patients with urine protein excretion greater than approximately 1.0 g/d.

Even at the levels of blood pressure and urine protein excretion associated with the lowest risk for kidney disease progression, our results show that antihypertensive regimens that included ACE inhibitors were more effective in slowing the progression of kidney disease than were regimens that did not include ACE inhibitors. Recent clinical trials of hypertensive patients at high risk for cardiovascular disease have reached conflicting conclusions about the beneficial effect of ACE inhibitors in preventing cardiovascular disease (36–38). Few patients in our database had cardiovascular disease outcomes, probably reflecting selection of patients with more severe kidney disease and less severe cardiovascular disease.

The patient characteristics (**Table 1**) are similar to those reported in other studies of nondiabetic kidney disease (6, 39). However, compared with the most recent report of the U.S. Renal Data System (40), our patients had a lower mean age (55 vs. 66 years) and a lower proportion of African Americans (7% vs. 32%). However, as discussed earlier, our results are consistent with the AASK, a study of African Americans (11). Moreover, our conclusions did not differ among patients according to age, sex, or baseline serum creatinine concentration. Thus, it is not likely that populations that differ by only these characteristics would show substantially different results. We acknowledge, however, that older patients may have a greater risk for cardiovascular disease than for progression of kidney disease.

In summary, we identified levels of blood pressure and urine protein excretion that are associated with the lowest risk for kidney disease progression. These levels might be appropriate targets for antihypertensive therapy. Our findings probably apply to patients with nondiabetic kidney disease, in whom the risk for progression of kidney disease is greater than the risk for cardiovascular disease. Confirmation of these findings in randomized, controlled trials comparing different targets for blood pressure and urine protein excretion or in other large clinical studies is necessary.

Note Added in Proof: Since submission of the manuscript, the seventh report of the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) has been published. This report defines chronic kidney disease as a "compelling indication" for aggressive antihypertensive therapy that includes ACE inhibitors and a lower blood pressure goal (<130/80 mm Hg) (41).

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