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Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease

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Background. Angiotensin-converting enzyme (ACE) inhibitors reduce urine protein excretion and slow the progression of renal disease. The beneficial effect in slowing the progression of renal disease is greater in patients with higher urine protein excretion at the onset of treatment. We hypothesized that the greater beneficial effect of ACE inhibitors on the progression of renal disease in patients with higher baseline levels of proteinuria is due to their greater antiproteinuric effect in these patients.

Methods. Data were analyzed from 1860 patients enrolled in 11 randomized controlled trials comparing the effect of antihypertensive regimens, including ACE inhibitors to regimens not including ACE inhibitors on the progression of non-diabetic renal disease. Multivariable linear regression analysis was used to assess the relationship between the level of proteinuria at baseline and changes in urine protein excretion during follow-up. The Cox proportional hazards analysis was used to assess the relationship between changes in urine protein excretion during follow-up and the effect of ACE inhibitors on the time to doubling of baseline serum creatinine values or onset of end-stage renal disease.

Results. Mean (median) baseline urine protein excretion was 1.8 (0.94) g/day. Patients with higher baseline urine protein excretion values had a greater reduction in proteinuria during the follow-up in association with treatment with ACE inhibitors and in association with lowering systolic and diastolic blood pressures (interaction $P < 0.001$ for all). A higher level of urine protein excretion during follow-up (baseline minus change) was associated with a greater risk of progression [relative risk 5.56 (3.87 to 7.98) for each 1.0 g/day higher protein excretion]. After controlling for the current level of urine protein excretion, the beneficial effect of ACE inhibitors remained significant [relative risk for ACE inhibitors vs. control was 0.66 (0.52 to 0.83)], but there was no significant interaction between the beneficial effect of ACE inhibitors and the baseline level of urine protein excretion.

Conclusions. The antiproteinuric effects of ACE inhibitors and lowering blood pressure are greater in patients with a higher baseline urine protein excretion. The greater beneficial effect of ACE inhibitors on renal disease progression in patients with higher baseline proteinuria can be explained by their greater antiproteinuric effects in these patients. The current level of urine protein excretion is a modifiable risk factor for the progression of non-diabetic renal disease. ACE inhibitors provide greater beneficial effect at all levels of current urine protein excretion.

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The level of blood pressure has long been recognized as a modifiable risk factor for the progression of renal disease. Recently, it has been shown that proteinuria is also an independent predictor of progression of renal disease. A higher level of urine protein at the onset of therapy is associated with a faster rate of progression, and a reduction in proteinuria during treatment is associated with slowing progression [1–7]. Lowering blood pressure is associated with reducing urine protein excretion, and angiotensin-converting enzyme (ACE) inhibitors are more effective than other antihypertensive agents in lowering urine protein excretion and in slowing the progression of renal disease [8–14]. The Modification of Diet in

Renal Disease (MDRD) Study showed that the beneficial effect of strict blood pressure control on the progression of non-diabetic renal disease was greater in patients with higher urine protein excretion at the onset of therapy [5]. We recently reported that the beneficial effect of ACE inhibitors on the progression of non-diabetic renal disease also was greater in patients with higher urine protein excretion at baseline [7]. Thus, the baseline level of urine protein excretion not only predicts the risk of progression of renal disease, but it also modifies the response to treatment with antihypertensive agents.

This analysis sought to explore the following two questions. First, what is the relationship between baseline proteinuria and changes in proteinuria during antihypertensive therapy? We hypothesized that patients with higher levels of proteinuria at baseline would have a greater reduction in proteinuria in association with treatment with ACE inhibitors and with lowering systolic and diastolic blood pressures. Second, what is the relationship among baseline proteinuria, changes in proteinuria, and the beneficial effect of ACE inhibitors on the progression of renal disease? We hypothesized that after controlling for the change in proteinuria during follow-up, there would be no relationship between the baseline level of proteinuria and the beneficial effect of ACE inhibitors on progression. If both these hypotheses are correct, then the greater beneficial effect of ACE inhibitors in patients with higher baseline urine protein excretion values is due to their greater antiproteinuric effect in patients with greater baseline proteinuria.

This conclusion would simplify the approach to management of non-diabetic renal disease. The current level of proteinuria, rather than the baseline level, could be used to assess the risk of progression and to guide therapeutic interventions. Interventions to reduce proteinuria in non-diabetic renal disease could target the current level of urine protein excretion, just as the current level of blood pressure is the target of antihypertensive therapy.

METHODS

Studies

Individual patient data were analyzed from randomized controlled trials testing the efficacy of ACE inhibitors in non-diabetic renal disease (personal communications, B.M. Brenner and R. Toto) [12, 14–22]. Criteria for inclusion of clinical trials in the individual patient data meta-analysis, search strategies for identification of clinical trials, and details of database formulation have been described previously [13]. Enalapril was used in seven studies (personal communications, B.M. Brenner and R. Toto) [16–19, 21]. Captopril [15], benazepril [12], cilazapril [20], and ramipril [14, 22] were used in one study each.

Justification for pooling the 11 clinical trials is based on the similarity of study designs and patient characteristics (Table 1), and has been discussed previously [7, 13]. Justification for pooling placebo-controlled and active-drug controlled trials is based on the presence of pre-existing hypertension and the use of antihypertensive agents in the vast majority of patients in the control groups in each clinical trial. Thus, the comparison of randomized groups in the pooled analysis addresses the clinically relevant question of whether antihypertensive regimens containing ACE inhibitors are more effective in slowing the progression of non-diabetic renal disease than antihypertensive regimens not including ACE inhibitors.

A total of 1946 patients were randomly assigned to antihypertensive regimens containing ACE inhibitors or those without ACE inhibitors: 983 in the ACE inhibitor group and 963 in the control group. Sixty-six patients were excluded because of non–insulin-dependent diabetes, and 20 patients were excluded because of missing baseline values for either blood pressure, serum creatinine, or urine protein excretion. Thus, the final study population for this analysis included 1860 patients: 941 in the ACE inhibitor group and 919 in the control group. Data were available for 22,613 visits. No baseline variables differed significantly between the 1860 patients included in the analysis and the 20 patients excluded because of missing values.

Target blood pressure was 140/90 mm Hg or less in all studies. All patients were followed at a frequency of at least once every three months for the first year and at least once every six months thereafter. Blood pressure assessment and laboratory parameters were repeated at each visit.

Supine systolic and diastolic blood pressure were measured after a five- to ten-minute rest in all studies, except one, which provided only sitting blood pressure readings [16]. Laboratory methods for measurement of urine protein varied across studies. Two of eleven studies performed a dipstick assessment for urine protein and performed quantitative measurement only if the dipstick was positive [17, 20]. For these two studies, all values of "dipstick negative" were assigned a value of 0.1 g/day. The remaining nine studies performed a quantitative measurement of urine protein for all patients. In all studies, results for urine protein excretion equal to or less than 0.1 g/day were also assigned a value of 0.1 g/day. Values of greater than 0.1 g/day were recorded as the exact values reported in the study.

Outcomes

Two primary outcomes were selected for our current analyses. First, a change in urine protein excretion during follow-up was defined as the baseline level minus the level during follow-up. For descriptive analyses, the level during follow-up was defined as the mean of all values recorded during follow-up. Repeated-measures analysis

Table 1. Study and patient characteristics in the randomized controlled trials included in the pooled analysis

Study number[a]	1	2	3	4	5	6	7	8	9	10	11
Reference	[15]	[16]	PC	PC	[17]	[18]	[19]	[20]	[21]	[12]	[14, 22]
Study characteristics											
Sample size	121	55	106	122	103	99	47	255	67	562	323
Planned duration of follow-up *years*	3	2	3	3	4	3	1	2	2	3	2.2
Study medicine in ACE-inhibitor group[b]	C	E	E	E	E	E	E	CL	E	B	R
Dose range of ACE inhibitor *mg/day*	12.5–50	≥2.5	5–40	5–40	10–40	5–10	5–20	2.5–5	5	10	1.25–5
Study medicine in control group[c]	S [n]	N	P	P	S [a]	S [a]	S [n]	S [a]	P	P	P
Concomitant anti-hypertensive medications in both groups[a]	DF	BCDG	BDEF	BDEFG	CD	CDF	BDE	BCD	BCDEF	BCDEFG	BCDEFG
Blinding	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Dietary advice	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Patient Characteristics[d]											
Men %	63	49	65	64	65	50	79	49	48	72	77
White %	100	100	44	40	99	100	100	100	100	100	99
Cause of renal disease %											
Glomerular disease	26	31	33	7	26	50	100	0	60	34	51
Hypertensive nephrosclerosis	29	0	36	90	29	7	0	100	0	17	13
Tubulointerstitial disease	20	29	5	3	22	19	0	0	2	19	7
Polycystic kidney disease	10	20	14	0	14	15	0	0	15	11	1
Other	15	20	12	0	9	9	0	0	23	19	28
Hypertension[e] %	100	93	98	100	100	100	100	100	100	92	84
Age *years*	55	50	47	52	51	51	48	63	46	51	49
Baseline serum creatinine *mg/dL*	3.0	5.0	2.7	2.6	1.8	3.0	1.4	1.0	4.2	2.1	2.2
Baseline SBP *mm Hg*	165	147	141	130	154	167	153	161	150	142	144
Baseline DBP *mm Hg*	100	90	91	82	91	102	95	94	88	88	89
Baseline urine protein *g/day*	1.7	1.9	2.3	0.7	1.6	2.2	1.7	0.1	2.1	1.8	3.4
Decline in SBP *mm Hg*	24	11	10	−3	16	13	18	4	7	2	4
Decline in DBP *mm Hg*	13	6	8	−1	11	11	10	4	2	2	2
Decline in urine protein *g/day*	0.1	0.5	0.8	−0.2	0.4	0.4	−0.1	0	0.2	0.2	0.3

Abbreviations are: ACE, angiotensin-converting enzyme; PC, personal communication; SBP, systolic blood pressure, DBP, diastolic blood pressure.

[a] Concomitant antihypertensive medications in both groups: B, beta-adrenergic blockers; C, calcium channel blockers; D, diuretics: E, peripheral alpha-adrenergic blockers; F, central alpha-adrenergic agonists; G, vasodilators

[b] Study medication in ACE inhibitor group: C, captopril; E, enalapril; CL, cilazapril; B, benazepril; R, ramipril

[c] Study medication in control group: S, specified; N, not specified; P, placebo; [n], nifedipine; [a], atenolol/acebutalol

[d] Values indicate percentages or means, as appropriate

[e] Hypertension was defined as either 1) SBP ≥ 140 mm Hg, 2) DBP ≥ 90 mm Hg, 3) taking antihypertensive medications prior to enrollment, or 4) classified as "hypertensive" by the clinical investigators

was not used to assess changes during follow-up because the times of follow-up measurements varied across studies. For multivariable models, measurements at each follow-up time were assessed. Second, progression of renal disease was defined as the combined endpoint of a doubling of baseline serum creatinine or onset of end-stage renal disease (ESRD). ESRD was defined as the onset of chronic dialysis therapy.

Statistical analyses

SAS (SAS Institute Inc., Cary, NC, USA) and S Plus (Stat Sci, a division of MathSoft Inc., Seattle WA, USA) were used for statistical analyses. For descriptive purposes, we compared the patients' baseline characteristics and outcomes during follow-up in subgroups of patients defined by their baseline urine protein excretion. The following four subgroups were defined a priori:

(1) Urine protein excretion <0.5 g/day. This cut point is just above the normal range in most clinical laboratories for urine protein excretion. Thus, patients in this category have normal or minimally elevated urine total protein excretion and would include most patients designated as having "microalbuminuria."

(2) Urine protein excretion 0.5 to 2.9 g/day. This category includes patients with "non–nephrotic-range proteinuria," which may be due to a wide variety of renal diseases.

(3) Urine protein excretion 3.0 to 6.0 g/day. Urine protein excretion greater than 3.0 g/day is generally considered "nephrotic-range proteinuria." Most, but not all, patients with this level of proteinuria have an underlying glomerular disease with clinical features of the nephrotic syndrome.

(4) Urine protein excretion >6.0 g/day. Patients with these high levels of proteinuria make up a small fraction of patients with chronic renal disease and may have clinical complications from hemodynamic and metabolic complications of nephrotic syndrome. For this reason, this subgroup was considered separately from other patients with nephrotic-range proteinuria. Only eight studies included patients with baseline proteinuria this high.

Baseline characteristics and outcomes were compared among these subgroups using analysis of variance or chi-square tests as appropriate.

For all other analyses, urine protein excretion on a

continuous scale was used; multivariable linear-regression analysis was used to assess factors associated with changes in urine protein excretion at each follow-up visit during which urine protein excretion was measured. The variables of interest were treatment assignment (ACE inhibitor group vs. control group), change in systolic blood pressure, change in diastolic blood pressure, baseline urine protein, and terms for interactions of each variable with baseline urine protein excretion. Potential covariates included baseline urine protein excretion, gender, race, natural logarithm of age, reciprocal of baseline serum creatinine, baseline systolic and diastolic blood pressures, treatment assignment (randomization to the ACE-inhibitor group vs. the control group), changes in systolic and diastolic blood pressures during follow-up, study variables, and terms for interactions of each covariate with baseline proteinuria. For consistency with our previous report (which could not include a term for each study), terms were included for studies 2, 5, 10, and 11 [7]. The cause of renal disease was not included as a covariate because it was not ascertained uniformly in different studies and because it is usually assigned based, in large part, on urine protein excretion rate.

The Cox proportional hazards regression analysis was used to assess the factors associated with the combined endpoints of doubling of baseline serum creatinine or onset of ESRD. The time associated with the endpoint achieved first was used. Variables of interest for these analyses were baseline urine protein excretion and treatment assignment (ACE inhibitor group vs. control group) as fixed variables and change in urine protein excretion as a time-dependent variable. As in previous analyses [7], we adjusted for the natural logarithm of age, gender, reciprocal of baseline serum creatinine, baseline systolic blood pressure, and terms for studies 2, 5, 10, and 11 as fixed covariates. An adjustment for changes in systolic blood pressure during follow-up also was made as a time-dependent covariate. The interaction term for the treatment effect and baseline urine protein excretion was tested in the model with and without the inclusion of change in urine protein excretion. Analyses were repeated after substituting the current level of urine protein excretion for baseline and change in urine protein excretion. The proportional hazards assumption was checked by computing the Schoenfeld residuals and determining that they exhibited no significant correlation with the ranked failure times [23–25]. 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. 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. We added 0.01 to those values predicted to equal zero in order to be able to calculate the log.

RESULTS

Studies and patients

Characteristics of studies and patients are given in Table 1. Mean baseline urine protein excretion varied from 0.1 to 3.4 g/day across the studies. Table 2 shows patient characteristics for the entire study group and for subgroups stratified by baseline urine protein excretion values. Sixty-five percent of the patients were male, and 94% were non-black. Causes of renal disease included glomerular disease (33%), hypertensive nephrosclerosis (33%), tubulointerstitial disease (12%), polycystic kidney disease (8%), and other (15%). Mean age was 52 years. Mean serum creatinine was 2.3 mg/dL, and mean systolic and diastolic blood pressures were 148 and 91 mm Hg, respectively. The mean (SD) urine protein excretion was 1.8 (2.3) g/day, while the median (interquartile range) urine protein excretion was 0.90 (0.18 to 2.3) g/day.

Baseline characteristics of patients varied according to baseline urine proteinuria. As shown, patients with higher baseline urine protein were younger, more likely to be men, had a greater prevalence of glomerular disease, and higher baseline serum creatinine values ($P \leq 0.001$ for all). Systolic and diastolic blood pressures did not differ among subgroups.

Mean (SD) decline in urine protein from baseline to follow-up was 0.20 (1.46) g/day: 0.43 (1.67) g/day in the ACE-inhibitor group versus −0.03 (1.16) g/day in the control group ($P < 0.001$). Higher baseline urine protein excretion was associated with a significantly greater decline in proteinuria during follow-up in both the ACE inhibitor and control groups ($P < 0.001$ for both). Table 2 and Figure 1 show the pattern of change in urine protein during follow-up. In both the ACE inhibitor and control groups, mean urine protein excretion declined in patients with higher baseline proteinuria and rose in patients with lower baseline proteinuria.

As described previously [7] and shown in Table 2, 176 patients developed ESRD (70 in the ACE inhibitor group vs. 106 in the control group, $P = 0.02$), and 311 patients developed the combined endpoint of a doubling of serum creatinine or onset of ESRD (124 in the ACE inhibitor group vs. 187 in the control group, $P = 0.001$). Patients with higher baseline proteinuria had a higher risk of both outcomes ($P < 0.001$ for both). These relationships were observed in both the ACE inhibitor and in the control groups ($P < 0.001$ for all).

Table 2. Comparison of baseline characteristics and outcomes in subgroups defined by baseline urine protein excretion

	Total	Urine protein excretion *g/day*				*P* value[b]
		<0.5	0.5–3.0	3.0–6.0	≥6.0	
Number of patients	1860	730	728	301	101	
Urine protein excretion *g/day*	1.8 (2.3)	0.15 (0.1)	1.5 (0.7)	4.2 (0.8)	8.7 (3.1)	
Baseline characteristics						
Men	1215 (65)	412 (56)	481 (67)	234 (78)	84 (83)	<0.001
Non-black race	1746 (94)	655 (90)	700 (96)	293 (97)	98 (97)	<0.001
Cause of renal disease						<0.001
Glomerular disease	611 (33)	73 (10)	302 (41)	169 (56)	67 (66)	
Polycystic kidney disease	142 (8)	81 (11)	49 (7)	9 (3)	3 (3)	
Hypertensive nephrosclerosis	614 (33)	434 (59)	146 (20)	28 (9)	6 (6)	
Tubulointerstitial disease	219 (12)	84 (12)	105 (14)	28 (9)	2 (2)	
Other	274 (15)	58 (8)	126 (17)	67 (22)	23 (23)	
Age *years*	51.9 (12.9)	56.9 (10.6)	49.4 (12.9)	47.6 (13.4)	47.2 (14.8)	<0.001
Serum creatinine *mg/dl*	2.3 (1.2)	1.8 (1.0)	2.6 (1.3)	2.6 (1.0)	2.9 (1.3)	<0.001
Systolic blood pressure *mm Hg*	148 (21.5)	149 (22.4)	147 (21)	150 (20.8)	150 (21.9)	0.23
Diastolic blood pressure *mm Hg*	91 (10.9)	90 (10.3)	91 (11.4)	91 (10.9)	90 (10.2)	0.04
Outcomes						
Decline in urine protein excretion *g/day*	0.20 (1.46)	−0.15 (0.49)	−0.06 (0.95)	0.83 (1.63)	2.89 (3.75)	<0.001
ACE inhibitor group	0.43 (1.67)	−0.10 (0.39)	0.14 (0.92)	1.18 (1.64)	3.93 (4.22)	<0.001
Control group	−0.03 (1.16)	−0.20 (0.58)	−0.26 (0.95)	0.48 (1.55)	1.57 (2.54)	<0.001
ESRD	176 (9.5)	22 (3.0)	91 (12.5)	44 (14.6)	19 (18.8)	<0.001
ACE inhibitor group	70 (7.4)	11 (2.9)	35 (9.6)	16 (11.4)	8 (14.6)	<0.001
Control group	106 (11.6)	11 (3.1)	56 (15.6)	28 (18.3)	11 (23.9)	<0.001
Doubling of serum creatinine or ESRD	311 (16.7)	51 (7.0)	146 (20.1)	81 (26.9)	33 (32.7)	<0.001
ACE inhibitor group	124 (13.2)	29 (7.7)	54 (14.8)	27 (19.2)	14 (25.5)	<0.001
Control group	187 (20.5)	22 (6.2)	92 (25.7)	54 (35.3)	19 (41.3)	<0.001

Results are given as *N* (%) or mean (SD) as appropriate.
[a] Ranges include left end point, but not right end point
[b] *P* values are for comparisons across subgroups defined by urine protein excretion

Factors associated with changes in proteinuria

We next considered the relationship of baseline urine protein excretion, ACE inhibitor therapy, and changes in systolic and diastolic blood pressure with changes in proteinuria during follow-up. Without controlling for other factors, higher baseline urine protein excretion was associated with greater reduction in proteinuria during follow-up. A 1.0 g/day higher baseline urine protein excretion was associated with a 0.39 (0.38 to 0.40) g/day greater reduction in proteinuria during follow-up.

After controlling for significant baseline covariates, in those treated with ACE inhibitors, a greater decline in systolic blood pressure and greater decline in diastolic blood pressure were each associated with a greater reduction in proteinuria ($P < 0.001$, $P < 0.001$, and $P = 0.10$, respectively). Separate multivariable models were used to test the interaction of each factor with baseline urine protein excretion. All three interaction terms were significant (interaction $P < 0.001$ for all). As shown in Figure 2A, there was a significantly greater decline in urine protein excretion with ACE inhibitors at higher levels of baseline urine protein excretion. A greater decline in urine protein excretion, albeit of much lesser magnitude, with changes in systolic and diastolic blood pressures (Fig. 2 B, C, respectively), also was observed at higher levels of baseline urine protein. Therefore, patients with higher baseline urine protein excretion experienced a greater antiproteinuric effect of ACE inhibitors and of lowering systolic and diastolic blood pressures.

These analyses were repeated after transforming baseline and follow-up urine protein excretion to the logarithmic scale. In this model, the decline in urine protein excretion during follow-up was independently associated with the use of ACE inhibitors versus control and with the decline in systolic and diastolic blood pressures. However, the interactions of each factor with baseline urine protein excretion were no longer significant. These findings are consistent with the interpretation that ACE inhibitors and lowering systolic and diastolic blood pressures are each associated with a constant fractional reduction in proteinuria, irrespective of the baseline level of proteinuria. The percent reductions (and 95% confidence intervals) for these three factors were 21 (19 to 23), 7 (6 to 8), and 4 (3 to 5), respectively.

Relationship of proteinuria to progression of renal disease

Next, we explored the relationship of urine protein excretion at baseline and changes during follow-up to the effect of ACE inhibitors on the progression of renal disease, as assessed from the combined outcome of doubling of baseline serum creatinine or onset of ESRD. As reported previously, the unadjusted relative risk for the combined outcome in the ACE-inhibitor group ver-

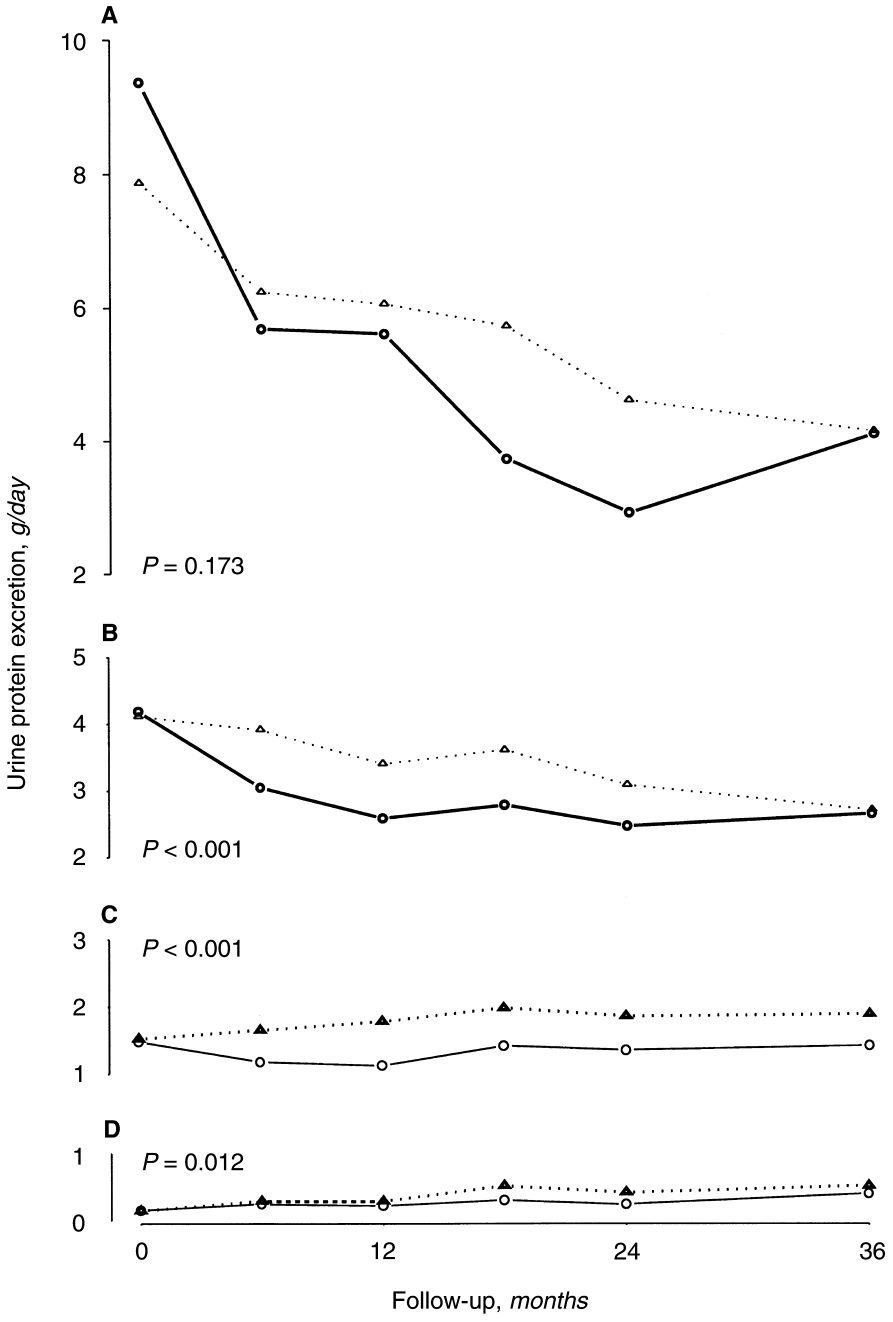

Fig. 1. Comparison between randomized groups of urine protein excretion during follow-up for each subgroup. Subgroups are defined in Table 2. (*A*) Subgroup with baseline urine protein >6.0 g/day ($N = 101$, mean baseline urine protein = 8.7 g/day). (*B*) Subgroup with baseline urine protein 3.0 to 6.0 g/day ($N = 301$, mean baseline urine protein = 4.2 g/day). (*C*) Subgroup with baseline urine protein 0.5 to 3.0 g/day ($N = 728$, mean baseline urine protein = 1.5 g/day). (*D*) Subgroup with baseline urine protein <0.5 g/day ($N = 730$, mean baseline urine protein = 0.15 g/day). (Note that ranges include the left end point but not the right end point.) Vertical axis depicts mean values for urine protein at baseline and various times after randomization for patients randomized to the ACE inhibitor group versus the control group. Horizontal axis depicts months after randomization. Follow-up measurements were reported more often during the first two years and less often thereafter. Not all patients had follow-up measurements of urine protein excretion at each visit. For statistical analyses, mean urine protein excretion during follow-up was defined as the mean of all available follow-up values for each patient. Change during follow-up (Δ) was defined as the baseline value minus the mean follow-up value for each patient. *P* values are for the comparison of change in urine protein excretion during follow-up between the ACE inhibitor group versus control group. Symbols are: (▲) control; (○) ACE inhibitor.

sus the control group was 0.64 (0.51 to 0.80) [7]. For these analyses, three different multivariable models were used: (*1*) controlling for baseline urine protein excretion, (*2*) controlling for the baseline level and changes in urine protein excretion during follow-up, (*3*) and controlling for the baseline level and the current level of proteinuria during follow-up. Each model also controlled for significant baseline factors.

In the first model, as reported previously [7], higher baseline urine protein excretion was a significant independent risk factor for the combined outcome [relative risk of 2.94 (2.05 to 4.22) per 1.0 g/day]. The beneficial effect of ACE inhibitors remained significant [relative risk of 0.59 (0.46 to 0.74)]. In addition, there was a significant interaction between baseline urine protein excretion and the treatment effect (interaction $P < 0.001$), with a greater benefit of ACE inhibitors (lower relative risk) in patients with higher baseline urine protein excretion (Fig. 3A).

In the second model, also as reported previously [7], a greater decline in urine protein excretion during follow-up was associated with a lower risk of the combined

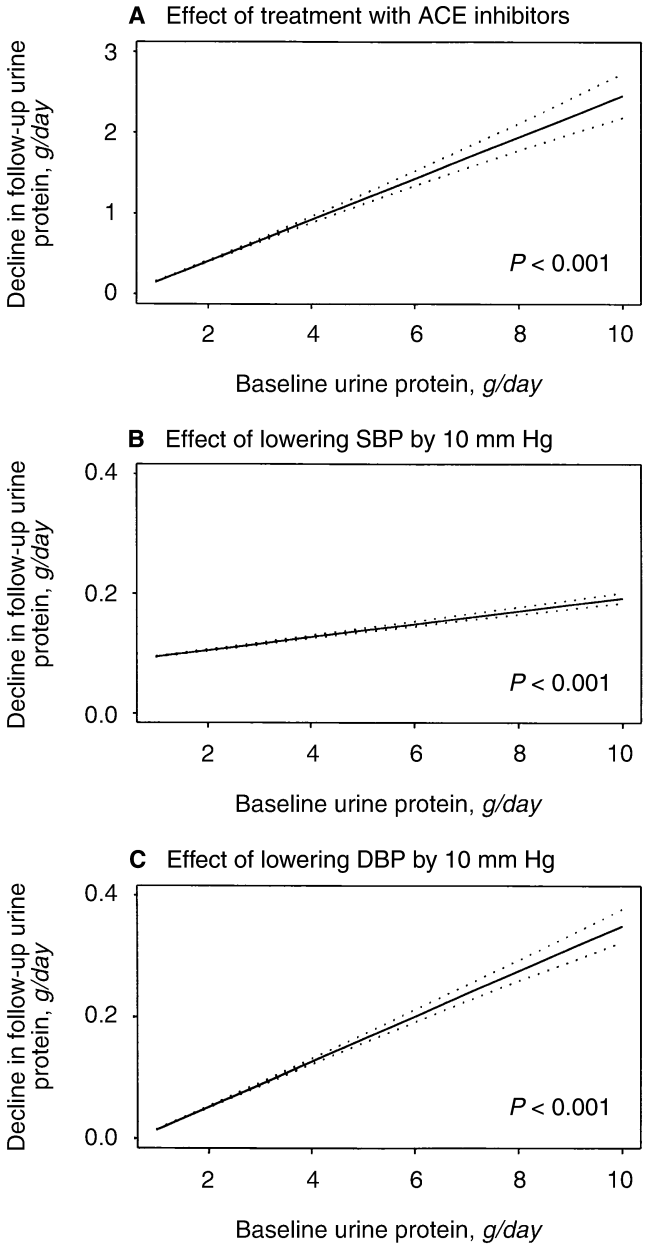

Fig. 2. Relationship of baseline urine protein excretion to changes in urine protein excretion during follow-up. Vertical axis indicates the decline in urine protein excretion from baseline to follow-up associated with treatment with ACE inhibitors versus control antihypertensive agents (*A*), lowering systolic blood pressure (SBP) by 10 mm Hg (*B*), and lowering diastolic blood pressure (DBP) by 10 mm Hg (*C*). Horizontal axis indicates baseline urine protein excretion. Diagonal lines indicate regression coefficient and 95% confidence interval for the relationship between baseline urine protein and decline in urine protein excretion for each intervention (interaction terms). Patients with higher baseline urine protein excretion have a significantly greater decline in urine protein excretion in association with each intervention. Results are derived from a multivariable linear regression model for the decline from baseline in urine protein excretion at each follow-up visit, controlling for gender (reference = male), natural logarithm of age (reference = 55 years), baseline urine protein excretion, reciprocal of serum creatinine (reference serum creatinine = 2.0 mg/dL), interaction between urine protein excretion and reciprocal of serum creatinine, SBP (reference = 150 mm Hg), DBP (reference = 90 mm Hg), treatment assignment (treatment with ACE inhibitors vs. control antihypertensive agents, reference = control), decline in SBP (reference = 0 mm Hg), decline in DBP (reference = 0 mm Hg), and study terms. Interactions were tested in separate models. $P < 0.001$ in all three panels.

outcome [relative risk of 0.20 (0.13 to 0.32) per 1.0 g/day]. In this model, the effect of baseline urine protein remained significant [relative risk of 6.18 (4.00 to 9.54) per 1.0 g/day], as did the beneficial effect of ACE inhibitors [relative risk of 0.70 (0.55 to 0.88)]. However, the interaction between the treatment effect and baseline proteinuria was no longer significant ($P = 0.26$; Fig. 3B). These results suggest three important conclusions. First, as reported before, the beneficial effect of ACE inhibitors is mediated by factors in addition to the antiproteinuric effect of ACE inhibitors [7]. Second, the greater beneficial effect of ACE inhibitors in patients with higher baseline urine protein excretion is due to the greater antiproteinuric effect of ACE inhibitors in these patients. Third, the current level of urine protein excretion during follow-up (the baseline level minus the change from baseline) is a better predictor of the risk of progression than the baseline level alone.

In the third model, these analyses were repeated substituting the current level of urine protein excretion during follow-up for the baseline urine protein excretion and change in urine protein excretion. Higher current urine protein excretion was an independent risk factor for the combined outcome [relative risk of 5.56 (3.87 to 7.98) for each 1.0 g/day]. After controlling for the current level of urine protein excretion, the beneficial effect of ACE inhibitors persisted [relative risk 0.71 (0.56 to 0.89)]. In this model, the interaction between the treatment effect and current urine protein excretion was not significant ($P = 0.93$; Fig. 3C). This indicates that ACE inhibitors are more effective than other antihypertensive agents in slowing progression at all levels of current urine protein excretion. The goodness of fit for this model was as high as the model including the baseline level of urine protein excretion and the change in follow-up, suggesting that the current level of urine protein excretion predicts the risk of progression as well as the baseline level plus the change during follow-up.

DISCUSSION

Hypertension and proteinuria are risk factors for the progression of chronic renal disease. We previously showed that regimens including ACE inhibitors were more effective than other antihypertensive regimens in lowering blood pressure, lowering urine protein excretion, and slowing the progression of renal disease in patients with non-diabetic renal disease [7]. The beneficial effect of ACE inhibitors on progression was greater in patients

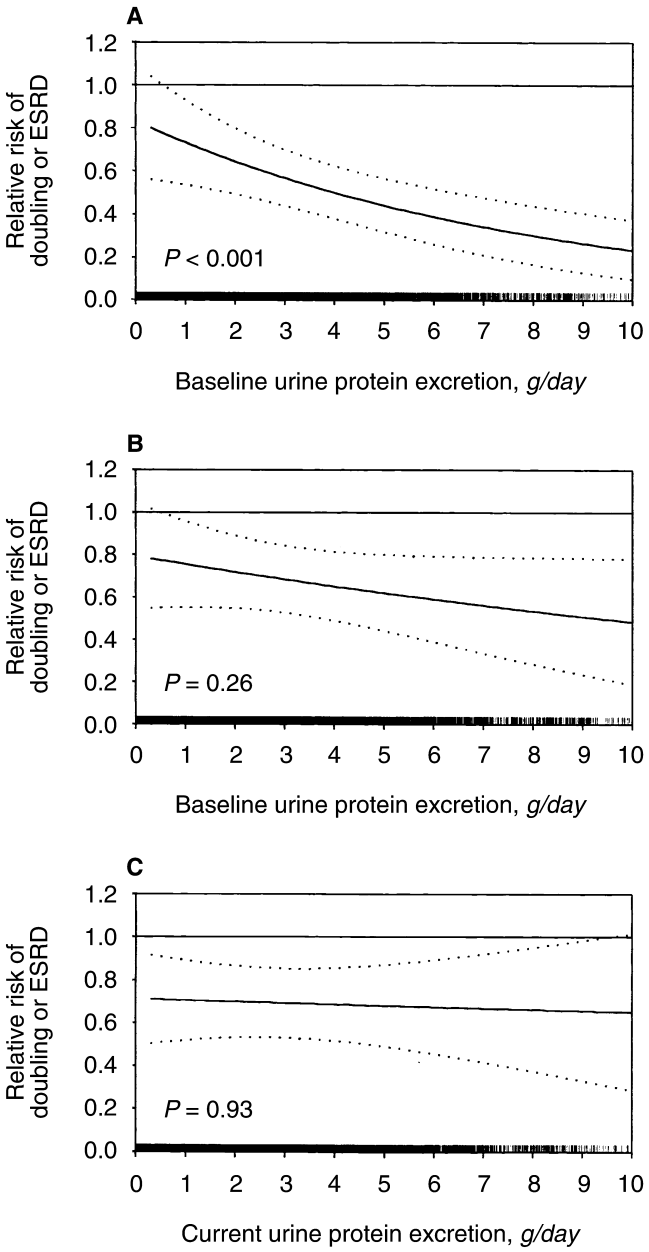

Fig. 3. Relationship of urine protein excretion to the effect of ACE inhibitors on doubling of baseline serum creatinine or ESRD. Vertical axis in all figures is the relative risk of the combined outcome of doubling of serum creatinine or ESRD in the ACE inhibitor group compared with the control group (treatment effect). Horizontal axis is either the baseline level or current level during follow-up of urine protein excretion. Solid and dotted lines indicate point estimates and 95% confidence intervals for the relative risks, respectively. (*A*) The relationship of the treatment effect to baseline urine protein in the multivariable model controlling only for significant baseline patient and study characteristics (modified from Figure 2) [7]. The beneficial effect of ACE inhibitors is greater (lower relative risk) at higher levels of baseline urine protein excretion. The test for interaction between baseline urine protein excretion and treatment was significant ($P < 0.001$). (*B*) The treatment effect after controlling for the change in urine protein excretion in addition to the baseline and study characteristics. The beneficial effect of ACE inhibitors remained significant (relative risk less than 1.0), but was not related to the level of baseline urine protein excretion (interaction $P = 0.26$). (*C*) The treatment effect after controlling for current urine protein excretion rather than the change from baseline. The beneficial effect of ACE inhibitors remains significant, but does not vary with current urine protein excretion (interaction $P = 0.93$). Results are from a multivariable proportional hazards model examining the effect of treatment assignment (ACE inhibitors vs. control antihypertensive agents) on time to doubling of baseline serum creatinine or onset of ESRD, controlling for baseline factors and follow-up factors. Baseline factors in the multivariable model include gender, logarithm of age, reciprocal of serum creatinine, systolic blood pressure, study terms, and urine protein excretion (as indicated). Follow-up factors include decline in systolic blood pressure and change in urine protein excretion or follow-up urine protein excretion (as indicated).

with higher urine protein excretion at the onset of treatment. Declines in blood pressure and urine protein during treatment were independently associated with a lower risk of progression; however, after controlling for these factors, the benefit of ACE inhibitors on progression remained significant. We concluded that the benefit of ACE inhibitors on progression of renal disease was not mediated solely by their antihypertensive and antiproteinuric effects. Thus, the greater beneficial effect of ACE inhibitors in patients with higher baseline proteinuria was unexplained. No other baseline factors modified the beneficial effect of ACE inhibitors on progression.

Our current study shows that antihypertensive regimens containing ACE inhibitors have a greater beneficial effect on lowering urine protein excretion than antihypertensive regimens not containing ACE inhibitors, and that the beneficial effect is greater in patients with higher baseline proteinuria (Figs. 1 and 2 and Table 2). Furthermore, after controlling for changes in proteinuria during follow-up, the beneficial effect of ACE inhibitors on progression is no longer related to the level of proteinuria at baseline (Fig. 3). We conclude that the greater beneficial effect of ACE inhibitors on progression in patients with higher baseline urine protein excretion reflects their greater antiproteinuric effect in these patients. While patients with higher urine protein excretion at baseline benefit more from ACE inhibition than patients with lower urine protein excretion, the level of proteinuria after treatment is begun is a better predictor of the risk of progression than the level at baseline. A lower level of urine protein excretion during follow-up predicts a lower risk. At all levels of urine protein during follow-up, the risk is lower in patients treated with ACE inhibitors.

Overall, these results simplify the approach to the management of non-diabetic renal disease. Lowering blood pressure, lowering urine protein excretion, and ACE inhibition are independent therapeutic goals in the treatment of non-diabetic renal disease. In addition, we show that the current level of proteinuria, rather than the level at the onset of treatment, should be the target of antiproteinuric therapy. To our knowledge, this is the first demonstration of this principle in a large, generalizable study using rigorous statistical methods.

Our database includes 11 of 14 studies and 1946 of the 2122 (92%) patients who met the inclusion criteria for our pooled analysis [7]. The study sample includes 22,613 visits in 1860 patients. This represents the largest set of data collected prospectively in patients with non-diabetic renal disease with longitudinal data on ACE inhibitor therapy, blood pressure, and urine protein excretion and outcomes of renal disease for the comparison of ACE inhibitors to other antihypertensive agents. The distribution of renal diagnosis is roughly similar to that observed for non-diabetic incident dialysis patients in the United States [26]. Thus, the results should be generalizable to the population of patients with non-diabetic renal disease. Both published and unpublished data were included, thereby minimizing publication bias, and only randomized trials that followed an intention-to-treat principle were included to minimize investigator bias. Multivariable regression models were used to identify factors associated with the level of urine protein excretion and renal disease progression, with fixed and time-dependent covariates to model baseline and follow-up factors. Interaction tests rather than subgroup analyses were used to assess "effect modification," which limits the risk of both type 1 and type 2 errors. Overall, these methods assure the internal validity of our results. Thus, we believe our conclusions are robust.

Our analysis confirms that a higher level of urine protein excretion, either at baseline or during treatment with antihypertensive agents, is an independent risk factor for the progression of non-diabetic renal disease. Thus, proteinuria should be considered a "modifiable" risk factor. Proteinuria may contribute to disease progression through a number of mechanisms, including direct mesangial toxicity, tubular overload, toxicity from specific filtered proteins, and induction of proinflammatory molecules [27, 28]. Our database cannot allow inferences regarding mechanisms of renal injury associated with proteinuria.

The analysis of factors associated with declining urine protein excretion during follow-up sheds light on potential therapies to slow the progression of renal disease. Treatment with ACE inhibitors and greater decline in systolic and diastolic blood pressure were independently associated with a greater decline in proteinuria, as has been noted by others [14]. Our results show that patients with higher baseline urine protein excretion have a greater reduction in urine protein excretion in response to each of these interventions (Fig. 2), indicating a subgroup of patients who are especially likely to benefit from antihypertensive therapy with ACE inhibitors.

There are a number of possible limitations of this analysis. First, urine protein was measured according to different protocols and using different laboratory methods in the various clinical trials. In principle, this may introduce measurement error in our pooled analysis, which could weaken the observed association of urine protein excretion with other variables. However, this would not be expected to lead to spurious associations. Second, patients were not assigned at random to different targets for urine protein excretion during follow-up. Thus, the association between higher urine protein excretion during follow-up and higher risk of progression may be confounded by other unmeasured variables or reflect reverse causation. However, the association detected was robust [relative risk of 5.56 (3.87 to 7.98) for each 1.0 gld, $P < 0.001$], even after controlling for other variables, including treatment with ACE inhibitors and baseline urine protein excretion. We suspect that higher urine protein excretion during follow-up truly is a risk factor for progression. The definitive test of this hypothesis would be a randomized clinical trial, comparing two target levels of urine protein excretion.

In addition, many important questions remain unanswered. For example, other than antihypertensive agents, there are few therapies to reduce urine protein excretion. Buter et al have shown that a low-salt diet or diuretics potentiate the antiproteinuric effect of antihypertensive agents [29]. Nonsteroidal anti-inflammatory agents that inhibit synthesis of vasodilator prostaglandins also lower urine protein excretion [30]. However, these drugs have many adverse effects on renal function in patients with chronic renal disease, including further reduction in glomerular filtration rate and reduction in renal potassium excretion [31]. In patients also treated with ACE inhibitors, nonsteroidal anti-inflammatory agents can lead to serious hyperkalemia or acute renal failure. They are also associated with gastrointestinal side effects, which can be serious in patients with chronic renal disease. In our judgment, clinical trials are necessary before these agents should be routinely recommended to reduce urine protein excretion. In addition, we have not analyzed whether the benefit of ACE inhibitors on lowering urine protein excretion is dose dependent. These analyses are underway. Finally, our analyses do not define the optimal target level for urine protein excretion during follow-up. This determination will require analysis of the risks as well as benefits of ACE inhibitors for various levels of urine protein excretion.

In summary, our analyses show that a higher level of urine protein excretion, either at baseline or during follow-up, is associated with a higher risk of progression of non-diabetic renal disease. Even after controlling for their antihypertensive effects, ACE inhibitors are more effective than other antihypertensive agents in lowering urine protein and slowing the progression of renal disease. These beneficial effects are greater in patients with higher urine protein excretion at baseline. The greater beneficial effect of ACE inhibitors in slowing progression in patients with higher baseline proteinuria reflects the greater antiproteinuric effect of ACE inhibitors in these patients. Thus, the level of urine protein during

follow-up is a more important predictor of the risk of progression than the baseline level. We conclude that the level of urine protein during follow-up, as well as the level of blood pressure, should be regarded as a "modifiable risk factor" in non-diabetic renal disease. Lowering blood pressure, reducing urine protein excretion, and treatment with ACE inhibitors are independent therapeutic goals to slow the progression of renal disease.

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