Effects of an Angiotensin-Converting Enzyme Inhibitor on Residual Renal Function in Patients Receiving Peritoneal Dialysis

A Randomized, Controlled Study

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Background: **Residual renal function is an important determinant of mortality and morbidity in patients receiving peritoneal dialysis. However, few studies have evaluated therapeutic approaches for preserving residual renal function after the initiation of dialysis.**

Objective: **To test the hypothesis that the angiotensin-converting enzyme (ACE) inhibitor ramipril slows the decline in residual renal function in patients with end-stage renal failure treated with peritoneal dialysis.**

Design: **Randomized, open-label, controlled trial.**

Setting: **Single-center study in the dialysis unit of a university teaching hospital.**

Patients: **60 patients receiving peritoneal dialysis.**

Measurements: **Patients were randomly assigned to ramipril (5 mg daily) or no treatment. The target blood pressure was 135/85 mm Hg or less. Rate of decline in residual glomerular filtration rate (GFR) and development of complete anuria were compared among groups.**

Results: **Over 12 months, average residual GFR declined by 2.07 mL/min per 1.73 m^2 in the ramipril group versus 3.00 mL/min per 1.73 m^2 in the control group ($P = 0.03$). The difference between the average changes in residual GFR in the ramipril and control groups from baseline to 12 months was 0.93 mL/min per 1.73 m^2 (95% CI, 0.09 to 1.78 mL/min per 1.73 m^2). At 12 months, 14 patients in the ramipril group and 22 in the control group developed anuria. With intention-to-treat multivariable analysis using the Cox model, it was estimated that at 3, 6, and 9 months, patients assigned to ramipril had a higher adjusted hazard of complete anuria than did patients assigned to no treatment. Of the 25 patients who still did not have complete anuria at 12 months, those assigned to ramipril had a better prognosis than did those assigned to no treatment (adjusted hazard ratio, 0.58 [CI, 0.36 to 0.94]). The rates of death from any cause, duration of hospitalization, and cardiovascular events did not differ significantly between groups.**

Conclusions: **Although the trial was small and had a limited ability to exclude effects of potential confounding factors, the angiotensin-converting enzyme inhibitor ramipril may reduce the rate of decline of residual renal function in patients with end-stage renal failure treated with peritoneal dialysis.**

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Residual renal function is an important determinant of mortality and morbidity in patients receiving peritoneal dialysis (1, 2). It contributes to measures of dialysis adequacy, including Kt/V (dialyzer clearance multiplied by time over volume) and creatinine clearance (3, 4), and accounts for most of the variability in dialysis requirement (5). Previous studies of patients receiving peritoneal dialysis showed that nutritional indices gradually deteriorate when residual renal function declines (2, 6). More important, the ADEMEX (Adequacy of Peritoneal Dialysis in Mexico) study, a recently published randomized, controlled trial, found that increases in doses of fluid for peritoneal dialysis had no effect on patient survival (7). Available data suggest that renal and peritoneal clearances are not equivalent (2, 8, 9) and that an increase in the exchange volume or frequency of peritoneal dialysis cannot completely compensate for loss of residual renal function. As a result, measures to preserve residual renal function are an important target in the treatment of patients receiving dialysis.

Residual renal function is better preserved with peritoneal dialysis than with hemodialysis (10, 11), but few studies have evaluated therapeutic approaches for preserving residual renal function after the initiation of dialysis. In one study, furosemide maintained the urine output of patients receiving peritoneal dialysis, but the rate of residual renal function decline was not altered (12). Recently, a retrospective study found that female sex, nonwhite race, history of diabetes, and history of congestive heart failure were predictors of loss of residual renal function (13). Patients treated with peritoneal dialysis had a 65% lower risk for losing residual renal function than did patients receiving hemodialysis. In addition, higher serum calcium levels, use of a calcium-channel blocker, and use of an angiotensin-converting enzyme (ACE) inhibitor were independently associated with decreased risk for loss of residual renal function (13).

Several trials have shown that ACE inhibitors reduce the rates of renal function deterioration in patients with diabetic nephropathy (14, 15) and chronic proteinuric nephropathy (16, 17). We present results of a randomized, open-label study that examined the efficacy of ramipril, an ACE inhibitor, in preserving the residual renal function of patients receiving peritoneal dialysis.

Context

Few studies assess preservation of residual renal function after initiation of dialysis.

Contribution

This open-label randomized trial in patients receiving peritoneal dialysis showed that ramipril reduced declines in glomerular filtration rate and decreased the hazard rate of anuria at 1 year. Five of 30 patients stopped taking ramipril because of dizziness or cough; none withdrew as a result of hyperkalemia.

Cautions

The trial did not use a placebo comparison group, involved patients from a single university teaching hospital, and was not powered to detect differences in health care utilization or morbidity or mortality.

–The Editors

METHODS

Patients

The Clinical Research Ethical Committee of the Chinese University of Hong Kong approved the study. We enrolled 60 stable patients from our hospital who were receiving peritoneal dialysis. All patients received traditional continuous ambulatory peritoneal dialysis, and all had standard peritoneal equilibration tests to determine peritoneal transport characteristics 1 month after dialysis was started. Within 3 months before randomization, blood pressure was measured, and serum and 24-hour urine samples were collected for the measurement of proteinuria and residual renal function to determine eligibility for the trial. We screened 217 patients in our dialysis unit; 72 met the enrollment criteria. On the basis of the sample size estimates, we invited 62 patients to participate in the study. Two declined for personal reasons.

Residual glomerular filtration rate (GFR) was defined as the average of 24-hour urinary urea and creatinine clearances (18). Enrollment criteria were as follows: 1) residual GFR of 2 mL/min per 1.73 m^2 or more, 2) blood pressure of at least 120/70 mm Hg, and 3) no history of taking an ACE inhibitor or angiotensin-receptor blockers for at least 6 months. Since all patients had been followed in our unit for at least 6 months before randomization, we had exact knowledge about the use of an ACE inhibitor or angiotensin-receptor blocker before the study. Exclusion criteria were as follows: 1) underlying medical conditions, such as congestive heart failure, that mandate therapy with an ACE inhibitor or angiotensin II–receptor antagonist; 2) myocardial infarction within the preceding 6 months; 3) clinically significant valvular disease; 4) malignant hypertension or Keith–Wagener grade III or IV hypertensive retinopathy; 5) history of hypertensive encephalopathy or cerebrovascular accident within the preceding 6 months; 6) any condition that may have precluded a patient from remaining in the study, such as alcohol or drug abuse, chronic liver disease, malignant disease, or psychiatric disorder; 7) known history of bilateral renal artery stenosis; and 8) history of allergy or intolerance to an ACE inhibitor. Patients with poor short-term likelihoods of survival, planned elective living related kidney transplantation, or planned transfer to another renal center within 6 months were also excluded.

Design

After obtaining informed consent and performing initial evaluations, we randomly assigned the 60 patients to either ramipril or no treatment. A computer-generated list that was maintained by a third party not involved in the conduct of the study was used for randomization. Investigators were unaware of the randomization schedule when recruiting patients, and both investigators and patients were not blinded during the follow-up period.

Thirty patients received 5 mg of ramipril daily, the dosage commonly used for treating proteinuric nephropathy (16, 17). Antihypertensive agents other than ACE inhibitors were allowed. Doses were adjusted appropriately to achieve and maintain the target blood pressure of 135/85 mm Hg or to avoid symptomatic hypotension. Thirty patients in the control group received identical clinical management, except that ramipril was not prescribed.

After randomization, patients were followed at 0, 3, 6, 9, and 12 months and at any time in between according to clinical need. At each clinic visit, serum creatinine and electrolyte concentrations, complete blood counts, and other serum biochemical values (uric acid, glucose, and liver enzymes) were measured. Residual GFR was assessed at 0, 3, 6, 9, and 12 months by 24-hour urinary collection (18). Indices of the adequacy of dialysis, including Kt/V and weekly creatinine clearance, were assessed at 0, 6, and 12 months by 24-hour dialysate and urinary collection (19). We recommended that all patients limit their sodium intake and that they eat 1.0 to 1.2 g of protein/kg of body weight daily. Persons who performed the 24-hour urinary assessments were unaware of the patients' assignment status. To further avoid bias in outcome assessment, the time at which anuria began was checked by both the investigators and clinic nurses; the nurses were unaware of the treatment assignment of patients.

Outcome Measures

The primary outcome measures were the longitudinal change in residual GFR and the time to anuria. Anuria was defined as total absence of urine output. Secondary outcome measures included urinary protein excretion, death from any cause, duration of hospitalization for any cause, and cardiovascular events. Cardiovascular events included death from cardiovascular causes, nonfatal myocardial infarction, cerebrovascular events with permanent neurologic deficit, and peripheral vascular disease requiring lower-limb amputation above the ankle. Data for secondary outcomes

were assessed by using the computerized Clinical Management System of the Hong Kong Hospital Authority and the Renal Registry Database, developed and maintained by the Central Renal Committee, Hong Kong. Patients assigned to the ramipril group were asked open-ended questions about adverse events at each clinic visit. Patients assigned to no treatment were not routinely asked open-ended questions about adverse events.

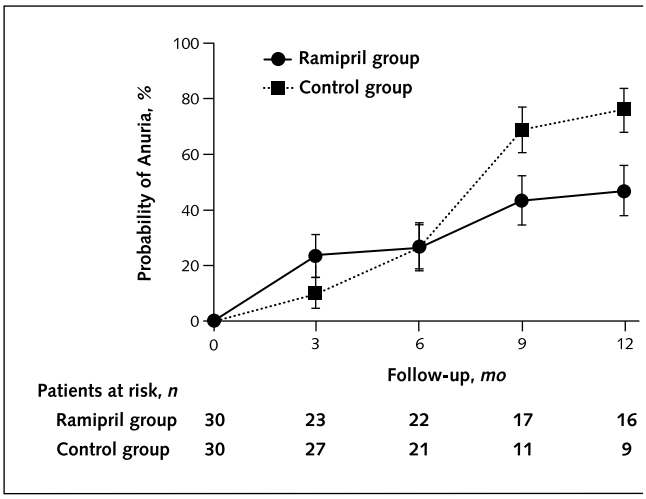
Statistical Analysis

The sample size was estimated before the study with Power Analysis and Sample Size software (PASS 2000, NCSS, Kaysville, Utah). Our previous study on the adequacy of peritoneal dialysis showed that the mean rate of residual GFR decline (±SD) in patients not taking an ACE inhibitor was approximately 0.3 ± 0.2 mL/min per 1.73 m^2 per month (2). Group sample sizes of 30 each would achieve an 83% power to detect a predefined meaningful difference of 0.15 mL/min per 1.73 m^2 per month between the null hypothesis that both group means are 0.3 mL/min per 1.73 m^2 per month (that is, a 50% reduction in the rate of decline) and the alternative hypothesis that the mean of the ramipril group is 0.15 mL/min per 1.73 m^2 per month, with a known group standard deviation of 0.2 and an α level of 0.05 using a two-sided, two-sample *t*-test.

Statistical analyses were performed by using SPSS statistical software, version 9.0 (SPSS, Inc., Chicago, Illinois). Results were expressed as the mean (±SD) unless otherwise stated. *P* values less than 0.05 were considered significant. All *P* values were two tailed. Analyses were done on an intention-to-treat basis, irrespective of adherence to treatment regimen. After 12 months, 26 patients in the ramipril group and 27 in the control group were available for analysis of longitudinal change in residual GFR.

The analysis of the effect of ramipril on longitudinal changes in residual GFR used repeated-measures analysis of covariance. Residual GFR was the repeated measure; treatment group was the between-group factor; a product term for treatment group by time interaction and diabetic status, body weight, net ultrafiltration from the peritoneal equilibration test, and baseline GFR, were the covariates. The model included other covariates because their baseline values seemed somewhat different between the treatment and control groups. All potential confounding variables were forced into the multivariable model. We did not include age, sex, serum calcium level, blood pressure, or antihypertensive therapy in the model because the baseline values in the treatment and control groups did not differ appreciably. Because the Mauchly test of sphericity was highly significant ($P < 0.001$), the degrees of freedom were adjusted by using the Huynh–Feldt epsilon. A significant interaction of a variable, such as treatment group with time in study, indicates that longitudinal changes in residual GFR differ between ramipril and control groups. Since this approach used only the patients who completed the follow-up period, 26 patients in the ramipril group and 27 in the control group were available for the analysis of longitudinal change in residual GFR.

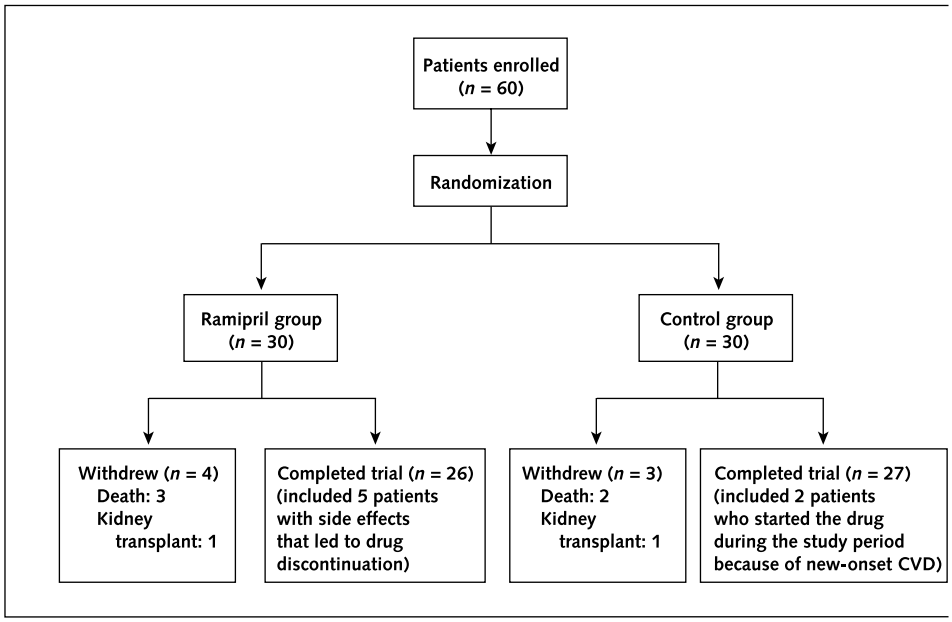
Figure 1. **Kaplan–Meier estimation of patients in the ramipril group and control group who progressed to complete anuria.**



Error bars denote SEs.

For the analysis of time to anuria, we constructed a multivariable Cox model. Since the time-to-anuria curves of the treatment and control groups cross each other (**Figure 1**), the proportional hazards assumption is not satisfied. To address this, we constructed a multivariable model that included terms for treatment group and a time-by-treatment interaction as well as the potential confounders described earlier. Data from all 60 patients were used for the Cox model construction (that is, patients were censored at dropout, development of anuria, or the end of 12 months). Because 36 patients developed complete anuria during the study period, only 3 independent variables could be included in the Cox model without overfitting. As a result, a propensity score to combine all the potential confounders was used for the Cox model analysis (20). We determined the propensity score by predicting treatment group allocation (that is, ramipril group vs. control group) from the potential confounding variables, which included diabetic status, body weight, net ultrafiltration from the peritoneal equilibration test, and baseline residual GFR, by using a logistic regression analysis. Each patient in the study then had an estimated propensity score, which was the estimated probability (as determined by that patient's covariate values) of being randomly assigned to the treatment versus control group. Thus, this propensity score is the single summarized confounding covariate that was forced into the multivariable Cox model for the time to complete anuria. In this analysis, only transplantation and transfer to hemodialysis were censoring events. On the basis of previous reports, transplantation and transfer to hemodialysis are independent of the times at which anuria occurs (2, 21). Specifically, transplantation is based on

Figure 2. **Randomization and patient flow in the trial.**



CVD = cardiovascular disease.

blood group and tissue typing as well as waiting-list time, not on the degree of residual renal function (22). Transfer to hemodialysis was needed only when peritoneal adhesion and failure to resume peritoneal dialysis occurred after an episode of severe peritonitis (which was a sporadic event unrelated to residual renal function or the study medication) (21). As a result, the censoring events in our analysis were considered noninformative, and a sensitivity analysis was not performed.

In all models, we examined the undue effect of influential observations by measuring the change in model parameters by deleting one point at a time. Deleting any of the 60 patients from analysis did not substantially change any model.

Table 1. **Baseline Characteristics**

Variable	Ramipril Group (*n* = 30)	Control Group (*n* = 30)
Men/women, *n/n*	19/11	19/11
Mean age ± SD, *y*	58.0 ± 14.0	59.1 ± 9.8
Mean duration of dialysis ± SD, *mo*	10.7 ± 10.4	10.3 ± 7.8
Mean body height ± SD, *m*	1.63 ± 0.08	1.62 ± 0.09
Mean body weight ± SD, *kg*	63.3 ± 12.4	61.3 ± 10.2
Mean body mass index ± SD, kg/m^2	23.6 ± 3.7	23.3 ± 3.8
Mean blood pressure ± SD, *mm Hg*		
Systolic	151.8 ± 14.5	150.5 ± 16.7
Diastolic	83.8 ± 10.2	83.3 ± 11.5
Mean	106.5 ± 9.9	105.7 ± 10.9
Patients taking antihypertensive medication, *n*		
Calcium-channel blocker	12	13
β-blocker	13	12
Methyldopa	4	5
Others	6	7
Diagnosis, *n*		
Glomerulonephritis	7	11
Diabetes	16	12
Polycystic kidney disease	0	1
Nephrosclerosis	2	0
Others or unknown	5	6

Role of the Funding Source

The funding source had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to submit the manuscript for publication.

RESULTS

Figure 2 shows the trial profile. Thirty patients were enrolled in the ramipril group and 30 in the control group. Baseline clinical characteristics are shown in **Table 1**. **Table 2** presents baseline renal function and indices of dialysis adequacy. The ramipril group had marginally more diabetic patients, higher body weights, lower net ultrafiltration from the peritoneal equilibration test, and lower baseline residual GFR than the control group. Blood pressure at baseline was nearly identical in the two groups, and the number of patients taking different types of antihypertensive agents at baseline was also similar in both groups. Two patients in the control group required an ACE inhibitor during the study period because of new-onset cardiovascular disease.

Decline in Residual GFR

Residual GFR gradually declined during the study period in both groups (**Figure 3**). Over 12 months, residual

Table 2. **Baseline Peritoneal Transport Characteristics, Residual Renal Function, and Dialysis Adequacy Indices***

Variable	Ramipril Group ($n = 30$)	Control Group ($n = 30$)
Peritoneal transport characteristics		
Net ultrafiltration, *L*	0.23 ± 0.43	0.46 ± 0.51
D/P4	0.65 ± 0.10	0.62 ± 0.14
MTAC, *mL/min per 1.73 m²*	9.32 ± 3.56	8.81 ± 4.47
Residual GFR, *mL/min per 1.73 m²*		
Mean ± SD	3.55 ± 2.13	3.74 ± 1.84
Median (range)	3.27 (2.00–7.87)	3.61 (2.01–7.67)
Urinary protein excretion, *g/d*	2.17 ± 3.12	2.27 ± 1.48
Serum albumin level, *g/L*	32.8 ± 6.2	33.0 ± 6.0
Serum creatinine level, *μmol/L (mg/dL)*	850 ± 287 (9.6 ± 3.2)	823 ± 246 (9.3 ± 2.8)
Total Kt/V	2.06 ± 0.63	2.12 ± 0.53
Total creatinine clearance, *L/wk per 1.73 m²*	78.7 ± 32.6	83.7 ± 31.4

* Unless otherwise noted, data are presented as means ± SDs. D/P4 = dialysate–plasma creatinine ratio at 4 hours; GFR = glomerular filtration rate; Kt/V = solute clearance as a dialysis adequacy index; MTAC = mass transfer area coefficient of creatinine.

GFR declined by 2.07 ± 1.12 mL/min per 1.73 m^2 in the ramipril group compared with 3.00 ± 1.86 mL/min per 1.73 m^2 in the control group ($P = 0.03$). The average decline in residual GFR was 0.93 mL/min per 1.73 m^2 (95% CI, 0.09 to 1.78 mL/min per 1.73 m^2) less in patients receiving ramipril than in control patients.

From the multivariable model (**Table 3**), the estimated adjusted mean residual GFR was 1.72 mL/min per 1.73 m^2 (CI, 1.13 to 2.30 mL/min per 1.73 m^2) at 12 months in the ramipril group and 0.64 mL/min per 1.73 m^2 (CI, 0.00 to 1.22 mL/min per 1.73 m^2) in the control group.

Twenty-two patients in the control group and 14 patients in the ramipril group developed complete anuria. **Figure 1** shows the Kaplan–Meier estimation of the unadjusted rate of developing anuria. As described earlier, we constructed a multivariable Cox model with the following covariates: treatment group, time-by-treatment interaction, and a propensity score that incorporated all the potential confounders. Data from all 60 patients were used for this part of the analysis. **Table 4** summarizes the results from the multivariable Cox model for the time to complete anuria. In this model, the terms for both treatment and treatment-by-time interaction group were statistically significant ($P < 0.001$), which was expected because the time-to-event curves cross (**Figure 1**). At 3, 6, and 9 months, patients assigned to ramipril had higher adjusted hazards of complete anuria than did those assigned to no treatment (**Table 4**). At 12 months, those assigned to ramipril had lower hazards of anuria than did those assigned to no treatment (adjusted hazard ratio, 0.58 [CI, 0.36 to 0.94]).

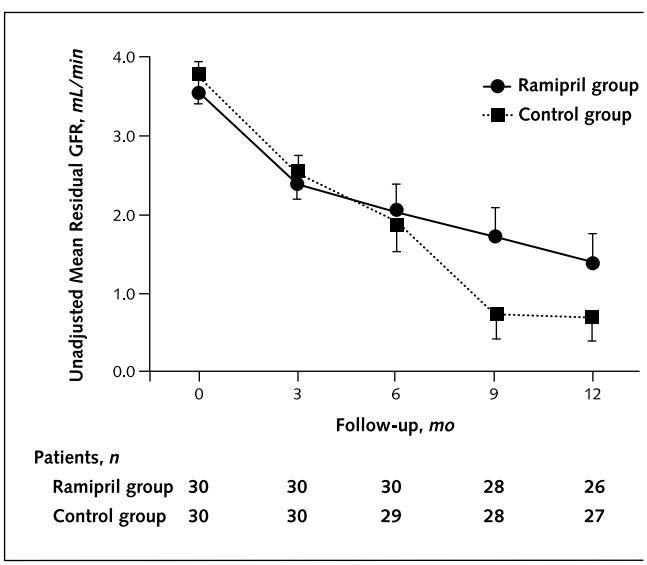
Secondary Outcomes and Adverse Events

Table 5 summarizes secondary outcomes. Because we adjusted antihypertensive treatment primarily by changing doses rather than by changing type of medication, the number of patients taking different antihypertensive medications remained similar in the two study groups throughout the follow-up period. Ramipril was well tolerated. Self-reported adherence was 85%. Five patients in the ramipril group withdrew from the study because of persistent dizziness ($n = 3$) or cough ($n = 2$). No patients developed hyperkalemia that necessitated withdrawal of ramipril.

Discussion

Our study suggests that treatment with ramipril reduces the rate of decline in residual renal function and possibly delays the development of complete anuria in patients receiving peritoneal dialysis. To our knowledge, this is the first randomized trial that examines the effect of an ACE inhibitor on the rate of decline in residual renal function in patients receiving long-term dialysis. Nevertheless, it is important to note that our trial was neither placebo controlled nor double blinded. In addition, the study was small, and our ability to determine whether potential confounding factors affected the observed results (for example,

Figure 3. **Unadjusted mean residual glomerular filtration rate (*GFR*) at baseline and follow-up in the ramipril group and the control group.**



Error bars denote SEs.

the use of other antihypertensive medications, which was not adjusted for in the multivariable analysis) was limited.

Our trial studied only patients with somewhat preserved residual renal function. We did not study new patients receiving continuous ambulatory peritoneal dialysis because a subgroup of patients lost residual renal function shortly after initiation of dialysis. Many of these patients had severe atherosclerosis and possibly ischemic nephropathy (13, 23) and were unlikely to benefit from ACE inhibitor therapy from a renal perspective.

Although our study found a small benefit in residual renal function, the clinical relevance of this finding may be substantial. Residual renal function is an independent predictor of actuarial patient survival. Each 1-mL/min of residual GFR is associated with nearly a 50% reduction in mortality rate (2, 24). It has also been estimated that each 1-mL/min of renal clearance can be translated into a Kt/V of 0.25 to 0.3 per week in a 70-kg man (25, 26). One 2-L dialysis exchange per day could be spared by preserving 1 mL/min of residual GFR, which could improve quality of life and decrease costs substantially (27).

Both the multivariable results on residual GFR (**Table 3**) and time to complete anuria (**Table 4**) indicate that patients assigned to ramipril seem to have lower average residual GFR and higher hazards of complete anuria at both 3 and 6 months. For example, at 3 months, of the 50 patients who still did not have complete anuria, those assigned to ramipril had a worse prognosis for having complete anuria (adjusted hazard ratio, 18.3) than those assigned to no treatment (**Table 4**). Similarly, at 6 and 9 months, of the 43 and 28 patients, respectively, who still did not have complete anuria, those assigned to ramipril had a worse prognosis (adjusted hazard ratios, 5.8 and 1.8, respectively) than those assigned to no treatment. The multivariable result is consistent with the general clinical impression that in a proportion of patients, the residual GFR declined more quickly than expected within 3 months of starting the ACE inhibitor (**Figure 1**), presumably because of the hemodynamic effect of the ACE inhibitor. The therapeutic benefit of the ACE inhibitor became obvious only after a follow-up period that allowed compensation for the initial decrease in residual GFR. Similar findings of an apparently delayed therapeutic effect have been observed in the treatment of diabetic nephropathy with an ACE inhibitor (28) and in progressive renal insufficiency treated with dietary protein restriction (29).

Similar to previous studies of diabetic nephropathy (14, 15) and other chronic proteinuric nephropathies (16, 17), our study found that the benefits of ramipril seem to be independent of systemic blood pressure. Average blood pressure during the study period was only minimally lower in the treatment than in the control group. Ample evidence from in vitro experiments shows that angiotensin II plays a pivotal role in the accumulation of extracellular matrix and progressive glomerulosclerosis (30, 31) and that the beneficial effect of ACE inhibitor therapy is related to the paracrine rather than hemodynamic effect of angiotensin II.

Unlike previous studies of diabetic nephropathy (14, 15) and chronic proteinuric nephropathies (16, 17), our study did not find that ramipril reduced proteinuria in patients receiving peritoneal dialysis. In fact, urinary protein excretion was marginally higher in the ramipril group after 6 months of therapy. This is probably explained by

Table 3. **Multivariable Analysis for the Serial Change in Residual Glomerular Filtration Rate by Analysis of Covariance for Repeated Measures***

Model Summary			*P* Value
Between-patient variables			
Treatment group			>0.2
Diabetes			>0.2
Body weight in kg			>0.2
Net ultrafiltration in L			>0.2
Baseline GFR in mL/min per 1.73 m^2			<0.001
Within-patient variables			
Time in mo			0.20
Time × treatment group			<0.001
Estimation of GFR	**Treatment Group**	**Control Group**	
Mean estimated GFR (95% CI), *mL/min per 1.73 m^2*			
0 mo	3.71	3.71	
3 mo	2.28 (1.60–2.96)	2.92 (2.26–3.59)	
6 mo	1.98 (1.22–2.74)	2.28 (1.53–3.02)	
9 mo	1.95 (1.30–2.59)	0.70 (0.00–1.33)	
12 mo	1.72 (1.13–2.30)	0.64 (0.00–1.22)	

* GFR = glomerular filtration rate.

Table 4. **Multivariable Cox Model for Time-to-Complete Anuria***

Model Summary Variable	Coefficient (B)	Adjusted Hazard Ratio	*P* Value
Treatment group†	4.057	57.79	<0.001
Treatment group × time in months	−0.384 × time	0.68^{time}	<0.001

Overall Adjusted Hazard Ratio at Different Time Points‡

Time, *mo*	Patients at risk for complete anuria, *n*	Adjusted Hazard Ratio (95% CI)
3	50	18.28 (5.63–59.33)
6	43	5.78 (3.10–10.77)
9	28	1.83 (1.71–1.96)
12	25	0.58 (0.36–0.94)

* A propensity score with the following variables was included in the Cox model: diabetic status, body weight, net ultrafiltration from the peritoneal equilibration test, and baseline glomerular filtration rate.
† B value and adjusted hazard ratio of the treatment group represent the corresponding parameter at time 0.
‡ Overall adjusted hazard ratio of ramipril treatment = $e^{(B1 + B2 \times time)}$; B1 is the B value of the treatment group at time 0, and B2 is the B value of treatment group × time. For example, the adjusted hazard ratio at 6 months = $e^{(4.057 - 0.384 \times 6)} = 5.77$; adjusted hazard ratio at 12 months = $e^{(4.057 - 0.384 \times 12)} = 0.58$. An adjusted hazard ratio above 1 indicates that ramipril is worse than no treatment; an adjusted hazard ratio below 1 indicates that ramipril is better than no treatment.

the high incidence of anuria in the control group, which inevitably results in an apparent reduction in proteinuria. Post hoc analysis confirmed that the degree of proteinuria correlated with the urine volume throughout the study period (details not shown).

Most of the patients in the our study were hypertensive at enrollment. The initial decline in residual GFR during the first 3 months of the study was steeper than the sustained decline during the remainder of the study period (**Figure 3**). This observation has been noted in other studies of ACE inhibitors (14–17, 32, 33). It was suggested that the faster initial decline in GFR is due to the hemodynamic effect of antihypertensive treatment (14, 15, 33). By contrast, the sustained but slower decline in GFR reflects the beneficial effect of the ACE inhibitor and possibly vigorous blood pressure control (34). The sustained rate of decline in kidney function found in our study was similar to that of studies in patients with chronic renal failure before the start of dialysis (14–17). We do not have comparison data on the rate of decline in GFR in our patients before enrollment into the study.

We advise caution before extrapolating our results to patients receiving hemodialysis. Residual renal function is better preserved with peritoneal dialysis than with hemodialysis (10, 11) because hemodialysis causes substantial hemodynamic disturbance and activates inflammation (25, 35), which may accelerate the loss of residual renal function. Therefore, patients receiving hemodialysis and those receiving peritoneal dialysis probably have a different therapeutic response to an ACE inhibitor. Nevertheless, peritoneal dialysis as initial renal replacement therapy and conversion to hemodialysis when the patient becomes anuric are increasingly being advocated (36, 37). Our finding suggests that an ACE inhibitor, ramipril, may slow the decline in residual renal function and contribute to the therapeutic success of peritoneal dialysis. Because most patients who begin peritoneal dialysis are hypertensive, our finding may be applicable to a substantial proportion of the dialysis population.

Table 5. **Secondary Outcomes**

Variable	Ramipril Group (n = 30)	Control Group (n = 30)
Average follow-up blood pressure, *mm Hg*	143/78	141/81
Patients taking other antihypertensive drugs, *n*	19	22
Median urinary protein excretion at 6 mo (range), *g/d*	0.28 (0–7.9)	0.30 (0–1.60)
Episodes of peritonitis, *n*		
Total	9	8
Treated with an aminoglycoside	6	5
Cardiovascular events, *n*		
Fatal	2	2
Nonfatal	3	3
Hospitalization		
Patients admitted, *n*	14	13
Median hospitalization (range), *d*	8 (0–58)	6 (0–96)

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