Original Article

Effects of Valsartan on the Progression of Chronic Renal Insufficiency in Patients with Nondiabetic Renal Diseases

Toshihiko ISHIMITSU, Tomoko KAMEDA, Akira AKASHIBA, Toshiaki TAKAHASHI, Norikazu ANDO, Satoshi OHTA, Masayoshi YOSHII, Hideki INADA, Kohju TSUKADA, Junichi MINAMI, Hidehiko ONO, and Hiroaki MATSUOKA

The present study tested the effects of valsartan, an angiotensin II receptor blocker, on the progression of renal insufficiency in patients with nondiabetic renal diseases. The study subjects were 22 patients with nondiabetic renal diseases whose serum creatinine (Cr) ranged from 1.5 to 3.0 mg/dl. Valsartan (40–80 mg) or placebo was given once daily for 1 year each in a random crossover manner. In both periods, antihypertensive medications were titrated when the blood pressure was not lower than 140/90 mmHg. Blood sampling and urinalysis were performed bimonthly throughout the study periods. The average blood pressure was comparable between the valsartan and the placebo periods (130±9/86±6 *vs.* 131±8/86±6 mmHg). Serum Cr significantly increased from 1.9±0.5 to 2.3±0.8 mg/dl ($p<0.001$) during the placebo period, but the change was insignificant in the valsartan period (2.1±0.6 to 2.2±0.9 mg/dl). The slope of decrease in the reciprocal of serum Cr was steeper in the placebo period than in the valsartan period (−0.064±0.070/year *vs.* −0.005±0.050/year, $p<0.01$). During the valsartan period, urinary protein excretion was less than that during the placebo period (0.75±0.73 *vs.* 1.24±0.92 g/g Cr, $p<0.001$). Serum K was significantly higher in the valsartan period than in the placebo period (4.6±0.5 *vs.* 4.4±0.5 mEq/l, $p<0.05$); however, no patients discontinued taking valsartan as a result of hyperkalemia. It is possible that long-term treatment with an angiotensin II receptor blocker, valsartan, is effective at retarding the deterioration of renal function in patients with nondiabetic renal disease by a mechanism independent of blood pressure reduction. (*Hypertens Res* 2005; 28: 865–870)

***Key Words*: valsartan, angiotensin II receptor blocker, chronic renal insufficiency, nondiabetic renal disease, proteinuria**

Introduction

According to the hyperfiltration theory, increases in glomerular capillary pressure, referred to as glomerular hypertension, play an important role in the progression of diabetic and nondiabetic renal diseases (*1*, *2*). Intraglomerular capillary pressure is affected by the tone of the glomerular arterioles as well as by the level of systemic arterial pressure. Because angiotensin II is a potent constrictor of the efferent arterioles, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), which inhibit the generation and/or action of angiotensin II, are effective at alleviating glomerular hypertension (*3*). On the other hand, calcium

From the Department of Hypertension and Cardiorenal Medicine, Dokkyo University School of Medicine, Tochigi, Japan.
Address for Reprints: Toshihiko Ishimitsu, M.D., Department of Hypertension and Cardiorenal Medicine, Dokkyo University School of Medicine, Mibu, Tochigi 321–0293, Japan. E-mail: isimitu@dokkyomed.ac.jp
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Table 1. Basic Characteristics of the Study Subjects

Pamameter	Value
Age (years)	56±13
Gender (men/women)	16/6
Body mass index (kg/m^2)	24.3±3.4
Renal disease	
Chronic glomerulonephritis	10
Nephrosclerosis	7
Polycystic kidney	2
Drug-induced nephropathy	2
Chronic pyelonephritis	1
Systolic blood pressure (mmHg)	131±8
Diastolic blood pressure (mmHg)	87±6
Pulse rate (bpm)	70±7
Antihypertensive medication	
Calcium channel blocker	16
Diuretics	7
ACE inhibitor	7
β-Blocker	3
α-Blocker	4
Others	2
Number of antihypertensive drugs	
0	4
1	7
2	5
3 or more	6

Data represent the mean±SD. ACE, angiotensin converting enzyme.

channel blockers (CCB) tend to dilate the afferent arterioles, and therefore tend to be less effective at reducing intraglomerular pressure, as compared to specific inhibitors of the renin-angiotensin system (*4*).

Multiple lines of clinical evidence have indicated that ACE inhibitors and ARBs exert protective effects against the progression of diabetic nephropathy (*5*, *6*). Moreover, as regards patients with nondiabetic renal diseases, it has been reported that long-term ACE inhibition reduced proteinuria and ameliorated the rate of deterioration of renal function (*7*). However, as compared to the amount of evidence available regarding ACE inhibitors, little evidence has been reported thus far regarding the long-term effects of ARBs on the progression of nondiabetic renal diseases. The number of ARB prescriptions has recently been increasing due to the higher risks of coughing as an adverse side effect associated with ACE inhibitors; thus, it appears important to establish evidence of the superiority of ARBs at slowing the progression of nondiabetic renal insufficiency.

In this random crossover study, we examined the effects of an ARB, valsartan, on the progression of renal dysfunction in patients with nondiabetic renal diseases.

Table 2. Average Blood Pressure and Pulse Rate during the Period of Administration of Placebo or Valsartan

Variable	Placebo period	Valsartan period
Systolic blood pressure (mmHg)	131±8	130±9
Diastolic blood pressure (mmHg)	86±6	86±6
Pulse rate (bpm)	71±5	70±6

Data are represented as the mean±SD.

Methods

We enrolled a total of 22 outpatients with nondiabetic renal insufficieny, the serum creatinine (Cr) levels of whom ranged from 1.5 to 3.0 mg/dl. The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Edinburgh version, 2000) and was approved by the institutional review board. The patients were informed that the study compares the effects of ARB and placebo administration on the progression of renal dysfunction, and informed consent was obtained from all subjects. Each patient underwent a 1-year period of treatment with valsartan and a 1-year period of treatment with placebo. Empty cellulose capsules were used as the placebo in this study, which was conducted in a single-blind manner. The order of study drugs was randomized blindly, and each drug was taken once daily after the subject had eaten breakfast. No patient had previously taken an ARB, and 7 patients had been taking ACE inhibitors before enrolling in the present study (Table 1). Among those patients who had been taking ACE inhibitors, the ACE inhibitor was replaced with valsartan or placebo. The antihypertensive medication dosage was chosen such that the blood pressure was decreased to a systolic value below 140 mmHg, and to a diastolic value below 90 mmHg. Valsartan was initiated at a 40-mg dose, which was increased to 80 mg if the combined blood pressure level was not lower than 140/90 mmHg. Then, the doses of other classes of antihypertensive drugs, with the exception of ACE inhibitors and ARBs, were added or increased in each case in order to achieve the target blood pressure. During the period in which the placebo was administered, the doses of antihypertensive drugs other than ARBs and ACE inhibitors were titrated such that the blood pressure was maintained below 140/90 mmHg. Blood pressure was measured by a sphygmomanometer at 2- to 4-week interval visits with the patient in a sitting position after the patient had rested for more than 20 min, also in a sitting position. The patients were instructed to reduce their salt intakes to less than 7 g/day, and their protein intake was to be restricted to less than 50 g/day throughout the study period; however, no limitation was required with respect to the intake of potassium.

During both of the study periods, blood and urine samples

Table 3. Changes in Body Weight, and Blood Hemoglobin and Serum Chemistry Data during the Administration of Placebo or Valsartan

Variable	Placebo period		Valsartan period	
	Month 0	Month 12	Month 0	Month 12
Body weight (kg)	64.3±11.1	64.3±11.3	64.2±11.3	64.4±10.6
Blood hemoglobin (g/dl)	13.3±1.7	13.2±1.7	13.2±1.6	13.1±1.7
Serum albumin (g/dl)	4.2±0.2	4.1±0.3	4.1±0.3	4.2±0.3
Serum Na (mEq/ml)	141±1.4	141±2.1	142±1.8	141±2.0
Serum K (mEq/l)	4.5±0.5	4.4±0.5	4.4±0.4	4.6±0.5*
Serum chloride (mEq/l)	105±3	106±2	106±2	107±2
Serum urea nitrogen (mg/dl)	26±7	31±10†	28±8	29±7
Serum creatinine (mg/dl)	1.9±0.5	2.3±0.8†	2.1±0.6	2.2±0.9
Serum uric acid (mg/dl)	6.6±1.0	6.9±0.8	6.9±1.2	6.9±0.9

Data represent the mean±SD. *$p<0.05$, †$p<0.001$ *vs*. month 0.

were collected bi-monthly to obtain blood cell counts, and to perform blood chemistry analysis and urine analysis. Blood samples were taken from the antecubital vein after the participant had fasted overnight. The first urine of the morning was used for the urine analysis. The urine samples were also collected consecutively at the last 3 visits of each study period. Urinary concentrations of protein and Cr were measured by colorimetry, and urinary protein excretion was expressed as a ratio to the urinary Cr concentration. The averaged values from the last 3 visits during each study period were used for the evaluation of urinary protein excretion.

Values are expressed as the means±SD. The clinical and laboratory data from the two groups were compared by Student's *t*-test for paired samples, and analysis of covariance was used to assess the influence of co-variables. A p value of less than 0.05 was considered to indicate statistical significance. The slope of time-course changes in the reciprocal of serum Cr was calculated by linear regression analysis.

Results

Table 1 shows the background characteristics of the study subjects. Chronic glomerulonephritis was the most frequent nondiabetic renal disease, followed by nephrosclerosis. The diagnoses were histologically verified in 7 out of 10 patients with chronic glomerulonephritis, in 2 out of 7 patients with nephrosclerosis, and in 1 out of 2 patients with drug-induced nephropathy. In the remaining 12 patients, the diagnosis of nondiabetic disease was based on the patient's medical history, physical findings, laboratory data, and findings on radiological and ultrasound images. The cause of drug-induced nephropathy in 2 patients was the long-term use of non-steroidal anti-inflammatory drugs for rheumatoid arthritis and compression fracture of the lumbar vertebra, respectively. In both of these latter cases, the use of non-steroidal anti-inflammatory drugs had been terminated more than a year before the patient participated in the present study, and the serum Cr levels of both of these subjects had remained stable for more than 6 months. The study was initiated with valsartan treatment in 1 of these patients (rheumatoid arthritis), and with placebo in the other patient (compression fracture of a lumbar vertebra). Eighteen patients had already been treated with antihypertensive drugs, and the average blood pressure of the study subjects was below 140/90 mmHg before the initiation of both study periods. CCBs were the most frequent antihypertensive drugs administered previously, followed by diuretics; in addition, 7 patients had been given ACE inhibitors, as noted above.

No patient experienced adverse side effects, and all 22 patients completed the study protocol. During the placebo period, a diuretic or β-blocker was added to the treatment protocol of 1 patient each, and a CCB was added or the dose of a CCB was increased in 6 patients, with the aim of reducing blood pressure to below 140/90 mmHg. During the valsartan period, the dose of valsartan was increased to 80 mg/day in 8 patients; in addition, the dose of the CCB was increased in 1 patient, and the dose of α-blocker was increased in one other patient. Table 2 lists the blood pressure and pulse rate of the patients in each treatment period. The average blood pressure was below 140/90 mmHg in both of the study periods, and the values observed in both periods were comparable. The average blood pressure remained below 140/90 mmHg in 17 patients during the placebo period and in 16 patients during the valsartan period.

Table 3 shows the changes in the physical and laboratory data of patients during each treatment period. Neither body weight, nor the concentration of either blood hemoglobin or serum albumin changed significantly during either of the treatment periods. Among the serum electrolytes, serum K was significantly increased during the valsartan period, whereas the serum K level did not significantly change during the placebo period. However, it should be noted that none of the patients discontinued taking valsartan due to hyperkalemia. As regards the indices of renal function, serum urea nitrogen and serum Cr levels were significantly increased during the placebo period, whereas the average values did not

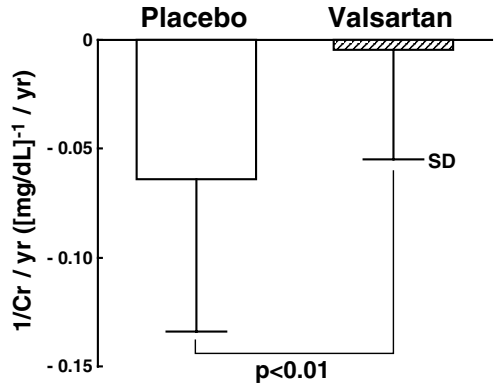

Fig. 1. *Bar graph comparing the slopes of decline in the reciprocal of serum creatinine levels during the periods of administration of placebo or valsartan.*

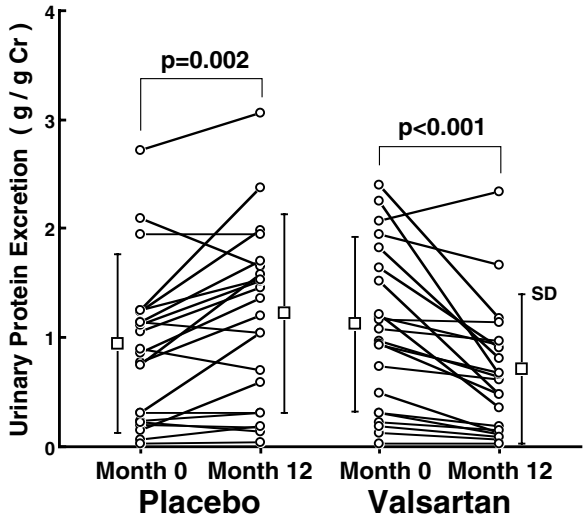

Fig. 2. *Changes in urinary protein excretion before and after the periods of administration of placebo or valsartan.*

change significantly during the 1-year-long valsartan period. According to the analysis of covariance, the changes in levels of serum Cr differed significantly between the placebo and the valsartan periods ($F=5.09$, $p=0.029$); however, these changes were not significantly related to the values observed before the respective periods ($F=1.03$, $p=0.316$). Figure 1 compares the average slopes of the time-course changes in the reciprocal of serum Cr levels during the two treatment periods. The slope of decline in the case of 1/Cr was less steep for the valsartan period than for the placebo period (-0.005 ± 0.050/year *vs*. -0.064 ± 0.070/year, $p<0.01$).

Figure 2 shows the changes in urinary protein excretion during each treatment period. Urinary protein excretion was significantly reduced during the valsartan period, *i.e.*, by 33% (1.12 ± 0.80 to 0.75 ± 0.73 g/g Cr, $p<0.001$), whereas urinary protein excretion increased during the placebo period (0.94 ± 0.82 to 1.24 ± 0.92 g/g Cr, $p=0.002$). However, the changes in urinary protein were not correlated with either systolic or diastolic blood pressure levels ($r=0.024$, $p=0.879$ and $r=0.236$, $p=0.122$; respectively). In the analysis of covariance, the changes in urinary protein excretion were significantly different between the placebo and the valsartan periods ($F=20.69$, $p<0.001$), but were not significantly related to the values observed before these periods ($F=2.28$, $p=0.139$).

Discussion

In order to protect the kidneys from diabetic and nondiabetic renal disease, it is important to prevent increases in glomerular capillary pressure. To this end, inhibitors of the renin-angiotensin system such as ACE inhibitors and ARBs are expected to improve glomerular hypertension by reducing the constrictive effect of angiotensin II on the efferent arterioles. Besides these hemodynamic effects, angiotensin II enhances production of free radicals, promotes cell growth, and increases the synthesis of inflammatory and profibrotic cytokines (*8*, *9*). Furthermore, recent studies have revealed that aldosterone also has mitogenic and pro-fibrotic properties (*10*, *11*). These non-hemodynamic effects of angiotensin II and aldosterone are deleterious to the kidney and cause inflammation, fibrosis, and scarring of the renal tissue, resulting in the deterioration of renal function (*12*). Therefore, the inhibition of the renin-angiotensin-aldosterone system by ACE inhibitors or ARBs is expected to ameliorate the non-hemodynamic pathogenesis of nephropathy, as well as reduce glomerular capillary pressure. ARBs have also been shown to alleviate podocyte injury and restore the expression of nephrin, the podocyte adhesion protein, in experimental models of hypertension and diabetes (*13–15*).

In accordance with these theoretical considerations, a considerable amount of clinical evidence has indicated that ACE inhibitors retard the progression of diabetic nephropathy (*16*). Moreover, comparable effects have been achieved by ARBs, as demonstrated by several studies such as the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) (*17*) and the Irbesartan Diabetes type 2 Nephropathy Trial (IDNT) (*18*). As regards nondiabetic renal diseases, the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) study (*19*) and the Ramipril Efficacy In Nephropathy (REIN) study showed that ACE inhibitors delay the progression of nondiabetic renal insufficiency. However, in contrast to the accumulation of evidence in these areas of study, an insufficient amount of evidence has been accumulated to unequivocally demonstrate the effectiveness of ARBs in the long-term management of patients with nondiabetic renal diseases. In the present random crossover study, the enrolled renal insufficiency patients with nondiabetic renal diseases exhibited the suppression of increases in serum Cr during the period in which the ARB valsartan was administered. Therefore, it appears that ARB, as well as ACE inhibi-

tors, is advantageous in terms of slowing the deterioration of renal function in patients with nondiabetic renal diseases.

It has been demonstrated previously that ACE inhibitors and ARBs are more effective at reducing proteinuria in patients with diabetic and nondiabetic renal diseases than are other classes of antihypertensive drugs (*5*, *20*, *21*). Moreover, in the present study, valsartan was found to reduce urinary protein excretion in patients with nondiabetic renal diseases. According to both the results of the Modification of Diet in Renal Disease (MDRD) study and the outcomes of the REIN study, the amount of urinary protein excretion was predictive of the rate of deterioration of renal function in patients with nondiabetic renal diseases (*22*, *23*). Proteinuria itself is detrimental to the kidney, as the ultrafiltration of proteins across the glomerular basement membrane brings about tubular protein overload, which in turn provokes inflammation, and ultimately results in glomerulosclerosis and tubulo-interstitial fibrosis (*24*, *25*). It is also known that proteinuria is associated with a risk of development of cardiovascular diseases, and proteinuria has also been recognized as a modifiable cardiovascular risk factor (*26–28*). Therefore, it would be expected that the decrease in urinary protein excretion brought about by treatment with ARBs not only inhibits the progression of renal tissue injury, it also reduces the incidence of cardiovascular events in patients with nondiabetic renal diseases.

ARBs are much less likely to induce a cough than are ACE inhibitors. Hyperkalemia is among the few adverse effects of the administration of ARBs. Indeed, in the present study, the mean serum K level was significantly higher (*i.e.*, by 0.2 mEq/l) in the valsartan period than in the placebo period. However, no patients were forced to discontinue treatment with valsartan due to the development of hyperkalemia. Therefore, hyperkalemia is unlikely to be a major problem associated with long-term ARB treatment of nondiabetic renal insufficiency patients with the maintenance of serum Cr levels below 3.0 mg/dl.

Although hypertension is generally not diagnosed when the blood pressure is lower than 140/90 mmHg, the latest guidelines for hypertension treatment recommend a lower upper limit for the target blood pressure level, namely, <130/80 mmHg for patients with reduced renal function (*29*, *30*). However, hypertension among patients with impaired renal function is often resistant to therapy, and in the present study, the average blood pressure was not lower than 140/90 mmHg in one-fourth of the patient. Thus, treatment with multiple antihypertensive agents appears to be necessary for the strict control of blood pressure in patients with renal diseases. The antihypertensive effects of ACE inhibitors and ARBs may not be prominent in patients with reduced renal function, because the renin-angiotensin-aldosterone system is generally suppressed due to the impaired excretion of Na and increased body fluid volume. However, according to the clinical evidence accumulated to date, inhibitors of the renin-angiotensin system should be included in the combination of antihypertensive drugs administered to patients with diabetic and nondiabetic diseases, unless the stage of renal dysfunction is advanced. The results of this study suggest that ARBs are effective at reducing the rate of deterioration of renal function as well in renal insufficiency patients suffering from nondiabetic renal diseases. Considering the low incidence of cough, ARBs are expected to be better tolerated than ACE inhibitors in the long-term treatment of chronic renal insufficiency.

In summary, the present study showed that valsartan, an ARB, is effective at reducing proteinuria and preserving renal function in patients with nondiabetic renal diseases. It is thought that these effects are, at least in part, independent of blood pressure changes, and that they are brought about by the inhibition of the renin-angiotensin system. The results of the present study should be reconfirmed by a prospective study of a larger number of patients and also by longitudinal follow-up studies.

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References

1. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981; **241**: F85–F93.
2. Brenner BM, Lawler EV, Mackenzie HS: The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; **49**: 1774–1777.
3. Romero JC, Ruilope LM, Bentley MD, Fiksen-Olsen MJ, Lahera V, Vidal MJ: Comparison of the effects of calcium antagonists and converting enzyme inhibitors on renal function under normal and hypertensive conditions. *Am J Cardiol* 1988; **62**: 59G–68G.
4. Carmines PK, Mitchell KD, Navar LG: Effects of calcium antagonists on renal hemodynamics and glomerular function. *Kidney Int Suppl* 1992; **36**: S43–S48.
5. Raij L: Recommendations for the management of special populations: renal disease in diabetes. *Am J Hypertens* 2003; **16**: 46S–49S.
6. Parving HH, Andersen S, Jacobsen P, *et al*: Angiotensin receptor blockers in diabetic nephropathy: renal and cardiovascular end points. *Semin Nephrol* 2004; **24**: 147–157.
7. Jafar TH, Schmid CH, Landa M, *et al*: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001; **135**: 73–87.
8. Wolf G: Angiotensin II as a mediator of tubulointerstitial injury. *Nephrol Dial Transplant* 2000; **15** (Suppl 6): 61–63.
9. Luft FC: Proinflammatory effects of angiotensin II and endothelin: targets for progression of cardiovascular and renal diseases. *Curr Opin Nephrol Hypertens* 2002; **11**:

59–66.
10. Juknevicius I, Segal Y, Kren S, Lee R, Hostetter TH: Effect of aldosterone on renal transforming growth factor-beta. *Am J Physiol Renal Physiol* 2004; **286**: F1059–F1062.
11. Hostetter TH, Ibrahim HN: Aldosterone in chronic kidney and cardiac disease. *J Am Soc Nephrol* 2003; **14**: 2395–2401.
12. Brewster UC, Perazella MA: The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. *Am J Med* 2004; **116**: 263–272.
13. Durvasula RV, Petermann AT, Hiromura K, *et al*: Activation of a local tissue angiotensin system in podocytes by mechanical strain. *Kidney Int* 2004; **65**: 30–39.
14. Mifsud SA, Allen TJ, Bertram JF, *et al*: Podocyte foot process broadening in experimental diabetic nephropathy: amelioration with renin-angiotensin blockade. *Diabetologia* 2001; **44**: 878–882.
15. Davis BJ, Cao Z, de Gasparo M, Kawachi H, Cooper ME, Allen TJ: Disparate effects of angiotensin II antagonists and calcium channel blockers on albuminuria in experimental diabetes and hypertension: potential role of nephrin. *J Hypertens* 2003; **21**: 209–216.
16. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; **329**: 1456–1462.
17. Brenner BM, Cooper ME, de Zeeuw D, *et al*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–869.
18. Lewis EJ, Hunsicker LG, Clarke WR, *et al*: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851–860.
19. Maschio G, Alberti D, Janin G, *et al*: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996; **334**: 939–945.
20. Ruggenenti P: Angiotensin-converting enzyme inhibition and angiotensin II antagonism in nondiabetic chronic nephropathies. *Semin Nephrol* 2004; **24**: 158–167.
21. Iino Y, Hayashi M, Kawamura T, *et al*: Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res* 2004; **27**: 21–30.
22. Peterson JC, Adler S, Burkart JM, *et al*: Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; **123**: 754–762.
23. Remuzzi G, Chiurchiu C, Ruggenenti P: Proteinuria predicting outcome in renal disease: nondiabetic nephropathies (REIN). *Kidney Int Suppl* 2004; **92**: S90–S96.
24. Abbate M, Benigni A, Bertani T, Remuzzi G: Nephrotoxicity of increased glomerular protein traffic. *Nephrol Dial Transplant* 1999; **14**: 304–312.
25. Abbate M, Zoja C, Morigi M, *et al*: Transforming growth factor-beta1 is up-regulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. *Am J Pathol* 2002; **161**: 2179–2193.
26. Kannel WB, Stampfer MJ, Castelli WP, Verter J: The prognostic significance of proteinuria: the Framingham study. *Am Heart J* 1984; **108**: 1347–1352.
27. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med* 2000; **109**: 1–8.
28. Dykeman-Sharpe J: Proteinuria, a modifiable risk factor: angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). *CANNT J* 2003; **13**: 34–38.
29. Chobanian AV, Bakris GL, Black HR, *et al*: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
30. European Society of Hypertension–European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1153.