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## The losartan renal protection study – rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)

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### Abstract

The RENAAL Study is a double-blind, placebo-controlled trial to evaluate the renal protective effects of losartan in Type 2 diabetic patients with nephropathy. The study has enrolled 1513 patients and is expected to continue for 3.5 years after the last patient has been entered. Eligible patients must have a urinary albumin:creatinine ratio of at least 300 mg/g and serum creatinine between 1.3 to 3.0 mg/dL. Eligible hypertensive or normotensive patients are randomised to receive either losartan or placebo, in addition to their existing antihypertensive therapy. Medications that block angiotensin production or action, are excluded. The primary endpoint is a composite of the time to first event of doubling of serum creatinine, end-stage renal disease, or death; secondary endpoints include cardiovascular events, progression of renal disease, and changes in proteinuria; tertiary endpoints include quality of life, healthcare resource utilisation, and amputations. Patients include Caucasians (48.6%), Blacks (15.2%), Asians (16.7%), and Hispanics (18.2%). Baseline urinary albumin:creatinine ratio and serum creatinine levels average 1867 mg/g and 1.9 mg/dL, respectively. Mean systolic and diastolic blood pressures are 153 and 82 mmHg, respectively. RENAAL will document whether blockade of the AII receptor with losartan produces clinical benefits in patients with Type 2 diabetes and nephropathy.

### Introduction

End-stage renal disease (ESRD) continues to represent a worldwide public health concern. The incidence of newly-treated cases of ESRD has risen over the last decade in the United States.<sup>1</sup> Recent estimates by the National Institute of Diabetes and Digestive and Kidney Diseases indicate that diabetes mellitus represents the single largest cause of ESRD requiring chronic dialysis or kidney transplantation and accounts for approximately 42% of new cases of ESRD in the U.S. in 1997.<sup>1</sup> The incidence of ESRD in patients with Type 2 diabetes has risen sharply in recent years in many regions of the world, including the United States.<sup>1-8</sup>

The prognosis of diabetic patients with ESRD is bleak – 30% of diabetic patients undergoing dialysis and 15% of diabetic patients receiving their first

cadaveric kidney transplants die within two years.<sup>9,10</sup> Preventing or delaying the progression of diabetic nephropathy to ESRD by dietary modification, medical therapy, and/or other means of lifestyle modification, is therefore an essential management goal.

Studies in experimental models of diabetic and nondiabetic renal disease show that losartan, a selective angiotensin II (Ang II) receptor antagonist (AIIA) reduces proteinuria and ameliorates pathological changes associated with the progression of renal disease.<sup>11-15</sup> Losartan has also been demonstrated to reduce proteinuria in diabetic and nondiabetic patients with renal disease, as well as in patients with renal transplant.<sup>16-19</sup>

Although these studies have shown a beneficial effect on proteinuria in patients with Type 2 diabetes, the RENAAL study is being performed in order to prove that blockade of the Ang II AT<sub>1</sub>-receptor may have a beneficial effect on the progression of renal disease by retarding deterioration of renal function and decreasing cardiovascular and overall mortality.

To further investigate the long-term renal protective effects of losartan, the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study was initiated in patients with Type 2 diabetes and nephropathy. The RENAAL study will investigate whether losartan, either alone or in combination with conventional antihypertensive therapy, will reduce the number of patients with Type 2 diabetes experiencing a doubling of serum creatinine, ESRD, or death compared with placebo-treated patients (with or without conventional antihypertensive therapy). In addition, the study will assess the effects of losartan *vs.* placebo on cardiovascular morbidity, mortality, progression of renal disease (slope of the reciprocal of serum creatinine), and proteinuria, as well as the impact of losartan therapy on quality of life and healthcare resource utilisation.

### Methods

This multinational, double-blind, randomised, placebo-controlled study is evaluating the renal protective effects of losartan in a total of 1513 patients with

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**Table 1** Principal inclusion and exclusion criteria for the RENAAL study.

#### Inclusion criteria

- Type 2 diabetes defined as:
  - >30 years of age at diagnosis (younger patients admitted on individual basis if C-peptide levels confirm Type 2 diabetes)
  - Insulin not required within six months of initial diagnosis
  - No history of diabetic ketoacidosis
  - Currently treated with diet, oral hypoglycaemics, or insulin
- Proteinuria (urinary albumin:creatinine ratio  $\geq 300$  mg/g) or 24-hour urine protein >500 mg
- Serum creatinine  $\geq 1.5$  to 3.0 mg/dL ( $\geq 1.3$  mg/dL for females)
- Hypertensive (sitting BP  $\leq 200/110$  mmHg) or normotensive (sitting systolic BP  $\geq 100$  mmHg)
- Glycosylated haemoglobin (A<sub>1c</sub>) <12%
- Aged 31 to 70 years
- Female patients of childbearing potential required to have a negative pregnancy test and use an approved birth control method
- All patients to give written informed consent before enrollment

#### Exclusion criteria

- Type 1 diabetes
- History of nondiabetic renal disease
- History of MI, CABG within past one month; CVA, PTCA within past six months; or TIA within the past 12 months
- History of heart failure
- Renal artery stenosis, primary aldosteronism, or pheochromocytoma

MI = myocardial infarction, CABG = coronary artery bypass grafting, CVA = cerebral vascular accident, PTCA = percutaneous transluminal coronary angioplasty, TIA = transient ischemic attacks, BP = blood pressure

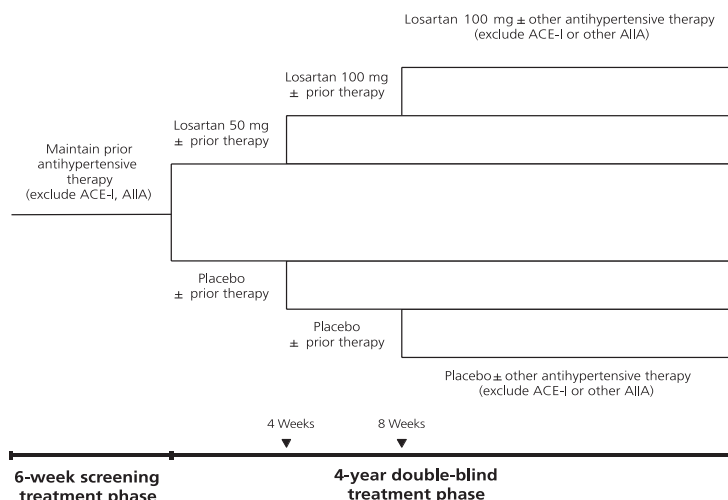
**Type 2 diabetes and nephropathy.** The study was initiated in 1996, and patient enrollment was completed in 1998. All patients will be followed for 3.5 years after the last patient has been randomised. To be eligible for enrollment in the study, male or female patients ranging in age from 31 to 70 years diagnosed with Type 2 diabetes must have had two qualifying urinary albumin:creatinine ratios on first morning specimen of at least 300 mg/g (or a 24-hour urine protein of greater than 500 mg) and two qualifying serum creatinines between 1.5 to 3.0 mg/dL (1.3 mg/dL for females) (Table 1). Eligible patients with Type 2 diabetes could have been either hypertensive or normotensive. Type 2 diabetes was defined as those patients who were diagnosed after the age of 30, who did not require insulin within six months of diagnosis, and who had no history of diabetic ketoacidosis. However, if one of these criteria

for Type 2 diabetes was not met, a C-peptide level must have been within normal range to confirm the diagnosis. Patients were excluded from the study if they had been diagnosed with Type 1 diabetes or nondiabetic renal disease, including renal artery stenosis. Patients with a history of heart failure, myocardial infarction, coronary artery bypass grafting, cerebral vascular accident, percutaneous transluminal coronary angioplasty, or transient ischaemic attacks within 1-12 months prior to study enrollment were excluded. Serum potassium levels <3.5 or >5.5 mEq/L, and chronic use of NSAIDs and aspirin >325 mg/day, also precluded patients from entering the study.

#### Statistical evaluation

The sample size calculation for this trial was based upon the assumption that the five-year rate of the

**Figure 1** Overview of the design of the RENAAL study.



first time to event of the composite endpoints of doubling of serum creatinine/ESRD/death in the placebo group would be 58% and that this rate would be reduced by 20% in the losartan group. In order to have 95% power at the 4.8% significance level (two-sided, adjusted for interim analyses), the trial required the enrollment of at least 1320 patients and follow-up of the last enrolled patient for 3.5 years.

In general, all primary efficacy analyses will be based on the intention-to-treat principle. All patients will be analysed according to the treatment to which they were randomly assigned.

A formal interim analysis is planned for efficacy when the last patient has been followed for two years or when half of the expected primary endpoints have occurred, whichever comes first. The interim analysis will be performed in accordance with recommendations from an independent Data and Safety Monitoring Board (DSMB). As a result of this interim analysis, the final  $\alpha$ -level for declaring a significant difference between treatment groups must be 0.048. In addition to reviewing the formal interim analysis, the DSMB is charged with identifying safety issues and interpreting emerging safety study data in order to make periodic recommendations on study continuation, termination or protocol modification.

An independent, blinded endpoint committee is adjudicating all potential clinical endpoints occurring from the time of randomisation until study termination, in order to determine whether an event is a true endpoint (as per the guidelines established in the RENAAL Endpoint Adjudication Manual).

### Study design

The RENAAL study began with an initial screening-treatment phase lasting six weeks (Figure 1). During this phase, in which placebo was not administered, hypertensive patients being treated with either an angiotensin-converting enzyme inhibitor (ACE-I) or AIIA within six weeks of trial enrollment discontinued these medications and received an alternative standard antihypertensive, (open-label diuretic, beta blocker, calcium-channel blocker [CCB], or alpha blocker) as appropriate, to control their hypertension. Hypertensive patients not being treated with an ACE-I or AIIA continued to receive their existing standard antihypertensive therapy. Patients with normal blood pressure did not receive any antihypertensive treatment during this phase. During the screening-treatment phase, patients underwent a medical history, physical examination, and electrocardiography. Electrocardiograms (ECGs) are performed in this study, not only as part of standard medical practice, but as a means to identify silent myocardial infarctions (MI), which are considered a secondary efficacy endpoint. A central ECG lab interprets all ECGs conducted throughout the study, exclusively for the detection of silent MI. Throughout the screening phase, patients also provide a random urine sample for urinalysis with microscopy, urine samples (first morning void) for determination of uri-

nary albumin/creatinine ratio and blood samples for serum chemistry and haematology parameters. With the exception of the urinalysis with microscopy, all urine and blood assessments are performed at a central laboratory. Trough blood pressure measurements are obtained at every visit.

The screening-treatment phase has been followed by a double-blind treatment phase which will last 3.5 years after the last patient has been randomised. The double-blind phase began with the randomisation of eligible patients to either losartan (50 mg daily) or placebo groups (Day 1). Patients were randomised according to a computer-generated random allocation schedule. The randomisation was stratified based on the level of baseline albuminuria. Patients will continue to receive study therapy (losartan or placebo), in addition to their existing antihypertensive therapy, for the duration of the study. On the morning of the clinic visit, the patients are instructed not to take their antihypertensive medications, including the study drug, until trough blood pressure has been measured. If the target trough blood pressure of less than 140/90 mmHg is not achieved after the first four weeks of therapy or at any phase during the study, the dose of losartan (or placebo) is increased to two pills (i.e., 100 mg) daily, however, if the 100 mg losartan dose is not sufficient to reduce trough blood pressure below target values, additional open-label antihypertensives are added. Open-label antihypertensives include diuretics, beta-blockers, calcium channel blockers, alpha blockers or centrally-acting agents. In addition, to assist in this aspect of the study, the Steering Committee has provided blood pressure treatment guidelines to investigators. Throughout the trial, patients continue to receive standard medical care for treatment of diabetes, including, but not limited to, blood pressure monitoring, routine measurements of HbA<sub>1c</sub> and fasting blood glucose concentrations. Patients from both losartan and placebo groups will not be permitted to receive ACE-I or other AIIAs throughout the study.

### Efficacy assessments

Patients return to the clinic for assessment at one week, one month and three months, and are continuing to return at intervals of three months over the 3.5-year study duration. Several key measurements are made at these time-points, including trough sitting blood pressure and heart rate, laboratory measurements (urinary albumin/creatinine ratio, blood chemistry, and haematology), healthcare resource utilisation, and yearly urinalyses, physical examinations and ECGs. In addition, quality of life questionnaires are completed by patients at each visit in the U.S. only. A subgroup of the total patient population will be analysed with regard to 24-hour urine collections at three-month intervals for total protein excretion and creatinine clearance determinations.

The primary efficacy parameter of the RENAAL study is a composite endpoint composed of the time to first event of doubling serum creatinine, ESRD, or death. ESRD has been defined as the need for chronic dialysis or renal transplantation.

**Table 2** Enrollment of patients in RENAAL according to region.

Region	%
<b>Asia</b> (Hong Kong, Israel, Japan, Malaysia, Singapore)	17.0
<b>Europe</b> (Austria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Portugal, Russian Federation, Slovakia, Spain, United Kingdom)	19.3
<b>Latin America</b> (Argentina, Brazil, Chile, Costa Rica, Mexico, Peru, Venezuela)	18.1
<b>New Zealand</b>	0.2
<b>North America</b> (Canada, United States of America)	45.5

Secondary efficacy endpoints include the assessment of cardiovascular events (e.g. MI, stroke, death from coronary heart disease, other cardiovascular-related death, coronary or peripheral revascularisation procedures, and hospitalisation for unstable angina, or heart failure), progression of renal disease (slope of the reciprocal of serum creatinine),<sup>20</sup> and changes in proteinuria, as measured by the urine albumin to creatinine ratio. Tertiary efficacy endpoints include health-related quality of life (U.S. patients only), healthcare resource utilisation, and incidence of amputation. Quality of life is being assessed using the SF-36 generic health profile instrument. The SF-36 is composed of numerous domains of health-related quality of life, including, but not limited to, physical function, bodily pain, general health, social function and mental health. The EQ-5D quality-adjusted life year instrument is being used to determine whether increasing the time to first event of doubling of serum creatinine, ESRD, or death leads to greater quality-adjusted life expectancy in patients treated with losartan compared with those on placebo.<sup>21,22</sup> Healthcare resource utilisation data (based on ICD-9-CM codes) will be calculated only for costly episodes of care (e.g. hospitalisations and medical procedures). Throughout the trial, the safety and tolerability of losartan is being assessed.

### Baseline characteristics

One thousand, five hundred, and thirteen (1513) patients have been enrolled in the RENAAL study. Approximately 50% of these patients were taking either an ACE-I or AIIA upon entering the screening treatment phase of the study. The greatest number of patients were enrolled in North America (45.5%), followed by approximately equal numbers in Asia, Europe and Latin America (Table 2). The patient population is comprised of 48.6% Caucasian, 15.2% Black, 16.7% Asian, 18.2% Hispanic, and 0.2% Native American (Table 3). Enrolled patients (63.2% male, 36.8% female) have a mean (SD) age of 59.6 (7.4) years. Urinary albumin:creatinine ratio and serum creatinine levels

**Table 3** Baseline characteristics of patients enrolled in RENAAL.

Baseline characteristic	N	%	Mean	SD
<b>Race</b>	1512*	100.0		
Caucasian	735	48.6		
Black	230	15.2		
Asian	252	16.7		
Hispanic	275	18.2		
Native American	3	0.2		
Other	17	1.1		
<b>Sex</b>	1512	100.0		
Female	556	36.8		
Male	956	63.2		
<b>Age</b>	1512	100.0	59.6	7.4
< 60	670	44.3	52.8	5.3
61-70	797	52.7	64.7	3.0
71-75	45	3.0	71.6	0.7
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	1472		29.7	6.3
<b>Blood pressure</b>	1512			
Systolic (mmHg)	1511		153	19
Diastolic (mmHg)	1511		82	10
<b>Laboratory values</b>	1510			
Urinary alb:creat (mg/g)	1509		1867	2699
Serum creat (mg/dL)	1510		1.9	0.5
HbA <sub>1c</sub> (% of total Hb)	1494		8.5	1.6
Serum cholesterol (mg/dL)	1494		228.0	55.5
ALT (u/L)	1494		18.0	11.4
AST (u/L)	1494		18.2	9.0
Serum bilirubin (mg/dL)	1494		0.6	0.2
Serum Potassium (mEq/l)	1510		4.6	0.5
Serum Uric Acid (mg/dl)	1510		6.7	1.7

\* Data from one patient was not incorporated into the database at the time of table generation. Alb:creat = albumin:creatinine ratio, creat = creatinine, Hb = haemoglobin, HbA<sub>1c</sub> = glycosylated haemoglobin A<sub>1c</sub>, ALT = alanine transaminase, AST = aspartate transaminase

averaged (SD) 1867 (2699) mg/g and 1.9 (0.5) mg/dL, respectively, and mean (SD) glycosylated haemoglobin (HbA<sub>1c</sub>) was 8.5 (1.6) %. Mean (SD) body mass index was 29.7 (6.3) kg/m<sup>2</sup>. Mean (SD) systolic and diastolic blood pressures at baseline were 153 (19) and 82 (10) mmHg (MAP=106 mmHg), respectively. Retinopathy (62%), lipid disorders (53.7%), neuropathy (49.2%), and cataracts (25.0%), represented the most common concurrent conditions observed at baseline (Table 4).

### Discussion

The key factors that prompted initiation of this long-term study of losartan in patients with Type 2 diabetes and nephropathy were the high prevalence of Type 2 diabetes throughout the world, the high incidence of ESRD in diabetic patients, and the lack of conclusive data on the effect of blockade of the renin-angiotensin-aldosterone system (RAAS) on the progression of renal disease and mortality in Type 2 diabetics with nephropathy.

Worldwide, an estimated 146 million people have Type 2 diabetes.<sup>23</sup> By 2010, the prevalence is expected to increase approximately 1.5-fold to a projected 210 million people around the world.<sup>23</sup> The rate of growth of Type 2 diabetes, which is reaching epidemic proportions in many countries throughout the world, can be attributed to a longer life span, obesity, diet and reduced exercise, among other factors.<sup>23</sup>

**Table 4** Baseline, concurrent conditions of patients enrolled in RENAAL.

Category	N	%
<b>Cardiovascular system</b>	715	47.4
Angina pectoris	142	9.4
Myocardial infarction	165	10.9
History of coronary revascularisation	138	9.1
Stroke	152	10.1
Transient ischaemic attack	29	1.9
Carotid disorders	54	3.6
<b>Hemic lymphatic</b>		
Anaemia	308	20.4
<b>Metabolic disorders</b>		
Lipid disorders	810	53.7
<b>Musculoskeletal</b>		
Amputation	107	7.1
<b>Nervous system</b>		
Neuropathy	743	49.2
<b>Ophthalmic system</b>	1113	73.8
Blindness	54	3.6
Cataracts	377	25.0
Glaucoma	104	6.9
Laser therapy and photocoagulation	138	9.1
Other ophthalmic disorders	161	10.7
Retinopathy	935	62.0
<b>Urogenital</b>		
Impotence and sexual dysfunction	169	11.2

A number of different treatment modalities have been evaluated to delay the progression of diabetic nephropathy, including modified protein intake,<sup>24,25</sup> strict glycaemic control,<sup>26-28</sup> and antihypertensive therapy.<sup>29-31</sup> The importance of tight blood pressure control in reducing the risk of macrovascular and microvascular complications in Type 2 diabetes is illustrated by the recent findings of the United Kingdom Prospective Diabetes Study (UKPDS) and the HOT study.<sup>31,32</sup> The UKPDS is a multicentre, randomised, controlled study that showed that tight blood pressure control (mean blood pressure, 144/82 mmHg) achieved a clinically important reduction in the risk of death and complications related to diabetes (e.g., non-fatal MI, angina, heart failure, renal failure, and amputations) and progression of diabetic retinopathy. The HOT study also provides evidence that strict blood pressure control plays an important role in reducing cardiovascular complications of diabetes.<sup>32</sup> In this study, a 51% reduction in major cardiovascular events (including MI, stroke, and cardiovascular mortality) was observed in patients with diabetes whose diastolic blood pressure was less than, or equal to 80 mmHg. In addition, Parving and colleagues demonstrated that antihypertensive therapy produced a reduction in blood pressure and albuminuria, as well as an attenuation in the decline of glomerular filtration rate (GFR) in patients with Type 1 diabetes.<sup>29</sup> A reduction in systemic blood pressure and the associated fall in intraglomerular pressure may be an important mechanism by which antihypertensive agents attenuate the progression of diabetic nephropathy.

In the RENAAL patient population, baseline mean blood pressure (namely systolic blood pressure) indicates suboptimal control prior to enrollment in the study. Based on the published literature, discussed previously, and the current recommendations for controlling blood pressure in patients with diabetes, it is imperative that we aim for aggressive reductions in blood pressure in this patient population. Furthermore, it is essential that blood pressure control in both treatment groups remain comparable. Assessment of the primary efficacy parameters would be difficult, if not impossible, with unequal blood pressure control between treatment groups.

Optimal blood pressure control with different classes of antihypertensive agents have shown that the progression of diabetic nephropathy can be delayed, and the risk of cardiovascular morbidity and mortality can be reduced. It has been suggested, however, that antihypertensive drugs that block the RAAS may be more effective in delaying the progression of diabetic nephropathy than conventional antihypertensive therapies. Ang II plays an important role in the progression of renal injury through haemodynamic and nonhaemodynamic mechanisms; therefore, it is believed that blockade of the Ang II receptor would offer renal protection beyond reduction in systemic blood pressure. Studies in patients with Type 1 diabetes have shown that ACE-I effectively diminish the progression of nephropathy above and beyond their blood pressure-lowering effects.<sup>33</sup> Also, in Type 1 diabetics with overt nephropathy, captopril therapy produced a 50% reduction in the risk of doubling of serum creatinine and the combined endpoints of ESRD and death compared with patients treated with placebo.<sup>34</sup> These findings suggest that blockade of the RAAS may offer renal protection in patients with Type 1 diabetes. Limited data exists on the effects of blockade of the RAAS on the progression of diabetic nephropathy in Type 2 diabetes. Although there are some similarities in the natural history of nephropathy between Type 1 and Type 2 diabetes, patients with Type 2 diabetes are typically older, with long-standing hypertension, advanced atherosclerotic changes, insulin resistance, and a high incidence of morbidity and mortality from cardiovascular disease.

At least two studies have been conducted in normotensive, Type 2 diabetic patients which demonstrated a long-term stabilising effect of ACE-I on plasma creatinine and proteinuria.<sup>35,36</sup> However, this effect was not associated with differences in glomerular filtration rate between treatment groups over the same time course.<sup>36</sup> Nevertheless, there are no studies with ACE-I demonstrating the beneficial effects of this class of drugs on ESRD and mortality in patients with Type 2 diabetes and kidney disease. In fact, data from the UKPDS did not show any difference between the effects of ACE inhibition and  $\beta$ -blockade on renal and cardiovascular endpoints.<sup>37</sup>

The AIIAs, such as losartan, represent the newest class of drugs to treat hypertension, and they appear to offer many of the therapeutic benefits of ACE-I with a more favourable side-effect profile.<sup>38-41</sup> Losartan is an orally active, highly specific antagonist

that blocks the binding of Ang II to the AT<sub>1</sub>-receptor subtype. Losartan has been shown to be well-tolerated in patients with varying degrees of renal dysfunction, including those on haemodialysis and those who have undergone renal transplantation.<sup>19,42-44</sup>

In patients with renal disease, both with and without diabetes, it has been demonstrated that losartan reduces proteinuria to a similar extent to ACE-I. In a pilot study and subsequent follow-up study performed in hypertensive patients with renal disease, Gansevoort and colleagues found that losartan treatment (50 or 100 mg daily) lowered blood pressure, decreased urinary protein excretion, and elevated renal plasma flow to a degree comparable to that found with ACE-I.<sup>16,17</sup> The anti-proteinuric effect of losartan has also been demonstrated in a double-blind, cross-over study comparing losartan with amlodipine in hypertensive patients with nondiabetic nephropathy.<sup>18</sup> In this study, both losartan and amlodipine significantly lowered blood pressure, but only losartan significantly reduced proteinuria after four weeks of treatment.<sup>18</sup> In patients with Type 2 diabetes, losartan has been shown to reduce proteinuria<sup>45</sup> and to reduce proteinuria similar to ACE-I.<sup>46</sup>

In recent years, the results of large, long-term clinical trials have been published, comparing the effects of ACE inhibition with those of conventional treatment on cardiovascular morbidity and mortality.<sup>47-50</sup> The most recently published Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that the risk of cardiovascular morbidity and mortality was significantly reduced with an ACE-I.<sup>50</sup> It is important to note that patients similar to those enrolled in the RENAAL study were excluded from HOPE. More specifically, increased levels of urinary protein and serum creatinine that characterise the RENAAL patients were not permitted in the HOPE study.<sup>50</sup> Additionally, only 47% of HOPE patients were hypertensive at baseline, unlike RENAAL, where approximately 94% were hypertensive. On the contrary, cardiovascular risk factors, such as established coronary artery disease and prior MI, were notably higher among patients in the HOPE study (80% and 53%, respectively) compared with those in RENAAL (19% and 11%, respectively).<sup>50</sup> Therefore, when assessing the relevance of such studies as HOPE to RENAAL, it is essential to consider that the risks and benefits of blockade of the RAAS have never been established in patients with Type 2 diabetes and advanced nephropathy. The RENAAL study will address such risks as hyperkalaemia and cardiovascular disease coupled with impaired renal function in patients taking a drug which inhibits the RAAS.

There are other long-term trials, that are currently underway, which will address the effects of blockade of the RAAS in high-risk patients with hypertension. Specifically, it will be interesting to compare the prospective results of the ALLHAT<sup>51</sup> study with those of RENAAL. The results of ALLHAT (diabetics: n=15,281 (36%))<sup>52</sup> will be more relevant to the RENAAL population, in that all patients enrolled in ALLHAT are hypertensive. In this study, all patients were treated with an antihypertensive drug, either

CCB, ACE-I, alpha-blocker or diuretic. The most recent news regarding ALLHAT is the termination of the alpha-blocker arm due to a higher incidence of cardiovascular events, especially congestive heart failure.<sup>53</sup> To date, there is no indication that the ACE-I arm is demonstrating superiority over the other treatment groups.

Considering the fact that approximately 90% of the diabetic population consists of patients with Type 2 diabetes, the results of the RENAAL study will have important clinical implications for physicians managing patients with diabetes mellitus. RENAAL is expected to underscore the clinical benefits of effective blockade of Ang II in progression of Type 2 diabetic nephropathy, as well as to help to determine whether simply lowering blood pressure in Type 2 diabetes with standard antihypertensives is adequate to achieve maximal renal protective benefits. If the results of the RENAAL study prove that blockade of the RAAS has a beneficial effect on delaying the progression of renal disease and mortality, it is likely that losartan will complement existing therapeutic options to improve survival and quality of life as well as reduce the healthcare burden of ESRD in patients with Type 2 diabetes and nephropathy.

## Appendix

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## References

1. USRDS: Annual Data Report, Chapter 2. Incidence and prevalence of ESRD. *Am J Kid Dis* 1999;34(suppl 1):S40-S50.
2. Ritz E, Keller CK, Bergis KH, Siebels M. Renal involvement in type II diabetes. *Curr Opin Nephrol Hypertens* 1994;3:137-44.
3. Bennett PH, Haffner S, Kasiske BL *et al*. Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the council on diabetes mellitus of the National Kidney Foundation. *Am J Kidney Dis* 1995;25:107-12.
4. Humphrey LL, Ballard DJ, Frohnert PP, Chu CP, O'Fallon WM, Palumbo PJ. Chronic renal failure in non-insulin dependent diabetes mellitus: a population-based study in Rochester, Minnesota. *Ann Intern Med* 1989;111:788-96.
5. Cordonnier DJ, Zmirou D, Benhamou P-Y, Halimi S, Ledoux F, Guiserix J. Epidemiology, development and treatment of end-stage renal failure in type 2 (non-insulin-dependent) diabetes mellitus. The case of mainland France and of overseas French territories. *Diabetologia* 1993;36:1109-12.
6. Zmirou D, Benhamou P-Y, Cordonnier D *et al*. Diabetes mellitus prevalence among dialysed patients in France (UREMIDIAB Study). *Nephrol Dial Transplant* 1992;7:1092-7.
7. Rettig B, Teutsch SM. The incidence of end-stage renal disease in type I and type II diabetes mellitus. *Diabetic Nephrop* 1984;3:26-7.
8. Pugh JA, Medina RA, Cornell JC, Basu S. NIDDM is the major cause of diabetic end-stage renal disease. More evidence for a tri-ethnic community. *Diabetes* 1995;44:1375-80.
9. USRDS: Annual Data Report. Chapter 5. Patient mortality and survival. 1995;pp59-77.
10. USRDS: Annual Data Report. Chapter 7. Renal transplantation: access and outcomes. 1995;pp91-108.
11. Lafayette RA, Mayer G, Park SK, Meyer TW. Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 1992;90:766-71.
12. Pollock DM, Divish BJ, Polakowski JS, Opgenorth TJ. Angiotensin II receptor blockade improves renal function in rats with reduced renal mass. *J Pharmacol Exp Ther* 1993;267:657-63.
13. Remuzzi A, Perico N, Amuchastegui CS *et al*. Short- and long-term effect of angiotensin II receptor blockade in rats with experimental diabetes. *J Am Soc Nephrol* 1993;4:40-9.
14. Kohzuki M, Yasujima M, Kanazawa M *et al*. Antihypertensive and renal-protective effects of losartan in streptozotocin diabetic rats. *J Hypertension* 1995;13:97-103.
15. Owen RA, Molon-Noblot S, Dorian C *et al*. Long-term effects of treatment with losartan [AT1-selective angiotensin II (AII) receptor antagonist] on renal function and structure in

- streptozotocin (STZ)-induced diabetic nephropathy. *J Am Soc Nephrol* 1995;6:880 (abstract).
16. Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system. *Kid Intl* 1994;45:861-7.
  17. Gansevoort RT, de Zeeuw D, Shahinfar S, Redfield A, de Jong PE. Effects of the angiotensin II antagonist losartan in hypertensive patients with renal disease. *J Hypertension* 1994;12 (suppl 2):S37-S42.
  18. Holdaas H, Hartmann A, Berg KJ, Lund K, Fauchald P. Renal protective effects of losartan and amlodipine in hypertensive patients with non-diabetic nephropathy. *Nephrol Dial Transplant* 1998;13:3096-102.
  19. Del Castillo D, Campistol JM, Guirado L *et al*. Efficacy and safety of losartan in the treatment of hypertension in renal transplant patients. *Kidney Int* 1998;54 (suppl 68):S135-S139.
  20. Mitch WE, Walser M, Buffington GA, Lemann J Jr. A simple method of estimating progression of chronic renal failure. *Lancet* 1976;2:1326-8.
  21. Ware JE, Sherbourne CD. The MOS 36-item Short Form Health Survey (SF-36). I conceptual framework and item selection. *Med Care* 1992;30:473-83.
  22. EuroQual Group. EuroQual-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
  23. Amos AF, McCarthy DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabetic Med* 1997;14:S7-S85.
  24. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1991;324:78-84.
  25. Raal FJ, Kalk WJ, Lawson M *et al*. Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: a 6-month prospective study. *Am J Clin Nutr* 1994;60:579-85.
  26. Diabetes Control and Complications Trial: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
  27. Kawazu S, Tomono S, Shimizu M *et al*. The relationship between early diabetic nephropathy and control of plasma glucose in non-insulin-dependent diabetes mellitus. *J Diab Comp* 1994;8:13-17.
  28. Ohkubo Y, Kishikawa H, Araki E *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103-17.
  29. Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *Br Med J* 1987;294:1443-7.
  30. Rossing P, Hommel E, Smidt UM, Parving HH. Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Intl* 1994;45(suppl 45):S145-S149.
  31. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998;317:703-13.
  32. Hansson L, Zanchetti A, Carruthers SG *et al*, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-62.
  33. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *Br Med J* 1992;304:339-43.
  34. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-2.
  35. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;118:577-81.
  36. Ahmad J, Siddiqui M, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 1997;20:1576-81.
  37. UK Prospective Diabetes Study Group. Effect of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *Br Med J* 1998;317:713-20.
  38. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with HCTZ, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol* 1995;75:793-5.
  39. Weir MR, Elkins M, Liss C, Vrecenak AJ, Barr E, Edelman JM. Efficacy, tolerability, and quality of life of losartan, alone or with hydrochlorothiazide, versus nifedipine GITS in patients with essential hypertension. *Clin Therapeut* 1996;18:411-28.
  40. Oparil S, Barr E, Elkins M, Liss C, Vrecenak A, Edelman J. Efficacy, tolerability, and effects on quality of life of losartan, alone or with HCTZ, versus amlodipine, alone or with HCTZ, in patients with essential hypertension. *Clin Therapeut* 1996;18:608-25.
  41. Lacourcière Y, Brunner H, Irwin R *et al*. Effects of modulators of the renin-angiotensin-aldosterone system on cough. *J Hypertension* 1994;12:1387-93.
  42. Toto R, Shultz P, Raij L *et al*, for the Collaborative Group. Efficacy and tolerability of losartan in hypertensive patients with renal impairment. *Hypertension* 1998;31:684-91.
  43. Sica DA, Lo M-W, Shaw WC *et al*. The pharmacokinetics of losartan in renal insufficiency. *J Hypertens* 1995;13(suppl 1):S49-S52.
  44. Saracho R, Martin-Malo A, Martinez I, Aljama P, Montenegro J. Evaluation of losartan in hemodialysis (ELHE) study. *Kidney Intl* 1998;54(suppl 68):S125-S129.
  45. Ragonesi PD, Belviso A, Tarata C, Taddei MT. The effects of angiotensin II antagonist losartan on urinary albumin excretion in non-insulin dependent diabetes mellitus. *Am J Hypertens* 1998;11(4 part 2):47 abstract.
  46. Lacourcière Y, Bélanger A, Godin C *et al*. Comparison of the long-term effects of losartan and enalapril on urinary albumin excretion (UAE) and glomerular filtration rate (GFR) in hypertensive subjects with type 2 diabetes and microalbuminuria. Submitted for presentation at the European Association for the Study of Diabetes, Belgium, September, 1999:1536 (abstract).
  47. Hansson L, Lindholm LH, Niskanen L *et al*. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP). *Lancet* 1999;353:611-6.
  48. Hansson L, Lindholm LH, Ekblom T *et al*. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6.
  49. The GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997;349:1857-63.
  50. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.
  51. Davis BR, Cutler JA, Gordon DJ *et al*. Rationale and design for the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). *Am J Hypertens* 1996;9:342-60.
  52. National Institutes of Health News Release: NHLBI stops part of study-high blood pressure drug performs no better than standard treatment. March 8, 2000.
  53. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2000;283:1967-75.