Renin Angiotensin Aldosterone System Blockade and Renal Disease in Patients With Type 2 Diabetes

An Asian perspective from the RENAAL study

JULIANA C.N. CHAN, MD, FRCP[1]
NELSON M.S. WAT, MBBS, MRCP[2]
WING-YEE SO, MBBS, MRCP[1]
KAREN S.L. LAM, MD, FRCP[2]
CHIN-TEONG CHUA, MRCP, FRCP[3]
KOK-SENG WONG, MMED, MRCP, FAMS[4]
ZAKI MORAD, MRCP, FRCP[5]
TANIA Z. DICKSON, PHD[6]
DARCY HILLE, EMBA[6]
ZHONGXIN ZHANG, PHD[6]
MARK E. COOPER, MBBS, MD, PHD, FRACP[7]
SHAHNAZ SHAHINFAR, MD[6]
BARRY M. BRENNER, MD[8]
KIYOSHI KUROKAWA, MD[9]
ON BEHALF OF THE ASIAN RENAAL STUDY INVESTIGATORS

OBJECTIVE — Asia is predicted to have the largest population of patients with diabetes who are at high risk for renal disease. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, ~17% of patients were Asians. In this subgroup analysis, we examined the characteristics, response, and adherence to treatment of the Asian population, as well as their baseline predictors of risk of renal end points.

RESEARCH DESIGN AND METHODS — A total of 252 Asian patients were enrolled in the RENAAL study, which compared losartan (50 mg titrated to 100 mg) to placebo in addition to conventional antihypertensive medications in type 2 diabetic patients with nephropathy. Mean follow-up was 3.2 years. The effect of losartan therapy on renal and cardiovascular outcomes was examined, and baseline predictors of risk were determined using a Cox proportional hazards model with prespecified baseline covariates.

RESULTS — Losartan reduced the risk of the primary composite end point composed of a doubling of serum creatinine, end-stage renal disease, or all-cause mortality in Asian patients by 35% ($P = 0.02$). No difference between losartan and placebo was observed for the cardiovascular composite outcomes. Losartan reduced the level of proteinuria by 47% ($P < 0.001$) and rate of decrease in renal function by 31% (0.0074). Discontinuations were lower in the losartan-treated patients. The strongest baseline predictors of risk of renal end points were proteinuria (hazard ratio 1.42, $P < 0.0001$) and low Hb (0.81, $P < 0.0001$).

CONCLUSIONS — In this subgroup analysis of the RENAAL study, losartan conferred significant renal benefits and was well tolerated in Asian patients with type 2 diabetes and clinical nephropathy. Baseline proteinuria and low Hb were strong predictors of risk of renal outcomes.

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In a 7-year follow-up study of the World Health Organization (WHO) Multinational Survey of Vascular Disease in Diabetes (MSVDD), end-stage renal disease (ESRD) accounted for 10–30% of deaths among diabetic Japanese and Hong Kong Chinese, especially women. This contrasts with a <5–10% risk of renal death in their Caucasian counterparts (1).

In most developed countries, 30–40% of patients currently on renal replacement therapy have diabetes, mainly due to type 2 disease (2). In Japan, the number of patients on renal replacement therapy has increased threefold in <15 years (3). In Hong Kong, the overall number of people on renal replacement therapy increased by 50% between 1995 and 1999, and in the diabetic group, a 100% increase was observed (4). These data suggest that Asian patients are predisposed to diabetic renal disease or that suitable interventional therapies may not be as effective in this patient population. Despite the potential cardiorenal protective effects of ACE inhibitors (5), Asian patients often have poor tolerance to these drugs due largely to adverse effects such as cough. The incidence of ACE inhibitor–associated cough in Chinese patients has been reported to range from 20 to 50% or some two- to fivefold higher than that in Caucasian patients (6).

Given the increased risk of progressive diabetic nephropathy in the Asian population, it is important to understand the characteristics and potential risk predictors in these patients. As such, the RENAAL study has taken on particular significance for the world's largest ethnic population, particularly in light of the growing diabetic population in Asia. The RENAAL study was a multicenter, multi-

From the [1]Department of Medicine and Therapeutics, The Chinese University Hong Kong, The Prince of Wales Hospital, Hong Kong, China; the [2]Department of Medicine, The Hong Kong University, Queen Mary Hospital, Hong Kong, China; the [3]University Malaya Medical Centre, Kuala Lumpur, Malaysia; [4]Singapore General Hospital, Singapore; [5]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [6]Merck Research Laboratories, West Point, Pennsylvania; the [7]Department of Medicine, Austin and Repatriation Centre, Medical Centre, University of Melbourne, Melbourne, Australia; the [8]Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the [9]Tokai University School of Medicine, Tokai, Japan.

Address correspondence and reprint requests to Dr. Juliana C.N. Chan, Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong. E-mail: jchan@cuhk.edu.hk.

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Z.M. is a member of the Asian Advisory Board for Merck Sharp & Dohme, which manufactures losartan, the drug used in this study; Z.M. received no honoraria. M.C. is a member of the RENAAL Steering Committee and has received honoraria from Merck. K.K. has received honoraria from Merck-Banyu for lectures related to RENAAL.

Abbreviations: AII, angiotensin II; DsCr, doubling of serum creatinine; ESRD, end-stage renal disease; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

ethnic, randomized, placebo-controlled study in which 17% of the 1,513 type 2 diabetic patients with clinical proteinuria were Asian (7). For the first time, it was possible to examine the characteristics of Asian patients with type 2 diabetes and nephropathy in a randomized, closely followed, and longer duration study (mean follow-up in the Asian population was 3.2 years). Furthermore, the RENAAL database affords the opportunity to examine potential baseline risk factors for progressive diabetic nephropathy specifically in the Asian population. In a recent post hoc analysis of the entire population of the RENAAL study, specific baseline variables, namely proteinuria, serum creatinine, Hb, and serum albumin, were found to be independent risk predictors for renal outcomes defined as ESRD and a doubling of serum creatinine (DsCr) concentration (8). In this subgroup analysis, the Asian population characteristics, response, and adherence to treatment are described. In addition, univariate and multivariate analyses were performed using prespecified baseline covariates to determine the baseline predictors of risk for renal end points in this population.

RESEARCH DESIGN AND METHODS

The RENAAL study was a double-blind, randomized, placebo-controlled study that compared the renal protective effects of the angiotensin II (AII) antagonist losartan plus conventional antihypertensive therapy with placebo plus conventional antihypertensive therapy in 1,513 patients with type 2 diabetes and nephropathy. In this multiethnic study, 252 patients were of Asian ethnicity; most of these patients resided in Asia ($n = 220$). Of these 220 patients, 96 were from Japan and the remainder were predominantly Chinese from Hong Kong ($n = 92$), Malaysia ($n = 21$), and Singapore ($n = 11$). The remaining 32 Asian patients were geographically located worldwide. The study rationale, design, and results have been described previously (8). Briefly, type 2 diabetic patients aged 31–70 years with nephropathy (presence, on two occasions, of urinary albumin-to-creatinine ratio from first morning specimen ≥300 mg/g or rate of urinary protein excretion of ≥0.5 g/day) and serum creatinine level of 115–265 μmol/l (133–265 μmol/l for men weighing >60 kg) were studied. Exclusion criteria have been described previously (7).

Table 1—*Baseline clinical, biochemical, and drug usage characteristics of the RENAAL study Asian population*

	Losartan	Placebo
n	117	135
Clinical characteristics		
Age (years)	59.7 ± 7.1	59.4 ± 7.5
Men	84 (71.8)	87 (64.4)
Smoking	29 (24.8)	23 (17.0)
Duration of diabetes (years)	15.0 ± 8.1	14.7 ± 8.3
Duration of diabetes ≥5 years	103 (88.0)	123 (91.1)
Duration of hypertension (years)	7.9 (8.1)	8.5 (8.0)
Duration of hypertension ≥ 10 years	33 (28.2)	40 (29.6)
BMI (kg/m^2)	25.2 ± 4.7	24.8 ± 4.3
Systolic blood pressure (mmHg)	152.1 ± 19.1	151.5 ± 19.6
Diastolic blood pressure (mmHg)	81.9 ± 10.5	82.9 ± 11.1
Mean arterial pressure (mmHg)	105.3 ± 10.8	104.6 (11.9)
Pulse rate (bpm)	76.3 (10.8)	75.2 (9.6)
Medical history		
Angina pectoris	9 (7.7)	13 (9.6)
Myocardial infarction	5 (4.3)	8 (5.9)
Amputation	3 (2.6)	5 (3.7)
Retinopathy	87 (74.4)	90 (66.7)
Laser therapy	25 (21.4)	26 (19.3)
Laboratory values		
Urinary albumin-to-creatinine ratio (mg/g)*	3.1 ± 0.5	3.1 ± 0.4
Calculated glomerular filtration rate (ml/min)	37.7 ± 9.8	37.5 ± 11.6
Serum creatinine (mg/dl)	1.9 ± 0.4	1.9 ± 0.5
Serum albumin (g/dl)	3.8 ± 0.5	3.8 ± 0.4
Total cholesterol (mg/dl)	228.8 ± 54.7	227.3 ± 48.2
LDL cholesterol (mg/dl)	144.2 ± 49.3	144.6 ± 46.8
HDL cholesterol (mg/dl)	45.7 ± 16.3	46.9 ± 17.4
Triglyceride (mg/dl)	208.1 ± 200.6	207.1 ± 161.1
Serum uric acid (mg/dl)	6.63 ± 1.4	6.9 ± 1.8
Hb (%)	12.3 ± 2.1	12.1 ± 2.0
GHb (%)	8.3 ± 1.5	8.0 ± 1.4
White blood cell count × 10^6/cc^9	7.5 ± 1.7	7.1 ± 1.7
Pattern of drug usage		
Dihydropyridine calcium channel blockers	84 (71.8)	101 (74.8)
Nondihydropyridine calcium channel blockers	12 (10.3)	10 (7.4)
Diuretics	43 (36.8)	44 (32.6)
β-Blockers	20 (17.1)	19 (14.1)
ACE inhibitors/AII antagonists	70 (59.8)	69 (51.1)
α-Blockers	23 (19.7)	26 (19.3)
Insulin	64 (54.7)	65 (48.1)

Data are means ± SE or *n* (%). *Log transformed.

The study was approved by all local research ethics committees, and all patients gave written informed consent before entry into the study.

Statistical analysis

Analysis of the primary and secondary end points was performed by the intention-to-treat method, and all of the data from the randomized Asian patients were included in the analysis. A Cox regression model (9) that included baseline proteinuria as a stratification factor and the geographical region as a covariate was used to determine the hazard ratio for the primary composite end point. The risk reduction was calculated as percent × (1 – hazard ratio). Event curves are based on Kaplan-Meier analysis (10).

The analyses of the progression of renal disease and changes in proteinuria were performed using an on-treatment approach. For the analysis of the progression of renal disease, we compared the slopes of the treatment groups using a linear random-effects model (11). Changes in the level of proteinuria in the two groups were compared by means of a mixed-effects model, the terms of which included the treatment at each point and the baseline level of proteinuria (12).

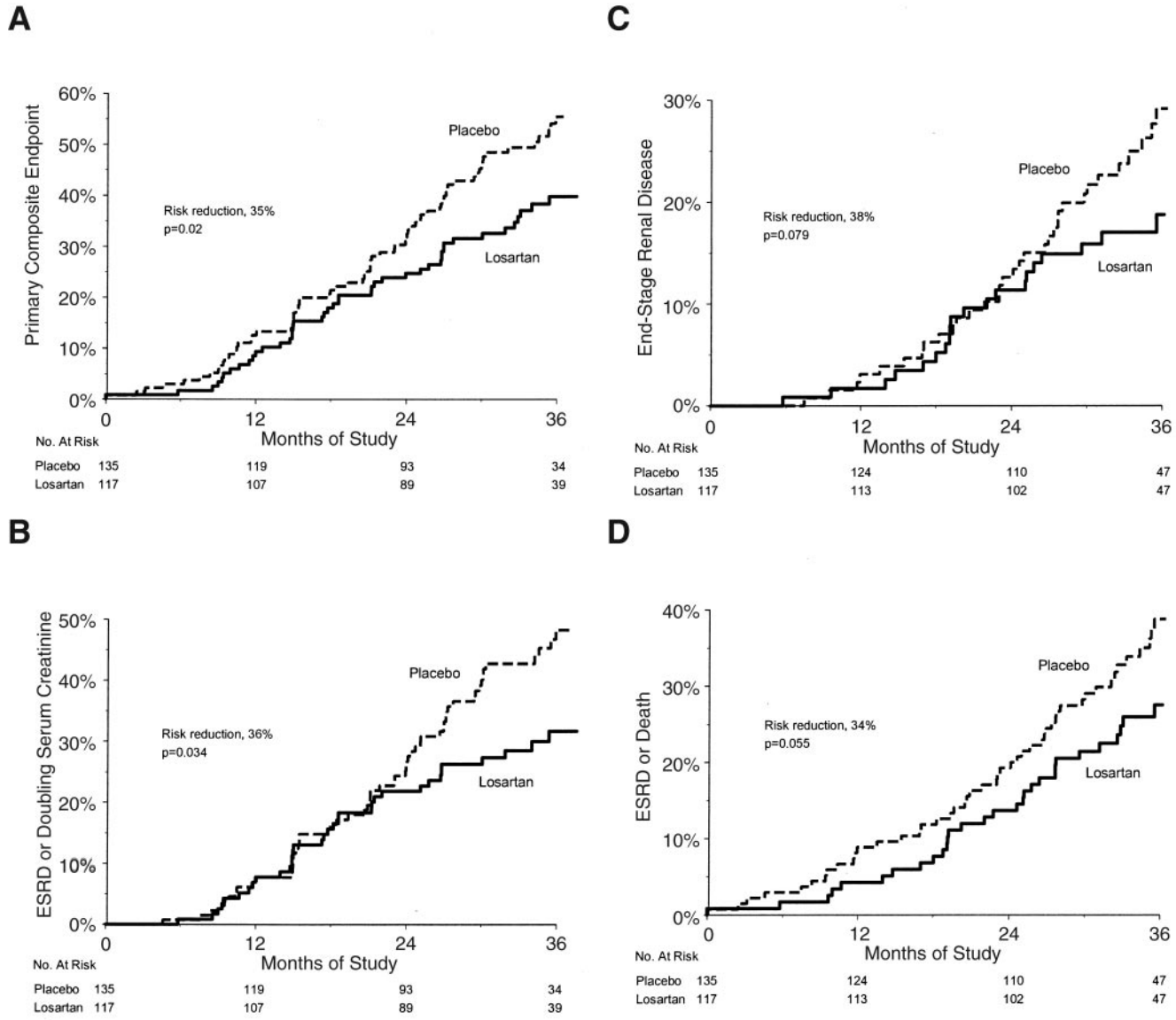

Figure 1—*Kaplan-Meier curves of the percentage of Asian patients with the primary composite end point of DsCr concentration, ESRD, or death* (A)*; the renal composite end point of DsCr concentration or ESRD* (B)*; ESRD alone* (C)*; and the composite end point of ESRD or death* (D)*.*

The calculated glomerular filtration rate was estimated using the formula based on the Modification of Diet in Renal Disease Study using body weight and serum creatinine (13). All data are expressed as mean ± SD or median (range). A Cox proportional model was performed to estimate the hazard ratio (95% CI) followed by a multivariate model to determine the baseline risk predictors for the renal end points using prespecified baseline covariates. A P value of <0.01 was required for the variable to remain in the model. The prespecified baseline covariates were age, sex, BMI, history of smoking, insulin use, systolic blood pressure, diastolic blood pressure, serum creatinine, estimated glomerular filtration rate, proteinuria, serum albumin, total cholesterol, lipoprotein(a), serum triglycerides, serum calcium, Hb, serum uric acid, GHb, white blood cell count, and dihydropyridine calcium channel blocker use. A P value <0.05 (two-tailed) was considered significant.

RESULTS

Baseline characteristics of the RENAAL Asian population

In the Asian subpopulation, the mean follow-up time for the RENAAL study was 3.2 years. The baseline characteristics of the two treatment groups were similar (Table 1). Dihydropyridine calcium channel blockers were used in >70% of patients at baseline; diuretics were the second most common antihypertensive medication used (34.5%).

Treatment effect of losartan in the RENAAL Asian population

At baseline, 92% of the Asian patients were receiving one or more antihypertensive medications (91% in the losartan group and 94% in the placebo group). The trough blood pressure declined in both treatment groups over the course of the RENAAL study from 152/82 to

Table 2—*Incidence of cardiovascular morbidity and mortality in the RENAAL study Asian population*

	Losartan (N = 117)		Placebo (N = 135)		Relative risk reduction	95% CI		P value
	Events	Event rate	Events	Event rate		Lower	Upper	
Primary composite end point	49	41.9	74	54.8	0.35	0.07	0.55	0.020
Components								
Doubling of serum creatinine	36	30.8	48	35.6	0.26	−0.01	0.52	0.167
ESRD	22	18.8	37	27.4	0.38	−0.06	0.63	0.079
Death	17	14.5	21	15.6	0.10	−0.71	0.52	0.753
Secondary composite end point*	35	29.9	43	31.9	0.11	−0.39	0.43	0.599
Components								
Cardiovascular death	9	7.7	10	7.4	0.01	−1.45	0.60	0.990
Heart failure	15	12.8	18	13.3	0.06	−0.87	0.53	0.864
Myocardial infarction	5	4.3	12	8.9	0.55	−0.29	0.84	0.137
Revascularization	7	6.0	7	5.2	−0.13	−2.22	0.60	0.820
Unstable angina	7	6.0	3	2.2	−1.61	−9.10	0.32	0.164
Stroke	9	7.7	14	10.4	0.29	−0.64	0.69	0.423

*Secondary composite end point of cardiovascular morbidity and mortality was a composite of myocardial infarction, stroke, hospitalization for heart failure, hospitalization for unstable angina, coronary and peripheral revascularization, and death due to cardiovascular causes. The relative risk reductions of losartan versus placebo were calculated with a Cox regression model, which was stratified by baseline proteinuria level. For the overall population, the model was also adjusted for region. (Positive relative risk reductions favor losartan.)

140/73 mmHg in the losartan group and from 152/83 to 144/74 mmHg in the placebo group (P = NS). During the study, 27% of the Asian patients were receiving losartan 50 mg once daily and 71% received losartan 100 mg once daily. The use of various classes of conventional antihypertensive medications changed between baseline and during the study with increased use of β-blockers (baseline 15.5 vs. 30.5% during the study), diuretics (baseline 35 vs. 67% during the study), and α-blocker (baseline 19.5 vs. 34.5% during the study). Dihydropyridine calcium channel blockers continued to be used in ~77% of the Asian patients. In accordance with the protocol, use of ACE inhibitors and other AII antagonists was discontinued at baseline.

Losartan was associated with a 35% risk reduction (P = 0.02) for the primary composite outcome in the RENAAL Asian population (Fig. 1*A*). In addition, losartan reduced the risk of the renal outcomes of ESRD or DsCr (36%, P = 0.034) (Fig. 1*B*). There was a difference in the incidence of ESRD and the composite of ESRD or death, but the risk reduction was not statistically significant (Fig. 1*C* and *D*). Death in Asian patients was lower in the losartan group; however, this was not statistically significant (Table 2).

Of Asian patients, ~30% (n = 78) had a cardiovascular event; hospitalization for heart failure was most common (~13%, 33 patients). In addition, <8% (n = 19) of the Asian patients died of cardiovascular causes. There was no significant difference in the treatment effect of losartan on the composite end point of cardiovascular morbidity and mortality (Table 2).

Losartan reduced the level of proteinuria (determined from the albumin:creatinine concentration in a morning spot specimen) by 47% (P < 0.001) (Fig. 2). In addition, the rate of decrease in renal function was reduced by 30.7% (P = 0.0074; median slope −0.0521 mg/dl per year in the losartan group, as compared with −0.0752 mg/dl per year in the placebo group).

In the Asian cohort, overall discontinuations throughout the study were lower in the losartan group than the placebo group (losartan 28% versus placebo 43%). Before the primary composite event, fewer patients treated with losartan discontinued treatment (losartan 10.3% versus placebo 17.8%, P = 0.089). Treatment compliance, defined as taking 80% or more of the test drugs determined by tablet counting, was 87.3% in the Asian population, and the mean length of time on the drug was 2.9 years. The most common adverse events experienced by the Asian subpopulation that led to discontinuation of the study drug (losartan and placebo combined) were ESRD (n = 9), renal insufficiency (n = 8), congestive heart failure (n = 4), myocardial infarction (n = 3), and cerebral infarction (n = 2). Losartan was not associated with increased incidence of cough when compared with placebo (losartan 22.2% versus placebo 20.0%, P = NS).

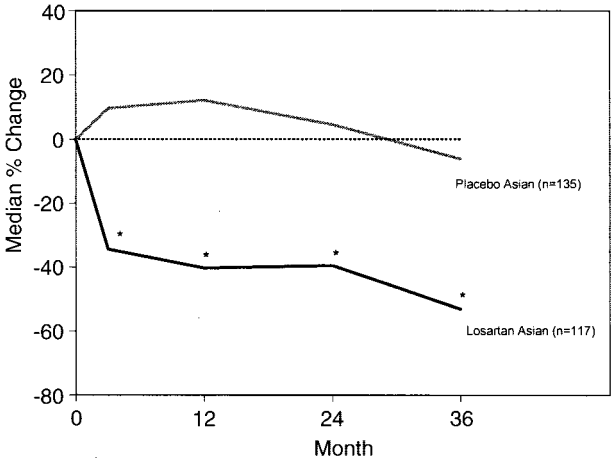

Figure 2—*Median changes from baseline in the level of proteinuria. Proteinuria was measured as the urinary albumin-to-creatinine ratio in a first morning specimen. *P < 0.05.*

Table 3—*Multivariate baseline predictors of risk for renal end points in the RENAAL study Asian population*

Renal event	Baseline risk factor	Hazard ratio	95% CI Upper	95% CI Lower	*P* value
Cox proportional hazards model using prespecified covariates*					
Primary composite	Proteinuria/1,000 mg	1.39	1.28	1.51	<0.0001
	Hemoglobin	0.82	0.74	0.91	<0.0001
DsCr or ESRD	Proteinuria/1,000 mg	1.42	1.30	1.55	<0.0001
	Hemoglobin	0.81	0.72	0.91	<0.0001
ESRD alone	Proteinuria/1,000 mg	1.24	1.39	1.11	<0.0001
	Calcium	0.34	0.63	0.18	0.001
	Age/10 years	0.54	0.79	0.54	0.002
	Hb	0.79	0.94	0.67	0.006
	Serum creatinine	2.25	4.18	1.22	0.010

*Prespecified covariates selected are as follows: age, sex, BMI, smoking, insulin use, systolic blood pressure, diastolic blood pressure, serum creatinine, estimated glomerular filtration rate, proteinuria, serum albumin, total cholesterol, lipoprotein(a), serum triglycerides, serum calcium, Hb, serum uric acid, GHb, white blood cell count, and dihydropyridine calcium channel blocker use.

Baseline risk predictors for renal outcomes in the RENAAL Asian subpopulation

By univariate analysis, the strongest baseline predictors of renal risk were proteinuria, serum albumin, serum calcium, Hb, lipoprotein(a), serum creatinine, and estimated glomerular filtration rate.

From this, we constructed a multivariate Cox proportional hazards model, which showed that baseline proteinuria and Hb were strong predictors of risk for both the primary composite end point (DsCr, ESRD, or death) and the renal composite end point (DsCr or ESRD) and ESRD alone (Table 3). Three additional baseline variables were significantly associated with the risk of ESRD: serum calcium, younger age (per 10 years), and serum creatinine (Table 3).

CONCLUSIONS — There is now consensus on the importance of optimal control of blood pressure to preserve renal function in high-risk patients such as those with diabetes and/or hypertension (14). Given the deleterious effects of AII on hemodynamics and cellular growth, inhibition of the renin angiotensin aldosterone system has been shown to have organ-protective effects beyond blood pressure reduction (5). Both the RENAAL study (7) and the Irbesartan Diabetic Nephropathy Trial (15) have now confirmed the renal protective effects of AII receptor antagonists in type 2 diabetic patients with established nephropathy. As a result of its multinational, multiethnic patient recruitment strategy, the RENAAL study database represents a unique resource for understanding the disease progression and treatment responses in different ethnic groups.

Losartan was effective in reducing the risk of developing the primary composite end point of DsCr, ESRD, and all-cause mortality in the Asian subpopulation of the RENAAL study. Although there was no interaction between race and treatment effect of losartan in the RENAAL study (8), the robust treatment effect of losartan in this Asian subpopulation was consistent with the results of the main study. This would support the importance of specific blockade of AII in addition to blood pressure reduction to reduce the continued decrease of kidney function in Asian patients with type 2 diabetes. No difference between losartan and placebo was observed for the secondary cardiovascular morbidity and mortality end point. This is most likely associated with the low number of cardiovascular events in the Asian population in general.

There are also reports suggesting that Asian patients with diabetes are at increased risk for renal complications (16–18). In addition, recent data from the Irbesartan Diabetic Nephropathy Trial suggest that calcium channel blockers, particularly dihydropyridine calcium channel blockers, are not the optimal antihypertensive agent for treating type 2 diabetic nephropathy (15). Despite the high use of dihydropyridine calcium channel blockers and their popularity in Asians (19), patients treated with losartan strongly benefited despite any potentially deleterious effects of dihydropyridine calcium channel blockers. Therefore, the demonstrated importance of adequate AII blockade must now, in addition to adequate control of blood pressure, become a major point of emphasis in this population.

The Asian patients had the lowest discontinuation rates of any subgroup in the RENAAL study. This is due, in part, to the tolerability of losartan in this patient population, which is supported by the similar incidence of cough in the losartan and placebo groups. The high adherence rate of Asian patients to losartan therapy has potential socioeconomic implications given the predicted increase in the incidence of type 2 diabetes in Asia over the next two decades. The increasing cost of ESRD to the healthcare sector in Asia is expected to be profound and is likely to overburden an already heavily taxed system. Economic evaluation of the overall RENAAL study shows that losartan therapy would result in a net savings of $3,522 per patient over 3.5 years (20). This may potentially bring some needed relief to the increasing cost of type 2 diabetic nephropathy in this region. In areas where access to renal replacement therapy is suboptimal, the delay in developing ESRD by losartan may also become very important to patient survival (21).

In a recent post hoc analysis of RENAAL data, the following risk factors for renal end points (DsCr or ESRD) were identified: proteinuria, serum creatinine, low serum albumin, and low Hb (8). In this respect, proteinuria and Hb were also identified as significant risk predictors for the same renal end points in Asian patients. The association between low Hb and renal end points requires further elucidation. Whereas low Hb might be a more sensitive marker for renal dysfunction, it is plausible that the relatively high prevalence of α- and β-thalassemia traits (reported to be 6–8% in Asians) (22) might have adverse effects on tissue function(s) through increased oxidative stress and iron overload. In this context, patients with thalassemia major, especially if hypertransfused, are known to have increased risk of insulin resistance (23) and diabetic nephropathy (24). More recently, thalassemia minor has been found

to be a risk factor for gestational diabetes (25), which was associated with excess maternal iron in Chinese women (26).

In conclusion, despite potential limitations due to its post hoc nature, our analysis shows that treatment with losartan significantly reduces the risk of developing the primary composite end point of DsCr, ESRD, and all-cause mortality in Asian patients with type 2 diabetes and nephropathy. In addition, losartan reduced proteinuria and the progression of renal disease and was well tolerated in these patients with a similar incidence of cough observed. In the Asian population of the RENAAL study, baseline proteinuria and Hb were significant predictors of risk for the renal end points of doubling of the serum creatinine concentration and ESRD. In light of the increasing epidemic of diabetes in Asia, our current results furnish important health care implications for Asian patients.

APPENDIX — The following investigators have participated in the RENAAL study in Asia.

Japan: R. Abe, Y. Ando, T. Fujita, T. Hanafusa, M. Haneda, T. Haneda, Y. Hashimoto, T. Ida, Y. Iino, S. Ishibashi, S. Ito, S. Kadoto, H. Kakuta, M. Kanazawa, T. Kanda, M. Kasuga, M. Kato, Y. Kida, T. Koike, H. Kurahachi, H. Kuzuya, F. Marumo, K. Matoba, K. Murakami, D. Nagasaku, K. Ohshiro, S. Oikawa, K. Okada, S. Owada, T. Saito, H. Sakai, T. Sawada, J. Seino, C. Shigemasa, K. Shikata, T. Shoji, M. Sone, C. Takahashi, T. Tamai, Y. Tsubakihara, N. Ujihara, N. Ura, T. Watanabe, N. Yamada, I. Yamaji, Y. Yamasaki, M. Yoshinari, N. Yoshioka; Hong Kong: J.C.N. Chan, W.Y. So, J.A.J.H. Critchley, M.K.W. Lo, K.F. Lee, G.T.C. Ko, W.B. Chan, K.S.L. Lam, N.M.S. Wat; Malaysia: C.T. Chua, Z. Morad; Singapore: K.S. Wong.

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