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Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

Michael Mauer[1,2], **Bernard Zinman**[3], **Robert Gardiner**[4], **Samy Suissa**[5], **Alan Sinaiko**[1], **Trudy Strand**[1], **Keith Drummond**[6], **Sandra Donnelly**[3], **Paul Goodyer**[6], **Marie Claire Gubler**[7], and **Ronald Klein**[8]

[1] Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota USA

[2] Department of Medicine, University of Minnesota, Minneapolis, Minnesota USA

[3] Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

[4] Department of Medicine, McGill University, Montreal, Quebec, Canada

[5] Departments of Epidemiology and Biostatistics and Medicine, McGill University, Montreal, Quebec, Canada

[6] Department of Pediatrics, McGill University, Montreal, Quebec, Canada

[7] Hôpital Necker-Enfants Malades, Paris, France

[8] Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Abstract

Background—Nephropathy and retinopathy remain important complications of type 1 diabetes. It is unclear whether early administration of drugs that block the renin-angiotensin system slows their progression.

Methods—The Renin Angiotensin System Study [RASS] was a multicenter controlled trial in 285 normoalbuminuric, normotensive type 1 diabetic patients who were randomized to losartan (100mg daily), enalapril (20mg daily) or placebo and followed for 5 years. The primary endpoint was change in glomerular mesangial fractional volume in kidney biopsies. The retinopathy endpoint was a 2-step or greater progression in retinopathy severity scale. Intention-to-treat data analyses used linear and logistic regression models.

Results—Ninety and 82% of patients had complete renal biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over 5 years in placebo (0.016 units) was not significantly different from enalapril (p=0.38) or losartan (p=0.26), nor were there significant changes in other biopsy assessed renal structural variables. Five-year cumulative microalbuminuria incidence was higher for losartan than placebo (14% *vs*. 4%; logrank p=0.015) but not for enalapril (6% *vs*. 4%; logrank p=0.96). Two-step or more retinopathy progression incidence was reduced by 65% in the enalapril (O.R. 0.35; 95% C.I., 0.14–0.85) and 70% in the losartan group (O.R. 0.30; 95% C.I., 0.12–0.73) independent of changes in blood pressure. There were three biopsy-related serious

Corresponding Author: Michael Mauer, MD, Departments of Pediatrics and Medicine, University of Minnesota, 420 Delaware Street S.E., MMC 491, Minneapolis, MN 55455, Phone: 612-626-2720; FAX: 612-626-1165, mauer002@umn.edu.

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adverse events that completely resolved. Chronic cough occurred in 12 enalapril, 6 losartan and 4 placebo patients.

Conclusions—Early renin-angiotensin system blockade did not modify nephropathy progression in type 1 diabetic patients, but had important effects in slowing retinopathy.

Diabetic nephropathy (DN), responsible for >45% of end-stage renal disease (ESRD) in the USA,[1] may be structurally advanced when albuminuria becomes detectable [2,3]. Renin-angiotensin system (RAS) blockers are more effective than other antihypertensives in slowing nephropathy progression in proteinuric diabetic patients with reduced glomerular filtration rate (GFR)[4–6] and can decrease proteinuria in diabetes.[7] Although proteinuria reduction in diabetes has been associated with a reduction in the rate of decline in the GFR, in small studies,[8] this association has not been systematically tested; and proteinuria reduction is not a generally accepted surrogate for hard clinical endpoints such as ESRD.[9] Intensive multifactorial intervention in type 2 diabetic patients with microalbuminuria nearly halved progression of proteinuria but did not alter the GFR decline.[10, 11] The present study asked whether the institution of RAS blockade prior to the onset of albuminuria in patients with type 1 diabetes mellitus (T1DM) could slow progression of early DN histologic lesions and was based on the concept that slowing the structural changes responsible for renal dysfunction in diabetes[2, 3] would delay or prevent clinical DN.

Recently, the DIRECT study reported that angiotensin receptor blockade (ARB) reduced retinopathy development in normotensive normoalbuminuric T1DM patients without diabetic retinopathy (DR),[12] but not in patients with mild to moderate DR. The Renin-Angiotensin System Study (RASS) assessed the effect of RAS blockade with either an angiotensin-converting-enzyme inhibitor (ACEI) or an ARB on both renal and retinal morphology in normotensive, normoalbuminuric T1DM patients.[13]

METHODS

Study Design

RASS[13] was a 5-year multi-center randomized, double-blind, placebo-controlled investigator-initiated trial comparing effects of the ACEI enalapril (Vasotec, Merck & Co.), the ARB, losartan (Cozaar, Merck & Co.) to placebo on early renal pathology in T1DM. The pre-specified primary study endpoint was change in the fraction of glomerular volume occupied by mesangium (mesangial fractional volume).[2, 14] Secondary renal endpoints included changes in other glomerular, vascular, tubular and interstitial parameters and changes in albumin excretion rate (AER) and GFR. Shortly after RASS began, a DR study with an *a priori* endpoint of two-step or more progression of DR was added.[13] Randomization was in computer-generated blocks of six, stratified by center and sex, into three groups: (1) enalapril, 10 mg daily; (2) losartan, 50 mg daily; or (3) placebos, daily. While the study was ongoing, dosages were doubled because of new data indicating greater proteinuria reduction with higher doses.[15] Patients were on the increased dose for 2.9±0.9 years. The study was designed by Drs. Mauer and Klein with input from Drs. Zinman, Drummond, and Suissa. Data gathered at the three study centers were forwarded to the Data Center based at McGill University where all analyses were done under Dr. Suissa's supervision and Drs. Mauer, Klein and Suissa vouch for the data and analyses. Dr. Mauer wrote the initial draft which was revised by the RASS writing committee (M. Mauer, B. Zinman, R. Gardiner, A Sinaiko and S Suissa). The RASS Executive Committee decided to publish the paper. There were no confidentiality agreements between the sponsors (Merck, USA and Merck Frosst, Canada) who provided partial support for this study and donated the study drugs, the authors or their institutions, nor did these sponsors have any role in study design, data accrual, data analysis or manuscript preparation. The study was approved by institutional review boards at the Universities of Minnesota, McGill, and Toronto,

and written informed consent obtained from each participant. The study was overseen by an NIH data safety monitoring board.

Study Patients

Patients had had T1DM for 2–20 years. Patients 18 or more years old were recruited from diabetes clinics and local advertising; Minnesota and Montreal centers included 32 (11%)15–17 year old participants from the Natural History of Diabetic Nephropathy Study (NHS). Of 1065 T1DM patients screened, 707 declined, 73 were ineligible, and 285 were randomized (Fig. 1); there were no demographic differences between those accepting and declining (Supplementary Appendix I)[13].

Exclusion criteria were hypertension [blood pressure (BP) >135/85 mmHg or on antihypertensive medications]; an albumin excretion rate above (AER) 20 μg/min; pregnancy; failure to take ≥85% of placebo pills during a two week run-in; GFR <90 ml/min/1.73m^2 (<80 ml/min/1.73m^2 if strictly vegan)[18]. Patients with baseline fundus photographs within one year after randomization without proliferative DR (PDR) were included in the DR studies.

Follow-up Measures

Patients were followed for five years. Pill count, BP, AER, and glycosylated hemoglobin (HbA_1C) were obtained quarterly and GFR, annually.[13] Study drugs were withheld during the 18 pregnancies that occurred (6 placebo, 4 enalapril, 8 losartan) in 14 patients (5 placebo, 4 enalapril, 5 losartan). HbA_1C was measured by DIAMAT analyzer (BioRad, Hercules, CA) until 2002 when the TOSOH method was introduced (Tosoh Medics, Inc, San Francisco, CA). BP was measured by DinamapR Monitor. If hypertension persisted for two weeks, non-RAS medication was initiated with the treatment goal <130/80 mmHg.

GFR was measured by iohexol plasma disappearance[19]. Baseline AER was the median of 3 pre-randomization samples[13]. Microalbuminuria was defined as at least 2 of 3 consecutive values between 20–200 μgm/minute.

Renal Biopsies and Morphometric Measures

Percutaneous biopsies[20] were performed prior to randomization and 5 years later. At least two glomeruli for electron microscopy were required for randomization. One baseline and three 5-years biopsies were repeated for inadequate tissue; one patient had inadequate tissue twice. Five exit biopsies had fixation problems; four were repeated. Electron microscopy was performed in 3.14 ± 0.53 glomeruli per biopsy (range 1–6; only one biopsy had a single glomerulus). All measurements were performed by one masked observer. Mesangial fractional volumes per glomerulus were estimated by point counting as reported elsewhere.[3, 20, 21] Peripheral glomerular basement membrane surface per glomerulus and glomerular basement membrane width were estimated as described.[3, 20] Two masked observers estimated the fraction of each cortical arteriolar wall replaced by hyaline in random light microscopy slides and the index of arteriolar hyalinosis was calculated.[16] The volume fractions of cortex which was interstitium and atrophic tubules per total cortical tubules, were estimated by point counting by one masked observer.[22]

Retinopathy Grading

Baseline and exit thirty degree stereoscopic fundus photographs of the seven standard Early Treatment Diabetic Retinopathy Study [ETDRS] fields[23] were graded by masked observers at the University of Wisconsin Ocular Epidemiology Reading Center using the modified Airlie House Classification and the ETDRS severity scale[24] (Supplementary Appendix II). For each eye, the maximum grade in any of the standard fields for each lesion was used in defining DR

(Appendix II). [20] If DR severity was ungradable in an eye (three instances), it was assigned a DR level equivalent to the other eye. DR level was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. This provided a 15-step DR severity scale.[20,23] The primary analyses considered a two-step or more and the secondary analyses a three-step or more increase on this scale, both clinically meaningful amounts of diabetic DR progression.[25].

Statistical Analysis

Baseline characteristics were compared using Chi-square tests and analysis of variance. HbA_1C and clinic BPs over the 5-year follow-up were compared using analysis of variance.

The difference between the 5-year and baseline values of the pre-specified primary study endpoint, namely mesangial fractional volume, was used to compute change over time. Mean changes between enalapril and placebo, and between losartan and placebo were first compared using simple linear regression. Multiple linear regression with the baseline mesangial fractional volume, T1DM duration, age at onset, sex, HbA_1C, systolic BP, diastolic BP, GFR and AER as covariates, used to improve precision of the estimates, was the pre-specified approach to analysis. This approach was used for all secondary structural outcomes.

For the secondary AER and GFR outcomes, the value at the time of the 5-year biopsy and the mean of all values over the five years were analyzed using multiple linear regression, with the baseline value of each endpoint as the only covariate. The Kaplan-Meier approach and the log rank test were used to estimate and compare the cumulative incidence functions of microalbuminuria.

Logistic regression was used to estimate the odds ratio of the secondary outcomes of two- and three-step or more DR progression. Odds ratios were estimated separately for losartan and enalapril, relative to placebo, adjusted for baseline characteristics, center and baseline DR level on the 15 step severity scale. To assess the independent effect of BP, we used BP during the 5 years as a *post-hoc* predictor of the odds of two- and three-step or more DR progression, adjusted for age, sex and center. Treatment was added to the model to quantify the change in the odds ratio related to BP.

A sensitivity analysis was performed for the primary renal and for the DR endpoints using multiple imputation techniques to assess effects of patients excluded for not having both biopsies or DR gradings, respectively. Assessment of the effect of doubling the dose during the study was performed by adding a term in the multiple regression analysis for the time from randomization to dose doubling, as well as for the time from randomization to the first fundus photographs, the latter only for DR analyses. The sample size of 86 patients per group was determined so that the study could detect a 50% reduction in mesangial fractional volume change over 5 years with 80% power and 5% significance, reduced to 2.5% to allow for the two contrasts of the primary analysis (losartan *vs.* placebo and enalapril *vs.* placebo)[13]. The sample size calculation used available data from 21 patients meeting the study's entry criteria, in whom the mean change mesangial fractional volume per glomerulus over 5 years was 0.0533 and the standard deviation was 0.0557 after regression on the baseline values at baseline of mesangial fractional volume, GFR, AER and diabetes duration. In anticipation of a 10% dropout rate, the study enrolled 95 patients per group. Data were entered at the Data Center based at McGill University, managed using Paradox, and analyzed using SAS version 9.1 with investigators and participants blinded to results until final analyses were completed.

RESULTS

Of the 285 patients randomized, 90 % (256) completed both renal biopsies (Fig. 1). There were no differences in baseline characteristics between the three groups (Table 1), for those completing both biopsies (Supplementary Appendix III), or for those with and without both baseline and exit biopsies (Supplementary Appendix IV). Medication compliance was ≈85% and visit attendance >93% in all groups (p=0.87 and 0.92, respectively).

HbA_1C (p=0.54) (Supplemental Appendix V) and insulin dose (p=0.29) during RASS were similar among groups. Clinic systolic and diastolic BP during the study were lower in enalapril (113±9/66±6mmHg) and losartan (115±8/66±6mmHg) groups than in placebo patients (117 ±8/68±5 mmHg) (p<0.001 and ≤0.02, respectively; Supplementary Appendix VI has further BP details). Hypertension developed in 9 placebo, 3 enalapril and 4 losartan patients (p=0.04).

The pre-specified primary study endpoint, mesangial fractional volume, increased by 0.016 units in the placebo (p<0.004) and 0.026 the losartan (p<0.001) groups but did not change significantly (0.005 units) in the enalapril group (Table 2a). These changes were not significantly different from placebo for either enalapril (p=0.16) or losartan (p=0.17). Inclusion of the time to the higher dose variable and the multiple imputation analyses accounting for patients with missing second biopsies did not change these findings. Secondary renal structural endpoints showed generally similar results (Supplementary Appendix VII).

AER increased significantly from baseline only in the losartan group (p=0.04). Compared with placebo, the 5-year average AER was higher with losartan by 4.0μg/min (p=0.033) but not with enalapril (p=0.47) (Table 2b). AER at 5-years was higher with losartan *vs.* placebo by 8.0μg/min (p=0.007) but not with enalapril (p=0.74). Microalbuminuria 5-year cumulative incidence was higher with losartan than placebo (17% *vs*. 4%; log rank p=0.015) but not with enalapril (6% *vs*. 4%; log rank p=0.96) (Fig. 2). GFR decreased similarly by 6.6 to 8.9 ml/min during RASS in all three groups (p <0.002 for each; Table 2b).

Thirty-two patients were excluded from the DR study; 28 had baseline photos >1 year after randomization, and 4 had PDR. 223 of the remaining 253 participants (92%) completed these studies (Fig. 1); 122 had baseline photographs before and 101 4.8 ± 4.8 months after randomization. There were no significant baseline differences in those with and without both baseline and exit photographs (Supplementary Appendix VIII) or among the groups that had both (Supplementary Appendix IX). At baseline, 34.0% of patients had no DR (Level 10), 39.5% had minimal non-proliferative DR (NPDR, Level 21), 17.5% had early NPDR (Levels 31–37), 9% had moderate to severe NPDR (Level 41 to 53). Baseline distributions of DR scores among groups were not statistically different (Supplementary Appendix X). Most of the 2-step or more and 3-step or more DR progression occurred in eyes with no or minimal NPDR (Levels 10–37, 93.5%) *vs.* eyes with more severe retinopathy (Levels 40–53, 6.5%). This pattern did not vary among groups. One placebo and 1 enalapril patient required laser therapy during RASS.

Two-step or more progression occurred in 38% of placebo *vs.* 25% of enalapril (p<0.03) and 21% of losartan patients (p<0.008) (Table 3). Two-step or more progression was reduced by 65% in the enalapril (odds ratio 0.35; 95% CI 0.14–0.85) and 70% in the losartan group (OR 0.30; 95% CI 0.12–0.73) (Table 3). Results were similar for 3-step or more progression (Table 4). These effects remained after adjustment for mean clinic BP during RASS, and for time to first retinal photographs and time to higher drug dose and after multiple imputation analyses accounting for patients with missing second photos.

Adverse Events

Serious adverse events were few and similar among groups (Table 4). There were 3 deaths: enalapril, ketoacidosis; losartan, traumatic cerebral hemorrhage; placebo, hypoglycemia. There were 2 perinephric hematomas and 1 large bladder clot, but no permanent sequalae. Numbers of participants with hypoglycemia and ketoacidosis were similar among groups. Chronic cough occurred in 12 enalapril, 6 losartan and 4 placebo patients; 2 discontinuing enalapril (Table 4). Transient hyperkalemia occurred in 1 enalapril patient and transient serum creatinine elevation in 1 losartan patient, neither requiring medication discontinuation (Table 4).

DISCUSSION

Mesangial fractional volume, the primary pre-specified renal endpoint in RASS, is the parameter most closely correlated with GFR loss in DN.[14]. Despite normal BPs and AERs, baseline DN structural abnormalities were present in RASS.[20]. Increased mesangial fractional volume in T1DM, as confirmed in RASS, primarily results from matrix rather than cellular expansion[21]. Thus, mesangial fractional volume and all DN glomerular structural parameters, except for mesangial cell fractional volume progressed in the placebo group and neither enalapril nor losartan significantly reduced these progression rates (Supplementary Appendix VII). These structural parameters do not vary with age in the age range of the RASS patients[26] There were also no treatment benefits on albuminuria and GFR loss. However, AER was higher in the losartan as compared to the placebo group during the study and at study exit, and more persons in the losartan group progressed to microalbuminuria. Long-term AER studies in ARB-treated normoalbuminuric type 1 diabetic patients have not been previously done and this unexpected and unexplained finding requires confirmation in other randomized controlled trials. Meanwhile, careful AER monitoring is recommended if ARBs are prescribed to similar diabetic patients. The rate of GFR loss was approximately twice that expected among normal people in the age range of participants in the present study,[27] but did not differ among groups. These early GFR declines may be important, since low GFR in normoalbuminuric T1DM patients are associated with worse lesions[28] and progressive GFR loss in microalbuminuric T1DM patients defines a phenotype whose AER increases over time.[29]

RAS blockade appears to be more effective than other antihypertensives in reducing time to serum creatinine doubling, dialysis or death in proteinuric T1DM[4] and T2DM[5],[6] patients with elevated serum creatinine levels. While ACEI slowed interstitial expansion in proteinuric T2DM patients,[30] the interstitium in RASS increased by more than 50% in all 3 groups (Supplementary Appendix VI). Thus, it may be misleading to extrapolate from more advanced to early DN stages and from T2DM to T1DM studies, especially given substantial differences in relationships of renal structure to albuminuria[31] and the frequent presence of hypertension, obesity and other albuminuria risk factors in T2DM[2]. Decreased progression of microalbuminuria to proteinuria in diabetic patients could result from direct effects of ACEIs on proteinuria[11, 32]. Thus, despite 8 years of treatment, two months after discontinuation of ACEI albuminuria differences from placebo were no longer significant[32], suggesting masking of progression of underlying injury. In a small study of patients with T1DM changes in renal biopsy morphologic parameters were similar in 7 ARB as compared to 3 placebo patients[33]. The present large randomized double blind placebo controlled trial examined the effects of RAS blockade on early renal structural changes in normoalbuminuric, normotensive patients with T1DM. Thus, while failure to detect benefits of RAS blockade on DN structural or functional outcomes may initially seem at odds with other studies, RASS is not comparable to earlier work. Since patients in our study were selected to have no baseline clinically detectable renal disease, patients at low DN risk were likely included. Moreover, while the rate of mesangial fractional volume progression in the placebo group of 0.016 was statistically

significant, this was less than the expected 0.053 change computed from 21 T1DM patients meeting our entry criteria who participated in an earlier study.[16] The impact on power can be seen from the lower bound of the 95% confidence interval for the difference in the rate of progression in mesangial fractional volume, suggesting that enalapril is at most 0.026 better than placebo, while losartan is at most 0.005 better than placebo. We estimate that the benefits we may have missed would be at most ½ to 1/10 of the mesangial fractional volume change needed to regularly result in proteinuria[3, 14]. There was no influence of T1DM duration on the primary outcome.

Important secondary structural variables, such as interstitial fractional volume[22], also showed no treatment benefit despite large increases from baseline in the placebo group. Currently, there are no accurate DN risk predictors for patients meeting the entry criteria for the present study. Thus, although a study which included only those normoalbuminuric normotensive T1DM patients at high risk for nephropathy might have provided different results, such study design is not currently feasible.

Enalapril and losartan were both associated with a reduction in two- and three-step or more DR progression by approximately 65 and 70 %, respectively. These reductions, unrelated to glycemia, might be from BP lowering or direct effects of retinal RAS blockade. Earlier trials[34,35] showed less DR progression in T2DM patients assigned to tight BP control, independent of ACEI use. Baseline DR severity in these normotensive RASS patients correlated with nocturnal systolic BP[36]. Although DR benefits remained after adjusting for the lower clinic BPs in the enalapril and losartan groups during the study, BP effects on these DR outcomes cannot be ruled out. Our findings are consistent with the DIRECT-Prevent 1 study where T1DM participants without DR randomly assigned to an ARB [candesartan] *vs.* placebo were less likely to develop DR [HR 0.82 (95% CI 0.67–1.00; p=0.0508)], but are inconsistent with DIRECT-Protect 1 where there was no benefit of candesartan in patients with non-proliferative DR [HR 1.02 (0.80–1.31, p=0.85)][12]. The reasons for these differences in DR progression are unknown and not easily explainable by differences in DR severity, BP, glycemia or diabetes duration at baseline between RASS and DIRECT- Protect 1.[12]

The RAS has been implicated in DR pathogenesis.[37] Angiotensin II synthesis occurs in ocular areas susceptible to DR.[38] Vitreous vascular endothelial growth factor levels, increased in eyes of patients with PDR,[39] are correlated with vitreous angiotensin converting enzyme activity[40]. Thus, enalapril and losartan DR benefits in the present study may represent direct effects on the eye, independent of systemic BP effects.

In summary, the RASS did not detect nephropathy structural or functional benefits in normoalbuminuric, normotensive T1DM participants randomized to RAS blockade with an ACEI or an ARB. Given current abilities to predict nephropathy risk, RAS blockade for the primary prevention of DN in T1DM is not supported by present evidence. In contrast, we found equally beneficial effects of the ACEI, enalapril, and the ARB, losartan, in reducing the risk of DR progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Diagram of Study Patients

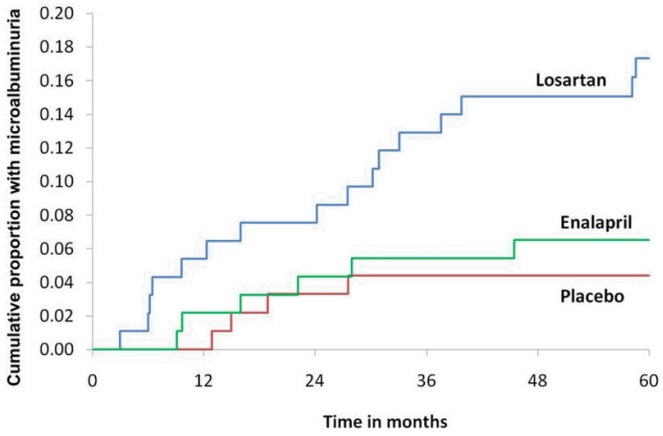

FIGURE 2.
Kaplan-Meier Curves of Time to Microalbuminuria

Table 1

Baseline Characteristics of All 285 Patients by Randomized Treatment

	Placebo (95)	Enalapril (94)	Losartan (96)
Age (years)	29.1±9.1	30.6±10.0	29.3±10.2
Diabetes duration (years)	11.2±4.5	11.7±4.9	10.7±4.8
Body Mass Index (kg/m^2)	25.4±3.7	25.6±3.4	26.1±4.0
Gender (% male)	45	48	46
Ethnicity (% Caucasian)	100	98	96
Glycosylated hemoglobin (%)	8.3±1.4	8.6±1.6	8.7±1.7
Systolic Blood Pressure (mmHg)	119±11.0	120±12.6	120±11.1
Diastolic Blood Pressure (mmHg)	70±8.4	71±8.4	70±8.4
Albumin Excretion Rate (μg/min)*	4.8	5.1	5.5
Glomerular Filtration Rate† (ml/min/1.73m^2)	126±22.4	129±20.0	131±17.8

*Albumin Excretion Rate is median; all other values are mean ± the standard deviation

†Glomerular Filtration Rate corrected up to 1.73m^2.

Table 2

a. Effects of Enalapril and Losartan Relative to Placebo on Mesangial Fractional Volume Change from the Baseline to the 5-Year Biopsy

	Placebo (N=85)	Enalapril (N=86)	Losartan (N=85)
Mean mesangial fractional volume at baseline	0.187	0.201	0.189
Mean change in mesangial fractional volume from baseline	0.016	0.005	0.026
Difference in change *vs*. placebo			
Mean difference	0 (reference)	−0.011	0.010
p-value		0.16	0.17
Adjusted* difference in change *vs*. placebo			
Mean difference	0 (reference)	−0.006	0.008
p-value		0.38	0.26

b. Effects of Enalapril and Losartan Relative to Placebo on Albumin Excretion Rate and Glomerular Filtration Rate During the Five-year Follow-up and at the Five-year Biopsy

	Placebo (N=85)	Enalapril (N=86)	Losartan (N=85)
Albumin Excretion Rate (μg/min)			
Mean at baseline	6.4±6	6.3±5	6.5±7
Mean over 5 yrs of follow-up	6.5±6	7.7±16	10.6±18
Mean difference *vs.* placebo*	0 (reference)	1.3	4.0
p-value*		0.47	0.033
Mean at the five-year biopsy visit	5.3±4	6.9±8	14.0±36
Mean difference *vs.* placebo*	0 (reference)	1.0	8.0
p-value*		0.74	0.007
Glomerular Filtration Rate (ml/min/1.73m^2)			
Mean at baseline	126±22	129±20	131±18
Mean over 5 yrs of follow-up	125±18	124±18	125±17
Mean difference *vs.* placebo†	0 (reference)	−2.6	−2.4
p-value†		0.11	0.14
Mean at the five-year biopsy visit	120±22	123±20	121±21
Mean difference *vs.* placebo†	0 (reference)	0.4	1.5
p-value†		0.88	0.54

Adjusted for baseline mesangial fractional volume, blood pressure, glycosylated hemoglobin, glomerular filtration rate, albumin excretion rate, age at onset, diabetes duration and sex

*Adjusted for baseline albumin excretion rate

†Adjusted for baseline glomerular filtration rate

Table 3

Effects of Enalapril and Losartan Relative to Placebo on Retinopathy as Measured by the Odds Ration of 2-Step or More and 3-Step or More Progression During the Five-year Follow-up

			Odds ratio		
	N	**Events (%)**	**Adjusted***	**95% CI**	**p-value**
2-Step or more progression					
Placebo	74	28 (38)	Reference	Reference	Reference
Enalapril	77	19 (25)	0.35	0.14–0.85	0.02
Losartan	72	15 (21)	0.30	0.12–0.73	0.008
3-Step or more Progression					
Placebo	74	21 (28)	Reference	Reference	Reference
Enalapril	77	15 (19)	0.39	0.15–0.98	0.045
Losartan	72	9 (13)	0.21	0.07–0.61	0.004

*Adjusted for the baseline characteristics, center and the baseline retinopathy grade on the 15-point scale.

Table 4

Serious Adverse Events and Adverse Events by System and Treatment

	Placebo		Enalapril		Losartan	
Serious Adverse Events	**No. of Events**	**No. of Patients**	**No. of Events**	**No. of Patients**	**No. of Events**	**No. of Patients**
Biopsy related	0	0	3	3	0	0
Body as a whole	2	2	2	2	1	1
Cardiovascular system	2	2	1	1	5	3
Digestive system	5	3	10	5	13	11
Endocrine	0	0	2	2	1	1
Hemo/lymphatic system	0	0	1	1	1	1
Metabolic and nutritional	9	7	23*	7	7	7
Musculoskeletal system	7	4	1	1	9	7
Nervous system	3	3	0	0	0	0
Respiratory system	1	1	2	2	1	1
Skin and appendages	4	2	3	3	3	3
Special senses	0	0	0	0	1	1
Urogenital system	4	2	5	3	6	6
Adverse Events						
Biopsy related	3	3	8	8	3	3
Body as a whole	35	32	26	21	36	26
Cardiovascular system	23	21	24	19	42	32
Digestive system	90	54	104	57	106	52
Endocrine	3	3	6	6	9	8
Hemo/lymphatic system	6	6	16	12	9	9
Metabolic and nutritional†	133	44	125	37	137	48
Musculoskeletal system	63	41	79	49	89	48
Nervous system	23	17	34	24	36	23
Respiratory system‡	112	59	158	72	148	60
Skin and appendages	53	37	40	29	49	34
Special senses	45	32	27	25	42	26
Urogenital system	70	36	74	34	88	41

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[*] 12 episodes of hyperglcemia and ketoacidosis occurred in a single patient

[†] Transient hyperkalemia occurred in 1 enalapril patient and transient serum creatinine elevation in 1 losartan patient, neither requiring discontinuation of study medication

[‡] Chronic cough occurred in 12 enalapril, 6 losartan, and 2 placebo patients. Two enalapril patients discontinued enalapril for this reason.