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CYP2C9 Genotype and Pharmacodynamic Responses to Losartan in Patients with Primary and Secondary Kidney Diseases

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Abstract

Losartan is used for anti-proteinuric as well as blood pressure effects in chronic kidney disease (CKD). It is metabolized by cytochrome P450 2C9 to active E-3174. Single nucleotide polymorphisms in *CYP2C9* that reduce catalytic activity could reduce clinical benefits. The study aims were to determine whether *CYP2C9* variant alleles (**2* and **3*) altered urinary protein excretion, glomerular filtration rate, and blood pressure in Caucasians prescribed losartan. Differences between baseline and six-month follow-up outcomes were compared by *CYP2C9* genotypes in 59 patients using unpaired T-test or Mann Whitney U test. Primary renal disease patients had a trend toward less favorable antiproteinuric response (−31.7±156 vs −125±323%; p=0.123) when carrying variant alleles. Patients with secondary renal diseases had less favorable diastolic blood pressure (9.8±16.0 mm Hg vs −3.2±10.6 mm Hg; p=0.043) and systolic blood pressure (16.2±27.1 mm Hg vs −5.5±17.5 mm Hg; p=0.044) with *CYP2C9* variants. Preliminary results suggest a possible influence of *CYP2C9* genotype on proteinuria and blood pressure in Caucasian CKD patients treated with losartan.

Keywords

Cytochrome P450 2C9; losartan; chronic kidney disease; proteinuria; blood pressure

Introduction

The primary strategies to slow or prevent progression of chronic kidney disease (CKD) include reduction in blood pressure and control of urinary protein excretion.[1] Proteinuria, in addition to being a risk factor for CKD progression also predicts cardiovascular outcomes. [2,3] Timely reduction of proteinuria, i.e. within the first 6–12 months of treatment is deemed crucial. [3] Treatment strategies for controlling proteinuria as well as reducing blood pressure in CKD include angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors. [4]

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Patient-related factors that may predict the likelihood of pharmacodynamic outcomes would be helpful for individualizing treatment strategies and possibly improving kidney outcomes.

Losartan is an angiotensin receptor blocker metabolized by cytochrome P450 2C9 (CYP2C9). Other CYP2C9 substrates include *S*-warfarin, phenytoin, torsemide, glipizide, nonsteroidal anti-inflammatory agents, and irbesartan. Point mutations or single nucleotide polymorphisms in the *CYP2C9* gene have been identified. The common coding mutations in *CYP2C9* are *CYP2C9*2* (Arg144Cys), and *CYP2C9*3* (Ile359Leu). [5,6] Approximately two-thirds of the Caucasian population express the wild-type genotype (*CYP2C9*1/*1*), one-third express either the **1/*2* or **1/*3* genotype, and less than 2.5% of individuals express the **2 /*2*, **2/*3*, and **3/*3* genotypes. [6] The frequency of the variant alleles (**2* and **3*) however, are lower (< 5%) in African-American and Asian populations, with greater than 95% of these individuals expressing the wild-type genotype. [6] Both *in vitro* and *in vivo* investigations suggest that *CYP2C9*2* and/or *CYP2C9*3* alleles result in decreased catalytic activity for losartan when compared to homozygosity for the **1* allele. [7,8] Several additional rare coding alleles of *CYP2C9* have been identified in Caucasians, although their drug metabolizing phenotypes have not yet been adequately examined *in vivo*. [9,10]

Given the knowledge concerning *CYP2C9* genotype and warfarin [11,12], we were interested in evaluating the effects of *CYP2C9* genotype on outcomes to losartan therapy in CKD patients. Unlike warfarin which is metabolized to the minimally or inactive alcohol and hydroxyl metabolites, losartan has a highly active 5-carboxylic acid metabolite, E-3174. [13] A reduced CYP2C9 activity phenotype for losartan as described by the **2* and **3* genetic variants would reduce the formation of E-3174, possibly shifting losartan's metabolism to inactive metabolites via other oxidative routes or glucuronidation. Individuals with the **2* or **3* variant alleles could have attenuated clinical responses. Our pilot study was designed to evaluate the effect of *CYP2C9* genotype on clinical responses to losartan therapy in Caucasian individuals with CKD due to primary and secondary etiologies. Specifically, we were interested in determining pharmacodynamic changes in urinary protein excretion, glomerular filtration rate (eGFR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with primary and secondary kidney diseases according to the presence or absence of variant *CYP2C9 *2* and/or **3* alleles.

Materials and Methods

Subjects and Clinical Data

The study was approved by the University Investigational Review Board (IRB) and complied with Health Insurance Portability and Accountability Act (HIPPA) regulations and the Declaration of Helsinki. Fifty-nine Caucasian subjects with CKD and prescribed losartan were targeted for enrollment from the outpatient Nephrology clinic. Patients were subsequently classified as having a primary renal disease (e.g. glomerulonephritis) or a secondary renal disease (e.g. type II diabetes mellitus, and/or hypertension). Additional inclusion criteria for study participation were 1) proteinuria, with or without renal function decline as assessed by eGFR [14], 2) documented date of losartan therapy initiation and data on drug dosing, 3) documented laboratory data, including urinary protein excretion and serum creatinine, and 4) documented blood pressure recordings from 30 days prior to the start of losartan initiation through six months of follow-up. Both laboratory and blood pressure recordings were required to be available from the 30 days prior to losartan commencement and six month time period. Exclusion criteria included a history of significant non-compliance with prescribed medications, receiving hemodialysis or peritoneal dialysis for Stage 5 CKD, and receiving potential CYP2C9 inducers or inhibitors.

Medical records were reviewed for demographics, blood pressure measurements, and laboratory parameters of interest (serum creatinine, urinary protein excretion or a urinary protein to creatinine ratio, eGFR) from losartan initiation and until 6 months of follow-up. Blood pressure measurements in the clinic are routinely performed in a sitting position after having the patient rest for five minutes. The measurement is repeated at least once for verification of the result. Subject medications were reviewed and concomitant medications with an indication for hypertension and diuresis were recorded. Medication lists were also reviewed to identify any potential CYP2C9-mediated interactions (i.e. drugs that inhibit or induce CYP2C9). Potential CYP2C9 inhibitors that were excluded were amiodarone, fluconazole, fluvoxamine, gemfibrozil, metronidazole, phenytoin, sulfamethoxazole, tamoxifen, valproic acid, sertraline, isoniazid, oral contraceptives, and zafirlukast. Potential CYP2C9 inducers that were excluded were rifampin, St John's Wort, and barbiturates.

Evaluation of Single Nucleotide Polymorphisms

A 5 mL whole blood sample was collected into an EDTA containing vacutainer and genomic DNA was isolated using a Flexigene Qiagen kit (Qiagen, Inc., Valencia, CA, USA) Pyrosequencing assays were used to determine the presence of the *CYP2C9 *1* (wild-type), **2* and **3* alleles as described by Limdi et al[11]. Briefly, amplification reactions of genomic DNA were generated for pyrosequencing by using 10–30 ng DNA in 40 μl volumes. Biotinylated forward primers and standard reverse primers (Eurogentec, San Diego, CA) in the amount of 0.2 pm/μl each were added and combined with final concentrations of 2mM $MgCl_2$, 0.5 mM dNTPs, 1× PCR buffer and 1 unit AmpliTaq Gold (Applied Biosystems, Foster City, CA). The reactions were cycled with an initial denaturation of 95°C for 8 min followed by 45 cycles of 95°C for 15 sec, 56°C for 30 sec, 72°C for 15 sec and final extension for 5 min at 72°C on a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA). The primers for amplifcation of *CYP2C9*2* were 5'-BT-AAACAGAGACTTACAGAGCTC-3' (BT: biotinylated) and 5'-CTAACAACCAGACTCATAATG-3', while the sequencing primer was 5'-GGGCTTCCTCTTGAAC-3'. For the *CYP2C9*3* allele, the forward and reverse amplification primers were 5'-BT-TGCACGAGGTCCAGAGAT-3' and 5'-GATACTATGAATTTGGGACTTC-3', while the sequencing primer was 5'-GCTGGTGGGGAGAAG-3'.

The biotinylated reaction products were immobilized on 3 ul (10 ug/ul) Streptavidin-Sepharose High Performance beads (Amersham Biosciences, Piscataway, NJ) in the presence of a 1× final concentration of Binding Buffer (Biotage, Foxboro, MA) by mixing for 10 min at room temperature. Biotinylated DNA strand separation was accomplished by using the Vacuum Prep Tool to capture beads and process through washes of Denaturation Solution and 1× Washing Buffer (Biotage). A PSQ Low Sequencing Plate was prepared with 1× Annealing Buffer (Biotage) and 20 pmoles of the appropriate sequencing primer in each well. The captured beads containing biotinylated DNA strands were dispersed into the wells and annealing with sequencing primer was allowed to proceed for 5 min at 95°C. The plate was cooled for 10 min at room temperature and then placed into the PSQ 96 MA Pyrosequencer (Biotage) along with a dispensing cartridge containing Enzyme Mixture, Substrate Mixture and dNTPs from a PyroGold Reagents Kit. Sequencing was performed and allele determination was performed with the Pyrosequencing Software.

Statistics/Planned Analyses

As previous data pertaining to *CYP2C9* genotype and pharmacodynamic responses was not available from the CKD population, *a priori* statistics were not conducted. Based on a review of several published studies that reported *CYP2C9* genotype frequencies, it was assumed that

our CKD cohort of fifty-nine Caucasian patients would be sufficient for an initial evaluation on pharmacodynamic responses to losartan therapy. [6,15]

Since kidney function as defined by urinary protein quantification and/or eGFR is/are commonly used in assessing the clinical benefits of drugs on the kidneys, we were interested in the association between the presence or absence of a variant *CYP2C9* allele and changes in urinary protein excretion, eGFR, and serum creatinine. Additionally, since blood pressure can effect kidney disease progression and losartan can reduce blood pressure, changes in systolic and diastolic blood pressures according to CYP2C9 genotype were also evaluated. The analyses by kidney disease groupings were included since variability in the response to therapies can be influenced by the type of the disease itself and this grouping system would increase the homogeneity of the evaluated populations. [16,17] Differences between baseline and six-month follow-up measures (delta values) in clinical variables (urinary protein excretion, eGFR, serum creatinine, SBP, and DBP) were assessed according to the presence or absence of a *CYP2C9* allelic variant by either a two-tailed t-test or nonparametric equivalent (Mann Whiney U test). Fisher's Exact Test was used to compare frequencies of prescribed diuretics, angiotensin converting enzyme inhibitors, and "other" medications between groups. All tests were two-tailed with an alpha value set at <0.05. Statistical analyses were conducted using Instat 3.05 (San Diego, CA).

Results

Demographics (mean ± SD) for the fifty-nine patients included age (53 ± 18 yrs), weight (84.0 ± 22 kg), and 64% female. Sixty-one percent of patients (n = 36) were classified as having a primary renal disease (e.g. glomerulonephritis) and the remaining 39% (n = 23) had secondary causes of renal disease (e.g. type II diabetes mellitus, hypertension). The mean ±SD baseline losartan dosage in the primary (59±31 mg/day) and secondary (60±26 mg/day) renal disease groups were similar. For patients included in the secondary renal disease grouping, 25% and 78%, respectively had a diagnosis of type II diabetes mellitus and hypertension (with overlap in one patient). Similar frequencies of diuretic, angiotensin converting enzyme inhibitor and "other" blood pressure agents were prescribed at baseline and follow-up within and between each chronic kidney disease category.

The frequencies for the *CYP2C9* allelic determinations at amino acid positions 144 (Arg to Cys) and 359 (Ile to Leu) and subsequent genotypes are shown in Table 1. We observed an allelic frequency of 5% for the **2 allele* and a frequency of 6% for the **3* allele in our sample population. As shown in Table 1, the combined frequency of having a heterozygous genotype for one of the variant **2* or **3* alleles was 20%, while the frequency of having a homozygous or heterozygous mutant genotype (**2/*2*, **2/*3*, or **3/*3*) was 2% and in this study was comprised of only the *2/*3 genotype. This data was in agreement with Hardy Weinberg equilibrium.

Baseline (pre-losartan) values for the clinical outcome parameters were generally similar within renal disease groups. (Table 2) There was, however, a trend in the primary renal disease grouping to have greater daily urinary protein excretion at baseline (p=0.07) in wildtype patients. Since this trend was recognized, the percentage change in urinary protein excretion was also calculated and compared. Differences in body weight trended toward higher values in variant groung of the primary renal disease category (96.8±13.7 kg) than the wildtype group (81.3±20.6 kg) p=0.05. No differences in baseline measures between wildtype and variant groups were appreciated within the secondary kidney disease group. Baseline systolic (156mm Hg) and diastolic (93mm Hg) blood pressure values for the *2/*3 subject (in the primary renal disease group) were higher than the mean values in the variant group as a whole. Baseline Scr

(2.0mg/dL) was within the range for the variant group and UP (160mg/day) was low for the variant group for the lone *2/*3 subject.

The changes in clinical parameters from baseline to follow-up were computed (denoted as delta values) and compared in each kidney disease group (primary and secondary) according to the presence or absence of variant *CYP2C9* alleles.(Table 3) In the primary kidney disease, e.g. glomerulonephritis, group there were no statistically significant differences in the clinical parameter changes from baseline to follow-up. However, the delta (−1278±4277 vs −458±1651 mg/day, p=0.14) and % delta (−125±323 vs −31.7±156%, p=0.12) urinary protein excretion exhibited a trend toward more improvement in the wildtype vs variant genotype groups, respectively. In the secondary renal disease, e.g. Type II diabetes mellitus and hypertension, group there was a statistically significant difference in the SBP (16.2±27.1 mm Hg vs −5.5 ±17.5 mm Hg; p=0.04) in the variant vs wildtype groups. A similar trend in diastolic blood pressure was appreciated (9.8±16.0 mm Hg vs −3.2±10.6 mm Hg; p=0.05) in the variant versus wildtype groups, respectively. The change in systolic (−23mm Hg) and diastolic (−16mm Hg) blood pressure values for the *2/*3 subject were greater than the mean values in the variant group. The change in Scr (−0.5mg/dL) was within the range for the variant group and UP (+76mg/day) was increased for the variant group for the lone *2/*3 subject.

Discussion

Our results generally supported the *a priori* hypothesis of this study that CKD patients with the *CYP2C9 *2* and *3* allelic variants would have associated attenuated clinical effects of losartan as opposed to patients classified as wildtype. In order to provide homogeneity to our population, we assessed *CYP2C9* genotype and pharmacodynamic outcomes to losartan according to primary and secondary kidney disease grouping. In the primary kidney disease group, there was a trend toward more improvement in urinary protein excretion in the presence of the *1/*1 genotype versus genotypes comprising the *2* and/or *3* alleles. No trends in improvements in blood pressure or eGFR were suggested. These results are encouraging for patients with glomerulonephritis, who often have moderate to significant proteinuria with minimal to mild baseline alterations in blood pressure. However, in the patients with secondary kidney diseases (e.g. Type II diabetes mellitus and hypertension), there were clinically significant reductions in DBP and SBP in wildtype patients and actual increases in blood pressure in the *2* and *3* variant group. In secondary kidney disease, improvements in eGFR and urinary protein excretion were not appreciated. This differential improvement on blood pressure in a group of CKD patients who often have moderate to significant hypertension, with minimal proteinuria reflects some beneficial targeting of responses.

The results of this study are important for patients with primary kidney diseases where disease-specific treatments are lacking. A key treatment strategy is reduction in proteinuria as this has been suggested to reduce eGFR decline. [1] As suggested by our results, variants in *CYP2C9* may be at least partially responsible for less than optimal antiproteinuric effects in patients receiving losartan therapy. Although the results are encouraging, evaluation of additional patients with primary kidney diseases will be required to validate statistical significance between wildtype vs *CYP2C9* variant genotypes and proteinuria reduction. As dosages of losartan were similar in the primary kidney disease patients with and without the *CYP2C9* variants, dosage-related effects are less likely. However, as patient weights were higher in the variant group and we did not measure plasma concentrations, it is conceivable that the achieved losartan plasma concentrations may have been lower in the variant group, possibly reducing the probability of a response. Since the prescription frequencies for angiotensin converting enzyme inhibitors, diuretics, and “other” blood pressure medication prescriptions were similar between genotype groups, these medications were not likely contributory in differential responses. As an adequate anti-proteinuric response to losartan therapy is of paramount

importance in the first 6–12 months of therapy, future determination of *CYP2C9* genotype, prior to prescribing medications, may be useful to help predict which patients are more likely to have the greatest impact on urinary protein reduction.

Regarding the clinical outcomes in patients with secondary kidney diseases, our results showed reductions in SBP and DBP in patients in the *CYP2C9* wildtype group as compared to the variant group. Secondary kidney diseases are defined by diseases that affect the kidney as a complication of their long-duration and poor control; e.g. Type II diabetes mellitus and hypertension. Since the frequencies of angiotensin converting enzyme inhibitors, diuretics, and "other" blood pressure medication usage were similar between the variant and wildtype groups, these medications were likely not related to any genotype differences. Our finding of favorable blood pressure effects is significant as in both type II diabetes mellitus and hypertension, blood pressure control is of paramount importance in preventing and/or slowing chronic kidney disease progression to end stage kidney disease. A previous study in a homogeneous population of Type I diabetic patients with nephropathy demonstrated a significant reduction in SBP ($p = 0.001$) after four months of losartan therapy in patients who did not carry the **3* variant alleles as opposed to those who were carriers. [16] The effects of the **2* variant on blood pressure were not reported and in fact, the authors grouped the **2* variant in with the wildtype patients for their analysis. While the authors provided no rationale for their decision to group in the manner that they did, it is curious given the previously published study results by Lee, et al. that described alterations in E-3174 formation clearance in both the **2* and **3* allelic variants. [18] A previous study that evaluated the association between another CYP2C9 substrate (e.g. tolbutamide) and genotype reported prolonged half-life in subjects whose genotypes exhibited the **3* allele, but not the **2* allele. [19] Hence, although grouping the **2* allele in with the wildtype vs the **3* group would be justified for tolbutamide analysis, it unclear at this point that this is the correct strategy for losartan analyses. However, Babaoglu et al, reported an increase in losartan to E3174 in the CYP2C9 *1/*3 group that was statistically greater than the *1/*2 or *1/*1 groups. [20] The study by Babaoglu (losartan) [20] and Kirchheiner (tolbutamide) [19] are similar in that they both show a moderate effect of *2 and major effect of *3 on outcome. The lack of a statistically significant effect in the Babaoglu study is likely secondary to a statistical phenomenon. e.g. while there were similar number of patients in the *1/*3 (n=12) and *1/*2 (n=10) groups, a larger effect (*3) would result in a significant value with smaller patient numbers than would a moderate effect (*2). Caution, should thus be exercised when grouping patients by genotype for analyses across different substrates for drug metabolizing enzymes.

Regarding blood pressure effects, the clinical significance of the *CYP2C9 *2* and **3* polymorphisms in patients prescribed another CYP2C9 substrate and angiotensin receptor blocker (irbesartan) has also been reported. [10] Irbesartan, contrary to losartan requires CYP2C9 for conversion to an inactive metabolite. In this study, carriers of the **2* variant *CYP2C9* allele experienced almost twice the reduction in both systolic and diastolic blood pressure compared to individuals with the wild-type genotype. [10] However, these investigators did not have sufficient patients with the **3* allelic variant to enable evaluation of the contribution of this variant on blood pressure responses. The results of the study suggest that the **2* allelic variant subjects had reduced catalytic activity of CYP2C9 as compared to wildtypes, resulting in an enhanced blood pressure lowering response.

While we did not perform pharmacokinetic assessments in our study, two previous publications addressed the association between *CYP2C9* genotype and losartan pharmacokinetics in healthy subjects. [7,8,18] Using an *in vitro* approach, Yasar et al. found that in human liver microsomes from a healthy liver bank, the rates of formation for losartan's active metabolite (E-3174) were significantly lower and the intrinsic clearance of losartan was reduced (mainly explained by a lower V_{max}) in carriers of at least one *CYP2C9* variant allele (**2* or **3*) as compared to

microsomes representing homozygosity for the wild-type genotype. [7] An *in vivo* by the same group showed a reduction in the maximum E-3174 plasma concentration in individuals with the *CYP2C9 *1/*3* and *2/*3* genotypes vs wildtypes and even lower E-3174 plasma concentration in the *CYP2C9 *3/*3* genotype. [8] The effects from the *1/*2 and *2/*2 genotypes were not able to be appropriately evaluated secondary to these subject groups being comprised of less than five patients each. A small pharmacokinetics study by Lee et al[18] reported no pharmacokinetic differences between *CYP2C9* wildtypes and **1/*2* and **1/*3* in healthy volunteers receiving losartan. However, the formation clearance of E-3174 by the *CYP2C9 *1/*2* genotypes was reduced as compared to the wildtype, with no differences appreciated in subjects with the **1/*3* genotype. Unlike the previous study, each genotype group was comprised of five patients, allowing appropriate statistical testing. No significant changes in blood pressures (SBP or DBP) between genotype groups were reported. [18] Effects on the parent to metabolite ratio supporting reduced formation of the E-3174 metabolite has also been reported for the *CYP2C9 *1/*3* vs wildtype homozygotes in healthy Turkish and Japanese subjects. [20,21] Based on the results supporting a role for both *CYP2C9 *2* and **3* variants in modifying the formation clearance of E-3174 we felt that inclusion of our *2 patients in the variant versus wildtype grouping was appropriate.

While our study is encouraging for clinicians who care for patients with primary and secondary kidney diseases, there were several limitations that require disclosure. The study itself was designed to evaluate trends in the effects of *CYP2C9* allelic variants vs wildtype homozygotes on clinical outcomes to losartan therapy. Hence by design, the study was limited in terms of statistical power. We also did not assess pharmacokinetics since other studies that evaluated losartan did not report significant changes in traditional pharmacokinetic parameters (area under the curve, half-life, and oral clearance) based on genotype. However, the formation clearance of E-3174 was reported to be reduced in the *CYP2C9* variants evaluated, yet one of these studies reported improvements in blood pressure as a clinical measure. Hence, there may not be a direct and predictable relationship between traditional pharmacokinetic variables and pharmacodynamic measures such as blood pressure and urinary protein excretion with losartan. A role of variations in additional rare *CYP2C9* alleles and *ACE* insertion/deletion genotype on clinical response to losartan therapy cannot be ruled-out as these genes were not assessed. Several newly recognized rare *CYP2C9* alleles have been discovered and *in vitro* studies suggest reduced catalytic activity toward tolbutamide (another CYP2C9 substrate). [9,22] However, many of these alleles are found in racial groups other than Caucasians and this makes it unlikely that they would contribute to the results of this study. The existing published data does not support a role of *ACE* insertion/deletion genotype on responses to losartan therapy. [23–25]

Conclusions

The results of this study demonstrated that there was a trend in reduction of urinary protein excretion in patients with primary kidney disease (comprised of glomerular diseases) receiving losartan when the *CYP2C9 *2* or **3* variants were absent. Patients with secondary kidney diseases tended to have significant reductions in DBP and SBP with losartan therapy when they were classified as *CYP2C9* wildtype vs *CYP2C9* variants. These preliminary results support future studies in larger numbers of patients with CKD to fully understand the role of *CYP2C9* genotype on clinical outcomes such as proteinuria and blood pressure in losartan-treated patients.

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Table 1

CYP2C9 Allelic and Genotype Distributions

Allelic Distributions n = 59 × 2=118		
	N	**Frequency**
*CYP2C9*1*	105	0.89
*CYP2C9*2*	6	0.05
*CYP2C9*3*	7	0.06
Genotype Distributions n = 59		
Genotype	N	Frequency
*CYP2C9*1/*1*	46	0.78
*CYP2C9*1/*2*	6	0.10
*CYP2C9*1/*3*	6	0.10
*CYP2C9*2/*3*	1	0.02

Table 2

Baseline Demographic and Clinical Measures by Disease Classification

	Primary Renal Disease		Secondary Renal Disease	
	WT (n=29)	**Variant (n = 7)**	**WT (n=18)**	**Variant (n=5)**
Age (yrs)	43.5 (17.8)	49.9 (15.7)	64.2 (14.1)	67.4 (8.05)
Weight (kg)	83.1 (20.6)	96.8 (13.7)+	89.7 (24.6)	71.7 (23.4)
Gender (%female)	65%	86%	50%	80%
Losartan dose (mg/day)	56 (29)	67 (38)	63 (29)	50 (0)
SBP (mm Hg)	131 (20.5)	136 (12.8)	141 (17.4)	128 (13.2)
DBP (mm Hg)	75.3 (9.77)	82.5 (6.57)	73.5 (13.0)	67.4 (14.8)
SCr (mg/dL)	1.63 (0.81)	1.57 (0.69)	2.03 (0.71)	2.04 (1.20)
eGFR (mL/min/1.73m^2)	41.6 (22.8)	36.2 (15.9)	30.2 (14.4)	29.8 (19.4)
UP (mg/day)	2632 (4710)	1365 (3061)*	2051 (2694)	340 (232)

Data presented as mean (standard deviation)

+ p value 0.05,

* p value 0.07

DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate via Modification of Diet in Renal Disease equation [14], SBP – systolic blood pressure; SCr – serum creatinine, UP – urinary protein to creatinine ratio, WT = wildtype Variant = presence of a **2* and/or **3* allele

Table 3

Changes in Clinical Parameters by Renal Disease from Baseline to Follow-up

Primary Renal Disease			
	WT (n = 29)	**Variant (n = 7)**	**P value**
Δ SBP (mm Hg)	−3.6 (26.3)	−1.7 (14.2)	0.863
Δ DBP (mm Hg)	−0.2 (13.8)	−1.2 (13.8)	0.879
Δ SCr (mg/dL)	0.2 (0.6)	0.2 (0.8)	0.606
Δ eGFR (mL/min/1.73m^2)	6.5 (13.6)	8.5 (14.5)	0.734
Δ UP (mg/day)	−1278 (4277)	−458 (1651)	0.139
Δ % UP	−125 (323)	−31.7 (156)	0.123
Δ Dose (mg)	9.8 (22.9)	0 (47.4)	0.540
Secondary Renal Disease			
	WT (n = 18)	Variant (n = 5)	P value
Δ SBP (mm Hg)	−5.5 (17.5)	16.2 (27.1)	0.044
Δ DBP (mm Hg)	−3.2 (10.6)	9.8 (16.0)	0.043
Δ SCr (mg/dL)	−0.02 (0.5)	−0.3 (0.9)	0.530
Δ eGFR (mL/min/1.73m^2)	2.7 (8.7)	5.2 (11.6)	0.493
Δ UP (mg/day)	−1161 (2192)	−5.7 (210)	0.611
Δ %UP	−67.3 (121)	1.4 (106)	0.521
Δ Dose (mg)	15.3 (24.5)	20.0 (27.4)	0.793

Data are presented as mean (standard deviation)

DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate via Modification of Diet in Renal Disease equation [14], SBP – systolic blood pressure; SCr – serum creatinine, UP – urinary protein to creatinine ratio, WT = wild type Variant = presence of a *2 and/or *3 allele