Impact of Angiotensin-Converting Enzyme Gene Polymorphism on Proteinuria and Arterial Hypertension

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A B S T R A C T

Proteinuria is the hallmark of renal disease. In essential hypertension the onset of de novo proteinuria is associated with faster rate of progression of disase. Some authors have suggested that the DD genotype of the angiotensin-converting enzyme (ACE) gene would be an adverse renal prognosis factor. It may also have different effects on the reduction of proteinuria by ACE inhibitors in patients with proteinuria. Observations on the association between the ACE gene polymorphism and hypertension have been inconsistent, which might be due to ethnic and geographical variations. In this study was to investigated the relationship between ACE gene polymorphism and antiproteinuric effect of ACE inhibitors (ramipril) and to evaluate the possible association between I/D polymorphism and hypertension. We recruited 66 hypertensive patients (male 42, female 24) with overt proteinuria (urinary protein excretion over 500 mg/day). Patients were classified into three groups in accordance with ACE genotypes (17 DD; 35 ID; 14 II). They were treated with ramipril and prospectively followed up for one year. Various clinical parameters including age, body mass index (BMI), 24-h urine protein, creatinine, creatinine clearance (Ccr), systolic and diastolic blood pressure (SBP and DBP), mean arterial pressure (MAP) were measured in the pre- and post-treatment periods. The ACE gene insertion/deletion(I/D) polymorphisms in intron 16 were determined by PCR. Results showed that there were no significant differences in the clinical parameters such as age, gender, serum creatinine, Ccr, SBP, DBP, MAP, and daily urinary excretion of protein among three groups (P>0.05). ID genotype patients were found to have lower BMI (p=0.031). ACE inhibition significantly reduced proteinuria in all genotype groups (p<0.05). The percentage reductions of 24-h urinary excretion of protein were significantly different between the genotype groups (p=0.042) and for DD genotype were significantly greater than in ID (79.2± 28.9% vs 49.2±64.8%, P=0.015). The slope of SBP was the main factor related to the slope of the percentage reduction of proteinuria, however, a significant negative correlation coefficient between these parameters was found (rs=−0.382, p= 0.002). We failed to find significant difference in outcomes of treatments with ACE inhibitor between male and female according the I/D polymorphism of the ACE gene. D allele in the ACE genotype could be a useful genetic marker with important clinical, therapeutic and prognostic implications in recognizing patients with proteinuria that are at greater risk of renal damage.

Key words: ACE-genotype, ACE inhibitors, antiproteinuric effect, arterial hypertension, proteinuria

Introduction

Although historically proteinuria has been considered as a simply a surrogate marker of the severity of underlying glomerular damage, clinical and experimental data reported during more than a decade of intensive investigation indicate that proteinuria is an independent risk factor and plays an important role in the pathogenesis of the progression of renal disease[1–3].

Recent evidence suggests that proteinuria can directly cause renal damage through lysosomal injury, growth factor induced tubular fibrosis and transcriptase genes

which trigger vasoactive and inflammatory renal damage[1–6].

The renin angiotensin system which releases angiotensin II, a most powerful vasoconstrictor and mediator of mesangial cell proliferation and matrix expansion, has been associated with progressive renal injury.

Angiotensin II, a central component of renin-angiotensin system (RAS), acts as a strong promoter that dramatically potentiates the ability of transforming growth factor β (TGF-β) to induce epithelial to mesenchimal transition (EMT) in tubular epithelial cells[7].

The relationship between proteinuria and poor prognosis in renal disease, as well as the link between renoprotection and protein traffic reduction by ACE inhibitors have been firmly established[8,9]. However, the antiproteinuric effect of ACE inhibitors on proteinuria is variable and the percentage of reducing proteinuria is in the range of 20–80% in a variety of renal disease and may be related to the type of the patient´s ACE genotype[10].

The ACE gen is located on the log arm of chromosome 17. Insertion or deletion of any of the 287 base pair fragments in the 16th intron of the ACE gene may determine its genotype.

These genotypes are used to characterize the polymorphism as DD, ID and II type[11].

It has been reported that each of these genotypes appeared to be a major determinant of plasma and tissue activities. Individuals with DD genotype have the greatest and those with II genotype the least ACE concentrations[11–13]. However, because the ACE I/D polymorphism is intronic, the mechanism of ACE overexpression in subjects with DD genotype is unclear; it is possible that this relationship is the result of tight linkage to another locus involved in the regulation of ACE gene expression[14].

Observations on the association between ACE polymorphism and essential hypertension have been inconsistent, which might be due to ethnic and geographical variations. No correlation has been found between plasma ACE levels and hypertension or between ACE DD genotype and hypertension[15–16]. A study of Zee et al.[17] showed a positive association between ACE polymorphism and hypertension, with a higher frequency of the I allele in hypertensive patients with a family history of hypertension, compared to normotensive controls.

Numerous studies have addressed the role of RAS gene polymorphisms in the development and progression of renal disease[18–27]. There is increasing evidence that the progression of diabetic nephropathy is more rapid in patients with DD genotype. Yoshida et al.[19] for example, report an OR for loss of renal function in diabetics with a DD genotype of 3.42 and consider ACE polymorphism to be a genetic marker for the progression to chronic renal failure in diabetics. They also showed a similar association in IgA nephropathy[20]. Administration of ACE inhibitors has been shown to lead to a significant decrease of proteinuria in chronic renal diseases, including nondiabetic renal diseases. The ACE genotype appears to pre-

dict the therapeutic efficacy of ACE inhibition of proteinuria; II genotype patients are resistant to this renoprotective therapy, whereas DD genotype patients have a significant reduction in the degree of proteinuria[19,20,25–28]. However there are also contradictory observation[21–24]. There is still no consensus on using ACE genotyping in the setting of diabetic and nondiabetic nephropathy, because reported studies to date are on limited size patient groups, and large prospective studies would be necessary to assess the impact of the ACE polymorphism on the response to renoprotective treatment.

In the present study we investigated the antiproteinuric effect of ACE inhibitors (ramipril) in relation to ACE I/D polymorphism and evaluated the possible association between I/D polymorphism and hypertension in an observational one year follow-up study of patients with overt proteinuria and hypertension.

Patients and Methods

Sixty-six patients with overt proteinuria (mean value of the urinary protein excretion over 500 mg/day in the baseline status) were recruited from the Department of Nephrology, Dubrava University Hospital, Zagreb, Croatia from 2007 to 2009. They were classified into three groups in accordance with their ACE genotypes (17 DD; 35 ID; 14 II). They were prospectively followed up for 12 months. Before enrollment in the study, all the patients signed informed consent forms. Previously used ACE inhibitors were withdrawn for at least one month, non-steroidal antiinflammatory drugs, corticosteroids or immunosuppressive drugs for et least six months before the study. Baseline proteinuria were measured using a 24-h urine collections. The mean values of the to measurements were taken as the baseline data. Blood pressure was measured following ESH/ECS guidlines using mercury sphyngomanometer. Mean arterial pressure (MAP) was calculated as the sum of two-thirds of the diastolic and one-third of the systolic blood pressure. A diagnosis of hypertension was made if the patient had two consecutive blood pressure readings >140/90 or if MAP was above 105 mmHg. Various clinical parameters including age, gender, body mass index (BMI), 24-h urinary excretion of sodium and protein, serum creatinine, creatinine clearance (Ccr) and MAP were measured in the pre- and post-treatment period (12 months) with standard laboratory techniques. During the one year study period patients were treated with ramipril (5 mg/day). The dose was doubled if blood pressure after 1 month was ≥140/90 mmHg. If the blood presure after 3 months was still ≥ 140/90 mmHg, another antihypertensive drug was added (indapamidum, calcium channel blockers, beta-blockers, furosemid). Dietary intake for sodium and patient medication were not changed during the study period. All patients with normal coagulation factors, whose ultrasound kidney size was greater than 9 cm and the thickness of renal parenchyma greater than 10 mm, after a good control of blood pressure underwent percutaneous renal biopsy. The main indications for renal biopsy were nephro-

tic syndrome, hematuria and/or non-nephrotic proteinuria and renal failure. Biopsy was done using continuous ultrasound guidance and a 16-gauge biopsy needle (Tru-Cut) in an automated gun (Biopty Bard, USA). All biopsies were processed for light, immunofluorescence and electron microscopy.

Genotyping of ACE I/D polymorphism

For determination of I/D polymorphism of ACE gene, genomic DNA was extracted from peripheral blood leukocytes. A 287-bp I/D polymorphism in the intron 16 of the ACE gene was examined by polymerase chain reaction (PCR). PCR was performed according to the method of Fernandez-Llama et al.[29] The sequence of the sense and the antisense primers were 5´-CTGGAGACCACT CCCATCCTTTCT-3´ and

5´-GATGTGGCCATCACATTCGTCAGAT-3' respectively. PCR was performed in a final volume of 25 µL that contained 200 ng of genomic DNA, 1.0 µm of each primer, 1.5 mmol/L $MgCl_2$, 50 mmol/L KCl, 0.25 mmol/L dNTP, 10 mmol/L Tris-HCl (PH 8.4), and 1 U Taq DNA polymerase. Amplification was carried out for 35 cycles with steps of denaturation at 94 °C for 2 min, annealing at 58 °C for 15 s, and extension at 72 °C for 30 s. The PCR products were subjected to electrophoresis in 1.5% agarose gels and stained by ethidium bromide for visualization. To avoid mistyping of the ID genotype as DD, we confirmed the accuracy of the genotyping results using an insertion-specific primer pair (5'-TGG GAC CAC AGC GCC CGC CAC TAC-3' i 5'-TCG CCA GCC CTC CCA TGC CCA TAA-3') according to the method of Shanmugam et al.[30]

Statistical analysis

All data are presented as X±SD except urinary protein. A one-way ANOVA test was used to analyse between group and within group differences. A paired Student´s t-test was used to test for differences between the baseline values and those after ACE inhibition therapy.

Variables with skewed distribution (e.g. creatinine) were logarithmically transformed and then tested by Student´s t-test. The non-parametric Mann-Whitney U test were used to analyze variable with skewed distributions in spite of logarithmic transformations (e.g. urinary protein excretion). Differences in frequency were determined by χ^2 analysis with the Yates correction. The correlation analysis was performed and the correlation coefficients were calculated. Simple linear regression analysis was applied when appropriate. Statistical significance was assumed at a 5% level. Statistical analysis was performed using SPSS 15.0 for Windows, computer software.

Results

The 66 participants included 42 men (63.6%) and 24 (36.4%) women. The frequency of ACE genotypes was 26%:53%:21%, respectively D allele frequency was 79%. The distribution of ACE genotypes observed were in agreement with the Hardy-Weinberg proportion and were consistent with other published reports.

Clinical and biochemical baseline characteristics of patients before initiating ACE inhibitors are shown in Table 1. There were no significant differences in the clinical parameters such as age, gender, systolic (SBP) and diastolic blood pressure (DBP), MAP, serum creatinine and creatinine clearance (Ccr) among three groups (p>0.005, Table 1). However, the median values of baseline daily urinary excretion of protein for DD genotype was greater than that of ID and II genotypes but statistically nonsignificant. ID genotype patients were found to have lower BMI (p=0.031). The majority of patients had glomerulonephritis (GN): focal segmental glomeruosclerosis (FSGS) in 27%, membranous GN in 21%, IgA nephropathy in 19.7%, crescentic GN in 3%, minimal change disease (MCD) in 1.5%, lupus nephritis in 3% and chronic GN in 6% cases. Tubulointerstitial nephritis was found in 3% cases, vascular disease and diabetic nephropathy in 3% case and nephroangiosclerosis in 6% case.

TABLE 1

CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PATIENTS WITH OVERT PROTEINURIA BY ACE GENOTYPES BEFORE TREATMENT WITH ACE INHIBITORS

Variables	DD	ID	II
No. of patients (M:F)	17 (13:4)	35 (20:15)	14(9:5)
Age (years)	50.6±14.2	43.1±16.6	53.0±14.8
BMI (kg/m²)	28.4±5.1	25.7±4.4*	28.9±3.8
Creatinine (µmol/L)[a]	101.0 (72–598)	105.0 (61–404)	125.5 (56–265)
Creatinine clearance (mL/min/1.73 m²)	76.4±27.1	71.8±28.4	76.0±37.7
24-h urinary protein excretion (g/day)[a]	4.8 (1.0–23.1)	4.4 (0.5–22.8)	5.6 (1.2–16.2)
Systolic blood pressure (mmHg)	140.2±26.1	133.9±20.9	138.9±19.2
Diastolic blood pressure (mmHg)	89.9±13.2	84.3±13.4	89.6±10.6
Mean arterial pressure (mmHg)	106.7±16.3	100.8±15.3	105.2±14.3

All data are expressed as X±SD except creatinine and urine protein, [a]median (minimum-maximum), BMI – body mass index, ACE – angiotensin-converting enzyme, *p<0.05, as compared to DD and II genotypes by one-way ANOVA test.

TABLE 2
COMPARISON OF CLINICAL FINDINGS AMONG THE THREE GENOTYPES AFTER TREATMENT WITH ACE INHIBITORS

Variables	DD	ID	II
Creatinine (µmol/L)[a]	152 (72–679)	100 (52–656)	115 (56–284)
Creatinine clearance (mL/min/1.73 m²)	81.6±39.4	90.9±45.5	78.3±48.9
24-h urinary protein excretion (g/day)[a]	0.5 (0–6)	1.0 (0–26)	1.1 (0–11)
Systolic blood pressure (mmHg)	141.8±19.7	141.3±18.1	136.3±14.1
Diastolic blood pressure (mmHg)	89.4±10.1	86.4±10.3	85.4±9.3
Mean arterial pressure (mmHg)	106.9±11.8	104.7±11.9	102.3±9.9
Proteinuria reduction rate (%)	79.2±28.9*	49.2±64.8	50.7±42.9
Ccr reduction (mL/min/1.73 m²)	5.2±46.0	19.0±34.1	2.3±32.3

All data are expressed as X±SD except creatinine and urine protein, [a]median (minimum-maximum), Ccr – creatinine clearance, ACE – angiotensin-converting enzyme, *p<0.05, as compared to ID and II genotypes by one-way ANOVA test.

After the 12-month treatment using ACE inhibitor (ramipril), there were no significant differences in the reduction of blod pressure and creatinine clearance among three groups (p>0.005, Table 2).

One year of ACE inhibition resulted in significant reduction of proteinuria in all three genotype groups. The magnitude of the responses varied between individuals. Comparison of proteinuria before and after treatment with ACE inhibitors in the three different genotypes are shown in Figure 1.
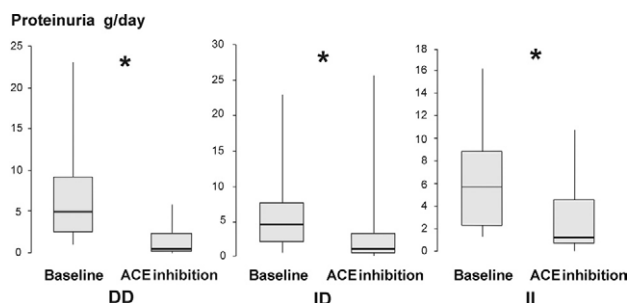
Fig. 1. Comparison of proteinuria before and after treatment with ACE inhibitors in the three genotypes. *p<0.05 by Wilcoxon paired test (ACE inhibitors vs baseline). Median values are indicated by the horizontal lines.

There were no statistically significant differences between values of protein excretion after ACE inhibition among the three groups (p>0.05, Table 2).

The percentage reductions of 24-h urinary excretion of protein were significantly different between the genotype groups (p=0.042) and for DD genotype were significantly greater than in ID (79.2±28.9% vs 49.2±64.8%, p=0.015). (Table 2, Figure 2). There was no statistically significant correlation between the levels of baseline proteinuria and the percentage reduction of proteinuria after ACE inhibition (r=0.143, p=0.252).

The slope of SBP was the main factor related to the slope of the percentage reduction of proteinuria, however, a significant negative correlation coefficient bet-
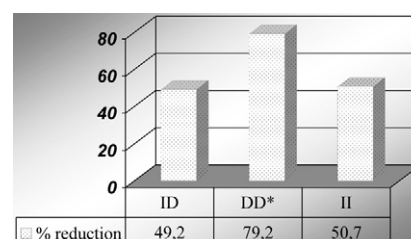
Fig. 2. Percentage reduction of proteinuria according to ACE genotype before and after treatment of ACE inhibitor. *p<0.05, compared to ID and II genotypes by one-way ANOVA test.

ween these parameters was found (rs=–0.382, p=0.002, Figure 3). To examine the sex-specific association of the ACE genotype in hypertensive patients with overt proteinuria we compared outcomes of treatments with ACE inhibitors according the I/D polymorphism of the ACE gene separately among men and women. However, the percentage reduction of proteinuria after treatment with ACE inhibitor for D allele was greater and equally in men and women than for I allele, statistically was not significant. We failed to find significant difference in outcomes of treatments with ACE inhibitor between male and female.

Discussion

In the present study, we evaluated whether the effect of ACE inhibition on proteinuria, blood pressure and renal haemodynamics were affected by the ACE genotypes in hypertensive patients with overt proteinuria. We found that patients with DD genotype are more susceptible to the antiproteinuric effect of ACE inhibition than those with ID or II.

Many of the previous association studies that focused on the association between ACE gene polymorphism and the development and progression of renal disease yielded conflicting results. In the study of Yoshida et al.[20] that included 53 Japanese patients with biopsy-proven IgA nephropathy, proteinuria was significantly decreased after ACE inhibitor administration in patients with DD
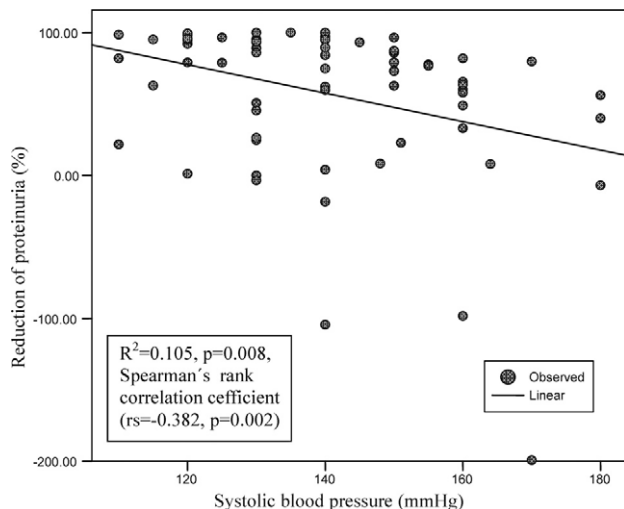
Fig. 3. Correlation between percentage reduction of proteinuria and systolic blood pressure after treatment of ACE inhibitors. Significant negative correlation between these parameters.

genotype but not in those with ID or II. The study of Sung-Kyu Ha et al.[26] also showed that the ACE DD genotype may have a significant role in the antiproteinuric effect of the ACE inhibitors. REIN trial[28] reported that polymorphism of ACE gene is a strong predictor of ACE inhibition-associated renoprotection., progression to ESRD and proteinuria were effectively reduced in patients with DD but not in those with ID or II genotype.

Moriyama et al.[10] found better antiproteinuric response to ACE inhibition in patients with II genotype in the study included 36 patients with various renal disorder. Penno et al.[22] reported from the EUCLID trial significant beneficial antiproteinuric effect of the ACE inhibitors also in patients with II genotype. Jacobsen at al.[21] concluded that hypertensive albuminuric patients with II genotype were particularly susceptible to renoprotective therapy. Our present observation does not coincide with EUCLID, Moriyama and Jacobsen studies, but concurs with many others[19,20,25–28]. The antiproteinuric effect of the ACE inhibitors has been thought to be independent of its antihypertensive effect on the systemic blood pressure. In this study we did not find any significant differences in SBP, DBP and MAP fall among the three genotype groups and our observation coincide with other reports[15,26,34]. However, the antiproteinuric effect of ACE inhibition in DD genotype was pronounced compared to II or ID genotypes.To exclude possibility that antiproteinuric effect of ACE inhibitors could be affected

by sodium intake, during the study period dietary sodium intake was not changed and sodium excretion was similar among three groups.

There was no statistically significant correlation between the levels of baseline proteinuria and the percentage reduction of proteinuria after ACE inhibition (r= 0.143, p=0.252). These findings suggest that the amount of baseline proteinuria do not affect the magnitude of the percentage reduction of proteinuria after ACE inhibition.

The slope of SBP was the main factor related to the slope of the percentage reduction of proteinuria, however, a significant negative correlation coefficient between these parameters was found (rs=–0.382, p=0.002).

Gender has been reported to have an impact on the development and progression of renal insufficiency[31], indicated that men with chronic renal disease of various etiologies show a more rapid decline in renal function with time than in women[32]. It has been speculated that direct receptor-mediated effects of sex hormones may determine susceptibility to renal damage[33]. Samuelsson et al.[25] reported that DD genotype was a significant predictor of a more rapid decline in renal function in male, but not female, patients while Ruggenenti et al.[27] found that ramipril uniformly decreased ΔGFR and incidence of ESRD in women either DD or II+ID genotype and in men with DD genotype but had no beneficiall effect in men with the II+ID genotype.

In the present study, the subgroup analysis of the allele distributions between males and females and analysis of gender-dependent interactions between the ACE gene and outcomes of treatments with ACE inhibitors failed to show any significance. Our observations may have been due to the small sample size of the female patient group compared to the male group.

In conclusion, the results of the present study show that the antiproteinuric effect of ACE inhibitors in DD genotype is significantly higher than that in ID or II genotypes.

As to the distribution of allele D and I, allele D is more frequent than allele I. This result corresponds with previous reports, suggesting an ethnic differences[35,36]. D allele in the ACE genotype could be a useful genetic marker with important clinical, therapeutic and prognostic implications in recognizing patients with proteinuria that are at greater risk of renal damage.

Although our study is limited by sample size, large prospective studies would be necessary to assess the impact of the ACE polymorphism on the response to renoprotective treatment.

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UTJECAJ POLIMORFIZMA GENA ANGIOTENZIN I KONVERTAZE (ACE) NA PROTEINURIJU I ARTERIJSKU HIPERTENZIJU

S A Ž E T A K

Proteinurija je najraniji znak oštećenja bubrega. U esencijalnoj hipertenziji pojava proteinurije povezana je s bržom progresijom bolesti. Neki autori su predložili da bi DD genotip angiotenzin I konvertaze mogao biti nepovoljan čimbenik prognoze u bubrežnih bolesti, ali i utjecati na učinke liječenja s ACE inhibitorima u bolesnika s proteinurijom. Rezultati dosadašnjih zapažanja o povezanosti polimorfizma ACE gena i arterijske hipertenzije često su oprečne i nekonzistentne, vjerojatno i zbog etničkih i geografskih varijacije. Cilj ove studije bio je ispitati utjecaj I/D polimorfizma ACE gena na ishod liječenja bolesnika s proteinurijom i povišenim krvnim tlakom s ACE inhibitorom (ramiprilom). U studiju je uključeno 66 bolesnika s proteinurijom (izlučivanje proteina urinom više od 500 mg dnevno) i arterijskom hipertenzijom. Bolesnici su bili podijeljeni u tri grupe prema ACE-genotipu (17 DD, 35 ID, 14 II) te liječeni ramiprilom i prospektivno praćeni godinu dana. Različiti klinički parametri uključujući dob, indeks tjelesne mase (IM), 24-h proteinuriju, kreatinin u serumu, klirens kreatinina (Ccr), sistolički i dijastolički krvni tlak (SKT i DKT), srednji arterijski tlak, izmjereni su prije i nakon liječenja. Insercijsko/delecijski polimorfizam ACE gena unutar introna 16 određen je metodom PCR. Rezultati su pokazali da nije bilo značajne razlike među genotipovima u kliničkim parametrima kao što su spol, dob, kreatinin, Ccr, SKT, DKT, 24-satna proteinurija (p>0,05). Bolesnici s ID genotipom imali su niži ITM (p=0,031). ACE inhibicija značajano smanjuje proteinuriju u svim skupinama (p<0,05). Utvrđena je statistički značajna razlika u postotku smanjenja proteinurije među genotipovima (p=0,042); za DD genotip bio je statistički značajno veći nego u ID (79,2±28,9% *vs.* 49,2±64,8%, p=0,015). Reductions in systolic and diastolic blood pressure did not differ significantly among genotypes.There was significant negative correlation between systolic blood pressure and percentage reductions of proteinuria (rs=–0,382; p=0,002).Nađena je statistički značajna negativna korelacija između sistoličkog krvnog tlaka i postotka smanjenja proteinurije (rs=– 0,382, p=0,002). Nismo uspjeli pronaći značajne razlike u ishodima liječenja s ACE inhibitorom između muškaraca i žena s obzirom na I/D polimorfizam ACE gena. D alel mogao bi biti koristan genski biljeg sa važnim kliničkim, terapeutskim i prognostičkim implikacijama u prepoznavanju bolesnika s proteinurijom koji imaju veći rizik za bubrežno oštećenje.