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ANTIHYPERTENSIVE DRUG USE AND URINARY ALBUMIN EXCRETION IN NON-DIABETIC HYPERTENSIVE POPULATION

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Summary. *Arterial hypertension together with proteinuria is one of the most important factors associated with the progression of both diabetic and nondiabetic chronic kidney disease. Reduction of blood pressure is an efficient way of slowing the progression of this damage whereas antihypertensive drugs vary in their proteinuria- and microalbuminuria-lowering effects. The objective of the present study was to determine the influence of different antihypertensive drug groups on urinary albumin excretion (UAE) as related to blood pressure in non-diabetic subjects. Subjects (n=39) with chronic renal disease accompanied by mild-to-moderate hypertension and varying degrees of proteinuria were included in the study. Patients were divided into three groups based on UAE values (normoalbuminurics, microalbuminurics and macroalbminurics) and were placed on usual care including nonpharmacological and/or treatment with an antihypertensive drug regime (consisting of one or more out of three different antihypertensive drugs (beta-blocker, ACE inhibitor or calcium-channel blocker) to achieve target blood pressure ≤ 130/85 mmHg. Periodic UAE measurements were performed until regression or significant reduction. A reduction in UAE was observed over time in most patients. However, it reached statistical significance only in the microalbuminuric group ($p < 0.01$). To further analyze the impact of different antihypertensive drugs on UAE, all patients were stratified into groups depending on the assigned therapy. They were divided into the following 5 groups: 0 – nonpharmacological treatment; 1 – assigned drug group 1; 12 – assigned drug groups 1 and 2; 13 – assigned drug groups 1 and 3; 123 – assigned all 3 drug groups where '1' stood for ACE inhibitors, '2' for beta blockers and '3' for calcium channel blockers. A statistically significant change in mean UAE values at the start and end of the study period in patients assigned to drug groups 12, 13 and 123 was achieved ($p<0.05$). Also, a statistically significant difference existed in the average reduction of proteinuria under varying antihypertensive drug regimens ($p<0.05$, ANOVA). Post hoc analyses revealed also a significant difference between groups 0 and 13 ($p<0.01$, Dunnett T3) as well as groups 1 and 13 ($p<0.01$, Dunnett T3). In patients with hypertension, changes in UAE depend on the initial UAE values and the type of antihypertensive treatment. ACE inhibitors combined with calcium channel blockers produced higher UAE reduction than other drug groups.*

Key words: *Antihypertensive drugs, urinary albumin excretion, proteinuria, hypertension, angiotensin-converting enzyme inhibitors, calcium channel blockers*

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. Arterial hypertension together with proteinuria is one of the most important factors associated with the progression of both diabetic and nondiabetic chronic kidney disease.

High blood pressure (BP) can be either a cause or a consequence of CKD. Hypertension is common in chronic renal disease and is a risk factor for the faster progression of renal damage. Therefore, reduction of BP is an efficient way of preventing or slowing the progression of this damage (1). Having this in mind, antihypertensive therapy is beneficial to slow down the progression of a variety of chronic renal diseases, no matter what the cause. (2)

In patients with primary renal disease, it has been shown that proteinuria predicts future renal function decline (3). This has been clearly demonstrated in nondiabetic renal disease by the Modification of Diet in Renal Disease study (4). The more proteinuria is lowered, the better the prognosis with regard to renal function.

Microalbuminuria in essential hypertension is associated with increased mortality, (5-7) and proteinuria seems to be an independent risk factor for cardiovascular and cerebrovascular disease (8). Interestingly, it has also been shown that in subjects with diabetes or hypertension, and even in the general population, urinary albumin excretion (UAE) predicts future cardiovascular events (9-11).

Clinical trials have demonstrated that different antihypertensive classes vary in their proteinuria- and mi-

croalbuminuria-lowering effects (12). Meta-analyses have shown that the angiotensin-converting enzyme (ACE) inhibitors are superior to other antihypertensives in lowering proteinuria and also microalbuminuria (12-15). These observations have led researchers in clinical practice to pursue a maximal antiproteinuric response on angiotensin-converting enzyme (ACE) inhibitors in renal patients by coprescribing treatments that are known to increase the antiproteinuric efficacy of this class of drugs, for example, sodium-restricted diet and diuretics (9). Later angiotensin II antagonists have been found to be equally effective in this regard as the ACE inhibitors (12, 16). In particular, for comparable average reductions in blood pressure, several studies demonstrated that ACE inhibitors improved glomerular barrier permselectivity and lowered proteinuria (12, 17) more than conventional therapy (diuretics and/or beta-blockers) or dihydropyridine calcium channel blockers (CCB), and were more renoprotective (17, 18). However, there is a disagreement concerning the calcium channel blockers (CCB), sometimes they are found to be more (13) and sometimes less effective (14).

Given these considerations, the objective of the present study was to determine the influence of different antihypertensive drug groups on urinary protein excretion of non-diabetic microalbuminuric or proteinuric hypertensive individuals with mild-to-moderate hypertension in a prospective follow-up.

Subjects and Methods

Patients (n=39) were recruited from the nephrology outpatient clinic of the Department of Internal Medicine, University Clinical Center, Nis, Serbia. Subjects had chronic renal disease accomapnied by mild-to-moderate hypertension and varying degrees of proteinuria. All participants gave written consent. They filled in a questionnaire regarding medical treatment for hypertension, hyperlipidemia and adverse drug reactions.

Blood pressure was measured at two outpatient visits, using a mercury sphyngomanometer following the recommendations of the British Hypertension Society. Measurements were performed after 10 minutes of rest in a supine position. Systolic and diastolic blood pressure were the average of three readings measured at 5-minute intervals at both visits.

At the second visit fasting blood samples were taken for direct measurement of glucose and cholesterol. The subjects also handed in two 24 h urine samples at the second visit. Urinary albumin concentration was determined by nephelometry (Behring diagnostics).

For the purpose of our study diabetics were excluded.

After enrollment, patients were divided into three groups based on urinary albumin excretion values (normoalbuminurics, microalbuminurics and macroalbminurics). Further, patients were placed on usual care including nonpharmacological treatment and/or treatment with an antihypertensive drug regime (consisting of one or more out of three different antihypertensive drugs (beta-blocker, ACE inhibitor or calcium-channel blocker) to achieve target blood pressure ≤ 130/85 mmHg (the current JNC VI recommendation in patients with coexistent hypertension and renal disease is for a reduction to a target blood pressure of 130/85 mm Hg, or to a lower value of 125/75 in patients with greater than 1 g proteinuria per day (16). Periodic UAE measurements were performed until regression or significant reduction (defined as a reduction of UAE to < 30 mg/24 h for microalbuminuric patients and < 300 mg/24 h for proteinuric patients).

Definitions and calculations

Microalbuminuria was defined as a urinary albumin excretion of 30-300 mg/24 h measured as the mean of two 24 h urine collections. An urinary albumin excretion > 300mg/24 h was defined as macroalbuminuria. Diabetes was defined as having a fasting glucose ≥ 7.8mmol/l, a nonfasting glucose ≥ 11.1 mmol/l or the use of antidiabetic medication. Mean arterial pressure (MAP) was calculated as 2/3 diastolic blood pressure + 1/3 systolic blood pressure.

Statistical analysis

Analyses were performed using the statistical software package SPSS version 13.0. Baseline characteristics are given as mean±SD. All data are expressed as mean with standard deviation. Differences between continuous variables were tested by use of Student's t-test or Mann-Whitney rank test in the case of skewed distribution. A p value of < 0.05 was considered statistically significant.

Differences in average age, MAP and cholesterol values between the three patient groups were determined using Student's t-test or Mann-Whitney rank test. Differences in gender between the three patient groups were determined using Fisher's test and Mantel-Haenszel's test with Yate's correction.

The influence of the use of one or more antihypertensive drug groups on UAE was determined using Fisher's test. Differences in mean proteinuria values at the start and end of the study period between patients assigned to various drug groups were determined using t-test, while differences in average reduction of proteinuria under varying antihypertensive drug use were determined using ANOVA. P values <0.05 and <0.01 were regarded as statistically significant.

Results

Patients were initially stratified into three groups according to urinary albumin excretion values (normo-, micro- and macroalbuminurics). The mean baseline patient characteristics are shown in Table 1. Both micro- and macroalbuminurics had higher blood pressure and cholesterol levels compared to normoalbuminurics and used significantly more cardiovascular drugs. However,

no significant difference existed between the average age of normoalbuminurics when compared to micro- and macroalbuminurics. Patients with macroalbuminuria were more often female, however this difference did not reach statistical significance.

Table 2 shows the number of users of different antihypertensive drug groups. The patients are divided into 3 groups based on urinary albumin excretion values. All patients (except 5) had mild-to moderate hypertension and were assigned appropriate antihypertensive agents to achieve a BP goal of ≤130/85.

Amongst the normoalbuminurics (n=13), 3 received nonpharmacological treatment, 10 received exclusively ACE inhibitors, 3 received an ACE inhibitor and beta-blocker, while only 1 patient received an ACE inhibitor, beta-blocker and calcium channel blocker combined.

Amongst the microalbuminurics (n=8), one patient was assigned nonpharmacological treatment, while 1 received exclusively an ACE inhibitor. 3 received an ACE inhibitor and beta-blocker, 1 received an ACE inhibitor and calcium channel blocker, whereas 2 patients received an ACE inhibitor, beta-blocker and calcium channel blocker.

Amongst the macroalbuminurics (n=18) one patient did not receive medication, 5 patients were assigned only an ACE inhibitor. Four received an ACE inhibitor and beta-blocker and 1 an ACE inhibitor and calcium channel blocker. Seven received all 3 drug groups-an ACE inhibitor, beta-blocker and calcium channel blocker.

Prescribed ACE inhibitors included fosinopril and enalapril. Amongst the beta-blockers metoprolol, carvedilol or bisoprolol were prescribed. Patients who required a calcium channel blocker to achieve BP goals were assigned only amlodipine.

In all three groups subjects received concomitant medication (comprising of diuretics) intermittently in order to achieve BP control. Out of 13 normoalbuminurics, 7 were occasionally assigned a diuretic (loop diuretic-furosemid). Amongst the microalbuminurics (n=8), 5 occasionally received a loop diuretic, whereas all macroalbuminurics were occasionally assigned diuretics (thiazide, potassium-sparing or loop diuretics) (Table 2).

During the course of the study changes in urinary protein excretion values under antihypertensive treatment were followed. Even though a reduction in UAE was observed over time in most patients, it reached statistical significance only in the microalbuminuric group ($p < 0.01$) (Table 3).

Table 1. Baseline characteristics of patients

Characterist1ic	Normoalbuminuria 0-30 mg/24 h	Microalbuminuria 30-300 mg/24 h	Macroalbuminuria > 300 mg/24 h
n	13	8	18
Age (years)	66.31 (14.87)	61.38 (12.66)	54.79 (20.58)
Male sex (%)	61.54	62.5	33.33
Blood pressure-mmHg			
Systolic	141.92 ± 20.16	114.22 ± 58.77	147.69 ± 18.67
Diastolic	78.46 ± 9.87	68.35 ± 37.96	77.85 ± 19.71
Mean arterial pressure	100 ± 16.73	83.64 ± 52.703	96.67 ± 5.77
Cholesterol- mmol l^{-1}	4.79 (1.16)	4.8 (1.1)	6.06 (1.84)*
Cardiovascular drug use			
No	3	1	1
1 drug group	10	7	17
2 drug groups	3	5	11
≥3 drug groups	1	3	8**

Continuous values are reported as means (s.d.), categorical values as percentages, MAP=mean arterial pressure.
*$p<0.005$ vs. normoalbuminuria
**Prevalence distribution for micro- and macroalbuminuria significantly ($p<0.05$) different from normoalbuminuria

Table 2. Antihypertensive drug use

Drug group	Normoalbuminuria 0-30 mg/24 h	Microalbuminuria 30-300 mg/24 h	Macroalbuminuria > 300 mg/24 h
Beta-adrenoceptor blockers	3	6	12
Diuretics			
Thiazide diuretic			1
Potassium- sparing			2
Loop diuretics	7	5	15
ACE-inhibitors	11	8	18
Dihydropyridine calcium channel blockers	1	3	8

**Prevalence distribution for micro- and macroalbuminuria significantly ($p<0.05$) different from normoalbuminuria

Table 3. Changes in mean UAE values at the start and ending of the study period

	Normoalbuminuria 0-30 mg/24 h		Microalbuminuria 30-300 mg/24 h		Macroalbuminuria > 300 mg/24 h	
Study period	Start	End	Start	End	Start	End
UAE	0.000± 0.000	0.050 ± 0.088	0.130 ± 0.083	0.030 ± 0.029	574.308 ± 1285.605	62.564 ± 262.654
p (t test)	0.065		0.007**		0.124	

Values are expressed as mean ±s.d. ** $p < 0.01$

When mean proteinuria values were compared at the beginning and end of the study period a statistically significant difference was found in these values for the group with microalbuminuria ($p<0.01$). In patients with macroalbuminuria UAE values showed a tendency to fall during the course of the study. However, this change in UAE values did not achieve statistical significance ($p > 0.05$).

In order to further analyze the impact of different antihypertensive drugs on UAE, all patients were further stratified into groups depending on the assigned therapy. They were divided into the following 5 groups: 0 – non-pharmacological treatment; 1 – assigned drug group 1; 12 – assigned drug groups 1 nd 2; 13 – assigned drug groups 1 and 3; 123 – assigned drug groups 1,2 and 3 (Tables 4 and 5) where drug group1 stood for ACE inhibitors, '2' for beta blockers and '3' for calcium channel blockers.

Table 4. Patients were divided into groups based on assigned therapy. 0- patients assigned nonpharmacological treatment; 1-drug group 1; 12-patients assigned drug groups 1 and 2; 13- pateints assigned drug groups 1 and 3; 123-patients assigned drug groups 1,2 and 3

Drug groups assigned	Frequency	Percentage (%)
0	5	12.8
1	13	33.3
12	9	23.1
13	2	5.1
123	10	25.6
total	39	100.0

Legend: drug group 1-ACE inhibitors
drug group 2- beta-blockers
drug group 3-calcium channel blocker

A statistically significant change in mean UAE values at the start and end of the study period in patients assigned to drug groups 12, 13 and 123 was achieved ($p<0.05$) (Table 5).

Also, we demonstrated that a statistically significant difference existed in the average reduction of proteinuria under varying antihypertensive drug regimens ($p<0.05$, ANOVA). Post hoc analyses revealed also a significant difference between groups 0 and 13 ($p<0.01$, Dunnett T3) as well as groups 1 and 13 ($p<0.01$, Dunnett T3) (Table 6).

Table 5. Differences in mean proteinuria values at the start and end of the study period between patients assigned to various drug groups

Drug groups assigned	$\overline{X} \pm SD$		P (t test)
	Therapy comencement	Therapy ending	
0	0.208 ± 0.392	0.312 ± 0.664	0.456
1	0.307 ± 0.553	0.244 ± 0.370	0.288
12	0.576 ± 0.673	0.020 ± 0.040	0.039*
13	0.800 ± 0.057	0.005 ± 0.007	0.036*
123	0.886 ± 0.982	0.114 ± 0.122	0.035*

*Statistically significant reduction in proteinuria values ($p<0.05$, t test)

Table 6. Differences in reduction of mean proteinuria values under various antihypertensive treatment

Drug groups assigned	$\overline{X} \pm SD$	F	P (ANOVA)	Dunnett T3
0	-0.104 ± 0.282			
1	0.060 ± 0.202			
12	0.556 ± 0.678	3.004	0.032*	A, B
13	0.795 ± 0.063			
123	0.772 ± 0.984			

*A statistically significant difference in average proteinuria reduction under antihypertensive treatment ($p<0.05$, ANOVA). Post hoc analysis reveals a significant difference between groups 0 and 13 ($p<0.01$, Dunnett T3) and 1 and 13 ($p<0.01$, Dunnett T3). A - $p<0.01$ 0 v.s. 13, B - $p<0.01$ 1 v.s. 13

Discussion

Hypertension is common in chronic renal disease and is a risk factor for the faster progression of renal damage, and reduction of blood pressure (BP) is an efficient way of preventing or slowing the progression of this damage. Proteinuria, which occurs as a consequence of elevated intraglomerular pressure, is also directly nephrotoxic. As well as protecting the kidneys by reducing BP, antihypertensive drugs can also have direct effects on intrarenal mechanisms of damage, such as increased glomerular pressure and proteinuria (1). Thus, BP control with antihypertensive medications is accompanied by a reduction (but not a normalisation) in UAE which we were able to demonstrate in our research (Tables 3, 5 and 6).

The results of recent studies show that antihypertensive drugs differ with respect to their action on UAE. Although some data are discordant, all of these studies

showed that reduction of BP with ACE-inhibitors, some calcium channel blockers, beta-blockers, diuretics, alpha-1-blockers and angiotensin-II receptor antagonists also reduces UAE (12). We confirmed this in our study where patients (normo-, micro- and macroalbuminurics) assigned ACE inhibitors alone, or in combination with a beta-blocker or calcium channel blocker showed statistically significant changes in UAE values (Tables 5, 6).

The superior antiproteinuric effects of ACE inhibitors have been acknowledged for a long time. Only in diabetic patients and in patients with renal disease has this characteristic of ACE inhibitors been shown to be independent of BP reduction (14, 19, 20).

Whereas BP-lowering effects are common to all antihypertensive drugs, intrarenal effects differ between classes and between individual drugs within certain classes. ACE inhibitors and angiotensin receptor blockers (ARB) have beneficial effects on proteinuria and declining renal function that appear to be mediated by factors additional to their effects on BP. These renin-angiotensin system (RAS) inhibitors are recommended as a first-line antihypertensive approach in patients with chronic kidney disease. In accordance with these facts all our patients were initially assigned ACE inhibitors. Despite the fact that ACE inhibitors alone can reduce UAE (15), in our study additional antihypertensive agents were administered not so much as to normalize proteinuria, but to achieve goal BP values. The results of our study showed that significant reduction of proteinuria was achieved in patients who were assigned at least 2 antihypertensive agents (groups 12, 13 and 123), i.e. patients receiving an ACE inhibitor plus a beta-blocker or calcium channel blocker, or all 3 drug groups combined. The highest reduction of proteinuria was reached in patients who were administered an ACE inhibitor and calcium channel blocker when compared to patients who did not receive any medication or when compared to patients receiving only ACE inhibitors. A reduction of UAE was also observed in patients receiving only ACE inhibitors, however this reduction did not achieve statistical significance.

The addition of diuretics and calcium channel antagonists to RAS inhibitor therapy is also considered to be a rational strategy to reduce BP and preserve renal function (1). Thus, our patients were occasionally assigned diuretics in order to achieve BP goals. The use of a diuretic is often helpful in patients who already have renal insufficiency, since fluid overload is an important cause of hypertension and may also enhance the effectiveness of drugs that interfere with the renin-angiotensin-aldosterone system (RAAS) (2).

Calcium channel antagonists are a highly heterogeneous class of compounds, and it appears that some agents are more suitable for use in patients with chronic renal disease than others. Our patients were assigned only amlodipine amongst the dihydropyridine calcium channel blockers in combination with an ACE inhibitor. A recent study showed that manidipine, a third-generation dihydropyridine (DHP) calcium channel antagonist that blocks both L and T-type calcium channels unlike older-generation DHPs, which preferentially act on L-type channels, has beneficial effects on intrarenal haemodynamics, proteinuria and other measures of renal functional decline in the first clinical trials involving hypertensive patients with chronic renal failure. Preliminary results from a trial in diabetic patients who had uncontrolled hypertension and microalbuminuria despite optimal therapy with an ACE inhibitor or an ARB suggest that manidipine may be an excellent antihypertensive drug in combination with RAS inhibitor treatment in order to normalise BP and albumin excretion in patients with diabetes (1). Calcium antagonists are effective for treating hypertensive patients with chronic renal impairment but have not been studied as intensively as ACE inhibitors with regard to their ability to slow the progression of renal insufficiency independently of their BP-lowering effects. The initial results for calcium antagonists and for combination calcium antagonist-ACE inhibitor therapy have been promising (16). Short-acting dihydropyridine calcium channel blockers (CCB) are not recommended. By comparison, long-acting dihydropyridines such as diltiazem and verapamil are less potent vasodilators and may primarily decrease the resistance of the efferent arteriole, similar to the ACE inhibitors. They may have an antiproteinuric activity. Yet, there is lack of large prospective randomized trials (2) .

ACE inhibitors seem to lower proteinuria more than other antihypertensive drugs, despite a similar BP lowering effect. Calcium antagonists likewise exert beneficial intrarenal effects, but with some differences among subclasses. Overall, data from clinical trials thus seem to indicate that ACE inhibitors and possibly calcium antagonists should be preferred in the treatment of patients with diabetic and nondiabetic nephropathies. However, further information is needed to understand renal protection (21). Similarly, in a multivariate analysis of controlled and uncontrolled trials it has been shown that long-term beneficial effects of antihypertensive agents on proteinuria and glomerular filtration rate are proportional to blood pressure reductions and are similar in diabetic and nondiabetic patients with renal disease. In addition, ACE inhibitors, and possibly nondihydropyridine calcium antagonists, have additional beneficial effects on proteinuria that are independent of blood pressure reductions (13) .

In some of our patients treatment goals for arterial hypertension were achieved when a beta blocker was added to an ACE inhibitor. A beta blocker as an antihypertensive agent is indicated as second- or third-line drug especially in patients with additional cardiovascular disease (2). In a study where the effects of four different antihypertensive drugs (the Ca (2+)-channel blocker felodipine, the beta-blocker metoprolol, the ACE inhibitor ramipril, and the alpha-blocking agent doxazosin) on microalbuminuria and renal hemodynamics were evaluated in 17 patients with mild-to-moderate essential arterial hypertension and microalbuminuria, it was found that all drugs reduced mean arterial

pressure and microalbuminuria to a similar and statistically significant extent (17).

There are some shortcomings in this study. Even though clinical and epidemiological data show that UAE is related to a number of clinical variables such as age, gender, race, hyperglycaemia, hyperlipaemia, hyperinsulinaemia, hypertension, smoking habit, diet, etc., (22) we could not establish a connection between all these variables in our study.

In summary, hypertension is common in chronic renal disease and is a risk factor for the faster progression of renal damage. Proteinuria is also directly nephrotoxic. All types of antihypertensive drugs under investigation reduced UAE in patients with mild-to-moderate arterial hypertension. Thus in the presence of increased UAE, having in mind its intrinsic significance (renal damage secondary to hypertension or underlying renal and systemic endothelial dysfunction) antihypertensive treatment should be intensified and blood pressure control optimised.

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UTICAJ UPOTREBE ANTIHIPERTENZIVA NA PROTEINURIJU KOD BOLESNIKA SA HRONIČNOM BUBREŽNOM INSUFICIJENCIJOM I HIPERTENZIJOM

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Kratak sadržaj: *Arterijska hipertenzija i proteinurija su glavni faktori koji utiču na progresiju hronične bubrežne insuficijencije (HBI). Sniženje vrednosti krvnog pritiska je efikasna mera kojom se može usporiti ova progresija. Antihipertenzivi variraju u svojoj sposobnosti da smanje vrednosti proteinurije i mikroalbuminurije. Cilj ovog rada je bio da*

se odredi uticaj raznih antihipertenziva na vrednosti proteina u urinu (UAE) kod pacijenata koji nisu dijabetičari, sa blagom do umerenom hipertenzijom i HBI. Studija je obuhvatila pacijente sa HBI (n=39), blagom-do-umerenom hipertenzijom i proteinurijom. Pacijenti su podeljeni u 3 grupe na osnovu vrednosti proteina u mokraći (pacijenti sa normoalbuminurijom, mikroalbuminurijom i makroalbuminurijom). Započeta je terapija nefarmakološkim merama i primenom jednog ili više antihipertenziva koji su bili na raspolaganju (beta-blokatori, ACE inhibitori i kalcijumski blokatori) kako bi se dostigle ciljne vrednosti tenzije od ≤130/85mmHg. Povremena merenja proteinurije su učinjena dok se nije zapazio pad ili značajno sniženje vrednosti. Smanjenje vrednosti proteina u mokraći registrovano je kod većine pacijenata, ali je ovo smanjenje bilo statistički značajno samo u grupi pacijenata sa mikroalbuminurijom ($p<0.01$). Kako bi se dalje analizirao uticaj antihipertenziva na UAE, pacijenti su podeljeni u grupe na osnovu ordinirane terapije. Podeljeni su u 5 grupa: 0 –nefarmakološke mere; 1 – oprimali lek 1. grupe; 12 – primali lekove iz 1. i 2. grupe; 13 – primali lekove iz 1. i 3. grupe; 123 – primali lekove iz sve 3 grupe, gde su grupu 1 činili ACE inhibitori, 2-beta blokatori i 3-kalcijumski blokatori. Statistički značajna razlika u prosečnim vrednostima UAE na početku i kraju studije zabeležena je u grupama 12, 13, i 123 ($p<0.05$). Postojala je i statistički značajna razlika u prosečnom smanjenju proteinurije pri upotrebi različitih grupa lekova ($p<0.05$, ANOVA). Post hok analizom utvrđeno je da je postojala razlika izmedju 0 i 13 grupe ($p<0.01$, Dunnett T3) i 1 i 13 grupe ($p<0.01$, Dunnett T3). Kod pacijenata sa hipertenzijom u sklopu HBI, promene u UAE zavise od početnih vrednosti i vrste propisanog antihipertenziva. ACE inhibitori u kombinaciji sa kalcijumskim blokatorima doveli su do većeg pada vrednosti UAE u odnosu na druge kombinacije antihipertenziva.

Ključne reči: *Antihipertenzivi, proteinurija, mikroalbuminurija, ACE inhibitori, kalcijumski blokatori*