Cent. Eur. J. Med. • 3(3) • 2008 • 287-293
DOI: 10.2478/s11536-008-0036-8

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Central European Journal of **Medicine**

Antiproteinuric effects of antihypertensive agents in non-diabetic hypertensive population

Research Article

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Received 14 November 2007; Accepted 4 April 2008

Abstract: Arterial hypertension and proteinuria are important factors associated with the progression of both diabetic and nondiabetic chronic kidney disease. 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 population. Subjects (n=39) with chronic renal disease accompanied by mild to moderate hypertension and varying degrees of proteinuria were divided into 3 groups based on UAE values and placed on nonpharmacological and/or treatment with an antihypertensive drug regimen (consisting of one or more antihypertensive drugs [beta blocker, ACE inhibitor or calcium-channel blocker]) to achieve a target blood pressure ≤ 130/85 mmHg. Periodic UAE measurements were performed. A reduction was observed over time in most patients, however, it reached statistical significance only in the microalbuminuric group ($P<0.01$). Patients were further stratified into 5 groups depending on assigned therapy: 0, nonpharmacological treatment; 1-drug group 1; 12-drug groups 1 and 2; 13-drug groups 1 and 3; 123- all 3 drug groups (1-ACE inhibitors, 2-beta blockers, 3-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, there was a statistically significant difference in the average reduction of proteinuria under varying antihypertensive drug regimens ($P < 0.05$). In conclusion, in patients with hypertension, changes in UAE depend on initial UAE values and administered antihypertensive treatment. ACE inhibitors combined with calcium channel blockers resulted in a higher UAE reduction than other drug groups.

Keywords: *Antihypertensive drugs • Urinary albumin excretion • Proteinuria • Hypertension • Angiotensin-converting enzyme inhibitors • Calcium channel blockers*

1. 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 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 blood pressure is an efficient way of preventing or slowing the progression of renal damage [1]. Indeed, antihypertensive therapy helps slow the progression of a variety of chronic renal diseases, regardless of the cause [2].

In patients with primary renal disease, proteinuria predicts future decline in renal function [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

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seems to be an independent risk factor for cardiovascular and cerebrovascular disease [8]. Interestingly, 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 drug classes have variable abilities to lower proteinuria and microalbuminurias [12]. Meta-analyses have revealed that the angiotensin-converting enzyme (ACE) inhibitors are superior to other antihypertensives at lowering proteinuria as well as microalbuminuria [12-15]. These observations have led clinical researchers to maximize the antiproteinuric response by ACE inhibitors in renal patients by prescribing concomitant treatments that enhance the antiproteinuric efficacy of these drugs, such as a sodium-restricted diet and diuretics [9]. Later, angiotensin II antagonists were found to be equally effective in this regard as the ACE inhibitors [12,16]. In particular, several studies showed that despite producing comparable average reductions in blood pressure, ACE inhibitors provide better improvements in glomerular barrier permselectivity and reduced proteinuria [12,17] than conventional therapy (*i.e.*, diuretics and/or beta blockers) or dihydropyridine calcium channel blockers and that they are better at protecting renal function [17,18]. However, there is disagreement concerning the effects of the calcium channel blockers; sometimes they are found to be more [13] and sometimes less effective [14] than ACE inhibitors.

Given these considerations, the objective of the present study was to determine the influence of different antihypertensive drug groups on urinary protein excretion by nondiabetic microalbuminuric or proteinuric hypertensive individuals with mild to moderate hypertension.

2. Materials 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 accompanied by mild to moderate hypertension and varying degrees of proteinuria. All participants gave written consent. They completed a questionnaire regarding medical treatment for hypertension and hyperlipidemia and any adverse drug reactions. Patients were diagnosed as having CKD based on reduced glomerular filtration rate values (GFR; 20–65 ml/min per 1.73 m^2). The GFR was computed using the simplified Modification of Diet and Renal Disease Study formula [19]:

Estimated GFR (ml/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 if female

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. In addition, at the second visit, the patient turned in two 24-h urine samples. 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). Furthermore, patients were provided 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 mmHg in patients with > 1 g proteinuria per day [16]). All patients included in this study, who were hypertensive, received an ACE inhibitor. A beta blocker as a second-line drug was added to manage hypertension in patients with accompanying cardiovascular diseases, and the other patients received a calcium channel blocker to maintain goal blood pressure values. Some patients required all three drug classes to maintain blood pressure goals.

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.

2.1. Definitions and calculations

Microalbuminuria was defined as a urinary albumin excretion of 30 to 300 mg/24 h measured as the mean of two 24-h urine collections. A urinary albumin excretion > 300 mg/24 h was defined as macroalbuminuria. Diabetes was defined as having a fasting glucose ≥ 7.8 mmol/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.

Table 1. Baseline Characteristics of Patients.

Characteristic	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	114.22±58.77	141.92±20.16	147.69±18.67
Diastolic	68.35±37.96	78.46±9.87	77.85±19.71
MAP	83.64±52.703	100±16.73	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 ± SD and categorical values as percentages. MAP, mean arterial pressure. *P < 0.005 vs. normoalbuminuria. **Prevalence distribution for micro- and macro-albuminuria was significantly different from normoalbuminuria (P < 0.05).*

2.2. Statistical analysis

Statistical analyses were performed using SPSS version 13.0. All data are expressed as means with standard deviations. Differences between continuous variables were tested using Student's t-test or the Mann-Whitney rank test for skewed distributions, and a *P* value below 0.05 was considered to indicate statistical significance. Differences in the average age, MAP, and cholesterol values between the three patient groups was determined using Student's t-test or the Mann-Whitney rank test. Differences in gender between the three patient groups was 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 was determined using a t-test, and differences in average reduction of proteinuria under varying antihypertensive drug use was determined by ANOVA, and *P* values below 0.05 and 0.01 respectively were regarded as statistically significant.

3. Results

Patients were initially stratified into three groups according to urinary albumin excretion values (normo-, micro-, and macro-albuminurics). The mean baseline patient characteristics are shown in Table 1. Both micro- and macro-albuminurics had higher blood pressure and cholesterol levels than normo-albuminurics and used significantly more cardiovascular drugs. However, there was no significant difference between the average age of normo-albuminurics and micro- or macro-albuminurics. Patients with macroalbuminuria were more often female, although this difference was not statistically significant.

Table 2 shows the number of users of different antihypertensive drug groups. The patients were divided into three groups based on urinary albumin excretion values. All patients (except no. 5) had mild to moderate hypertension and were assigned appropriate antihypertensive agents to achieve a blood pressure ≤ 130/85 mmHg. Of the normoalbuminurics (n=13), 3 received nonpharmacological treatments, 10 received exclusively ACE inhibitors, 3 received an ACE inhibitor and a beta blocker, and only 1 patient received a combination of an ACE inhibitor, a beta blocker, and a calcium channel blocker. Amongst the microalbuminurics (n=8), one patient was assigned nonpharmacological treatment, 1 received exclusively an ACE inhibitor, 3 received an ACE inhibitor and a beta blocker, 1 received an ACE inhibitor and calcium channel blocker, and 2 received an ACE inhibitor, a beta blocker, and a calcium channel blocker. Amongst the macroalbuminurics (n=18), 1 patient did not receive medication, 5 were assigned only an ACE inhibitor, 4 received an ACE inhibitor and a beta blocker, 1 received an ACE inhibitor and a calcium channel blocker, and 7 received all a combination of an ACE inhibitor, a beta blocker, and a 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 blood pressure goals were assigned only amlodipine.

In all three groups, subjects received concomitant medication (diuretics) intermittently to achieve blood pressure control. Out of 13 normoalbuminurics, 7 were

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	7	5	1215
Thiazide diuretic			
Potassium- sparing			
Loop diuretics			
ACE-inhibitors	11	8	18
Dihydropyridine	1	3	8
calcium channel blockers			

***Prevalence distribution for micro- and macro-albuminuria was significantly different from normoalbuminuria ($P < 0.05$).*

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	

Table 4. Patients were divided into groups based on assigned therapy.

Drug groups assigned*	Number of subjects	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

**0, patients assigned nonpharmacological treatment; 1, drug group 1; 12, patients assigned drug groups 1 and 2; 13, patients assigned drug groups 1 and 3; 123-patients assigned drug groups 1,2 and 3. Drug groups were as follows: 1, ACE inhibitors; 2, beta blockers; 3, calcium channel blockers.*

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	X ± SD		P(t test)
	therapy start	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 ($P < 0.05$ by t test).*

occasionally assigned a 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) (Tables 2 and 3).

During the course of the study, the changes in urinary protein excretion values during antihypertensive treatment were followed. Although 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). In patients with macroalbuminuria, UAE values showed a tendency to fall during the course of the study. However, this change in UAE values was not statistically significant.

To further analyze the impact of different antihypertensive drugs on UAE, all patients were further stratified into one of five groups depending on assigned therapy as follows: 0, nonpharmacological treatment; 1, assigned drug group 1; 12, assigned drug groups 1 and 2; 13, assigned drug groups 1 and 3; 123, assigned drug groups 1, 2, and 3 (1 refers to ACE inhibitors, 2 to beta blockers, and 3 to calcium channel blockers; Tables 4 and 5). There was a statistically significant change ($P < 0.05$) in mean UAE values between the start and end of the study period in patients assigned to drug groups 12, 13, and 123 (Table 5).

We also observed a statistically significant difference in the average reduction of proteinuria under varying antihypertensive drug regimens ($P < 0.05$ by ANOVA). Post-hoc analyses revealed also a significant difference between groups 0 and 13 ($P < 0.01$ by Dunnett T3 test) as well as between groups 1 and 13 ($P < 0.01$ by Dunnett T3 test) (Table 6).

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

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

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

4. Discussion

Hypertension is common in chronic renal disease and is a risk factor for the faster progression of renal damage. Reduction of blood pressure 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 blood pressure, antihypertensive drugs can directly affect intrarenal mechanisms of damage, for example by reducing glomerular pressure and proteinuria [1]. Thus, as found here, blood pressure control with antihypertensive medications is accompanied by a reduction but not a normalization of UAE.

The results of recent studies show that antihypertensives have different effects on UAE. Although there is some discrepancy in the results, all of the studies have shown that reduction of blood pressure with ACE inhibitors, some calcium channel blockers, beta blockers, diuretics, α1-blockers, and angiotensin-II receptor antagonists also reduces UAE [12]. Similarly, in the current studies, we found that patients assigned ACE inhibitors alone or in combination with a beta blocker or calcium channel blocker showed statistically significant changes in UAE values. Indeed, the superior antiproteinuric effects of ACE inhibitors have been acknowledged for many years. Only in diabetic patients and patients with renal disease has this characteristic of ACE inhibitors been shown to be independent of blood pressure reduction [14,20,21].

Although all hypertensive drugs can reduce blood pressure, the intrarenal effects differ between drug classes and between individual drugs within certain classes. ACE inhibitors and angiotensin receptor blockers have beneficial effects on proteinuria and declining renal function that appear to be mediated by factors additional to their effects on blood pressure. These inhibitors of the renin-angiotensin system are recommended as a first-line antihypertensives in patients with chronic kidney disease. In agreement with this, all our patients were initially assigned ACE inhibitors. Although ACE inhibitors alone can reduce UAE [15], in our study, additional antihypertensive agents were primarily administered to achieve blood pressure goals rather than to normalize proteinuria. In the current study, we found a significant reduction of proteinuria in patients assigned at least two antihypertensive agents (groups 12, 13, and 123), that is, patients receiving an ACE inhibitor plus a beta blocker or calcium channel blocker, or a combination of all three drug groups. The greatest 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 who received only ACE inhibitors. A reduction of UAE was also observed in patients receiving only ACE inhibitors, although the difference was not statistically significant.

The addition of diuretics and calcium channel antagonists to inhibitors of the renin-angiotensin system is considered to be a rational strategy for reducing blood pressure and preserving renal function [1]. Thus, our patients were occasionally assigned diuretics to achieve blood pressure goals. The use of a diuretic is often helpful in patients who already have renal insufficiency because fluid overload is an important cause of hypertension and because diuretics may also enhance the effectiveness of drugs that interfere with the renin-angiotensin-aldosterone system [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 receiving combination therapy with an ACE inhibitor received amlodipine, a dihydropyridine calcium channel blocker. In preliminary clinical trials in hypertensive patients with chronic renal failure, manidipine, a dihydropyridine calcium channel antagonist that, unlike older members of this class, blocks both L- and T-type calcium channels rather than only L-type channels, has beneficial effects on intrarenal haemodynamics, proteinuria, and other measures of renal function. In addition, preliminary results from a trial in diabetic patients with uncontrolled hypertension and microalbuminuria despite optimal therapy with an ACE inhibitor or angiotensin receptor blockers suggest that manidipine may be an excellent in combination with renin-angiotensin system inhibitors for normalizing blood pressure and albumin excretion [1]. Calcium antagonists are effective for treating hypertensive patients with chronic renal impairment but have not been studied as intensively as ACE inhibitors

Table 7. Blood pressure data at the end of the study period.

Characteristic	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	116.15±8.93	119.38±10.5	122.5±5.49
Diastolic	68.46±5.91	69.38±7.29	69.72±6.52
MAP	78.75±6.29	86.67±2.88	88.18±4.62

Continuous values are reported as means ± SD and categorical values as percentages. MAP, mean arterial pressure.

with regard to their ability to slow the progression of renal insufficiency independently of their blood pressure-lowering effects. Initial studies have produced promising results for the use of calcium antagonists and combinations of calcium antagonists and ACE inhibitors [16].

Short-acting dihydropyridine calcium channel blockers are not recommended. On the other hand, long-acting dihydropyridines such as diltiazem and verapamil are less potent vasodilators and may primarily decrease the resistance of the efferent arteriole, similar to ACE inhibitors. Although these may have antiproteinuric activity, large prospective randomized trials are needed to assess this possibility [2].

ACE inhibitors seem to lower proteinuria more than other antihypertensive drugs, despite a similar ability to lower blood pressure. Calcium antagonists likewise exert beneficial intrarenal effects, but with some differences among the various subclasses. Overall, data from clinical trials suggests that ACE inhibitors and possibly calcium antagonists should be preferred for the treatment of patients with diabetic and nondiabetic nephropathies. However, further information is needed to understand renal protection by these agents [22]. Similarly, multivariate analysis of controlled and uncontrolled trials has shown that the long-term benefits of antihypertensive agents on proteinuria and the glomerular filtration rate are proportional to the reduction in blood pressure 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 effects on blood pressure [13].

In some of our patients, arterial hypertension goals were achieved when a beta blocker was combined with 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]. A study evaluating the effects of four different antihypertensive drugs (the calcium channel blocker felodipine, the beta blocker metoprolol, the ACE inhibitor ramipril, and the alpha-blocking agent doxazosin) on microalbuminuria and renal hemodynamics in 17 patients with mild to moderate essential arterial hypertension and microalbuminuria found that all drugs reduced the mean arterial pressure and microalbuminuria to a similar and statistically significant extent [17].

The current study has some limitations. Although 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, and diet [23], we could not establish a connection between these variables in our study. Also, the number of patients was low, so that some of the results and their interpretations should be considered with care.

In summary, hypertension is common in chronic renal disease and is a risk factor for a more rapid 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, considering that increased UAE implies renal damage secondary to hypertension or underlying renal and systemic endothelial dysfunction, antihypertensive treatment should be intensified and blood pressure control optimized.

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