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Therapeutic Effects of a Selective Mineralocorticoid Receptor Blocker as an Additional Combination Antihypertensive Drug in Hypertensive Patients

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Summary

Among the components of renin-angiotensin-aldosterone system, aldosterone facilitates the progression of cardiovascular organ injuries not only by promoting renal tubular Na reabsorption but also by causing oxidative stress, inflammation and cardiovascular tissue hypertrophy and fibrosis. Therefore, mineral corticoid receptor blockers (MRB) supposedly exhibit protective effects against cardiovascular organ injuries in hypertensive patients. In this study, the therapeutic effects of MRB in the combination antihypertensive treatment were examined in hypertensive patients.

Fifty mg eplerenone (EPL) was added to 24 hypertensive patients under antihypertensive drug therapy who had not achieved the target blood pressure. The combination was continued for 3 to 4 months and the effects on blood pressure (BP) and laboratory data including renal function and cardiovascular endocrine system were evaluated.

After 3-4 months, office BP was lowered from 148/91 to 135/86 mmHg ($p<0.001/p=0.002$) as well as the home BP (morning 150/86 to 134/81, $p = 0.001/p = 0.033$; evening 139/80 to 127/74, $p = 0.005/p = 0.030$). Serum K (4.2 to 4.3 mEq/L, $p = 0.014$) and creatinine (0.82 to 0.87 mg/dL, $P<0.001$) increased slightly but significantly. Serum uric acid also increased significantly from 5.8 to 6.4 mg/dL ($p = 0.015$). However, the indices of glucose metabolism and serum lipids were not affected. In addition to the natural increases in plasma renin and aldosterone, plasma B-type natriuretic peptide (BNP: 23 to 17 pg/mL, $p = 0.028$) and urinary albumin excretion (111 to 70 mg/gCr, $p = 0.009$) were significantly decreased.

In the combination antihypertensive drug therapy, MRB is expected to reduce cardiac and renal injuries and the influences on glucose and lipid metabolisms seem negligible, however, care should be taken for the development of hyperuricemia and renal dysfunction in addition to hyperkalemia.

Key Words: hypertension, eplerenone, mineral corticoid receptor blocker, aldosterone, albuminuria

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Introduction

High blood pressure facilitates the progression of arteriosclerosis which increases the incidence of cardiovascular diseases such as stroke and coronary heart disease. Hypertension is also a major risk factor for the development of cardiovascular organ damages such as heart failure and renal dysfunction. The occurrence of these adverse cardiovascular events greatly impairs the quality of later life as well as shortening the life prognosis. Considering that hypertension is most prevalent lifestyle-related diseases, it is obviously important to control the blood pressure (BP) in optimal range and prevent the development of cardiovascular disorders[1-4].

According to the epidemiological follow-up studies, the lower BP is associated with lower risk of cardiovascular diseases such as cerebrovascular disease and ischemic heart disease even to the level as low as 115/75 mmHg[5]. The results of meta-analyses of randomized and controlled interventional studies also show that the strict BP control is more effective in reducing cardiovascular events and death than the usual BP control targeting <140/90 mmHg[4,6,7]. Therefore, the latest versions of guidelines for the management of hypertension recommend the strict target BP level lower than 130/80 mmHg in principle[8-10].

In order to achieve such strict target BP level, the combination of multiple antihypertensive drugs is usually needed in addition to lifestyle modification. Considering that the insufficient sodium excretion and the increased peripheral vascular resistance play pivotal roles in the etiology of hypertension, the use of diuretics is indispensable to lower BP effectively. For the purpose of antihypertensive therapy, the thiazide diuretics have been widely used so far because of the established evidence of improving the prognosis of hypertensive patients[11]. On the other hand, the evidence does not seem sufficiently accumulated as to the effects of mineral corticoid blockers, as diuretics, on the long-term prognosis of hypertensive patients.

In the present study, we evaluated the changes in cardiovascular risk profile by the addition of eplerenone (EPL), a selective antagonist of mineral corticoid receptor, in hypertensive patients.

Methods

The subjects enrolled in this study were 24 hypertensive outpatients whose blood pressure (BP) had not achieved the target level. The target BP was <130/80 mmHg for patients with diabetes mellitus or chronic kidney disease presenting proteinuria and <140/90 mmHg for other patients[10]. Patients with severe hypertension exceeding 180/110 mmHg or secondary causes of hypertension other than chronic kidney disease were excluded. According to the drug use regulations in Japan, we did not include patients diagnosed with diabetic nephropathy or patients with reduced renal function whose creatinine clearance (CCr) calculated by Cockcroft-Gault formula[12] indicated below was less than 50 mL/min.

CCr = (140 − age) × body weight (kg)/(72 × serum creatinine (mg/dL)) (× 0.85 for women)

We also excluded patients already taking mineral corticoid receptor blocker (MRB) such as spironolactone.

The patients were given 50 mg eplerenone (EPL) once daily in the morning for 12 to 16 weeks in addition to taking other drugs which are not changed during the study period. The medications having been given were not changed and continued during the study period. Office BP was measured with a sphygmomanometer in the sitting position after resting for at least 20 min at each visit every 4 weeks. Home BP was measured consecutively for 7 days before each visit using an arm-cuff oscillometric automatic manometer within 1 hour of awakening (before drug administration) as morning blood pressure and before going to bed as evening blood pressure, and the mean values were obtained. The patients used their own manometers equipped with arm cuffs.

Before and after 12 to 16 weeks starting EPL, nonfasting blood samples were drawn from the antecubital subcutaneous vein. In addition to the routine blood chemistry and blood cell counts, plasma renin activity (PRA) and plasma concentrations of aldosterone (PAC) and B-type natriuretic peptide (BNP) were determined by enzyme immunoassay, immune-radiometric assay and chemiluminescent enzyme immunoassay, respectively. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level (sCr)

Table 1 Baseline characteristics of the study subjects.

Age, years	58.4 ± 12.6
Gender, male/female	13 / 11
Body mass index, kg/m^2	26.7 ± 5.5
Systolic blood pressure, mmHg	147.5 ± 10.1
Diastolic blood pressure, mmHg	91.4 ± 10.3
Heart rate, bpm	75.0 ± 11.8
Duration of hypertension, years	13.2 ± 7.3
Complications	
Diabetes mellitus	8 (33.3%)
Dyslipidemia	10 (41.7%)
Hyperuricemia	4 (16.7%)
Chronic kidney disease	11 (45.8%)
Cardiovascular disease	3 (12.5%)

Data are the mean ± SD.

Table 2 Medications concurrently given with eplerenone in study subjects.

Drug	Number of subjects (%)
Antihypertensive drug	
Thiazide diuretic	3 (12.5%)
β-blocker	3 (12.5%)
α-blocker	3 (12.5%)
Calcium channel blocker	15 (62.5%)
ACE inhibitor	1 (4.2%)
Angiotenisn II receptor blocker	18 (75.0%)
Oral hypoglycemic agent	4 (16.7%)
Lipid-lowering drug	6 (25.0%)
Antihyperuricemic drug	2 (8.3%)
Antiplatelet drug	4 (16.7%)
Anticoagulant	1 (4.2%)
Antiarrhythmic drug	3 (12.5%)

and age by the following equation[8]: eGFR = 194 × Age$^{-0.287}$ × sCr$^{-1.094}$ (× 0.739 for females) mL/min/1.73 m^2. Casual urine samples were also collected at the visits before and after 12 to 16 weeks. Urinary albumin was measured by an immunoturbidimetric method and corrected using the urinary creatinine level. Then, the urinary albumin excretion (UAE) was expressed in mg albumin to g creatinine ratio (mg/gCr).

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Fortaleza version, 2013) and was approved by the institutional review board (C-260-02). Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means ± standard deviations (SD) or medians with interquartile ranges. Values before and after the study period were compared by paired t-test, however, Wilcoxon signed-rank test was applied for the data with skewed distribution. A P value of less than 0.05 was considered to be statistically significant.

Results

All the 24 patients who started EPL showed good adherence to the therapy and fulfilled the whole study periods. Table 1 shows the baseline characteristics of these 24 patients. The 12 patients were overweight with body mass index (BMI) higher than 25 kg/m^2 and 8 patients were obese with BMI higher than 30 kg/m^2 resulting in the overweight level of averaged BMI. The considerable percentage of patients were complicated with lifestyle-related diseases other than hypertension such as diabetes, dyslipidemia and hyperuricemia. In addition, 12.5% patients had cardiovascular disease such as arrhythmia and nearly half patients had been diagnosed with having renal diseases such as glomerulonephritis and nephrosclerosis.

Table 2 lists the drugs concurrently prescribed before and during the study period of 12 to 16 weeks. As antihypertensive medications, angiotenisn II receptor blockers and calcium channel blockers were frequently used. In addition, certain percentages of patients were taking drugs for lifestyle-related diseases such as diabetes mellitus, dyslipidemia and hyperuricemia. The doses of these drugs were unchanged throughout the study periods.

All the 24 patients showed good adherence to the therapy and fulfilled the whole study period. The physical findings of study subjects before and after taking EPL are shown in Table 3. Body weight was not significantly changed after the 12- to 16-week period given EPL. The systolic and diastolic office BP measured at hospital visits were significantly reduced by 12.7/4.8 mmHg after taking eplerenone for 12 to 16 weeks, while the heart rate was not significantly affected. Fig. 1 shows the effects of EPL on home BP in the morning and the evening. As well as the office BP, the morning and the evening home BPs were significantly lowered by 16.2/4.8 mmHg (p=0.001/0.033) and

Table 3 Blood pressure, heart rate and body weight before and after 12 to 16 weeks after starting eplerenone.

Variable	Before	After 12-16 weeks	P value
Systolic BP, mmHg	147.5 ± 10.1	134.8 ± 9.3	< 0.001
Diastolic BP, mmHg	91.4 ± 10.2	86.6 ± 10.2	0.002
Heart rate, bpm	75.0 ± 11.8	76.4 ± 11.2	0.498
Body weight, kg	68.5 ± 16.1	68.5 ± 15.1	0.862

Data are the mean ± SD. BP, blood pressure.

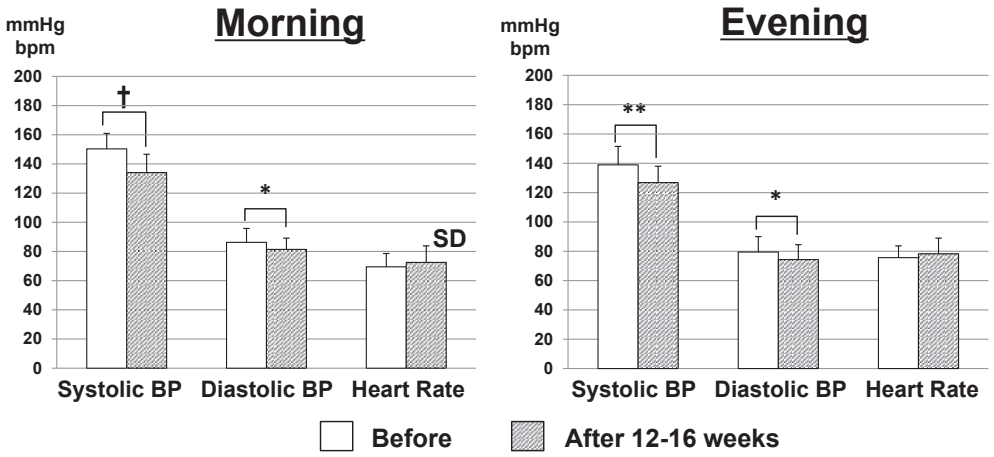

Figure 1 Average home blood pressure and heart rate before and after taking eplerenone for 12 to 16 weeks. Data are mean ± SD. * $p < 0.05$, ** $p < 0.01$, † $p < 0.005$.

12.1/5.2 mmHg (p=0.005/0.030), respectively, at the end of 12- to 16-week treatment period with EPL. However, the heart rates in the morning or the evening were not significantly different between before and after the EPL administration.

Table 4 shows the changes in blood cell counts before and 12 to 16 weeks after starting EPL. The number of erythrocytes, hemoglobin concentration, hematocrit and the numbers of white blood cells and platelets were not significantly changed by the EPL treatment. The changes in blood chemistry data are shown in Table 4. The serum total protein, albumin and liver enzymes such as aspartate transaminase (AST) and alanine transaminase (ALT) were not significantly changed after taking EPL for 12 to 16 weeks. also reduced significantly at the end of study period. Although the serum sodium (Na) was not significantly changed, the serum potassium (K) and uric acid were significantly increased after the 12 to 16 weeks of EPL therapy. As for the parameters of glucose and lipid metabolism, plasma glucose, hemoglobin A1c and serum lipids such as triglycerides and high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol were not significantly affected by EPL.

Fig. 2 depicts the changes in cardiovascular endocrine factors after taking EPL. As expected naturally, PRA and PAC were markedly enhanced from 2.2 ± 1.9 to 3.6 ± 2.5 ng/mL/hr (p=0.021) and from 112 ± 61 to 158 ± 50 pg/mL (p=0.019), respectively, by EPL, a selective blocker of mineral corticoid receptor. In addition, the plasma BNP was significantly reduced from 20.1 ± 14.5 pg/mL to 15.8 ± 11.9 pg/mL (p=0.044) after the 12 to 16 weeks of EPL treatment.

Fig. 3 shows the effects of EPL on renal parameters of study subjects. Corresponding to the increase in serum creatinine, the calculated eGFR was significantly decreased from to 69.4 ± 21.3 to 65.5 ± 21.0 mL/min/1.73 m^2 (p=0.001) after taking EPL for 12 to 16 weeks (Fig. 3, left panel). On the other hand, the UAE was significantly reduced from 287 ± 469 to 185 ± 412 mg/gCr (p< 0.001) by the EPL treatment Fig. 3, right panel).

Table 4 Data of peripheral blood cell counts and blood chemistry before and after 12 to 16 weeks after starting eplerenone.

Variable	Before	After 12-16 weeks	P value
White blood cell, $\times 10^3/mm^3$	6.08 ± 1.79	6.40 ± 1.79	0.242
Red blood cells, $\times 10^6/mm^3$	4.53 ± 0.42	4.42 ± 0.40	0.130
Blood hemoglobin, g/dL	14.0 ± 1.2	13.7 ± 1.2	0.162
Hematocrit, %	42.2 ± 3.7	41.4 ± 3.6	0.224
Platelet, $\times 10^3/mm^3$	257 ± 60	266 ± 54	0.382
Aspartate transaminase, U/L	26 ± 10	27 ± 9	0.552
Alanine transaminase, U/L	27 ± 9	26 ± 18	0.469
Total protein, g/dL	6.9 ± 0.4	7.0 ± 0.4	0.160
Albumin, g/dL	4.1 ± 0.4	4.1 ± 0.3	0.224
Na, mEq/L	140.9 ± 1.4	141.0 ± 1.7	0.784
K, mEq/L	4.2 ± 0.3	4.3 ± 0.3	0.014
Creatinine, mg/dL	0.82 ± 0.17	0.87 ± 0.18	< 0.001
Uric acid, mg/dL	5.8 ± 0.9	6.4 ± 1.1	< 0.001
Plasma glucose, mg/dL	105 (89-139)	101 (89-142)	0.179
Hemoglobin A1c, %	6.1 ± 1.1	6.0 ± 0.9	0.356
HDL-cholesterol, mg/dL	61 ±16	61 ±15	0.893
LDL-cholesterol, mg/dL	118 ± 27	112 ± 26	0.206
Triglycerides, mg/dL	128 (71-191)	121 (76-145)	0.141

Data are the mean ± SD or the median (interquartile range). AST: aspartate transaminase, ALT: alanine transaminase, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

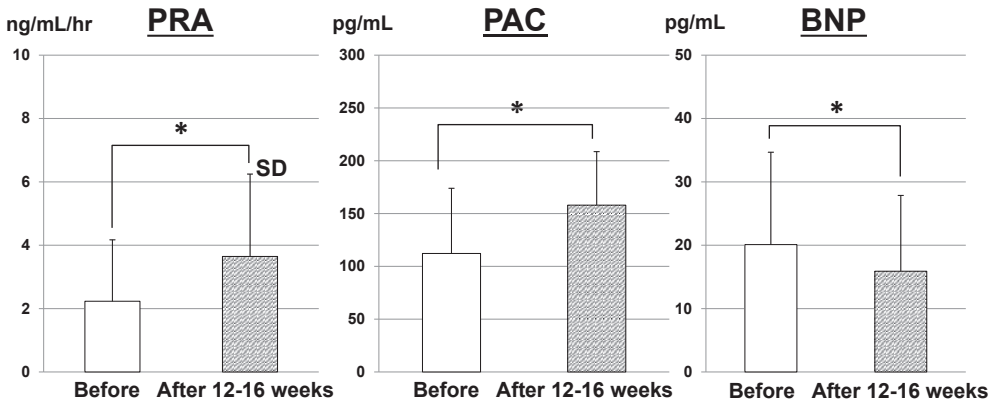

Figure 2 Changes in plasma renin activity (PRA, left panel), plasma aldosterone concentration (PAC, middle panel) and plasma B-type natriuretic peptide (BNP, right panel) before and after taking eplerenone for 12 to 16 weeks. Data are mean ± SD. * $p < 0.05$.

Discussion

Although strict BP control is required to sufficiently prevent the incidence of cardiovascular events in the treatment of hypertension, a large part of hypertensive patients have not been noticed, treated or have their hypertension controlled[13]. Even in patients under antihypertensive drug therapy, two thirds have been shown to fail to achieve BP levels lower than 140/90 mmHg[14]. For such cases, intensification of antihypertensive medication combining multiple agents is needed to achieve sufficiently low BP levels for the prevention of cardiovascular events. In combining the antihypertensive drugs, the addition of thiazide diuretics is effective in lowering BP by promoting natriuresis and strengthen the hypotensive effects of other classes of antihypertensive drugs concurrently given which generally have vasodilative actions and reduce periph-

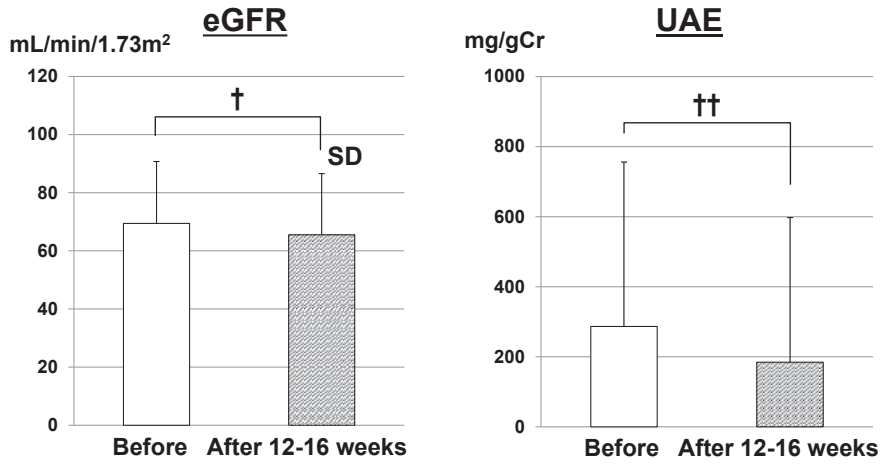

Figure 3 Changes in estimated glomerular filtration rate (eGFR, left panel) and urinary albumin excretion (UAE, right panel) before and after taking eplerenone for 12 to 16 weeks. gCr: g creatinine. Data are mean ± SD. † $p < 0.005$, †† $p < 0.001$.

eral vascular resistance.

MRB also cause diuresis by antagonizing the action of aldosterone and inhibiting Na reabsorption in the distal and collecting tubules of nephron. In PATHWAY-2 study[15], spironolactone, β-blocker (bisoprolol) or α-blocker (doxazosin) was added to patients with treatment-resistant hypertension whose systolic BP was not lower than 140 mmHg even with the combination of ACE inhibitors/ARB, calcium channel blockers and diuretics. As a result, spironolactone was most effective in lowering BP with the affordable occurrence rate of adverse events such as hyperkalemia. Also in the present study, the addition of EPL, a newer and selective MRB, significantly reduced not only the office BP but also the home BP in the morning and evening and no patients experienced needs for stopping or reducing the dose of EPL by the occurrence of any adverse effects. Thus, it is suggested that the addition of EPL, as well as spironolactone, is tolerable and useful for achieving the 24-hour BP control in hypertensive patients who needs the combination of multiple antihypertensive drugs[16,17].

The thiazide diuretics often cause adverse effects such as hypokalemia, hyperuricemia and unfavorable influences of glucose and lipid metabolism which are supposed to lessen the preventive effects against the incidence of cardiovascular diseases. Indeed, in the Systolic Hypertension in the Elderly Program (SHEP) used chlorthalidone for elderly hypertensive patients, the incidence of stroke or coronary artery disease failed to reduce significantly in participants who developed hypokalemia lower than 3.5 mEq/L or the increase in serum uric acid by 1 mg/dL or more [18,19].

In contrast to thiazide diuretics, MRB are known to increase serum K. EPL has high selectivity to mineral corticoid receptor and causes less side effects such as gynecomastia and menstruation disturbances than spironolactone. However, EPL increased serum K slightly but significantly in the present study and care should be taken for the development of hyperkalemia in the use of MRB including EPL especially when ACE inhibitors or angiotensin II receptor blockers (ARB) are concurrently used. The influences of EPL on the glucose and lipid metabolisms are not apparent in this study, but the serum uric acid was significantly increased with EPL and the development hyperuricemia is also a matter of concern in the use of EPL.

Aldosterone, as well as promoting Na reabsorption by renal tubules and increasing body fluid volume and BP, has been shown to cause deleterious effects on the cardiovascular tissues and organs such as vasoconstriction, cellular hypertrophy, tissue fibrosis and endothelial injuries[20-23]. In addition, cardiovascular tissues themselves are thought to have the ability to produce the components of renin-angiotensin-aldosterone (RAA) system, such as renin, angiotensinogen, ACE and aldosterone[24,25]. Furthermore, mineral corticoid receptors have been shown to express in the cardiac and vascu-

lar tissues[26,27]. Therefore, it is speculated that MRB is expected to exert protective effects against the development and progression of cardiovascular tissue and organ injuries by the mechanisms independent of BP reduction. In this context, the results of randomized and controlled large-scale clinical studies have indicated that MRB, including EPL, improve the prognosis of patients with heart failure or myocardial infarction [28,29]. Also in the current study, EPL reduced plasma BNP in the hypertensive patients. Circulating BNP, produced mainly in the cardiac ventricles, increases by pressure and volume load to the heart and is supposed to be a predictive factor of the prognosis of cardiac diseases[30-32]. Thus, it is speculated that EPL may reduce the incidence of heart failure in the long-term treatment of hypertensive patients.

With regard to the indices of renal function and injuries, thiazide diuretics have been shown to reduce the glomerular filtration rate (GFR) and albuminuria in hypertensive patients [33,34]. These renal effects were shared by EPL as a diuretic in this study. The reduction of blood volume by the diuretics may decrease renal blood flow and intraglomerular capillary pressure. On the one hand the reduction in albuminuria is supposed to reflect the alleviation of renal injury, on the other hand the reduction in GFR may bring about the progression of renal dysfunction. However, it has been indicated that the temporary decrease in GFR by ACE inhibitors or ARB is predictive of long-term preservation of renal function[35,36]. Similar effects have been observed in recent clinical studies enrolled diabetic patients and used sodium-glucose co-transporter (SGLT) 2 inhibitors which cause osmotic diuresis by promoting glucosuria[37-39]. The SGLT2 inhibitors such as empagliflozin and canagliflozin have shown to reduce albuminuria and long-term incidences of renal outcomes such as doubling of serum creatinine and needs for renal replacement therapy[37,38]. Even in non-diabetic patients with chronic kidney disease, dapagloflizin, a SGLT2 inhibitor, has been reported to exhibit similar effects on the risk of renal outcomes[39]. Taken together, the reductions in eGFR and UAE by EPL observed in this study are possibly associated with renoprotective effects in hypertensive patients.

In summary, the addition of EPL significantly lowered the office and home BP in hypertensive patients under antihypertensive medication in the present study. EPL did not significantly alter the indices of glucose and lipid metabolisms but the serum K and uric acid were significantly increased. The plasma BNP, eGFR and UAE were significantly reduced after the 3 to 4 months of EPL treatment. It is concluded that EPL is effective in intensifying the BP control in combination antihypertensive drug therapy with possibly beneficial effects on the risks of cardiac and renal events, however, care should be taken for the development of hyperkalemia and hyperuricemia.

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