Renal Protective Effects of Combination of Diltiazem and ACEI/ARB on the Progression of Diabetic Nephropathy: Randomized Controlled Trial

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Background: *Strict control of blood sugar and maintenance of normal blood pressure levels are the standard treatments shown to delay the progression of diabetic nephropathy in type 2 diabetic patients. The recommended antihypertensive medications for diabetic nephropathy are angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB). Previous studies have shown that a non-dihydropyridine calcium channel blocker (diltiazem) could reduce urinary protein excretion in type 2 diabetic patients.*
Objective: *To evaluate the effects of the combinations of diltiazem and ACEI/ARB treatment compared with ACEI/ARB alone in type 2 diabetic patients with diabetic nephropathy.*
Material and Method: *A prospective, randomized, double-blind, placebo-controlled multicenter trial was conducted at the out-patient departments of Rajavithi Hospital (Bangkok) and Ban-phaeo Hospital (Samut Sakhon). A total of 106 type 2 diabetic patients with hypertension and urine protein/creatinine (UPCr) >0.3 gm/gm who had received ACE/ARB were randomized into two groups: a diltiazem group (ACEI/ARB + sustained-release diltiazem 120 mg daily) (50 cases) and a placebo group (ACEI/ARB + placebo) (56 cases). Intention-to-treat analysis was utilized with the data of patients who withdrew from the study before its completion date.*
Results: *39 cases in the diltiazem group (78.0%) and 38 in the placebo group (67.9%) completed the 1-year treatment. The diltiazem group achieved better preservation of glomerular filtration rate and had lower proteinuria than the placebo group ($p < 0.05$), whereas blood pressure was similar in the two groups. Four patients in the diltiazem group and one patient in the placebo group developed severe pedal edema and discontinue treatment.*
Conclusion: *A combination of diltiazem and ACE/ARB could reduce proteinuria and preserve kidney function in type 2 diabetic patients with diabetic nephropathy.*

Keywords: *Diabetic nephropathy, Diltiazem*

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Diabetic nephropathy is a chronic kidney disease that is now commonly found in patients with diabetes mellitus in many countries including Thailand[1,2]. The early stages of diabetic nephropathy are microalbuminuria and macroalbuminuria while the advanced stage is kidney failure[3], which is life-threatening, and patients in this condition require costly treatments such as renal replacement therapy. Strict control of blood glucose and maintenance of normal blood pressure have been found to be greatly beneficial in slowing the progression of kidney disease in diabetic patients[4-6]. Previous studies have demonstrated that angiotensin-converting enzyme inhibitors (ACEI)[7] and angiotensin receptor blockers (ARB)[8] are the classes of antihypertensive drugs that greatly assist in delaying kidney damage in diabetic patients with normal or high blood pressure. Other classes of antihypertensive medication, such as dihydropyridine calcium channel blockers and beta adrenergic blockers, are not as effective as ACEI or ARB in delaying the progression of renal disease in hypertensive patients with diabetes mellitus. Although these two classes of antihypertensive medicines are recommended for diabetic nephropathy treatment, they can cause some serious adverse events. The side effects of ACEI include early reduction of glomerular filtration rate (GFR), hyperkalemia and intractable cough,

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and these may lead to discontinuation of the drug. ARB can also induce these adverse effects, but the incidence of cough resulting from ARB treatment is lower than that caused by ACEI[9]. Recently, there have been reports of renal protective effects in another class of antihypertensives called non-dihydropyridine calcium channel blockers, especially diltiazem, which has few adverse events. Manuel Perez-Maraver et al[10] conducted a 2-year study to evaluate the efficacy of diltiazem treatment in 13 type 2 diabetic patients with hypertension and persistent microalbuminuria. They reported that diltiazem in combination with captopril (ACEI), as opposed to captopril alone, was clearly effective in lowering the amount of protein in the urine (urine albumin/creatinine excretion-UAE). In the combination treatment group, the UAE baseline of 101 mg/day (range 39 to 298) was reduced to 74 mg/day (12 to 665) after a period of two years, compared with the UAE baseline of 118 mg/day (range 32 to 282) and the 2-year figure of 164 mg/day (15 to 1,161) in the group treated with captopril alone ($p<0.05$). The combination therapy had beneficial effects in delaying kidney function reduction by clearly preventing microalbuminuria from progressing into macroalbuminuria. 8% of combination treatment group developed macroalbuminuria while 40% of patients receiving captopril alone experienced such disease progression ($p<0.05$). Even though the study by Manuel Perez-Maraver et al suggested that diltiazem may delay chronic renal disease in diabetic patients when used with ACEI, the number of participating patients in their study was rather small, and further investigation to confirm such efficacy of combination therapy with diltiazem is thus required. In Thailand, diltiazem has been widely used to treat hypertension, but there has been no research on its kidney-protective benefits in patients with diabetes. The objective of this study was to compare the efficacy of the concomitant treatments of diltiazem and ACEI/ARB with monotherapy with ACEI/ARB in delaying the progression of chronic kidney disease in diabetic patients.

Material and Method

This prospective, randomized, double-blind, placebo-controlled, multicenter trial compared the efficacy of the concomitant treatments of diltiazem and ACEI/ARB with monotherapy with ACEI/ARB in type 2 diabetic patients. The study was approved by the ethics committee of Rajavithi Hospital (Bangkok) and Ban-phaeo Hospital (Nakhon Pathom Province). Type 2 diabetic patients, as defined by the American Diabetes Association's criteria[11], were recruited at the out-patient departments of Rajavithi Hospital and Ban-phaeo Hospital, and all patients voluntarily signed the consent form.

Inclusion criteria were patients at least 18 years of age and having received diabetic treatment from an endocrinologist with or without a nephrologist for at least one year. Patients were treated with the aim of controlling blood glucose levels (HbA1c less than 7%) and blood pressure (BP less than 130/80 mmHg). Subjects had been in a stable condition and had received treatment with ACEI or ARB without non-dihydropyridine calcium channel blockers at least 3 months. They had GFR values of greater than 15 ml/min/1.73 m^2 (using abbreviated Modification of Diet in Renal Disease formula[11]) and GFR which had not changed by over 10% within 3 months. Their urine had been tested for urine protein/urine creatinine ratio (UPCr) at least twice a year and results were abnormal (higher than 30 mg/gm). Exclusion criteria were 1 pregnant, 2 suffered from acute systemic diseases (such as cancer, infection, chronic heart failure, and malignant hypertension), 3 failed to follow urine collecting procedures, 4 refused to cooperate, 5 had medical/health conditions that interfered with urinalysis (such as infections, fever, menstruation or heavy physical work), 6 had kidney disease caused by medical conditions other than diabetes mellitus (such as glomerulonephritis and obstructive uropathy), 7 were using non-prescribed medications that could affect diabetes treatment (such as steroids or herbs) and 8 had mental health problems.

Patients were informed about the details of the study before voluntarily signing the consent form. They underwent screening through medical check-ups and laboratory tests at Rajavithi Hospital and Ban-phaeo Hospital. Block randomization of these patients were assigned to either the diltiazem group (ACEI/ARB and diltiazem) or the control group (ACEI/ARB and placebo). Patients in the diltiazem group received sustained-release diltiazem 120 mg (Cardil 120 mg controlled release tablet®, Orion Corporation Espoo, Finland) and patients in the control group received placebos throughout the one-year study period. The appearance and packaging of the placebos were identical to those of diltiazem. Neither the subjects nor the research teams knew which trial drug was being administered to the two groups. To monitor the patients' medication intake, the remaining medicines from their previous visit were counted before a new prescription

was given. The dosage of medications from other antihypertensive classes was adjusted so that the target blood pressure (130/80 mmHg) was maintained. After that, patients were scheduled for future clinical visits on a monthly or bimonthly basis for treatment and follow-up care, and they underwent laboratory testing every 3 months until the trial ended.

The patients' trial was terminated in the following circumstances: 1) they had received treatment and follow-up care for one year in accordance with the research methodology; 2) they had a clinically marked reduction in kidney function, namely a 50% drop in GFR; 3) they had a GFR of less than 15 ml/min/1.73 m^2 indicating that they had developed kidney failure or required renal replacement therapy; or 4) they had developed severe complications that were induced by the treatment in the trial or led to treatment discontinuation.

The outcome assessments were expressed in terms of: 1) reduction of kidney function assessed through serum creatinine testing and GFR (calculated using the abbreviated Modification of Diet in Renal Disease formula[11]); 2) progression of diabetic nephropathy assessed by monitoring changes in urine protein (UPCr), progression into end-stage renal failure, or the need for renal replacement therapy (hemodialysis or peritoneal dialysis); or 3) adverse events resulting from the treatment.

The data processing and analysis in the study was assisted by the computer program SPSS version 17. Statistical analysis of data from both groups was performed using unpaired t-test and general linear model (repeated measures). Intention-to-treat analysis was utilized with the data of patients who withdrew from the study before its completion date. The results were presented in terms of percentages or mean ± standard deviation. Factors analyzed for the comparison of results from the diltiazem and control groups were: 1) UPCr, 2) GFR, and 3) mean blood pressure. Statistical significance was set at a *p*-value <0.05.

Results

From January 2011 to July 2013, after five participants were excluded at the screening stage, research was conducted on a total of 106 type 2 diabetic outpatients, 18 at Rajavithi Hospital and 88 at Banphaeo Hospital. Table 1 shows the baseline characteristics of the participating patients. Males slightly outnumbered females. On average, the subjects were elderly (65.81±9.13 years old) and were supported by universal coverage program (83.96%). The subjects were overweight with high body mass index (26.88±5.06 kg/m^2). They all had well-controlled hypertension with acceptable blood pressure levels (systolic blood pressure of 140.00±22.01 mmHg and diastolic blood pressure of 70.30±13.02 mmHg), and they were being treated with ACEI or ARB in combination with other hypertensive medications. HbA1c level was slight high (7.76±1.67). Their kidney functions were in moderate impairment (GFR = 45.30±26.83 ml/min/1.73 m^2), and most subjects were suffering from chronic kidney disease stages 3 and 4 (48.1% and 32.1% respectively), with high levels of urine protein (UPCr = 2.05±2.25 gm/gm).

These 106 patients were randomly assigned to a placebo group (56 patients) and a diltiazem group (50 patients). There was insignificantly difference of clinical and laboratory data between the two groups (Table 2). Fig. 1 provides information about participation

Table 1. General information about the 106 participating patients

Characteristics	Patients (n = 106)
Male	56 (52.8)
Age (years)	65.81±9.13
Duration of diabetes (years)	13.14±9.88
Sources of medical care funding	
Universal coverage program	89 (84.0)
Personal funds	14 (13.2)
Social security office	2 (1.9)
Government/state enterprise	1 (0.9)
Height (cm)	159.91±8.76
Weight (kg)	68.97±14.84
Waist measurement (cm)	95.72±11.72
Body mass index	26.88±5.06
Systolic blood pressure (mmHg)	140.00±22.01
Diastolic blood pressure (mmHg)	70.30±13.02
Mean blood pressure (mmHg)	93.49±11.98
HbA1c (%)	7.76±1.67
Hemoglobin (g/dl)	12.07±1.60
Serum creatinine (mg/dl)	1.80±0.76
GFR (ml/min/1.73 m^2)	45.30±26.83
UPCr (g/g)	2.05±2.25
CKD staging	
Stage 1	9 (8.5)
Stage 2	12 (11.3)
Stage 3	51 (48.1)
Stage 4	34 (32.1)

Value were represented as n (%) and mean ± SD

Table 2. General information about the 50 patients in the diltiazem group and the 56 patients in the placebo group

Characteristics	Diltiazem (n = 50)	Placebo (n = 56)	*p*-value
Male	27 (54.0)	29 (51.8)	0.820
Age (years)	65.21±8.73	66.34±9.54	0.524
Duration of diabetes (years)	13.14±9.88	14.29±7.55	0.501
Height (cm)	159.92±8.85	159.91±8.76	0.996
Weight (kg)	68.61±17.81	69.30±11.73	0.812
Waist measurement (cm)	95.06±12.41	95.44±11.17	0.789
Body mass index	26.69±6.16	27.05±3.87	0.714
Systolic blood pressure (mmHg)	140.00±22.01	140.62±19.79	0.878
Diastolic blood pressure (mmHg)	70.30±13.02	71.04±11.24	0.755
Mean blood pressure (mmHg)	92.62±13.21	94.26±10.83	0.486
HbA1c (%)	7.85±1.75	7.67±1.60	0.560
Hemoglobin (g/dl)	12.11±1.67	12.04±1.54	0.844
Serum creatinine (mg/dl)	1.73±0.73	1.86±0.78	0.379
GFR (ml/min/1.73 m^2)	48.03±28.87	42.86±24.87	0.325
UPCr (g/g)	1.85±2.23	2.23±2.27	0.382
CKD staging			0.065
Stage 1	6 (12.0)	3 (5.4)	
Stage 2	4 (8.0)	8 (14.3)	
Stage 3	29 (58.0)	22 (39.3)	
Stage 4	11 (22.0)	23 (41.1)	

Value were represented as n (%) and mean ± SD

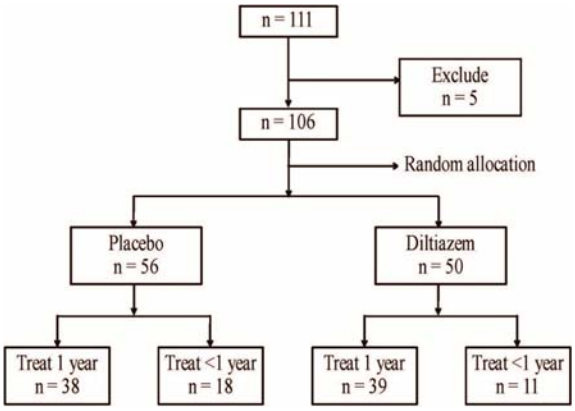

Fig. 1 Information about the subjects' participation in the research study.

in the research study. According to the data, 80 of the 106 patients received the complete one-year study protocol while the other 26 patients withdrew from the study as a result of marked reduction in kidney function in 21 cases (19.8%) and untolerated pedal swelling without kidney function reduction in 5 cases (4.7%).

The number of those treated and followed-up throughout the study was 38 (67.9%) in the placebo group and 39 (78.0%) in the diltiazem one. In the placebo group, 18 patients (32.1%) left the study as 11 (22.0%) in the diltiazem group. A clinically-marked decline in kidney function accounted for the withdrawal of 17 cases (30.4%) in the placebo group, compared with 7 cases (14.0%) in the diltiazem group. Increased pedal swelling unrelated to kidney function reduction was the reason for cessation of the study in the cases of one placebo patient (1.8%) and 4 diltiazem patients (8.0%).

Fig. 2 shows the change in kidney function (GFR) in the placebo and diltiazem groups over the one-year period of the study. Patients in the placebo group were found to experience a greater decline in kidney function than patients in the diltiazem group ($p<0.05$), and this suggests that diltiazem may delay progression of kidney function reduction.

Fig. 3 demonstrates the changes in urine protein levels (UPCr) during the study. The data shows that the patients in the diltiazem group had lower levels of urine protein than those in the placebo group ($p<0.05$); in other words, diltiazem may also decrease urine protein levels.

Fig. 4 compares the changes in patients' blood pressure, and shows that there was no significantly difference between the two groups ($p = 0.235$). HbA1c was no significantly different between both groups at last visit (7.38±1.48% in diltiazem group and 7.09±1.53%

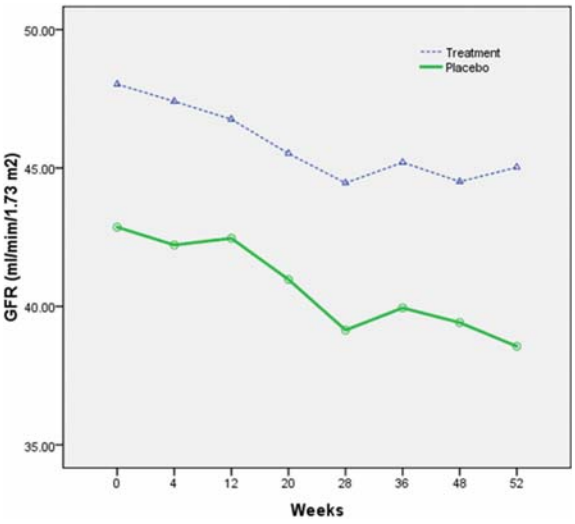

Fig. 2 Changes in kidney function (GFR) in both placebo and diltiazem groups over the one-year period. Diltiazem-treated patients (n = 50) were found to experience a smaller drop in kidney function than placebo-treated ones (n = 56) (p = 0.002).

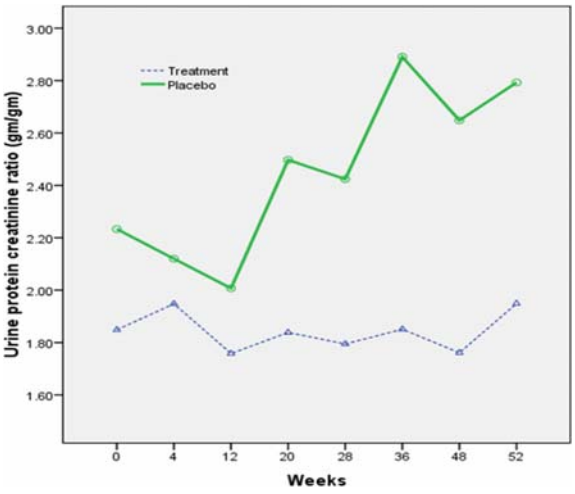

Fig. 3 Changes in protein levels (UPCr) in the patients' urine samples during the study. Diltiazem-treated patients (n = 50) were found to experience a greater drop in urine protein than placebo-treated ones (n = 56) (p = 0.003).

in placebo groups, p = 0.952). Compared with the placebo group, the retardation of patients' kidney function and lower urine protein levels in the diltiazem group did not correlate with changes in their blood pressures and blood sugar.

Discussion

It is well recognized that good blood glucose

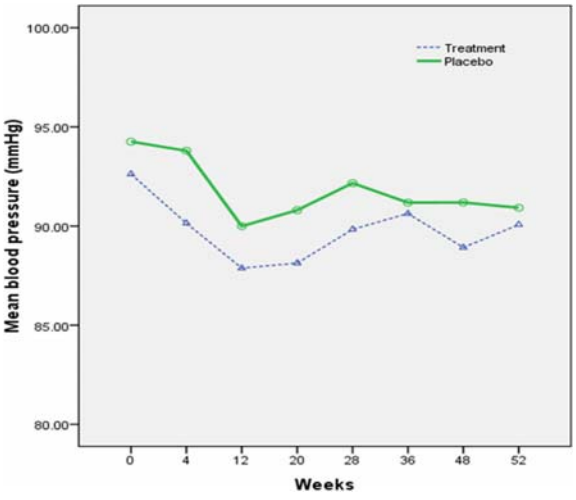

Fig. 4 Changes in the mean blood pressure of patients in both groups over the study period. The mean blood pressure of diltiazem-treated patients (n = 50) was similar to that of placebo-treated patients (n = 56) (p = 0.235).

control is essential in the management of chronic kidney disease caused by diabetes mellitus; in addition, maintaining normal blood pressure can slow the progression of kidney disease in diabetic patients. Previous studies have shown that antihypertensive medications, especially ACEIs or ARBs, are highly beneficial in retarding deterioration of kidney function and decreasing urine protein in diabetic patients with normal and high blood pressure. However, in some cases of ACEI/ARB-treated diabetic patients, ACEI or ARB still cannot return the amount of urine protein to its normal level, and kidney function is still reduced progressively. Hence, new medications, such as direct renin inhibitors (aliskiren) or antioxidant inflammatory modulators (bardoxolone methyl), have been developed, but they have not yet been proven to solve these problems in diabetic patients. With combinations of ACEI/ARB and aliskiren in diabetic patients, the incidence of renal events (end-stage renal disease, renal death, or doubling of serum creatinine) was similar to that of patients treated with ACEI/ARB and a placebo[12]. Adverse events, especially hyperkalemia, were significantly more frequent in subjects treated with aliskiren. With combinations of bardoxolone methyl and ACEI/ARB in diabetic patients, the primary endpoint (a composite of end-stage renal disease and cardiovascular death) was similar to that resulting after treatment with ACEI/ARB and placebo[13]. Combinations of bardoxolone methyl and ACEI/ARB

may increase estimated GFR, but they may also raise blood pressure and urine protein[14], and at present, these new drugs should not be used as standard treatment for patients with diabetic kidney disease.

This study suggested that diltiazem may retard the progression of diabetic nephropathy. Fig. 2 and 3 show that diabetic patients in the diltiazem group (diltiazem and ACEI/ARB) had better preservation of kidney function and excreted lower levels of protein in their urine than those in the placebo group (ACEI/ARB alone). As for the effect on kidney function, subjects who experienced clinically marked renal function reduction accounted for 14.0% of patients in the diltiazem group and 29.3% of those in the placebo group. This study endorsed the efficacy of diltiazem, when used with ACEI or ARB, in urine protein reduction and in kidney protection in patients with diabetic nephropathy. The findings were in agreement with those of previous reports[9], which found that the combination therapy of diltiazem and captopril (ACEI) was more effective in decreasing urine protein than monotherapy with ACEI. Diltiazem has long been used to treat hypertensive patients in Thailand. With its low cost and good effects on urine protein and kidney function, diltiazem is very beneficial to patients with diabetic nephropathy in Thailand.

With regard to adverse effects, pedal swelling was found in 4 patients from the diltiazem group and one from the placebo group, and this was the reason for their withdrawal from the study. Increased pedal swelling, which is not associated with the patients' kidney function reduction, has been reported as a common adverse effect of non-dihydropyridine calcium channel blocker drugs including diltiazem. Caution should be used in administering diltiazem to some diabetic patients with chronic kidney disease, as such adverse effects may lead to treatment interruption. Slowly titrated dosage of diltiazem, increasing diuretic treatment and salt restriction may be the proper management strategies for controlling this adverse effect.

This study had two main limitations. One was the rather small number of patients participating in the research. The other relates to the patients' medical conditions; more specifically, a number of participants already had greatly reduced kidney function at the start of the study. Baseline GFR of diltiazem group had insignificantly lower than the placebo group. Consequently, they either rapidly developed kidney failure or had to undergo a kidney replacement before completing the study protocol. These limitations call for further investigation in a larger population and with a greater duration.

Conclusion

The concomitant treatments of diltiazem and ACEI/ARB were more effective in decreasing urine protein and achieving stable kidney function than monotherapy with ACEI/ARB in type 2 diabetic patients with diabetic nephropathy.

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What is already known on this topic?

The recommended antihypertensive medications for diabetic nephropathy are ACEI or ARB. Some study suggested that the concomitant treatment of diltiazem and ACEI/ARB may retard the progression of chronic kidney disease in diabetic patients.

What this study add?

The concomitant treatment of diltiazem and ACEI/ARB was more effective in decreasing urine protein and achieving stable kidney function than monotherapy with ACEI/ARB in type 2 diabetic patients with diabetic nephropathy. This combination of diltiazem and ACEI/ARB may be the good recommendation for these patients.

Potential conflicts of interest

None.

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การชะลอการเสื่อมโรคไตในผู้ป่วยโรคเบาหวานด้วยยาลดความดันโลหิต

อุดม ไกรฤทธิชัย, วีระศักดิ์ ศรินนภากร, รุ่งระวี มหรรณพกุล, พลอยภัสสร อินทร์วัน

ภูมิหลัง: *การรักษาที่ช่วยชะลอการเสื่อมของโรคไตในผู้ป่วยโรคเบาหวาน ได้แก่ การควบคุมระดับน้ำตาลในเลือดและระดับความดันโลหิตให้เหมาะสม โดยเฉพาะยาในกลุ่ม angiotensin converting enzyme inhibitor (ACEI) หรือ angiotensin receptor blocker (ARB) มีการศึกษาแสดงว่ายาลดความดันในกลุ่ม non-dihydropyridine calcium channel blocker โดยเฉพาะ diltiazem สามารถช่วยชะลอการเสื่อมของไตในผู้ป่วยเบาหวานได้*

วัตถุประสงค์: *เพื่อศึกษาผลการชะลอการเสื่อมของไตเรื้อรังในผู้ป่วยเบาหวานจากการรักษาการใช้ยา Diltiazem ร่วมกับการรักษาด้วย ACEI/ARB เปรียบเทียบกับการรักษาด้วย ACEI/ARB*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาเชิงทดลองแบบสุ่มปกปิดข้อมูลทั้ง 2 ฝ่าย พหุสถาบัน ควบคุมด้วยยาหลอกในผู้ป่วยโรคเบาหวานชนิด 2 ที่เข้ารับการรักษาในแผนกผู้ป่วยนอกของโรงพยาบาลราชวิถี (กรุงเทพมหานคร) และโรงพยาบาลบ้านแพ้ว (สมุทรสาคร) จำนวน 106 ราย โดยเป็นผู้ป่วยที่ได้รับการรักษาความดันโลหิตสูงด้วยยา ACEI/ARB และมี urine protein/urine creatinine ratio (UPCr) มากกว่า 0.3 gm/gm ผู้ป่วยจะได้รับการสุ่มแบ่งเป็นสองกลุ่ม คือ กลุ่ม Diltiazem (ACEI/ARB + Sustained-release diltiazem 120 mg) (50 ราย) และกลุ่มยาหลอก (ACEI/ARB อย่างเดียว + ยาหลอก) (56 ราย) การวิเคราะห์ข้อมูลใช้หลักการ Intention-to-treat analysis*

ผลการศึกษา: *ผู้ป่วยกลุ่ม diltiazem (ACEI/ARB + sustained-release diltiazem 120 mg) 39 ราย (78.0%) และกลุ่มยาหลอก (ACEI/ARB อย่างเดียว + ยาหลอก) 38 ราย (67.9%) ได้รับการรักษาและติดตามนาน 1 ปี ผู้ป่วยกลุ่ม diltiazem จะมีการลดลงของหน้าที่ไตน้อยกว่า และลดปริมาณไข่ขาวในปัสสาวะมากกว่าผู้ป่วยกลุ่มยาหลอก ($p<0.05$) ส่วนระดับความดันโลหิตของทั้งสองกลุ่มไม่แตกต่างกัน ส่วนผลข้างเคียง ได้แก่ อาการบวมของขาพบในผู้ป่วยกลุ่ม diltiazem 4 ราย และกลุ่มยาหลอก 1 ราย*

สรุป: *การใช้ยา diltiazem ร่วมกับ ACEI หรือ ARB สามารถลดปริมาณ UPCr และช่วยชะลอการลดลงของหน้าที่ไตในผู้ป่วยโรคไตเรื้อรังจากเบาหวานได้*