Effects of Dual Blockade of Renin-Angiotensin System in Type 2 Diabetes Mellitus Patients with Diabetic Nephropathy

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Background: *Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) have been shown to delay the progression to proteinuria and kidney failure in hypertensive type 2 diabetic patients with diabetic nephropathy. Further synergistic effect may be obtained by combined therapy with both ARB and ACE inhibitors.*

Objective: *To evaluate the effect of dual blockage of the renin-angiotensin system by adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitors in type 2 diabetic patients with diabetic nephropathy.*

Material and Method: *Type 2 diabetic patients with urine protein/creatinine (UPCr) > 0.5 gm/gm and hypertension who received maximal recommended dose of ACE inhibitors (Enalapril 40 mg/day) over three months were randomized to two groups. ARB group received adding maximal recommended dose of ARB (Telmisartan 80 mg/day) and control group received previous ACE inhibitors only for 24 weeks.*

Results: *Eighty patients were enrolled. ARB group led to significantly reduced UPCr from baseline at week 8, 12, and 24 (2.65 $\pm$ 1.81, 2.24 $\pm$ 1.85, 2.24 $\pm$ 1.88, and 1.98 $\pm$ 1.73 gm/gm respectively, $p < 0.05$) but UPCr in the control group was unchanged (1.97 $\pm$ 1.56, 1.85 $\pm$ 1.27, 1.97 $\pm$ 1.11 and 1.96 $\pm$ 1.42 gm/gm respectively, $p > 0.05$). ARB group induced an additional reduction in proteinuria of 29.25% (95% CI 9.68-48.82) compared with control group. By the end of the present study, glomerular filtration rate had fallen from 41.76 $\pm$ 12.16 to 37.84 $\pm$ 13.59 ml/min/1.73 m^2 in ARB group and 50.89 $\pm$ 29.43 to 49.41 $\pm$ 29.85 ml/min/1.73 m^2 in control group ($p > 0.05$). Serum potassium had changed from 4.51 $\pm$ 0.48 to 4.58 $\pm$ 0.13 mEq/L in ARB group and 4.60 $\pm$ 0.58 to 4.40 $\pm$ 0.13 mEq/L in the control group ($p > 0.05$). No other serious adverse effects were reported during treatment.*

Conclusion: *Adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitors in type 2 diabetic patients can reduce proteinuria more than ACE inhibitors alone. This treatment is safe and well tolerated.*

Keywords: *Angiotensin-converting enzyme inhibitors, Angiotensin II type 1 receptor blockers, Diabetes mellitus, Type 2, Diabetic nephropathies*

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Patients with type 2 diabetes mellitus and kidney failure are increasing steadily in developed countries[1]. Recent studies showed kidney insufficiency rapidly progresses after there is overt diabetic nephropathy[2-4]. Despite improved treatment strategies, diabetic nephropathy has become the leading cause of end-stage kidney disease in Europe, Japan, and the US[5]. Diabetic nephropathy is characterized by persistent proteinuria, elevated blood pressure, a persistent decline in the glomerular filtration rate (GFR), and a high risk for cardiovascular morbidity and

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mortality[5]. Proteinuria and hypertension are predictors of poor renal and cardiovascular outcome in these patients[5,6]. The rennin angiotensin system (RAS) plays a central role in the initiation and progression of diabetic nephropathy and blockade of the RAS is now recommended as first-line therapy in diabetic patients with elevated urinary protein excretion[6]. Angiotensin-converting enzyme (ACE) inhibitors reduce the formation of angiotensin II by blocking the enzyme responsible for the conversion from angiotensin I. ACE inhibitors reduce arterial blood pressure, proteinuria, and the loss of kidney function and increase survival[7-10]. ACE inhibitors are recommended for all patients with type 1 diabetes and microalbuminuria, regardless of blood pressure[11]. Reduction in proteinuria and reduction in blood pressure during RAS blockade are surrogate endpoints for long-term renal preservation in diabetic nephropathy, and current recommendations suggest blood pressure readings below 130/80 mmHg and albuminuria values of less than 300 mg/24 h in such patients[12,13]. However, many patients with diabetic nephropathy do not reach blood pressure targets and have persistently elevated proteinuria, despite treatment with several antihypertensive agents, including recommended doses of ACE inhibitors. The advent of angiotensin II receptor blockers (ARB) provides an alternative approach to blocking the RAS. ARB antagonizes the angiotensin II type 1 receptor and may therefore interrupt the action of angiotensin II in a more effective way than ACE inhibitors. ARB have been shown to delay the progression to proteinuria and kidney failure[5,6,14]. ARB are now the initial agents of choice in hypertensive type 2 diabetic patients with microalbuminuria or clinical proteinuria, according to the American Diabetes Association[15]. Further effect may be obtained by combined therapy with both ARB and ACE inhibitors. Treatment with both ACE inhibitors and ARB may offer synergistic blockade of the RAS, not obtainable with either drug alone. Dual blockade of the RAS with both ACE inhibitor and ARB has been suggested as superior to monotherapy in diabetic patients with microalbuminuria[16] and in diabetic nephropathy[17,18]. The objective of the present study was to evaluate the effect of dual blockage of the RAS by adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitor in type 2 diabetic patients with diabetic nephropathy.

Material and Method

The institutional ethical committee approved the present study, and all patients gave written informed consent after reviewing a written summary of the study plan. At the out-patient department of Rajavithi Hospital, the authors recruited type 2 diabetic patients (American Diabetes Association's criteria)[15] with diabetic nephropathy and hypertension who received maximal recommended dose of ACE inhibitor (Enalapril 40 mg daily) over three months. Diabetic nephropathy was diagnosed clinically in patients with persistent urine protein/creatinine (UPCr) > 0.5 gm/gm, presence of diabetic retinopathy and absence of any other clinical or laboratory evidence of other kidney disease. Exclusion criteria were serum potassium more than 5.5 mEq/l, age less than 18 years, systolic blood pressure less than 100 mmHg, GFR less than 15 ml/min/1.73 m^2, pregnancy, breast feeding and acute systemic diseases (for example active infection, malignancy or heart failure).

They were randomized to two groups. The treatment group (ARB group) received adding maximal recommended dose of ARB (Telmisartan 80 mg daily) and the control group received previous ACE inhibitor only for 24 weeks. At randomized visit, patients in ARB group received Telmisartan 40 mg daily for two weeks. After two weeks, the dose of Telmisartan was increased to 80 mg daily and continued this regimen until week 24. Patients attended the clinic for five study-visits: one screening visit, randomized visit and subsequently 2,4,12 and 24 weeks after the beginning of each treatment period. Their clinical status were assessed, blood pressure was measured with sphygmomanometry using an appropriate cuff three times in the sitting position after at least 15 min rest and their fasting venous blood and spot urine samples were performed at each visit. HBA1c, plasma potassium and plasma creatinine levels were measured. From spot urine samples, protein and creatinine excretion in the urine were determined by an immunoturbidimetric method (Roche Diagnostics, Basel, Switzerland). Throughout the present study, all patients received the standard of care for the treatment of diabetes. Antihypertensive agents other than ACE inhibitor or ARB were used as needed in each group and the target blood pressure for all patients was the same (a systolic blood pressure of 130 mm Hg or less and a diastolic blood pressure of 80 mm Hg or less).

CKD staging was classified by the NKF-K/DOQI definition of CKD[19]. Calculated GFR was estimated using the abbreviated MDRD equation: GFR (ml/min/1.73 m^2) = 186.3 x serum creatinine (mg/dl)$^{-1.154}$ x age (year)$^{-0.203}$ x0.742 if female x 1.210 if African-American[20]. Serum creatinine was determined by

buffered kinetic Jeffe' reaction (compensated method for serum and plasma) using a COBAS INTEGRA 800® analyzer and original creatinine Jaffe generation-2 reagents (Roche Diagnostics, Indianapolis, IN, US). The cassette COBAS INTEGRA creatinine Jaffe' contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for quantitative determination of creatinine concentration in serum and plasma. This method sheet describes the applications for serum and plasma (compensated method). This laboratory is a participant in the quality assessment program for clinical chemistry from Bio-Rad Laboratories (9500 Jeronimo road, Irvine, California 92618, USA) and Randox International Quality Assessment Scheme (Randox Laboratories Ltd., 55 Diamond Road, Crumlin, Co. Antrim, BT29 4QY, United Kingdom).

The urinary protein concentration was determined by turbidimetric method and the urine creatinine concentration by Jaffe reaction with the use of a COBAS INTEGRA 800® analyzer. Glycosylated hemoglobin was measured by immunoturbidmetric method using a COBAS INTEGRA 800® analyzer. The primary endpoint was the changing of proteinuria and GFR. Secondary endpoints were total mortality, admission to hospital, cough, hyperkalemia, hypotension or other adverse events.

The critical statistic for this research was the determination factor shown as mean $\pm$ standard deviation. Changes in continuous variables from baseline values, by treatment group, were analyzed by ANOVA repeated method, adjusted for the baseline value. To compare the annual means of the various measurements between the two groups and within each group were used in t-test, Pearson Chi-square test and analysis of variance repeated method. A p-value less than 0.05 was considered as statistically significant. Analysis was made with the software program SPSS for Windows version 11.5 (SPSS Inc., Chicago, Illinois, USA).

Results

Eighty type 2 diabetic patients with diabetic nephropathy and hypertension, who received maximal recommended dose of ACE inhibitor, were randomized into two groups as ARB or control group. All patients completed the present study and were included in the statistical analysis. Baseline characteristics of participants in both groups were similar (Table 1). Blood pressure and blood sugar of these patients were controls.

Fig. 1 shows the UPCr in both groups during 24 weeks of treatment. In ARB group, UPCr at randomized visit, week 8,12 and 24 were 2.65 $\pm$ 1.81, 2.24 $\pm$ 1.85, 2.24 $\pm$ 1.88 and 1.98 $\pm$ 1.73 gm/gm respectively ($p < 0.05$). In control group, UPCr at randomized visit, week 8,12 and 24 were 1.97 $\pm$ 1.56, 1.85 $\pm$ 1.27, 1.97 $\pm$ 1.11, and 1.96 $\pm$ 1.42 gm/gm respectively ($p > 0.05$). Fig. 2 showed the percentage of UPCr reduction in both groups during 24 weeks of treatment. Dual blockage of the RAS by adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitor led to significantly reduce UPCr from baseline at week 8th, 12th and 24th ($p = 0.004$) but UPCr in control group unchanged. The ARB group induced an additional reduction in proteinuria of 29.25% (95% CI 9.68-48.82) compared with the control group. Changes

Table 1. Demographic features of all patients in this study

	All	ARB group	Control group	p-value
Number	80	40	40	
Male (%)	43 (53.75%)	18 (41.86%)	25 (58.14%)	0.12
Age (year)	55.67 $\pm$ 13.09	54.60 $\pm$ 12.08	56.75 $\pm$ 14.09	0.47
Duration of DM (year)	9.22 $\pm$ 7.56	10.68 $\pm$ 8.55	7.76 $\pm$ 6.19	0.09
Body weight (kg)	76.56 $\pm$ 16.68	76.24 $\pm$ 16.96	76.40 $\pm$ 8.96	0.50
Systolic BP (mmHg)	140.46 $\pm$ 17.87	140.98 $\pm$ 17.30	139.95 $\pm$ 18.63	0.80
Diastolic BP (mmHg)	75.47 $\pm$ 12.05	76.40 $\pm$ 8.96	74.55 $\pm$ 14.55	0.50
Mean BP (mmHg)	97.14 $\pm$ 11.58	97.93 $\pm$ 9.09	96.35 $\pm$ 13.70	0.55
HbA1c (%)	7.68 $\pm$ 1.03	7.80 $\pm$ 0.80	7.43 $\pm$ 1.37	0.19
Serum creatinine (mg/dl)	1.82 $\pm$ 0.95	1.76 $\pm$ 0.39	1.89 $\pm$ 1.28	0.53
Hemoglobin (gm/dl)	12.09 $\pm$ 1.93	12.02 $\pm$ 1.59	12.29 $\pm$ 2.70	0.64
GFR (ml/min/1.73m^2)	46.33 $\pm$ 22.84	41.76 $\pm$ 12.16	50.89 $\pm$ 29.43	0.07
Serum K (mEq/L)	4.53 $\pm$ 0.51	4.51 $\pm$ 0.48	4.60 $\pm$ 0.58	0.56
UPCr (gm/gm)	2.31 $\pm$ 1.71	2.64 $\pm$ 1.81	1.96 $\pm$ 1.57	0.07

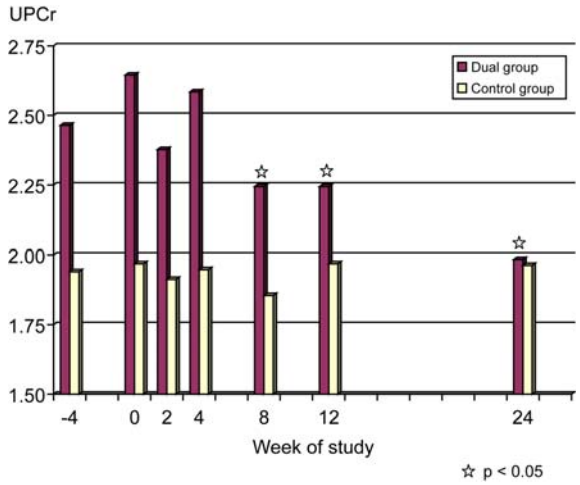

Fig. 1 The UPCr in ARB and control groups during 24 weeks of treatment

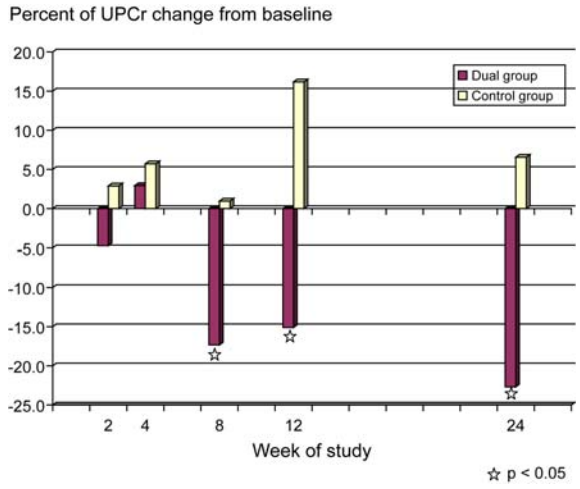

Fig. 2 The percentage of UPCr reduction in ARB and control groups during 24 weeks of treatment

of UPCr did not correlate with changes in blood pressure or GFR ($p > 0.05$).

Blood pressure decreased slightly more among participants on ARB than among those on placebo. By the end of the present study, systolic/diastolic blood pressure had fallen from 140.98 ± 17.30/76.40 ± 8.96 to 128.15 ± 19.94/72.22 ± 13.13 mmHg in the ARB group and 139.95 ± 18.63 / 74.55 ± 14.55 to 132.82 ± 19.94/75.40 ± 10.79 mmHg in the control group ($p > 0.05$). GFR was lowered in the ARB group compared with the control group. By the end of the study, GFR had fallen from 41.76 ± 12.16 to 37.84 ± 13.59 ml/min/1.73 m^2 in ARB group and 50.89 ± 29.43 to 49.41 ± 29.85 ml/min/1.73 m^2 in the control group ($p > 0.05$). Hemoglobin level decreased slightly in the ARB group. By the end of the present study, hemoglobin level had fallen from 12.02 ± 1.59 to 11.28 ± 1.47 gm/dl in the ARB group and 12.29 ± 2.70 to 12.84 ± 3.19 gm/dl in control group ($p > 0.05$). However, none of the patients needed treatment for anemia during the study. Dual blockade caused an insignificant change in plasma potassium. By the end of the present study, serum potassium had changed from 4.51 ± 0.48 to 4.58 ± 0.13 mEq/L in the ARB group and 4.60 ± 0.58 to 4.40 ± 0.13 mEq/L in control group ($p > 0.05$). No other serious adverse effects, *e.g.* death, admission to hospital or severe cough, were reported.

Discussion

Studies of diabetic and non-diabetic kidney disease suggest the initial degree of reduction in proteinuria after blockade of the RAS predicts an attenuated rate of decline in GFR[21]. Consequently, proteinuria may serve as a surrogate end point for monitoring treatment efficacy and prognosis in diabetic nephropathy[22]. Treatment of overt diabetic nephropathy aimed at reducing proteinuria and delaying the development of end-stage renal disease such as improved blood sugar or blood pressure control. Antihypertensive treatment has improved renal prognosis and survival in diabetic nephropathy. The beneficial effect of ACE inhibition or ARB in preventing the occurrence of nephropathy in type 2 diabetic patients has been documented in several trials[23-25]. ACE inhibitors are now a first-line therapy for patients with type 1 diabetes and diabetic nephropathy, whereas in patients with type 2 diabetes, ARB have been shown to protect the kidney. All diabetic patients with elevated urinary albumin excretion need blockade of the RAS by either ACE inhibitors or ARB. The current recommendations suggest blood pressure readings below 130/80 mmHg and albuminuria values of less than 300 mg/24 h in patients with diabetic nephropathy[12,13]. Dual blockade of the RAS may be helpful in reaching these goals in treatment-resistant patients with diabetic nephropathy. Short-term studies of dual blockade of the RAS in patients with diabetic nephropathy suggest superior efficacy in terms of the lowering of proteinuria in comparison with treatment using ACE inhibitors alone[16-18].

The authors performed the trial with dual blockade of the RAS (Telmisartan and Enalapril) in patients with type 2 diabetes and proteinuria who

received 24 weeks of treatment with ARB in addition to prior ACE inhibitor treatment. The main results of dual blockade therapy were additional reduction in proteinuria of 29.25% compared with the control group. Dual blockage therapy was a well-tolerated treatment without more adverse effects than therapy with ACE inhibitor alone. The presented study showed that the beneficial effect of dual blockage of the RAS by adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitor in type 2 diabetic patients with overt nephropathy. This result confirmed the previous studies. Recent randomized double-blind parallel and cross-over studies in type 2 diabetic patients with microalbuminuria or overt nephropathy suggested that the combination of ACE inhibition and ARB provides enhanced blood pressure reduction and antiproteinuric effect[16]. The effect of dual blockade of the RAS in patients with diabetes has been investigated in short-term studies using surrogate end-points for progression of diabetic nephropathy, *i.e.* antiproteinuric effects. Dual blockade of the RAS caused a significant reduction (25-43%) in proteinuria[17,26]. The original manifestation of this treatment concept was due to the Candesartan and Lisinopril Microalbuminuria (CALM) study-a prospective, randomized, double-blind study of patients with type 2 diabetes involving micro-albuminuria and hypertension. The present study found a more pronounced drop in urinary albumin excretion by 12 weeks of dual blockade (Candesartan and Lisinopril) in comparison with therapy with either agent alone[16].

The ONgoing Telmisartan Alone in combination with the Ramipril Global Endpoint Trial (ONTARGET) evaluated ramipril, telmisartan, and combination therapy in patients with high risk of cardiovascular events[27]. A combination of ACE inhibitor and ARB compared to ACE inhibitor alone was associated with significant increases in the following adverse effects: hypotensive symptoms, syncope, and renal dysfunction. These adverse effects may be due to patients who had a high risk of cardiovascular events and rapid treatment regimen initiation with both drugs. In the present study, dual blockage of the RAS did not produce more adverse effects (such as death, admission to hospital, cough, hyperkalemia, hypotension and renal impairment) than therapy with ACE inhibitor alone. Because these patients could tolerate maximal recommended dose of ACE inhibitor before the present study and they received ARB slowly, the incidence of cough did not increase after adding maximal recommended dose of ARB. The reason for insignificant changes in plasma potassium during dual blockage of the RAS therapy was that these patients had previously been given potassium-restricted food during therapy with maximal recommended dose of ACE inhibitor. Blood pressure and GFR were slightly lowered in the ARB group compared with the control group. Blocking of the RAS will dilate the efferent arteriole, lower intraglomerular pressure and reduce the GFR. A decline in GFR induced by an ACE inhibitor occurs within a few days after the beginning of therapy and ACE inhibitors are effective in slowing the rate of decline in GFR. Treatment with both ACE inhibitors and ARB offer synergistic blockade of the RAS. Because these patients had low risk of cardiovascular events and received ARB slowly, they had no hypotensive symptoms, syncope, or severe renal dysfunction. However, blood pressure, renal function, and plasma potassium should be monitored closely when dual blockage of the RAS is begun.

Despite treatment with ACE inhibitors or ARB, patients with diabetes and elevated urinary albumin excretion have a high risk of cardiovascular disease and end-stage kidney disease. Alternative and more effective ways of blocking the RAS may offer additional clinical advantages. Dual blockade of the RAS implies simultaneous treatment with both ACE inhibitors and ARB to obstruct both the synthesis and activity of angiotensin II. The further long-term study of dual blockage of the RAS for preventing cardiovascular disease and end-stage renal disease in patients with type 2 diabetes should be preformed.

Conclusion

The present study showed the renoprotective effects, as assessed by reduction in proteinuria, of dual blockage of the RAS by adding maximal recommended dose of ARB with maximal recommended dose of ACE inhibitor in type 2 diabetic patients with diabetic nephropathy. In patients with diabetes complicated with uncontrolled proteinuria and hypertension, dual blockade of the RAS may be helpful in reaching treatment goals.

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ผลของการรักษา dual blockage ของ renin-angiotensin system ในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะ diabetic nephropathy

อุดม ไกรฤทธิชัย, วิรัญญา ชัยสุวรรณรัตน์

ภูมิหลัง: *Angiotensin-converting enzyme (ACE) inhibitors หรือ angiotensin II receptor blockers (ARB) สามารถลด proteinuria และชะลอการเสื่อมของไตได้ในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะ diabetic nephropathy การใช้ยา ACE inhibitor ร่วมกับ ARB น่าจะเสริมประสิทธิภาพในการรักษามากยิ่งขึ้น*

วัตถุประสงค์: *ต้องการทดสอบประสิทธิภาพของการรักษา dual blockage ของ renin-angiotensin system โดยให้ยา ARB ขนาดสูงสุดเพิ่มในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะ diabetic nephropathy และได้รับยา ACE inhibitor ขนาดสูงสุด*

วัสดุและวิธีการ: *ผู้ป่วยเบาหวานชนิดที่ 2 ที่มี urine protein/creatinine (UPCr) มากกว่า 0.5 gm/gm และมีความดันโลหิตสูงที่ได้รับยา ACE inhibitors (Enarapil 40 mg) เป็นระยะเวลาอย่างน้อย 3 เดือน นำมาสุ่มแบ่งผู้ป่วยออกเป็นสองกลุ่ม คือ กลุ่ม ARB จะได้รับยา ARB เพิ่ม (Telmisartan 80 mg/day และ Enalapril 40 mg/day) ส่วนกลุ่มควบคุมจะได้รับยาเดิมของผู้ป่วย (Enalapril 40 mg/day) ติดตามผู้ป่วยไปนาน 24 สัปดาห์*

ผลการศึกษา: *ผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 80 คนแบ่งเป็น 2 กลุ่ม ผู้ป่วยในกลุ่ม ARB มีปริมาณ UPCr ลดลงตามระยะเวลาที่ได้รับยา ARB โดยพบความแตกต่างจากเวลาเริ่มต้นอย่างชัดเจนในสัปดาห์ที่ 8, 12 และ 24 (2.65 ± 1.81, 2.24 ± 1.85, 2.24 ± 1.88 และ 1.98 ± 1.73 gm/gm, $p < 0.05$) ในขณะที่ผู้ป่วยในกลุ่มควบคุมมีปริมาณ UPCr ไม่เปลี่ยนแปลง (1.97 ± 1.56, 1.85 ± 1.27, 1.97 ± 1.11 และ 1.96 ± 1.42 gm/gm, $p > 0.05$) โดยกลุ่ม ARB จะสามารถลด proteinuria of 29.25% (95% CI 9.68-48.82) เมื่อเปรียบเทียบกับกลุ่มควบคุม ส่วนหน้าที่ไตของกลุ่ม ARB ในสัปดาห์ที่ 0 และ 24 เท่ากับ 41.76 ± 12.16 และ 37.84 ± 13.59 ml/min/1.73 m^2 หน้าที่ไตของกลุ่มควบคุมในสัปดาห์ที่ 0 และ 24 เท่ากับ 50.89 ± 29.43 และ 49.41 ± 29.85 ml/min/1.73 m^2 ($p > 0.05$) ส่วน serum potassium ของกลุ่ม ARB ในสัปดาห์ที่ 0 และ 24 เท่ากับ 4.51 ± 0.48 และ 4.58 ± 0.13 mEq/L serum potassium ของกลุ่มควบคุมในสัปดาห์ที่ 0 และ 24 เท่ากับ 4.60 ± 0.58 และ 4.40 ± 0.13 mEq/L ($p > 0.05$) ภาวะแทรกซ้อนจากการรักษาอื่นพบว่าไม่มีความแตกต่างทั้งสองกลุ่ม*

สรุป: *การใช้ยา ACE inhibitors ร่วมกับ ARB มีประสิทธิภาพในการชะลอการเสื่อมของโรคไตในผู้ป่วยคนไทยที่เป็นโรคไตจากเบาหวานชนิดที่สองโดยสามารถลดปริมาณโปรตีนในปัสสาวะประมาณ 29.25% เมื่อเทียบกับการใช้ยา ACE inhibitors อย่างเดียวและสามารถนำไปใช้ได้อย่างปลอดภัย*