



Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease

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Abstract

Hypertension and proteinuria are well-known predictors of chronic kidney disease (CKD) progression. Therapeutic interventions have different magnitude of albuminuria and hypertension. This study was designed to evaluate the efficacy and safety of combined vs. single renin-angiotensin-aldosterone system (RAAS) blockade in chronic kidney disease. Forty (28 female) patients with chronic kidney diseases were collected from nephrology outpatient clinic, internal medicine department, Beni Suef University hospital. They were divided randomly into 2 groups. Group A was 24 (20 females) patients treated with Enalapril, as angiotensin converting enzyme inhibitor (ACE-I) alone. Group B was 16 (8 females) patients treated with combination of Enalapril and Irbesartan, as angiotensin receptor blocker (ARB). All patients were subjected to full history taking; thorough clinical examination; certain laboratory tests and renal function tests at the start of the study, 1.5 and 3 months later. Proteinuria, urinary albumin/creatinine ratio (UACR), systolic blood pressure (SBP) and glomerular filtration rate (GFR) were significantly ($p < 0.001$) decreased with dual therapy (ACE-I and ARB) compared to monotherapy. In return serum potassium level (Ser.K), serum creatinine level (Ser.Cr) were significantly increased ($p < 0.001$) with dual therapy (ACE-I and ARB) compared to monotherapy. The hypotensive and antiproteinuric effect of RAAS inhibitors should be compared with hyperkalemia and rise in serum creatinine level when prescribed as monotherapy or combination in patients with CKD. Decision of usage of RAAS blockade should be made based on the risk and benefit ratio.

Keywords: Renin-angiotensin-aldosterone system, proteinuria, chronic kidney disease (CKD), Angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), dual therapy, renal failure, hypertension, diabetic nephropathy and dual RAAS blockade, combination

Introduction

Chronic kidney disease (CKD) is a worldwide public health disease, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death [1].

The increase in prevalence of CKD is partly explained by the increase in a number of CKD risk factors, including aging of population, obesity, hypertension, and diagnosed diabetes [2].

Earlier stages of CKD are defined based on the combination of kidney damage (most often quantified using albuminuria) and decreased kidney function (quantified as glomerular filtration rate [GFR] estimated from the serum creatinine concentration) [2]. Kidney failure is not only the outcome of chronic kidney disease but complications of decreased kidney function and cardiovascular disease as well. Some of these adverse outcomes can be prevented or even delayed by early detection and treatment [3].

Proteinuria is a strong prognostic marker in renal disease [4]. It increases the risk for progression of chronic kidney disease and development of end-stage renal failure [5]. The anti-proteinuric effect has been initially attributed to the reduction of glomerular hypertension [6].

The role of RAAS in the progression of chronic kidney disease, especially if it is associated with increase in blood pressure (BP), is a well known and determinant of target-organ damage [7].

Inhibitors of the renin-angiotensin-aldosterone system (RAAS) reduce proteinuria by decreasing the systemic arterial pressure and the intraglomerular filtration pressure by changing pore size and charge of the glomerular filter [5]. Blockade of RAAS prevents the development and progression of diabetic kidney disease (DKD) [8].

Although RAAS blockade therapy in CKD is associated with a decrease in albuminuria and proteinuria, it is associated with a decrease in GFR and a higher incidence of hyperkalemia and hypotension [9]. This effect might increase by the combination of two or more of the RAAS blockade [9]. Hence, the aim of the present work was to

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examine the effect of combined vs. single RAAS blockade therapy on kidney related endpoints, BP parameters and other outcomes of interest in patients with proteinuria.

Materials and Methods

The study was conducted on forty (28 females) patients from the nephrology outpatient clinic, internal medicine department, Beni Suef University hospital. Local hospital research ethics committee approval was obtained.

Inclusion criteria:

- Patients with diabetic nephropathy or patients with chronic kidney disease (CKD), stages 1 and 2 with proteinuria for reasons other than diabetes mellitus
- Normal liver and cardiac examination

Exclusion criteria:

- Serum creatinine > 2 mg/dl
- Serum potassium > 5 mg/dl
- Arterial blood pressure below 110/70 mmHg
- Liver disease
- Organ failure e.g. cardiac failure
- Patients with concomitant bilateral renal artery stenosis

Patients were divided randomly into 2 groups. Group A received Enalapril 20 mg (Enalapril, October Pharm, Egypt) as angiotensin converting enzyme inhibitor (ACE-I) alone. Group B received combination of Enalapril, as ACE-I, and Irbesartan 150mg (Irbesartan, Mepaco Arab Co., Egypt) as angiotensin receptor blocker (ARB). All patients were subjected to the following:

- Full history taking
- Thorough clinical examination, including systolic and diastolic blood pressure measurement
- Measurement of all the next at the start of the study, 1.5 and 3 months later: Serum creatinine level (Ser.Cr), Serum potassium level (Ser.K), Albumin/Creatinine ratio in urine (UACR) and Estimated glomerular filtration rate (GFR), which was calculated from the modification of diet in renal disease (MDRD) equation:

$GFR (mL/min/1.73 m^2) = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$ (conventional units)

Statistical Analysis

All data were expressed by mean±SE and all statistical tests were done at p-values<0.05 using Released 2013 IBM software SPSS Statistics for Windows, Version 22.0 (IBM Corp., New York, USA). Repeated measure one way analysis of variance (ANOVA) was used to test significance between means of time groups for each drug (ACE-I or ACE-I\ARB) followed by Bonferoni's post hoc test to compare mean values pair-wise. Student independent T-test was used to compare significance

between means difference at each time of ACE-I and ACE-I\ARB groups.

Results

A number of 40 patients (28 female) completed the study. The underlying renal diseases included glomerular disease [in 15 (7 female) patients], diabetic and hypertensive [in 25 (21 female) patient]. 24 (20 female) patients received ACE-I alone while 16 (8 female) patients received ACE-I and ARB combination.

Table 1 shows the mean±SE of the effect of monotherapy and combination therapy on tested parameters during the study period. Figures 1-6 shows the effect of monotherapy and combination therapy on Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Ser.K, Ser.Cr., GFR and UACR.

Significant decreases (p<0.05) in SBP, DBP, GFR and UACR were observed in patient using monotherapy and combination therapies through the study period.

Significant increases (p<0.05) in Ser.K and Ser.Cr were observed in patient using monotherapy and combination through the study period.

Patients initiated on combination ACE-I and ARB therapy showed significant decrease in SBP compared to those used ACE-I as monotherapy (p<0.05) as illustrated at Table 1 and Figure 1.

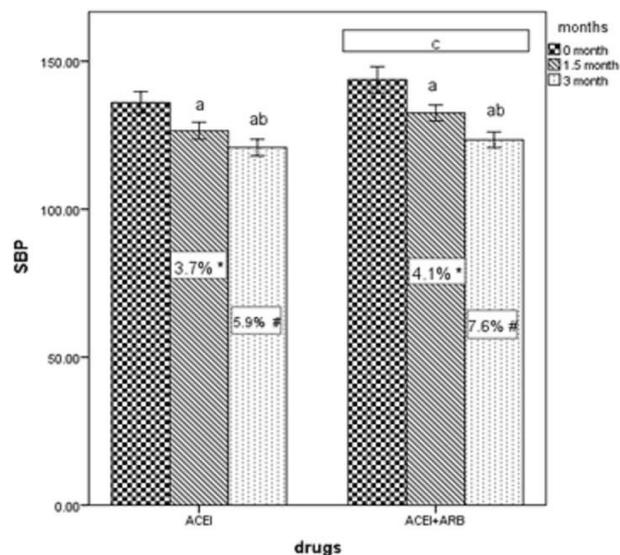


Figure 1. Mean± SE of SBP of patients using ACE-I and ACE-I+ARB at different time interval.

There was no statistical significant difference in DBP between the study groups throughout the study duration as shown in Table 1 and Figure 2.

The results illustrated in Table 1 and Figure 3 show that combination therapy significantly increased ($p < 0.05$) serum potassium level during 3 months (from 0 – 1.5 month, from 1.5 – 3 month and from 0 – 3 month) compared to monotherapy.

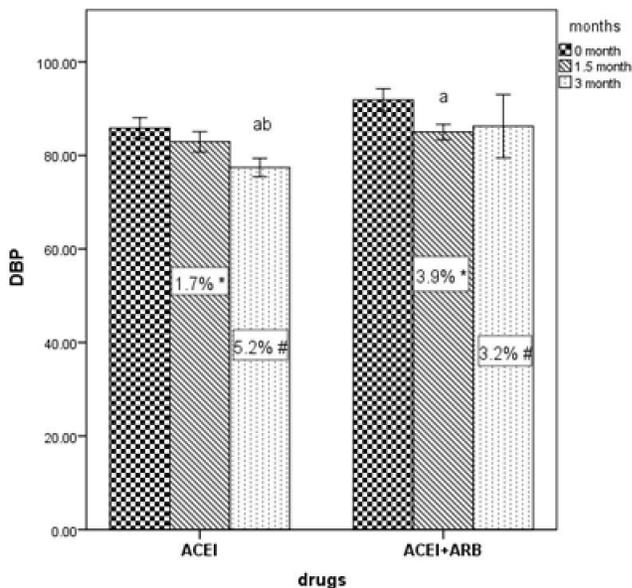


Figure 2. Mean± SE of DBP of patients using ACE-I and ACE-I+ARB at different time interval.

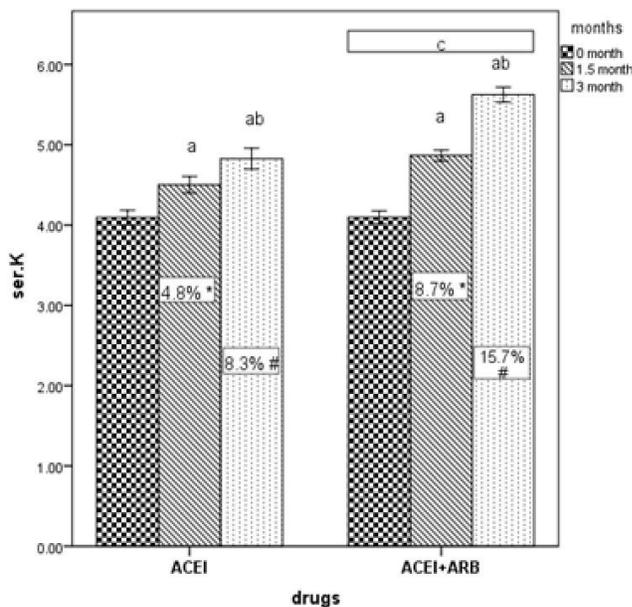


Figure 3. Mean± SE of Ser.K of patients using ACE-I and ACE-I+ARB at different time interval.

Dual therapy also showed significant increase ($p < 0.05$) in serum creatinine level compared to monotherapy from (0 –

1.5 month) and (0 - 3 month) as illustrated in Table 1 and Figure 4.

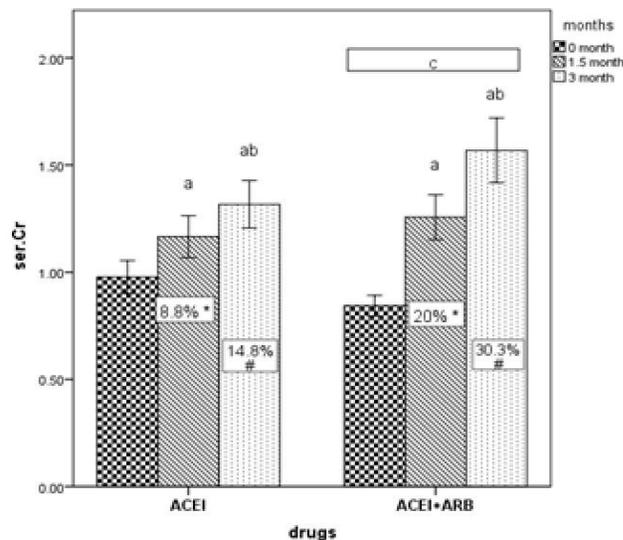


Figure 4. Mean± SE of Ser.Cr. of patients using ACE-I and ACE-I+ARB at different time interval.

There was a significant decrease ($p < 0.05$) in GFR in patients on combination therapy compared to those on monotherapy during 0 – 1.5 month only as illustrated in Table 1 and Figure 5. Comparing dual and monotherapy as shown in Table 1 revealed that the combination therapy significantly decrease UACR more than monotherapy during 3 month of study.

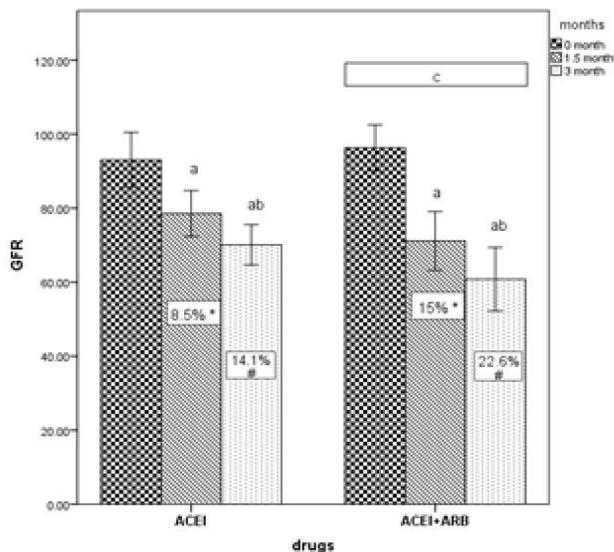


Figure 5. Mean± SE of GFR of patients using ACE-I and ACE-I+ARB at different time interval.

Discussion

Hypertension usually develops in patients with CKD. For those who have moderate or severe increased albuminuria, the guideline recommends that ACE-I or ARB to be used as first-line therapy in whom treatment with blood pressure (BP) lowering drugs is indicated [10].

From the present study, it is possible to confirm the previous recommendation of benefits of ACE-I or ARB in CKD patients which emphasized that treatment with an ACE-I or ARB improves kidney outcomes for patients with CKD with and without proteinuria [11]. However, the possible safety or efficacy of monotherapy and dual therapy, limit or encourage their use is still debated.

In the present study, use ACE-I and ARB with hypertensive patient with proteinuria adjusted their blood pressure and decreased their proteinuria especially in macroalbuminuria when both drug were used in combination. However, ACE-I and ARB were not able to prevent the development of microalbuminuria in normotensive individuals with diabetes [12].

Similar to previous literatures [13, 14], a significant reduction ($p < 0.05$) in systolic and diastolic blood pressure was observed in patient administrated ACE-I only and in patient administrated the combination therapy from (0 to 3 months). The decrease in SBP was in favor of dual therapy ($p < 0.05$), however, there was no statistical significant difference in DBP between the two groups throughout the study duration. This might be expected as ACE-I and ARB may decrease sympathetic activity, either by decreasing the effects of angiotensin pass way or by reducing renal afferent nervous activity through improving renal perfusion [14].

In the current study; there was a significant increase in serum potassium level ($p < 0.05$) with ACE-I treatment alone and with ACE-I and ARB treatment. Our data does not support the concept that detected in candesartan and lisinopril microalbuminuria II (CALM II) study as extension of CALM study where Andersen, N.H., et al., found no significant different in serum potassium levels between the two studied groups (Lisinopril and dual blockade Lisinopril and candesartan) [15]. That variation in results may be due to thiazide added in CALM II study as concomitant antihypertensive treatment due to insufficient blood pressure reduction. Hypokalemia is one of its adverse effects of thiazide, hence balance in potassium level might be achieved. Different type of ACE-I and ARB used may be another reason for this variation.

Similar to previous work [16], there was a significant increase ($p < 0.05$) in serum creatinine level in (0 -1.5 month) and (0 - 3 month). ACE-I and ARB treatment was significantly higher than that of ACE-I treatment alone ($p < 0.05$). It was not possible in this study to confirm

reports assuming that serum creatinine levels were not significantly affected differently by the two groups (Lisinopril and Dual blockade Lisinopril and candesartan) presented in CALM II study by Andersen, N.H., et al [15]. That variation in the result could be due to the calcium channel (CCB) which was added in CALM II study as concomitant antihypertensive treatment due to insufficient blood pressure reduction as mentioned in this study. To confirm this, Bunke, M. and B. Ganzel found that Serum blood urea nitrogen and creatinine levels decreased significantly when patients were treated with calcium channel antagonists ($p < 0.05$) [17].

The significant increase in serum creatinine level after 1.5 months ($p < 0.05$) and further after 3 months ($p < 0.05$) oppose the finding of Ligtenberg, G., et al [14]. They found that serum creatinine concentrations did not change significantly in patients taking enalapril for four to six weeks [14]. This might be because of short period of their study or difference in enalapril doses used.

ACE-I or ARB therapy in hypertensive diabetic patients with macroalbuminuria, microalbuminuria or normoalbuminuria had been repeatedly shown to improve cardiovascular mortality and reduce GFR decline [18-23]. In the present study, there was a significant reduction in GFR in enalapril alone and combination after 12 week ($p < 0.05$) with higher reduction by the combination therapy ($p < 0.05$). The rate of decrease in GFR in our study was progressive due to the great control in blood pressure which was found to be very important in slowing the rate of fall of GFR [12]. The great decrease might be due to some patients have overt diabetic nephropathy which is the hallmark of risk for a substantial continuous decline in GFR as reported by Mann, J.F., et al [16].

Similar to previous studies, [18, 24] There was a significant reduction in UACR by enalapril alone and combination after 3 months ($p < 0.05$) with much significantly higher decrease by combination ($p < 0.001$) with a high variation among treated population. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommended lowering salt intake to < 90 mmol (< 2 g) per day of sodium (5 g of sodium chloride) may also influence the effect of drugs such as RAAS blockers on surrogate markers such as BP and albuminuria, and low sodium intake enhances the antihypertensive and antialbuminuric effects of ACE-I/ARB [12]. Hence, the variation among treated population in this study may be affected by this lifestyle modification and low patient compliance. So, there is a high level of evidence for high dietary sodium intake to be associated with many adverse outcomes.

Clinical trials of ACE-I and ARB have shown that these drugs reduce albuminuria, as well as renal risk [16]. That was due to reduction of aldosterone levels by about 65%,

as dual RAAS blockade, with ACE-Is and ARB with improvement in blood pressure and proteinuria [25].

Kunz, R., et al found that reduction in proteinuria from ARB and ACE-I was similar, but their combination was more effective than either drug alone [5]. Remuzzi, G., et al., reported that ACE-I and ARB can be used in combination to maximize RAAS inhibition and more effectively reduce proteinuria and GFR decline [7].

In a study made by Maione et al., it was demonstrated that development of end-stage renal disease (ESRD) and progression of microalbuminuria to macroalbuminuria were reduced significantly with ACE-I versus placebo, ARB versus placebo but not with combined therapy of ACE-I and ARB versus monotherapy [24]. This could be because of the high dose of monotherapy, they used, when used alone versus dual therapy [24].

The present study was performed using patients with CKD especially stages 1 and 2. Several trials have shown that RAAS blockade was not only effective in late-stage renal disease in diabetes but also in early CKD and can prevent transition from microalbuminuria to macroalbuminuria, as well as from normoalbuminuria to microalbuminuria in hypertensive diabetic patients [12,26-29].

It was previously indicated that combination therapies of RAAS-blocking agents have been unsuccessful and harmful [12]. Also, ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET) showed no clear benefit of combining ACE-I and ARB for either cardiovascular (CV) or renal outcome [30]. It showed also that it was associated with an increased risk of hypotension, acute kidney injury and hyperkalemia, despite reductions in proteinuria [30]. Recently, the aliskiren trial in type 2 diabetes using cardio-renal endpoints trial (ALTITUDE) showed that a combination of either ACE-I or ARB with a direct renin inhibitors (DRI) in diabetes did not show any appreciable renal or cardiovascular protection, and may in fact be harmful [12,31].

Finally, veterans affairs nephropathy in diabetes trial (VA NEPHRON D) looking at combining ACE-I and ARB was prematurely stopped owing to safety concerns and demonstrated that combined angiotensin inhibition provided no overall clinical benefit and resulted in increased risk for hyperkalemia and acute kidney injury [12,32].

Ramipril efficacy in nephropathy (REIN) study found that patients with proteinuria of 2 g/day or greater gained the most benefit from ACE-I treatment [33]. Similarly, the African American study of kidney disease and hypertension (AASK) Study found that ramipril, as compared with amlodipine, retards renal disease

progression in patients with hypertension and proteinuria over 0.3 g/day [33].

Also, confirmed by Mercier, K., H. Smith, and J. Biederman, who reported the attractiveness of these combinations was based on recognition that: stage 2 hypertension (blood pressure >160/100 mm Hg) was difficult to treat to goal with monotherapy [18].

The thing that was not clear in other previous researches that; when should either monotherapy or dual therapy be given to the patient? That is the most important question that needs to be asked. From our results it is obvious that prescriber has to evaluate the risk and benefit ratio of using either combination or monotherapy of RAAS blockade.

Our current study was conducted on patients in three months to test drug safety and efficacy in comparison between mono and dual therapy in CKD patients. In the previous studies long term period of the study caused many problems including the increased side effects as hyperkalemia, increased serum creatinine level and decreased glomerular filtration rate and as a result more deterioration in renal function and finally decreased blood pressure especially with patients used dual therapy. As example, Mogensen, C.E, et al. found that not all patient would be included in the 24 week analysis because their diastolic blood pressure was below 80 mm Hg, so they were withdrawn from the study at the 12 week visit [13]. However, Ligtnerberg, G, et al, found that long term inhibition caused a larger decrease in blood pressure than short-term inhibition, in association with a fall in muscle sympathetic nerve activity [14]. Also, in ONTARGET study, Mann, J.F, et al, found combination of an ACE-I and an ARB reduces proteinuria to a greater extent than either drug alone. But they found also total number of patients in each trial was less than 30 on average, duration of therapy rarely exceeded one year and the effects on major renal outcomes, such as GFR changes or occurrence of dialysis, was not reported [16]. These limitations were also found in our study, although these would not bias the comparison between the groups.

Yet, the limitation of our study was small sample size, lack of sufficient information about placebo controlled population, short period of study, difference between laboratory results and inaccurate result as a result of patient noncompliance and other concomitant drug or food taken with our studied drug which might affect its therapeutic action positively or negatively. Therefore, these results must be verified by further studies to fill in gaps in this research.

Conclusion

Short term dual therapy was more effective than monotherapy in decreasing proteinuria and achieving a higher rate of regression to normoalbuminuria and was

associated with a significant higher increase in adverse events such as hyperkalemia, increase in serum creatinine and decrease in GFR. Hence, risk benefit ratio should be analysed carefully for each hypertensive chronic kidney disease patient before choosing his RAAS blockade therapy. Further studies should be performed on a large scale and larger populations for a longer duration.

Author Disclosure Statement

No Conflict of Interest and no competing financial interests exist.

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