

Combination of ACEI and ARB Confers Clinical Benefits in Chronic Kidney Disease

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ABSTRACT

Angiotensin Converting Enzyme Inhibitor (ACEI) is a novel drug and its prime role as renoprotective has been subject of intense interest in nephrology. Initially Angiotensin Receptor Antagonist (Type 1) came as a substitute for those who cannot tolerate ACEI or have intolerable side effects or have contraindications. Combining the two drugs to block effectively Ang II effects, a culprit in the relentless progression of renal injury has been subjected to intense investigation. The few initial studies, predominantly in Non Insulin Dependent Diabetes Mellitus (NIDDM), have been encouraging and shown remarkable risk reduction in loss of function.

Our study assessed the salutary effects of add-on Angiotensin Receptor Blocker (ARB) to 15 adult patients with various renal diseases already on ACEI therapy. We found remarkable benefits as there was significant reductions in mean arterial blood pressure (MAP), serum creatinine (SrCr) and urinary protein:creatinine ratio (UPCR) after adding ARB. There was associated concomitant elevation in serum albumin and potassium after adding ARB. We conclude that the use of combination therapy should therefore be advocated in the management of chronic renal disease whether diabetic or non-diabetic nephropathies to reduce the profound effects of activation of Renin-Angiotensin-Aldosterone (RAS) cascade on the kidneys. Combination therapy confers better blood pressure control, reduction in proteinuria, serum creatinine and improvement in serum albumin, however, a careful watch of serum potassium is advocated.

INTRODUCTION

Chronic glomerulonephropathy can result from variety of diseases and it is characterised by progressive sclerosis and interstitial fibrosis regardless of the nature of the initial renal injury. The renin-angiotensin system (RAS) plays a major pathophysiological role in the relentless progression of the glomerulopathies to end stage renal disease (ESRD) [1].

RAS consists of cascade of proteolytic events leading to the formation of angiotensin II (Ang II), a very powerful vasoconstrictor agent. Ang II has direct effect on vascular tone thus increases blood pressure (both systemic and intraglomerular pressure). Also Ang II has significant effect on intrarenal haemodynamics leading to increase in the filtration of protein and trafficking of macromolecules across the glomeruli and stimulates cell growth leading to fibrosis [1]. These effects are mediated through angiotensin receptor type 1 (AT1) which is present in the kidneys and other organs and tissues [2, 3, 4, 5].

With introduction of angiotensin converting enzyme inhibitor (ACEI) in the 80s the beneficial effects such as renoprotective, cardioprotective and antiproteinuric have been subjected to intense investigations. ACEI are effective drugs in preventing progression of renal injury and this is achieved by blocking the formation of Ang II from its precursor-Ang I [6, 7]. Unfortunately ACEI does not completely prevent the formation of Ang II. The reason for this has been found to be the activity of other enzymes beside ACE. These enzymes include chymases, cathepsins and aminopeptidases. They act on Ang I

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to synthesise Ang II [8, 9, 10]. In fact most Ang II synthesis outside kidneys is mediated by these non-ACE enzymes [8].

The development of orally active Angiotensin receptor blocker (ARB) type 1 (AT1) provided alternative route for inhibiting RAS. This drug blocks the attachment of Ang II to one of its receptors (ARB type 1) AT1 as against type 2 (AT2) leading to accumulation of AT2, a potent vasodilator [6, 7]. The combination of the two classes of drug, ACEI and ARB type 1 has been suggested as a way of maximising RAS blockade. It does so by reducing bioavailability of Ang II through ACEI and by blocking its activity at receptor level through ARB. Also the combination of the two drugs provided added advantage of increased vasodilatation through blockade of breakdown of bradykinins by ACEI and increased availability of AT2 through blockade of AT1.

The aim of this study was to evaluate the salutary effects the add-on of ARB would have on the progression of renal disease in patients who were already on ACEI.

MATERIALS AND METHODS

We looked at the records of all the patients aged 18 years and above attending our out-patient clinic (a University Teaching Hospital) for various chronic nephropathies who had been on ACEI therapy with good compliance over the previous 9 months. The diagnosis of various chronic nephropathies were made using internationally accepted standard criteria including histology. Fifteen of them were selected based on one or more of the following inclusion criteria, which include (1) increasing proteinuria (2) increasing blood pressure (3) increasing serum creatinine. They were given ARB AT1 blocker in addition to ACEI while other prescribed drugs were maintained. The surrogate indices of progression of renal disease were assessed and these include (a) Urine Protein / Creatinine Ratio (UPCR) as a measure of proteinuria, (b) Mean Arterial Blood pressure (MAP), (c) serum creatinine (SrCr), (d) serum urea (URE), (e) serum albumin (ALB) and (f) serum potassium (K). Mean of three values of each of these indices taken at three monthly intervals were recorded when the patients were on ACEI therapy. Similarly the parameters were reassessed at three monthly intervals after ARB type 1 (AT1) was added and the patients were followed up for 9 months. The data was analysed using SPSS version 10. Values of various indices used were presented as Mean $\pm$ standard deviation ($M \pm SD$). Standard errors of the

means as well as the differences between the indices prior to and after adding ARB were also determined. The means of the indices before and after adding ARB were compared using Mann-Whitney U test for non-parametric data. Level of significance was taken at $P < 0.05$. Graphs were used as appropriate.

RESULTS

A total of 15 patients were studied. A breakdown of the aetiologies of the nephropathies revealed 3 patients each with lupus nephritis, reflux nephropathy and chronic allograft nephropathy. Others include 2 patients each with diabetic nephropathy, IgA nephropathy and Alport's syndrome (Table 1). Table 2 shows the mean values of the indices of renal disease progression as well as the percentage reduction or increase when the angiotensin receptor antagonist was added.

Table 1: Aetiology of nephropathy in studied patients

Type	No of patients
IgA Nephropathy	2
Type 1 DM (DN)	1
Type 2 DM (DN)	1
Chronic Allograft Nephropathy	3
Alport's Syndrome	2
Reflux Nephropathy	3
Lupus Nephritis	3

Legend:

DM (Diabetes Mellitus)

DN (Diabetic Nephropathy)

Fig 1-6 shows the graphs of the data in Table 2. The results show statistically significant reductions in mean arterial blood pressure (MAP), serum creatinine (SrCr) and urinary protein : creatinine ratio (UPCR) before and after adding ARB. The reduction in proteinuria is further corroborated by the rise in serum albumin after adding ARB (Fig 4). However, there is tendency towards hyperkalemia in the combination therapy as seen in Fig 5. Fig 6 depicts serum urea as unreliable surrogate marker though with reduction in serum urea tending towards significance. Table 3 shows the difference between the means (i.e. before and after adding ARB) of the

six indices with the level of their standard error of the mean (SEM) and standard deviation (SD) and their corresponding P values.

Table 2: Percentage reduction / increase before and after adding ARB

	Mean Before	After	%age Reduction/ Increase
MAP (mmHg)	103	96	7%
SrCr (μ mol/L)	157	145	8%
Alb (g/L)	292	155	47%
UpCr Ratio(g/mg)	41	43	5%
K ⁺ mmol/L)	4.7	5	6%

Legend:

MAP = Mean Arterial Blood Pressure)

SrCr = Serum Creatinine)

Alb = Serum Albumin)

UpCr = (Urine protein creatinine)

K⁺ = serum Potassium)

play major role in the progression of renal disease either alone or in alliance with hypertension and proteinuria for which it contributes substantially to their initiation and sustainability [1,11], therefore inhibiting the synthesis of Ang II through the blockade of the enzyme responsible for its generation (ACE) has been found to confer salutary effects on the progression of renal disease in both diabetic and non-diabetic nephropathies [12, 13, 14].

The landmark study of Lewis *et al* in 1993 comparing captopril with placebo reduced the combined endpoints of death, dialysis and transplantation by 50% [12]. This was however in type 1 DM patients. The Angiotensin Converting Enzyme Inhibition in Progressive Renal Insufficiency (AIRPRI) [15] trial settled the question of whether the beneficial effects of ACE inhibitor is only restricted to type 1 DM because the studied subjects had progressive renal insufficiency caused by various renal diseases. And again the renal end points (doubling of serum creatinine or dialysis) were reduced by more than 50% [15]. Also Ramipril in Nephropathy (REIN) trial was stopped at the second interim analysis because the difference between the ACEI (ramipril) and placebo in the decline of GFR was highly significant [16]. Despite ACEI use, there is still generation of Ang II mainly because of the alternative enzymes which are available both within and outside the kidney parenchyma and this still contribute to progression of renal disease. Since introduction of ARB type 1 blocker as substitute for

Table 3: The difference between the means before and after adding ARB

Pair	Paired Diff Means	SEM	SD	Sig (2-tailed)
MAP	7.48	1.62	6.27	0.000
SrCr	11.40	5.31	20.55	0.050
Alb	-1.67	0.47	1.84	0.03
UpCrRatio	136.93	39.94	154.68	0.04
K ⁺	-0.27	0.06	0.25	0.1
Urea	1.40	0.79	3.07	0.06

DISCUSSION

Renin-angiotensin system (RAS) consists of cascade of proteolytic events leading to the formation of angiotensin II (Ang II), a very powerful vasoconstrictor. The synthesis of this agent takes place primarily in the kidney but can also be produced in other organs [2, 3, 4, 5]. Ang II has been found to

those patients with end-stage renal disease because of intractable cough, its renoprotective properties in diabetic nephropathy has been proved. The proven benefits of ARB in the progression of renal disease were seen in these landmark studies. Irbesartan Microalbuminuria in Type 2 Diabetes in Hypertensive patients study [17,18-20] [17]. Microalbuminuria

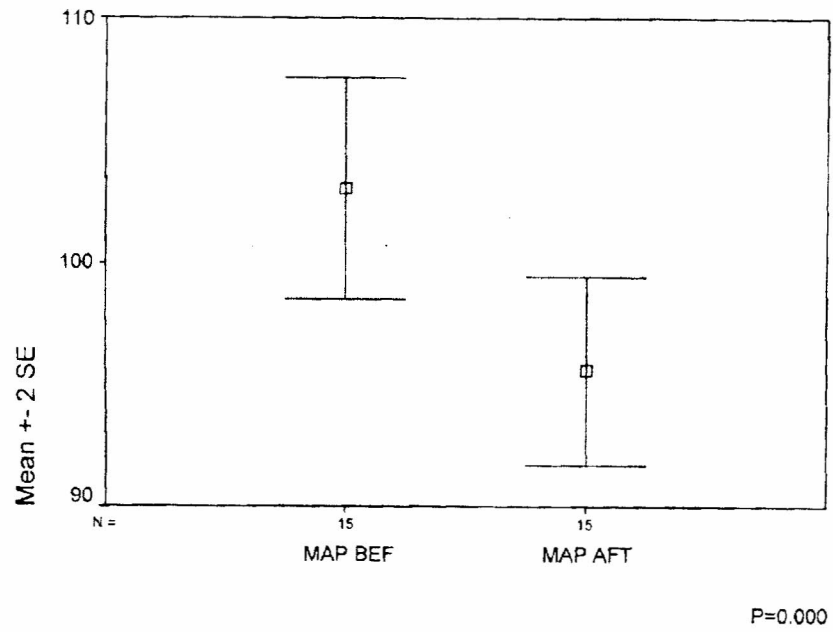


Fig. 1: MAP before and after adding ARB

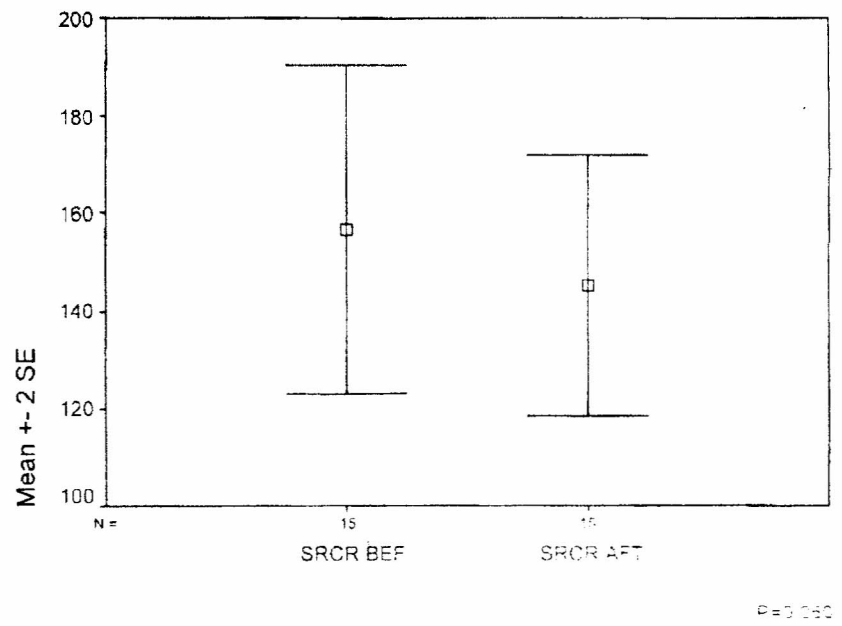


Fig. 2: SRCR before and after ARB

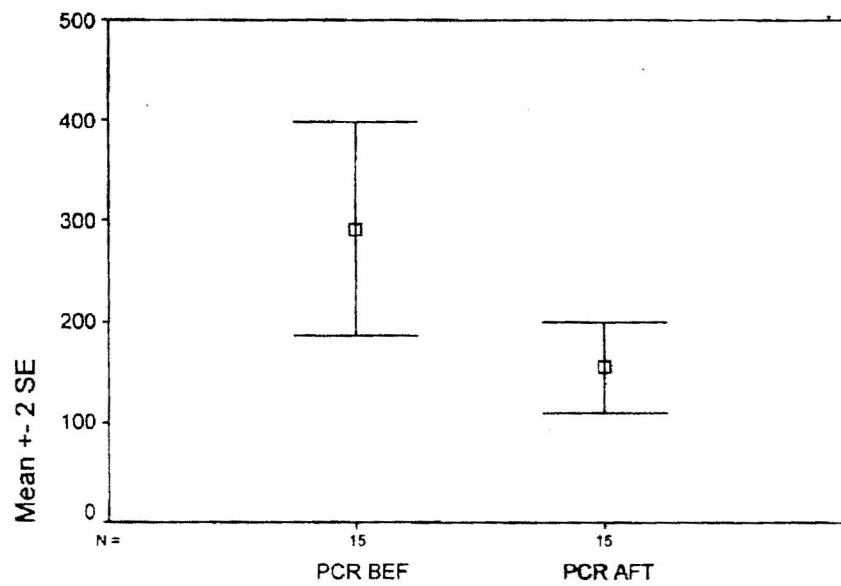
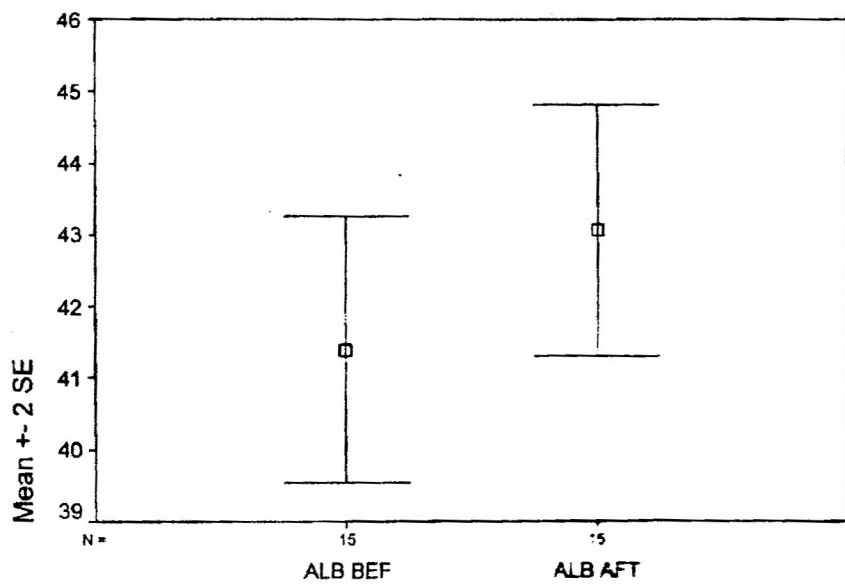
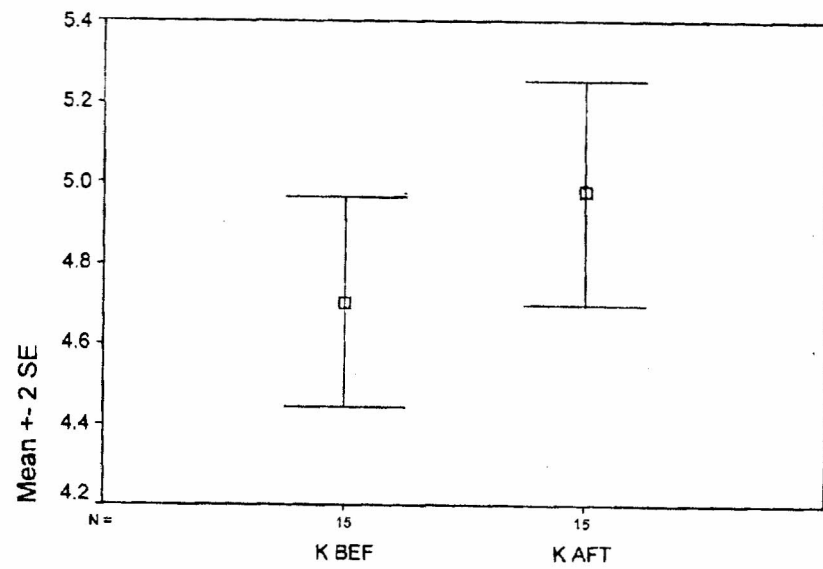


Fig. 3: Protein-Creatinine before and after ARB



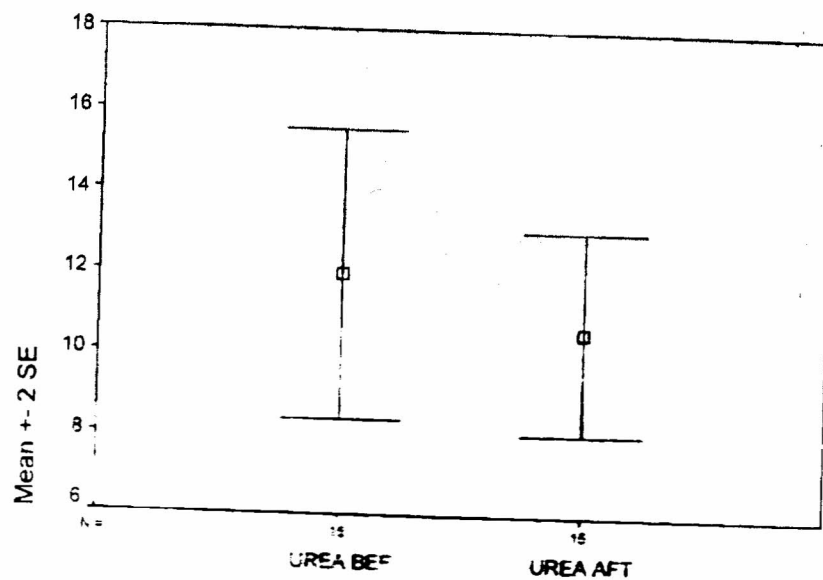
P=0.003

Fig. 4: Plasma Albumin before and after ARB



P=0.001

Fig. 5: Serum potassium before and after ARB



P=0.099

Fig. 2: Urea before and after ARB

Reduction with Valsartan study (MARVAL) [18], Losartan in diabetic nephropathy (IDNT) [19] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study [20].

Zoccali *et al* [21] first examined the salutary effects of combination therapy by adding losartan, an ARB type I blocking drug to treat 11 patients with various chronic renal nephropathies. Losartan caused a 30% reduction in proteinuria in patients who were already on ACE inhibitors. And from 1997 when Zoccali study was done there have been many other published works outlining the benefits of add-on ARBs to ACE inhibitors either as antiproteinuric, antihypertensive, antifibrotic (reduction in TGF- β) [22, 23, 24]. However, the work of Iodice *et al* [25] did not show any additional benefit conferred by the combination therapy.

This present study showed clearly the benefits of combination therapy in terms of reduction in proteinuria, blood pressure and serum creatinine which are recognised indices of progression of renal disease. There is also increase in serum albumin as a result of reduction in proteinuria and/or improvement in nutrition as a result of reduction in uraemic symptoms. Even though the number of studied patients was small, the beneficial effects were observed across all range of renal diseases including the hereditary, diabetic nephropathy and chronic allograft nephropathy. There is however tendency to hyperkalemia with the use of combination therapy; which is perhaps a synergistic effect.

The present study compared well with the work of Nakao *et al* [26] who also found a significant reduction in proteinuria but differed in terms of blood pressure control. The 47% reduction in proteinuria in our study was in the same range with the results of Ferrari *et al* [27] and Russo *et al* [28], although their patients were followed-up for 6 weeks and 2 months respectively which were much shorter than our follow-up period which was 9 months. Again Campbell *et al* [29] used the same parameters as surrogate markers as in our study but reductions in MAP, serum creatinine and albumin were not statistically significant though reduction in urinary protein excretion and increase in serum potassium reached statistical significance.

The use of combination therapy should be initiated early in the management of chronic renal disease whether diabetic or non-diabetic nephropathies to reduce the profound effects of activation of RAS cascade on the kidneys.

Combination therapy confers better blood pressure control, reduction in proteinuria, serum creatinine and improvement in serum albumin, however, a careful watch of serum potassium is advocated.

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