

**Original Article**

**A COMPARATIVE STUDY ON THE EFFECTIVENESS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIs) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) IN DIABETIC NEPHROPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS**

**N. SENTHILKUMAR<sup>1\*</sup>, ANANDHASAYANAM A.<sup>1</sup>, MOHAMMED SAFIL K.<sup>1</sup>, SHEMIMOL S.<sup>1</sup>**

Department of Pharmacy Practice, JKKMMRFs AJKK SA College of Pharmacy, Komarapalayam, Tamilnadu, India  
Email: senthilkumarjkk@gmail.com

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**ABSTRACT**

**Objective:** To observe the clinical outcomes on usage of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in type 2 diabetic nephropathy patients.

**Methods:** A total 70 patients diagnosed with diabetic nephropathy were treated with ACEIs or ARBs were enrolled in this study. The data was collected from the out patients and the physician. A data collection form was used for collecting patient data. The form was used to record the details of patient's demographics, history of diabetes mellitus, duration of diabetes mellitus co morbidities, food habits and laboratory parameters such as serum creatinine, HbA1c and all the relevant things. The study has obtained ethical clearance from the institution ethics committee (IEC).

**Results:** The study showed middle aged patients were more prone to diabetes and pre-existing hypertension is a major risk factor for diabetic nephropathy. Majority of the patients had long duration of diabetes mellitus which indicates the strong relation between duration of diabetes mellitus with diabetic nephropathy. Compared to ACE inhibitors, ARBs decreased the level of renal parameters. This reveals the better reno-protective effect of ARBs over ACE inhibitors. ARBs had more beneficial effects in reducing the major risk factor like proteinuria in diabetic nephropathy. A considerable reduction in HbA1c values were also observed in patients using ARBs.

**Conclusion:** While comparing the improvement in proteinuria and the laboratory outcomes, ARBs were beneficial relatively to the ACEs in patients with diabetic nephropathy.

**Keywords:** Diabetic nephropathy, Angiotensin Converting enzyme, Angiotensin Receptor blockers

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**INTRODUCTION**

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia. It is associated with abnormalities in carbohydrates, fat and protein metabolism and results in chronic complications including micro vascular and macro vascular disorders [1]. India has a high prevalence of diabetes mellitus and the numbers are increasing at an alarming rate. In India alone, diabetes is expected to increase from 40.6 million in 2006 to 79.4 million by 2030 [2]. The prevalence of type 2 diabetes is 4-6 times higher in urban than in rural areas [3]. The risk factors peculiar for developing diabetes among Indian include high familial aggregation, central obesity, insulin resistance and life style changes due to urbanization. Simple interventional strategies like "Eat less, Eat on time and Walk more" can go a long way in preventing these chronic disorders among present as well in future generation. There are 3 main type of diabetes: Type 1, Type 2 and Gestational diabetes mellitus. Type 2 is the most common form of diabetes and accounts for 90 to 95% of diabetes cases. Chronic hyperglycemia without proper management can also lead to various short term and long term secondary complications, both of small and big vascular nature may be determined as the main cause of mortality and morbidity in type 2 diabetic patients all over the world.

The long term effects of diabetes mellitus include progressive development of the specific complication of retinopathy with potential blindness, nephropathy that may lead to renal failure and neuropathy with risk of foot ulcers, amputation [4]. Complication of diabetes can be mainly divided into two: Micro vascular (Retinopathy, Neuropathy and Nephropathy) and Macro vascular (Cardiovascular disease and Peripheral vascular disease).

Diabetic nephropathy is the important cause of morbidity and mortality and affects almost 20-30 percent of patients with diabetes. It is also a leading cause of kidney failure in India and is seen in early stage with low level of albumin (micro albuminuria) in urine.

Clinical hallmark of diabetic nephropathy include a progressive increase in urinary albumin excretion and a decline in glomerular filtration rate (GFR), which occur in association with an increase in blood pressure, ultimately leading to end stage renal failure.

The Angiotensin II receptor blockers (ARBs) represent a new class of antihypertensive agent that was developed to overcome several deficiencies of ACE inhibitors, it may offer complete angiotensin II inhibition by interacting selectively with the receptor site [5]. All the 7 drugs in this class are approved by the food and drug administration for the treatment of hypertension either alone or in combination with other drugs. Uncommon uses include the treatment of congestive heart failure and diabetic nephropathy [6].

ACEIs decrease in GFR often increase serum creatinine concentration, and small increase should be anticipated. If large increases occur, ACE inhibitor therapy should be stopped or the dose reduced [7]. Some of the beneficial effects of bradykinin such as vasodilatation (which enhance BP lowering), regression of myocyte, hypertrophy and fibrosis and increased levels of tissue plasminogen activator are not present with ARB therapy [8].

In diabetes, both metabolic and hemodynamic factors interact to modify the glomerular microcirculation, creating an environment conducive to progressive glomerular injury. Patients with poor glycemic control show a greater reduction in intrarenal vascular resistance after blockade of RAS than that seen in subject with good metabolic control. Therefore with the wide spread use of agent that interrupts the RAS as first-line treatment in diabetic patients is at risk of diabetic nephropathy [9].

India is the diabetic capital of the world and hence the diabetic nephropathy management in India needs an assessment. ACEIs and ARBs are the more frequently used drugs in the management of diabetic nephropathy in India and hence a comparative study of both of them is needed.

The objective of the study was to find out the efficacy of ACEIs or ARBs reducing albuminuria in diabetic nephropathy patients. To find out the most preferable agent out of these two and to compare their blood pressure lowering effect. Along with reno-protective effects, effects on hyperglycemia and proteinuria also have to compare for finding out the comparative effectiveness of two drugs.

## MATERIALS AND METHODS

### Study site

The study was conducted at Nirmala Hospital at Calicut, a private tertiary level referral hospital in south Malabar region of Kerala.

### Study period

Comparative observational study over 10 mo period.

### Study population

Total population-70 patients

### Study criteria

#### Inclusion criteria

- Type 2 diabetic nephropathy patients who were on treatment with ACE inhibitors and ARBs.
- Age group: 18-80years.
- Outpatients.
- Patients with or without proteinuria were included.
- Patient with or without hypertension were included.
- Patients with other micro vascular disease like retinopathy, neuropathy, and foot ulcer were also included.

#### Exclusion criteria

- Type 1 diabetic patients were excluded.
- Pregnant women and pediatric patients were excluded.

#### Designing of data collection form

Reply to comment a3: The data collection form was for collecting the demographic as well as the medication details and lab results only.

A data collection form was used for all collecting patient data. This form containing the details of patient's demographics such as name, age, sex, history of diabetes mellitus, duration of diabetes mellitus, co-morbidities, food habit, complications and laboratory parameters such as creatinine, HbA1c, protein to creatinine ratio and all the relevant things.

#### Data collection

The data was collected from the out patients, physicians and other healthcare professionals.

- By direct interview with patients and care givers.
- From the out-patient files and prescriptions.

This study included 70 patients diagnosed with type 2 diabetic nephropathy who were on treatment with ACEI or ARB. They were grouped according to their therapy into 2 groups as the patients taking ACEI only or ARB only and were distributed in equal proportion (35 each). The patient's follow up was done every month, up to 10 mo. The main monitoring parameters like protein to creatinine ratio, blood pressure, Creatinine, urea, Hb, HbA1c, blood sugar level and potassium were monitored and recorded during the study period.

#### Data analysis

The recorded data was analyzed statistically. Student's T-test was used to compare quantitative and qualitative variables respectively. Data was expressed as mean and standard error. After six month of treatment, protein excretion and BP reduction were calculated as

the difference between final and baseline values for each patient and compared all the basic parameters in two groups.

Ethical committee approval and patients caregivers or patients consent was taken before data collection.

## RESULTS

In this study patient demographic data's were collected. The patients were classified according to age, gender, duration of diabetes mellitus and food habit.

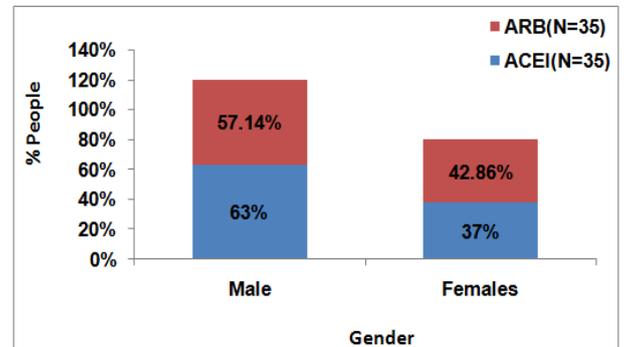


Fig. 1: Gender distribution among individual groups (N=70)

In patients who were treated with ACE inhibitors, out of 35 patients 63 % (N=22) were males and 37.14 % (N=13) were females. In patients who were treated with ARB out of 35 patients 57.14 % (N=20) were males and 42.86 % (N=15) were females.

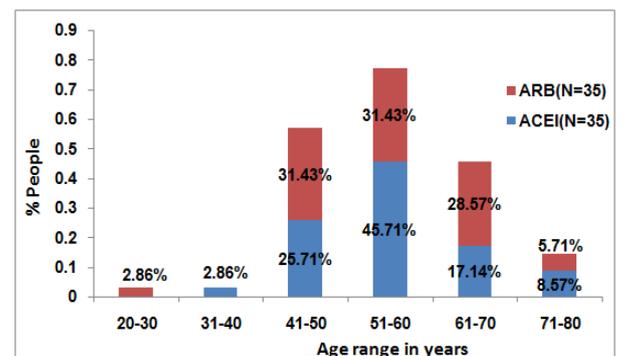
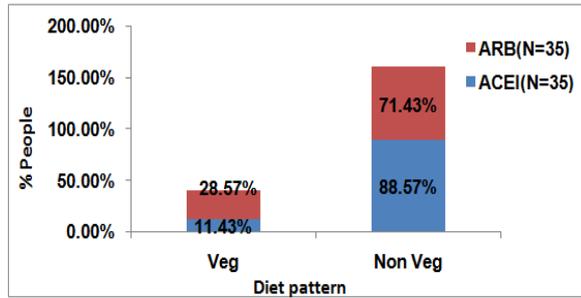


Fig 2: Age distribution among individual groups (N=70)

The most prominent age group in patients who were treated with ACEI were 51-60 y, which constituted 45.71% (N=16) of the patient population, followed by 41-50years, which constitute 25.71% (N=9), followed by 61-70 y which constitute 17.14% (N=6), followed by 71-80 y constitute 8.57% (N=3) and age group of 31-40 y constitute 2.86% (N=1). There were no patients below 30 y in ACEI treated patients.

In patients who were treated with ARB, the most prominent age groups were 41-50 y and 51-60years, both constitute similarly as 31.43% (N=11), followed by 61-70 y, which constitute 28.57% (N=10) and least number of patients were seen in the age groups 71-80 and 20-30 y which constitute 5.71% (N=2) and 2.86% (N=1) respectively. There were no patients in the age group 31-40years in ARB treated patients.

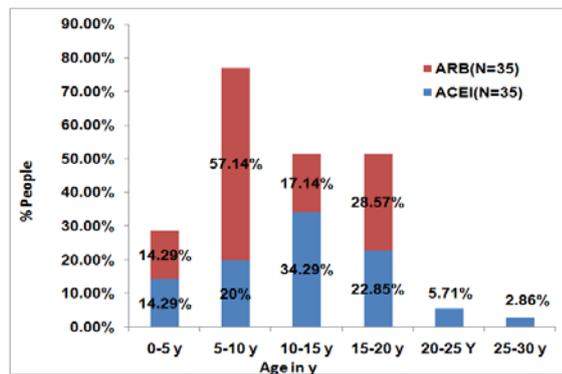
This reveals that middle aged populations suffer more from diabetic nephropathy.



**Fig. 3: Food habit among individual groups (N=70)**

Out of 35 patients who were treated with ACE inhibitors, 11.43 % (N=4) were vegetarians and 88.57 % (N=31) were non-vegetarian. Out of 35 ARB treated patients, 28.57 %

(N=10) were vegetarian and 71.43 % (N=25) were non-vegetarians.



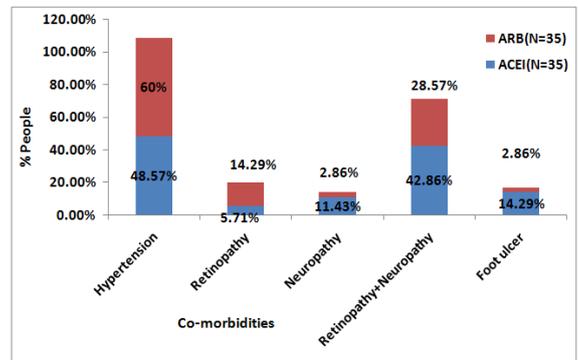
**Fig. 4: Duration of diabetics among individual groups (N=70)**

In patients who were treated with ACEI, the patients who had duration of diabetes mellitus between 10-15 y had more incidence i.e., 34.29% (N=12) of diabetic nephropathy. The patients in the 15-20 and 5-10 duration had the incidence of diabetic nephropathy 22.8 % (N=8) and 20 % (N=7) respectively. 14.29 % (N=5) patients were prone to diabetes mellitus between 0-5 y. 5.71 % (N=2) of patients

had diabetes mellitus since 20-25 followed by 2.86 % (N=1) of patients in 25-30 years.

In patient who were treated with ARB, the patient who had duration of diabetes mellitus between 5-10 years i.e., 57.14% (N=14), followed by 28.57 % (N=10) between 15-20 y duration and 17.14 % (N=6) between 10-15 y duration. 14.29 % (N=5) patients had duration of diabetes mellitus between 0-5 y.

Long standing diabetes mellitus is associated with increased prevalence of micro vascular disease. Duration of diabetes was one of the most important risk factor for diabetic nephropathy.



**Fig. 5: Distribution of co-morbidities in individual group (N=70)**

The most prevalent co-morbidity seen in diabetic nephropathy patients who were treated with ACEI were hypertension (HTN) which accounts for 48.57 % (N=17), followed by those suffering from both retinopathy and neuropathy 42.86 % (N=15). Patients with foot ulcer were 14.29 % (N=5) and patients with neuropathy only were 11.43 % (N=4).

The most prevalent co-morbidity seen in patients who were treated with ARB was hypertension which accounts for 60 % (N=21), followed by patients with both retinopathy and neuropathy account for 28.57 % (N=10). Patients with retinopathy only were 14.29 % (N=5) and neuropathy only and foot ulcer only were 2.86 % (N=1) each.

Here the most prevalent co-morbidity is hypertension in two groups. It reveals that pre-existing hypertension is a risk factor for developing diabetic nephropathy.

**Table 1: Drug usage in diabetic nephropathy patients (N=70)**

Drugs	Total (%) (N=70)	ACEI (%) (N=35)	ARB (%) (N=35)
Insulin	20%	22.86%	17.14%
Oral hypoglycemic	52.86%	57.14%	48.57%
Insulin+Oral hypoglycemic drugs	27.14%	20%	34.29%
Lipid lowering drugs	41.43%	34.29%	48.57%
Other antihypertensives	62.86%	60%	65.71%

The current recommendation for patients with diabetes is the treatment with an ACE inhibitors or ARB to reduce the risk of nephropathy [10]. Combination of an ACE inhibitor and ARB may potentially reduce the progression of diabetic nephropathy more than either agent alone [11].

Out of 70 patients 52.86 % (N=37) used Oral hypoglycemic (OHGs) as anti-diabetic drug, followed by insulin+oral hypoglycemic 27.14 % (N=19) and remaining 20 % (N=14) were used insulin alone as anti-diabetic agent.

In patients who were treated with ACEIs 57.14 % (N=20) used OHGs as anti-diabetic agent, followed by insulin 22.86 % (N=8), and remaining 20 % (N=7) used both insulin and OHGs.

In patients who were treated with ARB more number of patients used OHGs as anti-diabetic agent as in ACE inhibitors treated patients i.e., 48.57 % (N=17), followed by 34.29 % (N=12) used both insulin and OHGs, and remaining 17.14 % (N=6) used insulin as anti-diabetic agent.

Out of 70 patients 41.43 % (N=29) patients used lipid lowering drugs, which is 34.29 % (N=12) and 48.57 % (N=17) respectively in patients who were on ACEI and ARB.

Out of 35 patients who were treated with ACE inhibitors 92.31 % (N=24) were seen with decreased P/C ratio after 6 mo. The patient who were treated with ARB 94.29 % (N=33) patients were seen with decreased p/c ratio after 6 mo, so improved microalbuminuria.

**Table 2: Baseline clinical characteristics of patients (N=70)**

Variables	ACEI group (mean±S.E.)	ARB group (mean±S.E.)	P value
Urea(10-44 mg)	59.571±4.920	52.571±4.524	0.1468
Keratinize(0.4-1.4 mg/dl)	2.89±0.282	2.286±0.217	0.0256*
SBP(120 mmHg)	158.257±4.775	169.714±4.444	0.04*
DBP(80 mmHg)	87.143±1.767	86.57±1.687	0.4099
K+(3.5-5.1mEq/l)	4.834±0.122	4.888±0.118	0.3536
P/C ratio	2.528±0.278	2.438±0.2219	0.7991
Hb(12-15g/dl)	10.44±0.391	9.806±0.293	0.1971
RBS(70-140 mg/dl)	197.886±9.363	203±11.981	0.3838
HbA1c (4-6%)	6.861±0.221	7.145±0.331	0.3652

\*P<0.05 denotes significant difference, There was significant difference in the SBP and creatinine between the groups.

**Table 3: % Patients with improved clinical outcomes after 6 mo**

Variables	ACEI group	ARB group
Urea (10-45 mg/dl)	48.57%	54.29%
Creatinine(0.4-1.4 mg/dl)	40%	54.29%
SBP(120 mmHg)	74.29%	85.71%
DBP(80 mmHg)	68.57%	91.43%
K+(3.5-5.5mEq/l)	48.57%	60%
Hb(12-15g/dl)	34.29%	45.71%
Sugar(70-140 mg/dl)	65.71%	62.86%
HbA1c (4-6%)	65.71%	71.43%
P/C ratio	92.31%	94.29%

Out of 35 patients who were treated with ACE inhibitors group 48.57 % (N=17) were seen with decreased urea level after 6 mo. In ARB group 54.29 % (N=19) patients were seen with decreased urea level after the 6<sup>th</sup> month. So improved urea level was observed in ARB group after 6 mo.

## CONCLUSION

- Middle aged patients were more prone to diabetic nephropathy in this study group. Pre-existing hypertension and protein urea were the major risk factors in the progression of diabetic nephropathy.
- Majority of patients had long duration of DM which indicates the strong relation between duration of DM with diabetic nephropathy.
- Compared to ACE inhibitors, ARBs showed decrease in the levels of renal parameters such as blood urea, Creatinine and potassium. This study reveals that ARBs have favorable effect than ACEIs in treating diabetic nephropathy.
- Hemoglobin level was also increased in patients who were treated with ARBs compared to ACEIs, which reveals that ARB show better renoprotective effects than ACEIs.
- Blood sugar levels and HbA1c levels decreased more with ARB than ACE inhibitors.
- In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycemia. Any reduction in HbA1c is likely to reduce the risk of complications.

## Limitations

1. Short duration of the study
2. Time duration of consumption of ACEIs/ARBs were not taken into account.

## ABBREVIATION

ADA-American Diabetes Association, ACEIs-Angiotensin Converting Enzyme, ARBs-Angiotensin Receptor Blockers, BP-Blood Pressure, CKD-Chronic kidney Disease, CVD-Cardiovascular disease, DM-Diabetes Mellitus, DCCB-Dihydropyridine Calcium Channel Blockers, GDM-Gestational Diabetes mellitus, HbA1c-Glycosylated hemoglobin, GFR-Glomerular Filtration Rate, LDL-Low Density Lipoprotein, MAU-Microalbuminuria, RAAS-Renin Angiotensin Aldosterone System, UAE-Urinary Albumin Excretion

## CONFLICTS OF INTERESTS

Declared none

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