

## Efficacy of drugs in controlling microalbuminuria of diabetic nephropathy

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### ABSTRACT

**Background:** Beneficial effect in reducing microalbuminuria of diabetic nephropathy with angiotensin converting enzyme (ACE) inhibitor and angiotensin II receptor blockers (ARB) is proven. This study has directly compared the renoprotective effects of ARB and ACE inhibitors in persons with type-2 diabetes.

**Methods:** In this prospective, double-blind, controlled trial, 100 patients with type 2 diabetes mellitus were chosen and randomly assigned to either receive ACE inhibitor (ramipril 5 mg, 50 patients) or ARB (losartan 50 mg, 50 patients). The endpoint was a reduction in 24 hrs urine microalbuminuria after a period of 3 months treatment.

**Results:** At the end of 3 months treatment, the mean reduction of 24 hrs urine microalbuminuria in the ramipril group was 25 mg as compared to 38 mg in the losartan group; (t value=1.11, p=0.27). There was no statistical difference in the mean reduction when compared between the two groups. Significant reduction of blood pressure especially systolic blood pressure was noted in the losartan group as compared to those who received ramipril.

**Conclusion:** Losartan was not inferior to ramipril in providing renoprotection in subjects with type 2 diabetes and early nephropathy. Losartan showed a significant reduction in systolic blood pressure, though not much reduction was seen with ramipril. Despite this, both drugs have shown a reduction in microalbuminuria, which supports the fact that reduction in microalbuminuria is independent of the antihypertensive action of ramipril or losartan.

**Keywords:** Microalbuminuria, Diabetic nephropathy, Angiotensin converting enzyme inhibitor, Angiotensin II receptor blocker

### INTRODUCTION

The number of cases of diabetes worldwide in 2000 among adults more than 20 years of age is estimated to be 171 million. Prevalence is estimated to be 0.19% in population less than 20 years, 8.6% in those above 20 years and reaching 20.1% in those more than 65 years.<sup>1</sup> Globally, diabetes prevalence is similar in men and women, but it is slightly higher in men 60 years of age and in women at older ages. By 2030, it is estimated that the number of people with diabetes 64 years of age will be 82 million in developing countries and 48 million in developed countries.<sup>1</sup> India tops the list with 31.7 million people with diabetes and is estimated to grow up to 79.4 million diabetics by 2030.<sup>1</sup>

Diabetes mellitus (DM) remains the leading cause of end-stage renal disease, the world over. In persons with type 2 DM, hypertension and increased urinary albumin excretion are features of diabetic nephropathy. Increased urinary protein excretion is the earliest clinical finding of diabetic nephropathy. Diabetic patients with this complication are at increased risk for cardiovascular events and, if untreated, have a relentless decline in renal function leading to renal failure.

Angiotensin converting enzyme (ACE) inhibitors competitively block renin angiotensin system, decrease glomerular capillary pressure and prevent progression of microalbuminuria to overt proteinuria.<sup>1</sup> A similar beneficial effect of angiotensin II receptor blockers (ARB) in regression of microalbuminuria to overt proteinuria

has been seen in various studies.<sup>2-4</sup> There is a need for head-to-head comparison of ACE inhibitors and ARB in diabetic nephropathy.

The study is to evaluate and compare the efficacy of ACE Inhibitor versus ARB in controlling microalbuminuria of diabetic nephropathy

## METHODS

It is prospective, randomized, double-blind study with 100 patients of type 2 DM with evidence of microalbuminuria (urine albumin excretion rate of 30-300 mg/24 hrs) were chosen for the study. They were randomized into two groups of 50 each (Group A and Group B) in a double blind fashion. Group A patients received ACE inhibitor (ramipril 5 mg), Group B patients received ARB (losartan 50 mg) and the mean age group of 45-60 years (both males and females). Type I DM, overt proteinuria, history of hypertension, history of coronary heart disease, non-diabetic renal disease were excluded.

Subjects were followed up over a period of 3 months from the day of start of treatment. Albumin in 24 hrs urine was tested by the radio immuno-assay method - at the start of the study and at the end of 3 months of treatment with either an ACE inhibitor or an ARB. Diabetes was controlled with diet, oral hypoglycemic drugs or insulin.

At the end of 3 months, the collected data were analyzed for;

1. Reduced/absent microalbuminuria or
2. Persistent microalbuminuria (microalbuminuria of same or increased amount as compared to before the start of treatment).

## RESULTS

All the cases were randomized into either group (ACE inhibitor or ARB) and studied at the beginning and at the end of 3 months of treatment.

## DISCUSSION

A decline in the glomerular filtration rate is a key determinant of end-stage renal disease. Preventing (or delaying) the development of microalbuminuria is the key treatment goal for renoprotection. Recent clinical trials suggest that inhibition of the renin angiotensin system may actually prevent nephropathy. The *posthoc* analyses of the reduction in hypertension in the Heart Outcomes Prevention Evaluation Study<sup>5</sup> and in the losartan intervention for the end point study,<sup>6</sup> found a lower incidence of overt nephropathy in subjects with type 2 diabetes who received therapy that inhibited the renin angiotensin system than in controls.

Trials have supported the clinical equivalence of ARB and ACE inhibitors in delaying the progression of nephropathy in type 2 diabetes and in conditions that place them at high risk for cardiovascular events.<sup>7,8</sup> There has been a clinical study that has directly compared the effect of an ARB (losartan) with that of an ACE inhibitor (ramipril) in subjects with type 2 diabetes and early nephropathy.<sup>8</sup>

The present study is a similar study making head-to-head comparison of ACE inhibitor (ramipril) and ARB (losartan) in the regression of microalbuminuria in type 2 diabetics. The study has shown that both the drugs – ramipril and losartan reduce urinary albumin excretion (Table 1 & Figure 1) and within the group, the reduction in microalbuminuria is considerable and significant. However, the difference in reduction of microalbuminuria when compared between the two groups is statistically insignificant (Table 2).

Further, the study shows that losartan had better reduction in systolic blood pressure, as compared to the reduction seen with ramipril. (Table 2, 3 & Figure 2) though not significant difference was seen in the reduction of diastolic blood pressure (Table 2, 4 & Figure 3). Despite this difference on blood pressure, both the drugs have shown a reduction in microalbuminuria which supports the fact that reduction in microalbuminuria is independent of the antihypertensive action of the ramipril or losartan.<sup>9</sup> The study also shows that antihypertensive treatment reduces microalbuminuria and decreases the progression of albuminuria even in normotensive patients.<sup>10,11</sup>

This was a small study (100 subjects) done over a short follow-up period of 3 months duration. The two drug classes had an equivalent effect on the end point: Microalbuminuria reduction.

Diabetic nephropathy (progression of microalbuminuria) developed in eight of the patients – of which 6 were from the ramipril group (4 females, 2 male) and two (female) was from the losartan group. The non-superiority of either drug

**Table 1: Microalbuminuria (mg/24 hrs surine) gender in the two groups.**

	At the start			End of 3 months		
	Male	Female	Total	Male	Female	Total
<b>1. Ramipril</b>						
Mean	160	125	140	135	992	115
N	24	26	50	25	25	50
SD	60.1	96.9	81.8	56.1	82.8	73.3
<b>2. Losartan</b>						
Mean	176	112	145	114	99	107
N	25	26	50	24	26	50
SD	76.9	77.9	77.4	58.8	77.6	67.3

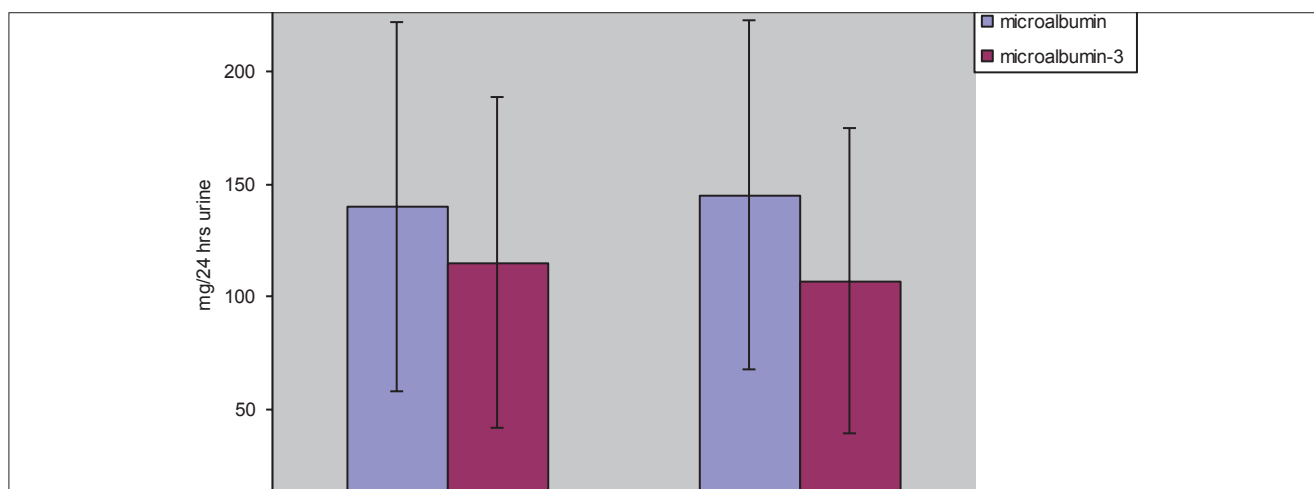


Figure 1: Microalbuminuria (mg/24 hrs urine) in the two groups.

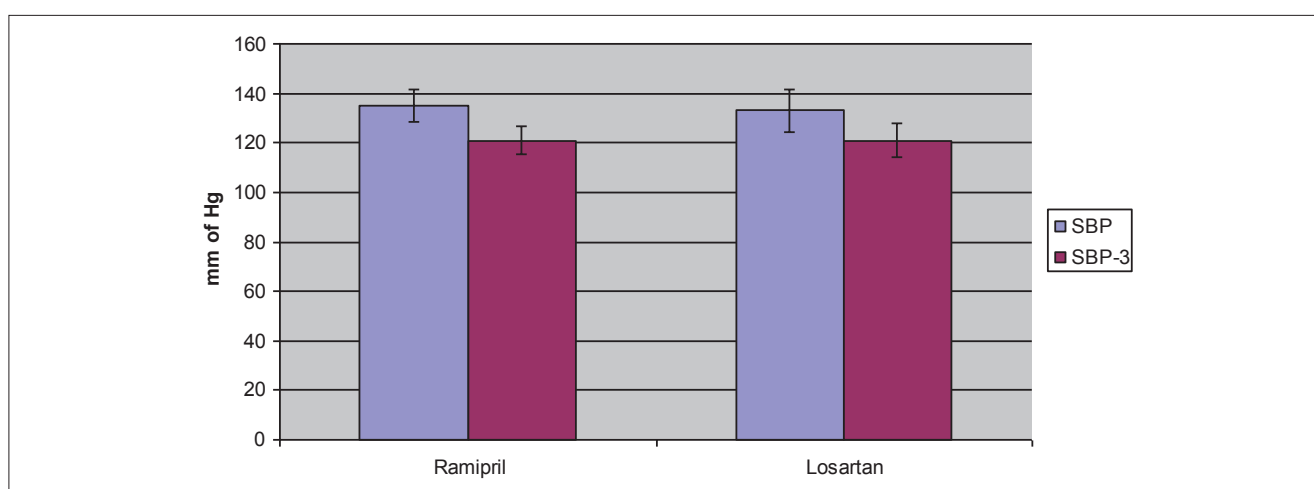


Figure 2: Systolic blood pressure before and after treatment in both groups.

Table 2: Blood pressure and microalbuminuria in the two groups.

	Ramipril		Losartan		T value	P value
	Mean	SD	Mean	SD		
SBP	135	6.5	133	8.6	0.85	0.4
SBP-3	121	5.6	121	7.0	3.05	<0.01
DBP	86	6.7	80	5.0	1.1	0.28
DBP-3	77	5.0	76	3.8	0.82	0.42
Microalbumin	140	81.8	145	77.4	0.16	0.87
Microalbumin-3	115	73.3	107	67.3	0.47	0.64

could be due to the fixed dose used – that is no titration to the maximum tolerated dose.<sup>12</sup> Two subjects on ramipril developed dry cough as an adverse effect, but there were no drop outs. No adverse effect was reported in the losartan group.

Our data indicate that losartan is not inferior to ramipril in providing renoprotection in subjects with type 2 diabetes and early nephropathy. This result is consistent with the emerging data that support the clinical equivalence of ARB

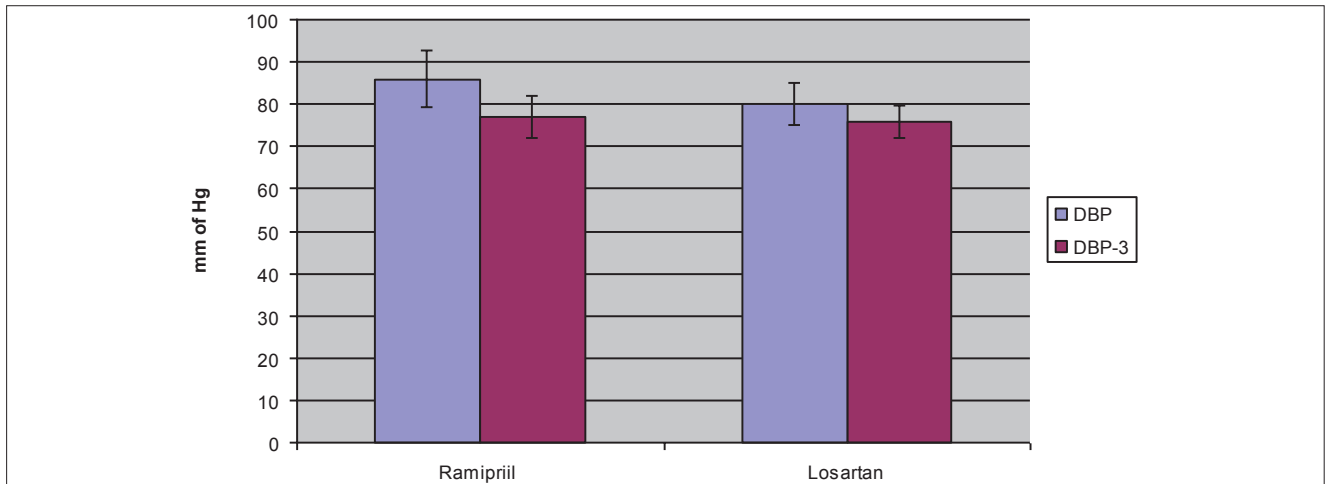
Table 3: Systolic blood pressure (mm of Hg) gender in the two groups.

	At the start			End of 3 months		
	Male	Female	Total	Male	Female	Total
1. Ramipril						
Mean	134	136	135	122	120	121
N	24	26	50	25	25	50
SD	5.1	7.3	6.5	5.1	6.0	5.6
2. Losartan						
Mean	136	128	133	122	119	121
N	26	25	50	26	24	50
SD	8.9	8.7	8.6	6.6	7.3	7.0

and ACE inhibitors in various conditions associated with high cardiovascular risk.<sup>8</sup>

### CONCLUSION

This study shows that both ramipril (ACE inhibitor) and losartan (ARB) reduced urinary albumin excretion; the differences



**Figure 3: Diastolic blood pressure before and after treatment in both groups.**

**Table 4: Diastolic blood pressure (mm of Hg) gender in the two groups.**

	At the start			End of 3 months		
	Male	Female	Total	Male	Female	Total
<b>1. Ramipril</b>						
Mean	87	84	86	78	76	77
N	24	26	50	25	25	50
SD	7.3	6.1	6.7	5.8	4.3	5.0
<b>2. Losartan</b>						
Mean	82	78	80	77	75	76
N	26	25	50	26	24	50
SD	5.9	3.4	5.0	4.4	3.4	3.8

between the two treatment regimens are not significant. Losartan is not inferior to ramipril in providing renoprotection in subjects with type 2 diabetes and early nephropathy.

Losartan showed a significant reduction in systolic blood pressure, though not much reduction was seen with ramipril. Despite this, both drugs have shown a reduction in albuminuria which supports the fact that reduction in microalbuminuria is independent of the antihypertensive action of the ramipril or losartan.

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