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**Original Research Article**

# A randomized, prospective, open label comparative study of the efficacy of azilsartan and ramipril in the management of hypertension in patients with type-2 diabetes mellitus

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## ABSTRACT

**Background:** Patients with diabetes are prone to have hypertension. Hypertension is risk factors for complications of the vascular system, cardiovascular diseases and leads to atherosclerosis. It has been estimated that the diabetics tend to have about two times more risk of having hypertension than the general population**.** Objective of current study is to study and compare the efficacy of azilsartan and ramipril in the management of Hypertensive patients with type 2 diabetes mellitus
**Methods:** randomized, prospective, open label comparative study was carried out among 60 known cases of diabetes mellitus type-2 with hypertension. Patients were randomly allocated into two groups: group-A (N=30) taking ACE Inhibitor tablet ramipril 5 mg Once daily orally. Group-B (N=30) taking angiotensin II receptor antagonist tablet azilsartan 40 mg once daily orally. At the commencement of the trial, patients were subjected to thorough clinical examination with necessary investigations and base line values were recorded.
**Results:** Both the groups were comparable for age, sex and treatment taken. There was a significant reduction in the mean arterial pressure (17.43 for azilsartan group vs. 14.5 for ramipril group) (mmHg), creatinine clearance (mean reduction of 18.8 for azilsartan group vs. 13.94 for ramipril group), and urinary albumin excretion (mean reduction of 29.74 in azilsartan group vs. 17.25 for ramipril group). In azilsartan group the reduction was more in all parameters compared to ramipril group without effecting renal parameters.
**Conclusions:** Azilsartan was more effective in reducing the mean arterial pressure (mmHg), creatinine clearance as well as urinary albumin excretion in Hypertensive patients with Type 2 diabetes mellitus without effecting renal parameters.

**Keywords:** Prospective, Efficacy, Azilsartan, Ramipril, Hypertension, Type -2 diabetes mellitus

## INTRODUCTION

Patients with diabetes are prone to have hypertension. Hypertension is risk factors for complications of the vascular system, cardiovascular diseases and leads to atherosclerosis. It has been estimated that the diabetics tend to have about two times more risk of having hypertension than the general population.[1] Disturbances in the renin-angiotensin-aldosterone-system (RAAS) lead to hypertension and subsequently to cardiovascular diseases.[2] Drugs that modulate RAAS are considered as best therapeutic agents for management of high blood pressure. They are more effective and at the same time are associated with few adverse effects. Angiotensin-converting enzyme (ACE) inhibitors are used to manage cardiovascular diseases including hypertension but their action is partial in the inhibition of angiotensin-II. In respect to this, angiotensin receptor blockers (ARB) have more selective action in the inhibition of RAAS. Angiotensin-II is a vasoconstrictor and stimulates

aldosterone release and thus promotes sodium retention. These are the drugs of first choice for treating all grades of hypertension without increasing the heart rate.[3] Ramipril belongs to ACE inhibitors and commonly used in the management of hypertension. Ramipril is a prodrug, cleavage of ester moiety by hepatic esterase transforms ramipril into ramiprilat, an ACE inhibitor that in vitro is about as potent as benazepril at and quinaprilat.[4] The antihypertensive efficacy of ramipril is maintained in patients with diabetes mellitus and preliminary data indicate that the drug has the beneficial effect of decreasing urinary albumin excretion in diabetic patients with nephropathy.[5] Azilsartan is highly selective angiotensin-II receptor-1 (AT1) antagonist with longer half-life, larger volume of distribution. Azilsartan has >10,000-fold greater affinity for the AT1 receptor than for AT2 receptor. Azilsartan medoxomil is given orally. It has inverse agonist properties and it dissociates slowly making it a therapeutic agent of choice in cases of cardiovascular diseases that are dependent on angiotensin-II. With this background, present study was carried out to study and compare the efficacy of azilsartan and ramipril in the management of hypertensive patients with type 2 diabetes mellitus.

## METHODS

A randomized, prospective, open label comparative study was carried out among known cases of diabetes mellitus type-2 with hypertensionat Department of General Medicine, Owaisi Hospital and Research centre. (OHRC) Hyderabadfrom January 2018 to December 2019

Patients with blood pressure more than 140 mm Hg systolic and more than 90 mm Hg diastolic with history of co-existing type-2 diabetes mellitus (with or without associated chronic complications); patient who gave informed consent; patients of 30-65yrs. age group of either sex, no gender bias; presence of clinical proteinuria (having urinary albumin excretion 20-200µg/min) were included in the present study.

Patients who were lactating; patients who did not give informed consent; patients with B.P more than 180 mm Hg systolic and 110 mm Hg diastolic; patients with Type-1 Diabetes Mellitus; patients with moderate to severe renal impairment; patients with moderate to severe congestive heart failure were excluded from the present study

### Methodology

Patients were randomly allocated into two groups; group-A (N=30) taking ACE Inhibitor tablet ramipril 5 mg once daily orally. Group-B (N=30) taking angiotensin II receptor antagonist tablet azilsartan 40 mg once daily orally. At the commencement of the trial, patients were subjected to thorough clinical examination with necessary investigations and base line values were recorded.

#### *Intervention*

Previous antihypertensive drug was stopped two weeks before the start of randomization. In some patients (if considered unsafe) the treatment was continued and it was stopped two days before randomization. After randomization patients of Group A (N=30) were started on 5 mg of ramipril and group B (N=30) were started with 40 mg of azilsartan. The dose was selected such that the mean arterial pressure was between 90-115 mmHg in supine position. The adjusted doses were kept constant in both groups throughout the 24-week trial. The measurement of B.P was followed up followed every 2, 4,6,8,12,16, 20 and 24 weeks. Before the study was started the status of glycemic control was assessed in the patients. The patients were included in the study only after glycemic control was achieved as follows: Glycosylated hemoglobin <8.0%, plasma glucose: Fasting <126 mg/dl; 2 hr. Post-prandial <200 mg/dl. Blood glucose control was maintained throughout the study period. All the patients were subjected to regular and frequent clinical examinations. The patients were also questioned to ensure that they had made no major modification in their diet or physical habit.

#### *Blood pressure measurement*

BP was measured with a standard mercury sphygmomanometer with the patients lying down. The cuff was applied to left arm after which pressure was recorded two times at 5 minute intervals, while the patient remained at rest. Diastolic blood pressure was recorded at the muffling of the Korotk off sounds. The mean of two readings differing by no more than 10 mm hg was recorded. Mean arterial pressure (MAP) was calculated as diastolic blood pressure (DBP) plus one third of difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). MAP=DBP+SBPDBP/3

#### *Laboratory tests*

Blood sugar estimation fasting and 2-hour post prandial method for true glucose O-toluidine method. Routine examination of urine including microalbuminuria and microalbuminuria. Blood urea estimation: diacetyl 1 monoxime method. Serum creatinine estimation: alkaline picrate method. 24-hour urinary protein estimation. Creatinine clearance=UV/P; where, U=creatinine concentration of urine V=minute volume of Urine and P=creatinine concentration of plasma,

#### *Statistical analysis*

Chi square test was used for proportions and t test for mean values, $p<0.05$ was taken as statistically significant.

## RESULTS

Both the groups were comparable for age and sex (Table 1). 33.3% of the study subjects were diabetic for 1-5 years and equal proportion for 6-10 years. 46.3% were known hypertensives for 1-5 years (Table 2). Both the groups were comparable in terms of proportion taking insulin and oral hypoglycemic drugs (Table 3). There was a significant reduction in the mean arterial pressure (mmHg) at the end of 24 months in both the groups but azilsartan group had more reduction than ramipril group indicating that both the it was more effective in reducing the mean arterial pressure (mmHg) (Table 4). There was a significant reduction in the creatinine clearance in both the groups but azilsartan group had more reduction than ramipril group indicating that both the it was more effective in reducing the creatinine (Table 5). There was a significant reduction in the urinary albumin excretion in both the groups but azilsartan group had more reduction than ramipril group indicating that both the it was more effective in reducing the urinary albumin excretion (Table 6).

**Table 1: Age and sex distribution of patients studied.**

| Variable | | Group A | Group B | t/Chi square | P value |
|---|---|---|---|---|---|
| **Age (years)** | | 56.06±5.6 | 54.03±5.4 | 1.429 | 0.1583 |
| **Gender** | Male | 16 | 15 | 0.066 | 0.7961 |
| | Female | 14 | 15 | | |

**Table 2: Distribution of study subjects as per duration of diabetes and hypertension.**

| Variable | | N | % |
|---|---|---|---|
| **Duration of diabetes (years)** | 1-5 | 20 | 33.3 |
| | 6-10 | 20 | 33.3 |
| | 11-15 | 15 | 25 |
| | > 15 | 5 | 16.6 |
| **Duration of hypertension** | 1-5 | 74 | 46.3 |
| | 6-10 | 62 | 38.8 |
| | 11-15 | 19 | 11.9 |
| | > 15 | 5 | 3.1 |

**Table 3: Anti-diabetic class of drugs prescribed.**

| Groups | Insulin | Oral hypo-glycemic drugs | Chi square | P value |
|---|---|---|---|---|
| **Group A** | 14 | 16 | 0.267 | 0.6054 |
| **Group B** | 17 | 13 | | |
| **Total** | 31 | 29 | | |

**Table 4: Effect of therapy on mean arterial pressure (mmHg) at the end of 24 months.**

| Groups | mean arterial pressure (mmHg) | | t value | P value |
|---|---|---|---|---|
| | Baseline | After 24 months | | |
| **Group B** | 121.83±12.1 | 104.4±10.2 | 4.4423 | <0.001 |
| **Group A** | 119.9±11.9 | 105.4±10.3 | 5.742 | <0.001 |

## DISCUSSION

The present non-interventional, prospective, observational study on prescribing pattern of type-2 Diabetes mellitus with co-existing hypertension was conducted in medicine department, Owaisi hospital and research centre over a period of 1 year 6 months had a total of 160 patients included in the study. In the present study, 51.3% of the study subjects were male and 48.8% were female. This difference was not statistically significant. This shows that gender difference in prevalence of hypertension with type-2 diabetes mellitus is narrowing down and by 2020 it is expected that more women would develop this condition than males. The mean age to develop type-2 diabetes mellitus with co-existing hypertension was 54.99±6.65 years. These results closely match with the findings in a study previously done by Zargar et al prevalence of type-2 Diabetes mellitus and impaired glucose tolerance with co-existing hypertension in the Kashmir valley of the Indian subcontinent, which showed that mean age in the study population was 51.89±8.81 years.[6] The present study revealed that 59.4% of the study subjects were from low socio-economic status and 40.6% were from middle class. This shows that disease was more common in lower socio-economic group. These results were consistent with those from a previous study by Agardh, Type-2 diabetes mellitus incidence and socioeconomic position.[7] These findings suggest that exposure to factors that are implicated in the causation of type-2 diabetes mellitus is more common in deprived areas. In our study none of them were from high socio economic status. In the present study, both the groups were comparable for age, sex and treatment taken. There was a significant reduction in the mean arterial pressure (mmHg), creatinine clearance, and urinary albumin excretion in both the groups but azilsartan group had more reduction than ramipril group indicating that both the it was more effective. Georgiopoulos et al carried out a systematic review of all relevant studies and found that azilsartan medoxomil (AZL-M) was more effective in reducing blood pressure compared to angiotensin II receptor blockers or ACE inhibitors.[8] It was also observed that AZL-M was associated with minimum side effects. To compare this ARB with another in the class, the authors

studied the effects of AZL-M and valsartan (VAL) in 984 patients with primary hypertension in a randomized, double-blind, multicentre study using ambulater and clinic blood pressure (BP) measurements.

**Table 5: Effect of therapy on creatinine clearance.**

| Groups | Creatinine clearance | | t value | P value |
|---|---|---|---|---|
| | Baseline | After 24 months | | |
| Group B | 73.56±7.3 | 54.76±5.4 | 7.5209 | <0.001 |
| Group A | 76.1±7.6 | 62.16±6.2 | 17.999 | <0.001 |

**Table 6: Effect of therapy on urinary albumin excretion.**

| Groups | Urinary albumin excretion | | t value | P value |
|---|---|---|---|---|
| | Baseline | After 24 months | | |
| Group B | 133±13.3 | 103.26±10.3 | 9.6833 | <0.001 |
| Group A | 111.78±11.1 | 94.53±9.45 | 6.455 | <0.001 |

The primary end point was change from baseline in 24-hour mean ambulatory systolic BP following 24 weeks of treatment. Hierarchical analysis testing for noninferiority was followed by superiority testing of AZL-M (80 mg then 40 mg) vs. VAL. The mean age of participants was 58 years, 52% were men, and 15% were black. Baseline 24-hour mean systolic BP was similar (approximately 145.6 mmHg) in each group. AZL-M 40 mg and 80 mg lowered 24-hour mean systolic BP (14.9 mmHg and 15.3 mm Hg, respectively) more than VAL 320 mg (11.3 mmHg; p<0.001 for 40-mg and 80-mg comparisons vs. VAL). Clinic systolic BP reductions were consistent with the ambulatory results (14.9 mm Hg for AZL-M 40 mg and 16.9 mm Hg for AZL-M 80 mg vs. 11.6 mm Hg for VAL; p=0.015 and p<0.001, respectively). The reductions in 24-hour mean and clinic diastolic BPs were also greater with both doses of AZL-M than with VAL (p=0.001 for all comparisons). Small, reversible changes in serum creatinine occurred more often with AZL-M than with VAL; otherwise, safety and tolerability parameters were similar among the three groups. These data demonstrate that AZL-M across the effective dose range had superior efficacy to VAL at its maximal recommended dose without any meaningful increase in adverse events.

These findings suggest that AZL-M could provide higher rates of hypertension control compared with other ARBs in the class. To compare this ARB with another in the class, the authors studied the effects of AZL-Mand valsartan (VAL) in 984 patients with primary hypertensionin a randomized, double-blind, multicenter study using ambulatory and clinic blood pressure (BP) measurements. The primary end point was change from baseline in 24-hour mean ambulatory systolic BP following 24 weeks of treatment. Hierarchical analysis testing for noninferiority was followed by superiority testing of AZL-M (80mg then 40mg) vs. VAL. The mean age of participants was 58 years, 52% were men, and 15% were black. Baseline 24-hour mean systolic BP was similar (approximately 145.6mmHg) in each group. AZL-M 40mg and 80mg lowered 24-hour mean systolic BP (14.9 mmHg and 15.3 mmHg, respectively) more than VAL 320mg 11.3mmHg; p<0.001 for 40mg and 80mg comparisons vs. VAL). Clinic systolic BP reductions were consistent with the ambulatory results (14.9 mmHg for AZL-M 40mg and 16.9 mmHg forAZL-M 80mg vs. 11.6 mmHg for VAL; p=0.015and p<0.001, respectively). The reductions in 24-hour mean and clinic diastolic BPs were also greater with both doses of AZL-M than with VAL (p=0.001for all comparisons). Small, reversible changes in serum creatinine occurred more often with AZL-M than with VAL; otherwise, safety and tolerability parameters were similar among the three groups. These data demonstrate that AZL-M across the effective dose range had superior efficacy to VAL at its maximal recommended dose without any meaning ful increase in adverse events.

These findings suggest that AZL-M could provide higher rates of hypertension control compared with other ARB sin the class. Bonner randomized patients in two groups. One group received AZL-M in the dose of 20 mg once in a day for two weeks and later on the dose was increased to 40-80 mg for 22 weeks. They found that the systolic blood pressure decreased by 20.6±0.95 mmHg for 20 mg dose of AZL-M while it decreased by 21.2±0.95 mmHg for higher doses. Both these differences were found out to be statistically significant. The incidence of the adverse effects was 4.8% in the ramipril group while it was only 2.4% with 20 mg of AZL-M dose and 3.1% with higher dose. The authors concluded that AZL-M was more effective in reducing systolic blood pressure compared to ramipril and also the side effects were less. Sica et al compared AZL-M with valsartan in a randomized controlled trial of 984 patients to see its effects on systolic blood pressure.[10] They found that AZL-M was able to lowered the systolic blood pressure in the dose of 40 and 80 mg more effectively when compared with valsartan which was administered in the dose of 320 mg. A study by Amira and Okubadejo on antihypertensive pharmacotherapy showed that ACE inhibitor (68.2%) was the most common drug prescribed for hypertension in diabetic patients.[11] A study by Amira and Okubadejo on antihypertensive pharmacotherapy showed that ACE inhibitor (68.2%) was the most common drug prescribed for hypertension in diabetic patients.[12] A study by Johnson et al on patterns of antihypertensive therapy among patients with diabetes mellitus showed that over 60% of patients received ACE inhibitor or angiotensin receptor blockers, followed by diuretics (38.1%), CCBs

(35.3%) and beta blockers (28.5%).[11] The findings are similar to the present study.[13]

### *Limitations*

This was a single centre study but the results are comparable to other larger studies carried out on similar theme. Authors did not consider the cost effective analysis of the two drugs which is an important parameter from the patient point of view as it will affect the treatment compliance this is another limitation of the present study. Hence other studies should be carried out as both drugs significantly reduced the study parameters. In such cases, the therapeutic choice is the cheaper drug so that patient treatment compliance can be improved.

## CONCLUSION

We conclude that both the drugs (azilsartan and ramipril) were effective in reducing the mean arterial pressure, serum creatinine and urine albumin excretion in hypertensive patients with type 2 diabetes mellitus over a period of 24 months. But azilsartan was able to reduce these parameters more compared to its study counterpart of ramipril. The reduction in the ramipril group was lesser compared to the reduction in the azilsartan group patients. Thus azilsartan was more effective in reducing the mean arterial pressure (mmHg), creatinine clearance as well as urinary albumin excretion in hypertensive patients with type 2 diabetes mellitus without effecting renal parameters

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