

Original Research Article

Monitoring Hypertension with Azilsartan Treatment With/Without Added Drug in Patients With/Without Comorbidity: An Observational Study

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ABSTRACT

Aims and Objectives of Study: Hypertension statistics had reported that approximately 9 million lives/per annum are at risk due to increased blood pressure. Azilsartan Medoxomil is an angiotensin inhibitor, widely used as a single treatment regime or in combination with other drugs is an FDA approved therapeutic that has a significant impact in hypertension patients. The present study is a prospective observational study with (a) Primary objective: to evaluate efficiency of Azilsartan (40mg / 80mg) as single treatment regime or with added drug, (b) Secondary objective: to assess the control statistics of hypertension in patients with/ without comorbidity.

Methodology: A total of 120 patients were screened and 100 subjects fulfilled the inclusion criteria with a hypertensive cut off value of 130/80 mmHg. Patients were subjected to Azilsartan monotherapy dosage (40mg/80mg) and combinatorial Azilsartan treatment with added drug. The following data was collected and analyzed for all study subjects enrolled in this observational study: Demographic details, Comorbidity associated with hypertension, Measurements of Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Measurements of Systolic blood pressure (SBP3m) and Diastolic blood pressure (DBP3m) after 3 months of drug treatment.

Results: The study population was predominantly of 51-60 years age group. Prevalence of hypertension at a gender level clearly showed that male population with 63% enrollment in study are at an increased risk in comparison to 37% patient enrollment noted in female population. Medical comorbidity ailments including Coronary Artery Disease, Diabetes Mellitus, Rheumatic Heart Disease. Azilsartan dosage (40mg/80mg) with either single treatment regime or combinatorial treatment regime with added drugs caused effective reduction in blood pressure during the study period.

Conclusion: Combinatorial treatment regimens of Azilsartan (40mg/80mg) along with added drug, proved more effective in significantly lowering blood pressure levels.

Keywords: Blood Pressure, Hypertension, Azilsartan, Comorbidity, Risk factors, Coronary artery disease(CAD), Diabetes mellitus, CAD/DM, Rheumatic heart disease (RHD).

INTRODUCTION:

High blood pressure or hypertension is well known as a 'silent killer', without exhibiting any major notable symptoms making it relatively undiagnosed. Hypertension is typically associated with a

myriad of medical comorbidities such as cardiovascular ailments, neurological complications (stroke), nephrological ailments (chronic kidney diseases).etc making it a prominent medical comorbidity at a global level. ^[1,2] Further, hypertension

statistics reported that approximately 9 million lives/per annum are at risk due to increased blood pressure. World Health Organization had prompted estimation that a 2mmHg decline in blood pressure at a population level would certainly prevent approximately 153000 deaths caused by cardiovascular ailments and 151000 deaths caused by neurological stroke. [1,3] Azilsartan Medoxomil is an angiotensin inhibitor, widely used as a single treatment regime or in combination with other drugs is an FDA approved therapeutic that has a significant impact in hypertension patients. [4] Azilsartan (40 mg and 80 mg) therapy in patients with 1–2 stage hypertension and metabolic syndrome effectively decreased to target blood pressure and had favorable effects on diastolic function and arterial stiffness. [5]

This study aimed at assessing the effectiveness of Azilsartan in hypertension patients with or without comorbidity. Further, role of age, gender, medical history and combinational treatment regime with Azilsartan had been examined. The present study is a prospective observational study with (a) Primary objective: to evaluate efficiency of Azilsartan (40mg / 80mg) as single treatment regime or with added drug, (b) Secondary objective: to assess the control statistics of hypertension in patients with/ without comorbidity.

METHODOLOGY

Investigation plan:

The study was conducted at VMMC & Safdarjung Hospital, New Delhi with a sample size of 120 evaluable patients. The prospective observational study is aimed with a focus to evaluate efficiency of Azilsartan (40mg / 80mg) as single treatment regime or with added drug, and also to assess the control statistics of hypertension in patients with/ without comorbidity.

Selection of study subjects:

The potential patients were identified and screened as per the inclusion and exclusion criteria set by clinical

research team. **Inclusion Criteria:** Hypertensive subjects with a cut off value of 130/80mmHg were enrolled in the study. **Exclusion Criteria:** Subjects with Chronic Kidney Disease - Stage 4, Pregnancy and subjects refusing to give informed consent were excluded in the study. Out of 120 study subjects, 100 patients fulfilled inclusion criteria. The study subjects / Legally Authorized Representatives signed a voluntary Informed Consent form, in order to facilitate collection of necessary data from the hospital records. The data collected was compiled centrally, cleaned and analyzed for outcome clinical report preparation.

Patients' data collection and

Measurements:

The following data was collected and analyzed for all study subjects enrolled in this observational study: Demographic details - Name, age, contact no, location, diagnosis/medical history, comorbidity associated with hypertension, measurements of Systolic blood pressure (SBP), Diastolic blood pressure (DBP) during enrolment, measurements of Systolic blood pressure (SBP3m) and Diastolic blood pressure (DBP3m) after 3 months of drug treatment. Azilsartan monotherapy dosage (40mg/80mg), combination drugs included - Metoprolol Succinate 25/50/100 mg, Cilnidipine 20 mg, Amlodipine 5 mg.

Statistical analysis:

The data were presented as proportions for categorical variables and range for continuous variables, as appropriate. BP control/non control in patients subjected to Azilsartan dosage (40mg / 80mg) with and without added drug treatments were analyzed by Pearson chi-square test and p value. A value of $p < 0.05$ was considered statistically significant.

Ethical Clearance:

Ethical approval was obtained from the independent research ethics committee at VMMC & Safdarjung Hospital, New Delhi.

RESULTS

Demographic details of the study population:

A total of 120 patients were screened, 100 subjects fulfilled the inclusion criteria and were enrolled. 20 subjects did not fulfill the inclusion / exclusion criteria and were excluded from the study.

Age group associated hypertension risk:

The study population was predominantly of 51-60 years age group (32 patients), followed by 61-70 years group (28 patients) and 41-50 years group (21 patients). Surprisingly, less than 30 - 40 years age group had an enrolment of 5 - 6 subjects showcasing the severity of hypertension at a younger age population. Distribution of age group and study subjects enrolled in study were represented in Figure 1.

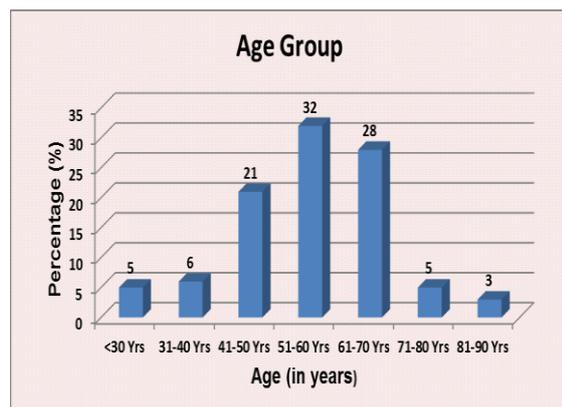


Figure 1: Age group based association of hypertension

Gender associated hypertension risk:

Prevalence of hypertension at a gender level clearly showed that male population with 63% enrollment in study are at an increased risk in comparison to 37% patient enrollment noted in female population. This observation proves that male populations are more susceptible to hypertension associated health risk factors. Gender associated hypertension risk were represented in Figure 2.

Comorbidity:

The study population was assessed for the impact of medical comorbidities associated with hypertension risk. Interestingly, Majority (69%) of study

subjects had no history or association of medical comorbidities along with hypertension. However, 13% subjects reported Coronary Artery Disease (CAD), 7% reported Diabetes mellitus (2), 10% showed a combined CAD/DM association with hypertension. Further, negligible 1% subjects reported rheumatic heart disease (RHD). Medical comorbidity ailments (CAD, DM, CAD/DM, RHD) associated with hypertension are represented in Figure 3.

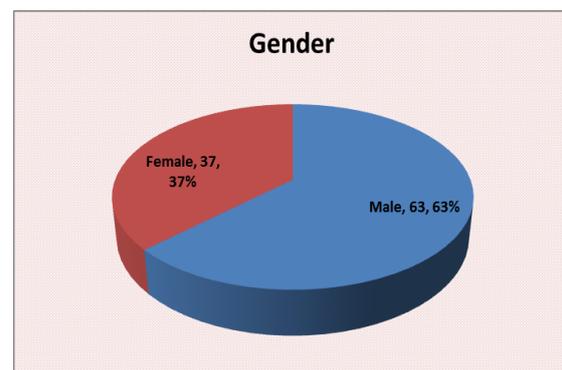


Figure 2: Gender based association of hypertension

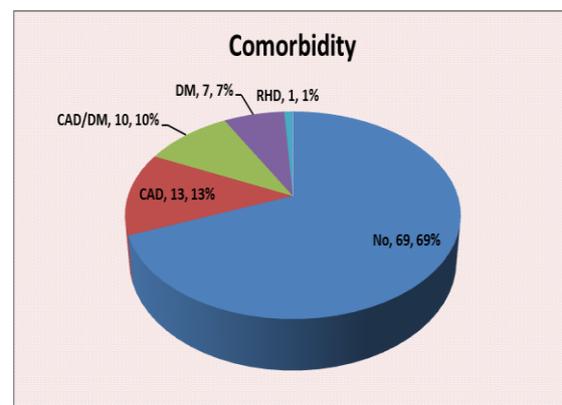


Figure 3: Medical comorbidities associated with hypertension. CAD - coronary artery disease, DM (Diabetes mellitus), RHD - rheumatic heart disease.

Azilsartan Monotherapy and Frequency of Subjects:

The study subjects were treated with Azilsartan - 40mg/ 80mg for hypertension and control statistics were monitored over a time period of 3 months. The frequency of 52% patient population was noted in Azilsartan dosage of 40mg as represented in Figure 4. Azilsartan monotherapy dosage (40mg/80mg) in both control and uncontrolled subjects showed reasonable

reduction as represented in Table 1. Further, effectiveness of combinatorial treatment with Azilsartan along with added drugs was assessed.

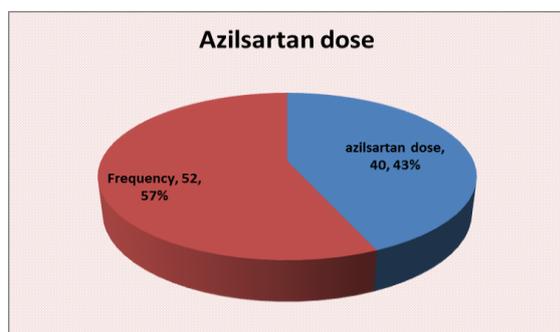


Figure 4: Azilsartan dosage and frequency of subjects.

uncontrolled subjects in comparison to Azilsartan monotherapy.

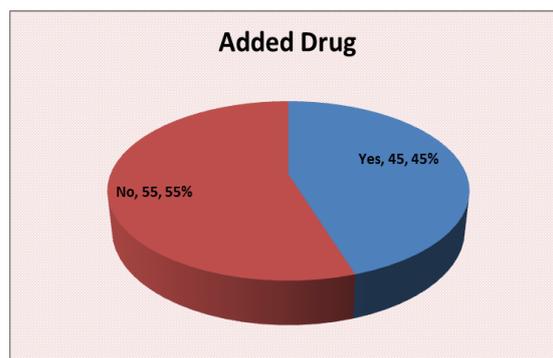


Figure 5: Azilsartan + added drug/without drug subjects.

Combinatorial treatment regime with Azilsartan + added drug:

Patients were given combinatorial treatment regime with added drug along with Azilsartan dosage. 45% of subjects were put under Azilsartan+ added drug, while 55% of subjects received only Azilsartan. Figure 5 shows the percentage of Azilsartan + added drug/without drug subjects.

Combinatorial treatment regime with Azilsartan dosage (40mg, 80mg) + added drug/without drug:

Subjects treated with 40mg / 80mg of Azilsartan in either single treatment or combinatorial treatment along with added drug were observed in both hypertension, control, uncontrolled subjects as represented in a tabulated form in Table 2. Combinatorial treatment regime showed enhanced BP reduction in both control,

Blood Pressure monitoring – Before and after 3 months Azilsartan treatment:

Blood pressure measurement recordings - Systolic blood pressure (SBP), Diastolic blood pressure (DBP) for normal subjects (baseline BP-normal) showed a value of 2 and subjects at the point of hypertension diagnosis (base line BP – raised) showed value of 98. Later, Azilsartan dosage (40mg/80mg) with either single treatment regime or combinatorial treatment regime along with added drug was provided. Further, after 3 months follow up blood pressure measurements showed that raised subjects had a decremental trend with a value of 77, while normal subjects exhibited value of 23. Overall combinatorial Azilsartan therapy with added drugs caused effective reduction in blood pressure as represented in Figure 6.

Table 1: BP Control/ noncontrol * azilsartan dose

		azilsartan dose		Total	Pearson Chi-Square	p-value
		40	80			
BP Control/noncontrol	Control	12	8	20	0.24	0.624
	Uncontrol	39	41	80		
Total		51	49	100		

Table 2: BP Control/ noncontrol * added drug * azilsartan dose crosstabulation

BP Control/noncontrol * added drug * azilsartan dose Crosstabulation							
Azilsartan dose			Added drug		Total	Pearson Chi-Square	p-value
			Yes	No			
40	BP Control/noncontrol	Control	4	8	12	0.785	0.376
		Uncontrol	18	21	39		
	Total		22	29			
80	BP Control/noncontrol	Control	3	5	8	0.091	0.762
		Uncontrol	18	23	41		
	Total		21	28	100		

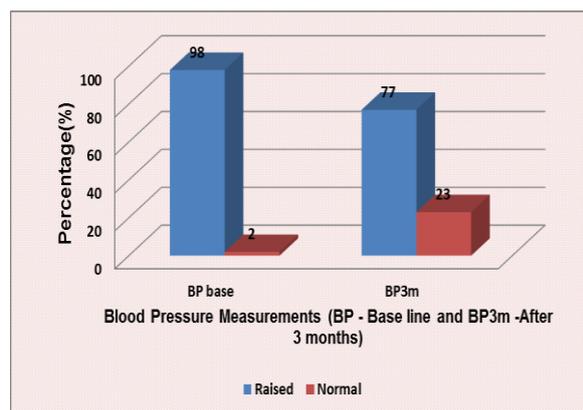


Figure 6: Blood Pressure monitoring – Before (BP baseline and after 3 months Azilsartan treatment (BP3m)

DISCUSSION

Retrospective audit based study was conducted to evaluate the effectiveness of Azilsartan monotherapy and in combination with other antihypertensive drugs in Indian population. A significant reduction in mean BP values with Azilsartan monotherapy (19.6/ 9.2 mm Hg) and combinatorial Azilsartan- drug therapy (30.2/13.5 mm Hg) was noticed in comparison to base line systolic/ diastolic BP values [6] and these findings were in accord with our current observations. Single-center, open-label, phase 1 parallel-group study to monitor pharmacokinetics and tolerability of Azilsartan 40 mg either as single-dose (day 1) and multiple-dose (days 4–8) in mild to moderate hepatic impairment patients revealed that Azilsartan dosage was well tolerated with no clinically meaningful effects. [7] Similarly, Azilsartan administration was well tolerated in our study patients. A prospective, observational, multicentric registry with a 12 month follow-up period was conducted to assess safety profile of Azilsartan in comparison to ACE inhibitors. Findings revealed that a significant BP control was achieved with Azilsartan in 61.1% patients in comparison to 56.4% with ACE inhibitors. [8] Double blind, randomized study to assess tolerability of Azilsartan (40 mg) either as a monotherapy and Azilsartan/Chlorthalidone (40/25 mg) combination in grade 2-3 essential hypertensive patients was carried out. Results confirmed that Azilsartan (40 mg) dosage was well tolerated in subjects.

Further, target BP was achieved with Azilsartan/ Chlorthalidone therapy in patients unresponsive to monotherapy. [9]

Retrospective cohort study was conducted by employing IMS® Disease Analyzer database to evaluate utilization patterns of Azilsartan in primary care setting of Germany. Study analysis performed in first wave (12 months before treatment) and second wave (6 months after treatment) confirmed that Azilsartan was prescribed both as a monotherapy and also in combination in subjects above 50 years and 75 years. [10] Randomized, double-blind, placebo-controlled trial was conducted to compare the efficiency of Azilsartan (40 mg, 80 mg), Valsartan 320 mg and Olmesartan 40 mg by employing ambulatory blood pressure and clinic BP monitoring. Investigations revealed that Azilsartan 80 mg was significantly effective in comparison to Valsartan, Olmesartan at maximal doses without any adverse events [11] and further, similar trend was observed among the current study subjects. Phase 3, randomized, double-blind, placebo-controlled study was carried out in Korean hypertensive patients to assess the efficacy of Azilsartan - 40 mg and 80 mg. A reduction in mean Systolic BP of 8.8mmHg in Azilsartan 40mg and 22.1mmHg in 80 mg was noted with a positive benefit-risk profile of Azilsartan in hypertension subjects. [12] 6-week, double-blind, randomized, placebo-controlled trial was conducted to examine the safety and efficiency of Azilsartan - 40 mg, 80 mg in African - American patients by employing ambulatory blood pressure and clinic BP monitoring. Investigations revealed that Azilsartan dosage was well tolerated and significantly decreased BP in a dose dependent manner. [13]

Randomized, double-blind, 6-week placebo-controlled study was carried out in stage 2 hypertensive subjects to assess the efficacy of Azilsartan - 40 mg and 80 mg in combination with Chlorthalidone and also Chlorthalidone monotherapy. Findings revealed that Azilsartan 40 mg or 80 mg

plus Chlorthalidone were significantly more efficient in lowering BP when compared to Chlorthalidone alone. [14] Randomized, double blind, 8-week titrate to target study was conducted to compare the hypertensive efficacy of Azilsartan - Chlorthalidone and Olmesartan - Hydrochlorothiazide in diabetic and chronic kidney disease subjects. Results confirmed that lower titration of Azilsartan – Chlorthalidone had a significant mean BP reduction of 37.6mmHg, while a higher mean value of 31.5mmHg was observed in Olmesartan - hydrochlorothiazide despite of greater titration dose. [15] Nonrandomized, phase 3, open-label, 56 week, treat-to-target cohorts study evaluated safety and tolerability of Azilsartan (40 mg, 80mg) over 8 weeks and further with drugs - Chlorthalidone (25mg) and Hydrochlorothiazide (12.5–25mg). Observations concluded that Azilsartan-Hydrochlorothiazide significantly lowered BP levels with a mean BP reduction by 24.2/17.9mmHg in comparison to a higher value of 25.2/18.4 mmHg noted in Azilsartan- Chlorthalidone. [16]

CONCLUSION

Azilsartan (40 mg / 80 mg) in a single treatment regime effectively decreased the raised blood pressure in hypertensive patients with/without comorbidity. Further, combinatorial treatment regimens of Azilsartan (40 mg /80 mg) along with added drug proved more effective in significantly lowering blood pressure levels below the base line value of 130 /80 mmHg. Further, Large population wide studies would provide more insights in optimizing the dosage and treatment management paradigms in hypertension patients with/with our medical comorbidities.

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Conflict of Interest: No conflict of interest among the authors.

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