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Efficacy and Safety of Azilsartan in Controlling Hypertension in Patients Attending a Tertiary Care Hospital of Odisha

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Introduction

Hypertension is one of the most important cardiovascular risk factors with very high prevalence. With uncontrolled hypertension there is high risk of myocardial infarction, stroke, atherosclerosis and renal failure.[1] As per the Registrar General of India (2017), CVD was the largest cause of deaths in males (33.8%) as well as females (34.3%) and out of that death due to hypertension happened in 14.2% of males and 16.2% of females.[2] The number of hypertensive patients in India is expected to double from 118.2 million in 2000 to 213.5 million by 2025. Henceforth India would be labelled as the "hypertension capital of the world".[3]

International guidelines suggests that in the general population, pharmacologic treatment should be initiated when blood pressure is 150/90 mm Hg or higher in adults 60 years and older, or 140/90 mm Hg or higher in adults younger than 60 years.[4] Successful treatment of hypertension leads to significant reduction of comorbidity and death.[5,6,7] According to the Eighth Joint National Committee (JNC 8), medications in the management of hypertension in adults, includes four major groups of drug. Among these, angiotensin II-receptor blockers (ARBs) have similar or greater efficacy compared with other classes of hypertensive agents but are much more tolerable.[8,9,10] ARBs have no negative metabolic effects and they cause no accumulation of bradykinin. They also have an ability to activate the angiotensin II type 2 (AT_2) receptors, which causes vasodilatation in the small vessels and presumably leads to additional cardiac and renal protection.

Despite the fact that all approved AT_1 receptor blockers can lower BP, many patients treated with currently available ARBs do not achieve BP treatment goals. So the FDA approved Takeda's Azilsartan medoxomil as the 8th ARB for the treatment of hypertension.[11]

Azilsartan medoxomil (AZL-M) is a prodrug which hydrolyses quickly in the gastrointestinal tract during its absorption to its active moiety Azilsartan. Azilsartan has high affinity for the angiotensin II type 1 receptor along with slower dissociation from the receptor.[12] It has an estimated bioavailability of 60%, with no relation to food, and an elimination half-life of approximately 11 h. No drug interactions have been observed till date in studies of AZL-M or Azilsartan.

With the above literature at the background, this study was conducted to evaluate the antihypertensive effect of Azilsartan against that of the standard ARB Telmisartan in hypertensive patients.

Objectives
Primary Objective
- To evaluate the efficacy of Azilsartan in patients with hypertension.

Secondary Objectives
- To compare the blood pressure lowering effect of Azilsartan to Telmisartan.
- To observe the safety profile of Azilsartan and Telmisartan.

Methodology
The study type was a hospital based prospective open label observational study which was carried out from 1st Aug. 2017 to 30th Sept. 2018, in the Department of Pharmacology in collaboration with Department of Cardiology of Srirama Chandra Bhanja (S.C.B.) Medical College & Hospital, Cuttack.

The protocol was submitted and approved by Institutional Ethics Committee (IEC) of SCB Medical College and Hospital prior to the beginning of the study. Written informed consent was taken from each patient before including them into the study after assessing the eligibility.

The Adverse drug reactions (ADRs) related to Azilsartan and Telmisartan were monitored and documented in Suspected ADR reporting form (IPC - PvPI).

Severity and causality of the ADRs were assessed by using Modified Hartwig and Seigel scale and WHOUMC Causality Assessment Scale, respectively. The Modified Hartwig and Siegel scale grades ADRs as Mild, Moderate, and Severe. The WHO-UMC Causalty Assessment Scale classifies ADR as Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified and Unassessable/Unclassifiable.

Statistical analysis of Data was done using SPSS 19. P-value <0.05 was taken as significant and P-value < 0.001 was taken as highly significant.
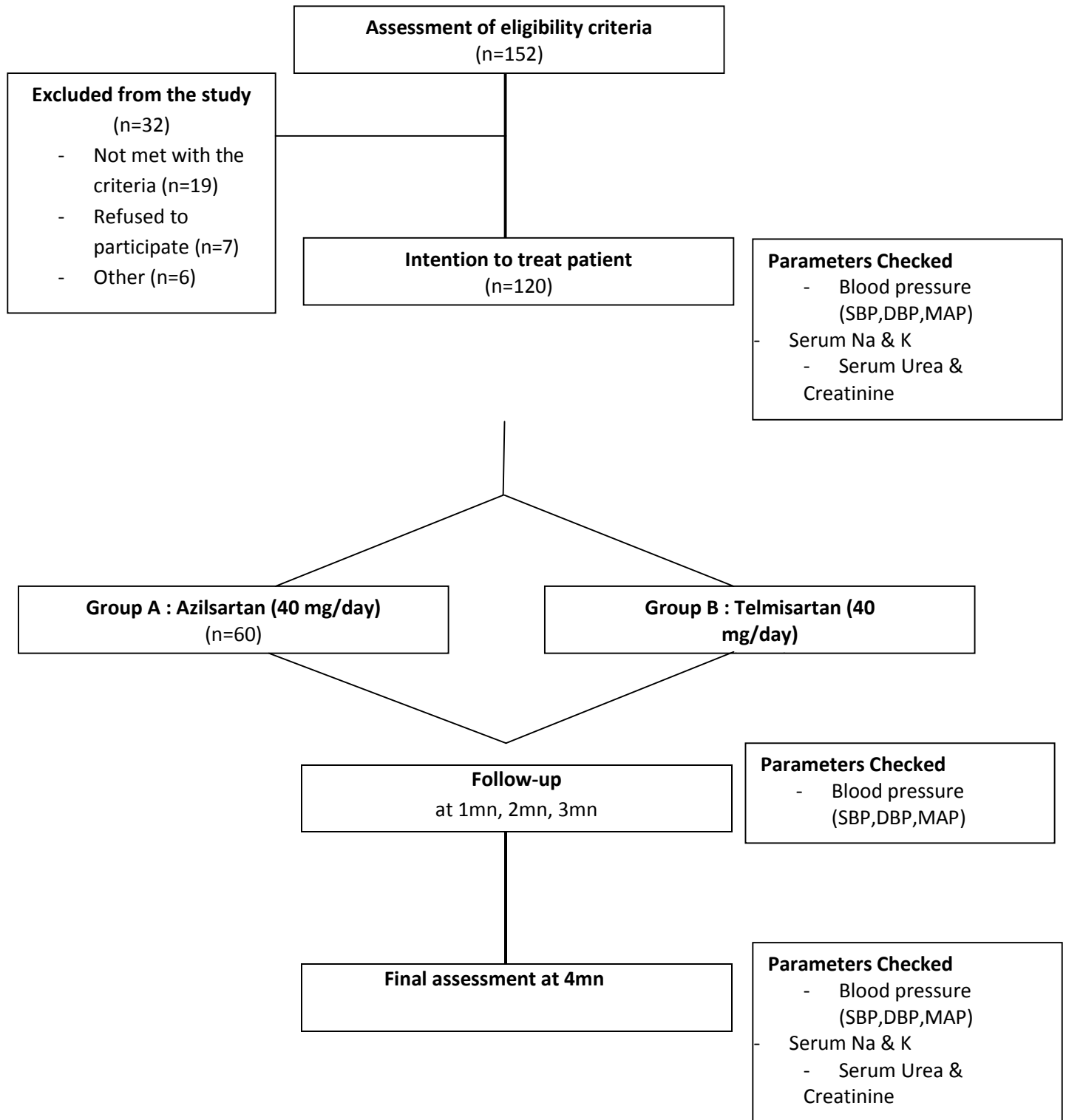
Inclusion Criteria
- All newly diagnosed cases of Hypertension (BP ≥140/90 mm of Hg in patients < 60 years and ≥150/90 mm of Hg in patients > 60 years) without prior treatment visiting the Cardiology OPD.
- Hypertensive patients resistant to other anti-hypertensive monotherapy (beta blockers, ACEIs, other ARBs, CCBs and diuretics).
- Patients intolerable to other first line drugs.
- Age >18 years of either sex.

Exclusion Criteria
- Secondary causes of Hypertension (Coarctation of Aorta, Reno vascular hypertension, Cushing syndrome, Adrenal tumors etc.)
- Pregnant women.
- Patients on Anti-hypertensive combination therapy.

Study Flow chart

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                          ┌─────────────────────────────┐
                          │ Assessment of eligibility    │
                          │ criteria                     │
                          │ (n=152)                      │
                          └─────────────────────────────┘
┌──────────────────────────┐
│ Excluded from the study  │
│        (n=32)            │
│  - Not met with the      │
│    criteria (n=19)       │
│  - Refused to            │        ┌─────────────────────────────┐   ┌──────────────────────────┐
│    participate (n=7)     │        │ Intention to treat patient  │   │ Parameters Checked       │
│  - Other (n=6)           │        │ (n=120)                     │   │  - Blood pressure        │
└──────────────────────────┘        └─────────────────────────────┘   │    (SBP,DBP,MAP)         │
                                                                        │ - Serum Na & K           │
                                                                        │  - Serum Urea &          │
                                                                        │    Creatinine            │
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Group A : Azilsartan (40 mg/day) (n=60)	Group B : Telmisartan (40 mg/day)

Follow-up
at 1mn, 2mn, 3mn

Parameters Checked
- Blood pressure (SBP,DBP,MAP)

Final assessment at 4mn

Parameters Checked
- Blood pressure (SBP,DBP,MAP)
- Serum Na & K
- Serum Urea & Creatinine

Results

Our study had a total of 120 patients with 60 patients each in Azilsartan and Telmisartan group.

None of the patients were lost during the follow-up period.

Table 1 Age Distribution of Patients

Age Group (years)	Group A(Azilsartan 40mg/day) (Total no of patients)N = 60		Group B(Telmisartan 40mg/day) (Total no of patients)N = 60	
	(no of patients) n	%	(no of patients) n	%
30-39	6	10	3	5
40-49	6	10	7	11.67
50-59	16	26.67	17	28.33
60-69	27	45	24	40
>70	5	8.33	9	15

It was observed that maximum numbers of patients belonged to the age group of 60-69 years in both the groups. The Mean age of Patients in Group A was 57.45 years and in Group B was 57.85 years.
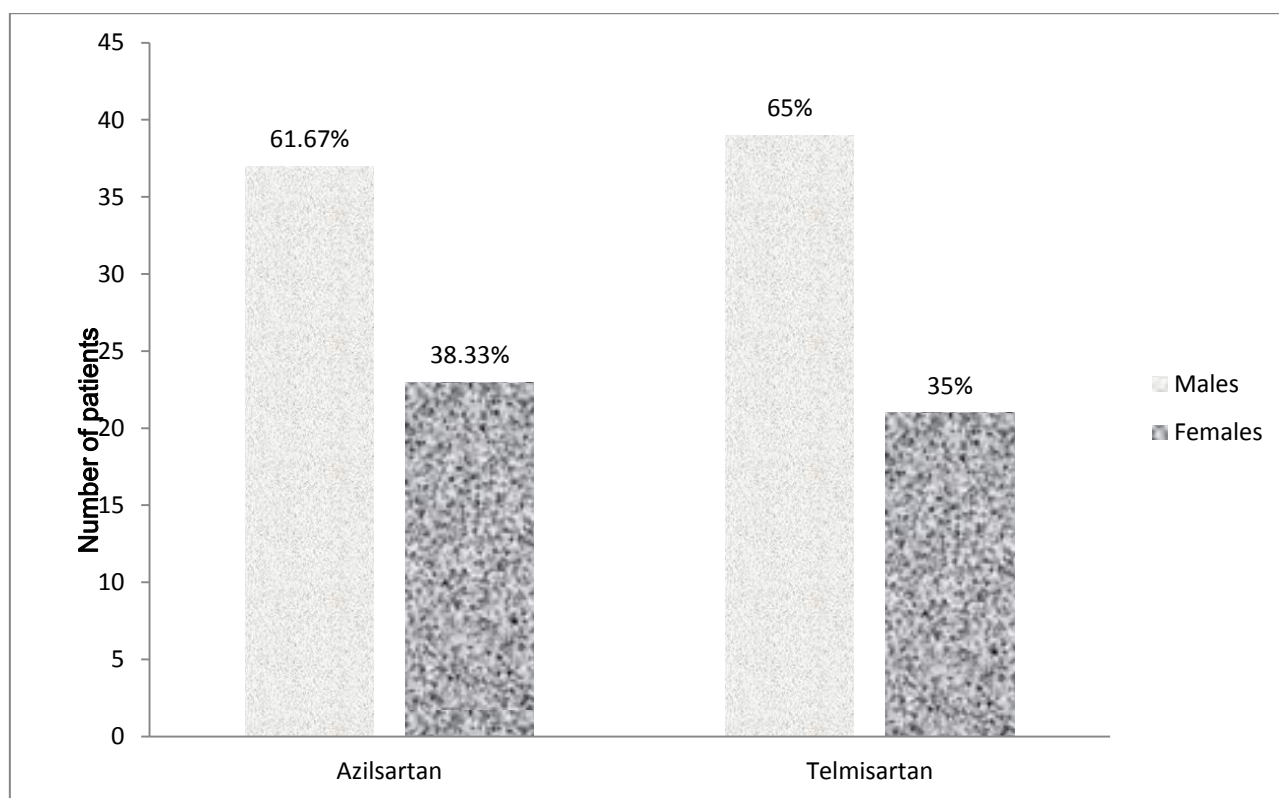
Figure 1 Bar Diagram Showing Gender Distribution of Patients

In Azilsartan group there were 37 males (62%) and in Telmisartan group there were 39 males (65%).

Average BMI in Azilsartan group was 30.16 and in Telmisartan group 29.67.

Table-2 Comparison of Blood Pressure Data between Groups at Monthly Intervals

Time \ Parameters	Mean SBP		Mean DBP		Mean Arterial BP	
	Azilsartan	Telmisartan	Azilsartan	Telmisartan	Azilsartan	Telmisartan
Baseline	161.9±13.4	164.7±13.79	94.13±6.17	93.5±6.17	116.72±7.16	117.27±7.1
1 month	153.36±12.05	155.3±11.95	86.13±4.78	87.13±5.01	108.54±5.74	109.85±5.9
2 month	145.96±11.9	147.03±11.95	80.96±5.20	81.5±5.37	102.63±6.5	101.44±6.3
3 month	136.53±8.63	136.3±7.57	76.3±3.85	76.66±4.02	96.37±4.53	96.54±4.21
4 month	126.31±4.28*	127±3.76*	74.86±3.86*	75.5±3.88*	91.44±3.71*	92.71±3.17*

*- paired t test

The p values on comparison between the groups at baseline and at follow-up intervals were non-significant. The Mean SBP, mean DBP and MEAN Arterial BP decreased at each follow up but was statically significant at 4 month in comparison to baseline for both the groups. ($p < 0.001$)

Table 3 Serum Parameters at Baseline and at 4 Month

Groups → Parameters ↓	AZILSARTAN (Group A)		TELMISARTAN (Group B)	
	BASELINE	4 MONTHS	BASELINE	4 MONTHS
Serum Na^+ (mmol/l)	140.75± 2.81	140.38±2.29	141.23±3.08	140.65±2.57
Serum K^+ (mmol/l)	4.18±0.53	4.25±.58	4.32±0.59	4.29±0.54
Serum Urea (mg/dl)	29.91±4.94	29.79±4.40	28.74±5.17	27.28±8.13
Serum Creatinine (mg/dl)	0.808±0.13	0.82±0.131	0.82±0.138	0.83±0.1323

Serum parameters measured at baseline and at the end of the study period showed no significant variation. ($p > 0.05$)

Table 4 Adverse Drug Reactions (ADR)

ADR	AZILSARTAN (Group-A)	TELMISARTAN (Group-B)
HEADACHE	0	2
GASTROENTERITIS	0	3

No ADRs were observed in Group A patients. In group B patients 3 patients suffered from gastroenteritis and 2 patients from headache.

All ADRs were mild in nature according to Modified Hartwig & Siegel scale and were probable according to WHO-UMC causality assessment scale.

Discussion

In the present study, both azilsartan (40mg once daily) and telmisartan (40mg once daily) were observed to be effective in reducing both systolic and diastolic BP throughout the study period when compared from the baseline with 1st, 2nd, 3rd and 4th month. When efficacy was compared, it was found that azilsartan was as effective as telmisartan in reducing systolic and diastolic BP ($p < 0.05$).When we compared the difference between Systolic, Diastolic and Mean Arterial blood pressure between both the treatment groups, at baseline and at monthly intervals for four months, the difference was not found to be

statistically significant.

Under the experimental conditions described by Ojima et al, azilsartan was found to be approximately twice as potent as either olmesartan or telmisartan, both of which are considered to be among the most potent of all clinically approved ARBs for blocking angiotensin II binding to AT1 receptors[13]. The greater potency of azilsartan for AT1 receptor blockade could help explain why azilsartan lowers BP more than maximum approved doses of other ARBs such as olmesartan and valsarta[14]. But current study failed to prove this.

The clinical BP trials of azilsartan or Azilsartan medoxomil published to date have been mainly conducted in patients without serious comorbidities, although 20% of the subjects in the study by Rakugi et al were diabetic[15].It remains to be determined whether azilsartan will also provide superior BP lowering action or any type of advantage over other ARBs in the treatment of hypertensive patients with serious co-morbidities such as cardiovascular disease or severe renal insufficiency. Although head-to-head comparisons of the BP lowering actions of different ARBs in high risk patients are certainly feasible, it is unlikely that large scale trials will ever be performed to compare the effects of different ARBs on clinical outcomes such as myocardial infarction, renal failure, stroke, etc[14].

Azilsartan, in clinically approved doses as Azilsartan medoxomil, has been shown to lower 24-hour BP in hypertensive patients significantly more than the maximum approved dose of olmesartan medoxomil, the latter being considered by some to be one of the most potent ARBs for lowering BP[16,17,18].

There was no difference among treatment groups in the incidence of clinical and laboratory adverse events. As a class, ARBs are noted for having a side effects profile similar to that of placebo[19].A placebo group was not included in the current study, but the total adverse events rare, is similar to that reported for the placebo group in several placebo controlled trials carried out in hypertensive patients[20,21].

In a study by Bhosle et al, where the safety profile of Azilsartan was compared to telmisartan, the majority of AEs were mild in severity, and the most commonly reported events with both drugs were nasopharyngitis, upper respiratory tract inflammation and gastroenteritis. There was a slightly higher incidence of treatment related AEs with azilsartan than with telmisartan (15% vs. 12.5%), mainly as a result of slightly higher incidences of postural dizziness (12.5% vs. 7.5%). However, these events were generally of mild intensity and resolved without intervention and, importantly, were not of clinical concern as they did not lead to any major health problem[18].

Conclusion

Patients with hypertension showed significant reduction in systolic, diastolic and mean arterial blood pressure in both the groups at the end of four months when compared to baseline. Serum electrolytes and urea and creatinine showed no significant change with the use of these drugs. Five ADRs were reported in Telmisartan group and no ADRs were reported in Azilsartan group and these were of mild in nature requiring no discontinuation of drugs.

So to conclude, both Azilsartan and Telmisartan are equally effective in reducing the blood pressure but Azilsartan is safer than Telmisartan.

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