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INTENSIVE BLOOD PRESSURE LOWERING WITH AZILSARTAN IN INDIAN HYPERTENSIVE PATIENTS IN REAL-WORLD CLINICAL SETTINGS: INTENSE STUDY

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ABSTRACT

Background: Hypertension (HTN) is ranked as third most important risk factor for attributable burden of cardiovascular disease. Azilsartan, because of highest responder rate, appears to be the most suited antihypertensive agent to achieve the target blood pressure (BP). As there is limited Indian clinical trial data and real-world studies on safety and effectiveness of azilsartan, this study was designed to investigate the 'real-world' effectiveness and safety of azilsartan in Indian hypertensive patients associated with various co-morbidities. **Methods:** This was a prospective, non-interventional, real-world study of Indian adult patients of diagnosed with essential HTN and prescribed with tablet azilsartan. Demographic data, details of treatment with azilsartan, changes in BP and occurrence of adverse events (AE) were noted during the follow-up visits (6 and 12 weeks). **Results:** Among 240 enrolled patients, mean reduction systolic BP from baseline with azilsartan was 16.2±11.1 mm Hg and 27.16±10.6 mm Hg ($p<0.001$) at Week 6 and Week 12 respectively. The proportion of patients achieving target systolic BP of ≤140 mm Hg was 56.70% at Week 12. The proportion of patients achieving aggressive target BP of <130/80 mm Hg was 40.42% at Week 12. In patients uncontrolled on telmisartan and shifted to azilsartan, the proportion of patients with target systolic BP of ≤140 mm Hg at Week 12 was 75%. **Conclusion:** The results of present real-world study suggest that azilsartan is effective and safe in the treatment of newly diagnosed treatment-naïve hypertensive patients as well as those uncontrolled on other antihypertensive agents including telmisartan with associated co-morbidities.

KEYWORDS: Hypertension, azilsartan, blood pressure, telmisartan.

INTRODUCTION

Hypertension (HTN) is ranked as third most important risk factor for attributable burden of cardiovascular disease (CVD).[1] It is amongst the frontline causes to contribute significantly to the public health burden of CVD in India.[2] The estimated worldwide age-standardized prevalence of HTN increased to 31.1% in 2010 in adults ≥20 years, with an increase of 5.2% over a period of 10 years, thus, affecting almost 1/3rd of the world population. The prevalence of HTN is higher in low and middle income countries compared to the high income countries.[3] The Global Health Observatory Data quotes 7.5 million (12.8%) deaths globally due to raised blood pressure (BP).[4] According to Global Burden of Disease Study, in India, increased BP attributes to 15.6% deaths and 7.8% DALYs.[5] It is estimated that by year 2025, the number of adults with HTN will increase by about 60% to a total of 1·56 billion.[6] A cross-sectional SITE Study has shown the prevalence of HTN in India as high as 46%.[7] Recently published data of cross-sectional, nationally representative, population-based study of 1.3 million Indian adults has shown that the crude prevalence of HTN in India is 25.3%.[8] Raised BP is, thus, one of the major health problems of the present and future times.

Epidemiological data from large scale studies provides strong evidence that HTN is associated with an increased risk of ischemic heart disease mortality, stroke mortality, vascular mortality and a range of other fatal and nonfatal vascular events.[9] Lowering of BP causes reduction of any cardiovascular (CV) risk, with greater risk reduction in patients who are at high CV risk.[10] Systolic Blood Pressure Intervention Trial (SPRINT) reported significantly lower relative risk of the primary composite CV outcome (25%), heart failure (38%), death from CV causes (43%) and death from any cause (27%) with intensive BP reduction (systolic blood pressure [SBP] less than 120 mm Hg) compared to standard BP lowering (SBP less than 140 mm Hg).[11] As per various guidelines

for HTN, among different therapies, renin angiotensin aldosterone system (RAAS) blockers like angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended among first choice therapy in treatment of HTN.[12-15]

Of the 8 ARBs available in the market, azilsartan is the latest one. It was approved by USFDA in 2011 and in India by DCGI at the end of 2016.[16,17] Azilsartan promises to reduce BP more effectively as compared to other known ARBs. Various randomised, double blind, controlled clinical trials have shown superior BP reduction with azilsartan than the maximum approved doses of available ARBs like olmesartan, valsartan, candesartan and ACEI (ramipril).[18-22] Azilsartan, because of highest responder rate, appears to be the most suited antihypertensive agent to achieve the target BP.

Though aggressive BP reduction and safety of azilsartan have been well established in several clinical trials done in European, Japanese and US population, there is dearth of clinical trial data on safety and effectiveness of azilsartan in Indian hypertensive patients. Moreover, data captured under these tightly controlled settings do not necessarily replicate actual experience in clinical practice. Real-life databases may suggest alternative information that reflects an uncontrolled real-world setting and supplements and expands on the findings of clinical trials. There have been no reports discussing the effectiveness of azilsartan in the 'real world' in the management of HTN. Hence, this study was designed to investigate the 'real world' effectiveness and safety of azilsartan in Indian hypertensive patients associated with various co-morbidities.

MATERIALS AND METHODS

This prospective, single center, non-interventional, real-world study was conducted at Rao Nursing Home, Pune during a period of 9 months from January 2017 to September 2017. Independent Ethics Committee approval was obtained before initiation of study. Indian adult patients $\geq$18 years of either sex and diagnosed with essential HTN; either newly diagnosed or uncontrolled HTN (uncontrolled HTN was defined as BP $\geq$140/90 mm Hg on current antihypertensive medications) and prescribed with tablet azilsartan as a part of routine clinical practice and approved prescribing information were included in the study. Pregnant and lactating women, and women in the child bearing age not willing to follow adequate contraceptive methods during study period, were excluded from the study. Withdrawal criteria included voluntary withdrawal by patient, inability to complete study and discretion of physician for discontinuation of study medication for better BP control or safety concerns. Written informed written consent was obtained from patients prior to enrolment in the study. A unique allotment number was given to all the enrolled patients to maintain his/her confidentiality. The unique identification number was not reassigned to any other patient, even if the patient withdrew consent or was dropped from the study.

Demographic data of patients was recorded. Associated comorbid illness and concomitant medications were noted. No examination or investigations beyond that normally required in routine clinical practice were done for the purpose of study. Baseline clinic BP recorded in sitting position (right arm) were entered in case report form (CRF). Details of treatment with azilsartan were also recorded in CRF. These patients were observed for a period of 12 weeks of initiating azilsartan therapy. BP readings, any change in the treatment, concomitant medications and occurrence of adverse events (AEs) as assessed by the investigator or spontaneously reported by patients were noted during the follow-up visits (6 and 12 weeks). Each AE was categorized as non-serious or serious, related to study medication or not and whether it resulted in discontinuation of study medication. If there was suboptimal response with azilsartan, investigator was liberated to add other antihypertensive agents as per clinical judgement. If BP still remained elevated, despite adherence to the treatment algorithm for study medication and additional antihypertensive agents, the investigator considered discontinuation of the patient at any time from study for offering other treatment options than study medication to these patients.

STATISTICS

Data was entered in a Microsoft excel sheet and was analysed using SPSS version 21 software. Descriptive data was noted as mean ± standard deviation (SD), frequencies and percentages. The BP in the patients at multiple intervals was compared using repeated measures ANOVA, followed by pairwise comparisons for significant results. The level of significance in the study was 0.05.

RESULTS

Total 240 patients of essential HTN were enrolled in the study. Mean age of patients was 62±11.9 years and body mass index (BMI) was 27.8±5.2 kg/m^2. Out of 240 enrolled patients, 218 (90.8%) patients were diagnosed with uncontrolled HTN and 22 (9.2%) patient were newly diagnosed hypertensives. Amongst various co-morbidities, most of the patients had type 2 diabetes mellitus (T2DM) (55%) and ischemic heart disease (13.8%). Overall, at the end of study, 57 patients were on azilsartan 40 mg once daily treatment; while 183 patients were on azilsartan 80 mg once daily, including those patients in whom azilsartan dose was up-titrated from 40 mg to 80 mg. The number of patients treated with azilsartan 40 mg once daily were 78 (32.5%), 61 (25.4%) and 57 (23.8%) at baseline, Week 6 and Week 12 respectively; while those treated with azilsartan 80 mg once daily were 162 (67.5%), 179 (74.6%) and 183 (76.2%) at baseline, Week 6 and Week 12 respectively. Demographics and baseline characteristics of patients are depicted in table 1.

Table 1 Demographics and baseline characteristics of patients (n = 240)

Variables	Values
Age (years)	62±11.9
Gender Males Females	 139 (57.9%) 101 (42.1%)
Weight (kg)	69.8±13.6
BMI (kg/m^2)	27.8±5.2
Newly Diagnosed Uncontrolled Hypertension	22 (9.2%) 218 (90.8%)
Presence of co-morbidities[a] Type 2 DM Renal Diseases Post MI Stroke/TIA Dyslipidemia Hepatic Diseases IHD Congestive cardiac failure Others[b]	 132 (55%) 9 (3.8%) 1 (0.4%) 10 (4.2%) 8 (3.3%) 5 (2.1%) 33 (13.8%) 2 (0.8%) 52 (21.7%)

[a] *values mutually exclusive of each other*
[b] *other co-morbidities included bronchial asthma, hypothyroidism, cirrhosis of liver, benign prostatic hypertrophy, supraventricular tachycardia, epilepsy, gout and osteoarthritis.*
Abbreviations: BMI – body mass index, DM – diabetes mellitus, MI - myocardial infarction, TIA – transient ischemic attack, IHD - ischemic heart disease

Effectiveness

There was statistically significant reduction in both systolic and diastolic BP from baseline at Week 6 and Week 12 ($p<0.001$) after treatment with azilsartan. The changes in BP of patients at Week 6 and Week 12 are depicted in table 2.

Table 2: Changes in blood pressure of patients at 6 and 12 weeks of azilsartan treatment.

Blood Pressure (BP)	Baseline	6 weeks	12 weeks
Systolic BP (mm Hg)	162.6±18.2	146.4±14.7***	135.44±13.3***$^{###}$
Diastolic BP (mm Hg)	92.3±8.7	84.7±5.9***	82.1±5.2***

*Repeated measures ANOVA, ***$p<0.001$ vs baseline, $^{###}p<0.001$ vs 6 weeks*

The mean reduction systolic BP from baseline with azilsartan was 16.2±11.1 mm Hg and 27.16±10.6 mm Hg ($p<0.001$) at Week 6 and Week 12 respectively. Similarly, the mean reduction in diastolic BP from baseline was 7.6±7.3 mm Hg and 10.2±7 mm Hg ($p<0.001$) at Week 6 and Week 12 respectively (Figure 1).

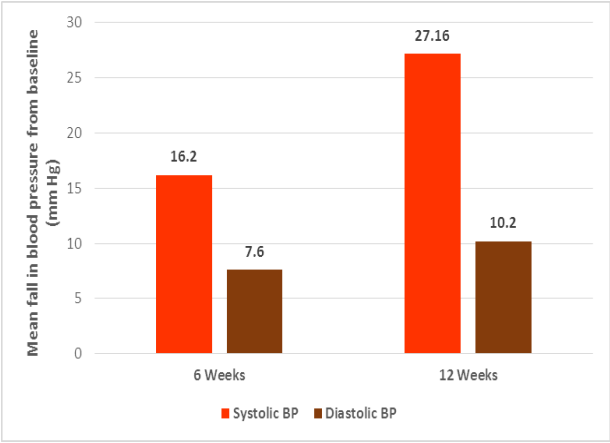

Figure 1: Mean reduction in blood pressure from baseline at Week 6 and Week 12 after treatment with azilsartan.

Responder Rates

The proportion of patients achieving target systolic BP of ≤140 mm Hg after treatment with azilsartan was 27.10% at Week 6 and 56.70% at Week 12. The mean reduction in systolic BP by ≥20 mm Hg was observed in 133 (55.40%) and 207 (86.30%) patients at Week 6 and Week 12 respectively. Overall, the total responder rates (defined as a patient whose systolic BP reached a target of ≤140 mm Hg and / or was reduced by ≤20 mm Hg from baseline) at Week 6 and Week 12 were 67.5% and 95.80% respectively (Figure 2). The proportion of patients achieving aggressive target BP of <130/80 mm Hg with azilsartan was 40.42% at Week 12.

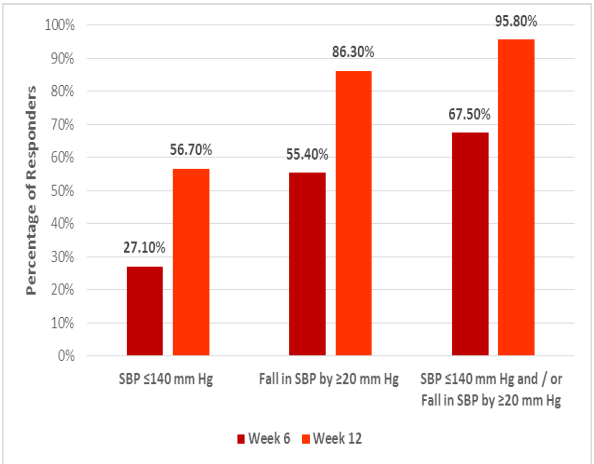

Figure 2: Responder rates after 6 and 12 weeks of treatment with azilsartan.

Changes in blood pressure in patients switched over to azilsartan from telmisartan

Out of 240 patients, 48 patients were on telmisartan at baseline; 40 patients were on telmisartan monotherapy and 8 patients were receiving dual or triple drug therapy

with amlodipine, metoprolol or prazosin. The baseline systolic and diastolic BP in these patients was 158.4±20 mm Hg and 90.1±7.8 mm Hg, respectively. These patients were shifted from telmisartan to azilsartan while continuing the previous antihypertensive agents if on combination therapy. In these patients shifted from telmisartan to azilsartan, there was statistically significant reduction in mean systolic BP from baseline at Week 6 and Week 12 (13.2±11.7 mm Hg and 26±14.4 mm Hg respectively, p<0.001). Also, there was statistically significant reduction in mean diastolic blood pressure at Week 6 and Week 12 (6±6 mm Hg and 9.7±7.1 mm Hg respectively, p<0.001).

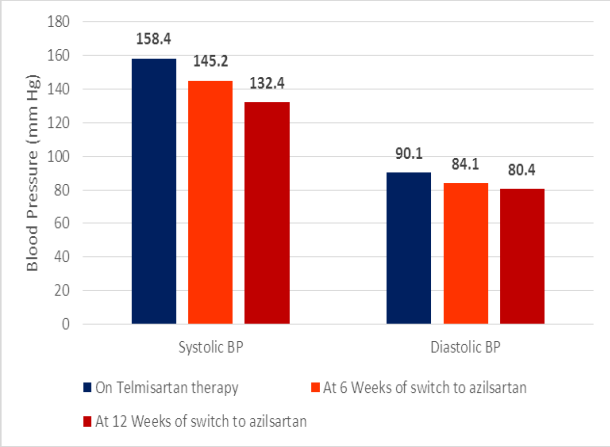

Figure 3: Changes in blood pressure after switching to azilsartan from telmisartan.

In patients uncontrolled on telmisartan and shifted to azilsartan, the proportion of patients with a target systolic BP of ≤140 mm Hg at Week 12 was 75% and those with a fall of ≥20 mm Hg was 75%. Overall, at Week 12, total responders in patients uncontrolled on telmisartan and shifted to azilsartan was 93.80%.

Concomitant antihypertensive drugs

Concomitant anti-hypertensive drugs were given in 168 (70%) patients along with azilsartan, while concomitant medications for other disorders were given in 177 (73.8%) patients. Azilsartan monotherapy was given to 72 (30%) patients, while 137 (57.1%) and 31 (12.9%) patients were initiated treatment with one and two antihypertensive drugs along with azilsartan respectively. Most common antihypertensive drugs given along with azilsartan were metoprolol (27.5%), amlodipine (23.3%) and prazosin (16.7%).

Safety

Adverse events were observed in 3 patients during the study period, 1 patient each with mild, moderate and severe AE. One patient had an ongoing serious AE (postural hypotension), which was not related to azilsartan. This patient was suffering from cirrhosis of liver and developed orthostatic hypotension as a result of autonomic dysfunction leading to hospitalization. One patient had taste intolerance (mild severity) and one patient had giddiness (moderate severity); both AEs were related to azilsartan.

DISCUSSION

The results of this real-world study indicate that azilsartan is an efficacious and well tolerated ARB in real world clinical practice. There was intensive drop in BP with azilsartan by 16.2±11.1/7.6±7.3 mm Hg at Week 6 and by 27.16±10.6/10.2±7 mm Hg at Week 12. This aggressive drop in BP was seen in newly diagnosed treatment-naive patients and patients uncontrolled on current antihypertensive drugs. Proportion of patients achieving target BP was also high (67.5% at Week 6 and 95.80% at Week 12). Another interesting finding of this study was 40.42% patients who were uncontrolled on telmisartan were able to achieve the target BP when shifted to azilsartan either as monotherapy or in combination with other antihypertensive agents. Aggressive drop in BP was achieved with azilsartan in all subsets of patients including those with dyslipidaemia, T2DM, ischemic heart disease, stroke, hepatic and renal diseases. Moreover, this high anti-hypertensive efficacy was not associated with worse adverse effect profile.

Aggressive drop in BP and high responder rates with azilsartan can be explained to a greater extent by its physico-chemical properties. Azilsartan has been developed by molecular modification in the structure of another ARB candesartan. A 5 member tetrazole ring of candesartan has been replaced with the 5 member oxo-oxadiazole ring in azilsartan. This modified chemical configuration has been reported to enhance the lipophilicity of azilsartan and potentially improve its oral bioavailability.[23] Azilsartan is the only ARB to have this unique oxo-oxadiazole ring in its structure. Moreover, it has very unusual capacity to persistently block AT1 receptor for prolonged period of time due to its slow dissociation from AT1 receptor.[23] Under experimental condition described by Ojima et al, azilsartan was found to be twice as potent as olmesartan or telmisartan, both of which are viewed as the most potent of all clinically approved ARBs for blocking AT1 receptors.[24] Also, azilsartan was found to be 5 to 20 times more potent than irbesartan & valsartan.[23] In a study by Ojima et al., 50% inhibitory concentration (IC50) of azilsartan was 2.6 nM, which is much lower than olmesartan, telmisartan, valsartan, and irbesartan (IC50 6.7, 5.1, 44.9, and 15.8 nM, respectively).[24] The greater potency of azilsartan for AT1 receptor blockade could help to explain aggressive drop in BP and more effective lowering of BP than maximum approved doses of other ARBs.

Another putative theory for aggressive drop in BP with azilsartan is related to its ability to augment Mas axis. The RAAS system is considered to be far more complex than what it was thought to be previously. In addition to the ACE/Ang II/AT1 receptor axis (classical), the RAAS possesses a counter-regulatory axis composed of ACE2,

angiotensin-(1-7) [Ang-(1-7)] and the Mas receptor. It has been reported that the effects of Ang-(1-7) are mediated via Mas receptor and exerts beneficial effects like vasodilation, inhibition of cell growth, anti-thrombosis and anti-arrhythmogenic effects.[25] An experimental study by Carroll et al has shown that plasma Ang-(1–7) levels were increased with azilsartan treatment.[26] Thus, amplification of ACE2 /Ang (1–7) / Mas signalling as exhibited by azilsartan, not only opposes the effects of the classical RAAS, but also additionally lowers BP and prevents or reverses related target organ damage. Moreover, increase in Ang-(1–7) level during AT1 receptor blockade and Mas receptor activation by azilsartan could result the induction of cardio-protective and reno-protective effects. In a study by Carroll et al, it was observed that the treatment with azilsartan prevented cardiac hypertrophy and attenuated renal damage.[26]

Several randomized controlled clinical trials have well established the efficacy and safety of azilsartan in the treatment of HTN. The overall responder rate seen in these trials varied from 44% to 60% with mean reduction in systolic BP as high as 24.2 mmHg at Week 8.[18-20] The clinical trials are conducted in controlled conditions, wherein the patients included are strictly bound by the eligibility criteria. However, in real-world settings, the patients may not be similar to that in the clinical trials; associated comorbidities, concomitant medications and lifestyle modifications suggested in routine clinical practice may affect its use or safety. Hence, it is important to note the effectiveness of azilsartan in real-world settings. The observation that effectiveness of azilsartan in reducing BP and achieving target BP goals in this real-world study was higher than previous clinical trial findings may be attributed to the fact that 90.8% patients were uncontrolled on existing antihypertensive agents and were either shifted to azilsartan or azilsartan was added to existing therapy. Around 30% patients were receiving azilsartan monotherapy, while 70% patients were treated with dual or triple drug therapy including azilsartan. However, these patients who were uncontrolled on existing anti-hypertensive agents and azilsartan was started as an add-on anti-hypertensive were benefited by the addition of azilsartan. The aggressive drop in BP with high responder rates in these patients can be ascribed to azilsartan as the overall reduction in BP is reflected from BP values at the time of continuation of other antihypertensive agents and addition of azilsartan to therapy.

In the EARLY registry, azilsartan monotherapy was given for 12 months, and such patients were grouped according to eligibility with the RCT criteria of the Bonner et al trial. The raw (unadjusted) fall in systolic BP in RCT eligible and non-eligible patients was 29.9 and 22.7 mm Hg, and in diastolic BP was 14.7 mm Hg and 11.6 mm Hg, respectively. This post-marketing study on azilsartan demonstrated more reduction in the BP than the clinical trials.[27]

Another finding of this study suggests that 70% patients who were on combination therapy of azilsartan with other antihypertensive agents like metoprolol, amlodipine, prazocin, etc. responded well to azilsartan therapy without major safety concerns. Thus, this observation further establishes azilsartan as an effective drug which can be safely used in combination with anti-hypertensive drugs from other classes.

In our study, substantial proportion of patients suffered from co-morbidities with T2DM being most common in 55% patients. Patients with co-morbidities tend to be on multiple medications, which increase the risk of the drug interactions, further increasing the potential of treatment failure or occurrence of adverse effects. In the present study, despite co-morbidities and concomitant medications, azilsartan was effective in achieving a high responder rate with a good safety profile. In the EARLY registry, azilsartan receiving patients had various comorbidities with most common being diabetes mellitus in 19.4%.[27] Compared to the EARLY registry, the higher proportion of T2DM patients in the present study alerts about the complex patient conditions, one may face in clinical practice. In a pooled analysis of 3821 hypertensive diabetic patients by White et al, azilsartan was found efficacious and safe to be used in patients with T2DM and pre-diabetes patients.[28] Thus, in this high-risk patient group, the observations of the present and previous studies suggest vital clinical implications. The significance of BP control in this subset of patients is documented as a means to reduce CV morbidity and mortality.[29] Hence, having the option of a well-tolerated ARB that provides an aggressive BP reduction is an important therapeutic advance for the treatment of patients of HTN with T2DM.

In a study by Okamura K et al, there was statistically significant reduction in systolic and diastolic BP in patients uncontrolled on telmisartan and shifted to azilsartan ($p<0.001$).[30] The results of our study also showed similar benefits of shifting the patients to azilsartan if patients are not controlled on telmisartan therapy. At Week 12, 75% patients uncontrolled on telmisartan therapy (baseline systolic BP of 158.4±20 mm Hg with telmisartan) were able to achieve the target systolic BP of ≤140 mm Hg.

We also observed that as against the usual target systolic BP goal of ≤140 mm Hg, in our study, the proportion of patients achieving aggressive target BP of less than 130/80 mm Hg with azilsartan was 40.42%. Recently, The American College of Cardiology (ACC) and the American Heart Association (AHA) have released a new guideline on hypertension in 2017. As against old 2003 JNC 7 guidelines, this new 2017 hypertension guidelines recommend a lower target goal BP of less than 130/80 mm Hg regardless of atherosclerotic cardiovascular disease (ASCVD) risk.[31] The level of evidence supporting this aggressive lowering of BP is stronger for patients with known CVD or an estimated 10-year

ASCVD risk of at least 10% than for patients without increased ASCVD risk. A recent systematic review and network meta-analysis showed there is progressive reduction in CVD risk (major cardiovascular events, stroke, coronary heart disease and all-cause mortality) with reducing the systolic BP to levels below currently recommended targets.[32] The findings of this systematic review and network meta-analysis support more intensive control of SBP among adults with HTN.

The Systolic Blood Pressure Intervention Trial (SPRINT) study also demonstrated targeting a systolic BP of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause in patients at high risk of CV events.[11] Based on the SPRINT data and the available literature on intensive BP lowering, we believe that intensive lowering of systolic BP should be considered for implementation in general clinical practice.

The publication of SPRINT study challenged the conventional approach to hypertension care. To achieve this intensive BP target, multiple antihypertensive drugs are needed as shown in SPRINT study. However, due to polypharmacy if compliance of the patient with antihypertensive therapy is poor, CV events are increased. Accordingly, it is considered reasonable to switch to a more potent antihypertensive agent with increased efficacy and fewer adverse effects like azilsartan as a strategy for improving the response to antihypertensive agents.

In the present study, AEs were noted in 1.25% patients, with azilsartan as the causal agent in 0.83% patients. The adverse effects were taste intolerance and giddiness. Compared to clinical trials of azilsartan, the incidence of AEs observed in the present study were much lower. This might be attributed to the fact that the AEs are actively pursued by the investigators in the trials, while in clinical practice they are noted whenever reported by patients; thus passive surveillance playing a key role in underreporting of AEs. Similar lower incidence of AEs was also observed in the EARLY registry.[27]

Limitations of Study

The present study had certain limitations. Firstly, the period of observation (12 weeks) was lesser than many of the clinical trials. Secondly, owing to the inherent characteristics of an observational study, treatment allocation was not randomised to two different doses of azilsartan and two diagnostic arms (newly diagnosed and uncontrolled HTN). Furthermore, because of frequent changes in the doses of azilsartan at infrequent intervals during the study period for achieving the target BP inherent to observational nature of study, we were not able to analyse separately the antihypertensive efficacy with different doses of azilsartan. Lastly, the BP was noted in the clinic and was not similar to 24 hour ambulatory BP which is much better predictor of antihypertensive efficacy as seen in previous trials.

CONCLUSION

The results of present real-world study suggest that azilsartan is effective and safe in the treatment of newly diagnosed treatment-naïve hypertensive patients as well as those uncontrolled on other antihypertensive agents including telmisartan. Azilsartan was effective in achieving a high responder rate with a good safety profile in all subsets of patients including those with co-morbidities and on other anti-hypertensives or concomitant medications. Thus, as a strategy for improving the response to current antihypertensive agents and for intensive lowering of BP to match-up with new lower BP target, azilsartan is a promising treatment option.

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