Evaluation Of Blood Pressure Reduction And Improved Lv Diastolic Function Among Hypertensive Patients With Diabetes Mellitus Type 2: Azilsartan Versus Losartan, Telmisartan And Olmesartan.

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Abstract

Background: Azilsartan is a new angiotensin receptor blocker with more continuous antihypertensive effects in diabetes mellitus type 2 patients. This study aimed to demonstrate the efficacy and safety of Azilsartan over other ARBs in diabetes mellitus type 2 patients with uncontrolled hypertension and with an evaluation of left ventricular diastolic function.

Methods: A cohort study was done to estimate the number of patients (N=411) with hypertension (SBP mean 161+/-9 mm Hg) along with diabetes mellitus type 2 and LV diastolic dysfunction who would achieve Systolic Blood Pressure (SBP) goal when treated with Azilsartan medoxomil (40 mg) versus other ARBs like Losartan (50 mg), Telmisartan (40 mg), or Olmesartan medoxomil(20mg) for 3 months.

Results: 2D Echocardiography results showed Azilsartan had better improvement in left ventricular diastolic function as compared to other ARBs and no comparative data was found regarding left ventricular wall thickness, however, LV wall thickness was slightly reduced by 0.3+/-0.12 mm.

Conclusion: Data suggest that more diabetic patients with hypertension treated with Azilsartan medoxomil than with Losartan, Telmisartan, or Olmesartan medoxomil are expected to reach the SBP goal. Further study at a large scale should address whether these differences in potency and efficacy.

Introduction

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) have been recognized as an effective approach to managing hypertension and these are recommended as first-line treatment by various guidelines. ACEI/ARB agents are particularly recommended for patients with comorbidities such as diabetes, heart failure, or renal insufficiency. Azilsartan is a new angiotensin receptor blocker with more continuous antihypertensive effects in diabetes mellitus type 2 patients. This study aimed to demonstrate the efficacy and safety of azilsartan over other ARBs in diabetes mellitus type 2 patients with uncontrolled hypertension and with an evaluation of left ventricular diastolic function.

Azilsartan medoxomil is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with an estimated bioavailability of 60% and an elimination half-life of 12 hours. The other major metabolite, M-II, is formed via CYP2C9 and has a low affinity for the angiotensin II type 1 receptor. Based on dose-ranging studies and supporting pharmacokinetic data, the expected plateau of BP reduction for azilsartan medoxomil in the large majority of patients with hypertension is 40 or 80 mg once daily.

Methods:

A cohort study was done to estimate the number of patients (N=411) with hypertension (SBP mean 161+/-9 mm Hg) along with diabetes mellitus type 2 and LV diastolic dysfunction who would achieve Systolic Blood Pressure (SBP) goal when treated with azilsartan medoxomil (40 mg) versus other ARBs like losartan (50 mg), telmisartan (40 mg), or olmesartan medoxomil(20mg) for 3 months.

Inclusion Criteria
- Age between 18 to 70 years of age
- Diabetes mellitus type 2
- Hypertension
- Homogenous group of medications
- Heart rate less than 100 beats/min, regular
- Normal LV Systolic function

Exclusion Criteria
- Structural heart disease
- Thyroid disorders
- Atrial fibrillation
- Pulmonary disease
- Renal disease or renal dysfunction
- Myocardial infarction, Significant Coronary Artery Disease
- Connective tissue disorders or systemic inflammatory diseases

Data Analysis
- Sample collection
- Used Amron instrument for BP measurement
- Used Standard Lab for Blood sugar and HBA1C level
- Used Vivid S6 machine for echocardiography data
- Used SPSS software for data analysis and statistics
- Others

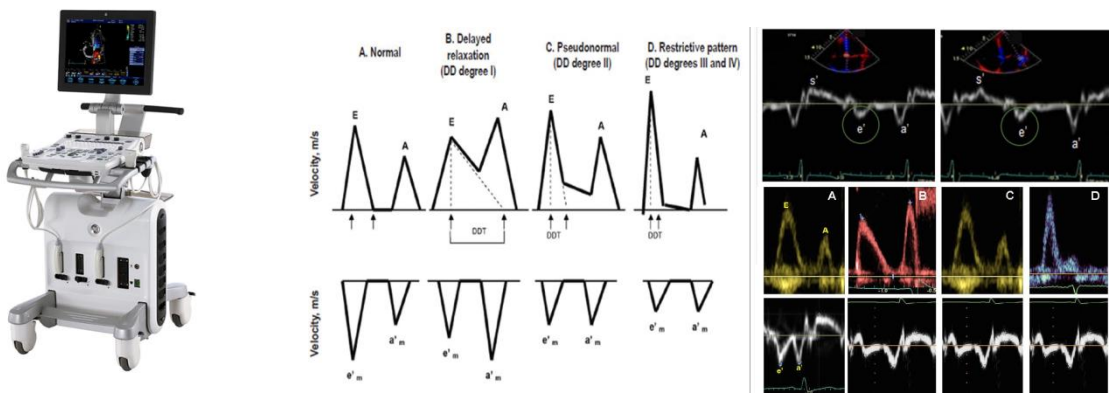

Figure 1 (2D Echocardiogram assessment)

2D Echocardiography performed at the time of study revealed LV wall thickness was 12.4+/-2.6 mm, E/A ratio 0.5+/-0.23, deceleration time (DT) 223+/- 12 msec, E/e' 9+/-4, Isovolumic relaxation time (IVRT) 113+/-4.5 msec and left atrial volume (LA) 34+/- 6 ml/m2 and LV Ejection fraction (LVEF) was 61+/- 9 %. We assessed goal attainment assuming that adherence was alternatively perfect and 2d Echocardiography performed for LV function.

Results

The study revealed mean±SD age 46±11 years, 61% male and 39% female, baseline SBP 169±9 mm Hg. 18 % of patients discontinued medications, and rest 82 % of patients (n=338) who continued their medications were found that 29.5% with azilsartan, 20.1% with losartan, 22.1% with telmisartan and 28.1% with olmesartan. Target SBP achieved azilsartan vs other ARBs after 3 months (35% for

Azilsartan, 23.5% for losartan, 26.6% for telmisartan, and 28.4% for olmesartan medoxomil, assuming perfect adherence; accounting for nonadherence, 23.2%, 12.9%, 14.7% and 16.6% of patients would reach SBP goals, respectively. 2D Echocardiography results showed azilsartan had better improvement in left ventricular diastolic function compared to other ARBs and no comparative data was found regarding left ventricular wall thickness, however, LV wall thickness was slightly reduced by 0.3+/-0.12 mm.

Variables	**Azilsartan Baseline**		**Azilsartan After treatment**		***P value***
Vitals					
Systolic blood pressure, mmHg	160	±15	140	±15	<0.02*
Diastolic blood pressure, mmHg	94	±9	83	±9	<0.02*
Heart rate, bpm	77	±18	9	±6	0.05*
Echocardiography					
IVS, mm	**11.8**	**±.9**	**9.9**	**±.7**	**0.82**
PW, mm	**10.5**	**±.6**	**9.6**	**±.4**	**0.83**
LVDd, mm	51	±10	49	±9	0.21
LVDs, mm	35	±10	32	±9	0.23
LVEF, %	61	±15	62	±14	0.62
LAd, mm	39	±6	39	±6	0.80
LAVi, mL/m^2	**39**	**±18**	**28**	**±14**	**0.19**
IVRT msc	**89**	**±23**	**75**	**±35**	**0.43**
TMF E, cm/s	71	±23	75	±35	0.59
TMF A, cm/s	86	±22	84	±22	0.56
TMF E/A	0.77	±0.3	0.82	±0.3	0.84
TMF DcT, ms	**238**	**±53**	**219**	**±47**	**0.65**
LV septal E/e′	**15.2**	**±6.2**	**13.4**	**±4.7**	**0.04***
LV lateral E/e′	**12.9**	**±4.1**	**10.3**	**±2.6**	**0.03***
Average LV E/e′	**14.0**	**±4.2**	**12.8**	**±3.7**	**0.04***

Table 1 (2D Echocardiogram assessment)

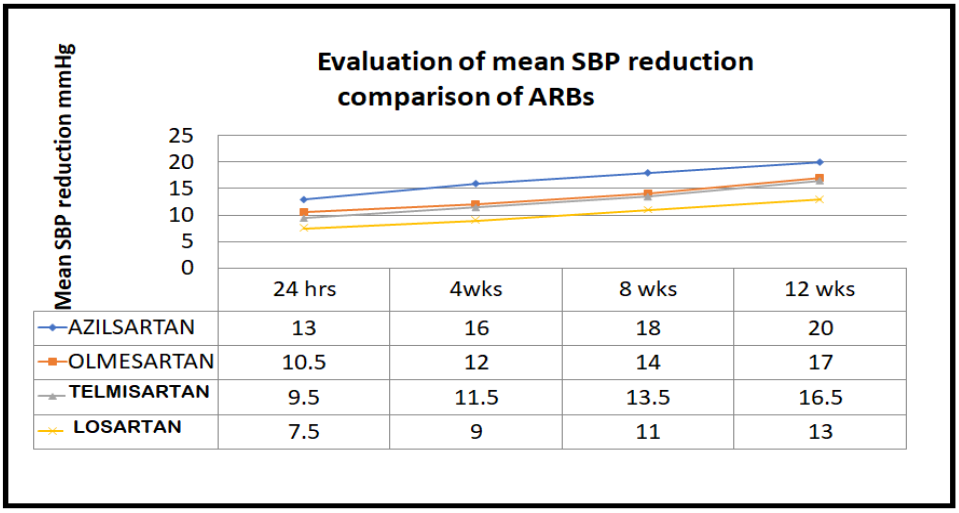

Figure 2 (SBP Reduction)

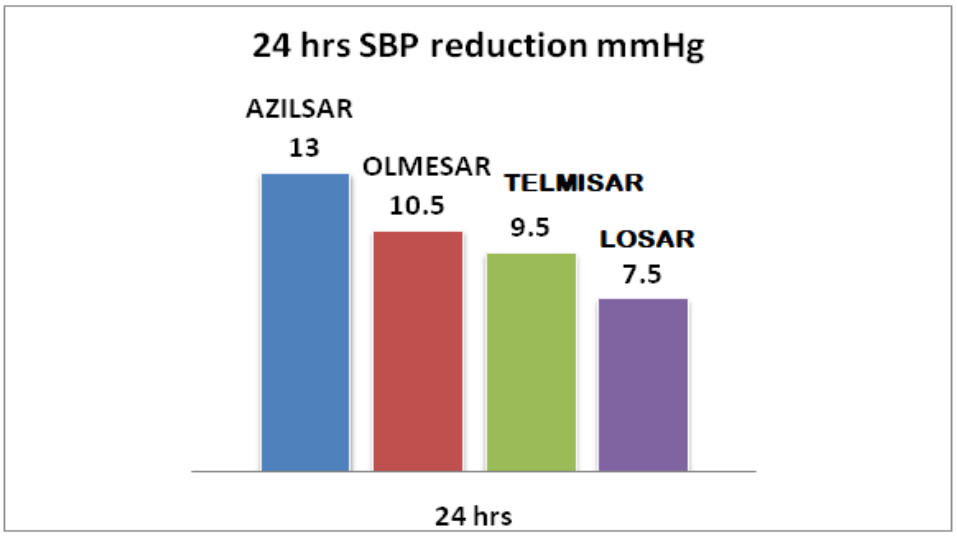

Figure 3 (SBP Reduction)

Variables	Azilsartan	Olmesartan	Telmisartan	Losartan
LVW Thickness mm	0.9+/-0.2	0.3+/-0.1	0.3+/-0.1	0.1+/-0.1
DT msec	19+/-6	11+/-4	10+/-3	6+/-4
E/e'	1.8+/-0.5	1.0+/-0.2	0.9+/-0.2	0.4+/-0.3
LAV ml/m2	11+/-4	6+/-2	5+/-2	3+/-2

Table 2 (2D Echocardiogram assessment)

Discussion

We hypothesized that azilsartan improves cardiac diastolic function in patients with hypertension. We proved this hypothesis, but the mechanisms underlying this effect need to be considered. First, a decrease in blood pressure may improve cardiac diastolic function. However, this was not the circumstance because losartan, which did not improve cardiac diastolic function, decreased the blood pressure to levels comparable to those in the azilsartan group. Second, a decrease in the heart rate may improve cardiac diastolic function. Azilsartan but not losartan indeed significantly decreased the heart rate.

This possible mechanism cannot be denied because decreases in the heart rate may affect LV diastolic properties by increasing the LV relaxation rate. Third, pharmacological travels specific to azilsartan may affect the myocardium such as reversing remodeling; changes in the LV end-diastolic volume and end-systolic volume alter the LV relaxation rate. Fourth, the only difference between azilsartan and losartan is the strength of their affinity to angiotensin II receptors and their affinity to the arterial vasculature. Affinity: Azilasartan > Olmesartan > Telmisartan > Losartan: Compared to losartan, azilsartan has a higher affinity for angiotensin II receptors and a higher affinity for vasculature because of the difference of one residue in the molecular structure. The effects on the arterial vasculature may affect the LV relaxation rate; this effect increases the capacitance of the aorta and delays the onset of ejection, & thus increasing the LV relaxation rate. In the present study, we did not measure aortic capacitance, but differences in the aortic diastolic pressure may reflect changes in the aortic capacitance.

The present study has several limitations. First, it was an open-label trial with a small sample size. However, to decrease this limitation, we used the objective end-point of the LV E/e′ ratio.
Second, the severity of HF pathophysiology may differ between retrospective and prospective studies. Therefore, we enrolled all HF patients with hypertension who received azilsartan in our department, which resulted in the absence of selection bias. Third, because azilsartan can also be used to treat hypertension, an improvement in LV E/e′ may be attributable to a decrease in high blood pressure. However, this does not seem to be the circumstance because lowering the blood pressure using losartan did not improve cardiac diastolic function. This suggests that the decrease in the LV E/e′ ratio is attributable to azilsartan-specific pharmacological actions, & not the secondary effects of decreased blood pressure.

Conclusion

Data suggest that more diabetic patients with hypertension treated with azilsartan medoxomil than with losartan, telmisartan, or olmesartan medoxomil are expected to reach the SBP goal. Further study at a large scale should address whether these differences in potency and efficacy.

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