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To Compare the Pleiotropic Effects of Telmisartan and Olmesartan in Hypertensive Patients with Metabolic Syndrome Based On ATP III Criteria

Dr. P. R. Anand Vijaya kumar[1] , Priya K[2], Piyush Srivastava[3] Dinsy Paul[4]
1. Professor, Department Of Pharmacy Practice, JSS College Of Pharmacy, Ooty, 2, 3, 4. PharmD JSS College of pharmacy, Ooty

***Abstract**: Metabolic syndrome (MetS) and cardiovascular disease is rapidly evolving.To treat hypertension, drug-classes with different glucometabolic effects are used but they have the potential for adverse metabolic effects. An open-label prospective crossover study was conducted to compare the PPAR- γ(peroxisome proliferative activated receptor γ) modulating activity of olmesartan (10 mg/day) and telmisartan (20 mg/day) on stage 1 hypertension, metabolic parameters and cardiovascular risk using Framingham risk score based on lipid profile. Twenty patients were recruited for two months according to ATP III (adult treatment plan), specific criteria used for the diagnosis of MetS. Analyzed the blood pressure lowering effects of each drug on an interval of 2 weeks. Simultaneously measured metabolic parameters on first visit & on last follow up. Telmisartan and olmesartan showed the pleiotropic effect by lowering metabolic parameters. Telmisartan shows more significant reduction in metabolic parameters and a significant increase in HDL (high density lipoprotein) values. Both the drugs show an increase in cardiovascular risk percentage. Our results recommend a future research in the use of telmisartan and olmesartan in cardiovascular risk patients with MetS.*

***Key Words*:** Adult treatment plan III, Metabolic syndrome, Peroxisome proliferative activated receptor gamma, Stage 1 hypertension, cardiovascular risk

I. Introduction

India is a major contributor to the global cardiovascular mortality and there is increasing trends in prevalence of various components of the Metabolic Syndrome (MetS) [1, 2]. MetS is a cluster of the most dangerous heart attack risk factors: diabetes or prediabetes, abdominal obesity, unfavorable changes in the lipid profile (low HDL-C, increased triglycerides and small-dense LDL) and high blood pressure [3]. Studies reported a high prevalence of the MetS in urban Asian Indians in the age group ≥40 years [4, 5] and are common in adult Asian Indians; 41% of subjects aged ≥20 years had features of the syndrome [6].

Recent evidence indicates that ARB Telmisartan structurally resembles the insulin sensitizer Pioglitazone, a thiazolidinedione ligand of PPAR- γ used for treatment of DM II [7, 8]. Telmisartan has been shown to improve endothelial dysfunction, insulin resistance & increasing serum adinopectin levels in several populations [9, 10, 11, 12]. Activation of PPAR -γ causes the receptor complex to affect the expression of key target genes that mediate beneficial effects on glucose and lipid metabolism [2]. Moreover PPAR -γ is an established therapeutic target in the treatment of insulin resistance, diabetes and metabolic syndrome [13, 14]. Olmesartan seems to have more potent blood pressure lowering than Telmisartan, but not similar effects on metabolic parameters [15]. Despite the availability of various types of ARBs, there are no comparative studies of their effects on cardiovascular risk patients with metabolic syndrome.

Cardiovascular disease represents a pathological continuum that begins with a predisposing, progressive pathological process such as Hypertension, Hyperlipidemia and Diabetes. Untreated, this process perpetuate the progression of end organ disease and present as new onset myocardial infarction, heart failure, end stage renal disease, stroke and/or death [3]. Patients with Impaired Glucose Tolerance (IGT) face a high risk to develop diabetes mellitus and accelerate atherosclerosis.

In hypertensive patients, prevalence of type II diabetes is higher than in general population. Thus to reduce cardiovascular events in patients with hypertension, treatment of diabetes in addition to blood pressure is important [4, 5] which emphasizes the importance of strict glycaemic control in patients with hypertension. The plausible mechanisms (**Pleiotropic effects**) are that angiotensin II promotes superoxide anion generation, endothelial dysfunction, blood pressure, fasting blood glucose & lipid profile. Current evidence focussing on Telmisartan suggest that pleiotropic effects manifest as improvement in endothelial dysfunction, reduction in LVH, Reno protection in normotensive & hypertensive subjects, improvement in metabolic parameter & potential benefits in Cerebrovascular disease [16].

NCEP/ATPIII (National Cholesterol Education Program/Adult Treatment Plan III) (2001) and the World Health Organization (1999) have established specific criteria for the clinical diagnosis of the MetS (Table 1). This syndrome complex is associated with a two to three-fold increased risk of cardiovascular mortality and a five- to nine-fold increased risk for developing type 2 diabetes [1] . Subjects having 3 or more of the 5 NCEP ATP III criteria were considered to have the MetS [17]. A few recent studies from USA have used the ATPIII criteria for identification of MetS [18, 19, 20]. Prevalence of MetS was higher in urban Indians (41.1%) in comparison with the population of USA, Aged>20years (22%) using similar criteria [8].

Table: .Modified ATP III criteria in urban Asian Indian adults but with a modified waist circumference (WC) appropriate for Indians

CLINICAL FEATURES	ATP III Criteria (2001), ≥3 of the criteria below
Impaired glucose Tolerance (Insulin Resistance)	Fasting Plasma Glucose ≥ 110 mg/ dl
Abdominal Obesity	Waist Circumference, Men ≥ 90 cm, Women ≥ 85 cm
Hypertriglyceridemia	≥ 150 mg/dl
Low HDL- C	< 40 mg/ dl in men, < 50 mg/ dl in women
High Blood Pressure	≥ 130/ 85 mmHg

Cardiovascular disease is the principle cause of morbidity and mortality. Evaluation of cardiovascular risk is the most appropriate way to discriminate between individuals who have risk factors requiring intensive control and those who at low risk. The cohort study based on the US city of Framingham began in 1948 and led to the publication of the most widely used risk equation: the Framingham 10-year risk score (FS10). The third report of the National Cholesterol Education Program (NCEP) Panel of Experts on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) incorporated FS10 as a basic tool for stratifying cardiovascular risk, on the basis of which objectives or therapeutic goals are determined. However, FS10 presents certain fundamental weaknesses, as it underestimates cardiovascular risk in populations such as the young or women. As most cardiovascular events occur in low- or moderate-risk populations, access to more efficient predictive tools is necessary. One option is to extend the period for predicting vascular events, thus giving physicians and patients a different perspective on the problem. A recently published score (FS30), which is based on descendants of the original Framingham cohort, extends the time-scale from 10 to 30 years [21] was used for the study.

In recent years, age-adjusted CVD death has been cut in half in developed countries. Much of the decline is due to reductions in risk factors that the Framingham Heart Study helped to identify. The absolute risk of CVD is strongly influenced by the combination of risk factors present, particularly a history of CVD, age, sex, diabetes, smoking, BP, and blood lipid concentrations. By the 1990s, major improvements were made with the addition of high-density lipoprotein (HDL) cholesterol; and the extended duration allowed for risk assessment in an older population up to the age of 74 years [22].

To gain insight into the respective properties of ARB for metabolic syndrome patients with hypertension, a prospective study was conducted to compare the efficacy of the starting doses of Telmisartan & Olmesartan on blood pressure and metabolic parameters. The need of the study is to check the metabolic parameters with the study drugs in Indian population and to check the safety in case of patients with cardiovascular risk along with Metabolic Syndrome.

1.1 Study Objective

Purpose of the study is to compare the pleiotropic effects of Telmisartan and Olmesartan in hypertensive patients with metabolic syndrome based on ATP III criteria. The objectives of the study includes

- To estimate the extent of Blood Pressure variability in Stage -1 Hypertensive patients on administration of Telmisartan and Olmesartan.
- To evaluate the effect of study drugs on Lipid Profile & Fasting Blood Sugar (FBS) among hypertensive patients.
- To assess the 30-year risk score for cardiovascular disease with Framingham risk score based on Lipid Profile.

1.2 Study Design

A prospective open label study was conducted in outpatient department of Govt. Head Quarters Hospital, a 420 bedded secondary care hospital, Ooty. Subjects were administered with the study drugs Tablet Telmisartan 20 mg and Tablet Olmesartan 10 mg once daily in morning after breakfast. A total of 40 patients were enrolled, 20 subjects in each group for study period of two months. Out of which 24 completed the study. Almost 16 dropped out of the study due to various reasons like inappropriate follow up and non-adherence. There were 12 patients in each study group who completed the study follow-ups, were analyzed for the effect like control of blood pressure, Fasting blood glucose (FBS) & Lipid profile. The data's are collected from the prescription and laboratory data. The approval for the study was obtained from Institutional Ethical Committee, JSS College of Pharmacy, Ooty.

1.2.1 Study Criteria

1.2.1.1 Inclusion criteria includes

- Male or female patients who are above 35 years & having Stage-1 Hypertension
- Metabolic syndrome patients who meet ATP III criteria based on WC, FBS, HDL-C, TGL-C & BP.

1.2.1.2 Exclusion Criteria Includes

- Patients who are on hypertensive medication
- Pregnant and lactating woman
- Patients who refuse to participate in the study or withdrawing informed consent
- Patient with severe renal & hepatic disease.

1.2.2 Study procedure

Patient meeting the study criteria will be requested to sign the Patient consent form and enrolled. Study population divided into two groups, each of 20 patients was recruited according to ATP III criteria with freshly detected Stage 1 hypertension for at two months. Group I is given with Telmisartan 20 mg OD. Group II is given with Olmesartan 10 mg OD. Blood pressure was measured at baseline, 7,21,35,49 & 60^{th} day of the treatment period. Lipid profile (TC, TGL, LDL, HDL, & VLDL) & FBS will be measured at the baseline and end of the study and comparison will be made in both the groups. Cardiovascular risk percentage using lipid profile was calculated after the end of the study using 30 years Framingham risk score (FS30). Blood samples were drawn after more than 12 hours of fasting. All lipid analysis & blood sugar analysis was performed in Clinical Laboratory of Govt. Head Quarters Hospital, Ooty.

1.2.3 Study instruments

Stethoscope(Microtone DX), Sphygmomanometer(Elkometer-Deluxe, Anita industries), Lipid profile kit (Trans Asia Bio-Medicals Ltd), Fasting Blood Sugar by Glucometer (Trans Asia Bio-Medicals Ltd)

1.2.4 Statistics

The data was assessed by using SPSS software (Statistical Package for Social Sciences) version 19.0, Epi Info 2010 and Microsoft Excel. Descriptive statistics was performed and data is presented as mean (SD). Independent student (t) test AND Paired t- test was used to compare the differences between lipid parameters, BP and fasting blood sugar level at baseline and after 8 weeks treatment period. A value of $p< 0.05$ was considered statistically significant.

2. RESULTS

A total of 16 females and 8 males completed the study and the average age of the study population was 49.08 years and whose body mass index (BMI) was 24.25kg/m2.The demographic characters of the study patients are presented in Table shown below (Treatment strategies A: telmisartan B: Olmesartan)

Table: Demographic Characteristics of subjects

SL.NO.	DEMOGRAPHY		STUDY GROUP A	STUDY GROUP B	TOTAL
1.	No. of patients enrolled		20	20	40
2.	Study Completers		12	12	24
3.	Number of Dropouts		8	8	16
4.	Sex	Male	4(33.33%)	4(33.33%)	8(33.33%)
		Female	8(66.67%)	8(66.67%)	16(66.67%)
5.	Age in yrs. (Mean±S.D)		48.83±7.27	49.33±7.18	49.08±7.23
6.	BMI in kg/m^2(Mean±S.D)		24.89±3.44	23.61±3.09	24.25±3.27
7.	Diet	Veg	4(33.33%)	4(33.33%)	8((33.33%)
		Non- Veg	8(66.67%)	8(66.67%)	16(66.67%)
8.	Smoking	Yes	2(16.67%)	3(25%)	5(20.83%)
		No	10(83.33%)	9(75%)	19(79.17%)
9.	Alcoholism	Yes	3(25%)	2(16.67%)	5(20.83%)
		No	9(75%)	10(83.33%)	19(79.17%)
10.	Education	Illiterate	1(8.33%)	1(8.33%)	2(8.33%)
		1-6	1(8.33%)	3(25%)	4(16.67%)
		7-12	9(75%)	7(58.33%)	16(66.67%)
		>12	1(8.33%)	1(8.33%)	2(8.33%)
11.	Occupation	Nil	0	0	0
		House- wife	8(66.67%)	8(66.67%)	16(66.67%)
		Industry	0	0	0
		Coolie	4(33.33%)	4(33.33%)	8(33.33%)
12.	Income	Nil	8(66.67%)	8(66.67%)	16(66.67%)
		1-12,000	4(33.33%)	4(33.33%)	8(33.33%)
		12,001-30,000	0	0	0
		>30,001	0	0	0

2.1 Effect of Telmisartan and Olmesartan on Hypertension.

Blood pressure was measured at each visit for all the patients and the variations in systolic and diastolic BP were monitored throughout the study. There was a comparable reduction in systolic blood pressure by both the study drugs (Fig:1). Telmisartan showed a constant decrease in blood pressure whereas Olmesartan showed deviation in second visit by a slightly increased blood pressure within 60 days which was insignificant.

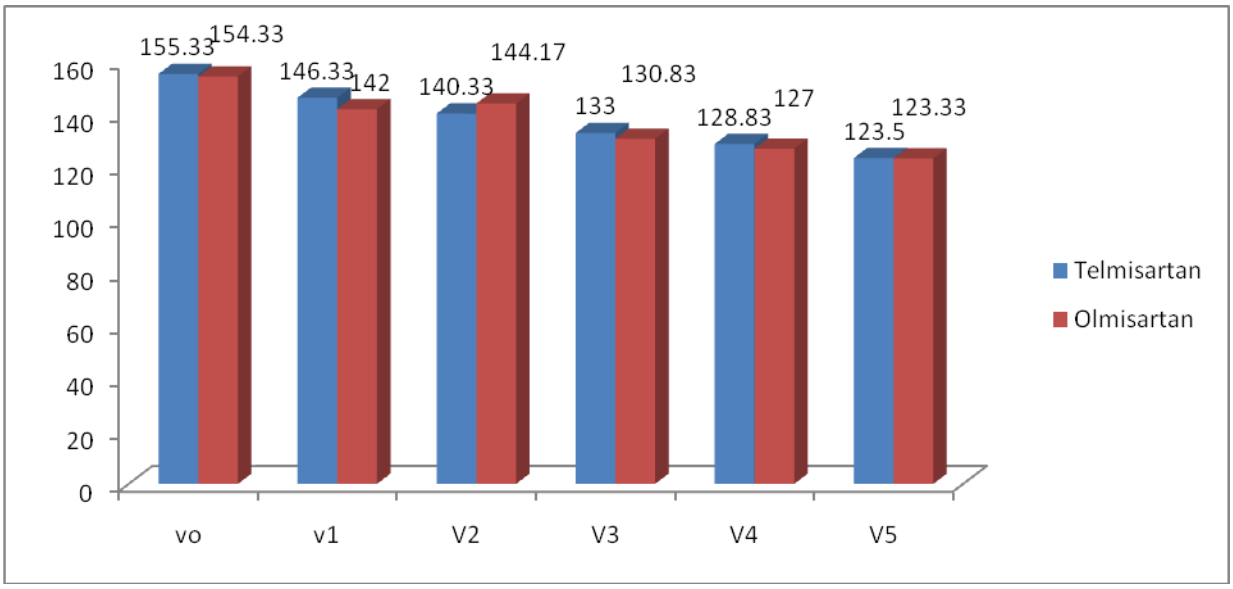

Figure 1: Variability In Systolic Blood Pressure in Patients Treated with Olmesartan and Telmisartan (Y-axis represents BP in millimeter of Hg & X-axis represent follow-ups).

Both Telmisartan and Olmesartan significantly reduced BP (systolic) from 155.33±6.88 to 123.50±8.36 mmHg (P=0.000) and 154.33±6.37 to 123.33±4.70 mmHg (P=0.015) respectively**.** Telmisartan showed a reduction of 31.83±1.48 mmHg and Olmesartan showed reduction of 31.00±1.67 mmHg in systolic blood pressure.

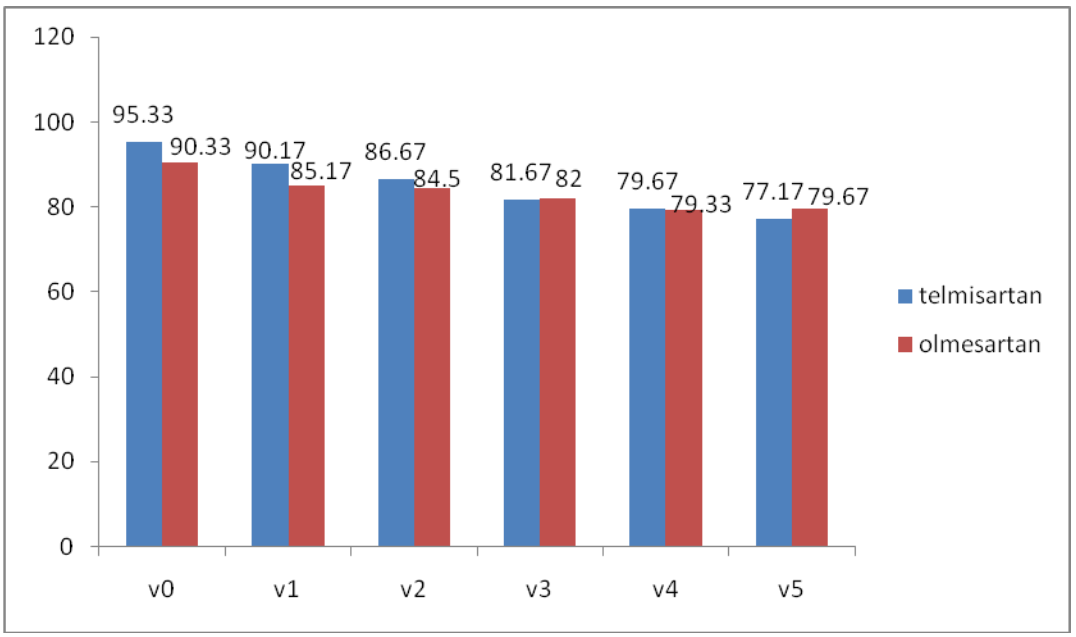

Figure 2: Variability In Diastolic Blood Pressure of the Study Groups during the Study (Y-axis represents BP in millimeter of Hg & X-axis represent follow-ups).

Telmisartan and Olmesartan significantly reduced BP (diastolic) from 95.33±10.93 to 77.17±6.18 mmHg (P=0.000) and 90.33±4.42 to 79.67±1.88 mmHg (P=0.000) respectively (Fig: 2). Telmisartan showed a reduction of 18.16±4.75 mmHg and Olmesartan showed reduction of 10.66±2.54 mmHg in diastolic blood pressure.

Table: Comparison of blood pressure between baseline & study end.

Study Drugs	Visits	Systolic blood pressure	P value	Diastolic blood pressure	P value
Telmisartan (n=12)	Baseline	155.33±8.88	< 0.05	95.33±10.93	< 0.05
	5th follow- up	123.50±8.36		77.17±6.18	
Olmesartan (n=12)	Baseline	154.33±6.37	< 0.05	90.33±4.42	< 0.05
	5th follow- up	123.33±4.70		79.67±1.88	

2.2 Effect of Telmisartan & Olmesartan in hypertensive patients on lipid profile

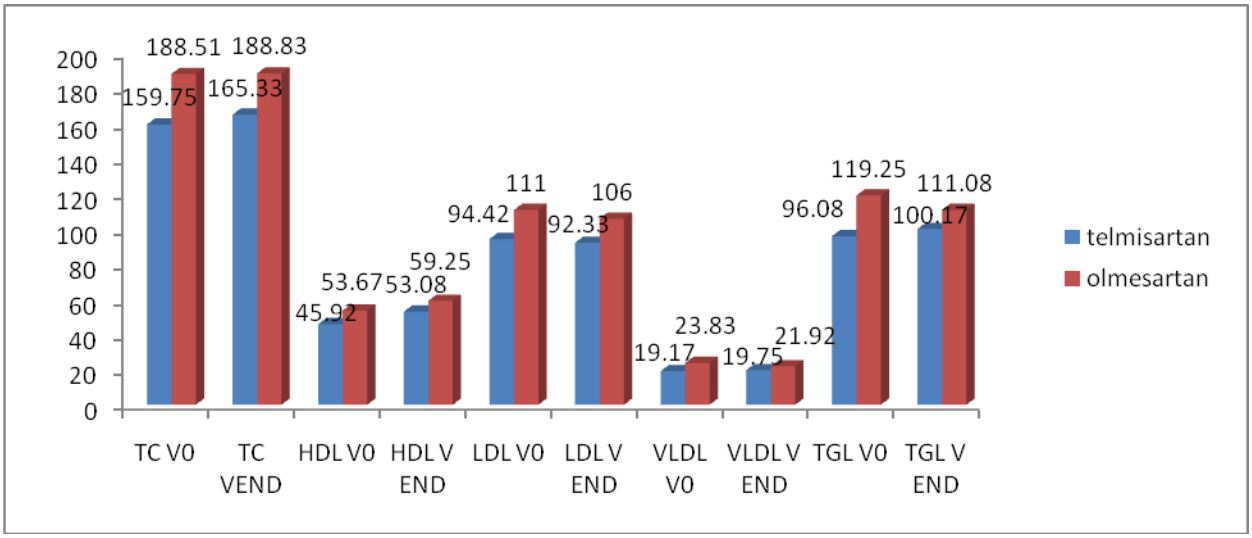

Figure 3 Change in Lipid Profile **(**Y-axis represents unit of lipid profile (mg/dl) & X-axis represents lipid profile at follow-ups).

Telmisartan increased the total cholesterol value from 159.75±27.93 to 165.33±18.4 mg/dl (P=0.198) and Olmesartan slightly increased the total cholesterol value from 188.50±26.25 to 188.83±32.29 mg/dl (P=0.972). The study has shown slight increase in the level of TC at the end of the study by both Telmisartan & Olmesartan, but the values were within the normal range. With independent t-test at baseline & at V end, the (P <0.05) was significant. Telmisartan reduced the LDL-C values from 94.42±24.70 to 92.33±18.20 mg/dl (P=0.555) & Olmesartan reduced the LDL-C values from 111±27.81 to 106±32.45 mg/dl (P=0.613). Telmisartan showed a slight decrease of 2.09±6.50 & Olmesartan showed a decrease of 5±10.64 mg/dl in LDL-C level. While comparing the LDL-C values of Telmisartan & Olmesartan, the independent t-test P value at baseline was 0.137 & at v end was 0.278. Telmisartan increased the VLDL-C value from 19.17±4.33 to 19.75±4.48 mg/dl (P= 0.306) and Olmesartan decreased the VLDL-C values from 23.83±5.49 to 21.92±5.67 (P=0.197) mg/dl. Telmisartan increased the VLDL-C value by 0.58±0.15 mg/dl and Olmesartan reduced the VLDL-C values by 1.91±0.18mg/dl. Telmisartan showed slight increase in VLDL-C values which was not significant & Olmesartan showed slight decrease in VLDL-C values which was also not significant (Fig: 3).

Table: Effect of Telmisartan & Olmesartan on HDL and TGL

DRUGS	HDL V0	HDL V END	P value	TGL V0	TGL V END	P value
Telmisartan(n=12)	45.92	53.08	0.003	96.08	100.17	0.113
Olmesartan(n=12)	53.67	59.25	0.011	119.25	111.08	0.270

Telmisartan significantly increased the HDL-C values from 45.92±8.82 to 53.08±4.74 mg/dl (P=0.003). Olmesartan also significantly increased the HDL values from 53.67±10.08 to 59.25±12.00 mg/dl (P=0.011). Telmisartan increased the HDL-C values by 7.16±4.08 mg/dl & Olmesartan increased the HDL-C values by 5.58±1.92mg/dl. While comparing the HDL-C values of Telmisartan with Olmesartan, the P value at baseline was 0.057 & P value at V end was 0.112 which was not significant. Telmisartan increased the TGL-C value from 96.08±21.54 to 100.17±22.19 mg/dl (P=0.113) & Olmesartan decreased the TGL-C value from

119.25±27.72 to 111.08±28.03 mg/dl (P= 0.270). Telmisartan increased the TGL-C value by 4.09±0.65 mg/dl & Olmesartan decreased the TGL value by 8.17±0.31 mg/dl. On comparing the changes in TGL-C with Telmisartan & Olmesartan using independent t-test, the P value was 0.032 at baseline & 0.302 at V end, which was not significant.

2.3 Effect of Telmisartan and Olmesartan on FBS value

Table Effect of Telmisartan and Olmesartan on FBS value

DRUGS	V0(mg/ dl)	V END(mg/ dl)	P- value
Telmisartan (n=12)	114.17	99.25	0.000***
Olmesartan (n=12)	109.75	98.42	0.000***
P- value	0.37	0.81	

***Strongly significant (P value: P≤0.01)

The mean FBS value for Telmisartan at Baseline was 114.17 mg/dl and the at V end the mean FBS value was 99.25 mg/ dl. The P- value of FBS for Telmisartan was highly significant (P<0.05). The mean FBS value for Olmesartan was 109.75 mg/dl at Baseline and 98.42 mg/dl at V end. The P- value of FBS for Olmesartan was highly significant (P<0.05).

2.4 Effect of Full and Hard Cardiovascular Disease on Framingham risk scores for patients having Hyperlipidemia.

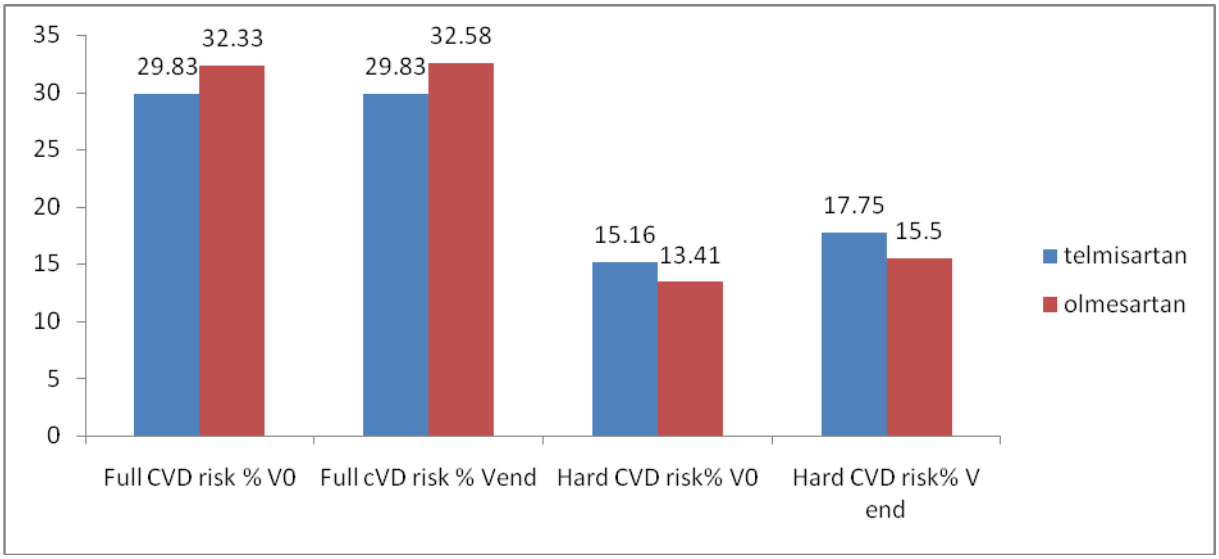

Figure 4: Changes in Framingham Risk Score during study (Y-axis represents risk score& X-axis represent Hard and Full CVD % risk score at V0 and Vend).

Telmisartan showed a mean value of 29.83% at Baseline and 29.83% at V end for Full CVD (hard CVD or coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication or congestive heart failure) risk%. The mean value for Olmesartan at Baseline was 32.33% and at Vend was 32.58% for Full CVD risk%. For Telmisartan the mean Hard CVD risk% (coronary death, myocardial infarction, fatal or non- fatal stroke) was 15.16% at Baseline and it increased to 17.75% at V end. For Olmesartan the mean Hard CVD risk% was 13.41% at Baseline and it increased to 15.5% at V end (Fig: 4).

Table COMPARISON OF CLINICAL PARARAMETERS

SL.NO	CLINICAL PARAMETER	V0	V END	P value
1.	BLOOD PRESSURE (mmHg)			
	(SYSTOLIC)			
	TELMISARTAN (n=12)	155.33±8.88	123.50±8.36	0.000***
	OLMESARTAN (n=12)	154.33±6.37	123.33±4.70	0.015**
	(DIASTOLIC)			
	TELMISARTAN (n=12)	95.33±10.93	77.17±6.18	0.000***
	OLMESARTAN (n=12)	90.33±4.412	79.67±1.88	0.000***
2.	LIPID PROFILE (mg/ dl)			
	TC			
	TELMISARTAN (n=12)	159.75±27.93	165.33±18.42	0.198
	OLMESARTAN (n=12)	188.50±26.25	188.83±32.29	0.972
	TGL-C			
	TELMISARTAN (n=12)	96.08±21.54	100.17±22.19	0.113
	OLMESARTAN (n=12)	119.25±27.72	111.08±28.03	0.270
	HDL-C			
	TELMISARTAN (n=12)	45.92±8.82	53.08±4.74	0.003***
	OLMESARTAN (n=12)	53.67±10.08	59.25±12.00	0.011**
	LDL-C			
	TELMISARTAN (n=12)	94.42±24.70	92.33±18.20	0.555
	OLMESARTAN (n=12)	111.00±27.81	106.00±38.45	0.613
	VLDL-C			
	TELMISARTAN (n=12)	19.17±4.33	19.75±4.48	0.306
	OLMESARTAN (n=12)	23.83±5.49	21.92±5.67	0.197

*Suggestive significance (P value: 0.05<P<0.10) ** Significant (P value: 0.01<P ≤ 0.05)***Strongly significant (P value: P≤0.01)

All the doses of Telmisartan & Olmesartan were well tolerated by the patients and no adverse event reported during treatment period.

3. Conclusion

In the absence of specific therapy, majority of the patients with metabolic syndrome are managed with Thiazide diuretics and β-blockers which have potential adverse effects on glucose & lipid metabolism. Telmisartan & Olmesartan as ARBs being very effective, widely available and easy to use without any major side effect may qualify as first line medication in these patients. Both the study groups had improved notably the clinical parameters from base line till two months of drug therapy. More improvement in blood pressure, HDL-C and FBS was seen with telmisartan when compared to olmesartan. The distinguishing finding compared to other studies is the significant increase ($p<0.05$) in the levels of HDL-C showed by Telmisartan after two months of treatment. Olmesartan failed to show significant reduction in HDL-C level. This may require a detailed study on a larger population.

The Pleiotropic effects of Telmisartan showed within two months of study recommend the use of the drug in metabolic syndrome patients. Even though the drugs are showing benefit on reducing predisposing factors of cardiovascular disease, study shows an increase in hard cardiovascular risk percentage according to Framingham risk score for 30 years based on lipid profile. This recommends a future large long term, randomized, multicenter trials are needed to determine necessary dosage adjustments for long-term utility of study drugs and the benefits among patients having cardiovascular risk with metabolic syndrome.

4. Summary

Treatment with Telmisartan & Olmesartan were found to be beneficial to a greater extend even with eight weeks of treatment with respect to disease, severity and dose. Both the drugs were found to be very effective in reducing Blood pressure, FBS, LDL-C and VLDL-C. While comparing the results of Cardiovascular risk (CVD) based on Framingham 30 year risk score based on lipid profile, both the drugs increases the risk percentage for full CVD (hard CVD or coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication or congestive heart failure) risk% and hard CVD risk% (coronary death, myocardial infarction, fatal or non- fatal stroke) shown in Fig (1). .Our result suggests that both the study drugs should be used with cautious in patients with cardiovascular risk in metabolic syndrome as it shows an increase in full CVD risk percentage. Telmisartan can be considered as an ideal agent in patients with elevated lipid profile because of its significant increase ($p<0.05$) in the levels of HDL-C after two months of treatment.

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