

## The Effect of Telmisartan and Irbesartan on Body Weight and its Contribution to Blood Pressure Control in Hypertensive Black Patients: a Retrospective Cohort Study.

Kanu Ekenedilichukwu<sup>1</sup>, Igbinogu Osas<sup>2</sup>, Ike Oyedimazu<sup>3</sup>

<sup>1</sup>M.Sc Clinical Research, Texila American University

<sup>2</sup>Edi International Hospital. 1 Coronation Drive, Benin city, Edo State, Nigeria.

<sup>3</sup>Lifeline Medicare Clinic. 8 Oza Street, Off Sakponba Road, Benin City, Edo State, Nigeria.

Corresponding author: Kanu Ekenedilichukwu

Email :- kekenedilichukwu@yahoo.com

### Abstract

No study has analyzed the extent of weight reducing ability among the “peroxisome proliferator activated receptor-gamma” (PPAR- $\gamma$ ) activating ARBs – Telmisartan and Irbesartan in black hypertensive of African origin. This retrospective cohort study was designed to delineate the extent of weight reducing effect of these PPAR- $\gamma$  activating ARBs and how it correlates with BP reduction observed with these ARBs in black hypertensive. A total of 26 case notes of patients (15 men, 11 women; mean age 58.9 $\pm$ 1.8 years) with diagnosis of hypertension were reviewed and the study attained a power of 96%. The patients whose case notes were reviewed were naïve to ARBs before commencing either telmisartan or irbesartan and did not have any metabolic disease like diabetes or thyroid disease which could interfere with body weight reading. They all took either telmisartan 80mg or irbesartan 150mg for at least a 6 month review period. Body weight were significantly reduced more in the telmisartan (n = 13) treatment group compared to the irbesartan (n = 13) treatment group [change from baseline; -1.51 $\pm$ 0.46Kg (-1.68%), P=0.006 vs. -0.96 $\pm$ 0.15Kg (-1.05%), P<0.001]. Both treatment effectively controlled blood pressure (mean BP after 6 months treatment: Telmisartan 126/83mmHg; Irbesartan 133/84mmHg). In the telmisartan group there were no correlation between either change in SBP and change in body weight (r = -0.220, P = 0.471) or change in DBP and change in body weight (r = -0.050, P = 0.870), but a significant positive correlation was observed between both change in SBP and change in body weight (r = 0.538, P = 0.058) and change in DBP and change in body weight (r = 0.610, P = 0.027) in the irbesartan treatment group. Both telmisartan and irbesartan reduced body weight in hypertensive black patients and this reduction in body weight may contribute to the power demonstrated by irbesartan to get patients to BP goal. Hence hypertensive blacks could also benefit from the established end-organ protection benefits of both telmisartan and irbesartan.

**Key words:** Hypertension; Telmisartan; Irbesartan; Body weight; Adiponectin; PPAR- $\gamma$ .

### INTRODUCTION

Hypertension is a global public health problem and has worldwide prevalence estimate of about 1 billion persons (Burt et al., 1995). Hypertension is the cause of about 7.1 million deaths per year and 4.5% of the disease burden which translates to 64 million disability adjusted life years (DALYs) (WHO., 2002). With projection that up to three quarter of the world hypertensive population will be in economically developing countries by the year 2025 (Kearney et al., 2005) of which Nigeria and many African countries are classed among.

Looking at one of the lifestyle modification parameter that has been found to affect BP control (Body weight), the effect of body weight reduction on BP control is well established in studies, as it is known that a 10kg loss in weight would give a corresponding 5-20mmHg reduction in BP (THPCRG, 1997 and He et al., 2000). In the light of recent finding about newer more potent ARB having interaction with PPAR- $\gamma$  receptor thereby causing a subsequent increase in plasma adiponectin and a decrease in plasma

adiponectin been established as an independent risk factor for obesity, this retrospective study tries to observe the effect on body weight of these newer ARBs to explain the clinical relevance of its interaction with PPAR- $\gamma$  receptors and proffer a likely mechanism through which these ARBs provide end-organ protection as established in the IDNT (Irbesartan Diabetic Nephropathy Trial) and the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) Study.

## **METHOD**

### **Settings**

This study is primarily an explanatory non-interventional retrospective cohort study. The study recruitment took place in two private hospitals in Benin-city Edo State, Nigeria where Telmisartan or Irbesartan were used to treat patients with essential hypertension that presents at the clinic.

The study consists of a qualitative component which involved review of 26 patients case note and this review was conducted to call up demographic information, blood pressure and weight before commencing ARBs, blood pressure and weight after 3, 4 and 6 months of commencing ARBs, underlying condition and any possible end-organ complication as indicated by fresh complain during the course of treatment with the ARBs.

### **Study End-points**

1. The primary end-point of the study is to determine the extent of weight reduction seen in black hypertensive patients placed on telmisartan or Irbesartan
2. The secondary end-point is to determine the correlation if any exist between body weight reducing effect of these ARBs and reduction in Blood pressure in black hypertensive.

### **Sample size and Power determination**

Statistical power is the probability of rejecting the null hypothesis while the alternative hypothesis is true. The sample size and power of a paired mean statistic that is normally distributed are interdependent and related by the following formulae:

$$P \{Z > Z_{\alpha/2} \text{ OR } Z < -Z_{\alpha/2} | \mu_1\} = 1 - \Phi \left( \frac{Z_{\alpha/2} - (\mu_1 - \mu_0)}{(\sigma/n)} \right) + \Phi \left[ \frac{-Z_{\alpha/2} - (\mu_1 - \mu_0)}{(\sigma/n)} \right]$$

From literature search, study on the effect of telmisartan on adiponectin levels and weight reduction in hypertensive patients with glucose intolerance showed a mean reduction in weight of 2.2%, thus estimating the standard deviation to be 4.4%. Hence from the study it was calculated that for this retrospective study to have a power of at least 50% at a level of significance of 0.05 to detect a 2.2% difference, 18 patient's case note would have to be reviewed. All statistics would have to be performed based on data from 18 patients case note each for the different treatment groups i.e. telmisartan and irbesartan treatment group (Makita et al, 2008).

### **Ethical Approval**

Ethical Approval was gotten from the Chief Medical directors of the two centers used for the retrospective cohort studies.

### **Study Inclusion Criteria**

1. ARB naïve patient with confirmed diagnosis of essential hypertension
2. Age 35 or Older
3. Disease duration less than five years
4. Body weight greater than 70kg

### **Study Exclusion Criteria**

1. Co-morbidity with type 1 or type 2 diabetes mellitus
2. Patients who have taken any form of ARB previously
3. Patients with any form of thyroid dysfunction (thyrotoxicosis or thyroid insufficiency)

### Study population and Data collection

Study population were know hypertensive patients in two private hospital in Benin – city, Edo state Nigeria. The two hospitals where chosen to give a rounded near representation of hypertensive patients in the state – as one of the hospital is known to attract people of very high means (high class) and the other a mix of low, middle and high class patients. The patients whose case reports were reviewed showed a fair representation of distribution from the six-geopolitical zones in Nigeria eliminating to a reasonable extent ethical variability in study data. 26 medical charts were reviewed and the following information were collected: Name, Age, Sex, and Weight before commencing therapy with ARB, Blood pressure before commencing ARB, Weight and blood pressure after 3 months, 4 months and 6 months respectively.

### Statistical Analysis

To determine the primary end-point, a paired t-test statistic was done to compare weight before commencement of treatment for either telmisartan or irbesartan and weight after an average of 6 months from commencement of ARB.

In other to determine the secondary end-point of the study a correlation statistic was performed between reduction in BP and reduction in weight among the two treatment groups

These statistic was tested at a  $P < 0.05$ . A P-Value of 0.05 or less was thus considered to be significant. Other statistics were also done on the data collected to determine center of tendency and dispersion and all data was expressed as Mean  $\pm$  SEM. All statistics were done using SPSS version 20.

### RESULT

Comparing the baseline characteristic between the two review groups it can be said that both groups were comparable (Table 1). The outcomes for these patients are summarized in Table 2 and 3.

**Table 1:** Baseline Characteristics of the patients

Characteristic	Telmisartan Group	Irbesartan Group	Confidence Interval %
Age - year	60.30 $\pm$ 1.52	57.53 $\pm$ 2.02	95
Male sex – no%	8(61.5%)	7(53%)	95
Body Weight	94.03 $\pm$ 3.70	91.30 $\pm$ 3.13	95
Blood Pressure			95
Systolic	158 $\pm$ 4.37	163 $\pm$ 5.78	
Diastolic	100 $\pm$ 2.64	98 $\pm$ 3.19	

**Table 2:** Outcomes in the Telmisartan Treatment Group

Parameter	Baseline	On therapy	Change	Change %	P-value
Body weight (Kg)	94.03 $\pm$ 3.70	92.53 $\pm$ 3.73	-1.51 $\pm$ 0.46	-1.61	0.006
Systolic BP (mmHg)	158.00 $\pm$ 4.37	126.00 $\pm$ 2.86	-32.00 $\pm$ 5.44	-20.25	0.000
Diastolic BP (mmHg)	100.77 $\pm$ 2.64	83.08 $\pm$ 2.00	-17.69 $\pm$ 4.07	-17.69	0.001

**Table 3:** Outcomes in the Irbesartan Treatment Group

Parameter	Baseline	On therapy	Change	Change %	P-value
Body weight (Kg)	91.30 $\pm$ 3.13	90.35 $\pm$ 3.15	-0.96 $\pm$ 0.15	-1.05	0.000
Systolic BP (mmHg)	163.07 $\pm$ 5.78	133.38 $\pm$ 2.33	-29.69 $\pm$ 7.23	-18.21	0.001
Diastolic BP (mmHg)	98.07 $\pm$ 3.19	84.23 $\pm$ 2.09	-13.85 $\pm$ 4.60	-14.13	0.011

### Clinical Management

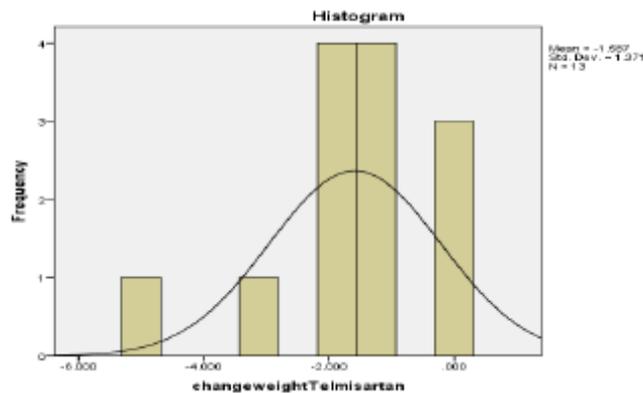
In the two groups, the proportion of patients in whom the expected blood pressure was achieved increased (62% in the Telmisartan 80mg daily group and 53% in the Irbesartan 150mg daily group) and the mean blood pressure decreased over the period of review; the mean blood pressure at visits after base

line was 126/83mmHg in the telmisartan group and 133/84mmHg in the irbesartan group. A greater decrease in SBP (-7.4mmHg) was seen in the telmisartan group over the irbesartan group though not significant ( $P=0.072$ ) and a greater decrease in DBP (-1.15mmHg) was also observed in the telmisartan group over the irbesartan group over the period of review though not statistically significant ( $P= 0.712$ ). The distribution of non-review drug used to control blood pressure – are primarily diuretic (hydrochlorothiazide 12.5mg daily) and calcium channel blocker (amlodipine 5mg daily) and was similar across group.

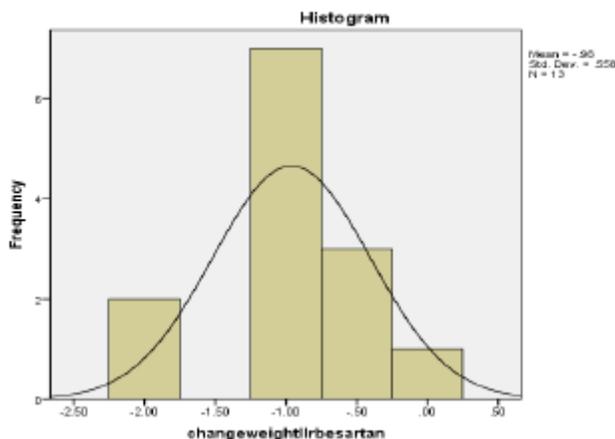
### Primary Endpoint

The mean weight of patients in the telmisartan review group before commencing telmisartan 80mg daily equals  $94.04\pm 3.70\text{kg}$ , mean weight after commencing telmisartan 80mg daily dropped to  $92.52\pm 3.73\text{kg}$  and the paired difference in mean weight before and after treatment with telmisartan decreased by  $-1.51\pm 0.46\text{kg}$  ( $P=0.006$ ) in the telmisartan treatment group over a six month review period. The reduction in weight across the telmisartan treatment group also had a normal distribution over the 6 months review period fig 1 below.

The mean weight of patients in the irbesartan review group before commencing irbesartan 150mg daily equals  $91.30\pm 3.14\text{kg}$ , mean weight after commencing irbesartan 150mg daily dropped to  $90.35\pm 3.15\text{kg}$  and the paired difference in mean weight before and after treatment with irbesartan decreased by  $-0.96\pm 0.15\text{kg}$  ( $P=0.000$ ) in the irbesartan treatment group over a six month review period. The reduction in weight across the irbesartan treatment group also had a normal distribution over the 6 months review period fig 2 below.



**Fig 1** Histogram of change in weight in the telmisartan treatment group

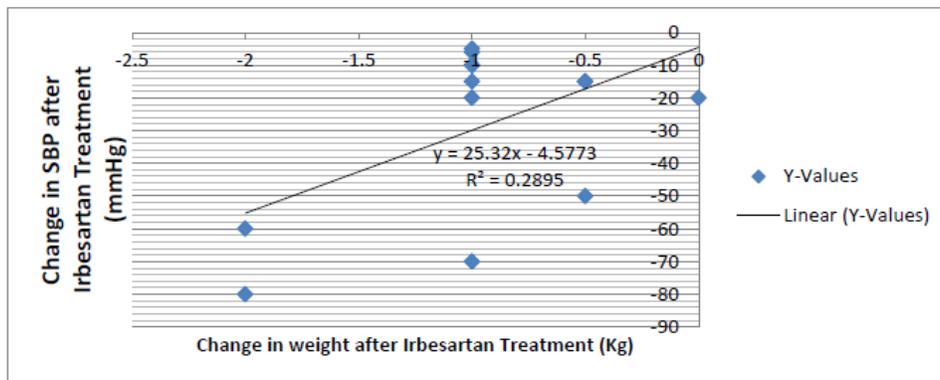


**Fig 2** Histogram of change in weight in the Irbesartan treatment group

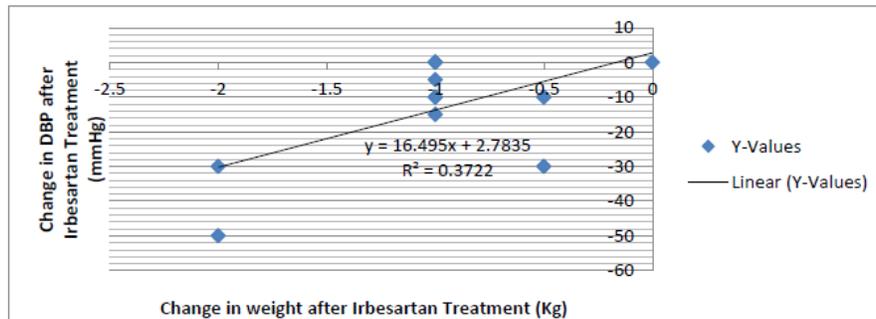
**Secondary Outcomes**

In the telmisartan review group there was a positive correlation between change in systolic blood pressure and change in diastolic blood pressure (Pearson correlation = 0.795, P = 0.001). The negative correlation that was seen between change in SBP and change in weight was not significant (Pearson correlation = -0.220, P = 0.471), same was the case between change in diastolic blood pressure and change in weight (Pearson correlation = -0.050, P = 0.870).

In the irbesartan review group there was a positive correlation between change in systolic blood pressure and change in diastolic blood pressure (Pearson correlation = 0.653, P = 0.016). A positive correlation was seen between change in SBP and change in weight (Pearson correlation = 0.538, P = 0.058), same was the case between change in diastolic blood pressure and change in weight (Pearson correlation = 0.610, P = 0.027). A regression plot of change in weight against change in systolic blood pressure in the irbesartan treatment group gave a positive slope, S = 25.32 and R<sup>2</sup> = 0.2895 fig 3, while a plot of change in weight against change in diastolic blood pressure gave a positive slope, S = 14.495 and R<sup>2</sup> = 0.3722 fig4.



**Fig 3** Plot of change in weight against change in diastolic blood pressure



**Fig 4** Plot of change in weight against change in diastolic blood pressure

**DISCUSSION**

It has been established that telmisartan and irbesartan causes increase in plasma adiponectin (Makita et al., 2008 and Clasen et al., 2005) level and low adiponectin level is correlated with obesity (Fasshauer et al, 2004). Makita et al., (2008) noted decrease in weight with telmisartan alongside increase in adiponectin level. A study done with obese zucker rat fed high fat diet alongside irbesartan also recorded decrease in weight and increase adiponectin level (de LasHeras et al, 2009). The DO-IT prospective observational study show a decrease in BMI and other metabolic parameter in hypertensive patients placed on irbesartan over a period of six month (Parhofer et al., 2007). Hence, this retrospective cohort study tried to see if either telmisartan or irbesartan have weight reducing effect in hypertensive black patients and if this correlates with BP reduction recorded with these ARBs.

The primary end-point i.e. body weight reduction was positive for both telmisartan and irbesartan. Telmisartan showed greater reduction in body weight -1.61% than irbesartan -1.05% this is similar with the study by Makita et al, (2008) in which telmisartan showed a -2.2% decrease in body weight. The secondary end-point i.e. correlation of weight reduction to decrease in blood pressure was positive for irbesartan, while no effect was noticed in the telmisartan treatment group.

The distant implication of this study for telmisartan is intricately related to the result seen in both the ONTARGET and the HOPE study (ONTARGET, 2008 and HOPE, 2000). Suffice to say that telmisartan and ramipril demonstrated cardiovascular protection and as such both share license indication for CV protection in hypertensive patients at high risk of cardiovascular complication. It is noted that telmisartan increases adiponectin level (Makita et al., 2008) as well as ramipril (Koh et al 2005). One of the effects of increase in adiponectin level by telmisartan is decrease in weight as decrease in plasma level of adiponectin correlative with obesity (Fasshauer et al., 2004). This study corroborates that in truth telmisartan thus have weight reducing effect in black hypertensive possibly due to its increase in plasma adiponectin level. A study reported in AHA, 2004 vividly shows that adiponectin adheres to blood vessel walls, possibly protecting them by fighting inflammation at cellular level, this result is further corroborated by Ouedraogo et al., (2007) who showed in an animal model that adiponectin helps prevent immune system white blood cells from binding to the inside of blood vessel walls, adiponectin acts not only on leucocytes adhering to blood vessel wall, but also on inflammatory cytokines by reversing effect of cytokines produced by injection of a pro-inflammatory mediator - TNF $\alpha$  and thus halting resulting inflammation. Inflammation is common in cardiovascular diseases, since telmisartan increase adiponectin level, this is possibly the mechanism through which telmisartan was able to show cardiovascular protection in high CV risk patients in the ONTARGET study. This is also true for ramipril which has been found to increase adiponectin level and hence also demonstrate cardiovascular risk protection in high CV risk patients in the landmark trial – HOPE study. This study avidly shows that the benefit of telmisartan in CV risk protection as demonstrated in the ONTARGET study can also be enjoyed by black hypertensive. Telmisartan also sells itself for black patients with metabolic syndrome – a triad of hypertension, obesity and insulin resistance.

For irbesartan the implication of this study is related to the result seen in the IRMA2 and IDNT. In these study irbesartan showed 70% relative risk reduction to micro-albuminuria and reversal of micro-albuminuria in a third of patients population been studied, a decrease in doubling of serum creatinine a marker of worsening kidney state and a delay to ESRD. Studies have shown that irbesartan has the ability to increase serum adiponectin level (Clasen et al., 2005). One of the effects of increased adiponectin level could be decrease in body weight (Parhofer et al., 2007) as adiponectin level has been well correlated with obesity (Fasshauer et al., 2004). The study thus confirms that irbesartan have weight reducing effect in black hypertensive placed on it. A study by Thomas Jefferson University Researchers, 2005, shows that those with low level of adiponectin may also have high level of a protein called albumin which in humans, may be a sign of kidney disease...to prove the relationship, they also studied mice without adiponectin “adiponectin knockout” compared to wild type mice whose levels were normal. The team found that the knockout mice had three times the level of urine albumin than the wild type mice. In a separate study the researchers measured the adiponectin levels of a group of obese African American adolescents and they found similar results – subjects who had a low level of adiponectin also had the condition known as albuminuria as indicated by high levels of the protein albumin in their urine. Albuminuria is an indicator for kidney disease and since irbesartan increases adiponectin level this possibly is the mechanism through which irbesartan was able to show reversal of microalbuminuria and renoprotection in the IRMA2 and IDNT respectively since it was observed that these effects were independent of it blood pressure lowering effects (Parving et al., 2001 and Lewis et al., 2001). This study thus goes to show that, “the benefits of irbesartan in reversal of microalbuminuria and renoprotection demonstrated in IRMA-2 and IDNT” might also be enjoyed by black diabetic hypertensive.

Amelioration of metabolic picture – a triad of obesity, insulin resistance and hypertension was reported to be improved in patients that were placed on Irbesartan 150mg/day and Telmisartan 80mg/day for 6 months and a greater effect was seen in the telmisartan group than the Irbesartan group (Negro et al 2006).

There was no change in BMI in a study conducted by Deroasa et al., (2006) to assess telmisartan and Irbesartan therapy in type 2 diabetic patients treated with rosiglitazone: effects on insulin resistance, leptin and tumor necrosis factor- $\alpha$ . There was a significant improvement of insulin sensitivity, decrease in leptin and TNF- $\alpha$  in both treatment groups after 6 and 12 months but greater decrease was seen in the telmisartan group than the Irbesartan group. It was observed that no change in BMI was seen in both telmisartan and irbesartan group after 6 and 12 month respectively, this finding can be explained by the study design, in which all patients were placed on rosiglitazone 4mg/day, remembering that TZDs have side effect of weight gain, it possibly explains why there was no change in BMI which is expected as shown in the study by mekita et al 2008.

Mori et al (2012), reports that higher doses of telmisartan gave increase in serum adiponectin level. The increase was evident particularly in a group of patients whose HMW adiponectin levels were less than 4.0 $\mu$ g/dl. A significant improvement in homeostasis model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance, was also observed in the telmisartan 80mg group only. Similarly Clasen et al., (2005) also demonstrated that AT2R activation and Irbesartan induce adiponectin in adipocytes, which was associated with an improvement of parameters of insulin sensitivity in vivo. Irbesartan induced adiponectin stimulation is likely to be mediated via PPAR- $\gamma$  activation involving post transcriptional mechanism.

## CONCLUSION

The present study shows that black hypertensive patients placed on either telmisartan or irbesartan would not only benefit with respect to blood pressure reduction but would also with respect to significant reduction in body weight. Body weight reduction correlates with blood pressure reduction with the ARB – Irbesartan. It can also be inferred that the end-organ protection benefits of telmisartan or irbesartan may equally be enjoyed in black hypertensive with either CV risk complication or diabetic nephropathy respectively since the benefits can be attributed to their ability to significantly increase serum adiponectin levels. Therefore that irbesartan or telmisartan can reduce body weight significantly is likely due to its confirmed ability to increase serum adiponectin levels.

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