Efficacy and safety of Olmesartan,Losartan, Valsartan, and Irbesartan in the Control of Essential Hypertension

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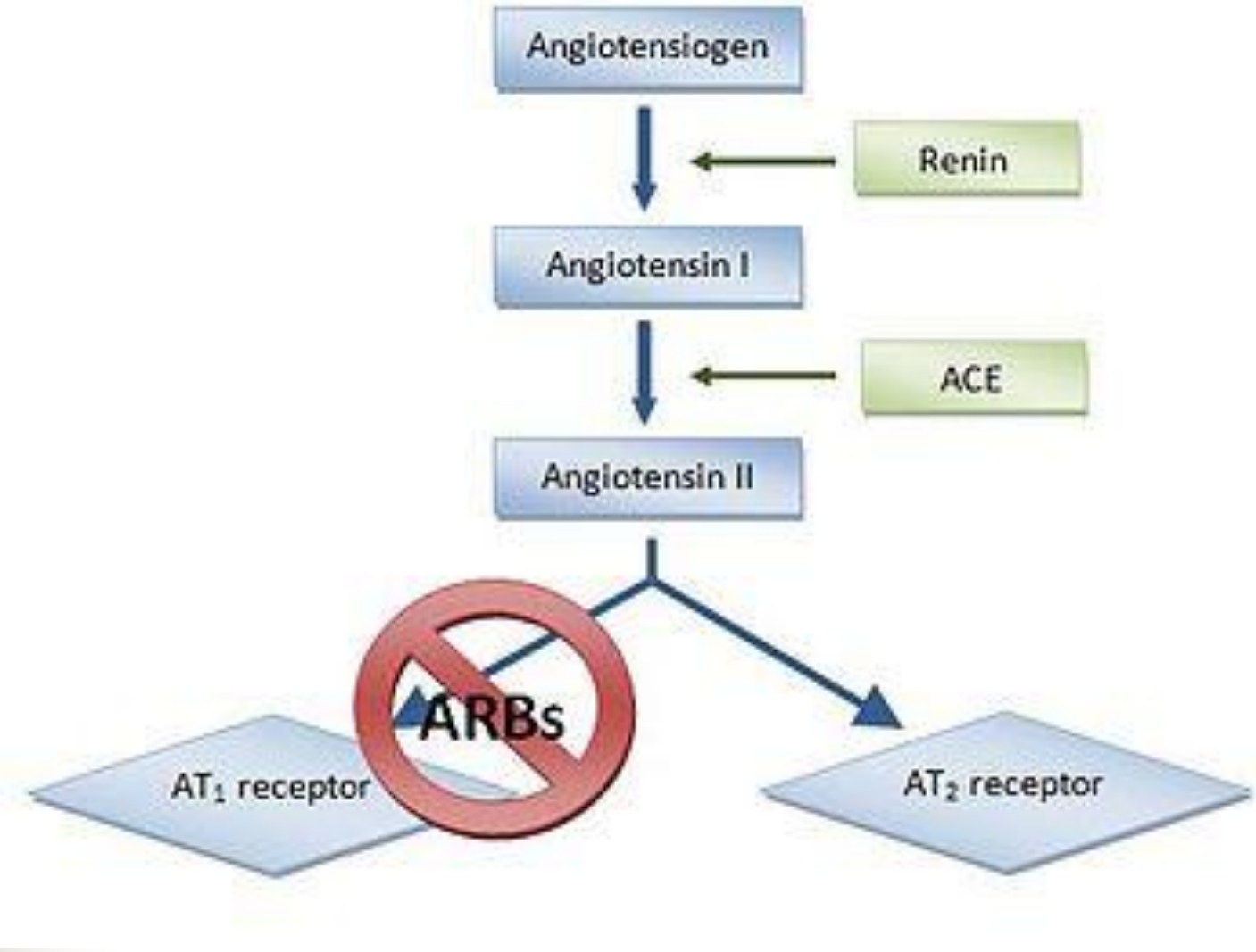
Collage of pharmacy

Clinical Question

In adult patient with **Hypertension** is a treatment with **Olmesartan** superior than other Angiotensin II receptor blockers (ARBs) in terms of efficacy and safety?

Introduction:

- Angiotensin II receptor blockers (ARBs) are the newest class of approved antihypertensive agents and the second class of drugs to exert their primary antihypertensive action by interrupting the renin-angiotensin system.
- ARBs prevent the hypertensive effects of angiotensin II by selective blockade of the angiotensin II type 1 (AT1) receptor.


Angiotensiogen
Renin
Angiotensin I
ACE
Angiotensin II
ARBs
AT1 receptor
AT2 receptor

Discovery and development of angiotensin receptor blockers

- **Valsartan, candesartan and irbesartan** were all developed in 1990.
- **LOSARTAN** was introduced in1995.
- **Olmesartan medoxomil** was developed in 1995 and is the newest ARB on the market, marketed in 2002.

Comparison between different ARBs

	Olmesartan medoxomil	Losartan	Valsartan	Irbesartan
Dosage for HTN	Start 20 mg po qd . Max 40 mg/day	start 50 mg po qd. Max 100 mg/day.	Start 80-160 mg po qd. Max 320 mg/day.	Start 150 mg po qd. Max 300 mg/day.
Renal dose	CrCl< 4o ml/min no adjustment. CrCl< 20 ml/min consider using lower initial dosage and not exceeding 20 mg/day	No adjustment .	No adjustment .	No adjustment .
Hepatic dose	No adjustment .	Hepatic impairment start 25 mg qd.	No adjustment .	No adjustment .
Metabolism Half life	Prodrug 13 hours	Prodrug 2 hours	Active drug 6 hours	Active drug 11–15 hours

combination	Olmesartan medoxomil/ Amlodipine/HCT 20/5/12.5 mg 40/5/12.5 mg 40/5/25 mg 40/10/12.5 mg 40/10/25 mg	Losartan/HCT 50/12.5 mg 100/12.5 mg 100/25 mg	Valsartan/ Amlodipine/HCT 160/5/12.5 mg 160/5/25 mg 160/10/12.5 mg 160/10/25 mg 320/10/25 mg	Irbesartan /HCT 150,300/12.5 mg
	Olmesartan medoxomil/HCT 20/12.5 mg 40/12.5 mg 40/25mg		Valsartan /HCT 80,160,320/12.5 mg 160,320/25 mg	
	Olmesartan medoxomil /Amlodipin 20/5 mg 40/5 mg 20/10 mg 40/10 mg		Valsartan /Amlodipine 160,320/5 mg 160,320/10 mg	

The Study of The Journal Club:

Comparative Efficacy of Olmesartan, Losartan, Valsartan, and Irbesartan in the Control of Essential Hypertension

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Study overview:

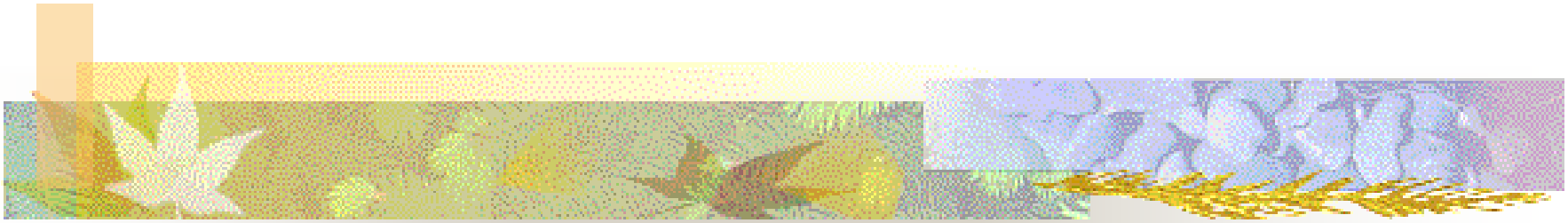
- **Aim of the study:** compared the efficacy of once-daily olmesartan with that of losartan, valsartan, and irbesartan in patients with uncomplicated essential hypertension.
- **PICO**

Population:	**1678patients with Hypertension.**
Intervention :	***once-daily treatment with the new angiotensin II type 1 receptor blocker (ARB) olmesartan (20 mg)***
Control :	***once-daily treatment with the old angiotensin II type 1 receptor blocker (ARB) losartan (50 mg), valsartan (80 mg) and irbesartan (150 mg)***
Outcomes:	**The primary efficacy outcome : was the change in sitting cuff DBP from baseline to the week 8 visit of the active treatment phase.**

Trial design

- This randomized, double-blind, parallel-group , multicenter clinical trial was conducted at 68 sites in the United States.
- The study was divided into three phases: initial screening, 4-week single-blind placebo run-in and 8-week double-blind active treatment.

Method

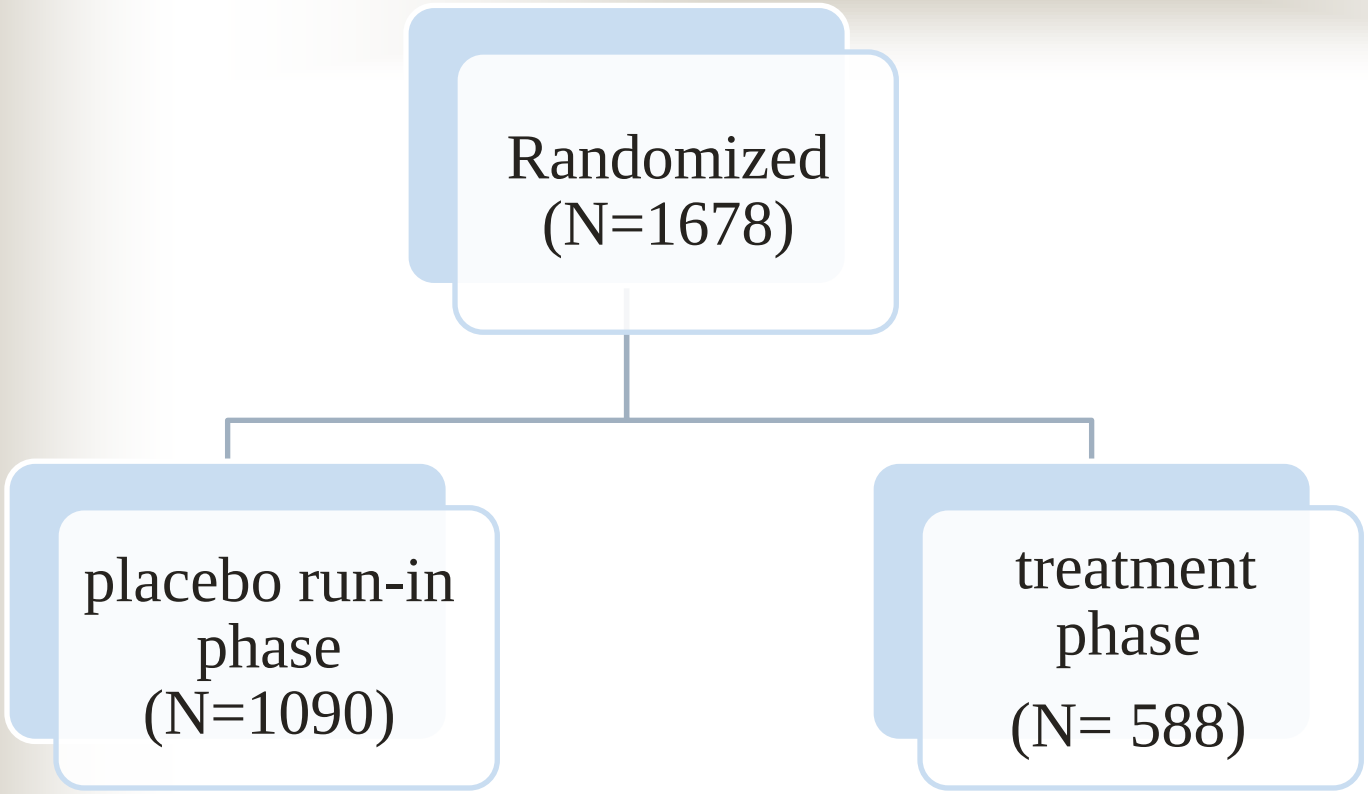


1-Randomization :

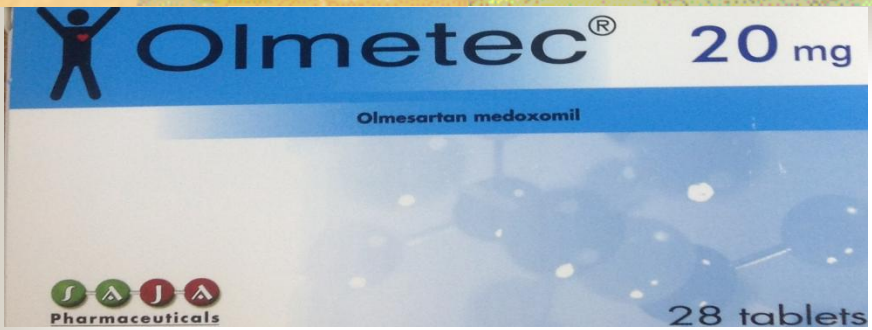
- Patients entering the active treatment phase of the study were randomly assigned to receive a once-daily dose of one of the following ARBs: 20 mg olmesartan ,50 mg losartan ,80 mg valsartan and150 mg irbesartan.
- All drugs were provided at the starting dose recommended by the manufacturer and were placed in identical capsules that matched the placebo capsules administered during the run-in phase of the study.
- All drugs were taken at breakfast except on examination days, when medication was not taken until after blood pressure had been measured.

2-Allocation

- A total of 1678 patients were screened for participation in the trial and 1090 were enrolled in the placebo run-in phase of the study ,while 588patients entered the treatment phase of the study .



588patients entered the treatment phase of the study and were randomized to:



Olmesartan 20 mg once daily (n=147).

Losartan 50 mg once daily (n=150).

valsartan 80 mg once daily (n=145).

Irbesartan 150 mg once daily (n=146).

3-blinding:

- investigators and study staff remained blinded to study medication.
- Blinding was maintained until a patient was excluded from the study.

4-Inclusion criteria :

- Male and female patients 18 years of age or older with essential hypertension.
- patients were required to have an average cuff diastolic blood pressure (DBP) of ≥100 and ≤115 mm Hg and a mean daytime DBP of ≥90 mm Hg and <120 mmHg.

5-Exclusion criteria :

- Women were nursing or were of child-bearing age and were not using a reliable means of birth control.
- any serious disorder that could limit the ability of the patient to participate in the trial, significant cardiovascular disease within the previous 6 months, and secondary hypertension.
- No antihypertensive medications, other than the drugs used in the study.

Table I. Summary of Baseline Demographic Characteristics and Blood Pressure of Patients in the Intent-to-Treat Population

	Olmesartan (20 mg)	Losartan (50 mg)	Valsartan (80 mg)	Irbesartan (150 mg)
N	145	146	142	145
Age (years)	52.4±8.95	51.6±9.30	51.7±9.62	51.9±9.63
Race (%)				
White	75.2	69.2	76.1	66.9
Black	13.8	13.0	10.6	16.6
Other	11.0	17.8	13.3	16.5
Gender (%)				
Male	66.9	62.3	57.7	58.6
Female	33.1	37.7	42.3	41.4
Baseline blood pressure				
Cuff DBP	104±3.5	104±3.5	104±3.3	104±3.6
Cuff SBP	157±13.3	157±11.9	155±12.1	156±12.8

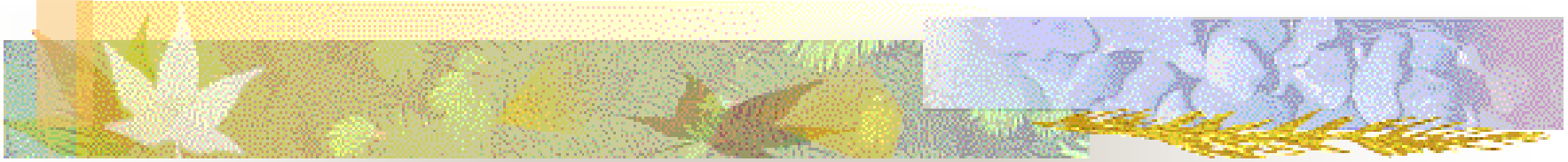
All values are means±SD. DBP=diastolic blood pressure; SBP=systolic blood pressure

There were no significant differences in the demographics of the different treatment groups.

Follow up

- Patients in the active treatment phase of the study were required to visit the clinic prior to taking their daily dose of medication 2, 4, and 8 weeks after commencing active treatment.
- At each visit sitting cuff blood pressure , heart rate was measured, compliance was assessed by pill count, and patients were queried for adverse events.

Result

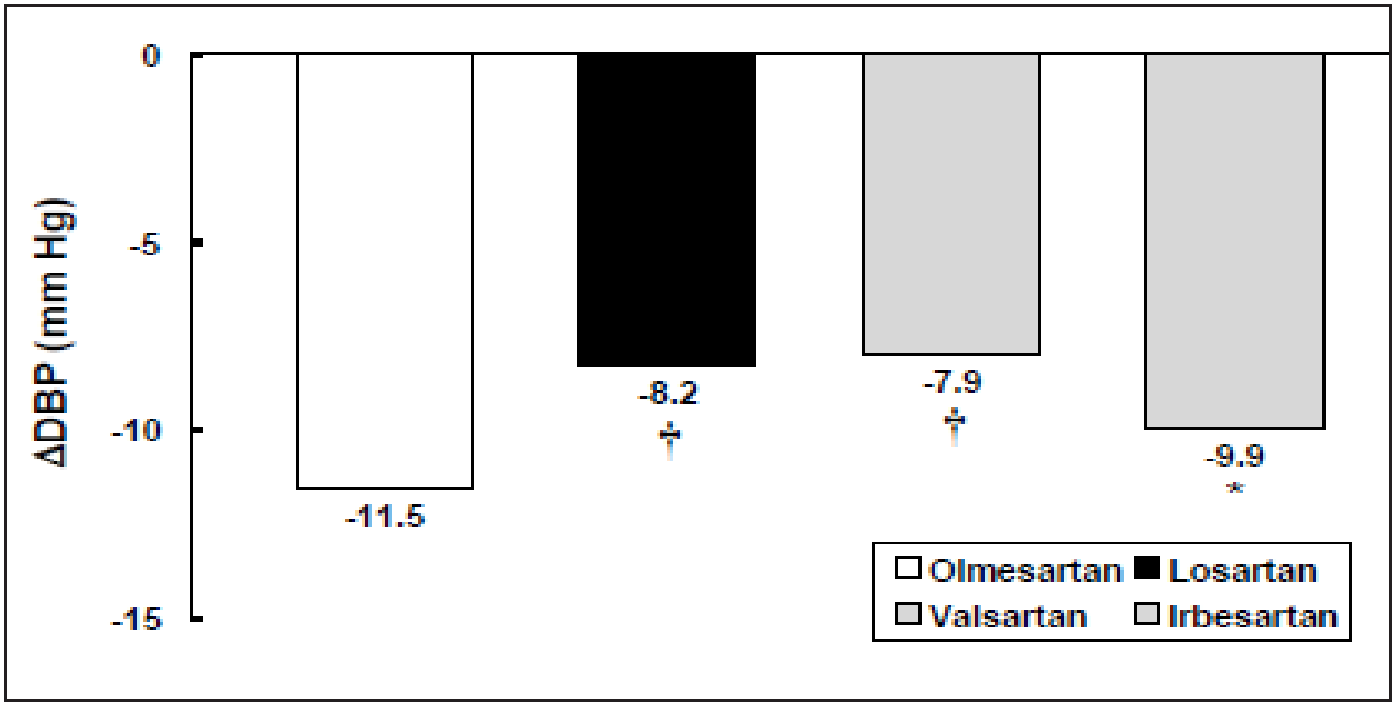


1-Cuff Blood Pressure and Heart Rate

- Treatment with all four ARBs resulted in significant decreases in both cuff DBP and SBP from baseline after 8 weeks of treatment (*$p<0.001$ for all groups).*

Drug	mean reduction in cuff DBP	P value
olmesartan	11.5 mm Hg	
losartan	8.2 mm Hg	*p=0.0002*
valsartan	7.9 mm Hg	*p<0.0001*
irbesartan	9.9 mm Hg	*p=0.0412*

Drug	Mean reduction in SBP	P value
olmesartan	13.0 mm Hg	
losartan	8.9 mm Hg	*p=0.001*
valsartan	9.2 mm Hg	*p=0.003*
irbesartan	10.8 mm Hg	*p=0.050*



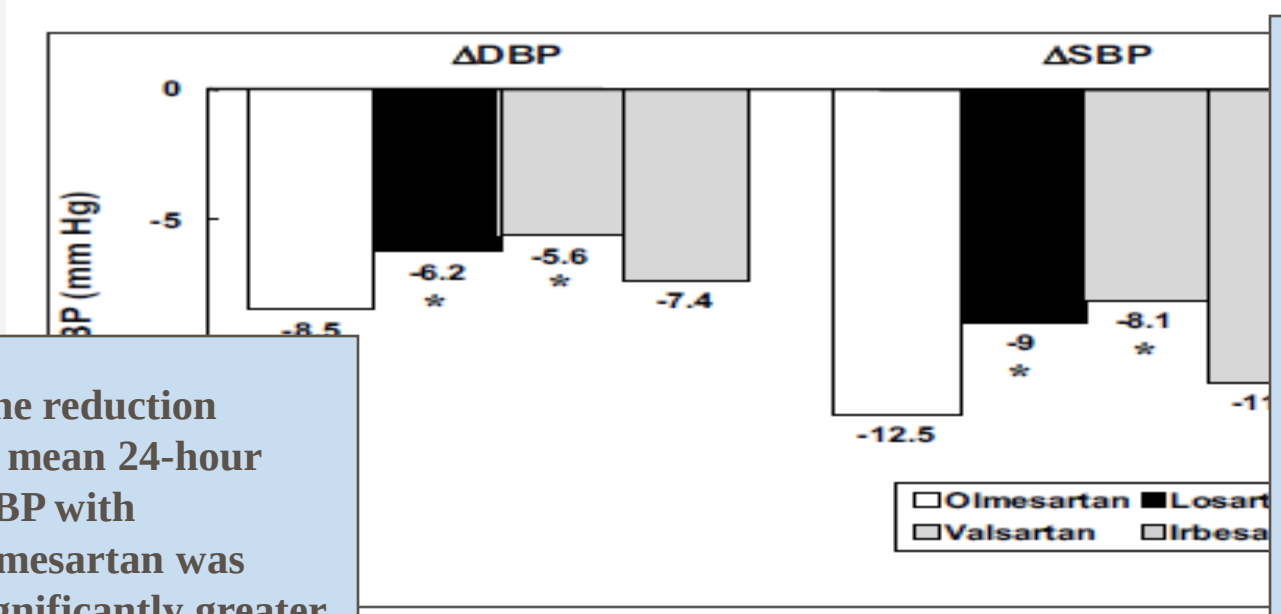
The mean reduction in cuff DBP achieved with olmesartan was significantly greater than that with losartan , valsartan and irbesartan.

Table II. Change in Cuff DBP and SBP After 2 and 4 Weeks of Treatment

	Olmesartan	Losartan	Valsartan	Irbesartan
2 Weeks				
Δ DBP	-10.7	-7.6†	-9.0*	-9.0*
Δ SBP	-13.0	-8.9**	-9.2**	-10.8*
4 Weeks				
Δ DBP	-11.4	-8.9†	-9.7*	-9.9*
Δ SBP	-13.4	-11.4	-10.6	-13.2

Olmesartan was also significantly more effective than all three comparison drugs in reducing SBP and DBPafter 2 weeks and at 4 weeks of treatment

2- Ambulatory Blood Pressure Monitoring



The reduction in mean 24-hour DBP with olmesartan was significantly greater than the reduction obtained with losartan and valsartan

The reduction in mean 24-hour SBP with olmesartan was significantly greater than the reduction obtained with losartan and valsartan

Table III. Change in Mean Daytime and Nighttime ABPM, DBP, and SBP After 8 Weeks of Treatment With Olmesartan, Losartan, Valsartan, or Irbesartan

	Olmesartan	Losartan	Valsartan	Irbesartan
Day				
Δ DBP	-10.2	-7.2**	-7.0†	-8.8
Δ SBP	-14.7	-10.9**	-10.2**	-13.8
Night				
Δ DBP	-6.8	-5.2	-4.2**	-5.9
Δ SBP	-10.3	-7.3*	-6.1**	-8.8

ABPM=ambulatory blood pressure monitoring; DBP=diastolic blood pressure; SBP=systolic blood pressure

All of the ARBs in this study had less effect on blood pressure during the night than during the day.

Safety

Table IV. Adverse Events During the Active Treatment Period

	Olmesartan N=147	Losartan N=150	Valsartan N=145	Irbesartan N=146
	N (%)			
Patients with ≥1 AE during active treatment				
Total AEs	45 (30.6)	48 (32.0)	65 (44.8)	52 (35.6)
Drug-related AEs*	12 (8.2)	14 (9.3)	13 (9.0)	11 (7.5)
Serious AEs (total)	1 (0.7)	1(0.7)	2 (1.4)	0 (0.0
Severe AEs (total)	4 (2.7)	2 (1.3)	3 (2.1)	3 (2.1)
Total AEs in ≥2% of patients in any treatment group				
URT infection	4 (2.7)	4 (2.7)	12 (8.3)	8 (5.5)
Headache	7 (4.8)	6 (4.0)	6 (4.1)	8 (5.5)
Fatigue	3 (2.0)	5 (3.3)	3 (2.1)	2 (1.4)
Back pain	1 (0.7)	5 (3.3)	3 (2.1)	2 (1.4)
Dizziness	2 (1.4)	1 (0.7)	2 (1.4)	5 (3.4)
Diarrhea	2 (1.4)	1 (0.7)	1 (0.7)	5 (3.4)
Arthralgia	1 (0.7)	3 (2.0)	3 (2.1)	1 (0.7)
Coughing	3 (2.0)	1 (0.7)	2 (1.4)	1 (0.7)
Pharyngitis	0 (0.0)	4 (2.7)	1 (0.7)	1 (0.7)
Influenza-like symptoms	1 (0.7)	0 (0.0)	1 (0.7)	4 (2.7)
Myalgia	0 (0.0)	1 (0.7)	4 (2.8)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	4 (2.8)	1 (0.7)
Peripheral edema	1 (0.7)	0 (0.0)	3 (2.1)	1 (0.7)
Migraine	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)

AE=adverse event; URT=upper respiratory tract; *adverse events considered by the investigator to be definitely, probably, or possibly related to study drug administration

CONCLUSION

- This study has shown that the reduction in cuff DBP resulting from 8 weeks of treatment with olmesartan is greater than that seen following treatment with losartan, valsartan, or irbesartan.
- Olmesartan also produced a reduction in cuff SBP & DBP more than losartan, valsartan, or irbesartan.
- *olmesartan, at its starting dose,is more effective than the starting doses of the other ARBs tested in reducing cuff DBP in patients with essential hypertension.*
- *so* , **Olmesartan** superior than other Angiotensin II receptor blockers (ARBs) in terms of efficacy and safety

jadad score

Yes, the patient were randomly assigned into 4 groups

Description	Point
Was the study described as random?	1
Was the randomization scheme described an appropriate?	1
Was the study described as double-blind?	1
Was the method of double blinding appropriate?	1
Was there a description of dropouts and withdrawals?	1

Yes, Randomization was performed with the use of interactive phone system .

Yes

Yes
Blinding investigators and PT

Yes

THANK YOU