

Efficacy, Safety and Tolerability of High dose Valsartan Hydrochloride in Essential Hypertension

MA Zaman

Department of Cardiology, Bangladesh Medical College Hospital, Dhaka, Bangladesh

Abstract

Key word:
Valsartan,
High dose,
Anti-hypertensive,
Safety, efficacy
and
tolerability.

Background: Studies across the world have demonstrated the efficacy of valsartan in lowering blood pressure in a variety of patient populations, several of them investigated higher doses of the drug. This study focuses on revealing safety and efficacy of valsartan at higher doses in Bangladeshi population. Current study is planned to evaluate the efficacy, safety and tolerability of daily dose of Valsartan 160 or 320 mg in the treatment of essential hypertension.

Method: This is a multi-center, open-label, observational, non-comparative, clinical decision based titration, involving about 31 centers in Bangladesh. A total of 334 newly diagnosed adult patients with essential hypertension received valsartan at a dose of 160 mg or 320 mg as deemed necessary by physician were included to allow for an assessment of efficacy, safety and tolerability. The total duration of treatment with valsartan was 16 weeks. Primary parameter for efficacy was percentage responders to valsartan at 16 weeks, reduction in Mean sitting systolic blood pressure (MSSBP) and Mean sitting Diastolic blood pressure MSDBP, control rate (% patients) achieving SBP <140 mmHg and DBP <90 mmHg at end point and Global assessment of efficacy and tolerability to valsartan treatment by the physician and patient.

Result: Mean age of the patient was 53.31 ± 8.8 years and 56.5% were male. A clearly evident decline is evident in mean Systolic BP and diastolic BP over the study duration. Average reduction of 30.4 ± 17.4 mmHg was seen in systolic BP, 18.4 ± 11.2 mmHg in diastolic BP and 3.5 ± 3.1 / minute in heart rate. The reduction was highly significant in both systolic BP and diastolic BP and heart rate as well ($P < .001$). At 16 weeks only 3.4% were found to be refractory to the treatment. Global assessment of safety and efficacy was assessed on four point scale, around 30.2% of the physician rated the efficacy as excellent, around 56% rated as very good and 13.8% rated as good. Tolerability of the treatment was also assessed based on the opinion of the patient and physician concerned on four point scale. Around 34.1% of the physician rated the tolerability as excellent, around 49.7% rated as very good and 16.2% rated as good.

Conclusion: Sixteen week treatment with valsartan at 160mg daily or 320 mg daily is an effective treatment for patients with essential hypertension. The drug is found to be well tolerated with minimal adverse event during the course of treatment.

(*Cardiovasc. j.* 2013; 5(2): 182-189)

Introduction:

Angiotensin II is a potent vasoconstrictor and also stimulates the release of aldosterone, which causes a further rise in blood pressure.¹ Valsartan is an angiotensin II receptor blocker for the treatment of hypertension, heart failure, and left ventricular failure or left ventricular dysfunction postmyocardial infarction. Its effects primarily result from selective blockade of the angiotensin type I receptor in vascular smooth muscle and adrenal gland.² Valsartan effectively reduces systolic blood pressure (SBP) and

diastolic blood pressure (DBP).³ Given its effects on angiotensin blockade, valsartan may also reduce proteinuria and have other beneficial effects in patients with underlying kidney disease.⁴ For these reasons, valsartan is an attractive drug for use in hypertension. Valsartan is a highly selective, orally available antagonist of the angiotensin Type 1 (AT₁) receptor. It is indicated for treatment of mild to moderate essential hypertension. Experimental studies have confirmed the abolition or attenuation of angiotensin II (AII)-related effects, such as

vasoconstriction, cell growth promotion and aldosterone release. In humans, valsartan is rapidly absorbed with maximal plasma concentrations occurring 1-2 h after oral administration. The elimination half-life comes to about 7- 8 h, valsartan is metabolised to a negligible extent and most of the drug is excreted via the faeces. There is no dose adjustment required for patients with a creatinine clearance >10 ml/min.

In comparison to other antihypertensive drugs valsartan therapy leads to similar blood pressure reductions, while exhibiting a favourable tolerability profile. Preliminary studies suggest beneficial effects in patients with hypertensive end-organ damage such as renal disease and left ventricular hypertrophy. Furthermore, the drug is evaluated for its efficacy in heart failure and patients' post-myocardial infarction.⁵ The efficacy, tolerability and safety of valsartan have been demonstrated in large-scale studies conducted in different population in hypertension, heart failure (HF) and post-myocardial infarction (MI). Many studies have demonstrated the efficacy of valsartan in lowering blood pressure in a variety of patient populations, several of them are investigated higher doses of the drug. This study focuses on revealing safety and efficacy of valsartan at higher doses in Bangladeshi population. From the data available now, daily dose of Valsartan 160 mg consistently provides greater BP-lowering efficacy than the 80-mg dose. Current study is planned to further evaluate the efficacy, safety and tolerability of daily dose of Valsartan 160 and 320 mg in the treatment of essential hypertension under normal practice conditions.

Methodology

Patients and materials

This is a multi-center, open-label, observational, non-comparative, clinical decision based titration, involving about 31 centers in Bangladesh. A total of 334 newly diagnosed adult patients with Stage I (SBP 140-159 mmHg/DBP 90-99 mmHg) or Stage II (SBP > 160 mmHg/DBP > 100 mmHg) essential hypertension received valsartan as determined by their

physician were included to allow for an assessment of efficacy, safety and tollerability. Pregnant or lactating mother, patient with severe medical condition(s) that in the view of the Investigator prohibits participation in the study and known Hypersensitivity to valsartan or any of the components in the formulation are excluded. The total duration of treatment with valsartan was 16 weeks. At week 0, patient received valsartan at a dose of 160 mg or 320 mg as deemed necessary by physician. At Visit 2, the Investigator decided the dose of valsartan which the patient continued for the remainder of the study, based on the blood pressure control. If the blood pressure was not controlled (SDBP ≥ 90 mm Hg and/or SSBP ≥ 140 mmHg) the Investigator titrated the dosage of valsartan to 320 mg. If the blood pressure was controlled (SDBP <90 mmHg and/or SSBP <140 mmHg), the dose of valsartan was also titrated to 320 mg in some patients, based on investigator's clinical judgment for a further reduction (better control) in blood pressure. This dose was then continued for the remainder of the study period. In general concomitant therapy was allowed with proper documentation however, Other anti-hypertensive agents (including diuretics), that might interfere with evaluation of efficacy and tolerability, was avoided as far as possible, and if used, the details were recorded.

Outcome assessment

Patients were assessed five times over the study period of 16 weeks. At the commencement baseline parameters as well concomitant treatment status was assessed along with the enrollment criteria. In the following three assessments in Week 4, 8, and 12 treatment response were assessed along with history of concomitant Treatment and adverse event. After completion of 16th week valsartan therapy in addition to the measurement taken in the previous assessments a global assessment of treatment outcome was done on a 4-point scale by the investigator and the patient.

Primary parameter for efficacy was percentage responders to valsartan at 16 weeks, defined as

SBP <140 mmHg and/or DBP <90 mmHg or a reduction >10 mmHg for DBP and/or >20 mmHg SBP versus baseline values. Reduction in MSSBP and MSDBP, Control rate (% patients) achieving SBP <140 mmHg and DBP <90 mmHg at end point and Global assessment of efficacy and tolerability to valsartan treatment by the physician and patient. Tolerability/safety assessments consisted of monitoring and recording all adverse events and serious adverse events. Global assessment of the physicians and patients evaluation about the efficacy and tolerability was done on a 4-point scale. Data collection activity was conducted abiding by the principles of Good Clinical Practice, the declaration of Helsinki. To protect the confidentiality of data and to preserve patient anonymity, each subject was assigned with a unique identifying number.

Data analysis

This is a descriptive intention to treat (ITT) analysis. Baseline characteristics were described by summary statistics. Assessment of efficacy was done based on the number of the patients with a controlled diastolic pressure and systolic pressure. The efficacy analysis of continuous variables was done descriptively by presenting summary statistics and confidence intervals. The safety and tolerance evaluation was done based on the frequency and nature of reported adverse events. Paired t test was used to assess mean BP between the measurement at baseline and end line.

Result

Patient characteristics

Out of 334 Adult hypertensive patients 7.2% were aged less than 40 years, 23.1% were aged between 40–49 years, 41.0% were aged between 50–59 years and 28.7% were aged above 60 years. Mean age of the patient was

53.31±8.8 years. Among them 56.5% were male and 43.4% were female. Around one percent of them had BMI <18.5 kg/m², 47.3% had BMI between 18.5 to 25 kg/m² and 51.8% had BMI over 25 kg/m².

Table-I
Age sex and BMI of patients of the study population

	Frequency	Percent
Age		
< 40 years	24	7.2
40 - 49 years	77	23.1
50 - 59 years	137	41.0
>= 60 years	96	28.7
Sex		
Male	189	56.6
Female	145	43.4
BMI		
< 18.5	3	0.9
18.5 - 25	158	47.3
> 25	173	51.8

Age Male 53.2±9.3 year Female 53.5±8.0 year

Treatment profile

Among the study subjects medication were changed at 2nd visit in 4.5%. The percentage was 2.4%, 1.8% and 2.4% in next three successive visits respectively. New concomitant treatment was started in 3.6% cases at 2nd visit and 1.3% in 3rd visit and in 1.2% at 4th visit. Adverse event was reported in three cases each (0.9%) at 2nd, 3rd visit and 4th visit and in 2 cases (2.4%) at 5th visit. Total adverse event occurred in 11 (3.3%) patients. At the commencement of the study 1.2% was prescribed with valsartan 320mg rest received Valsartan 160 mg. At 2nd visit 3.9% were given with Valsartan 320 mg. At 3rd, 4th and 5th visit patient requiring Valsartan 320 mg rose to 6.3%, 8.1% and 10.5% respectively. (Table II)

Table-II
Treatment profile of the study population

Treatment profile	Visit 1 (N=334)	Visit 2 (N=334)	Visit 3 (N=334)	Visit 4 (N=334)	Visit 5 (N=334)
Dose: 160mg once daily	330 (98.8)	321 (96.1)	313 (93.7)	307 (91.9)	299 (89.5)
Dose: 320 mg once daily	4 (1.2)	13 (3.9)	21 (6.3)	27 (8.1)	35 (10.5)
Change in medication	-	15 (4.5)	8 (2.4)	6 (1.8)	8 (2.4)
Concomitant treatment	-	12 (3.6)	4 (1.3)	4 (1.2)	-
Adverse event	-	03 (0.9)	3 (0.9)	3 (0.9)	2 (0.6)

*Figures in parenthesis denotes percentage

Assessment of BP reduction

A clearly evident decline is evident in mean Systolic BP and diastolic BP over the study duration (Figure 1). The fall of mean Systolic BP is steeper than that of Diastolic BP. Control rate is considered as percentage of patients with SBP <140 mmHg and DBP <90 mmHg at all 4 visits. At 2nd visit 19.8% had their BP controlled, at 3rd visit the percentage is 36.5% at 4th visit the percentage is 60.2% and at 5th visit 81.7% had their BP controlled (Figure 2). Change in BP and Heart rate was assessed at the end of the treatment in comparison to baseline parameters through paired t test. Average reduction of 30.4 ± 17.4 mmHg was seen in systolic BP, 18.4 ± 11.2 mmHg in diastolic BP and 3.5 ± 3.1 /minute in heart rate. The reduction was highly significant in both systolic BP and diastolic BP and heart rate as well ($P < .001$). At 16 weeks only 3.4% were found to be refractory to the treatment. (Table III)

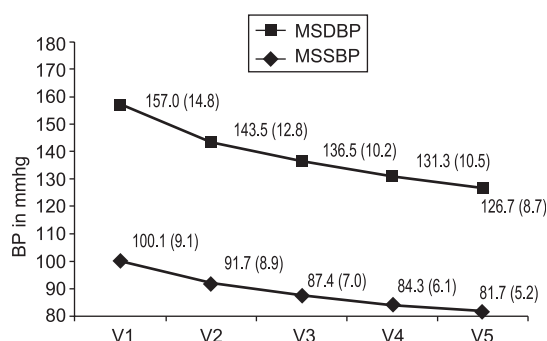


Fig.-1: Trend of blood pressure reduction

Global assessment of safety and efficacy

Efficacy of the treatment was assessed based primarily on the opinion of the patient and physician concerned on four point scale. Around 30.2% of the physician rated the efficacy as excellent, around 56% rated as very good and 13.8% rated as good. Regarding patient's opinion around 26.9% rated the efficacy as excellent, around 57.8% rated as very good, around 15.3% rated as good. Tolerability of the treatment was also assessed based on the opinion of the patient and physician concerned on four point scale. Around 34.1% of the physician rated the efficacy as excellent, around 49.7% rated as very good and 16.2% rated as good. Regarding patient's opinion around 36.8% rated the tolerability as excellent, around 47% rated as very good, around 16.2% rated as good. (Table IV)

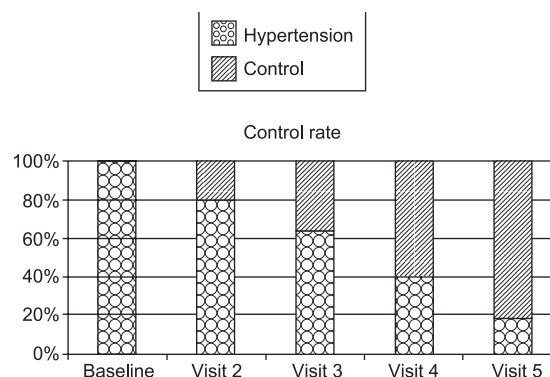


Fig.-2: Trend of control rate at each visit.

Table III
Reduction of BP after treatment

Variables	Assessment time		Paired mean difference		
	Baseline	End line	difference	t value	P value
SBP (N=334)	157.0±14.8	126.7 ± 8.7	30.4 ± 17.4	33.2	.001*
DBP (N=334)	100.1 ± 9.9	81.7 ± 5.4	18.4 ± 11.2	31.6	.001*
Heart rate (N=334)	77.8 ± 5.4	74.3 ± 5.2	3.5 ± 3.1	1.8	.001*

*Percentage responder at the end of the trial 96.6%

Table IV
Global assessment of efficacy and tolerability

Assessmentscale	Assessment of efficacy				Assessment of tolerability			
	Physician's assessment		Patient's assessment		Physician's assessment		Patient's assessment	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Excellent	101	30.2	90	26.9	114	34.1	123	36.8
Very Good	187	56.0	193	57.8	166	49.7	157	47.0
Good	046	13.8	051	15.3	054	16.2	054	16.2
Total	334	100.0	334	100.0	334	100.0	334	100.0

Discussion:

Hypertension is one of the most important preventable causes of premature death worldwide and it is one of the three most important risk factors for cardiovascular disease and is a major burden for global health.⁶⁻⁸ Prescribers are faced with many data from an expanding pool of large studies, yet, beyond the sheer time needed to update the evidence base, it can be difficult to translate and synthesize results into rational treatment decisions for individual patients.^{9,10} The benefits of antihypertensive drugs have been confirmed by the largest evidence base from clinical trials in medicine. Many classes of drugs are available for treatment, and debate has raged about whether the benefits of treatment are purely a function of the quality of blood pressure control or whether the type of drug used might also be a powerful determinant of outcome. A meta-analysis of trials of treatment for hypertension with the newer drugs found that ACE inhibitors and calcium channel blockers were likely to reduce cardiovascular morbidity and mortality by the same order of magnitude as β blockers or thiazides,¹¹ but such analyses have insufficient statistical power to detect cause specific outcomes with regard to specific drugs.

The renin angiotensin system (RAS) is a key element in the regulation of blood pressure as well as in electrolyte and fluid homeostasis. The active hormone of the RAS is angiotensin II, which is formed from angiotensin I by ACE. Angiotensin II binds to specific receptors which are located in the cell membranes of various

tissues. The receptor subtype AT1 is responsible for all the known actions of angiotensin II. Angiotensin II has a wide variety of physiological effects, principally those involved either directly or indirectly, in the regulation of blood pressure (BP). As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition it promotes sodium retention and stimulation of aldosterone secretion, and also stimulates thirst and release of antidiuretic hormone.

The use of ARB for first-line therapy for essential hypertension is well documented.¹² Valsartan, an angiotensin II receptor blocker with selectivity for the type I receptor subtype, is an established drug for the treatment of essential hypertension. It blocks the action of Angiotensin II irrespective of its origin.¹³ According to Black et al,¹⁴ in hypertension, valsartan exhibits dose-dependent efficacy in reducing both systolic and diastolic BP over the once-daily dose range of 80-320 mg; doses as high as 640 mg/day have been studied and found to be efficacious and safe. They reported that the magnitude of the BP lowering effect is comparable with that demonstrated with angiotensin-converting enzyme (ACE) inhibitors; however, they reported valsartan as more favorable and tolerable, with a significantly lower incidence of cough and only rare reports of angio-oedema.

Current study focused on the use of the high dose of valsartan in the treatment of essential hypertension with documented endpoint benefit in Bangladeshi population. The study only restricted to native patients with Stage I or Stage

II essential hypertension. The study used dose regimen of 160 mg and 320 mg. As the efficacy of the drug under study has already been documented in numerous clinical trials in different population, the primary goal of our current effort is to validate the treatment modality in Bangladeshi population. In the present study at the commencement 98.8% received valsartan 160 mg. Increment in dose, although minimum, demonstrates a relative under response or non response with the initial therapy, however leaves the ground for upward titration for achieving the target BP. These allows physician to minimize untoward effect exerted by administration of higher dose of single drug. At successive visits 3.9%, 6.3%, 8.1% and 10.5% received higher doses (320 mg) of valsartan.

In the study concomitant treatment for comorbidity or other conditions were allowed and additional concomitant treatment was added where warranted which have no potential for alter the anti-hypertensive activity. New concomitant treatment was started in 3.6% cases at 2nd visit and 1.3% in 3rd visit and in 1.2% at 4th visit.

One of the major outcome parameter set for the study was the percentage of participant having BP controlled that is a SBP <140 mmHg and DBP <90 mmHg or a reduction >10 mmHg for DBP and/or >20 mmHg SBP versus baseline values at 16 weeks. Percentage control at the end of the trial was 96.6%, which is quite high for response of a treatment regimen. Besides, Reduction in mean SBP and mean DBP was also assessed as efficacy parameter. A clearly evident decline is evident in mean systolic and diastolic BP. Reduction in mean systolic BP, diastolic BP and heart rate ($P < .001$) was evident through paired comparison from baseline to end of the study. Average reduction of 30.4 ± 17.4 mmHg was seen in systolic BP and 18.4 ± 11.2 mmHg in diastolic BP.

Efficacy of the treatment was also assessed based on the opinion of the patient and physician concerned on four point assessment scale. A potential limitation embedded in the design that might hinder the study goal was that for safety

data, as we had to depend on the turnout of patient at final follow-up. However, in the current study out of 334 participants no attrition was occurred. Around 30.2% of the physician rated the efficacy as excellent, around 56% rated as very good and 13.8% rated as good. Regarding patient's opinion around 26.9% rated the efficacy as excellent, around 57.8% rated as very good, around 15.3% rated as good. Regarding tolerability around 34.1% of the physician rated the efficacy as excellent, around 49.7% rated as very good and 16.2% rated as good. Regarding patient's opinion around 36.8% rated the tolerability as excellent, around 47% rated as very good, around 16.2% rated as good. Neither the patient nor the physician rated the efficacy or safety as poor.

According to the data of current study a large proportion of patients benefit from the high dose treatment of Valsartan. Considering the overall treatment effect, as many as 96.6% of patients showed a response to the treatment. All the three parameter used for efficacy assessment namely, mean BP reduction, percentage control and satisfaction by both physician and patients confirms the efficacy of valsartan as effective antihypertensive. ARBs are generally very well tolerated. The ELITE II study of 3,152 patients aged over 60 years with heart failure showed that patients taking ARB were significantly less likely to discontinue treatment because of adverse effects.¹⁵ With an asymptomatic condition such as hypertension, long-term compliance can be a problem and side effects have been shown to lead to non-compliance, or to under-treatment with suboptimal doses.¹⁶ Hypertensive patients tend to be elderly and often have other medical conditions. It is therefore important that long-term treatment with anti-hypertensive drugs do not interact with other medications.¹⁷

Safety and tolerability assessments focused on monitoring and recording of all adverse events and serious adverse events. At final follow-up, in addition to repetition of the baseline measurements and examinations, data on safety of the drug was collected by inquiring and

recording all adverse events or serious adverse events. Any untoward event in a patient or revealed through clinical investigation found in patient during the study period which may or may not have a causal relationship with given treatment was recorded and reported by participating physician. Total adverse event occurred in 11 (3.3%) patients. Which is quite low for the treatment of hypertension. Consistent with its angiotensin receptor-blocking effects, valsartan also reduces circulating levels of biochemical markers that are associated with angiotensin II-mediated endothelial dysfunction and Cardio Vascular risk. In clinical trials, adverse events during valsartan treatment were similar to those occurring with placebo.

Study by Oparil et al compared the efficacy and safety of valsartan 320 mg with placebo in the treatment of patients with essential hypertension and reported significant reductions in both MSDBP and MSSBP at end point compared with placebo. There were no clinically or statistically significant changes in laboratory values during treatment as well as no notable side effect. They concluded that valsartan is both effective and safe in reducing blood pressure in adults with essential hypertension.¹⁸Schaefer et al also demonstrated a good tolerability of the drug even in children with hypertension.¹⁹

Our study substantiate similar standpoint to the safety and efficacy of Valsartan at higher doses revealed in other population. Current study upholds the use of the drug at higher dose effective and safe antihypertensive treatment modality. Current study is a prospective observational study, neither randomized nor blinded, which to some extent limits credibility of the findings. However, the intent of the researcher was to assess the safety and efficacy of the treatment modality in our population which was already done by large, well designed and well powered studies in wide range of population and settings. Further investigation could preferably be done with better study design for even stronger evidences.

Conclusion:

16 week treatment with valsartan at 160mg daily or 320 mg daily is an effective treatment for patients with essential hypertension. The drug

is found to be well tolerated with minimal adverse event during the course of treatment.

Acknowledgement:

The study has received an unconditional grant and support from, Novartis Pharmaceuticals Bangladesh. The interventional drug for the study used in the study was Diovan[®] tablet containing 160 mg or 320 mg Valsartan is a registered product of Novartis.

Study Group:

Prof. MA Zaman, Prof. A.K.M Anwarullah, Prof M. N. Nag, Prof. Mian Mashud, Prof Dr. Md. Shahabuddin Khan, Dr. Abu Azam, Dr. Asia Khanam, Dr. Md. Nazrul Islam, Dr. M Mahabubur Rahman, Dr. Kazi Mohibur Rahman, Dr. M. Muhibur Rahman, Dr. Nabiul Hassan Rana, Prof. Dr. Shakwat Hossain, Dr. Md. Anisur Rahman, Dr. K.H. Haq, Dr. Tarikul Islam, Dr. G.C. Dhar, Dr. Nur M. Abdal, Dr.Md.Mahbubur Rahman, Dr.M. Rezaul Karim, Dr. Sukanta Aich, Dr. Md. Ibrahim Chowdhury, Dr. Shafiul Azam, Dr. M. A. Kashem, Dr. Shahabul Huda Chowdhury, Dr. S.U. Kumer Uttam, Dr. Shah Jamal Hossain, Prof. Mrinal Kanti Das, Dr. Moazzem Hossain, Dr. M.R. Khan, Dr. Jayanta Kumer Podder.

Reference:

1. Beevers G, Lip GYH, O'Brien E. The pathophysiology of hypertension. *BMJ* 2001;322: 912-916.
2. Novartis Pharmaceuticals Corporation. DIOVAN[®] Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; revised November 2007.
3. Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; 54: 299-311.
4. Chrysant SG, Chrysant GS. Clinical experience with angiotensin receptor blockers with particular reference to valsartan. *J Clin Hypertens (Greenwich)* 2004; 6: 445-451.
5. Liu PP, Maggioni A, Velazquez EJ. Use of valsartan in post-myocardial infarction and heart failure patients. *J Renin Angiotension Aldosterone Synt.* 2006; 7(1): 19-22.
6. Ezzati M, Lopez AD, Rodgers A, Vander Hoom S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;360:1347-1360.
7. He FJ, MacGregor GA. Cost of poor blood pressure control in the UK: 62,000 unnecessary deaths per year. *J Hum Hypertens* 2003; 17:455-457.
8. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;360:1347-1360.

9. Appel LJ. The verdict from ALLHAT - thiazide diuretics are the preferred initial therapy for hypertension. *JAMA* 2002;288:3039-3042.
10. Williams B. Drug treatment of hypertension. *BMJ* 2003;326:61-62.
11. Collaboration Blood Pressure Lowering Treatment Trialists. Effects of angiotensin converting enzyme inhibitors, calcium antagonists and other blood pressure lowering drugs on mortality and major cardiovascular morbidity. *Lancet* 2000;356:1955-1964.
12. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; 157: 2413-2446.
13. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; 54: 299-311.
14. Black HR, Bailey J, Zappe D, Samuel R. Valsartan: more than a decade of experience. *Drugs* 2009;69(17):2393-2414.
15. Pitt B, Poole-Wilson PA, Segal R et al . Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial - the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; 355:1582-1587.
16. Laeis P, Puchler K, Kirch W. The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction. *Journal of Hypertension*. 2001;19:S21-S32
17. Oparil S, Dyke S, Harris F, Kief J, James D, Hester A, Fitzsimmons S. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996;18(5):797-810.
18. Oparil S, Dyke S, Harris F, Kief J, James D, Hester A, Fitzsimmons S. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996 Sep-Oct;18(5):797-810.
19. Schaefer, F; Coppo, R; Kadwa, MY; Schlosshauer, R3; Zhang, Y. Efficacy and Safety of Valsartan in Hypertensive Children 6 Months To 5 Years of Age: A Randomized, Double-Blind, Dose-Response Study. *Journal of Hypertension* 2010; 28: 473