การเปรียบเทียบผลการลดความดันเลือด 24 ชั่วโมงของยาโลซาร์แทน และไฮโดรคลอโรไธอะไซด์เมื่อใช้เป็นยาเดี่ยวและใช้ร่วมกัน ในผู้ป่วยความดันเลือดสูงชนิดปฐมภูมิ

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COMPARATIVE 24-HOUR ANTIHYPERTENSIVE EFFECT OF LOSARTAN AND HYDROCHLOROTHIAZIDE AS MONOTHERAPY OR IN COMBINATION IN PRIMARY HYPERTENSIVE PATIENTS

Miss Kunyarat Chantrathada

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การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาเปรียบเทียบผลการลดความดันเลือด24ชั่วโมงของยาโลซาร์แทนเมื่อใช้เป็นยาเดี่ยวกับการใช้ร่วมกับยาไฮโดรคลอโรไธอะไซด์และผลต่อรูปแบบการลดความดันเลือดในผู้ป่วยที่มีความดันเลือดแบบ dippers หรือ nondippers โดยใช้เครื่องมือวัดความดันเลือดอัตโนมัติชนิดพกพาโดยศึกษาในผู้ป่วยความดันเลือดสูงชนิดปฐมภูมิขั้นอ่อนและปานกลาง 32 ราย ณ แผนกผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์ หลังจากรับประทานยาหลอกเป็นเวลา 1 สับดาห์ หรืออย่างน้อย 5 ครึ่งชีวิตของยาลดความดันเลือดที่ใช้อยู่ ผู้ป่วยที่มีค่าความดันเลือด systolic blood pressure(SBP)ขณะนั่ง140-179 มิลลิเมตรปรอท หรือdiastolic blood pressure(DBP) ขณะนั่ง 90-110 มิลลิเมตรปรอท และค่าความดันเลือดช่วงกลางวันจากเครื่องมือวัดความดันเลือดอัตโนมัติชนิดพกพา ≥ 130/80 มิลลิเมตรปรอท จะได้รับยาไฮโดรคลอโรไธอะไซด์ 12.5 มิลลิกรัมต่อวัน หรือยาโลซาร์แทน 50มิลลิกรัม ต่อวัน เป็นเวลา 4 สัปดาห์ และสลับชนิดยาในอีก 4 สัปดาห์ถัดมา หลังจาก 8 สัปดาห์ ผู้ป่วยจะได้รับการจัดเป็นกลุ่มที่มีความดันเลือดลดลงตามเกณฑ์เมื่อได้รับยาโลซาร์แทน 50มิลลิกรัม(sytolic/diastolic blood pressure <140/90 มิลลิเมตรปรอท) เมื่อวัดที่คลินิกในขณะนั่ง และกลุ่มที่ความดันเลือดไม่ลดลงตามเกณฑ์ ผู้ป่วยในกลุ่มแรกจะได้รับยาโลซาร์แทน 25มิลลิกรัม หรือ ยาผสมโลซาร์แทน 50มิลลิกรัม กับไฮโดรคลอโรไธอะไซด์ 12.5มิลลิกรัม ครึ่งเม็ด ต่อวันโดยการสุ่ม ส่วนกลุ่มหลังจะได้รับยาโลซาร์แทน 100 มิลลิกรัม หรือ ยาผสมโลซาร์แทน 50มิลลิกรัม กับไฮโดรคลอโรไธอะไซด์ 12.5มิลลิกรัม หนึ่งเม็ดต่อวัน อีกเป็นระยะเวลา 4 สัปดาห์ เมื่อรับประทานยาจนครบกำหนดตามเวลาแล้วจะทำการวัดความดันเลือดทั้งที่คลินิกและด้วยเครื่องวัดความดันเลือดอัตโนมัติชนิดพกพาทุกครั้ง

ยาโลซาร์แทนขนาด 50 มิลลิกรัมต่อวันสามารถลดความดันเลือดได้ตลอด 24 ชั่วโมง ขณะที่ยาไฮโดรคลอโรไธอะไซด์ขนาด 12.5 มิลลิกรัมต่อวันสามารถลดความดันเลือดได้เฉพาะเมื่อวัดที่คลินิกเท่านั้น ยาโลซาร์แทนขนาด 50 มิลลิกรัมสามารถลด BP loads ลงได้มากกว่ายาไฮโดรคลอโรไธอะไซด์ 12.5 มิลลิกรัมไม่ว่าจะพิจารณาในด้านความถี่ ขนาด หรือพื้นที่ใต้โค้งความดันเลือดที่อยู่เหนือเกณฑ์(AUC) นอกจากนี้ยังมีแนวโน้มที่จะทำให้ผู้ป่วยในกลุ่ม nondippers เปลี่ยนแปลงรูปแบบความดันเลือดไปเป็นรูปแบบ dipper ในกลุ่มผู้ป่วยที่ความดันเลือดลดลงถึงเกณฑ์ปกติด้วยยาโลซาร์แทนขนาด 50 มิลลิกรัม เมื่อลดขนาดยาเป็น 25 มิลลิกรัม พบว่าสามารถลดความดันเลือดลงได้ใกล้เคียงกับเมื่อได้รับยาโลซาร์แทนขนาด 50 มิลลิกรัม ในกลุ่มผู้ป่วยที่ความดันเลือดไม่สามารถลดลงสู่เกณฑ์ปกติด้วยยาโลซาร์แทนขนาด 50 มิลลิกรัม เมื่อเพิ่มขนาดยาโลซาร์แทนเป็น 100 มิลลิกรัม มีผลลดความดันเลือดเพิ่มขึ้นอีกน้อยมาก ขณะที่การให้ยาผสมโลซาร์แทน 50 มิลลิกรัมร่วมกับไฮโดรคลอโรไธอะไซด์ 12.5 มิลลิกรัมจะลดความดันเลือดตลอด 24 ชั่วโมงเพิ่มขึ้นอีกได้ดีกว่า นอกจากนี้อัตราการตอบสนอง และร้อยละของผู้ป่วยที่มีค่าความดันเลือดเข้าสู่เกณฑ์ปกติหลังจากได้รับยาผสมจะมีค่ามากกว่าการเพิ่มขนาดยา การใช้เครื่องมือวัดความดันเลือดอัตโนมัติชนิดพกพาสามารถแสดงผลการตอบสนองต่ายาได้ชัดเจนกว่าการวัดความดันเลือดที่คลินิก ค่า T:P ratio แตกต่างกันมากระหว่างผู้ป่วยแต่ละราย หลังจากได้รับยาโลซาร์แทน 50 มิลลิกรัมเป็นยาเดี่ยว หรือ ยาผสมโลซาร์แทน 50 มิลลิกรัม ร่วมกับยาไฮโดรคลอโรไธอะไซด์ 12.5 มิลลิกรัมวันละครั้ง ค่า T:P ratio ไม่ต่างกันมากนักและมีค่าเฉลี่ยอยู่ในช่วง 39-52% ขณะที่ค่า T:P ratio หลังจากได้รับยาไฮโดรคลอโรไธอะไซด์ 12.5 มิลลิกรัมในลักษณะยาเดี่ยววันละครั้ง ค่า T:P ratio อยู่ในช่วง 31-33% และผลการลดความดันเลือดเหล่านี้ไม่ได้ทำให้ผู้ป่วยเกิดภาวะหัวใจเต้นเร็วกว่าปกติ อาการข้างเคียง หรืออาการไอแต่อย่างใด

ภาควิชา.....เภสัชกรรม.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เภสัชกรรม.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา..... .2543..... ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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KUNYARAT CHANTRATHADA: COMPARATIVE 24-HOUR ANTIHYPERTENSIVE EFFECT OF LOSARTAN AND HYDROCHLOROTHIAZIDE AS MONOTHERAPY OR IN COMBINATIONIN PRIMARY HYPERTENSIVE PATIENTS. THESIS ADVISOR: ASSOC. PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D. THESIS CO-ADVISOR: Dr. SOMKIAT SANGWATANAROJ, M.D. 207 PP. ISBN 974-13-0769-1

The purpose of this study was to examine 24-hour antihypertensive effects of losartan as monotherapy or in combination with low dose hydrochlorothiazide and the effects of these medications on circadian blood pressure variation in dippers/nondipers hypertensive patients by using 24-hour ambulatory blood pressure monitoring(ABPM) machine. The study was achieved in thirty-two mild to moderate primary hypertensive patients in out-patient department at King Chulalongkorn Memorial Hospital. After one week placebo run-in period or on placebo for at least 5 T1/2 to wash out of any previously taken antihypertensive drugs, mild to moderate hypertensive patients whose office systolic blood pressure(SBP) 140-179 mmHg or diastolic blood pressure(DBP) 90-110 mmHg and mean daytime ambulatory BP≥130-80mmHg were allocated to receive 12.5mg dose of HCTZ or losartan 50mg once daily for 4 weeks and cross over for another 4 weeks. After 8 weeks, patients were categorized to losartan 50 mg normalized group(office SBP/DBP<140/90mmHg) and losartan 50mg non-normalized group. Patients in losartan normalized group were randomly allocated to receive either losartan 25mg or half tablet of losartan 50mg plus HCTZ12.5mg once daily. Either losartan 100mg or one tablet of losartan50mg plus HCTZ 12.5mg once daily were prescribed to losartan non-normalized patients for another 4 weeks. The office blood pressure and the ambulatory blood pressure were monitored at the end of each period.

Losartan 50 mg significantly reduced blood pressure of the patients throughout 24 hours while hydrochlorothiazide 12.5 mg could reduce office blood pressure only. Losartan 50 mg also induced higher reduction in BP loads when compared to hydrochlorothiazide 12.5 mg whether considering the frequency, magnitude or AUC above the normal range. Besides, with losartan 50 mg, the circadian rhythm of blood pressure of nondippers might be transformed to dipper patterns. In losartan 50 mg normalized group, decreasing dosage of losartan to 25 mg could reduce blood pressure to nearly the same extent as losartan 50 mg. In losartan 50 mg non-normalized group, increasing the dosage of losartan to 100 mg produce only small further reduction of blood pressure while using the combination of losartan 50 mg plus hydrochlorothiazide 12.5 mg could induce more pronounced further antihypertensive effects. Greater rate of response and higher percentage of normalized patients were also found after treatment with the combination drugs as compared to the increased doses of the single drug. Using ABPM machine could demonstrate the antihypertensive effects of the drug more thoroughly than the office measurement. T:P ratio varied extensively among individual patients. After losartan 50 mg or losartan 50 mg plus hydrochlorothiazide12.5 mg once daily, the T:P ratio was ranged 39 to 52 %, while the T:P ratio obtained after hydrochlorothiazide 12.5 mg once daily was ranged 31 to 33%. The antihypertensive effects were generated without the reflex tachycardia or intolerance effects or even cough.

Department……Pharmacy…….Student's signature……..…..…….
Field of study…….....Pharmacy……..…...Advisor's signature……..……..
Academic year……..….2000…… Co-advisor's signature……..…….

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LIST OF ABBREVIATIONS

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
AIIRA	angiotensin II receptor antagonist
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
bpm	beat per minute
BUN	blood urea nitrogen
cm	centimeter
Cr	creatinine
DBP	diastolic blood pressure
HDL	high density lipoprotein
HR	heart rate
Hr	hour
Ht	height
Kg	kilogram
MAP	mean arterial pressure
mg	milligram
mmHg	millimeter mercury
min	minute
no	number
SBP	systolic blood pressure
SD	standard deviation
T:P ratio	trough to peak ratio
Wt	weight
OBP	office blood pressure

CHAPTER I

INTRODUCTION

The 1994 US National Health and Nutrition Examination Survey(NHANES)III indicated that only 27 % of patients have their blood pressure controlled at the level of 140/90 mmHg .[1] A problem in the management of hypertension is the increasing number of treated but uncontrolled hypertensive patients. [2] These data are significantly important because data from MRFIT study indicated that cumulative risk for coronary artery disease increases with higher blood pressure levels. [3] It is quite clear that patients with adequately controlled blood pressure are at lower cardiovascular disease risk than those who are not. [4-5] The Hypertension Optimal Treatment(HOT) study has shown that the best results for reducing cardiovascular events were seen at a blood pressure of 139/83 mmHg. Important factors contributing to inadequate blood pressure control include the lower efficacy of some antihypertensive drugs and poor compliance . Although increasing the doses of some antihypertensive drugs may result in greater blood pressure reduction, the side effects profiles may become unacceptable. Thus , many antihypertensive drugs are limited in efficacy by dose-dependent side effects.

Whole day blood pressure recordings in healthy subjects are characterized by a nocturnal fall in blood pressure values. In patients with essential hypertension , it has been postulated that the lack of this nocturnal fall(nondipper) is associated with more serious end–organ damage, such as left ventricular hypertrophy, microalbumunuria, or

cerebrovascular diseases [6-9] than occurs in patients whose blood pressure falls during the night(dipper). Recently, study also showed that the nocturnal fall in blood pressure was less during high sodium diet with high sodium sensitivity. [10] Although the role of salt sensitivity in hypertension has not been fully clarified, proposed mechanisms include expansion of fluid volume [11], inappropriate suppression of renin-angiotensin system [12,13], abnormal response of sympathetic nervous activity [11,14] and the intracellular accumulation of sodium and calcium .[12] Data from Japanese study suggest that the NaCl loading blunted nocturnal decline in blood pressure[15] and the diminished nocturnal fall is restored by sodium restriction, indicating that the circadian rhythm of blood pressure shifted from a nondipper to a dipper pattern.[16] Diuretic-based treatment of patients with hypertension prevents the development of cardiovascular complications[17] and has been recommended as first line medication in management of hypertension, moreover, it has been shown that diuretics can restore nocturnal blood pressure decline in a manner similar to sodium restriction ,[18] thus diuretic-based treatment may have an additional therapeutic advantage of reducing risk for cardiovascular complications by transforming the circadian rhythm of blood pressure from nondipper to dipper.

Angiotension II Receptor antagonists are the newest class of antihypertensive agents, and there is growing evidence that they are efficacious and well tolerated. Losartan is the prototype of this class. The efficacy of Losartan have been proved in many studies that it is as effective and well–tolerated as enalapril. [19,20,21] Trough to peak ratios of the mean change in supine diastolic pressure indicated that losartan had sustained antihypertensive effects at 24- hours that were not the results of large peak

effects.[22] Findings in hypertensive patients with chronic renal disease also showed that once-daily Losartan, given as monotherapy or in combination with other antihypertensive drugs was effective in reducing blood pressure in these patients and was well tolerated including those on hemodialysis. [23] The addition of Hydrochlorothiazide to Losartan produced a significant and dose-related reduction in blood pressure at trough. [24] The data from comparative study and tolerability of Angiotensin II Receptor Antagonists showed that indeed cough is not an adverse effect of AIIRA . Losartan caused a low prevalence of spontaneous report of cough in patients with hypertension compare to lisinopril . [25] Moreover , Losartan has been shown to increase urinary uric acid in individuals who are normotensive and hypertensive patients. [24,26] The addition of Losartan has been shown to prevent the diuretic-induced increase in serum uric acid level. [24]

Blood pressure measurement is one of indicators for assessment the response of antihypertensive therapies. Findings from studies found that target-organ damage in essential hypertension is more closely associated with ambulatory than with clinic blood pressure .[27-28] Since target-organ damage is a powerful predictor of morbidity and mortalilty in hypertension , ambulatory might offer prognostic information beyond that provided by clinic blood pressure . An association between night time blood pressure and target–organ damage, reflecting the potential detrimental effect of a persistent pressure overload, has been shown in several cross-sectional studies . [29-31] Moreover ,ambulatory blood pressure study suggested that ambulatory blood pressure stratified cardiovascular risk in essential hypertension independent of clinic blood pressure and other traditional risk factors . Cardiovascular morbidity is low in white

coat hypertension and exceedingly high in women with ambulatory hypertension and absent or blunted blood pressure reduction from day to night.[32]

The previous works mentioned above had shown the importance of monitoring blood pressure response by 24-hour ambulatory measuremant and the effects of antihypertensive therapies on circadian blood pressure .However, data on the effects of Hydrochlorothiazide and Losartan on circadian blood pressure rhythm in Thai patients with essential hypertension are limited.

In this study, therefore we investigate the effects of angiotension II receptor antagonists , losartan ,as monotherapy or in combination with hydrochlorothiazide and hydrochlorothiazide therapies on circadian pattern of blood pressure and 24- hour blood pressure lowering effects in both dipper and nondipper hypertensive patients .

Objectives:

1. To examine 24-hour antihypertensive effects of Losartan as monotherapy or in combination with low dose Hydrochlorothiazide

2. To investigate the effects of low dose Hydrochlorothiazide and/or Losartan on circadian blood pressure variation in dipper/nondipper hypertensive patients

CHAPTER II

REVIEW OF LITERATURE

1.Hypertension

Hypertension is the most prevalent condition for which people receive prescription medications. Its occurences in the United States increases with age, and it is more prevalent in African American and in the lesser educated and lower socioeconomic classes.[33]

Blood pressure is a continuous variable, it is impossible to define a cutoff point below which blood pressure is normal and above which the pressure is abnormally high. After screening, the diagnosis of hypertension is confirmed when the average of two or more diastolic blood pressure(DBP) measurements visits are 90 mmHg or higher or the average of two or more systolic blood pressure measurements(SBP) is consistently greater than 140 mmHg. [34] Single, casual measurements of blood pressure may inacccurately classify individuals as having hypertension and cause unnecessary emotional, social and financial problems. [33]

1.1 Prevalence of hypertension [34,36]

The Center for Diseases Control and Prevention, National Center for Health Statistics, provided that an estimated 50 million Americans have high blood pressure ($\geq$ 140/90 mmHg). Blood pressure increases with age, but the onset of hypertension most often occurs during the third, fourth, and fifth decades of lifes. The prevalence of hypertension increases with age, is greater among blacks than whites, and is greater in less educated people. Men and women of the same race are affected approximately

equally. Data from the 1976 to 1980 and 1988 to 1991 of National Health and Nutrition Examination Survey(NHANES II& III) indicated that the prevalence of hypertension decresed from approximately 58 million to around 50 million. The NHANES III reported that 35% of those with hypertension were unaware and only 53% of those with hypertension were receiving antihypertensive therapy, and only 24% of those with hypertension had their blood pressure controlled to less than 140/90 mmHg.

1.2 Etiology of hypertension [36]

Hypertension is a heterogenous disorder that may result from either a specific cause(secondary hypertension) or some underlying pathophysiologic mechanism stemming from unknown etiology(primary or essential hypertension). Fewer than 5 % of people who suffer from high blood pressure have secondary hypertension. In the most of these, chronic renal diseases or renovascular disease is the cause of hypertension. Other conditions that are known to cause of hypertension include pheochromocytoma, Cushing' s syndrome, primary aldosteronism, and coarctation of the aorta. In some instances, exposure to various exogenous substances may produce hypertension. The most notable of these are estrogens, glucocorticoids, licorice, sympathomimetic amines, nonsteriodal anti-inflammatory agents, chronic alclhol use and tyramine-containing foods in combination with monoamine oxidase (MAO)inhibitors.

The pathogenesis of essential hypertension remains mysterious, a specific cause of sustained hypertension cannot be found. It is likely that several interrelated mechanisms rather than a single causative defect, control blood pressure in essential hypertension. The fact that hypertension often runs in families suggests that genetic

factors may play an important role in the development of essential hypertension. There is even some evidence that single genes might responsible for specific subtypes of hypertension. These include genetic traits for high sodium-lithium countertransport, a low urinary kalikrein excretion, increased aldosterone and other adrenal steriods, and high angiotensin levels. However, even with continued insights into the regulation of blood pressure, essential hypertension remains a process that must be controlled rather than a curable disorder.

1.3 Pathophysiology [36]

Multiple factors may contribute to the development of primary hypertension including abnormal neural mechanisms; defects in peripheral autoregulation; disturbances in sodium, calcium, and natriuretic hormone; and malfunctions in either humoral or vasodepressor mechanisms.

1.3.1 The neural mechanism [34-36]

Both the central(CNS) and the autonomic nervous system are intricately involved in the maintenance of arterial blood pressure. Stimulation of certain areas within the CNS(nucleus tractus solitarius, vagal nuclei, vasomotor center, and the area postrema) can result in either an increases or a decrese in blood pressure. For example, α-adrenergic stimulation within the CNS decreses blood pressure through an inhibitory effect on the vasomotor center. Increased angiotensin; on the other hand, increases sympathetic outflow from the vasomotor center, which eventuates in an increase in blood pressure. Located on the presynaptic surface of sympathetics terminals are a variety of receptors that either or inhibit norepinephrine release. The α and β presynaptic receptors play a role in negative and positive feedback to the

norepinephrine-containing vesicles located near the neuronal ending. Stimulation of presynaptic $\alpha(\alpha_2)$ receptors exerts a negative inhibition on norepineprine release. Stimulation of presynaptic β receptors facilitates further release of norepineprine. Stimulation of postsynaptic $\alpha(\alpha_1)$ receptors on arterioles and venules results in vasoconstriction. There are two types of postsynaptic β receptors, β_1 and β_2. Stimulation of β_1 receptors in the heart results in an increase in heart rate and contractlilty. When β_2 receptors in the arteriole and venules are stimulated, vasodilation occurs. The major negative-feedback mechanism controlling sympathetic activity is the system of baroreceptor reflexes. The baroreceptors respond extremely rapidly to changes in arterial pressure. In this system, an acute elevation in arterial pressure increases the rate of baroreceptor discharge, which results in vasodilation throughout the peripheral circulatory system and a decrease in heart rate and myocardial contractility. Conversely, low pressure has the opposite effect, causing reflex vasoconstriction and increase in heart rate and force of contraction. These baroreceptor reflex mechanism may blunted in elderly individuals.

Abnormalilties in either the renal or tissue autoregulatory processes could cause hypertension. In fact, it seems reasonable to postulate that individuals may first develop a renal defect for sodium excretion and then reset their tissue autoregulatory processes to a higher arterial blood pressure. An initial defect in the renal adaptive mechanism could lead to plasma volume expansion and increase blood flow to peripheral tissues even when blood pressure is normal. To offset the increase in blood flow, local tissue autoregulatory processes would induce arteriolar constriction to raise the peripheral vascular resistance. In time, a thickening of the arteriolar walls may

occur, resulting in a sustained elevation in peripheral vascular resistance. An increase in total peripheral vascular resistance is a common underlying problem in patients with primary hypertension.

1.3.2 The humoral mechanisms [34-36]

At least three possible humoral abnormalilties may be response for causing primary hypertension in some individuals.

1.3.2.1 *The renin-angiotensin-aldosterone system(RAS)*

The RAS is importance to the regulation of sodium, potassium, and fluid balance, and it significantly influences vascular tone and sympathetic nervous system activity.

In the kidney, renin is synthesized and restored in the juxtaglomerular cell, which are locate primarily in the media of the renal afferent arterioles. Several factors are known to control renin release. These can be grouped into intrarenal factors(such as perfusion pressure, catecholamines, angiotensin II) and extrarenal factors(such as sodium, chloride, and potassium). Decreased perfusion pressure leads to an increase in renin secretion. The flux of sodium and chloride across the cells influences renin release. A decrease in the amount of sodium and chloride delivered in the distal tubule stimulates renin release.

Angiotensin II has been shown to directly inhibit the release of renin through negative feedback. Cathecholamines increase renin release probably by directly stimulating the juxtaglomerular cells through an action involving the formation of cyclic AMP. Both potassium and calcium may also a direct role in renin release by the juxtaglomerular cells.

In blood, renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme(ACE). Angiotensin II exerts its biological effects in various tissues following binding to specific receptors classified as AT1 or AT2 subtypes. The AT1 receptors is located in brain, renal myocardial, vascular, and adrenal tissue. The AT2 receptors is located in adrenal medullary tissue, and brain. AT1 receptors mediate the majority of response critical to cardiovascular and renal function. An increase in circulating angiotensinII can cause an elevation in blood pressure through both pressor and volume effects. The pressor effects of angiotensin II include direct vasoconstriction, stimulation of cathecholamine release from the adrenal medulla, and a centrally mediated increase in sympathetic nervous system activity. Angiotensin II also stimulates the release of aldosterone from the adrenal gland, which leads to retention of both sodium and fluid, with a resultant increase in plasma volume and blood pressure(Figure 1). Clearly, any disturbance in RAS that leads to an increase on any or all three components could produce hypertension.

Both heart and brain contain a local RAS. In the heart, angiotensin II is also generated by a second enzyme, angiotensin I convertase(human chymase), which is not blocked by ACE inhibition. Activation of the myocardial RAS leads to increased cardiac contractility and stimulation of cardiac hypertrophy. The brain RAS has at least two functions. Angiotensin II modulates the production and release of hypothalamic and pituitary hormones. Angiotensin II also enhances sympathetic outflow from the medulla oblongata.

Local generation of biologically active peptides in peripheral tissues may play an important role in the increased vascular resistance often observed in hypertensive individuals. There is also some evidence that angiotensin produced by local tissue may interact with other humoral regulators and endothelium-derived growth factors to stimulate vascular smooth muscle growth and metabolism. This *in situ* generation of angiotensin peptides may, in fact, underlie the development of increased vascular resistance in forms of hypertension that are associated with low plasma renin activity. Component of tissue RAS may be responsible for long-term adaptation to hypertension (i.e., left ventricular hypertrophy, smooth muscle hypertrophy of blood vessels, and glomerular hypertrophy).

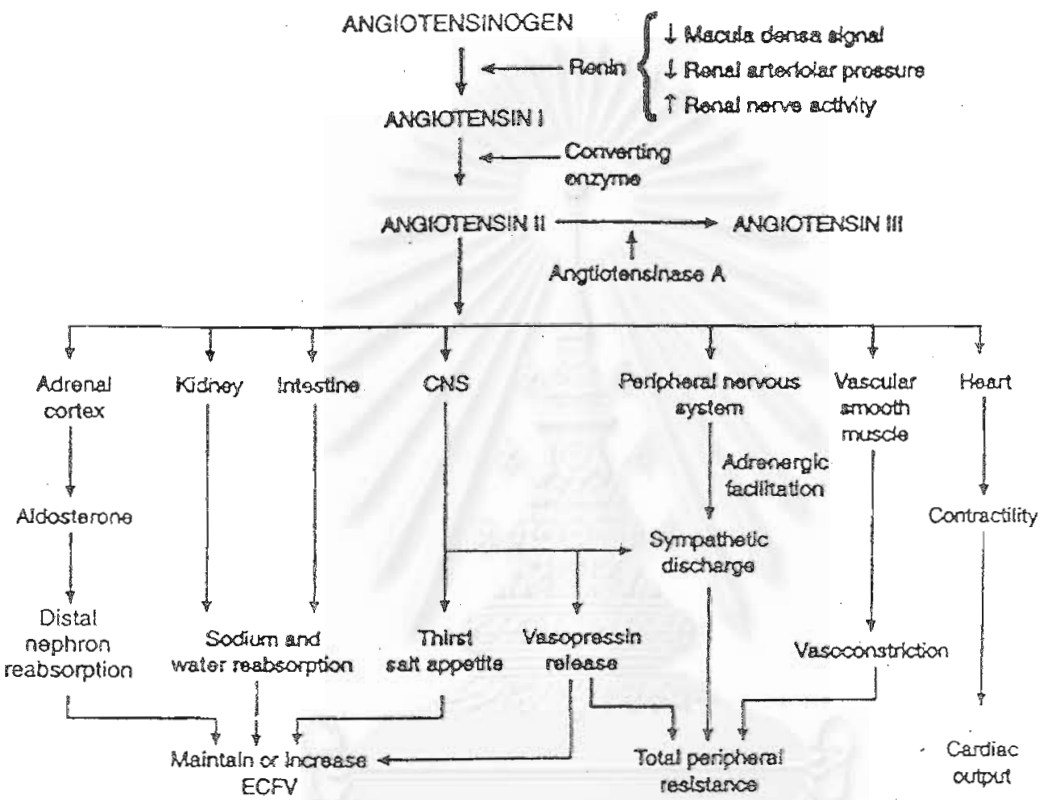


Figure 1: Schematic representation of the renin-angiotensin(RAS) [35]

1.3.2.2 *Natriuretic hormone*

Another humoral factor that may be involved in the developmemt of primary hypertension is the increased concentration of natriuretic hormone. The proposed role of natriuretic hormome is to inhibit Na^{+}/K^{+}-ATPase and , thus to interfere with sodium transport across cell membranes. It has been suggested that an inherited defect in the kidney's ability to eliminate sodium would cause an increase in extracellular fluid and plasma volume as discussed earlier. This may cause a compensatory increase in the concentration of circulating natriuretic hormone, which would increase urinary excretion of sodium and water. This same hormone, however, is also thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium would ultimately lead to vascular tone and hypertension.

1.3.2.3 *Insulin resistance and hyperinsulinemia*

Evidence linking insulin resistance and hyperinsulinemia to the development of hypertension is mounting. Several possiblilties by which hyperinsulinemia may lead to hypertension include renal sodium retention, enhanced sympathetic nervous system activity. and induction of vascular smooth muscle hypertrophy. Another possible way by which insulin could raise blood pressure is by increasing intracellular calcium concentration, which lead to increased vascular resistance. Hyperinsulinemia often accompanies upper body obesity, but even nonobese hypertensive individuals have been shown to be insulin resistant, glucose intolerant, and hyperinsulinemic. The mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. Hyperinsulinemia is also

associated with hypertriglyceridemia, which results in a decreased concentration of HDL cholesterol.

1.3.3 The vascular mechanisms

The abnormalities in the structure and function of the vasculature are increasing recognized as contributing to the hypertensive state by increasing total peripheral resistance. During the past decade, it has become obvious that the endothelium, single cell, innermost layer of blood vessels, is more than a passive barrier between the blood and the vascular smooth muscle cell. We now know that endothelium plays a crucial role in circulatory homeostasis responding not only to humoral and chemical signals, but also to change in the haemodynamics of blood flow such shear stress. Endothelium cells release chemical mediators that modulate the responses of numerous cells including vascular smooth muscle, platelets, and leucocytes. The endothelium serves a dual role in the control of vascular tone, endothelium cells produce and release a variety of vasoactive substances. These include both vasodilators, such as endothelium-derived relaxing factor(EDRF) which has not been identified as nitric oxide(NO), endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin, an vasoconstrictors, such as thromboxane A_2 and prostaglandin H_2, endothelin and angiotensin II. The interaction between these vasodilators and vasoconstrictors provides a local control mechanism that regulates vascular tone. Alterations in the production of these mediators are involved in the induction and persistance of hypertension in both experimental models and humans, in addition this

endothelial cell dysfunction has been reported in various forms. Plasma levels of endothelin, for example, have been reported to be significantly higher in patients with primary hypertension. In addition, both chemical-stimulated and basal releases of ERDF has been shown to be severely attenuated in hypertensive patients as well as in experimental models of hypertension. Another abnormality in the biology of vascular smooth muscle cells that may account for increased vasotone of hypertensives, is a disturbance in the physio-chemical properties of the cell membrane leading to abnormalities in ion handling. Reported abnormalities of cellular electrolyte homeostasis, for example, increased sodium influx due to elevation of sodium-hydrogen exchange activity, decreased sodium-potassium cotransport, increased lithium-sodium countertransport and decreased red cell membrane binding of calcium.

In parallel with studies on the function of vascular smooth muscle in the hypertensive state, considerable attention has been given to the importance of structural changes. The change in the geometry of the vessel wall that result in an increased vasoconstrictor response with the same degree of shortening of vascular smooth muscle in hypertensive patients is a decrease in the lumen(internal studies of the vessel). In studies of small resistance vessels from subcutaneous tissue from hypertensive subjects, an average 29% increase in the media thickness: lumen diameter ratio was found, closely matching the 32% elevation in the blood pressure. The increase in the wall thickness either due to smooth muscle cell proliferation, accumulation of glycoaminoglycans, or from the increasing evident support to the role of rearrangement of a normal amount of tissue around a small lumen, a process know as remodelling.

1.4 Clinical presentation [37]

Patients with uncomplicated, primary hypertension are usually asymtomatic initially. While a complete history and physical examination may help identify concerns that warrant further evaluation, a few basis tests should be performed in all hypertensive patients proir to initiating drug therapy. These include hemoglobin and hematocrit, urinalysis, serum potassium and creatinine, liver function test and electrocardiogram. Total and high-density-lipoproteined cholesterol, plasma glucose, and serum uric acid are indicated to assess other risk facrtors and top develop baseline data for monitoring drug-induced metabolic changes. As the hypertension processes, however, symptoms characteristic of cardiovascular, cerebrovascular, or renal diseases may occur as the patients develop target organ damage. Patients with secondary hypertension usually complain of symptoms suggestive of the underlying disorder. More than half of the patients with this form of secondary hypertension suffer episodes of orthostatic dizziness or syncope. In primary aldosteronism, hypokalemic symptoms usually manifest including muscle cramps and muscle weakness. Patents who present with hypertension secondary to Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregulatories, recurrent acne, or muscular weakness. The most common causes of secondary hypertension are summarized in Table 1.

Frequently, the only sign of primary hypertension is an elevated blood pressure. The rest of the physical examination may be completely normal. Again, as the hypertension progresses, sign of end-organ damage begin to appear. These are chiefly related to pathologic changes in the eye, brain, heart, kidneys, and peripheral blood vessels.

Table 1: Causes of secondary hypertension [71]

Systolic and diastolic hypertension

- Renal
  - Renal parenchymal disease
    - Chronic nephritis
    - Polycystic disease
    - Collagen vascular disease
    - Diabetic nephropathy
    - Hydronephrosis
    - Acute glomerulonephritis
  - Renal vascular disease
  - Renal transplantation
  - Renin-secreting tumors
- Endocrine
  - Adrenal
    - Primary aldosteronism
    - Overproduction of 11-deoxycorticosterone (DOC), 18-OH-DOC, and other mineralocorticoids
    - Congenital adrenal hyperplasia
    - Cushing's syndrome
    - Pheochromocytoma
  - Extra-adrenal chromaffin tumors
  - Hyperparathyroidism
  - Acromegaly
- Pregnancy-induced hypertension
- Coarctation of the aorta
- Neurologic disorders
  - Dysautonomia
  - Increased intracranial pressure
  - Quadriplegia
  - Lead poisoning
  - Guillain-Barre syndrome
- Postoperative
- Drugs and chemicals
  - Cyclosporine
  - Oral contraceptives
  - Glucocorticoids
  - Mineralocorticoid, including licorice and carbenoxolone
  - Sympathomimetics
  - Tyramine and MAO inhibitors

Isolated systolic hypertension

- Aging, with associated aortic rigidity
- Increased cardiac output
  - Thyrotoxicosis
  - Anemia
  - Aortic valvular insufficiency
- Decreased peripheral vascular resistance
  - Arteriovenous shunts
  - Paget's disease of bone
  - Beriberi

1.5 Complication of hypertension

The end of natural history of untreated hypertension is an increased likelihood of premature disability or death from cardiovascular disease. The risks of elevated blood pressure have been determined from large-scale epidemiologic surveys. MacMahon et al. performed a meta-analysis of all available major prospective observational studies relating diastolic blood pressure(DBP) level to the incidence of stroke and coronary heart disease(CHD). In the nine studies analyzed, almost 420,000 people were followed up for 6 to 25 years. A total of 599 fatal strokes and 4,260 deaths from CHD were recorded. The overall results demonstrated “direct, continuous and apparently independent associations” with “no associates with lower risks of stroke and CHD”. MacMahon et al. also estimated that a DBP that is persistently higher by 5.0 mmHg is associated with at least a 34% increase in stroke risk and at least a 21% in CHD risk. Table 2 provide a more detailed look at the causes of death in hypertension.

Hypertensive heart disease: the principal cardiac complications of hypertension are left ventricular hypertrophy, coronary heart disease, and congestive heart failure. These complication may lead to cardiac arrhythmias, angina, myocardial infarction, and sudden death. Coronary heart disease is the common cause of death in hypertensive patients.

Cerebrovascular disease: the types of cerebrovascular lesions most commonly seen in hypertensive individuals include lacunar infarcts caused by thrombolic occlusion of small vessel, intracerebral hemorrhage resulting from ruptured microaneurysms, and transient attacks secondary to atherosclerosis diseases in the carotid arteries.

Renal disease: Renal dysfunction, both structural and functional, is almost always demonstrable in hypertensive patients, even those with minimally elevated pressures, however renal involvement is asymtomatic and not demonstrable by usual clinical testing. The loss of renal function grows progressively as the blood pressure increases and the elevation continues, but only a minority of hypertensives die as a result of renal failure. Nevertheless, hypertension remains a leading risk for end-stage renal disease(ESRD), and is partly responsible for the much higher incidence of ERSD in blacks than in whites in the United States.

The damage hypertension to the eye is characterized by a variety of retinopathies. Nonspecific changes include an increased light reflex, increased tortusity of vessels, and arteiovenous thicking. These are all associated with the accelerated arterosclerosis that accompanies hypertension.

Table 2: Causes of death in primary hypertension [35]

	Year	No of Deaths	Percentage of Deaths			
			Heart Disease[a]	Stroke	Renal Failure	Nonvascular Causes
Untreated						
Janeway, 1913	1903–1912	212	33	14	23	30
Hodge and Smirk, 1967	1959–1964	173	48	22	10	20
Bechgaard, 1976	1932–1938	293	45	16	10	29
Smith et al., 1950	1924–1948	376				
Group 1[b]		100	28	9	3	60
Group 2		100	46	17	2	35
Group 3		76	52	18	16	14
Group 4		100	22	16	59	3
Bauer, 1976	1955–1974	144	41	34	15	10
Treated						
Breckenridge, 1970	1952–1959	87	18	28	44	10
Breckenridge et al., 1970	1960–1967	203	38	21	29	11
Strate et al., 1986	1970–1980	132	42	7	7	44
Bulpitt et al., 1986	1971–1981	410	51	18	3	28
Isles et al., 1986	1968–1983	750	52	23	?	25

[a]Includes ischemic heart disease and congestive failure.
[b]Grouping according to Keith-Wagener classification of hypertensive retinopathy.

Table 3: Complication of hypertension [35]

Hypertensive	**Atherosclerotic**
Accelerated-malignant hypertension (grade III and IV retinopathy)	Cerebral thrombosis
	Myocardial infarction
Encephalopathy	Coronary artery disaese
Cerebral hemorrhage	Claudication syndrome
Left ventricular hypertrophy	
Congestive heart failure	
Aortic dissection	

1.6 Definition and classification of hypertension [37]

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international authorities and particularly by the Joint National Committee(JNC) in the United States and the WHO-ISH Guidelines Committee. Accordingly, in order to reduce confusion and provide more consistent advice to clinicians around the world, the WHO-ISH Guidelines Committee has agrees to adopt in principle the definition and classification provided in JNC VI. This new definition defines the lower limits for the borderline subgroup of mild hypertension in the 1993 WHO-ISH Guidelines. The new guideline emphasize that the decision to lower the elevated pressure in a particular patients is not base on the level of blood pressure alone on assessment of the total cardiovascular risk in that individual.

Hypertension is therefore defined as a SBP of 140 mmHg or greater and/or DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adults over the age of 18 is provided in Table 4. The terms “grades 1 2 and 3” used by JNC VI, since the word “stage” implies progression over time in a way that does not necessarily apply here. Otherwise, the values chosen and the terms used are those used in JNC VI. The terms “mild”, “moderate” and “severe” used in previous versions of the WHO-ISH Guidelines, would correspond to grade 1,2 and 3 respectively. The widely used term “borderline hypertension” becomes a subgroup within grade 1 hypertension. It must be

emphasized that the term “mild hypertension” does not imply a uniformly benign prognosis, but is used simply to contrast with more severe elevations of blood pressure.

In contrast to the 1993 Guidelines, the present report does not deal separately with hypertension in the elderly nor with isolated systolic hypertension. Rather, discussion of these two conditions is now part of the main text, since it is widely agreed that the treatment of these conditions is at least as effective in reducing cardiovascular risk as the treatment of classical essential hypertension in middle-age subjects.

Table 4: Definition and classification of blood pressure levels(mmHg) [37]

Category	**Systolic**	**Diastolic**
Optimal	<120	<80
Normal	<130	<85
High-normal	130-139	85-89
Grade 1 hypertension(mild)	140-159	90-99
Subgroup: borderline	140-149	90-94
Grade 2 hypertension(moderate)	160-179	100-109
Grade 3 hypertension(severe)	>180	>110
Isolated systolic hypertension	>140	<90
Subgroup: borderline	140-149	<90

New(1999) WHO/ISH definition and classification of BP levels

When a patient’s systolic and diastolic blood pressure fall into different categories, the higher category should apply.

Stratification of patients by absolute level of cardiovascular risk

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk factors, concomitant diseases such as diabetes, target-organ damage and cardiovascular or renal disease, as well as other aspects of the patient's personal medical and social situation. To assist with this, guidelines provide a simple method by which to estimate the combined effect of several risk factors and conditions on the future absolute risk of major cardiovascular events. The estimates are based on age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular or renal disease. They were calculated from data on the average 10-year risk of cardiovascular death, nonfatal stroke or nonfatal infarction among participants(average initial age of 60 years; range 45-80 years) in the Framingham Study.

Four catagories of absolute cardiovascular disease risk are defined (low, medium, high, and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors present. So, for example, individual with very high levels of cholesterol or a family history of premature cardiovascular disease in several first-degree relatives will typically have absolute risk levels that are at the higher end of the range provided. Similarly, individuals with other risk factors listed in Table 5 may also have absolute risk levels that are towards the higher end of the range for the category.

How well these estimates predict the absolute risk of cardiovascular disease in Asian, African or other non-Western populations is uncertain. In those countries in which CHD incidence is relatively low and heart failure or renal disease is more common, the risk factors used to stratify risk in Table 6 should also be useful in stratify the risk of these diseases.

Low-risk group

The low-risk group includes men below 55 and women below 65 years of age with grade 1 hypertension and no other risk factor. Among individuals in this category, the risk of a major cardiovascular event in the next 10 years is typically less than 15 %. The risk will be paricularly low in patients with borderline hypertension.

Medium-risk group

This group includes patients with a wide range of blood pressure and risk factors for cardiovascular disease. Some have lower blood pressure and multiple risk factors. This is the patient group for which the clinical judgement of the responsible doctor will be paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next 10 years is typically about 15-20%. The risk will be closer to 15% in those patients with grade 1(mild) hypertension and only one additional risk factor.

High-risk group

This group includes patients with grade 1 or grade 2 hypertension who have three or more risk factors listed in Table 5, diabetes or target-organ damage and patients with grade3(severe) hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in the following 10 years is typically about 20-30%.

Very-high risk group

Patients with grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease(as defined in Table 5) carry the highest risk of cardiovascular events, of the order of 30% or more over 10 years, and thus qualify for the most intensive and rapidly instituted therapeutic regimens.

Table 5: Factors influencing prognosis [37]

Risk Factors For Cardiovascular Diseases	Target Organ Damage (TOD)	Associated Clinical Conditions (ACC)
I. Used for risk stratification • Levels of systolic and diastolic blood pressure (Grades 1–3) • Men >55 years • Women >65 years • Smoking • Total cholesterol >6.5 mmol/L (250 mg/dl) • Diabetes • Family history of premature cardiovascular disease II. Other factors adversely influencing prognosis • Reduced HDL cholesterol • Raised LDL cholesterol • Microalbuminuria in diabetes • Impaired glucose tolerance • Obesity • Sedentary lifestyle • Raised fibrinogen • High risk socioeconomic group • High risk ethnic group • High risk geographic region	• Left ventricular hypertrophy (electrocardiogram, echocardiogram, or radiogram) • Proteinuria and/or slight elevation of plasma creatinine concentration 106–177 mmol/L (1.2 – 2.0 mg/dl) • Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalised or focal narrowing of the retinal arteries	*Cerebrovascular disease* • Ischaemic stroke • Cerebral haemorrhage • Transient ischaemic attack *Heart disease* • Myocardial infarction • Angina pectoris • Coronary revascularisation • Congestive heart failure *Renal disease* • Diabetic nephropathy • Renal failure (plasma creatinine concentration >177 mmol/L) (>2.0 mg/dl) *Vascular disease* • Dissecting aneurysm • Symptomatic arterial disease *Advanced hypertensive retinopathy* • Haemorrhages or exudates • Papilloedema

Table 6: Stratifying risk and qualifying prognosis [37]

other risk factor & disease history	Blood Pressure(mmHg) Grade 1 (mild hypertension) SBP140-159 or DBP 90-99	Grade 2 (moderate hypertension) SBP 160-179 or DBP 100-109	Grade 3 (severe hypertension) SBP≥180 or DBP≥110
I. no other risk Factors	low risk	medium risk	high risk
II.1-2 risk factors(1)	medium risk	medium risk	high risk
III.3 or more risk Factors or TOD(2)	high risk	high risk	high risk
IV.ACC (3)	high risk	high risk	high risk

(1) See table 5

(2) TOD- target organ damage

(3) ACC- associated clinical conditions, including clinical cardiovascular or renal disease

2.Blood Pressure Measurement [34,38-43]

Conventional versus Ambulatory Blood Pressure Measurement:

Casual office–or clinic-based arterial pressure measurements, i.e. physician measures the patient's arterial pressure in his office or clinic, have been used since the turn of the century and remain the mainstay or standard method of diagnosis and management of hypertension even today. There are many reasons for this: normal and pathological values are defined and almost all we know about the prognostic impact of elevated arterial pressure relies on studies which used casual measurements, e.g. Framingham. The measurement itself and the situation in which it take place can be standardized,e.g. device, cuff size, vessel sounds, body position, time of day and thus equality of observation is achievable to a fair degree. Casual arterial pressure data can also be analyzed easily and aggregated to produce summary statistics without problems. Finally, the measurement is simple and inexpensive and thus even large samples can be examined. However, there are many limitations of casual measurements to determine the arterial pressure. Casual blood pressure measurements are often affected by the alerting reaction induced in patients by the doctor's presence, this reaction causes a rise in blood pressure which may be both large and unpredictable. Also known as the white-coat hypertension or office hypertension, which cannot be reproduced when self-measuring pressure at home or with an ambulatory blood pressure monitoring(ABPM) device. The reasons for white-coat hypertension are not well understood. The proportion of patients with white-coat hypertension varies between 20% and 30% of all patients with office-diagnosed hypertension. Mancia and colleagues showed that the average rise in pressure evoked by the presence of a physician was 23/18 mmHg. This

alerting reaction interferes with the evaluation of hypertensive treatment by clinic readings in two ways. Firstly, the alerting reaction may cause an overestimate of the initial blood pressure levels. Secondly, it may lead to an underestimate of the reduction in blood pressure achieved with treatment. Therefore, patients with white-coat hypertension must not be admitted to clinical trials. Another important disadvantage of casual measurements, especially in the clinical trial setting is its well described responsiveness to placebo. When arterial drops with placebo treatment, the observed difference compared with the active treatment group decreases and the variance increases. Sample size has to be increased to compensate for this power loss.

In addition, as the recognition of blood pressure variability that presents throughout the day, clinic blood pressure measurements are therefore limited in that the reading obtained may not be representative of the patient' s blood pressure. Hence, although the level of arterial pressure as measured at the clinic is an important risk factor in populations, its predictive value in individual patient is poor. These limitations can be reduced with the use of ABPM device.

Noninvasive intermittent blood pressure monitoring was first developed 30 years ago, with the improved technology, ambulatory devices are now pocket-sized, with almost noiseless pumps and are capable of automatically inflating the cuff and providing intermittent pressure over a 24-hour period. With this method of measurement, there are considerable advantages over conventional measurement including avoidance of observer error, either systematic error, terminal digit preference or observer prejudice, which limit accuracy of conventional measurements. Furthermore, ambulatory reduces white-coat effect, provides a series of blood pressure

readings over the time period rather than a one-off measurement and the use of ABPM in clinical trials seems to be no relevant arterial pressure response to placebo. There is convincing evidence that ABPM data have a higher reproducibility than casual clinic readings. With the distinct features of ABPM from conventional method make this advice almost a necessity in antihypertensive clinical trials. There are as follows

1. *Reliable identification of the target population*

24-hour ABPM provides an effective way of recognizing those patients whose blood pressure elevation is due to the white-coat effect. These patients who are not be exposed to possible adverse drug reactions, which are not balanced by the therapeutic benefit. Therefore, they should not receive any antihypertensive treatment. Likewise, patients with white-coat hypertension must not be admitted to clinical trials. In efficacy trials their inclusion would contribute to the reduction of arterial pressure in the placebo group, thus minimizing the difference in endpoint arterial pressure observed between the active and in the control group. In effectiveness studies the inclusion of white-coat hypertensives would dilute the effects of the antihypertensive treatment as a considerable subsample of the patients only casually experience elevated pressure. Therefore, increased sample sizes are necessary to achieve statistically significant results.

2. *Reduction of sample size*

24-hour ABPM does not respond to placebo and is highly reproducible. Thus the sample size required to show efficacy of an antihypertensive treatment can be reproduced markedly.

3. Assessment of dose-response relationship and duration of drug action

24-hour ABPM allows the BP of hypertensive patients to be measured under exposure to the variable physical and psychological stimuli in daily life not just in the artificial environment of the physician's office. Moreover the detailed or series of blood pressure reading also obtained over the time period with this device. As a result, it is possible that the exact time of the real, daily life of peak and trough antihypertensive effect will be identified. The persistence of the blood pressure reduction over 24-hour (drug's duration), during the night-time, or in the early morning hours on the blood pressure(BP) variables such as BP variability, BP load, mean 24-hour BP, mean night-time BP which are related with the end-organ damage in hypertension.

Prognostic Significant of 24-hour Blood Pressure(BP) Variables [41-43]

Twenty-four hour monitoring of blood pressure has been shown to be superior to casual(office) BP in predicting target organ involvement in patients with hypertension, particularly for the heart. Many types of information can be obtained by using 24-hour ABPM device, including an individual's true blood pressure level, amplitude of diurnal variation, short-term blood pressure variability and blood pressure load, all of which might have prognostic significance.

Prognostic significance of average 24-hour and daytime blood pressure

Sokolow et al showed that average daytime blood pressure values obtained noninvasively by a semi-automatic measuring device were correlated more closely with the overall end-organ damage in patients with hypertension than clinic blood pressure values. This finding was later confirmed by other investigators who provided the

following additional evidence:(1) both daytime blood pressure and the 24-hour average blood pressure are correlated more closely with end organ damage in hypertensive patients than clinic blood pressure;(2) the close correlation between 24-hour average blood pressure and end-organ damage can be seen when organ damage is measured by a comprehensive score base on patient history and clinic and laboratory examinations, and when different(and sometimes more sensitive) measures of individual end organ damage are considered. Thus, albuminuria, cerebral lacunae, left ventricular hypertrophy and retinopathy have all shown a greater correlation with 24-hour average values than with clinic values.

Prognostic significance of blood pressure variability

Parati *et al* demonstrated that blood pressure variations over 24-hour are correlated with end organ damage in hypertensive patients. In this study hypertensive patients were divided into five groups according to increasing 24-hour average blood pressure values as determined by intra-arterial ambulatory monitoring. Each group was then subdivided into two classes according to whether blood pressure variability (calculated as the standard deviation of the average of all half-hour mean values, i.e. the among half-hour standard deviation) was greater or lower than the average variability of the whole group. The greater incidence and severity of end-organ damage was seen in the class with greater blood pressure variability. Another support was shown by the study in 73 hypertensive patients using intra-arterial ambulatory monitoring. It was found that among the blood pressure reading taken at baseline, the short-term variability(defined as the standard deviation of consecutive half-hourly values during the daytime) was the best predictor of subsequence left ventricular mass. The other significant predictor was

an aggregate measure of target-organ damage based on the ECG, chest X-ray, examination of the fundus and the serum creatinine concentration. The variability in blood pressure also predicted aggregated target organ damage at follow-up, but blood pressure level was not a predictor.

Prognostic significance of the diurnal rhythm of blood pressure

Blood pressure usually follows a circadian rhythm with levels higher during the day and lower at night. In most people, blood pressure falls during the night by more than 10%, such people are often referred to as a dippers. But there are others(non-dippers) in whom the fall in blood pressure is smaller. This blunted circadian pattern has been reported to be associated with increased prevalence of left ventricular hypertrophy, atherosclerosis and stroke. In addition, a few cross-sectional studies have indicated that target organ damage is more pronounced in non-dippers than in dippers with comparable clinic blood pressure. It has also been suggested that this difference applies to women but not to men.

Prognostic significance of the daily blood pressure load

A study by White *at al* in 30 never previously treated patients with mild to moderate essential hypertension via 24-hour ambulatory BP monitoring indicated that percentage of elevated BP values that includes both the awake and sleep periods is predictive of cardiac target organ involvement. Elevated BP values during the awake hours(>140/90mmHg) and sleeping hours(>120/80mmHg) were used to calculate the total percentage of abnormal BP values(load) in each patient. It was found that the BP loads were related to left ventricular mass index and left arterial index more strongly than the mean 24-hour BP values. Moreover, if >40% of the ambulatory BP values

were elevated, the likelihood of increased mass or decreased filling was greater than 61%, whereas if <40% of the BP values were elevated, the incidence of an abnormal cardiac test result decreased to less than 17%.

Losartan potassium [44]

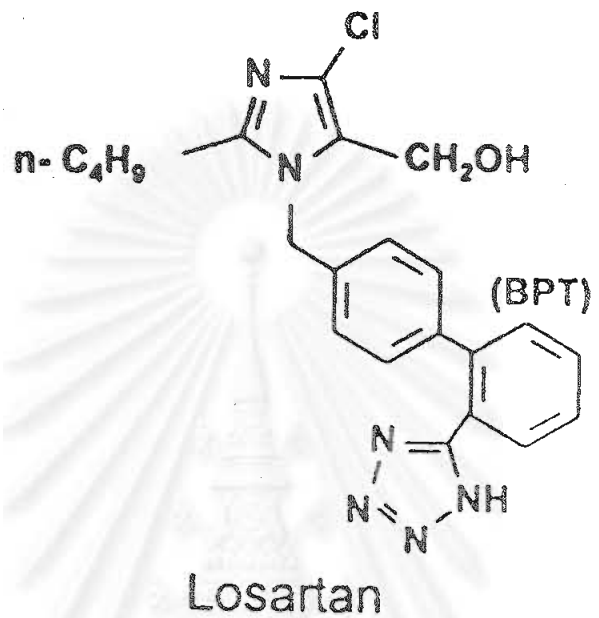


Figure 1: Chemical structure of losartan potassium [72]

Losartan potassium(Figure 1) is an orally administered nonpeptide angiotensin II (AII) antagonist. It is the first of a new class of antihypertensive drugs which act by directly blocking AII subtype 1(AT_1) receptors. This novel action is the basis for its application in patients with hypertension. An active metabolite, E3174, is largely responsible for the antihypertensive effect of the drug.

Losartan potassium is the prototype nonpeptide AT_1 receptor antagonist. As such, it has found considerable use as a pharmacological tool for investigation of the role of AII and its receptors in cardiovascular disorders.

1. Role of the Renin-Angiotensin System(RAS) in hypertension

The renin-angiotensin system(RAS) is central to blood pressure regulation, fluid volume homeostasis and electrolyte balance. Briefly renin is synthesised by the kidney and secreted into the systemic circulation. Renin acts on the substrate angiotensinogen to produce angiotensin I(AI), a decapeptide. AI is converted by ACE and other enzymes such as chymases to the active hormone AII, which in turn is hydrolysed to angiotensin III, another active substance, and to other fragments including angiotensin IV. The heart, vasculature and kidney are important sites for the local production of AII.

AII is the primary mediators of the RAS . Its binds to receptors located in virtually every tissue. The principle actions of AII critical in maintaining normal blood pressure control are: direct and intense vasoconstriction of the smooth muscle of the arterioles; release of aldosterone(and cortisol) from the adrenal cortex;: a direct antinatriuretic effect on the kidney to increase proximal tubular reabsorption of sodium, resulting in sodium and fluid retention .Among other actions, AII may cause positive inotropic effects and influences left ventricular function. It also facilitates norepinephrine release, and thus sympathetic activity, and induces cellular growth possibly implicated in left ventricular hypertrophy(LVH).

The exact role of the RAS in hypertension is complex and incompletely understood, although it is established that small increases in plasma levels of AII elevate blood pressure. Inhibition of AII has little effect on blood pressure in normotensive sodium-replete individuals, whereas in sodium-depleted individuals the

RAS is activated and blood pressure drops markedly upon AII blockade. Compensatory rise in plasma renin occur in response to decreased plasma AII levels.

ACE inhibitors are unable to block the effects of AII produced locally by systems other than the RAS or to prevent formation by enzymes other than ACE, including endopeptidase and chymases. The rational for developing specific AII receptor inhibitors is therefore, to antagonise the activity of this crucial effector hormone independent of its source.

2.Pharmacodynamic Properties

2.1 Inhibition of Angiotensin II(AII) Actvity

2.1.1 *Inhibition of receptor binding*

Two distinct type of AII receptor, subtype 1(AT_1) and subtype 2(AT_2), were first identified in rats and are now known to exist in humans. AT_1 receptors are located primarily in vascular and cardiac tissue but also in the brain, kidney and adrenal gland, notably in the aldosterone-secreting tissue of the zona glomerulosa. The function of the AT_2 receptor, which is present in brain, kidney and adrenal medullary tissue, is poorly delineated. This receptor is not thought to contribute to cardiovascular homeostasis, although a role has recently been proposed in renal haemodynamics and in smooth muscle cell proliferation.

Losartan potassium is highly and specifically bound to AT_1 receptors. It is 10,000 times more selective for the AT_1 than the AT_2 receptors. In rats Losartan potassium 10mg/kg/day significantly($p<0.05$) reduced the density of AT receptors from baseline in the liver, kidney, and adrenal cortex, sites of the AT_1 receptors, but not in the adrenal medulla, where AT_2 receptor predominate. The drug inhibits the specific binding of AII to the AT_1 receptor site in a monophasic, concentration-dependent fashion, yielding IC_{50} (concentration inhibiting 50% of binding) of 1 to $2*10^{-8}$ mol/L in isolated rat adrenal cortical microsomes and aortic smooth muscle cells. This contrasts with the IC_{50} of the 10^{-4} mol/L estimated for losartan potassium at the AT_2 receptor site. E3174 has 10-fold greater affinity than the parent drug for AT_1 receptor, as shown by an IC_{50} values of $1.1*10^{-9}$ mol/L in rat aortic smooth muscle cells.

In concentration of up to 10^{-5} mol/L losartan potassium has no affinity for any other receptor types in rat tissue,e.g. α_1-adrenoceptors in rat brain and Ca^{++} receptors in rat cardiac, or for other receptors(e.g.neurotensin, glycine, opoid, muscarinic) in various isolated tissue preparations.

2.1.2 *Functional Antagonism of AII activity*

Functional antagonism of AII activity, reflecting AT_1 blockade, has been demonstrated for Losartan potassium *in vitro, in vivo* and in healthy volunteers.

In Vitro and In Vivo

Binding of Losartan potassium to the AT_1 receptor is saturable, reversible, and competitive. In concentration of 10^{-8} to 10^{-7} mol/l losartan potassium caused parallel shifts to the right of the concentration-contractile response or pressor response curve to AII. The drug competitively blocked AII-induced contraction of rabbit aorta , guinea-pig ileum and rat uterus and AII-induced pressor response in conscious or spinally pith rats. In none of these test systems did the drug display any AII antagonist effects in the concentration tested(up to 10^{-5} mol/L) , and it has no effect on the enzymes of the RAS.

E3174 is also devoid of agonist activity, as shown in similar experiments. However, in contrast to Losartan potassium, the metabolite is a noncompetitive antagonist, causing nonparallel shifts to the right of the concentration-contractile response curve and display a pA_2 value of 10.09 in isolated rabbit aorta. E3174 is estimated to be approximately 15 to 20 times more potent than losartan potassium. This is based on ED_{30} values(intravenous dose required to decrease mean

arterial pressure by 30mmHg) of 0.04 mg/kg for E3174 vs 0.78 mg/kg for losartan potassium in renal hypertensive rats and on IC_{50} values for inhibition of AII-induced cell growth and increase in intracellular Ca^{++} levels *in vitro*.

In Healthy volunteers

In single oral dose of 20 and 100 mg losartan potassium blocked the vasoconstrictor response to exogenous AI and AII in healthy individuals, as measured by forearm blood flow and change in dorsal hand vein diameter. Similarly, the pressor response to exogenous AI and AII was inhibited by up to 95% in a dose-related fashion by single and multiple oral doses of losartan potassium 10 to 20 mg. With doses 40mg and higher this effect persisted for at least 24 hours.

2.2 Effects on RAS

Effects of losartan potassium on the RAS are consistent with inhibition of AII activity. In healthy volunteer, losartan potassium $\leq$ 100mg in single or multiple doses increased plasma renin activity and plasma AII levels but produced inconsistent effects on plasma aldosterone levels, compared with placebo. These dose-dependent effects are also apparent during several weeks' therapy with losartan potassium in patients with the exception that plasma aldoserone levels appear to decrease, at least temporarily, during prolonged therapy. Plasma aldosterone levels fell by 74% after 6 weeks' therapy with the 100mg/day doasge and by 17% and 47% after a month with losartan potassium 50mg/day. Increases in plasma renin activity and plasma AII levels peaked at about 2 weeks and declined thereafter in 1 study, whereas plasma renin activity remained elevated at the end of 4 weeks' therapy in patients with low baseline values. Plasma renin activity continued to rise over 12 months while plasma

aldosterone levels returned to normal in an other trial in which some patients also received diuretics. There was no active plasma renin glycoforms following 6 weeks of losartan potassium therapy.

Whether pretreatment plasma renin activity is related to the antihypertensive effect of losartan potassium is unknown. In hypertensive patients , Goldberg *et al*. found these changes in RAS parameters to be smaller than those previously observed in healthy volunteers, who have more responsive negative feedback system which are better able to inhibit renin release. Decreases in mean arterial pressure have been correlated with baseline levels of, and changes in plasma renin activity in a small study in patients with hypertension. Animal models showed that losartan potassium did not decrease blood pressure in low renin models of hypertension such as deoxycorticosterone acetate salt-hypertensive rats and the bilateral nephrectomised rat.

2.3 Haemodynamics and cardiovascular effects

Losartan potassium reduces systolic and diastolic blood pressure (SBP;DBP) in patients with essential hypertension. Placebo-adjusted trough-to-peak ratios in patients with hypertension were calculated as 60% for the 50mg dose, 72% for the 100mg dose and 62 to 85% for losartan potassium 50mg plus hydrochlrothiazide 6.25 or 12.5 mg. A ratio of $\geq$50% is considered indicative of a duration of activity permitting once-daily dosages, although the validity of this index has been questioned.

This aside, the effects of losartan potassium on blood pressure have been shown to extend throughout a 24-hour period. 24-hour ambulatory blood pressure monitoring in 14 patients given losartan potassium 50 to 100mg for 12

weeks demonstrated mean DBP decreases of 8mmHg during the day(07.00 to 09.00) and 6.8mmHg at night (19.00 to 07.00). Heart rate did not change substantially in healthy individuals or in patients with hypertension.

The blood pressure lowering effects of single doses of losartan potassium 50mg and captopril 50mg were similar in sodium-depleted normotensive male volunteers and were additive when the drugs were combined. In hypertensive patients receiving thiazides, the onset of action for a single dose of losartan potassium 50mg was slower in the first 3 hours than for captopril 25mg. The magnitude of the effect on DBP was smaller with losartan potassium but not significantly so.

The influence of losartan potassium on other haemodynamic parameters in patients with essential hypertension is not fully reported in the literature. Cardiac output, left ventricular ejection fraction and circulatory blood volume remained unchanged and peripheral vascular resistance decreased in 10 Japanese patients treated with losartan potassium 50 to 100 mg for up to 10 weeks. In spontaneously hypertensive rats with pressure overload left ventricular dysfunction, long term(12 weeks') administration of oral losartan potassium 30mg/kg/day decreased systemic arterial resistance, mean aortic pressure , myocardial contractility and left ventricular end diastolic pressure, and increased stroke volume and volumetic aortic flow, compared with placebo.

Losartan potassium enhanced the elasticity of a medium-sized artery in 20 patients with essential hypertension. Compliance of the radial artery, but not of the common carotid or femoral artery, increased by 50% after therapy with losartan potassium 50 mg daily for 4 weeks(p=0.02 vs placebo).

2.3.1 *Effects on the left ventricular hypertrophy*

In patients with hypertension, development of LVH amplifies the risk of end-organ damage and associated morbidity(e.g. myocardial infarction stroke and heart or renal failure). Preliminary data suggest losartan potassium administration is associated with regression of LVH. losartan potassium 50mg to 100mg administered daily to 15 patients for 12 weeks of a 16-week study reduced left ventricularmass(LVM) from 196 to 191.5g and produced small decreases (0.2mm) in interventricular septal thickness and posterior wall thickness.

The vast majority of studies using animal models, including those for low renin(renal aortic coarction) and high renin(2-kidney 1-clip renal hypertensive rats) hypertension, have demonstrated either a preventive or a regressive effect of losartan potassium against cardiac hypertrophy when the drug was administered in dosages of 0.5 to 40 mg/kg/day for 2 to 16 weeks.

2.3.2 Other effects

Losartan potassium has improved survival and prevented the development of cerebrovascular infarcts and cardiovascular and renovascular fibrinoid lesions in stroke-prone spontaneously hypertensive rats and salt-loaded Dahl S rats. The drug was adminstered orally by gavage in dosages of 1 to 30mg/kg/day for 8 to 20 weeks. The effect was evident during losartan potassium administration and persisted for 8 weeks after drug discontinuation. Losartan potassium (10mg/kg/day) reduced the collagen fibre content and thus myocardial fibrosis in the 2-kidney, 1-clip hypertensive model.

In other studies in rats, the drug inhibited the incorporation human low density lipoprotein(LDL) into hearts of normotensive animals and decreased ADP-induced aggregation and thrombus weight.

2.4 Effects on Renal Haemodynamics and function

Renal function is preserved during losartan potassium administration. Glomerular filtration rate, renal blood flow, urine volume or other renal parameters were unchanged in healthy volunteers following a single 100mg dose and in patients with hypertension given losartan potassium 50mg daily for periods of 7 days to 1 year. In patients with renal insufficiency, creatinine clearance was unaffected during losartan potassium therapy for1 to 12 weeks. Excretion of urinary electrolytes(including sodium and potassium) in healthy individuals on a low-salt diet was either increased or unaltered. Hyperkalemia has been reported infrequently in clinical trials.

Uricosuria demonstrated in normal, salt-loaded and salt-depleted volunteers who received single or multiple doses of losartan potassium $\leq$100mg was also observed in some but not in other trials in patients with hypertension. The mechanism of this effect is unknown. An albumin-sparing effect(lowering of proteinuria) in otherwise healthy patients with hypertension has also occurred in the presence of renal dysfunction(including nondiabetic patients with proteinuria< 2g/day) and in elderly patients with or without non-insulin-dependent diabetes mellitus (NIDDM) receiving losartan potassium.

2.5 Effects on Bradykinin

Degradation of the potent vasodilator bradykinin, and of substance P, is prevented by ACE inhibitors. The subsequence accumulation of bradykinin may

contribute to the mechnism of their antihypertensive action. Because losartan potassium does not inhibit ACE, it would not be expected to produce elevated levels of bradykinin which are also implicated in ACE inhibitor cough.

This expectation is borne out by the evidence to date. Losartan potassium in single oral doses of 20 and 100mg did not effect forearm vasodilation induced by exogenous bradykinin infusion in healthy volunteers. Eight-day administration of losartan potassium 10mg/kg every 12 hours intraperitoneally to rats decreased blood levels of bradykinin-(1-9) and bradykinin-(1-7), suggesting that increased bradykinin levels are not contributory to the drug's hypotensive action.

2.6 Metabolic and Neuroendocrine effects

Serum levels of lipids or lipoproteins[total cholesterol, high density lipoprotein(HDL)cholesterol and triglycerides] have remained unchanged during losartan potassium treatment for 4 weeks in patients with mild hypertension but without NIDDM. In contrast, in a small sample of 8 patients, including 4 with NIDDM, serum cholesterol levels dropped by 18% and LDL cholesterol levels fell by 28%. Serum total cholesterol levels were also reduced by 8.8% among 11 patients with nephrotic syndrome who received losartan potassium 50 to 100mg daily for 1 month.

The results of a small pilot study(n=5) showed improved insulin sensitivity and a 40% decrease in plasma norepinephrine levels during treatment with losartan potassium(50mg/day for 6 weeks) in patients with severe hypertension. These findings were not corroborated in larger placebo-controlled or placebo run-in trials which found no significant change in insulin sensitivity in patients with hypertension who were not diabetic, nor any reduction in plasma norepinephrine levels in patients

with mild to moderate hypertension. The possible influence of disease severity, prior therapy or duration of therapy on these results is unknown.

In Vitro, losartan potassium 100nmol/L stimulated prostaglandin (PG) I_2 releases in human saphenous vein during exposure to AII. However, losartan potassium 50mg daily for 4 weeks did not alter renal extrarenal PG synthesis in postmenopausal women with hypertension.

Lastly, losartan potassium 50mg/day for 9 days did not affect adrenal function, as measured by adrenal steriod biosynthesis , in patients with hypertension.

3.Pharmacokinetic Properties

Hepatic oxidation of losartan potassium yields the pharmacologically active carboxylic acid metabolite E3174. The pharmacokinetic of both losartan potassium and E3174 have been determined in healthy volunteers and in patients with renal impairment, using high performance liquid chromatography assay methods.

3.1Absorption and Distribution

Oral bioavailability of losartan potassium is approximately 33% because of first-pass metabolism and is largely unaffected by food. Peak plasma concentration(C_{max}) of a single dose of losartan potassium are dose-proportional within the range of 25 to 200mg. Time to achieve C_{max} is about 1 hour for losartan potassium and 3 to 4 hours for E3174. The area under the plasma concentration-time curve(AUC) for E3174 is about 4-fold to 8-fold greater than for losartan potassium. Multiple dose(up to 6 weeks) administration does not significantly alter the pharmacokinetics of losartan potassium or E3174.

Losartan potassium was undetectable in plasma at 10 hours post-dose whereas E3174 was measurable at 24 hours. Plasma concentrations of E3174 in healthy volunteers correlated more closely with blockade of the pressor response than did those of the parent compound. Inhibition of AII-induced pressor effects was dose-dependent within the range of 40 to 120mg and reached a plateau at E3174 concentrations of about 200μg/L.

Both compounds are >98% plasma protein bound (98.7% for losartan potassium vs 99.8% for E3174). The volume of distribution is 34L for losartan potassium and 12L for the metabolite. In rats, losartan potassium crossed the blood-brain barrier after a single intravenous dose (3mg/kg) but, of more clinical importance not after single(10mg/kg) or multiple(3mg/kg3 days) oral doses. Following a single oral dose, tissue losartan potassium concentrations in the rat were highest in liver and the intestine but were undetectable in muscle or fat. The drug did not cross the placenta in sheep, but not be applicable to humans. Because of the risk of fetal abnormalities losartan potassium is not recommended in pregnancy.

3.2 metabolism and elimination

Tests in rats demonstrate a significant first-pass effect for losartan Potassium and indicate that E3174 is formed during uptake from the intestinal lumen. About 14% of a dose (8% presystemic. 6% systemic) is converted to this metabolite in most individuals, and several metabolites are also produced. In a very small proportion of patients(<1%), enzymes necessary to metabolism to E3174 are deficient.

The terminal elimination half-life($t1/2_{\beta}$) is longer for E3174(about 4 hours in Japanese and 6 hours in Western individuals) than for losartan potassium(about

2 hours). Renal clearance is 4.3 to 5.6 L/h for losartan potassium 50mg and about 1.5L/h for its metabolite. About 35% of a radiolabelled oral dose is recovered in the urine and 65% in the feces.

Less than 5% of a losartan potassium dose is excreted unchanged renally with normal renal function. Clinically relevant effects of renal impairment on the pharmacokinetics of losartan potassium would therefore be expected to be minimal. This has been confirmed in patients with varying degrees of renal insufficiency given losartan potassium 100mg daily for 7 days. Renal clearance of losartan potassium and E3174 decreased significantly in the group with the greatest degree of renal dysfunction; however, AUC did not change. Furthermore, decreases in the percentage of losartan potassium excreted in the urine over 24 hours at steady state in patients with creatinine clearance<1.8L/h(30ml/min) and increases in $t1/2_{\beta}$(from 2.1 to 3.2 hours for losartan potassium and from 10 to 123 hours for the metabolite) were not considered to be important.

On the other hand, in patients with mild to moderate alcoholic cirrhosis plasma concentrations of losartan potassium and E3174 increased 5-fold and 1.7-fold, respectively, oral bioavailability was doubled and total plasma clearance was halved. Dose adjustment is therefore required in this population.

3.3 Drug interactions

The major oxidative enzyme pathway responsible for the biotransformation of losartan potassium is the cytochrome P450(CYP) system, predominantly CYP2C9 although CYP3A(4) has also been shown to catalyse the reaction *in vitro*. Studies in healthy volunteers showed that pretreatment with cimetidine

increased AUC values for losartan potassium (by about 20%) but did not affect the AUC for E3174 or C_{max} for either compound. Likewise, ketoconazole had no influence on the systemic conversion of losartan potassium to E3174 or on their plasma clearance. This suggests that significant drug interaction with other CYP34A inhibitors are unlikely.

Conversely, the CYP inducer phenobarbital(phenobarbitone) modestly but significantly reduced the AUC for both losartan potassium and E3174. The magnitude of change in this study was too small to be clinically relevant, but it was proposed that a more potent inducer might cause a significant interaction.

Conversion of losartan potassium to E3174 was markedly deficient in <1% of participants in clinical trials. Two individuals with this rare defect who converted<1% of the parent drug to the metabolte(compare with 14% in the general population) were found to be homozygous for a mutation in CPY2C9. Other work indicates that multiple phenotypic expression exist for the defect in cytochrome enzymes.

In healthy volunteers, losartan potassium did not alter the pharmacokinetics of single-dose warfarin or intravenous or oral digoxin. Hydrochlorothiazide had no effect on losartan potassium pharmacokinetics and *vice versa*.

4.Clinical Efficacy of losartan potassium in hypertension

Losartan potassium have been investigated both as monotherapy and in combination with hydrochlorothiazide in randomized double-blind multicenter clinical trial, usually of 8 to 12 weeks' duration, involving a total of approximately 3700

patients. All comparative investigations included a placebo washout or active control run-in period and a placebo or active control during the main body of the study. The drug was administered orally and, almost invariably, once daily.

Participants were diagnosed with mild, moderate or severe disease; the proportion of patients in each category was not described in some trials. With one exception, all studies were conducted in outpatients. The primary efficacy was mean absolute change from baseline in trough supine or sitting DBP and SBP. The percentage of patients rated as ‘responders’(trough DBP<90mmHg or DBP≥90mmHg but reduced by ≥10mmHg) has been assessed in some instances.

4.1 Losartan potassium monotherapy

4.1.1 *Dose-finding studies*

Nelson et al. first reported the efficacy of losartan potassium in dosage ≥ 50mg daily in hospitalised patients. Subsequently, losartan potassium in the 50mg/day dosage has proved to be efficacious and superior to placebo in large placebo-controlled dose-finding trials in outpatients.Benefit of the 100mg daily dosage were similar to those of 50 mg/day. This latter regimen has been adopted as the usual starting and maintenance dosage in patients with mild to moderate hypertension. Significantly, more losartan potassium recipients(41 to 54%) than placebo recipients(10%) were classified as responders at the end of 4 weeks’ therapy in 1 trial.

Table 7 : Efficacy of losartan potassium(L) in dose-finding studies and comparison with other antihypertensive drugs in patients with mild to moderate hypertension; all trial were randomized, double-blind and multicenter in design [44]

Reference	Disease severity	Dosage (once daily) (mg)	Study duration	No. of evaluable patients	Mean decreased in trough sitting SBP/DBP(mmHg)	Responders (%)	Comparative efficacy
Weber et al.	Mild to moderate	L50	4wk	29	9.2**/5.2**[b]	41*	L_{all}>placebo(for ambulatory and clinic measurements)
		L100		28	9.9**/6.4**[b]	54**	
		L50bid		30	13.2**/8.5**[b]	47*	
		Placebo		30	0.0/0.2[b]	10	
Nelson et al.	SupineDBP>95 mmHg	L50	5 days	20	12.0*/10.3**		L_{all}=E> placebo
		L100		18	17.5*/11.9**		
		L150		19	18.9*/10.8**		
		E10		18	15.3/10.3**		
		Placebo		20	10.0/3.6 (all supine)		
Gradman et al.	mild(76%) to moderate(24%)	L10	8wk	72	7.6[++]/7.9*[++]		L50=E> placebo
		L25		75	7.8*/6.8[++]		
		L50		76	13.0**/10.1**		
		L100		80	8.9**[++]/9.9**		
		L150		77	10.5**[++]/9.7**		
		E20		79	14.7**/11.2**		
		Placebo		67	3.8[+]/5.6[+] (all supine)		

[a] Defined as trough DBP≤90mmHg or DBP≥80mmHg but a decrease of>10mmHg at study end

[b] 24h ambulatory measurements

[c] Abstract. Patients were hospitalized

[d] For per protocol analysis(blood pressure measured at trough)

Abbreviation and symbols:ATE= atenolol; bid=twice daily;C= captopril; DBP= diastolic blood pressure; E=enalapril;FELER=felodipine extended release;SBP=systolic blood pressure wk=weeks;y=years;*p<0.05,**p<0.01 vs placebo;[+]p<0.05'[++]p<0.01 vs active comparator;>indicates superior efficacy for L or E based on statistical differencs for DBP and percentage responders where available,p≤0.05;=indicates equivalent efficacy

Table 7 : Efficacy of losartan potassium(L) in dose-finding studies and comparison with other antihypertensive drugs in patients with mild to moderate hypertension; all trial were randomized, double-blind and multicenter in design(continued)[44]

Reference	Disease severity	Dosage (once daily) (mg)	Study duration	No. of evaluable patients	Mean decreased in trough sitting SBP/DBP(mmHg)	Responders (%)	Comparative efficacy
Tikkanen et al.	mild to moderate	L50	12wk	200 (142)[d]	10.6/8.4 (10.9/8.4)[d]	51 (51)[d]	E>L(all patients' analysis)
		E20		199 (133)[d]	$12.9^{+}/10.6^{++}$ (12.8/9.7)[d]	59^{+} (53)[d]	L=E at trough(per protocol analysis)
Mallion et al.	mild (67%) to moderate(33%)	L50-100	12wk	109	$9.1/9.1^{++}$	50^{+}	L>C
		C50-100		34	7.5/5.7	29	
Dahof et al.	mild(66%) to moerate(34%)	L50-100	12wk	132	12.2/8.3	50	L=ATE
		ATE50-100		66	11.3/10.1	65	
Chan et al.	mild(73%) to moerate(27%)	L50-100	12wk	89	17.2/13.2	69	L=FEL ER
		FEL ER5-10		43	19.0/14.0	76	

[a] Defined as trough DBP≤90mmHg or DBP≥80mmHg but a decrease of>10mmHg at study end

[b] 24h ambulatory measurements

[c] Abstract. Patients were hospitalized

[d] For per protocol analysis(blood pressure measured at trough)

Abbreviation and symbols:ATE= atenolol; bid=twice daily;C= captopril; DBP= diastolic blood pressure; E=enalapril;FELER=felodipine extended release;SBP=systolic blood pressure wk=weeks;y=years;*p<0.05,**p<0.01 vs placebo;$^{+}$p<0.05;$^{++}$p<0.01 vs active comparator;>indicates superior efficacy for L or E based on statistical differencs for DBP and percentage responders where available,p≤0.05;=indicates equivalent efficacy

Although some patients with severe hypertension have been maintained with losartan potassium monotherapy after 12 weeks, most require addition of a diuretic with or without other antihypertensive agents.

4.1.2 *Comparison with other antihypertensive drugs*

Losartan potassium reduces trough blood pressure in patients with mild to moderate hypertensionto a similar extent to standard antihypertensive agents with which it has been compared. Supine or sitting DBP fell by a mean of about 8 to 13 mmHg during 8 to 12 weeks' treatment with losartan potassium 50mg to 100mg daily, compared with 10 to 14mmHg for the other drugs.

The largest mean decrease in DBP by losartan potassium (13.2mmHg) occurred in a study of 132 elderly patients. Dosage titration was needed at week 6 in 62% of losartan potassium recipients.

There has been one comparison with captopril which was given in a once-daily regimen. Losartan potassium produced a significantly larger decrease in DBP but not SBP at week 6 and 12. At week 12, the percentage of responders for losartan potassium(50%) was nearly twice that for captopril. These results are, however, unconvincing given that the dosage regimen used are not considered therapeutically equivalent; indeed, 82% of captopril recipients(vs 60% with losartan potassium ,p=0.001) required titration to a higher dose.

Although losartan potassium appeared to be less effective than enalapril according to an 'all patients treated' analysis in a large trial of nearly 400 patients, measurement of trough blood pressure values using a per protocol analysis

showed no differences in blood pressure reductions or percentage responders between the 2 drugs.

The antihypertensive effect of losartan potassium, like that of enalapril, is evident within 1 week of starting treatment. In a large comparison in 526 patients, clinically relevant reductions were manifest within 1 to 2 weeks of starting therapy with losartan potassium 50mg to 150mg daily or enalapril 20mg daily and were maximal at 3 to 6 weeks after treatment initiation. Similarly, Dahlof *et al*. found that antihypertensive efficacy reached a plateau at 6 weeks, with no further reduction discernable at 12 weeks.

4.2 Losartan potassium plus hydrochlorothiazide

4.2.1 *Noncomparative study*

Among 179 participants in the Losartan Severe Hypertension Study who began therapy with losartan potassium 50mg, 22% continued with losartan potassium monotherapy at week 12, 30% received losartan potassium plus hydrochlorothiazide 12.5 to 25 mg/day and 46% received this last regimen plus dihydropyridine calcium channel blocker or atenolol or both. The remaining 2% were prescribed regimen outside the protocol.

The overall decrease in blood pressure of 26/19 mmHg for all patients in this trial resembled the reduction of 18.4mmHg in DBP documented in a similar 12-week study of 131 patients. This latter result was obtained using a regimen

containing a tablet specifically formulated to contain losartan potassium 50mg/hydrochlorothiazide 12.5 mg, with provision for the doubling of dose plus addition of felodipine and/or atenolol. Approximately one-third of patients were controlled with the combination tablets only, but most also received felodipine.

4.2.2 Dose-finding and comparative trials

Weber et al found that the addition of hydrochlorothiazide 12.5mg daily for 2 weeks in patients unresponsive to losartan potassium lower DBP by a further 6.1 to 7.8 mmHg, similar to the decrease of 6.4mmHg in the placebo plus hydrochlorothiazide group. Adding hydrochlorothiazide in dose >12.5mg to losartan potassium 50mg reduces DBP by additional 4 to 6mmHg versus monotherapy with losartan potassium 50mg or with hydrochlorothiazide12.5mg or 25mg.

For example, DBP was decreased by 13.2mmHg with losartan potassium 50mg plus hydrochlorothiazide12.5mg versus 8.8mmHg with losartan potassium and 7.2mmHg with hydrochlorothiazide. Efficacy for the combination, as for losartan potassium monotherapy , was seen after 1 week and reached a maximum at 3 to 6 weeks. The percentage of patients responding in this trial was greatest for losartan potassium plus hydrochlorothiazide12.5mg(78%), similar for losartan potassium plus hydrochlorothiazide6.25mg(60%) and for losartan potassium (56%), and least for hydrochlorothiazide(47%).

As for monotherapy, regimen containing losartan potassium produce equivalent antihypertensive effects to those containing enalapril in direct comparisons. Hydrochlorothiazide was added in 53% of 132 patients with mild to moderate hypertension who initially received losartan potassium and 47% of enalapril

10mg group(n=36). Decreases in DBP were significantly larger in the losartan potassium group at 4 weeks, but not at study end, and response rates did not differ(68% vs 60%).

Similarly, in patients with severe hypertension, DBP fell by 27.7mmHg with losartan potassium plus one or more other drug(hydrochlorothiazide + calcium channel blockers $\pm$ atenolol) and by 30.9mmHg with a comparable regimen containing enalapril. None of the reductions in DBP differed between groups at any of the measured interval(week1,4 and 12). At study end, 94% of 50 losartan potassium and 83% of 25 enalapril recipients were receiving either drug plus hydrochlorothiazide and one other antihypertensive drug.

4.3 Special Patients groups

Elderly patients have responded well to losartan potassium . Blood pressure reductions were similar for losartan potassium and felodipine ER in a study conducted specifically in elderly patients, and response did not differ between patients older or younger than 75 years. Among 29 individuals(18% of total) aged$\geq$65 years in a comparison with captopril, age did not influence the antihypertensive effect of either treatment. Dahlof *et al*. also found no differences in response to losartan potassium between younger and elderly patients(>65 years) nor between male and female patients (no quantitative data were presented). Patients 65 years or older showed a larger mean reduction in DBP at 12 weeks with losartan potassium (n=25) than with enalapril(n=30) [12.7 vs 8.7mmHg, p=0.03], but percentage of responders was similar.

This was also the case for the Black patients analysed in this study (losartan potassium =32;enalapril=33). The DBP reduction was slightly but significantly

greater in the group(10 vs 8mmHg, p=0.02). The number of Black patients enrolled in other clinical trials(e.g.12% and 19%) has been too few to permit subgroup analysis.

Blood pressure decreased significantly from baseline(from 161/100 to 144/87mmHg) in 89 patients with hypertension and various degrees of renal failure who has received losartan potassium 50 to 100mg daily for 12 weeks. Similar results were earlier reported in 24 such patients treated for 7 days.

4.4 Long term Efficacy

In a noncomparative trial, the antihypertensive effects of losartan potassium persisted in the long term. 70.7%(41 of 58) of a losartan potassium monotherapy group(25 to 100mg daily) and 86.7%(26 of 30) of those receiving concomitant thiazide diuretics showed similar decreases in blood pressure at the end of a 52-week period to those recorded during the initial 8- to 10-week study. Extended clinical experience will assist an establishing the long term profile of losartan potassium several such trials are underway.

5. Tolerability profile

Dose, age, gender or race are reported to have no influence on the tolerablilty profile of losartan potassium; quantitative data for between-group comparisons are unavailable.

5.1 Losartan potassium monotherapy

As shown in double-blind trials, losartan potassium is very well tolerated. Among 2085 losartan potassium and 535 placebo recipients usually treated for 8 to12 weeks, losartan potassium monotherapy produced a similar incidence of drug-related overall events(15.3 vs 15.5%) and patients withdrawal(2.3 vs 3.7%) to

placebo. Drug-related events experienced most frequently with losartan potassium were headache(4.2%), asthenia/fatigue(2%) and also dizziness, which was the only drug-related event reported more frequently with losartan potassium than with placebo(2.4 vs 1.3%).

When a casual relationship of events to treatment was not considered, the most common reported unwanted events in patients receiving losartan potassium monotherapy were headache(14.1%), upper respiratory tract infection(6.5%), dizziness (4.1%), and asthenia/fatigue(3.8%). Cough was reported in 3.1% of the losartan potassium group.

The incidence of oedema with losartan potassium and ACE inhibitors was 1.7%, a rate similar to that placebo(1.9%). Orthostatic effects and first-dose hypotension appear uncommon, occuring in$\leq$0.5% of losartan potassium 25 to 50mg and 2.2% of 100mg recipients. One report has described classic migrain in a patients without a previous history of migrain. Symptoms developed within 6 hours of losartan potassium 50mg dose and were confirmed on rechallenge. Reversible ageusia also occurred in 1 patient receiving losartan potassium 25mg/day; this symptom appeared within 3 weeks of commencing therapy and resolved within 2 to 3 weeks of treatment discontinuation.

To date there have also been 2 reports of angioedema during losartan potassium therapy. A patient who was hypertensive to penicillin and aspirin developed facial rash and swelling considered by the investigator to be angioedema. Facial swelling and flushing without dyspnoea occurred within 30 minutes of ingestion a 50mg

dose of losartan potassium in another patient with glomerulosclerosis and no history of angioedema, who had discontinued captopril because of cough.

During long term losartan potassium treatment(≥1 year) in 306 patients, headache(3.6%), dizziness(2.9%) and asthenia/fatigue(2.6%) were the most common complaints. Rebound hypertension has not been reported in clinical trials which continued patient follow-up after abrupt losartan potassium withdrawal.

Levels of liver enzymes, usually alanine aminotransferase, have occasionally been elevated transiently during losartan potassium therapy(1.9%) and these increases necessitated drug withdrawal in one patient. Hyperkalemia(serum potassium>5.5mmol/L) was demonstrated on 1.5% of patients given ACE inhibitors but did not result in any patient being discontinued.

Apart from these alterations, no other changes in laboratory indices were reported in the clinical trials database. There were no changes in haematological or haemorrheological indices in 7 elderly patients treated with losartan potassium 50 to 100mg/day for 52 weeks. Losartan potassium did not reduce heart rate in healthy individuals or in patients involved in the clinical trials.

5.2 Losartan potassium plus hydrochlorothiazide

With losartan potassium plus hydrochlorothiazide, the incidence of any drug-related adverse event(14.8%) or event causing drug withdrawal(2.8%) is similar for losartan potassium alone and for placebo. The tolerability of the combination is difficult to assess when it is used with other drugs. In comparative studies, 23% of 131 patients who received losartan potassium plus hydrochlorothiazide with or without atenolol and felodipine had a drug-related adverse event. Similarly, headache occurred

in 26% of 180 patients with severe disease receiving polytherapy with losartan potassium plus hydrochlorothiazide with or without atenolol and a dihydropyridine calcium channel blocker. One trial comparing losartan potassium and enalapril, both plus hydrochlorothiazide and other drugs, found no differences in tolerability between the 2 approaches, but no quantitative values were given.

The rates of increased serum uric acid levels (3.5%) and decreased serum potassium levels(3.2%) with losartan potassium plus hydrochlorothiazide approximated those for diuretic alone(3.9% and 4.3%) when overviewed in all clinical trials.

6.Dosage and administration

The recommended starting and maintenance dosage of losartan potassium as monotherapy in patients with essential hypertension is 50mg once daily. Some patients may benefit from receiving 100mg once daily. A dosage of 25mg once daily should be given to patients with hepatic impairment or volume depletion or who are otherwise at high risk of hypotension. Hydrochlorothiazide 12.5mg daily may added in patients not responding completely to losartan potassium.

In Japanese studies, the initial dosage of losartan potassium for mild to moderate hypertension has been 25mg daily.

No initial dosage adjustment is necessary for elderly patients or those with renal impairment, including patients undergoing dialysis. However, in patients whose renal function may depend on an intact RAS, losartan potassium may be expected to be associated with worsening renal impairment. Losartan potassium may be given with or without food and with other antihypertensive agents.

Losartan potassium is not recommended in pregnant women because of risk of fetal and neonatal morbidity and death.

The combination of losartan potassium and hydrochlorothiazide is initiated at a dosage of 50mg/12.5mg daily. The dosage can be doubled to 2 tablets daily(the recommended maximum). The product is not recommended for initial therapy in patients with hypertension when monotherapy is the usual starting point, for patients with hepatic impairment or use in patients with creatinine clearance≤1.8L/h(30ml/min) , who should receive loop diuretics rather than hydrochlorothiazide. [44]

CHAPTER III

MATERIALS AND METHOD

Materials

1.Drug

Losartan potassium(COZAAR®) 50mg tablets

Losartan potassium 50mg plus hydrochlorothiazide 12.5mg tablets(HYZAAR®)

Hydrochlorothiazide 50mg tablets(DICHLORTIDE®)

from MSD(BLH TRADING CO.,LTD)

2.Instruments

-Mercury Sphygmomanometer

-24-hour Ambulatory blood pressure monitoring machine

(TM2421,A&D Company limited, Japan)

Patients

Subjects were recruited into the study based on the following criteria:

Inclusion criteria

-The patients were men or women with an aged older than 18 years old

-Primary hypertensive with the office seated SBP in the range of 140-179 mmHg and/or DBP in the range of 90-109 mmHg at the end of an initial 1-week placebo run-in period (at baseline) or antihypertensive drugs withdrawal and placebo run-in for at least 5 times of half life

-Mean daytime ambulatory blood pressure(ABP) showed

SBP≥130mmHg and/or DBP≥80mmHg after 2 weeks placebo run-in & washout period able to recruited.

-The patients were willing to be recruited in this study and sign consent form

Exclusion criteria

-hypersensitivity to losartan potassium or other angiotensin II receptor antagonists or hydrochlorothiazide

-secondary hypertension of any etiologies

-having a history of hypertensive encephalopathy or cerebrovascular accident

-significantly impaired renal function(serum creatinine>3.0 mg/dl)

-significantly impaired hepatic function(AST>76 U/L, and/or ALT>76 U/L)

-pregnancy or lactation

-having an evidence of advanced target-organ damage such as severe retinopathy(gradeIII, IV), or proteinuria(>1 gm / day)

Method

Study design

After a 1-week placebo run-in and washout from any previous antihypertensive therapy period, office seated blood pressure(OBP) were measured by mercury sphygmomanometer and 24-hour blood pressure were monitored by using ambulatory blood pressure monitoring(ABPM) machine. The patients were eligible for this study if their mean office systolic blood pressure(SBP) was 140-179mmHg and/or mean office diastolic blood pressure(DBP) was 90-109mmHg and their mean daytime SBP (09.00am-09.00pm) by ABPM machine was≥130mmHg and/or mean daytime DBP was≥80mmHg .

Patients were randomized to either 4 weeks treatment of losartan potassium 50 mg or hydrochlorothiazide12.5 mg once daily morning after meal for 4 weeks, and their OBP and 24-hour ABPM were evaluated. Patients in hydrochlorothiazide group would be prescribed to receive losartan potassium50 mg once daily morning after meal and vice versa for another 4 weeks treatment period. Office blood pressure was evaluated and 24-hour ABPM was performed after that.

Patients who achieved office systolic blood pressure and diastolic blood pressure ≥10% lower than baseline were classified as responders. SBP/DBP of<140/90 mmHg was determined as normalized BP.

Patients in losartan potassium BP normalized group were randomized to 2 parallel treatment groups: losartan potassium 25mg(COZAAR®1/2 tablets) or losartan potassium 25 mg plus Hydrochlorothiazide 6.25 mg(HYZAAR®1/2 tablets) once daily moring after meal for 4 weeks period. Patients in losartan potassium non-BP normalized

group were randomized to 2 parallel group: losartan potassium100 mg(COZAAR®2 tablets)or losartan potassium 50 mg plus Hydrochlorothiazide12.5 mg(HYZAAR®1 tablets) once daily morning after meal and their blood pressure were again evaluated after the patients were on the new dosage for at least 4 weeks.

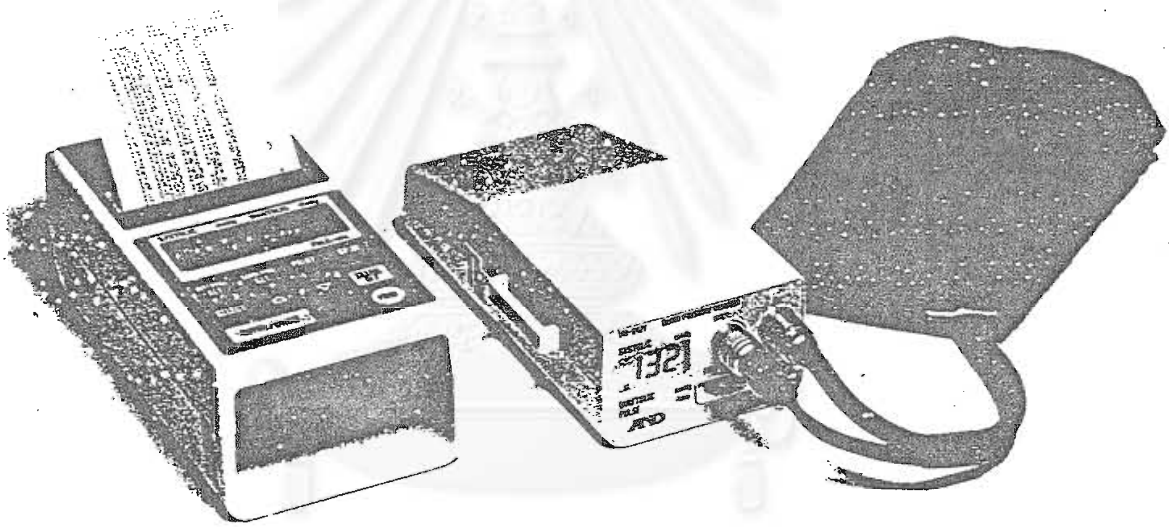


Figure 3: Ambulatory blood pressure monitoring machine

Procedures

Office Blood pressure measurement

Sitting SBP and DBP were measured with a mercury sphygmomanometer (korotkoff I and V for SBP and DBP, respectively) on the left arm after subjects had been rest in the sitting position for 5 minutes(min.). Three consecutive BP and heart rate (HR) were measured and recorded.

24-hour ambulatory Blood pressure measurement

24-hour ambulatory BP and HR were measured with a portable, non-invasive, fully automatic BP recording machine(TM2421;A&D company, Limited, Japan) which and be used alternatively between auscultatory and oscillometric methods. The adult cuff (range:20-31cm) was applied to the left arm of each subject. The recorder was programmed to had at 30-min intervals for the 06.00am.-10.00pm. period and at 60-min intervals for the 10.00pm.-06.00am. period . Subjects were allowed to have their normal daily activities. However, they were instructed to remain motionless each time a reading were taken and to note down the times they went to bed and woke up in the morning.

Data analysis

Office Blood pressure measurement

The average of the three BP and HR measurement was used for the evaluation. Sitting DBP was employed as an index of treatment response in that subjects who had a DBP and SBP reduction of $\geq$10% from baseline were defined as responders and those with a SBP<140mmHg and DBP<90mmHg at the end of the test treatment were defined as normalized. The mean arterial pressure (MAP) was calculated as DBP plus 1/3 of the difference between SBP and DBP.

24-hour ambulatory BP measurement

BP was detected by oscillometric method, however in the case whose oscillometric measurement was failure the korotkoff BP will be used instead for the analysis. Raw data of ambulatory BP and HR were transferred to a computer programme. Systolic readings of >250 or <70mmHg, diastolic readings of >130 or <30mmHg , pulse pressure (SBP-DBP) of >160mmHg or <20mmHg were deleted. And when actual values differ by 60 mmHg or more from each pre-measurement value within 1 hour , the data for the corresponding patient are picked up ,and individually examined.

Mean of SBP, DBP, MAP and HR were calculated for each hour, the entire 24-hour, during day-time period(09.00am-09.00pm) and during night-time (00.00a.m.-05.00a.m.). Mean hourly values were derived from the average of 3 readings obtained in each hour. For example, the values at 7.30 , 8.00 and 8.30 were used for the calculation of BP value at 8 o'clock, day-time and night-time periods were defined as 09.00 a.m.-09.00 p.m. and 00.00 a.m.-05.00 a.m., respectively.

BP difference during sleep and awake was determined by subtraction of the mean or the average night-time BP from that of the day-time BP. Percentage of the reduction relative to the average day- time BP was also calculated.

Dippers and Non-dippers

Dippers were defined as those patients who had the reduction in the night-time SBP and DBP $\geq$10% of their day-time values. Those whose night-time BP were not reduced by more than 10% were defined as non-dippers.

BP loads

BP loads were BP values that were higher than 140 or 120mmHg for SBP during day-time and night-time, respectively and 90 or 80mmHg for DBP. BP loads were expressed both as the frequency or percentage and the absolute value of blood pressure (mmHg).

Area under the blood pressure curve(AUC)

AUC was calculated by using area under the systolic or diastolic BP curve, with SBP cutoff values of 140 mmHg during the daytime and 120 mmHg during nighttime and DBP cutoff values of 90 mmHg during daytime and 80 mmHg during nighttime.

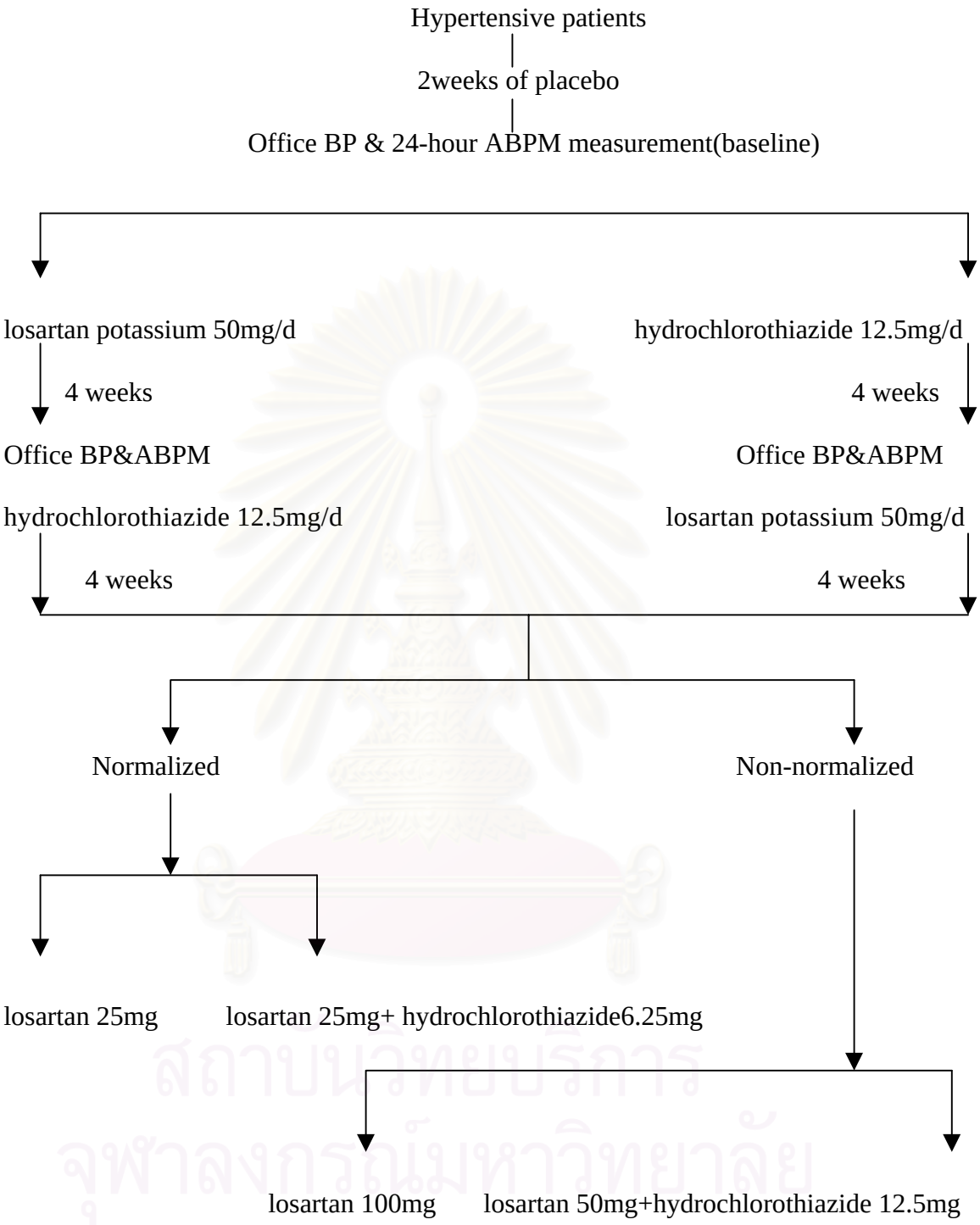
Trough to peak ratio(T:P ratio)

T:P ratio is the ratio between the antihypertensive effect at the end of the dosing interval(trough) and at the time of its maximum effect(peak). For each 24-hour ABP recording, trough SBP and DBP effects were BP reductions achieved between 23 and 24 hours after the dose, while peak SBP and DBP effects were the values averaged from the 2 adjacent hours giving maximum BP reduction which usually occur during 2-6 hour after the dose. T:P ratios were presented both as the mean of each individual T:P ratio obtained from using the mean trough and the mean peak values from all patients in the study.

Statistical analysis

-result are presented as mean±SD

-The OBP, 24-hour ABP measurements before and after treatment with losartan potassium 50mg and hydrochlorothiazide 12.5mg in cross over design and antihypertensive effects of losartan potassium and losartan potassium plus hydrochlorothiazide either dose titration or in combination were compared by using repeated measures analysis of variance(repeated measures ANOVA) and followed by the Bonferroni correction to calculate the significance of pairwise differences. Trough to peak ratio were calculated using both mean and the individual data



Note ;-normalize in this study mean office SBP<140 and DBP <90mmHg

Non-normalize mean office SBP≥140mmHg but DBP<90mmHg or SBP<140 but DBP≥90mmHg

Figure 4: The Study flow chart

CHAPTER IV

RESULTS AND DISCUSSION

1. Hypertensive patients

We began to recruit the patients during July 2000 and March 2001 at the out patient department, King Chulalongkorn Memorial Hospital. The screening process identified 42 patients who met the screening criteria for eligibility and entered the placebo run-in period. Nine patients were excluded for several reasons i.e., eight patients were diagnosed to be white coat hypertension(when we closely monitored with ambulatory blood pressure monitoring machine(ABPM), their mean day-time SBPs were less than 130 and/or DBPs were less than 80 mmHg), while one patient was excluded due to his blood pressure showed stage of severe hypertension.(BP$\geq$ 180/100 mmHg).The remaining thirty-three subjects, having day-time SBP and DBP $\geq$ 130/80 mmHg measured by ABPM, were recruited in the study. During the study, one patient was dropped out from the study due to uncomfortable with the machine. Finally, there were thirty-two patients who completed this study and their data only were used for statistical analysis.

Demographic data

Thirty-two hypertensive patients were enrolled in this study. Baseline demographic details are summarized in Table 9. There were eleven males and twenty-one females, with the average age of 52$\pm$9.7 years(range 30-69 years). The average weight, height and BMI values (mean$\pm$SD) were 63$\pm$10.9 kg., 157$\pm$8.2 cm.

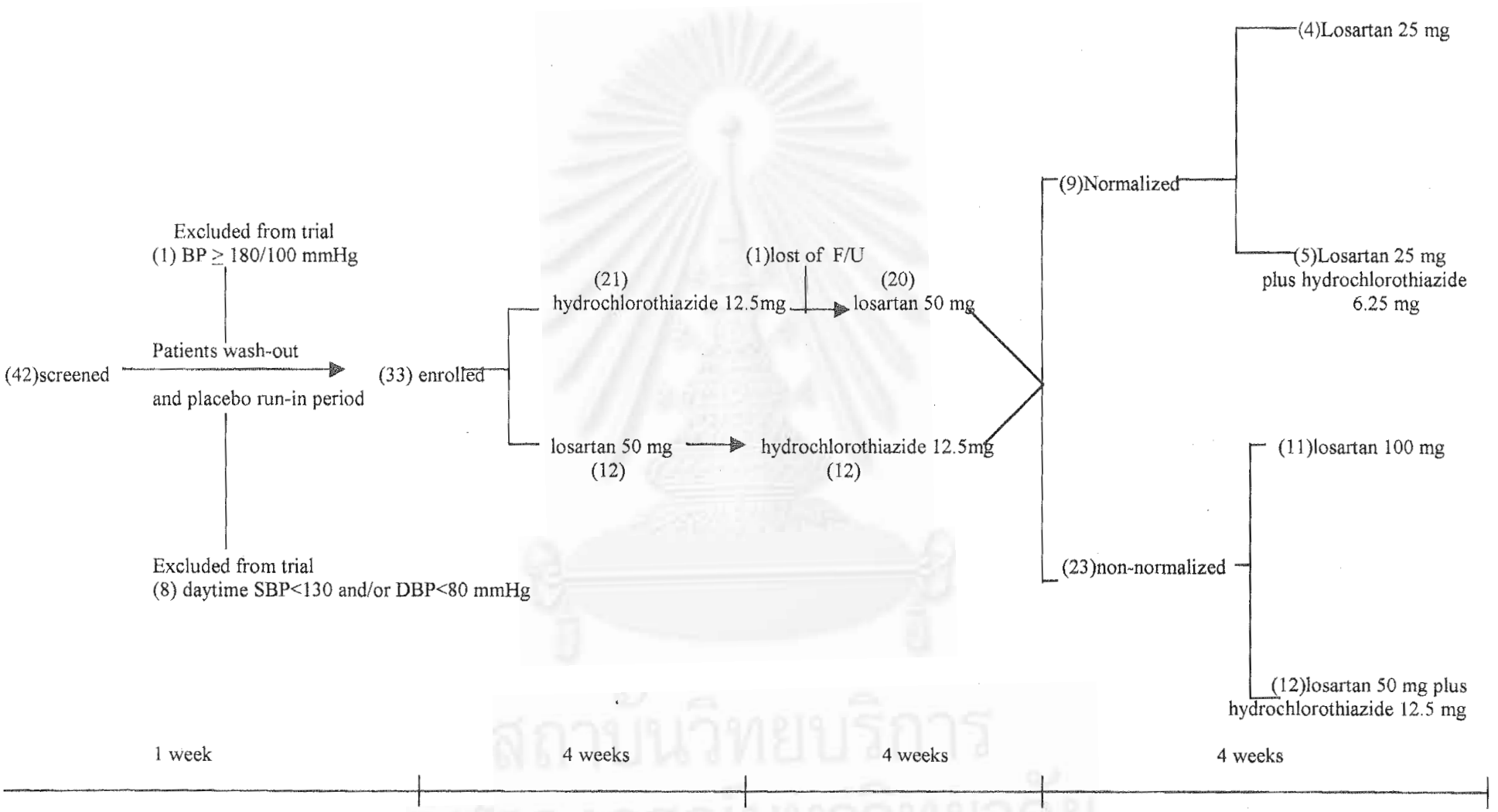


Figure 4: Study flow chart of treatment

Table 9 : Demographic data of the subjects

NO. of subjects	**32**
Sex(no.)	
male	11
female	21
Age(years)	
Mean $\pm$ SD	52$\pm$9.7
Range	30-69
Weight(kg.)	
Mean $\pm$ SD	63$\pm$10.9
Range	45-84
Height(cm.)	
Mean $\pm$ SD	157$\pm$8.2
Range	145-172
BMI(kg/m^2)*	
Mean $\pm$ SD	25$\pm$3.7
Range	19.6-37.2
Cigarettes smoking(no.)	1
Alcoholic(no.)	
social	5

* BMI =Body Mass Index= $\frac{weight}{(height)^2}$

Table 10 : Laboratory data of the subjects at baseline(n=32)

Test(normal range)[a]	Mean± SD	Range	
FPG(70-110 mg/dl)	94.8±12.2	74-121	
Cr(0.5-2.0 mg/dl)	0.92±0.25	0.5-1.5	
Uric acid(2.0-7.0 mg/dl)	5.97±1.52	3.5-9.1	
Cholesterol(150-240 mg/dl)	229±41.63	153-335	
Triglyceride(40-155 mg/dl)	130±64.9	54-321	
HDL(0-100 mg/dl)	54±12.1	32-74	(n=22)
LDL(130-159mg/dl)	146±34.5	96-221	(n=22)
AST(0-38 U/l)	24±11.2	13-70	
ALT(0-38 U/l)	26±16.1	7.0-71	

FPG= fasting plasma glucose

Cr= Creatinine clearance

AST=Alanine aminotransferase

ALT=Aspartate aminotransferase

[a]= normal range of King Chulalongkorn Memorial Hospital

and 25±3.7kg/m^2, respectively. One subject was currently cigarettes smoking and five subjects drank alcohol for social life.

Laboratory data at the end of the placebo run-in period are shown in table 10

Majority of these patients had normal levels of laborotory data. Eleven patients showed high cholesterol level(>240 mg/dl), while eight patients showed high triglyceride level(>155 mg/dl), among of them, six patients had both high levels of cholesterol and triglyceride. Five patients showed hyperglycemia(>126 mg/dl) while five patients showed hyperuricemia(>7.0 mg/dl). One patient showed high levels of liver function test, but not more than two times of the normal ranges. The demographic and laboratory data of each patients are demonstrated in appendices A and B.

2. Blood pressure data of the patients at baseline

Blood pressure after taking placebo was used as the baseline level for comparing the drug effects. Five patients had never been treated for their hypertension while twenty-seven of them had been administered with antihypertensive drug either monotherapy or combination therapy before they entered this trial. There were little differences in blood pressure between screening visit and after placebo run-in in new onset patients. In treated patients, none of them showed severe hypertension(SBP≥180 and/or DBP≥110 mmHg) after placebo run-in.

Some benefits of ambulatory BP measurement over the standard clinic or office blood pressure measurement in a clinic therapeutic trial have been well established. [41 –43] First, it is not substantially affected by the administration of placebo over

several weeks. Second, the error arising as the white-coat effect can also be avoid. Third, 24-hour mean blood pressure is more reproducible than clinic blood pressure . Thus, white-coat hypertensive patients could be identified and excluded from the antihypertensive drug trial with 24-hour ABP measurement.

Table 11 shows blood pressure at baseline measured both as office blood pressure and 24-hour ABP measurement. The mean office blood pressure was 155±12.7 / 97±7.3mmHg while the mean 24-hour blood pressure was 143±8.9 / 87±8.5mmHg and the mean daytime blood pressure was 148±10.0 / 90±9.1mmHg. The mean nighttime blood pressure or during sleep was 133±98 / 80±8.9mmHg. The mean nighttime blood pressures were 15 and 10mmHg less than the daytime blood pressures for SBP and DBP respectively.

Hypertensive patients recruited into this study had high BP both in the office and in their daily life. The average 24-hour BP value was lower than that of the office BP. This was essentially due to the large reduction in BP during the night. It was demonstrated that the fall in BP at night was the result of sleep and inactivity rather than the time of the day.

By using the 24-hour BP monitoring, blood pressure variability throughout the day could be observed. The SBP/DBP value that were higher than 140/90mmHg during daytime and 120/80mmHg during nighttime were judged as anomalous value or elevated values or BP loads. The frequency and absolute values of BP loads are also presented in table 11. It was found that the hypertensive subjects possed high percentage of BP loads which was presented both during daytime and nighttime. About 67% of SBP and 47% of DBP obtained during daytime were anomalous

Table 11 : Office BP and 24-hour ABP of the subjects after placebo run-in period (at baseline)(n=32)

	Office BP* (mmHg)	24-hour ABP*								
		Average BP(mmHg)			BP load**					
					24-hour BP		daytime BP		nighttime BP	
		24-hourBP	day-timeBP	night-time BP	frequency[a] (%)	absolute[b] (mmHg)	frequency[a] (%)	absolute[b] (mmHg)	frequency[a] (%)	absolute[b] (mmHg)
SBP	155±12.7	143±8.9	148±10.0	133±9.8	69±20.9	16±5.5	67±22.9	15±6.3	79±24.7	17±7.1
DBP	97±7.3	87±8.5	90±9.1	80±8.9	48±21.2	8±4.9	47±29.4	9±5.0	51±31.9	7±5.7
MAP	116±7.2	106±7.9	108±8.1	98±9.0						
HR(bpm)	76±8.4	77±9.1	81±9.1	68±10.8						

* data are shown as mean ± SD

** BP load were BP values that higher than 140 or 120 mmHg for SBP and 90 or 80 mmHg for DBP during daytime, nighttime respectively

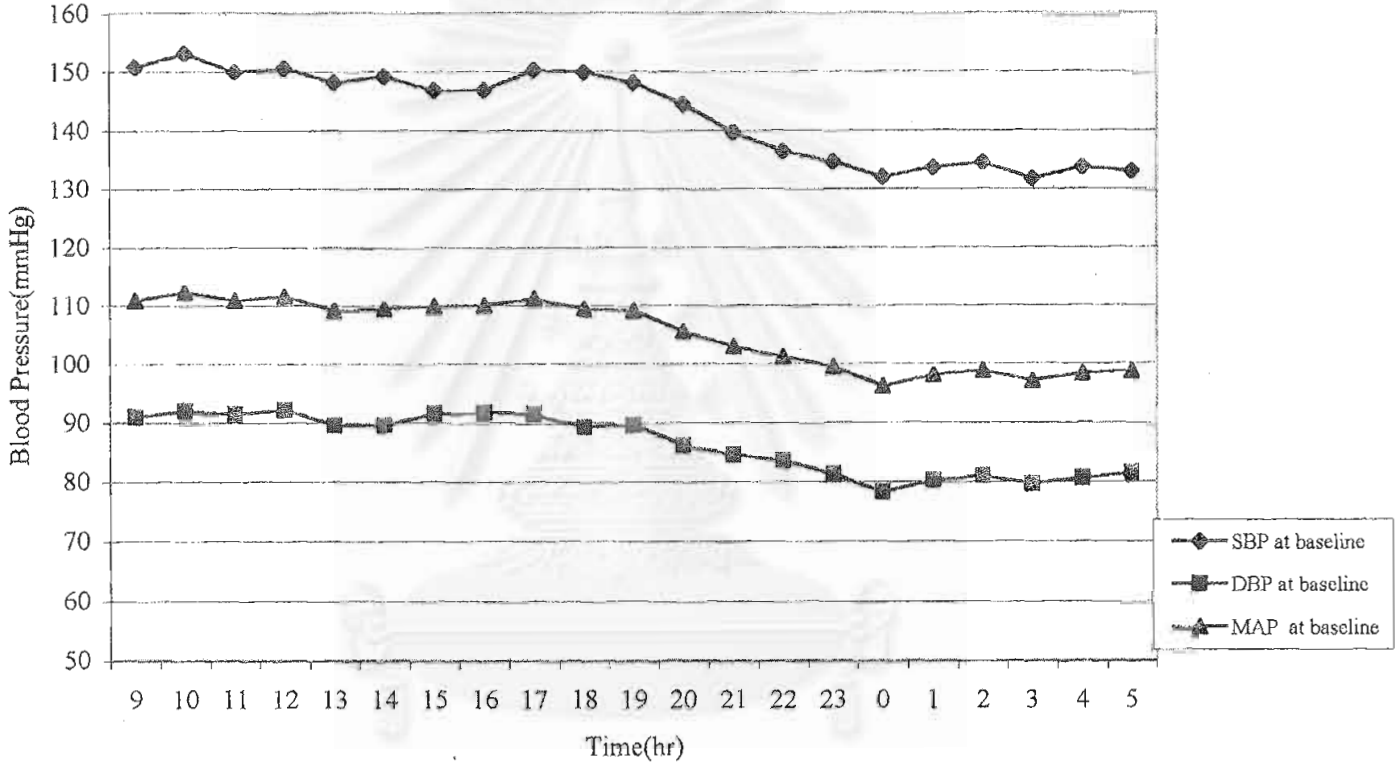
[a] frequency of BP loads is the percentage of BP load

[b] absolute of BP loads is the average of the BP values which were above the normal BP ranges

24-hour BP =average BP during 24 hours, daytime BP= average BP during09.00 a.m.-09.00p.m.,nighttime BP= average BP during 00.00a.m.-05.00a.m.by ambulatory blood pressure monitoring machine

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure(=DBP+1/3(difference between SBP and DBP)),HR= heart rate

Figure 6 :Ambulatory Hourly Blood Pressure Data of subjects at baseline(n=32)



values, they were higher than 140/90mmHg by 15±6.3 and 9±5.0mmHg for SBP and DBP respectively. Even higher percentages of anomalous values(SBP/DBP) of 79±24.7 / 51± 31.9 % were observed during nighttime. In addition, these BP loads during nighttime were 17±7.1 / 7±5.7mmHg higher than 120/80mmHg. When 24-hour BP was evaluated, the percentage of elevated BP values were 69±20.9 / 48±21.2 % while the magnitude of absolute deviated BP were 16 ±5.5 / 8±4.9 mmHg.

3.Antihypertensive effect evaluation

Step 1

Office blood pressure

After treatment with hydrochlorothiazide 12.5 mg once daily, it was found that office BP and DBP significantly decreased, from 155±12.7 / 97±7.3mmHg to 144±133.2 / 93±8.3mmHg (these BP were significantly different from the pre-treat values($p < 0.001$/ $p=0.04$). MAP was also significantly lowered from 116±7.2 to 109±9.6mmHg ($p<0.001$).

After losartan 50mg once daily administration, office SBP and DBP were significantly reduced from 155±12.7 / 97±7.3mmHg to 142±13.6 / 89±10.0mmHg ($p<0.001$). MAP was also significantly lowered from 116+7.2 to 107+10.1mmHg ($p<0.001$).

There were no significant differences in SBP and MAP between treatments, however DBP showed significant differences at $p=0.044$ level. HR showed no significant change after either regimens and were recorded to be 76±8.4

before treatment and was 77±10.4, 74±8.2 bpm after hydrochlorothiazide and losartan treatments respectively (table12).

Neither symptomatic nor postural hypotension or even cough were reported during treatment with these regimens.

Ambulatory blood pressure

Average 24-hour BP

By 24-hour evaluation, SBP and DBP were significantly reduced from 143±8.9 / 87±8.5 to 136±12.3 / 82±8.7mmHg with losartan treatment ($p<0.01$). MAP was also significantly lowered from 106±7.9 to 101±9.5mmHg ($p<0.01$) with this regimen. In controversy, with hydrochlorothiazide treatment, although SBP, DBP and MAP were also reduced from baseline to 140±9.3 , 85±8.6 and 103±8.3 respectively, but these reductions were too small that they were not statistically significant.

Average daytime BP

When the BP during daytime hours only were considered, the mean daytime SBP and DBP were significantly reduced from 148±10.0 / 90±9.1mmHg to 141±13.0 / 85±9.7mmHg with losartan 50 mg administration which show statistcally significant at p value<0.05 and p<0.01 respectively. MAP was also lowered from 108±8.1 to 104±10.9mmHg ($p=0.058$), while treatment with 12.5 mg of hydrochlorothiazide showed that the average daytime SBP, DBP and MAP were reduced to 145±9.6, 87±8.9 and 107±8.5 mmHg respectively which none was statistcally significant.

Table 12 : The mean office BP and ABP of the subjects at baseline, after 12.5 mg hydrochlorothiazide and after 50 mg losartan treatment (n=32)

Parameter	**baseline**	**hydrochlorothiazide 12.5 mg**	**losartan 50 mg**
	mean±SD	mean±SD[a]	mean±SD[b,c]
Office BP			
SBP(mmHg)	155±12.7	144±13.2****	142±13.6****, ns
DBP(mmHg)	97±7.3	93±8.31**	89±10.0****, *
MAP(mmHg)	116±7.2	109±9.6****	107±10.1****, ns
HR(bpm)	76±8.4	77±10.4[ns]	74±8.2[ns, ns]
24-hour ABP			
average 24-hour			
SBP(mmHg)	143±8.9	140±9.3 [ns]	136±12.3**, ns
DBP(mmHg)	87±8.5	85±8.6 [ns]	82±8.7**, ns
MAP(mmHg)	106±7.9	103±8.3 [ns]	101±9.5**, ns
HR(bpm)	77±9.1	77±8.0 [ns]	76±9.2 [ns, ns]
average daytime			
SBP(mmHg)	148±10.0	145±9.6 [ns]	141±13.0*, ns
DBP(mmHg)	90±9.1	87±8.9 [ns]	85±9.7**, ns
MAP(mmHg)	108±8.1	107±8.5 [ns]	104±10.9[$, ns]
HR(bpm)	81±9.1	84±8.9 [ns]	83±9.7 [ns, ns]

[a,b] versus baseline, [c] versus hydrochlorothiazide

A14 p<0.001, ** p<0.01 ,*=p< 0.05, [$] p=0.05-0.1 ,ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate respectively

Table 12 : The mean office BP and ABP of the subjects at baseline, after hydrochlorothiazide and after losartan treatment (n=32)(continued)

Parameter	**baseline**	**hydrochlorothiazide 12.5 mg**	**losartan 50 mg**
	mean±SD	mean±SD[a]	mean±SD[b,c]
average nighttime			
SBP(mmHg)	133±9.8	130±11.5 [ns]	125±11.9****, *
DBP(mmHg)	80±8.9	79±9.4 [ns]	75±7.8**, *
MAP(mmHg)	98±8.1	97±9.6 [ns]	92±8.2**, *
HR(bpm)	68±10.8	68±9.3 [ns]	68±11.4[ns, ns]

[a,b] versus baseline, [c] versus hydrochlorothiazide

**** p<0.001, ** p<0.01 ,*=p< 0.05, [$] p=0.05-0.1 ,ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Figure 7: Ambulatory Hourly Blood Pressure Data after HCTZ 12.5mg treatment(n=32)

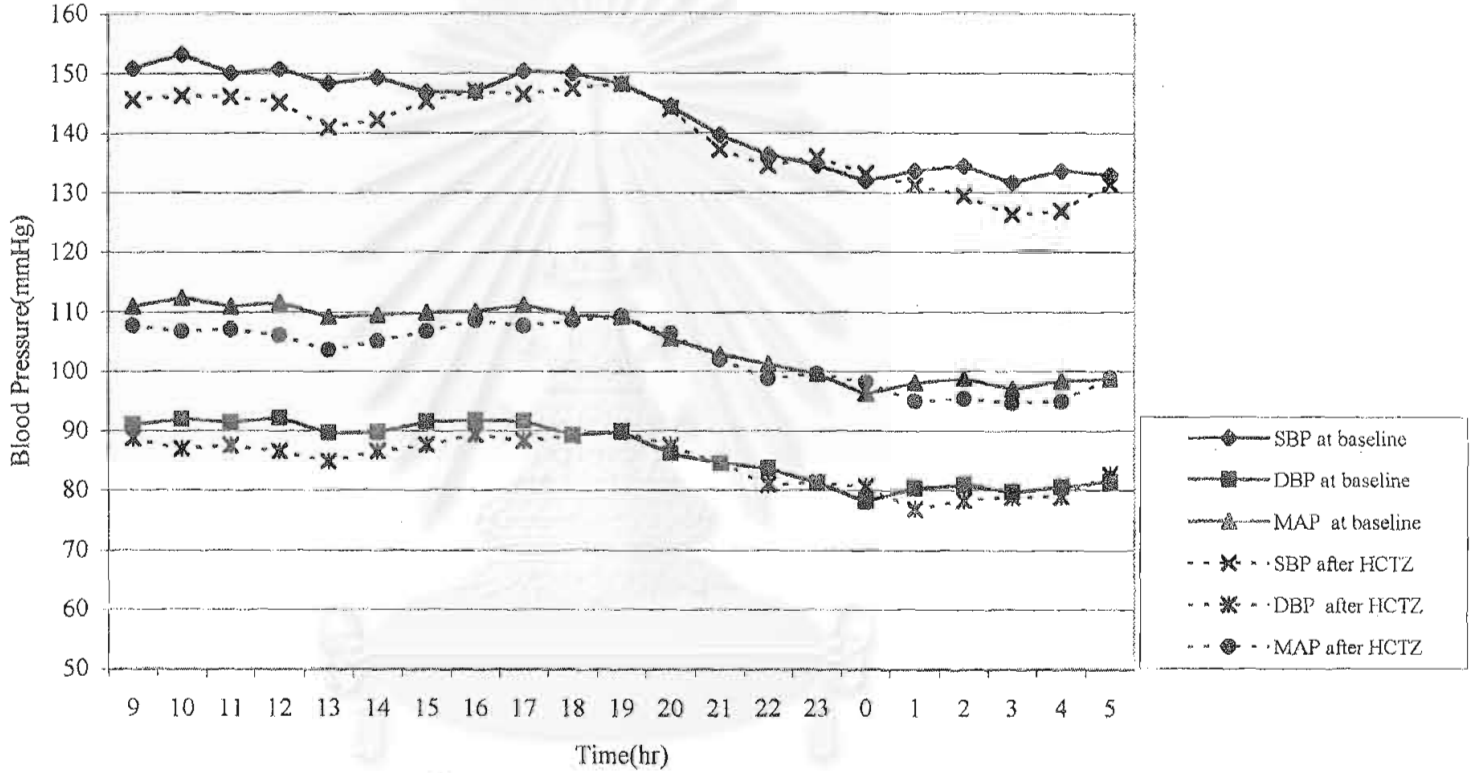
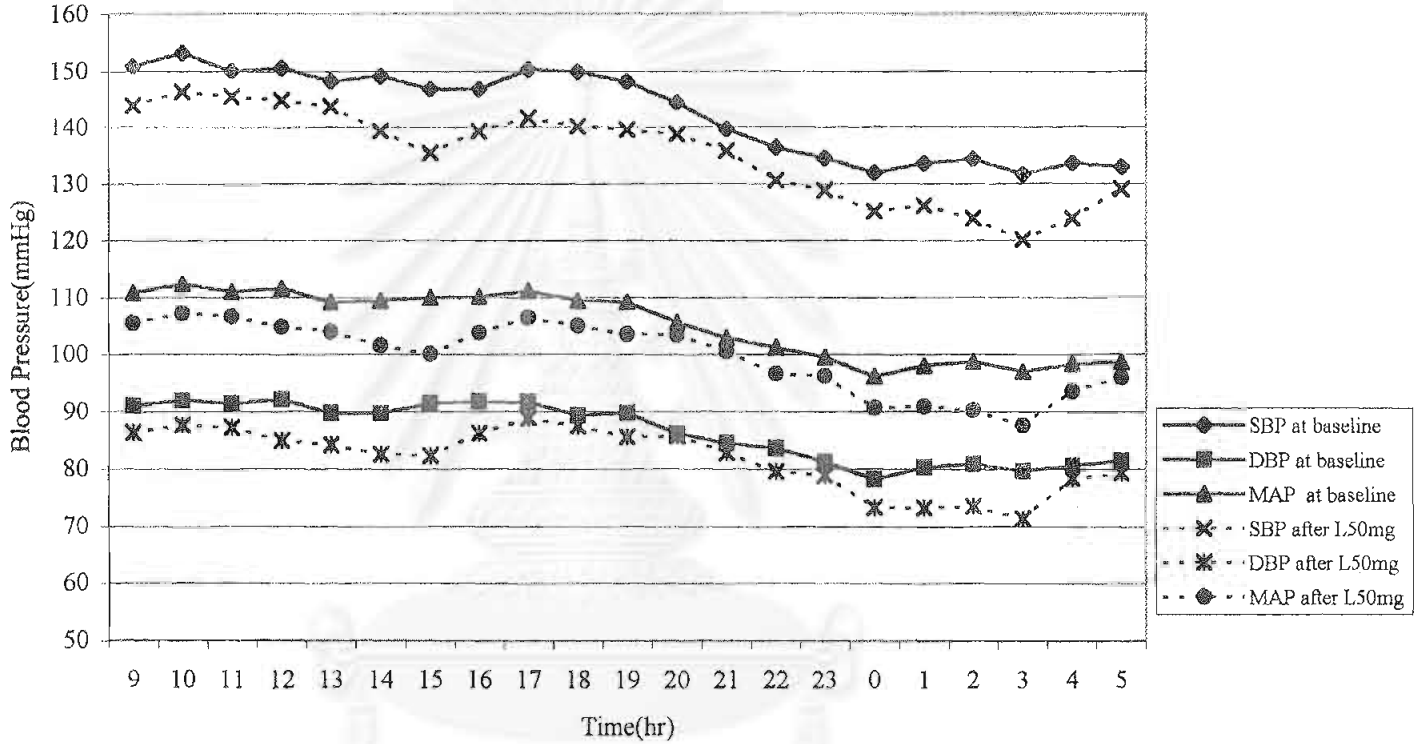


Figure 8: Ambulatory Hourly Blood Pressure Data after Losartan50mg treatment(n=32)



Average nighttime BP

With 50 mg losartan treatment, the average nighttime SBP, DBP and MAP were significantly reduced from 133±9.8, 80±8.9 and 98±8.1 to 125±11.9, 75±7.8 and 92±8.2 mmHg respectively, but with the administration of 12.5 mg of hydrochlorothiazide daily, SBP, DBP and MAP showed only small extent of reduction which were not statistically significant.

The result from this study showed that the antihypertensive efficacy of losartan 50 mg/day administration were distinct not only from office BP measurement, but also better reflected from the 24-hour ABP monitoring. This finding that losartan 50 mg accounted for the reduction of office blood pressure of 13/8 mmHg is similar to the results obtained from previous studies which investigated the efficacy of losartan potassium in either dose-finding studies or comparison studies with other antihypertensive drugs in patients with mild to moderate hypertension (table7). With 12.5 mg hydrochlorothiazide daily treatment, it was found that this dosage regimen provided reduction only in office BP. This could due in part to the reason that the dose was relatively low and the pharmacokinetic properties of the drug such as the half life is short. The office BP is probably the BP measured during the peak effect of hydrochlorothiazide or some patients may not be salt-sensitive hypertension and no good response to diuretic were observerd. However, hydrochlorothiazide 12.5-50mg once daily regimen has still been recommended for treatment of hypertension.

BP loads & AUC

Table13 show the frequency and the absolute value (the magnitude) of BP loads at baseline and after treatment with the two regimen. Both 50 mg losartan and 12.5 mg hydrochlorothiazide given once daily could induce significant reductions in the frequency of BP loads (percentage of abnormal BP values) in comparison to baseline whether the values were concentrated for daytime only or when the whole 24-hour were taken into consideration. During daytime, the frequency of SBP/DBP loads were dropped from 67±22.89/47±29.39% to 53+22.93/38+25.34% after treatment with 12.5 mg of hydrochlorothiazide and to 47±27.48 / 36±27.65% with 50 mg of losartan. Most of these reductions were statistically significant except for the reduction of DBP loads after treatment with hydrochlorothiazide. When 24-hour BP were considered, the frequency of SBP/DBP loads were dropped from 69±20.87 / 48±28.16% to 57±21.62 / 41±25.55% with 12.5 mg hydrochlorothiazide treatment and to 50±26.89 / 36±25.95% with losartan 50 mg treatment. Similar to the daytime BP loads, both 12.5 mg hydrochlorothiazide and 50 mg losartan reduced the frequency of 24-hour BP loads significantly except for the 24-hour DBP loads after hydrochlorothiazide treatment. However, when the nighttime hours were considered, the reduction in frequency of BP loads were not significant after hydrochlorothiazide treatment, while losartan 50 mg treatment produced statistically significant reduction in the frequency of BP loads SBP/DBP from 79±27.68 / 51±31.94 to 60±34.59 / 36±26.59% respectively.

Regarding the absolute or magnitude value of BP loads, only during nighttime after 50 mg losartan treatment which BP loads reduced significantly from 17±7.12 to 13±8.48 mmHg.

BP loads was used as one parameter to assess the antihypertensive efficacy of the medication. In this study, significant reduction of the percentage of abnormal values occurred during daytime after treatment with either 12.5 mg hydrochlorothiazide or 50 mg losartan once daily treatment. However, during nighttime, significant reduction in the percentage of abnormal values of both SBP/DBP and also the magnitude of systolic BP loads occurred only after 50 losartan treatment.

AUC was one of the parameters which was used to evaluate efficacy of antihypertensive drugs.[43] It could represent both frequency and magnitude of abnormal blood pressure. AUC was calculated by using area under the systolic or diastolic BP curve, with cutoff values of 140mmHg during daytime and 120mmHg during nighttime for SBP and 90mmHg during daytime and 80mmHg during nighttime for DBP. Figure 9 Show evaluation of antihypertensive therapy using the area under the systolic blood pressure curve.

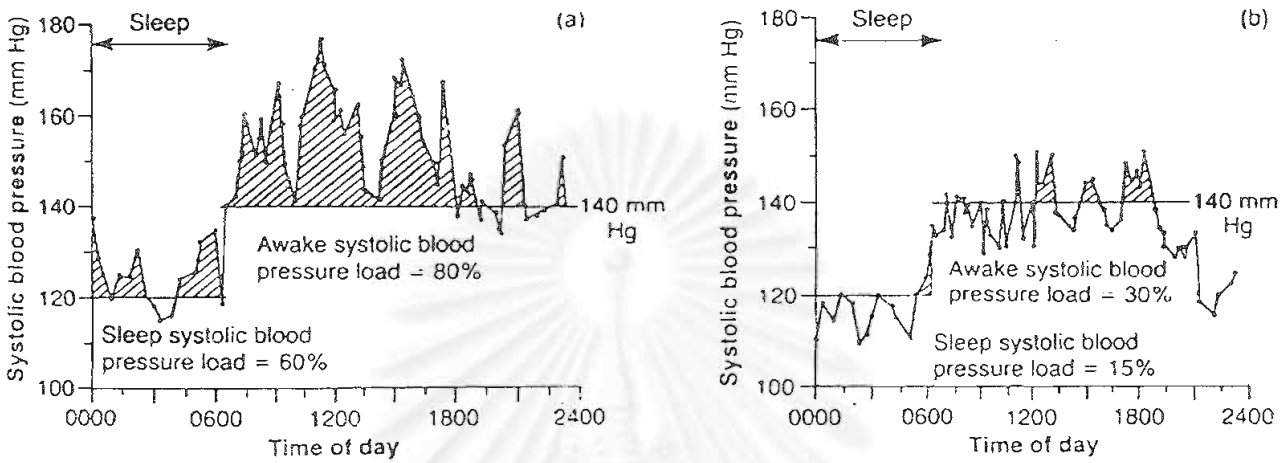


Figure 9: Evaluation of antihypertensive therapy using area under the systolic blood pressure curve with cutoff values of 140 mmHg during waking hours and 120 mmHg during sleeping for (a) placebo and (b) antihypertensive therapy

Data obtained from this study(table13) show that hydrochlorothiazide significantly reduced 24-hour AUC of SBP only from 202±118.5 to 148±102.5 mmHg.h, while losartan 50 mg treatment significantly reduced 24-hour AUC of both SBP/DBP from 202±118.5 / 84±83.7 to 129±117.5 / 48±69.9 mmHg.h. When the BP of daytime and nighttime hours were concentrated separately, AUC of SBP after losartan 50 mg treatment only was significantly lowered from 127±87.5 to 82±80.9 mmHg.h during daytime hours and from 75±49.4 to 46±44.8 mmHg.h during nighttime hours.

Table 13 :BP loads and the area above the normal blood pressure versus time curve (AUC)at baseline, after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment(n=32)

Parameter	baseline mean±SD	hydrochlorothiazide 12.5mg mean±SD[a]	losartan 50 mg mean±SD[b,c]
Frequency of BP load (%)			
24-hour BP load			
SBP	69±20.87	57±21.62*	50±26.89***, [ns]
DBP	48±28.16	41±25.55 [ns]	36±25.95***, [ns]
daytime BP load			
SBP	67±22.89	53±22.93*	47±27.48***, [ns]
DBP	47±29.39	38±25.34 [ns]	36±27.65 *, [ns]
nighttime BP load			
SBP	79±27.68	72±26.25 [ns]	60±34.59 *, [ns]
DBP	51±31.94	54±33.80 [ns]	36±26.59*,*
Absolute value of BP load(mmHg)			
24-hour BP load			
SBP	16±5.49	15±5.36 [ns]	14±6.71 [ns], [ns]
DBP	9±4.95	9±3.94 [ns]	7±4.53 [ns], [ns]
daytime BP load			
SBP	15±6.28	15±5.91 [ns]	14±7.41 [ns], [ns]
DBP	9±5.04	9±4.24 [ns]	7±4.71 [ns], [ns]
nighttime BP load			
SBP	17±7.12	16±8.14 [ns]	13±8.48 *, [ns]
DBP	7±5.70	8±5.56 [ns]	5±4.47 [ns], *

a,b versus baseline, c versus hydrochlorothiazide

***p< 0.005, * p< 0.05, [$] p=0.05-0.1, ns=not significant
SBP= systolic blood pressure, DBP= diastolic blood pressure

By using AUC for assessing effect of antihypertensive drug over time, several conclusions could be drawn.[49] First, the effect and duration of effect of the drug over the entire 24-hour period can be immediately visualized. Second, the blood pressure load can be calculated in mmHg.h. In mild hypertension, AUC could represent percentage of the blood pressure distribution. Thus data removal or smoothing method is unnecessary and quite simple statistical tests can be used to compare the treatment groups.

Step 2

After 4 weeks with hydrochlorothiazide 12.5 mg or 4 weeks with losartan 50 mg administration, according to the office BP, nine subjects were classified as losartan normalized group who had SBP<140 and DBP<90 mmHg after losartan 50 mg treatment, and the remaining twenty-three patients were classified as losartan nonnormalized group since these patients had SBP/DBP $\geq$140/90 mmHg after losartan 50 mg treatment. The mormalized patients and were randomly assigned to receive either losartan titrated to 100 mg or one tablet of HYZAAR® (losartan 50 mg in combination with hydrochlorothiazide 12.5 mg) once daily, while the normalized patients were randomly assigned to receive either losartan 25 mg or half a tablet of HYZAAR®(losartan 25 mg combined with hydrochlorothiazide 6.25 mg) once daily for another 4 weeks.

Losartan non-normalized group

Office BP

Among twenty-three patients in losartan non-normalized group, three of eleven patients administered with 100 mg losartan and four of twelve patients administered with one tablet of HYZAAR® once daily for 4 weeks were BP normalized. After losartan 100 mg administration, office SBP/DBP was significantly lowered from 160±15.0 / 97±7.3 to 141±11.4 / 89±5.8mmHg respectively($p<0.005$). MAP was also reduced from 118±7.5 to 106±6.0mmHg ($p<0.005$). Similar result was found in combination therapy (losartan 50 mg plus hydrochlorothiazide 12.5 mg) which SBP/DBP were lowered from 157±10.8 / 99±8.4 to 140±14.9 / 89±9.7 ($p<0.05$, $p<0.005$) respectively. MAP was also reduced from 119±7.3 to106±9.5 mmHg($p<0.005$) with this regimen(table14).

Ambulatory BP

Average 24-hour ABP

As shown in table14, SBP/DBP was decreased from 143±9.7 / 88±10.1 to 134±16.5 / 81±14.2 mmHg with 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment($p<0.05$), while with 100 mg losartan administration, SBP/DBP reduced from 148±6.2 / 88±6.1 to 138±13.7 / 85±8.5mmHg, but were not significantly different($p>0.05$). MAP after losartan plus hydrochlorothiazide also showed significant reduction from 106±9.1 to 98±14.3 mmHg($p<0.05$), while MAP after 100 mg losartan reduced from 108±5.0 to 102±9.2 mmHg, but were not statistically significant.

Table 14: The mean office BP and ABP of the subjects at baseline and after treatment with 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(HYZAAR)

Parameter	losartan 100 mg(n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)		
	baseline	losartan 50 mg	losartan 100 mg	baseline	losartan 50 mg	hyzaar
	mean±SD	mean±SD[a]	mean±SD[b,c]	mean±SD	mean±SD[d]	mean±SD[e,f]
Office BP						
SBP(mmHg)	160±15.0	149±10.2*	141±11.4***, *	157±10.8	145±11.7*	140±14.9*, ns
DBP(mmHg)	97±7.3	94±7.6 ns	89±5.8***, $	99±8.4	92±8.8***	89±9.7***, ns
MAP(mmHg)	118±7.5	112±6.3 ns	106±6.0***, *	119±7.3	111±7.3***	106±9.5***, ns
HR(bpm)	76±9.7	74±7.9 ns	74±6.3 ns, ns	78±6.0	77±8.5 ns	75±8.1 ns,ns
24-hour ABP						
average 24-hour						
SBP(mmHg)	148±6.2	138±12.0$	138±13.7$	143±9.7	140±11.4 ns	134±16.5*, ns
DBP(mmHg)	88±6.1	83±7.4 ns	85±8.5 ns,ns	88±10.1	85±9.8 ns	81±14.2*, ns
MAP(mmHg)	108±5.0	103±8.0 ns	102±9.2 ns,ns	106±9.1	103±9.6 ns	98±14.3*, ns
HR(bpm)	77±10.5	76±7.5 ns	78±6.2 ns,ns	77±7.7	78±8.5 ns	78±9.2 ns,ns
average daytime						
SBP(mmHg)	152±6.8	143±12.3 ns	143±15.2 ns,ns	148±10.5	145±12.1 ns	138±16.3*, ns
DBP(mmHg)	92±6.3	87±7.7 ns	88±10.1 ns,ns	91±10.1	89±11.3 ns	82±14.0*, ns
MAP(mmHg)	112±6.4	107±8.9 ns	106±11.4 ns,ns	110±9.3	107±11.2 ns	101±14.0*, ns
HR(bpm)	83±10.2	83±9.6 ns	84±8.9 ns,ns	82±7.4	82±8.4 ns	83±12.3 ns,ns

[a,b,d,e] versus baseline

[c,f] versus losartan 50 mg

*** p<0.005, * p< 0.05, $ p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Table 14: The mean office BP and ABP of the subjects at baseline and after treatment with 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(HYZAAR)(continued)

Parameter	losartan 100 mg(n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)		
	baseline	**losartan 50 mg**	**losartan 100 mg**	**baseline**	**losartan 50 mg**	**hyzaar**
	mean±SD	mean+SD[a]	mean+SD[b,c]	mean+SD	mean+SD[d]	mean+SD[e,f]
average nighttime						
SBP(mmHg)	139±9.1	128±12.8*	126±13.3*, ns	133±9.9	128±11.1 ns	126±18.8 ns,ns
DBP(mmHg)	82±5.2	76±7.8$	77±7.9 ns,ns	82±12.0	77±8.3 ns	77±15.4 ns,ns
MAP(mmHg)	100±5.0	95±8.1$	93±8.7*, ns	99±10.3	94±8.2 ns	93±16.3 ns,ns
HR(bpm)	66±12.1	67±11.5 ns	73±8.0 ns,ns	67±9.1	69±10.4 ns	75±15.1 ns,ns

[a,b,d,e] versus baseline

[c,f] versus losartan 50 mg

*** p<0.005, * p< 0.05, $ p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Figure 10: Ambulatory Hourly Blood Pressure data after losartan100mg treatment in patients who were non-normalized with 50 mg losartan treatment(n=11)

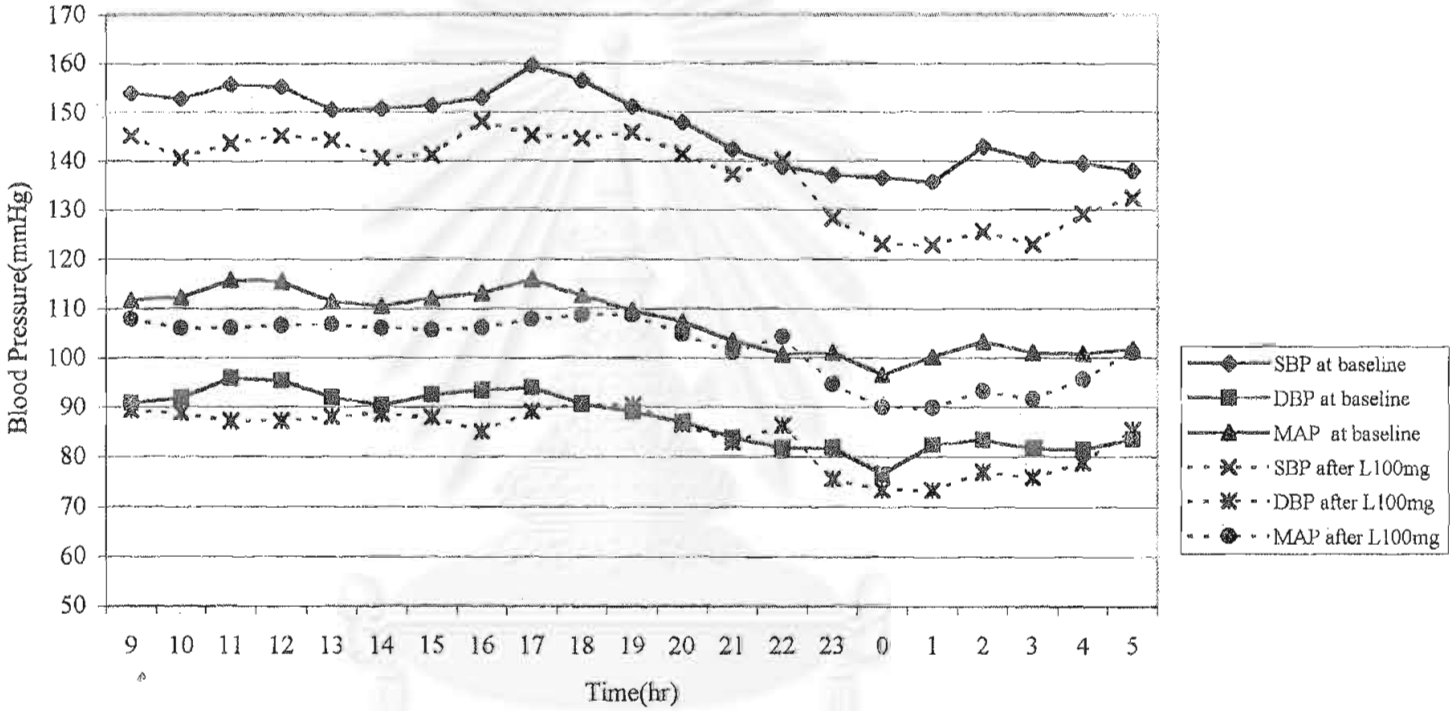
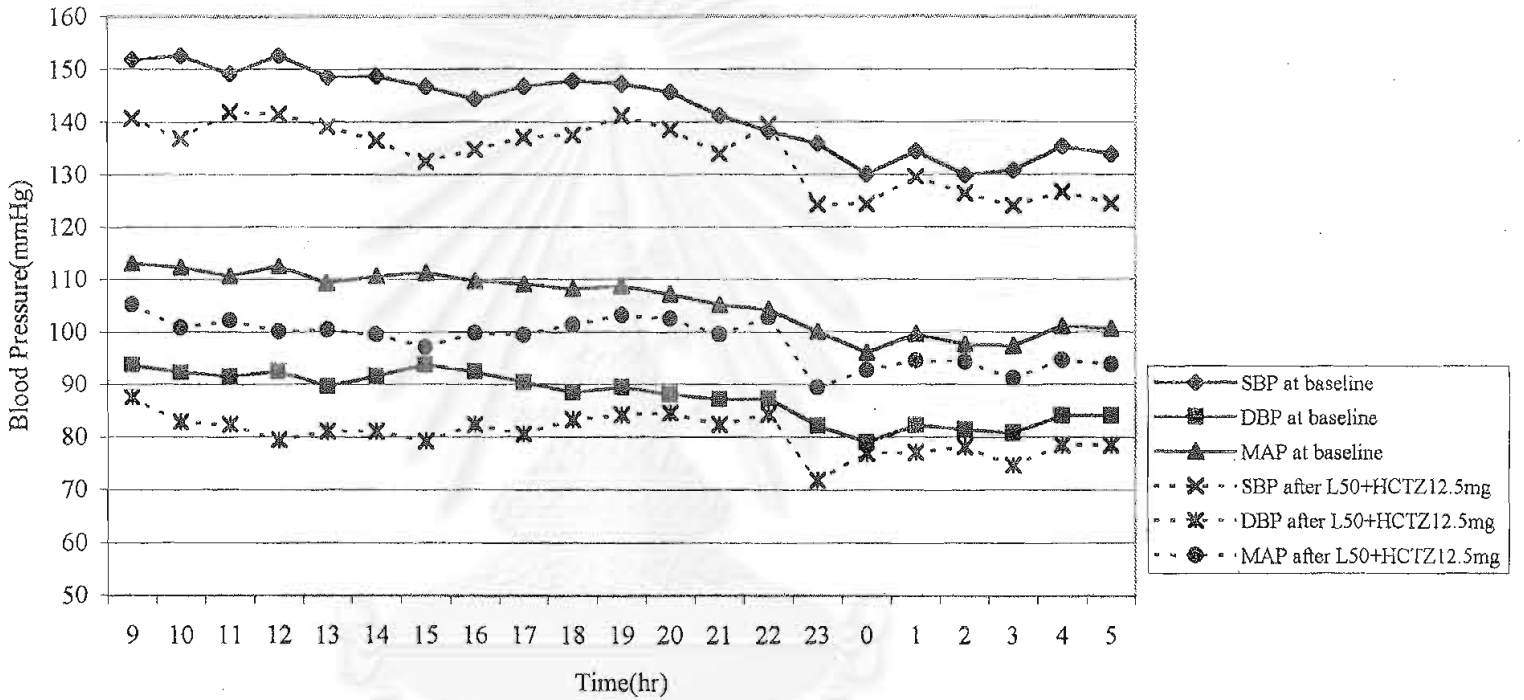


Figure 11: Ambulatory Hourly Blood Pressure data after losartan50mg plus HCTZ12.5mg treatment in patients who were non-normalized with 50 mg losartan treatment(n=12)



Average daytime ABP

The effects of either regimen on daytime ABP were similar to the effects on 24-hour ABP in that 50 mg losartan plus 12.5 mg hydrochlorothiazide significantly reduced SBP/DBP from 148±10.5 / 91±10.1 to 138±16.3 / 82±14.0 mmHg ($p<0.05$), while with losartan 100 mg treatment SBP/DBP decreased from 152±6.8 / 92±6.3 to 143±15.2 / 88±10.1 mmHg but these differences were not statistically significant($p>0.05$). MAP was also significantly reduced from 110±9.3 to 101±14.0 mmHg ($p<0.05$) after losartan plus hydrochlorothiazide treatment, but were not statistically significant reduced with the increased dose of losartan.

Average nighttime ABP

In this study, it was found that only with 100 mg losartan treatment that SBP and MAP were significantly reduced from 139±9.1 to 126±13.3 and 100±5.0 to 93±8.7 mmHg respectively. The other ABP even though were also lowered than baseline either after 100 mg losartan or 50 mg losartan plus 12.5 mg hydrochlorothiazide treatments, but these reductions were not statistically significant.

These findings are consistent with previous studies which indicated that the benefits of 100mg daily dosage of losartan were similar to those of 50 mg/day.[22] Nelson et al, first reported the efficacy of losartan in dosage ≥ 50 mg daily on hospitalized patients, subsequentially, losartan in the 50 mg /day dosage has proved to be efficacious and superior to placebo in large controlled dose-finding trials in out patients. This regimen has been adopted as the usual starting and maintenance dose in patients with mild to moderate hypertension. Effectiveness of

losartan plus hydrochlorothiazide in patients with severe hypertension has been proved in noncomparative trials. [65-66]. Dunlay et al, found that among 179 patients in the Losartan Hypertension Study who began therapy with losartan potassium 50 mg, 22% continued with losartan potassium monotherapy at week 12, 30% received losartan potassium plus hydrochlorothiazide12.5 mg to 25 mg/day and 46% received this last regimen plus a dihydropyridine calcium channel blocker or atenolol or both. The remaining 2% were prescribed regimens outside the protocol. The overall decrease in blood pressure of 26/19 mmHg for all patients in this trial [65], the same reductions of 18.4 mmHg in DBP were documented in a similar 12-week study [66] of 131 hypertensive patients (31%Blacks).

When the reductions of BP after each regimen were compared, it was found that when increasing the dose of losartan potassium from 50 mg to 100 mg, the effect of the adding dosage on further reduction of BP was lower especially on the ambulatory blood pressure either in daytime, nighttime or 24-hour (table14). In contrast to monotherapy, losartan 50 mg plus hydrochlorothiazide 12.5 mg seem to produce further reduction of BP compare with losartan 50 mg alone. This could be elucidated in ambulatory blood pressure even though the difference was not statistically significant when compared with losartan 50 mg treatment(table 15).

Weber et al, [67] found that the addition of hydrochlorothiazide12.5 mg daily for 2 weeks in patients unresponsive to losartan potassium given alone could lower DBP 6.1 to 7.8 mmHg further similar to the decrease of 6.4 mmHg in placebo plus hydrochlorothiazide group. Adding

Table 15 : The reduction of office and ABP after50 mg losartan, 100 mg losartan and 50 mg losartan plus12.5 mg hydrochlorothiazide(Hyzaar)

parameter	losartan 100 mg(n=11)			HYZAAR(n=12)		
	losartan 50 mg[a] step1 mean±SD	losartan50+50 mg[b] step2 mean±SD	c	losartan 50 mg [a] step1 mean±SD	losartan plus HCTZ 12.5 mg [b] step2 mean±SD	c
Office BP						
SBP(mmHg)	11.09±12.28	8.45±9.57	ns	10.17±9.57	7.08±13.89	ns
DBP(mmHg)	3.00±7.68	5±6.45	ns	7.00±5.26	3.25±5.31	ns
MAP(mmHg)	5.70±8.62	6.15±6.04	ns	8.06±5.03	4.53+6.72	ns
24-hour ABP						
average 24-hour						
SBP(mmHg)	9.36±12.27	0.18±6.35	$	2.75±10.15	6.08±17.12	ns
DBP(mmHg)	4.82±7.21	(-1.18)±6.32	$	2.75±6.90	5.58±12.25	ns
MAP(mmHg)	5.09±7.30	0.91±3.11	$	2.92±7.49	4.92±13.85	ns
average daytime						
SBP(mmHg)	9.45±13.62	(-0.27)±8.39	$	2.50±9.72	7.5±17.67	ns
DBP(mmHg)	5.45±8.10	(-1.09)±8.09	ns	2.17±5.95	6.25±12.89	ns
MAP(mmHg)	4.63±8.64	0.64±4.39	ns	2.41±7.20	6.50±14.35	ns
average nighttime						
SBP(mmHg)	10.82±11.02	2.18±5.95	$	4.33±11.53	2.42±17.86	ns
DBP(mmHg)	5.64±6.96	(-0.91)±5.77	ns	4.33±11.48	0.17±14.08	ns
MAP(mmHg)	5.45±7.17	1.91±5.99	ns	4.75±10.30	0.75±15.16	ns

[a] reduction of BP from baseline , [b] reduction of BP from BP after losartan 50 mg treatment(step1)

[c] difference between step1 and step2

[$] p=0.05-0.1, ns = not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure

Table 16 : The effect of sequence of treatment on the number and percentage of normalized and responded subjects based on office and 24-hour ambulatory blood pressure(24-hr ABP)

	Office blood pressure (OBP)				Ambulatory blood pressure(ABP)		
	total	**first regimen**	**latter regimen**		**total**	**first regimen**	**latter regimen**
Normalized [a] (losartan 50 mg)				**Normalized** [c] (losartan 50 mg)			
no.	(9/32)	(2/12)	(7/20)	no.	(8/32)	(3/12)	(5/20)
%	28.1	16.7	35	%	25	25	25
Normalized [a] (HCTZ12.5 mg)				**Normalized** [c] (HCTZ12.5 mg)			
no.	(8/32)	(5/20)	(3/12)	no.	(5/32)	(2/20)	(3/12)
%	25	25	25	%	15.6	10	25
Responders [b] (losartan 50 mg)				**Responders** [d] (losartan 50 mg)			
no.	(22/32)	(6/12)	(16/20)	no.	(15/32)	(5/12)	(10/20)
%	68.8	50	80	%	46.9	41.7	50
Responders [b] (HCTZ12.5 mg)				**Responders** [d] (HCTZ12.5 mg)			
no.	(20/32)	(14/20)	(6/12)	no.	(12/32)	(7/20)	(5/12)
%	62.5	70	50	%	37.5	35	41.7

a= OSBP<140 and ODBP<90 mmHg after treatment

b = OSBP<140 and ODBP<90mmHg and/or OSBP or ODBP falls >10 mmHg from baseline after treatment

c= 24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg after treatment

d =24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg and/or 24-hr SBP or 24-hr DBP falls >10 mmHg from baseline after treatment

hydrochlorothiazide in doses ≥12.5 mg to losartan potassium 50 mg reduced DBP by additional 4 to 6 mmHg versus monotherapy with losartan potassium 50 mg or with hydrochlorothiazide 12.5 mg[69] or 25 mg.[68] For example, DBP was decreased by 13.2 mmHg with losartan potassium 50 mg plus hydrochlorothiazide 12.5 mg versus 8.8 mmHg with losartan potassium and 7.2 mmHg with hydrochlorothiazide.[69] Efficacy of the combined therapy with losartan potassium monotherapy was shown after 1 week and reached a maximum effect at 3 to 6 weeks.[68] MacKay et al, found that the percentage of patients who responded to treatment in this trial was greatest in losartan potassium plus hydrochlorothiazide 12.5 mg group(78%), then 60% losartan potassium plus hydrochlorothiazide 6.25 mg group and 56% in losartan alone group, and 47% in hydrochlorothiazide group.[69]

Table 16 illustrated the effects of the sequence of treatment on the numbers and the percentage of normalized and responded subject based on office and ambulatory blood pressure. When patients were categorized as normalized and non-normalized groups according to their office BP(patients whose SBP/DBP <140/90 mmHg were categorized as normalized patients), it was found that the percentage of normalized patients after treatment with 50 mg losartan and 12.5 mg HCTZ were 28.1% and 25% respectively. When classified the patients into responder and non-responder groups (patients whose office BP became normalized or their office SBP or DBP decreased ≥ 10 mmHg after treatment with each regimen were classified as responders), the percentage of responded patients after 50 mg losartan was 68.8% while after 12.5 mg hydrochlorothiazide treatment was 62.5%. Consistent with the percentage of responders, the percentage of normalized patients after 50 mg

losartan were 28.1% which were higher than 25% of normalized after 12.5 mg hydrochlorothiazide treatment. When patients were classified based on their ambulatory blood pressure into normalized / non-normalized and reponders / non-responders groups (patients whose 24-hour SBP/DBP $\leq$ 130/80 mmHg were categorized as normalized subjects and patients whose BP became normalized or their 24- hour SBP or DBP decreased $\geq$ 10 mmHg after treatment with each regimen were categorized as responded patients), it was found that the percentage of normalized and responders either after 50 mg losartan or after 12.5 mg hydrochlorothiazide treatments were less than the percentages obtained when using the office blood pressure. Using 24-hour ambulatory blood pressure as the criterion to classify patients into normalized/non-normalized and responder/nonresponder groups have advantages in that the data covered the antihypertensive effects while the office BP covered only daytime or even peak time effect only . The percentage of normalized patients based on ABP after 50 mg losartan and 12.5 mg hydrochlorothiazide were 25 and 15.6 respectively, while the percentage of responders after 50 mg losartan and 12.5 mg hydrochlorothiazide were 46.9 and 37.5 respectively. The percentage of responders and normalized patients after 50 mg losartan treatment were found to be higher than the percentage obtained after 12.5 mg hydrochlorothiazide treatment whether the percentage were classified according to the office BP or ABP. Considering on the effect of sequence of treatment, it was found that, the percentage of normalized and responders of the drug seem to be higher when the drug was given as the latter regimen with either drugs, however, these were all non statistically significant. Part of the explanation could possibly due

to the patients were more familiar and relax with the monitor machine after the latter regimen and thus showed better antihypertensive response. Table16 and 17 showed the numbers and the percentage of responded and normalized patients after given the regimens in step2 to the patients in losartan non-normalized group and losartan normalized group respectively.

When 50 mg losartan non-normalized group were considered, it was found that the percentage of either responders or normalized patients were higher after 50 mg losartan plus 12.5 mg hydrochlorothiazide as compared to after 100 mg losartan based on the 24-hour ABP. When office BP were used, the same results as aforementioned was obtained for the percentage of normalized subjects but for the percentage of responders the results were vice versa(table 17).

In contrary, in losartan normalized group, the percentage of responders and normalized patients were all higher after losartan 25 mg monotherapy as compared to the percentage of responders and normalized patients after the combination of 25 mg losartan and 6.25 mg hydrochlorothiazide whether the data were based on office blood pressure or ambulatory blood pressure.(table 18)

Based on the assumption that when patients were normalized with 50 mg losartan treatment, they would also be normalized with 100 mg losartan treatment. The number of the expected patients normalized after 100 mg losartan of the whole thirty-two patients would be nine plus the six expected subjects normalized with 100 mg losartan(27.3% * 23 patients) which were 15 patients (46.9%). Applied the same assumption to 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment, the number of expected subjects normalized after this

Table 17 : The number and percentage of responded and normalized subjects after 100 mg losartan or 50 mg losartan plus 12.5 mg hydrochlorothiazic was given to the non- normalized(with 50 mg losartan) group based on office and 24- hour ambulatory blood pressure(24- hr ABP)

	Office blood pressure (OBP)		24- hour ambulatory blood pressure(24-hr ABP)	
	losartan 100 mg (n=11)	losartan 50 mg plus HCTZ 12.5 mg (n=12)	losartan 100 mg (n=11)	losartan 50 mg plus HCTZ 12.5 mg (n=12)
Responders[a]			**Responders**[c]	
no. of patients	9	9	no. of patients	5	6
%	81.8	75	%	45.5	50
Normalized patients[b]			**Normalized patients**[d]	
no. of patients	3	4	no. of patients	2	5
%	27.3	33.3	%	18.2	41.7

[a] = OSBP<140 and ODBP<90mmHg and/or OSBP or ODBP falls ≥10 mmHg from baseline after treatment

[b]= OSBP<140 and ODBP<90 mmHg after treatment

[c] =24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg and/or 24-hr SBP or 24-hr DBP falls ≥10 mmHg from baseline after treatment

[d]= 24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg after treatment

Table 18 : The number and percentage of responded and normalized subjects after 25 mg losartan or 25 mg losartan plus 6.25 mg hydrochlorothiaz was given to the normalized(with 50 mg losartan) group based on office and 24- hour ambulatory blood pressure(24- hr ABP)

	Office blood pressure (OBP)		24- hour ambulatory blood pressure(24-hr ABP)	
	losartan 25 mg (n=4)	losartan 25 mg plus HCTZ 6.25 mg (n=5)	losartan 25 mg (n=4)	losartan 25 mg plus HCTZ 6.25 mg (n=5)
Responders[a]			**Responders**[c]	
no. of patients	3	3	no. of patients	4	4
%	75	60	%	100	80
Normalized patients[b]			**Normalized patients**[d]	
no. of patients	3	2	no. of patients	3	1
%	75	40	%	75	20

[a] = OSBP<140 and ODBP<90mmHg and/or OSBP or ODBP falls ≥10 mmHg from baseline after treatment

[b]= OSBP<140 and ODBP<90 mmHg after treatment

[c]=24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg and/or 24-hr SBP or 24-hr DBP falls ≥10 mmHg from baseline after treatment

[d]= 24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg after treatment

Table 19 : The expected number and percentage of normalized subjects after each regimen based on office and 24-hour ABP

	losartan 25 mg (n=32)	losartan 50 mg (n=32)	losartan 100 mg (n=32)	HCTZ12.5 mg (n=32)	losartan 25 mg plus HCTZ12.5 mg (n=32)	losartan 50 mg plus HCTZ 12.5 mg (n=32)
Office Blood Pressure (OBP)						
normalized [a]						
no.	7	9	15	8	4	17
%	21.9	28	46.9	25	12.5	53
24-hour ambulatory Blood Pressure (24-hr ABP)						
normalized [b]						
no.	6	8	12	5	2	18
%	18.8	25	37.5	15.6	6.3	56.2

a= OSBP<140 and ODBP<90 mmHg after treatment
b= 24-hr SBP≤130 and 24-hr DBP≤ 80 mmHg after treatment

medication were nine plus eight expected subjects normalized with 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment(33.3%*23 patients) which were 17 patients(53%). The number of expected patients normalized with 25 mg losartan were seven patients(75%*9 patients) and the numbers of expected patients normalized with 25 mg losartan plus 6.25 mg hydrochlorothiazide were 4 patients (40%*9). From the expected patients normalized after each regimen obtained in this trial, it was found that 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment showed the greatest percentage of normalized patients(53%) and the second was 100 mg losartan(46.9%), and then 50 mg losartan(28%), 12.5 mg hydrochlorothiazide (25%), 25 mg losartan(21.9%) and the least was 25 mg losartan plus 12.5 mg hydrochlorothiazide(12.5%). When using 24-hour ambulatory blood pressure as the criterion, the percentage of normalized patients after every regimen were less than when using office blood pressure except with 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment which the percentage of normalized subjects were found to be higher(56.2% based on ABP vs 53% based on OBP). When the percentage of normalized patients were ranked based on ambulatory blood pressure for all regimens, the order was nearly the same as those obtained based on office blood pressure. The highest percentage of normalized subjects were 56.2% with 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment. The second were 37.5% with 100 mg losartan treatment and then 50 mg losartan (25%), 25 mg losartan (18.8%), 12.5 mg hydrochlorothiazide(15.6%) and the least were with 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment(6.3%). Most of the ranking were the same except for the results after 25 mg losartan and 12.5 mg hydrochlorothiazide

which the percentage of normalized subjects based on ABP was a little bit higher with 25 mg losartan as compared to 12.5 mg hydrochlorothiazide while the ranking was vice versa when based on office blood pressure(table19).

When compared the efficacy of losartan plus hydrochlorothiazide with the results from dose-finding and comparative studies with an active treatment of 12 weeks in patients with mild to moderate hypertension. It was demonstrated that office SBP/DBP decreased by 17.25/10.25 mmHg with losartan 50 mg plus hydrochlorothiazide 12.5 mg similar to those reported in previous investigations by Simpson et al and MacKay et al 69,70 who found that SBP/DBP reduced by 12/9 and 17.2/13.2 mmHg respectively with losartan 50 mg plus hydrochlorothiazide treatments.(table8)

When compared the reduction of office and ABP from baseline after treatment with hydrochlorothiazide 12.5 mg, losartan 50mg, losartan 100mg or losartan 50 mg plus hydrochlorothiazide12.5 mg(table20), the results showed that only the reduction of office DBP and MAP after treatment with losartan 100 mg and the reduction of office DBP after treatment with losartan 50 mg plus hydrochlorothiazide 12.5 mg were significantly different from the reduction after treatment with hydrochlorothiazide 12.5mg or losartan 50 mg alone, while there were no statistically significant difference in ABP after treatment with either losartan 100 mg or losartan 50 mg plus hydrochlorothiazide 12.5 mg except for the average nighttime SBP. Moreover, the ABP did not decreased further when increasing the dosage of losartan potassium from 50 to 100 mg, while adding hydrochlorothiazide 12.5 mg to the patients who initially received losartan 50mg as

monotherapy showed further reduction in their ABP. The result revealed that the patients who were nonresponded(i.e. responded only to a small extent) to losartan 50 mg were likely to respond further with the addition with hydrochlorothiazide 12.5 mg, while the patients who initially responded well to losartan 50 mg monotherapy probably responded less in the second step. Figure 12 to 23 compared office BP and ABP reduction from baseline after each regimen between losartan 100 mg and losartan 50 mg plus hydrochlorothiazide 12.5 mg groups.

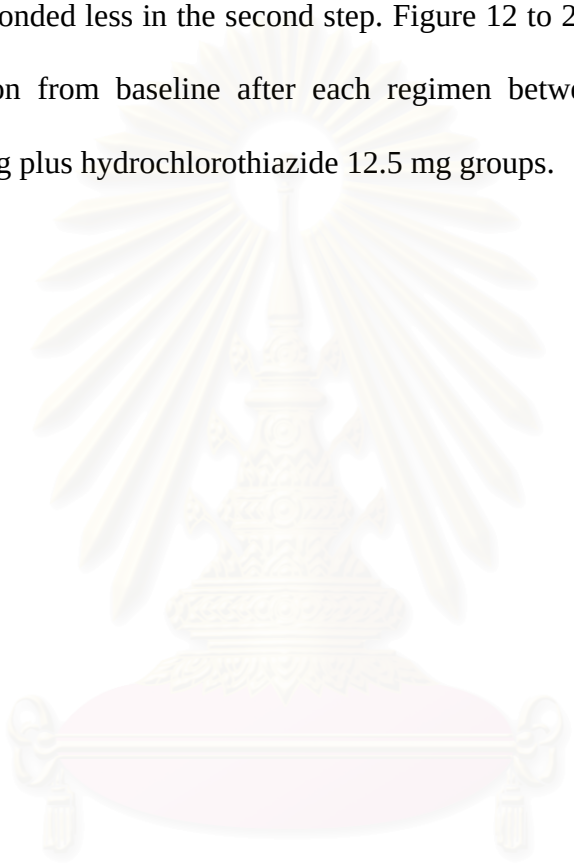


Table 20 : The reduction of office and ABP from baseline after 12.5 mg hydrochlorothiazide, 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide

parameter	losartan 100 mg(n=11)			HYZAAR(n=12)		
	HCTZ12.5mg	losartan50mg	losartan50+50mg	HCTZ12.5mg	losartan50mg	losartan50+HCTZ12.5mg
	mean±SD	mean±SD[a]	mean±SD[b,c]	mean±SD	mean±SD[a]	mean±SD[b,c]
Office BP						
SBP(mmHg)	13.73±14.22	11.09±12.28 [ns]	19.55±13.76[ns,*]	12.42±14.34	10.17±9.57 [ns]	17.25±15.86 [ns,ns]
DBP(mmHg)	2.36±6.68	3.00±6.08 [ns]	8.00±6.08***,$	5.50±7.57	7.00±5.26 [ns]	10.25±7.11*, [ns]
MAP(mmHg)	6.15±7.83	5.69±8.62 [ns]	11.85±7.25***,*	7.81±9.57	8.06±5.03 [ns]	12.58±9.35 [$,ns]
24-hour ABP						
average 24-hour						
SBP(mmHg)	6.82±9.48	9.36±12.27 [ns]	9.55±12.77 [ns,ns]	1.92±7.17	2.75±10.15 [ns]	8.83±10.21 [ns,ns]
DBP(mmHg)	1.18±5.33	4.82±7.21 [ns]	3.64±8.52 [ns,ns]	3.75±8.37	2.75±6.90 [ns]	7.17±6.78 [ns,ns]
MAP(mmHg)	3.09±5.91	5.09±7.30 [ns]	6.00±9.20 [ns,ns]	3.33±7.51	2.92±7.50 [ns]	7.83±8.84 [ns,ns]
average daytime						
SBP(mmHg)	6.45±9.73	9.45±13.62 [ns]	9.18±14.79 [ns,ns]	2.75±7.68	2.50±9.72 [ns]	10.00±10.32 [ns,ns]
DBP(mmHg)	2.36±4.84	5.45±8.10 [ns]	4.36±9.94 [ns,ns]	4.83±7.07	2.17±5.95 [ns]	8.42±8.73 [ns,ns]
MAP(mmHg)	3.09±6.45	4.64±8.64 [ns]	5.27±11.59 [ns,ns]	3.92±6.83	2.42±7.20 [ns]	8.92±8.83 [ns,ns]
average nighttime						
SBP(mmHg)	9.36±11.62	11.56±6.27 [ns]	13.00±10.95[ns,*]	0.92±9.51	3.90±7.11 [ns]	6.75±12.43 [ns,ns]
DBP(mmHg)	1.27±6.44	5.64±6.96 [ns]	4.73±7.54 [ns,ns]	2.08±13.01	4.33±11.48 [ns]	4.50±10.87 [ns,ns]
MAP(mmHg)	3.18±8.07	5.45±7.17 [ns]	7.36±8.15 [ns,ns]	1.75±10.28	4.75±10.30 [ns]	5.50±10.83 [ns,ns]

[a,b] versus hydrochlorothiazide 12.5 mg, [c] versus losartan 50 mg

***p<0.005, *p<0.05

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure

Figure 12: Office SBP reduction of losartan100mg group(n=11) and hyzaar group(n=12)

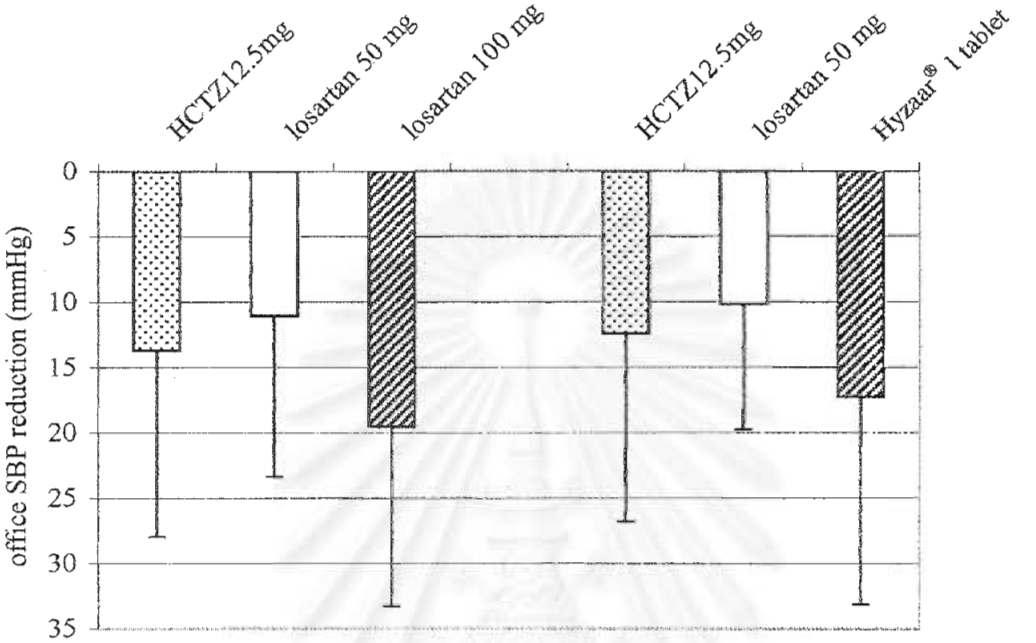


Figure 13: Office DBP reduction of losartan100mg group(n=11) and hyzaar group(n=12)

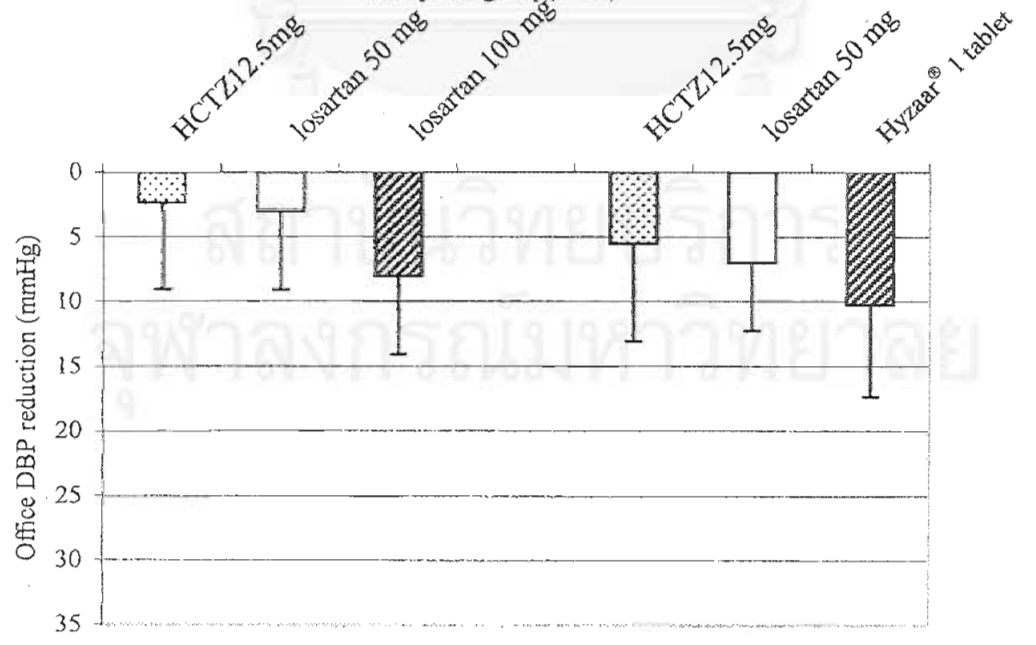


Figure 14: Office MAP reduction of losartan100mg group(n=11) and hyzaar group(n=12)

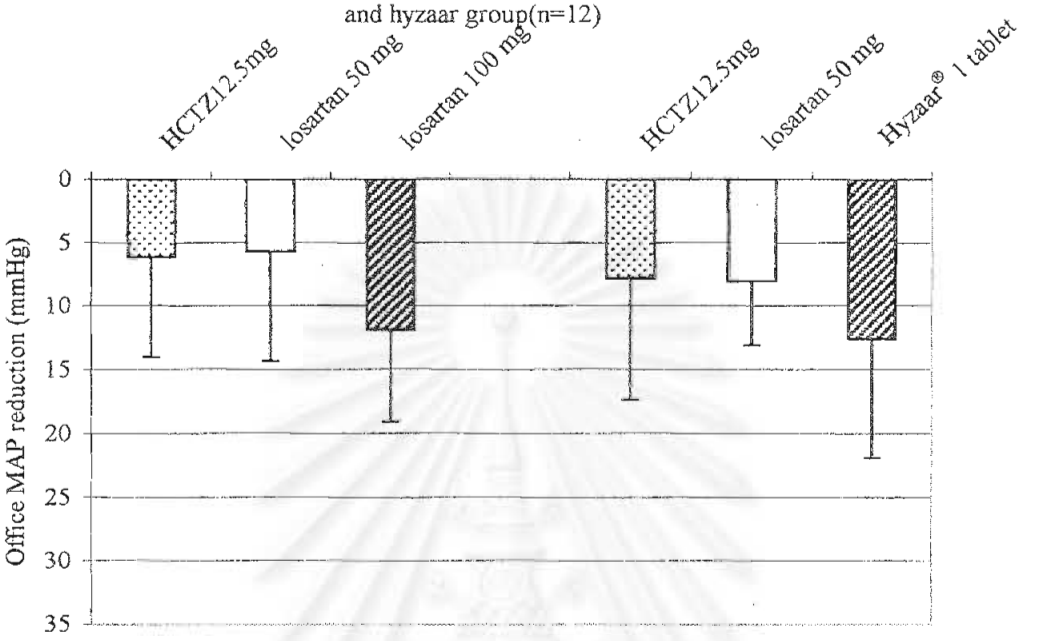


Figure 15: 24-hour SBP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

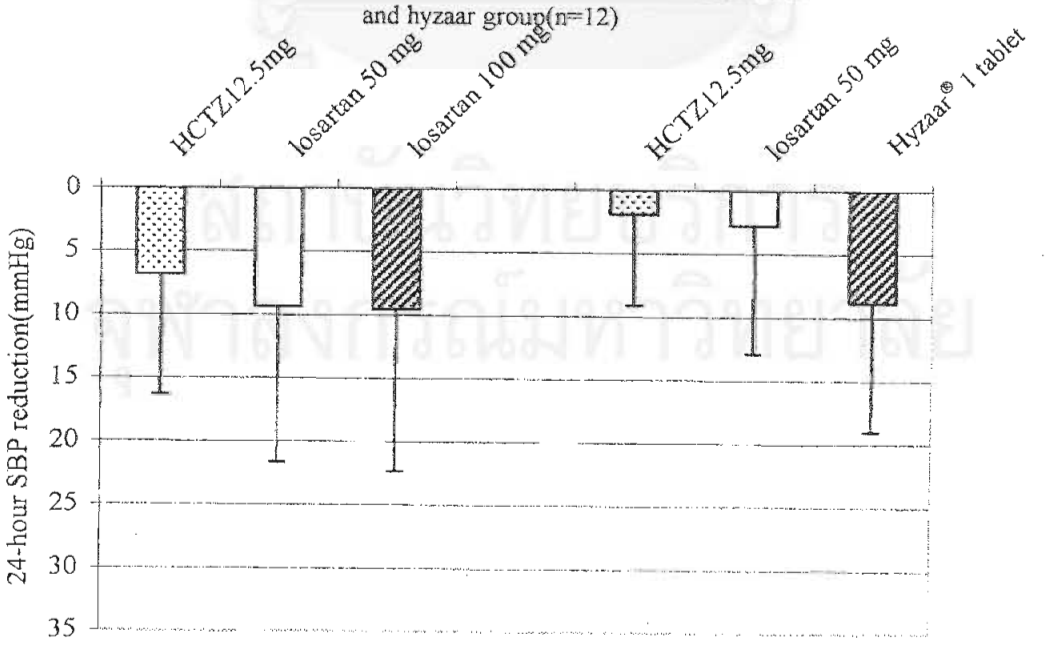


Figure 16: 24-hour DBP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

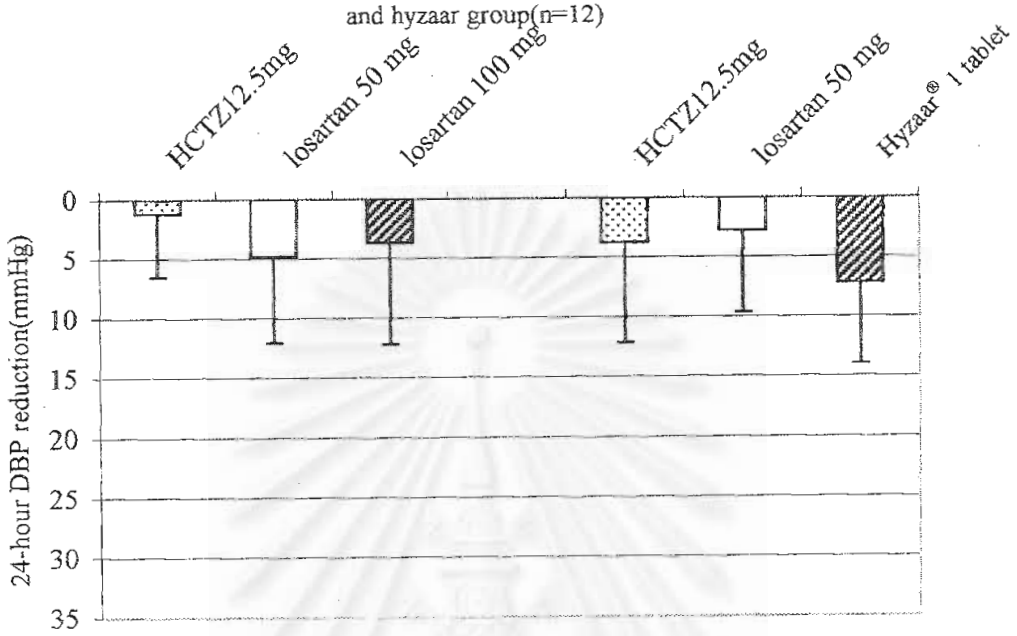


Figure 17: 24-hour MAP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

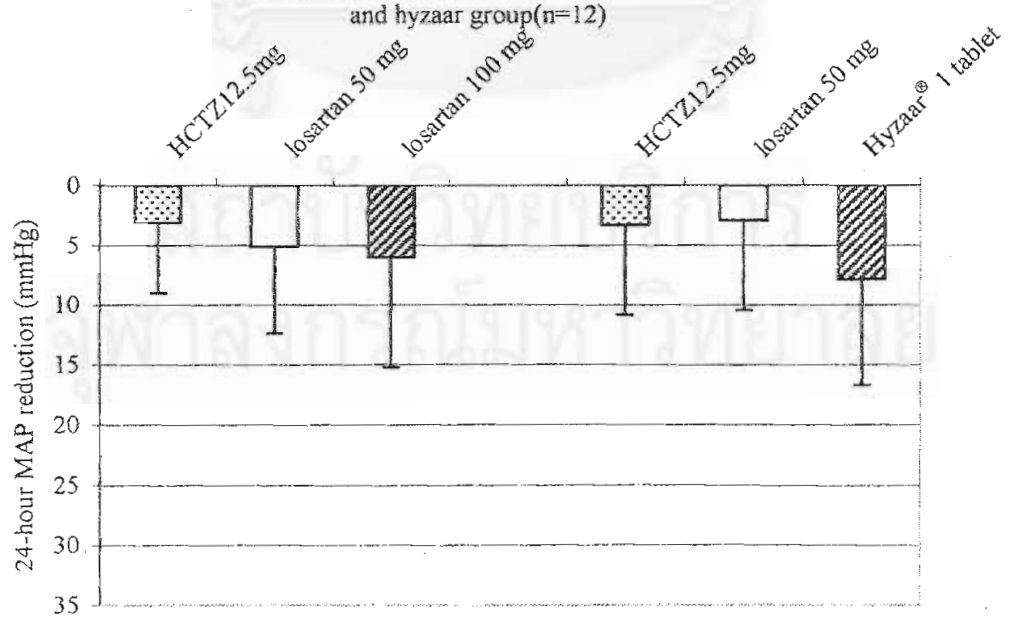


Figure 18: Daytime SBP reduction of losartan100mg(n=11) and hyzaar group(n=12)

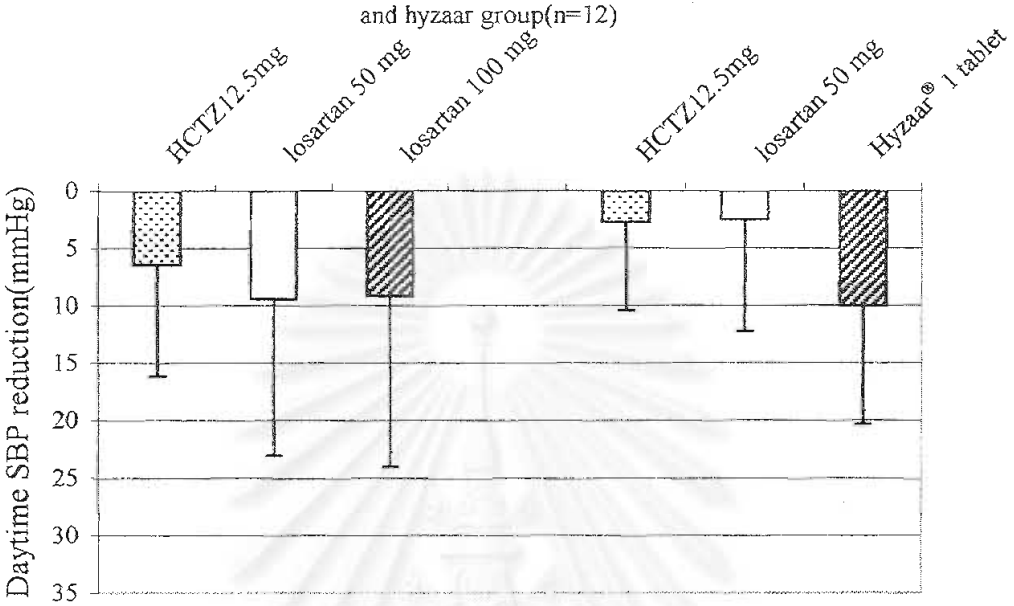


Figure 19: Daytime DBP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

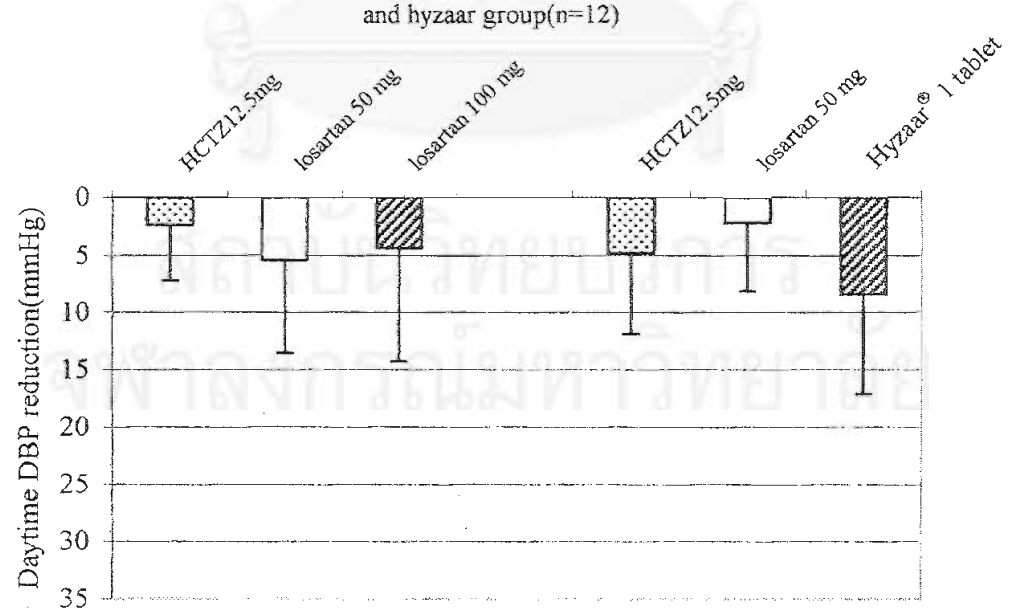


Figure 20: Daytime MAP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

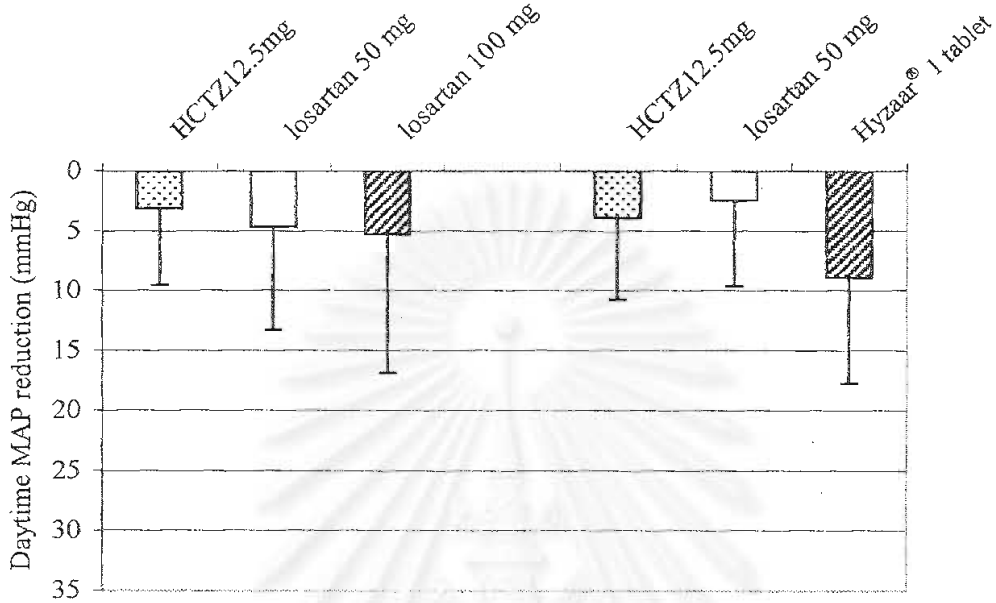


Figure 21: Nighttime SBP reduction of losartan100 mg group(n=11) and hyzaar group(n=12)

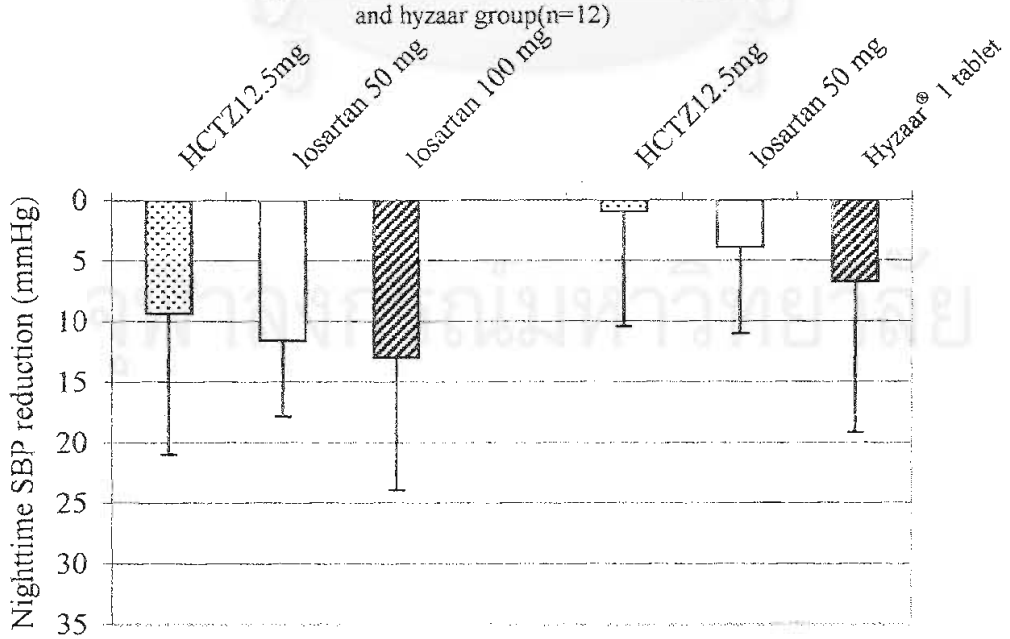


Figure 22: Nighttime DBP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)

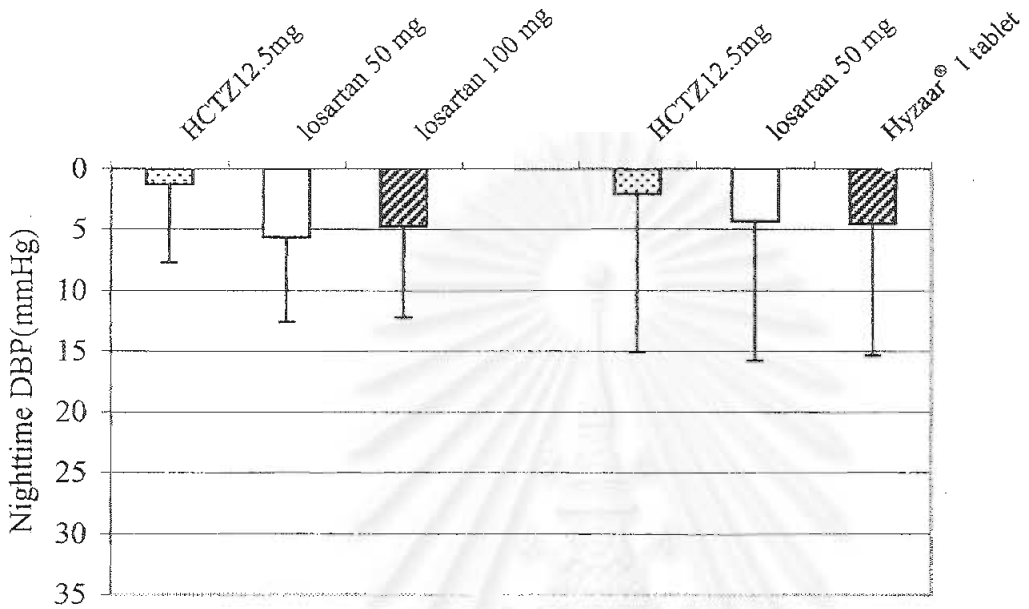
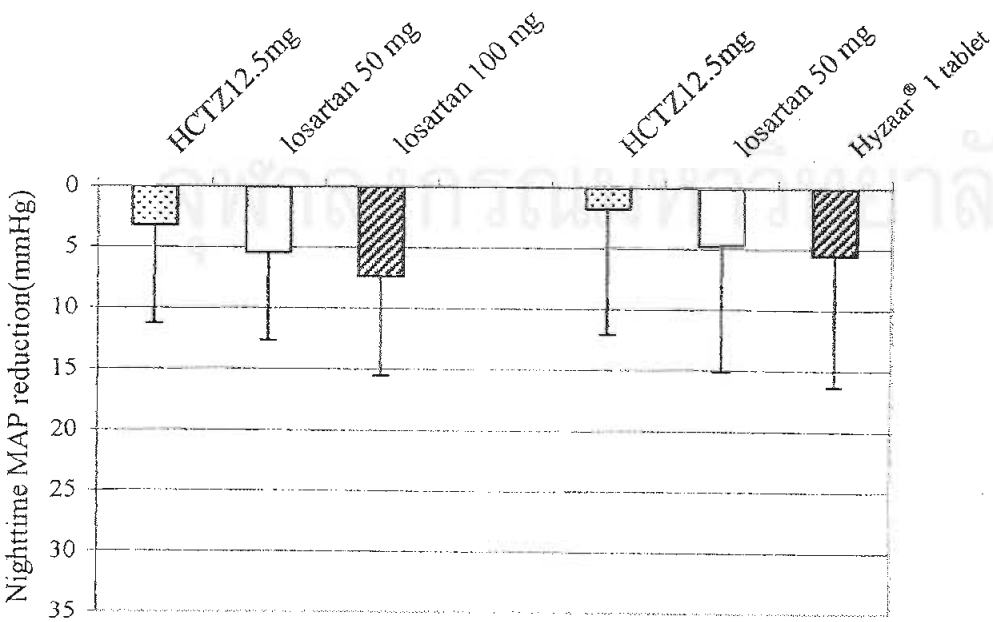


Figure 23: Nighttime MAP reduction of losartan 100 mg group(n=11) and hyzaar group(n=12)



BP loads & AUC

We found that losartan 50 mg plus hydrochlorothiazide 12.5 mg reduced 24-hour BP loads of SBP/DBP from 68±21.3/54±31.0 to 45±28.0/ 33±33.2%($p<0.05$). When considered only during daytime hours, this combination regimen also significantly lowered daytime BP loads of SBP/DBP from 65±22.3/ 54±32.4 to 42±28.0/31±31.0%, while during nighttime hours neither losartan monotherapy nor when used in combination with hydrochlorothiazide 12.5 mg reduced SBP/DBP significantly from baseline. With losartan 100 mg treatment, only SBP loads when considered the whole 24-hour SBP and daytime hours SBP were significantly reduced from 82±6.9% at baseline to 51±23.9% and from 82±8.9% at baseline to 37±27.4% respectively($p<0.05$).(table21)

As shown in table 22, after adding 50 mg more dose of losartan potassium in the second step, there were only 5.25±15.73 and 0.81±14.14% further reduction of SBP loads when focus on daytime hours and the average of the whole 24-hour after losartan potassium 100mg treatment respectively which shown statistically significant difference compared to the reduction obtained from losartan 50mg treatment($p<0.05$). Besides SBP loads mentioned above, the other BP loads no matter achieved after increasing the doses of losartan to 100 mg or adding 12.5 mg of hydrochlorothiazide showed no statistically significant difference from the reduction in frequency and magnitude of BP loads obtained after losartan 50 mg. The data obtained, either from office blood pressure or ambulatory blood pressure were all

Table 21 : BP loads and area above the normal blood pressure versus time curve (AUC) at baseline and after 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(Hyzaar)(losartan non-normalized group)

Parameter	losartan 100 mg(n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)		
	baseline	losartan 50 mg	losartan 100 mg	baseline	losartan 50 mg	hyzaar
	mean±SD	mean+SD[a]	mean+SD[b,c]	mean+SD	mean±SD[d]	mean+SD[e,f]
Frequency of BP load (%)						
24-hour BP load						
SBP	82±6.9	52±28.1*	51±23.9*,ns	68±21.3	58±21.9 ns	45±28.0*,ns
DBP	50±25.8	40±23.4 ns	37±24.0 ns,ns	54±31.0	45±28.9 ns	33±33.2*,ns
daytime BP load						
SBP	82±8.9	47±28.6*	47±25*,ns	65±22.6	56±23.5 ns	42±28.0*,ns
DBP	48±28.0	40±24.6 ns	37±27.4 ns,ns	54±32.4	46±31.0 ns	31±31.0*,ns
nighttime BP load						
SBP	83±24.7	70±34.8 ns	65±27.3 ns,ns	81±24.4	67±32.6 ns	58±38.6 ns,ns
DBP	56±29.1	41±25.1 ns	39±27.2 ns,ns	56±33.6	42±31.4 ns	43±41.1 ns,ns
Absolute value of BP load(mmHg)						
24-hour BP load						
SBP	18±4.2	14±5.2 ns	14±7.6 ns,ns	16±5.8	17±7.3 ns	13±7.9 ns,ns
DBP	9±3.8	8±3.7 ns	8±4.8 ns,ns	9±5.3	8±5.3 ns	6±6.6$
daytime BP load						
SBP	17±5.1	14±6.3 ns	14±9.2 ns,ns	15±6.3	18±8.1 ns	12±8.1 ns,$
DBP	9±4.0	8±3.9 ns	8±5.0 ns,ns	9±4.9	8±5.5 ns	6±6.3$,ns
nighttime BP load						
SBP	21±8.4	14±7.1$	12±9.7*,ns	16±6.7	16±9.5 ns	14±13.0 ns,ns
DBP	8±4.1	6±4.7 ns	6±6.1 ns,ns	9±7.5	5±4.7 ns	7±8.5 ns,ns

[a,b,d,e] versus baseline

[c,f] versus losartan 50 mg

***p<0.005, *p<0.05, $p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure

Table 21: BP loads and area above the normal blood pressure versus time curve (AUC) at baseline and after 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(Hyzaar)(losartan non-normalized group)(continued)

Parameter	losartan 100 mg (n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg		
	baseline	losartan 50 mg	losartan 100 mg	baseline	losartan 50 mg	Hyzaar
	mean± SD	mean± SD [a]	mean± SD[b,c]	mean± SD	mean± SD [d]	mean± SD[e,f]
24-hour AUC(mmHg.h)						
SBP	257±78.5	133±93.3*	130±122.8*, ns	201±125.2	174±144.2 ns	124±163.5 ns,ns
DBP	88±62.2	40±38.6$	48±55.6 ns, ns	98±101.7	80±100.2 ns	71±111.7ns,ns
daytime AUC(mmHg.h)						
SBP	155±63	72±53.5 *	87±92.8 ns,ns	126±89.6	117±104.0 ns	62±101.4$,ns
DBP	58±54.4	27±23.9 ns	34±45.8 ns,ns	64±64.0	64±80.4 ns	39±67.6 ns,ns
nighttime AUC(mmHg.h)						
SBP	102±50.0	61±45.0*	43±44.1***, $	75±47.6	57±48.4 ns	62±71.6 ns,ns
DBP	30±28.0	12±18.0 ns	13±13.5ns,ns	33±45.4	16±24.1 ns	32±46.1 ns,ns

[a,b,d,e] versus baseline

[c,f] versus losartan 50 mg

***p<0.005, *p<0.05, $p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure

Table 22 : The reduction of BP loads and area above the normal blood pressure time curve after 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(HYZAAR)

parameter	losartan 100 mg(n=11)			HYZAAR(n=12)		
	losartan 50 mg[a] step1 mean±SD	losartan50+50 mg[b] step2 mean±SD	c	losartan 50 mg [a] step1 mean±SD	losartan plus HCTZ12.5mg [b] step2 mean±SD	c
Frequency of BP load (%)						
24-hour BP load						
SBP	30.85±29.32	0.81±14.14	*	9.60±18.97	13.38±32.27	ns
DBP	9.64±20.86	2.48±18.71	*	8.86±16.52	12.67±30.58	ns
daytime BP load						
SBP	34.68±30.43	5.25±15.73	ns	8.66±20.68	14.51±36.49	ns
DBP	8.41±24.15	2.70±20.64	ns	7.72±17.18	15.42±31.58	ns
nighttime BP load						
SBP	13.63±34.79	4.55±18.38	ns	13.88±31.64	8.33±28.86	ns
DBP	15.18±32.87	1.50±34.53	ns	13.90±30.84	(-1.39)±36.54	ns
Absolute value of BP load(mmHg)						
24-hour BP load						
SBP	3.38±5.46	0.76±5.11	ns	(-1.52)±6.00	3.89+8.09	ns
DBP	1.19±4.72	(-0.08)±4.78	ns	1.13+4.68	1.43+6.41	ns
daytime BP load						
SBP	2.95±7.71	0.22±7.56	ns	(-2.37)+6.63	5.64+7.90	$
DBP	1.28±5.21	0.95±4.62	ns	0.56+4.69	2.33+6.16	ns
nighttime BP load						
SBP	7.14±9.16	1.83±4.93	ns	0.24+10.43	1.60+14.55	ns
DBP	1.56±6.27	(-2.33)±5.63	ns	3.90+7.11	(-2.05)+7.48	ns

[a] reduction of BP from baseline, [b] reduction of BP from BP after losartan 50 mg(step1), [c] difference between step1 and step2

*p<0.05, [$] p=0.05-0.1, ns= not significant

Table 22 : The reduction of BP loads and area above the normal blood pressure time curve after 50 mg losartan, 100 mg losartan and 50 mg losartan plus 12.5 mg hydrochlorothiazide(HYZAAR)(continued)

parameter	losartan 100 mg(n=11)			HYZAAR(n=12)		
	losartan 50 mg[a] step1 mean+SD	losartan50+50 mg[b] step2 mean+SD	c	losartan 50 mg [a] step1 mean+SD	losartan plus HCTZ12.5mg [b] step2 mean+SD	c
24-hour AUC(mmHg.h)						
SBP	123.89±111.81	3.68±87.60	*	26.27±137.99	50.25±209.27	ns
DBP	48.45±57.73	(-8.09)±26.54	*	17.94±89.52	9.06±137.09	ns
daytime AUC(mmHg.h)						
SBP	82.57±86.97	(-14.43)±74.27	*	9.04±86.55	54.67±140.82	ns
DBP	31.32±53.43	(-7.22)±31.67	ns	0.23±59.91	24.65±97.42	ns
nighttime AUC(mmHg.h)						
SBP	41.14±45.93	18.32±22.47	ns	17.29±57.88	(-4.40)±78.78	ns
DBP	17.14±32.91	(-0.86)±15.02	ns	17.71±45.95	(-15.58)±45.43	ns

[a] reduction of BP from baseline, [b] reduction of BP from BP after losartan 50 mg(step1), [c] difference between step1 and step2

*p<0.05, [$] p=0.05-0.1, ns= not significant

similar in that there was only slight further reduction of BP loads after dose titration, while adding hydrochlorothiazide 12.5 mg seem to cause more prominent reduction of BP loads. However, since the reductions of BP loads were different from the first step between two groups, this could effect result of the BP loads reduction in second step.

When considering the AUC, only the AUC of SBP attained for 24-hour and during nighttime after losartan 100 mg treatment showed significantly different from baseline AUC at p value of <0.05 level and <0.005 respectively. Although there were great differences of AUC reduction after either step 1 or step 2 therapy between losartan 100 mg group and losartan 50 mg plus hydrochlorothiazide 12.5 mg group, this is probably due to the effects of the differences of AUC at baseline. Nevertheless, AUC after step 2 therapy (losartan 100mg or losartan 50mg plus hydrochlorothiazide12.5mg) were finally showed quite no difference between these two groups. (table21-22)

Losartan normalized group

Office & ABP

After 25 mg losartan treatment, office SBP, DBP and MAP reduced from 144±7.70 to 126±17.80 mmHg, 96±6.22 to 80±10.14 mmHg and 112±5.64 to 95±12.54 mmHg respectively. With half a tablet of HYZAAR®(losartan 50 mg plus hydrochlorothiazide 12.5 mg) once daily treatment, office SBP, DBP and MAP reduced from 147±4.21, 94±5.26, 112±4.77 mmHg to 133±11.10, 86±5.94 and 102±7.42 mmHg respectively. Similar results were found when closely monitored with ambulatory blood pressure monitoring machine in that the average 24-hour ABP and either concentrated on daytime or nighttime hours were both lowered from baseline after losartan 25 mg and half a tablet of HYZAAR® treatment, however, all of these differences were not statistically significant. It could be seen from the results that after patients responded to losartan 50 mg, decreasing dosage to 25 mg losartan seems to produce more BP reductions than half a tablet of HYZAAR® once daily treatment.(table 23)

BP load & AUC

After patients were normalized BP with 50 mg losartan once daily treatment, it was found that the reductions of the frequency and magnitudes of BP loads with losartan in the dosage decreasing to 25 mg treatment were more than the reductions of BP loads with half a tablet of HYZAAR® once daily treatment. However, they showed no statistically significant difference which probably due to quite small in sample size in these groups. AUC with losartan 25 mg and half a tablet

Table 23: The mean office BP and ABP of the subjects at baseline and after 50 mg losartan, 25 mg losartan and 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment (losartan normalized group)

Parameter	losartan 25 mg(n=4)			losartan25 mg plus hydrochlorothiazide 6.25 mg(n=5)		
	baseline	losartan 50 mg	losartan 25 mg	baseline	losartan 50 mg	hyzaar1/2
	mean±SD	mean±SD[a]	mean±SD[b,c]	mean±SD	mean±SD[d]	mean±SD[e,f]
Office BP						
SBP(mmHg)	144±7.70	127±15.59[ns]	126±17.80[ns,ns]	147±4.21	129±10.88[ns]	133±11.10[ns,ns]
DBP(mmHg)	96±6.22	79±7.80[ns]	80±10.14[ns,ns]	94±5.26	78±4.02*	86±5.94[ns,$]
MAP(mmHg)	112±5.64	95±9.69[ns]	95±12.54[ns,ns]	112±4.77	95±6.12*	102±7.42[ns,ns]
HR(bpm)	71±5.00	70±3.79[ns]	76±7.3[ns,ns]	75±12.3	74±10.81[ns]	74±12.49[ns,ns]
24-hour ABP						
average 24-hour						
SBP(mmHg)	136±6.60	133±10.50[ns]	131±6.18[ns,ns]	140±10.83	126±13.89[ns]	133±8.23[$,ns]
DBP(mmHg)	84±10.34	81±6.61[ns]	78±7.14[ns,ns]	84±9.12	75±8.26[ns]	77±10.09[ns,ns]
MAP(mmHg)	101±8.06	98±4.55[ns]	96±5.91[ns,ns]	103±9.83	92±11.48[ns]	96±8.68*[,ns]
HR(bpm)	80±9.29	81±9.74[ns]	79±9.25[ns,ns]	71±9.36	69±12.26[ns]	72±10.11[ns,ns]
average daytime						
SBP(mmHg)	139±7.37	138±11.90[ns]	134±5.06[ns,ns]	148±13.40	132±15.57[ns]	139±13.85[ns,ns]
DBP(mmHg)	87±11.00	83±6.18[ns]	79±9.54[ns,ns]	88±12.01	78±10.36[ns]	80±13.13[ns,ns]
MAP(mmHg)	104±8.77	102±5.00[ns]	97±7.09[ns,ns]	102±3.77	95±13.73[ns]	100±11.70[ns,ns]
HR(bpm)	80±9.98	89±9.39[ns]	83±13.53[ns,ns]	74±9.24	76±11.63[ns]	79±12.79[ns,ns]

a,b,d,e versus baseline

c,f versus losartan 50 mg

* $p < 0.05$, $ p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Table 23: The mean office BP and ABP of the subjects at baseline and after 50 mg losartan, 25 mg losartan and 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment (losartan normalized group)(continued)

Parameter	losartan 25 mg(n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg(n=5)		
	baseline	losartan 50 mg	losartan 25 mg	baseline	losartan 50 mg	hyzaar1/2
	mean±SD	mean±SD[a]	mean±SD[b,c]	mean±SD	mean±SD[d]	mean±SD[e,f]
average nighttime						
SBP(mmHg)	130±6.81	121±8.06[ns]	123±14.13[ns,ns]	125±6.50	115±10.26[ns]	119±8.49[ns,ns]
DBP(mmHg)	77±10.05	75±7.14[ns]	74±5.29[ns,ns]	76±5.02	69±5.15[ns]	71±5.00[ns,ns]
MAP(mmHg)	95±8.23	90±4.62[ns]	91±7.27[ns,ns]	92±5.74	84±6.22[ns]	87±4.15[ns,ns]
HR(bpm)	74±11.09	74±11.03[ns]	76±4.69[ns,ns]	69±12.77	63±14.35*	69±12.40[ns,ns]

a,b,d,e versus baseline

c,f versus losartan 50 mg

* p< 0.05, $ p=0.05-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Table24 : BP loads and area above the normal blood pressure versus time curve at baseline and after 50 mg losartan,25 mg losartan and 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment.(losartan normalized group)

Parameter	losartan 25 mg(n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg(n=5)		
	baseline	losartan 50 mg	losartan 25 mg	baseline	losartan 50 mg	hyzaar1/2
	mean±SD	mean±SD[a]	mean±SD[b,c]	mean±SD	mean±SD[d]	mean±SD[e,f]
Frequency of BP load (%)						
24-hour BP load						
SBP	52±21.14	42±30.34 [ns]	34±11.7 [ns,ns]	56±25.59	31±29.72*	36±15.60 [ns,ns]
DBP	42±27.81	23±17.21 [ns]	28±20.31 [ns,ns]	34±30.04	16±19.83[ns]	24±25.57 [ns,ns]
daytime BP load						
SBP	43±23.11	39±31.6 [ns]	33±10.5 [ns,ns]	55±25.98	31±29.47*	37±19.59[ns,ns]
DBP	26±25.84	20±18.76 [ns]	25±16.94 [ns,ns]	35±31.27	17±21.69 [ns]	23±29.91 [ns,ns]
nighttime BP load						
SBP	88±15.96	54±28.46 [ns]	38±34.36 [ns,ns]	60±27.89	30±34.16[$]	33±11.79 [ns,ns]
DBP	46±41.67	38±15.96 [ns]	42±44.10 [ns,ns]	33±28.87	13±13.94 [ns]	27±14.91 [ns,ns]
Absolute value of BP load(mmHg)						
24-hour BP load						
SBP	12±3.96	11±6.49 [ns]	12±7.07 [ns,ns]	15±7.76	10±7.00 [ns]	18±7.32 [ns,ns]
DBP	7±4.51	6±1.87 [ns]	8±6.51 [ns,ns]	8±7.71	5±5.81 [ns]	8±4.31 [ns,ns]
daytime BP load						
SBP	11±5.68	11±7.05 [ns]	11±4.44 [ns,ns]	15±8.93	11±7.10 [ns]	17±8.86 [ns,ns]
DBP	8±4.69	6±1.49 [ns]	5±4.62 [ns,ns]	8±8.54	5±6.24 [ns]	5±6.10 [ns,ns]
nighttime BP load						
SBP	14±3.10	10±6.89 [ns]	11±16.82 [ns,ns]	13±2.91	5±6.48[$]	16±6.90 [ns,ns]
DBP	4±4.48	4±4.19 [ns]	11±15.95 [ns,ns]	4±2.56	2±3.49 [ns]	7±5.25[ns,$]

a,b,d,e versus baseline

c,f versus losartan 50 mg

* $p<0.05$, $ $p=0.05$-0.1, ns = not significant

Table24 : BP loads and area above the normal blood pressure versus time curve at baseline and after 50 mg losartan,25 mg losartan and 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment.(losartan normalized group)(continued)

Parameter	losartan 25 mg (n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg		
	baseline mean± SD	losartan 50 mg mean± SD [a]	losartan 25 mg mean± SD [b,c]	baseline mean± SD	losartan 50 mg mean± SD [d]	Hyzaar1/2 mean± SD [e,f]
24-hour AUC(mmHg.h)						
SBP	126±85	67±86.63 [ns]	70±68.77 [ns,ns]	146±163.59	58±76.83 [ns]	99±61.50 [ns,ns]
DBP	64±63.30	8±10.13 [ns]	10±7.26 [ns,ns]	57±108.59	20±27.03 [ns]	31±45.15 [ns,ns]
daytime AUC(mmHg.h)						
SBP	74±58.99	47±67.58 [ns]	33±26.91 [ns,ns]	111±139.69	48±62.00 [ns]	74±67.72 [ns,ns]
DBP	48±47.23	6±11.04 [ns]	15±14.79 [ns,ns]	52±99.40	19±25.31 [ns]	26±37.84 [ns,ns]
nighttime AUC(mmHg.h)						
SBP	53±38.02	20±23.23 [ns]	38±50.31 [ns,ns]	35±27.90	10±15.82 [ns]	25±21.81 [ns,ns]
DBP	16±27.19	2±2.36 [ns]	3±5.75 [ns,ns]	5±9.40	1±2.68 [ns]	5±8.59 [ns,ns]

a,b,d,e versus baseline

c,f versus losartan 50 mg

* p<0.05, $ p=0.05-0.1, ns = not significant

Figure 24: Ambulatory Hourly Blood Pressure data after losartan25mg treatment in patients who were normalized with 50 mg losartan treatment(n=4)

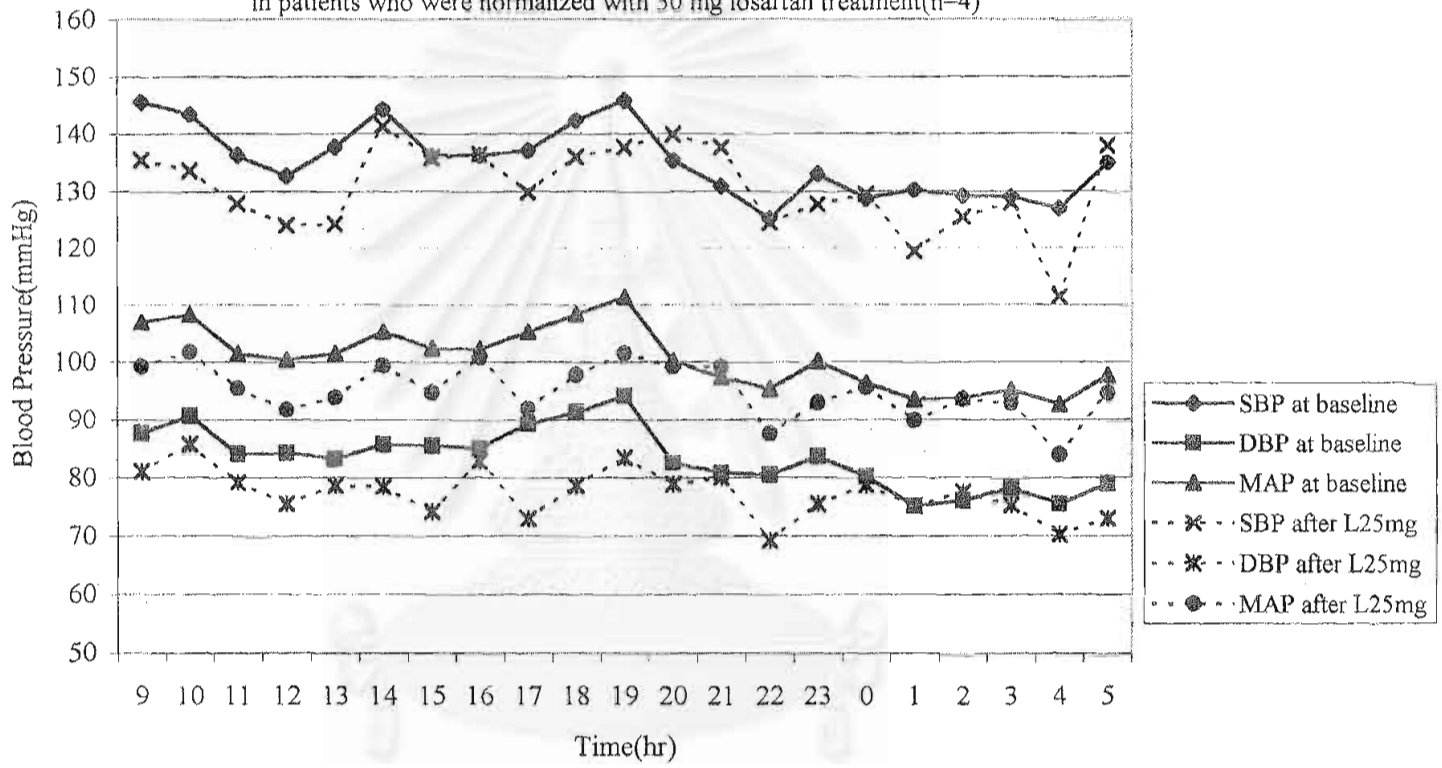
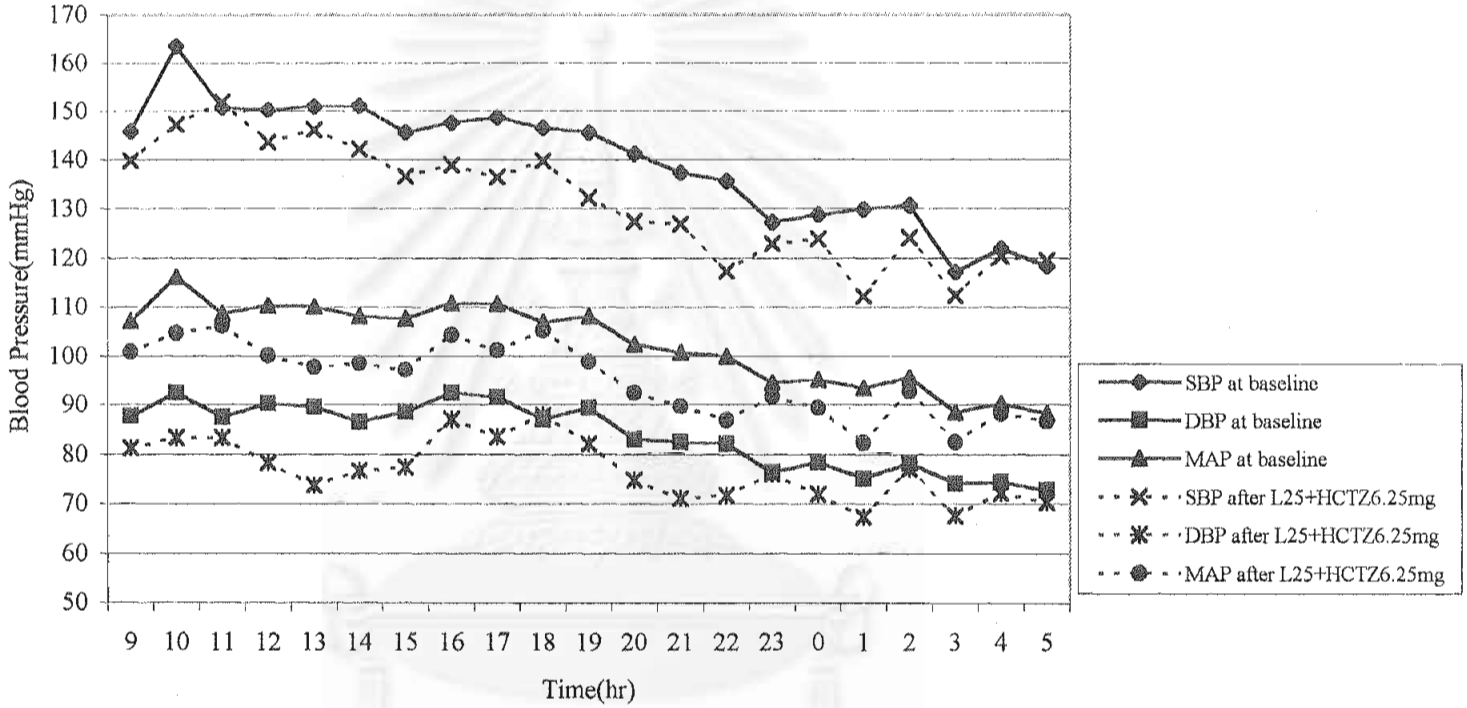


Figure 25: Ambulatory Hourly Blood Pressure data after 25 mg losartan plus 6.25 mg HCTZ treatment in patients who were normalized with 50 mg losartan(n=5)



of HYZAAR® treatment were also lowered from baseline with varied degree of AUC reduction since it is possibly due to the small number of subjects.(table24)

Dippers and nondippers

By using the 24-hour BP monitoring, BP variability throughout the day could be observed. According to the categorization of hypertensive patients as dippers or nondippers with the percentage of BP reduction of nighttime BP compare to daytime BP. Dippers were patients who had mean blood pressure fall during the night by more than 10% compared to daytime BP, but others in whom the fall in BP was less than 10% were nondippers. With this criterion, when groups were based on the nocturnal reduction of baseline SBP, twenty-one patients were dippers and eleven patients were nondippers. After treatment, it was found that, losartan 50 mg significantly increased nocturnal SBP reduction in nondippers from 3.46$\pm$3.98 to 9.18$\pm$5.55% at p value of <0.05 level (table25). When groups were based on nocturnal reduction of baseline DBP, fifteen patients were classified as dippers, while seventeen patients were classified as nondippers. With losartan 50 mg treatment, in nondippers, there was a significant increasing of nocturnal DBP reduction from 5.05$\pm$3.30 to 11.08$\pm$7.29% ($p<0.05$), but in dippers, nocturnal reduction of DBP was lowered from 17.17$\pm$3.62 to 11.40$\pm$5.72%($p<0.05$) after losartan 50 mg administration (table26). However, using this criterion, this nocturnal reduction of DBP after losartan50 mg still classified as dippers.This mae be due to more reduction of daytime DBP than nighttime DBP from losartan. When considered on MAP, seventeen patients were dippers and fifteen patients were nondippers. Consistent with previous result, with losartan 50 mg treatment, nocturnal reduction

of MAP was significantly increased from 5.42±3.37 to 10.60±6.24% in nondippers. Moreover, nocturnal reduction of DBP was also increased from 5.03±4.19 to 10.88±6.95% ($p<0.05$)(table 27). Figure 28 to 33 depict the effect of losartan 50 mg on SBP/DBP and MAP , nocturnal fall, and the interaction in dipper/nondippers.

The non-dipping or flat pattern of circadian BP variability is clinically important since recent studies suggest that these patients appear to have an increase in cardiovascular morbidity. In addition, there is some evidence that nondippers have a greater left ventricular mass than dippers.[45-47]

While earlier work noted that circadian rhythm of BP in nondipper type of essential hypertension shifted from nondipper to dipper with hydrochlorothiazide in salt-sensitive hypertension[18], the present study clearly showed that nocturnal fall in BP was restored by therapy with losartan 50 mg in nondippers indicating that the circadian rhythm of BP had a tendency to transform from nondippers to dipper patterns. Recently , it was found that BP failed to fall during the night in patients with sodium-sensitive essential hypertension[10] and also showed that sodium restriction shifted the circadian rhythm from nondippers to dippers in these patients.[48] The diurnal rhythm of BP was also disturbed in patients with primary aldosteronism, a typical form of sodium-sensitive secondary hypertension and sodium restriction enhanced nocturnal BP fall in these patients as well.[49] There are other sodium-sensitive types of hypertension, such as hypertension in Blacks,[50,51] glomerulonephritis,[52] and patients with diabetes mellitus.[53,54] The diurnal rhythm of BP is also reported to be disturbed in these pathophysiological states.[55-57] Thus,

Table 25 : Nocturnal reduction of BP at baseline and after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment (dippers/nondippers group based on nocturnal reduction of baseline SBP)(n=32)

parameter		baseline	hydrochlorothiazide 12.5 mg	losartan 50 mg
		mean±SD	mean±SD[d]	mean±SD[e,f]
SBP [a]	dippers(n=21)	13.76±2.87	11.53±5.35 [ns]	12.14±3.38 [ns,ns]
	nondippers(n=11)	3.46±3.98	7.18±6.52 [ns]	9.18±5.55*, [ns]
DBP [b]				
	dippers(n=21)	13.34±6.32	10.71±6.53 [ns]	12.30±5.48 [ns, ns]
	nondippers(n=11)	5.75±5.61	5.80±7.95 [ns]	9.18±8.00 [ns, ns]
MAP [c]				
	dippers(n=21)	13.47±4.39	10.94±5.31 [ns]	11.89±5.13 [ns, ns]
	nondippers(n=11)	4.77±3.89	6.44±6.07 [ns]	8.65±7.87 [ns, ns]

a,b,c =nocturnal reduction of SBP, DBP, MAP respectively (%)

d, e versus baseline, f versus hydrochlorothiazide

* $p<0.05$, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

Table 26 : Nocturnal reduction of BP at baseline and after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment (dippers/nondippers group based on nocturnal reduction of baseline DBP)(n=32)

parameter		baseline	hydrochlorothiazide 12.5 mg	losartan 50 mg
		mean±SD	mean±SD[d]	mean±SD[e,f]
SBP [a]	dippers(n=15)	12.99±4.79	13.26±5.36 [ns]	12.63±3.24 [ns,ns]
	nondippers(n=17)	7.78±5.87	7.19±5.24 [ns]	9.80±5.65 [ns,ns]
DBP [b]				
	dippers(n=15)	17.17±3.62	11.58±7.30 [$]	11.40±5.72 [*,ns]
	nondippers(n=17)	5.05±3.30	6.76±6.74 [ns]	11.08±7.29[*,ns]
MAP [c]				
	dippers(n=15)	15.25±3.74	12.13±5.25 [ns]	11.39±5.60 [$,ns]
	nondippers(n=17)	6.27±3.90	6.92±5.48 [ns]	10.24±6.94 [ns,ns]

a,b,c nocturnal reduction of SBP, DBP, MAP respectively(%)

d, e versus baseline, f versus hydrochlorothiazide

* $p<0.05$, [$] $p=0.05$-0.1, ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

Table 27 : Nocturnal reduction of BP at baseline and after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment (dippers/nondippers group based on nocturnal reduction of baseline MAP)(n=32)

parameter		baseline	hydrochlorothiazide 12.5 mg	losartan 50 mg
		mean±SD	mean±SD[d]	mean±SD[e,f]
SBP [a]	dippers(n=17)	14.01±3.33	12.44±5.49 [ns]	12.29±3.53 [ns, ns]
	nondippers(n=15)	5.93±5.29	7.31±5.62 [ns]	9.81±5.81 [$, ns]
DBP [b]				
	dippers(n=17)	15.75±4.80	11.81±6.55 [ns]	11.54±6.29 [ns, ns]
	nondippers(n=15)	5.03+4.19	5.86±7.02 [ns]	10.88±6.95* [, ns]
MAP [c]				
	dippers(n=17)	14.94±3.55	11.91±5.05 [ns]	10.93±6.49 [$,ns]
	nondippers(n=15)	5.42±3.37	6.55±5.61 [ns]	10.60±6.24* [, ns]

a,b,c nocturnal reduction of SBP, DBP, MAP respectively(%)

d, e versus baseline, f versus hydrochlorothiazide

* $p<0.05$, [$] $p=0.05$-0.1 , ns= not significant

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

Figure 26: Ambulatory Hourly Blood Pressure data after losartan50mg treatment in nondippers based on MAP(n=15)

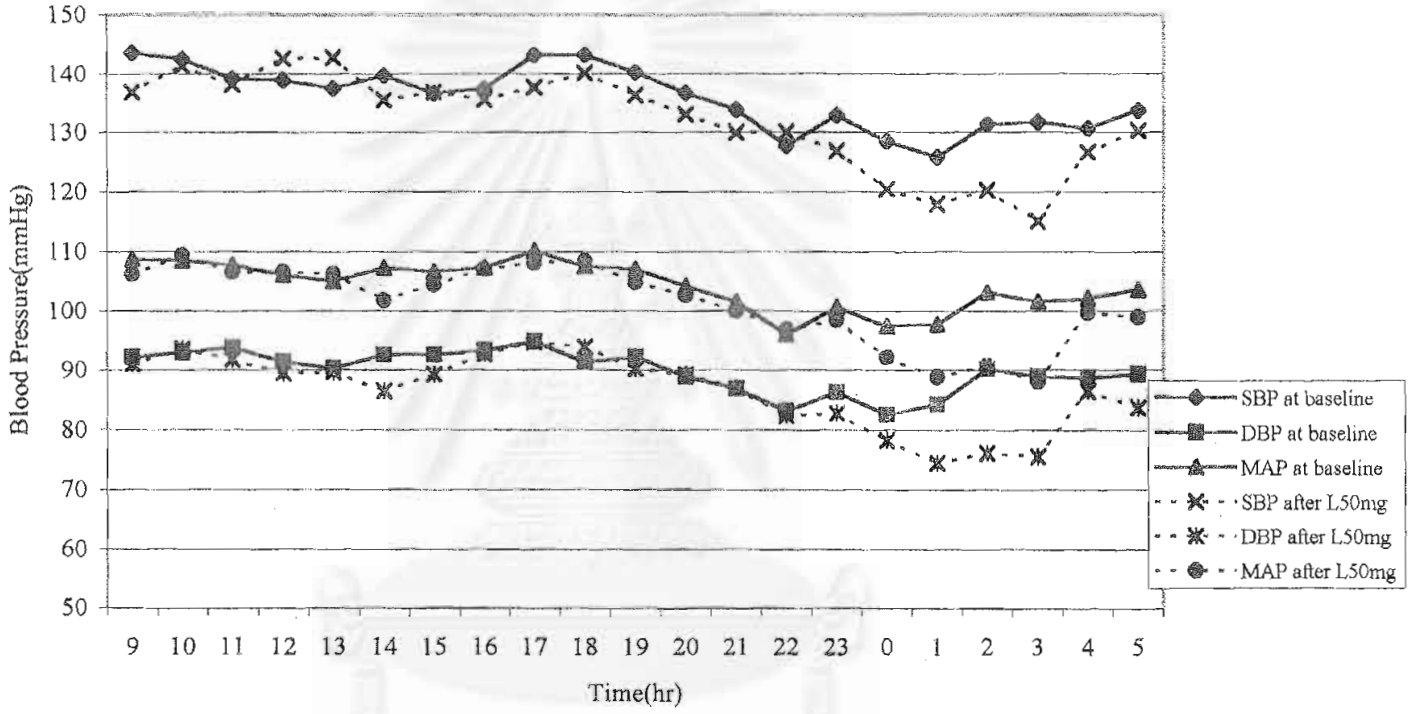


Figure 27 : Ambulatory Hourly Blood Pressure data after losartan 50mg treatment in dippers based on MAP(n=17)

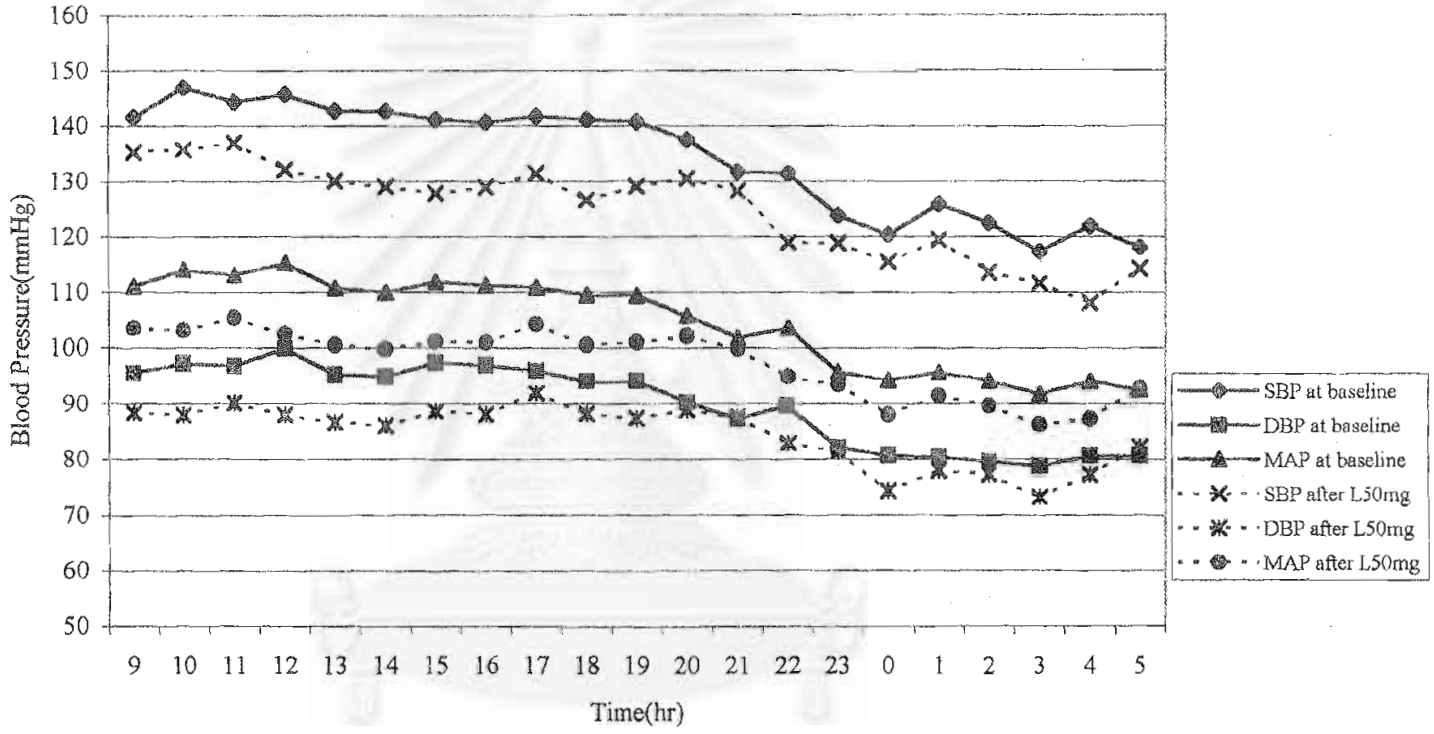


Figure 28: Daytime and nighttime SBP at baseline and after losartan50 mg treatmen; group based on nocturnal reduction of baseline SBP(dippers, n=21)

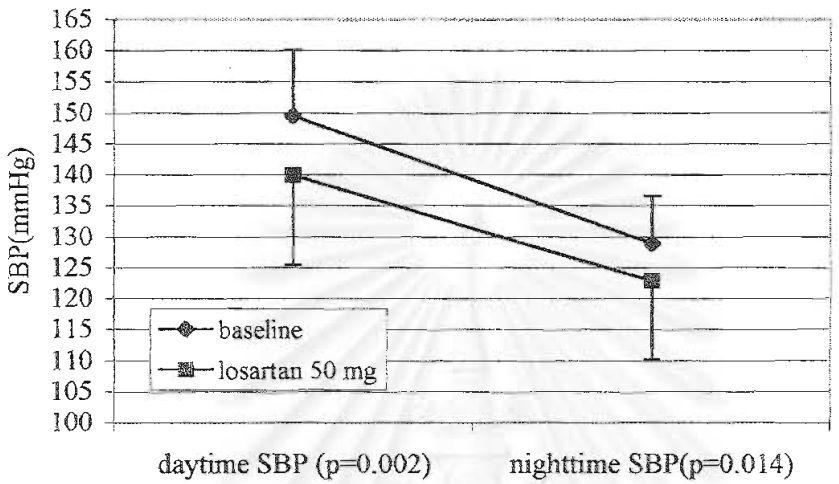


Figure 29: Daytime and nighttime SBP at baseline and after losartan 50 mg treatment; group based on nocturnal reduction of baseline SBP(nondippers, n=11)

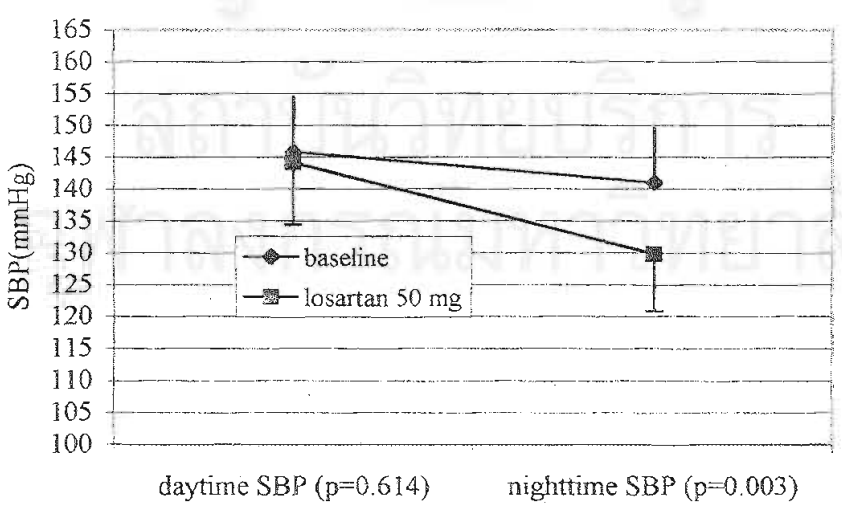


Figure 30: Daytime and nighttime DBP at baseline and after losartan 50 mg treatment; group based on nocturnal reduction of baseline DBP(dippers,n=15)

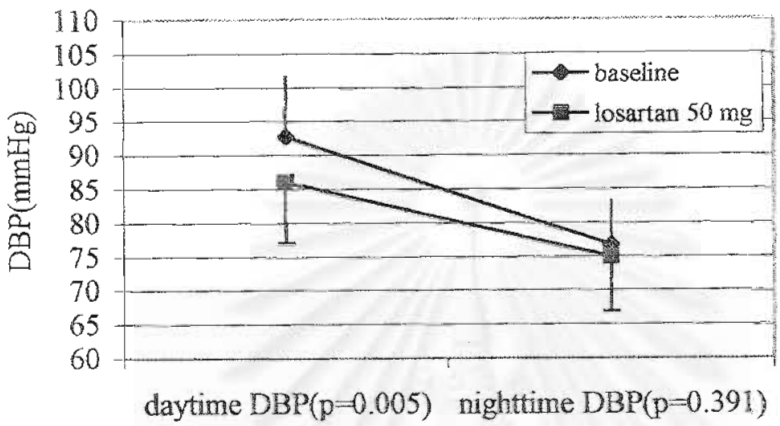


Figure 31: Daytime and nighttime DBP at baseline and after losartan 50 mg ;group based on nocturnal reduction of baseline DBP(nondippers,n=17)

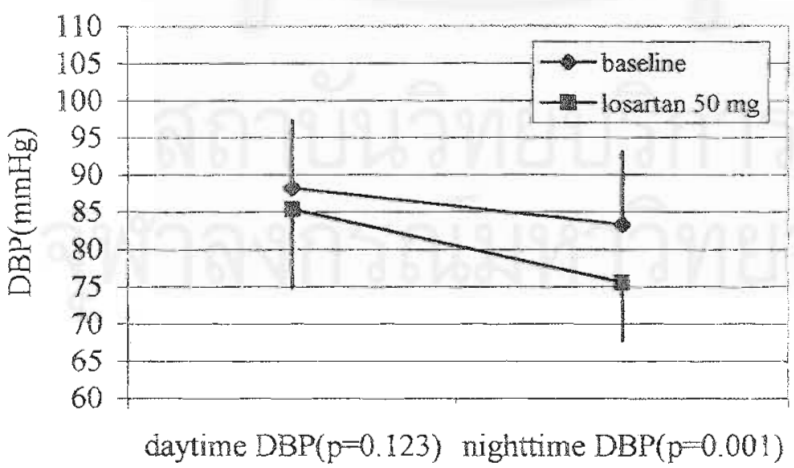


Figure 32: Daytime and nighttime MAP at baseline and after losartan 50 mg; group based on nocturnal reduction of baseline MAP(dippers,n=17)

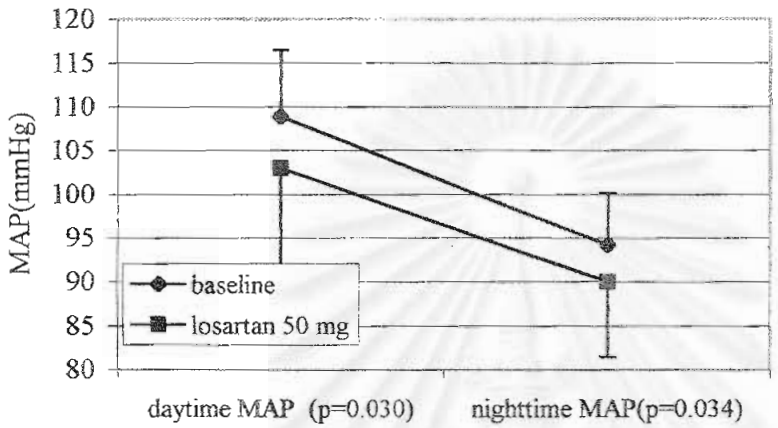
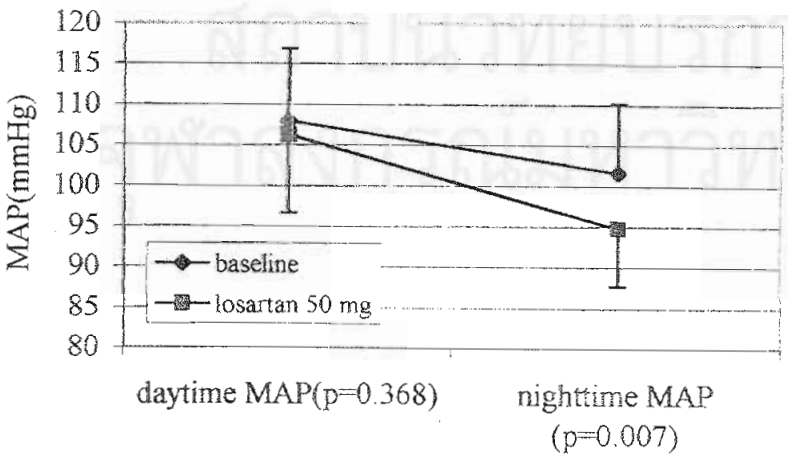


Figure 33: Daytime and nighttime MAP at baseline and after losartan 50 mg; group based on nocturnal reduction of baseline MAP(nondippers, n=15)



regardless of the mechanism of sodium sensitivity of BP, whether the ultrafiltration coefficient was reduced or tubular sodium reabsorption was enhanced [58], nocturnal BP fall diminished in all patients with sodium-sensitive types of hypertension who had relatively high sodium intake. Previous studies showed that hydrochlorothiazide effectively lowered 24-hour BP in nondippers and blacks, whose elevated salt sensitivity has been previously described. [48,50,59] In this study the dose of hydrochlorothiazide treatment was relatively low(12.5 mg daily), so antihypertensive effect based on its diuretic action on the kidney probably was a small extent and T:P ratio of hydrochlorothiazide 12.5 mg treatment was markedly lowered than those with losartan 50 mg treatment. In previous report[48], sodium restriction(mean reduction in sodium restriction of 176 mmol/day) lowered 24-hour MAP about 16.9 mmHg in patients with salt-sensitive essential hypertension). In this study, the mean value of 24-hour MAP reduction with 12.5 mg of hydrochlorothiazide was 3 mmHg and the patients are not all salt-sensitive essential hypertension . Thus adding 12.5 mg of hydrochlorothiazide may have a similar effect as a reduction in sodium intake of roughly 31 mmol/day in patients who are nondippers and/or have salt-sensitive essential hypertension. When examined the circadian rhythm of urinary sodium excretion and the effects of sodium restriction on it in both dipper and nondipper types of essential hypertension. It was found that the circadian rhythm of natriuresis is disturbed in nondippers.[50] These findings indicated that renal sodium handling may play a key role in determining the circadian rhythm of BP. When sodium intake is relatively high, the defect in sodium excretory capability , which elevates BP at night to compensate for diminished natriuresis during the day and to cause enhanced-pressure natriuresis at

night, becomes evident. When sodium intake is low, the effect remains latent, allowing BP to lower at night. These speculations, together with the well-known fact that in patients with renal dysfunction, nocturnal BP fall is lost.[60-63] , suggest that the circadian rhythm of BP is determined, at least in part, by the kidneys. It can be postulated from the findings that a renal defect in excreting sodium into the urine and the resulting sodium retention might be important determinants for impairments in nocturnal fall. The possibility that with this low dose hydrochlorothiazide in this study may have inadequate diuretic action on the kidney needs to be considered.

T: P ratio

Based on the assumption that patients with hypertension are likely to receive the greatest benefit from therapy when the antihypertensive effects do not fluctuate greatly during the dosing interval. The FDA guidelines indicated that the effect of an antihypertensive drug at the end of the dosing interval(trough) should be no less than half or two-thirds of the peak effect. Thus, a trough:peak ratio of 50-66% are required for the efficacy of antihypertensive agent to be considered satisfactory to its proposed dosage interval.

From the 24-hour ABP profiles of each patient, individual trough and peak antihypertensive effects were obtained. When 50mg and 100mg per day doses of losartan were considered, it was found that the magnitude of SBP/DBP decreased at peak drug effect were 24$\pm$12.5/18$\pm$10.9 mmHg with losartan 50mg and 27$\pm$14.1/7$\pm$8.6 mmHg after losartan 100mg treatment, while the magnitude of SBP/DBP reductions at trough after losartan 50 mg and losartan 100 mg were 12$\pm$8.3/ 7$\pm$5.1 mmHg and 12$\pm$7.0 / 7 $\pm$4.3 mmHg respectively. For treatment with

Table 28 : The changes in trough and peak BP changers and the T:P ratio of the subjects after hydrochlorothiazide, losartan and losartan plus hydrochlorothiazide treatment(Hyzaar)

Parameter	HCTZ 12.5 mg(n=32)	losartan 50 mg(n=32)	losartan 100 mg (n=11)	hyzaar(n=12)
SBP [a]				
Δ BP at Trough (mmHg)	7±4.83	12±8.3	12±7.0	13±8.8
Δ BP at Peak (mmHg)	21±10.59	24±12.5	27±14.1	25±10.4
T:P ratio of mean (%)	33	50	44	52
T:P ratio of individual (%)	38±26.6	51±20.2	44±14.9	53±22.1
(range)	(3-83)	(16-91)	(23-67)	(19-77)
DBP [a]				
Δ BP at Trough (mmHg)	5±4.6	7±5.1	7±4.3	8±8.5
Δ BP at Peak (mmHg)	16±8.7	18±10.9	17±8.6	17±9.6
T:P ratio of mean (%)	31	39	41	47
T:P ratio of individual (%)	33±18.6***	42±15.1	48±21.2	42±21.1
(range)	(6-64)	(22-69)	(15-89)	(12.5-84)

[a] data are shown as mean ± SD

***p<0.005 versus losartan50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure respectively

Table 29 : The number and percentage of subjects whose T:P ratio were higher than 50 % after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment (n=32)

Parameter		HCTZ 12.5 mg(n=32)	losartan 50 mg(n=32)
SBP			
	number	11	16
	%	34.4	50.0
DBP			
	number	8	10
	%	25.0	31.2

SBP= systolic blood pressure, DBP= diastolic blood pressure

Table 30 : The number and percentage of subjects whose T:P ratio were higher than 50 % after 50 mg losartan plus 12.5 mg hydrochlorothiazide and 100 mg losartan treatment(losartan non-normalized group)

Parameter		losartan 100 mg (n=11)	hyzaar(n=12)
SBP			
	number	3	8
	%	27.3	66.7
DBP			
	number	6	2
	%	54.5	16.7

SBP= systolic blood pressure, DBP= diastolic blood pressure

losartan 50mg plus hydrochlorothiazide 12.5 mg, the BP reductions both at peak and trough were close to those with losartan 50 and 100 mg treatment. By dividing the average changes at trough and peak drug effect, the T:P ratio of mean changes of 50% for SBP and 39% for DBP with losartan 50mg treatment were obtained, while T:P ratio of mean changes with losartan 100mg treatment were 44%/41% for SBP/DBP respectively. The T:P ratio of mean changes(SBP/DBP) with losartan 50 mg plus hydrochlorothiazide12.5 mg were 52%/47%.(table28).

The T:P ratio after hydrochlorothiazide treatment were much lower than the T:P ratio after losartan treatment, there were significant differences between T:P ratio after hydrochlorothiazide 12.5 mg treatment compared to losartan 50mg treatment especially for DBP which was 33±18.6% with hydrochlorothiazide 12.5 mg treatment and was 42+15.1% with losartan 50 mg which is not surprising since the half life of hydrochlorothiazide was quite short that the once daily dose could not be a suitable dosing interval.

When individual T:P ratio were calculated, the T:P ratio varied extensively after treatment with hydrochlorothiazide 12.5 mg, the SBP varied from 3 to 83% while the DBP ranged from 6 to 64%. With either losartan 100mg or losartan 50mg plus hydrochlorothiazide 12.5 mg treatment, the individual T:P ratio ranged from 15 to 89%.

Table 29 presents the numbers and percentage of the subjects whose their T:P ratio were more than 50% after 12.5 mg hydrochlorothiazide and 50 mg losartan treatment. It was found that when T:P ratio of systolic blood pressure and diastolic blood pressure was considered, 50 mg losartan treatment resulted in higher

percentage of patients either in systolic blood pressure(50.0% after 50 mg losartan vs 34.4% after 12.5 mg hydrochlorothiazide treatment) or diastolic blood pressure (31.2% after 50 mg losartan vs 25.0% after 12.5 mg hydrochlorothiazide treatment). In losartan 50 mg non-normalized group, it was found that for T:P ratio of systolic blood pressure, 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment seems to have antihypertensive effects covered 24-hour which were better than those of 100 mg losartan treatment(66.7% after 50 mg losartan plus 12.5 mg hydrochlorothiazide vs 27.3% after 100 mg losartan treatment), while the number and percentage of subjects whose T:P ratio were higher than 50% of diastolic blood pressure showed that 100 mg losartan seems to have better antihypertensive effects covered 24 hours than those after 50 mg plus 12.5 mg hydrochlorothiazide treatment(54.5% after 100 mg losartan vs 16.7% after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment)(table30). These T:P ratio obtained in this study show great variation either among patients and regimens. Trough SBP and DBP effects were BP reduction achieved at the times before the medications were taken, however, since in this study the patients were not told to record the exact time they took their medicine, so the trough SBP and DBP were calculated as the BP reduction during 02.00 a.m. to 04.00 a.m. which assumed that medicine had not been taken. The peak SBP and DBP effects were the values obtained from the time when the medication gave their maximum BP reduction which mostly were selected during 2-6 hours after the consumed losartan or losartan plus hydrochlorothiazide tablet and 1-3 hours after hydrochlorothiazide treatment(patients were told to take the medicine before coming to the hospital). Moreover, the number of subjects in step2 therapy(100 mg losartan

and 50 mg losartan plus 12.5 mg hydrochlorothiazide) were so small that the degree of variability among patients could affect the percentage of the subjects whose T:P ratio were higher than 50% after each regimen greatly.

CHAPTER V

CONCLUSION

1. Losartan 50mg administered once daily was effective in reducing both office SBP, DBP and MAP and ambulatory blood pressure when considered 24-hour as a whole or when concentrated on either daytime or nighttime hours, while hydrochlorothiazide 12.5 mg once daily treatment significantly reduced only office BP from baseline. HR after either regimens showed no statistically significant change.
2. Calculations of the frequency and absolute values of BP loads during daytime, nighttime and all 24-hour after treatment indicated that losartan 50mg once daily treatment induced significant reductions in the frequency of SBP and DBP loads for 24-hour, during daytime and nighttime hours, while with hydrochlorothiazide12.5 mg treatment, only 24-hour and daytime SBP loads were significantly reduced from baseline. Only the magnitudes of nighttime SBP loads were significantly reduced from baseline with losartan 50 mg treatment, while after hydrochlorothiazide 12.5 mg treatment, none of the magnitudes of BP loads were significantly reduced from baseline.
3. The area under the SBP and DBP curves which above normal BP were mostly significantly reduced from baseline with losartan 50 mg treatment except for AUC of daytime DBP which showed no statistically significant reduction. With hydrochlorothiazide12.5 mg treatment, only 24-hour AUC of SBP were significantly reduced from baseline.

4. Concerning on circadian rhythm of BP, it was found that nocturnal reduction of SBP was significantly increased in systolic nondippers administered with losartan 50 mg once daily. When categorized patients as dippers or nondippers according to their DBP and MAP, similar results was found. In diastolic nondippers patients, nocturnal reductions of DBP were increased with losartan 50 mg treatment. In mean arterial pressure nondippers, there were statistically significant increasing in nocturnal reductions of MAP, moreover, nocturnal reduction of DBP was also significantly increased from baseline. This findings clearly showed that nocturnal fall of BP was restored by therapy with losartan 50 mg in nondippers indicating that the circadian rhythm of BP was transformed from nondippers to dippers patterns.
5. In losartan 50 mg normalized group, Decreasing dosage of losartan to 25 mg seems to be able to decrease office and ABP in the extent close to BP reduction after losartan 50 mg treatment. With half a tablet of 50 mg losartan plus 12.5 mg hydrochlorothiazide once daily treatment, even though some antihypertensive effects could be seen, but they seem to be much smaller than with losartan 50 mg administration. However, all these differences (except the effect of half a tablet of 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment on MAP) were not statistically significant since the number of subjects in normalized group was so small. Further studies with more sample size are required.
6. In losartan non-normalized group, losartan 50 mg in the combination with hydrochlorothiazide12.5 mg caused statistically significant reductions in

office BP and ABP. Only during nighttime hours which the reduction in BP showed no statistically significant difference from baseline. Considerating on losartan with the dosage titrated to 100 mg, the office and ABP were found to be decreased from baseline with this treatment, however, only office BP and nighttime SBP, MAP were statistically different from baseline. Comparison between the results obtained after the initial 50 mg dose of losartan(first step) with the results achieved after adding another 50 mg dose of losartan(second step) revealed that the initial dose produce a more pronounced effect on the reduction of BP, frequency of BP loads and AUC than the consecutive dose. These results indicated that titrating dosage of losartan from 50 mg to 100 mg did not produce prominent further reduction of BP in this losartan non-normalized group. On the other hand, adding hydrochlorothiazide in the dosage of 12.5 mg to the initial 50 mg dosage of losartan appeared to show distinct further reduction of BP and frequency of BP loads in this same group.

7. The percentage of patients responded to 50 mg losartan treatment was higher than those after 12.5 mg hydrochlorothiazide treatment either when based on office blood pressure(68.8% after 50 mg losartan treatment vs 62.5% after 12.5 mg hydrochlorothiazide treatment) or 24-hour ambulatory blood pressure(46.9% after 50 mg losartan treatment vs 37.5% after 12.5 mg hydrochlorothiazide treatment).

In 50 mg losartan normalized group, the percentage of

responders after 25 mg losartan monotherapy was higher than those obtained from the combination of 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment whether the data were based on office blood pressure(75% after 25 mg losartan treatment vs 60% after 25 mg plus 6.25 mg hydrochlorothiazide treatment) or 24-hour ambulatory blood pressure (100% after 25 mg losartan treatment vs 80% after 25 mg plus 6.25 mg hydrochlorothiazide treatment).

In 50 mg losartan non-normalized group, the percentage of responders was higher after 50 mg losartan plus 12.5 mg hydrochlorothiazide as compared to after 100 mg losartan treatment only when based on 24-hour ambulatory blood pressure(50% after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment vs 45.5% after 100 mg losartan treatment), while the percentage of responders after 100 mg losartan treatment was higher when office blood pressure were used(81.8% after 100 mg losartan treatment vs 75% after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment).

When normalized rate are considered, it was found that the percentage of normalized patients after 50 mg losartan treatment was higher than after 12.5 mg hydrochlorothiazide treatment either based on office blood pressure(28.1% after 50 mg losartan treatment vs 25% after 12.5 mg hydrochlorothiazide treatment) or 24-hour ambulatory blood pressure(25% after 50 mg losartan treatment vs 15.6% after 12.5 mg hydrochlorothiazide treatment).

In 50 mg losartan normalized group, the percentage of normalized patients was higher after 25 mg losartan treatment as compared to those after the combination of 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment either based on office blood pressure(75% after 25 mg losartan treatment vs 40% after 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment) or 24-hour ambulatory blood pressure(75% after 25 mg losartan treatment vs 20% after 25 mg losartan plus 6.25 mg hydrochlorothiazide treatment).

In 50 mg non-normalized patients, the percentage of normalized patients after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment was higher than those obtained from 100 mg losartan treatment whether the data were based on office blood pressure(33.3% after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment vs 27.3% after 100 mg losartan treatment), or 24-hour blood pressure(41.7% after 50 mg losartan plus 12.5 mg hydrochlorothiazide treatment vs 18.2% after 100 mg losartan treatment).

8. The values of T:P ratio derived from the average trough and peak antihypertensive effects were ranged from 44 to 50% in SBP and 39-47% in DBP after losartan treatment. With losartan 50 mg plus hydrochlorothiazide 12.5 mg, T:P ratio of SBP/DBP were 52/47%. These findings offer support for the notion that losartan and losartan plus hydrochlorothiazide had sustained antihypertensive effect covered all 24-hours, consequently, once

daily dosing is appropriate. With hydrochlorothiazide 12.5 mg treatment, there were wide ranges of individual T:P ratio of SBP(3-83%) and DBP (6-64%), which probably due in part to the pharmacokinetic properties of the drugs itself. It had been suggested that in patients who had low T:P ratio, once daily treatment was not suitable for and these patients should be better treated with twice or even thrice daily regimens.

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APPENDICES

Appendix A : Demographic data of the individual subjects

Subjects no.	Age (years)	Wt. (kg.)	Ht. (cm.)	BMI (kg/m2)	Smoking	Alcohol
1	43	60.0	155.0	25.0	_	_
2	68	66.5	156.0	27.3	_	_
3	66	66.8	162.0	25.4	_	_
4	53	45.0	149.0	20.3	_	_
5	30	49.5	152.0	21.4	_	_
6	48	74.0	172.0	25.0	_	/
7	54	55.0	152.0	23.8	_	_
8	45	82.0	154.0	34.5	_	_
9	56	83.6	150.0	37.2	_	_
10	56	59.8	150.0	26.6	_	_
11	56	55.0	150.0	24.4	_	_
12	41	59.3	153.5	25.2	_	_
13	52	55.3	156.0	22.7	_	_
14	45	68.0	166.0	24.7	_	/
15	69	45.2	152.0	19.6	_	_
16	60	64.0	164.5	23.6	_	_
17	61	82.5	172.0	27.9	_	_
18	43	59.0	154.0	24.9	_	_
19	50	76.0	170.0	26.3	_	_
20	46	65.0	152.0	28.1	_	_
21	43	59.7	150.0	26.5	_	_
22	54	59.0	151.0	25.9	_	_
23	53	45.0	148.0	20.5	_	_
24	65	65.0	156.0	26.7	_	_
25	57	57.0	145.0	27.1	_	_
26	46	73.0	171.0	22.5	/	/
27	53	49.3	153.0	21.1	_	_
28	32	75.4	169.0	26.4	_	_
29	56	60.0	170.0	20.8	_	_
30	69	67.0	155.0	27.9	_	_
31	52	80.0	167.0	28.7	_	/
32	48	63.0	158.0	25.2	_	/

Appendix B : Laboratory data of individual subjects

Subjects no.	FPG (70-110mg/dl)	Creatinine (70-110mg/dl)	Uric acid (2.0-7.0mg/dl)	Chol (150-240 mg/dl)	TG (40-155 mg/dl)	HDL (0-100mg/dl)	LDL (130-159mg/dl)	AST (0-38U/l)	ALT (0-38U/l)
1	85	1.0	5.2	260	262	–	–	21	24
2	85	0.9	7.0	217	108	56	139	14	12
3	79	1.5	8.7	198	114	32	143	25	42
4	79	0.7	5.1	213	132	74	113	18	11
5	85	0.5	4.6	198	54	65	122	15	13
6	112	1.1	6.2	242	69	45	183	13	11
7	84	0.8	3.5	194	105	–	–	14	7
8	74	0.8	4.2	153	77	–	–	18	21
9	83	0.7	4.9	229	138	61	141	16	26
10	92	0.8	5.9	231	107	49	160	20	21
11	98	1.0	5.5	192	56	67	114	22	25
12	89	0.6	4.1	175	126	44	106	21	19
13	90	0.7	4.6	250	54	–	–	24	10
14	82	1.0	6.9	183	94	57	107	26	24
15	81	1.3	6.8	291	111	67	202	29	17
16	99	1.3	9.1	256	321	–	–	33	39
17	97	1.5	6.2	192	69	43	135	21	18
18	84	0.8	5.0	216	94	–	–	24	34
19	95	0.9	5.1	214	147	42	143	34	67
20	104	0.9	6.0	224	110	–	–	20	17
21	100	0.7	4.0	220	113	66	134	20	21
22	115	0.7	6.2	220	75	64	140	27	47
23	92	0.8	5.4	236	102	–	–	20	15
24	114	1.1	7.3	285	125	48	212	25	26
25	109	1.0	5.9	335	178	–	–	20	26
26	99	0.9	7.3	263	142	–	–	16	25
27	93	0.7	4.1	221	58	69	121	32	25
28	121	1.2	9.0	254	215	38	173	44	55
29	98	1.1	7.3	328	258	55	221	24	17
30	99	0.9	5.9	215	187	41	137	40	40
31	102	1.1	8.8	176	193	41	96	70	71
32	115	0.6	5.1	258	162	63	162	13	8

Appendix C : Office and 24-hour ABP measurements at baseline

Subjects no.	BP measurements at baseline(mmHg)							
	Office BP		Average 24-hour ABP					
			24-hour		daytime		nighttime	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
1	134	97	143	90	148	96	132	79
2	142	87	136	70	139	72	130	66
3	151	99	137	93	138	94	136	90
4	151	95	158	100	170	109	133	82
5	141	88	129	78	135	82	115	68
6	144	90	140	84	147	88	127	76
7	148	97	140	80	148	82	124	76
8	131	91	138	81	145	86	124	71
9	154	90	146	87	148	89	142	84
10	151	89	147	80	148	81	146	76
11	141	89	141	78	148	84	125	66
12	151	99	125	84	131	88	114	76
13	155	97	133	89	139	92	120	83
14	148	99	149	92	155	95	136	88
15	159	83	138	72	138	73	138	69
16	149	101	127	81	130	84	120	74
17	150	101	135	79	140	80	124	77
18	180	105	152	95	159	101	136	83
19	155	106	145	98	151	102	129	88
20	159	107	155	88	162	94	139	78
21	146	102	155	90	162	93	139	85
22	175	95	156	93	156	97	155	82
23	175	99	143	92	149	94	130	89
24	163	91	141	86	153	88	137	81
25	175	89	144	80	142	90	149	82
26	170	105	153	97	162	104	135	80
27	164	91	144	76	151	80	130	67
28	143	108	139	91	143	96	132	81
29	162	105	150	97	156	98	138	95
30	167	99	138	84	140	84	135	84
31	150	107	162	108	166	108	153	108
32	175	111	142	86	146	87	135	83

Appendix D : Office BP at baseline and after hydrochlorothiazide 12.5 mg and losartan 50 mg administration

Subjects no.	Office BP											
	baseline				hydrochlorothiazide12.5 mg				losartan 50 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	134	97	109	64	122	84	97	68	107	68	81	64
2	142	87	105	72	133	83	100	64	139	84	102	72
3	151	99	116	70	135	87	103	68	139	80	100	70
4	151	95	114	72	150	99	116	68	123	73	90	72
5	141	88	106	72	136	77	97	108	137	80	99	88
6	144	90	108	64	133	91	85	60	135	80	98	60
7	148	97	114	96	136	93	107	84	112	74	87	80
8	131	91	104	72	137	89	105	72	131	94	106	76
9	154	90	111	90	141	88	106	89	141	85	104	76
10	151	89	110	72	143	91	108	72	145	93	110	78
11	141	89	106	80	128	79	95	88	143	80	101	90
12	151	99	116	72	132	87	102	72	141	90	107	72
13	155	97	116	84	141	91	108	84	145	91	109	70
14	148	99	115	72	140	93	109	60	140	97	111	72
15	159	83	108	80	160	80	107	72	143	73	96	72
16	149	101	117	76	156	102	120	88	123	85	98	72
17	150	101	117	70	158	100	119	72	136	82	100	68
18	180	105	130	76	151	91	111	78	148	89	109	76
19	155	106	122	76	139	97	111	76	148	104	119	76
20	159	107	124	82	156	102	120	80	147	101	116	72
21	146	102	117	80	131	103	112	88	149	101	117	92
22	175	95	122	92	137	97	110	80	155	101	119	72
23	175	99	124	72	154	91	112	80	147	83	104	72
24	163	91	115	62	140	89	106	72	170	96	121	60
25	175	89	118	62	184	100	128	68	161	84	110	66
26	170	105	127	80	152	96	115	90	163	104	124	78
27	164	91	115	68	150	90	110	64	156	91	113	70
28	143	108	120	78	136	103	114	84	144	90	108	80
29	162	105	124	72	160	107	125	80	147	101	116	64
30	167	99	122	80	161	101	121	80	163	95	118	84
31	150	107	121	88	153	112	126	88	120	99	112	92
32	175	111	132	84	123	88	100	80	140	98	112	76

Appendix E: Average ABP at baseline and after hydrochlorothiazide 12.5 mg and losartan 50 mg administration

Subjects no.	Average 24-hour ABP											
	baseline				hydrochlorothiazide12.5 mg				losartan 50 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	143	90	108	75	144	87	106	75	130	82	98	73
2	136	70	92	72	133	79	97	81	145	72	97	81
3	137	93	108	93	135	80	98	70	136	88	104	76
4	158	100	120	71	143	89	107	63	145	83	104	83
5	129	78	95	85	133	83	100	85	117	74	89	82
6	140	84	103	60	136	78	97	67	131	83	99	59
7	140	80	100	74	134	84	101	85	109	63	74	63
8	138	81	101	68	130	72	92	72	117	74	89	70
9	146	87	107	88	142	85	104	92	141	88	106	84
10	147	80	102	68	151	84	106	75	132	81	98	76
11	141	78	99	81	134	77	96	86	141	77	98	84
12	125	84	98	80	119	73	88	83	121	80	94	78
13	133	89	104	69	130	78	95	71	147	90	109	93
14	149	92	111	77	137	82	100	73	137	90	106	68
15	138	72	94	72	141	70	94	75	131	68	89	73
16	127	81	97	81	143	94	112	88	120	80	93	95
17	135	79	98	66	147	82	103	70	130	74	93	59
18	152	95	114	81	142	95	111	79	118	77	91	77
19	145	98	114	72	143	98	115	77	142	91	109	74
20	155	88	110	92	129	80	97	87	138	72	110	87
21	155	90	112	83	147	96	113	77	139	88	105	79
22	156	93	114	87	142	87	106	83	156	96	116	80
23	143	92	109	82	128	87	101	77	140	83	102	81
24	141	86	107	60	142	87	105	65	146	87	107	63
25	144	80	102	67	151	86	108	68	150	80	103	65
26	153	97	115	77	156	104	121	79	157	101	119	81
27	144	76	99	66	140	79	99	67	139	78	98	68
28	139	91	107	72	143	95	111	73	135	89	104	83
29	150	97	115	71	160	98	118	72	162	101	121	70
30	138	84	102	83	144	90	108	88	141	82	102	80
31	162	108	126	90	158	93	115	92	141	86	104	89
32	142	86	105	89	129	70	90	85	129	79	96	69

Subjects no.	Average daytime ABP											
	baseline				hydrochlorothiazide12.5 mg				losartan 50 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	148	96	113	78	151	89	110	79	133	84	100	80
2	139	72	94	72	136	81	99	84	152	76	102	83
3	138	94	109	94	135	80	98	80	141	91	108	91
4	170	109	99	77	139	80	110	57	153	88	109	88
5	135	82	100	87	138	87	104	85	122	76	91	84
6	147	88	108	62	142	81	101	71	137	88	105	65
7	148	82	104	76	138	89	106	89	112	63	74	80
8	145	86	106	71	136	78	97	78	121	76	91	75
9	148	89	109	92	150	89	109	97	149	93	112	86
10	148	81	103	74	152	85	108	80	133	82	99	83
11	148	84	105	85	138	77	98	92	146	79	101	88
12	131	88	102	85	122	77	92	89	127	84	98	84
13	139	92	107	76	134	79	97	75	155	97	116	96
14	155	95	115	84	144	85	105	82	144	95	111	74
15	138	73	95	78	144	71	95	78	132	70	90	78
16	130	84	99	74	152	99	117	99	124	82	96	101
17	140	80	100	70	151	82	105	73	134	77	96	62
18	159	101	120	87	149	100	116	86	125	83	97	88
19	151	102	118	83	150	103	119	89	146	92	110	82
20	162	94	116	96	140	86	104	86	144	77	116	90
21	162	93	116	90	150	97	115	82	143	92	109	83
22	156	97	117	91	147	87	107	90	164	101	122	101
23	149	94	112	88	131	89	103	82	145	86	105	88
24	153	88	110	63	146	88	107	87	150	91	111	66
25	142	90	101	80	153	87	109	87	151	82	105	71
26	162	104	123	82	167	110	129	87	164	105	125	90
27	151	80	104	69	143	80	101	70	146	80	102	70
28	143	96	111	78	150	95	114	80	143	96	111	89
29	156	98	117	77	163	97	119	78	167	105	126	73
30	140	84	103	84	143	90	108	93	141	80	100	82
31	166	108	127	94	160	95	116	99	147	92	110	90
32	146	87	107	95	134	75	95	91	133	80	97	74

Subjects no.	Average nighttime ABP											
	baseline				hydrochlorothiazide12.5 mg				losartan 50 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	132	79	97	67	130	83	99	65	124	79	94	57
2	130	66	87	66	129	76	93	75	129	64	86	78
3	136	90	105	90	135	79	98	72	122	79	94	79
4	133	82	99	82	139	80	100	57	128	74	92	74
5	115	68	83	81	122	75	91	85	107	71	83	80
6	127	76	93	55	124	72	89	58	118	72	87	46
7	124	76	92	69	124	75	91	75	103	61	75	61
8	124	71	89	62	117	62	80	59	110	70	83	59
9	142	84	103	80	122	76	91	79	123	79	91	81
10	146	76	94	55	150	80	103	64	130	78	96	63
11	125	66	86	72	125	76	92	72	130	72	91	73
12	114	76	89	70	113	64	80	70	108	72	84	72
13	120	83	96	55	125	75	92	60	127	75	93	88
14	136	88	104	61	120	76	91	54	121	80	94	54
15	138	69	92	69	135	71	92	68	129	64	85	63
16	120	74	89	74	126	84	99	84	110	76	86	80
17	124	77	93	57	138	80	99	62	121	67	84	52
18	136	83	100	70	127	83	98	63	102	66	78	68
19	129	88	102	46	128	88	105	51	132	88	105	55
20	139	78	98	83	105	67	80	67	126	62	98	82
21	139	85	103	68	140	92	108	64	131	78	96	70
22	155	82	106	81	132	88	103	67	138	86	103	86
23	130	89	104	68	122	82	95	67	130	78	95	67
24	137	81	99	53	134	85	101	85	137	78	98	56
25	149	82	104	61	146	82	103	82	148	74	99	53
26	135	80	99	64	133	92	105	64	140	91	107	62
27	130	67	88	60	133	75	94	60	125	72	89	64
28	132	81	98	59	127	95	106	56	120	73	89	69
29	138	95	110	59	153	94	117	61	150	91	109	64
30	135	84	101	83	144	90	107	77	141	86	104	75
31	153	108	123	81	156	91	113	78	126	73	91	87
32	135	83	100	74	116	56	76	71	122	79	93	60

Appendix F : Average BP loads at baseline and after hydrochlorothiazide 12.5 mg and losartan 50 mg treatment

Subject no.	Average 24-hour BP loads											
	baseline				hydrochlorothiazide 12.5 mg				losartan 50mg			
	SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	78.8	14.3	60.6	13.1	60.6	19.5	39.4	8.2	33.3	12.2	21.2	4.7
2	36.4	15.8	6.1	3.0	42.4	11.0	21.2	8.7	78.8	17.2	12.1	6.5
3	57.6	11.8	66.7	9.5	48.5	14.5	30.3	7.5	48.5	11.3	48.5	8.2
4	87.9	28.4	84.8	20.8	66.7	12.2	51.5	10.5	72.7	18.0	39.4	12.8
5	24.2	13.5	21.2	4.4	45.5	9.9	33.3	7.2	6.1	11.5	6.1	0.0
6	69.7	12.5	39.4	7.3	45.5	14.6	15.2	6.3	30.3	14.4	36.4	9.1
7	36.4	9.9	15.2	2.0	39.4	14.9	42.4	9.5	0.0	0.0	0.0	0.0
8	81.8	10.3	27.3	3.5	27.3	11.8	3.0	9.0	3.0	5.0	12.1	8.0
9	75.8	15.4	36.4	9.7	69.7	15.4	63.6	6.7	63.6	14.3	45.5	12.3
10	78.8	16.3	21.2	3.0	84.8	19.3	30.3	8.0	27.3	10.7	21.2	4.2
11	66.7	15.6	27.3	7.6	36.4	13.4	6.1	3.5	60.6	12.9	3.0	1.0
12	18.2	6.6	45.5	6.7	6.1	3.0	6.1	10.0	24.2	5.9	30.3	4.4
13	51.5	9.8	60.6	7.5	33.3	9.1	12.1	4.0	69.7	19.4	57.6	12.7
14	78.8	21.4	72.7	10.8	42.4	15.8	42.4	7.3	63.6	11.2	42.4	7.9
15	57.6	10.4	0.0	0.0	54.5	19.6	3.0	7.0	45.5	8.3	6.1	0.0
16	33.3	6.8	33.3	5.3	69.7	15.7	69.7	12.0	6.1	1.7	12.1	4.0
17	60.6	9.7	12.1	3.0	78.8	18.0	36.4	4.2	45.5	6.8	0.0	2.0
18	93.9	21.6	87.9	12.7	72.7	14.9	81.8	11.7	6.1	9.0	30.3	7.0
19	81.8	15.0	81.8	14.9	84.8	14.6	81.8	16.1	63.6	15.9	69.7	8.9
20	78.8	24.1	21.2	11.3	30.3	15.4	36.4	6.3	51.5	14.3	6.1	1.0
21	81.8	22.2	57.6	10.9	63.6	17.7	66.7	11.8	57.6	14.3	54.5	10.4
22	93.9	21.6	75.8	10.4	63.6	14.0	54.5	10.3	81.8	24.8	78.8	14.0
23	72.7	17.9	69.7	9.0	24.2	9.0	51.5	6.0	51.5	15.1	36.4	4.7
24	87.9	17.1	42.4	7.7	72.7	11.5	42.4	7.4	78.8	15.8	57.6	7.5
25	78.8	14.1	24.2	5.2	75.8	19.0	30.3	6.9	81.8	19.2	27.3	7.2
26	90.9	21.5	87.9	13.8	97.0	25.1	100.0	18.9	97.0	23.5	93.9	14.8
27	69.7	15.6	18.2	3.0	60.6	9.9	15.2	2.2	51.5	20.7	42.4	4.0
28	57.6	13.9	75.8	10.1	78.8	14.5	69.7	13.4	60.6	12.4	63.6	11.4
29	90.9	19.4	90.9	11.6	78.8	25.8	63.6	15.1	93.9	30.4	87.9	16.6
30	60.6	13.4	39.4	7.0	51.5	25.5	48.5	9.6	45.5	20.2	33.3	7.0
31	93.9	26.7	93.9	20.9	78.8	24.6	57.6	12.8	57.6	24.3	60.6	9.6
32	78.8	11.8	36.4	9.0	30.3	7.3	9.1	1.3	30.3	15.2	21.2	5.0

Subject no.	Average daytime BP loads											
	baseline				hydrochlorothiazide 12.5 mg				losartan 50mg			
	SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	74.1	15.1	63.0	14.1	51.9	24.0	29.6	10.7	25.9	13.6	14.8	4.7
2	29.6	15.4	7.4	3.0	33.3	9.3	18.5	10.0	77.8	18.7	11.1	6.5
3	48.1	9.8	59.3	9.3	40.7	13.0	25.9	6.7	48.1	9.6	48.1	7.6
4	88.9	31.0	85.2	22.6	59.3	9.4	51.9	10.8	74.1	18.4	40.7	13.7
5	25.9	13.6	22.2	4.8	44.4	9.6	37.0	6.7	7.4	11.5	3.7	0.0
6	70.4	11.9	44.4	8.0	40.7	16.3	14.8	5.5	33.3	15.2	40.7	9.6
7	33.3	10.0	11.1	2.3	37.0	14.8	44.4	10.8	0.0	0.0	0.0	0.0
8	81.5	11.1	33.3	3.5	25.9	13.7	3.7	9.0	0.0	1.0	7.4	6.0
9	74.1	11.8	29.6	9.6	74.1	15.9	59.3	6.9	63.0	15.5	44.4	12.7
10	74.1	13.2	18.5	3.8	81.5	16.4	29.6	6.7	11.1	11.7	14.8	4.7
11	70.4	16.2	29.6	8.4	29.6	14.5	3.7	5.0	59.3	12.1	0.0	1.0
12	14.8	6.5	48.1	7.0	3.7	1.0	7.4	10.0	25.9	6.6	29.6	5.3
13	51.9	10.4	59.3	6.8	22.2	11.0	7.4	4.0	74.1	20.5	63.0	13.8
14	74.1	23.2	70.4	10.7	40.7	17.3	44.4	6.8	66.7	11.4	44.4	7.7
15	48.1	6.2	0.0	0.0	48.1	20.0	0.0	0.0	33.3	7.8	7.4	0.0
16	22.2	3.3	33.3	6.5	70.4	16.8	66.7	13.8	3.7	2.0	7.4	4.5
17	55.6	9.8	11.1	2.0	77.8	16.8	29.6	5.0	40.7	8.1	0.0	2.0
18	96.3	22.0	92.6	12.9	66.7	17.8	77.8	13.5	7.4	9.0	33.3	7.0
19	85.2	15.6	85.2	15.4	88.9	13.9	85.2	16.3	59.3	16.3	66.7	7.1
20	92.6	24.4	22.2	11.5	37.0	15.4	40.7	6.5	51.9	14.3	7.4	1.0
21	77.8	23.0	48.1	12.3	59.3	16.9	63.0	11.8	55.6	10.1	59.3	10.0
22	92.6	18.5	77.8	10.3	59.3	13.4	44.4	9.5	77.8	26.7	77.8	15.2
23	70.4	19.4	66.7	8.2	18.5	7.3	44.4	6.6	44.4	16.3	37.0	5.2
24	85.2	17.1	40.7	7.5	66.7	10.7	29.6	8.9	74.1	15.4	63.0	7.5
25	74.1	9.1	14.8	4.3	74.1	17.3	25.9	7.2	77.8	16.5	25.9	8.8
26	92.6	21.8	96.3	14.4	100.0	26.6	100.0	19.9	96.3	24.3	92.6	15.3
27	70.4	15.3	18.5	3.0	55.6	7.6	11.1	3.0	44.4	25.4	48.1	5.0
28	51.9	13.7	81.5	10.2	81.5	15.2	63.0	11.7	66.7	11.3	74.1	11.6
29	88.9	19.8	88.9	10.6	74.1	23.6	59.3	14.3	92.6	30.4	88.9	17.2
30	51.9	12.5	33.3	7.3	40.7	26.3	40.7	8.8	33.3	19.8	22.2	6.0
31	92.6	25.2	92.6	19.0	74.1	21.2	55.6	11.0	51.9	27.2	63.0	10.6
32	74.1	10.9	25.9	9.1	29.6	4.0	11.1	1.3	33.3	13.3	18.5	6.3

Subject no.	Average nighttime BP loads											
	baseline				hydrochlorothiazide 12.5 mg				losartan 50mg			
	SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	100.0	11.8	50.0	5.5	100.0	9.8	83.3	4.8	66.7	9.8	50.0	4.7
2	66.7	16.8	0.0	0.0	83.3	14.3	33.3	5.5	83.3	11.4	16.7	0.0
3	100.0	15.7	100.0	10.0	83.3	17.8	50.0	9.0	50.0	17.7	50.0	10.0
4	83.3	15.8	83.3	7.3	100.0	19.3	50.0	9.0	66.7	15.7	33.3	8.0
5	16.7	13.0	16.7	3.0	50.0	10.7	16.7	12.0	0.0	0.0	16.7	0.0
6	66.7	14.8	16.7	2.0	66.7	10.0	16.7	8.0	16.7	7.0	16.7	3.0
7	50.0	9.5	33.3	1.5	50.0	15.0	33.3	2.5	0.0	0.0	0.0	0.0
8	83.3	6.8	0.0	0.0	33.3	5.0	0.0	0.0	16.7	9.0	33.3	10.0
9	83.3	29.0	66.7	10.0	50.0	12.3	83.3	5.5	66.7	8.7	50.0	10.0
10	100.0	26.0	33.3	1.5	100.0	29.7	33.3	16.0	100.0	10.2	50.0	3.5
11	50.0	12.0	16.7	1.0	66.7	11.8	16.7	2.0	66.7	16.0	16.7	0.0
12	33.3	7.0	33.3	5.0	16.7	5.0	0.0	0.0	16.7	1.0	33.3	1.0
13	50.0	7.0	66.7	11.0	83.3	6.8	33.3	4.0	50.0	8.0	33.3	4.0
14	100.0	15.8	83.3	11.0	50.0	9.7	33.3	9.5	50.0	9.5	33.3	9.5
15	100.0	18.0	0.0	0.0	83.3	18.8	16.7	7.0	100.0	8.7	0.0	0.0
16	83.3	10.3	33.3	1.5	66.7	10.8	83.3	6.0	16.7	1.0	33.3	3.0
17	83.3	9.6	16.7	6.0	83.3	22.8	66.7	3.0	66.7	4.3	0.0	0.0
18	83.3	19.6	66.7	11.5	100.0	6.5	100.0	4.6	0.0	0.0	16.7	0.0
19	66.7	12.0	66.7	11.8	66.7	18.5	66.7	15.0	83.3	14.6	83.3	12.7
20	16.7	22.7	16.7	8.0	0.0	0.0	16.7	4.0	50.0	14.0	0.0	0.0
21	100.0	19.3	100.0	6.8	83.3	20.4	83.3	12.0	66.7	18.0	33.3	11.0
22	100.0	34.5	66.7	10.8	83.3	15.8	100.0	12.0	100.0	18.3	83.3	9.6
23	83.3	13.0	83.3	11.8	50.0	11.3	83.3	4.5	83.3	12.6	33.3	2.5
24	100.0	17.2	50.0	8.3	100.0	14.0	100.0	5.4	100.0	17.2	33.3	7.5
25	100.0	29.0	66.7	6.0	83.3	25.8	50.0	6.3	100.0	28.0	33.3	2.5
26	83.3	20.0	50.0	8.3	83.3	17.2	100.0	13.8	100.0	19.8	100.0	11.0
27	66.7	17.3	16.7	3.0	83.3	16.2	33.3	1.0	83.3	7.8	16.7	2.0
28	83.3	14.6	50.0	9.7	66.7	11.0	100.0	19.0	33.3	22.0	16.7	7.0
29	100.0	17.8	100.0	15.3	100.0	32.8	83.3	17.3	100.0	30.3	83.3	13.8
30	100.0	15.3	66.7	6.5	100.0	24.2	83.3	11.2	100.0	20.8	83.3	7.8
31	100.0	32.8	100.0	28.3	100.0	35.8	66.7	18.8	83.3	13.3	50.0	4.0
32	100.0	14.5	83.3	8.8	33.3	19.0	0.0	0.0	16.7	32.0	33.3	1.0

Appendix G: Area above the normal blood pressure versus time curve at baseline and after hydrochlorothiazide 12.5 mg and losartan 50 mg administration

Subject no.	Area above normal blood pressure versus time curve(24- hour)					
	baseline		hydrochlorothiazide12.5 mg		losartan 50 mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{SBP}
1	197.0	111.5	178.3	47.3	42.3	5.5
2	162.3	1.5	72.5	19.0	194.0	1.0
3	142.0	125.0	164.0	35.5	30.3	23.0
4	432.3	250.3	164.3	68.8	188.3	52.3
5	30.0	0.0	50.8	25.0	5.8	0.0
6	126.8	30.3	76.0	0.0	59.3	46.5
7	79.8	2.0	55.8	53.0	0.0	0.0
8	124.0	7.3	42.0	1.5	0.0	0.5
9	219.0	54.3	158.3	36.8	143.5	63.8
10	246.0	3.8	328.0	11.8	66.5	3.8
11	163.3	18.0	68.0	0.8	141.8	0.0
12	3.3	34.3	0.0	0.0	7.0	5.5
13	71.3	61.8	47.5	0.0	215.0	95.0
14	312.8	127.8	83.0	31.0	100.8	91.3
15	137.5	0.0	171.8	0.0	70.3	0.0
16	3.3	17.8	133.0	128.8	0.5	2.8
17	63.0	3.8	243.0	15.0	34.5	0.5
18	343.0	176.5	174.0	150.0	2.0	19.3
19	184.0	193.2	194.0	209.0	170.5	82.0
20	355.3	65.8	66.5	21.3	105.0	0.0
21	298.8	83.8	156.8	107.5	117.8	66.0
22	375.8	119.8	123.8	80.0	252.0	118.5
23	197.8	121.8	23.0	31.5	110.3	17.5
24	255.3	41.3	143.8	36.5	208.8	43.0
25	231.0	101.5	234.0	17.0	290.8	21.5
26	348.0	182.0	414.3	320.8	385.8	236.8
27	166.8	0.0	108.8	2.3	120.0	0.0
28	140.8	109.8	162.5	166.8	107.5	92.0
29	291.0	196.0	329.8	204.5	523.3	311.5
30	147.3	35.8	164.8	59.3	171.3	41.5
31	447.5	339.0	366.5	119.5	166.8	78.8
32	179.8	69.0	37.0	0.0	84.5	5.8

Subject no.	Area above normal blood pressure versus time curve (daytime)					
	baseline		hydrochlorothiazide12.5 mg		losartan 50 mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{SBP}
1	137.3	104.3	127.3	29.8	11.8	0.5
2	102.8	1.5	28.0	15.5	147.0	1.0
3	51.0	68.5	74.5	21.5	29.8	23.0
4	359.3	228.3	51.8	52.8	151.3	46.3
5	30.0	0.0	34.8	23.5	5.8	0.0
6	76.8	30.3	46.0	0.0	57.8	46.5
7	47.8	0.0	28.3	53.0	0.0	0.0
8	99.0	7.3	37.0	1.5	0.0	0.0
9	95.0	24.8	145.3	34.3	111.0	48.3
10	99.0	1.8	164.5	1.3	7.5	1.8
11	137.8	18.0	38.5	0.8	90.3	0.0
12	3.3	29.3	0.0	0.0	7.0	5.0
13	54.8	36.8	28.0	0.0	169.5	94.0
14	224.8	82.3	64.0	17.0	83.8	74.3
15	31.5	0.0	97.8	0.0	19.3	0.0
16	3.3	17.3	104.5	103.3	0.5	1.3
17	42.5	1.3	160.5	8.5	25.0	0.5
18	247.0	145.5	138.0	127.0	2.0	19.3
19	155.5	160.7	142.5	164.0	97.5	34.0
20	251.3	60.3	66.5	21.3	68.0	0.0
21	189.3	56.8	86.3	67.5	60.8	55.0
22	201.8	87.3	66.3	27.0	144.5	72.0
23	137.8	64.3	0.5	19.0	49.8	13.5
24	161.8	29.8	71.8	10.0	114.3	33.5
25	65.5	5.0	132.8	3.5	139.3	21.5
26	257.5	170.0	339.8	255.8	284.8	171.3
27	106.3	0.0	36.3	0.8	90.0	0.0
28	75.3	94.3	128.5	84.8	75.0	89.5
29	194.5	108.5	143.3	93.0	350.8	252.0
30	67.3	11.8	28.8	11.8	57.3	6.5
31	267.3	185.0	169.0	51.5	122.8	67.3
32	93.3	32.0	5.5	0.0	54.5	5.3

Subject no.	Area above normal blood pressure versus time curve (nighttime)					
	baseline		hydrochlorothiazide12.5 mg		losartan 50 mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{SBP}
1	59.5	7.0	51.0	17.5	30.5	5.0
2	59.5	0.0	44.5	3.5	47.0	0.0
3	91.0	56.5	82.5	14.0	0.5	0.0
4	73.0	22.0	112.5	16.0	37.0	6.0
5	0.0	0.0	16.0	1.5	0.0	0.0
6	50.0	0.0	30.0	0.0	1.5	0.0
7	32.0	2.0	27.5	0.0	0.0	0.0
8	25.0	0.0	5.0	0.0	2.0	0.5
9	124.0	29.5	13.0	2.5	32.5	15.5
10	147.0	2.0	163.5	10.5	59.0	2.0
11	25.5	0.0	29.5	0.0	51.5	0.0
12	0.0	5.0	0.0	0.0	0.0	0.5
13	16.5	25.0	19.5	0.0	45.5	1.0
14	88.0	45.5	19.0	14.0	17.0	17.0
15	106.0	0.0	74.0	0.0	51.0	0.0
16	0.0	0.5	28.5	25.5	0.0	1.5
17	20.5	2.5	82.5	6.5	9.5	0.0
18	96.0	31.0	36.0	23.0	0.0	0.0
19	28.5	32.5	51.5	45.0	73.0	48.0
20	104.0	5.5	0.0	0.0	37.0	0.0
21	109.5	27.0	70.5	40.0	57.0	11.0
22	174.0	32.5	57.5	53.0	107.5	46.5
23	60.0	57.5	22.5	12.5	60.5	4.0
24	93.5	11.5	72.0	26.5	94.5	9.5
25	165.5	96.5	101.5	13.5	151.5	0.0
26	90.5	12.0	74.5	65.0	101.0	65.5
27	60.5	0.0	72.5	1.5	30.0	0.0
28	65.5	15.5	34.0	82.0	32.5	2.5
29	96.5	87.5	186.5	111.5	172.5	59.5
30	80.5	24.0	136.0	47.5	114.0	35.0
31	180.5	154.0	197.5	68.0	44.0	11.5
32	86.5	37.0	31.5	0.0	30.0	0.5

Appendix H : Office BP at baseline and after step2 treatment

Subjects no.	Office BP																			
	baseline				losartan 25 mg				losartan 25mg+HCTZ 6.25mg				losartan 100 mg				losartan50mg +HCTZ 12.5 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	134	97	109	64	111	70	84	72												
2	142	87	105	72	151	92	112	68												
3	151	99	116	70	116	73	87	80												
4	151	95	114	72					133	90	104	68								
5	141	88	106	72					129	83	98	90								
6	144	90	108	64					144	88	107	60								
7	148	97	114	96					117	78	91	84								
8	131	91	104	72									123	85	98	70				
9	154	90	111	90									131	80	97	82				
10	151	89	110	72									153	80	104	72				
11	141	89	106	80													139	78	98	84
12	151	99	116	72													127	89	102	72
13	155	97	116	84													115	84	94	60
14	148	99	115	72													143	97	112	72
15	159	83	108	80													140	70	93	70
16	149	101	117	76	125	84	98	84												
17	150	101	117	70					143	93	110	68								
18	180	105	130	76									133	86	102	70				
19	155	106	122	76									131	93	106	80				
20	159	107	124	82									147	97	114	80				
21	146	102	117	80									137	93	108	80				
22	175	95	122	92									144	95	111	80				
23	175	99	124	72									143	88	106	68				
24	163	91	115	62									144	87	106	70				
25	175	89	118	62									163	92	116	64				
26	170	105	127	80													149	97	114	80
27	164	91	115	68													152	85	107	64
28	143	108	120	78													119	93	102	76
29	162	105	124	72													141	99	113	80
30	167	99	122	80													159	93	115	74
31	150	107	121	88													163	103	123	88
32	175	111	132	84													131	82	98	80

Appendix I : Average ABP at baseline and after step2 treatment

Subjects no.	Average 24- hour ABP																			
	baseline				losartan 25 mg				losartan 25mg+HCTZ 6.25mg				losartan 100 mg				losartan50mg +HCTZ 12.5 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	143	90	108	75	124	80	95	76												
2	136	70	92	72	130	67	88	75												
3	137	93	108	93	139	83	102	73												
4	158	100	120	71					144	90	108	68								
5	129	78	95	85					122	70	87	86								
6	140	84	103	60					130	86	101	63								
7	140	80	100	74					137	67	90	78								
8	138	81	101	68									118	73	88	76				
9	146	87	107	88									143	86	105	88				
10	147	80	102	68									135	79	98	81				
11	141	78	99	81													128	70	89	70
12	125	84	98	80													110	68	82	68
13	133	89	104	69													111	64	80	71
14	149	92	111	77													141	91	107	91
15	138	72	94	72													127	62	84	71
16	127	81	97	81	130	80	98	93												
17	135	79	98	66					131	74	92	63								
18	152	95	114	81									114	68	84	75				
19	145	98	114	72									131	95	107	81				
20	155	88	110	92									138	89	105	80				
21	155	90	112	83									153	87	109	78				
22	156	93	114	87									157	96	116	81				
23	143	92	109	82									134	86	102	82				
24	141	86	107	60									142	88	106	67				
25	144	80	102	67									152	83	106	68				
26	153	97	115	77													144	90	108	76
27	144	76	99	66													142	73	96	68
28	139	91	107	72													141	94	109	84
29	150	97	115	71													131	82	99	78
30	138	84	102	83													144	89	107	79
31	162	108	126	90													169	109	129	95
32	142	86	105	89													120	76	91	86

Subjects no.	Average daytime ABP																			
	baseline				losartan 25 mg				losartan 25mg+HCTZ 6.25mg				losartan 100 mg				losartan50mg +HCTZ 12.5 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	148	96	113	78	128	83	98	83												
2	139	72	94	72	131	65	87	65												
3	138	94	109	94	138	84	102	84												
4	170	109	99	77					155	97	116	97								
5	135	82	100	87					120	70	87	87								
6	147	88	108	62					140	91	107	68								
7	148	82	104	76					149	68	95	68								
8	145	86	106	71									120	74	89	77				
9	148	89	109	92									149	90	110	90				
10	148	81	103	74									138	80	99	80				
11	148	84	105	85													133	72	92	72
12	131	88	102	85													115	70	85	81
13	139	92	107	76													115	68	83	76
14	155	95	115	84													145	91	109	91
15	138	73	95	78													129	61	84	61
16	130	84	99	74	138	85	102	98												
17	140	80	100	70					132	74	93	74								
18	159	101	120	87									120	71	87	71				
19	151	102	118	83									135	99	111	99				
20	162	94	116	96									149	98	115	86				
21	162	93	116	90									163	92	116	92				
22	156	97	117	91									167	103	125	86				
23	149	94	112	88									138	86	103	86				
24	153	88	110	63									143	89	107	69				
25	142	90	101	80									152	85	108	85				
26	162	104	123	82													148	91	110	91
27	151	80	104	69													153	75	101	75
28	143	96	111	78													139	97	111	97
29	156	98	117	77													133	83	100	83
30	140	84	103	84													144	89	107	82
31	166	108	127	94													173	110	131	110
32	146	87	107	95													128	81	96	81

Subjects no.	Average nighttime ABP																			
	baseline				losartan 25 mg				losartan 25mg+HCTZ 6.25mg				losartan 100 mg				losartan50mg +HCTZ 12.5 mg			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
1	132	79	97	67	114	75	88	75												
2	130	66	87	66	128	71	90	70												
3	136	90	105	90	141	81	101	81												
4	133	82	99	82					120	74	89	74								
5	115	68	83	81					126	70	87	85								
6	127	76	93	55					108	76	87	52								
7	124	76	92	69					113	63	80	63								
8	124	71	89	62									114	72	86	72				
9	142	84	103	80									125	70	88	70				
10	146	76	94	55									130	76	94	76				
11	125	66	86	72													116	67	83	67
12	114	76	89	70													98	62	74	62
13	120	83	96	55													103	57	72	59
14	136	88	104	61													132	90	104	90
15	138	69	92	69													124	63	83	63
16	120	74	89	74	110	69	84	78												
17	124	77	93	57					128	72	91	72								
18	136	83	100	70									102	62	75	62				
19	129	88	102	46									118	87	95	87				
20	139	78	98	83									113	71	84	67				
21	139	85	103	68									132	78	96	78				
22	155	82	106	81									135	82	99	70				
23	130	89	104	68									127	85	99	85				
24	137	81	99	53									138	87	104	64				
25	149	82	104	61									149	77	101	77				
26	135	80	99	64													135	89	104	89
27	130	67	88	60													120	68	85	61
28	132	81	98	59													145	86	106	86
29	138	95	110	59													130	81	97	81
30	135	84	101	83													143	90	108	74
31	153	108	123	81													160	107	125	107
32	135	83	100	74													104	66	79	66

Appendix J: Average BP loads at baseline and after step2 treatment

subject no.	Average 24-hour BP loads																			
	baseline				losartan25 mg				losartan25mg+HCTZ6.25mg				losartan 100 mg				losartan50mg+HCTZ12.5mg			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	78.8	14.3	60.6	13.1	18.2	48.5	5.3	15.2												
2	36.4	15.8	6.1	3.0	39.4	0.0	9.6	0.0												
3	57.6	11.8	66.7	9.5	45.5	33.3	22.0	9.9												
4	87.9	28.4	84.8	20.8					54.5	54.5	24.0	13.6								
5	24.2	13.5	21.2	4.4					12.1	6.1	19.3	4.0								
6	69.7	12.5	39.4	7.3					42.4	48.5	12.9	9.6								
7	36.4	9.9	15.2	2.0					39.4	3.0	26.4	3.0								
8	81.8	10.3	27.3	3.5									6.1	9.1	3.0	2.0				
9	75.8	15.4	36.4	9.7									57.6	33.3	14.5	10.5				
10	78.8	16.3	21.2	3.0									48.5	18.2	8.3	3.9				
11	66.7	15.6	27.3	7.6													21.2	0.0	4.3	0.0
12	18.2	6.6	45.5	6.7													30.3	0.0	11.0	0.0
13	51.5	9.8	60.6	7.5													3.0	0.0	3.0	0.0
14	78.8	21.4	72.7	10.8													75.8	63.6	10.5	8.7
15	57.6	10.4	0.0	0.0													24.2	3.0	9.1	1.0
16	33.3	6.8	33.3	5.3	33.3	30.3	11.6	5.0												
17	60.6	9.7	12.1	3.0					33.3	6.1	8.9	7.5								
18	93.9	21.6	87.9	12.7									15.2	0.0	10.2	0.0				
19	81.8	15.0	81.8	14.9									39.4	75.8	7.3	11.0				
20	78.8	24.1	21.2	11.3									57.6	51.5	13.4	11.3				
21	81.8	22.2	57.6	10.9									72.7	48.5	25.7	8.8				
22	93.9	21.6	75.8	10.4									84.8	66.7	27.6	16.7				
23	72.7	17.9	69.7	9.0									45.5	42.4	9.3	4.3				
24	87.9	17.1	42.4	7.7									57.6	48.5	12.9	8.1				
25	78.8	14.1	24.2	5.2									72.7	18.2	17.8	7.8				
26	90.9	21.5	87.9	13.8													63.6	60.6	17.6	10.2
27	69.7	15.6	18.2	3.0													60.6	12.1	16.0	3.3
28	57.6	13.9	75.8	10.1													45.5	75.8	15.7	9.6
29	90.9	19.4	90.9	11.6													36.4	24.2	12.8	7.6
30	60.6	13.4	39.4	7.0													66.7	48.5	14.8	8.3
31	93.9	26.7	93.9	20.9													97.0	90.9	33.7	23.2
32	78.8	11.8	36.4	9.0													15.2	15.2	9.2	5.4

subject no.	Average daytime BP loads																			
	baseline				losartan25 mg				losartan25mg+HCTZ6.25mg				losartan 100 mg				losartan50mg+HCTZ12.5mg			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	74.1	15.1	63.0	14.1	18.5	6.0	37.0	3.7												
2	29.6	15.4	7.4	3.0	33.3	10.5	0.0	0.0												
3	48.1	9.8	59.3	9.3	40.7	16.8	29.6	11.1												
4	88.9	31.0	85.2	22.6					59.3	24.4	59.3	13.7								
5	25.9	13.6	22.2	4.8					7.4	15.0	0.0	0.0								
6	70.4	11.9	44.4	8.0					44.4	13.6	51.9	9.4								
7	33.3	10.0	11.1	2.3					44.4	27.9	3.7	3.0								
8	81.5	11.1	33.3	3.5									0.0	0.0	7.4	2.5				
9	74.1	11.8	29.6	9.6									59.3	15.7	40.7	10.5				
10	74.1	13.2	18.5	3.8									40.7	6.1	7.4	3.0				
11	70.4	16.2	29.6	8.4													22.2	4.2	0.0	0.0
12	14.8	6.5	48.1	7.0													37.0	11.0	0.0	0.0
13	51.9	10.4	59.3	6.8													0.0	0.0	0.0	0.0
14	74.1	23.2	70.4	10.7													74.1	8.9	59.3	7.3
15	48.1	6.2	0.0	0.0													14.8	10.7	0.0	0.0
16	22.2	3.3	33.3	6.5	40.7	11.6	33.3	5.3												
17	55.6	9.8	11.1	2.0					29.6	5.8	0.0	0.0								
18	96.3	22.0	92.6	12.9									14.8	12.5	0.0	0.0				
19	85.2	15.6	85.2	15.4									37.0	7.1	81.5	10.3				
20	92.6	24.4	22.2	11.5									59.3	15.0	55.6	12.3				
21	77.8	23.0	48.1	12.3									70.4	28.8	48.1	9.2				
22	92.6	18.5	77.8	10.3									81.5	31.0	74.1	16.5				
23	70.4	19.4	66.7	8.2									37.0	9.6	33.3	3.3				
24	85.2	17.1	40.7	7.5									48.1	10.5	44.4	8.0				
25	74.1	9.1	14.8	4.3									74.1	14.1	14.8	9.5				
26	92.6	21.8	96.3	14.4													59.3	16.4	55.6	8.7
27	70.4	15.3	18.5	3.0													59.3	18.2	11.1	3.7
28	51.9	13.7	81.5	10.2													37.0	7.1	74.1	9.7
29	88.9	19.8	88.9	10.6													25.9	12.8	18.5	8.4
30	51.9	12.5	33.3	7.3													59.3	11.6	40.7	6.5
31	92.6	25.2	92.6	19.0													96.3	32.3	88.9	22.2
32	74.1	10.9	25.9	9.1													18.5	9.2	18.5	5.4

subject no.	Average nighttime BP loads																			
	baseline				losartan25 mg				losartan25mg+HCTZ6.25mg				losartan 100 mg				losartan50mg+HCTZ12.5mg			
	SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP		SBP		DBP	
	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg	%	mmHg
1	100.0	11.8	50.0	5.5	16.7	2.0	100.0	34.3												
2	66.7	16.8	0.0	0.0	66.7	7.5	0.0	0.0												
3	100.0	15.7	100.0	10.0	66.7	36.2	50.0	6.7												
4	83.3	15.8	83.3	7.3					33.3	20.5	33.3	13.0								
5	16.7	13.0	16.7	3.0					33.3	23.5	33.3	4.0								
6	66.7	14.8	16.7	2.0					33.3	9.0	33.3	11.0								
7	50.0	9.5	33.3	1.5					16.7	8.0	0.0	0.0								
8	83.3	6.8	0.0	0.0									33.3	3.0	16.7	1.0				
9	83.3	29.0	66.7	10.0									50.0	8.3	0.0	0.0				
10	100.0	26.0	33.3	1.5									83.3	13.0	66.7	4.3				
11	50.0	12.0	16.7	1.0													16.7	5.0	0.0	0.0
12	33.3	7.0	33.3	5.0													0.0	0.0	0.0	0.0
13	50.0	7.0	66.7	11.0													16.7	3.0	0.0	0.0
14	100.0	15.8	83.3	11.0													83.3	16.8	83.3	13.2
15	100.0	18.0	0.0	0.0													66.7	7.5	16.7	1.0
16	83.3	10.3	33.3	1.5	0.0	0.0	16.7	2.0												
17	83.3	9.6	16.7	6.0					50.0	17.3	33.3	7.5								
18	83.3	19.6	66.7	11.5									16.7	1.0	0.0	0.0				
19	66.7	12.0	66.7	11.8									50.0	8.0	50.0	16.0				
20	16.7	22.7	16.7	8.0									50.0	5.0	33.3	3.5				
21	100.0	19.3	100.0	6.8									83.3	14.0	50.0	7.0				
22	100.0	34.5	66.7	10.8									100.0	15.3	33.3	18.5				
23	83.3	13.0	83.3	11.8									83.3	8.6	83.3	6.0				
24	100.0	17.2	50.0	8.3									100.0	18.0	66.7	8.5				
25	100.0	29.0	66.7	6.0									66.7	36.3	33.3	4.5				
26	83.3	20.0	50.0	8.3													83.3	21.4	83.3	14.6
27	66.7	17.3	16.7	3.0													66.7	7.3	16.7	2.0
28	83.3	14.6	50.0	9.7													83.3	33.0	83.3	9.0
29	100.0	17.8	100.0	15.3													83.3	12.8	50.0	6.3
30	100.0	15.3	66.7	6.5													100.0	23.5	83.3	12.4
31	100.0	32.8	100.0	28.3													100.0	39.7	100.0	27.2
32	100.0	14.5	83.3	8.8													0.0	0.0	0.0	0.0

Appendix K: Area above the normal blood pressure versus time curve at baseline and after step2 treatment

subject no.	Area above normal blood pressure versus time curve(24-hour)									
	baseline		losartan 25 mg		losartan25+HCTZ6.25mg		losartan 100 mg		losartan 50 mg+HCTZ12.5mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}
1	197.0	111.5	7.0	9.5						
2	162.3	1.5	56.0	0.0						
3	142.0	125.0	168.0	15.0						
4	432.3	250.3			172.8	106.3				
5	30.0	0.0			52.8	5.0				
6	126.8	30.3			52.8	41.0				
7	79.8	2.0			159.8	3.5				
8	124.0	7.3					0.0	0.0		
9	219.0	54.3					114.5	42.8		
10	246.0	3.8					71.5	8.0		
11	163.3	18.0							2.8	0.0
12	3.3	34.3							1.0	0.0
13	71.3	61.8							0.0	0.0
14	312.8	127.8							147.3	107.3
15	137.5	0.0							38.3	0.0
16	3.3	17.8	49.5	15.8						
17	63.0	3.8			57.5	0.0				
18	343.0	176.5					14.0	0.0		
19	184.0	193.2					30.3	121.0		
20	355.3	65.8					96.3	19.8		
21	298.8	83.8					291.3	45.3		
22	375.8	119.8					376.3	173.5		
23	197.8	121.8					48.8	33.5		
24	255.3	41.3					143.3	75.5		
25	231.0	101.5					240.5	5.5		
26	348.0	182.0							167.5	113.8
27	166.8	0.0							106.8	4.0
28	140.8	109.8							163.3	125.8
29	291.0	196.0							67.8	19.5
30	147.3	35.8							190.0	82.3
31	447.5	339.0							590.8	387.3
32	179.8	69.0							15.5	9.5

subject no.	Area above normal blood pressure versus time curve(daytime)									
	baseline		losartan 25 mg		losartan25+HCTZ6.25mg		losartan 100 mg		losartan 50 mg+HCTZ12.5mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}
1	137.3	104.3	6.0	9.5						
2	102.8	1.5	13.5	0.0						
3	51.0	68.5	61.0	35.0						
4	359.3	228.3			133.8	86.5				
5	30.0	0.0			8.8	0.0				
6	76.8	30.3			52.8	40.5				
7	47.8	0.0			158.3	3.5				
8	99.0	7.3					0.0	0.0		
9	95.0	24.8					105.0	42.8		
10	99.0	1.8					20.5	0.0		
11	137.8	18.0							2.8	0.0
12	3.3	29.3							1.0	0.0
13	54.8	36.8							0.0	0.0
14	224.8	82.3							76.3	50.8
15	31.5	0.0							11.8	0.0
16	3.3	17.3	49.8	15.8						
17	42.5	1.3			19.5	0.0				
18	247.0	145.5					12.5	0.0		
19	155.5	160.7					28.8	100.0		
20	251.3	60.3					83.3	15.8		
21	189.3	56.8					224.3	30.3		
22	201.8	87.3					287.3	139.0		
23	137.8	64.3					24.3	11.5		
24	161.8	29.8					52.3	39.0		
25	65.5	5.0					115.3	0.0		
26	257.5	170.0							78.0	50.8
27	106.3	0.0							92.8	3.0
28	75.3	94.3							23.8	88.8
29	194.5	108.5							17.3	8.0
30	67.3	11.8							63.5	24.3
31	267.3	185.0							366.3	234.3
32	93.3	32.0							15.5	9.5

subject no.	Area above normal blood pressure versus time curve(nighttime)									
	baseline		losartan 25 mg		losartan25+HCTZ6.25mg		losartan 100 mg		losartan 50 mg+HCTZ12.5mg	
	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}	AUC_{SBP}	AUC_{DBP}
1	59.5	7.0	1.0	0.0						
2	59.5	0.0	42.5	0.0						
3	91.0	56.5	107.0	11.5						
4	73.0	22.0			39.0	20.0				
5	0.0	0.0			44.0	5.0				
6	50.0	0.0			0.0	0.5				
7	32.0	2.0			1.5	0.0				
8	25.0	0.0					0.0	0.0		
9	124.0	29.5					9.5	0.0		
10	147.0	2.0					51.0	8.0		
11	25.5	0.0							0.0	0
12	0.0	5.0							0.0	0
13	16.5	25.0							0.0	0
14	88.0	45.5							71.0	56.5
15	106.0	0.0							26.5	0
16	0.0	0.5	0.0	0.0						
17	20.5	2.5			38.0	0.0				
18	96.0	31.0					1.5	0.0		
19	28.5	32.5					1.5	21.0		
20	104.0	5.5					13.0	4.0		
21	109.5	27.0					67.0	15.0		
22	174.0	32.5					89.0	34.5		
23	60.0	57.5					24.5	22.0		
24	93.5	11.5					91.0	36.5		
25	165.5	96.5					125.0	5.5		
26	90.5	12.0							89.5	63
27	60.5	0.0							14.0	1
28	65.5	15.5							139.5	37
29	96.5	87.5							50.5	11.5
30	80.5	24.0							126.5	58
31	180.5	154.0							224.3	153
32	86.5	37.0							0.0	0

Appendix L: Trough and peak antihypertensive effects and T:P ratio of hydrochlorothiazide 12.5 mg and losartan 50 mg admnistration

subject no.	Hydrochlorothiazide 12.5 mg						losartan 50 mg					
	SBP reduction			DBP reduction			SBP reduction			DBP reduction		
	T	P	T:P	T	P	T:P	T	P	T:P	T	P	T:P
	mmHg	mmHg	%	mmHg	mmHg	%	mmHg	mmHg	%	mmHg	mmHg	%
1	-5	-19	27	-8	-21	36	-13	-32	40	-5	-22	23
2	-8	-21	38	-4	-7	60	-5	-20	25	-1	-4	24
3	-6	-8	73	-12	-33	37	-4	-7	60	-8	-12	66
4	-3	-41	7	-2	-27	6	-23	-33	70	-20	-43	45
5	-10	-14	74	-3	-14	22	-12	-25	48	-7	-15	48
6	-8	-11	68	-1	-7	14	-5	-14	32	-6	-19	32
7	-10	-36	27	-8	-15	55	-26	-40	65	-9	-30	30
8	-13	-23	57	-4	-24	17	-22	-46	46	-9	-24	38
9	-6	-14	42	-7	-24	30	-6	-18	31	-8	-12	61
10	-8	-15	54	-3	-10	30	-20	-27	74	-6	-11	55
11	-6	-28	20	-4	-19	21	-3	-15	17	-5	-18	27
12	-3	-12	25	-5	-11	47	-10	-17	57	-10	-16	58
13	-3	-19	16	-13	-22	59	-4	-8	50	-2	-9	23
14	-3	-30	10	-8	-31	26	-13	-34	39	-5	-12	38
15	-18	-22	82	-3	-20	15	-11	-24	46	-8	-20	40
16	-1	-13	8	-3	-6	50	-6	-20	31	-4	-15	26
17	-12	-18	69	-1	-19	5	-13	-35	37	-4	-13	32
18	-16	-36	45	-2	-4	46	-35	-54	65	-10	-24	40
19	-11	-13	83	-2	-20	10	-15	-22	67	-6	-21	28
20	-17	-45	38	-13	-27	48	-21	-27	78	-8	-34	22
21	-3	-42	7	-3	-10	29	-22	-31	72	-16	-23	69
22	-8	-12	67	-22	-34	64	-13	-14	91	-3	-5	50
23	-7	-27	26	-7	-12	57	-12	-26	46	-10	-37	27
24	-1	-13	8	-7	-15	48	6	-22	28	-3	-7	46
25	-5	-14	37	-2	-6	33	-7	-10	65	-6	-8	69
26	-5	-6	79	-1	-2	59	-6	-12	51	-4	-6	67
27	-12	-25	49	-2	-8	25	-13	-15	85	-3	-10	31
28	-6	-10	60	-1	-22	5	-2	-13	16	-5	-12	42
29	-1	-13	8	-4	-19	21	-2	-10	21	-6	-11	55
30	-2	-16	12	-1	-6	17	-6	-8	75	-4	-9	40
31	-1	-34	3	-2	-18	11	-21	-46	45	-26	-42	62
32	-1	-25	4	-6	-11	51	-23	-41	56	-10	-35	29

Appendix M: Trough and peak antihypertensive effects and T:P ratio of losartan 100 mg and losartan 50 mg plus hydrochlorothiazide 12.5 mg

subject no.	losartan 100 mg						losartan 50 mg plus hydrochlorothiazide 12.5 mg					
	SBP reduction			DBP reduction			SBP reduction			DBP reduction		
	T mmHg	P mmHg	T:P %	T mmHg	P mmHg	T:P %	T mmHg	P mmHg	T:P %	T mmHg	P mmHg	T:P %
1												
2												
3												
4												
5												
6												
7												
8	-14	-36	39	-5	-24	21						
9	-6	-17	35	-8	-17	47						
10	-17	-26	67	-9	-15	58						
11							-6	-23	26	-9	-23	39
12							-4	-18	22	-9	-18	50
13							-26	-40	65	-27	-37	73
14							-7	-37	19	-1	-6	17
15							-9	-12	73	-2	-16	13
16												
17												
18	-28	-61	46	-18	-35	51						
19	-16	-31	50	-8	-15	52						
20	-6	-21	29	-6	-10	62						
21	-13	-21	63	-8	-21	36						
22	-4	-8	48	-9	-14	64						
23	-6	-26	23	-4	-23	15						
24	-9	-35	26	-3	-10	32						
25	-8	-14	58	-3	-3	89						
26							-30	-50	60	-10	-32	30
27							-7	-13	55	-8	-20	37
28							-12	-20	59	-3	-9	35
29							-25	-35	72	-22	-26	84
30							-15	-20	77	-3	-7	43
31							-9	-20	45	-3	-8	33
32							-28	-38	74	-6	-15	39

Appendix N: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP observed between treatment

p value	a	b	c
Office BP			
SBP(mmHg)	<0.001	<0.001	1.000
DBP(mmHg)	0.006	<0.001	0.044
MAP(mmHg)	<0.001	<0.001	0.509
HR(bpm)	1.000	0.868	0.124
24-hour ABP			
average 24-hour			
SBP(mmHg)	0.204	0.005	0.196
DBP(mmHg)	0.577	0.003	0.197
MAP(mmHg)	0.247	0.003	0.313
HR(bpm)	1.000	1.000	1.000
average daytime			
SBP(mmHg)	0.176	0.011	0.495
DBP(mmHg)	0.130	0.005	1.000
MAP(mmHg)	0.591	0.058	0.790
HR(bpm)	0.360	1.000	1.000

a hydrochlorothiazide versus baseline

b losartan 50 mg versus baseline

c losartan 50 mg versus hydrochlorothiazide 12.5 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Appendix N: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP observed between treatment (continued)

p value	a	b	c
average nighttime			
SBP(mmHg)	0.444	<0.001	0.040
DBP(mmHg)	1.000	0.008	0.027
MAP(mmHg)	1.000	0.001	0.029
HR(bpm)	1.000	1.000	1.000

a hydrochlorothiazide versus baseline

b losartan 50 mg versus baseline

c losartan 50 mg versus hydrochlorothiazide 12.5 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Appendix o: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above normal BP range observed between treatment

p value	a	b	c
Frequency of BP load (%)			
24-hour BP load			
SBP	0.010	0.001	0.460
DBP	0.298	0.002	0.755
daytime BP load			
SBP	0.014	0.001	0.771
DBP	0.129	0.011	1.000
nighttime BP load			
SBP	0.239	0.006	0.117
DBP	1.000	0.023	0.012
Absolute value of BP load(mmHg)			
24-hour BP load			
SBP	1.000	0.437	1.000
DBP	1.000	0.192	0.097
daytime BP load			
SBP	1.000	1.000	1.000
DBP	1.000	0.310	0.321
nighttime BP load			
SBP	1.000	0.044	0.205
DBP	1.000	0.108	0.010

a hydrochlorothiazide versus baseline

b losartan 50 mg versus baseline

Appendix o: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above normal BP range observed between treatment(continued)

p value	a	b	c
24-hour AUC(mmHg.h)			
SBP	0.032	0.005	0.969
DBP	0.303	0.029	0.413
daytime AUC(mmHg.h)			
SBP	0.063	0.019	1.000
DBP	0.187	0.160	1.000
nighttime AUC(mmHg.h)			
SBP	0.285	0.005	0.267
DBP	1.000	0.062	0.008

a hydrochlorothiazide versus baseline

b losartan 50 mg versus baseline

c losartan 50 mg versus hydrochlorothiazide 12.5 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure

Appendix P: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP observed between treatments losartan 50 mg) plus hydrochlorothiazide 12.5 mg (HYZAAR)

p value	losartan 100 mg (n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(Hyzaar)(n=12)		
	a	b	c	d	e	f
Office BP						
SBP (mmHg)	0.040	0.002	0.045	0.012	0.009	0.939
DBP (mmHg)	0.673	0.004	0.084	0.002	0.001	0.173
MAP (mmHg)	0.159	0.001	0.021	0.001	0.002	0.119
HR(bpm)	1.000	0.925	1.000	1.000	0.596	1.000
24-hour ABP						
average 24-hour						
SBP (mmHg)	0.090	0.098	1.000	1.000	0.036	0.732
DBP (mmHg)	0.153	0.562	1.000	0.585	0.049	0.767
MAP (mmHg)	0.130	0.167	1.000	0.613	0.032	0.734
HR(bpm)	1.000	1.000	0.457	1.000	1.000	1.000
average daytime						
SBP(mmHg)	0.132	0.200	1.000	1.000	0.019	0.509
DBP(mmHg)	0.149	0.528	1.000	0.700	0.020	0.363
MAP(mmHg)	0.316	0.486	1.000	0.809	0.015	0.435
HR(bpm)	1.000	1.000	1.000	1.000	1.000	1.000

a losartan 50 mg versus baseline, **b** losartan 100 mg versus baseline, **c** losartan 100 mg versus losartan 50 mg

d losartan 50 mg versus baseline, **e** Hyzaar versus baseline, **f** Hyzaar versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Appendix P: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP observed between treatments losartan 50 mg) plus hydrochlorothiazide 12.5 mg (HYZAAR)(continued)

p value	losartan 100 mg (n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(Hyzaar)(n=12)		
	a	b	c	d	e	f
average nighttime						
SBP(mmHg)	0.026	0.008	0.755	0.659	0.260	1.000
DBP(mmHg)	0.069	0.193	1.000	0.653	0.538	1.000
MAP(mmHg)	0.091	0.040	0.946	0.415	0.318	1.000
HR(bpm)	1.000	0.553	0.699	1.000	0.318	0.782

a losartan 50 mg versus baseline, **b** losartan 100 mg versus baseline, **c** losartan 100 mg versus losartan 50 mg

d losartan 50 mg versus baseline, **e** Hyzaar versus baseline, **f** Hyzaar versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate

Appendix Q: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP reduction observed between treatment

P value	losartan 50+50 mg(n=11)[c]	losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)[c]
Office BP		
SBP(mmHg)	0.622	0.561
DBP(mmHg)	0.616	0.125
MAP(mmHg)	0.910	0.123
24-hour ABP		
average 24-hour		
SBP(mmHg)	0.067	0.668
DBP(mmHg)	0.088	0.601
MAP(mmHg)	0.056	0.741
average daytime		
SBP(mmHg)	0.089	0.528
DBP(mmHg)	0.120	0.450
MAP(mmHg)	0.100	0.513
average nighttime		
SBP(mmHg)	0.067	0.813
DBP(mmHg)	0.062	0.548
MAP(mmHg)	0.285	0.568

[c] versus losartan 50 mg treatment(step1)
SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure

Appendix R: The statistical levels of significant difference(P value) when comparing the mean office BP and ABP reduction observed between treatment

P value	losartan 100 mg(n=11)			HYZAAR (n=12)		
	a	b	c	a	b	c
Office BP						
SBP(mmHg)	1.000	0.309	0.045	1.000	0.645	0.315
DBP(mmHg)	1.000	<0.001	0.084	1.000	0.021	0.173
MAP(mmHg)	1.000	0.002	0.021	1.000	0.074	0.119
24-hour ABP						
average 24-hour						
SBP(mmHg)	1.000	1.000	1.000	1.000	0.152	0.732
DBP(mmHg)	0.367	1.000	1.000	1.000	0.758	0.767
MAP(mmHg)	1.000	1.000	1.000	1.000	0.369	0.734
average daytime						
SBP(mmHg)	1.000	1.000	1.000	1.000	0.209	0.509
DBP(mmHg)	0.725	1.000	1.000	0.729	0.675	0.363
MAP(mmHg)	1.000	1.000	1.000	1.000	0.323	0.435
average nighttime						
SBP(mmHg)	0.120	0.881	0.013	1.000	0.438	1.000
DBP(mmHg)	0.211	0.645	1.000	1.000	1.000	1.000
MAP(mmHg)	1.000	0.434	0.946	0.983	0.737	1.000

[a] losartan 50 mg versus hydrochlorothiazide12.5 mg, [b] step2 (losartan 100 mg or hyzaar) versus hydrochlorothizide 12.5 mg

[c] step2 versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure

Appendix S: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above normal BP range observed between treatment

p value	losartan 100 mg (n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg(Hyzaar)(n=12)		
	b	c		d	e	f
Frequency of BP load (%)						
24-hour BP load						
SBP	0.018	0.006	1.000	0.323	0.032	0.536
DBP	0.469	0.586	1.000	0.272	0.041	0.565
daytime BP load						
SBP	0.011	0.005	1.000	0.526	0.048	0.587
DBP	0.822	0.839	1.000	0.445	0.029	0.356
nighttime BP load						
SBP	0.669	0.156	1.000	0.470	0.064	1.000
DBP	0.472	0.459	1.000	0.441	0.849	1.000
Absolute value of BP load(mmHg)						
24-hour BP load						
SBP	0.201	0.157	1.000	1.000	0.554	0.379
DBP	1.000	1.000	1.000	1.000	0.084	1.000
daytime BP load						
SBP	0.702	0.700	1.000	0.725	0.413	0.093
DBP	1.000	1.000	1.000	1.000	0.052	0.652
nighttime BP load						
SBP	0.082	0.029	0.742	1.000	1.000	1.000
DBP	1.000	1.000	1.000	0.252	0.835	1.000

a losartan 50 mg versus baseline, **b** losartan 100 mg versus baseline, **c** losartan 100 mg versus losartan 50 mg

d losartan 50 mg versus baseline, **e** Hyzaar versus baseline, **f** Hyzaar versus losartan 50 mg

Appendix S: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above normal BP range observed between treatment(continued)

p value	losartan 100 mg (n=11)			losartan 50 mg plus hydrochlorothiazide 12.5 mg (Hyzaar) (n=12)		
	a	b	c	d	e	f
24-hour AUC(mmHg.h)						
SBP	0.013	0.007	1.000	1.000	0.105	1.000
DBP	0.058	0.208	1.000	1.000	0.463	1.000
daytime AUC(mmHg.h)						
SBP	0.031	0.143	1.000	1.000	0.070	0.617
DBP	0.242	0.468	1.000	1.000	0.268	1.000
nighttime AUC(mmHg.h)						
SBP	0.042	0.001	0.067	0.969	1.000	1.000
DBP	0.345	0.327	1.000	0.626	1.000	0.779

a losartan 50 mg versus baseline, **b** losartan 100 mg versus baseline, **c** losartan 100 mg versus losartan 50 mg

d losartan 50 mg versus baseline, **e** Hyzaar versus baseline, **f** Hyzaar versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure

Appendix T : The statistical levels of significant difference when comparing the frequency, magnitude and AUC reduction above normal BP range observed between treatment

P value	losartan 100 mg(n=11)[c]	losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)[c]
Frequency of BP load (%)		
24-hour BP load		
SBP	0.028	0.782
DBP	0.401	0.779
daytime BP load		
SBP	0.017	0.705
DBP	0.558	0.555
nighttime BP load		
SBP	0.549	0.725
DBP	0.446	0.362
Absolute value of BP load(mmHg)		
24-hour BP load		
SBP	0.335	0.178
DBP	0.650	0.926
daytime BP load		
SBP	0.497	0.052
DBP	0.623	0.566
nighttime BP load		
SBP	0.152	0.845
DBP	0.627	0.154

[c] versus losartan 50 mg treatment(step1)
SBP= systolic blood pressure, DBP= diastolic blood pressure

Appendix T : The statistical levels of significant difference when comparing the frequency, magnitude and AUC reduction above normal BP range observed between treatment(continued)

P value	losartan 100 mg(n=11)[c]	losartan 50 mg plus hydrochlorothiazide 12.5 mg(n=12)[c]
24-hour AUC(mmHg.h)		
SBP	0.042	0.81
DBP	0.012	0.893
daytime AUC(mmHg.h)		
SBP	0.03	0.484
DBP	0.101	0.596
nighttime AUC(mmHg.h)		
SBP	0.250	0.572
DBP	0.176	0.203

[c] versus losartan 50 mg treatment(step1)

SBP= systolic blood pressure, DBP= diastolic blood pressure

Appendix U : The statistical levels of significant differences(P value) when comparing the mean office BP and ABP observed between treatment

P value	losartan 25 mg(n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg(n=5)		
	a	**b**	**c**	**d**	**e**	**f**
Office BP						
SBP(mmHg)	0.194	0.450	1.000	0.115	0.183	0.695
DBP(mmHg)	0.157	0.350	1.000	0.019	0.173	0.083
MAP(mmHg)	0.149	0.375	1.000	0.039	0.160	0.144
HR(bpm)	1.000	0.553	0.505	1.000	1.000	1.000
24-hour ABP						
average 24-hour						
SBP(mmHg)	1.000	1.000	1.000	0.106	0.059	0.930
DBP(mmHg)	0.797	0.250	0.275	0.184	0.169	1.000
MAP(mmHg)	1.000	0.463	1.000	0.164	0.035	0.914
HR(bpm)	1.000	1.000	1.000	1.000	1.000	1.000
average daytime						
SBP(mmHg)	1.000	1.000	1.000	0.104	0.125	1.000
DBP(mmHg)	1.000	0.285	0.866	0.252	0.173	1.000
MAP(mmHg)	1.000	0.528	1.000	0.992	1.000	1.000
HR(bpm)	0.765	1.000	0.758	1.000	1.000	1.000

a losartan 50 mg versus baseline, b losartan 25 mg versus baseline, c losartan 25 mg versus losartan 50 mg

d losartan 50 mg versus baseline, e Hyzaar1/2 versus baseline, f Hyzaar 1/2 versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate respectively

Appendix U : The statistical levels of significant differences(P value) when comparing the mean office BP and ABP observed between treatment

P value	**losartan 25 mg(n=4)**			**losartan 25 mg plus hydrochlorothiazide 6.25 mg(n=5)**		
	a	**b**	**c**	**d**	**e**	**f**
average nighttime						
SBP(mmHg)	0.168	0.893	1.000	0.128	1.000	1.000
DBP(mmHg)	1.000	1.000	1.000	0.236	0.453	0.463
MAP(mmHg)	0.406	0.690	1.000	0.141	0.433	0.670
HR(bpm)	1.000	1.000	1.000	0.040	1.000	0.401

a losartan 50 mg versus baseline, b losartan 25 mg versus baseline, c losartan 25 mg versus losartan 50 mg

d losartan 50 mg versus baseline, e Hyzaar1/2 versus baseline, f Hyzaar 1/2 versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure,HR= heart rate respectively

Appendix V: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above the normal BP range observed between treatment

P value	losartan 25 mg(n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg(n=5)		
	a	b	c	d	e	f
Frequency of BP load (%)						
24-hour BP load						
SBP	1.000	0.970	1.000	0.029	0.128	1.000
DBP	0.440	0.420	1.000	0.193	0.490	0.182
daytime BP load						
SBP	1.000	1.000	1.000	0.023	0.226	1.000
DBP	0.488	0.345	1.000	0.197	0.345	0.635
nighttime BP load						
SBP	0.483	0.275	0.924	0.064	0.233	1.000
DBP	1.000	1.000	1.000	0.326	1.000	0.298
Absolute value of BP load(mmHg)						
24-hour BP load						
SBP	1.000	1.000	1.000	0.367	1.000	0.500
DBP	1.000	1.000	1.000	0.514	1.000	0.123
daytime BP load						
SBP	1.000	1.000	1.000	0.565	1.000	0.875
DBP	1.000	0.917	1.000	0.585	0.673	1.000
nighttime BP load						
SBP	0.674	1.000	1.000	0.089	1.000	0.160
DBP	1.000	1.000	1.000	0.732	0.504	0.081

a losartan 50 mg versus baseline, b losartan 25 mg versus baseline, c losartan 25 mg versus losartan 50 mg

d losartan 50 mg versus baseline, e Hyzaar1/2 versus baseline, f Hyzaar 1/2 versus losartan 50 mg

Appendix V: The statistical levels of significant difference when comparing the frequency, magnitude and AUC above the normal BP range observed between treatment(continued)

P value	losartan 25 mg (n=4)			losartan 25 mg plus hydrochlorothiazide 6.25 mg		
	a	b	c	d	e	f
24-hour AUC(mmHg.h)						
SBP	0.813	1.000	1.000	0.276	1.000	0.775
DBP	0.418	0.515	1.000	1.000	1.000	1.000
daytime AUC(mmHg.h)						
SBP	1.000	1.000	1.000	0.476	1.000	1.000
DBP	0.499	0.697	0.255	1.000	1.000	1.000
nighttime AUC(mmHg.h)						
SBP	0.596	1.000	1.000	0.132	1.000	0.528
DBP	1.000	0.927	1.000	0.738	1.000	0.664

a losartan 50 mg versus baseline, b losartan 25 mg versus baseline, c losartan 25 mg versus losartan 50 mg

d losartan 50 mg versus baseline, e Hyzaar1/2 versus baseline, f Hyzaar 1/2 versus losartan 50 mg

SBP= systolic blood pressure, DBP= diastolic blood pressure

Appendix W: The statistical levels of significant difference(P value) when comparing the mean nocturnal reduction of SBP (dippers/ nondippers group based on nocturnal reduction of baseline SBP)(n=32)

P value		d	e	f
SBP	dippers(n=21)	0.383	0.167	1.000
	nondippers(n=11)	0.274	0.032	1.000
DBP				
	dippers(n=21)	0.239	1.000	1.000
	nondippers(n=11)	1.000	0.745	1.000
MAP				
	dippers(n=21)	0.125	0.824	1.000
	nondippers(n=11)	1.000	0.492	1.000

d hydrochlorothiazide versus baseline

e losartan versus baseline

f losartan versus hydrochlorothiazide

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

Appendix X: The statistical levels of significant difference(P value) when comparing the mean nocturnal reduction of DBP (dippers/ nondippers group based on nocturnal reduction of baselineDBP)(n=32)

P value		d	e	f
SBP	dippers(n=15)	1.000	1.000	1.000
	nondippers(n=17)	1.000	0.558	0.233
DBP				
	dippers(n=15)	0.050	0.008	1.000
	nondippers(n=17)	0.973	0.010	0.381
MAP				
	dippers(n=15)	0.177	0.068	1.000
	nondippers(n=17)	1.000	0.103	0.441

d hydrochlorothiazide versus baseline
e losartan versus baseline
f losartan versus hydrochlorothiazide

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

Appendix Y: The statistical levels of significant difference(P value) when comparing the mean nocturnal reduction of MAP (dippers/ nondippers group based on nocturnal reduction of baseline MAP)(n=32)

P value		d	e	f
SBP	dippers(n=17)	1.000	0.273	1.000
	nondippers(n=15)	1.000	0.084	0.311
DBP				
	dippers(n=17)	0.136	0.121	1.000
	nondippers(n=15)	1.000	0.018	0.280
MAP				
	dippers(n=17)	0.125	0.066	1.000
	nondippers(n=15)	1.000	0.008	0.176

d hydrochlorothiazide versus baseline

e losartan versus baseline

f losartan versus hydrochlorothiazide

SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP = mean arterial pressure

BIOGRAPHY

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