การเปรียบเทียบประสิทธิผลระหว่างยาโลซาร์ทานและเออร์เบซาทานในผู้ป่วยโรคความดันโลหิตสูง ที่โรงพยาบาลสระบุรี ประเทศไทย ปี 2551

นางสาววราภรณ์ เลิศวิมลชัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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COMPARISON OF EFFICACY BETWEEN LOSARTAN AND IRBESARTAN IN HYPERTENSIVE PATIENTS AT SARABURI HOSPITAL, THAILAND 2008.

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วราภรณ์ เลิศวิมลชัย: การเปรียบเทียบประสิทธิผลระหว่างยาโลซาร์ทาน และเออร์เบซาทาน ในผู้ป่วยโรคความดันโลหิตสูงที่โรงพยาบาลสระบุรี ประเทศไทย ปี 2551 (COMPARISON OF EFFICACY BETWEEN LOSARTAN AND IRBESARTAN IN HYPERTENSIVE PATIENTS AT SARABURI HOSPITAL, THAILAND 2008) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ.ดร.ฐิตินันท์ เอื้ออำนวย, 70 หน้า.

วัตถุประสงค์: 1.เพื่อตรวจสอบว่ายาโลซาร์ทาน ขนาด 50 มิลลิกรัม หรือ ยาเออร์เบซาทาน ขนาด 150 มิลลิกรัม สามารถลดค่าความดันโลหิตของค่าล่างขณะนั่งพักและค่าความดันโลหิตค่าบนขณะนั่งพักได้หรือไม่ 2. เพื่อเปรียบเทียบประสิทธิผลในการลดความดันโลหิตระหว่างยาโลซาร์ทาน 50 มิลลิกรัม และเออร์เบซาทาน 150 มิลลิกรัมโดยควบคุม (1) ค่าความดันโลหิตพื้นฐานของค่าล่างและค่าบนขณะนั่งพัก และ (2) อายุ 3.เพื่อเปรียบเทียบประสิทธิผลในการลดความดันโลหิตของยาโลซาร์ทาน 50 มิลลิกรัม และยาเออร์เบซาทาน 150 มิลลิกรัม ระหว่างเพศโดยควบคุม (1) ค่าความดันโลหิตพื้นฐานของค่าล่างและค่าบนขณะนั่งพัก และ (2) อายุ

วิธีวิจัย: เป็นการศึกษาแบบย้อนหลัง ข้อมูลถูกเก็บจากฐานข้อมูลหลักของโรงพยาบาลสระบุรีในระบบคอมพิวเตอร์ กลุ่มประชากรเป็นผู้ป่วยโรคความดันโลหิตสูงทั้งหมดซึ่งได้รับยาโลซาร์ทาน ขนาด 50 มิลลิกรัม วันละ 1 ครั้ง หรือยาเออร์เบซาทาน ขนาด 150 มิลลิกรัม วันละ 1 ครั้ง เพื่อรักษาโรคความดันโลหิตสูง ในระหว่างวันที่ 1 มกราคม 2551 ถึง 30 มิถุนายน 2551 เกณฑ์การคัดออก คือ โรคที่เป็นร่วม และการใช้ยาอื่นร่วม เช่น ยาที่มีผลต่อความดันโลหิต ซึ่งอาจรบกวนการประเมินประสิทธิผล การวิจัยนี้ใช้เทคนิคการสุ่มอย่างง่าย ใช้ค่า α 0.05, power 0.90 และ effect size 0.15 ได้ค่าตัวอย่าง 200 ตัวอย่าง ในแต่ละกลุ่ม (ทั้งหมด 400) ค่าความดันโลหิตพื้นฐานของค่าล่างและค่าบนขณะนั่งพักเฉลี่ยของกลุ่มที่ได้รับยาโลซาร์ทาน และกลุ่มที่ได้รับยาเออร์เบซาทาน คือ 81.57±8.56, 153.67±12.04 และ 83.25±12.24, 160.04±15.42 ตามลำดับ ค่าความดันโลหิตพื้นฐานของค่าล่างและค่าบนขณะนั่งพัก และ อายุ นำมาใช้เป็นตัวแปรกวน หลังจากได้รับยาเป็นเวลา 8 สัปดาห์ ค่าความดันโลหิตค่าล่างและค่าบนขณะนั่งพักถูกนำมาวัดและเปรียบเทียบ

ผลวิจัย: กลุ่มตัวอย่างทั้งหมด 400 คน (ร้อยละ 100) ส่วนใหญ่เป็นหญิง 270 คน (ร้อยละ 67.50), อายุเฉลี่ย 63.36 $\pm$ 12.42 ปี อาชีพส่วนใหญ่ของผู้ป่วย คือ ค้าขาย (ร้อยละ 35.00) หลังจากได้รับยา ค่าความดันโลหิตเฉลี่ยของค่าล่างขณะนั่งพักของกลุ่มที่ได้รับยาโลซาร์ทาน และ กลุ่มที่ได้รับยาเออร์เบซาทาน คือ 71.68±9.43 และ 69.35±9.64 มิลลิเมตรปรอท ตามลำดับ (p=0.000, Paired t-test, p=0.000, Paired t-test) หลังจากได้รับยา ค่าความดันโลหิตเฉลี่ยของค่าบนขณะนั่งพักของกลุ่มที่ได้รับยาโลซาร์ทาน และกลุ่มที่ได้รับยาเออร์เบซาทาน คือ 127.51±12.22 และ 126.44±15.16 มิลลิเมตรปรอท ตามลำดับ (p=0.000, Paired t-test และ p=0.000, Paired t-test) เมื่อควบคุมตัวแปรอายุ (ตัวแปรกวน) และเพิ่มตัวแปรเพศ (ปัจจัยคงที่) เข้าไปในแบบจำลอง ค่าเฉลี่ยของค่าความดันโลหิตของค่าล่างและค่าบนขณะนั่งพักของกลุ่มที่ได้รับยาโลซาร์ทาน และกลุ่มที่ได้รับยาเออร์เบซาทาน คือ 71.68±9.43, 127.51±12.22 และ 69.35±9.64, 126.44±15.16 มิลลิเมตรปรอท ตามลำดับ (p=0.017, Two way ANCOVA และ p=0.024, Two way ANCOVA) โดยปราศจากปฏิกิริยาของตัวแปรเพศ (p=0.927, p=0.714)

บทสรุป: ยาโลซาร์ทานขนาด 50 มิลลิกรัม วันละ 1 ครั้ง และยาเออร์เบซาทานขนาด 150 มิลลิกรัม วันละ 1 ครั้ง สามารถลดค่าความดันโลหิตค่าล่างและค่าบนขณะนั่งพักได้อย่างมีนัยสำคัญ (p=0.000, p=0.000, p=0.000, p=0.000, Paired t-test ตามลำดับ) ยาเออร์เบซาทานขนาด 150 มิลลิกรัม วันละ 1 ครั้ง สามารถลดค่าความดันโลหิตของค่าล่างและค่าบนขณะนั่งพักในผู้ป่วยโรคความดันโลหิตสูง ได้ดีกว่า ยาโลซาร์ทาน ขนาด 50 มิลลิกรัม วันละ 1 ครั้งอย่างมีนัยสำคัญ (p=0.017, p=0.024, Two way ANCOVA ตามลำดับ) ตัวแปรเพศไม่ทำให้เกิดความแตกต่างในประสิทธิผลของยาทั้ง 2 ชนิด คุณสมบัติของการศึกษานี้ การศึกษานี้ใช้กระบวนการทางสถิติที่มีประสิทธิภาพ คือใช้สถิติ Two way ANCOVA โดยควบคุมตัวแปรกวน 2 ตัว นั่นคือ ค่าความดันโลหิตพื้นฐานของค่าล่างและค่าบนขณะนั่งพัก และ อายุ อย่างไรก็ตาม ยังคงมีข้อจำกัดบางประการ คือ 1.การวิจัยนี้เป็นการศึกษาแบบย้อนหลัง ดังนั้นข้อมูลและตัวแปรทั้งหมดได้ถูกเก็บข้อมูลเรียบร้อยแล้ว หากการศึกษาเป็นแบบการศึกษาไปข้างหน้าซึ่งเป็นการออกแบบการวิจัยที่ดีกว่า ร่วมกับวิธีการวิจัยที่มีการควบคุมความผิดพลาด และตัวแปรกวน รวมถึงตัวแปรต้น และตัวแปรตามที่เชื่อถือได้อย่างเป็นระบบ การศึกษานั้นจะให้ผลที่ถูกต้องมากกว่า 2. การศึกษานี้เปรียบเทียบเพียงแง่มุมเดียว คือผลในการลดความดันโลหิต ถ้าจะเปรียบเทียบประสิทธิภาพของยา 2 ตัวนี้อย่างสมบูรณ์ การศึกษาในครั้งต่อไปอาจต้องเพิ่มการเปรียบเทียบในรายละเอียดอื่น ตัวอย่างเช่น ผลต่อระดับกรดยูริคในซีรั่ม ผลข้างเคียง และค่าใช้จ่าย เพื่อสรุปในท้ายสุดว่ายาตัวใดมีผลในผลการรักษาดีกว่า

คำสำคัญ: ยาโลซาร์ทาน ยาเออร์เบซาทาน ความดันโลหิตสูง ค่าความดันโลหิตพื้นฐานของค่าล่างขณะนั่งพัก ค่าความดันโลหิตพื้นฐานของค่าบนขณะนั่งพัก ค่าความดันโลหิตของค่าล่างขณะนั่งพัก ค่าความดันโลหิตของค่าบนขณะนั่งพัก, Paired t-test, One way ANOVA, Two way ANCOVA

ภาควิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต.....

สาขาวิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา 2552

507 68603 33 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS: LOSARTAN/IRBESARTAN/HYPERTENSION/BASELINE SEATED DIASTOLIC BLOOD PRESSURE/BASELINE SEATED SYSTOLIC BLOOD PRESSURE / SEATED DIASTOLIC BLOOD PRESSURE/ SEATED SYSTOLIC BLOOD PRESSURE /Paired t-test, One way ANOVA, Two way ANCOVA

WARAPORN LERTWIMONCHAI: COMPARISON OF EFFICACY BETWEEN LOSARTAN AND IRBESARTAN IN HYPERTENSIVE PATIENTS AT SARABURI HOSPITAL, THAILAND 2008. THESIS ADVISOR: ASSOC. PROF. TITINUN AUAMNOY, Ph.D., 70 pp.

Objectives: 1. To investigate whether 50 mg losartan or 150 mg irbesartan could reduce seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP). 2. To compare antihypertensive efficacy between 50 mg losartan and 150 mg irbesartan controlling for (1) baseline SeDBP and SeSBP and (2) age. 3. To compare antihypertensive efficacy of 50 mg losartan and 150 mg irbesartan between gender controlling for (1) baseline SeDBP and SeSBP and (2) age.

Method: A retrospective study design was performed. The data were collected from computerized Saraburi hospital main database. All hypertensive patients who were prescribed losartan 50 mg once daily or irbesartan 150 mg once daily for hypertensive treatment during January 1-June 30, 2008 were the population framework. Exclusion criteria included concomitant diseases and medications e.g., drugs known to affect BP that might interfere with the assessment of efficacy. Simple random technique was employed. The α 0.05, power 0.90 and effect size 0.15 were set to generate 200 samples in each group (total 400). The average baseline SeDBP and SeSBP of losartan group and irbesartan group were 81.57±8.56, 153.67±12.04 and 83.25±12.24, 160.04±15.42 respectively. Baseline SeDBP and SeSBP and age were used as covariates. After medications for 8 weeks SeDBP and SeSBP were measured and compared.

Results: Total 400 (100%) patients, mostly 270 (67.50%) were female. The average age was 63.36±12.42 years. The majority occupation of the patients was merchant (35.00%). After treatment, the average SeDBP of losartan and irbesartan groups were 71.68±9.43 and 69.35±9.64 mmHg respectively (p=0.000, Paired t-test and p=0.000, Paired t-test). After treatment, the average SeSBP of losartan and irbesartan groups were 127.51±12.22 and 126.44±15.16 mmHg respectively (p=0.000, Paired t-test and p=0.000, Paired t-test). When controlled age (covariate) and added gender (fixed factor) to the model, the average SeDBP and SeSBP of losartan group and irbesartan group were 71.68±9.43, 127.51±12.22 and 69.35±9.64, 126.44±15.16 mmHg respectively (p=0.017, Two way ANCOVA and p=0.024, Two way ANCOVA without gender interaction (p=0.927, p=0.714).

Conclusions: Both drugs, 50 mg losartan and 150 mg irbesartan once a day could significantly lower SeDBP and SeSBP (p=0.000, p=0.000, p=0.000, p=0.000, Paired t-test respectively). Irbesartan 150 mg once daily could significantly lower seated diastolic blood pressure and systolic blood pressure in hypertensive patients than losartan 50 mg once daily. (p=0.017, p=0.024, Two way ANCOVA respectively). Gender made no differences on efficacy of the two drugs. Qualifications of this study: This study used powerful statistical procedure, Two way ANCOVA controlling for two extraneous variables namely-baseline SeDBP and SeSBP and age. However there were still some limitations. 1. This research was a retrospective study consequently all data and variables were already collected. If it was a prospective design with a better protocol for systemically controlling errors and covariates including all reliable dependent and independent variables then it would yield better precise results. 2. This study proved only one aspect—lower blood pressure effect. To completely compare effectiveness of these two drugs, the future study may need comparing in more details such as effect to serum uric acid levels, side effects, and cost to ultimately conclude that which one is better.

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Academic year: .....2009.....

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LIST OF ABBREVIATIONS

AII	Angiotensin II
ACC	Associated Clinical Condition
ACE	Angiotensin Converting Enzyme
ADRs	Adverse Drug Reactions
ARBs	Angiotensin Recepter Blockers
BI	Behavioral Intension
BMI	Body Mass Index
BHS	The British Hypertension Society
BP	Blood Pressure
CAD	Coronary artery disease
COPD	Chronic Obstructive Pulmonary Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
ESH	The European Society of Hypertension-European Society of Cardiology
GFR	Glomerular Filtration Rate
HCTZ	Hydrochlorothiazide
HF	Heart Failure
HT	Hypertension
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
One way ANOVA	One way Analysis of Variance
post-MI	post-Myocardial Infarction
RAS	Renin-Angiotensin System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SeDBP	Seated Diastolic Blood Pressure

SeSBP	Seated Systolic Blood Pressure
SPSS	Statistical Package for the Social Sciences
Two way ANCOVA	Two way Analysis of Covariance
TOD	Target Organ Damage
WHO/ISH	The World Health Organization-International Society of Hypertension

CHAPTER I

INTRODUCTION

Hypertension (HT) is a medical condition in which the blood pressure is chronically elevated. In current usage, the word "hypertension" normally refers to systemic, arterial hypertension (Maton et al., 1993). Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure (Pierdomenico et al., 2009). Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated (Guyton and Hall, 2005). Beginning at a systolic pressure (which is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting) of 115 mmHg and diastolic pressure (which is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood) of 75 mmHg (commonly written as 115/75 mmHg), cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmHg (Chobanian et al., 2003).

Unless hypertension is severe, lifestyle changes are strongly recommended before initiation of drug therapy. Adoption of the DASH diet is one example of lifestyle change repeatedly shown to effectively lower mildly-elevated blood pressure. If hypertension is high enough to justify immediate use of medications, lifestyle changes are initiated concomitantly (U.S. Department of Health and Human Services, 2006).

1.1 Rational and background

Hypertension is an important public health challenge in both economically developing and developed countries. Analysis of the 1999-2004 United States

National Health and Nutrition Examination Survey database revealed that in 2003 to 2004, only 33% of hypertensive patients had controlled blood pressure and only 64% of patients treated for hypertension achieved control (Ong et al., 2007).

In 2004, Kearney and his team reported that the prevalence of hypertension varied around the world. The lowest prevalence was in rural India (3.4% in men and 6.8% in women) and the highest prevalence was in Poland (68.9% in men and 72.5% in women). Awareness of hypertension varied from 25.2% in Korea to 75% in Barbados. Receiving the proper treatment varied from 10.7% in Mexico to 66% in Barbados and the capacity in controlling the blood pressure <140/90 during the treatment varied from 5.4% in Korea to 58% in Barbados (Kearney et al., 2004).

In Thailand, the prevalence of hypertension and prehypertension studied in 2008 weighted to the national 2004 population was 22.0% and 32.8%, respectively. About 69.8% of hypertensive patients did not realize that they were facing hypertension. For the patients who were aware, 78.2% of them took antihypertensive drugs. Among these patients, 36.6% had lower than 140/90 mmHg after two weeks of drug taking. Rural populations from the poorer Northeast region were more likely to be unaware that they had hypertension than any other regions in Thailand (Wichai Aekplakorn et al., 2008).

1.2 Significant of the problem

Nowadays, there are many groups of antihypertensive medication in the market. These medications have different efficacies even they are in the same group. Angiotensin II receptor antagonist is an antihypertensive medication that has been prescribed increasingly.

Therefore, the current study was designed to compare the efficacy in terms of blood pressure reduction of two new angiotensin II receptor antagonists, losartan and irbesartan.

1.3 Objectives

The objectives of this study were

1. To investigate whether 50 mg losartan or 150 mg irbesartan could reduce seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP).

2. To compare antihypertensive efficacy between 50 mg losartan and 150 mg irbesartan controlling for (1) baseline SeDBP and SeSBP and (2) age.

3. To compare antihypertensive efficacy of 50 mg losartan and 150 mg irbesartan between gender controlling for (1) baseline SeDBP and SeSBP and (2) age.

1.4 Research questions

1. Could 50 mg losartan reduce SeDBP?
2. Could 50 mg losartan reduce SeSBP?
3. Could 150 mg irbesartan reduce SeDBP?
4. Could 150 mg irbesartan reduce SeSBP?
5. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeDBP better?
6. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeSBP better?

CHAPTER II

LITERATURE REVIEW

This chapter is composed of three sections. The first section describes hypertension and treatment. The second section is the overview of losartan and irbesartan. The third section is the literature review on losartan and irbesartan.

2.1 Hypertension and treatment

2.1.1 Definition of hypertension

Hypertension can be defined as a condition where blood pressure (BP) is elevated persistently above arbitrary normal values i.e. 139/89 mmHg (Alagappan, 2002).

Hypertension is a common chronic disease that leads to significant cardiovascular morbidity and mortality worldwide. BP control is critical in reducing the end organ complications, such as stroke, myocardial infarction, heart failure, and kidney disease (Lam and Choy, 2007).

The various other types of hypertension are defined below (Mark, 2007 and Alagappan, 2002).

1. Isolated systolic hypertension is hypertension in which only the systolic (upper) reading is high. This occurs in people over age 65 and it is caused by hardening of the arteries.

2. White coat hypertension is caused by a person's anxiety or stress levels being very high. Some people get anxious and have high BP readings whenever they see doctors.

3. Labile hypertension is hypertension that sometimes patients have arterial pressure within the hypertensive range.

4. Malignant hypertension is a rare form of hypertension that is an emergency situation. Its symptoms set in very quickly and there is a risk of seizures, stroke or even death.

5. Pseudo hypertension is a false increase in BP recording due to stiff and noncompliant vessels, occuring in old age. In these individuals, actual intra-arterial BP is lower than the BP measured by a sphygmomanometer.

6. Accelerated hypertension is a significant recent increase in BP over previous hypertensive levels, associated with evidence of vascular damage on fundoscopic examination, but without papilledema.

7. Hypertensive urgency is a situation in which the BP is markedly elevated, but without any evidence of end organ damage. In this condition the control of the elevated BP can be done gradually.

8. Hypertensive emergency is a situation in which the BP is markedly elevated, but with evidence of some end organ damage. In this condition, the control of the elevated BP has to be done immediately.

9. Transient hypertension is systemic hypertension seen for a transient phase of time when the patient is under stress or when he is having disorder with a transient hypertensive phase, as may occur in conditions like

a) Acute cerebrovascular accident
b) Acute myocardial infarction
c) Acute glomerulonephritis
d) Acute intermittent porphyria
e) Pregnancy.

10. Episodic or paroxysmal hypertension is seen in pheochromocytoma. However, a patient with pheochromocytoma may be normotensive, hypotensive or hypertensive.

11. Parodoxical hypertension is a form of hypertension, patients paradoxically shows an increase in BP, even when on antihypertensive drugs. For example patients with diabetes and hypertension, on beta blockers, on developing hypoglycemia show a paradoxical rise in over previously well-controlled BP. This is because the excess adrenaline released secondary to hypoglycemia, act unopposed the α-1 receptors and thereby rasing the BP.

12. Hypertensive state is situation in which there is a marked increase in both diastolic blood pressure (DBP), occuring in normal individuals as during sexual intercouse or on diving in to cold water.

13. Postural hypertension is a type of hypertension. When BP is recorded in different position i.e. in lying, sitting and standing position and if there is a fall in systolic blood pressure (SBP) of more than 20 mmHg after standing for three minutes from the lying posture, the patient said to have postural hypertension.

2.1.2 Classification of hypertension

2.1.2.1 JNC 7 Guideline

In 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 Guideline) defined BP between 120/80 mmHg as normal BP and 139/89 mmHg as prehypertension. Hypertension is likely to present when a person's SBP is consistently 140 mmHg or greater with or without DBP of 90 mmHg or greater. Further it states individuals with prehypertension are at high risk of developing hypertension (Chobanian et al., 2003). Classification of blood pressure is given in Table 2.1

Table 2.1 JNC 7 Guideline (Chobanian et al., 2003)

BP Classification	SBP (mmHg)	DBP (mmHg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 Hypertension	140-159	or 90-99
Stage 2 Hypertension	≥160	or ≥100

BP = blood pressure

SBP = systolic blood pressure

DBP = diastolic blood pressure

2.1.2.2 BHS, ESH and WHO/ISH Guideline

The classification of The British Hypertension Society (BHS), The European Society of Hypertension-European Society of Cardiology (ESH) and The World Health Organization-International Society of Hypertension (WHO/ISH) are similar. The details of these guidelines are shown in Table 2.2 (Williams et al., 2004, ESH Guideline, 2003 and WHO/ISH Guideline, 1999).

Table 2.2 BHS, EHS and WHO/ISH Guidelines (Williams et al., 2004, ESH Guideline, 2003 and WHO/ISH Guideline, 1999).

Category	SBP (mmHg)	DBP (mmHg)
Optimal BP	<120	<80
Normal BP	<130	<85
High-normal BP	130-139	85-89
Grade 1 Hypertension (mild)	140-159	90-99
Grade 2 Hypertension (moderate)	160-179	100-109
Grade 3 Hypertension (severe)	≥180	≥110
Isolated Systolic Hypertension (Grade 1)	140-159	<90
Isolated Systolic Hypertension (Grade 2)	≥160	<90

2.1.3 Etiology

In 95% of hypertensive causes are unknown and termed as essential hypertension. However in 5% cases have specific case and are called as secondary hypertension.

2.1.3.1 Primary hypertension (Tierrney et al., 2004)

Primary hypertension has a multifactorial etiology. Genetic factor play an important role. Children with one-and more so with two-hypertensive parents have higher BP. Environmental factors also are significant. Increased salt intake and

obesity have long been incriminated. These factors alone are probably not sufficient to raise BP to abnormal levels but are synergistic with a genetic predisposition. Other factors that may be involved in the etiology of hypertension are following

a) Sympathetic nervous system hyperactivity
b) Renin-angiotensin system
c) Defect in natriuresis
d) Intracellular sodium and calcium levels
e) Environmental factor like obesity, sodium intake, alcohol intake, smoking, stress

2.1.3.2 Secondary hypertension (Williams, 2001 and Black et al., 2001)

Secondary hypertension is hypertension that is caused by an underlying medical condition. There are several causes of secondary hypertension. The most common causes such as renal, endocrine, neurogenic drugs and others are summarized in Table 2.3.

Table 2.3 Cause of secondary hypertension (Williams, 2001 and Black et al., 2001)

Causes	Examples
Renal causes	Acute and chronic glumerulonephritis (e.g. Chronic pyelonephritis, Polycystic renal disease) Primary sodium retention (e.g. Liddle's syndrome) Renovascular stenosis Renin-producing tumors Severe renal diseases (e.g. Arteriolar nephrosclerosis, Diabetic nephropathy)
Endocrine causes	Adrenocortical hyperfunction (e.g. Cushing's syndrome, Primary hyperaldosteronism) Pheochromocytoma Acromegaly Hypo and Hyperthyroidism
Neurogenic causes	Diencephalic syndrome Familial dysautonomia Increased intracranial pressure Polyneuritis Psychogenic
Drugs and exogenous hormone	Adrenergic drugs, alcohol, cocaine, cyclosporine, erythropoietin, glucocorticoids, mineral corticoids, NSAIDs
Miscellaneous causes	Coarction of aorta Increased intravascular volume Polyarteritis nodosa Hypercalcemia

2.1.4 Diagnosis

The diagnosis of hypertension is completely based on the multiple BP measurements, taken on separate occasions under nonstressful circumstances, preferably over a period of several weeks unless it is too high i.e. >210/120 (Black et al., 2001).

Blood pressure measurement: Many expert panels have made recommendations regarding the methodology of BP measurement, that frequently do not agree in all details, but several general principles can be extracted: (Chobanian et al., 2003, ESH Guideline, 2003, Black et al., 2001, O'Brien, 2003 and Scottish Intercollegiate Guideline Network, 2001)

• Use a properly maintained, calibrated and validated device

• Allow the patients to sit for at least 5 minutes in chair with feet on the floor and arm supported at heart level in a quiet room before beginning BP measurement

• Abstain the patient from smoking or tobacco use, drinking caffeine or alcohol-containing beverages, and exercise within 30 min before a BP measurement

• Remove tight clothing, support arm at heart level, ensure hand relaxed and avoid talking during procedure

• Use proper size cuff (Table 2.4)

Table 2.4 Blood pressure cuff sizes (Chobanian et al., 2003)

Cuff	Width (cm)	Length (cm)
Newborn	2.5-4.0	5.0-9.0
Infant	4.0-6.0	11.5-18.0
Child	7.5-9.0	17.0-19.0
Normal adult	11.5-13.0	22.0-26.0
Large adult	14.0-15.0	30.5-33.0
Thigh	18.0-19.0	36.0-38.0

• Listening over the brachial artery by using the bell of the stethoscope with minimal pressure exerted on the skin

• The “peak inflation level” of the mercury column should be determined by using palpitation of the radial artery before the stethoscope is applied. For subsequent BP measurements, cuff typically should be inflated 20 mmHg higher than the pressure at which the palpable pulse at the radial artery disappears

• The deflection rate of column of mercury should be 2-3 mmHg. The lower rate of deflection should be used for persons with heart rate less than 72 beat per minute (bpm); the more rate of deflection is appropriate only for tachycardia. If the precision of measurement is to be at least 2 mmHg, observer should have the opportunity to hear at least one Korotkoff sound at each 2-mmHg gradation of the mercury column

• Measurements of BP in both arms typically are obtained at the initial visit, and the arm with the higher BP is used thereafter if the difference is greater than 10/5 mmHg

• Take the mean of at least two readings. More reading are needed if marked differences between initial measurements are found

• Check BP first by palpitation to avoid the “silent gap".

Recommendations for follow up: Recommendations for the follow up based on initial BP measurements for adults without acute end organ damage is described in below Table 2.5 (Chobanian et al., 2003 and Williams et al., 2004).

Table 2.5 Recommendation for follow up (Chobanian et al., 2003 and Williams et al., 2004).

Class of hypertension	Blood pressure	Follow up Recommendation
Normal	<130/85	Recheck in 5 years
High normal	130-139/85-89	Recheck in 1 year
Stage 1 Hypertension	140-159/ 90-99	Confirm within 2 months
Stage 2 Hypertension	≥160/100	Evaluate or refer to source of care within 1 month

2.1.5 Complications of hypertension (Tierrney et al., 2004 and WHO/ISH, 2003)

Hypertension is usually symptom less but should be treated to reduce the risk of developing complications. The major complications due to hypertension are

a) Cardiovascular complications: Like Myocardial Infarction (MI), angina, Congestive Heart Failure (CHF), Left Ventricular Hypertrophy (LVH), left ventricular dysfunction

b) Cerebrovascular diseases: Like ischemic stroke, hemorrhagic stroke, transient ischemic attack, and dementia.

c) Renal disease

d) Peripheral vascular disease

e) Aortic aneurysm

f) Retinopathy

g) Accelerated (malignant) hypertension.

2.1.6 Treatment of hypertension

2.1.6.1 Goals of treatment (Chobanian et al., 2003, Williams et al., 2004 and ESH Guideline, 2003): The goals of treatment of hypertensive patients are

a) Primarily to reduce the risk of cardiovascular and renal morbidity and mortality

b) Secondarily attaining of the target BP <140/90 mmHg to reduce the cardiovascular complications. In patients having hypertension with diabetes or renal disease the goal of attaining target BP is <130/80 mmHg.

Antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40 percent; myocardial infarction, 20–25 percent; and heart failure, more than 50 percent (Neal et al., 2000). It was estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional

cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years would prevent 1 death for every 11 patients treated (Lorraine et al., 2000).

The elderly patients (age >50 years old) with hypertension the primary focus should achieve the SBP goal. In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mmHg (American Diabetes Association, 2003 and National Kidney Foundation Guideline, 2002).

2.1.6.2 Approach to patient:

I.Patient evaluation: Patient evaluation should include the following

A. Assessment of hypertensive patient: In addition to BP measurement, the assessment of hypertensive patient should be focused on following

- Complete medical history
- Physical examination (Table 2.6)
- Routine laboratory test and diagnostic procedure (Table 2.7)

Table 2.6 Physical examination (Chobanian et al., 2003)

• Appropriate BP measurement
• Fundoscopic abnormality
• Heart rate, rhythms, pulse
• Features of Cushing syndrome
• Skin stigmata of neurofibromatosis
• Palpation of enlarged kidneys
• Auscultation of abdominal murmurs
• Auscultation of precordial or chest murmurs
• Diminished and delayed femoral and reduced femoral blood pressure

Table 2.7 List of laboratory investigation

Routine tests	Recommended tests
Blood Analysis • Blood glucose • Serum creatinine • Serum potassium • Lipid Profile o Total cholesterol o High-density lipoprotein cholesterol o Triglycerides • Serum uric acid • Hemoglobin and haematocrit Urine analysis Electrocardiogram	• Echocardiogram • X-rays • Carotid (and femoral) ultrasound • C-reactive protein • Microalbuminuria (essential test in diabetics) • Quantitative proteinuria (if dipstick test positive)

B. Assessment of cardiovascular risk (CVD), target organ damage (TOD) and associated clinical condition (ACC): Decision about the management of hypertensive patients should not only take BP levels into account, but also the presence of other cardiovascular risk factors, target organ damages and associated clinical conditions. The details of the cardiovascular risk, target organ damage, and associated clinical conditions are given in Table 2.8 (Chobanian et al., 2003, Williams et al., 2004, ESH Guideline, 2003 and WHO/ISH, 2003)

Table 2.8 Cardiovascular risk factor, target organ damage and associated clinical condition (Chobanian et al., 2003, Williams et al., 2004, ESH Guideline, 2003 and WHO/ISH, 2003)

Risk factors for cardiovascular disease	Hypertension (grades 1-3) Men > 55 years, Women > 65 years Smoking Family history of CVD Obesity (BMI $\geq$30 kg/m^2) Dyslipidemia
Target-organ damage	Heart LVH (ECG or ECHO) Angina/prior MI Heart Failure Brain Stroke Dementia Chronic kidney disease Peripheral arterial disease Retinopathy
Associated clinical conditions	Diabetes Cerebrovascular disease Ischemic stroke Cerebral hemorrhage Transient ischemic attack Heart disease Myocardial infarction Angina Coronary revascularization Congestive heart failure Renal disease Plasma creatinine concentration Female >1.4 or Male > 1.2 mg/dl Albuminuria > 300 mg /day Peripheral vascular disease

II. Risk stratification: Based on the above cardiovascular risk, target organ damage and associated clinical condition along with assessment of the blood pressure severity of hypertension, further patients can be allocated to a range of risk for cardiovascular disease. This includes three major risk cardiovascular events (fatal and non-fatal stroke and myocardial infarction) within the next 10 years: (I) Low risk – less than 15%; (II) Medium risk – 15-20%; and (III) High risk – greater than 20%. However some of guidelines extended it to fourth class i.e. very high risk when risk exceeds more than 30%. A modified risk stratification table is given in Table 2.9 (WHO/ISH Guideline, 1999, Scottish Intercollegiate Guideline Network, 2001 and WHO/ISH, 2003).

Table 2.9 Stratification of risk (WHO/ISH Guideline, 1999, Scottish Intercollegiate Guideline Network, 2001 and WHO/ISH, 2003)

Blood pressure	Risk factors and disease history		
	No risk factors	1 – 2 risk factors	3 or more risk factor or TOD, or ACC
Grade 1	Low risk	Medium risk	High risk
Grade 2	Medium risk	Medium risk	High risk
Grade 3	High risk	High risk	High risk

2.1.6.3 Lifestyle modifications: Lifestyle modifications are an important intervention both from a public health perspective and in the routine management of the individual hypertensive patient. Nevertheless, lifestyle modifications must be pursued as the first-line in the management of hypertension since such therapies are safe, inexpensive and, when combined with pharmacotherapy, may result in better BP control and improved quality of life. A variety of lifestyle modifications have been shown, in clinical trials, to lower BP (Ebrahim and Smith, 1998). Some of the important major lifestyle modifications are discussed below.

I. Weight reduction: The risk of hypertension and hypercholesterolemia were strongly associated with weight gain. A study suggests that for 10 kg weight loss, decreases of 4.6 mmHg and 6.0 mmHg in DBP and SBP respectively (Aucott et al, 2005). A higher intensity of medical treatment is needed to achieve BP control in obese hypertensive patients characterized by insulin resistance (Saito et al., 2003). Among hypertensive overweight adults already on antihypertensive medication, a comprehensive lifestyle intervention can substantially lower the BP and improve its control.

II. Smoking cessation: Smoking has been a risk factor for all-cause, non-cardiovascular and cancer mortality, as well as fatal and non-fatal stroke. However; smoking cessation is associated with small increase in BP (Janzon et al., 2004) the evidence shows that smoking aids the major risk factors for mortality from stroke and coronary heart disease among the elderly and very old hypertensive patient (Khalili, 2002). Thus, it is critical that person with raised BP are advised to stop smoking.

III. Physical activity: It is a sign of modern times that increasing rates of urbanization and associated behavioral changes have led to a higher prevalence of a sedentary lifestyle and less exercise. A sedentary lifestyle is associated with an increased risk of cardiovascular disease (Wannamethee, 1998). Meta-analysis of randomized controlled trial has shown that a regular aerobic physical activity can reduce 1.81-3.35 mmHg and 2.72-4.97 mmHg of DBP and SBP respectively (Whelton et al., 2002).

IV. Moderation of alcohol consumption: Daily alcohol consumption was associated with elevation in the BP. However, light consumption of alcohol does not affect BP (Okubo et al., 2001). A meta-analysis of randomized controlled trials shows that alcohol reduction for longer duration results in reduction of 3.24 and 2.22 mmHg of SBP and DBP respectively (Xin et al., 2001). So it has been recommended that alcohol moderaration should be a component of lifestyle modification for prevention and treatment of hypertension among drinkers.

V. Reduction in salt intake and other dietary change: Dash diet and reduced sodium intake lower BP substantially. The short-term reduction in sodium intake may be associated with a lower long-term risk of hypertension. Control diet lower sodium intake decreased BP by 7.0/3.8 mmHg in those older than 45 years of age and by 3.7/1.5 mmHg in those 45 years of age or younger (Vollmer et al., 2001).

2.1.6.4 Pharmacological treatment: There are many groups of antihypertensives, which—by varying means—act by lowering blood pressure (which lowers the blood pressure by different mechanism). However, these agents differ in side effect profiles, cost and efficacy; especially, the efficacy in preventing the important "endpoints" of hypertension such as heart attack, stroke and heart failure.

1. ACE inhibitors such as captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril
2. Angiotensin II receptor antagonists such as losartan, irbesartan, valsartan, candesartan, telmisartan,
3. Calcium channel blockers such as nifedipine, amlodipine, diltiazem, verapamil
4. Diuretics such as bendroflumethiazide, chlortalidone, hydrochlorothiazide (also called HCTZ), furosemide or spironolactone
5. Alpha blockers such as prazosin, terazosin, doxazosin
6. Beta blockers such as atenolol, labetalol, metoprolol, propranolol
7. Direct renin inhibitors such as aliskiren

The combination products usually contain HCTZ and one other drug. The advantage of fixed dose combinations resides in the fact that they increase compliance with treatment by reducing the number of pills taken by the patients. A fixed dose combination of the ACE inhibitor (perindopril) and the calcium channel blocker (amlodipine), recently been proved to be very effective even in patients with additional impaired glucose tolerance and in patients with the metabolic syndrome (Widimský 2009).

2.1.6.5 Choice of pharmacological agents: The JNC 7 Guideline gave recommendations for managing hypertension. According to the guideline, thiazide-type diuretic is the first-line antihypertensive choice for most patients. The other first-line treatment options are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium-channel blockers, beta-blockers, and combination therapy with >1 of these potential first-line treatment choices. For patients with compelling indications such as diabetes, heart failure (HF), post-myocardial infarction (post-MI), and chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, serum creatinine >1.3 mg/dL in women or >1.5 mg/dL in men, >200 mg albumin/g creatinine, or urinary albumin excretion >300 mg/d), the JNC 7 guideline included more specific recommendations regarding drug choice. The indications, contraindications and precautions for each class of drugs are given in Table 2.10 (Chobanian et al., 2003).

Table 2.10 Indication, precaution and contraindication of major class of drugs (Chobanian et al., 2003)

Drugs	Compelling indications	Precautions	Contraindications
ACE Inhibitors	Diabetic Nephropathy Coronary artery disease (CAD) Heart failure Post MI Stroke prevention Chronic renal disease	Renal impairment, Peripheral vascular disease	Pregnancy, renovascular disease
Angiotensin receptor blockers	ACE I Intolerance Diabetic nephropathy Heart failure Post MI Chronic renal disease	Renal impairment, peripheral vascular disease	Pregnancy, renovascular disease
Beta blockers	Angina Heart failure, Post MI	Diabetes, heart failure	Asthma / COPD, heart block
Calcium channel blockers	Angina ISH Post MI Elderly Diabetes	Use with beta blockers	Heart Block, Heart failure
Thiazide diuretics	Elderly ISH Heart failure Stroke prevention	Diabetes (high dose)	Gout
Alpha Blockers	Benign prostatic hypertrophy	Postural hypertension, Heart failure	Urinary Incontinence

In 2004, the British Hypertension society produced a comprehensive set of guidelines, endorsing the AB/CD algorithm. The AB/CD algorithm comed from the printed letters of the medicine group:

A= angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonists

B = beta blockers

C = calcium channel blockers

D = thiazide or thiazide-like diuretics

A is grouped with B and C is grouped with D (see figure 2.1). This grouping was based on the capacity of drugs to inhibit (A or B) or not inhibit (C or D) components of the renin-angiotensin system (RAS). In general, A or B drugs are more effective initial therapy in younger patients (< 55 years) in whom the RAS is generally more active. C + D drugs are generally more effective as initial therapy in older patients (≥55 years) and black adults at any age, in whom the RAS is usually less active. This formed the basis for initial drug selection at step 1. When there is a need to add a second drug (most patients), combining A or B with C or D will be suggested. In those requiring further medication, A or B + C + D are introduced at step 3. In patients with more resistant hypertension, the addition of an alpha-blocker, low dose spironolactone (i.e. 25 mg daily) or an alternative additional diuretic can be used. The AB/CD algorithm is a guidance to practice and provide a standardized template that allows physicians to select initial and subsequent treatments from all of the major classes of drug therapy. The algorithm is designed to place the emphasis on BP control (William et al, 2004).

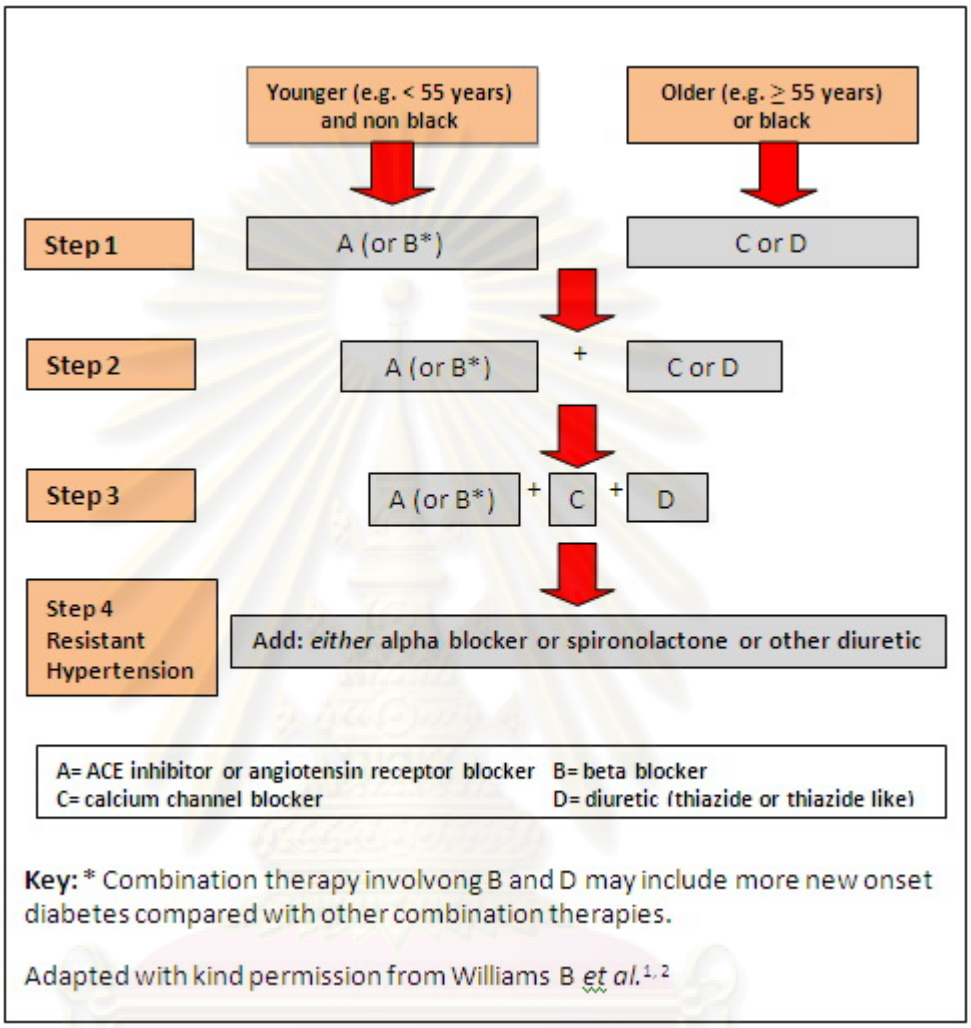

Figure 2.1: Illustration of AB/CD algorithm (William et al, 2004)

In 2006, The National Institute for Health and Clinical Excellence, launched "Hypertension: management of hypertension in adults in primary care Guideline". This guideline downgraded the role of beta-blockers due to their risk of provoking type 2 diabetes (The Newcastle Guideline Development and Research Unit, 2006)

2.1.7 Overview of Angiotensin II (AII) receptor blockers (ARBs)

2.1.7.1 Role of the Renin-Angiotensin System (RAS) in Hypertension

Renin is an enzyme secreted into the blood from specialized cells that encircle the arterioles at the entrance to the glomeruli of the kidneys (the renal capillary networks that are the filtration units of the kidney). The renin-secreting cells, which compose the juxtaglomerular apparatus, are sensitive to changes in blood flow and blood pressure. The primary stimulus for increased renin secretion is decreased blood flow to the kidneys, which may be caused by loss of sodium and water (as a result of diarrhea, persistent vomiting, or excessive perspiration) or by narrowing of a renal artery. Renin catalyzes the conversion of a plasma protein called angiotensinogen into a decapeptide (consisting of ten amino acids) called angiotensin I. An enzyme in the serum called angiotensin-converting enzyme (ACE) then converts angiotensin I into an octapeptide (consisting of eight amino acids) called angiotensin II. Angiotensin II acts via receptors in the adrenal glands to stimulate the secretion of aldosterone, which stimulates salt and water reabsorption by the kidneys, and the constriction of small arteries (arterioles), which causes an increase in blood pressure. Angiotensin II further constricts blood vessels through its inhibitory actions on the norepinephrine reuptake into nerve terminals (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2007).

The major breakthrough of the renin-angiotensin system is triggered by the development of orally active angiotensin-converting enzyme (ACE) inhibitors (Ferguson et al., 1977, Brunner et al., 1978, 1979, Turini et al., 1979, Faxon et al., 1980). ACE inhibitors, which block the formation of angiotensin II, are used in treating high blood pressure which is produced by excessive constriction of the small arteries. ACE inhibitors are recognized as an important therapeutic step to control blood pressure in hypertensive patients and to reduce morbidity and mortality in patients with congestive heart failure (The Consensus Trial Study Group, 1987). In addition, because of their ability to lower proteinuria, ACE inhibitors have become an essential component of the treatment of chronic renal diseases to delay the progression

of renal failure (Lewis et al., 1993). ACE inhibitors are also very effective in reducing cardiovascular morbidity and mortality in patients with a high cardiovascular risk profile, including diabetics (The Heart Outcomes Prevention Evaluation study investigators, 2000).

ACE inhibitors are unable to block the effect of angiotensin II produced locally by systems other than the RAS or to prevent formation of angiotensin II by enzymes other than ACE, including endopeptidase and chymases (Timmermans et al., 1995). The rationale for developing specific angiotensin II receptor inhibitors is, therefore, to antagonize the activity of this crucial effector hormone independently of its source.

ARBs inhibit the renin-angiotensin system by selectively blocking the AT1 subtype of AII receptors (Timmermans et al., 1993). ARBs are primarily used for the treatment of hypertension where the patient is intolerant of ACE inhibitor therapy. The characteristics of ARBs contribute to treatment success are twenty-four-hour blood pressure control, rapid treatment response, and excellent tolerability profiles. As surges in blood pressure occur in the early morning, 24-hour BP control is necessary to effectively reduce cardiovascular risk. Single doses of ARBs administered in ambulatory BP monitoring studies have been shown to control blood pressure throughout the day and night. In addition, BP reductions have been noted as early as 2 weeks after the start of treatment, and in an irbesartan trial, 33% of severely hypertensive patients reached the primary outcome of blood pressure control (DBP<90 mmHg) after 5 weeks of treatment (Venkata and Ram, 2008).

ARBs are also used for the treatment of heart failure in patients intolerant of ACE inhibitor therapy, particularly candesartan. Irbesartan and losartan have trial data showing benefit in hypertensive patients with type II diabetes, and may delay the progression of diabetic nephropathy. Candesartan is used experimentally in preventive treatment of migraine.

However in specific patient populations require caution. As ARBs modulate the renin-angiotensin system, the development of hypotension and hyperkalemia should be monitored carefully. Hypotension, for example, has been observed in volume- or salt-depleted patients, and dose adjustments should be considered for patients with impaired hepatic or renal function. ARBs also are contraindicated in pregnancy, hyperkalemia, and bilateral renal artery stenosis. Several other classes of antihypertensive drugs that do not modulate the renin-angiotensin system are available as alternatives for BP control in such patients.

ARBs differ in potencies in relation to BP control. When it is used in clinical practice, its uses may vary based on the degree of blood pressure response required.

2.1.7.2 Adverse effects

ARBs are usually well-tolerated, with common adverse drug reactions (ADRs) including: dizziness, headache, and hyperkalemia. Infrequent ADRs associated with therapy include: first dose orthostatic hypotension, rash, diarrhea, dyspepsia, abnormal liver function, muscle cramp, myalgia, back pain, insomnia, decreased haemoglobin levels, renal impairment, pharyngitis, and nasal congestion (Rossi, 2006).

They do not inhibit the breakdown of bradykinin or other kinins, so they are only rarely associated with the persistent dry cough and angioedema that limit ACE inhibitor therapy.

2.2 Overview of losartan and irbesartan

Despite ARBs have same common mechanism of action, pharmacologic differences that could result in different efficacy and tolerability profiles do exist among the AT1 blockers.

2.2.1 Losartan

Losartan is the first orally active competitive AT_1 receptor antagonist available on the market (Wong et al., 1990 and Christophe et al., 1995). It is currently marketed by Merck & Co. under the trade name Cozaar. Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is shown in Figure 2.2:

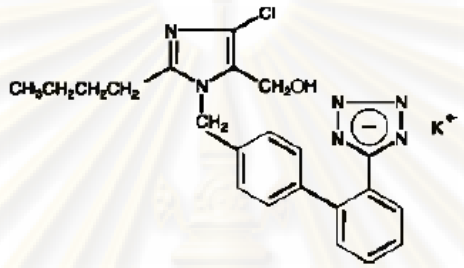

Figure 2.2: Illustration of structural formula of losartan

It is a prototype highly selective AT_1 receptor antagonist derived from the Takeda series of 1-benzylimidazole-5-acetic acid derivatives recognized to be weak angiotensin II antagonists (Dzau et al., 1993). Losartan and its metabolite are excreted by the kidney and in bile. Neither compound is dialysed.

Losartan is indicated for the treatment of hypertension. The recommended initial and maintenance dosage of losartan potassium as monotherapy in patients with essential hypertension is 50 mg once daily. Some patients may benefit from 100 mg per day. Losartan potassium may be given with or without food. In patients at high risk of hypotension or volume depletion and those with hepatic dysfunction, the initial dose should be 25 mg. No dosage adjustment is needed for the elderly or patients with renal impairment. Losartan potassium is not recommended for use in pregnant women because of the risk of fetal morbidity and mortality.

Losartan may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours) (Rossi, 2006).

ARBs are not usually considered first-line, because of the proven efficacy and lower costs of thiazide diuretics and beta blockers. However, losartan may be used first-line in patients with increased cardiovascular risk. The LIFE study demonstrated that losartan was significantly superior to atenolol in the primary prevention of adverse cardiovascular events (myocardial infarction or stroke), with a significant reduction in cardiovascular morbidity and mortality for a comparable reduction in BP (Dahlöf et al., 2002).

Much of the AII-inhibiting effect of losartan could be attributed to its active metabolite, EXP 3174,8,9 which is a noncompetitive AT1 blocker (Christophe et al. 1995 and Wong et al., 1990). The oral bioavailability of losartan is approximately 33% with nearly 14% of the administered dose being converted to the active metabolite (Lo et al., 1995 and Johnston et al., 1995). Food slightly delays its absorption (US FDA Medical Review for Cozaart, 1995). Losartan and EXP 3174 had plasma half-lives of 2 h and 6 to 9 h, respectively, and volumes of distribution of approximately 34 L for losartan and 10 L for EXP 3174.8–10. Due to the long duration of activity of EXP 3174, losartan might be administered once daily in the treatment of hypertension (Bauer et al., 1995).

Losartan is a uricosuric and can cause hyperkalemia. Hence, potassium supplements or salt substitutes containing potassium should not be used without consulting the prescribing physician or pharmacist.

Losartan potassium has been investigated both as monotherapy and in combination with hydrochlorothiazide in randomized double-blind multicenter clinical trials (Nelson et al., 1991, Gradman et al., 1995, Weber et al., 1995 and Dunlay et al., 1995) 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 hypertension. The primary efficacy measure was mean absolute change from baseline in trough supine or sitting DBP and SBP. The percentage of patients rates as 'responders' (trough DBP <90 mmHg or DBP ≥90 mmHg but reduced by ≥10 mmHg) has been assessed in some instances.

Nelson et al. first reported the efficacy of losartan potassium in dosage ≥50 mg daily in hospitalised patients. Subsequently, losartan potassium in the 50 mg per day dosage has proved to be efficacious and superior to placebo in large placebo-controlled dose-finding trials in outpatients (Nelson et al., 1991).

Benefits of the 100 mg daily dosage were similar to those of 50 mg per day (Gradman et al., 1995 and Weber et al., 1995). This latter regimen has been adopted as the usual starting and maintenance dosage in patients with mild to moderate hypertension.

Although some patients with severe hypertension have been maintained with losartan potassium monotherapy after 12 weeks, (Dunlay et al., 1995) most required addition of a diuretic with or without other antihypertensive agents.

2.2.2 Irbesartan

Irbesartan is a longer acting AT_1 receptor antagonist than Losartan. It also has a high affinity for the AT_1 receptor and no affinity for AT_2 receptors. Irbesartan was developed by Sanofi Research (now part of sanofi-aventis). It is jointly marketed by sanofi-aventis and Bristol-Myers Squibb under the trade names Aprovel, Karvea, and Avapro. Structurally, it contains an imidazolinone ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the C5 hydroxymethyl group of losartan (Reeves et al., 1998). Its empirical formula is $C_{25}H_{28}N_6O$, and its structural formula is shown in Figure 2.3

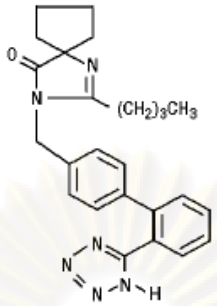

Figure 2.3: Illustration of structural formula of irbesartan

In contrast to losartan, irbesartan doesn't form any active metabolite. It is cleared predominantly by the bile (80%) and partly by the kidney (20%). Irbesartan has a large volume of distribution (53 to 93 L versus 12 L for EXP 3174 and 17 L for valsartan). Clinically, irbesartan has been evaluated at doses up to 900 mg/d. Irbesartan induced a dose-related blood pressure response, with a plateau at 300 mg (Reeves et al., 1998).

Irbesartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. Irbesartan may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, (Lewis et al., 2001) hypertension and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours) (Rossi, 2006).

Irbesartan is also available in a combination formulation with a low dose thiazide diuretic, hydrochlorothiazide, to achieve an additive antihypertensive effect. Irbesartan/hydrochlorothiazide combination preparations are marketed under similar trade names to irbesartan preparations, including Irda, CoIrda, CoAprovel, Karvezide, Avalide and Avapro HCT. A large randomized trial following more than 4100 men and women with heart failure and normal ejection fraction (>=45%) over 4 years found no improvement in study outcomes or survival with irbesartan as compared to placebo (Massie et al., 2008).

Irbesartan is a long acting AT1 blocker which does not require biotransformation for its pharmacologic activity (Cazaubon et al.1993). In vitro binding studies indicate that irbesartan is a competitive antagonist; however, in isolated rabbit aorta, it behaved as a noncompetitive (or insurmountable) antagonist of the AT1 receptor, i.e, it affects both the slope and the maximum response of the concentration and effect relationship (Vachharajani et al. 1995). The oral bioavailability of irbesartan ranged from 60% to 80% and its absorption is unaffected by food. Irbesartan is lipophilic and its volume of distribution averages from 53 to 93 L; it displays linear, dose-dependent pharmacokinetics and has a plasma half-life averaging 11 to 15 h (Necciari et al., 1994 and Marino et al., 1997).

Along with irbesartan pharmacological effects, they can cause unwanted side effects, which usually are improve as patients' bodies adjust to the new medicine. Possible side effects include diarrhea, indigestion, flushing, a fast fluttery heartbeat, cough, sexual problems, headache, ringing in the ears, changes in taste, feeling or being sick, muscle pain, fatigue, rare cases of allergic skin reactions, as well as localised swelling of the face, lips and tongue have been reported in patients taking irbesartan (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2007).

Once-daily administration of irbesartan provided 24-hour control of blood pressure. In patients with mild-to-moderate hypertension irbesartan was as effective as enalapril, atenolol and amlodipine, and more effective than valsartan in terms of absolute reduction in BP and response rates (Pool et al., 1998).

Early randomized, placebo-controlled studies showed that irbesartan 75-300 mg once daily for 6-12 weeks led to significantly ($p<0.01$) greater reductions in both DBP and SBP than placebo in patients with mild-to-moderate hypertension (Fogari et al., 1997, Pool et al., 1998 and Guthrie et al., 1998). Decreases in BP were apparent within weeks of commencing treatment, (Fogari et al., 1997, Pool et al., 1998 and Guthrie et al., 1998) with maximum reductions being achieved after 2-6 weeks and were dose-related, plateauing above 300 mg daily (Reeves et al., 1998). Irbesartan

150-300 mg once daily produce placebo-subtracted reductions in trough seated BP of approximately 8-10/5-6 mmHg (Reeves et al., 1998). Studies involving ambulatory BP measurements have confirmed that irbesartan maintains control of BP over 24 hours (Coca et al., 2002, and Mancia et al., 2002). A trough-to-peak ratio of at least 0.6 was generally achieved with once-daily dosages of 150 mg or above (Oparil et al., 2001, and Reeves et al., 1998).

2.3 Literature reviews on losartan and irbesartan

Losartan potassium reduced trough BP in patients with mild to moderate hypertension to a similar extent to the standard antihypertensive agents with which it has been compared e.g. enalapril, atenolol, felodipine extended release (ER). Supine or sitting DBP fell by an average of 8 to 13 mmHg during 8 to 12 weeks' treatment with losartan potassium 50 to 100 mg daily, compared with 10 to 14 mmHg for the other drugs (Weber et al., 1995, Nelson et al., 1991, Gradman et al., 1995, Tikkanen et al., 1995, Mallion et al., 1995, Dahlöf et al., 1995 and Chan et al., 1995).

The largest mean decrease in DBP by losartan potassium (13.2 mmHg) occurred in a study of 132 elderly patients: felodipine ER caused a reduction of 14 mmHg (Chan et al., 1995). A significant difference in DBP favoring felodipine at week 6 disappeared at week 12. Dosage titration was needed at week 6 in 62% of losartan potassium recipients and 51% of patients given felodipine ER.

Percentage responders did not differ significantly between the losartan potassium group (69%) or the felodipine group (76%) (Chan et al., 1995) or an atenolol group (50 vs 65%) (Dahlöf et al., 1995).

There has been one comparison with captopril which was given in a once daily regimen (Mallion et al., 1995). Losartan potassium produced a significantly larger decrease in DBP but not SBP at weeks 6 and 12. At week 12, the percentage of responders for losartan potassium (50%) was nearly twice that for captopril (29%).

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, (Tikkanen et al., 1995) measurement of trough blood pressure values using a per protocol analysis showed no differences in blood pressure reductions or percentage responders between the two 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, (Gradman et al., 1995) clinically relevant reductions were manifest within 1 to 2 weeks of starting therapy with losartan potassium 50 to 150 mg daily or enalapril 20 mg daily and were maximal at 3 to 6 weeks after treatment initiation. Similarly, Dahlöf et al. found that antihypertensive efficacy reached a plateau at 6 weeks, with no further reduction discernable at 12 weeks. (Dahlöf et al., 1995).

In randomized clinical trials against active comparators, once-daily irbesartan was as effective at reducing BP as enalapril, (Lacourciere, 2000, Mimran et al., 1998, Coca et al., 2002, Chiou et al., 2000), atenolol (Stumpe et al., 1998) and amlodipine (Neutel et al., 1999). It was significantly more effective than valsartan in the only trial that statistically compared the efficacy of these two drugs, (Mancia, et al., 2002) and at least as effective at reducing trough DBP as once-daily losartan, (Kassler-Taub et al., 1998 and Oparil et al., 1998) but less effective at reducing DBP than olmesartan (Oparil et al., 2001). Response rates with irbesartan 150-300 mg once daily were 36-72% compared with 43-68% for comparator agents.

Mancia et al. found that irbesartan 150 mg once daily was significantly more effective than valsartan 80 mg once daily for both absolute reduction in DBP and SBP and response rate (including normalisation rate) as assessed by mean seated BP and ambulatory BP. Mean reduction in ambulatory DBP at trough (the primary efficacy parameter) was 7 mmHg for irbesartan versus 5 mmHg for valsartan (p=0.035) (Mancia, et al., 2002).

Kassler-Taub et al. found that after 8 weeks of treatment, reductions from baseline in trough seated diastolic blood pressure (SeDBP) and trough seated systolic blood pressure (SeSBP) with 300 mg irbesartan were greater than with 100 mg losartan ($P < .01$ for both comparisons), by 3.0 and 5.1 mmHg, respectively; larger reductions were also demonstrated at weeks 1 and 4 ($P < .01$ and $P = .017$, respectively, for SeDBP). Throughout the study, the antihypertensive effect of 150 mg irbesartan did not differ significantly from that of 100 mg losartan (Kassler-Taub et al., 1998).

Oparil studied in a study in which doses were titrated according response, the change from baseline in DBP after 8 weeks' monotherapy was significantly greater (by 2 mmHg) in patients receiving irbesartan 150-300 mg once daily than losartan 50-100 mg once daily (Oparil et al., 1998). Differences in SBP and response rates (including normalisation) were not significant. Moreover, after a further 4 weeks, when add-on therapy was allowed, significantly greater effects on both DBP and SBP, and also response rate, were reported for the irbesartan group compared with those receiving losartan (Oparil et al., 1998).

Oparil et al. also investigated deeper in recipients who used olmesartan 20 mg once daily had a significantly greater reduction (by approximately 2 mmHg) in seated DBP than patients who received irbesartan 150 mg once daily after 8 weeks' treatment (Oparil et al., 2001). However, there was no significant between-group difference neither in the effect on SBP, nor for change in mean 24-hour ambulatory BP, assessed as a secondary parameter (11/7 vs 13/9 mmHg). For comparing between losartan and irbesantan, they found that the reduction of sitting cuff DBP of irbesartan was significantly greater than losartan (9.9 and 8.2 mmHg, respectively). The reduction in mean 24-hour DBP of losartan was lower than irbesartan (6.2 and 7.4 mmHg, respectively). The reduction in mean 24-hour SBP with irbesartan was significantly greater than losartan (11.3 and 9.0 mmHg, respectively) (Oparil et al., 2001).

The studies of Lacourciere, Coca et al. and Chiou et al have shown in terms of absolute reduction in BP and response rates for 8-12 weeks duration. Irbesartan 150-300 mg once daily shows similar efficacy to enalapril 10-20 mg once daily in patients with mild-to-moderate hypertension, including those aged ≥ 65 years; (Lacourciere, 2000, Coca et al., 2002 and Chiou et al., 2000) an other study found irbesartan 75-300 mg once daily to be similar to enalapril 10-40 mg once daily (Mimran et al., 1998). Whereas, irbesartan and enalapril also produced similar reductions in mean 24-hour ambulatory BP (Coca et al., 2002 and Chiou et al., 2000).

Stumpe et al. did a long-term study, in which dose titration was allowed from week 6 and add-on therapy from week 12. Irbesartan 75-150 mg once daily and atenolol 50-100 mg once daily showed similar efficacy at both 12 weeks (on monotherapy) and 24 weeks (after add-on therapy was allowed) (Stumpe et al., 1998).

Bays claimed his result of a 4-week, open-label, practice-based post-marketing surveillance study involving 7314 patients with mild-to-moderate hypertension (baseline SeDBP 90-115 mmHg) treated with irbesartan 150 mg once daily, the mean reduction in BP was 16/9 mmHg at the end of treatment, and the response rate was 77% (Bays et al., 1999). Subgroup analysis indicated that age, race and sex had no effect on the extent of BP reduction, but patients with a baseline DBP>110 mmHg had the greatest reduction in DBP (21 mmHg).

Littlejohn's long-term efficacy data study (≥ 12 months) total 821 patients from a pooled analysis of five open-label extension studies, during which irbesartan was started at a dosage of 75 mg once daily (150 mg once daily in one study) and titrated to a maximum of 300 mg once daily. If a target BP of 140/90 mmHg was not achieved, additional antihypertensive agents were added, most commonly hydrochlorothiazide. After 12 months, the mean reduction in seated BP from baseline (155/101 mmHg) was 21/16 mmHg and blood pressure had been normalised in 83% of patients. Of these patients, 64% were receiving irbesartan monotherapy and 21% were receiving irbesartan plus hydrochlorothiazide. At 24 months (130 evaluable patients), the mean BP reduction was 17/15 mmHg (Littlejohn III et al., 1999).

Ekman M et al. concluded that the results from his study indicate that irbesartan provides a cost-effective antihypertensive treatment strategy compared with losartan (Ekman et al., 2008)

Dang et al. studied by treatment patients for 4 weeks with losartan 50 mg or irbesartan 150 mg. After 4 weeks, patients with SeDBP <90 mmHg and SeSBP < 140 mmHg continued the same dose regimen for another 4 weeks. If blood pressure was not controlled after 4 weeks of treatment, the dose of either regimen was doubled to losartan 100 mg and irbesartan 300 mg. There were 351 patients randomized (176 to losartan and 175 to irbesartan), and of these, 325 patients completed the study (162 in the losartan group and 163 in the irbesartan group). They found that BP declined comparably in both groups from 151/92 mmHg at baseline to 137/83 and 135/83 (losartan and irbesartan, respectively, NS) (Dang et al., 2006).

In this study, we tried to prove whether 50 mg losartan and 150 mg irbesartan once a day can reduce SeDBP and SeSBP. Then we compared antihypertensive effect of the two drugs namely, 50 mg losartan and 150 mg irbesartan and gender (two independent variables) controlling for baseline BP and age (two covariates).

CHAPTER III

METHODOLOGY

3.1 Study design

This study was a retrospective study. The data were collected from computerized Saraburi hospital main database. The study was planned to prove whether losartan and irbesartan can reduce seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) and to compare efficacy of losartan and irbesartan—two AT1 receptor antagonists with different pharmacokinetic and pharmacodynamic profiles in lowering SeDBP and SeSBP in hypertensive patients at Saraburi hospital during January 1, 2008 to June 30, 2008.

3.2 Consideration of Patient Participation

The study protocol was reviewed for approval by the staff of Chulalongkorn Ethic Committee.

3.3 Population

The population framework for this study was all hypertensive patients who were prescribed losartan 50 mg once daily or irbesartan 150 mg once daily for hypertensive treatment during January 1, 2008 to June 30, 2008. Exclusion criteria included concomitant diseases and medications e.g., drugs known to affect blood pressure that might interfere with the assessment of efficacy. Simple random technique generated randomized sampling number by computer was employed to select samples from computerized Saraburi hospital main database. It yielded 1,051 patients.

3.4 Sample size

Sample size was calculated by using Cohen's table 4.6 page 348. The Type I error 0.05, power 0.90 and effect size 0.15 were set to generate 196 samples in each group (total n=392) (Cohen, 1988).

3.5 Sampling method

The samples were the patients who were prescribed losartan 50 mg once daily or irbesartan 150 mg once daily for hypertensive treatment during January 1, 2008 to June 30, 2008.

All data from computerized Saraburi hospital main data base were in Microsoft Office Access file from two different sources (files). The first file contained HN, birthday, age, gender, occupation, stockcode, dose, dosage, quantity, ICD-10 code (Figure 3.1).

HN	Birthday	Age	Gender	Occupation	STOCKCODE	Type	DoseT	DoseQTYC	Unit	Dose	Qn	ICDCODE
3902085	19-Aug-53	56.15	1	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	15	I10
3902085	19-Aug-53	56.15	0	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	30	I10
3902085	19-Aug-53	56.15	1	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	30	I10
3902085	19-Aug-53	56.15	1	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	30	I10
3902085	19-Aug-53	56.15	1	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	30	I10
3902085	19-Aug-53	56.15	0	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	10	I10
3902085	19-Aug-53	56.15	1	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	10	I10
3902085	19-Aug-53	56.15	0	พ่อบ้าน	2068110	T	กิน	1	เม็ด	od-pc	10	I10

Figure 3.1 Illustration of the first file in Microsoft Office Access from computerized Saraburi hospital main database

The second file contained HN and all laboratory data such as clinical chemistry, hematology, blood pressure (Figure 3.2).

HN	Visitdate	Group	Lab	Code	Result
3902085	03-Jan-08	Clinical Chemistry	Sodium	C005	141.6
3902085	03-Jan-08	Hematology	RDW		18.7
3902085	03-Jan-08	Hematology	Lympho %	H01DB	30
3902085	03-Jan-08	Hematology	Mono %	H01DC	4
3902085	03-Jan-08	BP	BP-Low	BP	100
3902085	03-Jan-08	BP	BP-high	BP	156
3902085	05-Mar-08	BP	BP-Low	BP	84
3902085	05-Mar-08	BP	BP-high	BP	122

Figure 3.2 Illustration of the second file in Microsoft Office Access from computerized Saraburi hospital main database

These two data files were linked by HN and were retrieved in one Microsoft Office Access file. We used key words 50 mg losartan or 150 mg irbesartan and ICD-10 code I10 (essential (primary) hypertension) or code I15 (secondary hypertension). It yielded 1,051 patients. Then all data were transferred from Microsoft Office Access form to Microsoft Office Excel form. We recruited only patients with SeDBP $\geq$ 90 mmHg or SeSBP $\geq$ 140 mmHg. It yielded only 951 patients. The two hundred random numbers were generated by Microsoft Office Excel program for each group of patients who were in 50 mg losartan or 150 mg irbesartan group. Finally we got four hundred patients and used SPSS Program for analyzing data.

Flow chart of collecting and analyze main database process in Saraburi Hospital

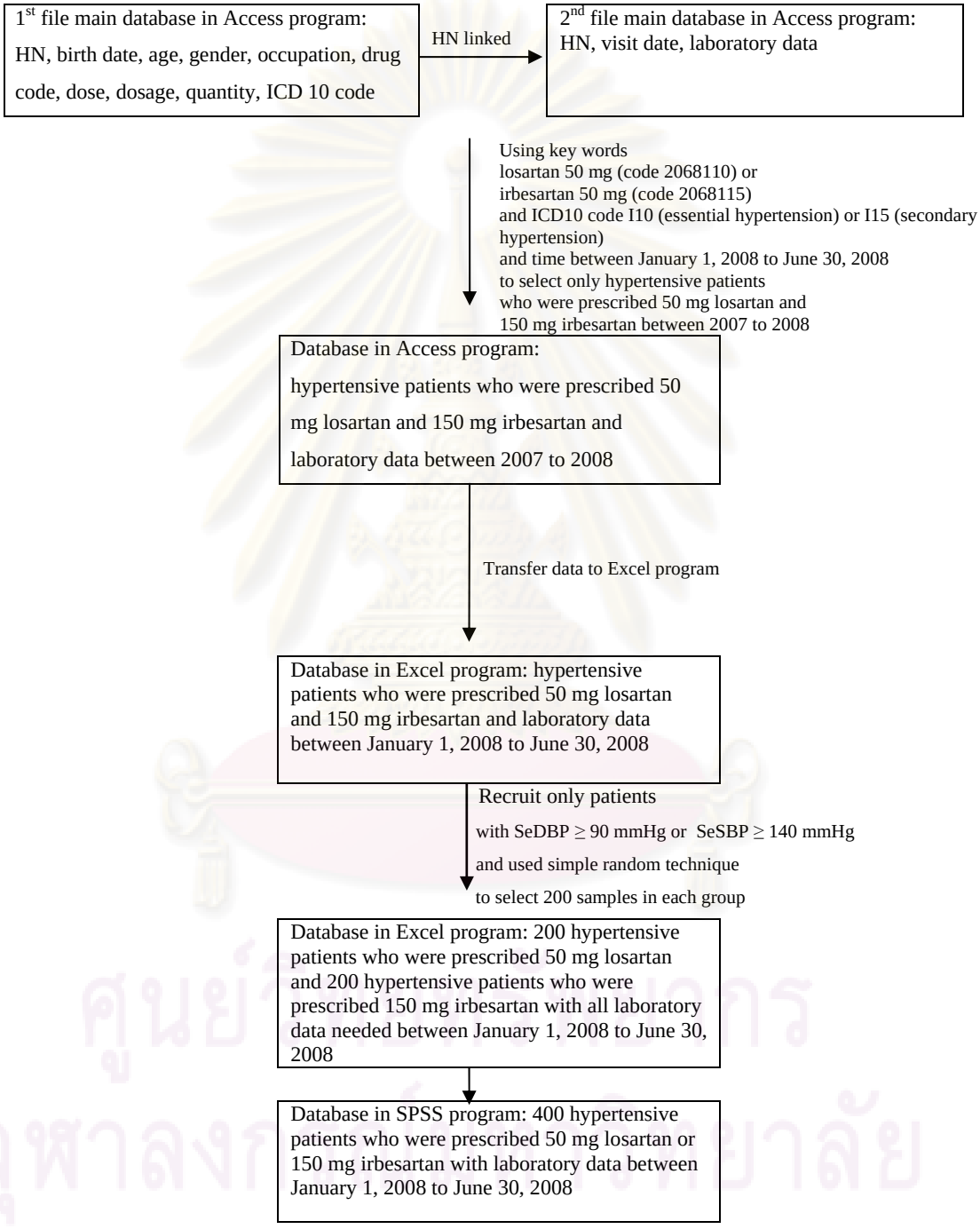

Figure 3.3 Illustration of the flow chart of collecting and analyzing main database process in Saraburi Hospital

3.6 Analysis Procedure

All data were reported in the aggregate to avoid inadvertent identification of an individual. Ten hypotheses were generated from this study. There were two dependent variables, two independent variables and two extraneous variables. Paired t-test, One way Analysis of Variance (One way ANOVA) and Two way Analysis of Covariance (Two way ANCOVA) statistical procedure was employed to analyze all data by using SPSS version 14.0. Demographic characteristics were expressed as frequency, percentage and means±SD. SeDBP and SeSBP after treatment with losartan 50 mg once daily and irbesartan 150 mg once daily for eight weeks and gender were compared controlling for baseline SeDBP and SeSBP and age by using Two way ANCOVA. These statistical tests were two-sided with a significance level of α=0.05

3.7 Research questions:

1. Could 50 mg losartan reduce SeDBP?
2. Could 50 mg losartan reduce SeSBP?
3. Could 150 mg irbesartan reduce SeDBP?
4. Could 150 mg irbesartan reduce SeSBP?
5. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeDBP better?
6. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeSBP better?

3.8 Variables

3.8.1 Dependent variables

Dependent variables in this study were SeDBP and SeSBP (mmHg) which were measured at the first time (before prescribing losartan 50 mg once daily or irbesartan 150 mg once daily) and after treatment with losartan 50 mg once daily or

irbesartan 150 mg once daily for eight weeks lowering blood pressure between January 1, 2008 to June 30, 2008. SeDBP and SeSBP were measured in Ratio scale by physicians or nurses and were recorded in patients' OPD cards. Finally, they were transferred to computerized Saraburi hospital main database.

3.8.2 Independent variables

There were two independent variables in this model. Those were: drug and gender.

3.8.3 Extraneous variables

The two covariates namely—1. baseline SeDBP and SeSBP measured in mmHg when using 50 mg losartan or 150 mg irbesartan for lowering blood pressure for the first time between January 1, 2008 to June 30, 2008 and 2. age. These two covariates were measured in Ratio scale.

3.9 Statistical analysis procedure

Data were illustrated as frequencies, percent, and means with standard deviations (SD).

Paired t-test was employed to compare the means of SeDBP or SeSBP before treatment and SeDBP or SeSBP after treatment with 50 mg losartan and 150 mg irbesartan.

One way ANOVA was used to compare the means of age of patients who were in losartan or irbesartan group. It was used to compare the means of SeDBP and SeSBP before treatment as well.

Two way Analysis of Covariance (Two way ANCOVA) controlling for baseline SeDBP and SeSBP and age was employed to compare the adjusted means of SeDBP and SeSBP of the two groups (50 mg losartan group and 150 mg irbesartan) and gender (Male). All analyses were performed by using the SPSS program version 14.0 with default setting— $\alpha<0.05$ —as the level of statistical significance.

Each of Hypotheses 1, and 2 contained two dependent variable— SeDBP and SeSBP of before and after treatment with 50 mg losartan. Therefore, Paired t-test was employed to compare the means of pre-test of SeDBP or SeSBP and post-test of SeDBP or SeSBP of 50 mg losartan (Figure 3.4).

(1) $\mu_{\text{losartan SeDBP Before}} = \mu_{\text{losartan SeDBP After}}$

(2) $\mu_{\text{losartan SeSBP Before}} = \mu_{\text{losartan SeSBP After}}$

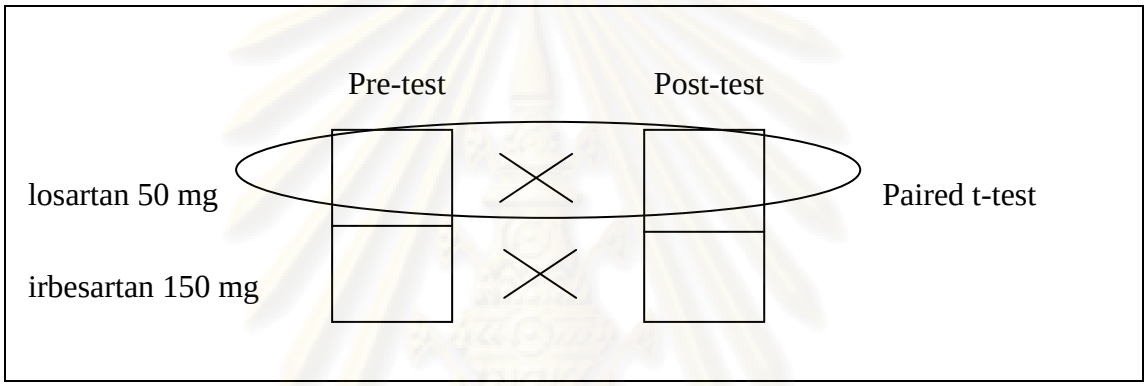

Figure 3.4 Illustration of the diagram of losartan 50 mg Paired t-test model

Each of Hypotheses 3, and 4 contained two dependent variable— SeDBP and SeSBP of before and after treatment with 150 mg irbesartan. Therefore, Paired t-test was employed to compare the means of pre-test of SeDBP or SeSBP and post-test of SeDBP or SeSBP of 150 mg irbesartan (Figure 3.5).

(3) $\mu_{\text{irbesartan SeDBP Before}} = \mu_{\text{irbesartan SeDBP After}}$

(4) $\mu_{\text{irbesartan SeSBP Before}} = \mu_{\text{irbesartan SeSBP After}}$

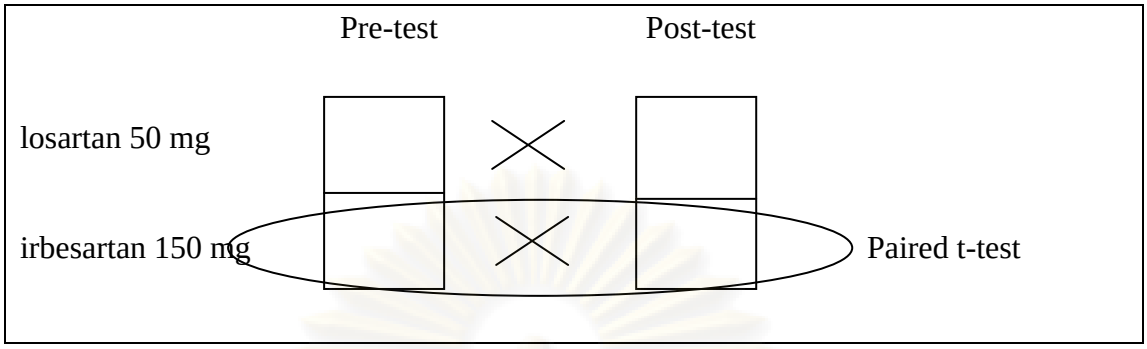

Figure 3.5 Illustration of the diagram of irbesartan 150 mg Paired t-test model

Each of Hypotheses 5, 6 and 7 contained one dependent variable— SeDBP after treatment for 8 weeks with 50 mg losartan or 150 mg irbesartan and two independent variable—50 mg losartan and 150 mg irbesartan (drug) (Nominal scale) and gender (Nominal scale) with two covariates— baseline SeDBP and age (Ratio scale). Therefore, Two way ANCOVA was employed to compare the adjusted means of SeDBP (after treatments for 8 weeks) between 1. two groups of patients using different drugs—50 mg losartan or 150 mg irbesartan and 2. Gender (Figure 3.6 and Table 3.1).

(5) $\mu_{\text{losartan SeDBP}} = \mu_{\text{irbesartan SeDBP}}$

(6) $\mu_{\text{male SeDBP}} = \mu_{\text{female SeDBP}}$

(7) $\mu_{\text{malelosartan SeDBP}} = \mu_{\text{femalelosartan SeDBP}}$

$= \mu_{\text{maleirbesartan SeDBP}} = \mu_{\text{femaleirbesartan SeDBP}}$

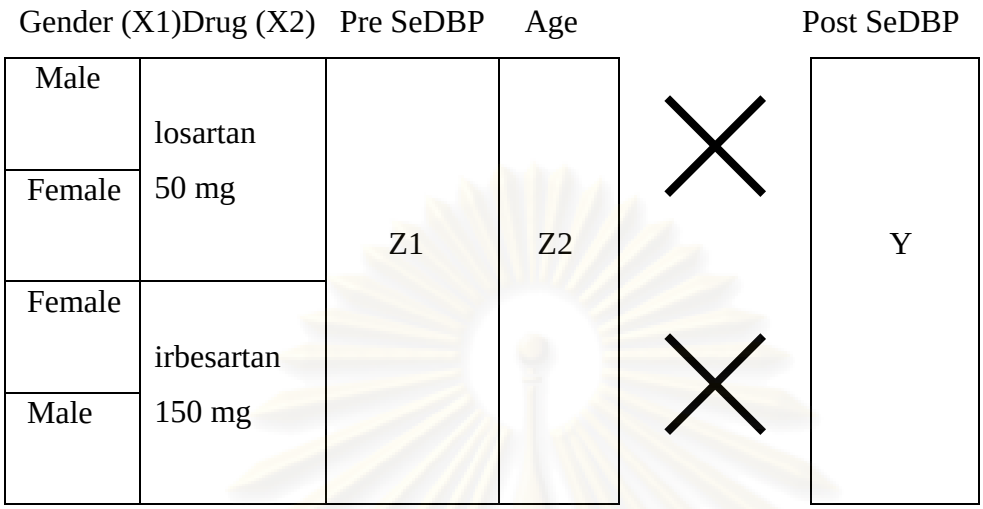

Figure 3.6 Illustration of the diagram of Two Way ANCOVA model

Table 3.1 The Two way ANCOVA

	Main effect 1		
Main effect 2	losartan 50 mg	irbesartan 150 mg	
male	$\mu_{\text{losartan male}}$	$\mu_{\text{irbesartan male}}$	Hypothesis 6
Female	$\mu_{\text{losartan female}}$	$\mu_{\text{irbesartan female}}$	
	Hypothesis 5		

Each of Hypotheses 8, 9 and 10 contained one dependent variable— SeSBP after treatment for 8 weeks with 50 mg losartan or 150 mg irbesartan and two independent variable—drug (2 groups) (Nominal scale) and gender (Nominal scale) with two covariates— baseline SeSBP and age (Ratio scale). Therefore, Two way ANCOVA was employed to compare the adjusted means of SeSBP (after treatments for 8 weeks) between 1. two groups of patients using different drugs—50 mg losartan or 150 mg irbesartan and 2. gender

(8) $\mu_{\text{losartan SeSBP}} = \mu_{\text{irbesartan SeSBP}}$

(9) $\mu_{\text{male SeSBP}} = \mu_{\text{female SeSBP}}$

(10) $\mu_{\text{malelosartan SeSBP}} = \mu_{\text{femalelosartan SeSBP}} = \mu_{\text{maleirbesartan SeSBP}} = \mu_{\text{femaleirbesartan SeSBP}}$

CHAPTER IV

RESULTS

This chapter demonstrated the results e.g. descriptive statistics such as demographic characteristics and socio-economic status data then an inference statistics was performed to analyze data. All ten hypotheses were tested. The study outcomes were explained including tables and graphs.

The first section summarizes descriptive analyses demographic characteristics. The second presents results of the evaluative analyses from the methods employed in this study: Paired t-test, One way Analysis of Variance (One way ANOVA) and Two way Analysis of Covariance (Two way ANCOVA).

Data process (coding and computer entry) was done by the investigators. Test for entry error was done by double check, throughout the entire sample, of every response item against its initial keyboard entry. Then the data were cleaned and inspected by two experts.

4.1 Data collection

Data from computerized Saraburi hospital main database were retrospectively collected restricted only the hypertensive patients who were prescribed losartan 50 mg once daily or irbesartan 150 mg once daily for hypertensive treatment for a period of six months during January 1, 2008 to June 30, 2008 yielded 1,051 patients (population frame). All 1,051 patients (population) were randomly selected by using computer generated 400 numbers to be samples. This study got 100% (n=400, 200 each) completed sample size.

4.2 Demographic Characteristics

Specific characteristics were presented in Tables 4.1 to 4.2. Most 270 (67.50%) were female, 130 (32.50%) were male (Table 4.1 and graph as shown in figure 4.1).

Table 4.1 Gender

Gender	Frequency	Percent
Female	270	67.50
Male	130	32.50
Total	400	100.00

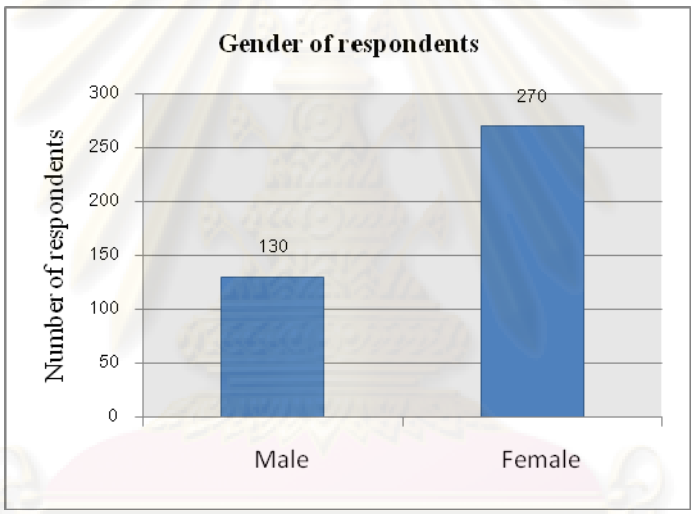

Figure 4.1 Illustration of Gender

The majority of patients were Merchant 140 (35.00%), Government Officer 72 (18.00%), Employee 55 (13.75%), Retired government official 47 (11.75%), Millitary service 33 (8.25%), Housekeeper 26 (6.50%), Agriculture 18 (4.50%). Much lesser were Priest 4 (1.00%), Student, Worker each 2 (0.50%) and Unknown 1 (0.25%) (Table 4.2 and graph as shown in Figure 4.2).

Table 4.2 Occupation

Occupation	Frequency	Percent
Merchant	140	35.00
Government officer	72	18.00
Employee	55	13.75
Retired government official	47	11.75
Military service	33	8.25
House keeper	26	6.50
Agriculture	18	4.50
Priest	4	1.00
Student	2	0.50
Worker	2	0.50
Unknown	1	0.25
Total	400	100.00

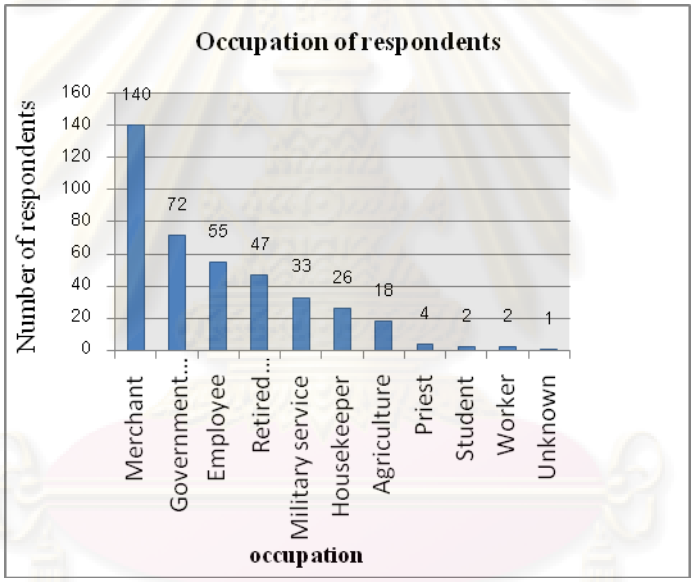

Figure 4.2 Illustration of Occupation

The female's average age was 63.58±11.87 years and male's average age was 62.90±13.53 years. The average age was 63.36±12.42 years.

The patients'minimum age was 23.70 years and patients'maximum age was 91.25 years.

Weight (kilogram) and height (metre) of patients were collected for calculating BMI and planned to use as another covariate. The average BMI was 26.11±2.52 (n=18) unfortunately only 18 patients (out of 400) had completed weight

and height the main data base therefore the BMI was not taken into account in this model.

The baseline SeDBP of female was 82.30±10.60 mmHg and male was 82.63±10.58 mmHg. The average baseline SeDBP was 82.41±10.58 mmHg.

The minimum baseline SeDBP of the patients was 63 mmHg and the maximum baseline SeDBP of the patients was 142 mmHg.

The baseline SeSBP of female was 158.78±14.79 mmHg and male was 152.85±11.92 mmHg. The average baseline SeSBP was 156.86±14.18 mmHg.

The minimum baseline SeSBP of the patients was 132 mmHg and the maximum baseline SeSBP of the patients was 243 mmHg.

SeDBP after treatment of female was 69.71±9.23 mmHg. SeDBP after treatment of male was 72.48±9.39 mmHg. The average SeDBP after treatment was 70.61±9.36 mmHg.

The minimum SeDBP of the patients was 51 mmHg and the maximum SeDBP of the patients was 110 mmHg.

SeSBP after treatment of female was 126.77±14.23 mmHg. SeSBP after treatment of male was 127.40±12.78 mmHg. The average SeSBP after treatment was 126.97±13.76 mmHg.

The minimum SeSBP of the patients was 95 mmHg and the maximum SeSBP of the patients was 220 mmHg.

The percent change of SeDBP of female was -0.14±0.13 mmHg. The percent change of SeDBP of male was -0.11±0.14 mmHg. The average percent change of SeDBP was -0.13±0.13 mmHg.

The minimum percent change of SeDBP of the patients was -0.43 mmHg and the maximum percent change of SeDBP of the patients was 0.35 mmHg.

The percent change of SeSBP of female was -0.20±0.09 mmHg. The percent change of SeSBP of male was -0.16±0.09 mmHg. The average percent change of SeSBP was -0.19±0.09 mmHg.

The minimum percent change of SeSBP of the patients was -0.40 mmHg and the maximum percent change of SeSBP of the patients was 0.15 mmHg. (Table 4.3)

Table 4.3 Descriptive statistics

Descriptive	Gender	N	Mean	SD	Min.	Max.
Age	Female	270	63.58	11.87	31.41	87.77
	Male	130	62.90	13.53	23.70	91.25
	Total	400	63.36	12.42	23.70	91.25
BMI		18	26.11	2.52	22.00	30.00
Baseline SeDBP	Female	270	82.30	10.60	63.00	126.00
	Male	130	82.63	10.58	68.00	142.00
	Total	400	82.41	10.58	63.00	142.00
Baseline SeSBP	Female	270	158.78	14.79	132.00	243.00
	Male	130	152.85	11.92	135.00	205.00
	Total	400	156.86	14.18	132.00	243.00
SeDBP after treatment	Female	270	69.71	9.23	51.00	96.00
	Male	130	72.48	9.39	55.00	110.00
	Total	400	70.61	9.36	51.00	110.00
SeSBP after treatment	Female	270	126.77	14.23	95.00	220.00
	Male	130	127.40	12.78	99.00	176.00
	Total	400	126.97	13.76	95.00	220.00
%changeSeDBP	Female	270	-0.14	0.13	-0.43	0.35
	Male	130	-0.11	0.14	-0.41	0.25
	Total	400	-0.13	0.13	-0.43	0.35
%changeSeSBP	Female	270	-0.20	0.09	-0.40	0.02
	Male	130	-0.16	0.09	-0.38	0.15
	Total	400	-0.19	0.09	-0.40	0.15

4.3 Results of analyses

4.3.1 Paired t-test

SeDBP before treatment with losartan was 81.57±8.56 mmHg and SeDBP after treatment with losartan was 71.68±9.43 mmHg (Table 4.4).

Table 4.4 SeDBP before and after treatment with losartan

SeDBP	Mean	SD
before treatment with losartan	81.57	8.56
after treatment with losartan	71.68	9.43

SeDBP before treatment with losartan and SeDBP after treatment with losartan were significantly different (p=0.000, Paired t-test) (Table 4.5).

Table 4.5 Paired t-test of SeDBP before and after treatment with losartan

SeDBP	Mean	SD	SE	t	df	p-value
before and after treatment	9.885	12.282	0.868	11.382	199	**0.000

** sig at p<0.01

SeSBP before treatment with losartan was 153.67±12.04 mmHg and SeSBP after treatment with losartan was 127.51±12.22 mmHg (Table 4.6).

Table 4.6 SeSBP before and after treatment with losartan

SeSBP	Mean	SD
before treatment with losartan	153.67	12.04
after treatment with losartan	127.51	12.22

SeSBP before treatment with losartan and SeSBP after treatment with losartan were significantly different (p=0.000, Paired t-test) (Table 4.7).

Table 4.7 Paired t-test of SeSBP before and after treatment with losartan

SeSBP	Mean	SD	SE	t	df	p-value
before and after treatment	26.160	14.513	1.026	25.491	199	**0.000

** sig at p<0.01

SeDBP before treatment with irbesartan was 83.25±12.24 mmHg and SeDBP after treatment with irbesartan was 69.35±9.64 mmHg (Table 4.8).

Table 4.8 SeDBP before and after treatment with irbesartan

SeDBP	Mean	SD
before treatment with irbesartan	83.25	12.24
after treatment with irbesartan	69.35	9.64

SeDBP before treatment and SeDBP after treatment with irbesartan were significantly different (p=0.000, Paired t-test) (Table 4.9).

Table 4.9 Paired t-test of SeDBP before and after treatment with irbesartan

SeDBP	Mean	SD	SE	t	df	p-value
before and after treatment	13.900	11.321	0.801	17.363	199	**0.000

** sig at p<0.01

SeSBP before treatment with irbesartan was 160.04±15.42 mmHg and SeSBP after treatment with irbesartan was 126.44±15.16 mmHg (Table 4.10).

Table 4.10 SeSBP before and after treatment with irbesartan

Variables	Mean	SD
SeSBP before treatment with irbesartan	160.04	15.42
SeSBP after treatment with irbesartan	126.44	15.16

SeSBP before treatment with irbesartan and SeSBP after treatment with irbesartan were significantly different (p=0.000, Paired t-test) (Table 4.11).

Table 4.11 Paired t-test of SeSBP before and after treatment with irbesartan

SeSBP	Mean	SD	SE	t	df	p-value
before and after treatment	33.605	15.256	1.079	31.151	199	**0.000

** sig at p<0.01

Conclusion: Both losartan 50 mg once a day and irbesartan 150 mg once a day could significantly lower SeDBP and SeSBP (p=0.000 Paired t-test and p=0.000, Paired t-test)

4.3.2 One way ANOVA

One way ANOVA statistical method was applied to compare means of age of patients in losartan group and irbesartan group. The results were shown in Table 4.12 and 4.13.

The average age of patients in losartan group was 64.93±12.78 years and the average age of patients in irbesartan group was 61.78±11.87 years (Table 4.12).

Table 4.12 Age of patients who were prescribed each drug group

Age of patients who were prescribed	Mean	SD
losartan	64.93	12.78
irbesartan	61.78	11.87
Patients' Age	63.36	12.42

The average age of patients in losartan and irbesartan group were significantly different (p=0.011, One way ANOVA) (Table 4.13). Therefore age was added as the second covariate.

Table 4.13 One way ANOVA analysis of age of patients who were prescribed each drug group

	Sum of Squares	Df	Mean Square	F	p-value
Between Groups	991.904	1	991.904	6.518	*0.011
Within Groups	60563.358	398	152.169		
Total	61555.262	399			

* sig at $p<0.05$

The average baseline SeDBP and SeSBP of losartan group were 81.57±8.56 mmHg, 153.67±12.04 mmHg and the average baseline SeDBP and SeSBP of irbesartan group were 83.25±12.24 mmHg, 160.04±15.42 mmHg respectively (Table 4.14).

The average baseline SeDBP of both drugs was not significantly different (p=0.111, One way ANOVA). But the average baseline SeSBP of both drugs was significantly different (p=0.000, One way ANOVA) (Table 4.14). However they were added as a covariate.

Table 4.14 One way ANOVA analysis of SeDBP and SeSBP before treatment

Blood pressure	losartan (mmHg)	irbesartan (mmHg)	p-value
SeDBP	81.57 ±8.56	83.25 ±12.24	0.111
SeSBP	153.67 ±12.04	160.04 ±15.42	*0.000

4.3.3 Two way ANCOVA: Seated Diastolic Blood Pressure (SeDBP)

When age was added as the additional covariate, the baseline SeDBP and age were controlled (used as two covariates). Then gender was added to the model as an additional category independent variable. After 8 weeks of treatment with 50 mg losartan or 150 mg irbesartan, the average SeDBP of losartan group in female and male were 70.66±9.41 mmHg and 73.08±9.34 mmHg respectively. The average SeDBP in losartan group was 71.68±9.43 mmHg. The average SeDBP of irbesartan in female and male groups were 68.81±9.52 mmHg and 71.17±9.90 mmHg respectively. The average SeDBP in irbesartan group was 69.35±9.64 mmHg (Table 4.15).

Table 4.15 Descriptive Statistics of Dependent Variable: SeDBP after treatment

Drugs	Gender	Mean	SD	N
losartan	Female	70.66	9.41	116
	Male	73.08	9.34	84
	losartan's group	71.68	9.43	200
irbesartan	Female	68.81	9.52	154
	Male	71.17	9.90	46
	irbesartan's group	69.35	9.64	200

There was no moderating effect (interaction effect) between drug and gender (Drug * Male) (p=0.927, Two way ANCOVA) therefore only the two main effects (drug and gender) were taken into account.

The baseline SeDBP was a significant covariate (p=0.000) whereas age was not a significant covariate (p=0.533). The average SeDBP of male and female were significantly different (p=0.030). However, the average SeDBP between losartan and irbesartan were significantly different (p=0.017, Two way ANCOVA) controlling for age and baseline SeDBP (Table 4.16 and Figure 4.3).

Table 4.16 Tests of Between-Subjects Effects

Dependent Variable: SeDBP after treatment

Source	Type III Sum of Squares	df	Mean Square	F	p-value
Corrected Model	4517.227 [a]	5	903.446	11.044	**0.000
Intercept	8244.755	1	8244.755	100.787	**0.000
Age	31.887	1	31.887	0.390	0.533
Baseline SeDBP	3012.725	1	3012.725	36.829	**0.000
Drug	473.706	1	473.706	5.791	*0.017
Male	389.705	1	389.705	4.764	*0.030
Drug * Male	0.687	1	0.687	0.008	0.927
Error	32230.683	394	81.804		
Total	2025694.000	400			
Corrected Total	36747.910	399			

a. R Squared = 0.123 (Adjusted R Squared = 0.112)

** sig at p<0.01

* sig at p<0.05

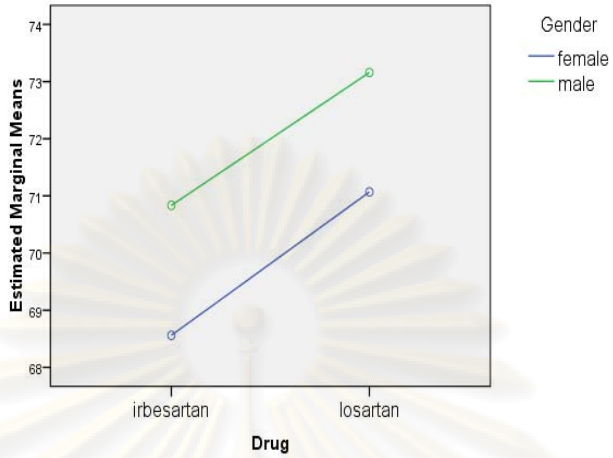

Figure 4.3 Illustration of estimated marginal means of SeDBP after treatment

4.3.4 Two way ANCOVA: Seated Systolic Blood Pressure (SeSBP)

When age was added as the additional covariate, the baseline SeSBP and age were controlled (used as two covariates). Then gender was added to the model as an additional category independent variable. After 8 weeks of treatment with 50 mg losartan or 150 mg irbesartan, the average SeSBP of losartan in female and male groups were 127.49±12.10 mmHg and 127.54±12.46 mmHg respectively. The average SeSBP in losartan group was 127.51±12.22 mmHg. The average SeSBP of irbesartan in female and male groups were 126.22±15.66 mmHg and 127.15±13.48 mmHg respectively. The average SeSBP in irbesartan group was 126.44±15.16 mmHg (Table 4.17).

Table 4.17 Descriptive Statistics of Dependent Variable: SeSBP after treatment

Drugs	Gender	Mean	SD	N
losartan	Female	127.49	12.10	116
	Male	127.54	12.46	84
	losartan's group	127.51	12.22	200
irbesartan	Female	126.22	15.66	154
	Male	127.15	13.48	46
	irbesartan's group	126.44	15.16	200

There was no moderating effect (interaction effect) between drugs and gender (Drug * Male) (p=0.714, Two way ANCOVA) therefore only the two main effects (drug and gender) were taken into account.

The baseline SeSBP was a significant covariate (p=0.000) whereas age was not a significant covariate (p=0.769). The average SeSBP of male and female were not significantly different (p=0.073). However, the average SeSBP between losartan and irbesartan were significantly different (p=0.024, Two way ANCOVA) controlling for age and baseline SeSBP (Table 4.18 and Figure 4.4).

Table 4.18 Tests of Between-Subjects Effects

Dependent Variable: SeSBP after treatment

Source	Type III Sum of Squares	df	Mean Square	F	p-value
Corrected Model	13825.837[a]	5	2765.167	17.650	**0.000
Intercept	9505.197	1	9505.197	60.671	**0.000
Age	13.583	1	13.583	0.087	0.769
Baseline SeSBP	13676.623	1	13676.623	87.297	**0.000
Drug	806.528	1	806.528	5.148	*0.024
Male	504.562	1	504.562	3.221	0.073
Drug * Male	21.047	1	21.047	0.134	0.714
Error	61726.861	394	156.667		
Total	6524359.000	400			
Corrected Total	75552.698	399			

a. R Squared = 0.183 (Adjusted R Squared = 0.173)

** sig at p<0.01

* sig at p<0.05

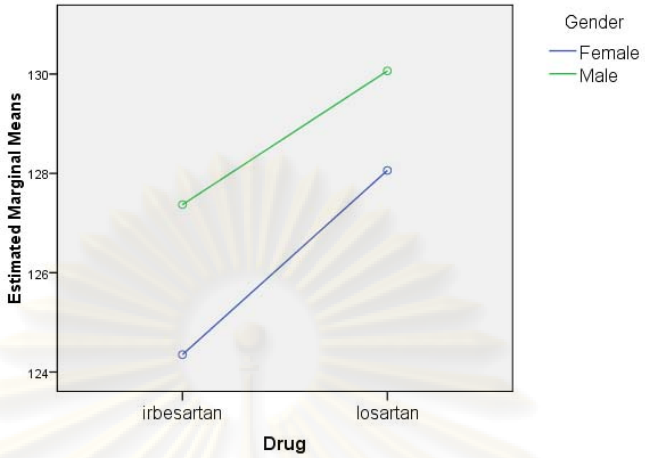

Figure 4.4 Illustration of estimated marginal means of SeSBP after treatment

Conclusions:

Losartan 50 mg once a day could significantly decrease SeDBP and SeSBP (p=0.000, Paired t-test and p=0.000, Paired t-test respectively).

Irbesartan 150 mg once a day could significantly decrease SeDBPand SeSBP (p=0.000, Paired t-test and p=0.000, Paired t-test respectively).

Irbesartan 150 mg once a day could significantly reduce SeDBP and SeSBP more than losartan 50 mg once a day did (p=0.017, Two way ANCOVA and p=0.024, Two way ANCOVA respectively). Gender made no differences on efficacy of these two drugs.

CHAPTER V

DISCUSSION AND CONCLUSION

This study was a retrospective study using computerized Saraburi hospital main data base. The study was performed to 1. To investigate whether 50 mg losartan or 150 mg irbesartan could reduce seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP). 2. To compare antihypertensive efficacy between 50 mg losartan and 150 mg irbesartan controlling for (1) baseline SeDBP and SeSBP and (2) age and 3. To compare antihypertensive efficacy of 50 mg losartan and 150 mg irbesartan between gender controlling for (1) baseline SeDBP and SeSBP and (2) age.

Data were discussed and presented according to the research questions as the followings:-

1. Could 50 mg losartan reduce SeDBP?
2. Could 50 mg losartan reduce SeSBP?
3. Could 150 mg irbesartan reduce SeDBP?
4. Could 150 mg irbesartan reduce SeSBP?
5. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeDBP better?
6. Which drug—50 mg losartan or 150 mg irbesartan could reduce SeSBP better?

Conclusion, qualifications of this study and future study were also provided.

We found that most of hypertensive patients who were in 50 mg losartan or 150 mg irbesartan were female (270, 67.50%). The patients' averages age was 63.36±12.42 years. The majority occupation of the patients was Merchant (35.00%).

5.1 Assessment of research question

5.1.1 The first question

The first question asked **"**Could 50 mg losartan reduce SeDBP?" Our study found that it could. SeDBP before treatment with losartan group was 81.57±8.56 mmHg and SeDBP after treatment with losartan was 71.68±9.43 mmHg. (p=0.000, Paired-T test). Therefore losartan could significantly lower SeDBP in hypertensive patients.

5.1.2 The second question

The second question asked **"**Could 50 mg losartan reduce SeSBP?" Our study found that it could. SeSBP before treatment with losartan group was 153.67±12.04 mmHg and SeSBP after treatment with losartan was 127.51±12.22 mmHg (p=0.000, Paired-T test). Therefore losartan could significantly lower SeSBP in hypertensive patients.

5.1.3 The third question

The third question asked **"**Could 50 mg irbesartan reduce SeDBP?" Our study found that it could. SeDBP before treatment with irbesartan was 83.25±12.24 mmHg and SeDBP after treatment with irbesartan was 69.35±9.64 mmHg (p=0.000, Paired-T test). Therefore irbesartan could significantly lower SeDBP in hypertensive patients.

5.1.4 The fourth question

The fourth question asked **"**Could 50 mg irbesartan reduce SeSBP?" Our study found that it could. SeSBP before treatment with irbesartan was 160.04±15.42 mmHg and SeSBP after treatment with irbesartan was 126.44±15.16 mmHg. SeSBP before treatment and SeSBP after treatment with irbesartan was significantly different

(p=0.000, Paired-T test). Therefore irbesartan could significantly lower SeSBP in hypertensive patients.

5.1.5 The fifth question

The fifth question asked “Which drug—50 mg losartan or 150 mg irbesartan could reduce SeDBP better?” Our study found that 150 mg irbesartan could better (lower) reduce SeDBP than 50 mg losartan did. The average SeDBP of patients who received irbesartan was 69.35±9.64 mmHg and losartan was 71.68±9.43 mmHg. Therefore 150 mg irbesartan could significantly lower SeDBP in hypertensive patients than 50 mg losartan controlling for age and baseline SeDBP (p=0.017, Two Way ANCOVA).

5.1.6 The sixth question

The sixth question asked “Which drug—50 mg losartan or 150 mg irbesartan could reduce SeSBP better?” Our study found that irbesartan could better (lower) reduce SeSBP than losartan did. The average SeSBP of patients who received irbesartan was 126.44±15.16 mmHg and losartan was 127.51±12.22 mmHg. Therefore 150 mg irbesartan could significantly lower SeSBP in hypertensive patients than 50 mg losartan controlling for age and baseline SeSBP (p=0.024, Two way ANCOVA).

5.2 Conclusion and discussion

Our finding supported what Graham and Allcock found in 2002, “Irbesartan was an appropriate substitution for valsartan or losartan.” (Graham and Allcock, 2002) and confirmed Kenneth Kassler-Taub, et al work “Comparative Efficacy of Two Angiotensin II Receptor Antagonists, Irbesartan and Losartan, in Mild-to-Moderate” in 1998 (Kenneth et al., 1998).

The result also confirmed Oparil's study in 1998 as well. Oparil found that in titrated doses according response, the change from baseline in DBP after 8 weeks, monotherapy was significantly greater (by 2 mmHg) in patients receiving irbesartan 150-300 mg once daily than losartan 50-100 mg once daily (Oparil et al., 1998).

Although our study found that irbesartan 150 mg once daily could significantly lower SeDBP and SeSBP in hypertensive patients better than losartan 50 mg once daily. Dang et al. found that irbesartan has more effective than losartan but this result has not significantly difference. They discovered that blood pressure declined comparably in both groups from 151/92 mmHg at baseline to 137/83 and 135/83 (losartan and irbesartan, respectively, NS) (Dang et al., 2006).

We investigated that both losartan 50 mg and irbesartan 150 mg once a day could significantly reduce SeDBP and SeSBP. However, this study proved that irbesartan 150 mg once a day could significantly lower SeDBP and SeSBP in hypertensive patients better (lower) than losartan 50 mg once a day. Gender made no differences on efficacy of these two drugs.

5.3 Qualifications of this study

This study used powerful statistical procedure, Two way ANCOVA controlling for two extraneous variables namely— baseline SeDBP and SeSBP and age however there were still some limitations that this study would like to pronounce. Those were the followings:-

Most of the variables weight and height of the patients were not complete thus we could only completely calculate BMI of only 18 patients. After consideration, we decided to ignore BMI. If not so the BMI would be used as another covariate that would generate a better accurate result.

This research was a retrospective study consequently all data and variables were already collected. If the future study can plan and do a prospective design with a better protocol for systematically controlling errors and covariates including all reliable dependent and independent variables, then it would yield much more better precise results.

This study proved only one aspect—lower blood pressure effect. To completely compare effectiveness of these two drugs, the future study may need comparing in more details such as effect to serum uric acid levels, side effects, and cost to ultimately conclude that which one is better result.

5.4 Future study

1. The future study should measure blood pressure every 8 weeks for 3 times to observe this trend in the long run and use Repeated Measure Two way ANCOVA instead this would yield a better precise explanation.

2. The future study should be done in many different sites to verify external validity then it could be generalized these finding to all Thai hypertensive patients as a whole.

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Vitae

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