CHAPTER 1

INTRODUCTION

1.1 Hypertension and its treatment

1.1.1 Epidemiology

The prevalence of hypertension varies among populations around the world. It increases with age, particularly systolic blood pressure, affecting 44% of adults aged 50-59 years and 65% of adults over 80 years but diastolic blood pressure is raised up until the age of 50 years and then declines (Burt et al., 1995; Staessen et al., 2003).

According to the third National Health and Nutrition Examination Survey (NHANES) from 1991-1994 in the USA, approximately 20% of adults aged 18-74 years had hypertension. NHANES III Phase 2 data showed that 68% of those with hypertension were aware of their condition, a 5% decrease from the NHANES III Phase 1, and optimal blood pressure control (<140/90 mm Hg) occurred in only 27% of hypertensive patients (National high blood pressure education program, 1997). The high prevalence of hypertension with its related mortality made hypertension a major healthcare problem in the US (National high blood pressure education program, 1993). It has been reported that there is a similar problem in Thailand. The death rate from hypertension and cerebrovascular disease has increased between 1999 and 2003 from 15.6 to 26.8 persons per 100,000 of the population and it was ranked third of the major causes of death in 2003 (Health Information Division Bureau of Health Policy and Plan, 2004). The morbidity rate of hypertension in hospitals per 100,000 of the population in the whole country except Bangkok was 389.83. In the Northern region it

was 521.32, in the North-eastern region 241.67, in the Central region excepting Bangkok 461.57 and in the Southern region it was 439.06 (Public Health Organization Thailand, 2004).

1.1.2 Definition

1.1.2.1 Blood pressure

Blood pressure (BP) refers to the pressure of the blood against the blood vessel walls (Shankie, 2001). It is indirectly measured in the brachial artery in the upper arm just above the elbow using a sphygmomanometer. Systolic blood pressure (SBP) is the pressure when the heart pumps blood out of the left ventricular chamber and through the circulation bed during systole. The pressure responsible for filling the left ventricular chamber during diastole is called diastolic blood pressure (DBP). BP is usually quoted as two values, for example, 130/80 mm Hg, 130 mm Hg being the SBP and 80 mm Hg being the DBP.

BP varies throughout the day. Under normal circumstance, BP has a diurnal rhythm. The peak BP occurs during the late morning to early afternoon, and then decreases throughout the day to reach a trough value around 3.00 am. A slow increase in BP is observed over the early morning hours before wakening (Figure 1.1).

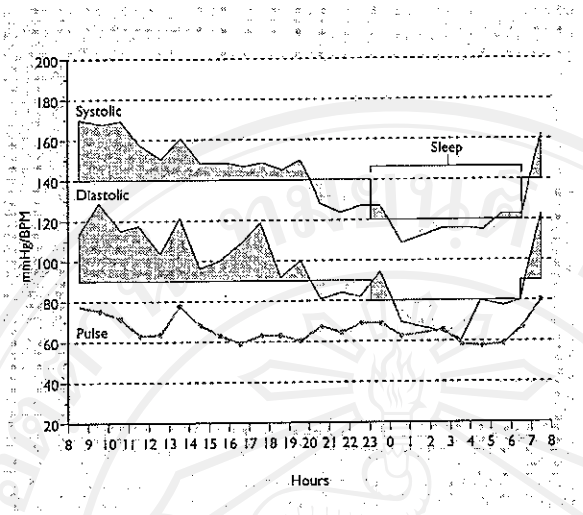

Figure 1.1 Example of ambulatory BP monitoring trace with normal nocturnal dip. (Poulter et al., 2000)

1.1.2.2 Classification of Hypertension

The classification for adults aged 18 or older has changed from time to time depending on evidence based reviews. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) defines an 'optimal BP' as systolic BP being lower than 120 mm Hg and diastolic BP being lower than 80 mm Hg. 'Normal BP' is defined as <130/80 mm Hg and above this up to 140/90 mm Hg it is defined as 'high-normal'. Patients who have a BP of at least 140-159/90-99 mm Hg are defined as 'stage 1 hypertension'. The range of 160-179/100-109 mm Hg is classified as 'stage 2 hypertension'. BPs of at least 180/110 mm Hg are called as 'stage 3 hypertension' (National high blood pressure education program, 1997).

In the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), Table 1.1, a further classification is added, prehypertension, 130-139/80-89 mm Hg and combined

stages 2 and 3 hypertension. The prehypertension patients are more at risk to progress to hypertension (National high blood pressure education program, 2003).

1.1.2.3 "White coat" hypertension

A white coat hypertension definition is imprecise but in general it describes individuals who have an elevated BP at a clinic visit but a normal BP at home or a lower BP with ambulatory monitoring. Most studies use the criteria of white coat hypertension when the BP is elevated to >140/90 mm Hg and when the daytime BP is below this value (Ben-Dov et al., 2004; Palatini et al., 1998; Soma et al., 1996). Some studies used additional criteria such as the systolic/diastolic pressure being at least 20/15 mm Hg or 20/10 mm Hg lower than the clinic reading (MacDonald et al., 1999; Myers et al., 1995). Nevertheless, a study which only shows the results of the difference between the clinic and the daytime average BPs does not reflect the alerting reaction and the pressure response elicited by the visit to the physician and is thus not a reliable measure of the white coat effect (Parati et al., 1998). The white coat effect refers to the transient pressure rise during clinic visits while white coat hypertension refers to the persistent high physician's office BP with normal BP readings returning outside the medical setting (Verdecchia et al., 1995).

Table 1.1 Classification and management of BP for adults*(National high blood pressure education program, 2003)

BP Classification	SBP* mm Hg	DBP* mm Hg	Lifestyle modification	Initial drug therapy	
				Without compelling indication	With compelling indications
Normal	<120	And < 80	Encourage	No antihypertensive drug indicated	Drug(s) for compelling indications.++
Prehypertension	120-139	Or 80-89	Yes		
Stage 1 hypertension	140-159	Or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or a combination	Drug(s) for the compelling indications. ++Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 hypertension	≥ 160	Or ≥ 100	Yes	Two-drug combination for most+ (usually Thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.
* Treatment determined by highest BP category.
+ Initial combined therapy should be used cautiously in those at risk of orthostatic hypotension.
++ Treat patients with chronic kidney disease or diabetes to BP goal of < 130/80 mm Hg

Many of the concerns with regard to white coat hypertension or white coat effect are to determine the association between this and cardiovascular outcomes or target organ damage (Gianfranco et al., 2000; Khattar et al., 1998; Muscholl et al., 1998; Palatini et al., 1998). However, it is still questionable as to whether doctors should treat or should not treat white coat hypertension.

Ambulatory BP monitoring becomes useful to exclude white coat hypertension from sustained hypertension and helpful to avoid misdiagnosis of resistant hypertension, unnecessary over treatment and expensive procedures to investigate for possible secondary hypertension (Mezzetti et al., 1997).

1.1.2.4 Hypertensive crises (Joseph and Carter, 2001)

Hypertensive crises refers to the situation where the BP exceeds 180/110 mm Hg. A further classification is hypertensive emergency which includes acute or chronic end-organ damage. Hypertensive urgency is without end-organ damage. Hypertensive emergency case should be hospitalized for immediate reduction of BP, but hypertensive urgency does not require immediate reduction but a slow reduction within 24 hours.

1.1.2.5 Isolated systolic hypertension

Isolated systolic hypertension (ISH) in the elderly is quite common. The Framingham Heart study showed that the prevalence of ISH increased in patients over 65 years (Wilking et al., 1988). Isolated hypertension is defined as an isolated elevation of systolic BP (SBP) with normal diastolic BP (DBP). The JNC-6 definition of ISH is SBP $\geq$140 mm Hg and DBP <90 mm Hg (National high blood pressure education program, 1997).

SBP is reported to be a better predictor of cardiovascular events than DBP (National high blood pressure education program, 1997; Swales, 2000).

1.1.2.6 Hypertension in special groups

Hypertension in the elderly

Hypertension mostly occurs in the elderly and approximately 70-80% of persons aged 50 years and over have hypertension, especially systolic hypertension (Franklin et al., 2001; Muhammad and Yousri, 2003). Systolic BP and pulse pressure

seem to be a better predictor than diastolic BP of cardiovascular events in the elderly (Kannel, 2000; Staessen et al., 1990; Vaccarino et al., 2001). Although most of the elderly have essential hypertension, secondary forms of hypertension should be specifically excluded especially in patients who have resistant high BP, or sudden onset high BP (Schwartz and Sheps, No date).

Special concerns are (1) pseudohypertension which occurs with false readings of systolic BP made with a cuff and results from calcification and loss of elasticity of peripheral arteries. Suspected persons include those who have high BP both in the clinic and at home without having target organ damage or having palpably stiff vessels; (2) white-coat hypertension which normally occurs in elderly women and for such people home BP monitoring or 24-hour monitoring should be encouraged; (3) orthostatic hypotension or postprandial hypotension which normally occurs in the elderly due to ageing and in diabetics due to autonomic dysfunction. For those people, BP measurement while standing has been recommended (National high blood pressure education program, 1997; Schwartz and Sheps, No date). Although long acting calcium channel blockers (CCB) or beta-blockers (BB) are considered to have a similar benefit to diuretics, angiotensin converting enzyme inhibitors (ACEI) may have better outcomes on the reduction in the risk of cardiovascular morbidity and mortality when compared to diuretics which are still recommended to use as the first line therapy in the elderly (Curb et al., 1996; Hansson et al., 1999; Kostis et al., 1997; National high blood pressure education program, 1997; National Intervention Cooperative Study in Elderly Hypertensives Study Group, 1999; SHEP Cooperative Research Group, 1991; Wing et al., 2003). Lifestyle modification should also be

encouraged because, due to age, the renal function is in gradual decline and greater salt sensitivity is common (Schwartz and Sheps, No date).

Hypertension with Diabetes

Hypertension with diabetes puts the patient at higher risk of macrovascular disease, such as stroke and coronary heart disease. Cardiovascular morbidity and mortality are reported to be greater than for diabetes alone (Guideline committee, 2003; Park et al., 2003). Hypertension reveals the onset of diabetic nephropathy in type 1 diabetes whereas type 2 diabetic patients are reported to still have normoalbuminuria at the time of the diagnosis of hypertension (Guideline committee, 2003).

Recent guidelines and many studies have shown the benefit of lowering BP lower than 130/80 mm Hg in patients with hypertensive diabetes (American Diabetes Association, 2003; Hansson et al., 1998; National high blood pressure education program, 2003). Lifestyle modifications, body weight reduction if overweight, moderate exercise to increase insulin sensitivity and to improve lipid profile, should all be encouraged (Schwartz and Sheps, No date). Randomized controlled trials have shown the benefits of ACEIs, angiotensin receptor blockers (ARBs), CCBs, thiazides and beta blockers against cardiovascular events and have resulted in reductions of such events (Mogensen et al., 2000; National high blood pressure education program, 2003; Tatti et al., 1998). ACEI and ARB-based treatments have given favorable reductions in microalbuminuria and ACEI has been recommended as first line therapy in type 1 diabetes and ARB in type 2 (American Diabetes Association, 2003; National high blood pressure education program, 2003).

Hypertension with heart disease

Patients with ischemic heart disease and hypertension are at risk to cardiovascular morbidity and mortality. The goal should be to control BP at lower than 140/90 mm Hg. The JNC-7 guidelines recommend starting treatment with BBs or alternatively with long acting CCBs in hypertensive patients with stable angina pectoris. BBs and ACEIs are recommended initially in patients with acute coronary syndromes (unstable angina and myocardial infarction). In patients with post myocardial infarction, ACEIs, BBs and aldosterone antagonists have been shown to be beneficial (National high blood pressure education program, 2003).

Heart failure, both systolic and diastolic, is a result of ischemic heart disease and left ventricular hypertrophy which are associated with systolic hypertension (Schwartz and Sheps, No date). In asymptomatic patients with ventricular dysfunction, ACEIs, BBs are recommended whereas in symptomatic ventricular dysfunction or end-stage heart failure, ACEIs, BBs, ARBs and aldosterone blockers given concomitantly with loop diuretics are recommended (National high blood pressure education program, 2003).

Hypertension with chronic kidney disease

Kidney disease can be both the cause and the consequence of hypertension (Schwartz and Sheps, No date). The goal of treatment in hypertensive patients with chronic kidney disease patients is to slow the deterioration of renal function and prevent cardiovascular mortality and morbidity by aggressive lowering of the BP to under 130/80 mm Hg (National high blood pressure education program, 2003).

Chronic kidney disease is defined by the estimation of glomerular filtration rate (GFR) below 60 ml/min per 1.73 m^2, or the presence of albuminuria of > 300 mg/day or 200 mg albumin/g creatinine (National high blood pressure education program, 2003).

ACEIs and ARBs are more effective in slowing the progression of renal function for which both drugs can be used in the presence of rising serum creatinine as long as it is not over 35 percent of the baseline value, unless hyperkalemia has developed. In advanced chronic kidney disease, estimated GFR <30 ml/min 1.73 m^2, equal to a serum creatinine of 2.5-3 mg/dL, loop diuretics are usually needed (National high blood pressure education program, 2003).

Hypertension in women

People who take oral contraceptives have 2-3 times more likelihood of developing hypertension than those who do not take them, especially in obese and older women (National high blood pressure education program, 1997). If it is necessary to continue an oral contraceptive, BP should be intermittently followed up. Hormone replacement therapy has also been reported to cause slight increases in the BP level but hypertension is not a contraindication for patients having postmenopausal estrogen replacement therapy (National high blood pressure education program, 2003).

Hypertension in pregnancy is important since it has been reported that it is the major cause of mother, fetal and neonatal morbidity and mortality. Lifestyle modification should be cautiously considered depending on the gestational age and the presence of maternal and fetal risk. Body weight reduction can cause neonatal weight

reduction and normal diet without salt restriction has also been advised (Guideline committee, 2003).

Methyldopa is extensively recommended as first choice for hypertension in pregnancy and pre-eclamsia because of long term use without reports of serious effects on the fetus. ACEIs or ARBs are contraindicated due to the possibility of oligohydraminos, renal failure and hypotension, which cause fetal abnormalities including intrauterine death (National high blood pressure education program, 1997; Ramsay et al., 1999). For emergency cases, ≥170/110 mm Hg, hospitalization is recommended and consideration should be given to giving intravenous labetalol, or oral methyldopa, or nifedipine. Hydralazine intravenously is no longer recommended due to perinatal adverse effects. Diuretics are also inappropriate because pre-eclampsia has reduced plasma volume. However, magnesium intravenously can prevent eclampsia and can be used in the treatment of seizure (Guideline committee, 2003).

1.1.3 Blood pressure measurement

1.1.3.1 History

The technique of measuring BP has a long and fascinating history. Stephen Hales (1677-1761) was the first person who described the direct measurement of BP. He measured horse BP with a brass cannula inserted into the horse's carotid artery. This brass cannula was connected to a glass manometer which gave BP reading in feet of water (Figure 1.2). A century later, Frederick Mahomed (1849-1884) reported elevated BP using an adapted Marey's sphygmograph which recorded the pulse wave.

Although it was not widely used, because it was crude, it showed that elevated BP could occur independently of the presence of renal disease.

Cipione Riva-Rocci (1863-1920) designed an air-filled rubber bladder as an occlusive cuff for measuring systolic BP. Nikolai Sergeyevich Korotkoff (1874-1920), a Russian military surgeon, observed the relationship between the arterial sound generated with the deflation of the Riva-Rocci cuff. The pressure at which the heart beat sound disappeared was described as the diastolic BP. He suggested that the simultaneous use of a stethoscope helped to measure both systolic and diastolic BP.

Figure 1.2 Hales making manometric measurements from the carotid artery of a horse in 1733 (Poulter et al., 2000)

1.1.3.2 Blood pressure measurement techniques

Hypertension detection begins with a proper measurement using accurate equipment. Although nowadays sphygmomanometer use is declining because of the safety and for health reasons, JNC-6 still prefers the sphygmomanometer for BP

measurement, otherwise, a calibrated aneroid manometer or a validated electronic device (National high blood pressure education program, 1997). Frequent retraining and meticulous technique are also required for accuracy in a person who performs a measurement (Table 1.2 and 1.3).

Self-measurement of BP at home is cheaper than ambulatory BP monitoring. If patients can do this after being instructed by a professional, self-measurement provides many advantages including the absence of the white coat syndrome, (when automated devices are used) and the absence of observer bias (Staessen et al., 2003).

The diagnosis is based on two or more properly performed measurements of seated BP readings at intervals dependent on the height of the BP, presence of target organ damage, and other cardiovascular risk factors. If there is a slightly elevated BP, the next measurement should be done within a few months, because of the possible regression to normal levels. If there is a marked elevation with evidence of hypertension-target organ damage, or a very high risk cardiovascular profile, repeated measurements should be obtained within days or weeks (Guideline committee, 2003).

Blood pressure monitoring devices

Manual sphygmomanometers

Aneroid devices are used as the home BP measurement device because the lack of mercury makes their use safer.

A mercury sphygmomanometer measures the pressure in the cuff. Sphygmos which is from the Greek means pulse. The Korotkoff description is heard by placing the stethoscope over the brachial artery (Figure 1.3). While the BP is lower than the

occluded pressure, the first sound is heard when the blood spurts along the artery from the point below the occlusion and this is taken as the systolic BP. As the pressure is allowed to fall, the sounds become muffled and disappear when the pressure is equal to the occluded pressure see Table 1.2.

Automated sphygmomanometers

There are a large number of automated devices used to measure BP, virtually all of which use the oscillometric technique. These devices use automated inflation and deflation of the cuff which is applied on the upper arm over the brachial artery. Recently the measurement devices have been used to measure BP over the radial artery at the wrist. This position is not at heart level and this makes these recent devices inaccurate to use. The same argument applies to the devices used over the radial artery at the finger. Additionally, the finger measurement may cause peripheral vasoconstriction. For these reasons neither the wrist or finger position are recommended for BP measurement (O'Brien et al., 2001).

Ambulatory BP monitoring (ABPM) reflects the BP pattern over the total 24-hour period. It is thought to be helpful for diagnosis of white coat hypertension. In this approach, ABPM is now approved for reimbursement by Medicare for detecting white coat hypertension. Medicare requires 3 home readings that show normal BP and 3 office readings showing high BP. There must not be any evidence of target organ damage and the patient has to be untreated. These criteria make it of restricted use because it is expensive and should be purchased with accompanying software (Victor, 2004).

Table 1.2 Techniques for BP measurement (O'Brien et al., 2002)

1. Patients should be seated in a chair with their backs supported and their arms bared and supported at heart level. Patients should refrain form smoking or ingesting caffeine during the 30 minutes preceding the measurement.
2. Under special circumstances, measuring BP in the supine and standing positions may be indicated.
3. Measurement should begin after at least 5 minutes of rest. The appropriate cuff size must be used to ensure accurate measurement. The bladder within the cuff should encircle at least 80% and the bladder width should be at least 40% of the arm (Joseph and Carter, 2001). Many adults will require a large adult cuff.
4. Measurement should be taken preferably with a mercury sphygmomanometer; otherwise, a recently calibrated aneroid manometer or a validated electronic device can be used.
5. Inflate the cuff to determine the SBP by observing the point at which the radial pulse is no longer palpable. Deflate the cuff and wait 15 to 30 seconds before reinflating (Joseph and Carter, 2001).
6. Position the stethoscope over the brachial artery and rapidly inflate the cuff to 20 to 30 mm Hg above the point determined in step 5. Deflate the cuff at a rate of 2 mm Hg per second, listening for phase I and phase V (phase IV for children) Korotkoff sounds. Phase V, at the disappearance of sound, is the DBP in adults. Listen for 10 to 20 mm Hg below phase V for any further sound, then deflate the cuff completely (Joseph and Carter, 2001).
7. Both SBP and DBP should be recorded. The first appearance of sound (phase 1) is used to define SBP. The disappearance of sound (phase 5) is used to define DBP.
8. Two or more readings separated by 2 minutes should be averaged. If the first 2 reading differ by more than 5 mm Hg, additional readings should be obtained and averaged.
9. Record the BP in even numbers and document the patient's position, arm used, and cuff size (Joseph and Carter, 2001).
10. Clinicians should explain to patients the meaning of their BP readings and advise them of the need for periodic measurement.

Table 1.3 Factors which may influence blood pressure measurement in the clinic setting adapted from reference (Kaplan, 1998)

Factors which increase recorded BP	Factors which decrease BP	Factors which have no effect on BP
RELATING TO THE EXAMINEE	RELATING TO THE EXAMINEE	RELATING TO THE EXAMINEE
Soft Korotkoff sounds	Soft Korotkoff sounds	Menstrual phase
Pseudohypertension	Meal eaten within 30 minutes	Chronic caffeine ingestion
White coat reaction to:	Missed auscultatory gap	Phenylephrine nasal spray
Physician	High stroke volume	Cuff self-inflation
Nonphysician	Habituation	
Paretic arm (due to stroke)	Shock	RELATING TO THE EXAMINEE AND EXAMINER
Pain, anxiety		
Acute smoking	RELATING TO THE SETTING OR EQUIPMENT	Discordance in sex or race
Acute caffeine		
Acute ethanol ingestion	Noisy environs	RELATING TO THE EXAMINATION
Distended bladder	Faulty aneroid device	
Talking: signing	Low mercury level	Thin shirtsleeve under cuff
	Leaky bulb	Stethoscope of bell vs. diaphragm
RELATING TO THE SETTING OR EQUIPMENT	RELATING TO THE EXAMINER	Cuff inflation per se
Environment noise	Reading to next lowest 5 or 10 mm Hg or expectation bias	
Leaky bulb valve	Impaired hearing	
Blocked monometer vents		
Cold hands or stethoscope	RELATING TO THE EXAMINATION	
RELATING TO THE EXAMINER	Noisy environs	
Expectation bias	Left vs. right arm	
Impaired hearing	Resting for too long (25 min)	
	Elbow too high	
RELATING TO THE EXAMINATION	Too rapid deflation	
Cuff too narrow	Excess bell pressure	
Cuff not centered	Parallax error (aneroid)	
Cuff over clothing		
Elbow too low		
Cuff too low		
Too short rest period		
Back unsupported		
Too slow deflation		
Too fast deflation		
Parallax error		
Using phase IV (adult)		
Cold season (vs. warm)		

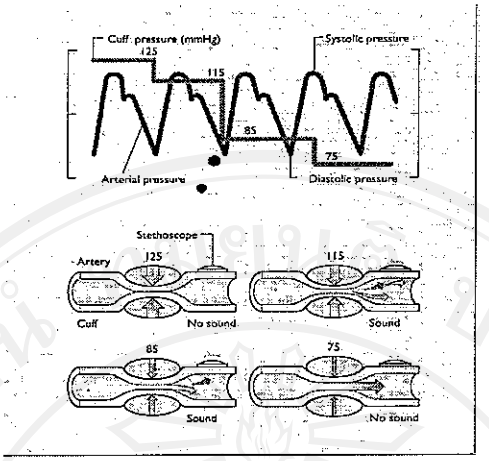

Figure 1.3 Sounds heard with application of the stethoscope over the palpable artery (Poulter et al., 2000)

Some studies use ABPM in their studies as a tool for determining isolated physician's office or surgery hypertension and as a stronger predictor of cardiovascular morbidity and mortality than conventional surgery BP measurement (Bjorklund et al., 2003; Gardner and Schneider, 2001).

1.1.4 Pathophysiology and etiology

There are a small number, between 2-5%, of underlying renal or adrenal diseases which cause hypertension called secondary hypertension (Beevers et al., 2001). The majority of specific underlying diseases are unknown but there are influences on hypertension resulting from heterogeneous genetic and environmental causes called essential hypertension or primary hypertension (Staessen et al., 2003).

1.1.4.1 Essential hypertension or primary hypertension

Although the etiology of essential hypertension is largely unknown, heredity is a predisposing factor. Environmental factors (e.g., dietary Na^+, obesity, stress) seem to act only in genetically susceptible people.

The pathogenic mechanisms lead to an increased cardiac output (CO) or to an increased total peripheral vascular resistance (TPR) or both. Figure 1.4 shows that these two factors maintain BP homeostasis. At the initial development of hypertension, the CO increases as the result of sympathetic nervous system overactivity. Later CO returns to normal because of the raised TPR which acts as a compensatory mechanism to the increased CO (Beevers et al., 2001).

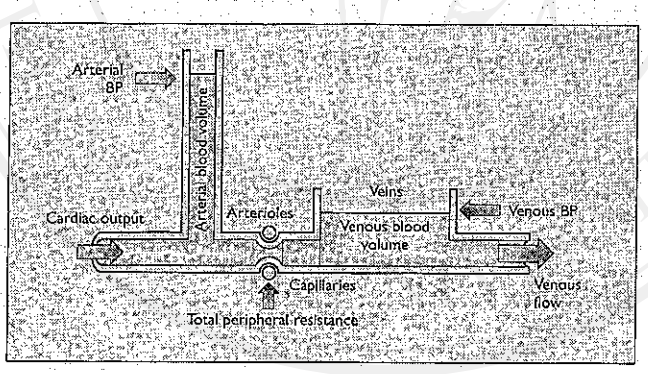

Figure 3.1. The regulation of BP within the cardiovascular system.

Figure 1.4 The regulation of BP within the cardiovascular system (Poulter et al., 2000)

1.1.4.1.1 Neural components

There is a close relationship between the nervous system, especially the sympathetic system and hypertension. The explanations include a similarity in

response between adrenalin and noradrenalin to cardiovascular modification in hypertension and, hypersensitivity to adrenalin in a hypertensive man. In addition hypertension is caused by pheochromocytoma, that is tumors in the adrenal medulla, which secrete excess adrenalin and noradrenalin. Antihypertensive drugs can also modify catecholamines, such as reserpine, reducing central and peripheral catecholamines, guanethidine reducing catecholamines in peripheral nerve endings, alpha-methyldopa producing a false transmitter at the nerve terminal, phenoxybenzamine and propranolol blocking alpha- and beta-adrenergic receptors respectively and clonidine having adrenergic and agonistic actions in the central nervous system (CNS) (Meyer, 1980).

Stimulation of the sympathetic nervous system raises BP more commonly in hypertensive or prehypertensive persons. A high resting pulse rate which may be a manifestation of increased sympathetic nervous activity, is a well-known predictor of subsequent hypertension (The Merck Manual of diagnosis and therapy, No date). The regulation by the CNS of arterial BP depends on the neurotransmitters, catecholamine-adrenalin, noradrenalin and dopamine, each of which has a different enzymatic content. For example, only adrenalin is found in the CNS because the peripheral neurons lack the enzyme which is necessary to convert noradrenalin to adrenalin.

BP regulation is also related to alpha and beta receptors (beta1 and beta2), which are located in pre and post synaptic neurons. In the brain, the stimulation of alpha receptors results in a BP decrease due to inhibition on the vasomotor center. However, the stimulation of alpha receptors on the postsynaptic arterioles and venules results in the BP being increased. Stimulation of beta1 receptors increases the heart

rate and results in contraction of the heart muscle, whereas, stimulation of beta2 receptors causes vasodilation.

Negative feedback controls, called baroreceptor reflexes, also form an important regulatory mechanism. Baroreceptor reflexes are nerve endings which are located in large arteries and respond to sudden changes in arterial BP. If a sudden change in BP occurs then baroreceptor reflexes will increase the discharge through the ninth cranial nerve and vagus nerve to the brain stem resulting in vasodilation through the peripheral circulation system and a decrease in the heart rate and strength of myocardium contraction. Baroreceptor reflexes may be blunted in elderly individuals (Hawkins et al., 1997).

Any defect of these neural components may lead to a sustained elevation in BP.

1.1.4.1.2 The renin-angiotension-aldosterone system (RAS)

Adrenal corticosteroids have been classified as mineralocorticoid or glucocorticoid. Both hormones are secreted from the adrenal cortex. Aldosterone is a hormone in the former group whereas cortisol is in the latter group. In the working of normal physiology, aldosterone is controlled by the renin-angiotensin system. Renin is a proteolytic enzyme that is synthesized and stored in the juxtaglomerular apparatus in the kidney. The release of renin activates angiotensinogen to form decapeptide angiotensin I. This is subsequently converted to angiotensin II by angiotensin converting enzyme (ACE), which is found mostly in the lung but also in the kidney, brain blood, vessels, adrenals, kidney, reproductive organs, and so on and is called tissue RAS (Gibbons, 1998; The Merck Manual of diagnosis and therapy. No date).

Angiotensin II is a potent vasoconstrictor which can elevate BP and also stimulate the release of aldosterone leading to sodium retention and potassium loss. The major triggers that stimulate renin release are perfusion pressure decrease, for example, hemorrhage, hypotension or a reduction of extracellular fluid volume after sodium depletion (Stewart, No date). This trigger leads to increased renin release and increased angiotensin II and aldosterone which increases BP and results in sodium retention.

Not only does angiotensin II stimulate aldosterone release but also ACTH and potassium. Acute ACTH secretion leads to increased aldosterone but chronic ACTH excess is associated with normal aldosterone levels. Hyperkalemia directly stimulates aldosterone synthesis.

In patients with essential hypertension, plasma renin activity (PRA) is usually normal but may be suppressed in about 25% of patients or elevated in about 15% (Stewart, No date). In black people and the elderly, PRA is quite low.

RAS as a pathogenesis of vascular syndromes is explained by the structure of the cardiovascular tree being dynamic and adaptive, and by ventricular and vascular remodeling in response to an initial injury. In addition angiotensin II is a toxic substance that promotes maladaptive changes such as hypertension, left ventricular hypertrophy (LVH) and congestive heart failure (CHF) (Gibbons, 1998).

The role of tissue RAS is unclear. The possible explanation is that the circulating RAS is related to the short-term changes in the regulation of acute vasoconstriction, chronotropic effects on the heart, or acute salt or water reabsorption in the kidney. Whereas the tissue RAS appears to be mostly involved with long-term changes such as the structure of cardiovascular tissue, the process of ventricular

remodeling in the heart and of vascular remodeling in the blood vessels, and the function of the kidney (Gibbons, 1998).

1.1.4.1.3 Vascular endothelial mechanisms

The vascular endothelium has an important role in regulating blood vessel tone by producing many vasoactive substances, eg. prostacyclin, bradykinin (a potent vasodilator), endothelium-derived relaxing factor (nitric oxide), angiotensin II, endothelin I (a vasoconstrictor producing a salt sensitive rise in BP) and ouabain (a steroid-like substance interfering with sodium and calcium transport) (Beevers et al., 2001; Hawkins et al., 1997). Dysfunction of the endothelium is related to essential hypertension.

Vascular endothelial mechanisms are an attractive therapeutic option to minimize the impaired production of nitric oxide, but not to improve the impaired endothelium dependent vascular relaxation or vascular response to endothelial agonists. This implies that endothelial dysfunction is irreversible after the hypertensive process has become established (Beevers et al., 2001).

1.1.4.1.4 Sodium and fluid balance

It seems that sodium and fluid balance and vasomotor tone are the cornerstones in BP regulation. The kidney plays a central part in the pathophysiology of essential hypertension.

The role of the kidney in the pathogenesis of hypertension should be distinguished from salt sensitivity (Staessen et al., 2003). Secondary forms of hypertension, for example, pheochromocytoma or hyperaldosteronism, can have an

influence to reduce the ability of the kidney to excrete a sodium load. In this case, the removal of the primary cause of hypertension can enhance sodium reabsorption. Genetic forms of hypertension, salt sensitivity may result from various mutations affecting cytoskeleton proteins, ion transporters, or endocrine factors that control renal sodium handling. In other forms of hypertension, salt sensitivity originates from an imbalance between the hormonal, nervous, or hemodynamic regulation which control sodium balance through glomerular filtration or tubular reabsorption.

Abnormal Na^+ transport is due to a defect in the Na-K pump (Na^+, K^+-ATPase) or to an increased permeability of Na^+. This leads to sensitivity to sympathetic stimulation because the Ca^{2+} follows Na^+ and is accumulated in the cell. Na^+, K^+-ATPase is responsible for the pumping back of noradrenalin into the neurons to inactivate this neurotransmitter (Stewart, No date). The inhibition of this mechanism enhances the effect of norepinephrine.

1.1.4.1.5 Genetic factors

There are multiple genes related to the contribution of essential hypertension. Nevertheless, a person who has one or two hypertensive parents is twice as likely to be hypertensive as normal (Beevers et al., 2001).

1.1.4.2 Secondary hypertension

There are several explanations of the cause of secondary hypertension which relate to renal parenchymal disease (e.g., chronic glomerulonephritis or pyelonephritis, polycystic renal disease, collagen disease of the kidney, obstructive uropathy) or pheochromocytoma, Cushing's syndrome, primary aldosteronism, hyperthyroidism,

myxedema, coarctation of the aorta, or renovascular disease Alcohol, oral contraceptives, sympathomimetics, corticosteroids, cocaine or licorice may also related to being the cause of hypertension (The Merck Manual of diagnosis and therapy, No date). Specific action to combat the causes of secondary hypertension with surgical or appropriate medical therapy can reverse the unwanted effects.

1.1.5 Diagnosis

Diagnosis is aimed at establishing the BP level, excluding secondary causes of hypertension (Table 1.4) and evaluating overall cardiovascular risk factors such as target organ damage and concomitant disease or accompanying clinical conditions (Guideline committee, 2003).

The procedures consist of (1) repeated BP measurements (2) medical history (3) physical examination and (4) laboratory and instrumental investigations.

Recommendations for routine laboratory tests to determine target organ damage and other risk factors include urinalysis, complete blood cell count, blood chemistry (potassium, sodium, creatinine, fasting glucose, total cholesterol, and high-density lipoprotein cholesterol), and a 12-lead electrocardiogram (National high blood pressure education program, 1997).

Table 1.4 Cardiovascular risk factors (Guideline committee, 2003)

Major Risk Factors	Target Organ Damage
Hypertension*	Heart
Cigarette smoking	Left ventricular hypertrophy
Obesity (body mass index ≥30 kg/m2)	Angina or prior myocardial infarction
Physical inactivity	Prior coronary revascularization
Dyslipidemia*	Heart failure
Diabetes mellitus*	Brain
Microalbuminuria or estimated GFR <60 ml/min	Stroke or transient ischemic attack
Age (older than 55 for men, 65 for women)	Chronic kidney disease
Family history of premature cardiovascular	Peripheral arterial disease
disease (men under age 55 or women under age	Retinopathy
65)	

GFR, glomerular filtration rate
* components of the metabolic syndrome

1.1.6 Treatment

Hypertension has a marked influence on stroke mortality and also adversely affects other cardiovascular problems (Wolf-Maier et al., 2003). The higher the BP, the greater is the chance of heart attack, heart failure, stroke and kidney disease (National high blood pressure education program, 2003).

The goal of the treatment is to reduce the risk of cardiovascular disease by decreasing BP. BP reductions maintained for a number of years, especially systolic BP reductions, have been reported to be associated with 30% and 23% reductions in the number of strokes and coronary events respectively (Staessen et al., 2000). This study also showed that a 10 mm Hg increase in systolic BP was significant and

independently correlated with an almost 10% in the risk of all fatal and non-fatal complications, except coronary events (Staessen et al., 2000).

1.1.6.1 Goal BP value

The goal in treating BP is to reduce potential complications and risk of cardiovascular morbidity and mortality. The JNC-7 states that for persons with hypertension aged ≥50 years, the primary focus should be on SBP. The target of treatment should be SBP and DBP <140/90 mm Hg because this helps to decrease cardiovascular disease (CVD) complications. In patients with diabetes or renal disease, the BP goal is < 130/80 mm Hg. This is different from the JNC-6 guidelines, (National high blood pressure education program, 1997) which were <130/85 mm Hg in diabetes and <125/75 mm Hg in renal disease with proteinuria more than 1 gram/day. The American Diabetes Association 2003 and other studies support the JNC-7 goals (American Diabetes Association, 1997; American Diabetes Association, 2003; Klag et al., 1997; Lazarus et al., 1997; National high blood pressure education program working group, 1994).

1.1.6.2 Pharmacological treatment

The initiation of pharmacological treatment depends on the presence of target organ damage, the degree of BP level, the other cardiovascular risk factors and the compelling indication (National high blood pressure education program, 1997).

For most patients, a low dose of the initial drug of choice should be used and then titrated up depending on the response, patient's age and needs. Optimal preparations of medicines should have 24-hour efficacy to maintain a smoothly

balanced BP, prevent the sudden death from heart attack and stroke which could result from an abrupt increase of BP when arising from overnight sleep. The preparation should also encourage adherence and be of low cost (National high blood pressure education program, 1997).

When it is needed to start pharmacological treatment, a thiazide diuretic is usually recommended as an initial monotherapy or as a combination with other drugs (ACEIs, ARBs, BBs and CCBs). Thiazide diuretics are useful in achieving BP, more affordable than other antihypertensive drug and can prevent cardiovascular diseases with a similar efficacy to ACEIs or CCB (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

The JNC-7 recommendation is to use at least 2 drugs as an initial therapy when the BP is more than 20/10 mm Hg above the goal (National high blood pressure education program, 2003). Particular caution should be advised for those who are at risk of hypotension especially diabetics, those with autonomic dysfunction and some older patients.

1.1.6.3 Nonpharmacological treatment

Lifestyle modifications are necessary in order to control BP. In stage 1 hypertension these consist of weight reduction to ideal levels, modest Na restriction to <2 g/day, and alcohol consumption to <1 oz/day. Such modifications may make drug therapy unnecessary (The Merck Manual of diagnosis and therapy, No date).

Weight and BP are strongly related especially in women (Sharabi et al., 2004). Weight reduction is recommended for those with general obesity or abdominal obesity to stabilize at normal body weight with body mass index (BMI) of 18.5-24.9 kg/m^2.

Ten kilograms in weight loss leads to at least a 5-20 mm Hg decrease in BP (National high blood pressure education program, 2003). Weight loss needs to be reinforced at every visit because maintaining optimal weight is more difficult than initiating weight reduction especially if eating habits have not been altered (Zellner and Sudhir, 1996).

Regular exercise is also recommended especially aerobic physical activity, e.g., brisk walking, biking, jogging and swimming at least 30 min per day, most days of the week (Guideline committee, 2003; National high blood pressure education program, 2003). Kazuko and colleagues showed that the suitable reduction in BP was obtained when 61-90 minutes/week was spent in exercise, although 30-60 minutes/week could be sufficient to reduce both systolic and diastolic BP in stage 1 or 2 essential hypertension (Kazulo et al., 2003).

Recommendations to reduce sodium intake less than 100 mmol per day (2.4 g sodium or 6 g sodium chloride) are widely supported due to the relation of BP reduction of 2-8 mm Hg (National high blood pressure education program, 1997; National high blood pressure education program, 2003; Sacks et al., 2001). However, Hooper and colleagues showed that the advice to reduce salt provided only a small reduction in BP and the effect on deaths and cardiovascular events were unclear (Hooper et al., 2002).

Alcohol has a pressor effect which leads to increase in BP, even in normotensive persons (Zellner and Sudhir, 1996). Daily intake should not be more than 2 drinks (1oz or 30 ml ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) in men and not more than 1 drink in women and people of lighter weight (National high blood pressure education program, 2003).

Smoking cessation should be strongly and repeatedly encouraged without hesitation in all patients. Although stopping smoking does not help BP control, antihypertensive drugs fail to protect against coronary artery disease and stroke in the presence of tobacco use (Zellner and Sudhir, 1996).

Caffeine has a strong, persistent, acute pressor effect and increases BP but not significantly. Vlachopoulos and colleagues showed that caffeine consumption acutely increase aortic stiffness in treated hypertensive patients. From this caffeine consumption was implicated to have an effect on cardiovascular risk in hypertension (Vlachopoulos et al., 2003). A review indicated that caffeine use could account for premature deaths in 14% of people with coronary heart disease and 20% of people with stroke (James, 2004).

1.2 Outcome Research

Outcomes research is a research method that has been increasingly used to measure the quality of care and the effectiveness of health care provided to patients.

The most recent model of health care outcomes provides a theoretical framework for systematic planning of outcomes research. This is the ECHO model. ECHO represents economic, clinical and humanistic outcomes. The model implies that pharmacists should take account of clinical outcomes when they are making decisions involving patients. The other two outcomes are wider in scope. Economic outcomes are defined as "the total costs of medical care associated with treatment alternatives, balanced against the costs and benefits of clinical or humanistic outcomes." Humanistic outcomes refer to "patient evaluations of the impact of treatment on their lives (e.g., health-related quality of life, satisfaction with care) (Kozma, 1995).

Outcomes in this study were mainly aimed to evaluate clinical and humanistic outcomes. These were BP control, BP reduction, patient satisfaction, patient knowledge and quality of life. Economic outcomes were assessed only for costs of medications.

1.2.1 Patient satisfaction

Patient satisfaction is one component of quality of care (Donabedian, 1980) and can also serve as a predictor of health-related behaviour (Pasco, 1983). Measuring patient satisfaction was the most important outcome measure about health services according to patients who evaluated those services (Williams, 1994). Patient expectation is one determinant of satisfaction which relates to the patient perception of the benefit of care and the extent to which the services meet the patient's expectation (Sitzia and Wood, 1997). There are many concepts of patients' satisfaction with pharmaceutical care. Nau and colleagues showed that patients who perceived benefit and value form pharmaceutical care showed enhanced satisfaction and returned for more services (Nau et al., 1997).

There have been many studies of patient satisfaction of medical care and some have specifically investigated pharmacy services. MacKeigan and Larson developed and validated a survey of patient satisfaction with pharmaceutical services using telephone interviews (MacKeigan and Larson, 1989).

Patient satisfaction has been classified in several ways. A definitive taxonomy of Ware and colleagues was described in the review of Sitzia and Wood (1997). The taxonomy is composed of eight dimension: (1) interpersonal manner; the way providers interact with patients, (2) technical quality of care; the competence and

adherence of providers in high treatment standard, (3) accessibility/convenience; factors involved to receive the care, (4) finances; factors involved with the medical payment, (5) efficacy/outcomes of care; the results after the service provided, (6) continuity of care; the consistency in providing care, (7) physical environment; the features of setting provided, (8) availability; the medical care resources (Sitzia and Wood, 1997).

1.2.2 Quality of life

Health related quality of life (HRQOL) is a specific term with regard to health and is a very useful and important indicator of patients' health perceptions resulting from their treatment. A strong association has been found between respondents' judgments of their health in general and mortality over a 12 year follow-up period (Idler and Angel, 1990). There is an increasing awareness of the importance of HRQOL and both researchers and clinicians are paying more attention to evaluating HRQOL as a substantial outcome to be measured routinely in clinical care (Guyatt et al., 1997). In chronic conditions, where prevention or cure is not possible, the provision of pharmaceutical care can have the aim of improving HRQOL as a realistic outcome (Kheir et al., 2004).

The content validity, criterion validity, construct validity, reliability and responsiveness of the instruments must be assessed before choosing a particular measurement. Most of the instruments in previous hypertension studies had been proven to be reliable and valid as reported in the study of Isabelle and colleagues (Isabelle et al., 2000). Their interesting comment was that if an instrument failed to

measure significant change in HRQOL, it might not be due to the instrument but rather to the ineffective intervention or inadequate statistical power.

Quality of life measures can be divided as generic or condition/disease-specific measures.

Generic measures are designed to assess HRQOL across different diseases or different populations. This broad application allows the comparison between groups or people with different conditions. But these instruments may lack the precision to either discriminate between specific groups of people or to be responsive to changes by treatment (Carr et al., 2003). The most frequently used instruments are the modified RAND Corporation Medical Outcome Study questionnaire, the Nottingham Health Profile (NHP), the Medical Outcomes Study 36-Item Short-Form Health Survey and the Sickness Impact Profile (Isabelle et al., 2000).

Disease specific measures focus on particular problems or diseases which can discriminate between specific groups and respond to change. These measures preclude their use in cross-disease comparison or populations because of ruling out unnecessary and irrelevant items (Carr et al., 2003). There are seven dimensions of health which are frequently used. Firstly, the cognitive function dimension in which the three most frequently used instruments were the Digit Span test, the Trial Making test and the Digit Symbol Substitution test. Secondly, the symptomatic well-being dimension in which the most frequently used instrument was the Physical Symptoms Distress Index (PSDI). Thirdly the sexual function dimension in which the Sexual Symptom Distress Index (SSDI) was the most often used instrument. Fourthly, the general well-being dimension in which the most popular instruments were the Psychological General Well-Being Index (PGWB), the General Well-Being Adjustment Scale (GWBAS), the

Symptom Rating Test (SRT) and the Profile of Mood State (POMS). Fifthly, the sleep dysfunction dimension was reported using the Sleep Dysfunction Scale. Sixthly, the social participation dimension which was measured by many instruments in which there was no one instrument dominant more than the others. Seventhly, the general health perception dimension in which the two instruments were frequently used which were the Health Status Index (HSI) and the General Perceived Health scale (GPH) (Isabelle et al., 2000).

In this study, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), a generic instrument, and the Digit Span test, a specific instrument, were selected. This was because SF-36 had been translated, validated and proved to be reliable to use in Thai version and one study showed significant changes compared between hypertensive patients and volunteers and between complicated hypertensive patients and uncomplicated hypertensive patients with the use of SF-36 in hypertensive patients (Leurmarnkul, 1997). A specific instrument, the Digit Span test, was selected in assumption of higher responsiveness in the change. In addition to antihypertensive medications, hypertension itself is strongly related to cognitive dysfunction (Kilander et al., 1998; Launer et al., 1995).

SF-36 measures quality of life in eight dimensions which cover physical and mental health. Physical health is composed of four dimensions; Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP) and General Health (GH). Mental health also contains four dimensions which are Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH). PF contains 10 items of 3a; vigorous activities, 3b; moderate activities, 3c; lift, carry groceries, 3d; climb several flights of stairs, 3e; climb one flight of stairs, 3f; bend, kneel, 3g; walk one mile, 3h; walk

several blocks, 3i; walk one block, and 3j; bathe, dress. RP has four items consisting of 4a; cut down time, 4b; accomplished less, 4c; limited in kind, 4d; had difficulty. BP has two items of 7; pain-magnitude and 8; pain-interfere. GH is composed of five items of 1; rating of general health, 11a; get sick easier, 11b; as healthy, 11c; health to get worse and 11d; health excellent. VT contains four items of 9a; life, 9e; energy, 9g; worn out, 9i; tired. SF has two items of 6; social-extent and 10; social-time. RE has three items of 5a; cut down time, 5b; accomplished less and 5c; not careful. MH contains of five items of 9b; nervous, 9c; down in dumps, 9d; peaceful, 9f; blue/sad and 9h; happy (Ware, 2000).

Digit span test is to test the patient's ability to concentrate. There are two sets of numbers, the first set is for a forward recall and the other is for a backward recall. The forward test begins with two numbers spoken clearly at a steady rate, then the patient is asked to repeat the numbers. If the repetition is right, the test continues with a series of three numbers and so on as long as the patient responds correctly. The test is stopped and a note made of the failure between repeating the numbers a second time. Then the other set of numbers is started beginning with two numbers and asking the patient to repeat the two numbers backwards after you. The test is stopped and a note made of the failure after the second failure. The normal range of forward numbers is 7 ± 2 and of backward numbers it is 5 ± 1. Causes of poor performance include delirium, dementia, mental retardation and performance anxiety (Bickley and Szilagyi, 2003).

1.3 Pharmaceutical care model

1.3.1 Definition

Pharmaceutical care was first defined in 1975 and has been continuously developed. Hepler and Strand in their paper in 1990 provided the definition: "Pharmaceutical care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for the patient's drug-related needs" (Cipolle et al., 1998). Two activities should be practiced by the pharmacist (1) they should determine the patient's specific wishes, preferences, and needs of his or her illness and (2) monitor the patient's outcomes after initiating treatment. These concepts lead to the descriptor: "pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Cipolle et al., 1998).

1.3.2 Pharmaceutical care in practice

Pharmaceutical care, both in theory and practice, is primary health care. The basic foci of pharmaceutical care and primary health care are the same. According to the definition, the pharmacist should engage in a systematic comprehensive service to accomplish three primary functions; (a) identify a patient's actual and potential drug related problems, (b) resolve the patient's actual drug related problems, and (c) prevent the patient's potential drug related problems from becoming actual problems (Strand et al., 1992).

The process to achieve the goal is (a) establish and maintain the pharmacist and the patient relationship (b) collect, synthesize, interpret and maintain patient

medical information (c) evaluate patient information by listing and ranking drug related problems, determining pharmacotherapeutic alternatives, choosing the best one for the individual and develop a therapeutic drug monitoring plan (d) assure that the patient has all necessary supplies, information and knowledge to carry out the drug therapeutic plan (e) review, monitor, modify and implement the therapeutic plan as necessary and appropriate with the patient and health care team (American Pharmacy Association, No date).

1.4 The role of pharmacist as a practitioner in primary health care

The role of the pharmacist in the provision of health care has changed throughout more than 700 years (Lunde and Dukes, 1989). Originally, medicines came from herbs or animal products which were prepared for individual use. In Europe, the charter to create a medical service was decreed by the German-Roman Emperor Frederick II in 1240. This was the foundation of the pharmaceutical system. In the late 19^{th} and early 20^{th} centuries, many medicines were developed and synthesized, such as the extraction of morphine from opium, a number of pain relieving and fever reducing agents, the production of pure adrenaline and insulin and development of the synthetic agent against syphilis known as salvarsan (Lunde and Dukes, 1989). All these developments led to a technological change of the chemical industry. Unfortunately tragedies were also attributable to new drugs, notably that caused by thalidomide. This resulted in more comprehensive toxicity testing and extensive clinical trials before releasing drugs for human use.

In primary care, pharmacists have developed new tasks which are involved with the provision of knowledge as well as direct or indirect participation in individual

patient care. This patient-oriented practice developed as clinical pharmacy. The practice of primary health care is a more "generalist" type of practice in which the focus has changed from illness to health, from cure to prevention and care (Cipolle et al., 1998). Primary health care is "based on the centrality of the patient rather than on an organ system or a disease, as is the case with specialism"(Cipolle et al., 1998).

Clinical pharmacists provide a wide range of ambulatory care in primary care setting which includes community pharmacies (American College of Clinical Pharmacy, 1994). The first type of practice pharmacists has responsibility for providing primary care to patients, usually between physician visits. For example, pharmacists have conducted patients' complete medical history, having made physical assessments and have ordered laboratory tests and determined when to start and stop or change a medication regimen. This is the practice in pharmacist-managed clinics, e.g., for hypertension, diabetes, hyperlipidemia, anticoagulation and pharmacy service clinics, in Veterinarians Affairs (VA) hospitals and medical centers. The second type of practice pharmacists work in interdisciplinary teams to care for patients in the same place as physicians (American College of Clinical Pharmacy, 1994).

Pharmacy practice has changed further in recent years and led to innovations to the working of interdisciplinary teams. Pharmacists in primary care have become involved with many clinics, including clinics for patients with hypertension and in this way influenced patient outcomes such as blood pressure control, blood pressure reduction, increased compliance, greater patient satisfaction, better quality of life, cost reduction or more cost effective medication.

Pharmacists' involvement in hypertensive patients have been reviewed over the past ten years, 1994-March 2005. There were 10 studies and two abstracts as shown in Table 1.5.

Table 1.5 Summary of studies of pharmacists' involvement with hypertensive patients

1. Implementation of a clinic for pharmacist review of hypertensive patients in primary care (Abstract) (Reid et al., 2003)	
Study	Edinburgh
Methods	One group pre post test design
Participants	352 patients with hypertension who were identified from the practice computer system and the diagnosis was confirmed by the medication notes
Interventions	A pharmacist led clinic for primary prevention of CHD and secondary prevention of atherosclerotic 10 months follow-up
Outcomes	BP control at target : proportion (BP control/total) at the pre test 72/206 patients at the post test 173/206 patients CHD risk management: for primary prevention (n=188) at the beginning there were 17 received an antiplatelet agent after intervention 101 received it ($p<0.01$); for secondary prevention (n=54) at the pre test 40 received an antiplatelet agent which increased to 52 ($p<0.01$)
2. Physician-pharmacist comanagement of hypertension: A randomized, comparative trial (Borenstein et al., 2003)	
Study	USA
Methods	RCT
Participant	Patients with a capitated health insurance from two main offices (a group medical practice of general internists and internal medicine subspecialists affilitated with a large community hospital); Inclusion: $\geq$ 18 years, diagnosis with a code of HT; Exclusion: advanced dementia, terminal illness, organ transplant and secondary hypertension Treatment gr. = 98 patients; Control gr. = 99 patients
Intervention	Algorithm for HT management was set up by physicians, pharmacists and nurses; Treatment group-pharmacists did practice followed the algorithm; Control group-no pharmacist involvement 12 months follow-up
Outcome	SBP showed significant decrease in Treatment gr. when compared with Control group DBP did not show any significant difference.
3. Evaluation of a pharmaceutical care program for hypertensive patients in rural Portugal (Garcao and Cabrita, 2002)	
Study	a private pharmacy serving a rural area in the western part of Portugal
Method	RCT
Participant	100 patients from the pharmacy who were taking HT medications furosemide and receiving care from physicians.

	Exclusion: patients who were unable to attend scheduled meeting, who were not interested in participating in the study, who had a spouse enrolled in the study in the other groups and who had been on HT medications < six months. Treatment gr. = 41 patients; Control gr. = 41 patients
Intervention	Pharmaceutical care; BP measured by the research pharmacist Six months follow-up
Outcomes	The proportion of patients who had BP control/total patients was 24/31 in Treatment gr. and 3/29 in Control gr., $p<0.05$. At the baseline, there were 31 in Treatment gr. and 29 in Control gr. who had uncontrolled BP.

4. Pharmacist-led hypertension drug use review (Abstract) (Braybrook et al., 2002)

Study	West Glucestershire Primary Care Trust
Method	One group design (not RCT, no control group)
Participants	HT patients identified by practice computer drug searches; Exclusion was patients with Raynaud's disease, uncontrollable angina/blood pressure, known to be resistant to change 211 patients (76% HT, 14% Angina, 10% HT+angina and 1% Raynaud's disease)
Interventions	medication review at the consultation and discussion as appropriate; Change CCB to felodipine
Outcomes	186 patients were changed to felodipine; DBP >90 mm Hg in 25 patients, 19 of these patients had better BP control after the Review

5. Effect of pharmacist intervention and initiation of home blood pressure monitoring in patients with uncontrolled hypertension (Mehos et al., 2000)

Study	a family medicine residency training clinic
Method	RCT
Participant	HT stage 1 or 2 (JNC-6)
	Inclusion: ≥ 35 years old, HT medication ≥ 1 item, ability for home BP, signing consent;Exclusion: stage 3 HT, secondary cause of HT, AF, pregnancy, current home blood pressure monitoring, failure to demonstrate correct use of monitoring device and drug or alcohol abuse
Intervention	Telephone contact after one month from the beginning to evaluate home BP if BP was >140/90 mm Hg, they were called at two months interval. Control group had no home BP machine Six months follow-up
Outcomes	BP decrease showed significant differences between groups in SBP, DBP and MAP. BP control <140/90 mm Hg after six months, the proportion of BP control/total were 8/18 in Treatment gr. and 4/18 in Control gr.; QOL did not show any significant difference.

6. Improving blood pressure control in a pharmacist-managed hypertension clinic (Vivian, 2002)

Study	VA Philadelphia, Pennsylvania
Method	RCT
Participant	56 patients (27 Treatment gr./29 Control gr.) 53 patients completed the study; Inclusion: HT stage 1, 2 or 3 (JNC-6), ≥ 18 years, diagnosis essential HT, receiving drugs from VA pharmacy, not receiving care at the pharmacist-managed clinic (until the study began); Exclusion: secondary cause of HT, missing more than three appointments in the last year, HT crisis, NYHA class III, IV, ESRD, a psychiatric disorder, severe hepatic dysfunction
Intervention	Pharmacist managed clinic
Outcomes	BP control <140/90 mm Hg, the proportion of BP control/ total was 21/26 in Treatment gr. and 8/27 in Control gr. (p=0.001); Compliance did not show significant difference. Patient satisfaction and quality of life (SF-36) did not show any significant difference either.

7. Pharmacoeconomic evaluation of a pharmacist-managed hypertension clinic (Okamoto and Nakahiro, 2001)

Study	a hypertension clinic and general medicine clinics with a managed care facility
Method	RCT
Participant	Inclusion: ≥ 18 years, a member of the managed care organization at least one year, filling prescriptions at the managed care organization's pharmacies, taking nifedipine/ verapamil/ captopril/diltiazem/ clonidine/ terazocine/ propranolol/ lisinopril or at least three HT medications; Exclusion: secondary HT, end organ disease (such that hospitalization was likely within the next few months) Treatment gr. = 164 patients; Control gr. = 166 patients
Intervention	Pharmacist-managed clinic (to determine the most appropriate HT regimen, to order lab as needed, to educate on non pharmacological treatment) Six months follow-up
Outcomes	Between groups comparison, there was significant differences both SBP and DBP. Within group comparison, only the Treatment gr. showed significant BP decrease, p <0.05. QOL: RF domain showed significant difference between groups.

8. Comparing standard care with a physician and pharmacist team approach for control hypertension (Bogden et al., 1998)

Study	The Queen Emma Clinic, Honolulu, Hawaii
Method	RCT
Participants	HT patients who had uncontrolled BP in the previous 6 months (JNC-5); Exclusion was when their medical conditions prevented them to receive the standard care. Treatment gr. = 49 patients, Control gr. = 46 patients
Interventions	(1) standard care (2) Physician and pharmacist as a team

Outcomes	One year study beginning in October 1993 BP reduction: mean reduction in BP 23±22/14±11 mm Hg, Treatment gr., and 11±23/3±11 mm Hg, Control gr. The proportion of BP control/total: Control gr. 9/46, Treatment gr. 27/49
9. Part 2 Clinical and economic outcomes in the hypertension and COPD arms of a multicenter outcomes study (Solomon et al., 1998)	
Study	VA Tennessee
Methods	RCT
Participants	133 patients (63 Treatment gr./70 Control gr.); Inclusion: receiving dihydropyridine or with diuretics, >=18 years old, understanding the study protocol, signing the consent, ability to read Eng; Exclusion: symptomatic of HF, taking other agents than dihydropyridine or with diuretics, alcohol or drug abuse, refusing informed consent, participating in any investigational drug within 30 days prior
Intervention	Pharmacist visit monthly over 6 months
Outcomes	BP decrease: Both groups showed decreases in mean SBP and DBP; after visit five SBP was significant lower in the Treatment gr. than Control gr.; Compliance self report was significant higher in the Treatment gr. than Control gr.
10. Blood pressure outcomes in a pharmacist-and-nurse-managed hypertension clinic: a team approach (Cookson et al., 1997)	
Study	VA California
Method	One group pre post test design (Not RCT)
Participant	22 new hypertensive patients (It did not clearly state the inclusion and exclusion criteria)
Intervention	12 months follow-up by a pharmacist and nurse management
Outcomes	Mean BP was 156 ± 19/ 96 ±10 mm Hg, next appointment was 142±15/ 89±14 which showed significant improvement ($p<0.05$)
11. Evaluation of hypertensive patients after care provided by community pharmacists in a rural setting(Carter et al., 1997)	
Study	Medical clinic, Taylorville, Illinois
Method	RCT single blind
Participant	HT patients; Inclusion: men and women in any racial group ≥ 18 years old, essential HT, signing informed consent, receiving care from one of the physicians in the medical center or the annex; Exclusion: secondary causes of HT, unwilling to return to the clinic pharmacy, BP > 210/115 mm Hg, having serious conditions Treatment gr. = 25 patients; Control gr.= 26 patients
Intervention	Pharmacist's monthly visit for six months

Outcome	BP control improved only in within group comparison, (not between group); Treatment gr., pre 151± 21/ 82± 9 mm Hg at the post test: 140± 14/80± 8 mm Hg; Control gr.: pre 145± 19/80± 9 at post test 143± 20/79± 10 mm Hg; QOL within group comparison showed sig. diff in PF, RF and BP domains only in the treatment group (t test). No difference between group comparisons was found.
12. Pharmacists' ability to influence outcomes of hypertension therapy (Erickson et al., 1997)	
Study	Internal medicine clinic of a University health center (Michigan)
Methods	RCT (a concurrent cohort design)
Participant	essential HT; Treatment gr. =40 patients, Control gr. = 40 patients
Intervention	Pharmaceutical care provided for 5 months by staff, students, fellows in each regular scheduled
Outcomes	BP control <140/90 mm Hg: Treatment gr. 18/40,Control gr. 12/40 (p=0.017) BP decrease showed significant difference between groups only in SBP. Within group comparison showed significant. BP improvement only in the treatment group. QOL did not show any significant difference between groups.

RCT = randomized control trial, QOL = quality of life, BP = blood pressure, gr.= group, HT = hypertension, RF = role limitation due to physical problem, JNC-5 = the Fifth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, VA = Veterans Affairs Medical Centers

In Thailand at present there are not many community pharmacists who work full time in a primary health care setting either in primary care units or community pharmacies. The role of pharmacists concentrate on working as a hospital dispenser or a drug seller until 2 Universities, Mahasarakham University (MSU) and Naresuan University, provided 6 year PharmD programs beginning in MSU in 1999. Since then the profession of pharmacy has gradually changed. The PharmD program aims to produce pharmacists with more clinical knowledge and competent to practice the pharmacy profession in the area of primary care in Thailand.

1.5 General aims of the study

The purpose of the study described in this thesis was to evaluate the clinical, humanistic and economic outcomes, for patients being treated for hypertension, resulting from introducing pharmaceutical care through a community pharmacy and in two primary care units (PCUs).

1.6 Research framework

Research framework is shown in Figure 1.5.

Figure 1.5 Research framework