CME Program For Health Professionals

HYPERTENSION

The Mother of Many Illnesses

Lt. General. (R) Manzoor Ahmad, HI(M)
MBBS, FCPS (Pak), Diplomate American
Board of Pathology, FRCP (Edin), FRC Path

Dr. Sami Saeed
MBBS, MCPS (Clin. Path)
M Phil (QAU), PhD

Dr. Atif Ahmad
MBBS, MCPS (Pak)

Dr. Sadia Atif Ahmad
MBBS, FCPS (Pak)

CHAPTER ONE

High Blood Pressure

WHAT IS HIGH BLOOD PRESSURE?

High blood pressure occurs when the arterioles narrow, which causes the blood to exert excessive pressure against the vessel walls. The heart must therefore work harder to maintain this higher pressure. Although the body can tolerate increased blood pressure for months and even years, eventually the heart can enlarge and be damaged (*resulting in hypertrophy*), and injury to blood vessels in the kidneys, the brain, and the eyes can occur.

Two numbers are used to describe blood pressure; the systolic and diastolic. For example, optimal blood pressure is less than 120/80 mm Hg (systolic/diastolic). The systolic pressure is measured as the heart contracts to pump out the blood. The diastolic pressure is measured as the heart relaxes to allow the blood to flow into the heart. Blood pressure is categorized as normal, high normal, mild, moderate, severe, and very severe. Normal pressure is below 130/85 and should be everyone's upper goal. High normal is considered to be 130-139/85-89 and hypertension is above 140/90. Any blood pressure above normal should be attended to with appropriate treatments; even high normal puts one at higher risk for heart events and stroke.

Hypertension itself is further categorized into four stages: mild (140-159/90-99); moderate (160-179/100-109); severe (180-209/110-119); very severe (over 210/120). If there is a disparity in these ranges, the higher category of either measurement should be used to determine severity. For example, if systolic pressure is 165 (moderate) and diastolic is 92 (mild), the patient would still be diagnosed with moderate hypertension. Mild systolic hypertension, in fact, may be a warning sign for more severe hypertension, even if diastolic pressure is normal. A child's blood pressure is normally much lower than an adult's. Children are at risk for hypertension if they exceed the following levels: 116/76 for ages 3-5; 122/78 for ages 6-9; 126/82 for ages 10-12; and 136/86 for ages 13-15.

The National Heart Blood and Lung Institute has now further categorized high blood pressure by risk groups denoted as A, B, and C to help determine treatment. For example, group A has no risk factors for heart disease or other medical problems; people in this risk group who have mild hypertension would use diet and exercise to try to reduce their blood pressure. Mild hypertension in group C, which covers major risk factors for heart disease, however, would probably require medication.

CONFIRMATION OF THE DIAGNOSIS OF HIGH BLOOD PRESSURE

Measuring Blood Pressure.

It is a rare physical examination that does not include blood pressure measurement. The process is familiar to everyone: an inflatable cuff is placed around the arm, and the person taking the blood pressure, listens with a stethoscope over the artery. Patients should not smoke or drink caffeinated beverages within 30 minutes of the measurement. Although this test has been used for 90 years, it is not completely accurate. A person who has recently exercised or a heavy smoker who has not smoked for awhile can have a temporarily *low* pressure reading. Temporary *high* pressure can result from an arm cuff that is too small, talking during the test, or from having recently eaten foods that raise blood pressure. If a first blood pressure reading is above normal, the health professional may take two or more measurements separated by two minutes with the patient sitting or lying down, as well as one taken after the patient has been standing for two minutes. Even if blood pressure remains mildly elevated, it may not indicate hypertension. A phenomenon called **white-coat hypertension** is a common occurrence in which a patient's blood pressure rises in the presence of a physician and, presumably, returns to normal at home.

Follow-Up. People with normal blood pressure (below 130/85) should be rechecked every two years. Anyone whose blood pressure is high normal (130-139/85-89) or above should have their blood pressure monitored at home and be evaluated for organ damage. If white-coat hypertension is suspected, home monitoring is especially important in order to avoid unnecessary drug treatments. Studies have suggested that white-coat hypertension actually may pose a risk for future heart problems, although the increased danger appears to be small (7.9%) compared with the risk in those with steady mild hypertension (22%). An individual with mild to moderate hypertension found during a first examination and who has no evident organ damage should be retested at least twice over several weeks. An average of all the measurements will be considered in the diagnosis of hypertension. Persons with very severe high blood pressure or those exhibiting any evidence of organ damage due to hypertension should consider drug therapy immediately.

Home Monitoring. A number of home tests are available for checking blood pressure between doctor visits. Manual cuffs and stethoscopes are fairly accurate, but they require practice to use, and the cuff must be the right size (one size does not fit all). Devices that use a digital readout and a cuff that can be electronically inflated and deflated are proving to be as accurate as a stethoscope. In general, everyone's blood pressure varies in the same way throughout a given day. It is usually highest at work and then drops slightly at home. Pressure decreases to its lowest level during sleep but suddenly increases at waking--the highest risk period for heart attack and stroke in those with severe high blood pressure. A physician may fit a patient with a portable unit that records blood pressure during a full day's activity. This test, known as ambulatory monitoring, is particularly useful for those who experience wide blood pressure swings, such as those who have white-coat hypertension or show resistance to drug therapy. Some physicians feel that such monitoring is not worth the expense, although one study indicated that when patients record and report their own blood pressure, they don't always tell the truth. Devices that take the pressure from the finger can be dangerously inaccurate.

Physical Examination for Complications of Hypertension.

If blood pressure is elevated, the physician should check the patient's pulse rate, examine the neck for distended veins or an enlarged thyroid gland, check the heart for enlargement and murmurs, and examine the abdomen and eyes.

Medical History.

If hypertension is suspected, the physician should obtain the following information:

(1) a family and personal medical history, especially incidence of high blood pressure, stroke, heart problems, kidney disease, or diabetes;

(2) risk factors of heart disease and stroke, including tobacco use, salt intake, obesity, physical inactivity, and unhealthy cholesterol levels;

(3) any medications being taken;

(4) any symptoms that might indicate secondary hypertension, such as headache, heart palpitations, excessive sweating, muscle cramps or weakness, or excessive urination; and

(5) any emotional or environmental factors that could affect blood pressure.

Laboratory and Other Tests.

If a physical examination indicates hypertension, additional tests may help determine whether it is secondary hypertension (caused by another disorder) or essential hypertension (no other disorder is present) and whether organ damage is present. These tests include a complete blood count, a urinalysis, and measurements of potassium, blood urea nitrogen, fasting blood glucose, serum cholesterol, and serum uric acid. An electrocardiogram (ECG) should also be performed. Of possible value is a blood test that measures high levels of renin an enzyme that stimulates production of angiotensin, which constricts blood vessels. High levels may predict heart attacks in white males with high blood pressure (although possibly not in women or African American men). A urine test that detects high levels of albumin, a protein, may be an indicator of complications. An exercise stress test could be important for those with borderline hypertension. Stress-induced blood pressure in such patients has been associated with a risk for left ventricular hypertrophy.

CAUSES OF HIGH BLOOD PRESSURE

Essential Hypertension.

Hypertension is referred to as essential, or primary, when the physician is unable to identify a specific cause. This is by far the most common type of high blood pressure, occurring in up to 95% of patients. Genetic factors appear to play a major role in essential hypertension. Several genetic factors, however are probably involved that regulate important physiologic processes and interact with environmental influences to produce essential high blood pressure. Experts appear to have located the chromosomes (13 and 18) that house the genes responsible for blood pressure regulation, although pinning down the range of specific genes involved in hypertension is more difficult.

Inherited Abnormalities in the Angiotensin-Renin System . Genes under intense study are those that regulate a group of hormones known collectively as the angiotensin-renin system, which include angiotensinogen, renin, and angiotensin converting enzyme. This system influences all aspects of blood pressure control, including blood vessel contraction, sodium and water balance, and cell development in the heart. Of particular interest is the so-called "salt gene", which regulates angiotensinogen, a key player in the relationship between sodium and hypertension. New studies indicate that people carry one of three different variations of the salt gene, which influences their sensitivity to salt. Patients with the AA salt gene are the most sensitive to the effects of sodium; they are at greatest risk for high blood pressure but they also respond best to a low-salt diet compared to those that carry the other two salt genes (GG and AG). The effects appear to be quite modest, however. Another study suggested that African Americans with hypertension, on average, experience a more dramatic fall in blood pressure after salt-restriction diets than whites, indicating they may tend to carry the salt-sensitive gene. Unfortunately, the study on the salt gene types was conducted only on Caucasian men and did not include African Americans or women, in whom the angiotensin-renin system may have different effects. For example, researchers have recently found a link between m utations in the genes for angiotensin converting enzyme (ACE) and hypertension in men (although not in women).

Inherited Abnormalities *in the Sympathetic Nervous System.* Studies suggest that some people with essential hypertension may inherit abnormalities of the sympathetic nervous system, which is the part of the autonomic nervous system that controls heart rate, blood pressure, and the diameter of the blood vessels.

Insulin Resistance. Insulin resistance occurs when the body is unable to use insulin, a hormone that is important for delivering blood sugar and amino acids into cells and helps determine whether these nutrients will be burned for energy or stored for future use. Insulin resistance is a primary feature in type 2 diabetes, which is often accompanied by high blood pressure, and metabolic abnormalities that cause insulin resistance occur in half of people with hypertension. Not all people with insulin resistance have hypertension, however, and not all those with high blood pressure have this problem, so any causal relationship is uncertain. One recent study suggested that a common factor linking the two in certain inherited cases may be enhanced secretion of and sensitivity to stress hormones. Another recent study, however, reported that obesity is the only element in common between insulin resistance and high blood pressure and that there is no cause-and-effect.

Low Levels of Nitric Oxide . Nitric oxide affects the smooth muscles cells that line blood vessels; it helps keep them relaxed, flexible, and may also help prevent blood clotting. Low levels of nitric oxide have been observed in people with high blood pressure (particularly in African Americans) and may be an important factor in essential hypertension.

Secondary Hypertension.

Secondary hypertension has recognizable causes, which are usually treatable or reversible.

Medical Conditions . Medical conditions that contribute to temporary hypertension are pregnancy, cirrhosis, kidney disease, or Cushing's disease. Many experts believe that a causal relationship exists between high blood pressure and sleep apnea, a disorder in which breathing

halts briefly but repeatedly during sleep. Patients with this disorder also have a poorer response to anti-hypertensive medications.

Medications. Certain prescription and over-the-counter drugs can cause temporary high blood pressure. Some prescription medications include cortisone, prednisone, estrogen, and indomethacin. Long term use of nonsteroidal anti-inflammatory drugs (NSAIDs) may cause kidney damage and can also interfere with treatments for hypertension, including diuretics and beta-blockers. Such drugs include aspirin, ibuprofen (Advil, Motrin, Rufen), indomethacin (Indocin), naproxen (Anaprox, Naprosyn, Aleve) and many others. Of these drugs, aspirin appears to have the least detrimental effect on blood pressure. Cold medicines containing pseudoephedrine have also been found to increase blood pressure in hypertensive people, although they appear to pose no danger for those with normal blood pressure. High blood pressure is known to be an uncommon side effect in a few women taking oral contraceptives (the Pill). Stopping the pill nearly always reduces blood pressure, although recent study suggests that oral contraceptive may produce a small but significant increase in diastolic pressure that persists in some older women who have been off the Pill for years. Cocaine is known to cause acute episodes of hypertension, although apparently not chronic hypertension.

Alcohol, Caffeine, and Smoking. An estimated 10% of hypertension cases are caused by alcoholic abuse--three alcoholic drinks a day or more--with heavier drinkers having higher pressure. In one study, binge-drinkers had even higher blood pressure than people who drank regularly. High blood pressure levels associated with alcohol abuse appear to remain elevated even after a reduction in alcohol intake. On the other hand, moderate drinking (one or two drinks a day) appears to have benefits for the heart and may even protect against some types of stroke.

Caffeine causes a temporary increase in blood pressure, which has been thought to be harmless in people with normal blood pressure. One study, however, suggested that long term and regular coffee drinking can boost blood pressure sufficiently to increase the risk for heart disease in healthy men. The study was small, however; evidence is stronger that regular intake of coffee has a harmful effect on blood pressure in people with existing hypertension and may even increase their risk for stroke. Drinking coffee increases excretion of calcium, which also may affect blood pressure. (Anyone who drinks coffee should maintain an adequate calcium intake.)

The dangers of caffeine on blood pressure, however, pale next to the risks from smoking. One study reported that smokers have blood pressures up to 10 points higher than nonsmokers. Although cigar smoking does not appear to cause coronary artery disease, it can double the risk of death from cardiomyopathy and hypertension.

Other Causes of Secondary High Blood Pressure . Temporary high blood pressure can result from stress, exercise, and long-term consumption of large amounts of licorice. Exposure to even low lead levels also appears to cause hypertension in adults. One small study showed that mobile phone use triggers a temporary rise in blood pressure, which may be harmful in people with existing hypertension.

WHO GETS HIGH BLOOD PRESSURE?

Age and Weight.

Studies show that the prevalence of high blood pressure in the U.S. is declining, mostly due to drug treatments in older people and lifestyle changes in younger adults. Still, an estimated 50 million Americans have high blood pressure--about 25% of all adults. Although the majority have mild hypertension, even this condition requires medical attention. About one-third of patients with high blood pressure are overweight; even moderately obese adults have double the risk of hypertension as nonobese individuals. In fact, the increase in blood pressure in aging Americans may be due primarily to weight gain. (In other cultures old age does not necessarily coincide with weight gain--or high blood pressure.) Children and adolescents who are obese and newborns who are underweight are at greater risk for high blood pressure when they reach adulthood.

Gender and Ethnic Difference.

More men than women have hypertension until age 55; after that ratio reverses and women are more likely to have high blood pressure than are men. In 1996, 58.5% of the deaths from hypertension were in women and 41.5% were in men. High blood pressure is significantly more prevalent and dangerous in African Americans than other groups. Over half of the men and slightly less than half of women in this group have hypertension, and it may account for 30% of all deaths in men and 20% of all women who are African American. Both whites and African Americans in the Southeast have a higher incidence of hypertension and stroke than people living in other parts of the country. Such populations are also at risk for many contributing factors found in lower socioeconomic groups, such as stress, anxiety, and depression, and for diets low in potassium and high in salt. Some studies have indicated that African American may have lower levels of nitric acid than whites; nitric oxide keeps arteries flexible and open, which may partially account for their higher proportion of hypertension. It should be noted, however, that one study of African villagers, whose diets were high in fish, reported only a 3% rate in high blood pressure. The prevalence of hypertension in Hispanic Americans appears to be similar to that in Caucasians, and the rate is much lower in Asian Pacific Islanders. In any case, hypertension appears to be dangerously undertreated in major minority groups, including African and Mexican Americans, and inadequately controlled hypertension is the major factor for the higher mortality rate from heart disease among African Americans.

Family History.

Some experts now believe that essential hypertension may be inherited in 30% to 60% of cases. According to a recent study, being a brother or sister of someone with premature coronary artery disease is a greater risk factor for hypertension than having a parent with the disease.

Emotional Disorders.

People who are anxious or depressed may have over twice the risk for high blood pressure than those without these problems. It is not clear whether these mood disorders contribute to high blood pressure due to some physiologic effect on blood vessels or if they may lead to behaviors, such as weight gain or alcohol abuse, which are also risk factors for hypertension. Anger does not appear to predict high blood pressure, although suppressed anger may.

Seasonal Factors.

Seasonal changes may influence variations in blood pressure, with hypertension increasing during cold months and declining during the summer, particularly in smokers. While cold may narrow blood vessels, lack of light has also been associated with higher blood pressure.

HOW SERIOUS IS HIGH BLOOD PRESSURE?

High blood pressure directly killed over 41,600 Americans in 1996 and may have contributed to 202,000 deaths. The mortality rate rose 6.8% over the previous ten years and the actual number of deaths increased by 34%. It is particularly deadly in African Americans.

Emergency Conditions.

Malignant hypertension, an emergency condition resulting from untreated primary hypertension, can be lethal [*see* What Are the Symptoms of High Blood Pressure, *below*].

Damage to Other Organs.

Because hypertension can cause certain organs to deteriorate over time, patients who do not control high blood pressure face a reduced life span. High blood pressure contributes to 75% of all strokes and heart attacks. Compared with normal individuals, hypertensive people can have as high as ten times the risk of stroke and five times the risk of a heart attack depending on the severity of the hypertension. The risk for developing congestive heart failure is also significantly higher with increased blood pressure. People whose high blood pressure has led to enlargement of the left side of the heart (left ventricular hypertrophy) remain at risk for strokes, heart attacks, sudden death, and heart failure even after their blood pressure is under medical control. Animal studies have indicated that when heart cells enlarge in response to high blood pressure, they undergo molecular changes that cause an abnormal release of calcium, a mineral crucial for healthy heart contractions. This defect appears to be irreversible, so detecting and reducing high blood pressure as soon as possible an extremely important preventive measure. High blood pressure causes 30% of all cases of kidney failure--a rate second only to diabetes. Hypertension also increases the elimination of calcium in urine that may lead to loss of bone mineral density, a significant risk factor for fractures particularly in elderly women.

Sexual Dysfunction.

Some form of sexual dysfunction occurs in 17% of hypertensive men. It is often caused by medications that treat high blood pressure, but there are indications that the disorder itself may impair sexual function. Impotence related to hypertension is treatable. Men who wish to take the oral drug sildenafil (Viagra) to restore erectile function, however, should be aware that the drug interacts with many medications that affect blood pressure, that it is associated with reports of fatal heart events, and early trials were not conducted using men with hypertension. A study found that women with high blood pressure, regardless of medications, found it difficult to achieve sexual satisfaction and had impaired vaginal lubrication.

Mental Deterioration.

Chronic high blood pressure is associated with mental deterioration in older people, including reduced short-term memory and attention, Alzheimer's disease, and dementia; The higher the blood pressure the greater the risk for mental impairment. Studies indicate, however, that controlling blood pressure may help ward off memory loss to begin with and treating blood pressure in older patients with elevated systolic pressure can reduce their risk of dementia.

Pregnancy and Preeclampsia.

Severe, sudden high blood pressure in pregnant women caused by a condition called preeclampsia can be very serious for both mother and child. It occurs in up to 10% of all pregnancies usually in the third trimester of a first pregnancy, and resolves immediately after delivery. According to one report women with existing hypertension are at higher risk for preeclampsia if they have high diastolic blood pressure, high blood pressure for at least 4 years, or have had preeclampsia in a previous pregnancy. New research suggests that this condition may be caused by a failure of the placenta to embed properly in the uterus, which causes it to misconnect with the mother's blood vessels. As a result, the fetus does not receive a sufficient blood supply and the mother's own blood pressure increases. Symptoms and signs of preeclampsia include protein in the urine and swollen ankles. The reduced supply of blood to the placenta can cause low birth weight and eye or brain damage in the fetus. Severe cases of preeclampsia can cause kidney damage, convulsion, and coma in the mother and can be lethal to both mother and child. New studies suggest that women at risk for preeclampsia may benefit from having an ultrasound of uterine arteries at 20 to 24 weeks' gestation followed, if abnormal, by 24-hour blood pressure monitoring.

Side Effects of Hypertension Treatments.

One of the most difficult issues that hypertensive patients face, particularly those with primary hypertension, is that the treatment may make them feel worse than the disease, which is almost always without symptoms. Patients face a life-long prospect of taking drugs with unpleasant side effects, reducing their salt intake, exercising, and watching their diet. Whatever the difficulties, compliance with a drug and lifestyle program is worth the effort and the cost.

SYMPTOMS OF HIGH BLOOD PRESSURE

Hypertension has been aptly called the silent killer, because it usually produces no symptoms. It is important, therefore, for anyone with risk factors to have their blood pressure checked regularly and to make appropriate lifestyle changes. Such recommendations are urged for individuals who have overall high-normal blood pressure, mild or above systolic pressure with normal diastolic, family histories of hypertension, are overweight, or are over forty years old.

Untreated hypertension increases slowly over the years. In rare cases (fewer than one percent of hypertensive patients), the blood pressure rises quickly (with diastolic pressure usually rising to 130 or higher), resulting in malignant or accelerated hypertension. This is a life-threatening condition and must be treated immediately. Symptoms may include drowsiness, confusion, headache, nausea, and loss of vision. Hypertensive individuals should call a physician immediately if these symptoms appear.

LIFESTYLE CHANGES NEEDED TO CONTROL HIGH BLOOD PRESSURE

Dietary Factors and Weight Loss.

The DASH Diet . A diet known as Dietary Approaches to Stop Hypertension (DASH) is now recommended as an important step in managing blood pressure. It is low in saturated fat (although includes calcium-rich dairy products that are no- or low-fat) and rich in whole grains, fruits, and vegetables. The diet includes a daily choice of nuts, seeds, or legumes and contains modest amounts of protein (preferably fish, poultry, or soy products). In one study, after eight weeks on the diet, subjects from a broad range of backgrounds (including 60% African Americans) experienced a significant reduction in blood pressure. The long-term effect on the heart is unknown. This diet is not only rich in important nutrients and fiber but also includes foods that contain two and half times the amounts of potassium, calcium, and magnesium--as are found in the average American diet. Important foods include most fruits, many vegetables (especially, carrots, spinach, celery, alfalfa, mushrooms, lima beans, potatoes, avocados, broccoli), chicken, liver, and no-fat or low-fat milk. According to a recent study a low-calorie oat or wheat diet may significantly reduce blood pressure, however more study is needed to confirm these findings. Many of these foods are also high in fiber, which is protective against many diseases. It should be noted that grapefruit (but not other citrus fruits) boosts the effects of calcium channel blocking drugs used for hypertension.

Weight Loss. Weight gain seems to be a primary determinant in blood pressure increase, and weight loss may be even more important than salt restriction in controlling blood pressure. Loss of weight, particularly in the abdominal area, immediately reduces blood pressure and helps reduce heart size. Weight loss, particularly accompanied by salt restriction, may allow patients with mild hypertension--even older people--to safely reduce or go off medications.

Salt Restriction. Diets high in salt accelerate hypertension in everyone as they age. Salt restriction is particularly important for those who are salt-sensitive and for elderly people. Slightly less than half of people with high blood pressure are salt-sensitive; that is salt intake is more likely to increase their blood pressure and salt restriction to lower it. People who are most likely to be very salt-sensitive are overweight, older, African American, and those who have low levels of renin--a hormone that prevents reduction of blood pressure. High salt diets in such people may harm the kidney and brain, even independently of high blood pressure. Restricting salt also enhances the benefits of nearly all standard antihypertensive drugs by reducing potassium loss, and may help protect against kidney disease in patients who are also taking calcium-blocker drugs. Although it is not clear whether restricting sodium adds any benefits for most people whose diets are rich in fruits, vegetables, and low-fat dairy products and who are not salt-sensitive, it is always wise to aim for a maximum of 2,000 mg sodium intake. Simply eliminating table and cooking salt can be beneficial. Salt substitutes, such as Cardia, containing mixtures of potassium, sodium, and magnesium are now available but are costly. It should be noted, however, that about 75% of the salt in the typical American diet comes from processed or commercial foods, so the benefits of table-salt substitutes are likely to be very modest. Some sodium is essential to protect the heart, but most experts agree that the amount is significantly less than that found in the average American diet.

Potassium, Magnesium, and Calcium. Some experts believe that sufficient intake of minerals, particularly potassium, magnesium, and calcium, may be more beneficial than salt restriction for reducing blood pressure. Studies have indicated that potassium deficiencies increase the risk for high blood pressure, and recent studies indicate that a potassium rich diet may reduce hypertension, and possibly even stroke, in groups as diverse as African American adolescents and middle-aged men. A number of studies have also shown that daily potassium supplements can modestly reduce blood pressure. The recommended goal is 3,500 mg of potassium a day. Some patients, such as those taking certain diuretics that do not spare potassium, may require supplements. Excess potassium level, however, can cause abdominal distress, muscle weakness, and, in rare cases, dangerous heart events. Some people should be particularly cautious about potassium supplements, including those with conditions, such as diabetes or kidney disease, that increase potassium levels or who are taking medications, such as ACE inhibitors or potassium-sparing diuretics, that limit the kidney's ability to excrete potassium. Most people should obtain this mineral from potassium-rich foods that include potatoes, avocados, bananas, nonfat milk products, red beans, oranges, prunes, and cantaloupes [*see* also Useful Foods, *above*].

Studies are also finding that magnesium supplements may induce small but significant reductions in blood pressure. No major studies, however, have been done on long-term benefits or risks of magnesium supplements.
Calcium regulates the tone of the smooth muscles lining blood vessels, and population studies have found that people who have sufficient dietary calcium have lower blood pressure than those who do not. Hypertension itself increases calcium loss from the body. Some, but not all, studies have found modest beneficial effects on blood pressure from calcium supplements. One study found protection against stroke in men whose diets were rich in magnesium and potassium but no similar effects from diets high in calcium. Sufficient calcium is important, in any case, for strong bones health.

Vitamin C . Vitamin C apparently has specific benefits for hypertension by preventing dangerous effects on nitric acid, the substance that keeps arteries flexible.

Caffeine Intake, Alcohol, and Smoking.

Everyone should quit smoking and if they drink alcohol at all, do so in moderation. In healthy people with normal blood pressure drinking a couple of cups of coffee a day is unlikely to do any harm. Caffeine drinkers, however, would do better to choose tea, which may have beneficial nutrients, and people with existing hypertension should avoid caffeine altogether.

Exercise.

Studies indicate that regular exercise helps keep arteries elastic, even in older people, which in turn keeps blood flowing and blood pressure low. Sedentary people have a 35% greater risk of developing hypertension than athletes do. No person with high blood pressure should start an exercise program without consulting a physician. Studies have shown that high-intensity exercise may not lower blood pressure as effectively as moderate intensity exercise. In one study, for example, moderate exercise (jogging two miles a day) controlled hypertension so well that more than half the patients who had been taking drugs for high blood pressure were able to discontinue the medication. Studies have indicated that T'ai Chi, an ancient Chinese exercise involving slow,

relaxing movements may lower blood pressure almost as well as moderate-intensity aerob exercises.

An estimated 1.5 million heart attacks occur every year; of these, 75,000, or about 5%, occ after heavy exertion, leading to 25,000 deaths. Isometric work-outs, such as snow shoveling, ten to stress the heart and raise blood pressure for a brief period; it can also cause spasms in th arteries leading to the heart. Some studies indicate that competitive sports, which couple intens activity with aggressive emotions, are more likely to trigger a heart attack than other forms o exercise. One major study found that sedentary people who throw themselves into a gruelin workout increase the risk of heart attack by 107 times over that which would occur with low or n exertion.

Certain antihypertensive medications, including diuretics and beta-blockers, can interfere wit exercise capacity. ACE inhibitors or calcium channel blockers are the best drugs for activ individuals. However, patients who must take drugs that interfere somewhat with exercis capability should still adhere to an exercise program and consult a physician on how best t balance medications with exercise.

Stress Reduction and Psychologic Therapy.

Emotional factors or psychologic stress are possible precursors to hypertension. One study foun that 73% of patients with mild to moderate hypertension who underwent cognitive-behaviora therapy were able to reduce their medication after 6 weeks; after 12 months, 55% required n medication. Two small studies also reported that religious faith and activity was associated wit healthy blood pressure levels, possibly indicating the benefits of a strong social network an reduced stress from spiritual activities. (Listening to religious services on the radio or watchin them on television had no impact on blood pressure.) In another study, a simple relaxatio technique called transcendental meditation (TM), which involves silent repetition of a singl sound, was shown to be effective in reducing blood pressure.

DRUG TREATMENTS FOR HIGH BLOOD PRESSURE

General Guidelines for Drug Therapy

Only 27% of American adults with high blood pressure have it under control; about the same percentage is on medications but not controlling their blood pressure, and nearly 15% of those with hypertension are not on medication at all. Aggressive drug treatment of long-term high blood pressure can significantly reduce the incidence of death from heart disease and other causes in both men and women. In people with diabetes, controlling both blood pressure and blood glucose levels prevents serious complications of that disease. If patients have mild hypertension and no heart problems, then lifestyle changes may suffice if carried out with determination. For more severe hypertension or for mild cases that do not respond to changes in diet and lifestyle within a year, drug treatment is usually necessary. A single-drug regimen can often control mild to moderate hypertension. More severe hypertension often requires a combination of two or more drugs. Prolonged-release drugs are being developed so that they are most effective during early morning periods, when patients are at highest risk for heart attack or stroke.

Dozens of antihypertensive drugs are available. They usually fall into the following categories: (1) diuretics, which cause the body to excrete water and salt; (2) ACE inhibitors, which reduce the production of angiotensin, a chemical that causes arteries to constrict; (3) beta-blockers, which block the effects of adrenaline, thus easing the heart's pumping action and widening blood vessels; (4) vasodilators, which expand blood vessels; and (5) calcium channel blockers, which help decrease the contractions of the heart and widen blood vessels.

Research now indicates that beta-blockers, diuretics, and ACE inhibitors all reduce the risk for fatal and nonfatal cardiovascular events. As first-line treatment experts generally recommend beta blockers or diuretics, which are inexpensive, safe, and effective, for most people with hypertension who have no complicating problems. Individuals, however, may have special requirements that call for specific drugs or combinations. Diuretics continue to be the best choice for most older adults and for many African Americans, who are more likely to be salt-sensitive and so respond well to these drugs. Isolated high systolic pressure is usually treated with a diuretic; adding a beta blocker may improve outcome. For diabetics, the best drugs are beta-blockers or angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors have been shown to delay the onset and progression of kidney disease by 30% to 60% and to limit progression of other complications. Beta blockers are less expensive and one study found that they were as effective as ACE inhibitors in reducing diabetic complications, although more studies are needed. Heart attack survivors are usually given beta blockers and sometimes ACE inhibitors to prevent a second attack. People with heart failure should be given ACE inhibitors and diuretics; specific drugs in these classes may be particularly beneficial for these patients because they reduce left ventricle hypertrophy.
All drugs used for hypertension have side effects, some distressing, and on-going compliance is difficult. Some physicians have been concerned about the long-term effects of anti-hypertensive drugs on mental processes. A recent study found that brain scans of people who took calcium channel blockers or loop diuretics detected changes in brain tissue; those who took beta blockers had no such changes. This is an isolated study and more research is needed to confirm it. In spite of this worrisome report and others reporting serious side effects associated with some calcium channel blockers, and despite recommendations by major expert group for wider use of beta blockers and diuretics, prescriptions for calcium-channel blockers have increased and beta blockers have decreased over recent years.

It is very important, in any case, to rigorously maintain a drug regimen. According to a recent study, patients who discontinue antihypertensive therapy, particularly smokers and younger adults, are at a significantly increased risk for stroke. On an encouraging note, one major study found that people taking blood pressure drugs did not experience any greater decline in the general quality of life or daily functioning over five years than did people who were not on blood pressure medication. In all cases, healthy lifestyle changes must accompany any drug treatment.

Diuretics.

For decades, diuretics, which cause reduction of water and sodium, have been the mainstays of antihypertensive therapy and are still considered the first choice by experts, especially for treating the elderly. Diuretics have reduced the incidence of stroke by a significant 40% and, to a lesser degree (about 16%), the incidence of hypertension-related heart attacks. They also may protect against blood clots. Diuretics come in many brands and are generally inexpensive. Some need to be taken once a day, some twice a day. A diuretic used as the initial single agent is particularly effective in elderly and African-American patients. Diuretics may also help reduce the rate of

fractures in elderly people who have taken them for a long time. It has been thought that long-term use of diuretics can be harmful to patients with diabetes; one large study, however, reported that a low-dose diuretic reduced the risk of major heart disease with few adverse effects in older patients who had type 2 diabetes and isolated systolic hypertension. Experts believe that diuretics should be the first line of therapy for such patients.

Three primary types of diuretics exist: thiazides, loop diuretics, and potassium sparing agents. Thiazides often serve as the basis for high blood pressure treatment, either taken alone for mild to moderate hypertension or used in combination with other types of drugs. There are many thiazides and thiazide-related drugs; some common ones are chlorothiazide (Diuril), chlorthalidone (Hygroton), and hydrochlorothiazide (Esidrix, HydroDiuril). Loop diuretics block sodium transport in parts of the kidney; they act faster than thiazides and have a great diuretic effect. It is important therefore to control the medication and avoid dehydration and potassium loss. Loop diuretics include bumetanide (Bumex), furosemide (Lasix), and ethacrynic acid (Edecrin).

The loop and thiazide diuretics deplete the body's supply of potassium, which can cause arrhythmias--heart rhythm disturbances that can, in rare instances, lead to cardiac arrest. In such cases, physicians will either prescribe lower doses of the current diuretic, recommend potassium supplements, or use potassium-sparing diuretics either alone or in combination with a thiazide. Some potassium-sparing diuretics include amiloride (Midamor), spironolactone (Aldactone), and triamterene (Dyrenium). Studies indicate that people who take a potassium-sparing diuretic with a low-dose thiazide have a lower risk for cardiac arrest than those taking either a beta-blocker or thiazide alone. Potassium-sparing drugs have their own risks, which include dangerously high levels of potassium in people with damaged kidneys or who have a high potassium intake from other sources. It should be noted, however, that, in general, all diuretics are more beneficial than harmful. (Arrhythmias can also occur as an interaction between diuretics and certain drugs, including some antidepressants, anti-arrhythmic drugs themselves, and digitalis.)

Common side effects of diuretics are fatigue, depression, irritability, urinary incontinence, loss of sexual drive, breast swelling in men, and allergic reactions. Diuretics can trigger attacks of gout; they may also increase the risk of gastrointestinal (GI) bleeding. They and may raise cholesterol level and, used alone, they have no effect on enlarged heart size (hypertrophy).

Beta Blockers.

Beta blockers affect the force and frequency of heart beats; they slow certain metabolic processes, ease the workload of the heart, and reduce pressure. They are very effective, and currently recommended along with or instead of diuretics as initial treatment. Beta blockers have been associated with a lower risk for a second heart attack or sudden death after a first heart attack, although one recent study indicated that beta-blockers did not reduce mortality rates in people over 60 years old. More research is needed on this surprising result. These drugs are not as effective as ACE inhibitors in people with or at risk for kidney disease. Because they can narrow bronchial airways and constrict blood vessels, patients with asthma should avoid them whenever possible. Many beta blockers are now available, including propranolol (Inderal), acebutolol (Sectral), atenolol (Tenormin), betaxolol (Kerlone), carteolol (Cartrol), metoprolol (Lopressor), nadolol (Corgard), penbutolol (Levatol), pindolol (Visken), and timolol (Blocadren). The drugs may differ in their effects and benefits. Carvedilol (Coreg), which is a mild beta blocker with some vasodilating properties has been found to improve very severe heart failure. It also

appears to have a better effect on insulin sensitivity than other beta blockers and so may prove to be a good choice for people with diabetes. A similar drug, bucindol, is in development. Atenolol has been found to reduce left ventricular hypertrophy and, when used with the diuretic chlorthalidone, was found to significantly reduce the risk for heart failure, particular in patients at high risk for it.

Some beta blockers tend to lower HDL cholesterol (the beneficial cholesterol) by about 10%; the effect is most marked in smokers. Fatigue and lethargy are the most common psychologic side effects. Some people experience vivid dreams and nightmares, depression, and memory loss. Exercise capacity may be reduced. Other side effects may include cold extremities, asthma, decreased heart function, gastrointestinal problems, and sexual dysfunction. If side effects occur, the patient should call a physician, but it is extremely important not to stop the drug abruptly. Angina, heart attack, and even sudden death have occurred in patients who discontinued treatment without gradual withdrawal.

Angiotensin Converting Enzyme Inhibitors and Similar Drugs.

Angiotensin Converting Enzyme Inhibitors. Angiotensin converting enzyme (ACE) inhibitors have successfully battled all types of hypertension. Many brands are available that are similar in efficacy and safety, as well as in price, which, unfortunately, is high. ACE inhibitors include captopril (Capoten), enalapril (Vasotec), quinipril (Accupril), benazepril (Lotensin), and lisinopril (Prinivil, Zestril). ACE inhibitors are recommended as first-line treatment for people with diabetes and kidney damage, for some heart attack survivors, and for patients with heart failure when taken with diuretics. A recent study offers sound medical proof that ACE inhibitors, like beta blockers and aspirin, can improve a patient's odds of surviving a heart attack. Captopril has also been found to reduce left ventricular hypertrophy. African-American patients usually do not respond to ACE inhibitors unless they are combined with diuretics. Although these drugs are expensive, one study demonstrated that enalapril decreased the risk of death by 18% and reduced hospital visits, saving over $1,500 per patient over a 40-month period.

Side effects are uncommon but may include an irritating cough, excessive drops in blood pressure, and allergic reactions. A recent study found that the drug picotamide can help reduce the frequency of coughs. Although ACE inhibitors can protect against kidney disease, they also cause the kidneys to retain potassium, which can result in cardiac arrest if levels become too high. Because of this action, they are not generally given with potassium-sparing diuretics or potassium supplements. A recent study shows that ACE inhibitors slow the progression of nondiabetic kidney disease through mechanisms other than their antihypertensive effects. Another study suggests that long term use of ACE inhibitors may even reduce the risk of cancer, particularly in women. One rare but severe side effect--granulocytopenia--has been observed, which is an extreme reduction in white blood cells.

Angiotensin II Receptor Antagonists. Drugs known as angiotensin II receptor antagonists, including losartan (Cozaar), candesartan (Atacand), telmisartan (Micardis), eprosartan, and valsartan (Diovan), have benefits similar to ACE inhibitors and may have fewer or less severe side effects, including coughing. They may also have positive effects on blood vessels. In one study, eprosartan was more effective than enalapril in reducing systolic pressure in African American patients. Also now available is a combination medication containing valsartan and the diuretic hydrochlorothiazide (Diovan HCT).

Vasodilators.

Vasodilators, which widen blood vessels, are often used in combination with a diuretic or a beta blocker. Representative vasodilators include hydralazine (Apresoline), prazosin (Minipress), clonidine (Catapres--available in tablets or as a skin patch), and Minoxidil (Loniten). Some of these drugs should be used with caution or not at all in people with angina or who have had a heart attack.

Calcium Channel Blockers.

Calcium channel blockers have an immediate effect on reducing blood pressure, but they have been linked to some severe problems and studies are reporting poorer results than with other, anti-hypertensive drugs. Patients being prescribed them should ask their physician if a beta blocker or diuretic would serve as well. (No one should ever, however, go off these drugs abruptly, because such action could dangerously increase the risk of high blood pressure.). These drugs include diltiazem (Cardizem, Dilacor), amlodipine (Norvasc), verapamil (Calan, Isoptin, Verelan), nisoldipine (Sular), nicardipine (Cardene), nifedipine (Adalat, Procardia), isradipine (DynaCirc), lercanidipine (Zanidip), felodipine (Plendil), and nitrendipine. Sustained-release calcium channel blockers provide stable and persistent low blood pressure. Side effects vary among different preparations, and may include fluid accumulation in the feet, constipation, fatigue, impotence, gingivitis, flushing, and allergic symptoms. Grapefruit juice appears to boost the effects of these drugs in some people, particularly the elderly. Newer drugs, such as lercanidipine may reduce or avoid many of these side effects. Studies have found a significantly increased risk for blood loss during surgery in patients taking these drugs. A higher risk for gastrointestinal bleeding was not confirmed in one major study and researchers believed that the higher incidence of bleeding previously observed was due to taking aspirin.

Of major concern were reports of an increased risk of death and serious heart events from abrupt drops in blood pressure in people taking short-acting forms of the calcium channel blocker nifedipine. A number of studies on long-acting forms of calcium channel blockers or other short acting forms, including diltiazem, do not report an increased risk for heart events or death. Studies that compare these drugs with ACE inhibitors in patients with type 2 diabetes, however, report more heart attacks and strokes in those taking the calcium channel blockers. Another study also reported that women who took calcium channel blockers had a significantly higher risk for heart attack than those on diuretics. This study, however, may not reflect the current trend toward taking long-acting calcium channel blockers. Other worrisome studies have pointed to a higher rate of cancer in those taking calcium channel blockers compared to people taking other anti-hypertensive medications, although a recent review of nearly 16,000 patients found no such greater risk. Another found changes in brain tissue on scans of people who had taken calcium channel blockers. Even long-acting calcium channel blockers should be used with caution or not at all by people who have had a recent heart attack, who have unstable angina, or who have or at risk for congestive heart failure. The negative effects of calcium channel blockers, even nifedipine, may be reduced when they are taken with a beta blocker or diuretics. One calcium channel blocker, mibefradil (Posicor) was taken off the market after reports of dangerous interactions with 25 medications including some deaths.

Alpha Blockers.

Labetalol (Normodyne, Trandate) is an alpha-beta blocker and is useful for hypertensive patients who also have angina. Alpha blockers, which include terazosin (Hytrin), doxazosin (Cardura) are also effective against high blood pressure, particularly in men who also have benign prostatic hyperplasia. Doxazoin reduces systolic pressure and may improve cholesterol levels.

Treatment During Pregnancy.

Most women who develop high blood pressure only during pregnancy (gestational hypertension) are at low risk for preeclampsia and require no treatment other than monitoring. Treating pregnant women who have chronic, mild hypertension is probably not necessary, although no large studies have been done to confirm this. Many of the standard anti-hypertensive drugs, particularly ACE inhibitors, have potentially harmful effects to a fetus. Women who have taken ACE inhibitors before pregnancy will not endanger the fetus if they discontinue therapy during the first trimester. Atenolol is also associated with adverse effects on the fetus; studies on other beta-blockers are conflicting. No significant or long-term studies have been conducted on pregnant women using calcium channel blockers. Treatment for preeclampsia ranges from monitoring to emergency treatments, depending on severity. It does not respond well to standard drug treatments. Preventive treatment using magnesium sulfate during labor is recommended by some experts. Experts hoped that aspirin might help prevent preeclampsia in high-risk women, but

CHAPTER TWO

Diagnosis of hypertension in adults

The diagnosis of hypertension in a patient is an important event, and it is essential that the diagnosis be accurate. Methods for the accurate diagnosis of hypertension were set out in the consensus report of the Canadian Hypertension Society (CHS) in 1984 In 1991 a new panel of CHS members with a special interest in the diagnosis of hypertension was struck as part of a general review of the recommendations of previous CHS consensus conferences. The panel reviewed the 1984 recommendations, retaining them when appropriate and updating pertinent references. In addition, it reviewed the evidence concerning the possible roles of echocardiography, self-assessment of blood pressure and ambulatory blood pressure monitoring in the diagnostic process.

The accurate measurement of blood pressure

The accurate determination of blood pressure is obviously the cornerstone of the diagnosis of hypertension. Over the past few years a number of scholarly reviewsreports of expert committeesand how to articleshave been published on the determination of blood pressure by sphygmomanometry; the recommendations of the American Heart Associationin particular provide an in-depth analysis. The 1984 CHS recommendationson taking blood pressure remain applicable, and there is emphasis on important points that are frequently missed by practitioners.[The special problems of measuring blood pressure in children were not considered but have been well described elsewhere] Because studies have shown that professional practice in blood pressure measurement falls far short of ideal, the last two recommendations are directed to faculties of health science and sponsors of continuing education for implementation.

1: Use a mercury manometer that has the mercury column at eye level.

2: Choose a cuff with appropriate bladder width (about 40% of arm circumference).

Adult arm size (cm)	Bladder size (cm)
Less than 33	12 x 23
Between 33 and 41	15 x 33
More than 41	18 x 36

3: Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centred over the brachial artery. The patient should be comfortable and the arm bared and well supported. There should be no talking, and the patient s legs should not be crossed.

4: Increase the pressure rapidly to 30 mm above the level at which the radial pulse is extinguished (to exclude the possibility of auscultatory gap).

5: Place the head of the stethoscope (the bell is preferred) gently but firmly over the brachial artery.

6: Open the control valve so that the rate of drop in the vicinity of the systolic and diastolic level is 2 mm per beat.

7: Record the systolic level the first appearance of a clear tapping sound (phase I Korotkoff) and the diastolic level the point at which the sounds disappear (phase V Korotkoff); as well, record the arm used and whether the patient was supine, sitting or standing.

8: If the sounds persist as the level approaches 0 mm Hg, then the point of muffling of the sound is used (phase IV) to indicate the diastolic pressure.

9: In the case of arrhythmias, additional readings may be required to estimate the average systolic and diastolic pressure. Isolated extra beats should be ignored. Note the rhythm and pulse rate.

10: Leaving the cuff partially inflated for too long will fill the venous system and make the sounds difficult to hear. To avoid venous congestion, it is recommended that at least one minute should elapse between readings. Conversely, if the sounds are difficult to hear initially, the veins can be emptied and the sound magnified if the patient raises the arm over the head with the cuff deflated. Milk the forearm down and inflate the cuff while the arm is still raised. Then quickly return the arm to the usual position and take the reading.

11: Blood pressure should be taken at least once in both arms and the higher pressure subsequently used.

12: All health care students who will be measuring blood pressure as part of their professional duties should have formal training in the proper technique and should be required to pass a skill-based examination to demonstrate their competence.

13: Health care professionals should review their technique and accuracy periodically and should undertake further instruction and testing if necessary.

Assessment of whether a patient has hypertension

The variability of blood pressure is such that one measurement, no matter how accurate, is inadequate to establish a diagnosis of hypertension, defined as sustained elevation of blood pressure above a certain cut-off value. Studies have shown that the number of visits at which blood pressure is assessed is far more important to accurate diagnosis than the number of measurements at any one visit. At one visit reasonable power in detecting hypertension is achieved by taking at least two measurements and using either the average or the minimum reading more than this number of measurements does not increase the diagnostic power appreciablyFurthermore, the duration of the observation period is important, since initially high pressures can continue to fall over several months of observation

The rate at which sustained hypertension develops in people with intermittent elevation of blood pressure (borderline hypertension has been shown to be about 1% yearly, and thus the frequency of follow-up should reflect this slow rate of increase in blood pressure. On the other hand, some people with mild elevations of blood pressure have target-organ damage, as indicated by left ventricular hypertrophy on electrocardiography, a history or electrocardiographic evidence of prior myocardial infarction, a history or clinical evidence of prior cerebrovascular accident or intermittent claudication, or impaired renal function. Because the value of treatment has been established for people with target-organ damage even when the elevation in diastolic blood pressure is mild, the search for such damage should begin soon after the raised blood pressure has been discovered.

Elevations in blood pressure can be caused by exogenous factors, such as use of oral contraceptive drugs, excess licorice consumption and use of nonsteroidal anti-inflammatory drugs. These possible contributory factors should be considered early in the course of evaluation.

Although the patient with hypertension whose blood pressure is not assessed or is underestimated on examination will be denied the benefits of therapy, this happens rarely in routine office-based screening for hypertension. Also, there has been an overenthusiatic prescription of therapy for mild hypertension, particularly in women. Many people appear to have been mislabelled as hypertensive by a misinterpretation of either the meaning of nonsustained elevations in blood pressure or of the term hypertension itself. People who are normotensive but who are informed that they are hypertensive on the basis of an incorrect or incomplete assessment cannot benefit from the therapy that is prescribed and will be subject to the adverse effects of both the label[35,36] and the treatment. A better balance between aggressively detecting hypertension and ensuring that people with normal blood pressure are not misinformed can be achieved if practitioners observe the need for multiple assessments before diagnosis and communicate this clearly to patients.

14: If the initial blood pressure is high in someone not previously known to have hypertension, then in the same session at least two readings should be taken according to the recommended procedure for accurate blood pressure determination (grade A).

15: If the blood pressure at a visit is mildly elevated but the patient does not meet the standards set out for the treatment of hypertension (i.e., there is no hypertensive organ or vessel damage), then the blood pressure should be measured at least twice on each of at least three occasions over a period of 6 months (grade A).

16: The search for target-organ damage and exogenous causes of elevated blood pressure should proceed as follows (grade D).

(a) On the first visit at which elevated blood pressure is detected the patient should be questioned and the medical record reviewed for mention of myocardial infarction, angina pectoris, transient ischemic attacks or cerebrovascular accident, peripheral arteriovascular insufficiency or renal insufficiency. If the patient has any of these conditions an appropriate physical examination and diagnostic tests should be done and the period of observation of blood pressure compressed, according to the severity of the condition(s) discovered.

In addition, if exogenous causes of hypertension are found, such as excess alcohol consumption or use of oral contraceptive drugs, conjugated estrogens or nonsteroidal anti-inflammatory drugs, and if the blood pressure remains high on follow-up, consideration should be given to stopping the use of these drugs.

(b) On the next visit, if the blood pressure is still high a physical examination should be done and electrocardiography, urinalysis and measurement of the serum creatinine level ordered to assess the possibility of target-organ damage. Again, if such damage is detected the period of observation of blood pressure should be compressed.

The existence and severity of other cardiovascular risk factors, including hyperlipidemia and glucose intolerance, could also be documented at this point.

17: If a patient s diastolic blood pressure is above 90 mm Hg on some occasions but not on others, he or she should be reassessed yearly. Such patients should not be told that they have hypertension (grade A for prognosis.

18: Practitioners should be careful to inform patients that a diagnosis of hypertension is reserved for those in whom hypertension is well established i.e., there is persistent elevation of blood pressure (grade D).

Initiating treatment for hypertension

Several large randomized controlled trials have demonstrated the overall benefits of antihypertensive therapy for patients with sustained pretreatment blood pressures of at least 140/90 mm Hg.

A large meta-analysis of hypertension trials addressing a long-standing controversy has shown that lowering blood pressure reduces the risk of not only cerebrovascular complications but also ischemic heart disease. Although there is strong evidence for a general recommendation about antihypertensive therapy, numerous subgroup analyses of treatment trials have shown that the absolute risk for the complications of hypertension is not uniform, and it may not be appropriate to treat all patients who have increases in diastolic blood pressure as if they were the same. Unfortunately, there have been no randomized trials focusing on the specific groups at risk, except for those with higher levels of blood pressure and elderly patients; thus, recommendations for patients at other levels of risk are supported only by lower-level evidence.

If the diastolic blood pressure is below 100 mm Hg, the patient's characteristics need to be taken into account. Patients with left ventricular hypertrophy or ischemic vascular impairment of the heart, brain, kidneys or peripheral arteries are at considerably increased risk for further complications if the blood pressure remains high. Thus, lowering the blood pressure in these patients is likely to do more good than harm, even if the elevation is mild.

Studies of hypertension in elderly patients have convincingly demonstrated that these patients also benefit from a reduction in blood pressure. Large randomized controlled trials with positive results have included patients up to the age of 84 years but have suggested diminishing benefits with increasing age. Thus, the preceding recommendations apply to adults up to at least 80 years of age.

New evidence adds an important indication for antihypertensive treatment in elderly patients. A large randomized trial] has shown that both men and women aged 60 years and over without major disease but with isolated systolic hypertension (diastolic blood pressure less than 90 mm Hg and systolic blood pressure greater than 159 mm Hg) benefitted from antihypertensive therapy. Only 14% of the patients were over 80 years of age at entry into the trial, but the benefit did not appear to diminish with increasing age.

For patients with diastolic pressures of 90 to 99 mm Hg who do not have systolic hypertension or evidence of target-organ damage, some large trials of antihypertensive therapy -- most clearly the British Medical Research Council trial-- have demonstrated a significant reduction in the risk of cerebrovascular accident. However, there were subgroups of patients, most notably women, for whom the risks of reduction in blood pressure appeared to outweigh the benefits.[34] Unfortunately, this evidence is not direct, in that no trials have been completed that include patients with mild hypertension selected for isolated protective or risk factors. Thus, decisions about whether to introduce antihypertensive therapy for those whose pressures are in the range of 140 to 159/90 to 99 mm Hg are still complex, and clinical judgement is needed that takes into account the number and severity of the patient s other risk factors, including male sex, black race, smoking habit, elevated cholesterol level and glucose intolerance. The greater the number of risk factors and the more severe they are, the lower the blood pressure level at which therapy should be implemented.

19: Overall, antihypertensive therapy does more good than harm for patients with diastolic blood pressures of 90 mm Hg or over (grade A).

20: Therapy for hypertension should be prescribed for all patients with diastolic blood pressure consistently 100 mm Hg or higher (grade A).

21: Therapy for hypertension should be prescribed for all patients with a diastolic blood pressure of 90 to 99 mm Hg and evidence of hypertensive target-organ damage (grade C). Target-organ damage is defined as one or more of the following: (a) left ventricular hypertrophy with strain demonstrated by electrocardiography, (b) a history or symptoms of angina pectoris, (c) a history or electrocardiographic evidence of myocardial infarction, (d) a history or symptoms of intermittent claudication and (e) a serum creatinine level higher than 150 µmol/L.

22: Therapy for hypertension should be prescribed for people 60 years of age and older with isolated systolic hypertension (diastolic blood pressure less than 90 mm Hg and systolic blood pressure 160 mm Hg or higher) (grade A).

23: The prescription of therapy for patients with systolic blood pressures averaging 140 to 159 and diastolic pressures averaging 90 to 99 mm Hg but no target-organ involvement should be based on the clinical judgement of the practitioner and should take account of the patient s absolute risk for cardiovascular disease according to the risk factors present (grade C).

The role of echocardiography

Echocardiography is more sensitive than electrocardiography or chest roentgenography in detecting left ventricular hypertrophy and thus presumably detects hypertensive cardiac response earlier in its course. As a result, some cardiologists feel that all patients with mild hypertension should undergo echocardiography, but there are important problems with this policy. First, there is inconsistency at present among some community and hospital echocardiography laboratories with regard to measurement of the thickness of the left ventricular wall (including the location of the measurement and the number of cardiac cycles used in making the measurement), and standardized equations are not used to calculate left ventricular mass. Furthermore, the reliability of echocardiography in different facilities has not been assessed. Thus, the information that some clinicians receive from echocardiographic reports is of uncertain quality.

Second, whether to use echocardiographic information to decide about prescribing antihypertensive therapy has not been answered directly by, for example, a placebo-controlled trial of such therapy in patients with mild hypertension and left ventricular hypertrophy detected by echocardiography. Even though it has been shown that echocardiographic findings can predict cardiovascular disease and death and left ventricular hypertrophy is an indication for intervention in mild hypertension, there are instances in medical therapeutics in which extrapolations from such indirect evidence have been wrong. A recent example of this was an increase rather than the expected decrease in the rates of death from suppression of cardiac arrhythmia. Thus, there is not sufficient evidence at present to make a firm recommendation on the general use of echocardiography in decisions about therapeutic intervention in patients with mild hypertension but no clinical evidence of cardiac disease. This is in accord with the decision of a joint committee of the American College of Cardiology and the American Heart Association.[54] Recommendations concerning the cost-effectiveness of echocardiography compared with electrocardiography must also await sound evidence of effectiveness.

24: Echocardiographers should adopt uniform standards for measuring the thickness of the left ventricular wall, calculating left ventricular mass and defining left ventricular hypertrophy. Studies should be conducted to determine the extent to which echocardiographic laboratories provide reproducible assessments and adhere to these standards.

25: There is insufficient evidence at present to recommend echocardiography for routine clinical use in evaluating mild hypertension or in making decisions about the initiation of treatment for mild hypertension.

26: Further studies should be undertaken to establish the prevalence of echocardiographic changes in patients with mild hypertension and no other indication for therapy, the role of echocardiography in the decision to implement therapy, and the effectiveness and cost-effectiveness of echocardiography in decisions about the introduction of antihypertensive therapy.

Self-measurement of blood pressure

Many investigators have found differences between blood pressure values obtained by health care professionals in a clinic and automated, self-determined measures obtained at home, the latter being on average about 8/4 mm Hg lower. The correlation between measurements at home and in the clinic has been reported to be as low as 0.21 for diastolic blood pressure.] In line with these low correlations Padfield and colleagues reported that the sensitivity and specificity of self-determined measures in diagnosing hypertension when compared with pressures measured in the clinic were 73% and 86% respectively. This finding assumes that the clinic pressures constitute a gold standard, which may not be the case. Thus is raised the issue of which readings, home or clinic, are more valid.

Studies have demonstrated that blood pressure measurements obtained at home can be highly reproducible. Reproducibility of readings is essential for accuracy, and these studies are therefore reassuring. Furthermore, Gould and colleagues found that the accuracy of self-determined readings at home and of professionally taken readings at the clinic were similar, as determined by intra-arterial pressures. However, the overriding issue here is the validity of self-determined measures of blood pressure in decisions about the diagnosis of hypertension and whether treatment should be initiated.

Self-monitoring of blood pressure has been advocated as an adjunct to diagnosis, particularly for the detection of white coat hypertension (defined as pressure that is persistently high when measured at the clinic but normal when measured elsewhere. Although there have been studies of home blood pressure monitoring as part of the management of treated hypertension, there have been few of self-monitoring as an adjunct to diagnosis and the initiation of therapy. Unfortunately, there is little information on the distribution of self-monitored pressures in the normotensive population, and there have been no prospective studies assessing the relation between level of self-monitored blood pressure and incidence of major illness or death from cardiovascular disease. The evidence from less rigorous cross-sectional assessments of monitoring at home and at the clinic is conflicting. Julius and colleagues have found that patients with high readings at the clinic and lower ones on self-assessment have hypertensive target-organ findings and cardiovascular risk factors similar to those of patients with sustained borderline elevation of blood pressure both at the clinic and at home. However, other investigators have found higher correlations of electrocardiographically determined left ventricular hypertrophy with self-determined blood pressure readings than with casual office readings[55] and higher correlations of echocardiographically determined left ventricular mass with blood pressure readings taken at home than with those taken at the clinic.

Given the consequences of both false-negative and false-positive diagnoses, the inaccuracy of many devices for the self-determination of blood pressure and the potential value of additional measurements in a patient s home, the accuracy of self-monitoring should be studied further and its value in diagnosis determined for those with mild elevations in blood pressure at the clinic.

If patients are asked to measure their blood pressure at home it is important that their equipment and technique be checked by health care professionals to ensure accuracy. Mercury sphygmomanometers are the most accurate and dependable devices and can be purchased for home use, but they are more difficult to master than the semiautomated or automated devices

that are widely available. Mercury devices should likely not be suggested for patients with young children at home in view of the possibility of a mercury spill. Patients with difficulty hearing or seeing should only be asked to use automated devices if someone else in the home can assist them. Some sphygmomanometers of all types are accurate, but most nonmercury devices are not. It is important that patients use the correct cuff size for their arm circumference. Thus, the given recommendations for blood pressure determination apply to the use of automated devices if they are found to be as accurate as mercury devices.

27: There is insufficient evidence at present to recommend self-monitoring of blood pressure for routine clinical use in the evaluation of patients with mild hypertension or in decision making about the initiation of treatment for mild hypertension.

28: The Department of National Health and Welfare should set standards for the performance and durability of blood pressure devices for use at home by the public and ensure that they are met (grade D).

29: Further study is needed of the value of self-measurement of blood pressure in the diagnosis of hypertension in patients with borderline hypertension or mild elevations of blood pressure. There should be prospective studies to compare the values of self-determined and clinic-determined readings in predicting cardiovascular disease and death.

30: If patients are measuring their blood pressure at home, health care professionals should ensure that the patients have adequate information about taking and interpreting blood pressure readings (grade D).

31: Health care professionals should regularly check patients accuracy in measuring their own blood pressure if they are using a mercury device, the accuracy of the device if it is automated, and the accuracy of both the patient and the device if the latter is aneroid and requires the patient to listen for pulse sounds (grade D).

Ambulatory blood pressure monitoring

The diagnosis and management of hypertension has traditionally been based on blood pressure measurements taken in the office. However, the inherent variability of blood pressure and its susceptibility to transient emotional influences in normotensive and hypertensive people undermine the ability of conventional clinical measurement to accurately reflect the usual level of blood pressure in some people. In contrast to other means of blood pressure assessment, including self-assessment, ambulatory monitoring provides information automatically and noninvasively about the effects of blood pressure load over time and under the various circumstances during which blood pressure is not usually measured (including work and sleep). Whereas self-assessments at home usually provide periodic measurements over many days and weeks, ambulatory monitoring provides numerous measurements over a period of hours, up to a day. Thus, the sampling of a person s blood pressure provided by the two means is quite different.

Although the accuracy of ambulatory monitoring is less than optimum, technical errors are relatively small compared with errors in the estimate of true pressure based on a small number of clinic readings and can be minimized if a standard protocol is followed, including calibration with a mercury sphygmomanometer immediately before and after the readings are taken.

It is important to note that even with excellent calibration there is substantial variability in the results of ambulatory monitoring when repeated after an interval of 2 to 8 weeks. Thus, monitoring may need to be done repeatedly to provide an average measure of a person s usual ambulatory blood pressure. The devices currently available vary in their reliability and accuracy.

We did not attempt a complete review of this subject, but those using ambulatory monitoring for clinical decisions should be familiar with the weaknesses of the devices they are using. Limited information is available from the review of O Brien and colleagues indicating that the SpaceLabs 90202 and 90207 (SpaceLabs Medical Equipment Inc., Redmond, Wash.) and the DIASYS 200 (Baxter Health Care Corp., Oakland, Calif.) monitors have met the standards of both the American Association for the Advancement of Medical Instrumentation and the British Hypertension Society.

Reference values for ambulatory monitoring in normotensive subjects are available from recent studies: daytime pressures range from 101/62 to 143/90 mm Hg, and a daytime average of 135/84 mm Hg corresponds to a clinic-based cut-off of 140/90 mm Hg. In view of the generally lower pressures obtained with ambulatory monitoring than at the clinic, patients with an average blood pressure of more than 135/84 mm Hg on ambulatory montitoring and without target-organ damage should be followed closely for the development of higher pressures or target-organ damage.

To date, ambulatory blood pressure monitoring has been primarily a research tool and has not had an established clinical role in the diagnosis and management of hypertension. Nevertheless, some clinical problems are better elucidated by this technique than by casual blood pressure readings, and ambulatory monitoring is being used increasingly in clinical decision making. Its most important clinical application is the detection of white-coat hypertension. Estimates of the prevalence of this syndrome vary from 20% to 39% Other clinical situations in which ambulatory monitoring might be of diagnostic value include borderline hypertension with target-organ involvement, episodic hypertensionand resistant hypertension.Many studies have shown a closer correlation of target-organ involvement (particularly left ventricular hypertrophy) with pressures obtained through ambulatory monitoring than with those obtained at the clinic, and there is also evidence that left ventricular hypertrophy occurs much less frequently in patients with white-coat hypertension than in those with confirmed essential hypertension. Other studies have shown that pressures obtained from ambulatory monitoring at work and the percentage of daily blood pressure loads correlate more strongly with left ventricular hypertrophy than do pressures measured at the clinic. The results of ambulatory blood pressure monitoring also appear to be a more potent predictor of cardiovascular disease and death in patients with hypertension than are casual blood pressure readings.

However, the evidence concerning the value of ambulatory blood pressure monitoring is not complete in some respects, and some procedural issues make its use less than straightforward. The main clinical trials of the benefits of lowering blood pressure have used measurements taken at the office or clinic to establish the diagnosis of hypertension and to gauge the effects of treatment. Ambulatory monitoring as a substitute has not been tested in studies large enough to determine whether it provides a better measure of diagnosis or of risk reduction. There are other factors to be considered: ambulatory monitoring devices are expensive (in terms of both equipment and personnel costs) in comparison with the usual sphygmomanometers, they are error-prone and need careful calibration, they are inconvenient for patients, few centres can provide them, there is enough variability in the measurements they provide for the same patient from time to time that more than one monitoring session may be needed, and the service is not approved for reimbursement by government health insurance plans in Canada. Thus, it is premature to recommend the widespread application of ambulatory monitoring for the diagnosis of patients with mild hypertension.

32: Devices for ambulatory blood pressure monitoring should be calibrated with a mercury sphygmomanometer immediately before and after use (grade B for diagnosis, according to a standardized protocol (grade A for diagnosis).

33: There is insufficient evidence at present to recommend ambulatory blood pressure monitoring for routine clinical use in the evaluation of mild hypertension or in decision making about the initiation of treatment for mild hypertension.

34: Further higher-quality research should be undertaken to determine if ambulatory blood pressure monitoring should replace or supplement traditional techniques for the diagnosis of mild hypertension.

35: Comparisons should be made of ambulatory blood pressure monitoring, self-measurement of blood pressure and echocardiography, alone and in combination, for the diagnosis and initiation of treatment in borderline and mild hypertension.

White-coat hypertension

Because the diagnosis of white-coat hypertension is generally based on ambulatory or self-monitoring supplemented by a demonstration of lack of target-organ involvement by echocardiography or other means and because the roles of ambulatory and self-monitoring and of echocardiography remain to be established, there is insufficient evidence at present to provide an operational definition of white-coat hypertension for routine clinical use. We have attempted to collect all the relevant research and summarize the findings faithfully in this report. Grade A recommendations based on level-I evidence can be considered as standards for practice that is, the evidence in support of them is so strong that it is unlikely to be supplanted by stronger evidence in the foreseeable future. Recommendations supported by lower levels of evidence have received lower grades. Although these may also survive the test of time and better studies, clinicians may wish to temper them with their own experience and to be alert for new evidence.

If the recommendations summarized here are implemented they will provide a sounder basis for the measurement of blood pressure, the appropriate labelling of people as hypertensive and the introduction of antihypertensive therapy for those most likely to benefit.

CHAPTER THREE

High Blood Pressure in Women

High Blood Pressure is a common problem in women. The special problems are posed due to child bearing. Not only do the women suffer from the usual injuries inflicted by this condition , a pregnant women is liable to develop temporary hypertension during pregnancy. This can endanger the unborn as well as the mother. A hypertensive woman on the other hand can pose similar dangers.

Pregnancy-Induced Hypertension (PIH) Hypertension in pregnancy is present when diastolic BP ˜ 90 mm Hg, systolic BP >140; systolic BP rises at least 30 mm Hg over baseline value or diastolic BP rises at least 15 mm Hg over baseline value.

Risk factors for PIH. The risk factors for PIH include first pregnancy, multiple gestation, polyhydramnios, hydatidiform mole, malnutrition, positive family history of PIH, underlying vascular disease. Molar pregnancy should be expected if PIH occurs early in gestation.

It is important that women undergo regular antenatal checkups

1. During pregnancy, it is not appropriate to use:
   a. Sympathetic ganglion blockers (orthostatic hypotension)
   b. Diuretics (aggravation of volume depletion)
   c. ACE inhibitors (associated with fetal defects and neonatal renal failure)
2. Laboratory evaluation is performed early in pregnancy.
3. Obstetric visits are scheduled every other week at 24 weeks and weekly after 30 weeks.
4. Early ultrasonogram is obtained for dating, and repeated periodically to look for evidence of IUGR.
5. Antenatal surveillance (NSTs) should begin at 34 weeks.
6. The pregnancy should not be allowed to go beyond 40 weeks. Delivery may be required earlier if there is evidence of IUGR or fetal distress or if hypertension cannot be controlled by bed rest and medication.
7. Intrapartum monitoring is required during labor.
8. If there is evidence of IUGR, cesarean section is preferable to a prolonged induction.
9. Complicated cases or women with superimposed preeclampsia should be handled at an appropriate referral center.

Hypertension

Although some women may develop PIH others might suffer from it due to reasons other than pregnancy. This imposes additional risks.

Maternal Risks. If no superimposed preeclampsia occurs, there is no additional maternal risk. In the presence of superimposed preeclampsia (20%), there is increased maternal mortality, frequently from intracranial hemorrhage.

Fetal Risks. There is an increased incidence of perinatal death, IUGR, and fetal distress.

Treatment of chronic hypertension can decrease maternal and, to some extent, fetal morbidity but cannot reduce the risks of superimposed preeclampsia. Appropriate medications include methyldopa, hydralazine, and beta-blockers

High blood pressure is a major risk factor for coronary heart disease and the most important risk factor for stroke and heart failure. High blood pressure causes three of every five cases of heart failure in women. High blood pressure also boosts the chances of developing kidney disease and blindness.

Older women have a higher risk of high blood pressure, with more than half of all women over age 55 suffering from this condition. Using birth control pills can contribute to high blood pressure in some women.

While all women can and should take steps to prevent or control high blood pressure, it is especially important for women who have heart disease to do so.

The harmful effects of elevated blood pressure do not necessarily begin at the 140/90 mmHg mark -- even blood pressures slightly under that can increase the risk of heart disease and stroke. Many older people, on the other hand, have a form of high blood pressure known as "isolated systolic hypertension". This occurs when the systolic pressure is high but the diastolic pressure) is normal. This too, if not controlled, increases the risk of heart attack and stroke.

Blood Pressure Categories in Women (18 Years and Older)*

*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category determines blood pressure status.

Blood Pressure Level in mmHg

Category	Systolic		Diastolic
Optimal**	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension			
- Stage 1	140-159	or	90-99
- Stage 2	160-179	or	100-109
- Stage 3	>=180	or	>=110

**Optimal blood pressure with respect to cardiovascular risk is <120/<80 mmHg. Unusually low readings should be evaluated for clinical significance.

Source: The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. NIH, NHLBI, 1997.

CHAPTER FOUR

Hypertension in Children

Hypertension though uncommon , does occur in children. More often than not it is secondary to a serious underlying disease. This is usually manifest but may sometimes require detailed and careful clinical examination and investigations. In addition , emergency situation may have to be faced.

A. Hypertensive emergencies exist when marked blood pressure elevation becomes a threat to function of vital organs including brain, heart, and kidneys. A major factor determining the outcome of children with hypertensive emergencies is the speed of initiating an effective plan to lower BP.

B. The objective of emergency treatment is prevention of hypertensionrelated adverse events (e.g., stroke, cardiac failure, encephalopathy). This usually requires only a modest reduction in BP. Attempts to rapidly achieve normal BP are contraindicated. In patients with chronic hypertension, a rapid lowering BP to "normal" can decrease needed perfusion to the heart and brain resulting in ischemia. For this reason, in individuals with longstanding hypertension or hypertension of unknown duration, an initial BP reduction (10-20%) followed by gradual normalization of BP is recommended. In acute hypertension, the therapy should be directed towards bringing the BP to normal values.

Causes of Pediatric Hypertension (partial listing)

A. Renal disease (80%)
   1. Nephritides
      a. Henoch-Schonlein Purpura
      b. Postinfectious glomerulonephritis
      c. Systemic lupus nephritis
      d. Rapidly progressive glomerulonephritis
   2. Vascular
      a. Hemolytic-uremic syndrome
      b. Renal artery stenosis & thrombosis*
      c. Renal vein thrombosis*
   3. Congenital Malformations
      a. Polycystic kidney disease*
      b. Tuberous sclerosis*
      c. Hydronephrosis*
      d. Renal hypoplasia*
      e. Obstructive uropathy*
   4. Miscellaneous
      a. Iatrogenic fluid overload*

b. Renal failure with fluid overload
c. Renal transplant (rejection or renal artery stenosis)
d. Reflux nephropathy
e. Renal tumors (Wilm's, Tuberous sclerosis, congenital nephroma)*, perirenal masses*

B. Endocrine
a. Pheochromocytoma*
b. Congenital adrenal hyperplasia*
c. Hyperthyroidism
d. Neuroblastoma*
e. Cushings Syndrome*
f. Renin-secreting tumor

C. Neurological
a. Meningoencephalitis
b. Tumor
c. Guillain-Barre syndrome
d. Dysautonomia
e. Increased intracranial pressure (trauma)
f. Seizures*

D. Cardiovascular
a. Aortic thrombosis*
b. Aortic coarctation*
c. Aortic insufficiency
d. Subacute bacterial endocarditis
e. Takayasu's arteritis

E. Others
Leg traction
Burns
Chronic lung disease*

Drugs*: including corticosteroids, NSAIDs, cocaine, amphetamines, theophylline, pancuronium, phenylephrine
"Rebound hypertension" -occurs with abrupt withdrawl of clonidine, angiotensin converting enzyme inhibitors or beta-blockers
**** are causes of neonatal hypertensive emergencies.***

Examination and investigations

A concise medical history, stressing renal, endocrine, cardiac and neurological systems, current medications or ingestions and hydration should be obtained..
Physical examination, emphasizing: cardiovascular, genitourinary, dermatologic and neurologic systems. Blood pressure should be measured in all extremities with correct sized cuff and that pain and anxiety are minimized.

Investigations

Baseline studies including: CBC and diff, urea , creatinine, serum electrolytes, calcium, glucose, phosphorus, triglycerides, cholestrol, lipoprotein analysis (HDL,

LDL) and urinalysis. Where indicated catecholamines, plasma renin activity (PRA), aldosterone, and urine culture.

Note: Catecholamines and PRA should be placed immediately on ice. These levels should be obtained before pharmacologic therapy is administered when possible.

It may also be necessary to get renal ultrasound, cardiac echocardiogram and depending on neurological status head CT.

The following 4 tables are from:

"The Report of the Second Task Force on Blood Pressure Control in Children 1987", PEDS, 79 (1), 1 - 25, 1987.

1. DEFINITIONS

TERM	DEFINITION
Normal BP	Systolic and diastolic BP's < 90th percentile for age and sex
High normal BP *	Average systolic and/ or average diastolic BP between 90th and 95th percentiles for age and sex
High BP (hypertension)	Average systolic and/ or average diastolic BPs ≥ 95th percentile fo age and sex with measurements obtained on at least three occasions

* If the BP reading is high normal for age, but can be accounted for by excess height for age or excess lean body mass for age, such children are considered to have normal BP.

2. Classification of Hypertension by Age Group

Age Group	Significant Hypertensio (mmHg)	Severe Hypertension (mmHg)
Newborn 7 day 8 - 30 days *	Systolic BP ≥ 96 Systolic BP ≥ 104	Systolic BP ≥ 106 Systolic BP ≥ 110
Infant (< 2 yr)	Systolic BP ≥ 112 Diastolic BP ≥ 74	Systolic BP ≥ 118 Diastolic BP ≥ 82
Children (3 - 5 yr)	Systolic BP ≥ 116 Diastolic BP ≥ 76	Systolic BP ≥ 124 Diastolic BP ≥ 84
Children (6 - 9 yr)	Systolic BP ≥ 122 Diastolic BP ≥ 78	Systolic BP ≥ 130 Diastolic BP ≥ 86
Children (10 - 12 yr)	Systolic BP ≥ 126 Diastolic BP ≥ 82	Systolic BP ≥ 134 Diastolic BP ≥ 90
Adolescents (13 - 15 yr)	Systolic BP ≥ 136 Diastolic BP ≥ 86	Systolic BP ≥ 144 Diastolic BP ≥ 92
Adolescents (16 - 18 yr)	Systolic BP ≥ 142 Diastolic BP ≥ 92	Systolic BP ≥ 150 Diastolic BP ≥ 98

<u>* also see tables that follow for neonates !</u>

3. Historical Information to Elicit

Information	Relevance
Family history of hypertension, preeclampsia, toxemia, renal disease, tumors	Important in essential hypertension, inherited renal disease, and some endocrine diseases (eg. familial pheo. with multiple endocrine adenopathy II)
Family history of early complications of hypertension and/ or atherosclerosis	Suggests likely course of hypertension and/ or presence of other coronary artery disease risk factors
Neonatal history	Use of umbilical artery catheter suggests need to evaluate renal vasculature and kidneys
Headaches, dizziness, epistaxis, visual problems	Nonspecific symptomatology, usually no etiologically helpful
Abdominal pain, dysuria, frequency, nocturia, enuresis	May suggest underlying renal disease
Joint pains/ swelling, facial or peripheral edema	Suggests connective tissue disease and/ or other forms of nephritis
Weight loss, failure to gain weight with good appetite, sweating, flushing, fevers, palpitations	In combination, symptoms suggest pheochromocytoma
Muscle cramps, weakness, constipation	May suggest hypokalemia and hyperaldosteronism
Age of onset of menarche, sexual development	May be helpful in suggesting hydroxylase deficiencies
Ingestion of prescription and over-the-counter drugs, contraceptives, illicit drugs	Drug-induced hypertension

4. Findings to Look for on Physical Examination

Physical Findings	Relevance
General:	
Pale mucous membranes, facial or Pretibial edema	Renal disease
Pallor, evanescent flushing, Increased sweating at rest	Pheochromocytoma vs. hyperdynamic essential hypertension
Cafe au lait spots, neurofibromas	Von Recklinghausen disease
Moon face, hirsutism buffalo hump, Truncal obesity, striae	Cushing syndrome
Webbing of the neck, low hairline, wide-spaced nipples, wide carrying angle	Turner syndrome
Elfin facies, poor growth, Retardation	Williams syndrome
Thyroid enlargement	Hyper- or hypothyroidism
Cardiovascular:	
Absent or delayed femoral pulses, low leg pressure relative to arm BP	Aortic coarctation
Heart size, rate, rhythm murmurs, Respiratory difficulty, hepato-Megaly	Murmur - coarctation; tachycardia and/ or arrhythmia - pheochromocytoma; large heart or heart failure - prolonged or severe hypertension
Bruits over great vessels	Arteritis or arteriopathy
Abdomen:	
Epigastric bruit	Renovascular diseases isolated or associated with Williams or Von Reck-linghausen syndromes, or arteritis
Unilateral or bilateral masses	Wilms tumor, neuroblastoma, pheochromocy-toma, polycystic kidneys, other tumors
Neurologic:	
Hypertenive funduscopic changes	Chronic hypertension
Bell palsy	Chronic hypertension (HTN)
Neurologic deficits (eg hemiparesis)	Chronic or severe acute HTN with stroke

Neonatal Systemic Hypertension:

The following 2 tables provide further information for neonates.

1. Systolic (S) and Diastolic (D) Blood Pressures in Low Birthweight Infants

Birthweight 600 - 999 g			Birthweight 1000 - 1249 g		
Day	S (± 2 SD)	D (± 2 SD)	Day	S (± 2 SD)	D (± 2 SD)
1	37.9 (17.4)	23.2 (10.3)	1	44 (22.8)	22.5 (13.5)
3	44.9 (15.7)	30.6 (12.3)	3	48 (15.4)	36.5 (9.6)
7	50 (14.8)	30.4 (12.4)	7	57 (14.0)	42.5 (16.5)
14	50.2 (14.8)	37.4 (12.0)	14	53 (30.0)	-
28	61.0 (23.5)	45.8 (27.4)	28	57 (30.0)	-
Birthweight 1250 - 1499 g			**Birthweight 1500 - 1750 g**		
Day	S (± 2 SD)	D (± 2 SD)	Day	S (± 2 SD)	D (± 2 SD)
1	48 (18.0)	27 (12.4)	1	47 (15.8)	26 (15.6)
3	59 (21.1)	40 (13.7)	3	51 (18.2)	35 (10.0)
7	68 (14.8)	40 (11.3)	7	66 (23.0)	41 (24.0)
14	64 (21.2)	36 (24.2)	14	76 (34.8)	42 (20.3)
28	69 (31.4)	44 (25.2)	28	73 (5.6)	50 (9.9)

from: Ingelfinger JR, Powers L, Epstein MF: Blood Pressure Norms in Low-birth-weight Infants Birth through 4 Weeks, Pediatr Res 17: 319A, 1983

2. Mean Arterial BP (MAP) in mmHg (+ SD) in Preterm and Term Ill Neonates

Birthweight (kg)	< 1.0 kg	1.0 - 1.5 kg	1.5 - 2.5 kg	> 2.5 kg
Birth	32.9 ± 15.4	39.1 ± 18.2	42.4 ± 19.6	48.8 ± 19.4
7 days	41.4 ± 15.4	47.2 ± 18.2	50.4 ± 19.6	60.2 ± 19.4
14 days	44.6 ± 15.4	50.1 ± 18.2	53.2 ± 19.6	64.2 ± 19.4
28 days	47.6 ± 15.4	53.0 ± 18.2	56.1 ± 19.6	68.3 ± 19.4

from: Stork EK, Carlo WA, Kliegman RM, et al: Hypertension redefined for critically ill neonates Pediatr Res 18: 321A, 1984

CHAPTER FIVE

1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension

1. Introduction

The present Guidelines come at a critically important time globally for the management of hypertension and the prevention of associated cardiovascular disorders. The second half of the twentieth century has seen a progressive decrease in cardiovascular mortality in North America, Western Europe, Japan and Australasia. At the same time, the control of hypertension in these regions has improved considerably. For example, the Health Examination Surveys in the USA have demonstrated that whereas 10% of hypertensive subjects had their blood pressure lowered to below 140/90 mmHg in 1976-80, by 1988-91 the proportion had risen to 27%.2 On the other hand it is important to note that this leaves over 70% of hypertensive subjects with imperfect control (or no treatment at all), as has been reported in many other countries, and that there are worrying signs that the rate of improvement has plateaued or even reversed in some cases. In the UK, a recent survey indicated that only 6% of hypertensive patients had their blood pressure lowered to below 140/90 mmHgAdditionally, in the USA there is recent evidence that age-adjusted stroke mortality rates have risen slightly and that the rate of decline of coronary heart disease (CHD) mortality has decreased. Moreover, given the ageing population structure of most developed countries, total numbers of strokes and CHD events are typically increasing or remaining static, even in those countries that continue to experience falling age-adjusted event rates.

Even more worrying is the rapid development of the "second wave" epidemic of cardiovascular disease that is now flowing through developing countries and the former socialist republics. It is evident that death and disability from CHD and cerebrovascular disease are increasing so rapidly in these parts of the world that they will rank No. 1 and No. 4 respectively as causes of the global burden of disease by the year 2020. Given the central role of elevated blood pressure in the pathogenesis of both CHD and stroke, it is clear that one of the biggest challenges facing public health authorities and medical practitioners is the control of hypertension worldwide, both in individual patients and at the population level.

1.1 Scope and purpose of Guidelines

The present Guidelines are written to guide specialist physicians responsible for the care of patients with high blood pressure. They are complemented by a companion set of "Practice Guidelines" for general practitioners and other clinicians caring for patients with hypertension in various regions around the world. The 1999 Guidelines again concentrate on the management of patients with "mild" hypertension, since there is often uncertainty among clinicians, and policy makers about how to manage this condition. Since the determinants of cardiovascular disease in hypertensive patients are substantially multifactorial, these Guidelines provide recommendations for risk reduction through blood pressure lowering, in a context that recognises the importance of

strategies for the management of other risk factors that commonly affect individuals with hypertension.

The Guidelines do not deal with the management of more severe hypertension except in the most general terms, nor with the management of patients with secondary forms of hypertension. Furthermore, these Guidelines do not deal with the primary prevention and control of hypertension at the population level. These strategies, which are dealt with elsewhere, are complementary to the clinical strategy that is the subject of this Report.

Box 1 The 1999 Guidelines

- These Guidelines provide recommendations that are based on the collective expert interpretation by the WHO-ISH Guidelines Subcommittee of the available evidence from epidemiological studies and from clinical trials.
- The primary aim is to offer balanced information to guide clinicians, rather than rigid rules that would constrain their judgement about the management of individual patients, who will differ in their personal, medical, social, ethnic and cultural characteristics.
- The WHO-ISH Guidelines are written for a global audience from communities that vary widely in the nature of their health system and in the availability of resources.
- It is hoped that national and regional experts will use them as a basis for drawing up recommendations that are specifically designed for the management of patients in their own region.

2. Determinants of Cardiovascular Disease Risk in Hypertensive Patients

It is well established that in Western populations, stroke, CHD and other common cardiovascular diseases, such as heart failure, have multiple determinants. The main established predictors of these diseases are described briefly in this section. How well these factors predict cardiovascular disease in non-Western populations is less certain, although recent evidence from Eastern Asian populations suggests that for blood pressure and blood cholesterol there may be similar associations in the East and West. There is very little direct evidence about the determinants of common cardiovascular diseases in other large populations such as those of sub-Saharan Africa, India or South America.

2.1 Effects of blood pressure on the risk of cardiovascular disease

2.1.1 Stroke

Blood pressure levels, both systolic and diastolic, have been shown to be positively and continuously related to the risk of stroke across a wide range of levels in populations from both Western and Eastern hemispheres. Among individuals of mostly middle age, a prolonged 5 mmHg lower level of usual diastolic blood pressure (DBP) was shown to be associated with a 35-40% lower risk of stroke, with no lower level identified below which the risks of stroke did not continue to decline. The slope of the association appears to decline somewhat with increasing age; however, because the incidence of stroke increases so rapidly with age (see below), the elderly still suffer the large majority of blood pressure-related cerebrovascular disease. Blood pressure levels are positively related to both cerebral haemorrhage and cerebral infarction, but the association appears to be somewhat steeper for haemorrhage than infarction

Box 2 Hypertension Versus Normotension

- Blood pressure levels are continuously related to the risks of cardiovascular disease and the definition of hypertension (or raised blood pressure) is, therefore, arbitrary.
- Much blood pressure-related disease occurs among individuals who would normally be considered "normotensive.
- Most of the evidence about the benefits and risks of lowering blood pressure comes from studies in patients selected on the basis of high blood pressure.
- It is not clear whether estimates of treatment effect obtained from trials in hypertensives can be extrapolated to individuals with lower blood pressure levels.
- There is a strong rationale for expecting high-risk patients without hypertension to benefit from blood pressure lowering and trials are required to investigate this possibility.

2.1.2 Coronary heart disease

Blood pressure levels have also been shown to be positively and continuously related to the risks of major CHD events (CHD death or non-fatal myocardial infarction). The strength of this association is about two-thirds as steep as that for stroke, and appears to be similar across a broad range of blood pressure levels, that includes both hypertensive and normotensive individuals. Once again, no lower level has been identified below which the risks do not continue to decline.

2.1.3 Heart failure and renal disease

The risks of heart failure and of renal disease have been observed to be related to blood pressure levels, but the sizes of the relationships are less well established than those for stroke and CHD. Nevertheless, there is evidence that patients with a history of hypertension have at least six times greater risk of heart failure than do individuals without such a history, and that each 5 mmHg lower level of DBP is associated with at least a one-quarter lower risk of end-stage renal disease.

2.1.4 Recurrent cardiovascular events

Among individuals with a history of cerebrovascular disease or previous myocardial infarction, there have been reports of both linearand non-linear ("J-shaped")associations between blood pressure levels and the risks of recurrent events. However, the associations in patients with prior cardiovascular disease are subject to confounding as a consequence of the effects of disease (or its treatment) on blood pressure and, independently, on the risks of recurrence. Studies that have attempted to control for this (either by excluding patients with more severe disease or by excluding early recurrent events) have consistently demonstrated continuous positive associations between blood pressure levels and the longer-term risks of stroke and CHD recurrence.

2.1.5 Pulse pressure and arterial distensibility

There is evidence that pulse pressure (the difference between systolic and diastolic blood pressure) is also positively associated with a variety of cardiovascular diseases. However, there remains uncertainty as to whether pulse pressure predicts disease risk independently of either systolic or diastolic blood pressure. Pulse pressure is one index of arterial distensibility. While there are theoretical reasons for expecting arterial distensibility to be independently predictive of cardiovascular disease riskthere are still few data demonstrating such an association.

2.2 Effects of other risk factors on the risk of cardiovascular disease

2.2.1 Age

In most populations, the risks of cardiovascular disease rise steeply with increasing age. For example, among British men, from age 45 to 74, there is a 3-4 fold increase in deaths from stroke and from CHD each decade. This powerful effect of age on disease risk has important consequences for the effects of blood pressure and other risk factors on disease occurrence. Specifically, while the relative effects of some risk factors decline as age increases, the absolute effects of these risk factors typically *increase* with age because of the markedly higher background risk of cardiovascular disease in older people.

2.2.2 Gender

At most ages, the risks of cardiovascular diseases are greater in men than women, although this difference declines with increasing age and is greater for CHD than for stroke. For example, in the United States from age 34 to 74, the risks of death from stroke are 30% higher in men than women, whereas the risks of death from CHD are 2-3 fold greater in men. After age 75, the risks of death from stroke and from CHD death are similar in men and women.

2.2.3 Pre-existing cardiovascular disease

A history of clinically manifest cardiovascular disease is a particularly important predictor of the future risk of major cardiovascular events. Patients with congestive heart failure, typically experience death rates of 10% or more annually. Patients with a history of stroke or TIA, experience stroke risks of 3 to 5% or more annually, and the risk of other major cardiovascular events is at least an additional few percent. Among patients with a history of myocardial infarction or unstable angina, the annual incidence of recurrent infarction or CHD death is 4% or more and the risk of other major cardiovascular events is an additional one or two percent.

Subclinical manifestations of cardiovascular disease in asymptomatic patients can also be important predictors of future risk. For example, high rates of major clinical events (a few percent per year) occur among patients with significant left ventricular dysfunction, ECG evidence of Q waves, or ECG evidence of left ventricular hypertrophy. Ultrasonographic evidence of left ventricular hypertrophy or carotid atherosclerosisis also associated with increased risks of cardiovascular disease events.

2.2.4 Renal disease and microalbuminuria

Renal disease manifested by raised serum creatinine and proteinuria is an important predictor not only of renal failure but also of major cardiovascular events. While most types of renal disease are associated with increased risk, diabetic nephropathy appears to confer the greatest risks. Typically, the risk of CHD events in patients with end-stage renal disease (irrespective of aetiology) is at least as great as that in patients with a clinical history of CHD. Among diabetics without frank renal disease, microalbuminuria has been observed to be associated with a 2-3 fold increase in the risk of major cardiovascular events.

2.2.5 Diabetes, hyperinsulinaemia and hyperglycaemia

Diabetes – whether insulin dependent or non-insulin dependent – increases the risks of CHD and ischaemic stroke, as well as the risk of renal disease. Overall, diabetes typically increases the relative risks of death from CHD and death from stroke about 3 fold. Additionally, among individuals without diabetes, the risks of CHD have been observed to be directly and continuously related to blood insulinand blood glucose levels.

Box 3 Contribution of Blood Pressure and Other Factors to Cardiovascular Disease Risk

- Among patients with mild hypertension, differences in the risks of cardiovascular disease are determined not only by the level of blood pressure, but also by the presence or levels of other risk factors.
- For example, a man aged 65 years with diabetes, a history of TIA, and a blood pressure of 145/90 mmHg will have an annual risk of a major cardiovascular event that is more than ***20 times greater*** than that in a man aged 40 years with the same blood pressure but without either diabetes or a history of cardiovascular disease.
- In contrast, a man aged 40 years with a blood pressure of 170/105 mmHg will have a risk of a major cardiovascular event that is about 2-3 times greater than that of a man of the same age with a blood pressure of 145/90 mmHg and similar other risk factor levels.
- Thus differences in the absolute level of cardiovascular risk between patients with hypertension will often be determined to a greater extent by other risk factors than by the level of blood pressure.

2.2.6 Smoking

Cigarette smoking increases the risk of CHD and ischaemic stroke at all ages, but is of particular importance in younger people. In men under 65 years, smoking has been observed to increase the risk of cardiovascular death 2 fold, while in men aged 85 years or older, the risk was observed to be increased by 20%. In addition to these effects of smoking on cardiovascular diseases, smoking also increases the risks of a wide variety of non-cardiovascular diseases, in particular respiratory and neoplastic diseases.

2.2.7 Lipids and lipoproteins

Increasing levels of both total and LDL cholesterol are associated with increases in the risks of CHD. The relative risks appear to decline with increasing age, although the absolute risks typically increase. A 0.6 mmol/l (23.2 mg/dl) lower total cholesterol in men aged 40 years has been observed to be associated with a 54% lower CHD risk, whereas the same difference in cholesterol in men aged 70 years was associated with a 20% lower risk. The effect of HDL cholesterol on CHD risk does not appear to be age-dependent; every 0.03 mmol/l (1.2 mg/dl) increase in HDL cholesterol appears to be associated with at least a 3% reduction in the risk of CHD. It is still unclear whether there is any independent effect of triglyceride levels on the risk of cardiovascular disease.

2.2.8 Obesity

Increased body mass index (BMI: kg/m^2) is associated with increased risks of CHD. Compared with lean men, men with BMI of 25-29 have been observed to have a 70% greater risk of CHD whereas men with BMI of 29-33 had almost a 3 fold greater risk of CHD. The strength of this association appears to decline with age. The risk associated with obesity is likely to be due in part to blood pressure elevation, but reduced HDL cholesterol and increased insulin and glucose may also be involved.

2.2.9 Fibrinogen

Blood levels of fibrinogen are positively associated with the risk of CHD and ischaemic stroke. In several studies, individuals with fibrinogen in the highest tertile had risks of CHD that were about twice as great as those among individuals with fibrinogen in the lowest tertile.

2.2.10 Alcohol

The risk of CHD appears to be reduced among regular consumers of alcohol (e.g. 1-3 standard drinks per day). In general, daily consumers of alcohol have a 30-40% lower risk of death from CHD than do non-drinkers. However, high levels of alcohol consumption can cause other cardiac disorders and are associated with increased risks of stroke (particularly after binge drinking), as well as higher blood pressure levels and higher risks of several non-vascular diseases and injury.

2.2.11 Physical activity

Regular aerobic exercise reduces the risk of CHD. Individuals performing about 20 minutes of light to moderate-intensity exercise daily have been observed to have about a 30% lower risk of death from CHD than do sedentary individuals. These benefits may be due in part to the blood pressure lowering effects of exercise, but other metabolic factors that may be activated by exercise, such as increased HDL cholesterol, may also be involved.

2.2.12 Hormone replacement therapy

In studies of Western populations, the use of hormone replacement therapy (HRT) has been shown to be associated with 30-50% lower risks of CHD among post-menopausal women. Whether this association reflects a true protective effects of HRT or of the selection of low risk women for HRT is uncertain. The results of a recent trial of HRT in women with CHD failed to demonstrate any protective effect of HRT for recurrent CHD events.

2.2.13 Socio-economic status

Socio-economic status – as judged from education, employment or income – is a powerful predictor of the risk of most common cardiovascular diseases. In many studies of a variety of mainly Western populations, lower levels of socio-economic status have been observed to be associated with higher risks of cardiovascular disease. The magnitudes of the associations vary between populations but in the US, individuals with income less than $18,500 in 1980 have been observed to have cardiovascular death rates that are 40% greater than in individuals with income greater than $32,000. These associations appear to be mediated, at least in part, by increased levels of most established risk factors, including smokingamong those in lower socio-economic groups. How widely such associations exist outside Western populations is uncertain; however, there is evidence within some Western populations of heterogeneity of associations among different ethnic groups.

2.2.14 Ethnicity

Ethnicity is also powerfully related to the risk of most common cardiovascular diseases. In many countries, ethnic minority groups – such as New Zealand Maori and United States Native Americans – have substantially higher risks of CHD than do the Caucasian majority. Moreover, there is evidence that African Americans are generally at greater risk of stroke, and of renal disease than are Caucasians from the US, and that South Asians in the UK but not Canadaare at higher risk of these diseases and CHD than are Caucasians from the same countries. There is uncertainty as to how much of these ethnic differences in risk can be ascribed to differences in levels of the established risk factors for cardiovascular diseases.

2.2.15 Geographic region

There are major differences between geographic regions in the incidence of cardiovascular diseases. Some particularly important trends include the high rates of both CHD and stroke in Eastern Europe, Russia and the Baltic states, and the high rates of stroke and the low rates of CHD in the People's Republic of China, compared to Western Eurcpe and North America. In some parts of Africa, there are high rates of stroke and renal disease, but low rates of CHD.

2.2.16 Other risk factors

Many other factors – including passive smoking, blood type, LDL particle size, apolipoproteins, plasma renin activity, blood homocysteine levels, blood uric acid levels, several common genetic polymorphisms, several infective agents, and several psychological factors – have been reported to be independently associated with the risks of cardiovascular diseases. For most of these factors, the evidence of an association with cardiovascular disease is less strong than for most of the factors listed above.

3. Interventions to Reduce Cardiovascular Risk in Hypertensive patients

3.1 Effects of blood pressure lowering treatments on mortality and morbidity from cardiovascular disease

3.1.1 Trials of diuretic and beta-blocker based regimens

Previous randomised controlled trials of diuretic- or beta blocker-based regimens, involving a total of about 47,000 patients with hypertension, have collectively demonstrated that, over an average of about 5 years, such treatment produced much of the epidemiologically-expected benefit of the achieved blood pressure reductions. A net reduction of 5-6 mmHg in usual diastolic blood pressure was associated with a 38% (SD 4) reduction in stroke risk and a 16% (SD 4) reduction in CHD risk, with similar effects on fatal and non-fatal events. The proportional reductions in the risks of stroke and CHD in these trials appeared to be broadly similar in patients with mild, moderate or more severe hypertension, in older or younger patients, and in patients with or without a history of cerebrovascular disease.

Because of the similarity of the relative risk reductions in different patient groups, the size of the absolute treatment benefits varied in direct proportion to the background level of risk (i.e. patients at highest absolute risk of stroke or CHD experienced the largest absolute reduction in risk). For example, there was a 34% reduction in the relative risk of stroke in trials conducted exclusively in older populations and a 43% relative risk reduction in the trials conducted predominantly in individuals of middle age. However, the annual absolute risk reduction was more than two times greater in the trials in older patients: specifically, there were 5 strokes prevented per thousand patients in the trials among older patients, compared with 2 strokes prevented per thousand patients in the trials among younger patients. The outcome was similar for CHD: there was a 19% reduction in relative risk in the trials among older patients and a 14% relative risk reduction in the trials among middle aged patients, but the annual absolute risk reduction was 3 events per thousand older patients and 1 event per thousand younger patients.

Box 4 Underestimation of the Effects of Blood Pressure Lowering Treatment in Randomised Controlled Trials

- Estimates of treatment effects in the trials of blood pressure lowering regimens generally provide conservative estimates of the full potential effects of treatment:
- In the trials, there was considerable "cross-over" between treatment groups:
- a proportion of patients assigned to active therapy groups stopped treatment; and
- a proportion of those assigned to control groups began active treatment.
- Such cross-over is likely to have reduced the average difference in diastolic blood pressure between groups by 1-2 mmHg, in which case, the full relative effects of treatment on stroke and CHD would be somewhat greater than the effects observed.
- The average duration of treatment in the trials was only about 5 years, and it is possible that longer-term treatment over many years, as is usual for hypertensive patients, might have led to larger relative risk reductions
- Low-risk patients were recruited to many trials, and the absolute effects of treatment among higher risk patients seen in broader clinical practice are, therefore, likely to be greater than those typically observed (see Box 3).

There was evidence of reduced stroke risks both in trials of diuretic-based regimens and in trials of beta blocker-based regimens. It has been observed that the evidence for reduced CHD risk was somewhat stronger for diuretic-based therapy than for beta blocker-based therapy, particularly in trials conducted in the elderly. However, data from the four trials that directly compared the effects of diuretic- and beta blocker-based regimens on the risks of stroke and CHD in younger and older patients provided no clear evidence of a difference between the regimens in their effects on stroke or CHD. Nevertheless, even in combination these studies lacked adequate statistical power to determine reliably any modest but potentially important treatment differences (e.g. a 10-15% difference in the relative risk of CHD).

While there are comparatively few data available from these trials about the effects of treatment on heart failure or renal disease, there was evidence of an approximate halving of the risk of heart failure in the trials of diuretic- and beta blocker-based based regimens. Additional evidence about the effects of beta-blockers on such outcomes is provided by the trials of these agents in patients with heart failure (see 6.4). Similarly, more evidence about the effects of beta blockers on CHD risk is provided by the trials of these agents in patients with prior myocardial infarction (see 6.4).

Box 5 Relative and Absolute Effects of Treatment

- The relative effect of treatment reflects the proportional difference between treatment groups in the incidence of disease events:
  - in the Systolic Hypertension in the Elderly (SHEP) trial, the incidence of major CHD events over 4.5 years in patients assigned active treatment was 4.4% while in those assigned placebo it was 5.9%. This represents a relative risk of 0.73 or a relative risk reduction of 27%.
- The absolute effect of treatment is generally of greatest interest to doctors and patients:
  - in the SHEP trial, the absolute reduction in CHD risk over 4.5 years was 1.4%. This indicates that 14 events were prevented among every 1000 patients assigned active treatment, and that one major CHD event was avoided among every 71 patients assigned active treatment.
- Estimates of *relative* treatment effects from randomised trials provide a guide to the likely relative effects of treatment in other non-study patient populations. However, estimates of *absolute* treatment effects from trials of blood pressure lowering are of limited generalisability because complex inclusion and exclusion criteria frequently resulted in the recruitment of patients at lower average risk than those seen in broader clinical practice
- The best predictor of absolute treatment effects for any individual patient will be provided by application of the estimate of the relative risk reduction from trials to an estimate of the absolute disease risk for the individual in question.
- A simple table for estimating the absolute cardiovascular disease risk of individual hypertensive patients is provided for use with these guidelines (see Table 3)

3.1.2 Trials of other treatment regimens

There are fewer data available from which to determine the effects on cardiovascular disease risks of blood pressure lowering regimens based on the newer classes of agents in hypertensive patients, although the available evidence is increasing rapidly. Data on the effects of calcium antagonists on cardiovascular disease risks in patients with hypertension are available from one moderate-to-large scale randomised, placebo-controlled trial: in the Syst-Eur trial, nitrendipine-based therapy produced an approximate 10/5 mmHg reduction in blood pressure in patients with systolic hypertension and a 42% reduction in the risk of stroke. Similar results were observed in two large, non-randomised, placebo-controlled trials (with alternate treatment assignment): the STONE Studyand the Syst-China trial. Collectively, these studies provide evidence that calcium antagonists reduce the risk of stroke, and that the magnitude of this effect appears to be similar to that seen in trials of diuretic- or beta-blocker-based therapy. However, there were few CHD events recorded in these trials and, as a consequence, it is not possible to assess reliably the effects of calcium antagonists on the risk of CHD in these trials. More evidence about the effects of calcium antagonists on CHD events is provided by trials of these agents in patients with a history of myocardial infarction (see 6.4).

To date, only one large-scale trial has provided evidence about the effects of ACE inhibitor-based therapy in patients with uncomplicated hypertension. The Captopril Primary Prevention Project (CAPPP) compared the effects of a captopril-based regimen with other therapy (principally diuretic- or beta-blocker-based regimens) among 10,985 patients with hypertension. However, imbalances in the assignment of treatment resulted in a 2 mmHg higher average diastolic blood

pressure level at entry in the group assigned captopril-based therapy. This difference in blood pressure alone would be sufficient to confer an increase of 20% in the risk of stroke and an increase in the risk of CHD of 10% among individuals of middle age, such as those included in this study. Hence the imbalance in blood pressure levels could mask real differences that may exist between the regimens in their effects on CHD, and could explain the greater risk of stroke observed among patients assigned the captopril-based therapy. The CAPPP study also reported a reduced risk of diabetes among patients assigned captopril-based therapy, a result that appears less likely to be explained by the observed imbalances at baseline. Additional evidence about the effects of ACE inhibitors on CHD risk is provided by trials in patients with left ventricular dysfunction or heart failure (see 6.4).

Two small studies have reported fewer CHD events among diabetic hypertensive patients randomised to ACE inhibitor-based versus calcium antagonist-based regimens. However, each of these studies recorded only a small number of CHD events, and, as a consequence, the apparent difference in the effects of these agents requires verification in larger studies. The UK Prospective Diabetes Study (UKPDS 39) involved 1148 hypertensive patients with Type 2 diabetes, and over a median follow-up period of 8 years, there were similar benefits of ACE inhibitor- and beta-blocker-based therapy for a variety of both macrovascular and microvascular disease outcomes (see 3.13 below). Additional evidence about the effects of ACE inhibitors in patients with diabetes is provided by trials of these agents in patients with renal disease (see 6.5).

At present, no reliable evidence is available from randomised controlled trials about the effects on cardiovascular disease risk of alpha-adrenergic blockers or angiotensin II antagonists. However, large-scale trials involving both these drug types are ongoing.

3.1.3 Trials of different blood pressure targets

The Hypertension Optimal Treatment (HOT) trial used a calcium antagonist (felodipine) -based regimen (with the stepped addition of ACE inhibitors, beta-blockers and diuretics) to investigate the effects of lowering blood pressure to three different targets (□ 80 mmHg, □ 85 mmHg and □ 90 mmHg) in 18,790 hypertensive patients. By the end of follow-up, blood pressure had been substantially reduced in all three groups but there were only modest differences in systolic and diastolic blood pressure (about 2 mmHg) between adjacent target groups. These blood pressure differences were less than expected, and the study was not able to determine reliably the most plausible effect of such modest blood pressure differences. There was a non-significant trend towards lower cardiovascular event risk and a marginally significant trend towards fewer CHD events in the group with the lowest target. In the subgroup with diabetes, the trend for total cardiovascular events reached statistical significance. This is consistent with evidence from the UK Prospective Diabetes Study (UKPDS 38), demonstrating that a lower blood pressure target (using either ACE inhibitor- or beta-blocker-based therapy) was associated with reduced risks of major macrovascular events as well as microvascular disease outcomes. In that study, the "tight' blood pressure control group achieved average blood pressures of 144/82 mmHg whereas the less tight control group achieved blood pressures of 154/87 mmHg. This 10/5 mmHg reduction in blood pressure was associated with a one-third reduction diabetic deaths, almost a halving of stroke risk, and a one third reduction in microvascular complications.

3.2 Effects of blood pressure lowering treatments on other major disease outcomes

The trials of diuretic- and beta-blocker-based therapy in patients with hypertension provide evidence of almost identical rates of death from non-cardiovascular causes in patients assigned

active treatment or control. The results of these trials therefore suggest that treatment with these agents is not only effective for cardiovascular disease prevention, but is also safe in terms of the overall risk of death from non-cardiovascular causes during the 5 years of treatment and follow-up in these trials. For the newer agents, there is less evidence from trials in hypertensive patients about the effects of treatment on non-cardiovascular outcomes. However, data from all trials in patients with either hypertension or CHD provide no clear evidence of any excess mortality from non-cardiovascular causes among patients assigned treatment with either ACE inhibitors or calcium antagonists. While there has been debate about possible adverse effects of calcium antagonists on cancer and bleeding risks and beneficial effects of ACE inhibitors on cancer risk, these observations have been generated primarily by results from a few, potentially biased non-randomised studies. Detailed review of the available evidence from observational studies and randomised trials did not provide clear evidence of an adverse effect of calcium antagonists on the risk of cancer or of bleeding. Recent data from the Syst-Eur trial suggest that a calcium antagonist-based blood pressure lowering regimen may reduce the risks of dementia in elderly patients with systolic hypertension.

3.3 Effectiveness of hypertension management as provided in community practice

3.3.1 Control of blood pressure

A number of studies have investigated the effectiveness of antihypertensive therapy for the control of hypertension in representative population samplesThe results of these studies indicate that in most populations studied, a moderate proportion of all hypertensive patients are untreated and a large proportion of treated hypertensive patients still have frankly elevated blood pressure, defined most frequently as SBP>160 mmHg or DBP>95 mmHg. On average, about half of all treated patients in these studies had continuing blood pressure elevation above 160/95 mmHg and three-quarters had blood pressure levels above 140/90 mmHg, although there was wide regional variation. Several studies have reported changes in blood pressure control over time, and these have generally shown trends towards improved control. Male gender and residence in a developing country have been identified as factors associated with poorer blood pressure control. The observations in Chinaand several other developing countries that only about 10% of treated hypertensive patients reached blood pressures below about 160/95 mmHg are particularly important in this regard. However, very low rates of blood pressure control have also been observed in some studies of Western populations

3.3.2 Control of cardiovascular risk

Despite the benefits of blood pressure-lowering treatment established in randomised controlled trials, several population studies have demonstrated that treated hypertensive patients continue to experience substantially higher risks of CHD, stroke and overall mortality than do non-hypertensive individuals some years after beginning antihypertensive drug therapy. These observations are consistent with other findings indicating more advanced atherosclerosis and more marked left ventricular hypertrophy among treated hypertensive patients compared with non-hypertensive controls. The reasons for this persisting risk of cardiovascular complications are uncertain but are likely to involve both modifiable and non-modifiable factors. Non-modifiable factors may include a more frequent history of prior cardiovascular disease, diabetes or a genetic predisposition to cardiovascular complications. Potentially modifiable factors could include blood pressure levels that remain in the upper part of the population distribution and metabolic abnormalities, such as reduced levels of HDL cholesterol and increased levels of LDL cholesterol,

insulin and glucose. Each of these modifiable factors is associated with obesity, which is also more frequent in treated hypertensive patients than non-hypertensive individuals.

3.4 Effects of modification of other risk factors on mortality and morbidity from cardiovascular disease

3.4.1 Smoking cessation

Smoking cessation confers reduced risks of a large number of diseases including stroke and CHD. In particular, there are large reductions in risk among those who quit in middle age or younger. Those who quit before 35 years or middle age typically have a life expectancy that is not different to that of lifelong non-smokers.

3.4.2 Cholesterol lowering

A large body of evidence has demonstrated that cholesterol lowering reduces the risks of CHD events in patients with high cholesterol levels or a history of CHD. Dietary restriction of saturated fats can produce modest reductions in cholesteroland the newer drug therapies reliably produce large reductions. The size of the reduction in CHD risk appears to be proportional to the size of the cholesterol reduction achieved, such that reductions of about 1-1.5 mmol/l (40-60 mg/dl) produced by HMG CoA reductase inhibitors reduce the risk of major CHD events by between a fifth and a third. The effects of these agents on fatal and non-fatal CHD events appear to be of similar magnitude. Reductions in stroke risk have also been observed in the trials of HMG CoA reductase inhibitors, but not in the trials of other cholesterol lowering agents. In the few trials that provided data on cerebral infarction, there was some evidence of reduction in the risk of this stroke subtype.

3.4.3 Treatment of diabetes

There has been uncertainty as to whether blood glucose control in diabetic patients alters the risks of macrovascular disease. The results of the UK Prospective Diabetes Study (UKPDS 33) among 3867 patients with newly diagnosed Type 2 diabetes indicated that therapy with insulin or sulphonylureas over 10 years produced a one-quarter reduction in microvascular disease events, but no clear reduction in macrovascular disease events, although there was a trend towards fewer CHD events in the intensive blood glucose control group. Similar results were achieved with metformin therapy in a separate trial by the same group in overweight patients with Type 2 diabetes (UKPDS 34). The UKPDS results indicate that blood pressure lowering therapy offers more definite reductions in macrovascular disease for diabetic patients than do interventions for blood glucose control.

3.4.4 Antiplatelet therapy

For patients with a history of CHD or cerebrovascular disease, there is strong evidence that long-term therapy with aspirin and some other antiplatelet agents reduces the risks of fatal and non-fatal coronary events, stroke and cardiovascular death. For patients without a history of cardiovascular disease, there is evidence of reduced risks of CHD but no clear evidence of reduced risks of stroke or of total cardiovascular death. The HOT Study investigated the effects of 75 mg aspirin daily on cardiovascular events in patients with hypertension, and demonstrated a one third reduction in the risk of CHD events, but no clear reduction in either ischaemic stroke or cardiovascular death. In this study and others, aspirin was shown to increase non-cerebral bleeding risks about two-fold. There was no detectable increase in the risk of cerebral haemorrhage in the HOT Study.

3.4.5 Other factors

The effects of modifying other factors that are known to determine cardiovascular disease risk are less certain. The evidence cited above (see 2.0)suggests the potential for modification of weight, exercise, alcohol intake, plasma fibrinogen to alter cardiovascular disease risks, but this has not yet been demonstrated in intervention studies. There has also been much recent interest in the possible effects of antioxidant vitamins such as vitamins E and C on the risks of CHD and stroke. While there is a rationale for believing that increased dietary intakes of these vitamins may confer worthwhile benefits and little risk, there is presently little direct evidence to support this. Several ongoing trials of vitamin supplements should provide reliable evidence about the effects of such interventions on a range of outcomes within the next few years.

4. Clinical Evaluation

The clinical and laboratory evaluation of the hypertensive patient should be conducted with four aims in mind:-

- to confirm a chronic elevation of blood pressure and determine its level.
- to exclude or identify secondary causes of hypertension.
- to determine the presence of target organ damage and to quantify its extent.
- to search for other cardiovascular risk factors and clinical conditions that may influence prognosis and treatment.

4.1 Clinical history

A comprehensive clinical history is essential and should include: -

- family history of hypertension, diabetes, dyslipidaemia, CHD, stroke, or renal disease.
- duration and previous levels of high blood pressure, and results and side effects of previous antihypertensive therapy.
- past history or current symptoms of CHD and heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, gout, dyslipidaemia, bronchospasm, sexual dysfunction, renal disease, other significant illnesses, and information on the drugs used to treat those conditions.
- symptoms suggestive of secondary causes of hypertension.
- careful assessment of lifestyle factors including dietary intake of fat, sodium and alcohol, quantitation of smoking and physical activity, and enquiry of weight gain since early adult life as a useful index of excess body fat.
- detailed enquiry of intake of drugs or substances that can raise blood pressure, including oral contraceptives, non-steroidal anti-flammatory drugs, liquorice, cocaine and amphetamines. Attention should be paid to the use of erythropoietin, cyclosporins or steroids for concomitant disorders.
- personal, psychosocial and environmental factors that could influence the course and outcome of antihypertensive care including family situation, work environment, and educational background.

.2 Physical examination

full physical examination is essential and will include careful measurement of blood pressure as escribed below. Other important elements of the physical examination include:-

- measurement of height and weight, and calculation of Body Mass Index (weight in kilograms divided by height in meters, squared).

- examination of the cardiovascular system particularly for heart size, for evidence of heart failure, for evidence of arterial disease in the carotid, renal and peripheral arteries, and for coarctations of the aorta.
- examination of the lungs for rales and bronchospasm and of the abdomen for bruits, enlarged kidneys, and other masses.
- examination of the optic fundi and of the nervous system for evidence of cerebrovascular damage.

4.3 Blood pressure measurement

Because blood pressure is characterised by large spontaneous variations, the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on several separate occasions.

4.3.1 Office or clinic blood pressure measurement

Blood pressure should be measured as described in standard textbooks, with the patient in a sitting position using a mercury sphygmomanometer or other non-invasive device. The accuracy of non-mercury devices should be ensured by comparison with values simultaneously obtained from a mercury sphygmomanometer. Since the medical use of mercury is likely to be progressively restricted around the world, the calibration and accuracy of non-mercury devices will become increasingly important.

When measuring blood pressure, particular care should be taken to:-

- allow the patient to sit for several minutes in a quiet room before beginning blood pressure measurement.
- use a standard cuff with a bladder that is 12-13 cm x 35 cm, with a larger bladder for fat arms and a smaller bladder for children.
- use phase 5 Korotkoff sounds (disappearance) to measure the diastolic pressure.
- measure the blood pressure in both arms first visit if there is evidence of peripheral vascular disease.
- measure the blood pressure in standing position in elderly subjects, diabetic patients and in other conditions in which orthostatic hypotension is common.
- place the sphygmomanometer cuff at heart level, whatever the position of the patient.

4.3.2 Home and ambulatory blood pressure measurement

Non-invasive semi-automatic and automatic devices are now available for blood pressure measurement at home and for ambulatory blood pressure monitoring over periods of 24 hours or more. Both of these approaches provide useful additional clinical information and have a place in the management of the hypertensive patient, but in both cases there are three important limitations:-

- first, there is limited data available about the prognostic value of both home and ambulatory blood pressure measurements. Further prospective studies are required to determine whether such measurements offer material advantages over conventional blood pressure measurements for the prediction of morbidity and mortality. Therefore information obtained from these methods must be regarded as supplementary to conventional measurements, not as a substitute;

- second, studies conducted in general populations and in hypertensive individuals have demonstrated that blood pressure values obtained by home measurements or by ambulatory monitoring are several mmHg lower than those obtained by office measurements with 24 hour average or home blood pressure values of around 125/80 mHg corresponding to clinic pressures of 140/90 mmHg;
- third, the devices used should be checked for accuracy and performance over time against other well-validated blood pressure measurement devices using standardised protocols. Currently available home devices that measure the pressure in the fingers or the arm below the elbow should be avoided.

The advantages of home blood pressure measurement are that it may provide numerous values on different days in a setting closer to daily life conditions than the doctor's office. It may also favourably affect patients perceptions of their "hypertension" problems and improve adherence to treatment. It may therefore be a valuable adjunct for checking the effectiveness of treatment.

Box 6 Situations In Which Ambulatory Blood Pressure Monitoring Should Be Considered:

- Unusual variability of blood pressure over the same or different visits
- Office hypertension in subjects with low cardiovascular risk
- Symptoms suggesting hypotensive episodes
- Hypertension resistant to drug treatment

Ambulatory blood pressure monitoring also offers the advantages of providing a more realistic setting for blood pressure measurements, and of improving patient perceptions and adherence to treatment. More important however, is the large body of evidence indicating that the target organ damage associated with hypertension is more closely related to 24 hour or day-time average blood pressure than to clinic blood pressure, particularly if only few office values are obtained. There is also evidence that pretreatment ambulatory blood pressure has a prognostic value and a recent prospective study suggests that regression of target organ damage such as left ventricular hypertrophy is more closely related to changes in 24 hour average than to changes in office blood pressure values. While ambulatory blood pressure monitoring is not a substitute for office measurement, it provides an important research tool for investigations of normal and deranged mechanisms of cardiovascular regulation, of the clinical relevance of phenomena such as blood pressure variability and nocturnal hypotension, and of the time-course and homogeneity of the antihypertensive effect of newer drugs or drug combinations.

Box 7 Isolated Office ("White Coat") Hypertension

- In some patients, office blood pressure is persistently elevated whereas day time blood pressure outside the clinic environment is not.
- This condition is widely known as "white coat hypertension" although the term "isolated office hypertension" is preferable because the office day-time blood pressure difference presumably depends on multiple factorsand does not correlate with the pressor response to blood pressure measurements by the doctor, i.e., the so-called "white coat" effect.
- It is likely that only a small fraction of the hypertensive population exhibits isolated office hypertension, if the diagnosis is restricted to subjects whose ambulatory blood pressure measurements are truly normal, i.e. below 125/80 mmHg.
- Furthermore, there is continuing debate as to whether isolated office hypertension is an innocent phenomenon or whether it carries an increased burden of cardiovascular risk.
- Physicians should aim at its identification (by use of home or ambulatory blood pressure measurements) whenever clinical suspicion is raised.
- The decision to treat or not should be based on the overall risk profile and the presence or absence of target organ damage. Close follow-up is essential for subjects with isolated office hypertension whom the physician chooses not to treat.

4.4 Laboratory investigations

In all regions of the world, routine investigations should include urinalysis for blood, protein and glucose, and microscopic examination of urine. Blood chemistry should include measurements of potassium, creatinine, fasting glucose, and total cholesterol. An electrocardiogram should also be performed. In some regions of the world this list of routine investigations is frequently expanded to include some of the optional investigations listed below.

Optional investigations will be guided by the findings from the history, examination and routine investigations. Such investigations should be conducted if the results are likely to have important implications for the management of the individual patient in question. These tests may include measurement of high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides, of uric acid, and of hormone assays such as plasma renin activity, plasma aldosterone and urinary catecholamines. Echocardiography should be performed whenever the clinical assessment reveals the presence of target organ damage or suggests the possibility of left ventricular hypertrophy or of other cardiac disease, since increased left ventricular mass is associated with increased cardiovascular risk and this information should be helpful in deciding whether to institute drug treatment. Similarly, vascular ultrasonography should be performed whenever the presence of arterial disease is suspected in the aorta, carotid or peripheral arteries. Assessment of arterial distensibility might also be considered in some patients although the complexity of the techniques involved, the lack of standardisation of procedures, and uncertainty about its place in management, makes it largely a research tool. Renal ultrasonography should be performed if renal disease is suspected. The cost of investigations should be considered in the context of the needs of the individual patient and the availability of resources in the particular health system or region.

4.5 Definition and classification of hypertension

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitrary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international authorities and particularly by the Joint National Committee in the USAand the WHO-ISH Guidelines Committee. Accordingly, in order to reduce confusion and provide more consistent advice to clinicians around the world, the WHO-ISH Guidelines Committee has agreed to adopt in principle the definition and classification provided in JNC VI. This new definition defines the lower limits of hypertension as 140 mmHg systolic and 90 mmHg diastolic, the same as the lower limits for the "borderline sub group" of mild hypertension in the 1993 WHO-ISH Guidelines. The new Guidelines emphasise that the decision to lower the elevated pressure in a particular patient is not based on the level of blood pressure alone but on assessment of the total cardiovascular risk in that individual.

Hypertension is therefore defined as a systolic blood pressure of 140 mmHg or greater and/or a diastolic blood pressure of 90 mmHg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adults over the age of 18 is provided inTable 3. The terms "Grade" 1, 2 and 3 have been chosen rather than the terms "Stage" 1, 2 and 3 used by JNC VI, since the word "stage" implies progression over time in a way that does not necessarily apply here. Otherwise, the values chosen and the terms used are those used in JNC VI. The terms "mild", "moderate" and "severe" used in previous versions of the WHO-ISH Guidelines, would correspond to Grades 1, 2 and 3, respectively. The widely used term "borderline hypertension", becomes a subgroup within Grade 1 hypertension. It must be emphasised that the term "mild hypertension" does not imply a uniformly benign prognosis, but is used simply to contrast with more severe elevations of blood pressure.

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

Table 1. Definitions and Classification of Blood Pressure Levels

CATEGORY	SYSTOLIC (mmHg)	DIASTOLIC (mmHG)
Optimal	<120	<80
Normal	<130	<85
High – Normal	130-139	85-89
Grade 1 Hypertension ("mild")	140-159	90-99
Subgroup: Borderline	140-149	90-94
Grade 2 Hypertension ("moderate")	160-179	100-109
Grade 3 Hypertension ("severe")	□ 180	□ 110
Isolated Systolic Hypertension	□ 140	<90
Subgroup: Borderline	140-149	<90

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

4.6 Stratification of patients by absolute level of cardiovascular risk

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

Four categories of absolute cardiovascular disease risk are defined (low, medium, high and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors present. So, for example, individuals with very high levels of cholesterol or a family history of premature cardiovascular disease in several first-degree relatives will typically have absolute risk levels that are at the higher end of the range provided. Similarly, individuals with other risk factors listed in Table 2may also have absolute risk levels that are towards the higher end of the range for the category.

How well these estimates predict the absolute risk of cardiovascular disease in Asian, African or other non-Western populations is uncertain. In those countries in which CHD incidence is relatively low and heart failure or renal disease is more common, the risk factors used to stratify risk in Table 3should also be useful in stratifying the risk of these diseases.

4.6.1 Low risk group

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

4.6.2 Medium risk group

This group includes patients with a wide range of blood pressures and risk factors for cardiovascular disease. Some have lower blood pressures and multiple risk factors, whereas others have higher blood pressures and no or few other risk factors. This is the patient group for which the clinical judgement of the responsible doctor will be paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next ten years is typically about 15-20%. The risk will be closer to 15% in those patients with Grade 1 (mild) hypertension and only one additional risk factor.

4.6.3 High risk group

This group includes patients with Grade 1 or Grade 2 hypertension who have three or more risk factors listed inTable 2, diabetes or target organ damage and patients with Grade 3 ("severe")

hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in the following ten years is typically about 20-30%.

4.6.4 Very high risk group

Patients with Grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease (as defined inTable 2) carry the highest risk of cardiovascular events, of the order of 30% or more over ten years, and thus qualify for the most intensive and rapidly instituted therapeutic regimes.

Table 2. Factors Influencing Prognosis

Risk Factors For Cardiovascular Diseases	Target Organ Damage[1]	Associated Clinical Conditions[2]
I. Used for risk stratification • Levels of systolic and diastolic blood pressure (Grades 1-3) • Men >55 years • Women >65 years • Smoking • Total cholesterol >6.5 mmo/l (250 mg/dl) • Diabetes • Family history of premature cardiovascular disease **II. Other factors adversely influencing prognosis** • Reduced HDL cholesterol • Raised LDL cholesterol • Microalbuminuria in diabetes • Impaired glucose tolerance • Obesity • Sedentary lifestyle • Raised fibrinogen • High risk socioeconomic group • High risk ethnic group • High risk geographic region	• Left ventricular hypertrophy (electrocardiogram, echocardiogram or radiogram) • Proteinuria and/or slight elevation of plasma creatinine concentration (1.2 - 2.0 mg/dl) • Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalised or focal narrowing of the retinal arteries	*Cerebrovascular disease* • ischaemic stroke • cerebral haemorrhage • transient ischaemic attack *Heart disease* • myocardial infarction • angina • coronary revascularisation • congestive heart failure *Renal disease* • diabetic nephropathy • renal failure (plasma creatinine concentration >2.0 mg/dl) *Vascular disease* • dissecting aneurysm • symptomatic arterial disease *Advanced hypertensive retinopathy* • haemorrhages or exudates • papilloedema

1. "Target Organ Damage" corresponds to previous WHO Stage 2 hypertension6
2. "Associated Clinical Conditions" corresponds to previous WHO Stage 3 hypertension.6

Table 3. Stratification of Risk to Quantify Prognosis

	BLOOD PRESSURE (mmHg)		
Other Risk Factors & Disease History	**Grade 1** (mild hypertension) SBP 140-159 or DBP 90-99	**Grade 2** (moderate hypertension) SBP 160-179 or DBP 100-109	**Grade 3** (severe hypertension) SBP □ 180 or DBP □ 110
I.. no other risk factors	LOW RISK	MED RISK	HIGH RISK
II. 1-2 risk factors	MED RISK	MED RISK	V HIGH RISK
III. 3 or more risk factors or TOD[1] or diabetes	HIGH RISK	HIGH RISK	V HIGH RISK
IV. ACC[2]	V HIGH RISK	V HIGH RISK	V HIGH RISK

Risk strata (typical 10 year risk of stroke or myocardial infarction): Low risk = less than 15%; medium risk = about 15-20% risk;
high risk = about 20-30%; very high risk = 30% or more

1. TOD – Target Organ Damage (Table 2)
2. ACC – Associated Clinical Conditions, including clinical cardiovascular disease or renal disease (Table 2)

5. Treatment

5.1 Goals of treatment

The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, such as smoking, raised cholesterol or diabetes and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure *per se*. The intensity with which the clinician treats these risk factors will plainly increase with the number and severity of risk factors, with the existence of associated clinical conditions, and with increasing absolute risks of major cardiovascular events, as indicated inTable 3.

Since the relationship between cardiovascular risk and blood pressure is continuous, without a lower threshold, the goal of antihypertensive therapy should be to restore blood pressure to levels defined as "normal;" or optimal" (Table1). Indeed there is evidence that a major determinant of the risk reduction conferred by antihypertensive therapy is the level of blood pressure achieved. Comparison of outcomes between the three randomised blood pressure target groups in the HOT Study (diastolic pressure <90, 85, or 80 mmHg) were unable to detect significant differences in the risk of cardiovascular disease between adjacent target groups. However, the results of that study confirm that there is no increase in cardiovascular risk in the patients randomised to the lowest target group (diastolic pressure <80 mmHg). Among diabetic patients in the HOT Study, there were significantly lower risks of cardiovascular disease in those patients assigned to the lowest blood pressure target. Similarly, the results of the UK Prospective Diabetes Study demonstrated that tight blood pressure control (with an average achieved blood pressure of 144/82 mmHg) conferred a substantial reduction in the risk of major cardiovascular events

compared to less tight blood pressure control (with an average achieved blood pressure of 154/87 mmHg). It would seem desirable to achieve optimal or normal blood pressures in young, middle aged or diabetic subjects (below 130/85 mmHg;Table 1) and at least high normal blood pressures in elderly patients (below 140/90 mmHg;Table 1).

Stratification of patients in terms of their total cardiovascular risk (Table 3) is not only useful for determining the threshold for initiating antihypertensive drug treatment, it is also useful for setting the goal blood pressure that should be achieved and the intensity with which this goal should be pursued. Plainly, the higher the risk, the more important it becomes to reach the goal blood pressure that is set, and to treat the other risk factors that have been identified.

When home or ambulatory blood pressure measurements are used to evaluate the efficacy of treatment, it must be remembered that day time values provided by these methods (compared with office measurements) are on average around 10-15 mmHg lower for systolic blood pressure and 5-10 mmHg lower for diastolic blood pressure. Treatment goals should therefore be modified appropriately when these methods are used.

5.2 Management strategy

Having assessed the patient and determined the overall risk profile, including the level of blood pressure elevation, the responsible physician should determine whether the patient is at low, medium, high or very high risk of cardiovascular disease events, as shown in Table 3.This will help the physician, in consultation with the patient, to determine whether to:-

- institute immediate drug treatment for the hypertension and the other risk factors or conditions present (high and very high risk groups).
- monitor blood pressure and other risk factors for several weeks and obtain further information before deciding whether to institute drug treatment (medium risk group).
- observe the patient over a significant period of time before deciding whether to institute drug treatment (low risk).

In situations where resources are limited it becomes imperative to direct drug treatment to individuals in the high and very high risk groups before considering their use in lower risk patients.

Having decided on the broad strategy for management, the physician should then determine the specific therapeutic goals for the individual patient, and draw up a comprehensive therapeutic plan to lower the blood pressure and reduce the overall cardiovascular risk in order to attain these goals. This plan will include consideration of:-

- monitoring - of blood pressure and other risk factors.
- lifestyle measures - to lower the blood pressure and control the other risk factors.
- drug treatment - to lower blood pressure and to control the other risk factors and clinical conditions present.

Lifestyle measures should be instituted wherever appropriate in all patients including those who require drug treatment.

5.3 Lifestyle measures

While there is no direct randomised evidence demonstrating that reducing blood pressure through lifestyle measures reduces the risk of cardiovascular disease, this seems likely given all the other evidence suggesting that the benefits of antihypertensive treatment are determined primarily by

the blood pressure reduction *per se* rather than by any other independent effect of particular treatment modalities.

Lifestyle measures (or non-pharmacological treatments) are used for a number of complementary reasons as outlined in the WHO Technical Report on Hypertension Controlto lower the blood pressure in the individual patient.

- to reduce the need for antihypertensive drugs and maximise their efficacy.
- to address the other risk factors present.
- for primary prevention of hypertension and associated cardiovascular disorders in populations.

Box 8 Lifestyle and Blood Pressure

- It is important that lifestyle measures be instituted within the framework of a structured plan that includes the use of counselling and monitoring by appropriate health professionals such as nurses, dieticians, clinical psychologists and other therapists, as well as the responsible physician.
- Recommendations should be tailored for each individual and greater use should be made of modern and well-validated counselling techniques.
- Lifestyle measures that are widely agreed to lower the blood pressure and that should be considered in all patients in whom they may apply are weight reduction, reduction of excessive alcohol consumption, reduction of high salt intake and increase in physical activity.
- Particular emphasis should be placed on cessation of smoking and on healthy eating patterns that contribute to the treatment of associated risk factors and cardiovascular diseases.

5.3.1 Smoking cessation

Smoking cessation is perhaps the single most powerful lifestyle measure for the prevention of both cardiovascular and non-cardiovascular diseases in hypertensive patients. All hypertensive patients who smoke should receive appropriate counselling for smoking cessation. Nicotine replacement therapy should also be considered, since it appears to augment other interventions for smoking cessation. **5.3.2 Weight reduction**

Excess body fat contributes to blood pressure levels from infancy and is the most important factor predisposing to hypertension. Weight reduction of as little as 5 kg reduces blood pressure in a large proportion of hypertensive individuals who are more than 10% overweight and also has a beneficial effect on associated risk factors such as insulin resistance, diabetes, hyperlipidaemia and left ventricular hypertrophy. The blood pressure lowering effects of weight reduction may be enhanced by simultaneous increase in physical exercise, by alcohol moderation in overweight drinkers, and by reduction of sodium intake in older hypertensive subjects (TONE Study). Weight loss of at least 5 kg should be recommended in the first instance, with further increments of 5 kg depending upon the response and the patients' weight.

5.3.3 Moderation of alcohol consumption

Notwithstanding the evidence that an alcohol intake of up to 3 "standard" drinks a day may lower the risk of CHD, there is a linear relationship between alcohol consumption, blood pressure levels, and the prevalence of hypertension in populations. Alcohol attenuates the effects of antihypertensive drug therapy but its pressor effect is, at least partially, reversible within 1-2

weeks by moderation of drinking by around 80%.Heavier drinkers (5 or more standard drinks a day) may experience a rise in blood pressure after acute alcohol withdrawal and be more likely to be diagnosed as hypertensive at the beginning of the week if they have a weekend drinking pattern. Accordingly, hypertensive patients who drink alcohol should be advised to limit their consumption to no more than 20-30 gm of ethanol per day for men, and no more than 10-20 gm of ethanol per day for women. They should be warned against the heightened risks of stroke associated with binge drinking.

5.3.4 Reduction in salt intake

Epidemiologic studies suggest that dietary salt intake is a contributor to blood pressure elevation and to the prevalence of hypertension. The effect appears to be enhanced by a low dietary intake of potassium containing foods. Randomised controlled trials in hypertensive patients indicate that reducing sodium intake by 80-100 mmol (4.7-5.8 gm) per day from an initial intake of around 180 mmol (10.5 gm) per day will reduce blood pressure by an average of around 4-6 mmHg systolic. However, individuals vary considerably in their responses to changes in dietary salt, with black, obese and elderly subjects the most sensitive. A recent study in older hypertensive patients showed no adverse effects of a reduction in sodium of 40 mmol (2.3 gm) per day and after 18 months there was a significant reduction in the need for antihypertensive drug therapy. The aim of dietary sodium reduction should be to achieve an intake of less than 100 mmol (5.8 gm) per day of sodium or less than 6 gm per day of sodium chloride. Patients should be advised to avoid added salt, to avoid obviously salted foods, particularly processed foods, and to eat more meals cooked directly from natural ingredients. Counselling by trained dieticians and monitoring of urinary sodium are necessary in most cases. The high sodium – low potassium content of many preserved foods is drawn to the attention of the food industry.

5.3.5 Complex dietary changes

Vegetarians have lower blood pressure than meat eaters and vegetarian dietary patterns can ower blood pressure in hypertensive patients. A series of controlled dietary trials indicate that hese effects depend on a combination of effects of fruit, vegetables, fibre and low saturated fat ntake rather than the presence or absence of meat protein. This conclusion has been confirmed n a recent study in which older subjects with mild or borderline hypertension were randomised for eight week periods to continue their normal diet, to increase fruit and vegetable consumption alone, or to also reduce their consumption of total and saturated fat. Increasing fruit and vegetable consumption alone caused blood pressures to fall by 3/1 mmHg while the added measure of reducing fat intake led to a fall of 6/3 mmHg. In the patients with higher initial blood pressures, there was a fall of 11/6 mmHg with the combined dietary regime. The presence of higher intakes of calcium, magnesium or potassium may have contributed to the beneficial effects of some of these diets. Regular fish consumption as part of a weight reducing diet may enhance blood pressure reduction in obese hypertensive patients and yield additional benefits on lipid profiles. Hypertensive patients should be advised to eat more fruit and vegetables, to eat more fish and to reduce their fat intake.

5.3.6 Increased physical activity

Sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis, such as a brisk walk or a swim for 30-45 minutes, 3-4 times a week. Such mild exercise may be more effective in lowering the blood pressure than more strenuous forms of exercise such as running or jogging, and may lower the systolic pressure by about 4-8 mmHg. Isometric exercise e.g. heavy weight lifting can have a pressor effect and should be avoided.

5.3.7 Psychological factors and stress

Psychological factors, personality factors and stress are associated with the adoption of many less healthy lifestyle patterns associated with hypertension and increased risk of cardiovascular disease. In this sense, helping individuals to cope with stress may have an important impact on their blood pressure and on compliance with antihypertensive medications. Whether there are more direct effects of sustained stress on long-term blood pressure levels is a subject requiring ongoing research. To date, trials of various stress management procedures for blood pressure control have been unconvincing.

5.3.8 Other measures

Lifestyle measures are fundamental for the management of diabetes and the treatment of hyperlipidaemia, and appropriate measures should be instituted when these disorders are present in the hypertensive patient. These will generally include a diet low in saturated fat and rich in vegetables and fruit.

Interventions with limited or unproven efficacy in lowering blood pressure include bio-feedback, micronutrient alterations and dietary supplementation with calcium, magnesium, and fibre.

5.4 Drug treatment for lowering blood pressure

The six main drug classes used, worldwide, for blood pressure lowering treatment are: diuretics, beta-blockers, calcium antagonists, ACE inhibitors, angiotensin II antagonists and alpha-adrenergic blockers. In some parts of the world, reserpine and methyldopa are also used frequently. There is no reliable or consistent evidence that indicates substantive differences between drug classes in their effects on blood pressure, although there are important differences in the side-effect profiles of each class. There are also important differences between classes in the amount of evidence available from randomised controlled trials on the effects of treatment on morbidity and mortality. While there is a large body of data demonstrating the benefits of the older agents such as diuretics and beta-blockers, there are fewer data available about calcium antagonists and ACE inhibitors, and no reliable data available about alpha-blockers or the most recent classes of agents such as angiotensin II antagonists.

Box 9 Benefits of Drug Treatment

- All classes of antihypertensive drugs have specific advantages and disadvantages for particular patient groups (see Table 4)
- There is as yet no evidence that the main benefits of treating hypertension are due to any particular drug property rather than to lowering of blood pressure *per se*.
- The randomised trials conducted to date have not provided any clear evidence of differential effects on outcome of different agents producing the same blood pressure reduction.
- However, most individual studies have been too small to detect plausibly modest differences in important outcomes such as stroke or myocardial infarction.

5.4.1 Principles of drug treatment

There is general agreement on the principles governing the use of antihypertensive drugs to lower blood pressure, independent of the choice of particular drugs. These principles include:-

- the use of low doses of drugs to initiate therapy, beginning with the lowest available dose of the particular agent, in an effort to reduce adverse effects. If there is a good response to a low dose of a single drug but the pressure is still short of adequate control, it is

reasonable to increase the dose of the same drug, provided that it has been well tolerated.

- The use of appropriate drug combinations(see Box11) to maximise hypotensive efficacy while minimising side effects. It is often preferable to add a small dose of a second drug rather than increasing the dose of the original drug. This allows both the first and second drugs to be used in the low dose range that is more likely to be free of side effects. In this context, the use of the fixed low dose combinations that are increasingly available in the USA and Europe, may be advantageous.
- Changing to a different drug class altogether if there is very little response or poor tolerability to the first drug used, before increasing the dose of the first drug or adding a second drug.
- The use of long-acting drugs providing 24-hour efficacy on a once daily basis. The advantages of such drugs include improvement in adherence to therapy and minimisation of blood pressure variability, as a consequence of smoother, more consistent blood pressure control. This may provide greater protection against the risk of major cardiovascular events and the development of target organ damage.

Box 10 Absolute Effects of Treatment on Cardiovascular Risk

- From the results of randomised controlled trials it appears that each reduction of 10-14 in systolic blood pressure and 5-6 mmHg in diastolic blood pressure confers about two-fifths less stroke, one-sixth less CHD, and in Western populations, one-third less major cardiovascular events overall.
- In patients with Grade 1 hypertension, monotherapy with most agents will produce reductions in blood pressure of about 10/5 mmHg. In patients with higher grades of hypertension, it is possible to achieve sustained blood pressure reductions of 20/10 mmHg or more, particularly if combination drug therapy is used.
- The estimated absolute effects of such blood pressure reductions on cardiovascular disease risks (fatal plus non-fatal stroke or myocardial infarction) are as follows:

Patient group	Absolute risk (CVD events over 10 yrs)	Absolute treatment effects (CVD events prevented per 1000 patient yrs) 10/5 mmHg	20/10 mmHg
Low risk patients	<15%	<5	<9
Medium risk patients	15-20%	5-7	8-11
High risk patients	20-30%	7-10	11-17
Very high risk patients	>30%	>10	>17

- Between these strata, the estimated absolute treatment benefits will range from less than 5 events prevented per thousand patient years of treatment (low risk) to more than 17 events prevented per thousand patient years of treatment (very high risk).
- The absolute benefits for stroke and CHD will be augmented by smaller absolute benefits for congestive heart failure and renal disease.
- These estimates of benefit are based on relative risk reductions observed in trials of about 5 years duration. Longer-term treatment over decades could produce larger risk reductions (see Box 4).

5.4.2 Initiation of drug treatment

For patients in the high and very high risk groups drug treatment should be instituted within a few days as soon as repeated measurements have confirmed the patient's blood pressure.
For patients in the medium and low risk groups the initiation of drug therapy will be influenced by:-

- consultation with the patient on preferred strategies;
- the degree of blood lowering achieved with lifestyle measures;
- the degree of control achieved for other risk factors
- the availability of resources in the prevailing health system;

For patients in the medium risk group it is desirable to continue with lifestyle measures and to reinforce these if necessary for at least 3 months before considering drug treatment. If however, goal blood pressures are not attained within a maximum of 6 months, drug treatment should be initiated.

For patients in the low risk group having Grade 1 (mild) hypertension, lifestyle measures should be used assiduously for 6 months before considering drug treatment. If however, goal blood pressures are not achieved, drug treatment should be instituted within 1 year.

The exception to this recommendation is for patients in the borderline subgroup with diastolic blood pressures between 90 and 94 mmHg or systolic blood pressure between 140 and 149 mmHg. In this group, the doctor, in consultation with the patient, may choose to persevere with lifestyle measures alone to lower the pressure and reduce cardiovascular risk.

There is one other group of patients that deserves special mention: this is patients with high-normal blood pressure (130-139/85-89 mmHg) who also have diabetes mellitus and/or renal insufficiency. For these patients early and active drug treatment should also be considered, since this has been shown to reduce the rate of loss of renal function (see section 6.5 and 6.6).

5.4.3 Choice of antihypertensive drugs

All available drug classes are suitable for the initiation and maintenance of antihypertensive therapy, but the choice of drugs will be influenced by many factors illustrated in Table 4 including:-

- socio-economic factors that determine drug availability in different countries or regions.
- the cardiovascular risk factor profile of the individual patient.
- the presence of target organ damage, of clinical cardiovascular disease, renal disease and diabetes.
- the presence of other co-existing disorders that may either favour or limit the use of particular classes of antihypertensive drugs.
- variation in individual patient responses to drugs from different classes.
- the possibility of interactions with drugs used for other conditions present in the patient.
- the strength of the evidence for reduction of cardiovascular risk with the drug class in question

The physician should tailor the choice of drug to the individual patient, after taking all these factors together with patient preference into account in each case. A practical framework for the management of patients with Grade 1 or Grade 2 hypertension is shown in Figure 1.

5.4.3.1 Diuretics

Diuretics constitute one of the most valuable classes of antihypertensive drugs. They are inexpensive, effective, generally well tolerated in low doses, and diuretic based treatment regimens have been clearly shown to prevent major cardiovascular events, including stroke and CHD, in a variety of hypertensive patient groups. Many of the unwanted side effects of diuretics such as potassium depletion, reduced glucose tolerance, ventricular ectopic beats and impotence were associated with the use of high doses of diuretics of the order of 50-100 mg daily of hydrochlorothiazide and chorthalidone in the 1970s and 1980s. While there is some evidence from observational studies that the risk of sudden cardiac death in patients treated with non-potassium sparing diuretics can be reduced by their combination with potassium sparing diuretics, this issue can only be resolved by prospective randomised controlled trials.

Diuretics should be used in low doses equivalent to a maximum of 25 mg daily of hydrochlorothiazide, and often half or less this dose, in order to reduce the adverse effects while still reaping the benefits. Diuretics are particular recommended for the treatment of elderly patients with systolic hypertensionand of black patients.

5.4.3.2 Beta-blockers

Beta-adrenoceptor-blocking drugs (beta-blockers) are safe, cheap and effective for use as monotherapy or in combination with diuretics, dihydropyridine calcium antagonists and alpha-blockers. Whereas heart failure used to be a clear contraindication to the use of beta-blockers in standard dosesthere is emerging evidence that they may have a beneficial effect when used in very low starting doses in some patients with heart failure. Beta-blockers should be avoided in patients with obstructive airways disease and peripheral vascular disease. There have been reports that beta-blockers can aggravate spastic or variant angina in Japanese patients. They are often less effective in black patients.

5.4.3.3 ACE inhibitors

ACE inhibitors are safe and effective in lowering blood pressure and they are now much less expensive than when first introduced. ACE inhibitors are particularly effective in reducing morbidity and mortality in heart failureand in retarding the progression of renal disease in patients with insulin dependent diabetes mellitus, especially in the presence of proteinuria. Their most common adverse effect is a dry cough and the their most serious adverse effect is very rare but life threatening occurrence of angioedema. They are often less effective in black patients.

5.4.3.4 Calcium antagonists

All subgroups of calcium antagonists are effective and well tolerated in lowering blood pressure. They are of demonstrated benefit for the prevention of stroke in elderly patients with systolic hypertension. The evidence about the effects of calcium antagonists on cardiovascular disease events is discussed in detail in sections 3 and. Long-acting calcium antagonists are preferred and rapid onset – short acting calcium antagonists should be avoided. Calcium antagonists are particularly recommended for elderly patients with systolic hypertension and for black patients. Adverse effects include tachycardia, flushing, ankle oedema and (with verapamil) constipation.

5.4.3.5 Angiotensin II antagonists

Angiotensin II - receptor antagonists are the latest major group of antihypertensive drugs to become generally available. They have many features in common with ACE inhibitors including particular value in patients with heart failure. There is still no reliable evidence of their effects on

cardiovascular risk in patients with hypertension. However, they have few side effects, which may encourage adherence to therapy and appear to offer one advantage over ACE inhibitors, that is the absence of cough as a side effect.

5.4.3.6 Alpha-blockers

Alpha-blockers are safe and effective in lowering blood pressure. There is still no evidence about their effects on cardiovascular risk in hypertensive subjects. Their main side effect is postural hypotension which may be a particular problem in elderly patients. Assessment of standing blood pressure is essential. These drugs may have advantages in subjects with dyslipidaemia or glucose intolerance.

5.4.3.7 Other drugs

A number of centrally acting drugs are also available, some of these are new such as the imidazoline receptor stimulants (agonists), rilmenidine and moxonidine, and others much older such as reserpine, methyldopa and clonidine. Methyldopa has a well documented and continuing place in the treatment of hypertension in pregnancy (seeSection6.2). However, the side effects profile of centrally acting agents is generally less favourable than that of the other main classes of available drugs. Where consideration of cost effectiveness favours the use of reserpine in low income populations, the doses used should be much lower than those used in earlier times.

The older vasolidator agents such as hydralazine are also widely used in some regions of the world. However, the side effects of direct vasolilators such as hydralazine and minoxidil - tachycardia, headache and sodium and water retention - make them less suitable for use as first line drugs.

Table 4 Guidelines for Selecting Drug Treatmen. of Hypertension

Class of Drug	Compelling Indications	Possible Indications	Compelling Contraindications	Possible Contraindications
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidaemia Sexually active males
Beta-Blockers	Angina After myocardial infarct Tachyarrhythmias	Heart failure Pregnancy Diabetes	Asthma and chronic obstructive pulmonary disease Heart block[a]	Dyslipidaemia Athletes and physically active patients Peripheral vascular disease
ACE Inhibitors	Heart failure Left ventricular dysfunction After myocardial infarct Diabetic nephropathy		Pregnancy Hyperkalaemia	Bilateral renal artery stenosis
Calcium Antagonists	Angina Elderly patients Systolic hypertension	Peripheral vascular disease	Heart block[b]	Congestive heart failure[c]
Alpha-Blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidaemia		Orthostatic hypotension
Angiotensin II Antagonists	ACE Inhibitor cough	Heart failure	Pregnancy Bilateral renal artery stenosis Hyperkalaemia	

[a] Grade 2 or 3 atrioventricular block
[b] Grade 2 or 3 atrioventricular block with verapamil or diltiazem
[c] Verapamil or diltiazem

Box 11 Monotherapy Versus Combination Therapy
Drug monotherapy

When drugs from the main classes available are used as monotherapy at the recommended doses, they produce very similar blood pressure reductions. In general, the sizes of the blood pressure reductions increase with the initial level of blood pressure, but typically the placebo-adjusted reductions average about 4-8% for both systolic and diastolic blood pressure. Thus for patients with blood pressures of about 160/95 mmHg, the usual reduction produced by monotherapy would be about 7-13 mmHg systolic and 4-8 mmHg diastolic. Clearly for many patients with hypertension, such reductions in blood pressure would not restore optimal or even non-hypertensive blood pressure levels.

Drug combination therapy

Combination therapy of several of the available drug classes has been shown to produce blood pressure reductions that are greater than those produced by any group of individual agents used alone. The HOT Study, in which blood pressure was lowered to below 90mmHg in over 90% of patients, demonstrated that combination therapy was necessary in 70% of participants. Combinations with fully additive hypotensive effects will deliver blood pressure reductions that are around twice as great as those obtained with a single drug, of the order of 8-15%, or 12-22 mmHg systolic and 7-14 mmHg diastolic for patients with blood pressure of 160/95 mmHg.

Effective drug combinations

- diuretic and beta-blocker.
- Diuretic and ACE inhibitor (or A-II antagonists).
- calcium antagonist (DHP) and beta-blocker.
- calcium antagonist and ACE inhibitor.
- alpha-blocker and beta-blocker.

Effective drug combinations utilise drugs from different classes in order to obtain the additive hypotensive effect that comes from combining drugs with different primary actions, while minimising the compensations that limit the fall in blood pressure. Combinations of limited value generally result from combining drugs that work through similar mechanisms so that their hypotensive actions may be less than additive, or drugs that have similar side effects so that the risk of adverse effects is increased.

5.5 Patient education and compliance with therapy

Good communication between the physician and the patient lies at the core of the successful management of hypertension. Since the treatment of hypertension is for life, it is essential that the physician establish a good relationship with the patient, provide the patient with information, both verbal and written, and answer any questions the patient may have. Good information about blood pressure and high blood pressure, about risks and prognosis, about the expected benefits of treatment and about the risks and side effects of treatment will be essential for satisfactory life long control of hypertension.

Failure to establish effective communications and relations will generally lead to poor adherence to antihypertensive therapy and unsatisfactory control of the raised blood pressure. The magnitude of this problem is reflected in population surveys that have demonstrated that hypertension is either untreated or inadequately controlled in around 70-75% of patients worldwide.

One of the best ways to improve adherence to therapy is to involve the patient in making decisions about treatment strategies. Another approach may be to use clinical pharmacists to inform the patient on the use of medications, and on side effects. Well trained clinic nurses will also contribute a great deal to improve compliance with therapy, as will other health professionals such as dieticians and trained counsellors who are experienced in the implementation of lifestyle measures.

Other measures that may help, include the use of home blood pressure measurement, and the involvement of the patient's family in the therapeutic plan.

5.6 Refractory hypertension

Hypertension may be termed refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of combination drug therapy in adequate doses, has failed to lower blood pressure below 140/90 mmHg in patients with classical essential hypertension, or below 140 mmHg systolic in patients with isolated systolic hypertension. In these situations, referral to a specialist should be considered

There are many causes for resistance to treatment, as illustrated in Box 12 below, including apparent causes such as isolated office ("white coat") hypertension and the failure to use an appropriately large cuff in a patient with a very fat arm. One of the most important causes of refractory hypertension may be poor compliance or adherence to therapy and in this situation, after all else fails, it can be very helpful to suspend all drug therapy while continuing to monitor blood pressure frequently. A fresh start with a new regime may help break a vicious cycle.

Box 12 Causes of Refractory Hypertension

- Unsuspected secondary cause (NB. renal and endocrine)
- Poor adherence to therapeutic plan
- Continued intake of drugs that raise blood pressure (NB. NSAIDS - but see4.1)
- Failure to modify lifestyle including
  - weight gain
  - heavy alcohol intake (NB: binge drinking)
- Volume overload due to
  - inadequate diuretic therapy
  - progressive renal insufficiency
  - high sodium intake

Causes of Apparently Refractory Hypertension

- Isolated office ("white coat") hypertension
- Failure to use large cuff on large arm

5.7 Other drug treatment

Since the aim of treatment is the reduction of the total cardiovascular risk it is at least as important to treat the other risk factors and clinical conditions present in the individual hypertensive patient. This means the physician should either refer the patient to appropriate clinics and specialists, or institute an appropriate regimen of lifestyle factors and drug treatment for associated conditions such as diabetes mellitus, hypercholesterolaemia, CHD, cerebrovascular disease, or renal disease.

5.7.1 Antiplatelet therapy

The use of aspirin, and of some other antiplatelet agents, has been well documented to reduce the risk of fatal and non-fatal coronary events, of stroke and of cardiovascular death in patients with established coronary or cerebrovascular disease. In the light of the results of the HOT Study, it is reasonable to recommend the use of low dose aspirin in hypertensive patients whose blood pressure has been rigorously controlled, who are at high risk of CHD, and who are not particularly at risk of bleeding from the gastro-intestinal tract or from other sites.

5.7.2 Cholesterol lowering therapy

Cholesterol reduction with a variety of agents has been shown to reduce the risks of initial and recurrent CHD events among patients with a wide range of initial cholesterol levels. Trials of HMG CoA reductase inhibitors, conducted primarily among patients with CHD, have also reported reductions in stroke risk. The relative effects of cholesterol lowering therapy appear to be similar in those with or without hypertension. In these circumstances, the use of cholesterol lowering therapy can be recommended for hypertensive patients who have elevated cholesterol or who are for other reasons at high risk of CHD.

5.8 Follow-up

During the period of evaluation and stabilisation of treatment, patients need to be seen at frequent intervals to monitor the changes in blood pressure and in the other risk factors and clinical conditions present, and to observe the effects of treatment. Follow-up visits should be used to establish good relations with the patient and to educate the patient on the nature of the condition of hypertension and of the other risk factors or disorders present. The patient should understand why control of hypertension is important, and that treatment should generally continue for a lifetime. The acceptance and implementation of changes in lifestyle in particular, need satisfactory explanation and reinforcement. For successful drug therapy, it is important to explain the possible adverse effects and emphasise the need for regular medication, with early reporting of any side effects.

The frequency of visits will depend on the overall risk category of the patient as well as on the level of blood pressure. Once the goals of therapy have been reached, including the control of other risk factors and the achievement of goal blood pressure, the frequency of visits can be reduced considerably. Patients with a low risk profile and milder degrees of blood pressure elevation (high normal or Grade 1), managed on a single drug could well be seen every six months. It is important that patients not on drug treatment understand the need for monitoring and follow-up and for periodic reconsideration of the need for drug treatment. In more complex cases, patients should be seen at more frequent intervals. If the therapeutic goals, including the control of blood pressure, have not been reached within 6 months, the physician should consider referral to a hypertension specialist.

Antihypertensive therapy is generally "for life". Cessation of therapy by patients who have been correctly diagnosed as hypertensive is usually followed, sooner or later, by the return of blood pressure to pre-treatment levels. Nevertheless, after prolonged blood pressure control it may be possible to attempt a careful progressive reduction in the dose or number of drugs used, particularly among patients strictly observing lifestyle (non-drug) measures. Such attempts to "step down" treatment should be accompanied by careful continued supervision of the blood pressure.

Since a hypertensive patient is typically treated for decades it is likely that the treatment regimen, including the choice of drugs, will undergo multiple changes. It is therefore advisable for all hypertensive patients to keep a record of all treatments used and of their outcomes, and it is the responsibility of doctors and health services to maintain adequate records of treated hypertensive patients and to make them readily available.

6. Special Populations

6.1 Ethnic minorities and high risk regions

The prevalence of hypertension and the incidence of blood pressure-related cardiovascular disease vary considerably between ethnic groups and geographic regions. Ethnic minority groups in many Western populations frequently have higher rates of hypertension, as well as higher rates of major cardiovascular events. The pattern of cardiovascular disease within minority ethnic groups appears to vary by region. For example, in some, but not all, African American populations, renal failure and strokeare particularly prevalent, In South Asian populations of the UK, CHD, stroke and renal failure rates are all high, whereas in Canada, the rates among South Asians are similar to or lower than those in caucasians.

The pattern of cardiovascular disease in ethnic majority groups also varies considerably between geographic regions. For example, in many Eastern Asian populations, stroke (particularly haemorrhagic stroke) is relatively common whereas CHD is relatively uncommon compared with that seen in Western populations. However, the proportional relationships of blood pressure with specific cardiovascular disease risks in Chinese and Japanese populations appears to be very similar to those observed in North American and European populations. The higher incidence of haemorrhagic stroke in Eastern populations appears to reflect, at least in part, a particularly strong association of this type of stroke with blood pressure. In other large non-Western populations such as those of sub-Saharan Africa, stroke and renal disease appear to predominate among cardiovascular diseases.

The available data provide no reason to believe that the relative effects of lowering blood pressure on specific disease risks will vary importantly between ethnic groups or regions, although there may be lesser effects of some specific agents (e.g. ACE inhibitors) in specific ethnic groups (e.g. African Americans). However, because ethnicity and geographic region are such important determinants of absolute risk, it is likely that the absolute effects of treatment will vary markedly between ethnic groups and geographic regions. For example, among individuals with similar levels of blood pressure, the absolute risk of cardiovascular disease will tend to be higher in individuals of South Asian descent in the UK or African Americans in the US compared to Caucasians in the same populations. Therefore, it could be expected that absolute treatment benefits conferred by any given reduction in blood pressure would also be greater in these groups.

The absolute benefits of blood pressure lowering therapy may be particularly great in groups in which there are high risks of events that are very strongly blood pressure-related (e.g. stroke or renal failure). Such populations include many of those in the Eastern Asian region, sub-Saharan Africa as well as African American populations in the US. The rates both of stroke and of CHD are high in Eastern Europe, Russia and the Baltic states, suggesting that the absolute effects of treatment in populations from these regions are also likely to be particularly large. Some ongoing randomised controlled trials will provide evidence about the comparative absolute benefits of blood pressure lowering treatments in such diverse populations.

For regions in which health care resources are particularly scarce, investment in population-based primary prevention strategies may yield the largest dividend. The most cost-effective hypertension treatment programmes will involve the use of the lowest cost drugs (e.g. diuretics, reserpine, beta-blockers, generic formulations of ACE inhibitors, angiotensin II antagonists, calcium antagonists, and other generic agents) in the highest risk groups. The selective treatment of patients with pre-existing cardiovascular or renal disease (irrespective of hypertension severity) or with severe hypertension (systolic >180 mmHg or diastolic >110 mmHg) will result in the greatest ratio of events prevented to numbers of patients treated.

6.2 Pregnancy

Hypertension in pregnancy is usually defined either by an absolute level of blood pressure (e.g. 140/90 mmHg or greater) or by a rise in blood pressure from pre-conception or first trimester levels (e.g. systolic blood pressure rise □ 25 mmHg and/or diastolic blood pressure rise □ 15 mmHg). Hypertension in pregnancy is typically classified as: chronic – essential or secondary hypertension; de novo – pre-eclampsia or gestational hypertension; or pre-eclampsia superimposed on chronic hypertension. Pre-eclampsia is a multi-system disorder in which raised blood pressure is but one sign. The major maternal abnormalities occur in kidneys, liver, brain and coagulation systems. Impaired uteroplacental blood flow may cause fetal growth retardation or intrauterine death.

It is generally agreed that blood pressures greater than about 170/110 mmHg should be lowered to protect the mother against risk of stroke or eclampsia. However, there is less agreement about the value of treatment for lower levels of blood pressure. The drugs that are most widely used to lower blood pressure acutely in pregnancy include nifedipine, labetolol, and hydralazine. Magnesium sulphate may produce some blood pressure lowering effects but is generally inadequate to treat severe hypertension in pregnancy. The drugs most widely used for chronic treatment of raised blood pressure in pregnancy include: beta-blockers; in particular, oxprenolol, pindolol, atenolol (associated with fetal growth retardation when used long-term throughout pregnancy), labetolol, methyldopa, prazosin, hydralazine, nifedipine and isradipine. Antihypertensive agents that are generally avoided during pregnancy include: ACE inhibitors, which are associated with fetal growth retardation, oligohydramnios, neonatal renal failure, and possibly abnormal fetal morphology ("fetal hypotensive syndrome"), and AII receptor antagonists, the effects of which may be similar to those of ACE inhibitors. Diuretics are also used infrequently because of concerns that they may further reduce the already compromised plasma volume, although they have been shown to be effective in randomised controlled trials.

Lowering blood pressure is only one aspect of the management of pre-eclampsia. Management ideally involves a multidisciplinary team. Maternal and fetal monitoring are essential for the detection of signs of advancing pre-eclampsia or of impending fetal demise, and, thereby, the need for delivery, which remains the definitive management for pre-eclampsia. Aspirin has not been shown to be effective in preventing pre-eclampsia. Oral calcium supplementation is not of benefit as prophylaxis against pre-eclampsia in calcium replete populations, but, although evidence is liimted, it is generally agreed that dietary calcium intake should be increased to recommended levels in populations with low calcium diets.

6.3 Very elderly

The results of randomised trials provide clear evidence of the benefits and safety of antihypertensive treatment in patients across a wide age range up to about 80 years. These trials have not provided any clear evidence of differential proportional effects of therapy in younger and

older patients, although the absolute effects are typically greater in older individuals because of their higher risk of cardiovascular events. Benefits of treatment have been demonstrated among older patients with classical hypertension (raised systolic and diastolic blood pressures), as well as among older patients with isolated systolic hypertension (raised systolic blood pressure alone).

However, most of the completed studies have included too few patients above this age to provide reliable evidence of benefits or safety. Among the trials reported to date, the oldest average age of patients was in the STOP-Hypertension trial (Swedish Trial in Old Patients with Hypertension) In that study, which demonstrated a marked reduction in cardiovascular events among patients assigned active treatment, participants were aged between 70 and 84 years at enrollment (mean 76 years). However, the number of patients in that study above age 80 years was too small for reliable conclusions to be drawn about the effects of treatment on cardiovascular disease risk in this subgroup. In the Syst-Eur trial of treatment for isolated systolic hypertension among patients aged 60 years or older, there was no clear evidence of an association between older age and the size of the treatment effects on combined fatal or non-fatal cardiovascular events, although there was a trend towards a lesser effect on fatal events with increasing age.

Because of the absence of direct evidence about the effects of blood pressure lowering in the very elderly, and the limited prognostic relevance of blood pressure levels when measured at very old ages, there is uncertainty about the value of antihypertensive treatment for patients over the age of 80 years. A large-scale randomised controlled trial has recently been initiated to assess the potential benefits of treatment of hypertension in very old patients. The Hypertension in the Very Old Trial (HYVET) is currently recruiting hypertensive patients aged over 80 years. Patients are randomised to receive either a diuretic-based regimen, a calcium antagonist-based regimen, or no treatment. In addition to this study, several other ongoing trials involving a broader patient group are recruiting some patients older than 80 years. The results of these trials should eventually provide reliable evidence about the effects of blood pressure lowering therapy in this very high risk population.

6.4 Co-existing cerebrovascular or cardiac disease

6.4.1 Cerebrovascular disease

Individuals with a history of stroke or TIA have very high risks of further cerebrovascular events. Among such patients, the typical stroke rate is 4% or more per year. Individuals with a history of ischaemic stroke or TIA also have high risks of CHD events. The risks of recurrent cerebrovascular events (as well as initial CHD events) appear to be directly related to levels of blood pressure. Consequently, even modest reduction in blood pressure among such patients could confer worthwhile reductions in the absolute risk of cardiovascular events. In trials among stroke survivors with hypertension, blood pressure lowering therapy produced a 29% (SD 9) reduction in stroke risk and a trend towards a reduction in CHD events. The proportional reduction in stroke risk was similar to that observed in patients without stroke; however, the absolute benefits were several times greater). In the three trials of blood pressure lowering agents among patients with a broad range of blood pressures at entry, the effects of treatment were less clear, although there was still a suggestion of benefit. The remaining uncertainty about the benefits of treatment for a broad range of patients with cerebrovascular disease should be resolved by PROGRESS (perindopril protection against recurrent stroke study), a trial of ACE inhibitor-based therapy in patients with a history of stroke or TIA.

6.4.2 Coronary heart disease

Individuals with a history of CHD have very high risks of further CHD events. Among patients with a history of myocardial infarction or unstable angina, the risk of CHD death or non-fatal myocardial infarction is 5% or more per year. Once again, the risk of these recurrent events appears to be directly related to the level of blood pressure. There are few data available about the effects of blood pressure lowering in hypertensive patients with CHD. However, many of the more common blood pressure lowering drugs have been assessed in broader groups of patients with CHD, albeit with objectives other than reduction of blood pressure. Beta-blockers have been shown to reduce the risks of both re-infarction and cardiovascular death by about a quarter in patients with myocardial infarction. Overall there is no clear evidence from clinical trials that calcium antagonists reduce recurrent CHD events outcomes, but there are suggestive, though not definitive, data demonstrating a reduced risk of myocardial infarction in patients treated with verapamil or diltiazem, and an increased risk in patients treated with immediate release nifedipine. Ongoing studies of verapamil, diltiazem and longer-acting dihydropyridine calcium antagonists in hypertensive and non-hypertensive patients with CHD should provide clearer evidence about the effects of these agents on recurrent CHD risk. Several large trials of ACE inhibitors in patients with heart failure or left ventricular dysfunction have provided evidence of a reduction of about one-fifth in the risk of myocardial infarction or sudden death. In both the trials of beta blockers and the trials of ACE inhibitors, the magnitude of the effects on CHD events appears greater than that which would be expected from the blood pressure lowering alone and seems likely to reflect, at least in part, other cardioprotective effects of these agents. The remaining uncertainty about the effects of ACE inhibitors on CHD events among high risk patients without heart failure or left ventricular dysfunction should be resolved by the HOPE (Heart Outcome Prevention Evaluation) study.

6.4.3 Congestive heart failure

Patients with congestive heart failure are at particularly high risk of death from cardiovascular disease. There are few data available about the effects of blood pressure lowering specifically among hypertensive patients with heart failure. However, the effects of various blood pressure lowering drugs have been assessed in a broad range of patients with heart failure. Several large trials of ACE inhibitors in patients with heart failure or left ventricular dysfunction have provided evidence of a reduction in mortality of about one-sixth and somewhat larger reductions in heart failure-related morbidity. Recent evidence also indicates that beta-blockers reduce the risk of cardiovascular death and the need for hospital admission by about a quarter in patients with heart failure, a group for which beta-blockers were previously thought to be contraindicated. Trials of calcium antagonists in patients with heart failure have produced no evidence of beneficial effects of treatments with these agents.

6.5 Renal disease

Hypertension is both a cause and a consequence of renal disease, and irrespective of aetiology, hypertension is a major determinant of renal disease progression. Malignant or accelerated hypertension, renal artery stenosis and athero-embolic disease are all important causes of renal disease secondary to hypertension. The role of less severe blood pressure elevations in the genesis of renal failure is less clear, although there is strong evidence of a role for such blood pressure elevations in some populations, e.g. African Americans. Primary renal parenchymal disease has been observed to be responsible for 3-4% of hypertension in some populations, and renovascular disease in around 1%. Most (80-90%) patients presenting to renal replacement programmes are hypertensive, but patients presenting with the combination of hypertension and

renal impairment require definition of macroscopic and/or microscopic renal and/or renovascular anatomy before hypertension can be regarded as the cause of the renal impairment. Diabetic nephropathy, hypertensive nephropathy and primary glomerulonephritis are the three most common causes of end-stage renal failure worldwide. Other important aetiologies include reflux nephropathy, polycystic kidney disease, analgesic nephropathy and secondary glomerulonephritis.

Irrespective of whether hypertension causes renal disease or vice versa, it is clear that hypertension is a major determinant of progression of renal disease and the risk of end-stage failure. There is also some evidence that any familial tendency to hypertension will increase the prevalence of renal failure in patients with primary renal disorders or with diabetes. There is little evidence from randomised trials in hypertensive patients to show that treatment modifies the slight risk of developing renal failure, but more compelling evidence that blood pressure control will slow progression in patients with renal failure. There has been much interest in the question of whether some classes of antihypertensive agents, in particular ACE-inhibitors, retard progression of renal disease over and above their effects on blood pressure loweringbut this remains unproven. Evidence from the Modification of Diet in Renal Disease Study suggests that more aggressive blood pressure lowering should be pursued in patients with chronic renal failure and proteinuria. Lower blood pressure targets have been proposed for patients with proteinuria >1G/d (125/75 mmHg) than for patients with lesser proteinuria (130/80 mmHg).

6.6 Diabetes mellitus

The prevalence of hypertension is 1.5 to 2 times greater in patients with diabetes mellitus compared with matched non-diabetic individuals. Type 1 diabetes mellitus is associated with hypertension only when albuminuria and early nephropathy develop, but Type 2 diabetes mellitus may be associated with hypertension at or even preceding diagnosis. Type 2 diabetes and hypertension are associated with an insulin resistant state (Syndrome X) characterised by hyperinsulinaemia, dyslipidaemia and obesity, but a causal relationship between insulin resistance and hypertension has not yet been established. The co-existence of diabetes mellitus and hypertension is important, as they are multiplicative risk factors for macrovascular and microvascular disease, resulting in increased risks of cardiac death, CHD, congestive heart failure, cerebrovascular disease and peripheral vascular disease. Macrovascular complications account for the majority of deaths in the diabetic population and the absence of hypertension is associated with long-term survival. Microvascular disease resulting in diabetic nephropathy and retinopathy leads to significant morbidity and mortality. The progressive decline in glomerular function that is seen in diabetic patients with hypertension, especially those with albuminuria, can be slowed with antihypertensive treatmentACE inhibitors have been shown to slow the rate of decline in renal function and reduce the risk of dialysis in normotensive Type 1 diabetic subjects with proteinuria. Hypertension is also associated with an increased incidence of diabetic retinopathy and treatment with ACE-inhibitors has been shown to reduce the progression of retinopathy in normotensive Type 1 diabetic subjects.

Non-pharmacological interventions such as weight loss have been shown to improve insulin resistance and blood pressure in hypertensive diabetic patients and similar lifestyle modifications are recommended for the initial treatment of hypertension and diabetes mellitus individually or when these diseases co-exist. Pharmacological treatment of hypertension in diabetic patients can potentially differ from the non-diabetic because of differing effects on lipid profiles, insulin sensitivity and glucose metabolism. Diuretics and beta-blockers are reported to reduce insulin sensitivity and increase triglyceride levels. However, diuretic-based regimens have been shown to reduce cardiovascular events in diabetic patients with hypertension. Beta-blockers potentially

mask hypoglycaemic awareness, but in practice this is not a major contraindication considering the clear evidence of benefits of beta-blockers in diabetic patients after myocardial infarction. ACE-inhibitors and calcium antagonists are thought not to alter insulin sensitivity or lipid profiles, but the CAPPP study has recently reported that hypertensive patients assigned captopril-based therapy had a lower risk of developing diabetes than did patients assigned diuretic- or betablocker-based therapy. Recently, the UK Prospective Diabetes Study (UKPDS 38 and 39) has demonstrated that there were similar benefits of ACE inhibitor- and beta-blocker-based therapy for a variety of both macrovascular and microvascular disease outcomes in patients with Type 2 diabetesTwo small randomised controlled trials have reported that ACE-inhibitors have a more favourable effect on CHD events compared with calcium antagonists in diabetic patients. These results are consistent with either a more favourable effect of ACE-inhibitors or, alternatively, an adverse effect of calcium antagonists, on vascular events in hypertensive diabetic patients. However, since these studies were small and their results less than definitive, further evidence is required to determine whether there are true differences between these drug classes in their effects on macrovascular events.

In the HOT Study of calcium-antagonist based therapy, there was evidence that lowering blood pressure to the lowest target level (diastolic <80 mmHg) in diabetic hypertensive patients resulted in lower risks of cardiovascular events. This finding is consistent with evidence from the UK Prospective Diabetes Study (UKPDS 38), demonstrating that a lower achieved blood pressure (144/82 mmHg vs 154/87 mmHg) was associated with significantly reduced risks of major macrovascular disease events as well as microvascular disease outcomes. The likelihood that diabetic hypertensive patients will benefit from low target blood pressures is consistent with the evidence from trials of blood pressure lowering in normotensive diabetic patients with or without renal disease.

7. Implementation

Translating the recommendations of clinical guidelines and the findings from research studies into daily clinical practice remains a daunting challenge, no less in the treatment of hypertension than in other fields. The rule of halves (only half of all hypertensive patients are aware that they have hypertension, only half of those aware are actually on treatment, and only half of those on treatment have their blood pressure well controlled) still applies in many countries around the world, and even the most affluent countries have only doubled the proportion of well controlled hypertensive patients to approximately one quarter (see3.1.1). This only serves to emphasise the validity of Alexander Lomas' statement "Words without action: the production, dissemination and impact of consensus recommendations".It is now plain that as a stand-alone tool, practice guidelines neither change clinical practice nor affect health outcomes. The evidence from many analyses has established that in order to improve physician performance or other health outcomes, it is necessary to put in place a range of measures reaching locally into the practice site and involving local medical practitioners in an active way. This is plainly beyond the direct capacity or resources of the WHO-ISH Guidelines Committee, but it is hoped to achieve far greater penetration to medical practitioners through alliances and partnerships with national and regional hypertension societies, leagues against hypertension and hypertension research councils.

These guidelines, which are being published in specialist medical journals will be accompanied by a much briefer companion set of "Practice Guidelines" intended for translation into many languages and distribution to local medical practitioners in many countries. The presidents of the leagues and societies affiliated with the International Society of Hypertension and the World

Hypertension League have agreed to assist in forming national alliances with government agencies, with professional medical associations and colleges and with public education groups in order to develop action programs for the implementation of the recommendations in these guidelines. The WHO-ISH Guidelines can serve as a model and a stimulus for the development of custom-built national recommendations, adapted to suit the local cultural, economic and social realities. It is hoped that such modified recommendations could be embedded in an implementation plan that reaches local medical practitioners and local communities alike. Such programs could embrace both the clinical strategies set out in these pages, and the mass strategies necessary for hypertension control at the population level.

8. Future Research

8.1 Blood pressure and cardiovascular disease in developing countries

There is a pressing need for observational epidemiological studies as well as randomised controlled trials in populations from Asia, Africa and Latin America, so as to provide direct evidence about the risks associated with blood pressure and other risk factors, and to determine the effects of blood pressure lowering treatments in patients from these large populations. The detection and quantification of any regional differences that may have relevance for decisions about the strategies adopted for both prevention and treatment of cardiovascular diseases.7 Importantly, such research would obviate the need to extrapolate from research conducted in other geographically and ethnically distinct populations..

8.2 Alternative blood pressure measurements and arterial distensibility

Reliable data are urgently needed on the prognostic significance of blood pressure values obtained by ambulatory blood pressure monitoring or by self-measurement, particularly at home. In this regard, the prognostic significance of isolated clinic ("white coat") hypertension also needs clarification. Further trials of ambulatory blood pressure measurement-guided treatment versus standard therapy would also be of value. More research is also required to determine the independent prognostic relevance of the various other indices of blood pressure and arterial distensibility that have been developed. This includes further investigation of pulse pressure in comparison with mean arterial pressure, diastolic pressure and systolic pressure. It should also include investigation of the prognostic relevance of other indices of arterial distensibility and stiffness.

8.3 Blood pressure lowering in high risk patients

It is essential to continue to extend trials of blood pressure lowering to include high risk groups with or without hypertension but with other major risk factors for cardiovascular events such as diabetes, renal insufficiency, cerebrovascular disease, CHD, peripheral vascular disease or atrial fibrillation. There is a strong rationale for expecting a wide range of patients – both hypertensive and normotensive – with these conditions to benefit from blood pressure lowering.

8.4 More versus less blood pressure lowering

The results of the UKPDS – together with the subgroup results for patients with diabetes in the HOT study – provide strong evidence that lower blood pressure targets among diabetic patients are associated with important reductions in cardiovascular risk. More research is required to

determine whether there are similar advantages of a lower blood pressure target in other high risk groups. Studies investigating the effects of combination therapy versus monotherapy in patients at high risk of cardiovascular events would be helpful in this regard.

8.5 Evaluation of surrogate endpoints

While there is reasonably good evidence about the independent prognostic significance of left ventricular hypertrophy (assessed by electrocardiogram or echocardiogram), there is a need for better evidence about the prognostic significance of other surrogate endpoints including carotid atherosclerosis, endothelial dysfunction and microalbuminuria (particularly among non-diabetic patients), for the separate risks of stroke and CHD events. Further trials evaluating the effects of blood pressure lowering treatments on the risks of cardiovascular events among individuals with these condftions would also be valuable. Furthermore, it would be of particular interest to determine whether different agents producing the same blood pressure reduction are differentially effective in reversing or retarding the progression of these conditions; and, if so, whether this has implications for cardiovascular disease.

8.6 Combined interventions for cardiovascular disease prevention

The causes of cardiovascular disease in hypertensive patients are clearly multifactorial, and there is a strong case for the conduct of factorial randomised trials investigating the separate and joint effects of blood pressure lowering treatments and other intervention modalities. For example, in active- or placebo-controlled trials of new blood pressure lowering agents, it would be of value to include factorial assignment to such interventions as cholesterol lowering, folic acid (for homocysteine lowering), and/or antioxidant vitamins

8.7 Effects of new blood pressure lowering agents

There are many ongoing trials of the new classes of blood pressure lowering agents, and more will be required as new drugs are developed. Most of the ongoing studies are head-to-head comparisons of older and newer agents in which the advantages and disadvantages of one or other treatment may be modest and difficult to detect. Another approach that is likely to evidence of clearer benefits is to randomise patients to new treatments or to placebo against a background of treatment with standard therapy. In this way the full effects of any new treatment will be demonstrated (i.e. the combined effects of blood pressure lowering plus any independent protective effects).

8.8 Genetically-targeted blood pressure lowering therapy

Despite the limited success of efforts to date, research is still required to identify both genetic factors that may be predictive of cardiovascular disease events, particularly in younger individuals, and genetic factors that may predict response to blood pressure lowering treatment.

CHAPTER SIX

Hypertension in Pakistan

Hypertension is a major problem affecting people in our country. A recent survey by Pakistan Medical Research Council is revealing in this context. To begin with only about thirty percent of people over twenty five years have had their blood pressure ever recorded. In the rural areas it is even less. For obvious reasons this proportion is higher in those with higher economic status. Eighty five percent of the urban females of higher class have had their blood checked while only 23 percent of their poor rural counter parts had ever done that.

The degree of awareness about hypertension is poor. Of those found to be hypertensive , 63 percent were unaware of their disease,17 percent were aware but not treated, 14 percent were treated but their blood pressure was not controlled. Only 6 percent had their blood pressure controlled with medication.

The Circulatory diseases in Pakistan cause over 100000 deaths a year, (12 percent of all deaths.) These are official figures, the real loss will be far higher. This is mainly due to adoption of life style prevalent in industrialized countries with increased risk factors like high blood pressure, high cholestrol, smoking, unhealthy diet and physical inactivity leading to obesity.

High blood pressure affects 17.9 percent of all adults over 25 years of age. For men and women hypertension increases with age ranging from a low of 3 percent in urban females to high of 65 percent in those aged 65 or over.

In females incidence is lower than males in younger age groups and then exceeding males after 35-44 years . Such increase also occurs in other populations like USA but at a later age.

Overall the prevalence in urban areas is higher than rural areas (21.5 vs 16.2 percent)

The disease affects urban dwellers earliar and prevalence in all age groups is higher.

Higher economic status is associated in urban males and rural residents with increased frequency, an association which is reverse of that seen in developed countries.

In Pakistan there are 5.5 million men and 5.3 women with high blood pressure. In case the disease is not controlled, it will lead to high incidence of circulatory diseases high morbidity and high mortality.

CHAPTER SEVEN

Investigation Facilities for Hypertension at Health Ways

Hypertension has been described as a silent killer. Although it primarily affects the small blood vessels, virtually all organs especially CV system and renal systems are involved . The secondary hypertension, on the other hand is due to the primary disease process in such organs as endocrines or elsewhere. It is difficult therefore to prescribe a set of tests in a hypertensive patient. A general guide for lab investigations is given in previous chapters. Health Ways have provided full state of the art facilities for hypertension cases. Some tests are rarely performed or not cost effective. Arrangements in such cases have been made to utilize the facilities available at referal institutions within the country or abroad.

A list of full range of tests available at Health Ways is given as under. It is obvious the not all tests are required to be done in hypertension.

NAME OF TEST	REQUIREMENT
A	
ABO & Rh Grouping	3-5 cc Clotted Blood
ACE (Angiotensin Converting Enzyme).	**3-5 cc Clotted Blood or serum**
Acetoaminophen (Paracetamol)	Serum or clotted blood 3-5 cc
Acid Fast Bacilli Culture (includes Smear)	Sample in sterile container
Acid Fast Bacilli Smear only	sterile containers are available in Lab.) Sample in sterile container.
Acid Phosphatase	Serum or clotted blood 3-5 cc
ACTH	**3 cc blood in EDTA tube (send in ice)**
Activated partial Thromboplastin Time (APTT)	Citrated tube available in lab
Aerobic Culture. (A&S)	Swab in transport medium
ALA (Amino Levulinic Acid)	Urine random/ 24 h.
Albumin	Serum or clotted blood 3-5 cc.
Alcohol	3cc blood in EDTA (without spirit)
Aldolase	Serum or clotted blood 3-5 c.c.
Aldosterone	Serum or clotted blood 3-5 c.c.
Alkaline Phosphatase	Serum or clotted blood 3-5 c
Alkaline Phosphatase Fractionation	Serum or clotted blood 3-5 cc
Alpha Fetoprotein (Amniotic Fluid)	1 ml Amniotic Fluid from second trimester
Alpha Fetoprotein (Serum)	Serum or Clotted Blood 3-5 c.c.
Alphahydroxybutyrate Dehydogenase(HBDH)	Serum or clotted blood 3-5 c.c.
Alpha- 1 Antitrypsin	Serum or clotted blood 3-5 cc
ALT (SGPT)	Serum or clotted blood 3-5 cc
Amikacin	Serum or clotted blood 3-5 cc
Amino Acid Screening	Random/24 h urine
Aminophylline (Theophylline)	Serum or clotted blood 3-5 cc
Amoebiasis IHA	Serum or clotted blood 3-5 cc
Amphetamine	Random Urine
Amylase, Serum	Serum or clotted blood 3-5 cc
Amylase, Urine	24 Hour or 2 Hour Urine
Anaerobic Culture. (C&S)	Swab in anaerobic transport medium or aspirate in Syringe
Androstenedione	Serum or clotted blood 3-5 cc
AntiCardiolipin - IgG	5 cc clotted blood
AntiCardiolipin - IgM	5 cc clotted blood
Anti Mitochondrial Antibody	Serum or clotted blood 3-5 cc
Antibody identification	7 cc clotted blood
Antibody Screening	Clotted blood 5cc
Antigen phenotyping	3 cc EDTA sample or clotted blood
Anti-DNA Antibodies. (Double Stranded)	Serum or clotted blood 3-5 cc
Anti-E.B.V. Antibodies (Infectious Mono)	Serum or clotted blood 3-5 cc
Anti-Nuclear Antibody	Serum or clotted blood 3-5 cc
Anti-Smooth Muscle Antibody	Serum or clotted blood 3-5 cc
Anti-Streptolysin-O Titre.	Serum or clotted blood 3-5 cc
Anti-Thrombin III	Citrate Blood same as (PT & APTT)
Aspirate from breast cyst - Potasium (BK)	Fluid
APTT	Citrate tube
Ascitic Fluid For R-E	(2-5 cc fluid)

NAME OF TEST	REQUIREMENT
Aspirate from Breast cyst - sodium (BNA)	Fluid
Aspirin (Salicylate) *	Serum or clotted blood 3-5 cc
AST (SGOT)	Serum or clotted blood 3-5 cc
Ascitic Fluid Albumin	
Australia Antigen (Hep. B. Surface Antigen)	Serum or clotted blood 3-5 cc
Auto Hemolysis	Special tube + EDTA Tube
A/G Ratio & Total Protein	Serum or clotted blood 3-5 cc
AFB Culture	
Acute Leukemia Phenotyping	1 citrate tube (APTT Tube)
Acetone Serum	Serum or clotted blood 3-5 cc
Anti Lupus Anti Coag.	Serum or clotted blood 3-5 cc
Anti-Gliadin IgA	Serum or clotted blood 3-5 cc
Anti Neutrophil Cytoplasmic Abs (ANCA)	Serum or clotted blood 3-5 cc
Acetycholine Receptor Ab.	Serum or clotted blood 3-5 cc
B	
Barr Bodies	Scrapping buccal mucosa fixed in 95% alcohol or spray fixed
Barbiturates	Random urine
Bence Jones Protein, Qual.	Random Urine
Benzodiazepines	Serum or clotted blood 3-5 cc
Beta HCG	Serum or clotted blood 3-5 cc
Bicarbonate	Serum or clotted blood 3-5 cc
Bile, Urine Qualitative	Random Urine
Bilirubin, Total & Direct	Serum or clotted blood 3-5 cc
Bilirubin, Total	Serum or clotted blood 3-5 cc
Biopsy (Large)	Formalin fixed tissue
Biopsy (Small)	Formalin fixed tissue
Bleeding Time	Send the patient to lab
Blood, Occult - Stool	Random Stool Gastric, Aspirate or vomit in clean container
Blood Culture	5cc blood in each culture bottle (Aerobic & Anaerobic) & send immediately to the lab.
Blood Group & Rh	Clotted blood 3-5 cc
Blood Indices	2-3 cc whole blood in EDTA
Blood Urea Nitrogen B.U.N	**Serum or clotted blood 3-5 cc**
Body Fluid , Cell Count	3-5 cc Body Fluid
Body Fluid Culture. (CSF, Pleural, & Joint etc)	Send fluid 3-5cc in sterile containers.
Bone Marrow	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow Culture	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow Non Specific/ ALPHA NAPH , ESTRERASE	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow Peroxidase	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow P.A.S. Stain	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow Special Stain	By appointment (Please call for appointment or Bone Marrow slides)
Bone Marrow Sudan Black	By appointment (Please call for appointment or Bone Marrow slides)
Bone Trephine	By appointment (Please call for appointment or Bone Marrow slides)
Brucella Antibody	Serum

NAME OF TEST	REQUIREMENT
B.U.N. (Blood Urea Nitrogen)	**5 cc Clotted blood**
B-12	Serum or clotted blood 3-5 cc.
B-12 Folate	3-5 cc clotted blood
Body Fluid Amylase	2-3 cc clotted blood
Body Fluid LDH	2-3 cc body fluid
Body Fluid pH	2-3 cc body fluid
Body Fluid Sp. Gravity	2-3 cc body fluid
Body Fluid Albumin	2-3 cc body fluid
Beta-$_2$ Microglobulin	2-3 cc body fluid
Bordetella Pertussis DNA detection	Serum or 3-5 cc clotted blood/Random Urine Nasopharyngeal secretions on a cotton swab
C	
CA125	Serum or 2-3 cc clotted blood
Calcium	Serum or clotted blood 3-5 cc
Calcuim, Urine	24 hours Urine
Calcitonin	5 cc clotted blood
Calculi Identification & Analysis. (Stone)	Submit the entire specimen, indicate source.
Cannabinoids	Random Urine
Carbamazepine (Tegretol)	Serum or clotted blood 3-5 cc
Carbon Dioxide, Total	Serum or clotted blood 3-5 cc
Carcinoembryonic Antigen (CEA)	Serum or clotted blood 3-5 cc
Catecholamines	**24 Hour Urine (Preservative added before collection)**
Cardiac Enzyme Profile	added before collection)
CCHF PCR	Serum or clotted blood 3-5 cc
Ceruloplasmin	5 cc Clotted blood
Cervical Smear Pap Smear,	Serum or clotted blood 3-5 cc
Endocervical, Endometrial)	95% Alohol or spray Fixed sides
Chlamydia trachomatis antigen test	25 ml urine in green top container
Chlamydia-Detection	Urethral or cervical swab
Chlamydia Trachomatis Antigen	Swab in 3 cc sterile
	normal saline or in transport media.
Chloride, C.S.F.	Urine, High Vaginal Swab
Chloride, Serum	2-3 cc C.S.F.
Chloride Urine.	Serum or clotted blood 3-5 cc
Cholestrol Total	24 hours Urine.
Cholinesterase, Serum	Serum or clotted blood 3-5 cc (FASTING)
Chromosomal Analysis :	Serum or clotted blood 3-5 cc
Blood	3-5 ml of peripheral blood with sodium heparin in a sterile white capped tube
Bone Marrow	Specimen should not be frozen 1-2 ml of bone marrow Aspirate with sodium heparin in a sterile white capped tube Frozen or clotted specimen will not work. Send specimen immediately to cytogenetics lab.
Amniotic Fluid	20 ml of amniotic fluid in a sterile tube. Bloody specimens are undesirable. Specimen should not be frozen. If cells do not grow, patient will be notified within 15 days of receipt.
	Obtain 1.0 cms of placenta (including chorionic villus) in a screw capped container with normal

NAME OF TEST	REQUIREMENT
	saline and 1 cc Gentamicin.
- Products of Conception (POC)	Do not add formalin. Culture failure will be notified within 15 days of recepipte.
- Chorionic Villus	20 mg of chorionic villus in a sterile screw capped container with normal saline and 1 cc Gentamicin. Do not add formalin culture . failure will be notified within 25 days of receipt.
CITRIC ACID	24 hours urine required.
CK (CPK)	3-5 cc Clotted blood
CK-MB.	Serum or clotted blood 3-5 cc
Clotting Time - Whole Blood	Send the patient to lab.
CMV IgM	Serum or clotted blood 3-5 cc
Cocaine	Random Urine
Cold Hemagglutinins Titre	5 cc Clotted blood
Complement. C3	Serum or clotted blood 3 cc
Complement. C4	Serum or clotted blood 3 cc
Complete Blood Picture (C.P)	**2-3 cc Blood in EDTA tube**
Coombs Test Direct	3cc clotted blood
Coombs Test, indirect (Antibody Screening)	3-5 cc clotted blood
Copper Serum	Serum or clotted blood
Copper , Urine	Urine (Random & 24 hours)
Coproporphyrins, Qualitative, Urinary	Random Urine 50-100 ml
Cortisol	**Serum or clotted blood 3-5 cc or hours or Drug.**
Creatinine. Serum, Urine	Serum / clotted blood 3-5 cc Random/24 h urine
Creatinine Clearance	24 Hrs, Urine and 3-5 cc Clotted blood + height and weight of patient
Cryoglobulins, Qualitative	Clotted blood 3-5 cc
CSF for RE	1 ml. of CSF fluid.
CSF Protein Electrophoresis	CSF-2-3 cc.
Culture & Sensitivity	Sample in sterile swab in transport medium
Cyclosporin	2-3 cc EDTA blood (whole blood)
Cysteine	Freshly voided 10-20 ml Urine
C.M.V. (Cytomegalovirus) IgG	Serum or clotted blood 3-5 cc
C.M.V. DNA detection by PCR	5 cc blood in PT tubes
C-Reactive Protein (C.R.P.)	Serum or clotted blood 3-5 cc
C.P.K (Creatinine Phosphokinase)	Serum or clotted blood 3-5 cc
C.S.F. for malignant cells	C.S.F.
C-Peptide	5 cc Fasting clotted blood
CA-15-3	3-5 cc clotted blood
Crimea Congo haemorrhagic Fever	3-5 cc clotted blood
Clostridium Difficle Antigen Detection Test	Fresh stool required
D	
Dehydroepiandrosterone (DHEA - SO_4)	Serum or clotted blood 3-5 cc Citrate tube or 3 cc EDTA
Dengue types 1-4 IgM	5 cc blood in plain tube
Dengue virus RNA detection in blood	5 cc blood in plain tube

NAME OF TEST	REQUIREMENT
Depakene (Valproic Acid)	Serum or clotted blood 3-5 cc
Diastase (Urine)	24 Hours or Random Urine
Differential Leucocytes Count (DLC)	2 Blood Film slides or 1-2 cc blood
Digoxin (Lanoxin)	**Serum or clotted blood 3-5 cc**
Dintrophenyl-Hydrazine (DNPH)	Random Urine
Direct Coombs Test	2 cc blood in EDTA tube
Disopyramide	Serum or clotted blood 3-5 cc
E	
Echinococcus Antibody	Serum or clotted Blood 3-5 cc
Electrolyte Panel	**Serum 3-5 cc**
Electrophoresis, Lipoprotein	Serum or clotted Blood 3-5 cc (Fasting)
Electrophoresis, Protein, Serum	Serum or clotted Blood 3-5 cc
Electrophoresis, Protein, Urine/CSF	Early morning first urine or 24 hr. Urnie collection/CSF 2-3 cc
Eosinophil Count	Whole blood 2-3 cc in EDTA bottle
Electrolyte Panel	**Serum 3-5 cc**
Erythrocyte Sedimentation rate (E.S.R.)	**Whole blood 2-3 cc in EDTA bottle**
Estradiol (Serum)	Serum or clotted blood 3-5 cc
Estriol (Serum)	Serum or clotted blood 3-5 cc
Estriol (Urine)	24 Hour Urine.
Estrogens, Total (Estradiol)	Serum or clotted blood 3-5 cc
E. Histolytica Antibodies	3-5 cc serum or clotted blood
ENA Profile (Anti-SM, Anti SM/RNP, Anti-RO (SS-A), Anti-SCL Anti-La (SS-B)	Serum or clotted blood 3-5 cc
Gynae cytology (Pap Smear)	2 Slide (UCE). Fixed with cytology fixative or 95% alcohol.
F	
Ferritin	Serum or clotted blood 3-5 cc
Fetoprotein (Alpha Feto Protein)	Serum or clotted blood 3-5 cc
Fibrinogen Degradation Products (F.D.P.)	Pls inquire (special tube will be provided for blood coll)
Fibrinogen level	Citrate tube
Fibrinogen Titre	Citrate tube
Fine needle aspiration	All palpable lumps & nodes fix in 95% alcohol
Fluoroescent Treponemal Antibody (FTA-ABS)	3-5 cc clotted blood
Fine needle aspiration with procedure (FNACP)	All palpable lumps & nodes. Pt. Is asked to come to the lab.
Fluid RE	2-3 cc Fluid
FNAB - Aspiration & needle biopsy	Spray fixed slides and tissue in formalin.
Folic Acid, R.B.C. (Folate)	2 ml whole blood in EDTA tube & also 2-3 ml clotted blood
Folic (Folic Acid) Serum	Serum or clotted blood 3-5 cc
Follicle Stimulating Hormone (FSH)	Serum or clotted blood 3-5 cc
Free T3	**Serum or clotted blood 3-5 cc**
Free T4	**Serum or clotted blood 3-5 cc**
Frozen Section	By appointment only

NAME OF TEST	REQUIREMENT
Fructosamine	5 cc clotted sample
FSH & LH	Serum or clotted blood 3-5 cc
F.S.H.	Serum or clotted blood 3-5 cc
FTA - ABS	Serum or clotted blood 5 cc
Fungus Culture	Specimen or scraping in sterile container
Fungus Smear	Specimen or scraping
Fast Hemoglobin (HbA_{1c}) (Glycos ylated Hemoglobin)	2-3 cc EDTA Whole Blood
Fat, Stool, Qualitative	Random Stool
Fecal Fat	Stool 24 Hrs or 72 Hrs collection
Fern, Test	2 slides with the specimen air dry fix
Ferric Chloride	Fresh random Urine
G	
G-6-PD	2 cc whole blood in EDTA
Gamma Globulin	Serum or clotted blood 3-5 cc
Gamma Glutamyl Transpeptidase (GGT)	Serum or clotted blood 2-3 cc
Gastric Content (Analysis for Acid. Pentagastric Test)	20-50 mg Gastric juice
Gastrin	Fasting serum or clotted blood 3-5 cc
GCT (Glucose ChallengeTest)	Please enquire from the lab.
Gentamycin	Serum or clotted blood 3-5 cc
Glucose, CSF	1-2 cc C.S.F.
Glucose Fasting	3-5 cc Serum
Glucose Random	3-5 cc Serum or in Fluoride tube Fasting condition
Glucose Tolerance Test	Serum or clotted blood 3-5 cc or in Fluoride tube
Gram Stain	Please inquire from the lab. 2 Air Dry smear made by rolling swabs across clean slide. Indicate specimen source
Group & Rh.	Clotted blood 3-5 cc
Growth Hormone	Serum or clotted blood 3-5 cc
GUAIAC Test	Random Stool Specimen.
G.C. Smear	2 Air dry smear made by rolling swab across clean slide ,indicate specimen source
Non Gyn. Gastric Washing	
Gross only	> 1.0 gram gall stone.
Gall Stone	
H	
HAA	Serum or clotted blood 3-5 cc
HAM's Test for PNH.	Whole blood 2 cc in EDTA tube
Haptoglobin.	Serum or clotted blood 3-5 cc
HBA_{1c} (Glycated hemoglobin)	**2 cc blood in EDTA tube**
Hb Electrophoresis (Acid pH)	2 cc blood in E.D.T.A. tube
Hemoglobin Electrophoresis	Whole Blood 2-3 cc blood in EDTA tube
Hemoglobin H Inclusions	Whole Blood 2-3 cc blood in EDTA tube

NAME OF TEST	REQUIREMENT
Hemoglobin & Hematocrit	2-3 cc Whole blood in EDTA tub
Hemosiderin (Urine)	Urine 10 cc
Hepatitis A Virus Antibody IgM	Serum or Clotted Blood 3-5 cc
Hepatitis B Core Antibody IgM	Serum or Clotted Blood 3-5 cc
Hepatitis B Core Antibody (IgM)	Serum or Clotted Blood 3-5 cc
Hepatitis Delta Antibody	Serum or Clotted Blood 3-5 cc
Hepatitis B Surface Antibody	Serum or Clotted Blood 3-5 cc
Hepatitis B Surface Antigen	Serum or Clotted Blood 3-5 cc
Hepatitis Be Antibody (HBeAb)	Serum or Clotted Blood 3-5 cc
Hepatitis Be Antigen (HBeAg)	Serum or Clotted Blood 3-5 cc
Hep. B Profile (incl. HBsAG, HBsAb, HbcAB, IgG, IgG, Igm, HbeAg & HbeAB)	Serum or Clotted Blood 3-5 cc
Hep. Profile (HbsAg, HBsAb, HBcAb (IgG, IgM), HbeAG, HBeAB, HAVAB-M), HBDAB, HCV, HEV)	Serum or Clotted Blood 7-10 cc
Hepatitis B Virus DNA	3 cc blood in plain tubes
Hepatitis C Virus (Antibody)	Serum or clotted blood 3-5 cc
Hepatitis C Virus RNA detection in serum	3cc blood in plain tubes
Hepatitis C Virus RNA in white blood cells	5cc blood in PT tubes
Hepatitis E Virus	Serum or clotted blood 3-5 cc
	Serum or clotted blood 3-5 cc
Hepatitus G Virus RNA	5 cc blood in plain tubes
Herpes IgM	Serum or clotted blood 3-5 cc
Helicobacter Pylori	Serum or clotted blood 3-5 cc
High Density Lipoprotein (HLD) Cholestrol	
HIV test (Aids) Human Immuneodeif.	Serum or clotted blood 3-5 cc Fasting
Homocystine & Cystine (Qualitative)	Serum or clotted blood 5 cc
Hormonal Evaluation	Random Urine Specimen
	Alcohol or spray fixed slides
H.B.D.H.	Serum or clotted blood 3-5 cc
H.G.G. (B)	**Serum or clotted blood 3-5 cc**
H.D.L. Cholesterol	Serum or clotted blood 3-5 cc (fasting)
H.G.H (Human Growth Hormone) (G.H.)	Serum or clotted blood 3-5 cc
Hess Test	Enquire with the Lab.
White Blood cells, liver biopsy	Liver Biopsy 25 mg
H.I.V. by western blot	5 cc clotted blood in plain tube
Homogentistic Acid (HMG)	Random Urine
HLA - B27 typing	5 cc blood in PT tubes
HBA_2 By Column	3 cc blood in EDTA tube
Hemoglobin Unstable	3 cc blood in EDTA tube
Hepatitis C Virus RNA (Quantitative)	5cc blood in EDTA
Herpes Simplex Virus Type 1& 2	5 ml clotted blood or 5 ml blood in EDTA tube
	1 ml CSF
Immunoelectrophoresis	Serum or clotted blood 3-5 cc
Immunoglobulins	Serum or clotted blood 3-5 cc
Indirect Coombs Test (Anti.screening)	Clotted blood 3-5 cc
InfectiousMononucleoses (Paul Bunnel)	Serum or clotted blood 3-5 cc
Inhibitor test A.P.T.T.	Citrated tube available in lab (ie sample send in 3 PT & ATT tube)

NAME OF TEST	REQUIREMENT
Insulin	Serum or clotted blood 3-5 cc (Fasting)
Iron/TIBC	Serum or clotted blood 5-7cc avoid Hemolysis
Iron Binding Capacity, Total	Serum or clotted blood 3-5 cc avoid Hemolysis
Iron Staimning (Bone Marrrow)	Bone marrow (slides)
I.g.A (immunoglobulin A) IgA	Serum or clotted blood 2-3cc
I.g.E.(immunoglobulin E) IgE	Serum or clotted blood 3-5 cc
I.g.G. (immunoglobulin G) IgG	Serum or clotted blood 3-5 cc
I.g.M. (immunoglobulin M) IgM	Serum or clotted blood 3-5 cc
Insulin Tolerance Test	3-5 cc clotted blood (Fasting/Random)
Immunoelectrophoresis Urine	Random urine or 24 hours urine
J	
K	
Knee Joint Fluid RE	2-3 cc Fluid
KOH Prep. For fungi	Specimen or scraping.
L	
Lactic Acid	2 cc blood in flouride Tube in ice
Lactic Dehydrogenase (L . D. H)	Serum or clotted blood 3-5 cc
Lactose Tolerance (Breath Hydrogen test)	Fasting condition. (Appointement required)
Lanoxin (Dioxin)	Serum or clotted blood 3-5 cc
Latex Particle Agglutination (LPA)	CSF
LEAD	4 cc blood in lithium Heparin
Leptospira Antibodies	5 cc clotted blood or serum
Leukocyte function test.	10 cc whole blood in EDTA tube
Leukocyte Phagocytic index	10 cc whole blood in EDTA tube
Leukocytes NBT (Nitro blue tetrazolium)	10 cc whole blood in EDTA tube
Leukocytes skin Window (Rebucks)	Patient
Lipase, serum	Serum or clotted blood 3-5 cc
➢ **Lipid Profile**	**Serum or clotted blood 3-5 cc (Fasting)**
➢ **Lipids, total**	**Serum or clotted blood 3-5 cc (Fasting)**
➢ **Liporotein Electrophoresis**	**Serum or clotted blood 3-5 cc (Fasting)**
Lithium	
Lupus Anticoagulant	Citrate tube available in lab (ie sample send in PT & APTT tube)

NAME OF TEST	REQUIREMENT
Luteinizing Hormone (L.H.)	Serum or clotted blood 3-5 cc
L.D.L. Cholesterol	Serum or clotted blood 3-5 cc (Fasting)
L.E. (Lupus Erythematosus) Cells	Request Special tube. (Lithium Heparin+5-6 glass beads)
L.F.T Profile	Serum or Clotted blood 3-5 cc
Lidocaine	Serum or clotted blood 3-5 cc
Lead	Urine 24 hours
M	
Magnesium	Serum or clotted blood 3-5 cc
Malaria (Smear)	Whole blood 1-2 cc in EDTA tube
Methaemoglobin	Whole blood 2-3 cc in EDTA tube
Methotrexate	Serum or clotted blood 3-5 cc
Microalbumin Urine	Random Urine sample
Microfilaria Smear	Whole blood in EDTA bottle (2-3cc)
Mixed Agglutination Reaction (MAR test)	Semen
Mantoux test	Skin test
Mono Specific Direct Coombs	3cc EDTA
MPS (Mucopolysaccharides)	24 Hour urine collection
Mycoplasma Antibodies (MPA)	Serum or clotted blood 5 cc
Myoglobulin Urine	Fresh Random urine
Myocobacterium Smear. (AFBS)	Sputum, 10 ml Blood in Pink Top tubes, CSF Bone
Mycobacterium Tuberculosis.	Sputum, 10 ml blood in EDTA, CSF, Marrow, Lymph node, Aspirate, Biopsy, Blood in 3 PT tubes(full)
MycobacteriumTuberculosis, MTB DNA detection	
Mix Antiglobulin test	Block Paraffin
Monoclonal Battery	
Mucin Clot test	5-10 cc knee joint fluid.
Myoglobulin Serum	2cc clotted blood
N	
Neonatal Bilirubin	3-5 cc clotted blood
Neonatal TSH	1-1/2 cc Clotted blood
Non-Gynae Bronchial	Fresh specimen
Non-Gynae Urine	Fresh specimen
Non-Gynae Spinal Fluid	Fresh specimen
Non-Gynae Breast	Syringe or slides
Norpase (Disopyramide)	Serum or clotted blood 3-5 cc
Non-Gynae Sputum	Early morning fresh deep cough specimen preferable

NAME OF TEST	REQUIREMENT
Non-Gynae Effusion	Fresh specimen preferable
Nitro Blue Tetrazolium	5 c blood in EDTA tube.
O	
Occult Blood - Stool	Random Stool Specimen.
Oligoclonal Bands	CSF 2cc
Opiates	Random Urine
Osmolality, Serum	**Serum or clotted blood 3-5 cc**
Osmotic fragility	Heparin tube
Ova & Parasites,	Fresh Stool Specimen
Complete Exam (Stool RE)	Stool Specimen
Oxalate, Urine	24 h. Urine Collection
P	
Pap Smear	Alcohol or spray fixed slides
Paracetamol (ACETOAMINOPHEN)	Serum or clotted 3-5 cc blood
Parathormone (INTACT)	Serum or clotted blood 3-5 cc
Parathyroid Hormone (INTACT)	Serum or clotted blood 3-5 cc
Partial Thromboplastin Time (P.T.T)	Citrated tube
Paul Bunnel Test (Infectious mononucleosis)	Serum or clotted Blood 3-5 cc
Pericardial Fluid RE	2-5 cc fluid
Peritoneal Fluid RE	2-5 cc fluid
Phenobarbital	Serum or clotted blood 3-5 cc
Phenyalanine (Urine Qual)	Random Urine Specimen
Phenylketonuria (PKU)	Urine
Phenytoin (Dilantin)	Serum or clotted blood 3-5 cc
Phosphate, Inorganic	Serum or clotted blood 3-5 cc
Phosphorus, Urinary	24 Hours urine
Pinworms (See Ova & Parasites)	Stool
Platelet Count	2 cc whole blood in EDTA tube
Pleural Fluid for RE	Fluid (2-5) cc
Porphobilinogen (Qualitative/Quantative) and Uroporphyrins)	Random or 24 Hours Urine collection
Potassium, Serum	24 Hours Urine Collection
Potassium, Urine	**Serum or clotted blood 3-5 cc**
Pre Albumin	Random or 24 hours urine
Pregnancy Test (Serum (BHCG)	Serum or clotted blood 3-5 cc
Pregnancy Test (Urine)	**Serum or clotted blood 3-5 cc**
	First morning urine specimen preferred

NAME OF TEST	REQUIREMENT
Procainamide (Pronestyl)	Serum or clotted blood 3-5 cc
Progesterone	Serum or clotted blood 3-5 cc
Prolactin	Serum or clotted blood 3-5 cc
Pronestyl (Procain Amide)	Serum or clotted blood 3-5 cc
Prostatic Acid Phosphatase	Serum or clotted blood 3-5 cc
Protein, Serum	Serum or clotted blood 3-5 cc
Protein, Total C.S.F.	C.S.F. 2-3 cc
Protein, Total & A/G RATIO.	Serum or clotted blood 3-5 cc
Protein, Urinary, Total	24 Hours Urine Collection.
Protein Electrophoresis Serum	Serum or clotted blood 3-5 cc
Protein (Bence Jones)	Freshly voided random urine
Prothrombin Time (PT)	Same as APTT sample
Protozoa Examination (Ova & Parasites)	Fresh stool required
P.C.T. (Post Coital Test)	Fresh slide with the specimen & send immediately.
P.T.H. (Parathyroid Hormone, Intact)	Serum or clotted blood 3-5 cc in ice.
Pyruvate Kinase	2cc blood in EDTA
Protein Electrophoresis Urine	Random urine or 24 hours urine
Protein Electrophoresis CSF	CSF
Q	
Quinidine.	Serum or clotted blood 3-5 cc
R	
Renal Calculi	**Submit entire specimen**
Reticulocyte	1-2 cc blood in EDTA tube.
Rh Factor & Blood Type.	3-5 cc clotted blood.
Rh Phenytype	5cc EDTA or clotted sample
Rh (Antibody Titre)	5cc clotted blood
Rheumatoid Factor Titre	Clotted blood 3-5 cc
Rheumatoid Factor (R.F.) Screen	Serum or clotted blood 3-5 cc
Rubella IgG Anibody	Serum or clotted blood 3-5 cc
Rubella IgM Anibody	Serum or clotted blood 3-5 cc
R.A. Test (Screen)	Serum or clotted blood 3-5 cc
R.P.R. (Rapid Plasma Reagin)	Serum or clotted blood 3-5 cc
R.B.C. Folate	5cc whole blood in EDTA & 2cc serum
Rota Virus	Random stool
S	
Salicylate	Serum or clotted blood 3-5 cc
Salmonella Antibodies (WIDAL)	Serum or clotted blood 5cc
Scrapings	Tongue Buccal Mucosa - any ulcerated lesion
Selectivity Index (SE)	Serum or clotted blood 3-5 cc & random urine
Semen Analysis	Deliver the specimen within half an hour of collection.

NAME OF TEST	REQUIREMENT
Semen Swim up	Fresh semen (abstinence 3 --7 days)
Serotonin Metabolite (Urine) (5-HIAA)	24 Hours Urine collection
SGOT (AST)	Serum or clotted blood 3-5 cc
SGOT (ALT)	Serum or clotted blood 3-5 cc
Sickle Cell Screen	1-2 whole blood in EDTA bottle
Slide for 2nd Opinion	Prepared slides with complete clinical history and previous histopathology report.
Smear, Eosinophils	Specimen or direct smears. Let air dry.
Smear, G.C.	
Smear, (A F B.)	
Sodium, Urine	Random or 24 h Urine collection
Sodium Serum	Serum or clotted blood 3-5 cc
Sperm Antibodies	Serum or clotted blood of wife, semen from husband.
Sperm Count	Deliver the specimen within half an hour of collection.
Special Stains	Paraffin blocks
Spinal Fluid Protein Electrophoresis	2-3 cc C.S.F. required.
Spot Urine Creatinine	Fresh Urine sample
Spot Urine Sodium	Fresh Urine sample
Spot Urine Potassium	Fresh Urine sample
Stool RE	Fresh stool sample
Stool Occult Blood	Fresh stool sample
Stool Fat Globules	Fresh stool sample
Stool Reducing Substances	Fresh stool sample
Stone, Kidney	Submit the entire specimen
Sugar Chromatography	Random Urine or 24 hours
Sulphhemogolbin	Whole blood 2-3 cc in EDTA bottles.
Synovial Fluid for RE	Fluid (2-5) cc
T	
Triglycerides	Serum or clotted 3-5 cc
T.S.H.	Serum or clotted blood 3-5 cc
Tegretol	Serum or clotted blood 3-5 cc
Testosterone, Serum	Serum or clotted blood 3-5 cc
Theophylline *	Serum or clotted blood 3-5 cc
Thyroglobulin Antibodies	Serum or clotted blood 3-5 cc
Thyroid Antibodies	Serum or clotted blood 3-5 cc
Tissue Biopsy (Large specimen)	Tissue specimen in 10 % buffered formalin.
Tissue Biopsy (Small specimen)	Tissue specimen in 10 % buffered formalin. (Formalin should be upto the level of specimen)
Torch Profile (CMV.IGM, Hep. IGM, Rub. (IGM, Tox. IGM)	Serum or clotted blood 3-5 cc

NAME OF TEST	REQUIREMENT
Total Iron Binding Capacity	Serum or clotted blood 4-6 cc
Total Lipids	Serum or clotted blood 3-5 cc (FASTING)
Total Protein & A/G Ratio.	Serum or clotted blood 3-5 cc
Total WBC Count (T.L.C.)	2-3 cc Whole Blood in EDTA bottle
Toxoplasma Antibodies IgM	Serum or clotted blood 3-5 cc
Toxoplasma Antibody IgG	Serum or clotted blood 3-5 cc
Trichomonas Smear.	Swab in Sterile Saline tube
Thyroid Profile	**Serum or clotted blood 3-5 cc**
T.I.B.C	Serum or clotted blood 3-5 cc
T.S.H.	Serum or clotted blood 3-5 cc
Thyroid Profile	Serum or clotted blood 3-5 cc
Trophozoites	CSF/aspirate 1cc
Typhi Dot	Serum or clotted blood 3-5 cc
Triple Test (Unconjugted Estradiol,AFP,BHCG)	Serum or clotted blood 3-5 cc
Troponin-T	3cc blood in Lithium heparin or EDTA tube
U	
Urine Chemical Analysis	Random Urine
Urine Microscopy	Random Urine
Urine Protein Electrophoresis	Early morning first urine or 24 h urine collection
Urine Bile Pigments	Spot Urine
Urine Reducing Substances	Spot Urine
Urine Urea Nitrogen	24 hours urine collection
Urea Nitrogen, Serum	Serum or clotted blood 3-5 cc
Urea Nitrogen, Urine	24 Hours Urine collection
Uric Acid, Serum	Serum or clotted blood 3-5 cc
Uric Acid, Urine.	24 Hours Urine collection
Urinalysis (Urine RE)	Random Urine Specimen.
Urobilinogen	Random Urine Specimen.
Urine IgG	Random Urine
V	
Vanlyl Mandelic Acid (V.M.A.)	**24 h Urine Collection**
Valproic Acid. (Epilim)	Serum or clotted blood 3-5 cc
Vitamin 3_{12}	Serum or clotted blood 3-5 cc
Vitamin B_{12} & Folic Acid	Serum or clotted blood 3-5 cc
V.D.R.L – C.S.F.	C.S.F. 1-2 cc
V.M.A.	24 Hours Urine Collection.
Vancomycin	3cc clotted blood