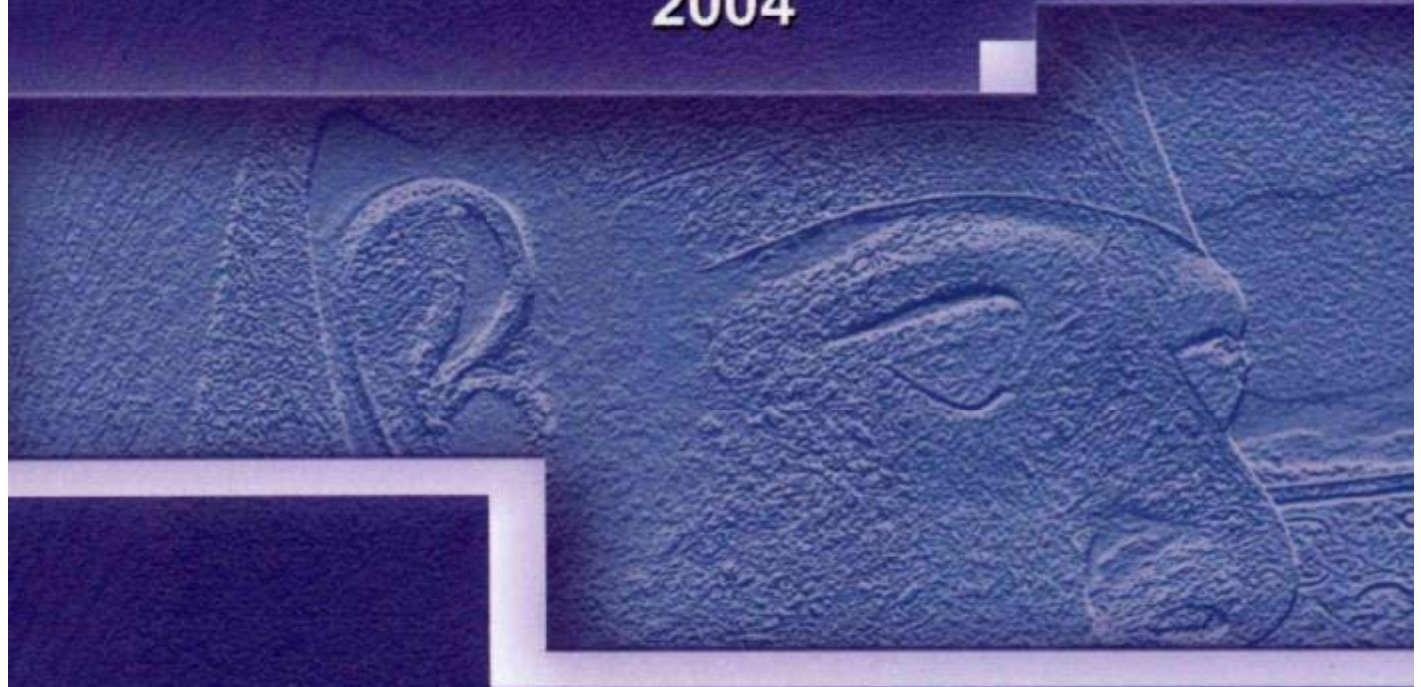


EGYPTIAN HYPERTENSION SOCIETY

**MANAGEMENT OF HYPERTENSION IN EGYPT  
AND DEVELOPING COUNTRIES**

**GUIDELINES**

2004



PRINCIPAL EDITOR

M. MOHSEN IBRAHIM, MD

السيد الزميل

يشكل مرض ارتفاع ضغط الدم أحد المشاكل الصحية الهامة في مصر وفي كثير من دول العالم الثالث، وعلى الرغم من هذا فإن المرض لا يلقى الاهتمام الكافي في مقررات الدراسة لطلبة الطب. بعد التخرج يجتهد الممارس والأخصائي باتباع الأسلوب العلاجي الذي قد يروق له بناءً على قراءته المحدودة في هذا المجال أو حسب خبرته الشخصية التي قد لا تعتمد على الدراسات العلمية. وقد اهتمت الجمعيات والهيئات العلمية في دول العالم الغربي بإصدار التوصيات والتوجيهات المختلفة لتشخيص وعلاج هذا المرض وتقوم هذه المؤسسات العلمية بمراجعة التوصيات بصفة دورية بناءً على ما استحدث في المجال العلمي، إلا أن التوصيات الموضوعة للأطباء في العالم الغربي لا تناسب الظروف الاقتصادية والاجتماعية في دول العالم الثالث هذا بالإضافة إلى اختلاف أسلوب المعيشة ونوعية الغذاء ومدى استجابة المرضى للعقاقير المختلفة لذلك كانت هناك ضرورة لإصدار توصيات خاصة لتشخيص وعلاج ضغط الدم للمرضى في مصر ودول العالم الثالث تأخذ في الاعتبار الفروق السابقة.

ولهذا قامت الجمعية المصرية لارتفاع ضغط الدم بوضع كتابها عن ضغط الدم المرتفع مساهمة منها في توعية الأطباء بالطرق العلمية الحديثة لتشخيص وعلاج هذا المرض وفيما يلي الملامح الرئيسية للتوصيات المصرية وما تتفرد به عن التوصيات العالمية الأخرى:

- التفرقة بين الحد الأدنى من الرعاية الطبية وبين الرعاية النموذجية، حيث تكون الظروف الاقتصادية والموارد المتاحة هي العامل الرئيسي في تحديد الفحوص المعملية ونوعية العلاج.
- الاهتمام الزائد بدقة قياس ضغط الدم.
- التركيز على ضرورة أخذ عدة قياسات للضغط وفي عدة زيارات مختلفة للطبيب.
- الاهتمام بعوامل الخطر الأخرى المؤدية إلى تصلب الشرايين والأزمات القلبية والمخية، واتخاذ القرار ببداية العلاج الدوائي وتحديد مستوى الضغط المطلوب الوصول إليه بناءً على هذه المعلومات.
- تحديد مستوى ضغط الدم المطلوب لبداية العلاج الدوائي.
- تغيير أسلوب المعيشة ونوعية الطعام كعامل رئيسي لعلاج مرض الضغط.
- اختيار العقاقير الأقل تكلفة كبداية لعلاج المرض.

# Main Features of Egyptian Hypertension Society Guidelines

## *Minimal VS Optimal Care*

Guidelines have to make a compromise between what is possible (minimal care) and what is ideal (optimal care). The limited resources of the health care system in developing countries will dictate that many of the recommendations developed in the wealthy industrial countries, have to be tailored and modified. It becomes imperative to direct drug treatment to individuals in the high and very high risk before considering their use in the lower risk patients. The EHS guidelines are introducing the new concept of minimal versus optimal care. The choice will depend upon available resources. Minimal care includes the least expensive diagnostic and therapeutic approaches while not compromising significantly the quality of care. For example, when it comes to assessment of high cardiovascular risk in a hypertensive subject, a minimal care policy will include only age, gender, family history, past history of atherosclerotic cardiovascular disease, smoking and body weight. Optimal care will require in addition lipid profile, blood sugar, ECG, serum creatinine and hs-CRP. The minimal care approach will depend on minimal laboratory investigations relying more on careful history and physical examination. A longer period of blood pressure monitoring before initiating drug therapy and higher threshold of blood pressure are recommended. It should be realized that even a small reduction in blood pressure is worthwhile if absolute targets prove difficult to achieve. Drugs for first choice are thiazide diuretics.

## *Blood Pressure Measurement*

Current guidelines stress the importance of accurate blood pressure measurement. It outlines the details of the technique and the precautions to be taken. Physicians and health professionals pay little attention to the conditions required for correct blood pressure readings. False and inaccurate readings are common due to inadequate preparation of the patient or to a faulty measurement technique. At least two measurements should be taken in an office visit and the lower reading is reported.

## *Repeated Blood Pressure Measurement*

A diagnosis of hypertension should be based upon a number of blood pressure readings, rarely it can be made during a single initial office visit. This will help avoid the white coat effect (isolated office hypertension).

A long period of follow-up and blood pressure monitoring is recommended before initiating drug therapy. Depending upon the initial blood pressure level and global risk profile, physician should monitor blood pressure over a period varying from one week to twelve month.

### *Global Risk Profile*

Similar to other guidelines the EHS stresses the importance of global risk assessment of hypertensive patients. Blood pressure unless it is very high is a poor predictor of future cardiovascular events. Evaluation of patients for presence of cardiovascular risk factors, TOD and associated cardiovascular atherosclerotic disease is mandatory for assessment of global risk profile. Patients in the high risk category need early and aggressive lowering of blood pressure. Treatment recommendations should be based on an absolute cardiovascular risk since benefits are related to reduction in absolute risk.

### *Blood Pressure Threshold for initiation of Drug Therapy*

This will depend upon the global risk profile. A more conservative approach is recommended with prolonged blood pressure monitoring and somewhat higher blood pressure threshold than other guidelines. This policy will increase cost effectiveness and avoid unnecessary treatment of low risk groups.

### *Life Style Modification*

Guidelines stress the role of dietary modification, exercise, weight control and limiting salt and alcohol intake. If followed carefully, this may limit the need and the dosage of drug therapy. Patient and public education is needed to avoid salty foods and reduce the amount of added salt in diet.

### *Drug Therapy*

Thiazide diuretics are the cornerstone of antihypertensive therapy. Unless there are very special indications for other agents they should be the initial treatment. However, the majority of patients will require drug combination such as thiazide- beta adrenergic blockers or thiazide-ACEI combination.

# GUIDELINES FOR MANAGEMENT OF HYPERTENSION IN EGYPT AND DEVELOPING COUNTRIES

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## Goal:

Improve hypertension detection, evaluation and management in Egypt and developing countries.

## Intended Users of Guidelines:

All internists, family physicians, general practitioners, cardiologists, obstetricians in Egypt and developing countries.

## Organization Responsible for Guidelines Development:

Egyptian Hypertension Society

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## INTRODUCTION

Six years ago, the Egyptian Hypertension Society produced its first guidelines for the management of hypertension. The success and popularity of this report were remarkable and it was in great demand. Since its publication in 1996, several guidelines for the management of hypertension were published. Many of these were recent revisions and updated versions of old ones that were modified according to new evidence from clinical trials. Research in the last decade provided an answer to many clinical questions. Now it is clear that isolated systolic hypertension in the elderly is dangerous and should be treated and that aggressive lowering of blood pressure is required in diabetic hypertensives. The optimal target blood pressure which should be achieved to obtain the best clinical outcome has been defined in many clinical situations. Blood pressure alone, unless very high, was a poor predictor of cardiovascular risk and the prognosis in hypertensive patients is influenced by other cardiovascular risk factors. Simple dietary interventions like providing plenty of fresh fruits and vegetables and limiting fat and dairy products can lower blood pressure even without decreasing body weight or limiting salt intake (DASH diet). There is accumulating new evidence supporting the favorable effect of the new classes of antihypertensive drugs on morbidity and mortality in hypertensive patients (ACE-inhibitors, calcium channel blockers, angiotensin receptor blockers). However, the recent results of ALLHAT study provide the proof that ACE-inhibitors, calcium channel blockers were equally effective as thiazide diuretics and on the contrary, thiazides were superior as first choice drugs regarding cost effectiveness.

The World Hypertension League and the International Society of Hypertension recommended that national hypertension societies develop their own guidelines that will adapt to the local circumstances and can be applied by the majority of clinicians in their everyday practice in their individual countries. This new edition of the Egyptian Hypertension Society guidelines took into consideration the cultural, and socioeconomic characteristics of Egyptians and many people in the developing world. In order to cover the wide spectrum of socioeconomic differences in developing countries, two approaches were selected for diagnosis and treatment depending upon the economic situation: the minimal and optimal hypertension care. The Egyptian Guidelines were designed to be user friendly,

written in a clear uniform style and in a reasonable concise size. The recommendations in guidelines are based upon the following sources:

1. Egyptian data: (a) Egyptian National Hypertension Project (NHP): This survey defined the prevalence of hypertension, other cardiovascular risk factors and hypertensive complications among Egyptians. (b) Results of the Egyptian multicenter antihypertensive drug study: The aim of the study was to compare the efficacy and tolerability of the four main antihypertensive groups: diuretics, ACE-inhibitors, beta blockers, and calcium antagonists. (c) The Egyptian physician and patient survey: The objectives of this survey were to identify physician and patient's attitudes and knowledge regarding hypertension, and reasons for non-compliance to therapy.
2. International literature, mainly the results of the recent randomized controlled studies.
3. Other national and international guidelines, the complete reports of the American JNC VI and JNC VII, British Hypertension Society Guidelines, Canadian Guidelines, WHO/ISH Guidelines, Japanese and South African Guidelines.

## Main Features of EHS Guidelines

### *Minimal VS Optimal Care*

Guidelines have to make a comparison between what is possible (minimal care) and what is ideal (optimal care). The limited resources of the health care system in developing countries will dictate that many of the recommendations developed in the wealthy industrial countries, have to be tailored and modified. It becomes imperative to direct drug treatment to individuals in the high and very high risk before considering their use in the lower risk patients. The EHS guidelines are introducing the new concept of minimal versus optimal care. The choice will depend upon available resources. Minimal care includes the least expensive diagnostic and therapeutic approaches while not compromising significantly the quality of care. For example, when it comes to assessment of high cardiovascular risk in a hypertensive subject, a minimal care policy will include only age, gender, family history, past history of atherosclerotic cardiovascular disease, smoking and body weight. Optimal care will require in addition lipid profile, blood sugar, ECG, serum creatinine and hs-CRP. The minimal care approach will depend on minimal laboratory investigations relying more on careful history and physical examination. A longer period of blood pressure

monitoring before initiating drug therapy and higher threshold of blood pressure are recommended. It should be realized that even a small reduction in blood pressure is worthwhile if absolute targets prove difficult to achieve. Drugs for first choice are thiazide diuretics.

### ***Blood Pressure Measurement***

Current guidelines stress the importance of accurate blood pressure measurement. It outlines the details of the technique and the precautions to be taken. Physicians and health professionals pay little attention to the conditions required for correct blood pressure readings. False and inaccurate readings are common due to inadequate preparation of the patient or to a faulty measurement technique. At least two measurements should be taken in an office visit and the lower reading is reported.

### ***Repeated Blood Pressure Measurement***

A diagnosis of hypertension should be based upon a number of blood pressure readings, rarely it can be made during a single initial office visit. This will help avoid the white coat effect (isolated office hypertension).

A long period of follow-up and blood pressure monitoring is recommended before initiating drug therapy. Depending upon the initial blood pressure level and global risk profile, physician should monitor blood pressure over a period varying from one week to twelve month.

### ***Global Risk Profile***

Similar to other guidelines the EHS stresses the importance of global risk assessment of hypertensive patients. Blood pressure unless it is very high is a poor predictor of future cardiovascular events. Evaluation of patients for presence of cardiovascular risk factors, TOD and associated cardiovascular atherosclerotic disease is mandatory for assessment of global risk profile. Patients in the high risk category need early and aggressive lowering of blood pressure. Treatment recommendations should be based on an absolute cardiovascular risk since benefits are related to reduction in absolute risk.

### ***Blood Pressure Threshold for initiation of Drug Therapy***

This will depend upon the global risk profile. A more conservative approach is recommended with prolonged blood pressure monitoring and somewhat higher

blood pressure threshold than other guidelines. This policy will increase cost effectiveness and avoid unnecessary treatment of low risk groups.

### *Life Style Modification*

Guidelines stress the role of dietary modification, exercise, weight control and limiting salt and alcohol intake. If followed carefully, this may limit the need and the dosage of drug therapy. Patient and public education is needed to avoid salty foods and reduce the amount of added salt in diet.

### *Drug Therapy*

Thiazide diuretics are the cornerstone of antihypertensive therapy. Unless there are very special indications for other agents they should be the initial treatment. However, the majority of patients will require drug combination such as thiazide-beta adrenergic blockers or thiazide-ACEI combination.

These guidelines were made through collaborative work of the twenty one members of the Egyptian Hypertension Society working group, whom I thank for their contribution. I would like to acknowledge the effort made by Dr. Karim Said, who made an outstanding job in helping me in the final editing of the guidelines manual. Also, I should mention the excellent secretarial work of Mrs. Rehab Mohamed. Finally, the support and generous grant offered by Aventis Egypt that helped in the production of this manual should be recognized.

Principal Editor,

M. Mohsen Ibrahim, MD  
Prof. of Cardiology- Cairo University  
President of the Egyptian Hypertension Society  
Cairo- April 2003

## METHOD OF PREPARATION OF THE GUIDELINES

Four specialized subgroups were formed in November 2001. Each subgroup was assigned to write a number of chapters and was chaired by a moderator section editor who represented the subgroup in the writing committee. Every author was asked to prepare a manuscript on the assigned subject. The guidelines working group met on several occasions discussing the contents of the individual chapters, reviewing literature and approving the writing policy. The preliminary guidelines were based upon the completed manuscripts. A pre-final document was prepared for discussion at the meeting held in Luxor during the period 6-9 December 2002. During this meeting each moderator read his assigned section to all the members of the working group, and then each subgroup revised separately the pre-final document. In a second plenary session, remarks, questions, comments and objections were discussed. Whenever there were points of disagreement, voting was applied and decisions were based upon majority approval. The pre-final document for each section was modified accordingly and was sent to the writing committee for the preparation of the final document.

When preparing the guidelines, authors were instructed that these guidelines are for the practicing physicians and not for the consultants, and should be written in a simple and clear language. Any important statements in guidelines should be supported, whenever possible, by evidence from literature.

# EXECUTIVE SUMMARY

## MAGNITUDE OF THE PROBLEM

- Hypertension is a major health problem in Egypt with a prevalence rate of 26.3% among the adult population ( $\geq 25$  years)<sup>1</sup>. Its prevalence increases with aging, approximately 50% of Egyptians above the age of 60 years suffer from hypertension. About seven million Egyptians had high blood pressure in the year 1993.
- Risks of hypertension include cardiovascular complications (heart failure, myocardial infarction, atrial fibrillation, aneurysms, dissection), renal (azotemia) and cerebrovascular (stroke, transient ischemic attacks "TIA", dementia), resulting in disability and premature death. These risks can be reversed by treatment and control of hypertension.
- Hypertension is poorly managed in Egyptians. The rates of awareness, treatment and control are low. Only 8% of hypertensive Egyptians have their blood pressure controlled<sup>1</sup>.

## NATIONAL GUIDELINES FOR DEVELOPING COUNTRIES

- Hypertension guidelines from rich industrial countries may not be applicable in developing and economically disadvantaged communities.
- Poverty, high illiteracy rate, inadequate health care system with limited access to medical insurance will limit hypertensive patient's care to the minimal acceptable level rather than the ideal or optimal western care recommended in international guidelines.
- Racial, genetic, life style and environmental differences between white Caucasian and black, dark or Asian populations will influence the hypertension mechanisms<sup>2</sup>, humoral profile<sup>3,4</sup>, type and extent of complications<sup>5,6</sup> (renal failure and stroke more common in blacks). Also, response to dietary therapy<sup>7,8</sup> (low salt, rich fruit and vegetable diet), and antihypertensive drugs (less control with ACE-inhibitors and beta adrenergic blockers in blacks)<sup>9,10</sup> varies.
- Risk factors for hypertension and atherosclerotic cardiovascular disease such as obesity, excess dietary salt intake, diabetes and cigarette smoking are particularly prevalent among Egyptians<sup>11</sup>.

- Compared to developed countries, hypertensive population in the developing world includes a large proportion of young and middle aged individuals because of the younger mean age<sup>1</sup>.

## MINIMAL VERSUS OPTIMAL CARE

- Resources more than science dictate the type of care that can be provided. Limited resources and economic factors will influence the level of management.
- Guidelines have to make a compromise between what is possible (minimal care) and what is ideal (optimal care), see tables 1, 2. This will have an impact on evaluation (getting the required information with the least expensive methods- relying more on detailed history and physical examination) and on the initiation and type of therapy (stressing dietary therapy, life style, use of less expensive drugs, and initiating therapy at higher thresholds of blood pressure).
- Even a small reduction in blood pressure is worthwhile if absolute targets prove difficult to achieve.

Table 1. Evaluation of Hypertensive Patients

	Minimal Care	Optimal Care
Detailed History- Physical Exam.	+++	++
Urine dipstick	+	+
Blood Sugar	±	+
ECG	±	+
Blood tests: urea, creatinine, lipid profile, K <sup>+</sup>	-	+
Optic Fundus	-	±

+++ : strongly recommended.

+: recommended.

- : not done

± : done if facilities are available.

Table 2. Therapy

	Minimal Care	Optimal Care
Duration of blood pressure monitoring before starting drug therapy	Weeks to months	Weeks to months
Life style and diet therapy	+++	++
Threshold Blood Pressure		
Low risk group	160/100	160/100
Intermediate risk group	150/90	140/90
High risk group	140/85	135/85
Drug of first choice	Small dose thiazide	Individualize
Target Blood Pressure		
Low & intermediate risk groups	< 140/90	< 140/90
High risk group	< 135/85	< 135/85

## DEFINITION AND CLASSIFICATION

- Levels of blood pressure 140 mmHg or more systolic and 90 mmHg or more diastolic represent the cut points for the current definition of hypertension.
- The following WHO/ISH classification of the levels of blood pressure (table 3) is recommended<sup>12</sup>.

Table 3. Classification of Blood Pressure Levels

Category	Systolic	Diastolic
Optimal	<120	< 80
Normal	<130	<85
High-normal	130-139	85-89
Grade 1 (Mild Hypertension)	140-159	90-99
Grade 2 (Moderate Hypertension)	160-179	100-109
Grade 3 (Severe Hypertension)	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	<90

## DIAGNOSIS OF HYPERTENSION

- Persistent elevation of systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg on at least five repeated blood pressure measurements in five office visits over a period varying from days

to months is required to make a diagnosis of hypertension. The frequency of visits and period of blood pressure monitoring will be dictated by the severity of hypertension and cardiovascular risk profile. Three visits are enough if the blood pressure is persistently above 160/100 mmHg or if target organ damage (TOD) is present.

- Failure to measure blood pressure accurately using a standardized technique and failure to realize the variable nature of blood pressure and office induced hypertension (white coat effect) will misclassify individuals.
- Levels of blood pressure measured at home or during daytime ambulatory recording should be less than 135/85 mmHg.

## BLOOD PRESSURE MEASUREMENT

- Use a calibrated, well maintained machine (mercury or aneroid).
- Examination done in a quiet room after five minutes rest in a relaxed position, avoiding talking, full bladder and withholding for two hours tobacco, eating and coffee.
- Use the appropriate cuff size, following a standardized measurement technique<sup>13</sup>, record the blood pressure to the nearest 2 mmHg in at least two measurements, take the lower reading.
- Use phase V (disappearance of sounds) for diastolic blood pressure.

## EVALUATION

- Assess cardiovascular risk and target organ damage (TOD) through a careful detailed history and physical examination with a detailed questioning about current medications. Body weight should be checked on each office visit.
- Urine dipstick analysis should be done in all patients and if possible blood sugar, and a standard 12 lead ECG.
- If blood testing facilities are available examine blood for urea, creatinine, potassium, hemoglobin, total cholesterol, HDL and LDL cholesterol and triglycerides.
- Echocardiography is not a part of the routine evaluation.
- An underlying cause (secondary hypertension) is suspected when hypertension is difficult to control (in spite of triple drug therapy), or if it is severe and of sudden onset particularly in a young subject or above the

age of 60 years or if there is rapid deterioration in kidney function. Referral to specialized facilities is needed in these conditions.

## RISK CATEGORIZATION

- Prognosis in hypertensive patients is highly variable depending largely on factors other than blood pressure such as sex, age, other risk factors, TOD, or history of cardiovascular disease<sup>14</sup>. Cardiovascular risk can vary more than ten folds at a given blood pressure level<sup>15</sup>.
- Hypertensive patients can be categorized according to their risk profile (adopted from JNC VI)<sup>16</sup>.

*Group A (low risk):* no TOD, no other risk factors and no associated cardiovascular disease.

*Group B (intermediate risk):* one or more additional risk factors but not diabetes or TOD (table 4).

*Group C (high risk):* diabetes, TOD and/or associated cardiovascular disease (table 5).

Table 4. Cardiovascular Risk Factors

- 
- Male gender.
  - Age > 65 years.
  - Current cigarette smoking.
  - Diabetes.
  - Total S- Cholesterol >240 mg/dl, HDL-C<40 mg/dl or LDL-C >160 mg/dl
  - Positive family history: atherosclerotic cardiovascular disease in first degree relative before the age of 40 years in males and 50 years in females.
- 

Table 5. Target Organ Damage and Associated Atherosclerotic Diseases

- 
- Left ventricular hypertrophy: by clinical, ECG, or echo.
  - Heart failure: clinical manifestations.
  - Coronary disease: angina, myocardial infarction, history of CABG or PCI.
  - Renal disease: serum creatinine >1.8 mg/dl, proteinuria.
  - Cerebrovascular disease: stroke, TIA, dementia.
  - Peripheral arterial disease.
  - Abdominal aortic aneurysm.
  - More than grade 1 optic fundus retinopathy.
-

## LIFE STYLE MODIFICATION

- Recommended in all hypertensive patients and should be the initial therapeutic approach in mild hypertension.
- Limit calorie intake in overweight individuals (BMI > 25 kg/m<sup>2</sup>) aiming at a weight reduction of 5 Kg.
- Limit salt (sodium chloride) intake to less than 6 gm/day.
- Encourage fruits and vegetables consumption (6-8 portions/day).
- Limit intake of total and saturated fats, encourage fish and fat free dairy products.
- Increase physical activity by regular exercise e.g. 30 minutes brisk walk/day.
- Combined diet, exercise and weight control may limit the need to drug therapy, allow step down or even discontinuation<sup>17</sup>.
- Limit alcohol intake and stop cigarette smoking.

## INITIATION AND MONITORING OF DRUG THERAPY

- Unless there is an emergency or blood pressure > 210/120 mmHg, no drug treatment should be instituted during the first two office visits so as to rule out the presence of "white coat" hypertension.
- Duration of blood pressure monitoring before initiating drug therapy varies depending upon blood pressure level, risk profile and response to life style modification.
- Threshold for antihypertensive drug treatment is 160/100 mmHg in low risk group, 140-150/90 mmHg for intermediate risk group and 135-140/85 mmHg in high risk group. The previous blood pressure cut points are the average of blood pressure readings taken on three separate office visits at least one week apart.
- Start with a small dose of thiazide diuretics in all patients with mild to moderate hypertension unless they are contraindicated or there are specific indications for other agents.
- In absence of adequate blood pressure response (fall in systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg) after one to two months of drug therapy, add another drug from a different pharmacologic group or use single dose combination.
- Treatment and follow-up should continue indefinitely.

- Recheck blood pressure at one to two monthly intervals until blood pressure remains at target level for two consecutive visits then recheck at 3 to 6 month intervals depending upon the risk profile.
- Antihypertensive drugs require a period of up to two months to achieve their maximal hypotensive effect<sup>18</sup>. Do not change drugs at short intervals.

## HYPERTENSION ASSOCIATED WITH TARGET ORGAN DAMAGE

- Treatment should be more aggressive in this group aiming at a target blood pressure less than 135/85 mmHg and initiated after a shorter monitoring period (two to four weeks).
- Drugs of first choice depend upon TOD:
  - Renal disease: ACE-inhibitors or angiotensin receptor blockers (ARBs)<sub>±</sub> thiazide diuretics (loop diuretic if serum creatinine is above 2.5 mg/dl).
  - Cerebrovascular disease: reduce the blood pressure after the acute phase of stroke by thiazide diuretic, and if necessary ACE- inhibitors, ARBs or Ca antagonist. Urgent blood pressure lowering is recommended in cerebral infarction if blood pressure is 220/120 mmHg or greater (180/105 mmHg in patients with cerebral hemorrhage). Do not lower mean blood pressure by more than 25% in the first two hours, then toward 160/100 mmHg within the next six hours.
  - Coronary disease: beta adrenergic blockers, ACE-inhibitors and if necessary Calcium antagonists.
  - Heart failure: ACE-inhibitors + thiazide diuretics.

## HYPERTENSION IN SPECIAL GROUPS

- Elderly: start with small dose of thiazide diuretics and add calcium antagonists or ARBs if necessary. Check blood pressure always in the supine and standing positions. Be aware of the marked fluctuations in blood pressure, the auscultatory gap when measuring blood pressure and the frequent comorbid conditions.
- Diabetes mellitus: initiate drug therapy within days after confirming the diagnosis of hypertension aiming at a target blood pressure of less than 140/85 mmHg, and even lower levels in presence of proteinuria. Start with ACE-inhibitors and add thiazide diuretics, calcium antagonists, beta

blockers or ARBs if necessary. In presence of proteinuria ARBs may replace ACE-inhibitors as initial therapy.

## COMPLIANCE

- Non compliance is probably the major cause of failure to control hypertension.
- Measures to improve compliance include patient education, use of less expensive medications, single daily dosage, fixed dose drug combination, continuous monitoring by spouse, nurse or doctor and home blood pressure self measurement.

## IMPLEMENTATION STRATEGIES

- Adoption of the guidelines by government agencies as the standard of care to be followed by physicians.
- Increase physician's awareness: printed material, seminars and meetings.
- Educational sessions with local opinion leaders nationwide.
- Reminder system and audit with feedback if available.

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# CHAPTER 1

## DEFINITION AND CLASSIFICATION OF HYPERTENSION

### DEFINITION

Upper acceptable limit for normal systolic blood pressure is less than 140 mmHg and for diastolic blood pressure less than 90 mmHg. These are arbitrary cut points since the relationship between blood pressure and cardiovascular risk is linear without a threshold and the risks start at levels as low as 110/80 mmHg.

### CLASSIFICATION

The classification followed in these guidelines is similar to that of the WHO/ISH with minor modifications (table 1).

The category of high normal blood pressure, although it is not within the spectrum of hypertension, should be identified and managed separately. Individuals with high normal blood pressure were found to be at significantly greater risk to develop future cardiovascular events than those with normal blood pressure. Clustering of cardiovascular risk factors (e.g., diabetes, dyslipidemia, obesity, impaired glucose tolerance) is more prevalent in this group than in individuals with normal blood pressure.

Table 1. Classification of Blood Pressure Levels

Category	Systolic	Diastolic
Optimal	<120	< 80
Normal	<130	<85
High-normal	130-139	85-89
Grade 1 (Mild Hypertension)	140-159	90-99
Grade 2 (Moderate Hypertension)	160-179	100-109
Grade 3 (Severe Hypertension)	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	<90

## DIAGNOSIS OF HYPERTENSION

- Diagnosis of hypertension is based upon at least five office visits over a period varying from days to months. The frequency of visits and period of blood pressure monitoring is dictated by the severity of hypertension and cardiovascular risk profile. Three visits are enough if the blood pressure is persistently above 160/100 mmHg or if target organ damage is present.
- Blood pressure should be measured accurately and under standardized conditions (see chapter 2).

## CHAPTER 2

### BLOOD PRESSURE MEASUREMENT

- ✓ Measure the blood pressure in the right arm while the patient is sitting with back supported or while lying flat on his back. Urine voided if needed. No food intake, coffee or smoking for two hour before the procedure. Talking should be avoided for 5 minutes prior to measurement.
- ✓ Appropriate cuff size and palpatory blood pressure measurement are essential.
- ✓ Take systolic blood pressure at first appearance of sounds at 3 consecutive beats. Take diastolic blood pressure at complete disappearance of sounds.
- ✓ Take the lower of at least two readings.

- Accurate blood pressure measurement is the only method for the diagnosis of hypertension.
- This procedure has many sources of inaccuracy, which commonly cause wrong decisions. Care must be given to all steps of the process.

#### THE SPHYGMOMANOMETER

There are three basic components to the sphygmomanometer: the manometer, the cuff and the connecting tubing, and the valve.

##### The Manometer

- The two commercially available types of manometer (mercury and aneroid) need periodic check.
- Aneroid manometers need to be calibrated against a subjected manometer using a T-tube. The mercury sphygmomanometer is subjected to mercury loss (leading to subnormal readings), introduction of air into the system (leading to bubbling and exaggerated readings), and breaking of the glass manometer tube (leading to injury and toxic hazards).
- With a deflated cuff, the manometer should read at the zero point. The mercury manometer should not bubble when the cuff is inflated while the

manometer is stable on a horizontal surface. The presence of air means that the manometer needs re-filling and re-calibration.

### The Cuff

- The cuff size must match the arm size to avoid tissue pressure dissipation that necessitates over-inflation, leading to false high readings if the cuff is too small.
- The width of the rubber bladder inside the fabric cuff (not the fabric itself) should be more than 40 % of the circumference of the mid-upper arm. The standard 12 cm cuff is good for most patients.
- For blood pressure measurement in adults, the physician should have at least one more cuff with 15 cm wide bladder for obese patients, and preferably a thigh cuff.
- Those taking care of children should possess a range of small cuffs.
- If the exact cuff size is lacking, it is better to use a larger than a smaller cuff.
- Rubber bladders and tubing may crack and leak with use, leading to poor control of inflation/deflation. The faulty piece must be changed.
- To exclude air leak from the system, make sure that the inflated cuff stays inflated at steady pressure when the valve is closed.

### The Valve

- Valve governs the deflation rate which is essential for accurate blood pressure measurement.
- To check for valve function, make sure that the inflated cuff stays inflated at steady pressure when the valve is closed and that it can be deflated smoothly and slowly with valve rotation between the index and thumb.

### THE STETHOSCOPE

- Tubing should be long enough for convenience but not more than 40 cm to prevent damping of sounds. There should be no air leak.
- The cone is better for listening to low frequency vibrations (the major component of the late stages of Korotkov sounds). The cone will – thus - be more accurate for sharp localization of sound disappearance, indicative of the diastolic blood pressure.
- The limitation of the cone is its limited field of reception. If it is not exactly over the brachial artery, it may miss some or all of Korotkov sounds.

- The diaphragm should only be used in the very obese arm when it becomes difficult to localize the brachial pulse in the antecubital region.

## BLOOD PRESSURE MEASUREMENT PROCEDURE

### Before Taking Blood Pressure

- The patient should avoid smoking, eating and coffee for at least two hours prior to measurement. Urine should be voided if necessary.
- Talking should be voided five minutes before and during blood pressure measurement.
- Blood pressure should be measured in a quiet room with comfortable temperature.

### Patient Position

- Blood pressure is to be measured in the supine or sitting positions. The abducted supinated arm should be at the heart level and supported on a pillow.
- In the sitting position, the back should be supported and the feet on the ground. The arm should be slightly flexed and supported on a desk.
- In the standing position, the arm should rest supported on either a high table, the shoulder of the examiner or in the armpit of the examiner, depending on the relative height of the patient and the examiner.
- In case of measuring the popliteal blood pressure, the patient should be in the prone position with the knee slightly flexed. The normal popliteal systolic blood pressure is about 20 mmHg higher than the brachial.

### The Procedure

- The cuff should be applied directly to the skin, with no clothing intervening. Tight sleeves should be taken off before cuff application.
- Palpate the brachial artery and center the bladder over the artery.
- Wrap the cuff tightly around the arm. The edge of the cuff should be 3 cm above the elbow crease.
- Close the valve and inflate the cuff first rapidly to about 70 mmHg, then by 10 mmHg at a time while the other hand feels for the radial pulse at the wrist. The pulse occlusion pressure (POP) is identified, and then release all pressure. Raise the arm above the level of the head for a few seconds to prevent venous engorgement.

- Close the valve and rapidly inflate the cuff to 30 mmHg above the POP identified from the previous step. Rapid inflation is essential to minimize venous engorgement which attenuates the Korotkov sounds. The cuff is then deflated slowly (at 2 mmHg/sec) while the cone of the stethoscope is firmly applied over the brachial artery but not touching the tubing or the cuff.
- The mercury manometer should be viewed from a distance of 1-3 feet and the eye level should be at the mid-point of the manometer. It is not essential to keep the manometer at heart level. The upper level of the convex top of the mercury column should be taken as the height of that column. For the aneroid sphygmomanometer, similar viewing distance should be observed.
- Record the blood pressure to the nearest 2 mmHg.

### The Korotkov Sounds

*Stage I:* appearance of sound, read as systolic blood pressure.

*Stage IV:* sudden reduction of sound, read as diastolic blood pressure when there is a wide pulse pressure (anemia, aortic incompetence, etc ...) or when sounds continue to zero blood pressure.

*Stage V:* disappearance of all sound, read as diastolic blood pressure in all other patients.

### *Augmentation of the Korotkov Sounds*

- Occasionally the Korotkov sounds are damped. This occurs when the cuff has been repeatedly inflated with incomplete deflation (resulting in venous stasis with poor reflow) and occasionally with an obese arm.
- Two maneuvers can augment Korotkov sounds:
  - Before inflation, raise the arm above head level to enhance venous emptying. Inflate the cuff with the arm still elevated. Lower the arm to the heart level and proceed as usual.
  - After inflation, ask the patient to open and clench the fist several times. This leads to metabolite-induced vasodilatation with better run-off with cuff pressure release.

## SPECIAL PRACTICAL ISSUES

### How Many Readings?

- Take the lower of at least two readings 1-2 minutes apart. If the difference in systolic or diastolic blood pressure between these two readings is more than 6 mmHg, a third reading is needed, and the lowest reading is taken.

### One or Both Arms? Which Arm?

- If the radial pulse volume is equal in both arms, the right arm blood pressure is measured.
- The arm with neuromuscular disease, skeletal deformity or vascular abnormality (venous or lymphatic obstruction, arteriovenous fistula or dialysis shunt) should be avoided.
- Use the same arm and same body position in the follow - up.

### Supine, Sitting or Standing Blood Pressure?

- There is usually no difference between supine and sitting blood pressures. However, the standing blood pressure should be taken in the following situations to detect postural hypotension:
  - First visit evaluation.
  - Elderly patients (above 60 years).
  - Diabetic patients of any age.
  - Patients with postural symptoms; dizziness, light headedness or faintness.
  - Patients on potent vasodilators or large doses of diuretics.
- The standing blood pressure should be measured two minutes after standing.

### Rhythm disturbances:

- With an irregular pulse (atrial fibrillation, frequent premature beats) take the average of four blood pressure readings or equate systolic blood pressure with the consistent presence of sounds.
- With a profoundly slow pulse (e.g., complete heart block):
  - Slower deflation is needed, drop pressure extremely slowly at about 2 mmHg/heart beat. Rapid cuff deflation can cause false low readings of both systolic and diastolic blood pressure.
  - Systolic hypertension is common with profound bradycardia. The clinical implication of these pressures is not known.

### Special Considerations for Elderly Patients:

- The auscultatory gap (a phase of silence after sound appearance, followed by reappearance) is more frequent in the elderly. This leads to a serious error if palpatory blood pressure is not taken prior to auscultation. Cuff

inflation to a level within this gap leads to under-estimation of systolic blood pressure.

- Stiff arterial walls may cause over-estimation of blood pressure (pseudohypertension). This phenomenon should be suspected when:
  - Target organ damage is absent despite high blood pressure readings.
  - Symptoms of hypotension while sphygmomanometer pressure is high.
  - Arterial wall is felt while inflating sphygmomanometer cuff above systolic pressure and absence of arterial pulsations (Osler maneuver).
  - Resistant hypertension in the elderly.

**Ambulatory Blood Pressure Monitoring** (see chapter 4).

**Home Blood Pressure Measurement** (see chapter 13).

## CHAPTER 3

### CLINICAL AND LABORATORY EVALUATION

- Hypertension, unless complicated, is asymptomatic disease. Diagnosis depends upon accurate and repeated measurements of blood pressure.
- The objective of clinical and laboratory evaluation is to establish the presence of hypertension, identify other cardiovascular risk factors, diagnose target organ damage, and detect secondary forms of hypertension.

#### AIM of EVALUATION

- Establishment of the diagnosis of hypertension.
- Assessment of global cardiovascular risk.
- Evaluation of target organ damage.
- Diagnosis of secondary causes of hypertension.

#### VALUE OF EARLY RECOGNITION OF HYPERTENSION

- Blood pressure level is linearly and continuously related to the risk of cardiovascular diseases and stroke.
- Target organ damage occurs early in the hypertensive process.
- Hypertension commonly occurs in association with other risk factors which interact synergistically to multiply cardiovascular risk.

#### MEDICAL HISTORY

- In most patients, uncomplicated hypertension causes no significant symptoms.
- Physician should inquire specifically about:
  - Previous levels of high blood pressure with and without treatment.
  - Symptoms of target organ damage.
  - Symptoms suggestive of secondary forms of hypertension (see chapter 4).
  - Current drug intake (e.g., contraceptive pills, non-steroid anti-inflammatory agents, etc.) (see chapter 5).

- Comorbid conditions (diabetes, bronchial asthma, gout, migraine, depression, sexual dysfunction, etc.).
- Family history of diabetes, coronary artery disease, stroke or renal disease.
- Life style factors: salt and fat intake, smoking, physical activity and alcohol consumption.

## CLINICAL EXAMINATION

- Establish the diagnosis of high blood pressure by using proper measurement procedure (see chapter 2).
- Peripheral pulses should be palpated. Document that the femoral pulse are not delayed beyond the radial pulse.
- Listen for neck bruits.
- Cardiac examination for left ventricular enlargement, third heart sound, loud aortic closure sound and ejection murmur over the aortic area. Carefully look for aortic incompetence murmur.
- Abdominal examination for renal enlargement, abdominal aortic aneurysm or bruits. Abdominal bruits are more suggestive of renal artery stenosis when they are lateralizing and continuous (systolic-diastolic).
- Chest examination for evidence of obstructive airway disease.
- Neurologic examination for level of consciousness, speech, motor power, lateralization and peripheral neuropathy. Profound muscle weakness with intact sensory function in a hypertensive patient should suggest primary aldosteronism.
- Optic fundi should be examined whenever possible (and in all patients with severe or resistant hypertension).
- Body weight and height to assess body mass index (normal value < 25 kg/m<sup>2</sup>). Waist circumference should be recorded whenever possible.

## LABORATORY TESTS

### The Standard-Optimal- Care

- Urine examination by dipstic and microscopic examination of the sediment.
- Serum potassium.
- Serum creatinine.
- Fasting plasma glucose

- Hemoglobin.
- Serum uric acid.
- Lipid profile (twelve hours fasting serum total cholesterol, HDL-C, LDL-C, and triglycerides).
- Standard 12-lead ECG.

#### The Minimum Evaluation Care

- Urine examination by dipstick.
- Electrocardiogram (if possible).
- Fasting plasma glucose (if possible).

#### Optional Tests

- More extensive investigations are indicated in the following conditions:
  - When secondary forms of hypertension are suspected.
  - To determine the significance of borderline hypertension by screening for target organ involvement.
  - When symptoms are suggestive of target organ damage.
- Extensive investigations include echocardiography, abdominal and peripheral ultrasonographic examination, testing for microalbuminuria, ambulatory blood pressure recording and specific (goal-oriented testing) for suspected secondary hypertension (see chapter 5) or a hypertensive complication (see chapter 9).

## CHAPTER 4

### SPECIAL DIAGNOSTIC METHODS

#### ECHOCARDIOGRAPHY

- Echocardiography is the most accurate non-invasive procedure to evaluate the cardiac effects of systemic hypertension. It is superior to radiography and electrocardiography in detection and quantification of left ventricular hypertrophy.
- A decision to initiate therapy may be based on the echocardiographic detection of left ventricular hypertrophy in borderline hypertensive patients without evidence of left ventricular hypertrophy by electrocardiogram.

#### Indications

- Echocardiography is not a routine test. The recommended indications in hypertension are:
  - Symptoms or signs of cardiovascular disease.
  - ECG abnormalities.
  - To guide therapeutic decision in some patients with mild or borderline hypertension.
- Echocardiography is not indicated for follow-up of left ventricular hypertrophy.

#### Limitations

- Operator dependent. Training and experience are required for precise measurement of internal chamber dimensions and wall thickness.
- Cost-effectiveness is questionable.

## AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory measurement provides a large numbers of measurements over prolonged periods of times, (usually 24 hours) which can give a profile of blood pressure. Ambulatory blood pressure monitoring provides three types of information:

- The average of true level of blood pressure which is the measure responsible for most of the adverse effects of hypertension.
- The diurnal rhythm of blood pressure.
- The short term variability of blood pressure.

### Equipment

- A large variety of use for that measurement are available. Physician should us only devices hat have been validated according to the standard protocol of the British Hypertension Society or the US Association for the Advancement of the Medical Instrumentation.
- In clinical practice, measurements are usually made at half hourly interval so as not to interfere with activity during the day and with sleep at night, but measurement can be made more frequently if necessary.
- Data display should include mean daytime and night-time and 24 hour systolic and diastolic blood pressure, as well as mean heart rate, and plot of the data in a diagram.

### Normal Value

- Normal mean 24 hour and awake ambulatory blood pressure values are less than 135/85 mmHg and 140/90 mmHg, respectively.

### Indications

- Suspected white coat hypertension.
- Resistant hypertension.
- Borderline hypertension with target organ damage.
- Symptoms suggestive of hypotension.
- Paroxysmal hypertension.

## Limitations

- Expensive.
- Repeated calibration is needed.
- Definitions of normal and abnormal are not established.
- There is insufficient evidence at present to recommend ambulatory blood pressure monitoring for routine clinical use or decision making.

## Recommendations

- Ambulatory blood pressure monitoring should be considered when indicated (listed above).
- Physician should only use ambulatory blood pressure monitoring devices that have been validated independently using established protocols.

## CHAPTER 5

# SECONDARY HYPERTENSION

### PREVALENCE

- Secondary hypertension accounts for less than 5% of all causes of hypertension.
- A higher prevalence may be present in tertiary care referral centers.

### CAUSES OF SECONDARY HYPERTENSION

#### Drugs

#### Renal Causes:

- Chronic renal parenchymal disease (3-5 %).
- Renal artery stenosis (1-2%).

#### Endocrinal Causes:

- Primary hyperaldosteronism (< 0.3%).
- Hyper- or hypothyroidism.
- Pheochromocytoma (<0.3%).
- Cushing syndrome.

#### Aortic Coarctation.

#### Other Causes:

- Central nervous system diseases e.g., brain tumor.
- Sleep apnea, acute porphyria, polycythemia vera.
- Rare congenital endocrinal and renal tubular disorders.

#### Drug-induced Hypertension:

A wide variety of medications may produce drug-mediated hypertension that is correctable once the condition is recognized and the offending agent withdrawn (table 2). These drugs can be divided into three categories:

#### *Vasoconstrictors*

Phenylephrine, pseudoephedrine, phenylpropanolamine (used in cough mixtures and cold medications) and other sympathomimetic amines, anti-adrenergic agents withdrawal, appetite suppressants, and monoamine oxidase inhibitors treatment combined with tyramine-containing foods or medications.

### *Volume expanders*

Glucocorticoids, estrogens especially at high doses as in oral contraceptives, non-steroidal anti-inflammatory agents that inhibit prostaglandins.

### *Miscellaneous*

Psychotropic drugs that interfere with sympatholytic antihypertensive agents, cyclosporine, immunosuppressants, and erythropoietin (used in treatment of anemia in end stage renal disease).

**Table 2. The Common Drugs That Cause or Exacerbate Hypertension**

- 
- Non-steroidal anti-inflammatory drugs
  - Contraceptive pills
  - Cold and flu medicines
  - Glucocorticoids
- 

## **EVALUATION FOR IDENTIFIABLE CAUSES OF HYPERTENSION**

Several clinical and laboratory features suggest a more extensive work-up for secondary hypertension (table 3). However, most of the features are non-specific and - in view of the low frequency of secondary hypertension - the selection of patients for further evaluation should be based on reasonable doubt.

### Table 3. Clues for Secondary Forms of Hypertension

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- Onset of hypertension before age 25 or after age 60 years.
  - Sudden onset, change from normal blood pressure to severe hypertension in less than a year.
  - Resistant hypertension.
  - Poor response to prior effective drug therapy.
  - Paroxysmal attacks of hypertension with palpitation, pallor, sweating and tremors.
  - Multiple system involvement on initial evaluation.
  - Delayed and weak femoral pulses with lower blood pressure in the lower extremities.
  - Continuous abdominal bruit.
  - Renal masses.
  - Advanced end organ damage: more than grade 2 retinopathy or serum creatinine >2.0 mg/dl .
  - Laboratory abnormalities: (e.g., hypokalemia, or hypercalcemia).
- 
- Table 4 summarizes the important clinical clues and diagnostic tests of some forms of secondary hypertension.

Table 4. Summary of Diagnosis and Treatment of Some Forms of Secondary Hypertension

Cause and Frequency	Clinical Clues	Screening Test	Definitive Test	Treatment
renal parenchymal hypertension (3-5 %)	<ul style="list-style-type: none"> <li>- History of renal disease</li> <li>- Abnormal urine sediments</li> </ul>	<ul style="list-style-type: none"> <li>Urinary sediments, pyuria, elevated creatinine.</li> </ul>	<ul style="list-style-type: none"> <li>- Abdominal ultrasonography.</li> <li>- Radiologic examination.</li> <li>- Renal biopsy.</li> </ul>	<ul style="list-style-type: none"> <li>- Drug therapy for hypertension.</li> <li>- Specific urologic treatment.</li> </ul>
renovascular hypertension. (< 2%)	<ul style="list-style-type: none"> <li>- Onset before 30 or after 50 years.</li> <li>- Abrupt onset.</li> <li>- Resistant hypertension.</li> <li>- Multi-site atherosclerosis.</li> <li>- Abdominal bruit.</li> <li>- Flash pulmonary edema.</li> <li>- Azotemia on ACE-I</li> </ul>	<ul style="list-style-type: none"> <li>Captopril renography                             <ul style="list-style-type: none"> <li>- <i>sensitivity</i> 83%</li> <li>- <i>specificity</i> 93%</li> </ul> </li> <li>Renal Duplex                             <ul style="list-style-type: none"> <li>- <i>sensitivity</i> 95%</li> <li>- <i>specificity</i> 93%</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Renal arteriography</li> <li>- Digital subtraction angiography.</li> <li>- Spiral CT*</li> </ul>	<ul style="list-style-type: none"> <li>- Angioplasty + stenting</li> <li>- Drug therapy</li> <li>- Surgery</li> </ul>
aortic Coarctation (< 0.5%)	<ul style="list-style-type: none"> <li>- Delayed / absent femoral pulse</li> <li>- ↓ arm / leg blood pressure difference</li> <li>- LVH**</li> <li>- Precordial systolic ejection murmur</li> <li>- Systolic / continuous back murmur</li> </ul>	<ul style="list-style-type: none"> <li>- Chest X-ray: rib notching</li> <li>- ECG: LVH**</li> <li>- Echocardiography</li> </ul>	<ul style="list-style-type: none"> <li>- Aortography.</li> </ul>	<ul style="list-style-type: none"> <li>- Surgical repair.</li> <li>- Balloon angioplasty.</li> </ul>

<p>Primary aldosteronism (<math>\leq 0.5\%</math>)</p>	<ul style="list-style-type: none"> <li>- Polyuria</li> <li>- Muscle weakness</li> </ul>	<ul style="list-style-type: none"> <li>- Hypokalemia</li> <li>- Excess urinary <math>K^+</math> loss</li> </ul>	<ul style="list-style-type: none"> <li>- High plasma and urinary aldosterone, not suppressible</li> <li>- Low renin, persistent with standing or frusemide</li> <li>- CT* / MRI†</li> </ul>	<ul style="list-style-type: none"> <li>- Surgical removal</li> <li>- Frusemide + spironolactone</li> </ul>
<p>Pheochromocytoma (<math>\leq 0.3\%</math>)</p>	<ul style="list-style-type: none"> <li>- Paroxysmal hypertension</li> <li>- Headache, chest or abdominal pain</li> <li>- Sweating, palpitations, pallor</li> </ul>	<ul style="list-style-type: none"> <li>- 24h urinary metanephrin &amp; normetanephrin (<i>sensitivity and specificity &gt;95%</i>).</li> </ul>	<ul style="list-style-type: none"> <li>- CT* / MRI† / MIBG scan‡</li> <li>- Angiography</li> </ul>	<ul style="list-style-type: none"> <li>- Surgical removal after medical preparation.</li> </ul>

\* CT: Computerized Tomography.

† MRI: Magnetic Resonance Imaging.

\*\* LVH: Left Ventricular Hypertrophy.

‡ MIBG:  $^{131}I$ - Metaiodobenzylguanidine.

## CHAPTER 6

### INITIATION AND MONITORING OF ANTIHYPERTENSIVE THERAPY

- ✓ Drug therapy is initiated after establishing:
  - The diagnosis of hypertension.
  - That life style modification alone is not enough to normalize blood pressure.
  - That treatment is cost effective.
- ✓ Unless there is an emergency or urgency, a period of observation and blood pressure monitoring varying from one week up to twelve months may be needed before starting drug treatment.
- ✓ Assessment of absolute cardiovascular risk i.e. probability of developing a serious cardiovascular event in the coming years will guide the need and urgency of drug therapy. Priority is given to high risk patients.
- ✓ Cardiovascular risk profile depends upon the presence of: 1. Clinical atherosclerotic cardiovascular disease. 2. Target organ damage. 3. Number and severity of other cardiovascular risk factors. 4. Diabetes mellitus 5. Level of blood pressure.
- ✓ Threshold blood pressure required to start drug intervention varies from 135/85 to 160/100 mmHg depending upon the global cardiovascular risk profile.

#### ASSESSMENT OF CARDIOVASCULAR RISK PROFILE

- While establishing the diagnosis of hypertension, the physician should assess the global risk profile of the patient. This approach will guide the therapeutic policy, timing and threshold for initiation of drug therapy and aggressiveness of blood pressure lowering.
- The risk of cardiovascular disease in patients with hypertension is determined not only by the level of blood pressure but also by the presence or absence of target organ damage, other cardiovascular risk factors, associated clinical conditions and diabetes. These factors independently modify the risk of

subsequent cardiovascular diseases and are used for empiric classification of patients with hypertension into risk groups for therapeutic decisions.

### Cardiovascular Risk Categorization

Depending upon the global risk profiling, hypertensive patients can be categorized into three groups:

**Risk Group A** (Low risk): patients with no other cardiovascular risk factors, no target organ damage or associated atherosclerotic cardiovascular diseases.

**Risk Group B** (Intermediate risk): patients with risk factors (not including diabetes) but with no target organ damage or associated atherosclerotic cardiovascular diseases.

**Risk Group C** (High risk): patients with diabetes, target organ damage or associated atherosclerotic cardiovascular diseases.

#### Table 5. Cardiovascular Risk Factors

- 
- Diabetes mellitus: fasting plasma glucose  $\geq 126$  mg/dl (blood glucose  $\geq 110$  mg/dL) on two occasions, or receiving treatment.
  - Age  $> 65$  years.
  - Total S- Cholesterol  $>240$  mg/dl, HDL-C $<40$  mg/dl or LDL-C  $>160$  mg/dl.
  - Current cigarette smoking.
  - Family history of atherosclerotic cardiovascular diseases in a first degree relative (parents or siblings) before the age of 40 years in males and 50 years in females.
  - Male gender.
- 

#### Table 6. Target Organ Damage and Associated Atherosclerotic Diseases

- 
- Left ventricular hypertrophy: by clinical, ECG, or echo.
  - Heart failure: clinical manifestations.
  - Coronary disease: angina, myocardial infarction, history of CABG or PCI.
  - Renal disease: serum creatinine  $>1.8$  mg/dl, proteinuria.
  - Cerebrovascular disease: stroke, TIA, dementia.
  - Peripheral arterial disease.
  - Abdominal aortic aneurysm.
  - More than grade 1 optic fundus retinopathy.
-

## INITIATION OF ANTIHYPERTENSIVE DRUG THERAPY

- Unless there is an emergency or blood pressure > 210/120 mmHg, no drug treatment should be instituted during the first two office visits so as to rule out the presence of "white coat" hypertension.
- Duration of blood pressure monitoring before initiating drug therapy varies depending upon blood pressure level, risk profile and response to life style modification (table 7).
- Threshold for antihypertensive drug treatment is 160/100 mmHg in low risk group, 140-150/90 mmHg for intermediate risk group and 135-140/85 mmHg in high risk group (table 8). The previous blood pressure cut points are the average of blood pressure readings taken on three separate office visits at least one week apart.

Table 7. Duration of Observation Period (life style modification) before Initiating Drug Therapy

Risk Group	Blood Pressure (mmHg)		
	140-159/90-99	160-179/100-109	≥180/110
Low Risk (A)	12 months	6 months	1-3 weeks
Intermediate Risk (B)	6 months	3 months	1 week
High Risk (C)	3 months	1 month	< 1 week

Table 8. Threshold for Initiating Therapy after an Observation Period

Risk Group	Threshold	
	Minimal Care	Optimal Care
Low Risk	160/100 mmHg	160-100 mmHg
Intermediate Risk	150/90 mmHg	140/90 mmHg
High Risk	140/85 mmHg	135/80 mmHg

## SELECTION OF ANTIHYPERTENSIVE AGENTS

- Start with a small dose of thiazide diuretics in all patients with mild to moderate hypertension unless they are contraindicated or there are specific indications for other agents.
- In severe cases (blood pressure > 180/110 mmHg), it is recommended to start by more than one drug or a fixed dose combination (should include a diuretic) and to increase the dose or add a third drug if blood pressure remains elevated above target level after 4-8 weeks.

### Factors Influencing Choice of First Drug

#### *Target Organ Damage and Associated Cardiovascular Diseases*

- Renal disease: ACE-inhibitors or angiotensin receptor blockers (ARBs)<sub>±</sub> thiazide diuretics (loop diuretics if serum creatinine is above 2.5 mg/dl).
- Coronary disease: beta adrenergic blockers, ACE-inhibitors and if necessary calcium antagonists.
- Heart failure: ACE-inhibitors and thiazide diuretics.
- After stroke: thiazide diuretics.
- Peripheral arterial disease: calcium antagonists.

#### *Other Cardiovascular Risk Factors*

- Elderly: start with small dose of thiazide diuretics and add calcium antagonists or ARBs if necessary. Check blood pressure always in the supine and standing positions. Be aware of the marked fluctuations in blood pressure, the auscultatory gap when measuring blood pressure and the frequent comorbid conditions.
- Diabetes mellitus: initiate drug therapy within days after confirming the diagnosis of hypertension aiming at a target blood pressure of less than 140/85 mmHg, even lower levels in presence of proteinuria. Start with ACE-inhibitors and add thiazide diuretics, calcium antagonists, beta blockers or ARBs if necessary. In presence of proteinuria, ARBs may replace ACE-inhibitors as initial therapy.
- Hypercholesterolaemia: alpha adrenergic blockers, central alpha agonists, calcium antagonists, ACE-inhibitors.

#### *Concomitant Disease*

- Obesity: thiazide diuretics.
- Benign senile prostatic hypertrophy: alpha adrenergic blockers.

- Migraine: beta-adrenergic blockers.
- Essential tremors: beta-adrenergic blockers.
- Anxiety, tachycardia, hyperdynamic heart: beta-adrenergic blockers.
- Supraventricular tachyarrhythmias: non- dihydropyridine calcium antagonists.

## TARGET BLOOD PRESSURE

- Target blood pressure varies from 135/85 to 140/90 mmHg depending upon risk profile:
  - *Low and intermediate risk groups:* below 140/90 mmHg
  - *High risk group:* below 135/85 mmHg.

## MONITORING OF DRUG THERAPY

- Antihypertensive drugs require a period of up to two months to achieve their maximal hypotensive effect. Do not change drugs at short intervals.
- Recheck blood pressure at one to two monthly intervals until blood pressure remains at target level for two consecutive visits then recheck at 3 to 6 month intervals depending upon the risk profile.
- In absence of adequate blood pressure response (fall in systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg) after one to two months of drug therapy add another drug from a different pharmacologic group or use single dose combination.
- Treatment and follow-up should continue indefinitely. The frequency of visits to doctors' office depends upon level of blood pressure and risk profile.

## CHAPTER 7

### NON PHARMACOLOGIC THERAPY OF HYPERTENSION

- ✓ Lose weight if overweight.
- ✓ Reduce salt intake to no more than 6 gm of sodium chloride/ day.
- ✓ Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
- ✓ Maintain adequate intake of dietary calcium for general health
- ✓ Encourage intake of diet rich in fresh fruits, vegetables, and in low-fat dairy products with a reduced content of saturated and total fat.
- ✓ Stop alcohol or limit intake to no more than one-two drinks/ day.
- ✓ Stop smoking.
- ✓ Increase physical activity (30-45 minutes) of brisk walking most days of the week.
- ✓ Limited evidence supports the role of calcium and magnesium, or stress management.
- ✓ Management of other cardiovascular risk factors.

- Non pharmacological interventions (life style modification) are beneficial in reducing a variety of cardiovascular risk factors including high blood pressure. They may also reduce the dosage requirements of antihypertensive drugs.
- Life style modification should be recommended in all hypertensive patients initially and as an adjunct to drug therapy.

*A reasonable generalized approach for all patients includes:*

1. Weight reduction for the overweight patient.
2. Reduced dietary intake of sodium, fat and increased calcium, potassium, vitamins, fish oil and fibres from food sources.
3. Regular physical activity.
4. Smoking cessation.
5. Moderation of alcohol consumption.

## WEIGHT REDUCTION

### Rationale

- Excess body weight (body mass index of 27 or greater) is correlated closely with increased blood pressure.
- Excess fat in the upper parts of the body (visceral or abdominal), defined as waist circumference  $\geq 85$ cm in women or  $\geq 98$ cm in men, increases the risk of hypertension, dyslipidemia, diabetes and cardiovascular mortality.
- One kilogram decrease in body weight is accompanied by an average reduction of 1.6 and 1.3 mmHg in systolic and diastolic blood pressure respectively.
- Possible mechanisms of hypertension in obesity include: increased blood volume, hyperinsulinaemia, and increased sympathetic activity.

### Recommendations

- All hypertensive patients should maintain normal body weight (body mass index: 18.5-24.9 kg/m<sup>2</sup>).
- A reasonable goal is to decrease body weight by 5 kg over 4-6 month period. This reduction in body weight will decrease the blood pressure and improve the cardiovascular risk profile.
- General guidelines to reduce calories:
  - Prepare all foods without addition of butter, margarine, fat, oil or sugar.
  - Limit servings to 3 meals a day and one small snack in the afternoon. Avoid continuous eating or snacking.
  - Limit portion sizes.
  - Avoid high caloric foods: Candy, cookies, pies, pastries, carbonated beverages (e.g., coca cola), nuts, chips, dried fruits.
  - Avoid appetizers.

## MODERATION OF DIETARY SODIUM

### Rationale

- Increased sodium in diet has been associated with increased incidence of future cardiovascular events.
- Sodium, in the form of sodium chloride or table salt, is linked to levels of blood pressure.
- Moderate sodium restriction increases the efficacy of all classes of antihypertensive drugs (with the exception of calcium channel blockers).

- Other favorable effects: protection from diuretic induced hypokalaemia, left ventricular hypertrophy regression, and improvement of renal function.

### *Salt Sensitivity:*

- Hypertensive patients can be classified into salt sensitive and salt resistant individuals.
- Salt sensitivity is present in 40% of patients with essential hypertension.
- Salt sensitivity is more common in the following groups:
  - Elderly.
  - Blacks.
  - Insulin dependent diabetes.
  - Secondary hypertension: hyperaldosteronism .

### Recommendations

Moderate sodium reduction to a daily level of no more than approximately 6 gm of sodium chloride is recommended (table 9).

**Table 9. Guidelines for Moderate Salt Restriction (6gm Na chloride/day)**

- Avoid foods containing more than 300 mg sodium per portion e.g. salted cheese, pickles, salted fish, sardines, anchovy, olives and salted nuts and popcorns.
- Substitute natural foods for processed foods.
- Do not add sodium chloride to food during cooking or on table.
- Avoid the use of fast foods e.g. hamburger, pizza, chips.
- Recognize the Na content of some antacids and other medications e.g. Alka-selzar contains more than 500 mg of Na.

## POTASSIUM INTAKE

### Rationale

- Epidemiologic and clinical studies have implicated potassium depletion in the pathogenesis and maintenance of essential hypertension.
- High dietary potassium intake may protect against developing hypertension and improve blood pressure control in patients with hypertension.

### Recommendations

- Maintenance of adequate potassium intake  $> 90$  mmol/d, preferably from dietary sources, is recommended for hypertensive persons.
- A diet rich in fruits and vegetables (DASH Diet) is superior to taking pills or other supplements as potassium sources (table 10).
- Potassium supplements should be avoided in patients with renal insufficiency, or those taking potassium sparing diuretics, ACE inhibitors, or ARBs.

Table 10. Foods Rich in Potassium

Highest content ( $> 1000$  mg [ $25$  mmol]/ $100$  g)

- Dried figs
- Molasses

Very high content ( $> 500$  mg [ $12.5$  mmol]/ $100$ g)

- Dried fruits (dates, prunes)
- Nuts
- Avocados
- Bran cereals
- Wheat germ

High content ( $> 250$  mg [ $6.2$  mmol]/ $100$  g)

- Vegetables: spinach, tomatoes, broccoli, winter squash, beets, carrots, cauliflower, potatoes.
- Fruits: bananas, cantaloupe, kiwis, oranges, mangos.
- Meat.

## CALCIUM AND MAGNESIUM INTAKE

There is currently no rationale for recommending calcium or magnesium supplements to prevent or treat hypertension. However, calcium or magnesium deficiency should be avoided.

## OTHER DIETARY FACTORS

- DASH Diet (table 11): the dietary approach to stop hypertension (DASH) trial showed a reduction in blood pressure of 11.4/5.5 mmHg in hypertensive persons maintained on a diet rich in fruits and vegetables and low fat dairy products compared with control subjects maintained on the so called usual American diet.
- Encourage intake of diet rich in fibres, fish (omega -3 fatty acids), garlic, low fat dairy products (e.g., cottages cheese, skimmed milk), fresh fruits, vegetables (especially raw) and fruit juices.
- Caffeine (consumed as coffee, tea, or cola drinks) raises blood pressure acutely. Tolerance to its pressor effect develops rapidly. There is no direct relationship between caffeine intake and persistent elevation of blood pressure.

## REGULAR PHYSICAL ACTIVITY

### Rationale

- Regular aerobic exercise has been shown to reduce blood pressure by 6/7 mmHg in borderline hypertension and by 10/8 mmHg in hypertension.
- Mechanisms of hypotensive action of physical activity include: weight reduction, attenuation of adrenergic activity and improved insulin sensitivity.

### Recommendations

- Moderate activity such as 30-45 minutes of brisk walking 3-5 times/week is beneficial.
- Exercise intensity can be set at a heart rate of 190 beats/min minus age.
- Training should be regular and progressive, avoiding exhaustion and sudden bursts of energy.
- Cardiovascular status should be carefully evaluated in the elderly hypertensive (> 65 years) before initiating an exercise program.

## TOBACCO AVOIDANCE

### Rationale

- A significant rise in blood pressure accompanies the smoking of each cigarette.
- The cardiovascular benefits of discontinuing tobacco use can be seen within a year in all age groups.
- Malignant hypertension is more common in smokers.

### Recommendations

Avoidance of tobacco in any form is essential.

## MODERATION OF ALCOHOL INTAKE

### Rationale

- Excessive alcohol intake is an important risk factor of high blood pressure and can cause resistance to antihypertensive therapy.
- Reduction in alcohol intake in individuals who consume 3 or more drinks /day is effective in lowering the blood pressure to a degree comparable with or greater than that achieved by most other effective life style interventions.

### Recommendations

- All hypertensive patients should be advised to limit alcohol intake not exceeding 1-2 drinks /day in men and one drink/day in women.

## RELAXATION AND BIOFEEDBACK

- Emotional stress can raise the blood pressure acutely.
- The available data does not support the use of relaxation therapies for treatment or prevention of hypertension.

## COMBINED THERAPIES

- When several life style modifications are combined, additional antihypertensive effects may occur.

Table 11. DASH Diet

Food Group	Daily Servings	Serving Sizes	Examples and Notes
Grains and grain Products	7-8	1 slice bread 1/2 cup (0.12L) dry cereal 1/2 cup(0.12L) cooked rice, pasta, or cereal	Whole wheat bread, pizza, bread, cereals, oatmeal
Vegetables	4-5	1 cup (0.24L) raw leafy vegetable 1/2 cup (0.12L) cooked vegetable 6 oz (180mL) vegetable juice	Tomatoes, potatoes, carrots, peas, squash, broccoli, turnip greens, spinach, beans, sweet potatoes
Fruits	4-5	6 oz (180mL) fruit juice 1 medium fruit 1/4 cup (0.06L) dried fruit 1/2 cup (0.12L) fresh, frozen, or canned fruit	Apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines
Low-fat or nonfat dairy foods	2-3	8 oz (240 ml) milk 1cup (0.24L) yogurt 1.5 oz (45 g) cheese	Skim or 1% milk, skim or low-fat buttermilk, nonfat or low-fat yogurt, part-skim mozzarella cheese, nonfat cheese
Meats, poultry, and fish	≤2	3 oz (84 g) cooked meats, poultry, or fish	Select only lean meats - trim away visible fats - roast, or boil, instead of frying - remove skin from poultry
Nuts, seeds, and legumes	4-5/week	1.5 oz (42 g) or 1/3 cup (0.08L) nuts 0.5 oz (14 g) or 2 tbs (3 mL) seeds 1/2 (0.12 L) cooked legumes	Almonds, fibers, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils

# CHAPTER 8

## ANTIHYPERTENSIVE DRUGS

### CLASSIFICATION

1. Diuretics.
2. Beta adrenergic blockers.
3. Calcium channel blockers.
4. Angiotensin converting enzyme inhibitors.
5. Angiotensin receptor blockers.
6. Sympatholytics and adrenergic blockers.
7. Direct arterial vasodilators.

### 1. DIURETICS

#### Types

- Thiazides and related diuretics.
- Loop diuretics.
- Potassium sparing diuretics.

#### Mechanism of Action

- Initial effects: through reduction of plasma volume and cardiac output.
- Long term effect: through decrease in total peripheral vascular resistance.

#### Advantages

- Documented reduction in cardiovascular morbidity and mortality.
- Least expensive antihypertensive drugs.
- Best drug for treatment of systolic hypertension and for hypertension in the elderly.
- Can be combined with all other antihypertensive drugs to produce synergetic effect.

#### Side Effects

- Metabolic effects (uncommon with small doses): hypokalemia, hypomagnesemia, hyponatremia, hyperuricemia, dyslipidemia (increased total and LDL cholesterol), impaired glucose tolerance, and hypercalcemia

(with thiazides).

- Postural hypotension.
- Impotence in up to 22% of patients.

### Practical Considerations

- Moderate salt restriction is the key for effective antihypertensive effect of diuretics and for protection from diuretic - induced hypokalaemia.
- Thiazides are not effective in patients with renal failure (serum creatinine > 2mg /dl) because of reduced glomerular filtration rate.
- Frusemide needs frequent doses ( 2-3 /day ).Thiazides can be given once daily or every other day.
- Potassium supplements should not be routinely combined with thiazide or loop diuretics. They are indicated with hypokalemia (serum potassium < 3.5 mEq/L) especially with concomitant digitalis therapy or left ventricular hypertrophy.
- Nonsteroidal antiinflammatory drugs can antagonize diuretics effectiveness.

### Special Indications

- Diuretics should be the primary choice in all hypertensives.
- They are indicated in:
  - Volume dependent forms of hypertension: blacks, elderly, diabetic, renal and obese hypertensives.
  - Hypertension complicated with heart failure.
  - Resistant hypertension: loop diuretics in large doses are recommended.
  - Renal impairment: loop diuretics.

Preparations and Dosage: see table 12.

## 2. BETA - ADRENERGIC BLOCKING AGENTS

### Mechanisms of Action

- Initial decrease in cardiac output, followed by reduction in peripheral vascular resistance.
- Other actions include decrease plasma renin activity, resetting of baroreceptors, release of vasodilator prostaglandins, and blockade of pre-junctional beta-receptors.

### Advantages

- Documented reduction in cardiovascular morbidity and mortality.
- Cardioprotection: primary and secondary prevention against coronary artery events (i.e. ischemia, infarction, arrhythmias, death).
- Relatively not expensive.

### Practical Considerations

- Beta blockers are used with caution in patients with bronchospasm.
- Contraindicated in more than grade I AV, heart block.
- Do not discontinue abruptly.

### Side Effects

- Bronchospasm and obstructive airway disease.
- Bradycardia
- Metabolic effects (raise triglycerides levels and decrease HDL cholesterol; may worsen insulin sensitivity and cause glucose intolerance). Increased incidence of diabetes mellitus.
- Coldness of extremities.
- Fatigue.
- Mask symptoms of hypoglycemia.
- Impotence.

### Special Indications

- First line treatment for hypertension as an alternative to diuretics.
- Hypertension associated with coronary artery disease.
- Hyperkinetic circulation and high cardiac output hypertension (e.g., young hypertensives).
- Hypertension associated with supraventricular tachycardia, migraine, essential tremors, or hypertrophic cardiomyopathy.

Preparations and Dosages: see table 12

### 3. CALCIUM CHANNEL BLOCKERS

#### Types

- Dihydropyridine: nifedipine, amlodipine, felodipine, nicardipine, lacidipine.
- Non dihydropyridine :
  - Phenylalkylamine: verapamil.
  - Benzothiazepine: diltiazem.

#### Mechanisms of action

- Decrease in the concentration of free intracellular calcium ions results in decreased contraction and vasodilation.
- Diuretic effect through increase in renal blood flow and glomerular filtration rate.
- Inhibition of aldosterone secretion.

#### Advantages

- No metabolic disturbances: no change in blood glucose, potassium, uric acid and lipids.
- May improve renal function.
- Maintain optimal physical, mental, and sexual activities.

#### Special Indications

- Ischemic heart disease: when beta blockers are ineffective or contraindicated and in vasospastic angina.
- Elderly hypertensives: second agent of choice after diuretics.
- Peripheral vascular disease (e.g., Raynaud's phenomenon).

#### Side Effects

- Dihydropyridine: flushing, headache, and lower limb oedema.
- Non dihydropyridine: aggravation of heart failure and heart block. Verapamil may cause constipation.

#### Practical Considerations

Short acting dihydropyridine should be combined with beta blockers in coronary artery disease, and should be avoided in stroke, and hypertensive crisis.

Preparations and Dosages: see table 12.

## 4. ANGIOTENSIN CONVERTING ENZYME INHIBITORS

### Types

- Class I: captopril
- Class II (prodrug) : e.g., ramipril, enalapril, perindopril
- Class III ( water soluble) : lisinopril.

### Mechanism of Action

- Inhibition of circulating and tissue angiotensin- converting enzyme.
- Increased formation of bradykinin and vasodilatory prostaglandins.
- Decreased secretion of aldosterone; help sodium excretion.

### Advantages

- Reduction of cardiovascular morbidity and mortality in patients with atherosclerotic vascular disease, diabetes, and heart failure.
- Favorable metabolic profile.
- Improvement in glucose tolerance and insulin resistance.
- Renal glomerular protection effect especially in diabetes mellitus.
- Do not adversely affect quality of life.

### Special Indications

- Diabetes mellitus, particularly with nephropathy.
- Congestive heart failure.
- Following myocardial infraction.

### Side Effects

- Cough (10 - 30%): a dry irritant cough with tickling sensation in the throat.
- Skin rash (6%).
- Postural hypotension in salt depleted or blood volume depleted patients.
- Angioedema (0.2%) : life threatening.
- Renal failure: rare, high risk with bilateral renal artery stenosis.
- Hyperkalaemia
- Teratogenicity.

### Practical Considerations

- Contraindications include bilateral renal artery stenosis, pregnancy, known allergy, and hyperkalaemia.

- High serum creatinine (> 3 mg/dl) is an indication for careful monitoring of renal function, and potassium. Benefits can still be obtained in spite of renal insufficiency.
- A slight stable increase in serum creatinine after the introduction of ACE inhibitors does not limit use.
- ACE-I are more effective when combined with diuretics and moderate salt restriction.

Preparations and dosages: see table 12.

## 5. ANGIOTENSIN RECEPTOR BLOCKERS

### Mechanism of action

They act by blocking type I angiotensin II receptors generally, producing more blockade of the renin - angiotensin - aldosterone axis.

### Advantages

- Similar metabolic profile to that of ACE-I.
- Renal protection.
- They do not produce cough.

### Practical Indications

Patients with a compelling indication for ACE-I and who can not tolerate them because of cough or allergic reactions.

Preparations and Dosages: see table 12.

## 6. SYMPATHOLYTICS AND ALPHA ADRENERGIC BLOCKERS

### Types

1. Alpha 1-receptor blockers: prazosin, doxazosin.
2. Centrally acting alpha 2- agonists: methyl dopa, clonidine.
3. Peripherally acting adrenergic antagonists: reserpine.
4. Imidazoline receptor agonists: rilmenidine, moxonidine.

### Advantages

- Alpha1- receptor blockers and imidazoline receptor agonists improve lipid profile and insulin sensitivity.

- Methyldopa: increases renal blood flow. Drug of choice during pregnancy.
- Reserpine: neutral metabolic effects and cheap.

#### Special indications:

- Diabetes mellitus: alpha1- receptor blockers, imidazoline receptor agonists.
- Dyslipidemia: alpha 1- receptor blockers, imidazoline receptor agonists.
- Prostatic hypertrophy: alpha 1- receptor blockers.
- When there is a need for rapid reduction in blood pressure: clonidine.

#### Side Effects

- Prazocin: postural hypotension, diarrhea, occasional tachycardia, and tolerance (due to fluid retention).
- Methyldopa: sedation, hepatotoxicity, hemolytic anemia, and tolerance.
- Reserpine: depression, lethargy, weight loss, peptic ulcer, diarrhea, and impotence.
- Clonidine: dry mouth, sedation, bradycardia, impotence, and rebound hypertension if stopped suddenly.

#### Practical Considerations

- Prazocin, methyldopa, and reserpine should be combined with a diuretic because of fluid retention.
- In Egypt, reserpine is only available as combination pill with thiazide (Brenardine) which contains 0.1 mg of reserpine per tablet.

Preparations and Dosages: see table 12.

## 7. DIRECT ARTERIAL VASODILATORS

Types: hydralazine, diazoxide, nitroprusside, and minoxidil (see chapter 10).

## PATIENTS' COMPLIANCE TO ANTIHYPERTENSIVE MEDICATIONS

Poor adherence to antihypertensive therapy remains a major therapeutic challenge contributing to the lack of adequate control of blood pressure in more than two thirds of patients with hypertension. One half of all patients discontinue antihypertensive medications within one year.

### CAUSES OF POOR COMPLIANCE

- Hypertension has no symptoms and treatment has to continue indefinitely.
- Poor communication with the patient. Very long intervals between follow-up visits, and frequent change of doctors impair the doctor-patient relationship.
- Logistic barriers e.g. expense of medications, inability to read instructions, complicated multi-dose regimens, etc....
- Adverse drug effects.

### STRATEGIES TO IMPROVE COMPLIANCE

- Educate patients about the disease and involve their families in the treatment.
- Stress that treatment is life-long.
- Consider cost while prescribing.
- Consider adverse effects at initial prescription and follow up visits.
- Prescribe simple once-daily regimens.
- Allow extra visits for blood pressure measurement at no extra charge to the patient.
- Arrange follow-up visits at intervals no more than three months apart, during the first year.
- Encourage life style modifications.

Table 12. Commonly Used Oral Antihypertensive Medications

Class	Generic Name	Daily Dose (mg)	Common Brand Name(s)	Tablet Size (mg)
Diuretics	Hydrochlorothiazide	12.5-50	Hydrex	25
			Aldactazide #	25
			Moduretic ++	25
	Indapamide	1.25-5	Natrilix	2.5
			Natrilix SR	1.5
	Chlorthalidone	25-50	Hygotone	50
Frusemide	20-400	Lasix	40	
Bumetanide	1-4 ( or more )	Burinex	1	
Beta adrenergic blockers	Atenolol	25-100	Tenormin	50, 100
			Blockium	50, 100
			Blockium Diu *	50
	Metoprolol	50-200	Betaloc	100
	Bisoprolol	2.5-10	Concor	5,10
Concor 5 Plus*			5	
Calcium antagonists	Verapamil	120-480	Isoptin retard	240
			Tarka ***	120
	Diltiazem	90-240	Tildium	60
			Altiazem	60
			Delaytiazem	90, 120, 180
	Nifedipine	20-80	Adalat retard	20
			Epilat retard	20
	Amlodipine	2.5-10	Norvasc	5, 10
Amilo			5	
Lacidipine	2-4 (or more )	Lacipil	2,4	

ACE inhibitors	Captopril	50-150	Capoten	25, 50
			Capozide *	50
	Enalapril	2.5-40	Captopril	25, 50
			Renetec	10, 20
			Co-renetec	10,20
			Ezapril	10,20
	Lisinopril	10-40	Zestril	5,10,20
	Ramipril	2.5-20	Zestoretic	20
			Tritace	1.25, 2.5, 5, 10
			Tritace comp *	5
	Perindopril	2-8	Tritace comp LS *	2.5
Coversyl			2,4	
Angiotensin Receptor blockers	Losartan	25-100	Cozaar	50
			Hyzaar *	50
			Losartan	50
			Fortzar*	100
	Valsartan	80-320	Tareg	80, 160
			Co-Tareg *	80, 160
			Co-Diovan*	160
Candesartan	4-32	Atacand	8	
Telmisartan	20-80	Micardis	40, 80	
Alpha-adrenergic blockers	Prazocin	1-16	Minipress	1,2
	Doxazocin	1-16	Cardura	1,4
Centrally acting drugs	Methyldopa	500-2000	Aldomet	250, 500
	Clonidine	0.1-1.2	Catapres	0.1, 0.2, 0.3
	Rilmenidine	1-2	Rilmenidine	1.0
	Reseraine	0.1	Brenardine	0.1

\* Combination with hydrochlorothiazide

\*\*\* Combination with ACE inhibitor

# Combination with spironolactone

++ Combination with triamterene

\*\* Combination with thiazide & vasodilator

## CHAPTER 9

# MANAGEMENT OF COMPLICATED HYPERTENSION

### CORONARY ARTERY DISEASE

- ✓ The level of blood pressure is continuously related to the risk of coronary artery disease.
- ✓ Hypertensive patients, particularly in the presence of left ventricular hypertrophy may present with angina pectoris without angiographic evidence of epicardial coronary artery disease.
- ✓ Exercise ECG and stress myocardial perfusion imaging occasionally yield false positive results in hypertensive patients.
- ✓ B-blockers are the drugs of choice for hypertension in patients with coronary artery disease. Calcium antagonists offer a good alternative for patients who cannot tolerate B-blockers. ACE-inhibitors are extremely useful in the presence of left ventricular dysfunction.
- ✓ Aspirin, statins and ACE inhibitors may reduce the risk of future cardiovascular events.
- ✓ Caution should be taken when aggressively lowering blood pressure in hypertensive patients with left ventricular hypertrophy and coronary artery disease.

### RELATION OF BLOOD PRESSURE TO CORONARY ARTERY DISEASE

- There is a continuous and graded relationship between blood pressure and risk for coronary artery disease. Lowering blood pressure can reduce this risk.
- Patients with coronary artery disease and hypertension are at particularly high risk for cardiovascular morbidity and mortality. The benefits and safety of antihypertensive therapy in such patients are well established.
- Concerns have been raised that lowering diastolic blood pressure too much may increase the risk of coronary events by lowering diastolic perfusion

pressure in the coronary circulation. The hypertension optimal treatment trial (HOT) has revealed that the optimal diastolic blood pressure level corresponding to minimal risk is approximately 83mmHg. Below this level there is little apparent further benefit in terms of reducing the number of major cardiovascular events.

## DIAGNOSIS OF CORONARY ARTERY DISEASE IN HYPERTENSIVE PATIENTS

- Some patients with hypertension, especially if associated with left ventricular hypertrophy, may have angina, positive exercise ECG, or perfusion defects in stress myocardial imaging without angiographic evidence of coronary artery disease.
- Stress echocardiography (most frequently with dobutamine) is more specific than exercise ECG or stress myocardial perfusion imaging.
- Coronary angiography is indicated when the results of non-invasive tests are inconclusive.

## MANAGEMENT OF HYPERTENSION IN PATIENTS WITH CORONARY ARTERY DISEASE

### Hypertensive patients with stable angina

- Beta-blockers may be specifically useful in patients with hypertension and stable angina.
- Calcium antagonists offer a good alternative therapy when beta-blockers are contraindicated or ineffective. Short-acting calcium antagonists should not be used.

### Hypertensive patients with acute coronary syndromes

- The appropriate initial treatment of severe hypertension should include IV nitrates.
- Beta-blockers may be valuable when the blood pressure is moderately raised.
- Sodium nitroprusside should be reserved for resistant cases, as it may exacerbates coronary ischemia.
- An ACE inhibitor may be administered when hypertension persists despite treatment with nitroglycerin and a beta blocker. It should be given as early as possible in patients with LV systolic dysfunction or congestive heart failure or large myocardial infarction.

- When beta blockers are contraindicated, a non-dihydropyridine calcium antagonist (e.g., verapamil or diltiazem) is recommended.
- Immediate release dihydropyridine calcium antagonists should be avoided in the absence of a beta blocker.

### Hypertension in the post-myocardial infarction patient

- Hypertension should be controlled to a blood pressure of 130/85 mmHg.
- Unless contraindicated, beta blockers should be used following a myocardial infarction. Beta blockers have been shown to reduce the risks of both reinfarction and cardiovascular death by about 25 %.
- ACE inhibitors are recommended after myocardial infarction especially in patients with left ventricular dysfunction or heart failure since they reduce by about one-fifth the risk of myocardial infarction or sudden death. They also retard the process of myocardial remodeling and may prevent progression of heart failure.
- There is no clear evidence from clinical trials that calcium antagonists (verapamil or diltiazem) reduce recurrent coronary heart disease events.
- Calcium antagonists (verapamil, diltiazem) may be used if beta blockers are ineffective or contra-indicated. In presence of left ventricular systolic dysfunction, they should better be avoided.

### PREVENTION OF CORONARY ARTERY DISEASE BEYOND BLOOD PRESSURE CONTROL

Since the aim of treatment of hypertension is the reduction in total cardiovascular risk, it is relevant as well to treat other cardiovascular risk factors and associated clinical conditions present in the hypertensive patient.

#### Anti-platelet Agents

In patients with well-controlled blood pressure, low dose (75 mg) aspirin may be used to reduce the risk of acute myocardial infarction without increasing the risk of cerebral bleeding. In the HOT study, a small dose (75 mg) of aspirin in addition to the antihypertensive treatment significantly reduced the number of major cardiovascular events and all myocardial infarctions compared with placebo.

### **Cholesterol Lowering Therapy:**

The results of several controlled trials have shown that statin treatment reduces the risks of initial and recurrent coronary heart disease events among patients with a wide range of initial cholesterol levels. Statin treatment also reduces the risk of stroke substantially in patients with coronary heart disease. The benefits were similar in hypertensive patients. Statins are recommended for hypertensive patients with hyperlipidemia and for those at increased risk of coronary heart disease.

### **Angiotensin Converting Enzyme Inhibitors:**

The heart outcome prevention evaluation study (HOPE) was carried out in high-risk patients who received ramipril (10 mg/day). Ramipril-treated patients experienced a 22 percent reduction in the composite endpoint, which resulted in a reduction in the risk of death from any cause. This effect appears largely independent of the ACE inhibitors blood pressure lowering effects. The benefits derived from ACE inhibitors are presumed to be primarily due to a direct protective mechanism upon the vascular wall, possibly by improving endothelial function and reducing plaque activation.

## HEART FAILURE

- Hypertension is the most common risk factor for heart failure, both with and without systolic dysfunction. Blood pressure control effectively prevents heart failure.
- Heart failure with normal left ventricular systolic function i.e. diastolic heart failure is the common type of heart failure in hypertensive patients.
- Echocardiography should be performed in all patients with heart failure. It will identify patients with normal systolic function, detect left ventricular hypertrophy, assess the degree of impairment of left ventricular contractility if present and diagnose unrecognized valvular disease, or myocardial scarring.
- A small elevation of blood pressure can cause serious deterioration and further impairment of left ventricular systolic function in patients with heart failure secondary to poor systolic function.
- Target blood pressure in patients with heart failure is less than 130/85 mmHg.
- Drugs of first choice are diuretics and ACE-I. Angiotensin receptor blockers may replace ACE-I if the latter are not tolerated. Additional drugs aiming at relieving myocardial ischemia and slowing the heart rate might be added.

## CEREBROVASCULAR DISEASE

- ✓ The main three cerebrovascular complications of hypertension are: stroke, hypertensive encephalopathy and dementia.
- ✓ The rates of recurrent cerebrovascular events appear to be directly related to levels of blood pressure.
- ✓ Ischemic strokes are more common (80%) than hemorrhagic strokes (20%).
- ✓ Antihypertensive therapy should be initiated in acute stroke patients if blood pressure exceeds 220 mmHg systolic and 120 mmHg diastolic. In hemorrhagic stroke initiate therapy at lower levels: >180 mmHg systolic and >105 mmHg diastolic. Do not lower mean blood pressure by more than 25% in the first two hours. In the next 2-6 hours, aim to lower blood pressure 160/100 mmHg.
- ✓ The drugs of choice are parenteral sodium nitroprusside and labetalol. In subarachnoid hemorrhage, nimodipine (calcium antagonist) is recommended.
- ✓ After achieving the target blood pressure with parenteral therapy, oral therapy with angiotensin receptor blockers or ACE-inhibitors in combination with a diuretic should be initiated and blood pressure is monitored to reach a target of <140/90 mmHg over the next two to four weeks.
- ✓ Other drugs; antiplatelets, statins, anticoagulant are added when indicated for secondary prevention of stroke.

## STROKE

- Hypertension is the single most important risk factor for stroke. This risk is "direct, continuous, and apparently independent". Other pertinent risk factors for stroke in hypertensive individuals are:

- Age.
- Atrial fibrillation.
- Diabetes mellitus.
- Previous stroke.
- Contraceptive pills.
- Black race.

In hypertensives, stroke is classified into:

- Ischaemic stroke (80%): caused by either
  - Athero-thrombosis.
  - Embolism.
- Hemorrhagic stroke (20 %)
  - Intracerebral hemorrhage (10 %)
  - Subarachnoid hemorrhage (10 %).

### *Ischaemic Stroke*

Hypertension predisposes to ischaemic stroke via:

- Acceleration of atherosclerosis in large cerebral arteries causing parenchymal cerebral infarctions.
- Arteriosclerosis (lipohyalinosis) of small penetrating cerebral arterioles causing lacunar infarctions.
- Cerebral embolism originating from the aortic arch, extracranial carotids, or the heart (e.g., atrial fibrillation).

### *Transient Ischemic Attacks (TIAs)*

- They are acute reversible episodes of focal loss of cerebral or visual functions lasting less than 24 hours, usually caused by small athermatous emboli.
- 30% of TIAs progress to a major stroke within 5 years.

## **HYPERTENSIVE ENCEPHALOPATHY (chapter 11)**

### **DEMENTIA**

Hypertension accelerates the development of dementia. Premature deterioration of cerebral cognitive function is more common in hypertensives than in normotensives.

## LOWERING OF BLOOD PRESSURE IN STROKE

### Lowering of Blood Pressure in Acute Stroke

- Markedly elevated blood pressure may increase risks for further cerebral ischaemia, cerebral oedema, rebleeding in subarachnoid hemorrhage, hemorrhagic transformation of the infarct and extension of hemorrhagic infarcts. However, management of markedly elevated blood pressure in the setting of cerebrovascular accidents is tempered by decreased flow to the areas surrounding the infarct (ischaemic penumbra), causing extension of infarct size.
- By the tenth day after stroke, two thirds of patients will be normotensive even without treatment.
- In ischaemic stroke antihypertensive drugs should be withheld unless the:
  - SBP is > 220 mmHg or,
  - DBP is > 120 mmHg.
- In hemorrhagic stroke, blood pressure lowering is initiated at lower threshold (180/105 mmHg).
- Blood pressure reduction should be gradual :
  - Reduce the mean blood pressure by no more than 25 % (within 30 minutes to 2 hours).
  - Then, reduce the blood pressure to the target level within 2 to 6 hours.
- Target blood pressure is 160/100 to 170/105 mmHg depending upon initial blood pressure.

### *Choice of antihypertensive agent*

- The drug of choice is parenteral sodium nitroprusside or labetalol.
- In cases of subarachnoid hemorrhage, nimodipine is recommended. It has value in reducing cerebral spasm. Treatment is not aimed at blood pressure control.
- Nitroglycerine and hydralazine increase cerebral blood flow and should not be used in cases with increased intracranial pressure.
- Diuretics should be avoided when patients with acute stroke are dehydrated.
- Sublingual nifedipine must be avoided because of unpredictable fall in blood pressure.
- Management should be performed in the ICU with careful monitoring of blood pressure and neurological status.

For long term management of hypertension after acute stroke the following is recommended:

- All hypertensive patients with previous stroke should receive antihypertensive therapy.
- The following agents have shown benefits in clinical trials:
  - ACE-Inhibitors.
  - Thiazide diuretics
  - Angiotensin receptor blockers.
  - B- adrenergic receptor blockers.
- Agents that are liable to produce orthostatic hypotension (e.g., alpha1-blockers) should be avoided. Additionally, measuring of blood pressure in the supine and standing position is recommended in all patients.

## BEYOND BLOOD PRESSURE CONTROL

### Antiplatelet Agents

#### *Aspirin*

- Primary prevention: Aspirin is used prophylactically in hypertensive patients with adequate blood pressure control.
- Secondary prevention: Patients with a prior ischaemic stroke or TIA should be treated with aspirin indefinitely unless there is definitive contraindication. The most appropriate dose is 75 – 325 mg daily.

#### *Thienopyridine agents (ticlopidine & clopidogrel)*

Clopidogrel (75 mg daily) appears to be at least as effective and safe as aspirin. It is therefore appropriate, but more expensive, alternative drug for patients intolerant to aspirin.

### Oral Anticoagulant Agents

- Hypertensive patients with atrial fibrillation should receive warfarin. An INR range of 2 to 3 is recommended provided that the blood pressure is adequately controlled.
- Oral anticoagulants are recommended in hypertensive patients with recurrent TIAs attacks despite aspirin therapy, or if there is a major cardiac source of emboli.

## Statins

- A reduction in stroke risk (between 30-50 %) with the use of statins has been confirmed in patients with known coronary artery disease and elevated cholesterol level.
- It is recommended that patients with coronary artery disease level should receive statins.

## ACE-Inhibitors

- Ramipril was found to reduce the incidence of strokes in high risk patients.

## RENAL DISEASE

- ✓ Patients with renal insufficiency should be encouraged to reduce dietary salt and protein intake.
- ✓ Target blood pressure is less than 135-130/85 mmHg. If patients have urinary protein of 1gm/day or greater, the target blood pressure should be, if tolerable, less than 125/75 mmHg.
- ✓ ACE-I, Angiotensin receptor blockers and Diuretics are the drugs of first choice for hypertensive patients with renal failure. Dose adjustment is required and when serum creatinine exceeds 3.0 mg/dl, ACE-inhibitors should be used carefully.
- ✓ Serum creatinine level often rise during the early phase of treatment with ACE-I in patients with renal disease.
- ✓ Calcium antagonists are useful and safe, especially in patients with severe renal dysfunction (serum creatinine > 3.0 mg/dl).
- ✓ Thiazide diuretics are ineffective in patients with serum creatinine greater than 3.0 mg/dl.
- ✓ In patients with severe renal failure (serum creatinine >3 mg/dl) intravenous frusemide 160 mg/day (or its equivalents, bumetanide or torsemide) or oral frusemide 320 to 400 mg may be required to control blood pressure when intravascular volume is expanded.

### GENERAL CONSIDERATIONS

- Renal insufficiency is defined as serum creatinine greater than 1.5 mg/dl in men and greater than 1.4 mg/dl in women.
- Elevation of serum creatinine may not occur until the glomerular filtration rate has fallen to less than 30% of normal; it is therefore of limited value in estimating the extent of renal damage.

### NEPHROANGIOSCLEROSIS

- It is the term applied to chronic renal disease primarily due to essential hypertension.
- Nephroangiosclerosis is the second most common cause of renal failure (30% of renal failure cases in the USA, around 24% in Egypt).

- Hypertension nephroangiosclerosis remains a diagnosis of exclusion, and it should be considered when other forms of progressive renal insufficiency have been systematically excluded.

## HYPERTENSION ASSOCIATED WITH RENAL DISEASES

- Most renal diseases are associated with hypertension.
  - Focal segmental sclerosis is associated with high incidence of hypertension. In contrast minimal change glomerulopathy has a low incidence.
  - Polycystic kidney disease as well as chronic obstructive uropathy is associated with high blood pressure.
  - Diabetic nephropathy cases are almost always hypertensive.
  - Most renal transplant cases as well as some regular hemodialysis cases are hypertensive.
- Hypertension is the single most important factor in the progression of renal disease.
- Hypertension is an important risk factor for cardiovascular and cerebrovascular diseases in renal failure cases whether pre or post renal replacement therapy.
- Hypertension in chronic renal insufficiency is secondary to salt and water retention caused by the decrease in renal excreting function. Other mechanisms include activation of the renin- angiotensin system, increased adrenergic activity, and loss of renal vasodilators.
- Erythropoietin therapy of anemic patients with chronic renal insufficiency may cause hypertension or exaggerate pre-existing hypertension.

## MANAGEMENT OF HYPERTENSION IN RENAL INSUFFICIENCY

### Special Considerations

- Proper control of blood pressure is mandatory. Control of other risk factors (e.g., diabetes, hyperlipidemia) is essential.
- The concept of intraglomerular pressure is important, particularly in grossly proteinuric cases. Drugs that reduce the intraglomerular pressure are preferred.
- There are pharmacokinetic changes (absorption, excretion, volume of distribution, and metabolism) due to the uremic state.
- There is a tendency to develop hyperkalemia.

- Uremic patients may suffer from autonomic neuropathy. They are susceptible to orthostatic hypotension.
- Uremic patients are already receiving many other medications and drug interactions should be considered.
- Associated medical problems (e.g., diabetes, heart failure, liver disease, hyperlipidemia and hyperuricemia) are commonly found in these patients.

### Target Blood Pressure

- To lower blood pressure to less than 135-130/85 mmHg and to less than 125/75 mmHg in patients with  $\geq 1$  g/day of proteinuria.

### Non Pharmacological Therapy

- Salt should be restricted. Protein intake should be limited according to body weight (0.8 mg/kg/day).
- Mild exercise as walking should be encouraged.
- Weight loss in obese patient should be encouraged.
- Smoking should be stopped; it is recognized as an aggravating factor for renal disease progression.

### Pharmacological Therapy

ACE-inhibitors, angiotensin II receptor blockers, non dihydropyridine calcium channel blockers, and diuretics are the drugs of first choice.

#### *ACE-inhibitors*

- Offer renoprotective effect especially in patients with heavy proteinuria.
- Low-sodium intake and dietary protein restriction enhance the anti-proteinuric effect of ACE-inhibitors.
- ACE-inhibitors are not contraindicated at any level of renal dysfunction, although they should be used cautiously when serum creatinine values exceed 3 mg/dl.
- Serum creatinine level often rise during the early phase of treatment with ACE-I in patients with renal disease. Elevation of serum creatinine greater than 20% of the initial value needs careful observation. In situations in which the initial increase in creatinine is greater than 30% or repeated measurements show a progressive increase, ACE-I therapy should be discontinued (table 13).

- ACE-inhibitors excretion is decreased in end stage renal disease, and a lower dose should be given, except for fosinopril.

Table 13: Causes of Exaggerated or Progressive Decline in Renal Function Associated with ACE-inhibitors or Angiotensin Receptor Blockers Use

<ul style="list-style-type: none"> <li>• Bilateral renal artery stenosis.</li> <li>• Renal artery stenosis to a single functioning kidney.</li> <li>• Polycystic kidney disease.</li> <li>• Absolute reduction in intravascular volume (gastroenteritis, aggressive diuresis)</li> <li>• Reduction in effective arterial volume (moderate to severe CHF).</li> <li>• Use of NSAIDs or cyclosporins (increased renal vasoconstriction).</li> </ul>
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#### *Angiotensin receptor blockers*

- Have similar effects as ACE-inhibitors. losartan and irbesartan in particular, proved to be renoprotective in diabetic nephropathy cases.

#### *Diuretics*

- Thiazide diuretics are effective as long as the serum creatinine is  $< 2$  mg/dl.
- In patients with serum creatinine  $>3$  mg/dl, intravenous frusemide 160 mg/day (or its equivalents; bumetanide or torsemide) or oral frusemide 320 to 400 mg may be required to control blood pressure when intravascular volume is expanded.
- Potassium retaining diuretics are used in early renal failure only, and with great caution particularly if ACE-inhibitors are concomitantly administered.
- With aggressive diuretics, potential irreversible worsening of renal function may occur, therefore, close observation is mandatory, with monitoring of body weight, orthostatic blood pressure, renal function and electrolytes.

#### *Calcium Channel Antagonists*

- Non dihydropyridine agents are renoprotective. They are safe with severe renal dysfunction (serum creatinine  $>3.0$  mg/dl).

### *Beta blockers*

- Adjust doses of drugs excreted through renal route (e.g., atenolol).

### *Alpha blockers and vasodilators*

- Not renoprotective and are associated with salt and water retention as well as postural hypotension.

## ANTIHYPERTENSIVE THERAPY IN HEMODIALYSIS PATIENTS

- Hypertension results in an increased incidence of myocardial infarction, cerebral accidents and contributes to left ventricular hypertrophy in hemodialysis patients. Therefore, proper control of blood pressure reduces mortality significantly.
- Excessive lowering of blood pressure may increase the mortality in hemodialysis patients.
- Hypervolemia plays a major role in the pathogenesis of hypertension in these cases. Proper adjustment of the dry weight is the first line of therapy in controlling hypertension in these patients.
- Dialysability of the various antihypertensives should be taken into account when drugs are prescribed.
- Salt restriction should always be observed.

## ANTIHYPERTENSIVE THERAPY IN RENAL TRANSPLANT PATIENTS

- Major causes of hypertension in renal transplant recipients include renal artery stenosis and drugs (cyclosporin and steroids).
- Beta blockers are cardioprotective but may disturb lipid metabolism which is already altered in these cases.
- Calcium channel blockers are useful and play a role in protecting the transplant from the deleterious effects of cyclosporin.
- ACE-inhibitors are renoprotective and may reduce cyclosporin induced fibrosis, but there is the risk of renal artery stenosis in these cases and a duplex sonography for the transplant renal artery is advisable before their use.
- Angiotensin receptor blockers probably have the same merits and effects of ACE-inhibitors.

- Diuretics are useful but one should avoid dehydration so as not to impair the transplant function.

## CHAPTER 10

# RESISTANT HYPERTENSION

### DEFINITION

- Persistent elevation of blood pressure above 140/90 mmHg in patients who are adhering to triple-drug regimen including a diuretic, and all three drugs are prescribed near maximum recommended doses for at least three months.
- For older patients with isolated systolic hypertension, resistance is defined as failure of an adequate triple-drug regimen to reduce systolic blood pressure below 160 mmHg.
- Although an inadequate response to antihypertensive therapy is unfortunately common, true resistant hypertension is rare.

### CAUSES OF INADEQUATE RESPONSIVENESS TO THERAPY

#### Poor Blood Pressure Measurement Technique

e.g., using a small cuff size in an obese arm (see chapter 2).

#### False High Blood Pressure

Twenty to 50% of patients referred to specialized clinics for evaluation have normal blood pressure on ambulatory monitoring. Three important causes are identified:

- *Office (white coat) Hypertension*  
15-30 % of patients diagnosed with hypertension actually have normal blood pressure at home (table 14).
- *Pseudo-hypertension*  
Seen in elderly patients with atherosclerotic arteries, and calcified brachial artery. The cuff pressure is inappropriately high compared with intra-arterial pressure.
- *Cuff Inflation Hypertension.*

Table 14. Features of White Coat Hypertension

Definition

- Abnormal office blood pressure  $\geq 140/90$  mmHg
- Normal daytime ABPM  $< 135/85$  mmHg

Prevalence of white coat hypertension

- 15-30 % of general population
- 30 % in pregnancy

Risks of white coat hypertension

- Considerably less than sustained hypertension
- Probable small risk compared to normotensives
- Possibly a pre-hypertensive state.
- May not be an entirely innocent condition

Clinical implications

- Few clinical characteristics to assist diagnosis
- Must be considered in newly diagnosed hypertensives
- Should be considered before drug prescription
- Must be placed in context of overall risk profile
- Reassurance for employment
- Reassurance for insurance and pension liability
- Common in the elderly and pregnancy
- Less drug prescription
- Need for follow up and re-monitoring

True High Blood Pressure

- *Inappropriate Drug Therapy*

A suboptimal medical regimen accounts for approximately 40% of patients referred to a tertiary care clinic for resistant hypertension.

- Incorrect drug combination: e.g., using drugs from the same pharmacologic group.
- Inadequate dosing: e.g., small dose, short acting preparation given once daily.

- *Poor compliance with treatment*

Poor adherence to the prescribed medical regimen is possibly the most common etiology of resistant hypertension. One-half of all patients discontinue antihypertensive medications within one year.

- Drugs: interruption, discontinuation, or irregular treatment.
- Lifestyle: high salt intake, alcohol excess, uncontrolled obesity, continuous stressful exposures.

- *Ingestion of substances that can elevate blood pressure (table 15)*

### True Resistant Hypertension

- *Extracellular Volume Expansion*

- Inadequate diuretic therapy
- Renal insufficiency.
- Direct vasodilators.
- Excessive sodium intake

- *Secondary Hypertension (see chapter 5).*

Table 15. Substances that Can Elevate Blood Pressure

- NSAIDs (nonsteroidal anti inflammatory drugs).
- Oral contraceptives.
- Glucocorticoids.
- Mineralocorticoids.
- Sympathomimetics (e.g., nasal decongestants, appetite suppressants).
- Licorice.
- Phenothiazines.
- Antidepressants.
- Cyclosporine.
- MAO inhibitors and tyramine rich foods.
- Erythropoietin.
- Cocaine.

## MANAGEMENT

- Blood pressure should be measured accurately according to guidelines. False-high blood pressure readings should be excluded. Vasopressor medications, and drug therapy needs to be reviewed for appropriateness of drug dose and combination. Deliberate explanation of the importance of compliance has to be offered at this stage (see chapter 8).
- When the above problems are adequately addressed and the blood pressure remains resistant to therapy, causes of extracellular volume expansion have to be considered:
  - Use a long-acting loop diuretic (e.g., torsemide) to replace thiazide
  - Monitor and correct serum electrolytes.
  - Gradually remove fluid until blood pressure is controlled or symptoms of extra-cellular volume depletion develop (orthostatic hypotension or rising blood urea).
  - Aggressive diuresis may be needed in resistant hypertension with renal failure. Intravenous frusemide 160 mg/day (or its equivalent, bumetanide) or oral frusemide 320 to 400 mg/day may be required to control blood pressure when intravascular volume is expanded.
  - Rarely, severe volume depletion is associated with high sympathetic activity, severe vasoconstriction, and sustained hypertension.
- Search for secondary causes of hypertension (see chapter 5).
- Consider referral of resistant hypertensive patients to a hypertension specialist.

# CHAPTER 11

## HYPERTENSIVE EMERGENCIES

- ✓ Hypertensive crisis is arbitrarily defined as severe elevation of blood pressure exceeding 220 mmHg systolic and/or 120 mmHg diastolic. It is considered an emergency when complicated by acute progressive target organ damage such as encephalopathy or cerebral hemorrhage.
- ✓ Patients who present with a hypertensive emergency should be hospitalized for rapid controlled lowering of blood pressure in the ICU. The mean arterial pressure is reduced to a level of 120 mmHg (160/100) over several hours. However the target blood pressure level and the rate of reduction depend on the nature of emergency, the age of the patient and the clinical response.
- ✓ The antihypertensive drugs of choice (sodium nitroprusside, nitroglycerin) are rapidly acting parenteral agents with a short duration of action which effectively reduce the systemic vascular resistance. Their action can be rapidly reversed in case of an adverse clinical response.
- ✓ Patients who present with severe elevation of blood pressure in the absence of acute target organ damage have hypertensive urgency. They can be managed as out-patients using a combination of rapidly acting oral antihypertensive drugs.

### DEFINITIONS AND CLASSIFICATION

- **Hypertensive crisis:** defined arbitrarily as a severe elevation in blood pressure, usually a systolic blood pressure exceeding 220 mmHg and/or a diastolic blood pressure greater than 120 mmHg. It includes hypertensive emergencies and urgencies.
- **Hypertensive emergencies:** severe elevation in blood pressure complicated by acute progressive target organ damage such as hypertensive encephalopathy or intracerebral hemorrhage. A hypertensive emergency represents an acute life-threatening situation which requires admission to the ICU for immediate but controlled

reduction of blood pressure using intravenous drug therapy under careful monitoring to avoid death or major irreversible target organ damage.

- **Hypertensive urgencies:** severe elevation of blood pressure in the absence of evidence of new progressive target organ injury. Immediate blood pressure reduction is not indicated and most cases can be managed as outpatients using combinations of oral hypertensive drugs to reduce the blood pressure over few days.
- **Malignant hypertension:** raised blood pressure in association with bilateral retinal hemorrhage and/or exudates with or without papilloedema.

**Table 16. Clinical Conditions Associated with Hypertensive Emergencies**

- Malignant hypertension with papilloedema
- Cerebrovascular
  - Hypertensive encephalopathy
  - Atherothrombotic brain infarction with severe hypertension
  - Intracerebral haemorrhage
  - Subarachnoid haemorrhage
- Cardiac
  - Acute aortic dissection
  - Acute left ventricular failure
  - Acute myocardial infarction
  - Coronary artery bypass graft surgery
- Renal
  - Acute glomerulonephritis
  - Renal crisis from collagen vascular disease
  - Severe hypertension after kidney transplantation
- Excessive circulating catecholamines
  - Pheochromocytoma crisis
  - Food or drug interactions with monoamine-oxidase inhibitors
  - Sympathomimetic drug use (cocaine)
  - Rebound hypertension after sudden cessation of antihypertensive drugs
- Eclampsia
- Surgical
  - Severe hypertension in patients requiring immediate surgery
  - Postoperative hypertension
  - Postoperative bleeding from vascular suture lines
  - Severe body burns

## HYPERTENSIVE ENCEPHALOPATHY

- A syndrome characterized by acute or subacute alteration in neurologic status that occurs as a result of elevated arterial blood pressure and that is reversed by lowering the blood pressure.
- Occurs when the blood pressure exceeds the upper limit of cerebral autoregulation, with consequent cerebral hyperperfusion, accompanied by disruption of blood brain barrier. Hypertensive encephalopathy can occur with any variant of hypertension. The most common cause is untreated essential hypertension.
- Tends to affect persons with previously normal blood pressure who have a rapid rise of blood pressure.
- The patient typically presents with generalized headache steadily increasing in severity over 48-72 hours accompanied by nausea, vomiting, visual disturbances, confusion, stupor and coma. Blood pressure is markedly elevated, usually a systolic pressure greater than 230-250 mmHg and a diastolic pressure exceeding 130-140 mmHg. An occasional patient may develop transient focal neurologic manifestations.
- Reduction of arterial pressure using an agent which decreases the systemic vascular resistance is accompanied by clearing of the sensorium and resolution of clinical manifestations.
- Severe retinopathy is frequently, but not universally, present.
- *CT-scan*: shows no abnormalities. It excludes other structural causes of neurological deficits (e.g., hemorrhage, infarcts,...).
- *MRI*: shows increased signal involving the subcortical white matter (consistent with the presence of edema).
- *Differential Diagnosis*
  - Acute stroke: CT-scan is diagnostic.
  - Drugs: e.g., intravenous amphetamines, cocaine and clonidine withdrawal .
  - Uremic encephalopathy.
- Sodium nitroprusside and labetalol are the drugs of choice.

## LABORATORY EVALUATION

- An ECG is performed to detect left ventricular hypertrophy and evidence of coronary heart disease.
- The fundus is examined for papilloedema, retinal haemorrhage and exudates.

- A chest x-ray is required in patients with pulmonary oedema.
- Echocardiography is used to determine left ventricular dimensions, wall thickness, global and regional function.
- A CT scan of the brain or MRI examination should be performed in patients suspected to have other causes of cerebrovascular accident.

## MANAGEMENT OF HYPERTENSIVE EMERGENCIES

### Goals of Therapy

- The goal of therapy is to reduce the mean arterial pressure in a calculated and controlled manner using potent rapidly acting antihypertensive agents with a short duration of action.
- Rapid controlled blood pressure lowering is recommended in cerebral infarction if blood pressure is 220/120 mmHg or greater (180/105 mmHg in patients with cerebral hemorrhage). Do not lower mean blood pressure by more than 25% in the first two hours, then to 160/100 mmHg within the next six hours.
- Rapid reduction of blood pressure to normal levels is indicated in patients with aortic dissection, acute pulmonary oedema or pheochromocytoma.

## ANTIHYPERTENSIVE DRUG THERAPY (Table 16)

### Sodium Nitroprusside

- This is the drug of choice in most hypertensive emergencies. It is a potent direct vasodilator which acts as a nitric oxide donor to reduce both the preload and the afterload.
- It should be administered in the ICU under close monitoring of arterial blood pressure, preferably through an arterial line. The dose ranges from 0.25-10 µg/kg/min. The infusion is started at 15 µg/min and cautiously increased by 5-10 µg/min every 3-5 minutes until the desired blood pressure is reached.
- The most common adverse reaction is hypotension. The physician should be extremely careful to avoid undesirable reduction of blood pressure.
- Thiocyanate toxicity occurs in patients with renal insufficiency, at high infusion rates or when therapy is prolonged > 72 hours. Toxic symptoms include nausea, vomiting, headache, delirium, disorientation and convulsions.

## Nitroglycerin

- This widely available direct vasodilator acts primarily by reduction of venous preload. However at high infusion rates, it also reduces the systemic vascular resistance.
- The dose ranges from 20-150 µg/min. Because of its favorable effect on myocardial ischemia, it is particularly effective in acute coronary syndromes and acute pulmonary oedema.

## *Practical Considerations*

- Intravenous diuretics should not be used as initial therapy in a hypertensive crisis unless the patient presents in acute pulmonary oedema or there is evidence of extracellular volume expansion. The haemodynamic profile of hypertensive crisis is characterized by a pronounced elevation of systemic vascular resistance and volume depletion. Intravenous loop diuretics will aggravate the hypovolaemia and further stimulate renin-angiotensin activity which may exacerbate hypertension and cause further deterioration in renal function. Oral diuretic therapy can be added for optimal long-term control of blood pressure after the acute stage of management.
- The practice of managing hypertensive crisis with a combination of a rapidly acting sublingual nifedipine plus an IV loop diuretic should be avoided. The uncontrolled reduction of arterial pressure using these drugs may result in organ hypoperfusion and catastrophic end-organ damage such as cerebral infarction, or acute myocardial infarction.
- Some physicians may not have hospital access to provide appropriate IV infusion therapy; it is possible to allow the administration of a single dose of sublingual captopril 12.5 mg (1/2 tablet of 25 mg) with close monitoring of blood pressure until the patient can be transferred to a properly equipped hospital. The action of sublingual captopril starts in 30 minutes, peaks at 50 minutes and lasts for 4-6 hours. It is not effective in all patients and is contraindicated in patients with suspected bilateral renal artery stenosis and in pregnancy. Clonidine alpha methyl dopa (aldomet) can bring rapid reduction in blood pressure (within three hours) after oral administration.

Table 17. Parental Agents for Treatment of Hypertensive Emergencies

Agent	Intravenous dose	Onset of Action	Duration of Action	Indications
Nitroprusside	0.25-10 µg/kg/min	Immediate	1-2 min	Most hypertensive emergencies
Nitroglycerin	20-150 µg/min	2-5 min	2-5 min	Angina, acute myocardial infarction, acute left ventricular failure
Labetalol	20-80 mg IV bolus q 10-15 min or infusion 0.5-2.0 mg/min	5-10 min	3-6 hr	Most hypertensive emergencies, including aortic dissection and catecholamine crisis
Esmolol	500 µg/kg/min for 1 min, then 50-300 µg/kg/min for 4 min; repeat sequentially	1-2 min	10-20 min	Perioperative hypertension, aortic dissection
Phentolamine	Bolus 5-10 mg q 5-15 min	1-2 min	3-10 min	Catecholamine crisis

Hydralazine	Bolus 5-10 mg q 20-30 min. total 30-40 mg	10-20 min	2-4 hours	Eclampsia
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## MANAGEMENT OF HYPERTENSIVE URGENCIES

- There is no evidence that acute lowering of blood pressure will improve short or long- term outcome. Most cases can be managed as out-patients using combination drug therapy based on a diuretic plus  $\beta$ - blockers, ACE-inhibitors or Calcium channel blockers to lower the blood pressure over few days.
- Again, the use of rapidly-acting sublingual preparations and IV loop diuretics in this situation is unnecessary and may result in catastrophic complications.

## PERIOPERATIVE HYPERTENSION

- Perioperative hypertension usually refers to severe hypertension  $\geq 200/110$  mmHg which develops in the perioperative period and which requires parenteral drug therapy because the patient cannot receive oral medication or because the surgical procedure cannot be deferred.
- Patients with severe or uncontrolled hypertension and those with target organ damage often develop hypertensive episodes during surgery particularly immediately after extubation and are at increased risk for perioperative myocardial infarction and congestive heart failure.
- Patients with mild to moderate hypertension who are well controlled on medical therapy should continue their prior antihypertensive regimen on the day of surgery and often run an uncomplicated course.
- It is important to exclude the possibility that a rise in blood pressure is a secondary response to stress, perioperative pain, bladder distension, hypoxemia, hypothermia or over-administration of inotropic agents.
- The agents of choice for management of perioperative hypertension include: esmolol, nitroglycerin, and sodium nitroprusside. Intravenous nitroglycerine is the drug of choice for management of postoperative hypertension following coronary artery bypass graft surgery.

## CHAPTER 12

### HYPERTENSION IN SPECIAL GROUPS

#### HYPERTENSION IN PREGNANCY

- ✓ Mild preeclampsia is managed by close observation of the mother and fetus preferably in hospital. If the diastolic blood pressure remains persistently >100 mmHg, oral antihypertensive drug therapy is instituted.
- ✓ Severe preeclampsia (SBP > 169 mmHg and/or DBP > 109 mmHg) is a medical emergency chiefly because of the high risk of maternal death and disability associated with intracerebral hemorrhage. The mother should be hospitalized for rapid lowering of the blood pressure using IV hydralazine, anticonvulsant therapy, and timely induction of labor after stabilization of the blood pressure.
- ✓ The oral antihypertensive drug of choice in pregnancy is methyldopa. Alternatives include b- blockers, labetalol, and nifedipine. Diuretics are better avoided. ACE-inhibitors and angiotensin receptor blockers are absolutely contraindicated.
- ✓ The drug of choice for parenteral therapy is hydralazine. Possible alternatives include nitroglycerin and labetalol.
- ✓ All antihypertensive drugs which are excreted in breast milk are present in very low concentrations except atenolol and nifedipine which attain high levels in breast milk and should be avoided in lactating mothers.

Hypertension complicates about 7-10% of all pregnancies. Apart from being the most common medical complication of pregnancy, it is the leading cause of maternal morbidity and mortality worldwide.

#### DEFINITIONS AND CLASSIFICATION

There are four major hypertensive disorders in pregnancy:

1. Preeclampsia- eclampsia.
2. Chronic preexisting hypertension.

3. Preeclampsia superimposed on chronic hypertension.
4. Gestational hypertension.

- Hypertension is defined as blood pressure exceeding 140/90 mmHg. Diastolic blood pressure is measured at Korotkov phase V.
- **Chronic preexisting hypertension:** hypertension that predates pregnancy or a blood pressure > 140/90 which develops before the 20<sup>th</sup> week of gestation. Rarely high blood pressure is the result of secondary causes as renal parenchymal disease.
- **Gestational hypertension:** is transient mild hypertension during the third trimester. It carries little risk to the mother or fetus. The hypertension typically resolves shortly after delivery, but tends to recur with subsequent pregnancies and may represent a risk factor for future development of essential hypertension.
- **Preeclampsia:** hypertension associated with proteinuria and generalized oedema which develops after the 20<sup>th</sup> week of gestation.
- **Eclampsia:** the development of convulsions unrelated to other cerebral conditions during the course of preeclampsia.

## PREECLAMPSIA- ECLAMPSIA

Preeclampsia complicates 3-14% of all pregnancies. Eclampsia occurs at a variable incidence of 1/300 to 1/3000 deliveries.

### Clinical Manifestations

- More common in nulliparas, older multiparas, hydatiform mole, twins and diabetic women.
- Proteinuria ( $\geq 300$  mg/d) is abnormal in pregnancy. it may be absent in early preeclampsia.
- Oedema alone is not abnormal in pregnancy.
- Eclampsia does not necessarily correlate with the severe features of hypertension. So, all women with preeclampsia are at risk.
- Ominous features in women with preeclampsia are listed in table 18.

Table 18. Ominous Features in Preeclampsia

- Systolic blood pressure >169 mmHg
- Diastolic blood pressure > 109 mmHg
- Proteinuria  $\geq$  2 gm/day or spot urine protein > 100 mg/dl
- Increasing serum creatinine (> 2 mg/dl)
- Platelet count < 100,000/mm<sup>3</sup>
- Evidence of haemolysis
- Epigastric or right upper abdominal pain
- Severe headache, or other cerebral signs
- Congestive heart failure
- Retinal hemorrhage, exudates, or papilloedema
- Intrauterine fetal growth retardation

## Management

### *Non pharmacologic Management and Preventive Measures*

- Adequate periods of rest.
- Normal diet. Salt restriction is not recommended.
- Weight reduction is not advised, since it may be associated with reduced fetal birth weight.
- Calcium supplementation (2 gm/day) may reduce the incidence of pregnancy related hypertension.
- There is no sufficient evidence to support the use of low-dose aspirin to prevent preeclampsia.

### *Mild Hypertension*

- There is no evidence that antihypertensive drug therapy alters maternal or foetal outcome.
- Pregnancy is allowed to mature as long as blood pressure is controlled and other signs of severe preeclampsia are absent.
- Patients with a diastolic pressure of 90-105 mmHg should be put under close observation. A short period of hospitalization may be required.
- If the diastolic blood pressure remains persistently > 100 mmHg, oral antihypertensive therapy can be started. Methyldopa is the drug of choice. Possible alternatives include  $\beta$ - blockers, labetalol and long acting nifedipine.

### *Severe Hypertension*

- Patients with systolic blood pressure >169 or diastolic blood pressure > 109 mmHg should be hospitalized. Management includes rapid lowering of blood pressure, prophylactic anticonvulsant therapy and timely induction of labour.
- In patients with ominous features of preeclampsia (Table 1), immediate delivery is mandatory.
- IV hydralazine is the drug of choice. Refractory cases can be given IV nitroglycerin, or IV labetalol.
- IV magnesium sulfate is the drug of choice for preventing eclamptic convulsions. It is administered slowly as a loading dose of 6 gm diluted in 150 ml glucose 5% over administered 20-30 minutes followed by continuous infusion of 2 gm/hr.

### MANAGEMENT OF CHRONIC PREEXISTING HYPERTENSION

- Preexisting hypertension is managed according to the same principles applied for management of preeclampsia.
- In general, patients can continue their previous medication except for ACE-I and Angiotensin receptor blockers.
- In patients with mild hypertension, the threshold to start drug therapy should be lowered to 140/90 mmHg under the following conditions:
  - Evidence of target organ damage.
  - Presence of intrinsic renal disease.
  - Preeclampsia superimposed on chronic hypertension.

### ANTIHYPERTENSIVE DRUGS IN PREGNANCY

#### Oral Drug Therapy

#### *Methyldopa*

This is the most widely used antihypertensive drug in pregnancy because of its long established safety to the foetus. The total daily dose varies from 500-2000 mg.

#### *b - Blockers*

- Metoprolol (100-200 mg) and oxprenolol (80-480 mg), are safe and effective when used in late pregnancy. An increased incidence of intrauterine growth retardation has been reported when treatment was started in early or mid

pregnancy. Other adverse effects to the fetus include bradycardia, hypoglycemia, and transient neonatal apnea.

- Atenolol is not the  $\beta$ - blocker of choice in pregnancy.

### *Labetalol*

Labetalol (combined  $\alpha$  and  $\beta$ - blocker) decreases the peripheral vascular resistance with little effect on maternal heart rate. It appears to be safe to the fetus although it was associated with intrauterine growth retardation. The oral daily dose varies from 200-600 mg.

### *Calcium Channel Blockers*

Nifedipine retard is used in a dose of 10-20 mg bid. It may decrease uterine contractions and prolongs the course of labour. Drug interaction with magnesium sulfate may cause severe hypotension.

### *Diuretics*

- Diuretics should be avoided in pregnancy because of its relatively low efficacy, risk of hypovolemia, stimulation of the renin-angiotensin system, hyperuricemia, hyponatremia and neonatal thrombocytopenia.
- Patients with chronic hypertension already on diuretic therapy can probably continue taking it through pregnancy as long as volume depletion can be avoided.
- The only established indication of diuretics in preeclampsia is the use of furosemide in the postpartum period to treat fluid overload and pulmonary oedema.

### *ACE-Inhibitors and Angiotensin Receptor Blockers*

These drugs are absolutely contraindicated in pregnancy since they cause a significant reduction in placental blood flow, foetal deformity, neonatal renal failure and intrauterine foetal death.

### *Hydralazine*

- Hydralazine is the parenteral drug of choice for management of severe hypertension in pregnancy.
- Action starts in 10-20 minutes, with a peak effect in 60 minutes and a duration of 2-4 hours. The total dose should not exceed 30-40 mg.

- Dose: given in intermittent IV boluses starting by 5 mg and increasing to 10 mg, and if necessary repeated every 20-30 minutes until the diastolic blood pressure is reduced below 100 mmHg.
- Side Effects:
  - Maternal tachycardia, headache, tremors, vomiting, and salt and water retention.
  - Excessive lowering of blood pressure is associated with reduced placental blood flow and foetal distress.

### *Nitroglycerin*

- IV nitroglycerin is indicated only in patients who do not respond adequately to hydralazine.
- Careful monitoring is necessary to avoid abrupt hypotension in volume depleted women which may lead to foetal distress.

### *Labetalol*

Given slowly as 20 mg bolus repeated every 10 minutes to a total dose of 300 mg.

### *Sodium Nitroprusside*

- This potent vasodilator is generally avoided in pregnancy since even small doses are associated with abrupt hypotension and paradoxical bradycardia in volume-depleted preeclamptic patients.
- It carries the risk of thiocyanate and cyanide toxicity to the mother and foetus.
- Its use should be restricted to refractory hypertensive crisis which failed to respond to other agents.
- The initial infusion dose should be 0.2 µg/kg/min.

## HYPERTENSION AND LACTATION

- Breast-feeding does not increase blood pressure in the nursing mother.
- Bromocryptine which is used to suppress lactation may induce hypertension.
- All antihypertensive drugs are excreted in breast milk. Most are present in very low concentrations except atenolol and nifedipine which attain high levels in breast milk and should be avoided in lactating mothers.

## HYPERTENSION IN CHILDREN AND ADOLESCENTS

- ✓ The prevalence of hypertension in children and adolescents varies from 1-2%.
- ✓ The blood pressure measurement in a child should be compared with the childhood reference data tables based on age, gender and height.
- ✓ High blood pressure (hypertension) in children is diagnosed when average systolic blood pressure or diastolic blood pressure (or both) is equal to or greater than the 95<sup>th</sup> percentile for age and gender.
- ✓ Younger children with severe blood pressure elevation more often have secondary hypertension, and need careful clinical evaluation. The major causes of secondary hypertension in children and adolescents are of renal parenchymal origin. Cardiovascular and renovascular causes are second in frequency.
- ✓ Treatment of essential hypertension is still empirical; the first step is restriction of excess caloric and sodium intake.
- ✓ In hypertensive children and adolescents in whom the blood pressure remains elevated despite life style modification, pharmacologic therapy is recommended with the initial choice being a diuretic or a beta-blocker in doses adjusted to body weight.

### PREVALENCE AND SIGNIFICANCE

- The prevalence of hypertension in children and adolescents varies from 1-2%.
- Childhood hypertension is associated with significant morbidity and mortality.

### BLOOD PRESSURE MEASUREMENT IN CHILDREN

- Routine blood pressure measurements by sphygmomanometer should be a part of the periodic physical examination by the age of 3, in older children and whenever the child is acutely ill or symptomatic.
- Fifth Korotkov sound is used as the best indirect reflection of the diastolic blood pressure.
- Choice of cuff size: small cuffs are available for use in children.

- Blood pressure measurement in a child should be compared with the childhood reference data tables based on age, gender and height.
- A quick reference table for the diagnosis of childhood hypertension at different ages is suggested in table 19.

Table 19. Suggested Quick Reference Table for Blood Pressure Levels above Which Hypertension in Child Should be Considered

Age (year)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg) *
1	105	70
6	115	76
12	125	84
18	135	90

\* Diastolic blood pressure is considered as 2/3 that of systolic blood pressure.

#### DEFINITIONS AND CLASSIFICATION

- **Normal blood pressure:** average systolic blood pressure and/or diastolic blood pressure less than the 90<sup>th</sup> percentile for age and gender.
- **High-normal blood pressure:** average systolic blood pressure and/or diastolic blood pressure between the 90<sup>th</sup> and 95<sup>th</sup> percentiles for age and gender.
- **High blood pressure (hypertension):** average systolic blood pressure and/or diastolic blood pressure equal to or greater than the 95<sup>th</sup> percentile for age and gender.
  - *Mild hypertension:* blood pressure level that is consistently 5 to 9 mm Hg above the upper limit.
  - *Severe hypertension:* blood pressure level that is consistently  $\geq 10$  mm Hg above the upper limit.

## CAUSES OF HYPERTENSION IN CHILDREN

- Table 20 lists the most common causes of hypertension seen in children in varying ages according to their prevalence.
- The major cause of secondary hypertension in children and adolescents is renal parenchymal diseases; cardiovascular (mainly coarctation of the aorta) and renovascular causes are second in frequency (collectively these account for 70-90 % of all cases).
- Essential hypertension is infrequent below six years.

Table 20. The Most Common Causes of Hypertension in Children According to Age\*

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*Newborn:*

Renal artery thrombosis  
Renal artery stenosis  
Renal vein thrombosis  
Congenital renal abnormalities  
Coarctation of the aorta

*First year of life*

Coarctation of the aorta  
Renovascular disease  
Renal parenchymal disease

*Age 1 to 12 years*

Renal parenchymal disease  
Renovascular disease  
Coarctation of the aorta  
Endocrine disease  
Essential hypertension (predominantly isolated systolic).

*Age 12 to 18 years*

Essential hypertension  
Prescribed drugs, drug abuse: steroids, CNS stimulants.  
Renal parenchymal disease  
Renovascular disease (less common)  
Coarctation of the aorta (less common)

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\* Listed in the order of frequency of occurrence.

Source: Bartosh SM, Aronson AJ Childhood hypertension: an update on etiology, diagnosis and treatment. *Pediatr Clin North Am*; 1999, 46: 935

## CLINICAL EVALUATION

- The initial workup of an asymptomatic child with elevated blood pressure is listed in table 21.

Table 21. Evaluation of Asymptomatic Children and Adolescents with Persistently Elevated Blood Pressure Levels

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### HISTORY

#### *Patient*

- Past or present history of events that influence blood pressure e.g., radiation to the kidney, recurrent urinary tract infection, drugs with pressor properties.
- Dietary habits; calories, sodium intake.

#### *Family*

- Essential hypertension and/or its complications.
- Obesity, hyperlipidemia.
- Genetic disorders associated with hypertension.
- Blood pressure elevation in siblings.

### PHYSICAL EXAMINATION

- Blood pressure in both arms and legs.
- Clues to secondary causes: coarctation, Cushing's syndrome, abdominal mass or bruits.
- Target organ damage: fundoscopic and cardiac examination.

### LABORATORY

- Urine analysis
- Hematocrit
- Urea / creatinine, electrolytes
- Renal ultrasound
- Lipid levels
- Echocardiography

- 
- The likelihood of identifying a secondary cause of hypertension is directly related to the degree of blood pressure elevation and is inversely related to

the age of the child. Thus, younger children with severe blood pressure elevation more often have secondary hypertension and need careful clinical evaluation and additional workup.

- Factors that amplify the tendency toward higher levels of pressure include obesity, lack of exercise, excessive sodium intake, tobacco or alcohol use, and exposure to drugs with pressor or nephrotoxic properties.

## TREATMENT

- The goal of treatment is reduction of blood pressure below the 95<sup>th</sup> percentile.
- Treatment of essential hypertension is still empirical; the first step in young children with persistently elevated level of pressure is life style modification: weight loss in obese children, increased physical activity and restriction of excess caloric and sodium intake. Potassium enriched diet may exert an additional protective effect.
- In hypertensive children and adolescents in whom the blood pressure remains elevated, pharmacologic therapy is recommended, with the usual initial choice being a diuretic or a beta-blocker. If either diuretic or a beta blocker in sufficient dosage does not provide blood pressure control, an angiotensin converting enzyme inhibitor or a calcium channel blocker may be warranted.
- The dosages of antihypertensive medications should be adjusted on the basis of the child's body weight. Recommended dosages are provided in table 22.

Table 22. Pediatric Doses of the Most Commonly Used Antihypertensive Drugs

Group	Drug	Dose	Frequency
Diuretics	Hydrochlorothiazide	1-2 mg/kg/24 hr	q 12-24 hrs
B-blockers	Propranolol	0.25-1.0 mg/kg/dose	q 6-8 hrs
ACE inhibitors	Captopril	0.1-0.3 mg/kg & increase to max 2mg/kg/dose	q 8 hrs
Calcium channel antagonists	Nifedipine	0.2-0.5 mg/kg max. 10-20 mg/dose	
Sympatholytics	Methyldopa	10 mg/kg/24 hrs	Q 6-8 hrs

## HYPERTENSION IN THE ELDERLY

- ✓ Hypertension is more common in older people and incurs a greater absolute cardiovascular risk.
- ✓ Treatment of isolated systolic hypertension in the elderly is associated with an even larger absolute reduction in cardiovascular complications compared to treatment of younger patients with conventional systolic and diastolic hypertension.
- ✓ Older patients tolerate antihypertensive drug therapy as well as younger ones.
- ✓ Low-dose thiazide diuretics and long acting dihydropyridine calcium antagonists constitute the first line treatment in elderly patients.

### PREVALENCE

- Individuals of 65 years or older are considered elderly.
- Hypertension is more prevalent in elderly people than in younger ones. In Egypt, data from National Hypertension Project indicates that two out of three elderly people have hypertension.

### AGE RELATED CHANGES IN BLOOD PRESSURE

- Systolic blood pressure rises linearly with advancing age, by an average of 25 mmHg in men and 35 mmHg in women between the fourth and ninth decades.
- The diastolic blood pressure tends to plateau before age 60 and drops thereafter. Therefore, older persons are more likely to present with isolated systolic hypertension and increased pulse pressure.

### CHARACTERISTICS OF HYPERTENSION IN THE ELDERLY

#### Pseudohypertension

- In elderly patients, blood pressure may be artificially elevated by the usual indirect cuff measurement technique as a result of increased stiffness of the large arteries, which interferes with compression and collapse of the brachial artery.
- Pseudohypertension should be suspected if:
  - Target organ damage is absent despite high blood pressure readings.

- Symptoms of hypotension while the sphygmomanometer pressure is high.
- Arterial wall is felt while inflating the sphygmomanometer cuff above systolic pressure and absence of arterial pulsations (Osler maneuver).
- Resistant hypertension in the elderly.

### Variability of blood pressure

- Manifested as excessive systolic blood pressure variability, post prandial hypotension and postural hypotension. This is caused by impaired baroreceptor function, reduced blood volume and diminished B-receptors responsiveness.
- White coat hypertension is common in elderly persons especially women.

### Auscultatory Gap

The auscultatory gap is more common in old age and may lead to underestimation of systolic blood pressure (see chapter 2).

## DIAGNOSIS

The main diagnostic goals are:

- To establish the diagnosis of hypertension:
  - Accurate and repeated measurements of blood pressure on several occasions in view of the excessive variability in blood pressure.
  - Blood pressure should be measured in the supine and standing positions. Elderly persons may have postural hypotension even before starting antihypertensive drug therapy.
  - The diagnostic pitfalls of pseudohypertension, auscultatory gap and white coat hypertension should be carefully considered.
- To determine the presence of target organ damage.
- To look for a possible aetiology in patients with suspected secondary hypertension. Common causes include renal parenchymal disease, renovascular hypertension and hypothyroidism.
- To consider the effects of co-morbid conditions. Elderly patients often have diabetes mellitus, left ventricular dysfunction, impaired renal function, cerebrovascular disease, depression, prostatic enlargement and osteoarthritis. These conditions may affect the selection, dosage and drug interactions of antihypertensive drug therapy.

## ISOLATED SYSTOLIC HYPERTENSION

### Definition

Systolic blood pressure greater than 160 mmHg with diastolic blood pressure less than 90 mmHg.

### Prevalence

Isolated systolic hypertension is the most common form of hypertension in the elderly.

### Significance

- Systolic blood pressure is a strong predictor of cardiovascular complications than diastolic blood pressure.
- Lowering of systolic blood pressure in the elderly is associated with significant reduction in cardiovascular mortality, stroke, heart failure, myocardial infarction, and dementia.

## ROLE OF NONPHARMACOLOGIC THERAPY

- The elderly hypertensive patients respond to non-pharmacological measures to lower blood pressure the same as younger patients. Life style modification is used as initial treatment in all patients, and should be continued even if drug therapy is instituted.
- The elderly (especially women) have increased sensitivity to salt. Blood pressure is readily increased by salt loading, and reduced by salt restriction.

## PHARMACOLOGICAL THERAPY

### *Benefits of Blood Pressure Reduction*

- An equivalent blood pressure reduction will produce a greater benefit in the elderly than in younger patients.
- Stroke is reduced by 30%, cardiovascular events by 20%, dementia by 50%, and mortalities by 13%.

### *Target Blood Pressure*

- For diastolic hypertension, reduce diastolic pressure to below 90 mmHg (same as young hypertensives).
- For systolic hypertension, reduce systolic pressure to below 160 mmHg.

### *Drugs to Use*

- Low-dose thiazide diuretics remain the drug of choice in the elderly patients.
- Calcium channel blockers are recommended as the second drug of choice.
- ARBs and ACE-I are effective in preventing hypertensive complications in the elderly hypertensive patients.

### *Drugs to Avoid*

- Centrally acting agents may cause drowsiness, depression or impaired cognitive function and should be avoided in old patients.
- $\alpha$ -adrenergic antagonists cause postural hypotension which is undesirable in these patients.
- Drugs which exacerbate hypertension e.g. nonsteroidal antiinflammatory drugs should be used with caution.

### *Practical Considerations*

- Start with smaller doses, at almost half the standard doses.
- Increase the dose gradually over several weeks.
- Check blood pressure always in supine and standing positions. Titrate doses according to standing pressures to avoid excessive orthostatic hypotension.
- Monitor renal function and electrolyte status in patients on diuretics or ACE-inhibitors.
- Adverse drug reactions are two to three times more common in the elderly.
- Follow-up visits should be scheduled every two to four weeks until blood pressure is controlled.
- Consider co-morbid conditions and poly pharmacy which are common in the elderly.

## CHAPTER 13

### HOME BLOOD PRESSURE MEASUREMENTS

- ✓ Home blood pressure measurement provides numerous measurements over several days in normal settings.
- ✓ Studies conducted in the general population and hypertensive individuals have consistently demonstrated that blood pressure values obtained at home are several mmHg lower than those obtained by the office measurements.
- ✓ There is a lower threshold value for hypertension when measured by home readings (< 135/85 mmHg).
- ✓ Major limitations include absence of consensus on normal values, most of the available devices are inaccurate, and there is limited information about its prognostic value.
- ✓ Useful when white coat hypertension is suspected or when there is inadequate response to therapy, or there is marked variability in blood pressure. Three to six measurements per week provide average out-of-office levels.

#### ADVANTAGES OF HOME MEASUREMENT OF BLOOD PRESSURE

- Provides numerous values on different days in a setting closer to daily life conditions than doctor's office.
- Distinguishes white coat hypertension from sustained hypertension.
- Has a positive impact on patients' perception of their hypertension problems and enhance adherence to medications.
- Helps in the assessment of the response to antihypertensive medications.
- Potentially reduces the costs.

#### LIMITATIONS OF BLOOD PRESSURE MEASUREMENT AT HOME

- There are limited data available about the prognostic value of home blood pressure measurements.
- The vast majority of the devices used have not been evaluated independently for accuracy.

- Anxiety: some patients become obsessed with the measurement of their blood pressure to the extent that they check it many times everyday. Patients should be informed that blood pressure is a biologic variable which is liable to change from one minute to another and fluctuations in blood pressure readings are expected.

#### UPPER LIMITS FOR NORMAL BLOOD PRESSURE

- Values of 135 mmHg systolic and 85 mmHg diastolic, based as an average of two measurements in the morning and an additional two in the evening for at least three working days.

#### RECOMMENDATIONS FOR HOME BLOOD PRESSURE MEASUREMENT

- Patients with significant white coat reaction, inadequate response to treatment, resistant hypertension, and patients with big variations of office values are the groups of patients who benefit most from home blood pressure measurement.
- Home blood pressure measurement must be regarded as supplementary to conventional office measurement, not a substitute for them.
- Physicians should advise patients to use only devices that underwent a validity check. These devices must be regularly checked against a device of known calibration as mercury column sphygmomanometer.
- Patients should be instructed how to check their blood pressure accurately.

# CHAPTER 14

## ECONOMICS OF HYPERTENSION CONTROL

### THE ECONOMIC BURDEN OF HYPERTENSION

Direct costs for detection, evaluation and management of hypertension.

Indirect costs of economic consequences of the illness, such as loss of productivity and earnings.

Intangible costs range from relatively small adverse effects on the quality of life resulting from hypertension treatment, to major impairment due to hypertension complications.

Hypertension related complications such as stroke, coronary heart disease and renal failure. All have devastating socioeconomic problems.

### COST EFFECTIVENESS

- In hypertension, cost effectiveness is used in reference to the cost of drugs, and other direct medical expenses required to prevent one myocardial infarction, stroke or death.
- Cost effectiveness is calculated as:  
*average drug price for 5 years + consultations + diagnostic tests) X number needed to treat for 5 years.*
- Cost effectiveness improves with older age, male sex, severity of hypertension and compliance.

### COST MINIMIZATION

- Patient selection: accurate diagnosis and classification of hypertension (chapter 6).
- Use of total risk concept: baseline risk assessment provides guidance on whether to treat milder forms of hypertension (chapter 7).
- Integrate the workup: simultaneously identify target organ changes, concomitant risk factors and possible cause of secondary hypertension, and limiting laboratory tests to those that are medically necessary.
- Encourage life style modifications (chapter 7)

- Optimize drug use: initiate antihypertensive treatment with diuretics in patients with no indications for other agents.
- Utilize drug efficiently: use proper drug dosages and combinations. Consider fixed combinations that cost less than separate drugs.
- Enhance compliance (chapter 8).
- Utilize trained nonphysician professionals e.g., nurse practitioners, who can ensure proper blood pressure measurements and enhance compliance with therapeutics and life style strategies.

### ECONOMIC MODELS TO CONTROL HYPERTENSION

There are two complementary approaches to reduce the level of blood pressure in a target population:

#### *The population strategy*

- Aims to shift the blood pressure distribution and hence reduce cardiovascular disease across the entire population even in those with lowest relative risk.

#### *The high-risk approach*

- Aims to reduce blood pressure in individuals who are by their level of blood pressure are at greatest risk of complications.
- This approach has important benefits on the individual but may have little impact on the population.

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