The Egyptian Heart Journal (2014) **66**, 79–132

Egyptian Society of Cardiology

The Egyptian Heart Journal

www.elsevier.com/locate/ehj
www.sciencedirect.com

The Egyptian Hypertension Society
EGYPTIAN HYPERTENSION GUIDELINES

Principal Editor
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2014

http://dx.doi.org/10.1016/j.ehj.2014.03.001

The main objectives of this document are to provide the practitioners in Egypt with up-to-date information regarding the management of hypertension in a poor resources setting and help answering practical questions seen in daily practice. The development of guidelines took into consideration the low socioeconomic status of the majority of the Egyptian patients, the defective health care system in our country- majority of public pay out of their own pocket to cover the health costs, in addition to the limited medical education in the field. The target physician population for these guidelines is the general practitioners, family doctors, internists and those who are taking care of hypertensive patients.

Principal Editor
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Cairo, October 2013

Abstract

This is the third version of the Egyptian Hypertension Society (EHS) Guidelines. The guidelines were developed by a working group of 28 members, including cardiologists, nephrologists and internal medicine specialists, who were divided into 6 writing groups and an implementation group. Members reviewed the recent world literature as well as other national and international guidelines. The working groups had a number of meetings over a period of one and half year, before finalizing the document. The Egyptian guidelines were based upon two principles: 1. Address practical issues, 2. Cost containment. They stressed the need for frequent office visits and careful measurement of blood pressure before making a diagnosis of hypertension. Higher threshold for diagnosis of hypertension (150/95 mmHg) was recommended. Ambulatory blood pressure monitoring (ABPM) was indicated in a selected group of patients. Laboratory work-up was kept to the minimum particularly when resources and facilities are limited. The need for lifestyle modification (LSM), controlling obesity and limiting salt intake were stressed.

Initiation of pharmacologic treatment, duration of blood pressure monitoring and frequency of office visits were based upon the global cardiovascular risk profile, level of blood pressure and response to LSM. In low risk patients, no drug therapy is recommended when blood pressure is less than 160/100 mmHg. Shorter period of blood pressure monitoring and lower blood pressure threshold (140/90 mmHg) is advised in moderate and high risk patients. In absence of compelling indications any of the five standard pharmacologic groups (diuretics, beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers) can be selected as initial therapy preferably a thiazide diuretic.

In absence of satisfactory control of blood pressure, it is recommended to ensure patient's adherence to therapy and lifestyle changes and that he is not taking pressor medications. Obstructive sleep apnea (OSA), white coat hypertension, inadequate diuretic therapy and secondary forms have to be considered as causes for resistant hypertension. Pharmacologic therapy should be modified according to the presence of chronic kidney disease, diabetes, coronary artery disease, heart failure and severity of hypertension. The guidelines addressed management of hypertension in special groups such as obese subjects, the elderly, pregnant women, hypertensive emergencies and patients with valvular heart disease.

KEYWORDS: Guidelines; Egypt; Hyptertension; Lifestyle; Antihypertensive drugs

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Guidelines were developed independent from funding organizations.
There is no conflict of interest of working group members.

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Problem of Hypertension in Egypt

Data from the Egyptian National Hypertension Project (NHP) [1–7] showed that hypertension is common among Egyptians. In the years (1991–1993), 26.3% of adult Egyptians have high blood pressure. More than 50% of individuals older than 60 years suffered from hypertension. At present, if the same prevalence rates did not change, it is predicted that with an Egyptian population of more than 80 millions, there are approximately 15 millions with hypertension and about 7 millions will be in need of lifelong drug treatment and regular follow-up. The problem is complicated by the low awareness rates, only 38% of hypertensive Egyptians were aware of having high blood pressure, only 24% were receiving treatment, whereas control rates ($<140/90$ mmHg) were 8%. Other cardiovascular risk factors namely hypercholesterolemia, increased LDL-cholesterol, low HDL-cholesterol, hypertriglyceridemia, diabetes, impaired glucose tolerance and obesity were present in 60% of hypertensive patients [8]. Target organ damage was present in patients with more than stage I hypertension ($\geqslant 160/100$ mmHg), e.g. ECG-LVH in 20%, coronary artery disease (CAD) 16%, systolic heart failure in 5% and renal failure in 3.2% [9]. Egyptians have one of the highest mortality rates secondary to CAD worldwide [10,11]. Hypertension is an established major risk factor for CAD.

These epidemiologic data underscore the need for developing national hypertension guidelines aiming at improving the rates of awareness, treatment and control of hypertension with the final goal of preventing or delaying target organ damage, hypertensive complications, cardiovascular and renal events and decreasing morbidity and mortality.

Because of its high prevalence, the treatment of hypertension puts economic pressure on Egyptian economy. Drug cost is the major determinant of cost of care, responsible for around 80% of total cost of hypertension care within the first year of treatment [12,13]. In Egypt, the drug cost of hypertension (total antihypertensive market) during the year 2011 was more than one billion Egyptian pounds, a dramatic increase from 600 millions in 2007 [14].

In view of Egypt's limited financial resources and the limited government spending on health which equals annually 42 USD per capita (year 2008), while total annual/capita expenditure on health is 124 USD compared with 3925 USD in USA [14], guidelines should give priority to cost of care. Furthermore, more than 58% of spending in Egypt on health care is out of pocket [14]. Choices must be made as to how limited budget is spent. Therefore, countries with limited resources can not treat everyone with BP beyond the defined threshold stated in the international guidelines. A higher threshold of $>150/95$ mmHg for initiation of therapy might be considered and priority should be given to high risk patients. On the other hand, drugs of first choice should be the least expensive such as thiazide diuretics, beta adrenergic blockers and generic forms. Patients will not adhere to drugs that they can not afford.

Problem of Hypertension Diagnosis

Diagnosis of hypertension depends upon accurate BP measurement and repeated BP readings. An accurate measurement will depend upon the equipment, technique, and approach whether office, home or ambulatory BP monitoring (ABPM). Repeated readings are taken through multiple office visits, repeated home measurements or 24 h ABPM.

Accurate measurement requires a well calibrated machine and a trained observer familiar with the details of the technique and precautions taken when checking BP. Many doctors have no formal education on how to measure BP accurately. Ignorance regarding cuff selection and application, incorrect cuff positioning and rapid cuff deflation rate, inadequate rest period, digit bias and lack of repeated measurements will provide inaccurate readings. Faulty equipment – sphygmomanometer (mercury and aneroid) will give wrong numbers. A study [15] showed that 44% of the aneroid sphygmomanometer used in hospital setting and 61% of them used in private medical practices were found inaccurate [15]. Lack of calibration and maintenance of the aneroid sphygmomanometer makes them highly doubtful for routine use in medical practice, unless maintenance and calibration is implemented.

Blood pressure variability is an important limitation of casual BP office readings. The great diurnal variability inherent in BP behaviour, makes office measurement of limited diagnostic value. There is a need for repeated BP measurements before diagnosing hypertension. A single BP measurement would over-diagnose hypertension in 20–30% of cases [16,17]. Many people with current diagnosis of hypertension might not in fact have hypertension. Routine BP values obtained in the office are generally higher than high quality research readings [18]. Blood pressure readings by primary care physicians tend to be higher than what it would be if measurements guidelines were strictly adhered to [18].

ABPM and home BP have a stronger prediction power than conventional office BP for CV events [19]. On the other hand, there is a gap between office and ABPM control. BP control is underestimated at the office (52% vs. 24%) [19]. The numbers of patients starting antihypertensive treatment could be reduced by 25% if ABPM is used instead of clinic blood pressure for diagnosis [20].

There is uncertainty around the current BP cut-off point (140/90 mmHg) leading to a huge number of people being misdiagnosed of having and not having hypertension. Over-diagnosis exposes people unnecessarily to considerable risk of adverse drug reactions.

The choice of a target BP < 140/90 mmHg regardless of underlying cardiovascular risk, intensity of treatment and underlying disease severity may not be a correct policy. Over-treatment and diastolic hypotension have been shown to be associated with worse cardiovascular outcomes [21,22].

The cutoff point for normal BP in the "real world" should be < 150/95 mmHg and not the value < 140/90 mmHg derived from research studies [18]. Patients at low absolute risk may be exposed to potential side effects of a treatment for little or no therapeutic benefit.

The decision to treat or monitor without treatment should be based on patient global CV risk. Low-risk patients have a lower-chance of gaining benefit from treatment. These patients should be given lower priority for treatment when resources are limited.

Need for National Hypertension Guidelines

Physicians in many countries treat hypertension according to their daily experience, drug industry promotion, limited information from medical school and random scientific meetings and publications. In absence of science based evidence and clear guidelines, patients will be mismanaged with irrational use of resources, over and under diagnosis, over and under treatment, exposure of patients to unnecessary laboratory procedures and unnecessary lifelong therapy. Different national and international organizations developed hypertension guidelines based, in the majority, on scientific evidence [23], though there are areas of agreement and disagreements. More importantly guidelines developed for rich industrial countries may not be applicable in developing and third world countries with a different health care system, lifestyle and dietary habits, genetic and ethnic background.

There is a need for practical guidelines designed specifically for use in resource-poor settings in place of the complex and largely impractical international guidelines developed for higher income countries.

The need for national Egyptian guidelines should not be underestimated. This is the third version of guidelines developed by the Egyptian Hypertension Society (EHS). The new guidelines will overcome some of the limitations of the previous one and will update recommendations based upon results of recent clinical trials. A simple, clear, realistic and easy to use guidelines were the main goal of this third version. Medical community should be familiar with guidelines and should implement them in their daily practice. Guidelines, in order to be implemented, should pay regard to the costs of treatment and should include drug affordability as main management component. Management depends on demographic and socioeconomic factors. Other factors to be considered when developing national guidelines include the system of medical education and the culture of the country and should make the best use of available resources.

What is Special about Egyptian Guidelines

Differences from Other Guidelines

The Egyptian guidelines were based on two principles 1. Address practical issues, 2. Cost containment. The main theme of the guidelines is to help answering, whenever possible, the main questions which the doctor faces when he decides that his patient has high blood pressure. Examples are: is his patient truly hypertensive- not simply white-coat or isolated office hypertension? Does he need drug therapy? When to initiate and how to select initial therapy? How to monitor and follow-up? What to do if there is unsatisfactory response to therapy?

Because of limited resources, cost consideration received great priority aiming at the most cost-effective approach in hypertension management. These influence guidelines preparation and make some issues different from other guidelines. The following areas might be different and not in complete agreement with other guidelines.

1. *Blood Pressure Measurement and Diagnosis of Hypertension*
   More frequent office visits and a larger number of blood pressure readings are needed before making a diagnosis of hypertension. The threshold for diagnosis from office readings was raised to 140/90–150/95 mmHg. Since it is not possible to apply ABPM as a standard diagnostic approach because of economic and logistic reasons and the difficulty of obtaining repeated accurate home blood pressure measurements, diagnosis will depend upon office readings which are vulnerable to office variability and diurnal fluctuations.
2. *Limited Laboratory Work-up*
   Global risk assessment can be defined through simple questions about history of cigarette smoking, diabetes, family history, symptomatic CV or renal disease, measurement of body mass index and urine dipstick. This can replace, when resources and facilities are limited, the detailed laboratory work-up recommended in international guidelines.
3. *Diet and Lifestyle*
   To limit the need and reduce the dosage of pharmacologic agents, attention should be paid to dietary regulations and lifestyle modification (LSM). Excess salt intake is common among Egyptians. Salty cheeses, pickles, canned and processed food, chips, salted nuts, ketchup and fast food should be completely avoided while limiting salt during cooking and on table. Intake of fresh fruits and vegetables with legumes (beans) should be encouraged together with exercise and control of obesity. Tobacco should be completely avoided; alcohol is not a problem in Egypt.

4. *Initiation of Drug Therapy*

Unless there is hypertension urgency, a long period of BP monitoring (6–9 months) is recommended before initiating a lifelong drug therapy. Low risk patients with grade I hypertension (BP 150–159/95–99 mmHg) can be followed while on lifestyle modification without drug therapy.A higher threshold is recommended when initiating therapy (160/100 mmHg) in low and intermediate risk groups, since BP alone is a weak predictor of future CV events. Priority of drug therapy is given to high risk patients.

5. *Type of Pharmacologic Treatment*

The monthly cost of drug therapy in Egypt varies from 5 to 180 Egyptian pounds when a single drug is used (monotherapy). Low cost drugs i.e. thiazide diuretics and beta adrenergic blockers should be recommended as initial therapy unless contraindicated or there are compelling indications for other agents. The use of generic CCB, ACEIs and ARBs should replace the expensive brand preparations. Drugs should be affordable and match the patient socioeconomic status.

6. *Measures to Improve Patient's Compliance*

Special emphasis on patient education and involvement, with prescription of simple and long acting affordable drugs while keeping the number of tablets to the minimum.

Guidelines Development

Panel Selection: Formation of Guidelines Working Group

There were two previous guidelines on hypertension developed by EHS in 1998 and 2004. This edition is the third in the series.

The president of the EHS, who is the guidelines main editor, selected a panel of 28 members from different specialties including cardiology, nephrology and internal medicine. Many of these members were involved in preparation of previous guidelines.

The new EHS Guidelines Working Group had its first meeting on May 25th 2012 at the Cairo Marriott Hotel attended by 28 members besides representatives of Ministry of Health and drug industry. During the meeting, there was a review of previous guidelines including important international guidelines, guidelines from other developing countries and the last Egyptian guidelines. The review addressed how guidelines were developed and areas of agreement and disagreement between different guidelines. Questions to be addressed in the new Egyptian guidelines were discussed. The plan of action was agreed upon. Eight different subgroups were formed; seven for writing and one for guidelines implementation. Each subgroup is led by a moderator or contact author who will be responsible for directing the activities of his group and for reporting to the EHS during future meetings. A writing group and an advisory board were selected from working group members.

Identification of Main Questions and Chapters' Contents

During its second meeting in Cairo on 14th June 2012, the contents of different chapters were reviewed and approved. The following 15 questions were thought to be critical in guidelines preparation:

1. How to measure blood pressure accurately? Technique of blood pressure measurement
2. How many measurements? And how frequent office visits?
3. What to do about blood pressure variability?
4. How to assess CV risk?
5. When to initiate pharmacologic treatment?
6. Which drug to choose as initial therapy?
7. When to see patient again?
8. When to change medication?
9. How to improve compliance?
10. What to do when there is lack or unsatisfactory blood pressure control?
11. What is the role of non-pharmacologic treatment?
12. How to manage a hypertensive emergency?
13. How to manage secondary hypertension?
14. How to monitor antihypertensive therapy?
15. How to manage hypertension in the elderly, during pregnancy and in adolescents?

Guidelines were grouped in 6 chapters under the main headings of:

1. Blood pressure Measurement- Hypertension diagnosis.
2. Evaluation.
3. Lifestyle modification.
4. Pharmacologic treatment.
5. Hypertension associated with other diseases.
6. Hypertension in special groups.

A seventh chapter was devoted to algorithm.

Preparation of the Preliminary Draft
The members reviewed available evidence from world literature and other national and international guidelines. The following guidelines were reviewed:

1. American: (JNC VII): 2003
2. Australian: 2008
3. Canadian 2011, 2012
4. Egyptian: 2004
5. European (ESC/ ESH): 2007
6. Indian: 2007
7. Japanese: 2009
8. Latin America: 2009
9. Malaysian: 2008
10. NICE (British): 2011
11. Sub-Saharan Africa (SSA): 2003
12. WHO/ISH: 2003
13. South African Hypertension Guideline 2011

The Final Document
The final document was sent to approximately 600 doctors mainly internists and general practitioners and to a group of experts from university professors with a check list for feedback and comments. Also guidelines with the check-list were put on EHS website for feedback and comments from medical community. The results of the doctors and experts' checklist survey were reviewed and the final document was modified accordingly.

The final draft of the guidelines, taken into consideration the comments and feedback from medical community was approved by all working group members.

Steps in Guidelines Development

1. **Panel selection: formation of guidelines working group**
   – A panel of 28 members from different specialties.

2. **Panel 1st meeting- May 25, 2012 (Cairo, Marriott)**
   – Formation of 7 writing groups and GL implementation group.
   – Identification of main questions to be addressed and approval of plan of action.

3. **Panel 2nd meeting- June 14, 2012 (Cairo, Marriott)**
   – Review and approval of individual chapters' contents.
   – Appointment of chapters' main authors.

4. **Preparation of the preliminary draft by the writing group**
5. **Review of the preliminary draft**
   – Two-day meeting in Alexandria (11-12 October 2012).
   – Assignment of separate reviewer to each chapter.

6. **Prefinal document**: Cairo meeting (22-23 November 2012).
   • Revised draft read and discussed by writing group members.

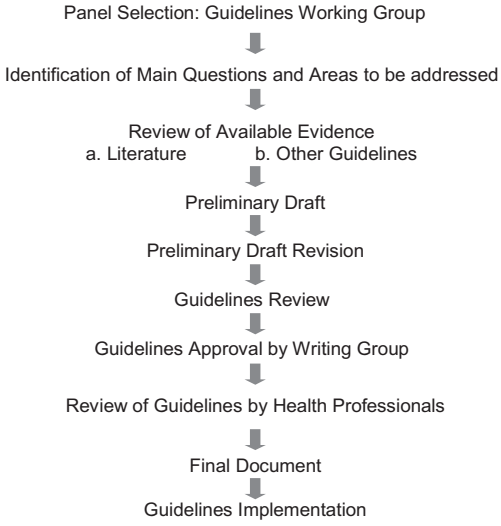
7. **Preparation of provisional final document**: Luxor meeting (19-21 December 2012)
   • All chapters read: provisional approval by WG members.

8. **GL central review committee meeting**: 21 March 2013
   • Agreement on unsettled questions.
   • Approval of all chapters.
   • Preparation of the education program.

9. **Medical community feedback**
   • Provisional final document distributed to about 600 doctors.
   • Checklist survey.

10. **Review of doctors checklist survey by central review committee & preparation of the final document**

11. **Final document approval by all members: Cairo meeting**



Summary Of Recommendations

BP Measurement and Diagnosis of Hypertension

A. Diagnosis of HT

1. Details of BP measurements at office according to guidelines should be followed. All necessary precautions are taken in order to obtain accurate readings.
2. At office measure BP at least 3 times, 30–60 seconds apart after resting quietly 3–5 min. Use the lower of the last 2 measurement to diagnose HT. If the initial readings are high (> 150/95 mmHg), have the patient rest for 5 min and repeat measurement.
3. If all BP measurements are 150/95 mmHg or higher, to confirm the diagnosis of HT choose one or more of the following:
   a. Repeat office BP measurements 3–5 times over 2–3 months depending on BP level.
   b. Offer 24 h ABPM and the use of the average daytime BP.
   c. Home BP monitoring, take as many measurements as possible preferably more than 14 measurements over one week.
4. Encourage the introduction of ABPM and automated BP measurement equipments to the medical community and its use in diagnosis of hypertension.

B. Cutpoints for diagnosing HT

1. Routine clinical practice: at office 140/90-150/95 mmHg
2. Daytime: ABPM: $\geqslant$ 135/85 mmHg
3. Average home BP readings: $\geqslant$ 135/85 mmHg

Evaluation

1. With optimal care check urine sediment and blood for sugar, electrolytes, lipid profile, urea, creatinine and ECG in all patients.
2. Pay more attention and rely on detailed history and physical examination.
3. Use simplified risk stratification method when resources are limited based upon:
   – Age – Smoking – Diabetes (history and urine dipstick) – BMI
   – Associated clinical conditions.
4. Global risk profiling depending upon number of RFs, TOD and symptomatic CVD to categorize patients into: low, moderate, high and very high risk.
5. Detailed laboratory evaluation is recommended in truly resistant hypertensive patients and when suspect secondary hypertension.

Lifestyle Modifications (LSM)

1. Details of dietary instructions should be explained to the patient preferably in writing.
2. Salt restriction (< 5 gm/day) is essential particularly in elderly, diabetics and CKD. List of food items rich in salt should be available in doctors' offices.
3. Weight reduction, smoking cessation and increased physical activity should be stressed in every office visit.
4. Adherence to LSM should be monitored.
5. LSM is recommended in all patients before and during therapy.

Pharmacologic Treatment

1. Drug therapy is life-long and should be considered after failure of LSM to lower BP and if global CV risk is high.
2. In absence of specific or compelling indications for a particular antihypertensive drug, low dose thiazide diuretics are recommended as initial therapy particularly in elderly patients. Patient's socioeconomic status, drug affordability, doctor's experience will influence drug choice.
3. Beta adrenergic blockers (BB) are recommended in young patients with hyperdynamic heart and in the presence of coronary artery disease or specific indications for BB.
4. Calcium channel blockers (CCBs) are recommended in elderly patients, in presence of angina, excessive BP variability or moderately severe hypertension.
5. RAS blockade (ACEIs and ARBs) are recommended in diabetic patients, proteinuria, presence of TOD, associated CV or CKD.
6. Combination therapy (2 or more drugs) is initiated in moderate and severe hypertension and in high risk patients.
7. Gradual reduction of BP and careful titration of drug dosage is essential.

Treatment of Hypertension Associated with CV, Renal Disease and Diabetes

1. Target BP is lower (< 130/80 mmHg) in patients with heart failure, aortic aneurysm, CKD or diabetes with gross proteinuria.
2. BB ± CCB are indicated in patients with angina.
3. BB and RAS blockade after MI.
4. RASB + diuretics in patients with HF, CKD and diabetes.

Hypertension in Special Groups

1. Secondary forms of hypertension (renal artery stenosis, renal parenchymal disease, endocrinal hypertension, coarctation of the aorta) are suspected in hypertension at young age (< 20 years old) or new onset HT above the age of 50 years, in symptomatic (sweating, headache, abdominal pain, weakness, etc) and difficult to control hypertension. Aortic coarctation is suspected when hypertension in young associated with weak and delayed femoral arterial pulse.
2. Factors contributing to resistant hypertension include white coat hypertension, inadequate therapy, lack of patient's compliance, failure of correction of obesity, sleep apnea, intake of pressor drugs and excess salt intake. If loop diuretics and spironolactone in addition to adequate dose of triple pharmacologic therapy fail, consider secondary forms. ABPM and details of laboratory evaluation is needed in this group.
3. Hypertension in the elderly is characterized by excess BP variability, postural changes, white coat effect, sensitivity to salt intake and associated co-morbidities. Diuretics and CCB are the drugs of first choice.
4. Hypertensive emergencies require hospitalization, parentral therapy and arterial pressure monitoring. They include severe hypertension associated with life threatening organ damage, examples are hypertensive encephalopathy, aortic dissection, acute left ventricular failure, brain infarction, intracerebral and subarachnoid hemorrhage. The recommended parental drugs are sodium nitroprusside, labetalol and nitroglycerin.

BLOOD PRESSURE MEASUREMENT

Diagnosis Of Hypertension

- BP must be measured in a standardized fashion using a properly validated, well maintained and recently calibrated device.
- Blood pressure is variable. The diagnosis of hypertension should be based on multiple BP measurements taken on several separate occasions.
- Cut-off point for defining hypertension during office measurement is 140/90–150/95 mmHg, while for average home readings and for daytime ambulatory blood pressure (ABP) is 130/85 mmHg.
- End organ disease and CV event rates correlate more closely with ABP than clinic measurements [24].

Blood Pressure Measuring Devices

Blood pressure can be measured by a mercury sphygmomanometer, aneroid sphygmomanometer, auscultatory or oscillometric semi-automatic devices and automated devices.

- Wrist devices should not be used (for a list of validated BP measuring devices, see: www.bhsoc.org).
- The mercury sphygmomanometer remains the gold standard against which new BP monitor accuracy is judged.
- Aneroid manometers and new devices should be calibrated regularly.
- Digital devices include: Automatic, semiautomatic and manual monitors.

Technique of BP Measurement by Sphygmomanometer

- The blood pressure should be measured in both arms in first visit 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 2 h before the procedure. Talking should be avoided for 5 min prior and during measurement.
- Remove tight clothing, ensure arm is relaxed and supported at heart level.
- Use cuff of appropriate size. BP measuring cuff bladder should cover 80% of the arm circumference of the patient. Larger cuffs are needed for obese subjects and smaller ones in pediatrics.
- Wrap the cuff tightly around the arm. The edge of the cuff should be 3 cm above the elbow crease.
- Inflate the cuff till disappearance of the radial pulse. Slowly deflate the cuff till reappearance of the radial pulse. The level at which the radial pulse starts to reappear is the palpable systolic blood pressure.
- Put a stethoscope over the brachial artery. Inflate cuff to 20–30 mmHg above palpated systolic BP.
- Lower column slowly, by 2 mmHg per second or per beat.
- Measure systolic pressure as first appearance of sounds (Korotkoff I) and diastolic pressure as disappearance of sounds (Korotkoff V). The sudden reduction of sound (Korotkoff IV) is read as diastolic blood pressures when there is a wide pulse pressure (anemia, aortic incompetence, etc …) or when sounds continue to zero blood pressure. Read BP to the nearest 2 mmHg.

Precautions to obtain correct BP reading

1. Choose the correct cuff size.
2. Avoid placing the cuff over clothes.
3. Arm must be at heart level.
4. Patient should rest quietly for 3–5 min before measurement in a quite room with comfortable temperature.
5. Avoid talking during measurement.
6. No caffeine or cigarette smoking at least 1 h before procedure.
7. Bladder should be evacuated.
8. Palpate radial pulse before auscultatory measurements (to avoid the auscultatory gap).
9. Do not deflate the cuff too quickly (2 mmHg/beat).
10. Do not re-inflate the cuff to repeat measurements before it has fully deflated.
11. Take more than one measurement.
12. If there is a difference of more than 10 mmHg between two measurements take more measurements.

Standing BP Measurement

- The standing blood pressure should be taken in the following situations:
  1. First visit evaluation.
  2. Elderly patients (above 60 years).
  3. Diabetic patients of any age.
  4. Patients with postural symptoms; dizziness, light headedness or faintness.
  5. Intake of drugs that can produce postural hypotension

- The standing blood pressure should be measured after 1–2 min of standing.
- 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.
- Orthostatic (postural) hypotension is diagnosed by $\geqslant$20 mmHg drop in systolic blood pressure and/or $\geqslant$10 mmHg drop in diastolic blood pressure within 2 min of standing up.

Methods To Diagnose Hypertension

Office BP Measurement

- Office measurement is the routine method for screening and follow-up of blood pressure. The current cut-off point of diagnosing hypertension in daily practice is based on office measurement.
- Mercury and digital (automated) blood pressure machines can be used in office measurements, but only validated devices are allowed. Mercury sphygmomanometer gives the most accurate BP reading.
- All sphygmomanometers require servicing at least once each year.
- Office measurements correlate poorly with blood pressure measured in other settings. The cut-off point for normal blood pressure in the ''real world'' should be $<$150/95 mmHg and not the value of less than 140/90 mmHg derived from research studies [18].
- The selection of the cut-off point of 150/95 mmHg for diagnosis of hypertension during office measurement is based upon the new data which showed that this level of blood pressure corresponds with the diagnostic threshold of 135/85 mmHg taken at daytime ambulatory blood pressure measurement [18]. This choice will avoid over diagnosis of hypertension since many people with a current diagnosis of hypertension might not, in fact, have hypertension.
- Recent studies showed a consistent difference between awake ABP and the routine office blood pressure greater than the normally recognized 5 mmHg (140/90 mmHg for office blood pressure vs. 135/85 mmHg for mean awake ABP) [18,19]. Thus, BP measured in routine clinical practice seems to be at least 10/5 mmHg higher than a research quality office BP.
- Blood pressure readings by primary care physicians tend to be higher that what it would be if measurement guidelines were strictly adhered to. Table 1 shows classification of hypertension based upon office measurements.

Home BP Measurement

- Self-measurement of BP at home is better than office measurements as it correlates with target organ damage (TOD), it detects white-coat and masked hypertension, it improves patient's adherence to therapy and it is cheaper than frequent office visits.
- Normal home BP measurement should be less than 135/85 mmHg. Measure blood pressure twice daily for 7 days and take average of the last 6 days [24].
- Home measurement should be discouraged if it causes anxiety to the patient or inducing self modification of antihypertensive medications.
- Home measurements should be regarded as supplementary to office readings, not a substitute for them.
- The patient should not stop, modify or change his medication without consulting his physician based on measurements taken outside the physician's office (pharmacy or home).

Rationale for 150/95 mmHg

- Better correlation with clinical outcome.
- Minimize over-diagnosis of HTN in clinical practice.
- Minimize the white-coat effect on BP in general practice.
- Establish a more practical and cost-effective strategies for managing patients in a society with limited health care resources.
- The diagnostic threshold of 140/90 mmHg is neither evidence-based nor universally accepted. At the 17th World Conference of Hypertension League Council (1997), 13 out of 27 national hypertension societies stayed with 160/95 mmHg [25].
- The distress about having hypertension wrongly diagnosed and possibly requiring unnecessary life-long drug therapy may lead to development of anxiety symptoms, costs and adverse drug reactions without any benefit.
- The threshold of 140/90 mmHg was based upon data from research studies and drug trials where BP readings were taken for research purposes and do not actually represent routine office measurements.
- Data derived from several large studies have equated a manual (research quality) office BP of 140/90 mmHg with a mean awake ABP of 135/85 mmHg [18,20,26–29]. There was a consistent difference between the mean awake ABP and the routine office greater than the usual recognized 5 mmHg (140/90 mmHg for office BP vs. 135/85 mmHg for mean awake ABP) [18,20,26–29]. BP measured in routine clinical practice seems to be at least 10/5 mmHg higher than the research-quality office BP.

Table 1 Definition and classification of hypertension.

Category	Systolic		Diastolic
Normal	< 140	And/or	< 90
High normal	140–149	And/or	90–94
Mild hypertension	150–159	And/or	95–99
Moderate hypertension	160–179	And/or	100–109
Severe hypertension	⩾180	And/or	⩾110
Isolated systolic hypertension	⩾160	And	< 90

Ambulatory BP Measurement (ABPM)

- The idea is applying an automatic BP measuring device to patient while allowing him to conduct normal life activities. The machine provides information on 24-h blood pressure as well as on mean values over more restricted periods such as the day, night or morning through checking BP every 15–30 min.
- ABP is the best method to diagnose hypertension but is not used for long-term follow-up. The major limitations are the cost and inconvenience to patient.
- Advantages of ABPM over office measurement [24,29–31]:
  1. Better correlation to end-organ damage.
  2. Better prediction of cardiovascular events.
  3. Better assessment of degree of BP reduction by antihypertensive medications.
  4. No white coat hypertension.

- Recent guidelines (NICE 2011) recommend treatment decisions based on ABPM [32].
- Normal ABPM averages are less than 135/85 mmHg for daytime readings and less than 120/70 mmHg for nighttime readings and less than 130/80 mmHg for 24 h [24,33].
- Currently the ABPM is not widely available in Egypt. The equipment is expensive and the procedure is inconvenient to the patient.

Blood Pressure Variability

- Blood pressure is characterized by large spontaneous variations from time to time in a hypertensive patient during the day and between days, months and seasons. Therefore the diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time [34].
- BP and heart rate should drop by 10–15% during sleep, a condition known as ''dipping''. Non dippers are at higher risk of future cardiovascular events [34–36].
- BP variability can be evaluated through ABPM, repeated home BP and office measurements. It is assessed through estimation of the standard deviation of mean blood pressure measurements.
- Enhanced BP variability independently contributes to target organ damage and the cardiovascular complications of hypertension.

The diagnosis of hypertension should be based on at least 3 blood pressure measurements 30–60 s apart after resting for at least 5 min and on repeated office visits. If there is a difference of ⩾10/5 mmHg between readings, take more measurements, take the lowest reading of the last 2 measurements. If the initial readings are high (> 150/95 mmHg), have the patient rest for 5 min and repeat measurement.

Number of Office Visits and Interval Between Visits will Depend upon the Level of BP and Patient's Risk Profile.

- For mild hypertension, the repeated measurements should be made over the subsequent 2–3 months. For moderate or severe hypertension, and/or evidence of target organ damage further assessments should be made over a shorter period e.g. 3–4 weeks.
- In low-risk patients (no other cardiovascular risk factors, TOD or associated cardiovascular or renal disease):
  - If BP is > 180/110 mmHg, exclude panic attack or severe anxiety and repeat measurements within 30 min at office. If blood pressure is persistent > 180/110 mmHg, diagnose hypertension.
  - If BP is 160–180/100–110 mmHg, check blood pressure at least 3 times within 4–8 weeks to confirm hypertension.

White Coat Hypertension

- In some patients office blood pressure is persistently elevated while daytime or 24-h blood pressure, or home blood pressure, are within normal range. This condition is known as 'white coat hypertension' or isolated office hypertension.
- It is present in 20–35% of patients who have elevated office BP [17,30].
- It is more common in grade 1 (mild) hypertension, in females, at older ages, and in hypertension of recent onset [34].
- When suspecting white coat hypertension, the physician should ask for a home or ambulatory BP measurements.

Masked Hypertension or Isolated Ambulatory Hypertension

- Clinic BP is normal while ambulatory BP is high.
- Masked hypertension should be suspected if TOD progresses or does not resolve, despite BP control in the clinic.
- It is not a benign condition and is associated with increased risk of future cardiovascular events [30,37].

One or Both Arms?

- BP should initially be measured in both arms as a significant number of patients, particularly the elderly, have large differences between arm (>10 mmHg) and the arm with the highest value used for subsequent measurements.
- Use the same arm and same body position in the follow - up measurements.

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.

Clinical and Laboratory Evaluation (See Table 2).

Objectives

a. Identify high risk patients
1. Detect other cardiovascular risk factors.
2. Assess target organ damage.
3. Diagnose associated cardiovascular or renal disease.

b. Identify secondary causes of hypertension and comorbid conditions.

Laboratory Tests

- Essential (in all patients):
  a. Urine: dipstick for protein, blood, sugar
  b. Blood tests: sugar, creatinine

- Recommended (if facilities are available)
  a. Blood lipid profile: total cholesterol, LDL, HDL, triglycerides
  b. Uric acid
  c. Serum potassium
  d. Hemoglobin
  e. ECG
  f. Special investigations in resistant or suspected secondary forms of hypertension (refer to Chapter # 6).
  g. Optic fundus in patients with severe hypertension.

Medical History

In most patients, uncomplicated essential hypertension causes no symptoms.
Physician should inquire specifically about:

1. Previous levels of high blood pressure with and without treatment.
2. Symptoms of target organ damage: shortness of breath, chest pain, edema of lower limbs, neurological complaints (TIA, stroke).
3. Current drug intake: antihypertensive and other drugs (e.g. contraceptive pills, non-steroid anti-inflammatory agents, etc.).
4. Co-morbid conditions (diabetes, bronchial asthma, gout, migraine, CKD, depression, sexual dysfunction, etc.).
5. Family history of hypertension, diabetes, coronary artery disease, stroke or renal disease.
6. Life style factors: salt and fat intake, smoking, physical activity and alcohol consumption.

Clinical Examination:

- Body weight and height. Waist circumference.
- Pulse: rate, irregularity, equality in 4 limbs.
- Skin and face: pallor, puffiness, rash
- Neck: carotid bruits, JVP, thyroid.
- Heart: LVH, gallop, valvular disease.
- Chest: pulmonary crepitations, COPD, bronchial asthma.
- Limbs: edema, pulsations
- Abdomen: masses, tenderness, organomegaly, abdominal bruits, aortic pulsations.

Optional Tests

More extensive investigations are indicated in the following conditions:

1. When secondary forms of hypertension are suspected (see Chapter # 6).
2. To determine the significance of mild elevation of BP by screening for target organ involvement.
3. When symptoms are suggestive of target organ damage or associated cardiovascular or renal disease.

Extensive investigations include

1. Echocardiography.
2. Abdominal ultrasound.
3. Duplex ultrasound for carotid arteries.
4. Ambulatory blood pressure recording.
5. Goal-oriented testing for suspected secondary hypertension.

Table 2 Frequency of Investigations.

Investigation	Clinic frequency
Body weight	Every visit
Height	First visit
Waist circumference	Every visit
Urine dipstick: for protein, blood and sugar	First visit, yearly if normal, repeat at next visit if abnormal on first visit
Blood tests	
– Creatinine	Yearly if normal
– Potassium	Yearly if normal, every 3–6 months if taking diuretics and ACE blockade
– Glucose (fasting)	Yearly if normal
– Random total cholesterol	Yearly if normal
ECG	Yearly if normal

Modified after South African Guidelines 2012 [38]

Special Diagnostic Methods

Echocardiography

Echocardiography is superior to radiography and electrocardiography in detection and quantification of left ventricular hypertrophy [39].

Indications

Echocardiography is not a routine test and is recommended if there is ECG abnormalities or symptoms or signs of cardiovascular disease.

Ambulatory Blood Pressure Monitoring *(See chapter on BP measurement)*

Indications [40]

1. Suspected white coat hypertension (isolated office hypertension).
2. Suspected masked hypertension.
3. Resistant hypertension.
4. Mild hypertension with target organ damage.
5. Symptoms suggestive of hypotension.
6. Paroxysmal hypertension or excessive office BP variability i.e. marked variability of BP readings during and between office (office to office) visits.

Assessment of Cardiovascular Risk Profile

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.

Cardiovascular Risk Factors

1. Diabetes mellitus: fasting plasma glucose >126 mg/dl, random plasma glucose >200 mg/dl or receiving treatment of diabetes or HbA1c $>$ 6.5 with symptoms of polyurea and polydypsia [41].
2. Males >55 years or Females >65 years.
3. Total S-Cholesterol $>$ 240 mg/dl, HDL-C <40 mg/dl or LDL-C >160 mg/dl.
4. Cigarette smoking.
5. Obesity (BMI $>$ 30 kg/m^2)
6. Serum creatinine $>$ 2 mg/dl.
7. Metabolic syndrome: combination of abdominal obesity (waist circumference >93.5 cm in men and >92.5 cm in women) [42], impaired glucose tolerance (fasting blood sugar 110–126 mg/dl), increased plasma triglycerides ($>$ 200 mg/dl) and low HDL-C (<40 mg/dl).
8. Family history of atherosclerotic cardiovascular diseases in a first degree relative (parents, siblings or brothers) before the age of 40 years in males and 50 years in females.

Silent Target Organ Damage

- Left ventricular hypertrophy (LVH):
  a. ECG criteria (Sokolow-Lyon $SV_1 + RV_5$ or $V_6 > 35$ mm, tall R in AVL $>$ 11 mm) [43].
  b. Echo criteria (wall thickness $\geqslant 12$ mm or LVMI in males $\geqslant 125$ gm/m^2 or in females $\geqslant 110$ gm/m^2 [44]
- Carotid bruits
- Proteinuria: microalbuminurea 30–300 mg/24 h
- Increased serum creatinine >1.4 mg/dl in females and >1.5 mg/dl in males
- Optic fundus changes: $>$ grade I retinopathy

Cardiovascular Risk Categorization

Depending upon the global risk profiling, hypertensive patients can be categorized into four 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 (moderate/intermediate risk): patients with additional 1 or 2 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 asymptomatic atherosclerotic cardiovascular diseases or patients with 3 or more risk factors or a very high level of a single risk factor.

Risk Group D (very high risk): Patients with ***symptomatic established*** cardiovascular or renal disease:

- Coronary artery disease (angina, MI, CABG, PCI).
- Cerebrovascular disease (stroke, TIA).
- Peripheral arterial disease.

- Heart failure.
- Abdominal aortic aneurysm.
- Renal failure: serum creatinine >2 mg/dl.

Identification of High Risk Individuals

The final aim of controlling hypertension is prevention of stroke, myocardial infarction, renal failure and heart failure. Preventive strategies, including lifestyle modification, will be most effective when they are targeted to individuals with a high risk of cardiovascular disease. High risk refers to a high probability of developing a CV event in the coming 5 or 10 years.

LIFESTYLE MODIFICATION

- Reduce weight if overweight by 5 kg over 4–6 month or achieve healthy body weight.
- Regular physical exercise of brisk walking (30–60 min) at least 5 days per week.
- Reduce salt intake to less than 5 g of sodium chloride/day.
- Encourage intake of healthy diet rich in fresh fruits, vegetables, and low fat dairy products with a reduced content of saturated and total fat.
- Stop smoking.
- Control stress with regular physical activity, behavior modification, change home and work environment conditions, if possible.
- Non-pharmacological interventions (lifestyle modification) are beneficial in reducing high blood pressure and a variety of other cardiovascular risk factors. They may also reduce the dosage requirements of antihypertensive drugs.
- Lifestyle modification should be recommended in all hypertensive patients initially and as an adjunct to drug therapy.

Weight Reduction

Recommendations

- All hypertensive patients should maintain normal body weight (body mass index of <25 kg/m^2).
- A reasonable goal is to decrease body weight by 10% or 5 kg over 4–6 month period. General guidelines to reduce calories:
  - Prepare all food 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, eat slowly and increase fiber intake (beans and vegetables).
  - Avoid high caloric foods: candy, cookies, pies, pastries, carbonated beverages (e.g. cola), nuts, chips, dried fruits.
  - Avoid appetizers.
  - Palm oil (rich in transfatty acids) is dangerous and should be avoided. It is present in cakes and biscuits.

Reduction of Dietary Sodium

Salt Sensitivity

- Salt sensitivity (excess rise in BP in response to salt intake) is present in 40% of patients with essential hypertension [45].
- Salt sensitivity is more common in the following groups [46]:
  - Elderly
  - Blacks
  - Insulin dependent diabetes
  - CKD.

Recommendations

- Limit salt intake to less than 5 g of table salt (about 1 teaspoon) and $<$ 3 g in the elderly ($>$ 70 years old).
- Substitute natural foods for processed foods and keep plenty of herbs and spices on hand to flavor your dishes. Use lemon, vinegar, cumin and pepper to replace salt.
- Do not add sodium chloride to food during cooking or on table.
- Avoid use of fast foods (e.g. beef burger, pizza, chips), pickles, salty snacks, cheese, preserved meat and fish, processed cheese and packed soups.
- Taste adaptation to reduced sodium intake occurs with time [47].

Potassium Intake

Recommendations

- Increased potassium intake reduces BP in adults with hypertension and is associated with a 24% reduced risk of stroke [48].
- Maintenance of adequate potassium intake, preferably from dietary sources, is recommended for hypertensive persons.
- A diet rich in fruits and vegetables (DASH Diet) is superior to pills or other supplements as potassium sources [49].

- Potassium supplements should be avoided in patients with renal insufficiency, or those taking potassium sparing diuretics, ACE-inhibitors, or ARBs.

Foods rich in potassium [50,51]

- Highest content (> 1000 mg/100 g).
  - Dried figs
  - Molasses
- Very high content (> 500 mg/ 100 g)
  - Dried fruits (dates, prunes)
  - Nuts
- High content (> 250 mg/100 g)
  - Vegetables: spinach, tomatoes, broccoli, winter squash, beets, carrots, cauliflower, potatoes
  - Fruits: bananas, cantaloupe, kiwis, oranges, mango

Healthy Diet
Recommendations

- A diet that emphasizes fruits, vegetables and low-fat dairy products, soluble fibers, whole grain and protein from plant sources and low in saturated fat and cholesterol [49,51] (see Table 3 for more details).
- Because the information conveyed during the few minutes available in the office setting is easily forgotten, it is helpful to provide educational materials, such as pamphlets, brochures, or booklets that patients can take home.

Food items to be avoided in hypertensive patients [51]

- Table salt (sodium chloride)
- Baking powder
- Sodium bicarbonate
- Fried food
- Salt preserved foods
  - Pickles and canned foods
  - Ketchup and sauces
  - Ready to eat foods (fast foods)
- Highly salted foods
  - Potato chips, cheese, peanut butter
  - Salted butter, salted nuts, salted fish
- Bakery products
  - Biscuits, cakes, salted breads

Table 3 Dietary approaches to stop hypertension (DASH) diet [49].

Food group	Servings	Examples and notes
Grains	7–8/day	Whole wheat bread, oatmeal, popcorn
Vegetables	4–5/day	Tomatoes, potatoes, carrots, beans, peas, squash, spinach
Fruits	4–5/day	Apricots, bananas, grapes, oranges, grapefruit, melons
Low-fat or fat-free dairy foods	2–3/day	Fat-free (skim) or low-fat (1%) milk, fat-free or low-fat yogurt, fat-free or low-fat cheese
Meats, poultry, fish	⩽2/day	Select only lean meats. Trim away fats. Broil, roast or boil. No frying. Remove skin from poultry
Nuts, seeds, dry beans	4–5/week	Almonds, peanuts, walnuts, sunflower seeds, soybeans, lentils
Fats and oils	2–3/day	Soft margarines, low-fat mayonnaise, vegetable oil (olive, corn, canola or safflower)
Sweets	5/week	Maple syrup, sugar, jelly, jam, hard candy, sorbet

Regular Physical Activity
Recommendations

- Moderate activity such as 30–45 min of brisk walking 5–7 times/week is beneficial.
- In previously inactive patients, an initial exercise program should be of a short duration (i.e. 10 min/day) of activity daily and gradually increase to 30 min/day of low-intensity activity. Intensity can be increased as the patient's strength and fitness improves.
- Exercise performed at home, rather than at a health club, reduces barriers of cost and travel time. Also, exercise does not need to occur in a single session to be beneficial as dividing activity into multiple, short bouts produces similar benefits and can enhance compliance.
- Use stairs instead of elevators.

Stress Management

- For hypertensive people in whom stress may be a contributing factor to blood pressure elevation, stress management by physical exercise in open air [52] or anxiolytic drugs when needed.

Caffeine
Recommendation

- It seems prudent to recommend moderation when it comes to the ingestion of caffeine containing beverages. There is little evidence to suggest that habitual consumption at the current average of the equivalent of 2–4 cups of coffee per day causes an increase in blood pressure of any clinical importance [53].
- Ingesting of larger amounts (e.g. 5–6 cups of coffee per day) should be discouraged in patients with hypertension or in those individuals having a pre-hypertensive state.

Herbal Dietary Supplements

- Licorice consumption in excess can increase BP and should be discouraged.
- Herbal therapy (Hibiscus) should be discouraged because there are no clinical trials to prove its efficacy and safety.

Alcohol

- Those who drink should limit alcohol intake specially in the elderly and women.

Tobacco Avoidance
Recommendations

- There are various strategies that can be used to promote smoking cessation, including advice from a physician, nicotine replacement therapy, behavior modification, and smoking cessation programs.

PHARMACOLOGIC TREATMENT OF HYPERTENSION

(SEE TABLES 4–8)

- Antihypertensive drugs can be classified into 3 big categories: 1. First line or drugs of first choice which include thiazides and thiazide derivatives (D), beta adrenergic blockers (BB), calcium channel blockers (CCB), angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). There is evidence from clinical trials that drugs in this group can improve prognosis and prevent TOD and disease progression.2. Second line or accessory drugs which include: loop and potassium sparing diuretics, central sympatholytics (methyldopa and clonidine), peripheral sympathalytics, (reserpine, guanethidine), α1 adrenergic blockers (prazosin and doxazosin) and direct arterial vasodilators (hydralazine and minoxidil).3. Drug combinations combining 2 drugs from different pharmacologic groups in a single pill.
- Initiation of drug therapy depends upon the patient global cardiovascular risk profile, level of BP and its response to lifestyle modification.
- Drug therapy should be started immediately in case of hypertensive emergencies and urgencies, otherwise a trial of non-pharmacologic treatment (lifestyle modification) for a period of weeks to months is recommended while monitoring BP on frequent office visits or at home before initiating drug treatment.
- The selection of the drug for initial treatment depends upon the presence of any compelling indications for a specific pharmacologic group such as coronary disease, heart failure, diabetes, chronic kidney disease (CKD) or associated co-morbid conditions.
- In patients with more than mild hypertension ($\geqslant$ 160/100 mmHg) and high risk patients, it is recommended to initiate therapy with a combination of two drugs.
- The BP target will depend upon the global risk profile of the patient and will vary from $<$150/95 mmHg in low risk patients to $<$130/80 mmHg in some high risk patients.

Table 4 When to Initiate Drug Therapy? Blood pressure threshold and duration of initial monitoring.

Population	LSM Duration	SBP	DBP
Low risk patients	3–6 m	160	100
Moderate and high risk (⩾2 RFs, DM, TOD, CKD)	3–6 w	140	90
Very high risk patients*	1–2 w	130	80
Elderly	3–6 w	150	95

• m: month, w: week, LSM: lifestyle modification.
* Associated CV disease: CAD, cerebrovascular, HF, peripheral arterial disease and aortic aneurysm. CKD with proteinuria > 1000 mg/24 h

- In patients with mild hypertension (BP 150–159/95–99 mmHg) with low risk profile, drug therapy may not be needed, lifestyle modification and regular BP monitoring is the recommended policy.

INITIATION AND MONITORING OF DRUG THERAPY

The Decision To Initiate Drug Therapy for High Blood Pressure Should Not Be Taken Lightly Since Once Initiated, therapy should continue indefinitely, as there is no cure from established essential hypertension, except in the unusual instances after developing a large MI, stroke or Addison's disease. Discontinuation of drug therapy leads to re-elevation of high blood pressure within days to months and is asymptomatic.

Initiation of drug therapy depends upon:

1. Level of blood pressure.
2. Global risk profile of patient.
3. Response to non-pharmacologic treatment.

Level of Blood Pressure

- Similar to recent NICE hypertension guidelines (2011) [54], Egyptian guidelines recommends a differential treatment initiation threshold where pharmacologic treatment is initiated If BP is >160/100 mmHg (home BP >150/95 mmHg) in low risk patients or if BP is > 140/90 mmHg (home BP >135/85 mmHg) in patients with target organ damage, cardiovascular, renal disease, diabetes or multiple risk factors.

TIMING OF INITIATION OF DRUG THERAPY

1. **Immediate: On First Office or Hospital Visit**

a. Hypertensive emergency.
b. BP >210/120 mmHg on 3 consecutive measurements 2–3 min apart after excluding a panic attack.
c. BP >180/110 mmHg on 3 consecutive measurements (2–3 min apart) in presence of:

- TOD: LVH (ECG, clinical, echo), proteinuria, elevated serum creatinine (>1.5 mg/dl in males, >1.4 mg/dl in females), optic fundus >gr I retinopathy, aortic aneurysm, carotid bruits.
- Symptomatic CVD (CAD, HF), stroke, transient ischemic attack (TIA), peripheral arterial disease (PAD), chronic kidney disease (CKD).

If suspect panic attack[1]

[1] ***Panic attacks*** [55] are episodes of intense fear or apprehension that are of sudden onset and of relatively brief duration. Panic attacks usually begin abruptly, reach a peak within 10 min, and are mainly over within 30 min. Panic attacks can be as short as 15 s, or can be cyclic, lasting for an extended period, sometimes hours, accompanied by at least 4 of the following 13 somatic and cognitive symptoms:

–Shortness of breath.
–Dizziness.
–Palpitations.
–Trembling.
–Sweating.
–Feeling of choking.
–Nausea/abdominal distress.
–Depersonalization.
–Paresthesias.
–Flushes/chills.
–Chest pain.
–Fear of dying.
–Fear of going crazy or fear of doing something uncontrolled.

1. Reassure the patient.
2. Give a minor tranquilizer e.g. diazepam.
3. Do not give antihypertensive drugs unless:

   - BP >180/110 mmHg + TOD
   - If it persists >210/120 mmHg in 3 consecutive readings during the visit (30–60 min).

1. **Within Days To Months After 1st Office Visit**

Timing of Initiation (office visits)	*BP Grade*	*Risk Category*
1–3 weeks (2 visits)	Grade III (severe)	Moderate
	Grade II (moderate)	High
	Grade I (mild)	Very high
1–3 m (2–4 visits)	Grade II (moderate)	Moderate
	Grade I (mild)	High
3–6 m (2–3 visits)	Grade I (mild)	Moderate
>6 m (2–3 visits)	Grade I (mild)	Low

BP grades: mild (150–159/95–99), moderate (160–179/100–109), severe (⩾180/110 mmHg)
Risk categories for hypertensive patients

– *Low risk:*
  - No additional CV risk factors
  - No TOD
  - No associated atherosclerotic CV or renal disease

– *Moderate or intermediate risk:*
  - 1–3 additional CV risk factors

– *High risk:*
  - >3 additional RFs, or TOD or DM or renal failure

– *Very high risk*
  - Symptomatic CVD and cerebrovascular disease

Initiation of drug therapy in patients with mild hypertension (150–159/95–99 mmHg)	
Depends on risk profile:	
– Low:	Lifestyle modification with follow-up can be the only therapy .
– Moderate:	Initiate therapy after 2–3 months if BP persists? 140/90 mmHg.
– High:	Initiate therapy after 2–3 weeks if BP persists? 140/90 mmHg.
– Very high:	Initiate therapy within 1 week.

Monitoring of drug therapy

– Antihypertensive drugs may require a period of up to two months to achieve maximal hypotensive effect [56]. However, a significant reduction in BP is obtained after 2 weeks of therapy with many antihypertensive drugs particularly combination therapy [56]. 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 3–6 month intervals depending upon the risk profile
– In absence of blood pressure response (fall in systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg) in mild and intermediate risk groups after one to two months of initiation of drug therapy, add another drug from a different pharmacologic group or use a single dose combination. In high and very high risk patients, if a satisfactory response to the initial combination therapy after two weeks is not obtained, add a third drug or a diuretic if not initially prescribed.
– Once blood pressure is at goal and stable, the patient should be seen usually at three- to six-month intervals to assess patient adherence, patient satisfaction and any changes in target organ status.

- Frequency of visits depends upon: comorbidities such as heart failure; associated diseases such as diabetes; and need for laboratory tests. Lifestyle modifications should be reviewed, reemphasized and documented annually.
- Treatment and follow-up should continue indefinitely.

Monitoring of drug therapy

Serum Potassium

- Patients receiving thiazide and loop diuretics are at increased risk of hypokalemia. Serum K estimation is recommended particularly if patients show heart rate irregularities (PVCS), ECG abnormalities (ST, T wave changes) or on digitalis therapy.
- Patients receiving K-sparing diuretic (spironolactone–aldactone) require regular serum K measurements because of risk of hyperkalemia (Serum $K > 5.5$ mEq/l).
- Patients at increased risk of hyperkalemia include those on RAS blockade (ACEIs or ARBs), patients with renal insufficiency or receiving K supplements.

Serum Creatinine (see Algorithm 5)

- Serum creatinine should be estimated 2–4 weeks after initiation of RAS blockade (RASB) specially in patients with CKD, HF or on aggressive diuretic therapy. A rise in serum creatinine up to 30% above initial level is expected in majority of patients [57–59]. Serum creatinine levels tend to revert to initial levels within 6–8 weeks in spite of continuation of therapy [57,58].
- If serum creatinine continues to rise on repeated measurements or if initial rise is greater than 50% stop RAS blockade and exclude hypovolemia (following aggressive diuresis or dehydration), intake of NSAIDs, polycystic kidney disease and renal artery stenosis [57,59]. Patients at increased risk of rise in serum creatinine are elderly patients (> 65 years) and patients with high baseline levels (> 1.4 mg/dl).
- If the increase in serum creatinine is between 30% and 50 % decrease the dose of ACEIs or ARB by 50% and recheck after 4 weeks if still more than 30% discontinue RAS blockade.

Table 5 Selection of antihypertensive drugs.

Class of drug	Indications	Contraindications	Caution/limited value
Thiazide diuretics	- Heart failure - Elderly patients - Black patients - Obese patients - Other low renin forms: diabetes, CKD	Gout	- Pregnancy - Dyslipidemia - Hypokalemia - Advanced RF
B- Blockers	- CAD - Tachyarrhythmia - Pregnancy - Increased adrenergic activity - Heart failure, hypertrophic cardiomyopathy - Associated: migraine, anxiety, tremors, hyperthyrodism	- Heart block (> grade I) - Bronchial asthma requiring inhalation therapy - Symptomatic bradycardia (< 50 beats/m)	- Blacks - Elderly
ACE inhibitors/ ARBs	- Heart failure - After MI - Diabetes - Microalbuminuria - Proteinuric CKD - Target organ damage (LVH, CV disease, PAD)	- Pregnancy - Bil renal artery stenosis - Sensitivity (angioneurotic edema)	- S. creatinine elevation - Blacks - Hyperkalemia - Acute renal failure
CCB	- Angina - Peripheral vascular disease - Elderly patients - Systolic hypertension - Black patients - Excessive BP fluctuations		
α_1*Blockers: Prazosin* (*combined with diuretics*).	- Bengin (senile) prostatic hypertrophy - Dyslipidemia		- Postural hypotension

Management of Patients with Transient Increases in Blood Pressure

Treatment should be directed to correction of the underlying cause (e.g. anxiety, excess salt intake, pressor drugs, interruption of treatment). Panic attacks can be associated with very high BP levels (200/120 mmHg).

Blood Pressure Targets

- < 150/95 mmHg in low risk patients and in elderly (> 65 years).
- < 140/90 mmHg:? 2 risk factors, diabetes, CKD, TOD.
- < 130/80 mmHg: HF, CKD or diabetes when associated with proteinuria > 1 g/24 h.

Aggressive Blood Pressure Lowering

- Treating patients to lower than standard BP targets (140–150/90–95 mmHg) does not reduce mortality and morbidity in patients with uncomplicated hypertension [60].
- No significant benefit to lower BP goals (< 130/80 mmHg) for the subset of patients with diabetes or chronic renal disease in absence of gross proteinuria > 1 g/24 h) [60–62].
- Moderate control of SBP < 150 mmHg may be sufficient in elderly hypertensives [63].

Selecting first-line therapy

In Absence of Compelling Indications for a Specific Pharmacologic Group:

- In mild-moderate hypertension (150–179/95–109 mmHg) without TOD or symptomatic CVD, initiate monotherapy from any of the 5 standard pharmacologic groups (diuretics, BB, CCB, ACEIs, ARBs) preferably a Thiazide diuretic. In elderly (age > 65 years) or in blacks, it is preferable to start with diuretic or CCB [64,65]. In young, particularly those with tachycardia start with BB.
- In moderate or high risk patients or those with BP ⩾180/110 mmHg, start with combination therapy.
- ACEIs or ARBs are **not** recommended as monotherapy in black patients in absence of compelling indications [66–68].

Compelling Indications

The choice of drug therapy will be individualized depending upon the patient risk profile, presence of TOD, associated disease or other comorbid conditions.

- Coronary artery disease
  - Angina: BB ± CCB ± RAS blockade
  - MI or after CABG: BB ± ACEIs or ARBs
- Heart failure: D + BB + RAS blockade ± spironolactone
- AF: BB, NDHP CCB, RAS blockade
- Cerebrovascular disease: RAS blockade + CCB ± D
- Peripheral arterial disease: RAS blockade + CCB
- Diabetes: RAS blockade ± D
- Renal disease: RAS blockade + D ± CCB
- Isolated systolic hypertension (ISH): CCB ± D
- LVH: RAS blockade
- Before non-cardiac surgery: BB
- Migraine, tremors, situational anxiety: BB
- Pregnancy: methyldopa, CCB
- Prostatic hypertrophy: α adrenergic blockers (doxazosin).

Recommended drug selection in absence of compelling indications

Escalating and modifying treatment at 4-week intervals according to BP response and patient's tolerance.
Step I: 1 or 2 or 3 or 4 or 5

1. HCT amiloride e.g. (moduretic) or chlorthalidone (hygroton) or HCT + spirinolactone (aldactazide) in the smallest dose e.g. half tablet (HCT: 12.5 mg) or indapamide in all patients particularly elderly, blacks and obese.
2. BB: cardio-selective with long activity e.g. bisoprolol 2.5–5.0 mg specially in young and female hypertensives and those with rapid and hyperdynamic heart.
3. Amlodipine: 2.5–5.0 mg specially in elderly patients.
4. ACEIs or ARBs.
5. Combine 1 + 2 or 1 + 3 or 2 + 3 or 1 + 4 if BP > 170/105 mmHg.

Step II: Combine 1 + two other groups if inadequate response in step I.
Step III: Increase dose of amlodipine to 10 mg, if used.
Step IV: Increase dose of ACEI or ARB, if used.
Step V: Use the four drug groups.
Step VI: Add loop diuretic preferably long acting e.g. torsemide (5-20 mg).
Step VII: Add spironolactone (12.5–25 mg).

– Aim at gradual BP reduction particularly in the elderly to achieve target BP in 2 months. In high-risk patients and in presence of severe hypertension, aim to achieve target BP at 2–4 weeks through combination therapy.

What to do if there is inadequate BP response?

a. Add another agent (different pharmacologic group).
b. Add thiazide if not given initially.
c. Stress salt reduction.
d. Substitute with another agent if the above measures fail.
e. Seek specialist's opinion.

Measures to improve patient's compliance:

1. **Patient Education:** Physician should spend few minutes with his/her patient during office visit to discuss the following facts:
   a. Hypertension is silent; one can not rely on symptoms to diagnose high blood pressure.
   b. Treatment of hypertension is lifelong and without interruption.
   c. Hypertension is not treated on demand i.e. give drugs when blood pressure is elevated and stop it when blood pressure is normal.
   d. Hypertension requires life-long monitoring. Blood pressure should be measured regularly at 3–6 months intervals, depending on risk profile and level of blood pressure.
   e. Lifestyle modification is an important component of the therapeutic regimen.
   f. Antihypertensive drugs can produce side effects.
2. **Prescribe Affordable Drugs.**
3. **Regular Follow-up (3–6 months).**
4. **Keep Care Inexpensive and Simple:**
   a. Do the least work-up needed.
   b. Add one drug at a time and use the least number of pills.
   c. Start with a small dose.

5. **Encourage Patient to Check his Blood Pressure at Home** provided that he has a reliable well-maintained device and he is well trained to measure blood pressure accurately. Home blood pressure measurement will improve compliance but not recommended if it causes anxiety and patient should be advised not to change his blood pressure medicines without the consultation of his physician.

Table 6 Antihypertensive Drugs

Chemical name	**Trade names (examples)**	Daily dose (mg/d)	Frequency /d	Notes
Diuretics				
Thiazides and thiazide-like diuretics				
Hydrocholothiazide (HCT)	Hydretic, hydrazide	12.5–50	1	Start with a low dose
Clorothalidone	Hygroton	12.5–25	1	
Indapamide	Natrilix, hypotense	1.5–2.5	1	
Loop diuretics				
Furosemide	Lasix	40–240	2–3	Short acting
Torsemide	Torseretic, examide	5–100	1	Long acting
Bumetanide	Burinex, edemex	0.5–4.0	2–3	
Ethacrinic acid	Edecrine	25–100	2–3	In pts with sulfonamide sensitivity
Potassium sparing diuretics				
Spironolactone	Aldactone, epilactone	12.5–100	1–2	
Diuretics combinations				
Amiloride(5 mg) + HCT(50 mg)	Moduretic, Yostiretic		1	
Spironolactone (25 mg) + HCT (25 mg)	Aldactazide		1	
Spironolactone (50, 100 mg) + Frusemide (20 mg)	Lasilactone		1	
Triamterene (30 mg) + Xipamide (10 mg)	Epitens		1	
Beta adrenergic blockers (BB)				
Selective BB				
Bisoprolol	Concor, Bistol, Bisocard	2.5–20	1–2	
Atenolol	Tenormin, Ateno, Blokium	25–100	1–2	
Metoprolol	Betaloc, Betalol, Low-press	25–200	1–2	
Non-Selective BB				
Propranolol	Inderal, indolol	10–240	2–3	
Sotalol	Sotacor, betacor	80–160	2	
Vasodilator BB				
Nebivolol	Nebilet, Nevilob	5	1	
Carvedilol	Dilatrend, Carvid, Carvedilol, Dilatrol	12.5-50	2	Alpha and beta blockers
Labetalol	Labetalol, Trandate	100-800	2	Alpha and beta blockers
Calcium channel blockers				
Dihydropyridines				
Amlodipine	Norvasc, Alkapress, Amilo, Myodura	2.5–10	1	Long duration
Felodipine	Plendil, Felocor	2.5–20	1	Less lower limb edema
Nifedipine	Adalat, Epilat, Epilat-retard	30–120	2–3	
	Adalat LA	30	1	
Nicardipine	Pelcard SR	30–60	2	
Lercanidipine	Caredipine	5–20	1	
Lacidipine	Lacipil	2–4	2	
Nimodipine	Nimotop	10–30	2	
Nondihydropyridine				
Diltiazem	Altiazem, Tildium, Delaytiazem	120–360	2–3	
Verapamil	Isoptin, Isoptin related	120–360	2	

Table 6 continued

Chemical name	**Trade names (examples)**	Daily dose (mg/d)	Frequency /d	Notes
Angiotensin converting enzyme inhibitors				
Captopril	Capoten, capotril, farcopril	75–300	2–3	
Enalapril	Ezapril, renitec	5–40	1–2	
Fosinopril	Monopril	10–40	1	
Lisinopril	Zestril, sinopril, mavipril	10–40	1	
Perindopril	Coversyl	4–16	1	
Ramipril	Tritace, ramitac	5–20	1	
Trandolapril	Mavik, gopten	2–8	1	
Benazepril	Cibacen	5–20	1	
Imidapril	Tanatril	5–10	1	
Angiotensin receptor blockers				
Losartan	Cozar, Amosar, Kanzar, Losar	50–100	1–2	
Valsartan	Tareg, Disartan	80–320	1	
Irbesartan	Aprovel, Kansartan, X-tension	150–300	1	
Telmisartan	Micardis, Biocardis	40–80	1	
Candesartan	Atacand, Candesar	8–32	1	
Eprosartan	Teveten	400–800	1	
Olmesartan	Erastapex	20-40	1	
Sympatholytics-Alpha-adrenoceptor blockers				
Methyldopa	Aldomed, Kadomet	500–3000	2–3	
Prozosin	Minipress	5–10	2–3	
Doxazosin	Cardura	4–16	1–2	
Clonidine	Catapress	0.1–0.8	2	

Table 7 Drug combinations

Chemical name	Trade names (examples)	**Frequency/d**
Thiazide and ACEIs		
Ramipril (2.5 or 5 mg) + HCT (12.5 or 25 mg)	Tritace Comp.	1
Captopril (25 or 50 mg) + HCT (12.5 or 25 mg)	Capozide, Farcopril Plus	1–2
Enalapril (10 or 20 mg) + HCT (12.5 or 25 mg)	Ezapril Co, Co-Renitec	1
Lisinopril (10 or 20 mg) + HCT (12.5 or 25 mg)	Zestoretic, Sinopril-Co	1
Monopril (10 or 20 mg) + HCT (12.5 or 25 mg)	Monozide	1
Benazepril (10 or 20 mg) + HCT (12.5 mg)	Cibadrex	1
Prindopril (2 or 4 mg) + Indapamide (1.25 or 0.625 mg)	Preterax, Biopretrax	1
Thiazide and ARBs		
Candesartan (16 or 32 mg) + HCT (12.5 mg)	Atacand Plus, Blopress Plus	1
Irbesartan (150 or 300 mg) + HCT (12.5 or 25 mg)	Co aprovel, Co aprovel Forte, X-tension Plus	1
Losartan (50 or 100 mg) + HCT (12.5 or 25 mg)	Hyzaar, Fortzaar, Kanzar-H	1
Telmisartan (40 or 80 mg) + HCT (12.5 mg)	Micardis Plus	
Valsartan (80, 160, 320 mg) + HCT (12.5 or 25 mg)	Co-Tareg, Co-Diovan, Disartan Co	1
Olmesartan (20 or 40 mg) + HCT (12.5 or 25 mg)	Erastapex plus	1
Thiazide and BBs		
Atenolol (50 or 100 mg) + chlorthalidone (25 mg)	Blokuim diu, Tenoret, Tenoretic	1
Bisoprolol (5 or 10 mg) + HCT (6.25, 12.5 or 25 mg)	Concor 5, 10 plus, Bistol Plus, Lodoz, Cardivocare	1
CCBs and ACEI		
Amlodipine (5 mg) + Benazepril (10 or 20 or 40 mg)	Amlo-ACE	1
Amlodipine (5 or 10 mg) + Perindopril (5 or 10 mg)	Coveram	1
Veramapil ER (180 or 240 mg) + Trandolapril (1, 2 or 4 mg)	Tarka, Tarka SR	1
CCBs and ARBs		
Amlodipine (5 or 10 mg) + Valsartan (160 or 320 mg)	Exforge, Blokatens.	1
CCB and BB		
Felodipine (5 mg) + Metoprolol (50 mg)	Logimax	1
CCBs + ARBs + HCT		
Amlodipine (5 or 10 mg) + Valsartan (160 or 320 mg) + HCT (12.5 or 25 mg)	Exforge HCT	1
Reserpine Comninations		
Reserpine (0.1 mg) + Clopamide (5 mg) + Dihydroergocistine (0.5 mg)	Brinerdin	1

MANAGEMENT OF HYPERTENSION

In association with cardiovascular, renal disease and diabetes

Hypertension associated with cardiovascular disease

- In chronic stable angina, target BP is < 140/90 mmHg. B-blockers, calcium channel blockers and ACE-inhibitors are 1st line drugs. Excessive lowering of diastolic BP (< 70 mmHg) should be avoided.
- In acute coronary syndromes associated with hypertension, B-blockers, non-dihydropyridine CCB, and IV nitrate are recommended.
- In systolic HF, target BP is < 130/80 mmHg. ACE-inhibitors (or ARB), B-blockers, and diuretics including aldosterone antagonists are recommended agents. Other agents include: amlodipine, felodipine, and hydralazine.
- Patients with evidence of left ventricular hypertrophy should receive an ACE inhibitor or ARB, complemented if necessary with a calcium antagonist.
- Treatment of hypertension with significant aortic stenosis should be done cautiously.
- Hypertension is a risk factor for atrial fibrillation and it is also a major risk factor for AF-related thromboembolism. Uncontrolled hypertension increases the bleeding risk in patients receiving anticoagulant therapy.

Chronic stable angina

Management

–***Target BP***: < 140/90 mmHg. Excessive lowering of diastolic BP (< 60–70 mmHg) may, however, reduce coronary perfusion and augment myocardial ischemia [69].

– ***Agents***:

– *BB + CCB are drugs of first drugs.*

a. BP should be lowered slowly without excessive diastolic BP lowering (< 60–70 mmHg) particularly in elderly patients with isolated systolic hypertension and those with critical coronary artery disease without revascularization.
b. Attention should be given to aggressive control of other vascular disease risk factors. Low dose aspirin and statins are needed by all patients.
c. All agents – except alpha adrenergic blockers and short acting dihydropyridine CCB may be used.
d. Beta adrenergic blockers are preferred drugs. In patients with a previous myocardial infarction (MI), they also reduce the incidence of recurrent MI, heart failure, and mortality [70].
e. Long acting calcium channel blockers relieve ischemia, can induce regression of LVH and delay the progression of atherosclerotic plaque.
f. ACE-inhibitors are also drugs of choice to reduce atherosclerotic vascular events, heart failure, and mortality in patients with or without previous MI and whether LV systolic function is normal or impaired [71,72].
g. Angiotensin receptor blockers should be used in patients who do not tolerate ACE inhibitors (e.g., due to cough or angioedema)

Acute coronary syndromes (ACS)

Management

- The agents of first choice are beta adrenergic blockers. They should be started as early as possible and should be titrated up until the heart rate is ⩽60 bpm.
- Non-dihydropiridine CCB (Verapamil, Diltiazem) may be used in patients with intact LV systolic function who cannot tolerate beta blockers.
- Acute reduction of BP by intravenous BB or nitroglycerin is indicated in patients with ST-segment elevation MI candidate for fibrinolysis with marked elevation of BP (> 180/110 mmHg).
- If the acute BP rise is suspected to be due to pain or anxiety, opiate analgesic or a benzodiazepine tranquillizer should be administered. Excessive use of tranquillizers may increase the risk of hypoxia, delirium, and CCU psychosis.
- Patients with acute severe mitral regurgitation (or septal rupture) should receive sodium nitroprusside infusion to reduce afterload.
- After stabilization, beta blockers should be continued, and an ACE inhibitor should be added (regardless of LVEF) unless there is clear hypotension.

Left ventricular systolic dysfunction

Management

– ***Target BP***: < 130/80 mmHg, however this level is still a controversy.

– ***Agents:***
  a. Patients with high BP and reduced LVEF (< 40%) should receive an ACE inhibitor and any of the following beta adrenergic blocker: Bisoprolol, Carvidelol, or Nebivelol regardless of the presence or absence of congestive symptoms [73] ARB should be prescribed to patients not tolerating ACE inhibitors.
  b. In presence of congestive symptoms or signs, a diuretic should be used with electrolyte monitoring.

- Spironolactone is another choice; however, its use may be associated with serious hyperkalemia.

Heart failure with preserved EF (diastolic heart failure)

- Hypertension is the most common cause of heart failure with preserved LVEF [30], and control of BP is the most effective way to prevent and/or treat patients with diastolic heart failure.

Management

- No particular class of antihypertensive drugs has been shown, convincingly, to reduce morbidity and mortality in these patients.
- Patients with evidence of left ventricular hypertrophy (LVH) should receive an ACE inhibitor or ARB [74], complemented if necessary with a calcium antagonist
- Patients with congestive symptoms are helped with a diuretic.
- Hypertensive patients with hypertrophic cardiomyopathy should be treated with a BB, with or without a non-DHP calcium antagonist. These patients may suffer severe LV outflow obstruction with the use of diuretics or vasodilators.
- Patients with rapid heart rate > 80 bpm usually benefit from rate reduction to improve LV filing. A beta adrenergic blocker or a non-DHP calcium antagonist may be used in this situation to control both BP and heart rate.

Aortic valve diseases

1. **Aortic Stenosis:**
   – Treatment of hypertension should be done cautiously using BB, small dose diuretics; or centrally acting agents. ACE-I can be used cautiously. Avoid direct vasodilators due the possible hypotensive effect of peripheral vasodilation with fixed valve obstruction.
   – Antihypertensive medications should be started at very low doses and slowly titrated to a therapeutic level.

2. **Aortic Incompetence:**
   – This is the commonest aortic valve lesion with hypertension. Severe lesion is associated with high systolic and low diastolic BP.
   – For severe AR, ACE-inhibitors or nifidipine are recommended for a diastolic pressure over 90 mmHg, which would be rare in severe AR.
   – These patients poorly tolerate beta adrenergic blockers, since bradycardia increases the regurgitant fraction and reduces forward cardiac output.
   – Hypertension and AR in the context of acute chest pain should raise the possibility of aortic dissection.
   – Aortic valve replacement may be followed by acute hypertension.

Atrial fibrillation (AF)

- Hypertension is a common risk factor for AF (preceded only by advancing age) [75].
- Antihypertensive treatment may contribute to reduce the risk of AF, and it seems ACE-inhibitors and ARBs are superior to others in the prevention of new-onset AF [76–78].
- Patients with atrial fibrillation treated by a rate control policy (i.e. slowing the ventricular response), should receive either beta adrenergic blockers or long acting non-DHP calcium antagonists (to control both BP and ventricular rate) [79].
- Patients with AF treated by a rhythm control policy (i.e restoration of normal sinus rhythm), may derive special benefit from ACE inhibitors or ARBs This is supported by some, but not all, studies addressing this issue.

Aortic aneurysm

- Uncontrolled hypertension is a risk factor for the development and rupture of aortic aneurysm.
- The antihypertensive drugs of choice are beta adrenergic blockers. They should be titrated to a dose enough to reduce the heart rate to < 60 bpm. If further BP reduction is needed, an ACE inhibitor should be used, and then a diuretic may be added. Target blood pressure is possible < 130/80 mmHg.

Peripheral arterial disease (PAD)

Management

a. Target Blood pressure is possibly < 130/80 mmHg.
b. The drugs of choice are ACE inhibitors [80] and long acting DHP calcium antagonists.
c. In presence of coronary artery disease, beta adrenergic blockers can be used in patients with claudication or asymptomatic PAD, but not in patients with rest pain or tissue loss [81,82]. The use of combined alpha and beta blockers (Labetalol, Carvedilol) may be safer [83].
d. Investigations for resistant hypertension in these patients should include screening for renal artery stenosis.
e. Aggressive lifestyle intervention including walking, cessation of smoking, and lipid lowering with a statin is needed.

Postural hypotension

- Postural hypotension (see chapter 1) should be suspected in elderly and diabetic hypertensives, and in those who develop dizziness or fatigue on antihypertensive therapy.
- In these patients it is better to discontinue or reduce the diuretic dose, reduce the dose of ACE inhibitors, avoid alpha adrenergic blockers. Beta adrenergic blockers and centrally acting agents may be used. Some patients benefit from the use of graded compression elastic stockings.
- Postural hypotension may be associated with severe supine hypertension. These patients are difficult to manage and should therefore be referred to a hypertension specialist.

Hypertension associated with renal diseases:

- Measurements of proteinuria at 6–12 months.
- Aim at reduction of micro-albuminuria by >30% within 6 months of starting treatment [84–87].
- Na restriction to 2–3 g/d will reduce urinary protein excretion.
- Need for lower BP in patients with >1 g protein excretion/d (<130/80 mmHg) and use of RASB [88].
- In absence of albuminuria BP target is <140/90 mmHg [89,90].
- Choice of diuretic should be guided by GFR, if 40 ml/min/1.73 m^2 use a loop diuretic [30].
- Patients with renal insufficiency should be encouraged to reduce dietary salt and protein intake [91,92].
- Target blood pressure is less than 140/90 mmHg. If patients have urinary protein of 1 g/day or greater, the target blood pressure should be, if tolerable, less than 130/80 mmHg [93,94].
- ACE-I, Angiotensin receptor blockers and loop 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 [95].
- Serum creatinine level often rises during the early phase of treatment with ACE-I or ARBs specially in patients with renal disease [57,59].
- Calcium antagonists are useful and safe, especially in patients with severe renal dysfunction (serum creatinine >3.0 mg/dl) [96].
- Thiazide diuretics are ineffective in patients with serum creatinine greater than 3.0 mg/dl [30].
- 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 320–400 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 [97].
- Hypertension is the single most important factor in the progression of early renal disease [97].
- 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 also essential for cardiovascular protection.
- The concept of intraglomerular pressure is important, particularly in grossly proteinuric cases. Drugs that reduce the intraglomerular pressure are preferred (RAS blockers).
- There is a tendency to develop hyperkalemia with some antihypertensive agents.
- 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 140/90 mmHg and preferably to less than 130/80 mmHg in patients with $\geqslant 1$ g/day of proteinuria [87].

Non Pharmacological Therapy

- Salt should be restricted. Protein intake should be limited according to body weight (0.8 g/kg/day) [91].
- 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 and angiotensin II receptor blockers are the drugs of first choice particularly in proteinuric cases [87]. Calcium channel blockers, diuretics, beta blockers and alpha blockers are additive drugs.
- 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.
- ACE-inhibitors excretion is decreased in end stage renal disease, and a lower dose should be given, except for fosinopril. ARBs need minimal dose regulation unless serum potassium rises.

Table 8 Causes of exaggerated or progressive decline in renal function associated with ACE-inhibitors or angiotensin receptor blockers use.

• Bilateral renal artery stenosis
• Renal artery stenosis to a single functioning kidney
• Polycystic kidney disease.
• Absolute reduction in intravascular volume (gastroenteritis aggressive diuresis)
• Reduction in effective arterial volume (moderate to severe CHF)
• Use of NSAIDs or calcineurine inhibitors e.g. cyclosporine (increased renal vasoconstriction)

Angiotensin Receptor Blockers

- Have similar effects as ACE-inhibitors. Losartan and irbesartan in particular, proved to be renoprotective in diabetic nephropathy patients [98,99].

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 300–400 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, potentially reversible 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 because they reduce proteinuria.
- Studies have shown superiority of ACEi combined with dihydropyridine CCBs compared to ACEi and diuretics [100,101].

Beta Blockers

- Adjust doses of drugs excreted through renal route (e.g., atenolol).
- Combined alpha and beta blockers (eg Carvidilol) are preferred.

Antihypertensive Therapy 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 [102].
- Excessive lowering of blood pressure may increase the mortality in hemodialysis patients. The target blood pressure is 140/90 mmHg, however other guidelines give no information for target BP lowering and reduction of mortality occurs only in patients with heart failure and that target BP could not be provided.
- Salt restriction should always be observed.

Diabetes and hypertension

Diagnosis

- Diagnostic criteria for diabetes:

  FBS 126 mg/dl and/or 200 mg/dl after oral glucose load; random blood sugar $\geqslant$ 200 mg/dl with symptoms suggestive of diabetes (e.g. polyurea) or HbA1C $>$ 6.5 mg % [41].

- Prediabetes
  - The levels of fasting glucose range between 100 and 125.9 mg/dl or plasma glucose 2 h after an oral glucose load (75 gm) is between 140 and 199.9 mg/dl.

- The diagnostic cutoff for the diagnosis of hypertension is lower in people with diabetes (140/90 mmHg) than those without diabetes or low risk patients (150/95 mmHg).
- Prevalence of hypertension is 1.5-fold higher in diabetic patients relative to non-diabetic patients.

Treatment:

- Treatment BP goal: $<$140/90–80 mmHg and $<$130/80 mmHg in presence of proteinuria ($>$1 g/24 h) [28–30]. Other Guidelines stated that it's mandatory to reduce SBP if it is $>$160 mmHg and that it is strongly recommended when it is $>$140 mmHg. DBP $<$85 and reduction of BP $<$130/80. However, lowering BP $<$130/80 was not supported by RCTs.
- Reduction of Na intake to $<$1500 mg/d ($<$4 g NaCl) is recommended.
- The management of diabetes and hypertension in patients with nephropathy mandates strict glucose and BP control [103].
- The target of HbA1C should be $<$6.5–7%, this can delay progression from microalbuminuria to macroalbuminuria [104].
- ACEIs and ARBs are superior to other agents in reducing cardiovascular events and deterioration of renal function [98].
- More than one antihypertensive drug is usually needed to control blood pressure [87,105].
- One antihypertensive medication to be given at bedtime.
- Dietary protein reduction in patients with diabetic nephropathy (0.6 g/kg/d).

HYPERTENSION IN SPECIAL GROUPS

Obstructive sleep apnea (OSA)

- OSA is considered one of the potentially reversible secondary causes of hypertension and among the causes of resistant hypertension [106].
- OSA is characterized by recurrent episodes of cessation of respiratory air?ow caused by upper airway inspiratory collapse during sleep, with a consequent decrease in oxygen saturation.
- Hypertension affects approximately 50% of patients with OSA [107].

When to Suspect OSA?

- Clinician should always ask for symptoms of obstructive sleep apnea especially in patient with resistant hypertension. Symptoms include choking episodes and interruption of breathing during sleep, nocturnal snoring reported by the bed partner, daytime somnolence, with impaired concentration.
- Large neck circumference with facial puffiness [108].

Treatment

- Weight loss in obese subjects ameliorates the syndrome [109].
- Treatment with continuous positive airway pressure (CPAP) devices is the most effective treatment for OSA. CPAP therapy reduces the systolic blood pressure by 2.5 mmHg and diastolic blood pressure by 1.8 mmHg [110].
- In addition to weight control and CPAP, spironolactone may be particularly effective in controlling blood pressure because of secondary hyperaldosteronism in patients with OSA [111].

Obesity

- Overweight is defined as a body mass index (BMI) $\geqslant$ 25 kg/m^2. BMI is body weight in kilograms divided by the height in meters squared. Obesity is defined as a BMI $\geqslant$30 kg/m^2; morbid obesity is a BMI $>$40 kg/m^2.
- Obesity and weight gain have been identified as one of the most important determinants of hypertension.
- False high blood pressure readings in obese patients may result from the use of inappropriate cuff (small) size.
- Central or visceral obesity leads to a substantial increase in cardiovascular disease (CVD) morbidity and mortality. It is assessed through measuring waist circumference.
- Upper limit for a normal waist circumference for Egyptian men $<$93.5 cm and $<$92.5 cm for women [42].

Management of Obesity

- Attempt weight loss treatment for all patients with BMI $\geqslant$30 kg/m^2 and for patients with a BMI between 25 and 29.9 or have a high waist circumference, and 2 or more risk factors [112].
- Therapy begins with lifestyle changes in diet and physical activity.
- An initial weight loss of 10% of body weight, achieved over 6 months is a recommended target and results in a decrease in blood pressure by 5–20 mmHg [113].
- After first six months of weight loss therapy, the priority should be weight maintenance, which is achieved through the combined changes in diet, physical activity and behavior.
- Weight-reduction through bariatric surgery in the morbidly obese with significant co-morbidities can result in improved metabolic parameters and blood pressure [114].

Management of Hypertension in Obese Patients

Pharmacologic Treatment

- Non-pharmacological treatment is usually insufficient and pharmacological treatment must be added to control BP in obese hypertensive patients.
- Low-dose thiazide diuretic is a good choice since they counter volume expansion and reduce BP effectively in obese patients.
- Modern b-blockers such as nebivelol and carvedilol, (vasodilator BBs), and bisoprolol; a highly selective beta blocker, have less adverse effects than the older ones.
- In patients with dysglycemia and/or dyslipidemia, drugs such as ACEIs, ARBs and calcium channel blockers might constitute the best choice

Resistant hypertension

- Resistant hypertension is defined as persistent elevation of blood pressure above 140/90–150/95 mmHg in patients who are adhering to triple-drug regimen including a diuretic, and all three drugs are prescribed in maximum recommended and tolerated doses for at least three months [115].
- 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 [116].
- The diagnosis of resistant hypertension requires accurate blood pressure measurement to confirm persistently elevated blood pressure levels.
- Referral to a specialist should be considered.
- Although an inadequate response to antihypertensive therapy is unfortunately common, true resistant hypertension is not common in general practice.

Table 9 Substances that Can Elevate Blood pressure [120].

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

Causes of Resistent Hypertension

- False high blood pressure.
- True high blood pressure.
- True resistant hypertension

False High Blood Pressure

- *Cuff hypertension: due to the use of inappropriate (small) cuff size*
- *Office (white coat) hypertension:* 15–30% of patients diagnosed with hypertension actually have normal blood pressure at home or on ABPM.
- *Pseudo-hypertension*: Seen in elderly patients with atherosclerotic arteries, and calcified brachial artery. The cuff pressure is inappropriately high compared with intra-arterial pressure.

True High Blood Pressure

- *Inappropriate Drug Therapy*

A suboptimal medical regimen is the commonest cause of resistant hypertension [117].

– 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 and lifestyle modification*

– Poor adherence to the prescribed medical regimen is possibly the most common etiology of resistant hypertension [118]. One-half of all patients discontinue antihypertensive medications within one year or receive irregular treatment [119].
– Lifestyle: high salt intake, alcohol excess, uncontrolled obesity, continuous stressful exposures.

- *Ingestion of substances that can elevate blood pressure (Table 9)*
- *Obstructive sleep apnea.*

True Resistant Hypertension

- *Extracellular volume expansion [121]*

– Inadequate diuretic therapy.
– Renal insufficiency.
– Therapy with direct arterial vasodilators.
– Excessive sodium intake.

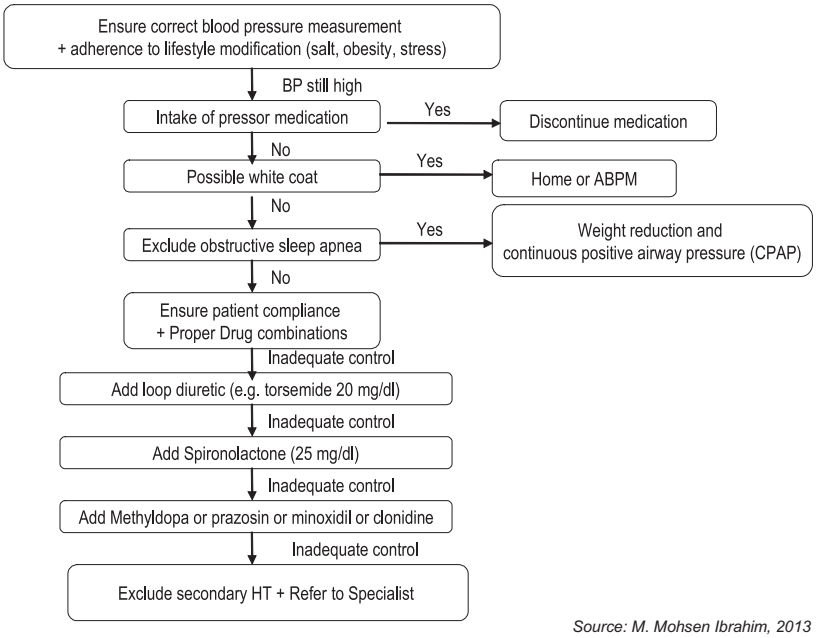
- *Secondary Hypertension*

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. Salt restriction, weight reduction and stress management are essential.
- Rule out white-coat hypertension by measurement of blood pressure at home or by ambulatory monitoring.

- Treat obstructive sleep apnea if present.
- Persistent volume expansion (even without edema) contributes to resistant hypertension. Effective diuretic (loop diuretic) use is almost always necessary to achieve blood pressure control [121].
- Spironolactone in a low dose usually 25 mg daily provides significant additional blood pressure reduction when added to multidrug treatment regimens [122].
- If these measures fail, consider taking the opinion of a specialist or hospitalization.
- Renal denervation by catheter-based radiofrequency ablation of the renal sympathetic nerves lowers though of the blood pressure in patients with resistant hypertension, it is still under investigation. Long-term data regarding efficacy and safety of radiofrequency ablation remain limited [123–125].

Resistant Hypertension



Source: M. Mohsen Ibrahim, 2013

HYPERTENSION IN THE ELDERLY

- BP goal in the elderly is $< 150/95$ mmHg
- Reduction in cardiovascular morbidity and mortality can be achieved with antihypertensive treatment in patients older than above 80 years.
- Low-dose thiazide diuretics and long acting dihydropridine calcium antagonists constitute the first line drug treatment in elderly patients.
- The diagnostic pitfalls of psuedohypertension, auscultatory gap and white coat hypertension should be carefully considered in these patients.
- Because of the increased risk of postural hypotension in the elderly, BP should always be measured also in standing posture.

Management of Elderly Hypertensive

- Start with smaller antihypertensive doses, at almost half the standard doses and 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.
- Check for adverse drug reactions which are two to three times more common in the elderly.
- Follow-up visits should be scheduled every 2–4 weeks until blood pressure is controlled.
- Consider co-morbid conditions and poly-pharmacy which are common in the elderly.
- Avoid centrally acting agents that may cause drowsiness, depression or impaired cognitive function
- Avoid drugs which exacerbate hypertension e.g. nonsteroidal anti-inflammatory drugs

Non Pharmacological Treatment

- The elderly (especially women) have increased sensitivity to salt [126]. Blood pressure is readily increased by salt loading, and reduced by salt restriction.
- Limit salt intake to less than 3–4 g NaCl/day [127,128].

Drug Therapy

- Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and long acting calcium antagonists as the drugs of choice [129].

Octogenarians (over 80 years)

- Successful treatment of hypertension in octogenarians was shown to reduce CV risk and mortality based on recently available data [130].
- Those with SBP more than 160 mmHg are candidates for antihypertensive drugs [130].
- Lowering of SBP less than 130 and DBP less than 65 mmHg should be avoided [130].

Isolated Systolic Hypertension

- Systolic blood pressure greater than 160 mmHg with diastolic blood pressure less than 90 mmHg.
- Systolic blood pressure is a strong predictor of cardiovascular complications than diastolic blood pressure [131,132].
- Lowering of systolic blood pressure in the elderly is associated with significant reduction in cardiovascular mortality, stroke, heart failure, myocardial infarction, and dementia [133].
- CCB, diuretics and ARBs are the drugs of choice [133].

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 , cerebral hemorrhage, pulmonary edema etc...
- 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.
- Patients who present with a hypertensive emergency should be hospitalized for rapid controlled lowering of blood pressure in the ICU. 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 parenteral antihypertensive drugs of choice (sodium nitroprusside, nitroglycerin and labetalol) are rapidly acting parentral 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.

General Principles

- Avoid using rapidly acting ***sublingual*** nifedipine and captopril that may result in uncontrolled reduction of arterial pressure and marked organ hypoperfusion leading to catastrophic end-organ damage such as cerebral infarction, or acute myocardial infarction [134,135].
- ***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 [135].
- Avoid rapid and uncontrolled reduction in blood pressure to the normal level within the first few hours, that may lead to target organs hypoperfusion. The mean arterial pressure should be reduced to a level of 120 mmHg (160/100) over several hourss [135]. In patients with acute pulmonary edema or aortic dissection, rapid lowering of BP (within <1 h) may be needed.
- Most patients with severe hypertension (DBP $\geqslant 110$ mmHg) have no acute end-organ damage. Rapid antihypertensive therapy may be associated with significant morbidity.
- In patients with hypertensive urgencies, BP is lowered gradually over a period of 24–48 h with oral medication [135].
- The immediate goal of IV therapy is to reduce the DBP by 10–15% or to less than 110 mmHg [135].
- All patients with a hypertensive emergency should be managed in an intensive care unit, where the patient can be closely monitored. Intra-arterial blood pressure monitoring may be required in patients with blood pressure that is labile and difficult to control.

Table 10 Types and Clinical Presentation of Hypertensive Emergencies [136]

- **Malignant hypertension with papilloedema**
- **Cerebrovascular**
  - Hypertensive encephalopathy
  - Atherothrombotic brain infarction with severe hypertension
  - Intracerbral haemorrhage
  - Subarachnoid haemorrhage
- **Cardiac**
  - Acute aortic dissection
  - Acute left ventricular failure
  - Acute myocardial infarction
- **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
  - Sympthomimetic drug use (cocaine)
  - Rebound hypertension after sudden cessation of antihypertensive drugs **e.g. clonidine.**
- **Eclampsia**
- **Surgical**
  - Severe hypertension in patients requiring immediate surgery
  - Postoperative hypertension
  - Postoperative bleeding from vascular suture lines
  - Severe body burns

Table 11 Diagnosis of Hypertensive Emergencies [137].

Diagnostic category	Diagnosis
Acute aortic dissection	Abnormal CTangiogram or transesophageal echocardiogram of the aorta
Acute pulmonary edema	Interstitial edema on chest radiograph
Acute coronary syndromes/ acute MI	Clinical diagnosis, and/or changes on electrocardiogram, and/or elevations of cardiac biomarkers
Acute renal failure	Elevated serum creatinine, proteinuria
Severe Pre-eclampsia, eclampsia	Proteinuria; hemolysis, elevated liver enzymes, low platelets; seizures, HELLP syndrome
Hypertensive encephalopathy	Clinical diagnosis including altered mental status associated with elevated blood pressure – may see papilledema, arteriolar hemorrhage or exudates on fundus exam; may note cerebral edema with a predilection for the posterior white matter of the brain on MRI after clinical diagnosis
Subarachnoid hemorrhage	Abnormal CT of the brain; red blood cells on lumbar puncture
Intracranial hemorrhage	Abnormal CT of the brain
Acute ischemic stroke	Clinical diagnosis including new neurological deficit, excluding other causes
Acute post operative hypertension	Clinical diagnosis including onset within 2 h of surgery, lasting 6 h or less
Sympathetic crisis*	Clinical diagnosis in the setting of sympathomimetic drugs including cocaine, amphetamine, positive urine drug screen, or pheochromocytoma demonstrated by 24 h urine for catecholamines and metanephrine

Abbreviations: CT = computed tomography, HELLP = hemolysis, elevated liver enzymes, low platelets, MRI = magnetic resonance imaging.
* In this syndrome, acute end organ dysfunction may not be measurable, but complications affecting the brain, heart, or kidneys may occur in the absence of acute treatment.

Table 12 Causes of secondary hypertension.

Renal causes:

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

Drugs

Endocrinal causes

- Primary hyperaldosteronism (5–12%)
- 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

Primary Aldosteronism

(see Algorithm 7)

- Most common form of secondary hypertension [146]
- Persistent elevations of aldosterone can result in end-organ damage [147]
- Prevalence among hypertensive patients [148,149]
  1. Unselected hypertensive patients: 4–5.9%
  2. Resistant hypertension: 11.3%
- Subtype differentiation
  1. Bilateral-adrenal hyperplasia 70% 2. Adenoma 30%
- Suspicion of primary aldosteronism [150]
  1. Spontaneous or unprovoked hypokalemia with renal K wasting
  2. Severe diuretic-induced hypokalemia (⩽3 mE/L) that does not normalize after discontinuation of diuretics [151]
  3. Hypertension with adrenal adenoma.
  4. Resistant hypertension with no other evidence of secondary cause
  5. Family history of primary aldosteronism
- Laboratory tests
  1. Hypokalemia: serum K < 3.5 mEg/L with 24 h urinary $K \geqslant 30$ mEq [152]
  2. Hypokalemia ⩽3.5 mEg/L provoked by a high salt intake
  3. Ratio of plasma aldosterone concentration (PA) to plasma renin activity (PRA) (PA: PRA) is the best screening test for primary aldosteronism [152,153].
  4. Combination of PA:PRA ratio > 30 and PA > 20 mg/dl had sensitivity of 90% and specifically of 91% [154]
- Drugs affecting plasma renin and aldosterone levels [155]
  1. BB → ↓ plasma renin → ↓ PA
  2. ACE and ARBs →↑renin, ↓PA
- Adrenal CT scan: high-resolution CT with contrast. Adenomas are < 3.0 cm, well circumscribed and homogenous, X-ray attenuation of ⩽10 Hounsfield units (HUS) [156].

Treatment

- Laprascopic adrenalectomy in confirmed unilateral adenoma [150].
- Spironolactone in adrenal hyperplasia.

Pheochromocytoma

Prevalence

- 0.3% of patients with hypertension [157]

Suspicion

- Family history of pheochromocytoma
- History of non-cardiogenic pulmonary edema
- Hypertension crisis with glucocorticoid or ACTH administration [158]
- Episodes suggestive of acute myocardial infarction with normal coronary angiography [159]
- Lactic acidosis in absence of shock
- Hypertension crisis during surgery

Clinical Characteristics

- Triad of episodic headaches, sweating, tachycardia
- Patient may be completely asymptomatic and have elevated circulating catecholamines [160]

Biochemical Testing [161]

- Plasma:
  1. Catecholamines > 2000 pg/ml
  2. Free metanephrine (MN) > 1.21 nmol/l
  3. Free non-metanephrine (NMN) > 2.21 nmol/l
- Urinary metanephrines > 1.8 mg/24 h
- If biochemical tests are in the indetermination range: use clonidine suppression test, does not suppress catecholamine release by supra-renal tumor. It acts at adrenergic nerve endings

  High Negative Predictive Value (exclude pheochromocytoma) if [161]
  1. Plasma free MN < 0.5 nmol/L, NMN < 0.9 nmol/l
  2. Plasma catechlamines < 1000 pg/ml
  3. Urinary metanephrine < 1.3 mg/ 24 h

Adrenal CT Scan

- Dense, vascular and heterogonous appearance with HUS ⩾ 22.

Treatment

- Surgical removal after preoperative preparation

- The most common clinical presentations of hypertensive emergencies are [135] cerebral infarction (24.5%), pulmonary edema (22.5%), hypertensive encephalopathy (16.3%), and congestive heart failure (12%). Other clinical presentations associated with hypertensive emergencies include intracranial hemorrhage, aortic dissection, and eclampsia, as well as acute myocardial infarction (see Tables 10 and 11).

Management of Hypertensive Emergencies

- The primary goal of the emergency physician is to determine which acute hypertensive patients are exhibiting symptoms of end-organ damage and require immediate intravenous (IV) parenteral therapy. In contrast, patients presenting with acutely elevated BP (systolic BP [SBP] > 200 mmHg or diastolic BP [DBP] > 120 mmHg) without symptoms and whose BP stays significantly elevated to this level on discharge, should have initiation of medical therapy and close follow-up in the outpatient setting.
- 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 [135].
- Rapid reduction of blood pressure to normal levels (< 140/90 mmHg) is indicated in patients with aortic dissection, acute pulmonary oedema, and in selected patients with cerebral hemorrhage (ICH).
- BP targets currently used for tissue plasominogen activator (< 180/110 mmHg) in patients with ischemic stroke could be beneficially extended to all patients within the first 24 h avoiding sharp BP reductions [135].
- Achieving SBP 130–140 mmHg over the initial 24 h in ICH was beneficial in the recent INTERACT study [138].
- For acute ischemic stroke, the preferred medications are labetolol and nicardipine. If the patient is not a candidate for thrombolytic therapy, withhold antihypertensive medications unless SBP is > 220 mmHg or DBP > 120 mmHg [139].
- For acute intracerebral hemorrhage, the preferred medications are labetalol, nicardipine and esmolol. Avoide nitroprusside and hydralazine [139].
- If there are signs of increased intracranial pressure (ICP), maintain SBP < 180 mmHg for the first 24 h after onset. In patients without increased ICP, maintain SBP < 160 mmHg for the first 24 h after symptoms onset [139].

Antihypertensive Drug Therapy

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 (IV infusion) in the ICU under close monitoring of arterial blood pressure, preferably through an arterial line. The dose ranges from 0.25 to 10 μg/kg/min. The infusion is started at 15 μg/min and cautiously increased by 5–10 μg/min every 3–5 min until the desired blood pressure is reached [140].
- It should be avoided whenever possible in patients with hepatic or renal failure.

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. The initial dose is 5 μg/min increased in increments of maximum rate of 200 μg/min.

Labetalol

- Beta and alpha adrenergic receptor blocker given as 50 mg bolus to be repeated every 5 min to a maximum of 200 mg, then intravenous infusion of 2 mg/min. The hypotension effect begins within 2–5 min after an IV dose and persists for about 2–4 h [140].

Clonidine

- Oral clonidine (0.1 mg every 20 min) used for the treatment of hypertensive urgencies. The onset of action is within 30 min–2 h, with duration of action of 6–8 h.

HYPERTENSION IN WOMEN

- The use of estrogen-containing oral contraceptive (OC) pills can cause secondary hypertension in young women.
- Newer progestins such as drospirenone contain a spironolactone-like moiety [141] with mild mineralocorticoid antagonist action; as a result, drospirenone-estrogen combinations generally cause a small decrease in BP.
- 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 intracerebral hemorrhage. The mother should be hospitalized for rapid lowering of the blood pressure using IV antihypertensive drugs , anticonvulsant therapy, and timely induction of labor after stabilization of the blood pressure.
- The oral antihypertensive drug of choice in pregnancy is methyldopa [142]. Alternatives include CCB 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.

Definition of Hypertension in Pregnancy

Hypertension in pregnancy is defined as blood pressure exceeding 140/90 mmHg. The diagnosis should be based on at least two high blood pressure readings on two separate occasions. Korotkoff phase V is now recommended for the measurement of diastolic blood pressure in pregnancy with phase IV being indicated only if Korotkoff sounds persist at cuff pressures approaching 0 mmHg.

Classification of Hypertension in Pregnancy

There are four major hypertensive disorders in pregnancy:

1. Preeclampsia–eclampsia.
2. Chronic preexisting hypertension.
3. Preeclampsia superimposed on chronic hypertension.
4. Gestational hypertension.

- **Chronic Preexisting Hypertension:** hypertension that predates pregnancy or a blood pressure >140/90 which develops before the 20th 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 which develops after the 20th week of gestation.
- **Eclampsia:** the development of convulsions unrelated to other cerebral conditions during the course of preeclampsia. Oedema occurs in up to 60% of normal pregnancies, and is no longer used in the diagnosis of pre-eclampsia.

Pharmacological Management of Hypertension in Pregnancy

Mild Hypertension

- 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 labetalol and long acting nifedipine.
- Never use ACEIs or ARBS during pregnancy due to its teratogenic effects.
- Avoid the use of diuretics during pregnancy because of its relatively low efficacy, risk of hypovolemia, stimulation of the renin-angiotensin system, hyperuricemia, hyponatremia and neonatal thrombocytopenia [143].

Severe Hypertension:

- Patients with systolic blood pressure >169 or diastolic blood pressure >109 mmHg should be hospitalized [143]. Management includes rapid lowering of blood pressure, prophylactic anticonvulsant therapy and timely induction of labour.
- In patients with ominous features of preeclampsia, immediate delivery is mandatory.
- IV nitroglycerin, or IV labetalol can be used in severe hypertension. IV hydralazine is no longer the parentral drug of choice because of its perinatal adverse effects
- IV magnesium sulfate is the drug of choice for preventing eclamptic convulsions. It is administrated slowly as a loading dose of 6 g diluted in 150 ml glucose 5% administered over 20–30 min followed by continuous infusion of 2 g/h.

Table 13 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%)	– History of renal disease – Abnormal urine sediments	Urinary sediments, pyuria, elevated creatinine	– Abdominal ultrasonography – Radiologic examination – Renal biopsy	– Drug therapy for hypertension – Specific urologic treatment
Renovascular hypertension (1–2%)	– Onset before 30 or after 50 years – Abrupt onset – Resistant hypertension – Multi-site atherosclerosis – Abdominal bruit – Flash pulmonary edema – Azotemia on ACE-I or ARBs	Captopril renography – *sensitivity 83%* – *specificity 93%* Renal Duplex – *sensitivity 95%* – *specificity 93%*	– Renal arteriography – Digital subtraction angiography – Spiral CT*	– Angioplasty + stenting – Drug therapy – Surgery
Aortic Coarctation (< 0.5%)	– Delayed/absent femoral pulse – ↓arm/leg blood pressure difference – LVH** – Precordial systolic ejection murmur – Systolic/continuous back murmur	– Chest X-ray: rib notching – ECG: LVH** – Echocardiography	– Aortography.	– Surgical repair. – Balloon angioplasty.
Primary aldosteronism (5–12%)	– Polyuria – Muscle weakness	– Hypokalemia – Excess urinary K^+ loss	– High plasma and urinary aldosterone, not suppressible – Low renin, persistent with standing or frusemide – CT* / MRI†	– Surgical removal – Spironolactone ± thiazide & loop diuretics
Pheochromocytoma (< 0.3%)	– Proxysmal hypertension – Headache, chest or abdominal pain – Sweating, palpitations, pallor	– 24h urinary metanephrin & nor-metanephrin (*sensitivity and specificity > 95%*)	– CT* / MRI† / MIBG scan‡ – Angiography	– Surgical removal after medical preparation

The following procedures should be ordered only by senior consultant

- Bariatric Surgery
- CPAP
- Confirmatory test for 2ry HTN

‡ MIBG: $^{131-}$I- Metaiodobenzylguanidine
† MRI: Magnetic Resonance Imaging.
* CT: Computerized Tomography
** LVH: Left Ventricular Hypertrophy

Hypertension in children and adolescents

- The prevalence of hypertension in children and adolescents varies from 1% to 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 95th percentile for age and gender [144].
- 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. Aortic coarctation can be easily diagnosed by careful examination of the lower limb pulsations (delayed and weak femoral compared with radial pulsations).
- 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.

Secondary hypertension

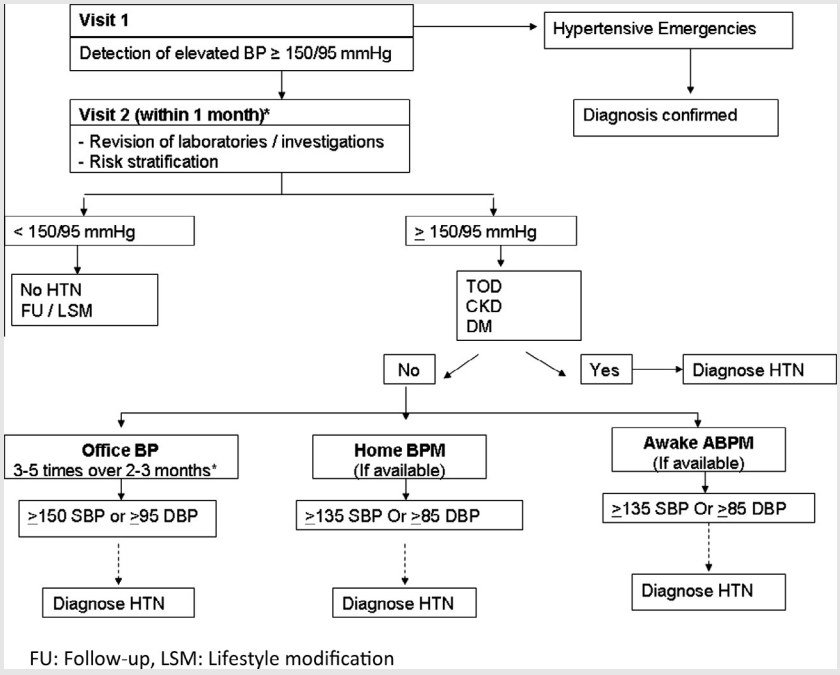
Patients Presenting with any of the Following Clinical Clues, should Suggest a Secondary Cause for Hypertension:

- 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).

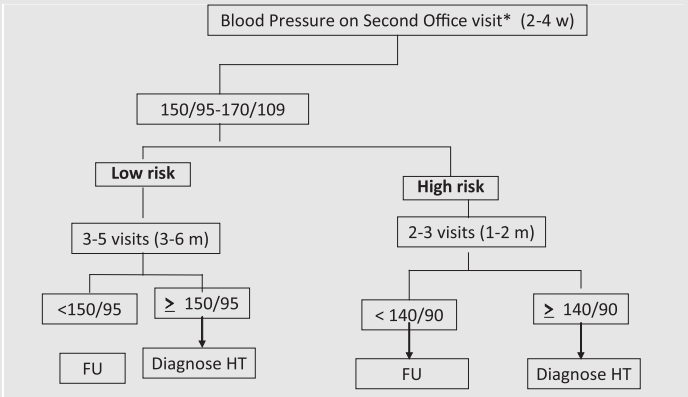
Secondary hypertension refers to high blood pressure from an identifiable underlying cause (see Tables 12 and 13). It may occur in 5–10% of hypertension cases, the most common causes are chronic renal disease, and primary hyperaldosteronism [145].

Algorithms

Algorithm 1. Diagnosis of hypertension (A)



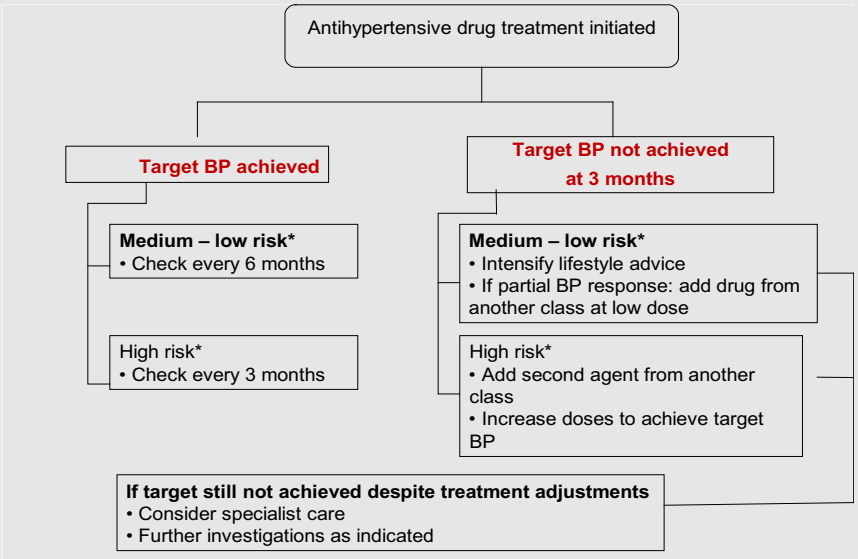
Algorithm 2. Diagnosis of hypertension (B)



*** Blood pressure measured on second office visit is usually lower than measurements taken on first visit (1)**

*Visits frequency and intervals depend upon blood pressure level and risk category

Algorithm 3. Follow-up after initiation of antihypertensive drug therapy

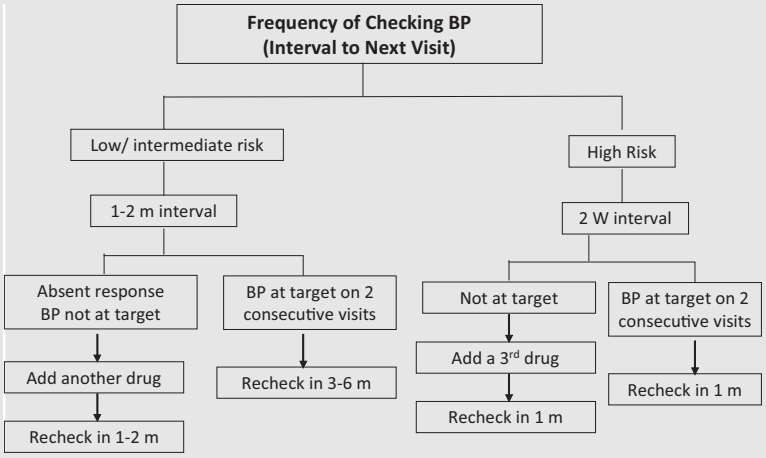


** Absolute cardiovascular risk assessed based upon number of risk factors, TOD, CV and CKD*

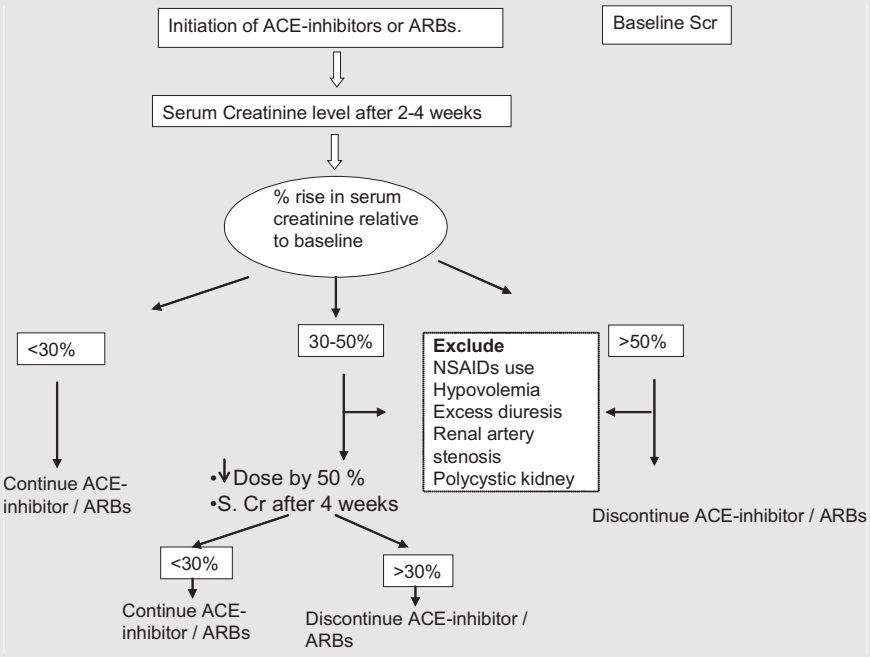
Modified from Australian guidelines 2008

*Visits frequency and intervals depend upon blood pressure level and risk category

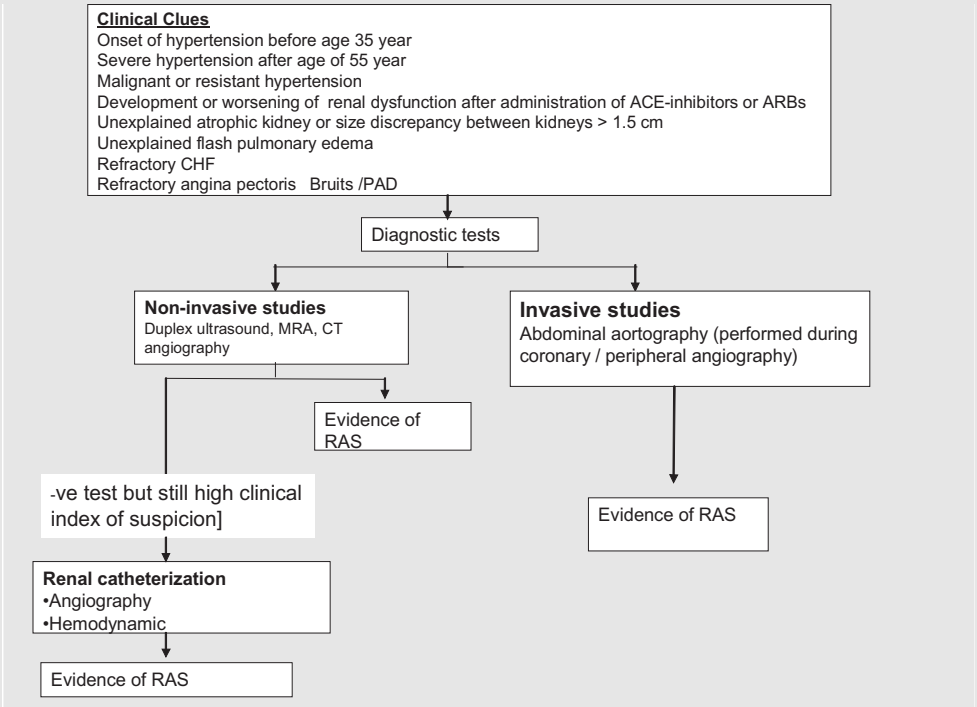
Algorithm 4. Monitoring of drug therapy



Algorithm 5. Monitoring and management of rising serum creatinine after initiation of ACE-inhibitors or ARBs.

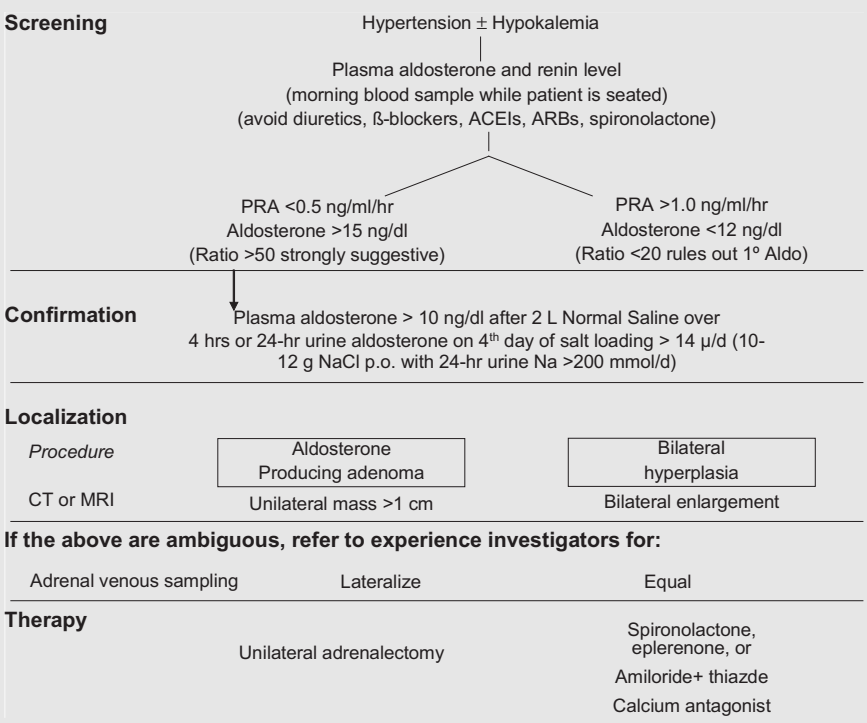


Algorithm 6. Diagnosis of renal artery stenosis. (See below-mentioned references for further information.)



Source: ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (162)

Algorithm 7. Diagnosis of primary hyperaldosteronism



Comments on Egyptian guidelines

Egyptian Guidelines Development

Developed by expert panel of 28 members (guidelines working group) which included writing group and advisory board. Six writing groups: reviewed pertinent literature and 13 recent national and international guidelines. Guidelines content were reviewed during a number of meetings for approval by working group members. Whenever there was a disagreement, voting was needed for reaching a consensus. Final draft was sent to 600 practitioners and internists and displayed on internet EHS website. Final document was prepared taken into consideration feedback and comments from medical community. Final document was approved by all working group members.

While preparing the guidelines, the following points were considered:

1. Guidelines should be relevant to the way in which health care is delivered.
2. Define practices that meet the needs of most patients in most situations.
3. Best patient care with least expensive management, limiting laboratory testing to a minimum and prescribing affordable drugs.
4. Limiting drug therapy to truly hypertensive patients particularly those at high risk.

Process of guidelines development differed. In developing countries such as Malaysia, the process was similar to ours initiated by the Malaysian Society of Hypertension. A committee of limited number of members including different specialties convened and guidelines were posted on websites for comments and feedback.

The Indian guidelines [163] were formulated by a core committee supported by a working group and the document was circulated to 250 doctors, whose input was incorporated in the final version. The updated guidelines have been reviewed by a panel of experts so as to arrive to a consensus.

The British NICE guidelines [32] were developed by a multidisciplinary guidelines development group comprising professional group members and consumer representatives of the main stakeholders.

Grading of Evidence

Majority of Egyptian recommendations were based on consensus of expert opinion. The main issue was the lack of applicability of guidelines developed in rich countries which are mainly evidence-based to less developed societies with limited resources [164,165]. There is limited literature and clinical trials from developing countries that provide evidence based decisions. Egyptian guidelines tried to adapt evidence-based recommendations to local economic, cultural and lifestyle circumstances. Recommended best practice based on the clinical experience of the guidelines development group. Evidence alone is never sufficient to make clinical decisions.

Size of the Document

Guidelines are not intended to be a text book on hypertension. Therefore a detailed document, though it may be a useful reference, is not practical and may be difficult to implement in the everyday practice of the busy practitioner. Important limitation of European, British and Japanese guidelines is the large size of the document. Egyptian guidelines made a compromise between a comprehensive and reasonable size document.

Guidelines were also produced in a small pocket-size summary. Basically, the practitioner needs to know, what to do and what not to do and how to do it in a particular situation.

Scope

While preparing guidelines, the main concern of the writing group was to address the important practical questions seen in everyday practice. The Egyptian guidelines differ from others by avoiding theoretical discussion, controversial issues and, in contrast to other guidelines, reference to clinical trials was kept to the minimum. More attention was paid to areas of thresholds for diagnosis, initiation and monitoring of drug therapy. Only a brief discussion addressed hypertension in children, since this is generally is not within the domain of general practitioner or internists.

The following areas were not covered in the Egyptian guidelines: arterial stiffness, pulse pressure, central aortic pressure, details of assessment of target organ damage, risk assessment charts, pharmacology of antihypertensive drugs as well as the details of management of patients with white coat, masked hypertension and secondary forms of hypertension.

Diagnostic Threshold for Hypertension: What is a Normal BP?

The risk associated with increasing blood pressure is graded and continuous. It begins as low as at 115/75 mmHg and increases gradually without a particular threshold that might discriminate between risk and no-risk circumstances. The choice of office blood pressure 140/90 mmHg as the diagnostic threshold for hypertension is neither evidence-based nor universally accepted. The Egyptian guidelines recommend a diagnostic threshold of 159/95 mmHg. The choice of 140/90 mmHg was based upon research studies of drug trials [26–29], where the benefits of treatment are out-weighted by its side effects. Blood pressure measurement during research studies by research personnel adhering to guidelines protocol and taking necessary precautions is different from measurements taken by practitioner in the busy everyday office practice [26–29,32], paying little attention to details of the procedure. Blood pressure readings taken during routine office measurements were consistently higher than research quality measurements [31].

Routine office BP of 150/95 mmHg is comparable to a research quality BP of 140/90 mmHg [18]. Research quality office BP of 140/90 mmHg = awake ABP of 135/85 mmHg. BP measured in routine clinical practice is 10/5 mmHg higher than a research-quality office BP.

There is uncertainty around the current blood pressure cut-off point (140/90 mmHg), a huge number of people being misdiagnosed of having hypertension [26–29]. Over-diagnosis exposes people unnecessarily to considerable risk for adverse drug reactions.

There is recent evidence to support the existence of a higher cut-point for diagnosing hypertension in routine clinical practice as seen in studies comparing office blood pressure with ambulatory blood pressure [18,27]. The real threshold for hypertension must be considered as flexible, being higher or lower based on the total cardiovascular risk of each individual.

In developing countries with limited resources, raising the diagnostic threshold should be more cost effective than the standard threshold of 140/90 mmHg. In high-risk patients, however, the threshold is reduced from 150/90 to 140/90 mmHg.

Risk Factors Thresholds

There is a disagreement between guidelines regarding the definition of abnormal lipid profile. The recent European guidelines (2013) defines as abnormal total cholesterol levels >190 mg/dl, LDL-C >115 mg/dl and triglycerides >150 mg/dl [166]. These levels are at variance from earlier guidelines e.g. the WHO/ ISH (2003) defines abnormal levels for total cholesterol, LDL-C as 240 mg/dl and 160 mg/dl respectively [167]. The Japanese guidelines (2009) took an intermediate LDL-C level of 140 mg/dl [168]. Egyptian Hypertension Society Guidelines advocates the conservative WHO/LSH guidelines high levels since this might be more cost-effective in risk stratification and for future management. On the other hand, many guidelines did not specify the diagnostic threshold for abnormal lipids.

The selection of waist circumference cut-off measurement defining risk of abdominal obesity was different from other guidelines, since waist circumference threshold depends on gender, ethnic differences and geographic regions. Egyptian guidelines were based on recent Egyptian data on definition of abdominal obesity at a cut-off of 93.5 cm for men and 92.5 cm for women [42].

Rationale for a Diagnostic Threshold of 150/95 mmHg:

- The diagnostic threshold of 140/90 mmHg is neither evidence-based nor universally accepted.
- At the 17^{th} World Conference of Hypertension League Council (1997), 13 out of 27 national hypertension societies stayed with 160/95 mmHg [25].
- The distress about having hypertension and possibly requiring life-long drug therapy may lead to development of anxiety symptoms.
- The threshold of 140/90 mmHg was based upon data from research studies and drug trials where blood pressure readings were taken for research purposes and do not actually routine office measurements.
- Data derived from several large studies [18,169] have equated a manual (research quality) office blood pressure of 140/90 mmHg with a mean awake ambulatory blood pressure (ABP) of 135/85 mmHg. There was a consistent difference between the mean awake ABP and the routine office blood pressure greater than the usual recognized 5 mmHg (140/90 mmHg for office blood pressure vs. 135/85 mmHg for mean awake ABP). Blood pressure measurement in routine clinical practice seems to be at least 10/5 mmHg higher than the research-quality office blood pressure.

Acknowledgement

The EHS Guidelines Working Group appreciates very much the excellent secretarial work of Mrs. Rehab El-Ashkar, who helped in the typing and preparation of the document and for running the logistics of working group meetings. Also, the efforts and help of Dr. Noha Abdel Shakor should be recognized.

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