EVALUATION, MANAGEMENT, AND CARDIOVASCULAR RISK REDUCTION IN ESSENTIAL HYPERTENSION

Hussien H. Rizk, MD

Most hypertensive patients present with a modest elevation in blood pressure. The diagnosis of hypertension is made in this setting only after an elevated and properly measured blood pressure has been confirmed on at least three separate occasions. Once this has occurred, an evaluation should be performed to ascertain the following information:

- To determine the extent of target organ damage.
- To assess the patient's overall cardiovascular risk status.
- To rule out identifiable (secondary) and often curable causes of hypertension

BASIC WORKUP

History – The history should search for facts that help determine the presence of precipitating or aggravating factors, the natural course of the blood pressure, the extent of target organ damage, and the presence of other risk factors for cardiovascular disease.

Physical examination – The main goals on the physical examination are to evaluate for signs of end-organ damage (such as retinopathy) and for evidence of a cause of identifiable hypertension. Thus, the various pulses should be palpated and the abdomen should be ausculted for a renal artery bruit. The presence of an upper abdominal bruit with a diastolic component that lateralizes toward one side is highly suggestive of renal artery stenosis

Laboratory testing – The only procedures that should be routinely performed are:

- Hematocrit, urinalysis, and routine blood chemistries (glucose, creatinine, electrolytes)
- Lipid profile (total and HDL-cholesterol, triglycerides)
- Electrocardiogram

The presence of hyperuricemia may also be a marker of cardiovascular risk in hypertensive patients as well as the general population. However, data from the Framingham Heart Study suggest that this relationship disappears after adjustment for other cardiovascular disease risk factors.

Additional tests – Additional tests may be indicated in certain settings. These include:

Limited echocardiography – Limited echocardiography is a more sensitive method to detect left ventricular hypertrophy than the ECG. The main indication for echocardiography is to detect possible end-organ damage in a patient with borderline blood pressure values. It will also identify some patients who would not be treated based upon clinical criteria alone.

Ambulatory blood pressure monitoring – Ambulatory BP monitoring is capable of reducing the costs of the management of hypertension by rapidly identifying the 20% of patients with "white-coat hypertension" and by ensuring adequacy of therapy. The main indication for its use is in the patient with persistent office hypertension but normal blood pressure readings in the ambulatory setting.

Microalbuminuria – The presence of microalbuminuria is an early manifestation of nephropathy in either diabetes mellitus or hypertension, and is associated with an increased incidence of cardiovascular disease. Testing for microalbuminuria is at present primarily limited to patients with diabetes to screen for early nephropathy. The value of measuring albumin excretion in patients with primary hypertension without diabetes is being increasingly advocated.

ASSESSMENT OF CARDIOVASCULAR RISK – As well defined by data from the Framingham study, a number of other risk factors interact with hypertension to determine the overall risk status of each individual patient. The presence or absence of other risk factors can influence the decision as to whether to institute antihypertensive medications in a patient with borderline values.

INTRODUCTION – The treatment of hypertension is the most common reason for office visits of non-pregnant adults and for use of prescription drugs. The number of patients with hypertension is likely to grow as the population ages, since hypertension occurs in over one-half of persons older than 65 y. An increased incidence of obesity will also increase the number of hypertensive individuals. Despite the prevalence of hypertension and its associated complications, control of the disease is far from adequate. The highest rate of BP control in the world is only 34% This failure reflects the inherent problem of maintaining long-term therapy for an asymptomatic condition, particularly when the therapy may interfere with quality of life and when immediate benefits may not be obvious to the patient. Thus, hypertension will likely remain the most common risk factor for heart attack and stroke.

DEFINITIONS – The following definitions have been suggested by the seventh report of the Joint National Committee (JNC 7). Based upon the average of $\geq$ 2 properly measured readings at each of two visits after an initial screen, the following classification is used:

- Normal BP: systolic <120 mmHg and diastolic <80
- Pre-hypertension: systolic 120-139 or diastolic 80-89
- Hypertension:
  - Stage 1: systolic 140-159 or diastolic 90-99
  - Stage 2: systolic > or =160 or diastolic > or =100

These definitions apply to adults on no antihypertensive drugs and who are not acutely ill.

ETIOLOGY/RISK FACTORS:

Essential hypertension has been associated with a number of risk factors:

- Hypertension is about twice as common in subjects who have one or two hypertensive parents and multiple epidemiologic studies suggest that *genetic factors* account for about 30% of the variation in blood pressure in various populations.
- Evidence for a relationship between *sodium intake* and essential hypertension continues to mount. It is likely that increased salt intake is a necessary but not sufficient cause for hypertension.
- Multiple studies show a clear association between *excess alcohol* intake and the development of hypertension.
- When hypertensive patients are compared to normal, one of the major differences is an increased prevalence of *obesity*. Furthermore, weight gain appears to be a main determinant of the rise in BP that is commonly seen with aging.
- Hypertension tends to be both more common and more severe in *blacks*.
- Hypertension may be more common among those with certain *personality traits*, such as hostile attitudes and time urgency/impatience.

COMPLICATIONS: Hypertension is associated with a number of serious adverse effects. The likelihood of developing these complications varies with the BP. The increase in risk begins as the BP rises above 110/75 mmHg and, at any BP, is importantly affected by the presence or absence of other risk factors.

- Hypertension is quantitatively the major risk factor for premature cardiovascular disease, being more common than cigarette smoking, dyslipidemia, and diabetes. In older patients, systolic pressure (and perhaps pulse pressure) are more powerful determinants of risk than diastolic pressure.
- Hypertension increases the risk of heart failure (HF) at all ages with the hazard increasing with the degree of BP elevation.
- Left ventricular hypertrophy (LVH) is common in patients with hypertension, and is associated with an increased incidence of HF, ventricular arrhythmias, death following myocardial infarction (MI), and sudden cardiac death.
- Hypertension is the most common and most important risk factor for stroke, the incidence of which can be markedly reduced by effective antihypertensive therapy.
- Hypertension is the most important risk factor for the development of intracerebral hemorrhage.
- Hypertension is a risk factor for chronic renal insufficiency and end-stage renal disease (ESRD). It can both directly cause renal disease (hypertensive nephrosclerosis) and accelerate the progression of a variety of underlying renal diseases (e.g. diabetic nephropathy)
- Marked elevations in BP can cause an acute, life-threatening emergency.

DIAGNOSIS: We recommend measuring BP at each office visit for all patients over 21 years.

BP Measurement:

- Proper measurement and interpretation of the BP is essential in the diagnosis and management of hypertension.
- In the absence of end-organ damage, the diagnosis of mild hypertension should not be made until BP has been measured on at least 3-6 visits, spaced over a period of weeks to months. Several studies showed that BP drops by 10-15 mmHg between visits 1 & 3 in patients with mild hypertension on a first visit to a new doctor, with a stable value achieved at about 6 visits in most cases.
- Many patients considered hypertensive at the initial visit are in fact normotensive.

White coat hypertension and ambulatory monitoring:

- About 20-25% of patients with mild office hypertension (DBP 90-104 mmHg) have "white-coat" or isolated office hypertension. Their BP is repeatedly normal when measured at home, at work, or by ambulatory BP monitoring. This problem is more common in the elderly, but is infrequent (< 5%) in patients with office diastolic pressures $\geq$105 mmHg.
- One way to minimize the white coat effect is to have the BP taken by a nurse or technician, rather than the physician.
- Ambulatory monitoring can be used to confirm the presence of white coat hypertension in patients with persistent office hypertension but normal blood pressure readings at home. Several studies have suggested that the risk of hypertensive cardiovascular complications (including both the development and regression of left ventricular hypertrophy) correlates more closely with ambulatory monitoring than with the office pressure.

- In addition to patients with suspected white coat hypertension, ambulatory monitoring should be considered in the following circumstances:
  - Significant office hypertension with little or no evidence of end-organ damage
  - Apparent resistance to increasing medication
  - Development of hypotensive symptoms (dizziness, weakness) on various medications, suggesting that the patient may be normotensive
  - Evaluation of episodic hypertension or autonomic dysfunction
  - Large variations in self-measured blood pressure values

EVALUATION – Once it has been determined that the patient has hypertension, an evaluation should be performed to ascertain the following information:

- To determine the extent of target organ damage.
- To assess the patient's overall cardiovascular risk status.
- To rule out secondary and often curable causes of hypertension.

Patients with essential hypertension undergo a relatively limited work-up because extensive laboratory testing is of limited utility. However, it is important to be aware of the clinical clues suggesting the possible presence of secondary hypertension. Many of these disorders can be cured, leading to partial or complete normalization of the blood pressure; but it is not cost-effective to perform a complete evaluation in every hypertensive patient.

History – The history should search for those facts that help determine the presence of precipitating or aggravating factors, the natural course of the BP, the extent of target organ damage, and the presence of other risk factors for cardiovascular disease.
One important consideration is the duration of hypertension. Simply asking the patient "How long have you had high blood pressure?" may lead to a misleading answer. Suppose, for example, that the patient says two years. This should be followed by the question: "When was the last time you were told your blood pressure was normal?" In some cases, the patient will not have a blood pressure measurement for many years. Thus, the patient may have had undiagnosed hypertension for many years.
Physical examination: The main goals on the physical examination are to evaluate for signs of end-organ damage and for evidence of a cause of secondary hypertension.
Laboratory testing – The only testing that should be routinely performed includes:

- Hematocrit, urinalysis, and routine blood chemistries (glucose, creatinine, electrolytes)
- Fasting lipid profile (total and HDL-cholesterol, triglycerides)
- Electrocardiogram

Additional tests may be indicated in certain settings:

- Testing for microalbuminuria is primarily limited to patients with diabetes to screen for early nephropathy.
- Limited echocardiography is a more sensitive method to detect LVH than ECG and is less expensive than a complete echocardiographic examination. The main indication for echocardiography is to detect possible end-organ damage in a patient with borderline BP. It will also identify some patients who would not be treated based upon clinical criteria alone.

TREATMENT

Benefits of BP control In clinical trials, therapy has been associated with 35-40% reduction in stroke; 20-25 % in MI; and > 50 % in HF. Hypertension control to < 140/90 mmHg could, in men & women, prevent 19 & 31 % of coronary events, respectively, while optimal control to < 130/80 mmHg could prevent 37 & 56 %, respectively.

Equal if not greater benefits have been shown with the treatment of elderly hypertensives (over age 65), most of whom have isolated systolic hypertension.

Who should be treated?

Using JNC 7 definition, the following approach can be used to determine which patients with hypertension require antihypertensive therapy:

- All patients should undergo appropriate lifestyle (non-drug) modification (discussed below). The following decisions about antihypertensive medications are generally not made until there has been an adequate trial of non-drug therapy.
- In the absence of end-organ damage, a patient should not be labeled as having hypertension unless BP is persistently elevated after 3-6 visits over several months. During the initial evaluation period (before a therapeutic decision is made), patients should be encouraged to measure their BP at home or work.
- Antihypertensive medications should generally be begun if SBP is persistently ≥140 mmHg and/or the DBP is persistently ≥ 90 mmHg in the office and at home despite attempted non-drug therapy.
- Starting with 2 drugs may be considered in patients with a baseline BP > 20/10 mmHg above goal. This strategy may increase the likelihood that target blood pressures are achieved in a reasonable time period, but should be used cautiously in patients at increased risk for orthostatic hypotension (such as diabetics and the elderly).
- In patients with diabetes or proteinuric chronic renal failure, antihypertensive therapy is indicated when SBP is persistently > 130 mmHg and/or DBP is > 80 mmHg.
- Based upon findings in the HOPE, EUROPA, and CAMELOT trials, we recommend a goal BP ≤130/80 mmHg in patients with cardiovascular disease.
- Patients with office hypertension, normal values at home, and no evidence of end-organ damage should undergo ambulatory BP monitoring to see if they are truly hypertensive.

Lifestyle modifications: Treatment of hypertension generally begins with non-drug therapy, including moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise.

- A low sodium diet will usually lower BP and may prevent the onset of hypertension.

The overall impact of moderate sodium reduction is a fall in BP in hypertensives and normotensives of about 5/2 & 2/1 mmHg, respectively.

The recommendation is to reduce dietary intake to 100 meq/day. [1 gram of NaCl = 17 meq Na]).

- Weight loss in obese individuals can lead to a significant fall in BP.
- Patients who drink alcohol should reduce intake to 2 drinks/D (1 drink/D in women).
- Long-term aerobic exercise has a beneficial effect on BP.

One additional important lifestyle modification is cessation of smoking. Although smoking itself does not appear to cause persistent hypertension, it markedly increases the cardiovascular risk in hypertensive patients.

Drug treatment:

Initial drug choice in uncomplicated hypertension:

We agree with JNC 7 report recommendation for initiating therapy in uncomplicated hypertensives with a low-dose thiazide diuretic based upon improved outcomes in ALLHAT and low cost unless there is a specific indication for a drug from another class.

This dose is associated with a low rate of metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia. If low-dose thiazide monotherapy fails to attain goal BP in uncomplicated hypertensives, an ACE inhibitor, ARB, beta blocker, or calcium channel blocker can be sequentially added or substituted.

Thiazides have other actions that may be desirable in specific patient populations. In particular, they lower urinary calcium excretion, which may be beneficial in patients with hypercalciuria and recurrent calcium stones and in those with osteoporosis.

The suggestion that calcium channel blockers may increase the risk of MI in hypertensive patients has not been confirmed in ALLHAT and other studies with long-acting dihydropyridines. The appropriate use of these drugs should therefore not be discouraged.

Indications for specific drugs – These general recommendations for initial therapy should be amended in certain clinical settings in which specific agents might offer particular benefit. These include the demonstration that ACE inhibitors improve outcomes in a number of high risk settings and that beta blockers improve survival in patients with systolic heart failure and a prior MI.

ACE inhibitors are first-line therapy in all patients with HF or asymptomatic LV dysfunction, ST elevation MI, anterior infarct, diabetes, or systolic LV dysfunction, and in patients with proteinuric chronic renal failure.

ARBs are particularly indicated in patients who do not tolerate ACE inhibitors (mostly because of cough).

Beta blockers – A beta blocker (without intrinsic sympathomimetic activity) should be given after an acute MI and to stable patients with HF or asymptomatic LV dysfunction (beginning with very low doses to minimize the risk and degree of initial worsening of myocardial function). The use of beta blockers in these settings is in addition to the recommendations for ACE inhibitors in these disorders.

Beta blockers are also given for rate control in patients with AF, for control of angina, and for symptom control in a number of other disorders (anxiety, panic disorder, migraine, and essential tremor).

Calcium channel blockers have no absolute indications in hypertensive patients. Like beta blockers, they can be given for rate control in patients with AF or to control angina. Calcium channel blockers may be preferred in patients with obstructive airways disease.

Other specific settings: Alpha blockers may be preferred in older men with prostate symptoms.

Combination therapy:

- If there is a suboptimal response to initial therapy, the alternatives are to push the first drug to maximum dosage or to add a second drug. The latter approach has the advantage of fewer side effects.
- Administering two drugs initially should be considered with BP of > 20/10 mmHg above goal BP. This may increase the likelihood that target BP is achieved faster, but should be used cautiously in patients at increased risk for orthostatic hypotension (such as diabetics and the elderly)
- If two drugs are required, use of a low dose of a thiazide diuretic as one of the drugs increases the response rate to all other agents. The combination of a thiazide diuretic with a beta blocker or an ACE inhibitor has a synergistic effect, controlling BP in up to 85 % of patients.

Goal BP

- In uncomplicated systolic/diastolic hypertension, the goal BP is < 140/90 mmHg.
- For hypertensives > 65 y. with isolated systolic hypertension, caution is needed not to inadvertently lower DBP to below 65 mmHg to attain a goal systolic pressure <140 mmHg, since this level of DBP has been associated with an increased risk of stroke. Thus, the level of SBP that is reached with two or three antihypertensive agents (even if > 140 mmHg) may be a more reasonable interim goal in such individuals.
- A goal BP of <130/80 mmHg is recommended in two clinical settings: patients with diabetes; and with chronic renal disease.
- Based upon findings in HOPE, EUROPA, & CAMELOT trials, we recommend a goal BP $\leq$ 130/80 mmHg in patients with cardiovascular disease.
- These recommendations assume that the blood pressure is being gradually reduced, since acutely lowering blood pressure in patients with severe underlying hypertension can clearly lead to deleterious cerebrovascular and coronary events.

Resistant hypertension:

- Resistance is usually defined as DBP > 95-100 mmHg despite intake of $\geq$ 3 antihypertensive medications.
- One or more of the following problems usually contributes to the inability to adequately lower the blood pressure (BP) in this setting:
  - Suboptimal therapy
  - Extracellular volume expansion
  - Poor compliance with therapy
  - Secondary hypertension
  - Office or "white coat" hypertension
  - Pseudohypertension
  - Ingestion of substances (or drugs) that can elevate BP

Discontinuing therapy:

- Anti-hypertensive therapy is maintained for life in the gross majority of patients.
- Gradual discontinuation of therapy is most likely to be effective in patients with mild initial hypertension who are well controlled on a single drug and who can often be maintained on non-drug therapy such as weight loss and sodium restriction.

Abrupt cessation of therapy with a short-acting beta-blocker (such as propranolol) or the short-acting alpha-2-agonist clonidine can lead to a potentially fatal withdrawal syndrome.
Gradual discontinuation of these agents over a period of weeks (including switching to longer-acting drugs of the same class such as atenolol or methyldopa) should prevent this problem.