

Hypertension

Hypertension (HTN) is an important public health problem with large numbers of people affected. It is a heterogeneous condition, its pathogenesis, and pathophysiology are incompletely understood. Because of these factors, we composed this article to assist busy medical practitioners in understanding the most current results, and treatment programs. We also provide definitive guidance explaining when we recommend referral to a nephrologist.

PATHOGENESIS AND EPIDEMIOLOGY

It is well known that the etiology of HTN is caused by a variety of genetic and environmental factors. Recently, Keller et al found that the kidneys from persons with HTN had significantly fewer glomeruli. Specifically, hypertensive patients' counts had a median of 702,379 compared with 1,429,200 in matched controls. Determining what controls these quantities is helpful in understanding the etiology of HTN. Updated research indicates that several factors are implicated in determining nephron quantities:

- 1) Fetal exposure to toxins
- 2) Protein calorie restriction
- 3) Decreased birth weight
- 4) Mutations in genes that are key to renal development, such as PAX genes (a transcription factor), WNT (Wilms' tumor 1, a zinc-finger nuclear factor) genes, renin angiotensin system genes and others.

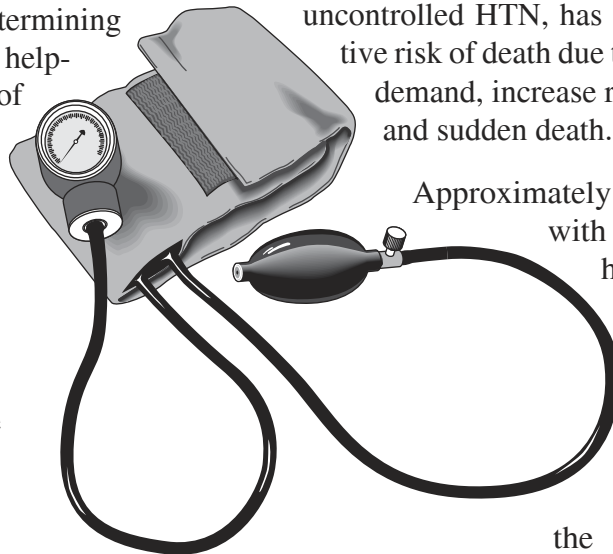
Simultaneously, glomerular volume has been found to be greater in hypertensive kidneys. This would suggest that the glomeruli in the persons with hypertension were overworking or hyperfiltrating.

Evidently, the physiological kidney architecture has far reaching consequences in the development of HTN, and may play a role in the development of chronic kidney disease.

HTN is strongly and independently associated with **cardiovascular morbidity and mortality**. Data from the famous Framingham heart disease study revealed that systolic blood pressure (SBP) higher than 140 and diastolic blood pressure (DBP) higher than 90 is associated with a 2.0 relative risk of death of cardiovascular heart disease. Left ventricular hypertrophy and increased left ventricular mass, a consequence of uncontrolled HTN, has an 11.4 high relative risk of death due to increase oxygen demand, increase risk of arrhythmias and sudden death.

Approximately 6% of patients with essential HTN have chronic kidney disease and are at risk for progression to end stage renal disease (ESRD). HTN is cited as

the cause of ESRD in about 30% of new cases in the United States and is the second leading cause of ESRD in African Americans.



HYPERTENSION

IMPROVING OUTCOMES

Outcomes could be improved for over 36 million, of the approximately 50 million people who are affected with HTN in the United States. Data from the Third National Health and Nutrition Examination phase III (NHANESIII) indicates that **32% of all patients with HTN are unaware** of their condition and are not receiving treatment, 15% are aware of it but are not receiving treatment, and 26% are treated, but their blood pressure is uncontrolled, leaving only **27%** with controlled HTN. Increased patient awareness could significantly improve outcomes.

Additional improvement could be achieved by treating cases currently deemed borderline 30% of the time. When diastolic blood pressure (DBP) is around 90 to 100 mmHg, or when systolic blood pressure (SBP) is between 140-160 mmHg, treatment is strongly recommended. This will prevent a significant number of hypertensive complications. Many people falling into this borderline category are elderly with isolated systolic HTN, women, and Mexican Americans. Studies show that 92% in this category are insured.

Another study by Berlowitz et al, in Veteran Affairs sites in New England showed that in a group of men with an average age of 65.5, approximately 40% of patients had blood pressure > 160/90 mmHg.

The Seventh Joint National Committee JNC VII has recently released the new classification for HTN for adults ages 18 and older (Table 1). This is based on the average of two or more properly measured, seated blood pressure readings on each of two or more office visits.

Table 1: Classification of Blood Pressure in Adults

BP Classification	Systolic Blood Pressure mmHg	Diastolic Blood Pressure mmHg	Lifestyle Modifications
Normal	< 120	And < 80	Encourage
Pre-HTN	120-139	80-89	Yes
HTN			
Stage 1	140-159	90-99	Yes
Stage 2	> 160	Or > 100	Yes
Stage 3	> 180	> 110	Yes

Once the diagnosis of HTN is established, certain laboratory tests are recommended before initiating therapy. These include:

- 1) Obtaining an electrocardiogram looking for left ventricular hypertrophy, or left atrial enlargement or left ventricular strain pattern. An optional study would be an echocardiogram to evaluate for left ventricular mass which makes the patient's prognosis worse, and will help in deciding drug therapy.
- 2) Evaluation of serum creatinine, and determination of glomerular filtration rate will help to determine the need for a nephrology referral (Table 2). Loop diuretics are probably a better choice with 50 percent or less of kidney function.
- 3) Serum electrolytes, such as decreased potassium or elevated serum calcium may correspond to secondary causes of HTN and will need evaluation.
- 4) Lipid profile, since hyperlipidemia has been related to worse cardiovascular outcomes.
- 5) Urinalysis to evaluate for significant proteinuria, hematuria, etc. If positive, this may represent hypertensive nephrosclerosis –generally less than a gram of protein- or a different nephropathy that will warrant further investigation.
- 6) Microalbuminuria is a high-risk marker for cardiovascular mortality. It can be assessed in a random sample of urine as the microalbumin/creatinine ratio (> 200 ug/g).

Once it is established that the patient has essential HTN, a careful review of lifestyle needs to be addressed, as will be discussed below. Another important step in the correction of HTN is to educate the patient that certain over the counter drugs, or prescribed medicines that the patient must take for a medical

reason, like in transplant patients, can cause HTN. Since these drugs could be the sole cause of HTN, and only discontinuing them will correct the problem, we recommend seriously evaluating withdrawal when possible. These include medications such as non-steroidals, cyclooxygenase 2 inhibitors, decongestants, anorectics, oral contraceptives, cyclosporine or tacrolimus, steroids, illicit drugs, licorice (including chewing tobacco) and selected over-the-counter dietary supplements and medicines (e.g. ephedra, ma haung, bitter orange, omega 3 fatty acids).

Table 2: Cockcroft and Gault Formula*

$\text{GFR ml/min} = \frac{(140 - \text{age in yrs}) \times \text{weight in kg}}{(72 \times \text{serum creatinine mg/dL}) \times 0.85 \text{ (if female)}}$		
Stage	Degree of Damage	GFR Level ml/min
1	Normal or High	>90
2	Mild	60-89
3	Moderate	30-59
4	Severe	15-29
5	Kidney Failure	<15

*Formula correction from previous newsletter

TREATMENT

An innovative method to assess management of HTN is ambulatory blood pressure monitoring, which provides information about blood pressure during daily activities and sleep. Recent studies have confirmed that cardiovascular outcomes in treated patients with hypertension are better predicted with this method, than by office blood pressure readings. Specifically 24 hour systolic blood pressure higher than 135 mmHg increases the risk of cardiovascular events by a factor of two, compared to systolic blood pressure less than 135 mmHg. Recently, cohort studies demonstrated that persons whose office blood pressure is elevated, but whose mean 24-hour ambulatory blood pressure is below 130/80 mmHg (white coat HTN), are no more likely than hypertensive patients to have a cardiovascular event. Further research is needed to assess the value of ambulatory monitoring in reducing drug prescription for white coat HTN and to better assess management of HTN in reaching levels that will prevent complications.

REFERRAL

Patients with a glomerular filtration rate less than 60 ml/min, and/or with significant proteinuria should be referred to a nephrologist.

Additionally, five important risk factors have been linked to the progression of end stage renal disease (ESRD).

Nephrology referral is warranted when patients show the following risk factors:

- 1) Systolic HTN proved to be an independent risk factor for all-cause ESRD in the analysis of the Multiple Risk Factor Intervention Trial.
- 2) Proteinuria is recognized as an important risk factor for progression of both diabetic and non-diabetic renal disease.
- 3) Decreased glomerular filtration rate, since renal disease continues to progress despite adequate blood pressure control.
- 4) Dyslipidemia is associated with hypertensive renal disease and correlates with glomerulosclerosis.
- 5) Cigarette smoking contributes to a faster decline in renal function.

Refer severe resistant HTN or cases where clinical laboratory findings suggest adrenal HTN (due to abnormal mineralocorticoid secretion or pheochromocytoma), or renovascular HTN, to a nephrology specialist for further evaluation.

LIFESTYLE MODIFICATIONS

The primary goal is the reduction of blood pressure to a level less than 140/90 mmHg and to less than 130/80 mmHg in patients with diabetes and chronic kidney disease.

Current national guidelines recommend lifestyle modifications such as:

- 1) Smoking cessation

- 2) Normal body weight: Blood pressure will decrease 1.6/1.1 mmHg for each kilo of weight loss
 - 3) Physical exercise, at least 30 minutes per day for 4-5 days a week will reduce blood pressure about 11.4/5.5 mmHg after 8 weeks
 - 4) Reduced alcohol consumption to a maximum of thirty milliliters per day, (fifteen milliliters per day in women with low body weight)
 - 5) Reduced intake of sodium chloride (salt), although controversial, it appears to be safe for all patients and is particularly effective in elderly people. This helps to diminish blood pressure by 4.2/2 mmHg
 - 6) Finally, the Dietary Approaches to Stop Hypertension (DASH). The DASH trial, published in 1997, demonstrated a reduction in systolic and diastolic blood pressure of 5.5 mmHg and 3.0 mmHg respectively, in patients who followed a diet rich in fruits, vegetables, and low-fat dairy products, and with reduced saturated fat and total fat.
- 1) Levels of systolic blood pressure / diastolic blood pressure
 - 2) Men older than 55 years
 - 3) Women older than 65 years
 - 4) Smoking
 - 5) Dyslipidemia
 - 6) Family history of premature cardiovascular disease
 - 7) Abdominal obesity
 - 8) C-reactive protein > than 1 mg/dl.

Guidelines, as the ones recently published, generate controversy. The panorama gets even more complicated when some of the major trials even show conflicting results. However, they are necessary to understand how the majority of the patients respond to treatment, and to determine which drugs are more effective in certain conditions.

Primary care physicians, then, must execute a global assessment of his/her patients and select a drug that is customized for each individual, as described in Table 3. Patients need to be educated about their risk factors to develop a stroke, myocardial infarction and/or chronic kidney disease.

Patients should be encouraged to take advantage of the great benefit of lifestyle modifications in the control of their blood pressure, and learn how compliance with their medical regimen will help reduce their cardiovascular morbidity and mortality. These measures will help to improve outcomes.

DRUG THERAPY

A significant amount of research is currently being done to develop more effective medicines for HTN. In the meantime, diuretics or beta-blockers, remain appropriate for the initial treatment of uncomplicated hypertension, as the JNC VII report recommends. However, with associated comorbidities alternative drugs are preferred (Table 2). In particular, ACE inhibitors and angiotensin-receptor antagonists are the recommended initial therapy in patients with diabetes mellitus, chronic kidney disease, or congestive heart failure. ACE inhibitors are also useful in patients with coronary artery disease and with prior myocardial infarction.

The European Commission recommends evaluating eight risk factors to stratify potential cardiovascular morbidity, and to choose a drug that can improve the overall outcomes. These risk factors include:

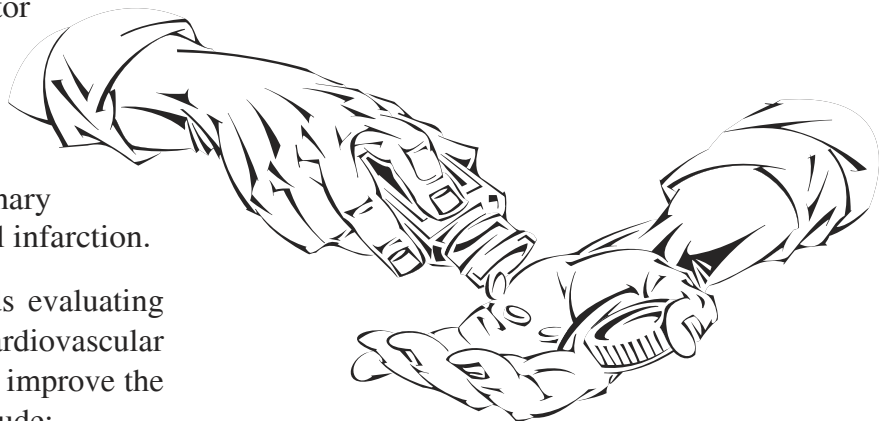


Table 3. Indications for the Use of Antihypertensive Drugs, Contraindications and Side Effects.

Class of Drug	Indications	Contraindications	Side Effects
Diuretics	Heart Failure Systolic HTN Advanced Age	Gout	Hypokalemia Hyperuricemia Glucose Intolerance Hypercalcemia Hyperlipidemia Hyponatremia Impotence
Beta blockers	Angina Heart Failure Previous Myocardial Infarction Migraine Tachyarrhythmias	Chronic Obstructive Pulmonary Disease Asthma Heart Block	Bronchospasm Bradycardia CHF PVD Hypertriglyceridemia Fatigue Insomnia
ACE Inhibitors	Heart Failure, Myocardial Infarction Congestive Heart Failure Nephropathy	Pregnancy Bilateral Renal Artery Stenosis Hyperkalemia	Cough Hyperkalemia Lack of taste Leukopenia
Calcium-channel Antagonists	Advanced Age Cyclosporine induced HTN Systolic HTN	Heart Block	Headache Flushing Gingival Hyperplasia Edema Short acting can produce angina
Alpha-blockers	BPH	Orthostatic Hypotension	Headache Drowsiness Postural hypotension
Angiotensin-receptor Antagonists	ACE-cough Nephropathy, Congestive Heart Failure	Pregnancy Bilateral Renal Artery Stenosis	Angioedema Hyperkalemia

CONCLUSIONS

Primary care physicians are well positioned to significantly improve outcomes affecting tens of millions of people with HTN. While the precise causes and potential severity of the condition will vary in each individual case, increasing the window of treatment and following the guidelines above in diagnostic and treatment procedures may allow to assist innumerable patients in improved quality of life and longevity. Refer to a nephrology specialist when the glomerular filtration rate is less than 60 ml/min, and/or the patient exhibits significant proteinuria.

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