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What's new in the treatment of hypertension

KEY POINTS:

Only 24% of hypertensive persons have their blood pressure under control.

Systolic blood pressure predicts risk more accurately than does diastolic blood pressure.

The current goal of lowering blood pressure to less than 140/90 mm Hg may not be aggressive enough; a prospective trial is underway to evaluate the effect of lower goal blood pressures.

It is important to identify and treat coexisting risk factors for atherosclerosis.

ABSTRACT: Twenty-five years after the establishment of the National High Blood Pressure Education Program, hypertension is still underdiagnosed and often inadequately treated. This article argues for more aggressive treatment and outlines a practical, office-based approach.

Despite impressive declines in coronary and stroke mortality in the United States over the last 20 years, evidence is emerging that hypertension is being undertreated. For example:

- Hospitalization rates for heart failure in older people have steadily increased over the last 20 years.[1]
- Cases of end-stage renal disease continue to increase, and hypertension is the second-leading cause, after diabetes.[2]
- A recent epidemiologic study from the Mayo Clinic found that the incidence of stroke, after declining for many years, has leveled off and may actually be increasing again.[3]
- In the most recent National Health and Nutrition Examination Survey (NHANES III),[4] only 24% of persons with hypertension had their blood pressures controlled to less than 140/90 mm Hg, and only 53% of hypertensive persons were receiving antihypertensive therapy. Thirty-five percent were unaware that they even had hypertension.

WHY HYPERTENSION IS UNDERTREATED

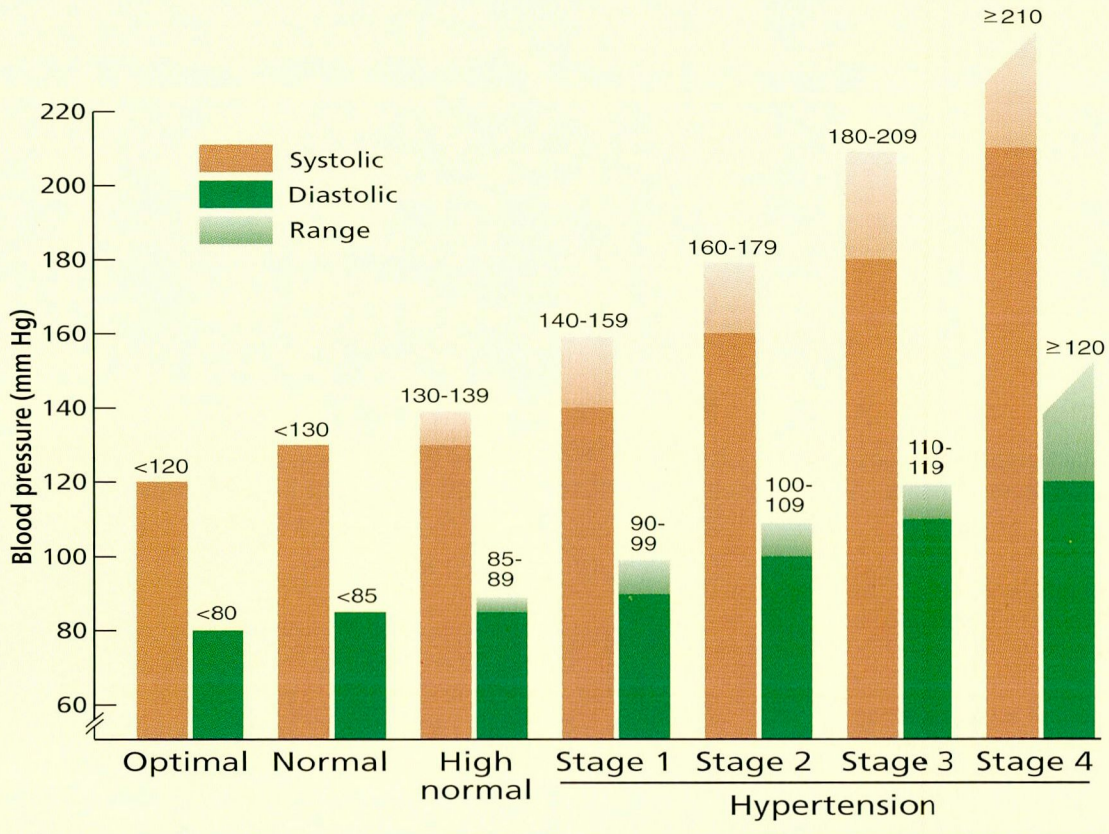
Besides indicating the need for greater detection efforts, these trends seem to indicate that patients are not being treated aggressively enough. In particular, I believe that physicians do not pay enough attention to the systolic blood pressure, and that the goal blood pressure is too high.

Systolic pressure is more important than diastolic pressure

Physicians have tended to base treatment decisions on diastolic pressure

FIGURE

A NEW CLASSIFICATION SYSTEM FOR HIGH BLOOD PRESSURE*



* Adapted from the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, reference 10

and ignore systolic pressure. Yet, systolic blood pressure more reliably predicts cardiovascular morbidity and mortality and all-cause mortality than does diastolic blood pressure.[5,6] The pulse pressure, which closely correlates with the systolic pressure, has also been implicated.[7]

For example, among the more than 300 000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) and followed for 6 years,[8] deaths from any cause increased with systolic blood pressure. Within every level of systolic blood pressure, the diastolic blood pressure did not affect the mortality rate at all. In the 12-year follow-up of the same group,[6] the highest rate of coronary mortality was in men who had systolic pressures higher than 160 mm Hg but diastolic pressures less than 70.

Why systolic hypertension is dangerous. High systolic pressures impose a greater burden on the heart than do high diastolic pressures, potentially leading to heart failure. Further, the "hammering" effect of the wide pulse pressure damages the arterial walls, contributes to atherosclerosis, and leads to target organ damage (see below).

140/90 is not low enough

Hypertension has been traditionally defined as beginning at 140/90 mm Hg. However, epidemiologic studies show that the optimal blood pressure is less than 120/80 mm Hg,[5,6] and I believe we should aim for this figure in treating hypertension.

Data from the Treatment of Mild Hypertension Study (TOMHS) support the

concept of "the lower the better."[9] All 902 participants in this study had "mild" hypertension—the average was 140/91 mm Hg. All underwent a vigorous program of nonpharmacologic therapy, reducing their weight, stopping smoking if they smoked, exercising regularly, and limiting their intake of sodium and alcohol. In addition, all were randomly assigned to receive either placebo or one of five antihypertensive medications: acebutolol, amlodipine, chlorthalidone, doxazosin, or enalapril.

As expected, lifestyle modifications lowered the blood pressure, to 132/82 mm Hg in the placebo group. Also as expected, medications lowered the blood pressure even more, to 124/79 mm Hg in the active-treatment groups.

Most physicians would consider a blood pressure of 132/82 mm Hg during therapy as acceptable. Yet, by 48 months, persons receiving active medications had experienced 31% fewer clinical events than the persons in the placebo group: 11.1% vs 16.2%, $P = .03$. The lower blood pressure made a difference.

A new classification system

To combat complacency about "mild" hypertension and to emphasize the importance of systolic blood pressure, the fifth Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V[10]) adopted a new classification system for blood pressure: (**FIGURE**)

- Optimal: 120/80 mm Hg or less.
- Normal: 130/85 or less.
- High normal: 130/85 to 139/89.
- Stage 1 (formerly "mild") hypertension: 140/90 to 159/99.
- Stage 2: 160/100 to 179/109.
- Stage 3: 180/110 to 209/119.
- Stage 4: 210/120 or greater.

When systolic and diastolic pressures fall into different categories, the higher category should be used.

Of note, 70% of persons with hypertension have stage 1 hypertension, and although their risk is not as great as for patients with more severe hypertension, so many more patients are at risk that the attributable risk is greatest in this group.

IF LOWER IS BETTER, WHAT ABOUT THE "J" CURVE?

The TOMHS results seem to run counter to those of numerous other reports that suggested that decreasing the diastolic blood pressure to less than 85 to 90 mm Hg may cause a paradoxical increase in coronary mortality, especially for patients who have evidence of ischemic heart disease before treatment is started.[11,12] This has been called the "J-" or "U-" shaped curve, because mortality increases as diastolic blood pressure decreases below 85 mm Hg or increases above 95 mm Hg.

Some groups have reported this phenomenon for systolic blood pressure (usually less than 140 mm Hg) as well as diastolic blood pressure, although most have confined their observations to the diastolic blood pressure. On the other hand, one study reported that the lower the systolic blood pressure during treatment, the lower the overall mortality rate (although there was a J-shaped relationship between systolic blood pressure and deaths from stroke, contrary to other studies).[13]

Some studies showed a J-curve in normotensive persons, and in hypertensive patients receiving placebo. Other studies did not show a J-curve at all. In a meta-analysis of observational studies, MacMahon et al[14] did not find evidence of an increase in mortality with diastolic blood pressure as low as 70 mm Hg. In the Systolic Hypertension in the Elderly Program (SHEP),[15] diastolic blood pressure was reduced to an average of 68 mm Hg in patients receiving active treatment, with no adverse effect.

In summary, the J-curve has been a retrospective observation in nonrandomized clinical trials, or randomized trials that were not designed to test this hypothesis. A prospective,

TABLE 1

CLUES THAT SUGGEST CURABLE CAUSES OF HYPERTENSION

Pheochromocytoma
Headache, palpitations, tachycardia, inappropriate perspiration, tremor, pallor (symptoms are usually, but not necessarily, paroxysmal)
Unusually labile blood pressure
Recent weight loss
Recent onset or discovery of diabetes
Malignant hypertension
Pressor response to antipressor drugs or during induction of anesthesia
Refractory hypertension

Renovascular hypertension
Age < 30 or > 60 years
Diastolic pressure ≥ 120 mm Hg
Recent onset or exacerbation of hypertension (< 2 years)
Malignant hypertension
Systolic-diastolic bruit in epigastrium or upper quadrants of abdomen
Refractory hypertension
Acquired resistance to antihypertensive therapy, especially in elderly patients

Primary aldosteronism
Unprovoked hypokalemia with inappropriate kaliuresis (24-hour urinary potassium ≥ 40 mEq and serum potassium ≤ 3.5 mEq/L)
Refractory hypertension

Cushing's syndrome
Characteristic body habitus with skin changes, especially of recent onset

Coarctation of the aorta
Absent, delayed or diminished arterial pulsations in lower extremities, especially in patients age < 30 years

TABLE 2

MANIFESTATIONS OF TARGET-ORGAN DISEASE

Cardiac
Coronary artery disease (eg, angina, myocardial infarction)
Left ventricular hypertrophy or "strain" by electrocardiography or left ventricular hypertrophy by echocardiography
Left ventricular dysfunction or cardiac failure

Cerebrovascular
Transient ischemic attack or stroke

Peripheral vascular
Absence of one or more major pulses in the extremities (except for dorsalis pedis) with or without intermittent claudication
Aneurysm

Renal
Serum creatinine ≥ 130 µmol/L (1.5 mg/dL)
Proteinuria (1+ or greater)
Microalbuminuria

Retinopathy
Hemorrhages or exudates, with or without papilledema

Source: Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, reference 10

controlled, randomized trial now underway should settle the issue.[16]

EVALUATING HIGH BLOOD PRESSURE

Except when hypertension is severe and life-threatening, evaluation should precede initiation of treatment.[10,17]

Purpose of evaluation

The pretreatment evaluation should answer four primary questions:

Does the patient have primary or secondary (possibly reversible) hypertension? Probably fewer than 5% of the 50 million hypertensive patients in the United States have a curable cause such as renovascular disease, pheochromocytoma, primary aldosteronism, or coarctation of the aorta. The younger or older the patient at the onset, and the more severe the hypertension, the more likely renovascular disease is the cause of the hypertension.

Indications for specialized diagnostic procedures to rule out curable hypertension are onset of hypertension before age 30 or after age 60, diastolic blood pressure greater than 120 mm Hg, abrupt onset of hypertension, resistant hypertension, or hypertensive retinopathy (Group III or IV by the criteria of Keith, Wagener, and Barker[18]).

TABLE 1 lists clues suggesting specific curable causes of hypertension.

Is target organ disease present? Target organ disease (**TABLE 2**) and other risk factors, such as family history of premature cardiovascular disease, dyslipidemia, diabetes mellitus, cigarette smoking, and sedentary lifestyle, put patients at greater risk of cardiovascular disease and death.

Are other cardiovascular risk factors present? Concomitant risk factors should be managed aggressively, along with the hypertension.

Is hypertension sustained? One should obtain repeated determinations of blood pressure for patients with borderline or labile hypertension before deciding whether to proceed with further evaluation. In general, patients who consistently have systolic blood pressure 140 mm Hg or greater or diastolic blood pressure 90 mm Hg or greater should undergo further evaluation.

History

The most important component of the pretreatment evaluation is a complete history and physical examination. The history should ascertain:

- Any family history of hypertension, premature cardiovascular disease, diabetes, or dyslipidemia.
- The duration of hypertension.
- Any symptoms of cardiovascular, cerebrovascular, or renal disease, or symptoms suggesting secondary hypertension.
- All prescribed and over-the-counter medications taken, especially nonsteroidal anti-inflammatory drugs and oral contraceptives.
- Any history of alcohol abuse.

Physical examination

In the initial physical examination, the clinician should:

- Measure the blood pressure at least twice (2 minutes apart) with the patient either supine or seated, and after standing for at least 2 minutes.
- Verify the blood pressure in the contralateral arm (if a significant and consistent difference is found, the higher value should be used).
- Examine the optic fundi, heart, and abdomen.

- Palpate the renal areas for masses.
- Auscultate for bruits in the neck and abdomen.
- Palpate the peripheral pulses.

Laboratory studies

The basic laboratory investigation should include:

- A complete blood count.
- A urinalysis.
- Determinations of serum creatinine, potassium, uric acid, calcium, fasting glucose, total and HDL cholesterol, and fasting triglycerides.
- An electrocardiogram (for most patients older than 30 years) to evaluate the heart as a target organ.

Ambulatory blood pressure monitoring, echocardiography, and measurement of plasma renin activity are not recommended for most patients.

TREATING HIGH BLOOD PRESSURE

Lifestyle modifications

For patients with stage 1 hypertension and no cardiovascular complications, the first therapeutic approach is to:

Restrict dietary sodium to 2 g of sodium (5 g NaCl) daily.

Reduce weight, if appropriate.

Limit alcohol intake to no more than 1 oz of ethyl alcohol daily.

Prescribe aerobic exercise, such as brisk walking for 30 to 45 minutes, three to five times per week.

Even patients with more severe hypertension should undertake lifestyle modifications to try to minimize the doses of antihypertensive agents required.

Pharmacologic therapy: when to start?

Hypertension of stage 2 or higher. There is general agreement that drug therapy is indicated initially, in addition to lifestyle modification, when the diastolic blood pressure is consistently above 100 mm Hg or the systolic blood pressure is consistently above 160 mm Hg (**TABLE 3**).

Stage 1 hypertension. Most physicians would prescribe drug therapy for patients with diastolic blood pressures of 95 to 100 mm Hg if lifestyle modifications fail to bring the diastolic blood pressure below 90 mm Hg within 3 to 6 months.

There is still controversy about whether drug therapy is indicated for patients with diastolic blood pressures 90 to 95 mm Hg or systolic blood pressures 140 to 150 mm Hg, in the absence of target organ disease or other major risk factors when lifestyle modifications fail.

TABLE 3

WHEN IS DRUG TREATMENT FOR HYPERTENSION INDICATED?

Classification	Target organ damage		Other major risk factors	
	Present	Absent	Present	Absent
High normal	No	No	No	No
Stage 1	Yes*	?	Yes*	?
Stages 2–4	Yes	Yes	Yes	Yes

*After trial of lifestyle modifications for 6 months has failed

I am inclined to give such patients drug therapy, for two reasons: to prevent target organ damage and to prevent hypertension from progressing to higher stages. A 35-year-old woman with stage 1 hypertension has only a minuscule risk of having a heart attack within the next 10 years, but what about 30 years from now? Untreated, the hypertension could silently damage her heart or kidneys and eventually cause heart failure or renal failure. Further, hypertension begets more hypertension. In an analysis of 12 studies that included 26 731 patients in all, Moser and Hebert[19] found that hypertension progressed to higher levels or caused left ventricular hypertrophy or congestive heart failure in 11.2% of patients who received placebo, compared with only 0.7% of patients who received active treatment.

A 35-year old woman with hypertension has a miniscule risk of having a heart attack in 10 years, but what about 30 years?

Most authorities agree that drug therapy is indicated even for patients with diastolic blood pressures of 90 to 95 mm Hg or systolic blood pressures 140 to 150 mm Hg if target organ disease is present or there are other major risk factors, or if the patient has an ominous family history of premature death or disability from cardiovascular disease.

What drug to use?

Diuretics, beta blockers preferred. In the JNC-V report,[10] we pointed out that only the diuretics and beta blockers have been shown in large randomized prospective trials to reduce cardiovascular disease and death,[20-23] and suggested that therefore these drugs be preferred as first-line agents, unless there are contraindications to them or special indications for using

TABLE 4

COEXISTING CONDITIONS FOR WHICH ANTIHYPERTENSIVE AGENTS HAVE BENEFICIAL EFFECTS (THE "TWO-FOR-ONE" CONCEPT)

Migraine headache
Beta blockers without intrinsic sympathomimetic activity (non-ISA beta blockers)
Verapamil
Diltiazem (possibly)

Angina pectoris
Non-ISA beta blockers
Long-acting calcium antagonists

Symptomatic benign prostatic hyperplasia
Alpha$_1$ blockers

Atrial fibrillation (to control ventricular rate)
Non-ISA beta blockers
Verapamil
Diltiazem

Paroxysmal supraventricular tachycardia, sinus tachycardia
Verapamil
Diltiazem
Non-ISA beta blockers

Irritable bowel with diarrhea
Verapamil

Recurrent renal calculi (calcium)
Thiazide diuretics

Senile tremor
Beta blockers

Cardiac awareness
Beta blockers

Glaucoma
Beta blockers

alternative drugs (ie, angiotensin-converting enzyme inhibitors, calcium antagonists, alpha$_1$ blockers, or alpha-beta blockers).

Although we believed we were advocating evidence-based medicine, we were roundly criticized for this recommendation.[24,25]

In defense of diuretics. There are concerns regarding the safety and long-term toxicity of diuretics and beta blockers. Although diuretics reduce cardiovascular risk by reducing blood pressure, they also may tend to increase cardiovascular risk by increasing the blood levels of lipids, glucose, and uric acid and decrease the potassium level. Thus, one may be substituting one risk factor for others.

Some suggest that some trials that used diuretics did not achieve the "expected" reduction in coronary events, but did show a decrease in the incidence of stroke, congestive heart failure, and dissecting aneurysms. Yet, several recent controlled trials in elderly patients did show impressive reductions in coronary events.[20,21]

Two reasons may explain the more-convincing effect of diuretics in decreasing coronary events in the recent trials compared to earlier ones. First, lower doses were used in the recent trials (12.5 to 25 mg of chlorthalidone or hydrochlorothiazide), thereby minimizing metabolic side effects. In addition, elderly patients are at greater risk for coronary events than are younger patients. Consequently, a randomized trial limited to 3 to 5 years of observation is more likely to reach a statistically significant conclusion in elderly patients than in younger ones, because they will suffer more events. To reach a statistically significant conclusion in a trial of young and middle-aged patients would require a longer trial or more participants, or both.[26]

"Expected" reductions in coronary events were calculated from long-term observational studies that extended for 10 to 30 years, whereas the randomized clinical trials were concluded after 5 years at the most.[27] Consequently, the surprising conclusion of the earlier clinical trials was that the reduction in strokes met expectations, not that the reduction in coronary events failed to do so.

Compelling indications for certain antihypertensive drugs. Angiotensin-converting enzyme (ACE) inhibitors, in randomized, placebo-controlled trials, improved the prognosis for patients with severe left ventricular dysfunction (ejection fraction < 40%) with or without congestive heart failure,[28-30] and slowed the rate of deterioration of renal function in patients with nephropathy caused by type I diabetes mellitus.[31] It is not clear whether this benefit also pertains to patients with nephropathy from type II diabetes mellitus.

Beta blockers without intrinsic sympathomimetic activity (atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, timolol) are indicated after a myocardial infarction because of their long-term cardioprotective effect.[32]

Drugs with two-for-one action. Some antihypertensive agents have beneficial effects on coexisting conditions or complaints, such as alpha$_1$ blockers for both symptomatic benign prostatic hyperplasia and hypertension or beta blockers for migraine headaches and hypertension (**TABLE 4**).[33] This is the "two-for-one" concept, in which two conditions are treated with one drug.

Avoid short-acting calcium antagonists. A case-control study by Psaty et al,[34] a meta-analysis by Furberg et al,[35] and a nonrandomized cohort study by Pahor et al[36-38] have raised enough concerns about the safety of short-acting calcium antagonists, especially nifedipine, to prompt the Food and Drug Administration (FDA) to issue a warning concerning the use of short-acting nifedipine. In fact, short-acting forms of nifedipine and diltiazem have never been approved by the FDA for treating hypertension. In general, it is best to avoid short-acting calcium antagonists of any class for treating either hypertension or angina. Particularly, the use of 10-mg capsules of nifedipine, either orally or sublingually, to control severe hypertension should be discouraged.[39]

Centrally-acting sympathetic inhibitors (methyldopa, clonidine, guanfacine, guanabenz) are not ideal step 1 drugs because they have many side effects and, except for guanfacine and the clonidine patch, must be given at least twice daily.

The new angiotensin-II receptor blockers (eg, losartan) should, in theory, be effective for the same group of patients whose hypertension has responded to ACE inhibitors. The chief advantage of the angiotensin-II receptor antagonists is that they are much less likely than ACE inhibitors to produce cough or angioedema, possibly because they do not interfere with the degradation of bradykinin as the ACE inhibitors do. However, for the same reason, they may in theory be less effective in controlling hypertension. They seem to be relatively free of side effects.[40]

Starting with two drugs. If the diastolic blood pressure is greater than 115 mm Hg initially or the systolic blood pressure is greater than 200 mm Hg, a single agent is unlikely to control the blood pressure satisfactorily. Under these circumstances it is reasonable to start therapy with two antihypertensive agents at the same time, usually a diuretic and a beta blocker, calcium antagonist, or ACE inhibitor.

Refractory hypertension

If hypertension does not respond to a rational triple drug regimen that includes a diuretic, the physician should suspect nonadherence to the regimen as the most likely cause.[41] Nonadherence may be manifested by failure to take drugs as prescribed or by consuming too much sodium or both.

Drug interactions should also be suspected. Leading the list of drugs that can interfere with an otherwise effective regimen are nonsteroidal anti-inflammatory drugs and oral contraceptives. Pseudohypertension and "white-coat" hypertension should be ruled out. Finally, the physician should reconsider the possibility that a secondary form of hypertension has been overlooked, such as pheochromocytoma, renovascular hypertension, or primary aldosteronism.

When it is apparent that the hypertension is truly resistant, changes in the regimen can be made empirically. Doses of all of the drugs in the regimen should be maximized. Consideration should be given to adding a fourth drug with a different mechanism of action. Minoxidil is one of the most potent agents available.

Sometimes it is necessary to evaluate the mechanism of the hypertension during treatment to see which drug or drugs are failing. This evaluation would include measurements of plasma renin activity, catecholamines, aldosterone, plasma volume, cardiac output, and total peripheral resistance. ■

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