Hypertension Guidelines: Revisiting the JNC 7 Recommendations

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Recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure are reviewed in this comprehensive article.

ABSTRACT

An estimated 73 million people in the United States live with hypertension. As many as 55,000 deaths are directly attributed to hypertension each year, and it is considered an underlying or contributing factor in at least another 300,000. In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) issued its seventh report, which provided guidelines for the diagnosis and management of this disease. Included in the guidelines were: a new classification system for hypertension; recommendations for lifestyle modifications; and recommendations for pharmacologic therapy. New JNC guidelines are expected in 2009, but until then, and to understand the forthcoming changes in recommendations, it is important to revisit and review those of JNC 7.

INTRODUCTION

As many as 1 billion people worldwide suffer from hypertension. In the United States, nearly 1 in 3 adults (approximately 73 million people) have some degree of high blood pressure. Hypertension is a contributing factor to many other diseases including myocardial infarction (MI), stroke, heart failure, renal failure, and retinopathy, and is a leading cause of death. In 2004, an estimated 55,000 deaths were directly attributed to hypertension, and it was considered an underlying or contributing factor in at least another 300,000.[1]

Awareness, treatment, and control of hypertension are suboptimal. Only two-thirds of patients with hypertension are aware of their status, which means that a large segment of the population has hypertension that is unrecognized and untreated. Even in patients with known hypertension, some are not treated for various reasons, including physician and patient under-recognition of the importance of treatment. Even with treatment, control of blood pressure can be difficult, with only one-third of treated hypertensives having a systolic blood pressure [SBP] that is less than 140 mm Hg.[1,2]

In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) issued its seventh report[2] with guidelines for treatment. These introduced important changes in the categorization and definition of hypertension, and recommended multiple lifestyle-based and pharmacologic strategies for treatment. New guidelines are expected in 2009, and to understand forthcoming recommendations and changes, it is important to revisit and review those of JNC 7.

DEFINITIONS OF HYPERTENSION

In the JNC 7 guidelines, the 7 categories of blood pressure defined in JNC 6 were simplified and reduced to 4 categories (Tables 1 and 2):

- Normal blood pressure: SBP <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg
- Prehypertension: These are patients on the cusp of developing hypertension. It is defined as a SBP of 120-139 mm Hg or a DBP of 80-89 mm Hg
- Stage I hypertension: SBP 140-159 mm Hg or DBP 90-99 mm Hg
- Stage II hypertension: SBP ≥160 mm Hg or DBP ≥100 mm Hg

TABLE 1. CHANGES IN BLOOD PRESSURE CLASSIFICATION.

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	< 120/80	Normal
Normal	120–129/80–84	Prehypertension
Borderline	130–139/85–89	
Hypertension	≥ 140/90	Hypertension
Stage 1	140–159/90–99	Stage 1
Stage 2	160–179/100–109	Stage 2
Stage 3	≥ 180/110	

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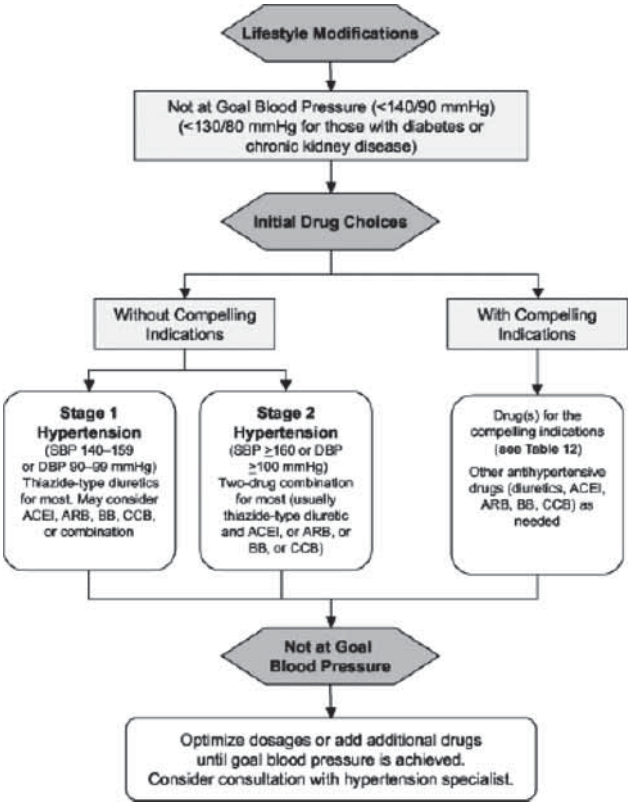
Follow-up and treatment strategies are based on the extent of blood pressure elevation. (Table 2 and Figure 1) In the prehypertensive stage, lifestyle modifications alone are recommended, whereas in Stage I hypertension lifestyle modifications combined with single-drug therapy (usually a thiazide-type diuretic) is recommended. In Stage II hypertension, lifestyle modifications are recommended, but initial therapy is aggressive, and typically includes a thiazide-type diuretic in combination with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or a beta-blocker.

Figure 1: Algorithm for treatment of hypertension.



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LIFESTYLE MODIFICATIONS

Lifestyle modifications can help prevent or delay the onset of hypertension and reduce blood pressure in already hypertensive patients. The JNC 7 recommendations are fairly universal to good health practices—maintain a normal body weight, do not smoke, exercise, etc. In addition to preventing or reducing high blood pressure, these modifications reduce the risk of other cardiovascular diseases.

Weight Reduction

Maintaining a normal body mass index (18.5-24.9 kg/m^2) helps control blood pressure. In fact, SBP can be reduced between 5-10 mm Hg for every 10 kg of body weight that is lost.

Diet

The Dietary Approaches to Stop Hypertension (DASH) diet is a plan that emphasizes eating fruits, vegetables, and low-fat dairy products, while discouraging the consumption of saturated and total fats. The diet is endorsed by the National Heart, Lung, and Blood Institute and the American Heart Association, and forms the basis for the United States Department of Agriculture's newest food pyramid. It is associated with reductions in SBP ranging from 8-14 mm Hg, and can help reduce and control weight and sodium intake. (More information is available at www.dashdiet.org.)

TABLE 2. CLASSIFICATION OF BLOOD PRESSURE IN ADULTS AND RECOMMENDED FOLLOW-UP.

BP classification*	SBP mm Hg	DBP mm Hg	Follow-up recommended†
Normal	<120	and <80	Recheck in 2 years
Prehypertension	120-139	or 80-89	Recheck in 1 year‡
Stage 1 hypertension	140-159	or 90-99	Confirm within 2 months‡
Stage 2 hypertension	≥160	or ≥100	Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g. >180/110 mm Hg), evaluate and treat immediately or within 1 week depending on clinical situation and complications

*If systolic and diastolic categories are different, follow recommendations for shorter time follow-up (e.g. 160/86 mm Hg should be evaluated or referred to source of care within 1 month).
†Modify the scheduling of follow-up according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.
‡Provide advice about lifestyle modifications.
Adapted from: Chobanian AV, et al. Hypertension. 2003;42:1206-1252.

Dietary Sodium Intake

The average American consumes 4000-6000 mg of sodium per day. I recommend that patients limit sodium intake to 2000 mg per day, which can reduce SBP by 5-10 mm Hg. This is a challenging endeavor: although most patients are compliant in avoiding and restricting table salt, few make the effort to read food labels and track intake. It is important to emphasize to patients that many medications, including ACE inhibitors and ARBs, are not as effective when sodium intake remains high.

Physical Activity

Fewer than 20% of Americans exercise regularly. However, regular aerobic activity—at least 30 minutes per day, most days of the week—can produce reductions in SBP of up to 9 mm Hg.

Alcohol Consumption

The JNC 7 define 2 drinks as 24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey. Consumption of 1-2 drinks per day may decrease SBP; however, more than 2 drinks per day increases blood pressure. The guidelines recommend that men limit alcohol consumption to 2 drinks per day, and women and lightweight people limit intake to 1 drink per day.

PHARMACOLOGIC TREATMENT

When lifestyle modifications fail to prevent or correct hypertension, pharmacologic therapy with 1 or more drugs is warranted. As many as two-thirds of patients with hypertension will not achieve optimal blood pressure levels with diuretic monotherapy and, as seen in multiple clinical trials, most patients require 2 to 4 agents. Discussing this fact with patients may help address the frequent complaint: "do I really need all those medications?"

Unless compelling indications favor one drug over another because of individual patient risk factors, history, or co-morbidities, JNC 7 recommends thiazide-type diuretics as the initial agent. Of course, the choice of initial and subsequent agents is based on the discretion of physicians. Issues such as cost, formulary, and complexity of regimen must be kept in mind. A simple rule to maximize the likelihood that patients will adhere to the treatment regimen is to try to use once-a-day formulations, generic drugs, and combination agents. If branded products are required, try to limit co-payments by adhering to formularies. If regimens are too complex or too expensive they surely will not be followed for an asymptomatic disease such as hypertension.

Diuretic Therapy

The rationale for thiazide-type diuretics as the preferred first-line treatment for uncomplicated hypertension[2] is based on randomized trials such as ALLHAT.[3] In this trial of 33,357 patients, the thiazide-type diuretic chlorthalidone was compared with the calcium channel blocker (CCB) amlodipine and the angiotensin converting enzyme (ACE) inhibitor lisinopril. (A fourth arm using doxazosin was stopped early because of efficacy concerns.) Over a mean follow-up period of 5 years, there was no difference in the incidence of fatal coronary heart disease (CHD) or non-fatal MI among the 3 treatments.

The major flaw of this study was the choice of chlorthalidone rather than hydrochlorothiazide (HCTZ). Although chlorthalidone produces superior blood pressure control to HCTZ, and is the true evidence-based choice, HCTZ, because of its familiarity and inclusion in most combination products, is the more widely prescribed agent in America. This suggests that the results of ALLHAT are not completely generalizable to the everyday practice of medicine. Side effects of thiazide diuretics include hypokalemia, hyperuricemia, hypercalcemia, impaired glucose tolerance, and erectile dysfunction (ranking second to beta-blockers).

Loop diuretics are also useful in the treatment of hypertension, particularly for patients with impaired renal function (glomerular filtration rate [GFR] <30-50 mL/min/m2), congestive heart failure, and resistant hypertension. The loop diuretic torsemide may be the preferable agent for hypertension because its long half-life allows once daily administration in most patients. Side effects also include hypokalemia and hyperuricemia.

Potassium Sparing Diuretics/Aldosterone Receptor Blockers

Potassium sparing diuretics have been available for many years and recently the aldosterone blockers (spironolactone and eplerenone) have gained much attention. While all agents in this class preserve potassium at the distal renal tubule, the sodium channel blockers (amiloride and triamterene) and aldosterone blockers work via different mechanisms. The former block sodium channels directly, whereas the latter bind to the aldosterone receptor in the distal tubule to prevent aldosterone activation of the distal sodium channel. Spironolactone and eplerenone also block aldosterone activity in the heart, kidney, and blood vessels, which may explain the improved outcomes in post-MI patients, and patients with heart failure.[4,5] Major limitations of these agents include hyperkalemia and – for spironolactone - progesterone-related effects

such as gynecomastia. Although eplerenone avoids gynecomastia, it exacts a very high price (usually >$100/month) for doing so.

ACE Inhibitors & ARBs

ACE inhibitors and ARBs, via different mechanisms, interfere with the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors block the conversion of the peptide angiotensin I to angiotensin II (a potent vasoconstrictor), whereas ARBs directly occupy angiotensin II subtype 1 receptors. Many agents in both classes are available (Table 3).

These classes of drugs are considered safe and equally effective, but ARBs, because of their more direct mechanism of action, may be associated with fewer side effects.[2,6] ACE inhibitors typically can cause angioedema, cough (up to 15% of patients), acute renal failure, hyperkalemia, anemia, cholestasis, and neutropenia. ARBs can also cause angioedema (although the incidence is approximately 1/100th that of ACE inhibitors), hyperkalemia, and acute renal failure. Both classes are contraindicated during pregnancy.

Multiple clinical trials have demonstrated the efficacy of ACE inhibitors in hypertensive patients, and there are compelling indications for their use post MI, and in patients with heart failure, diabetes, chronic kidney disease, and stroke. (Table 4) For example, in the HOPE trial, 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor (e.g., hypertension, smoking, hypercholesterolemia) were randomized to 10 mg daily of the ACE inhibitor ramipril or placebo.[7] The ACE inhibitor produced a relative 22% reduction in the composite endpoint of MI, stroke, or death from cardiovascular events (14% versus 17.8%, P<0.001). Other trials have demonstrated similar findings.[8]

Compelling indications for ARBs include heart failure, prior MI, diabetes, stroke and chronic kidney disease. (Table 4) In the recently completed large-scale ONTARGET trial (n=25,620), patients with vascular disease or high-risk diabetes were randomized to ramipril, the ARB telmisartan, or a combination of the two, and were followed for a median of 56 months for the composite endpoint of cardiovascular death, MI, stroke, or hospitalization for heart failure.[6] No statistically significant difference in the primary endpoint was observed among the treatments, and the strategies were considered equivalent by the investigators (16.5% versus 16.7% versus 16.3%, respectively). This trial has helped settle the debate regarding the equivalence of ACE inhibitors and ARBs. The investigators also concluded that the combination of the two classes is not warranted in the treatment of uncomplicated hypertension.

Direct Renin Inhibitor

The direct renin inhibitor aliskiren (Tekturna®, Novartis pharmaceuticals) is the first in a new class of antihypertensive agents to become available in over 10 years. Unlike ACE inhibitors and ARBs, which interfere with the RAAS at various points, aliskiren directly inhibits renin, thereby suppressing the RAAS cascade at its start, and theoretically eliminating some of the downstream production of angiotensin II seen with other agents.

Early data indicates that aliskerin is at least as effective as ACE inhibitors and ARBs, and possibly slightly better.[9] Aliskerin's side effects include hyperkalemia, renal failure, and diarrhea. Clinical trials in cardiovascular and renal disease are forthcoming and should help clarify aliskerin's role in the treatment of hypertension.

Beta-blockers

In early versions of JNC, beta-blockers were considered first-line therapy, but in JNC 7 beta-blockers were considered either add-on therapy to thiazide-type diuretics, or as initial therapy in patients with compelling indications. (Table 4) Recent European hypertension guidelines have relegated beta-blockers to fourth-line agents, after diuretics, RAAS blockers, and CCBs in patients with uncomplicated hypertension.[10]

There are 3 main types of beta-blockers: the older beta-nonspecific agents; the beta-1-specific agents; and beta-blockers with additional properties. The older nonspecific agents (e.g. propanolol) were associated with more adverse events (Table 3) so that over the last 20 years the beta-1-specific agents, including atenolol, metoprolol, and bisoprolol, became mainstays for hypertension. Their limitations are their constitutional symptoms, with frequent complaints of fatigue and erectile dysfunction.

The newer beta-blockers have additional properties, including antioxidant (carvedilol) and anti-endothelin (nebivolol) effects. These agents tend to produce better central aortic blood pressure control than other beta-blockers, which may explain why these agents, and particularly carvedilol, produce better outcomes.Since they seem to produce better outcomes with better tolerability

TABLE 3. COMMON ANTIHYPERTENSIVE MEDICATIONS AND RECOMMENDED DOSAGES.

Class	Drug	Usual dose range, mg/day	Usual daily frequency*
Diuretics			
Loop diuretics	Bumetanide	0.5-2	2
	Furosemide	20-80	2
	Torsemide	5-40	1
Potassium-sparing diuretics	Amiloride	5-10	1-2
	Triamterene	50-100	1-2
Thiazide and thiazide-like diuretics	Chlorthalidone	12.5-25	1
	Hydrochlorothiazide	12.5-50	1
	Indapamide	1.25-2.5	1
	Metolazone	0.5-5	1
ACE Inhibitors	Benazepril	10-40	1
	Captopril	25-100	2-3
	Enalapril	5-40	1-2
	Fosinopril	10-40	1
	Lisinopril	10-40	1
	Moexipril	7.5-30	1
	Perindopril	4-8	1
	Quinapril	10-80	1-2
	Ramipril	2.5-20	1
	Trandolapril	1-4	1
ARBs	Candesartan	8-32	1
	Irbesartan	150-300	1
	Losartan	25-100	1-2
	Olmesartan	20-40	1
	Telmisartan	20-80	1
	Valsartan	80-320	1
Aldosterone receptor blockers	Eplerenone	50-100	1
	Spironolactone	25-50	1
Beta-blockers	Atenolol	25-100	1-2
	Bisoprolol	2.5-10	1
	Metoprolol	50-100	1-2
	Nadolol	40-120	1
	Propranolol	40-160	2
	Carvedilol	12.5-50	2
Calcium channel blockers			
Dihydropyridine	Amlodipine	2.5-10	1
	Felodipine	2.5-20	1
	Isradipine	2.5-10	2
	Nifedipine (sustained released)	30-60	1-2
Nondihydropyridine	Diltiazem (extended release)	180-420	1
	Verapamil (ER)	120-360	1
Alpha-blockers	Doxazosin	1-16	1
	Prazosin	2-20	2-3
	Terazosin	1-20	1
Direct vasodilators	Hydralazine	25-100	2-3
	Minoxidil	2.5-80	1-2

*In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect). BP should be measured just prior to dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the *Physician's Desk Reference*, 57th ed.

Adapted from Chobanian AV, et al. Hypertension. 2003;42:1206-1252.

TABLE 4. CLINICAL TRIAL AND GUIDELINE BASIS FOR COMPELLING INDICATIONS FOR INDIVIDUAL DRUG CLASSES.

	Recommended Drugs						
Compelling indication	Diuretic	Beta-blockers	ACE inhibitors	ARBs	CCB	Aldosterone blockers	Clinical trial supporting
Heart Failure	●	●	●	●		●	ACC/AHA Heart Failure Guidelines, COPERNICUS, SOLVD, ValHEFT, CHARM, RALES
Post-MI		●	●	●		●	ACC/AHA Post MI Guidelines, Capricorn, SAVE, VALIANT, EPHESUS
High Coronary Risk	●	●	●	●	●		ALLHAT, HOPE, LIFE, EUROPA, ONTARGET
Chronic Kidney Disease	●		●	●			NKF HTN Guidelines, REIN, ROAD, RENAAL
Stroke	●		●	●			ALLHAT, PROGRESS, MOSES, LIFE
Diabetes			●	●			IRMA-2, Micro-HOPE
Elderly	●				●		SHEP, Sys-EURO

ACE = angiotensin converting enzyme, ARBs = aldosterone receptor blockers, CCB = calcium channel blocker.
Adapted from Chobanian AV, et al. Hypertension. 2003;42:1206-1252.

than the older agents, they may restore an important role for beta-blockers in hypertension, particularly in patients with classic compelling indications such as heart failure, prior MI, angina, and in those with high sympathetic drives, as seen with sleep apnea and anxiety.

Calcium Channel Blockers

Two types of CCBs are available for the management of hypertension: dihydropyridines and nondihydropyridines. (Table 3) The dihydropyridines such as amlodipine and nifedipine produce excellent blood pressure control by directly relaxing the smooth muscles surrounding muscular arteries. The same mechanism underlies their most common side effect, peripheral edema, which results from arterial vasodilation but not venous dilation. To combat this effect, patients require a venodilator such as an ACE inhibitor or ARB, which are balanced vasodilators, or long-acting nitrates such as isosorbide mononitrate. The dihydropyridines are also sold in combination with ACE inhibitors and ARBs.

The nondihydropyridines include verapamil and diltiazem. Both reduce blood pressure by inducing vasodilation and by decreasing myocardial contractility. Both are useful in patients with concomitant arrhythmias such as supraventricular tachycardias including atrial fibrillation. These agents may cause bradycardia (especially when given with beta-blockers), constipation, and edema. Compelling indications for CCB include high CAD risk and older age (Table 4).

Alpha Blockers

Alpha blockers lower blood pressure by inhibiting the alpha receptors of arterial smooth muscle. Agents of this class include doxazosin, prazosin, and terazosin (Table 3). All are primarily used as add-on therapy in unresponsive patients and in men with benign prostatic hyperplasia, and can cause orthostatic hypotension.

Direct Vasodilators

Patients with refractory hypertension may be helped by direct vasodilators like hydralazine or minoxidil, which directly dilate the vascular smooth muscle. Minoxidil is considered the more potent, but has more adverse events including serositis, hirsutism, and edema.

CONCLUSION

Hypertension is a major public health problem associated with debilitating and potentially deadly cardiovascular events such as MI and stroke. JNC 7 was a great leap forward in the treatment of hypertension, incorporating

many twenty-first century clinical trials. As with all things in medicine, the more knowledge we gather about hypertension, the more precisely we can treat it. JNC 8 will incorporate the groundbreaking clinical trials of the last 5 years to create a document with even more compelling indications for earlier treatment, and with different agents. Recommendations will probably include management of patients with the metabolic syndrome, and those with high cardiovascular risk based on family history and other typical risk factors. It is likely that RAAS blockade will be recommended as the new first-line therapy for the treatment of hypertension especially in high risk patients.

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Dr. Martin has disclosed that he is on the Speaker's Bureau for Novartis Pharmaceuticals.

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