

Clinical Practice Guidelines for the Management of Hypertension in the Community A Statement by the American Society of Hypertension and the International Society of Hypertension

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STATEMENT OF PURPOSE

These guidelines have been written to provide a straightforward approach to managing hypertension in the community. We have intended that this brief curriculum and set of recommendations be useful not only for primary care physicians and medical students, but for all professionals who work as hands-on practitioners.

We are aware that there is a great variability in access to medical care among communities. Even in so-called wealthy countries, there are sizable communities in which economic, logistic, and geographic issues put constraints on medical care. And, at the same time, we have been reminded that even in countries with highly limited resources, medical leaders have assigned the highest priority to supporting their colleagues in confronting the growing toll of devastating strokes, cardiovascular events, and kidney failure caused by hypertension.

Our goal has been to give sufficient information to enable healthcare practitioners, wherever they are located, to provide professional care for people with hypertension. All the same, we recognize that it will often not be possible to carry out all of our suggestions for clinical evaluation, tests, and therapies. Indeed, there are situations in which the most simple and empirical care for hypertension – simply distributing whatever antihypertensive drugs might be available to people with high blood pressure – is better than doing nothing at all. We hope that we have allowed sufficient flexibility in this statement to enable responsible clinicians to devise workable plans for providing the best possible care of hypertension in their communities.

We have divided this brief document into the following sections:

1. General introduction
2. Epidemiology
3. Special issues with black patients (African ancestry)
4. How is hypertension defined?

5. How is hypertension classified?
6. Causes of hypertension
7. Making the diagnosis of hypertension
8. Evaluating the patient
9. Physical examination
10. Tests

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11. Goals of treating hypertension
12. Nonpharmacologic treatment of hypertension
13. Drug treatment of hypertension
14. Brief comments on drug classes
15. Treatment-resistant hypertension

1. INTRODUCTION

- About one-third of adults in most communities in the developed and developing world have hypertension.
- Hypertension is the most common chronic condition dealt with by primary care physicians and other health practitioners.
- Most patients with hypertension have other risk factors as well, including lipid abnormalities, glucose intolerance or diabetes, a family history of early cardiovascular events, obesity, and cigarette smoking.
- The success of treating hypertension has been limited, and despite well established approaches to diagnosis and treatment, in many communities fewer than half of all hypertensive patients have their blood pressures adequately controlled.

2. EPIDEMIOLOGY

- There is a close relationship between blood pressure levels and the risk of cardiovascular events, strokes, and kidney disease.
- The risk of these outcomes is lowest at a blood pressure of around 115/75 mmHg.
- Above 115/75 mmHg, for each increase of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP), the risk of major cardiovascular and stroke events doubles.
- The high prevalence of hypertension in the community is currently being driven by two phenomena: the increased age of our populations, and the growing prevalence of obesity, which is seen in developing as well as in developed countries. In many communities, a high dietary salt intake is also a major factor.
- The main risk of events is tied to an increased SBP; after age 50 or 60, DBP may actually start to decrease, but systolic pressure continues to rise throughout life. This increase in SBP and decrease in DBP with aging reflect the progressive stiffening of the arterial circulation. The reason for this effect of aging is not well understood, but high SBPs in older people represent a major risk factor for cardiovascular and stroke events and kidney disease progression.

3. SPECIAL ISSUES WITH BLACK PATIENTS (AFRICAN ANCESTRY)

- Hypertension is a particularly common finding in black people.
- Hypertension occurs at a younger age and is often more severe in terms of blood pressure levels in black patients than in whites.

- A higher proportion of black people are sensitive to the blood pressure-raising effects of salt in the diet than white patients, and this – together with obesity, especially among women – may be part of the explanation for why young black people tend to have earlier and more severe hypertension than other groups.
- Black patients with hypertension are particularly vulnerable to strokes and to hypertensive kidney disease. They are three to five times as likely as whites to have renal complications and end-stage kidney disease.
- There is a tendency for black patients to have differing blood pressure responses to the available antihypertensive drug classes: they usually respond well to treatment with calcium channel blockers (CCBs) and diuretics, but have smaller blood pressure reductions with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β -blockers. However, appropriate combination therapies provide powerful antihypertensive responses that are similar in black and white patients. Most patients will require more than one antihypertensive drug to maintain blood pressure control.

4. HOW IS HYPERTENSION DEFINED?

- Most major guidelines recommend that hypertension be diagnosed when a person's SBP is 140 mmHg or higher, or their DBP is 90 mmHg or higher, or both, on repeated examination. The SBP is particularly important and is the basis for diagnosis in most patients.
- These numbers apply to all adults older than 18, though for patients aged 80 or older, a SBP up to 150 mmHg is now regarded as acceptable.
- The goal of treating hypertension is to reduce blood pressure to levels below the numbers used for making the diagnosis.
- These definitions are based on the results of major clinical trials that have shown the benefits of treating people to these levels of blood pressure. Even though, as discussed earlier, a blood pressure of 115/75 is ideal, there is no evidence to justify treating hypertension down to such a low level.
- We do not have sufficient information about younger adults (between 18 and 55) to know whether they might benefit from defining hypertension at a level below 140/90 mmHg (e.g., 130/80 mmHg) and treating them more aggressively than older adults. Thus, guidelines tend to use 140/90 mmHg for all adults (up to 80 years old). Even so, at a practitioner's discretion, lower blood pressure targets may be considered in young adults, provided the therapy is well tolerated.
- Some recent guidelines have recommended diagnostic values of 130/80 mmHg for patients with diabetes or chronic kidney disease. However, the clinical benefits of this lower target have not been established and so these patients should be treated to below 140/90 mmHg.

5. HOW IS HYPERTENSION CLASSIFIED?

- For people with SBPs between 120 and 139 mmHg, or diastolic pressures between 80 and 89 mmHg, the term ‘prehypertension’ can be used. Patients with this condition should not be treated with blood pressure medications. However, they should be encouraged to make lifestyle changes in the hope of delaying or even preventing progression to hypertension.
- Stage 1 hypertension: patients with SBP 140–159 mmHg, or DBP 90–99 mmHg.
- Stage 2 hypertension: SBP 160 mmHg or higher, or DBP 100 mmHg or higher.

6. CAUSES OF HYPERTENSION

Primary hypertension:

- About 95% of adults with high blood pressure have primary hypertension (sometimes called essential hypertension).
- The cause of primary hypertension is not known, although genetic and environmental factors that affect blood pressure regulation are now being studied.
- Environmental factors include excess intake of salt, obesity, and perhaps sedentary lifestyle.
- Some genetically related factors could include inappropriately high activity of the renin–angiotensin–aldosterone system and the sympathetic nervous system and susceptibility to the effects of dietary salt on blood pressure.
- Another common cause of hypertension is due to stiffening of the aorta with increasing age. This causes hypertension referred to as isolated or predominant systolic hypertension characterized by high systolic pressures (often with normal diastolic pressures) that is found primarily in elderly people.

Secondary hypertension:

- This pertains to the relatively small number of patients, about 5%, of all hypertension, where the cause of the high blood pressure can be identified and sometimes treated.
- The main types of secondary hypertension are chronic kidney disease; renal artery stenosis; excessive aldosterone secretion; pheochromocytoma and sleep apnea.
- A simple screening approach for identifying secondary hypertension is given later.

7. MAKING THE DIAGNOSIS OF HYPERTENSION

- Blood pressure can be measured by either a conventional sphygmomanometer using a stethoscope or by an automated electronic device. The electronic device, if available, is preferred because it provides more reproducible results than the older method and is not influenced by variations in technique or by the

bias of the observers. If the auscultatory method is used, the first and fifth Korotkoff sounds (the appearance and disappearance of sounds) will correspond to the SBP and DBP.

- Arm cuffs are preferred. Cuffs that fit on the finger or wrist are often inaccurate and should, in general, not be used.
- It is important to ensure that the correct size of arm cuff is used [in particular, a wider cuff in patients with large arms (>32 cm circumference)].
- At the initial evaluation, blood pressure should be measured in both arms; if the readings are different, the arm with the higher reading should be used for measurements thereafter.
- The blood pressure should be taken after patients have emptied their bladders. Patients should be seated with their backs supported and with their legs resting on the ground and in the uncrossed position for 5 min.
- The patient’s arm being used for the measurement should be at the same level as the heart, with the arm resting comfortably on a table.
- It is preferable to take two readings, 1–2 min apart, and use the average of these measurements.
- It is useful to also obtain standing blood pressures (usually after 1 min and again after 3 min) to check for postural effects, particularly in older people.
- In general, the diagnosis of hypertension should be confirmed at an additional patient visit, usually 1–4 weeks after the first measurement. On both occasions, the SBP should be 140 mmHg or higher, or the diastolic pressure 90 mmHg or higher, or both, in order to make a diagnosis of hypertension.
- If the blood pressure is very high (for instance, a SBP of 180 mmHg or more), or if available resources are not adequate to permit a convenient second visit, the diagnosis and, if appropriate, treatment can be started after the first set of readings that demonstrate hypertension.
- For practitioners and their staffs not experienced in measuring blood pressures, it is necessary to receive appropriate training in performing this important technique.
- Some patients may have blood pressures that are high in the clinic or office, but are normal elsewhere. This is often called ‘white coat hypertension.’ If it is suspected, consider getting home blood pressure readings (see below) to check this possibility. Another approach is to use ambulatory blood pressure monitoring, if it is available. In this procedure, the patient wears an arm cuff connected to a device that automatically measures and records blood pressures at regular intervals, usually over a 24-h period.
- It can be helpful to measure blood pressures at home. If available, the electronic device is simpler to use and probably more reliable than the sphygmomanometer. The average of blood pressures measured over 5–7 days, if possible in duplicate at each measurement, can be a useful guide for diagnostic and treatment decisions.

8. EVALUATING THE PATIENT

- Often a high blood pressure is only one of several cardiovascular risk factors that require attention.
- Before starting treatment of hypertension, it is very useful to evaluate the patient more thoroughly. The three methods are personal history, physical examination, and selective testing.

History

- Ask carefully about previous cardiovascular events because they often suggest an increased probability of future events that can influence the choice of drugs for treating the hypertension and will also require more aggressive treatment of all cardiovascular risk factors. Also ask patients whether they have previously been told they have hypertension and, if relevant, their responses to any drugs they might have been given.

Important previous events include the following:

- Stroke or transient ischemic attacks or dementia
Why is this information important? For patients with these previous events, it may be necessary to include particular drug types in their treatment, for instance, ARBs or ACE inhibitors, CCBs, and diuretics, as well as drugs for low-density lipoprotein (LDL) cholesterol (statins), and antiplatelet drugs.
- Coronary artery disease, including myocardial infarctions, angina pectoris, and coronary revascularizations.
Why is this important? Certain medications would be preferred, for instance β -blockers, ACE inhibitors or ARBs, statins, and antiplatelet agents (aspirin).
- Heart failure or symptoms suggesting left ventricular dysfunction (shortness of breath, edema)
Why is this important? Certain medications would be preferred in such patients, including ARBs or ACE inhibitors, β -blockers, diuretics, and spironolactone. Also, certain medications should be avoided such as nondihydropyridine CCBs (verapamil, diltiazem) in patients with systolic heart failure.
- Chronic kidney disease
Why is this important? Certain medications would be preferred, including ACE inhibitors or ARBs (though these two drug classes should not be prescribed in combination with each other), statins, and diuretics [loop diuretics may be required if the estimated glomerular filtration rate (eGFR) is below 30] and blood pressure treatment targets might be lower (130/80 mmHg) if albuminuria is present. Note: In patients with more advanced kidney disease the use of some of these drugs often requires the expertise of a nephrologist.
- Peripheral artery disease
Why is this important? This finding suggests advanced arterial disease that may also exist in the coronary or brain circulations, even in the

absence of clinical history. It is vital that smoking be discontinued. In most cases antiplatelet drugs should be used.

VI. Diabetes

Why is this important? This condition is commonly associated with hypertension and is associated with an increased risk of cardiovascular events. Certain medications such as ARBs and ACE inhibitors should be used, particularly if there is evidence for albuminuria or chronic kidney disease. Good blood pressure control, often requiring the addition of CCBs and diuretics, is also important in these patients.

VII. Sleep apnea

Why is this important? Special treatments are often required for these patients and their use may make it possible to improve blood pressure control as well as the other findings of this condition.

- Ask about other risk factors

Why is this important? Risk factors can affect blood pressure targets and treatment selection for the hypertension. Thus, knowing about age, dyslipidemias, microalbuminuria, gout, or family histories of hypertension and diabetes can be valuable. Cigarette smoking is a risk factor that must be identified so that counseling can be given about stopping this dangerous habit.

- Ask about concurrent drugs

I. Commonly used drugs (for indications unrelated to treating hypertension) can increase blood pressure and, therefore, should be stopped if possible. These include NSAIDs used for arthritis and pain relief; some tricyclic and other types of antidepressants; older high-dose oral contraceptives; migraine medications; cold remedies (e.g., pseudoephedrine). In addition, some patients may be taking herbal medications, folk remedies, or drugs of addiction (e.g., cocaine), which can increase blood pressure.

9. PHYSICAL EXAMINATION

- At the first visit, it is important to do a complete physical examination because often getting care for hypertension is the only contact that people have with a medical practitioner.
- Measuring the blood pressure: this has been discussed earlier.
- Document the weight and height and calculate body mass index (BMI). This can be done by going online to Google, searching BMI and entering the patient's weight and height as instructed (<http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm>). Why is this important? This helps to set targets for weight loss and, as discussed later, knowing whether a patient is obese or not obese might affect the choice of hypertension treatment. It should be noted that the risk of cardiovascular events, including stroke, paradoxically may be higher in lean hypertensive people than in obese.
- Waist circumference. Why is this important? Independent of weight, this helps determine whether a

patient has the metabolic syndrome and is at risk of type 2 diabetes. Risk is high when this measurement is more than 102 cm in men, or more than 88 cm in women.

- Signs of heart failure. Why is this important? This diagnosis strongly influences the choice of hypertension therapy. Left ventricular hypertrophy can be suspected by chest palpation, and heart failure can be indicated by distended jugular veins, rales on chest examination, an enlarged liver and peripheral edema.
- Neurologic examination. Why is this important? This may reveal signs of previous stroke and affect treatment selection.
- Eyes: If possible, the optic fundi should be checked for hypertensive or diabetic changes and the areas around the eyes for findings such as xanthomas.
- Pulses: It is important to check peripheral pulses; if they are diminished or absent, this can indicate peripheral artery disease.

10. TESTS

- Blood sample

Note: This preferably should be a fasting sample so that a fasting blood glucose level and more accurate lipid profiles can be obtained.

 - I. Electrolytes

Why is this important? There is a special emphasis on potassium: high levels can suggest renal disease, particularly if creatinine is elevated. Low values can suggest aldosterone excess. In addition, illnesses associated with severe diarrhea are common in some communities and can cause hypokalemia and other electrolyte changes.
 - II. Fasting glucose concentration

Why is this important? If elevated, this could be indicative of impaired glucose tolerance, or if sufficiently high, of diabetes. If available, HbA1C should be measured to further assess an elevated glucose level and help in making a diagnosis.
 - III. Serum creatinine and blood urea nitrogen

Why are these important? Increased creatinine levels are usually indicative of kidney disease; creatinine is also used in formulae for eGFR. When appropriate, use formulae designed for eGFR calculations in patients of African ancestry.
 - IV. Lipids

Why are these important? Elevated LDL cholesterol or low values of high-density lipoprotein (HDL) cholesterol are associated with increased cardiovascular risk; high LDL cholesterol can usually be treated with available drugs, usually statins.
 - V. Hemoglobin/hematocrit

Why are these important? These measurements can identify issues beyond hypertension and cardiovascular disease, including sickle cell anemia in vulnerable populations and anemia associated with chronic kidney disease.
 - VI. Liver function tests

Why are these important? Certain blood pressure drugs can affect liver function, so it is useful to

have baseline values. Also, obese people can have fatty liver disorders that should be identified and considered in overall management.

- Urine sample
 - I. Albuminuria

Why is this important? If present, this can be indicative of kidney disease and is also associated with an increased risk of cardiovascular events. Ideally, an albumin/creatinine ratio should be obtained, but even dipstick evidence of albuminuria (+1 or greater) is helpful.
 - II. Red cells, white cells

Why are these important? Positive findings can be indicative of urinary tract infections, kidney stones or other potentially serious urinary tract conditions, including bladder tumors.
- Electrocardiogram

Why is this important? The ECG can help identify previous myocardial infarctions or left atrial and ventricular hypertrophy (which is evidence of target organ damage and indicative of the need for good control of blood pressure). An ECG might also identify cardiac arrhythmias such as atrial fibrillation (which would dictate the use of certain drugs) or such conditions as heart block (which would contraindicate certain drugs, e.g., β -blockers, rate-slowing CCBs). An echocardiogram, if available, can also be helpful in diagnosing left ventricular hypertrophy and quantifying the ejection fraction in patients with suspected heart failure, although this test is not routine in hypertensive patients.

11. OVERALL GOALS OF TREATMENT

- I. The goal of treatment is to manage hypertension and to deal with all the other identified risk factors for cardiovascular disease, including lipid disorders, glucose intolerance or diabetes, obesity, and smoking.
- II. For hypertension, the treatment goal for SBP usually is less than 140 mmHg and for DBP less than 90 mmHg. In the past, guidelines have recommended treatment values of less than 130/80 mmHg for patients with diabetes, chronic kidney disease, and coronary artery disease. However, evidence to support this lower target in patients with these conditions is lacking, so the goal of less than 140/90 mmHg should generally be used, although some experts still recommend less than 130/80 mmHg if albuminuria is present in patients with chronic kidney disease.
- III. Are there other exceptions to less than 140/90 mmHg? Most evidence linking the effects on cardiovascular or renal outcomes to treated blood pressures has been based on clinical trials in middle aged to elderly patients (typically between 55 and 80). Some recent trials suggest that in people aged 80 or more, achieving a SBP of less than 150 mmHg is associated with strong cardiovascular and stroke protection, and so a target of less than 150/90 mmHg is now recommended for patients in this age group.

We have almost no clinical trial evidence about blood pressure targets in patients younger than 50; DBP may be important in this age group, so achieving less than 90 mmHg should be a priority. In addition, it is also a reasonable expectation that targets lower than 140/90 mmHg (e.g., <130/80 mmHg) could be appropriate in young adults, and can be considered.

- IV. It is important to inform patients that the treatment of hypertension usually is expected to be a life-long commitment and that it can be dangerous for them to terminate their treatment with drugs or lifestyle changes without first consulting their practitioner.

12. NONPHARMACOLOGIC TREATMENT

Several lifestyle interventions have been shown to reduce blood pressure. Apart from contributing to the treatment of hypertension, these strategies are beneficial in managing most of the other cardiovascular risk factors. In patients with hypertension that is no more severe than stage 1 and is not associated with evidence for abnormal cardiovascular findings or other cardiovascular risks, 6–12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. However, it may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. Also, in practice, settings in which patients have logistical difficulties in making regular clinic visits, it might be most practical to start drug therapy early. In general, lifestyle changes should be regarded as a complement to drug therapy rather than an alternative.

- I. Weight loss: in patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. Substituting fresh fruits and vegetables for more traditional diets may have benefits beyond weight loss. Unfortunately, these diets can be relatively expensive and inconvenient for patients, and can work only if patients are provided with a strong support system. Even modest weight loss can be helpful.
- II. Salt reduction: high salt diets are common in many communities. Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are 'salt-sensitive', which may be a fairly common finding in black communities. Often patients are unaware that there is a large amount of salt in foods such as bread, canned goods, fast foods, pickles, soups, and processed meats. This intake can be difficult to change because salty foods are often part of the traditional diets found in many cultures. A related problem is that many people eat diets that are low in potassium, and they should be taught about available sources of dietary potassium.
- III. Exercise: regular aerobic exercise can help reduce blood pressure, but opportunities to follow a structured exercise regimen are often limited. Still, patients should be encouraged to walk, use bicycles,

climb stairs, and pursue means of integrating physical activity into their daily routines.

- IV. Alcohol consumption: up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day.
- V. Cigarette smoking: stopping smoking will not reduce blood pressure, but as smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Patients should be warned that stopping smoking may be associated with a modest increase in body weight.

13. DRUG TREATMENT OF HYPERTENSION

- I. Starting treatment: (see the algorithm in the Fig. 1). Treatment with drugs should be started in patients with blood pressures at least 140/90 mmHg in whom lifestyle treatments have not been effective. (Note: as discussed earlier in Section 12 on Nonpharmacologic treatment, drug treatment can be delayed for some months in patients with stage 1 hypertension who do not have evidence for abnormal cardiovascular findings or other risk factors. In settings in which healthcare resources are highly limited, clinicians can consider extending the nondrug observation period in uncomplicated stage 1 hypertensive patients, provided there is no evidence for an increase in blood pressure or the appearance of cardiovascular or renal findings). In patients with stage 2 hypertension (blood pressure \geq 160/100 mmHg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes. Drug treatment can also be started immediately in all hypertensive patients in whom, for logistical or other practical reasons, the practitioner believes it is necessary to achieve a more rapid control of blood pressure. The presence of other cardiovascular risk factors should also accelerate the start of hypertension treatment.
- II. For patients aged over 80, the suggested threshold for starting treatment is at levels of 150/90 mmHg or above. Thus, the target of treatment will be less than 140/90 mmHg for most patients, but less than 150/90 mmHg for the older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mmHg can be considered).
- III. The treatment regimen:
 - o Most patients will require more than one drug to achieve control of their blood pressure.
 - o In general, increase the dose of drugs, or add new drugs, at approximately 2–3-week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an

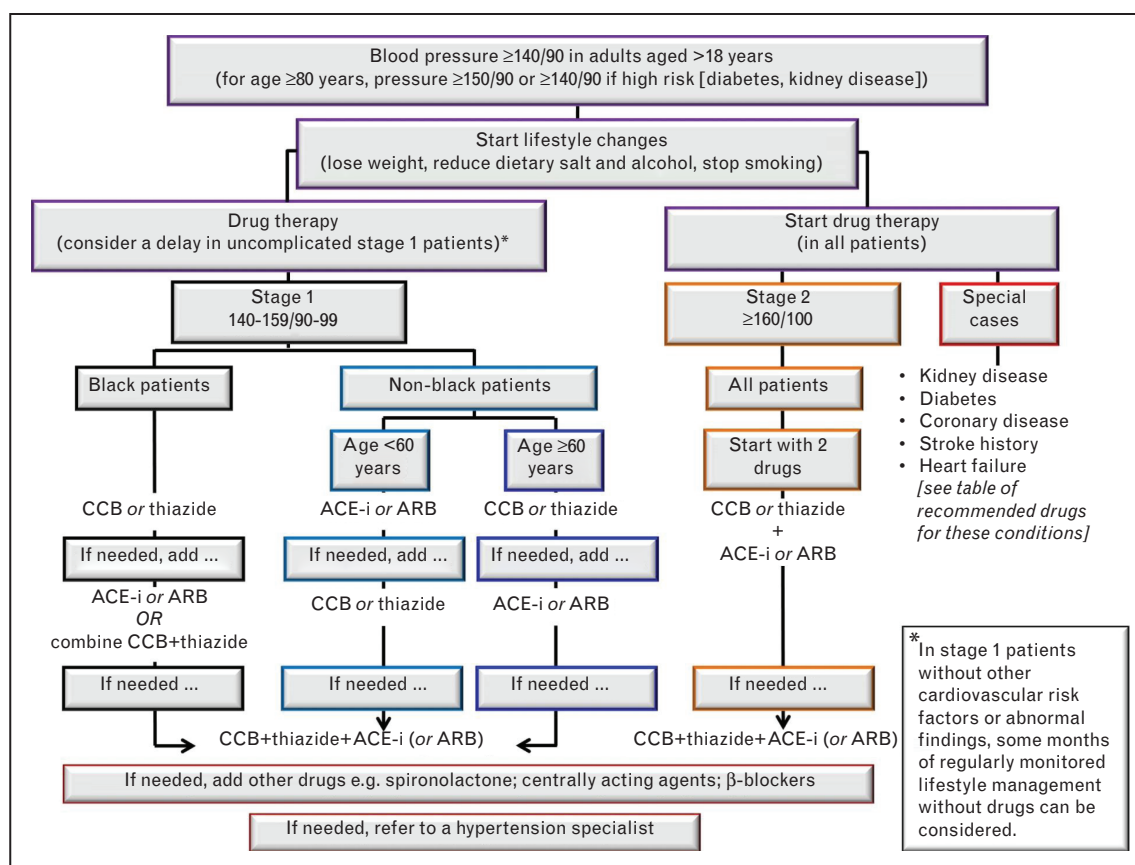


FIGURE 1 Algorithm summarizing the main recommendations of the guidelines. At any stage, it is entirely appropriate to seek help from a hypertension expert if treatment is proving difficult. In patients with stage 1 hypertension in whom there is no history of cardiovascular, stroke or renal events or evidence of abnormal findings, and who do not have diabetes or other major risk factors, drug therapy can be delayed for some months. In all other patients (including those with stage 2 hypertension), it is recommended that drug therapy be started when the diagnosis of hypertension is made. ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; thiazide, thiazide or thiazide-like diuretics. Blood pressure values are mmHg.

effective treatment regimen, whether one, two, or three drugs, within 6–8 weeks.

- If the untreated blood pressure is at least 20/10 mmHg above the target blood pressure, consider starting treatment immediately with two drugs.

IV. Choice of drugs:

- This should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient (see Table 1).
- The choice of drugs will also be influenced by the other conditions (e.g., diabetes, coronary disease, etc.) associated with the hypertension (see Table 2). Pregnancy also influences drug choice.
- Long-acting drugs that need to be taken only once daily are preferred to shorter acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen. For the same reason, when more than one drug is prescribed, the use of a combination product with two appropriate medications in a single tablet can simplify treatment for patients, though these products can sometimes be more expensive than individual drugs. Once-daily drugs can be taken at any time during the day, most usually either in the morning or in the evening before sleep. If

multiple drugs are needed, it is possible to divide them between the morning and the evening.

- The choice of drugs will further be influenced by their availability and affordability. In many cases, it is necessary to use whichever drugs have been provided by government or other agencies. For this reason, we will only make recommendations for drug classes, not individual agents, recognizing that there may be a very limited selection of drugs that can be prescribed by a practitioner. Even among generic drugs, there can be a wide variation in cost.
- Recommendations for drug selection are shown in Table 1 (Part 1) for patients whose primary problem is hypertension, and in Table 1 (Part 2) for patients who have a major comorbidity associated with their hypertension. The Fig. 1 displays an algorithm that summarizes the use of therapy for most patients with hypertension. The recommendations for particular drug classes are made with the recognition that sometimes only alternative drug classes will be available. However, most of the time, the use of any drugs that reduce blood pressure is more likely to help protect patients from strokes and other serious events than giving patients no drug at all.

TABLE 1. Drug selection in hypertensive patients with or without other major conditions

Patient type	First drug	Add second drug if needed to achieve a BP of <140/90 mmHg	If third drug needed to achieve a BP of <140/90 mmHg
(Part 1) Treatment regimens when hypertension is the only or main condition			
Black patients (African Ancestry): all ages	CCB ^a or thiazide diuretic	ARB ^b or ACE inhibitor (if unavailable can add alternative first drug choice)	Combination of CCB + ACE inhibitor or ARB + thiazide diuretic
White and other non-black patients: aged <60 years	ARB ^b or ACE inhibitor	CCB ^a or thiazide diuretic	Combination of CCB + ACE inhibitor or ARB + thiazide diuretic
White and other non-black patients: aged >60 years	CCB ^a or thiazide diuretic (though ACE inhibitors or ARBs are also usually effective)	ARB ^b or ACE inhibitor (or CCB or thiazide, if ACE inhibitor or ARB used first)	Combination of CCB + ACE inhibitor or ARB + thiazide diuretic
	First drug	Add second drug if needed to reach a BP of <140/90 mmHg	ADD third drug if needed to reach a BP of <140/90 mmHg
(Part 2) When hypertension is associated with other conditions			
Hypertension and diabetes	ARB or ACE inhibitor Note: in black patients, it is acceptable to start with CCB or thiazide	CCB or thiazide diuretic; Note: in black patients, if starting with CCB or thiazide, would now add ARB or ACE inhibitor	The alternative second drug (thiazide or CCB)
Hypertension and chronic kidney disease	ARB or ACE inhibitor Note: in black patients, good evidence for renal protective effects of ACE inhibitors	CCB or thiazide diuretic ^c	The alternative second drug (thiazide or CCB)
Hypertension and clinical coronary artery disease ^d	β-blocker with ARB or ACE inhibitor	CCB or thiazide diuretic	The alternative second step drug (thiazide or CCB)
Hypertension and stroke history ^e	ACE inhibitor or ARB	Thiazide diuretic or CCB	The alternative second drug (CCB or thiazide)
Hypertension and heart failure	Patients with symptomatic heart failure should usually receive an ARB or ACE inhibitor + β-blocker + diuretic + spironolactone regardless of blood pressure. Dihydropyridine CCB can be added if needed for BP control.		

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate.

^aCCBs generally preferred, but thiazides may cost less.

^bARBs can be considered because ACE inhibitors can cause cough and angioedema, though ACE inhibitors may cost less.

^cIf eGFR less than 40 ml/min, a loop diuretic, for example, furosemide or torsemide, may be needed.

^dIf previous myocardial infarction, a β-blocker and ARB/or ACE inhibitor are indicated regardless of blood pressure.

^eIf using a diuretic, there is good evidence for indapamide (if available).

14. BRIEF COMMENTS ON DRUG CLASSES

Note: There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other. We only mention individual agents if they have an important property that is not shared by the others in its class. Table 2 provides a list of commonly used antihypertensive drugs and their doses.

Angiotensin-converting enzyme inhibitors

- These agents reduce blood pressure by blocking the renin–angiotensin system. They do this by preventing conversion of angiotensin I to the blood pressure-raising hormone angiotensin II. They also increase availability of the vasodilator, bradykinin, by blocking its breakdown.
- ACE inhibitors are well tolerated. Their main side-effect is cough (most common in women and in patients of Asian and African background). Angioedema is an uncommon but potentially serious complication that can threaten airway function; it occurs most frequently in black patients.
- These drugs can increase serum creatinine by as much as 30%, but this is usually because they reduce pressure within the renal glomerulus and decrease filtration; this is a reversible change in function and is not

harmful. An even greater increase in creatinine sometimes occurs when ACE inhibitors are combined with diuretics and produce large blood pressure reductions. Again, this change is reversible, though it may be necessary to reduce doses of one or both drugs. If creatinine levels increase substantially, this can be due to concomitant treatment with NSAIDs, or it may indicate the presence of renal artery stenosis.

- The side-effects with ACE inhibitors are generally not dose-dependent; they occur as frequently at low doses as at high doses. Thus, it can be perfectly acceptable when using these agents to start at medium or even high doses. The one exception to this rule is hyperkalemia, which may occur more frequently at higher ACE inhibitor doses.
- These drugs have established clinical outcome benefits in patients with heart failure, post-myocardial infarction, left ventricular systolic dysfunction, and patients with diabetic and nondiabetic chronic kidney disease.
- In general, the ACE inhibitors are more effective as monotherapy in reducing blood pressure in white patients than in blacks, possibly because the renin–angiotensin system is often less active in black patients. However, these drugs are equally effective in reducing blood pressure in all ethnic and racial groups when combined with either CCBs or diuretics.

TABLE 2. Doses of commonly used antihypertensive drugs

	Daily doses (mg)	
	Low dose	Usual dose
Calcium channel blockers		
Nondihydropyridines		
Diltiazem	120	240–360
Verapamil	120	240–480
Dihydropyridines		
Amlodipine	2.5	5–10
Felodipine	2.5	5–10
Isradipine	2.5 twice daily	5–10 twice daily
Nifedipine	30	30–90
Nitrendipine	10	20
Drugs that target the renin–angiotensin system		
Angiotensin-converting enzyme inhibitors (ACEIs)		
Benazepril	5	10–40
Captopril	12.5 twice daily	50–100 twice daily
Enalapril	5	10–40
Fosinopril	10	10–40
Lisinopril	5	10–40
Perindopril	4	4–8
Quinapril	5	10–40
Ramipril	2.5	5–10
Trandolapril	1–2	2–8
Angiotensin receptor blockers (ARBs)		
Azilsartan	40	80
Candesartan	4	8–32
Eprosartan	400	600–800
Irbesartan	150	150–300
Losartan	50	50–100
Olmesartan	10	20–40
Telmisartan	40	40–80
Valsartan	80	80–320
Direct renin inhibitor		
Aliskiren	75	150–300
Diuretics		
Thiazide and thiazide-like diuretics		
Bendroflumethiazide	5	10
Chlorthalidone	12.5	12.5–25
Hydrochlorothiazide	12.5	12.5–50
Indapamide	1.25	2.5
Loop diuretics		
Bumetanide	0.5	1
Furosemide	20 twice daily	40 twice daily
Torsemide	5	10
Potassium-sparing diuretics		
Amiloride	5	5–10
Eplerenone	25	50–100
Spironolactone	12.5	25–50
Triamterene	100	100
β-Blockers		
Acebutalol	200	200–400
Atenolol	25	100
Bisoprolol	5	5–10
Carvedilol	3.125 twice daily	6.25–25 twice daily
Labetalol	100 twice daily	100–300 twice daily
Metoprolol succinate	25	50–100
Metoprolol tartrate	25 twice daily	50–100 twice daily
Nadolol	20	40–80
Nebivolol	2.5	5–10
Propranolol	40 twice daily	40–160 twice daily
α-Adrenergic receptor blockers		
Doxazosin	1	1–2
Prazosin	1 twice daily	1–5 twice daily
Terazosin	1	1–2
Vasodilators, central α-agonists, and adrenergic depleters		
Vasodilators		
Hydralazine	10 twice daily	25–100 twice daily
Minoxidil	2.5	5–10

TABLE 2 (Continued)

	Daily doses (mg)	
	Low dose	Usual dose
Central α-agonists		
Clonidine	0.1 twice daily	0.1–0.2 twice daily
Clonidine patch	TTS-1, once weekly	TTS-1, 2 or 3, once weekly
Methyldopa	125 twice daily	250–500 twice daily
Adrenergic depleters		
Reserpine	0.1	0.1–0.25

- Do not combine ACE inhibitors with ARBs; each of these drug types is beneficial in patients with kidney disease, but in combination they may actually have adverse effects on kidney function.
- When starting treatment with an ACE inhibitor, there is a risk of hypotension in patients who are already taking diuretics or are on very low salt diets or are dehydrated (e.g., laborers in hot climates, patients with diarrhea). For patients taking a diuretic, skipping a dose before starting the ACE inhibitor helps prevent this sudden effect on blood pressure.
- ACE inhibitors must not be used in pregnancy, especially in the second or third trimesters, as they can compromise the normal development of the fetus.

Angiotensin receptor blockers

- These drugs, like the ACE inhibitors, antagonize the renin–angiotensin system. They reduce blood pressure by blocking the action of angiotensin II on its AT1 receptor and thus preventing the vasoconstrictor effects of this receptor.
- The ARBs are well tolerated. As they do not cause cough and only rarely cause angioedema, and have effects and benefits similar to ACE inhibitors, they are generally preferred over the ACE inhibitors if they are available and affordable. Like the ACE inhibitors, the ARBs can increase serum creatinine (see comments about ACE inhibitors), but usually this is a functional change that is reversible and not harmful.
- These drugs do not appear to have dose-dependent side-effects, so it is perfectly reasonable to start treatment with medium or even maximum approved doses.
- These drugs have the same benefits on cardiovascular and renal outcomes as the ACE inhibitors.
- Like the ACE inhibitors, they tend to work better in White and Asian patients than Black, but when combined with either CCBs or diuretics, they become equally effective in all patient groups.
- Do not combine ARBs with ACE inhibitors; each of these drug types is beneficial in patients with kidney disease, but in combination they may actually have adverse effects on renal events.
- When starting treatment with an ARB in patients already on diuretics, it may be beneficial to skip a dose of the diuretic to prevent a very sudden fall in blood pressure.

- ARBs must not be used in pregnancy, especially in the second or third trimesters, as they can compromise the normal development of the fetus.

Thiazide and thiazide-like diuretics

- These agents work by increasing excretion of sodium by the kidneys and additionally may have some vasodilator effects.
- Clinical outcome benefits (reduction of strokes and major cardiovascular events) have been best established with chlorthalidone, indapamide, and hydrochlorothiazide, though the evidence for the first two of these agents has been the strongest.
- Chlorthalidone has more powerful effects on blood pressure than hydrochlorothiazide (when the same doses are compared) and has a longer duration of action.
- The main side-effects of these drugs are metabolic (hypokalemia, hyperglycemia, and hyperuricemia). The likelihood of these problems can be reduced by using low doses (e.g., 12.5 or 25 mg of hydrochlorothiazide or chlorthalidone) or by combining these diuretics with ACE inhibitors or ARBs, which have been shown to reduce these metabolic changes. Combining diuretics with potassium-sparing agents also helps prevent hypokalemia.
- The diuretics are most effective in reducing blood pressure when combined with ACE inhibitors or ARBs, although they are also effective when combined with CCBs.

Note: thiazides and β -blockers are also an effective combination for reducing blood pressure, but as both classes can increase blood glucose concentrations this combination should be used with caution in patients at risk of developing diabetes.

Calcium channel blockers

- These agents reduce blood pressure by blocking the inward flow of calcium ions through the L channels of arterial smooth muscle cells.
- There are two main types of CCBs: dihydropyridines such as amlodipine and nifedipine, which work by dilating arteries; and nondihydropyridines such as diltiazem and verapamil, which dilate arteries somewhat less but also reduce heart rate and contractility.
- Most experience with these agents has been with the dihydropyridines such as amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials.
- The main side-effect of CCBs is peripheral edema, which is most prominent at high doses; this finding can often be attenuated by combining these agents with ACE inhibitors or ARBs.
- The nondihydropyridine CCBs are not recommended in patients with heart failure, but amlodipine appears to be safe when given to heart failure patients receiving standard therapy (including ACE inhibitors) for this condition.

- Because the nondihydropyridine drugs, verapamil and diltiazem, can slow the heart rate, they can sometimes be preferred in patients with fast heart rates and even for rate control in patients with atrial fibrillation who cannot tolerate β -blockers. The nondihydropyridine drugs can also reduce proteinuria.
- The CCBs have powerful blood pressure-reducing effects, particularly when combined with ACE inhibitors or ARBs. They are equally effective in all racial and ethnic groups.
- The dihydropyridine, but not the nondihydropyridine, CCBs can be safely combined with β -blockers.

β -Blockers

- The β -blockers reduce cardiac output and also decrease the release of renin from the kidney.
- They have strong clinical outcome benefits in patients with histories of myocardial infarction and heart failure and are efficacious in the management of angina pectoris.
- They are less effective in reducing blood pressure in black patients than in patients of other ethnicities.
- The β -blockers may not be as effective as the other major drug classes in preventing stroke or cardiovascular events in hypertensive patients, but are drugs of choice in patients with histories of myocardial infarction or heart failure.
- Many of these agents have adverse effects on glucose metabolism and, therefore, are not recommended in patients at risk of becoming diabetic, especially in combination with diuretics. They may also be associated with heart block in susceptible patients.
- The main side-effects with β -blockers are reduced sexual function, fatigue, and reduced exercise tolerance.
- The combined α -blocker and β -blocker, labetalol, is widely used intravenously for hypertensive emergencies, and is also used orally for treating hypertension in pregnancy and in breastfeeding mothers.

α -Blockers

- The α -blockers reduce blood pressure by blocking arterial α -adrenergic receptors and thus preventing the vasoconstrictor actions of these receptors.
- These drugs are less widely used as first step drugs than other classes because clinical outcome benefits have not been as well established as with other agents. However, they can be useful in treating resistant hypertension when used in combination with agents such as diuretics, β -blockers, and ACE inhibitors.
- To be maximally effective, they should usually be combined with a diuretic. As the α -blockers can have somewhat beneficial effects on blood glucose and lipid levels, they can potentially neutralize some of the adverse metabolic effects of the diuretics.
- The α -blockers are effective in treating benign prostatic hypertrophy, and so can be a valuable part of hypertension treatment regimens in older men who have this condition.

Centrally acting agents

- These drugs, the most well known of which are clonidine and α -methyldopa, work primarily by reducing sympathetic outflow from the central nervous system.
- They are effective at reducing blood pressure in most patient groups.
- Bothersome side-effects such as drowsiness and dry mouth have reduced their popularity. Treatment with a clonidine skin patch causes fewer side-effects than the oral agent, but the patch is not always available and can be more costly than the tablets.
- In certain countries, including the United States, α -methyldopa is widely employed for treating hypertension in pregnancy.

Direct vasodilators

- Because these agents, specifically hydralazine and minoxidil, often cause fluid retention and tachycardia, they are most effective in reducing blood pressure when combined with diuretics and β -blockers or sympatholytic agents. For this reason, they are now usually used only as fourth-line or later additions to treatment regimens.
- Hydralazine is the more widely used of these agents. The powerful drug minoxidil is sometimes used by specialists in patients whose blood pressures are difficult to control. Fluid retention and tachycardia are frequent problems with minoxidil, as well as unwanted hair growth (particularly in women). Furosemide is often required to cope with the fluid retention.

Mineralocorticoid receptor antagonists

- The best known of these agents is spironolactone. Although it was originally developed for the treatment of high aldosterone states, it recently has become part of the standard treatment for heart failure. Eplerenone is a newer and better tolerated agent, although most experience in difficult-to-control hypertension has been with spironolactone.
- In addition, these agents can be very effective in reducing blood pressure when added to standard three-drug regimens (ACE inhibitor or ARB/CCB/diuretic) in treatment-resistant patients. This may be because aldosterone excess can contribute to resistant hypertension.
- Symptomatic side-effects of gynecomastia (swelling and tenderness of breasts in both men and women) and sexual dysfunction are common. These can be minimized by using spironolactone in a low dose (no more than 25 mg daily) or by using the more selective (but more expensive) agent, eplerenone. Hyperkalemia can also become a problem with these agents, particularly when added to ACE inhibitors or ARBs in patients with reduced renal function. These agents should be used with caution when the eGFR is below 50. In particular, when mineralocorticoid receptor blockers are combined with ACE inhibitors or ARBs,

potassium levels must be monitored within the first month of treatment and then on a regular basis (every 3–6 months).

15. TREATMENT-RESISTANT HYPERTENSION

- Hypertension can be controlled (blood pressure <140/90 mmHg in most patients) by using either one, two, or three drugs as described earlier (ACE inhibitor or ARB/CCB/diuretic) in full or maximally tolerated doses. The most widely used two-drug combination, ACE inhibitors either with CCBs or diuretics, or angiotensin receptor blockers either with CCBs or diuretics, can control blood pressure in about 80% of patients.
- Confirm that the blood pressure is truly uncontrolled by checking home pressures, or if available, by using ambulatory blood pressure monitoring.
- For patients not controlled on three drugs, adding a mineralocorticoid antagonist like spironolactone, a β -blocker, a centrally acting agent, an α -blocker, or a direct vasodilator will often be helpful.
- If blood pressure is still not controlled, it is important to make certain that patients are actually taking their medicines. Question their families, check their prescriptions, and ask questions about side-effects to help confirm compliance with treatment.
- Check whether patients are taking other medicines that can interfere with their hypertension treatment, for example, NSAIDs, cold remedies, and some antidepressants. Also ask about diet: blood pressures in some patients are especially sensitive to such factors as excessive salt intake.
- Consider secondary causes of hypertension if all these more simple approaches are unsuccessful.
 - Secondary hypertension can be suggested by the sudden onset of hypertension, or by the loss of blood pressure control in patients previously well managed or by the occurrence of a hypertension emergency
 - Chronic kidney disease: this common secondary cause of hypertension should normally be revealed by the initial patient evaluation (laboratory tests of creatinine, etc.). These patients, if possible, should be referred to a nephrologist.
 - Aldosterone excess: this is suggested by hypokalemia during the initial evaluation, though this condition can occur even when potassium levels appear normal. About 20% of patients whose blood pressures remain high despite taking three drugs have evidence for aldosterone excess. Confirming this diagnosis usually requires assistance from clinical hypertension specialists.
 - Sleep apnea: this is common in obese people. Not all patients with sleep apnea have hypertension, but there is a clear association. A preliminary diagnosis can be made by finding a history of snoring during sleep and daytime tiredness. A definitive diagnosis usually requires a sleep laboratory study.

- Other secondary causes of hypertension such as renal artery stenosis or coarctation of the aorta usually require evaluation by a specialist.

Final comment

The authors of this statement acknowledge that there are insufficient published data from clinical trials in hypertension to create recommendations that are completely evidence-based, and so inevitably some of our recommendations reflect expert opinion and experience.

We also should point out that because of the major differences in resources among points of care, it is not possible to create a uniform set of guidelines. For this reason, we have written a broad statement on the management of hypertension and have not presumed to anticipate the conditions or shortfalls that might exist in particular communities. We expect that experts who are familiar with local circumstances will feel free to use their own judgment in modifying our recommendations and to create practical instructions to help guide front-line practitioners in providing the best care possible.

A note to colleagues

The authors of this statement would welcome comments and suggestions from colleagues. We recognize that in this initial version of the guidelines, there will probably be omissions, redundancies, and inaccuracies. Please feel free to get in touch with us either by letters to the Journal or by personal communication.

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