Hypertensive Therapy: Part II

Veronica Franco, MD; Suzanne Oparil, MD; Oscar A. Carretero, MD

If the incidence of hypertension in the population could be reduced through lifestyle modification, much of the morbidity and mortality associated with coronary heart disease, renal disease, and stroke might be prevented. Randomized, controlled trials have shown that lifestyle modification can lower blood pressure (BP) in both hypertensive and high-risk normotensive (now called prehypertensive) persons and can prevent hypertension in the latter group. Accordingly, lifestyle modification is recommended for all persons (Table 1), either alone or in conjunction with pharmacological therapy (Table 2).

Lifestyle Modification

Weight Loss and Maintenance of Normal Body Weight

Weight loss is the most effective of all nonpharmacological measures to prevent and treat hypertension. This effect is independent of sodium restriction and is seen in both obese and nonobese hypertensive individuals. Clinical trial evidence suggests that weight loss interventions produce BP benefits that persist even after cessation of active therapy. Body mass index (BMI) should be maintained between 18.5 and 24.9 kg/m². Because sustained weight reduction is extremely difficult to achieve, emphasis should be placed on prevention of weight gain, particularly in younger individuals with prehypertension and in families with a high prevalence of hypertension.

Increased Physical Activity

At least 30 minutes of moderately intense physical activity, such as brisk walking, swimming, bicycling, or yard work, carried out at least 3 times per week (preferably once per day) can lower BP in both normotensive and hypertensive individuals. Studies suggest that such moderate activity may lower systolic BP (SBP) by 4 to 9 mm Hg. Additional benefits of regular physical activity include weight loss, enhanced sense of well-being, improved functional health status, and reduced risk of cardiovascular disease (CVD) and mortality from all causes. Accordingly, regular aerobic physical activity is recommended for all persons, but those with advanced or unstable CVD may require a medical evaluation before initiation of exercise or a medically supervised exercise program. Isometric exercise such as heavy weight lifting can have a pressor effect and should be avoided.

Dietary Modification

The Dietary Approaches to Stop Hypertension (DASH) trial showed overall reductions in BP of 11.4/5.5 mm Hg in hypertensive persons on a diet rich in fruits, vegetables, and low-fat dairy products compared with control subjects on a so-called usual American diet, whereas dietary sodium intake and weight were held constant. The DASH “combination diet” also produced reductions in BP of 3.5/2.1 mm Hg in subjects without hypertension. Remarkably, subgroup analysis of the DASH trial indicated that the combination diet lowered BP effectively in all participating groups examined, independent of race, sex, age, BMI, level of education, income, physical activity, family history of hypertension, and geographic location. Translation of the results of the DASH trial to advice for the general public or for the universe of hypertensive patients can be accomplished by recommending 4 servings of fruit, 4 servings of vegetables, and 2 to 3 servings of low-fat dairy products per day. The paradigm shift toward recognition of the powerful role of total diet (rather than individual nutrients) in the prevention and treatment of hypertension in particular and CVD in general deserves emphasis.

Sodium Reduction

High sodium intake has generally been related to BP elevation, particularly in hypertensive individuals, and this effect appears to be augmented by concomitant low potassium intake. When sodium restriction was added to the DASH diet in the DASH-sodium trial, the reduction in sodium intake from the high (150 mmol/d) to the intermediate (100 mmol/d) level reduced SBP by 2.1 mm Hg when participants were on a usual American diet and by 1.3 mm Hg on the DASH diet. Reducing the sodium intake from the intermediate to the low (50 mmol/d) level caused additional reductions of 4.6 mm Hg on the usual diet and 1.7 mm Hg on the DASH diet. The largest BP effect was observed with the combination of DASH diet and low sodium intake, although the effects were not fully additive. On the basis of these observations and the small but consistent BP-lowering effects observed in other clinical trials of dietary sodium reduction in hypertensive

From the Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham (V.F., S.O.), and the Hypertension and Vascular Research Division, Heart and Vascular Institute, Henry Ford Hospital, Detroit, Michigan (O.A.C.).

Correspondence to Veronica Franco, MD, ZRB 1024, 703 19th St South, University of Alabama at Birmingham, Birmingham, AL 35294. E-mail vfranco@uab.edu

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TABLE 1. Lifestyle Modifications to Manage Hypertension†

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate Systolic BP Reduction, Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI 18.5–24.9)</td>
<td>5–20 mm Hg/10-kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH diet eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8–14 mm Hg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter-weight persons</td>
<td>2–4 mm Hg</td>
</tr>
</tbody>
</table>

BMI indicates body mass index calculated as weight in kilograms divided by the square of height in meters; DASH, Dietary Approaches to Stop Hypertension.

†The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.

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subjects (particularly those who are obese, elderly, black, and/or female), avoidance of excessive sodium intake is recommended for hypertensive persons.¹² Additional benefits of sodium reduction include reduced diuretic-induced hypokalemia, greater ease of BP control with diuretic therapy, protection from osteoporosis and fractures by reducing urinary calcium excretion, and favorable effects on left ventricular hypertrophy. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a reduction in daily consumption of sodium chloride to ≤6 g and of sodium to ≤2.4 g.¹² This can be achieved by avoiding obviously salty foods, not adding salt at the table, and eating more meals cooked from natural ingredients. Whether this level of sodium reduction is helpful for the general population in preventing hypertension and related CVD morbidity and mortality is a matter of debate, considering the minimal effect of dietary sodium reduction on BP in normotensive subjects and possible adverse effects of reduced sodium intake on the cardiovascular system over time.⁴²

TABLE 2. Guidelines for Treatment of Hypertension Based on Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>High-Risk Conditions With Compelling Indications*</th>
<th>Recommended Drugs</th>
<th>Clinical Trial Basis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Diuretic, β-Blocker, ACE Inhibitor, ARB, Calcium Antagonist, Aldosterone Antagonist</td>
<td>ACC/AHA Heart Failure Guideline,⁴ MERIT-HF,⁵ COPERNICUS,⁶ CIBIS,⁷ SOLVD,⁸ AIRE,⁹ TRACE,¹⁰ ValHEFT,¹¹ RALES,¹² CHARM,¹³</td>
</tr>
<tr>
<td>Post–myocardial infarction</td>
<td>Diuretic, β-Blocker</td>
<td>ACC/AHA Post-MI Guideline,¹⁴ BHAT,¹⁵ SAVE,¹⁶ CAPRICORN,¹⁷ EPHEUS,¹⁸ ALLHAT,¹⁹ HOPE,²⁰ ANBP2,²¹ LIFE,²² CONVINCE,²³ EUROPA,²⁴ INVEST,²⁵</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>Diuretic, β-Blocker</td>
<td>NKF-ADA Guideline,²⁶,²⁷ UKPDS,²⁸ ALLHAT,¹⁹ NFK Guideline,²⁷ Captopril Trial,²⁹ RENAAAL,³⁰ IDNT,³¹ REIN,³² AASK,³³ PROGRESS,³⁴</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diuretic, β-Blocker</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>Diuretic, β-Blocker</td>
<td></td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve blood pressure goal to test outcomes.

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Pharmacological Treatment

Abundant clinical trial data indicate that lowering BP with antihypertensive drugs effectively reduces risk of a variety of CVD outcomes, including cardiovascular death, as well as total mortality.\(^{1,2,45-47}\) Outcome benefits have been seen with BP-lowering regimens based on thiazide-type diuretics or \(\beta\)-adrenergic receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, or angiotensin receptor blockers (ARBs). Meta-analysis of data from randomized, controlled trials has not shown significant differences in total major cardiovascular events between regimens based on ACE inhibitors, calcium antagonists, or diuretics or \(\beta\)-blockers, although there were some differences in cause-specific outcomes.\(^{46}\) For outcomes other than heart failure, differences in achieved SBP-lowering were related to the extent of risk reduction (Figure 1). An exception to this generalization is the Losartan Intervention for Endpoint Reduction (LIFE) trial, in which, because of a 25% reduction in stroke, CVD events were reduced significantly more by ARB (losartan) than by \(\beta\)-blocker (atenolol) treatment despite comparable BP reductions.\(^{48}\) Outcome data on the ARBs, the newest antihypertensive drug class, are sparse in patients with essential hypertension, although results of the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study will be available soon.\(^{49}\) No ARB–diuretic comparison yet has been carried out. Thus, for hypertensive patients as a whole, BP reduction appears to be generally more important than choice of antihypertensive drug(s) for reducing CVD risk. The key for a successful antihypertensive regimen is to include highly effective medication(s) that are well tolerated and affordable.

JNC 7 has keyed its antihypertensive treatment approach to the presence or absence of “compelling indications,” ie, high-risk comorbid conditions for which clinical trials have demonstrated benefit of specific classes of antihypertensive drugs (Figure 2, Table 2).\(^{1,2}\) For hypertensive persons with compelling indications, drug selections are dictated by the comorbid condition as well as the BP. In the absence of compelling indications, JNC 7 recommends that most patients use a thiazide-type diuretic, either alone or in combination with other classes of drugs (ACE inhibitor, ARB, \(\beta\)-blocker, or calcium antagonist) that have been shown to be beneficial in randomized, controlled outcome trials. In contrast, the European guidelines have taken the view that many regimens are effective in preventing cardiovascular outcomes and therefore have left drug choices up to the practitioner.\(^{55}\)

The basis for the somewhat controversial recommendation of preferred status for thiazide-type diuretics by JNC 7 is the extensive favorable experience with diuretics in outcome trials,\(^{19,50,51}\) the fact that diuretics enhance the antihypertensive efficacy of most other drug classes, and their low cost. Furthermore, volume overload related to inadequate or absent diuretic therapy is a common cause of resistance to BP control.\(^{52}\) Despite this powerful rationale, diuretics are underused in the United States, particularly by older patients.\(^{53}\)

For persons with BP \(>20/10\) mm Hg above goal (stage 2 hypertension), initial treatment with 2 drugs, usually including a thiazide-type diuretic, is recommended by JNC 7 because of the high risk of this patient group (Figure 2). Notably, randomized controlled trials have shown that single-drug treatment usually is not adequate to achieve goal BPs in most hypertensive patients, particularly those with systolic hypertension. For example, in the very large Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial (n=42 418), fewer than 30% of participants achieved goal BP (<140/90 mm Hg) on monotherapy.\(^{19}\) Data are similar for the LIFE trial,\(^{58}\) in which a minority of participants were on monotherapy at the end of the 5-year follow-up period. Initiating therapy with more than one agent offers the potential advantages of achieving BP control more rapidly and avoiding dose-related adverse effects of individual drugs by producing greater BP reduction at lower doses of the component agents. In addition, use of fixed-dose combinations may be more convenient, simpler to take, and less costly than the individual components prescribed separately. The starting dose of most fixed-dose combinations is usually below those used in clinical outcome trials, and doses of these agents should be titrated upward to achieve goal BP before adding other drugs. Caution is advised in taking this approach with patients at risk for orthostatic hypotension, eg, some
older persons, diabetic patients, and persons with autonomic dysfunction.

Compelling Indications

Compelling indications for specific therapy include high-risk conditions that can be direct sequelae of hypertension (heart failure, coronary heart disease, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes, high coronary heart disease risk). Therapeutic decisions in such individuals should be directed at both the compelling indication and BP lowering (Table 2).

Ischemic Heart Disease

Stable Angina and Silent Ischemia

Hypertensive persons are at increased risk for coronary events and may have a worse prognosis after myocardial infarction. Therefore, hypertension should be treated aggressively in persons with ischemic heart disease, with the caveat that lowering diastolic BP to ≤55 or 60 mm Hg may be associated with an increase in CVD events. Therapy generally should be initiated with a β-blocker. If angina and BP are not controlled with β-blockers alone, or if they are contraindicated (as in the presence of severe reactive airway disease, severe peripheral arterial disease, high-degree atrioventricular block, or the sick sinus syndrome), a calcium antagonist can be added or substituted. Long-acting dihydropyridine calcium antagonists are preferred for combination therapy with β-blockers. Short-acting dihydropyridine calcium antagonists should not be used because of their potential to increase risk of mortality, particularly in the setting of acute myocardial infarction.

High Coronary Disease Risk

Clinical trial data have provided evidence that several classes of antihypertensive agents, including diuretics, β-blockers, ACE inhibitors, and calcium antagonists, are beneficial in this clinical setting (Table 2). Notably, the ALLHAT trial and the meta-analysis of the Blood Pressure Lowering Treatment Trialists’ Collaboration showed no advantage of ACE inhibitors over other drug classes studied (diuretics, β-blockers, or calcium antagonists) in preventing coronary heart disease outcomes.

After Myocardial Infarction

β-Blockers, ACE inhibitors, ARBs, aldosterone antagonists, and non-dihydropyridine calcium antagonists have been shown to be beneficial (Table 2). This likely is due to a combination of antiischemic effects and effects on myocardial remodeling. The American Heart Association/American College of Cardiology guidelines recommend treatment with aspirin, β-blockers, lipid-lowering therapy, and ACE inhibitors. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) demonstrated that ARBs are as effective as ACE inhibitors in reducing the rates of death and other adverse cardiovascular outcomes after a myocardial infarction and should be considered as alternatives. The Eplerenone Post-acute myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS) showed that the addition of eplerenone to optimal medical treatment reduced overall mortality rate and rates of death and hospitalization from cardiovascular causes in patients with left ventricular dysfunction and heart failure.

Heart Failure

Hypertension precedes the development of heart failure in approximately 90% of patients and increases the risk for heart failure by 2-fold in men and 3-fold in women. Accordingly, aggressive treatment of hypertension plays an important role in preventing and managing heart failure. There are compelling indications for the use of all of the major classes of antihypertensive drugs in heart failure, with the exception of the calcium antagonists (Table 2). BP goals in heart failure have not been specifically defined on the basis of clinical trial data. However, reducing SBP to the range of 110 to 130 mm Hg...
appears to be beneficial. Some experts even advocate lowering SBP to <100 mm Hg or as low as tolerated, in part on the basis of results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.6

The Blood Pressure Lowering Treatment Trialists’ Collaboration meta-analysis46 compared the effects of regimens based on ACE inhibitors to those based on diuretics or β-blockers in hypertensive patients with heart failure (primary end point: death or need for hospitalization) and found no significant differences. However, compared with regimens based on calcium antagonists, those based on diuretics or β-blockers (33% [21% to 47%]) or on ACE inhibitors (18% [8% to 27%]) produced greater reductions in risk of heart failure. Compared with control regimens, ARB-based treatment reduced the risk of heart failure (16% [3% to 28%]). Aldosterone antagonists were not included in the analysis. Unlike other CVD outcomes, there was no relationship between extent of SBP reduction and heart failure prevention in these trials.

Diabetes
Diabetes is an independent risk factor for CVD (coronary heart disease and stroke), the cause of death in approximately two thirds of persons with diabetes. When patients with diabetes develop clinical CVD, they have a worse prognosis than do CVD patients without diabetes.59 In addition, patients with diabetes, particularly women, have more pronounced heart failure symptoms and a worse prognosis than those without diabetes.60 Diabetes is now the most common cause of end-stage kidney disease in the United States. Diabetic glomerulopathy is characterized by albuminuria, which is, in turn, associated with increased coronary heart disease, stroke, heart failure, and renal disease progression.59-62

Hypertension is common and carries a worse prognosis in diabetic patients.59,60 Randomized controlled clinical trials have shown that rigorous treatment of BP in patients with diabetes reduces macrovascular and microvascular disease and that diabetic patients are particularly sensitive to small reductions in BP.63 The goal BP recommended by JNC 7 and the American Diabetes Association is ≤130/80 mm Hg.1,2,64 JNC 7 lists diabetes as a compelling indication for diuretics, β-blockers, ACE inhibitors, ARBs, and calcium antagonists on the basis of clinical trial evidence (Table 2). Initial drug choices are moot, because most diabetic patients require 2 or more drugs to achieve BP control.61,62,64 ACE inhibitors and β-blockers are particularly useful for older diabetic patients at high risk for CVD or with established ischemic heart disease; ACE inhibitors and ARBs have been shown to delay deterioration in renal function and progression of proteinuria in type 2 diabetic patients with chronic kidney disease; whereas diuretics and calcium antagonists are useful in diabetic patients because of their ability to lower BP and reduce CVD events. Importantly, the adverse metabolic effects of diuretics (hypokalemia, reduced insulin sensitivity, increased cholesterol levels) have not been shown in randomized controlled trials to be reflected in adverse CVD outcomes in hypertensive diabetic patients, nor have ACE inhibitors been shown to offer particular advantages over other drug classes in this patient group as a whole.19 For the diabetic patient with albuminuria or chronic kidney disease, however, ACE inhibitors and ARBs offer advantages beyond BP lowering (see below).

Chronic Kidney Disease
CVD is the most common cause of death in persons with chronic kidney disease, itself an independent risk factor for CVD. Persons with an estimated glomerular filtration rate (GFR) <60 mL/min have an approximately 16% increase in CVD mortality, and those with estimated GFR <30 mL/min, a 30% increase.65,66 CVD risk exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50% increase in risk and the presence of macroalbuminuria a 350% increase.67 The American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention indicated that chronic kidney disease, whether manifested by proteinuria (albuminuria) or reduced GFR, appears to be an independent risk factor for CVD outcomes.66 They recommend that routine evaluation of patients with CVD or those at high risk for CVD include measurement of spot urine albumin-to-creatinine ratio and estimation of GFR by serum creatinine and prediction equations.68

JNC 7 includes chronic kidney disease as a compelling indication, with a target BP goal (<130/80 mm Hg) for specific treatment with ACE inhibitors or ARBs (Table 2).1,2 ACE inhibitors are more effective than other antihypertensive medications in slowing the progression of nondiabetic renal disease.69,70 The African American Study of Kidney Disease and Hypertension (AASK) of 1094 nondiabetic hypertensive African-American individuals with chronic kidney disease70 demonstrated that the decline in GFR was slower in the ACE inhibitor (ramipril) group than in the β-blocker (metoprolol) or the calcium antagonist (amlodipine) groups, irrespective of the degree of proteinuria.

Medications that block the renin–angiotensin–aldosterone system slow the progression of renal disease in patients with type 2 diabetes beyond the effect attributable to lowering BP. The Heart Outcomes and Prevention Evaluation (HOPE) study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy demonstrated that adding ramipril treatment lowered the risk of cardiovascular events and overt nephropathy in diabetic patients.71 The benefit of the ACE inhibitor in MICRO-HOPE and HOPE was much greater than can be attributed to its effects on BP. The Irbesartan Micro-Albuminuria study (IRMA II),72 a trial conducted in patients with type 2 diabetes mellitus and microalbuminuria, demonstrated that the ARB irbesartan reduced the rate of progression to proteinuria and diabetic nephropathy when compared with usual therapy, even though similar BPs were achieved. The Reduction in End Points in Non–insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study30 and the Irbesartan Diabetic Nephropathy Trial (IDNT)31 were conducted in diabetic patients with overt nephropathy, hypertension, and serum creatinine levels of 1 to 3 mg/dL. In both trials, adding the ARBs reduced the incidence of a doubling of serum creatinine compared with conventional antihypertensive...
Treatment, with nearly equal BP lowering in both treatment groups. In the RENAAL study, the incidence of end-stage renal disease was also lower in the losartan group than in those on conventional hypertensive therapy. The results of these trials support the use of ACE inhibitors and ARBs to prevent the deterioration in renal function, which is almost inevitable in the patient with untreated diabetic nephropathy.

The National Kidney Foundation recommends that patients with hypertension who have renal insufficiency, whether or not they are diabetic, should receive an ACE inhibitor or an ARB as a first antihypertensive agent (in most cases, a diuretic should be a second agent and a calcium antagonist a third) to control hypertension and to slow progressive renal failure. ACE inhibitors and ARBs also have been shown to slow the progression of proteinuria. There is no cutoff value for serum creatinine at which ACE inhibitor or ARB treatment is inappropriate unless the ACE inhibitor or ARB interferes with Ca\(^{2+}\) or anemia management. An initial transient decrease in GFR usually occurs during the first 3 months of treatment with either agent as BP is lowered. A limited increase in creatinine, as much as 30% to 40% above baseline, is acceptable and not a reason to withhold treatment unless hyperkalemia develops. Creatinine and potassium should be measured 2 to 4 weeks after starting treatment with an ACE inhibitor or ARB; if stable, the measurements should be repeated at 6 months and every 6 months thereafter. If there is an increase in serum creatinine, the patient should be evaluated to assess hydration status and query use of nephrotoxic medications. The creatinine and potassium should be remeasured after 6 weeks; if they remain persistently elevated, consideration should be given to the diagnosis of renal artery stenosis, and the ACE inhibitor or ARB should be discontinued. Furthermore, in kidney transplant recipients, ACE inhibitors and ARBs may exacerbate hyperkalemia caused by cyclosporine or tacrolimus. Thus, treatment of patients with chronic kidney disease with ACE inhibitors and ARBs requires knowledge of the expected benefits and risks of therapy and careful attention to BP, kidney function, serum electrolytes, and possible drug interactions.

**Conclusions**

Recently published observational and clinical trial data have underscored the importance of BP elevation as a public health problem. Linear positive relationships have been defined between both SBP and diastolic BP and death due to coronary artery disease and stroke over the entire BP range in middle-aged and elderly persons, and a very high lifetime risk of developing hypertension has been revealed. For these reasons, a new BP class known as prehypertension (BP 120 to 139/80 to 89 mm Hg) has been designated to identify individuals at high risk of developing hypertension and related target-organ damage. These persons require health-promoting lifestyle modifications to prevent a progressive rise in BP and development of CVD.

There is clear evidence from clinical trials that changes in lifestyle—including weight loss and maintenance of normal body weight; increased physical activity; dietary modification to include more fruits, vegetables, and low-fat dairy products; moderation of alcohol intake; and sodium reduction in salt-sensitive individuals—can lower BP in both hypertensive and prehypertensive persons and can prevent hypertension in the latter group. Accordingly, lifestyle modification is recommended for all persons, either alone or in combination with pharmacological treatment for hypertension. Lifestyle modification is difficult to achieve because it requires time, effort, and persistence on the part of the patient. Support from family, friends, and healthcare providers is helpful in this area.

Once hypertension develops, pharmacological treatment is needed to reduce BP and prevent CVD outcomes. Abundant clinical trial data indicate that lowering BP with antihypertensive drugs effectively reduces a variety of CVD outcomes, including stroke, coronary heart disease, heart failure, and cardiovascular death, as well as total mortality. Outcome benefits have been seen with antihypertensive regimens based on thiazide-type diuretics or \(\beta\)-blockers, ACE inhibitors, calcium antagonists, and ARBs. Meta-analyses of data from randomized controlled trials have not shown significant differences in total major cardiovascular events between regimens based on ACE inhibitors, calcium antagonists, or diuretics or \(\beta\)-blockers, although there were some differences in cause-specific outcomes. For outcomes other than heart failure, differences in achieved SBP-lowering are related to the extent of risk reduction, independent of treatment assignment. Thus, for hypertensive patients as a whole, reduction of BP (especially SBP) is more important than choice of antihypertensive drug(s) for reducing CVD risk.

Clinical trials have shown that 2 or more antihypertensive medications are required to achieve goal BP (<140/90 mm Hg in most; <130/80 mm Hg in those with diabetes or chronic kidney disease) in most hypertensive patients. Accordingly, initiation of therapy with 2 agents (in individual tablets or fixed-dose combination) should be considered for those at higher risk (BP >20/10 mm Hg above goal). US guidelines recommend using thiazide-type diuretics as first-line treatment in most hypertensives and in combination with other drug classes when multiple drugs are required. This differs from European guidelines, in which antihypertensive drug choices are left up to the healthcare provider. The rationale for the preferred status of the diuretics includes the abundance of favorable outcome trial data delineating their benefits, their ability to enhance the antihypertensive efficacy of most other drug classes, and their low cost. Their biochemical adverse effects (hypokalemia, reduced insulin sensitivity) are of uncertain clinical significance.

A hypertensive patient may also have a high-risk condition (eg, heart failure, recent myocardial infarction, diabetes, chronic kidney disease) that constitutes a compelling indication for use of other antihypertensive drug classes. In that case, initial treatment should be dictated by the compelling indication, bearing in mind that BP control is paramount. Treatment guidelines from JNC 7, as well as from the American Heart Association/American College of Cardiology, National Kidney Foundation, and American Diabetes Association, concurred on the drug-class choices for each compelling indication. Agents that interrupt the renin–angiotensin–aldosterone system have been shown to be beneficial...
in all of these conditions, as have β-blockers. In addition, thiazide diuretics and calcium antagonists are indicated in patients with high coronary artery disease risk or diabetes according to outcome data. Attainment of goal BP, in addition to correct choices of drug classes for compelling indications, is paramount in these hypertensive patients with concomitant cardiovascular or kidney disease.

CVD is the leading cause of morbidity and mortality in developed countries, and aggressive risk factor modification is needed to control this burgeoning public health problem. Tight BP control is fundamental for primary and secondary prevention of CVD. JNC 7 streamlines the recommended steps for treatment of hypertension. The new guidelines also include an appealing new BP classification with a prehypertension category. A heart-healthy lifestyle is vital, even if BP is normal. Healthcare providers and the population in general must think more seriously about high BP and take action to reduce this pervasive and pernicious risk factor.

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References
32. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on


34. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033–1041.


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