A 65-year-old man presented for evaluation of high blood pressure found on screening at a local health fair. History and physical examination did not show any signs or symptoms suggestive of a secondary cause, nor was there evidence of target end-organ damage except for grade 1 Keith-Wagener-Barker retinopathy. The patient denied taking any prescription or over-the-counter medications.

Hypertension is the most common disease-specific reason Americans visit a physician. Despite the risks associated with an elevated blood pressure (BP), there is still woefully low achievement of recommended BP goals. From 1991 to 1994, only 27.4% of hypertensive Americans aged 18 to 74 years had a BP <140/90 mm Hg, the current stated goal for most people with hypertension, and in those with diabetes, less than half that number (11%) were controlled to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VI (JNC VI) recommended goal of <130/85 mm Hg.1 The present update will provide an overview of the evaluation and management of essential hypertension and help to guide clinicians in developing a management plan for a patient like the one described above.

### Evaluation

Taking a proper BP is an important first step in the diagnosis of hypertension.2 Using the proper cuff size with patients resting quietly and comfortably (with back support if seated) for at least 5 minutes before measurement, 2 or more readings separated by 2 minutes should be taken and averaged. Initial elevated BP readings should be confirmed on at least 2 subsequent visits over a period of 1 week or more. A value that is consistently ≥140/90 mm Hg is diagnostic in healthy patients; a value >130/80 mm Hg should be used for those with diabetes or kidney disease and proteinuria.

Initial evaluation of the hypertensive patient focuses on the presence or absence of target organ damage (TOD) and includes a physical examination, blood urea nitrogen/creatinine evaluation, measurement of electrolytes, urinalysis, and an ECG. Further, an assessment of cardiovascular (CV) risk factors with a thorough history and chemistry panel (glucose, cholesterol, and triglycerides) is routinely administered.1 Although the patient in our case study did not exhibit signs or symptoms of a secondary cause of hypertension, this possibility must be entertained in every hypertensive patient.3

### Management

Goal BP management is determined by the presence or absence of TOD, diabetes and other CV risk factors, and other comorbidities. BP goal recommendations are based on results from randomized, controlled trials and recommendations from guidelines committees (Table 1). All patients with hypertension, except those with diabetes or evidence of TOD, should reduce their BP to ≤140/90 mm Hg.1 Those with diabetes mellitus or kidney disease with proteinuria (<1 g/d) should have a target BP of ≤130/80 mm Hg, and those with proteinuria >1 g/d should have a target BP of ≤125/75 mm Hg.1,4,5 Achieving these BP goals requires a combination of lifestyle modifications and pharmacological treatment. Patients with JNC VI stage 2 or 3 hypertension (systolic blood pressure [SBP] ≥160 mm Hg or diastolic blood pressure [DBP] ≥100 mm Hg) and those considered to be in a high-risk group (diabetics or subjects with clinical CV disease) should be prescribed antihypertensive drug therapy.1

Initial lifestyle modifications include weight loss for obese hypertensive patients, modification of alcohol intake to no more than 2 drinks per day, and limiting Na+ intake to ≤100 mmol/d. A number of trials, such as the first Trial of Hypertension Prevention (TOHP-1),6 the follow-up Trial of Hypertension Prevention (TOHP-2),7 the Treatment of Mild Hypertension Study (TOHMS),8 and the Dietary Approaches to Stop Hypertension (DASH) study,9
demonstrate that lifestyle modifications, especially weight loss and a reduction in Na\(^+\) intake, have salutary effects on BP. In the studies with a longer follow-up, there were significantly fewer CV events in the group with both pharmacological treatment and lifestyle modification. High rates of recidivism were seen in the long-term studies, and drug therapy had to be resumed. Thus, although lifestyle modifications can help reduce BP, it is clear that pharmacological therapy is needed to maintain the goal BP. The primary goal of BP reduction is to reach optimal BP by the least intrusive means possible. The choice of antihypertensive agent should be based on the ability of that agent to reduce morbidity and mortality, especially in the areas of cardiovascular and kidney disease. Three classes of drugs (thiazide diuretics, \(\beta\)-blockers, and angiotensin-converting enzyme [ACE] inhibitors) reduce CV events and mortality when used as the initial therapy for hypertension in appropriately designed and implemented clinical trials, and calcium antagonists reduce stroke mortality and morbidity in the elderly in the absence of proteinuria. Thus, calcium antagonists are very useful adjuncts to help achieve BP goals because it takes an average of 3 different antihypertensive medications to achieve BP goals in high-risk individuals.

### Cardiovascular Disease

The process of atherosclerosis is accelerated by hypertension, increasing an individual’s lifetime risk for adverse CV events 2- to 3-fold. The optimal therapy for a hypertensive patient with known coronary artery disease should do more than simply lower blood pressure. Ideally, the drug will help prevent development of ischemia and occurrence of future cardiovascular events. For patients with angina, an additional goal is reduction of symptoms. It is important to avoid antihypertensive agents that could potentiate myocardial ischemia. Vasodilators, specifically first- and second-generation dihydropyridine calcium-channel blockers (DHC-CBs) and hydralazine, cause significant vasodilation, with compensatory increases in heart rate and myocardial contractility. Once coronary blood flow supply is unable to match myocardial oxygen demand, ischemia, often manifested as angina, may result.

### \(\beta\)-Blockers

\(\beta\)-Blockers without intrinsic sympathomimetic activity remain the most effective class of drugs for primary and secondary cardioprotection and are the mainstay of therapy for hypertensive patients with ischemic heart disease. They decrease heart rate and inotropy, thereby reducing myocardial oxygen demand. As primary preventive therapy, \(\beta\)-blockers reduce CVD and all-cause mortality in hypertensive patients. In the post-myocardial infarction setting, \(\beta\)-blockers limit infarct size, suppress ventricular arrhythmias, reduce the incidence of angina, reinfarction and sudden cardiac death, and improve survival. Importantly, \(\beta\)-blockers have proven benefit regardless of the severity of left ventricular dysfunction, but they are typically withheld from heart failure patients until ACE inhibitors have been initiated and titrated.

### ACE Inhibitors

Initially, ACE inhibitors were recommended as standard therapy for all patients who suffered a myocardial infarction with resultant left ventricular dysfunction. Given the results of the Heart Outcomes Prevention Evaluation (HOPE) study, in which ramipril reduced the risk of CV events by 22% compared with placebo, however, ACE inhibitors should be considered for both primary and secondary prevention in all high-risk patients and may be considered as first-line therapy in those patients not able to tolerate \(\beta\)-blockers.

### Calcium Antagonists

Certain calcium-channel blockers (CCBs) can be used if anginal symptoms or hypertension are not controlled with \(\beta\)-blockers and ACE inhibitors or if patients cannot tolerate \(\beta\)-blockers. Verapamil is an approved alternative if \(\beta\)-blockers cannot be tolerated. Caution should be exercised whenever a non-dihydropyridine CCB is combined with a \(\beta\)-blocker. Significant side effects, including profound hypotension, symptomatic bradycardia, and heart block, may occur in 10% to 15% of patients, predominantly those over 65 years of age or with a preexisting heart block. Long-acting DHCCBs could be used to lower BP in this setting, but they do not reduce mortality from ischemic causes of heart failure.

### Kidney Disease/Diabetes

The National Kidney Foundation and the American Diabetes Association guidelines suggest that the target BP should be

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**TABLE 1. Recommended Target BP Goals**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Uncomplicated Hypertension</th>
<th>No TOD or Clinical CV Disease; at Least 1 CV Risk</th>
<th>Diabetes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC VI</td>
<td>&lt;140/90 mm Hg</td>
<td>&lt;140/90 mm Hg</td>
<td>&lt;130/85 mm Hg</td>
</tr>
<tr>
<td>NKF</td>
<td></td>
<td>≥130/80 mm Hg</td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td></td>
<td>≥130/80 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

NKF indicates National Kidney Foundation; ADA, American Diabetes Association.

*JNC VI BP goal also recommended for those with TOD or clinical CV disease.

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**Figure 1.** Recommended algorithm in screening for microalbuminuria.

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These recommendations were based on trials and epidemiological data that, taken together, suggested that the risk for both kidney and CV diseases starts to increase at a DBP as low as 83 mm Hg and a SBP as low as 127 mm Hg. There is now strong evidence that drugs that inhibit the renin-angiotensin system should be a prominent part of the antihypertensive regimen for those with diabetes and/or kidney disease. In a meta-analysis using individual subject data of those with nondiabetic kidney disease, not only did ACE inhibitors reduce the risk of attaining the primary outcomes of end-stage renal disease (ESRD) or doubling of serum creatinine, they also dramatically reduced the amount of proteinuria. Increased urinary albumin excretion or albuminuria is an independent risk factor for both CV and kidney disease, especially in high-risk individuals such as diabetics. Because of this, it is important to evaluate all diabetics, whether hypertensive or not, for albuminuria (Figure 1). We now can use “evidence-based” medicine to decide which class of antihypertensive agent to use. In type 2 diabetes with gross proteinuria, only the use of an angiotensin receptor blocker (ARB) has been proven to reduce the risk of developing ESRD or doubling of serum creatinine.

Conversely, ACE inhibitors or ARBs have been shown to blunt increases in microalbuminuria and, in some cases, normalize it; however, only ACE inhibitors have been shown to reduce the risk of CV events in diabetics, irrespective of whether microalbuminuria was present. An algorithm to achieve BP goal in diabetics is presented in Figure 2.

It is important to note that DHCCBs should not be used in the absence of an ACE inhibitor or ARB in the treatment of hypertension in those with type 2 diabetes or kidney disease. In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, there were fewer fatal and nonfatal myocardial infarctions with enalapril versus nisoldipine ($P=0.001$). In both the Irbesartan in Diabetic Nephropathy Trial (IDNT) and the African-American Study of Kidney Disease (AASK), both trials of participants with renal insufficiency and proteinuria, the amlodipine group had worse renal outcomes than the ACE inhibitor or angiotensin receptor blocker group.

### Elderly Patients

In a meta-analysis, it was found that in untreated subjects who were $\geq$60 years of age, the SBP was a more accurate predictor of mortality and CV events than DBP. This result may be due to the increased arterial stiffness that occurs with aging, leading to a higher SBP and lower DBP, and suggests that antihypertensive therapy in the elderly should focus on SBP rather than DBP, or even concentrate on the difference between the two, ie, pulse pressure. This meta-analysis also confirmed earlier results showing that treatment of hypertension in the elderly significantly reduced the incidence of strokes and coronary heart disease, irrespective of the medication used. JNC VI recommends that diuretics be the first-line therapy in the elderly, and there has been no evidence since its publication that has shown newer agents to be more effective. Of note, a meta-analysis published in 1998 questioned the use of $\beta$-blockers in the elderly, citing evidence that, except in subjects with coronary artery disease, they did not reduce CV morbidity or mortality.

### Conclusion

We presented an elderly man with probable essential hypertension. Assuming that his diagnosis of hypertension is $\leq 130/80$ mm Hg, these recommendations were based on trials and epidemiological data that, taken together, suggested that the risk for both kidney and CV diseases starts to increase at a DBP as low as 83 mm Hg and a SBP as low as 127 mm Hg. There is now strong evidence that drugs that inhibit the renin-angiotensin system should be a prominent part of the antihypertensive regimen for those with diabetes and/or kidney disease. In a meta-analysis using individual subject data of those with nondiabetic kidney disease, not only did ACE inhibitors reduce the risk of attaining the primary outcomes of end-stage renal disease (ESRD) or doubling of serum creatinine, they also dramatically reduced the amount of proteinuria. Increased urinary albumin excretion or albuminuria is an independent risk factor for both CV and kidney disease, especially in high-risk individuals such as diabetics. Because of this, it is important to evaluate all diabetics, whether hypertensive or not, for albuminuria (Figure 1). We now can use “evidence-based” medicine to decide which class of antihypertensive agent to use. In type 2 diabetes with gross proteinuria, only the use of an angiotensin receptor blocker (ARB) has been proven to reduce the risk of developing ESRD or doubling of serum creatinine.

### Table 2. Update and Modification of JNC VI List of Co-Morbid Conditions and Drugs That May Have Favorable Effects on Comorbid Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>$\beta$-blocker, calcium antagonist</td>
</tr>
<tr>
<td>Type 1 diabetes with or without proteinuria</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Type 2 diabetes with microalbuminuria</td>
<td>ACE inhibitor or ARB, not dihydropyridine calcium antagonist alone</td>
</tr>
<tr>
<td>Type 2 diabetes without proteinuria</td>
<td>ACE inhibitor or ARB, not dihydropyridine calcium antagonist alone</td>
</tr>
<tr>
<td>Type 2 diabetes with proteinuria</td>
<td>ARB, not dihydropyridine calcium antagonists alone</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACE inhibitor, ARB, $\beta$-blocker, potassium-sparing diuretic (spironolactone)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Labetolol, methyldopa, calcium antagonists</td>
</tr>
<tr>
<td>Prior myocardial infarction or CAD</td>
<td>$\beta$-blocker and ACE inhibitors</td>
</tr>
<tr>
<td>Prostatism</td>
<td>$\alpha$-blocker (not used alone)</td>
</tr>
<tr>
<td>Kidney insufficiency (nondiabetic)</td>
<td>ACE inhibitor (ARB if ACEI not tolerated)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.
confirmed, the benefits of controlling his BP to reduce both CV and renal disease risk are clear. It is important to identify other comorbidities that he may have, such as diabetes, renal disease, or evidence of TOD, because these will impact what his goal BP should be (Table 1), as well as which antihypertensive agents should be used (Table 2). For patients with coronary heart disease, β-blockers and ACE inhibitors are the first-line therapy, with the option of using a non-dihydropyridine CCB. For patients with nondiabetic renal disease, ACE inhibitors are the initial agent of choice. For patients with type 2 diabetes mellitus, ACE inhibitors reduce cardiovascular risk and ARBs reduce the risk of progression of renal disease in those with overt nephropathy. DHCCBs should not be used in these patients without the concomitant administration of either an ACE inhibitor or an ARB.

References


KEY WORDS: drugs diabetes mellitus coronary disease kidney aging
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