

Hypertension Treatment Guidelines: Practical Implications

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The focus of blood pressure (BP) lowering is to prevent or reduce the risk for cardiovascular and renal events. This rationale forms the basis for the recent guideline statements issued by the Seventh Joint National Committee, the American Diabetes Association, the European Society of Hypertension, and the Kidney Disease Outcomes Quality Initiative. The goal BP in the majority of hypertensive patients should be less than 140/90 mm Hg, with a lower goal of less than 130/80 mm Hg in patients with diabetes or kidney disease. Meta-analyses of clinical trials with renal end points make it clear that the presence of 1 gram or more of proteinuria mandates a BP approaching 115 mm Hg to slow the progression of advanced nephropathy adequately. Compelling indications also exist for the use of certain antihypertensive agents in the setting of kidney dysfunction, diabetes, heart failure, and coronary artery disease. Initiation with 2 antihypertensive agents should be considered strongly for patients with a BP of more than 20 mm Hg greater than the systolic BP goal. This means that those with a goal BP of less than 130 mm Hg should be started on 2 antihypertensive medications with complementary actions when the systolic BP is 150 mm Hg or greater. In patients with kidney disease, reaching the BP goal requires multiple agents that should include an appropriate diuretic and an agent that blocks the renin-angiotensin-aldosterone system to slow the progression of kidney disease.

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Treatment and management guidelines for hypertension have evolved since their inception in the 1970s. The primary purpose of guidelines is to establish a set of general principles that are applicable to the population at large to help reduce cardiovascular morbidity and mortality. Over the past few decades, however, they have become a sort of *holy grail* for some physicians as the only way to do things. In general, conclusions reached and statements made by such committees are derived from a combination of well-designed, published, clinical trials; opinions derived from experience and knowledge of the specific area; and general gestalt. In the end, the ingredients brought by each of the people on the committee are combined and a consensus is reached. Hence, guidelines are not the stone tablets on Mount Sinai but rather a set of general principles, subject to change over time as more data become available.

With that in mind, this article reviews the major guidelines including those from the Seventh Joint National Committee

on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), the American Diabetes Association, the European Society of Hypertension, and the Kidney Disease Outcomes Quality Initiative on blood pressure goals with an emphasis on applicability to patients with kidney disease.¹⁻⁴

Guidelines for Blood Pressure Management

The focus of blood pressure (BP) lowering should be to prevent or reduce the risk for cardiovascular and renal events. In general, guidelines have a number of principles in common; these are summarized in Table 1. JNC 7 tried to alert both patients and physicians to the risks for even small increases in BP levels. The reason for defining prehypertension as the range of systolic BP of greater than 120 and less than 140 mm Hg is that the risk for cardiovascular events doubles with each 20-mm Hg increase in systolic pressure, with the risk starting at 115 mm Hg.⁵ These individuals should undergo lifestyle modifications unless they have diabetes or kidney disease. If either of these conditions is present, treatment with pharmacologic agents should be initiated at a BP of greater than 130/80 mm Hg. In all situations, if there is a compelling

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Table 1 Common Principles and Differences Among Various Guidelines

Similarities
Achievement of a specific BP goal (<140 mm Hg in the general population and <130/80 mm Hg if diabetes or chronic kidney disease is present)
Support use of 2 or more agents if goal BP is not achieved after a reasonable dose adjustment of a single agent
Reduction of cardiovascular morbidity and mortality as an end point of BP reduction
Focus on special populations and specific goals, if any, in those groups
All emphasize lifestyle intervention
Differences
Definitions of risk for various BP differ, especially at the lower end of the scale (eg, prehypertension in JNC 7 and other guidelines)
Approaches to care: although all support use of ACEIs or ARBs for those with kidney disease or diabetes and β-blockers for those with CAD, the JNC 7 specifically supports thiazide diuretics as initial agents for achieving goal BP in most people in the general population, defined as those over 55 years of age

indication for the use of a specific type of antihypertensive drug it should be used (Table 2). The reason for a compelling indication is that a drug, when used as a part of an antihypertensive regimen in clinical trials, markedly reduces the risk for a specific event(s) (eg, angiotensin-receptor blockers in diabetic nephropathy).¹

The staging of BP beyond this range remains similar among all guidelines and is divided by 20-mm Hg increments in systolic BP and 10-mm Hg increments in diastolic BP, as represented by the JNC 7 (Table 3). Patients with stage 1 hypertension should receive lifestyle modifications and pharmacologic therapy (beginning with a thiazide-type diuretic, if appropriate) unless goal BP is achieved without drugs.¹ Patients with confirmed JNC 7 stage 2 hypertension strongly should be considered for initiation of treatment with 2 different antihypertensive medications, usually in combination (Tables 3 and 4).

BP Goal

In a majority of hypertensive patients, the goal should be a systolic BP of less than 140 mm Hg and a diastolic BP of less than 90 mm Hg. For patients with diabetes or kidney disease, the recommended goal is lower (systolic BP <130 mm Hg and diastolic BP <80 mm Hg).^{1,2,4} The United Kingdom Prospective Diabetes Study (UKPDS), which randomized 1,148 type 2 diabetic patients to a BP of either less than 180/105 or less than 150/85 mm Hg, showed that improved BP goals improves cardiovascular outcomes. After a median follow-up period of 8.4 years, those treated to the lower BP goal achieved an average BP of 144/82 mm Hg compared with those patients randomized to the higher goal, who achieved an average BP of 153/87 mm Hg. This 10/5-mm Hg decrease in BP resulted in 24% fewer diabetes-related end points, 32%

fewer deaths, 44% fewer strokes, and 37% fewer microvascular complications.⁶ The recommendation to achieve a diastolic BP of less than 80 mm Hg in diabetic patients is supported by the Hypertension Optimal Treatment study, in which the greatest reductions in major cardiovascular (CV) events were seen in those patients randomized to the diastolic BP target of 80 mm Hg or less.⁷ In addition, a review of renal outcome studies by the National Kidney Foundation showed a marked reduction in risk for CV events and kidney disease progression in those with diabetes when a lower BP (ie, <130 mm Hg systolic) is achieved (Fig 1).⁸

This lower level of BP can lead to major cost savings as noted in a cost-effectiveness analysis of American epidemiologic and clinical trial data. This analysis showed that, for diabetic patients age 60 and older, achieving a BP goal of less than 130/85 saved money overall, as long as the annual cost to lower BP from 140/90 mm Hg was less than \$414. This cost savings resulted from a reduction in high-cost complications of hypertension, including myocardial infarction (MI), stroke, ESRD, and heart failure.⁹

For patients with kidney disease, JNC 7 and Kidney Disease Outcomes Quality Initiative also recommend a BP target of less than 130/80 mm Hg. Data from meta-analyses of people with nondiabetic kidney disease, especially those with albuminuria greater than 300 mg/d, showed that achieving a systolic BP of 110 to 130 mm Hg is associated with optimal preservation of kidney function.¹⁰ This relationship is not as strong for people with stage 1 or 2 kidney disease and microalbuminuria, in which case a BP level between 130 and 139 mm Hg is quite reasonable based on data from the African-American Study of Kidney Disease and Appropriate Blood Pressure Control in Diabetes study.^{11,12}

One of the perceived limitations to achieving these lower levels of BP is the fear that lowering BP too far might be harmful, known as the *J curve*. It has been noted that patients with clinically apparent coronary disease treated to a diastolic BP level of less than 85 mm Hg had higher rates of MI than those whose on-treatment diastolic BP was between 85 and 90 mm Hg. However, trials such as the Systolic Hypertension in the Elderly Program treated individuals to an average diastolic BP of 67 mm Hg and prevented MIs compared with those treated to an average of 71 mm Hg.¹³ Similarly, analysis of the Systolic Hypertension in the Elderly Program provided no evidence for an increase in the risk for stroke with decreasing levels of on-treatment systolic BPs.¹⁴ Moreover, both the Hypertension Optimal Treatment and UKPDS 38 studies provided proof that intensive BP lowering was not harmful.

The *J-curve* effect also has been noted for kidney disease progression, especially for those with greater than 1 g/d of proteinuria. A systolic BP of greater than 110 mm Hg but less than 130 mm Hg should be maintained in such individuals or the benefits of lower BP are diminished.¹⁰

Lifestyle Modifications

Both guideline statements highlight the need for lifestyle intervention as a primary mode of lowering BP, although the adherence and compliance with such measures outside of

Table 2 Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

Compelling Indication*	Recommended Drugst					Clinical Trial Basis†
	Diuretic	β -Blocker	ACEI	ARB	Calcium-Channel Blocker	
HF	•	•	•	•		ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS SOLVD, AIRE, TRACE, Val HEFT, RALES, CHARM
Post-MI		•	•			ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHEBUS
High coronary disease risk	•	•	•		•	ALLHAT, HOPE, ANBP2, LIFE, CONVINCED, EUROPA, INVEST
Diabetes	•	•	•	•	•	NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•		NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	•		•			PROGRESS

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology /American Heart Association; ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin-receptor blocker; BHAT, Beta-Blocker Heart Attack Trial; CCB, calcium channel blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCED, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHEBUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial.

NOTE. A dot means this class of drugs was tested as part of an armamentarium of BP-lowering drugs in the given condition. It was shown to reduce either CV events or in the case of kidney disease the progression of nephropathy.

Modified from the JNC 7 guidelines.¹

*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 BP.

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

formal trials has been unsatisfying. The high points of controlled studies on BP as affected by lifestyle modification are summarized in Table 5.

Most guideline reports recommend weight loss for obese hypertensive patients, modification of dietary sodium intake to 100 mmol/d or less (2.4 g sodium or 6.0 g sodium chloride), and modification of alcohol intake to no more than 2 drinks per day.^{1,15} The recommendations for restriction of sodium intake and alcohol restriction are supported by multiple trials.¹⁶⁻²² Smoking cessation also has been recommended because the effects of tobacco have been shown to increase BP transiently.^{23,24} Additionally, guideline reports also recommend an increase in physical activity for all patients with hypertension who have no specific condition that would make such a recommendation not applicable or not safe.²⁵ For many patients, however, these suggestions are not acceptable or already have been implemented; therefore, drug therapy may be indicated even sooner in these situations.

The lack of proof for lifestyle modifications to reduce CV events does not mean that physicians should abandon non-drug treatments. The suggested lifestyle changes may well prevent or delay the virtually inevitable increase in BP that occurs, especially in those patient over age 40 who are prehypertensive (systolic BP >120 but <139 mm Hg).

Pharmacologic Approaches

The ultimate goal of hypertension treatment is to reduce cardiovascular and renal morbidity and mortality; the short-term goal is to achieve the recommended goal BP by using the least intrusive means possible. *Intrusive* has several interpretations: economic, office visits, adverse effects, and convenience. The choice of the drug with which to begin therapy is probably the most important decision the clinician must make when treating hypertensive patients. Approximately one third of patients will respond to the first choice and can tolerate most rational options. However, the majority of patients will need additional or

Table 3 Classification of BP Stages and Treatment Approaches for Adults

BP Classification	Systolic BP* mm Hg	Diastolic BP* mm Hg	Lifestyle Modification	Initial Drug Therapy	
				Without Compelling Indication	With Compelling Indications
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated	Drug(s) for compelling indications‡
Stage 1 hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB, or combination	Drug(s) for the compelling indications‡
Stage 2 hypertension	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed

Abbreviations: BB, β -blocker; CCB, calcium-channel blocker.

*Treatment determined by highest BP category.

†Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

Table 4 Fixed-Dose Combination Antihypertensive Drugs

Combination Type*	Fixed-Dose Combination, mg*
ACEIs and CCBs	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20) Enalapril-felodipine (5/5) Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25) Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25) Enalapril-hydrochlorothiazide (5/12.5, 10/25) Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5) Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25) Moexipril-hydrochlorothiazide (7.5/12.5, 15/25) Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5) Eprosartan-hydrochlorothiazide (600/12.5, 600/25) Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5) Losartan-hydrochlorothiazide (50/12.5, 100/25) Olmesartan medoxomil-hydrochlorothiazide (20/12.5, 40/12.5, 40/25) Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5) Valsartan-hydrochlorothiazide (80/12.5, 160/12.5, 160/25)
BBs and diuretics	Atenolol-chlorthalidone (50/25, 100/25) Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25) Metoprolol-hydrochlorothiazide (50/25, 100/25) Nadolol-bendroflumethiazide (40/5, 80/5) Propranolol LA-hydrochlorothiazide (40/25, 80/25) Timolol-hydrochlorothiazide (10/25)
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50) Reserpine-chlorthalidone (0.125/25, 0.25/50) Reserpine-chlorothiazide (0.125/250, 0.25/500) Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50) Spironolactone-hydrochlorothiazide (25/25, 50/50) Triamterene-hydrochlorothiazide (37.5/25, 75/50)

Abbreviations: BB, beta-blocker; CCB, calcium channel blocker.

Adapted from the JNC 7.¹

*Some drug combinations are available in multiple fixed doses.

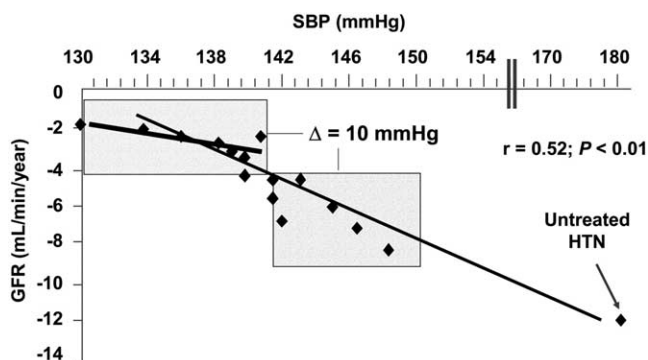


Figure 1 Relationship between decrease in GFR and BP achieved in clinical trials. Note that studies included in this analysis included IDNT, RENAAL, the Modification of Diet and Renal Disease, the Appropriate Blood pressure Control in Diabetes study, and long-term studies by Hannedouche and Bakris (unpublished data). Adapted from Bakris⁸

different treatment. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 60% of patients who achieved a BP of less than 140/90 mm Hg required 2 or more antihypertensive agents. The preferred first-line antihypertensive drug class for most patients now has been defined by data from clinical trials.¹

Practical Considerations in the Approach to Achieve BP Goal

A general approach to achieve BP goals is put forth by all guideline committees. A summary paradigm for those with kidney disease or diabetes is shown in Figure 2. Otherwise, a paradigm put forth by the JNC 7 certainly is appropriate for people age 50 or older (Table 3). In younger populations, a recent meta-analysis clearly showed that use of any antihypertensive drug class lowers CV risk as long as it achieves the BP goals.²⁶

Specific Indications for Pharmacologic Agents: Compelling Indications

All guidelines recognize that hypertensive patients often present with concomitant illnesses or conditions that benefit from therapy with specific antihypertensive drugs. Agents used to lower BP with such conditions have been derived from clinical trials and are shown in Table 2.

Perhaps most importantly, ALLHAT directly compared the thiazide-like diuretic, chlorthalidone, with 3 newer antihypertensive drugs: amlodipine (a calcium antagonist [CA]), doxazosin (an α -blocker), and lisinopril (an angiotensin-converting–enzyme inhibitor [ACEI]). The doxazosin arm was stopped early because it showed a significant increase (compared with the diuretic) in CV disease, an end point that included congestive heart disease, heart failure, and peripheral arterial disease.²⁷ Although there were no significant differences between the diuretic and either of the 2 remaining newer drugs in the primary end point (congestive heart disease, death, or nonfatal MI), chlorthalidone was significantly better at preventing heart failure than the other 2 drugs, and also better in reducing BP, stroke, and CV events than lisinopril. Because of its superiority in preventing 1 or more CV complications of hypertension in people over the age of 55 years and its lower cost, a thiazide-type diuretic was recommended as initial antihypertensive drug therapy by JNC 7 for most people with stage 1 hypertension and without compelling indications for other agents.

Note that the recent World Health Organization/International Society of Hypertension's Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis of all clinical CV outcome trials, including the ALLHAT, showed that all classes of antihypertensive agents tested reduced CV events and one class was not superior to the others—it is the level of BP reduction achieved that influences outcome.²⁸

In specific populations, certain antihypertensive agents may be preferable to others to reduce the risk for CV events.

Table 5 Summary of Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Recommendation	Approximate SBP Reduction (Range)*
Weight reduction	Maintain normal body weight (body mass index, 18.5–24.9 kg/m ²)	5–20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter-weight persons	2–4 mm Hg

NOTE. For overall cardiovascular risk reduction, stop smoking. Abbreviations: DASH, Dietary Approaches to Stop Hypertension. Adapted from JNC 7.¹

*The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

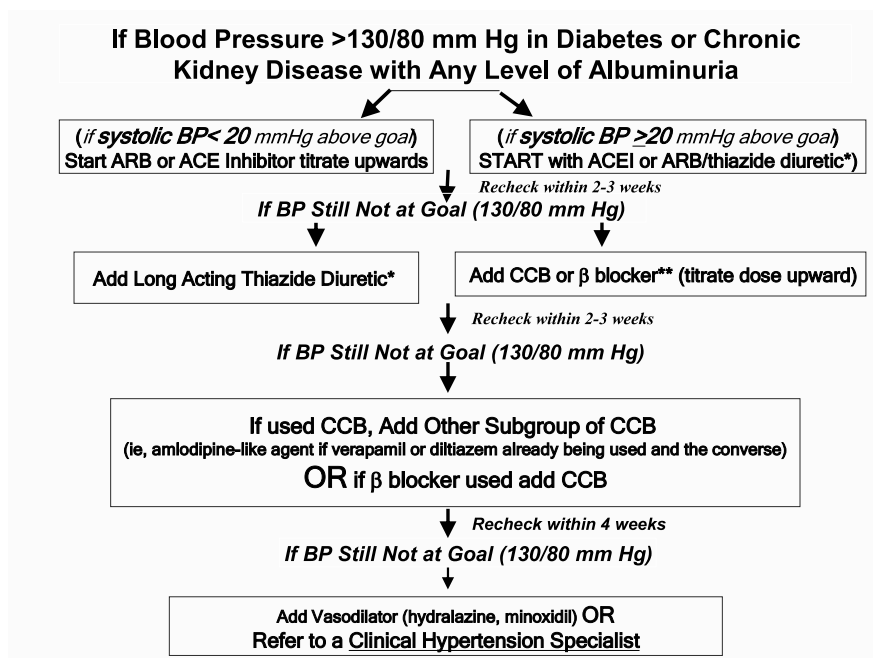


Figure 2 Proposed paradigm to achieve BP goals in people with diabetes or kidney disease.

In ALLHAT, African-American patients treated with lisinopril had poorer outcomes of stroke, BP reduction, and combined CV disease compared with African-American patients treated with chlorthalidone; however, this difference was not noted when comparing amlodipine with chlorthalidone. ACEIs, when used in the absence of diuretics, as was the case in ALLHAT, are not ideal for optimally lowering BP in African Americans.^{29,30}

Sequence of Additional Drugs in the Antihypertensive Cocktail

For those older individuals started on a diuretic, most people would consider an ACEI, angiotensin-receptor blocker (ARB), β -blocker, or CA to be a reasonable second choice. β -blockers have been the conventional second-line treatment in many previous clinical trials that used a diuretic as the initial treatment. An ARB (candesartan) was more effective than placebo and/or other treatments (not including an ACEI) after the initial diuretic in the recently completed Study on COgnition and Prognosis in the Elderly trial, which showed significant stroke reduction.³¹ The most successful trial of ACEI therapy in CV event protection was the Heart Outcomes Prevention Evaluation (HOPE), for which ramipril or placebo was given in addition to other required antihypertensive therapy (ie, as add-on treatment).³² Although the overall BP reduction with ramipril was said to be only 3/2 mm Hg compared with placebo, some patients were not hypertensive at enrollment, and this (as well as the possible addition of other antihypertensive drugs to the placebo arm) may have diluted the BP changes. Nonetheless, this trial showed significant reductions in the composite CV end point (stroke, MI, or CV death), as well as in each its individual components, in both diabetic and nondiabetic patients.

A number of fixed-dose combinations with diuretics exist including those with β -blockers, ACEIs, and ARBs. Such

combinations, either the individual agents or in fixed-dose, are suggested as second-line therapy by all major guideline groups.^{1,3} Moreover, although there are no outcome trials with such combinations as yet, the JNC 7 and guidelines by the American Diabetes Association and the National Kidney Foundation recommend their use for those who are greater than 20/10 mm Hg higher than the BP goal. The first data from a CV outcome trial to compare 2 different fixed-dose combinations will be completed in 2008, the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension trial.³³

Factors to Consider When Constructing an Antihypertensive Drug Regimen

The following factors always should be considered when antihypertensive drug therapy is chosen: efficacy, comorbidities, safety, patient demographics, special situations (eg, pregnancy), dosing schedule, drug interactions, adherence, mechanism(s) of action, and cost. These considerations are important not only in the choice of initial therapy, but also for subsequent antihypertensive agents. In recent clinical trials, most patients required a minimum of 2, and in many cases 3, drugs to achieve the goal BP; a recent meta-regression analysis suggested that there is only a 2.5% chance of achieving the target BP with monotherapy when the initial diastolic BP is greater than 10 mm Hg higher than the goal BP.

Efficacy

Five classes of medications (thiazide diuretics, β -blockers, long-acting CAs, ACEIs, and ARBs) have been shown to reduce CV or renal end points when used as initial therapy as part of a group of medications to lower BP in appropriately designed and implemented clinical trials. Other drugs such as peripheral sympatholytics (reserpine and guanethidine),

centrally acting α -agonists (α -methyl dopa), and vasodilators (hydralazine) also have been used in clinical trials as the second, third, or even fourth agent added to achieve BP control. None of these medications is an option for initial therapy because they are tolerated poorly or need to be taken together with other drugs to lower BP effectively in the long term.

α -blockers are a valuable adjunctive therapy, but not as initial therapy, based on the findings of ALLHAT.²⁷ α/β -blockers are well tolerated and effective as monotherapy, but have yet to be shown to reduce clinical end points in hypertensive patients without heart failure.

The blockade of aldosterone with low-dose spironolactone has been shown to reduce systolic and diastolic BP by 26/11 mm Hg at 6 months in patients with resistant hypertension.^{34,35} Selective blockade of aldosterone with eplerenone has been shown to be effective in the treatment of hypertension in patients with or without renin-angiotensin blockade.^{36,37} However, there have been no long-term trials to support its use to reduce CV end points as primary therapy.

Comorbidities and Other Risk Factors

The Joint National Committee recognized that individual patients may have certain comorbid conditions for which a specific agent may be appropriate, even though no clinical trial data exist to prove it. These specific indications try to codify clinical judgment, which any reasonable clinician would use to care for all the health needs of his or her patients. For the most part, these recommendations do not add classes of drugs to the list of those that already are favored because of a reduction in clinical end points, but instead alter the choice of which class should be selected for initial therapy (Table 2). Thus, other risk factors and active clinical problems sometimes can influence the choice of specific therapy for individual patients.

Presence of Albuminuria/Proteinuria

Microalbuminuria is an independent predictor of CV risk in patients with diabetes and in the healthy population.^{38,39,40} The achievement of BP goal with all commonly prescribed first-line drugs tends to reduce microalbuminuria (MA); however, ACEIs and ARBs have the most data showing reductions in MA and delaying its progression to proteinuria.^{1,41} Both ACEIs and non-dihydropyridine (DHP) CAs reduce albuminuria and together have additive antialbuminuric effects.^{42,43} The effects of different classes of antihypertensive agents on proteinuria in the context of kidney disease progression are summarized in Table 6.

The ACEIs and ARBs are the antihypertensive agents that reduce proteinuria most consistently and together have additive antiproteinuric effects without substantially lowering BP.⁴⁴ A high Na^+ intake blunts the antiproteinuric and antihypertensive effects of ACEIs and ARBs, so restricting dietary Na^+ is recommended for patients with microalbuminuria or proteinuria.⁴⁵

Kidney Dysfunction

Lowering BP will slow the progression of nephropathy. The recent African-American Study of Kidney disease and hyper-

Table 6 Relationship Between Changes in Proteinuria and Kidney Disease Progression With BP Treatment

Increased Time to Dialysis (30% to 35% Proteinuria Reduction)	No Change in Time to Dialysis (No Proteinuria Reduction)
Captopril Trial AASK Trial RENAAL IDNT	DHPCCB arm-IDNT DHPCCB arm-AASK

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; DHPCCB, Dihydropyridine Calcium Channel Blocker.

tension showed no additional benefit to lowering systolic BP to less than 130 mm Hg for nondiabetic renal disease, as compared with less than 140 mm Hg, but many of these people had microalbuminuria, not proteinuria. Conversely, in the Modification of Diet and Renal Disease study, the progression to ESRD in patients with proteinuria was reduced in those assigned to the intensive goal of a mean arterial BP of 92 mm Hg.⁴⁶ Based on current guidelines the greater the level of proteinuria the more important it is to achieve the currently recommended BP goal. ARBs and ACEIs will slow the progression of diabetic and nondiabetic nephropathy, assuming they are given with sufficient other drugs to reduce BP to less than 140/90 mm Hg.⁴⁷

The use of combination therapy with ACEIs and ARBs also has been evaluated in clinical trials. In the COOPERATE trial, patients with nondiabetic kidney disease and a mean protein excretion of 2.5 g/d were randomized to losartan 100 mg/d, trandolapril 3 mg/d, or a combination of the 2 drugs.⁴⁴ Patients in the combined treatment group had a 60% to 62% reduction in the primary end point of time to doubling of the serum creatinine concentration or ESRD compared with either the losartan or trandolapril groups.

Despite the preponderance of evidence from many long-term clinical trials, there is a general hesitancy among some clinicians to prescribe ACEIs (or ARBs) for patients with a serum creatinine level greater than 1.4 mg/dL because the level often increases after the drug is given. Analysis of long-term clinical trials has confirmed that this reduction in renal function plateaus within a month.⁴⁸ If the serum creatinine level increases by greater than 30%, or continues to increase after 3 months of therapy then volume depletion, unsuspected left ventricular (LV) dysfunction, or bilateral renal artery stenosis should be considered.

There also are concerns about hyperkalemia associated with an ACEI or ARB; this should be worrisome only if the serum K^+ increases 0.5 mEq/L or greater and the baseline level already is greater than 5 mEq/L. In the combination arm with losartan and trandolapril in the COOPERATE trial, the incidence of hyperkalemia was 8% (7 of 88 patients), which was treated successfully with dietary education or potassium binders.

Blockade of the renin-angiotensin-aldosterone system

with ACEIs or ARBs does not necessarily result in decreased plasma aldosterone levels.^{49,50} Levels of plasma aldosterone are increased in patients with chronic renal insufficiency and may play a role in renal injury.^{51,52} Furthermore, blockade of aldosterone in patients already treated with ACEIs may have beneficial effects in hypertension, chronic kidney disease, and cardiac disease.⁵³ Initial data suggest that the blockade of aldosterone results in decreased proteinuria in patients with renal insufficiency.^{54,55} Future studies are needed in larger groups of patients to elucidate further the effect of aldosterone blockade on renal end points and the safety of these medications in this patient population.

Thus, although any class of antihypertensive agent may be used to achieve the current recommended lower level of BP to preserve renal function, certain principles should be kept in mind: (1) BP will seldom, if ever, be controlled adequately in patients with significant renal impairment (serum creatinine >1.5 mg/dL) without the use of a loop diuretic; (2) a long-acting loop diuretic (such as torsemide) is preferred; furosemide or bumetanide should be given twice daily; and (3) combinations of antihypertensive medications will be needed to achieve the goal BP. One of these drugs should be an ACEI or ARB. Some investigators recommend both an ACEI and an ARB simultaneously, as it has been shown consistently to lower proteinuria levels further, although it may not lower BP further if maximal doses of both are used.

Glucose, Insulin, and New-Onset Diabetes Mellitus

Some antihypertensive drugs, namely diuretics and most β -blockers, affect glucose handling and either can worsen or improve insulin sensitivity.^{27,56,57} The magnitude and direction of the drug-induced changes seen in glucose and insulin are very similar to what occurs with lipids. Peripheral α -blockers and some ACEIs (eg, captopril, enalapril,trandolapril, and perindopril) improve insulin sensitivity.^{58,59} In the HOPE, the Captopril Primary Prevention Project, Losartan Intervention For Endpoint reduction in hypertension study, ALLHAT, International Verapamil-Trandolapril Study (INVEST), Candesartan in Heart Failure-Assessment or Reduction in Mortality (CHARM), and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) studies, incident diabetes was less common when an ACEI or ARB was the randomized choice.⁶⁰⁻⁶³ Patients at high risk for developing diabetes, that is, those who are obese with glucose intolerance or other components of the metabolic syndrome, may reduce their risk for new-onset diabetes by using ACEI or ARB treatment.

Hypertensive Patients With Diabetes Mellitus

The combination of hypertension and diabetes mellitus confers a much greater risk for CV events and renal failure than either one alone. According to all guideline statements, type 1 diabetic patients with renal impairment and proteinuria should receive a blocker of the renin-angiotensin system

along with a diuretic and other agents needed to achieve the BP goal.

All recently published guidelines for the treatment of hypertension in type 2 diabetic patients include a lower-than-usual goal for BP during treatment (<130/80 mm Hg, as discussed earlier) and a recommendation for a blocker of the renin-angiotensin system to be a component of the antihypertensive drug regimen (ie, initial drug therapy).¹⁻³ An ARB has been beneficial in 2 studies with renal end points (Irbesartan Diabetic Nephropathy Trial (IDNT), Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)), and for CV event prevention in the diabetic subset of the Losartan Intervention For Endpoint reduction in hypertension study.^{61,64,65} An ACEI provided impressive CV event reduction in the micro-HOPE study, although the number of patients reaching ESRD was only 18, and the data from outcome studies in people with established nephropathy are restricted to surrogate markers.^{41,66} In UKPDS 38, there was no significant difference between either captopril or atenolol as initial therapy, whereas the group achieving the lower BP did much better. These results also must be viewed in the context of achievement of the BP goal. Some argue that BP control, rather than how it is accomplished, is the key factor in reducing CV and renal events in patients with type 2 diabetes.

The role of CAs in the treatment of hypertension in diabetic patients has been controversial although some clear information is now available. The following statements about CA use in diabetes are defensible. First: differences in outcome exist between the 2 subclasses of CAs depending on the degree of initial proteinuria and kidney function. The use of DHP CAs in the absence of ACEIs or ARBs to reduce CV risk in people with normal kidney function in those with diabetes is warranted as evidenced by data from ALLHAT²⁶ and VALUE⁶³ and in the subgroup of those with diabetes and stage 2 nephropathy (ie, glomerular filtration rate, 60-89 mL/min) in the Syst-Eur study.⁶⁷ However, in those with advanced nephropathy (ie, stage 3 and beyond and glomerular filtration rate <60 mL/min), DHP CAs were significantly less effective in reducing renal events (but not CV events) when compared with an ARB in the IDNT study.⁶⁵ This also has been observed in post hoc analyses of other clinical trials.^{68,69} The use of DHP CAs, however, if used with an ACEI, ARB, or diuretic, does not distract from the benefit of the renin-angiotensin system–blocking agents and further lowers BP with resultant benefit of stroke reduction in all trials.

With regard to nephropathy progression, both the National Kidney Foundation and JNC as well as the American Diabetes Association recommend that DHP CAs be used as the third-line therapy after a diuretic and either an ACEI or ARB,^{2,4} favoring non-DHP CAs over DHP CAs because they further reduce proteinuria and slow the progression of diabetic nephropathy.^{4,68,69} Moreover, in the INVEST study, a comparison of non-DHP CAs with β -blockers in over 22,000 people with hypertension and coronary artery disease showed no difference in CV outcomes.⁷⁰

In those with diabetes, reducing the BP to goal may be a more important factor in reducing mortality and preserving

renal function than the initial drug chosen to do so because it usually takes several drugs to achieve the target BP of less than 130/80 mm Hg.

Heart Failure

Hypertension is also a major risk factor for the subsequent development of heart failure (HF), typically many years later.⁷¹ For many undertreated or untreated hypertensive patients, left ventricular hypertrophy (LVH) is an important intermediate step, resulting in hypertensive heart disease with impaired LV filling and increased ventricular stiffness. This type of HF (commonly seen in up to 40% of hospitalized patients with an antecedent history of hypertension) now is called HF with preserved systolic function.⁷² The treatment of hypertension in patients with HF and preserved systolic function has not been as well studied. Most investigators recommend using either diuretics and drugs that reduce the heart rate, increase diastolic filling time, and allow the heart muscle to relax more fully such as β -blockers or non-DHP CAs. The main long-term trial involving these patients is the third arm of the CHARM-Preserved trial evaluating congestive heart failure patients with ejection fraction greater than 40%, which showed that candesartan was associated with fewer hospitalizations than placebo.⁷³

The more common type of systolic dysfunction associated with a reduced LV ejection fraction often is caused by previous MI (for which hypertension is also an important risk factor). In a meta-analysis of placebo-controlled clinical trials in hypertension, there was a 42% reduction in HF incidence among hypertensive patients randomized to either a low-dose diuretic or a β -blocker.⁷⁴

Patients with low ejection fractions (systolic HF) improve both their BP and long-term prognosis with ACEIs and diuretics, to which β -blockers, spironolactone, and/or other drugs can be added as needed.^{75,76} Regarding blockade of the renin-angiotensin system, the ARB, valsartan, was as effective as captopril or the combination of the 2 drugs in patients with MI and HF in reducing mortality and cardiovascular mortality, although the combination of the drugs did not result in further mortality reduction.⁷⁷ However, the combination of ACEIs and ARBs in the Valsartan in Heart Failure and CHARM trials, showed that the combination resulted in a significant reduction in hospital admissions related to heart failure.^{73,78}

The use of DHP CAs in the absence of ACEIs or ARBs, although appropriate, remains controversial because no study has shown a benefit in heart failure or kidney disease progression outcomes with DHP CAs in the absence of an ACEI or ARB.⁴⁷ Moreover, the DHP CAs are associated with the highest incidence of new HF in hypertension trials.⁶²

The blockade of aldosterone with spironolactone or eplerenone may provide additional benefit in patients with severe LV dysfunction. In both the Randomized Aldactone Evaluation Study and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, mortality was reduced significantly by 30% with spironolactone and

15% with eplerenone compared with placebo.^{75,76} Selective blockade of the aldosterone receptor with eplerenone appears to reduce the sexual side effects (gynecomastia, menstrual irregularities, and decreased libido) typically associated with spironolactone. No difference in the incidence of gynecomastia, breast pain, or impotence was noted in the patients receiving eplerenone versus placebo in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.

Coronary Artery Disease

Because hypertension is a major risk factor for coronary artery disease (CAD), it is not surprising that a large number of patients have both conditions. It is unlikely on ethical grounds that a placebo-controlled trial will be performed with any single antihypertensive drug in such patients. The presence of CAD in a patient with hypertension is likely to influence both the choice of drugs used to treat the patient and the BP goal to be achieved. Because both β -blockers and CAs are effective antihypertensive agents with major antianginal efficacy, they are often the preferred agents for initial treatment, especially in the common setting of unstable angina pectoris.⁷⁹ A recent meta-analysis suggested that the former are more effective, although the latter are used more commonly.⁸⁰ The recent HOPE trial showed a large survival benefit for high-risk hypertensive patients (most of whom had known CAD) who were treated with ramipril. Likewise, in the European trial On reduction of cardiac endpoints with Perindopril in stable coronary Artery disease, the perindopril group had a relative risk reduction of 20% in the primary end point of composite CV death, nonfatal MI, and cardiac arrest with successful resuscitation.⁸¹ These findings have been interpreted by some as evidence in favor for this class of medications in the management of all hypertensive patients with CAD.

The issue of how low to reduce BP in the setting of CAD has been controversial until the results of INVEST.⁸² In this trial a strategy of a non-DHP CA, verapamil, was compared with a β -blocker, atenolol, for CV events and death. Both treatment groups were allowed to use the ACEI trandolapril; however, the verapamil group had a significantly increased usage of the ACEI compared the β -blocker group. The results showed no difference in outcome, with lower morbidity and less new-onset diabetes in the verapamil group. Because coronary artery filling occurs during diastole, reducing perfusion pressure at this time might increase coronary ischemia, thus agents such as verapamil or a β -blocker in concert with an ACEI should be included in the antihypertensive regimen of such patients.

CV disease is the most common cause of death in chronic kidney disease and renal insufficiency is an independent risk factor for CVD death.⁸³ Patients with ESRD have a 5-fold increase of in-hospital and postdischarge mortality compared with patients with normal renal function after acute MI, whereas those with even mild renal

insufficiency (creatinine clearance >50 mL/min and <75 mL/min) have a 2-fold increase of in-hospital and postdischarge mortality.⁸⁴ From the United States Renal Data System, treatment of classic risk factors for CV disease in dialysis patients is poor, with 18% of patients on aspirin, 21.9% on ACEIs, and 9.2% on statins.⁸⁵ Aggressive management of CV disease risk factors may improve the increased CV mortality of chronic kidney disease patients.

Medication Adherence

Overall, fewer than 50% of patients continue taking the initially prescribed antihypertensive drug therapy for 4 years.⁸⁶ The proportion of patients who properly adhere to therapy improves only modestly when the drugs and medical care are provided free of charge.⁶² About 10% of the overall expenditures on hypertension in the United States are wasted because of nonadherence to medical advice and antihypertensive drug therapy.

Summary and Recommendations

Drug therapy is indicated in all hypertensive patients if the goal BP ($<140/90$ mm Hg in hypertensive patients, $<130/80$ mm Hg in patients with diabetes and renal disease) is not reached with lifestyle modifications alone. For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, then the initiation of therapy with 2 agents should be considered. For patients with renal disease and nephropathy, reaching the BP goal often requires a diuretic, and blockade of the renin-angiotensin system with ACEIs or ARBs is essential in slowing the rate of progression of kidney disease.

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