

CARDIOLOGY I

HYPERTENSION: EVIDENCE-BASED UPDATES AND CLINICAL CONTROVERSIES

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Learning Objectives

1. Devise evidence-based treatment plans for managing hypertension.
2. Analyze the use of cardiovascular end points in outcome-based trials and apply these analyses to selecting antihypertensive drugs to reduce the incidence of various cardiovascular (CV) outcomes.
3. Analyze clinical trial findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Blood Pressure Lowering Arm.
4. Judge the value and limitations of the data derived from the subgroup analyses of the ALLHAT in the management of hypertension.
5. Justify pharmacotherapy regimens for treating hypertension in patients with a history of stroke, chronic stable angina, or chronic kidney disease based on new evidence and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendations.
6. Assess the relevant differences between hydrochlorothiazide and chlorthalidone in the management of hypertension.
7. Distinguish within class differences among β -blockers and their ability to reduce CV and other clinical outcomes in patients with hypertension.
8. Apply special considerations and analyze clinical controversies surrounding the treatment of hypertension in the elderly.

Introduction

The American Heart Association estimates that 65 million Americans have hypertension, making it the most common form of cardiovascular disease (CVD). Worldwide estimates indicate that this prevalence will increase 60% by the year 2025. Hypertension is considered a major cardiovascular (CV) risk factor, and reducing elevated blood

pressure (BP) is a primary strategy to reduce CV morbidity and mortality.

National guidelines for the diagnosis and treatment of hypertension are sponsored by the National Heart, Lung and Blood Institute. The most recent version is the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) published in 2003. Although JNC 7 provides consensus recommendations, more recent evidence must be considered when selecting antihypertensive pharmacotherapy. Newer data have either reinforced JNC 7 recommendations or created clinical controversies. The purpose of this chapter is to critically review newer evidence, compare findings to current recommendations, discuss and clarify certain treatment controversies, and ultimately to provide the reader with information to manage hypertension based on current best evidence.

Overview

Definitions

Systolic blood pressure (SBP) is more predictive of CVD than diastolic blood pressure (DBP) in patients age 50 or older and is frequently elevated in the elderly. The term elevated BP indicates a higher than normal BP measurement in a patient without the diagnosis of hypertension. Prehypertension describes patients who have BP measurements that are higher than normal but lower than the limit that defines hypertension. Patients with hypertension have repeated BP elevations within the diagnostic range for hypertension and subsequently have an increased risk of CVD that is incrementally related to their BP elevation. The risk of CVD doubles with every 20/10 mm Hg increase in BP starting at a value of 115/75 mm Hg.

Diagnosis

The diagnosis of essential hypertension is based on repeated BP measurements and only when secondary hypertension is ruled out. Table 1-1 explains the JNC 7 classification of BP. A diagnosis of hypertension requires a

Abbreviations in this Chapter

ACE	Angiotensin-converting enzyme	HOT	Hypertension Optimal Treatment
ACTION	A Coronary disease Trial Investigating Outcome with Nifedipine	JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial	MI	Myocardial infarction
ARB	Angiotensin receptor blocker	PEACE	Prevention of Events with Angiotensin Converting Enzyme inhibition
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial	PROGRESS	Perindopril Protection Against Recurrent Stroke Study
BP	Blood pressure	RAAS	Renin-angiotensin-aldosterone system
CAMELOT	Comparison of Amlodipine versus Enalapril to Limit Outcomes of Thrombosis	REIN-2	Ramipril Efficacy In Nephropathy 2
CCB	Calcium channel blocker	SBP	Systolic blood pressure
CHD	Coronary heart disease	SHEP	Systolic Hypertension in the Elderly Program
CV	Cardiovascular	VALUE	Valsartan Antihypertensive Long-term Use Evaluation
CVD	Cardiovascular disease		
DBP	Diastolic blood pressure		
EUROPA	EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease		

BP measurement greater than or equal to 140/90 mm Hg measured on different clinical encounters. Blood pressure should be measured at least twice during an individual clinical evaluation, with the average value used for classification purposes.

Quality Patient Care— National Treatment Guidelines

JNC 7 Goals and Treatment Recommendations Therapeutic Goals

The purpose of treating hypertension is to prevent associated morbidity and mortality. The JNC 7 recommends a goal BP of less than 140/90 mm Hg for most patients with hypertension. Although epidemiological studies suggest that lower BP values are associated with fewer CV events, prospective data have not demonstrated lower rates of CV events with BP goals below JNC 7 recommendations. The only exception is for patients with diabetes or chronic kidney disease; recommended goal BP values are less than 130/80 mm Hg in these patients. In patients with diabetes, this goal BP is based on strong evidence, primarily from the Hypertension Optimal Treatment (HOT) trial. In patients with chronic kidney disease, this goal BP is based on less definitive evidence, primarily from extrapolations of observational data and studies in other populations.

Pharmacotherapy Recommendations

The JNC 7 recommendations (Figure 1-1) were based on data available before 2003. Clinicians should assess patients

for the presence of comorbid conditions that are compelling indications for specific drug therapy, and recognize the importance of the magnitude of the BP elevation. Recommendations are differentiated according to the presence or absence of specific compelling indications.

Most Patients Without Compelling Indications

A thiazide diuretic is recommended as first-line therapy for most patients without compelling indications due to the results from landmark trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). An alternative antihypertensive drug may be considered when contraindications to thiazide diuretics are present (e.g., acute gouty arthritis and dehydration, hyponatremia). An angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), β -blocker, or calcium channel blocker (CCB) is listed as a potential alternative to a thiazide diuretic. Thiazide diuretics, along with these four drug classes, are considered primary antihypertensive drugs that have outcomes data demonstrating reduced CV events. With thiazide diuretics, supporting data are from placebo-controlled trials. Data evaluating the use of ACE inhibitors and CCBs are mostly from comparative studies, but do support similar effects on CV events when compared with thiazide diuretics. The ARBs have arguably the fewest data. Of note, other guidelines (i.e., the 2003 European Society of Hypertension–European Society of Cardiology guidelines) advocate that decreased hypertension-associated CV morbidity and mortality be primarily related to BP lowering, not to the antihypertensive drug class used. The guidelines do not consider thiazide diuretics the lone preferred first-line drugs.

Table 1-1. Classification of Blood Pressure in Adults (age ≥ 18 years) According to the JNC 7.

Classification ^a	Systolic Blood Pressure (mm Hg)	and	Diastolic Blood Pressure (mm Hg)
Normal	≤ 120	and	≤ 80
Prehypertension ^b	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥ 160	or	≥ 100

^aDetermined based on the average of two or more properly measured seated blood pressure measurements from two or more clinical encounters. If systolic and diastolic blood pressure values yield different classifications, the highest category is used for the purpose of determining a classification.

^bFor patients with diabetes mellitus or chronic kidney disease, values greater than or equal to 130/80 mm Hg are above goal.

JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–52.

Patients With Compelling Indications

Compelling indications listed in the JNC 7 are comorbid conditions where specific antihypertensive classes are recommended. Evidence supporting these recommendations is based on outcomes data demonstrating decreased morbidity and/or mortality related to the comorbid condition. The lines of demarcation between hypertension-associated complications and compelling indication-associated complications are not mutually exclusive. However, pharmacotherapy recommendations are based on the compelling indication, if present. Figure 1-2 depicts the six compelling indications listed in the JNC 7 and the antihypertensive classes of choice that are supported by evidence from outcome studies.

Role of Lifestyle Modifications

Lifestyle modifications are the cornerstone of hypertension prevention and treatment. Five modalities have been proven to lower BP and are recommended by JNC 7. These include weight loss, adopting the Dietary Approaches to Stop Hypertension eating plan, limiting dietary sodium, engaging in aerobic physical activity, and moderating alcohol consumption.

For patients with an established diagnosis of hypertension, lifestyle modifications in addition to pharmacotherapy should ideally be used to augment BP lowering and promote CV health. Lifestyle modifications enhance BP lowering seen with antihypertensive drugs, but BP lowering is a surrogate goal of treating hypertension. Although lifestyle modifications alone have not been proven in prospective controlled trials to reduce hypertension-associated morbidity and mortality, antihypertensive drug therapy has. Observational data demonstrate that lifestyle modifications are associated with decreased CV risk, but the evidence is stronger with drug therapy. It is reasonable to evaluate response to lifestyle modifications before starting

drug therapy (Figure 1-1), primarily in patients with no other CV risk factors and stage 1 hypertension. However, antihypertensive drug therapy should be initiated within 6–12 months if BP is not at goal in these lower risk patients with hypertension.

Treatment Plans

Goal BP attainment rates are estimated to be only 31% for the total hypertensive population based on the United States National Health and Nutrition Examination Surveys, so aggressive treatment is rational. A two-drug combination for initial therapy is an option for patients with stage 1 hypertension, but is strongly recommended for patients with stage 2 hypertension. Although only one commercially available two-drug combination product is indicated by the Food and Drug Administration for initial hypertension therapy, it is commonly accepted that starting with two drugs at low initial doses has a minimal risk of adverse effects.

Monotherapy and Combination Therapy Approaches

Traditional monotherapy approaches attain a goal BP of less than 140/90 mm Hg in only 50%–60% of patients based on data from the Veterans Administration Cooperative Studies Program. Average BP reduction with standard doses of one of the five primary antihypertensive drug classes is only 9.1/5.5 mm Hg (Table 1-2). Therefore, monotherapy is expected to be successful only when baseline BP is within 10/5 mm Hg of the goal value.

The benefits of using lower doses of drugs in combination include greater BP lowering, higher BP goal attainment rates, and fewer adverse effects. Long-term outcome trials in hypertension (e.g., ALLHAT) consistently demonstrated that most patients require multiple drugs to attain goal BP values. Table 1-2 depicts the expected magnitude of BP lowering with monotherapy and combination therapy at different doses. Combination therapy also has an efficacy benefit over higher dose monotherapy.

In general, second-line drugs should be added to first-line drugs, and third-line drugs added to first-line and second-line therapies (see Figure 1-2). Moreover, a significant dose-response relationship with adverse effects is seen with thiazide diuretics, β -blockers, and CCBs. Doubling the dose of each drug provides minimal additional BP lowering, but significantly increases the frequency of adverse effects. Conversely, a clinically relevant dose-dependent relationship with adverse effects is not seen with either ACE inhibitors or ARBs (both considered renin-angiotensin-aldosterone system [RAAS] blockers); however, similar to the other classes, little additive BP lowering occurs with higher monotherapy doses. Drug combinations with complementary mechanisms of action (e.g., ACE inhibitor/thiazide diuretic) generally provide better BP reductions than combinations with similar mechanisms of action (e.g., ACE inhibitor/ARB). The most efficacious antihypertensive drug combinations usually include a diuretic due to its ability to counteract compensatory increases in sodium or water retention seen with other antihypertensive drugs.

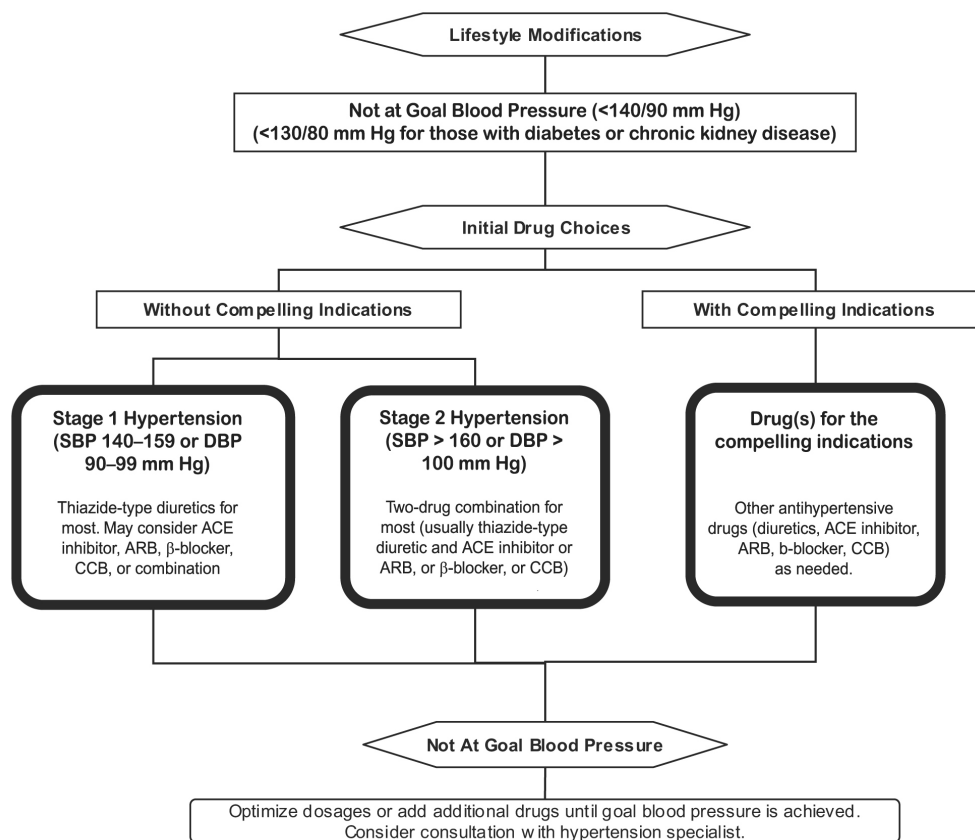


Figure 1-1. Algorithm for treatment of hypertension from JNC 7.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.

Evidence-Based Update and Controversies

The benefits of antihypertensive pharmacotherapy are irrefutable. However, debate continues over which drug is superior to another in a given situation. This debate questions whether within-class or among-class differences result in different long-term outcomes. Results of clinical trials have not completely clarified these controversies, but provide valuable information that clinicians and health policy makers should consider when making decisions. Multiple antihypertensive drugs are needed to treat hypertension, so contemporary comparative studies have incorporated combination therapy approaches in their study designs. These approaches make it challenging to directly compare data due to differences in study methodology.

Evolution of Long-Term Outcome Trials

Historical End Points Versus Combined Cardiovascular Events

Landmark clinical trials that demonstrated reduced morbidity and mortality with pharmacotherapy used specific CV outcomes as primary end points. Table 1-3 describes

these end points. Reductions in specific end points (e.g., stroke, myocardial infarction [MI], and CV death) using a placebo control were expected, and the absolute risk reductions were large. These data convincingly show that antihypertensive pharmacotherapy reduces morbidity and mortality.

Newer outcome studies comparing two or more active antihypertensive treatments should ideally use meaningful primary end points. One such end point is the incidence of fatal coronary heart disease (CHD) or nonfatal MI. This is commonly referred to as “hard CHD,” which is the 10-year Framingham risk scoring estimate. It is widely accepted as a gold standard CVD risk assessment tool in the United States. Studies that use the incidence of fatal CHD or nonfatal MI as their primary end point allow their results to be more easily extrapolated to clinical practice and compared to the cumulative body of evidence with antihypertensive pharmacotherapy.

Combined CV end points are being used in newer outcome studies because the expected absolute difference between active treatments is smaller than what is observed in placebo-controlled trials. For example, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) used a very broad composite primary end point (see Table 1-3). Other long-term trials assessing CVD used similar

Table 1-2. Average Blood Pressure Reduction With Monotherapy and Combination Antihypertensive Pharmacotherapy Based on Published Clinical Trials

Study Regimen and Treatment ^a	Average Placebo Corrected Reduction in Blood Pressure from Baseline	
	Systolic (mm Hg)	Diastolic (mm Hg)
Monotherapy with half the standard dose	7.1	4.4
Monotherapy with the standard dose	9.1	5.5
Monotherapy with twice the standard dose	10.9	6.5
Drug A alone	7.0	4.1
Drug B alone	8.1	4.6
Combination therapy with Drug A and Drug B	14.6	8.6

^aConsisting of one (for monotherapy) or two (for combination therapy) of the five primary antihypertensive drug classes: thiazide diuretics, β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers. Adapted with permission from the BMJ Publishing Group. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003;326:1427–34.

composite end points. The absolute and relative risk reductions demonstrated in these types of trials are not easily compared to other antihypertensive trials. Differences between treatment groups can overestimate the clinical relevance of study findings. Clinicians must appreciate this when assessing studies that use composite end points. The use of multiple combined CV end points may be defensible if the study aim is to demonstrate superiority for all types of associated morbidity and mortality. However, combining multiple CV events into one study end point can lead to an early statistically significant difference and early termination of the study. This approach often limits the ability to assess secondary end points and compare results to other trials where these end points were used.

End point assessment is ideally conducted using double-blind methodology to reduce potential bias. However, many newer outcome studies are using a prospective, open-label design with blinded end point analysis. Although the blinded end point analysis increases validity and is typically conducted by an independent adjudication committee, the

scientific rigor of this approach is lower than that of the double-blind methodology.

Use of Combination Regimens

Multiple antihypertensive drugs were used in long-term outcome trials to attain goal BP values and this creates a conundrum with interpretation. Comparator groups are never composed of only one antihypertensive drug class. When comparing treatment groups, it is best to view treatments as specific drug class-based regimens. Even landmark placebo-controlled trials should be viewed this way. For example, in the Systolic Hypertension in the Elderly Program (SHEP) study, patients were randomized to receive chlorthalidone or placebo. Patients receiving chlorthalidone had atenolol added if BP was not at goal after dose titrations. Therefore, this study really compared chlorthalidone-based therapy versus placebo. Because most patients in these trials required multiple antihypertensive drugs, some refer to a study group as first/second drug versus the comparator (e.g., chlorthalidone/atenolol vs. placebo). Recognizing this therapeutic approach when

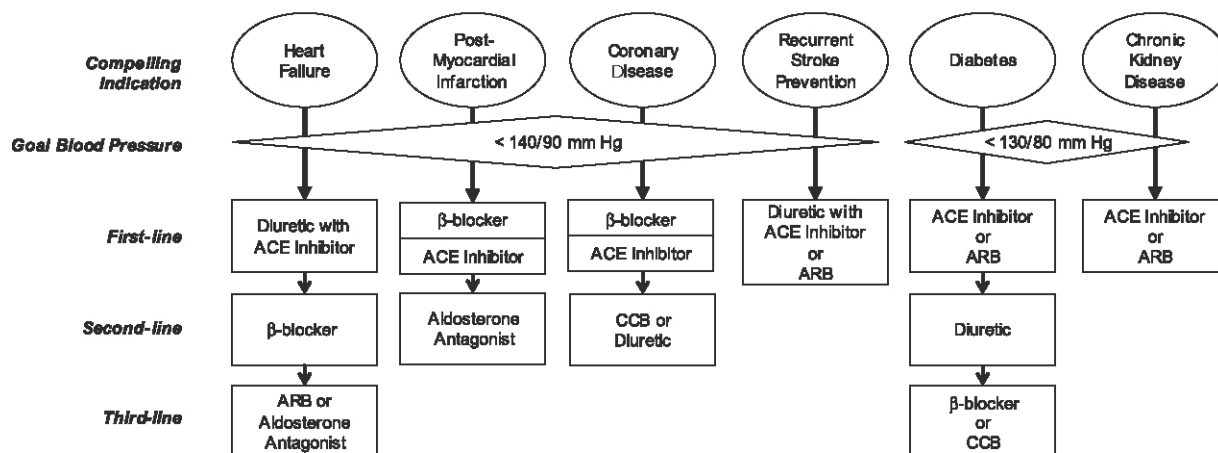


Figure 1-2. Compelling indications for specific pharmacotherapy.

Recommendations are based on evidence demonstrating reduced morbidity and/or mortality related to the compelling indication with recommended pharmacotherapy and adapted from JNC 7 recommendations. Blood pressure should be managed concurrently with the compelling indication using these drugs when possible.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

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Table 1-3. Comparison of Large Outcome-Based Clinical Trials in Hypertension

Study	Primary End Point(s)	Study Design	Comparison Groups
Systolic Hypertension in the Elderly Program (SHEP)	Stroke	Randomized, double-blind	Thiazide (chlorthalidone) versus placebo
Medical Research Council (MRC)	Stroke; coronary events; and all-cause mortality	Randomized, single-blind	Thiazide (hydrochlorothiazide) versus β -blocker (atenolol) versus placebo
Swedish Trial in Old Patients (STOP)	Stroke; MI; and CV death	Randomized, double-blind	β -Blocker (multiple)/thiazide versus placebo
Systolic Hypertension in Europe (Syst-Eur)	Stroke	Randomized, double-blind	CCB (nitrendipine) versus placebo
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)	Fatal CHD or nonfatal MI	Randomized, double-blind	Thiazide (chlorthalidone) versus ACE inhibitor (lisinopril), CCB (amlodipine) or α -blocker (doxazosin)
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)	Fatal CHD or nonfatal MI	Randomized, open-label	β -blocker (atenolol) versus CCB (amlodipine)
The Valsartan Antihypertensive Long-term Use Evaluation (VALUE)	Composite: sudden cardiac death, fatal or nonfatal MI, death during/after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure or recent MI, heart failure hospitalization, or emergency procedures to prevent MI	Randomized, double-blind	ARB (valsartan) versus CCB (amlodipine)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction.

SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265(24):3255–64.

MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304(6824):405–12.

Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekblom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338(8778):1281–5.

Saessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350(9080):757–64.

interpreting and applying these data is the most feasible and relevant means of making extrapolations.

Meta-Analysis of Blood Pressure-Lowering Trials

Meta-analyses have been conducted to assess and compare the incidence of specific CV events among antihypertensive drug classes. In 2003, the Blood Pressure Lowering Trialists' Collaboration Group completed a comprehensive analysis that included 29 randomized, clinical trials, representing 162,341 patients, and included outcome data available through July 2003.

Reduced incidence of CV events was demonstrated with the five major antihypertensive classes (thiazides, β -blockers, ACE inhibitors, ARBs, and CCB) versus placebo in the Blood Pressure Lowering Trialists' Collaboration Group analyses. Strong relationships were seen with ACE inhibitors and CCBs. Significant reductions in stroke, CHD, and major CV events were demonstrated with both of these classes compared with placebo. Relative risk reductions with ACE inhibitors and CCBs were 22% and 18%, respectively. However, only ACE inhibitors reduced the incidence of heart failure compared with placebo. Stroke, heart failure, and major CV events were reduced with ARB therapy. However, these data cannot be used to make reliable comparisons with other antihypertensive drugs because ARBs were compared with

controlled regimens that included both active treatments and placebo.

Multiple analyses compared ACE inhibitors and CCBs with each other and with thiazide diuretic/ β -blocker treatments. There were no differences in the incidence of total mortality, CV mortality, or major CV events. However, both ACE inhibitor and thiazide diuretic/ β -blocker regimens had a lower incidence of heart failure than CCBs. Conversely, patients receiving CCBs had fewer strokes than patients receiving ACE inhibitors. These data suggest no differences in the incidence of major events among the major antihypertensive drug classes (thiazide diuretics, β -blockers, ACE inhibitors, and CCBs), with only minor differences seen with specific clinical outcomes. These data justify careful evaluation of newer outcomes data to detect consistency with these findings. An often overlooked finding was the relationship between degree of BP lowering and CV end points. For all end points other than heart failure, there was a strong direct association between SBP and the incidence of the CV end point; higher SBP values were associated with higher CV event rates.

First-Line Pharmacotherapy

The first-line use of thiazide diuretics is supported by landmark placebo-controlled, clinical trials that demonstrated reduced morbidity and mortality, and the data are irrefutable. Future clinical trials should ideally compare

other treatment strategies to one that is thiazide diuretic-based (i.e., the gold standard). The ALLHAT is the only large outcome trial in recent years to use thiazide diuretic-based therapy as the gold standard comparator treatment.

Thiazide-Type Diuretics Versus Other Drugs *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*

The ALLHAT is the largest prospective, randomized, controlled trial to compare the incidence of fatal CHD or nonfatal MI (primary end point) in patients randomized to thiazide diuretic- (chlorthalidone), ACE inhibitor- (lisinopril), CCB- (amlodipine), or α -blocker (doxazosin)-based regimens. The original hypothesis of ALLHAT was that lisinopril, amlodipine, and doxazosin would be superior to chlorthalidone. A second antihypertensive drug, atenolol, was added to nearly all patients' initial drug regimen to attain goal BP values.

The ALLHAT results are summarized in the Annotated Bibliography. An interim safety analysis after a mean of 3.2 years of follow-up found that there was a 17% relative increase in risk of combined CVD with doxazosin compared with chlorthalidone. The doxazosin arm was terminated early based on the interpretation that chlorthalidone-based therapy was more protective than doxazosin-based therapy. At 4.9 years follow-up, final results showed no significant differences in the primary end point among groups. Lisinopril and amlodipine both failed to show superiority over chlorthalidone. Of importance, several secondary end points occurred at a lower rate with chlorthalidone.

Differences among treatment groups and study methodology have been cited as flaws of ALLHAT. Mean treatment BP values were lowest with chlorthalidone. The clinical validity regarding choice of the second drug is controversial. Most clinicians would not routinely select atenolol as the first add-on therapy for additional BP reduction. Differences in the incidence of heart failure significantly influenced secondary analyses and the overall study interpretation. Heart failure was neither a component of the primary end point, nor systematically assessed. When evaluating the entire body of evidence, the JNC 7 used ALLHAT as additional evidence supporting the use of thiazide diuretics as first-line drugs to reduce the incidence of CV events.

ALLHAT Subgroup Analyses in Special Populations

Several subgroup analyses of ALLHAT have been conducted to decipher whether lisinopril or amlodipine were superior in certain patient populations.

ALLHAT Subgroup: Blacks Versus Non-Blacks. Differences in BP response based on race have been well documented, but differences in CV outcomes have not. Black patients have a weaker antihypertensive response to RAAS blocking drugs and a stronger response to thiazide diuretics and CCBs. A comparison of CV outcomes between black and non-black patients was a prespecified subgroup analysis of the ALLHAT. As anticipated, black patients treated with lisinopril had mean SBP values that were 4 mm Hg higher than those of black patients treated with chlorthalidone. The incidence of the primary end point was statistically lower in black versus non-black patients, but

black patients had a higher incidence of stroke and total mortality (secondary end points). However, there were no differences in the primary end point among treatments in black patients. Therefore, the higher mean SBP values in black patients treated with lisinopril did not result in an increased rate of the primary end point.

Secondary end-point results comparing chlorthalidone with amlodipine were similar to the overall findings; the incidence of heart failure was higher with amlodipine. Secondary analyses comparing chlorthalidone with lisinopril were different; the incidence of heart failure, stroke, and combined CVD was all higher with lisinopril. These data support the use of all three drugs, but especially thiazide diuretic-based therapy, in black patients. They also indicate that differences in the incidence of stroke seen in the total ALLHAT population were driven by the black subgroup.

ALLHAT Subgroup: Diabetes, Impaired Fasting Glucose, and Normoglycemia. Clinical outcomes in ALLHAT patients with diabetes, impaired fasting glucose, or normoglycemia were compared in a subgroup analysis. The diabetes subgroup analysis was preplanned, but the impaired fasting glucose subgroup analysis was not. The diabetes subgroup was defined using contemporary American Diabetes Association criteria, but the impaired fasting glucose subgroup was defined using old criteria (fasting glucose of 110–125 mg/dL). In contrast to other outcomes data, there were no differences in the incidence of the primary end point with chlorthalidone versus lisinopril across these three subgroups, or with chlorthalidone versus amlodipine in the diabetes or normoglycemia subgroups. However, the incidence of the primary end point was 29% lower with chlorthalidone versus amlodipine in the impaired fasting glucose subgroup. This result is the only ALLHAT subgroup analysis to show a difference in the primary end point among treatments. This difference was not seen in the diabetes subgroup. Therefore, superiority claims supporting thiazide diuretics over ACE inhibitors or CCBs in patients with impaired fasting glucose are speculative.

Differences in BP were not prospectively controlled for and may have influenced these results. Mean achieved SBP was significantly lower throughout the study with chlorthalidone compared with lisinopril. Mean SBP values in patients with diabetes were 135.0 mm Hg, 136.3 mm Hg, and 137.9 mm Hg at 5 years with chlorthalidone, amlodipine, and lisinopril, respectively. It is possible that differences in CV outcomes would have been seen if patients had been treated to the recommended goal BP of less than 130/80 mm Hg.

This subgroup analysis questions the preferential use of an ACE inhibitor over a thiazide diuretic as first-line therapy for hypertension in patients with diabetes. The lack of superiority of lisinopril over chlorthalidone in patients with diabetes was not expected, but was observed nonetheless. Until definitive evidence indicates otherwise, clinicians should continue to follow JNC 7 guidelines and consider diabetes a compelling indication for an ACE inhibitor or ARB. Thiazide diuretics may have superior effects in reducing the incidence of CV events in patients with impaired fasting glucose (prediabetes). However, this subgroup analysis was not defined *a priori* and consisted of

a small portion of the total population. Therefore, these data cannot be considered conclusive.

ALLHAT Subgroup: Reduced Glomerular Filtration Rate. Antihypertensive drugs that block the RAAS are believed to have kidney protective effects in patients with reduced glomerular filtration rates. These drugs are recommended as first line by the National Kidney Foundation and JNC 7 to treat patients with hypertension and chronic kidney disease. A post hoc analysis of ALLHAT in patients with different ranges of estimated glomerular filtration rate compared the onset of kidney outcomes, end-stage kidney disease, and/or decrease in glomerular filtration rate of 50% or more. Kidney outcomes were similar among treatments regardless of baseline glomerular filtration rate.

These results are purely hypothesis generating as this was not a preplanned analysis. It is surprising that no differences between lisinopril and chlorthalidone were found, even in patients with the lowest glomerular filtration rate. Although not as robust as the subgroup analysis in patients with diabetes, these data question whether kidney protection is provided by ACE inhibitors in patients with reduced glomerular filtration rates. Nonetheless, these data are not strong enough to supersede the JNC 7 recommendation of an ACE inhibitor or ARB for the compelling indication of chronic kidney disease.

Anglo-Scandinavian Cardiac Outcomes Trial

The results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) contradict the results of ALLHAT and first-line JNC 7 recommendations. Both trials used the same primary end point, both used amlodipine-based therapy as a comparator, and both included patients with hypertension and additional CV risk factors. However, the study methodology and results of the two trials are quite different.

The ASCOT was a prospective, open treatment, and blinded end point study comparing amlodipine-based therapy with atenolol-based therapy. The trial was terminated early after secondary end-point analyses demonstrated lower incidences of stroke, coronary events, and all-cause mortality with amlodipine. The absolute risk reductions in these end points were modest, corresponding to numbers needed to treat of 100, 91, and 125, respectively. However, there were no significant differences in the incidence of the primary end point between groups.

Several differences between the two treatment groups were documented. Significant differences in BP and other metabolic parameters (e.g., cholesterol values) were noted after randomization, all of which favored amlodipine-based treatment. Mean achieved BP values were 2.7/1.9 mm Hg lower in the amlodipine-based group. After multivariate adjustments to account for clinically important differences between groups, the differences in secondary end points (stroke and coronary events) were reduced to an insignificant trend. These adjustments must be considered when evaluating the ASCOT data because they suggest that differences between treatments are clinically insignificant when other risk factors are managed (e.g., lipid-lowering therapy) and when BP is optimally lowered to goal values.

This study appears comparable to ALLHAT. However, ALLHAT was thiazide diuretic-based therapy versus ACE inhibitor-based and CCB-based therapy, and a β -blocker was the second drug added to all groups. In contrast, ASCOT was β -blocker-based versus CCB-based therapy. Recent meta-analyses assessing the use of atenolol make use of this drug as the primary comparator problematic (see Atenolol Versus Other β -Blockers section). The ASCOT would be less controversial and more reflective of clinical practice if the comparator group had been thiazide diuretic-based therapy (with β -blocker or, even better, with an ACE inhibitor as the add-on drug), and if hydrochlorothiazide had been used instead of bendroflumethiazide.

Women's Health Initiative Observational Study

There are no prospective, randomized, controlled trials evaluating CV events exclusively in women with hypertension. The Women's Health Initiative Observational Study was a large prospective cohort study of hypertensive women without CHD. Treatments were selected by the treating physician. Most women were treated with monotherapy regimens. There were no differences in occurrence of CVD mortality among drugs when used as monotherapy, except between CCBs and thiazide diuretics (higher with CCBs). Combination regimens that included a thiazide diuretic were more effective in lowering BP. In addition, thiazide diuretic/CCB combinations had higher occurrence of CVD mortality compared with thiazide diuretic/ β -blocker therapy. Adjustments were made to account for BP differences, but CVD mortality differences persisted.

Throughout this study, 58% of women had SBP less than 140 mm Hg, indicating better overall control than has been observed in the National Health and Nutrition Examination Surveys. However, participants in the Women's Health Initiative may represent women more likely to adhere with therapy due to the study's recruitment methodology and inclusion of patients already on pharmacotherapy. These data indicate mortality benefits and reinforce the role of thiazide diuretic-based regimens in women. However, these benefits may be seen only with optimal BP goal attainment.

Calcium Channel Blocker Versus Angiotensin Receptor Blocker

The newest antihypertensive drug class, ARBs, have only recently been evaluated in long-term hypertension outcome trials. The VALUE trial evaluated long-term CV outcomes in patients treated with valsartan-based therapy or amlodipine-based therapy. The hypothesis was that valsartan would be superior, given an equal magnitude of BP lowering. The incidence of very broadly defined CV outcomes was used as the primary end point (see Table 1-3). Patients with hypertension and additional CV risks were enrolled. Hydrochlorothiazide was the second drug added to either group for BP control. There was no difference in the incidence of the primary end point. The incidence of MI, a secondary end point, was significantly higher with valsartan, but this difference was small.

The assumption that there would be equal BP lowering in the two groups was not achieved throughout the VALUE

trial. Mean SBP and DBP values were significantly higher with valsartan. The most dramatic differences were observed during the first 3 months. It was during the first 6 months that more CV outcomes occurred with valsartan, and also the time periods of maximum BP differences between the groups. These data provide evidence that small differences in BP may correlate with risk of CV events. This finding alone is relevant to the overall management of hypertension and supports aggressive and timely BP lowering. The VALUE, Blood Pressure Lowering Trialists' Collaboration Group, ALLHAT, and ASCOT all provide evidence that support the use of CCBs, specifically dihydropyridines, in hypertension. Moreover, overall event rates were similar among the major antihypertensive drug classes. None can claim superiority based on overall efficacy in diverse patient populations.

Treatment of Hypertension With Comorbid Compelling Indications

The six compelling indications identified by JNC 7 represent comorbid conditions where specific antihypertensive drug classes have reduced CV morbidity and/or mortality. Outcomes that are reduced with antihypertensive therapy may be primarily attributed to the comorbid illness and secondarily to hypertension. It is important to acknowledge that reducing morbidity and mortality is relevant in any patient with hypertension. However, clinicians should appreciate that a compelling indication can increase the likelihood that patients will experience a specific type of CV outcome related to the compelling indication. Therefore, following pharmacotherapy recommendations that are based on evidence demonstrating compelling indication-specific outcome benefits is prudent (Figure 1-2).

Newer data have been published since JNC 7 regarding three of the six compelling indications. Some newer data provide evidence for a specific pharmacotherapy strategy that justifies compelling indication status. In other instances, newer data create controversy.

Coronary Disease: Chronic Stable Angina β -Blocker Versus Non-Dihydropyridine CCB

The International Verapamil-Trandolapril Study was a randomized, prospective, open-label, blinded, end-point study in 22,576 patients with hypertension and CHD. Verapamil-based and atenolol-based treatments were compared. There was no significant difference in the incidence of the composite primary end point (all-cause death, nonfatal MI, or nonfatal stroke). These data suggest that a CCB, specifically a non-dihydropyridine CCB, is equivalent to a β -blocker as first-line treatment for hypertension in patients with coronary disease. However, numerous studies demonstrated reduced CV events with β -blocker therapy in multiple forms of CHD. Therefore, based on the weight of evidence, CCB therapy should remain an acceptable alternative to β -blocker therapy in CHD.

β -Blocker Versus Dihydropyridine CCB

A coronary disease Trial Investigating Outcome with Nifedipine (ACTION) and Comparison of Amlodipine versus Enalapril to Limit Outcomes of Thrombosis

(CAMELOT) both used a placebo group in their prospective, randomized, double-blind designs. Most patients in these trials (75% in ACTION and 80% in CAMELOT) were already on β -blocker therapy at baseline. The ACTION included 7797 patients with chronic stable angina. No differences between nifedipine and placebo were observed in the incidence of the composite primary end point of all-cause death, acute MI, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularization.

In the CAMELOT trial, enalapril, amlodipine, and placebo were compared in 1991 patients with CHD and normal BP. The primary end-point comparisons and study methodology both changed. After recruitment was slow and the numbers of CV events in all groups were higher than expected, the targeted sample size decreased from 3000 to 2000 participants. In addition, the comparison between amlodipine and enalapril changed from a primary end point to a secondary end point. When results from all three treatment groups were compared, the incidence of the composite CV end point (occurrence of CV death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris or heart failure, stroke/transient ischemic attack, or new peripheral vascular disease) was lower with nifedipine than with placebo.

These trials are cited as relevant outcomes data in hypertension because they assessed antihypertensive drugs. However, the positive results seen in the CAMELOT are complicated by the fact that patients did not have hypertension and by the questionable study methodology. Data from ACTION and CAMELOT do not justify adding a dihydropyridine CCB to adequate anti-ischemic therapy in patients with chronic stable angina for the purpose of reducing CV events.

ACE Inhibitor Therapy

The primary evidence supporting the JNC 7 recommendation for ACE inhibitor therapy in patients with coronary disease was derived from the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA). This double-blind, placebo-controlled study evaluated 13,655 patients with stable CHD and no apparent heart failure. The primary composite end point was incidence of CV death, nonfatal MI, or cardiac arrest with successful resuscitation. The incidence of the primary end point was significantly lower with perindopril than with placebo (8.0% vs. 9.9%, respectively) and corresponded to a number needed to treat of only 53. However, the Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) trial showed different results. This randomized, placebo-controlled trial included 8290 patients with stable CHD, but was originally designed to enroll 14,100 patients. Because enrollment was slow, investigators decided to add coronary revascularizations to their primary end point to accommodate a smaller sample size. The incidence of the modified primary composite end point was similar in the trandolapril and placebo groups.

Data regarding using an ACE inhibitor in patients with chronic stable angina are conflicting. The PEACE trial included a patient population with higher CV risk than

EUROPA. Difference in severity of disease may explain differences in clinical outcomes. In addition, the PEACE study did not enroll the planned sample size, increasing the risk of a type 2 error. Overall, these data support CV event reduction with ACE inhibitor therapy in patients with chronic stable angina, and ACE inhibitors should remain as compellingly indicated drugs. However, ACE inhibitors should be used as add-on therapy with anti-ischemic therapy (β -blocker and/or CCB).

Recurrent Stroke Prevention

Thiazides and ACE inhibitors have compelling indications for secondary prevention of stroke according to JNC 7. This recommendation is based on findings from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) where these drugs provided a 28% relative risk reduction in the incidence of recurrent stroke compared with placebo. Of importance, this outcome benefit was demonstrated in patients receiving both the ACE inhibitor and a thiazide diuretic. Stroke reduction with thiazide diuretics had been previously demonstrated, but this study increased interest in investigating the cerebroprotective effects of RAAS blocking drugs.

The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention study provided strong evidence supporting ARB therapy for recurrent stroke prevention. This study demonstrated a significant reduction in the incidence of recurrent cerebrovascular events with eprosartan-based therapy compared with nitrendipine-based therapy in patients with hypertension and a history of a cerebrovascular event. About 66% of patients required the addition of a second or third drug for BP control, with a thiazide diuretic recommended as the preferred second drug. There was no difference in mean treated BP values between groups, in contrast to other long-term outcome studies comparing an ARB and CCB. In comparison to PROGRESS, which was the primary evidence supporting the JNC 7 recommendation of an ACE inhibitor and thiazide diuretic for secondary stroke prevention, Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study used an active antihypertensive comparator group. This methodology minimized potential differences in BP between groups and increased the external validity of the findings. These data are strong enough to support recurrent stroke prevention as a compelling indication for an ARB, with a thiazide diuretic added if BP control is not adequate.

Chronic Kidney Disease

The JNC 7, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, and the American Diabetes Association all recommend that patients with chronic kidney disease be treated to a BP goal of less than 130/80 mm Hg with a RAAS blocking drug as first-line therapy. Newer data question these recommendations.

The lower BP goal in patients without diabetes but with proteinuric nephropathies is based on results of the Modification of Diet in Renal Disease study. This study

demonstrated a slower rate of decline in the glomerular filtration rate in patients treated to a BP goal of less than 125/75 mm Hg compared with a BP goal of less than 140/90 mm Hg. However, 48% of patients in the lower BP group were receiving an ACE inhibitor versus 28% in the higher BP group, so the benefits cannot be solely attributed to BP lowering. The Ramipril Efficacy In Nephropathy 2 (REIN-2) trial evaluated different BP goals in patients with non-diabetic proteinuric nephropathies. This was a follow-up to the original REIN trial, which demonstrated less kidney disease progression in patients with non-diabetic kidney disease treated with ramipril compared with other antihypertensive drugs, given the same level of BP lowering.

In the REIN-2 trial, all patients were initially treated with ramipril and then were randomized to open-label conventional (DBP less than 90 mm Hg) or intensified (BP less than 130/80 mm Hg) treatment. There was no difference in the rate of progression to end-stage renal disease (the primary end point) at the end of study. Application of these results is limited by the small sample size, lack of blinding, and use of a low ACE inhibitor dose, but this trial was better designed than previous trials. These data highlight the lack of definitive data proving lower BP goals are beneficial in patients with non-diabetic forms of chronic kidney disease. Clinicians should not extrapolate these data to patients with diabetes where there are convincing data supporting a BP goal of less than 130/80 mm Hg.

Both ACE inhibitors and ARBs are believed to provide kidney protection because of efferent arteriole dilation. Data evaluating this hypothesis have been included in a meta-analysis comparing ACE inhibitors or ARBs with other antihypertensive drugs. Among all types of patients, there was a reduction in the incidence of serum creatinine concentration doubling and a lower incidence of end-stage renal disease with RAAS blocking drugs versus other antihypertensive drugs. When RAAS blocking drugs were compared with placebo, reductions in the incidence of adverse kidney outcomes were associated with reductions in BP. Patients with diabetic nephropathy were evaluated, and there was no difference in the incidence of serum creatinine concentration doubling or end-stage renal disease between RAAS blocking drugs and other drugs. Theoretical kidney protective effects of RAAS blockers in patients with diabetes beyond BP lowering are unproven.

Clinicians may be surprised by these data that indicate kidney protection from RAAS blockers appear to be largely from BP lowering. There may not be a significant class-specific benefit on kidney outcomes, which is in contrast to the proven benefits of ACE inhibitors on CV outcomes in patients with diabetes.

Other Clinical Controversies

Hydrochlorothiazide Versus Chlorthalidone

Several differences between hydrochlorothiazide and chlorthalidone are related to their pharmacokinetic and pharmacodynamic properties. The antihypertensive effects of chlorthalidone are more potent on a mg-per-mg basis, which can be explained by its longer elimination half-life and duration of action. Adverse effects are typically

dose-related with thiazide diuretics. Therefore, it is reasonable to assume that the rate of adverse metabolic effects (e.g., hypokalemia and insulin resistance) also may be higher with chlorthalidone on a mg-per-mg basis.

Hydrochlorothiazide, chlorthalidone, and other thiazide diuretics (e.g., bendroflumethiazide and indapamide) have been used in large outcome-based hypertension trials. However, studies using chlorthalidone have arguably been more robust and have had the greatest impact (e.g., ALLHAT). A 2004 report from investigators who conduct meta-analyses suggests that the incidence of CV outcomes is similar among all the thiazide diuretics used in placebo-controlled outcome trials. Two studies used chlorthalidone, and three studies used other types of thiazide diuretics in this meta-analysis, so the data are limited. However, it is unlikely we will see a prospective, comparative, clinical trial conducted.

The JNC 7 supports class effects when recommending antihypertensive drugs. It considers thiazide diuretics interchangeable from an outcomes benefit perspective. However, it is important for clinicians to consider potency, outcomes data, and potential safety differences between hydrochlorothiazide and chlorthalidone when interchanging these products. Whether all of the outcome benefits demonstrated with chlorthalidone can be extrapolated to hydrochlorothiazide remains controversial.

β-Blocker Therapy

Atenolol Versus Other β-Blockers

Differences among β-blockers in their ability to reduce CV outcomes in hypertension have been suggested. This difference has been seen in the setting of systolic heart failure where carvedilol, metoprolol, and bisoprolol have reduced the incidence of morbidity and mortality, but bucindolol has not. Atenolol, metoprolol, and carvedilol are all used for managing hypertension and/or certain CV conditions. However, their pharmacokinetics, pharmacodynamics, and outcome-based trial results are quite different (see Table 1-4). Landmark placebo-controlled trials often used atenolol or another β-blocker, but mostly as the second drug added to a thiazide diuretic. Newer comparative trials evaluating a β-blocker have used atenolol both as the first drug (e.g., ASCOT) or as the second drug (e.g., ALLHAT) for BP control.

A 2005 meta-analysis questions the efficacy of β-blockers in reducing the incidence of CV events in patients with hypertension. In this analysis, there were no differences in the incidence of MI or total mortality in the

studies comparing β-blocker therapy to placebo, but the incidence of stroke was significantly reduced. When β-blockers were compared to other antihypertensive drugs, there were no significant differences in the incidence of MI or total mortality, but an increase in the incidence of stroke was observed. Investigators sought to decipher whether these differences could be explained by the type of β-blocker used. When atenolol was compared with other antihypertensive drugs, the incidence of both stroke and total mortality was higher, but the incidence of MI was similar. These data indicate that it is reasonable to use RAAS blockers or CCBs before a β-blocker when an alternate first-line antihypertensive drug is needed. Atenolol may not provide the same CV benefits that other β-blockers do. However, clinicians should not extrapolate these findings to patients with hypertension and a compelling indication for a β-blocker.

Carvedilol Versus Metoprolol in Type 2 Diabetes

Although RAAS blocking drugs and thiazide diuretics are typically used first, many patients with diabetes are treated with a β-blocker as add-on therapy. Moreover, many patients with type 2 diabetes have a compelling indication to use a β-blocker as first-line therapy (i.e., post-MI and coronary disease). β-Blockers have traditionally been used cautiously in patients with diabetes because of adverse metabolic effects and possible masking of hypoglycemic symptoms. However, outcome benefits outweigh these risks in most patients.

The Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives trial has been widely cited as evidence to preferentially use carvedilol over metoprolol in patients with type 2 diabetes and hypertension treated with a RAAS blocking drug. Mean hemoglobin A1c values increased significantly from baseline with metoprolol, but not carvedilol. However, the absolute difference was small and likely not clinically significant. Of interest, the incidence of progression to microalbuminuria was lower with carvedilol despite similar mean BP values. Despite these data, preferential use of carvedilol over metoprolol in patients with type 2 diabetes requiring a β-blocker is controversial.

The Elderly Population

Elderly patients with hypertension are treated according to the philosophies and strategies recommended for adult patients in general. Within the elderly group, “older patients” are between the ages of 65 and 74. Very elderly

Table 1-4. Comparison of Commonly used β-Blockers for Hypertension

Drug	Daily Dosing Frequency	Half-Life (hour)	Lipid Solubility	Liver Metabolism	Cardio-selectivity	α-Blockade	Studied in Outcome Trials
Atenolol	1–2	6–7	Low	None	Yes	No	Yes, mostly hypertension trials
Carvedilol	1 ^a or 2	6–10	High	Extensive	No	Yes	Yes, mostly heart failure
Metoprolol succinate	1 ^a or 2	3–7	Moderate to high	Extensive	Yes	No	Yes, mostly heart failure
Metoprolol tartrate	2	3–7	Moderate to high	Extensive	Yes	No	Yes, post-myocardial infarction

^aOnly for the extended-release capsule formulation.

patients (age 75 or older) are a subgroup of the elderly and have many issues that can make selecting antihypertensive pharmacotherapy challenging.

Contrary to common belief, BP goals should not be adjusted in elderly patients based on age. Elderly patients with hypertension have a BP goal of less than 140/90 mm Hg, and a BP goal of less than 130/80 mm Hg is appropriate for elderly patients with diabetes or chronic kidney disease. Elderly patients are at higher risk for orthostatic hypotension with precipitous BP lowering or when certain primary antihypertensive drugs (ACE inhibitors, ARBs, and diuretics) are used, especially with high initial doses. Therefore, using lower initial doses and a longer titration period to attain goal BP values is a reasonable approach to minimize the risk of orthostatic hypotension. However, goal BP attainment should remain the ultimate therapeutic objective.

Elderly patients, especially the very elderly, often have isolated systolic hypertension (elevated SBP with DBP less than 80 mm Hg). Presence of this type of hypertension further increases the risk of orthostatic hypotension with antihypertensive therapy. However, the degree of SBP elevation is strongly correlated with the risk of CV events, especially stroke. Initiating therapy with two drugs in the elderly, especially those with isolated systolic hypertension, is discouraged. Even for patients with stage 2 hypertension, two drugs should almost never be simultaneously started in this population because of the potential for orthostatic hypotension.

Outcomes data with antihypertensive therapy in elderly patients have conclusively demonstrated a reduced incidence of CV events. However, there is a paucity of outcomes data evaluating the benefits of drug therapy and tight control of BP in the very elderly, particularly patients age 80 or older. The very elderly are underrepresented in outcome trials, and in some instances are systematically excluded due to fear of adverse events. A meta-analysis in 1999 indicated that, although antihypertensive pharmacotherapy does not decrease the incidence of total mortality or MI in the very elderly, the incidence of stroke is reduced. Without definitive outcome trials in the very elderly, it is acceptable to treat to the same clinical end points and BP goals as younger patients, but stroke reduction is the primary preventable CV outcome anticipated. Clinicians must provide close monitoring to detect drug-related complications in the very elderly and be willing to decrease the intensity of treatment based on the patient's response. The Hypertension in the Very Elderly Trial is a prospective, randomized, double-blind, placebo-controlled trial designed to evaluate the benefit of antihypertensive therapy on the incidence of stroke. However, the study results will not be available until after 2007.

Conclusion

Hypertension is a common condition, and its prevalence is increasing. Goal BP attainment rates are poor. Given that current treatment approaches have been inadequate in achieving treatment goals in many patients, more intense

treatment approaches and clinician education are needed. The JNC 7 guidelines are consensus opinions based the best available evidence. However, the body of evidence continues to grow. Clinicians should assess newer data in an ongoing manner to provide the best antihypertensive pharmacotherapy and always consider compelling indications. Newer outcome studies in hypertension use active treatments as comparators, which has led to controversy when extrapolating findings to clinical practice. Thiazide diuretics remain unsurpassed in their ability to reduce CV events in patients with hypertension, but other drugs (ACE inhibitors, CCBs, and ARBs) have data justifying their use as first-line therapy for hypertension in patients both with and without compelling indications. Although more effective than placebo, β -blockers for first-line treatment of hypertension without compelling indications may not be as effective in reducing the incidence of CV events compared with other antihypertensive drugs. It is to be hoped that future outcomes data will resolve more controversies than they create.

Annotated Bibliography

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This national consensus guideline, the JNC 7, is an essential reference for any clinician who treats patients with hypertension. Detailed background on hypertension and the evidence used to make pharmacotherapy recommendations are included. Lifestyle modifications that lower BP are fully explained. Thiazide diuretics are recommended as first-line therapy for most patients with hypertension. Potential alternative first-line drugs are ACE inhibitors, ARBs, β -blockers, and CCBs. For patients with a compelling indication, pharmacotherapy with specific antihypertensive drug(s) is recommended based on evidence available up to late 2002; results from ALLHAT are arguably weighted the most. Clinicians should not overlook the recommendation to consider starting therapy with two antihypertensive drugs in certain patients, particularly those with stage 2 hypertension. The JNC guidelines would be improved if evidence supporting each of their recommendations was ranked or graded so that clinicians could make more informed pharmacotherapy treatment decisions and appropriately incorporate new evidence into treatment strategies.

2. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003;326:1427–34.

This meta-analysis included 354 randomized, double-blind, placebo-controlled trials using thiazide diuretics, β -blockers, ACE inhibitors, ARBs, and CCBs in 55,696 patients. With monotherapy regimens, average SBP/DBP reductions were 9.1/5.5 mm Hg with standard doses and 7.1/4.4 mm Hg with half standard doses. Reductions were similar among all five classes. Higher baseline BP values were associated with

greater BP reductions; for each 10 mm Hg increase in baseline value, SBP/DBP reductions were 1.0/1.1 mm Hg greater. With monotherapy regimens, strong dose-related increases in the incidence of adverse effects were seen with thiazide diuretics, β -blockers, and CCBs, but not with ACE inhibitors or ARBs. With two-drug combination regimens, BP reductions were generally additive compared with each drug as monotherapy. The incidence of adverse effects with combination regimens increased only slightly compared with monotherapy. Clinicians can use these data to justify similar BP reduction among the five major drug classes as monotherapy regimens, and overall additive BP lowering without increased adverse event frequency with two-drug combination regimens. This analysis does not assess the efficacy of regimens among different races or sexes, nor of different combination regimens.

3. Turnbull F. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet* 2003;362:1527–35.

This was the second major meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration. The incidence of major CV events and death among different antihypertensive drug classes from 29 major randomized trials (n=162,341) was estimated. In placebo-controlled trials, the incidence of major CV events was reduced with ACE inhibitor-based (relative risk = 0.78; 95% confidence interval = 0.73–0.83) and CCB-based regimens (relative risk = 0.82; 95% confidence interval = 0.71–0.95). There were no differences in total major CV events when ACE inhibitors, CCBs, diuretics, or β -blockers were compared with one other. There were significant differences in the incidences of certain CV events; stroke was lower with diuretic/ β -blocker or CCB versus ACE inhibitor therapy; and heart failure was lower with diuretic/ β -blocker or ACE inhibitor versus CCB therapy. For every outcome except heart failure, the decrease in CV events was directly related to BP. The incidence of major CV events was lower with regimens attaining lower versus higher BP values (relative risk = 0.85; 95% confidence interval = 0.76–0.95). The incidence of major CV events was lower with ARB-based regimens compared with control regimens (relative risk = 0.90; 95% confidence interval = 0.83–0.96), which included both active drug regimens and placebo. Clinicians can use these results as evidence to support the use of commonly prescribed antihypertensive drug classes, especially ACE inhibitors and CCBs, as potential first-line treatments for hypertension. This meta-analysis is an important benchmark in the literature because it comprehensively assesses the entire body of antihypertensive pharmacotherapy outcomes data.

4. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–97.

The ALLHAT is the most robust prospective, randomized, controlled clinical trial in hypertension, and its results support the JNC 7 recommendation of thiazide diuretics as first-line therapy for most patients. It was sponsored by the National Heart, Lung, and Blood Institute and included 42,418 patients

with hypertension and at least one additional major CV risk factor. Patients were randomized to receive chlorthalidone-based, amlodipine-based, lisinopril-based, or doxazosin-based therapy with atenolol being the second drug added for BP control. The primary end point was the incidence of fatal CHD or nonfatal MI. This study was designed to demonstrate superiority of the newer antihypertensive drugs compared with chlorthalidone. After 3.3 years, patients randomized to doxazosin had a higher incidence of combined CVD than patients randomized to chlorthalidone (25.45% vs. 21.76%; $p<0.001$). After 4.9 years, amlodipine (relative risk = 0.98; 95% confidence interval = 0.90–1.07) and lisinopril (relative risk = 0.99; 95% confidence interval = 0.91–1.08) both failed to show superiority over chlorthalidone with regard to the incidence of the primary end point. The incidence of combined CVD was higher with lisinopril versus chlorthalidone (33.3% vs. 30.9%, respectively; $p<0.001$), as was the incidence of stroke (6.3% vs. 5.6%, respectively; $p=0.02$) and the incidence of heart failure (8.7% vs. 7.7%, respectively; $p<0.001$). The incidence of heart failure was higher with amlodipine versus chlorthalidone (10.2% vs. 7.7%; $p<0.001$). There were no differences among groups in the incidence of total mortality.

The ALLHAT has been criticized for the following weaknesses: the second drug added, atenolol, is not the most appropriate add-on drug for BP lowering, especially with lisinopril in most patients; mean SBPs were higher with amlodipine-treated (0.8 mm Hg; $p=0.03$) and lisinopril-treated (2 mm Hg; $p<0.001$) patients compared with chlorthalidone-treated patients; and the presence of heart failure, a component of the secondary end point, was not systematically assessed, yet it significantly influenced secondary outcomes. Moreover, differences in the rate of onset of new diabetes (11.6%, 9.8%, and 8.1% with chlorthalidone, amlodipine, and lisinopril, respectively) were not emphasized, but should be considered by clinicians. All clinicians managing patients with hypertension should read this landmark reference and identify it as the best available data demonstrating that ACE inhibitors and CCBs are not superior to thiazide diuretics. Application of these findings would have been simplified if ALLHAT investigators had chosen hydrochlorothiazide instead of chlorthalidone.

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This pre-specified subgroup analysis of the ALLHAT compared efficacy results in 11,792 black patients and 21,565 non-black patients. The incidence of nonfatal MI or fatal CHD (primary end point) was lower in black versus non-black patients (9.7% vs. 12.3%, respectively; $p<0.001$), but black patients had a higher incidence of stroke (6.5% vs. 5.3%, respectively; $p<0.001$) and total mortality (17.7% vs. 16.8%, respectively; $p=0.003$). There were no differences in the incidence of the primary end point among treatments in black patients. Differences in the incidence of certain secondary end points favored chlorthalidone, but there were no significant differences in treatment effects by race. This analysis is relevant to clinicians who treat black patients for the following reasons: there are limited outcomes data in this population; they have a higher risk of CVD than other populations; and BP lowering is less with ACE inhibitors than with CCBs or diuretics in black patients. These data support the use of diuretics in black patients.

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This subgroup analysis of ALLHAT analyzed patients according to glycemic status: diabetes (n=13,101), impaired fasting glucose (n=1399), and normoglycemia (n=17,012). Comparing patients with and without diabetes was a prespecified subgroup analysis, but the analysis of patients with impaired fasting glucose was not. A weakness of this analysis was defining impaired fasting glucose as 110–125 mg/dL, which is different from the definition recommended by the American Diabetes Association (100–125 mg/dL). No differences were seen in the incidence of the primary end point with chlorthalidone versus lisinopril among the three glycemic strata, or with chlorthalidone versus amlodipine in the diabetes or normoglycemia subgroups. However, in the impaired fasting glucose subgroup, the incidence of the primary end point was significantly lower with chlorthalidone versus amlodipine (7.7% vs. 10.8%; p=0.02) and was the only ALLHAT subgroup to show a difference in the primary end point. This analysis was important because it attempted to detect superiority of ACE inhibitors in patients with diabetes, which it did not. Rather, these data question the first-line use of an ACE inhibitor instead of a thiazide diuretic to prevent fatal CHD or nonfatal MI in patients with diabetes.

- Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT Jr, Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs. a diuretic. *Arch Intern Med* 2005;165:936–46.

This post hoc analysis of ALLHAT data was not prespecified. It compared the incidence of kidney outcomes among patients with different ranges of estimated glomerular filtration rate at baseline: normal/increased (greater than or equal to 90 mL/minute/1.73 m²; n=8,126), mildly decreased (60–89 mL/minute/1.73 m²; n=18,109), or moderately/severely decreased (less than 60 mL/minute/1.73 m²; n=5662). There were no differences among any treatments within any of these groups in the incidence of end-stage renal disease or a 50% decrease in glomerular filtration rate. This analysis would have been more useful if the mean achieved BP with each treatment were similar, to eliminate the influence of BP lowering on the incidence of end points. Although these results are hypothesis generating, they cast doubt on the kidney protective effects of ACE inhibitors.

- Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet* 2005;366:895–906.

This prospective, open treatment, and blinded end-point study compared the incidence of nonfatal MI or fatal CHD (primary end point) in 19,257 patients randomized to amlodipine-based (with or without perindopril) or atenolol-based (with or without bendroflumethiazide) therapy. Patients

had hypertension and multiple additional CV risk factors. Although the trial was stopped prematurely after 5.5 years, the incidence of the primary end point was similar (4.5% vs. 4.9% for amlodipine and atenolol, respectively; p=0.11). Secondary end points of fatal and nonfatal stroke (3.4% vs. 4.4%, respectively; hazard ratio 0.77; p=0.0003), coronary events (7.8% vs. 8.9%, respectively; hazard ratio 0.87; p=0.007), and all-cause mortality (7.7% vs. 8.5%, respectively; hazard ratio 0.89; p=0.025) were lower with amlodipine. Fewer patients developed diabetes with amlodipine-based therapy than with atenolol-based therapy (5.9% vs. 8.3%, respectively; p<0.0001). A weakness of this study was the use of a β -blocker (especially atenolol), not a thiazide diuretic, as the primary comparator. However, clinicians can use these data as support for using CCB-based therapy first-line, perhaps when an alternate to a thiazide diuretic is needed.

- Poulter NR, Wedel H, Dahlof B, Sever PS, Beevers DG, Caulfield M, et al; ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet* 2005;366:907–13.

This analysis of ASCOT assessed to what extent differences in secondary outcomes favoring amlodipine-based therapy were due to BP differences and other variables (e.g., cholesterol) while on treatment. This analysis was important because BP values were lower with amlodipine (mean SBP/DBP difference of 2.7/1.9 mm Hg; both p<0.0001). In addition, β -blocker with thiazide diuretic-based regimens can cause small but unfavorable metabolic abnormalities. All of these discrepancies could have influenced the trial results. Cox-regression models assessed differences in various measures (BP, high-density lipoprotein cholesterol, triglycerides, potassium, fasting blood glucose, heart rate, and bodyweight) and the incidence of CV events. Adjustments only for BP differences reduced the differences in the incidence of stroke and coronary events, but the results still statistically favored amlodipine. However, multivariate adjustment including other parameters eliminated the difference between treatment groups for the incidence of both stroke (hazard ratio 0.87; p=0.14) and coronary events (hazard ratio 0.94; p=0.35). All-cause mortality was not analyzed, but likely would not have been different after multivariate adjustments. This publication must also be considered to appropriately interpret ASCOT. Small differences in metabolic adverse effects coupled with differences in BP lowering influenced the incidence of CV events.

- Wassertheil-Smoller S, Psaty B, Greenland P, Oberman A, Kotchen T, Mouton C, et al. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. *JAMA* 2004;292:2849–59.

Occurrences of CVD mortality were observed in this prospective cohort of 30,219 postmenopausal women with hypertension but not CVD from the Women's Health Initiative Observational Study. At baseline, 66% of participants were on antihypertensive therapy, 72% on monotherapy, and 28% on combination therapy including an ACE inhibitor, β -blocker, CCB, or thiazide diuretic. After adjusting for covariates, the only difference with monotherapy regimens was a higher occurrence of CVD mortality with CCBs versus diuretics (hazard ratio 1.55; 95% confidence interval = 1.02–2.35). The combination of thiazide diuretic/CCB had a higher occurrence of CVD death

compared with thiazide diuretic/ β -blocker (hazard ratio 1.85; 95% confidence interval = 1.02–3.36). Regimens including a thiazide diuretic had the lowest BP values, which possibly explained mortality differences. Mean treated SBPs were 133.3–141.2 mm Hg, and 57.8% of participants had SBP values less than 140 mm Hg. A major criticism of this study was that SBP adjustments were done categorically, not continuously. These observational data in women reinforce the benefits of thiazide diuretic-based therapy seen in other trials.

11. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al; VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022–31.

In this double-blind trial, 15,245 high CV risk patients with hypertension were randomized to amlodipine-based or valsartan-based therapy, with 4.2 years of follow-up. The primary end point was time to first CV event, a broadly defined composite end point (see Table 1-3). There was no difference in the incidence of the primary end point (10.6% and 10.4% with valsartan and amlodipine, respectively; $p=0.49$). The incidence of MI, a secondary end point, was higher with valsartan (4.8% vs. 4.1%, respectively; $p=0.02$); BP also was significantly higher with valsartan (mean BP difference of 4.0/2.1 mm Hg during the first 3 months and 1.5/1.3 mm Hg after 1 year; $p<0.001$). The increased incidence of CV events with valsartan was mostly during the first 6 months, the time frame during which there were maximum BP differences. The incidence of new-onset diabetes was lower with valsartan compared with amlodipine (13.1% vs. 16.4%, respectively; $p<0.0001$). Clinicians treating patients with hypertension can use these data as evidence to justify diligent BP lowering to attain goal BP values because small changes in mm Hg differences may correlate with CV event differences.

12. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al; MOSES Study Group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention. Principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005;36:1218–26.

In this prospective, double-blind trial, 1405 patients with hypertension and a history of a cerebrovascular event were randomized to eprosartan-based or nitrendipine-based therapy for 2.5 years. The primary end point was the incidence of total mortality or any CV or cerebrovascular event. Reductions in BP were similar between groups. However, there were fewer primary events with eprosartan compared with nitrendipine (206 vs. 255, respectively; $p=0.014$), and fewer cerebrovascular events with eprosartan (102 vs. 134, respectively; $p=0.03$), but no difference in CV events (77 vs. 101, respectively; $p=0.06$). In comparison to other studies and results, this trial used an active antihypertensive comparator group and supports cerebroprotective effects of ARBs. This reference is important to individuals involved with either health care policy development or management of hypertension because it supports ARB therapy as a compelling indication for recurrent stroke prevention.

13. Ruggenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005;365:939–46.

In this controlled trial, 338 patients with non-diabetic proteinuric nephropathies receiving low-dose ramipril (2.5–5 mg/day) were randomized to open-label conventional (DBP less than 90 mm Hg) or intensified (BP less than 130/80 mm Hg) hypertension treatment. A CCB (felodipine) was added for BP control if needed. After 19 months, there was no difference in the incidence of progression to end-stage renal disease (the primary end point) between the intensified and conventional groups (23% vs. 20%, respectively; $p=0.99$). The open-label nature of this study, small sample size, and use of a low ACE inhibitor dose limits the clinical application of these findings. However, these data are useful to clinicians managing certain patients with chronic kidney disease in whom attaining a goal BP of less than 130/80 mm Hg is either complicated or unfeasible.

14. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on kidney outcomes: systematic review and meta-analysis. *Lancet* 2005;366:2026–33.

This meta-analysis evaluated evidence used to support the widely accepted assumption that ACE inhibitors and ARBs have renoprotective effects. Randomized trials (127 total) assessing antihypertensive drugs and progression of kidney disease were included. Comparisons of ACE inhibitors or ARBs with other antihypertensive drugs demonstrated only a trend toward a lower rate of decline in kidney function (serum creatinine concentration doubling (relative risk = 0.71; 95% confidence interval = 0.49–1.04), and a small but significant reduction in the development of end-stage renal disease (relative risk = 0.87; 95% confidence interval = 0.75–0.99). Comparisons of ACE inhibitors or ARBs with other antihypertensive drugs in diabetic nephropathy showed no difference in the incidence of serum creatinine concentration doubling (relative risk = 1.09; 95% confidence interval = 0.55–2.15) or end-stage renal disease (relative risk = 0.89; 95% confidence interval = 0.74–1.07). Placebo-controlled trials with ACE inhibitors or ARBs showed greater benefits than comparative trials on all kidney outcomes, but substantial reductions in BP favored the ACE inhibitor or ARB. Although surprising, these data indicate that the kidney benefits of ACE inhibitors or ARBs from placebo-controlled trials may be largely attributed to BP lowering and not intrinsic kidney protective effects. In patients with diabetes, additional kidney protective actions of ACE inhibitors and ARBs beyond BP lowering are, therefore, unproven.

15. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004;43:4–9.

This review article is provocative because hydrochlorothiazide is the most frequently used thiazide diuretic, but chlorthalidone has more evidence from outcome trials. The JNC 7 considers these two drugs interchangeable. Hydrochlorothiazide has an elimination half-life of 8–15 hours and duration of effect of 16–24 hours compared with 45–60 hours and 48–72 hours, respectively, with chlorthalidone. Chlorthalidone has 50% greater SBP lowering ability than hydrochlorothiazide (18 mm Hg and 12 mm Hg, respectively) with equal mg doses (25 mg/day). Evaluating adverse metabolic effects would have enhanced the application of this publication to clinical practice, especially considering these are expected to be higher with the more potent chlorthalidone on a mg-per-mg basis. Any clinician using a thiazide diuretic to treat hypertension should use this

reference as evidence suggesting that chlorthalidone is 1.5–2 times as potent as hydrochlorothiazide on a mg-per-mg basis. However, it does not mean that chlorthalidone should be preferentially used over hydrochlorothiazide in clinical practice.

16. Psaty BM, Furberg CD. Research letter: Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. *JAMA* 2004;292:43–44.

In this letter from two hypertension experts who conduct network meta-analyses, the incidence of CV events from five placebo-controlled trials in patients treated with low-dose thiazide diuretic therapy were compared. Two trials used chlorthalidone and three used other non-chlorthalidone thiazide diuretics. All thiazide diuretic treatments significantly reduced the incidence of coronary disease, stroke, and CVD events. A synergy index (SI) was used to compare groups and is interpreted similar to relative risk. When chlorthalidone-based studies were compared with non-chlorthalidone-based studies, there were no differences in the incidence of coronary disease (SI = 1.03; 95% confidence interval = 0.71–1.48), stroke (SI = 0.90; 95% confidence interval = 0.70–1.17), or CVD events (SI = 0.92; 95% confidence interval = 0.76–1.11). Although this is a preliminary analysis, it is the best available evidence justifying extrapolation of chlorthalidone outcome data to other thiazide diuretics. This publication is relevant to anyone involved with clinical practice considering the widespread use of hydrochlorothiazide. These data suggest that chlorthalidone and hydrochlorothiazide are equal in their ability to reduce CV events.

17. Lindholm LH, Carlberg B, Samuelsson O. Should beta-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;366:1545–53.

This meta-analysis included 13 randomized, controlled trials (n=105,951) comparing one of five β -blockers with other antihypertensive drugs, and seven randomized, controlled trials (n=27,433) comparing β -blockers with placebo. These trials were conducted in patients with hypertension with and without compelling indications. When β -blockers were compared with placebo, there was no significant difference in the incidence of MI or total mortality, but the incidence of stroke was lower (relative risk = 0.81; 95% confidence interval = 0.71–0.93). When β -blockers were compared with other antihypertensive drugs, there was no significant difference in the incidence of MI or total mortality, but the incidence of stroke was higher (relative risk = 1.16; 95% confidence interval = 1.04–1.30). Analysis of atenolol versus other antihypertensive drugs showed a significantly higher incidence of stroke (relative risk = 1.26; 95% confidence interval = 1.15–1.38) and total mortality (relative risk = 1.08; 95% confidence interval = 1.02–1.14), but not MI. This prominent publication highlights that using β -blockers, especially atenolol, for first-line therapy in patients with hypertension without compelling indications is controversial.

18. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, et al; GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004;292:2227–36.

In this double-blind, parallel-group trial, patients with type 2 diabetes and hypertension treated with an ACE inhibitor or ARB were randomized to carvedilol (n=498) or metoprolol (n=737). Mean hemoglobin A1c values were 7.2 mg/dL and increased after 5 months compared with baseline with metoprolol (absolute increase 0.15%; p<0.001), but not carvedilol (0.02%; p=0.65); BP lowering was similar between treatment groups. Insulin sensitivity, measured using Homeostasis Model Assessment-Insulin Resistance, improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less with carvedilol than with metoprolol (6.4% vs. 10.3%, respectively; p=0.04). The design of this study would have been improved by having a similar sample size between groups, and statistically comparing hemoglobin A1c values between treatment groups, as well as changes from baseline. Differences in hemoglobin A1c values may have been more drastic and clinically significant if patients had higher hemoglobin A1c values at baseline. Clinicians deciding between carvedilol or metoprolol to treat a patient with diabetes needing a β -blocker can use these data to argue that the changes in hemoglobin A1c values with metoprolol are very small and likely not clinically relevant in most patients with diabetes and hemoglobin A1c values near 7 mg/dL.

SELF-ASSESSMENT QUESTIONS

1. A 61-year-old woman has type 2 diabetes and gout. She is also status post myocardial infarction (MI). Her blood pressure (BP) is 154/98 mm Hg, heart rate 68 beats/minute, potassium 4.6 mEq/L, and serum creatinine 1.1 mg/dL. She started hydrochlorothiazide 12.5 mg/day 2 months ago, but stopped it 2 weeks later because of an acute gout attack. She is currently taking no antihypertensive therapy. Which one of the following is the most appropriate antihypertensive regimen for this patient?
 - A. Amlodipine.
 - B. Ramipril.
 - C. Ramipril with metoprolol.
 - D. Chlorthalidone with losartan.
2. A 50-year-old man was diagnosed with hypertension 3 months ago when his BP was 150/106 mm Hg. He instituted lifestyle modifications for 3 months and lost 7 kg. His current body mass index is 31 kg/m² and he smokes cigarettes. His BP today is 144/98 mm Hg. His only drug is simvastatin 40 mg/day. Which one of the following is the most appropriate recommendation at this time for the treatment of his hypertension?
 - A. Hydrochlorothiazide 12.5 mg/day.
 - B. Atenolol 25 mg/day.
 - C. An additional 3 months of his present lifestyle modifications, then add drug therapy.
 - D. Smoking cessation, then add drug therapy if BP is elevated after 3 months.

Questions 3–6 pertain to the following case.

You are preparing a continuing education lecture for a group of health care practitioners (nurse practitioners, physician assistants, pharmacists, and physicians) who treat patients with hypertension. The goals of this program are to review national treatment guidelines and provide evidence-based updates regarding antihypertensive pharmacotherapy.

3. Which one of the following concepts should be included in this lecture because it is the most important consideration to attain long-term benefits when approaching the treatment of patients with hypertension and compelling indications?
 - A. Treat patients with hypertension and chronic kidney disease, but without diabetes, to a goal BP of less than 130/80 mm Hg.
 - B. Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β -blockers, and calcium channel blockers (CCBs) all have similar reductions in cardiovascular (CV) events.
 - C. Lower systolic BP (SBP) as much as possible to maximize reduction in the risk of CV events.
 - D. Select specific pharmacotherapy regimens based on evidence demonstrating a reduced risk of stroke, MI, and CV death.
4. One of the learning objectives of this lecture you are to deliver is to identify, interpret, and apply data specifically from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). Which one of the following statements is most appropriate to include in your lecture to address this objective?
 - A. The two-drug combination regimens used in both treatment groups should be used in patients with hypertension because they were highly effective in lowering BP.
 - B. Differences in BP lowering and metabolic changes together can influence the incidence of CV events with antihypertensive therapy.
 - C. The primary end point of fatal coronary heart disease (CHD) or nonfatal MI was a very clinically relevant end point because it is similar to the Framingham risk scoring.
 - D. Using amlodipine-based and atenolol-based treatment groups makes comparisons of these data to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) invalid.
5. Part of this lecture includes a discussion of using a large combined CV end points as the primary end point in hypertension outcome trials. Which one of the following statements is the most clinically appropriate reason to use combined CV end points in clinical trials?
 - A. It is easier to detect a statistically significant difference between groups.
 - B. Open-label treatments can be used as long as assessment of the end point is blinded.
 - C. They are becoming more popular to use in studies rather than the end points that have been used in landmark clinical trials.
 - D. They may be more relevant than studies that use individual CV events as end points in assessing long-term complications.

Another objective of this lecture is to present cumulative data from meta-analyses demonstrating reduced incidence of CV events with the five major antihypertensive drug classes. You present a case scenario in which a large managed care organization is trying to incorporate these findings in the development of an institutional guideline for the treatment of hypertension. This guideline must reflect the data from the meta-analysis regarding reductions in CV outcomes with the five major antihypertensive drug therapies (ACE inhibitors, ARBs, β -blockers, CCBs, and thiazide diuretics).

6. Which one of the following recommendations most appropriately reflects the broad interpretation of these meta-analyses data to the overall population of patients with hypertension in this organization?
- Thiazide diuretics should be used before other drugs.
 - It is still inconclusive whether ARBs reduce CV events compared with other drugs.
 - All five classes have the ability to reduce the incidence of certain CV events.
 - All five classes can be used long term to provide similar reductions in BP.
- C. The ASCOT proved that amlodipine reduced secondary end points more than atenolol because it is a more potent antihypertensive drug.
- D. The ALLHAT reinforced the role of atenolol as the most rational second drug to add in an antihypertensive drug regimen.
10. Your colleague points out that extrapolating results seen with chlorthalidone to hydrochlorothiazide is problematic due to differences in efficacy, safety, and response between these drugs. Which one of the following statements is most appropriate to share with your colleague?

Questions 7 and 8 pertain to the following case.

An 81-year-old man has hypertension and a history of ischemic stroke. His BP today is 168/74 mm Hg, heart rate 68 beats/minute, height 70 inches, weight 70 kg, and serum creatinine 1.4 mg/dL. Last year his serum creatinine was 1.4 mg/dL. He is currently on lisinopril 20 mg/day, hydrochlorothiazide 12.5 mg/day and metoprolol 25 mg 2 times/day. He also smokes and drinks three ethanol-containing beverages daily.

7. Which one of the following treatment recommendations for this patient is best supported by outcomes data?
- Lowering BP to a goal of 140/90 mm Hg.
 - Lowering BP to a goal of 130/80 mm Hg.
 - Angiotensin-converting enzyme inhibitor with diuretic therapy.
 - β -Blocker with diuretic therapy.
8. In addition to his age, which one of the following factors increases his risk of orthostatic hypotension to the greatest extent?
- Diastolic blood pressure.
 - Serum creatinine concentration.
 - Smoking.
 - Metoprolol.

Questions 9 and 10 pertain to the following case.

One of your colleagues attended a lecture where ASCOT data were presented. Your colleague states that amlodipine is better at reducing CV events than other antihypertensive drugs, including ACE inhibitors, based on the results of the ASCOT trial. You cite the primary and secondary end point results of ALLHAT and the study methodology to refute that claim. Your colleague says this trial was also discussed at the presentation, but the presenter said it was not a "positive" trial.

9. Which one of the following is the most accurate application of the findings of these two trials to the treatment of hypertension?
- The ASCOT cannot be used to justify first-line treatment with amlodipine over a thiazide diuretic.
 - The ALLHAT doxazosin treatment arm was terminated early, so final results in the other groups are inaccurate.
11. A 60-year-old woman with a history of hypertension and chronic kidney disease is taking atenolol 100 mg/day and her BP is 150/82 mm Hg, heart rate 62 beats/minute, weight 90 kg, and height 65 inches. She does not have diabetes. Her serum creatinine is 2.3 mg/dL, her 24-hour urinalysis shows 1200 mg proteinuria, and her serum potassium is 4.5 mEq/L. Lisinopril 10 mg/day is added to her regimen. Four weeks later, her BP is 140/74 mm Hg, serum creatinine is 2.5 mg/dL, and potassium is 4.7 mEq/L. Based on recent evidence, which one of the following is the best approach to her current therapy?
- Continue to lower her BP further to a goal SBP of 140 mm Hg.
 - Switch lisinopril to ramipril for greater CV risk reduction.
 - Change the lisinopril dose to 5 mg/day.
 - Add losartan to lisinopril.
12. A 55-year-old woman was diagnosed with hypertension. Her BP at the time of diagnosis was 160/100 mm Hg, and her heart rate was 92 beats/minute. After 6 months of lifestyle modifications, her BP decreased to 150/96 mm Hg and hydrochlorothiazide 25 mg/day was started. It is now 4 weeks later, and her BP is 144/86 mm Hg and her heart rate is 90 beats/minute. Her only other medical condition is depression, which is controlled with fluoxetine 20 mg/day. In addition to continuing lifestyle modifications, which one of the following is most appropriate for the management of her hypertension?
- Switching hydrochlorothiazide to felodipine 5 mg/day.
 - Increasing hydrochlorothiazide to 50 mg/day.
 - Adding felodipine 5 mg/day.
 - Adding metoprolol 25 mg/day.

13. A 68-year-old woman is recovering from a stroke that occurred 3 months ago. She is currently stable and is seen for medical follow-up. She also has a history of hypertension that has been treated with hydrochlorothiazide 25 mg/day for the past 5 years. Her BP today is 154/80 mm Hg. She has previously taken enalapril and ramipril, but experienced an intolerable dry cough with both drugs. Which one of the following antihypertensive drug classes is the best choice to add to her current regimen to reduce her risk of a second stroke?
- An α -blocker.
 - An ARB.
 - A β -blocker.
 - A non-dihydropyridine CCB.
14. You are reviewing literature regarding ALLHAT. In addition to the primary study results paper, you also read several published subgroup analyses of ALLHAT. Which one of the following is justified based on an appropriate interpretation of the subgroup analyses data?
- Further studying the benefits of thiazide diuretics in patients with hypertension and prediabetes.
 - Avoiding β -blockers in patients with hypertension.
 - Preferential use of CCBs as first-line therapy in black patients with hypertension.
 - Guidelines should now recommend using ACE inhibitors as first-line therapy in patients with hypertension and diabetes.
17. Which one of the following is the most appropriate interpretation of evidence from outcome studies regarding β -blockers for the treatment of hypertension?
- Atenolol lowers the incidence of MI, but increases the incidence of stroke.
 - All β -blockers reduced the incidence of total mortality when used to treat hypertension.
 - β -blockers are best used as second-line drugs in most patients with hypertension after thiazide diuretics, ACE inhibitors, and CCBs.
 - There are no clinically relevant differences between atenolol and metoprolol because they both are cardioselective and do not block α -receptors.
18. You are a clinical pharmacist employed by a large managed care organization and are evaluating the use of thiazide diuretics. Nearly all the prescriptions for thiazide diuretics in your organization are for hydrochlorothiazide. However, a formulary decision has been made to replace hydrochlorothiazide with chlorthalidone. Which one of the following statements supports implementing this type of conversion?
- Chlorthalidone reduces the incidence of CV events more than other thiazide diuretics.
 - The largest hypertension outcome studies used chlorthalidone.
 - Hydrochlorothiazide is more likely to cause adverse metabolic effects than chlorthalidone.
 - Most fixed-dose combination products with a thiazide diuretic use chlorthalidone.

Questions 15 and 16 pertain to the following case.

A 67-year-old man has a history of hypertension, chronic stable angina, and type 2 diabetes mellitus. His current drugs are metoprolol XL 100 mg/day, isosorbide mononitrate 60 mg 2 times/day, nitroglycerin sublingual as needed, rosiglitazone 4 mg 2 times/day, metformin 1000 mg 2 times/day, atorvastatin 40 mg/day, and aspirin 81 mg/day. His BP is 154/84 mm Hg, and his heart rate is 60 beats/minute. Laboratory values are all normal and his hemoglobin A1c is 7.2 mg/dL. He has chest pain 2 times/week, which is relieved with one or two sublingual nitroglycerin tablets.

15. Which one of the following is the most appropriate therapy to reduce this patient's risk for CV events?
- Replace metoprolol with verapamil.
 - Replace metoprolol with atenolol.
 - Add perindopril.
 - Add perindopril and amlodipine.
16. Regardless of your recommendation, this patient's physician decides to switch metoprolol to carvedilol 12.5 mg 2 times/day. Based on newer data, which one of the following is the most likely patient outcome after changing metoprolol to carvedilol?
- Decreased progression to kidney failure.
 - Minimal to no change in his BP.
 - Decreased incidence of CV events.
 - A clinically significant decrease in his hemoglobin A1c value.
19. A 65-year-old woman with systolic dysfunction heart failure and hypertension was hospitalized 3 months ago for an acute MI. Her BP today is 130/84 mm Hg with a heart rate of 80 beats/minute. She is 68 inches tall and weighs 80 kg. Her serum creatinine is 0.8 mg/dL, serum potassium is 3.8 mEq/L, ejection fraction is 30%, and a 24-hour urinalysis shows microalbuminuria. Today she has moderate to severe peripheral edema. She is taking furosemide 40 mg 2 times/day, carvedilol 25 mg 2 times/day, and lisinopril 40 mg/day. In addition to heart failure, which one of the following also justifies ACE inhibitor therapy in this patient?
- Hypokalemia.
 - Peripheral edema.
 - Chronic kidney disease.
 - Post myocardial infarction.
20. A 79-year-old woman is diagnosed with chronic stable angina. She reports having chest pain once or twice weekly for the past month. Although she also has a diagnosis of hypertension, she has never been treated with antihypertensive pharmacotherapy. The only drug she is currently taking is enteric-coated aspirin 81 mg/day. Her current BP is 174/66 mm Hg, with a heart rate of 76 beats/minute. Which one of the following is the most appropriate initial antihypertensive therapy for this patient?
- Metoprolol.
 - Hydrochlorothiazide.
 - Metoprolol with hydrochlorothiazide.
 - Trandolapril with verapamil.

