



# Blood Pressure Management

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## LEARNING OBJECTIVES

1. Distinguish key differences between various national and international hypertension (HTN) guidelines.
2. Demonstrate appropriate drug selection and blood pressure goals for the treatment of HTN according to the presence of concomitant conditions.
3. Devise an evidence-based treatment strategy for resistant HTN to achieve blood pressure goals.
4. Justify the use of ambulatory blood pressure monitoring.
5. Develop treatment strategies for hypertensive urgency and emergency.
6. Construct appropriate drug therapy plans for the treatment of hypotension.
7. Assess the potential effect of pharmacogenomics on blood pressure.

## ABBREVIATIONS IN THIS CHAPTER

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
AGT	Angiotensinogen
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HF	Heart failure
HTN	Hypertension
JNC	Joint National Committee
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
OH	Orthostatic hypotension
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SNP	Single nucleotide polymorphism

[Table of other common abbreviations.](#)

## EPIDEMIOLOGY

Hypertension (HTN) is a persistent, nonphysiologic elevation in blood pressure; it is defined as (1) having a systolic blood pressure (SBP) of 140 mm Hg or greater; (2) having a diastolic blood pressure (DBP) of 90 mm Hg or greater; (3) taking antihypertensive medication; or (4) having been told at least twice by a physician or other health professional that one has HTN. According to WHO, almost 1 billion people had uncontrolled HTN worldwide in 2008. The American Heart Association (AHA) estimates that 41% of the U.S. population will have a diagnosis of HTN by 2030, an increase of 8.4% from 2012 estimates.

The prevalence of HTN increases from 7.3% in people aged 18–39 to 32.4% in people aged 40–59 and 65.0% in those older than 59 years. Data from the National Health and Nutrition Examination Survey (NHANES) show a higher prevalence of HTN in men than in women until age 45 years and similar rates thereafter.

The sobering reality for those who treat patients with HTN is that more than one-half of patients (53.5%) are inadequately controlled, and more than one-third (39.4%) are unaware that they have HTN (CDC 2012). A review of NHANES data shows that the percentage of hypertensive adults with optimal blood pressure increased from 13% to 19% from 2003 to 2012, whereas mean SBP decreased during the same time (Yoon 2015). However, with recent changes made to HTN guidelines (see the next section), the prevalence of uncontrolled HTN may be lower than these estimates (Sakhujia 2015). The improvements in HTN control among the U.S. population have correlated with the increased use of antihypertensive drugs, particularly combination therapy (Gu 2012).

A thorough knowledge of contemporary HTN management strategies is imperative for pharmacists participating in direct patient care, given the increased rates of atherosclerotic and atherothrombotic cardiovascular disease (CVD) in those with elevated blood pressure. Data analyses show that the risk of CVD is increased 2- to 3-fold in patients with HTN versus normotensive controls. It is estimated that 69% of individuals who have a first myocardial infarction (MI), 77% of those who have a first stroke, and 74% of those who have heart failure (HF) have HTN.

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- “White-coat” hypertension (HTN)
- Antihypertensive medications and their monitoring values
- Lifestyle recommendations for HTN
- Pharmacogenomics describes all genes within a genome that may relate to drug response, whereas pharmacogenetics focuses on single genetic polymorphisms

[Table of common laboratory reference values](#)

### ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Chobanian AV, Bakris GL, Black HR, et al. [Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure](#). *Hypertension* 2003;42:1206-52.
- American Diabetes Association (ADA). [Standards of medical care in diabetes – 2015](#). *Diabetes Care* 2015;38(suppl 1):S1-94.
- [KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease](#). *Kidney Int* 2013;5:337-414.
- James PA, Oparil S, Carter BL, et al. [2014 evidence-based guideline for the management of high blood pressure in adults](#). *JAMA* 2014;311:507-20.
- Weber MA, Schiffrin EL, White WB, et al. [Clinical practice guidelines for the management of hypertension in the community](#). *J Clin Hypertens* 2014;16:14-26.
- Rosendorff C, Lackland DT, Allison M, et al. [Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension](#). *Circulation* 2015;131:e435-70

## HTN GUIDELINES

Since the inception of the Joint National Committee guidelines on HTN, the National Heart, Lung, and Blood Institute (NHLBI) has sanctioned these publications. However, the last-sanctioned HTN guideline by the NHLBI was the Seventh Report of the Joint National Committee (JNC 7), published in 2003. The writing panel for the JNC 8 guideline was appointed in 2008; however, in 2013 the NHLBI transferred the HTN guideline development to the American Heart Association and the American College of Cardiology (AHA/ACC) (Gibbons 2013). The original JNC 8 writing panel published its recommendations in December 2013, acknowledging that it was not sanctioned or endorsed by the NHLBI (James 2014). In addition, the American Society of Hypertension/International Society of Hypertension (ASH/ISH) published guidelines in December 2013; some of these recommendations differ from those of the JNC 8 writing panel (Weber 2014). The official ACC/AHA guidelines for HTN management, which are intended to replace the last NHLBI guidelines, are expected in 2016.

The JNC 7 guidelines classified blood pressure as follows: normal (SBP less than 120 mm Hg and DBP less than 80 mm Hg), pre-HTN (SBP 120–139 mm Hg or DBP 80–89 mm Hg), stage 1 HTN (SBP 140–159 mm Hg or DBP 90–99 mm Hg), or stage 2 HTN (SBP 160 mm Hg or higher or DBP 100 mm Hg or higher) (Chobanian 2003). Table 1-1 compares blood pressure goals for different populations among various international guidelines, including several U.S. guidelines, the Canadian Hypertension Education Program, and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines.

### HTN Guideline Controversy

Although the various HTN guidelines differ, one controversial issue in these guidelines is the age that the blood pressure goal should be increased to less than 150/90 mm Hg for older adult patients. Published data are limited on the benefits of achieving a target blood pressure of less than 140/90 mm Hg in older adult patients. For patients 60 years and older, the JNC 8 panel recommends initiating treatment to achieve a goal blood pressure of less than 150/90 mm Hg (James 2014). The age chosen by the JNC 8 writing panel for a less aggressive blood pressure target is 20 years younger than the age defined as older adults, 80 years and older, in the 2013 ASH/ISH, Canadian Hypertension Education Program, ESH/ESC, and ACC/AHA/ASH guidelines, which target a blood pressure goal of less than 150/90 mm Hg (Rosendorff 2015; Weber 2014; Hackman 2013; Mancia 2013).

The JNC 8 panel authors cited the VALISH and JATOS studies as evidence for setting a goal SBP of higher than 140 mm Hg in patients older than 60 years. Neither the VALISH nor the JATOS study showed any difference between strict control (SBP of less than 140 mm Hg) and more modest control (SBP less than 150 mm Hg for VALISH; SBP less than 160 mm Hg for JATOS) (Ogihara 2010; JATOS 2008). However, both trials were underpowered to determine whether strict control was superior

**Table 1-1.** Comparison of International Guidelines on HTN Goals (mm Hg)

	Uncomplicated HTN	Diabetes	Cardiovascular Disease	Chronic Kidney Disease	Older Adults
JNC 7 (2003) <sup>a</sup>	< 140/90	< 130/80	< 140/90	< 130/80	Not specified
JNC 8 (2014) <sup>b</sup>	< 140/90	< 140/90	—	< 140/90	< 150/90, age ≥ 60 yr
ASH/ISH (2013) <sup>c</sup>	< 140/90	< 140/90	< 140/90	< 140/90	< 150/90, age ≥ 80 yr
CHEP (2013) <sup>d</sup>	< 140/90	< 130/80	< 140/90	< 140/90	< 150/90, age ≥ 80 yr
ESH/ESC (2013) <sup>e</sup>	< 140/90	< 140/85	< 140/90	< 140/90	< 150/90, age ≥ 80 yr
Disease-specific guidelines	Not applicable	< 140/90; ADA (2015) <sup>f</sup>	< 140/90; unless ≥ 80 yr, then < 150/90 ACC/AHA (2015) <sup>g</sup>	< 130/80 with proteinuria; otherwise, < 140/90; KDIGO (2012) <sup>h</sup>	Not specified; ACC/AHA (2011) <sup>i</sup>

<sup>a</sup>Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.

<sup>b</sup>James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. *JAMA* 2014;311:507-20.

<sup>c</sup>Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. *J Clin Hypertens* 2014;16:14-26.

<sup>d</sup>Hackam DG, Quinn RR, Ravani P, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2013;29:528-42.

<sup>e</sup>Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. *J Hypertens* 2013;31:1281-357.

<sup>f</sup>American Diabetes Association (ADA). Standards of medical care in diabetes – 2015. *Diabetes Care* 2015;38(suppl 1):S1-S94.

<sup>g</sup>Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *Circulation* 2015;131:e435-70.

<sup>h</sup>Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;2:337-414.

<sup>i</sup>Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2011;123:2434-506.

CHEP = Canadian Hypertension Education Program; HTN = hypertension.

to less stringent targets. Of interest, the authors of the JATOS trial noted that strict treatment may decrease CVD risk in patients younger than 75 (JATOS 2008). A minority of the JNC 8 writing panel published a report stating that there was no consensus on the age at which to increase the blood pressure goal in older adults. This report stated that the evidence supporting raising the target from 140 mm Hg to 150 mm Hg in people 60 or older was insufficient and inconsistent (Wright 2014).

The HYVET trial assessed various CV end points in 3845 patients 80 years and older (mean age 83) with an SBP of 160 mm Hg or greater treated with indapamide versus placebo. Perindopril or matching placebo was added to achieve a target blood pressure of 150/80 mm Hg. After 1.8 years, the mean SBP was 143.5 mm Hg in the treatment group and 158.5 mm Hg in the placebo group. The treated group had a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, -1 to 51; p=0.06), a 39% reduction in the rate of death from stroke (95%

CI, 1–62; p=0.05), and a 21% reduction in the rate of death from any cause (95% CI, 4–35; p=0.02) compared with the placebo group (Beckett 2008). This study supports increasing the blood pressure goal for patients older than 80 to less than 150/90 mm Hg because lowering blood pressure below this level decreased both death and stroke.

### New HTN Landmark Trial

In September 2015, the National Institutes of Health issued a press release about the SPRINT study, which it funded. The study was terminated early after a median of 3.26 years, and data were published in November 2015 (NIH 2015). More than 9300 patients 50 years or older with at least one CV risk factor or with renal disease (but no diabetes) were enrolled, and about 25% were 75 years or older. Patients were randomized to the intensive blood pressure arm (target SBP less than 120 mm Hg) or the conventional arm (target SBP less than 140

mm Hg). The primary composite outcome was MI, other ACS, stroke, HF, or death from CV causes.

In the intensive treatment group, the mean SBP was 121.4 mm Hg and in the standard treatment group, the mean SPB was 136.2 mm Hg at 1 year. During follow-up (3.26 years), the intensive group maintained a mean SBP of 121.5 mm Hg and the standard treatment group had a mean SPB of 134.6 mm Hg. The mean number of BP drugs was 2.8 and 1.8, respectively. The primary composite outcome in the intensive-treatment group was significantly lower than in the standard-treatment group (1.65% per year vs. 2.19% per year; HR 0.75; 95% CI, 0.64–0.89;  $p < 0.001$ ). Compared with the conventional arm, the intensive arm had a 38% reduction in HF, a 30% reduction in CV events, a 43% reduction in death from CV causes, and a 27% reduction in all-cause mortality. During the 3.26 years, the numbers needed to treat to prevent a primary outcome event, death from any cause, and death from CV causes were 61, 90, and 172, respectively. These benefits (primary outcome and death) were consistent across all subgroups, including participants aged 75 years or older.

Serious adverse events occurred in 38.3% of the intensive-treatment group and 37.1% of the standard-treatment group (HR 1.04;  $p = 0.25$ ). Rates of serious adverse events (hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure) were higher in the intensive-treatment group (4.7%) than in the standard-treatment group (2.5%) (HR 1.88;  $p < 0.001$ ). However, bradycardia and injurious falls were not seen more often in the intensive group, and orthostatic hypotension was seen significantly less in the intensive group. Among participants 75 years of age or older, adverse events were similar to those in the overall cohort (SPRINT 2015). Given the novelty of this information, the impact on guidelines is yet to be seen.

Therefore, although current national and international guidelines agree that the blood pressure goal should be increased to less than 150/90 mm Hg for older adult patients, the age at which this should be done is not universally agreed on. New evidence from the SPRINT trial may influence these recommendations in the future.

## UNCOMPLICATED HTN

### Blood Pressure Goals

The term *uncomplicated HTN* refers to HTN in the absence of diabetes, HF, chronic kidney disease (CKD), or known coronary artery disease (CAD). According to the guidelines, the blood pressure goal for uncomplicated HTN is less than 140/90 mm Hg. Lifestyle changes should be encouraged for patients with elevated blood pressure, including increased consumption of fruits and vegetables, moderation in alcohol and salt intake, participation in regular exercise, weight reduction to a healthy body mass (if needed), and tobacco cessation.

The benefits and risks of pharmacotherapy for stage 1 HTN (SBP 140–159 mm Hg and/or DBP 90–99 mm Hg) in primary

prevention were examined in two recent meta-analyses with conflicting conclusions. A Cochrane review examined four randomized controlled trials with more than 8900 patients, concluding that treatment with antihypertensive drugs for 4–5 years compared with placebo did not reduce total mortality (RR 0.85, 95% CI, 0.63–1.15), CAD (RR 1.12; 95% CI, 0.80–1.57), stroke (RR 0.51; 95% CI, 0.24–1.08), or total cardiovascular (CV) events (RR 0.97; 95% CI, 0.72–1.32). In addition, 9% of patients discontinued antihypertensive therapy because of adverse effects (Diao 2012).

However, a recent systematic review and meta-analysis updated this review with data from the Blood Pressure Lowering Treatment Trialists' Collaboration. This group completed a series of reviews of trials studying blood pressure lowering, with access to individual study participant data. This added 6361 eligible patients (96% had diabetes) for a study sample of more than 15,000 patients. After 5 years, patients in the treatment arms had a reduction in stroke (OR 0.72; 95% CI, 0.55–0.94), CV death (OR 0.75; 95% CI, 0.57–0.98), and total death (OR 0.78; 95% CI, 0.67–0.92). However, reductions in total CV events, coronary events, and HF were not statistically significant. Treatment withdrawal for adverse events was more common in the treatment groups; however, data were limited (Sundstrom 2015). Additional randomized controlled trials are needed in these patients to help clarify the benefits of treating stage 1 HTN in primary prevention.

### Antihypertensive Therapy

Thiazide diuretics decrease the incidence of mortality and CAD and have supporting evidence as first-line therapy for the treatment of HTN (Wright 2009). Control of blood pressure is more important than the drug class used in the primary prevention of complications from HTN (Staessen 2003; Wang 2003). Other recommended first-line options for uncomplicated HTN include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). In women of childbearing potential, ACE inhibitor and ARB therapy should be avoided because of possible teratogenic effects. If ACE inhibitor or ARB therapy must be used in young women, they should be counseled on the importance of using highly effective birth control methods.

$\beta$ -Blockers are no longer recommended as a first-line option for uncomplicated HTN. A meta-analysis of 13 randomized trials comparing  $\beta$ -blockers with other antihypertensive therapy in 105,951 patients reported an RR of stroke that was 16% higher for  $\beta$ -blockers (95% CI, 4%–30%;  $p = 0.009$ ) than for other drugs; there was no difference for MI (Lindholm 2005).  $\beta$ -Blockers may be useful in patients with uncomplicated HTN requiring antihypertensive drug therapy who also have atrial fibrillation, migraine, or essential tremor, but they should be avoided in patients with second- or third-degree heart block.

Table 1-2 compares U.S. guidelines on antihypertensive therapy recommendations, highlighting the variability among them. The JNC 8 panel guidelines and 2013 ASH/ISH

**Table 1-2. Comparison of U.S. Guidelines on Antihypertensive Therapy**

	Stage 1 HTN	Stage 2 HTN	Chronic Kidney Disease	Diabetes	Coronary Disease	Stroke	Symptomatic HF
	African American	Non-African American					
	< 60 yr	≥ 60 yr					
<b>JNC 7<sup>a</sup></b>							
Initial therapy	Thiazide diuretic	Two-drug therapy: thiazide diuretic PLUS CCB, ACE inhibitor or ARB, β-blocker	ACE inhibitor or ARB	Diuretic, β-blocker, ACE inhibitor or ARB, CCB	β-Blocker, ACE inhibitor, aldosterone antagonist	Diuretic, ACE inhibitor	Diuretic, β-blocker, ACE inhibitor or ARB, aldosterone antagonist
Subsequent therapy	CCB, ACE inhibitor or ARB, β-blocker						
<b>JNC 8<sup>b</sup></b>							
Initial therapy	Thiazide-type diuretic or CCB	Thiazide-type diuretic, CCB, ACE inhibitor or ARB	ACE inhibitor or ARB	—	—	—	—
<b>ASH/ISH<sup>c</sup></b>							
Initial therapy	CCB or thiazide diuretic (combine if necessary)	ACE inhibitor or ARB	CCB or thiazide diuretic (combine if necessary)	ACE inhibitor or ARB	β-Blocker PLUS ACE inhibitor or ARB	ACE inhibitor or ARB	Regardless of BP, ACE inhibitor or ARB PLUS β-blocker, diuretic, and spironolactone
Subsequent therapy	ACE inhibitor or ARB	CCB or thiazide diuretic (combine if necessary)	ACE inhibitor or ARB	CCB or thiazide diuretic (combine if necessary)	CCB or thiazide diuretic (combine if necessary)	CCB or thiazide diuretic (combine if necessary)	DHP CCB
<b>Disease-Specific Guidelines</b>							
Initial therapy	—	—	KDIGO <sup>d</sup>	ADA <sup>e</sup>	ACC/AHA CVD <sup>f</sup>	—	—
Subsequent therapy	—	—	Urine albumin excretion > 30 mg/24 hr: ACE inhibitor or ARB	ACE inhibitor or ARB	β-Blocker and/or ACE inhibitor and/or diuretics	—	—
Subsequent therapy	—	—	No proteinuria: no preferred antihypertensive drugs	Thiazide diuretic, β-blockers, and DHP CCB	Other antihypertensive drugs as needed to achieve BP goal	—	—

<sup>a</sup>Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

<sup>b</sup>James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. JAMA 2014;311:507-20.

<sup>c</sup>Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. J Clin Hypertens 2014;16:14-26.

<sup>d</sup>Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:337-414.

<sup>e</sup>American Diabetes Association (ADA). Standards of medical care in diabetes – 2015. Diabetes Care 2015;38(suppl 1):S1-S94.

<sup>f</sup>Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation 2015;131:e435-70.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DHP = dihydropyridine; HF = heart failure; HTN = hypertension.

guidelines both base antihypertensive therapy recommendations on race (African American vs. non-African American). For example, they advise a thiazide diuretic or CCB as initial therapy for African American patients (James 2014; Weber 2014). However, the ASH/ISH guidelines also factor in age (younger than 60 years and 60 years or older) for antihypertensive recommendations. For stage 2 HTN (i.e., greater than 160/100 mm Hg), guidelines recommend that patients be initiated on combination therapy (Weber 2014; Chobanian 2003). Finally, disease-specific guidelines (CKD, diabetes, and CVD) provide their own set of treatment recommendations.

## HTN WITH CONCOMITANT DISEASE STATES

### Coronary or Other Atherosclerotic Vascular Disease

Hypertension has long been recognized as an independent risk factor for CVD. In a large meta-analysis (almost 1 million primary prevention adults) there was a linear increase in vascular death from a blood pressure of 115/75 mm Hg to 185/115 mm Hg; the risk of CVD doubled for each 20-mm Hg increase in SBP (Lewington 2002). The mechanisms of blood pressure elevation and end-organ damage involving the heart include increased sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activity; decreased release or activity of vasodilators; changes in natriuretic peptides, growth factors, and inflammatory cytokines; increased vascular stiffness and endothelial dysfunction; and modifications in hemodynamic effects. Cardiac structure and function are primarily influenced by the physical forces on them (blood pressure and flow), which contribute to remodeling and atherosclerosis (Rosendorff 2015).

### Blood Pressure Goals

In 2015, AHA/ACC/ASH published updated blood pressure guidelines for patients with CAD (Rosendorff 2015). Although epidemiologic studies support a “lower-is-better” approach to blood pressure in patients with atherosclerotic cardiovascular disease (ASCVD), there is concern that lowering the DBP too much will result in decreased coronary perfusion. The coronary circulation autoregulates so that a decrease in perfusion pressure results in coronary vasodilation to allow consistent blood flow. However, it is theorized that the ability to compensate with vasodilation is limited once the perfusion pressure falls below a certain level. Unfortunately, beyond animal studies, no data on the DBP level correspond to the lower limits of autoregulation in humans with or without CAD. In addition, there is inconsistent evidence that lowering DBP beyond a certain level will compromise CV outcomes.

The 2007 ACC/AHA HTN guidelines for patients with ischemic heart disease use epidemiologic studies to set a blood pressure goal of less than 130/80 mm Hg for patients with CAD or CAD risk equivalents (Rosendorff 2007). In 2011, ACC/AHA published secondary prevention guidelines that updated

the blood pressure goal from less than 130/80 mm Hg to less than 140/90 mm Hg (Smith 2011). The 2012 ACC/AHA guidelines for patients with stable ischemic heart disease again recommend a goal of less than 140/90 mm Hg (Fihn 2012). The 2015 ACC/AHA/ASH blood pressure guidelines for patients with CAD also support the goal of less than 140/90 mm Hg (class I, level of evidence A), with caveats: a goal blood pressure of less than 130/80 mm Hg may be appropriate in some individuals with CAD, previous MI, stroke or transient ischemic attack, or CAD risk equivalents (carotid artery disease, peripheral artery disease, abdominal aortic aneurysm) according to some epidemiologic data and several post hoc analyses of clinical trials (class IIb, level of evidence C). Caution is advised in causing DBP to drop below 60 mm Hg in any patient with diabetes mellitus or who is older than 60. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (less than 60 mm Hg) (class IIa, level of evidence C). Despite a lack of data to support a specific blood pressure goal, a blood pressure target of less than 150/80 mm Hg may be seen as reasonable for patients with CAD who are older than 80 (Rosendorff 2015).

### Antihypertensive Therapy

Box 1-1 highlights first- and second-line treatment options for patients with ischemic heart disease (Rosendorff 2015). The benefits of  $\beta$ -blockers in these patients are likely caused by a decrease in oxygen demand resulting from a lower heart rate and blood pressure, decreased risk of ventricular arrhythmias, and prolonged diastole leading to improved diastolic perfusion. However, recommendations for  $\beta$ -blocker therapy have been updated to reflect evidence that their efficacy is greatest among patients experiencing an MI (or acute coronary syndrome) within the previous 3 years and/or left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] less than 40%). In normotensive patients without these class I indications,  $\beta$ -blocker therapy is optional (class IIa or IIb) (Smith 2011). No large trials have shown a survival benefit or reduction in coronary event rates with  $\beta$ -blocker therapy in patients with stable ischemic heart disease. If  $\beta$ -blocker therapy is needed to adequately control blood pressure or heart rate, it should be continued unless contraindications or tolerance issues develop. In this situation, alternative antihypertensive drugs should be used.

Clinical trials have shown that ACE inhibitors provide CV-protective effects by reducing the risk of future ischemic events, particularly in high-risk patients (Fox 2003; Yusuf 2000). The decrease in angiotensin II and increase in bradykinin may contribute to the reductions in left ventricular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis, as well as improved myocardial oxygen supply/demand. As first-line antihypertensive therapy, ACE inhibitors should be initiated and continued indefinitely in all patients with HTN having coronary or atherosclerotic vascular disease (Rosendorff 2015). In addition, ACE inhibitors are recommended for patients with ASCVD and an LVEF of less than

40%, diabetes, or CKD, unless contraindicated. The use of ARBs is recommended as first-line antihypertensive therapy in patients who are ACE inhibitor intolerant and have HF or in those who have had an MI with an LVEF of less than 40% (Rosendorff 2015; Fihn 2012; Smith 2011).

Other first-line antihypertensive therapies for patients with ASCVD are thiazide and thiazide-type diuretics (e.g., chlorthalidone, indapamide); in several clinical trials, these have shown benefit in reducing cardio- and cerebrovascular events (Rosendorff 2015).

## Diabetes

Most patients with diabetes are affected by HTN, and it is a risk factor for macro- and microvascular complications. Because CVD is the No. 1 killer of, and main source of morbidity in, patients with diabetes, controlling CV risk factors such as HTN in patients with diabetes is of utmost importance.

Controlling CV risk factors prevents or slows the development of CVD (ADA 2015).

## Blood Pressure Goals

The blood pressure goal for patients with diabetes has changed several times in recent years. In January 2013, the American Diabetes Association (ADA) recommended a higher SBP goal of less than 140 mm Hg (previous goal: less than 130 mm Hg). The 2013 ASH/ISH blood pressure guidelines and JNC 8 also recommended this higher SBP goal for patients with diabetes (James 2014; Weber 2014).

The former SBP goal (less than 130 mm Hg) was based only on epidemiologic data, not randomized controlled trials. The ACCORD study aimed to determine whether an SBP target of less than 120 mm Hg reduces major CV events in participants who have type 2 DM and a high risk of CV events. More than 4700 patients were randomly assigned to intensive or standard therapy, targeting an SBP of less than 120 mm Hg or

### Box 1-1. Antihypertensive Therapy Recommendations for Patients with Ischemic Heart Disease

#### Acute Coronary Syndrome

First-line options – Drugs of choice

- ACE inhibitor or ARB – Particularly if MI, LVSD, DM, or proteinuria is present
- $\beta$ -Blocker – Metoprolol or bisoprolol (oral); esmolol (intravenous)
- Diuretic – Chlorthalidone is preferred, unless HF (NYHA III or IV) or CrCl < 30 mL/minute/1.73 m<sup>2</sup>, then loop diuretic preferred

Second-line options – Add-on therapy

- Dihydropyridine CCB
- Non-dihydropyridine CCB – Do not use if LVSD or HF with reduced ejection fraction present. Caution when combining with  $\beta$ -blocker
- Nitrates (long-acting)
- Aldosterone antagonists – If left ventricular dysfunction, HF, or DM present

#### Stable Angina

First-line options – Drugs of choice

- ACE inhibitor or ARB – Particularly if MI, LVSD, DM, or proteinuria is present
- $\beta$ -Blocker
- Nitrates
- Diuretic – Chlorthalidone is preferred, unless HF (NYHA III or IV) or CrCl < 30 mL/minute/1.73 m<sup>2</sup>, then loop diuretic preferred

Second-line options – Add-on therapy

- Dihydropyridine CCB
- Non-dihydropyridine CCBs – Do not use if LVSD or HF is present. Caution when combining with  $\beta$ -blocker
- Aldosterone antagonist

#### Heart Failure with Reduced Ejection Fraction

First-line options – Drugs of choice

- ACE inhibitor or ARB
- $\beta$ -Blocker – Carvedilol, metoprolol succinate or bisoprolol
- Aldosterone antagonist – If left ventricular dysfunction, HF, or DM

Second-line options – Add-on therapy

- Nitrates
- Hydralazine/isosorbide dinitrate

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DM = diabetes mellitus; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Information from: Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease. A scientific statement from the American Heart Society, American College of Cardiology and American Society of Hypertension. *Circulation* 2015;131:e435-70.

less than 140 mm Hg, respectively. After 1 year, the mean SBP was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard therapy group. The annual rate of the primary outcome (composite nonfatal MI, nonfatal stroke, or death from CV causes) was similar between groups: 1.87% in the intensive therapy group and 2.09% in the standard therapy group ( $p=0.20$ ). There was also no difference between groups in all-cause mortality or CV death. Strokes were reduced in the intensive therapy group compared with the standard therapy group (0.32% vs. 0.53%; HR 0.59; 95% CI, 0.39–0.89;  $p=0.01$ ). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group ( $p<0.001$ ). With the exception of lower stroke risk (absolute difference 0.21%), the results of this study showed no additional CV or mortality benefit of a lower SBP goal (less than 120 mm Hg) but an increased rate of adverse events (Cushman 2010).

The 2015 ADA guidelines increased the DBP goal from less than 80 mm Hg to less than 90 mm Hg. The previous DBP goal of less than 80 mm Hg was based primarily on a post hoc analysis of the Hypertension Optimal Treatment trial (Hansson 1998). According to other higher-quality evidence, the ADA raised the DBP goal in 2015 to less than 90 mm Hg, which coincides with the 2013 ASH/ISH blood pressure and JNC 8 panel guidelines recommendations (James 2014; Weber 2014). However, the ADA contends that lower blood pressure targets (less than 130/80 mm Hg) are appropriate for younger patients if they can be achieved without “undue treatment burden” (ADA 2015).

### **Antihypertensive Therapy**

Inhibitors of the RAAS may have unique advantages in the initial or early therapy for HTN in individuals with diabetes. The HOPE trial showed that ACE inhibitors reduce major CVD outcomes (e.g., MI, stroke, death) in patients with diabetes (HOPE 2000). The ADVANCE trial showed that the combination of perindopril and indapamide reduced not only macrovascular complications, but also microvascular outcomes and mortality, with lower blood pressure (Patel 2007). The compelling benefits of RAAS inhibitors in patients with diabetes and albuminuria provide added rationale for their use.

The 2015 ADA and the 2013 ASH/ISH blood pressure guidelines recommend that therapy for patients with diabetes and HTN include either an ACE inhibitor or an ARB (ADA 2015; Weber 2014). If one class is not tolerated, the other class may be substituted if not contraindicated. Multidrug therapy is usually required to achieve blood pressure targets. If additional blood pressure lowering is needed after ACE inhibitor or ARB therapy is optimized, a thiazide diuretic,  $\beta$ -blocker, and/or CCB should be added and optimized.

### **Heart Failure**

Hypertension is one of the most important modifiable risk factors for both HF with preserved ejection fraction and HF with reduced ejection fraction. Individuals with HTN have a much higher risk of

developing HF than do normotensive men and women. The incidence of HF is greater with higher blood pressure readings, older age, and longer duration of HTN. Long-term treatment of both systolic and diastolic HTN reduces the risk of HF by around 50%.

Hypertension is an important contributor to acute decompensated HF. A registry that tracks hospitalized patients with acute decompensated HF showed that almost 50% of patients admitted with HF had a blood pressure level greater than 140/90 mm Hg, and almost 75% had a history of HTN. Patients who were admitted for HF were more often significantly hypertensive with preserved systolic function than hypotensive with reduced systolic function (Adams 2005). In addition, the abrupt discontinuation of antihypertensive therapy may precipitate worsening HF.

### **Blood Pressure Goals**

The 2013 ACC/AHA HF guidelines recommend that clinicians lower both SBP and DBP in accordance with JNC 7 (Yancy 2013). According to JNC 7, blood pressure targets in HF have not been firmly established, but lowering SBP is almost uniformly beneficial. In most successful trials, SBP was lowered to 110–130 mm Hg (Chobanian 2003). For example, the COPERNICUS trial showed the benefits of carvedilol (27% reduction in the combined risk of death or CVD [ $p<0.001$ ] and 31% reduction in the combined risk of death or HF hospitalization [ $p<0.001$ ]) in patients who had a mean baseline blood pressure of 123/76 mm Hg, suggesting that lower blood pressure is desirable in some patients (Packer 2001). However, the benefits seen in this trial may be the result of treatment with carvedilol, rather than the blood pressure level. In the 2015 ACC/AHA CAD blood pressure guidelines, a blood pressure goal of less than 140/90 mm Hg is recommended for patients with HF (class IIa, level of evidence B) (Rosendorff 2015). Other recently published guidelines (e.g., JNC 8 2013 ASH/ISH) do not address a blood pressure goal for patients with HF.

### **Antihypertensive Therapy**

Choice of antihypertensive therapy should be guided by HF-specific options and tailored to concomitant medical problems. Diuretic-based antihypertensive therapy prevents HF in a wide range of patients. One trial of indapamide-based therapy showed a number needed to treat of 52 over 2 years to prevent one HF event (Beckett 2008). Other effective treatments to decrease the risk of HF include ACE inhibitors, ARBs, and  $\beta$ -blockers.

### **HF with Reduced Ejection Fraction**

Therapies that reduce morbidity and mortality in patients with HF also reduce blood pressure. Evidence-based  $\beta$ -blockers (metoprolol succinate, carvedilol, or bisoprolol) and ACE inhibitors should be used in all patients with a reduced ejection fraction (unless contraindicated) to prevent symptomatic HF, even if they have no history of MI. In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated. Aldosterone receptor antagonists are recommended in patients

with New York Heart Association (NYHA) classes II–IV who have an LVEF of 35% or less and in patients after an acute MI with an LVEF of 40% or less with HF symptoms. Loop diuretics do not reduce mortality in patients with HF with reduced ejection fraction, but they are recommended in patients with fluid retention to achieve euvolemia.

### **HF with Preserved Ejection Fraction**

Blood pressure control remains the most important consideration in patients with HF with preserved ejection fraction. In patients with HTN having HF with preserved ejection fraction, aggressive treatment (usually requiring multidrug regimens) is recommended. Although strong evidence is lacking, ACE inhibitors or ARBs are often used to treat HTN (Yancy 2013).

The TOPCAT study examined the effect of spironolactone versus placebo on HF with preserved ejection fraction. Patients had a median ejection fraction of 54% and a median blood pressure of 130/80 mm Hg. After a 3-year follow-up, there was no difference in the primary outcome (composite of CV death, aborted cardiac arrest, or HF hospitalization). However, the spironolactone group had a significantly lower rate of hospitalization for HF than did the placebo group (12.0% vs. 14.2%; HR 0.83; 95% CI, 0.69–0.99;  $p=0.04$ ). In an exploratory post hoc analysis, marked regional variations in outcomes were seen in the placebo group: patients from Russia and Georgia had a much lower likelihood of a primary outcome event than patients in the Americas. This may partly explain why a decrease in the primary outcome was seen in the spironolactone arm for patients enrolled in the Americas (27.3% vs. 31.8%; HR 0.82; 95% CI, 0.69–0.98;  $p=0.026$ ) but not for patients enrolled in Russia or Georgia (Pitt 2014). Although the TOPCAT study was not a blood pressure–lowering trial, it may guide the use of spironolactone in these patients, and the expected benefit may go beyond blood pressure control.

### **Chronic Kidney Disease**

Both HTN and CKD can cause and worsen each respective disease state. In patients with CKD (but not on dialysis), higher blood pressure levels are usually associated with a higher CVD risk. Treating HTN is fundamental to caring for patients with CKD because premature CVD is a primary cause of death and morbidity (KDIGO 2012).

#### ***Blood Pressure Goals***

For all adults (including those with diabetes) who have CKD and a urine albumin excretion of less than 30 mg/24 hours (or equivalent), recent guidelines recommend the use of drugs to maintain blood pressure consistently less than 140/90 mm Hg (James 2014; Weber 2014; KDIGO 2012). Several previous guidelines recommended a blood pressure target of less than 130/80 mm Hg for all patients with CKD, irrespective of urine protein concentration. However, recent randomized controlled trials have shown no benefit of lower blood pressure targets in patients without proteinuria.

For example, in the AASK study, participants were randomized to treatment to a mean arterial pressure of either less than 92 mm Hg (equivalent to 125/75 mm Hg) or 102–107 mm Hg (equivalent to 135/85–140/90 mm Hg). During the long-term follow-up of participants, benefit was associated with the lower blood pressure target among patients with a urine protein/creatinine ratio of greater than 220 mg/g, but not if the urine protein/creatinine ratio was 220 mg/g or less (Appel 2010). In fact, in some analyses, there was a trend toward worse outcomes with a low blood pressure target and ratio of 220 mg/g or less. Therefore, in adults with or without diabetes who have CKD and a urine albumin excretion greater than 30 mg/24 hours (or equivalent) and an office blood pressure consistently greater than 130 mm Hg systolic or greater than 80 mm Hg diastolic, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment to maintain a blood pressure consistently lower than 130/80 mm Hg. However, this lower goal for patients with albuminuria is not mentioned in either the JNC 8 or the 2013 ASH/ISH guidelines.

#### ***Antihypertensive Therapy***

Although the KDIGO guidelines suggest an ACE inhibitor or ARB for adults with diabetes, CKD, and a urine albumin excretion of 30–300 mg/24 hours (or equivalent), they recommend an ACE inhibitor or ARB for patients with or without diabetes who have CKD and a urine albumin excretion of greater than 300 mg/24 hours (or equivalent). Vasodilation of the efferent and afferent glomerular arterioles (particularly the efferent) results in decreased intraglomerular pressure and hence reduction in both glomerular filtration rate and urine albumin excretion. This is believed to result in some degree of long-term renoprotection in patients with albuminuria.

Blood pressure control in patients with CKD often requires the use of three or more agents. With the exception of ARB or ACE inhibitor use in patients with CKD and high concentrations of protein excretion, KDIGO finds no strong evidence to support the preferential use of any particular agent in controlling blood pressure in CKD, nor are there data to guide the clinician in the choice of second- and third-line agents. However, other recent guidelines continue to recommend an ACE inhibitor or ARB as initial therapy for patients with CKD (James 2014; Weber 2014). Ultimately, the choice of agents is less important than the actual reduction in blood pressure achieved. The ACE inhibitors or ARBs are valuable antihypertensive agents in patients with CKD and are safe to combine with most other blood pressure–reducing agents, though the risk of significant hyperkalemia warrants caution. In CKD, aldosterone antagonists reduce urine albumin concentrations and may be used as an adjunct to other antihypertensive agents in treating resistant HTN (Epstein 2006). Impaired renal excretion of spironolactone and eplerenone can increase the risk of hyperkalemia; hence, their use should be limited to patients with a CrCl greater than 30 mL/minute/1.73 m<sup>2</sup>.

Of the currently available antihypertensive agents, thiazides and thiazide-like diuretics are most often used and have been assessed in many randomized controlled trials involving patients with CKD. Although thiazides are excreted by the kidney, no dose adjustment is recommended in patients with a CrCl above 30 mL/minute/1.73 m<sup>2</sup>. As the glomerular filtration rate falls below about 30–50 mL/minute/1.73 m<sup>2</sup>, the ability of thiazides to overcome fluid retention is diminished, though their antihypertensive benefit may be preserved. Most clinicians switch to a loop diuretic in patients with a CrCl of less than 30 mL/minute/1.73 m<sup>2</sup> because of the thiazide's lack of effectiveness, particularly if the blood pressure is becoming resistant to therapy or if edema becomes a problem. On initiation of diuretics and RAAS blockers, a transient reduction in CrCl of up to 30% (and accordingly, a 30% increase in SCr concentration) has been regarded as reasonable because of the physiologic mechanism of vasodilation in the kidney. Greater CrCl reductions may suggest underlying renal artery stenosis or other renal disease, in which case therapy should be adjusted.

## RESISTANT HTN

Resistant HTN is defined as either a blood pressure of 140/90 mm Hg or greater while using optimally dosed antihypertensive agents from three different drug classes (including a diuretic); or as taking agents from four or more antihypertensive drug classes regardless of blood pressure. In the 2003–2008 NHANES data, 8.9% of U.S. adults with HTN met the criteria for resistant HTN (Persell 2011).

### Pseudo-resistant HTN

Pseudo-resistant HTN should be ruled out before treating resistant HTN. Causes of pseudo-resistance include drug nonadherence and “white-coat” HTN (Calhoun 2008). If patients are chronically nonadherent, modifying their antihypertensive regimens without addressing this issue will not result in blood pressure control. Adherence rates with antihypertensive drugs are reported to be 50%–70% (Calhoun 2008). In a systematic review of randomized trials, the most successful strategy in improving adherence was simplifying the antihypertensive treatment regimen, including reducing the number of total daily doses. Motivational strategies (e.g., daily drug reminder charts, modified packaging, social support, telephone reminders) were partly successful. Patient education strategies alone were largely unsuccessful (Schroeder 2004). However, one study found that nonadherence was related to patients' lack of understanding of the causes and effects of HTN, as well as concerns about adverse effects, and the authors called for targeted educational interventions (Marshall 2012).

The [Million Hearts “Team Up. Pressure Down” program](#) is an educational effort sponsored by the U.S. Department of Health and Human Services and the CDC. This program promotes team-based blood pressure care and offers support for

health care professionals in helping patients improve adherence and better manage their blood pressure. Moreover, the program provides several ideas on how best to incorporate this program into pharmacies. [Million Hearts](#) has resources for pharmacists (e.g., posters, discussion tool, blood pressure guide, video vignette, continuing pharmacy education) and for patients (e.g., blood pressure journal, medication-tracking cards). Program implementation involves three tiers: general awareness, medication adherence messaging, and blood pressure counseling services.

### Causes of Resistant HTN

Box 1-2 details various causes of pseudo-resistant and resistant HTN, including drugs and diseases. Once a patient has been given a diagnosis of resistant HTN, it is desirable to rule out disease-related causes. This will allow either a more targeted treatment strategy (e.g., with primary aldosteronism) or the ability to resolve the issue without additional antihypertensive medication (e.g., with hyperthyroidism). Some conditions are especially prevalent in patients with resistant HTN; for example, sleep apnea (60%–70%) can be treated, in part, with continuous positive airway pressure (Vongpatanasin 2014).

It is also important to address other causes of pseudo-resistant and resistant HTN. Improper blood pressure measurement and white-coat HTN may not necessitate any changes to the antihypertensive regimen, whereas volume overload may need to be addressed by lifestyle modification or optimization of diuretic therapy.

Some clinicians may overlook drug-related causes of resistant HTN. If a patient is prescribed inappropriate drug combinations or inadequate doses of antihypertensive agents, the HTN may not be truly resistant to therapy. Health care provider education may be the most efficient way to address these issues.

Nonsteroidal anti-inflammatory drugs, which inhibit prostaglandins, have been implicated in increasing blood pressure and CVD risk. Prostaglandins promote vasodilation and improve the excretion of sodium and water; their inhibition contributes to vasoconstriction and volume retention, and the blood pressure level can increase. In addition, NSAIDs can antagonize the effects of some antihypertensive agents and cause complications when used concurrently. The use of NSAIDs with several antihypertensive agents (a thiazide diuretic plus an ACE inhibitor or an ARB), acute kidney injury (AKI) may occur. In a retrospective nested case-control cohort study, use of a double-therapy combination (either diuretics and NSAIDs or ACE inhibitors/ARBs and NSAIDs) was not associated with an increased rate of AKI. In contrast, use of a triple-therapy combination was associated with an increased rate of AKI (rate ratio 1.31; 95% CI, 1.12–1.53). The authors hypothesized that this occurs because of a decreased volume into the kidney from the diuretic and the NSAID, and the renal blood flow cannot be compensated for because of blockade of the RAAS by the ACE inhibitor or ARB, resulting in an increased risk of AKI (Lapi 2013).

For patients with HTN and CAD, NSAIDs may increase the risk of morbidity and mortality. In a post hoc analysis of the INVEST trial, which enrolled patients with HTN and CAD, the primary outcome (all-cause death, nonfatal MI, or nonfatal stroke) occurred at a significantly higher rate in the chronic NSAID group than in the nonchronic NSAID group (adjusted HR 1.47; 95% CI, 1.19–1.82;  $p=0.0003$ ). This difference was caused by an increase in CV mortality (adjusted HR 2.26; 95% CI, 1.70–3.01;  $p<0.0001$ ) (Bavry 2011). Thus, for patients with HTN, it may be advisable to avoid NSAIDs, if possible, to decrease the risk of worsening HTN, kidney disease, and CV morbidity and mortality. However, these risks must be weighed against benefits such as pain control.

## Treatment of Resistant HTN

### *Spironolactone*

Several investigators have studied spironolactone as a strategy for treating resistant HTN. In 2002, a study of 25 patients showed that adding spironolactone 1 mg/kg/day significantly decreased blood pressure ( $p<0.013$ ) and the mean number of antihypertensive drugs required per patient ( $p<0.001$ ) without requiring spironolactone discontinuation because of adverse renal effects (Ouzan 2002). In a larger study ( $n=76$ ), spironolactone (12.5–25 mg/day) was added to each subject's antihypertensive regimen, and if blood pressure remained uncontrolled, the spironolactone dose was titrated to 50 mg/day. A significant mean decrease in blood pressure occurred, as did a significant decrease in the mean number of prescribed antihypertensive medications from baseline compared with 6-month follow-ups ( $p<0.05$ ) (Nishizaka 2003).

In a post hoc analysis of 1411 patients taking spironolactone enrolled in the ASCOT-BPLA trial, spironolactone was mainly used as a fourth-line antihypertensive agent for uncontrolled blood pressure, with a median dose of 25 mg/day. During spironolactone therapy, the mean blood pressure fell a mean difference of 21.9/9.5 mm Hg ( $p<0.001$ ). Spironolactone was generally well tolerated, with 6% of participants discontinuing the drug because of adverse effects (Chapman 2007).

The ASPIRANT trial was a double-blind, placebo-controlled, multicenter study that randomly assigned 117 patients to receive spironolactone 25 mg/day ( $n=59$ ) or placebo ( $n=58$ ) in addition to their antihypertensive drugs for 8 weeks. The primary end point (a difference in the mean fall in blood pressure on daytime ambulatory blood pressure monitoring [ABPM]) showed a significant reduction for SBP ( $p=0.024$ ) between the groups (Václavík 2011).

Finally, the efficacy, safety, and tolerability of eplerenone were compared with that of spironolactone in patients with primary aldosteronism and HTN in a multicenter, randomized, double-blind study. Patients were randomized to a 16-week treatment of spironolactone 75–225 mg once daily ( $n=71$ ) or eplerenone 100–300 mg once daily ( $n=70$ ) using a titration-to-effect design (doses were titrated if DBP remained greater than 90 mm Hg). The mean

eplerenone dose was 214 mg/day, and the mean spironolactone dose was 152 mg/day. Changes from baseline in the eplerenone group were SBP -9.9 mm Hg ( $\pm 2.3$  mm Hg) and DBP -5.6 mm Hg ( $\pm 1.3$  mm Hg), whereas changes in the spironolactone group were SBP -27.0 mm Hg ( $\pm 2.3$  mm Hg) and DBP -12.5 mm Hg ( $\pm 1.3$  mm Hg). The lowering of both SBP and DBP was significantly greater in the spironolactone group, but there were no significant differences in the overall rate of adverse events between eplerenone and spironolactone (Parthasarathy 2011). Each study shows that spironolactone can be effective at lowering blood pressure.

## Box 1-2. Causes of Resistant and Pseudo-resistant HTN

### Disease Related

- Sleep apnea
- CKD/renovascular disease
- Primary aldosteronism
- Cushing syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease
- Obesity
- Intracranial tumor

### Drug Related

- Nonadherence
- Inadequate antihypertensive doses
- Inappropriate antihypertensive combinations
- Chronic glucocorticoid steroid therapy
- Nonsteroidal anti-inflammatory drugs
- Stimulants
  - Methylphenidate and other prescription stimulants
  - Cocaine, amphetamines, other illicit drugs
  - Sympathomimetics
  - Decongestants, anorectics
  - Select OTC dietary supplements (e.g., licorice, ephedra, ma huang, bitter orange)
- Oral contraceptives
- Adrenal steroids
- Cyclosporine and tacrolimus
- Erythropoiesis-stimulating agents

### Other

- Improper blood pressure measurement
- Volume overload
  - Excess sodium intake
  - Volume retention
  - Inadequate diuretic therapy
- Excess alcohol intake
- White-coat HTN

CKD = chronic kidney disease; HTN = hypertension.

Information from: Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117:e510-e526; and Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.

### **Thiazide Diuretics – Chlorthalidone vs. Hydrochlorothiazide**

The use of chlorthalidone for HTN is supported by the results of the ALLHAT study. This randomized controlled trial compared chlorthalidone, lisinopril, and amlodipine in more than 41,000 patients with HTN. At a mean follow-up of 4.9 years, the primary outcome (fatal CAD or nonfatal MI) was the same in the three arms. However, the chlorthalidone arm had a significantly lower rate of HF than did the amlodipine and lisinopril arms, and a significantly lower rate of combined CVD outcomes than did the lisinopril arm (ALLHAT 2002). Conversely, there is little, if any, trial evidence to show that hydrochlorothiazide alone reduces CV events.

Chlorthalidone is about 1.5–2.0 times more potent than hydrochlorothiazide and has a longer duration of action (24–72 hours vs. 6–12 hours). A small randomized crossover trial showed that this longer duration of action may result in a greater fall in nighttime blood pressure with chlorthalidone (-13.5 mm Hg with 12.5 mg/day [force-titrated to 25 mg/day]) versus hydrochlorothiazide (-6.4 mm Hg with 25 mg/day [force-titrated to 50 mg/day]) (Ernst 2006). There are no randomized

trials directly comparing chlorthalidone with hydrochlorothiazide. A meta-analysis of nine trials that included more than 50,000 patients indirectly compared hydrochlorothiazide with chlorthalidone by evaluating their efficacy against common comparator drugs (e.g., ACE inhibitors). Compared with hydrochlorothiazide, chlorthalidone significantly reduced the risk of CV events (RR 0.79; 95% CI, 0.72–0.88) and HF (RR 0.77; 95% CI, 0.61–0.98). To prevent one CV event, 27 patients would need to be treated with chlorthalidone instead of hydrochlorothiazide for at least 5 years (Roush 2012).

However, observational data analyses comparing hydrochlorothiazide with chlorthalidone are mixed. Results of observational data from the MRFIT trial are consistent with the aforementioned meta-analysis. In that trial, the 2392 hypertensive men treated with chlorthalidone had fewer CV events than did the 4049 men treated with hydrochlorothiazide (HR 0.79; 95% CI, 0.68–0.92) in 6 years of follow-up (Dorsch 2011). In contrast, other investigators found that among almost 30,000 adults 66 years and older, chlorthalidone (mean dose 27 mg/day) was associated with an increased risk of hospitalization for hypokalemia (HR 3.06; 95% CI, 2.04–4.58) and hyponatremia (HR 1.68;

### **Patient Care Scenario**

A 52-year-old man (height 71 inches, weight 85 kg) is referred to the clinic for further evaluation of his blood pressure. His medical history is significant for type 2 DM for 5 years and HTN for 10 years. His drugs include hydrochlorothiazide 25 mg daily, candesartan 32 mg daily, amlodipine 10 mg daily, clonidine 0.2 mg twice/day, metoprolol succinate 100 mg daily, atorvastatin 40 mg daily, fenofibrate 145 mg daily, and metformin 1000 mg twice daily. His examination reveals no evidence of end-organ damage and nothing remarkable except for mild arteriolar narrowing in the fundus. The patient's only

#### **ANSWER**

Resistant HTN is defined by either having a blood pressure of 140/90 mm Hg or greater and using optimally dosed antihypertensive medications from three different drug classes (including a diuretic) or taking medications from four or more antihypertensive drug classes regardless of blood pressure. Given his seated office blood pressure values, this patient meets this definition of resistant HTN. Ambulatory blood pressure monitoring should be performed to verify the office readings and confirm the diagnosis. In addition, sources of pseudo-resistance such as nonadherence and drug-induced causes should be considered. A review of his drug list identifies no sources of drug-induced HTN. His symptoms of fatigue and dry mouth are likely from adverse drug reactions (metoprolol

complaints are of fatigue and dry mouth. In the clinic, his seated blood pressure taken from his right arm is 154/90 mm Hg with a heart rate of 70 beats/minute. His laboratory results reveal K 4.1 mEq/L, SCr 1.3 mg/dL, Na 140 mEq/L, and no albuminuria. His blood pressure was unchanged when standing.

The patient is given a preliminary diagnosis of resistant HTN. What should be the next steps to confirm this diagnosis, and what treatment plan should be designed for him moving forward?

and clonidine). Tests to identify sources of secondary hypertension, such as serum aldosterone concentrations and plasma renin activity (to determine an aldosterone/renin ratio) can also be recommended. A mineralocorticoid receptor antagonist (e.g., spironolactone) can be added to his regimen. Future considerations can also be given to tapering off clonidine and metoprolol if adverse events continue; however, metoprolol would need to be tapered and discontinued before clonidine could be tapered to avoid the potential for rebound hypertension. The patient should be closely followed up to check his renal function, serum potassium concentrations, and response of his blood pressure to the drug regimen changes.

1. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117:e510-26.

2. Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007;49:839-45.

95% CI, 1.24–2.28). Chlorthalidone was not associated with a reduced risk of death or CV hospitalization (HR 0.93; 95% CI, 0.81–1.06) compared with hydrochlorothiazide (mean dose 18 mg/day). However, because chlorthalidone is more potent than hydrochlorothiazide, the mean daily doses in this trial may not be comparable (Dhalla 2013).

In the absence of head-to-head trials, chlorthalidone appears to be superior to hydrochlorothiazide in potency and, in most studies, in reducing CV events, but it may increase the risk of electrolyte abnormalities. These factors should be considered when choosing a thiazide diuretic.

### **Dosing at Bedtime**

The circadian rhythm contributes to the 24-hour variation in blood pressure and can affect the pharmacokinetics of drugs. Because of this, ingestion time differences in hypertensive medications may change how the body responds to them. Blunted asleep blood pressure decline is associated with an increased incidence of fatal and nonfatal CVD events; moreover, the asleep blood pressure mean is a better predictor of CVD risk than the awake or 24-hour blood pressure mean. The 2010 MAPEC study was designed to determine whether a regimen of bedtime chronotherapy with at least one antihypertensive drug (bedtime group) exerted better blood pressure control and CVD risk reduction than when subjects took all medications in the morning (awakening group). After a median follow-up of 5.6 years, patients in the bedtime group had a significantly lower risk of total CVD events (RR 0.39 [0.29–0.51];  $p < 0.001$ ) (Hermida 2010). These findings provided the basis for subsequent studies in this field.

In 2012, the ADA added a recommendation to administer one or more antihypertensive drugs at bedtime (level of evidence A). This was based on a prospective randomized study comparing patients with HTN and type 2 diabetes mellitus taking bedtime doses of at least one hypertensive agent ( $n=216$ ) with patients taking all antihypertensive drugs in the morning ( $n=232$ ) to determine whether blood pressure control and CV risk reduction were improved. After a median follow-up of 5.4 years, patients using the bedtime dosing had a significantly lower mean asleep blood pressure ( $115.0 \pm 17.1$  vs.  $122.4 \pm 21.8$ ;  $p < 0.001$ ) and a higher prevalence of controlled ambulatory blood pressure (62.5% vs. 50.9%;  $p=0.013$ ). However, differences between groups in clinic and awake blood pressure were small and nonsignificant. Similar to patients in the MAPEC study, patients treated at bedtime had a lower CV risk (adjusted by age and sex) than taking all drugs on awakening (HR 0.33 [95% CI, 0.21–0.54];  $p < 0.001$ ). There was a significant 12% CV risk reduction for each 5-mm Hg decrease in asleep SBP during follow-up ( $p < 0.001$ ) (Hermida 2011a).

Patients with CKD also benefited when at least one of their antihypertensive drugs was administered at bedtime. After a median follow-up of 5.4 years, patients with CKD using the bedtime treatment strategy had a significantly lower mean sleep-time blood pressure, and a greater proportion had

control of their ambulatory blood pressure (56% vs. 45%;  $p=0.003$ ). In addition, patients who took at least one blood pressure–lowering drug at bedtime had a reduced risk of total CV events (a composite of death, MI, angina, revascularization, HF, arterial occlusion of lower extremities, occlusion of the retinal artery, and stroke) than did patients who took all drugs on awakening (adjusted HR 0.31; 95% CI, 0.21–0.46;  $p < 0.001$ ) (Hermida 2011b).

Changing the administration time of at least one antihypertensive medication is a cost-effective (no additional medication required), simple strategy that results in improved ambulatory blood pressure control and significantly reduced CV morbidity and mortality in patients. Often, practitioners do not consider a patient's blood pressure during sleep, but these studies show that blood pressure during this period is important.

## **AMBULATORY AND HOME BLOOD PRESSURE MONITORING**

In ambulatory blood pressure monitoring, the patient wears a portable blood pressure–measuring device on the nondominant arm for 24 hours. This provides information on blood pressure during daily activities as well as at night during sleep. Average daytime, nighttime, and 24-hour blood pressure readings are the most commonly used variables in practice. A systematic review and meta-analysis concluded that 24-hour SBP is a strong predictor of CV events, providing prognostic information independently of conventional office blood pressure (Conen 2008).

A more recent systematic review performed for the U.S. Preventive Services Task Force (USPSTF) examined the predictive accuracy of various blood pressure measurement methods for CV events. Independent of office blood pressure, ABPM independently predicted CV outcomes (HR range 1.28–1.40 in 11 studies). After an elevated blood pressure reading in the office, 35%–95% of patients (across 27 studies) remained hypertensive with confirmatory testing. The authors concluded that ABPM should be used as the reference standard for confirming elevated office blood pressure readings (Piper 2015).

Because of this and other studies, the USPSTF issued a statement on Screening for High Blood Pressure in Adults in October 2015. The recommendation stated that for patients with an elevated blood pressure level in the office, clinicians should confirm the hypertension diagnosis with readings outside of the clinical setting (24-hour ABPM or home blood pressure readings). Using this approach will help decrease the number of patients with a false diagnosis of HTN because of short-term elevations in blood pressure (e.g., from stress, pain, or caffeine intake), white-coat HTN, or errors in blood pressure measurement. However, outside confirmation may not be needed in all cases, such as with very high blood pressure (greater than 180/110 mm Hg), in patients with signs of end-organ damage, or in patients with HTN because of an underlying condition (e.g., CKD) (USPSTF 2015). The USPSTF expanded its recommendations to include home

blood pressure measurement, in addition to ABPM, for confirmatory BP readings because of the potential financial burden of ABPM for some patients. The USPSTF still considers ABPM as the reference standard for confirmation of a HTN diagnosis.

Home blood pressure monitoring involves self-measurement of blood pressure, which offers advantages over office-measured blood pressure because home measurements can be taken for several days at different times in the patient's own environment. Moreover, there is evidence that home blood pressure monitoring is a significant predictor of CV morbidity after adjusting for office blood pressure (Ward 2012). However, patients should be instructed on proper technique. Individuals should be seated with their feet flat on the floor and their back and arm supported for 5 minutes of rest. Two measures should be taken 1–2 minutes apart and the results recorded in a logbook. Values reported by the patient may not always be reliable, but many devices now come with downloadable memory storage capabilities. Use of telemonitoring and smartphone applications for home blood pressure monitoring may provide further advantage. Devices worn on the wrist or finger are currently not recommended because of concerns about accuracy (Pickering 2008).

The HyperLink study examined whether an intervention combining home blood pressure telemonitoring with pharmacist case management improves blood pressure control compared with usual care, and whether blood pressure control is maintained 6 months after the intervention is discontinued. The patients in the intervention group received home blood pressure telemonitors that transmitted blood pressure data to pharmacists, who then adjusted their antihypertensive therapy. The SBP decreased more from baseline among patients in the telemonitoring intervention group at 6 months (-10.7 mm Hg; 95% CI, -14.3 to -7.3 mm Hg;  $p < 0.001$ ) and 12 months (-9.7 mm Hg; 95% CI, -13.4 to -6.0 mm Hg;  $p < 0.001$ ) than did the SBP among patients in the usual care group. This decrease persisted at 18 months (-6.6 mm Hg; 95% CI, -10.7 to -2.5 mm Hg;  $p = 0.004$ ) (Margolis 2013). The HyperLink study highlights the value a pharmacist can bring to the care team. Other studies have also shown that team-based care can lower blood pressure better than standard care (Magid 2013; Green 2008).

## HYPERTENSIVE URGENCY AND EMERGENCY

*Hypertensive crisis* is a broad term encompassing hypertensive urgency and emergency; it is defined by JNC 7 as an SBP of 180 mm Hg or greater and/or a DBP of 120 mm Hg or greater (Chobanian 2003). When individuals meet the qualifications for hypertensive crisis and also have evidence of end-organ damage, it is a *hypertensive emergency*. Those without end-organ damage are classified as having *hypertensive urgency*. Risk factors for developing hypertensive crisis include female sex, obesity, presence of either hypertensive or coronary

heart disease, presence of a somatoform disorder, high number of antihypertensive drugs, and medication nonadherence (Saguner 2010). The true incidence of hypertensive emergency and urgency remains largely unknown. However, recent data from Italy show that of 1000 ED visits, 4.6 were because of hypertensive crises; of these, three-fourths were urgencies and one-fourth were emergencies (Pinna 2014). Distinguishing between these two distinct conditions is critical in formulating a treatment strategy because the pharmacotherapy used to treat them differs dramatically.

### Treatment of Hypertensive Emergency

Hypertensive emergencies typically present as sudden, precipitous elevations in blood pressure associated with acute target organ dysfunction. Common presentations include hypertensive encephalopathy, malignant HTN, acute coronary syndromes, eclampsia, aortic dissection, acute cerebrovascular events, acute pulmonary edema, and acute renal dysfunction. Thus, although the blood pressure itself can often be quite high (greater than 180/greater than 120 mm Hg), these clinical signs and symptoms more commonly denote the emergency. The initial examination of patients should include a focused history and funduscopic, CV, and mental examinations as well as pertinent laboratory values. Once the hypertensive emergency has been diagnosed, and even before laboratory results are available, drug therapy should be initiated.

Specific blood pressure targets do not exist for patients with hypertensive emergency. Individuals with chronic HTN often tolerate very high blood pressure levels because of autoregulatory structural and functional changes. Thus, blood pressure reduction should be achieved in a more controlled fashion to avoid sudden drops that can precipitate or exacerbate target organ damage.

Unfortunately, goal blood pressure reductions are not guided by clinical trial data. Most experts recommend no more than a 20%–25% reduction in SBP within the first 2 hours of presentation (Chobanian 2003). Reducing the DBP by 25% within the next 2–6 hours toward an overall goal of 160/100 mm Hg is also reasonable. If this level of reduction is well tolerated and the patient is clinically stable, slow reductions can continue over the next 24–48 hours with a transition to oral drugs when appropriate. This oral transition should be made after the patient has had a 12- to 24-hour period of clinical stability, to allow for restoration of normal autoregulation. Notable exceptions to these targets include patients with acute aortic dissection (goal SBP less than 120 mm Hg over 20 minutes), acute intracerebral hemorrhage (goal SBP less than 140 mm Hg within 5–10 minutes), and acute ischemic stroke (goal blood pressure depends on the revascularization strategy chosen) (Anderson 2013).

Various parenteral pharmacologic agents are available for treating hypertensive emergency (Table 1-3). However, relatively few have been directly compared in randomized

controlled trials. A meta-analysis published in 2008 included data from 15 studies evaluating seven drug classes for treating hypertensive emergencies. Only minor differences in blood pressure were seen between select drug classes, with analyses severely limited by a low number of studies, short durations of follow-up, and few included patients (Perez 2008).

A pooled analysis of three clinical trials compared the dihydropyridine L-type CCB clevidipine with nitroglycerin, sodium nitroprusside, or nicardipine in 1500 patients with post-cardiac

surgery acute HTN. Clevidipine maintained blood pressure within the prespecified range better than either nitroglycerin ( $p=0.0006$ ) or sodium nitroprusside ( $p=0.003$ ) and was similar to nicardipine (Aronson 2008). A more recent trial of 226 ED patients with acute HTN showed that nicardipine use resulted in greater achievement of target blood pressure than labetalol (91.7 vs. 82.5%;  $p=0.039$ ) within 30 minutes (Peacock 2011).

The choice of pharmacologic agent is influenced by the clinical situation. For patients with aortic dissection who

**Table 1-3.** Parenteral Pharmacologic Agents for Treatment of Hypertensive Emergencies

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects	Additional Information
Clevidipine	1–16 mg/hr	2–4 min	5–15 min	Headache, nausea, vomiting, reflex tachycardia	Weight-independent dosing; given in lipid emulsion through dedicated IV line
Enalaprilat	1.25–5 mg IV (q6hr)	15–30 min	6–12 hr	Acute hypotension, variable response	Avoid in bilateral renal artery stenosis, pregnancy
Esmolol	250–500 mcg/kg/min (IV bolus); then 50–100 mcg/kg/min	1–2 min	10–30 min	Nausea, heart block, HF	Avoid in cocaine-induced hypertension; appropriate for aortic dissection
Fenoldopam	0.1–5 mcg/kg/min	< 5 min	~20 min	Reflex tachycardia, nausea, vomiting, flushing, increased ocular pressure	Caution with glaucoma; can be used for most hypertensive emergencies
Hydralazine	10–20 mg (IV)	10–20 min	1–4 hr	Tachycardia, flushing, headache, vomiting, angina pectoris	Avoid in CAD, aortic dissection
Labetalol	20–80 mg (IV bolus); then 0.5–2 mg/min	5–10 min	3–6 hr	Nausea, vomiting, flushing, heart block, OH	Avoid with heart block, asthma, pregnancy, acute HF
Nicardipine	5–15 mg/hr	5–10 min	15–30 min, may exceed 4 hr	Tachycardia, flushing, headache	Avoid in acute HF; weight-independent dosing
Nitroglycerin	5–100 mcg/min	2–5 min	5–10 min	Headache, vomiting, tachyphylaxis, methemoglobinemia	Unpredictable antihypertensive effects
Phentolamine	5–15 mg	1–2 min	3–10 min	Tachycardia, flushing, headache, OH	Avoid in preexisting CAD; useful for catecholamine excess <sup>a</sup>
Sodium nitroprusside	0.25–8 mcg/kg/min	~20 s	1–2 min	Nausea, vomiting, muscle spasm, cyanide and/or thiocyanate toxicity, coronary steal syndrome	Caution with high intracranial pressure, hepatic or renal failure; avoid in pregnancy; shield from light

<sup>a</sup>Cocaine, monoamine oxidase inhibitor crisis, pheochromocytoma.

CAD = coronary artery disease; IV = intravenous(ly); MI = myocardial infarction; OH = orthostatic hypotension; q = every.

Information from: Sarafidis PA, Georgianos PI, Malindretos P, et al. Pharmacologic management of hypertensive emergencies and urgencies: focus on newer agents. *Expert Opin Investig Drugs* 2012;21:1089-106; Elliott WJ, Rehman SU, Vidt DG, et al. Hypertensive emergencies and urgencies. In: Black HR, Elliott WJ, eds. *Hypertension: A Companion to Braunwald's Heart Disease*, 2nd ed. Philadelphia: Saunders, 2013:390-5.

require a blood pressure decrease to less than 120 mm Hg within 20 minutes of presentation, a common recommendation is short-acting  $\beta$ -blockers such as esmolol and labetalol. In patients with pulmonary edema and/or HF, either nitroglycerin or sodium nitroprusside can be preferred, with diuretics added in cases of volume overload. In patients with catecholamine excess, either the nonselective  $\alpha$ -blocker phentolamine or the  $\beta$ -blocker (with  $\alpha$ -blocking properties) labetalol is recommended. For individuals presenting with acute coronary syndromes, vasodilators such as nitroglycerin, sodium nitroprusside, nicardipine, or clevidipine can be used. Thus, the specific agent for treating patients presenting with a hypertensive emergency depends on both the end-organ dysfunction and the patient comorbidities.

### Treatment of Hypertensive Urgency

Hypertensive urgency has also been called blood pressure elevations without ongoing target organ damage. Of note, however, hypertensive urgency can still be associated with headache, thoracic pain, and dyspnea despite the lack of overt organ damage. The most common cause is either inadequate antihypertensive treatment or drug nonadherence. Despite its name, there is no great urgency to reduce blood pressure quickly. In 2013, the American College of Emergency Physicians stated that acute treatment of blood pressure without target organ damage may not be required (Wolf 2013). However, the statement did provide a consensus recommendation that select patients, such as those with poor outpatient follow-up, can be treated in the ED and then referred for continued care.

Patients with significant blood pressure elevations without ongoing target organ damage should have their pressure decreased over 24–48 hours with oral agents. This can also be accomplished in the ED over a few hours without the need for hospital admission. If short-acting agents are desired, commonly used options include captopril, clonidine, and labetalol. Barring contraindications, no specific agent appears to have a major advantage over another.

## HYPOTENSION

No specified blood pressure level is considered too low in asymptomatic patients not taking antihypertensive therapy. As long as the patient is not having symptoms (e.g., dizziness, fatigue, syncope), there is no concern. Overtreatment with antihypertensive therapy can cause hypotension. There is no evidence of benefit from an SBP less than 110 mm Hg, and the risk of adverse effects increases with unnecessary drugs. If this occurs, consider tapering therapy unless therapy has benefits beyond blood pressure lowering, such as medications used to treat left ventricular systolic dysfunction.

The definition of orthostatic hypotension (OH) is a sustained reduction of at least 20 mm Hg in SBP or of 10 mm Hg in DBP within 3 minutes of standing. In healthy people, about 700 mL of venous blood goes to the peripheral circulation on standing,

which causes a transient decrease in cardiac output and blood pressure. The baroreflex-mediated compensatory sympathetic system activates with a decreased parasympathetic activation, which increases heart rate and vascular resistance to restore cardiac output and blood pressure. However, when the autonomic system fails to trigger these compensatory mechanisms, OH can occur. Peripheral damage of the autonomic nerves (e.g., by diabetes or Parkinson disease) commonly contributes to OH. Autoimmune and neurodegenerative autonomic dysfunction can cause more pronounced OH, but this rarely occurs. Older adults are especially prone to OH because their compensatory mechanisms diminish over time. Baroreflex sensitivity, heart rate response, and vasoconstriction become blunted as patients age (Shibao 2013).

Symptoms of OH (e.g., dizziness, fatigue, dim or blurred vision, pain in the back of the neck/shoulders) occur within a few seconds of standing. These symptoms are not present in the supine position and should be relieved after sitting or lying down. Symptoms are usually worse on awakening because of nighttime pressure natriuresis, making morning orthostatic measurements sensitive to detecting OH. The prevalence of OH among patients 65 years and older is about 16%; this increases as patients age. Risk factors for OH include age, comorbid conditions, and number of drugs used (particularly antihypertensive agents). Major CV events have been associated with OH, and it is a risk factor for syncope and falls (Shibao 2013). In older adults, it has been identified as an independent predictor of mortality (Luukinen 1999).

The initial evaluation for OH includes blood pressure measurements at both 1 minute and 3 minutes of standing after the patient has been supine for at least 5 minutes. This helps determine whether there is an immediate decline in blood pressure, when patient falls are most likely to occur, and if there is delayed onset of blood pressure lowering. It is also important to measure heart rate at each of these periods because there is a compensatory mechanism for the heart rate to increase with certain types of OH. Diagnosis may require several measurements.

The goals of therapy are to decrease the patient's symptoms, improve functional status, and decrease the risk of falls and syncope. The goal is not to achieve a certain blood pressure target. Once a diagnosis of OH has been confirmed, nonpharmacologic therapy should be initiated. These interventions include eliminating any offending agents (e.g.,  $\alpha$ -blockers), increasing fluid and salt intake, avoiding standing too quickly, and initiating exercise. Pharmacologic therapy options include fludrocortisone (which increases intravascular volume) and adrenergic agent hypertensives (e.g., midodrine, pyridostigmine, pseudoephedrine, atomoxetine). Fludrocortisone or midodrine can be used in patients who are not hypertensive. Midodrine can also be used in combination with either fludrocortisone or pseudoephedrine if monotherapy is ineffective.

Droxidopa is a newly approved agent that is a structural analog of norepinephrine. In clinical trials, efficacy

was measured by a questionnaire describing dizziness, light-headedness, faintness, and symptoms of syncope. Studies showed a treatment effect (decrease in dizziness) at week 1, but no study showed a treatment effect beyond 2 weeks (Biaggioni 2015; Kaufmann 2014). Therefore, this agent's place in therapy is uncertain.

Patients with OH and HTN present a special treatment situation. There is a 2.5 times higher risk of falls in older adult patients with OH and HTN than in patients with OH without HTN (Ooi 2000). It is important to continue antihypertensive therapy in patients with OH and HTN because adequately controlling blood pressure does not increase the risk of OH. Antihypertensive agents should be initiated at low doses and titrated slowly. Angiotensin-converting enzyme inhibitors or ARBs may be beneficial in these patients because of improved blood pressure regulation and cerebral blood flow (Lipsitz 2005).

## HTN AND PHARMACOGENOMICS

There is interindividual variation in blood pressure response to antihypertensive agents. One potential explanation for this variation is genetic polymorphisms that can lead to alterations in either the pharmacokinetic or pharmacodynamic actions of these agents. Thus, optimization of the pharmacologic management of HTN using pharmacogenetic and pharmacogenomic information has received considerable attention. Although this research is promising, most of the information is not ready for clinical implementation. The following sections highlight the current state of knowledge, organized by major drug class.

As previously discussed, inhibitors of the RAAS (e.g., ACE inhibitors, ARBs) play an important role in the pharmacologic management of HTN. Variations in several steps in the RAAS, including the angiotensinogen enzyme (AGT), angiotensin I enzyme, angiotensin II receptor type 1 (*AGTR1*), angiotensin II receptor type II (*AGTR2*), and bradykinin receptor, have been assessed for their relation to drug response. In a study of 1447 patients receiving benazepril from a 3-year postmarket surveillance trial, the AGT rs7079 (C/T) single nucleotide polymorphism (SNP) was significantly associated with reductions in the DBP response to benazepril (Su 2007). In total, the response to benazepril explained by variations in the AGT SNP and *AGTR1* haplotype groups were 13% for SBP and 9%–9.6% for DBP. Polymorphisms in the bradykinin receptors as well as ACE insertion/deletion polymorphisms are also associated with ACE-induced cough and angioedema (Mahmoudpour 2013).

Genome-wide association studies have also identified SNPs associated with candesartan response (Turner 2012). However, much of these data have not been replicated, and further studies are needed in varying populations before they can be translated to clinical practice.

Although current guidelines have recommended a lesser role for routine  $\beta$ -blocker use, studies have shown an association between polymorphisms in the  $\beta_1$ -adrenergic receptor gene

(*ADRB1*) and treatment response (Johnson 2011). A study of white, African American, and Hispanic subjects showed greater reductions in DBP in Arg homozygotes for Arg389Gly versus Gly carriers ( $p=0.0018$ ) (Johnson 2003). Similarly, a substudy of INVEST found that individuals with the Ser49ARG389 haplotype had the greatest blood pressure response to metoprolol (Pacanowski 2008). Moreover, individuals with this haplotype of *ADRB1* had higher death rates; treatment with atenolol reduced this mortality risk versus verapamil. These two SNPs show promise regarding the association between the *ADRB1* gene and blood pressure response to  $\beta$ -blockers; however, additional confirmatory studies are required.

The *CACNA1C* and *CACNB2* genes have pharmacogenomic data showing association with CCB use and blood pressure. These genes code for the calcium channel, voltage-dependent, L-type,  $\alpha$ -1C and  $\beta$ -2 regulatory subunits, respectively. Another substudy of INVEST evaluated eight different SNPs on the *CACNA1* coding region. The rs1051375 SNP had a significant interaction with treatment strategy ( $p=0.0001$ ), with AA homozygotes showing a 46% reduction in the primary end point (death, nonfatal MI, or nonfatal stroke) in patients receiving verapamil sustained release versus those receiving atenolol (Beitelshees 2009). A similar study showed that individuals with the rs2357928 GG SNP on the *CACNB2* gene receiving verapamil sustained release were more likely to have an adverse CV outcome than were those receiving atenolol (Niu 2010). This finding was consistent across white, African American, and Hispanic populations. Thus, it appears that these two genes are important, not only for the regulation of blood pressure but also for related CV outcomes in patients receiving CCBs. Ongoing studies are aimed at further examining and replicating these relationships.

The thiazide diuretics are another antihypertensive drug class with a fair amount of pharmacogenomic data. Most of this information has focused on the effect of the *NEDD4L* gene and the association with hydrochlorothiazide and blood pressure. The *NEDD4L* gene encodes regulatory proteins that remove sodium from the epithelial cell surface in the kidney. Data from the NORDIL study showed a greater reduction in SBP ( $p=0.047$ ) and adverse clinical outcomes (fatal and nonfatal stroke, fatal and nonfatal MI, and other CV deaths;  $p<0.0001$ ) in patients receiving thiazide diuretics or  $\beta$ -blockers who were G carriers for the rs4149601 SNP of the *NEDD4L* gene (Svensson-Farbom 2011). These findings were replicated using data from white participants enrolled in the INVEST and PEAR trials, with a greater SBP response to hydrochlorothiazide seen in the G-C haplotype of *NEDD4L* (McDonough 2013).

## CONCLUSION

Several HTN-related studies and guidelines have been published since JNC 7. Studies contributing to knowledge regarding blood pressure goals, preferred therapies for concomitant disease states and specific populations, dosing of

antihypertensive drugs, and treatment of resistant HTN have been completed. This chapter summarizes some of the more recent changes to guidelines and therapy recommendations. However, a single U.S. guideline with majority consensus to manage HTN is eagerly awaited.

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## Practice Points

- For patients with coronary or other atherosclerotic vascular disease, the blood pressure goal is less than 140/90 mm Hg according to the AHA/ACC, and initial therapy should be with  $\beta$ -blockers and ACE inhibitors (or ARBs if ACE inhibitor therapy is not tolerated).
- For patients with diabetes, the blood pressure goal is less than 140/90 mm Hg.
- For patients with HF, there is no set blood pressure goal, but lower blood pressure is likely beneficial. For HF with reduced ejection fraction, blood pressure should be treated with evidence-based  $\beta$ -blockers, ACE inhibitors (or ARBs if ACE inhibitor therapy is not tolerated), and aldosterone antagonists.
- Consider a blood pressure goal of less than 150/90 mm Hg for older adult patients.
- For patients with CKD, the blood pressure goal is less than 140/90 mm Hg in those without proteinuria and less than 130/80 mm Hg in those with proteinuria, according to KDIGO.
- Spironolactone is useful for blood pressure reduction in patients with resistant HTN.
- Chlorthalidone is likely a more effective thiazide diuretic medication for HTN than is hydrochlorothiazide.
- Dosing at least one medication at bedtime is an efficacious way to lower nighttime blood pressure and may reduce the risk of CVD.
- Patients presenting with very high blood pressure should be treated according to the presence or absence of end-organ damage.
- Pharmacogenomic data show that certain polymorphisms are related to blood pressure response with drug therapy; however, replication and clinical outcomes studies are lacking.

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# Self-Assessment Questions

## Questions 1 and 2 pertain to the following case.

A.K., a 63-year-old white man (height 70 inches, weight 113.6 kg), presents to the clinic after not seeking health care for 5 years. He knows he has diabetes, but he is not sure how well it is controlled. Today, his blood pressure is 138/88 mm Hg, with repeat 138/85 mm Hg, and his heart rate is 80 beats/minute. A.K.'s laboratory test results are A1C 11.1%, SCr 1.3 mg/dL (CrCl [ideal body weight (IBW)] 60 mL/minute/1.73 m<sup>2</sup>), urine albumin excretion 100 mg/24 hours, K 3.9 mEq/L, and Na 141 mEq/L. His physician has a plan for A.K.'s diabetes treatment but would like to know what, if anything, should be done for the patient's blood pressure according to the latest KDIGO guidelines.

- Which one of the following is best to recommend regarding A.K.'s blood pressure?
  - Blood pressure is at goal; no action is required.
  - Blood pressure is at goal; the KDIGO guidelines do not apply because he does not have chronic kidney disease (CKD).
  - Blood pressure is above goal; initiate lisinopril 10 mg/day.
  - Blood pressure is above goal; initiate atenolol 50 mg/day.
- One year later, A.K. presents for a follow-up. He was admitted to the hospital last week with an ST-segment elevation myocardial infarction (STEMI) and discharged after stent placement. He now takes prasugrel 10 mg/day, aspirin 81 mg/day, enalapril 2.5 mg/day, and metoprolol succinate 12.5 mg/day. His blood pressure is 105/70 mm Hg, with similar repeat; his heart rate is 65 beats/minute, and his ejection fraction is 50%. He has no symptoms of orthostatic hypotension (OH), but he asks whether his blood pressure is too low. Which one of the following is the best response to A.K.'s inquiry?
  - His blood pressure is too low; discontinue metoprolol succinate.
  - His blood pressure is too low; discontinue enalapril.
  - Reassure him that his blood pressure should be this low; no changes are needed.
  - Reassure him that there is no concern for his blood pressure; no changes are needed.
- A 59-year-old African American woman with diet-controlled diabetes presents to the clinic for a follow-up. She is concerned about her cardiovascular (CV) risk because her mother died of a myocardial infarction (MI) at age 54. The patient's blood pressure is 138/86 mm Hg, and her heart rate is 85 beats/minute; she reports similar home blood pressure readings. Every morning, she takes lisinopril 20 mg, chlorthalidone 12.5 mg, and atorvastatin 40 mg. Her laboratory results are K 4.1 mEq/L, Na 142 mEq/L, SCr 1.3 mg/dL, CrCl 66 mL/minute/1.73 m<sup>2</sup>, total cholesterol 160 mg/dL, HDL 45 mg/dL, TG 115 mg/dL, and LDL 92 mg/dL. She is adherent to her therapy but would prefer not to take any additional agents. Her diabetes is well controlled, and she does not smoke. Which one of the following would best address this patient's concern about her CV risk?
  - Change the lisinopril dose to nighttime.
  - Increase the chlorthalidone dose to 25 mg/day.
  - Change all her antihypertensive medications to nighttime.
  - Reassure the patient that no medication changes are needed.
- A 75-year-old man (height 66 inches, weight 68 kg) with hypertension (HTN), gastroesophageal reflux disease (GERD), and osteoarthritis presents to the clinic. The patient is frustrated with trying to control his blood pressure. He is adherent to a low-sodium diet, antihypertensive drugs, and regular exercise. Today, his blood pressure is 155/90 mm Hg, and his heart rate is 80 beats/minute. His laboratory test results include K 4.8 mEq/L, Na 138 mEq/L, Cr 1.5 mg/dL, CrCl 38 mL/minute/1.73 m<sup>2</sup>, and ALT 25 mg/dL. His home drugs are carvedilol 25 mg twice daily, hydrochlorothiazide 25 mg/day, losartan 100 mg/day, amlodipine 10 mg/day, ibuprofen 800 mg twice daily, and omeprazole 20 mg twice daily. What is the next best step to address this patient's blood pressure control?
  - Increase his carvedilol dose to 50 mg twice daily.
  - Discontinue ibuprofen and start acetaminophen.
  - Start spironolactone 12.5 mg/day.
  - Increase his hydrochlorothiazide dose to 50 mg/day.
- A 69-year-old Hispanic woman (height 65 inches, weight 79.5 kg) with heart failure (HF) with preserved ejection fraction presents to the clinic. She reports her home blood pressure readings have been steadily increasing for the past several months. She has been adherent to her drugs: candesartan 32 mg/day and furosemide 40 mg twice daily. She is euvolemic. Her blood pressure today is 145/80 mm Hg, with similar repeat; her heart rate is 62 beats/minute; and her last ejection fraction was 55%. Her laboratory results are K 4.0 mEq/L, Na 140 mEq/L, SCr 1.1 mg/dL, and CrCl (IBW) 43 mL/minute/1.73 m<sup>2</sup>. Which one of the following is the best step to take to address this patient's blood pressure?
  - Increase furosemide to 80 mg twice daily.
  - Start spironolactone 12.5 mg/day.
  - Start metoprolol succinate 50 mg/day.
  - Start eplerenone 25 mg/day.

6. A 51-year-old white man presents for a blood pressure recheck. During his annual physical examination 3 months ago, his blood pressure was elevated (155/90 mm Hg). His only significant medical history is chronic gout, for which he takes allopurinol. He has been trying to lower the sodium in his diet and to increase exercise. Today, his blood pressure is 152/92 mm Hg, with similar repeat, and his heart rate is 75 beats/minute. His electrolytes and renal function are normal. Which one of the following is the best step to take next to treat this patient's blood pressure?
- Start lisinopril 10 mg/day.
  - Start chlorthalidone 25 mg/day.
  - Start metoprolol succinate 50 mg/day.
  - Start terazosin 5 mg at bedtime.
7. An 81-year-old woman with atherosclerotic cardiovascular disease (ASCVD) (STEMI with 4-vessel coronary artery bypass grafting 7 years ago), HTN, and CKD presents with dizziness on standing. Last week, she almost fell after getting out of bed. She has tried increasing her fluid and salt intake, but this has not helped. Today, her blood pressure is 138/74 mm Hg and her heart rate is 60 beats/minute while sitting; 1 minute later she stands and her blood pressure is 115/70 mm Hg and her heart rate is 76 beats/minute. She takes metoprolol tartrate 50 mg twice daily, lisinopril 20 mg/day, aspirin 81 mg/day, and atorvastatin 40 mg/day. Which one of the following is the next best step to treat this patient's blood pressure?
- Start midodrine 2.5 mg three times daily.
  - Discontinue all her antihypertensive drugs.
  - Start droxidopa 100 mg three times daily.
  - Lower her metoprolol dose to 25 mg twice daily.

**Questions 8 and 9 pertain to the following case.**

P.J., a 58-year-old man (height 72 inches, weight 100 kg) with type 2 diabetes mellitus (DM) and CKD, presents to the clinic for a follow-up. His blood pressure today is 152/86 mm Hg, with similar repeat, and his heart rate is 80 beats/minute. His laboratory test results are: A1C 6.9%, SCr 1.7 mg/dL, CrCl (IBW) 42 mL/minute/1.73 m<sup>2</sup>, K 4.0 mEq/L, Na 135 mEq/L, and urine albumin excretion 20 mg/24 hours. His home drugs are insulin glargine, insulin aspart, and pravastatin 40 mg/day.

8. Which one of the following represents the best blood pressure goal for P.J.?
- Less than 130/80 mm Hg
  - Less than 140/80 mm Hg
  - Less than 140/90 mm Hg
  - Less than 150/90 mm Hg
9. Which one of the following is best to initiate to address P.J.'s blood pressure?
- Losartan 25 mg/day
  - Lisinopril/hydrochlorothiazide 20/25 mg/day

- Hydrochlorothiazide 25 mg/day
  - Spironolactone 25 mg/day
10. A 61-year-old woman with ASCVD (stent placement 1 year ago) presents today for follow-up. Her blood pressure is 148/86 mm Hg, with a similar repeat, and her heart rate is 85 beats/minute. Her laboratory values are: K 4.6 mEq/L, Na 142 mEq/L, and SCr 0.9 mg/dL. She takes lisinopril/hydrochlorothiazide 20 mg/25 mg once daily and metoprolol succinate 50 mg/day, and she reports being adherent to her regimen. She is reluctant to take more blood pressure drugs because when she uses her home blood pressure monitor the readings are usually less than 125/70 mm Hg. Which one of the following is best to recommend for this patient's blood pressure management?
- Start felodipine 2.5 mg/day.
  - Decrease her lisinopril/hydrochlorothiazide dose to 10/12.5 mg once daily.
  - Order 24-hour ambulatory blood pressure monitoring.
  - Ask her to check her home blood pressure both sitting and standing.

**Questions 11 and 12 pertain to the following case.**

T.S., a 57-year-old man with a 13-year history of HTN, presents to the ED with a blood pressure of 210/120 mm Hg and a heart rate of 110 beats/minute. T.S. describes a sudden onset of severe chest pain as "sharp and tearing." A diagnosis of a thoracic aortic aneurysm dissection is made.

11. Which one of the following represents the best goal for T.S.'s blood pressure reduction?
- Achieve 170–150 mm Hg SBP within the first 2 hours of presentation.
  - Achieve 90 mm Hg DBP over the first 2–6 hours of presentation.
  - Reduce SBP to less than 120 mm Hg within 20 minutes of presentation.
  - Reduce SBP to less than 140 mm Hg over 24–48 hours.
12. Which one of the following would best manage T.S.'s hypertensive emergency?
- Diazoxide
  - Esmolol
  - Hydralazine
  - Minoxidil
13. You are giving a continuing education lecture to a local group of community pharmacists on the recent HTN guidelines. During the question and answer portion, an attendee asks your thoughts on treating HTN in patients older than 80 years. Which one of the following is the best evidence-based response to this question?

- A. Meta-analyses have shown fewer adverse CV outcomes with aggressive blood pressure lowering to less than 140 mm Hg in 70- to 85-year-old patients.
- B. The VALISH trial showed that achieving an SBP of less than 150 mm Hg in patients 70–84 years of age improved outcomes.
- C. The JATOS trial showed that achieving an SBP of less than 160 mm Hg in patients 65–85 years of age improved outcomes.
- D. The HYVET trial showed lower adverse CV outcomes with lowering the blood pressure to less than 150/80 mm Hg in patients older than 80 years.
14. A 57-year-old man is brought to the ED with significant shortness of breath, evidence of volume overload, and a blood pressure of 220/110 mm Hg. His medical history is significant for hyperlipidemia, gout, diabetes, HF with reduced ejection fraction, and coronary artery disease (CAD). Which one of the following would best manage this patient's hypertensive emergency event?
- A. Esmolol
- B. Labetalol
- C. Nicardipine
- D. Sodium nitroprusside
15. A patient who is homozygotic for the Arg389Gly phenotype of the *ADRB1* gene requires blood pressure reduction. Which one of the following would have the greatest blood pressure–lowering effect for this patient?
- A. Chlorthalidone
- B. Metoprolol
- C. Trandolapril
- D. Verapamil
16. According to the JNC 8 panel author recommendations, for which one of the following patients would a goal blood pressure of less than 150/90 mm Hg be most appropriate?
- A. A 56-year-old woman with a medical history of DM (5 years) and CKD (2 years)
- B. A 62-year-old man with a medical history of hypercholesterolemia (4 years)
- C. A 58-year-old man with a recent MI (2 months ago)
- D. A 45-year-old man with uncomplicated HTN
17. A 54-year-old man presents to the clinic for a follow-up of his hypertensive drug regimen. His medical history is significant for HTN and CAD. To control his blood pressure, he takes amlodipine 10 mg/day, lisinopril 40 mg/day, and chlorthalidone 25 mg/day. Today in the clinic, his vital signs include blood pressure 154/96 mm Hg and heart rate 55 beats/minute, and his laboratory values are all within normal values. Which one of the following would best manage this patient's HTN?
- A. Switch chlorthalidone to hydrochlorothiazide.
- B. Increase amlodipine to 15 mg/day.
- C. Add spironolactone 25 mg/day.
- D. Send him for a consult for a renal denervation procedure.
18. While completing paperwork in the clinic, a third-year medical student asks your opinion on initiating atenolol 25 mg/day in a patient with newly diagnosed uncomplicated HTN. Which one of the following is the best response to this question?
- A.  $\beta$ -Blockers are no longer recommended as first-line options.
- B. Carvedilol would be a better  $\beta$ -blocker to initiate as a first-line option.
- C. Initiating atenolol sounds like a reasonable plan.
- D. Make sure that a baseline corrected QT interval is obtained before initiating atenolol.
19. Which one of the following best justifies the initiation of chlorthalidone over hydrochlorothiazide in a patient with HTN?
- A. The ALLHAT trial showed that chlorthalidone reduced blood pressure better than hydrochlorothiazide.
- B. Direct head-to-head trials showed lower mortality with chlorthalidone.
- C. Meta-analyses of indirect data showed improved CV outcomes with chlorthalidone.
- D. The MRFIT trial showed a higher risk of developing diabetes with hydrochlorothiazide.
20. The ALLHAT was a randomized, double-blind, active-controlled clinical trial that enrolled 33,357 patients with HTN and at least once other coronary heart disease (CHD) risk factor to receive chlorthalidone, amlodipine, or lisinopril. The primary outcome was a combination of fatal CHD or non-fatal MI. One of the secondary outcomes was HF. The following table summarizes the data for amlodipine compared with chlorthalidone:

	Relative Risk	95% CI
Primary end point	0.98	0.90–1.07
Heart failure	1.38	1.25–1.52

Which one of the following best describes how amlodipine compares with chlorthalidone in the ALLHAT data?

- A. Decreases the primary end point but increases HF
- B. Decreases both the primary end point and HF
- C. Has no significant effect on the primary end point or HF
- D. Has no significant effect on the primary end point but increases HF

Learner Chapter Evaluation: Hypertension.