Update on the Therapeutic Management of Hypertension

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Learning Objectives

1. Assess patient risk factors and comorbidities to determine an appropriate blood pressure (BP) goal according to various international guidelines.
2. Develop an individualized evidence-based treatment plan considering medication benefits and potential for adverse effects.
3. Design a treatment strategy for patients with resistant hypertension (HTN) to achieve BP goals.
4. Demonstrate apropriate medication selection, dose, and duration for treatment of HTN according to compelling indications.
5. Account for the role of medications that increase BP when treating patients with HTN.
6. Justify the employment of ambulatory HTN monitoring.

Baseline Knowledge Statements

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

- White-coat hypertension (HTN)
- Antihypertensive medications and their monitoring parameters
- Lifestyle recommendations for HTN

Additional Readings

The following free resources are available for readers wishing 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.
- Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease. Circulation 2007;115:2761-88.
- American College of Cardiology/American Heart Association (ACC/AHA). 2011 Expert Consensus Document on Hypertension in the Elderly [homepage on the Internet].
- American Diabetes Association (ADA). Standards of medical care in diabetes – 2014. Diabetes Care 2014;37(suppl 1):S14-80.
- Go AS, Bauman MA, King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. Hypertension 2013 Nov 15. [Epub ahead of print].
- 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.

Abbreviations in This Chapter

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
AKI	Acute kidney injury
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHD	Coronary heart disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DHP	Dihydropyridine
HF	Heart failure
HTN	Hypertension
OH	Orthostatic hypotension

Epidemiology

Hypertension (HTN) 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. Around 78 million adults in the United States (33.0%) have HTN (Go 2013b). The prevalence of HTN is higher in patients with cardiovascular disease (CVD) than in those without (51% vs. 28.5%). The American Heart Association (AHA) has projected that the prevalence of HTN will increase by 7.2% between 2013 and 2030.

Blood pressure (BP) is controlled to goal in just more than 50% of adults with documented HTN, and 75% are using medication to treat their BP. Eighteen percent of adults with HTN are unaware they have high BP. Although the control of HTN remains suboptimal, national data show that control and treatment have improved; the National Health and Nutrition Examination Survey (NHANES) found that for the periods 1988–1994 and 2007–2008, HTN control rates improved from 27.3% to 50.1%, and treatment improved from 54.0% to 73.5% (Go 2013b).

In 2009 the overall death rate from HTN was 18.5 of 1000. In the Harvard Alumni Health Study, higher BP in early adulthood was associated with a higher risk of all-cause mortality, CVD mortality, and coronary heart disease (CHD) mortality several decades later (Gray 2011). At age 50, normotensive men and women have a life expectancy about 5 years longer than their hypertensive counterparts. Estimates from various studies show 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 BP levels exceeding 140/90 mm Hg.

International Guidelines

The last sanctioned guideline by the National Heart, Lung, and Blood Institute (NHLBI) was the Seventh Report of the Joint National Committee (JNC 7), published in 2003. The writing panel for JNC 8 was appointed in 2008 by the NHLBI. However, in 2013, the NHLBI transferred HTN guideline development from this writing panel to that of the American Heart Association and the American College of Cardiology (AHA/ACC) (Gibbons 2013). Members of the original JNC 8 writing panel published their recommendations in December 2013, acknowledging that they were not sanctioned or endorsed by the NHLBI (James 2014). In addition, the AHA/ACC and the Centers for Disease Control and Prevention (CDC) issued a joint science advisory in November 2013, and the American Society of Hypertension/International Society of Hypertension (ASH/ISH) published guidelines in December 2013, which have several recommendations that differ from those in the JNC 8 guidelines (Weber 2014; Go 2013a). The official guidelines for HTN management, which are intended to replace the last NHLBI guidelines, are expected in 2015.

The JNC 7 guidelines classified BP 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 provides a comparison of the BP goals for different populations among various international guidelines, including several U.S. guidelines and the Canadian Hypertension Education Program (CHEP) and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines.

Uncomplicated HTN

BP Goals

The term uncomplicated HTN refers to HTN in the absence of diabetes, HF, chronic kidney disease (CKD), or known CHD. According to the guidelines, the BP goal for uncomplicated HTN is less than 140/90 mm Hg (see Special Populations section, which addresses elderly patients). Patients with an elevated BP should be encouraged to make lifestyle changes, including increased consumption of fruits and vegetables, moderation in alcohol and salt intake, participation in regular exercise, weight reduction to a healthy body mass index of less than 25 kg/m^2, and smoking cessation.

Antihypertensive Therapy

Recently, it has been debated about when pharmacotherapy should be initiated in patients with uncomplicated HTN. A 2012 Cochrane review examined the risks and

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

	JNC 7 (2003)[a]	JNC 8 (2014)[b]	ASH/ISH (2013)[c]	CHEP (2013)[d]	ESH/ESC (2013)[e]	Disease-Specific Guidelines
Uncomplicated HTN	< 140/90	< 140/90	< 140/90	< 140/90	< 140/90	Not applicable
Diabetes	< 130/80	< 140/90	< 140/90	< 130/80	< 140/85	< 140/80; ADA (2013)[f]
CVD	< 140/90	—	< 140/90	< 140/90	< 140/90	< 140/90; ACC/AHA (2011)[g]
CKD	< 130/80	< 140/90	< 140/90	< 140/90	< 140/90	< 130/80 with proteinuria; otherwise, < 140/90; KDIGO (2012)[h]
Elderly individuals	Not specified	< 150/90, age ≥ 60 years	< 150/90, age ≥ 80 years	< 150/90, age ≥ 80 years	< 150/90, age ≥ 80 years	Not specified; ACC/AHA (2011)[i]

CKD = chronic kidney disease; CVD = cardiovascular disease; HTN = hypertension.

[a]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.

[b]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.

[c]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.

[d]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.

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

[f]American Diabetes Association (ADA). Standards of medical care in diabetes – 2013. Diabetes Care 2013;36(suppl 1):S1-S110.

gSmith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. Circulation 2011;124:2458-73.

[h]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.

[i]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.

benefits of pharmacotherapy for mild HTN (SBP 140–159 mm Hg and/or DBP 90–99 mm Hg) in primary prevention patients; the review concluded that, compared with placebo, antihypertensive drugs did not reduce total mortality (relative risk [RR] 0.85, 95% confidence interval [CI], 0.63–1.15), CHD (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). Moreover, 9% of patients treated with antihypertensive drugs discontinued therapy because of adverse effects (Diao 2012). Additional trials are needed in this population to help answer whether the benefits of treatment outweigh the harm.

Thiazide diuretics decrease mortality as well as CHD and have supporting evidence as first-line therapy for the treatment of HTN (Wright 2009). Meta-analyses have shown that, in the primary prevention of complications from HTN, BP lowering is more important than the drug class used (Staessen 2003; Wang 2003). Other first-line options recommended 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.

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

Table 1-2 compares U.S. guidelines on antihypertensive therapy recommendations, highlighting the variability among them. Both the JNC 8 and the 2013 ASH/ISH guidelines base their antihypertensive therapy recommendations on race (African American and non–African American). For example, both guidelines advise

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

	Stage 1 HTN			Stage 2 HTN	CKD	Diabetes	Coronary Disease	Stroke	Symptomatic HF
	African American	Non–African American							
		< 60 years	≥ 60 years						
JNC 7[a]									
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								
JNC 8[b]									
Initial therapy	Thiazide-type diuretic or CCB	Thiazide-type diuretic, CCB, ACE inhibitor or ARB		—	ACE inhibitor or ARB	—	—	—	—
ASH/ISH[c]									
Initial therapy	CCB or thiazide diuretic (combine if necessary)	ACE inhibitor or ARB	CCB or thiazide diuretic (combine if necessary)	Two-drug therapy: CCB or thiazide diuretic PLUS ACE inhibitor or ARB	ACE inhibitor or ARB	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	Three-drug therapy: CCB PLUS thiazide diuretic PLUS 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)	CCB or thiazide diuretic (combine if necessary)	DHP CCB

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

	Stage 1 HTN			Stage 2 HTN	CKD	Diabetes	Coronary Disease	Stroke	Symptomatic HF
	African American	Non–African American							
		< 60 years	≥ 60 years						
ACC/AHA HTN[d]									
Initial therapy	Thiazide diuretic			Thiazide diuretic PLUS CCB, ACE inhibitor, or ARB; ACE inhibitor PLUS CCB	ACE inhibitor or ARB	ACE inhibitor or ARB, thiazide diuretics, β-blocker, CCB	β-Blocker PLUS ACE inhibitor	Thiazide diuretic, ACE inhibitor	Systolic: ACE inhibitor or ARB, β-blockers, aldosterone antagonists, thiazide diuretics Diastolic: ACE inhibitor or ARB, β-blockers, thiazide diuretics
Subsequent therapy	CCB, ACE inhibitor or ARB								
Disease-Specific Guidelines					**KDIGO[e]**	**ADA[f]**	**ACC/AHA CVD[g]**		
Initial therapy	—			—	Urine albumin excretion > 30 mg/24 hours: ACE inhibitor or ARB	ACE inhibitor or ARB	β-blocker and/or ACE inhibitor	—	—
Subsequent therapy					No proteinuria: No preferred antihypertensive drugs	Thiazide diuretic, β-blockers, and DHP CCB	Other antihypertensive drugs as needed to achieve BP goal		

CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; DHP = dihydropyridine; HF = heart failure; HTN = hypertension.

aChobanian 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.

bJames 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.

[c]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.

[d]Go AS, Bauman MA, King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. Hypertension 2013 Nov 15. [Epub ahead of print]

[e]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.

[f]American Diabetes Association (ADA). Standards of medical care in diabetes – 2013. Diabetes Care 2013;36(suppl 1):S1-S110.

[g]Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. Circulation 2011;124:2458-73.

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.

The science advisory from the AHA/ACC/CDC includes a template outlining a general approach for a treatment algorithm (Go 2013a). As initial therapy, this advisory recommends a thiazide diuretic for most patients, with an ACE inhibitor, ARB, or CCB as an alternative. For stage 2 HTN (greater than 160/100 mm Hg), several guidelines recommend that patients be initiated on combination therapy (Weber 2014; Go 2013a; Chobanian 2003). Finally, disease-specific guidelines (CKD, diabetes, and CVD) provide their own set of treatment recommendations.

Concomitant Disease States

Specific disease states are direct sequelae of HTN or are commonly associated with HTN. Antihypertensive therapy should be individualized according to age; race; coexisting CVD, diabetes, CKD, or HF; risk of disease progression; and tolerance of antihypertensive treatment.

Coronary or Other Atherosclerotic Vascular Disease

Hypertension is an independent risk factor for CVD. In a large meta-analysis of almost 1 million primary prevention adults, there was a linear increase in vascular death from a BP 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). Fortunately, studies have shown the benefit of antihypertensive drugs on CVD risk.

BP Goals

In 2011, ACC/AHA published secondary prevention guidelines that updated BP management for patients with coronary or other atherosclerotic vascular disease. The most notable modification from previous guidelines was the change in BP goal from less than 130/80 mm Hg to less than 140/90 mm Hg (Smith 2011). The 2007 ACC/AHA HTN guideline for patients with ischemic heart disease had lowered the goal to less than 130/80 mm Hg on the basis of epidemiologic studies. This goal was recommended for patients with coronary artery disease (CAD) or CAD risk equivalents (Rosendorff 2007). The 2012 ACC/AHA guideline for patients with stable ischemic heart disease again recommend a goal of less than 140/90 mm Hg. Reasons listed for this goal change were excessive reductions in DBP that compromised coronary perfusion in patients with stable ischemic heart disease and the link between low DBP and coronary events (Fihn 2012).

Antihypertensive Therapy

Antihypertensive treatment recommendations in guidelines have not recently changed extensively, except for recommendations regarding β-blocker therapy. Previously, β-blocker therapy post-MI or post–acute coronary syndrome was recommended indefinitely unless contraindications to therapy were present, because β-blockers demonstrated a reduction in deaths and recurrent MIs in patients with a history of MI. The benefits of β-blockers in this patient population are likely caused by a decrease in oxygen demand from lower heart rate and blood pressure, decreased risk of ventricular arrhythmias, and prolonged diastole leading to improved diastolic perfusion.

However, recommendations for β-blocker therapy have been updated to reflect recent 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 (ejection fraction [EF] less than 40%). In patients without these class I indications, β-blocker therapy is optional (class IIa or IIb) (Smith 2011). A survival benefit or reduction in coronary event rates with β-blocker therapy in patients with stable ischemic heart disease has not been shown in any large trials.

In patients with HTN and coronary or other atherosclerotic vascular disease, elevated BP should be treated initially with β-blockers and/or ACE inhibitors, with the addition of other drugs such as thiazide diuretics or CCBs as needed to achieve the goal BP (Smith 2011). Therefore, if β-blocker therapy is needed to adequately control BP or heart rate, it should be continued unless contraindications or tolerance issues develop. In this situation, alternative antihypertensive agents should be used.

Several clinical trials have shown ACE inhibitors to have CV protective effects by reducing the risk of future ischemic events. The reduction 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 the improved myocardial oxygen supply/demand. Unless contraindicated, ACE inhibitors should be initiated and continued indefinitely in all patients with coronary or atherosclerotic vascular disease with a left ventricular ejection fraction (LVEF) of less than 40% and in those with HTN, diabetes, or CKD. The use of ARBs is recommended in patients who have HF or in those who have had an MI with an LVEF of less than 40% and are ACE inhibitor intolerant (Fihn 2012; Smith 2011).

Diabetes

Most patients with diabetes are affected by HTN. Because CVD is the No. 1 killer of, and main source of morbidity in, patients with diabetes, controlling CV risk factors such as HTN is of utmost importance in patients with diabetes. Studies of patients with diabetes have shown that controlling CV risk factors prevents or slows the development of CVD (ADA 2014).

BP Goals

The BP goal for patients with diabetes also changed recently. In January 2013, the American Diabetes

Association (ADA) recommended a higher SBP goal of less than 140 mm Hg (from the previous goal of less than 130 mm Hg). The 2013 ASH/ISH BP guidelines and JNC 8 also recommended this higher SBP goal for patients with diabetes (Weber 2014; James 2014). The lower SBP goal was based only on epidemiologic data and was not obtained from randomized controlled trials.

The ACCORD study objective was to determine whether an SBP target of less than 120 mm Hg reduces major CV events in participants with type 2 diabetes mellitus at a high risk of CV events. More than 4700 patients were randomly assigned to intensive (SBP target less than 120 mm Hg) or standard therapy (SBP target less than 140 mm Hg). 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 (HR with intensive therapy 0.88; 95% CI, 0.73–1.06; p=0.20). There was also no difference between groups in all-cause mortality or CV death. Fewer strokes were seen with intensive therapy than with standard therapy (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 exception of lower stroke risk (absolute difference 0.21%), study data 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 2014 ADA guidelines maintain the DBP goal of less than 80 mm Hg (ADA 2014). Two earlier studies, the UKPDS and HOT trials, showed a reduction in CHD events and nephropathy with this diastolic goal (Adler 2000; Hansson 1998; UKPDS 1998). In contrast, the 2013 ASH/ISH BP and JNC 8 guidelines recommend a DBP goal of less than 90 mm Hg for patients with diabetes, stating that the clinical benefits with the lower goal have not yet been established (James 2014; Weber 2014).

Antihypertensive Therapy

Inhibitors of the renin-angiotensin system 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 (Heart Outcomes Prevention Evaluation Study Investigators 2000). The compelling benefits of renin-angiotensin system inhibitors in patients with diabetes and albuminuria provide additional rationale for their use.

The ADA and the 2013 ASH/ISH BP guidelines recommend that pharmacologic therapy for patients with diabetes and HTN include either an ACE inhibitor or an ARB (ADA 2014; Weber 2014). If one class is not tolerated, the other class should be substituted. Multidrug therapy is usually required to achieve BP targets. If additional BP lowering is needed after ACE inhibitor or ARB therapy is optimized, a thiazide diuretic, β-blocker, and/or CCB should be added and optimized. To overcome clinical inertia, additional antihypertensive therapy should be initiated and titrated in a timely manner to achieve BP goals.

Heart Failure

One of the most important modifiable risk factors for both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) is HTN. 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 BP 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. Data from the first 107,000 patients in the ADHERE registry (which tracks patients hospitalized with acute decompensated HF) showed that almost 50% of patients admitted with HF had a BP greater than 140/90 mm Hg, and almost 75% of patients 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, abrupt discontinuation of antihypertensive therapy may precipitate worsening HF.

BP 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, BP 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 (reduction in the combined risk of death or CVD by 27%; p<0.001) and the combined risk of death or HF hospitalization by 31% (p<0.001)) in patients with a mean baseline BP of 123/76 mm Hg, suggesting that lower BP may be desirable in some patients (Packer 2001). However, the benefits seen in this trial are likely caused by the treatment with carvedilol rather than the BP level. Other recently published guidelines such as the JNC 8 and the 2013 ASH/ISH guidelines do not address a BP goal for patients with HF.

Antihypertensive Therapy

Choice of antihypertensive therapy should be guided by HF-specific options and tailored to concomitant medical problems such as diabetes or CAD. Diuretic-based antihypertensive therapy has repeatedly been shown to prevent HF in a wide range of patients. One trial of indapamide-based therapy showed a number needed to treat of 52

to prevent one HF event in 2 years (Beckett 2008). Angiotensin-converting enzyme inhibitors, ARBs, and β-blockers are also effective in decreasing the risk of HF.

Patients with HFrEF

Therapies that reduce morbidity and mortality in patients with HF also reduce BP. Evidence-based β-blockers (metoprolol, carvedilol, or bisoprolol) and ACE inhibitors should be used in all patients with a reduced EF (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 HF 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 have not been shown to have a mortality benefit in patients with HFrEF but are recommended in patients with fluid retention to achieve euvolemia. Although the aforementioned agents can help treat HTN, caution must be used to ensure symptomatic hypotension does not develop.

Patients with HFpEF

Blood pressure control remains the most important consideration in patients with HFpEF. In hypertensive patients with HFpEF, aggressive treatment (usually requiring multidrug regimens) is recommended. The ACE inhibitors or ARBs are often considered first-line agents (Yancy 2013). Specific BP targets in HFpEF have not been firmly established; thus, the recommended targets are either less than 140/90 mm Hg or according to concomitant comorbid conditions, if present.

Chronic Kidney Disease

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

BP Goals

For adults with or without diabetes who have CKD and a urine albumin excretion of less than 30 mg/24 hours (or equivalent), together with an office BP readings consistently greater than SBP 140 mm Hg or DBP 90 mm Hg, recent guidelines recommend treatment to maintain a BP consistently less than 140/90 mm Hg (James 2014; Weber 2014; KDIGO 2012). Previous guidelines recommended a BP target of less than 130/80 mm Hg for all patients with CKD, irrespective of urine protein level. However, recent randomized controlled trials have not shown a benefit of lower BP targets in patients without proteinuria. For example, in the African American Study of Kidney Disease and Hypertension (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) (Appel 2010). During the long-term follow-up of participants, benefit was associated with the lower BP target among patients with a urine protein/creatinine ratio of greater than 220 mg/g; for patients with a urine protein/creatinine ratio of 220 mg/g or less, there was either no benefit or a trend toward worse outcomes. Therefore, in adults with and without diabetes who have CKD and a urine albumin excretion greater than 30 mg/24 hours (or equivalent) whose office BP is consistently greater than 130 mm Hg systolic or greater than 80 mm Hg diastolic, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment with BP-lowering drugs to maintain a BP 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

An ACE inhibitor or ARB is suggested in adults with diabetes, CKD, and a urine albumin excretion of 30–300 mg/24 hours (or equivalent). In addition, an ACE inhibitor or ARB is recommended for patients with or without diabetes who have CKD and a urine albumin excretion greater than 300 mg/24 hours (or equivalent). Vasodilatation of the efferent and afferent glomerular arterioles (particularly the efferent) results in decreased intraglomerular pressure and hence reduction in both glomerular filtration rate (GFR) 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 having high levels of protein excretion, KDIGO contends that there is no strong evidence to support the preferential use of any particular agent in controlling BP in CKD, nor are there data to guide 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; Go 2013a). Ultimately, the choice of agents is less important than the actual reduction in BP achieved. The ACE inhibitors or ARBs are valuable antihypertensive agents in patients with CKD and are safe to combine with most other BP-reducing agents, although the risk of significant hyperkalemia warrants caution. In CKD, aldosterone antagonists reduce urine albumin levels and are 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.

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, either as the primary investigational agent or as add-on therapy. Although thiazides are excreted by the kidney, no dose adjustment is recommended in patients with a CrCl above 30 mL/minute. As the GFR falls below about 30–50 mL/minute/1.73m2, the ability of thiazides to overcome fluid retention is diminished, although their antihypertensive benefit may be preserved. Most clinicians switch to a loop diuretic in patients with a CrCl of less than 30 mL/minute because of the thiazide's lack of effectiveness, particularly if the BP level is becoming resistant to therapy or if edema becomes a problem.

Potentially nephrotoxic and renally excreted drugs should be temporarily discontinued in individuals with a CrCl of less than 60 mL/minute who have a serious intercurrent illness that increases the risk of acute kidney injury (AKI). These agents include antihypertensive drugs such as the RAAS (renin-angiotensin-aldosterone system) blockers (including ACE inhibitors, ARBs, aldosterone inhibitors, and direct renin inhibitors) and diuretics. However, on initiation of these therapies, a reversible 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.

HTN in Special Populations

Elderly Patients

Published data are limited on the benefits of reaching a target BP of less than 140/90 mm Hg in elderly patients. Neither the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study – which included 3079 patients between 70 and 84 years of age – nor the Japanese Trial to Assess Optimal Systolic BP in Elderly Hypertensive Patients (JATOS) – which included 4418 patients between 65 and 85 years of age – showed any difference between strict control (SBP of less than 140 mm Hg) compared with more modest control (SBP less than 150 mm Hg for VALISH; SBP less than 160 mm Hg for JATOS) (Ogihara 2010; JATOS 2008). The overall rate of the primary cardiovascular composite end point in the VALISH study was 10.6 per 1000 patient-years in the strict control group versus 12 per 1000 patient-years in the moderate control group (p=0.38) (Ogihara 2010). VALISH was underpowered to determine whether strict control was superior to less stringent targets because the incidence of the primary outcome was less than half of the estimated value from the power calculation (Ogihara 2010). In JATOS, also underpowered, the primary end point (composite of CVD and renal failure) was similar in the two groups (86 patients in each group; p=0.99) (JATOS 2008). The authors did note that strict treatment may be more favorable in patients aged less than 75 years (JATOS 2008).

The Hypertension in the Very Elderly Trial (HYVET) assessed various CV end points in 3845 patients 80 years and older with an elevated SBP of 160 mm Hg or greater treated with the diuretic indapamide compared with placebo. Perindopril or matching placebo was added to achieve a target BP of 150/80 mm Hg. After 1.8 years, 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).

In elderly patients with an initial SBP of greater than 160 mm Hg, there is strong evidence of benefit of lowering BP by antihypertensive treatment to SBP less than 150 mm Hg but not less than 140 mm Hg. For patients 60 years and older, JNC 8 recommends initiating treatment to achieve a goal BP of less than 150/90 mm Hg (James 2014). The age chosen by the JNC 8 writing panel for a less aggressive BP target is 20 years younger than the population defined as elderly (80 years and older) in the 2013 ASH/ISH, CHEP, and ESH/ESC guidelines, which target a BP goal of less than 150/90 (Weber 2014; Hackman 2013; Mancia 2013). The choice of antihypertensive therapy should be driven by comorbidities. In the absence of comorbidities, thiazides and CCBs are useful in isolated systolic HTN (Chobanian 2007).

A potential concern with using antihypertensive therapy in elderly patients is the risk of orthostatic hypotension (OH). The diagnosis of OH can be made by measuring BP and heart rate supine and after 1 and 3 minutes of standing. Orthostatic hypotension is defined as a reduction in SBP of 20 mm Hg or a reduction in DBP of 10 mm Hg within 3 minutes of standing. Symptoms of OH include dizziness or light-headedness immediately on standing that can be relieved by sitting or lying down. Orthostatic hypotension is a risk factor for syncope and falls. Those performing a medication review should look for any potential offending agents including α-blockers, diuretics, vasodilators, and tricyclic antidepressants (Shibao 2013).

Pregnant Patients

Hypertension complicates 5%–7% of all pregnancies. Hypertension in pregnancy can be categorized as chronic (BP 140/90 mm Hg or greater before pregnancy or before 20 weeks' gestation and usually lasting more than 12 weeks postpartum), gestational (HTN without proteinuria developing after 20 weeks' gestation), preeclampsia-eclampsia (HTN with proteinuria greater than 300 mg/24 hours), or preeclampsia superimposed on chronic HTN (Lindheimer 2008). Hypertension in pregnancy is associated with an increased risk of preterm and small-for-gestational-age births. Preeclampsia is associated with maternal and fetal complications. Management

of preeclampsia focuses on early diagnosis of the condition and, ultimately, delivery of the placenta, which is curative.

It is unclear whether antihypertensive therapy is useful in mild to moderate HTN during pregnancy. In women with severe chronic HTN (SBP of 160 mm Hg or greater or DBP of 110 mm Hg or greater), antihypertensive therapy should be initiated or continued to reduce the risk of maternal stroke. The American Congress of Obstetricians and Gynecologists recommends labetalol 200–2400 mg/day in two or three divided doses as first-line treatment of chronic HTN in pregnancy because of the low rate of adverse effects and good efficacy (ACOG 2012). Methyldopa has been used for decades to treat HTN in pregnancy and appears safe. Methyldopa can be dosed at 0.5–3 g/day in two divided doses; however, maternal sedation can limit its use. The CCBs have also been used in chronic HTN, the most commonly studied of which is nifedipine 30–120 mg/day in the slow-release preparation. Thiazide diuretics may be continued if they were initiated before the pregnancy. Atenolol, a pure β1-antagonist, has been associated with growth restriction in infants and is not currently recommended for the treatment of chronic HTN in pregnancy. The ACE inhibitors and ARBs are contraindicated in this population.

Resistant HTN

Resistant HTN is defined as either a BP of 140/90 mm Hg or greater while using optimally dosed antihypertensive medications from three different drug classes (including a diuretic) or taking agents from four or more antihypertensive drug classes regardless of BP. The 2003–2008 NHANES data show that 8.9% of U.S. adults with HTN met the criteria for resistant HTN, which is 12.8% of the population taking antihypertensive medication (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 BP control. Adherence rates with antihypertensive drugs are reported to be 50%–70%. In a systematic review of randomized trials, the most successful strategy in improving medication 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, telephonic 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, engaging 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 BP care and offers support for health care professionals in helping Americans improve their medication adherence and more effectively manage their BP. Moreover, the program provides several ideas on how best to incorporate this program into pharmacies. Million Hearts has resources for pharmacists (including posters, a discussion tool, a BP guide, a video, and continuing pharmacy education) and patients (e.g., a BP journal, medication tracking cards). Program implementation involves three tiers: general awareness, medication adherence messaging, and BP counseling services (Million Hearts 2012).

Causes of Resistant HTN

Box 1-1 details various causes of pseudo-resistant and resistant HTN, including drug- and disease-related causes. 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., primary aldosteronism) or the ability to resolve the issue without additional antihypertensive medication (e.g., hyperthyroidism). It is also important to address other causes of resistant HTN. Improper BP measurement and white-coat HTN may not necessitate any changes to the antihypertensive regimen, whereas volume overload may require lifestyle modification or optimization of diuretic therapy.

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

Stimulants

Although some patients may experience significant increases in BP or heart rate, one stimulant medication (e.g., methylphenidate, amphetamines) usually causes only modest increases in average BP (about 2–4 mm Hg) and average heart rate (about 3–6 beats/minute). However, patients should be monitored for changes in heart rate and BP because response to these agents is unpredictable and may have untoward consequences.

Caution is indicated in patients with underlying medical conditions that could be compromised by increased BP or heart rate (e.g., preexisting HTN, HF, recent MI, ventricular arrhythmia). Sudden death, stroke, and MI have been reported in adults taking stimulant drugs at usual doses, although the causality of stimulant use in these cases has not been determined. In general, adults with serious structural cardiac abnormalities, cardiomyopathy, serious

heart rhythm abnormalities, CAD, or other serious cardiac problems should not be treated with stimulant drugs. Stimulants, and medications with stimulant properties, are present in a variety of products, both prescription and over the counter (OTC), as well as in illicit forms. Patients may be taking several drugs with stimulant properties without realizing it, thereby making BP control unusually difficult and perhaps increasing patients' CV risk (Calhoun 2008).

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been implicated in increasing BP and CVD risk. Prostaglandins promote vasodilation as well as enhance the excretion of sodium and water. Because NSAIDs inhibit prostaglandins, the benefits of prostaglandins are diminished, contributing to vasoconstriction and volume retention, and the BP level can increase. In addition, NSAIDs can antagonize the effects of some antihypertensive drugs and cause complications when used in combination. This pharmacodynamic interaction may involve attenuation of the antihypertensive agents secondary to the ability of NSAIDs to interfere with the production of vasodilator and natriuretic prostaglandins (which are stimulated by select antihypertensive agents).

When NSAIDs are used with several antihypertensive drugs (a thiazide diuretic plus an ACE inhibitor or an ARB), AKI may occur. In a retrospective nested case-control cohort study of almost 500,000 patients, combinations of ACE inhibitors/ARBs, diuretics, and NSAIDs were evaluated to determine the risk of AKI. After a mean follow-up of 5.9 years, current use of a double-therapy combination containing 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 renin-angiotensin system by the ACE inhibitor or ARB (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, 882 self-reported chronic NSAID users were compared with 21,694 self-reported nonchronic NSAID users. At a mean follow-up of 2.7 years, the primary outcome (all-cause death, nonfatal MI, or nonfatal stroke) occurred at a rate of 4.4 events per 100 patient-years in the chronic NSAID group versus 3.7 events per 100 patient-years in the nonchronic NSAID group (adjusted HR 1.47; 95% CI, 1.19–1.82; p=0.0003). This difference was because of 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, the benefits of NSAIDs (e.g., pain control) must be weighed against the risk of worsening HTN, kidney disease, and CV morbidity and mortality. To mitigate these risks, strategies may include the following: (1) monitoring BP, renal function, and new-onset or worsening edema; (2) recommending lifestyle changes and nonpharmacologic therapies for pain; (3) choosing the lowest effective NSAID dose; (4)

Patient Care Scenario

A 35-year-old woman with a 10-year history of chronic HTN calls the clinic with her recent home BP readings. She is 36 weeks pregnant and reports adherence to nifedipine extended release (ER) 60 mg once daily. She states she developed preeclampsia with a previous pregnancy at 37 weeks. Her clinician must decide the next course of action.

Day	1	2	3	4	5
BP (mm Hg)	157/92	159/93	161/94	162/95	161/96

Answer

Proteinuria must be present to diagnose preeclampsia definitively because use of BP criteria alone causes a misdiagnosis of preeclampsia in some women with chronic HTN. Preeclampsia is a serious disease, for which obstetricians have particular experience in diagnosing and treating. Suspected preeclampsia may warrant close obstetric follow-up, fetal monitoring, and possible hospitalization.

In a prospective study of 763 women with chronic HTN, 193 (25%) developed superimposed preeclampsia. The frequency of preeclampsia was greater in women who had experienced HTN for at least 4 years (31% vs. 22%; odds ratio [OR] 1.6 [CI, 1.1–2.2]) and in those with preeclampsia during a previous pregnancy (32% vs. 23%; OR 1.6 [CI, 1.1–2.3]).

This patient should be evaluated in the clinic by her obstetrician for a verification of her BP reading as well as an assessment for proteinuria as a work up for preeclampsia.

1. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1998;339:667-71.

2. American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 125: chronic hypertension in pregnancy. Obstet Gynecol 2012;119:396-407.

changing to an NSAID with a lower propensity to worsen CV risk (e.g., naproxen); and (5) modifying antihypertensive therapy and diuretic management as needed to maintain target BP (Whelton 2011).

Treatment of Resistant HTN

Spironolactone

Several studies have investigated spironolactone for treatment of resistant HTN. A 2002 study (n=25) showed that adding spironolactone 1 mg/kg/day significantly decreased BP (SBP from 152 ± 2 mm Hg to 128 ± 2 mm Hg, p<0.001; DBP from 86 ± 2 mm Hg to 76 ± 2 mm Hg; p<0.013) as well as the mean number of antihypertensive drugs required per patient (from 3.2 ± 0.2 to 2.1 ± 0.2; p<0.001). Furthermore, no patient required spironolactone discontinuation because of adverse renal effects (Ouzan 2002).

A larger study enrolled 76 subjects, 34 of whom had biochemical primary aldosteronism. Spironolactone (12.5–25 mg/day) was added to each subject's antihypertensive regimen, and if BP remained uncontrolled, the spironolactone dose was titrated to 50 mg/day. A significant mean decrease from baseline to 6-month follow-up occurred (SBP, –25 ± 20; DBP, –12 ± 12 mm Hg). The BP reduction was similar in patients with and without primary aldosteronism; however, patients with primary aldosteronism required higher spironolactone doses. There was also a significant decrease in the mean number of prescribed antihypertensive drugs from baseline to 6-month follow-up (from 4.0 ± 1.0 to 3.5 ± 1.2; p<0.05) (Nishizaka 2003).

In a post hoc analysis of 1411 patients taking spironolactone enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial, spironolactone (median dose of 25 mg/day) was mainly used as a fourth-line antihypertensive agent for uncontrolled BP. During spironolactone therapy, the mean BP fell from 156.9/85.3 mm Hg (±18.0/11.5 mm Hg) to 135.1/75.8 mm Hg (±18.8/10.7 mm Hg), a difference of 21.9/9.5 mm Hg (95% CI, 20.8–23.0/9.0–10.1 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 medication for 8 weeks. The primary end point (a difference in the mean fall of BP on daytime ambulatory BP monitoring) demonstrated a 5.4 mm Hg reduction for SBP (95% CI, –10.0 to –0.8, p=0.024) and a 1.0 mm Hg reduction for DBP (95% CI, –4.0 to 2.0, p=0.358) between the groups. (Václavík 2011).

Finally, the efficacy, safety, and tolerability of eplerenone and spironolactone were compared in patients with primary aldosteronism and HTN in a multicenter, randomized, double-blind study. Patients were randomized to 16 weeks 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 (±2.3 mm Hg) and DBP –5.6 mm Hg (±1.3 mm Hg), whereas changes in the

Box 1-1. 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
NSAIDs; cyclooxygenase 2 inhibitors
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
Erythropoietin

Other

Improper BP measurement
Volume overload:
- Excess sodium intake
- Volume retention
- Inadequate diuretic therapy

Excess alcohol intake
White-coat HTN

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.

spironolactone group were SBP –27.0 mm Hg (±2.3 mm Hg) and DBP –12.5 mm Hg (±1.3 mm Hg). The lowering of both SBP and DBP was significantly greater in the spironolactone group, and there were no significant differences between eplerenone and spironolactone in the overall rate of adverse events. Each study shows that spironolactone can be effective at lowering BP.

Diuretics – Chlorthalidone vs. Hydrochlorothiazide

The use of chlorthalidone for HTN is supported by results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). 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 CHD 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 BP from baseline 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). No randomized trials have directly compared 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 (relative risk [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 comparing hydrochlorothiazide with chlorthalidone are mixed. Results of observational data from the Multiple Risk Factor Intervention Trial (MRFIT) are consistent with the aforementioned meta-analysis. In MRFIT, the 2392 hypertensive men treated with chlorthalidone experienced 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). By contrast, another study found that among almost 30,000 adults ages 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; 95% CI, 1.24–2.28). However, 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 BP and can affect the pharmacokinetics of medications. Because of this, ingestion-time differences in hypertensive medications may change how the body responds to them. Studies have shown an association between blunted asleep BP decline and increased incidence of fatal and nonfatal CVD events; moreover, studies have shown that the asleep BP mean is a better predictor of CVD risk than the awake or 24-hour BP mean. The 2010 MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares) study was designed to determine whether a regimen of bedtime chronotherapy with at least one antihypertensive medication (bedtime group) exerted better BP control and CVD risk reduction compared with a regimen in which 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 relative risk of total CVD events than those in the awakening group (0.39 [0.29–0.51]; p<0.001) (Hermida 2010). These findings provided the basis for subsequent studies in this field (see Pivotal Study box).

In 2012, the ADA added a recommendation to administer one or more antihypertensive medications 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 medication (n=216) with patients taking all medications in the morning (n=232) to determine whether BP control and CV risk reduction were improved. After a median follow-up of 5.4 years, patients using the bedtime dosing showed a significantly lower mean asleep BP than did patients using the morning dosing (115.0 ± 17.1 vs. 122.4 ± 21.8; p<0.001) and had a higher prevalence of controlled ambulatory BP (62.5% vs. 50.9%; p=0.013). However, differences between groups in clinic and awake BP 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 did patients ingesting all medications 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 hypertensive medications was administered at

Pivotal Study That May Change Practice

Hermida RC, Ayala DE, Mojón A, et al. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int 2010;27:1629-51.

Setting: Previous studies have shown an association between blunted asleep BP decline and increased incidence of fatal and nonfatal CVD events. In addition, studies have shown that the asleep BP mean is a better predictor of CVD risk than the awake or 24-hour BP mean. However, reductions in CVD morbidity and mortality risk, if any, by a bedtime versus an on-awakening antihypertensive treatment schedule had not been evaluated prospectively before this trial.

Design: The prospective MAPEC study was designed to determine whether bedtime chronotherapy with one or more antihypertensive medications (bedtime group) exerts better BP control and CVD risk reduction than a regimen in which all medications are taken in the morning (awakening group). The study had 2156 hypertensive subjects – 1044 men and 1112 women 55.6 years of age (±13.6 years) – who were taking a mean of two antihypertensive medications and randomized to ingest all of their hypertensive medications on awakening or one or more at bedtime.

Outcomes: Despite the lack of difference in the mean ambulatory BP between the groups at baseline (awakening group 154.4 mm Hg vs. bedtime group 155.7 mm Hg; p=0.144), subjects in the bedtime group had a significantly lower mean sleep-time BP. In addition, subjects in the bedtime group had a reduced prevalence of non-dipping (defined as a sleep-time SBP decline of less than 10%; 34% vs. 62%; p<0.001) and an increased prevalence of controlled ambulatory BP (62% vs. 53%; p<0.001). Differences between groups in the mean awake BP were small and nonsignificant. After a median follow-up of 5.6 years, subjects in the bedtime group had a significantly lower relative risk of total CVD events than those in the awakening group (0.39 [0.29–0.51]; p<0.001). The difference between the treatment-time groups in the relative risk of major events (including CVD death, MI, ischemic stroke, and hemorrhagic stroke) was also significant (0.33 [0.19–0.55]; p<0.001), favoring the bedtime dosing group.

Limitations: Limitations of this study include its open-label design and overall small number of CV events.

Impact: This was the first randomized controlled trial to show that taking at least one antihypertensive medication at bedtime not only lowers the sleep-time BP but also the risk of total and major CVD events. This study paved the way for additional studies in specific populations, as in patients with diabetes and CKD, and subsequent changes in practice guidelines.

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 BP, and a greater proportion had control of their ambulatory BP (56% vs. 45%; p=0.003). In addition, patients who took at least one BP-lowering medication 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) compared with patients who took all medications 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, simple strategy that results in improved ambulatory BP control and significantly reduced CV morbidity and mortality in patients. Often, practitioners do not consider a patient's BP during sleep, but these studies show that BP during this period is important.

Concomitant Dihydropyridine and Nondihydropyridine CCBs

The two distinct classes of CCBs affect their sites of action to varying degrees. The contractile processes of cardiac muscle and vascular smooth muscle depend on the movement of extracellular calcium ions into these cells through specific ion channels. The dihydropyridine (DHP) CCBs selectively inhibit the influx of calcium ions into vascular smooth muscle and, to a lesser degree, cardiac muscle. This results in peripheral arterial vasodilation, reducing peripheral vascular resistance and BP. The non-DHP CCBs (diltiazem and verapamil) nonselectively inhibit calcium ions from entering the "slow channels" of vascular smooth muscle and myocardium; this relaxes vascular and cardiac smooth muscle, resulting in decreased peripheral vascular resistance as well as potent dilation of coronary arteries, both epicardial and subendocardial.

The pharmacodynamic interaction between the two types of CCBs results in greater vasodilation than if only a single CCB is used. A small study showed DHP and non-DHP CCB combination therapy provided significant additional antihypertensive benefit compared with monotherapy but with more frequent constipation and minor leg edema (Saseen 1996). The pharmacokinetic interaction between the two types of CCBs involves both verapamil's and diltiazem's inhibition of the cytochrome P450 3A–mediated biotransformation of DHP CCBs. This interaction can result in up to a 60% increase in amlodipine systemic exposure.

Recently, a meta-analysis of six studies (total of 153 patients) examined the efficacy and safety of dual CCB therapy. The efficacy outcomes of decreased SBP and DBP measurements from baseline, changes in heart rate, and adverse effects were compared between dual CCB therapy and DHP alone or non-DHP alone. Dual CCB produced a significantly greater reduction in SBP from baseline (21.6 ± 9.2 mm Hg) than DHP (10.3 ± 6.3 mm Hg) or non-DHP

(8.9 ± 4.2 mm Hg). Dual CCB therapy also more significantly reduced DBP from baseline than either monotherapy (dual CCB 17.5 ± 10.2 mm Hg vs. DHP 11.6 ± 8.7 mm Hg and non-DHP 10.5 ± 5.6 mm Hg). Dual CCB therapy showed significantly lower heart rates compared with DHP ($p<0.001$) but was comparable with non-DHP ($p=0.12$). Dual CCB therapy did not increase adverse effects: there was no significant increase in edema, headache, or flushing rates compared with either monotherapy, and the incidence of constipation was lower in the dual CCB group than in the non-DHP CCB group (Alviar 2013).

Dual CCB blockade may be of benefit in patients with limited options for BP lowering for various reasons, including allergies or intolerance to several antihypertensive agents (Sever 2011). Concomitant DHP and non-DHP CCBs may be better tolerated than other fourth- or fifth-line antihypertensive agents (e.g., clonidine, hydralazine). If this combination is used, patients should be monitored for hypotension, peripheral edema, and constipation. To date, no outcome data are available for dual CCB therapy, and long-term safety remains unknown. According to the AHA, insufficient information is available to recommend the use of same-class combinations over the use of agents from different classes (Calhoun 2008). Large-scale, long-term trials are needed to further evaluate this strategy.

Renal Denervation

The renal sympathetic nerves contribute to the complex physiology of HTN. Patients with HTN usually have an increased efferent sympathetic drive to the kidneys and an increased rate of sympathetic nerve firing, possibly modulated by afferent signaling from renal sensory nerves. The SYMPLICITY trials have looked at renal denervation as a means to treat resistant HTN, both in nonrandomized (SYMPLICITY-1) and randomized (SYMPLICITY-2) manners. The SYMPLICITY-1 trial examined 153 patients (mean age, 57 years) with resistant HTN (SBP of 160 mm Hg or greater taking three or more antihypertensive drugs, including a diuretic) who were treated with catheter-based renal sympathetic denervation at 19 international centers. Patients' baseline mean office BP was 176/98 mm Hg (±17/15 mm Hg), and patients were taking a mean of five antihypertensive drugs. Postprocedure office BPs were reduced by 23/11 mm Hg at 12 months and 32/14 mm Hg at 24 months; however, only 42% of the original cohort reached the 12-month follow-up, and just 12% of the cohort reached the 24-month follow-up. The procedure complication rate was 3% (4 of 153), which included three groin pseudoaneurysms and one renal artery dissection (Symplicity HTN-1 Investigators 2011).

The SYMPLICITY-2 trial was a multicenter prospective, randomized study that enrolled 106 patients (mean age, 58 years) with baseline SBP measurements of 160 mm Hg or more (150 mm Hg or greater for patients with type 2 diabetes mellitus). Patients were randomized to a renal denervation group (n=52) or control (maintaining previous treatment alone, n=54). Office-based BP measurements at 6 months in the renal denervation group were reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, $p<0.0001$), whereas no change from baseline occurred in the control group. Between-group differences in BP at 6 months were significant ($p<0.0001$). Patients in the intervention and control groups were taking a mean of five antihypertensive drugs at baseline and follow-up. No serious procedure- or device-related complications were noted (Symplicity HTN-2 Investigators 2010).

In January 2014, Medtronic, the company that markets the Symplicity renal denervation system, issued a press release regarding the SYMPLICITY-3 trial. This study enrolled more than 500 patients with resistant HTN to examine the safety and efficacy of renal denervation in patients compared with a sham control group of patients. The press release stated that the study failed to meet its primary efficacy end point, change in office BP from baseline to 6-month follow-up, but no data were published. According to Medtronic, the results have yet to undergo peer review to allow for presentation at a scientific meeting or publication in a peer-reviewed journal. Until these results are available, data from the SYMPLICITY-1 and SYMPLICITY-2 trials should be interpreted with caution. Enrollment in ongoing and future studies of renal denervation by Medtronic has been suspended.

Ambulatory Measurement

Ambulatory BP monitoring is performed with the patient wearing a portable BP measuring device, usually on the nondominant arm, for 24 hours. This monitoring is to provide information on BP during daily activities as well as at night during sleep. Average daytime, nighttime, and 24-hour BP 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 BP (Conen 2008). The authors suggest that BP measured more frequently outside the physician's office improves BP assessment and CV risk stratification.

Home BP monitoring involves self-measurement of BP, which offers advantages over office-measured BP because home measurements can be taken for several days at different times in the patient's own environment. Moreover, there is evidence that home BP monitoring is a significant predictor of CV morbidity after adjusting for office BP (Ward 2012). However, patients should be instructed on proper technique. Individuals should be seated with their feet flat on the floor with 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 BP monitoring may provide further advantage. Devices worn on the wrist or finger are currently not recommended because of concerns about accuracy (Pickering 2008).

The Home Blood Pressure Telemonitoring and Case Management to Control HTN (HyperLink) study was conducted to determine whether an intervention combining home BP telemonitoring with pharmacist case management improves BP control compared with usual care and to determine whether BP control is maintained 6 months after the intervention is discontinued. The patients in the intervention group received home BP telemonitors and transmitted BP 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) compared with 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). Studies have shown that team-based care can lower BP better than standard care (Green 2008, Magid 2013). The HyperLink study highlights the value a pharmacist can bring to the care team.

Quality Metrics

Quality measure development begins with identifying high-priority opportunities for health care. The Pharmacy Quality Alliance (PQA) develops measures of safe and appropriate medication use and medication management services, several of which are associated with HTN. One example is an adherence measure looking at the percentage of patients 18 years and older who meet the proportion of days covered threshold of 80% during the measurement period for β-blockers, renin-angiotensin system antagonists, and CCBs. Another PQC measure is for the appropriate treatment of HTN in patients with diabetes, which reviews the percentage of patients who receive an ACE inhibitor, ARB, or direct renin inhibitor.

The Healthcare Effectiveness Data and Information Set (HEDIS) tool is used by health plans to measure performance on important dimensions of care and service. The controlling high BP measure is the percentage of members 18–85 years of age who have a diagnosis of HTN and whose most recent office SBP is less than 140 mm Hg, with a DBP of less than 90 mm Hg. If no BP is recorded in the measurement year, the patient's BP is considered uncontrolled. The HEDIS tool does not currently recognize home readings for this measure. Another HEDIS measure is annual monitoring for patients taking persistent medications, including ACE inhibitors, ARBs, and diuretics. Members 18 years or older must complete a potassium and SCr or BUN test to meet this measure.

The Centers for Medicare & Medicaid Services created ratings that show the quality of Medicare plans on a scale of 1 star (lowest) to 5 stars (highest). The star ratings are important because they are tied to quality bonus payments, and more stars equal higher bonus payments. A pharmacist can be an essential component of the team to help meet these quality metrics.

Conclusion

Many HTN-related studies have been published since JNC 7 in 2003. For example, studies contributing to knowledge regarding BP goals, preferred therapies for concomitant disease states and specific populations, dosing antihypertensive medication, and treating resistant HTN have been completed. Although this chapter summarizes some of the more recent changes to guidelines and therapy recommendations, a single U.S. guideline with majority consensus to manage HTN is needed.

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Practice Points

- For patients with coronary or other atherosclerotic vascular disease, the BP goal is less than 140/90 mm Hg per the AHA/ACC, and initial therapy should be with β-blockers and ACE inhibitors (or ARBs if ACE inhibitor therapy is not tolerated).
- For patients with diabetes, the BP goal is less than 140/80 mm Hg, and initial therapy should be with ACE inhibitors (or ARBs if ACE inhibitor therapy is not tolerated), according to the ADA.
- For patients with HF, there is no set BP goal, but the lower BP levels are likely beneficial. For HFrEF, BP should be treated with evidence-based β-blockers, ACE inhibitors (or ARBs if ACE inhibitor therapy is not tolerated), and aldosterone antagonists.
- Consider a BP goal of less than 150/90 mm Hg for elderly patients.
- For patients with CKD, the BP 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 BP reduction in patients with resistant HTN.
- Chlorthalidone is likely a more effective diuretic medication for HTN than is hydrochlorothiazide.
- Dosing at least one medication at bedtime is an efficacious way to lower nighttime BP and reduce the risk of CVD.
- Labetalol is the antihypertensive therapy of choice in pregnancy.
- In patients with stage 2 HTN (greater than 160/100 mm Hg), consider initiating combination therapy.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

J.J. is a 63-year-old man who comes to your office for a blood pressure (BP) follow-up. He has coronary heart disease (CHD) (MI and stent placement 5 years ago), hypertension (HTN), and hypothyroidism. Today, his vital signs include BP 150/83 mm Hg, with 147/81 mm Hg on repeat; heart rate 58 beats/minute; and ejection fraction (EF) 55%. His fasting laboratory results show the following: glucose 101 mg/dL, potassium 3.2 mEq/L, sodium 140 mg/dL, SCr 1.5 mg/dL, CrCl 45 mL/minute, thyroid-stimulating hormone 0.02 mIU/mL (normal 0.32–5.5 mIU/mL), and creatinine/microalbumin ratio 20 (normal less than 30). J.J. is frustrated about the erectile dysfunction that has been present since his MI as well as his difficult-to-control BP. His current drug regimen, which has been stable for the past 6 months, consists of metoprolol succinate 25 mg/day, lisinopril 20 mg/day, chlorthalidone 25 mg/day, levothyroxine 137 mcg/day, and aspirin 81 mg/day.

1. According to AHA/ACC, which one of the following would be the best BP goal for J.J.?

   A. Less than 125/75 mm Hg.
   B. Less than 130/80 mm Hg.
   C. Less than 140/80 mm Hg.
   D. Less than 140/90 mm Hg.

2. Which one of the following would best address J.J.'s concerns about erectile dysfunction and his difficult-to-control BP?

   A. Stop metoprolol and lower levothyroxine dose to 125 mcg/day.
   B. Increase metoprolol succinate to 50 mg/day and chlorthalidone to 50 mg/day.
   C. Continue current regimen and add amlodipine 5 mg/day.
   D. Stop metoprolol and increase chlorthalidone to 50 mg/day.

3. A 55-year-old woman with type 2 diabetes mellitus presents for her well woman examination. She has HTN and currently takes amlodipine 10 mg/day. Today, her BP is 142/78 mm Hg (with similar repeat), and her heart rate is 78 beats/minute. Her laboratory tests today reveal the following: potassium 4.0 mEq/L, sodium 144 mg/dL, SCr 1.0 mg/dL, CrCl 65 mL/minute, and creatinine/albumin ratio 100. Which one of the following is best to recommend for this patient's BP?

   A. No action is needed.
   B. Stop amlodipine and start lisinopril 10 mg/day.
   C. Continue current therapy and start lisinopril 10 mg/day.
   D. Stop amlodipine and start HCTZ 25 mg/day.

4. A 45-year-old woman (height 67 inches, weight 72 kg) has HTN and is frustrated with efforts to control her BP. She reports adherence to her low-salt diet, exercise regimen, and medications. Because her mother died of a stroke, she would like her BP controlled as soon as possible. She currently takes chlorthalidone 25 mg/day, enalapril 40 mg/day, felodipine 10 mg/day, and carvedilol 25 mg twice daily. No changes have been made to her drugs for the past 6 weeks. Today, her BP is 150/95 mm Hg (with similar repeat), and her heart rate is 62 beats/minute. Her laboratory results reveal potassium 3.3 mEq/L, sodium 135 mg/dL, SCr 0.8 mg/dL, and CrCl 86 mL/minute. Which one of the following would best address this patient's BP?

   A. Increase carvedilol to 50 mg twice daily.
   B. Increase chlorthalidone to 50 mg/day.
   C. Start spironolactone 12.5 mg/day.
   D. Start diltiazem XR 120 mg/day.

5. A 62-year-old man with diabetes presents to the clinic for a follow-up. He is concerned about his CV risk because his father died of an MI at 45 years of age. Today, his BP is 141/92 mm Hg and heart rate 85 beats/minute, and he reports similar home BP readings. He currently takes metformin 1000 mg twice daily, losartan 100 mg every morning, hydrochlorothiazide 50 mg every morning, aspirin 81 mg/day, and simvastatin 40 mg every morning. His laboratory results reveal potassium 3.9 mEq/L, sodium 142 mg/dL, SCr 1.3 mg/dL, and CrCl 66 mL/minute. He is adherent to his medications but, if possible, would prefer not to take any additional agents. His diabetes and cholesterol are well controlled. Which one of the following actions would best address this patient's concern about CV risk?

   A. Reassure the patient that no medication changes are needed.
   B. Change the losartan dose to nighttime.
   C. Lower the hydrochlorothiazide dose to 25 mg/day.
   D. Start terazosin 1 mg/day.

6. A 50-year-old woman comes to the clinic inquiring about renal denervation. She is tired of taking BP medication and "just wants it fixed." Currently, she

takes amlodipine 5 mg/day for her BP; today, her BP is 145/80 mm Hg. Which one of the following responses would be best for this patient?

A. Renal denervation has been studied only in patients with resistant HTN, and she would not be a candidate at this time.
B. Renal denervation has been shown to improve BP in all patients, and she would be a candidate.
C. Renal denervation has been studied only in patients older than 60, so she would not be a candidate at this time.
D. Renal denervation has been shown to maintain significant BP reduction for more than a decade, and she would be a candidate.

7. A 66-year-old woman with a history of HTN and gastroesophageal reflux disease (GERD) comes to her first visit with you today. She has chronic constipation, lower extremity edema, fatigue, and high BP. She currently takes pantoprazole 40 mg/day, nifedipine ER 60 mg/day, diltiazem XR 240 mg/day, furosemide 40 mg/day, docusate daily, and a fiber supplement daily. She reports that her furosemide dose was increased 2 months ago, but her edema has not improved. According to her records, her SCr 2 months ago was 1.5 mg/dL. Today, her BP is 155/90 mm Hg, heart rate is 55 beats/minute, and SCr is 1.9 mg/dL. Which one of the following is best to recommend for this patient?

A. Increase furosemide to 40 mg twice daily.
B. Stop diltiazem and start ramipril 5 mg/day.
C. Increase nifedipine ER to 90 mg/day.
D. Start ramipril 5 mg/day.

8. A 68-year-old man (height 70 inches, weight 83 kg) with heart failure with reduced ejection fraction (HFrEF) (NYHA class III, EF 30%) presents to the clinic for a BP follow-up. He has been adherent to his medications, but his BP continues to be above the goal set by his cardiologist (less than 130/80 mm Hg). He eats a low-salt diet and exercises as much as he can. His current medication regimen is carvedilol 25 mg twice daily, lisinopril 20 mg/day, aspirin 81 mg/day, atorvastatin 40 mg/day, furosemide 40 mg twice daily, and potassium 20 mEq/day. Today, he is euvolemic; his BP is 149/85, with similar repeat; and his heart rate is 60 beats/minute. His laboratory tests show potassium 4.0 mEq/L, sodium 144 mg/dL, and SCr 1.5 mg/dL. Which one of the following would best address this patient's BP?

A. Start amlodipine 5 mg/day.
B. Start diltiazem 240 mg/day.
C. Change furosemide to hydrochlorothiazide 25 mg/day.
D. Start spironolactone 12.5 mg/day and discontinue the potassium supplement.

9. A 63-year-old woman (height 64 inches, weight 59 kg) presents for a BP follow-up. She has osteoarthritis, chronic kidney disease, and HTN. Last month, she came to the clinic because her home BP readings had been in the 160s/100s. This was confirmed at the clinic. At that time, her laboratory values were as follows: potassium 4.6 mEq/L, sodium 140 mg/dL, and SCr 1.3 mg/dL. She was initiated on lisinopril/hydrochlorothiazide 20/12.5 mg/day in addition to her other drugs (naproxen 500 mg twice daily and amlodipine 10 mg/day). Today, when she comes in for a follow-up, her BP is 138/89 mm Hg, heart rate is 85 beats/minute, and laboratory values reveal potassium 5.1 mg/dL, sodium 141 mg/dL, SCr 1.9 mg/dL, and creatinine/albumin ratio 20. Which one of the following is best to recommend for this patient?

A. No change is needed at this time.
B. Hold lisinopril/hydrochlorothiazide.
C. Increase the lisinopril/hydrochlorothiazide dose to 40/25 mg/day.
D. Start atenolol 50 mg/day.

10. A 40-year-old woman (height 65 inches, weight 95 kg) with HTN presents to your clinic for an initial visit and a well woman examination. She has had insomnia and congestion with rhinorrhea for the past week, which she has self-treated with OTC loratadine and pseudoephedrine. She takes felodipine 10 mg/day and chlorthalidone 12.5 mg/day in addition to an OTC herbal supplement daily for weight loss. She also consumes several "energy drinks" daily because of daytime sleepiness. Today, her BP is 150/95 mm Hg, and her heart rate is 95 beats/minute. She does not monitor her BP at home. Her laboratory values are as follows: potassium 4.1 mEq/L, sodium 145 mg/dL, and SCr 1.0 mg/dL. Which one of the following, in addition to stopping the weight-loss supplement would be best to recommend for this patient?

A. Increase chlorthalidone to 25 mg/day.
B. Start valsartan 80 mg/day.
C. Stop pseudoephedrine and energy drinks.
D. Stop loratadine.

Questions 11 and 12 pertain to the following case.

S.K. is a 27-year-old woman who presents to the clinic to follow up on her BP after working on lifestyle changes for the past several months. Her BP today is 152/96 mm Hg and her resting heart rate is 61 beats/minute. Other pertinent history includes chronic persistent asthma, which is controlled with fluticasone. S.K. was recently married and shares that she and her husband want to start

a family "in the next few years." Her father has resistant HTN, and S.K. wants to make sure she is protecting herself from future CV complications.

11. Which one of the following best describes the BP goal for S.K. according to the CHEP guidelines?
    A. Less than 135/85 mm Hg.
    B. Less than 150/90 mm Hg.
    C. Less than 140/90 mm Hg.
    D. Less than 140/80 mm Hg.

12. Which one of the following is the best initial treatment option for S.K.?
    A. Labetalol 200 mg twice daily.
    B. Nifedipine ER 30 mg once daily.
    C. Lisinopril 10 mg once daily.
    D. Methyldopa 250 mg twice daily.

13. A 59-year-old man presents to his physician for a repeat BP check. The patient's BP was elevated at his annual physical examination 1 month ago. Today, his BP is 163/85 mm Hg and heart rate is 59 beats/minute. He currently takes no prescription medications. However, after eating spicy food, he has occasional GERD. Which one of the following is best to recommend for managing this patient's BP?
    A. Lisinopril/hydrochlorothiazide 10/12.5 mg once daily.
    B. Atenolol 25 mg once daily.
    C. Terazosin 1 mg once daily.
    D. Amlodipine 10 mg once daily.

14. A 36-year-old woman with a history of diabetes and HTN currently takes lisinopril 10 mg once daily and chlorthalidone 25 mg once daily. Her BP is 140/79 mm Hg. After having her intrauterine device removed next month, she will be trying to conceive. Which one of the following is the best option for managing this patient's BP?
    A. Continue lisinopril and chlorthalidone as directed.
    B. Increase lisinopril to 10 mg daily.
    C. Stop lisinopril and start labetalol.
    D. Discontinue antihypertensive therapy.

15. A prospective randomized controlled trial compared a new combination antihypertensive drug with chlorthalidone. The primary end point was the composite of CV outcomes, including CV death, nonfatal stroke, or nonfatal MI. The secondary end points were CV death, nonfatal stroke, or nonfatal MI individually. The following table summarizes the trial outcomes.

	Hazard Ratio (HR) of New Drug vs. Chlorthalidone	**95% Confidence Interval**
Composite of CV death, nonfatal stroke, or nonfatal MI	0.89	0.81–0.95
CV death	0.87	0.79–0.98
Nonfatal stroke	0.76	0.68–0.91
Nonfatal MI	0.98	0.71–1.18

Which one of the following statements most accurately describes how this new drug compares with chlorthalidone?
    A. It decreases nonfatal stroke but increases nonfatal MI.
    B. It decreases composite CV end point and has no significant effect on nonfatal MI.
    C. It has no significant effect on CV death but decreases nonfatal stroke.
    D. It decreases the composite CV end point as well the individual end points of CV death, nonfatal stroke, and nonfatal MI.

16. A 34-year-old pregnant woman (37 weeks' gestation) has been taking labetalol 200 mg twice daily for gestational HTN diagnosed 2 months ago. She borrows her father's home BP monitor and calls the clinic concerned about her recent readings of 158/96 mm Hg and 159/98 mm Hg. Which one of the following is the best course of action for this patient?
    A. Refer her to the nearest emergency department for evaluation of her blood pressure and probable delivery.
    B. Obtain a verbal order from her physician to increase labetalol to 400 mg twice daily.
    C. Coordinate prompt evaluation with her obstetrician to rule out preeclampsia.
    D. Ask her to make an appointment with her primary care physician.

17. An 82-year-old man presents to his physician for a wellness check. Today, his BP is 159/87 mm Hg with a similar repeat. He still lives independently; however, he mentions he does not feel as stable on his feet and has had some recent falls. When you are asked by the physician in your clinic about treating BP in the elderly, which one of the following is your best response according to the available literature?
    A. Lowering BP in the elderly is beneficial if BP is reduced to less than 150 mm Hg but not less than 140 mm Hg.
    B. Elderly patients should be treated to a BP goal of less than 140/90 mm Hg as stated in JNC 7.

C. Diuretics are the only class of antihypertensive agents that have shown benefit in the elderly.
D. BP lowering is not recommended in the elderly because of the increased risk of orthostatic hypotension (OH) and falls.

18. A 72-year-old woman with a history of osteopenia is presenting for her regular checkup. Today, her BP is 158/88 mm Hg (with a similar repeat), and her heart rate is 78 beats/minute. Her laboratory values are as follows: potassium 4.4 mEq/L, sodium 144 mg/dL, and SCr 1.0 mg/dL. She states that her resting home BP is usually less than 135/80 mm Hg and that she always seems to have higher BP readings in the clinic. Which one of the following is the best recommendation for her BP management?

A. No action is needed because her home BP is at goal.
B. Start lisinopril/hydrochlorothiazide 20 mg/25 mg once daily.
C. Order 24-hour ambulatory BP monitoring.
D. Request that she check her BP at home both sitting and standing.

19. The medical director at your clinic attended a recent conference on improving quality measures and pay for performance. She asks for ways in which a pharmacist could contribute to improving a quality measure related to HTN control rates. Which one of the following pharmacist actions would be most helpful toward this goal?

A. Gather patients' home BP readings for reporting to HEDIS to assist in improving their BP control rate.
B. Provide patient educational sessions on the proper technique for home BP monitoring.
C. Perform medical record reviews and recommend appropriate BP goals for each patient according to current guidelines.
D. Participate in adjusting antihypertensive medications to help more patients reach their BP goal.

20. A 76-year-old man presents to his physician for a wellness check. Today, his BP seated and resting for 5 minutes is 142/79 mm Hg, and his standing BP after 3 minutes is 118/70 mm Hg. His current drugs include hydrochlorothiazide 25 mg/day and amlodipine 10 mg/day. Which one of the following is the best recommendation for managing this patient's BP?

A. Increase hydrochlorothiazide to 50 mg/day.
B. No change is needed.
C. Stop hydrochlorothiazide.
D. Stop amlodipine.