Hypertension

By Toni L. Ripley, Pharm.D., FCCP, BCPS, AHSCP-CHC;
and Anna Barbato, Pharm.D., BCPS, AHSCP-CHC

Reviewed by Adam Bress, Pharm.D., MS; David L. Nickerson, Pharm.D., BCPS; and Kathryn Rice, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Distinguish between the recommendations for hypertension management among recent hypertension- and disease-specific guidelines.
2. Justify blood pressure goals for individual patients on the basis of the primary literature and hypertension guidelines.
3. Apply understanding of blood pressure results and measurement technique to a patient case.
4. Design an evaluation and treatment plan for a patient presenting with hypertension.

ABBREVIATIONS IN THIS CHAPTER

AAFP	American Academy of Family Physicians
ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACP	American College of Physicians
AHA	American Heart Association
AOBP	Automated office blood pressure
ASCVD	Atherosclerotic cardiovascular disease
CV	Cardiovascular
JNC	Joint National Committee
MRA	Mineralocorticoid receptor antagonist
RAS	Renin-angiotensin system
TOD	Target organ damage

Table of other common abbreviations.

INTRODUCTION

Hypertension Overview

Blood pressure elevations are associated with an increased risk of cardiovascular (CV) disease in a linear fashion. Starting at a blood pressure of 115/75 mm Hg, every increase of 20 mm Hg in systolic blood pressure (SBP) and/or increase of 10 mm Hg in diastolic blood pressure (DBP) is associated with a doubling of the risk of death from stroke, heart disease, or other vascular disease (Lewington 2002). Increases in SBP have the strongest link with CV disease, though other blood pressure components have been linked to CV disease as well, including DBP, pulse pressure, blood pressure variability, and mean arterial blood pressure (Whelton 2018; Muntner 2015).

This chapter will review the new recommendations for blood pressure management and will focus on the pharmacotherapy of hypertension. Because hypertension is largely managed with drug therapy, clinical pharmacists often participate in management, especially when hypertension may be difficult to manage because of factors such as adverse effects or resistant hypertension.

Hypertension Epidemiology

The prevalence of hypertension in U.S. adults has continued to increase. In 2018, the American Heart Association (AHA) heart disease and stroke statistics update reported that about 34% of U.S. adults had hypertension, using a diagnostic SBP/DBP threshold of 140/90 mm Hg (Benjamin 2018). However, the American College of Cardiology and AHA (ACC/AHA) 2017 blood pressure guidelines lowered the threshold for the diagnosis of hypertension to an SBP/DBP of 130/80 mm Hg, which led to a new hypertension prevalence of 46% of U.S. adults. Despite the 12 percentage point increase in prevalence with the lower diagnostic threshold, the 2017 ACC/AHA blood pressure guideline estimates that only an additional 2% of patients will be recommended antihypertensive medications because the new guideline does not recommend that all patients with blood pressure

readings of 130–139/80–89 mm Hg should receive drug therapy (Muntner 2018).

Hypertension prevalence increases as patients age. Using the lower threshold as defined by the 2017 ACC/AHA guidelines, the prevalence of hypertension for patients 20–44 years of age is 30% in men and 19% in women. This increases to 77% for men and 75% for women 65–74 years of age (Whelton 2018).

Hypertension prevalence also differs on the basis of ethnicity and sex. Overall, hypertension is more prevalent in blacks, with an estimated prevalence of 59% and 56% in black men and women, respectively. White, Asian, and Hispanic men have a prevalence of 47%, 45%, and 44%, respectively, and white, Asian, and Hispanic women have an estimated prevalence of 41%, 36%, and 42%, respectively (Whelton 2018). These numbers are based on the 2017 ACC/AHA guidelines and are higher than previous estimates because of the lower diagnostic threshold for hypertension in the new guidelines.

CLINICAL GUIDELINE UPDATE

In 2017, the long-awaited ACC/AHA guidelines for the prevention, detection, evaluation, and management of high BP in adults were published. These are the first comprehensive, evidence-based guidelines for hypertension in the United States.

BASELINE KNOWLEDGE STATEMENTS

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

- Pathophysiology of hypertension.
- Knowledge of oral pharmacologic agents used to treat hypertension.
- Knowledge of parenteral agents used to treat hypertension.
- Consequences of poor blood pressure control.
- Standard process of blood pressure measurement.

Table of common laboratory reference values

ADDITIONAL READINGS

The following resources have additional background information on this topic:

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-672.
- 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
- ASCVD risk calculator.
- 2017 ACC/AHA hypertension guidelines.

Joint National Committee Guidelines

The Joint National Committee (JNC) published the first hypertension management guidelines in the 1970s. These guidelines were constructed primarily as an expert consensus rather than an evidence-based set of recommendations.

Nonetheless, the JNC guidelines were the authoritative recommendations for hypertension until 2013, when the National Heart, Lung, and Blood Institute (NHLBI) announced the transfer of responsibility for guideline development to other organizations. At that time, the ACC and AHA accepted responsibility for leading the development of comprehensive and evidence-based hypertension guidelines. At the same time, the NHLBI published the recommendations of the JNC 8 committee.

Although this was a controversial publication, the intent of the JNC 8 committee was to bridge the gap between JNC 7 and the new ACC/AHA guidelines that were in development, given that JNC 7 was published in 2003 and many believed it to be outdated. For example, JNC 7 recommended β-blockers as an acceptable first-line therapy, whereas by 2017, most hypertension experts considered β-blockers to be inferior to other first-line hypertension medications in the absence of compelling indications.

The JNC 7 guidelines were a comprehensive expert consensus of the prevention, detection, evaluation, and treatment of high blood pressure in adults (Chobanian 2003), whereas the JNC 8 guidelines were an evidence-based, focused set of recommendations. The JNC 8 panel chose three critical questions on which to focus its update (Box 1) and revised the process such that recommendations were graded on the basis of the available evidence, as is the contemporary guideline standard.

One unique aspect of JNC 8 was the evidence included in its review to inform its recommendations. Only randomized controlled clinical trials were reviewed; meta-analyses, systematic reviews, and epidemiologic analyses were excluded. Although the intention to restrict review to the gold standard evidence of randomized trials is understandable, the process was criticized for not considering the totality of evidence for managing hypertension.

Box 1. Critical Questions Addressed in JNC 8

In adults with hypertension:

1. Does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. Does treatment with antihypertensive pharmacologic therapy to a specified BP goal improve health outcomes?
3. Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

BP = blood pressure.

Information from: James PA, Oparil S, Carter BL, et al. 2014 evidence-based guidelines for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.

The JNC 8 guidelines contained nine recommendations surrounding the three critical questions. The most controversial recommendation was to relax the target blood pressure for adults without diabetes or chronic kidney disease, age 60 and older, to less than 150/90 mm Hg. In fact, a group within the JNC 8 committee separately published a "minority view" supporting the continued goal of less than 140/90 mm Hg for adults 60 and older (Wright 2014). These authors cited concerns about the adverse effects on public health if blood pressure goals were relaxed in older patients because older age is a risk factor for CV disease. Although no randomized controlled trials supported treating patients 60 and older to less than 140/90 mm Hg, they contended that there were also no data at the time to support the higher blood pressure target.

Other Hypertension Guidelines

The delay in comprehensive U.S. guidelines led to a surge in blood pressure recommendations from several groups. Many of these guidelines were focused on subgroups, such as those with heart failure, coronary artery disease, or stroke. Guidelines such as these were developed by the ACC; therefore, it is reasonable to consider that the goals recommended by the 2017 ACC/AHA guidelines supersede former blood pressure recommendations by past ACC-endorsed guidelines.

However, some guidelines remain that were not developed in collaboration with the ACC or AHA that continue to support clinical practice. The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) published recommendations for managing hypertension in adult patients 60 and older in early 2017, before release of the 2017 ACC/AHA guidelines (Qaseem 2017). After publication of ACC/AHA guidelines, the ACP and AAFP published a statement that they would not be endorsing the ACC/AHA hypertension recommendations (Crawford 2017). Hence, the ACP/AAFP 2017 guidelines should be considered a current and active set of recommendations.

Finally, the role of the JNC 8 panel recommendations remains less clear. Some groups such as ACP and AAFP have endorsed the JNC 8 recommendations. However, JNC 8 is not a comprehensive guideline and leaves many questions unanswered. Table 1 presents highlights from the guideline recommendations.

BP = blood pressure; TIA = transient ischemic attack.

2017 ACC/AHA Recommendations for Managing Hypertension in Adults

The 2017 ACC and AHA updated guidelines were endorsed by many other organizations. The guidelines are extensive, and several recommendations are new and worthy of discussion.

Table 1. Comparison of BP Target Recommendations

	BP Targets	BP Categories[a]	SBP (mm Hg)	DBP (mm Hg)
JNC 7, 2003	< 140/90 mm Hg < 130/80 mm Hg for those with diabetes or chronic kidney disease	Normal	< 120	< 80
		Prehypertension	120–139	80–89
		Stage 1 hypertension	140–159	90–99
		Stage 2 hypertension	≥ 160	≥ 100
JNC 8, 2014	< 150/90 mm Hg for patients ≥ 60 < 140/90 mm Hg for patients < 60, diabetes, and chronic kidney disease	Was not a comprehensive set of recommendations, and did not discuss hypertension diagnostic thresholds		
ACP/AAFP, 2017	< 150/90 mm Hg for patients ≥ 60 < 140/90 mm Hg for patients at higher CV risk, or with a history of stroke or TIA	Was not a comprehensive set of recommendations and did not discuss hypertension diagnostic thresholds Did not address recommendations in patients < 60		
ACC/AHA, 2017	≤ 130/80 mm Hg	Normal	< 120	< 80
		Elevated	120–129	< 80
		Stage 1 hypertension[b]	130–139	80–89
		Stage 2 hypertension	≥ 140	≥ 90

[a]Patients with SBP and DBP in two different categories should be classified in the higher category.

[b]Antihypertensive medication should be initiated in stage 1 hypertension only in patients with clinical CV disease, a 10-year risk of ASCVD of 10% or higher, diabetes mellitus, or chronic kidney disease.

BP = blood pressure; TIA = transient ischemic attack.

New Diagnostic Criteria and Staging

The 2017 guidelines lowered the threshold for the diagnosis of hypertension to 130/80 mm Hg from the 140/90 mm Hg standard of the past several decades. The JNC 7 guidelines categorized patients with a blood pressure of 130–139/80–89 mm Hg as "pre" hypertensive on the basis of cohort data showing a gradient of increased CV risk as SBP crossed the threshold of 120 mm Hg. The lower threshold for the diagnosis of hypertension increased the prevalence of hypertension, as previously discussed.

The 2017 guidelines also updated the blood pressure categories (see Table 1) and highlighted the blood pressure measurement technique (discussed below).

Risk Assessment

The 2017 ACC/AHA guidelines recommend incorporating CV risk estimates with blood pressure levels to determine when to initiate antihypertensives. The guidelines suggest initiating medication in those at high CV risk when SBP is 130 mm Hg or greater or DBP is 80 mm Hg or greater. In those at lower CV risk, they suggest initiating antihypertensives when SBP is 140 mm Hg or greater or DBP is 90 mm Hg or greater (Whelton 2018).

High CV risk is defined as a history of clinical CV disease or an estimated 10-year atherosclerotic CV disease (ASCVD) risk of 10% or higher according to the pooled cohort equations. Clinical CV disease is defined as coronary artery disease, heart failure, or stroke.

The inclusion of risk estimation in determining when to initiate antihypertensives comes, in part, from SPRINT, which included CV risk assessment as part of the inclusion criteria. Using the 10-year Framingham risk score, the SPRINT investigators set the threshold for high CV risk at 15%, which has been estimated to be similar to a 10-year ASCVD risk of 6–7% according to the pooled cohort equations (Whelton 2018).

Use of the pooled cohort equations has been controversial, given that their role for estimating the risk of initiating antihypertensives has not been formally evaluated in a clinical trial. Conversely, the pooled cohort equations have become more common in clinical practice and are integrated into some electronic medical records for efficient risk assessment. The pooled cohort equations are also used to determine the appropriate drug therapy for dyslipidemia and have played a role as the contemporary CV risk estimator, in place of Framingham, since 2014.

Although evidence to evaluate the pooled cohort equations in hypertension is beginning to surface, their use and the thresholds to consider for various risk levels continue to be debated. Regardless of the method used to assess CV risk, clinicians must be aware that CV risk should be considered in hypertension management, given that the benefits of treating hypertension are greatest in those with the highest CV risk (Muntner 2017).

TREATMENT GOALS

Epidemiologic evidence has shown that the risk of vascular death increases as blood pressure increases above 115/75 mm Hg (Lewington 2002).

Blood pressure goals have been intensely debated since 2013, when the JNC 8 recommendations became available. Whereas the thet JNC 8 recommendation to relax the SBP goals from less than 140 mm Hg to less than 150 mm Hg in patients older than 60 without diabetes or kidney disease was met with criticism, the 2017 ACC/AHA hypertension guidelines now call for stricter blood pressure control. A review of clinical trials that have tried to tackle this challenging question regarding optimal blood pressure targets follows. Of importance, several well-conducted meta-analyses have further explored this issue (Bundy 2017; Reboussin 2017). A comprehensive review of this complicated question is beyond the scope of this chapter.

SPRINT

The Systolic Blood Pressure Intervention Trial (SPRINT) was a sentinel clinical trial that compared CV outcomes in patients diseasewith increased CV risk who were randomized to an intensive blood pressure goal of less than 120 mm Hg or a standard blood pressure goal of less than 140 mm Hg (Wright 2015). This trial has affected hypertension management and clinical guidelines more than any other trial since the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

In the SPRINT study, more than 9000 patients were randomized.).)To be included, patients had to be 50 or older and have an increased CV risk, defined as clinical or subclinical CV disease, chronic kidney disease, or a 10-year CV risk of 15% or more on the basis of the Framingham risk score, or be 75 or older. On average, patients were 68 years of age with a baseline blood pressure of 140/78 mm Hg, about 28% were 75 or older, 17% had clinical CV disease, and the average 10-year CV risk score was 25%.

Diastolic BP was not a criterion for inclusion in SPRINT. Eligibility was based on a combination of SBP and the number of antihypertensive medications being taken at enrollment. Patients with an SBP of 130–180 mm Hg and taking no more than four antihypertensives were included.

Patients with a history of stroke or diabetes, symptomatic heart failure or heart failure with an ejection fraction less than 35%, severely elevated blood pressure (defined as SBP greater than 180 mm Hg), orthostasis (defined as an SBP decrease to less than 110 mm Hg after 1 minute of standing) and nursing home patients were excluded from the SPRINT trial.

Exclusion of patients with diabetes was based on the ACCORD trial, which was ongoing at the time SPRINT was designed, with the thought that intensive blood pressure control in patients with diabetes was already being adequately evaluated.

Of note, 14,692 patients were screened for enrollment, and 5331 were ineligible to participate. Forty-three percent of the

excluded patients were excluded because they took too many medications or had an SBP out of the range noted previously.

The primary composite outcome was myocardial infarction (MI), non-MI acute coronary syndromes, stroke, heart failure, or death from CV causes.

The trial was terminated early, after 3.26 years of follow-up, because of the significant benefits in those randomized to the intensive blood pressure arm. Patients in the intensive group achieved an average SBP of 121.5 mm Hg compared with 134.6 mm Hg in patients in the standard care group, taking an average of 2.8 and 1.8 antihypertensive medications, respectively.

The intensive group had a 25% relative risk reduction for the primary composite end point compared with the standard care group (HR 0.75; 95% CI, 0.64–0.89; p<0.001). The results were largely driven by a reduction in heart failure in the intensive group (HR 0.62; 95% CI, 0.45–0.84; p=0.002). No differences occurred between the groups in MI, acute coronary syndrome, or stroke.

Overall serious adverse events were similar between the groups, but the intensive group had more hypotension, syncope, electrolyte abnormalities, and acute kidney injury than the standard care group. The standard care group had more asymptomatic orthostasis (18.3% vs. 16.6%, p=0.01).

Blood pressure measurement in SPRINT differed from the standard of most clinical practices. Blood pressure in SPRINT was assessed using an automated device that measured blood pressure after the patient rested for 5 minutes, which then provided the average of three blood pressure measurements. Blood pressure assessed using this method is around 10 mm Hg lower than the measurements used in most office settings. Discussion of blood pressure measurement technique will be provided in another section.

The conclusion from SPRINT is that intensive blood pressure reduction is more effective than standard blood pressure reduction at reducing CV events and all-cause mortality in patients without diabetes or stroke who are at risk of CV disease. However, the measurement technique used in SPRINT may limit extrapolation of the findings to settings that do not use similar automated blood pressure measurement devices.

ACCORD BP Study

Another important clinical trial that has influenced contemporary hypertension management is the Action to Control CV Risk in Diabetes BP (ACCORD BP) trial (Cushman 2010). In ACCORD BP, 10,521 patients were randomized to intensive or standard glycemic control. Patients were then further randomized in a 2 x 2 factorial design to intensive versus standard care of either blood pressure or lipids. The results of the blood pressure arm, in which 4733 patients were randomized, will be discussed here.

Patients in ACCORD BP had uncontrolled type 2 diabetes and an SBP of 130–180 mm Hg on three or fewer antihypertensives. Included patients were age 40–54 with CV disease, or age 55 and older with subclinical CV disease, albuminuria, or CV risk factors. The primary outcome was the first occurrence of a CV event, defined as a composite of nonfatal MI, nonfatal stroke, or CV death.

On average, patients were 62 years of age and had a baseline blood pressure of 139/76 mm Hg; 33.7% had CV disease. Patients were followed for an average of 5 years.

Patients in the intensive arm achieved a blood pressure of 119.3/64.4 mm Hg and patients in the standard arm, 133.5/70.5 mm Hg. Despite the blood pressure difference, the primary composite outcome was similar between the intensive and standard blood pressure treatment groups (1.87%/year vs. 2.09%/year; HR 0.88; 95% CI, 0.73–1.06; p=0.20). However, intensive blood pressure reduction did reduce the rate of stroke, one of the prespecified secondary outcomes, compared with standard treatment (0.32%/year for intensive vs. 0.53%/year for standard treatment; HR 0.59; 95% CI, 0.39–0.89; p=0.01).

Patients in the intensive blood pressure treatment arm had more hypotension, syncope, bradycardia, increases in serum creatinine, and hypokalemia than did patients in the standard treatment group.

The conclusion from the ACCORD BP trial is that intensive blood pressure management in patients with type 2 diabetes does not improve CV end points, despite improved blood pressure values.

HYVET Study

The Hypertension in the Very Elderly Trial (HYVET) was one of the first large-scale clinical trials to establish the benefit of lowering blood pressure in patients 80 and older (Beckett 2008). The HYVET trial adds to our understanding of blood pressure targets by evaluating blood pressure control in older patients at high risk of CV events and adverse drug events.

HYVET was a non–U.S.-based study that evaluated the occurrence of fatal or nonfatal stroke in 3845 adults with a baseline SBP of 160 mm Hg or greater taking indapamide 1.5 mg daily or placebo. Perindopril 2 or 4 mg daily or placebo was added to the intervention or placebo groups, respectively, if needed, to target a goal blood pressure of less than 150/80 mm Hg.

Patients were, on average, 84 years of age with a baseline blood pressure of 173/91 mm Hg. Median follow-up was 1.8 years. Blood pressure fell in both groups. After 2 years, the mean seated blood pressure reduction in the placebo group was 14.5 ± 18.5/6.8 ± 10.5 mm Hg and was 29.5 ± 15.4/12.9 ± 9.5 mm Hg in the intervention group.

There was a nonsignificant reduction in the primary endpoint with active treatment (p=0.06). However, there was a 39% reduction in death from stroke (p=0.046), a 21% reduction in all-cause death (p=0.02), a 74% reduction in heart failure (p<0.001), and a 34% reduction in the occurrence of any CV event (p<0.001).

The conclusion from HYVET supports targeting a blood pressure goal of less than 150/80 mm Hg for patients with hypertension who are older than 80.

SPRINT Study – Adults 75 and Older Subanalysis

Evaluation of the adults 75 and older enrolled in the SPRINT trial was a prespecified analysis. Patients in this subanalysis were 80 years of age on average and had a blood pressure of 142/71 mm Hg (Williamson 2016).

Thirty-one percent of patients were classified as frail, according to a 37-item index. The average 10-year risk of CV disease was similar to that in the whole SPRINT cohort and was 24% and 25% in the intensive and standard care groups, respectively.

During follow-up, SBP was 123 mm Hg in the intensive arm and 135 mm Hg in the standard care arm.

The primary outcome was 34% lower in the intensive arm than in the standard care group (HR 0.66; 95% CI, 0.51–0.85). Similar to the main study results, improvement in this cohort was primarily driven by a reduction in heart failure.

The most common question in treating older patients to a more intensive blood pressure goal appears to be their tolerability of the lower blood pressure, especially frail patients, and this analysis sought to address that question.

Patients who were classified as "less fit" had a reduction in the primary composite outcome with intensive blood pressure reduction compared with standard reduction (HF 0.63; 95% CI, 0.43–0.91; p=0.01). Patients who were "less fit" or "frail" also had less all-cause mortality with intensive treatment, whereas patients who were classified as "fit" had no benefit with intensive blood pressure reduction. No difference occurred in adverse outcomes with intensive blood pressure treatment using markers of frailty.

Overall, this subanalysis helps inform hypertension management in older patients and supports a more intensive strategy than was suggested with the recommendations from the panel appointed to the JNC 8 committee.

DBP Considerations

Another area of debate within hypertension management is the threshold to which DBP can safely be lowered while targeting the lower SBP goals recommended in the 2017 ACC/AHA guidelines.

The diastolic J- or U-curve phenomenon suggests that CV and stroke risk increase as DBP is reduced. The rationale for increased risk is that most coronary and cerebral blood flow occurs during diastole. Therefore, excessively low DBP could cause ischemia.

However, evidence is mixed about this phenomenon. A post hoc analysis of SPRINT found a U-curve association for baseline DBP, but the benefit of intensely lowering SBP was not influenced by the baseline DBP. Other nonrandomized analyses show no increased risk when DBP is lowered to achieve SBP goals. Data from observational studies and secondary analyses suggest that a combination of low DBP and wide pulse pressure is associated with increased vascular events (Ahmed 2018).

Individual characteristics should be considered when estimating the risk of lowering DBP. For example, in older patients, arterial stiffness leads to elevated SBP and lower DBP. However, lowering DBP to less than 65 or 70 mm Hg in this specific group may increase vascular risk, and prudence is warranted (de Boer 2017).

BLOOD PRESSURE MEASUREMENT

The 2017 ACC/AHA guidelines place more emphasis on proper blood pressure measurement than do previous guidelines. The impetus for this comes from the recognition that blood pressure measurement is error prone and there is potential for harm if a provider titrates medications to the lower blood pressure target recommended by the guidelines using a falsely elevated blood pressure measurement (Whelton 2018).

Proper Measurement Technique

Standard techniques for blood pressure measurement are well established and can be done with manual auscultation or with an automated oscillometric device. Interest in using automated office blood pressure (AOBP) devices has continued to grow, given the belief that some measurement errors (e.g., auscultatory errors) can be eliminated. Furthermore, AOBP devices can be programmed to minimize the white-coat effect by delaying blood pressure measurement such that the health care professional can leave the room and the patient can be resting for a prescribed period (typically 1–5 minutes) before measurement. The AOBP devices can also provide an average of three readings.

Given that there are different methods of measuring blood pressure, different blood pressure results should be expected, depending on the procedure. Providers involved with managing hypertension should be familiar with the differences and should consider these during clinical decision-making. Manual office blood pressure measurements average about 10 mm Hg higher than measurements from daytime ambulatory blood pressure monitoring (ABPM) or AOBP, whereas ABPM and AOBP usually provide similar results (Sica 2016).

Of note, AOBP was used in SPRINT. Because the mean SBP achieved with intensive treatment in SPRINT was 121.4 mm Hg, the 2017 ACC/AHA guidelines factored in that many offices are not using AOBP and recommended an SBP goal of less than 130 mm Hg, rather than 120 mm Hg.

It is vital to recognize the potential sources of error during blood pressure measurement and how the error could affect the blood pressure reading. Using AOBP does not remove the potential for all errors. Indeed, attention still needs to be given to proper procedure, and patients should be instructed to maintain the correct body position and avoid talking during measurement.

Box 2 provides examples of factors that can cause inaccurate blood pressure readings and the direction of effect on SBP and DBP.

Box 2. Selected Causes of BP Measurement Errors

Factors that can falsely increase SBP and DBP:
- Bladder distension
- Cuff too small
- Insufficient rest period
- Talking during measurement

Factors that can falsely decrease SBP and DBP:
- Cuff too large

Factors that have mixed errors on SBP and DBP measurements:
- Deflating the cuff too quickly
- Standing or supine position rather than sitting position
- White-coat effect

Information from: Kallioinen N, Hill A, Horswill MS, et al. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. J Hypertens 2017;35:421-41.

Out-of-Office Measurement

Emphasis on proper blood pressure measurement includes both office and out-of-office measurement. In fact, out-of-office measurements are strongly recommended to confirm the hypertension diagnosis as well as to titrate medications.

Controversy exists about which method of blood pressure assessment is best correlated with clinical outcomes. Three types of blood pressure assessment can be used: (1) office blood pressure measurement with a manual sphygmomanometer or automated oscillometric device; (2) ABPM; (3) and home blood pressure monitoring. Of these, ABPM is considered the gold standard, given that elevations in 24-hour blood pressure on ABPM are clearly associated with stroke and CV events.

Ambulatory blood pressure monitoring is a form of concentrated blood pressure monitoring over 24–48 hours. A blood pressure device is worn constantly, and blood pressure is usually measured every 20–30 minutes, including during sleep. Information gained from ABPM is unique because blood pressure is assessed during activities of daily living. Data from ABPM include average awake and asleep blood pressure values, range of blood pressure, and nocturnal blood pressure. These data can inform underlying causes of hypertension. For example, a "non-dipping" pattern, in which blood pressure does not decrease by at least 10% during sleep, suggests sleep-disordered breathing (e.g., obstructive sleep apnea). In addition, ABPM can assess response to medication and degree of blood pressure control. When available, ABPM should be used to confirm the initial diagnosis but is also a valuable tool during treatment, especially in difficult-to-treat or resistant hypertension.

However, ABPM is not easily accessible in some practices, and cost can be a barrier to use. As such, home blood pressure measurement is a viable alternative. Elevated home blood pressure readings are also associated with CV events, though there is less evidence than with ABPM.

Box 3. Instructions for Home BP Measurement

Step 1: Obtain an appropriate home BP measurement device.
- Choose a fully automated device (avoid auscultatory home devices).
- Choose an arm device (brachial BP). Use wrist monitors only for patients whose arm circumference prevents proper fitting of a brachial measurement device.
- Choose validated devices, if possible.
- Ensure correct cuff size.

Step 2: Prepare for BP measurement.
- Empty bladder; refrain from drinking caffeine or smoking 30 min before measurement.
- Rest at least 5 min before BP measurement.
- Sit with back supported and feet flat on the floor (legs uncrossed).
- Place cuff directly above the antecubital fossa.

Step 3: Measure BP.
- Take two readings 1 min apart.
- Avoid unnecessary movement or talking during measurement.
- Minimize excessive measurements.

Step 4: Record BP values with date and time, noting anything unusual (e.g., pain, stress, illness, missed medication).

Patients measuring home blood pressure must be properly trained on selecting a device and blood pressure measurement procedure. Box 3 summarizes key training points.

Masked and White-Coat Hypertension

Including out-of-office blood pressure measurement as part of the hypertension diagnosis allows diagnosticians to identify patients with masked or white-coat hypertension.

Patients with masked hypertension are not hypertensive in a health care setting but are hypertensive in the home or ambulatory setting. This may occur in up to 15–20% of patients without a hypertension diagnosis. Of importance, masked hypertension is associated with an increased risk of CV disease, and patients with confirmed out-of-office hypertension should be treated with lifestyle changes and antihypertensives.

The association between white-coat hypertension and CV risk is less well established. However, patients with white-coat hypertension have a risk of progressing to sustained hypertension. As such, patients with white-coat hypertension should be counseled on lifestyle modifications and screened annually with either ABPM or home blood pressure monitoring for sustained hypertension.

DRUG THERAPY

Fundamentals of initial pharmacologic therapy of hypertension have not changed significantly with the 2017 ACC/AHA guidelines. Recommended options for initial therapy still include angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), calcium channel

blockers (CCBs), or thiazide-type diuretics, given that these classes reduce the risk of adverse CV and/or renal outcomes. Patient- and drug-specific characteristics may guide selection for initial monotherapy (Whelton 2018). For patients whose hypertension is uncontrolled with an appropriate combination of first-line agents, several other medication classes are potentially appropriate as add-on therapy.

First-line Treatment

Initial treatment of all patients should include lifestyle modifications designed to lower blood pressure. Evidence-based lifestyle modifications include moderation in alcohol intake, regular exercise, weight loss in overweight patients or patients with obesity, decreased sodium intake, and increased intake of potassium-rich foods. The Dietary Approaches to Stop Hypertension (DASH) diet limits sodium, incorporates high-potassium foods, and can facilitate weight loss. Adherence to a DASH-style dietary pattern has been associated with an SBP decrease of about 11 mm Hg; this effect is magnified when combined with stricter sodium reduction and/or weight loss (Whelton 2018).

For patients with stage 1 hypertension whose 10-year ASCVD risk score is less than 10%, lifestyle modification alone is reasonable. A combination of lifestyle modification and antihypertensives should be used in patients with stage 1 hypertension with established CV disease or a 10-year ASCVD risk score greater than 10%, and in those with stage 2 hypertension.

ACEIs and ARBs

The two primary pharmacologic classes targeting the renin-angiotensin system (RAS) are ACEIs and ARBs. Treatment with one of these agents is a necessary part of guideline-directed medical therapy for patients with heart failure or overt proteinuria (greater than 300 mg albumin/24 hours or the equivalent).

Patients with greater RAS activation should theoretically have a more robust response to RAS blockade, and initial therapy with an ACEI or ARB is logical in these patients. Increased RAS activation is more common in patients restricting salt intake, as well as younger, white patients, and/or those with higher measured renin concentrations. Consistent with this theory, evidence shows that African American patients have a diminished blood pressure response to RAS blockade as monotherapy (Helmer 2018). However, data on the benefits of choosing the initial therapy on the basis of these considerations are not conclusive, and other patient factors may outweigh race or age in some individuals. Measurement of plasma renin activity is not routinely recommended before beginning therapy.

Although ACEIs are usually well tolerated, a dry cough may occur in up to 20% of patients treated with these drugs; cough is more common among Asian Americans. Angioedema is an infrequent but more serious risk that is 2–4 times more common in African American patients than in whites (3.9 cases per 1000 person-years among African American vs. 0.8 cases per 1000 person-years among whites) (Taler 2018). Historically, ACEIs offered a significant cost advantage over ARBs, as well as more robust outcomes data. Now, almost all ARBs are available in generic form in the United States, and a large body of literature supports their benefit in CV and renal outcomes. Consequently, many practitioners now prefer ARBs to ACEIs as initial therapy, particularly in patients at a higher risk of cough or angioedema (Messerli 2018).

Patients who experience cough with ACEIs may safely be changed to ARBs. Those who experience ACEI-induced angioedema should discontinue the ACEI for at least 6 weeks. If RAS blockade is still indicated, these patients may then begin ARB therapy in most cases, though there is a small risk of cross-reactivity (Whelton 2018).

Both ACEIs and ARBs decrease the activity of angiotensin II. The clinically important ramifications of this include arterial and venous dilation, increased potassium concentrations, and reduced glomerular filtration pressure. Some of these effects are particularly beneficial when ACEIs and ARBs are used in combination with other first-line drugs. Venous dilation occurs with both classes but appears to be more pronounced with ACEIs. This pharmacodynamic effect can help offset CCB-induced edema. Increased potassium may help offset potassium losses when these agents are used in combination with thiazides. Reduced glomerular filtration pressure is responsible for the small, expected, and often transient physiologic increase in serum creatinine that follows initiation of either of these classes, as well as their renoprotective effects in patients with proteinuria.

Both ACEIs and ARBs are fetotoxic and should be avoided in pregnant women; women of childbearing age should be counseled regarding effective contraception before beginning ACEI or ARB therapy.

Calcium Channel Blockers

The two major subgroups of CCBs are the dihydropyridine (DHP) type and the non-dihydropyridine (non-DHP) type. Both subgroups are safe and well tolerated in most patients, including those with chronic kidney disease and, unlike many other classes of antihypertensive medications, have a low risk of electrolyte abnormalities. These subgroups help treat vasospastic conditions such as Raynaud disease and Prinzmetal angina. By reducing myocardial oxygen demand, CCBs can also improve symptoms in chronic stable angina. Peripheral edema can occur with either subgroup, though this is significantly more common with the DHPs. Management of CCB-induced edema is discussed later.

The DHP CCBs have no direct effect on heart rate, though indirect reflex tachycardia sometimes occurs. The non-DHP CCBs are less potent vasodilators than the DHPs. The hypotensive effects of the non-DHP CCBs occur by combining vasodilation with reduced cardiac output through negative

inotropic and chronotropic effects. Non-DHPs can maintain rate control in atrial fibrillation; however, their negative inotropic effects are harmful in patients with heart failure with reduced ejection fraction. Non-DHPs should also be avoided in patients with bradycardia.

Thiazide and Thiazide-like Diuretics

The term *thiazide* is usually considered to include both thiazide-type and thiazide-like diuretics, which have identical sites of action despite differing molecular structure (Olde Engberink 2015). Since the publication of ALLHAT, thiazides have been well recognized as a major first-line class of antihypertensives. The three thiazides most commonly used for hypertension in clinical practice are hydrochlorothiazide, chlorthalidone, and indapamide. Of these three, hydrochlorothiazide is the most widely prescribed. Hydrochlorothiazide is also the least effective at lowering blood pressure and has the shortest duration of action, with the antihypertensive benefit generally lasting less than 24 hours (Roush 2015). A meta-analysis comparing head-to-head trials of hydrochlorothiazide with other antihypertensive drugs showed that hydrochlorothiazide is consistently inferior to other antihypertensive drugs at lowering ambulatory blood pressure (Messerli 2011). Both chlorthalidone and indapamide have robust data supporting their benefit in improving CV outcomes. Conversely, evidence showing an outcomes benefit with hydrochlorothiazide is limited, despite its widespread use. For most patients, therefore, chlorthalidone and indapamide are preferred. Although thiazides are usually well tolerated, electrolyte abnormalities, including hyponatremia, can occur. In patients at a higher risk of problems, indapamide may be more convenient because it offers greater flexibility in available dosage strengths.

Virtually all thiazide-containing fixed-dose combination regimens, including both of the FDA-approved triple-therapy (ARB plus CCB plus thiazide) tablets, use hydrochlorothiazide. In some patients, the benefits of these combinations with respect to improved adherence and reduced pill burden may outweigh the reduced intrinsic efficacy of the thiazide component.

β-Blockers

β-Blockers have been shown to be inferior to other first-line agents in patients with uncomplicated hypertension. However, these data are largely based on trials that used atenolol. Outcomes evidence is insufficient with more contemporary β-blockers (e.g., carvedilol or nebivolol) to determine whether the inferiority is a class effect or is limited to atenolol. Nonetheless, no β-blocker is appropriate for initial hypertension therapy except when another indication requires β-blocker use, such as heart failure, rate control, MI, or migraine prophylaxis.

Combination and Add-on Therapy

Patients who do not tolerate a medication from one first-line class should discontinue it and begin an agent from a different first-line class. If the initial dose of the first medication does not reduce blood pressure sufficiently, the dose can be increased, or a regimen containing a combination of two or more of the recommended initial drug classes can be prescribed. Most patients with hypertension will require two or more medications to reach their blood pressure goal. Guidelines recommend initiating treatment with two or more drug classes in patients with stage 2 hypertension. However, in patients with a history of drug intolerance or at high risk of adverse effects, establishing tolerability with one agent before adding a second may help avoid removing both classes as therapeutic options. In patients who are already tolerating two medications, or in those in whom adherence is a concern, fixed-dose combination regimens are convenient to reduce pill burden, though optimal dosing or drug selection may not be available.

Relatively few head-to-head trials of different drug combinations are available. Thiazide diuretics often cause compensatory up-regulation of the RAS, and combining them with RAS blockers may have synergistic benefit. However, the clinical significance of this synergy was challenged by the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. This study compared benazepril plus amlodipine with benazepril plus hydrochlorothiazide. Benazepril plus amlodipine was more beneficial in both blood pressure lowering and CV outcomes (Jamerson 2008). Whether this improvement would have been maintained if a more efficacious thiazide had been used is unknown.

Some combinations should be avoided. In general, two drugs within the same class should not be combined. A combination of an ACEI and an ARB, or either of these agents combined with a direct renin inhibitor, increases the risk of hyperkalemia and renal impairment without improving CV or renal outcomes (Whelton 2018). However, combinations of different classes of diuretics, or DHP plus non-DHP CCBs, can sometimes be appropriate (Whelton 2018).

Fourth-line Drugs

Most patients should be initiated on a RAS inhibitor, a CCB, and/or a diuretic (usually a thiazide), with second and third agents from the remaining classes. For most patients, good adherence to well-chosen drugs in these classes, at appropriate doses, will ensure adequate blood pressure control.

However, around 12–13% of patients have true resistant hypertension despite this combination (Benjamin 2018); the percentage will be higher with lower blood pressure goals. Some patients may also have intolerances or contraindications that limit dosing or preclude the use of one or more classes altogether. Consequently, for some, a fourth medication is necessary to achieve blood pressure control. Two recent trials have been published to guide clinicians in selecting fourth-line agents. Both suggest spironolactone is an effective and well-tolerated add-on therapy for appropriately selected patients.

Mineralocorticoid Antagonists

The PATHWAY-2 study was a randomized, double-blind, crossover trial comparing spironolactone with placebo, bisoprolol, or doxazosin as add-on therapies for patients with drug-resistant hypertension, defined as a home SBP over 130 mm Hg on maximally tolerated doses of an ACEI or an ARB plus a CCB and a diuretic. Care was taken to rule out nonadherence as a cause for resistance. Spironolactone reduced SBP by an additional 10.2 mm Hg relative to placebo; SBP was 5–6 mm Hg lower in the spironolactone group than in the doxazosin and bisoprolol groups ($p<0.0001$) (Williams 2015).

More recently, the Resistant Hypertension Optimal Treatment (ReHOT) trial compared spironolactone with clonidine as fourth-line therapy for resistant hypertension in an open-label, randomized study (Krieger 2018). Of note, about 85% of screened patients were excluded because their blood pressure became controlled during the 12-week lead-in when they were placed on standard therapy, leaving the trial underpowered. Patients were randomized to treatment with clonidine or spironolactone. The percentage of patients achieving their goal blood pressure was similar between the two arms, though overall blood pressure control using office readings was low (around 21% of patients). Both drugs were surprisingly well tolerated in this trial; no gynecomastia was reported with spironolactone, and discontinuations because of somnolence with clonidine were rare. However, the authors suggested that although efficacy was comparable between the drugs, spironolactone has simpler dosing, making it the more attractive fourth-line agent for most patients.

Although both of these trials concluded that spironolactone was beneficial as a fourth-line agent, mineralocorticoid receptor antagonists (MRAs) are clearly not appropriate in all patients, particularly those with impaired renal function. The mean estimated glomerular filtration rate (eGFR) of patients in the PATHWAY-2 trial was 91.1 mL/minute/1.73 m^2; patients with an eGFR of less than 45 mL/minute/1.73 m^2 were excluded. Patients randomized in ReHOT had similarly good renal function, with a mean eGFR of 88.9 mL/minute/1.73 m^2. Close monitoring of potassium and renal function, particularly in patients with chronic kidney disease or those receiving concomitant ACEI/ARB therapy, is critically important, particularly with initiation of therapy or dose adjustment. Similar to ACEI or ARB initiation, a small increase in serum creatinine is expected when initiating an MRA, and serum creatinine should be monitored to ensure that it remains stable or moves back toward baseline. Some very common medications can have serious drug interactions when used together with MRAs. For example, additive hyperkalemia can result from use of MRAs with sulfamethoxazole/trimethoprim or drospirenone-containing contraceptives. Acute kidney injury can result from MRA use in combination with high-dose NSAIDs.

Mineralocorticoid receptor antagonists have additive benefits in reducing proteinuria when combined with an ACEI or ARB, though long-term outcomes benefit data are lacking (Mavrakanas 2014). For patients with primary aldosteronism, one of the most common and often under-recognized causes of secondary hypertension, MRAs are the medical treatment of choice.

Two MRAs are currently marketed. Spironolactone is well studied, inexpensive, and commonly well tolerated and should be the MRA of choice in most cases. However, because of its structural similarity to progesterone, dose-dependent antiandrogenic effects can occur. These can be exploited for clinical benefit; spironolactone is widely used to decrease acne and hirsutism in women. However, they can also be responsible for gynecomastia and erectile dysfunction in men, can cause breast pain or tenderness in both sexes, and can lead to menstrual irregularities in premenopausal women. Spironolactone is contraindicated in pregnancy because of the risk of feminizing male fetuses.

For patients with resistant hypertension who do not tolerate spironolactone, eplerenone is a good alternative. Eplerenone is more selective for the aldosterone receptor and typically avoids the hormonal adverse effects. Eplerenone is less potent than spironolactone and has a shorter half-life; for resistant hypertension, twice-daily dosing is often necessary. Although eplerenone has been available as a generic for at least 10 years, it still costs more than spironolactone, and insurance coverage is less universal.

Miscellaneous Approaches for Difficult-to-Treat Hypertension

Individual patient characteristics will play a large role in determining which fourth-line therapy is most appropriate, particularly for patients in whom MRAs are contraindicated. Table 2 compares characteristics that may influence the choice to select or avoid particular agents in a given patient.

Controversies and Special Populations

The 2017 ACC/AHA guidelines provide recommendations for treating patients with comorbidities or in certain high-risk groups. However, not all groups endorse the recommendations provided in the 2017 ACC/AHA update.

Hypertension and Diabetes

The 2017 ACC/AHA guidelines suggest treating patients with diabetes to a goal blood pressure of less than 130/80 mm Hg, whereas the American Diabetes Association (ADA) 2018 guidelines for CV disease and risk management recommend a blood pressure target of less than 140/90 mm Hg. The ADA suggests reserving a blood pressure target of less than 130/80 mm Hg for patients at high risk of CV disease (de Boer 2018).

The ADA recommendation for the blood pressure targets of less than 140/90 mm Hg is largely based on the ACCORD BP and Hypertension Optimal Treatment (HOT) trials (Cushman 2010; Hansson 1998). As previously discussed, the

Table 2. Fourth-line and Beyond Antihypertension Options

Therapy	Potential Population	Precautions	Notes
MRA	Hypokalemia, HFrEF, proteinuria, edema	Advanced kidney disease, hyperkalemia, hormonal effects with spironolactone	Spironolactone is better studied in resistant hypertension; consider eplerenone for spironolactone intolerance because of antitestosterone effects
β-Blocker	HFrEF, MI, atrial fibrillation, tachycardia, migraine prophylaxis, tremor	Bradycardia, asthma	
α-Blocker	BPH, ED, PTSD/ nightmares	Orthostatic hypotension	
Hydralazine	HFrEF (in combination with nitrates)	Adherence problems with TID dosing, drug-induced lupus, increased BP variability, reflex tachycardia	
Minoxidil	Very resistant hypertension	Often profound salt and water retention. Reflex tachycardia, hirsutism, pericardial effusion	Give in conjunction with loop diuretic and rate control agent
Central α-agonist	Anxiety disorders, ADHD	Anticholinergic effects, sedation, and cognitive effects may be especially pronounced in older adult patients. Rebound hypertension and/ or bradycardia may be exacerbated in patients receiving β-blockers. Skin irritation and/or adhesion problems with clonidine patch	

ADHD = attention-deficit/hyperactivity disorder; BPH = benign prostatic hyperplasia; ED = erectile dysfunction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; PTSD = posttraumatic stress disorder; TID = three times daily.

Patient Care Scenario

A 68-year-old woman was in the ED 1 week ago with a blood pressure of 192/98 mm Hg and no symptoms of TOD. She was given two doses of clonidine 0.1 mg, and 1 hour later, her blood pressure was 152/80 mm Hg. She was released with a prescription for clonidine to take as needed for blood pressure over 180/100 mm Hg. Her regular antihypertensives include lisinopril 20 mg/hydrochlorothiazide 12.5 mg daily (fixed-dose combination) and amlodipine 5 mg daily. Her laboratory values today are Na 130 mEq/L, K 4.2 mEq/L, and SCr 1.1 mg/dL. Her blood pressure in the clinic today is 164/88 mm Hg. How should this patient's antihypertensive regimen be modified?

ANSWER

The first step in determining the best modification to the patient's regimen is to confirm the accuracy of the blood pressure results. For example, ensure that the patient was resting for at least 5 minutes before blood pressure measurement, that she was properly positioned, and that she was not talking during measurement. Furthermore, if the blood pressure reading is a single measurement, repeat it and use the average of two readings.

Next, assess adherence, especially before the ED visit. If antihypertensives have been discontinued, reinstating medication rather than adding or increasing doses may be best. It is also important to determine how much "as-needed" clonidine she has taken since the ED visit.

The patient is hyponatremic, likely from hydrochlorothiazide. Therefore, hydrochlorothiazide cannot be titrated to treat the uncontrolled hypertension and should be discontinued. If this patient were not hyponatremic, changing from hydrochlorothiazide to chlorthalidone as the more effective thiazide diuretic could be considered.

The most rational adjustments to her regimen would be to discontinue the fixed-dose lisinopril/hydrochlorothiazide and to change to lisinopril at the higher dose of 40 mg daily. Given that this alone is unlikely to lower blood pressure sufficiently to her goal of less than 130/80 mm Hg, titration of amlodipine to 10 mg daily is also needed. However, that adjustment could be done at a follow-up visit within 1–2 weeks if there are concerns about making additional medication changes in one visit.

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71:e127-e248.
2. Leung AA, Wright A, Pazo V, et al. Risk of thiazide-induced hyponatremia in patients with hypertension. Am J Med 2011;124:1064-72.

ACCORD BP trial was the largest prospective comparison of intensive with standard hypertension treatment in patients with type 2 diabetes. No difference occurred in the primary endpoint between the treatment groups, though a subanalysis showed a reduction in stroke. Conversely, a subanalysis of the HOT trial found that targeting a DBP of 80 mm Hg or less, rather than 90 mm Hg or less, was associated with a 51% reduction of CV events in patients with diabetes (de Boer 2017). Of importance, patients with diabetes were excluded from SPRINT.

The rationale for recommending the more intensive goal of less than 130/80 mm Hg in the 2017 ACC/AHA guidelines is largely based on ASCVD risk assessment. The position of the guideline authors is that most adults with diabetes have a 10-year ASCVD risk that is at least 10%, thereby making them part of the higher-risk category (Whelton 2018).

Other Comorbidities

The 2017 ACC/AHA guidelines advocate a goal of less than 130/80 mm Hg across other comorbidities and high-risk groups with one exception. The guidelines suggest that in those who have had a stroke or transient ischemic attack (TIA), a blood pressure goal of less than 130/80 mm Hg is reasonable, but evidence is limited to support initiating treatment when blood pressure is less than 140/90 mm Hg. As such, the recommendations for blood pressure targets in those with stroke or TIA are not as strongly endorsed.

HYPERTENSIVE CRISIS

Hypertensive crisis includes two types of patients with severely elevated blood pressure (greater than 180 mm Hg SBP or greater than 120 mm Hg DBP). Patients with hypertensive emergency have severely elevated blood pressure plus new or worsening target organ damage (TOD) (Box 4). Patients with hypertensive urgency have severely elevated blood pressure with no evidence of TOD. differentiatedIt is important to distinguish these conditions because their management differs.

Both types of hypertensive crisis lack robust clinical trials to guide management, and most clinical recommendations are based on consensus expert opinion.

Box 4. Types of Target Organ Damage Related to Acute Hypertension

- Acute coronary syndrome
- Acute ("flash") pulmonary edema
- Acute renal failure
- Aortic dissection
- Cerebrovascular event (ischemic or hemorrhagic)
- Eclampsia
- Encephalopathy
- Papilledema

Hypertensive Emergency

The goal of treating patients with hypertensive emergency is to prevent or limit further TOD. Treatment of hypertensive emergency should include ICU admission for immediate reduction of blood pressure using a parenteral antihypertensive, plus treatment of the acute TOD.

Of importance, blood pressure should not be lowered too quickly. Most patients should have their blood pressure lowered by 25% within the first hour, though some circumstances (e.g., acute aortic dissection) may require more rapid blood pressure lowering. Guidelines differ on which blood pressure marker to use for monitoring during acute hypertensive emergencies. The 2017 ACC/AHA guidelines use SBP to guide therapy, but mean arterial pressure may also be used to monitor acute blood pressure–related emergencies (Adebayo 2015).

Although a complete review of managing hypertensive emergencies is beyond the scope of this chapter, it helps to be aware of the parenteral agents used in managing hypertensive emergency (Table 3).

Hypertensive Urgency

Treatment of hypertensive urgency is discretely different from that of hypertensive emergency. No evidence shows that immediate reduction of blood pressure in those with a severe asymptomatic blood pressure elevation improves clinical outcomes. Current consensus recommendations state that patients with an asymptomatic blood pressure elevation should be treated by adjusting or reinstating chronic medications, ideally within 24–48 hours (Wolf 2013).

It is especially important to ensure proper measurement of blood pressure and medication adherence and to minimize excessive blood pressure lowering. In addition, patients prone to anxiety may need to avoid excessive blood pressure measurement.

SECONDARY HYPERTENSION

Around 10% of patients with hypertension have a specific, identifiable cause for their elevated blood pressure. Patients with resistant hypertension or other suggestive clinical factors should be screened for secondary causes. A chart describing the known causes of secondary hypertension as well as when and how to test for them is available in the 2017 AHA hypertension guidelines.

Pharmacists are in a unique position to identify and address medications that may be inducing or exacerbating hypertension. Several commonly encountered classes of medications raise blood pressure, including NSAIDs, decongestants, attention-deficit/hyperactivity disorder medications (atomoxetine as well as amphetamine derivatives), estrogens, and serotonin-norepinephrine reuptake inhibitors. Patients should also be questioned about supplement use because some supplements (e.g., licorice, yohimbine, bitter orange) can also exacerbate hypertension. Mirabegron, a relatively new treatment for overactive bladder, is a β_3-agonist that may

Table 3. Intravenous Antihypertensives for Hypertensive Emergencies

Class	Drug	Comments
DHP CCBs	Nicardipine	Avoid in aortic stenosis Can be titrated every 5–15 min to achieve BP control Fluid may be excessive in those with acute pulmonary edema or acute heart failure Can cause phlebitis
	Clevidipine	Avoid in those with allergy to soy or eggs, those with severe aortic stenosis or with defective lipid metabolism Effects occur within 2–4 min Cost may affect availability
Vasodilators	Sodium nitroprusside	Fast onset of action Caution for cyanide toxicity with prolonged use and/or high doses Avoid in cerebrovascular events
	Nitroglycerin	Avoid in right ventricular infarction Good choice in pulmonary edema
	Hydralazine	Option for eclampsia or preeclampsia
β-Blockers	Esmolol	Good option for aortic dissection
	Labetalol	Ideal choice in eclampsia or preeclampsia
α-Blocker	Phentolamine	Preferred in sympathetic overload (e.g., pheochromocytoma)
Dopamine agonist	Fenoldopam	Ideal for nephropathic emergencies. Cost may affect availability
ACEI	Enalaprilat	Does not require hepatic activation; enalaprilat is the active form of enalapril and is 10–20 times as potent as captopril Avoid in acute coronary syndrome

DHP = dihydropyridine.

Information from: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71:e127-e248.

also raise blood pressure. Corticosteroids raise blood pressure through their mineralocorticoid effects; MRAs may be especially beneficial in patients with resistant HTN related to chronic corticosteroid use. Atypical antipsychotics, particularly olanzapine and clozapine, cause a variety of metabolic derangements, including hypertension. If alternative drugs cannot be substituted, aggressive lifestyle interventions and intensification of pharmacotherapy are usually necessary.

Vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab induce nitric oxide deficiency. Endothelial nitric oxide deficiency inhibits arterial vasodilation; inhibiting renal nitric oxide signaling adds salt and fluid retention as an additional mechanism for exacerbating hypertension. Hypertension is well recognized as a problem among patients using these drugs for cancer treatment. However, smaller-dose, intravitreal injections of VEGF inhibitors used for retinal disorders are also commonly associated with hypertension (Fiebai 2017). Calcium channel blockers and diuretics are often effective for treating hypertension related to VEGF inhibitors; in refractory cases, nitrates or nebivolol may be appropriate because they specifically address the nitric oxide deficiency (Touyz 2018).

DIFFICULT-TO-TREAT HYPERTENSION

Resistant Hypertension

Resistant hypertension is defined as blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of different classes. Ideally, one of these agents should be a diuretic, and the other agents should be prescribed at maximally tolerated doses. A companion definition of resistant hypertension is blood pressure that requires four or more medications to maintain control (Calhoun 2008).

The exact prevalence of resistant hypertension is unknown, in part because of pseudoresistance, in which blood pressure is uncontrolled because of factors such as nonadherence,

poor blood pressure measurement technique, or a white-coat effect. Temporary or persistent volume overload related to inadequate diuresis can also cause pseudo-resistant hypertension. However, current estimates are that truly treatment-resistant hypertension occurs in 12–13% of patients with hypertension (Benjamin 2018).

A clinical pharmacist involved in hypertension management will undoubtedly have to consider alternative diagnoses in patients referred for treatment-resistant hypertension. To effectively treat these patients, the pharmacist must consider underlying causes or other factors contributing to the resistance, such as secondary hypertension.

An early step in treating patients with apparently resistant hypertension is to assess and address medication adherence. When adherence is a concern, addressing causes such as adverse effects, cost, or misperceptions about medications is necessary. Once barriers to adherence have been addressed, ensure the regimen includes antihypertensives that are maximally effective. For example, change from hydrochlorothiazide to chlorthalidone for more potency (Roush 2015). In addition, consider changing to an agent with a longer duration of action, simplifying regimens, or changing to fixed-dose combinations, when feasible.

Once patients have been evaluated for underlying causes of resistance, if blood pressure remains uncontrolled, adding fourth-line agents, especially spironolactone, is reasonable.

Managing Adverse Effects

Many common adverse effects from blood pressure medications, such as β-blocker–induced bradycardia and ACEI cough, are clinically troublesome but straightforward to detect and treat. Other complications of therapy may be more difficult to manage.

Hypokalemia

Several antihypertensives cause electrolyte abnormalities. Diuretic-induced hypokalemia is well recognized and can generally be avoided or treated by rational medication combinations. Combining low-dose thiazides with an ACEI or ARB is often sufficient to balance potassium concentrations. If hypokalemia persists, an MRA may provide blood pressure lowering as well as potent potassium-sparing effects. Triamterene and amiloride are alternatives to potassium supplements in patients with hypokalemia whose blood pressure is already at or near goal.

Hyponatremia

One of the most common, troublesome, and underrecognized problems with thiazide diuretics is hyponatremia. In one retrospective study, 30% of patients taking a thiazide over 5 years developed a serum sodium concentration of 130 mmol/L or lower (Leung 2011). Risk of hyponatremia is related to treatment intensity, with higher doses and more efficacious agents such as chlorthalidone posing a higher risk. Several other risk factors for hyponatremia exist, including older age, lower BMI, female sex, and use of other hyponatremia-inducing medications such as NSAIDs or selective serotonin reuptake inhibitors, as well as a history of hyponatremia or a low-normal baseline sodium concentration (Rodenburg 2013). If a thiazide is needed in patients with hyponatremia risk factors, the clinician should begin with a low dose (e.g., indapamide 0.625–1.25 mg daily). In addition, serum sodium concentrations should be checked 1–2 weeks after initiating treatment and intermittently thereafter, especially if there is any acute change in water intake or fluid handling (e.g., UTI, acute GI illness, heart failure exacerbation). High-risk patients should be counseled against excessive water consumption. Those who develop hyponatremia should be changed to another class of drugs. If a diuretic is still required, a low dose of a long-acting loop diuretic (e.g., torsemide 2.5–5 mg daily) is as effective as usual thiazide doses at treating hypertension and has minimal effects on electrolyte concentrations, though outcomes data are more limited (Baumgart 1993).

Edema

Edema is common in patients undergoing treatment for hypertension, with several possible etiologies that may commonly coexist. Many patients with hypertension present with salt sensitivity that predisposes them to mild hypervolemia and edema. Hypertension is a risk factor for many comorbidities that can induce edema, including chronic kidney disease, heart failure, and venous insufficiency; these should be considered before assuming that edema is medication induced. Nevertheless, edema is the most common adverse effect in patients taking DHP CCBs. Because CCBs have intrinsic mild natriuretic properties, this effect is not related to overall salt and water retention. Rather, the primary mechanism seems to be arteriolar dilation without concomitant venodilation; the increased venous pressure can lead to capillary leak and increased interstitial fluid. Unless the edema is multifactorial, adding a diuretic usually does not provide significant relief. Women may be particularly susceptible to CCB-induced edema. Peripheral edema can be minimized by decreasing the dose, foot elevation, compression stockings, changing to a non-DHP CCB, or using CCBs in combination with venodilating agents such as ACEIs (Gradman 1997).

In contrast, edema from direct vasodilators such as hydralazine and minoxidil is related to salt and water retention. Minoxidil is particularly notorious and usually requires coadministration of a loop diuretic to prevent hypervolemia.

Erectile Dysfunction

Erectile dysfunction is estimated to affect at least 30% of men with hypertension (DeLay 2016). Because both hypertension and erectile dysfunction are essentially disorders of endothelial dysfunction, many of the risk factors and common comorbidities, such as diabetes mellitus, CV disease, and metabolic syndrome, overlap. Although hypertension itself can lead to erectile dysfunction, erectile dysfunction is also commonly a treatment-emergent adverse event. Thiazide diuretics are the most commonly implicated class in clinical trials, though

β-blockers are also associated with increased risk. Nebivolol, with its increase in endothelial nitric oxide, is an exception, and in several small studies has been found to have neutral to positive effect on erectile function, particularly in men with previous erectile dysfunction related to other β-blockers. Limited data suggest that ARBs actually benefit sexual function. Calcium channel blockers and ACEIs appear to be neutral in this respect (Nunes 2012).

Although α-blockers are inappropriate as monotherapy, they may also be helpful add-on antihypertensives for patients with erectile dysfunction or benign prostatic hyperplasiaplasia. In the Treatment of Mild Hypertension Study, doxazosin was associated with improved erectile function in men both with and without reported problems at baseline (Grimm 1997). Although α-blockers were initially contraindicated with phosphodiesterase type 5 (PDE5) inhibitors, that prohibition has now been relaxed to a caution to monitor for additive antihypertensive effect. Preliminary evidence suggests that the combination of α-blockers and PDE5 inhibitors improves both erectile dysfunction and lower urinary tract symptoms compared with either class alone (Yan 2014).

Multiple Medication Intolerances

Although many patients have treatment-emergent adverse effects, one subset of patients has difficulty tolerating multiple agents. Many of these reported adverse effects may be common, nonspecific symptoms that are only questionably the result of drug therapy (Colloca 2011). Several approaches to this difficult clinical situation may be considered. All patients benefit from positive lifestyle modifications, but these should be particularly encouraged in patients who have difficulty taking medications. Many patients tolerate moderate doses of two drugs better than high-dose monotherapy, and this approach has been extended in one center to try fractional doses of two or more medications, often including alternative dosage forms such as liquids or transdermal formulations to improve tolerability (Antoniou 2016). Finally, the importance of the nocebo effect cannot be overlooked. Nocebo effect, the inverse of placebo, is strongly associated with patient expectations of the benefits and harms of therapy. Positive framing of the expected risks, focusing on the large percentage of patients who do tolerate the medication, may help modify patient expectations and improve tolerability (Wells 2012).

Non–drug-specific intolerance to several unrelated antihypertensive drugs is significantly more common in patients with psychiatric conditions such as anxiety disorders and depression (Davies 2003). In patients who present with a long list of unrelated drug intolerances, recognition and treatment of any psychiatric comorbidities may be necessary before antihypertensive therapy is successful.

Labile Hypertension

Physiologic blood pressure variation occurs in healthy individuals from beat to beat and is affected by factors such as time of day, season, body position (e.g., sitting vs. standing), and stressors. However, in some individuals, this variation is magnified.

Blood pressure variation, which is often a marker for increased arterial stiffness, has been found in observational trials to be associated with an increased CV risk (Eguchi 2012). Blood pressure variability can be measured as visit-to-visit variation or using 24-hour ambulatory measurement. However, although the problem is relatively easy to recognize, it is comparatively more difficult to treat.

Several approaches to reducing blood pressure variation can be tried, depending on the individual's blood pressure pattern. One of the most straightforward explanations for visit-to-visit blood pressure variability is sporadic adherence to blood pressure medications and lifestyle recommendations; identifying and addressing these problems should clearly be the initial step. Similarly, pharmacokinetic differences among agents can play a role. Drugs with relatively constant plasma concentrations over 24 hours or longer may cause less variability than drugs with shorter half-lives or with large peak-to-trough plasma ratios. Choosing long-acting medications may reduce blood pressure variability even in patients with good medication adherence (Parati 2010). Drug class may also affect blood pressure variability independent of the specific agent chosen within the class. One meta-analysis found that CCBs (both DHPs and non-DHPs) and, to a lesser extent, thiazide diuretics, were associated with reduced blood pressure variability. Therapies with ACEIs, ARBs, and β-blockers were associated with increased variability (Webb 2010). Clonidine deserves special mention in this respect. Because of its rapid onset of action, clonidine is often prescribed for as-needed use in patients with a history of hypertensive urgency. However, with frequent use, clonidine can exacerbate the problem and become an underrecognized iatrogenic cause of severe blood pressure variability.

Ensuring regular adherence to antihypertensive therapy and choosing medications with "smooth" pharmacokinetics will improve blood pressure variability in many patients. Other patients may pose a greater challenge. No universally accepted definition of "highly labile" or "variable" hypertension exists. However, from a practical management standpoint, blood pressure variability is a problem when an individual patient's day-to-day blood pressure range includes readings that are too high to safely leave untreated in conjunction with readings that are too low to safely allow for increased antihypertensive therapy. Measurement error should be ruled out to avoid unnecessarily treating spurious readings. Ambulatory blood pressure monitoring, in combination with a detailed diary of activity, medications, and symptoms, can help identify patterns. Patients with a consistent pattern of predictable highs and lows (e.g., "non-dippers" or others with abnormal circadian variability) can sometimes be treated with judicious use of short-acting medications.

Patients who describe episodic, severely elevated blood pressure, especially if associated with tachycardia, headache,

Table 4. Short- and Long-Acting Antihypertensives

	Drug Class	Drug
Drugs with expected duration ≤ 12 hr[a]	ACEI	Captopril
	β-Blocker	Metoprolol tartrate
	DHP CCBs	Nicardipine
		Isradipine
	Non-DHP CCBs	Diltiazem IR
		Verapamil IR
	Diuretics	Hydrochlorothiazide
		Furosemide[b]
	Miscellaneous agents	Prazosin
		Clonidine
		Hydralazine
		Nitrates
Drugs with expected antihypertensive duration ≥ 24 hr	ACEIs	Trandolapril
		Perindopril
	ARBs	Eprosartan
		Telmisartan
	β-Blockers	Nadolol
		Betaxolol
		Nebivolol
	CCB	Amlodipine
	Diuretics	Chlorthalidone
		Indapamide
	α-Blocker	Doxazosin
	α-Agonist	Clonidine patch

[a]Immediate-release nifedipine is not appropriate for hypertension treatment in most patients.

[b]Antihypertensive effect usually lasts longer than diuretic effect, but is still usually < 24 hr.

palpitations, diaphoresis, and/or pallor, should be tested to rule out pheochromocytoma. However, most patients, even those with classic pheochromocytoma symptoms, do not have this disorder. A much more common disorder, termed *paroxysmal hypertension* or *pseudopheochromocytoma*, is characterized by sudden and often dramatic rises in blood pressure, often accompanied by pheochromocytoma-type symptoms or flushing, in the absence of any recognizable trigger. Unlike patients with panic disorder or with large blood pressure swings triggered by emotional distress, these patients usually state that their anxiety is a consequence of the hypertensive episode, rather than a cause. Nevertheless, the treatment approach is similar; limited data suggest benefit from anxiolytics and/or combined α/β-blockade (Mann 2015).

Autonomic dysfunction can present as severe, frequent blood pressure fluctuations within minutes or hours. Patterns of orthostatic hypotension and supine hypertension, as well as postprandial hypotension, are common, though many of the dramatic blood pressure fluctuations in these patients are unpredictable. Dysfunctional autonomic blood pressure regulation is most common in neurologic disorders such as Parkinson disease, or as a consequence of trauma or radiation to the carotid baroreceptors, but can sometimes occur in patients without obvious predisposing factors. Referral to a neurologist and/or tertiary care center is necessary for these patients.

Pharmacokinetic differences among agents can become particularly important when managing labile hypertension. Drugs with longer durations of action help ensure 24-hour blood pressure coverage and may be particularly beneficial in patients with nonadherence. Conversely, some patients have blood pressure fluctuations that may benefit from shorter-acting, more targeted treatments, either at consistent times of day (e.g., evening dosing for patients with nocturnal hypertension) or as needed (Table 4).

Practice Points

Clinical pharmacists involved in treating hypertension are often presented with complex hypertension cases. Newly available guidelines can be a resource while caring for patients with challenging hypertension situations. Consider applying these practice points:

- **Incorporate lifestyle changes in all patients with hypertension.**
- **Initiate antihypertensives in patients with stage 1 hypertension if they have clinical CV disease, an ASCVD risk score of 10% or higher, diabetes mellitus, or chronic kidney disease.**
- **Initiate antihypertensives in patients with stage 2 hypertension, regardless of their risk factors.**
- **Target a goal of less than 130/80 mm Hg for most patients, but consider individual factors (e.g., older adult patients with wide pulse pressures, fall risk) that could affect safety with titrating medication to meet this goal.**
- **Optimize first-line treatments by choosing the most evidence-based antihypertensives and titrating the dose on the basis of safety and efficacy.**
- **Choose combination treatments that have synergistic or complementary mechanisms of action, such as an ACEI plus a CCB.**
- **Consider fourth-line agents such as MRAs, direct-acting vasodilators, or α-blockers in patients whose hypertension is still uncontrolled despite optimized first-line antihypertensives. Spironolactone has the most evidence in this population.**
- **Consider long-acting agents and/or CCBs to manage sporadic adherence or labile blood pressure readings.**
- **Be prepared to manage hyponatremia in patients taking thiazide diuretics by changing to other first-line agents or a low-dose loop diuretic.**

CONCLUSION

Pharmacists have many opportunities to manage the care of patients with hypertension. Emerging research continues to support a role for clinical pharmacists as a vital member of a health care team managing hypertension.

Because almost one-half of the U.S. adult population now has hypertension, the importance of having a strong working knowledge of hypertensive pharmacotherapy transcends specialty areas and health care settings.

Pharmacists should continue to advocate the optimization of first-line hypertension medications and to address adherence issues and adverse events.

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Self-Assessment Questions

1. A 50-year-old African American man has had an average blood pressure of 136/78 mm Hg and heart rate of 72 beats/minute over the past two visits. He is a smoker but has no other relevant medical history. His TC is 240 mg/dL and HDL is 32 mg/dL. Which one of the following is best to recommend to manage this patient's blood pressure?

   A. Lifestyle modifications only
   B. Lifestyle modifications plus chlorthalidone 25 mg daily
   C. Lifestyle modifications plus hydrochlorothiazide 12.5 mg and lisinopril 20 mg daily
   D. Lifestyle modifications plus atenolol 50 mg daily

2. A patient with hypertension and lower-extremity edema is being treated with amlodipine 10 mg once daily. Her blood pressure in the clinic today is 152/90 mm Hg and heart rate is 68 beats/minute. Which one of the following is best to recommend for this patient's amlodipine-induced lower-extremity edema?

   A. Decrease amlodipine to 5 mg daily.
   B. Discontinue amlodipine.
   C. Add furosemide 20 mg daily.
   D. Add lisinopril 10 mg daily.

3. A 78-year-old woman with an average clinic blood pressure of 142/82 mm Hg is referred to your clinic. Her antihypertensive regimen includes telmisartan 40 mg daily. The patient is somewhat resistant to adding medications because of concern that more medications will worsen her daytime fatigue. She undergoes ambulatory blood pressure monitoring (ABPM) for further evaluation before medication is added, with average daytime blood pressure 144/80 mm Hg and average nighttime blood pressure 140/78 mm Hg. Which one of the following best assesses this patient's blood pressure?

   A. White-coat hypertension
   B. Masked hypertension
   C. Non-dipping blood pressure pattern, consistent with sleep-disordered breathing
   D. Sporadic hypertension, consistent with pheochromocytoma

4. A patient calls your clinic, worried because his blood pressure was 192/98 mm Hg on his home blood pressure monitor. He repeated it to confirm and had a similar result. He denies feeling any symptoms and denies missing any of his regular antihypertensives. The patient takes chlorthalidone 25 mg daily and amlodipine 5 mg daily. In addition to arranging for prompt outpatient follow up, which one of the following is best to recommend for this patient?

   A. Increase amlodipine to 10 mg daily.
   B. Go to the ED for evaluation of hypertensive emergency.
   C. Initiate clonidine 0.1 mg every hour until blood pressure is normalized.
   D. Take one extra dose of chlorthalidone 25 mg today only.

5. A 55-year-old woman has a new diagnosis of hypertension. Her average blood pressure on her ABPM was 158/92 mm Hg. She has implemented dietary changes, but her blood pressure remains elevated. You are consulted to initiate hypertension treatment. Her other medical history is significant for allergic rhinitis and hypothyroidism. Her laboratory values are all within normal limits. Which one of the following is best to recommend initiating in this patient?

   A. Metoprolol succinate 50 mg daily
   B. Chlorthalidone 25 mg plus lisinopril 10 mg daily
   C. Hydrochlorothiazide 25 mg daily
   D. Metoprolol succinate 50 mg plus chlorthalidone 25 mg daily

Questions 6 and 7 pertain to the following case.

H.G. is a 61-year-old man with heart failure with reduced ejection fraction, dyslipidemia, diabetes, and hypertension. His home blood pressure readings have recently increased to 152–168/72–84 mm Hg over the past 7–10 days. Six months ago, his home and clinic average blood pressure reading was 128/70 mm Hg. H.G. takes carvedilol 25 mg twice daily, lisinopril 40 mg daily, and torsemide 50 mg daily. He denies missing doses of his medication, which is confirmed by assessing his refill history. He admits recently eating out for several days and not watching his dietary sodium intake. H.G. also admits feeling short of breath and having more lower-extremity edema. His weight in the clinic today is 70 kg, a 10-kg increase from his last visit. His blood pressure in the clinic is 156/86 mm Hg; his laboratory values are all within normal limits.

6. Which one of the following best assesses H.G.'s blood pressure?

   A. Treatment-resistant hypertension
   B. Pseudo-resistant hypertension
   C. White-coat hypertension
   D. Masked hypertension

7. Which one of the following is best to recommend for H.G.'s recent uncontrolled blood pressure?

   A. Increase carvedilol to 50 mg twice daily.
   B. Add clonidine 0.1-mg/hour patch; change once weekly.

C. Add hydrochlorothiazide 25 mg daily.
D. Increase torsemide to 100 mg daily for 3–5 days.

8. A 78-year-old woman is seen for a hypertension follow-up. She takes hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, and nifedipine XL 30 mg daily. Her home and clinic blood pressure readings have been 142–154/64–72 mm Hg. Pertinent laboratory values from today are Na 128 mEq/L and K 4.9 mEq/L. Physical examination reveals 1+ bilateral lower-extremity edema. Which one of the following is best to recommend regarding this patient's hypertension regimen?

   A. Discontinue hydrochlorothiazide and replace with chlorthalidone 25 mg daily.
   B. Discontinue hydrochlorothiazide and replace with torsemide 5 mg daily.
   C. Discontinue nifedipine and replace with diltiazem CD 120 mg daily.
   D. Increase lisinopril to 40 mg daily.

9. A 59-year-old man with labile hypertension is seen in your clinic. He takes amlodipine 10 mg daily and chlorthalidone 25 mg every morning. He reports having blood pressure elevations starting at 4 p.m. that last until 10 p.m. The patient keeps excellent home blood pressure records; his average blood pressure during this time is 160/90 mm Hg, and his blood pressure during the morning and early afternoon is 118–126/62–70 mm Hg. Which one of the following is best to recommend to manage this patient's blood pressure elevation during this limited time?

   A. Start lisinopril 10 mg at 3 p.m.
   B. Start lisinopril 10 mg in the morning.
   C. Start captopril 12.5 mg at 3 p.m.
   D. Start captopril 12.5 mg in the morning.

10. A physician is caring for a frail 75-year-old woman with hypertension. The patient's blood pressure is 145–150/70–78 mm Hg on amlodipine 10 mg daily and hydrochlorothiazide 25 mg daily. The physician asks your opinion on whether he should target the blood pressure goal suggested by the 2017 ACC/AHA hypertension guidelines or the goal suggested by the AAFP guidelines. Which one of the following is best to recommend for this patient?

    A. Evidence shows that reducing SBP to lower than 150 mm Hg in patients 75 and older increases the risk of falls.
    B. Evidence shows that reducing SBP to lower than 150 mm Hg in patients 75 and older decreases the quality of life.
    C. Evidence shows that reducing SBP to lower than 130 mm Hg in patients 75 and older improves CV outcomes.
    D. Evidence shows that reducing SBP to lower than 130 mm Hg in patients 75 and older increases the risk of falls.

11. A 53-year-old man with a history of hypertension, dyslipidemia, and type 2 diabetes is discharged from the hospital 2 weeks after an acute MI. His home drugs include aspirin 81 mg daily, prasugrel 10 mg daily, and atorvastatin 40 mg daily. During his hospitalization, the patient's blood pressure was low; his blood pressure medications were discontinued and were not resumed on discharge. Today, his blood pressure is 146/80 mm Hg and heart rate is 52 beats/minute. Which one of the following is best to initiate in this patient today?

    A. Lisinopril 10 mg daily
    B. Chlorthalidone 25 mg daily
    C. Amlodipine 5 mg daily
    D. Metoprolol succinate 50 mg daily

12. A 73-year-old woman has difficult-to-treat hypertension. Her current regimen includes lisinopril 40 mg daily, chlorthalidone 25 mg daily, and amlodipine 10 mg daily. She also takes mirabegron 50 daily, rosuvastatin 10 mg daily, and loratadine 10 mg daily. Her blood pressure has been 150–155/75–78 mm Hg and heart rate 58–60 beats/minute during the past three visits, which did not improve with the last medication adjustment. Pertinent laboratory values today are Na 136 mEq/L, K 4.7 mEq/L, and SCr 1.4 mg/dL. Which one of the following is best to recommend for this patient's hypertension?

    A. Discontinue mirabegron.
    B. Add doxazosin 4 mg daily.
    C. Increase chlorthalidone to 50 mg daily.
    D. Add carvedilol 12.5 mg twice daily.

13. A 50-year-old woman was recently given a diagnosis of hypertension caused by her prednisone therapy for rheumatoid arthritis. She takes prednisone 40 mg daily; she has not yet been initiated on an antihypertensive. Her blood pressure is 148–156/80–85 mm Hg and heart rates are 62–70 beats/minute. On physical examination, she has 2+ pitting edema bilaterally. Pertinent laboratory values today are Na 140 mEq/L, K 3.4 mEq/L, and SCr 1.0 mg/dL. Which one of the following is best to recommend for this patient's hypertension?

    A. Chlorthalidone 25 mg daily
    B. Metoprolol succinate 100 mg daily
    C. Amlodipine 10 mg daily
    D. Spironolactone 25 mg daily

14. A 44-year-old man with hypertension takes chlorthalidone 25 mg daily. His blood pressure in the clinic today is 128/70 mm Hg and heart rate is 76 beats/minute. His laboratory values are within normal limits. However, he has concerns of new-onset erectile dysfunction. Which one of the following is best to recommend for this adverse effect in this patient?

    A. Change to telmisartan 40 mg daily.
    B. Change to doxazosin 2 mg daily.
    C. Change to metoprolol succinate 100 mg daily.
    D. Change to isosorbide mononitrate ER 30 mg daily.

15. A 55-year-old woman takes hydrochlorothiazide 25 mg daily and amlodipine 10 mg daily. She presents for a follow-up of her hypertension. Her blood pressure readings have been 146–152/70–75 mm Hg. Pertinent laboratory values include Na 140 mEq/L, K 4.8 mEq/L, and SCr 0.9 mg/dL. Which one of the following is best to recommend for this patient's hypertension?

    A. Add lisinopril 40 mg daily.
    B. Add spironolactone 25 mg daily.
    C. Change from hydrochlorothiazide to furosemide 40 mg daily.
    D. Change from hydrochlorothiazide to chlorthalidone 25 mg daily.