Essential Hypertension

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LEARNING OBJECTIVES

1. Evaluate evidence-based recommendations from recent hypertension and disease specific guidelines.
2. Apply recent guideline recommendations for blood pressure goals and thresholds to the management of essential hypertension.
3. Evaluate blood pressure measurement techniques for the management of hypertension.
4. Develop an individualized assessment and management plan for a patient with essential hypertension.

ABBREVIATIONS IN THIS CHAPTER

AAFP	American Academy of Family Physicians
ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
ACP	American College of Physicians
AHA	American Heart Association
ARB	Angiotensin II receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AOBP	Automated office blood pressure
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HBPM	Home blood pressure monitoring
HCTZ	Hydrochlorothiazide
JNC	Joint National Committee
MI	Myocardial infarction
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
SBP	Systolic blood pressure

Table of other common abbreviations.

INTRODUCTION

Despite advances in health care, cardiovascular disease (CVD) remains the leading cause of death in the United States (Herron 2019). From 1980–2010, the number of deaths attributed to CVD declined; however, the mortality rate has continuously increased since 2010. High blood pressure contributes to about 90,000 cardiovascular-related deaths per year and is one of the most high-impact risk factors for CVD prevention (Virani 2020). It is estimated that more than 30% of cardiovascular deaths could be prevented with appropriate management of blood pressure (Patel 2015).

In 2017, the American College of Cardiology (ACC) and American Heart Association (AHA) released guidelines that redefined the baseline for high blood pressure as 130/80 mm Hg (Whelton 2018). This definition expanded the prevalence of hypertension to 46% in adults age 20 years and older (Virani 2020). Although blood pressure control rates were less than ideal before the ACC/AHA guidelines changed, estimates using the new, lower blood pressure goals reduced the overall control rate in the United States to about 25% (Virani 2020). Furthermore, the blood pressure control rates are even lower in certain populations, including 17% in African American men and 12% in Hispanic men. These statistics highlight the need to improve poor blood pressure control rates in the United States as well as the disparities within the health care system (Virani 2020). The financial impact of uncontrolled blood pressure is estimated to cost the U.S. health care system $55.9 billion annually, and costs are projected to increase to $220 billion by 2035 (Virani 2020; Heidenreich 2011).

CLINICAL GUIDELINE EVOLUTION

The development of hypertension practice guidelines was traditionally the responsibility of the Joint National Committee (JNC), which was funded by the National Heart Lung and Blood Institute (NHLBI). This group released a series of comprehensive guidelines, the seventh

and most recent of which is known as *JNC7* (Chobanian 2003). During production of Eighth JNC Report (JNC8), the NHLBI transferred future guideline development responsibilities to ACC and AHA and then disbanded the JNC8 Panel. However, the authors previously appointed to JNC8 released their recommendations without NHLBI endorsement in 2014. Many practitioners refer to this set of guidelines as *JNC8*; although this document is not society endorsed, it instead served as a welcome update helping to inform practice patterns until release of the comprehensive practice guideline endorsed by ACC/AHA NHLBI in 2017. The major changes in this 2017 document related to classification, measurement technique, thresholds, and targets were largely based on the Systolic Blood Pressure Intervention Trial (SPRINT) and meta-analysis data (Whelton 2018; The SPRINT Research Group 2015). Although a large group of multidisciplinary organizations endorsed the ACC/AHA guidelines, neither ACP nor AAFP endorsed these new guidelines, and AAFP instead opted to continue their endorsement JNC8. Therefore, practice variations remain with notable differences in primary care compared with other specialties. This section compares the recent guideline recommendations and summarizes the key differences among them.

BASELINE KNOWLEDGE STATEMENTS

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

- Pathophysiology of hypertension and its impact on cardiovascular disease
- The mechanisms of action for medications commonly used to treat hypertension
- Treatment goals and thresholds from recent hypertension guidelines

Table of common laboratory reference values.

ADDITIONAL READINGS

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

- 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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13-115.
- Bundy JD, Mills KT, Chen J, et al. Estimating the association of the 2017 and 2014 hypertension guidelines with cardiovascular events and deaths in US adults: an analysis of national data. JAMA Cardiol 2018;3:572.
- Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association Hypertension. Hypertension 2019;73:e35-66
- Wagner TD, Jones MC, Salgado TM, et al. Pharmacist's role in hypertension management: a review of key randomized controlled trials. J Hum Hypertens 2020;34:487-94.

JNC Recommendations

In 2003, JNC7 was published and remained the standard of care for hypertension management for more than 10 years (Chobanian 2003). The release of recommendations from authors previously appointed to the JNC8 Panel in 2014 was intended to provide an update to JNC7 with a focus on three key questions related to treatment goals and pharmacologic therapy. The evidence-based recommendations of the JNC8 Panel focused strictly on RCTs because they are subject to the least amount of bias and represented the highest quality of evidence (James 2014). The exclusion of other study designs was a common criticism of the JNC8 update because of the gaps in evidence presented by considering current RCTs alone. Nevertheless, this revision process created new recommendations to simplify hypertension management.

Perhaps the most significant practice-changing recommendations from JNC8 were the reduction of blood pressure goals and thresholds across patient populations. The JNC8 Panel recommendations established 140/90 mm Hg as the standard blood pressure goal for the general population, including individuals with CKD and diabetes. The exception to the 140/90 mm Hg goal was the older adult population (age >60 years) without comorbidities, for whom the assigned treatment goal was <150/90 mm Hg. These recommendations were based strictly on RCTs, which raised concerns among clinicians about the relationship between higher blood pressure values for the general population and the effect on CVD event rates for cases in which subclinical CVD may be present. These potential concerns were even echoed by several guideline authors who particularly opposed the higher blood pressure goals in older patients (Wright 2009). Regardless of the disagreement among the JNC8 Panel, both ACP and AAFP later supported a treatment goal and threshold of 150/90 mm Hg in older adults (Qaseem 2017).

Another major change recommended by the JNC8 Panel regarded the first-line medication selection for the treatment of essential hypertension. Specifically, β-blockers were no longer recommended as initial therapy in absence of a compelling indication. This decision was based on the inferior efficacy of this drug class to lower blood pressure and the concern for higher rates of stroke compared with ARBs (Dahlof 2002). Thiazide diuretics, dihydropyridine (DHP) calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs) and ARBs all remained appropriate first-line options (James 2014).

Ultimately, the JNC8 Panel intended to simplify treatment and improve outcomes—both for the general hypertensive population and the subpopulations with hypertension—using the best available evidence. For non-African American patients, any of the first-line medications were recommended. However, thiazides and DHP CCBs were given preference for African American patients. This recommendation included patients with diabetes, unless albuminuria was present, in which case an ACEI or ARB was preferred. Both recommendations were dramatic shifts in the treatment approach for high blood pressure (James 2014).

The classification of blood pressures was a major area that was the JNC8 Panel did not address. The JNC7 Guideline defined *normal blood pressure* as <120/80 mm Hg, whereas blood pressure between 120–139/80–89 mm Hg was considered *prehypertension*. Once blood pressure exceeded 140/90 mm Hg patients were classified as having *stage 1 hypertension*, unless their blood pressure reached the threshold for *stage 2 hypertension* at 160/100 mm Hg (Chobanian 2003). Because these ranges and definitions were not addressed by the JNC8 Panel, categorization of hypertension remained unchanged from the JNC7 guideline.

ACP and AAFP Guideline Recommendations

Shortly before the ACC/AHA guidelines were released in 2017, ACP and AAFP published guidelines for managing hypertension in older adults age >60 years (Qaseem 2017). The primary purpose of these recommendations was to compare the benefits and risks of treating older adults to a goal systolic blood pressure (SBP) of <150 mm Hg versus <140 mm Hg. Importantly, the guidelines did not compare more aggressive targets such as a goal SBP of <130 mm Hg versus <150 mm Hg. Based on a review of the evidence by ACP/AAFP, a goal SBP of <150 mm Hg was recommended for most adults age >60 years and a lower goal SBP of <140 mm Hg was considered for patients at high risk of CVD or who had a history of stroke. When the ACC/AHA guidelines were released, neither ACP nor AAFP endorsed the new recommendations, and AAFP opted instead to continue with the JNC8 Panel recommendations in conjunction with the ACP/AAFP recommendations for older adults (Qaseem 2017).

ACC/AHA Guidelines

The long-awaited comprehensive blood pressure management guidelines from ACC/AHA were published in 2017. Major changes in recommendations were largely based on the SPRINT findings, which was published after the JNC8 Panel recommendations (The SPRINT Research Group 2015). Changes in blood pressure measurement techniques, staging, and goals were all updated (Whelton 2018). Before the ACC/AHA guidelines were released, many of these questions had not been addressed in recommendations from the JNC8 Panel; therefore, practice remained based on guidance from JNC7 (James 2014; Chobanian 2003).

Table 1. Blood Pressure Classification Guideline Comparison

Blood Pressure	JNC7 Stages	ACC/AHA Stages
<120/80 mm Hg	Normal	Normal
120–129 mm Hg/ <80 mm Hg	Prehypertension	Elevated Blood Pressure
130–139/80–89 mm Hg	Prehypertension	Stage 1 Hypertension
140–159/90–99 mm Hg	Stage 1 Hypertension	Stage 2 Hypertension
Greater than 160/100 mm hg	Stage 2 Hypertension	Stage 2 Hypertension

ACC, American College of Cardiology; AHA, American Heart Association; JNC7, Joint National Committee, seventh edition of the hypertension practice guidelines.

Information from: Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 2003;289:2560-71; 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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;7:e13-115.

The ACC/AHA classification system for blood pressure included several notable changes from the JNC7 recommendations (Table 1). Whereas the *normal blood pressure* classification remained unchanged at <120/80 mm Hg, all other stages were updated. A SBP of 120–129 mm Hg and diastolic blood pressure (DBP) <80 mm Hg would now classify as *elevated blood pressure*, essentially replacing the *prehypertension* category used in JNC7 guideline. Similarly, *stage 1 hypertension* was lowered to a threshold of 130/80 mm Hg, and the new diagnostic threshold for *stage 2 hypertension* became 140/90 mm Hg (Whelton 2018).

DETERMINING BLOOD PRESSURE TREATMENT THRESHOLDS AND GOALS

ACC/AHA Guidelines Approach to Hypertension Management

Concern for overtreatment is a common criticism of the ACC/AHA recommendations. However, this new approach to pharmacologic treatment thresholds was expected to increase medication prescribing by only 4.7% compared with JNC8 (Bundy 2018). Thus, the ACC/AHA recommendation of a

target a blood pressure <130/80 mm Hg was not expected to increase inappropriate medical therapy. Furthermore, nonpharmacologic therapy was recommended in all patients with elevated blood pressure. Patients with stage 1 hypertension are not initially indicated for medication treatment unless they have a history of atherosclerotic cardiovascular disease (ASCVD) or a 10-year risk for ASCVD that exceeds 10%. Because most patients with diabetes and CKD are expected to have high ASCVD risk, a threshold of 130/80 mm Hg was assigned to patients with these comorbidities. In addition, patients with stage 2 hypertension were also recommended to receive drug therapy. Regardless of the threshold, all patients should be treated to a blood pressure <130/80 mm Hg as tolerated (Whelton 2018).

The basis of these treatment stages, goals, and thresholds was to identify people most likely to benefit from pharmacotherapy. Observation data estimate that the risk of CVD increases for each 20 mm Hg increase in SBP or 10 mm Hg increase in DBP >115/75 or mm Hg (Lewington 2002). More recent analysis suggested the development of ASCVD may begin at SBP of 100 mm Hg (Whelton 2020). Hence, the change in terminology from *prehypertension* to *elevated blood pressure* may serve to better communicate risk. The SPRINT data also indicate that patients who have the highest risk of ASCVD benefit the most from intensive treatment (Attar 2019). However, a major gap in the evidence from RCTs is the lack of inclusion of patients age <40 years whose ASCVD risk is low.

Risk-Based Approach

The 2017 ACC/AHA guidelines selected the ACC/AHA Pooled Cohort Risk Calculator to estimate a patient's 10-year risk for developing ASCVD. It is important to acknowledge the limitations of this instrument related to hypertension management. This risk tool was validated in patients age 45–79 years without statin therapy, an approach that may miscalculate the risk of hypertension for patients who do not meet these criteria. The ACC/AHA guideline authors selected a 10% risk threshold for 10-year ASCVD based on clinical trials that showed patients with SBP >130 mm Hg and/or DBP >80 mm Hg have a 0.9% per year rate of cardiovascular events (Whelton 2018; Xie 2016)—an event rate of 0.9% per year is roughly equivalent to a 10% risk in 10 years. No universal risk threshold exists for patients to receive hypertension therapy. Instead, clinicians use risk estimates together with blood pressure measurements when deciding to treat hypertension. In the ACC/AHA Guidelines, patients with stage 2 hypertension are categorially high risk, which warrants treatment at diagnosis, whereas those with stage 1 hypertension require further risk assessment with the Pooled Cohort Risk Calculator to guide treatment. (Whelton 2018). The use of both blood pressure measurements and risk calculation has the potential to improve the cost effectiveness of hypertension management, but important gaps in evidence remain.

As mentioned previously, one of the greatest challenges to hypertension management is selecting the optimal approach for low-risk individuals. Most RCTs enroll high-risk patients, and generally those who are at the highest risk benefit the most from pharmacologic treatment (Attar 2019; Montgomery 2003). Modeling studies suggest treating younger patients (low-risk) to lower targets would reduce complications of hypertension; however, the number needed to treat to achieve a benefit is much higher than for those with established CVD or at high risk of CVD (Montgomery 2003). More evidence is needed for hypertension management in low-risk patients; however, risk calculation is a useful tool in conjunction with blood pressure readings to identify the patients who are most likely to benefit from treatment (Lonn 2016).

Important Clinical Trials for Hypertension Management

SPRINT

Perhaps the most influential trial cited in the ACC/AHA guidelines is SPRINT, which examined the effect of an intensive SBP target <120 mm Hg compared with <140 mm Hg. All enrolled patients were age ≥50 years with SBP 130–180 mm Hg and an elevated risk of CVD. Other inclusion criteria required patients to meet one of the following conditions: subclinical or established CVD, CKD, a Framingham risk score of ≥15%, and age ≥75 years. Important exclusion criteria included diabetes mellitus, stroke, and heart failure with an ejection fraction <35%. The primary composite outcome was MI, non-MI acute coronary syndrome, stroke, decompensated heart failure, or death from cardiovascular causes (The SPRINT Research Group 2015).

The intent of the SPRINT was to study more-intensive SBP targets than the standard of care at the time of trial inception. Beyond simply comparing two blood pressure targets, the SPRINT inclusion criteria ensured that the study would enroll patients at high-risk for short-term cardiovascular events. Of the 9361 patients who underwent randomization, the average age was 68 years, with 28% ≥75 years; 28% with CKD; and 20% who met the criteria for CVD or CVD risk. The average 10-year Framingham risk score was 20%, and the average baseline blood pressure was 140/78 mm Hg (The SPRINT Research Group 2015).

The SPRINT study outcomes must be taken in context with its protocol. First, automated office blood pressure (AOBP) measurements were taken at each visit. Patients were seated and the measurement device was programmed to take 3 seated measurements after 5 minutes of rest before each measurement. The results were averaged to report the blood pressure at the study visit (Ambrosius 2014). As discussed later in text, AOBP values are generally lower than those obtained in standard clinical practice or research and thus can assist with unmasking the white coat effect. Study participants were also given a rigorous blood pressure monitoring plan.

Both groups began with 3 monthly visits, and then visits were scheduled every 3 months thereafter unless the patient's SBP was poorly controlled. Patients in the intensive arm were seen monthly until they reached a target SBP of <120 mm Hg or until no additional titration was planned. The same practice was conducted in the standard treatment group until the patient had a SBP of <160 mm Hg or consecutive visits with SBP >140 mm Hg. Laboratory monitoring was extensive at the beginning of the trial and during the medication titration period. It is important to note the aggressive titration of medications coincided with intensive monitoring and careful blood pressure measurement technique.

The median follow-up for time of SPRINT was 3.26 years, shorter than the 5 years planned. Because of the significantly better interim results of the primary outcome in the intensive treatment arm, the Data and Safety Monitoring Board stopped the trial early. A 25% relative risk reduction was observed for the primary outcome in the intensive arm (hazard ratio [HR] 0.75, 95% CI, 0.64–0.89; p<0.001). The absolute risk difference for the primary outcome was 1.6%, favoring the intensively treated group—a 1.6% absolute risk difference yields a number needed to treat of 63 patients over 3.26 years. Significant differences were also observed for heart failure, death from all causes, and death from cardiovascular causes in favor of the intensive-treatment group. Importantly, the median SBP was 121.5 mm Hg in the intensive arm and 134.6 mm Hg in the standard arm. Despite substantial differences in SBP between the groups, the intensive arm failed to reach a median SBP goal of <120 mm Hg. Failure to reach the SBP goal was a major limitation of the study. Further reductions in SBP in the intensively treated group may have led to lower event rates, but potentially higher rates of adverse effects.

Composite serious adverse events were similar between groups. One reason for the similar results in adverse effects was the appropriate screening for orthostatic hypotension in all patients before enrollment. Higher rates of hypotension, acute kidney injury, and electrolyte abnormalities were noted in the intensive arm. These outcomes would be expected considering that the intensive arm used 3 antihypertensives and the standard treatment arm used 2 antihypertensives for most patients. Surprisingly, a small absolute increase of 1.7% for orthostatic hypotension events was observed in the standard treatment arm; however, an identical 7.1% rate of injurious falls occurred in both treatment arms (The SPRINT Research Group 2015).

The results from SPRINT show that intensive SBP lowering in patients without stroke or diabetes decreases cardiovascular morbidity and mortality compared with those treated to standard SBP goals (i.e., that standard SBP at the time of the study). However, the rigorous study protocol for blood pressure measurement and monitoring may limit the generalizability to clinical practices that approach hypertension management differently. The limitations on generalizability particularly applies to the methods used for measuring blood pressure in SPRINT. Because use of an AOBP device provides more accurate measurements compared with manual measurements, the blood pressures measured in SPRINT may be lower than the values obtained in many practice settings still using manual measurement techniques. Careful consideration of the approach to blood pressure measurement, follow-up, and monitoring should be considered before applying to real-world practice.

SPRINT CKD

The SPRINT Research Group conducted several pre-specified analyses, including one in patients with CKD at baseline. Before SPRINT, questions remained regarding intensive blood pressure control on kidney and cardiovascular outcomes in patients with CKD without diabetes. A total of 2646 study participants or 28% of the total study population had CKD at baseline and were included in subgroup analysis. All-cause death was incrementally lower in the intensive group compared with the standard group (1.61% vs. 2.21% per year). No benefit was seen for the primary kidney outcome, and the yearly rate of change in the eGFR was larger in the intensive-treatment group compared with the standard group (−0.47 mL/min/1.73m^2 vs. −0.32 mL/min/1.73m^2). Serum potassium derangements and acute renal failure were also more common in the intensive group. Overall, the estimated number need to treat to prevent all-cause death in the CKD subgroup at 4 years was 28 patients compared with an estimated number needed to harm of 35 patients for acute renal failure (Cheung 2017). These results emphasize the careful balance that must be managed in this population.

ACCORD

The Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD) was a multicenter RCT in patients with type 2 diabetes at high risk of CVD (ACCORD Study Group 2010). The methodologic approach and study design were similar to the SPRINT Trial, with one major difference: A 2 × 2 factorial design randomized patients to an intensive SBP arm (<120 mm Hg) or standard SBP arm (<140 mm Hg) in addition to an intensive hemoglobin A1C arm (<6%) or a standard arm hemoglobin A1C (7%–7.9%). Of the 4733 patients enrolled, 2362 were randomized to intensive treatment and 2371 to standard treatment. The results of the 2 blood pressure arms showed no difference in cardiovascular events and mortality, except for stroke. Patients in the intensive arm were less likely to have a stroke (1.6% vs. 2.6%) with an estimated number needed to treat of 89 patients over 5 years. In addition, participants in the intensive arm had more adverse drug effects from additional antihypertensive treatment. Serious adverse effects such as hypotension and electrolyte abnormalities occurred in 3.3% of patients in the intensive treatment arm compared with 1.27% in the standard arm. The number needed to harm or experience one major one major adverse effect from intensive treatment over 5 years was 31(ACCORD

Study Group 2010). One important limitation of ACCORD to consider when interpreting the results is the low event rate of the primary outcome. An event rate of 4% per year in the standard group was required to meet adequate power for the study; however, the actual event rate was only 2.09% per year which may have underpowered the trial's ability to assess differences between arms. Regardless of the limitations of ACCORD trial, it was a major influence on the JNC8 Panel recommendations and questioned the need for more intensive blood pressure targets in patients with diabetes.

Reconciling ACCORD and SPRINT Data

Questions remain on how to apply the SPRINT and ACCORD results to clinical practice because these similarly designed trials found seemingly different results for intensive blood pressure targets. No pathophysiologic mechanisms have explained the discordant results between SPRINT and ACCORD. An analysis by Brouwer and colleagues used patient-level data to analyze a pooled cohort of 14094 SPRINT and ACCORD patients. The primary end point for the pooled cohort was MI, stroke, or cardiovascular death, and the data were evaluated for the same duration as SPRINT (3.26 years). The primary end point occurred in 8% of patients in the standard treatment arm compared with 6.6% in the intensive group. Data were further analyzed to evaluate the effect of diabetes on the primary outcome. Intensive treatment to SBP <120 mm Hg was found to be beneficial to patients regardless of their diabetes history. This analysis suggested that intensive SBP is beneficial in patients irrespective of diabetes history, and it does not support diabetes as the reason for differences in SPRINT and ACCORD (Brouwer 2018).

The 2 × 2 factorial design has been hypothesized as a major confounding factor accounting for the differences in cardiovascular outcomes in ACCORD and SPRINT. As mentioned previously, patients in the ACCORD trial were randomized to either intensive or standard blood pressure groups and intensive or standard hemoglobin A1C groups. A post-hoc analysis by Buckley and colleagues evaluated outcomes of 1284 patients meeting the SPRINT criteria (excluding diabetes) treated to standard glycemic control. The primary outcome assessed was cardiovascular death, nonfatal MI, nonfatal stroke, any revascularization, and heart failure. Patients in ACCORD treated to a target A1C of 7%–7.9% and SBP <120 mm Hg experienced lower rates of the primary outcome (3.48% per year vs. 4.22% per year) (Buckley 2017). This post-hoc analysis supports the hypothesis that intensive glucose control has negative effects on cardiovascular outcomes and attenuates the benefits of intensive SBP control.

Buckley and colleagues conducted the same analysis on the follow-on study to ACCORD, the ACCORDION trial (ACCORD Study Group 2016). After completion of the initial ACCORD trial, an observational follow-up study monitored patients for an average duration of 4 years after the trial ended and a combined 9 years overall. At the end of the ACCORDION trial, the SBP for the intensive and standard blood pressure groups was 132±16 and 134±16, respectively. The beneficial effects of intensive treatment in the standard glycemic group during ACCORD persisted over the long-term follow-up for the main composite outcome of cardiovascular death, nonfatal stroke, and nonfatal MI. The main outcome occurred at a rate of 2.7% per year and 3.36% per year for the intensive and standard treatment groups, respectively (Buckley 2018). The long-term follow-up in the ACCORDION trial further adds to support that intensive blood pressure treatment in conjunction with appropriate glycemic control in people with diabetes improves cardiovascular outcomes.

Other Trials Including Older Adults

Recommendations for hypertension management in older adults have led to greatest controversy in the post-JNC7 era. Specific management recommendations are discussed in detail later in this chapter. This section focuses on studies related to blood pressure interventions in adults age ≥75 years, the subgroup analysis for older adults from SPRINT, and the Hypertension in the Very Elderly Trial (HYVET) (Williamson 2016; Beckett 2008).

HYVET

The HYVET study design randomized 3845 patients age ≥80 years with SBP ≥160 mm Hg at baseline to receive treatment with indapamide or placebo. Participants in the active arm also received perindopril 2 or 4 mg if their blood pressure remained above the treatment target of 150/80 mm Hg. The primary endpoint for HYVET was stroke; secondary endpoints were death from cardiovascular causes and death from any cause. Patients were followed for a median of 1.8 years. At the end of the study, those in the active arm had lower blood pressure values for both SBP and DBP with an average decrease of 15/6.1 mm Hg. Because the treatment group showed a reduction in death from any cause (HR 0.76; 95% CI, 0.62–0.93; p=0.007) and stroke (HR 0.59; 95% CI, 0.4–0.88; p=0.009) in favor of the active arm, the Data and Safety Monitoring Board ended the trial early for ethical reasons. Ending the trial early was also responsible for the fewer patient-years needed (10500) to achieve a power of 90%. The final analysis of the trial data showed lower event rates for fatal stroke of 6.5 and 10.7 and death from any cause of 47.2 and 59.6 per 1000 patient-years for the active and placebo groups, respectively. Despite the use of additional antihypertensives in the active arm, no differences in adverse effects were observed between the active and placebo arms. The generalizability of the adverse effect results were limited by the screening process in the study protocol. All patients screened were required to have a standing blood pressure >140 mm Hg, which may potentially select a population better able to tolerate antihypertensive therapy. A further limitation of HYVET were the 3670 of 3845 patients from China and Eastern Europe, a population not reflective of

the demographics in the United States. This study suggests individuals age ≥80 years have an incremental benefit from antihypertensive treatment (Beckett 2008).

SPRINT Adults Older Than 75 years

The SPRINT Trial included 2636 individuals age ≥75 years who were examined in a pre-specified subgroup analysis. These participants' mean age was 79.9 years, and almost 45% had an eGFR <60 mL/min/1.73m^2. The benefits of intensive blood pressure targets (SBP <120 mm Hg) versus standard (SBP <140 mm Hg) were also observed in this SPRINT subgroup. Similar to the full trial population, the intensive arm failed to reach a SBP <120 mm Hg. The mean SBP achieved in the intensive arm was 123.4 mm Hg versus 134.8 mm Hg in the standard arm. Nevertheless, intensive control led to 1.2% absolute risk reduction for the primary composite outcome (2.59% vs. 3.85% per year) as well as 0.85% absolute risk reduction for all-cause mortality. (1.78% vs. 2.63% per year). Furthermore, the HR was 0.64 with a 95% CI of 0.51–0.85, which was numerically lower than the HR of 0.75 (95% CI, 0.64–0.89) observed in the main trial. Together, these results suggest intensively treating SBP shows a greater benefit in adults age ≥75 years (The SPRINT Research Group 2015; Williamson 2016).

Serious adverse effects were also similar among groups. A trend for higher rates of acute kidney injury, electrolyte abnormalities, and syncope was noted, but none of these outcomes met statistical significance. Similar to the main study findings—although not statistically significant in this subgroup of older patients—a lower rate of injurious falls and orthostatic hypotension in patients randomized to intensive treatment was observed (Williamson 2016). It is unclear why the intensive treatment led to fewer injurious falls, and these data still support the need for careful monitoring for hypotension when managing hypertension in older adults.

An exploratory analysis of outcomes based on frailty and gait speed was also completed to better understand who was likely to experience from adverse effects of intensive treatment. Adverse effects increased with increased frailty status and decreased gait. However, within each frailty or gait stratum, the absolute number of adverse events tended to favor the intensive treatment arm. The subgroup analysis in older adults of the SPRINT Trial suggests that intensive blood pressure targets are beneficial with similar adverse effects rates compared with standard blood pressure targets, regardless of frailty status (Williamson 2016). Nevertheless, frailty status is only one consideration clinicians must contemplate when determining blood pressure goals in older adults.

In summary, contemporary evidence suggests that initiation of antihypertensive therapy in the older adults can reduce the risk of cardiovascular events and that intensive blood pressure reduction may enhance this risk reduction. Individualized patient selection, including assessment of standing blood pressure, and engagement of the patient in shared decision-making should be part of the process of determining which older adult patients to consider for aggressive blood pressure management.

MEASURING AND ASSESSING BLOOD PRESSURE

Clinic-Based Blood Pressure Measurement

Patient assessment for diagnostic decision-making relies on proper techniques for blood pressure measurement. The traditional approach to blood pressure measurement uses manual auscultatory methods, but errors are common with this approach. Incorrect blood pressure technique is estimated to alter treatment decisions in 20%–45% of cases (Padwal 2019). Oscillometric devices have largely replaced manual approaches to measurement in many practice settings. Some oscillometric devices even allow for several automated readings, referred to as *automated office blood pressure devices* (Muntner 2019). A recent meta-analysis compared blood pressure measurement using AOBP versus other types of devices and found that AOBP measurement resulted in a 14.5 mm Hg lower mean difference (95% CI, 11.8–17.2 mm Hg, p<0.001) (Roerecke 2019). Automatic readings alleviate the clinician–patient interaction during measurement that may contribute to increasing a patient's blood pressure. Because SPRINT is one example of a recent major trial using AOBP measurements, clinicians should consider their site's approach to measuring blood pressures before implementing any study findings.

The ACC/AHA guidelines recommend taking an average of at least two readings 1–2 minutes apart. Many clinical trials, including SPRINT, used AOBP and an average of 3 readings in their protocols (Johnson 2018). An average of several readings alleviates the problems of a single reading. One study found that 35% of patients initially presented with a blood pressure of 140–159/90–99 mm Hg, but after 3 readings the average was <140/90 mm Hg (Handler 2012). These data highlight the importance of several measurements and the need for more automated devices that can efficiently and accurately take several readings each visit (Muntner 2019).

Every clinic should develop a standard for measuring blood pressure and calibrating validated devices. To ensure accuracy, patients should wait 3–5 minutes in a seated position with their back supported and their feet flat on the floor. Caffeine, tobacco, and exercise should be avoided within 30 minutes before assessment. Neither clinic personnel nor patients should speak during the measurements, and the monitor cuff sizes should be appropriate for the patient's arm circumference. The patient's arm being measured should be supported, and any clothing that covers the arm should be removed. Deviations from these procedures will lead to inaccurate measurements (Muntner 2019).

Out-of-Office Monitoring

Out-of-office blood pressure readings provide additional information that cannot be evaluated by clinic measurements and have a stronger association with cardiovascular outcomes compared with office-based measurements (Perloff 1983). Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are two options that can aid decision making by providing data from outside of clinic. Out-of-office readings help rule out white coat syndrome and can identify masked hypertension. *White-coat hypertension* is defined as having elevated blood pressure in the clinic setting and normal blood pressure outside of the clinic. Estimates suggest that as many of 15%–30% of patients new to hypertension treatment and up to 40% of patients on treatment experience this syndrome. A less-often discussed phenomenon with potentially more severe outcomes is *masked hypertension* or normal blood pressure in clinic and elevated blood pressure outside of clinic. Masked hypertension is estimated to also occur in 15%–30% in patients with undiagnosed hypertension. Although HBPMs and ABPMs have the potential to provide more data, uptake of these devices by the health care system in the United States has been limited by availability and reimbursement. Lack of reimbursement for ABPM especially makes it challenging for use in low-income individuals. Regardless of the limitations, the ACC/AHA Guidelines recommend out-of-office readings for all patients with blood pressure >130/80 mm Hg and <160/100 mm Hg to confirm the diagnosis of hypertension. Treatment should not be delayed in patients presenting with a blood pressure >160/100 mm Hg (Muntner 2019).

To fully use out-of-office readings, clinicians must be familiar with the measurements provided by ABPM and HBPM. Several categories have emerged for blood pressure monitoring outside the clinic, including daytime, nighttime, and 24-hour values. *Daytime blood pressure* is an average of readings during the awake period, whereas *nighttime blood pressure* is an average of values taken while the patient sleeps, as measured by an ABPM. The *24-hour average* of all values can also be used to assist in decision-making. The ACC/AHA guidelines provide corresponding out-of-office readings to clinic-based measurements (Table 2). It is important to note that these recommendations were based on outcome trials using a blood pressure of 140/90 mm Hg for diagnosis and initiation of therapy. Therefore, the specific corresponding values listed in the ACC/AHA Guidelines have not been studied in an RCT. Because these values are only obtainable through ABPM, the ability to capture 24-hour, daytime, and nighttime values requires tools not routinely available in most practice settings (Muntner 2019).

An ABPM is a device programmed to measure blood pressure at regular intervals over a 24-hour period. This strategy is the only approach to measurement that captures daytime, nighttime, and 24-hour values. Most guidelines recommend that 70% of the readings must be valid to use the data. A commonly used monitor setting is to check blood pressure every 15–60 minutes during the day and every 30 minutes while the patient sleeps. Studies have used a variety of protocols and to provide flexibility in measurement intervals. Set intervals must be made in conjunction with the patient's quality of life in mind to avoid excess measurements while also following best practices (Muntner 2019).

Table 2. Corresponding Clinic/Office and Out-of-Office Measurements

Blood pressure (mm Hg)				
Office	HBPM	ABPM Daytime	ABPM Nighttime	ABPM 24-Hour
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

HBPM = home blood pressure monitoring.

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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;7:e13-115.

Home Blood Pressure Monitoring and Wearable Technologies

An alternative to ABPM for patients and clinicians is HBPM. Compared with ABPM, HBPM is more accessible, better tolerated, and less costly. Patients using HBPMs should be advised to use validated devices. Wearable health technologies are widely available by cell phone manufacturers, and other wearable smart devices may serve to motivate patients to improve their health. However, clinicians should avoid treatment decision-making based on the use of devices that have not received FDA approval. Unlike ABPM devices, which typically undergo rigid protocols, the quality of HBPMs is highly variable (Muntner 2019). This includes wrist monitors, which, until recently, did not undergo validation protocols. Most wrist monitors remain unvalidated, but validated devices may be an option for patients with larger arms in conjunction with training on the proper technique. Validated devices are listed on the British and Irish Hypertension Society and Dabl Educational Trust websites.

Compared with office-based readings, HBPM is a better predictor of cardiovascular outcomes (Ward 2012). However, patient counseling on proper technique is required to obtain valid results, especially because the readings are user initiated. The procedures for the patient are the same as if they were measuring their blood pressure in clinic—feet flat on the floor, measurement arm supported, and no talking (Muntner

2019). Beyond technique, patients should record 2 readings on awakening before medication administration and 2 readings shortly before dinner. Each reading should be 1 minute apart (Muntner 2019; Whelton 2018). Guidelines continue to recommend ABPM over HBPM, but HBPM may offer a more practical approach for most patients and clinicians. However, not all patients, particularly those with cognitive decline, are appropriate for HBPM unless the patient has adequate social support.

Reimbursement for Out-of-Office Readings

Reimbursement has traditionally been the main barrier to using ABPM in primary and specialty care settings. Until recently, reimbursement was only offered for assessing white coat hypertension in a limited capacity. In July 2019, the Centers for Medicare and Medicaid Services (CMS) released an updated memo covering ABPM once yearly and lessening the criteria for reimbursement. The expanded coverage follows the ACC/AHA recommendations for white coat and masked hypertension, making most patients eligible for the service (Centers for Medicare and Medicaid Services 2019). Notably, HBPM was not included in the CMS memo, and it is not eligible for reimbursement per this guidance. Although reimbursement is now easier to obtain, the rate for reimbursement remains low (Muntner 2019).

CIRCADIAN RHYTHM OF BLOOD PRESSURE

Blood pressure follows a distinct circadian pattern, influenced by both external and internal factors. External factors may include substance use (e.g., alcohol, caffeine), physical activity, and sleep/wake patterns, whereas internal factors may include the RAAS and sympathetic nervous system. The circadian pattern for blood pressure over 24-hours is characterized by a decrease or "dip" in blood pressure during nighttime hours (usually 10%–20% compared with daytime) and a marked increase on awakening, termed the *morning surge*. Increased sympathetic activity, including increased renin activity and secretion of catecholamines and cortisol, leads to an elevation in morning blood pressure compared with nighttime pressure. A morning blood pressure surge—typically occurring between 6:00–10 a.m.—that is beyond the normal physiologic increase of 10%–20% confers an increased cardiovascular risk. A meta-analysis of seven studies evaluating the relationship between morning surge and cardiovascular risk found a higher risk of all-cause mortality, stroke, and cardiovascular events in those who experience a morning surge, although only all-cause mortality was statistically significant (Xie 2015). Conversely, it is normal for blood pressure to decrease or dip during sleep, when sympathetic activity regresses. For unknown reasons, some people lack this natural dip in nighttime blood pressure and are therefore called *nondippers*. Nondipping blood pressure is associated with autonomic dysfunction, renal dysfunction, glucose intolerance, and obstructive sleep apnea (Bowles 2018). An estimated 32%–46% of adults with hypertension are nondippers, leading to an increased 24-hour blood pressure (Salles 2016). Increased 24-hour blood pressure is associated with left ventricular hypertrophy, urinary albumin excretion, and cerebrovascular disease (Giles 2006).

Chronotherapy

Chronotherapy is generally defined as treatment of a disease that uses the body's natural patterns and cycles. In treatment of hypertension, chronotherapy is centered around the body's circadian rhythm of blood pressure, attempting to maximize efficacy and minimize adverse effects. This strategy takes into account the circadian rhythm of blood pressure plus the administration time-dependent pharmacokinetic factors of the medications. Most of the studies focus on patients with hypertension who have an abnormal circadian rhythm of blood pressure, such as the nondippers and those with exaggerated morning surges. Medications from almost every antihypertensive class have been examined, yielding different findings both between and within classes. The most studied are CCBs and ACEIs. A few studies have examined other classes such as alpha-adrenergic antagonists, β-adrenergic blockers, loop diuretics, and ARBs. The best data are available for bedtime dosing of medications that affect the RAAS. Studies comparing morning versus bedtime dosing of several ACEIs and an ARB found that evening administration resulted in a larger effect on nocturnal blood pressure and a significant reduction in the prevalence of nondipper status (Hermida 2007). In the MAPEC study, patients with essential hypertension without CVD who took at least one of their antihypertensives at bedtime had a significantly lower rate of cardiovascular morbidity and mortality compared with those who took all of their antihypertensives in the morning (10% vs. 22%, respectively). Of all study participants at baseline, >50% of were considered to be nondippers, and the number of nondippers in the bedtime dosing arm significantly decreased by the end of the study (Hermida 2010). A subsequent validation study in several primary care centers with a median 6.3-year follow-up showed an 8% absolute reduction in total CVD events with bedtime therapy compared with therapy on awakening (16% vs. 24%, respectively) (Hermida 2019).

Nondippers seem to benefit the most from chronotherapy. Identifying nondippers can be difficult given that the most effective method for doing so is through ABPM, which is not readily available or feasible in most settings. Nondipping is more likely to occur in those with secondary hypertension from medical conditions such as obstructive sleep apnea, CKD, and diabetes than those with essential hypertension (Hermida 2007). Groups with altered sleep/wake cycles, such as shift workers, may also benefit from modifying their antihypertensive administration times relative to their waking and bedtimes. It is important to consider how changing medication administration times may impact adherence and also to be mindful of dropping nighttime blood pressure too low, which can put patients at risk for falls if sudden changes

Patient Care Scenario

M.M. is a 58-year-old African American woman with a 20-year history of type 2 diabetes (A1C 8%, proteinuria 300 mg/day). She received a diagnosis of essential hypertension last month and started amlodipine 5 mg/day. At her follow-up appointment today at the family medicine clinic, she has 2 in-office readings by an automated cuff: 156/94 mm Hg, heart rate 80 beats/minute; and 150/96 mm Hg, heart rate 76 beats/minute. She takes amlodipine every morning and she reports some new recent ankle swelling that developed since starting the medication. She says that she limits salt in her diet and walks 5 days per week around her neighborhood. In this interdisciplinary clinic, you have been asked to develop a medication strategy for this patient's hypertension. Determine her blood pressure goal and design an appropriate medication regimen for her, including adverse effect monitoring.

ANSWER

The first step is to assess the patient's hypertension control and blood pressure goal. She currently has uncontrolled stage 2 hypertension with a goal blood pressure of <130/80 mm Hg. Lifestyle modifications are recommended for all patients with hypertension, so a discussion about her diet and exercise should always be a part of the clinic visit. Pharmacologic therapy is indicated based on the ACC/AHA guidelines stage 2 hypertension. She is already on a first-line recommended therapy that is proven to be effective in African-Americans for lowering blood pressure and reducing cardiovascular risk. She is experiencing a common adverse effect of the medication, pedal edema, which is a dose-dependent adverse effect. Therefore, increasing her dose of amlodipine to provide better blood pressure control is inappropriate. In addition, ACC/AHA guidelines recommend 2 medications in adults with stage 2 hypertension and an average blood pressure >20/10 mm Hg above their goal blood pressure. When a second medication is added, preference should be given to other first-line therapies and those with complimentary activity. Both ACEIs and ARBs are recommended for adults with proteinuria ≥300 mg/day to reduce proteinuria and risk of CKD. They can also reduce the adverse effect of pedal edema from CCBs, which the patient is currently experiencing. Thiazide diuretics are the other first-line recommended therapy, but will likely not help in reducing the CCB-induced pedal edema. In addition, the combination of CCB/ACEI results in a lower cardiovascular risk than combination HCTZ/ACEI for patients at high cardiovascular risk, such as those with diabetes. In the ACC/AHA guidelines, ACEIs are recommended first and ARBs are recommended in ACEI-intolerant patients. Lisinopril is a generic once-daily ACEI available through many community pharmacy discount programs. A usual starting dose is 10 mg/day. Adding this drug to her amlodipine 5 mg/day is an appropriate plan for today's visit.

The patient should be counseled on the known adverse effect of pedal edema with amlodipine and informed that starting lisinopril may help reduce the swelling. Monitoring for reduction and resolution of the ankle swelling is important. If the swelling becomes unacceptable to the patient, dose reduction to amlodipine 2.5 mg/day or discontinuing the amlodipine should be considered. Regarding lisinopril, the patient should be counseled on the risk of angioedema, how to monitor for this effect, and what to do if she experiences these symptoms. Blood should be drawn in clinic today to determine the patient's baseline serum creatinine and potassium before starting the new therapy, and monitoring 2–4 weeks after initiation of lisinopril is necessary to assess for an increase in serum creatinine and hyperkalemia.

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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13-115.
2. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417-28.
3. Ojji DB, Mayosi B, Francis V, et al. Comparison of dual therapies for lowering blood pressure in black Africans. N Engl J Med 2019;380:2429-39.
4. Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. Am J Med 2011;124:128-35.

in posture occur during the night. Overall, chronotherapy for hypertension is a potential strategy to improve 24-hour blood pressure and reverse nondipping in those with altered circadian rhythm blood pressure. Large trial data support a cardiovascular risk reduction when some of part of a patient's antihypertensive pharmacotherapy regimen is dosed in the evening or at bedtime.

TREATMENT OF ESSENTIAL HYPERTENSION

Hypertension treatment focuses on lowering blood pressure to reduce the risk of future cardiovascular morbidity and mortality through a combination of nonpharmacologic and pharmacologic therapies. Lifestyle modifications focusing mainly on diet and exercise are recommended for adults with elevated blood pressure and all stages of hypertension. Dietary sodium intake and alcohol consumption are restricted whereas dietary potassium intake is encouraged. The Dietary Approaches to Stop Hypertension (DASH) diet, which restricts sodium and emphasizes fresh produce, whole grain, and low-fat dairy products, can reduce blood pressure by 11.4/5.5 mm Hg (Appel 1997). Aerobic or resistance exercise for 90 to 150 minutes per week and weight loss for overweight or obese individuals complete these strategies, all of which

reduce SBP by 4–8 mm Hg (Whelton 2018). Nonadherence to these strategies is common in a real-world population and is affected by factors such as lack of family support, barriers to accessing food and exercise facilities, and even the lack of behavioral modification training among health care providers. Educating patients and their families, creating a patient support system, and identifying resources to help with financial constraints are possible strategies to improve adherence for any antihypertensive therapy. Initiation of antihypertensive medication is recommended for any person with clinical CVD and stage 1 hypertension. For adults without clinical CVD, initiation of medication therapy is based on cardiovascular risk and blood pressure values. Adults with high CVD risk should be started on antihypertensive medication when they reach stage 1 hypertension and those with low CVD risk can be managed with lifestyle modifications until they reach stage 2 hypertension (Table 3).

Table 3. ACC/AHA Blood Pressure Categories and Recommendations for Treatment

Blood Pressure Category	Nonpharmacologic Therapy	Pharmacologic Therapy
Normal BP; SBP < 120 mm Hg AND DBP < 80 mm Hg	Not recommended	Not recommended
Elevated BP; SBP 120-129 mm Hg AND DBP < 80 mm Hg	Recommended	Not recommended
Stage 1 Hypertension; SBP 130-139 mm Hg OR DBP 80-89 mm Hg	Recommended	Recommended if ASCVD or 10-year risk ≥ 10%
Stage 2 Hypertension; SBP ≥ 140 mm Hg OR DBP ≥ 90 mm Hg	Recommended	Recommended

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; ASCVD = atherosclerotic cardiovascular disease.

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: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;7:e13-115.

First-Line Agents

Medications proven to reduce clinical events are preferred, first-line agents. These include thiazide diuretics, ACEIs, ARBs, and CCBs. In the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), amlodipine and lisinopril had similar 6-year rates of combined fatal coronary heart disease or nonfatal MI compared with the thiazide-like diuretic, chlorthalidone (11.3%, 11.4%, and 11.5%, respectively) Furthermore, the development of heart failure was lowest in chlorthalidone-treated patients (7.7%) compared with those treated with lisinopril (8.7%) and amlodipine (10.2%) (ALLHAT 2002). A recent systematic review and meta-analysis of clinical trial data for many available classes of antihypertensives confirmed the cardiovascular benefit of all 3 first-line classes and reported ACEIs to be most effective in reducing the risk of MI and thiazide diuretics to be the most effective in reducing revascularization (Wei 2020). Importantly, each 10/5 mm Hg reduction in blood pressure was significantly associated with a reduced risk of cardiovascular death, stroke, and overall cardiovascular events (Wei 2020). This analysis illustrates the powerful benefit of blood pressure lowering, regardless of the agent used. When initiating a medication, consideration should be given to comorbid conditions and other patient-related variables for which specific classes of medications are indicated.

Thiazide and Thiazide-Like Diuretics

Thiazides and thiazide-like diuretics have a unique mechanism of action. In the short term, they lower blood pressure through natriuresis, which decreases plasma volume and cardiac output. With prolonged treatment (i.e., >1 month), blood pressure reduction remains while plasma volume returns to pre-thiazide levels. It is thought that reduced peripheral vascular resistance through direct vasodilation occurs with long-term use, making thiazides effective antihypertensives. This relationship may explain why thiazides can be effective with eGFR decreased to 30 mL/min/1.73m^2, and possibly even lower for thiazide-like diuretics. Whereas HCTZ and chlorothiazide are true thiazide diuretics, chlorthalidone and indapamide are thiazide-like diuretics. Most positive studies used thiazide-like diuretics and found them to be at least as effective as other medications for reducing renal and cardiovascular outcomes and more effective at preventing heart failure (Wright 2009). Chlorthalidone and indapamide have long durations of action, providing consistent, durable blood pressure reduction over a 24-hour period. The most commonly used thiazide, HCTZ, has a <24-hour duration of action and is less effective than thiazide-like diuretics at reducing blood pressure (Roush 2015). Chlorthalidone is preferred because it has a long duration of action and proven cardiovascular benefit, as documented in ALLHAT. However, the usual starting dose of 12.5 mg requires halving the lowest

dosage form manufactured, which can lead to inconsistent/inaccurate dosing. A strategy of 25 mg taken every other day takes advantage of the drug's long duration of action and eliminates pill cutting. Thiazides may be particularly effective in those with salt-sensitive hypertension, such as African Americans, obese individuals, and older adults.

All adverse effects of thiazides are dose- and time-dependent. Diuresis and vasodilation may lead to dehydration and orthostatic hypotension, especially when paired with other diuretics. It is important to use caution with thiazides in older adults, who may be more prone to these adverse effects. Electrolyte imbalances include hypokalemia, hyponatremia, hypomagnesemia, and hypercalcemia. Thiazides can also lead to hyperuricemia and carry a high risk of gout compared with other common antihypertensives, with a multivariate relative risk of 2.36 (2.21–2.52) (Choi 2012). Laboratory monitoring at initiation and at dose increases is recommended.

ACEIs and ARBs

Both ACEIs and ARBs are recommended as first-line agents and have compelling indications for patients with heart failure, CKD, and overt albuminuria (≥300 mg/day or ≥300 mg/g creatinine). These medications block part of the RAAS, which results in decreased blood pressure by vasodilation, decreased epinephrine, and blocked sodium and water reabsorption. Both ACEIs and ARBs have a nonlinear dose-response curve, such that increasing the dose will extend the drug's duration of action rather than its potency. First ACEIs are recommended, with ARBs being prioritized in ACEI-intolerant patients. This approach was historically based on the presumed lower cost of ACEIs, which is not as applicable today given that most ARBs are available as generic formulations. Considering the available evidence to date, little, if any, difference exists between the efficacy of ACEIs and ARBs, but ARBs are better tolerated (Messerli 2018).

High-sodium diets can diminish renin levels and lead to a blunted effect from medications that affect the RAAS. Salt-sensitivity, genetics, and other factors suggest that African American patients may be more likely to have low-renin hypertension, for which RAAS inhibitors are less effective. Indeed, studies show that African American patients have a reduced blood pressure response to ACEIs and ARBs as monotherapy compared with white patients, who may have renin-driven hypertension (Helmer 2018). However, ACEIs and ARBs remain useful because they are protective in heart failure with reduced ejection fraction and among those with proteinuria.

Although generally well tolerated, dry cough can develop in up to 20% patients taking ACEIs (Taler 2018). Cough is much less common with ARBs. Angioedema is a rare and serious complication that is 2–4 times more common among African American patients compared with white patients (3.9 vs. 0.8 cases per 1000 person-years) (Taler 2018). If angioedema occurs with an ACEI, an ARB can be considered, with allowance for a 6-week washout period. By stimulating efferent arteriolar vasodilation, ACEIs and ARBs decrease intraglomerular pressure, which results in reduced eGFR (2% to 25% from baseline) in the first 2–4 weeks of initiating or increasing the dose of an ACEI or ARB. Blocking the RAAS, and specifically aldosterone, leads to impaired renal potassium excretion. Hyperkalemia is more common in patients with renal dysfunction and those taking several medications that can lead to potassium retention, which may be common for patients with type 2 diabetes, CKD, and heart failure. The VA NEPHRON-D study examined combination losartan and lisinopril versus losartan alone for reducing progression of kidney disease in people with diabetic nephropathy. The trial was stopped early due to safety concerns of increased hyperkalemia (6.3 vs. 2.6 events per 100 person-years with monotherapy) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years with monotherapy) in the combination group (Fried 2013). For these reasons, ACEIs and ARBs should generally not be used together as combination therapy (Whelton 2018). Laboratory testing to assess serum electrolytes and renal function is recommended within 2–4 weeks of starting an ACEI or ARB. In pregnant patients, ACEIs and ARBs are contraindicated because of an associated increased risk of fetal complications. Women of child-bearing age should have a negative pregnancy test before starting therapy.

Calcium Channel Blockers

Calcium channel blockers work on the L-type calcium channel, which normally activates excitatory skeletal, smooth, and cardiac muscle cells. Dihydropyridines (DHPs) are more potent peripheral vasodilators and reduce systemic vascular resistance. Nondihydropyridines (NDHPs) are more cardioselective and reduce cardiac output by decreasing heart rate and contractility. Despite their indications, the combination of DHPs and NDHPs in the same patient must be avoided because of the vasodilatory-mediated hypoperfusion and hypotension that may precipitate rebound tachycardia. For essential hypertension, the long-acting DHPs are well tolerated and most commonly prescribed, and dihydropyridine was the formulation of CCB used in ALLHAT. As add-on therapy in patients with stable ischemic heart disease and angina CCBs are recommended. In the ACCOMPLISH trial, the combination amlodipine/benazepril resulted in a 2.2% absolute risk reduction in the composite cardiovascular end point compared with the combination HCTZ/benazepril in patients at high risk of CVD, supporting the role of DHPs as first-line therapy (Jamerson 2008). The NDHPs are effective in establishing heart rate control in patients with atrial fibrillation. Because CCBs have a linear dose-response curve, initial doses should be low, and then doses are progressively increased based on the individual's response and tolerance to the drug.

All CCBs are associated with dose-related pedal edema, which have a reported incidence of 10%–30% in studies and can lead to drug discontinuation (Brown 2000; Makani 2011a).

The pedal edema is not associated with salt and water retention, making diuretics a futile antidote. Instead, the edema develops from capillary leak into the interstitium and is multifactorial. Strategies to prevent or reduce pedal edema include nighttime drug administration, dose reduction, and adding complimentary agents such as ACEIs and ARBs. Blockade of the RAAS can decrease postcapillary resistance and intracapillary pressure. In a meta-analysis, the addition of an ACEI or ARB to a CCB lead to a 38% relative risk reduction in the incidence of pedal edema and a 62% lower risk of withdrawal because of pedal edema compared with CCB monotherapy (Makani 2011b). Reflex tachycardia can be seen with short-acting DHPs as a result of their potent vasodilation. The negative inotropic effects of NDHPs make them especially concerning in patients with heart failure and reduced ejection fraction. It is generally best to avoid combination of NDHPs and β-blockers because of their additive risk of bradycardia and heart block. Important drug–drug interactions exist for both types of CCBs. The NDHPs (diltiazem and verapamil) are CYP3A4 substrates and moderate CYP3A4 inhibitors. The DHPs are CYP3A4 substrates and can be affected by major inhibitors (e.g., systemic azoles, clarithromycin) and inducers (e.g., carbamazepine, rifampin, phenytoin). Notably, doses of simvastatin cannot exceed 20 mg/day when given with amlodipine.

Second-Line Agents

Whereas first-line agents are regarded as beneficial for most patients with essential hypertension, second-line agents are reasonable for specific comorbidities. β-Blockers, once considered a first-line class, lack evidence to support their initial use in essential hypertension, unless the patient has ischemic heart disease, has heart failure with reduced left ventricular function, or requires a rate control agent for atrial arrhythmias. If stopped abruptly, β-blockers can exacerbate ischemic symptoms because of rebound sympathetic activity and discontinuation may lead to rebound hypertension and possibly heart rate elevations. Loop diuretics are the preferred diuretic in patients with symptomatic heart failure and are effective at reducing blood pressure from volume overload in patients with moderate to severe CKD. Potassium-sparing diuretics are minimally effective as monotherapy. Mineralocorticoid receptor antagonists (MRAs) are effective add-on therapy for resistant hypertension and are the drug of choice for primary aldosteronism, a type of secondary hypertension. Also, MRAs are recommended as add-on therapy for heart failure patients with reduced ejection fraction. All diuretics can cause electrolyte depletion and should be used with caution in acute kidney injury. Direct vasodilators such as hydralazine and minoxidil are associated with sodium and water retention and reflex tachycardia. Minoxidil should generally be given with a loop diuretic, and, because of the risk of reflex tachycardia, may require a concomitant β-blocker. α-1 Blockers may be useful in patients with benign prostatic hyperplasia, but they can also contribute to orthostatic symptoms or orthostatic hypotension, particularly in older adults. Central α-2 agonists have significant adverse effects for the central nervous system because of the reduction in sympathetic outflow (i.e., decreased norepinephrine release) and are generally considered a last-line agent for essential hypertension. To avoid rebound hypertension, clonidine should be tapered before stopping therapy, usually over 1–2 weeks.

Combination and Add-On Therapy

Most patients with hypertension need at least 2 medications to reach their target blood pressure. It is prudent to initiate 1 medication first, which is the preferred approach for patients with stage 1 hypertension and for older adults, regardless of blood pressure, because of their potential sensitivity to medicines. Those with stage 2 hypertension and an average blood pressure >20/10 mm Hg above their target blood pressure may be started on 2 medications simultaneously. First-line therapies should be prioritized as well as medications with different mechanisms of action that may have complimentary activity. Several combinations are particularly effective. Not only does the combination of ACEI/CCB reduce CCB-induced pedal edema, but it can also reduce cardiovascular events and decrease CKD progression compared with the combination ACEI/thiazide (Jamerson 2008; Bakris 2010). It is rational to use drugs that block the RAAS with diuretics as an approach targeting the RAAS stimulation that is a reaction to volume depletion while also counterbalancing electrolyte adverse effects. The ACEIs, ARBs, and/or direct renin inhibitors are potentially harmful when used together, and their combination therapy should be avoided. Many fixed-dose combinations are available, but not always at the target dose needed for optimal blood pressure lowering. It is reasonable to add a second agent before titrating the initial medication to its maximal dose. When adding a third agent and beyond, initial combination therapies should be optimized first. If the patient's financial concerns or lack of insurance coverage is an issue, it is important to note that they can take advantage of specific pharmacy discount programs and to prioritize generic formulations.

Special Populations and Comorbid Conditions

Race

In the United States, hypertension prevalence and control varies by race according to available resources and health care access. Non-Hispanic African Americans have the highest incidence of hypertension and lowest blood pressure control rates, with 54.1 deaths/100,000 deaths compared with whites (23.0 deaths/100,000 deaths) and Hispanics (21.8 deaths/100,000 deaths). The increased rates of high blood pressure in African Americans are thought to be a result of limited access to health care and nutritious foods as well as financial considerations affecting basic living necessities. These data highlight the disparities related to hypertension

for non-Hispanic African Americans in the U.S. health care system (Whelton 2018).

The Barbershop study was a landmark trial investigating a new type of intervention in African American patrons at barbershops. The barbershops in the study were randomized to either have a pharmacist on site for hypertension management or to serve as a control group. Participants in the control group were encouraged by the barbers to follow-up with their primary care providers. Pharmacists interviewed and evaluated patients at the barbershops for the active arm. Under a collaborative practice agreement, they initiated and modified drug regimens with point-of-care testing for laboratory monitoring as needed. The primary outcome for the study was change in SBP at 6 months. Results shows –27 mm Hg SBP change in the active arm and –9.3 mm Hg in the control group. The difference in SBP between the groups was 21.6 mm Hg (95% CI, 14.7–28.4; p<0.001) (Victor 2018). These findings highlighted new strategies to improve blood pressure control and reduce health care disparities by expanding access to care, positioning trusted health care professionals in everyday settings, and reimagining care settings.

The ACC/AHA Guidelines recommend that non-Hispanic African American adults without heart failure or CKD, including those with diabetes, receive a CCB or thiazide-type diuretic as monotherapy or the initial medication in a multi-drug regimen. Thiazide-type diuretics and CCBs are more effective than ACEI, ARB and BB therapy at lowering blood pressure and preventing cardiovascular events. However, most patients will require multi-drug regimens, including an ACEI or ARB in combination with either a thiazide or CCB. These recommendations largely arose from analyses of ALLHAT; however, new data from the Barbershop and CREOLE Trial have become available since publication of the ACC/AHA Guidelines (Ojji 2019; Victor 2018). The Barbershop protocol started patients on amlodipine and an ARB followed by a thiazide diuretic and aldosterone antagonist as needed. The CREOLE trial studied patients from sub-Saharan African. Participants were randomized to receive amlodipine plus HCTZ, amlodipine plus perindopril, or perindopril plus HCTZ. Both arms receiving amlodipine experienced greater reductions in blood pressure compared with perindopril plus HCTZ (Ojji 2019). These new data strengthen the recommendations made by ACC/AHA to use CCBs, and possibly thiazide diuretics, as first-line agents in African American patients without heart failure or CKD.

Stable Ischemic CVD

A blood pressure target and threshold of 130/80 mm Hg is appropriate in patients with stable ischemic heart disease. These patients should receive guideline-directed therapy for their underlying CVD. For patients who have experienced an MI, β-blockers are recommended as well as ACEI or ARB therapy for additional blood pressure lowering. β-Blockers are most beneficial within 3 years of a cardiac event, and may be continued long term. Thiazides, CCBs, and aldosterone antagonists can all be considered for add-on therapy (Whelton 2018).

Diabetes

Hypertension is an important and modifiable risk factor in patients with diabetes that must be adequately treated to lower CVD risk, and it is more common in patients with versus without type 2 diabetes. The combination of hypertension and diabetes increases the risk of developing heart failure, pulmonary artery disease, coronary heart disease, and stroke and the risk of cardiovascular death (Whelton 2018). Evidence for treatment targets in patients with diabetes is limited and low in quality. As described in detail earlier in this chapter, the ACCORD trial was randomized and controlled but underpowered and confounded by the 2 × 2 factorial design and lower-than-expected event rates. Meta-analysis data support an ideal blood pressure of about 133/76 mm Hg to reduce both macrovascular and microvascular complications, but these results do not clearly establish a singular blood pressure goal (Xie 2016). A lack of definitive RCT data on blood pressure goals in patients with type 2 diabetes continues to lead to varying recommendations and practice.

The ACC/AHA guidelines recommend a blood pressure target of 130/80 mm Hg in people with diabetes. These recommendations also acknowledge most patients with diabetes are at elevated risk and will therefore benefit from a treatment threshold of 130/80 mm Hg for medication therapy. Risk assessment using the ASCVD risk estimator was also recommended to further guide treatment decisions (Whelton 2018).

The American Diabetes Association (ADA) standards of care provide an alternative approach to blood pressure targets and thresholds. The ADA Standards acknowledges the post hoc analyses of the ACCORD and SPRINT Trials, without endorsing their findings. Instead the ADA recommends a blood pressure target and threshold of 140/90 mm Hg in most patients unless they have a history of clinical ASCVD or a 10-year ASCVD risk of 15% or higher. Despite a different approach, the ADA recommendations received ACC endorsement. Both organizations are aligned on the more intensive treatment for high-risk individuals (American Diabetes Association 2020). Regardless of the guideline used in practice, clinicians must use a patient-centered approach to goal setting in people with diabetes ((American Diabetes Association 2020).

Unlike the varying goals for blood pressure across organizations and guidelines, first-line pharmacologic treatment for people with diabetes is now consistent. First-line treatment includes CCBs, ACEIs/ARBs, and thiazide diuretics because most agents among these drug classes have proven cardiovascular benefits in diabetes. Most patients with diabetes will require several medications to reach their treatment goals; therefore, a combination of the first-line agents is recommended in most cases, including ACEIs or ARBs. The ACEI and ARB drug classes are preferred when albuminuria

is present, although not concomitantly (American Diabetes Association 2020; Whelton 2018). Both ACEIs and ARBs reduce the progression of albuminuria and end-stage renal disease for patients with albuminuria (Brenner 2001; Lewis 1993). Primary prevention of albuminuria also occurs with ACEI therapy, but studies have failed to show an improvement in CVD, a decrease in eGFR decline, and slower progression to end-stage renal disease compared with thiazide diuretics and CCBs in non-selected patients with diabetes (Bangalore 2016).

Chronic Kidney Disease

Hypertension is the second leading cause of CKD in the United States, and unmanaged hypertension accelerates CKD progression. The Modification of Diet in Renal Disease (MDRD) Study and the African American Study of Kidney Disease and Hypertension trial provided some of the first evidence that lowering blood pressure decreases mortality in patients with CKD, with an unadjusted relative risk of death of 0.87 based on extended follow-up data from both studies (Ku 2017). What is less clear, however, is the optimal target blood pressure for this particular group. Pre-SPRINT trials used variable cutoffs for the intensive-treatment groups, making it difficult to show a consistent benefit in patients with CKD. Not until after SPRINT was a blood pressure goal of <130/80 mm Hg recommended based on an all-comers design for patients with CKD in practice guidelines. A meta-analysis of these trials found a 0.6% absolute risk reduction for all-cause mortality in the more treatment-intensive groups (average SBP 132 mm Hg) than the less-intensive groups (average SBP 140 mm Hg) and found that the number needed to treat to prevent one death was 167 patients (Malhotra 2017). Patients with CKD and albuminuria benefit the most from intensive blood pressure control. In the MDRD study, a more intense blood pressure control (goal 125/75 mm Hg) resulted in a slower eGFR decline compared with a less intense blood pressure control (goal 140/90 mm Hg) in patients with albuminuria >1 g/day (–4 mL/minutes/year vs. –7.5 mL/minutes/year, respectively) (Peterson 1995). Patients with end-stage renal disease and history of kidney transplant should be considered separately.

Both ACEIs and ARBs provide renal protection for patients with CKD independent of their effect on lowering blood pressure and are therefore the preferred first-line therapies. Indeed, ACEIs or ARBs and diuretics were the most common medications for patients with CKD in SPRINT. Although patients with CKD receive great benefit from ACEIs and ARBs, they are also more susceptible to their adverse effects. Attention must be paid to decreases in eGFR together with the higher risk of hyperkalemia, which makes careful monitoring critical for this population. Both thiazide and loop diuretics can be effective in patients with CKD, particularly when volume overload is present.

Older Adults

Blood pressure increases linearly for almost 60 years, when a new pattern commonly emerges (Duprez 2008). Older adults age ≥60 years often present with low or normal DBP and elevated SBP, known as *isolated systolic hypertension* (ISH). Many definitions exist for ISH, and early studies used an SBP >160 mm Hg with DBP <95 or <90 mm Hg. The pathophysiologic mechanism behind ISH is attributed to increased atherosclerosis and calcification of arteries, resulting in decreased arterial compliance. Comorbid conditions such as diabetes, CKD, hyperlipidemia, and smoking may worsen arterial stiffness, thus exacerbating the difference in SBP and DBP (Bavishi 2016). Several studies have shown that treating ISH decreases cardiovascular morbidity and mortality (The SPRINT Research Group 2015; Beckett 2008). However, older adults also experience higher rates of adverse effects, such as syncope, orthostatic hypotension, and falls. Therefore, individualized care and careful consideration are warranted when managing hypertension in older patients (Whelton 2018).

Perhaps the most noticeable changes in the ACC/AHA guidelines was an SBP treatment goal and threshold for noninstitutionalized patients age ≥65 years (Whelton 2018). The recommendation for class I (strong) level A (high-quality evidence) was largely based on the SPRINT and HYVET Trials, as previously discussed. The average participant ages in the HYVET and SPRINT Trials were about 84 and 68 years, respectively. Both trials were stopped early because of substantial cardiovascular benefit in the intensive treatment arms. In addition, the intensive-treatment arms experienced similar or fewer adverse effects compared with the less-intensive arms. One important caveat was the exclusion of nursing home patients; these data do not apply to institutionalized individuals (The SPRINT Research Group 2015; Beckett 2008). Concern for overtreatment led ACP and AAFP to not endorse this recommendation, leading to a variety of blood pressure targets currently used by primary care clinicians (Qaseem 2017). However, the data support an SBP target of 130 mm Hg in ambulatory community-dwelling older adults. Clinical judgement must still be used in the decision-making process when setting blood pressure targets in older adults. As performed both in SPRINT and HYVET, screening patients for orthostatic decreases in blood pressure may help select those most likely to tolerate blood pressure lowering.

Caution is needed when intensifying antihypertensive therapy in older adults. Risk calculation is appropriate; however, most patients age >65 years will exceed a 10% risk and thus are indicated for therapy. Initiation of 1 agent is preferred in most cases, and this approach is consistent with the SPRINT protocol, which recommended single-drug therapy to start in patients age ≥75 years (The SPRINT Research Group 2015). In general, the same first-line medications are recommended for older adults, including thiazides, CCBs, and ACEIs/ARBs. For patients with severe ISH, a DHP CCB, or thiazide-diuretic

should be considered first unless other compelling indications exist. The RAAS is also thought to contribute to ISH and ACEIs or ARBs are also potential options (Bavishi 2016). Regardless of the treatment selection, close follow-up and laboratory monitoring are important to identify adverse effects of therapy and to prevent clinical inertia.

Pregnancy

Hypertension classification during pregnancy is divided into 4 categories according to the American College of Obstetrics Guidelines (ACOG): preeclampsia/eclampsia; chronic hypertension, of any cause; chronic hypertension with superimposed preeclampsia; and gestational hypertension (ACOG 2013). *Preeclampsia* is new-onset hypertension after 20 weeks of gestation in the presence of proteinuria, which can be harmful to both the mother and the fetus. *Gestational hypertension* is new-onset hypertension that occurs after 20 weeks of gestation. Severe hypertension requires urgent treatment to prevent end-organ damage, such as stroke and heart failure, and damage to the fetus. Severe hypertension can occur with or without preeclampsia (Whelton 2018). Because acute changes in blood pressure impact both maternal and infant outcomes, screening should occur at every prenatal visit.

During the first trimester, blood pressure generally decreases and then it gradually increases throughout pregnancy. Women with hypertension who are pregnant or planning for pregnancy should be converted to treatments that are safe and effective during pregnancy. Specifically, ACEI, ARBs, and direct renin inhibitors are contraindicated. Safe alternatives include methyldopa, nifedipine, and/or labetalol. The goal of hypertension management in pregnancy is to prevent severe hypertension and to allow additional time for fetal maturation before delivery. The ACOG recommendations differ from the ACC/AHA guidance, and both acknowledge the low quality of evidence associated with their guidance. Until a threshold of 160/105 mm Hg is reached, ACOG does not recommend blood pressure treatment. Once treatment begins, blood pressure should not decrease <120/80 mm Hg to avoid reduced feto-placental blood flow (ACOG 2013).

Team-Based Care and the Role of the Pharmacist

Team-based care received a class 1A recommendation in the ACC/AHA guidelines. *Team* was defined as a patient, a primary care provider, and other health care professionals, including pharmacists. A recent meta-analysis showed collaborative care models with pharmacists reduce SBP by –7.6 mm Hg (95% CI, –9.0 to –6.3) and DBP by –3.9 mm Hg (95% CI –5.1 to –2.8) compared with controls (Santschi 2014). Several RCTs have also showed that pharmacists improve blood pressure control using telemedicine or by community-based intervention (Victor 2018; Margolis 2013). Overall the data support incorporating pharmacists to improve patient outcomes for patients with hypertension.

CONCLUSION

The publication of the 2017 ACC/AHA guidelines was a practice-changing document, well overdue. For the first time since JNC7, a comprehensive guideline is available for the management of hypertension. These recommendations provided much-needed updates with new blood pressure targets and thresholds. Additional emphasis was placed on blood pressure measurement (both in and out of office) while acknowledging the use of new technology in ABPM and HBPM practices. Such

Practice Points

The clinical pharmacist is a cornerstone member of team-based care for patients with essential hypertension. New data continue to emerge regarding how to assess, classify, and manage essential hypertension. As a result, guidelines/recommendations, approaches to blood pressure measurement, indications for existing medications in special populations, and safety issues continue to evolve:

- **The role of hypertension guideline development has transitioned from the JNC to ACC and AHA, which released comprehensive guidelines in 2017. Major changes include lowering the definition of high blood pressure, emphasis on measurement techniques, using a risk-based approach to management, and tighter blood pressure goals based on the pivotal SPRINT study.**
- **The various guidelines differ in their recommendations in treating hypertension, and the clinical pharmacist must be aware of these important differences.**
- **Assessment of blood pressure for treatment decision-making should rely on standard techniques, several readings, and use readings from several settings. Automated office blood pressure devices increase measurement accuracy when used correctly. Out-of-office blood pressure readings are strongly associated with cardiovascular outcomes and should carry as much weight as in office readings when making patient care decisions.**
- **First-line recommended medications for hypertension treatment include thiazide diuretics, ACEIs, ARBs, and CCBs because of their proven reduction in cardiovascular events. When more than 1 agent is required, medications with different mechanisms of action that may have complimentary activity should be prioritized.**
- **Initial therapy in African American patients should be a CCB or thiazide diuretic because these agents are the most effective at lowering blood pressure and preventing cardiovascular events in this population.**
- **Both ACEIs and ARBs can reduce progression of proteinuria and of end-stage renal disease in patients with type 2 diabetes or CKD. These agents should not be used together because of an increased risk of hyperkalemia and acute kidney injury.**
- **A SBP goal of 130 mm Hg is recommended in ambulatory, community-dwelling older adults. It is essential to use caution when intensifying medications for older adults because they are more prone to adverse effects such as orthostatic symptoms and syncope.**
- **Team-based care improves patient outcomes, and the clinical pharmacist is an essential member of the team.**

changes are consistent with the latest data in hypertension management; however, gaps in RCT evidence remain.

Whereas many organizations have adopted the ACC/AHA guidelines, several major medical groups have not endorsed the guidelines, leading to inconsistencies in hypertension management with public health implications at a time when hypertension and cardiovascular-related mortality are increasing. A projection of the outcomes associated with implementing ACC/AHA guidelines found these recommendations would result in about 340,000 (95% CI, 241,000–349,000; p<0.001) fewer cardiovascular events and 156,000 (95% CI, 77,000–235,000; p<0.001) fewer deaths annually in the United States. These positive clinical outcomes projected with ACC/AHA Guidelines also come with an expected increase in 62,000 (95% CI, 37,000–86,000) additional hypotensive events and 79,000 (95% CI, 25,000–134,000 acute kidney injury events (Bundy 2018). The current conclusion is that the cardiovascular benefits of improved management far exceed the risks of adverse events. In addition, pharmacist can be key members of the team to implement best practices in primary care and specialty clinics to improve hypertension outcomes.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

J.T., a 50-year-old African American man with a 20 pack-year smoking history, was recently diagnosed with hypertension. His in-office blood pressure today is 138/84 mm Hg and his estimated 10-year ASCVD risk is 12%.

1. For which one of the following blood pressure thresholds is it best to recommend initiation of pharmacotherapy for J.T.?

   A. 120/80 mm Hg
   B. 130/80 mm Hg
   C. 140/90 mm Hg
   D. 150/80 mm Hg

2. Which one of the following is best to recommend as initial blood pressure-lowering therapy for J.T.?

   A. Smoking cessation
   B. Lisinopril
   C. Chlorthalidone
   D. Indapamide and amlodipine

Questions 3 and 4 pertain to the following case.

T.R. is a 50-year-old man with hypertension and CKD stage 3 (eGFR 44 mL/min/1.73m^2). He was started on losartan 50 mg orally daily 3 months ago and is coming to clinic for a follow-up appointment. T.R.'s pertinent laboratory values from today are Na 138 mEq/L, K 4.4 mEq/L, BUN 12 mg/dL, SCr 1.9 mg/dL, eGFR 40 mL/min/1.73m^2, urine albumin-creatinine ratio 400 mg/g (reference range 0–30 mg/g).

3. Based upon findings from SPRINT, which one of the following would T.R. be most likely to experience with intensive blood pressure lowering?

   A. Lower risk for acute kidney injury
   B. Lower risk for progression to end stage renal disease
   C. Lower risk of electrolyte abnormalities
   D. Lower risk for all-cause death

4. T.R. reports that his home blood pressure readings over the past 2 weeks have been 152–168/82–90 mm Hg and he is adherent with his losartan. His physician wants to adjust his antihypertensive regimen. Which one of the following is the best to recommend for T.R.?

   A. Increase losartan.
   B. Add aliskiren.
   C. Switch losartan to amlodipine.
   D. Add chlorthalidone.

5. A woman with a medical history that includes hypertension, diabetes, and CKD stage 2 comes to clinic seeking better control of her blood pressure. The patient has reduced her sodium intake and started exercising 2–3 times a week. She reports taking her medications in the morning as prescribed: these include HCTZ 25 mg daily, valsartan 160 mg twice daily, and atenolol 100 mg daily. The patient undergoes ambulatory blood pressure monitoring (ABPM) using an automated cuff for further evaluation, showing an average daytime blood pressure of 146/88 mm Hg and an average nighttime blood pressure of 148/84 mm Hg. Her blood pressure in clinic today is 144/86 mm Hg, heart rate of 64 beats/minute with an automated cuff. On the basis of her ABPM data, which one of the following best assesses this patient's blood pressure?

   A. Masked hypertension
   B. Non-dipping blood pressure
   C. Dipping blood pressure
   D. White-coat hypertension

Questions 6–8 pertain to the following case.

W.B. is a 70-year-old African American man with a medical history of atrial fibrillation, dyslipidemia, hypertension, and benign prostatic hyperplasia. In clinic he reports higher than normal home blood pressure. W.B.'s blood pressure log in the electronic health record shows a range from 138–148/66–80 mm Hg and a heart rate of 55–65 beats/minute. His home drugs include metoprolol 75 mg twice daily, atorvastatin 40 mg daily, warfarin 3 mg daily, and tamsulosin 0.4 mg daily. Today in clinic W.B.'s blood pressure is 146/70 mm Hg using an automated cuff and heart rate is 62 beats/minute.

6. Which one of the following is best to recommend for W.B.'s hypertension?

   A. Add amlodipine 2.5 mg daily.
   B. Increase metoprolol to 100 mg twice daily.
   C. Add diltiazem 120 mg daily.
   D. Switch tamsulosin to doxazosin 4 mg at night.

7. After selecting a new antihypertensive for W.B., his provider is concerned about the associated fall risk potential with hypotension. Which one of the following is best to recommend for W.B. to use in assessing his blood pressure out of the office?

   A. Ambulatory blood pressure monitor
   B. Pharmacy kiosk
   C. Wrist monitor
   D. Generic home monitor

8. W.B. returns to clinic reporting that he could not wear his ABPM all day because it was uncomfortable. He wishes to buy a monitor to check his blood pressure at home.

Which one of the following monitors is best to recommend for W.B.?

A. A&D UA-705 Blood Pressure Monitor
B. SGreater Goods Blood Pressure Monitor
C. IProven Blood Pressure Monitor
D. Paramed Blood Pressure Monitor

9. A primary care practice would like to improve patient blood pressure metrics and has recruited the pharmacist to develop a best practices protocol focusing on blood pressure measurement. Which one of the following procedures is best to recommend to improve the accuracy of blood pressure measurement?

A. Complete the medication reconciliation during the measurement.
B. Take an average of 2 or 3 measurements using an automated device.
C. Use a clinician certified in auscultatory measurement to check the blood pressure.
D. Ensure each patient has blood pressure measured within 2 minutes of the start of their appointment.

Questions 10 and 11 pertain to the following case.

F.S. is a 58-year-old African American man with a medical history of hypertension and type 2 diabetes mellitus (diagnosed more than 10 years ago). His home drugs include insulin glargine 30 units daily and metformin 1000 mg twice daily. F.S.'s A1C today is 5.8% and three blood pressure values from clinic (measured with an AOBP without clinicians in the room) are 146/92 mm Hg, 138/82 mm Hg, and 136/84 mm Hg.

10. Based on the ACCORD and SPRINT Trial and the patient presentation, which one of the following is the most likely outcome if F.S. is treated to a SBP less than 120 mm Hg compared with a SBP less than 140 mm Hg?

A. Because his A1C is below 6%, he is unlikely to benefit from intensive blood pressure treatment.
B. Because he has diabetes, he is unlikely to benefit from intensive blood pressure treatment.
C. He will be more likely to develop a stroke if treated to a SBP less than 120 mm Hg.
D. He will be less likely to experience adverse effects because he has intensively managed blood glucose.

11. Two months later, F.S. calls into the pharmacist-run telehealth clinic. He now takes glargine 20 units daily, metformin 1000 mg twice daily, and losartan 50 mg daily. At home F.S. is using a validated home blood pressure monitor and reports values of 132–148/86–96 mm Hg throughout the day. The average of these blood pressures is 144/92 mm Hg. Which one of the following is best to recommend for F.S.'s Stage 2 blood pressure?

A. Come into the clinic to verify home blood pressure.
B. Increase losartan to 100 mg daily.
C. Continue losartan and add amlodipine 5 mg daily.
D. Stop losartan and start amlodipine 5 mg daily.

Questions 12 and 13 pertain to the following case.

K.J. is a 78-year-old woman with a medical history of hypertension, NSTEMI (3 years ago), and dyslipidemia. Her last ECHO reported an ejection fraction of 50%. K.J. lives at home independently and manages her living situation well. Today she reports that she is able to walk 30 minutes every day without stopping and she does not have any chest pain or shortness of breath. K.J.'s home drugs include atorvastatin 80 mg, ASA 81 mg, lisinopril/HCTZ 20/12.5 mg (2 tabs daily), and metoprolol 50 mg twice daily. Her average blood pressure and heart rate, using an oscillometric device in clinic today, are 144/78 mm Hg and 62 beats/minute.

12. Given her health history, which one of the following is the best SBP goal to recommend for K.J.?

A. Less than 130 mm Hg
B. Less than 140 mm Hg
C. Less than 145 mm Hg
D. Less than 150 mm Hg

13. Based on K.J.'s blood pressure, she presents with isolated systolic hypertension. Which one of the following is best to recommend for improving K.J.'s blood pressure?

A. Increase metoprolol.
B. Start clonidine.
C. Start hydralazine.
D. Start amlodipine.

Questions 14 and 15 pertain to the following case.

T.Y. is a 34-year-old woman receiving care at a family medicine clinic. She has a medical history of well managed blood pressure. Today T.Y. arrives to clinic for routine follow-up after becoming pregnant 1 month ago. After multiple readings, her average manual auscultatory blood pressure is 162/95 mm Hg and her urine dipstick is (-) for protein. T.Y. denies any chest pain, headaches, or shortness of breath.

14. Which one of the following best classifies T.Y.'s presentation?

A. Chronic hypertension
B. Gestational hypertension
C. Preeclampsia
D. Chronic hypertension with superimposed preeclampsia

15. Which one of the following is best to recommend for T.Y.'s high blood pressure?

A. Start with a monitoring plan.
B. Start HCTZ 25 mg once daily.
C. Start nifedipine ER 30 mg once daily.
D. Start Carvedilol 6.25 mg twice daily.