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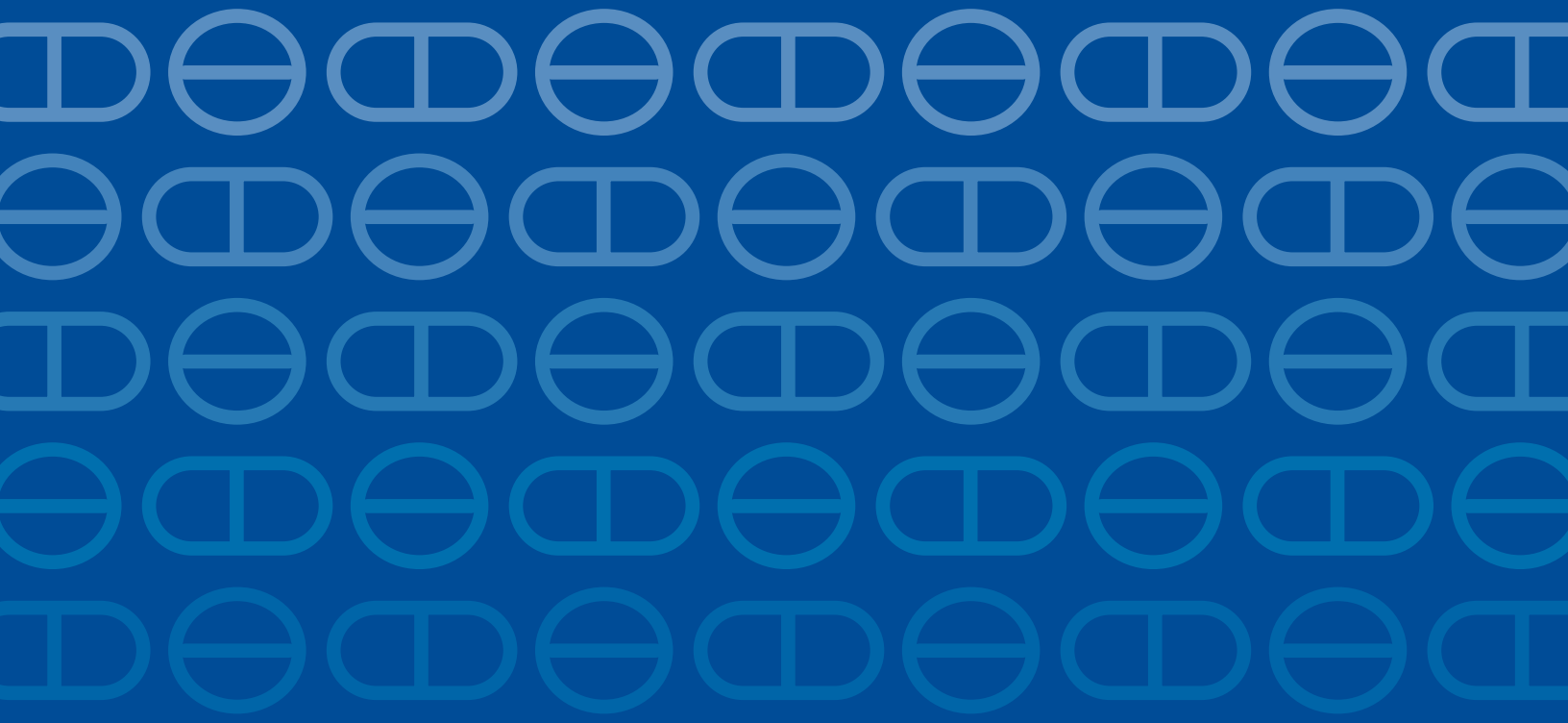
Don’t let the pressure get to you

Managing blood pressure in older adults



Don’t let the pressure get to you:

Managing blood pressure in older adults

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient’s clinical condition.

Alosa Health

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Activity Overview:

The goal of this activity is to educate prescribers about the most recent evidence relating to defining and diagnosing hypertension, recommended blood pressure targets, and the efficacy of different pharmacologic and non-pharmacologic interventions used to achieve blood pressure goals with a specific focus on the risks and benefits of maintaining intensive blood pressure control in older adults.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of top 4-5 key messages
- “Academic detailing” educational sessions in physicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear-off sheets)

The program’s goal is to critically review and synthesize the most current clinical information on these topics into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Perform accurate blood pressure measurement to identify and manage patients with elevated blood pressure and meeting criteria for hypertension
- Identify patients with hypertension who are more likely to benefit from intensive blood pressure lowering according to the latest guidelines
- Select drug and non-drug therapies with consideration of cardiovascular risk, risk of adverse events, blood pressure goals, and patient preferences
- Assess treatment response and intensify therapy to achieve the blood pressure goal
- Counsel patients about diet and medication adherence throughout treatment

Disclosure Policy:

All individuals in a position to control the content of this activity have been asked to disclose any relationship they have with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients. All relevant financial relationships have been mitigated.

This material is provided by Alosa Health, a nonprofit organization which accepts no funding from any pharmaceutical company. No commercial support has been received for this activity. The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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All other individuals including course directors, planners, reviewers, faculty, staff, etc., who are in a position to control the content of this educational activity have reported no relevant financial relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, ANCC contact hours, or Continuing Pharmacy Education (CPE) participants must receive a minimum score of 70% on the post−test.

Tests should be submitted to Alosa Health via email, mail or fax; to complete the evaluation and claim your certificate visit myce.hms.harvard.edu. Credits for pharmacists will be uploaded into CPE Monitor® within 60 days from the date the learner completed the activity.

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The activity will take approximately 1.25 hours to complete.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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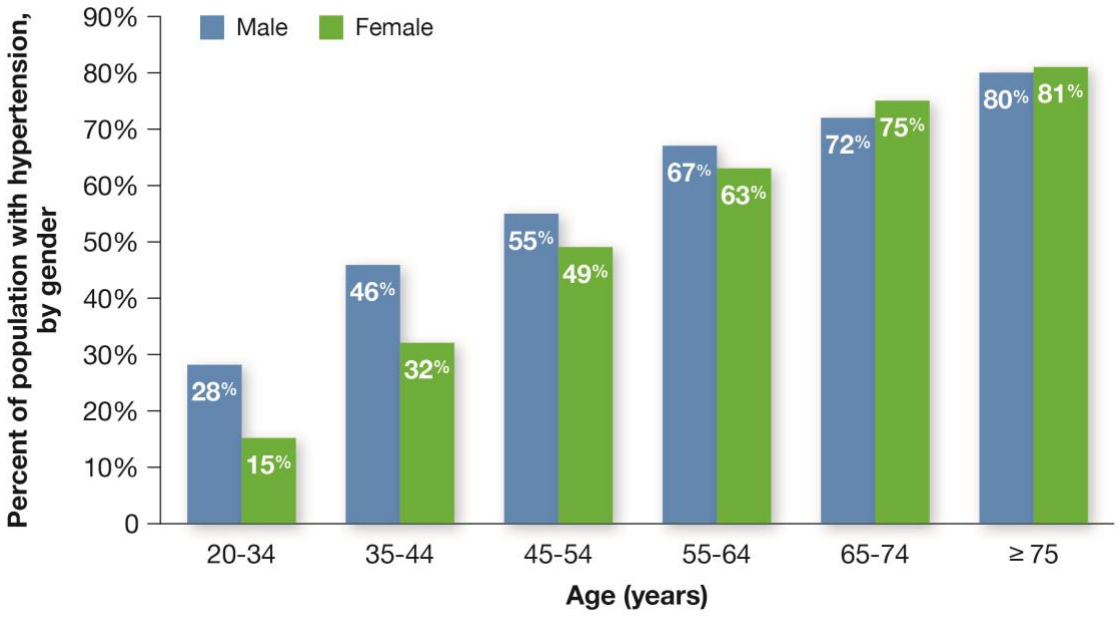
Introduction

Hypertension, defined as a blood pressure (BP) of 130/80 or greater, is the most common condition seen in primary care; over half of people 55 and older have a diagnosis of hypertension.[1,2] While the exact BP cutoff used to define hypertension has changed over time, recent national survey data estimates that 47% of American adults have high blood pressure (historically defined for surveillance purposes as a systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg the lower threshold of 130/80 mmHg used in clinical practice, patient currently taking antihypertensive medicine, or patient told at least twice by a health care professional that he/she has hypertension). This corresponds to about 122 million people in total.[2]

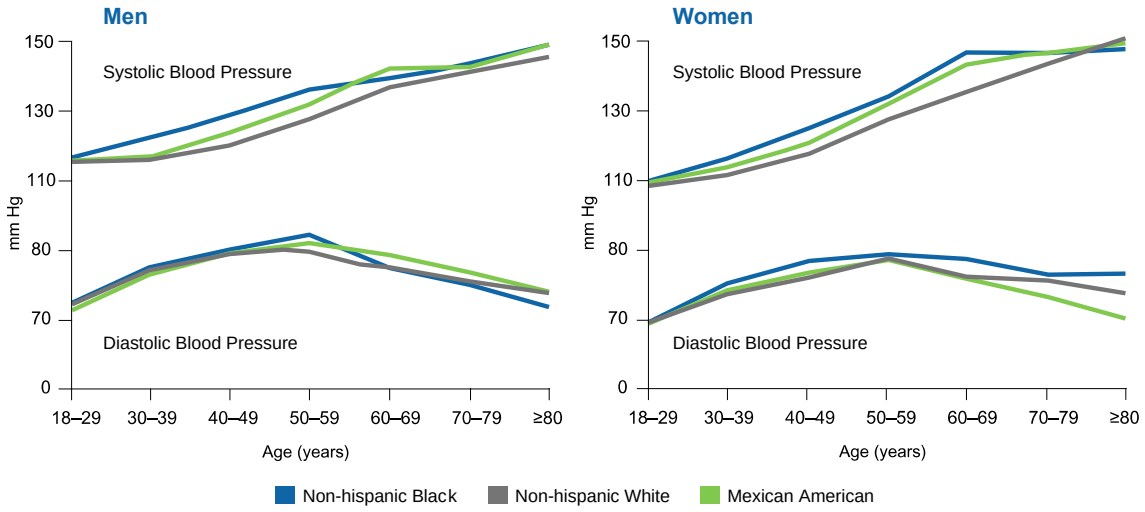
A higher percentage of men than women have hypertension until 65 years of age, at which point the prevalence switches (Figure 1). Overall, more men (62.8 million) than women (59.6 million) have hypertension.[2] In 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) published a new hypertension guideline re-defining Stage 1 hypertension as 130/80 mm Hg – a reduction from 140/90 mm Hg based on contemporary evidence.[3,4] According to these guidelines, 91.7 million U.S. adults met criteria for pharmacotherapy for hypertension between 2015 and 2018. Of these adults, only half were using medications and only 26% had adequately controlled blood pressure.[5]

Figure 1: Prevalence of hypertension among U.S. adults from 2017 to 2020[2]



The prevalence of hypertension rises dramatically with age.[6] The components of blood pressure change differently during aging so that, on average, SBP usually increases with age while DBP decreases with age (Figure 2). The incidence of developing hypertension with increased age is high among all US adults, though there are notable differences by self-reported race and ethnicity. Among participants 45 years of age without hypertension of the population-based cohort Multi-Ethnic Study of Atherosclerosis study, the 40-year risk of developing hypertension was 93% for African-American, 92% for Hispanic, 86% for non-Hispanic White, and 84% for Chinese-American adults.[7]

Figure 2: Trends in SBP and DBP with age[8]



SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Left untreated, hypertension raises the risk of heart attack, stroke, renal failure, and death.[9] For individuals 40–70 years of age, across ranges of <115 mm Hg to >180 mm Hg for SBP and <75 mm Hg to >105 mm Hg for DBP, each increment of 20 mm Hg in SBP or 10 mm Hg in DBP doubles the risk of cardiovascular disease (CVD).[10] Evidence from numerous clinical trials shows that treating patients for hypertension significantly reduces CVD and death.[9,11]

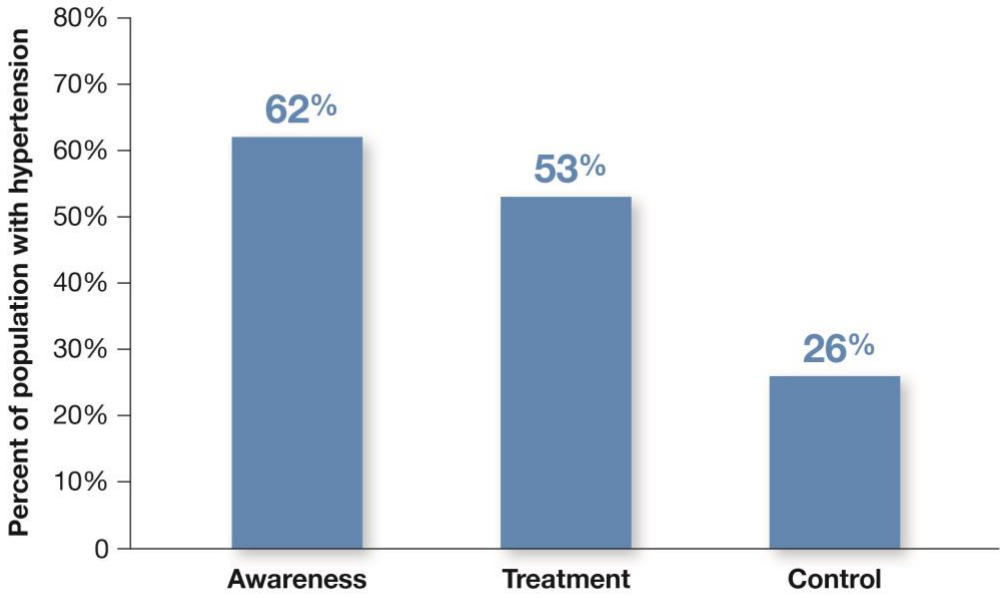
Table 1: Impact of active antihypertensive treatment in reducing cardiovascular events[8,12,13]

Outcome	Average percent relative reduction
Stroke	35-40%
Myocardial infarction (MI)	15-25%
Heart failure	Up to 64%

Randomized clinical trials among individuals with hypertension have demonstrated that for every 10 mm Hg SBP lowering with medical therapy, there was a relative reduction in CVD events by 20%, coronary heart disease (CHD) by 17%, stroke by 27%, and heart failure by 28%.[14]

Although the percentage of patients with hypertension receiving treatment and achieving adequate blood pressure control improved slowly through the early 2000s, including some reductions in disparities between groups, there has more recently been a decline in rates of control with the lowest levels of blood pressure control are among U.S. adults who do not identify as non-Hispanic White.[15] Of those currently being treated for hypertension, only 54% have their hypertension under control, defined as a BP <140/90 mm Hg consistent with historical guideline-recommendations (Figure 3).[16] Notably not all US adults with hypertension are aware of their disease. Data from the 2017 to 2020 National Health and Nutrition Examination Survey (NHANES) found that 38% of U.S. adults with hypertension are not aware they have the condition.[2,17]

Figure 3: AHA statistics for hypertension awareness and treatment (2017 to 2020)[2]



The importance of accurately diagnosing and adequately treating hypertension cannot be overstated; between 2017 and 2020, more Americans died from cardiovascular disease than from cancer and chronic lung disease combined.[2] Race-based disparities in cardiovascular mortality have also persisted, with Black adults far more likely to die from a cardiovascular condition than their White counterparts.[18]

In recent years, new evidence from large, well-controlled clinical trials has given clinicians valuable information about how to help patients set blood pressure goals and about the pharmacological and non-pharmacological options for reaching them. In addition, data supporting lower blood pressure targets in older adults continue to emerge, suggesting that treatment of hypertension, while individualized, should not necessarily less intensive in older adults.

In conjunction with nine other health organizations, the ACC/AHA published the 2017 guidelines for the prevention, detection, evaluation and management of hypertension in adults.[9] This was the first release of a major guideline in hypertension since the Seventh Report of the Joint National Committee (JNC7), which was published in 2003.[8] The updated ACC/AHA recommendations address the framework for defining hypertension, blood pressure thresholds for initiation of antihypertensive medication, and blood pressure treatment goals.[9]

This evidence document consolidates all the available evidence for optimal management of hypertension and provides a clear roadmap for the diagnosis and treatment of this common cause of morbidity and mortality.

BOTTOM LINE: Hypertension is common and, if untreated, is the single most important cause of cardiovascular and cerebrovascular disease. Approximately 38% of U.S. adults with hypertension are not aware they have it, and only 26% of adults with hypertension have controlled blood pressure. Primary care providers can play a vital role in helping to reduce the burden of untreated or under-treated hypertension.

Classifying blood pressure

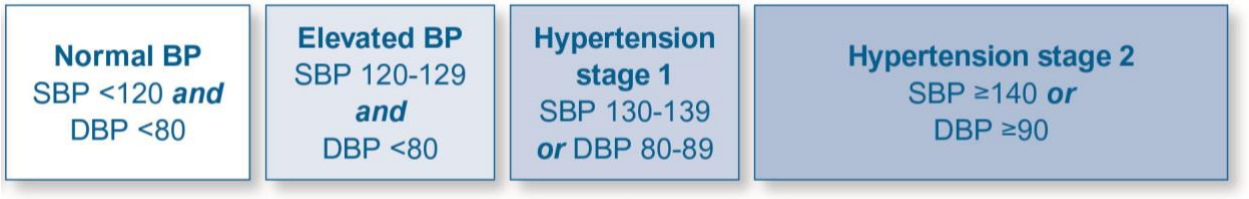
Elevated blood pressure and hypertension are associated with increased risk of CVD, end stage renal disease (ESRD), subclinical atherosclerosis, and all-cause death. Accurate classification of a patient's blood pressure status allows for careful monitoring over time and facilitates both initial treatment decisions and assessment of the response to management interventions.

Definitions and classifications of hypertension have evolved over the past few decades. Since the 1970's, the Joint National Committee (JNC) guidelines were widely consulted for hypertension definitions and treatment approaches. JNC7 (2003) introduced the concept of "prehypertension" for SBP between 120 and 139 mm Hg, based on the idea that earlier adoption of healthy lifestyle may reduce progression to hypertension. The JNC8 never completed its work, but a subset of panelists published a guideline in 2014 that recommended raising target SBP goals from 140 to 150 mmHg in subjects aged ≥60 years, as well as removing prior recommendations for tighter blood pressure control in individuals with diabetes or chronic kidney disease. However, this report relied exclusively on systematic review of randomized controlled trials and omitted data from nonrandomized and observational studies. While it was endorsed by the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP), it was not otherwise widely endorsed or implemented.[1,8,19] The 2017 guidelines on hypertension from the ACC/AHA advocated a paradigm shift in the way blood pressure is defined and managed. These guidelines recommended lowering the blood pressure threshold for the diagnosis of hypertension and incorporation of CVD risk into decisions on treatment initiation and goals.[9]

Blood pressure definitions

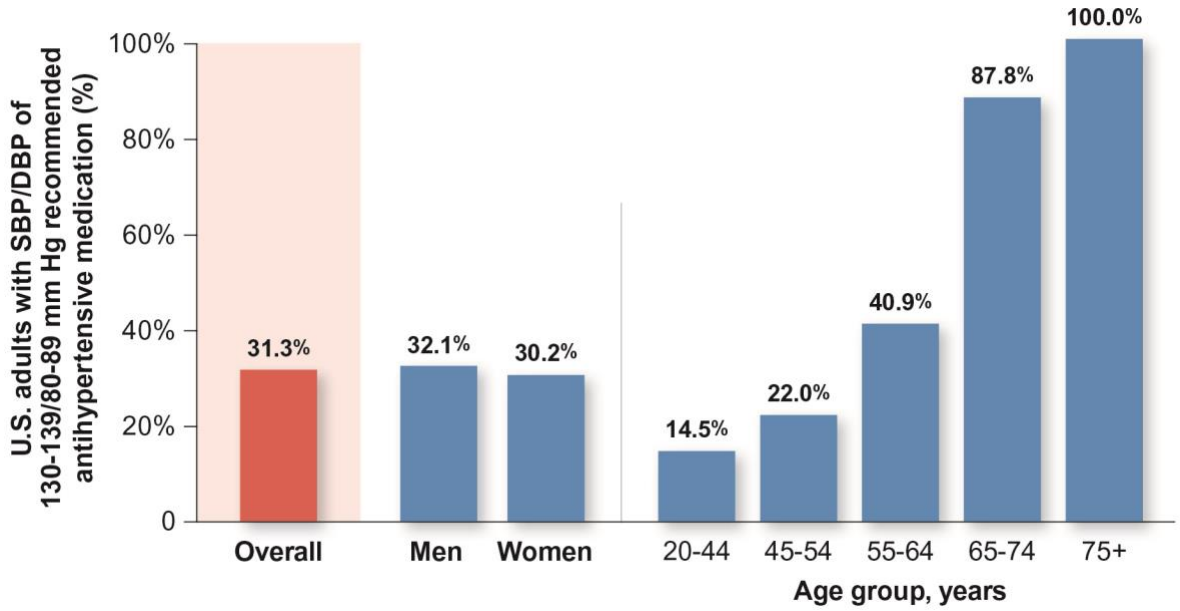
The 2017 ACC/AHA guidelines differ from previous reports by defining hypertension at a lower blood pressure level. In contrast to the previous JNC8 (2014) guidelines, in which hypertension was classified as a blood pressure of 140/90 mm Hg or higher (and >150/90 in older adults), the AHA/ACC 2017 guidelines define hypertension as blood pressure of 130/80 mm Hg or higher, regardless of comorbidities. The new guidelines also divide the JNC7-created category of "pre-hypertension" (SBP 120–139 mm Hg/DBP 80–89 mm Hg) into 2 categories: a new category of "elevated BP" (SBP 120–129 mm Hg/DBP <80 mm Hg) and Stage 1 hypertension (SBP 130–139 mm Hg/DBP 80–89 mm Hg) (Figure 4).[8,9] SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg are defined as Stage 2 hypertension. The diastolic threshold, however, does not apply for adults age 65 and older.

Figure 4: Categories of blood pressure classification in adults in the 2017 ACC/AHA guidelines[9]



The redefinition of the hypertension categories was based on a pragmatic interpretation of blood pressure-related CVD risk and the benefit of blood pressure reduction in clinical trials, which demonstrated a gradient of progressively higher CVD risk going from normal to elevated blood pressure (hazard ratio (HR): 1.1–1.5) and from elevated to Stage 1 hypertension (HR: 1.5–2.0).[9]

Figure 5: Percentage of U.S. adults recommended for antihypertensive medication according to the 2017 ACC/AHA guideline[3]



BOTTOM LINE: The 2017 hypertension guidelines changed the definition of hypertension to a blood pressure of 130/80 mm Hg or higher, regardless of comorbidities, and advocate for incorporating CVD risk status into the decision to start antihypertensive medication.

Measuring blood pressure accurately

Blood pressure determination is one of the most important measurements in clinical medicine and yet it is often performed inaccurately.[20] Surveys show that clinicians and other health care professionals rarely follow established guidelines for blood pressure measurement; however, when they do, the readings correlate much more closely with externally validated measures of blood pressure than the usual clinic readings.[20] Accurate measurement and proper recording of blood pressure are essential for categorizing blood pressure level, ascertaining CVD risk, and guiding management of hypertension.

Best practices for blood pressure measurement

Measurement accuracy

Proper technique for blood pressure measurement is vital not just for proper diagnosis but because, when measurements are used to guide medication and dosing decisions, errors could result in either over- or under-treatment.[9] Common mistakes that can lead to inaccurate blood pressure measurements include failure to allow for a rest period, talking with the patient during or immediately before the recording,

inappropriate cuff size, improper patient positioning, rapid cuff deflation (for auscultatory readings), and measuring blood pressure only once.[21]

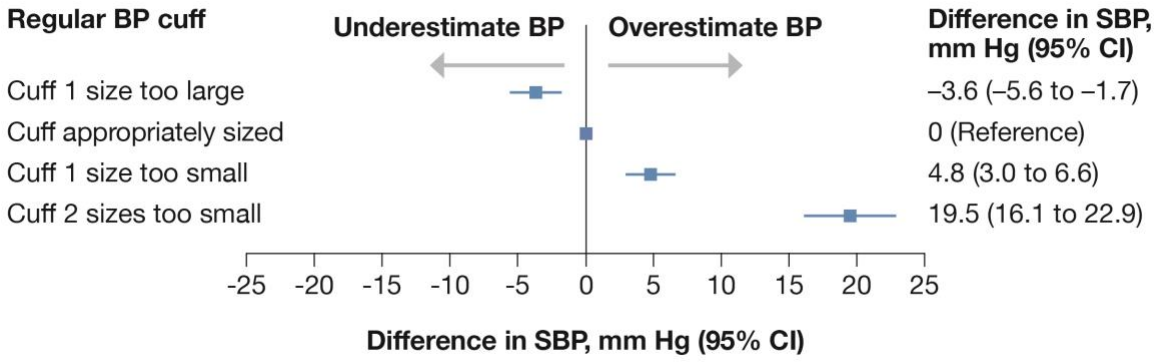
The 2017 ACC/AHA guidelines recommend that healthcare providers follow a standard checklist of best practices when taking blood pressure measurements.[9]

Table 2: ACC/AHA checklist for accurate measurement of blood pressure[9]

Steps	Specific instructions
Properly prepare the patient	• Have the patient relax, sitting in a chair (feet on the floor, back supported) for >5 min. • The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. • Ensure patient has emptied his/her bladder. • Neither the patient nor the observer should talk during the rest period or during the measurement. • Remove all clothing covering the location of cuff placement. • Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
Use proper technique for BP measurements	• Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically. • Support the patient's arm (e.g., resting on a desk) • Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). • Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger or smaller than normal cuff size is used. • Either the stethoscope diaphragm or bell may be used for auscultatory readings.
Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	• At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. • Separate repeated measurements by 1-2 min. • For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20-30 mm Hg above this level for an auscultatory determination of the BP level. • For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds.
Properly document accurate BP readings	• Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. • Note the time of most recent BP medication taken before measurements.
Average the readings	• Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Provide BP readings to patient	• Provide patient's SBP/DBP readings both verbally and in writing.

Appropriate cuff size is integral to accurate blood pressure measurement. A cuff size that is too large leads to an underestimate of actual SBP, while having a cuff size that is too small leads to an overestimation (Figure 6). A 2023 randomized cross-over trial of a diverse group of 195 community-dwelling patients quantified how important cuff size is for accurate BP readings.[22]

Figure 6: Impact of inaccurate cuff size on SBP measurement[22]

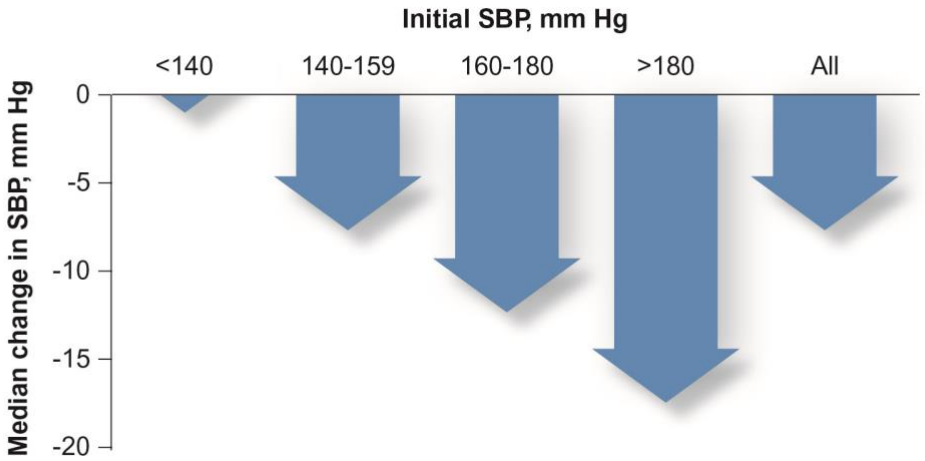


Measurement frequency

Blood pressure varies within an individual over short time intervals and multiple measurements are necessary for deciding the status of patients. The ACC/AHA recommends repeating a blood pressure measurement at the same clinic visit with at least one minute between readings and using the average of two or more readings for classification instead of relying on a single value.[9] In busy primary care practices, blood pressure is often only measured once, and switching to a validated and automated BP cuff to measure repeat blood pressures appropriately spaced can allow for integration of this approach without significant change to clinical work flow.

A repeat blood pressure measurement during the same office visit may result in a lower SBP. In patients with hypertension, repeated measurement of an initially elevated blood pressure was associated with a median of 8 mm Hg improvement in SBP and increased hypertension control rate from 61% to 73%. This change in SBP is approximately equal to the effect of adding a new antihypertensive medication (i.e., clinically meaningful). The change in SBP was positively associated with the initial blood pressure value; the higher the initial SBP, the greater the change in final SBP (Figure 7).[23] Since these results suggest that repeating a blood pressure measurement within the same clinic visit resulted in lower blood pressure, it Is important to obtain repeat measurements for accurate assessment.

Figure 7: Median change in SBP on repeat measurement by initial SBP subgroup[23]



Types of blood pressure measurements

Types of non-invasive blood pressure measurements include office-based, home-based blood pressure monitoring (HBPM), ambulatory blood pressure monitoring (ABPM), and research protocol measurement. HBPM is used to obtain a record of out-of-office blood pressure measurements taken by a patient. ABPM is used to obtain automated out-of-office blood pressure readings at set intervals throughout the day to provide daytime, nighttime and 24-hour averages.

Both ABPM and HBPM can estimate blood pressure based on multiple measurements. Although APBM is generally accepted as the best out-of-office measurement method, insurance coverage can be difficult to obtain, so HBPM is often more practical in routine settings while maintaining the ability to accurately measure blood pressure with a high degree of certainty.[24]

Blood pressure measurements vary based on the setting in which they are recorded; measurements taken in the office are higher than those taken by ABPM or HBPM, especially at higher blood pressure levels.[9]

Table 3: Equivalent corresponding values of SBP/DBP by measurement type and location[9]

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-hour ABPM
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

In-office blood pressure measurement

In-office blood pressure measurement has been historically used for diagnosis and management of hypertension, and generally involves a patient, an administrator (usually doctor or nurse), and a device to measure blood pressure. In-office measurements are usually conducted with auscultatory or automated devices that are used without reference to rest, position, number of readings, or averaging method.

Office-based measurements are generally higher than research setting measurements by 6 to 14/4 to 10 mm Hg (SBP/DBP).[25] Oscillometric devices have become the clinical standard for measuring blood pressure in the office, using a sensor that detects oscillations in pulsatile blood volume during inflation and deflation of the cuff. Many newer devices automatically inflate multiple times at set intervals, which allows patients to be undisturbed during measurement and may reduce measurement bias.[9,26] Randomized controlled trials have shown that measuring blood pressure using an automated device better correlates with ambulatory blood pressure and reduces the likelihood of white coat hypertension compared to manual blood pressure measurement.[27]

Many factors can affect the levels of blood pressure measured, such as the number of visits, number of readings, sitting posture, device type and measurement method, administrator error and bias, administrator presence, and talking during rest period and measurement. For these reasons, in-office measurements are prone to multiple sources of error, such as inaccurate devices and failure to standardize the circumstances of measurement.[21] Given the heterogeneity of BP measurement methods in clinical practice, the 2017 ACC/AHA guidelines recommend in-office measurement solely as a screening method for the identification of hypertension and out-of-office blood pressure measurement (ABPM or HBPM) to confirm the diagnosis.[9]

Home-based blood pressure measurement

Self-monitoring of blood pressure (regular measurement by an individual at home or elsewhere outside the clinic setting) is recommended to confirm the diagnosis of hypertension and for titration of blood pressure-lowering medication. Self-measurement of blood pressure at home or at work can provide useful information about differences between in-office and out-of-office blood pressure as well as response to therapy. Patients who self-monitor blood pressure should be provided with clear instructions on blood pressure measurement and obtain blood pressures using a validated measurement device (see www.validatebp.org for a list of validated BP devices).[9]

For patients with suspected white coat hypertension (elevated office blood pressure with normal blood pressure when measured at home), self-monitoring should be used before or in place of ABPM. Patients should take duplicate morning and evening self-measurements using a validated upper arm blood pressure device for seven days and calculate the average after discarding measurements on the first day. Patients unable to use an upper arm device can use wrist devices instead. Finger devices are not recommended due to concerns that peripheral vasoconstriction can skew results.[28] For additional information and resources on blood pressure measurement resources, such as a home blood pressure measurement patient instruction handout, visit AlosaHealth.org/Hypertension.

Ambulatory blood pressure monitoring

Automated ABPM is used to obtain out-of-office blood pressure measurements at set intervals (e.g., every 15 to 30 minutes during day and every 15 minutes to 1 hour during night), usually over a 24-hour period. It requires the patient to wear a cuff on the arm, typically, and carry a monitor with a pouch or on a belt as individuals go about their normal daily activities. The most common indication for ABPM is suspected white coat hypertension.

APBM may also be useful in evaluating patients with suspected masked hypertension (normal office blood pressure with elevated blood pressure when measured at home), drug-resistant hypertension, episodic hypertension, or hypotensive symptoms with antihypertensive medication.[8] APBM is reimbursed by Medicare for the evaluation of suspected white coat or masked hypertension (with appropriate

documentation) but may not be covered for other indications depending on type of insurance.[29] Individual ABPM providers may be reluctant to bill insurance directly given the need for medical documentation prior to reimbursement by CMS.

APBM provides a more comprehensive assessment of blood pressure and, though there is still debate, may better predict health outcomes than measurements taken in the clinic or at home. Specifically, it may predict long term CVD risk and all-cause mortality more accurately than office-based blood pressure monitoring. An analysis of data from the Spanish Ambulatory Blood Pressure Registry of a large cohort of patients in primary care (n= 63,910) examined the associations of blood pressure measured in the clinic and 24-hour ABPM with all-cause and cardiovascular mortality. 24-hour SBP measurements from ABPM were found to be more strongly associated with all-cause mortality (HR 1.58 per 1-SD increase in pressure; 95% CI: 1.56-1.60) after adjustment for clinic blood pressure than clinic SBP (HR 1.02; 95% CI: 1.00-1.04) after adjustment for 24-hour blood pressure. Masked hypertension was more strongly associated with all-cause mortality (HR 2.83; 95% CI: 2.12-3.79) than sustained hypertension, defined as elevated clinic and elevated 24-hour ambulatory blood pressure (HR 1.80; 95% CI: 1.41-2.31) or white-coat hypertension (HR 1.79, 95% CI: 1.38-2.32). The ability to predict all-cause mortality was significantly better with ambulatory SBP than clinic SBP (discriminatory ability 0.94 vs. 0.79).[30] A U.S. Preventive Services Task Force (USPSTF) systematic review similarly demonstrated that ABPM independently predicts CV risk and mortality, in addition to its utility in differentiating white-coat or masked hypertension phenotypes.[31]

Research protocol blood pressure measurement

Monitoring blood pressure in clinical trials is conducted differently than in clinical practice. Measurement of blood pressure in the SPRINT trial, a pivotal trial of blood pressure lowering in patients with hypertension comparing an SBP goal of <120 mm Hg to a goal of <140 mm Hg, was representative of research protocol measurement.[13] Measurement was performed after a mandatory seated rest in a quiet room for 5 minutes, after which 3 recordings were made at 1-minute intervals. The average of these recordings was used to determine the blood pressure of study participants. See Appendix 2 for more information about SPRINT. In these types of measurements, methodology is carefully standardized, follows a protocol, and requires careful training. In everyday clinical office and home-based settings, these meticulous methods are likely not implemented.[32]

Variation of blood pressure measurement by setting

Hypertension can be differentiated into several clinically useful categories depending on the setting of blood pressure measurement:[9]

Table 4: Blood pressure patterns based on office and out-of-office measurements

	Office/clinic/healthcare setting	Home/nonhealthcare/ABPM setting
Normotensive	No hypertension	No hypertension
Sustained hypertension	Hypertension	Hypertension
Masked hypertension	No hypertension	Hypertension
White coat hypertension	Hypertension	No hypertension

White coat hypertension is characterized by elevated office blood pressure but normal readings when measured outside the office with either ABPM or HBPM. The prevalence of white coat hypertension averages approximately 13% and as high as 35% in some hypertensive populations, such as the elderly, females, and nonsmokers.[9,31]

White coat hypertension has been associated with a two-fold increased risk of CVD complications and all-cause mortality risk. In 1% to 5% of cases per year, white coat hypertension can convert to **sustained hypertension**, defined as elevated blood pressure readings in both office and out-of-office settings.[30] There is a higher incidence of conversion in patients with elevated blood pressure, older age, obesity, or self-identified Black race. Careful consideration of non-pharmacologic and pharmacologic interventions may be warranted for patients of these demographics.

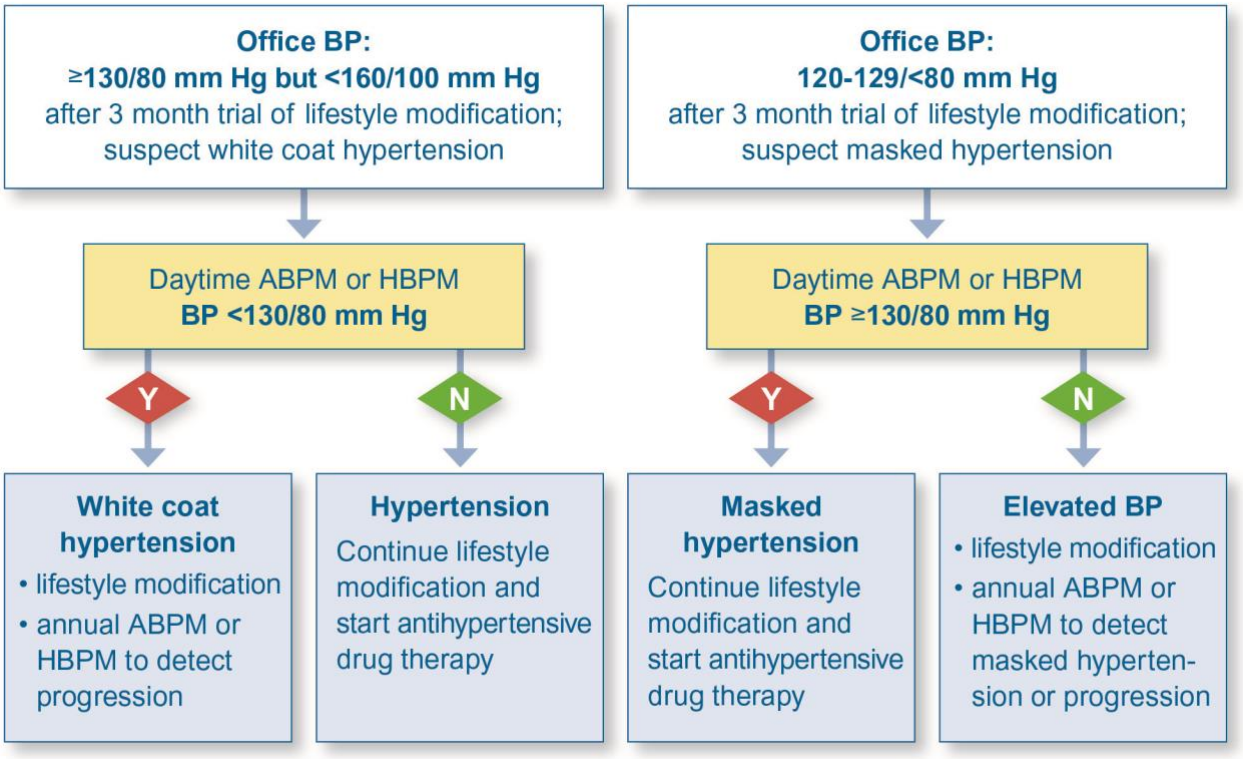
In adults with an untreated SBP >130 but <160 mm Hg or DBP >80 but <100 mm Hg, it is reasonable to screen for the presence of white coat hypertension using either daytime ABPM or HBPM before diagnosis of hypertension. In adults with white coat hypertension, periodic monitoring with either ABPM or HBPM can detect transition to sustained hypertension.[9]

Masked hypertension is characterized by office readings suggesting normal blood pressure accompanied by out-of-office (ABPM/HBPM) readings that are consistently above normal. The prevalence of masked hypertension varies from 10% to 26% (mean 13%) in population-based surveys and from 14% to 30% in normotensive clinic populations and increases with higher office blood pressure readings.[9]

Although masked hypertension is less prevalent than white coat hypertension, it is associated with a CVD and mortality risk twice as high as those seen in normotensive individuals. In patients with treated hypertension, this condition is referred to as masked uncontrolled hypertension. Patients with increased CVD risk or target end-organ damage should use HBPM to screen for masked uncontrolled hypertension. In adults with elevated office blood pressure (SBP 120-129 mm Hg and DBP <80 mm Hg) without a diagnosis of hypertension, screening for masked hypertension using HBPM may identify patients who would benefit from a more aggressive treatment approach.

Neither white coat hypertension nor masked hypertension are well-captured by relying on in-office blood pressure measurements. In patients where either clinical scenario is suspected, a HBPM or ABPM should be used to clarify the diagnosis. Further, among adults with hypertension and taking antihypertensive medication, discordance between office blood pressure readings and HBPM readings, ABPM can be useful.

Figure 8: Approach for suspected white coat hypertension or masked hypertension in patients not on drug therapy[9]



Resistant hypertension

According to the AHA, patients have resistant hypertension when they have BP ≥ 130/80 mm Hg despite being prescribed three or more anti-hypertensive agents of different therapeutic classes or if they require 4 or more anti-hypertensive agents regardless of whether they have achieved disease control.[33] The first steps to diagnosing resistant hypertension is to ensure the patient does not have pseudoresistant hypertension by checking if the patient is adhering to their prescribed medications and checking if out-of-office blood pressure measurements confirm persistently elevated blood pressures. If true resistant hypertension is diagnosed, the workup for secondary hypertension (e.g., primary hyperaldosteronism, Cushing syndrome, renal artery stenosis, chronic kidney disease) is guided by patient history and exam.

BOTTOM LINE: Out-of-office methods such as home-based or ambulatory blood pressure monitoring are appropriate for both diagnosis and management of hypertension and may help distinguish between white coat hypertension and masked hypertension in untreated patients. However, when out-of-office blood pressure measurement is not possible, treatment should not be delayed if clinical suspicion and multiple in-office measurements suggest a diagnosis of hypertension.

Patient evaluation

Once a patient has been identified as having hypertension, evaluation should include:

- assessing potential lifestyle factors that may be elevating blood pressure,
- identifying other cardiovascular risk factors or concomitant disorders that will guide treatment,
- searching for identifiable secondary causes of high blood pressure, and
- determining the presence and extent of end-organ damage.

Many lifestyle factors influence blood pressure, including diet, physical activity, and alcohol consumption. Some of the diet-related factors associated with high blood pressure include overweight and obesity, excess sodium intake, and insufficient intake of potassium, calcium, magnesium, protein, fiber, and fish fats.

There is a strong association between higher blood pressure and increased CVD risk, especially in older persons. The population-attributable risk of outcomes associated with hypertension, such as heart disease, stroke, and end-stage renal disease (ESRD), is high.

Secondary causes of hypertension are uncommon. Consider a work-up for secondary hypertension in patients with any of the following: abdominal bruit, accelerated or resistant hypertension, recurrent flash pulmonary edema, renal failure, or onset of hypertension under age 30 without a family history.

Potential causes of secondary hypertension include:

- sleep apnea
- alcohol or non-prescribed substances
- adverse effect of medication
- chronic kidney disease
- primary aldosteronism
- renovascular disease
- chronic steroid therapy or Cushing’s syndrome
- pheochromocytoma
- coarctation of the aorta
- thyroid or parathyroid disease

Prescription or over-the-counter medications may raise blood pressure within the normal range or cause overt hypertension, as can stimulants used recreationally. The most common medications with this potential are oral contraceptives (particularly with higher doses of estrogen), NSAIDs, antidepressants, glucocorticoids, decongestants (especially pseudoephedrine), stimulants (including weight loss medications containing stimulants), and cyclosporine.

Laboratory testing is recommended in all patients newly diagnosed with hypertension in order to identify common comorbid conditions and prior to initiating medications. Recommended laboratory testing includes serum electrolytes and renal function, fasting glucose or hemoglobin A1c, urinalysis, and lipid profile. In addition, a baseline electrocardiogram should be obtained in order to assess for left ventricle hypertrophy (LVH) or silent ischemic heart disease.

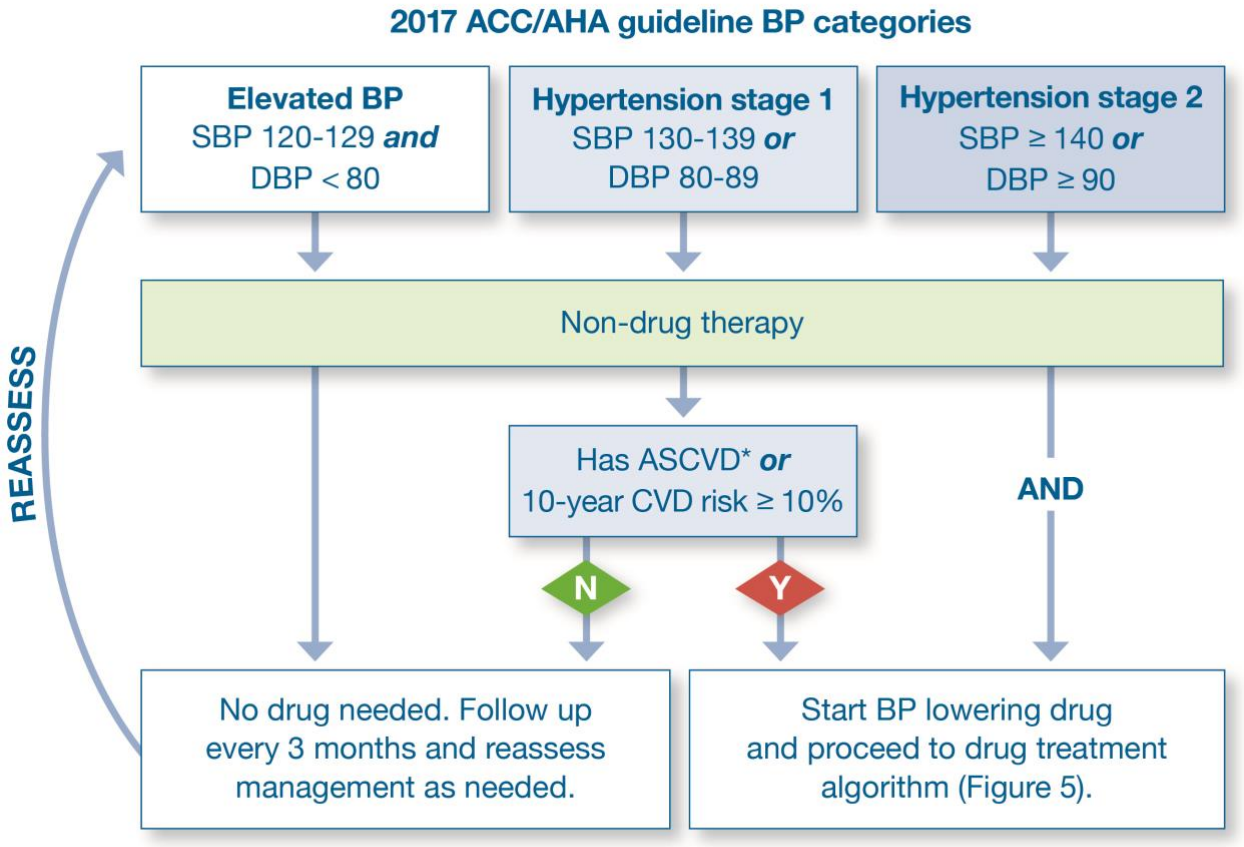
BOTTOM LINE: Assess patients for modifiable risk factors, comorbidities, potential secondary causes, and end-organ damage prior to developing a treatment plan for hypertension.

Managing hypertension

When to start treatment

Lifestyle or non-drug therapies such as dietary modifications, physical activity, and weight loss are the backbone of any hypertension management plan (see page 20 for more detail on these interventions). The 2017 ACC/AHA guideline recommends these interventions for anyone with a BP >120/80 mm Hg.[9] The decision to start pharmacologic therapy is based on blood pressure alone for all patients with Stage 2 hypertension and for patients with Stage 1 hypertension with either existing CVD or an elevated risk of developing CVD.

Figure 9: Algorithm for initiating management based on blood pressure



*ASCVD (atherosclerotic cardiovascular disease) includes acute coronary syndrome, myocardial infarction, angina, revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease.

Role of cardiovascular risk assessment

Considering both absolute CVD risk and blood pressure levels to guide treatment has been shown to be effective at reducing risk of CVD.[34] The 2017 ACC/AHA guidelines recommend initiating pharmacologic blood pressure treatment for adults with Stage 1 hypertension in the context of CVD risk by estimating 10-year risk of ASCVD with the pooled cohort equation to establish the blood pressure threshold for treatment.[9] This CVD risk assessment is similar to how guidelines recommend risk stratification and treatment decisions for hyperlipidemia. However, use of global assessments to estimate CVD risk thresholds is still infrequent in routine clinical practice to date, as it does represent a more complex approach than using blood pressure measurements alone to guide treatment.

Thresholds for starting pharmacologic therapy

In line with their modified definitions of hypertension, the 2017 ACC/AHA guidelines maintain that the blood pressure threshold of 130/80 mm Hg can be used to determine whether a patient should be considered a candidate for treatment.[3,9] Special comorbidities are also aligned with current blood pressure treatment thresholds, except when used in secondary prevention of non-lacunar strokes.

Table 5: Blood pressure thresholds for starting antihypertensive treatment by clinical condition[3,9]

	ACC/AHA (2017) (mm Hg)
General	
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80
No Clinical CVD and 10-year ASCVD risk <10%	≥140/90
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)
Special comorbidities	
Diabetes mellitus	≥130/80
Chronic kidney disease after renal transplantation	
Heart failure	
Stable ischemic heart disease	
Peripheral artery disease	
Secondary stroke prevention (lacunar)	
Secondary stroke prevention	≥140/90

*No specific BP threshold is provided in the guideline for this population. The other thresholds listed from the guideline should be applied, as appropriate. †High cardiovascular risk

BOTTOM LINE: Patients with BP >120/80 mm Hg should receive non-drug therapy. Both blood pressure level and CVD risk factors should be used to guide the decision to start pharmacologic therapy in patients with Stage 1 hypertension. Patients with Stage 2 hypertension should receive drug and non-drug management.

Blood pressure treatment goals

A common blood pressure goal of 130/80 mm Hg was defined in the 2017 ACC/AHA guideline to simplify treatment targets for most patients.[9] In patients aged 65 and over, the DBP goal was eliminated, but the common SBP goal of <130 mm Hg is retained. This goal is for patients who are ambulatory, community dwelling, and without morbidities such as dementia that would exclude them from clinical trials.

Table 6: Comparison of blood pressure goals recommended by ACC/AHA[8,9]

	ACC/AHA (2017) (mm Hg)
General population	<**130/80** (aged <65)
Older adult population	<**130*** (aged ≥65)
Diabetes	<**130/80**
Kidney disease (CKD)	<**130/80**

*Isolated SBP goal for adults ≥65 years of age without a history of CVD, DM, or CKD and a 10-year predicted ASCVD risk <10%.

These same treatment goals apply to patients already on antihypertensive medication.[9,16] Intensification of therapy may be required to meet new blood pressure goals.

Evidence supporting 2017 ACC/AHA blood pressure goals

The 2017 ACC/AHA guidelines evaluated evidence emerging after the publication of the JNC7 guidelines from pivotal trials such as ACCORD BP, SPRINT, and SPS3. The lower target blood pressure set by the 2017 ACC/AHA guideline is predominantly based on evidence for systolic blood pressure goals. See appendices 2, 3, and 4 respectively for further explanation of the findings of SPRINT, ACCORD and SPS3 trials, respectively. In brief:

- ACCORD BP investigated a composite outcome of fatal and nonfatal major cardiovascular events, and found no difference in patients with intensive SBP lowering (<120 mm Hg) compared with standard SBP (<140 mm Hg) in patients with type 2 diabetes and elevated cardiovascular risk, although patients reported a significant increase in treatment-related side effects.[9,35]
  - However, the ACCORD BP trial did demonstrate a 41% reduction in secondary outcome of stroke in the intensive management group. Other trials, including the STEP trial and the ADVANCE trial, also focused on patients with diabetes and found decreased CV events with lowering to SBP<130-135 mm Hg, and the American Diabetes Association guidelines concur with 2017 ACC/AHA about a goal BP <130/80 mm Hg.[36,37]

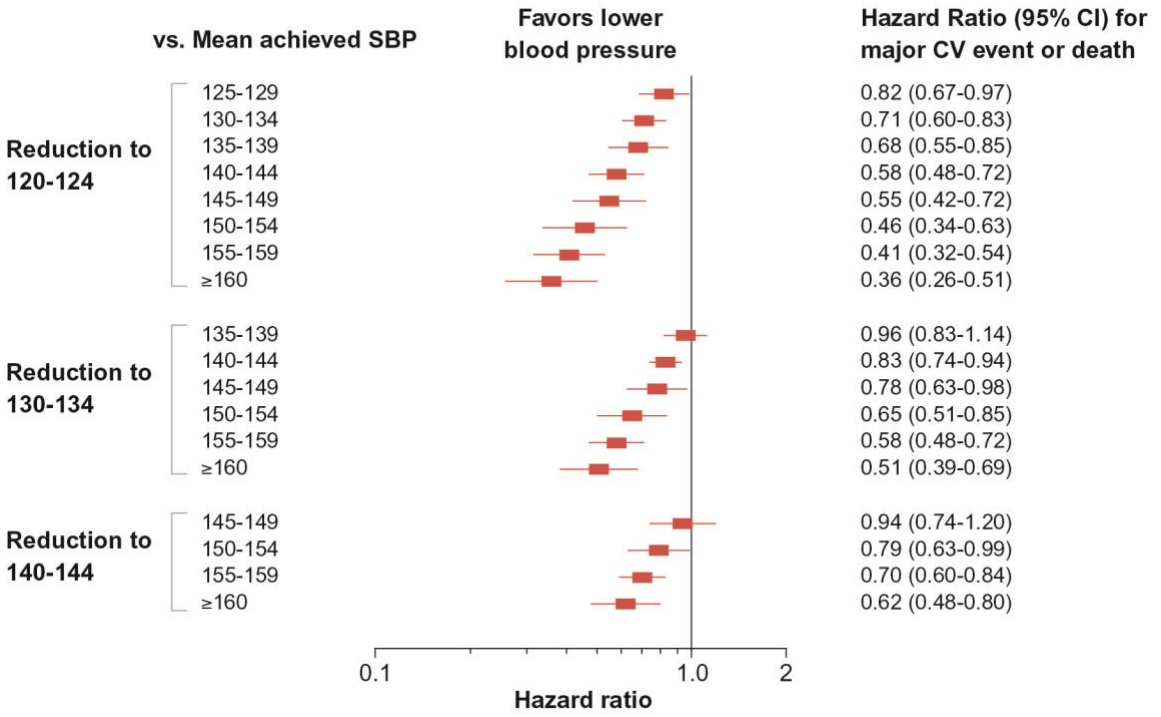
- SPRINT examined the incidence of MI, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes, and found a 25% relative risk reduction in patients with intensive SBP lowering to <120 mm Hg compared to standard SBP lowering (<140 mm Hg) in non-diabetic patients with elevated cardiovascular risk, and an even greater benefit in patients age 75 and over (relative risk reduction 34%).[13,38] Adverse events including hypotension, syncope, electrolyte abnormalities, and acute kidney injury were more common in the intensive treatment group but the risk of injurious falls was not statistically different. Notably, within the

subgroup of older adults (75 and older), there was no significant difference in the rates of serious adverse events between intensive and standard treatment groups.[39]

- SPS3 evaluated SBP lowering to <130 mm Hg vs. <140 mm Hg in patients with recent lacunar stroke, finding no difference in the risk of recurrent stroke between these two thresholds for most patients, but benefit in patients with lacunar strokes.[40]
  - Since the publication of 2017 guidelines, new data has emerged supporting SBP goal <130 to reduce risk of recurrent stroke or TIA (secondary prevention). A large 2023 meta-analysis of 10 randomized controlled trials (RCTs) found an overall reduction in stroke with more intensive BP lowering (RR 0.83; 95% CI: 0.78-0.88).[41]

Evidence continues to indicate that more aggressive reduction of SBP reduces CVD risk. A 2017 network meta-analysis of 42 trials including 144,220 patients assessed whether achieved SBP correlated with CVD or all-cause mortality in adults with hypertension who were treated with antihypertensive therapy. The study found a linear association between mean achieved SBP and risk of cardiovascular disease (Figure 10), as well as with SBP and all-cause mortality.[4] All-cause mortality is lowest for an achieved SBP of 120 to 124 mm Hg (HR 0.73; 95% CI: 0.58-0.93) compared with those with a mean achieved SBPs of 130 to 134 mm Hg, with even greater reductions when compared to 140 to 144 mm Hg, and ≥160 mm Hg.[4] These results support tighter control of blood pressure among adults with hypertension, as long as the treatment is well tolerated.[4,9]

Figure 10: Reducing blood pressure prevents CVD events, with even greater reductions at lower blood pressure targets.[4]



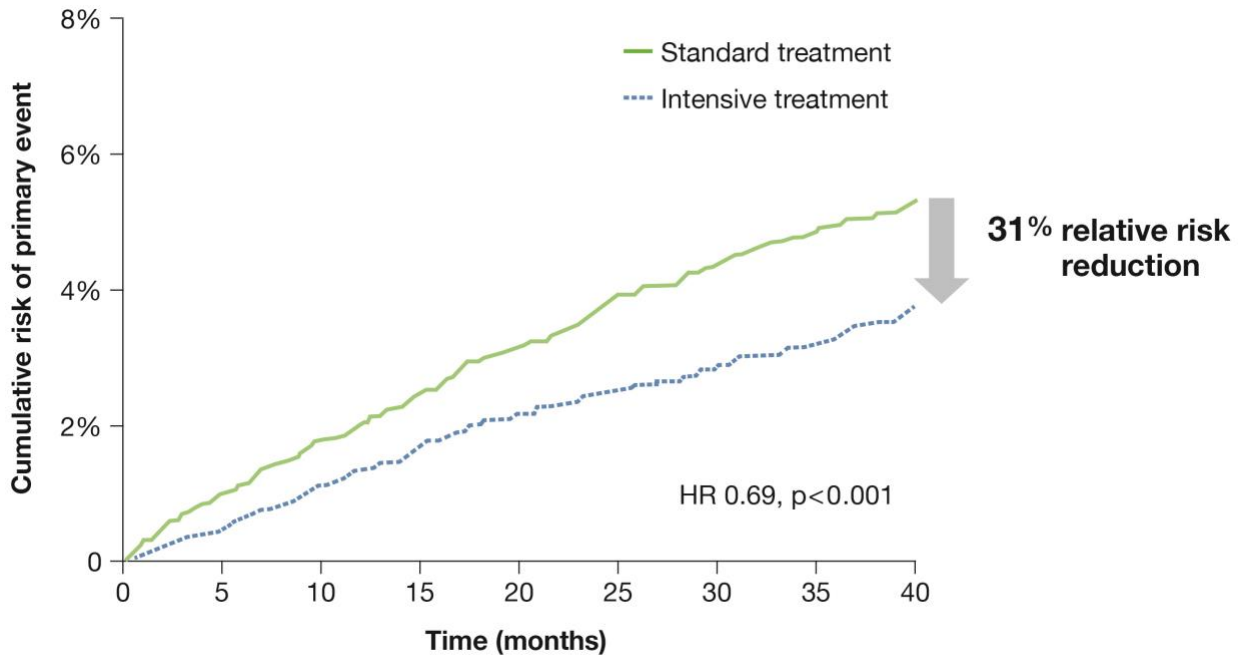
The 2017 ACC/AHA guidelines took the above and other findings into consideration when establishing a common blood pressure goal. As blood pressure measurement technique in RCTs differs from routine clinical practice in way that can result in lower readings, the recommended SBP target (<130 mm Hg) was

higher than what was used in SPRINT (<120 mm Hg). The AHA/ACC guidelines also provide a single SBP target for all conditions.[9]

Since the publication of the 2017 guidelines, new data has emerged supporting the recommended BP targets. Yano et al., showed that, in a prospective cohort of adults 18-30 years old, hypertension as defined by the 2017 guidelines was strongly associated with CVD and mortality later in life, a testament to the value of the updated classifications.[42] The SPRINT MIND investigators showed in a multicenter RCT that more intensive control (SBP target of <120) was associated with a lower likelihood of mild cognitive impairment and a trend (though not statistically significant) toward lower risk of dementia.[43]

A secondary analysis that followed SPRINT participants up to 10 years after the trial ended determined that there were no significant differences between the intensive and standard treatment groups in blood pressure control, mortality due to cardiovascular disease, or all-cause mortality.[44] This study demonstrates the importance of persistent longitudinal management of hypertension in order to maintain the benefit of lower BP. Given that the mortality benefits from better BP control may take years to accrue whereas the harms may occur in the short term, one study attempted to determine the time to clinical benefit of intensive blood pressure lowering examined adults aged 60 and older. They determined that 19.1 months and 34.4 months were needed to avoid 1 cardiovascular event for 200 and 100 patients, respectively, suggesting reasonably quick time-to-benefit from obtaining well-controlled blood pressures.[45] This time-to-benefit data in conjunction with other data from the SPRINT trial suggest continued cardiovascular benefits to targeting intense blood pressure targets even for older adults.

Figure 11: Like all adults, older adults also benefit from intensive BP lowering[45]



BOTTOM LINE: In the general population of non-institutionalized, ambulatory adults, including older adults, treating hypertension will reduce mortality and targeting a blood pressure goal of <130/80 mm Hg is shown to reduce major cardiovascular events.

Response to the ACC/AHA guidelines

The “one size fits all” intense blood pressure target of <130/80 mm Hg blood pressure target has been met with mixed reactions. Some organizations, such as the ACP/AAFP, had taken the position that a single blood pressure treatment target for a broad population of older adults was not supported by sufficient evidence and may result in suboptimal care. This is because the risks associated with high blood pressure form a continuum and patient individualization is critical to proper treatment. While some individuals may benefit from more stringent targets, these targets may also lead to unnecessary treatment and potential side effects in other individuals.[19,46]

As such, in 2017, the ACP/AAFP jointly published clinical guidelines based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.[19] These guidelines support a relaxed SBP goal of <150 mm Hg in older adults those without CV risk, diabetes, or prior stroke.[19] However, more recently the 2022 the AAFP guidelines embraced a single BP target regardless of age though they continued to advocate for targeting standard blood pressure targets (now <140/90 mmHg) rather than the more intense ACC/AHA target of <130/80.[47] They specifically cite multiple meta-analyses showing that there is no difference in mortality between targeting standard versus intense blood pressure targets, putting less emphasis on the ability of more intense blood pressure targets to reduce cardiovascular events alone. In general, the benefits of reducing the risk of CV events by lowering blood pressure must be weighed against increased risks of side effects with intensive therapy.

It is important to realize that the SPRINT population consists of non-institutionalized, ambulatory, community-dwelling adults. Common reasons for exclusion from the trial included conditions that cause concern regarding safety of the protocol, such as CVD event or procedure, symptomatic heart failure, a medical condition likely to limit survival, or dementia, which resulted in exclusion of some, though not all, multimorbid, frail older adults who could’ve been at highest risk of adverse events from intensive blood pressure lowering.[13,48] Moreover, self-reported outcomes of physical and mental health did not differ significantly between intensive and standard blood pressure lowering groups.[49] Therefore, a target SBP <130 mm Hg should only be recommended after considering the individual’s benefit, risk of adverse events, and preferences.

Taken together, blood pressure guidelines are a starting point, but do not represent a mandate that should be used for uniform evaluation of clinicians or systems. Rather than being imposed bluntly as a means of dictating decisions, they should be used to support clinical practice. Focusing on the larger goal of ensuring that those with substantially elevated blood pressures receive appropriate diagnosis and treatment rather than debates about specific blood pressure target values will yield the greatest overall improvements in health outcomes.[50]

BOTTOM LINE: Competing recommendations for BP goals from various societies reflect the complexity of interpreting the many studies of hypertension but should not obscure the important benefits of hypertension treatment, especially for patients with very elevated BP. These position statements should be used to support clinical practice while incorporating the needs and preferences of individual patients and are not intended to be used for performance evaluation for all patients.

Treatments for hypertension

Non-pharmacologic treatment

According to the 2017 ACC/AHA guidelines and a 2021 AHA scientific statement, non-pharmacologic lifestyle interventions are recommended in those with elevated blood pressure (SBP>120 mm Hg), with reassessment in 3 to 6 months.[51] Clinicians should recommend modification of lifestyle factors that may be contributing to hypertension and these efforts should continue concurrently with any other treatments pursued. Modifications shown to reduce blood pressure and lower CV risk include weight loss, the DASH (Dietary Approaches to Stop Hypertension) diet, sodium reduction, potassium supplementation, increased physical activity, and reduced alcohol consumption. These interventions may be sufficient to prevent hypertension in patients with elevated blood pressure and contribute to reaching blood pressure goals in managing patients with Stage 1 and 2 hypertension. For instance, the DASH diet has been associated with statistically significant BP reduction in RCTs.[52] Behavioral strategies that are aimed at lifestyle change can also reduce blood pressure.[9]

Although the amount of blood pressure reduction that can be expected from any single lifestyle intervention is relatively modest, the cumulative effect of multiple interventions can be significant and may allow for the avoidance or minimization of pharmacological therapy in motivated patients.

Table 7: Nonpharmacological interventions for prevention and treatment of hypertension[9]

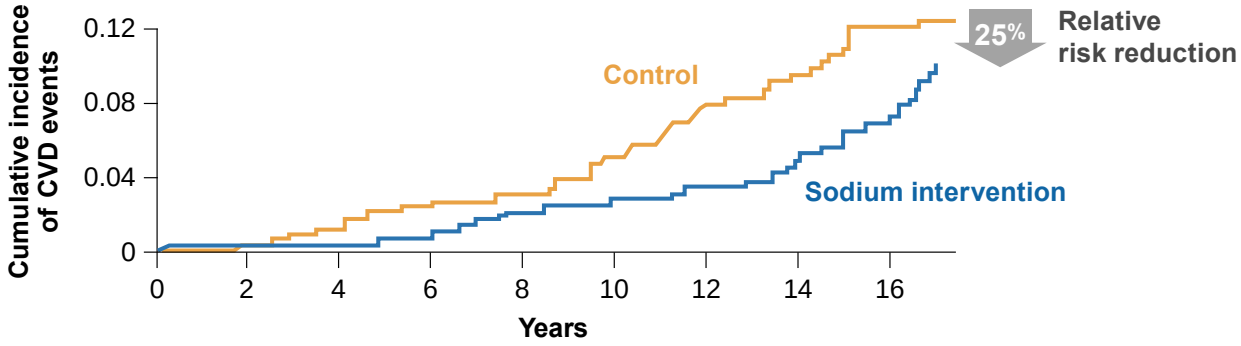
Intervention	Goal	Approximate reduction in BP	
		Hypertension	Normotension
Weight loss	Aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight	5 mm Hg	2-3 mm Hg
Healthy diet	DASH dietary pattern: Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat	11 mm Hg	3 mm Hg
Reduced intake of dietary sodium	At least a 1000-mg/d reduction in most adults (ideally <1500 mg/d)	5-6 mm Hg	2-3 mm Hg
Enhanced intake of dietary potassium	3500–5000 mg/d	4-5 mm Hg	2 mm Hg
Physical activity	90–150 min/week aerobic activity	5-6 mm Hg	2-4 mm Hg
Moderation in alcohol intake	Men: ≤2 drinks daily Women: ≤1 drink daily	4 mm Hg	3 mm Hg

The positive effects of aerobic exercise on blood pressure were demonstrated in a meta-analysis of 54 randomized, controlled trials (2419 participants) involving aerobic exercise interventions such as walking, jogging, or biking for time durations varying from 32 – 350 minutes weekly, with the most common duration of exercise being about 120 minutes weekly.[53] Aerobic exercise was associated with a reduction in mean SBP and DBP (-3.84 mm Hg [95% CI, -4.97 to -2.72 mm Hg] and -2.58 mm Hg [95% CI, -3.35 to

-1.81 mm Hg], respectively). Blood pressure reductions were seen in patients with and without hypertension, as well as in overweight and normal-weight participants.

Counseling patients on reducing dietary sodium can produce clinically significant results. The Trials of Hypertension Prevention (TOHP I and II) tested the efficacy of non-pharmacological interventions for reducing blood pressure in people with high-normal blood pressure, including counseling on how to identify sodium in the diet, and how to prepare lower sodium foods. The people randomized to the sodium reduction arm (n = 327) had a 25% - 30% reduction in cardiovascular events compared to those in the control arm (n = 417).[54]

Figure 12: Reduction in CV events with sodium restriction[54]



BOTTOM LINE: Weight loss may decrease the risk of developing hypertension among those at increased risk. Both counseling and adherence to a low sodium diet may also reduce blood pressure and improve CV outcomes. Although the amount of blood pressure reduction that can be expected from any single lifestyle intervention is relatively modest, the cumulative effect of multiple interventions can be significant.

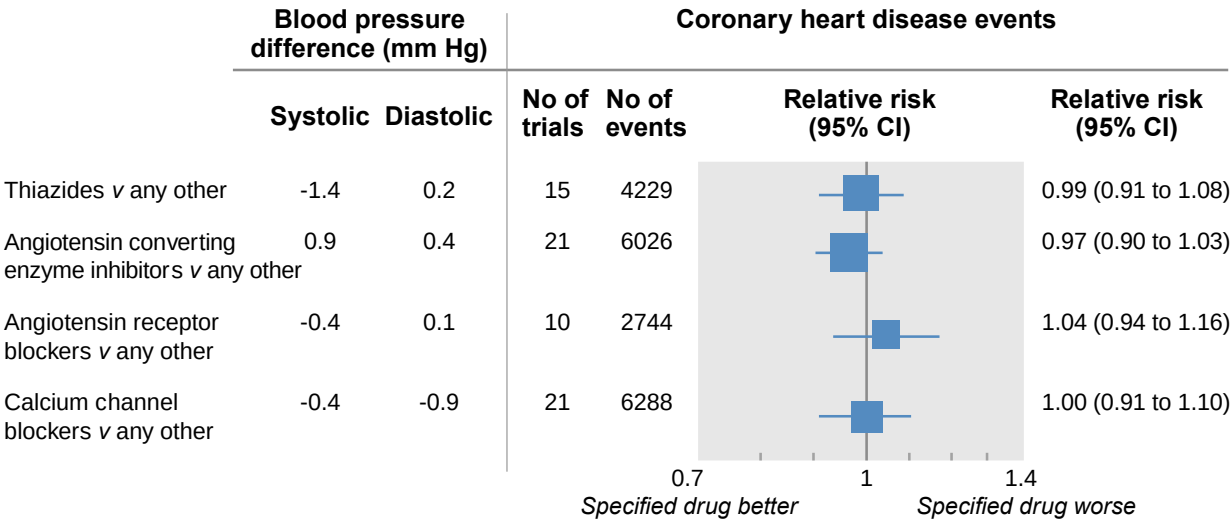
Pharmacologic treatment

Hypertension can be treated with medications from multiple classes, each with different mechanisms of action. The recommended classes for first-line antihypertensive medications are: thiazide type-diuretics, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). Over two-thirds of patients with hypertension will eventually require more than one medication.[55] For example, in the SPRINT trial, patients randomized to intensive treatment required on average three medications to achieve a target SBP <120 mm Hg.[13] According to the 2017 ACC/AHA guidelines, for patients with Stage 2 hypertension or baseline blood pressure more than 20/10 mm Hg above target, it may be appropriate to start 2 first-line agents, either separately or as a fixed-dose combination.[9]

In the past four decades, numerous clinical trials have compared individual antihypertensive medications to placebo, using blood pressure lowering as a major outcome.[56,57,58] Meta-analyses have combined these data to calculate the average effect on blood pressure of each of the four main classes of antihypertensive medication. The results show similar blood pressure-lowering effects for standard-dose anti-hypertensives in each major drug class.[59,60]

In general, unless other compelling indications exist (e.g., the use of beta-blockers for patients with recent MI), there is no strong evidence to favor any one particular antihypertensive drug or class over another for initial therapy. One meta-analysis published in 2009 examined the 46 trials that directly compared one drug class against another for the prevention of coronary heart disease events (defined as fatal or nonfatal MI or sudden cardiac death) or stroke.[61] Those authors concluded that all the classes of blood pressure lowering drugs have a similar effect for a given reduction in blood pressure.

Figure 13: Relative risk estimates of CHD events in 46 drug comparison trials[61]



On the basis of this meta-analysis and the protocols of more recently published large pivotal trials, we suggest that the choice of pharmacologic agent is less important than achieving the appropriate blood pressure goal. Given this approach, adherence is more important than drug choice, creating a preference for generics/affordability, once daily dosing, and combination pills. That said, calcium channel blockers (CCBs) may have minor additional benefits for stroke prevention compared to other antihypertensive agents (see CCB section below).

While not standard practice now, in the future it may be possible to appropriately select an antihypertensive based on an patients' individualized probability of responding to a given agent. A recent randomized controlled trial showed there is actually heterogeneity in response to blood pressure medications. In this double-blinded trial, 270 patients with Stage 1 hypertension at low risk of cardiovascular events were randomized to receive either lisinopril (and ACEI), candesartan (an ARB), hydrochlorothiazide (a thiazide diuretic), or amlodipine (a CCB) for a median of 56 days before being randomized another three times to the other medication classes. While on each treatment patients were followed and ambulatory daytime systolic blood pressure measurements were recorded. The results showed that blood pressure response to different treatments varied considerably by individual and it was estimated that a personalized treatment choice would have on average lead to a 4.4 mm Hg-lower systolic blood pressure than always selecting a fixed first choice. Developing predictive tools that can accurately match patients with the medication class to which they are most likely to respond would drastically change the manner in which hypertension is treatment from largely class-agnostic to very much class-targeted.[62]

Thiazide-type diuretics

Thiazide-type diuretics inhibit about 5% of sodium reabsorption and are longer-acting and exert greater antihypertensive effect than loop diuretics. The landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial randomized nearly 40,000 patients with hypertension into one of four treatment groups and compared clinical outcomes.[63] The four drug classes were diuretics, CCBs, ACEIs, and alpha-blockers. The alpha-blocker arm was stopped early because of increased risk of CVD, especially heart failure compared with diuretic arm.

The ALLHAT trial found that thiazide-type diuretics were equivalent to ACEIs and CCBs for preventing the primary CV outcome. However, **thiazides were superior to either ACEIs or CCBs in preventing heart failure** (a secondary outcome). At the time the study was conducted, thiazides were substantially less expensive than the other two drug classes and thus the JNC7 guidelines recommended thiazides as the initial drug of choice. See Appendix 1 for the costs of various antihypertensives by class.

The blood pressure lowering effect of thiazides is not immediate. Most patients will respond with a reduction in blood pressure within four weeks, although a minority of patients will not achieve maximum reduction for up to 12 weeks.[32] If blood pressure control is inadequate after a reasonable time period, rather than increase the dose of the diuretic, it is better to add another drug from a different class, and to re-emphasize the importance of lifestyle changes. For patients who require more than one drug to control their hypertension, thiazides should generally be part of the regimen.

Until recently, few head-to-head trials have compared different thiazides with one another in terms of clinical outcomes, although both chlorthalidone and hydrochlorothiazide (HCTZ) lower blood pressure effectively.[64] Indirect comparisons of thiazides had suggested that both agents had equal effects on reducing rates of serious CV events, and both appear equally safe.[65] Despite the lack of direct comparisons and relative equipoise in the literature, some experts espouse that because of pharmacologic features, such as a longer half-life, and its use in the ALLHAT trial, chlorthalidone was the superior drug in the thiazide class.[66] However, in 2022 a pragmatic randomized trial was conducted to finally assess whether this sentiment that chlorthalidone was superior to hydrochlorothiazide.[67] In this pragmatic trial carried out in the Veterans Affairs health system, 13,523 patients over 65 years of age were randomized to either continue HCTZ or to switch to chlorthalidone and monitored for a primary outcome that was a composite measure of nonfatal myocardial infarction, stroke, heart failure resulting in hospitalization, urgent coronary revascularization for unstable angina, and non-cancer related death. After a median follow-up time of 2.4 years, there was no difference in the occurrence of primary outcome events between the chlorthalidone group (10.4%) and the hydrochlorothiazide group (10.0%; p=0.45), and blood pressure remained similar in both patients who continued on HCTZ and were switched to chlorthalidone. Alternatively, chlorthalidone use was associated with a higher incidence of electrolyte abnormalities; specifically, there was more hypokalemia in the chlorthalidone group (6.0%) compared with the HCTZ group (4.4%). The results from this trial suggest it is very unlikely that clinicians should preference chlorthalidone over HCTZ – whichever the patient prefers, is affordable, and they will take, is the most reasonable choice.

Concerns about metabolic side effects of thiazides such as hypokalemia, hyperglycemia, hyperuricemia, or hyponatremia were based on early studies in which higher doses of thiazides were used (e.g., 50–100 mg/d of HCTZ). At lower doses (e.g., 12.5 mg/day of HCTZ), thiazides provide very effective blood pressure control and side effects rates that are indistinguishable from other classes of anti-hypertensives (and only 2% more than placebo).[68,69]

In patients with chronic kidney disease and hypertension, ACEIs and ARBs have long been preferred (see following sections), though a recent RCT showed that in stage 4 CKD, chlorthalidone was effective in lowering BP relative to placebo, suggesting thiazides may also play a role in the management of hypertension in patients with CKD.[70]

Angiotensin converting enzyme inhibitors (ACEIs)

No randomized head-to-head trials have compared the effect of different ACEIs on clinical outcomes in patients with hypertension, although many studies have compared specific ACEIs with placebo, or with drugs from other antihypertensive classes. These trials have not found any consistent advantage of any one ACEI over another.[71] Several trials compared the rates of adverse events from ACEIs in patients with hypertension and found no important differences among them in rates of common side effects such as hypotension, cough, angioedema, hyperkalemia, or elevated serum creatinine.[72]

- A meta-analysis of 26 trials, involving 152,290 patients, found no difference in CV events between ACEIs or ARBs when compared against other antihypertensives in patients with reduced glomerular filtration rates (eGFR).[73]
- Among patients with diabetes, a meta-analysis of 19 RCTs involving over 25,000 patients with diabetes that compared Renin-Angiotensin-Aldosterone-System (RAAS) antagonists against other antihypertensives showed no differences in the risk for adverse clinical outcomes such as death, CV outcomes, or end stage renal disease.[74]
- ACEIs may not be preferred monotherapy for patients with a history of stroke. Based on the results of PROGRESS[75], ACEIs were no different than placebo in reducing recurrent stroke.
- When compared with ARBs, ACEIs have several-fold higher incidence of side effects at most doses, the most common being a dry, irritating cough.[76] In a meta-analysis of 125 studies including 198,130 patients, the pooled weighted incidence of cough for enalapril was found to be 11.48% (95% CI: 9.54%-13.41%). The pooled weighted withdrawal rate resulting from cough for enalapril was 2.57% (95% CI: 2.40%-2.74%).[77]

Many clinicians have been taught that RAAS inhibitors are efficacious for patients with CKD based on the results from some older clinical trials. For example, the African American Study of Kidney Disease and Hypertension (AASK) trial showed that ramipril was superior to metoprolol or amlodipine among hypertensive African-Americans with renal impairment in reducing a composite outcome that included GFR decline, ESRD and death.[78] Unfortunately, these findings on renoprotection have either not been consistently replicated or do not extend to hard clinical outcomes such as CV events or ESRD. However, the 2017 ACC/AHA guidelines recommend treatment with an ACEI to slow kidney disease progression in adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]).[9]

The American Diabetes Association also suggests the use of RAAS inhibitors as a preferred first-line agent for patients with diabetes, especially those with microalbuminuria or known CAD.[79] This recommendation was first made due to results from the HOPE study and MICRO-HOPE substudy, which randomized 3577 patients with diabetes and cardiovascular risk factors (though not necessarily hypertension) to ramipril and placebo or Vitamin E and placebo. After 4.5 years of follow-up those randomized to the ramipril group had 37% lower risk of cardiovascular death (95%CI 21%-51%) and 24% lower risk of developing overt nephropathy (95%CI 3%-40%) among other cardiovascular benefits even after controlling for the drug's blood pressure lowering affects.[80] More recently, additional professional

societies have also recognized RAAS inhibition as an appropriate first-line anti-hypertensive for patients with diabetes despite recent evidence that these drugs may not offer benefits over existing regimens.[74,81]

An observational study suggests that ACEI may be worse than CCBs or diuretics in some populations. This 2015 propensity-score matched cohort study of community-dwelling African-Americans on a range of antihypertensives found that ACEIs were associated with a higher risk of cardiovascular events (CV death, MI, and stroke) compared with CCBs or thiazide diuretics.[82] In particular, the RAAS in Black adults has typically been perceived to be less active than in White adults, as evidenced by a lower average BP reduction to monotherapy with ACEIs and ARBs in Black adults. Some evidence suggests that thiazide-type agents are superior to drugs that inhibit the RAAS (i.e., ACEIs, ARBs, renin inhibitors, and beta blockers) for prevention of selected clinical outcomes in Black adults.[9,83] For example, in ALLHAT, lisinopril (an ACEI) was less effective than chlorthalidone (a thiazide-type diuretic) and a CCB in lowering BP and in preventing many major clinical outcomes in Black participants.[83] Though there is no evidence that race-based prescribing necessarily improves rates of HTN control among Black adults, in Black adults with hypertension but without heart failure or CKD, including those with diabetes mellitus, it is still reasonable to preference an initial antihypertensive regimen that includes a thiazide-type diuretic or CCB.[9,84]

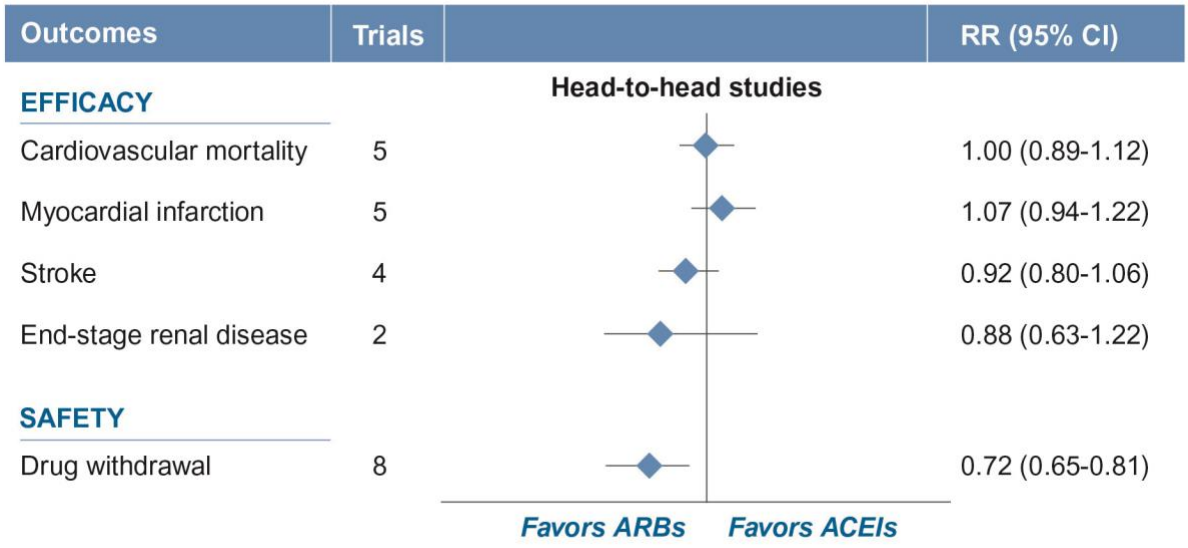
Angiotensin receptor blockers (ARBs)

ARBs were studied and introduced into routine practice more recently than ACEIs. Compared to ACEIs, ARBs present a lower risk for inducing cough (approximately 10% vs. 3%) or angioedema.[1] Common side effects include dizziness, headache, drowsiness, nausea, and diarrhea. There have been no head-to-head trials of the different ARBs that have measured clinical outcomes or safety.[85] The existing data do not suggest any meaningful differences among different ARBs.[86]

Many trials have found that ACEIs and ARBs are equally effective at lowering blood pressure.[87] A systematic review also found that ACEIs and ARBs had similar effects on quality of life, progression to diabetes, progression of renal disease, left ventricular function, cardiovascular events, and mortality.[87] One trial (LIFE) compared the ARB losartan against a beta-blocker atenolol among over 9000 patients with hypertension and left-ventricular hypertrophy. That trial found that losartan was more effective at preventing a composite CV endpoint than atenolol (HR 0.87; 95%CI: 0.77-0.98).

A 2018 meta-analysis of ACEI and ARB clinical trials compared outcomes and adverse events between ACEIs and ARBs in patients with hypertension, and found no difference in efficacy between the two classes with regard to the surrogate endpoint of blood pressure and outcomes of all-cause mortality, cardiovascular mortality, MI, heart failure, stroke, and end-stage renal disease. However, ARBs showed the highest reduction in SBP and DBP compared with ACEIs and direct renin inhibitors. Additionally, withdrawal rates because of adverse events were lower with ARBs than with ACEIs. Secondary analysis of ACCORD-BP and SPRINT demonstrated similar reductions in CV mortality, though overall mortality was lower among participants initiated on an ARB vs. ACEI.[88] Although historically ACEIs had been preferred as first-choice therapy patients with CVD, and ARBs were considered an alternative for ACEI–intolerant patients, the results from this study suggest that starting with an ARB may be preferred.[76] A separate meta-analysis of RCTs comparing ACEIs and ARBs to each other and active controls in patients with CKD and hypertension demonstrated that ACEIs reduced likelihood of renal failure by 35% (OR 0.65; 95% 0.51-0.89) and ARBs reduced the likelihood by 25% (OR 0.75; 95% 0.54-0.97); similar reductions in MACE occurred between ACEIs and ARBs (OR 0.82; 0.71-0.92 and OR 0.76; 95% CI: 0.62-0.89, respectively.[89]

Figure 14: Efficacy and safety of ACEIs vs. ARBs [76]



Calcium channel blockers (CCBs)

Two types of CCBs exist: dihydropyridine CCBs (e.g., amlodipine, felodipine) and non-dihydropyridine CCBs (e.g., diltiazem, verapamil). While both are approved for the treatment of hypertension, non-dihydropyridine CCBs are also used for other compelling indications like rate control in atrial fibrillation.

Although no trials have compared CCBs to one another in the treatment of hypertension, trials of CCBs to treat other conditions do not suggest any important differences in efficacy.[90] Indirect comparisons of CCBs suggest they are all relatively safe when used to treat hypertension.[90] A 2009 meta-analysis that included data for both dihydropyridines and non-dihydropyridine CCBs suggests that CCBs may be more effective than the other antihypertensive classes in preventing stroke.[61] Common side effects for dihydropyridine CCBs include peripheral edema, fatigue, and pulmonary edema, while dizziness, constipation, first degree AV block, and bradycardia are more common with non-dihydropyridine CCBs. CCBs should be started at a lower dose in older patients or patients with hepatic impairment.

BOTTOM LINE: In general, thiazides, ACEIs/ARBs, and CCBs are equally effective first line antihypertensives. In patients without other comorbidities, achieving the blood pressure goal is more important than the specific first-line drug class used to get there. In patient with comorbidities, there is some evidence that choice of agent may also matters. For example, in patients with diabetes or early-stage CKD, an ACEI or ARB is a preferred first-line agent, but ACEIs are not recommended for monotherapy for secondary prevention of stroke. There are no clinically significant differences between ACEIs and ARBs outcomes, but ARBs show a more favorable safety profile.

Beta-blockers

In early versions of the JNC guidelines, beta-blockers were recommended as first-line agents for treating uncomplicated hypertension. But since 2005 several reviews have highlighted limitations of beta-blockers

as medications to reduce high blood pressure in patients without a history of myocardial infarction.[91,92,93] These analyses found that while beta-blockers were superior to placebo for lowering blood pressure, they were inferior to the other major antihypertensive drug classes in preventing stroke, and were borderline inferior to other drug classes in preventing other cardiovascular outcomes such as MI. These differences were especially notable for older patients.[91]

Side effects of beta-blockers include fluid retention, fatigue, sexual dysfunction, bradycardia, heart block, and hypotension. Absolute contraindications include third degree heart block and a history of severe bronchospasm (although patients with mild-to-moderate bronchospasm may tolerate a beta-1 selective beta blocker). Relative contraindications include bradycardia, symptomatic hypotension, and severe peripheral artery disease.

Beta-blockers continue to have an important role in treating patients with both hypertension and a compelling indication such as CAD or heart failure (HF), but they are no longer considered a first choice agent for uncomplicated hypertension.[1] In the absence of a competing indication, patients taking a beta-blocker for hypertension should be evaluated for initiating an alternative therapy with proven CVD benefit.

One beta-blocker that was commonly used in the past should be avoided is atenolol. A 2004 meta-analysis demonstrated no difference in all-cause mortality, CV mortality or MI after 4.6 years with placebo and higher mortality (including stroke and cardiovascular mortality) with atenolol compared to other active treatments despite equivalent BP lowering.[94]

Renin inhibitors

Direct renin inhibitors block the conversion of angiotensinogen to angiotensin I. Aliskiren was approved by the U.S. Food Drug Administration in 2007 for treatment of primary hypertension. Direct renin inhibitors have the purported advantage of not affecting kinin metabolism, and therefore posing a lower risk for cough or angioedema than ACEIs.[95] A meta-analysis found that standard doses of aliskiren lower SBP to an extent similar to other anti-hypertensive classes.[96]

Aliskiren has not been compared in head-to-head trials with either ACEIs or ARBs for efficacy or safety, however the ALTITUDE[97] and ATMOSPHERE[98] trials showed that adding aliskiren to standard RAAS therapy (an ACEI or ARB) increased the risk of adverse events, including hypotensive symptoms, elevated serum creatinine, and elevated potassium levels. Aliskiren reduces the albumin-to-creatinine ratio in diabetics when added to an ARB, indicating it could have reno-protective effects independent of blood pressure control,[97] however the ALTITUDE trial showed no benefit on cardiorenal outcomes and possible increases in adverse events in patients with diabetes.[97]

Other agents

A number of agents may be considered for patients with resistant hypertension, defined as suboptimal blood pressure control despite treatment with at least three antihypertensive agents.[99] Evidence from PATHWAY-2, a double-blind placebo-controlled trial of 230 patients, demonstrated that in the absence of competing indication for alternative therapy, spironolactone, a mineralocorticoid antagonist and potassium-sparing diuretic, is the preferred medication to add in patients with resistant hypertension. which may be due to the underrecognized prevalence of primary hyperaldosteronism in the general population.[99,100] Alternative agents may be particularly useful for patients with hypertension and comorbid conditions for which these agents may be prescribed: alpha-blockers (e.g., doxazosin, prazosin,

terazosin); centrally-acting drugs (e.g., clonidine, methyldopa, reserpine, guanfacine); or direct vasodilators (e.g., hydralazine, minoxidil).

BOTTOM LINE: Beta-blockers and renin inhibitors are not considered first-line antihypertensives, although each may have utility for patients with selected comorbidities. Spironolactone is effective therapy for many patients with resistant hypertension.

Combination therapy

Since most antihypertensive medications at standard doses will lower SBP by 9-10 mm Hg, combination therapy is often required to achieve blood pressure goals. In the SPRINT trial, patients in the intensive treatment arm used an average of three medications to achieve the target blood pressure levels. In the ALLHAT trial, only about a quarter of patients were controlled on monotherapy.[101]

Most hypertension clinical trials allow for the addition of a second medication to reach target blood pressure levels. The combined data from these trials provide estimated effects of such combination therapy. Systematic reviews and meta-analyses have demonstrated that for the vast majority of antihypertensive combinations, the effect of combining two drug different classes equals the additive impact of each individual agent.[59,102]

Combination therapy requires a careful evaluation of each drug's dose-response relationship and dose-side effect relationship. Fortunately, most side effects are not additive across drug classes. The important exceptions to this include the increased risk of bradycardia with beta-blocker/CCB combinations, and the risk of hyperkalemia, hypotension, syncope, and renal dysfunction with ACEI/ARB combinations.

A 2008 randomized controlled trial of an ACEI and an ARB in high-risk patients (vascular and patients with diabetes), found that combination therapy did not reduce rates of a composite outcome (cardiovascular death, MI, stroke, or HF hospitalization).[103] However, the combination did produce significantly higher rates of adverse events than did either single agent, including hypotension, syncope, and renal dysfunction.[103]

One large trial (ACCOMPLISH) randomized 11,506 patients with hypertension at high risk of CV events to the combination of an ACEI+CCB or the combination of an ACEI+thiazide. Forty percent of patients were over 70 years old and over 60% had diabetes. This trial was stopped early because interim results showed that the ACEI+CCB was significantly better than the ACEI+thiazide. On the basis of ACCOMPLISH, assuming no other compelling indications, it is reasonable to start patients requiring two antihypertensives on an ACEI+CCB.

The PROGRESS trial also explored combination therapy in patients who had a stroke in the previous 5 years.[75] 3051 patients were randomized to active treatment of either and ACEI + thiazide or an ACEI alone; another 3054 patients were randomized to placebo.

Active treatment reduced blood pressure by 9/4 mm Hg (achieved BP: 138/82 mm Hg). 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction [RRR] 28%; 95% CI: 17–38; p<0·0001). Active treatment also reduced the risk of total major vascular events (RRR 26%; 95% CI:16–34). Combination therapy produced larger blood pressure reductions and larger risk reductions than did single drug therapy (ACEI alone was no better than placebo).

Importantly, the prescription of combination pills instead of separate medications has been shown to improve adherence and persistence (time to discontinuation), which may mediate some of the demonstrated benefits in above trials.[104] Nonadherence to antihypertensive therapy is common, with significant disparities among adults who self-identify as race or ethnic minorities, and adults living in low-healthcare access regions. A 2016 review of Medicare claims data of 18.5 million individuals found that 26.3% of patients (4.9 million) who had been started on antihypertensives were nonadherent to their regimen.[105] Nonadherence differed by multiple factors, including medication class (range: 16.9% for angiotensin II receptor blockers to 28.9% for diuretics); race-ethnicity (24.3% for non-Hispanic whites, 33.8% for Hispanics, 35.7% for blacks, and 38.8% for American Indians/Alaska Natives); and state of residence (range 18.7% for North Dakota to 33.7% for the District of Columbia).[105]

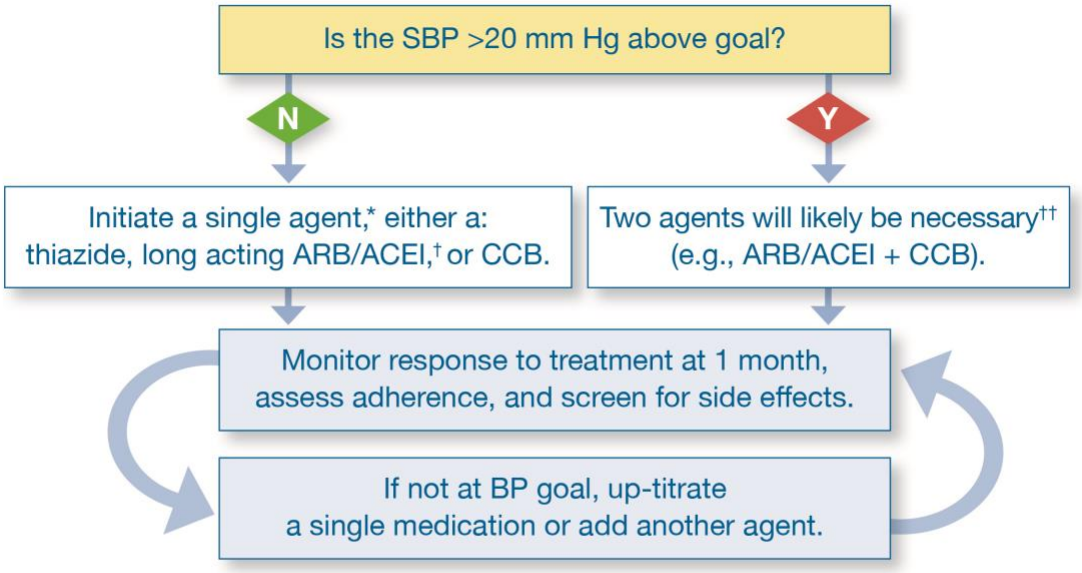
Finally, combination pills demonstrate greater cost-effectiveness than single agent therapy, and may reduce out-of-pocket costs due to a single copay instead of multiple separate copays.[106]

Practical steps for starting medications in patients with hypertension

For most patients a systolic blood pressure >20 mm Hg goal, initiating two antihypertensives will be required to achieve appropriate blood pressure reduction. For many patients who are age 75 or over, it may be reasonable to start one agent at a time. Titration upwards of doses at the subsequent visits will likely be required to achieve blood pressure goals. This practice is in accordance with the SPRINT protocol. This stepped approach is reasonable in a patient population that has higher risk of adverse events.

With 26% of Medicare beneficiaries not adhering to antihypertensive regimens, factors such as reducing the number of pills (using combinations when clinically appropriate) and having one prescriber managing blood pressure treatment increase the likelihood of patients adhering to therapy. Patients should be educated about non-pharmacological interventions such as reduced salt diet, exercise, weight loss and medication adherence throughout their treatment.

Figure 15: Initiating and managing patients on pharmacologic therapy



* For African Americans, initiate a thiazide or CCB.
† Combining an ACEI and an ARB confers no additional benefit and may increase adverse events. ARBs confer far less risk of cough or angioedema, and are preferred over ACEI.
†† For older patients, start one medication and intensify therapy at the first follow-up visit.

For patients on long-standing pharmacologic treatment for hypertension, prescribed medications should be reviewed to determine if patients will require de-escalation or discontinuation of medications based on their current status. Re-evaluation is critical for patients who experience changes such as weight loss, renal dysfunction, and/or hepatic impairment, which are all factors that could impact drug efficacy.

In the past, some have suggested that the timing of antihypertensives (i.e., whether they are taken in the morning versus evening) may affect the therapeutic benefit, akin to statins. However, an RCT of over 24,000 patients recently found no difference in cardiovascular death or hospitalization for non-fatal MI or stroke between groups randomized to morning compared to evening dosing of antihypertensives.[107] Counseling at time of prescription can therefore encourage that medications be timed based on convenience and minimizing adverse effects.

BOTTOM LINE: Many patients will require more than one antihypertensive agent to achieve their blood pressure goal. Absent other clinical indications or contraindications, ACCOMPLISH provides some evidence to support choosing an ARB (or ACEI)+CCB when 2-drug therapy is needed. However, the best multi-drug regimen is the one that a patient can adhere to.

Putting it all together

Hypertension is the most common condition seen in primary care. Because many effective treatments are available, hypertension represents one of the most important opportunities for clinicians to significantly reduce patients' risk of illness and disability. Healthcare teams should review their procedures for measuring and monitoring blood pressure to accurately identify patients needing treatment.

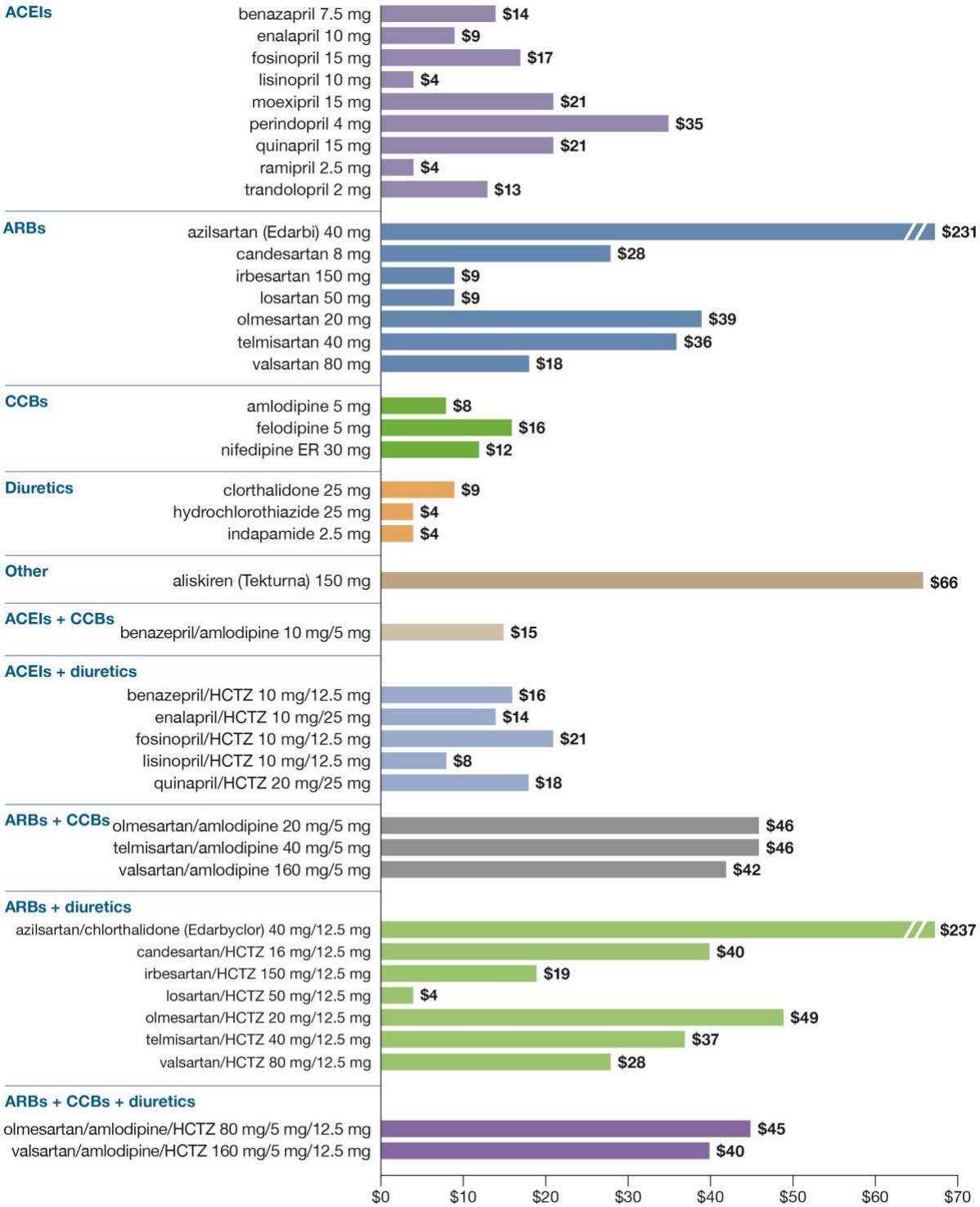
The available evidence provides a solid foundation for the creation of an evidence-based algorithm that can help guide clinical decision making. The process involves assessing each patient, then setting a reasonable, individualized blood pressure goal. The common goal of 130/80 mm Hg can be used as a clinical benchmark for treatment efficacy, to be modified at the discretion of the healthcare provider based on individual factors, such as diabetes, prior stroke, overall CV risk, and frailty.

Once patients are determined to have hypertension, a management plan should be created. Non-drug approaches such as a low sodium diet, aerobic exercise as tolerated, and weight loss are key components of a comprehensive treatment plan to lower blood pressure.

All major classes of hypertension medications lower blood pressure by a similar degree (~8-10 mm Hg) and have similar, though not identical, risks of adverse events. Some drug classes may be preferred for specific comorbid conditions. Overall, achieving the blood pressure goal is more important than the choice of drug. Clinicians should regularly assess response to treatment by asking about adherence, screening for side effects, and intensifying treatment with the goal of achieving a patient's target blood pressure.

Appendix 1. Cost of antihypertensives

Price of a 30-day supply of drug classes commonly used to treat hypertension.



Prices from goodrx.com, May 2023. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

Appendix 2. Systolic Blood Pressure Intervention Trial (SPRINT) key findings

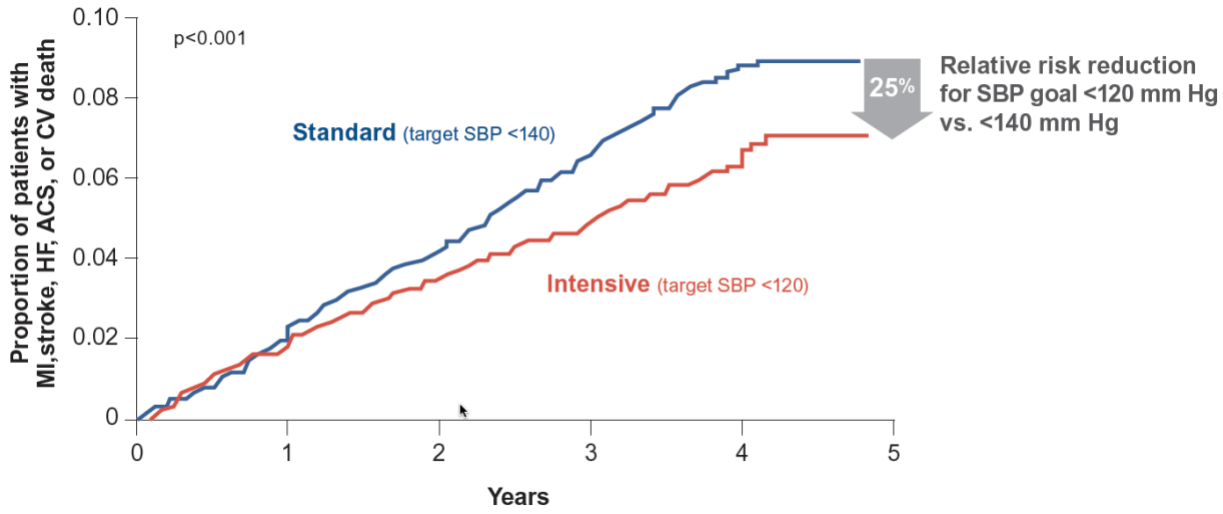
The results from both the SPRINT trial[13] and the SPRINT 75 subgroup trial[38] show that among patients at high risk for cardiovascular events but *without* diabetes or prior stroke, targeting an SBP <120 mm Hg, as compared <140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death. The trial randomized 4678 patients to intensive therapy (SBP ≤120 mm Hg) and 4683 patients to standard therapy (SBP ≤140 mm Hg). The primary outcome was a composite outcome of myocardial infarction (MI), acute coronary syndrome (ACS), stroke, acute decompensated heart failure or death from CV causes.

Table A1: Key inclusion and exclusion criteria for the SPRINT trial

Inclusion criteria	Exclusion criteria
• Age ≥50 years • SBP 130-180 mm Hg • Increased CV risk — clinical or subclinical CVD, except stroke — chronic kidney disease (eGFR 20-59 mL/min/1.73m^2) — Framingham risk score ≥15% — age ≥75 years	• Patients with: — diabetes — dementia — prior stroke — heart failure — end stage renal disease • Life expectancy <3 years • Residence in a nursing home

The trial was stopped early, after a median follow-up of 3.3 years, due to the significantly lower numbers of CV outcomes in the intensive group. At the end of the study, patients in the intensive treatment arm had a 1.6% absolute risk reduction in cardiovascular outcomes, corresponding to a 25% relative risk reduction (HR 0.75; 95% CI: 0.64-0.89; p<0.001).

Figure A1: Primary efficacy outcome for SPRINT[13]



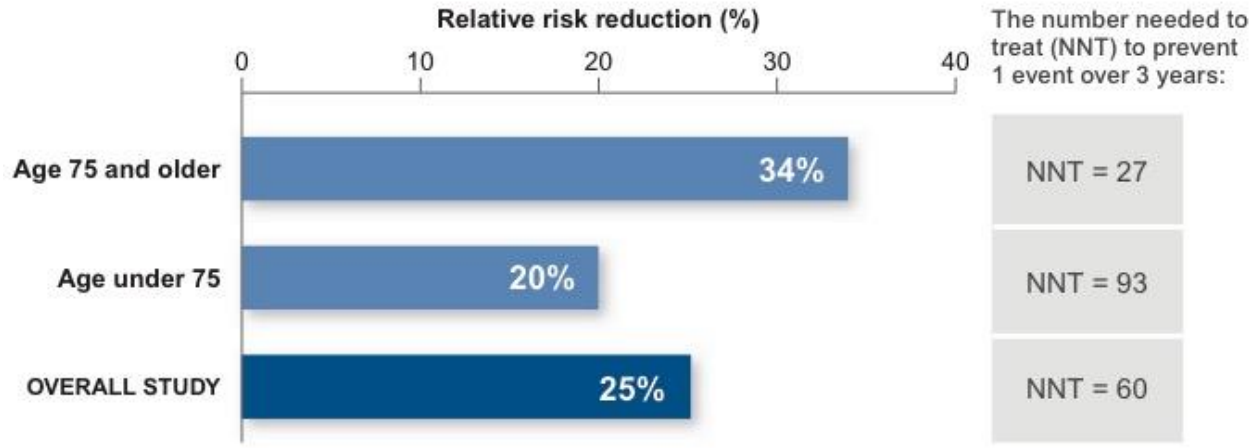
The open label trial design allowed for medication selection from a formulary, with most patients in the study receiving ACEIs/ARBs, thiazide diuretics, and CCBs. Intensive treatment required more medications (mean 2.8 vs. 1.8) and was associated with an increased risk of adverse events including: hypotension, syncope, acute kidney injury, and electrolyte abnormalities, although the higher risk of such events did not offset the observed decreases in the risk of cardiovascular outcomes. Serious adverse events, defined as those requiring hospitalization, were more common in those randomized to intensive therapy among all participants in SPRINT (number need to harm: 45). However, the rate of orthostatic hypotension (with or without dizziness) and injurious falls was not more common with intensive treatment. See Figure A3).

Older patients

Twenty-eight percent of the SPRINT trial comprised patients age ≥75, and these older individuals were evaluated in a pre-specified subgroup analysis. The results indicate that these patients benefitted from intensive SBP lowering even more than younger patients did. Lower BP goals reduced risk of CV events by about a third in many patients over 75 years of age (Figure A2).

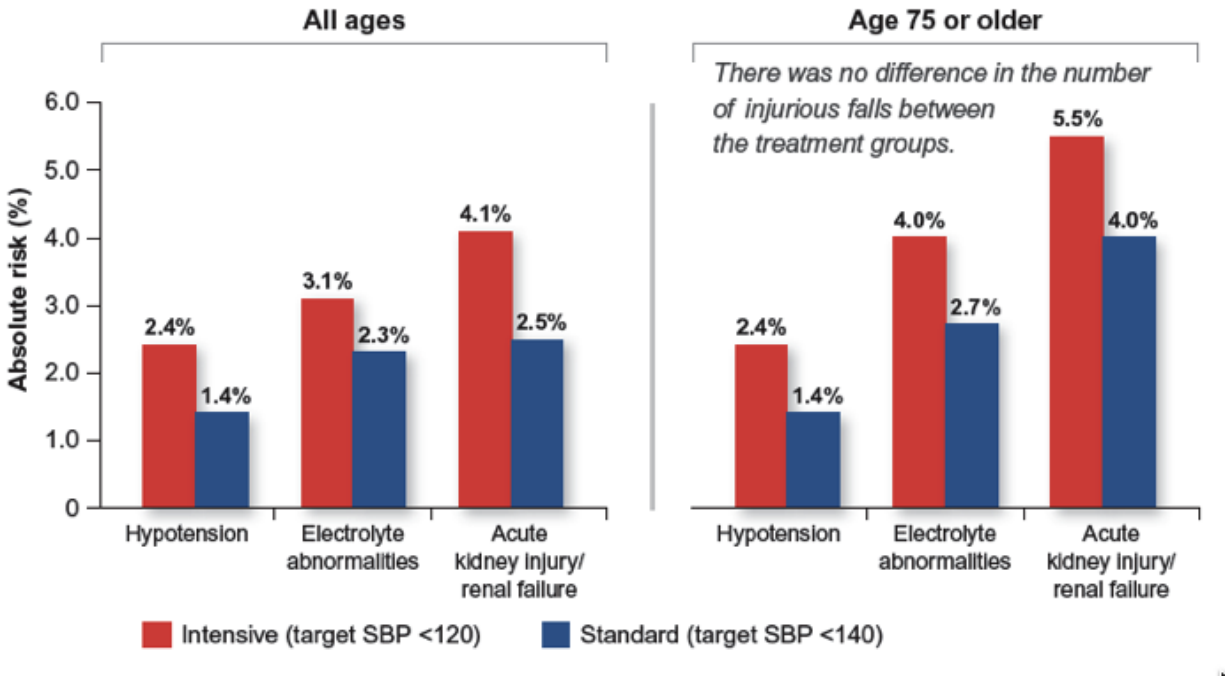
In SPRINT, the 2636 enrolled patients age 75 and over* had a greater relative risk reduction in CV outcomes that overall study participants from intensive (goal SBP <120 mm Hg) than standard (goal SBP <140 mm Hg) treatment.

Figure A2: Compared to the overall study and younger patients, fewer patients ≥75 need to be treated to prevent one CV event.



The rates of serious adverse events in both the intensive and standard treatment groups were high, with 48.4% and 48.3% of patients in the intensive and standard arms, respectively, reporting serious adverse events. There was no significant difference between the treatment arms in the rates of individual adverse events, including hypotension, syncope and the risk of falls.

Figure A3. Serious adverse events in SPRINT by age group[13]



While the results of SPRINT offer convincing evidence for lower SBP targets in patients who are either >75 or at increased cardiovascular risk, some important caveats must be kept in mind:

- The results of SPRINT do not re-define the threshold for diagnosing hypertension to an SBP greater than 120 mm Hg.
- SPRINT did not compare pharmacologic agents, hence the trial results do not provide guidance for medication choices.
- Randomization of the trial did not follow age stratification
- The trial was stopped early due to clinical impact, which limits evaluation of long term safety

Patients with chronic kidney disease (CKD)

CKD affects 10-15% of the general adult population and is associated with an increased risk of kidney failure and CV disease. Blood pressure is often elevated in patients with CKD and previous guidelines have recommended lower blood pressure goals in these patients.[8]

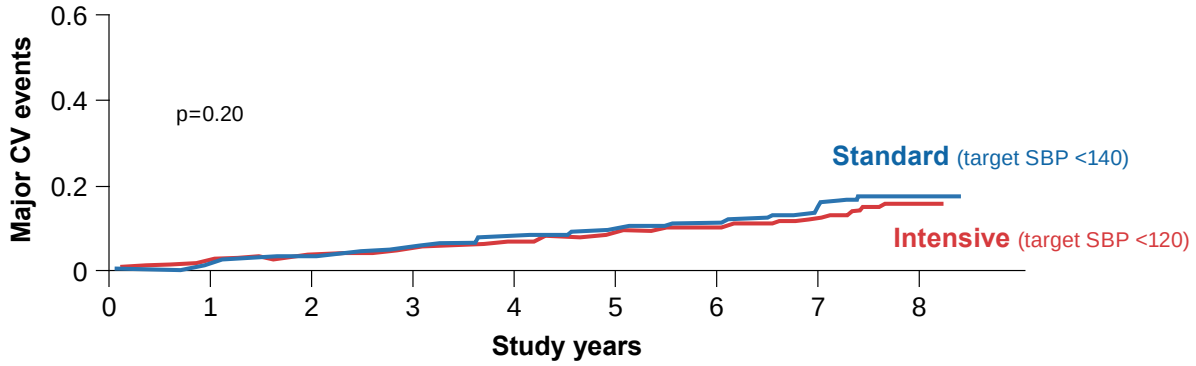
Until the publication of results from SPRINT, most guidelines for blood pressure targets in patients with CKD favored treatment to a blood pressure of <140/90 mm Hg, with consideration of the lower target of <130/80 mm Hg for those with more severe proteinuria (≥300 mg albuminuria in 24 hours or equivalent), if tolerated. In SPRINT, intensive blood pressure management in patients with stage 3 to 4 CKD (eGFR of 20 to <60 mL/minute/1.73 m^2), which comprised 28% of the SPRINT study population, seemed to provide the same benefits for reduction in the CVD composite primary outcome and all-cause mortality as were seen in the full study cohort. The 2017 ACC/AHA guidelines cites evidence from SPRINT to suggest a lower target of <130/80 mm Hg for all patients with CKD.[9]

Appendix 3. Action to Control Cardiovascular Risk in Diabetes (ACCORD) key findings

The U.K. Prospective Diabetes Study (UKPDS 38) found that a BP <150/85 mm Hg reduced diabetes-related endpoints, stroke, and microvascular disease compared to less intensive control (BP <180/105 mm Hg). The ACCORD BP trial was designed to investigate whether additional blood pressure lowering effect would provide additional cardiovascular benefit. This study randomized 4733 older patients with diabetes to intensive therapy (<120 mm Hg) or standard therapy (<140 mm Hg).[35] Mean age was 62 and mean SBP was 139. The mean follow-up was 4.7 years.

Figure A4. Intensive treatment to an SBP <120 mm Hg did not prevent more CV events than an SBP <140 mm Hg.[108]

The major results of ACCORD revealed:



- no difference in the primary outcome of major CV events comparing intensive versus standard blood pressure control.
- some reduction in stroke risk (a prespecified secondary outcome) in the intensive treatment group (HR 0.59; 95% CI: 0.39-0.89; p=0.01).
- lower blood pressure goal required more medications (3.4 vs. 2.4 in the intensive vs. standard, respectively) and patients experienced more adverse events attributed to blood pressure medications (3.3% vs. 1.27% in the intensive vs. standard groups, respectively). These events included: hypotension, syncope, bradycardia or arrhythmia, hypokalemia and elevations in serum creatinine.

Appendix 4. Secondary Prevention of Small Subcortical Strokes (SPS3) key findings

The Secondary Prevention of Small Subcortical Strokes (SPS3) study examined whether targeting an SBP <130 mm Hg was beneficial for patients with recent lacunar stroke.[40] 1519 patients were randomized to intensive therapy (SBP target <130 mm Hg), and 1501 patients were randomized to standard therapy (SBP target 130-149 mm Hg). The primary endpoint was reduction in all recurrent stroke (including ischemic strokes and intracranial hemorrhages).

After a mean follow-up of 3.7 years, the rate of recurrent stroke in the intensive therapy group was 2.25% (n=125) compared to 2.77% (n=152) in the standard therapy group, a difference that did not reach statistical significance (p=0.08). Similar trends were observed for reductions in disabling/fatal stroke and in the composite outcome of stroke, myocardial infarct or vascular death. Intracerebral hemorrhage, however, was reduced by 63% in those assigned to intensive therapy (HR 0.37; 95% CI: 0.14-0.89; p=0.03). Serious complications of blood pressure lowering were infrequent and not significantly different in frequency between groups.

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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