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Treatment of Hypertension
A Review

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IMPORTANCE Hypertension, defined as persistent systolic blood pressure (SBP) at least 130 mm Hg or diastolic BP (DBP) at least 80 mm Hg, affects approximately 116 million adults in the US and more than 1 billion adults worldwide. Hypertension is associated with increased risk of cardiovascular disease (CVD) events (coronary heart disease, heart failure, and stroke) and death.

OBSERVATIONS First-line therapy for hypertension is lifestyle modification, including weight loss, healthy dietary pattern that includes low sodium and high potassium intake, physical activity, and moderation or elimination of alcohol consumption. The BP-lowering effects of individual lifestyle components are partially additive and enhance the efficacy of pharmacologic therapy. The decision to initiate antihypertensive medication should be based on the level of BP and the presence of high atherosclerotic CVD risk. First-line drug therapy for hypertension consists of a thiazide or thiazidelike diuretic such as hydrochlorothiazide or chlorthalidone, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker such as enalapril or candesartan, and a calcium channel blocker such as amlodipine and should be titrated according to office and home SBP/DBP levels to achieve in most people an SBP/DBP target (<130/80 mm Hg for adults <65 years and SBP <130 mm Hg in adults ≥65 years). Randomized clinical trials have established the efficacy of BP lowering to reduce the risk of CVD morbidity and mortality. An SBP reduction of 10 mm Hg decreases risk of CVD events by approximately 20% to 30%. Despite the benefits of BP control, only 44% of US adults with hypertension have their SBP/DBP controlled to less than 140/90 mm Hg.

CONCLUSIONS AND RELEVANCE Hypertension affects approximately 116 million adults in the US and more than 1 billion adults worldwide and is a leading cause of CVD morbidity and mortality. First-line therapy for hypertension is lifestyle modification, consisting of weight loss, dietary sodium reduction and potassium supplementation, healthy dietary pattern, physical activity, and limited alcohol consumption. When drug therapy is required, first-line therapies are thiazide or thiazidelike diuretics, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, and calcium channel blockers.

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Multimedia

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Hypertension, a major risk factor for cardiovascular morbidity and mortality, is defined by the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline as systolic blood pressure (SBP) at least 130 mm Hg or diastolic BP (DBP) at least 80 mm Hg, or reported treatment with antihypertensive medication.[1,2] The prevalence of hypertension in US adults is approximately 44% to 49%.[3,4] Based on self-reported data from a survey of hypertension prevalence in 533 306 adults, it was estimated that eliminating hypertension in women would reduce population mortality by approximately 7.3% compared with 0.1% for hyperlipidemia, 4.1% for diabetes, 4.4% for cigarette smoking, and 1.7% for obesity.[5] Eliminating hypertension in men would reduce population mortality by approximately 3.8% compared with 2.0% for hyperlipidemia, 1.7% for diabetes, 5.1% for cigarette smoking, and 2.6% for obesity.[5]

Despite the well-established risks of hypertension and benefits of antihypertensive treatment,[6,7] an analysis of data from the National Health and Nutrition Examination Survey (NHANES) that included 18 262 US adults demonstrated that the age-adjusted percentage of the general adult population with hypertension (defined in the report as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication) whose SBP/DBP was controlled to less than 140/90 mm Hg was 48.5% in 2007-2008, 53.8% in 2013-2014, and 43.7% in 2017-2018.[8] This Review summarizes current evidence regarding treatment of hypertension, emphasizing the 2017 ACC/AHA high BP guideline recommendations.[2]

Methods

We searched the PubMed database for studies in English published since release of the 2017 ACC/AHA BP guideline from January 2018 to September 2022. References of selected articles were manually searched for additional relevant studies. Emphasis was given to

randomized clinical trials, systematic reviews and meta-analyses, clinical practice guidelines, scientific statements, and articles relevant to general medical practice. Of 457 reports identified, 45 were included, consisting of 18 randomized trials, 15 meta-analyses, 2 longitudinal observational studies, 6 cross-sectional studies, and 4 scientific statements.

Nonpharmacologic Management of Hypertension

Established nonpharmacologic interventions for the prevention and treatment of hypertension are losing weight, reducing dietary sodium, increasing potassium intake, consuming a heart-healthy diet, engaging in physical activity, and reducing alcohol consumption (**Table 1**).[10-23] Although difficult to achieve and sustain, behavior change is feasible, especially in motivated patients counseled by trained professionals with clinician reinforcement. Each of these interventions can reduce mean SBP by approximately 5 mm Hg in adults with hypertension and approximately 2 to 3 mm Hg in adults without it.[2] Greater BP reductions are possible in individuals with a higher initial BP when lifestyle interventions are combined.[24-26] Nonpharmacologic interventions also augment BP lowering by pharmacologic agents, including in patients with drug-resistant hypertension. A reasonable approach is to implement the intervention(s) most likely to be successful, based on lifestyle factors that are most suboptimal and on the patient's willingness to adopt the intervention(s).

Weight Loss

Weight loss is best achieved by combining calorie reduction and physical activity.[27] The ideal approach is gradual and results in durable weight loss, with a weekly reduction goal of 1 to 2 kg. An SBP reduction of approximately 1 mm Hg is expected for every kilogram of weight lost.[11] Among individuals with obesity and hypertension who meet the appropriate criteria (body mass index >35 [calculated as weight in kilograms divided by height in meters squared] and poorly controlled hypertension), bariatric surgery can induce substantial weight loss and meaningfully improve BP.[28]

Dietary Sodium and Potassium Intake

Any decrease in sodium intake is helpful because the association between sodium and BP reduction is approximately linear, with a 1000-mg sodium reduction resulting in SBP lowering of approximately 3 mm Hg.[15,25,29,30] As an optimal target, clinicians can recommend sodium intake of less than 1500 mg/d.[2] Eating patterns associated with lowering dietary sodium intake include eating fresh rather than processed foods, reducing portion size, avoiding foods especially high in sodium content, reading food labels for packaged and prepared foods, choosing condiments and seasonings with low sodium content, and attempting sodium substitutions by using herbs, spices, or potassium-enriched salt substitutes.[31]

Randomized clinical trials have demonstrated that potassium supplementation significantly lowers BP.[32] Most clinical trials demonstrating benefit added approximately 60 mmol/d. However, increasing foods high in potassium (ie, fruits and vegetables) is preferred because of the additional health benefits associated with this change. Potassium supplementation has greater effects on BP in people with a higher initial BP, people who are Black, and those consuming sodium at more than 2500 mg/d.[32] A clinical trial in rural China that randomized participants with a history of stroke or aged 60 years or older and with high BP in clusters (villages) to either a salt substitute (75% sodium chloride and 25% potassium chloride) or continued regular salt reported significantly lower rates of stroke (29 vs 34 events per 1000 person-years), major cardiovascular events (49 vs 56 events per 1000 person-years), and death from any cause (39 vs 45 events per 1000 person-years) in those randomized to salt substitute.[31] Rates of serious adverse events attributed to hyperkalemia were not significantly different in the salt substitute and regular salt groups (3 vs 3 events per 1000 person-years). However, the results of this study may not be entirely applicable in the US, where a larger proportion of sodium is consumed in processed foods as opposed to salt added during cooking or eating.

Whole Dietary Patterns

Heart-healthy diets, such as the Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH), consist of whole grains, vegetables, legumes, fish, olive oil, fruits, nuts, seeds, herbs, and moderate alcohol consumption (defined as ≤1 standard drink per day for women and ≤2 for men). In 1 clinical trial, 459 people with mean BP at baseline of 132/85 mm Hg were randomized to a diet high in fruits and vegetables (n = 154); a DASH diet high in fruits and vegetables and low-fat dairy foods and low in saturated fat, total fat, and cholesterol (n = 151); or a control diet typically consumed by US adults (n = 154).[18] The diets were prepared in a research kitchen and participants were asked not to eat other foods. After 8 weeks of adherence to the assigned diets, changes in SBP/DBP were −2.7/−1.9 mm Hg in the fruits and vegetables diet group and −5.5/−3.0 mm Hg in the DASH diet group compared with the control group. In the subgroup with hypertension, the SBP/DBP changes were −7.3/−2.9 mm Hg in the DASH group compared with the control group.

Physical Activity

Most clinical trials demonstrating a BP-lowering effect of physical activity have used aerobic exercise such as brisk walking, swimming, dancing, or gym exercises. However, dynamic resistance exercise such as hand grip or yoga is also beneficial.[33] Medium- to high-intensity exercise, such as running, and low-intensity aerobic exercise, such as walking, can lower BP.[34] According to clinical trial evidence, an exercise duration of 40 to 60 minutes at least 3 times per week may be optimal for BP lowering.[34]

Alcohol Consumption

Epidemiologic studies have repeatedly documented a progressive, direct, quantitative, dose-response relationship between alcohol consumption and level of BP, as well as the incidence of hypertension.[35] It is reasonable to continue small amounts of alcohol (≤2 drinks daily for men and ≤1 for women), but alcohol consumption should not be encouraged because of the risk of accidents, injuries, and liver disease and the potential for alcohol dependency.[2]

Role of Cardiovascular Disease Risk in the Management of Adults With High BP

In prospective observational studies, mean SBP was directly associated with risk of atherosclerotic cardiovascular disease (ASCVD) across SBP ranging from 90 to 180 mm Hg.[36-38] However, at any level

Table 1. Most Effective Nonpharmacologic Interventions to Lower Blood Pressure

Lifestyle characteristic	Association with high BP	Intervention	Regimen/dosage	Expected BP improvement
Weight loss	Prevalence of overweight (BMI 25-<30) and obesity (BMI ≥30) in US adults: >70% (>40% obesity)[10]	Combined calorie reduction and physical activity, preferably provided by someone trained to deliver behavioral interventions	Achieving ideal weight is optimal, but any reduction in weight is beneficial In most clinical trials, an average ≈4.5-kg (10-lb) weight loss has been achieved with behavior-change interventions, but long-term maintenance of weight loss has been challenging	In a meta-analysis of 25 randomized clinical trials, average weight loss was 5.1 kg (11.2 lb) and average reduction in SBP/DBP was 7.00/5.49 mm Hg in patients treated with antihypertensive medication and 3.77/2.97 mm Hg in those who were not[11] When expressed per kilogram of weight loss, the reductions in SBP/DBP were 1.05/0.92 mm Hg
	In a meta-analysis of 10 prospective cohort studies (N = 173 828), the risk ratio of hypertension in adults with overweight and obesity compared with normal weight was 1.52 and 2.17, respectively[9]	Bariatric surgery reserved for individuals with BMI ≥40 or ≥35 with ≥1 obesity-related comorbidity		In a single-center trial (N = 144), addition of weight loss to the DASH diet resulted in an additional SBP/DBP reduction of 4.9/2.4 mm Hg at 4 mo
Sodium intake	In the INTERSALT cross-sectional study (10 079 adults; 32 countries), increased sodium intake of 2300 mg/d (100 mmol) was associated with a level of SBP 3-6 mm Hg higher[14]	Reduced dietary sodium consumption counseling, preferably provided by someone trained to deliver behavioral interventions	The ACC/AHA recommends an optimal sodium intake of <1500 mg/d The USDA Dietary Guidelines for Americans recommends <2300 mg/d and the WHO recommends <2000 mg/d Most US adults consume sodium well in excess of these recommendations. Because of the linear dose-response relationship between sodium intake and BP, any reduction in sodium intake is beneficial	Meta-analyses of sodium reduction trials have identified an SBP reduction of ≈5 mm Hg for adults with hypertension and 2.5 mm Hg in adults without it[13] Dose-response meta-analysis has identified an approximately linear association, with a 1000-mg reduction in dietary sodium resulting in ≈3- and 1-mm Hg SBP reduction in adults with and without hypertension, respectively[15]
	In a 2005-2010 NHANES analysis, SBP was 2.4 mm Hg higher for a sodium intake that was higher by 2300 mg[12]	Elements for success: selecting food carefully, favoring fresh foods and minimizing processed foods and those known to be high in salt content; reading food labels when purchasing food products; moderating portion size; using salt substitutes such as potassium-rich salts, herbs; minimizing fast food or sit-down restaurant food consumption; requesting no added salt when ordering		
	The INTERSALT investigators suggested that every year of exposure to a daily sodium intake increase of 2300 mg might result in an increase of 0.5 mm Hg in SBP, partly explaining the age-related increase in BP common in most populations			

(continued)

Table 1. Most Effective Nonpharmacologic Interventions to Lower Blood Pressure (continued)

Lifestyle characteristic	Association with high BP	Intervention	Regimen/dosage	Expected BP improvement
Potassium intake	In the INTERSALT study, a daily potassium intake increase of 50 mmol (1955 mg) was associated with a decrease in SBP of 3.4 mm Hg	Fruits, leafy greens, beans, nuts, dairy foods, and starchy vegetables (potatoes, winter squash) are a rich source of potassium The DASH diet provides potassium at 4700 mg/d. Potassium pill supplements (60 mmol/d) are effective for BP lowering but do not provide the additional benefits of a dietary supplementation approach	A potassium intake of 3500-5000 mg/d, preferably through diet, is the optimal approach but any increase is good	Meta-analyses have repeatedly documented a BP-lowering effect of potassium supplementation, whether achieved by diet or pill supplementation In a 2017 meta-analysis of 25 randomized clinical trials, SBP and DBP were reduced by an average of 4.5 and 3.0 mm Hg, respectively[16] In a meta-analysis of 32 trials, a nonlinear *U*-shaped dose-response relationship was identified but there were only a limited number of trials informing the upper end of the relationship[17]
	In the 2005-2010 NHANES report, the fully adjusted equivalent was a decrease in SBP of 2.4 mm Hg for a daily potassium intake increase of 50 mmol (1955 mg)			
Whole dietary patterns	Many observational studies have documented lower BP in adults consuming a vegetarian compared with nonvegetarian diet and have suggested that vegetarians experience a lower age-related increase in BP Vegetarian individuals tend to exhibit lifestyle characteristics that favor a lower BP, making it difficult to estimate the quantitative role of nonvegetarian dietary consumption as a cause of hypertension	DASH specifically maximizes BP lowering, but all vegetarian diets tend to lower BP, whether specific or a component of heart-healthy diets such as Mediterranean, vegan, or low carbohydrate	The DASH diet is high in fruits, vegetables, and whole grains It allows for consumption of fat-free or low-fat dairy products, fish, and poultry The standard DASH diet contains sodium at ≈2300 mg/d Dose-response meta-analyses have demonstrated a significant association between DASH diet adherence and risk of stroke, as well as all-cause and cause-specific mortality	In an 8-wk feeding study, the DASH diet lowered SBP/DBP by 5.5/3.0 mm Hg[18]
				In a 6-mo behavioral intervention trial, the DASH diet reduced SBP/DBP by 4.3/2.6 mm Hg compared with advice only, and by 0.6/0.9 mm Hg compared with "established recommendations (weight loss, physical activity, reduced sodium intake, and moderation in alcohol consumption)"[19]
Physical activity	In a meta-analysis of 29 longitudinal cohort studies (330 222 adults with 67 698 cases of incident hypertension during follow-up), both leisure time and total physical activity demonstrated an inverse linear association with the risk of incident hypertension, with the risk being 6% lower in those who met the minimal level of physical activity recommended in guidelines (exercise at 150 min/wk) compared with those who were inactive[20]	Most physical activity, including aerobic (endurance) and resistance (strength) exercises, lowers BP	Common forms of aerobic exercise include brisk walking, running, swimming, dancing, gym workout, or some combination 5-7 times/wk (approximately 30-60 min/session; ≥150 min/wk), with gradual start/warm-up and postexercise cool-down[21] Many studies have documented clinically important reductions in BP with physical activity of only modest intensity.	In a network meta-analysis of 391 trials (197 evaluating exercise and 194 evaluating antihypertensive drug therapy), SBP was reduced, compared with control, by 4.88 mm Hg with aerobic exercise, 3.50 mm Hg with resistance exercise, and 6.49 mm Hg with the combination In patients with hypertension, the BP reduction magnitude was similar to that obtained with different antihypertensive medications (average SBP difference = 0.18 mm Hg)[21]

(continued)

Table 1. Most Effective Nonpharmacologic Interventions to Lower Blood Pressure (continued)

Lifestyle characteristic	Association with high BP	Intervention	Regimen/dosage	Expected BP improvement
		Most trials have used aerobic exercise, most commonly prescribed for prevention and treatment of hypertension	Common forms of dynamic resistance exercise include weightlifting, use of a weight machine, push-ups, squats, bicep curls, and circuit training They should be performed at least 2-3 times/wk (90-150 min)	
		Although less well studied, dynamic resistance exercise seems to provide BP lowering of similar magnitude to aerobic exercise and is often used as a complement to aerobic exercise	Common forms of isometric resistance exercise include the plank, side bridge, wall sit, hand grip, and yoga poses. They should be practiced at least 3-4 times/wk	
		Isometric resistance exercise, also known as static strength training, involves holding a position rather than moving. Although less well studied, it seems to provide effective BP lowering		
Alcohol consumption	Epidemiologic studies have repeatedly documented a progressive, direct dose-response relationship between alcohol consumption and level of BP, as well as prevalence and incidence of hypertension, with a doubling of hypertension prevalence for individuals consuming ≥3 alcoholic drinks/d compared with people who do not drink alcohol[22]	Interventions have included behavioral counseling, use of reduced alcohol (eg, light beer) or alcohol-free drinks (eg, mineral water or dealcoholized wine), and abstinence	Most interventions have aimed for a reduction rather than elimination of alcohol consumption and have targeted individuals consuming an average of ≥2-3 alcoholic drinks/d, with the goal of consuming ≤2 standard drinks/d in men and ≤1 standard drink/d in women However, any reduction in alcohol consumption is beneficial	Reducing or eliminating alcohol intake results in BP lowering, with an approximately linear dose-response pattern In a meta-analysis of 31 alcohol reduction trials, average SBP/DBP was reduced by 5.5/3.97 mm Hg in individuals consuming ≥2 drinks/d[23] There was no significant reduction in BP in those drinking <2 alcoholic beverages/d at baseline

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; NHANES, National Health and Nutrition Examination Survey; SBP, systolic BP; USDA, US Department of Agriculture; WHO, World Health Organization.

Table 2. Recent Randomized Trials of Drug Treatments for Hypertension

Source	Design	Size	Sample	Mean age, y	SBP/DBP, mm Hg[a]			Results	
					Baseline	SBP targets	Achieved	Primary outcome	Primary outcome results
SPRINT, 2015[48] and 2021[49]	2-Arm parallel RCT	9361	Adults with high BP and high risk of CVD No patients with diabetes or survivors of stroke Strong representation of older adults and patients with CKD	68	140/78	<120 and <140	119/- and 136/- (Median after 6 mo)	CVD composite	Significant benefit for the primary outcome of composite CVD events: 1.65% per year in the intervention group vs 2.19% in the standard treatment group and 25% reduction in all-cause mortality
STEP,[50] 2021	2-Arm parallel RCT	9624	Adults 60-80 y with high BP High CVD risk cohort	66	146/82	110-129 and 130-149		CVD composite	Significant 26% benefit in the primary outcome for intensive pharmacologic treatment group (3.5% vs 4.6%)
Neal et al,[31] 2021	Open-label, cluster RCT	20 995	Adults with a history of stroke or ≥60 y with high BP in 600 villages (clusters) in rural China Salt substitute (25% potassium and 75% sodium) vs regular salt intake High CVD risk cohort	65	154/89	NA	151/- (Median after 60 mo)	Stroke	Significant reduction in stroke rates in the salt substitute vs the regular salt intake group (29.14 events/ 1000 person-years vs 33.65 events/1000 person-years)
ACCORD,[51] 2010	2 × 2 Factorial RCT (BP and glycemic interventions)	4733	Adult patients with diabetes who were at high risk for CVD	62	139/76	<120 and <140	119/64 and 133/70	CVD composite	No significant treatment difference (1.87% event rate in intervention group vs 2.09% in control) Nominal SPRINT-like benefit for intensive BP lowering in normoglycemic subgroup
SPS3,[52] 2013	2 × 2 Factorial RCT (BP and antiplatelet interventions)	3020	Adults with recent lacunar stroke	63	143/79	<130 and 130-149	127/- and 138/-	Recurrent stroke	Nonsignificant lower event rate (2.25% vs 2.77%, P =.08) in the intensively treated group, compared to control

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic BP; NA, nonapplicable; RCT, randomized clinical trial; SBP, systolic BP.

[a] Dashes indicate no values were provided for DBP.

of BP, the risk of ASCVD varies approximately 30-fold, depending on the presence of other CVD risk factors.[39] For example, at a mean SBP of 130 mm Hg, the 10-year predicted risk of ASCVD varies from 1.1% to 38.4%.[39] In one of several similar meta-analyses of antihypertensive drug treatment trials, a reasonably constant reduction in CVD relative risk (risk ratio of 0.82 to 0.85) has been noted in adults with different levels of CVD risk at baseline (5-year risk of CVD from <11% to >21%).[40] However, the corresponding absolute reduction in CVD risk was greater in individuals with a higher level of baseline CVD risk compared with a lower one (reduction in CVD events per 1000 people over 5 years of 38 vs 14 events). Meta-analyses and modeling studies of observational data showed associations of antihypertensive drugs with improved cardiovascular risk across baseline SBP from less than 120 mm Hg to at least 170 mm Hg.[41] This has led some researchers to recommend treating adults only according to high risk of ASCVD[42,43] rather than treating individual CVD risk factors, such as high BP,[44] or using population-wide strategies such as sodium intake reduction or smoking cessation.[45] The ACC/AHA and most other BP guidelines recommend basing treatment decisions on a combination of ASCVD risk and pretreatment BP level.[2]

The 2017 ACC/AHA high BP guideline reclassified BP into the following categories: normal BP (SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (SBP 120-129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg), and stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg).[2] For stage 1 hypertension, the ACC/AHA BP guideline recommends estimating 10-year ASCVD risk in adults aged 40 to 79 years who have not had a CVD event by using the pooled cohort equations calculator, which has been validated in US Black and White adults. The calculator is accessible on websites[46] and may be downloaded as a mobile phone application or embedded in clinical information system software. For antihypertensive drug therapy decisions, a history of a CVD event or a calculated 10-year risk of ASCVD at least 10% in adults without a history of clinical CVD reflects high ASCVD risk and is an indication to prescribe antihypertensive drug therapy in adults with stage 1 hypertension.[2] The knowledge that clinicians may not always formally estimate ASCVD risk led the ACC/AHA BP Guideline Writing Committee to accept aged 65 years or older, diabetes, and chronic kidney disease as surrogate indicators of high ASCVD risk, an approach that was validated in an NHANES analysis.[47]

Pharmacologic Treatment of Hypertension

Table 2 shows the major randomized clinical trials informing this narrative review. Randomized clinical trials have established that pharmacologic BP lowering reduces the risk of CVD events and death in adults with hypertension.[6,7] Lowering SBP by 10, 20, or 30 mm Hg to achieve the treatment goal of 120 to 124 mm Hg was associated with a reduction in CVD event rates of 29%, 42%, and 54%, respectively.[7] For adults with stage 2 hypertension, lifestyle modification combined with antihypertensive drug therapy using 2 complementary agents from different pharmacologic classes is recommended.[2] These patients should be treated regardless of whether they have a history of CVD, and the 2 antihypertensive drugs should be combined in 1 pill, if available. For patients with stage 1

hypertension and either history of CVD or at increased risk for CVD, a combination of lifestyle modification and pharmacologic therapy with a single drug is recommended.

The SBP/DBP goal during antihypertensive therapy in adults younger than 65 years is less than 130/80 mm Hg. Intensive BP control in older adults with hypertension has been controversial owing to concerns about adverse consequences of treatment such as orthostatic hypotension, falls, electrolyte abnormalities, acute kidney injury, and hypoperfusion of vital organs, including the heart and brain. However, in the SPRINT randomized trial, adults aged 75 years or older, even those who were frail or with slow gait, significantly benefited from treatment to an SBP target of less than 120 mm Hg compared with one of less than 140 mm Hg.[53]

The STEP randomized clinical trial of 8511 patients aged 60 to 80 years demonstrated that intensive antihypertensive treatment to an SBP target of 110 to less than 130 mm Hg reduced CVD events (stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from a cardiovascular cause) compared with treatment to an SBP target of 130 to less than 150 mm Hg.[50] After 1 year of treatment, the mean SBP was 127.5 mm Hg in the intensive treatment group and 135.3 mm Hg in the standard treatment group. During a median follow-up period of 3.34 years, primary outcome events occurred in 3.5% of the intensive treatment group and 4.6% of the standard treatment group (hazard ratio for intensive vs standard treatment, 0.74; 95% CI, 0.60-0.92; $P < .007$). This trial was stopped early because of treatment benefit. Hypotension, defined as SBP less than 110 mm Hg or DBP less than 50 mm Hg, was higher in the intensive treatment group compared with the standard treatment group (3.4% vs 2.6%), but there were no significant differences in rates of dizziness, syncope, or fractures. There was no difference between the 2 treatment groups in rates of estimated glomerular filtration rate decline by 30% or greater or by 50% or greater or the number with an incident estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

In the SPRINT clinical trial, there were no significant differences between the intervention and control groups in rates of orthostatic hypotension (5.7% vs 5.0%), electrolyte abnormalities (2.7% vs 3.7%), injurious falls (6.6% vs 7.5%), or acute kidney injury (2.5% vs 4.3%).[54,55] These results were consistent with the 2017 ACC/AHA BP guideline recommendation of an SBP treatment goal of less than 130 mm Hg for noninstitutionalized ambulatory community-dwelling adults aged 65 years or older.[2] However, titration to a lower BP goal requires careful monitoring and use of properly performed out-of-office or in-office BP measurements to avoid clinical decision making based on inaccurate, elevated values.

Although randomized clinical trial data are unavailable for young adults (18-40 years) with hypertension, recent observational studies have demonstrated an association of hypertension with higher rates of subclinical CVD in young adults with hypertension, including in those with a low 10-year ASCVD risk.[56,57] For adults with stage 1 hypertension, no history of CVD, and a 10-year ASCVD risk less than 10%, a 6-month trial of intensive lifestyle modification is recommended. If BP less than 130/80 mm Hg is not attained after approximately 6 months (overall success rate with first attempt, 27%),[25] clinicians should consider pharmacologic therapy with a single first-line antihypertensive agent (ie, diuretic, calcium channel blocker, or renin-angiotensin system inhibitor).[58] Consideration should be given to earlier initiation of pharmacologic therapy in patients with a concomitant family history of premature CVD, personal history of hypertension during pregnancy, or history of having been born prematurely (born significantly before their due date).[58]

First-line pharmacologic therapy for hypertension consists of thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (**Table 3**), or available 2-drug combinations.[2,60] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should not be administered simultaneously (Table 3).[2,60] Unless the patient has a history of ischemic heart disease or heart failure, β-blockers are generally not recommended as first-line agents because of their reduced benefit for stroke prevention compared with the previously mentioned first-line agents.[2,60]

BP Treatment Target

The optimal BP goal for individuals balances the benefits of BP reduction to prevent CVD events with the risks of adverse effects at that level of BP.[2,61] Evidence supporting an SBP goal of less than 130 mm Hg for most adults comes from the SPRINT and STEP clinical trials, as well as multiple systematic reviews and meta-analyses.[48,49,62-65] Although to our knowledge recent trials have not focused on DBP, a value of less than or equal to 80 mm Hg is a reasonable goal and recommended as a target for adults younger than 65 years. Thus, the new optimal BP goal for adults with hypertension is less than 130/80 mm Hg except in adults aged 65 years or older when the goal is SBP less than 130 mm Hg without regard to DBP.

For adults with diabetes and hypertension, clinical practice guidelines support an SBP goal of less than 130 mm Hg.[2,61,66,67] For adults with chronic kidney disease who are not undergoing dialysis, with or without diabetes, the most recent Kidney Disease: Improving Global Outcomes guidelines recommended an SBP goal of less than 120 mm Hg when tolerated,[68] but other guidelines recommend less than 130 mm Hg.[2,61] The BP goal for patients with other comorbidities (eg, stroke, ischemic heart disease, peripheral artery disease, heart failure) is less than 130/80 mm Hg.[2]

BP Monitoring and Dose Titration to Achieve Target

Suboptimal medication adherence and failure by clinicians (ie, physicians, nurse practitioners, and physician assistants) to appropriately increase medication doses are common causes of not achieving the BP goal and can prevent optimal reduction in CVD risk and death.[69] Successful attainment of the ideal BP level requires continuous accurate BP monitoring (by patients and their clinicians), appropriate pharmacologic dose titration in response to current BP levels, and, in those who fail to respond to dose escalation, assessment of adherence to the antihypertensive regimen.[70] Optimally, office-based BP monitoring should be combined with out-of-office measurements, such as home BP monitoring recordings obtained by a carefully instructed patient who uses the proper BP measurement technique and provides cumulative BP readings to the clinician's office. In a study of community-dwelling adults (N = 318), 2 readings taken in the morning and evening for a minimum of 3 d/wk were sufficient for reliable estimation of out-of-office BP.[71] This method not only enhances treatment adherence and improves treatment control but also helps to avoid overtreating white coat hypertension (BP high in the office but normal at home) and allows detection of

Table 3. Major Drug Classes in the Treatment of Hypertension

Medication class	Selected medication examples	Dose range, mg, (frequency per day)	Mechanism of action	SBP reduction, mm Hg[57,58] vs placebo (95% CI)	Most common a dverse effects	Overall AE rate/class, %[a]	Additional comments
First-line							
Diuretic (thiazide or thiazidelike)	Chlorthalidone	12.5-25 (once)	Block renal distal tubule sodium reabsorption by inhibiting NCC	12.4 (18.8-6.0) for diuretics	Hyponatremia, hypokalemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia	Similar to placebo	Chlorthalidone preferred (prolonged half-life and proven CVD reduction)
	Hydrochlorothiazide	12.5-50 (once)					
	Indapamide	1.25-2.5 (once)					
ACE inhibitor	Benazepril	10-40 (once or twice)	Inhibit ACE activity and angiotensin II formation	12 (20.5-3.6) for ACE inhibitors	Hyperkalemia in CKD, reduced GFR, AKF in severe bilateral RAS, hypotension, cough, angioedema	Similar to placebo	Do not use in combination with ARB; contraindicated in pregnancy
	Enalapril	5-40 (once or twice)					
	Lisinopril	10-40 (once)					
	Ramipril	2.5-20 (once)					
	Trandolapril	1-4 (once)					
ARB	Azilsartan	40-80 (once)	Inhibit angiotensin II binding to the angiotensin type 1 receptor	10.7 (20.0-1.4) for ARB class	Hyperkalemia in CKD, reduced GFR, AKF in severe bilateral RAS, hypotension	Similar to placebo	Do not use in combination with ACE inhibitor; contraindicated in pregnancy
	Candesartan	8-32 (once)					
	Losartan	50-100 (once or twice)					
	Olmesartan	20-40 (once)					
	Valsartan	80-320 (once)					
CCB (dihydropy-ridine)	Amlodipine	2.5-10 (once)	Block voltage-gated (L-type) calcium channels preventing cellular calcium entry	15.9 (22.2-9.5) for dihydropy-ridine class	Dose-dependent peripheral edema, gingival hyperplasia		Amlodipine preferred CCB if tolerated; avoid CCB in HFrEF
	Felodipine	2.5-10 (once)					
	Nifedipine LA	30-90 (once)					
CCB (nondihy-dropyridine)	Diltiazem ER	120-360 (once)	Block voltage-gated (L-type) calcium channels preventing cellular calcium entry	4 (9.1-2.1) for nondihy-dropyridine class	Bradycardia, nausea, constipation		Avoid use with β-blocker; do not use in patients with HFrEF. Contraindicated in high-grade AV or SA block
	Verapamil delayed-onset ER	100-300 (once in evening)					
Second-line							
MRA	Eplerenone	50-100 (twce)	Block mineralocorticoid receptor activity	21.9 (23.0-20.8) for MRA	Hyperkalemia, especially in CKD and during potassium supplementation. Spironolactone: gynecomastia and erectile dysfunction in men.		Preferred in low-renin states and resistant hypertension
	Spironolactone	25-100 (once)				8.6-20	
β-Blocker	Metoprolol succinate		Block β-adrenergic receptors	10.1 (14.2-5.1)	Asthma, bradycardia, fatigue, exercise intolerance, impaired concentration and memory, worsening depression	Similar to placebo	First-line only in IHD and HF; contraindicated in high-grade SA or AV block
	Carvedilol phosphate	50-200 (once)					
	Nebivolol						
		20-80 (once)					
		5-40 (once)					

(continued)

Table 3. Major Drug Classes in the Treatment of Hypertension (continued)

Medication class	Selected medication examples	Dose range, mg, (frequency per day)	Mechanism of action	SBP reduction, mm Hg[57,58] vs placebo (95% CI)	Most common adverse effects	Overall AE rate/class, %[a]	Additional comments
Potassium-sparing diuretic	Amiloride	5-10 (once or twice)	Block cortical collecting duct sodium reabsorption by inhibiting ENaC	NA	Hyperkalemia, especially in CKD	Similar to placebo for potassium-sparing diuretics	Minimally effective in BP reduction. Commonly used to counteract hypokalemia during diuretic use.
	Triamterene	50-100 (once or twice)					
Loop diuretic	Furosemide	20-80 (twice)	Inhibit sodium reabsorption in the thick ascending limb of the loop of Henle by inhibiting NKCC2		Volume depletion, hypokalemia, hyperuricemia	Similar to placebo for loop diuretics	Preferred in CKD with GFR <30, in symptomatic HF, and when potent direct vasodilator minoxidil is used
	Torsemide	5-10 (once)		NA			
α_1-Antagonist	Doxazosin	1-16 (once)	Inhibit α_1-adrenergic receptors	10.6 (19.8-1.4)	Orthostatic hypotension, especially in older adults	9	Use when increased SNS activity suspected
Central α_2-agonist and other centrally acting drugs	Clonidine (oral)	0.1-0.8 (twice)	Stimulate CNS α_2-adrenergic receptors		Sedation, dry mouth, bradycardia, fatigue, constipation, orthostatic hypotension	6-19 for the drug class	Last line owing to CNS effects and potential for hypertensive crisis on withdrawal
	Clonidine patch	0.1-0.3 (1/wk)		NA			
	Guanfacine	0.5-2 (once)					
Direct vasodilator	Hydralazine	100-200 (2 or 3)	Dilate peripheral arterioles	NA	Reflex tachycardia; fluid retention		Hydralazine: use with diuretic and β-blocker
	Minoxidil	5-100 (1-3)			Hydralazine: drug-induced lupus syndrome	Up to 80 for direct vasodilators	Minoxidil: use with loop diuretic and β-blocker
					Minoxidil: hirsutism in women		

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; AE, adverse event; AKF, acute kidney failure; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; CVD, cardiovascular disease; ENaC, epithelial sodium channel; ER, extended release; GFR, glomerular filtration rate; HF, heart failure; HFrEF, HF with reduced ejection fraction; IHD, ischemic heart disease; LA, long acting; MRA, mineralocorticoid receptor antagonist; NA, not available; NCC, sodium chloride cotransporter; NKCC2, sodium-potassium 2 chloride cotransporter; RAS, renin-angiotensin system; SA, sinoatrial; SBP, systolic BP; SNS, sympathetic nervous system.

[a] Information obtained from Food and Drug Administration labeling.[59]

masked hypertension (BP normal in the office but high at home). Upper arm automated cuff measures are generally preferred over wrist measures for home BP monitoring.[72] Direct transmission or electronically entered BP values can facilitate prompt titration of medications in response to home BP measures.[73] After initiation of antihypertensive drug therapy, reassessment at 1 month is indicated and subsequently at 1-month intervals until the BP goal is achieved, after which follow-up visits should be at 3-month intervals until BP stability at or below target with minimal to no adverse effects is accomplished.[2] Although in-person follow-up is optimal, telephone or virtual follow-up may be used when necessary. Once control is achieved, the maximal interval between office visits for a patient taking antihypertensive medications should be 6 months.

Effective BP control begins with agreement between the clinician and patient on the BP target. Use of fixed-dose single-pill combinations and 90-day (rather than 30-day) prescription refills reduces complexity, enhances adherence to the antihypertensive regimen, and facilitates earlier achievement and maintenance of goal BP compared with initial monotherapy and subsequent addition of supplemental drugs with the stepped-care approach.[74] Recent data suggest that initiation of therapy with low-dose combinations may be as effective as usual-dose monotherapy in reducing BP.[75] Compared with shorter-acting diuretics such as hydrochlorothiazide, longer-acting agents such as chlorthalidone or indapamide are more effective for BP lowering and CVD protection.[76-79]

Resistant Hypertension

Resistant hypertension is defined by lack of adequate BP control during treatment with 3 antihypertensive agents of different classes, prescribed at optimal doses and dosing intervals, in patients with good adherence.[80] Erroneous BP measurement, often caused by failure to use validated devices or by observers who have been inadequately trained or certified for BP measurement, must be excluded before a patient is classified as having resistant hypertension.[72,81,82] Similarly, the white coat effect, defined as office BP at least 130/80 mm Hg but out-of-office BP less than 130/80 mm Hg, must be ruled out before resistant hypertension is diagnosed.[80] Successful BP reduction to goal that requires 4 or more antihypertensive agents indicates

controlled resistant hypertension.[80] Clinicians should evaluate patients with resistant hypertension by probing for poor adherence to lifestyle and antihypertensive medication practices and use of drugs that interfere with antihypertensive medication effectiveness such as nonsteroidal anti-inflammatory agents, oral contraceptives, hormone therapy, or glucocorticoids.[80] Patients with true resistant hypertension should be screened for secondary hypertension and undergo assessment of target organ damage with a basic metabolic profile (levels of serum sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, and creatinine) and urinalysis.[80] If the patient takes a thiazide diuretic, a long-acting thiazidelike diuretic (chlorthalidone or indapamide) should be used in place of a shorter-acting agent such as hydrochlorothiazide (estimated mean SBP reduction, 5.6 mm Hg),[78] followed by addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone) as the fourth drug if BP remains uncontrolled.[80] If BP remains elevated, stepwise addition of antihypertensive agents with complementary mechanisms of action, such as a β-blocker or α_1-adrenergic antagonist, is indicated, with consideration of referral to a clinician with expertise in difficult-to-control hypertension.[80]

Addressing Social Determinants of Health to Improve BP Control

In the US, where an estimated 28 million people (8.6%) lack health insurance and 1 in 4 do not have access to a primary care clinician,[83,84] it is easy to assume that poor hypertension control nationwide is primarily due to lack of health insurance or access to health care. However, more than 90% of patients with hypertension have health insurance and access to a usual source of medical care.[85] Lack of health insurance and access to care were not explanations for the recently reported decline in national hypertension control.[85]

The 2020 US surgeon general's Call to Action to Control Hypertension recognized that "the conditions in which people are born, live, learn, work, play, worship, and age directly impact opportunities" to control hypertension in US communities.[86,87] In practice, these determinants include not only health care system factors such as insurance coverage and access to health care and pharmacies but also community factors such as access to safe affordable housing, healthy foods, quality schools, safe walkable streets, bicycle lanes, gyms, parks, and transportation. Social determinants of health affect risk of developing hypertension and BP control in people living with hypertension.[88,89] In 2382 adults participating in the Multi-Ethnic Study of Atherosclerosis, neighborhood healthy food availability was associated with a 12% lower rate of hypertension (hazard ratio, 0.88; 95% CI, 0.82-0.95).[90] In a nationally representative sample of US adults, those with hypertension who did not have a routine place for health care had a 72% lower prevalence of controlled BP than those who did, and those without insurance had a 34% lower prevalence of controlled BP than those with insurance coverage.[88]

Hypertension treatment may be more effective and sustainable when delivered at sites near where patients live and conducted in collaboration with community partners trusted by patients. In a randomized clinical trial of 319 Black male barbershop patrons aged 35 to 79 years from Los Angeles who had uncontrolled hypertension, a pharmacist-barber collaboration lowered mean SBP by 21.6 mm Hg[91] compared with barber-led hypertension education and physician referral alone. In a separate study of 318 Black patients with uncontrolled hypertension in 32 New York City churches, a motivational interviewing and lifestyle change curriculum delivered by church members compared with a health education only control group lowered mean SBP by 5.8 mm Hg.[92]

Organizing and Conducting Team-Based Care of Hypertension

In team-based hypertension care, a physician coordinates patient care with a health care team that may include nurses, pharmacists, lifestyle counselors, medical assistants, social workers, community health workers, and other clinicians with specialized hypertension training who are able to contact patients directly and overcome obstacles to achieving their BP goals. In a meta-analysis of 119 randomized trials and 920 participants, compared with usual care, team-based hypertension care led by trained nonphysician health care professionals was associated with a mean decrease in SBP of 7.1 mm Hg in patients with hypertension, and team-based care increased the proportion of patients with controlled BP by a median of 8.5%.[93,94]

Optimizing Treatment Adherence in Hypertension

Pharmacy claims data from the US suggest an antihypertensive medicine nonadherence rate (defined as proportion of days an individual had prescription medication available <80%) of 31.0%.[95] Clinicians and health systems can facilitate improved medication adherence.

Traditionally, medication adherence has been assessed in clinical practice by either patient self-report (ideally using a standard, validated adherence instrument) or by a count of the number of pills from the patient's pill bottle. Self-report alone has limited accuracy compared with more objective adherence measures. Agreement between a self-reported adherence scale and a criterion standard mass spectrometry assay of urine drug metabolites appears to be very weak (Cohen κ of −0.01),[96] and self-report scales underpredict nonadherence by 50% or more compared with an objective pill-count adherence record.[97] Because objective measures of adherence are more reliable, health systems or pharmacies with pharmacy claims databases should use the timing of prescription refills to objectively measure and provide clinician and patient feedback on medication adherence as the medication possession ratio or proportion of days covered.

Adherence support, consisting of interventions such as patient coaching support and automated reminders, can be delivered to patients who start with limited motivation to treat a chronic, asymptomatic condition; those with mental health challenges, cognitive deficits, or other comorbid conditions; and those facing financial or social barriers. Measures implemented at the health system and individual patient levels improve antihypertensive medication adherence.[98]

Limitations

This Review has several limitations. First, the literature search excluded articles not published in English. Second, it may have missed some relevant publications. Third, not all aspects of hypertension treatment were covered. Fourth, some of the included literature consisted of clinical practice guidelines and scientific statements, which are based in part on expert opinion.

Conclusions

Hypertension affects approximately 116 million adults in the US and more than 1 billion adults worldwide and is a leading cause of CVD morbidity and mortality. First-line therapy for hypertension is lifestyle modification, consisting of weight loss, dietary sodium reduction and potassium supplementation, healthy dietary pattern, physical activity, and limited alcohol consumption. When drug therapy is required, first-line therapies are thiazide or thiazidelike diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and calcium channel blockers.

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