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Pharmacology: Evidence Meets Practice

Making Sense of Hypertension Guidelines

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Hypertension is a leading risk factor for heart disease, stroke, kidney failure, and diabetes and is a predisposing risk factor for most cardiovascular chronic illnesses. The risk for major cardiovascular events drops significantly when guideline-based blood pressure targets are achieved. Several different societies and organizations have released guidelines during the past 6 years, and significant clinical trial data have been recently released. Here, we summarize existing guidelines and recent pertinent clinical trial data to assist practitioners in identifying optimal treatment strategies for the successful management of hypertension.

KEY WORDS: advanced practice nursing, blood pressure management, evidence-based care, hypertension guidelines

In the United States, one-third of all adults have hypertension (HTN), and 35.8 million of those are uncontrolled.[1] As a leading risk factor, high blood pressure (BP) is a predisposing factor for almost 80% of all cardiovascular chronic illnesses. The risk for major, debilitating cardiovascular disease (CVD) events (heart failure, myocardial infarction [MI], and stroke) drops significantly when BP reaches the guideline-based target (140 mm Hg systolic) or lower.[2,3] Randomized controlled trials (RCTs) have found that lowering BP by as little as 10 mm Hg in patients with HTN can reduce a person's lifetime risk for cardiovascular and stroke death by 25% to 40%.[4] Over the last 50 years, extensive effort has been given to determining the optimal BP target for adults with HTN.[5]

Despite recent improvements in prescribing practices for evidence-based antihypertensive medication therapy, many diagnosed cases remain "uncontrolled."[1] Data from the National Health and Nutrition Examination Survey showed that, of those people 20 years or older with HTN, 76.5% were under current treatment, 54.1% had their BP controlled, and 45.9% did not have it controlled.[1] Even when HTN is detected and appropriate treatment is prescribed, medication and lifestyle nonadherence can undermine success.

Ample opportunity exists for improvement in the management of HTN in the United States. The purpose of this article is to review recent guidelines directed toward prevention, detection, evaluation, and management of high BP in adults and provide easily accessible guideline-based comparisons and recommendations for identifying BP treatment targets, lifestyle, and medication management of patients with HTN.

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Recognizing a Need for a Revised Guideline

Several recent trials have evaluated whether a more aggressive approach to a lower BP target could reduce the risk for CVD, particularly in higher-risk populations and older individuals.[6,7] These trial results introduced both optimism and controversy over establishment of more aggressive BP targets.

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial was a large trial evaluating the effects of intensive BP control in a population of patients with diabetes. The ACCORD BP trial targeted a more intensive systolic BP (SBP) goal of less than 120 mm Hg.[7] In this trial, 4733 adults with type 2 diabetes, an additional risk of CVD, and an average SBP of 130 to 180 mm Hg were enrolled. The composite CVD

outcome (MI, stroke, or CVD death) was 12% lower in the intensive treatment group, but the difference was not statistically significant compared with the commonly recommended target of less than 140 mm Hg (P = .20).[7] A nominally significant difference in the rate of stroke was seen in the intensive therapy group, compared with standard therapy (0.32% vs 0.53% per year; hazard ratio, 0.59; 95% confidence interval [CI], 0.39–0.89; P = .01). The rate of serious adverse events in the intensive therapy group of ACCORD BP was significantly higher and driven largely by medication-associated adverse effects, hypokalemia, and alterations in measures of kidney function.[7]

After completion of ACCORD BP, the National Institute of Health conducted the Systolic Blood Pressure Intervention Trial (SPRINT)[6] designed to highlight BP management of adults 50 years and older. This trial evaluated an intensive treatment approach versus a standard treatment approach comparing the effects of antihypertensive treatment with an SBP goal of less than 120 mm Hg (intensive treatment) versus SBP less than 140 mm Hg (standard treatment) in 9631 adults with HTN. Patients with an SBP of 130 to 180 mm Hg could be included if they were 50 years or older with an increased CVD risk without diabetes or previous stroke. Although any medication class could be used, the treatment protocol encouraged the use of drug classes with the strongest evidence for reduction in cardiovascular complications (diuretics, calcium channel blockers, and angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]).[8] The primary composite outcome of SPRINT was MI, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

During follow-up at 1 year, the mean SBP was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group. The trial was stopped after a median follow-up of 3.26 years because of a significantly lower rate of MI, the primary composite end point, in the intensive treatment group. At 3 years, the intensive group maintained an SBP of 121.5 mm Hg and the standard group had a mean SBP of 134.6 mm Hg. The mean numbers of antihypertensive medications were 2.8 in the intensive treatment group and 1.8 in the standard treatment group. These results indicated that achievement of a more aggressive BP-lowering target (<120 vs <140 mm Hg) compared with the previous targets of less than 150 mm Hg significantly lowered rates of death (by nearly 25%), stroke, MI and heart failure (by nearly one-third).[6] All-cause mortality was reduced by approximately 27% and significantly lower in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60-0.90; P = .003). The medication classes most used in the intensive treatment group were ACE inhibitors or ARBs, diuretics, calcium channel blockers, and β-blockers. Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure were higher in the intensive treatment group. It is unclear how medication management changed in the setting of adverse events or the long-term consequences of these adverse effects.[8]

The benefits of intensive BP lowering in older adults were further confirmed in a separate analysis of SPRINT.[9] In a prespecified subgroup of ambulatory adult enrollees 75 years or older, treating to an SBP target of less than 120 mm Hg, compared with an SBP target of less than 140 mm Hg, resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause.[9] Because participants 75 years or older did not experience a higher rate of adverse events, the existing guideline recommendation of a higher BP target (<150/90 mm Hg) for those 80 years or older was controversial because it appears that this population benefits from intensive BP management as well.

In this context, a systematic review and meta-analysis sought to identify the optimal target for reduction of SBP for reduction of CVD and mortality among persons with HTN.[10] Forty-two trials, including 144 220, patients were included. Diverse populations, including those with type 2 diabetes, were included. In this analysis, the lowest risks for major CVD, coronary heart disease, all-cause mortality, and CVD mortality were at a mean achieved SPB of 120 to 124 mm Hg, whereas the lowest risk for stroke was at a mean achieved SBP of less than 120 mm Hg.[10] Adverse events were not examined in this analysis; however, because comorbidities such as stroke and diabetes were included in the analysis, the authors concluded that the results were generalizable to populations at large with HTN.[10] The results of this analysis suggested that treating patients to lower BP targets than what the current guidelines recommended could significantly reduce the risk of CVD and all-cause mortality. They also supported intensive BP control and the need for revising existing clinical guidelines for the management of HTN.

Finally, identification of the appropriate BP target for high-risk patients with HTN became the focus of another systematic review and meta-analysis[11] commissioned for the development of the 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Geriatrics Society/American Pharmacists Association/American Society of Hypertension/American Society for Preventive Cardiology/National Medical Association/Preventive Cardiovascular Nurses Association Guideline.[12] This analysis was limited to trials that compared an SBP target of less than 130 mm Hg

with any higher target.[11] From this analysis, patients benefited in terms of major cardiovascular events (relative risk [RR], 0.84; 95% CI, 0.73–0.99) and stroke (RR, 0.82; 95% CI, 0.70–0.96) but not MI (RR, 0.85; 95% CI, 0.73–1.00) or all-cause mortality (RR, 0.92; 95% CI, 0.79–1.06). The evidence review committee concluded that their meta-analysis supported BP lowering to a target of SBP less than 130 mm Hg that may reduce the risk of several important outcomes including stroke, heart failure, and major cardiovascular events.[11]

In November 2017, the ACC/AHA/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Geriatrics Society/American Pharmacists Association/American Society of Hypertension/American Society for Preventive Cardiology/National Medical Association/Preventive Cardiovascular Nurses Association Task Force on Clinical Practice Guidelines writing committee released the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (hereafter referred to as the ACC/AHA guideline).[12] This guideline is a comprehensive update to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure last released in 2003 and aims to provide practical guidance while incorporating new supporting data.[13,14]

Guideline Recommendations

Several significant guideline recommendations regarding the management of HTN have been released since 2011.[3,12,15–18] Important highlights from these guidelines, when HTN is the main indication for treatment, are reported in Table 1 (see Supplemental, Digital Content 1, http://links.lww.com/JCN/A54). Table 2 (see Supplemental, Digital Content 1, http://links.lww.com/JCN/A55) presents guideline-recommended BP goals and preferred initial treatment options in the setting of additional comorbidities that present additional risk.

Therapeutic Treatment Options

Lifestyle Modification

Lifestyle modifications can contribute to clinically significant reductions in BP; however, the challenges of long-term adherence limit the use of this strategy as a sole means for managing BP.[19] All of the referenced guidelines incorporate lifestyle changes in summarized recommended treatment approaches.[3,12,15–18,20–22] All guidelines recommend varying degrees of sodium restriction, weight management, and physical activity.[3,12,16–18,20–22] Some of the guidelines specifically recommend combining the Dietary Approaches to Stop Hypertension diet, which includes reduced amounts of red meat and sugar-containing beverages, while emphasizing consumption of vegetables, fruits, whole grains, low-fat dairy, fish, and nuts[23] or other "healthy diet" combined with sodium restriction.[12,16,18,21,22] All recommend limiting alcohol consumption except the Eighth Joint National Committee guideline, which made no recommendation regarding alcohol consumption.[3,21] Most guidelines recommend smoking cessation in those patients who smoke; the 2017 ACC/AHA guidelines recognize nicotine as a drug that might be a cause of secondary HTN.[12] The Canadian Hypertension Education Program recommends that stress management be considered; however, the 2017 ACC/AHA guidelines cite insufficient evidence of stress reduction to support a long-term BP-lowering effect.[12,16,24] All guidelines recommend that lifestyle interventions be initiated immediately upon recognition of high BP, alone or in combination with guideline-directed drug therapy.

Medication Therapy

Antihypertensive therapy has a major role in the primary and secondary prevention of cardiovascular and renal diseases, both in the general population and in at-risk populations such as those with diabetes.[22] The guideline-recommended approaches to medication therapy are presented in Tables 1 (see Supplemental, Digital Content 1, http://links.lww.com/JCN/A54) and 2 (see Supplemental Digital Content 2, http://links.lww.com/JCN/A55). Existing medication classes and doses of therapeutic treatment options are briefly summarized in Table 1. Most antihypertensive treatment options can be divided into 9 classes: ACE inhibitors, ARBs, β-blockers, calcium channel blockers, thiazide diuretics, mineralocorticoid receptor antagonists, direct arterial vasodilators, central α-2 agonists, and α-1 blockers. Many treatment options are currently available as fixed dose combinations of separate medication classes for improved BP control and improved patient adherence through reduced pill burden. Significant heterogeneity in adherence to antihypertensive therapy has been reported, with ACE inhibitors, ARBs, and calcium channel blockers showing the best adherence.[32] A retrospective cohort study evaluated the relationship between adherence to antihypertensive medication and use of healthcare resources and costs.[33] The authors found that 25.4% of insured patients were nonadherent to antihypertensive medication and these patients were more likely to have 1 or more hospitalizations or emergency department visits, as well as higher total healthcare costs.[33] The high prevalence of uncontrolled HTN results in an estimated 30 billion dollars in preventable healthcare costs annually.[33]

Guideline recommendations of first-line medication classes for the treatment of high BP are derived from outcomes of large RCTs. Current

TABLE 1 Doses and Considerations of Selected Medications in Guideline Directed Medication Therapy[3,17,25–30]

Medication Class	Medication and Total Daily Dosing Range, mg[a]	Precautions or Contraindications	Clinical Considerations
Angiotensin-converting enzyme inhibitors (ACEIs)[b]	Captopril 50–150 mg/d Enalapril 5–20 mg/d Lisinopril 10–40 mg/d Quinapril 5–40 mg daily Ramipril 2.5–10 mg/d	If cough develops, patient may tolerate ARB. Monitor renal function and potassium. Angioedema may occur at any time in therapy; do not use in patients with a history of angioedema.	Avoid combining ACEI with ARBs. Monitor renal function and potassium. ACEI may be preferred in patients with LV systolic HF and patients with DM.
Angiotensin receptor blockers (ARBs)[b]	Eprosartan 400–800 mg/d Candesartan 4–32 mg/d Irbesartan 150–300 mg/d Losartan 50–100 mg/d Telmisartan 20–80 mg/d Valsartan 80–320 mg/d	Monitor renal function and potassium. Angioedema may occur at any time in therapy; do not use in patients with a history of angioedema.	Avoid combining ARBs with ACEI. ARBs may be preferred in patients with LV systolic HF and patients with DM.
β-Adrenergic receptor blockers (β-blockers)[b]	Atenolol 25–100 mg/d Bisoprolol 2. 5–10 mg/d Carvedilol 12. 5–50 mg/d Metoprolol 25–400 mg/d	Heart block or bradycardia may limit use in some patients. Adverse effects of fatigue, reduced exercise tolerance, and reduced sexual function may occur.	Preferred in patients with systolic HF and a history of MI. Less effective in reducing blood pressure in black patients.
Calcium channel blockers (CCBs)[b]	Dihydropyridine: Amlodipine 2.5–10 mg/d Felodipine 2. 5–10 mg/d Nifedipine ER 30–90 mg/d Nondihydropyridine: Diltiazem extended release 120–480 mg/d Verapamil 180–480 mg/d	Peripheral edema is a common adverse effect. Heart block or bradycardia may limit use of nondihydropyridine CCB.	Avoid use of nondihydropyridine CCB in patients with LV systolic dysfunction. May be preferred for HR control in atrial fibrillation with preserved LV function.
Diuretics[b]	Chlorthalidone 12.5–25 mg/d Hydrochlorothiazide 12.5–50 mg/d Indapamide 1.25–2.5 mg/d	Monitor electrolytes and glucose carefully.	Most effective when combined with ACEI, ARB, or CCB
Mineralocorticoid receptor antagonists	Spironolactone 50–100 mg/d Eplerenone 50–100 mg/d	Monitor renal function and potassium closely, particularly if used in combination with ACEI or ARB. Use cautiously in patients with an underlying renal impairment.	Gynecomastia may limit use of spironolactone. May be preferred in patients with HF.
Arterial vasodilators	Hydralazine 40–300 mg/d Minoxidil 5–40 mg/d	Not a first step recommendation for hypertension. Reflex tachycardia may occur.	Hydralazine may be preferred in patients with LV systolic dysfunction HF in combination with nitrates.
Central α-2 agonists	Clonidine 0.2–0.6 mg/d Clonidine patch TTS-1-TTS-3 (0.1–0.3 mg/24 h) applied once weekly	Not a first step recommendation for hypertension. Methyldopa may cause hemolytic anemia; monitor CBC. Use methyldopa cautiously in patients with an underlying renal disease. Methyldopa is contraindicated with an active hepatic disease.	Clonidine may worsen sinus node dysfunction and AV block and reduce heart rate. Avoid abrupt discontinuation of clonidine because of risk of rebound hypertension. This class may cause drowsiness or dry mouth.
α-Adrenergic blockers	Doxazosin 1–16 mg/d Prazosin 2–20 mg/d Terazosin 1–20 mg/d	Not a first step recommendation; clinical outcome benefits are not well established.	May be useful in managing HTN in men with BPH.

Abbreviations: AV, atrioventricular; BPH, benign prostatic hypertrophy; CBC, complete blood count; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HF, heart failure; HTN, hypertension; LV, left ventricular; MI, myocardial infarction.
[a]Daily dosing ranges provided for the indication of hypertension in the adult population.
[b]Preferred medication class for the initial pharmacologic treatment of hypertension as directed by guidelines.
[c]Dosing recommendations are presented for oral route of administration, except clonidine TTS (Transdermal Therapeutic System).[31]

recommendations of preferred first-line pharmacotherapeutic treatment options in the setting of selected comorbidities (diabetes, chronic kidney disease, coronary artery disease, recent MI, heart failure, and stroke) are presented in Table 2 (see Supplemental Digital Content 2, http://links.lww.com/JCN/A55). For specific

TABLE 2 2017 High Blood Pressure Clinical Practice Guideline: Categories of BP in Adults[12]

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

If SBP and DBP in 2 categories, measurement should be designated in the higher category.
Abbreviations: BP, blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions); DBP, diastolic blood pressure; SBP, systolic blood pressure.

comorbidities, preferred medication classes are listed as initial therapy. These treatment options should be further refined based on patient-specific features, such as additional patient comorbidities and organ function, race and ethnicity, patient intolerances, complexity of medication administration and schedule, and cost of the medication regimen relative to patient resource availability. In general, the medication classes that are preferred treatment options interfere with the renin-angiotensin-aldosterone system pathway and the activity of the sympathetic nervous system and its effects or potentiate dilation of the arterioles.

A recent systematic review and meta-analysis including 123 randomized trials of BP lowering for prevention of CVD and death combined data from all published large-scale BP-lowering trials.[34] Five classes of BP-lowering drugs were examined: ACE inhibitors, ARBs, β-blockers, diuretics (particularly thiazide diuretics), and calcium channel blockers. The different classes of medications were of similar effectiveness for the prevention of studied outcomes. However, β-blockers were less efficacious than other medications for the prevention of major CVD events (RR, 1.17; 95% CI, 1.11–1.24), stroke (RR, 1.24; 95% CI, 1.14–1.35), renal failure (RR, 1.19; 95% CI, 1.05–1.34), and all-cause mortality (RR, 1.06; 95% CI, 1.01–1.12).[34] The results of this analysis also suggested that calcium channel blockers were superior to other medication classes for the prevention of stroke (RR, 0.90; 95% CI, 0.85–0.95) but were inferior to the other classes for the prevention of heart failure symptoms (RR, 1.17; 95% CI, 1.11–1.24). Diuretics were superior to other classes for heart failure prevention (RR, 0.81; 95% CI, 0.75–0.88). Although these results are not entirely in line with comorbidity-specific guideline recommendations, the authors acknowledge the possibility that the concurrent use of multiple medication classes in many trials included in this analysis may have modified apparent differences between drug classes.[34]

Will the 2017 Guideline be Sufficient to Effect Change?

A recent analysis of 2011 and 2014 National Health and Nutrition Examination Survey data was completed to evaluate the potential impact of the new classification scheme recommended by the 2017 ACC/AHA guideline[12] (Table 2).[35] The purpose was to estimate the percentage and number of US adults with HTN and the percentage recommended for pharmacological antihypertensive treatment according to the new 2017 ACC/AHA guideline compared with the earlier Seventh Joint National Committee (JNC 7) guideline.[14] The prevalence of HTN among US adults is substantially higher when the definition in the present guideline is used versus the JNC 7 definition (46% vs 32%). However, lifestyle modification or nonpharmacological treatment is recommended for most US adults who have HTN as defined in the present guideline but who would not meet the JNC 7 definition for HTN. As a consequence, the new definition of high BP results in only a small (1.9%) increase in the percentage of US adults for whom antihypertensive medication is recommended in conjunction with lifestyle modification.[35] However, opportunities for care optimization remain because greater than 50% of US adults taking antihypertensive medication do not meet the SBP/diastolic BP goal of less than 130/80 mm Hg proposed in the 2017 guideline, which will necessitate intensification of their prescribed therapies to attain the recommended BP control.[35]

Prospectively, the success of the guideline is not simply individual BP reduction but also maximal CVD risk reduction in individuals and populations. The 2017 ACC/AHA high-BP guideline, if widely adopted and applied to appropriate populations, moves the approach to HTN treatment in this direction.[36]

Recommendations for Practice

Recently released and revised guidelines have incorporated the beneficial results of more recent RCT data and large-scale observational analyses to determine the optimal BP target for individual patients. Consideration of age and patient comorbidities remain important factors that may influence individual BP goals, recognizing that there is little high-quality evidence to support clear BP targets in some populations such as the frail and/or institutionalized older adults.[6,7] The balance of the potential benefits of HTN management with medication costs, potential adverse effects, and polypharmacy must be individually reconciled. Current recommendations for appropriate medication classes for first- and second-line therapy remain mostly consistent across guidelines and RCT data; however, consideration of patient-specific features remains essential to achieve optimal outcomes and minimize adverse effects. Patient adherence to

prescribed therapies and lifestyle intervention will significantly improve achievement of individual BP goals. Patient and family education and consideration of factors such as medication adverse effects, cost, and complexity of administration regimen will increase the chances for successful adherence to recommended therapies.[37,38] A growing body of evidence suggests that a team-based approach is needed to improve adherence.[22,39,40]

Multidisciplinary approaches have been shown to improve outcomes and timeliness of achieving BP treatment targets,[39] and the 2017 ACC/AHA guideline places more emphasis on team-based systems for managing HTN.[12] Multidisciplinary collaboration and task sharing can improve (1) collaboration regarding patient-specific targets for BP goals, (2) identification of optimal medication treatment choices based on patient-specific features and collaboration regarding medication titration opportunities, (3) improved communication regarding medication-related adverse effects and interactions, and (4) shared patient education and decision-making for adherence, monitoring, and use of concomitant medications to reduce the risk of heart disease, stroke, kidney failure, and diabetes.

Conclusions

Widespread acceptance and use of guideline-based recommendations and consideration of more recent RCTs and large-scale analyses can improve population outcomes. Finding the optimal BP target and treatment regimens, particularly in high-risk populations,[41] could have far reaching implications for the reduction of CVD and premature death in general populations.

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