New Guidelines for the Treatment of Hypertension: Re-emergence of Chlorthalidone in the Treatment of Hypertension

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Abstract

Hypertension is the most common modifiable risk factor for cardiovascular diseases, stroke, and renal dysfunction. Its treatment is the main focus of primary and secondary disease prevention strategies. The guidelines for the treatment of hypertension continue to evolve over the past few decades for early detection, risk stratification, and better control to improve clinical outcomes. This article highlights the newer guidelines for the treatment of hypertension and the role of diuretics.

Key words: Cardiovascular diseases, hypertension, renal dysfunction, stroke

Introduction

Hypertension is the major risk factor for cardiovascular deaths and stroke. It accounts for an estimated 57% of all strokes and 24% of all ischemic heart disease events in India. [1] Hypertension prevalence in India accounts for 33% of urban and 25% of rural population. [2] In spite of this awareness, treatment and adequate control of hypertension is far from complete. The first comprehensive guideline for detection, evaluation, and management of high blood pressure (BP) was published in 1977, under the sponsorship of the National Heart, Lung, and Blood Institute. [3] In subsequent years, a series of Joint National Committee (JNC) BP guidelines were published to assist the clinicians to improve prevention, awareness, treatment, and control of high BP. [4] To address the existing controversies and to account for the evidence from the new randomized controlled trials on hypertension, the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology/European Society of Hypertension (ESC/ESH) have come up with new guidelines for hypertension. [5,6] The newer guidelines emphasized on the accuracy as well as out-of-office BP measurement, classification of BP, new approach to decision-making for treatment that incorporates underlying cardiovascular risk, lower targets for BP, and strategies to improve BP control during treatment with an emphasis on lifestyle approaches.

Classification

In a meta-analysis of 61 prospective studies, the risk of cardiovascular diseases (CVD) increased in a log-linear fashion from systolic blood pressure (SBP) levels <115 mmHg to >180 mmHg and from diastolic blood pressure (DBP) levels <75 mmHg to >105 mmHg. [7] In that analysis, 20 mmHg higher SBP and 10 mmHg higher DBP were each associated with a doubling in the risk of death from stroke, heart disease, or other vascular diseases. Although the relative risk of incident CVD associated with higher SBP and DBP is smaller at older ages, the corresponding high BP-related increase in absolute risk is larger in older persons (>65 years) given the higher absolute risk of CVD at an older age.

Although a continuous association exists between higher BP and increased CVD risk, it is useful to classify BP levels for clinical and public health for decision-making. In 2017, the ACC/AHA classified on the basis of average office BP into
Evaluation of Hypertension

The newer guidelines emphasize on the evaluation of hypertensive individuals for the risk factors and the evidence for the end-organ damage. The risk factors to be considered are smoking, diabetes, dyslipidemia, sedentary lifestyle, abnormal diet, alcohol intake, obesity, sleep apnea, and stress. Although secondary hypertension accounts for around 10% of hypertensive individuals, multiple clinical scenarios given in Table 2 should alert the physician to search for them. Screening includes testing for common causes such as renal diseases, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug- and alcohol-induced hypertension. Testing for less common causes such as pheochromocytoma, Cushing’s syndrome, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism, and aortic coarctation to be considered based on clinical indications.

When to Initiate Treatment

The treatment of high BP involves non-pharmacological, pharmacological, and recently device therapies. The non-pharmacological therapy is indicated in all categories of hypertension. The newer guidelines recommend the use of estimating 10-year ASCVD risk of >10% for decision-making in initiation of pharmacotherapy. The limitation of ACC/AHA CVD risk assessment equation is that it is not applicable for very elderly (>79 years) and it overestimates risk in Asians. The Joint British Society 3 risk score or the World Health Organization-International Society of Hypertension modified risk scores for Southeast Asian region are suited better for Indian population and may be used instead for our patients.\(^\text{[8]}\)

The use of pharmacological therapy is recommended for:
- Stage 1 hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg) and an estimated 10-year ASCVD risk of 10% or higher
Table 2: Indicators for secondary hypertension

<table>
<thead>
<tr>
<th>Resistant hypertension</th>
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<tbody>
<tr>
<td>Sudden onset of hypertension</td>
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<tr>
<td>Hypertension onset &lt;30 years of age</td>
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<tr>
<td>Onset of diastolic hypertension &gt;65 years</td>
</tr>
<tr>
<td>Target organ damage disproportionate to severity of hypertension</td>
</tr>
<tr>
<td>Unprovoked or excessive hypokalemia</td>
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<td>Accelerated/malignant hypertension</td>
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</table>

- Stage 1 hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg) and clinical CVD
- Stage 2 hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg).

Make 130 the New 140 Target Goal

Meta-analyses and systematic reviews of multiple trials comparing an aggressive versus standard BP goals have shown a consistent reduction in stroke, coronary events, and major adverse cardiovascular events. The SPRINT trial showed significant reduction in composite cardiovascular deaths and mortality in the more intense BP control group compared to standard BP group.

The guidelines recommend a BP goal of 130/80 mmHg in persons who are on treatment for hypertension. Treatment of hypertension with an SBP treatment goal of 130–139 mmHg is recommended for non-institutionalized ambulatory community-dwelling older adults (>65 years of age) if they tolerate well. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, the clinical judgment, patient preference, and a team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

Non-Pharmacological Therapy

The non-pharmacological therapies have very important role in controlling BP and recommended in all stages of hypertension. These interventions help in 2–10 mmHg reduction of BP. The maximum benefit of BP reduction of 11 mmHg is seen with Dietary Approaches to Stop Hypertension (DASH) diet which includes diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat. The other interventions include tobacco cessation, weight reduction, low sodium intake of <1.5 g/day, increased potassium intake of 3.5–5 g/day, physical activity, and moderation of alcohol intake.

Pharmacological Therapies

The pharmacological therapies in addition to lifestyle modifications form the primary basis for achieving the target BP goal. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics are recommended as the first-line antihypertensive agents as they reduce CVD and strokes. Beta-blockers and alpha-blockers may not be the first-choice drugs as they were the only drug classes that were not significantly superior to any other drug, for any outcomes.

The choice of agents depends on the comorbid factors in an individual. In adults with chronic kidney disease, ACE inhibitors/ARBs are preferred. In diabetes mellitus with hypertension, ACE inhibitors or ARBs are considered in the presence of albuminuria. Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease. The addition of spironolactone for the treatment of resistant hypertension is considered, unless contraindicated.

The combination of two renin–angiotensin system (RAS) blockers is not recommended due to increased risk of hyperkalemia, cardiovascular events, and reduction in renal function. Similarly, the beta-blockers and thiazide diuretic combinations are not recommended due to metabolic adverse effects.

Reemergence of Chlorthalidone

Thiazide and thiazide-like diuretics have been the mainstay of therapy for primary hypertension since 1960. The BP reduction with diuretics occurs due to initial reduction in plasma volume and cardiac output. The fall in BP later is blunted by hypovolemia-induced RAS activation. Long-term maintenance of the decrease in BP is associated with partial reversal of the initial hemodynamic changes: The plasma volume and cardiac output partially rise toward the baseline level, while the systemic vascular resistance falls.

The initial use of high dose of thiazides to reduce BP resulted in metabolic complications such as hypokalemia, hyponatremia, dyslipidemia, and hyperuricemia, leading to increased incidence of sudden cardiac deaths. Later, the thiazides and thiazide-like diuretics are typically used at low doses of 12.5–25 mg/day of chlorthalidone and hydrochlorothiazide or 1.25 mg/day of indapamide to minimize metabolic complications while maintaining the antihypertensive response. The low-dose chlorthalidone and indapamide are long acting and have shown significant reduction in BP as compared to hydrochlorothiazides with lesser metabolic disturbances. The reductions in cardiovascular events have been noted with chlorthalidone in ALLHAT trial.

Due to the longer duration of action with significant reduction in BP and cardiovascular events with lesser metabolic disturbances, the chlorthalidone has emerged as low-dose diuretic of choice in the treatment of hypertension.

Strategies to Improve Hypertension Treatment and Control

Various strategies are planned to achieve sustained BP control below the target BP to reduce CVD and strokes. Initiation with a single antihypertensive drug is reasonable in adults with Stage...
Hypertension (130–139) and in frail very elderly persons in whom sequential addition of other agents is done to achieve the BP target. Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a single pill combination (SPC), is recommended in adults with hypertension >140/90 mmHg and an average BP >20/10 mmHg above their BP target. The use of SPCs leads to reduction in pill burden, improve compliance, and better control of BP. The preferred combinations are ACEI or ARBs with CCB or diuretics as shown in Figure 2. HBPM, ABPM, team-based care, and telehealth strategies all should be used based on availability for better monitoring of BP control and patient compliance.

Device-Based Hypertension Treatment

Various device-based therapies for the treatment of resistant hypertension are under trial to understand the efficacy and safety. Carotid baroreceptor stimulation (pacemaker and stent), renal denervation, and creation of central iliac arteriovenous fistula are tried but are not recommended as there efficacy and safety need to be proved.

Conclusions

Hypertension is the major non-communicable risk factor for increased cardiovascular events. It needs to be detected early and treated adequately to reduce the cardiovascular morbidity and mortality. In this regard, the newer guidelines emphasize on accurate measurement of BP with liberal use of out-of-office BP monitoring methods. The target BP has been reduced to 130/80 mmHg in all hypertension individuals including in those with age >65 years if they tolerate well. The incorporation of CV risk assessment helps in better decision making in the treatment of hypertension. Lifestyle modification is emphasized in all stages of hypertension. The ACE inhibitors, ARBS, CCB, and diuretics are considered as the first-line antihypertensives with chlorthalidone as the diuretic of choice. The use of SPCs is promoted for better control of BP and to improve the compliance. Overall, the newer guidelines emphasized on accuracy of BP measurement, lower BP targets, incorporation of cardiovascular risk assessment in deciding treatment, and strategies to improve BP control which help the clinicians for better management of hypertension.

References

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