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C Venkata S Ram

Special Issue of the Journal from Mumbai, Maharashtra, India

Guest Editor:
Satyavan Sharma

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AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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From the Desk Of Guest Editor

Special Issue on Hypertension from "Aamchi Mumbai"

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Hypertension (HTN) is an increasing threat to global public health, a leading cause of premature death, and an important modifiable risk factor for coronary artery disease (CAD), stroke, and renal failure. The global burden of HTN is expected to increase from the current estimate of 1 billion affected individuals to 15.6 billion affected individuals by 2025.[1] Aggressive lifestyle modifications are recommended in all subjects with HTN irrespective of age, gender, race, risk factors, or associated comorbidities. Statins for primary prevention of CAD are often needed in patients with HTN. The special issue of HTN from "Aamchi Mumbai" (our Mumbai) includes contribution from diverse specialties and provides insights into specific issues which a cardiologist, internist, pulmonologist, neurologist, interventional cardiologist, or pediatrician encounter. Clinicians from across the Mumbai have put forward their views on subjects varying from BP levels to therapeutic interventions. Management of HTN in specific circumstances (e.g., pregnancy, obstructive sleep apnea (OSA), resistant and secondary HTN) have been eloquently addressed.

There has been extensive debate about the most recent American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines.[2-5] Overall both guidelines agree on majority of the issues. The most important distinction is that ACC/AHA guidelines maintain that all people with blood pressure (BP) >130/80 mmHg have HTN, and BP should be lowered to <130/80 mm in all. In contrast, BP >140/90 mmHg is considered HTN by European guidelines with the goal to reduce BP <140/90 mm for all and targeting to lower levels in those with high cardiovascular (CV) risk.

Newer and aggressive BP goals to control HTN have been controversial. How low systolic blood pressure (SBP) should be lowered continues to be hotly debated by various specialists. A discussion point is the balance of potential benefits versus likely harm or adverse effects. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial with a mean follow-up of 4.7 years, a target BP of <120 compared with 140 mmHg was not associated with a reduced risk of composite of CV events (heart attack, a stroke, or a CV death).[6] However, the incidence of stroke was significantly less. The evidence that excessive lowering with diastolic blood pressure (DBP) may compromise the cardiac outcomes (the J curve) is inconsistent.[7] Evidence with respect to BP targets in chronic kidney disease (CKD) is complex.

Epidemiological studies have shown that an elevated BP is the most important determinant of the risk of stroke. The risk is almost linear and the lowering of high BP is a major factor in the impressive reduction in the stroke death rates in the recent years.[8] Meta-analyses of antihypertensive trials have demonstrated that BP lowering is more important than the particular drug class in preventing the complications such as stroke and CAD.[9] Management of HTN during hemorrhagic, ischemic, or recurrent stroke is truly challenging. During an acute phase of stroke, BP is often elevated as a protective mechanism and often declines without intervention. Secondary prevention of HTN is a key to reducing long-term morbidity and disabilities of stroke events. Similarly, strong epidemiological correlation exists between CAD and HTN. Randomized controlled trials (RCTs) have shown that BP lowering in patients with HTN produces rapid reduction in CV risk.[10] The appropriate SBP and DBP targets in patients with established CAD remain debatable. There are certain groups of drugs (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], and beta-blockers) which have shown particular efficacy in secondary prevention of CAD. HTN is a major risk factor in the development and progression of CKD, irrespective of cause of CKD. Reduction of albuminuria as a therapeutic target whether this parameter is a proxy for CV event reduction remains unresolved. BP lowering reduces renal perfusion pressure, it is expected and not unusual for e-GFR to be reduced by 10–20% in patients treated for HTN. This decline usually occurs in the first few weeks of treatment and then stabilizes. A cautious approach is needed to treat HTN keeping in mind age, comorbidities, end-organ damage, and individual response. The nuances of dealing with HTN in cerebrovascular disease and CAD have been addressed in this issue.

HTN affects women in all phases of life and is prone to develop HTN after the third decade of life. The pathophysiology of HTN is different with unique forms of HTN associated with

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menopause, pregnancy, and the use of oral contraceptive pill. The vascular protective effect of estrogen vanishes after menopause with increase in rates of HTN. These women are usually older with nontraditional risk factors such as abdominal obesity and renal disease. Hypertensive disorders of pregnancy affect 5–10% of pregnancies and remain a major cause of maternal, fetal, and neonatal mortality and morbidity. Pregnancy-related vascular complications such as gestational HTN or preeclampsia contribute to increased risk of postpartum HTN and long-term CV disease.[11] States of estrogen imbalance such as polycystic ovarian disorder, premature ovarian insufficiency, and infertility too contribute to HTN. Current evidence supports similar BP threshold for initiating treatment, and choice of drugs with the exceptions because of pregnancy and sex-specific side effects of some drugs.[12]

On a population level, HTN in children is on the rise with unhealthy lifestyle and obesity being the main reasons. Prevalence of confirmed pediatric HTN in children has ranged from 2% to 4%. In 2017, the American Academy of Pediatrics formulated new clinical guidelines for diagnosis, evaluation, and treatment of HTN.[13] There is an increasing evidence that adult HTN has its antecedents during childhood, as childhood BP predicts adult BP. HTN in children and adolescents contributes to atherosclerosis and early development of CVD. Identifying and successfully treating HTN in children may have an important impact on long-term outcomes of CV disease. Lifestyle alterations remain the cornerstone of treatment and pharmacotherapy with ACEI/ARB or other agents being reserved to those who fail to respond to non-pharmacological measures.

OSA is highly prevalent, estimated to affect 34% of men and 17% of women in the general population in 40–60% with CV disease.[14] OSA has been associated with many different forms of CV disorder including HTN, stroke, CAD, atrial fibrillation, and heart failure. OSA is considered as a potential treatable cause of HTN and can often present with resistant HTN.

Resistant HTN is a vexing problem and accounts for 10% of patients with HTN. HTN is defined resistant to treatment when the recommended strategy fails to lower office BP values below 140/90 mmHg. The common causes apart from OSA include primary hyperaldosteronism, CKD, or renal artery stenosis. Renal denervation is an attractive option in selected patients. Secondary HTN is seen in 10% of cases and is treatable with an intervention specific to the cause. Percutaneous intervention or surgery can be curative if secondary causes such as coarctation of aorta, fibromuscular dysplasia, or pheochromocytoma can be diagnosed early.

Hopefully, the readers will find the articles useful in managing their patients with HTN in a wide range of clinical scenarios. My special thanks to Dr. C. Venkata Ram, Editor-in-Chief for giving an opportunity to team MUMBAI to compile this issue. Our special thanks to Mr. Abhinav Kumar, for his help and valuable inputs in the editorial process.

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ℛeview ᴀrticle

Considerations in the Management of Hypertension in Cerebral Vascular Diseases

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Abstract

Hypertension is a well-established modifiable risk factor for stroke. As the prevalence of hypertension is increasing over the past few decades, it is becoming increasingly important to diagnose hypertension early and adjust the treatment vigilantly. A distinct pathologic process is involved in hypertensive individuals leading to stroke. Hypertension causes alteration of blood–brain barrier by affecting endothelial and smooth muscle cells, resultant vascular remodeling, and hypertrophy which prompt atherosclerosis and lipohyalinosis in large and small vessels, respectively. Therapy in the first few hours of stroke has evolved very rapidly and thrombolysis and thrombectomy are being routinely employed. These require specific blood management which avoids complications. Poorly managed blood pressure (high as well as low) in acute and/or chronic settings leads to disastrous outcomes of stroke in terms of mortality and long-term morbidity. Different non-pharmacological and pharmacological measures are available for hypertension management in the primary and secondary prevention of stroke. Well-managed hypertension over long periods of time leads to reduction in the long-term morbidity and mortality from strokes. Various guidelines and trials are available for the management of hypertension in stroke. In this paper, we discuss the various updates of the management of hypertension in cerebral vascular diseases for prevention, recurrence, and acute and chronic management.

Key words: Hypertension, pathophysiology of hypertension, prevention, stroke, treatment

Introduction

Stroke is a one of the leading causes of mortality, morbidity, and disability globally.[1] While a variety of diseases such as diabetes, dyslipidemia, hyperhomocysteinemia, and various vasculopathies are associated with cerebral vascular diseases, most experts consider hypertension to be the most common and perhaps most important modifiable risk factor in stroke. Management of hypertension is a very important for prevention, recurrence, and in treatment of stroke.

Epidemiology of Stroke in India

Truly representative national surveys and comprehensive stroke registries are not available for the prevalence of hypertension in India, but from various regional studies have documented the prevalence of hypertension to vary from 23.2% to 32% in rural and 29.7 to 37.8% in urban areas.[2] The stroke rates have varied in various regional studies. Information is available from Maharashtra, Kolkata region, Karnataka, Kashmir, and Haryana and these investigations showed different crude prevalence and incidence rates of stroke.[3] A single systemic review showed prevalence of stroke in different part of India to be 44.29–559/1,00,000 persons. In this study, the case fatality rate within a week was alarmingly high at 42% and 46% in urban and rural areas, respectively. The prevalence of hypertension was a risk factor in 60.8% of patients with ischemic stroke.[4] Another recent study showed a somewhat higher prevalence (65%) of hypertension as risk factor in ischemic as well as hemorrhagic vascular events.[5]

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Pathophysiology of Stroke and Hypertension

Hypertension increases the risk of stroke through various mechanisms.[6] Stress on endothelial cells and smooth muscle cells of intracerebral arteries increases. This leads to change in permeability in blood–brain barrier, resulting in brain edema. Such local and multifocal brain edema has been demonstrated in rat models.[7] Altered blood cell-endothelial cell interactions enhance leucocyte adhesion and can lead to the formation of local thrombi and ischemic lesions. In small penetrating blood vessels of 100–400 microns, hypertension accentuates fibrinoid necrosis, stenosis, and occlusions which result in lacunar infarcts. Such medial hypertrophy and lipohyalinosis secondary to hypertension commonly affect penetrating lenticulostriate branches from middle cerebral arteries, anterior perforating branches arising from anterior cerebral arteries, penetrating arteries arising from anterior choroidal arteries, thalamoperforating and thalamogeniculate arteries arising from posterior cerebral arteries, and paramedian perforating branches from basilar artery. Accentuation of arteriosclerotic changes occurs in the large extracranial arteries as well. This is the harbinger of strokes through stenotic and embolic mechanisms. Adaptation of resistance vessels causes increase in the peripheral vascular resistance which is detrimental to collateral circulation. It increases the risk of ischemic events in the events of hypotension. Thus, both intracranial and extracranial vascular changes in large and small arteries occur in the hypertensive individuals, increasing their stroke risk. Intracranial tandem lesions in association with extracranial large vessel disease are believed to occur more commonly in Indian patients.[4] Leukoaraiosis is a term used to describe white matter changes in brain imaging and is thought to be related to small vessel disease. Leukoaraiosis associated with stroke[8] and unfavorable prognosis in acute setting as well as poor long-term outcome.

Pathophysiological mechanisms for intracerebral hemorrhages were elucidated initially by Charcot and Bouchard. They demonstrated microaneurysms in intracerebral arteries of patients who died from hypertensive intracerebral hemorrhage.[9] These form weak spots from where the hemorrhages take place. Modern neuroimaging techniques are known to show such bleeding points "the spot sign" in a proportion of patients.[10] Common sites for hypertensive bleed are deep gray matter (putamen, globus pallidus, and thalamus), subcortical white matter, pons, and cerebellum. Small arteries in these areas are more prone to hypertension-induced vascular injuries as vessels run perpendicular here, an anatomical disadvantage in pressure transmission. Altered flow dynamics and histopathological changes in blood vessels both contribute to bleed in hypertension.

Hypertension is seen in nearly half of the patients with subarachnoid hemorrhage. Hypertension is a very commonly associated with aneurysms, especially saccular ones, and acute hypertension can also be responsible for rupture. Production of saccular aneurysm by experimental induction of renal hypertension and carotid artery ligation to alter hemodynamic stress in the circle of Willis in rats and monkeys has been demonstrated.[11]

Management of Hypertension

As hypertension is a major risk factor for stroke, treatment of hypertension is an inseparable part of the management of stroke in acute as well as chronic setting for prevention and recurrence of stroke. Management of hypertension differs in acute and chronic phases of stroke.

Diagnosis of Hypertension

At the ground level, accurate measurement of blood pressure (BP) is very important and attention needs to be given to patient preparation, correct technique, calibration of the BP apparatus, multiple readings, and averages.[12] One should be careful not to miss white coat and masked hypertension. Workup to rule out secondary hypertension is done as and when required. Investigations to look for long-standing hypertension such as electrocardiogram, ophthalmological evaluation (hypertensive retinopathy), 2 D ECHO (left ventricular hypertrophy), renal ultrasonography, urine routine, and microscopy also give an idea of the end-organ damage.

Treatment of Hypertension in Acute Ischemic and Hemorrhagic Stroke Events

In acute stroke, the first step is to differentiate hemorrhagic and ischemic stokes with the help of imaging, as treatment of the two is entirely different. In acute ischemic stroke (AIS), elevated BP may be due chronic hypertension, sympathetic response to the acute stroke, or various other phenomena.[13] As cerebral autoregulatory mechanisms are not fully functional, perfusion pressure distal to the obstructed vessel gets dependent on systemic BP. The baseline systolic blood pressure (SBP), therefore, becomes important.

BP management in AIS is a vital in salvaging reversible ischemic penumbra. For patients requiring thrombolysis and/or mechanical thrombectomy, BP must be kept at ≤185/110 mmHg before initiation of therapy. BP should be maintained <180/105 mmHg during and after thrombolysis and/or thrombectomy.[14] Various observational studies showed higher risk of hemorrhage in patients with higher levels and fluctuating BP.[15] Monitoring of BP should be carried out at every 15 min for 2 h, then every 30 min for 6 h and every hourly until 24 h from initiation of thrombolysis. Frequency of BP measurement may be increased if BP tends to remain higher. Selection of a particular antihypertensive agent or regimen is not clearly defined. Maintaining SBP between 150 and 180 mmHg before reperfusion and <140 mmHg after reperfusion is recommended in patients undergoing thrombolysis and/or thrombectomy. Various intravenous (IV) antihypertensive drugs offering ease of titration and rapid reversibility of action are used in accordance with comorbid conditions. Labetalol, nicardipine, clevidipine, hydralazine, and enalapril have been commonly used. Large head-to-head trials of various antihypertensive agents in AIS are not available. A single-center prospective study comparing nicardipine to labetalol in acute setting showed that reduction

of BP to the intended levels was faster with nicardipine, but no superiority in terms of other benefits was seen.[16]

In patients who are not eligible for thrombectomy and/or thrombolysis, aggressive BP lowering (15% reduction in the first 24 h from stroke onset) is recommended in such patients, who have BP more than 220/120 mm Hg. The same is true for those having comorbidities such as aortic dissection, ischemic coronary disease, heart failure, hypertensive encephalopathy, preeclampsia, or eclampsia.[14] In patients with BP >140/90 mmHg who are neurologically stable (usually after 24–48 h), the recommendation is to start or reinstate antihypertensive drugs during hospital stay. Starting the antihypertensive therapy should be delayed in patients having unstable neurodeficits such as fluctuating weakness or progressive deterioration. Caution is necessary in patients having extracranial or intracranial vessel stenosis, in whom lowering of BP can be counterproductive. In stenotic lesions, slower reduction of BP (over 7–14 days after acute stroke) or sometimes minor elevation of BP levels to maintain cerebral blood flow may be carefully considered.

In intracranial hemorrhage, elevated BP is often associated with hematoma expansion and worsening of outcomes in terms of mortality and disabilities.[17] Hence, IV infusion is used in patients with SBP >220 mmHg with the target levels of 140–160 mmHg.[18] Further, reduction is not associated with outcome differences but may be associated with renal ischemia (INTERACT 2 and ATTACH 2 trials).[19,20]

Optimal treatment of BP in subarachnoid hemorrhage (SAH) is unclear. Risk of rebleeding and ischemia is important considerations in the management of BP in SAH patients. In SAH patients with vasospasm, brain oxygen tension depends on cerebral perfusion pressure (CPP) which leads to higher chances of infarction with decrease CPP. CPP monitoring, when available, is helpful in titration of antihypertensives. Clinical evaluation and transcranial Doppler are also useful in the absence of availability of CPP. SBP of <160 mmHg or mean arterial pressure of <110 mmHg is recommended.[21]

The summary of therapeutic paradigm is provided in Figure 1.

Primary and Secondary Prophylaxis of Stroke[22]

Primary prophylaxis is recommended in hypertensive patients without prior history of stroke or transient ischemic attack (TIA) to lower BP to <140/90 mmHg. Secondary prophylaxis is indicated in individuals with prior history of stroke or TIA who, after the first several days, have an established BP ≥140/90 mmHg. Lowering of SBP <130 mmHg may be recommended in recent lacunar stroke. For patients with known cardiovascular disease (CVD) or a 10 years atherosclerotic CVD risk 10% or higher, target of <130/80 mmHg is recommended.

Drug selection

Monotherapy is initiated when BP is <20/10 mmHg above that of the target BP. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics can be considered for monotherapy. Older (≥60 years) patients have good response to diuretics and CCBs.[23] Beta-blockers not beneficial in stroke prevention. Diabetics and chronic kidney disease patients respond better to ACE inhibitors and ARBs. Selection of drug is done according to age and comorbid conditions. Observation of response to
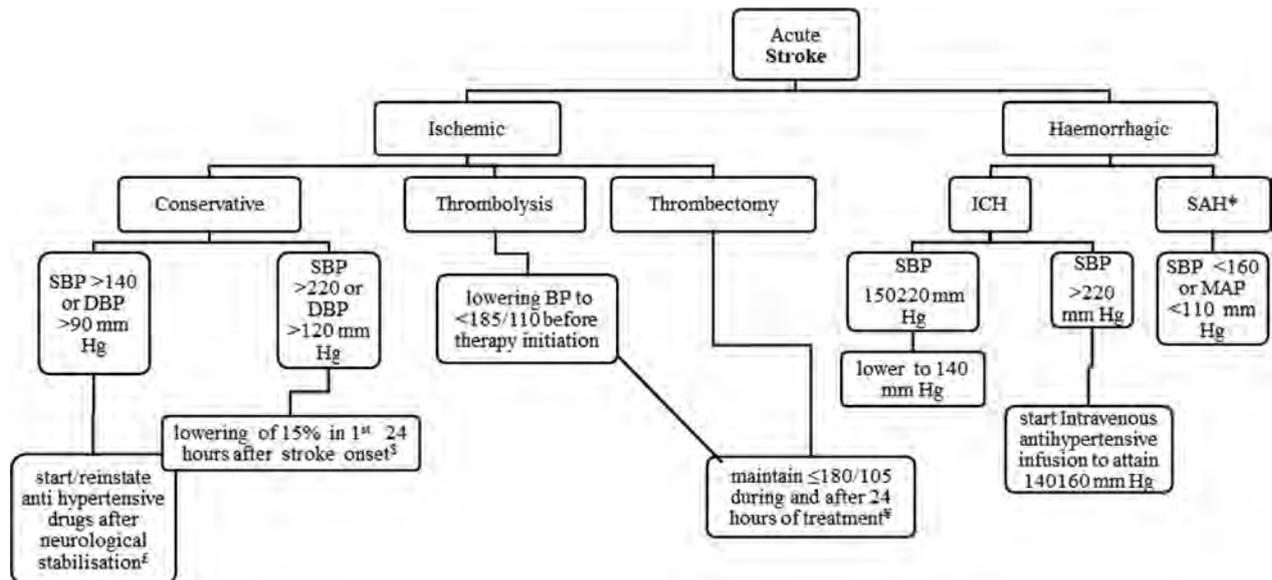
Figure 1: Algorithm for the management of hypertension in acute stroke. $In patients with aortic dissection, ischemic coronary disease, heart failure, hypertensive encephalopathy, preeclampsia, eclampsia also, *optimal therapy not clear, based on ASA/AHA guidelines, ¥In thrombectomy BP should be lowered ≤185/110 mmHg, £usually after 24–48 h in hospital stay only in neurologically stable patients (to be cautious in extra or intracranial stenosis of vessels)

Table 1: Trials of antihypertensive drugs[25-34]

Trial	Drug	Findings
ADVANCE	Indapamide and perindopril	Reduction of micro- and macrovascular events including stroke in Type 2 DM
PROGRESS	Indapamide and perindopril	Reduction of strokes recurrence in nearly normotensive patients with prior history of stroke or TIA
SCOPE	Candesartan	Significant risk reduction of stroke in elderly patients with isolated systolic hypertension
PRoFESS	Telmisartan	No lowering of stroke recurrence or other major cardiovascular event
PATS	Indapamide	Lowering of stroke recurrence
HOPE	Ramipril	Cardiovascular events reduction in elderly patients with vascular disease and diabetes
VALIANT	Valsartan and captopril	Equal effectiveness in reduction of atherosclerotic events in high-risk patients with myocardial infarction
LIFE	Losartan	Significant reduction of new-onset atrial fibrillation and associated stroke
ONTARGET	Telmisartan and ramipril	Equal effectiveness in reducing left ventricular mass, myocardial infarction, and stroke in high-risk cardiovascular patients
ACCESS and CAST	Candesartan	No beneficial effects on functional outcome

DM: Diabetes mellitus, TIA: Transient ischemic attack

adequate monotherapy is carried out over 4–6 weeks. Patients in whom there is a failure of monotherapy to achieve satisfactory BP reduction or drug toxicity emerges, consideration of changing monotherapy agent, gradual dose titration, adding second drug, or combination therapy should be considered.

Initial combination therapy should be considered when BP is elevated beyond >20/10 mmHg above goal[12] or Stage 2 hypertension (≥140/90 mmHg). Single-pill combination preparations improve patient compliance, BP control and may reduce side effects (as individual drugs tend to be used in lower doses). Orthostatic hypotension needs to be keep in the mind while using combination therapy.

Nocturnal "non-dipping" (failure of BP to drop by 10% in sleep) is a strong predictor for adverse cardiovascular outcome than daytime BP so medication timings have to be adjusted accordingly.[24] However, EUROPA and CONVINCE trials showed no specific consensus about optimal timing of medications. Table 1 enumerates important drug trials of antihypertensive agents in relation to stroke.

Non-pharmacological management[12]

There is an increasing recognition of the role of non-pharmacological management in the control of BP. Dietary approaches to stop hypertension diet, weight loss, sodium intake <2.4 g/day, dietary potassium of 3.5–5 g/day (cautious in CKD and drugs causing hyperkalemia), moderate alcohol consumption, control of blood sugar and lipids, and moderate to vigorous physical activity 3–4 days a week averaging 40 min/session have a role and augment the benefits of pharmacotherapy.

Conclusions

Cerebrovascular diseases pose specific challenges with respect to the management of BP. As acute stroke care is changing remarkably, the BP management in acute situations of thrombolysis and thrombectomy are becoming increasingly relevant. To a large extent, increase in BP is a protective response and needs to be handled carefully. Primary and secondary prevention of hypertension is the key to reducing long-term morbidity and disabilities of stroke events.

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Review Article

Hypertension in Children

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Abstract

Prevalence of hypertension (HT) in children is increasing. Part of the reason is the rise in the population of children with obesity and part is better screening for HT though far from ideal. Neonatal and infantile HT remains relatively poorly described in terms of epidemiology, normative data, and available antihypertensive medications. The 2017 American Academy of Pediatrics guidelines on the management of HT in children have used data from children with normal body mass index thereby lowering the cutoffs for definition of HT compared to earlier. HT is now staged as elevated, Stage 1 and Stage 2, making earlier terminologies obsolete. Elevated blood pressure (BP) is important as studies show that an elevated BP as a child increases risk of developing HT as an adult as well as metabolic syndrome. Ambulatory BP monitoring in pediatrics is increasingly being used in various situations though so far there is no normative data for children <120 cm in height. Investigations into the cause of HT may be limited when the patient is over 6 years of age and is overweight or obese or has family history of HT and the physical examination is normal. The two major causes of secondary HT in pediatrics are renal/reno-vascular and endocrine. Lifestyle modification plays a major role in therapy. It includes weight reduction/control by increasing physical activity, nutritious, and low-fat diet and reducing salt intake. The first-line medications for oral therapy are angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics, and calcium channel blockers. Lifelong follow-up is essential for care of the pediatric patient with HT.

Key words: Blood pressure, hypertension, management, pediatrics

Introduction

Hypertension (HT) in children is an important cause of morbidity in childhood.[1] It is a precursor to HT and atherosclerosis related diseases in adulthood. Its prevalence is estimated to be 3.5% in the pediatric population. It is key to choose an appropriate cuff size and be meticulous while obtaining blood pressure (BP) in children. Unlike adult population, in the absence of obesity and family history, HT in young children is more likely to be secondary to renal or endocrine causes. The initial laboratory evaluation of children is tailored with that in mind. Additional investigations are performed as demanded by unique historical and clinical features of the child. Lifestyle modification plays a major role in control of pediatric HT associated with obesity. Initiating pharmacotherapy has to be a well thought out decision as the child may need lifelong medication. The range of medicines available to treat pediatric HT is limited.

Definition of HT

HT in pediatrics is diagnosed when abnormal BP reading (as defined below) is obtained at three separate visits using an appropriate BP cuff and manual auscultatory method. The cutoffs for children are defined by outliers from data collected from children with normal weights. This is unlike the definition of adult HT. Abnormal BP measurements are categorized into three stages: Elevated, Stage 1, and Stage 2. Each level has a particular management strategy. The software application MDCalc (downloadable app) has a BP tool developed in partnership with the American Academy of Pediatrics for use in children aged 1–17 years. It classifies the entered BP value into normal/ elevated/Stage 1 or Stage 2 HT based on age, sex, and height. The practice guidelines issued by the American Academy of Pediatrics in 2017[1] also have an easy reference table for office practice. This tabulates the screening BP values

requiring further evaluation in boys and girls from age 1 to 13 years.

Age 0–12 months

This is a challenging subset for definition of HT for a myriad of reasons, especially in neonates. There is gestational age specific normative data available for neonates inclusive of premature babies and infants.[2,3]

Age 1 year–13 years

- Normal BP – Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) <90th percentile.
- Elevated BP – SBP and/or DBP is between 90 and 95th percentile, or 120/80 mmHg to 95th percentile.
- A BP reading above 95th percentile defines Stage 1 and Stage 2 HT. It is Stage 1, if it is up to 12 mmHg over the 95th centile. It is Stage 2, if it is more than 12 mmHg over the 95th centile:
- Stage 1 hypertension – SBP and/or DBP ≥95th percentile to <95th percentile + 12 mmHg, or 130/80–139/89 mmHg.
- Stage 2 hypertension – SBP and/or DBP ≥95th percentile + 12 mmHg, or ≥140/90 mmHg (whichever is lower).

Age more than 13 years

- Static cutoff numbers (no percentile charts) are similar to adult cutoff values for HT:
- Normal BP – BP <120/80 mmHg.
- Elevated BP – SBP 120–129 with a DBP <80 mmHg.
- Stage 1 hypertension – BP between 130/80 and 139/89 mmHg.
- Stage 2 hypertension – BP ≥140/90 mmHg.

The group of "elevated BP" is important as there is progression to persistent HT in adulthood in almost a third of affected children.[4,5]

The above definition is followed in the United States. The European union uses adult guidelines for children aged 16 years and older, instead of 13 years.[6]

Masked HT is defined as HT at home but not in the office. White coat HT is defined as HT in the office but not at home.

Measurement Protocol

Two measurements to be taken at each visit, after the child is calm and quiet and seated, with at least 2–3 min gap between measurements. The child should have the right arm supported, and at the heart level. The diaphragm of the stethoscope should be kept on the brachial pulse.

An appropriately sized cuff is selected. The selected cuff's bladder length should encircle the bare arm 80–100% and the width of the bladder should be at least 40% of the mid-arm circumference.

The manual auscultatory method with an aneroid sphygmomanometer is preferred; normative data used for defining HT is based on manual auscultation. The cuff is inflated 30–40 mmHg above the level of disappearance of sounds. It should then be slowly deflated till Korotkoff sounds reappear (SBP) and then disappear (DBP).

The automated oscillometric devices are easier to use but have been shown to have higher readings. Hence, manual measurements are always preferable. A hypertensive reading obtained by the oscillometric device has to be rechecked by the manual method.

A lower limb BP should also be recorded in the initial evaluation. The normal lower limb BP is 10–20 mmHg higher than the upper limb.

Screening for HT

Diagnosis of HT in pediatrics is missed because there are lack of symptoms or inability to convey symptoms. Hence, screening for HT is essential. In the absence of any risk factor, BP measurement should be taken annually starting from age 3 years. In the presence of any risk factor, BP measurement should be taken at every clinic visit irrespective of age.

Risk Factors for Developing HT

Premature birth has been linked to HT in children, including abnormal circadian BP pattern. Relevant family history, childhood obesity, dyslipidemia, hyperglycemia, high salt intake, low potassium intake, and obstructive sleep apnea (OSA) are risk factors in children.[7,8] There is a four-fold increase in HT if the body mass index (BMI) is >99% percentile and a 2 fold increase in HT if BMI is >95% percentile.[9] The prevalence of HT in children with OSA is 3–14%.

Ambulatory BP Monitoring in Pediatrics

There are limited data of ambulatory BP monitoring (ABPM) in pediatrics.[10,11] ABPM is monitored by oscillometric method and has separate cutoffs for definition of HT. Normative data for ABPM in pediatric age groups is available.[8] There is no reference for children <120 cm tall. In addition, in most parts of the third world, availability of ABPM apparatus is a challenge.

Possible indications of ABPM in pediatrics include:
1. White coat HT
2. Masked HT (prevalent in obese children)
3. Persistent HT in the Elevated range
4. Stage 1 or 2 HT with a high suspicion of secondary HT not detected with routine tests
5. Chronic kidney disease
6. Long-term follow-up of patients post-correction of coarctation of the aorta
7. Dysautonomic syndromes
8. BP response to medical therapy.

Etiology of HT

HT could be primary HT or secondary to identified causes. It is essential to differentiate the two using historical, clinical, and

laboratory parameters. Diagnosing secondary HT permits better control or potential resolution of the HT.

Primary HT used to be considered a diagnosis of exclusion. However, numerous studies have demonstrated that in hypertensive children aged more than 6 years of age, coexistent over-weight status/obesity, family history of HT, and absence of any physical findings consistent with secondary HT or end organ damage may suggest that secondary HT is very less likely. Accordingly, the American Academy of Pediatrics 2017 clinical practice guideline for screening and management of HT in children and adolescents[1] states that extensive work up is not required in such instances.

A step-wise approach to diagnosing secondary HT is essential.

Age-wise Distribution of Causes of Secondary HT

Neonates

1. Lower gestational age and low-birth weight
2. Administration of antenatal steroid or post natal use
3. NICU related factors: Fluid overload conditions, periprocedural pain, suctioning, prolonged TPN, and ECMO
4. Umbilical artery catheter related thrombus (renal artery flow is disturbed)
5. Bronchopulmonary disease
6. Coarctation of the aorta
7. Congenital Adrenal Hyperplasia
8. Hyperthyroidism
9. Renal diseases
   a. Renal vein thrombosis
   b. Renal artery stenosis: Fibromuscular dysplasia, neurofibromatosis, William syndrome, and congenital Rubella infection
   c. Polycystic kidney disease
   d. Obstructive uropathy
   e. Wilms tumor, neuroblastoma.

Children and Adolescents

The prevalence studies have shown that adolescents are more likely to have primary (essential) HT. The other most common reasons would renal or endocrine causes. On the other hand, in the age group <12 years, the most likely cause of HT would be renal and endocrine, followed by primary HT.

These are the various causes of secondary HT.

1. Renal Disease: About half of the cases of secondary HT may be renal in origin.[12,13] HT is a common feature of chronic renal failure, end-stage renal disease, and post-renal transplant status. Chronic kidney disease has a 37% prevalence of HT.
   a. Renal parenchymal disease: Glomerulonephritis, acute tubular necrosis, hemolytic-uremic syndrome, polycystic kidney disease, recurrent urinary tract infections, and obstructive uropathy.
   b. Renal vascular disease: This cause is identified in 5–10% of children and adolescents with HT and affected patients present frequently with Stage II HT. Fibromuscular dysplasia, aorto-arteritis (Takayasu arteritis), neurofibromatosis, William syndrome, congenital Rubella infection, extrinsic compression on the renal vessels by a mass, and renal venous thrombosis due to a prothrombotic state are common causes.
2. Coarctation of the aorta.
3. Endocrine disturbances: Pheochromocytomas, congenital adrenal hyperplasia, Cushing disease, hyperthyroidism, hypothyroidism (diastolic HT), diabetes (type I and II), and primary hyperaldosteronism.
4. OSA.
5. Exogenous medications: Steroids, caffeine, over-the-counter medications for cold (ephedrine, and pseudoephedrine), medications for attention deficit hyperactivity disorder, tacrolimus, cocaine, oral contraceptive pills, and recreational drugs.
6. Central causes of HT: Space occupying lesions, and disturbances of the vasomotor center.

Evaluation of HT in Children and Adolescents

A stepwise approach to evaluation is critical for satisfactory management of HT [Table 1].

Management of HT

Elevated BP reading: Advise lifestyle changes. Repeat measurement in 6 months. If still in elevated BP range, then consider ambulatory BP monitoring.

Stage 1 Hypertension: Lifestyle changes if applicable. Repeat measurement in 1–2 weeks as appropriate. Consider diagnostic workup.

Stage 2 Hypertension: If the patient is symptomatic or if the BP is elevated by more than 30 mmHg above the 90th percentile, referral should be made to emergency care dept. If the patient is asymptomatic, the BP is repeated in 1 week and then work up and treatment initiated. Symptoms of HT include headache, visual disturbances, seizures and focal neurological deficits, and symptoms of underlying disease in cases of secondary HT laboratory investigations of children and adolescents with Stage 2 HT [Table 2].

An echocardiogram is recommended when initiating antihypertensives. Left ventricular hypertrophy (LVH) is diagnosed if indexed LV mass is >115 g for boys and 95 g for girls. An ECG has low sensitivity to diagnose LVH. However, it gives information on pulse rate and electrolyte disturbances. Ambulatory BP monitoring may be performed as part of work up. Subtle clues in favor of secondary HT such as elevated diastolic pressure readings in daytime and elevated systolic BP readings at night time may be picked up on ABPM. Some units advocate plasma renin activity as part of initial laboratory work up. This would diagnose renal causes

Table 1: Evaluation of a child with hypertension

Component	Details	Remarks
History	Birth/Antenatal history	Maternal history of HT, low birth weight, other factors (see neonatal HT section)
	Family history	HT, early (<55 years age) onset ischemic heart disease, familial hyperlipidemia, sudden cardiac death, hereditary renal, or endocrine syndromes
	Family Structure	Nuclear/joint/both parents working. May determine ease of following dietary or activity advice given
Diet	Intake of high sodium, high fat, caffeine	
Physical activity level	Exercise/field sports/cycling/skating, etc.	
Screen time	Time spent on mobile phone/laptop/tablet/television	Inversely proportional to physical activity level. Hence, important to crosscheck.
Sleep	Less sleep, snoring, day time sleepiness	Obstructive sleep apnea
Physical exam	Weight/Height/BMI	Obesity, endocrine/renal causes
	Dysmorphology	Endocrine causes
	Peripheral/periorbital edema	Renal causes
	Enlarged thyroid	
	Skin lesions: Acne, acanthosis nigricans, xanthelasmas, xanthomas, café au lait spots	Obesity, hyperlipidemia, Cushing syndrome, neurofibromatosis
	Pulse volume and rate	Coarctation, arteritis, hyperthyroidism
	Apical heave, murmur	End organ affect left ventricular hypertrophy
	Abdominal bruit/mass	Arteritis, renal-suprarenal mass
	Joints	Arthritis in certain autoimmune causes of glomerulonephritis
	Ambiguous genitalia	Congenital adrenal hyperplasia

HT: Hypertension, BMI: Body mass index

Table 2: Laboratory investigations of children and adolescents with Stage 2 hypertension

Test	Details	Remarks
Blood	Complete blood count, serum sodium, potassium, chloride levels; serum blood urea nitrogen, serum creatinine, estimated eGFR; lipid profile	In obese patients: Serum fasting blood sugar, HbA1c, serum ALT, serum AST
Urine	Routine and microscopic	
Imaging	Renal ultrasound with Doppler	The Doppler component is more reliable in non-obese children and children above 8 years of age. The alternative to renal Doppler is CT angiography or MR angiography
	CT angiogram or MR angiography	Complete visualization of the aorta and branches including renal vessels. Additional information in mass lesions. Radiation dose should be minimized in CT
	Echocardiogram	When considering antihypertensives

eGFR: Estimated glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CT: Computed tomography, MR: Magnetic resonance, MR

of HT and also help choose antihypertensives. A high plasma renin level prompts usage of an angiotensin converting enzyme (ACE) inhibitor as drug of first choice.[14] Additional testing is determined by index of suspicion for secondary cause of HT.

Treatment of HT

Asymptomatic HT: The goal of therapy is to obtain BP readings that are <90th percentile for age[1]. For children with end-stage renal failure, the goal should be to obtain readings at 50th percentile for age.

Lifestyle Modifications

This includes activity and dietary changes and reduction in stress.[1,15] The entire family has to adapt to the change for success. Encourage outside activity/sports involving moderate physical exertion for 40–60 min at least 3–5 times

in a week, reduction in screen time and age appropriate sleep time.[16]

Diet

In general, the DASH diet (dietary approach to stop HT) can be applied to children.[17] Such a diet is high in minimally processed food, whole grains, lentils, vegetables and fruits, low fat milk and milk products, and fish and lean red meat. There should reduction in refined sugar containing products and salt. Salt reduction implies no table salt and avoiding salty snacks and processed foods. Sodium intake should be <2.3 g (1 teaspoon of salt) per day.[18] A high potassium diet has also been advocated.[19] Avoid caffeinated drinks. Weight control/reduction with a dietician consultation should be availed as appropriate. There is a fall in BP by an estimated 2–4 mmHg for every kg weight reduction in obese adolescents.[20]

Drug Therapy

The preferred medications for pediatric HT are ACE inhibitors, angiotensin receptor blockers, thiazide diuretics, and calcium channel blockers.[21] Beta blockers are not preferred as first line as their side effect profile is not favorable. See Table 3 for common oral antihypertensive medications used in pediatrics. Calcium channel blockers can be safely started on children while

they undergo investigations for secondary HT as these do not interfere with the renin-angiotensin axis. Thiazide diuretics are less effective in children with glomerular filtration rate <30 ml/min/1.7 m^2.

Patients should be seen monthly for titrating drugs. A second or a third drug is rarely required. Second or third line antihypertensives include beta blockers, arterial vasodilators, alpha blockers, and central alpha agonists. See Table 4 for second and third line drugs. Despite all measures, if the child is persistently hypertensive while on three antihypertensives (resistant HT), a trial of spironolactone may be made. Certain disease states benefit from a particular class of antihypertensives. For example, ACE inhibitors are preferred in children with chronic kidney disease with proteinuria. There are data on the efficacy of ramipril in such children, aged 1.9–19 years.[22] Clonidine is helpful in HT due to brain injury and autonomic disorders. Labetalol is useful in pheochromocytoma induced HT, after phenoxybenzamine or prazosin is used.

Contraindications and Common Side effects of Oral Antihypertensives

ACE inhibitors

They are contraindicated in females at risk of becoming pregnant and patients with bilateral renal artery stenosis. Important side

Table 3: First line oral anti-hypertensives for pediatric hypertension

Drug	Dose range (initiating to maximum)	Doses per day	Remarks
Enalapril	0.05–0.3 mg/kg/dose	Twice	>Age 1 month (max dose range: 5 mg–40 mg/day)
Lisinopril	0.07–0.6 mg/kg/dose	Once	Age >6 years (max dose range: 5 mg–40 mg/day)
Ramipril	1.6–6 mg/m^2/dose	Once	Max dose in adults: 2.5 mg–20 mg/day. Has been used in children above 18 months of age
Candesartan	0.01–0.2 mg/kg/dose	Twice	Age 1–5 years (max dose range: 8 mg–32 mg/day)
	4–16 mg/dose	Twice	Age >6 years (max dose range: 8–32 mg/day)
	8–16 mg/dose	Twice	Age >6 years and weight >50 kg (max dose range (8–32 mg/day)
Olmesartan	10–20 mg/dose	Once	Age >6 years, weight <35kg
	20–40 mg/dose	Once	Age >6 years, weight >35 kg
Losartan	0.7–1.4 mg/kg/dose	Once	Age >6 years (max dose range: 50–100 mg/day)
Valsartan	0.4–3.4 mg/kg/dose	Once	Age 1–5 years and weight >8kg: Max dose: 40 mg (<18 kg) to 80 mg (>18 kg)/day
	1.3–2.7 mg/kg/dose	Once	Age: >6 years Max dose range: 40–160 mg/day
Hydrochlorothiazide	0.5–1 mg/kg/dose	Twice	Max dose range: 25–75 mg/day
Chlorothiazide	5–10 mg/kg/dose	Twice	Max dose for age <2 years: 375 mg/day Max dose for 2–12 years: 1000 mg/day Max dose for >12 years: 2000 mg/day
Amlodipine	0.1–0.6 mg/kg/dose	Once	Age 1–5 years. (max dose 5 mg/day)
	2.5–10 mg/dose	Once	Age >6 years. (max dose 10 mg/day)
Nifedipine (extended release)	0.1–1.5 mg/kg/dose	Twice	Max dose: 60 mg twice a day

effect is hyperkalemia and acute renal failure especially in infants. Chronic cough is not as frequent as in adults.

Angiotensin receptor blockers

They are more teratogenic than ACE inhibitors. Side effects are the same; cough is even less frequent.

Thiazide diuretics

They can cause hypokalemia and volume depletion. Prescribe with caution in athletes.

Calcium channel blockers

Peripheral edema and headache. Short acting Nifedipine should be avoided in office practice as it can cause precipitous drop in BP.

Beta blockers

They can reduce endurance in athletes. They are contraindicated in children with severe asthma or diabetes. Rebound HT and tachycardia are seen with abrupt withdrawal of beta blockers.

Alpha blocker (Prazosin)

Syncope with first dose; dry mouth, headache, and weakness.

Central alpha agonist (clonidine)

Drowsiness is a common side effect.

Emergency Treatment of HT

A patient presenting with symptoms/signs of HT, such as headache, delirium, seizures, visual disturbances, or heart failure will require admission to the intensive care unit. Alongside starting medications for control of HT, attempt must be made to thoroughly investigate for secondary HT. Specifically intracranial mass or injury has to be ruled out. Differentiating hypertensive encephalopathy from signs and symptoms of an intracranial mass or a hemorrhage or thromboembolism may require urgent neuro-imaging. The target BP should be at the 95th percentile for age/sex/height of the child. The aim of BP control in a hypertensive emergency is to achieve 25% of the desired reduction over 8 h and the remaining over the next 12–24 h. Intravenous medications used in hypertensive emergencies are tabulated in Table 5. In general, a continuous infusion of nicardipine or labetalol is preferred.

Sports Participation

Physical exercise improves cardiac health in children.[23] Children with elevated or Stage 1 HT should not be restricted. Athletes with Stage 2 HT should be restricted from participating in high static activities such as weight lifting, boxing, and wrestling until BP control is achieved. Athletes should be evaluated for effects on the heart, kidneys, and retina before lifting restrictions.

Summary

Protocols for pediatric HT evaluation and management have evolved over the past some decades. The currently recommended protocols for defining and treating HT have simplified care to a large extent. To achieve control of HT, substantial emphasis should be on encouraging physical activity and low sodium, nutritious diet. Initiating drug therapy has to be a well thought out decision. The array of anti hypertensives available for use lags behind drugs available for adults with HT.

Table 4: Second line oral anti-hypertensives for pediatric hypertension

Drug	Dose range (initiating to maximum)	Doses per day	Remarks
Atenolol	0.25–1 mg/kg/dose	Twice	Max dose range: 50–100 mg/day
Metoprolol	0.5–3 mg/kg/dose	Twice	Max dose range: 100–200 mg/day
Metoprolol extended release	1–2 mg/kg/dose	Once	Max dose range: 50–200 mg/day
Propranolol	0.5–1.2 mg/kg/dose	Thrice	Max dose range: 80–640 mg/day
Labetalol	0.5–10 mg/kg/dose	Twice	Max dose range: 200–1000 mg/day
Prazosin	0.02–0.15 mg/kg/dose	Thrice	Max dose range: 2–20 mg/day
Clonidine	2.5–5 mcg/kg/dose	Twice	Max dose range:200–900 mcg/day

Table 5: Intravenous drugs for pediatric hypertensive emergencies

Drug	Dose	Remarks
Nicardipine infusion	0.5–4 mcg/kg/min	Reflex tachycardia is a side effect. Can be used even in infants.
Labetalol infusion	0.25–3 mg/kg/h	Bolus or infusion is contraindicated in asthma and frank heart failure.
Labetalol bolus	0.2–1 mg/kg/dose. Max 40 mg/dose	Can be repeated every 10 min.
Sodium nitroprusside	0.5–3 mcg/kg/min. max dose 10 mcg/kg/min	Avoid in chronic renal disease.
Hydralazine bolus	0.1–0.2 mg/kg/dose. Max 0.4 mg/kg/dose	Onset of action is slower. Can be repeated every 4 h. Can be given intramuscularly as well. Tachycardia is a side effect. Can be used in infants.

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Review Article

Hypertension in Women

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Abstract

Hypertension (HTN) in women has generated more focus in view of reports of increased prevalence. Women compared with men exhibit a steeper increase in blood pressure (BP) as early as in the third decade and continue in a linear time course thereafter. HTN is the most common medical disorder during pregnancy. Pre-existing HTN is defined as HTN diagnosis before pregnancy, early in pregnancy (before 20 weeks of gestation), or HTN continues after 6 weeks postpartum. Gestational hypertension (GH) is defined as HTN first diagnosis during pregnancy after 20 weeks of gestation. Antihypertensive medications should be initiated at BP ≥150/95 mmHg for patients with pre-existing HTN and >140/90 mmHg for patients with gestational HTN with or without proteinuria. BP target should be <140/90 for all hypertensive pregnant women. Women who take antihypertensive treatments other than ACE inhibitors, ARBs, thiazide or thiazide-like diuretics, and limited evidence available have not shown an increased risk of congenital malformation with such treatments. Labetalol is first-line medication during pregnancy and lactation. Antihypertensives should be restarted after delivery and tapered slowly only after days 3–6 postpartum. Most antihypertensive medicines taken while breastfeeding is safe. Women with established strong clinical risk factors for preeclampsia should be treated ideally before 16 weeks with low-dose aspirin 75–162 mg/day. Women with GH or preeclampsia have increased risks of cardiovascular disease and recurrence of preeclampsia and GH in future pregnancies.

Key words: Gestational hypertension, hypertension during pregnancy, hypertension, labetalol, preeclampsia, proteinuria

Introduction

The prevalence of hypertension (HTN) in women is an increasing concern. Data from 5,26,336 participants aged 40–79 years in the high-income countries have shown a prevalence of HTN across all women participants aged 40–79 years from 33% to 52%. In the age group of 40–49 years, HTN prevalence ranged from 12% to 20% and in 70–79 years from 61% to 82%.[1]

Blood pressure (BP) was recorded for 180,335 participants with a mean age 40.6 ± 14.9 years in India which included 33.2% of women. The prevalence among women was 23.7%. Higher predisposition was noted during the menopausal age. In the age group of 45–54 years, the prevalence of HTN was 34.6% with systolic blood pressure (SBP) of 126.7 ± 18.0 mmHg and diastolic blood pressure (DBP) of 80.3 ± 10.9 mmHg.[2,3]

HTN in Women

Sympathetic activity, increased arterial stiffness may play an important role in the increased prevalence of HTN after menopause.[4,5] Women with HTN are noted to develop more heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, and dementia compared to men.[6,7]

Gender-specific analysis of existing data of four community cohort studies in 32,833 individuals over four decades and inclusive of 54% of women done recently has brought forth some important information on the trajectories of BP elevation. Women compared with men exhibited a steeper increase in BP that began as early as in the third decade and continued through the life course (likelihood ratio test $\chi^2 = 531$ for systolic BP; $\chi^2 = 123$ for diastolic BP; $\chi^2 = 325$ for mean arterial pressure [MAP]; and $\chi^2 = 572$ for PP; for all $P < 0.001$). MAP which is a vascular marker of small artery function also had a greater increase in women as they aged.[8]

Considering the assumption that vascular physiology may or may not fundamentally differ between women and men, these data revealed the early onset and more rapid progress of high BP in women and the manifestations of cardiovascular diseases in their later life.

Underlying genetic expression at the cellular level is a plausible hypothesis.[9]

Hypertensive Disease of Pregnancy (HDP)

HTN is the most common medical disorder during pregnancy, with a prevalence of 5–10% of all pregnancies worldwide.[10]

The discussion in the further text is based on the guidelines of American College of Obstetricians and Gynecologists, ESC/ESH guidelines, ISHHP guidelines, and the NICE guidelines[11-14] for the benefits of healthcare professionals. The discussion is mainly pertinent to HTN and BP lowering drugs and not on other pregnancy-related complications including eclampsia, which is beyond the purview of this article.

Classification of HDP

European guidelines have classified the severity of hypertension as mild HTN (SBP 140–159 mmHg and/or DBP 90–109 mmHg) and severe HTN (BP ≥160/110 mmHg). Classification of hypertension during pregnancy is described in Table 1.

Aneroid devices are used commonly for BP measurement, but they may be inaccurate and need to be regularly calibrated. In a smaller study, 50% of aneroid devices had at least 1 BP reading >10 mmHg out of range compared with the same error in only 10% of mercury devices.[15]

Diagnosis of HTN during pregnancy is based on the standard office BP measurements. Standard procedure for measurement of BP in pregnancy is described in Table 2. Ambulatory blood pressure monitoring (ABPM) which is an important tool in diagnosis and outcome studies in clinical practice[16] is not recommended because they may record lower BP readings and are unreliable in preeclampsia.[17] Also, the diagnosis of hypertension in the ambulatory phase relies on the non–outcome-derived cutoffs from normotensive pregnancies, or the defined threshold values in non-pregnant adults. Paucity of prospective multi-centric studies in different ethnicities of adequate sample size and ABPM outcome-derived thresholds makes ABPM recommendations difficult in HDP. With ongoing studies and data generation ABPM role in pregnancy should not be undermined.

Twenty-four hours ABPM or home BP monitoring has a utility in confirming office or clinic HTN after repeated measurements over hours at the same visit or on two consecutive antenatal visits to eliminate a diagnosis of white coat HTN. Normal values for 24 h ABPM in pregnancy have been determined.[18] Before 22 weeks, BP values should be below: 24 h average 126/76 mmHg; awake average BP 132/79 mmHg;

and sleep average BP 114/66 mmHg. These values are slightly lower than those used as thresholds for diagnosing HTN in non-pregnant women.

ISSHP does not recommend routine testing for any secondary cause of HTN in the absence of clinical clues to these conditions as they are less common.

Complications of Hypertension during Pregnancy are described in Table 3. Eclampsia is a severe form of preeclampsia associated with generalized tonic-clonic seizures. Preeclampsia may develop in the early postpartum period in few cases. If women with chronic HTN are suspected of developing preeclampsia,

Table 1: Classification of hypertension

Preexisting hypertension
HTN diagnosis before pregnancy, early in pregnancy (before 20 weeks of gestation), or HTN continues after 6 weeks postpartum.
Gestational hypertension
HTN first diagnosis during pregnancy, after 20 weeks of gestation; it usually resolves within 6 weeks postpartum. Gestational HTN is considered a form of secondary HTN
Preexisting hypertension plus superimposed gestational hypertension with proteinuria
Preeclampsia
Antenatally unclassifiable hypertension
HTN is first diagnosed after 20 weeks of gestation and it is unclear if hypertension was preexisting and reassessed after 6 weeks postpartum

HTN: Hypertension

Table 2: Blood pressure measurement and HDP

Defined as systolic BP ≥140 and/or diastolic BP ≥90 mmHg. BP should be repeated to confirm true hypertension
BP should be confirmed within 15 min if systolic BP ≥160 and/or diastolic BP ≥110 mmHg
BP to be measured with a liquid crystal sphygmomanometer and if unavailable, validated and appropriately calibrated automated device
Correct cuff size is important, large cuff to be used if the mid upper arm circumference is >33 cm

HDP: Hypertensive disease of pregnancy, BP: Blood pressure

Table 3: Complications of hypertension during pregnancy

Preeclampsia
HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count)
Placental abruption
Disseminated intravascular coagulation.
Intrauterine growth retardation (25% cases of preeclampsia)
Prematurity (27% cases of preeclampsia)
Intrauterine death (4% cases of preeclampsia)
Chronic hypertension (4-fold higher risk)
Stroke and ischemic heart diseases (2-fold higher risk)
Preterm delivery (12.5% in women with gestational hypertension)

placental growth factor-based testing is recommended to help rule out preeclampsia between 20 weeks and up to 35 weeks of pregnancy.

Principles of antihypertensive therapy

Antihypertensive medications should be initiated at BP ≥150/95 mmHg for patients with preexisting HTN and >140/90 mmHg for patients with gestational HTN (with or without proteinuria) and patients with subclinical HTN-mediated organ damage.

BP target should be <140/90 for all hypertensive pregnant women. Physiological drop of BP is noted in the second trimester and some pregnant women may require reduction of dose or sometimes withdrawal of their antihypertensive medication. It is desirable to maintain BP 110–140/85 mmHg.

CHIPS trial (control of HTN in pregnancy study) studied the effects of tight control of BP (DBP <85 mmHg and SBP <160 mmHg). Diastolic BP of 85 mmHg was associated with reduced likelihood of developing accelerated maternal HTN and no demonstrable adverse outcome for babies compared with targeting higher diastolic BP in the CHIPS trial in chronic hypertensive women.[19]

Development of severe HTN was associated with significantly greater likelihood of adverse outcomes in the mother (thrombocytopenia, abnormal liver enzymes with symptoms, and longer hospital stay) and neonate (low birth weight, prematurity, death, and morbidity requiring neonatal unit care) in the follow-up of women in the CHIPS trial. Severe HTN in the less tight control was associated with significantly more serious maternal complications.[20]

Cochrane review on antihypertensive therapy for mild-to-moderate HTN during pregnancy (BP 140–169 mmHg/90–109 mmHg) found that initiating treatment halved the risk of progression to severe HTN but had no effect on the risk of preeclampsia.[21]

Drug therapy for mild HTN

Rigorous salt restriction and weight loss are not recommended during pregnancy due to the risk of volume contraction and neonatal growth restriction, respectively.[22,23] Recent reexamination of the high-risk aspirin trial data during pregnancy reported that the newly identified Stage 1 HTN in pregnancy was associated with increased risk of preeclampsia compared with normotensive women (39% vs. 15%) and that randomization to aspirin reduced this risk (24% vs. 39%).[24]

ISSHP recommends that women with established strong clinical risk factors for preeclampsia (i.e., prior preeclampsia, chronic HTN, pregestational diabetes mellitus, maternal body mass index >30 kg/m², antiphospholipid syndrome, and receipt of assisted reproduction) be treated, ideally before 16 weeks but definitely before 20 weeks, with low-dose aspirin (defined as 75–162 mg/day, as studied in randomized controlled trials). Pre-pregnancy advice for BP lowering drugs in women is described in Table 4.

Table 4: Pre-pregnancy advice for blood pressure lowering drugs

ACE inhibitors or ARBs are associated with an increased risk of congenital abnormalities if taken during pregnancy
ACE inhibitors or ARBs should be stopped preferably within 2 working days of notification of pregnancy
Thiazide or thiazide-like diuretics may have an increased risk of congenital abnormalities and neonatal complications
Antihypertensive treatments other than ACE inhibitors, ARBs, thiazide, or thiazide-like diuretics have not been shown to have an increased risk of congenital malformation

Pregnancy and lactation labeling rule system must be checked before prescribing any drugs to pregnant women. BP lowering drugs and drugs for urgent BP control are described in Tables 5 and 6 respectively. Acceptable initial antihypertensives include labetalol, oxprenolol, methyldopa, nifedipine, diltiazem, prazosin, and hydralazine are usually used as the second- or third-line agents. Atenolol should be avoided in pregnancy as it is associated with fetal growth impairment and this effect is related to duration of therapy. Recent studies suggest that exposure to ACEI early in pregnancy during the period of organogenesis does not confer an increase in the risk of malformations.[25]

Timing of birth and intrapartum antihypertensive treatment

Women with preeclampsia should be delivered if they have reached 37 weeks' (and 0 days) gestation or if they develop repeated episodes of severe HTN despite maintenance treatment with three classes of antihypertensive agents (ISSHP). Planned early birth before 37 weeks is not recommended to women with chronic HTN whose BP is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications. For women with chronic HTN, whose BP is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician. If planned early birth is necessary, antenatal corticosteroids and magnesium sulfate, if indicated, may be given in line with the NICE guideline on preterm labor and birth.

Oral antihypertensives should be given at the start of labor. HTN should be treated urgently with oral nifedipine or either intravenous labetalol or hydralazine if BP rises ≥160/110 mmHg. Total fluid intake should be limited to 60–80 mL/h. Absorption of antihypertensives after oral administration can be hampered because of reduced gastrointestinal motility. Intravenous antihypertensives may be needed to control severe HTN. Short term and long term measures in the post partum phase are described in Table 7.

Antihypertensive treatment during lactation

Antihypertensive medicines can pass into breast milk. Most antihypertensive medicines taken while breastfeeding only lead to very low levels in breast milk, so the amounts taken in by babies are very small and would be unlikely to have any

Table 5: Antihypertensive drugs during pregnancy

Drug	Recommended	Dose	Side effects/concerns
Labetalol	Yes (first choice)	100–200 mg bid, maximum 1200 mg in four doses	Fetal bradycardia or intrauterine growth retardation
Alpha methyldopa	Yes	0.5–3.0 g in 2–4 doses	Sleepiness, dry mouth, general malaise, hemolytic anemia, and hepatopathy[26]
Calcium channel blockers, for example, nifedipine	Yes	20–120 mg long-acting single dose	Headache, pedal edema, dizziness
Hydralazine	Yes	40–200 mg/day in up to four doses	Fetal thrombocytopenia Reflex sympathetic activation
Thiazide and potassium-sparing diuretics	No	--	Potential risk of oligohydramnios
ACEIs and ARBs	No	--	Renal dysplasia, pulmonary hypoplasia, growth restriction[27]

Table 6: Drug therapy for urgent BP control[13]

Drug	Dose	Side effects
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 min to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV; onset of action 1–2 min	Bradycardia
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 min maximum dose 20 mg; or constant infusion of 0.5–10 mg/h; onset of action 10–20 min	Maternal hypotension, headaches, and abnormal fetal heart rate tracings
Nifedipine immediate release	10–20 mg orally, repeat in 20 min if needed; then 10–20 mg every 2–6 h; maximum daily dose is 180 mg; onset of action 5–10 min	Tachycardia, headache

Table 7: Postpartum follow-up – short term and long term

Blood pressure should be monitored at least every 4 h while awake in view of high risk for preeclamptic complications for the first 3 days.

Antihypertensives administered antenatally should be continued and withdrawn slowly over 3–6 days

Antihypertensive therapy may be given for any hypertension before day 6 postpartum

Review recommended at 3 months postpartum by which time BP, urinalysis, and all laboratory tests should have normalized

Women with gestational hypertension should be advised that they have approximately a 4% risk for developing preeclampsia[28]

clinical effect.[29,30] Most medicines are not tested in pregnant or breastfeeding women, so disclaimers in the manufacturer's information are not because of any specific safety concerns or evidence of harm.

Methyldopa, labetalol, and propranolol are considered safe. Beta-blockers such as metoprolol and atenolol can achieve high levels in breast milk and therefore should be avoided. Methyldopa should be avoided because of the risk of postpartum depression.

Angiotensin-converting enzyme inhibitors captopril and enalapril are considered safe given their low concentrations in breast milk. Enalapril can be offered to treat HTN in women during the postnatal period, with appropriate monitoring of maternal renal function and maternal serum potassium. Calcium channel blockers have a limited data and nifedipine is commonly used during breastfeeding. Diuretics are discouraged because of the risk of reducing breast milk production.

HTN in Pregnancy – Future Cardiovascular Implications

Progression to chronic HTN postpartum has been reported in 42% of women with preeclampsia and 39% of women with gestational hypertension (GH) after mean follow-up of 2.5 years as compared to 1% among women with normotensive pregnancies.[31] Women with GH or preeclampsia should be advised that they have increased risks of cardiovascular disease, death, stroke, diabetes mellitus, venous thromboembolic disease, and CKD compared with women who have had normotensive pregnancies.[32,33]

Women with a history of preeclampsia have 71% increased risk of CV mortality, a 2.5-fold increase in risk of coronary artery disease (CAD), and a 4-fold increase in the development of heart failure when compared to normal cohorts as shown in a recent meta-analysis.[34,35] Nurse's Health Study II reported that women with GH and pre-eclampsia had a 3-fold and 6-fold increased rate of chronic HTN. Women with HTN during their first pregnancy had 70% increased risk of type 2 diabetes and 30% increased prevalence of hypercholesterolemia later in life.[36] Norwegian study with a mean follow-up of 17.2 years found that women with preeclampsia alone had a 2-fold increased risk of a major CV event.[37]

Conclusions

High-income countries have reported prevalence of HTN in women aged 40–79 years from 33% to 52% and in India of 23.7%. Higher predisposition is noted during the menopausal age. Vascular physiology may or may not fundamentally differ between women and men but recent evidence has focused on the early onset and more rapid progress of high BP in women and the manifestations of cardiovascular diseases in their later life. HDP which includes all the entities preeclampsia, GH, and chronic HTN is associated with significantly increased risk of CVD in the first decade postpartum and in the long term.

HTN is the most common medical disorder during pregnancy, with a prevalence of 5–10% of all pregnancies worldwide. Progression to chronic HTN postpartum has been reported in close to half of women with preeclampsia and substantial number of women with GH. Women with a history of preeclampsia have a high risk of CV mortality, a 2.5-fold increase in risk of CAD, and a 4-fold increase in the development of heart failure. Labetalol, CCB's, and methyldopa are safe drugs in HDP and ACE inhibitors, ARBs, thiazide, or thiazide-like diuretics are to be avoided. Women with HTN who need to take antihypertensive medication can be adapted to accommodate breastfeeding without any harm.

Acknowledgment

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*R*eview *A*rticle

Interventional Treatment of Secondary and Essential Hypertension

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Abstract

The cornerstone of treatment in hypertension is lifestyle management and pharmacotherapy. A remedial cause of hypertension called as secondary is present in small number of patients. Percutaneous or surgical treatment can be curative or highly effective in controlling the blood pressure in these cases. Balloon angioplasty and stent implantation provide excellent blood pressure control in coarctation of aorta and nonspecific aortoarteritis. There is considerable debate regarding stent deployment in atherosclerotic renal artery stenosis and its use should be restricted to select group. The results of percutaneous interventions are remarkable in fibromuscular dysplasia and post renal transplant graft restenosis .Surgery has a definite role in endocrine disorders like pheochromocytoma ,adrenal adenoma and cushing's disease. Renal denervation is an attractive therapy for patients with essential hypertension who are refractory to pharmacotherapy. Ongoing studies will provide real world indications for this technique.

Key words: Aortic stenting, hypertension, renal denervation, renal stenting, transcatheter interventions

Introduction

Systemic hypertension (HTN) is a major public health problem. India had 41.5 million people with HTN in 2000 and the burden is projected to increase by another 5 million by 2025.[1] HTN is divided in to primary and secondary and vast majority (≥90%) of cases belong to former group.[2] The management consists of lifestyle alterations along with judicious use of pharmacotherapy. A remedial cause of HTN, termed secondary can be identified in approximately 10% of cases. The treatment of specific cause can achieve normalization or better control of blood pressure (BP) with improved outcomes. Table 1 shows causes of secondary HTN amenable to surgical or percutaneous interventions. Various device-based therapies have emerged principally targeted at the treatment of resistant HTN. The therapeutic interventions used in secondary and essential HTN will be discussed in following subheads:

1. Endovascular renal interventions
2. Aortic interventions
3. Role of surgery
4. Renal denervation (RND).

Endovascular Renal Interventions

Atherosclerosis remains the dominant etiology though several important conditions also cause renal artery stenosis (RAS) [Table 2]. Renovascular HTN results from stimulation of renin angiotensin aldosterone system following impairment of renal blood flow by RAS.

Atherosclerotic RAS (ARAS)

ARAS is the leading cause of secondary HTN and frequently coexists with coronary and peripheral atherosclerosis. The prevalence ranges from 10.5% among patients undergoing coronary angiography to 54% among those with congestive heart failure.[3] ARAS may lead to refractory HTN, progressive decline in renal function and cardiac destabilization syndromes.

The diagnosis of significant RAS is crucial to optimal treatment. A physical examination may rarely reveal systolic/diastolic abdominal bruit radiating to flank. Table 3 provides clues to the diagnosis and a detailed evaluation should be restricted to those who are potential candidates for revascularization. Doppler ultrasound is noninvasive, cost

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effective, and excellent diagnostic tool but the yield depends on the operator expertise. A peak systolic velocity (PSV) of >200 cm/s is associated with 95% sensitivity and 90% specificity of >50%.[4] Computed tomographic angiography or magnetic resonance angiography is highly sensitive and specific but are expensive with issues of contrast and radiation. Invasive renal angiography is appropriate for patients who are likely to need intervention and in those undergoing angiography for other indications. Adequate hydration and minimal use of contrast are recommended. On angiography, the stenosis can be categorized as mild (≤50%), moderate (50–70%), and severe (≥70%). The lesion is considered hemodynamically significant when resting or hyperemic translesional systolic pressure gradient of ≥ of 20 mmHg, or a mean gradient of ≥

Table 1: Causes of secondary HTN

Disorder	Major findings
Renovascular HTN	See Table 3
COA	Inequal pulses, young patients <30 years
NSA	Inequal pulses, young female HTN (<30 years)
PCC	Paroxysmal HTN, established HTN with spells, headache, sweating
Conn's syndrome	HTN, Hypokalemia, incidental detection of adrenal mass
Acromegaly	Skeletal features, DM
CD	Typical obesity, DM

HTN: Hypertension, PCC: Pheochromocytoma, CD: Cushing's disease, NSA: Non-specific aortoarteritis, COA: Coarctation of aorta, DM: Diabetes mellitus

Table 2: Common causes of RAS

Atherosclerosis
Nonspecific aortoarteritis
FMD
Transplant related
Atheroembolic renal disease
Aortorenal dissection
Trauma

RAS: Renal artery stenosis, FMD: Fibromuscular dysplasia

Table 3: Indications for diagnostic testing in RAS

Increase in serum creatinine of at least 50% within a week of starting ACEI or ARB therapy
Onset of severe HTN (e.g., >180 mm systolic, >120 mm diastolic) in young patients or those above 55 years
Renal bruit, severe HTN in patients with unilateral small kidney
Severe HTN in patients with known atherosclerosis
Severe HTN in patients with recurrent flash pulmonary edema

RAS: Renal artery stenosis, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, HTN: Hypertension

of 10 mmHg, or renal fractional flow reserve ≤0.8.[4,5] These measurements help to identify patients with refractory HTN who are likely to have favorable BP reduction with stenting.[6,7] Estimation of gradients is also useful in patients with moderate stenosis on angiography.

Treatment options include pharmacotherapy with or without renal revascularization. Percutaneous trans-luminal renal angioplasty (PTRA) with stent placement (PTRAS) is an option for control of HTN and preservation of renal function. A review of seven randomized controlled trials comparing PTRAS plus continued medical treatment (MT) versus MT alone failed to support a beneficial effect of PTRAS on clinical outcomes.[3] Three major trials, STAR,[8] ASTRAL,[9] and CORAL[10] failed to document a definite subset of patients who may benefit from percutaneous treatment. The impact of these studies was considerable reduction in use of PTRAS from its peak in 2006 to selective use.[11] These trials have been strongly criticized for several flaws in selection criteria, inconsistent definitions of improvement, endpoints, and procedural techniques.[4,5] Given the controversies, it is a challenge to select a suitable patient who will respond favorably to the intervention. According to Society for Cardiovascular Angiography and Interventions (SCAI) expert consensus document[5] and review of American College of Cardiology (ACC) and American Heart Association guidelines,[4] PTRAS is recommended for symptomatic patients with significant RAS who have refractory HTN despite guideline directed MT. PTRAS is also effective for prevention of progressive ischemic nephropathy, heart failure, or sudden pulmonary edema (cardiac destabilizing syndrome). Figure 1 shows marked reduction in trans-stenotic gradient with angiographic improvement in renal narrowing in a patient with refractory HTN secondary to ARAS.
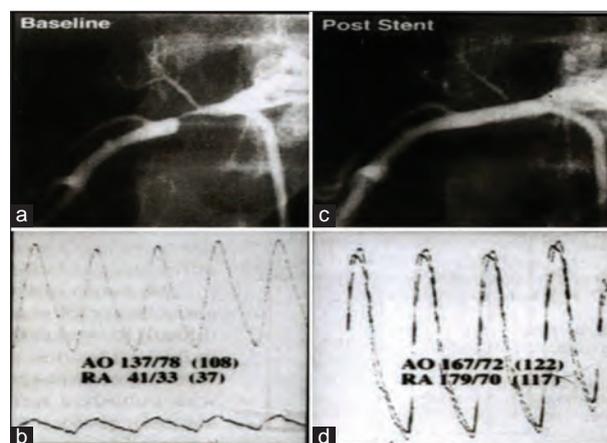
Figure 1: Selective right renal angiography depicts over 90% narrowing (a) with marked trans-stenotic gradient (b) in a patient with severe ARAS in basal state. Remarkable angiographic (c) and hemodynamic (d) improvement after renal stenting. AO: Ascending aorta, RA: Radial artery, ARAS: Atherosclerotic renal artery stenosis

Fibromuscular Dysplasia (FMD)

FMD is a non-inflammatory, non-atherosclerotic arterial disease that predominantly affects carotid, renal, and femoral arteries. Renal artery FMD is often found incidentally in asymptomatic individuals but has a 2–6% prevalence with a female preponderance and can lead to HTN.[12] Medial hyperplasia accounts for 70% of cases and is mostly bilateral. "String of pearls" appearance on angiography is characteristic of FMD. The stenosis can be subtle and only detectable on pressure gradient measurement or by intravascular ultrasound imaging. PTRA without stent implantation is very effective and is recommended for patients who have uncontrolled BP or deteriorating renal function. The procedure is very effective in curing or controlling HTN.[13]

Non-specific Aortoarteritis (NSA)

NSA is common in our country and obstructive lesions of renal artery result in renovascular HTN which is often resistant to pharmacotherapy. There is localized or diffuse involvement of the proximal segment or ostia of renal arteries. PTRA was found to be safe and effective but the high rates of restenosis limited its utility. Cutting or high pressure balloon has been utilized in tough ostial lesions. Stent implantation provides better angiographic results, effective control of BP and is recommended for *de novo* lesions, dissection and in patients with suboptimal results to PTRA.[14]

Transplant RAS (TRAS)

TRAS is a unique subset of RAS and is the most common vascular complication following renal transplantation. There are important differences in the pathology of ARAS and TRAS. Early stenosis with in 1st year of transplantation is related to vascular injury whereas late TRAS resembles severe bilateral ARAS.

Refractory HTN, unexplained rise of serum creatinine or flash pulmonary edema are presenting manifestations. Doppler ultrasound finding of PSV of >2 mm raises strong suspicion. TRAS is a potentially treatable/curable cause of HTN with excellent therapeutic outcomes following percutaneous trans-luminal angioplasty with or without stent.[15,16]

Aortic Interventions

Balloon angioplasty (BA) with or without stent implantation has been used to treat aortic obstruction in coarctation of aorta (COA) and NSA.

COA accounts for 5% of congenital heart disease. Neonates and infants usually present with heart failure and surgical correction is the best option. COA can cause HTN in children but presentation is usually delayed until adulthood. Adult patients with COA are either asymptomatic or present with HTN and its complications. Classic signs include delayed or absent femoral
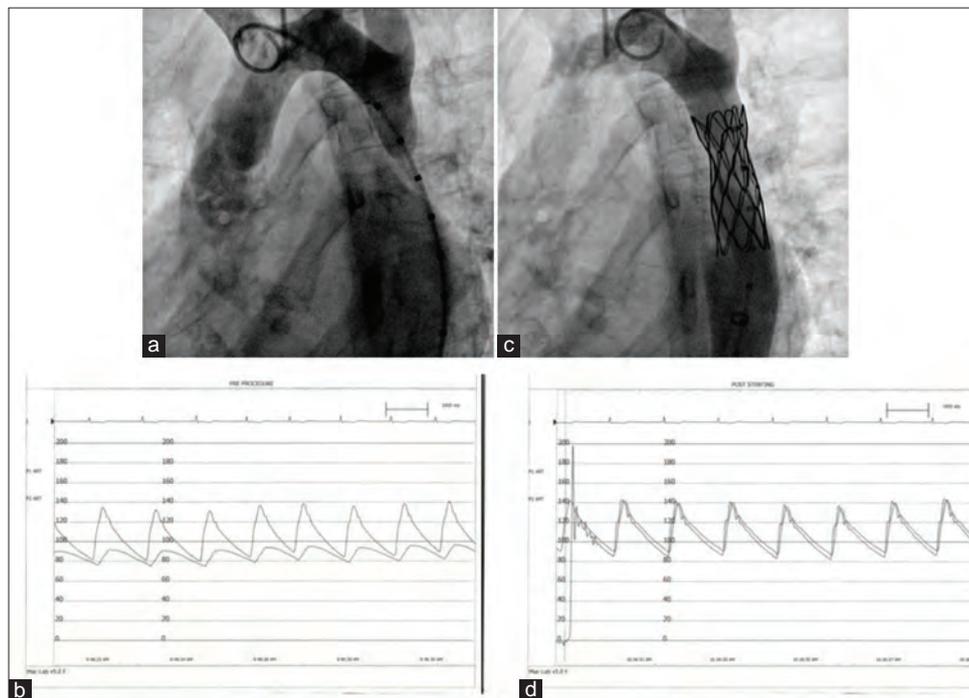
Figure 2: Ascending aortography in left anterior oblique view demonstrates severe aortic narrowing (a) and gradient across descending and ascending aorta (c) in an adult with coarctation of aorta. Stent deployment results in excellent angiographic (b) and hemodynamic (d) improvement

pulses, upper extremity HTN, low or unrecordable BP in the lower extremity and a murmur. Therapeutic options for COA have evolved from surgical correction through BA[17] to stent implantation.[18] The initial application of BA was to successfully dilate post-surgical COA. The dense scar tissue surrounding the recurrent COA makes the re-operation difficult and provides support against aortic rupture during balloon dilatation. BA is the preferred approach for the management of post-operative COA. In older children and adolescents, BA has been widely used as the primary form of therapy. There are variable rates of recurrence and aneurysm formation. In general, the results of balloon dilatation are better and long lasting in discrete COA. In adults, stent is offered as the first choice of treatment. Figure 2 demonstrates angiographic aortic narrowing in an adult with HTN and remarkable angiographic and hemodynamic benefits after stent deployment. Stenting results in effective and predictable relief of the obstruction with effective control of BP in short- and long-term. Accumulated experience including the COAST trial[18] support the use of bare metal stents for most patients with COA, with covered stents usually reserved for those deemed to be high risk or with aneurysm formation.

NSA is a chronic inflammatory arteritis of unknown etiology affecting aorta and its main branches with resultant HTN. Revascularization should be attempted only after suppressing the disease activity. BA, stent, or stent graft placement has been used as percutaneous treatment options. The procedure outcome depends on the site, length, lesion characteristics, and stage of arterial stenosis. BA produced excellent results for short segment lesions.[19] The rigid, noncompliant lesions may yield only to a high pressure dilatation or result in significant residual stenosis .Stents are an important adjuvant to BA when there is vessel recoil or dissection but have been extensively used electively with high procedural success and restenosis rate of 20%. Stent grafts are better than uncovered metal stents or BA with low restenosis and sustained patency.

Role of Surgery

Surgery remains a feasible and effective option in selected patients with COA, NSA, and RAS with complex anatomy or failed percutaneous intervention. Operative options in COA include resection with end to end anastomosis, patch aortoplasty, or bypass graft. Vascular surgery has been the traditional modality in NSA and several procedures including aortorenal bypass are in vogue.[20] The role of surgery in rare endocrine disorders will be discussed briefly.

Pheochromocytoma (PCC)

PCC and paragangliomas are catecholamine producing endocrine tumors arising from chromaffin cells in the adrenal glands and the ganglia. Clinical manifestations such as HTN, headache, palpitations, and pallor are due to catecholamines release. Rarely, patients can present with life threatening hypertensive crisis. Approximately 95% of patients have HTN which can be paroxysmal or sustained. In some patients, hypertensive paroxysms will occur in a background of sustained HTN. Demonstration of elevated levels of catecholamines and/or its metabolites in urine or plasma is essential for the diagnosis. Imaging by computed tomography (CT), magnetic resonance imaging (MRI), or metaiodobenzylguanidine scan is needed to confirm the diagnosis. Laparoscopic techniques are currently in vogue for adrenal removal surgery. Pre-operative alpha and beta blockade and intraoperative hemodynamic monitoring are crucial for a favorable outcome.[21]

Primary Hyperaldosteronism (Conn's syndrome)

Hyper-aldosteronism can result from adrenal adenoma, unilateral or bilateral adrenal hyperplasia, and rarely carcinoma. Adenoma (Conn's syndrome) is Characterized by increased aldosterone secretion from the adrenals, suppressed plasma renin, hypokalemia, and HTN. Hypokalemia in a patient with HTN is the usual clue to consider hyper-aldosteronism, but potassium can remain normal in one-third of patients. These patients have uncontrolled BP, increased vascular risk, and early death. High aldosterone: Renin ratio suggests primary hyper-aldosteronism to be confirmed by CT, MRI, or selective adrenal venous sampling. Laparoscopic surgical adrenalectomy results in significant improvement in 95% and complete cure in one-third.[22]

Cushing's Disease (CD)

CD is caused by a pituitary adenoma that secrets adenocorticotropin (ACTH) autonomously, leading to excess cortisol secretion from the adrenal glands. Adenoma accounts for 70% of patients with endogenous Cushing Syndrome, the remaining 30% are secondary to ectopic ACTH syndrome, adrenal tumors, or hyperplasia. These patients show a cluster of systemic manifestations including abdominal obesity, HTN, and cardiovascular abnormalities. High BP is present in 70–80% of patients and attributed to stimulation of mineralocorticoid and glucocorticoid receptors, insulin resistance, and over expression of renal angiotensin system. CD is associated with increased mortality and morbidity primarily as a consequence of increased risk of CVD. Diagnosis of adenoma is confirmed by MRI. Trans-sphenoidal pituitary surgery is the first line of treatment and carries a favorable prognosis.[23]

Acromegaly

Acromegaly is usually caused by a growth hormone secreting pituitary adenoma which causes a disorder with disproportionate skeletal tissue and organ growth. HTN is among the most frequent cardiovascular complication. Resection of adenoma using highly sophisticated endonasal trans-sphenoidal approach improves outcomes.[24]

RND Therapy

HTN contributes to a significant mortality and morbidity attributable to cardiac, cerebrovascular, and renal complications. Drug therapies are effective but adverse effects; intolerance and non-adherence pose major challenge in effective control of BP. To overcome these limitations, a number of interventional technologies are being evaluated

Chronic elevation of sympathetic nervous system activity has been identified as an important pathological mechanism in the initiation and maintenance of hypertensive state. Historically, surgical splanchniectomy has been used to interrupt sympathetic nerves in the lower thoracic and lumbar regions for treating severe HTN.[25] Sympathomedullary approaches such as RND, baroreflex activation therapy, and endovascular baroreflex modulation have been used to lower BP. Percutaneous RND became possible through the development of a catheter based radio-frequency ablation resulting in selective renal sympathectomy. The procedure effectively modulates the effects of elevated sympathetic activity both by reducing the efferent renal sympathetic control of kidney function (renin release, sodium excretion, and renal flow) and by removing the renal afferent sympathetic contribution to BP control. The initial studies showed effective reduction of office BP. However, the first randomized sham-controlled trial, SYMPLICITY HTN-3[26] did not show significantly lower office or 24 h ambulatory systolic BP compared with sham treatment. The results dampened the enthusiasm and raised questions about the efficacy and the procedural protocols.

The second generation of placebo-controlled trials of renal sympathetic denervation has moved from including the patients with resistant HTN receiving intensive pharmacological treatment to including patients with mild-to-moderate HTN in the presence or absence of antihypertensive medications. Refined radio frequency based and ultrasound based RND systems were used. Three recent sham controlled trials: SPRYAL HTN OFF MED, SPRYAL HTN ON MED, and RADIANCE-HTN provide data supporting the use of RND as a treatment of HTN.[27-29] Ambulatory BP was used as the end point in all these trials. SPRYAL HTN-OFF MED pivotal trial data in 331 patients released in virtual ACC 2020 showed superiority of catheter based RND compared with a sham procedure to safely lower BP in patients off medication.[30] These trials have provided the proof of principle for the BP lowering efficacy of radio frequency based and ultrasound based RND in patients with or without concomitant pharmacotherapy. Clinically relevant and consistent reduction in ambulatory BP and office BP in the short term (2–3 months) and mid-term (6 months) was documented. Future studies will answer the remaining questions regarding the precise mechanism, the most eligible group, procedure protocols, and the duration of efficacy.

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Review Article

Newer and Aggressive Blood Pressure Goals to Treat Hypertension

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Abstract

The benefits of blood pressure (BP) lowering treatment for the prevention of cardiovascular disease are well established. However, aggressive control of BP is controversial, as it leads to a reduction in organ perfusion and function, thereby increasing overall morbidity and mortality. An elusive balance is now being sought between deleterious effects of hypotension and protective autoregulatory mechanism. Here, we perform a systematic review of data and the current status of aggressive control of BP in various clinical settings.

Key words: Aggressive blood pressure control, autoregulatory mechanisms, hypotension

Introduction

Historically, clinicians believed that the rise in systolic blood pressure (SBP) in older age groups was a benign physiological response to age-related arterial stiffening.

However, this view changed and was largely forgotten in the subsequent 2–3 decades, due to the results of various antihypertensive treatment trials, showing beneficial effects of BP reduction on cardiovascular morbidity and mortality.[1-5]

The possibility of antihypertensive treatment causing more harm than benefit resurfaced in the late 70s and 80s. Cruickshank *et al.* (1987) showed that excessive lowering of diastolic BP (DBP) (below 85 mmHg) in patients with severe hypertension resulted in an increased risk of myocardial infarction (MI) and death.[6] This also emphasized the fact that BP reduction and incident cardiovascular risk or events is a J-shaped curve rather than a linear relationship.

The prevalence of hypertension has increased among the Indian population in the past 25 years. The latest data show that the prevalence of hypertension in urban areas is 33.8% and 27.6% in rural areas, with an overall prevalence of 29.8%. Ramakrishnan *et al.* found a high prevalence of hypertension among young Indian adults (20–44 years), and this prevalence was more than twice the prevalence found in a similar population in the United States (22.4% vs. 10.5%, respectively).[7]

J-curve Hypothesis

A J-shaped relationship between BP and cardiovascular morbidity and mortality has been described. Organs, such as brain, heart, and the kidneys, have autoregulatory mechanisms which cause vasodilatation to maintain constant perfusion when the BP is reduced. However, any further reduction below a threshold is accompanied by a steep reduction in blood flow, leading to organ damage. In hypertensives, this threshold is reset to a higher level, making it more difficult to maintain BP within a narrow range without causing end-organ dysfunction.

J-curve phenomenon in hypertension is as yet unresolved since the optimal BP may vary between individuals, across various organs, and with associated conditions. The J-curve phenomenon, for DBP, was first observed in connection with MI in patients on hypertension treatment. It describes an inverse relationship between low DBP and angina, MI, cardiovascular morbidity, and mortality [Figure 1]. Stewart reported that the incidence of MI was 5 times higher in the patients with DBP <90 mm of Hg, compared with those with a DBP between 100 and 109 mm of Hg ($P < 0.01$).

Evidence in Favor of Aggressive Management of BP

The focus on aggressive BP control was rekindled by the results of the SPRINT (SBP Intervention Trial). SPRINT enrolled

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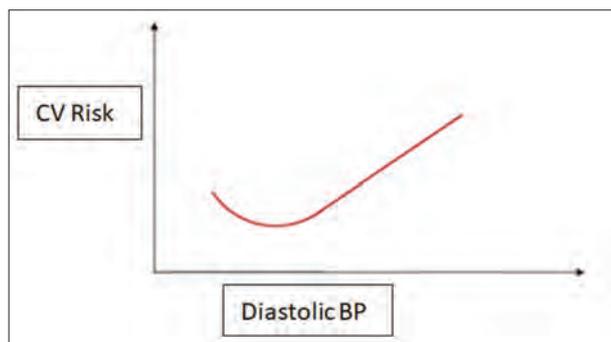
Figure 1: Lowering diastolic blood pressure below a threshold causes higher cardiovascular risk and morbidity: J-curve phenomena

more than 9300 participants aged 50 years and above, in about 100 medical centers and clinical practices throughout the USA and Puerto Rico. SPRINT investigators randomly divided the study participants into two groups that differed according to targeted levels of SBP. The standard group received an average of two different BP medications to achieve a target of <140 mmHg. The intensive treatment group received an average of three BP medications to achieve a target of <120 mm of Hg. The significant preliminary results of SPRINT were announced on September 11, 2015. The trial showed that the lower target of BP (<120 mm Hg) reduced cardiovascular events by 25% and overall risk of death by 27%.[8]

SPRINT is the largest study of its kind to date to examine how maintaining SBP at a lower than currently recommended level will impact cardiovascular and renal disease. The study population is diverse and includes women, racial/ethnic minorities, elderly, chronic kidney disease (CKD), and pre-existing cardiovascular disease. However, SPRINT excluded patients with diabetes, prior stroke, or polycystic kidney disease. On the basis of SPRINT and few other studies, the American College of Cardiology (ACC)/American Heart Association (AHA) 2017 guidelines on hypertension targeted an aggressive BP goal of 130/80 for those with high or elevated cardiovascular risk estimated by atherosclerotic cardiovascular disease risk (ASCVD).

Wang *et al.*, using recursive partitioning of all clinical variables in a derivation cohort within the SPRINT trial, developed a three-step decision tree composed of age ≥74 years, urinary albumin to creatinine ratio or Urinary albumin to creatinine ratio (UACR)≥ 34, and history of prior CVD, to distinguish patients at high or low risk of major adverse coronary event (MACE). Only the high-risk subgroup had a significant risk reduction with intensive versus standard BP treatment. The improvement in cardiovascular outcomes associated with a lower BP target in the high-risk group was not accompanied by an increase in serious adverse events, thus maximizing the net benefit of intensive BP reduction in this group. Thus, they were successful in identifying the group of hypertensive patients who would derive the most favorable risk-benefit profile from intensive BP lowering.[9]

Clinicians should also consider how the results of SPRINT compare with other trials that have asked similar questions when comparing intensive versus standard treatment for BP control. Cochrane Collaboration's Hypertension Review group observed that aiming for targets lower than 140/90 mmHg did not result in overall benefit to the patient.[10] The meta-analysis of seven trials of more than 22,000 patients found that even though giving drugs did achieve lower BP; this strategy did not prolong survival or reduce strokes, MI, heart failure, or renal failure. Although various researchers have been eager to incorporate the evidence from SPRINT to modify current recommendations, the systematically reviewed evidence suggests that a more careful and individualized approach is needed to manage BP.

How Aggressive should BP Reduction be in Various Clinical Settings?

Although lowering the BP decreases cardiovascular events, too much reduction may actually be detrimental. The benefits of BP reduction on cardiovascular events are not bottomless, as it tends to plateau or even reverse, below a critical level. Various clinical guidelines have been established to provide a general framework to guide clinicians in the diagnosis and treatment of hypertension. Although there exist some differences in the definition of hypertension between ACC/AHA and European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines [Figure 2], both agree to the treatment goal of BP <130/80 mm of Hg.

BP reduction in myocardial ischemia

The normal epicardial coronary arteries are conductance vessels, which do not provide any resistance to blood flow, and there is no detectable pressure drop along the entire vessel length. Coronary circulation is more susceptible to reduced perfusion pressure, especially in the presence of atherosclerotic plaques and impaired flow reserve. The presence of left ventricular hypertrophy (LVH) also increases susceptibility to ischemia, along with lowered DBP.[11] Treatment-induced diastolic hypotension, which is more common in older patients and those with diabetes, has been associated with an increased risk of adverse cardiovascular events in both observational studies and *post hoc* analyses of various trials. The CLARIFY international cohort study (the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease) and INVEST study (the International Verapamil-Trandolapril Study) in patients with stable coronary disease found that cardiovascular risk doubled when DBP was <60 mm of Hg and 70 mm of Hg, respectively. Similar findings were also noted in the SYST-EUR trial (Systolic Hypertension in Europe), where elderly population were targeted to achieve SBP to <150 mm of Hg. However, this demonstrated a J-curve effect, when the diastolic pressure was reduced below 70 mm of Hg, resulting in higher cardiovascular morbidity.

Arterial stiffness, frailty in the elderly, heart failure, malnutrition, and malignancy may also contribute to the J-shaped relationship between low diastolic pressure and the composite

	ACC/AHA	ESC/ESH
Definition of Hypertension (mm Hg)	≥ 130/80	≥ 140/90
Normal Blood Pressure ranges (mm Hg)	Normal: < 120/80 Elevated: 120-129/<80	Optimal: < 120/80 Normal: 120-129/80-84 High normal: 130-139/85-89
Hypertension Stages (mm Hg)	Stage 1: 130-139/80-89 Stage 2: ≥ 140/90	Grade 1: 140-159/90-99 Grade 2: 160-179/100-109 Grade 3: ≥ 180/110
Age Specific Blood pressure targets (mm Hg)	< 65 years: < 130/80 ≥ 65 years: < 130/80	< 65 years < 120-129/70-79 ≥ 65 years < 130-139/70-79

Figure 2: Differences between American and European definition of hypertension with age-specific targets

cardiovascular events. A sub-analysis of the EPHESUS study showed that patients after acute MI (AMI) with a low DBP were at an increased risk of all-cause mortality than patients with higher DBP. These patients also were older, which had previous acute coronary events, heart failure, lower ejection fraction, higher Killip class, and a higher rate of revascularization. Analysis has revealed that the unfavorable outcome in the low DBP group was almost predominantly limited to those patients who had not been revascularized. These patients showed an increase in all-cause death, cardiovascular death, or cardiovascular hospitalization, whereas no such trend was seen in those who were revascularized, and their outcomes were independent of DBP. It is for this reason that guidelines recommend caution in reducing DBP to <60 mm of Hg in patients with CAD.[12-14]

However, data suggest that patients with CVD who undergo effective myocardial reperfusion strategy, lower DBP does not produce a greater risk than persons without CVD. Patients with hemodynamically significant aortic regurgitation (AR) have low DBP. Such patients exhibited mortality which rose steeply, in inverse proportion to DBP ranging from 70 mm of Hg to about 55 mm of Hg.[15]

BP reduction in stroke

Hypertension is the most important modifiable risk factor for stroke. Recent data indicate that treatment with antihypertensive drugs reduces the incidence of all strokes in men (by 34%), women (by 38%), and the elderly (by 36%), including those older than 80 years (by 34%), younger persons, those with systolic and diastolic hypertension, persons with isolated systolic hypertension, and those with a history of stroke or transient ischemic attack (by 28%). Aggressive antihypertensive therapy has been proven to be highly effective in reducing the risk of stroke.

An overview of published reviews noted that 10 mmHg reduction in SBP was associated with a decrease in the risk of stroke in approximately one-third of subjects (60–79 years). This association continues up to BP levels of at least 115/75 mm Hg and is seen across sexes, regions, and stroke subtypes as well as for fatal and nonfatal events.[16] In action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a SBP reduction to <120 mmHg did not have any significant effect on MI but reduced the risk of stroke substantially. A similar benefit was seen in the Perindopril Protection against Recurrent Stroke Study, where a reduction in the incidence of stroke recurrence was seen at a baseline SBP between 120 and 139 mmHg.

BP reduction in CKD

Hypertension is an important risk factor for the development of the end-stage renal disease. Hypertension is present in 60–90% of patients on hemodialysis. Control of BP has been shown to reduce or delay the onset of urinary protein excretion and attenuate the progressive decline in renal function. BP reduction is a must in both pre-dialysis phase of CKD and patients on dialysis. Pohl et al.[17] noted that all-cause mortality was higher in patients with SBP <120 mmHg, but the progression of renal deterioration was low.

However, in few observational studies, paradoxical results were also obtained, wherein mortality was observed to be highest in patients with low pre- or post-dialysis BP values, particularly in the presence of high pulse pressure. Low SBP, both pre- and post-dialysis, was associated with increased CV and non-CV mortality. Hence, a "U-shaped" relationship between BP and mortality was observed, with excess mortality risk in patients with the lowest and highest BP. Pre-dialysis systolic hypertension was not associated with an increase in either CV or non-CV mortality.

Management of BP in dialysis patients requires attention to both management of fluid status and adjustment of antihypertensive medication. In patients with difficult-to-control hypertension, the dialyzability of antihypertensive medications (such as metoprolol, atenolol, ACEI, alpha-methyldopa but not ARB's or calcium channel blockers) should be considered. A clinician should keep in mind that intensive BP lowering may be beneficial in further reducing CV outcomes, but reduction below 120/70 mmHg may actually be harmful.

BP control in diabetes

Patients with diabetes have accelerated vascular aging manifested by poor vascular compliance, increased BP variability, impaired blood flow autoregulation, and increased microvascular disease. Pioneering trials, such as the United Kingdom Prospective Diabetes Study, highlighted the benefits of "intensive BP lowering" (<150/85) in diabetics with 32% risk reduction in mortality related to diabetes and 44% reduction in the incidence of strokes.[18] The results of INVEST and ONTARGET trials have also been encouraging.

The ACCORD trial focused on SBP targets (aggressive therapy SBP <120 mmHg vs. standard therapy SBP <140 mmHg) rather than DBP due to the increasing recognition of SBP as an important CVD risk factor. The primary outcomes were non-fatal MI, non-fatal stroke, or cardiovascular death. Intensive antihypertensive therapy in the ACCORD BP trial did not significantly reduce the primary cardiovascular outcome or the rate of death from any cause. Intensive BP management did, however, reduce the rate of two secondary outcomes total stroke and non-fatal stroke. There were some reports of possible harm associated with intensive BP control, including some side effects (dizziness, hypotension, syncope, injurious falls, and acute kidney injury) that were significantly higher in the intensive-therapy group than in the standard therapy group.

The BP targets to adopt in the diabetic population are controversial, with conflicting recommendations from different guideline-issuing groups. The 2017 update of the ACC/AHA BP treatment guidelines recommends universal intensive BP treatment for adults with DM (target BP <130/80 mmHg). The 2018 Standards of Care in Diabetes from the American Diabetes Association, however, recommend a target of <140/90 mmHg for most patients. Adults with advanced microvascular disease and endothelial dysfunction from diabetes may, therefore, be more likely to experience adverse effects from aggressive BP lowering. ADA guidelines recommend that lower SBP and DBP targets (<130/80 mmHg) may be appropriate for individuals at high risk of cardiovascular diseases. Thus, it is important to consider the entire spectrum of patients with diabetes, as well as their age, rather than placing everyone under one umbrella.[19]

In diabetic patients, the SBP target should be <140 mmHg according to the ACCORD trial. However, for patients with protein-creatinine ratio >500 mg/g (albumin-creatinine ratio >300 mg/g), with or without diabetes, a lower SBP target for renal protection aiming for SBP <130 mm of Hg is recommended as per kidney disease improving global outcomes guidelines.

BP reduction in elderly

A 2018 ESC/ESH BP guidelines categorize older adults in two subgroups; "elderly" refers to patients between the ages of 65 and 79 years while "very old" refers to those ≥80 years. A recent evaluation of the NHNES Health database revealed that nearly 50% of hypertensive US adults (≥ 80 years of age) have uncontrolled

hypertension. The Korean Society of Hypertension recommends a BP goal <140/90 mmHg for fit older adults between 65 and 79 years old. The office BP treatment threshold for adults ≥80 years old or frail elderly hypertensives is ≥160/90 mmHg, but if they tolerate treatment, it is reasonable to aim for <140/90 mmHg. These targets are similar to the European guideline, but much less aggressive than the American guideline that recommends BP <130/80 mmHg for most adults ≥65 years old.

In INFINITY (Intensive vs. Standard Ambulatory BP Lowering to Prevent Functional Decline in the Elderly) study, researchers assessed the older adults' mobility, cognitive function, their brain's white matter progression with magnetic resonance imaging, and tracked the occurrence of any adverse events. The results of INFINITY demonstrate that a lower ambulatory BP goal for older adults is likely to conserve future brain function and health. A large prospective observational study on 415,980 people above 75 years has projected that the lowest mortality risk in adults above 75 years was at SBP 140–160 mmHg and diastolic of 80–90 mmHg. However, they also noted that there was excess mortality in this same group with SBP <130 mmHg irrespective of baseline frailty.

This study suggested frailty assessment in the elderly should be coupled with BP levels to decide the feasibility of aggressive hypertension treatment. If an elderly individual is independent and needs no assistance in activities of daily living, aggressive reduction of BP can be considered, keeping a close watch on postural BP change, symptoms of cerebral ischemia or rise in creatinine levels[20]. Lower targets are relevant in elderly patients if no orthostatic hypotension occurred, and in patients with non-proteinuric CKD (eGFR < 60 ml/mn/1.73 m^2) or cardiovascular disease with Framingham score more than 15%.

BP reduction in young

Hypertension in the young is often unrecognized and neglected. Between the period of 1999 and 2014, the various aspects of hypertension control (hypertension diagnosed by average BP of >140/90 mmHg or the use of antihypertensive medication) were lower among young adults(18–39 years) compared with middle-aged (40–59 years) or older adults (>60 years) (74.7% vs. 81.9% vs. 88.4% for awareness; 50.0% vs. 70.3% vs. 83.0% for treatment; and 40.2% vs. 56.7% vs. 54.4% for control). However, if one uses current guidelines cutoff, the incidence will be higher. A 20-year prospective Chinese cohort study found that Stage 1 hypertension, as defined by the 2017 ACC/AHA hypertension guidelines (130-139/80-89), was associated with a significantly increased risk of CVD compared with normal BP, and this group accounted for 26.5% of cardiovascular deaths and 13.4% of cardiovascular events in young Chinese adults aged 35–59 years.

In the short-term, hypertension in the young is associated with higher rates of LVH, alterations in brain volume, and white matter hyperintensities. In the long-term, multiple studies have demonstrated increased rates of cardiovascular disease and mortality in young people with hypertension. Coronary Artery Risk Development in Young Adults longitudinal study showed that

Clinical Conditions	BP Threshold (mm Hg)	BP Goals (mmHg)
General		
Clinical CVD or 10 Year ASCVD risk ≥ 10 %	≥ 130/80	<130/80
No clinical CVD and 10 Year ASCVD risk <10%	≥ 140/90	<130/80
Older persons (≥ 65 Yrs of age; ambulatory ,non-institutionalized, community-living adults	≥ 130 (SBP)	<130 (SBP)
Specific co-morbidities		
Heart Failure (HF)	≥ 130/80	<130/80
Stable Ischemic heart disease	≥ 130/80	<130/80
Diabetes mellitus	≥ 130/80	<130/80
Chronic kidney disease (CKD)	≥ 130/80	<130/80
CKD after renal transplantation	≥ 130/80	<130/80
Secondary stroke prevention	≥ 140/90	<130/80
Peripheral artery disease	≥ 130/80	<130/80

Figure 3: Threshold and goals to be achieved in various clinical settings

elevated SBP at baseline was more predictive of coronary artery calcium 15 years later and a significantly higher risk of cardiovascular disease. The higher risk seen in the younger subgroup suggests incremental risk over time when risk factors are left untreated and, hence, need for lifestyle change measures (which are the mainstay of treatment for this cohort) together with intensive BP control therapy even in Stage 1 hypertension in young.

The ACC/AHA guidelines advocate treating all Stage 2 young hypertensives (SBP >140 and DBP >90 mm Hg) regardless of 10-year cardiovascular risk. However, in Stage 1 hypertension (SBP, 130–139 or DBP, 80–89 mm Hg), guidelines advice treating only those with ASCVD 10-year cardiovascular risk ≥10%, or the presence of diabetes mellitus or CKD.[21] In patients at low or intermediate risk, without cardiovascular disease, SBP should be treated when it is above 140 mmHg, and when treated, target BP should be <140 mmHg as reported by HOPE-3 trial. There is, however, limited evidence if these interventions can reduce the risk of cardiovascular events or adverse changes in brain structure.

BP control in atrial fibrillation (AF)

Another cohort not often discussed is patients with non-valvar AF and hypertension. In the Korean AF cohort, applying the new 2017 ACC/AHA guidelines redefined 17.2% of patients with AF as newly hypertensives. AF can be a result of uncontrolled hypertension, and the presence of hypertension increases the risk of complications in patients with AF. Patients with AF and newly redefined hypertension were at significantly higher risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission compared to non-hypertensive patients.

Patients with AF would receive the greater benefit if BP target range of 120–129/<80 mm of Hg is achieved, compared to that of 130–139/80–89mm of Hg, regardless of their estimated CVD risk.[22]

Summarizing, the first target of anti-hypertensive treatment should be to achieve BP lower than 140/90 mmHg. Once that target is achieved, BP can be further reduced to 130/80 mmHg. However, one must always be vigilant to avoid organ hypoperfusion manifested as orthostatic hypotension, orthostatic dizziness, weakness, and elevation in serum creatinine level BP. The threshold and goals to be achieved in various clinical settings have been described [Figure 3].

Conclusion

Hypertension remains the most important risk factor for cardiovascular disease. BP targets have been a subject of great controversy. The "lower – the better dogma" has been strongly advocated, especially after data reported from recent trials. However, aggressive BP control in low-risk patients did more damage than benefit. Various meta-analysis and guidelines have shown that a more nuanced approach is needed to treat hypertension, keeping in mind age, comorbid conditions, end-organ damage, and individual response to treatment. It is important to emphasize that there can be no one-size-fits-all approach in the control of BP.

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$\mathcal{R}$eview $\mathcal{A}$rticle

Newer Drug Choices in Hypertension Treatment

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Abstract

Life style alterations and drug therapy are the main stay in the treatment of hypertension (HTN). Five classes of drugs, for example, angiotensin-converting enzyme inhibitor (ACEI), aldosterone receptor blocker (ARB), beta-blocker (BB), calcium channel blocker (CCB), and diuretics have been recommended by various guidelines and these agents are standard of care. This review focusses on certain agents which have become available or new data have emerged with the existing compound. Azilsartan, a recently approved ARB, has been shown to provide sustained and superior antihypertensive effect as compared to existing sartans. Nebivolol, a third-generation long-acting BB with vasodilatory effects, provides excellent hemodynamic and side effect profile. A number of third- and fourth-generation CCB (benidipine, azelnidipine, and cilnidipine) are available in our country. These compounds are highly vascular selective and display organ protection effects. The use of these agents can be individualized depending on the likely benefits. Spironolactone, an old drug with modest blood pressure lowering effects, has proved to be an excellent add-on fourth agent in patients with resistant HTN.

Key words: Azelnidipine, azilsartan, benidipine, hypertension treatment, nebivolol

Introduction

Hypertension (HTN) continues be a major health problem with considerable mortality and morbidity resulting from the resultant vascular complications.[1] There are two well-established strategies to lower blood pressure (BP): Lifestyle alterations and drug treatment. Meta-analysis of randomized controlled trials (RCTs) has shown that a 10 mm reduction in systolic BP (SBP) or a 5 mm reduction in diastolic BP (DBP) is associated with significant reduction in all major cardiovascular (CV) events, all-cause mortality, stoke, coronary events, and heart failure (HF).[1] There are well-established classes of drugs used in the treatment of HTN as per guidelines.[2,3] This review intends to discuss new drugs/choices which are now available for the treatment of HTN in our country. It is not intended to review the well-established compounds.

Five groups of drugs, for example, angiotensin-converting enzyme inhibitors (ACEIs), aldosterone receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide), are recommended based on proven ability to reduce BP, reduce CV events, and overall CV morbidity and mortality. There are some specific differences between various drug groups. BBs cause less stroke prevention, whereas less HF prevention is documented by CCBs. The new drug choices will be discussed in the following sections [Table 1].

1. Blockers of the renin-angiotensin system
2. Newer BBs
3. Third- and fourth-generation CCBs
4. Anti-aldosterone agents (aldosterone antagonists).

Blockers of renin-angiotensin system

Both ACEI and ARBs are among the most widely used classes of antihypertensive drugs. Both groups have similar effectiveness in terms of CV event and mortality reduction. Both ACEI and ARB reduce albuminuria and are effective in preventing chronic kidney disease (CKD). ARBs are associated with significantly lower discontinuation rates for adverse rates than other group Wof drugs. ARBs are extensively used for the treatment of HTN

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Table 1: Newer drug choices in HTN

Class of drug	Compound
ARB	Azilsartan
BB	Nebivolol
CCB	Benidipine, azelnidipine, cilnidipine
Aldosterone antagonist	Spironolactone

ARB: Aldosterone receptor blocker, HTN: Hypertension, CCB: Calcium channel blocker, BB: Beta-blocker

as monotherapy and in combination with other group of drugs. Losartan was the first ARB to be used and many compounds are now available. *Azilsartan medoxomil* is the eight ARB approved by FDA for the treatment of HTN. It is highly selective with a 10,000 times higher affinity for angiotensin (AT) 1 receptor than AT 2 receptor. Azilsartan exerts some of its effects through peroxisome proliferator-activated receptors gamma pathway activation. There are considerable data which have accumulated comparing this compound with ACEI or other ARBs.[4] A meta-analysis of seven RCT including a total of 6152 patients treated with 40 mg azilsartan versus control therapy with other sartans revealed a significant reduction in clinic and 24 h SBP and DBP in the azilsartan group.[5] The initial dose of azilsartan is 40 mg once daily (20 mg for patients >75 years of age) which may be increased to 80 mg once daily with full effect reached by 4 weeks. Adverse effects include dizziness (8.9%), increase in serum creatinine (3.6%), fatigue (2%), diarrhea (2%), hypotension (1.7%), and syncope (0.3%).[4] A fixed-dose combination (FDC) with chlorthalidone has been approved as it reduced 24 h ambulatory SBP more effectively than olmesartan combined with hydrochlorothiazide.[6] ARBs have an excellent patient safety profile as assessed by low discontinuation rates.[7] Any ARB including azilsartan has been recommended in ACC guidelines for the treatment of HTN.[1]

Newer BBs (BBs)

Some years ago, BBs were relegated to the 2nd or 3rd line positions by HTN societies. Current RCTs and meta-analyses demonstrate that when compared with placebo, BBs significantly reduce the risk of HF and major CV events in hypertensive patients. When compared with other BP lowering groups, BBs are equivalent in preventing major CV events, except for less effective control of stroke.[3] BBs are not a homogenous class. In recent years, the use of vasodilating BB such as labetalol, nebivolol, celiprolol, and carvedilol has increased. Nebivolol is a third generation, long-acting and highly selective B1 adrenoreceptor antagonist that also exhibits nitric oxide-mediated vasodilatory effects. It is an effective anti-HTN agent with long duration of action. *Nebivolol* has a unique pharmacological profile, despite showing similar BP lowering effects, and has certain advantages in the treatment of HTN compared to previous generation of BBs. It has favorable effects on endothelial function, central BP, and aortic stiffness. The side effect profile is favorable with negligible risk of new-onset diabetes mellitus and less risk of erectile dysfunction.[8,9]

Nebivolol at doses of 1.25 mg–40 mg/day has been evaluated for the treatment of HTN both as monotherapy and in combination of other drugs. The usual initial is 5 mg daily. The compound is beneficial and widely prescribed for sexually active man and in those with comorbidities such as type 2 diabetes mellitus, metabolic syndrome, and chronic obstructive lung disease. Nebivolol has been approved by FDA as monotherapy and also a FDC of nebivolol and valsartan (5/80 mg). ESC guidelines recommend use of nebivolol for the treatment of HTN although long-term outcome data in HTN are not available.[3]

Third- and fourth-generation CCBs

Based on chemical structure, CCBs are categorized into three subgroups; benzothiazepines, phenylalkylamines, and dihydropyridines (DHPs). The first two groups have negative chronotropic and inotropic effects and are used for the treatment of stable coronary artery disease and in certain arrhythmias. Main action of DHP group of CCBs is peripheral vasodilatation and these drugs are used for the treatment of HTN. The CCBs, a diverse group of CV drugs, exert their effect by inhibiting the L-type (or other type T, N, and L/N) calcium channel and cause vasodilatation in the heart and the smooth muscles. Although the CCBs have common antihypertensive action, they have vast difference in their pharmacological actions, pharmacokinetic profile, and adverse reactions. The CCBs have evolved from first to fourth generation.[10] The first-generation CCBs have a rapid onset of action, need frequent dosing, and cause significant tachycardia by baroreceptor reflex mechanism. These drugs reduce both myocardial contractility and conduction of electrical impulses to the heart. Nifedipine is the first-generation DHP specifically blocking L-type calcium channel in heart and blood vessels. The second generation of drugs has a better pharmacokinetic profile and also reduced baroreceptor activation. This group has less negative inotropic effect and reduced effect on atrioventricular conduction system. Nifedipine extended release is prototype of this group and benidipine is an intermediate compound between generation two and three. The third-generation drugs with slow and prolonged action limit reflux tachycardia. They are lipophilic, inhibit L-type calcium channel, have stable pharmacokinetic, and are well tolerated in HF and CKD. Amlodipine, azelnidipine, and lercanidipine represent this group. The fourth-generation CCBs possess both L- and N-type calcium channel blocking action and are highly lipophilic. These drugs can completely attenuate the activation of sympathetic system. Cilnidipine represents this generation. Clinical application of CCBs is dependent on antihypertensive and vasodilatory actions, duration of benefits, profile of end-organ protective effects, and incidence of adverse events. CCBs are a heterogeneous class of agents. Most RCTs demonstrating the benefits of CCBs on outcomes have used DHP, especially amlodipine. CCBs are widely used for the treatment of HTN and have similar effectiveness as other major drug classes on BP, major CV events and mortality outcomes. CCBs have a

greater effect on stroke reduction than expected for the BP reduction, but may also be less effective for preventing HF with preserved ejection fraction. Based on large data, amlodipine remains a safe and effective drug of choice in the treatment of chronic HTN owing to its slow, prolonged duration of action and lesser incidence of reflux tachycardia. The newer CCBs, although similar to amlodipine in BP lowering effect, have several pharmacological advantages. However, it is important to understand that there is lack of robust data with the newer agents and head-to-head comparative data with amlodipine are lacking. Three compounds, benidipine, azelnidipine, and cilnidipine, will be discussed briefly and are already in use in our country. *Benidipine*: This agent was marketed in Japan 15 years back and has highest affinity for binding sites among all CCBs, blocks N, L, and T calcium channels, and has vascular selectivity 20 times more that of amlodipine.[11] The blockage of N- and T-type calcium channels inhibits the catecholamine with resultant reduction in tachycardia. This agent is renoprotective as it promotes natriuresis, reduces apoptosis of renal tubule and proteinuria. Anti-atherosclerotic properties have also been demonstrated. The dose is 2–4 mg daily and maximum dose being 8 mg daily. Side effects include palpitations, headache, rash, itching, gynecomastia, and photosensitivity. Three benidipine-based regimens, benidipine + ARB, benidipine +BB, and benidipine + thiazide, were equally effective in lowering BP and preventing cardiac events in a substudy of COPE trial.[12] Benidipine-thiazide regimen provided better CV outcomes, BP control, and stroke reduction than the benidipine-BB combination in another subanalysis.[13] *Azelnidipine*: The compound is lipophilic and inhibits both L- and T-type calcium channels. The drug has high affinity to vascular tissues resembling nifedipine except for being long acting with slow onset and no tachycardia. Like benidipine, it displays anti-atherosclerosis, anti-oxidative properties and reduces proteinuria. A meta-analysis of 19 studies (1482 patients) revealed similar efficacy and safety of both azelnidipine and amlodipine for reducing BP in mild-to-moderate HTN.[14] In an open-labeled randomized short-time study, a combination of olmesartan with azelnidipine was superior to combination of candesartan and amlodipine and provided better morning BP, heart rate, and glycemic control.[15] The dose is 8 mg once a day and can be increased up to 16 mg. Adverse effects include headache, hot flashes. and nausea. Cilnidipine: The drug belongs to the fourth generation of the DHP-CCB and is a dual L/N type CCB. *Cilnidipine* reduces excessive excitation of the sympathetic nervous system and the release of norepinephrine from sympathetic nerve endings and consequently suppresses reflective tachycardia and stress-induced BP elevation more efficiently than amlodipine.[16] In white coat and morning HTN, there is excessive sympathetic activity and cilnidipine can be a preferred choice. It is postulated that cilnidipine provides superior renal protection attributable to reduced activation of renin-angiotensin-aldosterone system. In a short-term study, lower incidence of edema was observed with cilnidipine as compared to amlodipine.[17] Anti- ischemic, pleiotropic, and favorable glycemic effects have been reported.

The dose is 5–10 mg daily and can be increased to 20 mg a day. The side effects include fever, rashes, gastric reflux, flushing, myalgia, and increased urination.

Anti-aldosterone agents (aldosterone antagonist)

Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects when elevated can contribute to the development of HTN. There is a strong postulate that sodium retention plays a dominant role in resistant HTN. Mineralocorticoid receptor antagonist (MRA), spironolactone which has modest BP lowering efficacy has been used in resistant HTN.[18] There is a growing evidence to suggest that the fourth-line treatment in HTN should involve a blockade of the biological effects of aldosterone through the use of MRAs. PATHWAY-2 is the first RCT to compare different BP lowering treatments in patients with resistant HTN.[19] The patients enrolled in this trial had uncontrolled BP despite being on triple drug therapy involving an ACEI/ARB, CCB, and a diuretic. In the study, spironolactone was compared with alternate fourth-line treatments targeting different pathogenetic mechanism: The alpha-1 adrenoreceptor blocker, doxazosin, acting to reduce peripheral resistance and the beta-1 adrenoreceptor blocker, bisoprolol, which inhibits the release of renin and reduces cardiac output. The 25–50 mg daily dose of spironolactone in PATHWAY-2 was well tolerated and was superior to other groups in achieving BP control within 3 months. The use of spironolactone should be restricted to patients with eGFR above 45 ml/min and plasma potassium concentration of ≤4.5 mmol/l. Guidelines recommend the use of spironolactone as add-on treatment for resistant HTN.[3]

The equivalence and efficacy of all five groups of drugs are well established as monotherapy and in certain combinations. The drugs discussed above can be used judiciously by the clinician as an alternative to the existing compounds. A number of new BP lowering drugs (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, and endothelin antagonists) are investigational and have not been discussed.

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Review Article

Obstructive Sleep Apnea, Hypertension, and Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) accounts for significant morbidity and mortality globally. Obstructive sleep apnea (OSA) is the repeated stoppage of inspiratory airflow due to oropharyngeal obstruction during sleep. This results in lack of oxygen, disturbance to sleep, and adrenergic nervous system stimulation. Consequently, the blood pressure rises, there are tachycardia, vascular dysfunction, widespread inflammation, and resistance to insulin. All these changes are said to contribute to the development of CVD. A large volume of evidence has accumulated in favor of OSA linking it to hypertension, coronary artery disease, cardiac failure, and various cardiac arrhythmias. Increased public awareness of OSA and its early detection, prompt diagnosis, and institution of appropriate treatment, including continuous positive airway pressure, would help in adequate control of this potentially modifiable risk factor in the era of increasing CVD.

Key words: Cardiovascular disease, hypertension, obstructive sleep apnea

Introduction

Globally, cardiovascular disease (CVD) contributes majorly to increased morbidity and mortality. In addition to the research directed toward the development of newer and more effective treatments, there is also serious thought and research toward modifying risk factors for primary and secondary prevention of CVD.

In the ongoing search for such modifiable risk factors, obstructive sleep apnea (OSA) is one main risk factors for several CVDs such as hypertension (HTN), cardiac failure (CF), cardiac arrhythmias, and coronary artery disease.[1] In a society, where there is an ever-increasing aging population compounded with the obesity epidemic, OSA prevalence has increased by 30% and thereby its increased association with CVD.

OSA is the repeated stoppage of inspiratory airflow due to oropharyngeal obstruction during sleep. It affects 34% of males and 17% of females in the USA.[2] This upper airway obstruction results in lack of oxygen, disturbance to sleep, and adrenergic nervous system stimulation. Consequently, there is a rise in blood pressure with tachycardia, vascular dysfunction, widespread inflammation, and resistance to insulin. All these changes are

said to contribute to the development of CVD.[3] A large volume of evidence has accumulated in favor of OSA linking it to drug-resistant HTN, coronary artery disease, congestive CF, and atrial fibrillation [Table 1].

Pathophysiology

Due to OSA, there is recurrent oropharyngeal airflow obstruction and the consequent intermittent hypoxia and hypercapnia leads on to myocardial ischemia (resulting from decreased myocardial oxygen delivery), pulmonary and systemic vasoconstriction with increased afterload (due to stimulation of the adrenergic nervous system) which leads to the onset of pulmonary and systemic HTN and their obvious consequences.

OSA gives rise to increased sympathetic activity which, in turn, causes tachycardia and HTN. There are several mechanisms which induce the increased sympathetic activity such as chemoreflex stimulation by hypoxia and hypercapnia, baroreflexes, pulmonary afferents, impairment in venous return to the heart, cardiac output alterations, and possibly the arousal response itself.[3]

The cortical arousal due to OSA results in sympathetic and parasympathetic stimulation with the release of increased of

Table 1: Prevalence estimates of sleep apnea in various cardiovascular conditions[3]

Cardiovascular conditions	Prevalence estimates (%)
Angina	30
Coronary artery disease	30
Type 2 diabetes	35
All HTN	35
Atrial fibrillation	50
Congestive heart failure	50
Drug-resistant hypertension	80

HTN: Hypertension

catecholamines into the circulation, along with increased vagal activity, leading to cardiac hypertrophy, diastolic and systolic myocardial dysfunction, and ultimately cardiac arrhythmias and CF.[3]

The negative intrathoracic pressure from repetitive episodes of OSA results in increased transmural gradient causing atrial stretch, left ventricular (LV) wall tension, structural remodeling, and increased oxygen demand, all of which ultimately lead to cardiac arrhythmias and CF.[3] Endothelial dysfunction may also play a role.[4]

OSA is a significant risk factor for CVD and is associated with increased cardiovascular morbidity and mortality.[5,6] Several clinical trials have been conducted to study the effect of continuous positive airway pressure (CPAP) therapy in OSA on cardiovascular effects.[7,8] One of the largest multicenter randomized clinical trials (RCTs), sleep apnea cardiovascular endpoints study (in 2717 patients with moderate-to-severe OSA) and CVD, observed the effect of CPAP on the incidence of CVD. Despite adequate control of OSA (apnea-hypopnea index [AHI] reduced from 29 to 3.7), there was no significant decrease in CV episodes. Several meta-analyses of RCTs of OSA patients also did not reveal a statistically significant decrease of risk in CV episodes. This could have been attributed to the overall low adherence rate to CPAP of <4 h per night.[9]

Diagnosis of OSA

To suspect OSA, a contributory history and clinical examination should be forthcoming in the background of certain risk factors. Some of these risk factors are (1) age 40–70 years, (2) family history of OSA, (3) male:female ratio: 3:1, (4) obesity with body mass index (BMI) >35 kg/m², (5) postmenopausal women not on hormone therapy, and (6) retrognathia.

Predictive clinical history include "choking"/gasping episodes during sleep, morning headaches, excessive daytime sleepiness, loud snoring, and a neck circumference of >40 cm.

There are several questionnaires for screening for OSA. Epworth Sleepiness Scale, Berlin questionnaire, and STOP-BANG questionnaire are the ones which are often used.

Physical examination to look for a short neck with a large circumference (>40 cm), a high BMI (>35 kg/m²), retrognathia,

and a narrow, "crowded" oropharyngeal opening with a large tongue all of which may suggest the presence of OSA.

OSA is confirmed by performing an overnight sleep study (polysomnography) in a sleep laboratory (Type I study) or at home, which can detect and quantify the AHI. Apnea occurs when a complete cessation of airflow for >10 s is recorded. Hypopnea is a partial obstruction to airflow lasting for >10 s and desaturation of >3%. The AHI is calculated by adding all the apneas and hypopneas and dividing by the total sleep time. An AHI of 5 or <5 is normal, 5–15 is mild, 15–30 is moderate, and >30 is diagnostic of severe OSA.[10]

OSA and HTN

In OSA patients, when compared with controls, there is a higher frequency of HTN. Around 50% of OSA patients have coexisting HTN.[11-13] Furthermore, in patients with resistant HTN, there is a higher frequency of OSA. In resistant HTN patients, 71% had OSA whereas only 38% of patients had OSA in well-controlled systemic HTN.[14] OSA is a well-recognized secondary cause of HTN.[15]

Several mechanisms have been put forward to explain the effects of OSA on the evolution and worsening of HTN. Recurrent episodes of hypoxemia and hypercapnia cause reflex stimulation of the adrenergic nervous system with associated increase in adrenaline/noradrenaline levels resulting in increases of blood pressure. Furthermore, hypoxic vasoconstriction occurs as a result of release of various chemical mediators.[16]

The use of CPAP in patients with OSA has contributed immensely to the control of HTN. Marin *et al.* studied 1889 patients of OSA without HTN and demonstrated the 5 times higher possibility of developing HTN in OSA patients who were not treated with CPAP.[17] Pedrosa *et al.* also reported significant reductions in systolic and diastolic BP. The Joint National Committee concluded from the results of all these studies that OSA is a preventable liability for the development of HTN.[18]

OSA and Coronary Heart Disease

Severe OSA is an underlying risk factor and is associated with an increased incidence of CAD. In the Sleep Heart Health Study of over 6000 patients, there was an independent association of OSA and the CAD incidence.[19] Other studies by Shah *et al.* of 1436 patients also showed a significant association between OSA and CAD.[20] Worse outcomes with higher incidence of cardiac deaths and reinfarction were also seen in another study by Yumino *et al.*[21]

Various mechanisms have been proposed for atherosclerosis in OSA. Repeated hypoxic events can induce oxidative stress, systemic inflammation, and endothelial dysfunction and the consequent decreased nitric oxide production causing lack of vascular relaxation.[22] Other studies have provided evidence of OSA increasing platelet aggregation and decreasing the breakdown of fibrin which may lead to acute coronary syndromes.[23]

The application of CPAP in OSA to reduce the incidence of CAD and acute coronary syndrome has been extensively researched. McEvoy *et al.* studied 2687 patients with OSA (being treated with CPAP) and CAD, and there was no statistically significant benefit in endpoints.[9] The RICCADSA (randomized intervention with CPAP in CAD and OSA) trial of 244 patients established that the routine use of CPAP in patients with CAD with non-sleepy OSA did not significantly reduce long-term adverse cardiovascular outcomes. However, CPAP therapy in OSA does control HTN and CV episodes if used for at least 4 h per night.[7]

OSA and CF

There is a higher prevalence of CF in OSA patients, particularly in those with decreased ejection fraction. About 30% of those patients with CF and low ejection fraction and around 35% of those with preserved ejection fraction were found to have OSA. Furthermore, in patients with existing CF and untreated OSA, the mortality rates were significantly higher.[16]

The pathophysiology of OSA and CF has a number of mechanisms. Negative intrathoracic pressure due to obstruction of upper air flow (apnea) and consequent hypoxia and sympathetic hyperstimulation results in increase in the LV transmural pressure which, in turn, decreases LV preload and increased afterload. The net result of these changes is myocardial strain and impairment in contractility, LV hypertrophy leading onto the development and progression of CF.[3]

The use of CPAP in OSA patients with CF significantly improves the symptoms. In a small study of 24 patients of severe CF with OSA, the application of CPAP produced 9% improvement in cardiac function.[24] Another study by Mansfield *et al.* also showed 5% improvement in the LV ejection fraction, lower urinary catecholamine levels, and improved quality of life compared to controls.[25]

OSA and Cardiac Arrhythmias

A strong association exists between OSA and cardiac arrhythmias. Their incidence depends on the stage of OSA and frequency of hypoxic episodes. Several studies have shown the increased prevalence of nocturnal arrhythmias, atrial fibrillation, sinus arrest, ventricular premature contractions, and ventricular tachycardia in patients with OSA. Guilleminault *et al.* studied 400 patients with OSA of whom, 48% had cardiac arrhythmias. Tracheostomy was done in 50 of these patients which completely relieved them of any cardiac arrhythmias.[26] A four-fold increase in cardiac arrhythmias was seen in severe OSA patients when compared to controls in the subgroup analysis of patients from the Sleep Heart Health Study.[27] There was a two-fold increase in atrial fibrillation in OSA patients when compared to controls in a meta-analysis of 19,837 patients by Youssef.[28]

Many different explanations have been offered for the increased incidence of cardiac arrhythmias in OSA. Repeated episodes of hypoxemia during upper airway obstructive events induce baroreflex and chemoreflex activation resulting in abnormal electric remodeling of the atria and the myocardium. This could explain the high incidence of AF in OSA. Increased sympathetic activity could also trigger cardiac arrhythmias. Reflex cardiac vagal stimulation due to repeated apneic-hypopneic events could explain the basis of the development of bradyarrhythmias in OSA patients.[3]

The incidence of sudden cardiac death (SCD) in severe or untreated OSA may increase due to fatal cardiac arrhythmias. The rate of SCD decreased with the application of CPAP in such patients when compared with those who discontinued CPAP therapy.[29]

The effect of CPAP therapy in OSA on the occurrence of cardiac arrhythmias has been studied in 3000 patients of AF and found 11% decrease in AF recurrence.[30] Ryan *et al.* showed 58% decrease in the occurrence of cardiac arrhythmias in 18 patients of OSA treated with CPAP compared to controls.[31]

OSA and Pulmonary HTN (PH)

Advanced stages of OSA are associated with a higher prevalence of PH to the tune of approximately 20%. It is usually mild when there is no associated lung disease. Other risk factors for PH in this setting are comorbid lung disease, obesity hypoventilation syndromes, and increasing severity of OSA along with daytime hypoxemia.[32]

OSA-PH has a lower functional capacity and quality of life.[33] The increased mortality seen in PH is more due to the nocturnal hypoxia than due to OSA with higher apnea-hypopnea index.[34]

The regular application of CPAP in patients with OSA-PH reduced PH and resistance in the pulmonary circuit in a period of 3–4 months. Bariatric surgery-induced significant weight loss may also lead to decrease in pH. The effects of other modes of treatment in OSA such as the use of oral devices, oral surgery, tracheostomy, and pharmacotherapy are unknown.[35]

OSA and Venous Thromboembolism (VTE)

There is a two- to three-fold higher incidence of VTE in OSA. That OSA could contribute independently to the occurrence of VTE which has been revealed in a review of 15 studies.[36] There is a hypercoagulable state as evidenced by detection of increased markers such as fibrinogen and plasminogen activator inhibitor-1 in OSA patients with VTE. The impact of use of CPAP in OSA on VTE is unknown.[37]

Conclusion

OSA is a potentially treatable risk factor for CVD. The inflammatory, autonomic, hemodynamic, and metabolic consequences of OSA have contributed to the pathogenesis and worsening of many CVDs such as coronary artery disease, CF, HTN, and various often fatal cardiac arrhythmias. The

appropriate and timely management of OSA decreases the incidence and prevalence of these cardiovascular disorders. Increased public awareness of OSA and its early detection, prompt diagnosis, and institution of appropriate treatment including CPAP lead to prompt control of this potentially modifiable risk factor in the era of increasing CVD.

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ℛeview ℐrticle

The Perplexing Problem of Resistant Hypertension – Evaluation and Treatment

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Abstract

Resistant hypertension (HT) is a vexing problem and accounts for approximately 10% of all cases of HT. According to European and American Heart Association/American College of Cardiology guidelines, it is defined as blood pressure (BP) above target levels despite optimal dosing of three antihypertensive medications of which one is a thiazide diuretic. The other two are most often a calcium channel blocker and an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. It is imperative to first rule out all causes of pseudoresistant HT such as inaccurate BP measurement, prominent white coat effect, poor medication compliance, and inadequate optimization of treatment. Contributing lifestyle factors and secondary causes of HT must also be looked for and corrected before labeling the patient as having resistant HT. Investigations should include basic tests to evaluate for end-organ damage and in selected cases tests to rule out the common secondary causes such as sleep disorders, primary hyperaldosteronism, chronic kidney disease, and renovascular HT. When treating such patients, the first step is to change from hydrochlorothiazide to chlorthalidone or indapamide which are more effective diuretics. If a fourth drug is to be added, the strategy of choice is to add a mineralocorticoid receptor antagonist such as spironolactone eplerenone or amiloride. Beta-blockers, alpha-blockers, centrally acting drugs such as clonidine, and vasodilators such as hydralazine are other medicines that can be used for very resistant cases. For patients with very stubborn HT, newer interventional modalities may be tried. Among these, the most investigated is renal (sympathetic) denervation by either ultrasound or radiofrequency ablation. Another newer target is carotid baroreceptor modulation. Although an exciting frontier in the treatment of resistant HT, their efficacy, safety, and exact role await further randomized studies.

Key words: Drug therapy mineralocorticoids, interventional treatment, pseudoresistant hypertension, resistant hypertension

Introduction

Hypertension (HT) is the leading risk factor for cardiovascular disease and ranks as a leading cause of disability worldwide.[1] In many patients, it remains poorly controlled and above the goal defined in various guidelines.[2] A smaller percentage of patients suffers from resistant HT, defined as the failure to reduce the systolic and/or diastolic blood pressure (BP) below 140 mmHg and 90 mmHg, respectively, despite the use of three or more anti-HT agents in optimal (best tolerated) doses. These must include an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a calcium channel blocker, and a thiazide/thiazide-type –diuretic.[3,4] As stated in

the guidelines, home or ambulatory BP measurements should be used to confirm inadequate BP control and one needs to exclude pseudoresistant HT and secondary HT to establish the diagnosis of resistant HT.[3,4] When using such a strict definition, the overall incidence of true resistant HT is about 10%.[3,4] However, as per the recent American College of Cardiology (ACC)/ Heart Association (AHA) guidelines published in 2017, Stage 1 HT is defined as a systolic BP between 130 and 139 mmHg and/or a diastolic BP between 80 and 89 mmHg.[5] As the AHA statement defines resistant HT as failure to achieve target BP, if one was to follow these guidelines rather the than the ESC-ESH guidelines, prevalence of resistant HT would be

bound to increase. Irrespective of the guidelines that one follows, resistant HT is associated with increased risk of cardiovascular morbidity and mortality, chronic kidney disease (CKD), and other HT -mediated target organ damage.[6] When treating such a patient, it is imperative that the physician approaches the problem in a systematic way to ensure adequate control of the BP. This should be carried out in four stages.

1. Rule out pseudoresistance and confirm BP measurements and adherence to treatment
2. Identify contributing lifestyle factors
3. Rule out secondary causes of HT
4. Optimize treatment measures including addition of medication in their optimal doses.

Pseudoresistance

The exclusion of pseudoresistance is paramount for diagnosing resistant HT accurately. Pseudoresistance is defined as persistently high uncontrolled BP at the clinic for reasons other than true resistance to drug treatment.[7] These could be due to numerous factors.

Erroneous BP measurement technique: This is a common cause and includes using a wrong size cuff, recording only a single reading, not baring the arm during measurement, or not having the patient in the proper position during the measurement.[3,4,7,8]

White coat effect

Studies indicate that white coat HT (where clinic BP measurements are persistently elevated while out-of-office readings are significantly lower) is as common in patients with resistant HT as it is in the more general hypertensive population.[9] In a large Spanish study involving over 12,000 patients, a third of the patients initially diagnosed as resistant HT, were reclassified as having white coat resistant HT when subjected to a 24 h ambulatory blood pressure test.[10] Thus, it is imperative to perform this test before labeling patients as having resistant HT.

Poor adherence to medications

Non-adherence to antihypertensive drug therapy is another common cause of lack of BP control,[3,4,7,11] with a prevalence of 31.2% in a pooled analysis of 24 studies in patients with treatment resistant HT was.[11] This prevalence varies depending on the mode of assessment and tends to increase with the longer the duration of treatment. During a 5–10 year follow-up, less than 40% of patients persist with their prescribed antihypertensive medication.[12] In a referral clinic setting, this phenomenon is less common, but it is still an important contributing factor to poor BP control in up to 16% of patients.[13] HT is a chronic disease often requiring the taking of multiple pills lifelong. Usually, more number of drugs prescribed less likely is the patient to adhere to those medications. Witnessing drug intake, though ideal, is not always possible and a variety of methods has been used to identify this problem such as patient interview and

diaries, pill counting, and examining prescription refill records.[7] Therapeutic drug monitoring, by repeatedly measuring serum or urine drug concentrations, has also been found to be a cost-effective way to ensure proper pill intake.[7]

Physician-related problems

Physician inertia is one of the important contributors to apparent drug-resistant HT.[14] It has been found that doctors are reluctant to maximize therapy by either switching medications or increasing the dose of drugs to reach target levels. There is a huge discrepancy between guideline recommendations and their implementation in everyday practice which results in suboptimum blood pressure control.[14] Another physician-related cause of resistant HT is the use of irrational drug combinations some of which do not even contain a diuretic in the prescription.[15] Bridging this gap between knowledge and implementation could go a long way in effectively treating HT.

Identify Modifiable Lifestyle Factors

Addressing contributing lifestyle factors are the second step in the approach to managing patients with resistant HT. These factors could be broadly classified into lifestyle factors, concomitant drug ingestion, and diagnosing secondary HT.

Lifestyle factors

Obesity
This is more commonly associated with severe and resistant HT and the need for multiple medications.[16] The pathophysiological mechanisms responsible are varied and include defective sodium excretion, in addition to increased activation of the sympathetic and the renin-angiotensin-aldosterone axis (RAAS).[17]

Physical inactivity
Reduced physical activity and a sedentary lifestyle are important independent risk factors for HT, however, there is a lack of clinical studies linking physical inactivity to resistant HT.[4] Indirect evidence that activity plays a role comes from a study which demonstrated that a regular exercise program resulted in significant lowering of ambulatory BP readings in patients with RH.[18]

Dietary salt
Apart from directly contributing to high BP, increased dietary salt is also responsible for blunting the BP lowering action of antihypertensive mediation.[19] This is more important in the salt sensitive populations such as the elderly, African-Americans, and those with CKD. Although increased salt intake is widespread, it has been especially identified in patients with resistant HT.[4,20]

Alcohol intake
Increased alcohol ingestion (>30–50 g/day) has been recognized as an important risk factor for HT across many populations.[3,4,7,21]

Poor adherence to drug therapy is another reason why BP control is more difficult to achieve in heavy drinkers.

Treatable/Secondary HT

Drug-induced HT

Despite its frequent occurrence, primary care physicians often miss the diagnosis and hence a rare opportunity to treat this iatrogenic form of HT.[22] A variety of prescriptions and over-the-counter medications may induce HT [Table 1] or contribute to treatment resistance, and therefore, a detailed history of concomitant drug ingestion is important. The mechanisms whereby these drugs increase the BP are multiple.[22]

Other causes of secondary HT

Before labeling a patient as having resistant HT, it is imperative to rule out the treatable causes of secondary HT. These are seen in about 5–10% of patients with HT.[7] Secondary HT is to be suspected when HT is first encountered at extremes of age, or is resistant, or presents as accelerated or malignant HT, when there is a disproportionate target organ damage for the degree of HT, or unprovoked or excessive hypokalemia.[23] A list of the possible causes is enumerated in Table 2, but among these, the most common are primary aldosteronism (PA), obstructive sleep apnea (OSA), CKD, and renovascular causes.[22,23] The diagnostic work-up for secondary HT is exhaustive and beyond the purview of this paper but some important tests that need to be carried out in suspected cases are listed in Table 3. Particular attention should be paid to a detailed history and physical examination, especially with regard to a history of snoring, daytime sleepiness and neck thickness, presence of abdominal bruits and peripheral pulses to rule out renal artery stenosis, aortic coarctation, and aortoarteritis. Assessment of end-organ damage, hypokalemia, active urinary sediment,

Table 1: Drugs responsible for increase in blood pressure

Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors

Oral contraceptives

Sympathomimetics

Illegal drugs such as cocaine, amphetamines, ecstasy (MDMA and other derivatives)

Glucocorticoids

Mineralocorticoids

Immunosuppressants – cyclosporine, tacrolimus

Erythropoietin

Supplements – containing ginseng, licorice, yohimbine

Antidepressants – venlafaxine, bupropion, desipramine

VEGF inhibitors

Cancer drugs such as bevacizumab

COX-2: Cyclooxygenase 2, MDMA: 3,4-methylene-methamphetamine, VEGF: Vascular endothelial growth factor

blood chemistry, and kidney size on ultrasound to rule CKD is important as is tests to rule out the endocrine causes HT if clinically suspected.[7,23]

OSA

This is another risk factor that has been documented to be associated with resistant HT.[3,4,7,24] The pathophysiological basis includes intermittent hypoxia, sympathetic stimulation, and intrathoracic pressure swings all of which lead to fluid overload, aldosterone excess, and resultant HT.[24] Diagnosis is established with the help of a questionnaire (STOP-Bang, Berlin, Epworth Sleepiness Scale), measurement of neck circumference (>40 cm), and performance of a sleep study.[7] Continuous positive airways

Table 2: Causes of secondary HT

Drug induced

Renal
    Renovascular
    Renal parenchymal

Neurological
    Increased intracranial pressure
    Dysautonomia
    Lead poisoning, porphyria
    OSA
    Guillain-Barre syndrome

Endocrine
    Primary hyperaldosteronism
    Pheochromocytoma

Cushing's disease
    Thyroid disorders
    Acromegaly

Aortic disease

Coarctation of aorta

Aortoarteritis

HT: Hypertension, OSA: Obstructive sleep apnea

Table 3: Basic testing in a patient with resistant HT

Ambulatory BP monitoring

12-lead electrocardiogram/chest X-ray

Transthoracic echocardiogram

CBC and blood chemistry (including urea, creatinine, electrolytes)

Urine analysis (proteins, erythrocytes, leukocytes)

Plasma aldosterone concentration and renin

Free plasma metanephrine/normetanephrine

Thyroid-stimulating hormone

Renal ultrasound

Renal artery Doppler

CBC: Complete blood count, HT: Hypertension

pressure although mildly useful in hypertensive patients is strongly recommended in those with resistant hypertension (RHT) and at least moderate OSA.[7] A recent study, however, brought into question the effectiveness of this therapy.[25]

Primary hyperaldosteronism

This is now considered as one of the most common causes of secondary HT accounting at least for 20% of all cases of resistant HT.[7] In a recent large study from Greece involving 1616 patient with true resistant HT, high aldosterone/renin ratios were detected in 21% of cases.[26] Of these, only about half had true PA as confirmed by salt suppression test or response to spironolactone. It usually occurs between the ages of 30 and 60 years and only about 40% have hypokalemia.[27] Diagnosis is established by measuring the plasma aldosterone renin ratio, currently considered the most sensitive marker for diagnosing this disease. The result is affected by prior drug ingestion, age, and the method of collection.[7,27] A low ratio of morning plasma aldosterone in ng/dl to plasma renin activity in ng/ml/h (normal level between 20 and 40) is a test with a high negative predictive value.[7]

CKD

The relationship between CKD and HT is bidirectional. More than 75% of patients with CKD have HT and the prevalence of resistant HT in CKD patient is more than 50%.[28] The cause of resistance is multifactorial, the most important factor being salt and water retention. In addition, there is activation of the sympathetic and the RAAS and renal ischemia due to structural and functional alterations in the kidney vasculature.[22,23] Another important contributory factor to HT seen in these patients is the restriction in the use of diuretics and the fact that when the glomerular filtration rate (GFR) is <40 ml/min; thiazide diuretics are ineffective.[22]

Renovascular HT

This is predominantly atherosclerotic in origin and is common in older patients, with diabetes and evidence of atherosclerosis in other vascular beds.[7] In younger females (10% of this population), fibromuscular dysplasia is the etiological factor. In India, it is not uncommon to see renal artery stenosis due to aortoarteritis. Non-invasive diagnosis of this condition is tricky and remains an unfulfilled challenge for primary care physicians.[4,22]

Management of Resistant HT

Management of resistant HT requires a multipronged approach. Before labeling the patient as having true resistant HT, we need to rule out pseudoresistant HT by correctly measuring the BP and corroborating the readings with a 24 h ambulatory BP record. Next, one should pay careful attention and address and all modifiable factors alluded to above.

Maximize adherence

Simplification of the patient's prescription so that the number of pills he has to take decreases helps improves patient compliance. This is most easily done by prescribing long-acting formulations and also using combination medications where possible. Educating and counseling patients on the importance of adhering to their medication are also extremely important. A multidisciplinary approach using nurses, pharmacists, and nutritionists can improve the results of treatment care but is not always possible due to financial or other logistical considerations. Liberal use of home monitoring readings also helps to ensure compliance.[7,29]

Non-pharmacological methods

Weight loss: This should be encouraged in all patients, especially those who are obese and overweight. It has been shown that a 10 kg loss in weight is associated with a 6.0 mmHg decrease in systolic and a 4.6 mmHg decrease in diastolic pressures in patients with HT.[30] Although not studied in patients with resistant HT, it is logical to conclude that this intervention would benefit patients with resistant HT and also help decrease the overall cardiovascular risk of the patient.

Dietary advice and salt restriction

A reduced salt intake is well proven to decrease BP. A recent meta-analysis showed that a 1.0 g (43.5 mmol) reduction in daily sodium intake produces a 2.1 and 1.2 mmHg decrease in systolic BP in hypertensive and normotensive patients, respectively.[4] Although this has not been studied specifically in resistant HT, it is not unreasonable to advise salt restriction in this subgroup of patients. This would be especially in those with a high salt intake and those whose BP is salt sensitive such as elderly and African-American patients. It is advised that all patients with resistant HT should decrease the sodium intake to <100 mmol/24 h (2.3 g/day)[4] and to <65 mmol/day (1.5 g/day) in some recalcitrant cases. This requires a detailed history of the diet of the patient to allow adjustments so as to achieve this target. In accordance with the DASH diet, high intake of vegetables, fruit, nuts, and low-fat dairy products with a decreased consumption of saturated fats is effective in further reducing the BP.[4]

Other lifestyle measures

Smoking cessation is a must as is curbing excessive caffeine use. Curtailing the alcohol intake to not more than 2 drinks per day in males and one drink in females or lighter weight people helps control BP better.[3-5] It is advisable that patients with resistant HT perform some aerobic exercise of at least 30 min duration on most days of the week.[4,7] This has been proven to decrease BP in all patients with HT including those with resistant HT. In addition, meditation and yoga techniques have been proven to improve the overall well-being of the patient and aid control of the BP.[4] All these adjustments in lifestyle, if properly adhered to, could go a long way in managing these patients without resorting

to increased medication or other new invasive modalities of treatment.

Treatment of the secondary causes of HT

If an endocrine cause of HT such as PA, pheochromocytoma, or Cushing's disease is diagnosed, these patients should be referred to a specialist for effective treatment of that particular disease. If ingestion of drugs known to be responsible for BP is identified, the treating physician should ideally stop them altogether or lower their dosage or find a suitable alternative.

Treatment of OSA

The greatest benefit is seen in those patients with severe OSA who are already on medication for HT. Although it is strongly recommended in those with RHT and at least moderate OSA,[4,7] data regarding its use in resistant HT are sparse. More recently, the efficacy of this has brought into question the effectiveness of this therapy.[25]

Treatment of Renal artery stenosis

Intervention in the form of balloon angioplasty and stenting is almost always curative in those with fibromuscular dysplasia and is strongly recommend in this subset of patients. Restenosis rates can approach 20% at the end of 1 year.[7] In those with a stenosis due to atherosclerosis, results of clinical studies surprisingly show no great benefit and may be even harmful.[31,32] The overall consensus thus is that in this subgroup of patients, intervention is reserved for those with truly resistant HT and those with a demonstrated decline in renal function.[3,4,7]

Pharmacological Treatment of Resistant HT

Patients with resistant HT are by definition on at least three antihypertensive agents. Common sense dictates that the drugs should preferably act by different mechanism and possibly have a synergistic action. The most widely used drug combination is of an ACEI or ARB with a calcium channel blocker (preferably of the dihydropyridine type) and a thiazide diuretic.[3,4,7] When deciding which drug to use, the clinical profile of the patient plays an important role.[3,5,29] For example, a patient with ischemic heart disease would benefit by addition of a beta-blocker while patients of African origin may not respond to RAS blockers. Before adding another drug to the therapeutic regimen of patients with resistant HT is to make sure, the patient is on a maximum dose of the three primary drugs. It must be remembered that the dose of diuretic is GFR dependent and often the dose of diuretic used is subtherapeutic which needs to be first addressed.[4] The next step is to change from hydrochlorothiazide to chlorthalidone or indapamide as these appear to be more effective antihypertensive agents.[3,4,7,33,34] A dose of 25 mg of chlorthalidone is equivalent to 50 mg of hydrochlorothiazide. If the GFR is <30–40 ml/min, then addition of a loop diuretic in single or multiple doses may help.

Which Fourth Line Drug?

It is now realized that activation of the RAAS and consequent fluid retention is the important pathogenetic mechanism of resistant HT.[3,4,7] It, therefore, stands to reason that if a fourth drug is required, a mineralocorticoid receptor antagonist spironolactone or eplerenone would be the drug of choice.[3-5,7] This has now been incorporated in all recent guidelines.[3,4,5] The PATHWAY 2 trial clearly demonstrated the effectiveness and also superiority of such a strategy over using other antihypertensive drugs such as a beta-blockers and alpha receptor blockers (bisoprolol and doxazosin, respectively, which were used in this trial).[35] In this study, which was a double-blind four-way crossover trial, spironolactone in a dose of 25–50 mg was compared to bisoprolol (5–10 mg), doxazosin (5–10 mg) or placebo.[35] Spironolactone was found to be superior to all the other strategies with a mean reduction of mean BP by 8.78 mmHg with spironolactone versus 4.48 mm Hg with bisoprolol and 4.03 mmHg with doxazosin. Importantly, the percentage of patients achieving BP control was 60%, 43.3%, and 41.5% with spironolactone, bisoprolol, and doxazosin, respectively.[35] Important clinical data were also gleaned from three substudies conducted in these patients.[36] The first was that spironolactone was most effective in patients with low renin levels. Second, with this treatment, the thoracic fluid content decreased significantly by 6.6% highlighting the importance of fluid retention in the etiopathogenesis of resistant HT. Finally, in one substudy, amiloride was used instead of spironolactone with equally effective if not better results.[36] As a result of these findings, the European guidelines propose the use of amiloride in those in whom spironolactone is either not tolerated or is contraindicated.[3] Use of the newer agents such as eplerenone can also be used but because of a shorter half-life usually requires a twice daily dosage.[4]

Other second-line drugs

These are only used if diuretics or mineralocorticoids cannot be administered and are usually not as effective as spironolactone. Alpha-blockers are vasodilators with an added benefit in patients with benign prostatic hyperplasia. If beta-blockers are to be used, those with additional alpha blocking properties such as carvedilol or labetalol may be preferred.[7] Bisoprolol and doxazosin were both found to be effective in the PATHWAY 2 trial.[35] Direct vasodilators such as hydralazine and centrally acting drugs such as clonidine and moxonidine have been used but there are problems of patient adherence due to multiple dosing required with these drugs and also side effects such as fluid retention and symptomatic hypotension.[7] To assess their efficacy, the resistant HT optimal treatment study compared the impact of clonidine and spironolactone in 187 patients with resistant HT.[37] The BP control as assessed in the office and with 24 h BP recordings was similar, however, the magnitude of 24 h reduction and also the reduction in daytime diastolic readings was more with spironolactone.[37] Many newer drugs such as endothelin receptor blocker (darusentan), aldosterone synthase inhibitors, canrenone, and neprilysin inhibitors are being developed for the

treatment of HT, however, there are little data regarding their use in patients with resistant HT.[7]

Interventional treatment of resistant HT

Due to inadequate BP control even after optimal drug treatment, there have been new developments in technology resulting in a number of interventional procedures under review for the treatment of resistant HT.[38] These include renal nerve ablation (RNA), carotid baroreceptor stimulation, central arteriovenous anastomosis, carotid bulb restoration, and aortic stimulation.

RNA

Catheter-based renal denervation acts by modulating the efferent sympathetic signals to the kidney that leads to reduced renal flow, RAAS activation, and fluid retention. It also decreases the afferent signals to the brain which are responsible for sympathetic action on the heart, vascular bed, and neurohumoral loops.[38] Initial studies (SYMPLICITY 1 AND 2) demonstrated significant reductions in BP and generated huge interest in this modality in the treatment of HT.[38] However, the SYMPLICITY 3 prospective, randomized trial comparing this procedure to sham studies did not reveal any significant difference in BP outcome between the two groups.[39] The study suffered from several pitfalls, but the lack of complete denervation involving a four quadrant interruption of the sympathetic nerve fibers was considered the main factor responsible for the negative outcome of this study.[40] To overcome these shortfalls, three new studies were carried out to retest this hypothesis. One of these studies, using a special designed spiral multielectrode catheter (SPYRAL HTN ON study), recruited patients whose BP was not controlled by one to three medications.[41] When compared to a sham procedure, RNA was associated with a greater improvement in office and ambulatory BP recorded readings. There was no documented damage to the renal artery or deterioration in renal function. Another recent study compared two different methods of carrying out RNA – namely, ultrasound ablation versus the radiofrequency method.[42] The former was associated with a greater decrease in BP as compared to the radiofrequency group. However, many questions continue to remain unanswered. Which modality is best (radiofrequency or ultrasound ablation), whether one needs to perform only the main artery RNA or to access all side branches and accessory arteries, which patients are likely to benefit the most. Till such time that these issues are not addressed, RNA will not become part of the mainstream treatment of resistant HT.

Iliac vein and artery anastomosis

This is performed by placement of an arteriovenous coupler. The ROX CONTROL HTN study compared this procedure versus pharmacological treatment and it was found to be associated with a better control of both systolic and diastolic BP and the benefit persisted up to 1 year post-procedure.[43] However, the procedure suffered from a serious adverse effect in the form of iliac vein stenosis requiring stenting in up to 33% of patients.[43] This procedure has, therefore, been abandoned.

Carotid baroreceptor activation therapy

Stimulation of the carotid baroreceptors results in a sympatholytic response which results in lower BP due to a decreased heart rate and peripheral vasodilatation. The first device was studied in the RHEOS study in patients with resistant HT.[44] Although it resulted in a significant amelioration in blood pressure lasting for up to 1 year, it was associated with a significant procedure related facial nerve injury.[38] The newer device (the Barostim Neo) from the same company is much smaller and has shown good long-term effects both in resistant HT and heart failure.[45] This modality has become approved in Europe for the treatment of resistant HT, but in the US, it is only approved for the treatment of heart failure.[38,45] However, it is more invasive than RNA and the safety of the procedure has not been well established to be included in the mainstream therapies for resistant HT.[38] The MobiusHD carotid bulb expansion device which acts by stretching the carotid artery at the bulb, thereby reducing the BP, is a newer device used to treat HT.[38] Two trials are underway for exploring its use in difficult-to-treat HT and the results are eagerly awaited.

Conclusion

During the past several years, newer data have emerged regarding various therapeutic options available to treat resistant HT. Before resorting to these, it is imperative for the treating physician to rule out pseudo-HT and identify and implement lifestyle modifications that will bring down the BP. It is also important to clinically assess and evaluate thoroughly for secondary causes of HT. If a fourth drug is to be added, studies show that a mineralocorticoid inhibitor such as aldosterone is the most effective and the drug of choice. For those who are intolerant to or develop side effects with spironolactone, eplerenone or amiloride are reasonable alternatives with a similar mode of action. Beta-blocker, alpha-blockers, centrally acting drugs, direct vasodilators, and some of the newer drugs are usually tried in only the very resistant cases. Several interventional and device-based modalities have been developed and are being investigated and recent studies have renewed interest in RNA in therapy of resistant HT. Carotid receptor stimulation and modulation are another emerging therapy which needs long-term studies to assess effectiveness and also address safety aspects. With all this armamentarium available to the treating physicians, the future outlook of patients with resistant HT appears to be bright.

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$\mathcal{R}$eview $\mathcal{A}$rticle

Managing Hypertension in Coronary Artery Disease

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Abstract

Hypertension remains the strongest risk factor for development of coronary artery disease (CAD) and often both these conditions co-exist. Genetic and environmental factors interact to determine whether an individual may develop hypertension and related CAD. Blood pressure lowering itself reduces cardiovascular disease (CVD) risk in patients with hypertension ,however a residual cardiovascular risk persists and necessitates better evaluation and treatment of these individuals. For primary prevention of CAD, the key factor is lowering of blood pressure rather than the choice of the drug, whereas for secondary prevention there is merit in choosing the appropriate agent. From a practical standpoint, an office BP of <130/80 is the target for most patients, if well tolerated (except for people above age 65 years, for whom the 2018 ESC/ESH guidelines recommend a target of <140/80). Care needs to be taken to keep DBP above 70 mm in some patients. Certain drugs should be avoided in CAD with heart failure and in CAD without HF. While statins are recommended for secondary prevention of CVD in all hypertensives, they are recommended in those at moderate to high risk for primary prevention. Aspirin is indicated in all patients for secondary prevention, but has restricted recommendation for primary prevention.

Key words: Hypertension, Coronary artery disease, blood pressure targets, primary and secondary prevention

Introduction

Hypertension is one of the most important risk factors for coronary artery disease (CAD) which, in turn, is commonly its first presenting complication. The present review will address the following key questions:

1. What are the epidemiological relationships between hypertension and CAD?
2. What are the pathophysiologic mechanisms underlying the risk of CAD due to hypertension?
3. How effective is blood pressure (BP) treatment for reducing the risk of CAD?
4. Does the benefit of treatment accrue only from BP lowering effect or also from some additional uniquely protective actions of specific classes of drugs?
5. Why is there a residual risk of cardiovascular disease (CVD) and CAD despite optimal treatment of hypertension?
6. What are the systolic BP (SBP) and diastolic BP (DBP) targets that are appropriate in patients

    (i)   With established CAD?
    (ii)   Without established CAD?
7. How low should you go? Is there a J curve?
8. Which are the antihypertensive drugs that have shown particular efficacy (and should be used) in the secondary prevention of acute and chronic (stable) coronary syndromes and heart failure (HF) caused by CAD?
9. Which BP lowering drugs are inadvisable in patients with CAD?
10. Should all hypertensive people be on a statin? On aspirin?

Epidemiological Relationships with CAD

The INTERHEART study[1] showed that hypertension accounted for about ~25% of the population attributable risk of myocardial infarction. In another registry-based study[2] of over 1 million patients, angina and myocardial infarction were the cause of almost half (43%) the CVD free years of life lost over 5 years, from the age of 30 years, due to hypertension.

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A meta-analysis of 61 studies involving almost 1 million adults[3] showed that BP ranging from 115/75 to 185/115 for all ages was associated with fatal CAD such that the risk of a fatal coronary event doubled with each increase in SBP of 20 mmHg or in DBP of 10 mmHg. Although systolic hypertension (especially after age 50 years) and combined systolic diastolic hypertension (especially in the young) are associated with heightened CVD risk, there is a divergence of opinion with regard to the risk posed by isolated diastolic hypertension.[4,5]

Hypertension is associated with greater number of cardiovascular (CV) risk factors than normotension and these risk factors multiply the risk associated with hypertension. One or more coexistent risk factors are found in more than 80% of hypertensives and two or more in 55% of them.

Besides the concomitant presence of classical risk factors, some factors that have been found to be predictive of heightened chances of CAD and CVD in hypertensive people are as follows:

Coronary artery calcium (CAC) score,[6] biomarkers such as NT pro-BNP and troponins,[7] morning home BP,[8] serum uric acid,[9] inter-arm difference in BP,[10] exaggerated (>180) SBP rise on a treadmill test,[11] and early age of onset of hypertension.

Pathophysiologic Mechanisms Underlying the CAD Risk of Hypertension

There is an interplay of genetic and environmental factors through neurohormonal pathways (sympathetic nervous system, renin–angiotensin–aldosterone system activity, insulin resistance, vasodilators and vasoconstrictors, growth factors, and inflammatory cytokines), hemodynamic effects, structural and functional abnormalities in the arterial system, endothelial dysfunction, inflammation and oxidative stress to determine the risk of development of hypertension, and consequent CAD.

When the left ventricular hypertrophy (LVH) occurs in addition, it reduces coronary flow reserve, increases metabolic demands of the myocardium, and favors the development of ventricular arrhythmias. Diastolic dysfunction reduces the perfusion of the myocardium.

Antihypertensive Rx for Primary Prevention of CAD: How Effective?

Randomized trials[12] have shown reductions in CV risk that BP lowering brings about in hypertensive people.

In a meta-analysis of 123 studies with 613 815 participants, CAD was reduced by 17%,[13] stroke by 27%, HF by 28%, and all-cause mortality by 13% for every 10 mmHg reduction in SBP. Others[14] have shown a similar risk reduction with more intensive BP control.

The above-mentioned meta-analysis also showed that for prevention of major CVD events, stroke, and renal failure, β-blockers were inferior to other drugs. Calcium channel blockers were better for the prevention of stroke and diuretics for the prevention of HF, for which calcium channel blockers were inferior to other drug classes.

A beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on CVD outcomes in individuals with established CVD or at high risk for its development has been shown in hypertensives and non-hypertensives in studies such as heart outcomes prevention evaluation, survival and ventricular enlargement, and European Trial on Reduction of Cardiac Events With Perindopril in Stable CAD.

ACCORD and SPRINT (see below) are recent trials that have shown the efficacy of hypertension treatment for primary prevention of CVD in patients with mean basal SBP of 139 mmHg.

Does the Benefit of Treatment Accrue Only from BP Lowering Effect or also From Some Additional Uniquely Protective Actions of Specific Classes of Drugs?

As per meta-analyses of most antihypertensive trials, BP lowering appears to be more important than a particular drug class for primary prevention of CAD.

On the other hand, for secondary prevention in individuals with underlying comorbid illnesses such as IHD, CKD, or recurrent stroke, different drug classes have shown differing levels of benefit [Table 1].

Why is There a Residual Risk in Treated Hypertensives?

Even after the office BP is controlled, a hypertensive patient under treatment has a substantial residual risk of any CV event. Indeed, there is up to 50% increased risk[15,16] in treated hypertensives as compared to untreated normotensives, which is why risk scores include "treatment for hypertension" as one of the risk factors in the equations. More specifically, the increase in risk was 46% for coronary disease, 75% for stroke, and 62% for CV death.

The reason for this increased risk could be multifold:

Higher underlying subclinical CVD burden in treated hypertensives

Indeed, as shown by Nadir et al.,[17] 34% of optimally treated hypertensives have silent, underlying cardiac abnormalities out of which LVH was the most prevalent (29%), followed by LV diastolic dysfunction (LVDD; 21%), left atrial enlargement (LAE; 15%), LV systolic dysfunction (LVSD; 6%), and silent myocardial ischemia (SMI; 6%) as assessed by resting and dobutamine 2 D echocardiography.

About 13% of all treated hypertensives have ≥3 silent cardiac abnormalities. Out of those with cardiac abnormalities, 1 abnormality was seen in 29%, 2 in another 31%, 3 in another 29%, and ≥4 in 10% of patients.

It has been suggested by them[17] that combined screening of treated hypertensives with BNP and hs TnT with cutoff values at 15 pg/mL and 5·9 ng/L, respectively, had a sensitivity and specificity of 87% and 65% for diagnosing underlying disease

Table 1: Antihypertensive drugs that have shown particular efficacy (and should be used) in the secondary prevention of CAD and its subsets

Hypertension with →	Stable CAD	ACS including unstable angina, NSTEMI, and STEMI	HFrEF with CAD	HFpEF with CAD
First-line therapy	GDMT BB*, ACE/ARB, (Non DHP CCB if BB contraindicated in normal LV fn.)	BB**, NTG, ACEI/ARB, (Non DHP CCB if BB contraindicated in normal LV fn.)	GDMT BB***, ACE/ARB/ARNI, AA, thiazide-type diuretics for HT, loop diuretics for volume control	Thiazide-type diuretics for HT, loop diuretics for careful volume control
Add-on therapy	LA DHP CCB for angina and HT Thiazides, AA, for HT	LA DHP CCB for residual angina and HT, thiazide-type diuretics for HT, loop diuretics for volume control, AA after STEMI in patients with LV dysfn. with LVF or diabetes	Hydralazine plus isosorbide dinitrate in Africans and those resistant or contraindicated to RAAS blockers	ACEI/ARB, BB, DHP CCB, (Non-DHP CCB if BB contraindicated, without concomitant DHB CCB)

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, AA: Aldosterone antagonist, ARNI: Angiotensin receptor-neprilysin inhibitor, BB: Beta-blocker, LA: Long acting, NTG: Nitroglycerine (intravenous), DHP: Dihydropyridine, CCB: Calcium channel blocker, ACS: Acute coronary syndrome, HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HT: Hypertension. *GDMT BB guideline-directed management and therapy of stable IHD with beta-blockers (carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol), **A short-acting β1-selective beta-blocker without intrinsic sympathomimetic activity (metoprolol tartrate) or bisoprolol should be initiated orally within 24 h of presentation, provided that there is no contraindication. ***Guideline-directed management and therapy of HFrEF with beta-blockers (carvedilol, metoprolol succinate, or bisoprolol)

burden listed above. Thus, initial screening of hypertensives with these two biomarkers, followed by further testing of individuals with abnormal biomarker values to find specific cardiovascular abnormality and tailoring the treatment toward the same, may help to further reduce the risk.

This idea matches well with the findings of Pandey *et al.*[7] alluded to earlier that a biomarker-led based approach to CV risk assessment may help identify individuals with elevated BP or Stage 1 hypertension who may benefit from BP –lowering therapy but who are otherwise at low risk based on pooled cohort equation and would not have been recommended antihypertensive medication according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guideline.

Indeed, in the study, approximately one-third of adults with elevated BP or Stage 1 hypertension had elevated high-sensitivity cardiac troponin T or NT-pro-BNP (N-terminal pro-B-type natriuretic peptide), putting them at more than 10% risk of atherosclerotic CVD (ASCVD) or HF over the 10-year follow-up period. Antihypertensive medication would not have been recommended to these patients according to the 2017 ACC/AHA BP guideline.

Another way to redefine risk for the sake of taking treatment decisions is by measuring CAC score. Although as per the new ACC/AHA guidelines, ASCVD risk score of 10% is the cutoff value to guide antihypertensive treatment, it has been shown in a recent analysis[6] that CAC can recategorize risk around this threshold; within the low-risk group defined by ASCVD risk score <10%, CAC >100 identified individuals with higher risk of CVD and CHD death compared with those in the higher risk group (ASCVD ≥10%) who had lower CAC scores.

Reliance on office BP alone for optimal BP control

Conditions such as masked hypertension, nocturnal hypertension, reduced or reversed nocturnal dip, morning surge, and BP variability are all significant predictors of risk

which may be missed if only office BP is relied on for optimal BP control.[18-21] Indeed, non-dippers (night-time fall in BP <10%) have been reported to have a CV risk, which is significantly higher than normal dippers.[22]

Presence of other risk factors

Elevated BP seldom occurs without concomitant presence of other CVD risk factors. As said earlier, their combined risk is multiplicative rather than additive and may be one reason why even treated hypertensives remain at higher risk.

BP Targets

There is an apparent difference between the BP targets suggested by the two major guidelines across the Atlantic.[23,24]

For example, the 2017 ACC/AHA guidelines mention an office BP of <130/80 as the target for all patients, whereas according to 2018 ESC/ESH guidelines, the numbers are <140/90.

However, as said, the difference is more apparent than real. This is because (i) ESC/ESH recommends that the first step in management should be to reduce BP below 140/90 in all patients and, if the treatment is well tolerated, treated BP targets should be 130/80 mmHg or lower in most patients (except people above age 65 in whom the target is <140/80) and (ii) the strategy for managing people in the zone between 130/80 and 140/90 is the same in both guidelines, namely, non-pharmacological therapy for 3 and 6 months in low-risk people (at a 10-year ASCVD risk of <10%), and pharmacological therapy along with lifestyle changes with a goal of reaching 130/80 and below for people at higher risk or with CVD or target organ damage. Risk may be redefined as mentioned earlier by selective application of additional tests like biomarkers.

This BP goal of <130/80 has been arrived on the basis of two large recent trials, namely, SPRINT (A Randomized Trial of Intensive Versus Standard Blood-Pressure Control)[25] and

ACCORD (Action to Control CV Risk in Diabetes),[26] and a recent meta-analysis[27] of 42 trials and 44,220 patients which showed a linear relationship between mean achieved SBP and risk of CVD mortality, the lowest risk being at SBP of 120 and 124 mmHg.

Since the method of BP measurement in SPRINT and ACCORD studies was more stringent (Automated Office BP Measurement unattended in SPRINT and attended in ACCORD) than what is done in clinical practice, the SBP target recommended by guidelines (<130 mmHg) is set at somewhat higher level than that which was found to be beneficial in these studies (~ 120 mmHg in SPRINT for all end points and in ACCORD for stroke).

How Low Can You Go While Reducing BP? Is There a J Curve?

In hypertensive patients with CAD – the relationship between BP and CV events is J shaped, especially for DBP, with an increased risk of CV events (except stroke) among patients with DBP <70 mmHg as per *post hoc* analyses of randomized controlled trials[28,29] and observational studies.[30,31]

This could be especially relevant for secondary prevention of CAD, as coronary perfusion occurs in diastole which could be impaired with very low DBP worsening myocardial ischemia and causing events.

On the other hand, two recent randomized controlled trials showed no harm,[26] or a reduced harm[25] in the lowest BP groups up to a DBP of 60 mmHg, although the hazard ratios for CVD including IHD were 1.68 (1.16–2.43, $P = 0.006$) in patients without and 1.52 (0.99–2.34, $P = 0.06$) in patients with prior CVD,, respectively,[32] for diastolic pressure <55 mmHg versus 55–90 mmHg.

However, two factors can confound the relation between low DBP and CV outcomes.

1. The problem of reverse causality whereby low DBP would be a result of underlying poor health, rather than its cause, with the underlying physical condition itself leading to increased morbidity and mortality. Although dedicated randomized interventional trials will be required to disprove this, at least one study showed increased risk with lower (<70 mmHg) and higher (≥80 mmHg) DBP risk for the primary outcome, myocardial infarction, stroke, HF hospitalization, and all-cause mortality, which persisted after several sensitivity analyses ruled out the possibility of "reverse causality."[33]
2. Whether low DBP has an effect independent of the confounding impact of associated wide pulse pressure (PP) is not known. The CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable CAD)[34] followed up 22,672 hypertensive patients with CAD for a median of 5.0 years, and the relationship between PP and DBP, alone or combined, and the primary composite outcome (CV death or myocardial infarction) was analyzed using multivariable Cox proportional hazards models.

It was found that the J-shaped relationship between DBP (with increasing risk below and above 70 and 80 mmHg DBP, respectively) and CV events in hypertensive patients with CAD persisted in patients who were in the lowest risk PP range and is therefore unlikely to be solely the result of an increased PP associated with advanced vascular disease.

The Framingham Heart Study[35] found that DBP below 70 mmHg was linked with increased events, but the risk was greater among those with combined low DBP and wide PP.

What about the Impact of Low SBP on the J Curve of DBP?

In the INternational VErapamil-Trandolapril Study, Wokhlu *et al.*[36] categorized 17,131 hypertensive patients from the US cohort, aged at least 50 years with CAD, by tertiles of mean achieved SBP (<120, 120–<130, 130–<140, and ≥140 mmHg) and DBP (low, middle, and high per SBP category) during mean follow-up of 11.6 years.

DBP <70 mmHg was associated with excess mortality in older patients with CAD when SBP was <120 mmHg, but not when SBP ≥120–<140 mmHg. These findings point to an increased risk of lowering DBP when SBP is <120 mmHg.

Thus, BP targets should not be below 120 mmHg systolic or below 70 diastolic, especially in non-revascularized CAD patients (as some studies show lack of harm in revascularized CAD patients), the elderly, those with wide PP and those with SBP <120 mmHg.

1. Tailored treatment for secondary prevention of CAD and its subsets
   The antihypertensive drugs that are known to be effective (and should be used) in the secondary prevention of CAD and its subsets are shown in Table 1:[23,24,37]
2. Hypertensive drugs to be avoided in patients with CAD
   These are delineated in Table 2.
3. Should all hypertensives be advised a statin? An aspirin?

Primary prevention of hypertensives with statins

There is undisputable evidence showing benefit of statins in hypertensive patients who are at moderate to high CV risk.[38]

Primary prevention of hypertensives with aspirin

The authors of a Cochrane systematic review[39] which included four randomized trials with a combined total of 44,012 patients concluded that overall, for primary prevention of hypertensive people, aspirin did not reduce stroke or CV events compared with placebo.

Hence, aspirin is not recommended for primary prevention in hypertensive patients without CVD by the 2016 European Society of Cardiology guidelines.[40]

Three recent trials and a meta-analysis[41-44] have shown that aspirin for primary prevention reduces non-fatal ischemic events in some people (at high 10-year CVD risk and below 70 years age), but is counter balanced by significant increase in serious non-fatal bleeding events (gastrointestinal and intracranial), with no difference in mortality or cancer.

Table 2: Hypertensive drugs to be avoided in patients with CAD

CAD with HFrEF	CAD without HF (SCAD or ACS)
Non-DHP CCB (such as verapamil or diltiazem)	Hydralazine (may provoke angina).
Clonidine	Short acting nifedipine (except in prinzmetal or vasospastic angina)
Moxonidine	
Hydralazine alone without a nitrate	
a-Adrenergic blockers such as doxazosin (to be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses)	

HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, SCAD: Stable coronary artery disease, DHP: Dihydropyridine, CCB: Calcium channel blocker

Hence, low-dose aspirin (75–100 mg orally daily) may be considered only among adults 40–70 years of age who are at higher risk of CVD but not at increased risk of bleeding by shared decision-making after a risk/benefit discussion as per the 2019 ACC/AHA guidelines[45] on the primary prevention of CVD. However, low-dose aspirin is not recommended on a routine basis for primary prevention of CVD among adults over 70 years of age or among adults of any age who are at increased risk of bleeding.

Thus, low-dose aspirin may be advisable for primary prevention in hypertensives below 70 years age for preventing non-fatal ischemic events only if their bleeding risk is low, BP is well controlled and ischemic risk is high.

Secondary prevention of hypertensives with statins

The presence of CVD places the patient at high or very high risk in which case statins show immense benefit and hence should be administered to target LDL-C levels below 70 mg/dL or 50 mg/dl or to below 50% of the baseline.

Secondary prevention of hypertensives with aspirin

For secondary prevention, the use of aspirin has shown greater benefit than harm in all clinical forms of IHD in hypertensives and is recommended. In patients who are unable to take aspirin and in those with a history of gastrointestinal bleeding, clopidogrel is a reasonable alternative.

A P2Y12 inhibitor is recommended to be added in patients with ACS or who undergo PCI.

With regard to CABG, as per the 2017 EACTS guidelines on perioperative medication in adult cardiac surgery, dual antiplatelet therapy (DAPT) after elective CABG may not benefit all patients but only the select group of patients of ACS or those that undergo coronary endarterectomy or off-pump surgery.

Conclusion

1. One of the strongest risk factors for developing CAD and hypertension frequently coexists with other risk factors and together they have a multiplicative effect on development of CAD.
2. The development of hypertension and related CAD is determined by an interplay of genetic and environmental factors working through neurohormonal activation, increased expression of growth factors and inflammatory cytokines, increased vascular stiffness, and endothelial dysfunction. LVH adds to the pathophysiology of ischemia.
3. BP lowering produces rapid reductions in CAD risk in hypertensive people.
4. BP lowering is more important than the particular drug class used for primary prevention of CAD.
5. An on-treatment hypertensive still has a substantial residual risk of any CV event due to various reasons listed which requires better evaluation and treatment of hypertension.
6. An office BP of <130/80 is the target for all patients, if well tolerated (except for people above age 65 years, for whom the 2018 ESC/ESH guidelines recommend a target of <140/80). The use of drugs in addition to lifestyle changes depends on (i) the level of BP (>140/90) and (ii) presence of CVD or 10-year risk above 10% by ASCVD risk calculator (for levels between 130/80 and 140/90). Low-risk patients with these latter levels to be observed for 3–6 months on lifestyle changes.
7. Care should be taken to keep DBP above 70 mm, especially in non-revascularized CAD patients, the elderly, those with wide PP and those with SBP <120 mmHg.
8. For secondary prevention in individuals with underlying comorbid illnesses such as CAD, CKD, or recurrent stroke, all drug classes have not shown optimal or even the same level of benefit.
9. Certain drugs are not advisable in CAD with HF and in CAD without HF.
10. While statins are recommended for secondary prevention of CVD in all hypertensives, they are recommended in those at moderate-to-high risk for primary prevention. Aspirin is indicated in all patients for secondary prevention, but has restricted recommendation for primary prevention.

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