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Guest Editor: Sudha Vidyasagar

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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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*M*essage

MANIPAL
ACADEMY *of* **HIGHER EDUCATION**
(Institution of Eminence Deemed to be University)

Lt Gen (Dr) M. D. Venkatesh, VSM (Retd)
Vice Chancellor

MESSAGE

Greeting from Manipal Academy of Higher Education (MAHE), Manipal, an Institution of Eminence, Deemed to be University. Ranked 8th in the NIRF Rankings MAHE has been constantly ranked among the top universities in the country. Kasturba Medical College (KMC), Manipal is the flagship institution of MAHE and enjoys a great reputation within India and abroad. With an enviable academic and research record, KMC, Manipal is ranked 7th in the NIRF ranking and has been constantly placed in the top ten medical colleges in the country.

I am very happy to note that KMC, Manipal has been entrusted with the responsibility of coming out with the MAHE edition of Hypertension Journal and it is being edited by Dr. Sudha Vidyasagar, Professor of Medicine, KMC, Manipal. This recognition is a true reflection of the quality of faculty at MAHE and their rich clinical and research experience. I am extremely happy to note that the articles that are being published are of a very high standard covering diverse aspects of this silent killer "Hypertension". I compliment the authors and the editor for bringing out MAHE edition of Journal of Hypertension with excellent articles which I am sure will benefit the readers and add great value to published literature on Hypertension.

Lt. Gen. (Dr.) M. D. Venkatesh
Vice-Chancellor

*G*uest *E*ditorial

Target Blood Pressure in Clinical Settings

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Hypertension (HTN) is a common risk factor for atherosclerosis in all vascular systems and has consequences on the heart, brain, kidney, and peripheral vessels. It is also well known that control of HTN makes a huge impact on prevention of vascular events which cause significant morbidity and mortality.

Over the years, the definition of HTN has changed based on data generated by large clinical trials.[1] The level at which to begin treatment has been based on the level at which complications tend to occur. There have been controversies in this area with these thresholds being changed time to time, with every joint national committee (JNC) report, from JNC 6 to JNC 8.

The bigger question has been to identify the target blood pressure (BP) to be achieved by therapy, to prevent complications. There have been differences of opinion between cardiologists who are looking at BP target in cardiac failure and ischemic heart disease and the neurologists who deal with hemorrhagic and ischemic stroke.[2] Further, there is the question of targets for systolic and diastolic BP, as circulations such as coronary are dependent on diastolic BP, whereas the cerebral blood flow varies according to systolic pressure. The "J"-shaped curved in HTN translates into higher mortality at both very high and very low BP, as lower diastolic pressures compromise the coronary flow.[3] Heart failure in hypertension, which can be with reduced or preserves ejection fraction, demands an approach which takes into account the type of heart failure, as the targets for these groups are likely to be different.[4]

Diabetics for a significant proportion of hypertensives and this combination of comorbidities are double trouble for all vascular complications, especially causing faster progression of diabetic kidney disease.[5] The cardiovascular impact is also significant, and hence, the American Diabetic Association and the American Heart Association have both asked for stringent control of BP

in this subgroup. However, the systolic BP intervention trial (SPRINT) did not address this subgroup at all, and hence, there is lack of clarity in targets in diabetics.[6]

Chronic kidney disease is yet another group of patients, whose renal function which depends on their glomerular filtration, which varies according to their BP. They may also have diabetes or maybe elderly, overlapping with the other important subgroups. The target BP must take into account the best glomerular filtration rate (GFR) to protect renal function, yet prevent progression of diabetic nephropathy.[7]

The elderly form an entirely different population, with their tendency to have orthostatic hypotension, with and without treatment of HTN, which may result in giddiness and falls, when the sitting BP, and not the standing BP is used as target. In addition, their lower diastolic pressures causing coronary compromise may predispose them to coronary events, and their declining GFR may affect renal function with lowering of systolic BP.[8] These have to be balanced against the clinical gains made by strict BP control, as shown in the SPRINT trial.

There is also the question of treating BP in special populations such as pregnancy. The consideration in this group is different and needs to address the morbidity in the mother and the intrauterine environment for growth for the fetus *in utero*.[9] In the pediatric age group, the causes of HTN are mostly secondary, and these must be addressed. However, in those without correctable causes and long-term gains of treating BP in children must be weighed against their side effects.[10]

Hence, this series of articles is written by practicing clinicians dealing with all the subgroups mentioned above. Each is a perspective from that specialists point of view. All of them address the same question of what is the ideal target BP in their patient, and take a call on that, putting together the current evidence.

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There are important questions raised and answered, and some still await further evidence and clarity. They are all important for the practicing clinician who deals with hypertensive patients every day in their day-to-day practice.

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Review Article

Target Blood Pressure Goals for Treating Hypertension in Pregnancy

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Abstract

There are different clinical types of hypertensive disorders in pregnancy. The management mainly lies in the hands of an obstetrician; however, a physician's role is often sought specially in chronic hypertension and when blood pressure (BP) remains uncontrolled. There is no doubt that severe hypertension ≥160/110 mm Hg will be treated expeditiously to prevent complications. It is in less severe hypertension, where the questions arise – what should be the cutoff to treat with medications, and what must be the goal of control that has to be achieved? The dilemma is due to the observations of increased incidence of small for gestational age newborns among those treated for mild hypertension. Research in the recent past has shown that strict control reduces severe hypertension though there was no significant benefit in terms of reduction in pregnancy loss, high-level neonatal care, or overall maternal complications. There is no clear consensus between various guidelines on indication to initiate medication for the control of hypertension and the target BP to be achieved. Considering the recent developments in the field, it appears prudent to control even mild-to-moderate hypertension effectively. Regardless of the type of hypertensive disorder of pregnancy, persistent BP ≥140/90 mmHg in clinic (or ≥135/85 mmHg at home) should be treated, aiming for a target BP of 110–140/85 mmHg in the office to reduce the likelihood of developing severe maternal hypertension, and other complications. However, in gestational hypertension and preeclampsia, strict surveillance to identify worsening of the condition so as to take appropriate interventions

Key words: Blood pressure; hypertension, pregnancy-induced, preeclampsia, pregnancy outcome

Introduction

With a prevalence of 10–15%, hypertension is one of the leading causes of maternal mortality and morbidity.[1-3] Pregnancy-related hypertension has a unique pathogenesis unlike hypertension in the general population. The disease begins as a result of defective placentation, due to insufficient invasion of trophoblasts into the uterine spiral arterioles, thereby initiating a cascade of events leading to hypertension. Hypertension is just one of the manifestations of a far fetching placental disorder, which can also affect several organs such as kidneys, liver, eyes, brain, and the fetus.

The extensively researched subject continues to intrigue clinicians and researchers. The etiopathogenesis has a number of theories and hypothesis involving complex humoral and immunological factors, with the core problem of vasoconstriction, endothelial dysfunction, and resulting multiorgan impairment.

National High Blood pressure (BP) Education Program Working Group on High BP in pregnancy has suggested the following classification of hypertensive disorders in pregnancy:[4]

- Chronic hypertension: Elevated BP in the mother that predated the pregnancy; can also be diagnosed in retrospect, when hypertension fails to normalize 12 weeks after delivery.
- Preeclampsia-eclampsia: Appearance of hypertension in pregnancy accompanied by new-onset proteinuria, defined as ≥300 mg per 24 h.
- Preeclampsia superimposed on chronic hypertension
- Gestational hypertension: *De novo* hypertension arising after mid-pregnancy and is distinguished from preeclampsia by the absence of proteinuria and severe complications related to hypertension

International Society for the Study of Hypertension in Pregnancy (ISSHP) Classification categorizes hypertension into two main categories as (1) hypertension known before

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pregnancy or present in the first 20 weeks and (2) hypertension arising *de novo* at or after 20 weeks of pregnancy. It further adds white coat hypertension, masked hypertension, and transient gestational hypertension to the categories.[5]

Definition of preeclampsia has also undergone modification due to the observations of severe complications even before the onset of proteinuria. Therefore, the latest definition adds "the presence of severe features with or without proteinuria" to the existing definition of preeclampsia.[6]

Chronic Hypertension

The goal of treatment of chronic hypertension would be (1) to prevent superimposed preeclampsia and (2) to minimize the devastating complications such as cerebral hemorrhage directly related uncontrolled hypertension *per se*.

It is well established that diastolic BP (DBP) ≥110 mm Hg is associated with fetoplacental complications such as placental abruption and fetal growth restriction. On the other hand, the systolic BP (SBP) ≥160 mm Hg is associated with maternal complications such as intracerebral hemorrhage. The degree of systolic hypertension is found to be the most important predictor of cerebral injury and infarction.[7,8] Thus, there is no doubt about hypertension 160/110 mm Hg requiring to be controlled as an emergency.[9,10] Here, the goal of pharmacologic treatment should be a DBP of <100–105 mm Hg and an SBP <160 mm Hg. Similarly, it is accepted beyond doubt that women with preexisting end-organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication.[11]

There is dilemma regarding whether or not to treat the BP values at or just beyond the diagnostic cut off of 140/90 mm Hg; and if treatment is required what should be the target BP control. The guidelines as recently as 2010 recommended not to treat mild hypertension and to consider treatment only when BP was consistently above 150/100 mm Hg.[12] This was well in line with the fact that prolonged antihypertensive treatment resulted in poor placental circulation thereby causing fetal growth restriction. Women with chronic hypertension, who received at least one antihypertensive in third trimester had a higher rate of intrauterine growth restriction (7.2% vs. 2.1%, respectively; adjusted odds ratio, 4.37; 95% confidence interval, 3.00–6.36; $P < 0.001$) compared to those who did not receive antihypertensive medication. They found similar observations between chronic hypertensive – no treatment group against non-hypertensives.[13]

The Control of Hypertension in Pregnancy Study (CHIPS) trial including 987 women with non-proteinuric preexisting hypertension, or gestational hypertension with office DBP of 90–05 mm Hg (85–105 mm Hg if the woman was on antihypertensive medications) evaluated the benefits and risks of tight (85 mmHg) versus less tight (100 mmHg) DBP control. They observed that fewer women in the tight control group developed severe hypertension (27.5 vs. 40.6%). However,

there was no significant between-group differences in the risk of pregnancy loss, high-level neonatal care, or overall maternal complications.[14]

In the *post hoc* analysis of CHIPS data to determine whether clinical outcomes differed by occurrence of severe hypertension, it was found that severe hypertension was associated with perinatal loss or high-level neonatal care for >48 h, serious maternal complications, birth weight <10th percentile, pre-eclampsia, and delivery at <34 or <37 weeks, platelets <100 × 109/L, elevated liver enzymes with symptoms, and maternal length of stay ≥10 days.[15]

These observations have led researchers to suggest tight control for minimizing the incidence of severe hypertension.

Further analysis of the data in CHIPS study, to find the role of gestational age at the time of randomization to "tight" control and "less tight" control groups, showed that there is no gestational age at which less tight (vs. tight) control is the preferred clinical option for women with chronic or gestational hypertension. Delaying the treatment to gestational age of beyond 24 weeks did show benefit in minimizing the small for gestation newborns; however, this benefit was countered by increase in severe hypertension and related premature delivery.[16]

Meta-analyses including Cochrane review also inferred that antihypertensives in mild-to-moderate hypertension prevented development of severe hypertension. However, it had little or no influence on perinatal outcome in terms on fetal death, prematurity, small for gestation newborns, and neonatal complications; neither was there any significant effect on maternal outcome like preeclampsia/eclampsia.[17,18]

Despite the recent observations, differences in guidelines prevail. In Ireland, clinical practice guidelines (2016, revised in 2019) recommend that for pregnant women with chronic hypertension without underlying medical problems, antihypertensive drug therapy should aim at BP below 150 /80–99 mm Hg and for those with underlying medical problems, such as diabetes or renal disease, tighter control with the goal of maintaining BP below 140/80–90 mmHg.[19] ISSHP and National Institute for Health and Care Excellence (NICE) guidelines pragmatically recommend a common goal of 140/85 mm Hg 135/ 85 mm Hg, respectively, for control of BP for all types of hypertensive disorders in pregnancy.[5,20]

ACOG Practice Guidelines 2019 recommendations for chr hypertension.[21]

Preeclampsia and Gestational Hypertension

Although gestational hypertension and preeclampsia are two different categories of pregnancy hypertension, their management in the absence of severe features is similar; and both require enhanced surveillance. Up to 50% of women with gestational hypertension will eventually develop proteinuria or other end-organ dysfunction consistent with the diagnosis of preeclampsia especially when hypertension is diagnosed at

<32 weeks of gestation.[22] For all practical purposes, the two categories may be discussed as one entity.

Gestational hypertension and preeclampsia have placental origin; here, hypertension is due to increased vascular resistance secondary to increased sensitivity of the vasculature to angiotensin. Defective secondary wave of trophoblastic invasion of myometrial spiral arterioles during placentation results in failure of establishing a desired low resistance placental circulation, initiates the process of increased vascular resistance, endothelial damage, and platelet dysfunction all leading to maternal multiorgan dysfunction. On the fetoplacental side, vascular resistance causes poor perfusion. Initial response to this insult is brain-sparing adjustment by the fetus, at the cost of compromising other vital organs such as kidneys and liver. The fetus will become growth restricted; poor renal perfusion will result in oligohydramnios. The fetal effect may become evident much before high BP becomes evident on maternal side. Antihypertensive treatment will add to the already existing hypoperfusion at placental bed, especially when given for longer duration.

Similarly severe maternal complications may occur even without very high BP levels. Seizures can occur without other severe features of preeclampsia and with a normal BP; 15% of women with eclampsia have a DBP <90 mm Hg.[23]

The latest ACOG interim guidelines emphasize on intensive surveillance for women with gestational hypertension and preeclampsia with less severe BP and in the absence of severe features; the guidelines speak of antihypertensive medications only in case of severe hypertension.[22]

However, NICE and ISSHP recommend pharmacological treatment if BP remains above 140/90 mm Hg with an aim for BP of 135/85 mm Hg or less for preeclampsia, gestational hypertension.[5,20] In all cases, care should be taken to avoid reducing the BP below the lower limits (110/80 mmHg) which would lead to a risk of placental underperfusion.[24]

Postpartum Management

Pregnancy hypertension is not just the problem of pregnancy; the risk extends even into the postpartum period. Community-Level Interventions for Pre-eclampsia trials in 27 geographical clusters in less-developed countries observed substantial proportion (40%) of pregnancy hypertension diagnosed postpartum.[25] More dreaded are the complications of hypertension such as eclampsia and cerebrovascular events which are not uncommon after delivery; rather, 20–28% of eclampsia happens in postpartum period.[23,26]

Similarly, it is observed that preeclampsia/eclampsia was present in 57.5% of the patients with hemorrhagic stroke and 36% of the patients with ischemic stroke related to obstetrics.[27] More interesting is that stroke associated with preeclampsia occurs most often in postpartum period.[28,29]

This emphasizes the need to be vigilant in identifying postpartum hypertension and treating those who already had hypertension antepartum. After delivery, women with

preeclampsia require ongoing close BP monitoring. As in antepartum management, BP 160/110 mm Hg should be treated with acute antihypertensive management. Persistent BP above 155/105 mm Hg will require oral antihypertensive treatment.

In case of chronic hypertension, persistent BP ≥ 140/90 mm Hg needs antihypertensive treatment with the goal of maintenance of BP at ≤140/90 mm Hg. Medications will be reduced as BP falls below 130/80 mmHg. 19

Summary Points

1. Regardless of the hypertensive disorder of pregnancy, severe hypertension (>160/110 mmHg) requires urgent immediate acting antihypertensive agents.
2. BPs consistently ≥140/90 mmHg in clinic (or ≥135/85 mmHg at home) may be treated, aiming for a target DBP of 85 mmHg in the office (and SBP of 110–140 mmHg). However, in gestational hypertension and preeclampsia, intensive surveillance to identify proteinuria and/ or other features of end organ involvement needs to be emphasized.
3. Women with preexisting end-organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication and a strict control of BP.
4. Monitoring of BP and control of hypertension after delivery is not less important.

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Review Article

How Tight Should Hypertension Control in CAD Be? – A Review

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Abstract

Guidelines for the management of hypertension have been constantly updated and with them targets for hypertension control have been evolving. There has been special concern for targets to achieve in hypertensive with coronary artery disease (CAD). Concern has been raised whether too low a value is harmful especially with concept of J curve being emphasized. This review attempts to analyze data for and against existence of a J curve and dissects various trials for and against this concept and attempts to come to a conclusion on ideal target for hypertension control in CAD patients. The data have been a little different in diabetics with CAD and trials in this field are also analyzed. Special concerns of tight hypertension control in the elderly are looked into. Mechanisms proposed for explaining J curve postulate are also discussed in the review. Approach of striking an ideal balance in therapy between good controls of systolic blood pressure with not so low diastolic blood pressure is proposed. Finally, an attempt has been made to zero in on ideal target blood pressure in various clinical spectra of vascular disease.

Key words: Coronary artery disease, hypertension, treatment targets

Background

It is well proved that hypertension (HTN) is a risk factor for coronary artery disease (CAD), heart failure, and stroke. It is a more powerful risk factor for acute myocardial infarction (MI) than diabetes mellitus (DM) as per data from INTERHEART study. High BP accelerates atherosclerosis and destabilizes vascular lesions and precipitates acute coronary syndromes (ACS).[1] Risk of having a fatal coronary event doubles for every 20/10 mm rise in blood pressure (BP). Hypertensive heart disease with the left ventricular hypertrophy (LVH) has impaired coronary autoregulation and reduced coronary flow reserve causing ischemia with normal coronary arteries (INOCAs).

In this context, it is logical to assume that control of BP should reduce coronary risk. However, there are differing opinions on how much to reduce BP and what target to keep. Is lower the better? Are there any concerns if BP is lowered beyond a limit? This review tries to address these concerns and zero in on a target value to achieve for systolic BP (SBP) and diastolic BP (DBP) in hypertensive with CAD.

Current ACC/AHA guidelines[2] recommend a blood pressure target of <130/80 mm of Hg in hypertensive with relaxation up to <140/80 mm of Hg in the elderly. The core practical concern is that attempts to lower SBP below 130 mm of Hg often lower DBP to levels as low as <60–70 mm of Hg, which may be harmful in CAD. Framingham study showed that low DBP and wide pulse pressure increase cardiovascular events.

Why is Low Blood Pressure Harmful?

Lower DBP has been linked to worsening angina in CAD. Coronary perfusion pressure the difference between aortic diastolic pressure and left ventricular end-diastolic pressure (LVEDP). If diastolic BP falls, coronary perfusion pressure should fall outside limits of autoregulation. Normal response to low DBP is autoregulation due to dilation of coronary resistance vessels. If DBP is very low, resistance vessels are already maximally dilated and if DBP falls further, coronary perfusion will suffer.[3] Coronary autoregulation gets exhausted in low DBP in setting of atherosclerotic narrowing of epicardial coronaries. Hypertensive

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with LVH is more vulnerable to have subendocardial ischemia when coronary perfusion falls. In patients with chronic total occlusions and collateral donor artery stenosis, a U-shaped pattern is seen between blood pressure and development of coronary collaterals. As DBP falls below 80 mm of Hg, it is shown that difference in pressure between central aortic pressure and intracoronary pressure distal to occluded segment falls. This reduces collateral flow. This fall is approximately 20% if DBP is 70–79 mm of Hg, 28% if DBP is 60–69 mm of Hg, and 38% if DBP is <60 mm of Hg.[4]

Does That Mean That A J Curve Exists?

JM Cruickshank first reported J curve phenomenon in the treatment of hypertension in which J-shaped relationship was noted between DBP during therapy and occurrence of myocardial infarction (MI) with lowest point of the J at DBP 85–90 mm of Hg. This suspicion was mirrored by data from many trials.

HOT TRIAL[5] evaluated the J curve phenomenon prospectively and had three DBP targets – 90, 85, and 80 mm of Hg. The decline in major cardiovascular event rate in a patient with CAD at baseline was not different between three groups. However, the group with <80 DBP had 43% lesser strokes. The drawbacks were that the trial did not assess the effects of lowering DBP < 80 as only 8% in the study group reached that level.

In Syst-Eur trial,[6] cardiovascular event rates were found to be higher when DBP fell <70 in patients 60 years and above, and it was statistically significant when DBP fell <60 mm of Hg.

The landmark diabetic study ACCORD[7] done in 40–79 years old diabetics showed no difference in composite outcome of cardiovascular death, non-fatal MI, and non-fatal stroke between intensive (<120 mm of Hg) and standard BP control (<140 mm of Hg). Intensive BP control group had 2% increase in absolute risk for adverse events (3.3% vs. 1.3%). However, the study was confounded by low event rate even in standard therapy group.

In ACCOMPLISH trial,[8] major CVS events were lower in those with SBP < 130–140 mm of Hg, but composite endpoint of MI, hospitalized angina, or sudden death (not stroke) increased when SBP fell below 120 mm of Hg. Similar findings supporting J curve were found in INVEST trial[9] with death and MI at nadir at BP of 119/84, TNT trial[10] where SBP < 110–120 or DBP < 60–70 increased non-stroke cardiovascular events and PROVE-IT TIMI 22 trial[11] where BP < 110/70 caused harm.

Registry data too like CLARIFY registry[12] showed that SBP > −140 and DBP > −80 increased cardiovascular events, but SBP < 120 and DBP < 70 too increased composite endpoint of death, MI, and stroke.

A Taiwanese study[13] of 2045 stable CAD patients of Chinese ethnicity who underwent PCI showed that SBP < 120 and > −160 or DBP < 70 is associated with major cardiovascular events at 12 months and 24 months.

However, one should remember that J curve may be different in hypertensive and normotensive. Hypertension shifts autoregulation rightwards to a higher range and LV mass also is higher. Both may explain higher risk of adverse events at lower BP values. Hence, inflection of J curve may occur at lower BP values in normotensive than hypertensive.[12]

Data against J Curve – Sprint and the Rest

One of the initial data against existence of J curve came from an interesting intravascular ultrasound study called CAMELOT trial[14] done in patients who underwent PCI or had angiographic diameter stenosis >50%. Study found that most favorable rate of atheroma progression occurred in those with SBP < 120/80.

However, the strongest data against J curve came from the landmark NIH funded RCT – SPRINT trial.[15] This study randomized 9361 non-diabetic patients >50 years age to SBP target < 120 (achieved 121.4) versus SBP target < 140 (achieved 136.2) with 3.26 years follow-up. It showed that intensive treatment reduced primary composite outcome (MI/cardiovascular death/stroke/acute decompensated heart failure) by 25% and all-cause mortality 27%. However, this trial had only 16.7% of patients with clinical cardiovascular disease and cannot be extrapolated fully to CAD group. However a meta-analysis of SPRINT showed that intensive BP control resulted in similar risk reduction in both CAD and non-CAD group. Intensive treatment increased side effects such as hypotension, syncope, reversible acute renal failure, and electrolyte defects. Number needed to treat NNT for preventing one primary outcome was 61, death 90, and cardiovascular death 172. Largest data against J curve have recently been presented in BPLTTc meta-analysis data[16] at ESC congress 2020. It analyzed 48 trials including 348,854 patients and analyzed seven groups with achieved BP < 120, 120–129, 130–139, 140–149, 150–159, 160–169, and >−170. Study showed that antihypertensive drug therapy reduced MI and stroke in all seven groups. Neither the presence of cardiovascular disease or blood pressure at study entry modified effect of therapy.

One should, however, remember that J curve may be more important in DBP targets rather than SBP targets and these trials do not refute the possibility that a DBP < 70 may be more harmful than a SBP < 130. It is possible that lower DBP may be a marker of frailty or medical illness and need not be the cause for higher events. Even non-cardiac mortality may be higher in this population.[3]

Are Targets Different in Diabetics?

Diabetes is considered a marker of baseline risk of CAD, which, in turn, could affect relative treatment effect of intrinsic BP lowering. Furthermore, since diabetics have more diffuse disease, multivessel disease, and chronic total occlusions, the risk of lowering diastolic BP may be more in diabetics than non-diabetics.

Current recommendation of target BP in diabetics is <130/80; <140/80 in the elderly.[2] INVEST study[9] showed that

cardiovascular risk is reduced in type 2 diabetics with diastolic BP < 90, but increased when DBP is <70. All-cause mortality increased in diabetic hypertensive above 50 years treated to SBP < 115. This RCT had 22,576 patients with hypertension and CAD, and the subgroup with SBP < 130 had higher all-cause mortality than the groups with SBP130–139 and >139. Similar increase in adverse events except stroke was seen with SBP <120 which was seen in ONTARGET[17] and TRANSCEND[18] trials too. The data of the large ACCORD study arguing against strict hypertension control in diabetics have already been discussed before.

In diabetics with ACS, data from EXAMINE trial[19] showed a U relationship between BP and cardiovascular outcomes in diabetic. BP of < 130/80 worsened cardiovascular outcomes and degree of risk was more if BP < 120/70 was achieved.

Hence, caution is needed before accepting the concept that lower is the better in hypertensive patients with DM and CAD. One should also be aware of the fact that risk of stroke behaves differently and risk falls when BP is < 120/70. PROGRESS trial showed that stroke risk falls even with SBP < 115, probably due to excellent cerebral autoregulation with hardly any evidence of J curve in cerebral circulation. Similarly, "SPRINT eligible diabetics" (with additional risk factor) may benefit from stricter BP targets as seen in ACCORD-BP trial.

The discordance between the major trials SPRINT and ACCORD may be because latter was based on BP recordings made in the presence of an observer (white coat effect) and not on home BP as in SPRINT, and hence, ACCORD patients would have actually had lower BP at start of study than SPRINT and hence benefits were diminished. Furthermore, an interesting analysis of SPRINT eligible patients of ACCORD-BP trial (those diabetics who had an additional cardiovascular risk factor) showed that intensive BP control reduced composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, revascularization, and heart failure.

Are There Special Issues in the Elderly?

The elderly often have high SBP with low DBP reflecting increased aortic stiffness. In this scenario, lowering SBP < 140 has shown benefit even though DBP falls further. If patient has CAD, it may be prudent to keep DBP >60–70 while using anti-angina drugs such as beta-blockers and calcium channel blockers. The special concern of J curve in very elderly >80 years was addressed in systolic hypertension in elderly trial (SHEP)[20] where benefit of BP lowering was reduced once DBP fell below 60.

Which is More Important in Cad – Systolic Goal or Diastolic Goal?

CLARIFY registry[12] of 5956 stable CAD patients with average BP < 140/90 showed that in patients with stable CAD, a DBP 80–90 was associated with higher cardiovascular risk compared to DBP 70–79. However, SBP 130–139 did not increase risk compared to SBP 120–129. This suggested that lower diastolic BP achievement is more important than systolic BP goal achievement in stable CAD. This registry suggested that it is more important to achieve DBP< 80 than achieving SBP < 130. Similar inference was made from *post hoc* analysis of ONTARGET and TRANSCEND trials where in patients who achieved a SBP 120–139, a DBP of 80–89 had higher risk of stroke and heart failure hospitalization compared to 70–79.

Can We Arrive at a Reasonable Conclusion with Plethora of Data?

In hypertensive with CAD, it may be prudent to aim BP <130/80, but not <120/70. Target can be relaxed up to 140/90 in those with acute coronary syndromes or chronic total occlusions. While achieving SBP target <130, it may be prudent to ensure that DBP remains in 70–79 range. DBP < 60 is likely to be harmful in CAD. If angina relief is a concern at these DBP levels, it may be prudent to use ranolazine/ trimetazidine/ivabradine like drugs without hemodynamic effect.[21]

Dilemma occurs in patients with SBP >140 on therapy, where DBP has already fallen below 70. Framingham study has identified that this group with low DBP and wide pulse pressure has high cardiovascular risk.

Based on the current data,[22-26] target BP goals in hypertensives with CAD can be summarized as follows.

Group	SBP goal (mm of Hg)	DBP goal (mm of Hg)
Unspecified hypertensive	120–130	70–80
General CAD population	120–130	70–80
ACS	130	80
Diabetic CAD	120–130	70–80
Post-stroke/TIA	120–130	70–80
Carotid disease/peripheral vascular disease/aortic aneurysm	130	70–80
Very elderly >80	130–140	80

However, outcomes of trials do not always translate into real world practice, and often, clinical judgment of risk and patient choice too would get reflected in prescription patterns, especially regarding achieving target BP goals.

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Target Blood Pressure Goals for Treating Hypertension in the Elderly: A Review

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Abstract

Hypertension is a common disease in elderly people, and prevalence increases with age. It is associated with substantial morbidity and mortality. Newer, lowered definitions of hypertension further increase prevalence. There is no consensus between the hypertension guidelines on the precise definition of the elderly and the target blood pressure (BP) for the elderly. Due to the heterogeneity of this population, the goal of optimum BP regulation is also controversial. In this article, we review current data on hypertensive treatment guidelines, try to define the target BP, optimize treatment strategies in the elderly and summarize the challenges health provider face when dealing with this population.

Key words: Blood pressure, Cardiovascular, Elderly, Geriatrics, Hypertension

Introduction

The 2015 Global Burden of disease study[1] reported that high systolic blood pressure (SBP) was one of the largest contributors to global morbidity and mortality, accounting for 10.2 million (9.16–11.3 million Uncertainty interval [UI]) deaths and 208 million (UI 188–227 million) disability-adjusted life years (DALYs). Most of the burden of high systolic BP (SBP) was due to stroke and ischemic heart disease, with 56.5% (UI 49.0–63.2) and 55.5% (UI 48.0–62.7) of DALYs being attributed to stroke and ischemic heart disease, respectively. The INTERHEART[2] and INTERSTROKE[3] studies also showed similar findings, with hypertension accounting for 34.6% and 17.9% of the population attributable risk for stroke and coronary artery disease, respectively. A systematic review of hypertension in India highlighted the increasing prevalence of hypertension in both rural and urban India.[4] With the decrease in BP levels in the 2018 American Heart Association/American College of Cardiology guidelines[5] and an increase in the number of elderly people, the prevalence of those with hypertension, especially the elderly, is likely to increase.

There are a number of controversies in the management of hypertension in the elderly, such as the optimum BP at which there are maximum preventive benefits and at the same time minimal complications, the categorization of the BP stage, to rule out pseudo hypertension, white-coat hypertension, masked hypertension, orthostatic, postprandial hypertension and exclude secondary causes in cases of resistant hypertension, the choice of first-line therapy, and the role of combination therapy. In addition, many factors, such as high prevalence of several comorbidities, poly-pharmacy, frailty and minimal inclusion of the elderly in hypertension trials, and leave a variety of unresolved clinical issues to clinicians who offer treatment for this age group. The purpose of this review article is to address the difficulties of evaluating and treating hypertension in older adults and to analyze the evidence and recommendations of different professional societies.

Pathophysiology of Age-related Hypertension

Several factors contribute to the development and worsening of existing hypertension in elderly people. These include arterial stiffening, mechanical hemodynamic changes, neuro-hormonal dysregulation, autonomic dysfunction, ageing of the kidneys, and secondary causes of hypertension.[6]

Over time, arterial intimal hyperplasia and damage of the elastic lamellae occur, leading to arterial stiffening. The stiffened arteries have reduced recoil and capacitance, leading to difficulties in dealing with changes in volume during the cardiac cycle. After the age of 60, SBP tends to increase while diastolic BP (DBP) reduces due to a predominant increase in central arterial stiffness. This leads to isolated systolic hypertension, which is more important than elevated DBP as a risk factor for both cardiovascular disease (CVD) and renal disease.[7]

Pulse pressure, rises with age, regardless of mean BP and other factors, and is a marker for large artery stiffness, early vascular ageing and is a risk factor for CVD.[8]

Pseudohypertension, characterized by systolic and DBP ≥10 mmHg higher than the concurrently measured intra-arterial BP, is a potential cause of hypertension in this age group with a reported prevalence of 4%. This should be taken into account during the treatment of the elderly hypertensives, as false BP due to arterial calcification can lead to over-treatment and increased adverse reactions.[9]

Increased use of home BP monitoring and ambulatory BP monitoring has showed an increased occurrence of "white coat" hypertension and "reversed white coat" hypertension, which is important challenges in determining target BP and optimizing therapy.[10]

Orthostatic hypotension, described as a decrease in SBP by at least 20 mmHg or DBP by at least 10 mmHg within 3 min of standing, is common in elderly people with a prevalence of 18% in older adults and is associated with increased risk of falls and cerebrovascular events.[11] This is due to reduced arterial compliance, decreased sensitivity of the baroreceptors with age and reduced cardiovascular sensitivity to catecholamines. This is further exacerbated by beta-blockers, which are associated with an increased risk of developing orthostatic hypotension because elderly people rely on increased cardiac output due to increased heart rate, as compared to adjustments in their already stiff arteries, to achieve postural homeostasis. However, a randomized clinical trial reported that non-institutionalized elderly patients with SBP <120 mmHg were not associated with a substantially elevated risk of orthostatic hypotension.[12]

Post-prandial hypotension is an under-recognized cause of syncope in geriatric patients. It appears to be related to a reduced response of the autonomic nervous system to meals. Monitoring of ambulatory BP and symptoms can help with the diagnosis. These patients can be managed with increase water intake before eating or having six smaller meals daily instead of three larger meals. Patients with heart failure, end-stage renal disease on hemodialysis, Parkinson's disease, and autonomic dysfunction are more prone to post-prandial hypotension.[13]

Secondary causes of hypertension, such as atherosclerotic renovascular disease, chronic kidney disease, thyroid disease, obstructive sleep apnea, and drugs such as nonsteroidal anti-inflammatory drugs, anabolic steroids, and antidepressants, are also more prevalent in this population.[9] Pseudo-resistant hypertension due to drug non-adherence due to various causes,

such as cognitive decline and lack of social and financial support, is also an important consideration in this age group.[9]

Risk Assessment of Older Adults with Hypertension

In the geriatric population with hypertension, a thorough history, physical examination, and selected investigations should be carried out to determine the global risk of CVD. In addition, the clinical examination should evaluate the global functioning of the patient, including comorbidity, frailty, autonomy, medications, and social and financial support.[14]

Although the same general rules, as for the general hypertensive group apply, certain specificities should be taken into account for older adults. These include (a) risk calculators such as atherosclerotic CVD risk calculator,[15] are standardized for individuals of age 40–75 years, (b) personal rather than family history is of importance, (c) orthostatic hypotension may be a significant contributor to increased cardiovascular risk, (d) assessment of arterial stiffness and intima-media thickness, although of weak evidence, may be of help to better identify risk, (15) (e) presence of other cardiovascular risk factors, such as smoking and high cholesterol, diabetes mellitus, and (f) presence of target organ damage such as left ventricular hypertrophy, stroke, retinopathy, and renal insufficiency.

The risk of functional decline, morbidity, and mortality should also be assessed by the examination. Groups with considerations of risk/benefit balance of aggressive and chronic treatment should also be defined. Functional profiles using tools such as canadian health study and aging frailty scoring system[16] would provide additional objective measures to guide treatment decisions in the frail elderly.

Current evidence: Clinical Trials and Guidelines on Treating Hypertension in the Elderly

While the benefits of BP control are irrefutable, it was not clear whether or not intensive BP reduction was superior to modest control in the geriatric population. Numerous studies have, therefore, assessed the benefits of antihypertensive drug therapy in reducing cardiovascular events in elderly people with hypertension and have sought to obtain an ideal BP target. Some of the studies are described in Table 1.

Earlier studies such as systolic hypertension in the elderly program,[17] systolic hypertension in Europe (Syst-Eur)[18] and hypertension in the very elderly trial[20] showed significant cardiovascular benefits in elderly patients with isolated systolic hypertension for lowering SBP. However, all four of these studies had defined a SBP cutoff of 160 mmHg to initiate treatment.

The systolic blood pressure intervention trial (SPRINT) trial recently demonstrated the benefits of a lower BP target of SBP <120 mmHg even in the subgroup of patients over 75 years of age.[22] However, the SPRINT trial did not include patients with diabetes mellitus, which is a common comorbid condition in the elderly hypertensives. In comparison, the

Table 1: Analysis of studies showing the benefits of different blood pressure targets in elderly patients

Study (year)	Study characteristics	Initial blood pressure	Target blood pressure (mmHg)	Conclusions
Systolic hypertension in the elderly program (1989)[17]	Age of included population ≥60 years Average follow-up (years): 4.5 years Study design: Double-blind randomized placebo-controlled trial Number of patients: 4736	SBP level of 160–219 mmHg and DBP less than 90 mmHg	SBP <160 Or reduction of ≤ 20 mmHg	Antihypertensive drug therapy reduced ischemic stroke by 37%, hemorrhagic stroke by 54%, reduced heart failure by 49% and by 80% in patients with prior myocardial infarction, reduced major cardiovascular events by 32%, as well as all-cause mortality by 13%
Systolic hypertension in Europe trial (Syst-Eur) (1997)[18]	Age of included population ≥ 60 years Average follow-up (years): 2 years Study design: Double-blind randomized placebo controlled trial Number of patients: 4695	Sitting SBP: 160 to 219 mmHg Sitting DBP below 95 mmHg and Standing SBP of at least 140 mmHg	Sitting SBP < 150mmHg	In the median follow-up of 2 years , the incidence of stroke decreased by approximately 42% and cardiovascular endpoints by 31% in the active treatment group.
Systolic hypertension in China trial (2000)[19]	Age of included population ≥ 60 years Average follow-up (years): 3 years Study design: Double-blind randomized placebo controlled trial Number of patients: 2394	Sitting SBP: 160 to 219 mmHg Sitting DBP below 95 mmHg	SBP <150 Or reduction of ≤20 mmHg	Stroke rates decreased by 38%, all cardiovascular endpoints by 37% and all-cause mortality by 39% in the active treatment group.
Hypertension in the very elderly trial (2008)[20]	Age of included population ≥80 years Average follow-up (years): 1.8 years Study design: Randomized controlled trial Number of patients: 3845	SBP >160 mm Hg	SBP <150 DBP <80	Blood pressure < 150/80 mmHg decreases risk of fatal stroke, heart failure, any cardiovascular events, and all-cause mortality
Valsartan in elderly isolated systolic hypertension study (2010)[21]	Age of included population ≥ 70 Average follow-up (years): 3 years Study design: Randomized, open-label trial Number of patients: 3260	Sitting SBP 160 to 199 mm Hg	Two groups: strict blood pressure control (< 140 mm Hg) and moderate blood pressure control (≥ 140 mm Hg to < 150 mm Hg)	No difference was seen between strict blood pressure (SBP <140 mmHg) control versus mild blood pressure control (SBP 140–150) in terms of composite cardiovascular diseases
Systolic blood pressure intervention trial (2016)[22]	Age of included population ≥ 75 Average follow-up (years): 3 years Study design: Randomized control trial Number of patients: 2636 were ≥ 75	Systolic blood pressure of 130 mm Hg or higher	Intensive treatment group: SBP target of less than 120 mm Hg Standard treatment group: SBP target of less than 140 mm Hg	Systolic blood pressure target of <120 mmHg was associate with lower rates of cardiovascular events and deaths, as compared to a SBP target of <140 mmHg
Delgado et al. (2017)[23]	Age of included population ≥80 Average follow-up (years): 4.4 years Study design: Observational cohort analysis Number of patients: 79,376	SBP >140 mmHg DBP >90 mmHg	SBP was grouped in 10-mmHg increments from less than 125 to 185 mmHg or more	Patients with systolic blood pressures ranging between 135 and 154 mmHg had the lowest mortality rate

analysis of the elderly diabetics with hypertension in the action to control cardiovascular risk in diabetes-BP study[24] showed that targeting SBP to less than 120 mm Hg, as compared with less than 140 mm Hg, did not affect the rate of fatal and nonfatal major cardiovascular events. In addition, increased adverse events such as hypotension, syncope, and renal insufficiency, and electrolyte disturbances were also observed in the SPRINT trial in patients who received intensive BP control. These adverse events will reduce the tolerability of therapy, particularly in older adults, which may result in decreased long-term adherence and discontinuation of treatment, masking the beneficial effects of intensive BP control.[25]

Further studies, such as the observational cohort analysis published in 2017 by Delgado *et al.*,[23] reported that patients with SBPs ranging from 135 to 154 mmHg had the lowest mortality rate.

This evidence has been incorporated into the recent guidelines and recommendations of various professional societies. A summary of the guidelines for initiation of therapy and target BPs is mentioned in Table 2.

Management Considerations in the Elderly

Non-pharmacological interventions

Data from the trial of non-pharmacological interventions in the elderly study[30] have suggested that non-pharmacological lifestyle interventions should be promoted as preventive treatment for the development of hypertension and adjunctive therapy in patients already diagnosed with hypertension. Diets such as dietary approaches to stop hypertension and Mediterranean diets which have been proven to be heart-healthy should be recommended. Patients should be advised regarding reduction in sodium consumption (1000 mg/day), potassium supplementation, increased fiber, reduced carbohydrate, increased protein intake,

Table 2: Summary of the recommendations for the threshold to initiate therapy for hypertension, the target blood pressure in the elderly and drug choices (office blood pressure monitoring)

Clinical condition	Threshold to initiate medical therapy	Target blood pressure	Initial Drug choices in the elderly
JNC – 8[26]			
Age ≥ 60 years	SBP ≥150 mmHg or DBP ≥90 mmHg	SBP <150 mmHg and DBP <90 mmHg.	No separate recommendation
2017 American college of cardiology/American Heart Association[5]			
Older persons (≥ 65 years of age; non-institutionalized, ambulatory, community living adults)	SBP ≥ 130	SBP < 130 mmHg	No separate recommendation
2018 European society of cardiology/European society of hypertension[27]			
Age ≥80 years	SBP ≥ 160 mmHg	SBP: 130–139 mmHg	No separate recommendation
National Institute for Health and Care guideline (2019)[26]			
Age ≥ 80 years	SBP ≥ 150 mmHg DBP ≥ 90 mmHg	SBP < 150 mmHg DBP < 90 mmHg	In patients > 55 years of age: Calcium channel blocker Thiazide diuretic, if calcium channel blocker is not appropriate or poorly tolerated
Indian guidelines on hypertension – IV (2019)[28]			
Age ≥ 60	SBP >140 mmHg DBP >90 mmHg	SBP: 130–140 mmHg DBP: 80–90 mmHg Higher target blood pressure may be acceptable for frail elderly, those with postural hypotension and those at high risk for falls	No separate recommendation
Hypertension Canada (2020)[29]			
High risk of cardiovascular disease (clinical or subclinical cardiovascular risk, chronic kidney disease, estimated 10-year global cardiovascular risk ≥ 15%, or age ≥ 75 years)	SBP ≥130 mmHg	SBP <120 mmHg	Monotherapy with • Thiazide/Thiazide –like diuretic • ACE-I/ARB (in non-black) • Long acting calcium channel blocker Or a single pill combination of • CCB + ACE-I or ARB •ACE-I or ARB + diuretic

ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker

decreased caffeine intake, and weight loss.[6] Aerobic exercises, dynamic resistance exercises, and isometric resistance exercises have shown statistically significant reductions in both SBP and DBP in older adults. However, these reductions have not reached clinically significant thresholds and cannot be recommended as anti-hypertensive mono-therapy in the majority of individuals.[31] Current recommendations also advocate the cessation of smoking, the reduction of stress and the prevention of excessive alcohol intake.[28] Regular home BP monitoring and follow-up through tele-consultation have also been shown to better control BP.

Pharmacological Therapy: Special Considerations in the Elderly[14,32,33]

While angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blockers (ARB), and thiazide diuretics and calcium channel blocker (CCB) have all shown benefit on cardiovascular outcomes in the elderly and have been recommended as first line agents by most professional guidelines [Table 2],[5,26-29] factors to be evaluated prior to prescription of medicines include comorbidities including renal function and electrolytes, frailty, comprehension, complexity of the treatment, drug interactions and adverse effects, and social support. Table 3 summarizes important considerations while prescribing these drugs.

Management in the Elderly with Orthostatic Hypotension

Current guidelines for hypertension do not provide specific recommendations for the diagnosis and management of orthostatic hypertension in the elderly. However, because orthostatic hypertension is common in elderly hypertensives, has been shown to be associated with increased cardiovascular risk, and has not been excluded from clinical trials, similar targets, as for the rest of the elderly hypertensive population may be used. Monitoring of ambulatory BP may be particularly helpful in guiding the subsequent management of this population. There is a lack of evidence that patients with orthostatic hypertension benefit from a specific class of drugs in terms of cardiovascular risk protection. Treatment of orthostatic hypotension should be aimed more at improving symptoms, functional status, quality of life, and prevention of injury. It is reasonable not to lower BP in elderly patients with orthostatic hypotension or recurrent falls. Maintaining the supine SBP <120 mmHg increases the risk of orthostatic hypotension more adverse outcome. Using the diuretics which sometimes exacerbate central hypovolemia should be used with caution in this population.[34]

Management in the Elderly with Isolated Systolic Hypertension

The ideal BP targets for patients with isolated systolic hypertension are debated. While various studies have shown that reduction of SBP reduces cardiovascular mortality, aggressive BP lowering may be harmful in elderly patients with isolated systolic hypertension due to the risk of target organ hypoperfusion. Excessive reduction in BP could result in a J-curve phenomenon such that reduction of DBP could increase the risk of coronary heart disease and other adverse events. People aged 65 years and

Table 3: Antihypertensive drugs: Considerations in the elderly

Class of drug	Co-morbidities	Precaution
ACE- I/ ARB	Preferred in non-black elderly with ischemic heart disease, heart failure with reduced ejection fraction, diabetes mellitus, chronic kidney disease, dyslipidemia, hyperuricemia, previous strokes, and peripheral vascular disease	Monitor creatinine and potassium Caution when diuretics and aldosterone antagonists are used concurrently Avoid simultaneous NSAID use
Calcium channel blockers	Di-hydro-pyridines calcium channel blockers may be preferred in patients with previous stroke, chronic kidney disease, diabetes mellitus, dyslipidemia, hyperuricemia, peripheral vascular disease Non-dihydropyridine CCBs are preferred in atrial fibrillation for rate control	Avoid non-dihydropyridine CCBs in heart failure, second or third degree heart block and combination with beta-blockers
Diuretics	Preferred in heart failure (loop diuretics), chronic kidney disease (loop diuretics, if CrCl <30 mL/min/1.73 m²), previous stroke and osteoporosis (thiazide)	Monitor creatinine and electrolytes Use with caution in the elderly as they are more prone to hyponatremia Increased risk of severe hyponatremia with concomitant use of SSRI antidepressants May worsen existing urinary incontinence
Beta-blockers	Avoid as first-line medications May be used in Ischemic heart disease, atrial fibrillation or thyrotoxicosis	Avoid in second or third degree heart block Avoid combination with non-dihydropyridine CCBs and acetylcholinesterase inhibitors (for Alzheimer's disease)
Alpha-blocker	Avoid as first-line medication May have beneficial effect in benign prostatic hypertrophy	Increased predisposition to falls
Central α-adrenoreceptor agonists	Avoid as first-line medication	High risk of delirium and confusion

older with SBP of 130 mm Hg or higher or a DBP of 80 mm Hg or higher with lifestyle measures plus antihypertensive drug to lower the BP to less than 130/80 mm Hg. Preferred drugs in the treatment of this subgroup are like CCBs, Thiazide-like diuretics and ACE-I or ARBs being preferred, alone, or in combination. Beta-blockers are avoided due to lack of efficacy in lowering central aortic BP and possible pro-fibrotic effects.[32,35]

Management in the Elderly with Loss of Autonomy or Limited Life Expectancy

This subpopulation includes patients with multiple comorbidities, dementia, several geriatric syndromes, and lack of functional independence. The main objectives of therapy in this group are the preservation of quality of life and the relief of symptoms. SBP of 130–150 mmHg may be targeted in these patients, taking care to avoid lowering SBP to less than 130 mmHg and orthostatic hypotension. De-prescription of anti-hypertensive drugs should be considered as necessary.[14]

Conclusion

There is a lack of consensus between the hypertension guidelines on the definition of elderly people and target BP recommendations for the elderly. The most recent guidelines suggested a treatment goal of 130/80 mmHg in patients older than 65 years. There is also a lack of data on frail elderly people age >85 years. With the lowering of the threshold for diagnosis of hypertension, the increasing survival of the elderly and the increasing prevalence of the disease, this issue is becoming more relevant. There is great benefit in the successful treatment of hypertension in the elderly population. Encouraging lifestyle changes is the first-line treatment. Medications should be started as appropriate. Therapy may, therefore, need to be tailored to these patients, using clinical judgment and a team-based approach, in consultation with the patient, family, and caregivers, until further studies provide more definite answers.

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*R*eview *A*rticle

Target Blood Pressure Goals in Cerebrovascular Disease

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Abstract

Stroke continues to be a globally leading cause of morbidity and mortality in today's scenario despite increasing awareness and newer interventions. Modifiable risk factors such as hypertension provide opportunities for early identification and optimal treatment to prevent stroke and improve outcomes if stroke occurs. The management of hypertension in stroke is multifaceted and requires proper identification and accurate definition of therapeutic goals. The goal of optimal blood pressure management in stroke has to balance target BP goals, cerebral perfusion and autoregulation to prevent worsening of tissue perfusion by aggressive BP lowering. The advent of intravenous and intra-arterial thrombolysis also requires emphasis on emergent management of accelerated hypertension to facilitate thrombolysis and post-thrombolysis care. This review aims at looking in depth at the traditional and newer clinical practices and evidence-based data on targets and methods of blood pressure control in cerebrovascular disease.

Key words: Cerebrovascular disease, target BP goals, thrombolysis

Magnitude of the Problem

The second most attributed cause of mortality and morbidity globally is stroke and it accounts for the third most common cause of disability.[1] Elevated blood pressure is a common modifiable risk factor as confirmed in several studies. Hypertension is observed in an estimated 64% of stroke patients with approximately 51% of stroke mortality being attributed to hypertension worldwide.[2,3] Screening and early optimal treatment of hypertension at community level presents many missed opportunities to reduce the burden of stroke. Hypertension contributes as a major risk factor for both ischemic and hemorrhagic stroke.[3] The relationship between hypertension and cerebrovascular disease risk is well established and the causal association has been confirmed with a progressively graded association with increasing BP values.[2] The relationship between BP and cerebrovascular events is continuous, making the distinction between normal BP and hypertension, based on cutoff BP values, somewhat ambiguous. Progressively higher BP value entails greater risk of stroke in both non-hypertensive and hypertensive range of BP values. The definition of hypertension is the level of raised BP above normal values at which the benefits

of treatment (either with lifestyle interventions or drugs) unequivocally outweigh the risks of treatment, as documented by clinical trials. More than two-third of individuals above age of 65 years are diagnosed to have hypertension. Although awareness and treatment of hypertension has improved over the past two decades, control rates are around 50%. The European Guidelines for the Management of Hypertension recommend aiming to achieve a target systolic BP to <140 mmHg for all patient categories, including independent elderly patients, with an ideal target of 130 mmHg for all patients if tolerated [Table 1].[4] Isolated systolic hypertension in the elderly also contributes to the risk of stroke. The deleterious contribution of hypertension as a risk factor in stroke is based on a continuum rather than a threshold effect. Epidemiological studies have concluded that optimal BP control reduces the risk of stroke and for every 10 mmHg control of systolic blood pressure by one-third in patients aged 60–79 years. This benefit is sustained up to BP level of 115/75 mmHg and is observed in all stroke subtypes, both genders, and all age groups. SBP ≥ 140 mmHg contributes to about 70% of the mortality and disability burden. Both office BP and home or ambulatory BP have an independent and

Table 1: Target BP goals in stroke or TIA

Age groups (years)	Systolic (mmHg)	Diastolic (mmHg)
18–65	Target to 130 or lower if tolerated	<80–70
65–79	Target to <140–130 if tolerated	<80–70
≥80	Target to <140–130 if tolerated	<80–70

continuous relationship with the incidence of cerebrovascular events. SBP has been found to be a better predictor of events than DBP after the age of 50 years.

Definitions and Pathophysiology

Acute hypertensive response in stroke is the elevation of blood pressure values above normal and baseline values within 24 h of onset of stroke symptoms.[5] About 75% of patients present with a concomitant acute hypertensive response in stroke and 50% have pre-existing hypertension.[6] JNC criteria define hypertension as persistent BP recordings > 140/90 mmHg on multiple separate occasions several days apart.[6] However to identify uncontrolled new-onset hypertension in stroke patients, acute hypertensive response is defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg demonstrated on two recordings taken 5 min apart within 24 h of stroke symptom onset. New-onset hypertension without a history of same is observed in 20% of patients with stroke. Although some of these patients may represent undetected and untreated chronic hypertension, transient stroke-specific mechanisms contribute to the BP rise in the immediate post-stroke period. Apart from pathophysiological mechanisms involved in chronic pre-existing hypertension, an increase in sympathetic tone with release of renin and constriction of arterioles results from stroke-related damage to sympathetic neurons in the brain located in prefrontal cortex and insula. Dysfunction of parasympathetic pathways also reduces carotid baroreceptor sensitivity in acute stroke. Acute headache, stress-induced catecholamine release infection, and other factors may further exacerbate the BP rise.[7] Raised ICP with compression of brainstem structures as part of Cushing's reflex also elevates the blood pressure. In the presence of raised ICP, a MAP of > 60 mmHg may be insufficient to maintain cerebral blood flow in the capillary bed. Hence, to avoid decline in tissue perfusion in the ischemic penumbra, rapid reduction of BP should be avoided. BP spontaneously decreases in two-thirds of patients in the 1st week following stroke, but one-third remain hypertensive and have a poor neurological outcomes.[8] *Post hoc* analyses from several acute stroke clinical trials suggest that as well as increased SBP, other hemodynamic variables including higher peak SBP, mean arterial pressure (MAP), pulse pressure, and increased SBP variability are each associated with poor functional outcome, early neurological deterioration, recurrent stroke, and death.[9]

Decision to Treat

One of the oldest and most vexing debates in stroke management pertains to the decision to treat hypertension in the immediate stroke period.[10] Although the debate has opposing views, no definitive answer has been firmly established even today. Several trials have compared active intensive lowering of blood pressure versus guideline-based lowering.[11] How, when, and speed of lowering blood pressure were more important than specific agent used for BP control.[12] Type of stroke and additional effects of antihypertensive agents on cerebral vasculature also influence outcomes. Intervention to control BP has to be initiated within the hyperacute stages of stroke, that is, < 6 h of onset for any beneficial effects to be seen.

The optimal treatment of elevated blood pressure in stroke is based on BP recordings, timing, type of stroke, presence of raised ICP, use of thrombolysis, coexisting medical disorders, and pharmacologic variables of antihypertensives.[13] The decision and strategy to treat hypertension in stroke do not have a one size fits all approach and have to be customized as per individual patient requirements.[13] AHA/ASA guidelines recommend maintaining a cerebral perfusion pressure of 60–80 mmHg in patients with suspected increase in ICP. The salvageable ischemic penumbra is prone to further irreversible damage if rapid drops in BP occur on institution of antihypertensive therapy.

Blood Pressure and Ischemic Stroke [Table 2]

In thrombolysis window period

Raised BP values are noted in approximately 60% of patients within 1 h of stroke symptom onset. Uncontrolled hypertension affects the decision making process and eligibility for thrombolysis in acute ischemic stroke which is time sensitive. Patients with only elevated BP as precluding factor for thrombolysis must be managed in an emergent manner to facilitate thrombolysis and a door to needle time of <60 min. Approximately 10% of patients who are otherwise eligible for t-Pa fail to meet thrombolysis eligibility due to acute hypertensive response. The management of hypertension in the acute stage depends on whether the patient is being planned for intravenous or intra-arterial thrombolysis or not.[13] The pre-thrombolytic BP goal of <185/110 has to be achieved rapidly using multiple agents and intravenous preparations and infusions if required.[13] Post-IV thrombolysis target BP <180/105 mmHg is the goal in first 24 h after treatment.[13] However, factors such as tissue perfusion, cerebral perfusion pressure, raised ICP, and avoidance of hypotension should be kept in mind in achieving these targets. Intra-arterial thrombolysis requires more stringent control and pre-procedure BP values <180/100 mmHg are recommended. During procedure, target BP values <10–20% of admission BP are an accepted goal if intra-arterial thrombolysis is used as monotherapy or BP <180/105 mmHg if used adjunctively with IV t-PA.[14] Extreme care should be exercised in patients undergoing endovascular treatment to avoid hypotension especially if general anesthesia is used. Systolic BP > 140 mmHg is required during procedure as lower values are predictors

Table 2: Blood pressure management and stroke

A. Ischemic stroke /TIA	
1. Acute setting	Treatment plans and target
- Patient eligible for IV thrombolysis	For BP ≥185/110 mmHg: Administer labetalol 10 mg over 1–2 min, may repeat 1 time; or start nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes for maximum 15 mg/h; or add other agents (hydralazine and enalaprilat)
- During and after reperfusion therapy	BP goal ≤180/105 mmHg
- Patients not eligible for acute reperfusion therapy	For SBP ≥220 mmHg or DBP 121–140 mmHg, administer labetalol IV or nicardipine as IV infusion, aiming for 10%–15% reduction of BP
	If DBP≥140 mmHg, give sodium nitroprusside as IV infusion, titrating the dose for a 10%–15% reduction of BP
2. Subacute setting	
- Patients with SBP ‡140 mmHg or DBP ‡90 mmHg (not treated previously)	Initiate BP therapy (Class I; level of evidence B)
- Patients with SBP <140 mmHg and DBP <90 mmHg	Initiation of BP therapy is of uncertain benefit (Class IIb; level of evidence C)
	Resume BP therapy (Class I; level of evidence A)
- Previously treated patients with known hypertension	Reasonable to achieve BP ≤140/90 mmHg as a target – except specific indications (Class IIa; level of evidence B
3. Specific indications	
- Recent lacunar stroke	SBP ≤130 mmHg (Class IIb; level of evidence B)
- Intracranial atherosclerosis (50%–99% stenosis major artery)	Target SBP ≤140 mmHg (Class I; level of evidence B)
B. Intracerebral hemorrhage	When SBP is 150–220 mmHg, acute lowering to 140 mmHg is reasonable.

of poor neurologic outcome post-endovascular treatment. Post-endovascular treatment if complete recanalization has been achieved a target SBP of 120–140 mmHg is maintained to lower the risk of reperfusion hemorrhage. If only partial recanalization has been achieved, only then SBP of up to 185 mmHg is maintained to facilitate collateral flow and clear microemboli from distal vasculature. BP control must maintain adequate cerebral perfusion and minimize reperfusion injury and spontaneous ICH.

Acute ischemic stroke not being considered for thrombolysis

In acute ischemic stroke not eligible for thrombolysis, optimal BP management should sustain collateral flow and minimize tissue damage in ischemic penumbra. Current guidelines recommend 15% reduction in BP values over 24 h only if BP values exceed 220/120 mmHg.[13] About > 20% reduction in MAP rapidly can compromise cerebral blood flow. Early initiation of antihypertensive therapy within 6 h is beneficial but later introduction of antihypertensive beyond 15 h may not change stroke outcomes. In view of the acute hypertensive response, patients with ischemic stroke and BP < 180/105 mmHg can be monitored and may not benefit from introduction of antihypertensive therapy. If the BP remains elevated > 140/90 mmHg, even after 72 h of stroke should be considered as hypertensive and treatment initiated.

Specific Situations in Acute Ischemic Stroke

Small vessel disease

Hypertension and lipohyalinosis play an important pathophysiological role in lacunar infarcts and small vessel disease. Achieving a target SBP< 130 mmHg has been shown to reduce the rate of all strokes, fatal strokes, and intracerebral hemorrhage in patients with MRI proven acute lacunar infarcts.[4]

Large vessel occlusion

A cautious reduction of 10/5 mmHg BP should be attempted with monitoring for neurological symptoms in patients with large vessel occlusion which is hemodynamically significant.[15] If neurologic symptoms attributable to a stenotic large artery develop on BP reduction, below a threshold BP should be maintained above the threshold and BP targets individualized. Patients with minor strokes and TIAs due to large vessel occlusion of 70–99% had lesser cerebrovascular events within 30 days had persisting benefits at 3 years if SBP was maintained in the range of 130–140 mmHg by antihypertensive therapy and lifestyle and aggressive medical management of other risk factors.

Raised Intracranial Pressure

Intracranial pressure is another important parameter to be considered in patients with large infarcts and cerebral hemorrhage. Systolic BP values more than 180 mmHg and

clinical suspicion of elevated intracranial pressure require cerebral perfusion pressure to be maintained between 61 and 80 mmHg. If there is no suspicion of raised intracerebral pressure, a moderate lowering of BP (160/90 mmHg) is adequate. If the systolic BP is in the range of 150–200 mmHg, acute lowering to 140 mmHg is probably safe.

Restarting Antihypertensives in Chronic Hypertension

The AHA/ASA guidelines recommend continuing earlier antihypertensive agents within 24 h of stroke in previously hypertensive patients with non-disabling strokes who are neurologically stable without signs of raised intracranial pressure and no hemodynamic mechanism of stroke.

- Recurrent stroke: In patients with pre-existing hypertension, a target BP of <140/90 mmHg or systolic pressure <130–135 mmHg is advisable as per the current guidelines.[16]
- For patients with recent lacunar ischemic stroke, lowering the systolic BP <130 mmHg may reduce the risk of a future intracerebral hemorrhage.

Intracerebral Hemorrhage

Hypertension plays a significant role in the pathogenesis of intracerebral hemorrhage and also hematoma expansion. Approximately a third of patients presenting with intracerebral hemorrhage develop hematoma expansion within 24 h. If SBP > 200 mmHg and MAP > 150 mmHg, aggressive reduction with IV antihypertensives or infusions is required.[8] A SBP > 180 mmHg or a MAP > 130 mmHg and ICP are suspected to be high then continuous ICP monitoring should be initiated and BP reductions initiated to maintain cerebral perfusion pressure between 60 and 80 mmHg. Lower BP levels for intervention may be considered if there are associated organ damages due to hypertensive urgency or emergency such as hypertensive encephalopathy, acute cardiac failure, and concomitant cardiac ischemia which are present. Studies have concluded that rapid reduction to a target of SBP < 140 mmHg in patients with intracerebral hemorrhage with BP values in the range of 150–220 mmHg SBP is safe.[17-20] In addition to absolute BP values, variations during the acute period also influence outcomes. Intravenous calcium channel blockers such as nicardipine or IV beta-blockers like labetalol are the drugs of choice in rapid control of BP because of short half-life and ease of administration. Nitrates can cause intracranial vasodilatation and have a propensity to increase ICP and hence are not used as primary agents. A MAP goal of 110 mmHg is recommended in patients with intracranial hemorrhage without raised ICP. Oral antihypertensive agents should be overlapped with IV preparations to transition from acute care to long-term BP goals. During acute-phase BP values may be persistently high due to a sympathoadrenal response and may require multiple antihypertensive agents but a downregulation of these drugs may be needed to prevent hypotension a few days or weeks later.[20-24]

Table 3: Take home points as per current guidelines

- Patients presenting with acute ischemic stroke and are otherwise eligible for IV tPA (except for severely elevated BP) can become thrombolysis candidates with rapid and efficient BP treatment.
- When thrombolysis is not an option, acute management of BP is a balancing act between maintaining cerebral perfusion and avoiding systemic adverse events due to persistently elevated BP.
- In the acute setting of ICH, rapidly lowering BP to <140/90 mmHg is safe and may be associated with improved radiographic and clinical outcomes.
- In the hyperacute setting of both ischemic and hemorrhagic strokes, initiation of continuous IV administration of newer agents may achieve treatment goals rapidly.

Choice of Antihypertensive Agents

All major categories of antihypertensive patients diminish stroke risk. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are more effective than other classes in some studies in preventing recurrent stroke. The choice of antihypertensive is based more on associated comorbid conditions rather than specific antihypertensive class. When emergent therapy is required for thrombolysis eligible candidates, short-acting IV preparations such as labetalol, hydralazine, esmolol, metoprolol, nicardipine, enalaprilat, nitroglycerin, and nitroprusside-clevidipine and nicardipine-urapidil are preferred. Oral therapy is discouraged as it may not achieve rapid BP control in thrombolysis eligible patients. If situations requiring rapid lowering of systolic BP, such as aortic dissection or pheochromocytoma, are not present, guidelines aim at reducing blood pressure by a maximum of 25% over the first hour, then to 160/100–160/110 mmHg over the next 2–6 h, then to normal over the next 24–48 h. For post-stroke long-term BP control, patients with other metabolic risk factors such as diabetes and dyslipidemia are relative contraindications for beta-blockers and thiazide diuretics which promote dyslipidemia and disruption of glycemic control.

Conclusion

Uncontrolled hypertension continues to be a modifiable risk factor with missed opportunities in prevention of strokes and achieving better outcomes in established stroke. Optimal BP control has to be customized based on individual patient factors such as age, pre-existing hypertension, absolute BP values and variability, time since stroke symptoms, thrombolysis eligibility, raised ICP, and available pharmacological agents. Better outcomes in stroke are achieved only when balance between BP control and cerebral and tissue perfusion is achieved [Table 3].

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*R*eview *A*rticle

Target BP Goals in Children/Adolescents

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Abstract

Ever increasing pandemic of obesity, hypertension (HTN), and other factors that may contribute significantly to the cardiovascular morbidity and mortality in adulthood has shifted the focus from management of HTN to its prevention. Tracking of adult HTN from childhood HTN, increasing recognition of reversible childhood markers of target organ damage and effective interventions, both pharmacological and non-pharmacological, have made it mandatory for the clinicians to control childhood HTN more aggressively although deleterious effects of HTN may not be as commonly seen as in adults. A thorough literature search was conducted to formulate the target blood pressure (BP) goals in children/adolescents, mainly based on the European and American guidelines. Reduction in systolic and diastolic BP to <90th percentile in children and <130/80 mm mercury in adolescents more than or equal to 13 years old is a consensus target BP goals in children. Reduction in BP levels <90th percentile in children and <130/80 in adolescents is a good control to prevent further progression. Prevention of early determinants of HTN, factors that determine BP tracking in childhood to adulthood and of end organ damage shall be the field of further research in this arena.

Key words: Childhood hypertension, goals, targets, treatment

Introduction

Childhood hypertension (HTN), increasingly being detected and being prevalent, has become a significant public health problem not only posing a therapeutic challenge but also being associated with increased fatality and morbidity. Cutoffs for different age groups for the diagnosis, difficulties with accurate measurements in childhood, poor adherence to medication due to dependency, and absence of enough evidences for target organ damage of this disease, which is less prevalent in children when compared to adults, makes monitoring of HTN and of its associated morbidities more complicated in pediatric population. Predisposition to adult HTN and increased cardiovascular events in adults mandate the clinician to treat and monitor the childhood HTN more aggressively.[1-2]

The Need for the Target BP Goals in Children and Adolescents

In adults, medication management reduces incidence of cerebrovascular accidents by 35–40%, myocardial infarction

by 15–25%, and cardiac failure by 64%.[3-6] Adequate and safe control of HTN in childhood and adolescents will have beneficial effects on these comorbidities as evidenced by the following.

a. HTN has been shown to track (or persist) from childhood to adulthood. The origins of HTN in adulthood extend to childhood ages, and the frequency of increased blood pressure (BP) in adolescence progresses to HTN by 7% yearly.[1,7,8] However, the strength of tracking has been shown to vary between studies and depends on baseline age, length of follow-up, and susceptibility alleles. It is evidenced that approximately 10% of adult HTN can be prevented if elevated BP in childhood can be controlled. In view of the global burden of disease attributable to adult HTN, even a small shift in the control of pediatric BP levels (left or right) will have a significant impact on morbidity and financial cost.[9]

b. HTN in childhood and adolescence, no more considered as a benign disease, is known to have significant target organ damage at diagnosis. Although clinically detectable

ischemic heart disease is rare in childhood, it is known that the extent of target organ damage is the main risk factor for future cardiovascular events.[10] Current evidence suggests that preclinical markers of cardiovascular health in adulthood associate with multiple early-life risk factors such as birth size and adiposity, BP, own and parental smoking, blood lipid levels, family history, and socioeconomic factors (among others). Therefore, primary prevention by controlling the early-life risk factors could lead to a lifelong benefit in the growing era of pandemic of obesity and HTN[9,11-13]

c. Cardiovascular disease begins early in life in children with HTN and other comorbidities and has a long manifest stage before clinical end-points such as myocardial infarction and stroke present.[9]

Current Guidelines for Control and Monitoring of BP in Children and Adolescents

American academy of Paediatrics published "Clinical Practice Guideline for Screening and Management of High BP in Children and Adolescents" by Flynn *et al*. in the year 2017.[14] These guidelines provide clear-cut recommendations on diagnosis, evaluation, and management of childhood HTN aiming at practicing clinicians seeing outpatients. Salient features are as follows:

a. To start BP measurement at age 3 years (No change in old recommendation) and annual measurement is recommended unless risk factors (to be measured at every health-care visits if obesity, are taking medications known to increase BP, have renal disease, a history of aortic arch obstruction or coarctation, or diabetes) are present

b. Doctors and other health care workers should make a diagnosis of HTN if a child or adolescent has auscultatory confirmed BP readings ≥95th percentile (or ≥130/80 in adolescents ≥13 years of age) at three different visits

c. Ambulatory BP Monitoring (ABPM) should be performed for confirmation of HTN in children and adolescents with office BP measurements in the elevated BP category for ≥1 year or with Stage 1 HTN over three clinic visits. Routine performance of ABPM should be strongly considered in children and adolescents with high-risk conditions to assess the severity of HTN and determine if abnormal circadian BP patterns are present, which may indicate increased risk for target organ damage. ABPM may be used to assess treatment effectiveness in children and adolescents with HTN, especially when clinic and/or home BP measurements indicate insufficient BP response to treatment

d. Home BP monitoring should not be used to diagnose HTN, masked HTN or white-coat HTN but may be a useful adjunct to office and ambulatory BP measurement after the diagnosis

e. There is no need to evaluate extensively for secondary causes for HTN in children and adolescents ≥6 years of age, if they have a positive family history of HTN, are overweight or obese, and/or do not have history or physical examination findings suggestive of a secondary cause of HTN

f. Echocardiography to be performed to assess for cardiac target organ damage (left ventricular mass, geometry, and function) at the time of consideration of pharmacologic treatment

g. At the time of diagnosis, clinicians should provide advice on the Dietary Approaches to Stop HTN (DASH) diet and recommend moderate to vigorous physical activity at least 3 to 5 days per week (30–60 min per session) to help reduce BP

h. Definition of HTN (Term prehypertension deleted) refer to Table 1

i. New BP table (with age and height percentile) refer to Table 2

j. Patient evaluation and management by BP level refer to Table 3.

Target BP in Management of HTN in Children and Adolescents

The remarkable increase in the prevalence of pediatric HTN over the last two decades mirroring the rise in obesity and sleep disorders in children mandates the clinicians to be familiar with the management of HTN in children by pharmacological and non-pharmacological means. However, absence of large, well-structured safety and efficacy trials in children, challenges in understanding of pharmacokinetics and unknown risk of life-long exposure to antihypertensive medications, and pharmacotherapy in childhood HTN challenging.[15]

The following point's needs to be considered while deciding the target BP goals in children

a. The extent of antihypertensive interventions to will depend largely on the relative risk of BP levels and the pathological changes in target organs. Thus, well conducted longitudinal studies are required in hypertensive pediatric population to determine the advantages and risks of interventions in preventing cardiovascular and other short- and long-term end-organ injury related to the level of BP.

b. The cause and effects of HTN in kidney diseases need to be clearly understood as they are the major target organs in pediatric population.

Table 1: Definition of hypertension[14]

For children aged 1–13 years	For children aged >13 years
Normal BP: <90th percentile	Normal BP <120/<80 mmHg
Elevated BP: >90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	Elevated BP: 120/<80–129/40 mmHg
Stage 1 HTN: >95th percentile to <95th percentile + 12 mmHg, or 130/80–139/89 mmHg (whichever is lower)	Stage 1 HTN: 130/80–139/89 mmHg
Stage 2 HTN: >95th percentile + 12 mmHg, or >140/90 mmHg	Stage 2 HTN: >140/90 mmHg (whichever is lower)

Table 2: New BP table (with age and height percentiles)[14]

Age (years)	BP percentile	SBP (mmHg) Height percentile or measured height							DBP (mmHg) Height percentile or measured height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th+12 mmHg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th+12 mmHg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th+12 mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76

Table 3: Patient evaluation and management by blood pressure level[14]

BP category	BP screening schedule	Lifestyle counseling (weight, nutrition)	Check upper and lower extremity BP	ABPM	Diagnostic evaluation	Initiate treatment	Consider sub-specialty referral
Normal	Annual	X					
Elevated BP	Initial measurement	X					
	Second measurement: Repeat in 6 months	X	X				
	Third measurement: Repeat in 6 months	X		X	X		X
Stage 1 HTN	Initial measurement	X					
	Second measurement: Repeat in 1–2 weeks	X	X				
	Third measurement: Repeat in 3 months	X		X	X	X	X
Stage 2 HTN	Initial measurement	X	X				
	Second measurement: Repeat/refer to specialty care within 1 week	X		X	X	X	X

c. Management of hypertensive emergencies is another area of concern in pediatric population in view of significant mortality and morbidity associated with it.

d. Absence of a well-tolerated, affordable and cost effective, and antihypertensive intervention in reducing the mortality and morbidity in this vulnerable pediatric population makes it still more difficult to define the targets.

e. More than 50% of hypertensive adults have additional risk factors. The common ones are diabetes mellitus (15–20%), lipid disorders (elevated low-density lipoprotein-cholesterol and triglycerides (30%)), overweight-obesity (40%), hyperuricemia (25%) metabolic syndrome (40%), and unhealthy lifestyle habits (e.g., smoking, high alcohol intake, and sedentary lifestyle). The presence of one or more

additional cardiovascular risk factors proportionally increases the risk of coronary, cerebrovascular, and renal diseases in hypertensive adults.[3,16] Many of these comorbid lifestyle related diseases are also associated with HTN in children and hence, the increased risk.

Hence, the goals for the treatment of HTN in pediatric population, include achieving a level that decreases the risk for target organ damage (which are, to a large extent reversible) and reduces the risk for HTN and related cardiovascular diseases in adulthood.[14]

The Treatment Goal of Antihypertensive Therapy

"Clinical Practice Guideline for Screening and Management of High BP in Children and Adolescents" by Flynn *et al.* in the year 2017 published by American academy of Paediatrics has given the following practical guidelines.[14] We, In India, follow the same guidelines as these guidelines are applicable in Indian children also.

Target BP Goals in Children and Adolescents, in General

- Key action statement 19 "Reduction in systolic and diastolic BP to <90th percentile in children and <130/80 mm mercury in adolescents more than or equal to 13 years old (Grade C, moderate recommendation).

  These recommendations were based on the predictions and progression of childhood HTN into adult HTN and effects of childhood HTN on cardiovascular health in adults.[17-19] In a cohort of 4210 participants (mean follow-up, 23 years), Juhola *et al.* had concluded that individuals with persistently elevated BP from childhood to adulthood had increased risk of carotid atherosclerosis. This risk was reduced if elevated BP during childhood resolved by adulthood.[18] Sladowska *et al.* found that antihypertensive treatment leads to significant improvement and normalization of the left ventricular geometry. However, patients with concentric hypertrophy are less prone to normalized geometry and may require more intensive treatment[10,19]
- Key Action Statement 22: ABPM may be used to evaluate treatment effectiveness especially when clinic and/or home measurements indicate insufficient response (Grade B, moderate recommendation).

  These recommendations were based on the effectiveness of ABPM in achieving the target control of HTN in children.[20-22]

Target BP Goals in Children/Adolescents, with Kidney Diseases

- Key Action Statement 23: Children and adolescents with Chronic kidney disease should be evaluated for HTN at each medical visit; children with HTN should be treated to lower 24-h Mean arterial pressure to <50th percentile by

ABPM; and regardless of apparent control of BP with office measures, children, and adolescents with chronic kidney disease and a history of HTN should have BPs assessed by ABPM at least yearly to screen for masked HTN (Grade B; strong recommendation).

Intensified BP control confers a substantial benefit with respect to renal function among children with chronic kidney disease.

The recommendations were based on the fact that the treatment of childhood and adolescent HTN with chronic kidney disease might slow the progression of or reverse end organ damage.

In a study of 385 children, 3–18 years of age, with chronic kidney disease, Wuhl *et al.* described that achievement of BP targets and a decrease in proteinuria were significant independent predictors of delayed progression of renal disease.[23,24]

Target BP Goals in Children/Adolescents, with Diabetes Mellitus

- Key action statement 26: Children and adolescents with diabetes should be evaluated for HTN at each medical visit and treated if BP is ≥95th percentile or >130/80 mmHg in adolescents ≥13 years of age (Grade C, moderate recommendation).

These recommendations were based on the evidences that early detection and treatment of childhood HTN with type 1 and type 2 diabetes mellitus might reduce future cardiovascular and kidney disease. The prevalence of elevated BP in youth with type 1 diabetes mellitus was 5.9% ($n = 3691$); and in type 2 was 23.7% ($n = 410$) ($P < .0001$), hence, the need for intense screening.[25-27]

Target BP Goals in Children/Adolescents, with Acute Severe HTN

- Key Action Statement 27: In children and adolescents with acute severe HTN and life-threatening symptoms, BP should be reduced by no more than 25% of the planned reduction over the first 8 h (grade expert opinion D, weak recommendation). The ultimate short-term BP target in such patients should generally be around the 95th percentile.

These recommendations were based on the fact that acute severe HTN may precipitate encephalopathy, acute kidney injury, and congestive heart failure in children and a rapid reduction in the BP my result in further complications.[24,28] Patel *et al.* in their review observed that a larger rapid reduction in pressure can worsen end-organ function, leading to worsening neurological status, and possibly cause cerebrovascular compromise and should therefore be avoided.[28]

Target BP Goals in Children/Adolescents, who are in Competitive Sports

- Key Action Statement 29 – Children and adolescents with HTN should receive treatment to lower BP below Stage 2

Table 4: Summary of key action statements (KAS) for target BP in children and adolescents

No	KAS	Recommendations	Quality of evidence	Strength of recommendations	References
1	19	Reduction in systolic and diastolic BP to <90th percentile in children and <130/80 mm mercury in adolescents more than or equal to 13 years old	Grade C	Moderate	[17-19]
2	22	ABPM may be used to evaluate treatment effectiveness especially when clinic and/or home measurements indicate insufficient response	Grade B	Moderate	[20-22]
3	23	Children and adolescents with chronic kidney disease should be evaluated for HTN at each medical visit; children with HTN should be treated to lower 24-h Mean arterial pressure to <50th percentile by ABPM; and regardless of apparent control of BP with office measures, children and adolescents with chronic kidney disease and a history of HTN should have blood pressures assessed by ABPM at least yearly to screen for masked HTN	Grade B	Strong	[23,24]
4	26	Children and adolescents with diabetes should be evaluated for HTN at each medical visit and treated if BP is ≥95th percentile or >130/80 mmHg in adolescents ≥13 years of age	Grade C	Moderate	[25-27]
5	27	In children and adolescents with acute severe HTN and life-threatening symptoms, BP should be reduced by no more than 25% of the planned reduction over the first 8 h.	Grade D	Weak	[24-28]
6	29	Children and adolescents with HTN should receive treatment to lower BP below Stage 2 thresholds before participating in competitive sports	Grade C	Weak	[29,30]

(Derived from Flynn et al., Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[14]).
HTN: Hypertension; ABPM: Ambulatory blood pressure monitoring; BP: blood pressure

thresholds before participating in competitive sports (Grade C, weak recommendation)

- Black et al. in their research article stated that both systolic and diastolic pressures increase during resistance (static or isometric) exercise, and strenuous aerobic or resistance exertion may precipitate myocardial infarction and sudden death in susceptible, untrained people. In a person with normal BP at rest, a rise in systolic BP to >200 mm Hg during an exercise treadmill test may suggest underlying HTN. This person may benefit from further investigation, including 24-h ABPM, to document true sustained HTN. A hypertensive responsive to exercise testing may also indicate an independent risk for cardiovascular events and mortality.[29] Similar observations were also made by McCambridge et al.[30]

These are summarized in Table 4

Conclusions

There are enough evidences to prove the assumptions that BP tracks from childhood to adulthood and that an increased BP in childhood is likely to help predict adult HTN. The end organ damage that may predispose the adverse outcome in children and adolescents begins in the childhood and is reversible to a very large extent, if target BPs could be achieved with an early diagnosis, prompt management (both pharmacologically and non-pharmacologically) and a close follow-up. Future studies should concentrate on early determinants of HTN in children, on identifying the factors that determines BP tracking in infancy, childhood, and adolescence and on early markers of end organ damage.

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Review Article

Hypertension and Heart Failure

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Abstract

Background: Hypertension is the leading cause of heart failure worldwide leading to adverse cardiovascular outcomes. However, little is known about the target blood pressure goals in patients with heart failure. **Body:** Chronic hypertension leads to the left ventricular hypertrophy and further remodeling may cause heart failure with preserved ejection fraction and eventually heart failure with reduced ejection fraction. Various societal guidelines have come forward to decide on target blood pressure goals in specific high-risk populations. However, only some evidence is available on target blood pressure goals in heart failure patients and most of these data have been extrapolated from other studies. With the data currently available, treating hypertension at a level of 140/90 mmHg and titrating to 130/80 mmHg in patients with heart failure looks well justified. However, targeting blood pressure below 120/70 mmHg remains a gray zone and should ideally be avoided. **Conclusion:** Further prospective studies are needed to define target blood pressure goals in patients with heart failure.

Key words: Heart failure, Hypertension, J Curve

Introduction

Hypertension is defined as blood pressure above 140/90 mmHg and is a leading cause for the development of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[1] Although equally prevalent in both the forms of heart failure, it remains more common in HFpEF patients with prevalence of up to 90%, compared to HFrEF.[2-4] Various guidelines have recommended not only different staging systems for hypertension but also the target blood pressure (BP) goals and therapeutic drug usage in specified populations. Although the target BP goals and therapeutic strategies for BP control in HF patients have been mentioned in different guidelines, robust data are still lacking. Most of the recommendations for optimal BP control in HF patients have been extrapolated from other high-risk populations where intensive BP control showed better long-term cardiovascular (CV) outcomes, however, at an increased risk of adverse effects. Chronic hypertension causes pressure overload leading to ventricular hypertrophy which is initial compensatory mechanism and preserves cardiac output. Subsequently, the left

ventricle (LV) dilates as remodeling occurs and LV starts to decompensate. Remodeling occurs due to activation of renin-angiotensin system, sympathetic nervous system, and deposition of extracellular matrix. Diastolic dysfunction or the so-called HFpEF is the primary manifestation of hypertensive heart failure. It is only in the later stages that dilated cardiomyopathy leading to HFrEF sets in. Long-term prognosis is poor with increased mortality in hypertensive patients with HF. Treating hypertension can significantly reduce incident of HF and HF hospitalization, especially in old population.[5-7]

Prevalence of Hypertension in Patients with Heart Failure

The Framingham Heart Study, which involved 5143 patients (20 years follow-up) showed that the hypertension precedes the progression of heart failure among 91% newly diagnosed heart failure patients. Male and female cohorts showed 2- and 3-fold increase risk of developing heart failure, respectively, compared to normotensive individuals.[8] The Korean Heart Failure (KorHF) study (2004–2009) recruited 3200 patients with HF

and showed that 36.7% of the patients had hypertensive HF.[9] ATTEND registry (2002–2011) conducted in Japan with 4842 patients suggested that majority of hospitalized heart failure patient are the elderly with either new-onset hypertension or a history of hypertension (overall 70% were hypertensive).[10] In KorAHF study (2011–2014), 62% of patients had a history of hypertension, however, only 4% decompensation were attributed to hypertension.[11] ESC-HF-LT (2011–2013) registry involving 12,440 subjects suggested the coexistence of hypertension and heart failure among 65.6% of patients.[12] Similarly, ASIAN-HF showed 55.4% coexistence of heart failure and hypertension.[13] The ADHERE (2002–2004) registry, involving 1,59,168 subjects, suggested that 69% of subjects with heart failure with reduced ejection fraction and 77% of the subjects with heart failure with preserved ejection fraction had hypertension.[14] However, contrary to other studies, ADHERE registry showed that almost 30% of the acute decompensation were caused by hypertension and this was more common in patients with preserved ejection fraction.

Why We Need Optimal BP Control in HF Patients?

There is clear evidence for linear association between hypertension and cardiovascular event in the general population. However, association between blood pressure and clinical outcomes in HF patients is poorly understood, which creates a challenge in managing them. The J curve effect reflects an inverse relationship between low blood pressure and cardiovascular outcomes. This effect is seen predominantly in patients with preexisting coronary artery disease (CAD) and hypertension and does not appear in stroke or renal disease as the coronaries are perfused during diastole, whereas the renal arteries and carotids are perfused in systole. However, as most of the data are derived from trials without HF patients, it is difficult to extrapolate the existence of J-shaped curve and optimal blood pressure for HF patients. J shape relationship between systolic blood pressure (SBP) and diastolic blood pressure (DBP) with all-cause and cardiovascular mortality among HF patients has been demonstrated in observational study. That means cardiovascular events may increase at both too high and too low levels of blood pressure. One of the observational studies demonstrated that at a nadir of SBP/DBP of 132/74 mm of Hg, there was a reverse J association between on treatment BP and long-term mortality in HF patients. This suggests that the too low BP can be actually harmful for the HF patients and cannot be considered optimum target.[15,16] Low BP might be related to severe LV dysfunction and low cardiac output which are actual causes for the adverse clinical outcome rather than BP itself. This is supported by evidence for resynchronization therapy which demonstrated significant increase in BP and reduced in mortality and HF hospitalization in patients with lower baseline BP which improved due to device-related improvement in cardiac function. Whether the relationship between SBP and mortality in HF patients follows a linear or non-linear trend is still controversial.[17-19]

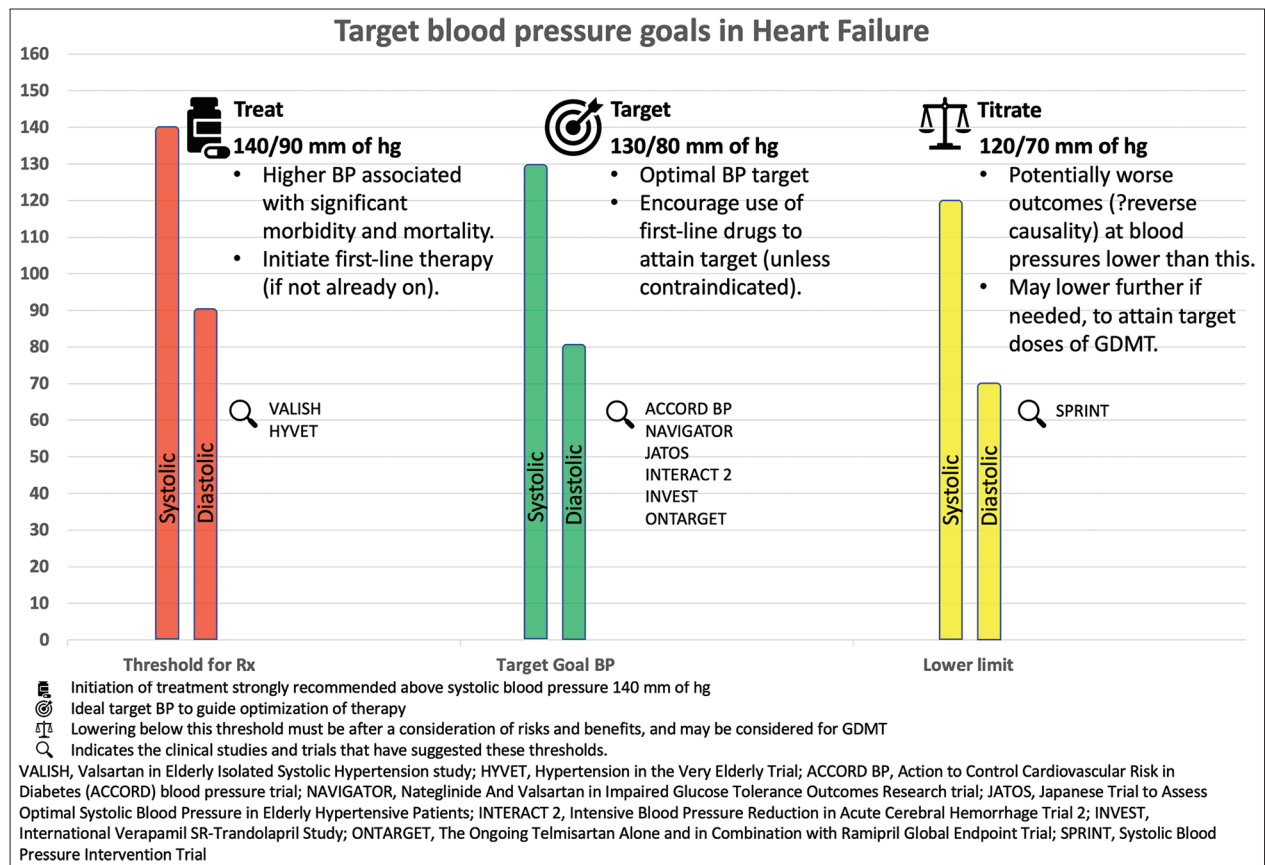### Guideline-recommended Treatment for Hypertension in HF

Many randomized controlled trials (RCTs) and guidelines exist currently for the management of arterial hypertension including European Society of Cardiology (ESC) 2018 hypertension guidelines, American College of Cardiology/American Heart Association (ACC/AHA) 2017 hypertension guidelines, and International Society of Hypertension(ISH) 2020 guidelines.[1,20,21] Although the drugs used in all these guidelines remain the same, there may be subtle alterations in step-wise management. There are no RCTs comparing the different antihypertensive drugs and treatment goal in HF patients. Most of the data existing are from the heart failure trials and guidelines where these drugs have shown mortality benefits in patients with HFrEF. All recommendations have been derived from other trials in which intensive BP reduction showed significant benefit in CV outcomes. This suggests BP reduction if the baseline BP ≥ 140/90 mmHg, similar to general population without HF. However, ideal BP target in HF has not been studied in RCTs.[1]

Target BP in Patients with HFrEF and HFpEF

No RCTs have been done in patients with hypertension and heart failure to evaluate the ideal BP targets. Hence, the current recommendations are based solely on the expert consensus. According to major guidelines, target SBP of <130 mmHg in HFrEF and HFpEF patients on the basis of systolic blood pressure intervention trial (SPRINT) trial is recommended. The trial compared intensive BP control to standard BP control. However, it was prematurely terminated at 3 years as intensive BP group showed superiority in the form of primary outcome of CV event, stroke, HF, and CV mortality. However, it is not justifiable to extrapolate the results of SPRINT trial to HF patients as the trial had excluded HF patients with EF less than 35% or who had symptomatic heart failure 6 months before enrollment.[7] Apart from this, these targets might have been formulated from trials where other high-risk population were studied such as coronary artery disease, peripheral vascular disease, stroke or TIA, and diabetes mellitus[22-29] [Figure 1].

The 2017 ACC/AHA/Heart Failure Society of America (HFSA) guidelines for the management of HF have recommended a BP goal of <130/80 mmHg, whereas the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), and the ESC HF guidelines have opted not to follow an intensive BP target of <130/80 mmHg.[30] According to ESC 2018 hypertension guidelines, in patients with HFrEF, BP should be lowered if baseline BP is ≥140/90 mmHg. However, it remains a matter of debate how low the BP should be lowered in HF patients. However, as per most of the published data, outcome for HF patients with BP <120/70 mmHg remains poor.[14] [Figure 2].

HFpEF patients commonly have multiple comorbidities and that may adversely affect outcome and complicate management. Same BP threshold and drugs used for HFrEF are advised for HFpEF.[1,20,21]

Target blood pressure goals in Heart Failure

Treat
140/90 mm of hg
- Higher BP associated with significant morbidity and mortality.
- Initiate first-line therapy (if not already on).

VALISH
HYVET

Target
130/80 mm of hg
- Optimal BP target
- Encourage use of first-line drugs to attain target (unless contraindicated).

ACCORD BP
NAVIGATOR
JATOS
INTERACT 2
INVEST
ONTARGET

Titrate
120/70 mm of hg
- Potentially worse outcomes (?reverse causality) at blood pressures lower than this.
- May lower further if needed, to attain target doses of GDMT.

SPRINT

Threshold for Rx   Target Goal BP   Lower limit

Initiation of treatment strongly recommended above systolic blood pressure 140 mm of hg
Ideal target BP to guide optimization of therapy
Lowering below this threshold must be after a consideration of risks and benefits, and may be considered for GDMT
Indicates the clinical studies and trials that have suggested these thresholds.
VALISH, Valsartan in Elderly Isolated Systolic Hypertension study; HYVET, Hypertension in the Very Elderly Trial; ACCORD BP, Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial; NAVIGATOR, Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research trial; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; INTERACT 2, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2; INVEST, International Verapamil SR-Trandolapril Study; ONTARGET, The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; SPRINT, Systolic Blood Pressure Intervention Trial

Figure 1: Diagram summarizing the various targets BP in non-heart failure high-risk population along with the evidence

AHA Hypertension Guidelines 2017

- Threshold to start Rx 130/80 mm of hg
- Target BP <130/80 mm of hg
- **HFrEF**
  - ARNI, ACEis, ARBs, MRAs, diuretics, beta-blockers
  - Non-dihydropyridine CCBs harmful/ no benefit
- **HFpEF**
  - First line: diuretics for hypertension if symptoms of volume overload
  - Second line: ACEis, ARBs, MRAs
  - Third line: beta blockers, CCBs, alpha blockers
  - Avoid nitrates

ESC/ESH Hypertension Guidelines 2018

- **HFrEF**
  - Threshold BP≥140/90 mmHg if not already on treatment
  - Avoid BP < 120/70 mm Hg (unless further lowering is a result of GDMT)
  - First line: Beta-blockers, ACEI/ARB, ARNI, and MRA
  - Second line: dihydropiridine CCB
  - Diuretics for symptomatic relief
  - Avoid Non-dihydropiridine CCB, alpha-blockers, centrally acting agents
- **HFpEF**
  - Optimal strategy not known
  - Target systolic BP < 130 mm of hg

ISH Hypertension Guidelines 2020

- Threshold for treatment 140/90 mm of hg
- Target for treatment < 130/80 but > 120/70 mm of hg
- **HFrEF**
  - First line: ARNI, ACEis, ARBs, Beta-blockers MRAs
  - Second Line: dihydropyridine CCBs
  - Diuretics for symptomatic relief
- **HFpEF**
  - Similar threshold and target values
  - Optimal strategy not known

AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blocker; BP, blood pressure; CCB, calcium-channel blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure

Figure 2: Summary of recommendations for target blood pressure goals by key guidelines in heart failure patients

Management of Hypertension IN Patients with HFrEF and HFpEF

Most of the drugs which are approved in guideline directed medical therapy of HFrEF such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), beta-blockers, angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs) have potential to reduce BP. However, this CV benefit is

directly related to BP reduction or not is still controversial.[31-38] Antihypertensive medication is commonly needed for HFpEF patients but optimum strategy is unknown. Till date, no drug has clearly shown benefit in the form of decrease in morbidity and mortality in HFpEF patients. Hence, optimal therapy remains symptomatic improvement and improving quality of life. Reduction in BP can lead to the regression of the left ventricular hypertrophy (LVH), accompanied by a reduction of CV events and mortality. ACE/ARB and CCB are more effective for LVH regression than beta-blockers or diuretics.[39-41] Although evidence for the management of HTN in HFpEF is limited, guidelines recommend RAAS blocker such as ACEI/ARBS as first-line drugs.[42-45]

Management of Hypertension in Special Population

Hypertension should not only be seen as a comorbid condition which can present with HFpEF but the management of hypertension in other comorbid conditions which can present with heart failure deserves a mention. This special population includes advanced age, patients with chronic kidney disease (CKD), patients with diabetes mellitus, and patients with atrial fibrillation.[46] In patients with advanced age, optimal BP control not only reduces the chances of major events such as intracranial hemorrhage and cerebral infarction but may also reduce the risk of dementia. One should ideally aim for conservative targets like SBP <140 mmHg and avoid achieving intensive goals. In patients with diabetes mellitus, ACEIs/ARBs remain to be the first-line therapy in view of their ability to regress left ventricular hypertrophy and prevent the progression of microalbuminuria. In patients with chronic kidney disease, ACEIs/ARBs remain the first-line therapy (when not contraindicated) along with dihydropyridine CCB. Hypertension remains to be an important risk factor for the development of atrial fibrillation and minimum three blood pressure recording should be for accurate diagnosis and treatment. Beta-blockers and non-dihydropyridine CCB are recommended for rate control in AF with fast ventricular rate, however, latter should be avoided in patients with HFrEF.

Summary

Uncontrolled hypertension beyond a threshold of 140/90 mmHg is clearly associated with an increase in long-term risk of adverse events in the general population. Data on the effect of hypertension and benefit from treatment on the long-term outcomes in heart failure are primarily extrapolations from studies that excluded patients with heart failure. Further thoughtfully designed and adequately powered studies are required to determine optimal targets for blood pressure reduction in heart failure (HFrEF as well as HFpEF). At present, however, major societal guidelines recommend a threshold of 140/90 mm of Hg for initiation of treatment in heart failure as well. A systolic blood pressure of 130 and diastolic of 80 mm of Hg should be targeted. Lowering beyond a blood pressure of

120/70 must be accompanied by a risk–benefit analysis and may be considered if further drug therapy is necessary to improve the overall prognosis in patients with heart failure.

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*R*eview *A*rticle

Target Blood Pressure in Diabetes Mellitus: A Review

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Abstract

Hypertension and diabetes mellitus (DM) are major risk factors for atherosclerotic cardiovascular diseases (ASCVD). The prevalence of hypertension is more in people with DM compared to general population augmenting the risk of ASCVD. A systolic blood pressure (SBP) reduction below 140 mmHg in diabetes subjects is known to reduce cardiovascular events and mortality beyond doubt in several trials. A SBP ≤130 mmHg should be targeted in individuals with high ASCVD risk scoring with careful monitoring for electrolyte imbalances and renal function. A target SBP of 130–139 should be targeted in elderly diabetes individuals with less strict control in patients with autonomic neuropathy and low diastolic BP (DBP). A DBP target of ≤80 mmHg should be attained in diabetes subjects with hypertension.

Key words: Diabetes mellitus, Hypertension, Artherosclerotic cardiovascular diseases

Introduction

Individuals with diabetes mellitus (DM) are 2–4 times more prone to develop atherosclerotic cardiovascular diseases (ASCVD) than general population and often are affected at younger age. ASCVD is the leading cause of mortality and morbidity in diabetes patients. ASCVD accounts for 25% of all deaths in India, higher than the global average as per Global Burden of Disease study.[1] Several clinical trials have established the relation of high blood pressure (BP) with ASCVD. A BP of ≥140/90 mmHg was strongly associated with stable angina, myocardial infarction, and intracerebral hemorrhage even in non-diabetes subjects.

Hypertension is more common in people with type 2 diabetes than in the general population and *per se* is a major risk factor for ASCVD. The prevalence of hypertension in adult DM patients is estimated to be 73.6% in the US population. Similar hypertension prevalence was found by Gupta *et al.* among Indian diabetes population with ASCVD risk.[2,3] Patients with DM often have metabolic syndrome comprising hypertension, obesity, and dyslipidemia. The coexistence of DM and hypertension leads to major adverse cardiovascular events such as myocardial infarction, stroke, and microvascular complications such as retinopathy and nephropathy.

The United Kingdom Prospective Diabetes Study (UKPDS36) group evaluated the effect of high BP on macrovascular and microvascular complications. A systolic BP (SBP) of ≥160 mmHg had twice as high macrovascular complications as individuals with SBP <120 mmHg. There was an increase in both microvascular and macrovascular complications above SBP of 120 mmHg.[4] This trial highlights the association between hypertension in diabetics and complications of diabetes potentially opening a window for further trials.

Effect of BP Control in Type 2 DM

UKPDS 38 evaluated the potential benefit of BP regulation in DM. Subjects in the intensive BP control arm with target BP ≤150/90 mmHg had significantly reduced all-cause mortality compared to less tight control arm in whom BP target was ≤180/105 mm of Hg. The median BP achieved in the intensive arm and less tight control arm were 144/82 mmHg and 154/82, respectively. The risk of stroke, myocardial infarction, and heart failure was significantly lesser in the intensive BP control arm. There was a linear relationship between SBP reduction up to 120 mmHg and adverse outcomes. This trial opened up the

potential benefits of BP regulation in DM individuals in the early 2000.[5]

The Action in Diabetes and Vascular Disease trial: ADVANCE trial compared intensive BP reduction versus placebo in diabetes individuals with pre-existing macrovascular or microvascular risk complications. The mean BP at entry to the trial was 145/81 mmHg and 41% patients had BP<140/80 mmHg. A SBP reduction of 5.6 mmHg and a diastolic BP (DBP) reduction of 2.2 mmHg were seen in the active arm compared to placebo. A relative risk of major and minor cardiovascular event reduction of 9% was seen in the active arm during follow-up for 4.5 years. There was no significant reductions in major and minor cardiovascular events when assessed individually.[6]

A BP target of 130/80 mmHg recommended by Joint National Committee (JNC) on prevention, detection, and evaluation of high BP in 2007 in the JNC7 report. This was widely prescribed by the scientific bodies such as American Diabetic Association (ADA), European Society of Cardiology (ESC), and European Society of Hypertension (ESH). However, the evidence for this target were based on small observational studies.[7,8] The Normotensive Appropriate BP Control in Diabetes failed to show reduction in cardiovascular events or nephropathy in patients with intensive BP target of ≤130/80 contrary to JNC7 recommendation. However, there was reduction in stroke, retinopathy progression, and albuminuria in these patients.[9]

The Action to Control Cardiovascular Risk in Diabetes-BP arm (ACCORD-BP) study of 2010 targeted a much lower target of BP, <120 mmHg. At 4.7 years follow-up, there was no difference in the cardiovascular diseases (CVD) outcomes in the intensive group (SBP target <120 mmHg) versus the standard group (SBP target <140 mmHg). Incidence of stroke was less in the intensive group. These beneficial effects were upset by increased incidence of side effects such as hyperkalemia, syncope, arrhythmias, and increased serum creatinine levels.[10] Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial showed no CVD benefit in SBP reduction below 130 mmHg. There was an increase in CVD mortality in the intensive study group (SBP <125 mmHg).[11]

In the SBP Intervention Trial (SPRINT), intensive SBP target of <120 mmHg versus standard SBP control of <140 mmHg was studied. Intensive SBP target group had 25% reduction in the risk of MI, stroke, heart failure, and death due to CVD. The main benefit of this study was in the age group of >75 years. There was increase in acute kidney injury, syncope, and electrolyte abnormalities in the intensive control group.[12] Diabetes individuals with hypertension were excluded from this trial. A meta-analysis of 13 randomized control trials on hypertension with DM by Bangalore et al showed 10% reduction in all-cause mortality with intensive SBP control <130mmHg. However, there was no difference in micro- and macrovascular events. In another meta-analysis of 49 studies, SBP reduction from initial BP >150 mmHg showed reduction in all-cause mortality, stroke, and myocardial infarction. There was no benefit of BP reduction in individuals with baseline SBP <140 mmHg.[13,14]

Benefits of lowering the DBP in diabetics were shown in hypertension on target (HOT) trial. DBP lowering beyond 80 mmHg showed reduction in incidence of stroke, MI, and CVD-related deaths.[15]

Recommendations by Various Bodies on Target BP in Type 2 DM

The eighth JNC 8 report of 2014 recommends initiating treatment for hypertension in patients with diabetes with BP is >140/90 mmHg. A SBP target of <140 mmHg and DBP target of <90 mmHg is recommended.[16] International Diabetes Federation clinical practice recommendation for managing type 2 DM of 2017 suggests a SBP target between 130 and 140 mmHg and DBP target of <80 mmHg. IDF recommends to reduce SBP below 130mmHg in patients with microvascular complications, especially albuminuria.[17]

The 2017 AHA/ACC guidelines recommend initiation of antihypertensive therapy at BP levels >130/80 mmHg or higher to target a BP <130/80 mmHg.[18] ESC and ESH guidelines of 2018 recommend treatment for people with DM with BP ≥140/90 mmHg. Following recommendations were given for people with DM and hypertension. A SBP target of <130mmHg and >120mmHg should be tried in DM patients with hypertension. A target DBP below 80mmHg and not less than 70mmHg should be attempted.[19] NICE guidelines recommend initiation of BP therapy at a threshold of 135/85 mmHg in diabetes patients. In diabetes patients with a BP>130/80mmHg, NICE recommends initiation of treatment in the presence albuminuria or two and more features of metabolic syndrome.[20]

ESC guidelines on diabetes, pre-diabetes, and CVD published in 2019 recommend following BP targets in DM subjects and emphasizes on individualization of target BP. The BP goal is to target SB to 130 mmHg in patients with DM and <130 mmHg if tolerated, but not <120 mmHg considering the expected adverse events with further reduction. A target SBP of <130mmHg should be achieved in diabetes patients with chronic kidney disease and high risk of cerebrovascular disease. In older people (aged >65 years), the SBP goal is to a range of 130–139 mmHg. The DBP target is <80 mmHg, but not <70 mmHg in view of anticipated increase in orthostatic hypotension.[21] The ADA in the standards of care 2020 has made following suggestions. In diabetics with hypertension at higher cardiovascular risk (existing ASCVD or 10-year ASCVD risk ≥15%), a BP target of 130/80 mmHg can be targeted safely. In those with 10-year ASCVD risk, <15% target BP for treatment should be <140/90 mmHg, Table 1.[13,14,22,29-32]

BP Target in Type 1 DM

ADA recommends to start therapy for BP >140/90 mmHg in type 1 DM.

Hypertension target in elderly

The elderly are more sensitive than younger population for low BP and as perfusion to vital organs such as brain and heart is

Table 1: Summary of BP target recommendations by various professional bodies and the basis for recommendations

Recommending organization	Target BP	Year of publication	Basis for recommendation
ADA	• ≤130/80 mmHg for individuals with 10-year ASCVD risk score ≥15% • <140/80 mmHg for individuals with 10-year ASCVD risk score <15%	2020	• ACCORD • ADVANCE • HOT • SPRINT
ESC	• SBP <130 mmHg for age <65 • SBP 130–139 mmHg for age >65 • DBP <80 mmHg, not <70 mmHg	2019	• ADVANCE • ESH guidelines 2018 • Meta-analysis[13,29]
ESH/ESC	• SBP <130 mmHg, but not <120 mmHg • DBP <80 mmHg, but not <70 mmHg	2018	• Meta-analysis[14,21,32]
AHA/ACC	• <130/80 mmHg	2017	• ACCORD • Meta-analysis[29-31]
NICE	• 135/85 mmHg • <130/80 in case of albuminuria/two or more features of metabolic syndrome	2019	• ACCORD • SPRINT
IDF	• SBP <140 mmHg • SBP <130 mmHg in case of albuminuria • DBP <80 mmHg	2017	
JNC8	<140/80 mmHg	2014	• ACCORD • ADVANCE • UKPDS38

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ASCVD: Atherosclerotic cardiovascular disease, BP: Blood pressure

BP dependent. Further, orthostatic hypotension, postprandial hypotension, CKD, and isolated systolic hypertension with low DBP complicate BP control threshold. The Hypertension in the Very Elderly Trial demonstrated reduction in stroke, heart failure, and CVD in subjects above 80 years of age.[23] The Japanese Trial to Assess Optimal SBP in Elderly Hypertensive Patients included subjects of 65–85 years age group (11.8% of these subjects were diabetics) at 2 years follow-up there was no significant difference in the rates of CVD, renal events, and mortality in the group with SBP <140 mmHg and SBP of 140–160 mmHg.[24]

Systolic Hypertension in the Elderly Program in elderly patients >60 years with isolated systolic hypertension, treatment with chlorthalidone showed significant benefits in diabetics and non-diabetics and no additional benefit was seen in reducing SBP <140 mmHg.[25] SPRINT study has shown that lowering SBP <120 mmHg has reduced all-cause mortality predominantly in the age group of >75 years. However, the same was not implied by ACCORD trial. However, SPRINT trial had no diabetes subjects.

Isolated systolic hypertension defined as SBP>140 mmHg with DBP<90 mmHg is common in elderly patients, presents in 30% of the elderly in a study done in the USA.[26] DBP in these individuals is lower and treatment of SBP can precipitate a low DBP. This is the potential mechanism of J-shaped curve association between DBP and CV events at DBP lower than 60–70 mmHg.[27] Hence, in elderly patients with diabetes with isolated systolic hypertension, SBP target lowering should be attempted in individuals with DBP >60 mmHg. A higher SBP cutoff of 160 mmHg should be targeted in diabetics with DBP <60 mmHg. In elderly diabetics with CAD, a BP target of <140–

150/90 mmHg should be tried. Evidence to this is reduction in the vascular events with BP reduction below 143/82 mmHg in the Second Manifestations of ARTerial disease trial. Target BP should be carefully chosen to avoid positional hypotension which could lead to falls and syncope.[27,28]

Majority of the bodies on hypertension in 2014 recommended a BP target of ≤150/90 mmHg in elderly diabetics aged more than 80 years.[26,27] ESC and ESH guidelines recommend a SBP target of 130–139 mmHg in people with diabetes and age ≥65 years.[19,21,24]

Conclusion

From the several RCT and guidance from various professional bodies, it's evident that lowering the SBP below 130 mmHg results in reduction of cardiovascular events and microvascular complications. Further, lowering SBP below 120 mmHg has shown only reduction in the occurrence of strokes with several adverse events such as syncope, orthostatic hypotension, and electrolyte imbalances such as hyperkalemia and worsening of renal functions. Hence, individualization of BP target should be considered based on cardiovascular risk factors and diabetes-related complications.

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Review Article

Target Blood Pressure Goals in Patients with Chronic Kidney Disease: Where Do We Stand in this Era of Evidence-based Medicine?

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Abstract

Chronic kidney disease (CKD) is highly prevalent globally and is strongly associated with cardiovascular disease (CVD). Hypertension affects the vast majority of patients with CKD and increases the risk of CVD, end-stage kidney disease, and mortality. Control of hypertension in CKD is very important in our clinical practice to slow the progression of CKD as well as to reduce CVD risk. Over the past 10 years, three major guidelines have dealt with blood pressure (BP) thresholds and targets for antihypertensive drug therapy in CKD patients: The 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for the management of BP in CKD; the 2017 American College of Cardiology/American Heart Association 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High BP in Adults; and the 2018 European Society of Cardiology and the European Society of Hypertension guidelines for the Management of arterial hypertension. These guidelines do not offer a consensus on optimal BP targets and have varying recommendations for BP goals in patients with CKD. It may leave practicing physicians and patients in a dilemma. Therefore, it is necessary to understand the existing evidence used to create these guidelines to deliver personalized management and achieve BP targets in CKD.

Key words: Blood pressure measurement techniques, Chronic kidney disease, Hypertension guidelines, Hypertension, Target blood pressure

Introduction

Hypertension is common in patients with chronic kidney disease (CKD) and, depending on the stage of CKD and its etiology, its prevalence ranges from 60 to 90%. It can be a consequence or cause of CKD. The mechanisms of hypertension in CKD are multifactorial which includes salt retention, volume overload, sympathetic over activity, endothelial dysfunction, and alterations in hormonal systems especially the renin-angiotensin-aldosterone axis which regulates blood pressure (BP).[1,2] Hypertension is a strong risk factor for cardiovascular disease (CVD), end-stage kidney disease, and mortality. There is a linear relationship between BP and cardiovascular risk in CKD.[3-5] Therefore, the management of hypertension is particularly important in patients with CKD. The BP control in CKD is very poor. According to data from the National Health and Nutrition Examination Survey, only 32% had BP controlled among CKD.[2]

Over the past two decades, many hypertension trials in the general population and CKD have been published leading to a debate on target BP goals.[6-13] After 2010, there are three major guidelines for BP thresholds and targets for antihypertensive drug therapy in CKD patients: The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the management of BP in CKD; the 2017 American College of Cardiology/American Heart Association 2017 (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High BP in Adults; and the 2018 European Society of Cardiology and the European Society of Hypertension (ESC/ESH) Guidelines for the Management of Arterial Hypertension.[14-16] There are disagreements and no consensus between these guidelines for hypertension management concerning the optimal BP target in patients with CKD. There is also a lot of emphasis in the last decade about BP measurement techniques. BP measurement by automated BP instruments or

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standardized BP techniques is gaining more importance especially for screening for hypertension in adults. The 24-h ambulatory BP (ABPM) measurement and home BP (out of office BP measurements) are also promising to be better in the management of hypertension.[10-16] Here, we review the results of recent trials, different guidelines after KDIGO 2012, their BP goals, and hypertension treatment recommendations in the CKD population.

Hypertension in CKD – Non-Dialysis

Hypertension targets recommended by various guidelines for non-dialysis CKD patients are based on trials with CKD patients or having a subset of CKD patients along with the general population. The three major BP trials in non-diabetic CKD patients that focused on the progression of CKD as a primary outcome are shown in Table 1.[6,7,17]

The Modification of Diet in Renal Disease (MDRD) study is the first large, randomized, controlled trial to evaluate a lower BP target in CKD. In this study, intensive BP lowering had no significant effect on CKD progression. However, in the subset of patients with proteinuria >1 g/day, there was a significantly slower glomerular filtration rate (GFR) decline in intensive arm (target mean arterial pressure [MAP] 92 mmHg compared to standard BP arm target MAP 107 mmHg). However, no such benefit was seen in those without proteinuria.[17]

Similar to the MDRD study, the African American Study of Kidney Disease and Hypertension, 2002 (AASK) study in non-diabetic African American CKD (eGFR 20–65 ml/min/1.73 m²) patients showed no benefit in renal outcome with intensive BP control with only patients having proteinuria >1 g/day, showing benefits in the intensive control arm.[6,17]

In the Ramipril Efficacy in Nephropathy-2 study, CKD patients with >1 g proteinuria were randomized to either intensive BP control with the addition of a dihydropyridine calcium channel blocker (CCB) felodipine to those already established on an angiotensin-converting enzyme (ACE) inhibitor or standard BP control with an ACE inhibitor alone. The addition of a CCB did reduce BP; however, this did not translate into improved renoprotection[7] [Table 1]. It is important to note that the duration of study in all these three trials was short with an average of 1.3–3.8 years.

Taking evidence from these trials, guidelines published suggested intensive BP control for only those patients with significant proteinuria (>1 g/day).[14] In the absence of proteinuria a higher target BP <140/90 may be appropriate. These studies, however, did not consider the potential benefits of intensive BP control on cardiovascular endpoints.

The other landmark trials on hypertension in the general population which included CKD patients as a subgroup in the last decade are shown in Table 2.

The trials on diabetic CKD are sparse for intensive BP control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared intense (target systolic BP <120 mmHg) BP control to standard (target systolic BP <140 mmHg) BP control on cardiovascular outcomes (myocardial infarction [MI], stroke, or death from CVD) in patients with type 2 diabetes mellitus. It had 1325 (28%) stage 1–2 CKD patients and 401 (8%) stage 3 CKD patients.[10] The probability of death from CVD did not vary substantially in this analysis (Hazard Ratio [HR], 0.88; 95% confidence interval, [0.73–1.06]). However, there was a lower risk of stroke. The ACCORD trial, on the other hand, was underpowered for the intended result. In 9361, non-diabetic patients with elevated CVD risk, the landmark Systolic BP Intervention Trial (SPRINT) compared a systolic BP target of 140 mmHg with a more intensive systolic goal of 120 mmHg.[12] The primary outcome, a combination of MI, acute coronary syndrome, stroke, heart failure, or death from CVD, was reduced by a statistically significant percentage in the intensive care arm. There was also a substantial decrease in the secondary outcome of death from any cause, prompting the trial stoppage within 3 years. Intensive BP management decreased all-cause mortality with an impact size close to that observed in the overall cohort ($n = 2646$, mean GFR 47.9 mL/min/1.73 m²). Despite this, no impact on renal outcomes, such as the rate of eGFR decline, was observed. Those with an eGFR of <20 mL/min/1.73 m² and/or proteinuria >1 g/day were removed from the SPRINT study. Patients with diabetes, which accounts for up to 45% of CKD in the developing world,[18] were also left out. Nonetheless, SPRINT indicates that in those with CKD, intensive BP monitoring decreases CVD morbidity and mortality.

Table 1: Major RCTs on target blood pressure in CKD with primary renal outcomes

Trial and type of instrument used	Participants and study criteria	Target BP	Follow-up	Outcomes
MDRD – 1994 (Sphygmomanometer)	255+585, All CKD (eGFR 13–55 ml/min) Predominant non-diabetic	MAP<92 mmhg versus MAP<107 mmhg	2.2 years	No difference in mean GFR slope overall Subgroup analysis suggested MAP<92 target beneficial for those with proteinuria >1 g/d
AASK – 2002 (Hawskley random zero sphygmomanometer)	1094 (all African American), eGFR (20–65 ml/min), Excluded – DM, UPCR>2.5	MAP<92 versus MAP<102–107 mmHg	3.8 years	No difference in mean GFR slope or clinical composite kidney outcome (50% GFR decline, ESKD, or death)
REIN – 2 – 2005 (standard sphygmomanometer)	338, all proteinuric CKD (>1 g/day) Excuded: DM	DBP<90 or SBP/DBP<130/80	1.6 years	No difference in the incidence of ESKD

MDRD: Modification of diet in renal diseases, AASK: African-American Study of Kidney Disease and Hypertension REIN-2: Ramipril Efficacy in Nephropathy trial 2, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, MAP: Mean arterial pressure, DM: Diabetes mellitus, UPCR: Urine protein-creatinine ratio, ESKD: End-stage kidney disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2: Major RCTs after 2010 with CVD outcomes having subset of CKD patients

Trial and type of instrument used	Participants and study criteria	Target BP	Follow-up	Renal outcomes	CVD outcomes
ACCORD-2010 (Omron HEM-907) Automated device	4733 patients, All DM 36% (1726) with CKD stage 1–3,	SBP<120 mmhg v/s SBP<140 mmhg	4.7 years	Not reported	No difference in primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular cause
SPS 3 – 2013 (Colin 8800C) Automated device	2916 participants, 14% (411) with CKD, Recent lacunar stroke	SBP<130 versus SBP 130–149 mmhg	3.7 years	Not reported	No difference in all-cause mortality or major vascular events
SPRINT 2015 (Omron HEM-907) automated device	9361 participants, non-DM, 28% with CKD (eGFR 20–59 ml/min)	SBP<120 v/s SBP<140	3.3 years	Significance in 30% eGFR decline in intensive target group but no difference in 50% eGFR decline or ESKD	Significant decrease in all cause death and composite CVD outcomes in the intensive target group

ACCORD: Action to Control Cardiovascular Risk in Type 2 Diabetes, SPS3: The Secondary Prevention of Small Subcortical Strokes, SPRINT: Systolic Blood Pressure Intervention Trial, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, MAP: Mean arterial pressure, DM: Diabetes mellitus, ESKD: End-stage kidney disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CVD: Cardiovascular disease

In 2017, the AHA/ACC recommendations proposed a 130/80 mm Hg BP target for patients with CKD, regardless of the degree of proteinuria, based on evidence from this study.[15] The required BP goal for patients with CKD who do not meet the SPRINT inclusion criterion (including those with diabetes mellitus) is, however, still a point of contention. It is important to note that the intensive control arm had a greater risk of adverse effects such as acute kidney injury, eGFR decline >30%, hypokalemia, hyponatremia, and hypotension. Patients with CKD stages 4 and 5 were scarce.[12,18] They used automated BP measurements which are usually less than routine manual office BP measurements by 5–10 mmHg.[12,19] Hence, The ESC/ESH guideline in 2018 recommended 130–39/70–79 mmHg, a slightly higher target than ACC/AHA[16] so whether to target <120/80 mm Hg in CKD is still debatable. Overall, individualized BP targets should be set only after weighing potential risks and benefits of treatment.

Guidelines and Recommendations for Non-dialysis CKD

In 1997, the Joint National Committee on Detection, Evaluation, and Treatment of High BP (JNC)-VI recommended a BP target of 125/75 mm Hg for proteinuric CKD and 130/85 mm Hg for non-proteinuric CKD, respectively.[20] JNC-VII later revised the BP goal for all patients with CKD to 130/80 mmHg in 2003.[21] The KDIGO guidelines from 2012 recommended a BP target of 130/80 mm Hg only for those with albuminuric (albumin-to-creatinine ratio >30 mg/g) CKD,[14] while the 2013 ESH/ESC guidelines[22] and the recommendation from the panel members assigned to JNC-8 recommended a BP target of 140/90 mm Hg.[21] The ACC/AHA 2017 Hypertension recommendations, which were based on the SPRINT study, redefined the BP target of 130/80 mm Hg in patients with CKD and those at high cardiovascular risk.[15] The ACC/AHA guidance committee preferred a systolic BP target of 130 mm Hg rather than 120 mm Hg because automatic BP measurements

were found to be 5–10 mmHg lower than routine clinic measurements. However, the 2018 ESH/ESC recommendations propose a systolic BP target of 130–139 mm Hg and a diastolic BP target of 70–79 mm Hg, which is significantly higher than the ACC/AHA guidelines [Figure 1].[16]

The available evidence does not provide a clear consensus for optimal BP targets in CKD. The 2017 ACC guidelines used the results of SPRINT as the basis for a more intensive BP target. However, the 2018 ESC/ESH guidelines have not adopted this more intensive approach. The KDIGO is also revising the previous KDIGO 2012 guideline and the draft has been put on the ISN website for public opinion. Since it also has to be based on the SPRINT trial, the question remains still whether to target 120/80 mmHg or 130/80 mmHg. It looks by the evidence that the target BP should be based on the type of BP measurement. If you are using automated BP measurement and standardized BP measurement like that of SPRINT or AASK trials, targeting <120/80 mmHg in CKD may be beneficial. If management is based on routine office BP measurement then it is preferable to target 130/80 mmHg in our clinical practice.

Hypertension in CKD 5D (Dialysis)

Sodium and water overload are major mechanisms of hypertension in hemodialysis patients. Despite aggressive ultrafiltration, hypertension often persists.[24,25] There is inadequate data to direct BP targets in this group of patients. In this cohort, reduced BP does not always imply better survival, as it does in the general population and those with pre-dialysis CKD.[26] According to the latest KDIGO controversies conference on BP and Volume Control in Dialysis, concrete recommendations on BP care goals cannot be made based on current evidence. It also suggested that pre- and post-HD BP should not be used alone for diagnosing and managing hypertension. The use of 24-h ABPM and home BP monitoring for interdialytic BP management was suggested.[27]

Hypertension in Kidney Transplantation

There are currently no randomized clinical trials evaluating an evidence based approach to treat hypertension after kidney transplantation, just as there are not any for hemodialysis. Hypertension is a typical post-transplant complication that can be caused by a variety of reasons. Nearly 70–90% of kidney transplant patients on a calcineurin inhibitor-based immunosuppression treatment will develop hypertension after the transplant.[28,29] Higher BP is linked to lower graft outcomes and a higher risk of CVD, which is the main cause of death after kidney transplantation.[30,31] Both KDIGO and the ACC/AHA guidelines currently prescribe a BP target of 130/80 mm Hg, but it is unknown whether lower BP targets will delay the development of CKD or decrease CV risk. There are established particular first-line agents recommended for antihypertensive therapy.[14,15]

BP Measurement Techniques and its Importance in CKD

For the management of hypertension to be effective, accurate BP measurements are essential. Technique of BP measurement will have a significant impact on the outcome of any trial. The use of automated oscillometric devices and standardized BP measurements is gradually replacing manual BP measurement in the office, and recent clinical trials have moved toward automated BP measurements.[10-12] CKD is associated with

Figure 1: Target blood pressure recommendations in chronic kidney disease as per various guidelines

significant abnormal ambulatory BP patterns, including elevated ambulatory BP and non-dipping, masked, and sustained hypertension.[32-34] Thus, out of office measurements such as home BP and 24-h ABPM should also be considered in CKD when we suspect masked hypertension and white coat effect.[35,36]

Conclusion

The recent guidelines differ in their approach and do not include a consensus on acceptable BP targets, but they are based on evidence that supports either renoprotection or cardioprotection treatments. In patients with CKD, a BP target of 130/80 mm Hg can be a rational, evidence-based goal, and existing evidence indicates that lowering BP to 130/80 mm Hg decreases potential CVD and mortality risk. Despite the SPRINT study, the available data does not support a strong consensus on the intensive BP goal of 120/80 mm Hg. A one size fits all target approach may not be feasible because implementation of an intensive BP goal in CKD will require increased attention to appropriateness of BP measurement techniques, assessment of patient preferences, and comorbidities.

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