Newer and Aggressive Blood Pressure Goals to Treat Hypertension

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Abstract

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

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

Introduction

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

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

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

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

J-curve Hypothesis

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

J-curve phenomenon in hypertension is as yet unresolved since the optimal BP may vary between individuals, across various organs, and with associated conditions. The J-curve phenomenon, for DBP, was first observed in connection with MI in patients on hypertension treatment. It describes an inverse relationship between low DBP and angina, MI, cardiovascular morbidity, and mortality [Figure 1]. Stewart reported that the incidence of MI was 5 times higher in the patients with DBP <90 mm of Hg, compared with those with a DBP between100 and 109 mm of Hg (P < 0.01).

Evidence in Favor of Aggressive Management of BP

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

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

more than 9300 participants aged 50 years and above, in about 100 medical centers and clinical practices throughout the USA and Puerto Rico. SPRINT investigators randomly divided the study participants into two groups that differed according to targeted levels of SBP. The standard group received an average of two different BP medications to achieve a target of <140 mmHg. The intensive treatment group received an average of three BP medications to achieve a target of <120 mm of Hg. The significant preliminary results of SPRINT were announced on September 11, 2015. The trial showed that the lower target of BP (<120 mm Hg) reduced cardiovascular events by 25% and overall risk of death by 27%.²

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

Wang et al., using recursive partitioning of all clinical variables in a derivation cohort within the SPRINT trial, developed a three-step decision tree composed of age ≥74 years, urinary albumin to creatinine ratio or Urinary albumin to creatinine ratio (UACR) ≥34, and history of prior CVD, to distinguish patients at high or low risk of major adverse coronary event (MACE ). Only the high-risk subgroup had a significant risk reduction with intensive versus standard BP treatment. The improvement in cardiovascular outcomes associated with a lower BP target in the high-risk group was not accompanied by an increase in serious adverse events, thus maximizing the net benefit of intensive BP reduction in this group. Thus, they were successful in identifying the group of hypertensive patients who would derive the most favorable risk-benefit profile from intensive BP lowering.²

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

How Aggressive should BP Reduction be in Various Clinical Settings?

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

BP reduction in myocardial ischemia

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

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

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

**BP reduction in stroke**

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

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

**BP reduction in CKD**

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

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

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

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

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

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

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

BP reduction in elderly

A 2018 ESC/ESH BP guidelines categorize older adults in two subgroups; “elderly” refers to patients between the ages of 65 and 79 years while “very old” refers to those ≥80 years. A recent evaluation of the NHNES Health database revealed that nearly 50% of hypertensive US adults (≥ 80 years of age) have uncontrolled hypertension. The Korean Society of Hypertension recommends a BP goal <140/90 mmHg for fit older adults between 65 and 79 years old. The office BP treatment threshold for adults ≥80 years old or frail elderly hypertensives is ≥160/90 mmHg, but if they tolerate treatment, it is reasonable to aim for <140/90 mmHg. These targets are similar to the European guideline, but much less aggressive than the American guideline that recommends BP <130/80 mmHg for most adults ≥65 years old.

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

This study suggested frailty assessment in the elderly should be coupled with BP levels to decide the feasibility of aggressive hypertension treatment. If an elderly individual is independent and needs no assistance in activities of daily living, aggressive reduction of BP can be considered, keeping a close watch on postural BP change, symptoms of cerebral ischemia or rise in creatinine levels. Lower targets are relevant in elderly patients if no orthostatic hypotension occurred, and in patients with non-proteinuric CKD (eGFR <60 ml/mn/1.73 m²) or cardiovascular disease with Framingham score more than 15%.

BP reduction in young

Hypertension in the young is often unrecognized and neglected. Between the period of 1999 and 2014, the various aspects of hypertension control (hypertension diagnosed by average BP of >140/90 mmHg or the use of antihypertensive medication) were lower among young adults (18–39 years) compared with middle-aged (40–59 years) or older adults (>60 years) (74.7% vs. 81.9% vs. 88.4% for awareness; 50.0% vs. 70.3% vs. 83.0% for treatment; and 40.2% vs. 56.7% vs. 54.4% for control). However, if one uses current guidelines cutoff, the incidence will be higher.

A 20-year prospective Chinese cohort study found that Stage 1 hypertension, as defined by the 2017 ACC/AHA hypertension guidelines (130-139/80-89), was associated with a significantly increased risk of CVD compared with normal BP, and this group accounted for 26.5% of cardiovascular deaths and 13.4% of cardiovascular events in young Chinese adults aged 35–59 years.

In the short-term, hypertension in the young is associated with higher rates of LVH, alterations in brain volume, and white matter hyperintensities. In the long-term, multiple studies have demonstrated increased rates of cardiovascular disease and mortality in young people with hypertension. Coronary Artery Risk Development in Young Adults longitudinal study showed that...
elevated SBP at baseline was more predictive of coronary artery calcium 15 years later and a significantly higher risk of cardiovascular disease. The higher risk seen in the younger subgroup suggests incremental risk over time when risk factors are left untreated and, hence, need for lifestyle change measures (which are the mainstay of treatment for this cohort) together with intensive BP control therapy even in Stage 1 hypertension in young.

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

BP control in atrial fibrillation (AF)

Another cohort not often discussed is patients with non-valvar AF and hypertension. In the Korean AF cohort, applying the new 2017 ACC/AHA guidelines redefined 17.2% of patients with AF as newly hypertensives. AF can be a result of uncontrolled hypertension, and the presence of hypertension increases the risk of complications in patients with AF. Patients with AF and newly redefined hypertension were at significantly higher risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission compared to non-hypertensive patients. Patients with AF would receive the greater benefit if BP target range of 120–129/<80 mm of Hg is achieved, compared to that of 130–139/80–89 mm of Hg, regardless of their estimated CVD risk.

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

**Conclusion**

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

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