

## Review Article



# Ideal Target Blood Pressure in Hypertension

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 OPEN ACCESS

**Received:** Aug 11, 2019

**Accepted:** Aug 13, 2019

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### Funding

This research was supported by a research grant from the Fire Fighting Safety & 119 Rescue Technology Research and Development Program funded by National Fire Agency (grant number: MPSS-FireSafety-2015-80), a research grant from the Korea Centers for Disease Control & Prevention (grant number: 2018ER630200).

### Conflict of Interest

The author has no financial conflicts of interest.

## ABSTRACT

In the Systolic Blood Pressure Intervention Trial (SPRINT), intensive blood pressure (BP) lowering was associated with significant reduction in composite cardiovascular (CV) outcomes in hypertension. Subsequently, several meta-analyses have corroborated the findings from SPRINT and these benefits were more prominent in subjects with higher cardiovascular risk at baseline. As such, the recent American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guideline and the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guideline recommended the lowering of target BP to less than 130/80 mmHg in most hypertensive subjects. However, one should keep in mind the potential harm of too much BP lowering. Post hoc analysis of clinical trials have demonstrated increased cardiovascular mortality and events with too much BP lowering. Therefore, although intensive BP lowering may be beneficial in further reducing CV outcomes, too much reduction below 120/70 mmHg may actually harmful. In conclusion, although intensive BP lowering to achieve target BP below 130/80 mmHg is beneficial in reducing CV outcomes, one should do so cautiously as to avoid adverse events. As such, the first target of anti-hypertensive treatment should be to achieve BP lowering below 140/90 mmHg. Once that target is achieved, one could target BP below 130/80 mmHg keeping in mind to avoid signs of organ hypoperfusion such as orthostatic hypotension, orthostatic dizziness, weakness and serum creatinine elevation.

**Keywords:** Hypertension; Blood pressure; Cardiovascular diseases

## INTRODUCTION

Recent changes in the American and European guidelines on the management of arterial hypertension have resulted in emphasis of intensive blood pressure (BP) lowering below 130/80 mmHg for most hypertensive patients.<sup>1,2)</sup> The 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/American Society of Hypertension (ASH) hypertension guideline recommended that treatment goal of all hypertensive patients should be lowered to below 130/80 mmHg and that high risk patients with stage 1 hypertension, whose BP is between 130/80 to <140/90 mmHg with ASVD risk score of more than 10% or cardiovascular disease (CVD), should be considered for drug treatment.<sup>1)</sup> The 2018 European

guideline recommends a strict target systolic blood pressure (SBP) goal of at or below 130 mmHg for most hypertensive patients except for those with chronic kidney disease (CKD) and elderly over the age of 65 and recommended that diastolic blood pressure (DBP) should be controlled to between 70–80 mmHg.<sup>2)</sup> Similarly, in the 2018 Korean Society of Hypertension guidelines for the management of hypertension, a target SBP of 130 mmHg was recommended for high risk hypertensive patients such as hypertensive patients associated with coronary artery disease, congestive heart failure, CKD with proteinuria and diabetes mellitus with CVD.<sup>3)</sup> In this review, we will discuss the evidence that serves as the basis for these recent changes in target BP.

## **ESTABLISHMENT OF TARGET BLOOD PRESSURE OF 140/90 MMHG AS TREATMENT TARGET IN HYPERTENSION**

Although we take for granted the efficacy of anti-hypertensive treatment in preventing cardiovascular (CV) events, the establishment of the current recommendations of BP targets have a long history. Before the publication of the seminal Veterans Administration Cooperative Study (VA Cooperative Study) in 1967, the only evidence of benefit for treating hypertension was above the level of what we would today consider to be severe, emergent hypertension. The VA Cooperative study enrolled 143 male hypertensive patients with DBP between 115–129 mmHg, patients whose DBP levels were thought to be mild forms of hypertension at that time and randomized them to active treatment versus placebo. The clear benefits of active treatment demonstrated in this study paved the way for clinical trials in the 1970s and 1980s that established 140/90 mmHg as the target BP in hypertension.<sup>4)</sup> In the 2nd VA cooperative study on the effects of treatment on morbidity in hypertension, 380 male hypertensive patients with DBP between 90–114 mmHg were randomized to active treatment and control. The results, for the first time, demonstrated that BP lowering in hypertensive patients with DBP above 90 mmHg was beneficial in reducing CV events and mortality.<sup>5)</sup> Subsequent studies such as the Hypertension detection and follow-up program I, Hypertension-Stroke Cooperative Study, Australian Therapeutic Trial in Mild Hypertension and Medical Research Council (MRC) trial of mild hypertension enrolled hypertensive subjects with DBP above 90 mmHg and demonstrated the beneficial effect of anti-hypertensive treatment in reducing CV events.<sup>6-9)</sup> As such, the diagnostic threshold of hypertension was established as BP above 140/90 mmHg based on the definition of hypertension being the level of BP above which the benefits of treatment unequivocally outweighs the risks of treatment.<sup>2)</sup> Also, a therapeutic target of BP below 140/90 mmHg was established as well.

## **RECOMMENDATION FOR INTENSIVE BLOOD PRESSURE LOWERING IN PATIENTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE**

The first clinical trial to determine whether further intensive lowering of BP reduces CV outcomes was the hypertension optimal treatment (HOT) study.<sup>10)</sup> In this study, 18,790 patients age 50–80 with baseline DBP of 100–115 mmHg were randomized to target DBP of

≤90, ≤85, and ≤80 mmHg. Overall, there was no significant difference in CV events among the three treatment arms with the lowest incidence of major CV events occurring at mean achieved DBP of 82.6 mmHg. However, in 1,501 patients with diabetes mellitus, there was a 51% reduction in major CV events in the DBP ≤80 mmHg treatment target arm compared to the DBP ≤90 mmHg arm.<sup>10)</sup>

For patients with CKD, the modification of diet in renal disease (MDRD) randomized 840 patients with non-diabetic chronic renal disease to usual BP treatment target (mean BP, 107 mmHg) versus intensive BP target (mean BP, 92 mmHg). The study showed that in subjects with proteinuria of more than 1 g/day, intensive BP lowering was associated with significantly slower decline in the glomerular filtration rate.<sup>11)</sup> In 2003, based on the above mentioned evidence, the JNC 7 recommended a treatment target BP of 140/90 mmHg and BP goal of less than 130/80 mmHg for patients with diabetes and chronic renal disease.<sup>12)</sup>

## **REVISION OF TARGET BLOOD PRESSURE TO 140/90 MMHG FOR ALL HYPERTENSIVE PATIENTS REGARDLESS OF ASSOCIATED CONDITIONS**

The recommendation put forth by the JNC 7 was generally accepted until the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in 2010, which was the first study to explore the benefits of intensive BP lowering specifically in patients with diabetes mellitus.<sup>13)</sup> Although strict BP lowering had been recommended for hypertensive patients with diabetes, it was based on a subgroup analysis from the HOT trial and expert consensus that high risk hypertensives needed to be treated with more intensive BP lowering. The ACCORD study randomized 4,733 to either intensive SBP lowering (<120 mmHg) or standard BP lowering (<140 mmHg) with a mean follow up of 4.7 years. Surprisingly, intensive BP lowering did not reduce the rate of a composite of fatal and non-fatal CV outcome while reducing the rate of fatal or non-fatal stroke.<sup>13)</sup> For CKD, the evidence for benefit of intensive BP lowering was also unclear. In both the Blood-pressure Control for Renoprotection in Patients with Non-diabetic Chronic Renal Disease (REIN-2) study and the African-American Study of Kidney Disease and Hypertension (AASKD), intensive BP control failed to show benefit in slowing the progression of kidney disease.<sup>14)15)</sup> Based on these evidence, both the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) arterial hypertension guideline and the 2014 JNC 8 guideline recommended that regardless of associated conditions, the target BP should be 140/90 mmHg with the European guideline recommending a target DBP of 85 mmHg for subjects with diabetes mellitus.<sup>16)17)</sup>

## **BACK TO 130/80 MMHG: INTENSIVE BLOOD PRESSURE TREATMENT TARGET FOR ALL HYPERTENSIVES**

In 2015, the publication of the Systolic Blood Pressure Intervention Trial (SPRINT) changed the landscape of the hypertension treatment guideline.<sup>18)</sup> The objective of the study was to determine whether intensive SBP lowering below 120 mmHg lowers the risk of CV outcomes compared to conventional SBP lowering below 140 mmHg in individuals with SBP above 130 mmHg without diabetes. The 9,361 persons enrolled in the study were relatively high

risk, with the inclusion criteria of the SPRINT study being individuals above the age of 50 with at least 1 of the following: 1) history of clinical/subclinical CVD, excluding stroke, 2) Framingham risk score of more than 15, 3) age of 75 years of age or more 4) CKD with estimated glomerular filtration rate between 20–60 mL/min/1.73 m<sup>2</sup>. The clinical trial was stopped after a median follow-up of 3.26 years due to the significant, 25% lowering of the primary composite outcome in the intensive treatment group compared to the standard treatment group (hazard ratio [HR] with intensive treatment, 0.75; 95% confidence interval [CI], 0.64–0.89;  $p=0.003$ ).<sup>18)</sup> One thing to keep in mind for the SPRINT study was that unattended automated office blood pressure (AOBP) measurement was used for clinical office BP measurement. As studies have shown that AOBP is 5–15 mmHg lower than usual office BP measurements, AOBP SBP target of 120 mmHg would most likely corresponded to usual clinical office SBP of 130 mmHg.<sup>19)20)</sup>

Subsequently, meta-analysis of BP lowering clinical trials have demonstrated the benefit of intensive BP lowering. In a recent meta-analysis of 123 BP lowering intervention studies with 613,815 participants, Ettehad et al.<sup>21)</sup> demonstrated the every 10 mmHg reduction in SBP is associated with 20% reduction in the risk of major CV events, 17% reduction in the risk of coronary heart disease, 27% reduction in the risk of stroke 28% reduction in the risk of heart failure and 13% reduction in all-cause mortality. The proportion risk reduction did not differ for those with lower baseline SBP of less than 140 mmHg, suggesting that there is further benefit in reducing SBP to less than 130 mmHg.<sup>21)</sup> Also, the benefits of intensive BP lowering in high risk patients were demonstrated in a meta-analysis by Xie et al.,<sup>22)</sup> in which 19 clinical trials including 44,989 patients were analyzed. In this meta-analysis, the average CV event rate was approximately 0.9%/year, corresponding to 9–10%/10 year and the average BP of the intensive BP lowering arm and the usual treatment arm was 133/76 mmHg versus 140/81 mmHg, respectively. The results showed that intensive BP lowering was associated with 14% reduction in CV events, 13% reduction in MI, 22% reduction in stroke, 10% reduction in albuminuria and 19% reduction in retinopathy progression without any significant reduction in heart failure, CV death, total mortality, or end-stage renal disease.<sup>22)</sup> Finally, Thomopoulos et al.<sup>23)</sup> performed a meta-analysis of randomized controlled trials of BP lowering treatment published between 1966 and 2015. Among the trials comparing the effects of more intense BP lowering versus less intense BP lowering, the standardized relative risk of SBP lowering of 10 mmHg in achieved SBP of <130 mmHg in the more intense group BP lowering group was associated with 21% reduction of stroke. For the standardized relative risk of DBP lowering of 5 mmHg in achieved DBP of <80 mmHg in the more intense BP lowering group, there was a 27% reduction in stroke and 27% reduction in CV death. Additional analysis comparing the effects of more intense BP lowering versus placebo or less intense BP lowering, the standardized relative risk of SBP lowering of 10 mmHg in achieved SBP of <130 mmHg in the more intense BP lowering group was associated with 21% reduction of stroke, 14% reduction of coronary heart disease, and 20% reduction in CV death.<sup>23)</sup> Taken together, the evidence strongly suggests that intensive BP lowering reduces CV events, especially in those at high CV risk.

One thing to keep in mind is that since most of the clinical trials for BP lowering have been performed in subjects with high CV risk, there is some limitation to generalize the results from the clinical trials to all hypertensive subjects. Recently, Lee et al.<sup>24)</sup> analyzed 148,761 low risk, treated stage 1 hypertensive subjects from the National Health Insurance Service Health Examination Database. The results showed that the lowest adjusted risk of all-cause mortality was observed in subjects with average SBP of 120 to <130 mmHg and average DBP of 70 to <80 mmHg, which is in line with the target BP recommendation of the newest ACC/

AHA and ESH/ESC arterial hypertension guideline and supports the generalization of the recommended target BP in the general hypertensive population.<sup>24)</sup>

## BLOOD PRESSURE TARGET IN THE ELDERLY

The efficacy of anti-hypertensive treatment in reducing CV events in the elderly was established after the publication of the Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe (Syst-Eur) Trial and the Systolic Hypertension in China (Syst-China) trial.<sup>25-27)</sup> The enrollment criteria of these 3 clinical trials was hypertensive subjects over age 60 with SBP between 160–219 mmHg and DBP below 90 mmHg for SHEP and DBP below 95 mmHg for Syst-Eur and Syst-China trials and the achieved SBP for the active treatment group was between 140–150 mmHg for all 3 trials. For the very elderly, defined as hypertensive subjects over the age of 80, the Hypertension in the Very Elderly Trial (HYVET) demonstrated that for subjects with baseline SBP  $\geq$ 160 mmHg, active treatment was associated with significant reduction in fatal or non-fatal stroke, stroke mortality, CV mortality, and heart failure. The achieved SBP in the HYVET trial was also between 140–150 mmHg.<sup>28)</sup> However, both the Japanese Trial to Assess Optimal Systolic Blood Pressure in the Elderly Hypertensive Patients (JATOS) and Valsartan in Elderly Isolated Systolic Hypertension study failed to demonstrate the benefit of lowering SBP below 140 mmHg in the elderly.<sup>29)30)</sup> As such, the target SBP in the elderly in the major clinical guidelines remained at 150 mmHg until most recently.<sup>16)17)</sup>

This all changed with the publication of the SPRINT trial. In the SPRINT elderly trial, which analyzed the results from 2,636 participants in the SPRINT trial who were over the age of 75, intensive SBP lowering (SBP target  $<$ 120 mmHg) was associated with 34% reduction in primary composite outcome compared to the standard SBP lowering (SBP target  $<$ 140 mmHg).<sup>31)</sup> Based on these results, the ACC/AHA arterial hypertension guideline recommended a target SBP  $<$ 130 mmHg for elderly hypertensive patients.<sup>1)</sup> However, because the achieved BP in the SPRINT elderly trial was 124/62 mmHg versus 135/67 mmHg and because unattended automatic office BP measurement was used in the SPRINT study, both the 2018 ESH/ESC guideline and the 2018 Korean Society of Hypertension guideline suggested that the mean SBP of 124 mmHg in the intensive treatment arm more probably reflects a conventional office SBP between 130–139 mmHg and recommended a target SBP of 130–140 mmHg in elderly hypertensive subjects above the age of 65.<sup>2)3)</sup>

## CONSIDERING THE LOWER LIMITS OF BLOOD PRESSURE REDUCTION DURING INTENSIVE BLOOD PRESSURE LOWERING

The harmful effect of too much BP lowering, the J curve effect, has been a long-standing issue of debate. In a post hoc analysis of the International Verapamil-Trandolapril (INVEST) study, which was a randomized trial evaluation 22,576 patients with hypertension with coronary artery disease, Messerli et al found increased risk of MI in subjects who had lower DBP below 70 mmHg. An interaction between lower DBP and history of revascularization was observed with relatively lower risk for primary outcomes in patients with lower DBP and history of revascularization compared to patients with lower DBP without history of revascularization.<sup>32)</sup>

These results were recently corroborated by a pooled analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trial.<sup>33)</sup> In this analysis, 30937 subjects at high CV risk were analyzed for CV outcomes according to the on treatment SBP and DBP. The results showed that on treatment SBP of less than 120 mmHg was associated with increased risk of composite CV outcome (HR, 1.14; 95% CI, 1.03–1.26), CV death (HR, 1.29; 95% CI, 1.12–1.49), and all cause death (HR, 1.28; 95% CI, 1.15–1.42) compared to subjects with on treatment SBP between 120–140 mmHg. Also, mean DBP below 70 mmHg was associated with increased risk of composite primary outcome (HR, 1.31; 95% CI, 1.20–1.42), MI (HR, 1.55; 95% CI, 1.33–1.80), hospitalization for heart failure (HR, 1.59; 95% CI, 1.36–1.86) and all-cause mortality (HR, 1.16; 95% CI, 1.06–1.28) compared to subjects with mean DBP 70–80 mmHg.<sup>33)</sup> Further supporting these findings was an analysis of 1,234,435 participants of the Korean Cancer Prevention Study cohort, in which the hazard ratios of mortality from atherosclerotic CVD was 1.37 (95% CI, 1.20–1.37) for those with DBP <60 mmHg compared to those with DBP of 70–79 mmHg.<sup>34)</sup> Taken together, although intensive BP lowering may be beneficial in further reducing CV outcomes, too much reduction below 120/70 mmHg may actually be harmful. One should be especially careful in DBP going below 70 mmHg in those with underlying multivessel coronary artery disease who did not undergo revascularization or in those with left ventricular hypertrophy.

Also, one should be aware that aggressive BP lowering may lead to increased risk of adverse events leading to treatment discontinuation. In a meta-analysis of 50 BP lowering randomized clinical trials which provided data on treatment discontinuation for adverse events and treatment associated serious adverse events, SBP/DBP reduction of 10/5 mmHg was associated with 24% reduction of major CV events and 89% increase in the risk of treatment discontinuation. Furthermore, SBP reduction below 130 mmHg was associated with smaller reduction in CV events with greater risk of adverse events resulting in treatment discontinuation.<sup>35)</sup> As adherence to medication is an important, but often forgotten factor for reducing CV events,<sup>36)</sup> one should make every effort to minimize adverse events, even if it means that the target BP is not below the current recommended levels.

## CONCLUSION

Although intensive BP lowering to achieve target BP below 130/80 mmHg is beneficial in reducing CV outcomes, one should do so cautiously as to avoid adverse events. As such, the first target of anti-hypertensive treatment should be to achieve BP lowering below 140/90 mmHg. Once that target is achieved, one could target BP below 130/80 mmHg keeping in mind to avoid signs of organ hypoperfusion such as orthostatic hypotension, orthostatic dizziness, weakness and serum creatinine elevation.

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