INDIAN SOCIETY OF HYPERTENSION
CURRENT MEDICAL CONCEPTS

10.5005/jp-journals-10043-0041

PATHOPHYSIOLOGY

Prehypertension: Does It Still Matter?

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ABSTRACT

Prehypertension was introduced in the JNC staging of blood pressure in 2003. The rationale for this classification was the progressive nature of hypertensive disease. Recently clinical trials have demonstrated clear benefits of treatment to blood pressure levels of 120/80 mm Hg, which is the lower threshold of prehypertension. Furthermore other trials suggest that early treatment may be more important in long-term risk reduction rather than immediate risk reduction. These new findings raise questions regarding the current classification and use of medication in the range of prehypertensive blood pressure.

Keywords: Blood pressure, Hypertension, Prehypertension.

How to cite this article: Nesbitt SD. Prehypertension: Does It Still Matter? Hypertens J 2016;2(3):109-112.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

In 2003, the term "prehypertension" was coined to refer to blood pressures between 120 and 139 mm Hg for systolic, and 80 and 89 mm Hg for diastolic to simplify the classification of blood pressure, and to highlight the nature of progression in hypertensive disease.[1] Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) concluded that the ideal systolic blood pressure goal for most patients is 120 mm Hg.[2] If hypertension should be treated to a goal of 120 mm Hg, then does prehypertension still matter? Even more importantly, how should the early stages of blood pressure elevation be addressed? Is the evidence for early treatment now stronger than ever?

Effect of Prehypertension on Outcomes

Prehypertension has been associated with an escalating risk of cardiovascular events. The risk increases with age, gender, and exposure time. The most striking difference in risk is related to the baseline level of blood pressure. The risk of events with blood pressure range of 130–139/85–89 mm Hg is significantly greater than 120–129/80–85 mm Hg.[3] Shimbo et al[4] have shown that there is considerable diagnostic overlap of prehypertension and masked hypertension. Masked hypertension is the presence of normal clinic blood pressure with elevated out of office blood pressures. In a community cohort with a mean age of 45 years, 83% of masked hypertensives had prehypertension, while 34% of prehypertensives had masked hypertension. Moreover, the prevalence of masked hypertension was higher in prehypertensives with blood pressures of 130–139/85–89 mm Hg than 120–129/80–85 mm Hg, at 51 and 26% respectively. In a study of multiple populations, prehypertension carried an increased risk of 41% in cardiovascular endpoints and 92% increase in cerebrovascular endpoints compared to normotensives. Furthermore, the presence of masked hypertension in normotensives or prehypertensives increased the hazard ratio of cardiovascular events similar to nearly 3.[5] Likewise, in African-Americans who are at the highest risk of hypertensive consequences, the prevalence of prehypertension was 62% among participants with normal clinic blood pressure. Masked hypertension was present in 12% of normotensives and in 36% of prehypertensives, and it was associated with a significantly increased LV mass index, microalbuminuria, and common carotid artery thickness.[6,7]

Prior to 2003, prehypertension was known as "high normal blood pressure" (130–139/85–89 mm Hg) and normal blood pressure (120–129/80–89 mm Hg). High normal blood pressure carries higher risk of adverse consequences and higher risk of progression to Stage 1 hypertension.[3,8,9] In the Trial of Prevention Hypertension (TROPHY) study, an angiotensin receptor blocker (ARB) (candesartan cilexetil) was administered to participants with high normal blood pressure in a randomized, controlled, double-blinded 4-year trial. The TROPHY study was the first trial of treatment in individuals who had not yet been diagnosed with hypertension. This novel study demonstrated that early treatment with an ARB was safe, well tolerated, and it reduced the relative risk of progression to stage 1 hypertension by 15.6% in the 2 years following drug discontinuation.[10]

Because SPRINT suggests that nearly all high-risk hypertensives benefit from reducing blood pressure

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to 120 mm Hg, it is the now important to reexamine the question of whether treatment ought to begin at a lower level for all. Large epidemiology studies show that lower blood pressure is associated with lower event rates.[11] Yet Lonn et al[12] have shown that in an intermediate risk mild hypertensive population, such as the HOPE3 trial group, treating with candesartan hydrochlorothiazide (HCT) 16/12.5 mg does not reduce the risk of cardiovascular events compared to placebo. In fact, the subgroup analysis showed that only the group with baseline systolic blood pressure >143 mm Hg had a significant reduction in the co-primary outcomes of cardiovascular disease death, nonfatal myocardial infarction, and stroke; or these events plus heart failure, revascularization, and cardiac resuscitation. The baseline blood pressure was 138/82 mm Hg in HOPE3. Thus perhaps, it is purely baseline risk that drives the decision to treat of which blood pressure is only one component.

Benefit of Short-term *vs* Long-term Risk Reduction

Most clinical trials are focused on interventions to reduce the immediate risk of cardiovascular events in a 4 to 5-year period. This approach is justifiable because of demonstrated improvement in survival, quality of life, and cost savings. The length of clinical trials is dictated by the cost of conducting the trial, difficulty in maintaining follow-up of the study population, and controlling confounders in the trial.[13,14] Yet the longer term benefit or risk of an intervention has potential to be greater than early benefits shown in trials. For example, the early benefits of breastfeeding are clear in improving immunity for young children; however, later in life breastfed children have higher academic performance compared to formula-fed children.[15-17] While both TROPHY and HOPE3 trials introduced antihypertensive medication to "prehypertensive" individuals, the pretense of treatment was quite different. The TROPHY trial sought to assess the "preventive" aspect of early treatment. Early changes in the vasculature of prehypertensives that may be reversible become fixed changes in the vasculature of later stage hypertensives.[18-20] HOPE3 sought to assess the immediate reduction in risk. Both studies provide critical information regarding treatment benefit and risk in low to intermediate risk patients. However, the results of HOPE3 do not abrogate the results of TROPHY. The potential of reducing the progression to hypertension from prehypertensive levels remains a key question to investigate particularly since nonpharmacologic interventions continue to fail to show long-term success.[21]

Risks of Treatment

The argument to treat earlier must be tempered by the concern for excess treatment, side effects, adverse events, and cost. What happens when blood pressure is treated to this level? The side effect and adverse event profile in both SPRINT and : Action to Control Cardiovascula Risk in Diabetes (ACCORD) trials showed hypotension and syncope to be among the most common in the groups treated to a more intensive goal of 120 mm Hg.[2,22] Yet there was no difference in hypotension and syncope in the TROPHY study between treatment and placebo. In addition, HOPE3 showed no difference in overall side effects between the treatment groups, but there was a significant difference in hypotension between treatment and placebo arms.[12] The key differences between these trials are the number of drugs administered, age of the population, and the baseline blood pressure treatment status of the study populations. At baseline the number of participants on antihypertensive therapy was 87% in ACCORD, 91% in SPRINT, and 0% in TROPHY. By the end of these trials, the number of drugs used in both ACCORD and SPRINT trials outnumbered the number in the TROPHY trial to achieve a blood pressure goal of 120 mm Hg. ACCORD required 2.3 (1–5) medicines to achieve the intensive treatment goal, in SPRINT it was 3 (1–5), while in TROPHY only 1 drug leads to a similar blood pressure. The average age of participants was also different with ACCORD at 62 years old, SPRINT at 67.8 years old, and TROPHY at 48 years old. The baseline clinic blood pressure using an automated device in ACCORD, SPRINT, and TROPHY was 139/76, 139/78, and 134/84 mm Hg respectively. The baseline blood pressure in HOPE3 was 138/82 mm Hg and the achieved blood pressure in the treatment arm was 128/76 mm Hg. The achieved systolic blood pressure in the intensive treatment arms of ACCORD and SPRINT were 119 and 121 mm Hg respectively. The achieved blood pressure in the TROPHY treatment arm at the end of 2 years was approximately 123/76 mm Hg. More medication in an older population with underlying vascular disease leads to greater frequency of side effects. However, SPRINT has clearly shown that despite these challenges, the benefit of tighter control is significant. Although ACCORD could not demonstrate a statistically significant benefit in the primary outcome, tighter control showed benefit in the secondary outcomes, stroke. While SPRINT and ACCORD represent high-risk populations, HOPE3 and TROPHY represent low to intermediate risk groups, yet TROPHY used less medicine (candesartan hct *vs* candesartan) and achieved lower blood pressure with lower incidence of side effects than the HOPE3 study. This may be explained by the lack of differentiation between white

coat hypertensives from prehypertensives in HOPE3 compared to TROPHY.

Final Thoughts

Guidelines for diagnosing and managing hypertensive disease will most assuredly be affected by the results of these pivotal new trials. The urge to be more aggressive in all hypertensives based on SPRINT is balanced by the modest effects of ACCORD and HOPE3. Canadian guidelines have already shifted to reflect the observations from SPRINT, favoring lower treatment goals (<120/80) for higher risk patients with systolic blood pressure >130 mm Hg; and removal of the limited goal of 150/90 for patients over 80 years old unless clinically necessary. Furthermore, the use of automated blood pressure devices for measurement is endorsed as the ideal for clinical use.[23] It is likely that other guidelines and consensus groups will provide new recommendations in the coming year reflecting the implications of these new trials. Perhaps the most important revelation from these trials is the difference in responses and risks based on the population studied. A more individual approach based on risk rather than pure level of blood pressure seems plausible. However, out of office blood pressure assessment has great utility in the proper identification of prehypertension, masked hypertension, and white coat hypertension. Preventing hypertension with early treatment is yet unanswered although these trials help to narrow the scope of individuals for whom early pharmacologic treatment is at issue. Perhaps it is also time to rethink the classification of prehypertension altogether. It may be necessary to take a step back in time to consider prehypertension as blood pressures of 130–139 mm Hg and/or 85–89 mm Hg.

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