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THERAPEUTIC IMPLICATION

Clinical Implications of Recent Therapeutic Trials in Hypertension: Insights from SPRINT and HOPE-3 Trials

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ABSTRACT

Hypertension is a global pandemic of ever growing proportions. It is the most important population attributable risk-factor for ischemic heart disease, stroke and cardiovascular mortality. Appropriate blood pressure (BP) control with antihypertensive agents reduces these cardiovascular complications but very tight BP control can lead to adverse effects like hypotension and renal dysfunction, especially in the elderly. Moreover, the relationship between BP and ischemic heart disease and all-cause mortality follows a J-shaped curve with a signal of higher mortality at low BP ranges. Blood pressure targets across various age and cardiovascular risk groups are not well defined. In the paucity of clinical trial data, many of the BP targets suggested by panels like the Joint National Committee are based on expert consensus. Two recent randomized clinical trials, Systolic Blood Pressure Intervention Trial (SPRINT) and Heart Outcomes Prevention Evaluation (HOPE-3), have extended our knowledge of the BP control paradigm. The SPRINT trial evaluated the benefits of intensive BP reduction to a target systolic BP of 120 mm Hg by addition/up-titration of various antihypertensive medications in a high-risk patient population. The HOPE-3 trial was a primary prevention trial that evaluated the utility of BP lowering in intermediate-risk patients without known cardiovascular disease using a fixed dose drug combination. These trials are discussed in detail in this review.

Keywords: Blood pressure, Clinical trials, Hypertension control.

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INTRODUCTION

Hypertension is the most common medical condition in the world. The global pandemic of hypertension affects more than a fourth of the world population. In the year 2000, 26.4% of the world's adults were estimated to have hypertension with a further 60% increase predicted by 2025.[1] Based on 2009 to 2012 data, 32.6% (80 million) of US adults have hypertension.[2] With urbanization, the prevalence of hypertension is rapidly catching up in Southeast Asian countries. An overall prevalence for hypertension in India is estimated to be around 29.8% with significantly more hypertensive populations in urban (33%) than rural (25%) India.[3] Hypertension is the leading risk factor for global disease burden and among the top three risk factors for disease burden in India.[4,5] It is also the primary population attributable risk-factor for ischemic heart disease, stroke, and cardiovascular (CV) mortality.

Clinical trial data shows that treatment with any commonly used antihypertensive regimen reduces the risk of major CV events.[6] Blood pressure (BP)-lowering therapy can affect a 35 to 40% reduction in stroke, 20 to 25% reduction in myocardial infarction, and more than 50% reduction in incident heart failure.[7]

HOW LOW SHOULD BLOOD PRESSURE GO?

With the benefits of BP reduction well documented, the next obvious question is how low should it go? Observational studies suggest that benefits of BP lowering may extend to levels below 120 mm Hg. A meta-analysis of individual data for one million adults from 61 prospective studies showed a direct and linear relationship between BP and vascular and the overall mortality throughout middle and old age.[8] There was no evidence of a lower threshold for risk of mortality in this analysis, and lowest mortality was seen with BP as low as 115/75 mm Hg.[8] These findings were consistent in all age groups, including those from 60 to 90 years of age. Is it reasonable then, to aim for BP goals well below the average normal of 120/80 mm Hg?

First of all, it is crucial to realize that although the observational data from meta-analysis, such as the one by Lewington et al provide useful information about the relationship between BP and the clinical outcome, one needs to be cautious in directly translating these findings to the treatment targets in the patients. The only reliable and definitive way to do that will be to conduct randomized controlled trials (RCTs) to document the benefits of therapeutic intervention(s) directed to a specific goal (in this case BP level) and demonstrate the efficacy and safety of the intervention used. We have learned from the large number of RCTs conducted in hypertension that BP can be lowered to a specific target but requires multiple

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antihypertensive drugs. Tighter BP control comes at a high price due to increased risk of drug-related adverse experiences. The relationship between BP and ischemic heart disease and all-cause mortality follows a J-shaped curve rather than a linear pattern. The rates of coronary events, such as myocardial infarction and cardiac mortality decrease with BP lowering but reach a nadir at diastolic BP of around 85 mm Hg, and then start rising as BP drops further.[9,10] Stroke rates, on the contrary, have a linear relationship with BP lowering, such that at lower diastolic BP ranges there is much more myocardial infarction than stroke.[10] Tighter BP control can also lead to significant medication-related adverse effects like orthostatic hypotension, syncope, renal insufficiency, and electrolyte imbalances. Side effects are particularly pronounced in the elderly and with polypharmacy. From a system's standpoint, high costs of potentially unnecessary medications, increased need for intensive monitoring leading to more frequent clinic visits, and poor patient compliance from complicated antihypertensive regimens are a real issue. Clearly, there needs to be a balance at which the risk/benefit ratio of antihypertensive therapy is most favorable for the outcomes without causing any serious adverse effects.

THE CURRENT BLOOD PRESSURE GUIDELINE RECOMMENDATIONS

In 2003, the Joint National Committee (JNC) on prevention, detection, evaluation, and treatment of high blood pressure presented the JNC 7 report, which recommended target BP goal of < 140/90 mm Hg in most hypertensive patients and < 130/80 mm Hg in those with diabetes mellitus or chronic kidney disease.[11] These BP targets were based on a range of findings from RCTs and expert consensus opinions and have guided the clinical practice of BP management for over a decade. In 2014, the panel members appointed to JNC 8 published some important changes to the BP targets.[12] While advocating the BP target of < 140/90 mm Hg for persons < 60 years of age (including diabetics and kidney disease patients), they recommended relaxation of BP target to < 150/90 mm Hg for those > 60 years. This decision to relax BP goals in the elderly was based not on any new data since JNC 7, but rather lack of evidence from specific RCTs of benefit beyond this threshold. This decision has been quite controversial to say the least. Some JNC 8 panel members published a separate "minority report," contending that relaxation of BP goals could potentially increase CV mortality and, specifically, rates of strokes in the elderly, and undo the progress made toward hypertension control over the years.[13] This dissenting opinion from the JNC 8 panel members did acknowledge that there was little evidence to recommend appropriate systolic BP (SBP) goals for those > 60 years of age, and goal < 140 mm Hg was primarily based on expert opinion. New trial evidence was therefore needed to resolve some of these contentious issues. The recent findings from the SPRINT does provide further insights in this area and will be discussed and compared with another recent trial, the Heart Outcomes Prevention Evaluation (HOPE-3) study.[14-16]

THE SPRINT TRIAL

The SPRINT trial was a multicenter, randomized, controlled and open-label clinical trial to evaluate if a treatment strategy aimed at reducing SBP to lower (SBP < 120 mm Hg) than the currently recommended goal (SBP < 140 mm Hg) would reduce the occurrence of CV events.[14,15] The trial was conducted at 102 centers in the USA with randomized 9,361 hypertensive adults aged ≥ 50 years with SBP of 130 to 180 mm Hg (treated or untreated) and at least one of the following CV disease risk factors: (1) Clinical or subclinical CV disease, (2) chronic kidney disease [estimated glomerular filtration rate (eGFR) 20 to 60 mL/minute/1.73 m^2], (3) Framingham 10-year risk score ≥ 15%, or (4) Age ≥ 75 years. Patients with stroke, diabetes, heart failure, proteinuria > 1 gm/day, severe chronic kidney disease (eGFR < 20 mL/minute/1.73 m^2), and those with adherence concerns were excluded (Table 1).

Various evidence-based antihypertensive medications (and their combinations) were added and/or titrated at each study visit to achieve the prespecified BP goal. Mean baseline BP was 139.7 mm Hg. Through the median follow-up period of 3.26 years, the mean SBP of 121.5 mm Hg was achieved in the intensive-treatment arm and 134.6 mm Hg in the standard-treatment arm. The composite outcome of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from CV cause occurred less frequently in the intensive-treatment arm [hazards ratio (HR) 0.75, 95% confidence interval (CI) 0.64–0.89, p < 0.001; NNT 61]. This difference in primary outcome was driven mainly by less CV mortality and less heart failure with intensive therapy. Similarly, all-cause mortality was lower in the intensively treated patients (HR 0.73, 95% CI 0.60–0.90, p = 0.003; NNT 90) (Table 2).

Not unexpectedly, antihypertensive medication-related serious adverse effects of hypotension, syncope, electrolyte abnormalities, and acute kidney injury occurred more frequently in the intensive treated group (HR 1.88, p < 0.001). The authors concluded that lowering of SBP to a goal of < 120 mm Hg compared with < 140 mm Hg in high-risk patients (without diabetes or

stroke) resulted in lower rates of fatal and nonfatal CV adverse events at the cost of minor increase in medication-related adverse effects.

HOPE-3 TRIAL

The HOPE-3 trial addressed the question of BP lowering in primary prevention.[16] This trial evaluated the role of antihypertensive therapy in intermediate risk patients (annual risk of major CV events ≅ 1%) without known CV disease and with SBP < 160 mm Hg. Unlike SPRINT, where different BP-lowering medications and their combinations were used to target BP goals, HOPE-3 compared a fixed dose combination of candesartan 16 mg and hydrochlorothiazide 12.5 mg daily with placebo. Using a 2-by-2 factorial design, another part of this study evaluated the role of statin therapy in these patients (not discussed here).

This multinational, randomized, double-blinded trial enrolled 12,705 intermediate risk patients from 228 centers in 21 countries, including India. The study population comprised men ≥ 55 years and women ≥ 65 years of age with at least one of the following CV risk factors: (1) Elevated waist-to-hip ratio, (2) low high-density lipoprotein cholesterol, (3) tobacco use, (4) dysglycemia, (5) family history of premature coronary disease, and (6) mild renal dysfunction. Women ≥ 60 years of age that had two or more risk factors were also included (Table 1). Persons with known CV disease, moderate to severe renal dysfunction, and contraindications to the trial drugs were excluded.

After a run-in period of 4 weeks, 12,707 persons were randomized to candesartan/hydrochlorothiazide or placebo and followed for 5.5 years. A mean BP difference of 6/3 mm Hg was achieved between comparison groups. At the end of the study period, there were no

Table 1: Comparison of SPRINT and HOPE-3 trials – design and baseline patient characteristics

	SPRINT	*HOPE-3*
Trial design	Randomized control trial	Randomized control trial
Blinding	Open label	Double blinded
Participation	USA (including Puerto Rico)	21 countries
Study population	9,361	12,705
Population characteristics		
Mean age	68 years	66 years
Female sex (%)	36%	46%
White	58%	20%
Black	31%	2%
Hispanic	10%	27%
Chinese	< 2%	29%
South Asian + other Asian	< 2%	20%
Chronic kidney disease	28%	None
Cardiovascular disease	20%	None
On antihypertensive therapy	91%	22%
Cardiovascular risk	2.2%	0.8%
Run-in period	None	4 weeks
Trial strategy	Treat-to-target	Fixed dose *vs* placebo
Antihypertensive medications	Various. Average 2.8 medications in intensive-treatment group and 1.8 in standard-treatment arm	Combination of 16 mg of candesartan + 12.5 mg of hydrochlorothiazide
Funding	National Heart, Lung and Blood Institute	Industry

Table 2: Comparison of SPRINT and HOPE-3 trials – results

	SPRINT	*HOPE-3*
Median follow-up	3.3 years	5.6 years
Adherence at the end of the trial (%)	93%	77%
Mean blood pressure reduction at the end of the trial	13 mm Hg	6 mm Hg
Outcomes	Composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular cause (HR, 0.75; 95% CI, 0.64–0.89; p < 0.001)	1. Composite of cardiovascular death, myocardial infarction, or stroke (HR, 0.93; 95% CI, 0.79-1.10; p = 0.40) 2. Composite of the above and resuscitated cardiac arrest, heart failure, and revascularization (HR, 0.95; 95% CI, 0.81–1.11; p = 0.51)

statistical difference noted in the first co-primary outcome (composite of CV death, myocardial infarction, or stroke; HR 0.93; 95% CI 0.79–1.10, p = 0.40), second co-primary outcome (first co-primary endpoint plus resuscitated cardiac arrest, heart failure, or revascularization; HR 0.95, 95% CI 0.81–1.11, p = 0.51), or any of the secondary endpoints (Table 2).

COMPARING SPRINT AND HOPE-3 TRIALS

Benefits of BP Reduction as a Function of CV Risk

The SPRINT and HOPE-3 trials addressed different questions in different populations and their results should not be considered incongruent (Table 1). SPRINT targeted a high-risk patient population with preexisting clinical/subclinical CV disease, chronic kidney disease, and a mean Framingham 10-year CV risk score of 20 and showed benefits of intensive BP reduction to a target SBP of 120 mm Hg. On the other hand, the HOPE-3 trial was a primary prevention trial that targeted intermediate-risk patients without known CV disease or significant renal dysfunction that were at ≅ 1% annual risk of CV events and failed to show significant CV risk reduction in this group. Findings from these trials emphasize that benefits of BP reduction are a function of baseline patient risk. High-risk populations, perhaps, have most to benefit from aggressive antihypertensive therapy while average-risk population may not gain as much.

Benefits of BP Reduction are seen Only in Hypertensive Patients

Though mean SBP at the outset of the trial was similar in both studies (140 mm Hg in SPRINT, 138 mm Hg in HOPE-3), there are important differences that need to be highlighted. The SPRINT enrolled patients with documented hypertension with more than 90% on therapy and a majority on two antihypertensive drugs at baseline. On the other hand, HOPE-3 did not have hypertension as an enrollment criterion. In fact, only 38% of patients in HOPE-3 reported a history of hypertension and a mere 22% were on BP-lowering medications at baseline. It is not surprising that benefits of antihypertensive therapy were seen in SPRINT patients with preexisting hypertension (controlled or uncontrolled) rather than HOPE-3 patients, a majority of who were prehypertensive at best. To further prove the point, a subgroup of patients in HOPE-3, with baseline SBP > 143 mm Hg, showed reduced CV co-primary outcomes with BP lowering, despite the overall negative results of the trial. Though results of subgroup analysis should be interpreted with caution, these findings suggest that current targets for initiating therapy at SBP > 140 mm Hg may be appropriate for average-risk general population. By the same token, HOPE-3 also proves the futility of BP lowering in persons who are not hypertensive (SBP< 140 mm Hg).

Magnitude of BP Reduction

It is well documented that larger reductions in blood pressure produce larger reductions in CV events.[6] The SPRINT trial, with a "treat-to-target" strategy, achieved an average difference of 15 mm Hg between groups compared with the 6 mm Hg difference seen in HOPE-3 that used a "fixed-dose" strategy. Many experts are of the opinion that, all things being equal, an excess 9 mm Hg reduction of BP could potentially explain the statistically significant results of SPRINT and the lack thereof in HOPE-3. However, due to the very different goals and study designs of the two trials, this remains a conjecture.

Choice of Antihypertensive Medication

The SPRINT trial largely used evidence-based antihypertensive drug combinations for BP control, and chlorthalidone was encouraged as the primary thiazide-like diuretic. Chlorthalidone has been extensively studied in randomized trials and has proven efficacy in reducing CV events.[17] In a network meta-analysis of nine randomized trials, it was shown to be better than hydrochlorothiazide by a substantial margin in reducing CV events.[18] It is a more potent and longer acting diuretic than hydrochlorothiazide. A recent small randomized trial showed 12.5 mg of hydrochlorothiazide (the dose used in HOPE-3) not only to be inferior to 6.25 mg of chlorthalidone but essentially ineffective in reducing 24-hour ambulatory BP.[19] Similarly, the benefits of angiotensin receptor blockers in reducing CV events are not as clear as angiotensin converting enzyme inhibitors.[20,21] Thus, use of fixed combination of hydrochlorothiazide and candesartan used in HOPE-3 might not have been the ideal first-line therapy to reduce CV endpoints and could possibly explain the nonsignificant outcomes.

ISSUES AND CONTROVERSY

The SPRINT trial has attempted to fill the knowledge gaps in antihypertensive therapy goals in persons >60 years of age and answer the very important question raised by the JNC 8 panel's "minority report". It enrolled a significant proportion of elderly patients. The mean age of participants was 67.9 years and more than a fourth (28.2%) were above the age of 75. Intensive treatment to a SBP goal of 120 mm Hg was shown to reduce significant CV

endpoints, and most importantly mortality. Furthermore, a substudy of SPRINT in 2,636 adults ≥ 75 years of age (mean age 80 years) showed an even greater benefit (HR 0.66) from intensive therapy compared with the overall SPRINT cohort (HR 0.75) without significant differences in the rate of serious adverse events.[22]

These data directly contradict the JNC 8 panel's recommendation of relaxing BP targets to < 150/90 mm Hg in those > 60 years of age and provide evidence to do exactly the opposite. Should we then revert to the target of < 140/90 mm Hg in the elderly and perhaps even go beyond and shoot for near normal BP target of 120 mm Hg? The answer may not be simple and one should not hasten to draw conclusions without knowing specific details of the trial.

We have briefly visited the J-curve at the beginning of this review. Though this phenomenon has not been reported in the SPRINT patients, real-world data suggests that this is a cause of concern. Outcomes of 22,672 hypertensive patients with coronary artery disease (CAD) from 45 countries enrolled in the CLARIFY registry were recently published.[23] After a median follow-up of 5 years, those with SBP < 120 mm Hg and diastolic BP < 70 mm Hg were found to be at a higher risk of all-cause mortality, CV mortality, and myocardial infarction. Thus, real-world outcomes are not necessarily congruent with the results of the SPRINT trial, where apparently, the J-curve phenomenon was not observed despite achievement of a mean SBP of 121.5 mm Hg in the aggressive treatment arm. This raises serious concerns about generalizability of SPRINT, especially in the elderly, many of whom might have clinically asymptomatic CAD. How does one reconcile these findings?

Differences in the methodology of BP measurement in research and real-world settings may offer a possible explanation. For example, BP in SPRINT trial patients was measured after 5 minutes of quiet rest, in an unattended room and repeated three times. The average of the three BP readings was used as the BP for that visit. Postrest and unattended BP measurements used in research trials tend to be lower by as much as 15 to 20 mm Hg than the clinical setting due to the avoidance of "white-coat" effect.[24,25] Though desirable and recommended, instituting such elaborate BP measurement strategies may be impractical in most busy outpatient clinic settings. Implementing SPRINT BP goals without using the specific SPRINT BP measurement methodology may prove dangerous. It has been suggested that BP measured in the SPRINT trial may be 10 to 15 mm Hg lower than that measured in the usual clinical setting and aiming for SPRINT targets may lead to overshooting and can cause even more hypotensive episodes.[26]

The benefits of intensive BP lowering in the SPRINT came at the price of increased hypotensive complications.[27] This phenomenon is prominently seen in high-risk elderly patients who have most to gain from BP control but are also most susceptible to hypotension, syncope, electrolyte abnormalities, and acute kidney injury if not monitored closely.

CLINICAL IMPLICATIONS

In summary, it is important to recognize that hypertension is a complex disease syndrome that affects a heterogeneous group of people, and a "one glove fits all" strategy may not work for a given patient. New evidence from the SPRINT and HOPE-3 studies emphasizes individualization of BP control based on the CV risk as well as the concern of adverse clinical consequences of excessive lowering of BP and the associated side effects of the drugs needed to achieve it. Blood pressure control perhaps needs a paradigm shift from age-based stratification to risk-based stratification. Antihypertensive therapy should be initiated in average risk individuals at a SBP of 140 mm Hg and not before. Current goals of therapy to bring BP < 140 mm Hg seem appropriate for most patients. Tighter goals in patients with high CV risk should be attempted when feasible and with extreme caution. Though the primary goal is to reduce CV morbidity and mortality, elderly needs special attention to avoid adverse effects of orthostatic hypotension, acute kidney injury, and possibility of the J curve phenomenon in those with underlying CAD from tight BP control. Such patients need close follow-up, with frequent office visits, ambulatory, and home BP monitoring as well as avoidance of rapid up-titration of antihypertensive regimens. Let us remind ourselves of the central tenet of the Hippocratic Oath "above all do no Harm".

DISCLAIMER

The views expressed by the authors in this article are their own and do not represent the official position of the affiliated institutes.

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