The Case for Low Blood Pressure Targets

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The “totality” of hypertension clinical trial endpoint data has shown that the absolute benefit of pharmacological blood pressure (BP) lowering is directly related to the BP level and baseline cardiovascular risk, albeit with attenuation of the relative risk reduction per unit of BP lowering in patients with diabetes and chronic kidney disease. Absolute risk reductions with pharmacological treatment are greater with advancing age. Cardiovascular risk and mortality reductions attributable to pharmacological BP lowering have been demonstrated for progressively lower BP levels extending well below the conventional BP threshold (140/90 mm Hg) for hypertension. Hypertension endpoint trials have shifted from determining the relative clinical benefits of various antihypertensive drugs to exploring whether lower than conventional BP targets in persons with BP levels spanning the prehypertensive to much higher BP strata confer clinical benefit. The more recent of these trials were “relatively” agnostic to the drugs used for BP lowering although several trials provided, but did not mandate the use of, specific agents. Pharmacological treatment benefit has been demonstrated at pretreatment BP levels even lower than the intensive SPRINT BP target (<120 mm Hg) and a growing body of evidence suggests that substantial risk reduction can be achieved by maintaining a normal BP over time (rather than waiting for BP to exceed 140/90 mm Hg before treating). Thus there is a compelling rationale to lower the BP threshold not just for a therapeutic goal but also for the initiation of pharmacological intervention.

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Initially, the relatively small placebo-controlled VA Cooperative study Group study1–2 demonstrated cardiovascular (CVD) risk reductions (not coronary) in persons with moderate to severe (diastolic blood pressure (BP) of 105–114 mm Hg) but not milder levels hypertension. Over the years, larger hypertension endpoint trials have tested and shown clinical benefit from pharmacological treatment at progressively lower BP levels3–9 This has been possible because the focus moved beyond simply demonstrating that pharmacological BP lowering lowers CVD risk as well as beyond whether one drug class is superior to another. Contemporary hypertension trials5,6,8–11 have formally tested whether differing BP targets below the conventional 140/90 mm Hg, at times including persons with BP well below 140/90 mm Hg, reduces CVD events with acceptable risk. The SPRINT trial12 results may also provide support for separating the BP threshold for initiating pharmacological treatment from the therapeutic BP target (or target range).

In recent years, the debate over the most appropriate BP targetsresholds for hypertension treatment in general as well as for specific subgroups has become increasingly controversial. No consensus has evolved around the type of evidence, other than selected clinical trials, to be considered (meta-analyses5,4,12 Mendelian randomized BP cohorts13) and their rank–order of importance, when determining BP treatment thresholds/therapeutic targets. This is largely a result of the absence of an agreed upon conceptual framework to guide the interpretation of the body of data deemed relevant for consideration. A similar conundrum exists for the interpretation of randomized clinical trial data.

The SPRINT trial13 provides high-level clinical endpoint data confirming that intensive (<120 mm Hg) rather than conventional (<140 mm Hg) on-treatment targets, at least in those without diabetes, provide greater CVD and mortality reductions than higher BP target levels in middle-aged persons 50–80 years of age with a baseline systolic BP 130–180 mm Hg. Several pre-SPRINT studies14,15 of randomized hypertension endpoint trials and Mendelian BP cohorts13 (i.e., persons with gene polymorphisms associated with low BP, who when followed for extended periods of time serve as a proxy for long-term pharmacological BP control) provided similar, albeit less definitive, evidence in support of lower than conventional BP thresholds/targets. The relative homogeneity of proportional CVD reduction with various pharmacological BP agents across a broad range of BPs and co-morbidities, as well as the established treatment benefit when pharmacological BP lowering is initiated at much lower than the conventional hypertension diagnostic
BP threshold of 140/90 mm Hg, should substantively inform new hypertension treatment guidelines.

Herein, we review the convincing body of data supporting lower than conventional (<140/90 mm Hg) treatment threshold/targets. We also suggest guiding principles for the types of data that are relevant to the clinical use of hypertension therapeutics, and the interpretation of randomized controlled trial data. Lastly, we propose several strategies for updating the recommended timing and intensity of antihypertensive drug therapy.

**The evidence base supporting lower than conventional BP thresholds/targets**

**Epidemiological data.** Epidemiological data have convincingly demonstrated a log-linear relationship with BP level and cardiovascular outcomes that begins at incrementally higher BP levels, well below 140/90 mm Hg. The upward inflection point of CVD risk in such epidemiological studies (~115 mm Hg systolic) is very close to the SPRINT systolic BP (SBP) target in the intensive treatment group (<120 mm Hg). A recent analysis of the Framingham Offspring and Atherosclerosis Risk in Communities study showed the existence of substantial excess cardiovascular risk for individuals whose baseline systolic BP was above normal but below traditional hypertension treatment thresholds (i.e., >120 but <140 mm Hg). Perhaps more importantly, data from the Coronary Artery Risk Development in Young Adults Study and the Multi-Ethnic Study of Atherosclerosis suggest that the current, threshold based approach to initiation of antihypertensive therapy cannot adequately restore risk to ideal levels, even if the intensive SPRINT target is achieved.

**Mendelian randomized BP cohorts.** Mendelian randomization within epidemiological cohorts takes advantage of the multiple gene polymorphisms linked to lower BP that are distributed approximately randomly at conception. As a result, much longer follow-up periods are inherent to this type of study, providing new insight into the unconfounded effect of systolic BP on pressure-sensitive CVD outcomes. Mendelian randomized observational cohorts can thus serve as a long-term proxy for pharmacological BP control. Using such an approach, we reported that long-term exposure to lower BP (attributable to a cluster of genetic alleles) had more than 2-fold greater impact on coronary heart disease than the identical BP difference in nearly one million persons in 61 longitudinal cohort studies; it was also noted that the impact of low BP on coronary heart disease risk reduction was cumulative. The impact on coronary heart disease in this Mendelian randomization for the same magnitude of BP difference observed in randomized clinical trials of pharmacological therapy in a meta-analysis of 27 short-term randomized controlled trials in over 100,000 pharmacologically treated hypertensives without known CVD (SBP 8.5 mm Hg lower in the low-BP group over 4.4 years of average follow-up) was nearly 3-fold greater. The age-related rise in systolic BP was significantly lower in those naturally randomized to the cluster of genetic alleles linked to lower BP. This observation is consistent with higher levels of BP, even within the so-called normal range, being a substantive cause of the steeper slope in the rise BP with advancing age.

Epidemiological studies and Mendelian randomizations make complementary contributions, albeit not as convincingly as “adequately powered” randomized controlled trials and meta-analyses, to our understanding of hypertension and CVD risk. Mendelian randomized cohorts with differential BP levels followed over the long term also have implications for the duration of hypertension control. The CVD risk reductions are substantively larger than those observed in short-term randomized controlled trials or epidemiological studies for a given magnitude of BP reduction. Mendelian randomized BP cohorts should not have similar CVD risk as pharmacologically treated hypertensive cohorts achieving the same BP level because of the residual CVD risk that drug treatment does not appear to eliminate.

**Meta-analyses of pharmacological hypertension treatment trials**

Meta-analyses represent a pragmatic, useful way to aggregate and display hypertension outcomes data spanning many decades in very large numbers of pharmacologically treated patients with hypertension. Meta-analyses have shown clear benefit from pharmacological treatment at pretreatment BP levels well below 140/90 mm Hg. The absolute treatment benefit is proportional to the height of the pretreatment CVD risk level, in persons with and without vascular disease, across a broad range of BP levels from the prehypertensive range to well into stage 2 hypertension. Relative risk reductions for CVD are also similar across a broad range of BP in participants with and without CVD, although RR reductions per unit of SBP lowering are less in hypertensives with diabetes and CKD than in those without these conditions. The SPRINT results are entirely consistent with the pre-SPRINT meta-analysis of 147 randomized trials published in 2009 by Law.

**THE SPRINT STUDY**

The SPRINT study was a landmark unblinded randomized clinical trial that included 9,361 high-risk hypertensives 50 years and older with SBP 130–180 mm Hg and compared an intensive (systolic BP < 120 mm Hg) relative to a standard BP target (systolic BP < 140 mm Hg) on the risk for a composite primary outcome (myocardial infarction, acute coronary syndrome, stroke, heart failure, or CVD death). Persons with prior stroke and diabetes mellitus were excluded. All major antihypertensive drug classes were available without charge to participants. Though the protocol did not mandate the use of specific drugs, the use of drug classes with the most evidence for CVD risk reduction was encouraged; chlorthalidone and amldopine, respectively, were the preferred thiazide-type diuretic and calcium antagonist. Systolic BP averaged 121.5 and 134.6 mm Hg, respectively, in the intensive and standard BP target groups; 62% of participants in the intensive group had systolic BP <120 mm Hg. After median follow-up of 3.26 years, SPRINT was stopped.
early because of a 25% lower rate of the composite primary outcome, and a 27% lower all-cause mortality in the low-BP target group. The average number of prescribed antihypertensive medications was 2.8 in the low and 1.9 in the higher BP target groups. Despite visually separated point estimates in some predefined subgroups, there was no convincing evidence (statistical interaction) of differences in treatment benefit for any subgroup. The use of unattended automated office BP (AOBP) in SPRINT has caused significant angst in regards to how the positive results in this trial should inform recommendations to clinical practitioners. Specifically, the main concern centers on the proven systematically lower BP readings obtained with unattended AOBP relative to manual office BP (MOBP) determinations.

**BP MEASUREMENT TECHNIQUES**

Research BP measurement techniques used in clinical trials and epidemiological studies have “never” produced BP readings that were directly comparable to MOBP measurements obtained in clinical practice. Accordingly, an analysis by Myers et al.\(^\text{19}\) combined data from 6 studies to compare mean MOBP readings with research BP determinations; the mean BP in the former was 154/91 mm Hg compared to 145/85 mm Hg, a 9/6 mm Hg difference (MOBP higher). Another study\(^\text{20}\) compared AOBP to solitary MOBP readings. AOBP readings averaged 141/83 mm Hg compared to 155/90 mm Hg for solitary MOBP readings, a 14/7 mm Hg difference. A report by Myers et al.\(^\text{19}\) summarized the contrast of AOBP and awake ambulatory BP (AABP) measurements across 9 studies involving 2,692 participants with BP measurements obtained with both modalities; the average BP was identical being 137/79 with AOBP and AABP. The difference (relative to MOBP) in obtained BP readings “might” be slightly greater with AOBP; however, both methods produce BP readings that are systematically and significantly lower than manual BP readings obtained in the clinician’s office. AOBP readings are almost identical to AABP readings\(^\text{19}\) over a wide range of BP when measured in both clinic exam rooms and waiting rooms.\(^\text{20}\) AOBP, AABP, and home BP readings are approximately equivalent and all are lower than typical MOBP.

**Adverse effects of intensive hypertension treatment**

In a large meta-analysis published by Xie et al., serious adverse events (SAEs) occurred more often in participants randomized to intensive compared to standard BP control though the absolute difference in risk is very small.\(^\text{3}\) In SPRINT,\(^\text{4}\) SAEs occurred similarly in the intensive and standard BP groups though hypotension, acute kidney injury, and syncope occurred more frequently in the low-BP target group; nevertheless, the frequency of occurrence of these condition-specific AE’s was 4.1% or less in both treatment groups. Of note, orthostatic hypotension was slightly more common (18.3% vs. 16.6%, \(P = 0.013\)) in the standard rather than the intensive treatment group. In the ACCORD study,\(^\text{5}\) there were more SAEs in the intensive compared to the standard therapy group that were attributable to antihypertensive medications (3.3% vs. 1.27%, \(P < 0.001\)); specifically, there was more hypotension (0.7% vs. 0.04%, \(P < 0.001\)), and bradycardia or arrhythmia (0.5% vs. 0.13%), though overall adverse hemodynamic effects were uncommon. There was also more hyperkalemia (0.4% vs. 0.04%, \(P = 0.01\)) and more occurrences of reduced kidney function defined as an estimated glomerular filtration rate <30 ml/min/1.73 m\(^2\) (4.2% vs. 2.2%, \(P < 0.001\)). In SPS3 trial,\(^\text{11}\) 3,020 patients (average age 62 years) with prior history of nondisabling lacunar stroke were randomized to SBP <130 mm Hg or 130–149 mm Hg, there was a nonsignificant reduction in recurrent stroke (−19%, 95% confidence interval −36% to 3%, \(P = 0.08\)) and a significant reduction in intracerebral hemorrhage (−63%, 95% confidence interval −85% to −5%, \(P = 0.03\)). SAEs were numerically but not significantly higher in the lower compared to higher BP target group (0.40% vs. 0.26% per patient year, \(P = 0.20\)). Notably, there was no difference in unsteadiness, dizziness, or light-headedness with postural change. In aggregate, data suggest that lower BP targets are relatively safe (small increase in SAEs, other adverse events, and biochemical abnormalities). However, at present, there is no consensus formula for weighing the risk of SAEs with the benefits of treatment.

**Proposed conceptual framework for the interpretation of hypertension randomized controlled endpoint trials**

**Randomized controlled trials.** Adequately powered well-executed randomized controlled trials are considered to be the highest level of evidence available when utilizing data to make therapeutic decisions. Such trials often have prespecified subgroups across which the treatment effect is displayed, typically as whisker plots with 95% confidence intervals. Examining the subgroups for consistency is routinely done. However, one must be careful given the fact that many prespecified subgroup analyses are inadequately powered and, indeed, may not reach statistical significance solely as a consequence of their small sample size. Thus, positive subgroup results convey substantively more information than negative subgroup findings but are also susceptible to being falsely positive, especially when the number of nonrandomized contrasts is high. In the SPRINT study, the intervention result was not statistically significant in African Americans but was in the larger group of Whites. However, there was no evidence of an interaction of treatment status with race. Accordingly, the “difference” in statistical significance of the intensive intervention does not equate, with any confidence, to the proving that the effect of intensive treatment on the SPRINT primary outcome differed by race. Well executed but inadequately powered randomized controlled trials do not provide high-level evidence for the absence of a treatment effect.\(^\text{6}\) Indeed, in the ACCORD trial,\(^\text{1}\) a well planned and executed study, the primary composite endpoint rate was only half of the anticipated rate. Consequently, the trial could have missed a favorable intervention effect of intensive BP control relative to standard therapy of as much as 27% (slightly more than the treatment benefit documented for intensive BP lowering on the SPRINT primary composite endpoint). Moreover, the point estimate of the intensive BP lowering intervention was in the direction of benefit.
Undertaking (typically post-hoc) analyses of randomized controlled trials with the intervention results presented according to strata of the response variable (BP) is potentially problematic. This has been done in an attempt to identify the optimal on-treatment BP in trials where such information was not the focus of the implemented study design.\textsuperscript{21,22} In these type of analyses, there will be less statistical power than in the overall study meaning that negative results may simply reflect inadequate statistical power. Positive results should also be viewed with caution because of the possibility that the results are confounded by important patient characteristics, possibly present at baseline, that are associated differentially with the on-treatment SBP response.

Meta-analyses. Meta-analyses of hypertension endpoint trials should not be excluded from consideration when synthesizing the expansive hypertension database. These analyses do not provide the level of evidence obtainable from an adequately powered randomized controlled trial but do reflect the summation of effects on common endpoints, often across a range of populations. As a result, they provide relevant, complementary information and can document trends that are not as easily observed in a single trial. Findings from meta-analyses may be particularly beneficial to clinicians trying to determine the best practice approach for their individual patients.

Synthesizing the expansive hypertension database into rationale treatment recommendations

In 2010, we published the first update of the International Society on Hypertension in Blacks (ISHIB) consensus statement on the treatment of hypertension in Blacks.\textsuperscript{23} It was recommended that for primary prevention of CVD, pharmacological hypertension treatment should be initiated at 135/85 mm Hg and, in turn, those already on treatment should use 135/85 mm Hg as their target BP. This recommendation evoked a blistering criticism based on the notion that our recommendation was not evidence based.\textsuperscript{24} Seemingly though with the publication of SPRINT, the hypertension community now has enough high-level evidence to recommend more intensive pharmacological therapy for hypertensive patients. The following are “examples” of approaches that might be taken to develop and promulgate simple, straightforward BP treatment recommendations.

A BP-centric, conventional approach would be to lower the BP threshold for the diagnosis of hypertension. MOBP consistently 135/85 mm Hg or higher would be considered hypertensive as would BP 130/80 mm Hg or higher if documented by at least 12 averaged home BP readings, AABP, or unattended AOBP. A BP treatment target range of 115–125 mm Hg would eliminate the focus on a single BP level and the provision of a lower end should allay concerns regarding overzealous and potentially harmful treatment. The upper part (120–125 mm Hg) of this range could be used for those with MOBP and the lower part of the range for those with BP measured by home BP, AABP, or AOBP. Alternatively, a slightly higher target treatment range (120–130 mm Hg) could be considered for those with hypertension diagnosed with MOBP.

An alternative worth considering is to utilize absolute CVD risk to determine which patients merit treatment. For example, a 7.5% 10-year risk for atherosclerotic CVD could be used to identify patients eligible for treatment.\textsuperscript{18} The treatment goal would be to achieve the same aforementioned BP target range. This approach focuses on the prevention of global CVD and utilizes pharmacological BP treatment as a strategy for CVD risk reduction while also forcing the consideration of a broader range of CVD risk factors that collectively define global risk. One attractive feature of such an approach would be to end the on-going and seemingly unresolvable arguments that trial results cannot be used in groups that were not enrolled in the trials themselves. The likelihood, for example, of a large-scale randomized hypertension endpoint trial in persons younger than 50 years, or solely in Blacks or Latinos, is small, yet such individuals who are at sufficient CVD risk are surely to derive benefit from efforts to normalize BP and mitigate cumulative exposure to excess pressure loads.

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