

Blood Pressure goals of hypertension therapy in 2017: Which patient and which goal?

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ABSTRACT

The goal of hypertension treatment in 2017 and beyond will be a systolic BP <120 mmHg, for all high risk patients with hypertension who can tolerate it, with no symptoms or significant laboratory changes. Blood pressure measurements need to be taken the SPRINT way. If alternative methods are used target values should be adjusted. In general, systolic BP between 120 and 129 mmHg will be acceptable and no medication adjustment will be recommended. For lower risk patients or patients younger than the age of 50 years similar guidelines may be adopted, but more flexible.

 **Key words:** Hypertension, SPRINT, treatment, control, goal, blood pressure, measurement, j-curve

Results of the recently published Systolic Blood Pressure Intervention Trial (SPRINT)¹, demonstrated in a powerful and convincing way that targeting systolic BP to less than 120 mmHg is better than targeting a systolic BP <140 mmHg. The study randomized 9,361 high risk patients >50 years of age to a standard treatment group (<140 mmHg) or to an intensive treatment group (<120 mmHg). It was discontinued prematurely in only 3.5 short years because, it had achieved its primary purpose: In the intensive treatment group the primary endpoint was 25% lower than the standard group and all-cause mortality was 27% lower. Most of the secondary end points (except for stroke) were also significantly lower in the intensive group. Beneficial results were apparent across the board, in all pre-specified subgroups and among all ages including the elderly. In fact, patients over the age of 75 years appear to better benefit from intensive treatment (at least numerically). Benefits extended to patients with and without baseline CKD and to all high-risk subgroups. Fragility does not seem to have been a problem. Intensive therapy did not affect the

rate of decline of gait speed. Furthermore, intensive therapy was well tolerated. No major adverse effects were reported, except for higher rate of eGFR decline in patients with no baseline CKD, but even that was probably due to the intensity of treatment, BP reduction and hemodynamic changes in the first 6 months (all mostly reversible). All in all, the SPRINT study demonstrated in a non-disputable way that lower is better, and targeting systolic BP <120 mmHg saves lives. The impact of the SPRINT results is largely enhanced by the fact that it was a well-designed and well executed study, sponsored by the National Institute of Health, and paid by the American tax payers. Although drugs were donated by the industry, SPRINT was not a drug study and the choice of medicine was left to the local investigators. Blood pressure measurements were taken using a validated automated BP device thus called “Automated Office BP” measurement (AOBP). The SPRINT BP measurements are uniquely reliable, objective and unbiased and remained unaltered throughout the study and similar in all participating centers. There was no ob-

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server bias, no environmental impact, and the alert effect was minimized. Furthermore, the measurement procedure included most if not all recommendations for good clinical practice in BP measurements: Patient seated in a quiet room for at least 5 minutes, legs uncrossed, back supported etc, and BP taken in triplicates one minute apart. The achieved average BP was 121.5 mmHg in the intensive group and 134.6 mmHg in the standard group. In short, the SPRINT AOBP may be considered the modern version of the Smirk's basal blood pressure concept that is BP measured in the absence of all external physical and emotional stimuli. Smirk demonstrated more than 70 years ago that basal BP was 7 to 8 mmHg lower than casual BP². Thus, the fear of targeting clinic BPs to <120 mmHg (casual) may be too much and may actually increase mortality and CV events.

The J shape curve phenomenon

The J shape curve has been described and discussed for several years now. It has been hypothesized that low BP at some point, will be associated with decreased organ perfusion, mostly myocardial perfusion and increased risk of myocardial infarction, cardiovascular events and cardiovascular mortality. The only prospective randomized trial to test the hypothesis of J shape curve was the HOT study³, which randomized 18,790 patients to three levels of diastolic BP: <90 mmHg, <85 mmHg or <80 mmHg. The achieved diastolic BP however was 81,83 and 85 mmHg and the systolic was 139,141 and 143 mmHg. There was no difference in CV events and J shape curve could not be demonstrated. An important meta-analysis of 7 prospective randomized studies, by the INDANA investigators⁴ examined the optimal systolic and diastolic BP in treated groups and controls. They found that the lowest total, cardiovascular and non-cardiovascular mortality was associated with a systolic BP between 130 and 140 mmHg or a diastolic BP of 85 to 95 mmHg. Lower systolic or diastolic BPs were associated with higher mortality risk and CV events. The authors concluded however that the increased mortality noted with low BPs was due to reverse causality and not to treatment for high blood pressure or low BP itself. In one of our studies from the VA data sets (AHA 2016), we examined the association of the average blood pressure over a 15-year period with all-cause mortality in more than 6 million patients with con-

firmed hypertension. We found that the lowest mortality was associated with an average BP between 120-130 mmHg. Mortality appeared to increase with BPs <120 mmHg. It should be noted however that both the INDANA data and data from the VA data base are based on casual clinic BP measurements that are most likely higher than the AOBP measured in SPRINT. In SPRINT the achieved mean systolic BP in the intensive group was 121 mmHg, which means that about 1/2 of the patients achieved systolic BP <120mmHg and no signals of increase mortality have been reported (This analysis has not been completed yet). Data from the achieved diastolic BP in SPRINT are not available at this point, but analyses are underway. Not to be mistaken, the J shape curve exists for both systolic and diastolic BP but the optimal Nadir point has not been determined. Data from SPRINT (and ACCORD) indicate that the Nadir point for systolic AOBP is well below 120 and probably below 110 mmHg.

There is no question that publication of the SPRINT results created controversies on the applicability of its findings in patients with hypertension. The main question asked is "how does the AOBP as measured in SPRINT translates into clinical practice". The argument is that AOBP is consistently lower than conventional office BP by as much as 5-10 mmHg⁵ and thus overestimates BP levels. Conventional office BP is supposedly best represented by the average daytime ambulatory BP and ABPM is a better correlate of outcomes and as such should be the preferred standard. Things are not so clear however. Office BP measured the conventional way has its own shortcomings and problems. First "conventional office BP" is not standardized, it can mean one measurement, average of three measurements, average of last two out of three measurements, BPs taken at first contact with the patients, after waiting 3 minutes or 5 minutes, using automated, device or auscultatory method, attended or semi-attended (operator sitting in the room quietly). Most importantly conventional office BP incorporates the white coat effect in some patients, which falsely represents the hypertension load. In a recent editorial Parati et al⁶ published BP differences between daytime ABPM and clinic BPs⁷. In the SPRINT study, AOBP was lower by -7/-6 mmHg as compared to day time ambulatory

BP, in the intensive group and -3/-5 in the standard group (as recently reported, Drews et al⁷. In the HOPE study placebo arm the conventional office BP was lower by -10/-6 mmHg, whereas in other studies conventional office BP was higher than daytime ambulatory BP by 7 to 29 mmHg. The problem with most of the reported studies is that conventional clinic BP and ambulatory BP were not measured at the same time thus introducing bias. Even in SPRINT ABPM was done within 3 weeks from month 27th visit, thus introducing visit to visit variability in those comparisons. The only study in which ambulatory BP monitoring was obtained at the same time with office BP in all randomized patients was the ELSA study⁸. That trial reported that clinic BP was higher than ambulatory BP in the higher range of clinic BP distribution, but the difference between office and ambulatory BP values became progressively smaller at lower clinic BP values. The opposite was noted in the SPRINT comparison of AOBP and ambulatory BP. There were greater differences in the intensive group as compared to standard group. A recently published study⁹ compared average office BP (measured in triplicates in 3 separate visits) to ambulatory daytime BP in 888 healthy, employed, middle aged men and women on no antihypertensive medication and screening BP <160/105. Interestingly results of this study indicate that clinic BP was on average -7/-2 mmHg lower than the awake ambulatory BP, very similar to SPRINT intensive group.

The bottom line is that conventional measurement of office BP is not a better correlate of ambulatory (awake) BP than AOBP and it is not certain if it is indeed higher and by how much. The question then to asked then should be. "how can we adjust conventional clinic BPs to correlate better with AOBP as measured in SPRINT and not how AOBP correlates with conventional office BP". Furthermore, the question should not be how to translate the SPRINT results into clinical practice, by how to adjust clinical practice to achieve the results achieved in SPRINT.

My personal opinion is that we should slowly but surely converge into measuring BP in the office the SPRINT way. Check triplicate BPs with the patient seated in a comfortable chair in a quiet room, with the legs uncrossed, after 5 minutes waiting and preferably with the patient alone in the room. Do-

ing so we'll have clear targets and clear goals. The AOBP technique is simple, standardized and reproducible. It takes away confounders, the alert effect and speculations. The medical community gets it and slowly but surely the guidelines will adopt. I am confident that in the very near future we'll see leadership from more hypertension societies and adaptation of guidelines. The Australians and the Canadians are so far leading the way.

The SPRINT closed a very important chapter opened by the VA co-operative studies published in 1967 and 1971. Those studies^{10,11} revolutionary for their time, were designed and executed by the VA co-operative study group, headed by Dr Eduard D. Freis (my mentor and boss for >20 years). At that time, it was believed that elevated BP is needed in high risk patients so to maintain organ perfusion, and physicians were advised to not reduce BP aggressively because of fear of strokes and MIs. The first VA study assessed patients with diastolic BP 115-129 mmHg and patients were randomized to treatment or placebo. It only took 18 months in a small number of patients (n=143) to demonstrated dramatic reduction of CV events (21 vs 1 event) and the study was concluded and never repeated. The second study included patients with mild to moderated diastolic hypertension (DBP 90 -114 mmHg). In this study patients were again randomized to treatment or placebo and in about 3.5 years it was demonstrated that treatment reduced CV events by 67% (48 vs 16 events in placebo vs active groups). These studies were carefully done, patients were hospitalized for titration and medicine was carefully monitored. Compliance confirmed by urine test and closely enforced throughout the study. Ed Freis noted then that benefits were limited to patients with diastolic BP >100 mmHg and benefit needed confirmation for patients with diastolic BP <100 mmHg. Of note diastolic BP was chosen instead of systolic, because it was more stable and varied less between visits (personal communication). Later it was realized that systolic BP is probably more predictive of events especially in persons >50 years of age.

The SHEP study done in patients with isolated systolic hypertension (ISH)¹² confirmed benefits with only reduction in systolic BP. Since the early VA Co-op studies and for the next 45 years myriad studies were done trying to define the best goal for

BP control. Most of the studies however did not achieve BP levels low enough or differences between controls and treated groups to establish lower goals. The HOT³ study for example randomized patients to three diastolic BP goals, <90, <85 or <80 mmHg. Although it was a large study with adequate follow up, the achieved BPs were not spread enough to be meaningful (81, 83 and 85 mmHg) and CV events were similar between groups. Systolic BPs were similarly close with small differentials. Meta analyses and Cochrane reviews^{13,14} identified studies that attempted to assess best BP goals for optimal reduction of outcomes. The guidelines wondered from lower is better, to earlier is better and then, tolerate higher pressures is better, until results from the SPRINT were published. And then hell broke loose. Everybody got an opinion on the matter. But guidelines need to adopt and goals need to be resettled, the SPRINT way.

My opinion

While we should target systolic BPs <120, systolic BPs between 120-130 mmHg should be acceptable. If office BP is measured the SPRINT way treatment should be initiated at systolic BPs >130 mmHg in high risk patients.

Who should be included in these goals?

- Certainly those high-risk patients who meet the SPRINT inclusion exclusion criteria. Patients over the age of 50 yo, with comorbidities, systolic BP >130 mmHg on or off antihypertensive medication
- Should Younger patients (<50 yo) be included? Difficult to address at this point. They were not included in SPRINT and we have no data. Most of them are low risk with low event rates. Diastolic BP is more relevant in this group of patients. I am inclined to accept current guidelines (<140/90 mmHg), but if treatment is initiated and BP falls to the 120s should be acceptable.
- Should the elderly be included? For sure. Patients over the age of 75 yo were a pre-specified subgroup in the SPRINT study. They are high risk patients with high event rates and high mortality. Results have shown that the benefit may even be greater in this subgroup of patients. The caveat is that these patients are more fragile and caution needs to be exercised when titrating their meds to achieve goal BP. The goal for these patients should be the lowest tolerated.
- Should diabetics be included? Cannot commit at this point, as these patients were excluded from SPRINT. The ACCORD data however indicate that point estimates of benefits in the intensive group of ACCORD were similar to point estimates in SPRINT except that the confidence intervals were wider due to smaller number of patients in SPRINT. And ACCORD was underpowered to answer the question (ACCORD, N=4733 pts, SPRINT, N=9361 pts). Patients with diabetes however are high risk and should benefit from intensive BP control. More ammunition may be acquired soon from a new analysis (underway) of the SPRINT patients with pre-diabetes (baseline fasting glucose >100 mg/dl).

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