

Target Blood Pressure for Treatment Should Current Recommendations Be Changed?

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The guidelines on the management of hypertension released by European and US Task Forces in 2013 and 2014^{1,2} recommend target blood pressure (BP) levels below 140/90 mm Hg in most hypertensive patients, with higher values (<150/90 mm Hg) in the elderly.

However, recent randomized trials as well as new meta-analyses of the available data have obtained results that are not consistent with these recommendations, rather supporting the possibility for antihypertensive treatment to pursue much lower BP goals in both middle-age and old individuals. Aim of this editorial is to review the results of these recent studies to assess whether any change of BP target during antihypertensive treatment may be proposed.

The Systolic Blood Pressure Intervention Trial

The Systolic Blood Pressure Intervention Trial (SPRINT) was performed in 9361 patients with a high cardiovascular risk and an entry systolic BP (SBP) of 130 to 180 mm Hg³ who were randomized to an intensive (SBP <120 mm Hg) or a standard BP goal (SBP <140 mm Hg). After a treatment duration longer than 3 years, the intensively treated group showed a 25% and 27% lower risk of cardiovascular and all-cause death, respectively, than the standard treatment one, for which reason the trial was prematurely stopped with the conclusion that an intensive BP reduction leads to a greater benefit than the currently recommended one. Because one fourth of the patients were aged ≥ 75 years, this applied to elderly patients as well, in striking contrast with the higher BP target recommended by current guidelines.³ Despite the early termination, SPRINT adjudicated >500 primary events, which gives its conclusion an adequate statistical power. Yet, as mentioned in several commentaries,^{4,5} some aspects and results of the trial are not easy to be interpreted, suggesting to deal with its conclusion with a degree of caution. For example, SPRINT did not enroll patients with diabetes mellitus, a history of stroke, a marked proteinuria, and unstable angina or institutionalized elderly subjects,⁶ which means that its results do not apply to all hypertensive patients, regardless their clinical characteristics.

However, according to a recent study of Bress et al, based on data from the National Health and Nutrition Examination Survey, a substantial percentage of US adults (ie, 7.6% or 8.2 million adults) may meet the eligibility criteria for SPRINT.⁷

Furthermore, and in contrast with the results of many previous trials, the intensively treated patients did not show a significant reduction in the risk of myocardial infarction and stroke, its outcome results being largely driven by a marked reduction in the incidence and risk of heart failure, a benefit possibly magnified by the masking effect of diuretics on this outcome, given that diuretics were predictively much more frequently used in aggressively than in standard-treated patients.⁸

In addition, no patient enrolled in SPRINT had high pulse pressure, and only 23% of those in the intensive-treated group had SBP <120 mm Hg.

Finally, it is worth mentioning that in SPRINT, office BP was measured with an automatic device in absence of a physician or a nurse, thus avoiding the white coat effect, that was on the contrary probably present in previous trials in which BP was measured by more conventional approaches. Because on average the white coat effect may amount to ≥ 10 mm Hg, this implies that the target BP values observed in SPRINT may have been closer to those of previous trials than what appears from the published values.^{9,10}

New Meta-Analyses

The results of SPRINT are in line with those of recent meta-analyses that have been able to include both early and late randomized trials, for a huge number of patients and outcomes, and thus with an extremely large statistical power. Xie et al¹¹ have pooled data from 19 trials (44 989 participants), which evaluated the effect of more- versus less-intensive BP-lowering treatment on cardiovascular and renal outcomes. Although the absolute on-treatment BP varied widely between trials (118/75–144/82 mm Hg in the more and 124/80–154/87 mm Hg in the less intensively treated patients), on average, the intensive BP-lowering treatment was accompanied by a significantly lower BP (133/79 mm Hg compared with 140/81 mm Hg in the control group). This was not accompanied by a between-group difference in cardiovascular mortality, all-cause mortality, and end-stage renal disease. It was accompanied, however, by a significant reduction in the risk of major cardiovascular events, myocardial infarction, stroke, and, in diabetic patients, albuminuria or progression of retinopathy. The benefits resulted more evident in elderly patients as well as in patients with diabetes mellitus or renal disease, suggesting a greater protective effect of more aggressive antihypertensive treatment strategies and lower achieved on-treatment BP values. The above conclusion is in line with the results of 2 other meta-analyses, which have pooled data from a huge

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number of patients and outcomes. In one of them, Ettehad et al¹² included 123 trials and 613 815 patients to relate the effect of BP lowering on cardiovascular risk to baseline BP values, comorbidities, or drug classes. In all conditions, a 10 mmHg reduction in SBP significantly reduced the risk of cardiovascular morbid and fatal events, with also a significant (–13%) reduction of all-cause mortality. A proportionally similar risk reduction was observed in trials with higher and lower mean baseline SBP, including a baseline SBP of <130 mmHg. Furthermore, a significant benefit was seen also in patients with diabetes mellitus and chronic kidney disease, although in either condition the risk reduction was somewhat smaller than in the overall analyzed population.

Similar results have been obtained in the other meta-analysis, which has included 34 randomized trials, one of which being SPRINT.¹³ In >138 000 patients, a more intensive decrease of SBP and diastolic BP (10 and 5 mmHg, respectively) reduced stroke, coronary events, and cardiovascular mortality, irrespectively of whether the initial SBP was 150, 140, or 130 mmHg, although for most outcomes, the absolute risk reduction was smaller at the lower baseline and target BP values.

The beneficial effects of more-intensive BP reductions reported in SPRINT and the above meta-analyses should be considered also with regard to the greater number of serious side effects that have regularly been associated with lower on-treatment BP values. In SPRINT, patients treated to <120 mmHg SBP had much more hypotension, syncope, electrolyte disturbance, acute renal injury, and failure. Moreover, in 5 trials included in the meta-analysis of Xie et al,¹¹ a greater incidence of severe hypotension has been reported. Although the investigators claim that the absolute benefits of treatment surpass the absolute harms, this cannot be minimized because in the setting of everyday clinical practice, serious side effects lead to treatment discontinuation, which is accompanied by a much greater incidence of events.^{6,14}

Hypertension and Diabetes Mellitus

Patients with hypertension and type 2 diabetes mellitus carry a much greater cardiovascular risk, as well as a greater susceptibility to hypertension-related complications. Whether in these patients lower BP targets should be recommended is still matter of debate, however, because with few exceptions, reducing BP more aggressively has not been found to increase the protective effect of antihypertensive treatment. This has been clearly the case in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which an SBP reduction to ≈120 mmHg was not accompanied by a lower risk of cardiovascular events and death compared with an SBP reduction to ≈135 mmHg.¹⁵ This conclusion should be tempered by the observation that, considering the factorial design of the ACCORD study, both intensive BP reduction and intensive glycemic treatment alone were associated with a better cardiovascular disease outcome in comparison with standard treatment, but there was no additional benefit from combining the 2.¹⁶ However, different conclusions have been reached by a recent review of the relation between BP-lowering treatment and cardiovascular events, based on 100 354 diabetic hypertensive patients from 40 trials.¹⁷ Each 10 mmHg lower SBP

was associated with a significantly lower risk of death (–13%), cardiovascular events (–11%), coronary events (–12%), and stroke (–27%). No significant decrease of heart failure and renal failure was observed, but retinopathy (–13%) and albuminuria (–17%) were also significantly less frequent in the more aggressively treated patients. Furthermore, although the outcome reduction was mostly seen when SBP was reduced from ≥140 mmHg SBP to an on-treatment value that laid between 130 and 140 mmHg, SBP reductions to <130 mmHg were accompanied by a further reduction in the risk of stroke and in the progression of albuminuria, suggesting that a more aggressive antihypertensive treatment strategy may maximize the benefit also in patients in whom diabetes mellitus coexists with a BP elevation. Another recent meta-analysis including 73 778 participants in 49 trials concluded that antihypertensive treatment reduces cardiovascular morbidity and mortality in patients with diabetes mellitus if baseline SBP is >140 mmHg. However, if SBP is already below 140 mmHg, further treatment might be harmful. Indeed, it seems that the proposal of an adequately powered, conclusive randomized clinical trial in hypertensive diabetic patients would be appropriate.^{18,19}

HOPE-3 Trial: Antihypertensive Treatment at High Normal BP and in Grade 1 Hypertension at Intermediate Cardiovascular Risk

The Heart Outcomes Prevention Evaluation (HOPE-3) trial²⁰ has recently investigated the effects of BP lowering in 12 705 people with an intermediate cardiovascular risk level and a baseline mean BP of 138/82 mmHg who were randomized to take active drug treatment (a combination of an angiotensin receptor antagonist and a diuretic) or placebo during a median follow-up of 5.6 years. Compared with placebo, active treatment decreased SBP by 6 mmHg and diastolic BP by 3 mmHg. This was not associated with a lower risk of major cardiovascular events. In fact, the incidence of cardiovascular events was superimposable in the actively treated and in the placebo groups. However, when analyzed according to the baseline BP value, active treatment was accompanied by a 23% reduction of cardiovascular outcomes in patients in whom the initial SBP was >143.5. Because only a small number of subjects recruited for the HOPE-3 trial were taking antihypertensive drugs at baseline, these results provide evidence that BP reductions may carry little or no benefit in subjects with a high normal BP whose risk is not elevated. They also show, however, that in patients with grade-1 hypertension, antihypertensive treatment may be beneficial even when their risk is not elevated, a finding that importantly adds to previous available evidence. Similar conclusions have been reached by a meta-analysis of 32 trials on 104 359 individuals in which BP-lowering interventions have been reported to significantly lower cardiovascular risk in grade 1 hypertensive patients with a low-to-moderate initial risk.²¹

Conclusions

In summary, the results of randomized clinical trials as well as of large-scale systematic reviews on the effects of BP reduction on cardiovascular risk provide new important ground for discussing the target BP to aim at by antihypertensive treatment, as well the BP level at which antihypertensive drug

administration should be started. All these studies have largely focused on SBP, although how low diastolic BP should be targeted remains to be explored by further specific trials.

There seems to be no evidence that using antihypertensive drugs in intermediate risk patients with high normal BP is associated with a reduction of cardiovascular events, at least when follow-up is limited to few years. On the contrary, cardiovascular events may be significantly reduced by BP reductions in patients with grade 1 hypertension even when their cardiovascular risk is not elevated. Based on SPRINT and meta-analyses, a more aggressive BP reduction may further reduce cardiovascular events in high-risk hypertensive patients. However, the data available to date and their specific design do not permit to establish a precise target BP. More precise information could be obtained by trials that explore the protective effect of 3 instead of 2 different SBP treatment targets, such as in the ongoing Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke (ESH_CHL_SHOT) trial.²² Further studies are certainly needed to identify those patients who may benefit by lower BP. Specific trials in groups of patients with careful characterization of their phenotypic manifestations and possibly also of genetic markers may be the most useful and precise approach for assessing when to start treatment and how low BP should be reduced.

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