EDITORIAL

Redefining Blood-Pressure Targets — SPRINT Starts the Marathon

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Blood pressure is a potent determinant of cardiovascular risk, but the most appropriate targets for blood-pressure lowering have long been debated. Observational studies with a low risk of confounding have shown a linear relationship between blood pressure and cardiovascular risk down to 115/75 mm Hg,[1] but some observational studies with a greater potential for confounding, involving persons at increased risk, have suggested a J-shaped curve — that is, below a given blood pressure, risk would increase. When trials of blood-pressure–lowering drugs have shown benefits in patients without hypertension, these effects have often been ascribed to alternative mechanisms. The widespread uncertainty about blood-pressure targets was increased when the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed no significant overall difference in cardiovascular events between patients with type 2 diabetes assigned to a systolic blood-pressure target of less than 120 mm Hg and those assigned to a target of less than 140 mm Hg.[2]

The eagerly awaited results of the Systolic Blood Pressure Intervention Trial (SPRINT), now reported in the *Journal*,[3] are certain to have far-reaching implications. SPRINT randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk to a target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). People with difficult-to-control blood pressure were excluded and will require separate study. The mean blood pressure at baseline was 139.7/78.2 mm Hg in the intensive-treatment group and 139.7/78.0 mm Hg in the standard-treatment group, and the mean pressure at 1 year was 121.4/68.7 mm Hg and 136.2/76.3 mm Hg in the respective groups. During follow-up, the average difference in systolic pressure was 13.1 mm Hg, and the mean number of blood-pressure medications was 2.8 in the intensive-treatment group and 1.8 in the standard-treatment group.

The trial was stopped early, after a median follow-up of 3.26 years. Overall, participants assigned to the intensive-treatment group, as compared with those assigned to the standard-treatment group, had a 25% lower relative risk of major cardiovascular events (95% confidence interval [CI], 11 to 36), with consistent results across subgroups defined according to age, sex, race, medical history, and baseline blood pressure. In addition, the intensive-treatment group had a 27% lower relative risk of death from any cause (95% CI, 10 to 40). Rates of some serious adverse events, including hypotension and acute kidney injury or failure, were higher in the intensive-treatment group than in the standard-treatment group, but these higher rates appear unlikely to outweigh the benefits overall.

Are the results reliable? Small trials can overestimate benefits when stopped early,[4] but this is unlikely for SPRINT, which had more than 500 primary outcome events. Lack of blinding is inevitable in trials involving blood-pressure targets, but this was mitigated by structured assessment of outcomes and adverse events. Some findings require further elucidation and follow-up, particularly the renal outcomes. The lack of effect on injurious falls will surprise many but is consistent with the finding of the largest trial involving the elderly.[5]

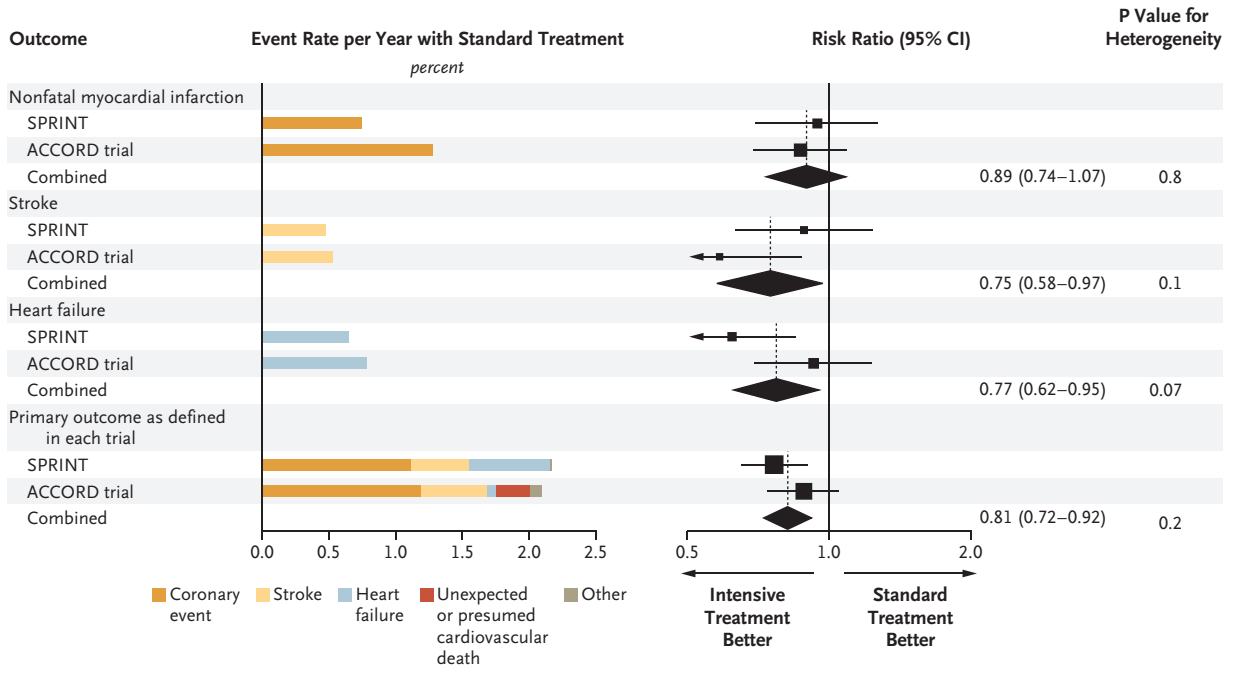

Figure 1. Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials.

In both the Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the systolic blood-pressure target in the intensive-treatment group was less than 120 mm Hg, and the target in the standard-treatment group was less than 140 mm Hg. The primary outcome in the ACCORD trial was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The primary outcome in SPRINT also included acute coronary syndrome not resulting in myocardial infarction and nonfatal episodes of heart failure. For the ACCORD trial only, death from cardiovascular causes included "unexpected death presumed to be due to ischemic cardiovascular disease" and "presumed cardiovascular death," which together accounted for 81 (69%) of the deaths from cardiovascular causes in that trial.

Are the results of SPRINT different from those of the ACCORD trial? As shown in Figure 1, the effects on individual outcomes in SPRINT and the ACCORD trial are generally consistent. The main differences were that the ACCORD trial had less statistical power than SPRINT, and its primary outcome included a higher proportion of events that are less sensitive to blood-pressure reduction. Previous trials have also shown similar-sized benefits in persons with diabetes and those without diabetes.[6] More broadly, labeling trials as "positive" or "negative" is seductive but ultimately counterproductive; it is more helpful to look at the totality of available data. Several previous large trials of blood-pressure lowering[7,8] included participants at high cardiovascular risk, about half of whom had a baseline systolic blood pressure below 140 mm Hg. These trials also showed benefits for people with a pressure of at least 140 mm Hg and those with a pressure below 140 mm Hg. The benefits seen in SPRINT are also consistent with those seen in previous trials of more intensive versus less intensive blood-pressure control[9] and, more broadly, in previous trials in which differences in blood pressure were achieved between groups.[1]

SPRINT provides another cautionary reminder about using data from nonrandomized trials or biologic plausibility to assess efficacy and safety. We are reminded that real-world data, such as J-curve associations, can be really wrong. Randomized trials are required to reliably assess treatment effects. SPRINT also brings into focus approaches to synthesizing trial evidence for guidelines. The Eighth Joint National Committee took a targeted approach to consideration of previous trials and concluded that systolic blood-pressure targets should be below 140 mm Hg, or

below 150 mm Hg in those 60 years of age or older. More inclusive trial reviews have indicated benefits of blood-pressure lowering in persons at high cardiovascular risk without hypertension.[1] Current guidelines and guideline processes require revision.

Clearly, our current concept of hypertension is insufficient to determine who benefits from blood-pressure lowering or how far to lower blood pressure.[10] SPRINT strongly supports pharmacotherapy decisions based on absolute risk levels, in a similar way to current recommendations for lipid lowering. For people at high cardiovascular risk, a systolic goal of less than 120 mm Hg is appropriate. Substantial effort and resources are required: initial combination therapy was the norm in SPRINT, with monthly visits until blood pressure was at the target level. Even with intensive lifestyle modification and medical therapy, blood pressure will remain above target in many patients, which suggests the need for population-level initiatives (e.g., reduced sodium content in food), new therapies, and multifactorial intervention. In SPRINT, less than half the patients were taking statins, 13% were still smoking, and most were overweight or obese.

SPRINT redefines blood-pressure target goals and challenges us to improve blood-pressure management. Success will require a marathon effort.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
2. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85.
3. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. DOI: 10.1056/NEJMoa1511939.
4. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010;303:1180-7.
5. Peters R, Beckett N, Burch L, et al. The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). Age Ageing 2010;39:609-16.
6. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005;165:1410-9.
7. Brugts JJ, Ninomiya T, Boersma E, et al. The consistency of the treatment effect of an ACE-inhibitor based treatment regimen in patients with vascular disease or high risk of vascular disease: a combined analysis of individual data of ADVANCE, EUROPA, and PROGRESS trials. Eur Heart J 2009;30:1385-94.
8. Sleight P, Yusuf S, Pogue J, Tsuyuki R, Diaz R, Probstfield J. Blood-pressure reduction and cardiovascular risk in HOPE study. Lancet 2001;358:2130-1.
9. Lv JC, Neal B, Ehteshami P, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med 2012;9(8):e1001293.
10. MacMahon S, Neal B, Rodgers A. Hypertension — time to move on. Lancet 2005;365:1108-9.

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