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## SPRINT Trial Results: Latest News in Hypertension Management

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### For the SPRINT Study Research Group

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We thank the editors of *Hypertension* for the invitation to discuss aspects of the recently published Systolic Blood Pressure Intervention Trial (SPRINT) main results.<sup>1</sup> This commentary focuses on generalizability of the findings and what is known about serious adverse effects that may be related to the SPRINT intervention. SPRINT compared the effects of antihypertensive treatment to a systolic blood pressure (SBP) target of <120 mm Hg (intensive treatment) versus <140 mm Hg (standard treatment) in 9,361 hypertensive adults 50 years of age who had an average SBP of 130-180 mm Hg (the acceptable upper limit decreasing as the number of pre-trial antihypertensive medications increased) and were at additional risk for cardiovascular disease (CVD).<sup>2</sup> SPRINT was designed to recruit study participants with an average CVD risk of approximately 2% per year, equivalent to a Framingham 10-year CVD risk score of 20%.

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The main finding in SPRINT was that a primary composite outcome of myocardial infarction (MI), non-MI acute coronary syndrome, stroke, acute decompensated heart failure, and CVD death was reduced by approximately 25% in the intensive-treatment group compared with the standard-treatment group. Similarly, all-cause mortality was reduced by approximately 27% in the intensive-treatment group.

During follow-up, the mean SBP was 121.5 mm Hg in the intensive-treatment group and 134.6 mm Hg in the standard-treatment group.<sup>1</sup> Although many classes of medications were available, emphasis was placed on using classes with the best outcomes in large clinical trials: thiazide-type diuretics, calcium channels blockers, and angiotensin converting-enzyme inhibitors or angiotensin receptor blockers. Other agents, including spironolactone, amiloride,  $\beta$ -blockers, vasodilators, or alpha-receptor blockers, could be added if necessary. The mean numbers of antihypertensive medications were 2.8 and 1.8 in the intensive-treatment and standard-treatment groups, respectively.

On balance, the intensive intervention was well tolerated. The trial was designed to identify serious adverse effects expected to be related to more intensive treatment of hypertension.<sup>2</sup> The SPRINT protocol pre-specified conditions of interest, including orthostatic hypotension, syncope, bradycardia, electrolyte abnormalities, injurious falls, and acute kidney injury or failure. Orthostatic hypotension, defined as a drop in SBP  $\geq$  20 mm Hg or drop in diastolic BP  $\geq$  10 mm Hg 1 minute after standing, was significantly more common in the standard compared to the intensive arm. There was no significant difference between the two treatment groups in orthostatic hypotension with dizziness during standing BP measurement, injurious falls, or bradycardia. Hospital reports of acute kidney injury or failure were significantly more common in the intensive (4.1%) compared to the standard (2.5%) arm. Electrolyte abnormalities also occurred more often in the intensive (3.1%) compared to the standard (2.3%) arm. The long-term consequences of these adverse effects are unclear, but the potential for harm was offset by the positive effects of more intensive compared to standard treatment on total mortality (3.3% versus 4.5%, respectively) and the primary outcome (5.2% versus 6.8%, respectively). The potential benefit compared to harm was similar when both emergency room visits and hospitalizations were included in the analysis, and when adverse events were restricted to those thought to be related to the intervention.

It is possible that our estimates of frequency for these conditions of interest were biased. Clinic staff were unblinded to randomized assignment, and adverse events could be reported at any visit. In contrast, the trial outcomes were ascertained only at quarterly visits and adjudicated by a committee that was blinded to treatment assignment. During follow-up, participants in the intensive arm were seen for unscheduled clinic visits about 20-30% more often than those in the standard arm, mostly for BP management. This provided greater opportunity for participants in the intensive arm to report adverse events.

By design, SPRINT enrolled a diverse population of adults at sufficiently high risk for CVD events to ensure adequate statistical power. Individuals with diabetes, stroke, and polycystic kidney disease were excluded because of other ongoing NIH-funded trials. One of the most common questions about SPRINT will likely be whether the trial results apply to adults with

diabetes. The Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial<sup>3</sup> (ACCORD BP) used the same SBP goals employed in SPRINT to determine the value of intensive compared to standard BP reduction in 4,733 adults with diabetes, additional risk of CVD, and an average systolic BP of 130-180 mm Hg. In ACCORD BP, the composite CVD outcome (MI, stroke, or CVD death) was 12% lower in the intensive-treatment group, but this difference was not statistically significant (Table). Although SPRINT and ACCORD BP shared several common features, the two trials had important differences. The sample size in SPRINT was about twice as large as that employed in ACCORD BP; the participants in SPRINT were older than those in ACCORD BP (mean age 68 years vs. 62 years, respectively); SPRINT included a cohort with chronic kidney disease (CKD) whereas a serum creatinine >1.5 mg/dl was an exclusion in ACCORD BP; and there was a slight difference in the primary composite outcome used in the two trials. The 95% confidence interval for the primary outcome in ACCORD BP included the possibility of a 27% reduction, which is consistent with the 25% CVD benefit observed in SPRINT. The factorial design used in ACCORD BP, which simultaneously compared the value of intensive compared to standard glycemic therapy, may have negatively impacted the opportunity to test the effect of the BP intervention. In a post-hoc analysis of the ACCORD results, the primary CVD outcome was 26% lower in participants randomized to the intensive BP and standard glycemia goals compared to those assigned to the combined standard BP and glycemia treatment goals.<sup>4</sup> Such a benefit is consistent with CVD reductions observed in other trials that studied the effect of BP lowering in patients with hypertension and diabetes<sup>5</sup>.

It is possible, but we believe unlikely, that there is an inherent difference in the CVD benefits of intensive SBP lowering in diabetic and non-diabetic adults. Since the ACCORD BP trial was not definitive, it would be ethical to conduct another trial of intensive BP-lowering on major CVD outcomes in diabetics. Enrollment of a higher risk group (e.g., participants of older age and those with CKD) and enlarging the sample size would help to ensure adequate statistical power to answer this question. In the meantime, guideline committees and the medical community will have to decide whether the SPRINT results should be generalized to patients with hypertension and diabetes.

For several large groups of individuals with SBP 130-180 mm Hg, the SPRINT results are directly relevant: these include nearly all adults 75 years and three groups who are 50 years: those with subclinical or clinical CVD; those with a 10-year CVD Framingham risk score of at least 15% and those who have CKD with an estimated glomerular filtration rate 20-59 mL/min/1.73 m<sup>2</sup>. One possible extension of the SPRINT findings might be to individuals who are 50 years old with a SBP 130-180 mm Hg and who are at similar risk for CVD as some of the participants in SPRINT because of CVD risk indicators that were not part of the SPRINT inclusion criteria. One could make a case for extending the SPRINT findings to younger individuals with hypertension, especially those at high risk for CVD. Examples might include younger individuals with CKD or subclinical or clinical CVD, a substantially increased CVD risk score, or genetic CVD risk factors such as familial hypercholesterolemia. For many individuals the number needed to treat will likely be higher than that noted in SPRINT, but they may still derive a benefit from a lower SBP than is currently recommended, especially if this could be accomplished with few serious adverse

effects. Another group to whom the SPRINT intensive-therapy goal may be appropriate, but difficult to achieve, are those who have an average SBP >180 mm Hg.

There are several groups, who in aggregate constitute a large percent of the adult population, for whom extension of the SPRINT findings would be more speculative. This includes adults with an average untreated SBP 120-129 mm Hg, and those with an average SBP 130-139 mm Hg who have a Framingham 10 year CVD risk score <15%. Practical considerations related to sample size and duration of follow-up make conduct of trials like SPRINT in these populations an unlikely possibility. For now, practitioners will have to decide whether the SPRINT results should be extrapolated to individuals with these characteristics.

No matter who are chosen for application of the SPRINT intensive BP lowering treatment strategy, it is important to be mindful of the manner in which BP was measured in the trial: an average of 3 office BP readings taken with proper cuff size, participants seated with their back supported, 5 minutes of rest prior to measurement, and no conversation during the rest period or BP determinations. In SPRINT this was achieved using an automated manometer (Omron Healthcare, Lake Forest, IL) that was preset to wait for 5 minutes prior to measurement as well as to take and average the 3 readings. BP measurements taken without observing these conditions are likely to overestimate BP<sup>6</sup> and result in overtreatment, with the potential for higher rates of serious adverse effects and greater utilization of resources. This issue should be carefully considered in the development of any practice-based performance measures for BP control in hypertension that are derived from the SPRINT results. Finally, although the intensive-treatment goal in SPRINT was <120 mm Hg, the majority of our participants did not achieve a SBP that was consistently below this level. The expectation in many practice settings that average SBP in most adults with hypertension be controlled below a particular goal should be considered carefully if the SPRINT intensive-treatment SBP goal is applied to this type of performance measure.

The results of SPRINT are likely to have a major impact on the treatment of hypertension. However, there are a number of important lessons to be learned from SPRINT in order to apply the results in a safe and effective manner.

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**Table**  
**Cardiovascular outcome event rates in ACCORD BP and SPRINT**

Event	Standard % per year		Intensive % per year		Hazard ratio	
	ACCORD	SPRINT	ACCORD	SPRINT	ACCORD	SPRINT
All Deaths	1.19	1.40	1.28	1.03	1.07	0.73
Death from cardiovascular causes	0.49	0.43	0.52	0.25	1.06	0.57
Non-fatal myocardial infarction	1.28	0.77	1.13	0.63	0.87	0.82
All Stroke	0.53	0.47	0.32	0.41	0.59	0.89
Non-fatal Stroke	0.47	0.45	0.30	0.39	0.63	0.88
All heart failure	0.78	0.67	0.73	0.41	0.94	0.62
ACCORD primary outcome*	2.09	1.52	1.87	1.15	0.88	0.75

\* Results for application of the ACCORD composite in both SPRINT and ACCORD.

ACCORD BP: Action to Control Cardiovascular Risk in Diabetes Blood Pressure

SPRINT: Systolic Blood Pressure Intervention Trial