SPRINT
What Remains Unanswered and Where Do We Go From Here?
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The Systolic Blood Pressure Intervention Trial (SPRINT) main results were recently published and presented at the American Heart Association Scientific Sessions. These data provide insight into the important question of the most appropriate treatment goal for systolic blood pressure (BP). The results of this study will have a large and lasting impact on the management of patients with hypertension. The study answers a critical question, but important questions remain.

The large over-riding question remaining from the SPRINT trial is this: How generalizable are the results? The J-curve relationship between systolic BP and risk is present in every individual and every group. What has been uncertain is where the inflection point on the J curve is and how the J curve relationship is impacted by chronic hypertension, age, diabetes mellitus, chronic kidney disease, and atherosclerotic disease leading to stroke and heart disease. The SPRINT has answered some of these questions, but some remain unanswered.

Perhaps, the most important question coming from the SPRINT involves a group of patients not included in the trial: patients with diabetes mellitus. A few years earlier, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was done to determine the appropriate goal systolic BP for patients with diabetes mellitus. ACCORD did not demonstrate a benefit for a systolic BP goal of 120 versus 140 mm Hg. On the basis of those results, most current guidelines call for lowering BP to the range of 135 to 140 mm Hg in diabetic patients. If the interpretation of the ACCORD results is correct, is the reason for lower BP goals leading to better results in SPRINT related to the influence of diabetes mellitus on the vasculature? Could diabetes mellitus have some negative influence on arteriolar function and blood flow autoregulation that shifts the J curve or the pressure/flow relationship? We know that blood flow is related to BP and that flow in organs, such as the brain, heart, and kidneys, remains relatively constant over a wide range of BPs in healthy people without target organ injury. But there is a precipitous decrease in flow when BP reaches a critical low point. Some speculate that arteriolar dysfunction with hampered autoregulation in diabetics might account for the difference in results for SPRINT and ACCORD. And some argue that the unexpected difference in outcomes might be related to the ACCORD study design. ACCORD had lower event rates than initially predicted because of a lower cardiovascular risk profile in participants. The exclusion of participants aged >80 years led to a younger group of patients in ACCORD than in SPRINT. The mean age for ACCORD was 62 years and for SPRINT was 68 years. Participants in the BP arm were also at lower risk because patients with dyslipidemia were assigned to the lipid arm and excluded from the BP arm. Finally, because of the use of metformin in the treatment of diabetes mellitus, participants with a serum creatinine concentration >1.5 mg/dL were excluded.

Another significant difference in the design of the SPRINT and ACCORD studies was the use of diuretics. The treatment regimen for hypertension in the ACCORD study often used hydrochlorothiazide, and the SPRINT study primarily used chlorthalidone. And the complexity of the factorial design in ACCORD may have made it less likely that a statistically significant difference could be demonstrated.

Another study addressing the issue of goal BP in treating diabetic patients with a different study design might need to be considered. Because of the issues previously noted, the ACCORD study was not sufficiently powered to detect a significant 20% reduction in the primary outcome in the more intensively treated group. Support for this consideration is the finding in ACCORD of a 40% reduction in stroke in the intensively treated group. A related question on diabetes mellitus is the recommendation for the upcoming American College of Cardiology/American Heart Association guidelines for treatment of diabetic patients with hypertension. Should the goal systolic BP be 140, 135, 130, or 120 mm Hg? Adequate evidence to guide this recommendation will not be available for the upcoming set of guidelines. The recommendation will be based on expert opinion. It is reassuring that adverse events in ACCORD were low for both randomized groups. So one might argue that risk for harm for a systolic BP goal of 120 mm Hg might be low.

Other questions in need of further study include goal BP for patients with preserved ejection fraction heart failure and for patients with low ejection fraction heart failure. Another interesting question that arises from SPRINT is whether to perform more clinical trials in patients with untreated systolic BP from 120 to 140 mm Hg. Would it be prudent to evaluate that patient population again to determine whether there is a benefit of drug treatment to a lower systolic BP? Previous studies may have demonstrated no benefit because overall risk was low in this patient group. Or might it be similar to ACCORD in that that power of the study design may have been insufficient to demonstrate benefit? Important unanswered questions unrelated to goal BP but important in hypertension management include issues related to obesity and precision medicine. Will
we discover meaningful ways to prevent and manage obesity that will lead to dramatic changes in the prevalence of high BP? The development of new science and new therapies for hypertension over the past 50 years offers hope that science will yield similar good options for obesity management. Fifty years ago what was available to manage hypertension were a small number of mostly undesirable drugs and lifestyle recommendations that were difficult to implement. That is pretty much where we are today in obesity knowledge and management.

Also the growing investment in precision medicine may offer opportunities to refine optimal BP management including goal BP for individuals or more narrowly defined groups.

Where do we go from here? Certainly, the SPRINT results should be considered by the writing committee for the upcoming American College of Cardiology/American Heart Association BP guidelines. The most critical decision relates to the treatment goal for systolic BP, including goal systolic BP for subgroups such as patients with diabetes mellitus, patients <50 years, and those with untreated systolic BP of 120 to 140 mm Hg. Given that SPRINT only included patients with, or at high risk for, cardiovascular disease, the committee might consider whether treatment recommendations should be based on global cardiovascular risk rather than BP alone. The writing committee may also want to consider implications for classification of BP. We should increase efforts in hypertension research including basic science, translational science, clinical trials, and population science. The impact of the results of SPRINT, Systolic Hypertension in the Elderly Program (SHEP), and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) should encourage funders and investigators to continue the use of high-quality, event-based, randomized clinical trials. Research should include expanded use of better BP measurements, including improved methods for ambulatory BP measurements. We need to better understand the risk associated with various components of BP, such as variability, nighttime dipping, and pulse pressure. We should consider whether clinical trial results could be improved if we had more accurate and more complete BP measurements. We should consider how we might address the question of whether treatment to 120/80 mm Hg early in life prevents the intermediate end points that may predict later target organ injury or earlier intermediates such as albuminuria and vascular stiffness. We should continue and increase efforts in hypertension-related research including obesity and precision medicine. We should continue efforts to better implement what we know now including lifestyle therapy with a strong focus on prevention in early childhood and on improving the food and physical activity environment. This includes consideration of the use of regulation. And we should not fail to pause momentarily to appreciate the progress in the field of hypertension including the remarkable results of the SPRINT. The investigators, the National Institutes of Health, and participants of the SPRINT are commended and congratulated for this important contribution.

Disclosures
None.

References
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