Sucesses of SPRINT, but Still Some Hurdles to Cross

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The Systolic Blood Pressure Intervention Trial (SPRINT; ClinicalTrials.gov identifier NCT01206062) tested the hypothesis that an intensive antihypertensive strategy that targets systolic blood pressure (SBP) to <120 mm Hg is superior to a target of 140 mm Hg in reducing the risk of cardiovascular disease.1 Studying >9000 hypertensive patients in the United States, >50 years who were at risk for heart disease or who had kidney disease, the study clearly indicated that achieving a target SBP of 120 mm Hg reduced cardiovascular events by ≈30% and reduced the risk of death by ≈25%. These profound and clinically relevant results, which were already evident 3 years in advance of the planned 6-year closure of the study, warranted early termination of the study and early communication of the results to inform healthcare providers, patients, and the public.

The SPRINT findings will have major impact at many levels, including evidence-based clinical guidelines, medical care, prescribing patterns, insurance and reimbursement schemes, and of course overall cardiovascular health at the individual and population levels. The SPRINT trialists and the National Institutes of Health funding agency are truly applauded for the significant and major contribution to the field of clinical hypertension, which could not only change the landscape on how healthcare providers manage patients with hypertension but also on how we define normal blood pressure and what levels of (systolic) blood pressure constitute hypertension.

Although overall cardiovascular event rates were lower in the intensive-treated group versus the standard care–treated group (P<0.001), the major protective cardiovascular effect was evident primarily for heart failure (P<0.002), with no significant effect on event rates for myocardial infarction (P=0.19), non–myocardial infarction acute coronary syndrome (P=0.99), or stroke (P=0.50).2 These findings not only highlight the importance of intensive treatment of hypertensive patients with heart failure but also indicate that blood pressure may be an important driving force in the evolution of heart failure, at least in the SPRINT cohort studied. The heart failure outcomes may be especially important in patients with heart failure and preserved ejection fraction, where hypertension has been identified as a particularly significant risk factor.3,5 What we still do not know from the SPRINT study, at least at the present time, is what percentage of patients with heart failure had heart failure and preserved ejection fraction.

As an additional bonus beyond highlighting the treatment benefits of intensive treatment of hypertension, SPRINT has provided us with an excellent opportunity, in the clinical setting, to learn more about the pathophysiological relationship between blood pressure and heart failure.6 Notwithstanding the striking results of this important clinical trial, the largest of its kind, there are still some caveats that warrant careful and further consideration. In particular, the patients treated to SBP <120 mm Hg exhibited significantly more hypotension (P<0.001), syncope (P=0.05), electrolyte disturbances (hyponatremia [P<0.001] and hypokalemia [P=0.006]), acute renal injury, and acute renal failure (P<0.001). Some of these effects may be directly because of the antihypertensive drugs used, such as electrolyte disturbances secondary to excessive diuretic use, whereas other effects, including syncope and acute renal injury/failure, are likely because of significant blood pressure–lowering and possible kidney hypoperfusion and renal ischemia. Although the trial investigators claim that the potential benefits of intensive blood pressure lowering to SBP <120 mm Hg exceed the potential for harm, this still remains to be demonstrated and confirmed. The adverse outcomes of SPRINT should not be overlooked lightly, especially because hypotension and acute kidney disease are associated with their own morbidity and mortality.7,8 In particular, low blood pressure and syncope may predispose to falls and dizziness, especially in the elderly,7 and acute renal injury/failure is now recognized as an important risk factor for new onset chronic kidney disease and acceleration in progression to end-stage renal disease,3,9 with its own challenges of poor quality of life, disability, and long-term costs of care.8,9 Hence, although we may prevent overall cardiovascular events by treating hypertensive patients to a target of <120 mm Hg, as suggested by SPRINT, this needs to be considered in the context that we may be creating new morbidities linked to electrolyte imbalances (predisposing to cardiac arrhythmias), hypotension, and renal disease. As such patients treated with the intensive care strategy will need to be carefully monitored for such adverse events.

There are some other aspects about SPRINT that still need clarification. The trial, by definition, focused on lowering of SBP. However, at the time of writing this editorial commentary, the effects on diastolic blood pressure (DBP) are unclear. This is important because it is likely that in the intensively treated cohort, not only was SBP reduced but also DBP. Considering the evidence demonstrating a J-shaped relationship between DBP and increased risk for cardiovascular disease in some cohorts,10 caution should be exercised whether DBP is reduced <70 mm Hg. This is further supported by findings from a secondary analysis of the Interventional Verapamil-Trandolapril Study...
(INVEST), in which ≈23,000 patients with coronary artery disease and hypertension were studied and were found to have higher risk of all-cause death and cardiac events, when DBP was low (<70–80 mm Hg). On the contrary, in a cohort of high-risk patients (>15,000), in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, no significant adverse cardiovascular events were observed at DBP<70 mm Hg, indicating no J-shaped relationship. Together these findings underscore the need to know the DBP, and hopefully this will be further elaborated as the SPRINT data are published.

Further limitations that need to be considered in the SPRINT study relate to the facts that patients with diabetes mellitus or a previous history of stroke were excluded. Unlike SPRINT, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not show cardiovascular prevention in diabetic hypertensive patients treated intensively to SBP<120 mm Hg compared with standard treatment (140 mm Hg). However, the recent ACCORD-BP demonstrated that the risk of left ventricular hypertrophy was reduced in the intensive target arm when compared with the standard target arm, supporting, in general, the SPRINT findings. With respect to stroke, a meta-analysis of 45 trials including >105,000 patients with diabetes mellitus and hypertension demonstrated that lowering SBP by 10 mm Hg was associated with reduced incidence of stroke. Other aspects that still demand careful evaluation in the SPRINT study concern the long-term outcomes in the elderly and importantly the effects of intensive blood pressure lowering on cognition. The community looks forward to the completion of the SPRINT-MIND trial, which is a substudy that will evaluate the effects of reducing SBP on cognitive function and all-cause dementia. Taken together, despite the caveats and limitations of the study, the fact that intensive treatment in the SPRINT study reduced cardiovascular morbidity by almost one third and the risk of death by almost one quarter clearly indicates that treating SBP to a lower goal (120 mm Hg) than what most clinical guidelines suggest (140 mm Hg) is favorable. The challenge now, however, is how do we get the numbers down in every day clinical practice, when currently less than half of those patients with hypertension who are treated actually are achieving targets of 140 mm Hg. As stated in the past addressing, both patient adherence and provider intensification simultaneously and insisting on healthy lifestyle choices would most likely result in better blood pressure control. Perhaps the important findings of SPRINT will further alert healthcare providers and patients that being proactive about blood pressure lowering is a health priority.

Disclosures

None.

References


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