SPRINT Proves that Lower Is Better for Nondiabetic High-Risk Patients, but at a Price

Ernesto L. Schiffrin,1,2 David A. Calhoun,3 and John M. Flack4

The release of the results of the Systolic Blood Pressure Intervention Trial (SPRINT, ClinicalTrials.gov number, NCT01206062) at Scientific Sessions of the American Heart Association on 9 November 2015 and online publication of the main results in the New England Journal of Medicine are a source of new knowledge that should increase our ability to treat hypertension more effectively and improve outcomes for hypertensive patients.1

SPRINT was a well designed and executed randomized clinical trial funded by the National Institutes of Health (NIH) in which 9,361 hypertensive patients at high risk of cardiovascular disease with blood pressure (BP) above 130 mm Hg and below 180 mm Hg, were randomly assigned to be treated to a goal systolic BP (SBP) of less than 140 vs. less than 120 mm Hg. The trial recruited hypertensive individuals in the United States who were older than 50 years of age and had never had a stroke and were not diabetic, but were either older than 75 years of age (28% of subjects), had chronic kidney disease with estimated glomerular filtration rate (eGFR) <60 and >20 ml/min/1.73 m² of body surface (28% of subjects), or had clinical or subclinical cardiovascular disease or a Framingham score indicating 10-year risk of >15% of cardiovascular disease. By 1-year post-randomization, the trial achieved SBPs of 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group, a difference that was maintained throughout the trial. SPRINT was stopped early after a median follow-up of 3.26 years because of a 25% relative risk reduction in the intensive treatment group of the primary endpoint (myocardial infarction or other coronary syndromes, stroke, heart failure, or death from cardiovascular causes) and 27% in all-cause mortality. In order to achieve these results, patients in the intensive therapy group took a mean of approximately 3 vs. 2 antihypertensive drugs in the standard therapy group. About 3,000 patients in each group completed 3 years of the trial, a little more than 1,000 completed 4 and slightly less than 300 in each group completed 5 years of the trial.

The beneficial results were found across all prespecified groups. However, it is noteworthy that individuals older than 75 years of age appeared to benefit more than younger subjects. Is it possible that these older individuals were “survivors,” who although at high cardiovascular risk, were able to benefit more than the more “mixed” younger group? As well, those subjects who entered the trial with SBP of <132 mm Hg also benefited more than those who entered the trial with higher SBP, both in terms of relative and absolute risk reduction. The protocol required that individuals assigned to the standard therapy group who entered with lower BP than goal have their antihypertensive medication down-titrated.2 In contrast, those assigned to the intensive therapy group would be up-titrated. No specific drug algorithm was used and the broad range of antihypertensive drugs utilized were provided to participants free of charge. Since among secondary endpoints 2 were highly significant in favor of the intensive therapy group, heart failure, and death from cardiovascular disease, as well as all-cause mortality, is it possible that in a high-risk population down-titration of medication, perhaps renin–angiotensin inhibitors, vs. use of a high dose of these in the intensive therapy group, progressively uncovered latent heart failure contributing to the results observed? The rise in BP after down-titration may also have contributed to the higher event rates for these conditions.

Importantly, serious adverse effects deemed related to treatment were twice as frequent in the intensive therapy group than in the standard therapy group, and although not trivial and sometimes requiring hospitalization, these remained however only moderately frequent. Indeed, 220 patients in the intensive therapy group (4.7%) and 118 in the standard therapy group (2.5%) had serious adverse events that were classified as “possibly” or “definitely” related to the intervention. Adverse effects included hypotension and syncope, and acute kidney injury, as well as hypotension and hypokalemia. Interestingly, a greater incidence of ≥30% reduction in eGFR to <60 ml/min/1.73 m² was found in the intensive therapy group in the subjects without chronic kidney disease at entry into the trial than in the standard treatment group. This may be functional, related to reversible intrarenal hemodynamic effects of the BP reduction, and the greater use of potent diuretics such as chlorothalidone, and use of high-dose renin–angiotensin inhibitors. It is unclear whether in the long run these renal effects of intensive treatment may lead to further compromise...
of renal function. The study did not recruit elderly individuals from nursing homes. It is likely that the elderly subjects enrolled in the trial were in “good shape” and not frail. This may explain that there was no difference in injurious falls in the intensive therapy group compared with the standard treatment group. Indeed, no difference in orthostatic hypotension was found between the 2 groups. However, this should raise a word of caution regarding elderly subjects who may be frail and who may not represent the type of elderly subject who was part of the trial and might therefore not necessarily benefit from similar intensive therapy in the real world of a general practitioner’s office.

As already mentioned, no diabetic subjects participated in the trial. It is important therefore to compare these results with those of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial. In ACCORD there was no significant benefit for the intensive therapy group targeting a SBP of 120 vs. 140 mm Hg, except for stroke that was more frequent in the standard therapy group. Why the difference is unclear, although ACCORD recruited half the number of slightly younger patients. Importantly, in SPRINT the projected event rate in the less intensively treated group was virtually identical to the primary endpoint composite event rate in the study while, in ACCORD, the projected event rate of the primary composite endpoint was approximately half as much as projected. Therefore, ACCORD was almost assuredly underpowered to show a benefit from intensive BP lowering. Also, the factorial design of the study including arms of standard vs. intensive glucose control may have confounded the results. There is no doubt that diabetic subjects are at high cardiovascular risk, and it is therefore in light of the results of SPRINT, difficult to interpret the absence of significant benefit in ACCORD. The differences in study outcomes between these 2 well-executed trials are unlikely to be the result of some fundamental difference in pathobiology of the cardiovascular system in diabetics vs. nondiabetic subjects. Whether some of the conclusions derived from SPRINT will be extended to diabetic subjects will have to be considered and vigorously debated by those putting together clinical guidelines.

One aspect that has received only passing mention is the method of measurement of BP. This was performed using automated office BP (AOBP) measurement using an Omron device and measuring BP 3 times unobserved. This is critically important, since SBP when measured this way may be 5–10 mm Hg lower than when measured with a manual instrument or even when patients are being observed or talking, or in a room that is not quiet. Thus in community practice, lowering SBP to 120 mm Hg may mean that, if not done according to the correct protocol of AOBP, SBPs could actually be far lower than 120 mm Hg, with unknown consequences. Furthermore, it should be noted that more than 50% of patients in the intensive treatment group did not achieve a SBP lower than 120 mm Hg, which may indicate that intensifying BP control even if these targets are not reached will result in the improved outcomes reported in the trial.

SPRINT provides extraordinary new knowledge on how to manage hypertension. It also challenges the long-held belief that evidence was lacking for initiating antihypertensive treatment in hypertensive patients at BP threshold of <140/90 mm Hg, despite the previously published meta-analysis by Law suggesting that this was indeed the case. The SPRINT data should prompt critical reexamination of recently released guidelines suggesting that BP targets be relaxed for high-risk patients. These exciting, high-quality data also raise the counter-intuitive possibility that the greatest benefit might be derived from earlier initiation of pharmacological treatment before BP elevations have caused more vascular and target-organ injury.

However, the knowledge in principle needs to be applied to the population recruited to SPRINT, meaning that it does not apply to diabetic subjects or subjects without cardiovascular risk. As mentioned above, although it applies to elderly individuals, it does not apply perhaps to frail elderly subjects. The questions that crafters of best practices will have to deal with now are not easy. However, it is clear that optimizing the protocol for BP measurement and optimizing control of BP are evident conclusions that can be drawn from this study, and NIH and the authors of SPRINT as well as the more than 9,000 participants have to be congratulated for providing us with this extraordinary trial and strong evidence. Should conclusions drawn from SPRINT be extended to other populations of subjects, such as younger persons, diabetics, blacks, hypertensive subjects at lower cardiovascular risk, or with higher SBP? How do we balance the benefits observed with the adverse effects recorded in SPRINT? Patient preference and tolerance for adverse effects, weighing benefits and risks involved, will certainly have to play a role. We already achieve control of BP with difficulty in about 50% of subjects, more often in some jurisdictions. Intensifying treatment will mean that patients will have to take more antihypertensive agents, maybe more visits to practitioners’ offices will be needed, and there will be a greater cost to the health care system, albeit compensated by reduced morbidity and mortality of hypertensive subjects. However, it is thanks to the SPRINT main results just published, and the many other analyses of the trial that will surely follow including those regarding cognition, that we can now start dealing with all these questions, hopefully leading to improved outcomes for our hypertensive patients.

REFERENCES
