Managing Hypertension in Patients with CKD: A Marathon, Not a SPRINT

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ABSTRACT

In this manuscript, nephrologist-investigators from one of five Clinical Center Networks of the Systolic Blood Pressure Intervention Trial (SPRINT) provide background information and context on the intensity of anti-hypertensive therapy in conjunction with the release of detailed results from SPRINT’s primary analysis. The authors highlight published evidence on the safety and efficacy of differing intensities of anti-hypertensive therapy in mild to moderate CKD, where SPRINT will help to inform practice, as well as where gaps in evidence will remain. The authors also challenge the nephrology community to renew its attention and efforts on hypertension clinical care and research.


The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to determine whether more intensive antihypertensive therapy was superior to conventional (standard) hypertension control. The BP metric on which the intervention was based was a target in-clinic systolic BP <140 mmHg (standard) or <120 mmHg (intensive). SPRINT recruited subjects from November 2010 to March 2013 at 102 sites organized within five Clinical Center Networks, one of which primarily involved clinical sites directed by nephrologists and focused on recruiting participants with CKD. SPRINT was sponsored by four institutes within the National Institutes of Health, with the National Heart, Lung and Blood Institute being the primary sponsor and additional support coming from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Aging, and the National Institute of Neurologic Disorders and Stroke. The trial intended to recruit one third of its subjects with CKD. Patients with diabetes mellitus, polycystic kidney disease, and a history of stroke were excluded along with patients with heavy proteinuria (>1 g/d urine protein excretion).

HYPERTENSION MANAGEMENT IN MILD TO MODERATE CKD

The optimal BP goal, whether systolic or diastolic, in the treatment of hypertension remains controversial. Observational data consistently show lower risks of death and cardiovascular events among persons with lower rather than higher systolic BP.1 However, the observation that lower ambient BPs are associated with lower risks of death and cardiovascular events does not necessarily indicate that the treatment of hypertension to these same values reduces risks proportionately or even at all. Notable examples where observational data were incorrectly relied on to change clinical practice include the provision of antiarrhythmic agents for the treatment of premature ventricular beats after myocardial infarction (a strategy countered by results from the Cardiac Arrhythmia Suppression Trial),2 the provision of estrogen replacement therapy in postmenopausal women to reduce cardiovascular risk (countered by results from the Heart and Estrogen/Progestin Replacement Study3 and the Women’s Health Initiative),4 and intensive glycemic control in type 2 diabetes mellitus (countered by results from the Action to Control Cardiovascular Risk in Diabetes Trial).5 Cohort studies and secondary analyses of randomized clinical trials comparing different drug classes have yielded mixed results. For example, in an analysis of data from the Irbesartan in Diabetic Nephropathy Trial, Berl et al.6 showed lower rates of cardiovascular death and heart failure with lower achieved systolic BPs, although few subjects had <120 mmHg (the trial target was <130/85 mmHg). More recently, a cohort study

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of 77,765 veterans with eGFR < 60 ml/min and uncontrolled hypertension showed a 1.7-fold increase in the risk of death comparing veterans with systolic BPs < 120 mmHg with those with systolic BPs ranging from 120 to 139 mmHg. Before the initiation of SPRINT, data from randomized clinical trials on the intensity of antihypertensive therapy on cardiovascular outcomes in patients with (and without) CKD were sparse.

In the Hypertension in the Very Elderly Trial (HYVET), 3845 subjects ≥ 80 years of age with systolic BPs > 160 mmHg received the diuretic indapamide (with or without perindopril) or placebo, aiming to reduce BPs to < 150/80 mmHg. The active treatment group had an average achieved systolic BP during follow-up of approximately 145 mmHg and experienced substantially lower rates of all-cause and cardiovascular death, stroke, and heart failure. It should be noted that the systolic BP goal in the active treatment arm of the HYVET (< 150 mmHg) was higher than that of both treatment arms in SPRINT. Although persons with serum creatinine concentrations > 1.7 mg/dl were excluded from the HYVET, > 30% of the HYVET population had eGFR < 60 ml/min per 1.73 m² by virtue of the age inclusion criterion and the published distribution of serum creatinine concentrations.

In the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) Trial, 4733 subjects with type 2 diabetes and hypertension were randomly assigned to systolic BP targets of < 120 mmHg (intensive) or < 140 mmHg (standard). There was a nonsignificant 12% reduction (95% confidence interval, − 27% to + 6%) in the primary composite end point (time to first occurrence of nonfatal myocardial infarction, stroke, or cardiovascular death), a nominally significant 41% (95% confidence interval, 11% to 61%) reduction in the risk of stroke, and a 2.5-fold increase in the risk of serious adverse events with the more intensive BP-lowering strategy. Patients with serum creatinine concentrations > 1.5 mg/dl were excluded, and the mean age of study subjects was 62.2 years old. Although the mean serum creatinine and its distribution were not reported, the participants’ ages and expected serum creatinine distributions suggest that a relatively small proportion of the ACCORD-BP Trial population would have been classified as having stage 3 or 4 CKD in contrast to the HYVET and the CKD trials described below.

Two moderate-sized randomized clinical trials have examined the intensity of antihypertensive control in distinct CKD populations without diabetes mellitus, namely the Modification of Diet in Renal Disease (MDRD) Study and the African American Study of Kidney Disease and Hypertension (AASK). Both trials focused on progression of kidney disease as the primary outcome, and both found no significant differences comparing mean change in measured (iothalamate) GFR from baseline to the end of the treatment between standard (approximately 140/90 mmHg) and more intensive (approximately 125/75 mmHg) BP target groups during the intervention portion of the trial. It should be noted that neither the MDRD Study nor the AASK had nearly sufficient statistical power to evaluate effects of the more intensive BP intervention on major cardiovascular events.

PRELIMINARY SPRINT FINDINGS

SPRINT randomized 9361 persons with hypertension with systolic BPs between 130 and 180 mmHg, including 2648 (28%) with eGFR of 20– < 60 ml/min per 1.73 m², 1877 (20%) with a history of cardiovascular disease, and 2636 (28%) aged ≥ 75 years old (proportions not mutually exclusive). By preliminary report, there was an approximately 30% relative reduction in the risk of the primary composite end point (first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death) and an approximately 25% reduction in all-cause mortality in the entire cohort. Although data on cognitive and kidney function have not been released, whatever their direction or magnitude, they were not likely to be of sufficient concern (or optimism) to prompt their dissemination before reporting of the primary trial results or acquisition of end of trial data. We await additional results on progression of CKD in patients with CKD at baseline, incident CKD (i.e., CKD in subjects without CKD at baseline defined as a ≥ 30% reduction in eGFR to < 60 ml/min per 1.73 m²), and safety data related to episodes of AKI during the trial.

ALERT: SPRINT IS NOT A TYPICAL CKD TRIAL

Clinical trials in nephrology have been few and far between, and we should celebrate SPRINT’s success. However, we should recognize what SPRINT is and what it is not. SPRINT is a cardiovascular trial in which a sizeable fraction of patients with mild to moderate CKD was included. SPRINT is not a typical CKD trial. SPRINT is not a trial of CKD progression. SPRINT is a trial comparing the effects of standard versus more intensive antihypertensive therapy in persons with preexisting cardiovascular disease or at high risk for cardiovascular disease, including the elderly and persons with mild to moderate CKD, the latter of which was included by virtue of reduced eGFR. It should be emphasized that persons with advanced CKD or significant (> 1 g/d) proteinuria (patients who are more likely to experience CKD progression and generally more likely to be seen by nephrologists) were excluded from SPRINT.

CAVEATS

In addition to the caveats usually ascribed to randomized clinical trials, SPRINT was restricted to persons > 50 years old and enriched with persons considerably older. Inclusion criteria ensured enrollment of a population at relatively high risk for death and cardiovascular events. Relative risk reduction was initially
reported. Although the absolute benefits experienced by subjects randomized to the <120-mmHg systolic BP target were not reported, we would anticipate lower event rates in lower-risk populations. Therefore, the absolute benefits afforded to persons with hypertension at lower risk for cardiovascular disease may be smaller than those gained in SPRINT. Although substantial relative risk reductions in the composite cardiovascular end point and all-cause mortality should never be ignored, the potential for a smaller relative benefit and the certainty of a smaller absolute benefit in lower-risk populations might prompt some providers and patients to balance effects of more intensive antihypertensive therapy on overt cardiovascular disease with effects on health-related quality of life, cognitive and sexual function, and the like, depending on the direction and magnitude of effects of the intervention on these outcomes and others. It is unlikely that SPRINT intervention will be rigorously and specifically tested in a lower-risk population in the near future, owing to feasibility and fiscal issues (a trial of lower-risk participants would likely require ≥40,000 enrollees).

**PRESENT ACTION AND FUTURE DIRECTION**

For now, nephrologists and other providers should continue the evidence-based strategy of using inhibitors of the renin-angiotensin-aldosterone system (i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, or direct renin inhibitors) with or without thiazide or thiazide-type diuretic agents as the foundation of antihypertensive therapy in CKD, adding third- and fourth-line agents (e.g., dihydropyridine calcium channel blockers, β- and/or α-adrenergic antagonists, and other drug classes) as necessary to achieve systolic BP targets toward or slightly to somewhat <120 mmHg. Providers and patients will need to balance the anticipated benefits of therapy with adverse effects, recognizing that the absolute benefit of BP lowering should be greater for patients at higher risk. As in SPRINT, careful attention should be given to lifestyle factors, including physical activity, dietary sodium intake, obesity, sleep apnea, and alcohol use. The post-SPRINT era should be one focused on prevention and treatment of hypertension to enhance longevity and reduce cardiovascular mortality and morbidity. The American Society of Nephrology and other professional societies in nephrology should expand efforts in the hypertension domain with a renewed focus on preventive medicine. Finally, after relinquishing much of dialysis care and virtually all inpatient care to others (dialysis providers and hospitalists, respectively), nephrologists should take their rightful lead in hypertension research and clinical care. We should consider formally and rigorously testing an intervention similar to that evaluated in SPRINT among patients with moderate to advanced (stages 3b and 4) CKD and patients with and without diabetes for cardiovascular, renal, cognitive, physical function, and other outcomes. Determining the optimal BP targets for all patients with CKD will likely take one to two decades of effort: a marathon, not a sprint. We owe the effort to our profession, our professional organization, and especially, our patients.

**DISCLOSURES**

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**REFERENCES**


