

## Questions Not Answered by SPRINT

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Hypertension guidelines since 2011 have recommended a blood pressure target goal of less than 140/90 mm Hg in patients younger than 80 years of age and of less than 150/90 mm Hg in patients aged 80 years and older [1-7] and of less than 140 mm Hg in persons with diabetes mellitus or chronic kidney disease older than 60 years of age and less than 150/90 mm Hg in persons without diabetes mellitus or chronic kidney disease older than 60 years of age [8]. The 2014 American Society of Hypertension/International Society of Hypertension guidelines recommended considering lowering the blood pressure to less than 140/90 mm Hg in elderly diabetics aged 80 years and older [6]. We reported data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study [9]. This study included 4,181 persons aged 55-64 years, 3,737 persons aged 65-74 years, and 1,839 patients aged 75 years and older (mean age 79.3 years) on antihypertensive drug therapy. Data from this study also support a blood pressure goal of less than 140/90 mm Hg in elderly persons [9].

The new guidelines for the management of patients with hypertension will be strongly influenced by the results from the Systolic Blood Pressure Intervention Trial (SPRINT) [10]. SPRINT randomized 9,361 patients with a systolic blood pressure of 130-180 mm Hg and an increased cardiovascular risk but without diabetes mellitus, history of stroke, symptomatic heart failure within the past 6 months, a left ventricular ejection fraction of less than 35 %, and an estimated glomerular filtration rate less than 20 ml/min/1.73 m<sup>2</sup> to a systolic blood pressure target of less than 120 mm Hg or to a systolic blood pressure target of less than 140 mm Hg [10-16]. The patients were aged 50 years and older with a mean age of 67.9 years. Of the 9,361 patients, 2,636 (28.2 %) were aged 75 years and older, 3,332 (35.6 %) were women, 5,399 (57.7 %) were non-Hispanic white, 2,947 (31.5 %) were black, and 984 (10.6 %) were Hispanic. Cardiovascular disease was present in 1,877 patients (20.1 %), and the Framingham 10-year cardiovascular disease risk score was  $\geq 15$  % in 5,737 patients (61.3 %).

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group. The intervention was discontinued early after a median follow-up of 3.26 years [10].

The primary composite outcome was myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes and was lowered 25% ( $p < 0.001$ ) by intensive blood pressure treatment [10]. All-cause mortality was lowered 27% ( $p = 0.003$ ) by intensive blood pressure treatment. Heart failure was reduced 38% ( $p = 0.002$ ) by intensive blood pressure treatment. Death from cardiovascular causes was lowered 43% ( $p = 0.005$ ) by intensive blood pressure treatment. The primary composite outcome or death was lowered 22% ( $p < 0.001$ ) by intensive blood pressure treatment. Intensive blood pressure treatment insignificantly lowered myocardial infarction by 17%, caused the same incidence of other acute coronary syndrome, and insignificantly lowered stroke by 11%. Intensive blood pressure treatment significantly lowered the primary outcome 33% in patients aged 75 years and older and significantly lowered the primary

outcome 20% in patients aged 50 to 74 years [10].

Serious adverse events were similar in both treatment groups [10]. However, intensive blood pressure treatment was associated with more hypotension (2.4% versus 1.4%,  $p = 0.001$ ), more syncope (2.3% versus 1.7%,  $p = 0.05$ ), more electrolyte abnormality (3.1% versus 2.3%,  $p = 0.02$ ), and more acute kidney injury or acute renal failure (4.1% versus 2.5%,  $p < 0.001$ ). The incidence of bradycardia, injurious falls, and orthostatic hypotension with dizziness was similar in both treatment groups [10].

The new hypertension guidelines will have to answer on the basis of expert medical opinion many questions not answered by SPRINT. One of these questions is what should be the target diastolic blood pressure? These data are available for analysis by the SPRINT investigators. Hopefully, these data will be analyzed and published.

With the current data from SPRINT, there is no evidence of permanent kidney injury associated with the lower target systolic blood pressure [10]. However, long-term follow-up of adverse renal outcomes needs to be performed.

The SPRINT investigators planned a comparison of the effects of the 2 systolic blood pressure targets in the elderly on the incidence of dementia, changes in cognitive function, and cerebral small-vessel ischemic disease [10]. We are awaiting publication of these very important data.

Randomized clinical trial data are needed to investigate the effects of the 2 systolic blood pressure targets on clinical outcomes in patients with heart failure and a reduced left ventricular ejection fraction, in patients with heart failure and a preserved left ventricular ejection fraction, and in patients with a left ventricular ejection fraction below 35% since these patients were excluded from SPRINT. We investigated the effect of baseline systolic blood pressure on clinical outcomes in patients with mild to moderate heart failure with a reduced left ventricular ejection fraction and in patients with a preserved left ventricular ejection fraction in the Digitalis Investigation Group trial using a propensity-matched design [11]. We found that a baseline systolic blood pressure of 120 mm Hg or lower was associated with increased cardiovascular and heart failure mortalities and all-cause, cardiovascular, and heart failure hospitalizations which was independent of other baseline characteristics [11]. On the basis of our data, I favor that the target systolic blood pressure in patients with heart

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failure and a reduced left ventricular ejection fraction, in patients with heart failure and a preserved left ventricular ejection fraction, and in patients with a left ventricular ejection fraction less than 35 % should be less than 140 mm Hg.

Patients with a prior stroke and patients with an estimated glomerular filtration rate less than 20 ml/min/1.73 m<sup>2</sup> were also excluded from SPRINT. Until randomized clinical trial data are available for the optimal systolic blood pressure in these patients, I recommend that the target systolic blood pressure in these patients should be less than 140 mm Hg.

Patients with diabetes mellitus were also excluded from SPRINT. In The ACTION to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial, lowering the systolic blood pressure to less than 120 mm Hg in 4,733 persons insignificantly lowered the composite primary outcome of myocardial infarction, stroke, or cardiovascular death 12% but significantly lowered the incidence of stroke (a prespecified secondary outcome) 41% ( $p = 0.01$ ) [12]. The sample size was much larger in SPRINT (9,361 persons) than in ACCORD BP (4,733 persons), and there were important methodological differences between both trials [12-15]. The patients in SPRINT were older (mean age 67.9 years) than in ACCORD BP (mean age 62.2 years). The patients in ACCORD BP were at lower risk than the patients in SPRINT. Patients with dyslipidemia were assigned to the lipid arm and excluded from the blood pressure arm in ACCORD BP. Patients with a serum creatinine above 1.5 mg/dL were also excluded from ACCORD BP. In addition, the use of diuretics was different in these trials. ACCORD BP often used hydrochlorothiazide, whereas SPRINT primarily used chlorthalidone (my preference) [15].

A post-hoc analysis of the results from ACCORD BP also found that the primary cardiovascular disease outcome was 26% lower in patients randomized to intensive blood pressure treatment and standard glycemia goals than in patients randomized to standard blood pressure treatment and standard glycemia goals [14]. In addition, targeting a systolic blood pressure of less than 120 mm Hg in ACCORD BP was associated with a 39 % lower risk of electrocardiographic left ventricular hypertrophy ( $p = 0.008$ ) [16].

In conclusion, a randomized clinical trial using a similar number of patients enrolled in SPRINT and the design used in SPRINT needs to be performed in diabetics with hypertension to determine whether the target systolic blood pressure in this population should be lowered to less than 120 mm Hg or to less than 140 mm Hg. On the basis of the available data, I recommend lowering the systolic blood pressure in diabetics at increased cardiovascular risk to less than 120 mm Hg. However, because of a higher incidence of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure in patients treated to a systolic blood pressure target goal less than 120 mm Hg, these patients will require more intensive monitoring for serious adverse events with an increased cost of care.

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