

## EDITORIAL

# SPRINT Results in Older Patients

## How Low to Go?

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**In this issue of *JAMA*,** Williamson and colleagues<sup>1</sup> report the results of a preplanned, appropriately powered subgroup analysis of data from the Systolic Blood Pressure intervention Trial (SPRINT) in persons aged 75 years or older.



### Related article

SPRINT was a randomized, clinical, open-label study of community-dwelling older adults with systolic blood pressure (SBP) in the 130 to 180 mm Hg range in whom the effects of reducing SBP to less than 120 mm Hg (intensive treatment group) were compared with those associated with SBP lowering to less than 140 mm Hg (standard treatment group).<sup>2</sup> The primary end point was a composite of cardiovascular disease (CVD) events, including myocardial infarction, acute coronary syndrome, heart failure, stroke, or death from cardiovascular causes. Exclusion criteria included diabetes, history of stroke or heart failure, and SBP less than 110 mm Hg after 1 minute of standing.

As in the overall SPRINT cohort, the subgroup of participants aged 75 years or older showed impressive reductions in CVD events and total mortality with intensive as compared with standard therapy.<sup>1,2</sup> The primary outcome occurred in 102 patients in the intensive treatment group versus 148 in the standard treatment group (hazard ratio, 0.66 [95% CI, 0.51-0.85]), with 73 deaths in the intensive treatment group and 107 in the standard treatment group (hazard ratio, 0.67 [95% CI, 0.49-0.91]).

Hypertension in older persons is a major clinical problem worldwide. In the United States, more than 75% of individuals aged 75 years or older have hypertension, and the lifetime risk of developing hypertension exceeds 90% if a person lives long enough.<sup>3,4</sup> In addition, hypertension remains a major cause of coronary heart disease, congestive heart failure, stroke, and renal failure in older patients. Considerable uncertainty has existed regarding the target level of SBP with treatment in older patients. Observational studies have indicated that the risk for both stroke and ischemic heart disease increases progressively from levels of SBP as low as 115 mm Hg to as high as 180 mm Hg, even among individuals aged 80 to 90 years.<sup>5</sup> The Systolic Hypertension in the Elderly Program demonstrated that lowering SBP to less than 150 mm Hg in patients 60 years or older with isolated systolic hypertension was beneficial in reducing stroke,<sup>6</sup> and the Hypertension in the Very Elderly Trial, which involved patients 80 years or older with hypertension and an SBP treatment target of less than 140 mm Hg, showed significant reduction in incidence of stroke and heart failure with active as compared with placebo therapy.<sup>7</sup>

Nevertheless, many clinicians still have concerns about reducing SBP to less than 160 mm Hg in older patients, with their reluctance based on such factors as the very high prevalence of systolic hypertension in their practices, potential adverse effects of medications in older persons, the need to use 2 or more antihypertensive medications to achieve recommended blood pressure (BP) goals, and hesitation of both clinicians and patients to add more drugs to regimens that already may include several other medications for treating concomitant illnesses.

Adding to the treatment dilemma has been the differing recommendations on BP goals provided in various national and international guidelines. The report from the panel members appointed to the JNC 8 committee is a particular example in this regard.<sup>8</sup> The JNC 8 report focused primarily on the results of randomized clinical trials rather than on the totality of relevant clinical data on hypertension, as had been done by prior JNC committees.<sup>4</sup> The report also recommended raising the SBP goal to less than 150 mm Hg for patients aged 60 years or older, but this decision was controversial not only in the clinical community but among the JNC 8 committee, and some members of the committee published a minority report to advocate an SBP goal of less than 140 mm Hg.<sup>9</sup>

SPRINT is an important study that should have a substantial influence on future clinical practice. The impressive decreases in CVD events and mortality reported in *JAMA* for the subgroup older than 75 years warrant the reconsideration of optimal BP goals for patients in this age group. However, as with all important clinical trials, SPRINT also raises several questions. Because of the trial exclusion criteria, the current results may not be applicable to individuals with diabetes, heart failure, prior stroke, or postural decreases in BP. Also, despite the impressive benefits observed in the intensive group that had an SBP target of less than 120 mm Hg, the mean SBP actually achieved in this group was 123 mm Hg, indicating that not all patients in the study attained the preset SBP goal of less than 120 mm Hg. Furthermore, only ambulatory, community-based persons were recruited into the study, so the results may not be relevant to frail individuals and others restricted to their homes or to institutions. The investigators tried to address the frailty issue by performing post hoc secondary analyses in which the effect of levels of frailty and functional ability on the primary outcome was estimated. Although the findings did not appear to show an influence of these factors on the benefits of intensive BP treatment, such analyses can only be considered exploratory in nature.

The available safety data in the subgroup of patients 75 years or older in this trial are somewhat reassuring, in that no substantial increase in major clinical adverse events were apparent with intensive treatment. Small increases in incidence of hypotension, syncope, or acute changes in renal function were observed, but these appeared to be more than offset by the large benefits of treatment. However, patients recruited in clinical trials are often not representative of the broader population that would have a wider range of concomitant diseases and medications than study participants. Moreover, the full effect of the trial results may not become apparent until further data become available on the already known adverse events as well as on other important areas such as the influence of treatment on cognitive function.

The results from the overall SPRINT cohort differ from those of the ACCORD trial, which used a similar study protocol for intensive blood pressure lowering, except that only patients with type 2 diabetes were included in ACCORD but were excluded from SPRINT. No difference in primary outcome with intensive vs standard therapy was found in ACCORD, although a significant reduction in stroke incidence was observed.<sup>10</sup> There was a nonsignificant reduction in incidence of CVD events in the ACCORD intensive group, and it has been speculated that ACCORD may not have been powered adequately to detect significant treatment effects on primary outcome.<sup>2</sup>

The study by Williamson et al also may help ease longstanding concerns relating to excessive lowering of diastolic blood pressure in older patients, particularly among those with coronary heart disease.<sup>4</sup> The mean diastolic blood pressure achieved in the intensive group was 62 mm Hg, or 5 mm Hg less than in the standard group, yet CVD events in the intensive group were more than 30% lower than with standard care.

What should clinicians now recommend for the management of hypertension in most patients 75 years or older?

Although the story is incomplete, the available evidence supports a stepwise approach to treatment beginning with an initial SBP goal of less than 140 mm Hg. If lowering SBP to that level is tolerated well, further titration with careful monitoring should be considered to achieve an SBP goal of less than 130 mm Hg. The choice of antihypertensive medications can vary depending on clinician and patient preference, considering that several studies have shown that the major benefit of treatment depends on BP lowering rather than type of antihypertensive medication used.<sup>11</sup> In general, however, the preferred first-line drugs should be diuretics, calcium antagonists, angiotensin receptor antagonists, and angiotensin-converting enzyme inhibitors.  $\beta$  Receptor antagonists are also valuable as first-line agents in patients with coronary heart disease, arrhythmias, and heart failure. Combination drug preparations are useful because therapy often will involve multiple drugs. Since older persons with SBP less than 110 mm Hg while standing were excluded in SPRINT, the risk of syncope and falls may have been underestimated, and particular attention should be given to avoidance of orthostatic hypotension with treatment.

Currently, more than 40% of persons with hypertension in the United States do not have their blood pressure controlled to levels less than 140/90 mm Hg, and if the goal SBP were reduced to less than 130 mm Hg, more than one-half of persons with hypertension would be considered to have uncontrolled blood pressure. Achieving the SBP goal of less than 130 mm Hg may be challenging for clinicians, because doing so could require use of additional medications, more careful monitoring, and more frequent clinic visits. Nevertheless, the important results reported by Williamson et al in this issue of *JAMA* cannot be discounted, and unless unexpected adverse effects are observed on further examination of the trial data, then major changes in treatment goals for patients 75 years or older with hypertension will be warranted.

#### ARTICLE INFORMATION

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