

Blood pressure targets

(MARCH 2016)

TO THE EDITOR: I read with great interest the article by Thomas et al, “Interpreting SPRINT: How low should you go?”¹

Hypertension is the most prevalent modifiable risk factor, affecting almost one in every three people in the United States.² Moreover, only half of people with hypertension have their blood pressure under control to the current standard of lower than 140/90 mm Hg.² The Systolic Blood Pressure Intervention Trial (SPRINT) tested a lower goal systolic pressure, ie, less than 120 mm Hg, and found it more beneficial than the standard goal of less than 140 mm Hg.³

A drawback of SPRINT that Thomas et al did not address in their interpretation of the trial is that the two study groups were not homogeneous in terms of the antihypertensive drugs used. Antihypertensive drugs do not only lower blood pressure—some of them have additional pleiotropic effects, making their use more advantageous in special situations. For example, renin-angiotensin-aldosterone system (RAAS) blockers—ie, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists—are disease-modifying drugs in heart failure, as are certain beta-blockers.⁴ The cardiovascular benefit seen in the intensive-treatment group in SPRINT compared with the standard-therapy group was primarily due to a reduction in heart failure (a 38% relative risk reduction, $P = .0002$),³ for which RAAS blockers and beta-adrenergic blocking drugs have been shown consistently to be beneficial. But the intensive- and standard-therapy groups were not homogeneous in terms of the use of RAAS blockers and beta-blockers.

So, was the cardiovascular benefit attained in the intensive-treatment group in SPRINT due to the benefit of lower blood pressure or to the drugs used?

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TO THE EDITOR: In their review,¹ Thomas et al noted that the benefits of intensive blood pressure lowering seen in the SPRINT study² were not observed in the Action to Control Cardiovascular Risk in Diabetes-Blood pressure (ACCORD BP) trial³ or in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial.⁴ In addition to the reasons discussed in their review, the discrepancy may be due to the surprisingly low rate of statin use in the patients enrolled in SPRINT. Even though 61% of the patients in SPRINT had a 10-year Framingham risk score greater than 15%, only 44% of the patients were on statin therapy. In comparison, rates of statin use in ACCORD BP and SPS3 were 65% and 83%, respectively.

A possible interaction between statin use and intensive blood pressure lowering is consistent with previous data on angiotensin-converting enzyme (ACE) inhibitor use in high-risk populations.

The Heart Outcomes Prevention Evaluation (HOPE) trial,⁵ in which only 29% of patients received lipid-lowering therapy, found that ACE inhibitor use was associated with a significant reduction in a composite cardiovascular outcome, whereas the Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) trial,⁶ in which 70% of patients were on lipid-lowering therapy, did not show a benefit for ACE inhibitor therapy. In addition, there are many drug interactions between statins and calcium channel blockers, potentially limiting options for simultaneous aggressive treatment

of lipid levels and blood pressure.

In summary, aggressive use of statins may confer sufficient cardiovascular protection when aggressive antihypertensive therapy provides little or no incremental benefit. Hopefully, further analyses of these trials will shed light on this important question.

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IN REPLY: We thank the readers for their important and insightful comments and questions.

Dr. Yilmaz raises the point that there was no mandate in the SPRINT trial to preferentially use any specific class of antihypertensive medications in either group. However, there was greater use of all drug classes (including diuretics and renin-angiotensin-aldosterone blockers) in the intensive-treatment group.¹ (This information was included as a supplementary appendix in the main paper, and as **Table 1** in our review.) Could this have contributed to the primary cardiovascular outcome benefit seen in the intensive-therapy group, largely driven by a decreased incidence of heart failure, or could it even have masked the symptoms of heart failure rather than preventing it^{2,3}? While this is plausible, since the SPRINT trial was designed as a “treat to target” study and not as an antihypertensive medication efficacy

study, it is difficult to conclusively answer the question of potential pleiotropic effects of antihypertensive medications influencing the trial results. The authors did not comment on this in the main paper, and we agree that further analysis would be helpful in exploring this important question.

Dr. Edwards raises the question whether antihypertensive therapy confers additional cardiovascular benefit over aggressive use of statins. Statin use in the SPRINT cohort (both intensive and standard groups) was low at baseline, despite this being a population at high cardiovascular risk.¹ It is unclear whether treatment practices pertaining to lipid management could have changed during the course of the trial in participants within the SPRINT cohort, particularly after the new lipid guidelines were published. The recently published HOPE-3 trial indicated cardiovascular benefit with statins used as a primary prevention strategy in older persons with intermediate cardiovascular risk.^{4,5} Notably, outcomes with combination therapy in this trial using a statin plus antihypertensive therapy were not significantly better than with statin alone, except in the subgroup of participants who were in the upper third of systolic blood pressure levels, where combination appeared to benefit more. This study, of course, was done in a population with lower cardiovascular risk than in SPRINT, and the antihypertensive medications used (candesartan and hydrochlorothiazide) were not at maximal doses. There is also a question of whether use of chlorthalidone in HOPE-3 may have been more effective.

We agree with Dr. Edwards that this is an important question that merits further exploration, especially in the broader context of treatment based on cardiovascular risk.

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