

## CORRESPONDENCE



## A Randomized Trial of Intensive versus Standard Blood-Pressure Control

**TO THE EDITOR:** Wright et al. (Nov. 26 issue)<sup>1</sup> report on the Systolic Blood Pressure Intervention Trial (SPRINT). By focusing on blood-pressure levels, rather than on specific antihypertensive agents, this trial follows a rich heritage of government-funded, noncommercial, randomized trials in hypertension that address major public health issues. The clear differences in outcomes, including lower rates of death among patients who were randomly assigned to intensive treatment than among those assigned to standard treatment, underscore the major impact of implementing this lower blood-pressure target for the appropriate population.

Achievement of a difference of 15 mm Hg between patients who were randomly assigned to the intensive-treatment group (target systolic blood pressure <120 mm Hg) and patients who were randomly assigned to the standard-treatment group (target <140 mm Hg) was central to testing the authors' hypothesis. Their design article specifies that in the standard-treatment group, antihypertensive therapy should be withdrawn in a patient whose systolic blood pressure is less than 130 mm Hg on any occasion or less than 135 mm Hg on two consecutive visits.<sup>2</sup> Since withdrawal of antihypertensive therapy in

asymptomatic patients in whom these pressures are achieved is not necessarily considered to be standard, interpretation of the overall trial results could be affected by knowledge of how often, and in how many patients, this nonstandard action was taken.

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2. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* 2014;11:532-46.

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**TO THE EDITOR:** SPRINT was terminated early because of a survival benefit in the intensive-treatment group. We question the wisdom of this decision to truncate the trial.

In a systematic review and meta-regression analysis, Bassler et al.<sup>1</sup> compared 91 truncated randomized, controlled trials with 424 matching nontruncated randomized, controlled trials addressing the same clinical questions. They found that the truncated trials had, on average, a 29% reduction in relative risk as compared with the nontruncated trials. The number of primary-outcome events (which was lower in the truncated trials) was a significant factor in explaining differences in effect.

If we assume that SPRINT had a moderate overestimation of effect similar to that seen in the study by Bassler et al., the adjusted hazard

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ratio with intensive treatment would increase to 0.85 (95% confidence interval [CI], 0.73 to 1.01). This adjusted hazard ratio suggests either that intensive treatment is not significantly beneficial or that it is of much less benefit than the authors report. Before termination of a randomized, controlled trial for therapeutic benefit alone, the risks of outcomes bias that have been established in truncating studies should be considered — or researchers will have to accept the risk of committing a type 1 error.

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**TO THE EDITOR:** SPRINT addresses what is perhaps the most important question in the management of hypertension: what systolic blood-pressure levels should be targeted in patients who do not have diabetes? In this trial, targeting a systolic blood pressure of less than 120 mm Hg, as compared with a systolic blood pressure of less than 140 mm Hg, reduced the primary composite outcome by 25%.

The observed benefits, with a number needed to treat of 61, may redefine blood-pressure targets in clinical practice. However, clinicians should bear in mind that for each primary outcome event prevented in the intensive-treatment group, 1.3 patients had a serious adverse event related to the intervention (by our calculations, the number needed to harm was 46); this suggests the need for caution.

These results will probably reopen the discussion on benefit–risk balance in the management of hypertension, and it would thus be of clinical importance to identify patient subgroups with the

highest hazard from tight blood-pressure control in daily practice. The benefit–risk balance appears to be more favorable in patients who are older than 75 years of age. Therefore, we urge the SPRINT investigators to analyze the risk of serious adverse events related to the intervention according to age, baseline and achieved systolic and diastolic blood pressure, medication use, and coexisting conditions.

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**TO THE EDITOR:** The blood-pressure measurement technique in SPRINT has received insufficient attention. The use of a programmed automated oscillometric blood-pressure meter, which mandates 5 minutes of rest followed by three readings, results in approximately 8 minutes of rest. This longer rest time alone will reduce blood pressure.<sup>1</sup> In addition, the requirement for “quiet rest” almost certainly meant that the operator would not have been in the room, so that blood-pressure reactivity would have been further reduced.<sup>2</sup>

An automated oscillometric blood-pressure method that is similar to that used in SPRINT has been shown to result in readings that are lower than resting manual readings by up to 8 mm Hg in systolic blood pressure and up to 8 mm Hg in diastolic blood pressure.<sup>3,4</sup> As such, the achieved systolic blood pressure of 121 mm Hg and diastolic blood pressure of 69 mm Hg in the intensive-treatment group may be equivalent to a systolic blood pressure of 129 mm Hg and a diastolic blood pressure of 77 mm Hg if the blood pressure is measured manually. This is an important caveat for the large number of practitioners who continue to rely on manual blood-pressure measurement. Of even greater concern, in the standard-treatment group, the systolic blood pressure could have been as high as 144 mm Hg and the diastolic blood pressure could have been as high as 84 mm Hg when measured manually. These levels exceed current recommendations.

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**TO THE EDITOR:** Wright et al. found that aiming for a systolic blood pressure of less than 120 mm Hg, as compared with a target of less than 140 mm Hg, reduced the rate of adverse cardiovascular events among patients at high risk for cardiovascular events who did not have diabetes. However, it remains important to evaluate the effects of intensive blood-pressure lowering on cognition.

Fuster<sup>1</sup> designated heart-brain interaction as one of the top 10 cardiovascular concerns for the next decade. The relationship between hypertension and cognitive function is complex and not completely understood, and the results of clinical trials of antihypertensive therapies on cognitive function are not consistent. Some studies indicate that lower blood pressure increases the risk of cognitive decline among elderly persons.<sup>2,3</sup>

The SPRINT Memory and Cognition in Decreased Hypertension study and its magnetic resonance imaging (MRI) substudy were designed to determine whether intensive versus standard blood-pressure lowering would affect cognitive decline and structural abnormalities in the brain.<sup>4</sup> However, the trial was discontinued early because of the benefit of the intervention with respect to reductions in cardiovascular disease. This trial was stopped before most of the 4-year data on cognitive function were collected. We hope that these remaining data can be collected and the question of the effects of intensive blood-pressure lowering on cognition can be answered.

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**TO THE EDITOR:** The article on SPRINT acknowledges that the prevalence of hypertension is especially high among the elderly. However, the trial excluded patients with dementia, those who resided in assisted-living facilities or nursing homes, and those who were broadly specified to have a condition estimated to limit survival to less than 3 years. Therefore, the results are not generalizable to many older people with multiple coexisting conditions, frailty, and disability. This is especially disappointing because observational studies have shown that, paradoxically, mortality may be increased among older people with frailty who have tightly controlled blood pressure.<sup>1</sup>

The systematic exclusion of older people with frailty and nursing-home residents who may be at greater risk for adverse events and death because of tight blood-pressure control is regrettable. This exclusion risks misapplication of the otherwise robust trial findings to populations who might not benefit and indeed may be harmed.

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**TO THE EDITOR:** Wright et al. conclude that among patients at high risk for cardiovascular events who did not have diabetes, the most appropriate systolic blood-pressure target was less than 120 mm Hg. Among the secondary outcomes, heart failure, death from cardiovascular causes, and death from any cause were significantly lower in the intensive-treatment group than in the standard-treatment group.

There were obviously important differences between the intensive-treatment group and the standard-treatment group with respect to the proportion of patients who received antihypertensive medications from each individual drug class. Several of these classes (in particular, angiotensin-converting-enzyme inhibitors,<sup>1</sup> beta-blockers,<sup>2</sup> and aldosterone-receptor blockers<sup>3</sup>) have previously been shown to lead to significant reductions in fatal and nonfatal cardiovascular events among patients with heart failure or left ventricular dysfunction. The proportions of patients who received each of these three classes were significantly higher in the intensive-treatment group than in the standard-treatment group. In the Discussion section of the article, the authors do not consider that this higher use of medications from beneficial drug classes could at least in part explain the magnitude of the benefit, even independent of the magnitude of blood-pressure lowering.

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**TO THE EDITOR:** In their editorial accompanying the article by Wright et al., Perkovic and Rodgers<sup>1</sup> state that “labeling trials as ‘positive’ or ‘nega-

tive’ is seductive but ultimately counterproductive; it is more helpful to look at the totality of available data.” On the basis of this principle, they compare SPRINT and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

In the few outcomes presented (stroke, myocardial infarction, heart failure, and the primary outcome), the test for interaction for SPRINT and ACCORD was not significant; this indicated similar effects in the two trials. However, analyses of the most important outcomes in SPRINT, death and cardiovascular death, reveal a different story. The test for interaction was significant for death (*P* for interaction=0.02) and cardiovascular death (*P* for interaction=0.003), and the pooled analyses from these trials show no differences in the risk of death (relative risk, 0.88; 95% CI, 0.62 to 1.23; *I*<sup>2</sup> statistic, 80.4%) or cardiovascular death (relative risk, 0.77; 95% CI, 0.43 to 1.39; *I*<sup>2</sup> statistic, 79.1%) with the use of intensive blood-pressure control versus standard blood-pressure control.

These findings make any extrapolation of the SPRINT results to an ACCORD-like cohort of patients with diabetes inappropriate. Thus, the analysis of Perkovic and Rodgers does not alleviate concerns that a blood pressure that is too low in a patient with diabetes and hypertension may increase the risk of cardiovascular events.<sup>2,3</sup>

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**THE AUTHORS REPLY:** Pfeffer asks how often antihypertensive medications were discontinued in asymptomatic participants in the standard-treatment group who had a systolic blood pressure of less than 130 mm Hg or less than 135 mm Hg. Antihypertensive therapy in the standard-treatment group often required adjustment; 87% of participants required at least one reduction in the dose of medication to maintain systolic blood pressure in the range of 135 to 139 mm Hg. Withdrawal of medication was required in less than 7.5% of participants. Such adjustments, although not standard in clinical practice, were required to adequately test the SPRINT hypothesis.

Vipler et al. suggest that stopping the SPRINT intervention early might have caused bias in the estimated intervention effect. All trial events were scrutinized by an independent data and safety monitoring board, and as shown in Figure S3 in the Supplementary Appendix (available with the full text of the article at NEJM.org), the intensive-treatment group exceeded the predetermined stopping boundary on two consecutive occasions, the second time by a substantial margin. The sequential boundary used is known to produce less early stopping bias, and estimates from trials such as SPRINT, with a large number of events, are known to be less biased by early stopping. Before publication of our article, we computed an alternative estimate of the intervention effect, the median unbiased estimate.<sup>1</sup> This estimate indicated that our inferences were unaffected by an early stopping bias.

Muskiet et al. ask whether certain subgroups of patients may be at greater risk for adverse events with a systolic blood pressure of less than 120 mm Hg. Detailed safety and quality-of-life monitoring were conducted in our trial. The health outcomes in older patients and other subgroups are important questions.

McCormick et al. question whether sufficient attention has been paid to the technique of blood-pressure measurement in SPRINT. Measurement of blood pressure in the trial followed recommended procedures more closely than is typical in clinical practice. More attention should be paid to recommended techniques of blood-pressure measurement in clinical settings. In response to Dai and Guang: analyses of data on cognitive function and results of MRI are under way.

Todd and Clegg express concern that residents of nursing homes and patients with dementia

were excluded. We had difficulty obtaining informed consent in the latter group. SPRINT did include an older population with diverse levels of fitness, and approximately 28% of the participants were classified as frail.<sup>2</sup> The SPRINT findings according to the level of frailty in this population were recently reported.<sup>3</sup>

Pierard suggests that differences in drug use according to treatment group in the trial may have influenced the results. The distribution of antihypertensive drug classes was similar between the randomized groups, except for the 10 to 20% greater use of each major class in the intensive-treatment group. Previous studies comparing the effect of antihypertensive drug classes have shown little difference with respect to overall cardiovascular outcomes distinct from lowering blood pressure, except in patients with proteinuric nephropathy, coronary heart disease, or heart failure.<sup>4,5</sup> Patients with heart failure were excluded, and appropriate drug therapy was recommended according to the protocol for other indications, regardless of the effect on systolic blood-pressure targets.

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Since publication of their article, the authors report no further potential conflict of interest.

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**THE EDITORIALISTS REPLY:** In reply to Bangalore et al.: in SPRINT and the ACCORD trial, we noted similar results with respect to cause-specific outcomes (stroke, coronary disease, and heart failure). Since the degree of benefit varies across these outcomes and the proportions of the events in the composite outcomes (including death from cardiovascular causes and death from any cause) are different across trials, differences in composite outcomes are expected. In the ACCORD trial, more events were coronary, so composite outcomes were less sensitive to blood pressure.

We suggest three causes of undue concern regarding blood-pressure lowering in diabetes. First, there is an overemphasis on individual trials or patient subgroups. We recommended consideration of all randomized evidence, which shows no heterogeneity in cause-specific outcome effects in patients with or without diabetes and that blood-pressure lowering above and below 140 mm Hg reduces cardiovascular events.<sup>1</sup> A second cause is J-shaped curve associations from nonrandomized analyses; these are inconsistent with randomized trials<sup>1,2</sup> and hence due to confounding. Third, meta-analyses<sup>3</sup> can obscure the benefits of established blood-pressure-lowering regimens by giving undue weight to trials of dual renin-

angiotensin blockade. Dual renin-angiotensin blockade, which is now contraindicated because of specific harms, achieves minimal blood-pressure reduction. Hence, trials of this therapy should play little or no role in considerations of the benefits of blood-pressure lowering in patients with diabetes or those with a systolic blood pressure below 140 mm Hg.

The totality of randomized evidence indicates that lower blood-pressure targets benefit people with diabetes and people without diabetes. Our focus should move to implementation.

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## Corrections to Report of a Trial of Burch Colposuspension

**TO THE EDITOR:** On the basis of a report of an investigator who was using the public data set to replicate our reported data, we identified a coding error related to the urinary stress test used in our trial. We report corrections related to our original research article (April 13, 2006, issue).<sup>1</sup>

The overall conclusions of the trial remain supported by the corrected percentages, which are as follows: 3 months after surgery, 33.6% of the women in the Burch group and 57.4% of the women in the control group met one or more of the criteria for stress incontinence ( $P < 0.001$ ). A detailed correction notice in this issue of the *Journal* contains additional changes. The article has been corrected at NEJM.org. We wish to acknowledge the data coordinating center at RTI International and the Pelvic Floor Disorders Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Develop-

ment for correcting the data set and providing the analysis of the corrected data set.

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