

Review of the Systolic Blood Pressure Intervention Trial for Hypertension Management

How Low to Go for Patients With Stroke?

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One of the great successes of modern medicine is the development of effective pharmacological treatments to lower blood pressure (BP). Of the modifiable risk factors for cardiovascular disease, elevated BP or hypertension has the highest population attributable risk,¹ and a near continuous relationship with rates of stroke and coronary heart disease from levels of 115 mmHg systolic and 75 mmHg diastolic BP.² Overviews of randomized trials are consistent in showing that lowering systolic BP by 5 to 10 mmHg reduces the risk of stroke by one third, irrespective of disease history, initial BP level, or type of agent used.³⁻⁵ Moreover, more intensive long-term BP lowering can result in additional benefits proportional to the size of fall in BP.⁴⁻⁶

Despite this body of evidence, there has been longstanding controversy (and consternation) over the levels to which BP should be brought down by treatment for the prevention of cardiovascular disease. Because there has been limited randomized evidence, guideline committees have been challenged in defining BP targets below 130 to 140 mmHg to manage individual patients.⁷ Concerns over diminishing net benefit being overtaken by excessive harm with increasing reductions in BP is supported by a physiological argument over critical thresholds for organ perfusion and secondary analysis of randomized trials suggesting a J-shaped relationship with cardiovascular events.⁸ Moreover, recent trials of more intensive BP lowering, including the Action to Control Cardiovascular Risk on Type 2 Diabetes (ACCORD)⁹ and Secondary Prevention of Small Subcortical Strokes (SPS3),¹⁰ failed to show significant reductions in rates of ischemic stroke with systolic BP reductions below 120 and 130 mmHg, respectively.

The main result of the Systolic Blood Pressure Intervention Trial (SPRINT)¹¹ has, therefore, created a new paradigm in hypertension management and is affecting on hypertension management guidelines around the world. The headline summary was that people at high cardiovascular risk who received more intensive BP-lowering treatment to target systolic levels below 120 mmHg had fewer cardiovascular events than those who were treated to a target of below 140 mmHg. For stroke

physicians, the key question is whether these results apply to their patients.

SPRINT was a carefully conducted clinical trial, sponsored by the National Heart, Lung and Blood Institute of the United States, that involved 9361 hypertensive patients (mean age, 68 years) who were treated to 2 systolic BP treatment targets (<120 versus <140 mmHg). The key inclusion criteria were an age ≥ 50 years, systolic BP of 130 to 180 mmHg, and evidence of increased cardiovascular risk based on either a 10-year Framingham risk estimate of at least 15% or markers of vascular disease including chronic renal disease in approximately one third of participants; but people with diabetes mellitus or stroke were specifically excluded. The study was stopped earlier than planned after a mean follow-up of 3.26 years, on the recommendation of the data and safety monitoring board. During the study period, a mean systolic BP reduction to 121.4 mmHg in the intensive-treatment group, when compared with a mean systolic BP to 134.6 mmHg in the standard-treatment group, resulted in a significant relative reduction in the primary composite cardiovascular end point (first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death caused by cardiovascular disease) by 25% (1.65% per year versus 2.19% per year; $P < 0.01$), and in all-cause mortality by 27%.

The treatment effect was driven primarily by a reduction in heart failure and death; the annual stroke rate was 0.41% in the intensive-treatment group versus 0.47% in the standard-treatment group (hazard ratio, 0.89; 95% confidence interval, 0.63–1.25; $P = 0.50$). The SPRINT Research Group noted their trial was comparable with ACCORD and SPS3 in showing a reduction in stroke with lower BP targets; the lack of statistical significance was most likely because of limited power to detect small effects in a population at relatively low risk of stroke (two thirds were aged <75 years and most had cardiovascular risk factors, rather than a previous cardiovascular event). As such, the absolute benefit with respect to this end point would equate to 6 strokes prevented per 10000 people treated annually.

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The main hazard observed with more intensive BP lowering in SPRINT was an increased risk of kidney dysfunction as measured by glomerular filtration rate (1.21% per year versus 0.35% per year; $P < 0.001$). Hypotension, syncope, electrolyte abnormalities, and acute renal failure also occurred more commonly in intensive-treatment group. These events are a potential concern in older people, but those aged ≥ 75 years (28% of participants) had similar benefit from more intensive treatment to those younger. Whether the benefits extend to octogenarians and nonagenarians, rapidly growing segments of the population at higher absolute risk of cardiovascular events than younger people, is unclear. Results of a cognitive function substudy are eagerly awaited as observational studies suggest a U-shaped relationship between BP and cognitive impairment. Some studies show clear benefits from lowering BP in those with systolic BP > 140 mmHg,¹² whereas others suggest potential harm with reductions below 126 to 128 mmHg^{13,14} and diastolic BP below 70 mmHg.¹³

Data from the 2007 to 2012 National Health and Nutrition Examination Survey suggest that 7.6% of the US population meet the SPRINT eligibility criteria, which equates to > 16 million people.¹⁵ Thus, a large segment of the population who could potentially benefit from more intensive BP management. However, we recommend caution in generalizing the SPRINT results, and particularly so to patients with a history of stroke for the following reasons.

1. SPRINT specifically excluded patients with stroke. In SPS3, which compared a target systolic BP < 150 mmHg (mean 138 mmHg at 1 year) versus a target BP < 130 mmHg (mean 127 mmHg at 1 year) in patients with magnetic resonance imaging-proven lacunar stroke, there was no mortality benefit,¹⁰ nor any benefit on cognition over a median follow-up of 3 years.¹⁶
2. The intensive clinic assessments, with BP measurement taken with an automated device after 5 minutes rest in a seated position, every month for the first 3 months, and then every 3 months thereafter postrandomization in SPRINT, will be challenging to achieve in routine care around the world.
3. The balance of benefits and harms of more intensive BP lowering may be more critical in patients with stroke than in other types of patients with high cardiovascular risk.
4. The major cause-specific event reduced by intensive BP lowering in SPRINT was heart failure (38 heart failure events prevented of a total of 76 cardiovascular events prevented), which is not a common outcome in stroke survivors.

In summary, the SPRINT study provides good news about the effects of additional BP lowering in a broad high cardiovascular risk population and hypertension guidelines are likely to be updated accordingly. The results should also prompt additional research in secondary stroke prevention through the enrollment of patients into clinical trials of more intensive BP targets. Two such trials include the ongoing Stroke in Hypertension Optimal Treatment (SHOT) trial of the European Society of Hypertension and the Chinese Hypertension League,¹⁷ and the soon to commence Triple Therapy Prevention of Recurrent Intracerebral Disease Events

Trial (TRIDENT) funded by the National Health and Medical Research Council of Australia. HOT is an open trial which plans to enroll 7500 patients aged ≥ 65 years with a history of hypertension and stroke/transient ischemic attack to 3 systolic BP targets, < 135 to 145 mmHg, 125 to 135 mmHg, and < 125 mmHg, for the prevention of recurrent stroke. TRIDENT is a double-blind, placebo-controlled, trial using a fixed low-dose combination of BP-lowering agents (Triple Pill strategy) for stroke prevention in 4200 patients with intracerebral hemorrhage and systolic BP levels defined as high normal to borderline high. SPRINT provides a strong rationale for such research gaining complimentary data on the question of optimal BP control in patients with a history of stroke.

Disclosures

Dr Silver reports being a surveyor for the Joint Commission, and adjudicator for the Women's Health Initiative and SOCRATES (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) trials; medico-legal expert review; and honoraria for Ebix, Medscape, and Medlink. Dr Anderson reports being a Principal Investigator of the Triple therapy prevention of Recurrent Intracerebral Disease Events Trial study supported by the National Health and Medical Research Council of Australia, is a member of advisory committees for Astra Zeneca and Medtronic, and he has received honoraria and travel reimbursement from Takeda China.

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