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Optimal target for blood pressure control – how low should we go?

[1]RL Soiza, [2]L Shields
[1]Consultant Physician, [2]Specialty Registrar in Geriatric Medicine and General Internal Medicine, Aberdeen Royal Infirmary, Aberdeen, UK

TITLE A randomized trial of intensive versus standard blood pressure control

AUTHORS SPRINT Research Group

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Correspondence to RL Soiza
Department of Acute Geriatric Medicine
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN
UK

e-mail roy.soiza@nhs.net

SUMMARY

The SPRINT trial randomised 9,361 people (64% male, mean age 68.9 years) with systolic blood pressure (SBP) between 130–180 mmHg and high cardiovascular risk to either 'intensive' treatment with a target of <120 mmHg or 'standard' treatment with a target of <140 mmHg.[1] The trial had a cluster-randomised design and involved 102 centres in the USA, and included Puerto Rico. Those with diabetes, previous stroke or age <50 years were excluded. Most (90%) participants were already taking antihypertensive therapy (mean 1.8 agents per patient) at baseline. Participants were seen monthly for the first three months and then every three months thereafter. A treatment protocol was followed although specific therapies were not mandated. The intensive treatment arm had medications adjusted on a monthly basis. The standard treatment arm had therapy adjusted to a target of 135–139 mmHg; this included reducing their treatment if their SBP was less than 130 mmHg at a single visit or 130–134 mmHg on two consecutive visits.

The primary outcome measure was a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes. Secondary outcome measures included all-cause mortality and the individual components of the composite outcome. In addition to serious adverse events, a short-list of monitored events such as syncope and injurious falls were reported if they resulted in emergency department attendance. Participants and all study personnel were unblinded. Outcome adjudicators were blinded and relied on standard proformas completed by the unblinded study personnel. Follow-up was planned for 5 years.

The study was stopped early after a median follow-up of 3.26 years due to a significantly lower incidence rate of the primary composite outcome in the intensive treatment arm (1.65% vs 2.19% per year, p<0.001). All-cause mortality was lower in the intensive treatment arm (1.03% vs 1.40% per year, p=0.003). Differences in the primary outcome rate between groups became apparent at 1 year and, for death, separation occurred at 2 years. Serious adverse events deemed 'probably' or 'definitely' attributable to the intervention were reported in 4.7% of cases on the intensive treatment arm and 2.5% of the standard therapy arm (p<0.001). Rates of reported serious adverse events overall were only marginally higher in the intervention arm (38.3% v 37.1%, p=0.25). However, rates of monitored and objectively measured serious adverse events were significantly higher in the intervention arm, including emergency department visits for hypotension (3.4% v 2.0%, p<0.001), syncope (3.5% v 2.4%, p=0.003), electrolyte abnormalities (3.8% v 2.8%, p=0.006) and acute kidney injury (4.4% v 2.6%, p<0.001). Rates of injurious falls were similar in both groups.

OPINION

The findings of the study resulted in calls for changes in guidelines and clinical practice, with media reports claiming the study had 'conclusively' shown lower blood pressure (BP) targets are better and would save many lives.[2] The commendable inclusion of a relatively large number of older people (26.8% of participants were over 75) placed special focus on this group as most guidelines advise a higher SBP target in this population. Pre-planned sub-group analyses showed those aged over 75 were the most likely to benefit from intensive treatment,[1] although the relative risk of serious adverse events was not reported. The result is in keeping with that in other trials of BP lowering therapy in older people, showing that lower BP leads to fewer cardiovascular events.[3-5] However, none of these trials had a treatment target as low as 120 mmHg. The only

other trial to have tested the 120 mmHg and 140mm Hg targets (ACCORD) was undertaken in people with diabetes and failed to show any benefit from intensive BP lowering.[6] So should SPRINT now lead to a major change in the treatment of hypertension? A number of issues merit further consideration.

First, is the result credible? SPRINT has many strengths, such as its large size and inclusiveness (particularly participant age and race profile). However, over half the participants in the intervention arm did not reach their SBP target of 120 mmHg despite the intensive monitoring and polypharmacy (mean of 2.8 antihypertensive medications per participant). This suggests that a target of 120 mmHg will probably be unachievable for most in the real world and its safety for those achieving the lower target has not been conclusively proven by SPRINT. An even bigger concern is the unusual treatment of the 'standard' therapy arm, where patients with a history of well-controlled hypertension had their medication reduced to achieve a higher SBP of 135–139mmHg. This could have inflated event rates in the standard therapy arm. The lack of participant and investigator blinding could have easily introduced important biases, particularly ascertainment bias. It is highly unlikely that this would be eliminated by the blinded endpoint adjudication panel. The effect on overall mortality deserves further scrutiny. Deaths from cardiovascular causes accounted for a minority of fatal events in both groups and for only half of the 'excess' deaths in the standard therapy group. It is possible that the apparent benefits come from other salutary effects of BP-lowering agents, rather than the lower BP itself.

Second, is the result relevant to clinical practice? In addition to the usual concerns that trial results are not always replicated in real practice, the choice of composite outcome may expose the study to criticism that it was designed more to prove a point about the dangers of hypertension than to improve patient welfare. We know nothing about the effects of each target on more person-centred outcomes such as quality of life or functional ability.[7] Concerns about the effects of hypotension on cognitive decline are well described[8] and SPRINT's protocol includes assessments in this domain, but the investigators have not reported them at the time of writing. The implications for healthcare cost of additional management to achieve the lower BP threshold and deal with the higher rates of serious adverse events have not been described. The additional burden on patients from the extra visits, monitoring and treatment that will be required to achieve such a low BP should not be underestimated.[9] Care should be taken in extrapolating the results to patient groups not included in the trial. In particular, the trial did not include anyone with low overall vascular risk or those with a life expectancy below three years, those with significant cognitive impairment, or people with diabetes.

Arguably, SPRINT confirms many 'standard wisdoms'. It adds to the existing evidence base that lowering BP as near to 120 mmHg as possible results in fewer major cardiovascular events and saves lives but also causes additional serious adverse events. The results will provide plenty of encouragement both to those who advocate aggressive BP lowering and to those who argue the use of arbitrary cut-offs for hypertension results in avoidable harm. While continuing to pursue good control of hypertension, clinicians should still use their judgment and treat patients as individuals when making decisions on antihypertensive treatment. Important considerations should include patient preference and goals, overall vascular risk and risk of adverse events such as syncope or renal impairment. The vast majority of individuals on antihypertensive treatment will never benefit from it – even the most optimistic interpretation from the SPRINT trial investigators suggests just 1 in every 61 treated in the intensive intervention will avoid an event after three years of treatment.[1] Therefore, we suggest neither patient nor clinician should lose sleep when a higher BP cut-off is needed to avoid adverse drug events, minimise symptom or medication burden, or improve quality of life. This is particularly pertinent for those especially susceptible to indiscriminate use of guidelines or policies to intensively control BP, such as frail older people and those nearing the end of life.[10]

REFERENCES

1 The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med* 2015; 373: 2103–16. http://dx.doi.org/10.1056/NEJMoa1511939

2 Kolata G. Lower blood pressure guidelines could be 'life-saving', federal study says. *New York Times* 11 September 2015. http://www.nytimes.com/2015/09/12/health/blood-pressure-study.html (accessed 26/11/15).

3 Staessen JA, Fagard R, Thijs L et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; 350: 757–64.

4 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; 265: 3255–64.

5 Beckett NS, Peters R, Fletcher AE et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; 358:1887–98. http://dx.doi.org/10.1056/NEJMoa0801369

6 Cushman WC, Evans GW, Byington RP et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575–85. http://dx.doi.org/10.1056/NEJMoa1001286

7 Roberts H, Khee TS, Philp I. Setting priorities for measures of performance of geriatric medical services. *Age Ageing* 1994; 23:154–7.

8 Duthie A, Chew D, Soiza RL. Non-psychiatric comorbidity associated with Alzheimer's disease. *QJM* 2011; 104:913–20. http://dx.doi.org/10.1093/qjmed/hcr118

9 Mair F. Thinking about the burden of treatment. *BMJ* 2014; 349:g6680. http://dx.doi.org/10.1136/bmj.g6680

10 Caslake R, Soiza RL, Mangoni AA. Practical advice for prescribing in old age. *Medicine* 2013; 41: 9–12. http://dx.doi.org/10.1016/j.mpmed.2012.10.006