

Optimum Blood Pressure Target After Lacunar Stroke

Con Side of the Argument

Ernesto L. Schiffrin

The recent report of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, a randomized controlled clinical trial of secondary prevention of stroke targeting systolic blood pressures (BPs) <130 versus 130 to 149 mm Hg in patients with recent but not acute subcortical lacunar stroke,¹ and the associated Comment² conclude that “Although the reduction in stroke was not significant, our results support that in patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial.”¹ Indeed, the Comment underlined that “the SPS3 trial was underpowered to identify or exclude confidently a slight, but nevertheless clinically important, increase in serious complications of hypotension with systolic blood pressure lower than 130 mmHg.”² However, the cover of August 10 to 16, 2013 issue of *The Lancet* that carries the article on SPS3 and the associated Comment reads “The implications of SPS3 are that clinicians should endeavour to achieve and maintain systolic blood pressures lower than 130 mmHg in patients who have survived 2 weeks or more after subcortical lacunar ischemic stroke.” This assertion is essentially based on the consistency of results across subgroups, the consistency of results (19% reduction in events) with other studies of primary or secondary prevention of different types of stroke, at similar differences of systolic BP between groups, in this particular trial 11 mmHg between the achieved BP of the high-target group (138 mmHg) and the low-target group (127 mmHg), among the 3020 subjects with MRI-proven lacunar strokes followed for 3 to 6 years.

However, in an era of “evidence-based medicine,” the BP target after results that are not statistically significant in a trial possibly underpowered to detect either benefit or harm should

remain in a situation of equipoise, with cautious recommendations that stress that the evidence is weak. The results were consistent across subgroups, and specifically hemorrhagic stroke prevention did achieve statistical significance ($P=0.03$); nevertheless, the latter was a secondary end point, and the primary end point of prevention of all strokes was nonsignificant ($P=0.08$).

The vascular biology underlying lacunar strokes may differ from that of other types of stroke such that BP lowering may be less effective in prevention of repeat stroke post lacunar stroke certainly than hemorrhagic stroke as shown in this trial and other strokes or all strokes as demonstrated in the Perindopril Protection against Recurrent Stroke Study (PROGRESS)³ and in a small group of subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.⁴ Recurrence of lacunar strokes may be more sensitive to more important lowering of BP (J-curve effect), eliminating the benefit of lower BPs seen for strokes in general. The Comment in *The Lancet* brings up the greater use of β -blockers in the lower target group than in the higher target group and that this could result in an increase in visit-to-visit variability in systolic BP. Indeed, enhanced visit-to-visit variability in systolic BP has been shown by Rothwell et al⁵ to raise the risk of stroke independently of mean BP. However, there was increased use of calcium channel blockers in the lower target group. Calcium channel blockers reduce visit-to-visit BP variability^{6,7} and could accordingly counteract the action of excess use of β -blockers. But all this remains speculative. The important fact is that the primary end point did not achieve statistical significance.

It would seem that it is premature for blanket statements recommending treatment targets to appear in the article, the

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Comment, and on the cover of a major journal when these are not substantiated by a significant primary end point, and particularly because of the journal's impact, they will undoubtedly influence the practice of physicians around the world. We have seen recently how guidelines from different organizations have backtracked on lower targets for chronic kidney disease and diabetes mellitus for which evidence was weak, mostly expert opinion, and not supported by data.⁸ Furthermore, it has become evident that in other conditions such as chronic kidney disease⁹ and in diabetes mellitus,⁴ systolic BP targets <130 mmHg may be harmful, even though in the latter, a small group of diabetic patients did have a reduced incidence of stroke in ACCORD.⁴

In conclusion, the Comment and the original article as well as *The Lancet's* cover should have been more cautious in their interpretation of the data, and the message that is communicated regarding BP targets in the secondary prevention of strokes after a lacunar stroke. At present, it cannot be recommended that physicians lower systolic BP <130 mmHg for secondary prevention after lacunar strokes. It is unlikely that organizations issuing guidelines for the management of hypertension will recommend physicians to follow the advice issued in the article of *The Lancet* reporting the SPS3 trial. Despite the commendable effort carried out by the SPS3 investigators, larger future randomized double-blind trials will be needed to ensure that the study has the power to detect either benefit or harm from equivalent BP reductions as tested in the SPS3 trial and define the evidence-based targets required to protect patients from recurrence of ischemic brain infarction post lacunar stroke. We are in a situation of equipoise with respect to this question, with

no solid evidence to support recommending lowering BP <130 mmHg to prevent stroke recurrence after lacunar stroke.

Disclosures

None.

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Response to Optimum Blood Pressure Target After Lacunar Stroke: Con Side of the Argument

Graeme J. Hankey, Ben Lacey

We agree with Schiffrin that the Secondary Prevention of Small Subcortical Strokes (SPS3) trial primary end point did not reach the arbitrary threshold of statistical significance of $P < 0.05$.¹ However, we also agree with Hackshaw and Kirkwood that borderline significance in the primary end point of trials does not necessarily mean that the intervention is not effective.² Borderline P values, such as in SPS3, can occur when there is a clinically meaningful treatment effect but a large SE because of an insufficient number of outcome events. The SPS3 trial was powered to reliably identify a reduction in the relative risk of recurrent stroke by 25%, but not by the observed 19%. Nevertheless, the SPS3 results still offer some evidence of a beneficial effect in targeting a systolic blood pressure <130 mmHg compared with 130 to 149 mmHg; the 95% confidence intervals indicate that recurrent stroke may be reduced by as much as 36% or increased by as much as 3%.

We also agree with Schiffrin that the evidence from the SPS3 trial is weak, if it is interpreted in isolation. However, the evidence from SPS3 is compelling when it is interpreted in the context of meta-analyses of large numbers of cohort studies and clinical trials that have not identified a threshold below which blood pressure lowering is not associated with a reduced risk of stroke, down to $\geq 115/75$ mmHg.^{3,4} Further, there is no strong evidence to indicate that this varies in different subtypes of stroke. Although awaiting the outcome of future randomized trials, the totality of evidence suggests that targeting a systolic blood pressure <130 mmHg is likely to be safe and more effective than a systolic blood pressure of 130 to 149 mmHg in patients with recent (but not acute) lacunar ischemic stroke.

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