

## Optimum Blood Pressure Target After Lacunar Stroke

### *Pro Side of the Argument*

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Lacunar stroke is a small (<20 mm axial diameter), subcortical infarct or hemorrhage in the deep white matter, internal capsule, thalamus or ventral pons, in the territory of supply of an intracerebral small penetrating / perforating artery.<sup>1</sup>

Lacunar strokes are most commonly ischemic (ie, infarcts) and are caused by disease of intracerebral small (40–200  $\mu$ m diameter) penetrating arteries.<sup>2</sup> Intracerebral small artery diseases causing lacunar ischemic stroke include intrinsic cerebral arteriolar occlusive disease (eg, arteriolosclerosis, lipohyalinosis, fibrinoid necrosis, and arteritis) and, in a small minority (10%) of cases, occlusion by embolism from a proximal source. Intracerebral small artery diseases causing lacunar hemorrhagic stroke include amyloid angiopathy, fibrinoid necrosis, and arteritis.

The pathogenesis of intracerebral small vessel disease is largely unknown and may primarily reflect endothelial dysfunction and failure.<sup>2</sup> However, the pathological processes leading to the arteriolar disease are associated with prolonged exposure to vascular risk factors, particularly hypertension.<sup>2</sup> Hence, tight control of vascular risk factors such as hypertension underpins the management of the  $\approx$ 25% of patients (varying 10% to 40% in different populations) with ischemic stroke who have lacunar stroke attributable to intracerebral small vessel disease as the underlying cause.<sup>3–8</sup>

### **What Is the Evidence That Lowering Usual Blood Pressure After Stroke, and After Lacunar Stroke, Reduces Recurrent Stroke?**

A meta-analysis of 45 randomized controlled trials (RCTs) of blood pressure (BP)-lowering drugs found that reducing mean BP by 10 mmHg systolic, or 5 mmHg diastolic, reduced the

risk of stroke by  $\approx$ 40% (relative risk reduction [RRR] 41%; 95% confidence intervals [CI, 33–48]).<sup>9</sup> The strength of association was slightly less extreme in the 13 trials that based their recruitment on a history of stroke (RRR, 34%; 95% CI [21–44]) compared with the 25 trials that solely recruited participants with no history of vascular disease (RRR, 46%; 95% CI [35–55]).<sup>9,10</sup> There was also evidence of modification by age in this meta-analysis, with less extreme associations at older ages; the overall mean age on entry into these trials was 64 years, and it did not materially differ between the subsets of trials with and without a history of stroke.<sup>9</sup>

The mechanism of the effect of lowering usual BP on recurrent stroke is likely to be a reduction in hemorrhagic stroke attributable to hypertension-induced intracranial aneurysms and small penetrating artery disease, and a reduction in ischemic stroke attributable to hypertension-induced atrial fibrillation, atherosclerosis, and intracranial small penetrating artery disease. However, until last year, only one trial, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), had examined the effect of lowering usual BP on recurrent stroke according to the pathological and pathogenetic subtypes of stroke as a qualifying event or as an outcome event.<sup>11,12</sup>

The PROGRESS trial reported that random allocation to perindopril $\pm$ indapamide realized a reduction in BP by 9/4 mmHg (SE, 0.3/0.2 mmHg) and a corresponding reduction in recurrent stroke by 28% (95% CI [17–38]) compared with placebo during a mean of 3.9 years follow-up of 6105 patients with previously symptomatic cerebrovascular disease.<sup>11,12</sup> The relative risk of any stroke during follow-up was reduced by 26% (95% CI [12–38]) among patients whose qualifying cerebrovascular event was an ischemic stroke (mean age at entry 64 years) and

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by 49% (95% CI [18–68]) among those whose qualifying event was an intracerebral hemorrhage (mean age entry 61 years). There are no data reported in this study for patients whose qualifying cerebrovascular event was a lacunar ischemic stroke.

Prolonged exposure of a 9/4 mm Hg lower BP in PROGRESS was associated with a reduction in the outcomes events, ischemic stroke by 24% (95% CI [10–35]) and hemorrhagic stroke by 50% (26%–67%).<sup>11</sup> The study further classified ischemic stroke outcome events according to pathogenetic subtypes, although the small number of events for each subtype meant there was only weak evidence of variation in the strength of these associations: a 9/4 mm Hg lower BP was associated with a reduction in lacunar ischemic stroke by 23% (95% CI [–7 to 44]), large-artery ischemic stroke by 39% (95% CI [5–61]), cardioembolic ischemic stroke by 23% (95% CI [–38 to 57]), and unclassified ischemic stroke by 19% (95% CI [0–35]).<sup>11</sup>

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial reported that random allocation to telmisartan (80 mg daily) realized a reduction in BP by 3.8/2.0 mm Hg and a corresponding nonsignificant reduction in recurrent stroke by 5% (95% CI [–4 to 14];  $P=0.23$ ) compared with placebo during a mean of 2.5 years follow-up of 20 332 patients with recent (median 15 days) ischemic stroke. The qualifying ischemic stroke was a lacunar stroke caused by small artery occlusion in 52% of the patients; however, analysis of the effect of telmisartan versus placebo in the lacunar stroke subgroup has not been published.<sup>13</sup>

Consequently, there has been substantial uncertainty as to the effect of BP lowering after lacunar stroke. Furthermore, there has also been reason for caution in lowering BP in some patients with stroke, such as those with bilateral severe carotid or vertebrobasilar occlusive disease, in whom lowering of BP, <150 mmHg systolic, may increase the risk of recurrent stroke.<sup>14,15</sup> The mechanism of recurrent stroke in these patients is hemodynamic because of ultimate failure of compensatory dilatation (autoregulation) of the intracranial arteries to maintain constant cerebral perfusion as the systemic BP falls.<sup>16</sup> Hence, for each patient with stroke there is likely to be a sweet spot, or threshold lower BP, at which the benefits of lowering BP in preventing recurrent stroke are maximized before the risks of hemodynamic ischemic stroke increase. For the broader range of patients with stroke, the target lower BP is unknown.

In the PROGRESS trial, lowering BP with perindopril±indapamide produced similar proportional reductions in risk of stroke among each of 4 subgroups defined by baseline BP of <120, 120 to 139, 140 to 159, and ≥160 mmHg ( $P$  homogeneity=0.5).<sup>17</sup> The analyses of achieved follow-up BP showed that the lowest absolute risk of recurrence was among the one quarter of participants with the lowest follow-up BP levels (median of 112/72 mmHg), and that absolute risks rose progressively with higher follow-up BP levels. Minor adverse effects were progressively more common at lower BP levels ( $P$  homogeneity=0.04), but there was no excess of serious complications (all  $P$  homogeneity>0.2).<sup>17</sup>

Observational analysis of the PROGRESS trial cohort found no evidence of a J-curve relationship between follow-up BP levels and risk of recurrent stroke. This is consistent with the findings from large meta-analyses of prospective cohort studies, in participants without a history of vascular disease, which

have described strong, direct, log-linear associations between BP levels and stroke throughout middle and old age, with no evidence of a threshold down to ≥115/75 mmHg.<sup>18</sup>

In contrast, an observational analysis of the PROFESS trial cohort of patients with recent noncardioembolic ischemic stroke reported that there was a J-curve relationship between BP level and stroke risk. In this study, levels of systolic BP during follow-up in the low-normal (<120 mmHg), high (140–150 mmHg), or higher (≥150 mmHg) range were associated with an increased risk of recurrent stroke compared with low-normal (120–130 mmHg) and high-normal (130–140 mmHg).<sup>19</sup> The recurrent stroke rates were 8.0% (95% CI [6.8–9.2]) for the low-normal BP level group, 7.2% (95% CI [6.4–8.0]) for the low-normal BP group, 6.8% (95% CI [6.1–7.4]) for the high-normal BP group, 8.7% (95% CI [7.9–9.5]) for the high BP group, and 14.1% (95% CI [13.0–15.2]) for the high BP group.<sup>18</sup> Compared with patients in the high-normal BP group, the risk of recurrent was higher for patients in the low-normal BP group (adjusted hazard ratio [AHR], 1.29; 95% CI [1.07–1.56]), in the high BP group (AHR, 1.23; 95% CI [1.07–1.41]), and in the high BP group (AHR, 2.08; 95% CI [1.83–2.37]).<sup>19</sup> The findings of this study should be interpreted with caution, however, given that reserve causality may well explain the increased risk of stroke recurrence at lower BP levels.

For nonstroke patients with diabetes mellitus and elevated BP, a systematic review of 5 RCTs comparing lower BP targets (any target <130/85 mmHg) with standard BP targets (<140–160/90–100 mmHg) during a mean follow-up of 4.5 years in 7314 participants found no evidence to support BP targets lower than the standard targets, but recommended more randomized trials.<sup>20</sup> In one trial (Action to Control Cardiovascular Risk in Type 2 Diabetes [ACCORD]) that compared clinical outcomes associated with lower (<120 mmHg) or standard (<140 mmHg) systolic BP targets, the group assigned to lower systolic BP achieved a significantly lower BP (119.3/64.4 mmHg versus 133.5/70.5 mmHg,  $P<0.0001$ ) and lower incidence of stroke (relative risk [RR], 0.58; 95% CI [0.39–0.88]) but no reduction in mortality (RR, 1.05; CI [0.84–1.30]) and a significant increase in several other serious adverse events (RR, 2.58; 95% CI [1.70–3.91]).<sup>21</sup> In the 4 trials that compared clinical outcomes associated with different diastolic BP targets, the group assigned to lower diastolic BP achieved a significantly lower BP (128/76 mmHg versus 135/83 mmHg,  $P<0.0001$ ) but no reduction in stroke (RR, 0.67; 95% CI [0.42–1.05]), myocardial infarction (RR, 0.95; 95% CI [0.64–1.40]), or mortality (RR, 0.73; 95% CI [0.53–1.01]).<sup>20</sup>

Although it is acknowledged that larger reductions in systolic and diastolic BP are positively associated with a greater reduction in the risk of recurrent stroke and that a systolic BP level of <120 mmHg is normal, the optimal usual target BP is not known. Hence, guidelines state “an absolute target BP level and reduction are uncertain and should be individualized ... (Class IIa; Level of Evidence B).”<sup>22,23</sup>

### What Is the Evidence for an Optimal Usual BP Target After Lacunar Stroke? What Did the SPS3 Trial Show?

The only RCT to investigate the effect of different BP targets on the rate of recurrent stroke in patients with recent lacunar

stroke is the recently published Secondary Prevention of Small Subcortical Strokes (SPS3) trial.<sup>24</sup>

The SPS3 investigators randomly assigned 3020 patients with recent (2 weeks to 6 months previously) symptomatic lacunar ischemic stroke, confirmed by MRI of the brain, to a higher systolic BP target of 130 to 149 mmHg (n=1510) or to a lower systolic BP target of <130 mmHg (n=1501). Patients with acute ischemic stroke (ie, 0–2 weeks) were excluded because the safety and effectiveness of BP lowering in acute ischemic stroke has not been established.<sup>25</sup> The mean age of the patients at entry was 63 (SD 11) years. The treatment allocation was open label.

After a year, mean systolic BP was lowered to 138 mmHg (95% CI [137–139]) in the higher target group and to 127 mmHg (95% CI [126–128]) in the lower target group. This difference of 11 mmHg in mean systolic BP between the treatment groups was sustained throughout the study (mean of 3.7 years), and 95% of patients in each treatment group achieved their allocated target systolic BP, as measured by a standardized automated electronic device, at least once during follow-up.

Random allocation to a lower systolic BP target of <130 mmHg was associated with a nonstatistically significant reduction in recurrent stroke by 19% (95% CI [–3 to 36];  $P=0.08$ ).<sup>24</sup> This primary result was consistent among pre-specified subgroups, including baseline systolic BP. It was also consistent among the secondary outcomes of disabling or fatal stroke (hazard ratio [HR] 0.81, 95% CI [0.53–1.23]) and the composite of stroke, myocardial infarction, or vascular death (HR, 0.84; 95% CI [0.68–1.01]). The study found only weak evidence of difference in RRs between recurrent ischemic/unknown stroke (HR, 0.84; 95% CI [0.66–1.09];  $P=0.19$ ) and intracerebral hemorrhage (HR, 0.37; 95% CI [0.14–0.89];  $P=0.03$ ). There was no interaction between the BP target intervention and the other intervention (antiplatelet therapy) in the SPS3 trial.<sup>26</sup>

There was no evidence of difference between the treatment groups in overall mortality (1.80% versus 1.74% per year, in the lower and higher target groups, respectively; HR, 1.03, 0.79, 1.35;  $P=0.82$ ) or serious complications of hypotension, such as symptoms of presyncope, syncope, and hemodynamic stroke or myocardial infarction (0.40% versus 0.26% per year; HR, 1.53, 0.80, 2.93;  $P=0.20$ ).

### Are the Results of SPS3 Trial Valid Internally?

There are 3 main threats to the internal validity of the SPS3 study.

First, participants and investigators were aware of the treatment allocation. This could have introduced a bias in the awareness and notification by patients of symptoms of recurrent stroke, and in the ascertainment (eg, investigation) and reporting of recurrent stroke and major outcome events by investigators.

Second, 5% of participants in each treatment group failed to achieve their allocated BP target on any occasion during follow-up, which may have compromised the statistical power of the study to reliably assess the effect a lower target BP on recurrent stroke.

Third, 3% of participants were lost to follow-up, and another 3% ended follow-up early for other reasons. If the

relative rate of recurrent stroke between different BP target groups was different in this group of patients from that in the patients who were not lost to follow-up, the overall results of the trial could be different.

These relatively minor caveats may have been the difference between a nonstatistically significant and statistically significant reduction in the RR of recurrent stroke with a lower versus higher BP target, and 11 mmHg reduction in systolic BP in the lower BP target group. However, they are unlikely to account for the somewhat shallower association between mean BP and stroke in SPS3 (ie, RRR, 19% and 95% CI [–3 to 36] for a 11 mmHg lower systolic BP)<sup>24</sup> compared with the large meta-analysis of 13 trials, see above (RRR, 34% and 95% CI [21–44] for a 10 mmHg reduction in systolic BP).<sup>9</sup>

Several factors might explain this difference.

First, the difference in estimated stroke rate reduction in SPS3 compared with the meta-analysis may be because of random error; the 95% CIs for both estimates of recurrent stroke reduction are wide and overlap.<sup>9,24</sup>

Second, the SPS3 estimate could be confounded by a greater use in the lower target group than in the higher target group of  $\beta$ -blockers (31% versus 25%) and angiotensin-converting enzyme (ACE)-inhibitors or angiotensin-receptor blockers (ARBs; 80% versus 63%).<sup>24</sup> Because  $\beta$ -blockers, ACE-inhibitors, and ARBs all increase visit-to-visit variability in systolic BP, which is associated with an increased risk of stroke for any given mean BP, the greater use of  $\beta$  blockers, ACE-inhibitors, and ARBs in the lower-target group (31%) than in the higher target group (25%) may have increased the rate of stroke for any given BP in the lower target group, and thereby reduced the margin of benefit with a lower usual BP.<sup>27,28</sup> However, there was also greater use in the lower target group than the higher target group of calcium-channel blockers (43% versus 20%) and thiazide diuretics (58% versus 43%), which reduce variability in systolic BP. Furthermore, the meta-analysis of all RCTs that compared the effects of BP-lowering drugs on stroke outcomes reported that the 5 main classes of BP-lowering drugs (thiazides,  $\beta$ -blockers, ACE-inhibitors, ARBs, and calcium-channel blockers) were similarly effective (within a few percentage points) in preventing strokes, with the exception that calcium-channel blockers had a greater preventive effect on stroke when compared directly with any other class of BP-lowering drug (RR, 0.91; 95% CI [0.84–0.98]).<sup>9</sup>

Third, the strength of the association between systolic BP and stroke risk might be weaker (ie, shallower) with lower systolic BPs, <130 mmHg, as observed in the SPS3 trial,<sup>24</sup> than with higher systolic BPs, >130 mmHg, such as the mean of 138 mmHg achieved in the PROGRESS trial.<sup>11,12</sup> If so, this could explain the smaller reduction in recurrent stroke observed in SPS3, for a reduction in mean systolic BP of 11 mmHg, than observed in other BP-lowering trials. However, a J-shaped association curve with shallowing/flattening of the association between BP and stroke risk at systolic BPs <130 mmHg is not supported by the observation analysis of the PROGRESS trial, or findings from large meta-analyses of prospective cohort studies.<sup>18</sup>

Fourth, lowering BP could be less effective in preventing recurrent stroke among patients with lacunar ischemic stroke than for patients with some of the other subtypes of ischemic

stroke. Unfortunately, there are no trials of BP lowering among patients with a history of stroke for whom the different subtypes of ischemic stroke have been classified at entry, to allow a direct comparison.

The failure to reach conventional significance at the  $P=0.05$  level is probably because the trial was underpowered to reliably identify or exclude the RRR of 19% at the  $P=0.05$  level.<sup>29</sup> The observed rate of recurrent stroke was only half of what was anticipated ( $\approx 11\%$  during 3.7 years versus 21% during 3.0 years), probably because of expert secondary prevention throughout the trial but perhaps also because the original estimate may have been an overestimate because of the lack of reliable data on the long-term risk of recurrent lacunar stroke. The observed annual rate of serious complications of hypotension, however, was also low (0.40% and 0.26% in the lower target and higher target groups, respectively). Although these safety results are consistent with other observational studies,<sup>30</sup> the SPS3 trial was underpowered to identify or exclude confidently a modest, but nevertheless clinically important, increase in serious complications of hypotension with systolic BP <130 mmHg, particularly in patients at risk such as the elderly and with bilateral carotid occlusive disease.

### Are the Results of SPS3 Trial Valid Externally (Generalizable)?

The SPS3 trial results are most generalizable to the type of patients enrolled, that is,  $\approx 60$ -year-old patients, with recent symptomatic small deep ischemic strokes, residing in North America, Latin America, and Spain. The results are also likely to be generalizable more broadly to patients of similar or older age, with lacunar stroke, residing in other parts of the world. However, caution is required with intensive BP lowering, particularly in patients with bilateral, severe, occlusive cerebrovascular, or coronary artery disease; elderly patients with stiff, poorly compliant arteries; and patients with acute ischemic stroke.

### Conclusions

For patients with lacunar stroke, clinicians know that the risk of recurrent stroke can be reduced by lowering the patient's usual BP. However, clinicians do not know how far to lower the BP. In routine clinical practice, they have traditionally aimed for a systolic BP target between 130 and 149 mmHg. However, the SPS3 trial recently reported that random allocation to a systolic BP target of <130 mmHg, and achieving a mean systolic BP of 127 mmHg (95% CI [126–128]) after a year, was associated with a nonstatistically significant reduction in recurrent stroke by 19% (95% CI [–3 to 36];  $P=0.08$ ) compared with the more traditional strategy of targeting 130 to 149 mmHg systolic and achieving a mean systolic BP of 138 mmHg (95% CI [137–139]) after a year. We think that, when the SPS3 results are interpreted in context of all other randomized trials of BP lowering after stroke, the totality of evidence suggests that targeting a systolic BP of <130 mmHg is likely to be safe and more effective than a systolic BP of 130 to 149 mmHg in patients with recent (but not acute) lacunar ischemic stroke. More RCTs are needed to examine the external validity of the SPS3 trial results in other patient populations with previous stroke.

While awaiting the outcome of future randomized trials of lower usual BPs in patients with previous stroke, clinicians should endeavor to achieve and maintain usual systolic BP <130 mmHg in patients who have survived  $\geq 2$  weeks after subcortical lacunar ischemic stroke. Systolic BP should be lowered gradually and cautiously, in view of the potential for serious complications related to hypotension, particularly in at-risk individuals, such as the elderly and those with bilateral carotid occlusive disease.

### Disclosures

None.

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

Ernesto L. Schiffrin

The preceding scholarly discussion by Hankey and Lacey<sup>1</sup> proposes a target systolic blood pressure <130 mmHg for individuals who have had a lacunar stroke to prevent recurrent stroke on the basis of a trial (Secondary Prevention of Small Subcortical Strokes [SPS3]) that showed that achieving a mean systolic blood pressure of 127 mmHg (95% confidence interval, 126–128) after 1 year was associated with a nonstatistically significant reduction in recurrent stroke. The argument of these authors is based on the totality of the evidence, including that from nonlacunar stroke trials that showed significant prevention of recurrent stroke with lower blood pressures. However, Hankey and Lacey<sup>1</sup> recognize the difference in treatment between both groups in SPS3, the loss to follow-up, and provide a lengthy explanation of why the trial did not achieve statistical significance, because it may have been underpowered to demonstrate either benefit or harm. They discuss the pathophysiology of lacunar stroke resulting from small vessel disease in the deep white matter, internal capsule, thalamus, or ventral pons, in the territory of supply of an intracerebral small penetrating/penforating artery, which is different from the pathophysiology of the different forms of nonlacunar stroke. How can they then extrapolate from one to the other and recommend a guideline based on a nonsignificant result with such weak evidence?

Guidelines according to the Institute of Medicine are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances, and evidence-based medicine is the integration of best researched evidence and clinical expertise with patient values.<sup>2</sup> The objective is to enhance the quality of clinical care leading to better patient outcomes with cost-effective approaches. SPS3, despite the extraordinary effort of the authors of the study, the rigor and care with which it was performed, and the argument of its defenders, does not meet these criteria and can therefore not be included as the basis for a recommendation except with extreme caution and many caveats, and a plea for more trials to be able to make a more definitive recommendation. Specifically, the Canadian Hypertension Education Program (CHEP) Recommendations for 2014,<sup>3</sup> which like all previous CHEP recommendations are rigorously evidence based, chose to ignore SPS3 because of the weaknesses mentioned. To push for lower blood pressures and therefore more medication and greater cost to patients, their families, and the healthcare system, exposing patients to potential harm, without significant incontrovertible evidence that they will benefit, does not seem either cost-effective or appropriate. *Primum non nocere*. For more on this, see my argument of the Con position.

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## Optimum Blood Pressure Target After Lacunar Stroke: Pro Side of the Argument Graeme J. Hankey and Ben Lacey

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