SPS3: Lower systolic blood pressure <130mmHg vs Higher systolic blood pressure 130-149mmHg target in patients with recent symptomatic, MRI-identified lacunar stroke

Secondary Prevention of Small Subcortical Strokes

**BOTTOM LINE**

In SPS3 (systolic blood pressure intervention), for patients with recent (median 62 days) symptomatic, MRI-identified lacunar stroke:

- Lowering systolic blood pressure (SBP) to <130 mmHg, compared to 130-149 mmHg, over 3.7 years, did NOT reduce recurrent stroke.
- SBP <130 mmHg may ↓ intracerebral hemorrhage in a small number of patients (NNT 154 x 3.7 years) without significantly ↑ SAE related to hypotension or blood pressure management
- At this time, the Canadian Stroke Best Practices Recommendations 2014 do not recommend BP <130 mmHg. They recommend a target of <140/90 mmHg for patients who have had a stroke or TIA (Evidence Level B).

**BACKGROUND**

- Hypertension is an important risk factor for stroke, especially small vessel disease (SVD). Treatment with antihypertensive medications can prevent stroke and its recurrence. However, lowering SBP too much may compromise autoregulation and the ability to maintain cerebral perfusion. Thus the optimal blood pressure target is unknown.
- Lacunar strokes (small subcortical strokes) account for approximately 25% of ischemic strokes, and usually result from small penetrating artery disease.
- Since an RCT for secondary prevention after MRI-identified lacunar stroke has not been conducted, SPS3 was designed to determine if SBP <130 mmHg was more effective & safer than SBP 130-149 mmHg as secondary prevention in reducing the incidence of recurrent stroke.

**TRIAL BACKGROUND**

**DESIGN:** randomized, stratified by centre and baseline hypertensive status, open label (SBP intervention), multicenter (n=81), intention-to-treat, 2x2 factorial (antiplatelet intervention and targeted systolic blood pressure intervention).

**Funding:** National Institute of Neurological Disorders and Stroke (NINDS).

**INTERVENTION:** “lower” SBP <130 mmHg versus “higher” SBP 130-149 mmHg

- BP assessed at least monthly, until in target range for ≥ 2 consecutive visits then BP assessed q3months. If at any time SBP was outside target, patients were to return for assessment within 1 month.
- Antihypertensive medications were prescribed by the local study physician and supplied via study formularies

**INCLUSION:** ≥ 20 years old, normotensive or hypertensive, symptomatic lacunar stroke confirmed by MRI pre-specified criteria

**EXCLUSION:** surgically amenable ipsilateral carotid artery disease, major risk factors for cardioembolic sources of stroke, modified Rankin score ≥4 (disabling stroke), previous intracranial hemorrhage from non-traumatic causes, cortical ischemic stroke

**POPULATION** at baseline: n=3020, median time to randomization 62 days, qualifying event: TIA 1%, ischemic stroke 99%; North America 65%, n=1960, Latin America 23%, n=694, Spain 12%, n=366

- Non-modifiable risk factors for stroke or TIA: 63%, mean age ~63 years old, previous stroke or TIA 15%, black ethnicity 16%
- Modifiable risk factors for stroke or TIA: hypertension 75%, mean SBP ~143 mmHg, hyperlipidemia 49%, diabetes 37%, current smoker 20%
- There were no substantial differences between the two treatment groups at baseline
- Use of statin during follow-up ~83%
- Permanent discontinuation of blood pressure therapy (high SBP target 17%, low SBP target 16%, NS)

**RESULTS** follow-up: mean 3.7 years

**TABLE 1: EFFICACY** (efficacy outcomes confirmed by central adjudication committee unaware of treatment assignments)

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>130-149 MMHG n=1519</th>
<th>&lt;130 MMHG n=1501</th>
<th>HR 95% CI</th>
<th>ARR/ARI</th>
<th>NNT/NNH x3.7 YRS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT</td>
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<tr>
<td>Stroke recurrence (ischemic, intracranial hemorrhage)*</td>
<td>10% (n=152) (2.77%/pt-year)</td>
<td>8.3% (n=125) (2.25%/pt-year)</td>
<td>0.81 (0.64-1.03)</td>
<td>1.7%</td>
<td>NS</td>
<td>Kaplan-Meier for primary endpoint. This NS result is consistent across various subgroups (age, gender, diabetes, race, baseline SBP)</td>
</tr>
<tr>
<td>Ischemic stroke or unknown</td>
<td>8.6% (n=131) (2.4%/pt-year)</td>
<td>7.5% (n=112) (2%/pt-year)</td>
<td>0.84 (0.66-1.09)</td>
<td>1.1%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1.4% (n=21) (0.38%/pt-year)</td>
<td>0.9% (n=13) (0.23%/pt-year)</td>
<td>0.61 (0.31-1.22)</td>
<td>0.5%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1.1% (n=16) (0.29%/pt-year)</td>
<td>0.4% (n=6) (0.11%/pt-year)</td>
<td>0.37 (0.15-0.95)</td>
<td>0.7%</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td>12.4% (n=188) (3.46%/pt-year)</td>
<td>10.7% (n=160) (2.91%/pt-year)</td>
<td>0.84 (0.68-1.04)</td>
<td>1.7%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death (vascular, nonvascular, unknown)</td>
<td>6.6% (n=101) (1.74%/pt-year)</td>
<td>7.1% (n=106) (1.80%/pt-year)</td>
<td>1.03 (0.79-1.35)</td>
<td>0.4%</td>
<td>NS</td>
<td>Causes of death NS between groups.</td>
</tr>
</tbody>
</table>

*ischemic stroke = focal neurological deficit of sudden onset >24hr and no hemorrhage on neuroimaging, intracranial hemorrhage = intracerebral, subdural, epidural, subarachnoid on neuroimaging
## STRENGTHS, LIMITATIONS, & UNCERTAINTIES

### STRENGTHS:
- This was a well-defined, homogeneous group of patients (lacunar stroke)
- Sample size of 3000 was achieved
- Even though there was open label BP management, there was an event adjudication committee, blinded to treatment allocation, to confirm efficacy outcomes (the publication did not mention whether safety endpoints were adjudicated through this committee)
- This study mimicked real world practice, and allowed clinicians to use any antihypertensive[s] to treat to SBP target
- Although 4.8% did not achieve SBP target, this is similar to other studies

### LIMITATIONS:
- The period of time after a stroke is important, as the estimated risk of recurrent stroke is 11.5% at 7 days, 15% at one month, and 18.5% at 3 months after a minor stroke.\(^3\) In SPS3, the earliest time antihypertensive therapy was initiated was 2 weeks, with a median time to randomization of 62 days. This delay resulted in the enrollment of patients at lower risk of recurrent stroke, who are less likely to benefit.
- There was a high rate of discontinuation of antihypertensives (high SBP 17%, low SBP 16%). It is unknown whether this was due to efficacy, safety or other reasons.
- Lost to follow up, ended follow up early (withdraw consent, centre closed, MD request, other) 18%
- Although at 1 year, mean SBP were within target (higher target group 138 mmHg (CI 137-139), lower target group 127 mmHg (CI 126-128)), 75% in the higher target group versus 65% in the lower target group had BP within the assigned target ranges.
- Patients in the lower target group used more medications at 1 year and at last visit (1.8 for higher target group, 2.4 for lower target group).

### UNCERTAINTIES:
- The rate of recurrent stroke in the comparator arm, higher SBP 130-149 mmHg, was low (2.77%/pt-year) thereby minimizing the difference between the two arms. The authors and others suggest whether this was due to good secondary prevention: usage of statins (~85%), adherence to antiplatelet therapy (94%)\(^6\), and good BP control (<5% did not achieve BP within target at any point) contributed to this.\(^7\)
- The types of antihypertensives used were different between groups and may confound the results. Some may increase variability in SBP (beta-blocker) while others less variability in SBP (calcium-channel blockers and diuretics).\(^7\) Additionally, thiazides may be beneficial in stroke prevention.\(^4\)
- It's unknown whether the association of SBP and stroke risk is weaker with SBP <130 mmHg than with higher SBP.\(^7\)
- The subgroup analysis did not include all risk factors for stroke (missing previous stroke or TIA, hypertension, smoking, hyperlipidemia), so it is unknown what the hazard ratio for recurrent stroke is in these subgroups.
- This was stated in the SPS3 antipatelet intervention, but not the blood pressure intervention publication: For stroke recurrence, no significant interaction between the antiplatelet and blood pressure lowering intervention was found.
- There were minor discrepancies between the patient baseline characteristic numbers & the two SPS3 publications (i.e. antiplatelet and SBP results) (e.g. ischemic stroke as qualifying event 97% vs 99%). With a 2x2 factorial design, it is uncertain why there were differences, but the small differences likely did not impact results.

## RxFiles RELATED LINKS


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References


