SPS3: Lower systolic blood pressure <130mmHg vs Higher systolic blood pressure 130-149mmHg target in patients with recent symptomatic, MRI-identified lacunar stroke[1]

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).[2]

BACKGROUND

- Hypertension is an important risk factor for stroke, especially small vessel disease (SVD). Treatment with antihypertensive medications can prevent stroke and its recurrence.[3] 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" SPB 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: ≥30 years old, normotensive or hypertensive, symptomatic lacunar stroke confirmed by MRI pre-specified criteria ≥2 weeks to ≤180 days

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%,[4] 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)

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

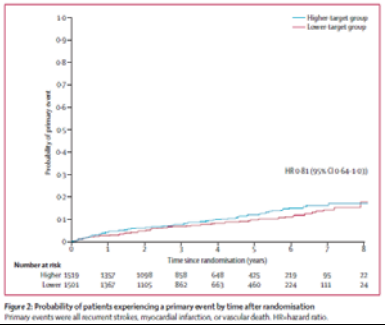

Figure 2: Probability of patients experiencing a primary event by time after randomisation
Primary events were all recurrent strokes, myocardial infarction, or vascular death. HR=hazard ratio.

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

TABLE 2: SAFETY & NONCLINICAL ENDPOINTS			
CLINICAL ENDPOINTS	130-149 MMHG n=1519	<130 MMHG n=1501	COMMENTS
SAFETY			
Serious adverse events related to hypotension	~1%, NS between groups.		
Side-effects potentially related to BP management	Unsteadiness ~25%, dizziness ~22%, others, were NS between groups.		
NONCLINICAL ENDPOINTS			
SBP (mean) @ 1 year	138 mmHg (CI 137-139)	127mmHg (CI 126-128)	11 mmHg difference between treatment arms
BP within assigned range @ 1year	75% {n=1139}	65% {n=976}	
Did not achieve BP targets within range at any time	4.6% {n=70}	4.9% {n=74}	
# antihypertensive meds at study entry (mean)	1.7 (SD 1.2)	1.7 (SD 1.2)	
# antihypertensive meds at 1 year (mean)	1.8 (SD 1.4)	2.4 (SD 1.3)	Differences were significant
Antihypertensive meds at last visit			
Thiazides	38% {n=569}	54% {n=804}	Differences were significant
ACEI/ARB	60% {n=894}	78% {n=1156}	
Calcium-channel blocker	39% {n=438}	43% {n=637}	
BB	28% {n=424}	35% {n=521}	

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 adjudicate 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.[5] 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 (withdrew 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).

UNCERTAINITIES:

- 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 antihypertensive 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. [8]
- 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 antiplatelet 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

- RxFiles DAPT & Triple Therapy newsletter & chart: http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT%20and%20Triple%20Therapy%20Newsletter%20and%20Chart.pdf
- Canadian Family Physician Journal – RxFiles article on DAPT post stroke: http://www.cfp.ca/content/62/8/640.full.pdf+html?sid=aa5c799f-c58e-4ca9-ad79-f96a3abe4367
- **SPS3** Antiplatelet Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/SPS3%20antiplatelet-Trial%20Summary.pdf
- **MATCH** Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/MATCH-Trial%20Summary.pdf
- **CHANCE** Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/CHANCE-Trial%20Summary.pdf

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♂=male **BP**=blood pressure **CI**=confidence interval **mos**=months **SAE**=serious adverse events **SBP**=systolic blood pressure **pt-years**=patient years

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References

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