SPS3: Clopidogrel + ASA ASPIRIN versus ASA ASPIRIN in Patients with recent symptomatic, MRI-identified lacunar stroke[1]

Secondary Prevention of Small Subcortical Strokes

BOTTOM LINE

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

- Dual antiplatelet therapy with clopidogrel + ASA, compared to ASA alone, over 3.4 years, did NOT reduce recurrent stroke but increased all-cause mortality (NNH=44) and major extracranial hemorrhage (NNH=32).
- Clopidogrel and aspirin should not be combined long-term for secondary prevention after lacunar stroke (unless there is another indication). This is consistent with the Canadian Stroke Best Practices Recommendations 2014, and American guidelines which recommend monotherapy (ASA or clopidogrel) or dipyridamole + ASA.[2 (CSBPR'14 [A]),3 (AHA/ASA'14 IA/IB),4]

BACKGROUND

- Lacunar strokes (small subcortical strokes) account for approximately 25% of ischemic strokes, and usually result from small penetrating artery disease.
- ASA is the recommended antiplatelet therapy for lacunar strokes. In *cardiac* conditions (atrial fibrillation, acute coronary syndrome) adding clopidogrel to ASA reduces stroke recurrence, but dual antiplatelet therapy (DAPT) increases bleeding.[5,6]
- Since an RCT for secondary prevention after MRI-identified lacunar stroke has not been conducted, **SPS3** was designed to determine if DAPT for secondary prevention reduced incidence of recurrent stroke.

TRIAL BACKGROUND

DESIGN: randomized stratified by centre and baseline hypertensive status, double blind (antiplatelet intervention), multicenter n=82, intention-to-treat, 2x2 factorial (antiplatelet intervention and targeted systolic blood pressure intervention). Enrollment: 2003 to Aug 2011. Funding: National Institute of Neurological Disorders and Stroke (NINDS). Sanofi-Aventis & Bristol-Myers-Squibb donated clopidogrel and matching placebo but had no involvement in design, execution, analysis or reporting of data.

INTERVENTION: clopidogrel 75mg daily + ASA EC 325mg daily vs. ASA EC 325mg daily

INCLUSION: ≥30 years old, 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, recent or remote cortical infarct, large subcortical infarct >1.5cm, history of intracerebral hemorrhage other than microbleeding, modified Rankin score ≥4 (disabling stroke), previous intracranial hemorrhage from non-traumatic causes, cortical ischemic stroke

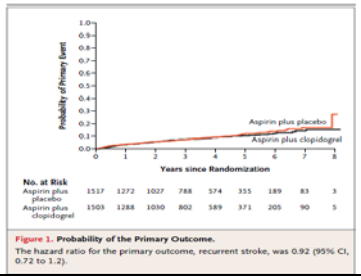
POPULATION at baseline: n=3020, median time to randomization 62 days, qualifying event: TIA 3%, ischemic stroke 97%; North America 65%, n=1960, Latin America 23%, n=694, Spain 12%, n=366

- Non-modifiable risk factors for stroke or TIA: 63% ♂, mean age 63 (SD ±11) years old, previous stroke or TIA 15%, black ethnicity 17%, coronary artery disease 10%
- Modifiable risk factors for stroke or TIA: hypertension 75%, mean SBP 143±19 mmHg, hyperlipidemia ~49%,[7] diabetes 37%, current smoker 20%
- There were no significant differences between the two treatment groups at baseline
- Use of ASA at time of qualifying event 28%, use of statin at any follow-up visit 84%; proton pump inhibitor use was not reported

RESULTS

follow-up: mean 3.4 years

TABLE 1: EFFICACY (confirmed by central adjudication committee unaware of treatment assignments and classified ischemic strokes on basis of available diagnostic studies)

CLINICAL ENDPOINTS	ASA 325MG + PLACEBO DAILY n=1503	CLOPIDOGREL 75MG + ASA 325MG DAILY n=1517	HR 95% CI	ARR/ARI	NNT/NNH /x3.4 YRS	COMMENTS
PRIMARY ENDPOINT						
Stroke recurrence (ischemic stroke, intracranial hemorrhage)* assessed 3 to 6 months after initial stroke	9.2% {n=138} (2.7%/year)	8.2% {n=125} (2.5%/year)	0.92 (0.72-1.16)	0.9%	NS	Kaplan-Meier for primary endpoint. This NS result is consistent across various subgroups (age, gender, diabetes, race, ASA at index stroke).  Figure 1. Probability of the Primary Outcome. The hazard ratio for the primary outcome, recurrent stroke, was 0.92 (95% CI, 0.72 to 1.2).
SECONARY ENDPOINTS						
Stroke type						
Ischemic stroke	8.3% {n=124} (2.4%/year)	6.6% {n=100} (2%/year)	0.82 (0.63-1.09)	1.7%	NS	
Intracranial stroke	0.86% {n=13} (0.25%/year)	1.4% {n=21} (0.42%/year)	1.65 (0.83-3.31)	0.5%	NS	
Unknown	0.07% {n=1} (0.02%/year)	0.26% {n=4} (0.08%/year)	3.97 (0.44-35.47)	0.2%	NS	
All-cause mortality	5.1% {n=77} (1.4%/year)	7.4% {n=113} (2.1%/year)	1.52 (1.14-2.04)	2.3%	NNH 44	Authors surprised by this outcome; causes of deaths NS between groups.
Major vascular event (stroke, MI, vascular death)	11.6% {n=174} (3.4%/year)	10.1% {n=153} (3.1%/year)	0.89 (0.72-1.11)	1.5%	NS	Other efficacy outcomes were NS (disabling or fatal stroke, TIA without stroke, MI, other thromboembolic events)

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

RESULTS continued

follow-up: mean 3.4 years

TABLE 2: SAFETY (confirmed by central adjudication committee unaware of treatment assignments and classified ischemic strokes on basis of available diagnostic studies)

CLINICAL ENDPOINTS	ASA 325MG + PLACEBO DAILY n=1503	CLOPIDOGREL 75MG + ASA 325MG DAILY n=1517	HR 95% CI	ARR/ARI	NNT/NNH /x3.4 YRS
SAFETY					
Major hemorrhage (no definition provided)	3.7% {n=56} (1.1%/year)	6.9% {n=105} (2.1%/year)	1.97 (1.41-2.77)	3.2%	NNH 32
Intracranial hemorrhage	1.0% {n=15} (0.28%/yr)	1.5% {n=22} (0.42%/yr)	1.52 (0.79-2.93)	0.5%	NS
Major extracranial hemorrhage*	2.8% {n=42} (0.79%/year)	5.7% {n=87} (1.7%/year)	2.15 (1.49-3.11)	2.9%	NNH 35
Gastrointestinal hemorrhage (determined by local investigator)	1.9% {n=28} (0.52%/year)	3.8% {n=28} (1.1%/year)	2.14 (1.36-3.36)	1.9%	NNH 53

*serious or life-threatening bleed requiring transfusion of RBC or surgery or resulting in permanent functional sequelae or death

- The SPS3 antiplatelet intervention was terminated early after the 2nd planned interim analysis due to increase harm and minimal benefits.
- For stroke recurrence, no significant interaction between the antiplatelet and blood pressure lowering intervention was found.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- This was a well-defined, homogeneous group of patients (lacunar stroke)
- Sample size of 3000 was achieved
- There was an event adjudication committee, blinded to treatment allocation, to confirm efficacy and safety outcomes
- Interim analyses were preplanned
- Average rate of adherence to assigned antiplatelet 94%
- For stroke recurrence, no significant interaction between the antiplatelet and blood pressure lowering intervention was found

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.[8] In SPS3, the earliest time antiplatelet therapy was initiated was 2weeks, 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.
- The SPS3 antiplatelet intervention was terminated early due to increase harm and minimal benefits.
- There was a high rate of discontinuation of antiplatelet therapy between the two groups (clopidogrel + ASA 30%, ASA 27%, p=0.02)
- lost to follow up, withdrew consent, centre closed 13.3%[9]

UNCERTAINITIES:

- The rate of recurrent stroke in the comparator arm, ASA alone, was low (2.7%) thereby minimizing the difference between the two arms. The authors suggest whether high usage of statins (84%) or good blood pressure control contributed to this.
- Was the dose of ASA EC325mg too high for combination therapy? It is 25mg when used with dipyridamole as part of **AGGRENOX**, thus minimizing benefit and increasing bleeding.
- 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.
- Would earlier treatment with antiplatelets, for a shorter duration be beneficial in lacunar strokes?
- We await the results of an ongoing study called the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (**POINT**) trial, which may provide guidance on earlier administration of dual antiplatelet therapy.
- 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** Systolic Blood Pressure Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/SPS3%20SBP-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 **ASA** **EC**=enteric coated acetylsalicylic acid **DAPT**=dual antiplatelet therapy **MI**=myocardial infarction **MRI**=magnetic resonance imaging **mRS**= modified Rankin score (scale 0-6) **NNH**=number need to harm **NS**=not significant **RCT**=randomized controlled trial **SBP**=systolic blood pressure **SD**=standard deviation

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