The SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012;367:817.

Trial's clinical question: In patients with recent lacunar stroke, does adding clopidogrel to aspirin reduce stroke recurrence?

Context:

- Lacunar strokes make up about 25% of ischemic strokes and typically stem from intrinsic disease of cerebral arterioles
- Compared to other ischemic stroke subtypes, lacunar strokes are associated with milder maximal neurological deficits and lower post-stroke Rankin scores[1]
- Current practice for secondary prevention of lacunar stroke includes antiplatelet therapy and the treatment of hypertension[2]

Methodology

Study design	RCT
Sequence generation	Appropriate (permuted-block design, variable block size) • Stratified by clinical centre and baseline hypertensive status
Allocation concealment	Adequate (web-based randomization)
Blinding	• Patients, practitioners and adjudicators blinded • Matching placebo to clopidogrel pills
Loss to follow-up	13%
Population analyzed	Intention-to-treat
Intervention	• Intervention: ASA EC 325 mg PO daily + clopidogrel 75 mg PO daily • Control: ASA EC 325 mg PO daily + placebo PO daily
Outcomes	• Death – vascular, non-vascular, unknown cause • Stroke recurrence – ischemic or hemorrhagic (primary outcome) • Major extracranial hemorrhage • MI
Duration	Mean follow-up of 3.4 years (range of 0-8.2 years)
Additional Details	• Stopped early: for futility in terms of the primary outcome and evidence of harm. Two planned interim analyses were performed by an independent Data and Safety Monitoring Committee (DSMC), and the study was stopped after the second interim analysis, 10 months before the planned end date. • Subgroup analyses: ethnic group, use of aspirin at time of qualifying event, diabetes status (prespecified); age, sex and region (not pre-specified)
Funding	• National Institute of Neurological Disorders and Stroke: grant • Sanofi-Aventis and Bristol-Meyers Squibb provided clopidogrel and matching placebo

Participants

Setting	82 clinical centres (North America, Latin America, Spain)
Inclusion criteria	• ≥ 30 years • Symptomatic lacunar stroke or transient lacunar ischemic attack 14-180 days before randomization • Stroke confirmed by MRI, TIA confirmed by diffusion-weighted MRI
Relevant exclusion criteria	• Disabling stroke (modified Rankin score ≥ 4) • Major risk factors for cardioembolic sources of stroke • Ipsilateral carotid artery disease appropriate for surgery • Subcortical infarction > 1.5 cm in diameter • MRI-confirmed recent or remote cortical infarction • Cortical ischemic stroke • History of intracerebral hemorrhage other than microbleeding or intracranial hemorrhage other than traumatic hemorrhage
Study size	• Unknown how many patient assessed for eligibility • 3020randomized

"Average" patient	• Male 63%
	• Patient populations:
	  ○ North American 65%
	  ○ Latin American 23%
	  ○ Spanish 12%
	• Mean age 63 years
	• Comorbidities:
	  ○ Hypertension 75%
	  ○ Diabetes 37%
	  ○ Previous stroke/TIA 15%
	  ○ Current smoker 20%
	  ○ IHD 10.5%
	• Ethnicity:
	  ○ White 52%
	  ○ Hispanic 31%
	  ○ Black 17%
	• Mean age 63 years
	• Qualifying event:
	  ○ Ischemic stroke 97%
	  ○ TIA 3%
	• Use of aspirin at time of qualifying event 28%
	• Use of statin at any follow-up visit 84.5%

No clinically relevant baseline between-group differences.

Results				
Outcomes	ASA + Placebo %/year	ASA + Clopidogrel %/year	Hazard Ratio	Absolute risk reduction (NNT)
All deaths	1.4%	2.1%	1.52 (1.14-2.04)	ARI: 2.3% (NNH = 43)
Vascular	0.35%	0.51%	1.46 (0.81-2.64)	
Stroke	2.7%	2.5%	0.92 (0.72-1.16)	
Ischemic stroke	2.4%	2.0%	0.82 (0.63-1.09)	
Intracranial hemorrhage	0.25%	0.42%	1.65% (0.83-3.31)	
Major hemorrhage	1.1%	2.1%	1.97 (1.41-2.71)	ARI: 3.2% (NNH = 31)
Extracranial hemorrhage	0.79%	1.7%	2.15 (1.49-3.11)	ARI: 2.9% (NNH = 34)

Major Limitations:

Results

- **Increased mortality with dual antiplatelet treatment**
  - Risk of death in dual antiplatelet group was 2.1%/year versus 1.4%/year in the ASA-only group.
  - Fatal hemorrhages (intracranial and extracranial) accounted for some but not all of the increased death rate

Generalizability

- **Delay between initial lacunar stroke and start of clopidogrel**
  - Antiplatelet treatment was not started until, at minimum, 14 days after stroke or TIA.There is an 8-12% risk of stroke recurrence within the first 7 days after initial event.[7] In a 90-day observational study of TIA recurrences, over half of recurrent TIAs happened within the first 2 days of initial event.[8]

- **ASA dosing**
  - ASA 325 mg po daily was used in both groups
    In secondary prevention of vascular events, doses of ASA greater than 75 mg daily do not appear to render any additional benefit, but do increase risk of bleeding

Conclusions & Application:

- Long-term dual antiplatelet therapy with ASA+clopidogrel started 14-180 days after a lacunar stroke or TIA carries a clinically-important increased risk of bleeding and death, with no apparent reduction in stroke recurrence in patients who:
  - Are receiving vigorous management of blood pressure
  - Are most likely receiving statin therapy
  - Had a specific subtype of ischemic stroke stemming from intrinsic disease of small vessels of the brain (not large-vessel or atherosclerotic in origin)
- These findings are not applicable in the decision for antiplatelet treatment for a patient immediately following a lacunar stroke, nor for short-term courses of dual antiplatelets (such as the one discussed in CHANCE)

References:
1. Petty GW, et al. Stroke 2000;31:1062.
2. Lacunar Stroke. In *DynaMed* [database online]. EBSCO Information Services. http://web.ebscohost.com.ezproxy.library.dal.ca/dynamed/detail?vid=5&sid=1a16f00a-8753-4729-9466-f1a328106806%115834. Updated August 19, 2013. Accessed August 21, 2013.
3. Lovett JK, et al. Neurology. 2004;62:569.
4. Aminoff MJ, Kerchner GA. Chapter 24. Nervous System Disorders. In: Papadakis MA, McPhee SJ, Rabow MW, eds. *CURRENT Medical Diagnosis & Treatment 2014*. New York: McGraw-Hill; 2013. http://www.accessmedicine.com/content.aspx?aID=12507. Accessed August 18, 2013.5.Palacio S, et al. Stroke. 2012;43:2157.
6. Diener HC, et al. Lancet 2004;364:331.
7. Coull AJ, et al. BMJ 2004;328:326.
8. Johnston SC, et al. JAMA 2000;284:2901.
9. Antithrombotic Trialists' Collaboration. BMJ 2002;324:141.