Wang Y, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11-19.

Trial's clinical question: In patients with acute minor ischemic stroke or high-risk TIA, does combination antiplatelet treatment with clopidogrel and aspirin versus aspirin alone reduce the risk of recurrent stroke?

Context:

- The risk of early recurrent stroke in patients with TIA or minor stroke is very high (10-20% within 3 months), most occurring within the first 2 days
- Previous RCTs of ASA alone started within 48 hrs of acute ischemic stroke demonstrated a 0.7% reduction in the rate of stroke recurrence within the first 4 weeks[1]
- Pharmacologically, ASA and clopidogrel act synergistically to inhibit platelet aggregation, which has been shown to reduce cardiovascular events in patients ACS or coronary stent placement
- Previous RCTs (MATCH, SPS3) demonstrated no reduction in recurrent ischemic events when dual antiplatelet therapy was started non-acutely post-stroke versus a single antiplatelet, but did show increased bleeding rates[3,4]
- Only a handful of small trials assess dual antiplatelet therapy started acutely after ischemic stroke, but their findings suggest short-course dual therapy may have a role[5,6,7]

Methodology

Study design	RCT

Sequence generation	Appropriate (automated system to randomly assign #s)
	• Stratified according to
	  ○ Clinical centre
	  ○ Time between symptom onset and enrolment (<12 hrs vs 12-24 hrs)

Allocation concealment	Adequate (automated telephone system)
Blinding	• Patients, clinicians, adjudicators blinded • Double-dummy design
Loss to follow-up	0.7%
Population analyzed	Intention-to-treat (based on all patients who underwent randomization)
Intervention	• Clopidogrel-ASA Group: ○ Day 1: ASA 75-300 mg PO + clopidogrel 300 mg PO ○ Days 2-21: ASA 75 mg PO + clopidogrel 75 mg PO ○ Days 22-90: Placebo ASA PO + clopidogrel 75 mg PO • ASA Group: ○ Day 1: ASA 75-300 mg PO + placebo clopidogrel PO ○ Days 2-21: ASA 75 mg PO + placebo clopidogrel PO ○ Days 22-90: ASA 75 mg PO + placebo clopidogrel PO
Outcomes	• Death from any cause • Death from CV cause • Composite: Stroke, MI, CV-death • Stroke - ischemic or hemorrhagic (primary outcome) • Severe bleed • TIA • MI • Moderate bleed • Mild bleed
Subgroup analyses	• 11 predefined subgroups
Funding	• Supported by grants from the Ministry of Science and Technology of the People's Republic of China

Participants

Setting	114 clinical centres (China)
Inclusion criteria	• ≥ 40 years • Acute minor ischemic stroke (NIHSS score of ≤3) or TIA (focal ischemia with resolution of symptoms within 24 hrs and ABCD[2] score of ≥4) • Able to start study drug within 24h of symptom onset
Relevant exclusion criteria	• High bleed risk: current hemorrhage, vascular malformation, prior ICH, GI bleed/major surgery within past 3 months, • Tumor, abscess, other non-ischemic brain disease • Isolated visual changes/dizziness/vertigo with no evidence of acute infarct on baseline CT or MRI • Modified Rankin scale score >2 before stroke/TIA Indication for anticoagulation (presumed cardiac source of embolus) • Anticipated need for long-term NSAID use or non-study antiplatelet • Use of heparin or oral anticoagulant within 10 days before randomization • Planned or probable angioplasty or vascular surgery within 3 months after screening • Planned surgery/interventional treatment requiring cessation of study drug • TIA/minor stroke caused by angiography or surgery
Study size	• 41,561 assessed for eligibility • 5170 included/randomized (12%)

"Average" patient	• Male 66.2%
	• Comorbidities:
	  ○ Hypertension 65.7%
	  ○ Diabetes 21.1%
	  ○ Current/former smokers 43.0%
	  ○ Previous stroke/TIA ~23%
	  ○ Previous MI ~2%
	• Chinese patients
	• Mean age 62 years
	• Qualifying event:
	  ○ Minor stroke ~72%
	  ○ TIA ~28%
	• Median time from onset to randomization 13 hrs

	No clinically-relevant baseline between-group differences

Results

Outcomes	ASA	Clopidogrel-ASA	Hazard Ratio	Absolute risk reduction (NNT)
Death at 90 days	0.4%	0.4%	0.94 (0.24-3.79)	
from CV cause	0.2%	0.2%	1.16 (0.35-1.79)	
Stroke	11.7%	8.2%	0.68 (0.57-0.81)	3.5% (NNT = 29)
Ischemic stroke	11.4%	7.9%	0.67 (0.56-0.81)	3.5% (NNT = 29)
Hemorrhagic stroke	0.3%	0.3%	1.01 (0.38-2.70)	
All bleeding (GUSTO)	1.6%	2.3%	1.41 (0.95-2.10)	ARI: 0.7% (NNH = 142)
Severe bleed	0.2%	0.2%	0.94 (0.24-3.79)	
Moderate bleed	0.2%	0.1%	0.73 (0.16-3.26)	
Mild bleed	0.7%	1.2%	1.57 (0.88-2.79)	

Major Limitations:

Generalizability

- **Careful patient selection is crucial!**
  - Only 12% of patients assessed for this trial were eligible
  - Use of the ABCD2 score in TIA and NIHSS assessment in stroke, as well as ruling out bleeding risk, are essential to properly evaluate patients for initiation of this intervention.
- **Absolute benefits & harms may differ in a non-Chinese population**
  - Ethnically-Chinese patients have a greater risk of ischemic and hemorrhagic stroke than white patients[7]
  - Higher rate of genetic polymorphism affecting bioactivation of clopidogrel in ethnically-Chinese versus white (i.e. stronger antiplatelet effect in whites, and thus greater risk of bleeding)
- **Stroke prevention was NOT optimized**
  - Only ~35% were on antihypertensive therapy during the 90-day follow-up
    - Unknown how many were on a thiazide, the single most effective agent for stroke prevention
  - Only 40% were on lipid-lowering therapy (presumably mostly statins) during the 90-day follow-up

Conclusions & Application:

- A 21-day course of clopidogrel + ASA reduces the risk of stroke by a clinically important difference over 90 days in a carefully selected patient population.
- Use of the ABCD[2] tool in TIA and NIHSS assessment in stroke should be mandatory prior to initiation of this regimen.
- Stroke patients should NOT receive greater than 21 days of dual antiplatelet therapy.
  - Pharmacists should investigate all stroke patients on dual antiplatelet therapy for duration of therapy and alternative appropriate indications (ACS, coronary or other stent, atrial fibrillation, etc)
- The POINT trial, a similar ongoing trial in a North American population, will expand our understanding of this strategy in white patients and, presumably, in a population with more extensive use of pharmacological co-interventions

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