재발 고위험군 뇌경색에서 항혈소판제 사용

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Antithrombotic treatment for high-risk stroke patients

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- DAPT with aspirin+clopidogrel
  - High vs Low risk stroke patients
- Other antiplatelets
  - aspirin+cilostazol
  - Ticagrelor/prasugrel

- Acute DAPT trials
  - FASTER
  - ⬇
  - CHANCE
  - POINT

◆Key take-aways:
Ischemic risk highest in acute period,
whereas bleeding risk is constant over time.

Thus:
- Treatment should be initiated as soon as possible
- Long-term treatment (>3 months) associated with negative benefit-risk

Q. Same treatment?

✓ High risk of recurrent stroke ?
-Acute and Minor…

1) Multiple risk factors
2) Prior aspirin users
3) Old age
4) …

✓ Low risk of recurrent stroke ?
-Acute and Minor…

1) Less risk factors
2) No vascular diseases
3) Young age
4) …

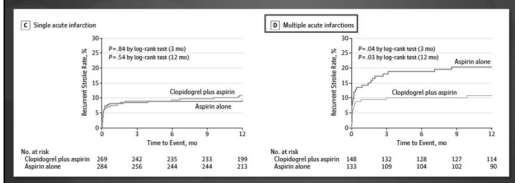

JAMA Neurology | Original Investigation

Dual Antiplatelet Therapy in Transient Ischemic Attack and Minor Stroke With Different Infarction Patterns
Subgroup Analysis of the CHANCE Randomized Clinical Trial

Jing Jing, MD, PhD; Xia Meng, MD, PhD; Xingquan Zhao, MD, PhD; Liping Liu, MD, PhD; Anxin Wang, MD; Yumeng Pan, MD; Hao Li, PhD; David Wang, DO; S. Claiborne Johnston, MD, PhD; Yongjun Wang, MD; Yilong Wang, MD, PhD

Are the efficacy and safety of C+A
consistent in different infarction patterns after TIA or minor stroke?

	Asp	Asp+Clop	Adjusted HR	P
Outcome				
Stroke	18.8%	10.1%	0.50 (0.3-0.96)	0.04
Combined outcome	19.6%	10.1%	0.50 (0.3-0.92)	0.03
Ischemic stroke	18.8%	10.1%	0.50 (0.3-0.96)	0.04

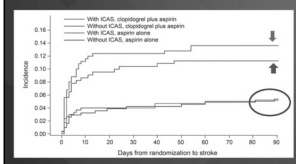


Dual antiplatelet therapy in stroke and ICAS

Subgroup analysis of CHANCE

Neurology 2015;85:1154-1162

- ✓ Objective: investigate whether the efficacy and safety of clopidogrel + ASA vs ASA alone were consistent between patients with and without intracranial arterial stenosis (ICAS).
- ✓ 1089 patients with MRA images available in CHANCE
- ✓ 608 patients (55.8%) with ICAS and 481 (44.2%) without



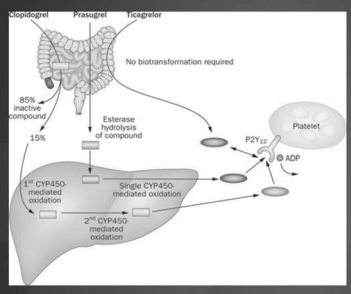
Outcome	Without ICAS (n = 608)		With ICAS (n = 481)		
	Placebo plus aspirin (n = 308)	Clopidogrel plus aspirin (n = 300)	Placebo plus aspirin (n = 230)	Clopidogrel plus aspirin (n = 232)	p Value*
Efficacy outcomes					
Primary efficacy outcome, stroke	17 (5.5)	16 (5.3)	34 (14.8)	26 (11.2)	<0.0001
Secondary efficacy outcomes					
Composite efficacy outcome†	19 (6.2)	18 (6.0)	34 (14.8)	26 (11.2)	0.0001
Ischemic stroke	17 (5.5)	16 (5.3)	34 (14.8)	26 (11.2)	<0.0001
Hemorrhagic stroke	0 (0)	0 (0)	0 (0)	0 (0)	NA
Myocardial infarction	2 (0.7)	0 (0)	0 (0)	0 (0)	0.208
Vascular death	1 (0.3)	0 (0)	0 (0)	0 (0)	0.374
Death from any cause	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0.208
TIA	7 (2.3)	5 (1.7)	9 (3.9)	4 (1.7)	0.425
mRS score at 90 d					<0.0001
0-2	299 (97.4)	297 (99.0)	221 (89.8)	204 (89.5)	
3-6	8 (2.6)	10 (3.4)	28 (11.2)	24 (10.5)	

- ▶ 2 main limitations
  - ▶ Non-minor stroke
  - ▶ Higher risk vs lower risk

Is DAPT with A+C Enough for early treatment in high risk patients?

- ▶ Aspirin vs Ticagrelor
- ▶ Aspirin+Ticagrelor

Drug	Clopidogrel	Prasugrel	Ticagrelor
Drug Class	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine
Prodrug	Yes	Yes	No (active drug)
Mechanism of Action	Irreversible inhibition of $P2Y_{12}$ ADP receptor	Irreversible inhibition of $P2Y_{12}$ ADP receptor	Reversible inhibition of $P2Y_{12}$ ADP receptor
Absorption	C_{max}: 30 min-1 hour	C_{max}: 30 min	C_{max}: 1.5 hours (ticagrelor), 2.5 hours (active metabolite)
Metabolism	Hepatic (CYP2C19)	Hepatic (primarily CYP3A4 and CYP2B6)	Hepatic (CYP3A4)
Elimination	Urine 50%, feces 46%	Urine 68%, feces 27%	Urine 26%, feces 58%
Half-life	~6 hours (clopidogrel); ~30 min (active metabolite)	~7 hours (active metabolite; range = 2-15 hours)	~7 hours (ticagrelor); ~9 hours (active metabolite)
Dosage Form	75-, 300-mg tablets	5-, 10-mg tablets	90-mg tablets
Daily Maintenance Dose	75 mg	10 mg	90 mg twice daily



Clopidogrel

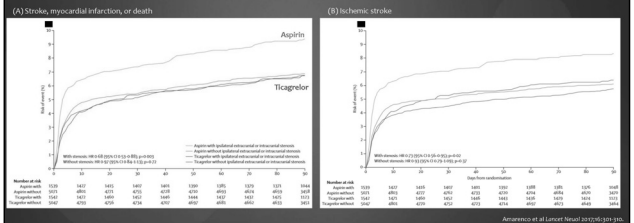
Inactive prodrug

two-step oxidation by the hepatic CYP450 system to generate its active compound

CYP2C19, CYP3A4/5, CYP1A2, CYP2B6, and CYP2C9

SOCRATES

Efficacy was greater in patients with ipsilateral extra-or intracranial stenosis

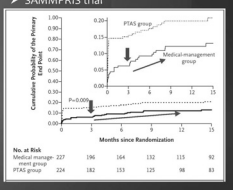


Amarenco et al Lancet Neurol 2017;16:301-310.

Is short-term A+C Enough for 2nd prevention?

- DAPT for prevention of recurrent stroke in high-risk stroke patients
- Still high risk of recurrent stroke, even in acute phase
- High risk of bleeding for long-term prevention
  - ✓ More potent in acute phase…
  - ✓ Less bleeding, but still potent in subacute to chronic phase…

- SAMMPRIS trial



Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial

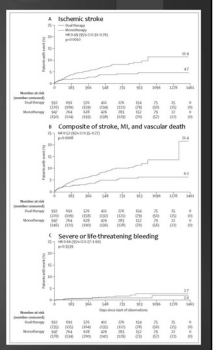
Kazunori Toyoda, Shinichiro Uchiyama, Takenori Yamaguchi, Donald M Easton, Kazumi Kimura, Haruhiko Kishima, Nobuyuki Sakai, Yasushi Okada, Kentaro Tanaka, Hideki Origasa, Hiroaki Nagura, Kiyohiro Houkin, Keiji Yamaguchi, Masanori Iwabe, Kazuo Minematsu, on behalf of the CSPS.com Trial Investigators

Lancet Neurol 2019; 18: 136–46

	Dual therapy		Monotherapy		HR (95% CI)	p value
	Number of patients	Annual event rate	Number of patients	Annual event rate		
Primary efficacy outcome	n=932		n=947			
Ischaemic stroke*	29 (3%)	2·2	64 (7%)	4·5	0·49 (0·31–0·76)	0·0010
Secondary efficacy outcomes	n=932		n=947			
Any stroke	34 (4%)	2·6	71 (7%)	5·0	0·53 (0·34–0·77)	0·0012
Haemorrhagic stroke*	5 (1%)	0·4	7 (1%)	0·5	0·77 (0·24–2·42)	0·65
Ischaemic stroke or transient ischaemic attack	32 (3%)	2·4	69 (7%)	4·9	0·50 (0·33–0·76)	0·00091
Death from any cause	6 (1%)	0·5	7 (1%)	0·5	0·92 (0·31–2·73)	0·88
Composite of stroke, myocardial infarction, and vascular death	38 (4%)	2·9	78 (8%)	5·5	0·52 (0·35–0·77)	0·0007·9
All vascular events	47 (5%)	3·6	90 (10%)	6·4	0·56 (0·39–0·80)	0·0011
Safety outcomes	n=930		n=921			
Severe or life-threatening bleeding	8 (1%)	0·6	13 (1%)	0·9	0·66 (0·27–1·60)	0·35
Intracranial haemorrhage	8 (1%)	0·6	13 (1%)	0·9	0·66 (0·27–1·60)	0·35
Haemorrhagic adverse events	38 (4%)	2·9	33 (4%)	2·4	1·23 (0·77–1·96)	0·38

Annual event rate indicate the number of events per 100 person years. HR=hazard ratio. *Two patients who developed ischaemic stroke (one in each of the two treatment groups) and two patients who developed haemorrhagic stroke (one in each of the two treatment groups) had fatal outcomes.

Table 3: Efficacy and safety outcomes

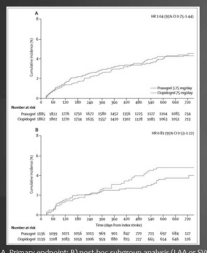


Comparison of prasugrel and clopidogrel in patients with non-cardioembolic ischaemic stroke: a phase 3, randomised, non-inferiority trial (PRASTRO-I)

Akira Ogawa, Kazunori Toyoda, Kazuo Kitagawa, Takanari Kitazono, Takehiko Nagao, Hiroshi Yamagami, Shinichiro Uchiyama, Norio Tanahashi, Masayasu Matsumoto, Kazuo Minematsu, Izumi Nagata, Masakatsu Nishikawa, Shinsuke Nanto, Kenji Abe, Yasuo Ikeda, PRASTRO-I Study Group*

2019 Lancet Neurol.

PRASTRO-I



	Prasugrel group (n=1885)		Clopidogrel group (n=1862)		Hazard ratio (95% CI)
	Events (n)	Incidence	Events (n)	Incidence	
Life-threatening bleeding, clinically relevant bleeding, clinically overt major bleeding	115	6·1% (5·1–7·3)	110	5·9% (4·9–7·0)	1·02 (0·79–1·33)
Life-threatening bleeding	18	1·0% (0·6–1·5)	23	1·2% (0·8–1·8)	0·77 (0·41–1·42)
Major bleeding	2	0·1% (0·0–0·4)	4	0·2% (0·1–0·5)	0·49 (0·09–2·64)
Clinically relevant bleeding	98	5·2% (4·2–6·3)	85	4·5% (3·6–5·5)	1·15 (0·86–1·55)
Bleeding event leading to treatment discontinuation	30	1·6% (1·1–2·3)	33	1·8% (1·2–2·5)	0·89 (0·54–1·46)

Table 3: Safety endpoints

- Although the cumulative incidence of IS, MI, and death from other vascular causes was similar between the 3.75 mg/day of prasugrel and 75 mg/day of clopidogrel groups, non-inferiority could not be confirmed in Japanese patients with non-CE stroke.
- Of note, the incidence of bleeding events, which was assessed as part of the safety evaluation, was not significantly different between groups.

A. Primary endpoint; B) post-hoc subgroup analysis (LAA or SVO)

- Summary
  - DAPT with A+C: may be a choice for early secondary prevention
  - High risk stroke patients
    - Acute minor stroke
    - Arterial steno-occlusion
    - Multiple infarcts
    - …

More intense antiplatelet effect
+ Less bleeding risk

; Acute periods
_ aspirin+clopidogrel
_ ongoing trial for aspirin+ticagrelor

; subacute-to-chronic periods
_ clopidogrel, aspirin mono in general
_ aspirin+cilostazol in high risk groups