CHANCE: Clopidogrel PLAVIX + ASA ASPIRIN versus ASA ASPIRIN in patients with acute minor stroke or high-risk transient ischaemic attack (TIA)[1]

Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events

BOTTOM LINE

- In **CHANCE**, Chinese patients with minor ischemic stroke NIHSS ≤3 or high-risk TIA ABCD^2 ≥4, seen within 24hr symptom onset who received clopidogrel + ASA x 21 days then clopidogrel alone for a total of 90 days, compared to ASA alone x 90 days:
  - had ↓ risk of recurrent stroke (NNT=29) without an ↑ risk in hemorrhagic events or all-cause mortality
- The Canadian Stroke Best Practices Recommendations 2014 are cautious on recommending this routinely for the general Canadian population, CSBPR'14 (C) and they await the results of the **POINT** trial (clopidogrel + ASA vs ASA alone x 90 days in North America, Australia, and Europe).[2] The use of ASA alone, clopidogrel alone or dipyridamole + ASA are preferred for secondary stroke prevention.[2] CSBPR'14 (A)
- If choosing to use the results from **CHANCE**, then patients must be chosen carefully as only a small number (12%) of Chinese patients may benefit. Therapy must be given within 24 hours of symptom onset, and the dosing regimen followed, for patients at low risk for bleeds with minor ischemic stroke NIHSS ≤3 or high-risk (for stroke recurrence) TIA ABCD^2 ≥4 (also see other inclusion & exclusion criteria) who did not receive thrombolysis.

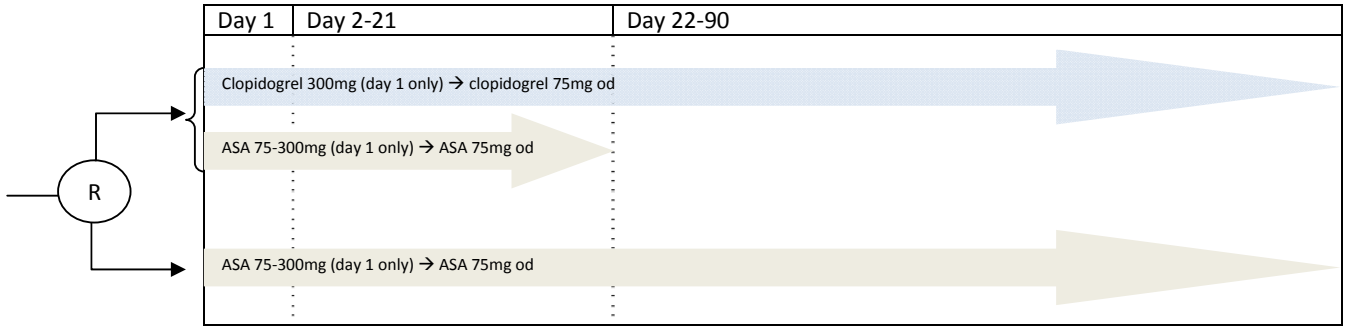
BACKGROUND

- The risk of stroke is high after TIA or minor stroke, with approximately 20% recurrence rate at 3 months;[3] following a TIA most strokes will occur within the first 2 days.[4] Antiplatelet therapy is beneficial as secondary prevention, with ASA as the usual choice as it's easily accessible and less expensive. Although combining clopidogrel + ASA reduces recurrent ischemic events in ACS,[5,6] this combination has not been successful and increases the risk of bleeding & mortality when used in stroke patients (e.g. **MATCH**, **SPS3**).[7,8] However these trials delayed administering secondary prevention until 1-2 months after the index stroke, and only few patients with TIA were included. **CHANCE** was designed to determine if clopidogrel + ASA was better than ASA alone at reducing risk of recurrent stroke, if given acutely to patients with high-risk TIA or minor ischemic stroke.

TRIAL BACKGROUND

DESIGN: randomized stratified by centre & interval between symptom onset & enrollment <12hr vs. 12-24hr, double-blind, double-dummy, placebo-controlled, multi-centre n=114, ITT study with concealed allocation conducted in China,
Funding: Ministry of Science and Technology of People's Republic of China

INTERVENTION: clopidogrel 300mg (day 1), 75mg daily (day 2-90) **+ ASA** 75-300mg (day 1), 75mg daily (day 2-21) **vs. ASA** 75-300mg (day1), 75mg daily (day 2-90)



INCLUSION: ≥40 years old, acute minor ischemic stroke NIHSS ≤3 or TIA focal brain ischemia with symptom resolution <24hr plus ABCD^2 ≥4, start therapy <24hr symptom onset

EXCLUSION: CT or MRI showing hemorrhage, vascular malformation, tumour, abscess, major nonischemic brain disease; isolated sensory symptoms, isolated visual changes, isolated dizziness or vertigo without evidence of acute infraction on CT or MRI; modified Rankin scale >2 (disabling stroke) before index event, NIHSS ≥4, clear indication for anticoagulation, contraindication to clopidogrel or aspirin, history of intracranial hemorrhage, anticipated requirement for long-term antiplatelets or NSAIDs, heparin or oral anticoagulation within 10 days before randomization, GIB or major surgery within previous 3 months, planned or probable revascularization within 3 months after screening, planned survey or interventional treatment requiring cessation of study drug, TIA or minor stroke caused by angiography or surgery, severe non-cardiovascular coexisting condition with life expectancy <3 months, women not practicing reliable contraception, pregnant women, patient receiving investigational drugs or devices, received thrombolysis around time of randomization

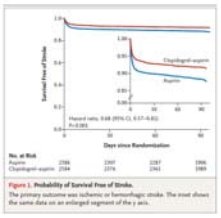
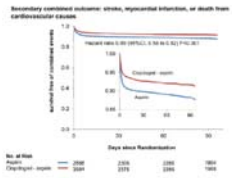
POPULATION at baseline: n=5170 enrolled (screened 41,561), mean time to randomization 13 hours

- qualifying event: TIA 27.9%, minor stroke 72.1%; median ABCD^2 score 4 (IQR~4-5); NIHSS baseline score not reported
- Main reasons screened patients not enrolled: delay ≥24hr 26.4%, other 15.2%, moderate and major ischemic stroke 10.4%, ICH 7%, low risk TIA 6.5%[9]
- Non-modifiable risk factors for stroke or TIA: 66.2% ♂, median age 62 years old, previous ischemic stroke 20%, previous TIA 3.4%
- Modifiable risk factors for stroke or TIA: hypertension 65.7%, smoking (past or current) 43%, diabetes 21.1%, hypercholesterolemia 11.1%
- Baseline characteristics were balanced between the two groups
- on ASA within 24hr before hospital admission 11.3%
- concomitant meds within 90 days: lipid lowering ~42%, antihypertensives ~35%, other ~30%, traditional Chinese medicine ~24%, antidiabetics ~13%, ASA ~1%, clopidogrel 0.5% [9]

RESULTS

follow-up: 90 days

TABLE 1: EFFICACY & SAFETY (confirmed by central adjudication committee unaware of group assignment)

CLINICAL ENDPOINTS	DAY 1: LOADING DOSE‡ DAYS 2-90: ASA 75MG DAILY n=2586	DAY 1: LOADING DOSE‡ DAYS 2-21: CLOPIDOGREL 75MG + ASA 75MG DAILY DAYS 22-90: CLOPIDOGREL 75MG DAILY n=2584	HR 95% CI	ARR/ARI	NNT/NNH /x 90 DAYS	COMMENTS
PRIMARY ENDPOINT						
Recurrent stroke (ischemic or hemorrhagic)	11.7% {n=303}	8.2% {n=212}	0.68 (0.57 - 0.81)	3.5%	NNT 29	Kaplan-Meier for 1° endpoint. Most of the benefits occurred within first few days. 
Ischemic stroke	11.4% {n=295}	7.9% {n=204}	0.67 (0.56-0.81)	3.5%	NNT 29	
Hemorrhagic stroke	0.3% {n=8}	0.3% {n=8}	1.01 (0.38-2.7)	0%	NS	
Fatal or disabling stroke	6.8% {n=177}	5.2% {n=135}	0.75 (0.6-0.94)	1.6%	NNT 63	
SECONDARY ENDPOINTS						
TIA	1.8% {n=47}	1.5% {n=39}	0.82 (0.53-1.26)	0.3%	NS	
Stroke, MI, cardiovascular death	11.9% {n=307}	8.4% {n=216}	0.69 (0.58-0.82)	3.5%	NNT 29	
MI	0.1% {n=2}	0.1% {n=3}	1.44 (0.24-8.63)	0%	NS	Kaplan-Meier for stroke, MI, CV death 
Death from all causes	0.4% {n=10}	0.4% {n=10}	0.97 (0.4-2.33)	0%	NS	
Vascular death (due to stroke, systematic hemorrhage, MI, CHF, PE, sudden death, arrhythmia)	0.2% {n=5}	0.2% {n=6}	1.16 (0.35-3.79)	0%	NS	
SAFETY						
Moderate-to-severe bleed*	0.3% {n=8}	0.3% {n=7}	Not reported	0%	NS	"Adverse events" and "serious adverse events" were similar between the two groups.
Any bleeding	1.6% {n=41}	2.3% {n=60}	1.41 (0.95-2.1)	0.7%	NS	

‡ Loading dose for ASA alone treatment arm was ASA 75-300mg; loading dose for clopidogrel + ASA treatment arm was clopidogrel 300mg + ASA 75-300mg
**Severe hemorrhage* (GUSTO) = fatal or intracranial or other causing hemodynamic compromise requiring blood/fluid/inotropes/surgical intervention
Moderate hemorrhage (GUSTO) = require transfusion but no hemodynamic compromise requiring intervention

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Sample size of 5100 was achieved
- There was an event adjudication committee, unaware of group assignment, to confirm efficacy and safety outcomes
- 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, and 8%, 11.5% and 17.3% respectively after a TIA.[3]
  In **CHANCE**, the mean time to randomization was 13 hours. This early enrollment ensured that that there would be lots of patients at higher risk of recurrent stroke, with the potential to benefit from therapy.
- Loss to follow up was low (0.7%)
- The rate of discontinuation was low (clopidogrel + ASA 6.4%, ASA 5.6%)

LIMITATIONS:

- Other risk factors for stroke (ethnicity and family history of stroke) not reported at baseline. However as other baseline characteristics imbalances were not detected, it is unlikely these were imbalanced.
- This study is generalizable to only 12.4% of minor strokes or high-risk TIAs, because initiating therapy had to occur ≤24 hours and there were strict eligibility criteria.
- The following were not reported: baseline NIHSS score, type of contraceptives used (i.e. estrogen containing?), mean loading dose of aspirin, stroke subtypes

UNCERTAINITIES:

- Antiplatelet therapy is usually recommended for secondary prevention after stroke or TIA.
  If using the results from **CHANCE** for the first 3 months, can antiplatelet therapy be given indefinitely after 90 days?
- The subgroup analysis did not include all risk factors for stroke (missing smoking, hyperlipidemia, ethnicity), so it is unknown what the hazard ratio for recurrent stroke is in these subgroups.
- Is this study only applicable to Chinese patients (e.g. different polymorphisms of CYP-450 affecting clopidogrel metabolism, use traditional Chinese medicine) treated in China (e.g. suboptimal secondary prevention medications, different standards of care)
- ABCD^2 was used in **CHANCE** to identify TIA patients who were at high-risk for another stroke. However a Canadian study found this tool was not sensitive enough to assess risk, nor did it accurately predict stroke risk.[10] Thus the Canadian Stroke Best Practices Recommendations 2014 do not recommend using ABCD^2. This makes it difficult to apply the findings from **CHANCE** in Canada when an important entry criterion relies on a tool that is not endorsed.
- We await the results of other studies to help guide therapy: dual therapy in non-Chinese patients (e.g. **POINT**), triple therapy (e.g. **TARDIS**), and new antiplatelet or anticoagulant agent s[11,12]

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
- **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

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♂=male **ACS**=acute coronary syndrome **CHF**= congestive heart failure **GIB**=gastrointestinal bleed **hr**=hour **IQR**=interquartile range **MI**=myocardial infarction **PE**=pulmonary embolism **TIA**=transient ischaemic attack

ACKNOWLEDGEMENTS: Contributors & Reviews: Lynette Kosar, Brent Jensen, Loren Regier, Jialin Liu, Josh Poteet, Brenna Gallagher **Prepared By**: Anne Nguyen PharmD

References

1. Wang Y, Zhao X, Liu L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* Jul 04 2013;369(1):11-19.
2. Coutts SB, Wein TH, Lindsay MP, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014. *Int J Stroke.* Apr 2015;10(3):282-291.
3. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ.* Feb 07 2004;328(7435):326.
4. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA.* Dec 13 2000;284(22):2901-2906.
5. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* Nov 20 2002;288(19):2411-2420.
6. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* Aug 16 2001;345(7):494-502.
7. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* Jul 24-30 2004;364(9431):331-337.
8. Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med.* Aug 30 2012;367(9):817-825.
9. Supplement to: Wang Y, Zhao X, Liu L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* Jul 04 2013;369(1):11-19.
10. Perry JJ, Sharma M, Sivilotti ML, et al. Prospective validation of the ABCD2 score for patients in the emergency department with transient ischemic attack. *CMAJ.* Jul 12 2011;183(10):1137-1145.
11. Hankey GJ. Dual antiplatelet therapy in acute transient ischemic attack and minor stroke. *N Engl J Med.* Jul 04 2013;369(1):82-83.
12. Sharma M, Khandelwal P. Clopidogrel with aspirin in minor stroke or transient ischemic attack. *N Engl J Med.* Oct 03 2013;369(14):1375-1376.