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

**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

**INCLUSION:** ≥40 years old, acute minor ischemic stroke NIHSS ≤3 or TIA focal brain ischemia with symptom resolution <24hr plus ABCD² ≥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 clopidogrel or aspirin, history of intracranial hemorrhage, anticipated requirement for long-term antiplatelets or NSAIDs, heparin

**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 ABCD² 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%, intracranial hemorrhage 9.2%, age ≥80 years 6.7%, history of major nonischemic stroke 5.1%, other 14.8%

**MAIN REASONS SCREENED PATIENTS NOT ENROLLED:** delay ≥24hr 26.4%, other 15.2%, moderate and major ischemic stroke 10.4%, intracranial hemorrhage 9.2%, age ≥80 years 6.7%, history of major nonischemic stroke 5.1%, other 14.8%

**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%

**TIMELINE**

**STUDY OBJECTIVE:** 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.
RESULTS

follow-up: 90 days

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

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

‡ 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. In CHANCE, the mean time to randomization was 13 hours. This early enrollment ensured 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 imbalances.
- 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

UNCERTAINTIES:
- 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 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. Thus the Canadian Stroke Best Practices Recommendations 2014 do not recommend using ABCD. 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
RxFILES RELATED LINKS

- 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

X = 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 
h = hour 
IQR = interquartile range 
MI = myocardial infarction 
PE = pulmonary embolism 
TIA = transient ischaemic attack

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Prepared By: Anne Nguyen PharmD

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References