THE ROLE of CILOSTAZOL

*in* ISCHEMIC STROKE

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This presentation is supported by
Thai Osuka
CONTENT

1. Mechanism of cilostazol
2. Acute Ischemic Stroke \textit{(within 48h)}
3. Secondary Prevention \textit{and} Recurrence
4. Bleeding Complication
ACUTE ISCHEMIC STROKE (WITHIN 48H)

SECONDARY PREVENTION AND RECURRENCE

MECHANISM OF CILOSTAZOL

BLEEDING COMPLICATION
Increase cAMP → reduce platelet function
Decrease cAMP → increase platelet function
PDE enzyme change cAMP to 5-AMP
Inhibit PDE enzyme → increase cAMP
→ reduce platelet function
Phosphodiesterase inhibitor

Cilostazol
Dipyridamole
9 family of PDE enzyme (PDE1-9)

PDE-3
Site: platelet, heart, vascular SM, adipose tissue
Inhibitor: Cilostazol

PDE-5
Site: platelet, heart, vascular SM, corpus carvernosum
Inhibitor: Dipyridamole, Sidenafil
### Distribution of PDE Isozyme

<table>
<thead>
<tr>
<th>Cell</th>
<th>Platelet</th>
<th>Heart</th>
<th>Vascular SMC</th>
<th>Adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Subordinate</td>
<td>II</td>
<td>V</td>
<td>I II IV</td>
<td>I II</td>
</tr>
</tbody>
</table>

- Inhibit PDE-3
  - antiplatelet action
  - vasodilatation → **headache**?
  - inhibit vascular SMC proliferation
  - tachycardia and palpitation
  - increase HDL and decrease TG
Which antiplatelet drug that can use in acute ischemic stroke?

1. ASA 81 mg
2. ASA 300 mg
3. Clopidogrel
4. Dipyridamole+ASA
5. Cilostazol
1. Mechanism of cilostazol
2. Acute Ischemic Stroke (within 48h)
3. Secondary Prevention and Recurrence
4. Bleeding Complication
reduce mortality rate 9/1,000 OR 0.92 (0.87-0.98)
good functional outcome 7/1,000 OR 1.02 (1.01-1.04)
increase severe bleeding (within 2-4 wk) 4/1,000 OR 1.69 (1.35-2.11)
no evidence for difference dose of ASA
ASPIRIN plus CLOPIDOGREL


- ASA v ASA+clopidogrel (loading 300 mg then 75 mg/d)
- patient with AIS or TIA within 24h
- not significant in recurrence rate
- mild increase rate of bleeding in combination group

ASPIRIN plus ER-DIPYRIDAMOLE


- ER-DP v ASA+ER-DP
- not difference in efficacy and safety
CILOSTAZOL

CAIST
Cilostazol in Acute Ischemic Stroke Trial

- ASA 300 mg v Cilostazol 200 mg duration 90d
- 458 AIS patients within 48h
- Recurrence stroke ASA 4% v Cilostazol 3% (p=0.41)
- Bleeding ASA 13% v Cilostazol 11% (p=0.43)
- Drug withdrawal ASA 7% v Cilostazol 10% (p=0.32)
- Cilostazol is feasible in AIS

CONCLUSION for ACUTE ISCHEMIC STROKE

ASA 160-300 mg/d (mostly 300mg/d) is recommended in AIS within 48h

May be reduce to 75-100 mg/d after 2wk for reduce bleeding complication

Cilostazol, ASA+clopidogrel or ASA+ER-DP is the alternative treatment
## Anti-platelet agents for acute ischemic stroke

<table>
<thead>
<tr>
<th>Anti-platelet agent</th>
<th>Quality of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 160-325</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cilostazol 200</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Thai Stroke guideline: revised 2012*

- Antibiotic therapy for infection should be started within 48 hours of onset (+, 1-1)
- Adjunctive therapy for Cilostazol 200 mg/day (+, 2-1)
- Pre-emptive treatment with Aspirin or any other second-line thrombolytic therapy) should be started within 48 hours of onset (+, 1-1)
Effects of Clopidogrel added to Aspirin in Patients with Recent Lacunar Stroke

- ASA 375 alone mg/d vs add clopidogrel 75 mg/d
- Recurrence stroke 2.7% vs 2.5% (HR 0.92, 95% CI 0.72-1.16)
- Hemorrhage 1.1% vs 2.1% (HR 1.97, 1.41-2.71)
- Mortality combine group > ASA group (HR 1.52, 1.14-2.04)

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA
- clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg/d for 90 d + aspirin 75 mg/d for the first 21d vs placebo plus aspirin (75 mg/d for 90 days)
- primary outcome: stroke (ischemic or hemorrhagic) during 90d

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- Combine gr. 8.2% as compared with 11.7% of those in aspirin group (HR, 0.68; 95%CI, 0.57 - 0.81; p<0.001).
- Moderate or severe hemorrhage: 0.3% in combine gr. v 0.3% in the aspirin group (p=0.73)

In TIA or minor stroke the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage.

Which antiplatelet drug that is worst in 2º stroke prevention?

1. ASA
2. Clopidogrel
3. Clopidogrel + ASA
4. Dipyridamole + ASA
5. Cilostazole
Acute Ischemic Stroke (within 48h)

Secondary Prevention and Recurrence

Bleeding Complication

Mechanism of cilostazol
RECURRENCE ISCHEMIC STROKE

- risk factors and drug compliance
- new or miss risk factors
  - cardio-embolic-anticoagulant
  - carotid stenosis-carotid intervention
- adjusted medications
CAROTID DOPPLER ULTRASOUND
<table>
<thead>
<tr>
<th>Study</th>
<th>Stenosis Range</th>
<th>Benefit</th>
<th>2y Stroke Rate</th>
<th>3y Stroke Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET</td>
<td>&lt; 50%</td>
<td>no benefit</td>
<td>9%</td>
<td>26% (0.7%/mo)</td>
</tr>
<tr>
<td></td>
<td>50-99%</td>
<td>marginal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70-99%</td>
<td>significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECST</td>
<td>&lt; 30%</td>
<td>no benefit</td>
<td>10.3%</td>
<td>16.3%</td>
</tr>
<tr>
<td></td>
<td>30-69%</td>
<td>no benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70-99%</td>
<td>significant</td>
<td></td>
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</tbody>
</table>

## CE in SYMPTOMATIC PATIENTS

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Recommendation</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99%</td>
<td>CE effective for recently previous stroke (A)</td>
<td>within 6 Mo</td>
</tr>
<tr>
<td>50-69%</td>
<td>CE may be considered with clinical status (A)</td>
<td>recommended the patient have:  - at least 5y life expectancy  - peri-op stroke/death &lt; 6%  - age &lt; 80y  - mild to moderate disability</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>CE should not be considered (A)</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>CE show small benefit in 2y</td>
<td>but not clear long term benefit (C)</td>
</tr>
</tbody>
</table>

CAROTID ARTERY STENOSIS (CAS)

Carotid Endarterectomy *in* Asymptomatic Stenosis

**ACAS** 1
- 825 CEA+medications *v* 834 only medications
- outcome: stroke 5y and selective surgeon+exclude high risk patients
- Sx 5.1% *v* medications 11% (sig.)
- post-op death 0.14%, stroke within 30d 1.1%
- NNT 17, ARR 5.9% (1% in 1y)
- prevent 1 stroke in 1y = 85 Sx

**ACST** 2
- same protocol as ACAS
- no surgeon selection, not control U/S quality and less exclusion criteria
- ARR 5.4%
- post-op death 1.11%, stroke within 30d 3%

<table>
<thead>
<tr>
<th>CE in ASYMPTOMATIC PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60-99%</strong> reasonable to consider CE in (A)</td>
</tr>
<tr>
<td>- patients age between 40-75y</td>
</tr>
<tr>
<td>- life expectancy &gt; 5y</td>
</tr>
<tr>
<td>- post-op stroke/death &lt; 3%</td>
</tr>
<tr>
<td><strong>100%</strong> medication</td>
</tr>
</tbody>
</table>
CE in SOME PATIENTS

- women with 50-69% symptomatic stenosis not show clear benefit in previous trial (C)
- hemispheric TIA or stroke benefit > retinal ischemia (C)
- operate within 2wk of TIA or minor stroke had greater benefit
- no emergency CE in patient with progressive neurological deficit contralateral occlusion
- associated with increase peri-operative risk but persistent small benefit (C)
Cilostazole Regression of Carotid Atherosclerosis

Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) Study

- compare cilostazol v ASA of progression of atherosclerosis
- 329 type 2 DM with PAD were enrolled (163 and 166 subjects)
- outcome: intimal media thickness in 2y
- significant regress in cilostazol group
  \[-0.088 \pm 0.260 v 0.059 \pm 0.275 \text{ mm} (p < 0.01)\]

Compare with ASA, cilostazol potently inhibit progression of carotid intima-media thickness in DM type2 patients

Circulation 2012;121:2584-91.
CAROTID STENOSIS *plus* INTRACRANIAL STENOSIS

- common in patients with extracranial carotid disease
- likely as a marker of a severe systemic vascular disease
- requiring further diagnostic tools, as MRA, CTA, TCD or angiography
- tandem lesions or intracranial aneurysms not alter the decision to perform a CEA
- surgical risk is not high (about 0.5%)
Prevalence of ICAS among populations

- Singapore: 48%
- Thai: 47%
- Chinese: 42%
- Korean: 18%
- US: 10%

The Open Atherosclerosis & Thrombosis Journal 2010;3:3-7.
Cilostazole *in* Intracranial Arterial Stenosis

**Trial of CilOstazol in Symptomatic Intracranial Stenosis (TOSS)**

- 135 patients with *acute symptomatic stenosis of middle cerebral artery or the basilar artery*
- assessed by using MRA and transcranial Doppler (TCD) at the time of recruitment and 6 months later
- Cilostazole 200 mg/d+ASA 100 mg/d v ASA 100 mg/d
- In cilostazol group, 6.7% progressed and 24.4% regressed. In placebo group, 28.8% progressed and 15.4% regressed (*p*=0.008)

**Progression of symptomatic IAS in cilostazol group was significantly lower than that in placebo group (*p*=0.008)**

*Stroke 2005;36:782-6.*
Cilostazole in Intracranial Arterial Stenosis

Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis II (TOSS-2)

- 480 patients with acute symptomatic stenosis of middle cerebral artery or the basilar artery within 2wk
- assessed by using MRA and transcranial Doppler (TCD) at the time of recruitment and 6 months later
- Cilostazole 200 mg/d+ASA 100 mg/d vs Clopidogrel 75 mg/d+ASA 100 mg/d
- In cilostazol group, 9.9% progressed and 30.2% regressed.
  - clopidogrel group, 15.4% progressed and 23.7% regressed ($p=0.049$)
- hemorrhagic complications 0.86% vs 2.67% ($p=0.16$)
- not difference in total CV event, new stroke, AMI and death

Progression of symptomatic IAS in cilostazol group was significantly lower than that in clopidogrel group

RECURRENCE ISCHEMIC STROKE

- risk factors and drug compliance
- new or miss risk factors
  eg. cardio-embolic-anticoagulant
  carotid stenosis-carotid intervention
- adjusted medications
CAROTID STENOSIS

MEDICATIONS TREATMENT
ANTIPLATELETS
ASPIRIN

- ASA 75-100 mg/d
  - reduce mortality rate 5/1,000 OR 0.91 (0.81-1.0)
  - reduce recurrence rate 25/1,000 OR 0.81 (0.71-0.92)

ASA resistance

- increase bleeding* 7/1,000 OR 2.69 (1.25-5.76)
  - * non-fatal major extracranial hemorrhage

Which antiplatelet drug that is chose beyond ASA?

1. Clopidogrel
2. Clopidogrel + ASA
3. Dipyridamole + ASA
4. Cilostazole
5. Cilostazole + ASA
CLOPIDOGREL

CALEEIRE
Clopidogrel versus ASA in Patient at Risk of Ischemic Events

- ASA 325 mg/d v clopidogrel 75 mg/d
- Ischemic stroke, MI, peripheral vascular disease
- reduce overall mortality \((p=0.043)\)
- ischemic stroke \((p=0.26)\), MI \((p=0.66)\), PVD \((p=0.0028)\)

Compare with ASA

- reduce mortality rate 1/1,000 OR 0.98 (0.89-1.1)
- reduce recurrence rate 10/1,000 OR 0.91 (0.78-1.07)
- increase bleeding* 1/1,000 OR 0.94 (0.72-1.23)

* non-fatal major extracranial hemorrhage

CLOPIDOGREL plus ASPIRIN

**MATCHS**
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.

- ASA 325 mg/d + clopidogrel 75 mg/d v clopidogrel 75 mg/d
  - not reduce in recurrence rate
  - significantly increase bleeding in combination group (1.3%, p< 0.001)

**Compare with clopidogrel**
- reduce mortality rate 0/1,000 RR 1.00 (0.83-1.21)
- reduce recurrence rate 5/1,000 RR 0.95 (0.82-1.1)
- increase bleeding* 15/1,000 RR 2.55 (1.88-3.46)
  * non-fatal major extracranial hemorrhage

ASPIRIN plus ER-DIPYRIDAMOLE

ESPS II
European Stroke Prevention Study Group

- ASA 50 mg/d + ER-DP 400 mg/d v ASA 50 mg/d v placebo
- outcome: recurrence rate compare with placebo
  - combination decrease 37% ($p=0.001$)
  - ASA alone decrease 18% ($p=0.013$)
- not significantly increase bleeding in combination group

Compare with placebo

- reduce mortality rate 1/1,000 RR 0.97 (0.83-1.13)
- reduce recurrence rate 24/1,000 RR 0.77 (0.67-0.89)
- increase bleeding* 1/1,000 RR 1.08 (0.75-1.54)
  * non-fatal major extracranial hemorrhage

ASPIRIN plus ER-DIPYRIDAMOLE v CLOPIDOGREL

PRoFESS
Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study

ASA 50 mg/d+ER-DP 400 mg/d v clopidogrel 75 mg/d
- no difference in recurrence stroke ($p=0.38$)
- more hemorrhagic event in ASA+ER-DP group

Compare with clopidogrel
- not difference in recurrence ischemic stroke
- but increase hemorrhagic complications

Lancet Neurol 2008; 7: 875-84.
CSPS-2

Cilostazol for Secondary Prevention of Stroke

cilostazol 200 mg/d v ASA 81 mg/d for 1-5y
- recurrence stroke 2.76% v 3.71% (HR 0.74, CI 0.56-0.98, p=0.035)
- all hemorrhage 0.77% v 1.78% (HR 0.46, CI 0.30-0.71, p=0.004)
- more headache, dizziness, palpitation in cilostazol group

Compare with ASA
- reduce mortality rate 6/1,000 RR 0.89 (0.45-1.74)
- reduce recurrence rate 35/1,000 RR 0.67 (0.52-0.86)
- decrease bleeding* 3/1,000 RR 0.74 (0.61-0.90)
  * non-fatal major extracranial hemorrhage

**ACCP 2012:**

In patients with non-cardioembolic ischemic stroke or TIA

<table>
<thead>
<tr>
<th>Anti-platelet agents</th>
<th>Comparator</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 75-100 mg OD</td>
<td>No anti-platelet</td>
<td>1A</td>
</tr>
<tr>
<td>Clopidogrel 75 mg OD</td>
<td>No anti-platelet</td>
<td>1A</td>
</tr>
<tr>
<td>ASA+Dipyridamole ER (25 mg/200 mg bid)</td>
<td>No anti-platelet</td>
<td>1A</td>
</tr>
<tr>
<td>Cilostazol 100 mg bid</td>
<td>No anti-platelet</td>
<td>1A</td>
</tr>
<tr>
<td>Oral anti-coagulants</td>
<td>No anti-platelet</td>
<td>1B</td>
</tr>
<tr>
<td>Clopidogrel+ASA</td>
<td>No anti-platelet</td>
<td>1B</td>
</tr>
<tr>
<td>Triflusal</td>
<td>No anti-platelet</td>
<td>2B</td>
</tr>
<tr>
<td>Clopidogrel or ASA+Dipyridamole ER (25 mg/200 mg bid)</td>
<td>ASA</td>
<td>2B</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>ASA</td>
<td>2C</td>
</tr>
</tbody>
</table>
Which antiplatelet drug that is less bleeding?

1. ASA
2. Clopidogrel
3. Cilostazole
4. Cilostazole + Clopidogrel
5. Cilostazole + ASA
1. Mechanism of cilostazol
2. Acute Ischemic Stroke *(within 48h)*
3. Secondary Prevention *and* Recurrence
4. Bleeding Complication
Bleeding Completitions

Effect on platelet function of cilostazol, clopidogrel, and aspirin, each alone or in combination

- from patients with peripheral vascular disease
- bleeding time in ASA, clopidogrel and cilostzole alone, two-combination, three-combination
<table>
<thead>
<tr>
<th>Bleeding Time</th>
<th>Baseline</th>
<th>ASA</th>
<th>Clopi</th>
<th>Cilos</th>
<th>ASA+Clopi</th>
<th>ASA+Cilos</th>
<th>Cilo+Clopi</th>
<th>Three combine</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.39</td>
<td>6.93*</td>
<td>10.52*</td>
<td>5.50*</td>
<td>17.43#</td>
<td>8.50*</td>
<td>12.61*</td>
<td>18.69#</td>
<td></td>
</tr>
</tbody>
</table>

* Significant from baseline  # Significant from cilostazol+other antiplatelet

CONCLUSION for SECONDARY PREVENTION of ISCHEMIC STROKE

Clopidogrel    ASA+ER-DP    Cilostazol

ASA

Cilostazol+ASA ??

Clopidogrel+ASA

ASA+ER-DP    Clopidogrel

Cilostazol  Cilostazol+ASA

ASA

Cilostazol
CONCLUSION for CLINICAL USE OF CILOSTAZOL in ISCHEMIC STROKE

- Repeated stroke and failure to ASA
- Risky to hemorrhagic events
- Intracranial stenosis with and without DM
- Allergic to ASA
THANK YOU for YOUR ATTENTION
Special Conditions
ASPIRIN *plus* CLOPIDOGREL

**CARESS**
Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis

- microembolic signal from TCD at carotid artery in AIS
- clopidogrel loading 300 mg then 75 mg/d + ASA 75 mg/d vs ASA 75 mg/d alone
- reduce MES at 1wk (RRR 39.8%, *p*=0.046)
Effects of Clopidogrel added to Aspirin in Patients with Recent Lacunar Stroke

- ASA 375 alone mg/d v add clopidogrel 75 mg/d
- Recurrence stroke 2.7% v 2.5% (HR 0.92 95%CI 0.72-1.16)
- Hemorrhage 1.1% v 2.1% (HR 1.97, 1.41-2.71)
- Mortality combine group > ASA group (HR 1.52,1.14-2.04)

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA
- clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg/d for 90 d + aspirin 75 mg/d for the first 21d) vs placebo plus aspirin (75 mg/d for 90 days)
- primary outcome: stroke (ischemic or hemorrhagic) during 90d

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

- Combine gr. 8.2% as compared with 11.7% of those in aspirin group (HR, 0.68; 95%CI, 0.57 - 0.81; \( p<0.001 \)).
- Moderate or severe hemorrhage: 0.3% in combine gr. v 0.3% in the aspirin group (\( p=0.73 \)).

In TIA or minor stroke the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage.

Which drug that is the best for stroke prevention in AF?

1. ASA
2. ASA + clopidogrel
3. Warfarin alone
4. Warfarin + ASA
5. Rivaroxaban
ASPIRIN plus CLOPIDOGREL in ATRIAL FIBRILLATION without WARFARIN

- ASA 75-100 mg/d v ASA+clopidogrel 75 mg/d
- AF without warfarin patients, time follow 3-6y
- less ischemic stroke in combination group 3.3% v 2.4% (RR 0.72, CI 0.62-0.83, p < 0.001)
- more hemorrhagic event in combination group 2.0% v 1.3% (RR 1.57, CI 1.29-1.92, p < 0.001)