Antithrombotic Drugs in Stroke

- Antiplatelet drugs in stroke
  - Mechanisms of actions, evidence-based recommendations in acute stroke, and for secondary prevention
  - Novel antiplatelet drugs
  - ASA resistance?, clopidogrel resistance?
- Anticoagulants in stroke
  - VKA
  - NOACs

Antithrombotic Drugs in Acute Ischemic Stroke

- Antiplatelets in Stroke
  - Aspirin
    - Rapid absorption at stomach and proximal small bowel
    - Max. drug level reach after 30-40 min. of oral ingestion
    - Able to inhibit platelet aggregation at 1 hour
    - Half life 15-20 min.
    - Irreversible COX-1 inhibitor
    - Aspirin resistance?
  - Triflusal
    - Block cyclooxygenase -> inhibit TXA2, preserve prostacyclin, increased NO synthesis
    - Block phosphodiesterase -> increase cAMP
    - Antithrombotic effect; inhibit plt aggregation, vasc. Inflammation
    - Did not increase bleeding time
    - 600mg/d

- Antithrombotic Drugs in Acute Ischemic Stroke
  - Intravenous/intraarterial thrombolytic drugs +/- mechanical thrombectomy

- Ticlopidine
  - Thienopyridine
  - Active metabolite of ticlopidine-> inhibit platelet aggregation via blockage of ADP receptors
  - 250 mg bid
  - SE: diarrhea 12%, rash, neutropenia 2%, reports of thrombotic thrombocytopenic purpura (TTP)

- Clopidogrel
  - Pro drug -> oxidized by CYP2C19**, CYP3A4 -> active metabolite
  - Platelet inhibition; max. at day 2-5
  - Load 300 mg -> inhibit plt. 6 hrs.
  - Load 600 mg -> inhibit plt. 2 hrs.
  - Clopidogrel resistance?
**Action of antiplatelets: P2Y12 inhibitors**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Thienopyridine</th>
<th>Thienopyridine</th>
<th>Thienopyridine + thienopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2Y12 receptor blockade</td>
<td>Reversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Twice a day</td>
<td>Twice a day</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Percentage of active metabolite</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Onset of action</td>
<td>2-4 hrs</td>
<td>2-4 hrs</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td>Offset of action</td>
<td>3-5 days</td>
<td>3-5 days</td>
<td>3-5 days</td>
</tr>
<tr>
<td>Interactions with CYP-targeted drugs</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Possible interactions with P-glycoprotein transporters</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP1A2 or CYP3A4</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Onset of antithrombotic effect</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Antiplatelets in Stroke**

- **Ticagrelor**
  - Potent antiplatelet; reversibly binds and inhibits P2Y12 receptors on platelet
  - Loading dose 180 mg -> 90 mg twice a day
  - Antiplatelet effect; inhibits >40% of plts in 30 min, and peak effect in 2 hrs.
  - H.l. 8-12 hrs, steady state after 2-3 d.
  - Offset 3-5 d.
  - Avoid coadministration of simvas/lovastatin >40 mg

**Antiplatelet Trials in Acute Stroke**

<table>
<thead>
<tr>
<th>Year</th>
<th>Antiplatelet</th>
<th>Trials</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Aspirin 160-325 mg within 48 hours 10-28 days</td>
<td>IST</td>
<td>Decreased mortality and morbidity 5%</td>
</tr>
<tr>
<td>2007</td>
<td>Clopidogrel 300 mg &gt;75 mg + ASA 81 mg, 90 days</td>
<td>CAST</td>
<td>Recur stroke: 7.1% vs 10.8%, ARR 3.7%, P&lt;0.01</td>
</tr>
<tr>
<td>2010</td>
<td>ASA 25&lt;mg (dipy 200) bid vs ASA 100, 7 days &gt;then both ASA 25&lt;mg (dipy 200) bid, 90 days</td>
<td>EARLY Lancet 2010</td>
<td>MRS0: 1% vs 5%, P=0.45</td>
</tr>
<tr>
<td>2011</td>
<td>Clopidogrel 300 mg + ASA 75 mg</td>
<td>CAST CO 2010</td>
<td>MRS0-2; 7% vs 7.5% (non-int/Trial, p=0.0004)</td>
</tr>
<tr>
<td>2013</td>
<td>Clopidogrel 300 mg + ASA 75 mg</td>
<td>CHANCE</td>
<td>Recur stroke: 8.2% vs 11.7%, p=0.001</td>
</tr>
<tr>
<td>2016</td>
<td>Ticagrelor 180 mg &gt;90 mg bid vs ASA 300 mg &gt; 100 mg, 90 days</td>
<td>SOCRATES</td>
<td>Stroke, MI, death 6.7% vs 7.5%, p=0.07</td>
</tr>
</tbody>
</table>

**Antiplatelet in Stroke**

- **Cilostazol**
  - Inhibit PDE -> increase local adenosine -> increase cAMP -> inhibit platelet aggregation
  - Onset of action 4 hrs.
  - H.l. 11-13 hrs, steady state d 4.
  - Reversible antiplatelet function at 48 hrs. after last dose

- **Dipyridamole**
  - Inhibit PDE -> increase local adenosine -> increase cAMP -> inhibit platelet aggregation
  - Average time to peak concentration: 75 min
  - H.l. approximate 10 hours

**CHANCE**

**Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack**

<table>
<thead>
<tr>
<th>Primary outcome: stroke/MI/death</th>
<th>SOCRALES</th>
<th>6.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute IS (NIHSS ≤ 5) or high-risk TIA (ABCD2 ≥ 4) or symptomatic intra/extracranial arterial stenosis within 24 hrs</td>
<td>Ticagrelor 180 mg -&gt; 90 mg bid, N=6589</td>
<td>7.5% + HR 0.89, 95%CI 0.78-1.01, p&lt;0.07</td>
</tr>
<tr>
<td>ASA 300 mg -&gt; 100 mg, N=6610</td>
<td>F/U 90 days</td>
<td>Ischemic stroke: 5.8% (T) vs 6.7% (A), HR 0.87, 95%CI 0.76-1.00</td>
</tr>
<tr>
<td>Major bleeding: 0.5% (T) vs 0.6% (A), ICH: 0.2% (T) vs 0.3% (A)</td>
<td>Johnston SC, et al. N Engl J Med 2016; 375: 35-43.</td>
<td></td>
</tr>
</tbody>
</table>

**CHANCE**

- Primary outcome: any new stroke
- 8.2%
Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT)

- Minor stroke
- NIHSS<3 or TIA (ABCD2=4, within 12 h)
- N=5840

Clopidogrel 600 mg then 75mg/d-89+Aspirin 50-325mg

Follow up 90 days

Estimated Study Completion Date Dec 2018

Anticoagulant Drugs in Acute Ischemic Stroke

- Reasons for use
  - To halt neurological worsening
  - To prevent early recurrent embolization
  - To improve neurological outcomes
  - Anticoagulants often were prescribed to prevent early recurrent cardioembolic stroke
  - Risk of early recurrent embolization was 12% among untreated pts with embolic stroke
  - IST-3; UFH within 48 hrs
  - Although heparin lowered the risk of early recurrent stroke, an increased bleeding rate negated this benefit.
  - Did not find a benefit from heparin in lowering the risk of recurrent stroke among those with AF

Current RECOMMENDATION: ACUTE ISCHEMIC STROKE

- Evidence-based
- ASA √
- Cilostazol √
- ASA+Clopidogrel √

 ASA/AHA recommendations:
- ASA 325mg within 24-48hrs (I, A) (Stroke 2013;44:870-947.)
- Combination of ASA and Clopidogrel might be considered for initiation within 24 hours of a minor stroke or TIA and for continuation for 90 days (llb, B) (Stroke 2014;45:2160-2236.)

- Thai Stroke Society recommendations (2016)
- ASA 325 mg within 48 hrs.
- ใบกินยาไม่สามารถใช้ aspirin ได้ จึงพิจารณาใช้ cilostazol 200 mg/d

Antithrombotic Drugs in Acute Ischemic Stroke

- Acute ischemic stroke
  - *Thrombolytic
  - *Antiplatelet
  - *ASA,
  - *ASA+Clopidogrel
  - *Cilostazol
  - *Anticoagulant?

Anticoagulant Drugs in Acute Ischemic Stroke

- Low-molecular-weight heparins (LMWHs) or danaparoid in AIS
  - Early increased hemorrhage risk found in most early LMWH trials, outweighing the early prevention benefits.
  - 10-day, 2 doses of nadroparin
  - Dalteparin: more effective than ASA in preventing recurrent events, but more bleeding
  - Certoparin, tinzaparin: no differences in the rate of favorable outcomes
  - IV danaparoid in pts with NIHSS>15; increased risk of SICH, not lessen risk of recurrent stroke or neurological worsening or improve outcomes at 3 months
  - Meta-analysis of trials that tested ASA or LMWHs: LMWHs significantly reduced the risk of VTE, but increased the risk of symptomatic bleeding.

Antithrombotic Drugs in Stroke

Prevention of recurrent Ischemic stroke/TIA

- *Antiplatelet agents - Monotherapy*
  - **Aspirin**
  - **Clopidogrel** • CAPRIE (aspirin 325 mg vs clopidogrel 75 mg)
  - **Cilostazol** • CSPS (cilostazol 100 mg bid vs placebo)
  - **Dipyridamole** • ESPS 2 (dipyridamole 400 mg/d vs aspirin 50 mg/d vs [combination] vs placebo)
  - **Triflusal** • TACIP (triflusal 600mg/d vs ASA 325 mg/d): non-sig. diff. in composite endpoint, IS, lower risk of bleeding

**Antiplatelet**
- ASA
- Clopidogrel
- Dipyridamole+ASA
- Cilostazol
- Terutroban

**References**

CATS 1989
TASS 1989
AAASPS 2003
CAPRIE 1996
CSPS 2000
CSPS 2008
TOSS 2005
MATCH 2006
CHARISMA 2006
CARESS 2005
CSPS2 2010
ESPS 1996
ESPRIT 2006
PROFESS 2008

**A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) Primary outcome is ischaemic stroke, MI, vascular death 5.32%**

- **Atherosclerotic vascular diseases**
- **Cilostazol** 75 mg
  - 5.83%
  - RRR 8.7% 95%CI (0.3-16.5)

Aspirin 325 mg
Mean F/U 1.91 years
Patients selection
Informed consent
Examination & Test
Judgment of Patients’ condition
Initiation & randomization

Study Period
Treatment Period (1~5 year)
12w
12w
24w
Cilostazol
100mg bid (N=1337)
Aspirin
81 mg (N=1335)

Regular Check-up
Completion of Study & Adverse event
Completion of Treatment

Study Design
(CSPS 2)
A multi-center, double-blind, parallel-group, randomized, prospective comparative study
2,757 non-cardioembolic stroke patients from 278

European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke
H.C. Diener, L. Casu, C. Forbes, J. Sivenias, P. Stents, A. Lowenthal

Prior stroke/TIA
6602 pts.
Aspirin 50 mg/d
Dipyridamole 400 mg/d
Primary outcome: risk of stroke/death

Follow up 2 years

(CSPS 2)

Relative risk reduction (%)

Aspirin + Clopidogrel
MATCH (aspirin75mg+clopidogrel 75mg vs clopidogrel 75 mg)
CHARISMA (aspirin75-162mg+clopidogrel 75mg vs aspirin75-162mg)

Cilostazol + Aspirin
TOS (aspirin 100 mg/d+cilostazol 200 mg/d vs aspirin 100 mg/d)

Dipyridamole + Aspirin
ESPS 2 (dipyridamole 400 mg/d vs aspirin 50 mg/d vs combination vs placebo)
ESPRIT (aspirin 30-325 mg/d vs aspirin 30-325 mg/d + dipyridamole 400 mg/d)
PROFESS (dipyridamole 400 mg/d +aspirin 50 mg/d vs clopidogrel 75 mg/d)

RRR 23%
RRR 20%

Aspirin 50 mg/d
Dipyridamole 400 mg/d
Placebo

Pairwise comparisons:
ER-DP + ASA vs. placebo
ER-DP vs. placebo
ASA vs. placebo
ER-DP + ASA vs. ASA

ESPS 2: effects on stroke – relative risk reduction
ER-DP + ASA is significantly more effective than ASA or ER-DP alone

Diener et al. (Stroke 1996;143(1-2): 1-13)
Antithrombotic Drugs in Stroke

**Prevention of recurrent Ischemic stroke/TIA**

*Antiplatelet*
*ASA*
*Clopidogrel*
*Dipyridamole+ASA*
*Cilostazol*
*Terutroban*

Choose by Stroke Subtypes?

---

**Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial**

*The ESPRIT Study Group*.

**Aspirin 30-325 mg**

TIA, minor stroke of presumed arterial origin within 6 months

N =1363

Aspirin 30-325 mg

Primary outcome: Composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding

RRR 16%

Complications

Mean follow up 3.5 years

*Antioxidant Agent*  
*Vitamin E*  
*Vitamin C*  
*Folic acid*  
*Polyunsaturated fatty acids (PUFA)*

---

**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**


Aspirin 75 mg

Recent ischemic stroke, TIA + >1 vascular RF

7599 pts.

Primary endpoints:

16% Composite of ischemic stroke, MI, vascular death,
rehospitalization from acute ischemia

Follow up 18 months

Life threatening bleeding 3%vs1%, p<0.00

RRR 6.4%

p=0.244
**Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke**

**Primary outcome:** any recurrent stroke

**Clopidogrel 75 mg**

+ Aspirin 325 mg

- Aspirin 325 mg

Median follow up 3.4 yrs

Major hemorrhage 2.1% vs 1.1% per yr, p<0.001

**Recent symptomatic lacune, mrs <3**

**N=3020**

**SPS3**

**Antplatelet: Secondary prevention of non–CST stroke/TIA**

**Recommendations**

<table>
<thead>
<tr>
<th>ESO</th>
<th>AHA 2014</th>
<th>THAI 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, A</td>
<td>I, A</td>
<td>++</td>
</tr>
</tbody>
</table>

**Patients should receive antithrombotic**

**Initial therapy:** ASA 50-325 mg/d

**Combination ASA25mg+ERDP**

**Clopidogrel 75 mg od**

**Triflusal**

**Cilostazol**

**Allergic to ASA**

**Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)**

**Primary outcome:** Stroke and Death within 30 d

**5.8%**

**N=451**

**PTAS + medical**

**F/U 90 days**

**LAA (ICS)**

**Acute IS (non-disabling) or TIA with 70-99% intracranial stenosis within 30 days**

**Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)**

**Primary outcome:** Stroke and Death within 30 d

**5.8%**

**N=451**

**PTAS + medical**

**F/U 90 days**


**Subanalysis of CSPS2 study**

**Ischemic stroke**

**Cilostazol**

**Aspirin**

**Hemorrhagic stroke**

**Aspirin Resistance: Definition, Prevalence**

- ‘Aspirin resistance’ has been defined as inability of aspirin to protect individuals from thrombotic complications or to produce an anticipated effect on one or more in vitro tests of platelet function.

- ‘Aspirin non-responders’ or ‘low response’ or ‘high residual platelet reactivity’, have been used.

- Prevalence of aspirin non-responders is 5.5-45% in patients with various cardiovascular diseases.

**Aspirin ‘resistance’ and risk of cardiovascular morbidity: systematic review and meta-analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exclusion criteria</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al. 2015</td>
<td>N=44</td>
<td>No coronary artery disease</td>
<td>Stroke and death within 30 days</td>
<td>Cardiovascular events</td>
<td>1.1 (0.7-1.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Cattaneo et al. 2004</td>
<td>N=100</td>
<td>No history of stroke</td>
<td>Stroke and death within 30 days</td>
<td>Cardiovascular events</td>
<td>1.2 (0.8-1.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Nouri et al. 2007</td>
<td>N=100</td>
<td>No history of stroke</td>
<td>Stroke and death within 30 days</td>
<td>Cardiovascular events</td>
<td>1.3 (0.8-2.1)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

**BMJ 2008;:6-9**
Aspirin Resistance: Mechanisms

- Non-atherothrombotic causes of vascular events
- Reduced bioavailability of aspirin
  - Inadequate intake of aspirin (poor compliance)
  - Inadequate dose of aspirin
  - Concurrent intake of certain NSAIDs
- Alternative pathways of platelet activation
- Increased turnover of platelets
- Genetic polymorphisms

Aspirin nonresponders: patients with ischaemic stroke
Pompatr A. Dharmasaroja\textsuperscript{a}, Sombat Muengtaweepongsa\textsuperscript{a} and Suvarnaporn Sae-Lin\textsuperscript{b}

Aspirin nonresponders:
- *less favourable outcome*
  (54 vs. 83\%, OR 0.24; 95\% CI 0.11–0.51, \(P<0.001\))
- *marginally higher CV events*
  (11 vs. 2\%, OR 4.48; 95\% CI 0.92–21.37, \(P=0.045\))
- *higher mortality*
  (12 vs. 1\%, OR 10.52; 95\% CI 1.3–85.28, \(P=0.0007\))

Aspirin nonresponders in patients with ischaemic stroke
Pompatr A. Dharmasaroja\textsuperscript{a}, Sombat Muengtaweepongsa\textsuperscript{a} and Suvarnaporn Sae-Lin\textsuperscript{b}

*21 patients, who were aspirin nonresponders from the first urine samples, had another urine test, which showed persistent aspirin nonresponse in eight patients (8/21, 38%).*
*Suggestive of increased platelet activity during the acute phase of atherothrombosis, and the normal daily dose of aspirin might not be adequate to completely suppress the platelet activity.
Stroke Recurrence while taking ASA: What should we do?

- The outcomes of
  - Continue ASA
  - Switch to another antiplatelet
  - Add another antiplatelet
  - Adjust antiplatelet following the results of antiplatelet function?
  - Recommendation?

Stroke Recurrence while taking ASA: What should we do?

Primary outcome:
- Death, MI, stroke, urgent revascularization

Different Antiplatelet Strategies in Patients With New Ischemic Stroke While Taking Aspirin

AIS, non CE, within 48hr+ on ASA within 7d of stroke onset

N=1172

Maintain ASA N=212 (18.1%) 14.5%
Switching to nonASA N=246(21%) 7.4% HR 0.5 (0.27–0.92; P=0.03)
Add another antipit N=714(60.9%) 6.7% HR 0.4 (0.24–0.66; P=0.001)
Follow up 1 years


Primary outcome:
- Death, MI, stent thrombosis, stroke, urgent revascularization

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Primary outcome:
- Death, MI, stent thrombosis, stroke, urgent revascularization

N=2440 pts scheduled for coronary stenting

Modifying doses of antiplatelet

VerifyNow P2Y12, ASA

*34.5% clopi nonresponder
*7.6% ASA nonresponder

Median dose of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure

Major bleeding did not differ significantly.

Stroke Recurrence while taking ASA: What should we do?

- The outcomes of
  - Continue ASA
  - Switch to another antplatelet
  - Add another antplatelet
  - Adjust antplatelet following the results of antplatelet function?
- Recommendation?
- AHA 2014:
  - For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin.
**Efficacy**

Rivaroxaban

AF

IIa

mg

Class,

Apixaban (I, A)

= warfarin

mg

risk for hemorrhagic

Major bleeding

Major bleeding

VKA (IA)

ml/min: 15

Should initiate OAC

attack despite

warfarin

150

<

CrCl <15 ml/min

adding

> warfarin

B

Recommendation

Edoxaban*

(I, A),

to ASA

IIa

mg bid > warfarin

Apixaban

< warfarin

CrCl <15 ml/min

≥

ASA

Rivaroxaban

= warfarin

1

CrCl  <30 ml/min

AF

within 14 d

P et al.. Heart J  2016

kg: 2.5

to delay OAC beyond 14d

mg bid < warfarin

150 mg bid

Safety

Rivaroxaban

ml/dl,

of an antithrombotic agent

mg

Conversion

High

AF

Unable to take OAC

Nonvalvular

(paroxysmal/permanent)

Nonvalvular

Stroke/

Atrial fibrillation : American Stroke Association 2014

Stroke/ TiA with

Recommendation

Class, LOE

Nonvalvular AF (paroxysmal/permanent) VKA (I,A), apixaban (I,A), dabigatran (I,B) I, A

Nonvalvular AF Rivaroxaban Ila, B

Unable to take OAC ASA Or adding clopidogrel to ASA Iib, B

The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.

**Secondary Stroke Prevention**

**Recommendations**

<table>
<thead>
<tr>
<th>NOACs</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>DABIGATRAN</td>
<td>150 mg bid &gt; warfarin</td>
<td>Major bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICH Rivaroxaban &lt; warfarin</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>Rivaroxaban = warfarin (non-inferiority) Major bleeding</td>
<td>Rivaroxaban = warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban &lt; warfarin</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>Apixaban &gt; warfarin Major bleeding</td>
<td>Apixaban &lt; warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apixaban &lt; warfarin</td>
</tr>
</tbody>
</table>

**Double antiplatelet drugs (ASA+clopidogrel) may be benefit in high risk TiA (ABC2D score) or minor stroke (NIHSS<3)***

**Acute ischemic stroke patients should admit in stroke unit***

**Consider non-vitamin K antagonist anticoagulant in patients with AF and ischemic stroke with High risk of bleeding (HASBLED score >3)**

**Poor coated INR**

**Consider cardiac endarterectomy or angioplasty in carotid stenosis >70-95% 50-75% within 6 months (++) or within 2 weeks (+)**

**In case who had contraindication for surgery, treatment with antiplatelet and statin with control risk factor is reasonable.**

**Notes**

*High: red; moderate: orange; low: green; not available: blue. 
**Class: evidence and level of recommendation. 
***Not recommended for patients with high risk TiA (ABC2D score) or minor stroke (NIHSS<3).

**Patients with Chronic Kidney Disease**

**Dabigatran**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Adjusted (mg/d)</th>
<th>Dosage (mg/d)</th>
<th>VRA</th>
<th>Additional dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>150</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>110</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Apixaban**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Adjusted (mg/d)</th>
<th>Dosage (mg/d)</th>
<th>VRA</th>
<th>Additional dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rivaroxaban**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Adjusted (mg/d)</th>
<th>Dosage (mg/d)</th>
<th>VRA</th>
<th>Additional dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Estimated daily dose of dabigatran, apixaban and rivaroxaban in patients with chronic kidney disease.**
NOACs and intravenous thrombolysis

**ASA 2013**

- The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA (Class III, Level of Evidence C).

**EHRA 2016**

- Patients presenting with acute ischaemic stroke under (NOAC) therapy present an even greater clinical conundrum.
- Until there are reliable and sensitive rapid (point-of-care) tests for the individual NOAC, we would discourage the use of thrombolytics in situations with uncertainty about the anticoagulation status or when NOACs have been administered within the last 24–48 h. Mechanical recanalization of occluded vessels with stent retrievers may be considered as an alternative treatment option, although no prospectively collected data exist in patients under NOAC therapy.

---

**Conclusions**

- Increase RCT of potent antiplatelet in acute ischemic stroke, but still limit for short-term usage
  - ASA 325mg, ASA+Clopidogrel 3 weeks, or ticagrelol?
- Should provide antiplatelet medication in all IS, TIA patients with non-cardioembolic causes
  - ASA, clopidogrel, ticlopidine, ASA+ERDP, or cilostazol
- Should provide OAC in IS patients with AF
  - VKA, NOACs

---

### No increased risk of ICH with thrombolysis or intra-arterial treatment in patients on NOACS vs warfarin or no OAC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NOAC (n=78)</th>
<th>VKA (n=441)</th>
<th>No OAC (n=8938)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ICH, %</td>
<td>18.4</td>
<td>26.8</td>
<td>17.4</td>
</tr>
<tr>
<td>Symptomatic ICH, %</td>
<td>2.6</td>
<td>6.5</td>
<td>5.0</td>
</tr>
<tr>
<td>ECASS-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS</td>
<td>3.9</td>
<td>9.3</td>
<td>7.2</td>
</tr>
</tbody>
</table>

- No significant differences between groups after propensity-score matching

Treatment with a NOAC does not appear to increase bleeding complications with thrombolysis vs those seen in warfarin-treated or non-anticoagulated patients