NOAC trials for AF: A review

Chern-En Chiang, MD, PhD, FACC, FESC
General Clinical Research Center
Division of Cardiology
Taipei Veterans General Hospital
National Yang-Ming University
Taipei, Taiwan
Presenter Disclosures

- Research Grant: nothing to disclose
- Honorarium: has spoken at symposia sponsored by and served on scientific advisory boards for Astrazeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi-aventis, Servier, Tanabe, Takeda, TTY
- Stockholding: None
Outlines

- Role of aspirin in Asians
- Role of warfarin in Asians
- Role of NOACs in Asians
- Reversal agents
- Asian algorithm
1. ASA is not effective in cohort studies in Asia
Aspirin and warfarin in Chinese

- 9,727 AF patients in HK, mean age 77 y, FU 3.2 years

**CHADS\(_2\)**

**Aspirin**

- 18.7%

**Warfarin**

- 52.7%

**CHA\(_2\)DS\(_2\)-VASc**

**Aspirin**

- 18.7%

**Warfarin**

- 52.7%

2. ASA is not effective in RCT in Asia
Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With Atrial Fibrillation: Japan Atrial Fibrillation Stroke Trial

Hiroshi Sato, Kinji Ishikawa, Akira Kitabatake, Satoshi Ogawa, Yukio Maruyama, Yoshiyuki Yokota, Takaya Fukuyama, Yoshinori Doi, Seibu Mochizuki, Tohru Izumi, Noboru Takekoshi, Kiyoshi Yoshida, Katsuhiko Hiramori, Hideki Origasa, Shinichiro Uchiyama, Masayasu Matsumoto, Takenori Yamaguchi and Masatsugu Hori

JAST

Stroke 2006;37;447-451
Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With Atrial Fibrillation: Japan Atrial Fibrillation Stroke Trial

Hiroshi Sato, Kinji Ishikawa, Akira Kitabatake, Satoshi Ogawa, Yukio Maruyama, Yoshiyuki Yokota, Takaya Fukuyama, Yoshinori Doi, Seibu Mochizuki, Tohru Izumi, Noboru Takekoshi, Kiyoshi Yoshida, Katsuhiko Hiramori, Hideki Origasa, Shinichiro Uchiyama, Masayasu Matsumoto, Takenori Yamaguchi and Masatsugu Hori

<table>
<thead>
<tr>
<th>TABLE 2. Primary and Secondary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (n=426)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Primary end points</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Cardiogenic embolism</td>
</tr>
<tr>
<td>Thrombotic infarction</td>
</tr>
<tr>
<td>Lacunar infarction</td>
</tr>
<tr>
<td>TIA</td>
</tr>
<tr>
<td>Secondary end points</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
</tr>
<tr>
<td>Peripheral emboli</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
</tbody>
</table>
3. ASA is worse than NOACs
AVERROES Trial

ASA
(81-324 mg daily; up to 36 mo/end of study)

Apixaban
(5 mg twice daily; 2.5 mg in selected patients; up to 36 mo/end of study)

Unsuitable for warfarin therapy
N=5600

Double-blind

**AVERROES: Stroke or Systemic Embolic Event**

- **Cumulative Risk**
  - Cumulative Risk graph showing the risk over time for ASA and Apixaban.
  - Cumulative Risk values are presented for each month from 0 to 21.

- **RR=0.45**
  - Risk ratio for Apixaban compared to ASA, with a 95% CI of 0.32-0.62.
  - Significant at P<.001.

- **No. at Risk**
  - Table showing the number of patients at risk for each month:
    - ASA: 2791, 2720, 2541, 2124, 1541, 626, 329
    - Apixaban: 2809, 2761, 2567, 2127, 1523, 617, 353

- **Apixaban is not FDA approved.**

- **AVERROES: Stroke or Systemic Embolic Event**
  - Stroke or Systemic Embolic Event data from Connolly S, N Engl J Med 2011;364:806

- **Connolly S, N Engl J Med 2011;364:806**

**Graph Details:**
- **ASA** line starts lower and remains below the **Apixaban** line throughout the months, indicating a lower cumulative risk.
- **Apixaban** starts higher but crosses over **ASA** around 18 months, showing a decrease in cumulative risk.
- **-55%** signifies a 55% reduction in risk for Apixaban compared to ASA.
Fewer hemorrhagic stroke and ICH in Apixaban group

Annual incidence of ICH
Real Life data from Hong Kong

Chi-Wai HO, ...Chung-Wah Siu, Stroke, 2015 Jan;46(1):23-30
Outlines

• Role of aspirin in Asians
• Role of warfarin in Asians
• Role of NOACs in Asians
• Reversal agents
• Asian algorithm
1. It is very difficult for Asians to maintain optimal INR (2.0-3.0)
# Global Atrial Fibrillation Registry

## INR Control by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean TTR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>50.9</td>
</tr>
<tr>
<td>South America</td>
<td>46.8</td>
</tr>
<tr>
<td>Western Europe</td>
<td>62.4</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>56.0</td>
</tr>
<tr>
<td>India</td>
<td>33.7</td>
</tr>
<tr>
<td>China</td>
<td>35.5</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>36.0</td>
</tr>
<tr>
<td>Middle East</td>
<td>42.2</td>
</tr>
<tr>
<td>Africa</td>
<td>32.7</td>
</tr>
</tbody>
</table>

2. A lower INR, which is common in Asia, could not protect your patients from Stroke!
Low INR is not protective from stroke

Adjusted Odds ratio

INR

* P<0.05

3. In Asians, even a lower INR could not protect you from bleeding!
Major bleeding (Warfarin)

More bleeding occurs even at lower INR range

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Intra-cranial hemorrhage (Warfarin)
More bleeding occurs even at lower INR range

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
4. In Asians, even a high TTR could not protect you from hemorrhagic stroke!
Time in Therapeutic Range for Warfarin-treated Patients

INR 1.6─2.6 ≥70 years

% Time in therapeutic range (median)

- INR 2.0─3.0
- INR 1.8─3.2
- INR 2.0─3.0 <70 years/

INR 1.6─2.6 ≥70 years

East Asian
n = 629

67.1

82.6

Non-East Asian
n = 6268

68.6

83.1

Japan
n = 336

72.3

87.1

75.9

Yukihiro Koretsune, JCS2014
5. Intra-cranial hemorrhage (ICH) is more catastrophic in Asians!
Warfarin associated intracerebral hemorrhage in Hong Kong Chinese

- The mean INR on presentation was $2.9 \pm 1.0$
- The mortality rate at 3-6 months for WICH was 62.0%
Outlines

• Role of aspirin in Asians
• Role of warfarin in Asians
• Role of NOACs in Asians
• Reversal agents
• Asian algorithm
Non-vitamin K antagonist Oral Anti-Coagulants (NOACs)

Dabigatran\textsuperscript{a}
- RE-LY
- Reported September 2009

Apixaban\textsuperscript{c}
- ARISTOTLE
- Reported September 2011

Rivaroxaban\textsuperscript{b}
- ROCKET-AF
- Reported November 2010

Edoxaban\textsuperscript{d}
- ENGAGE
- Report November 2013

---

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials


- 4 trials
- N= 71,683 patients

Global
• 5 trials
  – Asians = 8,928 patients
  – Non-Asians = 64,033 patients

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Standard doses

- Dabigatran 150 mg
- Rivaroxaban 20 mg
- Apixaban 5 mg
- Edoxaban 60 mg
Stroke and systemic embolism

Global

-19%

P<0.0001

Lancet. 2014;383:955
Stroke and systemic embolism

<table>
<thead>
<tr>
<th></th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asian</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>25/933</td>
<td>53/926</td>
<td>0.45 (0.28-0.74)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>21/468</td>
<td>27/464</td>
<td>0.76 (0.42-1.37)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>44/988</td>
<td>60/1005</td>
<td>0.73 (0.49-1.09)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>34/646</td>
<td>47/644</td>
<td>0.71 (0.45-1.11)</td>
</tr>
<tr>
<td><strong>Non-Asian</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>109/5143</td>
<td>149/5096</td>
<td>0.72 (0.56-0.92)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>248/6813</td>
<td>279/6626</td>
<td>0.89 (0.74-1.06)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>168/8132</td>
<td>205/8076</td>
<td>0.81 (0.66-1.00)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>262/6389</td>
<td>290/6392</td>
<td>0.90 (0.76-1.07)</td>
</tr>
<tr>
<td><strong>Overall Effect</strong></td>
<td></td>
<td></td>
<td>0.65 (0.52-0.83)</td>
</tr>
</tbody>
</table>

Interaction P=0.045

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
All-cause mortality

Global

-10%

P=0.0003

Lancet. 2014;383:955
All-cause mortality

interaction P=0.219

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Major bleeding

Global

-14%

P=0.06

Lancet. 2014;383:955
Major bleeding

<table>
<thead>
<tr>
<th></th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asian</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>39/933</td>
<td>66/926</td>
<td>0.57 (0.38-0.85)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>23/466</td>
<td>35/462</td>
<td>0.63 (0.37-1.09)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>33/981</td>
<td>63/1002</td>
<td>0.52 (0.34-0.80)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>42/642</td>
<td>68/641</td>
<td>0.59 (0.39-0.88)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>Q= 0.4 (P= 0.949)</td>
<td>F= 0.00%</td>
<td>0.57 (0.44-0.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-Asian</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>360/5143</td>
<td>355/5096</td>
<td>1.01 (0.86-1.17)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>372/6645</td>
<td>351/6663</td>
<td>1.07 (0.92-1.24)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>294/8107</td>
<td>399/8050</td>
<td>0.72 (0.62-0.84)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>376/6370</td>
<td>456/6371</td>
<td>0.81 (0.71-0.94)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>Q= 16.7 (P= 0.001)</td>
<td>F= 82.1%</td>
<td>0.89 (0.76-1.04)</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td>P= 0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Hemorrhagic stroke

Global

-51%

P<0.0001
Hemorrhagic stroke

Interaction $P=0.046$

Asian

<table>
<thead>
<tr>
<th>Study</th>
<th>Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 150mg</td>
<td>3/933</td>
<td>0.23 (0.06-0.80)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>4/468</td>
<td>0.39 (0.12-1.26)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>6/988</td>
<td>0.25 (0.10-0.61)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>8/646</td>
<td>0.41 (0.18-0.95)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>-68%</td>
<td></td>
</tr>
</tbody>
</table>

Non-Asian

<table>
<thead>
<tr>
<th>Study</th>
<th>Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 150mg</td>
<td>9/5143</td>
<td>0.28 (0.13-0.58)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>29/6613</td>
<td>0.62 (0.39-0.98)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>34/8132</td>
<td>0.62 (0.41-0.96)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>41/6389</td>
<td>0.58 (0.39-0.85)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>-44%</td>
<td></td>
</tr>
</tbody>
</table>

Interaction $P=0.046$

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Gastrointestinal bleeding

Global

+25%

P=0.043
Gastrointestinal bleeding

Asian

<table>
<thead>
<tr>
<th></th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 150mg</td>
<td>17/933</td>
<td>24/926</td>
<td>0.70 (0.37-1.31)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>15/642</td>
<td>16/641</td>
<td>0.93 (0.46-1.91)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>Q= 0.4 (P= 0.546)</td>
<td></td>
<td>0.79 (0.48-1.32)</td>
</tr>
<tr>
<td></td>
<td>ρ= 0.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-Asian

<table>
<thead>
<tr>
<th></th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 150mg</td>
<td>170/5143</td>
<td>101/5096</td>
<td>1.69 (1.32-2.17)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>217/6370</td>
<td>174/6371</td>
<td>1.26 (1.03-1.54)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td>Q= 3.3 (P= 0.070)</td>
<td></td>
<td>1.44 (1.12-1.85)</td>
</tr>
<tr>
<td></td>
<td>ρ= 69.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interaction P=0.041

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Low doses

• Dabigatran 110 mg
• Rivaroxaban 15 mg (J-ROCKET)
• Edoxaban 30 mg
Global

-67%

-69%
Ischemic stroke

Global

$P = 0.046$

$+28\%$

Ruff, Lancet. 2014;383:955
Ischemic stroke

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Myocardial infarction

Global

P = 0.019

+25%
Myocardial infarction

Asian

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 110mg</td>
<td>9/923</td>
<td>10/926</td>
<td>0.90 (0.36-2.23)</td>
</tr>
<tr>
<td>J-ROCKET AF</td>
<td>3/637</td>
<td>1/637</td>
<td>3.01 (0.31-29.01)</td>
</tr>
<tr>
<td>ENGAGE AF, 30mg</td>
<td>6/653</td>
<td>8/644</td>
<td>0.74 (0.25-2.14)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.92 (0.48-1.79)</td>
</tr>
<tr>
<td>Q= 1.2 (P= 0.544)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$ = 0.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interaction $P=0.352$

Non-Asian

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 110mg</td>
<td>89/5092</td>
<td>65/5096</td>
<td>1.38 (1.00-1.90)</td>
</tr>
<tr>
<td>ENGAGE AF, 30mg</td>
<td>163/6381</td>
<td>133/6392</td>
<td>1.23 (0.98-1.56)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>1.28 (1.06-1.55)</td>
</tr>
<tr>
<td>Q= 0.3 (P= 0.587)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$ = 0.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interaction $P=0.352$

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
NOACs in Asia

• Standard dose
  ◆ Efficacy:
  ◆ NOACs>>>Warfarin
  ◆ Safety:
  ◆ NOACs>>>warfarin

• Low dose
  ◆ Efficacy:
  ◆ NOACs=Warfarin
  ◆ Safety:
  ◆ NOACs>>>warfarin

Wang, Lip, Lin, and Chiang, Stroke. 2015 Sep;46(9):2555-61
Stroke and SEE in **Asian** vs **non-Asian** in 4 RCTs

V

Dabigatran 150mg b.d.
- **Asian**
- **Non-Asian**

Dabigatran 110mg b.d.
- **Asian**
- **Non-Asian**

Rivaroxaban 20mg o.d.
- **Asian**
- **Non-Asian**

Apixaban 5mg b.d.
- **Asian**
- **Non-Asian**

Edoxaban 60mg o.d.
- **Asian**
- **Non-Asian**

Edoxaban 30mg o.d.
- **Asian**
- **Non-Asian**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Asian</th>
<th>Non-Asian</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150mg</td>
<td>0.45 (0.28-0.72)</td>
<td>0.72 (0.56-0.92)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110mg</td>
<td>0.81 (0.54-1.21)</td>
<td>0.93 (0.74-1.17)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20mg</td>
<td>0.78 (0.44-1.39)</td>
<td>0.89 (0.75-1.05)</td>
<td></td>
</tr>
<tr>
<td>Apixaban 5mg</td>
<td>0.74 (0.50-1.10)</td>
<td>0.81 (0.66-0.99)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60mg</td>
<td>0.71 (0.46-1.10)</td>
<td>0.88 (0.75-1.05)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30mg</td>
<td>1.08 (0.73-1.61)</td>
<td>1.14 (0.97-1.61)</td>
<td></td>
</tr>
</tbody>
</table>

**NOACs better**  **Warfarin better**

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Ischemic stroke in Asian vs non-Asian in 4 RCTs

- Dabigatran 150mg b.d.
  - Asian: 0.55 (0.32-0.95)
  - Non-Asian: 0.82 (0.61-1.10)
- Dabigatran 110mg b.d.
  - Asian: 1.01 (0.63-1.61)
  - Non-Asian: 1.17 (0.89-1.53)
- Rivaroxaban 20mg o.d.
  - Asian: 0.94
  - Non-Asian: 0.94 (0.75-1.17)
- Apixaban 5mg b.d.
  - Asian: 1.17 (0.74-1.85)
  - Non-Asian: 0.86 (0.68-1.10)
- Edoxaban 60mg o.d.
  - Asian: 0.64 (0.28-1.46)
  - Non-Asian: 1.01 (0.83-1.22)
- Edoxaban 30mg o.d.
  - Asian: 1.77 (0.93-3.36)
  - Non-Asian: 1.38 (1.15-1.64)

NOACs better    Warfarin better

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Hemorrhagic stroke in **Asian** vs **non-Asian** in 4 RCTs

- **Dabigatran 150mg b.d.**
  - Asian: 0.22 (0.06-0.77)
  - Non-Asian: 0.28 (0.13-0.58)
- **Dabigatran 110mg b.d.**
  - Asian: 0.15 (0.03-0.66)
  - Non-Asian: 0.37 (0.19-0.72)
- **Rivaroxaban 20mg o.d.**
  - Asian: 0.40 (0.13-1.27)
  - Non-Asian: 0.59 (0.37-0.93)
- **Apixaban 5mg b.d.**
  - Asian: 0.25 (0.10-0.62)
  - Non-Asian: 0.62 (0.41-0.96)
- **Edoxaban 60mg o.d.**
  - Asian: 0.40 (0.18-0.92)
  - Non-Asian: 0.57 (0.39-0.84)
- **Edoxaban 30mg o.d.**
  - Asian: 0.36 (0.15-0.86)
  - Non-Asian: 0.32 (0.20-0.51)

**NOACs better**  **Warfarin better**

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Efficacy and safety endpoints of different NOACs in **Asians**

<table>
<thead>
<tr>
<th></th>
<th>Stroke/SSE</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>Myocardial infarction</th>
<th>All-cause death</th>
<th>Major bleeding</th>
<th>Intra-cranial hemorrhage</th>
<th>GI bleeding</th>
<th>Bleeding of any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Dabigatran 110 mg</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V</td>
<td>NR</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Apixaban</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>NR</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Edoxaban 60 mg</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Edoxaban 30 mg</td>
<td>V</td>
<td></td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
</tbody>
</table>

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Efficacy and safety endpoints of different NOACs in non-Asians

<table>
<thead>
<tr>
<th></th>
<th>Stroke/SSE</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
<th>Myocardial infarction</th>
<th>All-cause death</th>
<th>Major bleeding</th>
<th>Intra-cranial hemorrhage</th>
<th>GI bleeding</th>
<th>Bleeding of any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110 mg</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td></td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60 mg</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30 mg</td>
<td>X</td>
<td>V</td>
<td></td>
<td></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td></td>
</tr>
</tbody>
</table>

Real-life data of dabigatran in Asia: Taiwan experience

• Dabigatran (n=9940) and warfarin (n=9913) non-valvular atrial fibrillation patients
• 88% taking dabigatran 110 mg
Ischemic stroke

Logrank $P < 0.0001$

-38%

Acute myocardial infarction

Logrank $P = 0.1445$
-56%
Low dose dabigatran (110 mg)

<table>
<thead>
<tr>
<th></th>
<th>Ischemic stroke</th>
<th>All-cause mortality</th>
<th>Major bleeding</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global RE-LY</td>
<td>11%</td>
<td>9%</td>
<td>20%</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian meta-analysis</td>
<td>3%</td>
<td>43%</td>
<td>43%</td>
<td>79%</td>
</tr>
<tr>
<td>Wang</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Chan</td>
<td>71%</td>
<td></td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td>Taiwan NHIRD Chan</td>
<td>38%</td>
<td>55%</td>
<td>42%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Outlines

- Role of aspirin in Asians
- Role of warfarin in Asians
- Role of NOACs in Asians
- Reversal agents
- Asian algorithm
Non-valvular AF

CHA$_2$DS$_2$-VASc score

0 (male) or 1 (female) i.e. ‘low risk’

No antithrombotic therapy

1 (male)

NOACs Dabigatran Apixaban

≥ 2

NOACs Dabigatran Edoxaban Apixaban Rivaroxaban

Lip GYH, Wang KL, Chiang CE. Int J Cardiol 2015 Feb 1;180C:246
Summary (I)

- Aspirin has no role in stroke prevention in AF in Asians
- Warfarin should only be spared for those in whom NOAC is contraindicated
- In our meta-analysis, standard-dose NOACs were more effective and safer in Asians than in non-Asians. The increased risk of GI bleeding was not found in Asians.
- Low-dose NOACs performed similarly in efficacy in both populations, but the safety was much better than warfarin in both populations. Increased risk of myocardial infarction was not found in Asians.
- All NOACs are preferable over warfarin
- NOACs is now revolutionizing SPAF in Asians
Thank you