새 항응고제를 1차 선택 약으로 먼저 사용하면 안 된다

아주 의대
황교승
Treatment of Atrial Fibrillation (AF)

- Rate control
- Rhythm control
- Stroke prevention

Stroke prevention with safe and effective antithrombotic therapy is a critical goal in the AF population
## Risk of Stroke in AF Stratified by CHADS2 Score*

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>No. of Patients (n = 1733)</th>
<th>No. of Strokes (n = 94)</th>
<th>NRAF Crude Stroke Rate per 100 Patient-Years</th>
<th>NRAF Adjusted Stroke Rate, (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>3.6</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>6.4</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.0</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>7.7</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>44.0</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

*CHADS2 score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.

†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

Gage, B. F. et al. JAMA 2001;285:2864-2870
HAS-BLED bleeding risk score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points

Eur Heart J. 2010;31:2369-2429
Stroke Prevention With Warfarin

• reduces the stroke risk by 64%

• increases the risk of all major bleeding by 69%

• warfarin is hampered by
  - slow onset of action
  - narrow therapeutic range
  - requirement for regular monitoring
  - drug and food interactions
  - pharmacogenetic variability
  - risk of hemorrhage

Stroke Prevention With Warfarin

The good, The bad, and The ugly

Risk reduction: 44-81%

F/36, AF, Rheumatic mitral valve
INR: 1.9-3.0

M/69, AF, mitral stenosis
INR: 2.9

Stroke Prevention With Warfarin
Vitamin-K Antagonists (VKA)

Dicumarol

Warfarin

In 1940

Sweet clover

In 1954
The Coagulation Cascade

**Diagram:***

- **IXa**
- **VIIa**
- **VIIIa**
- **Xa**
- **TF**
- **Va**
- **II**
- **IIa**
- **fibrinogen**
- **fibrin**

**Note:**
- **warfarin**
Disadvantage of VKA

- **Dietary restrictions** regarding the amount of vitamin-K–containing foods

- Significant **interactions** with numerous **medications**

- **Narrow therapeutic window**, with a poorly predictable dosing range

- The **delayed onset and delayed reversal** of VKA-induced anticoagulation
Dabigatran vs Warfarin in Patients with AF: the RE-LY trial

Rivaroxaban vs Warfarin in Nonvalvular AF (ROCKET AF)

The Coagulation Cascade

**Rivaroxaban**

**Dabigatran**

**Fibrinogen** → **Fibrin**
New Oral Anticoagulants (OACs) Currently Available or in Development for Prevention of Stroke in AF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Relevant Clinical Trial/Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibitor</td>
<td>ARISTOTLE, AVERROES$^{26,28}$</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>ROCKET-AF$^{24}$</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>ENGAGE-AF$^{27}$</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Direct factor Xa inhibitor</td>
<td>EXPLORE-Xa$^{25}$</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>RE-LY$^{22,23}$</td>
</tr>
</tbody>
</table>
Both doses of dabigatran (In RE-LY)

• Associated with significantly higher rates of dyspepsia and a trend toward increased rates of myocardial infarction

• Higher 2-year discontinuation rates of both doses of dabigatran (21%) compared with warfarin (17%)

New OACs vs VKA

• Dabigatran has a 12- to 17-hour half-life, lapses of dabigatran therapy could be more problematic than lapses of warfarin

• Lack of an effective antidote

• The lack of a reliable serum test (either to assess for treatment failure or on compliance or to titrate the intensity of therapy)

• Bottled medication must be used within 60 days of opening

Thromb Haemost. 2010;103(6):1116-1127
Safety Considerations

For patients with chronic kidney disease

• The lower dabigatran dose of 75 mg was FDA approved for CrCl between 15 and 30 mL/min despite never being tested in a randomized fashion

• Testing renal function prior to starting therapy and annually thereafter in patients 75 years of age or older or patients with CrCl <50 mL/min.

Safety Considerations

There is no reported data for new OACs

- patients with mechanical prosthetic heart valves

- coronary stent implantation requiring dual antiplatelet therapy

- during pregnancy
Drug Interactions

• Dabigatran is a substrate of the efflux transporter P-glycoprotein [P-gp] inhibitors

• **Rifampin** (P-gp inducers) and dabigatran should not be used in combination

  Thromb Haemost. 2010;103(6):1116-1127

• In RE-LY, amiodarone and verapamil (inhibitors of P-gp) : no specific increase in bleeding in patients taking these P-gp inhibitors and concurrent dabigatran compared with concurrent warfarin

  EuroIntervention. 2010;6(2):220-226
Drug Interactions

• Dronedarone: increase the serum concentration of dabigatran (about 1.7- to 2.0-fold) suggesting a dose of 75 mg bid when dronedarone and dabigatran are prescribed together in patients with moderately reduced renal function.

• Concomitant use of P-gp inhibitors in patients with severe renal dysfunction (CrCl 15-30 mL/min) is contraindicated.

Cost-Effectiveness for AF Population

In USA
warfarine: $1 for 1 day’s generic dose
dabigatran: $9 per day at the 150 mg bid dosing

Circulation. 2011;123(22):2562-2570

In Korea
warfarin 2 mg: 39원
warfarin 5 mg: 82원
dabigatran: 6000원/day
rivaroxaban: ?
Cost-Effectiveness for AF Population

Considering

- the added cost of serum coagulation testing

- any saved costs and productivity from loss of work
  avoided strokes
  avoided bleeds
  hospitalizations saved
Representation of the Decision Model (Markov Model)

Shah S V, Gage B F Circulation 2011;123:2562-2570
Two-way Sensitivity Analysis of Stroke and Hemorrhage Risk With Cost Effectiveness

Base-case scenario

TTR < 57.1%

TTR > 72.6%

Shah S V, Gage B F Circulation 2011;123:2562-2570
Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in AF

• For patients already taking warfarin who have excellent INR control, dabigatran 150 mg (twice daily) was not cost-effective.

• The benefits of dabigatran outweigh costs in AF patients at moderate to high risk of stroke and/or hemorrhage unless their INR control with warfarin therapy would be excellent.
Elective Cardioversions of AF

• Pretreatment with warfarin for at least 3 weeks at target range INR followed by cardioversion or early cardioversion guided by transesophageal echocardiogram to exclude left atrial thrombus

• Anticoagulation is then continued for at least 4 weeks following the cardioversion

Elective Cardioversions of AF

RE-LY substudy in which close to 2000 cardioversions in 1270 patients: D110, D150, and warfarin

- The rates of stroke and systemic thromboembolism (SSE) at 30 days were similar (0.8%, 0.3%, and 0.6%, respectively), as were the rates of major bleeding events (1.7%, 0.6%, and 0.6%, respectively).

- However, retrospective study, no randomized data

Peri-AF Ablation Anticoagulation to Prevent Thromboembolic Events

• In patients undergoing AF ablation, periprocedural dabigatran use significantly increases the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.


• Dabigatran did not cause bleeding complications and there were no thromboembolic events. Dabigatran appears to be an alternative to warfarin after AF ablation

Questions?

- Are new OACs as effective as warfarin, when administered as long-term therapy beyond the initial 6 to 12 months?

- How will the risk-to-benefit profile change when new OACs are administered in a more heterogeneous patient population (e.g., renal insufficiency, obesity, pediatric patients)?

- What are the roles of new OACs in patients with AF and concomitant malignancy of using long-term dabigatran or rivaroxaban?

- When these newer agents are more widely used, will they have rare but severe side effects?
RE-LY Trial Exclusion Criteria

- Severe valvular disorder
- Stroke in last 14 days, or severe stroke in last 6 months
- Conditions that increase risk of hemorrhage
- Active liver disease
- Pregnancy
- Creatinine clearance less than 30 mL per minute
Conclusions

• Warfarin is still considered a first line agent for the prevention of stroke and systemic thromboembolism in AF

• In the case of variable control on warfarin, the New OACs can be considered especially with patient preference, high stroke and hemorrhage risk
New OACs
Warfarin