8th Annual Scientific Session of Korean Heart Rhythm Society Luncheon Symposium 1

Stroke Prevention of the Patients with Atrial Fibrillation – New Options for Anticoagulant Therapy –

Wataru Shimizu

Professor and Chairman
Department of Cardiovascular Medicine
Nippon Medical School
KHRS 2016

COI Disclosure

Name of First Author : Wataru Shimizu

①Consultation fees: none
②stock ownership/profit: none
③patent fees: none
④remuneration for lecture: Daiichi Sankyo., Ltd.
Tanabe Mitsubishi Pharma Corporation
Nippon Boehringer Ingelheim Co., Ltd.
Bayer Yakuhin, Ltd.
Bristol-Myers K.K.
Pfizer Japan Inc.
Ono Pharma Corporation

⑤manuscript fees: none
⑥trust research/joint research funds: none
⑦scholarship fund: Daiichi Sankyo., Ltd.
Tanabe Mitsubishi Pharma Corporation
Nippon Boehringer Ingelheim Co., Ltd.
Bristol-Myers K.K.

⑧Affiliation with Endowed Department: none
⑨Other remuneration such as gifts: none
Increase of Patients with Atrial Fibrillation (AF) in Japan

- AF becomes more prevalent by age.
- AF patients are expected to increase up to 1 million in near future.


Method: Based on the age group-specific prevalence of AF, the future number of patients with AF was estimated with reference to the changes of the general population.

Ohsawa M, et al.: J Epidemiology 15; 194, 2005
Individual NOAC is recommended based on the evidence demonstrated in phase III study.

If antithrombotic therapy is indicated, novel oral anticoagulants are preferable to warfarin for patients with the same level of risk.

*1: Vascular disease includes a history of myocardial infarction, aortic plaque, and peripheral artery disease.
*2: Prosthetic valve includes mechanical and biological valves.
*3: Not approved for the national health insurance scheme as of December 2013.

Guidelines for Diagnosis and Treatment of Cardiovascular Disease (2012 Report of the Joint Working Group)
Guidelines for Pharmacotherapy of Atrial Fibrillation (2013 revised version)
FUSHIMI AF REGISTRY - Control level of PT-INR

Distribution of PT-INR level in the age groups

Target INR

Circ J 2014 Aug 25;78(9):2166-72
Warfarin
J-RHYTHM & FUSHIMI AF Registry

- Appropriate use (CHADS\textsubscript{2} score, etc.)
  Warfarin is not appropriately prescribed for individual patient who needs the therapy.

- Target INR for Japanese patients
  \begin{itemize}
  \item <70 years old: INR = 2.0 – 3.0
  \item \geq 70 years old: INR = 1.6 – 2.6
  \end{itemize}

Warfarin underdose is a common issue, especially in patients aged under 70 years.
Issues with Warfarin Therapy

- Warfarin therapy is difficult to manage due to multiple different restrictions, but more serious side effect, intracranial hemorrhage limits use of warfarin.

- Narrow therapeutic range (INR: 2-3)
- Restricted intake of vitamin K-containing foods
- Routine coagulation monitoring required
- Interactions with many drugs
- Slow onset and offset
- Drug resistance

Novel Oral Anticoagulant (NOAC)

Coagulation cascade

Initiation

TF-VIIa → VII

Propagation

X → IX

VIIa → IXa

Va → Xa

II → Prothrombin

Fibrin formation

Thrombin → Fibrin

Fibrinogen

Anticoagulation

Vitamin K antagonist

Warfarin

FXa inhibitor

Rivaroxaban

Apixaban

Edoxaban

Direct thrombin inhibitor

Dabigatran

Selection of Novel Oral Anticoagulant (NOAC)
Pharmacological Profile of Various Anticoagulants

- T1/2 for each NOAC are almost the same around 12 ho, however, dosing regimen is different by product, once daily for ribaroxaban and edoxaban or twice daily for dabigatran and apixaban.
- Renal excretion rate and protein binding rate are different from one to another.

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>tmax (hr)</td>
<td>3-9</td>
<td>0.5-2</td>
<td>0.5-4</td>
<td>1-4</td>
<td>1-2</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>36</td>
<td>12-14</td>
<td>9-13</td>
<td>8-15</td>
<td>10-14</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Daily dosage</td>
<td>Individualized with large variation</td>
<td>150 mg × 2</td>
<td>15 mg</td>
<td>5 mg × 2</td>
<td>60 mg or 30 mg</td>
</tr>
<tr>
<td>Reduced daily dosage</td>
<td>110 mg × 2</td>
<td>10 mg</td>
<td>2.5 mg × 2</td>
<td>30 mg or 15 mg</td>
<td></td>
</tr>
<tr>
<td>Metabolism via CYP R-form: 1A2, 2C19, 3A4</td>
<td>Not involved</td>
<td>3A4, 2J2</td>
<td>3A4</td>
<td>Virtually not involved (&lt;4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S-form: 2C9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal excretion rate</td>
<td>0%</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Protein binding rate</td>
<td>99%</td>
<td>35%</td>
<td>92-95%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>6.5%</td>
<td>80-100%</td>
<td>49%</td>
<td>62%</td>
</tr>
</tbody>
</table>
### Precautions for Use of NOAC

- Dose reduction criteria for each NOAC takes into account different patient-related factors.
- Contraindications according to renal function is different between Dabigatran and FXa inhibitors.

<table>
<thead>
<tr>
<th>Criteria for dose reduction</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Ccr ≤ 50 mL/min</strong></td>
<td>• Ccr ≤ 50 mL/min</td>
<td>• Age ≥ 80 years</td>
<td>• Weight ≤ 60 kg</td>
<td>• Ccr ≤ 50 mL/min</td>
</tr>
<tr>
<td><strong>• Age ≥ 70 years</strong></td>
<td>• History of GI hemorrhage</td>
<td>• Serum Cr ≥ 1.5 mg/dL</td>
<td>• Concomitant use of oral p-glycoprotein inhibitors (quinidine, verapamil, erythromycin, cyclosporine)</td>
<td>• Concomitant use of oral p-glycoprotein inhibitors</td>
</tr>
<tr>
<td><strong>• History of GI hemorrhage</strong></td>
<td>• Concomitant use of oral p-glycoprotein inhibitors</td>
<td>• Reduce the standard dose if the patient meets at least two of the above criteria.</td>
<td>• Reduce the standard dose if the patient meets any of the above criteria.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Con med that may require dose reduction</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Oral p-glycoprotein inhibitors</strong></td>
<td>• Fluconazole</td>
<td>• Erythromycin, clarithromycin</td>
<td>• HIV protease inhibitors</td>
<td>• Oral p-glycoprotein inhibitors</td>
</tr>
<tr>
<td><strong>• Contraindications</strong></td>
<td>• Ccr &lt; 30 mL/min</td>
<td>• Ccr &lt; 15 mL/min</td>
<td>• Ccr &lt; 15 mL/min</td>
<td>• Ccr &lt; 15 mL/min</td>
</tr>
<tr>
<td><strong>• Liver disease with coagulation disorder</strong></td>
<td>• Liver disease corresponding to Child-Pugh B or C</td>
<td>• Liver disease with abnormal coagulation and/or bleeding risk</td>
<td>• Liver disease with abnormal coagulation</td>
<td>• Liver disease with abnormal coagulation</td>
</tr>
<tr>
<td><strong>• Liver disease</strong></td>
<td>• Itraconazole</td>
<td>• HIV protease inhibitors</td>
<td>• Azole antifungals except fluconazole</td>
<td>• Acute bacterial endocarditis</td>
</tr>
<tr>
<td><strong>• Itraconazole</strong></td>
<td>• None</td>
<td>• None</td>
<td>• None</td>
<td></td>
</tr>
</tbody>
</table>

Ccr = creatinine clearance, Cr = creatinine, HIV = human immunodeficiency virus
Selection of appropriate NOAC

- Severity of underlying risk factors, such as patient’s age, body weight, and renal function needs to be considered when making a decision on the most appropriate NOAC to use.
Consideration for choosing NOAC
(Strength: ○, Weakness: ×)

**Dabigatran**
- ○ Useful for patients with mild underlying risk factors (age <75 years, normal to mild renal impairment [CCr ≥50 mL/min]).
- × Moderate or severe renal impairment, gastrointestinal symptoms.

**Rivaroxaban**
- ○ Evidence of efficacy is available for patients with a CHADS$_2$ score ≥2. Once-daily dosing.
- × No superiority vs. warfarin. Limited evidence of efficacy at low doses.

**Apixaban**
- ○ Useful for patients with moderate to severe underlying risk factors (age ≥65 years, mild to severe renal impairment [CCr <80 mL/min]).
- × Limited evidence of efficacy at low doses.
Effective anticoagulation with factor xA next GEneration In Atrial Fibrillation – Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48)
[Study population]
A total of 21,105 subjects (including 1,010 Japanese subjects) confirmed to have non-valvular atrial fibrillation (NVAF) by electrocardiography within 12 months before enrollment and had a CHADS<sub>2</sub> score ≥2 points, indicated for anticoagulant therapy.

Randomization

- **Edoxaban**
  - 60 mg once-daily (dose reduced to 30 mg if applicable*)
  - n=7,035

- **Edoxaban**
  - 30 mg once-daily (dose reduced to 15 mg if applicable*)
  - n=7,034

- **Warfarin**
  - (PT-INR 2.0–3.0)
  - n=7,036

Follow-up period: 2.8 years (median)

* Dose reduction criteria (applicable when at least one of the following conditions was satisfied)
  - CCr = 30–50 mL/min
  - Body weight ≤60 kg
  - Concomitant use of p-glycoprotein inhibitors (e.g., verapamil, quinidine)

Study design
- Randomized, double-blind, double-dummy, event-driven study

Primary efficacy endpoint
- Incidence of stroke or systemic embolic events

Primary safety endpoint
- Incidence of major bleeding

NDA dossier
Phase II Study: Safety of Four Fixed Doses of Edoxaban in AF Patients (Non-Japanese Patients)

Incidence of major bleeding or clinically relevant non-major bleeding

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Warfarin</th>
<th>Edoxaban 30 mg once daily</th>
<th>Edoxaban 60 mg once daily</th>
<th>Edoxaban 30 mg twice daily</th>
<th>Edoxaban 60 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>8/250</td>
<td>7/235</td>
<td>9/234</td>
<td>19/244</td>
<td>19/180</td>
</tr>
</tbody>
</table>

Follow-up period: 12 weeks
*p<0.05, **P<0.01 vs. warfarin, Fisher’s exact test

Cohort: 1,146 patients with NVAF or risk of stroke.
Methods: Subjects were randomized to 5 groups: edoxaban 30 mg once-daily group, edoxaban 30 mg twice-daily group, edoxaban 60 mg once-daily group, edoxaban 60 mg twice-daily group, or warfarin group (target PT-INR: 2.0-3.0). Follow-up was performed for 12 weeks.
Dosing Regimen and Adherence to Treatment

- Systematic review of 76 reports on adherence assessed with an electronic monitoring system.

### Daily dosing frequency

- **Once daily (od)**: 79%
- **Twice daily (bid)**: 69%
- **Three times daily (tid)**: 65%
- **Four times daily (qid)**: 51%

### Mean adherence rate

Methods: 76 reports based on electronic monitoring of adherence were extracted from studies reported between 1986 and 2000 by searching MEDLINE, psychInfo, HealthStar, Health&Psychosocial Instruments, and the Cochrane Library. Then data on adherence from these reports were compiled by dosing regimen.

p=0.008 (od vs. tid), p<0.001 (od vs. qid), p=0.001 (bid vs. qid)

Mean ± SD

Which Feature of Medication is Linked with Good Adherence/Ease of Use?

- Once daily dosing
- No concern about side effects (risk of bleeding)
- No concern about side effects (GI disorders)
- Less frequent visits to hospital
- No concern about interactions with other drugs
- No restriction on foods (such as fermented soybeans Natto, green and yellow vegetables, etc.)
- Easy to swallow
- More effective than prior prophylaxis
- Less frequent collection of blood samples
- Less care needed when family members prepare meals
- Nothing particular
- Other features

Kenko Nippon 21 (Healthy Japan 21) Forum
Cumulative Incidence of Stroke or Systemic Embolic Events (Primary Efficacy Endpoint; ITT Analysis)

Edoxaban was non-inferior to the well-controlled warfarin in the prevention of stroke or systemic embolic events

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS₂ score ≥ 2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: C_{CR} = 30-50 mL/min, body weight ≤ 60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier
Cumulative Incidence of Major Bleeding (Primary Safety Endpoint)

Incidence of major bleeding was significantly lower in both 60mg, 30mg Edoxaban group compared to that in the well-controlled warfarin group.

No. at Risk
- Edoxaban 60-mg group: 7,012
- Edoxaban 30-mg group: 7,002
- Warfarin group: 7,012

TTR (median) = 68.4%

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: CCR = 30-50 mL/min, body weight ≤ 60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS² score ≥ 2, indicated for anticoagulant therapy.

Efficacy and Safety of the Patient Groups W/ or W/O Clinical Features for Dose Reduction

Dose reduced edoxaban preserved its relative efficacy to warfarin, and tended to prove even greater safety compared to warfarin.

### Stroke or Systemic Embolic Events

<table>
<thead>
<tr>
<th></th>
<th>No Edoxaban Dose Reduction</th>
<th>Edoxaban Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg</td>
<td>1.00</td>
<td>1.29</td>
</tr>
<tr>
<td>WF</td>
<td>1.79</td>
<td>2.21</td>
</tr>
<tr>
<td>Reduced to 30 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Major Bleeding

<table>
<thead>
<tr>
<th></th>
<th>No Edoxaban Dose Reduction</th>
<th>Edoxaban Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg</td>
<td>2.66</td>
<td>3.02</td>
</tr>
<tr>
<td>Reduced to 30 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WF</td>
<td>4.85</td>
<td></td>
</tr>
</tbody>
</table>

*Patients satisfying dose reduction criteria: The dose was reduced to 30 mg in the edoxaban 60-mg group.

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS\textsubscript{2} score \(\geq 2\), indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) \(n=7,012\), an edoxaban 60 mg once-daily group \(n=7,012\), and an edoxaban 30 mg once-daily group \(n=7,002\). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: \(C_{\text{CR}} = 30-50 \text{ mL/min}\), body weight \(\leq 80 \text{ kg}\), concomitant treatment with a \(P\)-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.
Annual Incidence of Major Bleeding Stratified by Renal Function

Compared with warfarin, edoxaban showed consistent reduction of major bleeding across different renal function groups.

- **Edoxaban group:** 60 mg (dose reduced to 30 mg if applicable)
- **Warfarin group**

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Annual incidence of major bleeding (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{CR} \geq 30 - \leq 50</td>
<td>3.91 \text{ (n=1,302 I n=1,305) }</td>
</tr>
<tr>
<td>C\text{CR} &gt;50 - &lt;80</td>
<td>3.20 \text{ (n=3,007 I n=3,048) }</td>
</tr>
<tr>
<td>C\text{CR} \geq 80</td>
<td>1.77 \text{ (n=2,633 I n=2,608) }</td>
</tr>
</tbody>
</table>

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS\textsubscript{2} score \geq 2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0 (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: C\text{CR} = 30-50 mL/min, body weight \leq 60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier (Summary of Clinical Safety)
Annual Incidence of Major Bleeding
Stratified by Body Weight

Compared with warfarin, edoxaban showed consistent reduction of major bleeding regardless of body weight.

- **Edoxaban group:** 60 mg (dose reduced to 30 mg if applicable)
- **Warfarin group**

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS\textsubscript{2} score $\geq 2$, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: $C_{\text{Cr}} = 30-50$ mL/min, body weight $\leq 60$ kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier (Summary of Clinical Safety)
Compared with warfarin, edoxaban showed consistent reduction of major bleeding regardless of age.

**Cohort:** 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS\(_2\) score ≥2, indicated for anticoagulant therapy.

**Methods:** Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: \(C_{\text{cr}} = 30-50\) mL/min, body weight ≤60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

**NDA dossier (Summary of Clinical Safety):**

Compared with warfarin, edoxaban showed consistent reduction of major bleeding regardless of age.
ENGAGE AF-TIMI 48
East Asian Sub-analysis
## Demographics and Baseline Clinical Characteristics in East Asian Sub-analysis

<table>
<thead>
<tr>
<th></th>
<th>East Asian (n = 1,943)</th>
<th>Non-East Asian (n = 19,162)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>70.1 ± 8.7</td>
<td>70.7 ± 9.5</td>
<td>0.0085</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>545 (28.0)</td>
<td>7495 (39.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>67.0 ± 12.6</td>
<td>85.6 ± 20.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation, n (%)</td>
<td>373 (19.2)</td>
<td>4993 (26.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score, mean ± SD</td>
<td>2.9 ± 1.0</td>
<td>2.8 ± 1.0</td>
<td>0.17</td>
</tr>
<tr>
<td>≤3, n (%)</td>
<td>1487 (76.5)</td>
<td>14850 (77.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>4–6, n (%)</td>
<td>456 (23.5)</td>
<td>4312 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction at randomization, n (%)</td>
<td>912 (46.9)</td>
<td>4444 (23.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CrCl ≤50 mL/min, n (%)</td>
<td>583 (30.0)</td>
<td>3491 (18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight ≤60 kg, n (%)</td>
<td>594 (30.6)</td>
<td>1489 (7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of verapamil or quinidine, n (%)</td>
<td>128 (6.6)</td>
<td>633 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous use of VKA for ≥60 days, n (%)</td>
<td>1153 (59.3)</td>
<td>11288 (58.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Medication at time of randomization, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>543 (27.9)</td>
<td>5637 (29.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>60 (3.1)</td>
<td>427 (2.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>85 (4.4)</td>
<td>2407 (12.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Digoxin or digitalis preparation</td>
<td>576 (29.6)</td>
<td>5751 (30.0)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

CHADS<sub>2</sub> = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, prior Stroke or transient ischemic attack; CrCl = creatinine clearance; SD = standard deviation; VKA = vitamin K antagonist.
Primary Efficacy Endpoint
(East Asian Sub-analysis, mITT Population, On-treatment)

Higher dose of Edoxaban 60mg group showed significantly lower rates in the incidence of stroke/systemic embolic events compared to warfarin group.

- **Edoxaban 60-mg group (1.34%, HR = 0.53, 95% CI 0.31–0.90), P = 0.02**
- **Edoxaban 30-mg group (2.52%, HR = 0.98, 95% CI 0.63–1.54), P = 0.93**
- **Warfarin (2.62%)**

![Graph showing the incidence of stroke/systemic embolic events over years for different groups](image-url)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Warfarin 641</th>
<th>615</th>
<th>604</th>
<th>590</th>
<th>580</th>
<th>439</th>
<th>251</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60-mg group</td>
<td>642</td>
<td>633</td>
<td>623</td>
<td>612</td>
<td>597</td>
<td>464</td>
<td>263</td>
<td>53</td>
</tr>
<tr>
<td>Edoxaban 30-mg group</td>
<td>652</td>
<td>635</td>
<td>617</td>
<td>605</td>
<td>594</td>
<td>449</td>
<td>254</td>
<td>46</td>
</tr>
</tbody>
</table>

Primary Safety Endpoint
(East Asian Sub-analysis)

Both edoxaban 60mg and 30mg groups led to significant reductions in major bleeding compared to warfarin group.

- Warfarin (4.80%)
- Edoxaban 60-mg group (2.86%, HR = 0.61, 95% CI 0.41─0.89), \( P = 0.011 \)
- Edoxaban 30-mg group (1.59%, HR = 0.34, 95% CI 0.21─0.54), \( P < 0.001 \)

ENGAGE AF-TIMI 48
Elderly Sub-analysis
Proportion of Dose Reduction by Age (Elderly Sub-analysis)

- <65 years (n=5,497) - 10%
- 65-74 years (n=7,134) - 18%
- ≥75 years (n=8,474) - 41%

Dose reduction criteria (applicable when at least one of the following conditions was satisfied):
- CCr = 30–50 mL/min
- Body weight ≤60 kg
- Concomitant use of p-glycoprotein inhibitors (e.g., verapamil, quinidine)

Efficacy and Safety Outcomes Comparing Edoxaban With Warfarin by Age (Elderly Sub-analysis)

<table>
<thead>
<tr>
<th>Incidence Rate</th>
<th>&lt;65 years</th>
<th>65-74 years</th>
<th>≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or SEE  (Primary efficacy Endpoint) Interactive p = 0.84</td>
<td>1.1</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Ischemic Stroke Interactive p = 0.48</td>
<td>0.9</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Major Bleeding Interactive p = 0.78</td>
<td>1.5</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>ICH Interactive p = 0.11</td>
<td>4.8</td>
<td>4.0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

TTR median: (<65 years) 67.2%, (65-74 years) 68.4%, (≥75 years) 69.6%
Proportion of patients satisfying dose reduction criteria: (<65 years) 10%, (65-74 years) 18%, (≥75 years) 41%
Efficacy and Safety Outcomes in Patients aged ≥ 80 years and 85 years (Elderly Sub-analysis)

≥ 80 years old
(n = 3,591)
(% of dose reduced patients: 53%)

≥ 85 years old
(n = 899)
(% of dose reduced patients: 67%)

In both age sub-groups, Edoxaban preserved its relative efficacy and safety to warfarin regardless of age.

Efficacy and Safety Outcomes in Patients aged ≥ 80 years and 85 years (Elderly Sub-analysis)

Major Bleeding
Stroke or SEE (%/Year)

Incidence Rate

Edoxaban 60 mg group
Warfarin (median TTR: [≥ 80 years old] 69.5%, [≥ 85 years old] 68.4%)

HR: Hazard Ratio ( ):95% CI
Interpretation of the ENGAGE AF-TIMI 48 study

- Edoxaban shows comparable (non-inferior) efficacy to well-controlled warfarin with superior safety.

- Edoxaban is associated with less bleeding risk than warfarin irrespective of the severity of underlying risk factors (renal function, age, body weight, and concomitant antiplatelet therapy).

- Edoxaban has a consistent efficacy and safety profile even including dose reduced patient population.
Patients Receiving Edoxaban Therapy at the Department of Cardiovascular Medicine of Nippon Medical School (N=358) October 2014 – October 2015
Percentage of Patients Treated for Atrial Fibrillation (AF) Among 358 Patients at Nippon Medical School (October 2014 – October 2015)

Number of patients analyzed: 358

DVT / PE 302 (84%)
AF 56 (16%)

Edoxaban was the first approved drug for DVT/PE, but the 4th approved one for AF in Japan market.
### Clinical Profile of 56 AF Patients Treated with Edoxaban at Nippon Medical School (October 2014 – October 2015)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 56)</th>
<th>60 mg sid (n = 16)</th>
<th>30 mg sid (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 ± 10</td>
<td>67 ± 12</td>
<td>74 ± 9</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>≥75 yr, n</td>
<td>28 (50%)</td>
<td>5 (31%)</td>
<td>23 (58%)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥80 yr, n</td>
<td>17 (30%)</td>
<td>3 (19%)</td>
<td>14 (35%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Women, n</strong></td>
<td>20 (36%)</td>
<td>1 (6%)</td>
<td>19 (48%)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>64 ± 17</td>
<td>79 ± 16</td>
<td>58 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;50 kg, n *</td>
<td>9 (16%)</td>
<td>0</td>
<td>9 (23%)</td>
<td>0.052</td>
</tr>
<tr>
<td>&lt;60 kg, n *</td>
<td>26 (46%)</td>
<td>0</td>
<td>26 (65%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sustained atrial fibrillation/flutter, n</strong></td>
<td>25 (45%)</td>
<td>7 (44%)</td>
<td>18 (45%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>CHADS2 score</strong></td>
<td>1.8 ± 1.5</td>
<td>1.6 ± 1.5</td>
<td>1.9 ± 1.6</td>
<td>0.51</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>15 (27%)</td>
<td>3 (19%)</td>
<td>12 (30%)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>CHA2DS2–VASc score</strong></td>
<td>3.2 ± 1.9</td>
<td>2.4 ± 1.8</td>
<td>3.5 ± 1.9</td>
<td>0.07</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>31 (55%)</td>
<td>7 (44%)</td>
<td>24 (60%)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Body weight was missing for 1 patient (1.8%).
### Clinical Profile of 56 AF Patients Treated with Edoxaban at Nippon Medical School (October 2014 – October 2015)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 56)</th>
<th>60 mg sid (n = 17)</th>
<th>30 mg sid (n = 39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke/TIA, n</td>
<td>8 (14%)</td>
<td>2 (13%)</td>
<td>6 (15%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.93 ± 0.25</td>
<td>0.98 ± 0.26</td>
<td>0.91 ± 0.25</td>
<td>0.37</td>
</tr>
<tr>
<td>≥1.5 mg/dL, n</td>
<td>3 (5%)</td>
<td>2 (13%)</td>
<td>1 (3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>65 ± 27</td>
<td>85 ± 26</td>
<td>58 ± 23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤50 ml/min, n *</td>
<td>15 (27%)</td>
<td>1 (7%)</td>
<td>14 (35%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Patient satisfying dose reduction criteria, n</td>
<td>28 (50%)</td>
<td>1 (6%)</td>
<td>27 (68%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior anticoagulant therapy, n</td>
<td>29 (52%)</td>
<td>101 (42%)</td>
<td>78 (52%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Concomitant antiplatelet therapy, n</td>
<td>3 (5%)</td>
<td>0</td>
<td>3 (8%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Concomitant dual antiplatelet therapy, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Body weight was missing for 1 patient (1.8%).
Anticoagulants Used Before Edoxaban in 56 AF Patients at Nippon Medical School (October 2014 – October 2015)

- None: 27 (48%)
- Warfarin: 11 (20%)
- Dabigatran: 7 (13%)
- Rivaroxaban: 7 (13%)
- Apixaban: 4 (7%)

Number of patients analyzed: 56
CHADS\textsubscript{2} Scores of 56 AF Patients at Nippon Medical School (October 2014 – October 2015)

- CHADS\textsubscript{2} 0-1 point = 49%
- CHADS\textsubscript{2} 2 points = 25%
- CHADS\textsubscript{2} 3-6 points = 27%

Number of patients analyzed: 56
Dose Regimen of Edoxaban and Age Distribution of 56 AF Patients at Nippon Medical School (October 2014 – October 2015)

67 ± 12 vs. 74 ± 9
P = 0.03

Number of patients (n)

Age (yr)

60 mg sid (n = 16)
30 mg sid (n = 40)
Concurrent Diseases of 56 AF Patients at Nippon Medical School (October 2014 – October 2015)

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Major bleeding, n</th>
<th>Fatal outcome, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause bleeding events</td>
<td>2 (3.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous hemorrhage</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(with a suspected drug)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 (5.4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Follow-up period: 137±103 days
Incidence of Efficacy Endpoint Events in 56 AF Patients at Nippon Medical School (October 2014 – October 2015)

<table>
<thead>
<tr>
<th>Incident Type</th>
<th>No. of patients, n</th>
<th>Fatal outcome, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular embolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic embolic events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>

Follow-up period: 137±103 days

Nippon Medical School
Clinical Decision on Optimal NOACs Considering the Patient Profile

**Individual patient groups and characteristics**

- **Asian**
  - Consider agents with reduced risk of ICH and major haemorrhage in Asian populations

- **Elderly**
  - Consider comorbidities and agents with lower extracranial haemorrhage among elderly (age>75)

- **Renal impairment**
  - Consider agents with lower haemorrhagic complications in moderate-severe renal impairment

- **Previous GI bleeding**
  - Consider agents with no increased risk of GI haemorrhage

- **High bleeding risk (HAS-BLED ≥3)**
  - Consider agents with lower incidence of extracranial haemorrhage

- **Recurrent stroke despite well-managed VKA**
  - Consider agent with demonstrable benefit in reducing both ischaemic AND haemorrhagic stroke

- **Preference for low pill burden**
  - Consider once daily formulations

- **Patient less likely to do well on VKA (SAMeTT²R² score >2)**
  - Avoid ‘trial of warfarin’ and consider NOAC upfront when deciding on OAC in newly diagnosed patient

**NOACs with characteristics beneficial to target group**

- **Apixaban**
  - Dabigatran
  - Edoxaban

- **Apixaban**
  - Edoxaban

- **Apixaban**
  - Dabigatran
  - Edoxaban 110 mg

- **Apixaban**
  - Dabigatran
  - Edoxaban

- **Apixaban Dabigatran 110 mg**
  - Edoxaban

- **Dabigatran 150 mg**
  - Rivaroxaban

- **Edoxaban**
  - Any NOAC, but consider patient characteristics when choosing agent

Edoxaban could be an option for a wide range of patient groups based on its robust evidence in ENGAGE AF study.

**Individual patient groups and characteristics**

- **Asian**
  - Consider agents with reduced risk of ICH and major haemorrhage in Asian populations

- **Elderly**
  - Consider comorbidities and agents with lower extracranial haemorrhage amongst elderly (age >75)

- **Renal impairment**
  - Consider agents with lower haemorrhagic complications in moderate-severe renal impairment

- **Previous GI bleeding**
  - Consider agents with no increased risk of GI haemorrhage

- **High bleeding risk (HAS-BLED ≥3)**
  - Consider agents with lower incidence of extracranial haemorrhage

- **Recurrent stroke despite well-managed VKA**
  - Consider agent with demonstrable benefit in reducing both ischaemic AND haemorrhagic stroke

- **Preference for low pill burden**
  - Consider once daily formulations

- **Patient less likely to do well on VKA (SAMeTT2R2 score >2)**
  - Avoid ‘trial of warfarin’ and consider NOAC upfront when deciding on OAC in newly diagnosed patient

**NOACs with characteristics beneficial to target group**

- **Apixaban**
  - Dabigatran
  - Edoxaban

- **Apixaban**
  - Edoxaban

- **Apixaban**
  - Edoxaban

- **Apixaban**
  - Dabigatran 110 mg

- **Apixaban**
  - Dabigatran 150 mg

- **Rivaroxaban**
  - Edoxaban

Any NOAC, but consider patient characteristics when choosing agent

끝까지 경청해 주셔서 감사합니다.
Efficacy and Safety of the Patent Groups W/ or W/O Clinical Features for Dose Reduction

Stroke or systemic embolic events

<table>
<thead>
<tr>
<th></th>
<th>Annual incidence of stroke or systemic embolic events (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Edoxaban Dose Reduction</td>
<td></td>
</tr>
<tr>
<td>Edoxaban group: 60 mg (dose reduced to 30 mg if applicable)</td>
<td>1.00</td>
</tr>
<tr>
<td>Warfarin group</td>
<td>1.29</td>
</tr>
<tr>
<td>Edoxaban Dose Reduction</td>
<td></td>
</tr>
<tr>
<td>Reduced to 30 mg</td>
<td>1.79</td>
</tr>
<tr>
<td>WF</td>
<td>2.21</td>
</tr>
</tbody>
</table>

Major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Annual incidence of major bleeding (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Edoxaban Dose Reduction</td>
<td></td>
</tr>
<tr>
<td>Edoxaban group: 60 mg (dose reduced to 30 mg if applicable)</td>
<td>2.66</td>
</tr>
<tr>
<td>Warfarin group</td>
<td>3.02</td>
</tr>
<tr>
<td>Edoxaban Dose Reduction</td>
<td></td>
</tr>
<tr>
<td>Reduced to 30 mg</td>
<td>3.05</td>
</tr>
<tr>
<td>WF</td>
<td>4.85</td>
</tr>
</tbody>
</table>

*Patients satisfying dose reduction criteria: The dose was reduced to 30 mg in the edoxaban 60-mg group.

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS2 score >2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: C_Cr = 30-50 mL/min, body weight ≤60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.
**Annual Incidence of Major Bleeding Stratified by Renal Function**

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Edoxaban group: 60 mg (dose reduced to 30 mg if applicable)</th>
<th>Warfarin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;CR&lt;/sub&gt; ≥30 - ≤50</td>
<td>3.91</td>
<td>5.23</td>
</tr>
<tr>
<td>C&lt;sub&gt;CR&lt;/sub&gt; &gt;50 - &lt;80</td>
<td>3.20</td>
<td>3.55</td>
</tr>
<tr>
<td>C&lt;sub&gt;CR&lt;/sub&gt; ≥80</td>
<td>1.77</td>
<td>2.52</td>
</tr>
</tbody>
</table>

(n=1,302 | n=1,305)  (n=3,007 | n=3,048)  (n=2,633 | n=2,608)

Annual incidence of major bleeding (%/year)

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS<sub>2</sub> score ≥2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: C<sub>CR</sub> = 30-50 mL/min, body weight ≤60 kg, concomitant treatment with a P-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier (Summary of Clinical Safety)
Annual Incidence of Major Bleeding Stratified by Body Weight

Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS₂ score ≥2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: Cr = 30-50 mL/min, body weight ≤60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier (Summary of Clinical Safety)
Cohort: 21,026 patients who had AF confirmed within 12 months before enrollment and a CHADS\(_2\) score ≥2, indicated for anticoagulant therapy.

Methods: Subjects were randomized to 3 groups: a warfarin group (PT-INR: 2.0-3.0) (n=7,012), an edoxaban 60 mg once-daily group (n=7,012), and an edoxaban 30 mg once-daily group (n=7,002). They were followed for a median of 2.8 years. The dose of edoxaban was reduced by half if the subject had any of the following dose-limiting conditions at randomization: C\(_{\text{Cr}}\) = 30-50 mL/min, body weight ≤60 kg, concomitant treatment with a p-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). Dronedarone has not been approved in Japan.

NDA dossier (Summary of Clinical Safety)
Primary Efficacy Endpoint
(East Asian Sub-analysis, mITT Population, On-treatment)

Edoxaban 60-mg group (1.34%, HR = 0.53, 95% CI 0.31—0.90), P = 0.02
Edoxaban 30-mg group (2.52%, HR = 0.98, 95% CI 0.63—1.54), P = 0.93
Warfarin (2.62%)

Patients with stroke or systemic embolic event (%)

Number at Risk
- Warfarin 641
- Edoxaban 60-mg group 642
- Edoxaban 30-mg group 652

Years

Primary Safety Endpoint
(East Asian Sub-analysis)

Warfarin (4.80%)
Edoxaban 60-mg group (2.86%, HR = 0.61, 95% CI 0.41–0.89), P = 0.011
Edoxaban 30-mg group (1.59%, HR = 0.34, 95% CI 0.21–0.54), P < 0.001

Number at Risk
Warfarin 641 607 587 567 548 406 234 35
Edoxaban 60-mg group 642 621 610 599 576 448 250 50
Edoxaban 30-mg group 652 640 623 610 598 452 255 45

Primary Net Clinical Outcome* Comparing Edoxaban With Warfarin (Elderly Sub-analysis)

Absolute Risk Difference

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Warfarin (%/yr)</th>
<th>Edoxaban 60mg (%/yr) vs Warfarin</th>
<th>HR (95% CI)</th>
<th>p-int</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>4.9</td>
<td>4.8</td>
<td>0.99 (0.82 – 1.18)</td>
<td>0.48</td>
</tr>
<tr>
<td>65-74 years</td>
<td>7.3</td>
<td>6.4</td>
<td>0.87 (0.76 – 1.00)</td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>11.2</td>
<td>9.7</td>
<td>0.88 (0.79 – 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

*P <0.05 vs warfarin, ** Primary net clinical outcome: Stroke or SEE, major bleeding, all-cause mortality
CI = confidence interval; E60 = higher-dose edoxaban regimen (60/30 mg once-daily); HR = hazard ratio ; yr = year.