Relationship Between Edoxaban Dose, Concentration, Anti-Factor Xa Activity, and Outcomes in the ENGAGE AF-TIMI 48 Trial

Christian T. Ruff, MD, MPH
On behalf of the Executive Committee and Investigators

TIMI Study Group
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA
Disclosures

Research Support:
Daiichi-Sankyo, AstraZeneca, Bristol-Meyers Squibb, Sanofi-Aventis, Merck, Eisai, Intarcia

Consultant and Advisory Boards:
Boehringer Ingelheim, Daiichi-Sankyo, Bristol-Meyers Squibb, Alere, Beckman Coulter
Study Design

21,105 PATIENTS with AF and CHADS$_2$ ≥2

RANDOMIZATION

Low Dose Edoxaban
30* mg QD

High Dose Edoxaban
60* mg QD

Warfarin
(INR 2.0–3.0)

1º Efficacy Endpoint = Stroke or SEE
1º Safety Endpoint = Major Bleeding (ISTH criteria)

*Dose reduced by 50%:
- CrCl 30–50 mL/min
- Weight ≤ 60 kg
- Strong P-gp inhibitor

Cl = confidence interval; CrCl = creatinine clearance;
ISTH=International Society on Thrombosis and Haemostasis;
P-gp = P-glycoprotein; SEE=systemic embolic event
Primary Efficacy and Safety Results
(2.8 years median f/u)

Stroke/SEE: Noninferiority Analysis (mITT, On Treatment)

Hazard ratio (97.5% CI)

- **edoxaban noninferior**

**P Values**

- Non-inferiority: $P<0.0001$
- Superiority: $P=0.017$
- $P=0.005$
- $P=0.44$

**ISTH Major Bleeding: (Safety Cohort, On Treatment)**

- **edoxaban superior**
- **edoxaban inferior**

**Warfarin TTR 68.4%**

- **High Dose Edoxaban* vs. Warfarin**
- **Low Dose Edoxaban* vs. Warfarin**

* Dose reduced 50% in selected patients

Background

- Initial appeal of NOACs
  *Fixed dosing without the need for routine monitoring*

- Emerging concern:
  *Does optimizing risk / benefit of NOACs requires measuring drug concentration and / or anticoagulant activity?*

- Pharmacokinetic modeling and simulation from Phase I/II studies of edoxaban*:
  - *Identified clinical features that increased edoxaban exposure*
  - *Trough concentration closely correlated with bleeding*

Methods

- Trough plasma samples 1-mo. post randomization*:
  - Edoxaban Concentration (N=6,780)
    - Quintiles Bioanalytical and ADME Labs
  - Anti-Fxa Activity (N=2,865, Substudy)
    - Rotachrome Heparin Assay
    - Stago STAR Evolution Platform

- Correlated edoxaban dose, concentration, and anti-FXa activity.

- Compared efficacy and safety outcomes with warfarin stratified by dose reduction status.

* Samples excluded if value < lower limit of detection, handling errors, drawn outside protocol time window, endpoint occurred before sample drawn
**Mean Edoxaban Trough Concentration (N=6,780)**

- **High Dose Edoxaban**
  - No DR: 48.5 ± 45.8 ng/mL
  - DR: 34.6 ± 30.9 ng/mL

- **Low Dose Edoxaban**
  - No DR: 24.5 ± 22.7 ng/mL
  - DR: 16.0 ± 14.5 ng/mL

**Mean Trough Anti-FXa Activity (N=2,865)**

- **High Dose Edoxaban**
  - No DR: 0.85 ± 0.76 IU/mL
  - DR: 0.64 ± 0.54 IU/mL

- **Low Dose Edoxaban**
  - No DR: 0.44 ± 0.37 IU/mL
  - DR: 0.35 ± 0.28 IU/mL

DR = Dose Reduction
Correlation of Trough Edoxaban Concentration & Anti-FXa Activity

$r = 0.96 \quad P < 0.0001$

Trough Anti-FXa Activity [IU/mL] vs. Trough Edoxaban Concentration [ng/mL] for different regimens.
## Stroke or SEE (% / Year)

### High Dose Edoxaban vs. Warfarin
- **No Dose Reduction:** HR 0.78 (0.61 - 0.99)
- **Dose Reduction:** HR 0.81 (0.58 - 1.13)

$P_{interaction} = 0.85$

### Low Dose Edoxaban vs. Warfarin
- **No Dose Reduction:** HR 1.07 (0.86 - 1.34)
- **Dose Reduction:** HR 1.07 (0.79 - 1.46)

$P_{interaction} = 0.99$

---

**Edoxaban Dose Reduction**

<table>
<thead>
<tr>
<th>Edox Conc (ng/mL)</th>
<th>Edoxaban Dose Reduced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>HD Edox 30 mg</td>
</tr>
<tr>
<td>HD Edox 60 mg</td>
<td>34.6</td>
</tr>
<tr>
<td>LD Edox 30 mg</td>
<td>16.0</td>
</tr>
<tr>
<td>LD Edox 15 mg</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>0.35</td>
</tr>
</tbody>
</table>

**No Edoxaban Dose Reduction**

<table>
<thead>
<tr>
<th>Edox Conc (ng/mL)</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD Edox 60 mg</td>
<td>NA</td>
</tr>
<tr>
<td>LD Edox 30 mg</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>24.5</td>
</tr>
</tbody>
</table>

**Anti-Fxa (IU/mL)**

<table>
<thead>
<tr>
<th>Anti-Fxa (IU/mL)</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD Edox 60 mg</td>
<td>NA</td>
</tr>
<tr>
<td>LD Edox 30 mg</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>0.44</td>
</tr>
</tbody>
</table>

HD = High Dose
LD = Low Dose
Edox = Edoxaban
Major Bleed (% / Year)

High Dose Edoxaban vs. Warfarin
No Dose Reduction: HR 0.88 (0.76 - 1.03)
Dose Reduction: HR 0.63 (0.50 - 0.81)

\[ P_{\text{interaction}} = 0.02 \]

Low Dose Edoxaban vs. Warfarin
No Dose Reduction: HR 0.55 (0.46 - 0.65)
Dose Reduction: HR 0.31 (0.23 - 0.42)

\[ P_{\text{interaction}} = 0.002 \]

HD = High Dose
LD = Low Dose
Edox = Edoxaban
**ICH (% / Year)**

**High Dose Edoxaban vs. Warfarin**
- No Dose Reduction: HR 0.47 (0.32 - 0.68)
- Dose Reduction: HR 0.46 (0.27 - 0.78)

**Low Dose Edoxaban vs. Warfarin**
- No Dose Reduction: HR 0.40 (0.27 - 0.60)
- Dose Reduction: HR 0.11 (0.04 - 0.28)

P_{interaction} = 0.94

P_{interaction} = 0.01

**No Edoxaban Dose Reduction**
- Warfarin: 0.73
- HD Edox 60 mg: 0.34
- LD Edox 30 mg: 0.29

**Edoxaban Dose Reduced**
- Warfarin: 1.26
- HD Edox 30 mg: 0.57
- LD Edox 15 mg: 0.14

*HD = High Dose, LD = Low Dose, Edox = Edoxaban*
Edoxaban Trough Concentration & Outcomes

Major Bleed

Probability of Event Over 3 Years

Trough Edoxaban Concentration [ng/mL]
Edoxaban Trough Concentration & Outcomes

Probability of Event Over 3 Years

- Major Bleed
- Stroke or SEE

Trough Edoxaban Concentration [ng/mL]
Edoxaban Trough Concentration & Outcomes

- Probability of Event Over 3 Years
  - Major Bleed
  - Stroke or SEE
  - ICH

Trough Edoxaban Concentration [ng/mL]
Patients meeting clinical criteria for edoxaban dose reduction were at high risk*:

*Increase in stroke and bleeding events in warfarin patients (placebo edoxaban dose reduction)*

Dose reduction by 50% based on clinical features reduced mean edoxaban exposure 29-35% and anti-FXa activity 20-25% compared to the population who were not dose reduced.

Dose reduction of edoxaban compared with warfarin:

- Preserved relative efficacy
- Provided even greater safety

The therapeutic window (dose response curve) of edoxaban:

*Major Bleeding* - narrowest (steepest)
*Stroke or SEE* - wider (shallower)
*ICH* – widest (nearly flat)

* Dose reduced by 50%: CrCl 30–50 mL/min, weight ≤ 60 kg, Strong P-gp inhibitor
Conclusions

- Tailoring the dose based on clinical features alone: *Prevented excess edoxaban drug levels*

- Dose modification of edoxaban in ENGAGE AF-TIMI 48: *Helped optimize the balance between ischemic and bleeding events without measuring drug levels or anticoagulation activity*