Edoxaban versus Warfarin in Atrial Fibrillation Patients with Low, Mid and High Body Weight: Analysis of Outcomes in the ENGAGE AF TIMI 48 Trial

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*Disclosure: modest speaker’s fees from Boehringer, Boston, Medtronic.
**Background:** Impact of extremes of body weight on outcomes with NOACs in patients with AF has not been well-characterized.

**Aim:** To analyse the pharmacokinetic, pharmacodynamics, and outcomes of pts at the extremes of weight from a large RCT of pts with AF.

**Methods:** In ENGAGE AF-TIMI 48, 21,105 pts with CHADS$_2$ $\geq$2 were randomized to warfarin or edoxaban and followed for 2.8 years (median).

3 subgroups identified according to weight at baseline:
- Low body weight (0-5th percentile): $\leq$ 55 kg
- Middle body weight (45-55th percentile): 79.8-84 kg (reference)
- High body weight (95-100th percentile): $> 120$ kg

**NOTE:** Edoxaban dose was ↓50% if CrCl $< 50$ ml/min, body weight $< 60$ kg, or strong P-gp inhibitor used
### Baseline Characteristics by Weight Category

<table>
<thead>
<tr>
<th>Weight category</th>
<th>Low (0-5th percentile) &lt; 55 kg</th>
<th>Middle (45-55th percentile) 79.8-84 kg</th>
<th>High (95-100th percentile) &gt; 120 kg</th>
<th>Weight category</th>
<th>Low (0-5th percentile) &lt; 55 kg</th>
<th>Middle (45-55th percentile) 79.8-84 kg</th>
<th>High (95-100th percentile) &gt; 120 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts</td>
<td>1082</td>
<td>2153</td>
<td>1093</td>
<td>Number of pts</td>
<td>1082</td>
<td>2153</td>
<td>1093</td>
</tr>
<tr>
<td>Age (median)</td>
<td>76</td>
<td>73</td>
<td>62</td>
<td>Risk factors (%)</td>
<td>Age ≥75 yr</td>
<td>57</td>
<td>46</td>
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<tr>
<td>Women (%)</td>
<td>76</td>
<td>35</td>
<td>18</td>
<td>- Hx stroke /TIA</td>
<td>41</td>
<td>29</td>
<td>17</td>
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<tr>
<td>Region (%)</td>
<td></td>
<td></td>
<td></td>
<td>- CHF</td>
<td>53</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td>- N America</td>
<td>10</td>
<td>19</td>
<td>53</td>
<td>- Diabetes</td>
<td>19</td>
<td>35</td>
<td>62</td>
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<tr>
<td>- Asia/Pac/SAF</td>
<td>56</td>
<td>11</td>
<td>4</td>
<td>- HTN</td>
<td>83</td>
<td>95</td>
<td>97</td>
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<tr>
<td>- W Europe</td>
<td></td>
<td></td>
<td></td>
<td>CrCl &lt; 50 ml/min</td>
<td></td>
<td></td>
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<tr>
<td>- E Europe</td>
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<td></td>
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<td>Weight &lt; 60 kg</td>
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<tr>
<td>- Latin Am</td>
<td></td>
<td></td>
<td></td>
<td>P-gp therapy</td>
<td></td>
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<tr>
<td>CHADS₂ 4–6 (%)</td>
<td>27</td>
<td>25</td>
<td>13</td>
<td>Dose reduced* (%)</td>
<td>99.8</td>
<td>16</td>
<td>4</td>
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<tr>
<td>Median CrCl (ml/min)</td>
<td>45</td>
<td>70</td>
<td>130</td>
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<tr>
<td>VKA naive (%)</td>
<td>51</td>
<td>41</td>
<td>29</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**P <0.001 for all 3-way comparisons**

* Edoxaban dose was ↓50% if CrCl < 50 ml/min, body wgt < 60 kg, or strong P-gp inhibitor used

**Very large differences between lightest 5% and heaviest 5%**

Lightest pts: 4x female, most from Asia, 2x prior stroke/TIA, CrCl median 45 ml/min, 2x VKA naïve

Heaviest pts: 14 years younger, most from NA, 3x higher rate of DM, CrCl median 130 ml/min
**PRIMARY EFFICACY END POINT: STROKE/SEE**
P int=0.52

- LBW: HR 1.08 (0.61-1.88) P=0.80
- MBW: HR 0.75 (0.44-1.25) P=0.27
- HBW: HR 1.3 (0.46-3.57) P=0.62

**PRIMARY SAFETY END POINT: MAJOR BLEEDING**
P int=0.35

- LBW: HR 0.55 (0.31-0.97) P=0.05
- MBW: HR 0.77 (0.51-1.15) P=0.20
- HBW: HR 0.99 (0.56-1.73) P=0.97

**MACE: MI/stroke/SEE/CV death**
P int=0.39

- LBW: HR 0.78 (0.53-1.1) P=0.16
- MBW: HR 0.8 (0.59-1.09) P=0.16
- HBW: HR 1.12 (0.69-1.81) P=0.64

**NET CLINICAL OUTCOME: Stroke/SEE/Major Bleeding/Death**
P int=0.087

- LBW: HR 0.67 (0.5-0.9) P=0.007
- MBW: HR 0.89 (0.7-1.14) P=0.35
- HBW: HR 1.09 (0.77-1.55) P=0.62
Pharmacokinetics and Pharmacodynamics of Higher Dose Edoxaban Regimen by Weight Groups

**Trough Edoxaban concentrations (ng/mL)**

- **P = 0.33**
- LBW: n = 141
- MBW: n = 317
- HBW: n = 171

**Trough Exogenous Anti-Factor Xa Activity (IU/ml)**

- **P = 0.13**
- LBW: n = 61
- MBW: n = 138
- HBW: n = 102

**% Inhibition Endogenous FXa activity at Peak (Day 29)**

- **P = 0.22**
- LBW: n = 59
- MBW: n = 157
- HBW: n = 103

**% Inhibition Endogenous FXa activity at Trough (Day 29)**

- **P = 0.93**
- LBW: n = 63
- MBW: n = 162
- HBW: n = 107
Conclusions

In an analysis of extremes of body weight from the ENGAGE AF-TIMI 48 trial:

- Low body weight subjects (<55kg) were older, with more risk factors, consistent with a more fragile clinical status, and had higher rates of stroke, bleeding, CV events, and death.

- Approved edoxaban regimen (60/30 mg o.d.) achieved similar efficacy regardless of weight, while bleeding and net outcomes were most favourable in pts with low body weight, compared to warfarin.

- Use of recommended criteria for edoxaban dose adjustment resulted in consistent drug concentrations and inhibition of Factor Xa across extremes of body weight.