Engage AF-TIMI 48

Edoxaban in AF: What can we expect?

John Camm
St. George’s University of London
United Kingdom

Advisor / Speaker: Astra Zeneca, Gilead, Merck, Menarini, Sanofi Aventis, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionics, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda
# 4 Phase III Trials of Novel Anticoagulants in AF

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>150, 110</td>
<td>20 (15)</td>
<td>5</td>
<td>60, 30</td>
</tr>
<tr>
<td><strong>Freq</strong></td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>15,000</td>
<td>21,500</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Open</td>
<td>2x blind</td>
<td>2x blind</td>
<td>2x blind</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Stroke/SEE</td>
<td>Stroke/SEE</td>
<td>Stroke/SEE</td>
<td>Stroke /SEE</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>1.46</td>
<td>Not publ.</td>
<td>1.38</td>
<td>1.38</td>
</tr>
</tbody>
</table>

SEE = systemic embolic event (i.e., non-CNS)
## Phase III AF Trials: Results To Date

<table>
<thead>
<tr>
<th></th>
<th>RE-LY¹</th>
<th>ROCKET-AF²</th>
<th>ARISTOTLE³</th>
<th>ENGAGE AF-TIMI 48⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>110 BID</td>
<td>150 BID</td>
<td>20 QD</td>
<td>5 BID</td>
</tr>
<tr>
<td><strong>Stroke + SEE</strong></td>
<td>Non-inferior</td>
<td>Superior</td>
<td>ITT : non-inferior</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td>On Rx : superior</td>
<td></td>
<td>On Rx : superior</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>Superior</td>
<td>Superior</td>
<td>Superior</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>Lower</td>
<td>Similar</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Similar</td>
<td>P=0.051</td>
<td>Similar</td>
<td>Sup: p=0.047</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>Similar</td>
<td>Lower</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td><strong>Mean TTR</strong></td>
<td>64 %</td>
<td>55 %</td>
<td>62 %</td>
<td></td>
</tr>
<tr>
<td><strong>Stopped drug</strong></td>
<td>21 %</td>
<td>23 %</td>
<td>23 %</td>
<td></td>
</tr>
<tr>
<td><strong>WD consent</strong></td>
<td>2.3 %</td>
<td>8.7 %</td>
<td>1.1 %</td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale of ENGAGE AF-TIMI 48: Thrombolysis in Myocardial Infarction (TIMI) 48: ENGAGE AF-TIMI 48 (ENGAGE AF-TIMI 48). A multicenter, randomized, double-blind, double-dummy, multinational, non-inferiority design, phase 3 trial comparing 2 exposure strategies of edoxaban to warfarin. Approximately 20,500 subjects will be randomized to edoxaban high exposure (60 mg daily, adjusted for drug clearance), edoxaban low exposure (30 mg daily, adjusted for drug clearance), or warfarin titrated to an international normalized ratio of 2.0 to 3.0. The edoxaban strategies provide for dynamic dose reductions in subjects with anticipated increased drug exposure. Blinded treatment is maintained through the use of sham international normalized ratios in patients receiving edoxaban. Eligibility criteria include documentation of atrial fibrillation < 12 months and a CHADS2 score ≥ 2. Randomization is stratified by CHADS2 score and anticipated drug exposure. The primary objective is to determine whether edoxaban is noninferior to warfarin for the prevention of stroke and systemic embolism. The primary safety end point is modified International Society on Thrombosis and Haemostasis major bleeding. Recruitment began in November 2008. The expected median follow-up is 24 months.

Protocol Schema

Figure 1

INR Blinding

Because the anticoagulant activities of warfarin and other VKAs are monitored by measuring the INR, once subjects start study drug, INR measurements are performed using a point-of-care device supplied to (DMC) and Study Oversight Committee.

Ruff et al. Am Heart J 2010;160:635-641
Study Design

AF on electrical recording ≤ 12 mo
Intended oral anticoagulant
CHADS$_2$ ≥ 2

Exposure strategy: patients anticipated to have increased drug exposure received a 50% dose reduction

Low exposure strategy
Edoxaban 30 mg QD

High exposure strategy
Edoxaban 60 mg QD

Median duration of follow up 24-months

Primary objective
*Edoxaban: therapeutically as good as warfarin*

Active control:
warfarin (INR 2.0 – 3.0)

Ruff et al. Am Heart J 2010;160:635-641

1º endpoint = stroke or SEE (non-inferiority boundary HR 1.38)
2º endpoint = stroke or SEE or all-cause mortality
Safety endpoints = major bleeding, hepatic function

AF, atrial fibrillation, mo, months; QD, once daily; HR, hazard ratio
SEE, systemic embolic event; INR, International Normalised Ratio
Global Participation

~ 6 Continents
~ 46 Countries
~ 1400 Sites

North America
350 Sites

South America
165 sites

Europe
560 sites

Africa
20 sites

Asia
300 sites

Australia/NZ
24 Sites
Inclusion Criteria

- Male or female, age ≥21 years
- AF documented by an electrical tracing within the prior 12 months and for which anticoagulation is indicated and planned
- Subjects with paroxysmal, persistent or permanent AF
- Subjects with or without previous VKA experience
  - Anticipated that ~40% of subjects will be VKA naïve (< 60 days of continuous anticoagulation at anytime before randomization)
- CHADS$_2$ index score ≥2

AF, atrial fibrillation; VKA, vitamin K antagonist

Ruff et al. Am Heart J 2010;160:635-641
Major Exclusions

- Rheumatic mitral stenosis or mechanical valve
- Anticoagulation contraindicated or not planned
- Patients at high-risk of bleeding
- Need for dual antiplatelet therapy (e.g., recent stent, ACS, stroke) or strong PGP inhibitors
- Pregnancy, severe comorbidities (e.g., cancer, severe renal failure, life-expectancy < 12 mths)
Patients randomized to either of the two edoxaban groups anticipated to have an increased drug exposure received a 50% dose reduction (e.g. from 30 mg to 15 mg)

ARISTOTLE dose reduction only at randomization:
Apixaban 5 mg b.i.d. to 2.5 mg b.i.d.
≥2 of the following:

- age ≥80 years,
- body weight ≤60 kg
- serum creatinine level ≥1.5 mg/dL (133 μmol/L)

Total of 3 doses studied with over a 4-fold range of doses (60, 30, 15 mg)

CrCl, creatinine clearance; P-gp, P-glycoprotein

Ruff et al. Am Heart J 2010;160:635-641
ENGAGE AF- TIMI 48
TTR Approach

- Reviewed worldwide experience with VKA
- Monthly monitoring of TTR at level of
  - Trial, Region, Country, Individual Center
- Review of centers with TTR <40 %
- Letters to centers with TTR <60 % and >80 %
- Lessons learned:
  - Fixed (usually too low) initial dose selection
  - Insufficient, infrequent INR monitoring
  - Excessively cautious dose adjustment when INR sub-therapeutic
- Solutions: Reporting, Education, Algorithm
## Baseline Characteristics

**First 15,000 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>– Mean age (years)</td>
<td>72 (64-77)</td>
</tr>
<tr>
<td>– Age ≥75 years (%)</td>
<td>39</td>
</tr>
<tr>
<td>– Female (%)</td>
<td>38</td>
</tr>
<tr>
<td><strong>CHADS$_2$ 2-3 (%)</strong></td>
<td>81</td>
</tr>
<tr>
<td><strong>CHADS$_2$ 4-6 (%)</strong></td>
<td>19</td>
</tr>
<tr>
<td><strong>Warfarin naïve (%)</strong></td>
<td>39</td>
</tr>
<tr>
<td><strong>AF category</strong></td>
<td></td>
</tr>
<tr>
<td>– Paroxysmal (%)</td>
<td>26</td>
</tr>
<tr>
<td>– Persistent (%)</td>
<td>23</td>
</tr>
<tr>
<td>– Permanent (%)</td>
<td>52</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong>*</td>
<td></td>
</tr>
<tr>
<td>– Any reason (%)</td>
<td>25</td>
</tr>
<tr>
<td>– Weight ≤60 kg (%)</td>
<td>10</td>
</tr>
<tr>
<td>– CrCl ≤50 mL/min (%)</td>
<td>19</td>
</tr>
<tr>
<td>– Concomitant p-gp inhibitors (%)</td>
<td>4</td>
</tr>
</tbody>
</table>

*May have >1 reason for dose adjustment, thus, the total of the individual reasons is >25%. AF, atrial fibrillation; CrCl, creatinine clearance.

Ruff et al. Am Heart J 2010;160:635-641
## Additional Scientific Investigations

<table>
<thead>
<tr>
<th><strong>Name</strong></th>
<th><strong>Objective</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics/Pharmacodynamics in all patients</td>
<td>Characterise the relationship between exposure and response to edoxaban</td>
</tr>
<tr>
<td>Health economics/Quality of life</td>
<td>Cost-effectiveness of edoxaban therapy</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td>Identify genetic polymorphism that identify patients at higher risk for recurrent AF, thromboembolism and bleeding</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Correlate concentrations of biomarkers of thrombosis, inflammation, necrosis and haemodynamic status with efficacy and safety</td>
</tr>
<tr>
<td>Continuous and static electrocardiography</td>
<td>Determine the varying risk associated with different burdens of AF</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Determine if left atrial size predicts thromboembolic risk</td>
</tr>
</tbody>
</table>

*Ruff et al. Am Heart J 2010;160:635-641*
ENGAGE AF-TIMI 48
Expected strengths

1. Scientifically sound design incorporates
   - Two doses (30 mg, 60 mg) selected on phase II PK data
   - Dosing is adjusted for drug clearance
   - Entry criteria identify moderate-high risk patients

2. Posing several interesting questions
   - Doses that are as safe (or safer) than current Rx
   - Built in investigations of PK, PD, genetics, health economics
   - Ancillary studies of biomarkers, echo, holter, ECG

3. Investigation of two dose regimens could result in superior net clinical benefit (efficacy/bleeding) compared to other oral anticoagulants, especially to other direct factor Xa inhibitors.
ENGAGE AF- TIMI 48
Unique features

- The largest (>21,000) single RCT in AF with a novel oral anticoagulant
- Longest follow-up (median 2.5-3.0 yrs)
- 2 once-daily dosing regimens (60 & 30 mg)
- First study with dose adjustment after titration
  - 60 → 30 mg
  - 30 → 15 mg
- Data on 3 doses spanning a 4-fold range
Summary

• High unmet needs for the replacement of VKAs in AF from physician’s and patient’s perspective

• Predictable pharmacological profile and convenient once-daily dosing regimen of edoxaban

• Edoxaban the only Factor Xa inhibitor with a large Phase II dose finding study in AF

• Largest Phase III study programme in AF

• Strategy with 2 dose regimens and dose adjustments might allow selection of best dose on an individual basis