Effective anticoagulation with factor xA next GEneration in Atrial Fibrillation – TIMI 48

Primary Results

Robert P. Giugliano, MD, SM, FAHA, FACC

On behalf of the ENGAGE AF-TIMI 48 Executive Committee and Investigators
Background

- Warfarin in AF: ↓stroke 64% vs placebo
- Warfarin ↑bleeding and has well-known limitations
- 3 NOACs at least as effective; ↓hem. stroke by 51%\(^1\)

**Direct oral FXa inhibitor**

62% oral bioavailability

Peak 1-2h

\(t_{1/2} \sim 10-14h\)

**Edoxaban seated in Factor Xa catalytic center**

**Once** daily

~50% renal clearance

Dose↓ 50%\(^2\) if:
- CrCl 30-50 mL/m
- Weight ≤ 60kg
- Strong P-gp inhib

AF=atrial fibrillation; CrCl=creatinine clearance; FXa=Factor Xa; NOAC=new oral anticoagulant; P-gp=p-glycoprotein

**Study Design**

**21,105 PATIENTS**
AF on electrical recording within last 12 m
CHADS\(_2\) \(\geq 2\)

**RANDOMIZATION**
1:1:1 randomization is stratified by CHADS\(_2\) score 2–3 versus 4–6 and need for edoxaban dose reduction*

**Double-blind, Double-dummy**

**Warfarin**
(INR 2.0–3.0)

**High-dose Edoxaban**
60* mg QD

**Low-dose Edoxaban**
30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight \(\leq 60\) kg
- strong P-gp inhibitor

**1\(^{\circ}\) Efficacy EP = Stroke or SEE**

**2\(^{\circ}\) Efficacy EP = Stroke or SEE or CV mortality**

**1\(^{\circ}\) Safety EP = Major Bleeding (ISTH criteria)**

Non-inferiority
Upper 97.5% CI <1.38

*[Ruff CR et al. Am Heart J 2010; 160:635-41.]*

**CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE=systemic embolic event**
**Trial Organization**

**TIMI Study Group**
- Eugene Braunwald (Study Chair)
- Elliott M. Antman (Principal Investigator)
- Robert P. Giugliano (Co-Investigator)
- Christian T. Ruff (Co-Investigator)
- Suzanne Morin (Director)
- Stephen D. Wiviott (CEC)
- Sabina A. Murphy (Statistics)
- Naveen Deenadayalu (Statistics)
- Laura Grip (Project Director)
- Abby Cange (Project Manager)

**Executive Committee**
- Eugene Braunwald
- Elliott M. Antman
- Robert P. Giugliano
- Michele Mercuri
- Stuart Connolly
- John Camm
- Michael Ezekowitz
- Jonathan Halperin
- Albert Waldo

**Sponsor: Daiichi Sankyo**
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- Hans Lanz
- Indravadan Patel
- Minggao Shi
- James Hanyok

**CRO: Quintiles**
- Maureen Skinner
- Shirali Patel
- Dean Otto
- Joshua Betcher
- Carmen Reissner

**Data Safety Monitoring Board**
- Freek W. A. Verheugt (Chair)
- Jeffrey Anderson
- J. Donald Easton
- Allan Skene (Statistician)
- Shinya Goto
- Kenneth Bauer
**Populations**

- mITT*, On-Treatment†
- Intent-to-Treat (ITT)
  All randomized
- Safety, On-Treatment†

**Analyses**

- Primary efficacy
  (Non-inferiority)
- Superiority
  All events
- Principal Safety
  Major Bleeding (ISTH definition)

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* mITT = All patients who took at least 1 dose
† On-Treatment = 1st dose → last dose +3 days or end of double-blind treatment
ISTH=International Society on Thrombosis and Haemostasis
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [IQR]</td>
<td>72 [64, 78]</td>
</tr>
<tr>
<td>Female sex</td>
<td>38%</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>25%</td>
</tr>
<tr>
<td>CHADS$_2$ (mean ± SD)</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>CHADS$_2$ ≥ 3</td>
<td>53%</td>
</tr>
<tr>
<td>CHADS$_2$ ≥ 4</td>
<td>23%</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>57%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>94%</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36%</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>28%</td>
</tr>
<tr>
<td>Dose reduced at randomization</td>
<td>25%</td>
</tr>
<tr>
<td>Prior VKA experience</td>
<td>59%</td>
</tr>
<tr>
<td>Aspirin at randomization</td>
<td>29%</td>
</tr>
<tr>
<td>Amiodarone at randomization</td>
<td>12%</td>
</tr>
</tbody>
</table>

**No differences across treatment groups**

CHF = congestive heart failure; IQR = interquartile range; TIA = transient ischemic attack; VKA = vitamin K antagonist
## Key Trial Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received drug / enrolled</td>
<td>99.6%</td>
</tr>
<tr>
<td>Completeness of follow-up</td>
<td>99.5%</td>
</tr>
<tr>
<td>Final visit or died / enrolled</td>
<td>99.1%</td>
</tr>
<tr>
<td>Off drug (patients per yr)</td>
<td>8.8%</td>
</tr>
<tr>
<td>Withdrew consent, no data</td>
<td>0.9%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>n=1</td>
</tr>
<tr>
<td>Median time in therapeutic range [Interquartile range]</td>
<td>68.4% [56.5-77.4]</td>
</tr>
</tbody>
</table>

**Countries and Researchers**

- **UNITED STATES (3907)**
  - E. Antman; R. Giugliano
  - W. Ruzyllo
  - J. Spinar
  - M. Ruda
  - A. Parkhomenko
  - E. Paolasso
  - V. Mitrovic
  - J.C. Nicolau
  - B. SomaRaju
  - A. Goudev

- **CHINA (469)**
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  - J. Voitk
  - M. Ostojic
  - T. Moccetti
  - S. Chen
  - N. Chung
  - D. Alexopoulos

- **DENMARK (219)**
  - P. Grande
  - J. Camm
  - M. Horna
  - J.J. Blanc
  - P. Sritara
  - T. Oude Ophuis
  - M. Nieminen
  - D. Atar
  - S. Juul

- **CROATIA (127)**
  - M. Bergovec
  - J. Morais
  - A. Oto
  - N. Babilonia
  - J.L. Zamorano

- **POLAND (1278)**
  - HUNGARY (464)
  - ESTONIA (191)
  - PHILIPPINES (125)
  - CZECH REPUBLIC (1173)
  - ROMANIA (410)
  - MEXICO (190)
  - THAILAND (115)
  - RUSSIAN FEDERATION (1151)
  - SLOVAKIA (405)
  - PORTUGAL (180)
  - TURKEY (111)
  - UKRAINE (1148)
  - UNITED KINGDOM (400)
  - PERU (173)
  - FRANCE (110)
  - ARGENTINA (1059)
  - ISRAEL (283)
  - ITALY (169)
  - AUSTRALIA (102)
  - JAPAN (1010)
  - SERBIA (277)
  - SPAIN (166)
  - GREECE (51)
  - BRAZIL (707)
  - SWEDEN (252)
  - COLOMBIA (141)
  - SWITZERLAND (5)
  - CANADA (774)
  - CHILE (254)
  - BELGIUM (149)
  - NORWAY (34)
  - SOUTH AFRICA (277)
  - NETHERLANDS (153)
  - FINLAND (42)
  - SOUTH KOREA (230)
  - NEW ZEALAND (131)

21,105 Patients, 1393 Centers, 46 Countries
Primary Endpoint: Stroke / SEE (2.8 years median f/u)

Noninferiority Analysis (mITT, On Treatment)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (97.5% CI)</th>
<th>P Value Non-inferiority</th>
<th>P Value Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60* mg QD</td>
<td>0.79</td>
<td>0.0001</td>
<td>0.017</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30* mg QD</td>
<td>1.07</td>
<td>0.005</td>
<td>0.44</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Superiority Analysis (ITT, Overall)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (97.5% CI)</th>
<th>P Value for Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60* mg QD</td>
<td>0.87</td>
<td>0.08</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30* mg QD</td>
<td>1.13</td>
<td>0.10</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Dose reduced by 50% in selected pts

Warfarin TTR 68.4%

Edoxaban 60* mg QD vs warfarin

Edoxaban 30* mg QD vs warfarin

edoxaban noninferior

edoxaban superior

edoxaban inferior
Key Secondary Outcomes

**Hem. Stroke**
- Edoxaban 60 mg QD vs warfarin: 0.33
- Edoxaban 30 mg QD vs warfarin: 0.54
- Warfarin TTR 68.4%

**Ischemic Stroke**
- HR (95% CI) E-60 vs warfarin: 0.97, <0.001
- HR (95% CI) E-30 vs warfarin: 0.97, <0.001

**2° EP: Stroke, SEE, CV death**
- HR (95% CI) E-60 vs warfarin: 0.95, 0.32
- HR (95% CI) E-30 vs warfarin: 0.95, 0.32

**Death or ICH**
- HR (95% CI) E-60 vs warfarin: 0.92, 0.08
- HR (95% CI) E-30 vs warfarin: 0.92, 0.08

**All-cause mortality**
- HR (95% CI) E-60 vs warfarin: 0.87, 0.013
- HR (95% CI) E-30 vs warfarin: 0.87, 0.013

**CV death**
- HR (95% CI) E-60 vs warfarin: 0.86, 0.006
- HR (95% CI) E-30 vs warfarin: 0.86, 0.006

**Myocardial infarction**
- HR (95% CI) E-60 vs warfarin: 0.94, 0.13
- HR (95% CI) E-30 vs warfarin: 0.94, 0.13

*Dose reduced by 50% in selected pts*
Main Safety Results
- Safety Cohort on Treatment -

ISTH Major Bleeding

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P Value vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60 mg QD</td>
<td>0.47</td>
</tr>
<tr>
<td>Edoxaban 30 mg QD</td>
<td>0.55</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Fatal Bleeding

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P Value vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60 mg QD</td>
<td>0.35</td>
</tr>
<tr>
<td>Edoxaban 30 mg QD</td>
<td>0.47</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P Value vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60 mg QD</td>
<td>0.30</td>
</tr>
<tr>
<td>Edoxaban 30 mg QD</td>
<td>0.47</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P Value vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60 mg QD</td>
<td>0.25</td>
</tr>
<tr>
<td>Edoxaban 30 mg QD</td>
<td>0.5</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* Dose reduced by 50% in selected pts

Safety cohort = all patients who received at least 1 dose by treatment actually received
**Net Clinical Outcomes**

**Edoxaban 60* mg QD vs warfarin**

**Edoxaban 30* mg QD vs warfarin**

**Warfarin TTR 68.4%**

**Hazard ratio (95% CI)**

**P Value vs warfarin**

**Stroke, SEE, death, major bleeding**

- **Edoxaban 60* mg QD**
  - Hazard ratio: 0.89
  - P Value: 0.003

- **Edoxaban 30* mg QD**
  - Hazard ratio: 0.83
  - P Value: 0.001

- **Warfarin**
  - Hazard ratio: 0.83
  - P Value: 0.001

**Disabling stroke, life-threatening bleeding, death**

- **Edoxaban 60* mg QD**
  - Hazard ratio: 0.88
  - P Value: 0.008

- **Edoxaban 30* mg QD**
  - Hazard ratio: 0.83
  - P Value: 0.001

- **Warfarin**
  - Hazard ratio: 0.83
  - P Value: 0.001

**Stroke, SEE, life-threatening bleeding, death**

- **Edoxaban 60* mg QD**
  - Hazard ratio: 0.88
  - P Value: 0.003

- **Edoxaban 30* mg QD**
  - Hazard ratio: 0.89
  - P Value: 0.007

- **Warfarin**
  - Hazard ratio: 0.89
  - P Value: 0.007

*Dose reduced by 50% in selected pts
SEE=systemic embolic event
Tolerability and Adverse Events

- **P < 0.001 for each edoxaban dose vs warfarin**

  - **Warfarin (n=7012)**
  - **Edox 60* mg (n=7012)**
  - **Edox 30* mg (n=7002)**

  *Dose reduced by 50% in selected pts

- **Severe adverse event**
  - **Warfarin**: 18.4%
  - **Edox 60* mg**: 17.3%
  - **Edox 30* mg**: 18.3%
  - **P = NS**

- **AST or ALT >3x ULN**
  - **Warfarin**: 2.1%
  - **Edox 60* mg**: 2.2%
  - **Edox 30* mg**: 2.1%
  - **P = NS**
Transition Period Outcomes

- All pts transitioned → VKA or NOAC
- If VKA: Frequent INRs, overlapped VKA + edox (30 or 15 mg) for ≤ 2 wks until INR ≥ 2.0
- If NOAC: start when INR < 2.0

<table>
<thead>
<tr>
<th>Events After Transition to Open-label Anticoagulant</th>
<th>Warfarin (n=4503)</th>
<th>High-dose Edoxaban (n=4526)</th>
<th>Low-dose Edoxaban (n=4613)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or SEE* through 30d</td>
<td>7 (0.16%)</td>
<td>7 (0.15%)</td>
<td>7 (0.15%)</td>
</tr>
<tr>
<td>Major Bleeds through 14d</td>
<td>6 (0.13%)</td>
<td>4 (0.09%)</td>
<td>5 (0.11%)</td>
</tr>
</tbody>
</table>

Data shown include all patients on blinded study drug at the end of the treatment period.

SEE = systemic embolic event. No SEEs occurred during the 30-day transition period.
Summary

Compared to well-managed warfarin (TTR 68.4%) once-daily edoxaban:

- Non-inferior for stroke/SEE (both regimens)
  - High dose ↓ stroke/SEE on Rx (trend ITT)
- Both regimens significantly reduced:
  - Major bleeding (20%/53%) - ICH (53%/70%)
  - Hem. stroke (46%/67%) - CV death (14%/15%)
- Superior net clinical outcomes

No excess in stroke or bleeding during transition → oral anticoagulant at end of trial
Thank you to our patients, investigators and coordinators, data safety committee members, clinical endpoint committee members, core laboratories, operational teams, monitors, Quintiles, and Daiichi Sankyo.