Effective anticoagulation with factor $\text{f}$ 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

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

**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

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° Efficacy EP = Stroke or SEE
2° Efficacy EP = Stroke or SEE or CV mortality
1° Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI $< 1.38$

Cl = 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
- Michele Mercuri
- 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
Population/Analysis Definitions

**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)

---

* 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
21,105 Patients, 1393 Centers, 46 Countries

<table>
<thead>
<tr>
<th>Key Trial Metrics</th>
<th>United States (3907)</th>
<th>China (469)</th>
<th>Denmark (219)</th>
<th>Croatia (127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received drug / enrolled</td>
<td>99.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completeness of follow-up</td>
<td>99.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final visit or died / enrolled</td>
<td>99.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off drug (patients per yr)</td>
<td>8.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrew consent, no data</td>
<td>0.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>n=1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time in therapeutic range [Interquartile range]</td>
<td>68.4% [56.5-77.4]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The table includes data from various countries with their respective patient counts and contributors.
Primary Endpoint: Stroke / SEE (2.8 years median f/u)

Noninferiority Analysis (mITT, On Treatment)

- **Warfarin TTR 68.4%**
- Edoxaban 60* mg QD vs warfarin
- Edoxaban 30* mg QD vs warfarin

---

**Hazard ratio (97.5% CI)**

- Edoxaban 60* mg QD: 0.79
- Edoxaban 30* mg QD: 1.07
- Warfarin: 1.38

---

**P Values**

- Non-inferiority: Edoxaban noninferior
  - Edoxaban 60* mg QD vs warfarin: P<0.0001
  - Edoxaban 30* mg QD vs warfarin: P=0.005

- Superiority: Edoxaban superior
  - Edoxaban 60* mg QD vs warfarin: P=0.017
  - Edoxaban 30* mg QD vs warfarin: P=0.44

---

Superiority Analysis (ITT, Overall)

- Edoxaban 60* mg QD vs warfarin
- Edoxaban 30* mg QD vs warfarin

---

**Hazard ratio (97.5% CI)**

- Edoxaban 60* mg QD: 0.87
- Edoxaban 30* mg QD: 1.13
- Warfarin: 1.42

---

**P Value for Superiority**

- Edoxaban superior
  - Edoxaban 60* mg QD vs warfarin: P=0.08
  - Edoxaban 30* mg QD vs warfarin: P=0.10

---

*Dose reduced by 50% in selected pts*
**Key Secondary Outcomes**

**Edoxaban 60* mg QD vs warfarin**

- **Hem. Stroke**
  - HR (95% CI): 0.33 [0.94, 1.19]
  - P vs warfarin: 0.08

- **Ischemic Stroke**
  - HR (95% CI): 0.87 [0.60, 1.13]
  - P vs warfarin: 0.013

- **2° EP: Stroke, SEE, CV death**
  - HR (95% CI): 0.82 [0.33, 1.00]
  - P vs warfarin: 0.004

- **Death or ICH**
  - HR (95% CI): 0.92 [0.94, 1.00]
  - P vs warfarin: 0.97

- **All-cause mortality**
  - HR (95% CI): 0.87 [0.82, 0.95]
  - P vs warfarin: <0.001

- **CV death**
  - HR (95% CI): 0.86 [0.85, 0.87]
  - P vs warfarin: <0.001

- **Myocardial infarction**
  - HR (95% CI): 0.80 [0.60, 1.00]
  - P vs warfarin: 0.32

*Dose reduced by 50% in selected pts

**Edoxaban 30* mg QD vs warfarin**

- **Hem. Stroke**
  - HR (95% CI): 0.54 [1.00, 1.41]
  - P vs warfarin: <0.001

- **Ischemic Stroke**
  - HR (95% CI): 0.54 [1.00, 1.41]
  - P vs warfarin: <0.001

- **2° EP: Stroke, SEE, CV death**
  - HR (95% CI): 0.87 [0.94, 1.19]
  - P vs warfarin: <0.001

- **Death or ICH**
  - HR (95% CI): 0.87 [0.82, 0.95]
  - P vs warfarin: <0.001

- **All-cause mortality**
  - HR (95% CI): 0.87 [0.82, 0.95]
  - P vs warfarin: <0.001

- **CV death**
  - HR (95% CI): 0.92 [0.94, 1.00]
  - P vs warfarin: 0.005

- **Myocardial infarction**
  - HR (95% CI): 0.92 [0.94, 1.00]
  - P vs warfarin: 0.32
Main Safety Results
- Safety Cohort on Treatment -

**ISTH Major Bleeding**
- Edoxaban 60* mg QD vs warfarin: Hazard ratio (95% CI) = 0.80 (P<0.001)
- Edoxaban 30* mg QD vs warfarin: Hazard ratio (95% CI) = 0.47 (P<0.001)

**Fatal Bleeding**
- Edoxaban 60* mg QD vs warfarin: Hazard ratio (95% CI) = 0.55 (P=0.006)
- Edoxaban 30* mg QD vs warfarin: Hazard ratio (95% CI) = 0.35 (P<0.001)

**Intracranial Hemorrhage**
- Edoxaban 60* mg QD vs warfarin: Hazard ratio (95% CI) = 1.23 (P=0.03)
- Edoxaban 30* mg QD vs warfarin: Hazard ratio (95% CI) = 0.47 (P<0.001)

**Gastrointestinal Bleeding**
- Edoxaban 60* mg QD vs warfarin: Hazard ratio (95% CI) = 0.67 (P<0.001)
- Edoxaban 30* mg QD vs warfarin: Hazard ratio (95% CI) = 0.30 (P<0.001)

*P Value vs warfarin

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

*Dose reduced by 50% in selected pts

Warfarin TTR 68.4%

edoxaban superior edoxaban inferior
Net Clinical Outcomes

Edoxaban 60 mg QD vs warfarin
Edoxaban 30 mg QD vs warfarin
Warfarin TTR 68.4%

Hazard ratio (95% CI)

Stroke, SEE, death, major bleeding
- Hazard ratio: 0.89 vs warfarin
  - P Value: 0.003
  - SEE=systemic embolic event

Disabling stroke, life-threatening bleeding, death
- Hazard ratio: 0.83 vs warfarin
  - P Value: <0.001

Stroke, SEE, life-threatening bleeding, death
- Hazard ratio: 0.88 vs warfarin
  - P Value: 0.003

* Dose reduced by 50% in selected pts

*See=systemic embolic event
Tolerability and Adverse Events

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

*Dose reduced by 50% in selected pts

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

Never interrupted

Severe adverse event

AST or ALT >3x ULN
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
Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D.,

Comprehensive Meta-Analysis Comparing the Efficacy and Safety of NOACs with Warfarin in AF

Ruff CT, et al. [in press]

Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48

Deepak K. Gupta¹, Amil M. Shah¹, Robert P. Giugliano², Christian T. Ruff²,

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