Edoxaban vs Enoxaparin/Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation – The Randomized ENSURE-AF Study

Declaration of interest

• **AG** has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; and as a speaker for AstraZeneca, Bayer, Berlin-Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi-Aventis
Background

• In AF patients undergoing cardioversion, current guidelines recommend ≥3 weeks of therapeutic anticoagulation prior to cardioversion and a continuation of anticoagulation for ≥4 weeks post-cardioversion and longer in patients at risk of AF recurrence or if stroke risk factors are present\(^1,2\)

• VKAs have traditionally been used as oral anticoagulation pericardioversion,\(^1,2\) but VKAs are associated with inter- and intrapatient variability, requiring regular monitoring to ensure a target INR range of 2.0 to 3.0

• Current data from post hoc analyses of the phase 3 NOAC studies\(^3-6\) and 1 randomized trial (X-VeRT)\(^7\) suggest NOACs could be a safe alternative to VKAs for pericardioversion anticoagulation

AF = atrial fibrillation; INR = international normalized ratio; NOAC = nonvitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist

Purpose and key points about methods

A prospective randomized trial, assessing the efficacy and safety of edoxaban compared to the best possible conventional therapy (enoxaparin/warfarin) in patients with NVAF undergoing cardioversion.

The ENSURE-AF study aimed to demonstrate that once-daily edoxaban is a treatment option for patients undergoing cardioversion.

**Patients with documented NVAF planned for cardioversion**

- **Delayed cardioversion** (non-TEE-guided stratum)
- **Early cardioversion** (TEE-guided stratum)

**RANDOMIZATION**

1:1 randomization into 2 anticoagulation treatment groups per stratum

- Edoxaban (60/30 mg once daily)\(^a\)
- Enoxaparin\(^b\) + Warfarin (INR, 2.0–3.0)
- Edoxaban (60/30 mg once daily)\(^b\)
- Enoxaparin\(^b\) + Warfarin (INR, 2.0–3.0)

Duration of follow-up = 28 + 30 days

---

\(^a\)Patients meeting ≥1 of the following criteria: CrCl ≥15 mL/min and ≤50 mL/min; low body weight (<60 kg); or concomitant use of P-gp inhibitors (with the exception of amiodarone)

\(^b\)Patients with INR at randomization ≥2 did not require enoxaparin

CrCl = creatinine clearance; INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation; TEE = transesophageal echocardiography


Prof. Andreas Goette
Results – Primary efficacy outcomes

Composite of Stroke, SEE, MI, and CV Death, %

- Edoxaban
- Enoxaparin + Warfarin (mean TTR = 70.8%)

**OR (95% CI):**
- 0.46 (0.12–1.43)
- 0.40 (0.04–2.47)
- 0.50 (0.08–2.36)

*Composite of stroke, SEE, MI, and CV mortality assessed in the ITT population during overall period*

CI = confidence interval; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; OR = odds ratio; SEE = systemic embolic event; TEE = transesophageal echocardiography; TTR = time in therapeutic range
### Results – Adjusted safety outcomes

**Event Rate, % (n/N)**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Edoxaban</th>
<th>Enoxaparin + Warfarin</th>
<th>Edoxaban vs Enoxaparin + Warfarin</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Major or CRNM Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total by Treatment</td>
<td>1.5 (16/1067)</td>
<td>1.0 (11/1082)</td>
<td>1.48 (0.64–3.55)</td>
<td></td>
</tr>
<tr>
<td>TEE Stratum</td>
<td>1.9 (11/570)</td>
<td>0.9 (5/577)</td>
<td>2.3 (0.72–8.31)</td>
<td></td>
</tr>
<tr>
<td>Non-TEE Stratum</td>
<td>1.0 (5/497)</td>
<td>1.2 (6/505)</td>
<td>0.85 (0.20–3.35)</td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total by Treatment</td>
<td>0.3 (3/1067)</td>
<td>0.5 (5/1082)</td>
<td>0.61 (0.09–3.13)</td>
<td></td>
</tr>
<tr>
<td>TEE Stratum</td>
<td>0.5 (3/570)</td>
<td>0.3 (2/577)</td>
<td>1.52 (0.17–18.27)</td>
<td></td>
</tr>
<tr>
<td>Non-TEE Stratum</td>
<td>0</td>
<td>0.6 (3/505)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td><strong>CRNM Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total by Treatment</td>
<td>1.3 (14/1067)</td>
<td>0.6 (7/1082)</td>
<td>2.04 (0.77–6.00)</td>
<td></td>
</tr>
<tr>
<td>TEE Stratum</td>
<td>1.6 (9/570)</td>
<td>0.5 (3/577)</td>
<td>3.07 (0.76–17.00)</td>
<td></td>
</tr>
<tr>
<td>Non-TEE Stratum</td>
<td>1.0 (5/497)</td>
<td>0.8 (4/505)</td>
<td>1.27 (0.27–6.45)</td>
<td></td>
</tr>
<tr>
<td><strong>Any Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total by Treatment</td>
<td>3.0 (32/1067)</td>
<td>3.2 (35/1082)</td>
<td>0.93 (0.55–1.55)</td>
<td></td>
</tr>
<tr>
<td>TEE Stratum</td>
<td>3.0 (17/570)</td>
<td>2.9 (17/577)</td>
<td>1.01 (0.48–2.13)</td>
<td></td>
</tr>
<tr>
<td>Non-TEE Stratum</td>
<td>3.0 (15/497)</td>
<td>3.6 (18/505)</td>
<td>0.84 (0.39–1.79)</td>
<td></td>
</tr>
</tbody>
</table>

*In the safety population assessed during the on-treatment period

CI = confidence interval; CRNM = clinically relevant nonmajor; NC = not calculated; OR = odds ratio;
TEE = transesophageal echocardiography

---

www.ascardio.org

Prof. Andreas Goette
## Results – Net clinical outcome

### Event Rate, % (n/N)

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>Enoxaparin + Warfarin</th>
<th>Edoxaban vs Enoxaparin + Warfarin</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>0.7 (8/1095)</td>
<td>1.4 (16/1104)</td>
<td></td>
<td>0.50 (0.19–1.25)</td>
</tr>
<tr>
<td><strong>By CrCl, mL/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>0 (0/83)</td>
<td>2.63 (2/76)</td>
<td></td>
<td>NC</td>
</tr>
<tr>
<td>&gt;50–&lt;80</td>
<td>0.99 (3/304)</td>
<td>2.22 (7/315)</td>
<td></td>
<td>0.44 (0.07–1.95)</td>
</tr>
<tr>
<td>≥80</td>
<td>0.62 (4/643)</td>
<td>0.94 (6/636)</td>
<td></td>
<td>0.66 (0.14–2.79)</td>
</tr>
</tbody>
</table>

*Composite of stroke, SEE, MI, CV mortality, major bleeding assessed in the ITT population during the entire study duration.*

CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; NC = not calculated; OR = odds ratio; SEE = systemic embolic event.
Conclusions

ENSURE-AF study is the largest prospective randomized clinical trial to date of anticoagulation for electrical cardioversion in NVAF

- Overall, the rates of the composite primary efficacy endpoint and of major or CRNM bleeding were similarly low in both treatment arms, irrespective of a TEE-guided strategy.
- The net clinical outcome was numerically lower but not statistically different in the edoxaban arm vs enoxaparin/warfarin arm.
- Edoxaban is an effective and safe alternative to treatment with enoxaparin/VKA strategy for patients undergoing electrical cardioversion of nonvalvular AF and may allow prompt cardioversion to be performed following the start of anticoagulation (≥2 hours for TEE-guided strategy; ≥3 weeks for non-TEE).
Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial

Andreas Goette*, Jose I Merino, Michael D Ezekowitz, Dmitry Zamoryakhin, Michael Melino, James Jin, Michele F Mercuri, Michael A Grosso, Victor Fernandez, Naith Al-Saadly, Natalya Pekhri, Bela Markely, Sergey Zenin, Mykola Kushyr, Jindrich Spinar, Valeriy Betushkin, Joris R de Grooth, Gregory Y H Lip*
Additional slide: Embolic events in AF

- In AF, random electrical pulses are generated in the atrium that override the normal pacemaker and cause the atria to beat in a rapid and uncoordinated way (fibrillation).\(^1\)
- The main complication of AF is an increased risk of stroke, with one in five of all strokes occurring as a result of AF.\(^2\) The risk of stroke also increases with age and strokes in those with AF are nearly twice as likely to be fatal than strokes in those without AF.\(^2,3\)

ESC AF Guidelines

- Updated on 27 August 2016
- Due to the risk of thromboembolic events in the peri-procedural period, clinical guidelines recommend anticoagulation before and after cardioversion in patients with AF.\(^4,5\)
  - Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF. For cardioversion of AF, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.\(^4\)
  - In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.\(^4\)