Edoxaban- vs vitamin-K-antagonist-based anti-thrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): A randomised, open-label, phase 3b trial

Andreas Goette, Marco Valgimigli, Lars Eckardt, Jan Tijssen, Thorsten Lewalter, Giuseppe Gargiulo, Valerii Batushkin, Gianluca Campo, Zoreslava Lysak, Igor Vakaliuk, Krzysztof Milewski, Petra Laeis, Paul-Egbert Reimitz, Rüdiger Smolnik, Wolfgang Zierhut, Pascal Vranckx
Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; and a speaker for AstraZeneca, Bayer, Berlin-Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, and Omeicos.)
Disclosures

Honoraria:

Astra Zeneca
Bayer Healthcare
Berlin Chemie
Biotronik
BMS/Pfizer
Boehringer Ingelheim
Boston Scientific
Cordis
Daiichi-Sankyo
Medtronic
Omeicos
Background

• Approximately 15% of AF patients also require PCI with stent placement to treat obstructive coronary artery disease
• Current guidelines recommend oral anticoagulation for AF and dual antiplatelet therapy (DAPT) with acetylsalicylic acid (aspirin) and P2Y\(_{12}\) inhibitors after PCI
• DAPT in combination with oral anticoagulation (triple therapy) is associated with high rates of bleeding
• Edoxaban has established efficacy and safety for stroke prevention in AF
• Three randomised trials evaluated standard or reduced doses of NOAC in AF patients undergoing PCI while aspirin was abandoned
• The effects of edoxaban in combination with a P2Y\(_{12}\) inhibitor in the setting of PCI are unexplored
Primary objective: To compare a 12-month antithrombotic regimen of
• edoxaban plus a P2Y<sub>12</sub> inhibitor versus
• VKA plus a P2Y<sub>12</sub> inhibitor plus aspirin for 1-12 months
in patients with AF and ACS or stable CAD following successful PCI with stent
placement for the incidence of major or clinically relevant non-major bleeding
(ISTH)

Two hypotheses for the primary bleeding objective are tested consecutively:
1. The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based
   antithrombotic regimen
2. The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic
   regimen

Secondary objectives (exploratory):
– Main efficacy endpoint: Composite of cardiovascular (CV) death, stroke, systemic embolic
  events (SEE), spontaneous myocardial infarction (MI), and definite stent thrombosis
ProBE design: Prospective, Randomized, Open label, Blinded endpoint Evaluation in 1500 AF patients with ACS or stable CAD

**Inclusion Criteria:**
- OAC indication for AF for at least 12 months
- Successful PCI with stent placement (goal of at least 25% ACS)

**Study Design Diagram:**
- **Edoxaban 60 mg/day**
- **P2Y<sub>12</sub> inhibitor** (without aspirin)
- **Vitamin K Antagonist***
- **P2Y<sub>12</sub> inhibitor aspirin 1 - 12 months****

**Primary outcome:**
ISTH major or clinically relevant non-major bleeding

* Edoxaban dose reduction to 30 mg OD
  - if CrCl≤50 ml/min
  - BW≤60 kg
  - certain P-gp inhibitors

** Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily. Predeclared at randomization

*** VKA, target INR 2-3

**** aspirin 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), CHA<sub>2</sub>DS-VASc<sub>2</sub> and HAS_BLED

---

*OAC: Oral Anticoagulant, PCI: Percutaneous Coronary Intervention, CrCl: Creatinine Clearance*

**HAS_BLED:**
- **H**igh blood pressure
- **A**ge 75+ years
- **S**moking
- **B**leeding history or diathesis
- **L**eukemia, lymphoma, myeloma
- **E**lderly
- **D**iabetes

**CHA<sub>2</sub>DS-VASc<sub>2</sub>:**
- **C**erebrovascular disease
- **H**ypertension
- **A**ge 65-75 years
- **D**iabetes
- **S**moking
- **V**ascular disease
- **A**ge 75+ years
- **C**ardiovascular disease

**PROBE**: Prospective Randomized Open label Blinded Evaluation
1506 randomised

751 to edoxaban regimen (ITT)
- 746 received study medication (On-treatment)
  - 147 received the reduced dose
- 616 completed regular treatment period as planned
  - 130 did not complete regular treatment period as planned

755 to VKA regimen (ITT)
- 740 received study medication (On-treatment)
- 580 completed regular treatment period as planned
  - 160 did not complete regular treatment period as planned

186 centres
18 countries
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban regimen (N=751)</th>
<th>VKA regimen (N=755)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (Q1; Q3)</td>
<td>69 (63; 77)</td>
<td>70 (64; 77)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>194 (25.8)</td>
<td>192 (25.4)</td>
</tr>
<tr>
<td>Weight (kg), median (Q1; Q3)</td>
<td>80 (71; 93)</td>
<td>83 (72; 94)</td>
</tr>
<tr>
<td>Type of AF, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>402 (53.5)</td>
<td>358 (47.5)</td>
</tr>
<tr>
<td>Persistent</td>
<td>140 (18.6)</td>
<td>146 (19.4)</td>
</tr>
<tr>
<td>Long-standing persistent or permanent</td>
<td>209 (27.8)</td>
<td>250 (33.2)</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc score, median (Q1; Q3)</td>
<td>4.0 (3; 5)</td>
<td>4.0 (3; 5)</td>
</tr>
<tr>
<td>HAS-BLED score, median (Q1; Q3)</td>
<td>3.0 (2; 3)</td>
<td>3.0 (2; 3)</td>
</tr>
<tr>
<td>CrCL (mL/min), median (Q1; Q3)</td>
<td>71.8 (53.7, 91.1)</td>
<td>71.7 (54.0, 90.9)</td>
</tr>
<tr>
<td>Clinical presentation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>388 (51.7)</td>
<td>389 (51.5)</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>363 (48.3)</td>
<td>366 (48.5)</td>
</tr>
<tr>
<td>OAC prior to index PCI, n (%)</td>
<td>408 (68.0)</td>
<td>413 (65.1)</td>
</tr>
<tr>
<td>Time (hours) between end of PCI and randomisation, median (Q1; Q3)</td>
<td>45.1 (22.3; 75.6)</td>
<td>44.8 (22.1; 76.5)</td>
</tr>
<tr>
<td>Type of P2Y$_{12}$ antagonist, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>696 (92.8)</td>
<td>695 (92.1)</td>
</tr>
<tr>
<td>Prasugrel or Ticagrelor</td>
<td>54 (7.2)</td>
<td>60 (7.9)</td>
</tr>
</tbody>
</table>
Primary Study Endpoint
ITT Analysis (N=1506), overall study period

<table>
<thead>
<tr>
<th>Edoxaban regimen</th>
<th>VKA regimen</th>
<th>Hazard Ratio (2-sided 95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome of major or CRNM bleeding (ISTH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat analysis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>751</td>
<td>755</td>
<td></td>
</tr>
<tr>
<td>Number of patients with event (%)</td>
<td>128 (17)</td>
<td>152 (20)</td>
<td></td>
</tr>
<tr>
<td>Annualised event rate (% per year)</td>
<td>20.7</td>
<td>25.6</td>
<td>0.83 (0.65; 1.05)</td>
</tr>
</tbody>
</table>

Hierarchical test procedure (confirmatory statistics):
STEP 1: 1.047 < 1.20 ➔ The edoxaban regimen is non-inferior to the VKA regimen

STEP 2: 1.047 > 1.00 ➔ superiority of edoxaban regimen could not be demonstrated
Primary Study Endpoint
ITT Analysis (N=1506), overall study period

- Cumulative incidence of outcomes over days from randomization
- Comparison between Edoxaban and VKA
- Number of events:
  - Edoxaban: 128/751
  - VKA: 152/755
- HR (95% CI): 0.83 (0.65: 1.05)
- P-value (non-inferiority): 0.0010
- P-value (superiority): 0.1154

Number at risk:
- EDOXABAN: 751, 688, 665, 646, 629, 618, 609, 600, 590, 584, 575, 565, 506
- VKA: 755, 678, 648, 625, 603, 588, 578, 568, 561, 552, 543, 538, 485
Main Efficacy Endpoint
ITT Analysis (N=1506), overall study period

<table>
<thead>
<tr>
<th>Main efficacy outcome (composite of CV death, stroke, SEE, MI or definite stent thrombosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat analysis:</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Number of patients with event (%)</td>
</tr>
<tr>
<td>Annualised event rate (% per year)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
## Bleeding Outcomes (ISTH, TIMI, BARC)

### ITT Analysis (N=1506), overall study period

<table>
<thead>
<tr>
<th>Bleeding (ISTH, TIMI, BARC): Time to first event</th>
<th>95% CI Lower Limit</th>
<th>HR</th>
<th>95% CI Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major or CRNM bleeding (ISTH)</td>
<td>0.654</td>
<td>0.83</td>
<td>1.047</td>
</tr>
<tr>
<td>Major bleeding (ISTH)</td>
<td>0.628</td>
<td>0.95</td>
<td>1.422</td>
</tr>
<tr>
<td>CRNM bleeding (ISTH)</td>
<td>0.636</td>
<td>0.83</td>
<td>1.093</td>
</tr>
<tr>
<td>Minor bleeding (ISTH)</td>
<td>0.723</td>
<td>0.93</td>
<td>1.200</td>
</tr>
<tr>
<td>Any bleeding (ISTH)</td>
<td>0.698</td>
<td>0.84</td>
<td>1.009</td>
</tr>
<tr>
<td>Major or minor bleeding (TIMI)</td>
<td>0.666</td>
<td>0.85</td>
<td>1.077</td>
</tr>
<tr>
<td>Major bleeding (TIMI)</td>
<td>0.326</td>
<td>0.62</td>
<td>1.186</td>
</tr>
<tr>
<td>Minor bleeding (TIMI)</td>
<td>0.687</td>
<td>0.89</td>
<td>1.142</td>
</tr>
<tr>
<td>Minimal bleeding (TIMI)</td>
<td>0.696</td>
<td>0.89</td>
<td>1.148</td>
</tr>
<tr>
<td>Any bleeding (TIMI)</td>
<td>0.697</td>
<td>0.84</td>
<td>1.011</td>
</tr>
<tr>
<td>Type 2, 3, or 5 bleeding (BARC)</td>
<td>0.666</td>
<td>0.85</td>
<td>1.077</td>
</tr>
<tr>
<td>Type 3 or 5 bleeding (BARC)</td>
<td>0.549</td>
<td>0.86</td>
<td>1.342</td>
</tr>
<tr>
<td>Type 3 bleeding (BARC)</td>
<td>0.582</td>
<td>0.92</td>
<td>1.464</td>
</tr>
<tr>
<td>Type 2 bleeding (BARC)</td>
<td>0.680</td>
<td>0.89</td>
<td>1.165</td>
</tr>
<tr>
<td>Type 1, 2, 3, or 5 bleeding (BARC)</td>
<td>0.697</td>
<td>0.84</td>
<td>1.011</td>
</tr>
</tbody>
</table>
Post Hoc Landmark Kaplan-Meier Analysis

Primary Study Endpoint

Cumulative rate of events

Days from randomization

Phase 1 (≤ day 14) HR (95% CI): 2.42 (1.27; 4.63)
Phase 2 (> day 14) HR (95% CI): 0.68 (0.53; 0.88)
Interaction P-value: <0.0001

Number at risk:

**EDOXABAN**
- 751
- 707
- 688
- 665
- 646
- 629
- 618
- 609
- 600
- 590
- 584
- 575
- 565
- 506

**VKA**
- 755
- 721
- 678
- 648
- 625
- 603
- 588
- 578
- 568
- 561
- 552
- 543
- 538
- 485

ESC Congress
Paris 2019
World Congress of Cardiology
INR in VKA regimen in first 5 weeks

Time from PCI to Randomisation:
- shortest – 0.2 h
- median – 45 h

Overall study period: median TTR = 63.1%
Meta-Analysis:
Comparative NOAC AF PCI trials
ISTH Major or CRNM Bleeding

ISTH Major or Clinically Relevant Non-Major Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC DAT</th>
<th>VKA TAT</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>84</td>
<td>1143</td>
<td>210</td>
<td>1123</td>
</tr>
<tr>
<td>ENTRUST AF-PCI</td>
<td>128</td>
<td>751</td>
<td>152</td>
<td>755</td>
</tr>
<tr>
<td>PIONEER AF-PCI</td>
<td>117</td>
<td>696</td>
<td>178</td>
<td>697</td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>305</td>
<td>1744</td>
<td>264</td>
<td>981</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4334</td>
<td>3556</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>634</td>
<td>804</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.07; Chi² = 22.84, df = 3 (P <0.0001); I² = 87%
Test for overall effect: Z = 3.47 (P = 0.0005)
Myocardial Infarction and Stent Thrombosis
- Endpoints as defined by each of the NOAC AF PCI trials -

Stent Thrombosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC DAT Events</th>
<th>NOAC DAT Total</th>
<th>VKA TAT Events</th>
<th>VKA TAT Total</th>
<th>Weight</th>
<th>M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUGUSTUS</td>
<td>21</td>
<td>1153</td>
<td>12</td>
<td>1154</td>
<td>40.0%</td>
<td>1.75 (0.87, 3.54)</td>
<td></td>
</tr>
<tr>
<td>ENTRUST AF-PCI</td>
<td>8</td>
<td>751</td>
<td>6</td>
<td>755</td>
<td>17.9%</td>
<td>1.34 (0.47, 3.84)</td>
<td></td>
</tr>
<tr>
<td>PIONEER AF-PCI</td>
<td>5</td>
<td>694</td>
<td>4</td>
<td>695</td>
<td>11.6%</td>
<td>1.25 (0.34, 4.64)</td>
<td></td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>22</td>
<td>1744</td>
<td>8</td>
<td>981</td>
<td>30.6%</td>
<td>1.55 (0.69, 3.46)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4342</td>
<td>3585</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.55 (0.99, 2.41)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 56
Total events: 30

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)
Limitations

• TTR for the patients who received VKA was modestly lower than in ENGAGE AF-TIMI 48 but comparable to other NOAC AF PCI studies. The observed TTR in NOAC AF PCI trials reflects the challenges with VKA treatment in routine clinical practice.

• The number of patients on a more potent P2Y$_{12}$ inhibitor is limited; therefore, our trial must primarily be viewed as a comparison of clopidogrel-based antiplatelet therapies, which is consistent with all prior NOAC AF PCI trials.

• Furthermore, our study was designed as an open-label study, with potential treatment or reporting bias, which may explain why more patients withdrew from the VKA arm. However, patient data were 100% monitored for unreported events and all potential events were blindly adjudicated.

• Finally, in concert with the other trials, the enrolment of 1506 patients in ENTRUST-AF PCI was not large enough to detect small but potentially important differences in the incidence of the main efficacy outcome.
Conclusions

- The ENTRUST-AF PCI trial showed that, among patients with AF who underwent successful PCI, a full-dose anticoagulation therapy with edoxaban 60 mg once daily plus a P2Y12 inhibitor is noninferior to a triple therapy with VKA (ASA given for 1 to 12 months) regarding the risks of major or CRNM bleeding events at 12 months.

- The edoxaban-based dual therapy regimen, as compared to the triple VKA-based regimen, showed similar rates with respect to the main efficacy outcome, a composite of death from cardiovascular causes, stroke or SEE, MI, or definite stent thrombosis.

- Of note, all NOAC AF PCI trials show numerically increased rates of MI and stent thrombosis in patients with early withdrawal of aspirin.

- In conclusion, in patients with AF who underwent PCI, the edoxaban-based dual antithrombotic therapy was noninferior for bleeding compared with VKA-based triple antithrombotic regimen without significant differences in ischaemic events.
### Steering Committee
1. Prof. Dr. Pascal Vranckx (Hasselt, Belgium) (Co-principal investigator)
2. Prof. Dr. Andreas Goette (Paderborn, Germany and Atrial Fibrillation Network (AFNET) (Co-principal investigator)
3. Prof. Jan Tijssen, PhD (Amsterdam, The Netherlands; and Cardialysis, Rotterdam, The Netherlands)
4. Prof. Dr. Lars Eckhardt (Muenster, Germany and Atrial Fibrillation Network (AFNET))
5. Prof. Dr. Thorsten Lewalter (Munich and Bonn, Germany)
6. Dr. Ron van Amsterdam (Cardialysis, Rotterdam, The Netherlands)
7. Prof. Dr. Marco Valgimigli, PhD (Bern, Switzerland)

### Data and Safety Monitoring Board
1. Prof. Dr. Freek W.A. Verheugt (Amsterdam, Netherlands) (Chair)
2. Prof. Dr. med. Helmut U. Klein (Rochester, NY, USA)
3. Prof. Dr. Tim Friede (Göttingen, Germany)

### Country Leaders
<table>
<thead>
<tr>
<th>Country</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Dr. Kurt Huber</td>
</tr>
<tr>
<td>Belgium</td>
<td>Dr. Tom Vandendriessche</td>
</tr>
<tr>
<td>Spain</td>
<td>Prof. Francisco Marin</td>
</tr>
<tr>
<td>France</td>
<td>Dr. François Schiele</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Dr. Adesh Ramsewak</td>
</tr>
<tr>
<td>Germany</td>
<td>Prof. Christian Hamm</td>
</tr>
<tr>
<td>Hungary</td>
<td>Dr. Imre Ungi</td>
</tr>
<tr>
<td>Ireland</td>
<td>Dr. Ross Murphy</td>
</tr>
<tr>
<td>Italy</td>
<td>Dr. Andrea Rubboli</td>
</tr>
<tr>
<td>South Korea</td>
<td>Dr. Hyo-Soo Kim (NLI)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Dr. Ramunas Unikas</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dr. Jur ten Berg</td>
</tr>
<tr>
<td>Poland</td>
<td>Prof. Adam Wittkowski</td>
</tr>
<tr>
<td>Portugal</td>
<td>Prof. Pedro Monteiro</td>
</tr>
<tr>
<td>Romania</td>
<td>Prof. Dr. Dragos Vinereanu</td>
</tr>
<tr>
<td>Serbia</td>
<td>Dr. Goran Stankovic</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Dr. Chern-En Chiang</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Dr. Igor Kraiz</td>
</tr>
</tbody>
</table>

### Data Coordination Centres
1. Daiichi Sankyo Europe GmbH (Munich, Germany) (Sponsor)
2. European Cardiovascular Research Institute (ECRI) (Rotterdam, The Netherlands) (Academic Research Organization)
3. Kompetenznetz Vorhofflimmern e.V. (AFNET e.V.) (Münster, Germany) (Academic Research Organization)
4. Cardialysis (Rotterdam, The Netherlands) (Academic Research Organization)
5. Chiltern International (Neuilly sur Seine, France) (Contract Research Organization)

### Data and Safety Monitoring Board
1. Prof. Dr. Freek W.A. Verheugt (Amsterdam, Netherlands) (Chair)
2. Prof. Dr. med. Helmut U. Klein (Rochester, NY, USA)
3. Prof. Dr. Tim Friede (Göttingen, Germany)

### Blinded Independent Clinical Event Committee
1. Prof. G. Andersen (Aarhus, Denmark)
2. Prof. em. Dr. med. Dr. h.c. G. Breithardt (Münster, Germany)
3. PD Dr. med. K. G. Häusler (Würzburg, Germany)
4. Prof. C. Hanet (Yvoir, Belgium)
5. Dr. E. McFadden (Cork, Ireland)
6. Prof. Dr. med. U. Tebbe (Detmold, Germany)
Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

Pascal Vranckx, Marco Valgimigli, Lars Eckardt, Jan Tijssen, Thorsten Lewalter, Giuseppe Gargiulo, Valerii Batoshkin, Gianluca Campo, Zorelava Lysak, Igor Vakaliuk, Krzysztof Mliekski, Petra Laeis, Paul-Egbert Reimitz, Rüdiger Smolnik, Wolfgang Zierhut, Andreas Goette

Summary
Background We aimed to assess the safety of edoxaban in combination with P2Y12 inhibition in patients with atrial fibrillation who had percutaneous coronary intervention (PCI).

Methods ENTRUST-AF PCI was a randomised, multicentre, open-label, non-inferiority phase 3b trial with masked outcome evaluation, done at 186 sites in 18 countries. Patients had atrial fibrillation requiring oral anticoagulation, were aged at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome. Participants were randomly assigned (1:1) from 4 h to 5 days after PCI using concealed, stratified, and blocked web-based central randomisation to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a vitamin K antagonist (VKA) in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months). The