The ePAD Study: RCT comparing edoxaban and aspirin to clopidogrel and aspirin in SFA and proximal popliteal interventions

Frans Moll, MD, PhD
On behalf of the ePAD Steering Committee and Investigators
Disclosures

Dr. Moll reports research grants from Daiichi Sankyo during the conduct of the study.
Current Medical Treatment Recommendations

• Increasing research gains have improved both devices and operator technique for peripheral EVT
• Unlike PCI, there is limited research in medical therapy after peripheral EVT
• Guideline recommendations after EVT vary and range from aspirin only to clopidogrel + aspirin for 1 to 3 months followed by long-term aspirin\textsuperscript{1-3}
• Treatment recommendations focus on platelet aggregation, and exclude the role of the coagulation cascade in thrombus formation

EVT, endovascular treatment; PCI, percutaneous coronary intervention.

Loss of Patency

- Loss of patency after EVT remains high (range 17 to >40% with DAPT)\(^1-^5\)
- There is catheter-induced damage to endothelium during EVT
- Damage exposes tissue factor-rich subendothelium to the bloodstream creating a thrombogenic environment
- Platelets and coagulation factors are activated

DAPT, dual anti-platelet therapy; EVT, endovascular treatment.

Figure used with permission from Robbins and Cotran Pathologic Basis of Disease, Professional Edition.

Hypothesis and Objective

• A regimen which targets all major components of the arterial thrombi may be a more optimal approach to preserve EVT-restored patency in PAD patients with a low risk of bleeding

• The objective of this proof-of-concept study was to test the safety and efficacy of edoxaban and aspirin vs conventional DAPT treatment (clopidogrel and aspirin) in maintenance of vessel patency in PAD patients following femoropopliteal EVT

  • This is the first study to utilize a non-vitamin K antagonist oral anticoagulant in a dual antithrombotic regimen in patients with PAD

DAPT, dual antiplatelet treatment; EVT, endovascular treatment; PAD, peripheral artery disease.
Study Design

Successful EVT

Randomization 1:1

Follow up visits at months 1, 2, 3, 4, and 6

Edoxaban 60₀ mg once daily for 3 months
+ Aspirin 100 mg once daily for 6 months

Clopidogrel; 300 mg loading dose followed by 75 mg once daily for 3 months
+ Aspirin 100 mg once daily for 6 months

Prospective, randomized, open-blinded endpoint (PROBE design) proof-of-concept study (NCT01802775)

*For patients randomized to receive edoxaban, the dose was reduced to 30 mg once daily if the patient had a low body weight (≤60 kg), moderate renal impairment (CrCl ≥30 mL/min to ≤50 mL/min Cockcroft-Gault formula) or concomitant use of select P-gp inhibitors at randomization or during the 3 months of active treatment.

CrCl, creatinine clearance; EVT, endovascular treatment; P-gp, P-glycoprotein.
Patient Selection

• Key inclusion criteria:
  • Patient provided written informed consent
  • Symptomatic PAD (Rutherford class 2–5)
  • Successful EVT (defined as ≤ 30% residual stenosis)
  • Superficial femoral artery and proximal popliteal lesions

• Key exclusion criteria:
  • CrCl < 30 mL/min
  • Active bleeding or high bleeding risk
  • Ongoing other indication for DAPT or anticoagulant treatment

CrCl, creatinine clearance; DAPT, dual antiplatelet treatment; EVT, endovascular treatment; PAD, peripheral artery disease.
Study Design and Oversight

- **Steering Committee**
  - Design and continued oversight of study

- **Data Monitoring Committee**
  - Experts in vascular surgery, cardiovascular medicine, interventional radiology and statistics

- **Clinical Events Committee**
  - Blinded adjudication of clinical and bleeding events
  - University Medical Center Utrecht, Utrecht, NL

- **Core Laboratory**
  - Blinded
  - VasCore (Massachusetts General Hospital, Boston, MA) – duplex ultrasound

- **Clinical Sites and Data Management**
  - Medpace, Cincinnati, OH
Study Endpoints

• Primary safety endpoint:
  • Blinded, adjudicated bleeding using TIMI and ISTH criteria\(^1,2\)
    • Safety population

• Primary efficacy endpoint:
  • Restenosis or reocclusion at month 6, defined as peak systolic velocity ratio ≥ 2.4 at the treated segment obtained using duplex ultrasonography\(^3\)
    • Modified intent-to-treat population

ISTH, International Society of Thrombosis and Haemostasis; TIMI, Thrombosis in Myocardial Infarction.

Patient Disposition

Screened Subjects
N = 275

Screen Failure
n = 72

Randomized
N = 203

Clopidogrel
n = 102

mITT 1/Safety
n = 101

Completed
n = 96

never took study drug
n = 1

Permanently discontinued
n = 5

AE = 1
Lost to f/u = 1
Withdrawn consent = 2
Physician decision = 1

Edoxaban
n = 101

mITT 1/Safety
n = 100

Completed
n = 89

never took study drug
n = 1

Permanently discontinued
n = 11

AE = 1
Lost to f/u = 2
Death = 3
Withdrawn consent = 5

AE, adverse event; f/u; follow up; mITT 1, modified intent-to-treat including all randomized subjects who received ≥1 dose of study drug.
## Baseline Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Clopidogrel N = 102</th>
<th>Edoxaban N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.7 (8.55)</td>
<td>68.0 (10.36)</td>
</tr>
<tr>
<td>≥65, n (%)</td>
<td>69 (67.6)</td>
<td>71 (70.3)</td>
</tr>
<tr>
<td>≥75, n (%)</td>
<td>16 (15.7)</td>
<td>23 (22.8)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>24 (23.5)</td>
<td>34 (33.7)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (SD)</strong></td>
<td>27.69 (4.90)</td>
<td>27.10 (4.61)</td>
</tr>
<tr>
<td><strong>History of diabetes, n (%)</strong></td>
<td>40 (39.2)</td>
<td>41 (40.6)</td>
</tr>
<tr>
<td>HbA1c, mean (SD)</td>
<td>8.07 (1.79)</td>
<td>7.92 (1.84)</td>
</tr>
<tr>
<td><strong>Baseline CrCl, mL/min, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 and ≤50</td>
<td>15 (14.7)</td>
<td>19 (18.8)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>87 (85.3)</td>
<td>82 (81.2)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CrCl, creatinine clearance; HbA1c, glycated hemoglobin; SD, standard deviation.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Clopidogrel N = 102</th>
<th>Edoxaban N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>0 or 1 – Asymptomatic or mild claudication</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2 – Moderate claudication</td>
<td>30 (29.4)</td>
<td>29 (28.7)</td>
</tr>
<tr>
<td>3 – Severe claudication</td>
<td>56 (54.9)</td>
<td>59 (58.4)</td>
</tr>
<tr>
<td>4 – Ischemic rest pain</td>
<td>11 (10.8)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>5 – Minor tissue loss</td>
<td>5 (4.9)</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>6 – Ulceration or gangrene</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
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<th>Category</th>
<th>Clopidogrel N = 102</th>
<th>Edoxaban N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion location, n/N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>94/102 (92.2)</td>
<td>92/99 (92.9)</td>
</tr>
<tr>
<td>Popliteal</td>
<td>8/102 (7.8)</td>
<td>7/99 (7.1)</td>
</tr>
<tr>
<td><strong>Lesion length, cm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.0 (10.04)</td>
<td>12.5 (10.11)</td>
</tr>
<tr>
<td>Max</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Lesion length, cm, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>42 (41.2)</td>
<td>38 (38.0)</td>
</tr>
<tr>
<td>7–12</td>
<td>20 (19.6)</td>
<td>22 (22.0)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>40 (39.2)</td>
<td>40 (40.0)</td>
</tr>
<tr>
<td><strong>Lesion severity, n/N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>66/102 (64.7)</td>
<td>64/100 (64.0)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>36/102 (35.3)</td>
<td>36/100 (36.0)</td>
</tr>
</tbody>
</table>
RESULTS
Adjudicated Bleeding Events in the On-Treatment period – Safety Set

<table>
<thead>
<tr>
<th>Category</th>
<th>Clopidogrel N = 101</th>
<th>Edoxaban N = 100</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>TIMI Criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>9 (8.9)</td>
<td>5 (5.0)</td>
<td>0.56 (0.19, 1.62)</td>
</tr>
<tr>
<td>ISTH Criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or CRNM bleeding</td>
<td>8 (7.9)</td>
<td>11 (11.0)</td>
<td>1.39 (0.58, 3.31)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (5.0)</td>
<td>1 (1.0)</td>
<td>0.20 (0.02, 1.70)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>28 (27.7)</td>
<td>30 (30.0)</td>
<td>1.08 (0.70, 1.67)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ISTH, International Society of Thrombosis and Haemostasis; RR, relative risk; TIMI, thrombolysis in myocardial infarction.
Kaplan-Meier Cumulative Event Rate Estimates for Adjudicated Bleeding Events per TIMI Criteria (Safety Analysis Set, Overall Study Period)

RR (95%CI) for any bleeding : 0.56 (0.19, 1.62)

Clopidogrel N = 101; Edoxaban N = 100.

CI, confidence interval; TIMI, thrombolysis in myocardial infarction; RR, relative risk.
Kaplan-Meier Cumulative Event Rate Estimates for Adjudicated Major Bleeding Events per ISTH Criteria (Safety Analysis Set, Overall Study Period)

<table>
<thead>
<tr>
<th>Days</th>
<th>Clopidogrel N = 101</th>
<th>Edoxaban N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>30</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>60</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>90</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>120</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>150</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>180</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

RR (95%CI) for major bleeding: 0.20 (0.02, 1.70)

CI, confidence interval; ISTH, International Society of Thrombosis and Haemostasis; RR, relative risk.
Kaplan-Meier Cumulative Event Rate Estimates for Adjudicated Major and Clinically Relevant Nonmajor Bleeding Events per ISTH Criteria (Safety Analysis Set, Overall Study Period)

RR (95%CI) for major and CRNM bleeding: 1.39 (0.58, 3.31)

Subjects with major and CRNM bleeding (%)

Days

Clopidogrel N = 101; Edoxaban N = 100.

CI, confidence interval; CRNM, clinically relevant nonmajor bleeding; ISTH, International Society of Thrombosis and Haemostasis; RR, relative risk.
Six-month composite endpoint event rates in patients with PAD who have undergone EVT treatment (mITT)

- Restenosis/Reocclusion
- Restenosis/Reocclusion + TLR
- Restenosis/Reocclusion + TLR + Amputation
- Restenosis/Reocclusion + TLR + Amputation + MACE

CI, confidence interval; EVT, endovascular treatment; MACE, Major adverse cardiovascular event, including non-fatal MI, non-fatal stroke, and CV death; mITT, modified intent-to-treat; PAD, peripheral artery disease; RR, relative risk; TLR, target lesion revascularization.
Six-month composite endpoint (re-stenosis, re-occlusion, TLR, and amputation) event rates in patients with PAD who have undergone EVT treatment (mITT)

- Gender: Female
- Gender: Male
- Lesion Length: $\leq 7$ cm
- Lesion Length: $> 7$ cm
- Age: $\leq 65$ years
- Age: $> 65$ years
- Region: Europe
- Region: USA

CI, confidence interval; EVT, endovascular treatment; mITT, modified intent-to-treat; PAD, peripheral artery disease; TLR, target lesion revascularization.
Conclusions

• This proof of concept study results suggest that in PAD patients who have undergone EVT treatment both the risk for major and life threatening bleeding events and the risk of restenosis/reocclusion events may be lower with the combination of edoxaban and aspirin compared to the combination of clopidogrel and aspirin.

• An adequately sized trial will be needed to confirm this potentially paradigm shifting treatment approach.
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- The Study Steering Committee: Frans Moll, Iris Baumgartner, Michael Jaff, Erich Minar, Gary Ansel, George Adams, Chuke Nwachuku, Marco Tangelder, Michael Grosso, Hans Lanz

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Backup slides
### ISTH vs. TIMI Bleeding Definitions: CEC Adjudicated

<table>
<thead>
<tr>
<th>ISTH</th>
<th>TIMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td><strong>Major</strong></td>
</tr>
<tr>
<td>- Associated with a fall in Hgb of 2 g/dL</td>
<td>- Any ICH or any clinically overt bleeding, (including bleeding evident in imaging studies) associated with a fall of Hgb of ≥ 5gm/dL</td>
</tr>
<tr>
<td>- Leading to transfusion of ≥ 2 units of packed red cells or whole blood</td>
<td></td>
</tr>
<tr>
<td>- Occurring at a critical site [ICH, ISH, IOH, Pericardial, Intra-articular, intra-muscular or compartment syndrome, retroperitoneal</td>
<td></td>
</tr>
<tr>
<td>- Contributing to death</td>
<td></td>
</tr>
<tr>
<td><strong>CRNM</strong></td>
<td></td>
</tr>
<tr>
<td>- Overt bleeding not meeting major bleeds, but requires medical intervention, unscheduled contact (visit or telephone call) with a physician, temporary cessation of study treatment or associated with any discomfort such as pain or impairment of ADL.</td>
<td></td>
</tr>
<tr>
<td>- Several examples including intramuscular hematomas; subcutaneous skin hematomas</td>
<td></td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>- All other overt bleeding episodes not meeting the criteria of major or CRNM</td>
<td>- Any clinically overt bleeding associated with a fall in Hgb ≥ 3gm/dL but &lt; 5 gm/dL</td>
</tr>
<tr>
<td><strong>Minimal</strong></td>
<td><strong>Minimal</strong></td>
</tr>
<tr>
<td>- Any clinically overt bleeding associated with a fall in Hgb &lt;3gm/dL</td>
<td>- Any clinically overt bleeding associated with a fall in Hgb &lt;3gm/dL</td>
</tr>
</tbody>
</table>
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