VOYAGER PAD trial

RCT investigating efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic PAOD undergoing revascularization – the concept of an event driven trial

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Disclosures

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- **Research Support / Principal Investigator:**
  - Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Leo, Pfizer, Portola

- **Consultant & Speakers Bureau:**
  - Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer
Prevalence of PAD is high and increases significantly with age

The Rotterdam Study

- Patients aged ≥55 years
- 19.1% had PAD
- Prevalence higher in women (20.5%) than in men (16.9%)
- Clear increase of PAD with age
- >50% of patients aged ≥85 years have PAD

PAD=Peripheral artery disease.
Prevalence of PAD is high and continues to increase since 2000

Natural history – 5-year follow-up

- **No symptoms (20–50%)**
- **Interm. claudication (10–35%)**
- **Other leg pain (30–40%)**

**Limb prognosis**
- Stable: 70–80%
- Further reduced WD: 10–20%
- Critical limb ischaemia: 5–10%
- Amputation: <1% annually

**General prognosis**
- Mortality: 10–15%
- (CV: 75%)
- MI/stroke: 20%

CV=Cardiovascular; MI=Myocardial infarction; WD=Walking distance.
CAD and PAD: Overlapping conditions

The REACH registry showed 3 out of 5 patients with PAD also have CAD and/or CVD.

- 8322 patients had PAD
  - ~39% had PAD only
  - ~38% had PAD and CAD
  - ~10% had PAD and CVD
  - ~13% PAD, CAD and CVD

CAD=Coronary artery disease; CVD=Cerebrovascular disease; PAD=Peripheral artery disease.

## Current treatment strategies for patients with PAD

<table>
<thead>
<tr>
<th>Symptom Improvement</th>
<th>CV risk reduction</th>
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<tr>
<td>Exercise training</td>
<td>Lipid-lowering drugs (e.g. statin)</td>
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<td>Pharmacological treatments (e.g. cilostazol, pentoxifylline)</td>
<td>Antihypersensitive drugs (e.g. ACE inhibitor)</td>
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<td>Endovascular intervention (e.g. stent placement)</td>
<td>Diabetes therapies</td>
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<td>Surgery (e.g. revascularisation)</td>
<td>Smoking cessation</td>
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<tr>
<td>Antiplatelet drugs (e.g. ASA, clopidogrel)</td>
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ACE=Angiotensin-converting-enzyme; ASA=Acetylsalicylic acid; CV=Cardiovascular; PAD=Peripheral artery disease.
Antithrombotic treatment after intervention

• Cochrane Review conclusions
  • Limited evidence suggesting that restenosis/reocclusion is reduced by antiplatelet drugs;
  • information on bleeding and side effects is lacking.
  • Trials are small and of variable quality and side effects are not addressed.
  • Further good quality, large-scale RCTs are required.

Antithrombotic treatment after intervention Guidelines

- ACC/AHA and ESC are divergent
- Recommendations often extrapolated from CAD, or expert opinions
- ACCP recommend single antiplatelet over DAPT post angioplasty/ and stent in PAD (2C)
- ESC: DAPT with aspirin / thienopyridine for ≥ 1 month after infrainguinal BMS (IC)
- Anticoagulation after infrainguinal PTA/ stenting was assessed in 3 RCTs: None showed significant improvement in patency => anticoagulation cannot be recommended

NOAC (triple) treatment after ACS

CV death, MI, or stroke
Stent thrombosis
Major bleeding
Major or minor bleeding

Apixaban 5 mg bid therapeutic dose on top of:
- Aspirin Only
- Aspirin + Clopidogrel
NOAC (triple) treatment after ACS

NOAC (triple) treatment after ACS (TIMI 51)
Very low dose Rivaroxaban (2.5 mg bid)

CV = Kardiovaskulär; HR = Hazard Ratio; MI = Myokardinfarkt; NNT = Number needed to treat
NOAC (triple) treatment after ACS (TIMI 51) Stent thrombosis

Estimated Cumulative incidence (%)

Placebo

Rivaroxaban (both doses)

Natural history – 5-year follow-up

- **No symptoms** (20–50%)
  - Stable: 70–80%
  - Further reduced WD: 10–20%
  - Critical limb ischaemia: 5–10%
  - Amputation: <1% annually

- **Interm. claudication** (10–35%)

- **Other leg pain** (30–40%)

**Limb prognosis**

**General prognosis**

- **Mortality**: 10–15%
- (CV: 75%)
- **MI/stroke**: 20%

CV=Cardiovascular; MI=Myocardial infarction; WD=Walking distance.
Official study title: An International, Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial Investigating the Efficacy and Safety of Rivaroxaban to Reduce the Risk of Major Thrombotic Vascular Events in Patients with Symptomatic Peripheral Artery Disease Undergoing Lower Extremity Revascularization Procedures

Objective:
Efficacy and safety of rivaroxaban for the reduction of thrombotic vascular events in subjects with PAD undergoing peripheral revascularisation procedures

Population:
Patients with symptomatic PAD undergoing peripheral revascularisation

Study design:
Rivaroxaban 2.5 mg bid + ASA 100 mg od

Event-driven study (1.015 events)
MI, ischemic stroke, CV death, ALI, and major amputation (vascular etiology)

Day 1
DAPT

ASA 100 mg od

Up to 7 days

Mean 30 months

*Mean treatment duration ~30 months. ASA=Acetylsalicylic acid; bid=Twice daily; MI=Myocardial infarction; od=Once daily; PAD=Peripheral artery disease; R=Randomisation; TIMI=Thrombolysis in myocardial infarction.

Primary endpoints and inclusion/exclusion criteria

**Primary efficacy endpoints**

- Composite of MI, stroke or CV death, ALI, and major amputation due to vascular etiology

**Key inclusion criteria**

- Age ≥50 years
- Symptomatic and haemodynamic PAD
- Technically successful peripheral infrainguinal revascularisation within last 7 days prior to randomisation

**Primary safety endpoints**

- TIMI major bleeding events

**Key exclusion criteria**

- Asymptomatic PAD or mild claudication
- Major tissue loss/gangrene beyond the forefoot
- Prior revascularisation within 8 weeks
- ALI within 2 weeks
- Planned DAPT >30 days
- Planned DAPT for any other indication
- Systemic anticoagulation

ALI=Acute limb ischaemia; CV=Cardiovascular; DAPT=Dual antiplatelet therapy; MI=Myocardial infarction; PAD=Peripheral artery disease; TIMI=Thrombolysis in myocardial infarction.

Study design (contd)

- **Randomisation / stratification** by procedure and clopidogrel use

- Event-driven (~1015 endpoint events)
- ITT
- ≈6,500 patients
- Enrollment period: ~18 months
- Start: Q4 2015; last patient: Q1 2017

ASA = acetylsalicylic acid; ITT = intention-to-treat.
ClinicalTrials.com Identifier: NCT02504216.
Committee chairs

**Executive Committee**
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University of Colorado and CPC  
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Unmet needs in PAD

- PAD remains a frequent and serious disorder with a high rate of severe thrombotic complications, including AMI, stroke, CV death, ALI and amputation.

- The risk is particularly high in incident patients, i.e. patients undergoing revascularisation.

- VOYAGER PAD is the largest antithrombotic trial ever performed in PAOD patients undergoing revascularization.

- VOYAGER PAD will also provide important long-term and large-scale outcome data in patients undergoing revascularisation procedures for PAD.
Thank you very much for your attention!
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7. FRANKFURTER GERINNUNGSSYMPOSIUM

2. – 3. SEPTEMBER 2016