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.
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

Symptom Improvement

- Exercise training
- Pharmacological treatments (e.g. cilostazol, pentoxifylline)
- Endovascular intervention (e.g. stent placement)
- Surgery (e.g. revascularisation)

CV risk reduction

- Lipid-lowering drugs (e.g. statin)
- Antihypersensitive drugs (e.g. ACE inhibitor)
- Diabetes therapies
- Smoking cessation
- Antiplatelet drugs (e.g. ASA, clopidogrel)

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

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


HR 0.69
(0.51-0.93)

ITT  p = 0.008

2.9%
2 Yr KM Estimate

2.3%

Estimated Cumulative incidence (%)

Placebo

Rivaroxaban
(both doses)

ARC Definite/probable: HR=0.65, mITT p=0.017, ITT p=0.012

Months After Randomization

0
4
8
12
16
20
24

0
1
2
3

0.69
(0.51-0.93)
Natural history – 5-year follow-up

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CV=Cardiovascular; MI=Myocardial infarction; WD=Walking distance.
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

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
Up to 7 days
Mean 30 months

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

*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

#### Primary safety endpoints
- TIMI major bleeding events

#### Key inclusion criteria
- Age $\geq$ 50 years
- Symptomatic and haemodynamic PAD
- Technically successful peripheral infrainguinal revascularisation within last 7 days prior to randomisation

#### 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

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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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Conclusion
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