Update on the Voyager-PAD

Eike Sebastian Debus, Hamburg
Disclosure

Speaker name:
Univ.-Prof. Eike Sebastian Debus, FEBS, FEBVS

- Executive Member VoyagerPAD trial / Bayer
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

Natural history – 5-year follow-up

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Limb prognosis
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Key Points in PAD Treatment with Revascularization

Post-revascularization PAD than stable PAD

PAD antithrombotic practice patterns vary widely
  Likely influenced by CAD treatment patterns
    Little data to support varying DAPT prescribing patterns

• We are still searching for the best way to care for post-revascularization PAD
  DAPT is not supported by trial evidence in this setting, demonstrating the uncertainty of current treatment decisions
DAPT equivalent to ASA alone after PAD Surgical Bypass (CASPAR-trial)

- n= 851 below-knee bypass ASA + clopidogrel vs. ASA alone
- Primary EP: graft occlusion, revascularization, amputation, death
- DAPT failed to decrease risk of limb events or death

Belch et al. Journal of Vascular Surgery. 2010
Anticoagulation fails to prevent graft occlusion, increases bleeding (Dutch BOA-trial)

- 2,690 infra-inguinal bypass (vein 59%, prosthetic 33%, other 8%)
- Warfarin INR 3.0-4.5 versus aspirin 80 mg/d started within 5 d
- FU 21 months

**Hemorrhagic risk**

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<tr>
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<th>Warfarin</th>
<th>ASA</th>
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<tr>
<td>Major bleed</td>
<td>4.7%/yr</td>
<td>2.5%/yr</td>
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<tr>
<td>Fatal bleed</td>
<td>0.7%/yr</td>
<td>0.5%/yr</td>
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Lancet 2000;355:346-51
Guideline Recommendations
Management of Antithrombotics in the setting of revascularization

**ACC-AHA 2011 update.** Aspirin or clopidogrel for reduction of ischemic risk; silent on the optimal antithrombotic approach to revascularization

**TASC 2007** - Aspirin or clopidogrel for reduction of ischemic risk; silent on the optimal antithrombotic approach to revascularization

**Chest 2012** - For patients undergoing peripheral artery angioplasty recommend long term aspirin (75-100 mg/day) or clopidogrel (75 mg/day) (Grade 1A). **For patients undergoing peripheral artery PTA with stenting, suggest single rather than dual antiplatelet therapy (Grade 2C)**

- ESC – DAPT for 1 month after infrainguinal BMS (1C)
- ESC – Aspirin ± dipyridamole after infrainguinal bypass (1A)
Status of Antithrombotic Therapy in PAD

- There is really very little evidence for current practice patterns in the PAD revascularization setting.
- There have been no positive data published in the PAD revascularization setting since the Antithrombotic Trialists Collaboration 1994 report (> 20 years!!)

VOYAGER is an opportunity to change that!
Unmet Need In PAD

The optimal antithrombotic management of patients with PAD undergoing revascularization is unknown

- DAPT after endovascular interventions is unproven but standard practice
- DAPT failed in a surgical revascularization trial
- Full dose warfarin after surgical bypass shows no benefit over aspirin alone
- Interesting initial data on Vorapaxar – an novel antithrombotic drug

VOYAGER Trial Rationale:
- The direct acting factor Xa inhibitor rivaroxaban has shown benefit in ACS
- Will rivaroxaban in combination with aspirin improve limb and systemic outcomes in PAD undergoing revascularization?
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)

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

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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 (cont.)

- Randomisation / stratification by procedure and clopidogrel use

  - Surgical
    - Rivaroxaban & ASA
    - Placebo & ASA
  - Endovascular w/Clopidogrel
    - Rivaroxaban & ASA
    - Placebo & ASA
  - Endovascular w/o Clopidogrel
    - Rivaroxaban & ASA
    - Placebo & ASA

- 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.
## Executive Committee

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<td>United Kingdom</td>
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Global Site Status (Americas)
Global Site Status (Asia Pacific)

- **China**: Sites Selected - 40, Sites Opened - 10
- **Japan**: Sites Selected - 50, Sites Opened - 50
- **South Korea**: Sites Selected - 10, Sites Opened - 10
- **Taiwan**: Sites Selected - 5
- **Thailand**: Sites Selected - 5

Legend:
- Blue: Sites Selected
- Red: Sites Opened
- Green: Sites Closed
Global Site Status (Europe)
Regional Enrollment To Date (25Jan2017)
Conclusion:

- 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
  - Objective: reduce severe thrombotic complications

- VOYAGER PAD will also provide important long-term and large-scale outcome data in patients undergoing revascularisation procedures for PAD
European Society for Vascular Surgery
Specialists in Vascular HealthCare

Forward. Together.

Join us in Lyon, France!
Sept 19-22 2017
Update on the Voyager-PAD

Eike Sebastian Debus, Hamburg