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

Rupert M. Bauersachs
Dept. of Vascular Medicine
CTH – Professorship for Vulnerable Individuals and Populations (VIP)

Gefäßzentrum Darmstadt

KlinikumDarmstadt GmbH
Akademisches Lehrkrankenhaus

CTH
Centrum für Thrombose und Hämostase Mainz

Disclosures

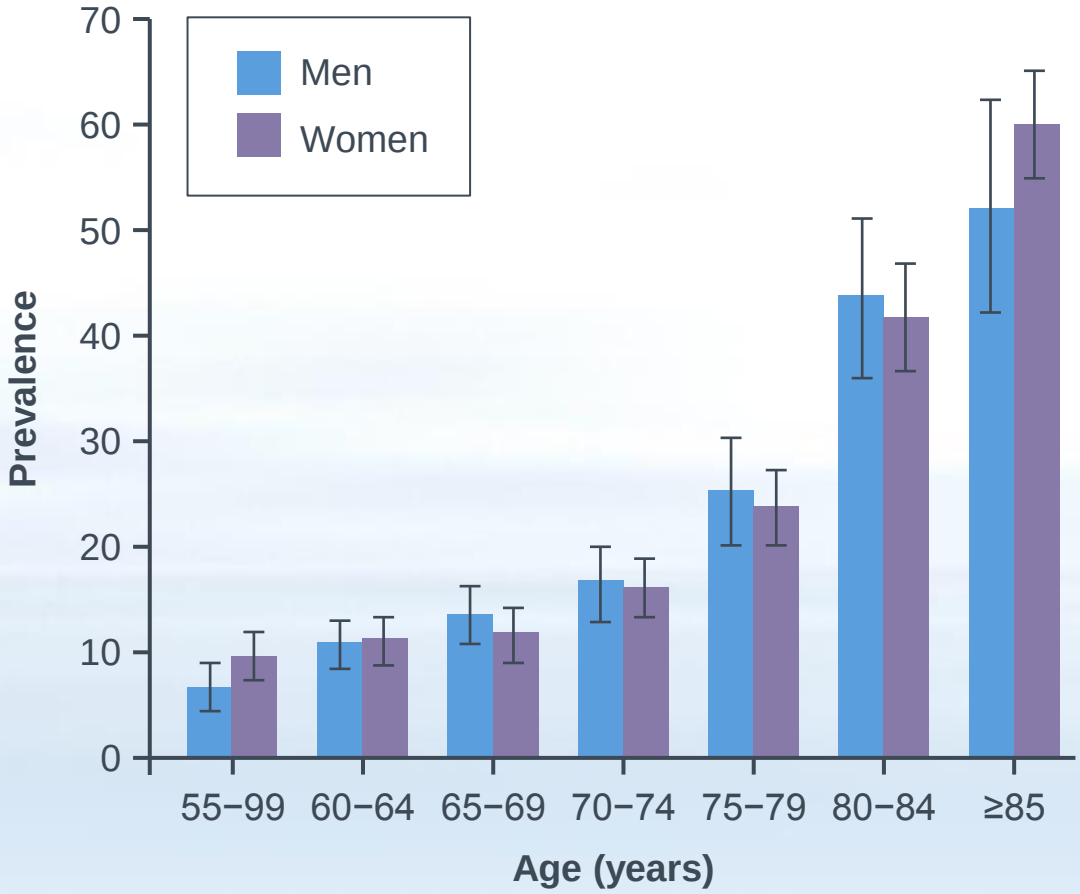
Rupert M. Bauersachs

- **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

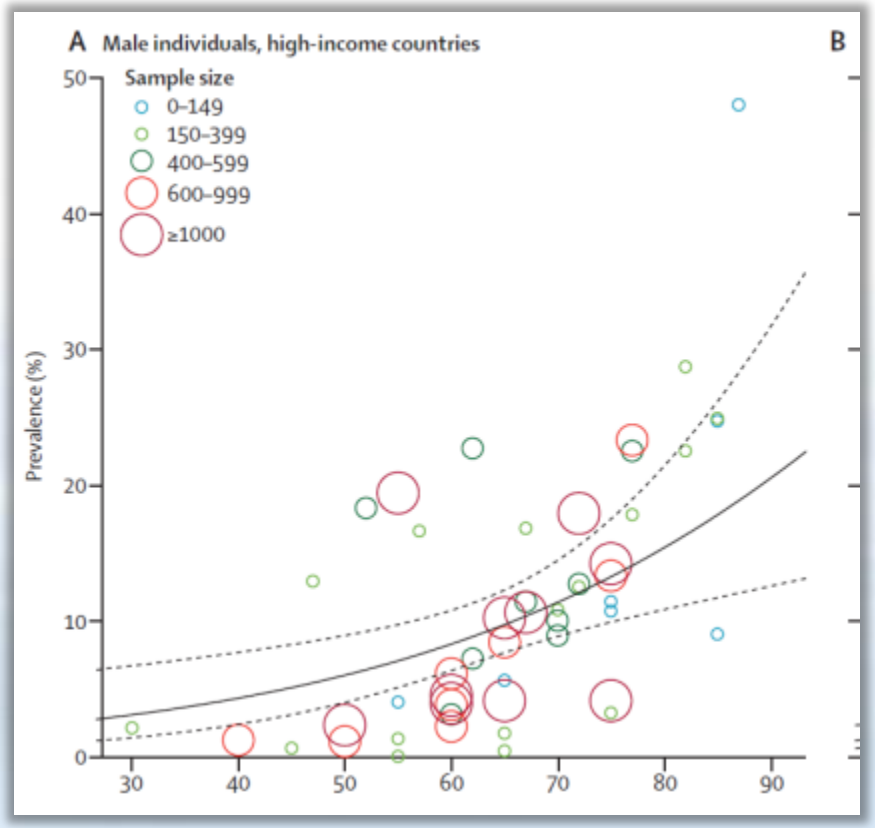
- Patients aged ≥55 years
- 19.1% had PAD
- Prevalence higher in women (20.5%) than in men (16.9%)
- Clear increase of PAD with age
- >50% of patients aged ≥85 years have PAD

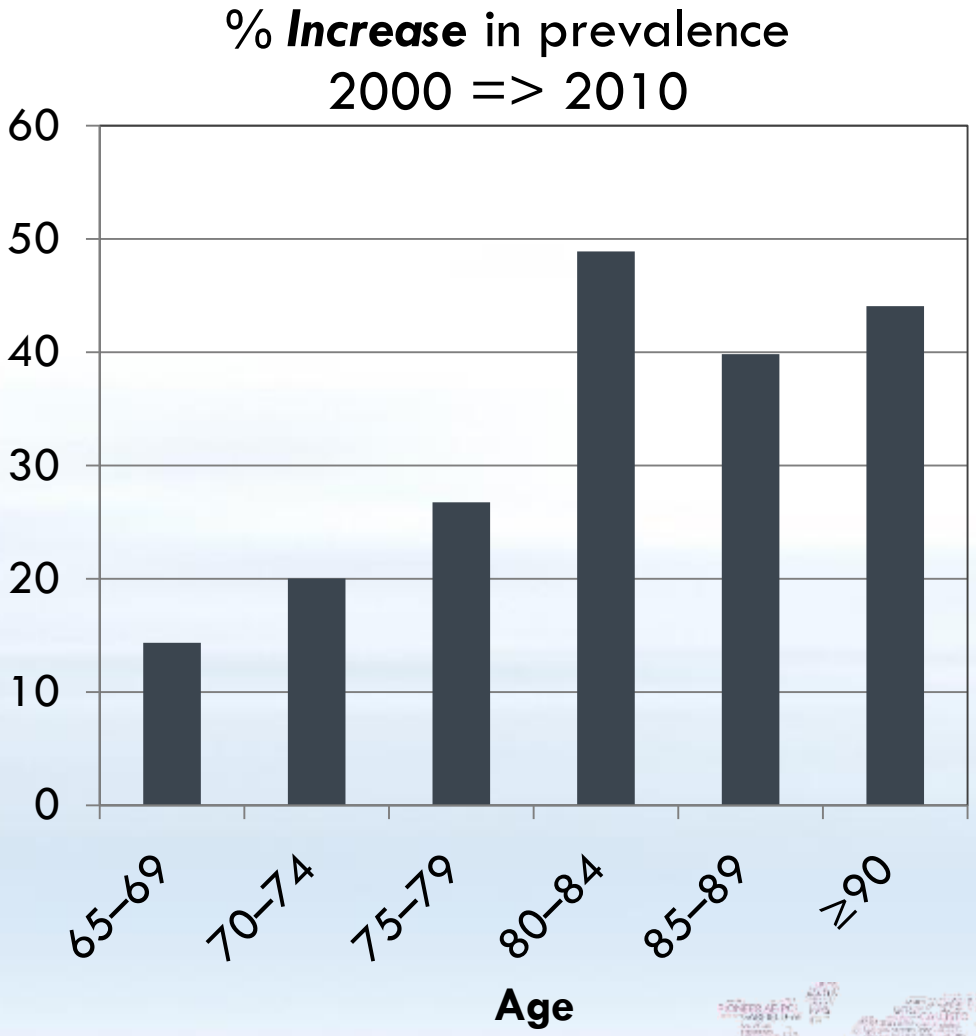


PAD=Peripheral artery disease.

Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185–92.

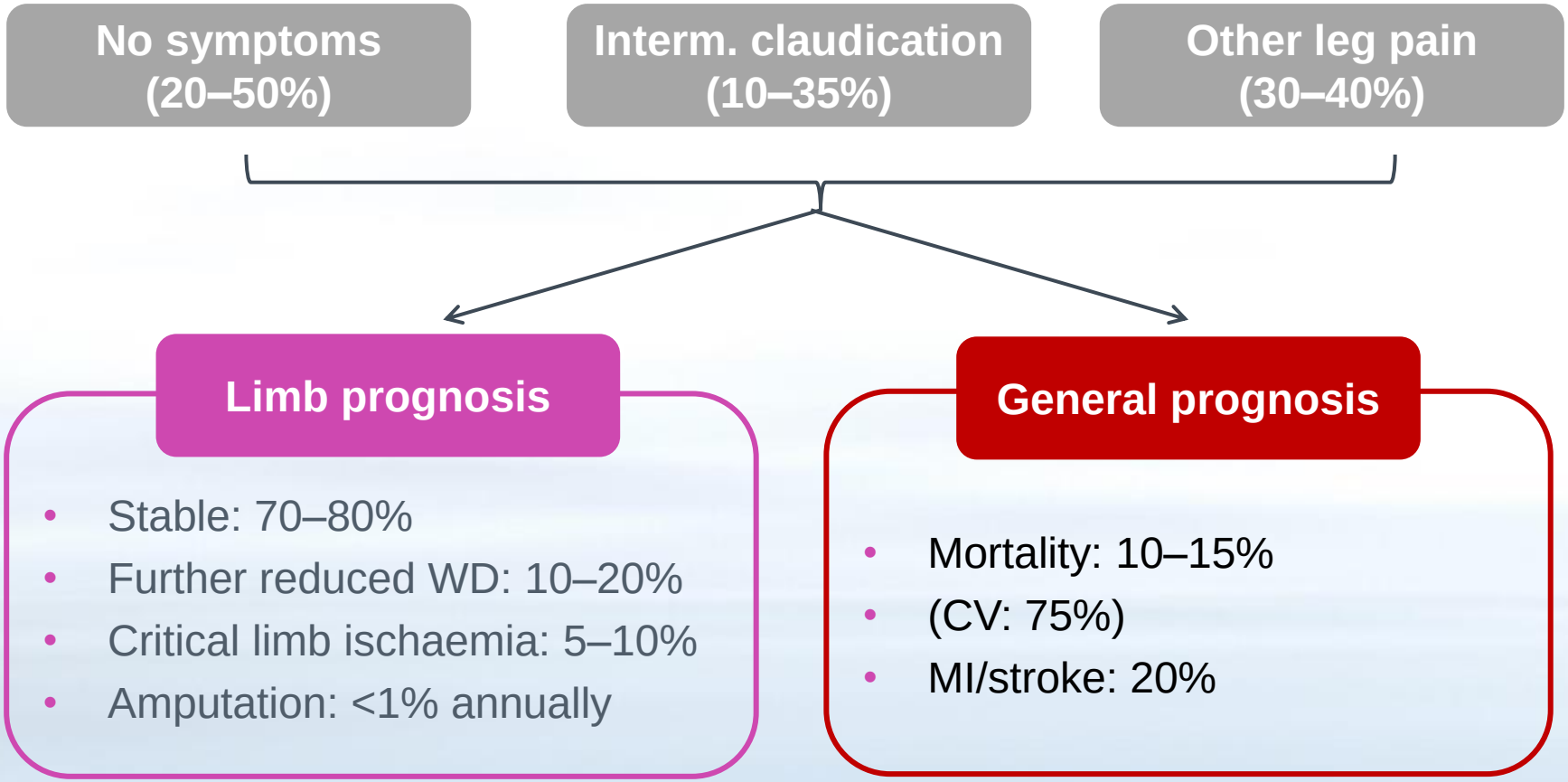
Prevalence of PAD is high and continues to increase since 2000





Fowkes FG, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013 Oct 19;382(9901):1329-40.

Natural history – 5-year follow-up



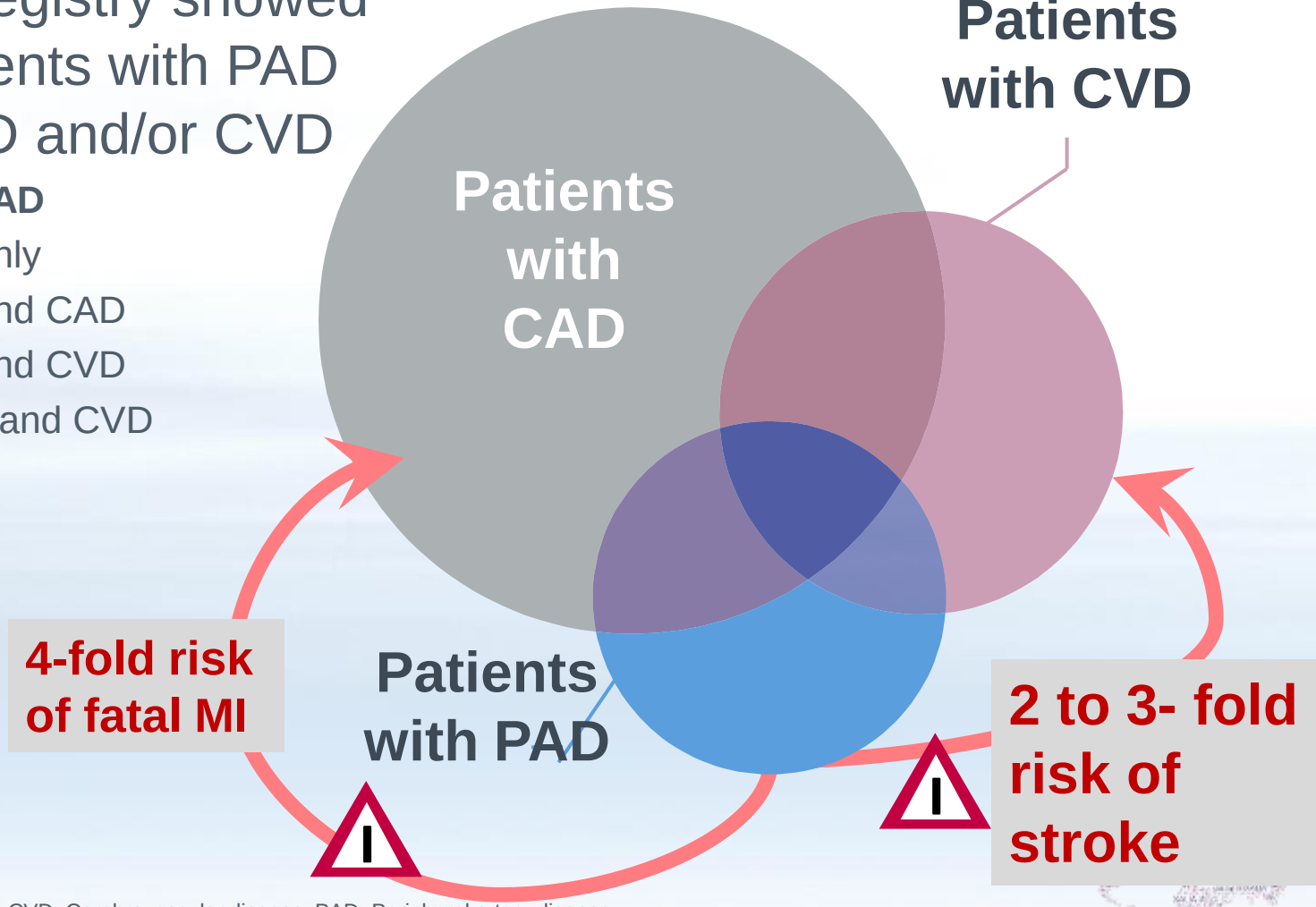
CV=Cardiovascular; MI=Myocardial infarction; WD=Walking distance.
Norgren L, et al. *J Vasc Surg*. 2007;45 Suppl S:S5–67.

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.
Cacoub PP, et al. *Atherosclerosis*. 2009;204:e86–92.

Current treatment strategies for patients with PAD

Symptom Improvement	CV risk reduction
• Exercise training • Pharmacological treatments (e.g. cilostazol, pentoxifylline) • Endovascular intervention (e.g. stent placement) • Surgery (e.g. revascularisation)	• 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.

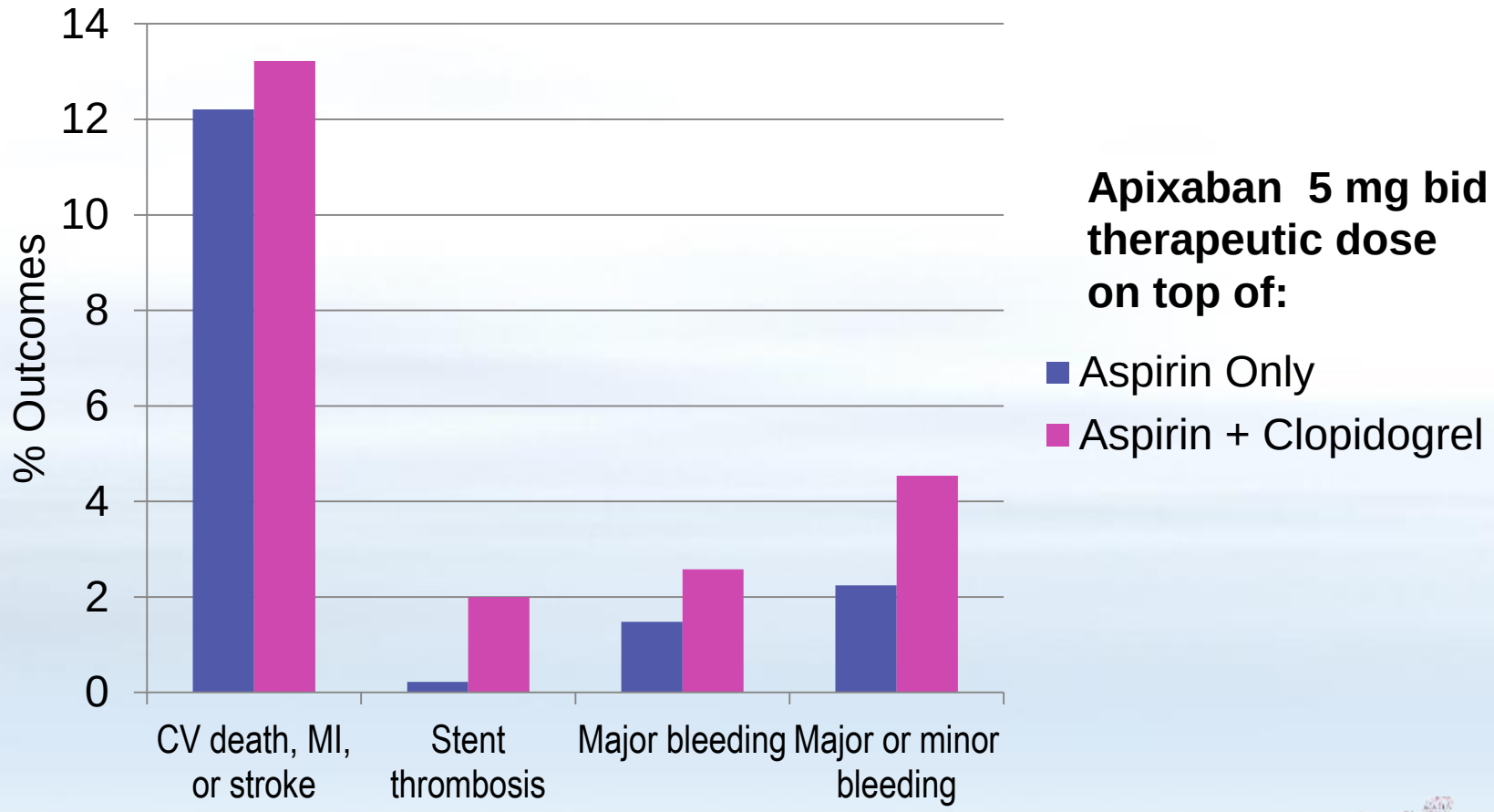
Robertson L, Ghouri MA, Kovacs F. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD002071. DOI: 10.1002/14651858.CD002071.pub3.

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

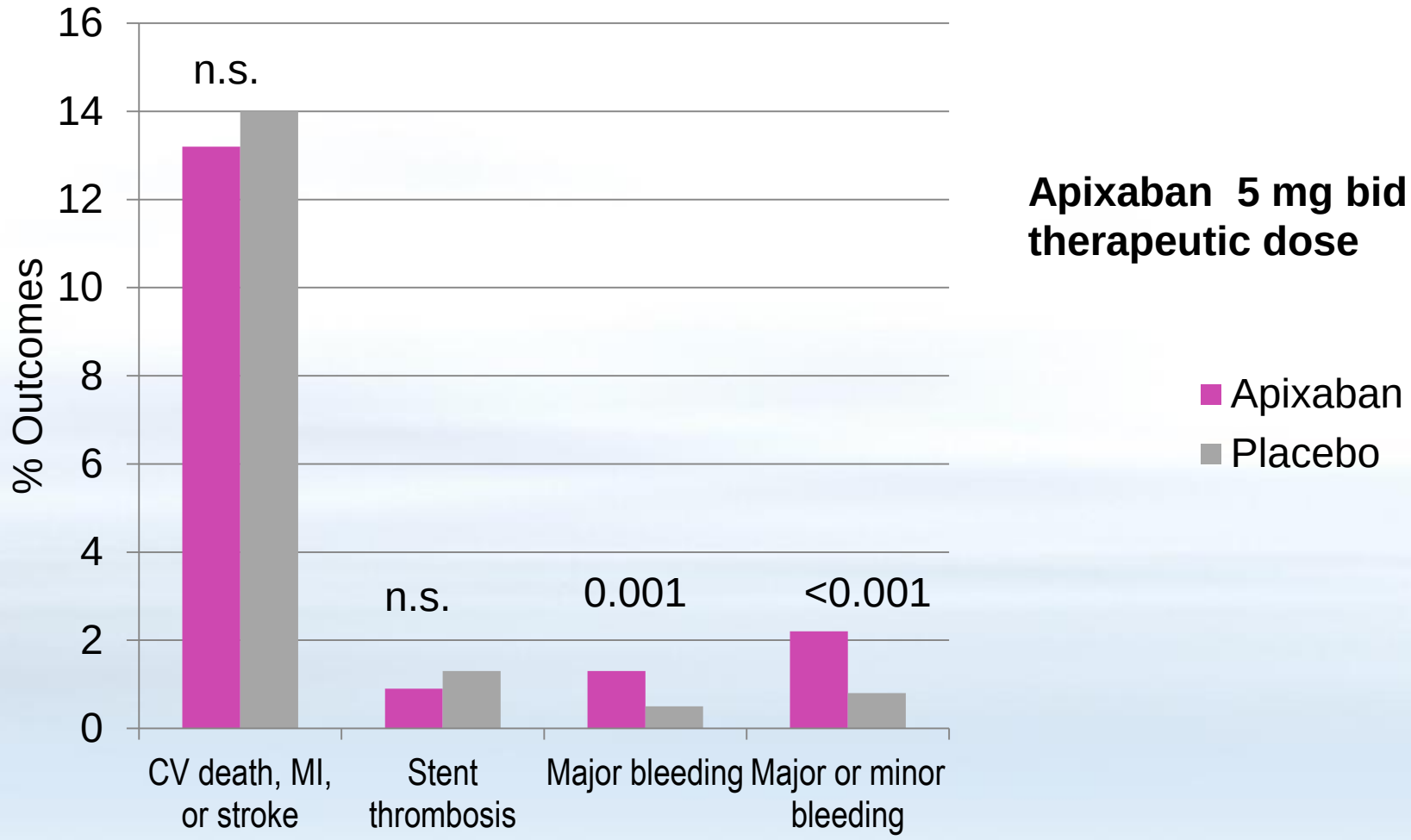
ACCF/AHA [Anderson et al. 2013] and ESC [Tendera et al. 2011] ACCP [Alonso-Coello et al. 2012].

NOAC (triple) treatment after ACS



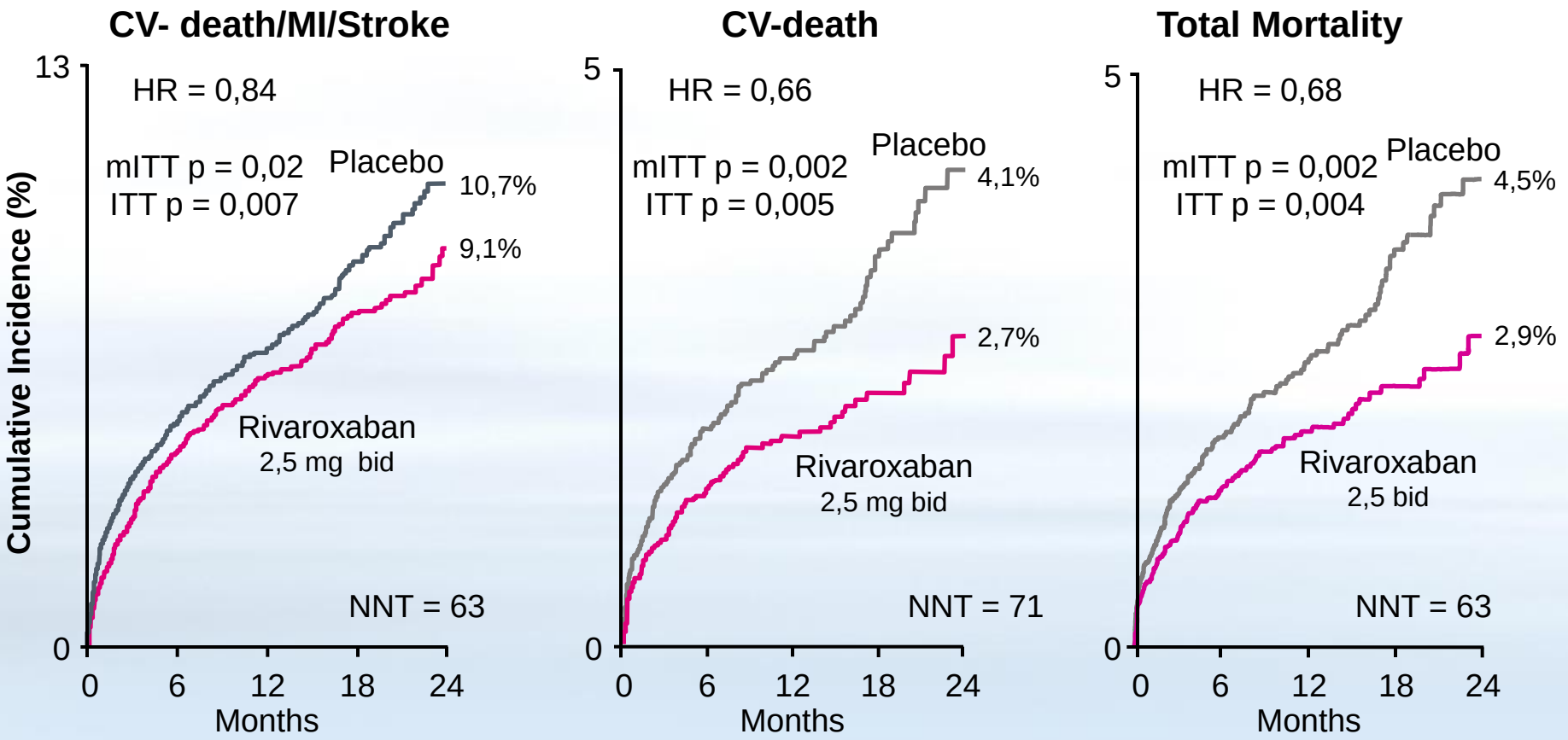
Hess CN, James S, Lopes RD, Wojdyla DM, Neely ML, Liaw D, Hagstrom E, Bhatt DL, Husted S, Goodman SG, Lewis BS, Verheugt FW, De Caterina R, Ogawa H, Wallentin L, Alexander JH. Apixaban Plus Mono Versus Dual Antiplatelet Therapy in Acute Coronary Syndromes: Insights From the APPRAISE-2 Trial. J Am Coll Cardiol. 2015 Aug 18;66(7):777-87.2015/08/14..

NOAC (triple) treatment after ACS



Hess CN, James S, Lopes RD, Wojdyla DM, Neely ML, Liaw D, Hagstrom E, Bhatt DL, Husted S, Goodman SG, Lewis BS, Verheugt FW, De Caterina R, Ogawa H, Wallentin L, Alexander JH. Apixaban Plus Mono Versus Dual Antiplatelet Therapy in Acute Coronary Syndromes: Insights From the APPRAISE-2 Trial. J Am Coll Cardiol. 2015 Aug 18;66(7):777-87.2015/08/14..

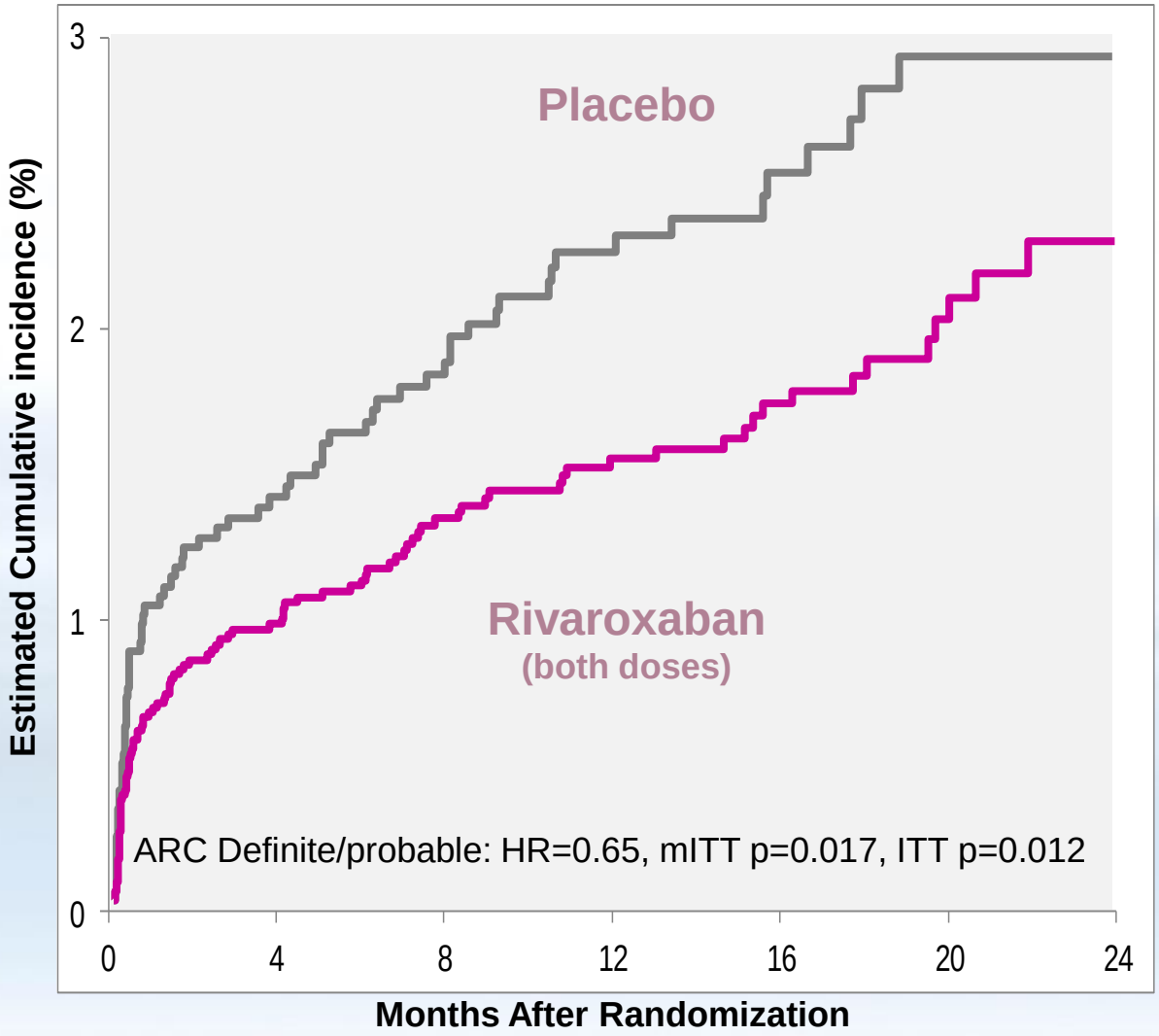
NOAC (triple) treatment after ACS (TIMI 51)
Very low dose Rivaroxaban (2.5 mg bid)



CV = Kardiovaskulär; HR = Hazard Ratio; MI = Myokardinfarkt; NNT = Number needed to treat

Mega JL et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1112277; Gibson CM et al. Presented at AHA Scientific Sessions 2011

NOAC (triple) treatment after ACS (TIMI 51) Stent thrombosis



2.9%

2 Yr KM Estimate

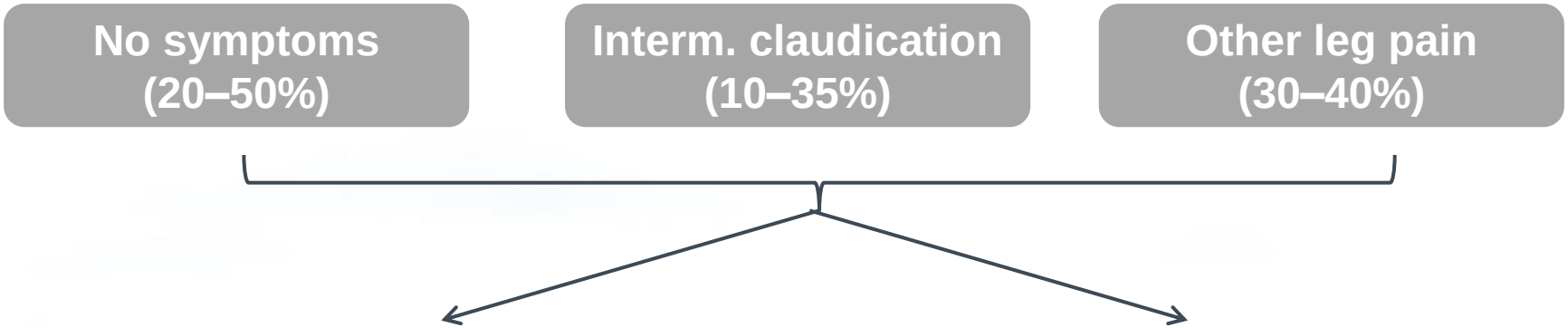
2.3%

HR 0.69
(0.51- 0.93)

ITT p = 0.008

Mega JL et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1112277; Gibson CM et al. Presented at AHA Scientific Sessions 2011

Natural history – 5-year follow-up



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%

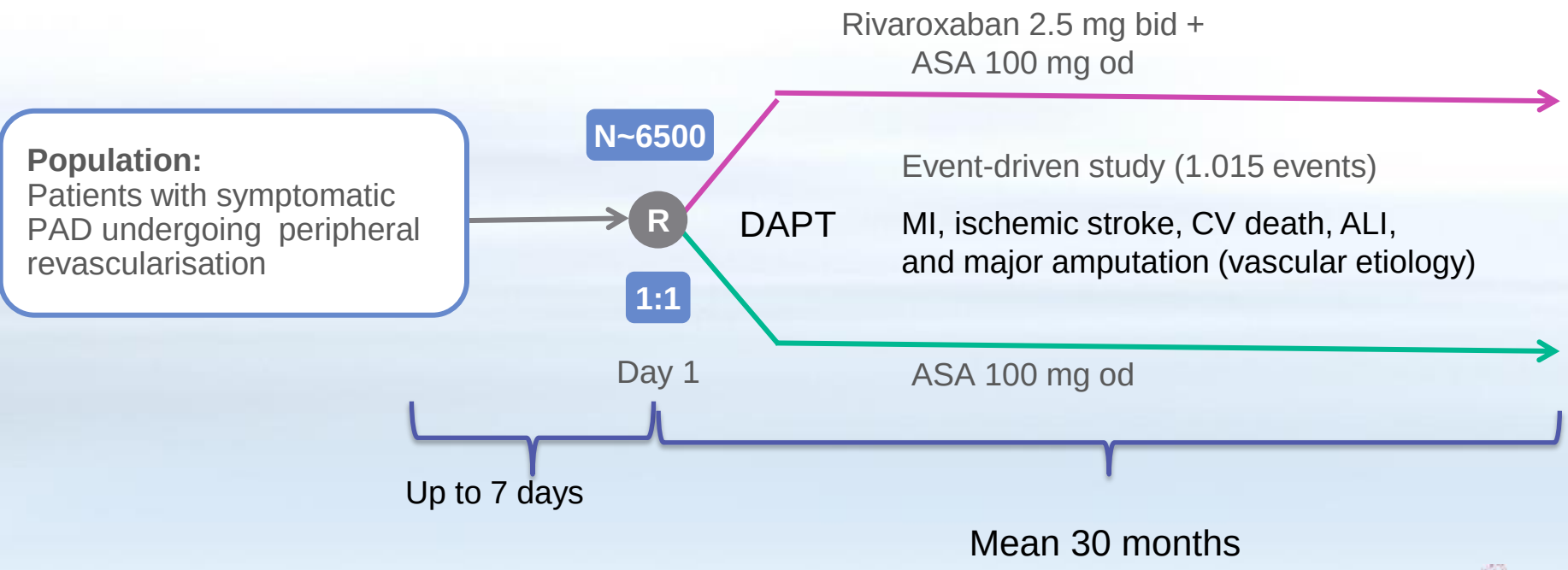
CV=Cardiovascular; MI=Myocardial infarction; WD=Walking distance.

Norgren L, et al. *J Vasc Surg*. 2007;45 Suppl S:S5–67.

Study design

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



*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.
ClinicalTrials.com Identifier: NCT02504216. Available at https://clinicaltrials.gov/ct2/show/NCT02504216 (accessed November 2015).

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

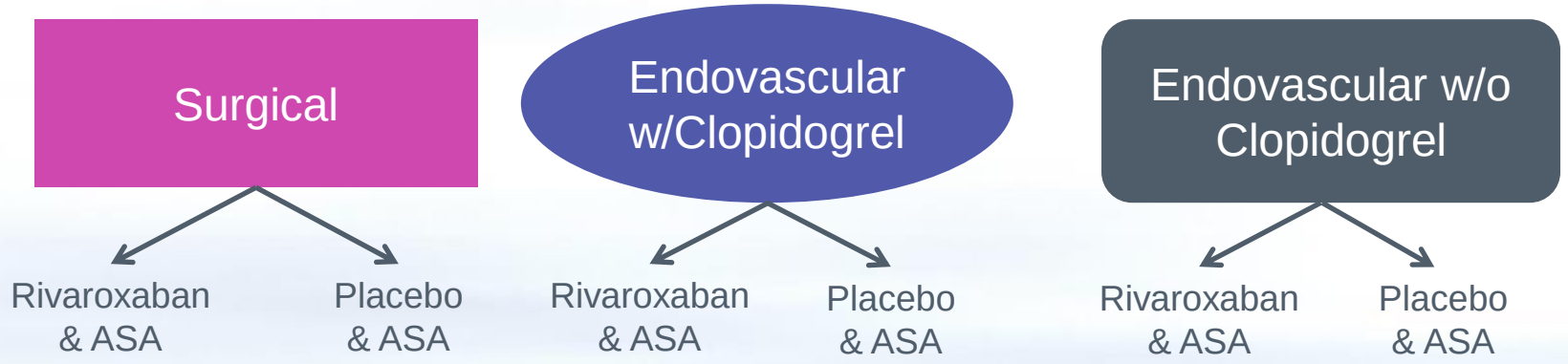
- Asymptomatic PAD or mild claudication
- Major tissue loss/gangrene beyond the forefoot
- Prior revascularisation within 8 weeks
- ALI within 2 weeks
- Planned DAPT >30 days
- Planned DAPT for any other indication
- Systemic anticoagulation

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

ClinicalTrials.com Identifier: NCT02504216. Available at https://clinicaltrials.gov/ct2/show/NCT02504216 (accessed November 2015).

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

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Rupert M. Bauersachs, MD – Co-Chair	Klinikum Darmstadt GmbH

Independent Data Monitoring

John Dormandy, MD – Chair	St. George's Hospital Medical School

Independent Clinical Adjudication

Warren Capell, MD – Chair	CPC Clinical Research

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National lead investigators

Argentina
A. Alarcon

Austria
M. Brodmann

Belgium
F. Vermassen

Brazil
D. Brasil

Bulgaria
V. Chervenkoff

Canada
D. Szalay

China
TBD

Czech Republic
K. Roztocil

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H. Sillesen

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Taiwan
S. Wang

Thailand
P. Mutirangura

United Kingdom
G. Hamilton

United States
R. Powell, A. Hirsch, J. Mustapha & J. Mills

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