

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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Populations (VIP)



Disclosures

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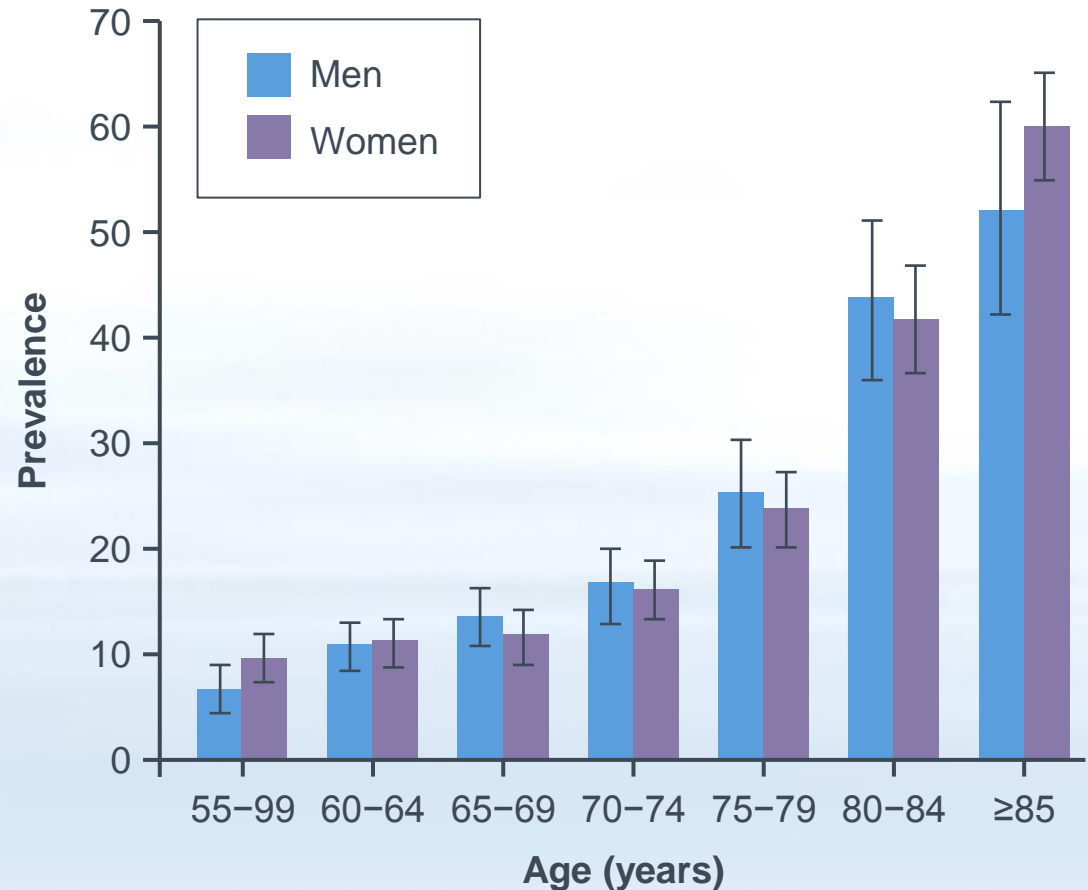
- **Research Support / Principal Investigator:**
 - Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Leo, Pfizer, Portola
- **Consultant & Speakers Bureau:**
 - Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer



Prevalence of PAD is high and increases significantly with age

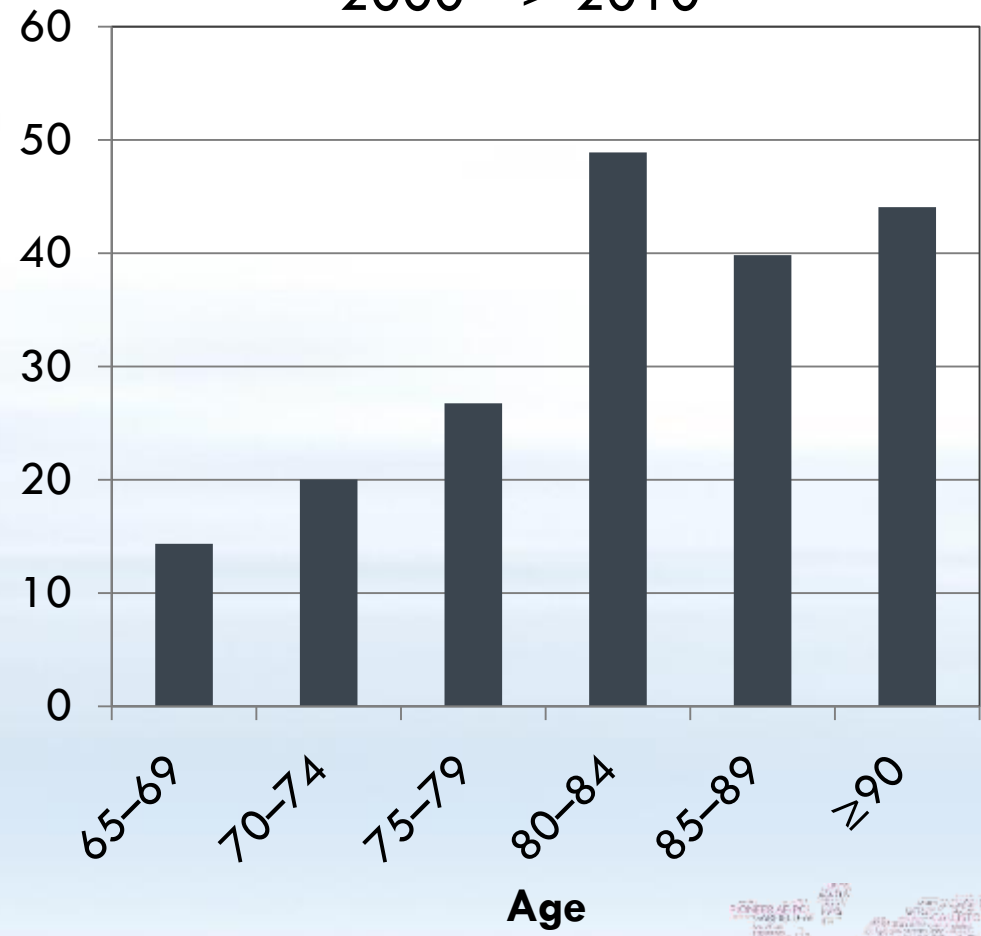
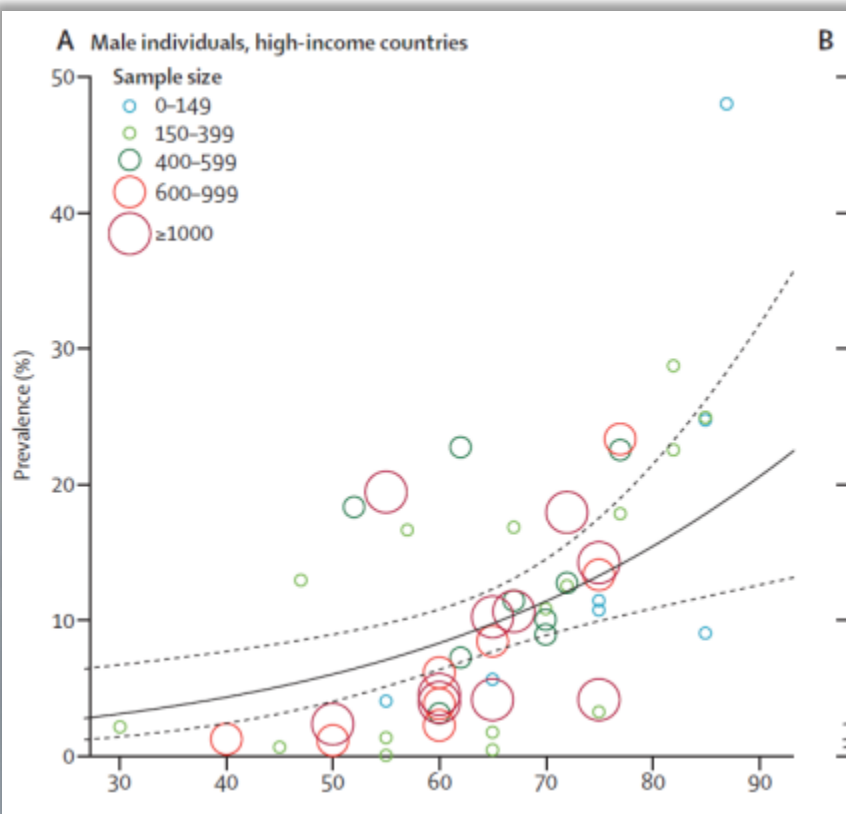
The Rotterdam Study

- 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

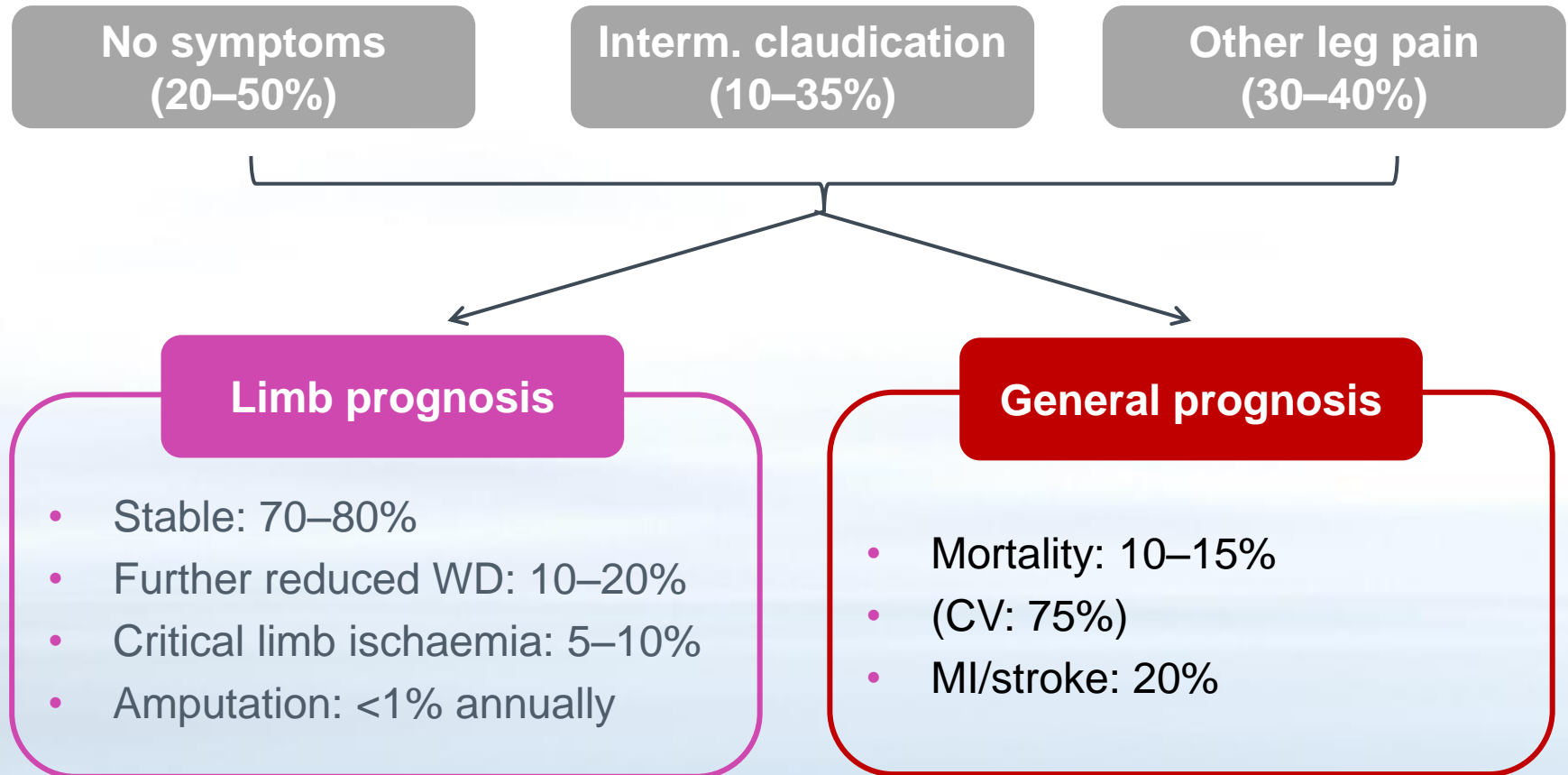


Prevalence of PAD is high and continues to increase since 2000

% Increase in prevalence
2000 => 2010



Natural history – 5-year follow-up

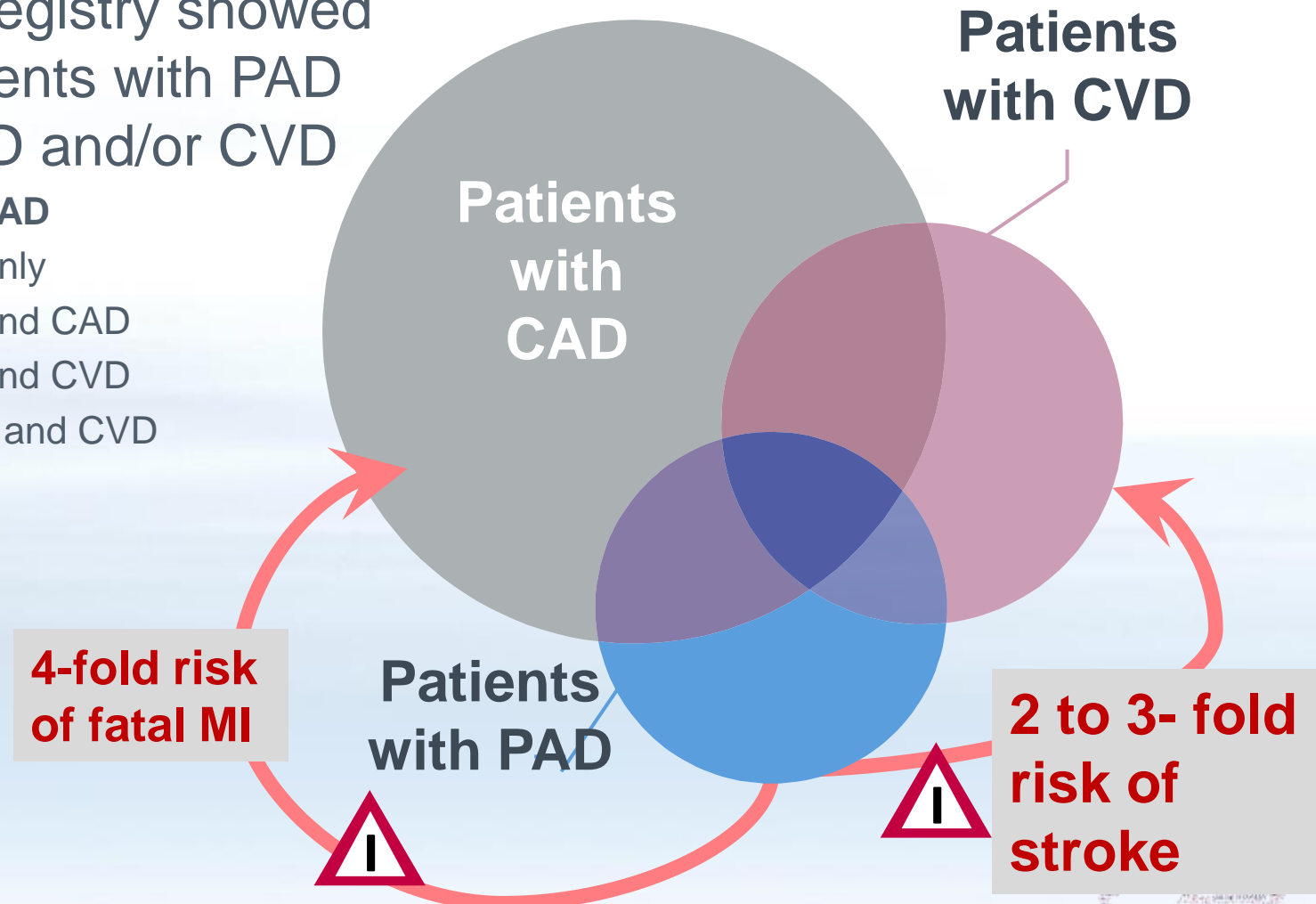


CAD and PAD: Overlapping conditions

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



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)
- Antihypertensive drugs (e.g. ACE inhibitor)
- Diabetes therapies
- Smoking cessation
- Antiplatelet drugs (e.g. ASA, clopidogrel)



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.



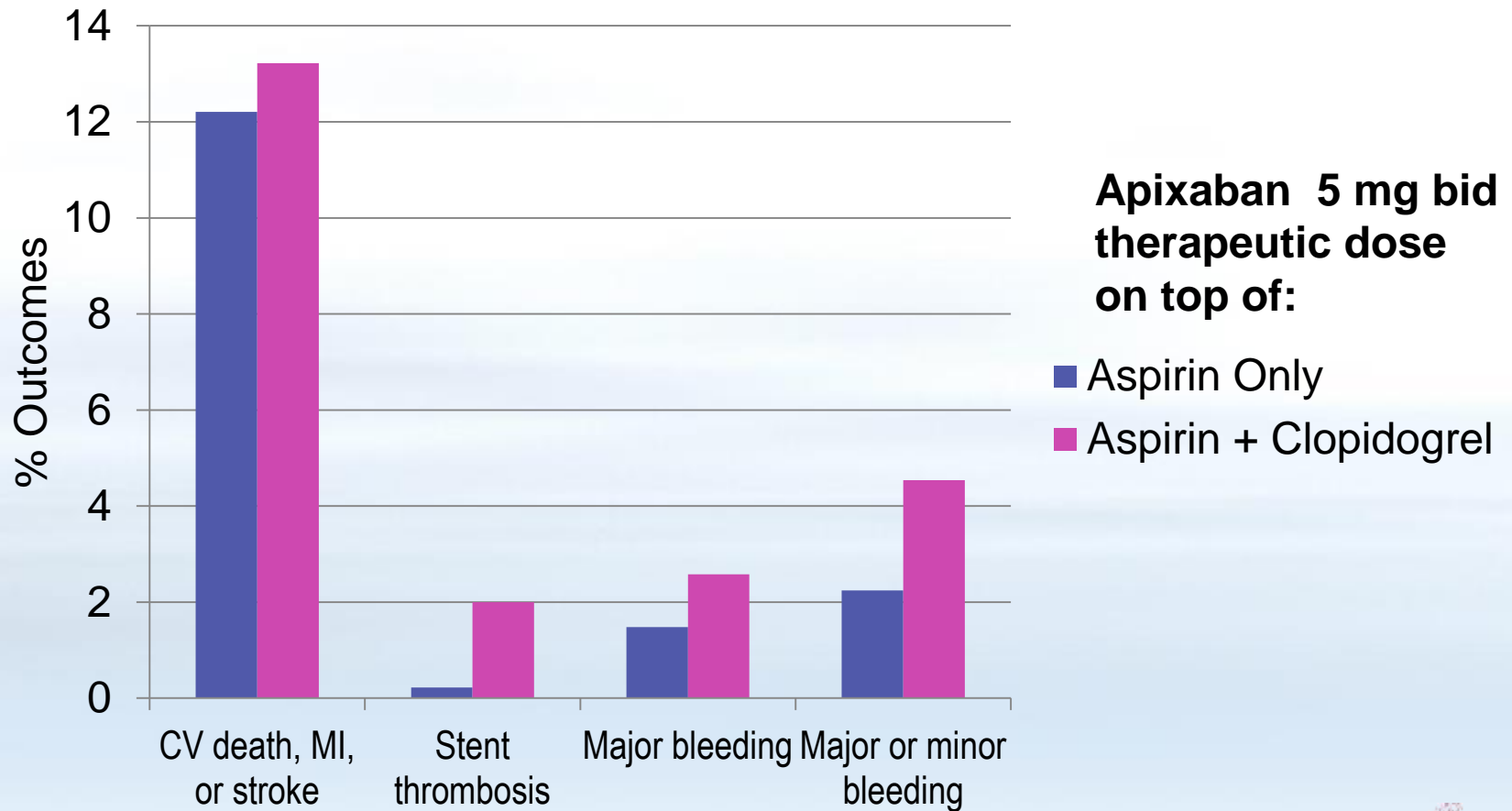
Antithrombotic treatment after intervention

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 (1C)
- Anticoagulation after infrainguinal PTA / stenting was assessed in 3 RCTs: None showed significant improvement in patency
=> anticoagulation cannot be recommended



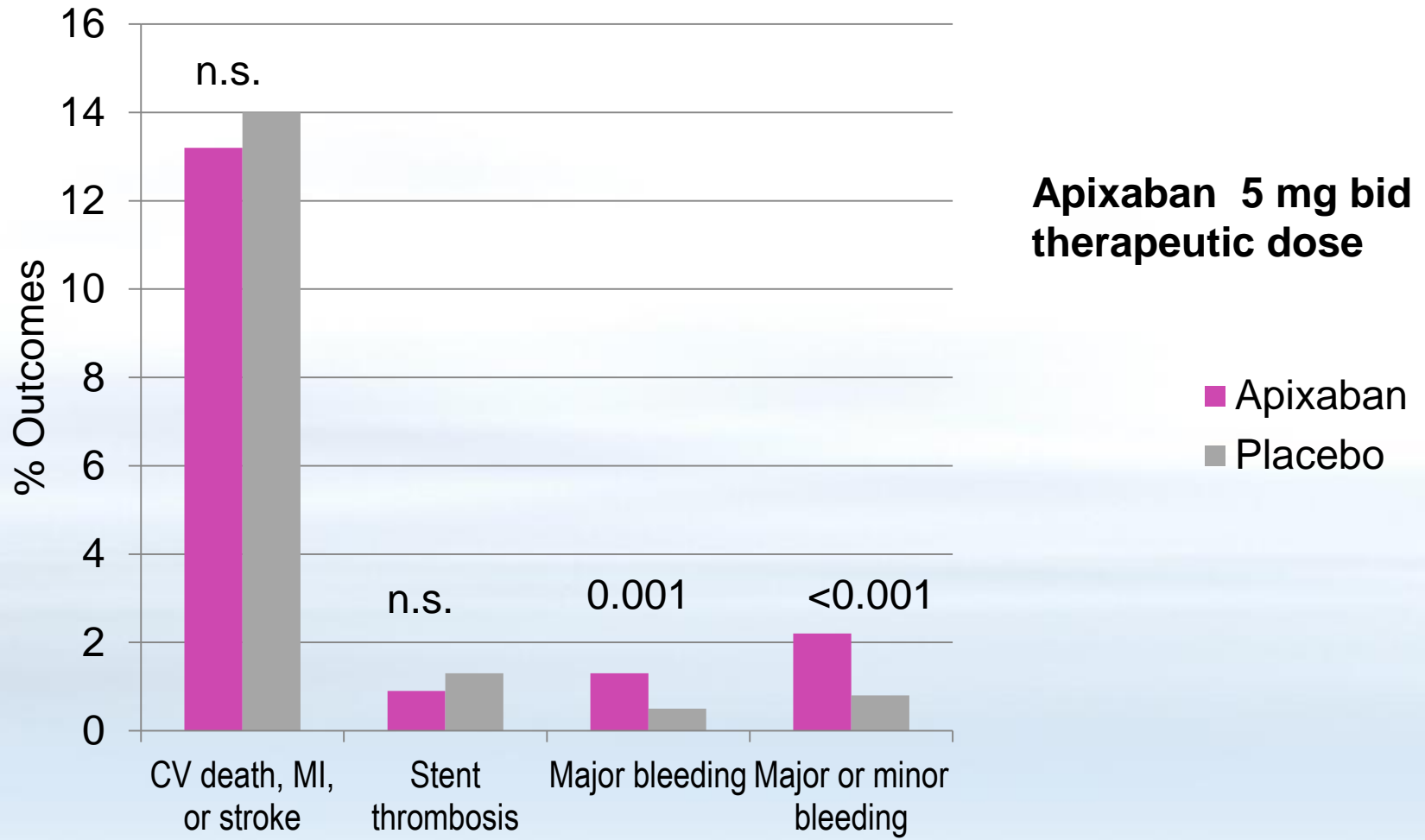
NOAC (triple) treatment after ACS



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..

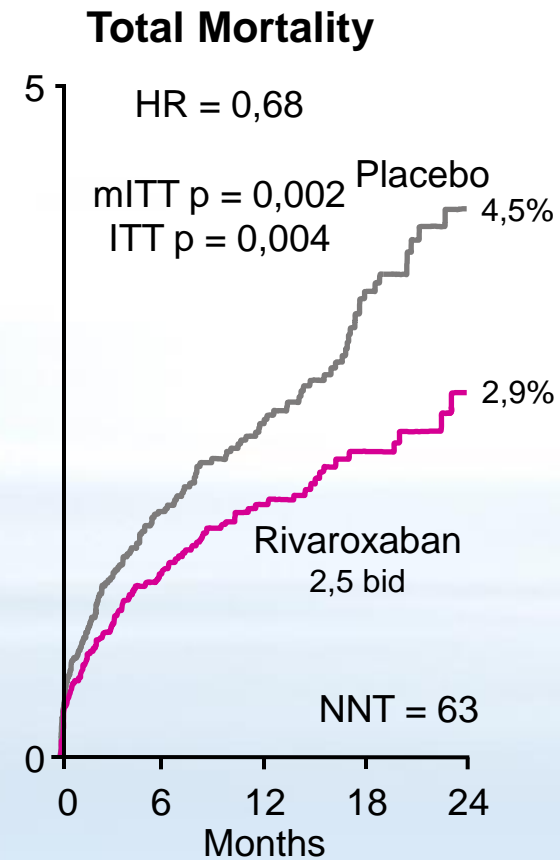
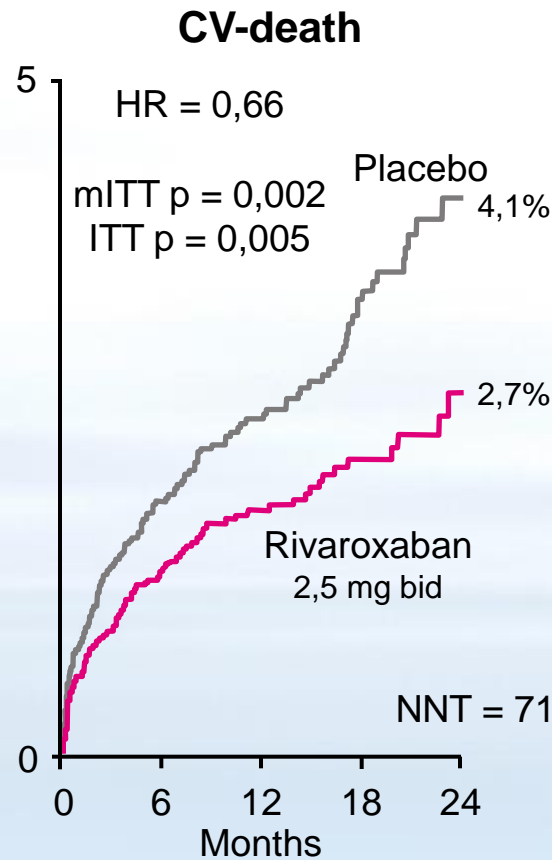
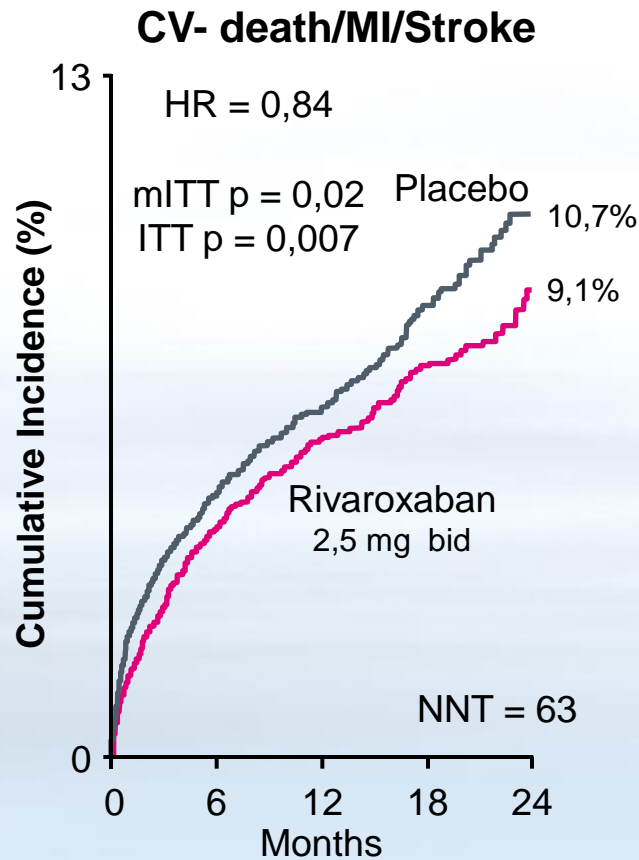


NOAC (triple) treatment after ACS

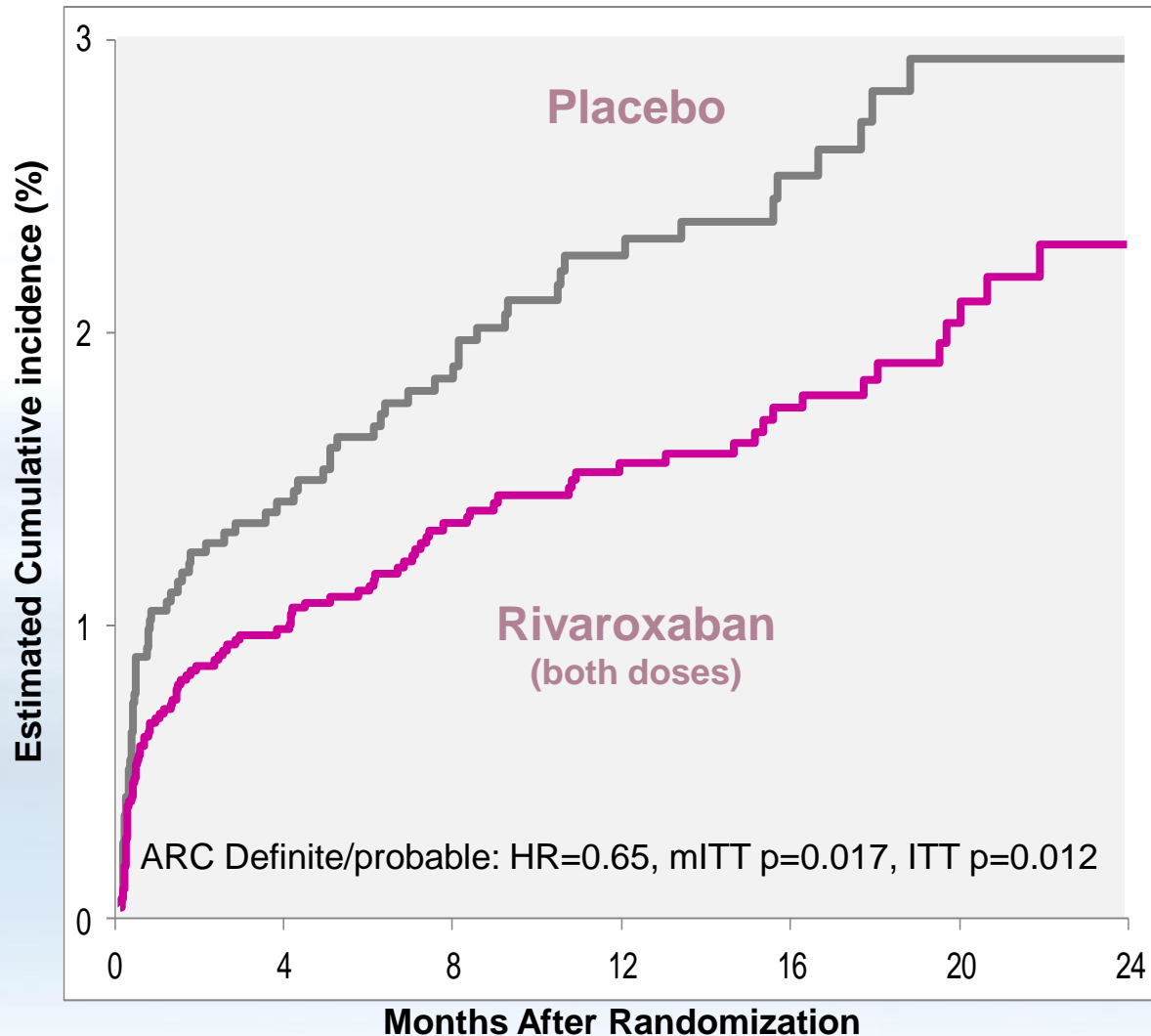


NOAC (triple) treatment after ACS (TIMI 51)

Very low dose Rivaroxaban (2.5 mg bid)



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



2.9%

2 Yr KM Estimate

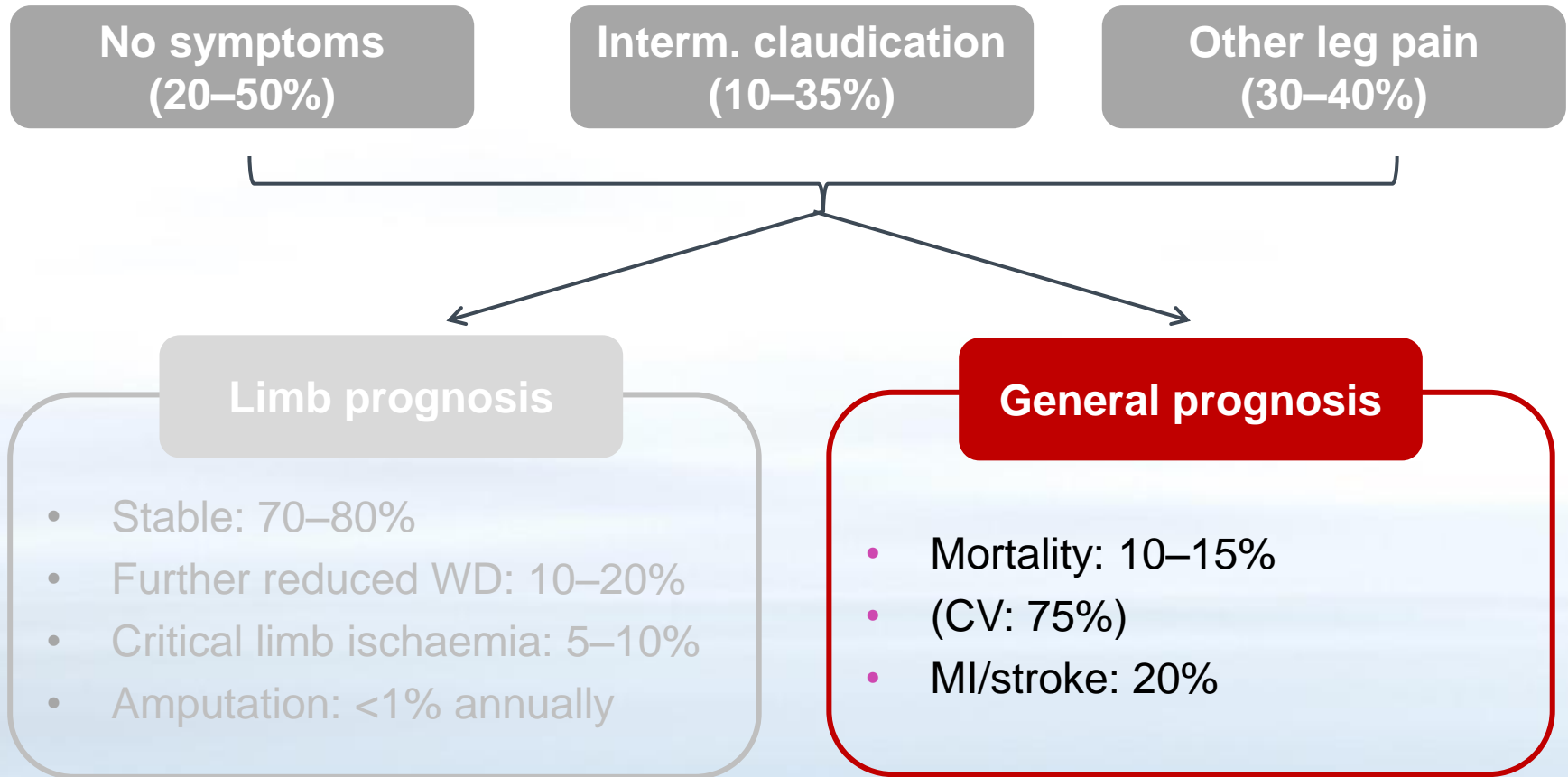
2.3%

HR 0.69
(0.51- 0.93)

ITT p = 0.008



Natural history – 5-year follow-up



Study design

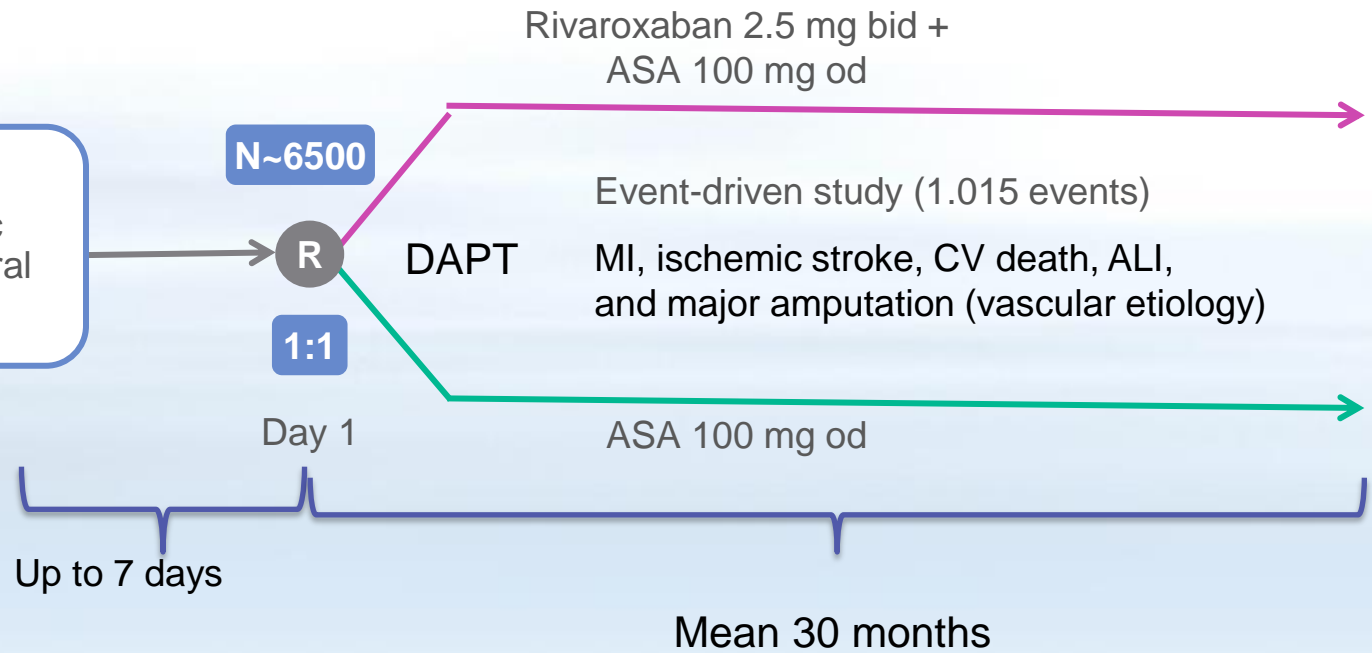
Official study title: An International, Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial Investigating the Efficacy and Safety of Rivaroxaban to Reduce the Risk of Major Thrombotic Vascular Events in Patients with Symptomatic Peripheral Artery Disease Undergoing Lower Extremity Revascularization Procedures

Objective:

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

Population:

Patients with symptomatic PAD undergoing peripheral revascularisation



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

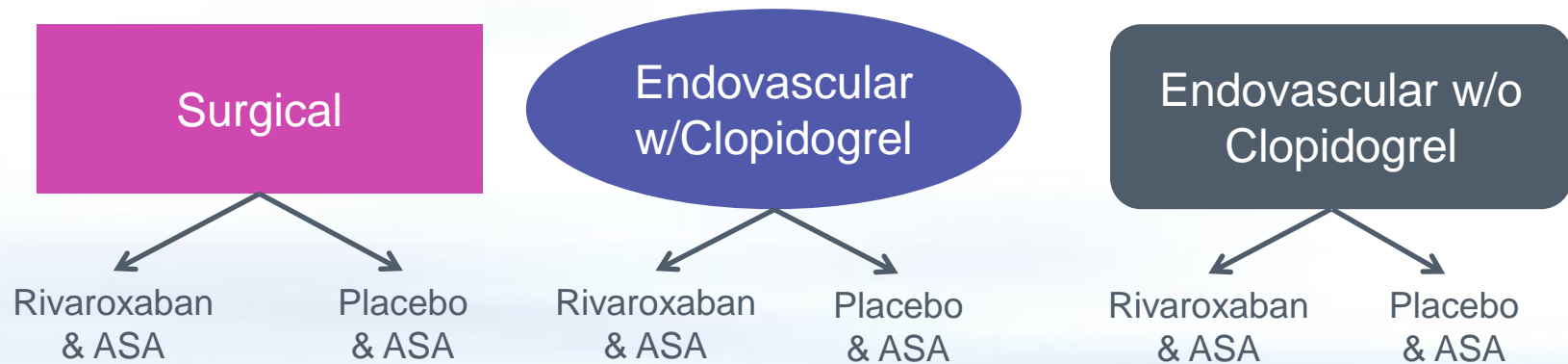
ALI=Acute limb ischaemia; CV=Cardiovascular; DAPT=Dual antiplatelet therapy; MI=Myocardial infarction; PAD=Peripheral artery disease; TIMI=Thrombolysis in myocardial infarction.

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



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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
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2. – 3. SEPTEMBER 2016