PAD: From Post-Intervention to the Chronic State

Professor Dr Rupert Bauersachs

Klinikum Darmstadt, Germany

Centre of Thrombosis and Haemostasis, University of Mainz, Germany

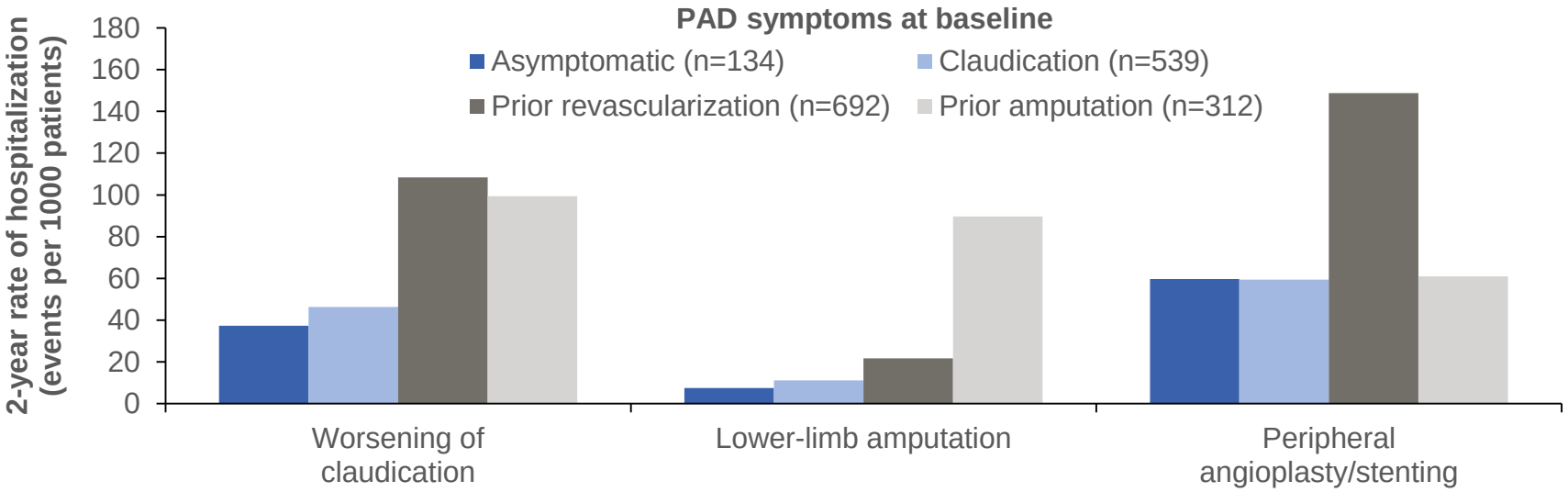
G.MA.GM.XA.01.2018.2056
L.DE.MA.01.2018.1715

Disclosures

- Principal investigator:
  - Bayer, BMS, Boehringer, Daiichi Sankyo, Leo, Portola
- Consultant and speakers bureau:
  - Bayer, BMS, Boehringer, Daiichi Sankyo, Pfizer

Post-Interventional PAD Has a Higher Thrombotic Risk than Chronic PAD

REACH registry: 2-year hospitalization rates are highest in patients with a history of revascularization or amputation[1]

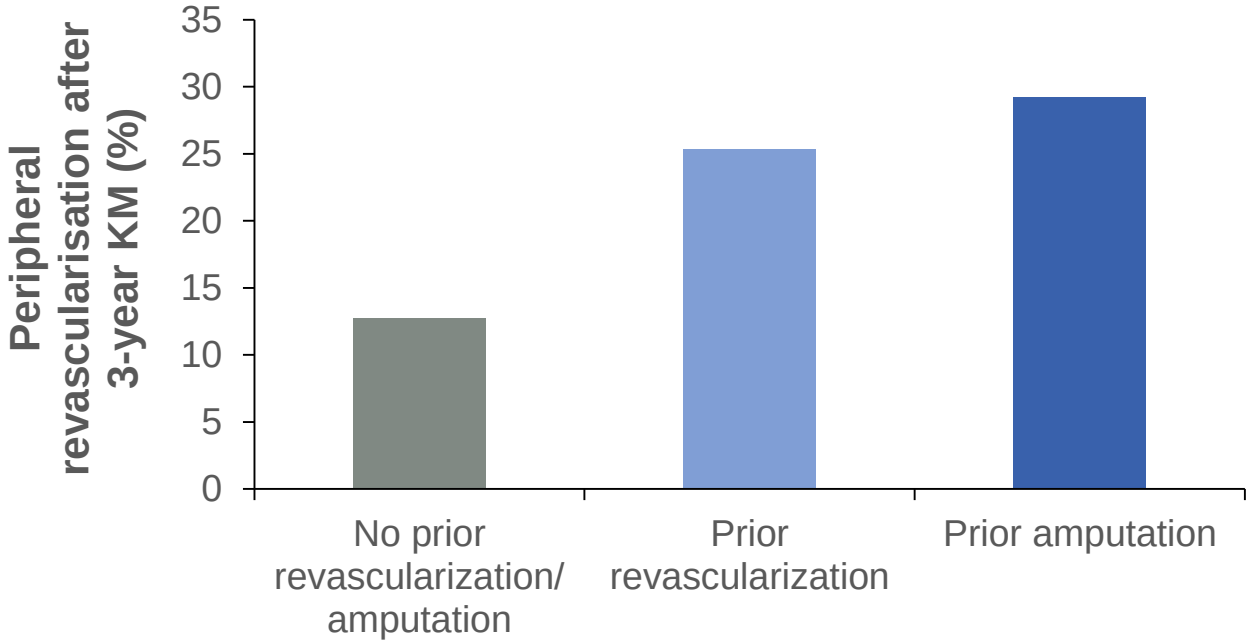


In a study of 3925 infrainguinal surgical revascularization procedures, the rate of postoperative mortality and/or limb loss was 9.2% in the first 30 days after surgery[2]

1. Mahoney EM *et al*, *Circ Cardiovasc Qual Outcomes* 2010;3:642–651; 2. Biancari F *et al*, *World J Surg* 2007;31:217–225

After Revascularisation or Amputation PAD Patients are at Higher Risk

Rates of peripheral revascularisation in patients randomised to placebo in the TRA°2P–TIMI 50 trial



Bonaca MP, et al. *JACC Cardiovasc Interv* 2016; 9:2157–2164

The VOYAGER PAD and COMPASS Trials Cover a Broad Range of Patients with Lower-Extremity PAD

COMPASS[1]

Chronic PAD

- Patients with intermittent claudication or a history of revascularization/amputation
- Most patients were not enrolled within 30 days of revascularization because of a high bleeding risk or a requirement for DAPT[3]

VOYAGER PAD[2]

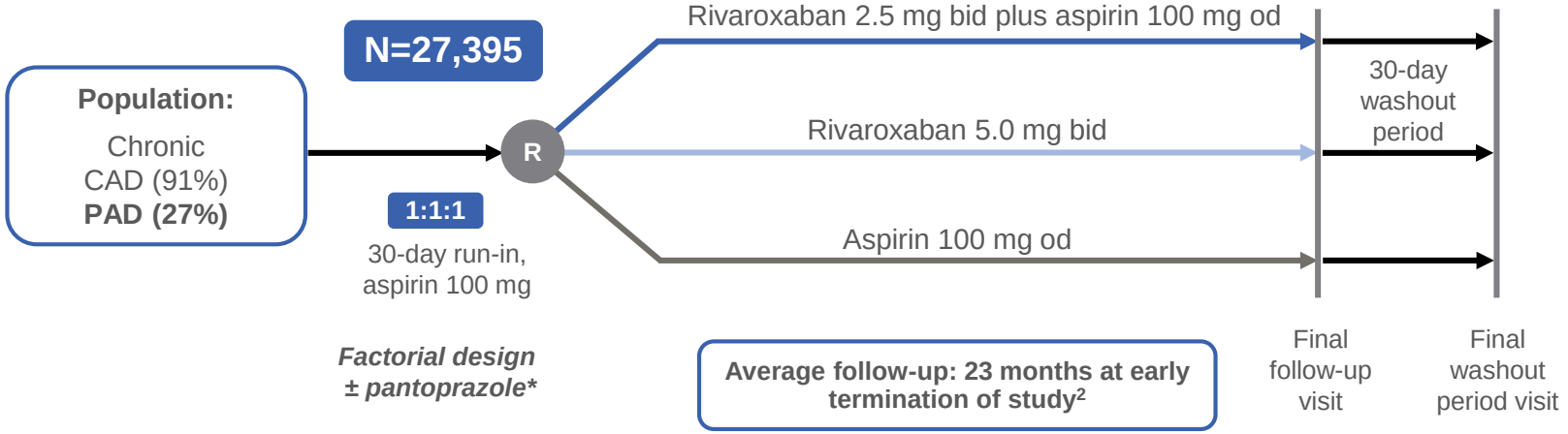
Acute post-interventional PAD

- Patients enrolled ≤10 days after revascularization

1. Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1; 2. Bayer. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed 12 Jan 2018];
3. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

COMPASS Investigated a Dual Pathway Approach in Patients with Chronic PAD and/or CAD

Objective: To determine the efficacy and safety of rivaroxaban 2.5 mg bid plus aspirin, rivaroxaban 5 mg bid alone or aspirin alone for reducing the risk of CV death, MI and stroke in patients with CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in February 2017 because of overwhelming efficacy in the rivaroxaban vascular dose 2.5 mg bid plus aspirin arm[2]

*Patients who were not receiving a PPI were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035; 2. Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319-1330

COMPASS

COMPASS Included Over 7000 Patients with Symptomatic PAD or Concomitant CAD and PAD

	Number of patients
All patients with PAD	7470
Symptomatic lower-extremity PAD	4129
Carotid disease	1919
CAD plus asymptomatic PAD (ABI <0.90)	1422

- PAD was defined according to patient presentation at enrolment
- In addition, a patient could be classified as having PAD based on medical history and/or measurement of ABI at the baseline visit
  - The latter category added patients with CAD and asymptomatic PAD into the overall PAD subgroup
- Median follow-up: 21 months

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Baseline Characteristics Were Consistent Across Treatment Arms

Characteristic or baseline medication*	Rivaroxaban 2.5 mg bid plus aspirin (N=2492)	Aspirin (N=2504)
Age, years, mean ± SD	67.9±8.5	67.8±8.5
Current smoker	682 (27.4)	685 (27.4)
Former smoker	1147 (46.0)	1143 (45.6)
Diabetes	1100 (44.1)	1104 (44.1)
Hypertension	1966 (78.9)	2017 (80.6)
Prior CAD	1656 (66.5)	1641 (65.5)
Prior stroke	171 (6.9)	154 (6.2)
Lipid lowering	2088 (83.8)	2074 (82.8)
ACE inhibitor/ARB	1715 (68.8)	1765 (70.5)

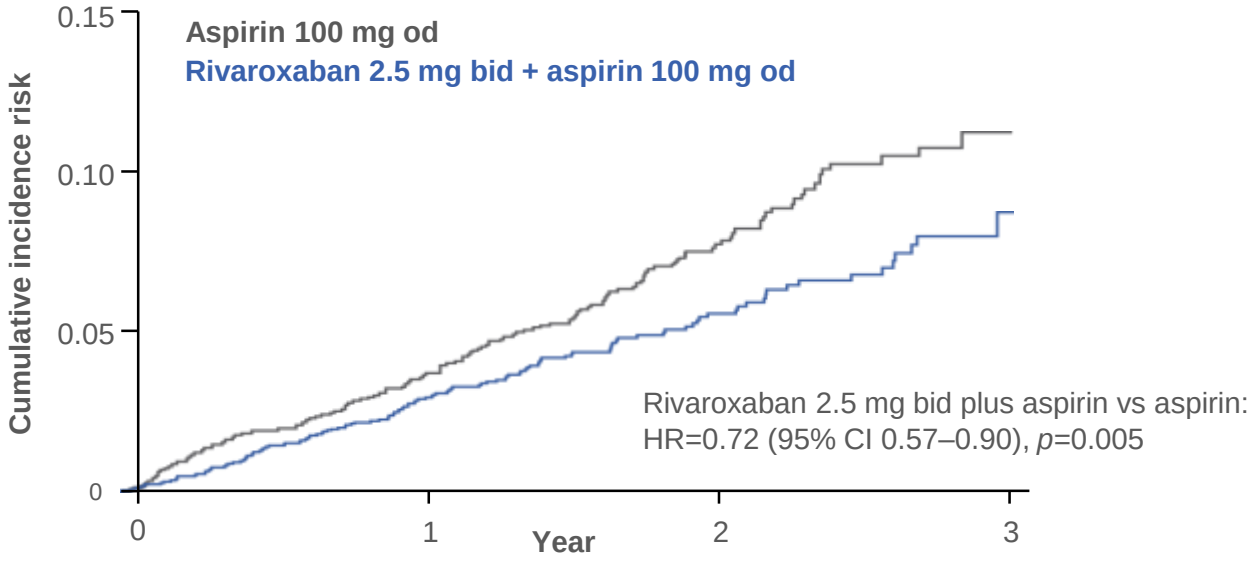
*Values are n (%) unless stated otherwise

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Significant Reduction in Risk of MACE with Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone

CV death, MI or stroke



Number at risk				
Rivaroxaban + aspirin	2492	2086	907	127
Aspirin	2504	2065	930	119

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Significant Reduction in the Risk of MACE with Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (N=2492)	Aspirin (N=2504)	Rivaroxaban 2.5 mg bid plus aspirin vs aspirin	
	n (%)	n (%)	HR (95% CI)	*p*-value
MACE	126 (5)	174 (7)	0.72 (0.57–0.90)	0.0047
CV death	64 (3)	78 (3)	0.82 (0.59–1.14)	–
MI	51 (2)	67 (3)	0.76 (0.53–1.09)	–
Stroke	25 (1)	47 (2)	0.54 (0.33–0.87)	–

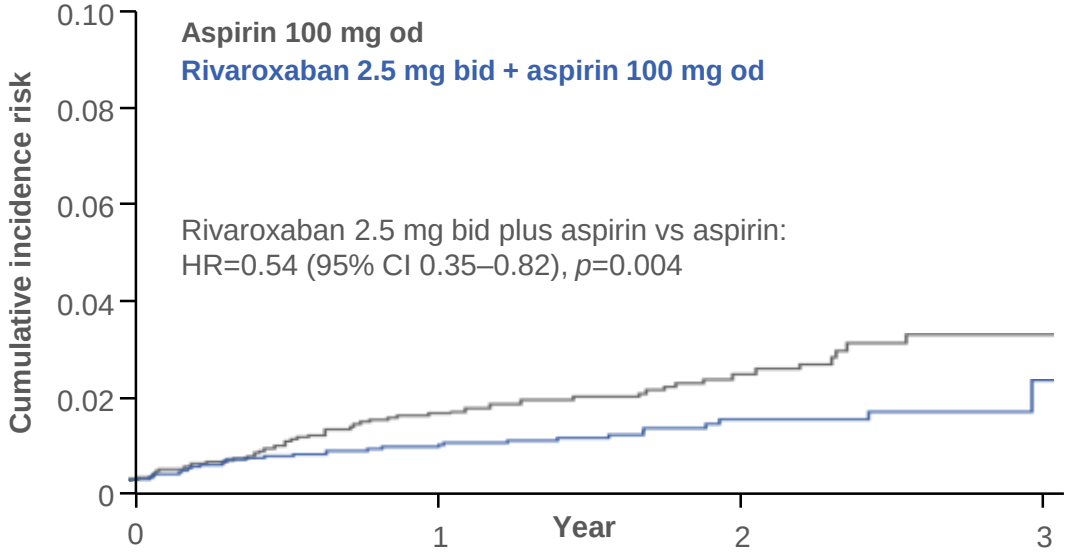
Dual pathway inhibition with rivaroxaban vascular dose 2.5 mg bid plus aspirin reduced the risk of MACE by 28% versus aspirin alone

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Significant Improvement in MALE with Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone

MALE including major amputation



Number at risk				
Rivaroxaban + aspirin	2492	2099	919	129
Aspirin	2504	2072	951	120

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Significant Reduction in Risk of Limb Outcomes with Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (N=2492)	Aspirin (N=2504)	Rivaroxaban 2.5 mg bid plus aspirin vs aspirin	
	n (%)	n (%)	HR (95% CI)	*p*-value
MALE	30 (1)	56 (2)	0.54 (0.35–0.84)	0.0054
Major amputation	5 (<1)	17 (1)	0.30 (0.11–0.80)	0.011
MALE plus major amputation*	32 (1)	60 (2)	0.54 (0.35–0.82)	0.0037

Rivaroxaban vascular dose 2.5 mg bid plus aspirin
significantly reduced major amputation by 70% versus aspirin alone

MALE, major adverse limb events (composite of acute and chronic limb ischaemia)
*An additional 11 major amputations of a vascular cause were unrelated to acute or chronic limb ischaemia: two in the rivaroxaban 2.5 mg bid plus aspirin group, five in the rivaroxaban 5 mg bid group, and four in the aspirin alone group

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

Increased Major Bleeding, but not Fatal Bleeding or ICH, with Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (N=2492)	Aspirin (N=2504)	Rivaroxaban 2.5 mg bid plus aspirin vs aspirin	
	n (%)	n (%)	HR (95% CI)	*p*-value
Modified ISTH major bleeding*	77 (3)	48 (2)	1.61 (1.12–2.31)	0.0089
Fatal	4 (<1)	3 (<1)	–	–
ICH	5 (<1)	9 (<1)	0.56 (0.19–1.66)	–
Fatal or symptomatic bleeding into a critical organ	21 (1)	19 (1)	1.10 (0.59–2.05)	–

Bleeding rates increased but remained low with rivaroxaban 2.5 mg bid plus aspirin versus aspirin alone, with no differences seen in fatal and intracranial bleeding

*Defined as fatal bleeding, bleeding into a critical organ, surgical site bleeding requiring reoperation or bleeding requiring hospitalization

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

COMPASS Offers a New Approach for the Treatment of Chronic PAD

- Rivaroxaban vascular dose 2.5 mg bid plus aspirin vs aspirin alone:
  - Reduced MACE by 28%
  - Reduced MALE by 46%
  - Reduced major amputations by 70%
  - Increased major bleeding without increasing fatal or critical organ bleeding
- The COMPASS results represent a major advance in the management of PAD
- Rivaroxaban 2.5 mg bid plus aspirin is the only antithrombotic regimen shown to significantly reduce both MACE and MALE

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1

COMPASS

What About Patients Undergoing Revascularization?

- Patients undergoing revascularization were mostly excluded from COMPASS because of a need for dual antiplatelet therapy or a high risk of bleeding

Key COMPASS exclusion criteria[1,2]

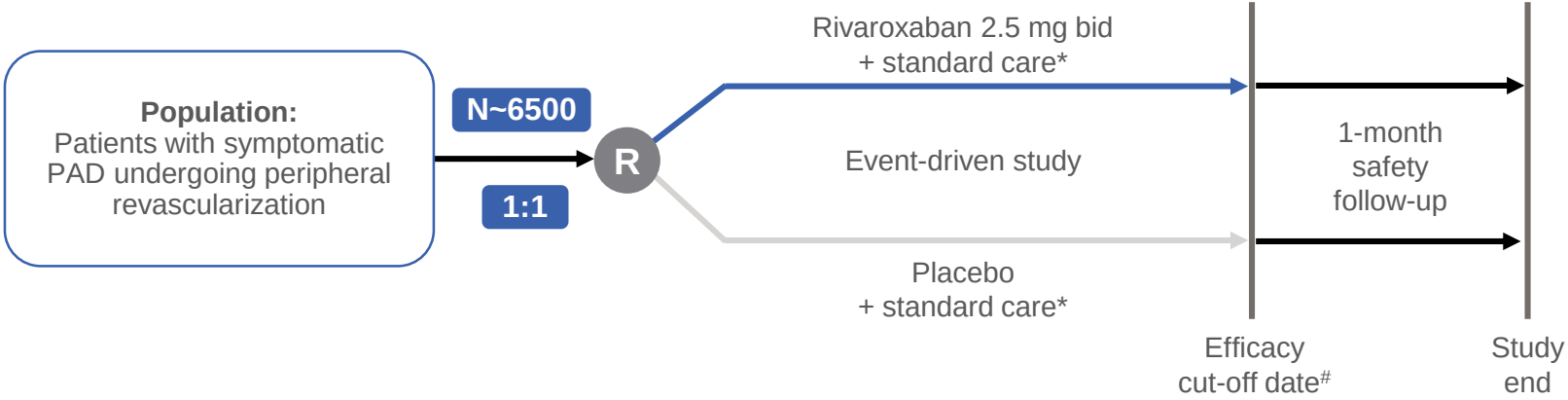
- **High risk of bleeding**
- Stroke within 1 month
- History of haemorrhagic/lacunar stroke
- Severe heart failure (ejection fraction <30%)
- eGFR <15 ml/min
- **Need for dual antiplatelet therapy**
- Need for non-aspirin antiplatelet therapy
- Indication for anticoagulation therapy

1. Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1; 2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

COMPASS

The VOYAGER PAD Trial Is Investigating Dual Pathway Inhibition in the Acute Phase After Lower-Limb Revascularization

Objective: To evaluate the efficacy and safety of rivaroxaban 2.5 mg bid plus aspirin compared with aspirin alone to reduce the risk of major thrombotic vascular events in patients with PAD undergoing peripheral (lower extremity) revascularization procedures



Primary endpoints:
Efficacy: CV death, MI, ischaemic stroke, ALI or major amputation
Safety: TIMI major bleeding

Indication:
Symptomatic PAD

End of recruitment: Q4-17
Completion date: Q1-19

*Aspirin 100 mg alone or aspirin plus clopidogrel for ≤6 months after index revascularization; #mean treatment duration per patient: ~2 years

Bayer. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed 13 Dec 2017]

VOYAGER PAD

Patients in VOYAGER PAD Are Randomized Within 10 Days of Peripheral Revascularization

Key inclusion criteria

- Age ≥50 years
- Confirmed moderate-to-severe symptomatic lower extremity occlusive PAD* within 3 months of screening
- Technically successful peripheral infra-inguinal revascularization for symptomatic PAD within the last 10 days prior to randomization

Key exclusion criteria

- Patients undergoing revascularization to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis
- Prior revascularization on index leg within 10 days of the qualifying revascularization
- Planned use of DAPT with clopidogrel plus aspirin for >6 months after the qualifying revascularization
- Planned use of any additional antiplatelet agent other than clopidogrel and aspirin after the qualifying revascularization

*Limb haemodynamic and angiographic or imaging evidence of occlusive PAD

Bayer. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed 13 Dec 2017]

VOYAGER PAD

Conclusions

COMPASS[1]

- First trial of an antithrombotic to show a significant reduction in both MACE and MALE in patients with chronic PAD
- Rivaroxaban vascular dose 2.5 mg bid plus aspirin was associated with a 28% reduction in MACE and a 46% reduction in MALE

VOYAGER PAD[2]

- Examines the same drug regimen as COMPASS (rivaroxaban 2.5 mg bid plus aspirin) but in a post-revascularization population
- Will be the first trial of an antithrombotic in acute symptomatic PAD with a combined CV and limb endpoint

1. Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1; 2. Bayer. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed 13 Dec 2017]

Thank you very much for your attention!

PAD: From Post-Intervention to the Chronic State

Professor Dr Rupert Bauersachs

Klinikum Darmstadt, Germany

Centre of Thrombosis and Haemostasis, University of Mainz, Germany

G.MA.GM.XA.01.2018.2056
L.DE.MA.01.2018.1715