A new era in the treatment of peripheral artery disease (PAD) ?

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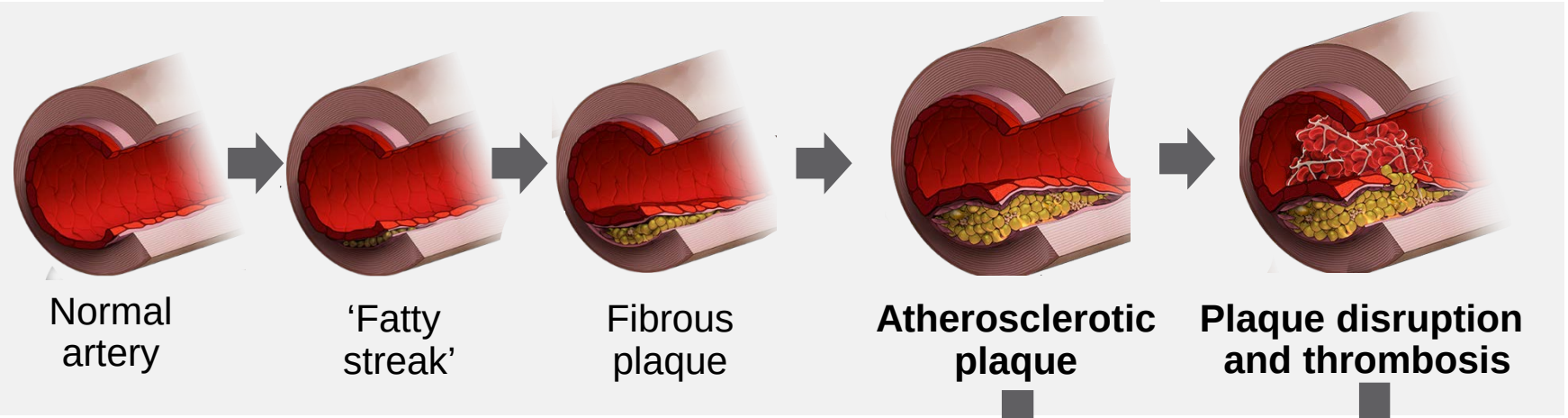
Atherosclerosis Is a Progressive Disease Leading to Atherothrombosis and Ischaemia



Flow-limiting stenosis
Symptoms with exercise, e.g. stable angina and intermittent claudication

Atherothrombosis

- **MI**
- **Stroke**
- **CV death**
- **Limb ischaemia**

1. Insull W Jr, *Am J Med* 2009;122(1 Suppl):S3–S14; 2. Bradberry JC *et al*, *J Am Pharm Assoc* 2004;44:S37–S45

Current Vascular Protection Strategies Aim to Reduce Risk of Atherothrombotic CV and Limb Events in Patients with PAD

Vascular protection[1–4]

Control of cardiovascular risk factors to limit atherosclerosis progression and stabilize existing plaques

Prevention of blood clot formation over any ruptured/eroded atherosclerotic plaques

Lifestyle changes

- Smoking cessation
- Regular exercise
- Healthy diet
- Weight management
- Psychosocial support

Medical therapies

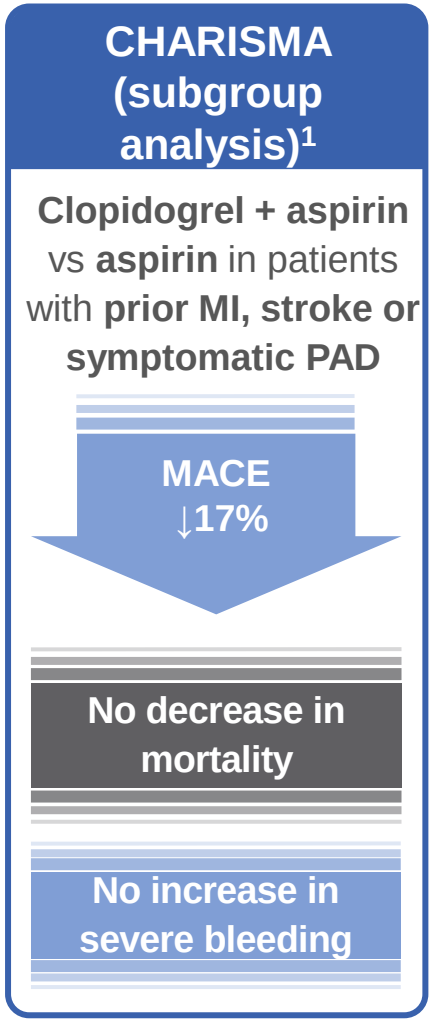
- Lipid control – statins
- Hypertension control – ACE inhibitors/ARBs
- Diabetes control – insulin/anti-glycaemic drugs

Antithrombotic therapy

- Single antiplatelet therapy with aspirin or clopidogrel

1. Aboyans V *et al*, *Eur Heart J* 2017; doi: 10.1093/eurheartj/ehx095; 2. Aboyans V *et al*, *Eur J Vasc Endovasc Surg* 2017: doi:10.1016/j.ejvs.2017.07.018; 3. Gerhard-Herman MD *et al*, *J Am Coll Card* 2016: doi:10.1016/j.jacc.2016.11.007;
4. Cortés-Beringola A *et al*, *Eur J Prevent Cardiol* 2017;24:22–28

Trials Investigating Intensified Antiplatelet Therapy in Patients with PAD Show Mixed Results



*Hospitalization for ALI or lower limb revascularization (individual endpoints); #Composite of ALI or peripheral revascularization; ‡No mortality benefit in the overall trial population[5]

1. Bhatt DL *et al*, *J Am Coll Cardiol* 2007;49:1982–1988; 2. Bonaca MP *et al*, *Circulation* 2013;127:1522–1529; 3. Hiatt WR *et al*, *N Engl J Med* 2017;376:32–40; 4. Bonaca MP *et al*, *J Am Coll Cardiol* 2016;67:2719–2728; 5. Bonaca MP *et al, N Engl J Med* 2015;372:1791–1800

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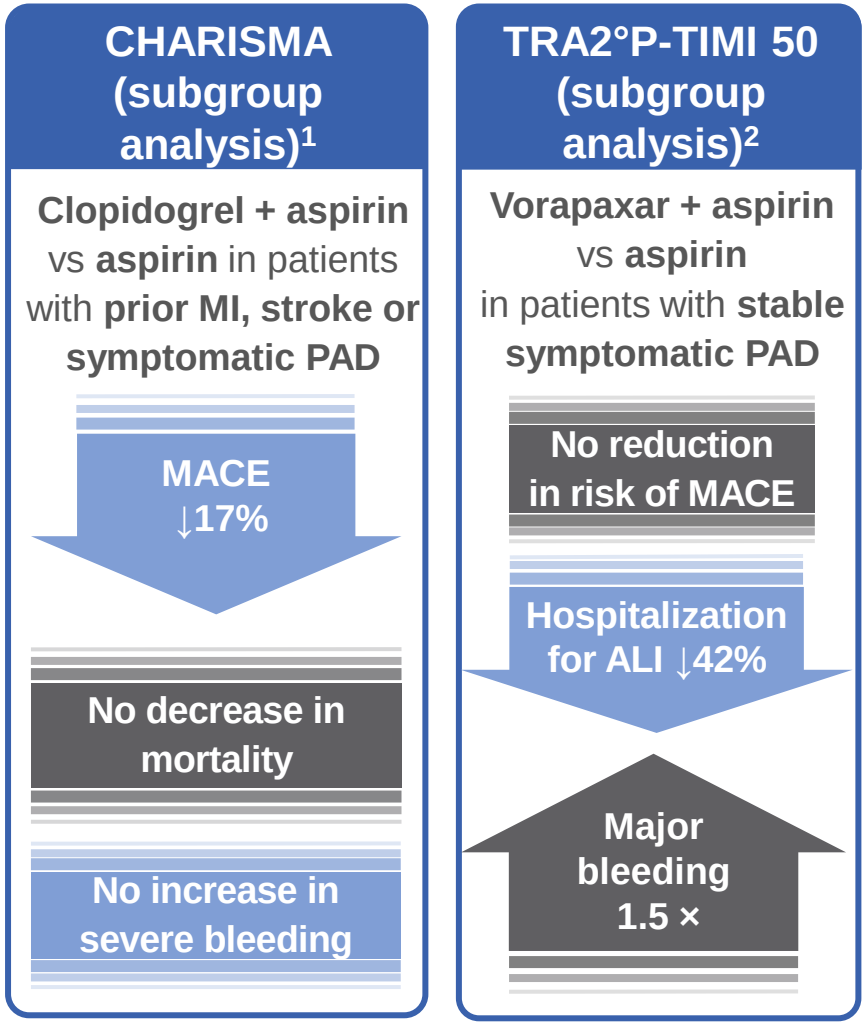

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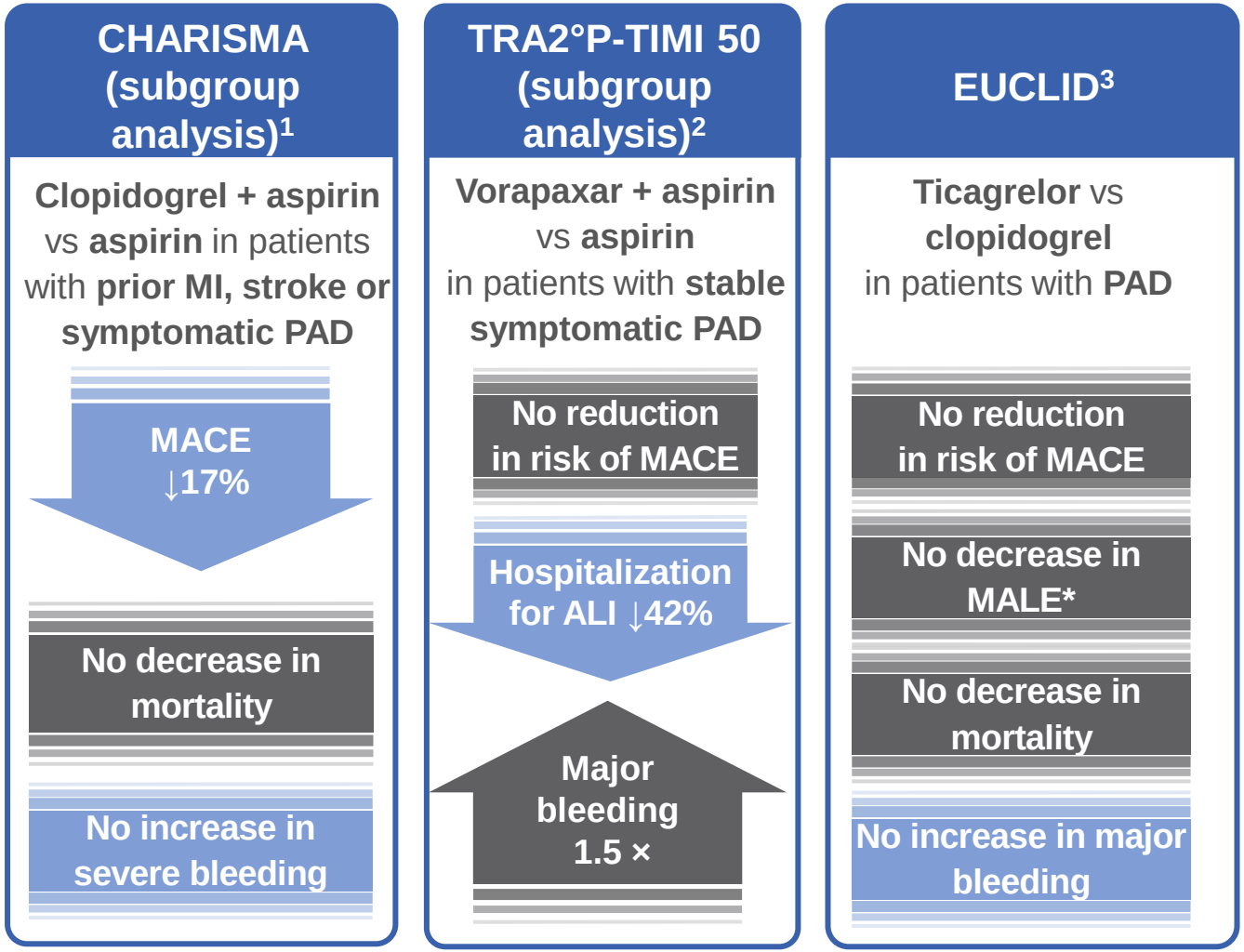

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Trials Investigating Intensified Antiplatelet Therapy in Patients with PAD Show Mixed Results

CHARISMA (subgroup analysis)[1]

Clopidogrel + aspirin vs **aspirin** in patients with **prior MI, stroke or symptomatic PAD**

- MACE ↓17%
- No decrease in mortality
- No increase in severe bleeding

TRA2°P-TIMI 50 (subgroup analysis)[2]

Vorapaxar + aspirin vs **aspirin** in patients with **stable symptomatic PAD**

- No reduction in risk of MACE
- Hospitalization for ALI ↓42%
- Major bleeding 1.5 ×

EUCLID[3]

Ticagrelor vs **clopidogrel** in patients with **PAD**

- No reduction in risk of MACE
- No decrease in MALE*
- No decrease in mortality
- No increase in major bleeding

PEGASUS (subgroup analysis)[4,5]

Ticagrelor + aspirin vs **aspirin** in patients with **prior MI + PAD**

- MACE ↓31%
- No decrease in MALE#
- Mortality ↓48%‡
- No increase in major bleeding

*Hospitalization for ALI or lower limb revascularization (individual endpoints); #Composite of ALI or peripheral revascularization; ‡No mortality benefit in the overall trial population[5]

1. Bhatt DL *et al*, *J Am Coll Cardiol* 2007;49:1982–1988; 2. Bonaca MP *et al*, *Circulation* 2013;127:1522–1529; 3. Hiatt WR *et al*, *N Engl J Med* 2017;376:32–40; 4. Bonaca MP *et al*, *J Am Coll Cardiol* 2016;67:2719–2728; 5. Bonaca MP *et al, N Engl J Med* 2015;372:1791–1800

The Current ESC Guidelines for PAD Management Recommend Treatment of Symptomatic PAD

2017 ESC guideline recommendations for antithrombotic therapies in patients with PAD

- **SAPT is recommended for all patients with symptomatic PAD**
- **DAPT is recommended only for a limited period of time after certain revascularization procedures**

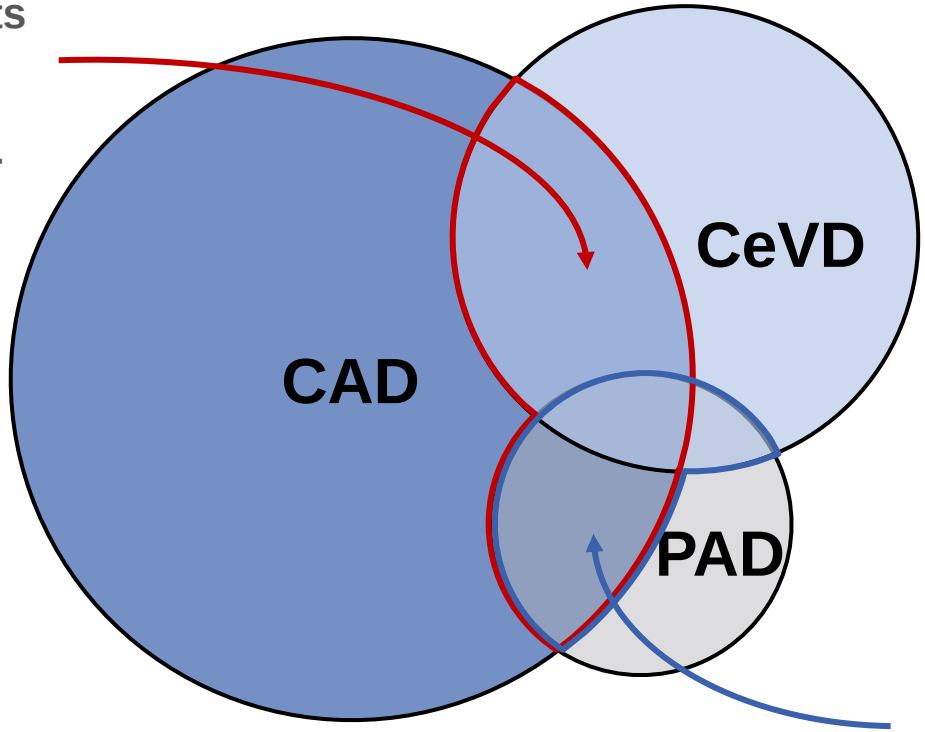
Patients with…	Recommendation	Class
Symptomatic PAD	Antiplatelet therapy is recommended	Ic
Lower extremity PAD	In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin	IIb
	Anticoagulation with VKAs may be considered after autogenous vein infrainguinal bypass	IIb
	DAPT (aspirin plus clopidogrel) for ≥1 month should be considered after infra-inguinal stent implantation	IIa
	DAPT (aspirin plus clopidogrel) may be considered in the case of below-knee bypass with a prosthetic graft	IIb
	Long-term SAPT is recommended in all patients who have undergone revascularization	Ic
	SAPT is recommended after infrainguinal bypass surgery	Ia

1. Aboyans V *et al*, *Eur Heart* J 2017: doi:10.1093/eurheartj/ehx095; 2. Aboyans V *et al*, *Eur J Vasc Endovasc Surg* 2017: doi:10.1016/j.ejvs.2017.07.018

Atherosclerosis Is a Polyvascular Disease

REACH: More than 3 in 5 patients with PAD have atherothrombotic disease also in other arterial territories

24.7% of patients with CAD had concomitant disease in other vascular beds



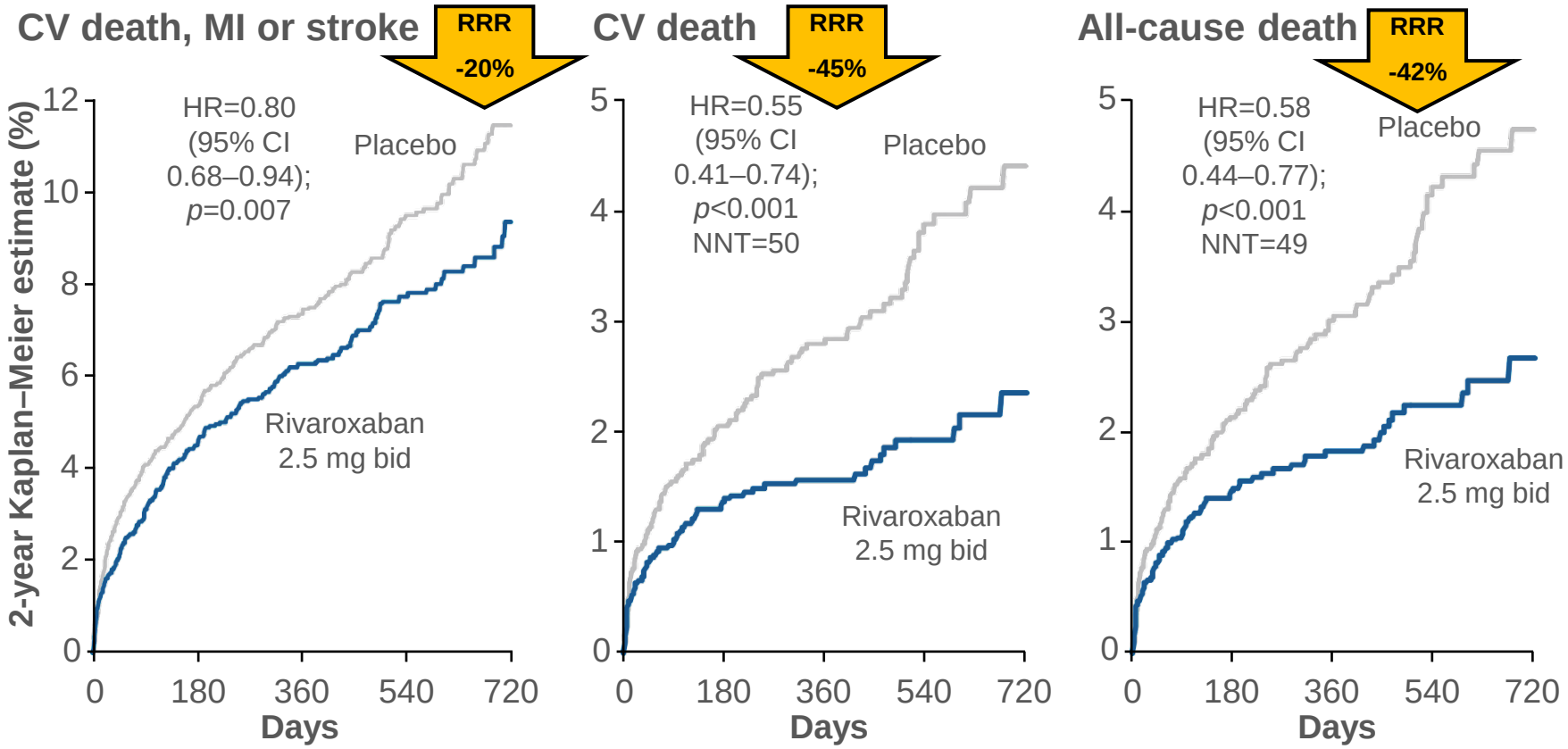
61.5% of patients with PAD had concomitant disease in other vascular beds

Percentages are calculated from the total population included in the REACH registry. N=67,888

Bhatt DL *et al*, *JAMA* 2006;295:180–189

ATLAS : Adding Rivaroxaban 2.5 mg BID to (D)APT Reduced CV Events and Death in Patients with ACS

Patients with elevated cardiac biomarkers and no prior stroke/transient ischaemic attack



CI, confidence interval; HR, hazard ratio; NNT, number needed to treat
Patients also received antiplatelet standard of care: ASA + thienopyridine (~93%) or ASA alone (~7%)

Mega JL *et al*, *Eur Heart J* 2014;35(Suppl.):992. Abstract P5518 (poster presentation)

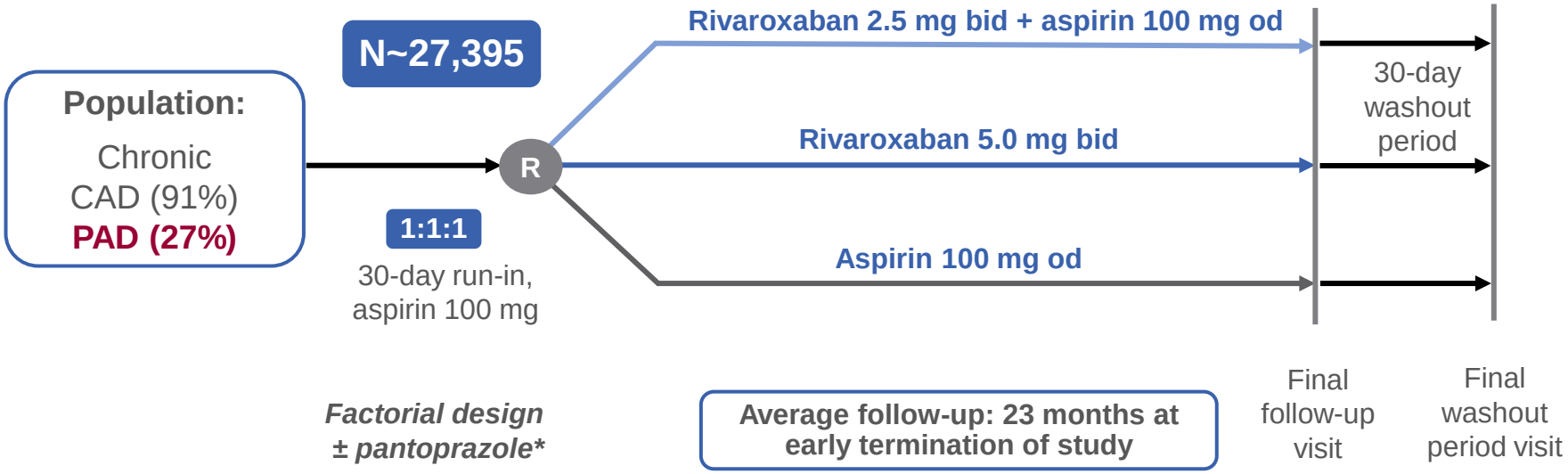
ATLAS ACS TIMI 51

COMPASS:
Could rivaroxaban 2.5 mg BID in addition to (D)APT also reduce CV events and Death in stable CAD + PAD patients ?

COMPASS PAD Analysis

COMPASS: Adding rivaroxaban 2.5 mg BID zu (D)APT in Patients with stable CAD or PAD

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban vascular dose 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (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. Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319–1330; 2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

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Inclusion and Exclusion Criteria Ensure That Patients with Chronic PAD are Enrolled

Key inclusion criteria

- Previous peripheral artery revascularization
- Previous limb or foot amputation for arterial vascular disease
- Intermittent claudication plus:
  - Low ABI (<0.90), or
  - Significant peripheral artery stenosis (≥50%)
- Previous carotid revascularization, or asymptomatic carotid artery stenosis ≥50%
- CAD + low ABI (<0.90)

Key exclusion criteria

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

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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PAD-Specific Limb Outcomes Were Added to Main Study Outcomes for COMPASS

- Primary cardiovascular outcome was MACE, defined as:
  - Composite of cardiovascular death, stroke or MI

- Key composite outcomes for PAD:
  - **Primary limb outcome was major adverse limb events (MALE), defined as development of ALI or CLI and major amputations not included in ALI or CLI**
  - The composite of MACE and MALE
  - The composite of MACE, MALE and major amputations not included in ALI or CLI

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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Major Adverse Limb Events and Major Amputation Were Included in PAD-Specific Net Clinical Benefit

- Primary safety outcome: modified ISTH
  - Major bleeding defined as:
    - Fatal bleeding, or
    - Bleeding into a critical organ, or
    - Surgical site bleeding requiring reoperation, or
    - Bleeding requiring hospitalization
- Net clinical benefit outcome defined as:
  - MACE
  - MALE including major amputation
  - Fatal bleeding
  - Bleeding into a critical organ

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

COMPASS: >7000 Patients with symptomatic PAD or CAD+PAD

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

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

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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Baseline Characteristics Were Consistent across Treatment Arms and in Line with Those Usually Seen in Patients with PAD

Characteristic	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504
Age, years, mean ± SD	67.9±8.5	67.8±8.5	67.8±8.5
Current smoker, n (%)	682 (27.4)	685 (27.7)	685 (27.4)
Former smoker, n (%)	1147 (46.0)	1154 (46.6)	1143 (45.6)
Diabetes, n (%)	1100 (44.1)	1083 (43.8)	1104 (44.1)
Hypertension, n (%)	1966 (78.9)	1939 (78.4)	2017 (80.6)
Prior CAD, n (%)	1656 (66.5)	1609 (65.0)	1641 (65.5)
Prior stroke, n (%)	171 (6.9)	177 (7.2)	154 (6.2)
Lipid lowering, n (%)	2088 (83.8)	2074 (83.8)	2074 (82.8)
ACE inhibitor/ARB, n (%)	1715 (68.8)	1757 (71.0)	1765 (70.5)

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly Reduced Major Amputation by 70% Versus Aspirin Alone

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MALE	30 (1)	35 (1)	56 (2)	**0.54 (0.35–0.84)**	**0.0054**	0.63 (0.41–0.96)	0.032
Major amputation	5 (<1)	8 (<1)	17 (<1)	**0.30 (0.11–0.80)**	**0.011**	0.46 (0.20–1.08)	0.068
MALE plus major amputation*	32 (1)	40 (2)	60 (2)	**0.54 (0.35–0.82)**	**0.0037**	0.67 (0.45–1.00)	0.046
MACE or MALE including major amputation	157 (6)	188 (8)	225 (9)	**0.69 (0.56–0.85)**	**0.0003**	0.83 (0.69–1.02)	0.077

*An additional 11 major amputations of a vascular cause were done that were unlinked to acute or chronic limb ischaemia, two in the low-dose rivaroxaban plus aspirin group, five in the rivaroxaban alone group, and four in the aspirin alone group

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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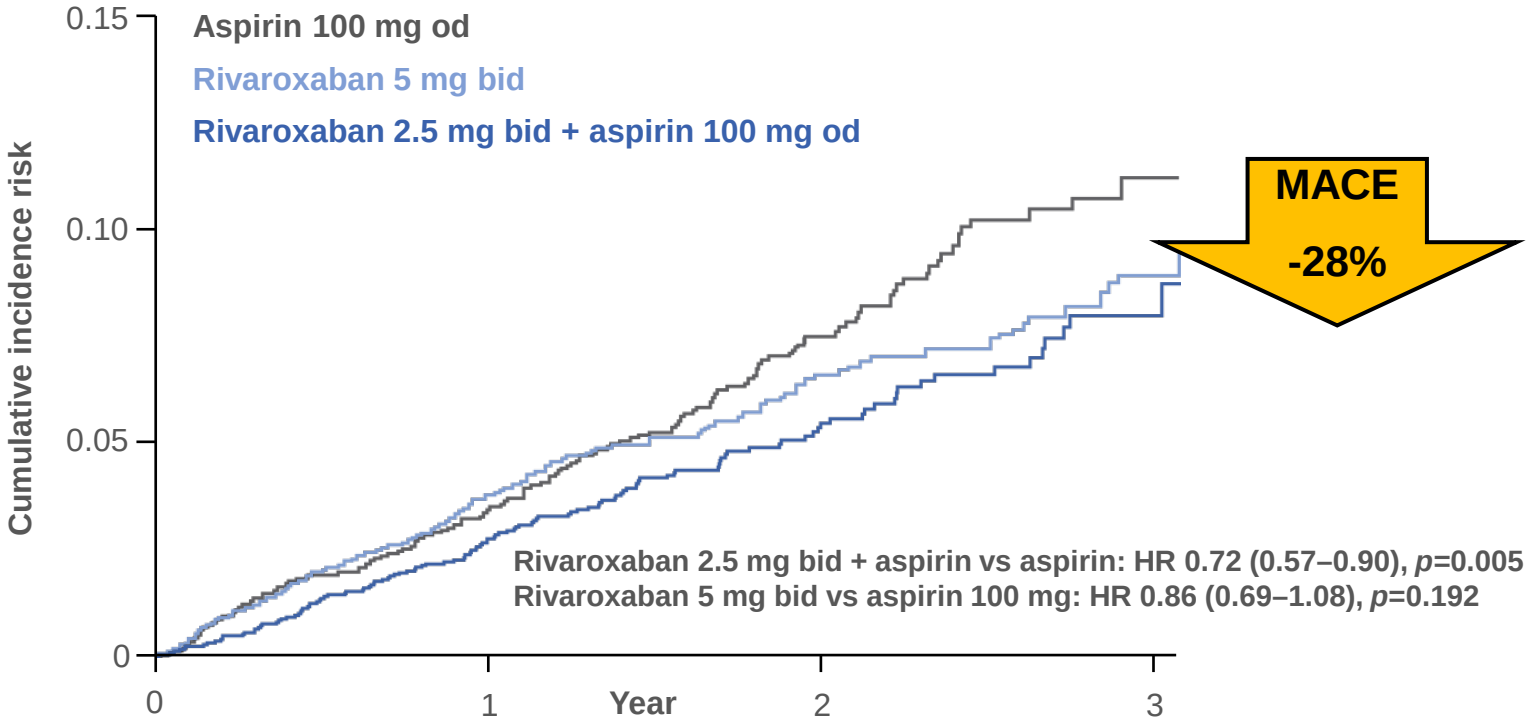
MACE with Rivaroxaban 2.5 mg bid + ASA versus ASA alone

Stroke/MI/cardiovascular death



Number at risk				
Rivaroxaban + aspirin	2492	2086	907	127
Rivaroxaban	2474	2044	870	147
Aspirin	2504	2065	930	119

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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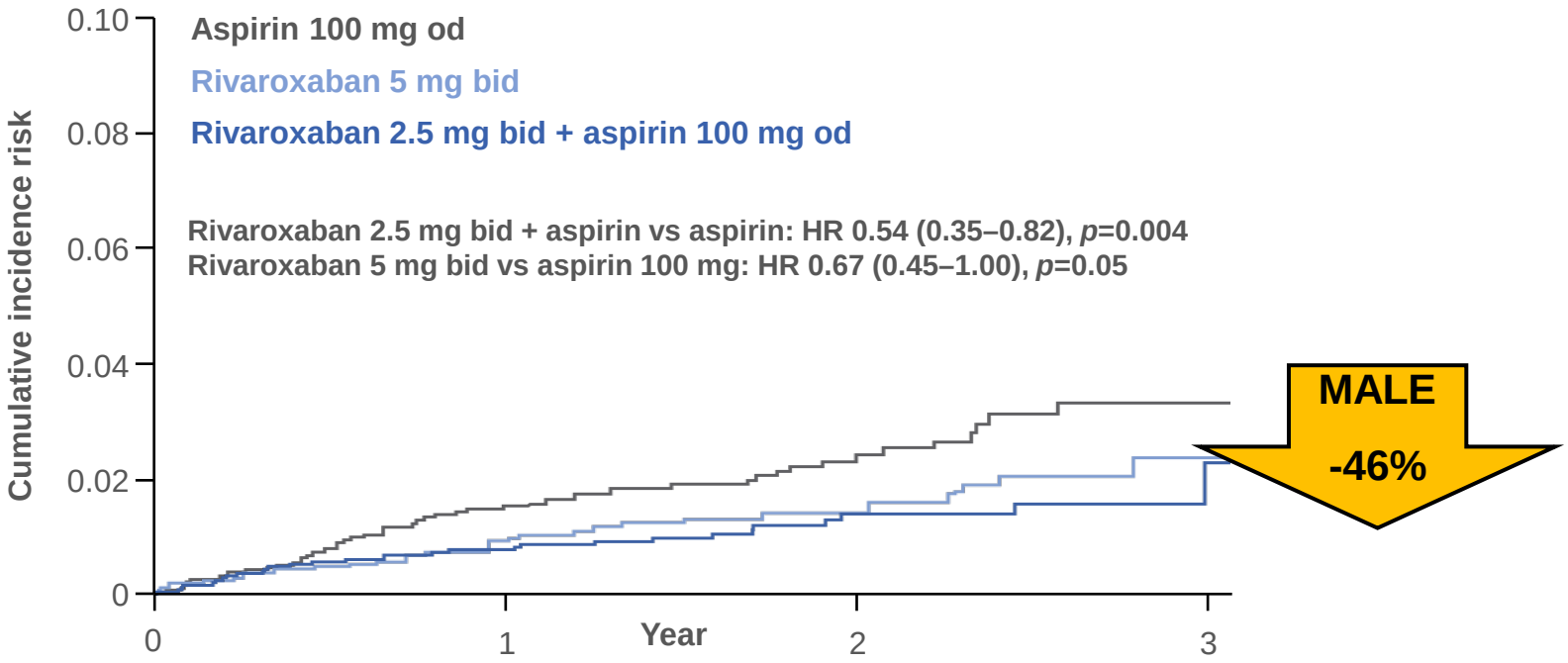
MALE (including Major Amputation) with Rivaroxaban 2.5 mg bid + ASA versus ASA alone

MALE including major amputation



Number at risk				
Rivaroxaban + aspirin	2492	2099	919	129
Rivaroxaban	2474	2071	902	151
Aspirin	2504	2072	951	120

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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Bleeding Increased with Rivaroxaban 2.5 mg bid + ASA versus ASA alone (but no differences fatal bleeding and ICB)

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Major bleeding	77 (3)	79 (3)	48 (2)	1.61 (1.12–2.31)	0.0089	1.68 (1.17–2.40)	0.0043
Fatal	4 (<1)	5 (<1)	3 (<1)	–	–	–	–
Intracranial	5 (<1)	6 (<1)	9 (<1)	0.56 (0.19–1.66)	–	0.68 (0.24–1.91)	–
Fatal or symptomatic bleeding into a critical organ	21 (1)	26 (1)	19 (1)	1.10 (0.59–2.05)	-	1.39 (0.89–3.09)	-

Anand SS *et al, Lancet* 2017;doi:10.1016/S0140-6736(17)32757-5

Composite Outcome with Rivaroxaban 2.5 mg bid + ASA versus ASA alone

28% RRR for the combined endpoint of CV death, MI, stroke, MALE, major amputation, fatal bleeding or critical organ bleeding

Rates at median follow-up of 21 months	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Composite net clinical benefit outcome*	169 (7)	207 (8)	234 (9)	0.72 (0.59–0.87)	0.0008	0.89 (0.74–1.07)	0.23

- For every 1000 patients with PAD treated with rivaroxaban plus aspirin, 27 MACE or MALE (including major amputation) events would be prevented, and 1 fatal and 1 critical organ bleed would be caused over a 21-month period

*Defined as CV death, MI, stroke, MALE, major amputation, fatal bleeding or critical organ bleeding

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

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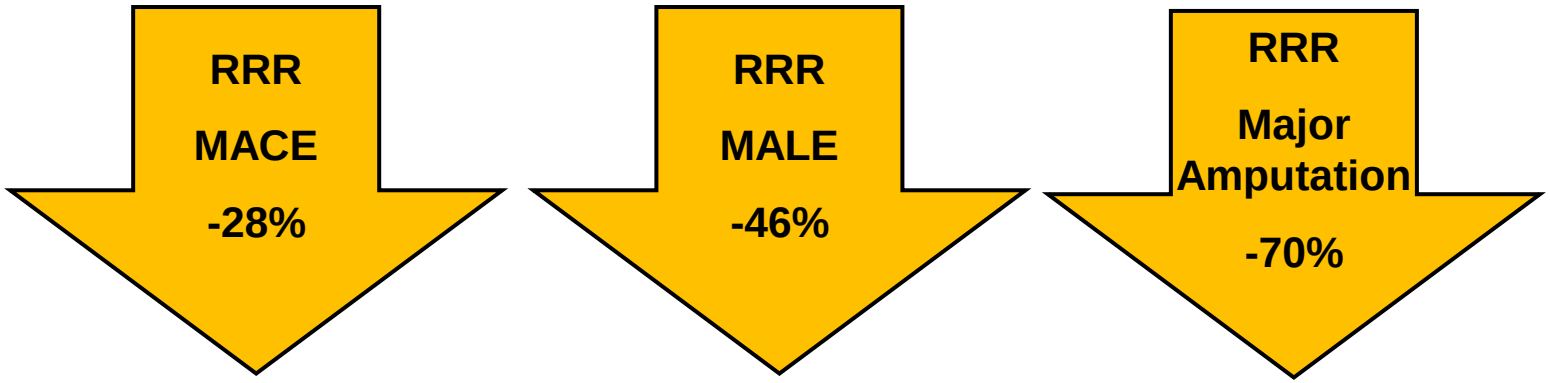
Rivaroxaban 2.5 mg BID achieved Improved Outcomes for PAD Patients

- Rivaroxaban 2.5 mg bid plus ASA (vs. ASA alone):



- Increase in major bleeding (incidence 3 vs. 2%), but not in fatal (incidence both <1%) or critical organ bleeding (incidence both <1%)

- This dual pathway inhibition with rivaroxaban and aspirin represents a major advance in the management of PAD and is the only available therapeutic option to significantly reduce both MACE and MALE

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

COMPASS