Applying novel antithrombotic therapy in the secondary prevention of chronic CVD

COMPASS CAD & PAD

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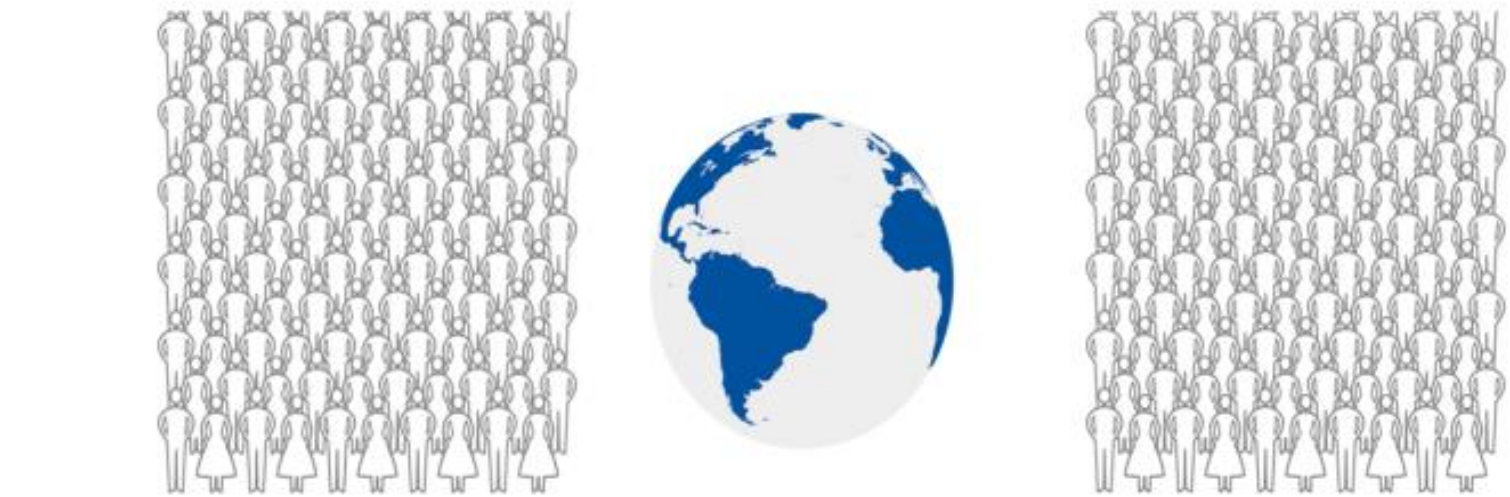
Dual pathway inhibition in Stable Cardiovascular Disease

(Rivaroxaban 2.5 mg BD + Aspirin 75-100 mg OD)



154 MILLION
PATIENTS WITH CAD

120 MILLION
PATIENTS WITH PAD

Key trials of anti-thrombotic therapy in chronic coronary syndrome patients

Dual Anti platelet therapy extension after 1 year

DAPT Trial

ASA vs ASA + Clopidogrel

PEGASUS Trial

ASA vs ASA +Ticagrelor

Dual pathway inhibition after 1 year

FDA APPROVED

COMPASS Trial

ASA vs ASA +Rivaroxaban 2.5 mg BD

Important points:

Only in COMPASS Trial:

- ✓ The study was completed earlier
- ✓ Patients had chronic CAD & PAD
- ✓ 27% of Patients had PAD
- ✓ 22% of patients had heart failure (EF > 30)
- ✓ COMPASS Trial had Less Discontinuation Rate

Cardiovascular Outcomes for People Using Anticoagulation Strategies

The NEW ENGLAND JOURNAL of MEDICINE

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

COMPASS trial
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Inclusion Criteria

- Presence of CAD or PAD
  - CAD defined as any of:
    - MI within the last 20 years
    - Multivessel CAD with symptoms or with history of stable or unstable angina
    - Multivessel PCI/CABG
  - PAD defined as any of:
    - Previous limb bypass surgery or PTCA
    - Previous limb or foot amputation for arterial vascular disease
    - History of claudication (with either of ABI < 0.90 or ≥ 50% stenosis of peripheral artery by angio. or US
    - Previous carotid revascularization or asymptomatic carotid stenosis ≥ 50% by angio. or US
- If included for CAD, also requires either of:
  - Age ≥ 65 years
  - Age < 65 years with documented atherosclerosis or revascularization involving at least 1 additional vascular bed or presence of at least 2 of:
    - Current smoker / Diabetes / eGFR < 60mL/min/ Heart failure/ Non-lacunar stroke ≥ 1 month

N Engl J Med 2017; 377:1319-1330

COMPASS trial
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Exclusion criteria

- high bleeding risk
- a recent stroke or previous hemorrhagic or lacunar stroke
- severe heart failure
- advanced stable kidney disease (estimated GFR <15 ml per minute)
- the use of dual antiplatelet therapy, anticoagulation, or other antithrombotic therapy
- Non cardiovascular conditions deemed by the investigator to be associated with a poor prognosis.

N Engl J Med 2017; 377:1319-1330

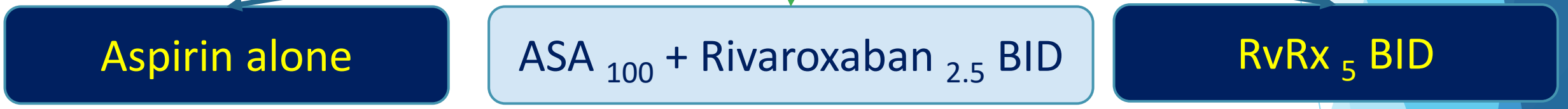
BLEEDING RISK

Table 7 **Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met)**

Major	Minor
• Anticipated use of long-term OAC[a]	• Age ≥ 75 years
• Severe or end-stage CKD (eGFR <30 mL/min)	• Moderate CKD (eGFR 30–59 mL/min)
• Haemoglobin <11 g/dL	• Haemoglobin 11–12.9 g/dL for men or 11–11.9 g/dL for women
• Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	• Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
• Moderate or severe baseline thrombocytopenia[b] (platelet count <100 × 10^9/L)	• Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
• Chronic bleeding diathesis	• Any ischaemic stroke at any time not meeting the major criterion
• Liver cirrhosis with portal hypertension	
• Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	
• Previous spontaneous intracranial haemorrhage (at any time) • Previous traumatic intracranial haemorrhage within the past 12 months • Presence of a brain arteriovenous malformation • Moderate or severe ischaemic stroke[d] within the past 6 months	
• Recent major surgery or major trauma within 30 days prior to PCI • Non-deferrable major surgery on DAPT	

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease (PAD, CAD)

Prospective, multi-center, double-blind,
3-by-2 partial factorial design, randomized controlled trial,
N=27,395, 602 centers in 33 countries



- Rivaroxaban and aspirin (n=9152)
- Rivaroxaban alone (n=9117)
- Aspirin alone (n=9126)

- **Mean follow-up**: 3-4 years
- **Primary outcome**: Cardiovascular death, stroke, or nonfatal MI

N Engl J Med 2017; 377:1319-1330

MAJOR CARDIOVASCULAR EVENTS†

24%
RELATIVE RISK REDUCTION

HR (95% CI): 0.76 (0.66-0.86)
P<0.001

†Major cardiovascular events were a composite of stroke, myocardial infarction (MI), and cardiovascular (CV) death.

STROKE‡

42%
RELATIVE RISK REDUCTION

HR (95% CI): 0.58 (0.44-0.76)

MYOCARDIAL INFARCTION‡

14%
RELATIVE RISK REDUCTION

HR (95% CI): 0.86 (0.70-1.05)

CARDIOVASCULAR DEATH‡§

22%
RELATIVE RISK REDUCTION

HR (95% CI): 0.78 (0.64-0.96)

Bleeding Events

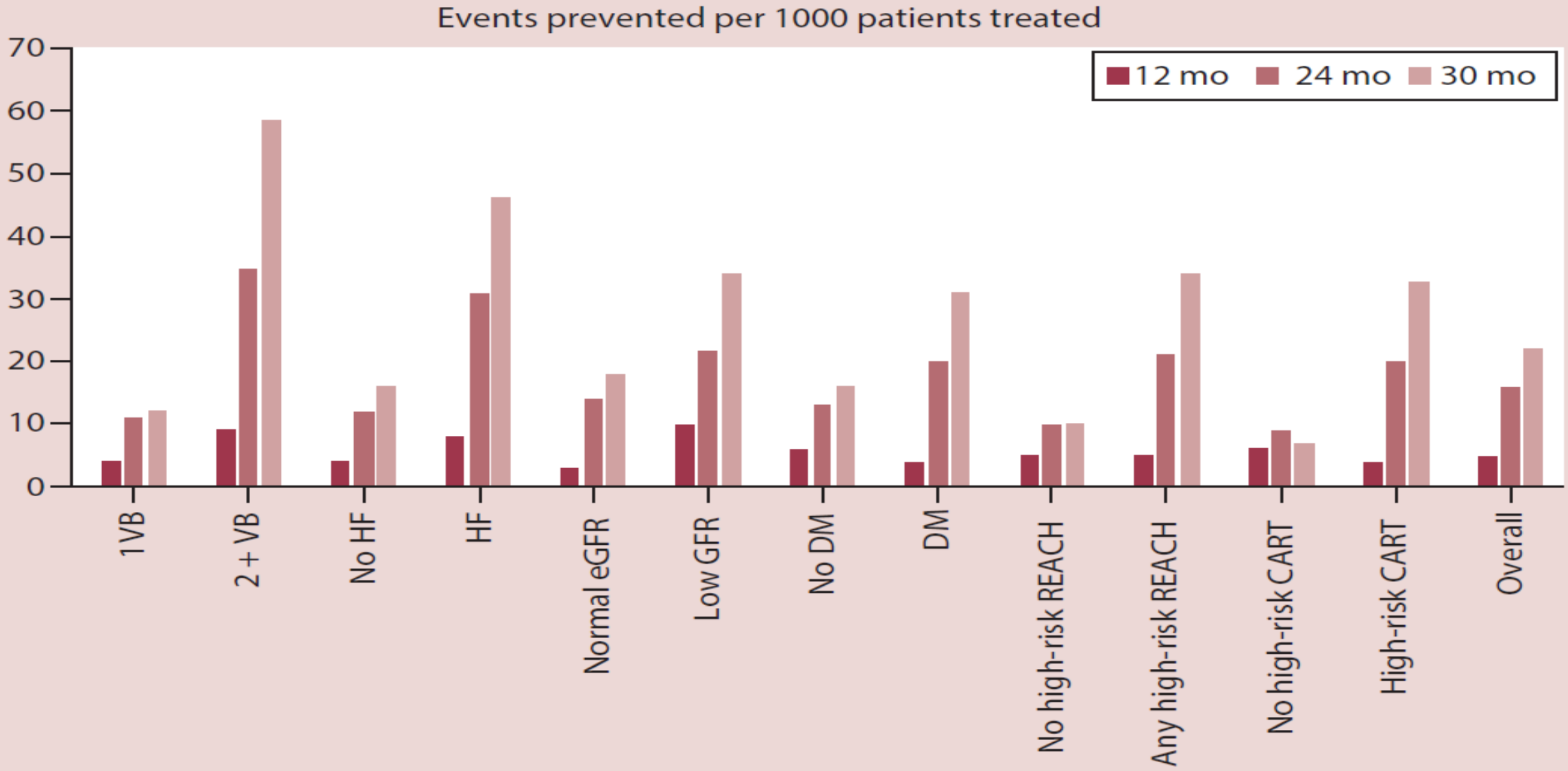
Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value
	number (percent)				
Major and minor bleeding					
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09

NET Clinical benefit

Cardiovascular death, stroke, myocardial infarction, fatal bleeding or symptomatic bleeding into a critical organ	392 (5%)	462 (6%)	494 (6%)	0·78 (0·69–0·90)	0·0003	0·94 (0·82–1·06)	0·31

22%

Net clinical benefit per 1000 patients



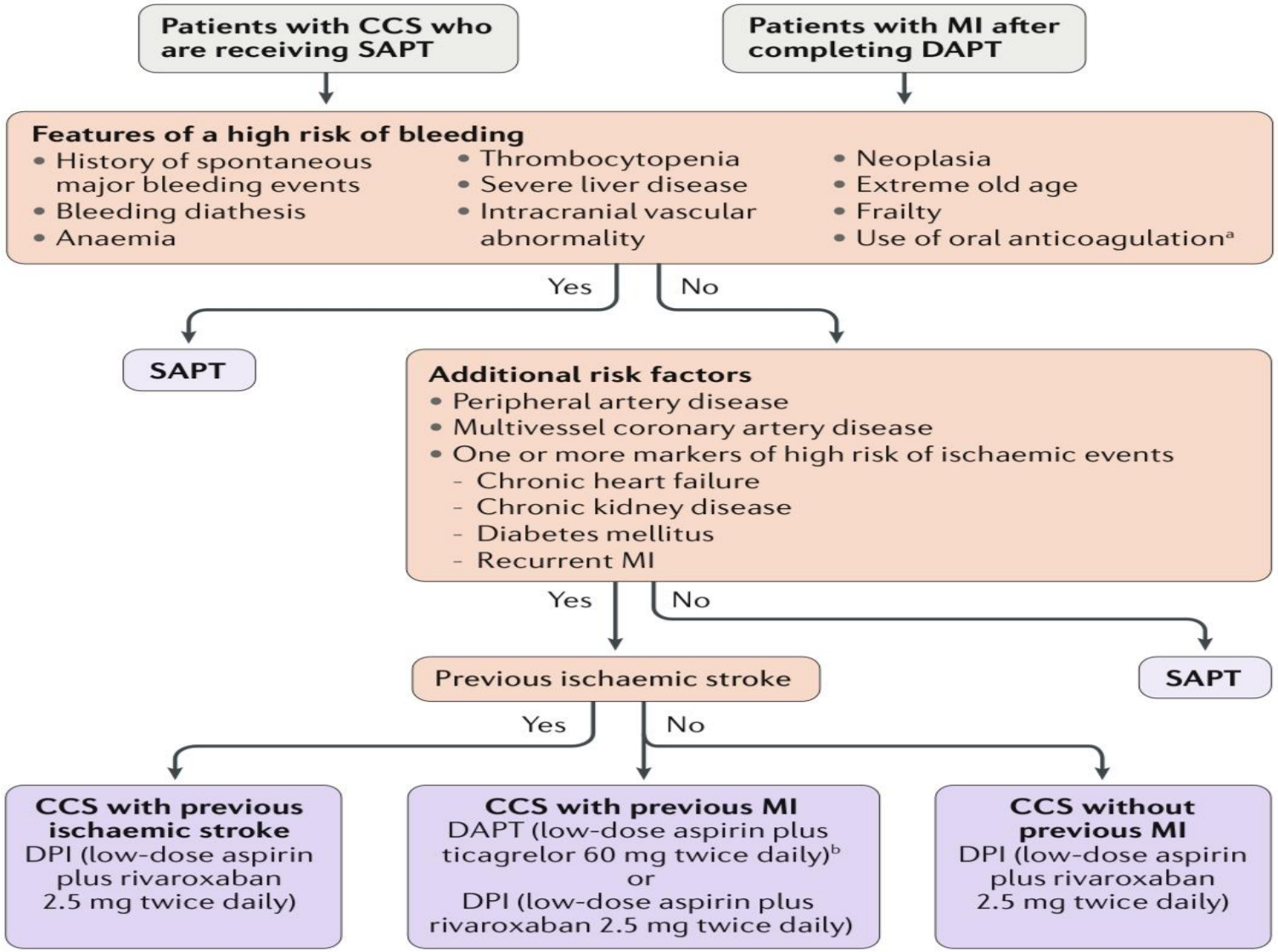
2020 ESC Guidelines

Prolonging antithrombotic treatment duration		
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223]	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223]	IIb	A

2020 ESC Guideline

High thrombotic risk (Class IIa)	Moderate thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	**Non-complex CAD and at least 1 criterion**
Risk enhancers	
Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
History of recurrent MI	History of recurrent MI
Any multivessel CAD	Polyvascular disease (CAD plus PAD)
Polyvascular disease (CAD plus PAD)	CKD with eGFR 15–59 mL/min/1.73 m^2
Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	
Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	
CKD with eGFR 15–59 mL/min/1.73 m^2	
Technical aspects	
At least 3 stents implanted	
At least 3 lesions treated	
Total stent length >60 mm	
History of complex revascularization (left main, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel)	
History of stent thrombosis on antiplatelet treatment	

complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy.



Dual- pathway inhibition for secondary and tertiary antithrombotic prevention in cardiovascular disease, Nature Reviews Cardiology volume 17, pages242–257(2020)

ADA 2021

Combination therapy with aspirin plus low-dose rivaroxaban should be considered for patients with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

Diabetes Care Volume 44, Supplement 1, January 2021

Dual pathway inhibition in Peripheral Artery Diseases

(Rivaroxaban 2.5 mg BD + Aspirin 75-100 mg OD)

Current Challenges in PAD

- Under-recognized and underdiagnosed
- Little progress in management during the last few decades
- High burden of disease and complications in patients with PAD
  - Increased risk of all-cause mortality, CV mortality, and morbidity (MI, stroke)

Global Burden of PAD

Global Prevalence[a]

- 120,000,000
  - 25.6% global burden of CV disease

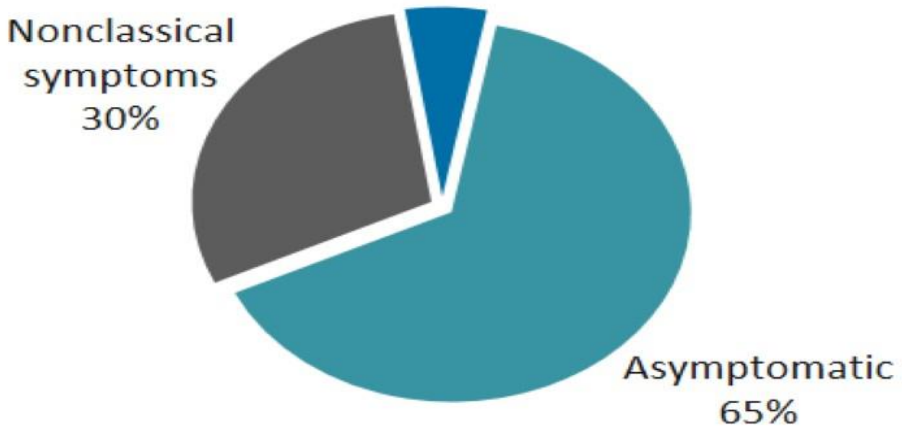
1999–2000 US NHNE Survey[b]

- PAD (ABI < 0.90) prevalence
  - ≥ 40 years: 4.3%
  - ≥ 70 years: 14.5%

US Healthcare Insurer Database[c]

- Mean annual prevalence
  - 10.7%

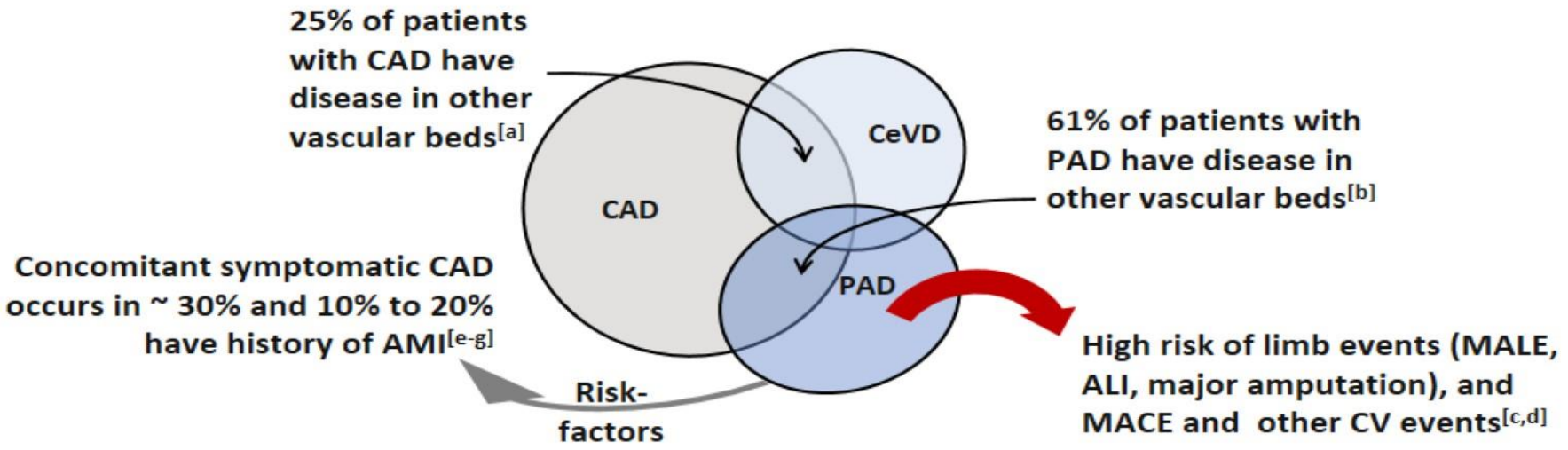
~ 5% of patients with PAD have classical symptoms of intermittent claudication[d]



a. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211-1259; b. Selvin E, et al. *Circulation*. 2004;110:738-743; c. Nehler MR, et al. *J Vasc Surg*. 2014;60:686-695; d. McDermott MM et al. *J Am Heart Assoc*. 2013;2:e000257.

Polyvascular Disease
Substantial Overlap Between CAD and PAD

REACH registry: enrolled 67,888 patients with CAD, PAD, and CeVD[a]



a. Bhatt DL, et al. *JAMA*. 2006;295:180-189; b. Cacoub PP, et al. *Atherosclerosis*. 2009;204:e86-e92;
c. Bonaca MP, et al. *Circulation*. 2013;127:1522-1529; d. Kumbhani DJ, et al. *Eur Heart J*. 2014;35:2864-2872;
e. Hiatt WR, et al. *N Engl J Med*. 2017;376:32-40; f. Mega JL, et al. *N Engl J Med*. 2012;366:9-19;
g. Yusuf S, et al. *N Engl J Med*. 2001;345:494-502.

Current Treatment Strategies For Patients With PAD

Symptom Improvement

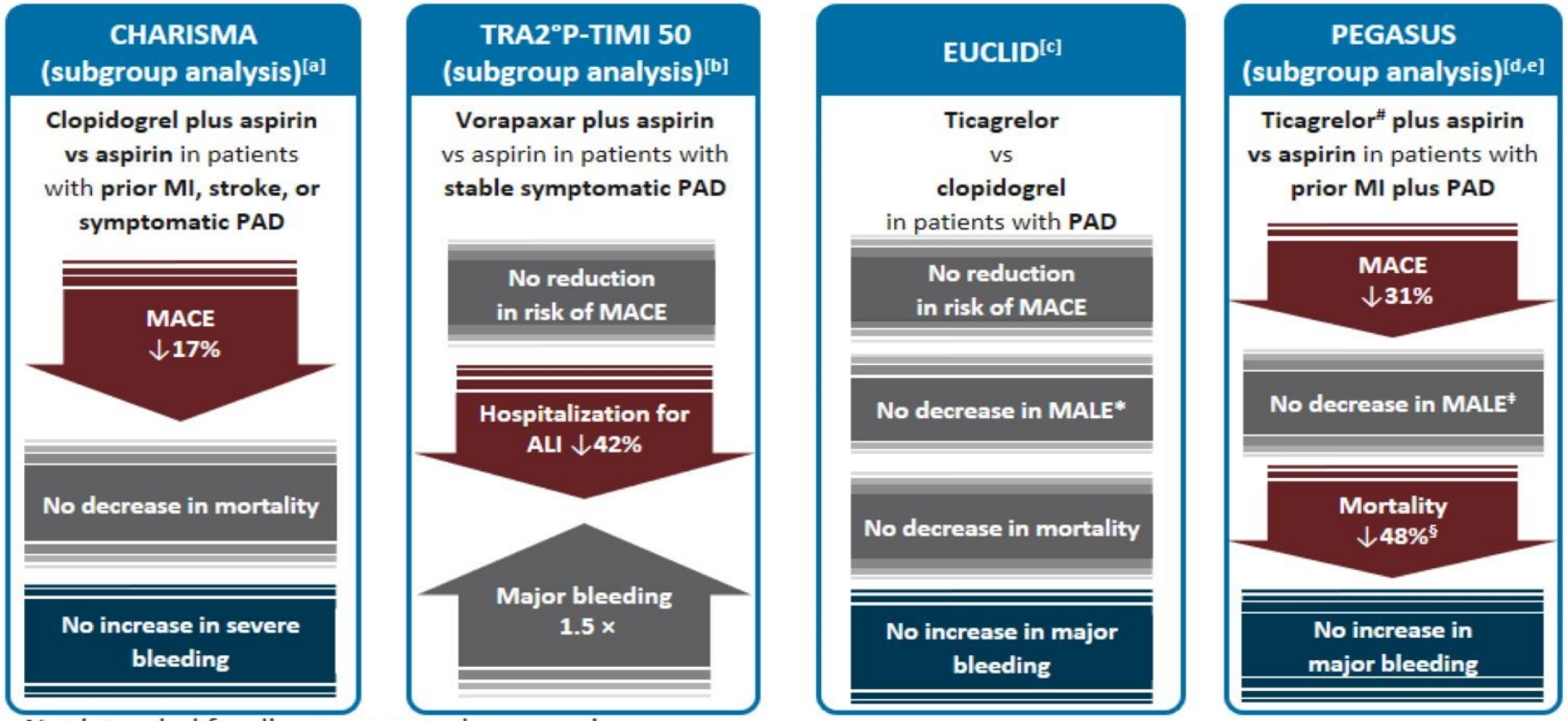
- Exercise training
- Pharmacologic treatments (eg, cilostazol)
- Endovascular intervention (eg, stent placement)
- Surgery (eg, revascularization)

CV Risk Reduction

- Lipid-lowering drugs (eg, statin)
- Antihypertensitive drugs (eg, ACE inhibitor)
- Diabetes therapies
- Smoking cessation
- Antiplatelet drugs (eg, aspirin, clopidogrel)

Aboyans B, et al. *Eur Heart J*. 2018;39:763-821.

Trials on Intensified Antiplatelet Therapy in Patients With PAD Showed Mixed Results



Not intended for direct cross-study comparison

*Hospitalization for ALI or lower limb revascularization (individual endpoints); #Results presented are for the 60 mg twice daily dose; ‡Composite of ALI or peripheral revascularization; §No mortality benefit in the overall trial population[e]

a. Bhatt DL et al. *J Am Coll Cardiol.* 2007;49:1982-1988; b. Bonaca MP, et al. *Circulation.* 2013;127:1522-1529;
c. Hiatt WR *et al, N Engl J Med.* 2017;376:32-40; d. Bonaca MP *et al, J Am Coll Cardiol.* 2016;67:2719-2728;
e. Bonaca MP, et al. *N Engl J Med.* 2015;372:1791-1800.

IN PEGASUS 5% of patients had PAD

THE LANCET

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni , Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators**

- Multicentre, double-blind, randomised placebo-controlled trial
- 7470 patients with peripheral artery disease from 558 centers

Lancet. 2018;391:219–229

PAD Patients in COMPASS

PAD Groups	Number of patients
All Patients	7,470
Symptomatic PAD Limbs	4,129
Carotid Disease	1,919
CAD + Low ABI (<0.90) only	1,422

Mean Follow-up: 21 months

eligible for trial inclusion **(COMPASS-PAD)**

were required to have one of the following:

1) **Previous revascularization of peripheral arteries**

2) **limb or foot amputation** for arterial vascular disease

3) **Intermittent claudication** and one or more of either an **ABI< 0·90** or a **peripheral artery stenosis (≥50%)**

4) **Asymptomatic carotid artery stenosis of at least 50%** diagnosed by duplex ultrasound or

5) **Previous revascularization of carotid artery**

Rivaroxaba
peripheral
randomise

Sonia S Anand, Jackie Bos
Katalin Keltai, Aldo P Mag
Dragos Vinereanu, Nana F
Alvaro A Avezum, Edmon
*Investigators**

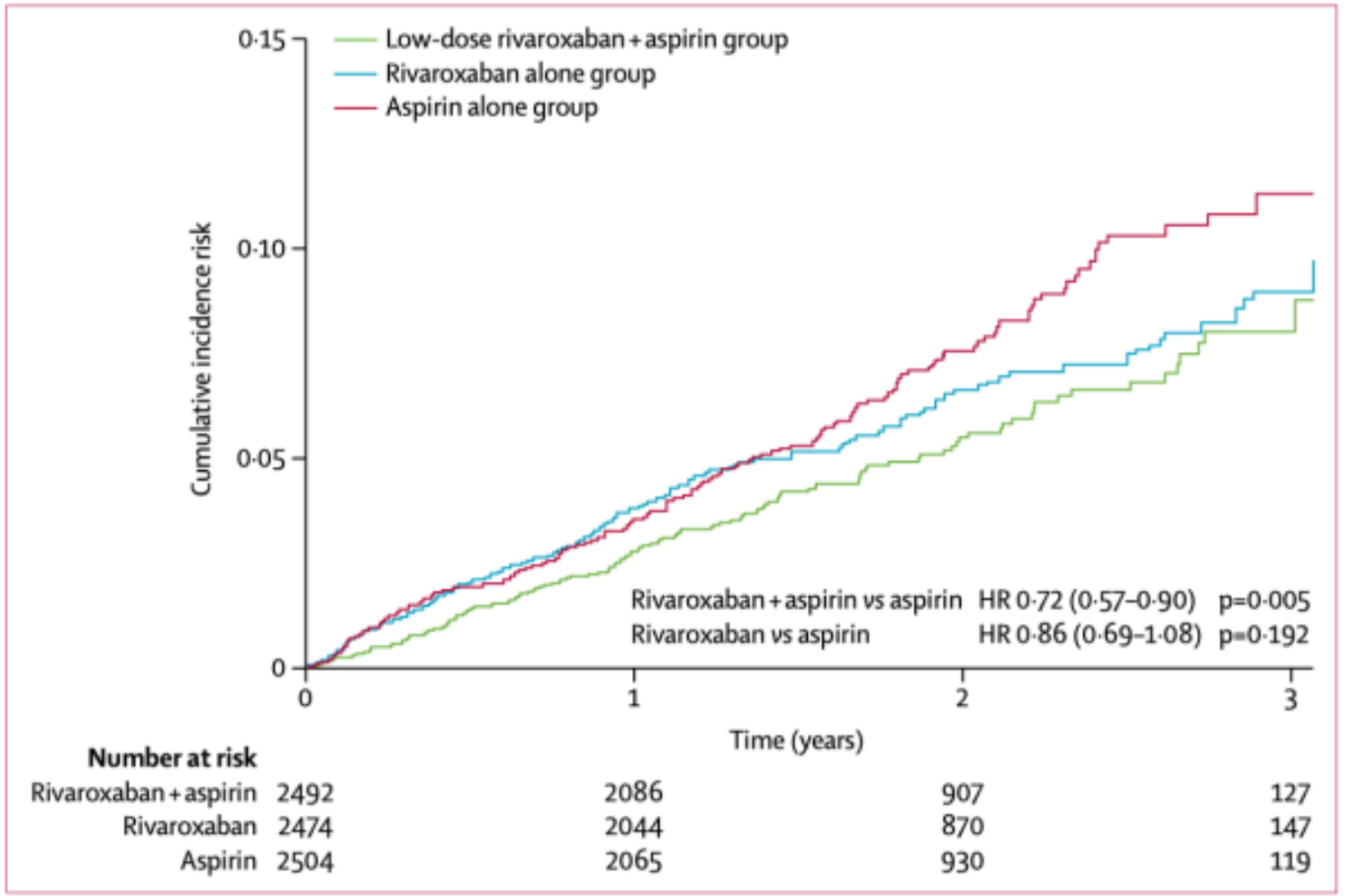


Figure 2: **Cumulative incidence of the primary efficacy outcome**

Primary Efficacy Outcome:
Cardiovascular Death,
Myocardial Infarction,
Stroke

28%

Lancet. 2018;391:219–229

THE LANCE

Rivaroxaba
peripheral c
randomised

Sonia S Anand, Jackie Bosch,
Katalin Keltai, Aldo P Maggi
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*Investigators**

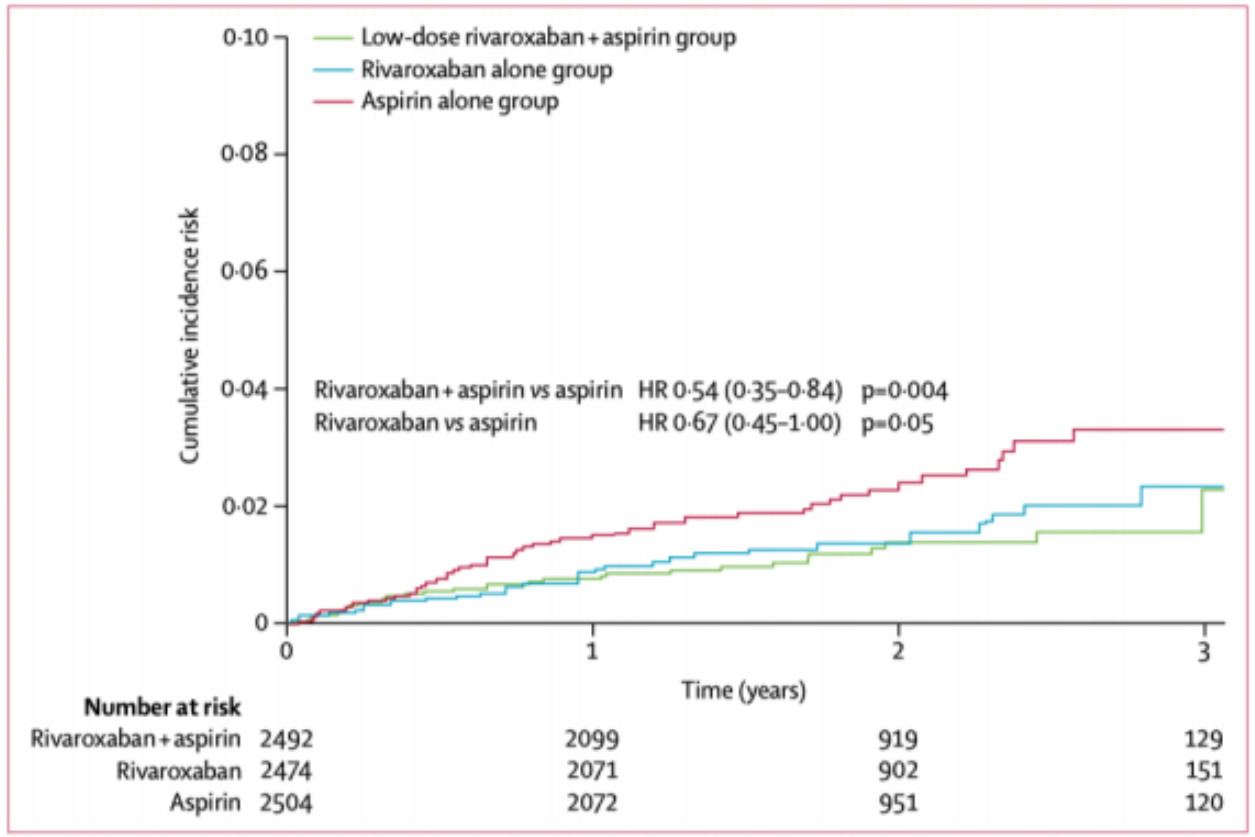


***Figure 3*: Cumulative incidence of individual components of major adverse limb events including major amputation**

Major adverse limb events: acute or chronic limb ischemia over the course of the trial follow-up

46%

Lancet. 2018;391:219–229

COMPASS
PAD Subgroup

Primary Outcomes	Rivaroxaban + Aspirin n = 2492 %	Aspirin n = 2504 %	Rivaroxaban + Aspirin vs Aspirin HR (95% CI)	*P*
MACE[a]	5	7	0.72 (0.57, 0.90)	< .005
MALE including major amputation[a]	1	2	0·54 (0.35, 0.82)	.005
Vascular intervention[b]	n = 2139 5.5	n = 2123 7.1	0.76 (0.60, 0.97)	.03

a. Anand SS, et al. *Lancet*. 2018;391:219-229; b. Anand SS, et al. *J Am Coll Cardiol*. 2018;71:2306-2315.

28% MACE

46% MALE

70% Major Amputation

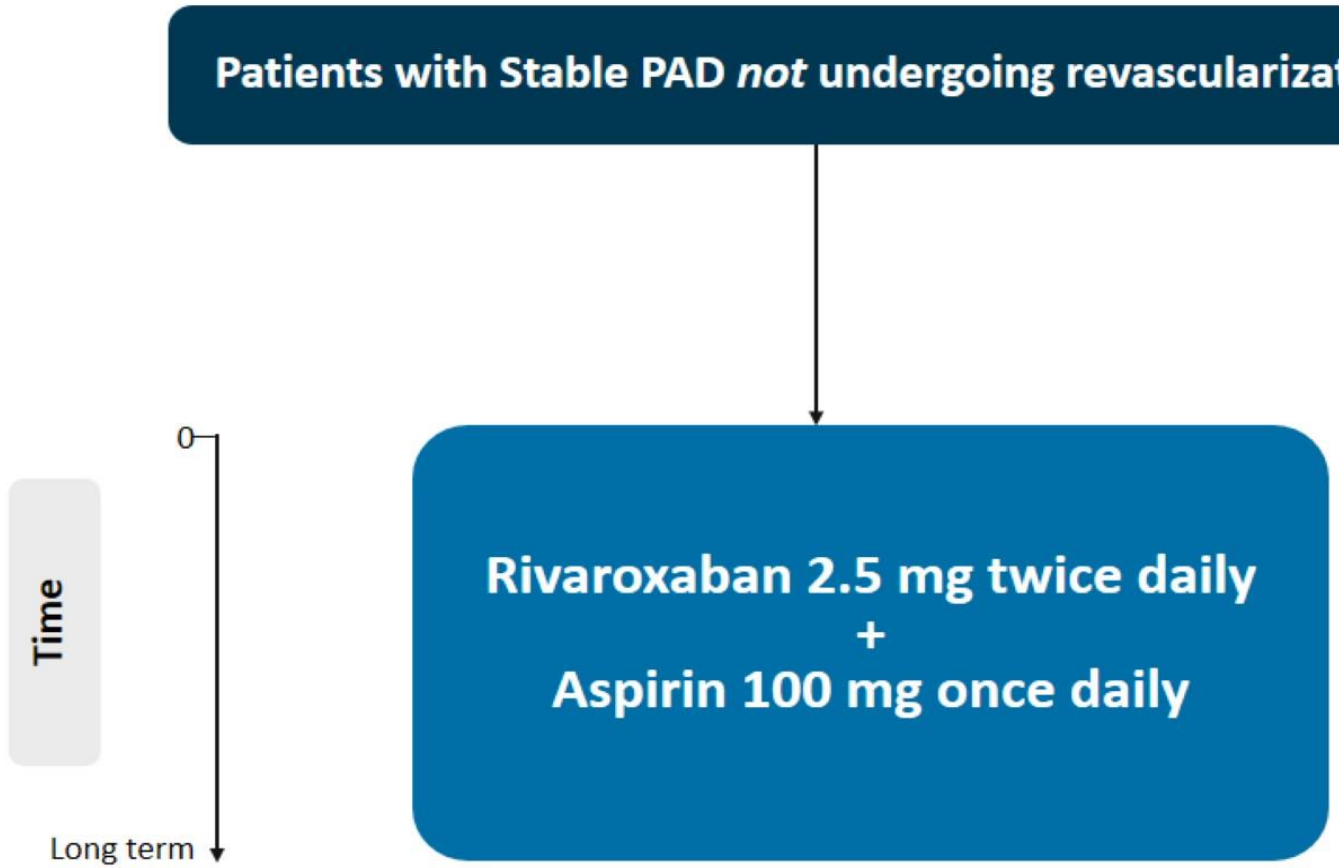
THE LANCET

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

	Low-dose rivaroxaban plus aspirin group (n=2492)	Rivaroxaban alone group (n=2474)	Aspirin alone group (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus asprin alone	
				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 bleeding	4 (<1%)	5 (<1%)	3 (<1%)	..	..	..	..
Non-fatal symptomatic intracranial haemorrhage	4 (<1%)	3 (<1%)	8 (<1%)	..	..	..	..
Non-fatal, non-intracranial haemorrhage symptomatic bleeding into a critical organ	13 (1%)	18 (1%)	8 (<1%)	1·55 (0·64–3·74)	0·33	2·15 (0·94–4·96)	0·065
Other major bleeding (surgical site bleeding requiring reoperation or bleeding leading to hospitalisation	56 (2%)	53 (2%)	29 (1%)	1·94 (1·24–3·04)	0·0031	1·86 (1·18–2·92)	0·0064
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)	..
Fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to re-operation	25 (1%)	29 (1%)	22 (1%)	1·13 (0·64–2·01)	..	1·34 (0·77–2·52)	..
ISTH major bleeding	64 (3%)	53 (2%)	40 (2%)	1·61 (1·08–2·39)	..	1·34 (0·89–2·02)	..

Lancet. 2018;391:219–229

New Antithrombotic Therapy Option for Stable PAD



European Society for Vascular Medicine

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/337679564

ESVM Guideline on Peripheral Arterial Disease

Article *in* VASA.: Zeitschrift für Gefässkrankheiten. Journal for vascular diseases · December 2019
DOI: 10.1024/0301-1526/a000834

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

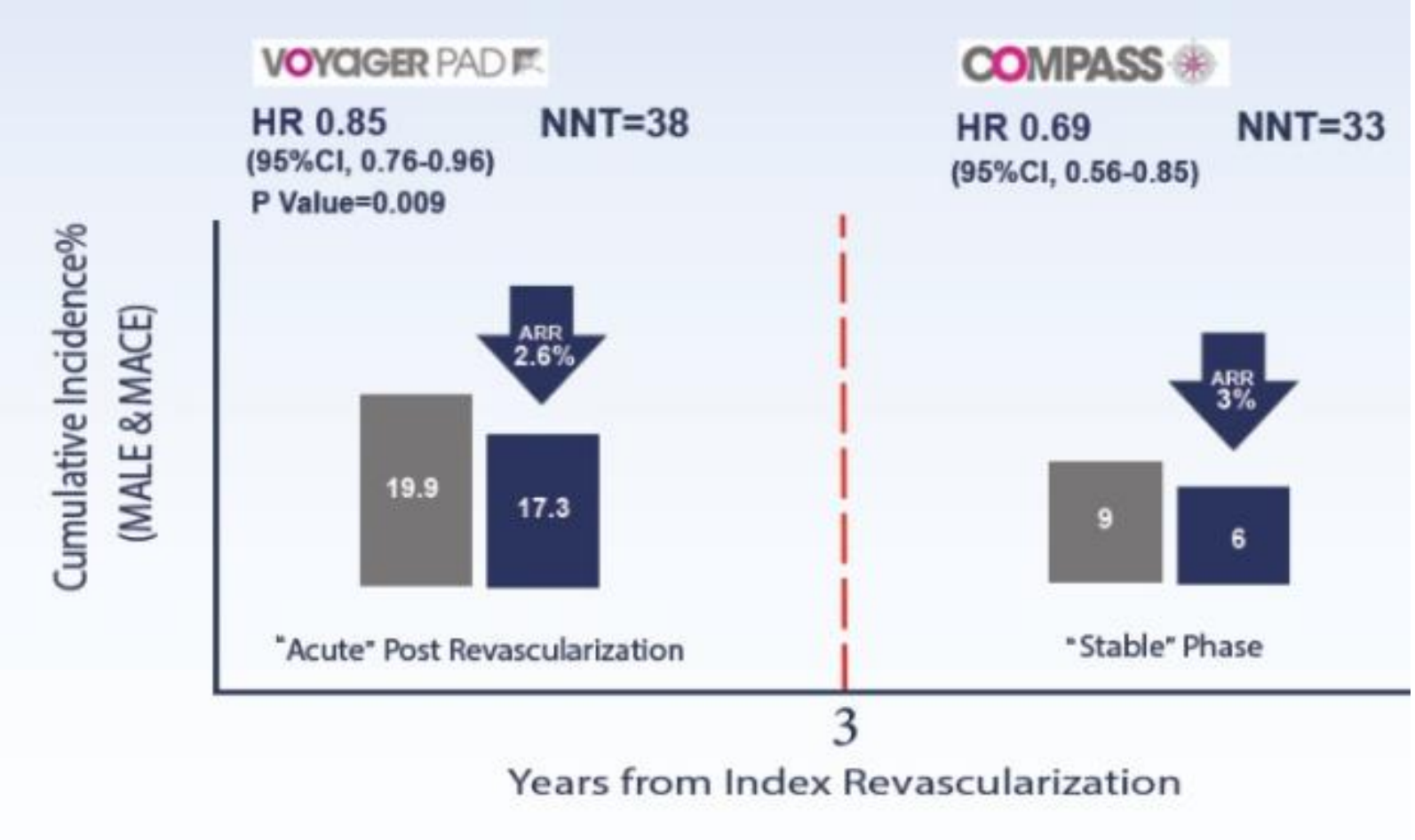
The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

RECOMMENDATIONS	CLASS	EVIDENCE LEVEL
2019 ESVM guidelines on the management of PAD The combined therapy of aspirin 100 mg od and rivaroxaban 2.5 mg bid should be considered in PAD patients without a high risk of bleeding or other contraindications	IIa	B
2019 ESC-EASD guidelines on diabetes, pre-diabetes and CVD In patients with diabetes and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg bid) and aspirin (100 mg od) should be considered	IIa	B

Concluding Remarks

- Rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily is a more efficient antithrombotic strategy than current options for patients with PAD
- The efficacy of this combination is consistent during the different periods of the disease course
- There is no need to change this combination or its dose for the different periods of the disease, which is important for long-term treatment adherence

Rivaroxaban 2.5 mg in PAD CLINICAL TRIAL



Not eligible for **AXABIN 2.5 mg**:

1. High risk of bleeding
2. Stroke within 1 month
3. Any history of haemorrhagic stroke
4. Any history of lacunar stroke
5. Severe heart failure with a known ejection fraction of less than 30%
6. eGFR of less than 15 mL/min
7. Need for dual-antiplatelet therapy or for any nonaspirin antiplatelet therapy

ADA 2021

Combination therapy with aspirin plus low-dose rivaroxaban should be considered for patients with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

Diabetes Care Volume 44, Supplement 1, January 2021

Thanks for your attention