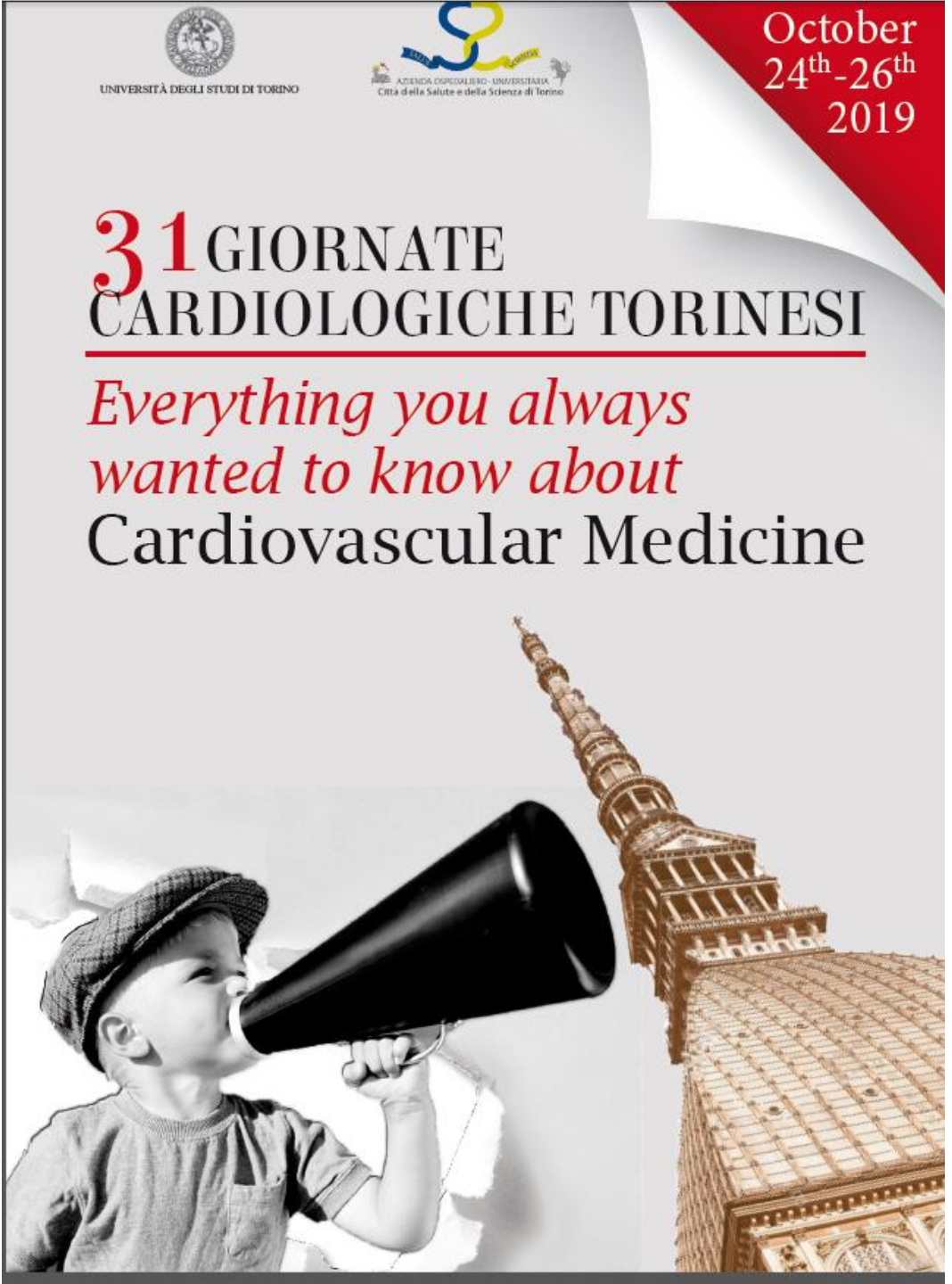


DOACs in chronic ischemic heart disease and peripheral arteriopathy

Giuseppe Favretto

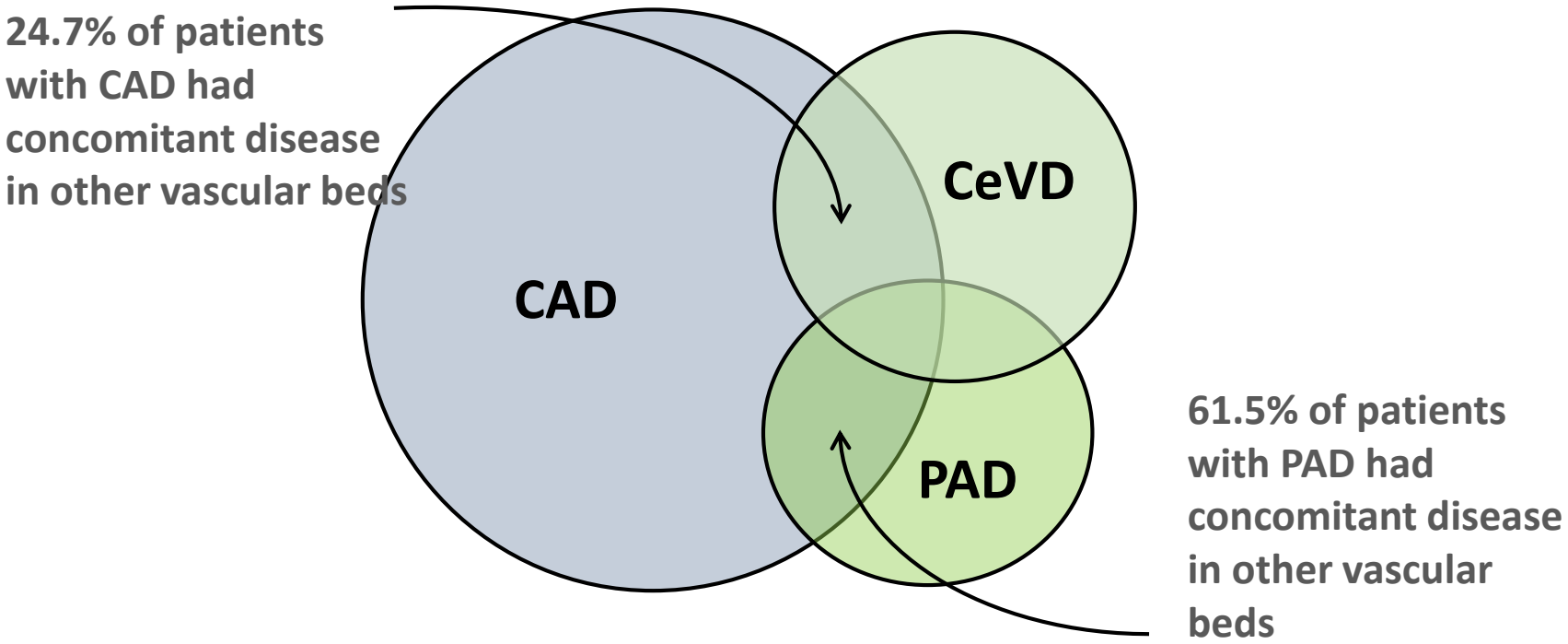
UO di Cardiologia Riabilitativa e Preventiva

O. Riabilitativo di Alta Specializzazione

Motta di Livenza (TV)

Atherothrombosis Is a Polyvascular Disease with Substantial Patient Overlap Between CAD and PAD

- **REACH registry**: enrolled 40,258 patients with established CAD, 8273 patients with established PAD, and 18,843 patients with established cerebrovascular disease from 44 countries*



CeVD, cerebrovascular disease
*Note: definitions of CAD and PAD in REACH are not identical with COMPASS

Bhatt DL *et al*, *J Am Med A, 2006*

Coronary artery disease (CAD)

Acute coronary syndrome (ACS)

- STEMI
- NSTEMI
- Unstable angina

2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

SIHD

2013 ESC guidelines on the management of stable coronary artery disease

SCAD

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Juhani Knuuti* (Finland) (Chairperson), William Wijns* (Ireland) (Chairperson), Antti Saraste (Finland), Davide Capodanno (Italy), Emanuele Barbato (Italy), Christian Funck-Brentano (France), Eva Prescott (Denmark), Robert F. Storey (United Kingdom), Christi Deaton (United Kingdom), Thomas Cuisset (France), Stefan Agewall (Norway), Kenneth Dickstein (Norway), Thor Edvardsen (Norway), Javier Escaned (Spain), Bernard J. Gersh (United States of America), Pavel Svitil (Czech Republic), Martine Gilard (France), David Hasdai (Israel), Robert Hatala (Slovak Republic), Felix Mahfoud (Germany), Josep Masip (Spain), Claudio Muneretto (Italy), Marco Valgimigli (Switzerland), Stephan Achenbach (Germany), Jeroen J. Bax (Netherlands)

From ‘stable’ to ‘chronic’: Changing definitions in CAD

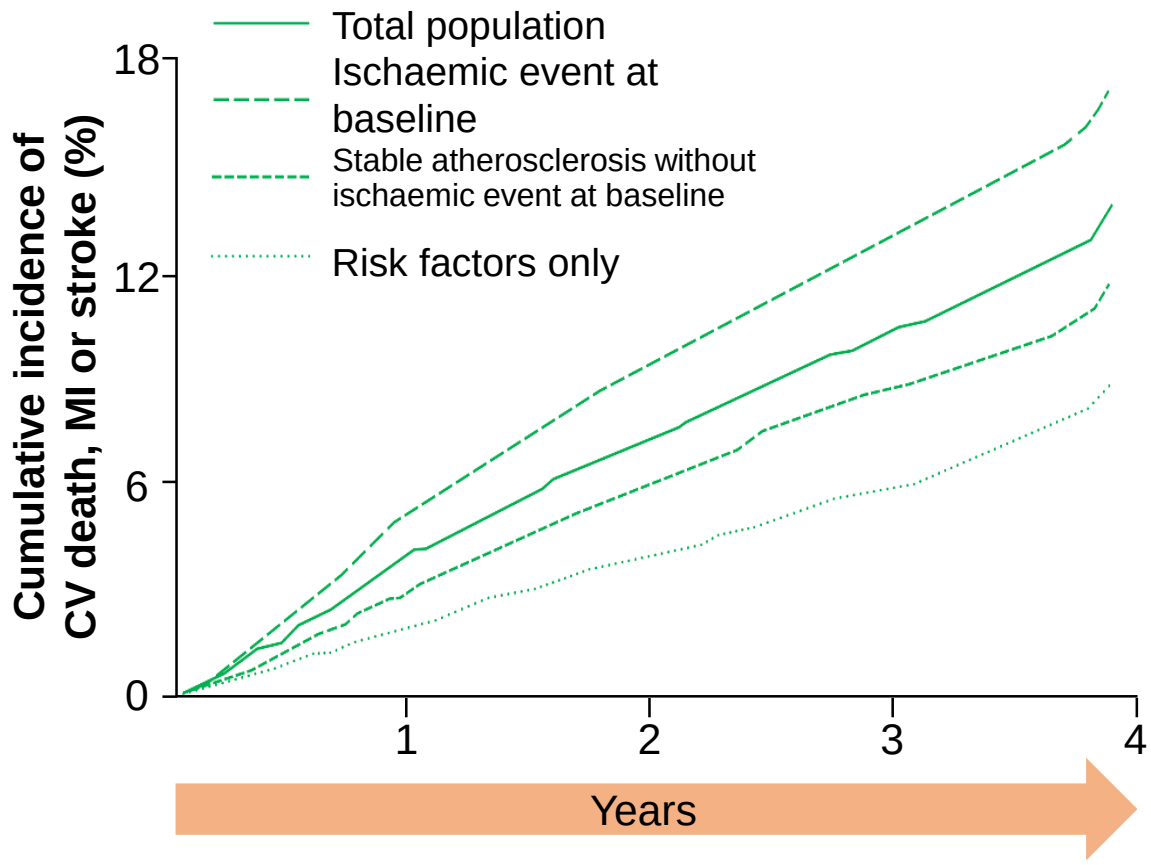
Chronic Coronary Syndrome ESC Update 2019

dispel the myth

the patient with atherosclerotic cardiovascular disease is not a stable patient

Despite guideline-recommended therapy, patients with previous ischaemic events are at high risk of recurrence

Incidence of MACE according to the history of ischaemic events in the REACH registry



4-year incidence of MACE in patients with a prior ischaemic event: 18.3%

Bhatt *et al*, *JAMA* 2010;304:1350–1357

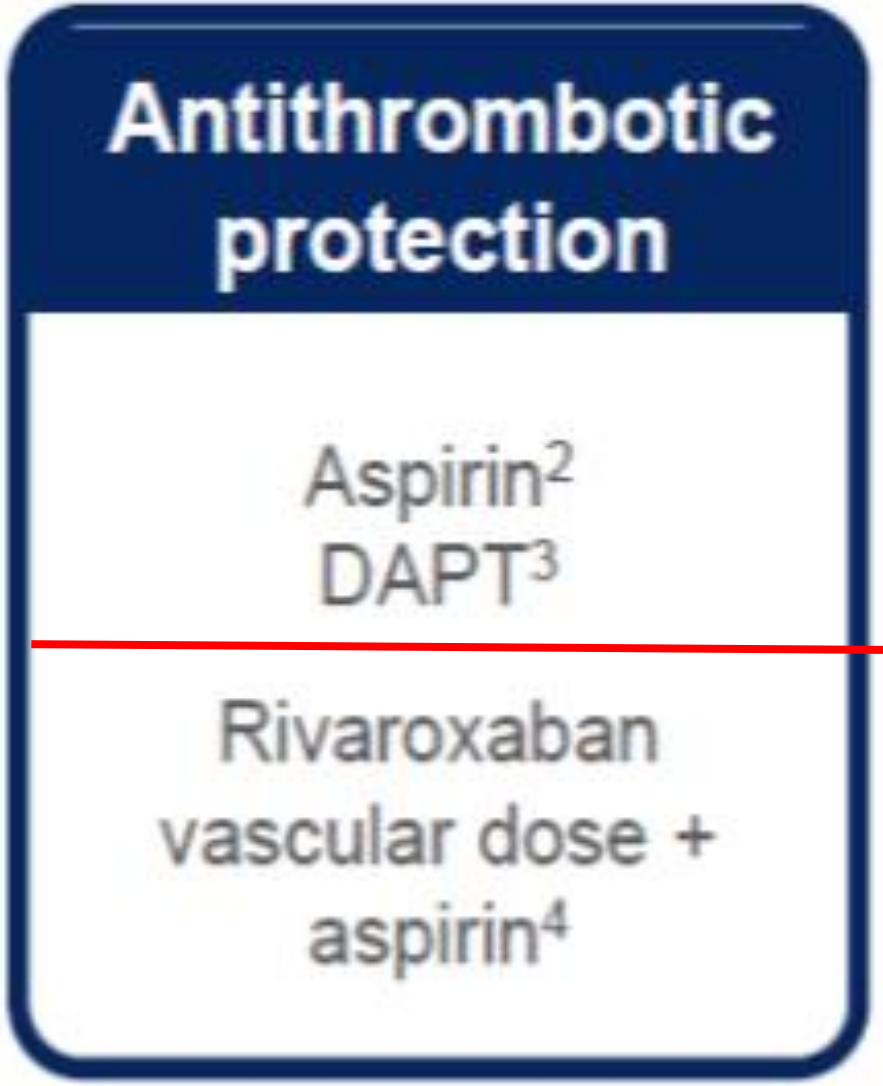
RESIDUAL RISK REDUCTION

“Residual Metabolic Risk”

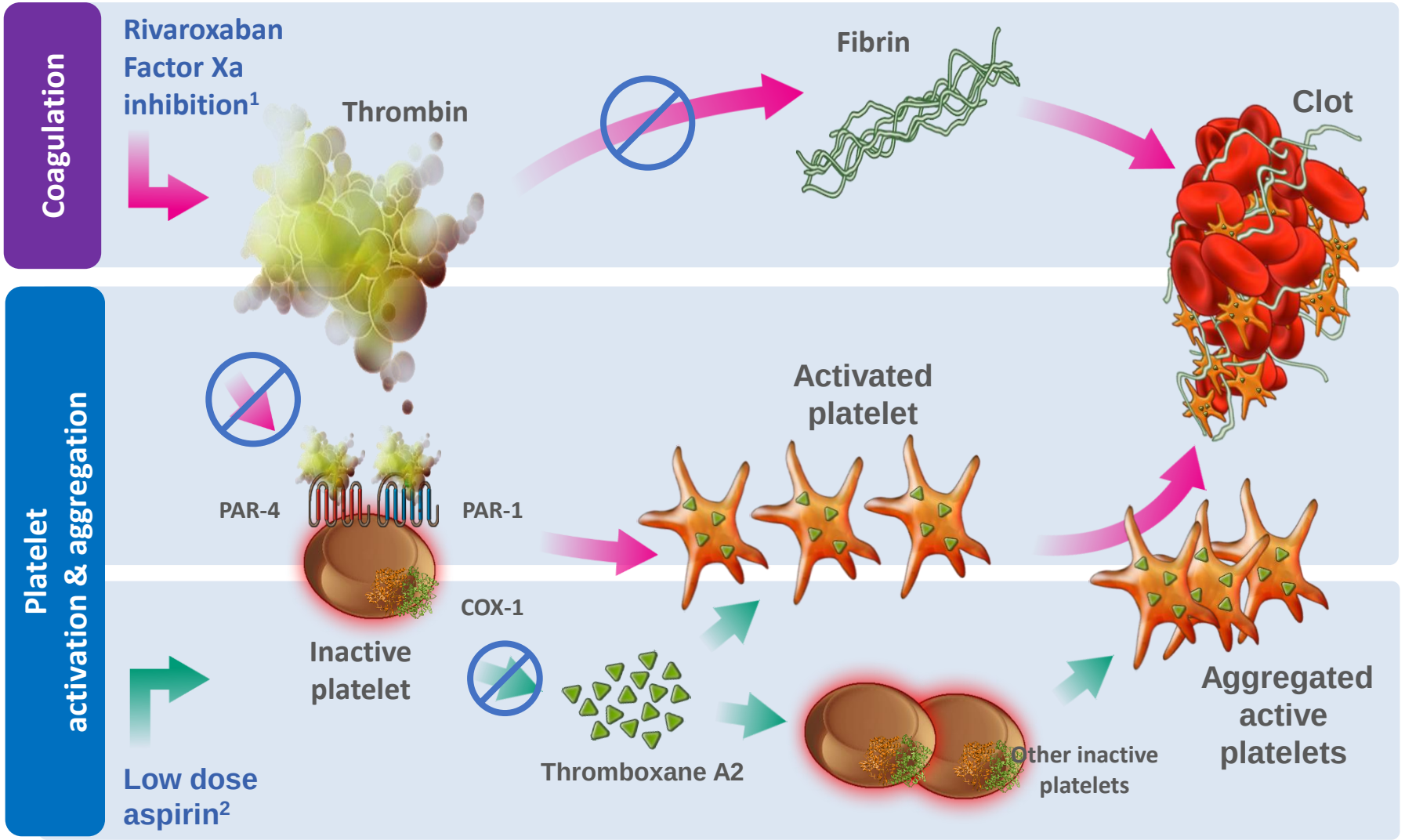
“Residual Thrombotic Risk”

“Residual Inflammatory Risk”

Residual Antithrombotic Risk

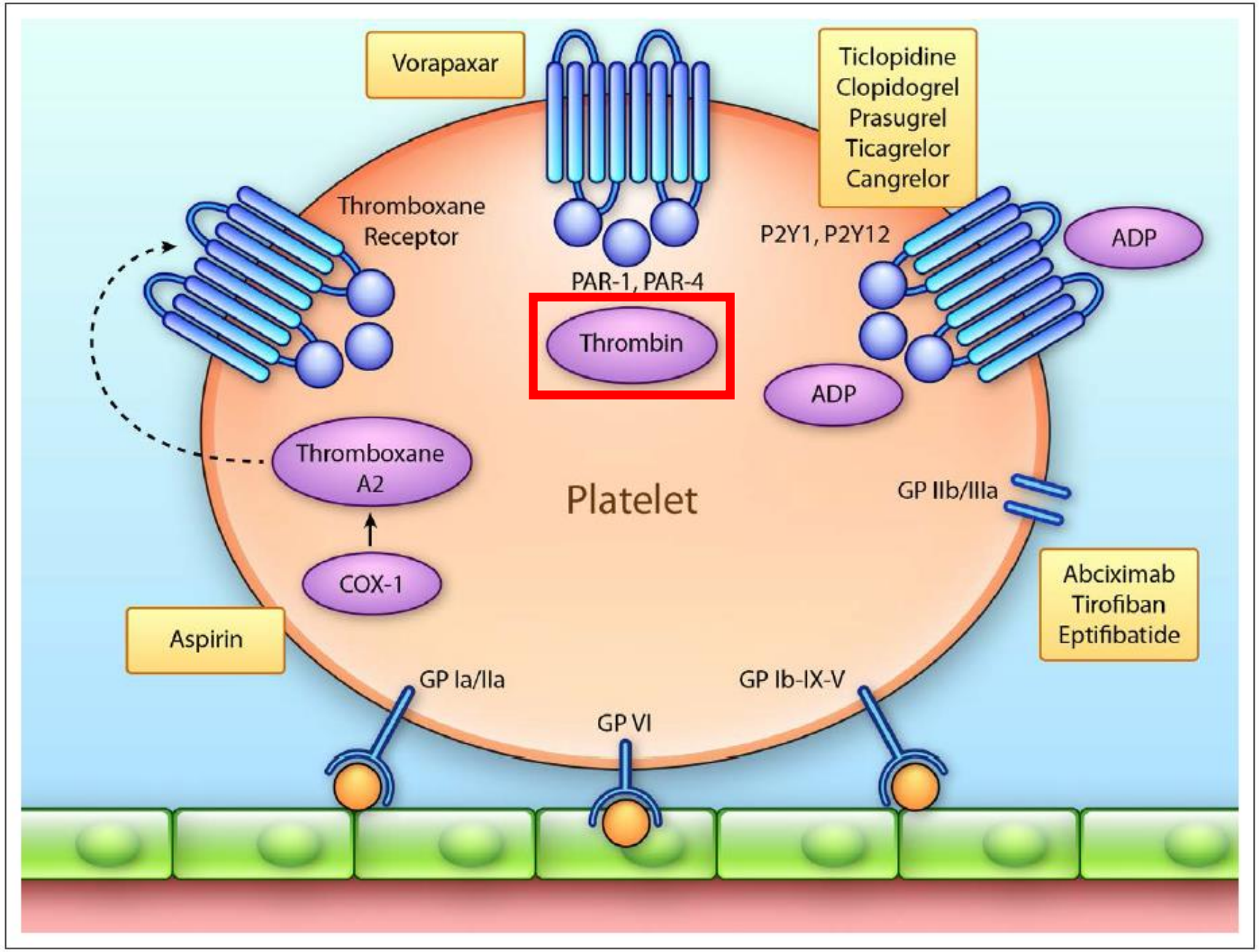


Rivaroxaban and Aspirin Synergistically Target Essential Components of Atherothrombosis



Rivaroxaban impacts not only fibrin formation, but also platelet activation

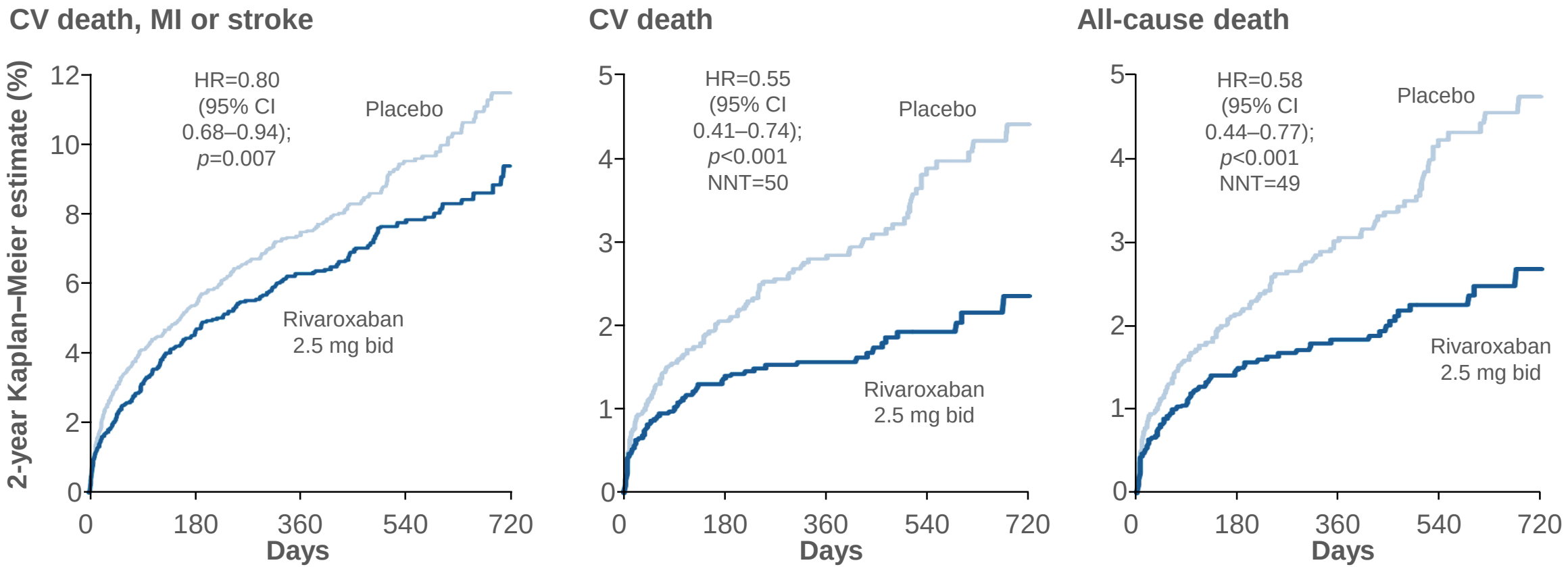
1. Adapted from Angiolillo DJ *et al. Eur Heart J* 2010;31:17–28; 2. Adapted from Mitchell JRA. *BMJ* 1981;282:590–594


Vorapaxar
Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor
Cangrelor
Thromboxane
Receptor
PAR-1, PAR-4
P2Y1, P2Y12
ADP
Thrombin
ADP
Thromboxane
A2
Platelet
GP IIb/IIIa
COX-1
Abciximab
Tirofiban
Eptifibatide
Aspirin
GP Ia/IIa
GP Ib-IX-V
GP VI

ATLAS ACS 2 TIMI 51: Rivaroxaban Vascular Dose Reduced CV Events and Death in Patients with ACS

Therapeutic scheme: Rivaroxaban 2,5 mg bid + DAPT (in 95% pts)

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%)

Korjian S *et al, Eur Heart J Acute Cardiovasc Care* 2017: doi:10.1177/204887261774500

ATLAS ACS TIMI 51

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

- double-blind, double-dummy, event-driven trial conducted at 602 centers in 33 countries

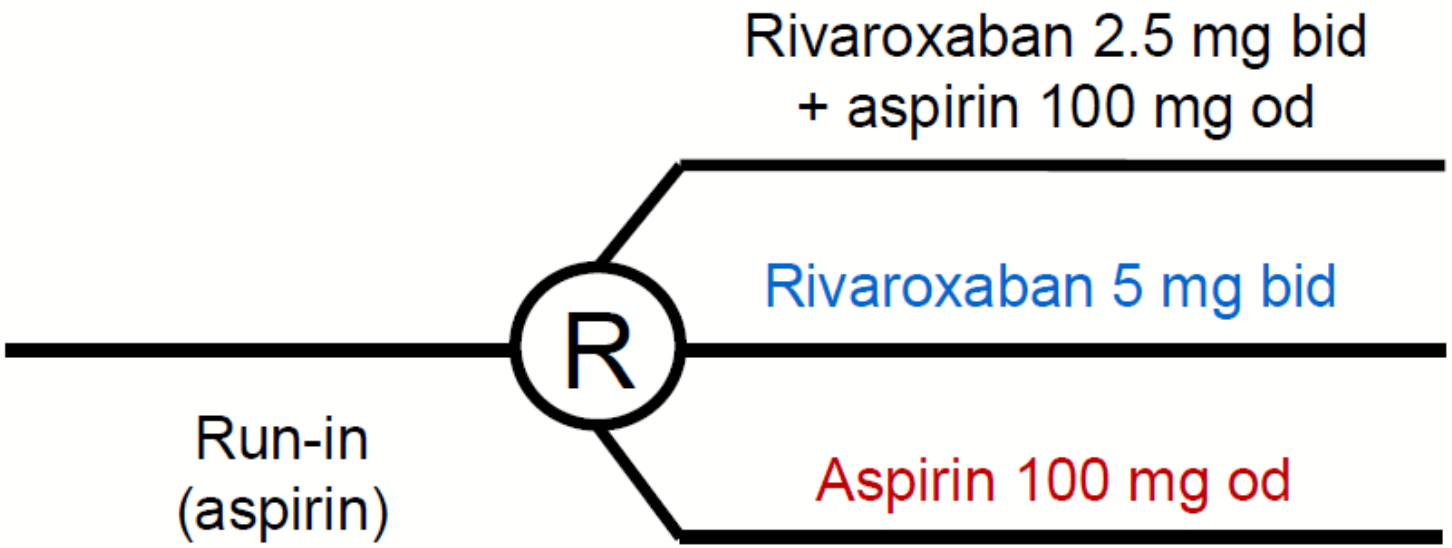
- a total of 27.392 pts with stable atherosclerotic vascular disease were enrolled from March 2013 through May 2016

This article was published on August 27, 2017, at NEJM.org.

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

COMPASS Design

Stable CAD or PAD
2,200 with a primary outcome event



Expected follow-up
3–4 years

Average follow-up: 23 months at early termination of study

COMPASS Population

Inclusion criteria ensured that a high-risk population was enrolled

Patients with ***established*** atherosclerotic disease with a ***high risk*** of incident cardiovascular disease

CAD (N=24,824)

- Multivessel CAD and/or prior MI
- For patients <65 years two vascular beds or two additional cardiovascular risk factors

PAD (N=7470)

- Previous interventions of peripheral bypass surgery or PTCA
- Limb or foot amputation
- Symptomatic intermittent claudication with ankle/arm blood pressure ratio <0.90 or significant peripheral artery stenosis
- Previous carotid revascularization or asymptomatic carotid artery stenosis ≥50%

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

Exclusion criteria[†]

- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known ejection fraction < 30% or New York Heart Association class III or IV symptoms
- Estimated glomerular filtration rate < 15 mL/min
- Need for dual antiplatelet therapy, other nonaspirin antiplatelet therapy, or oral anticoagulant therapy
- Known noncardiovascular disease that is associated with poor prognosis (eg, metastatic cancer) or that increases the risk of an adverse reaction to study interventions
- History of hypersensitivity or known contraindication for rivaroxaban, aspirin, pantoprazole, or excipients, if applicable
- Systemic treatment with strong inhibitors of CYP 3A4 as well as p-glycoprotein (eg, systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4 (ie, rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine)
- Any known hepatic disease associated with coagulopathy
- Subjects who are pregnant, breastfeeding, or are of childbearing potential, and sexually active and not practicing an effective method of birth control (eg, surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization)
- Previous assignment to treatment during this study
- Concomitant participation in another study with investigational drug
- Known contraindication to any study-related procedures

Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

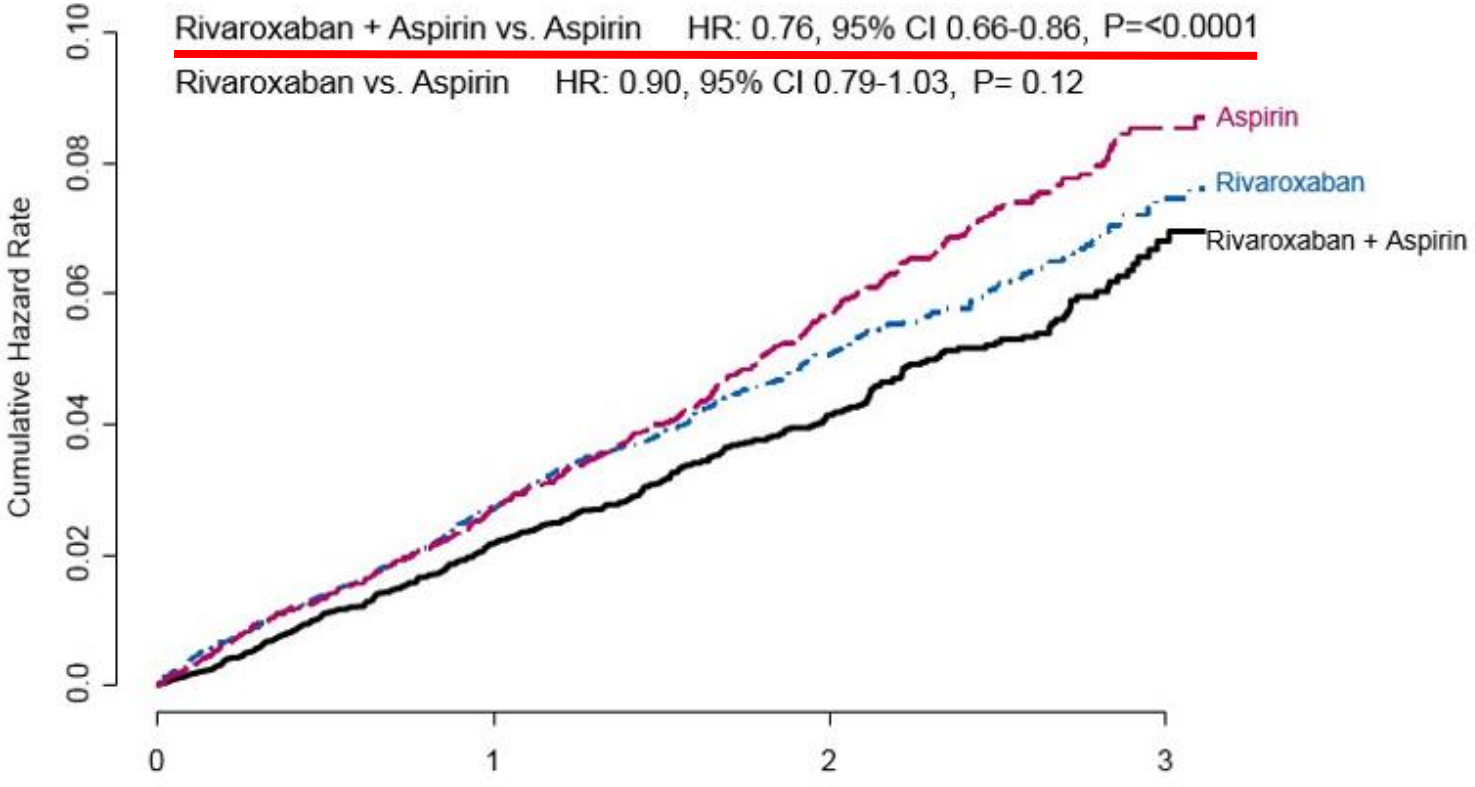
COMPASS

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)
Estimated GFR — no. (%)¶			
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)

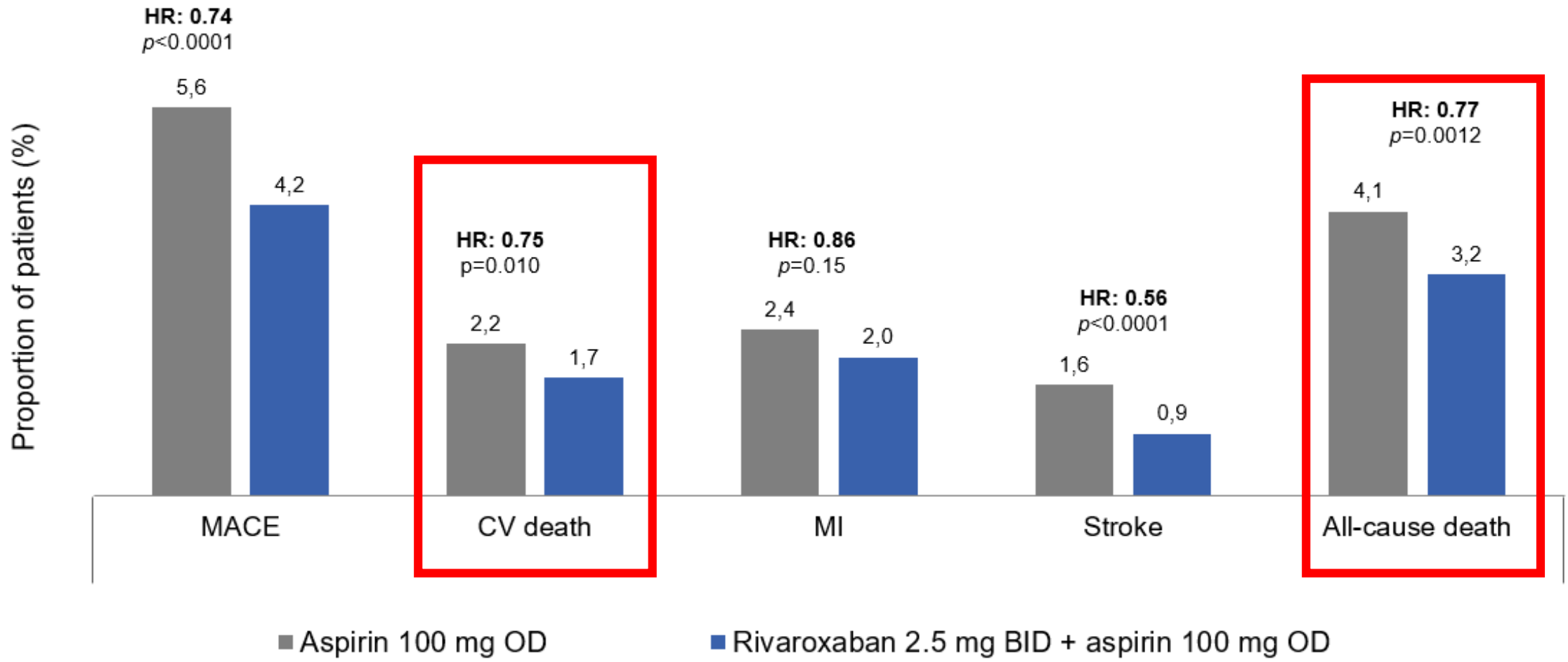
Primary: CV death, stroke, MI

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE



No. at Risk				
Rivaroxaban + Aspirin	9152	7904	3912	658
Rivaroxaban	9117	7824	3862	670
Aspirin	9126	7808	3860	669

Rivaroxaban Vascular Dose + Aspirin Decreased Major Adverse Cardiovascular Events & Mortality



Connolly SJ et al. *Lancet* 2018;391:205–218.

COMPASS

Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		
	N (%)	N (%)	N (%)	HR (95% CI)	P	
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	**Primary safety outcome**
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	

* symptomatic

COMPASS study

Major bleeding

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P
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* symptomatic

The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 5, 2017 VOL. 377 NO. 14

NET CLINICAL BENEFIT / IRREVERSIBLE HARM

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin Vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
Net clinical benefit (Primary + Sever bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

Subgroup	Rivaroxaban+ Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All participants	379/9152 (4.1)	496/9126 (5.4)	0.76 (0.66–0.86)	
Age				0.20
<65 yr	79/2150 (3.7)	126/2184 (5.8)	0.63 (0.48–0.84)	
65–74 yr	179/5078 (3.5)	238/5045 (4.7)	0.74 (0.61–0.90)	
≥75 yr	121/1924 (6.3)	132/1897 (7)	0.89 (0.69–1.14)	
Sex				0.75
Male	300/7093 (4.2)	393/7137 (5.5)	0.76 (0.66–0.89)	
Female	79/2059 (3.8)	103/1989 (5.2)	0.72 (0.54–0.97)	
Geographic region				0.56
North America	63/1304 (4.8)	80/1309 (6.1)	0.78 (0.56–1.08)	
South America	93/2054 (4.5)	111/2054 (5.4)	0.84 (0.63–1.10)	
Western Europe	117/2855 (4.1)	141/2855 (4.9)	0.82 (0.64–1.05)	
Eastern Europe	59/1607 (3.7)	90/1604 (5.6)	0.65 (0.46–0.90)	
Asia–Pacific	47/1332 (3.5)	74/1304 (5.7)	0.62 (0.43–0.89)	
Race				0.37
White	235/5673 (4.1)	306/5682 (5.4)	0.76 (0.64–0.90)	
Black	2/76 (2.6)	8/92 (8.7)	0.30 (0.06–1.46)	
Asian	54/1451 (3.7)	81/1397 (5.8)	0.64 (0.45–0.90)	
Other	88/1952 (4.5)	101/1955 (5.2)	0.87 (0.65–1.16)	
Body weight				0.64
≤60 kg	41/901 (4.6)	45/836 (5.4)	0.83 (0.55–1.27)	
>60 kg	335/8241 (4.1)	448/8285 (5.4)	0.75 (0.65–0.86)	
Estimated GFR				0.95
<60 ml/min	132/2054 (6.4)	177/2114 (8.4)	0.75 (0.60–0.94)	
≥60 ml/min	247/7094 (3.5)	319/7012 (4.5)	0.76 (0.64–0.90)	
Baseline tobacco use				0.29
Yes	80/1944 (4.1)	122/1972 (6.2)	0.66 (0.50–0.88)	
No	299/7208 (4.1)	374/7154 (5.2)	0.79 (0.68–0.92)	
Baseline diabetes				0.77
Yes	179/3448 (5.2)	239/3474 (6.9)	0.74 (0.61–0.90)	
No	200/5704 (3.5)	257/5652 (4.5)	0.77 (0.64–0.93)	
History of hypertension				0.68
Yes	317/6907 (4.6)	409/6877 (5.9)	0.76 (0.66–0.89)	
No	62/2245 (2.8)	87/2249 (3.9)	0.71 (0.51–0.98)	
Baseline dyslipidemia				0.47
Yes	325/8239 (3.9)	428/8158 (5.2)	0.74 (0.64–0.86)	
No	54/913 (5.9)	68/968 (7)	0.85 (0.60–1.22)	
Coronary artery disease				0.47
Yes	347/8313 (4.2)	460/8261 (5.6)	0.74 (0.65–0.86)	
No	32/839 (3.8)	36/865 (4.2)	0.89 (0.55–1.43)	
Peripheral arterial disease				0.61
Yes	126/2492 (5.1)	174/2504 (6.9)	0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)	0.77 (0.66–0.91)	

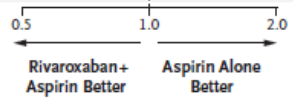
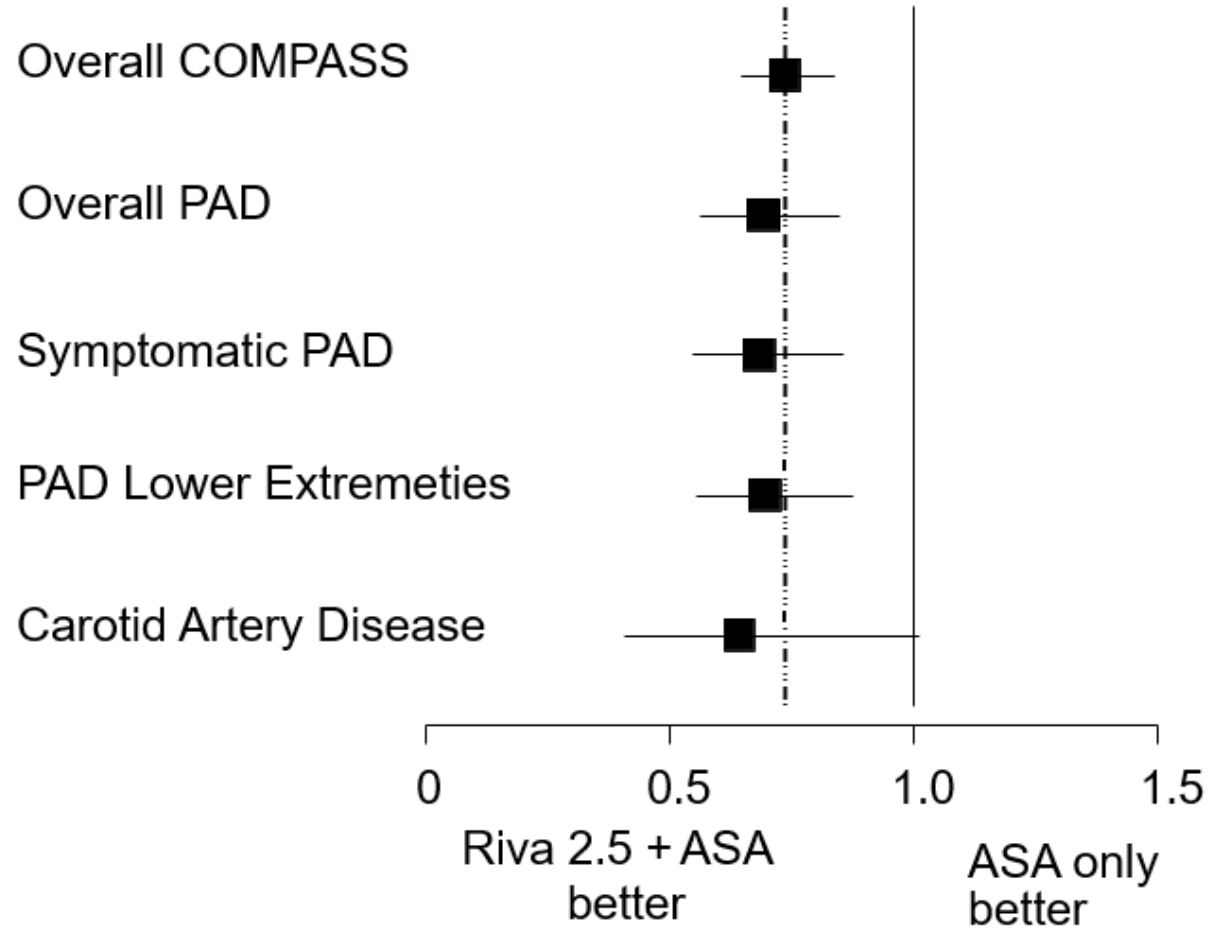


Figure 2. Subgroup Analyses for the Primary Outcome for the Comparison of Rivaroxaban plus Aspirin with Aspirin Alone.

The size of each box is proportional to the number of events. Arrows indicate that the limits of the confidence interval are not shown. The subgroup labeled "Western Europe" also includes participants in Israel, Australia, and South Africa. GFR denotes glomerular filtration rate.

NEJM, 2017

MACE, MALE or Major Amputation



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, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan [illegible], Ajay K Kakkar, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators

NET CLINICAL BENEFIT / IRREVERSIBLE HARM

	Low-dose rivaroxaban plus aspirin group (n=2492)	Aspirin alone group (n=2504)	HR (95% CI)	p value
Cardiovascular death, myocardial infarction, stroke or major adverse limb events, major amputation, or fatal or critical organ bleeding	169 (7%)	234 (9%)	0·72 (0·59–0·87)	0·0008

www.thelancet.com Published online November 10, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32409-1

26 July 2018
EMA/CHMP/515065/2018
Committee for Medicinal Products for Human Use (CHMP)

U.S. FDA approves Bayer's Xarelto® for patients with coronary or peripheral artery disease

15 Oct 2018 | Source: Bayer AG

Xarelto, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease or peripheral artery disease / Xarelto, in combination with aspirin, is the only non-vitamin K antagonist oral anticoagulant (NOAC) indicated for this patient group / Approval in the U.S. follows regulatory clearance in both Europe and Canada

The U.S. Food and Drug Administration (FDA) has approved rivaroxaban (Xarelto®), 2.5 mg twice daily, plus aspirin low dose once daily to reduce the risk of major cardiovascular events including cardiovascular (CV) death, heart attack or stroke in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

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ANTITHROMBOTIC THERAPY	
25 RECOMMENDATIONS	
Class I	9
Class IIa	8
Class IIb	7
Class III	1

DUAL ANTITHROMBOTIC THERAPY
CCS GL ESC 2019

HIGH ISCHAEMIC RISK	IIa A (SHOULD BE)	NO
MODERATE ISCHAEMIC RISK	IIb A (MAY BE)	NO
	NON HIGH BLEEDING RISK	HIGH BLEEDING RISK

Chapter 5 is an excerpt from the Guideline on peripheral arterial disease.
The correct citation is: European Society for Vascular Medicine (ESVM). Guideline on peripheral arterial disease. Vasa. 2019;48, Supplement 102, doi 10.1024/0301-1526/a000834.

5 Conservative treatment for PAD – Risk factor management

Ulrich Frank[a] (Switzerland), Sigrid Nikol[a] (Germany), and Jill Belch[a] (UK) for the European Society of Vascular Medicine

PAD Guideline Writing Group

[a]all co-first authors

Recommendation	Class of recommendation	Level of evidence
Based on the results of the COMPASS trial, the combined therapy of ASA 100 mg/d and rivaroxaban 2 × 2.5 mg/d should be considered in PAD patients without a high risk of bleeding, or other contraindications.	IIa	B

Vasa (2019), *48* (Supplement 102/excerpt), 1–12