Queen Mary Hospital

Hong Kong College of Cardiology ASM 2020

Emerging role of NOAC in the treatment of CAD & PAD

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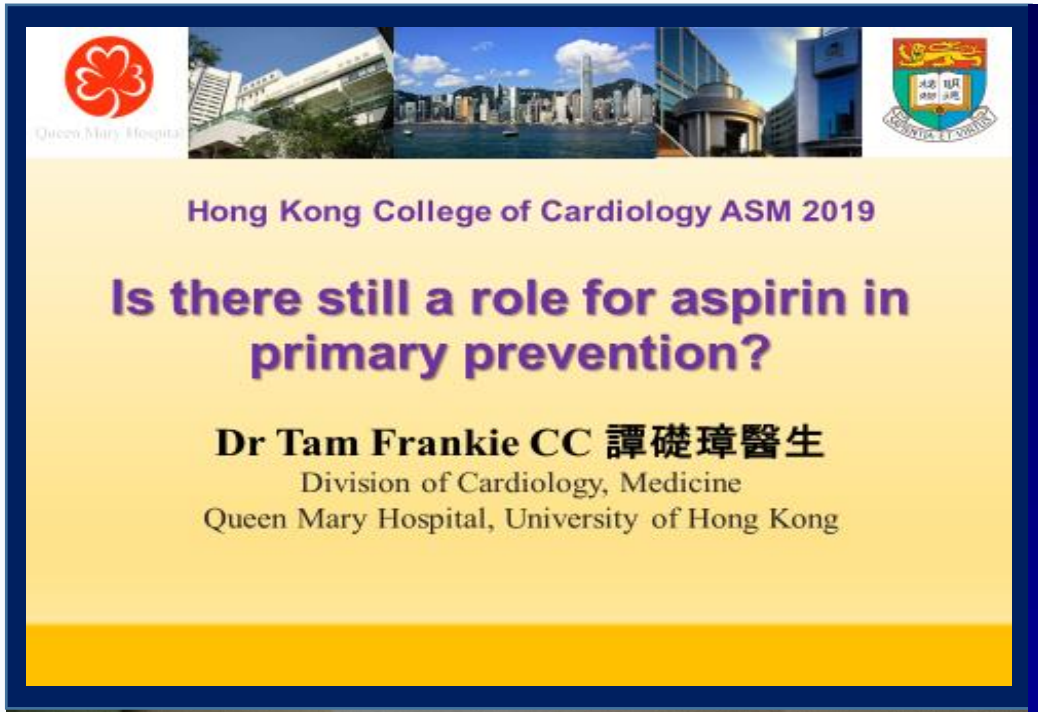
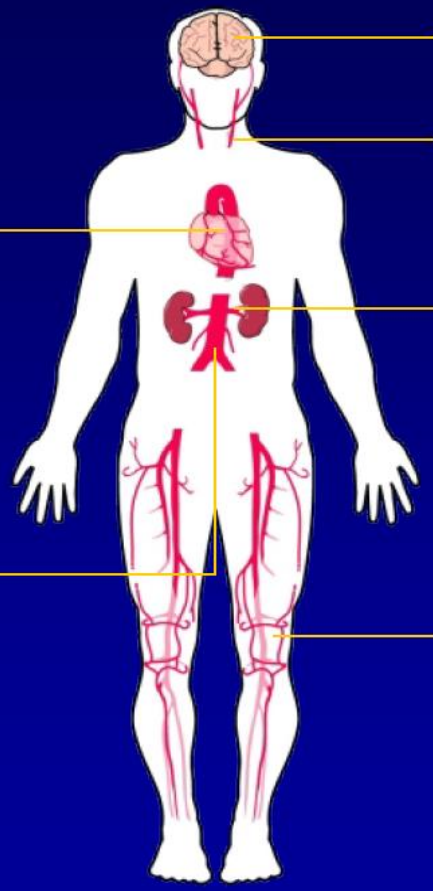


Acute coronary syndromes
- STEMI
- NSTEMI
- Unstable angina

Stable CAD
Atrial Fibrillation
Angioplasty
Bare metal stent
Drug eluting stent
CABG

Abdominal aortic aneurysm (AAA)



Stroke
TIA
Intracranial stenosis

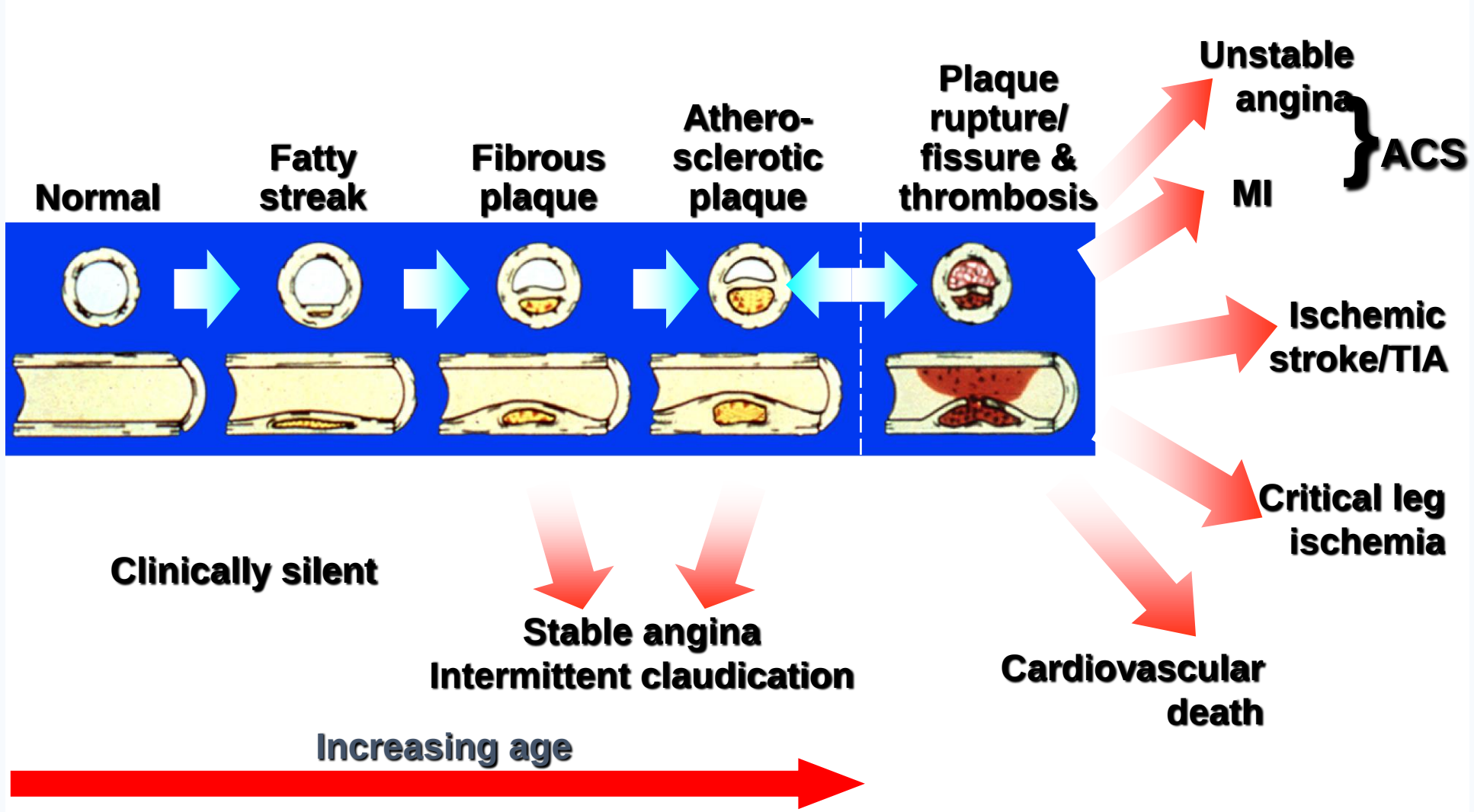
Carotid artery stenosis
CEA
Carotid stenting

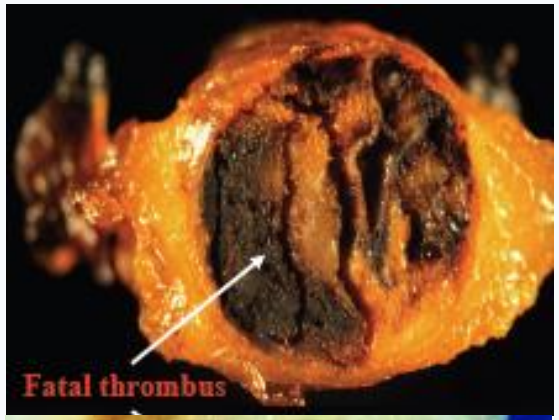
Renal artery stenosis
Renal artery stenting

Peripheral arterial disease
Acute limb ischemia
Claudication
Amputation
Endovascular stenting
Peripheral bypass
Abnormal ABI

Aspirin inhibits platelets, reduces chance of thrombosis

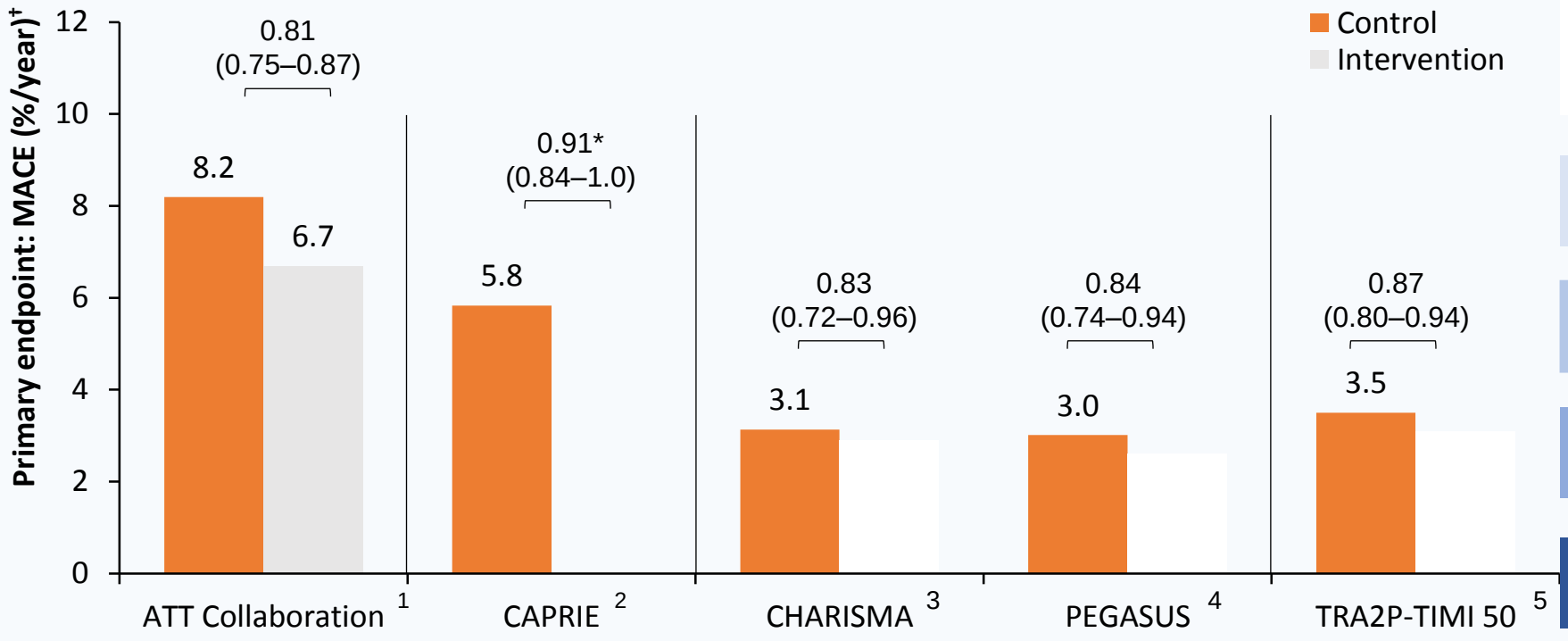
Aspirin as the main player in Atherothrombosis for more than 50 years





Is Aspirin good enough?

Chronic Coronary Syndrome CCS



	ATT Collaboration 1	CAPRIE 2	CHARISMA 3	PEGASUS 4	TRA2P-TIMI 50 5
% Use of key therapies in intervention arm	Control ‖ Aspirin	Aspirin ‖ Clopidogrel	Placebo + Aspirin ‖ Clopidogrel + Aspirin	Placebo + Aspirin ‖ Ticagrelor + Aspirin	Vorapaxar + Aspirin ‖ Placebo + Aspirin ± Thienopyridine
ACEI/ARB	*Meta-analysis of 16 trials*	*NR*	*up to 85.3*	*80.4*	*73.5*
Statin/ lipid-lowering		*NR*	*77.1–89.3*	*92.4*	*91.0*

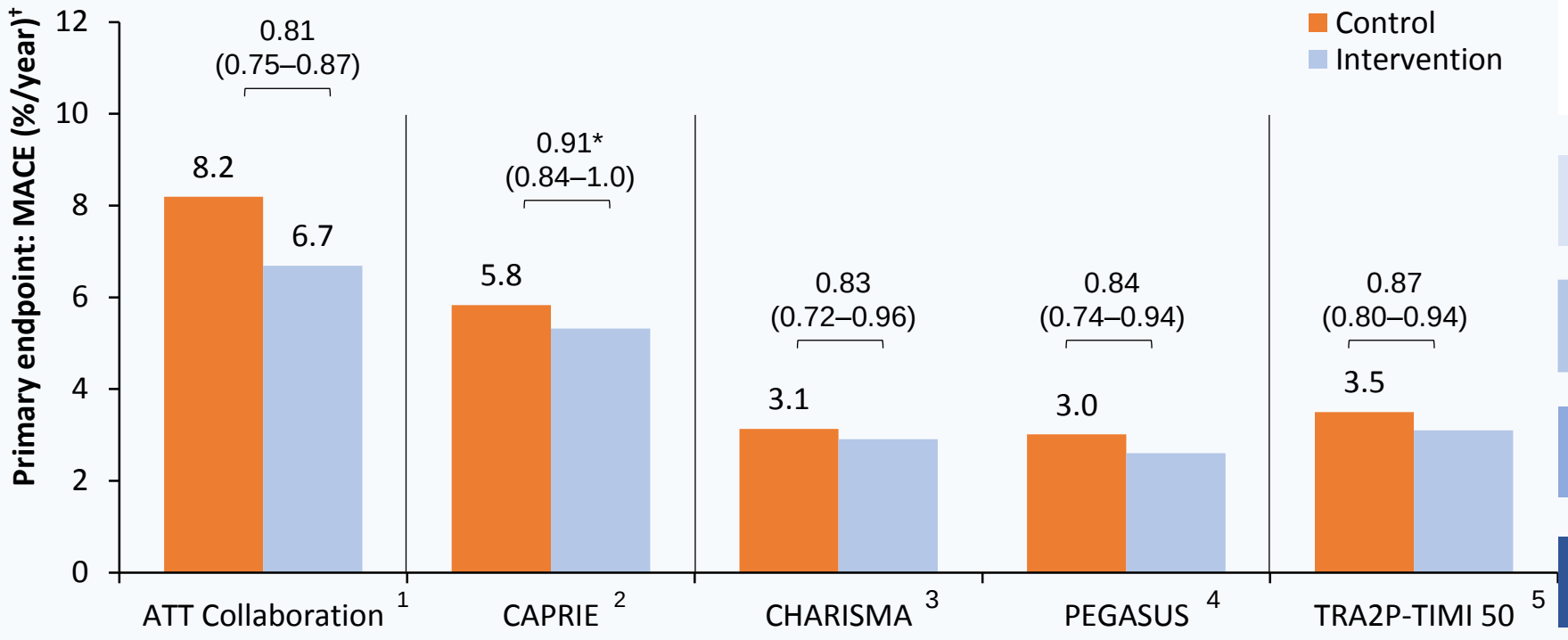
*Estimate calculated from reported relative risk reductions; †Estimate calculated from reported overall % across 28 months of median follow up for CHARISMA; and from reported 3-year Kaplan-Meier event rates for PEGASUS & TRA2P-TIMI50

Searching for more potent anti-platelet agents

- Aspirin
- Clopidogrel instead of Aspirin
- Clopidogrel + Aspirin
- Ticagrelor + Aspirin
- Vorapaxar + Aspirin

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

Chronic Coronary Syndrome CCS



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ACEI/ARB					
Statin/ lipid-lowering					

*Estimate calculated
CHARISMA; and fro

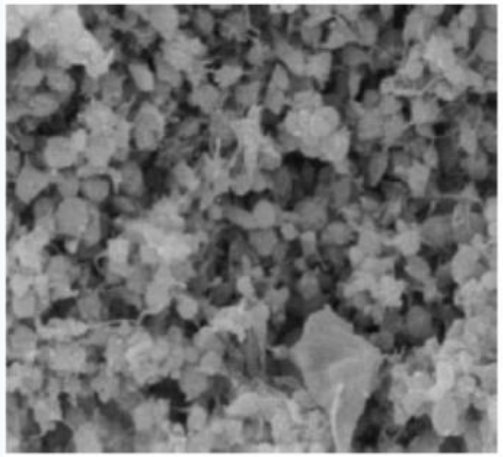
Searching for more potent anti-platelet agents

- Aspirin
- Clopidogrel instead of Aspirin
- Clopidogrel + Aspirin
- Ticagrelor + Aspirin
- Vorapaxar + Aspirin

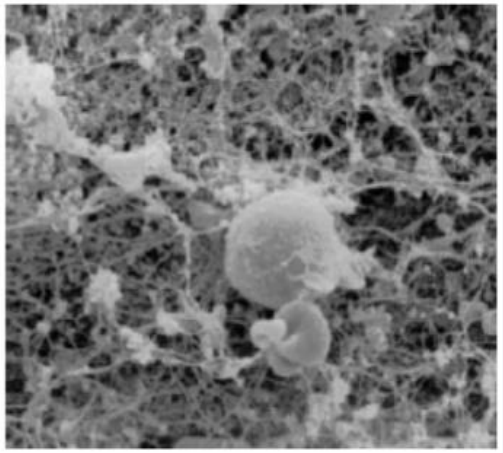
Addition of anti-platelet agent seems can reduce ischemic risks, at the expense of increase in bleeding

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

Pathogenesis of Atherothrombosis

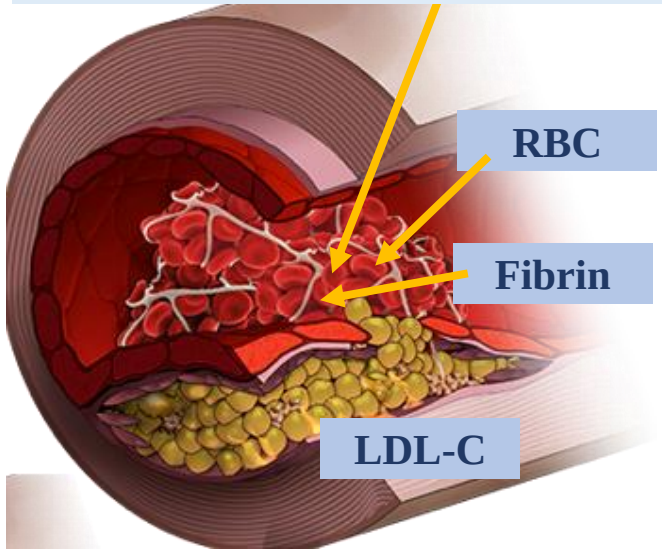


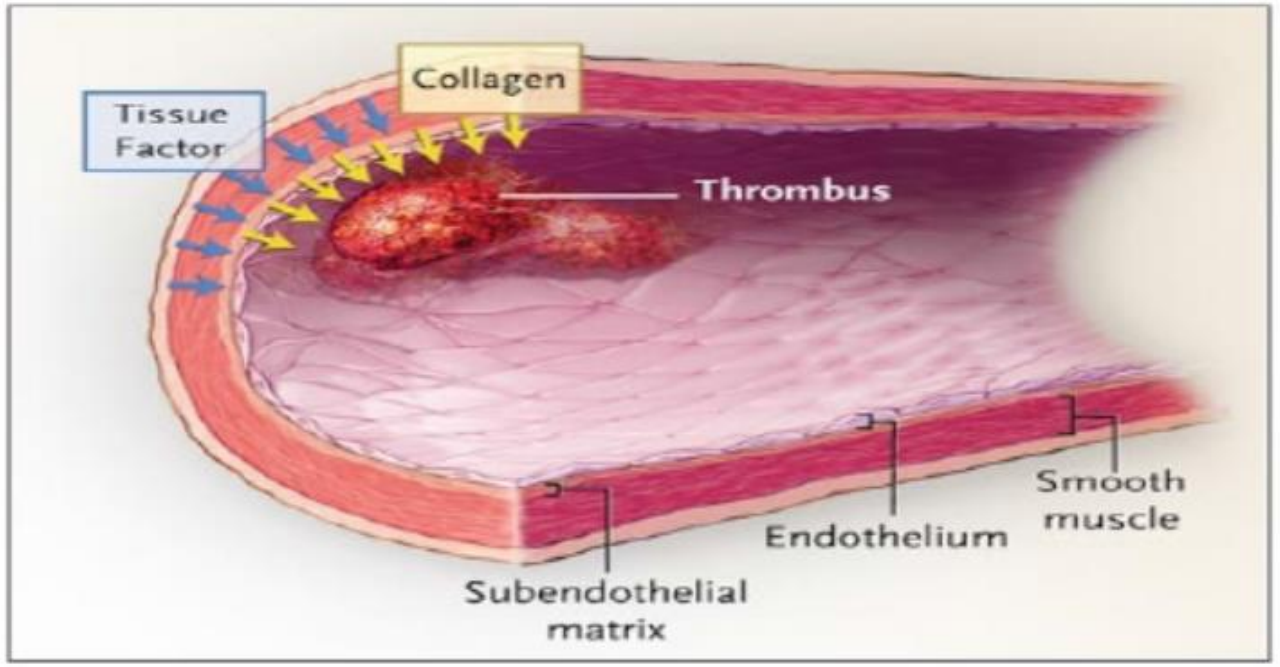
White thrombus
Platelet + fibrinogen



Red thrombus
Red cells + fibrin

All thrombi contain fibrin OR fibrinogen

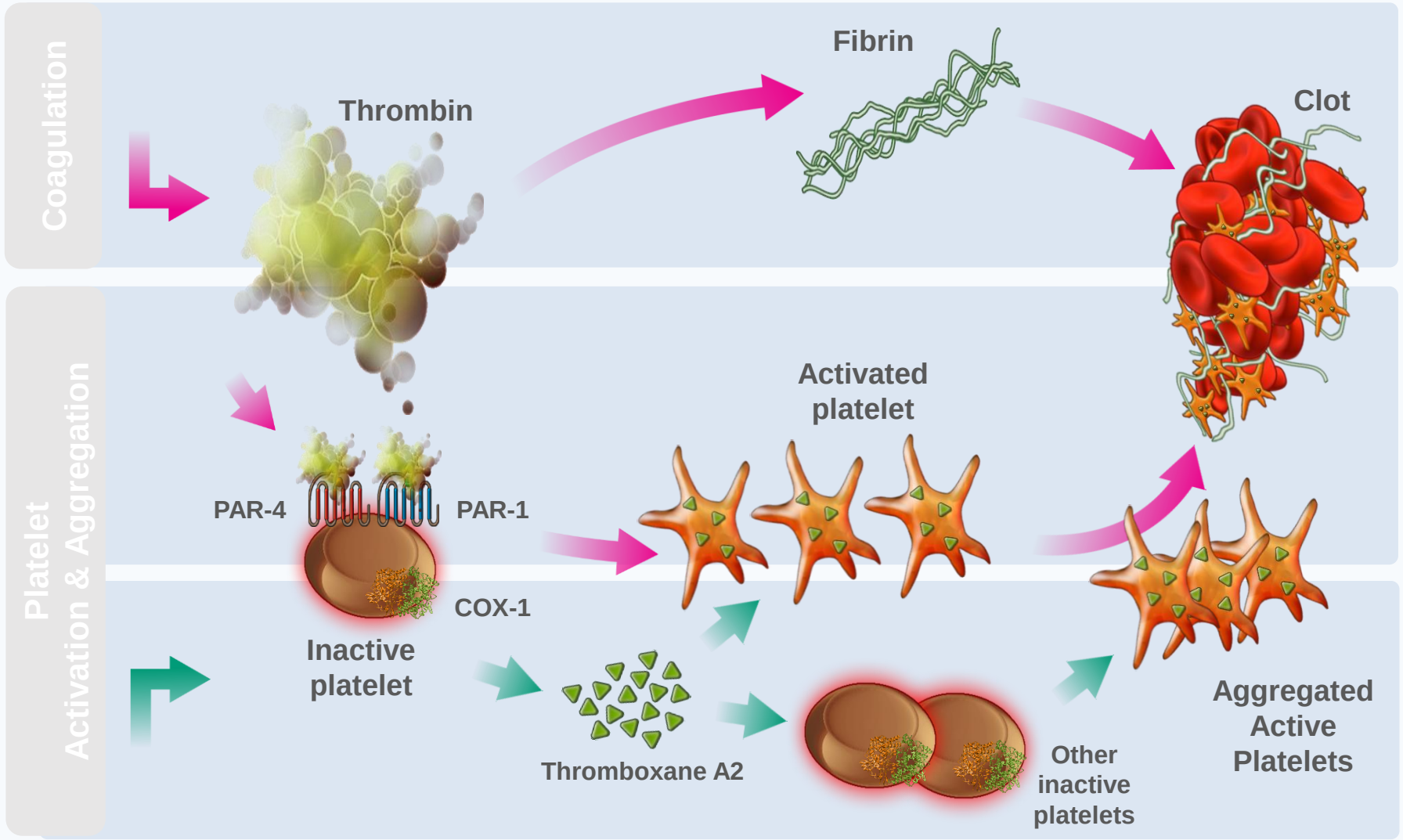


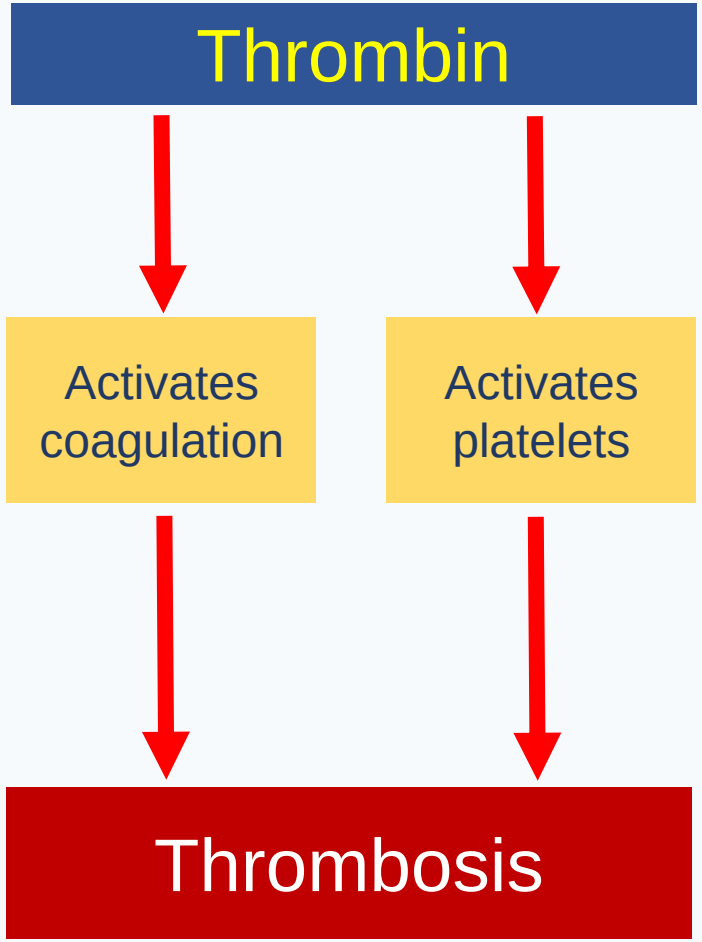


Fissured-plaque thrombosis more likely initiated by Tissue factor-coagulation pathway
(Plaque Erosion)

1. Weisel et al. JBC 1992. 2. Beygui et al. Circulation 2006. 3. Furie NEJM 2008

THROMBIN is a potent platelet agonist





Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28

Anticoagulation for atherothrombosis

Did we use it? Should we use it?

- We give Enoxaparin or heparin for ACS
- Before P2Y12 inhibitors, we used warfarin for post PCI/stenting patients
- We used warfarin for post MI patients many years ago
- Warfarin has some efficacy as primary prevention

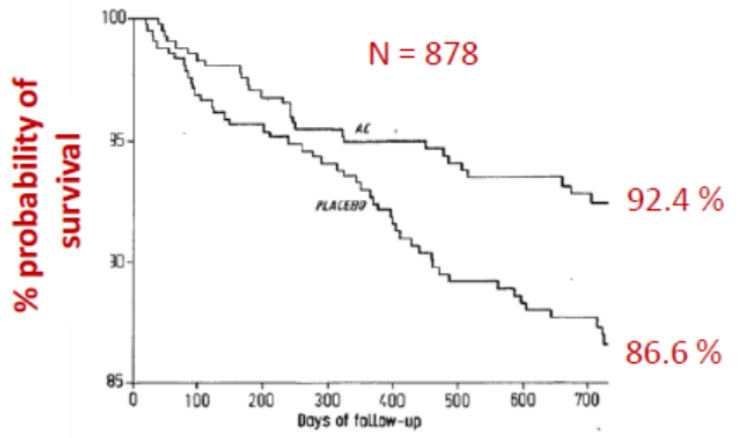
Medical Research Council. Low dose warfarin vs low dose aspirin in I prevention of IHD in 5000 high risk men followed for 7 yrs. Lancet 1998; 351: 233-41

	WA	W	A	P
MI (%)	8.7	10.3	10.2	13.3
Stroke (%)	3.6	2.7	2.2	3.2
Death (%)	12.4	11.4	13.6	13.1
Maj Blee (N)	12	9	8	4

Anticoagulation in NSTE-ACS

Recommendations	Class	Level
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B
In patients on fondaparinux (2.5 mg s.c. daily.) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

post-MI in 60+ trial



Lancet 1980;ii:98923:26-30

NOAC as game changer for NVAF

Stable pharmacokinetics
Less interaction with drugs/food

No need routine monitoring
Lower risk of major bleeding

NOACs are associated with improved outcomes for patients with NVAF compared with warfarin

	Dabigatran[1,2] (RE-LY) 150 mg BID	Dabigatran[1,2] (RE-LY) 110 mg BID	Apixaban[3] (ARISTOTLE) 5/2.5 mg BID	Rivaroxaban[4] (ROCKET AF) 20/15 mg OD	Edoxaban[5] (ENGAGE AF-TIMI 48) 60/30 mg OD
Major bleeding	Similar	↓ 20%	↓ 31%	Similar	↓ 20%
ICH	↓ 59%	↓ 70%	↓ 58%	↓ 33%	↓ 53%
Stroke/SE	↓ 35%	Similar	↓ 21%	Similar	Similar
Ischaemic stroke	↓ 24%	Similar	Similar	Similar	Similar
CV mortality	↓ 15%	Similar	Similar	Similar	↓ 14%
Mortality	Similar	Similar	↓ 11%	Similar	Similar

Not for direct comparison between studies

Relative risk reductions vs warfarin. ICH, intracranial haemorrhage; SE, systemic embolism. 1. Connolly et al. N Engl J Med 2014; 2. Connolly et al. N Engl J Med 2010; 3. Granger et al. N Engl J Med 2011; 4. Patel et al. N Engl J Med 2011; 5. Giugliano et al. N Engl J Med 2013

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

ABSTRACT

BACKGROUND

Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

RESULTS

Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.05). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).

CONCLUSIONS

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mega at the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at jmega@partners.org.

*Investigators in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1112277) was published on November 13, 2011, at NEJM.org.

N Engl J Med 2012;366:9-19.

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ACS

ATLAS ACS 2 TIMI 51

Recent ACS: STEMI, NSTEMI, UA

Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo	Rivaroxaban	Rivaroxaban
n=5,176	2.5 mg BID n=5,174	5.0 mg BID n=5,176

PRIMARY ENDPOINTS:

EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

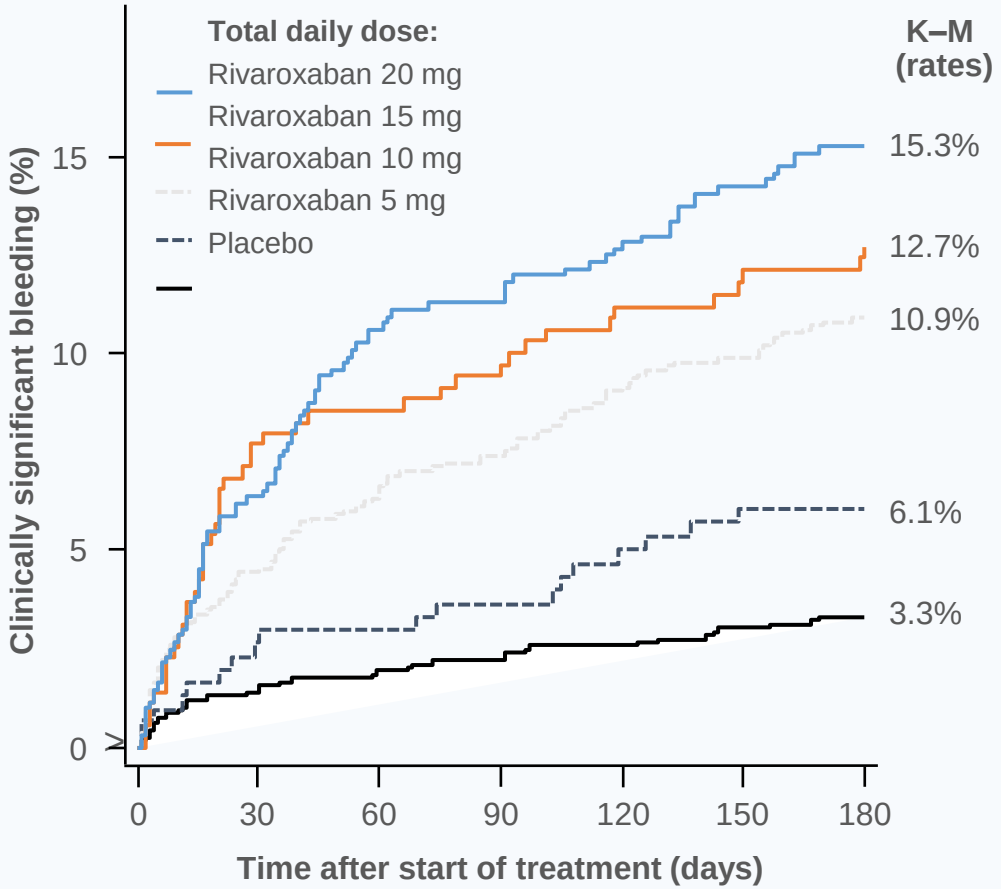
SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

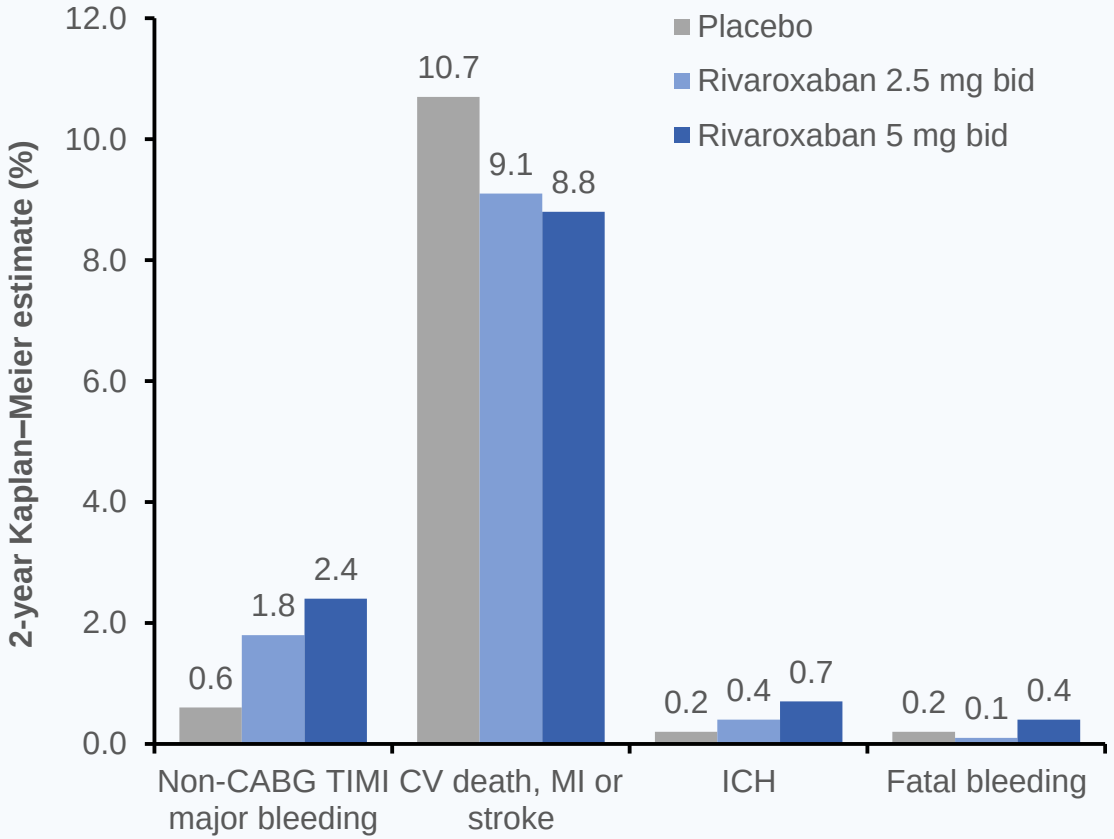
Mega et al, N Engl J Med 2012; 366:9-19

Rivaroxaban 2.5 mg BID Resulted in Best Balance of Safety and Efficacy when added to Aspirin or DAPT in ACS Patients

ATLAS ACS TIMI 46: safest dose of rivaroxaban with Aspirin or DAPT was 5 mg daily[1]



ATLAS ACS 2 TIMI 51: best balance of safety and efficacy for rivaroxaban 2.5 mg bid[2]



- Twice-daily dosing is required for daily doses below 10 mg to ensure 24-h coverage[3]

1. Mega JL *et al*, *Lancet* 2009;374:29–38; 2. Mega JL *et al*, *N Engl J Med* 2012;366:9–19;
3. Kubitza D *et al*, *Clin Appl Thromb Hemost* 2016;22:412–422

COMPASS

The NEW ENGLAND JOURNAL of MEDICINE

CCS

Stable phase of CAD

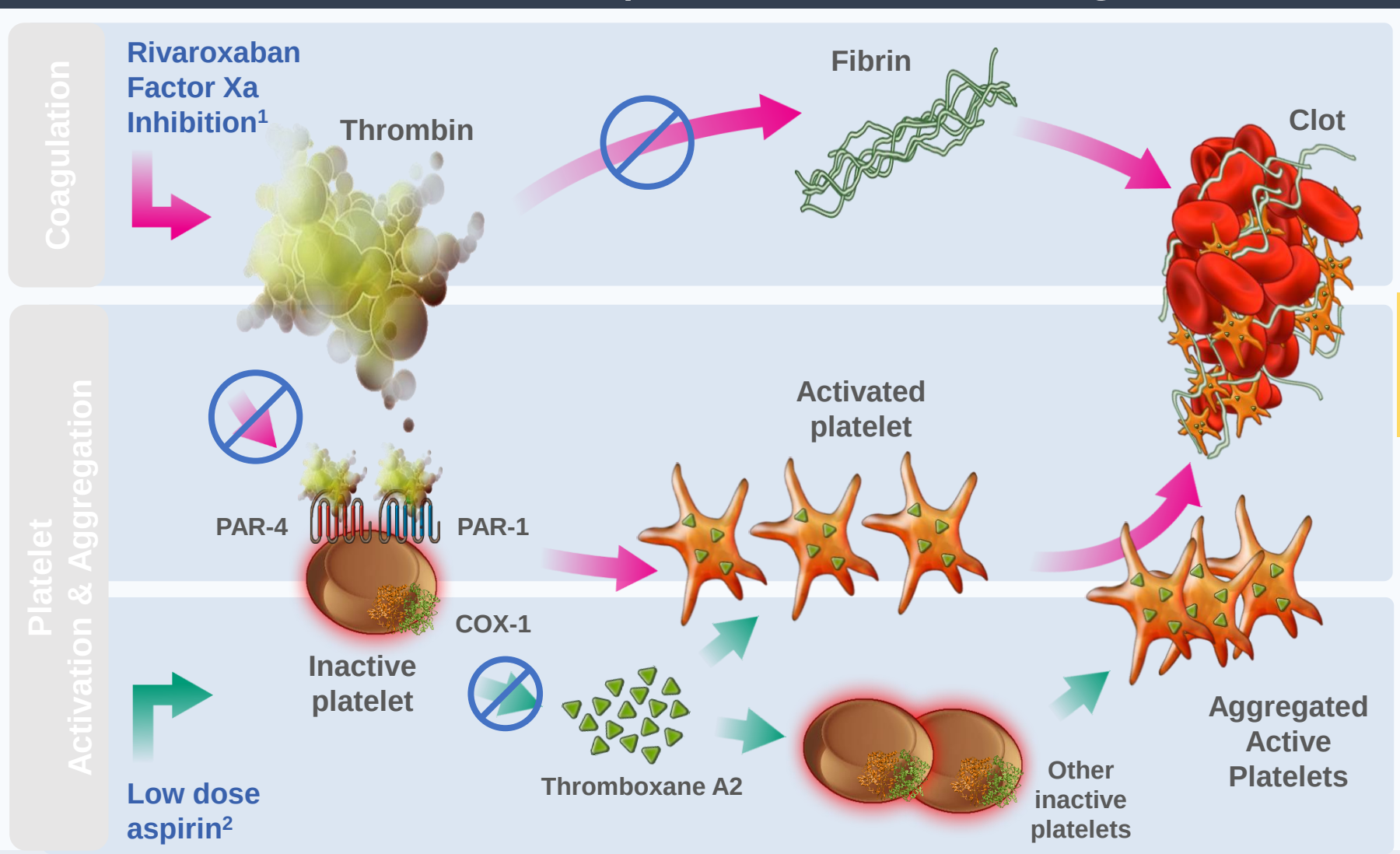
ORIGINAL ARTICLE

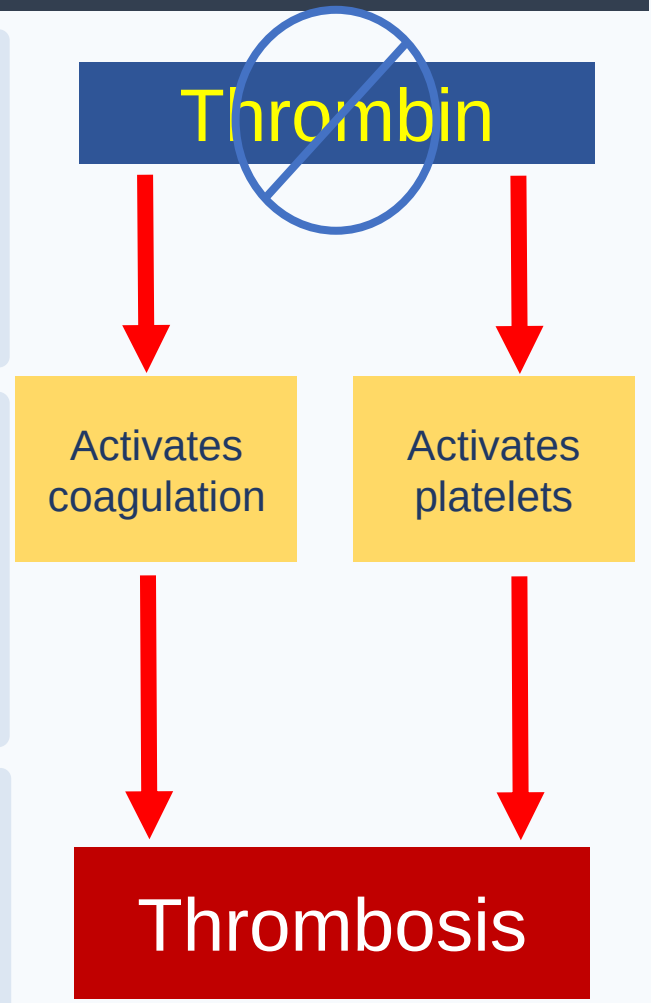
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

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. 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*

Dual Pathway Approach

Anti-platelet + Anti-coagulation





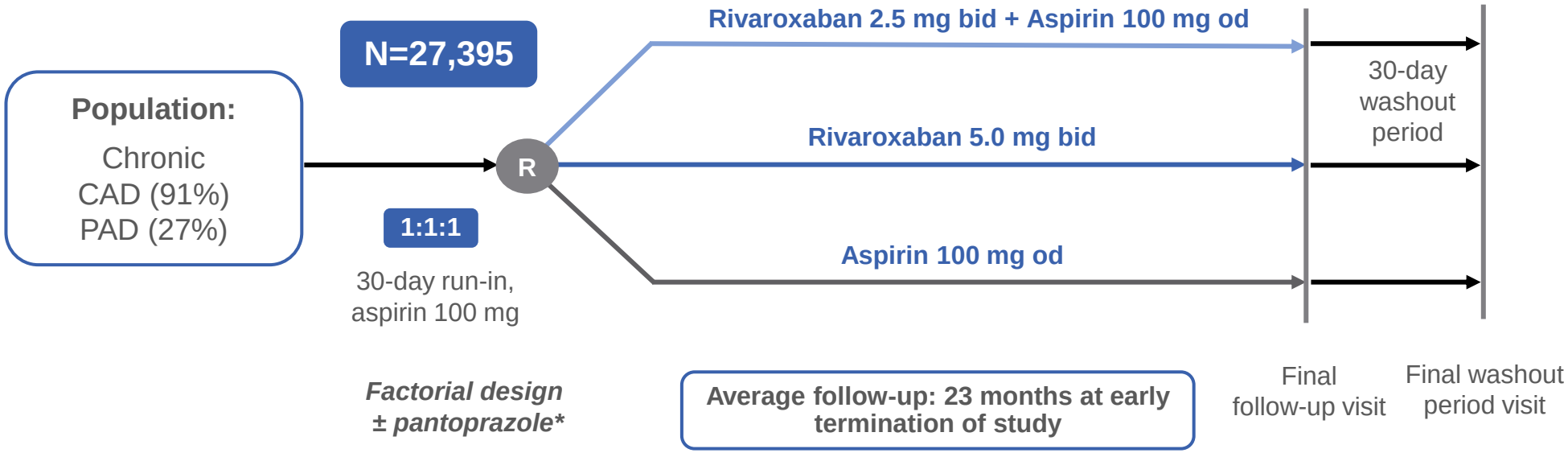
Rivaroxaban impacts not only fibrin formation, but also platelet activation

Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28

CAD PAD

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

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 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; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

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Inclusion and Exclusion Criteria Ensure That Patients Are Chronic CAD and PAD Patients

Key inclusion criteria*

- PAD
- CAD with ≥1 of:
  - Age ≥65 years
  - Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR<60 ml/min)
    - Heart failure
    - Non-lacunar ischemic stroke ≥1 month ago

Key exclusion criteria‡

- Stroke ≤1 month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
- **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy**
- eGFR <15 ml/min

[#]Including but not limited to; [‡]any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

www.clinicaltrials.gov/ct2/show/NCT01776424 [accessed 21 Mar 2017];
Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

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COMPASS: Study Population

Definition of CAD

- Previous MI

  OR
- Stable angina or unstable angina with documented multi-vessel CAD, >50% stenosis in at least 2 major coronary arteries on coronary angiography, or positive stress test (electrocardiogram) or nuclear perfusion scintigram

  OR
- Multi-vessel percutaneous coronary intervention

  OR
- Multi-vessel coronary artery bypass grafting surgery within 1 week or at least 4 years ago or with recurrent angina or ischaemia at any time following surgery

Definition of PAD

- Previous aorto-femoral bypass surgery, limb bypass surgery or percutaneous transluminal angioplasty of the iliac or infrainguinal arteries

  OR
- Previous limb or foot amputation for arterial vascular disease*

  OR
- History of intermittent claudication and either an ankle/arm blood pressure ratio ≤0.90 or significant peripheral artery stenosis (>50%) documented by angiography or non-invasive testing by duplex ultrasound

  OR
- Asymptomatic carotid artery stenosis[#] >50% as diagnosed by duplex ultrasound or angiography

*i.e. excludes trauma; [#]i.e. no ipsilateral stroke or transient ischaemic attack within 6 months

Clinical study protocol BAY 59-7939/15786

Main Study Outcomes

Primary efficacy outcome

- Composite of MI, stroke or CV death

Secondary efficacy outcomes

- Composite of major thrombotic events
  - Coronary heart disease death, MI, ischaemic stroke, acute limb ischaemia
  - Cardiovascular death, MI, ischaemic stroke, acute limb ischaemia
- Mortality (all cause)

Primary safety outcome

- Modified ISTH major bleeding
  - Fatal bleeding, *and/or*
  - Symptomatic bleeding in a critical area or organ, such as intracranial, *or*
  - Bleeding into the surgical site requiring re-operation, *and/or*
  - Bleeding leading to hospitalization

A stricter bleeding definition

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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Key Baseline Characteristics Are in Line With Those Usually Seen in Patients With Chronic CAD or PAD

Characteristic	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Rivaroxaban 5 mg bid N=9117	Aspirin 100 mg N=9126
Age, years	68	68	68
Blood pressure, mmHg	136/77	136/78	136/78
Total cholesterol, mmol/L	4.2	4.2	4.2
CAD, %	91	90	90
PAD, %	27	27	27
Diabetes, %	38	38	38
Lipid-lowering drugs, %	90	90	89
ACE inhibitors/ARB, %	71	72	71

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

*Excluding <7 days before randomization

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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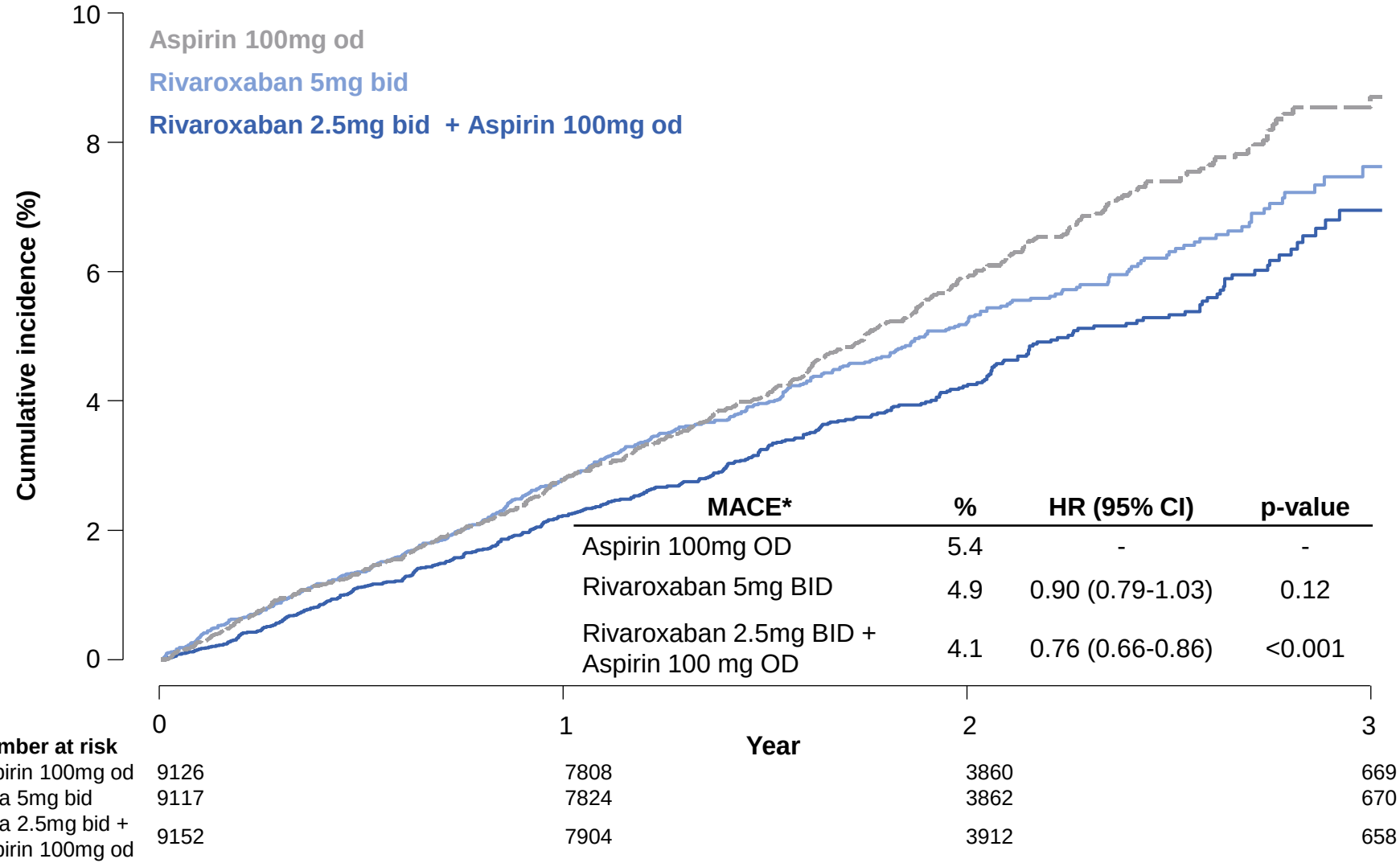
Patients in COMPASS Were Receiving High Standard of Care

Baseline medication	Total N=27,395 n (%)
ACE inhibitor/angiotensin receptor blocker	19,518 (71.2)
Calcium channel blocker	7269 (26.5)
Diuretic	8139 (29.7)
Beta-blocker	19,184 (70.0)
Lipid-lowering agent	24,601 (89.8)
NSAID	1470 (5.4)
Non-study PPI	9798 (35.8)

Modern medical care

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

CAD PAD

Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin: Significantly Reduced CV Events

Outcomes, n (%)	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
CV death, stroke, or MI	379 (4.1)	496 (5.4)	0.76 (0.66–0.86)	<0.001
CV death	160 (1.7)	203 (2.2)	0.78 (0.64–0.96)	0.02
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44–0.76)	<0.001
MI	178 (1.9)	205 (2.2)	0.86 (0.70–1.05)	0.14

Reduction of hard CV endpoints (Ischemic)

Outcomes, n (%)	Rivaroxaban 5 mg bid N=9117	Rivaroxaban 5 mg bid vs aspirin 100 mg	
		HR (95% CI)	*p*-value
CV death, stroke, or MI	448 (4.9)	0.90 (0.79–1.03)	0.12
CV death	195 (2.1)	0.96 (0.79–1.17)	0.69
Stroke	117 (1.3)	0.82 (0.65–1.05)	0.12
MI	182 (2.0)	0.89 (0.73–1.08)	0.24

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Bleeding Rates

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Rivaroxaban 5 mg bid N=9117	Aspirin 100 mg N=9126
Modified major ISTH bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)
Non-fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg		Rivaroxaban 5 mg bid vs aspirin 100 mg	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Modified ISTH major bleeding	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Non-fatal ICH*	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Non-fatal other critical organ*	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

The use of the standard ISTH major bleeding definition would have led to approximately one third fewer major bleeding events than with the use of the modified ISTH definition

Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. For each outcome, the first event experienced per patient is considered. Subsequent events of the same type are not shown. Therefore subcategories do not necessarily sum up to overall category. *Symptomatic

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Net Clinical Benefit: 20% RRR with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin

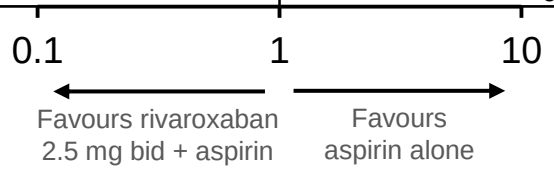
- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
  - **In other words, net clinical benefit represented the composite of fatal and non-fatal events of irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Subgroup analysis

Subgroup	Rivaroxaban 2.5 mg bid + aspirin n/N (%)	Aspirin alone n/N (%)	HR (95% CI)	*p*-value
All participants	379/9152 (4.1)	496/9126 (5.4)	0.76 (0.66–0.86)	
Age				0.20
<65 years	79/2150 (3.7)	126/2184 (5.8)	0.63 (0.48–0.84)	
65–75 years	179/5078 (3.5)	238/5045 (4.7)	0.74 (0.61–0.90)	
≥75 years	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)	
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)	
CAD				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)	
PAD				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)	

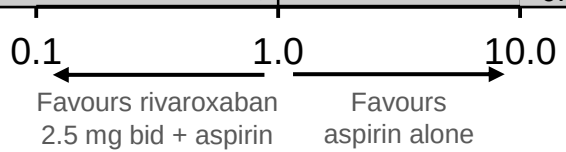


Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Demonstrated a Clear Benefit Across All Subgroups

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Subgroup analysis

Subgroup	Rivaroxaban 2.5 mg bid + aspirin n/N (%)	Aspirin alone n/N (%)	HR (95% CI)	*p*-value
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 or ethnic group				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)	
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)	
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)	
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)	
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)	



Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Demonstrated a Clear Benefit Across All Subgroups

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Consistent Benefit Of Rivaroxaban 2.5 mg bid + Aspirin Supported by Secondary Outcomes, Including All-Cause Mortality

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
CHD death, ischaemic stroke, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63–0.83)	<0.001
CV death, ischaemic stroke, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65–0.85)	<0.001
Mortality (all-cause)	313 (3.4%)	378 (4.1%)	0.82 (0.71–0.96)	0.01

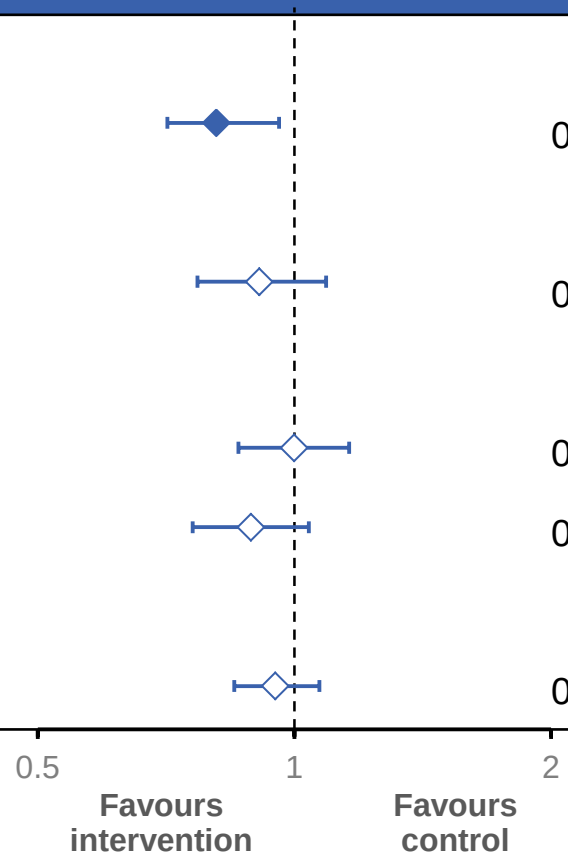
The first anti-thrombotic to show all-cause mortality benefit in chronic coronary syndrome

CHD coronary heart disease death: death due to acute MI, sudden death, or CV procedure

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Rivaroxaban 2.5 mg bid + Aspirin Improved Overall Survival in Patients with CAD or PAD

Study / Treatment arm	Control %/year	Intervention %/year	HR	HR (95% CI)	*p*-value
COMPASS[1]					
Rivaroxaban 2.5 mg bid	2.1†	1.8†	0.82		0.01
CHARISMA[2]					
Clopidogrel 75 mg od	2.3‡	2.1‡	0.91		0.32
PEGASUS[3]					
Ticagrelor 90 mg bid	1.7¶	1.7¶	1.00		0.99
Ticagrelor 60 mg bid	1.7¶	1.6¶	0.89		0.14
TRA2P-TIMI 50[4]					
Vorapaxar 2.5 mg od	1.8¶	1.7¶	0.95		0.41



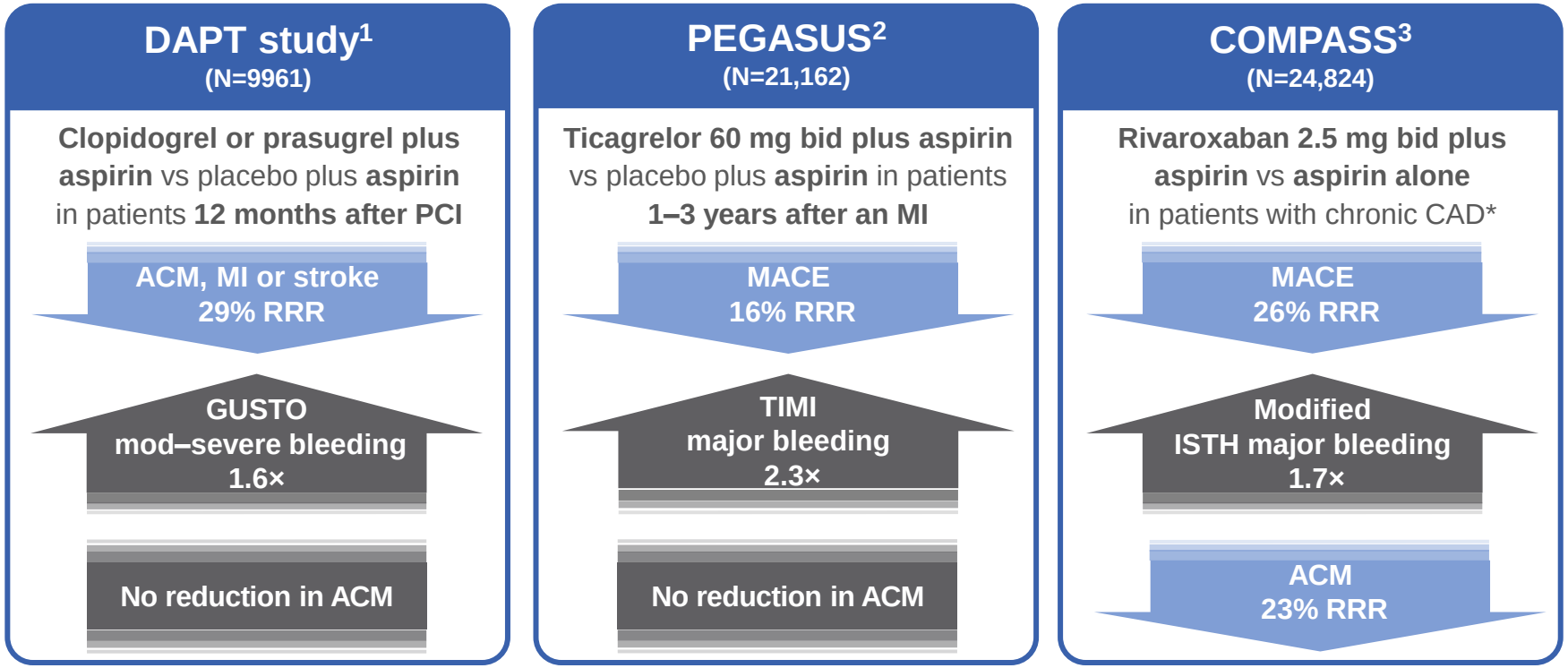
The first anti-thrombotic to show all cause mortality benefit in CCS patients

†Estimate calculated from reported overall % across 23 months of mean follow up; *p-value nominally significant because the study was stopped approximately 1 year ahead of schedule due to overwhelming efficacy; threshold for formal significance p=0.0025* ‡Estimate calculated from reported overall % across 28 months of median follow up; ¶Estimate calculated from reported 3-year Kaplan-Meier event rates

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118; 2. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988;
3. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 4. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

COMPASS Demonstrated a Favourable Benefit–Risk Ratio Compared with Other Antithrombotic Strategies After MI/PCI

CAD, Chronic Coronary Syndrome

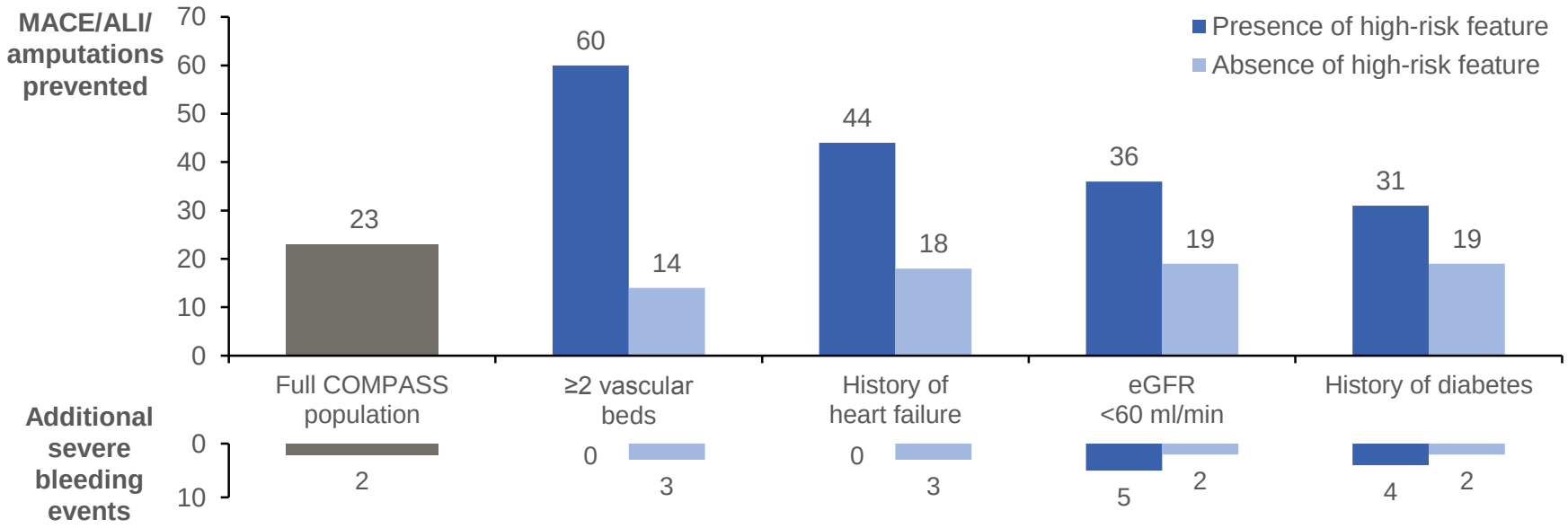


*Defined as MI ≤20 years, multivessel CAD with symptoms or history of angina, previous multivessel PCI or previous multivessel CABG
Follow-up periods were as follows: DAPT study, 18 months by design; PEGASUS, median 33 months, COMPASS, mean 1.95 years

1. Mauri L *et al*, *N Engl J Med* 2014;371:2155–2166; 2. Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800; 3. Connolly SJ *et al*, *Lancet* 2018;391:205–218

Absolute Benefit of Rivaroxaban Vascular Dose 2.5 mg bid plus Aspirin Is Highest in High-Risk Patient Groups

Ischaemic events prevented and bleeding events caused per 1000 patients over 30 months with addition of rivaroxaban 2.5 mg bid to aspirin in high-risk groups*



*Identified through two independent methods (a modified REACH score and a CART analysis)

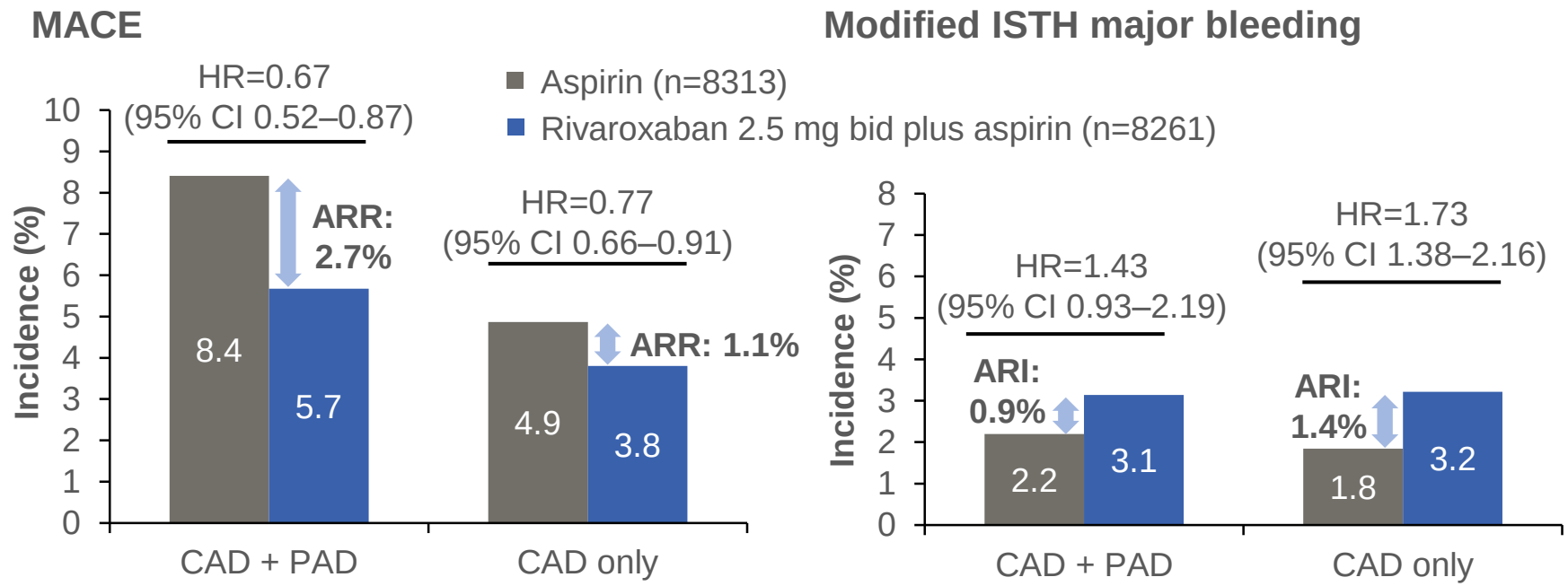
Anand SS *et al*, *J Am Coll Cardiol* 2019;73:3271–3280

COMPASS

Polyvascular disease, Heart Failure, DM, CKD

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with Polyvascular Disease

Incidence of the primary efficacy and safety outcomes in patients with CAD plus PAD and in patients with CAD only in COMPASS



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

Polyvascular disease: CAD, PAD, Cerebrovascular (prior stroke or asymptomatic carotid artery stenosis >= 50%/revascularization)

Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Significantly Reduced MACE by 28% and MALE by 46% Versus Aspirin

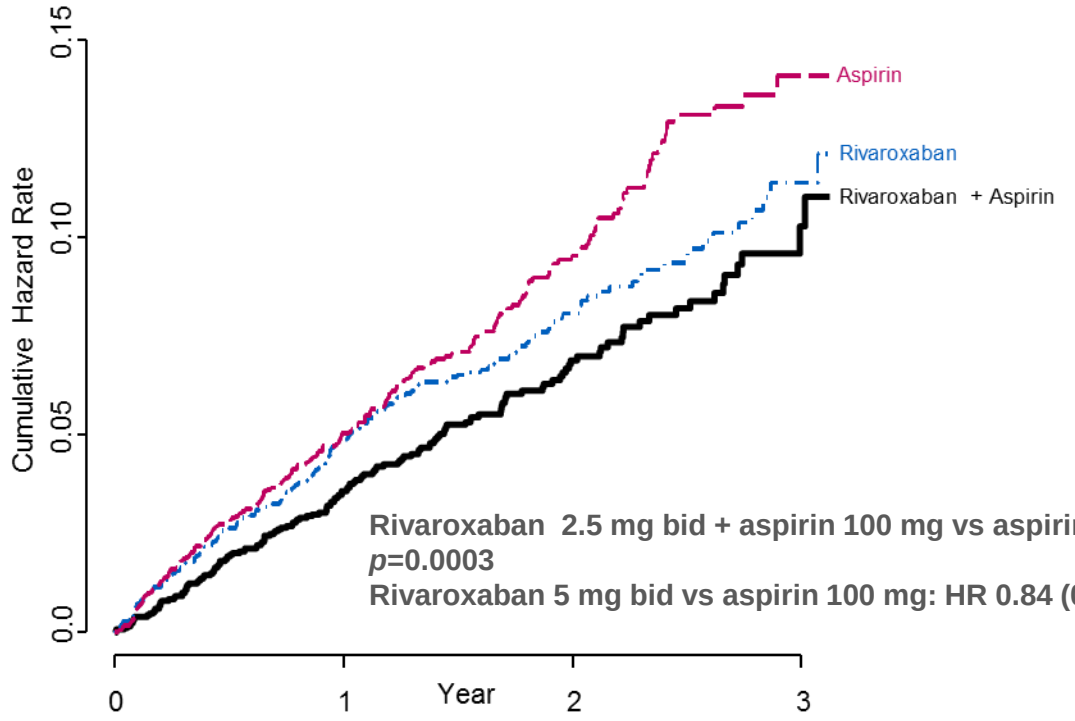
Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2,504	Rivaroxaban 2.5 mg bid + aspirin vs. aspirin		Rivaroxaban 5 mg bid vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57–0.90)	0.005	0.86 (0.69–1.08)	0.19
CV death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59–1.14)	-	0.86 (0.62–1.19)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33–0.87)	-	0.93 (0.61–1.40)	-
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53–1.09)	-	0.84 (0.59–1.20)	-
MALE	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35–0.84)	0.005	0.63 (0.41–0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11–0.80)	0.01	0.46 (0.20–1.08)	0.07

Rivaroxaban 2.5 mg bid + aspirin significantly reduced major amputation by 70% versus aspirin

Anand SS *et al.* ESC 2017, Abs 1157; Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1220&sessId=22247&subSessId=0;

COMPASS

31% RRR in MACE or MALE Including Major Amputation with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin in Patients with PAD



Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg: HR 0.69 (0.56–0.85), *p*=0.0003

Rivaroxaban 5 mg bid vs aspirin 100 mg: HR 0.84 (0.69–1.02), *p*=0.08

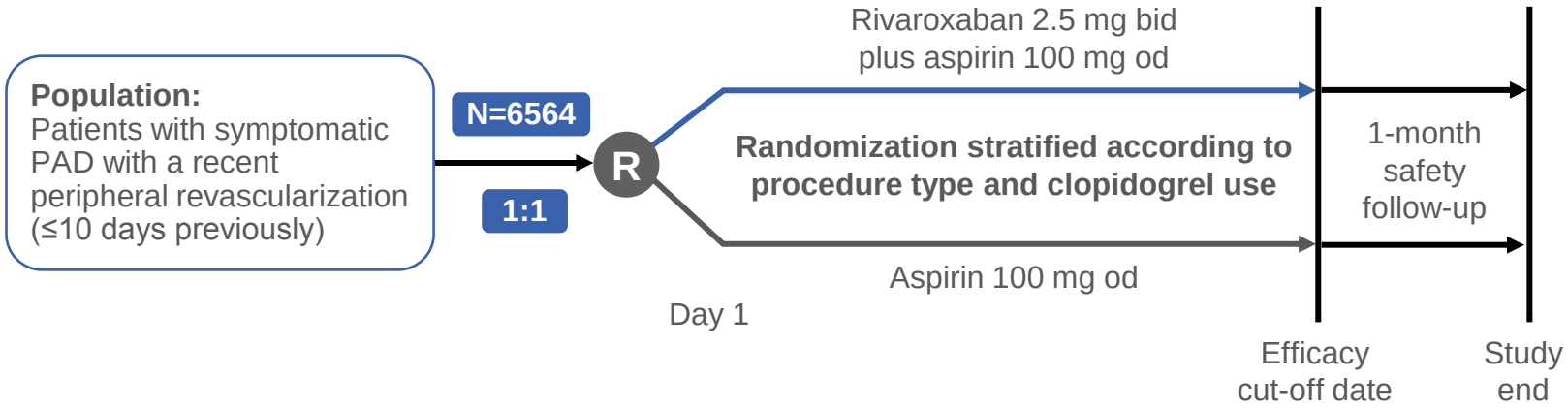
Number at risk				
Rivaroxaban + aspirin	2492	2069	893	124
Rivaroxaban	2474	2023	864	147
Aspirin	2504	2034	911	113

Anand SS *et al.* ESC 2017, Abs 1157; Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1220&sessId=22247&subSessId=0;

COMPASS

VOYAGER PAD: Study Design

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



Short design: Randomized, double-blind, phase III, controlled trial

Indication: Symptomatic PAD

Completion date: December 2019

Mean treatment duration per patient: ~30 months.

Capell WH *et al*. *Am Heart J* 2018;199:83–91. Bayer 2019. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed Dec 2019].

VOYAGER PAD Enrolled Patients with Symptomatic PAD Undergoing Lower Extremity Revascularization

Key inclusion criteria	Key exclusion criteria
◆ Age ≥50 years ◆ Confirmed moderate-to-severe lower extremity occlusive PAD* ◆ Technically successful peripheral infrainguinal revascularization for symptomatic PAD within the last 10 days prior to randomization	◆ Prior revascularization on index leg within 10 days of the qualifying revascularization ◆ ALI within 2 weeks prior to the qualifying revascularization ◆ Planned post-procedural co-administration of thienopyridines along with aspirin[#] ◆ Confirmed ACS within last 30 days ◆ Medically documented history of ICH, stroke or TIA

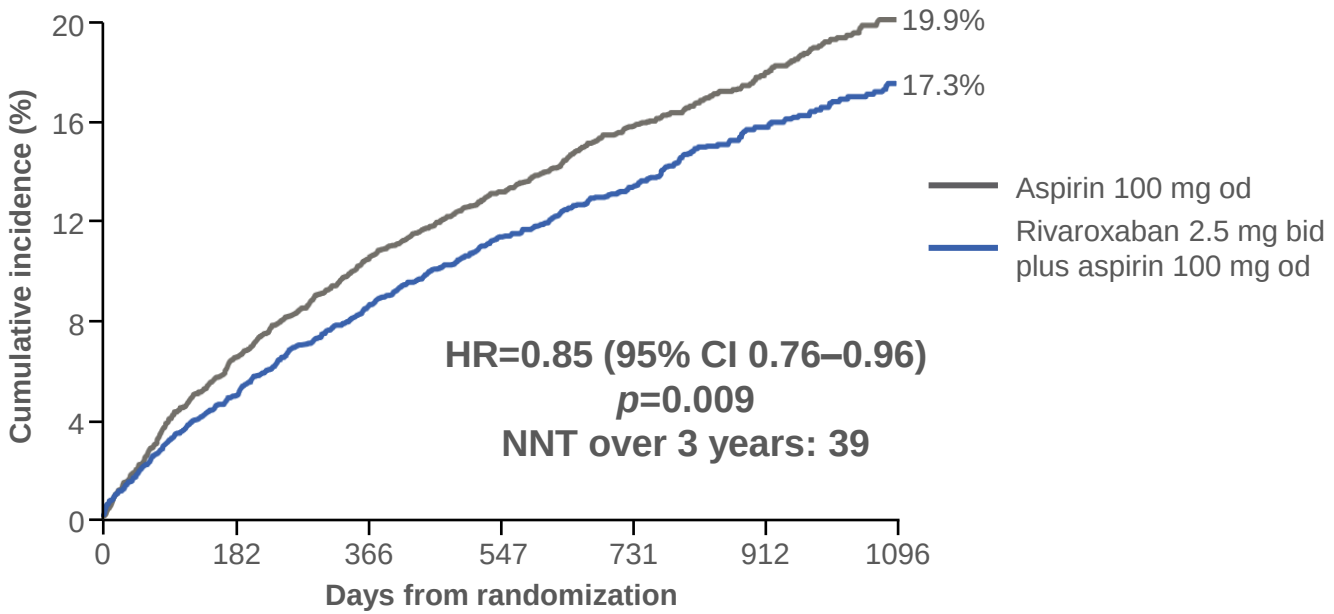
*Based on clinical, anatomical and haemodynamic evidence; [#]except clopidogrel for up to 6 months after the qualifying revascularization.

Capell WH *et al*. *Am Heart J* 2018;199:83–91.

VOYAGER PAD

Rivaroxaban Vascular Dose plus Aspirin Significantly Reduced Risk of the Composite Primary Endpoint by 15% Versus Aspirin

Cumulative incidence of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death (Median follow-up: 28 months)



Number at risk

Rivaroxaban plus aspirin	3286	3082	2938	2834	2219	1415	684
Aspirin	3278	3030	2881	2773	2151	1351	642

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Reduction in the Primary Endpoint Was Driven by a 33% Reduction in Risk of ALI with DPI Versus Aspirin

Endpoint	Rivaroxaban 2.5 mg bid + aspirin (N=3286)		Aspirin (N=3278)		HR (95% CI)	*p*-value
	Patients with event n (%)	K-M Estimate at 3 years	Patients with event n (%)	K-M Estimate at 3 years		
ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
ALI	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation of vascular aetiology	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
MI	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischaemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
CV death	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	

The study was not powered to test for significance in the individual components of the primary endpoint.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

Dual Pathway Inhibition with Rivaroxaban & Aspirin Should be Seen as Part of the Overall Vascular Protective Strategy

RRR	Lipid lowering (1 mmol/L)[1,2]	BP lowering (10 mmHg)[3]	ACEI (HOPE)[4]		COMPASS[5]
MACE	21%	20%	22%	**+ Riva 2.5 mg bid & aspirin 100 mg**	**26%**
Stroke	15%	27%	32%		**44%**
MI	24%	17%	20%		**14%***
Death	9%	13%	16%		**23%**

*Trend towards reduction, not statistically significant

Benefits of dual pathway inhibition are on top of standard control of lipids, blood pressure and RAAS blockade & therefore should be used as part of the overall vascular protective strategy

1. CTT Collaboration. *Lancet* 2015;385:1397–1405; 2. Collins R et al. *Lancet* 2016;388:2532–2561; 3. Ettehad D et al. *Lancet* 2016;387:957–967; 4. HOPE Investigators. *N Engl J Med.* 2000;342:145–153; 5. Connolly SJ et al. *Lancet* 2018;391:205–218.

Vascular Protection Requires a Combination of Optimal Antithrombotic Therapy and Risk Factor Management

THROMBOSIS PREVENTION

- Antithrombotic therapy

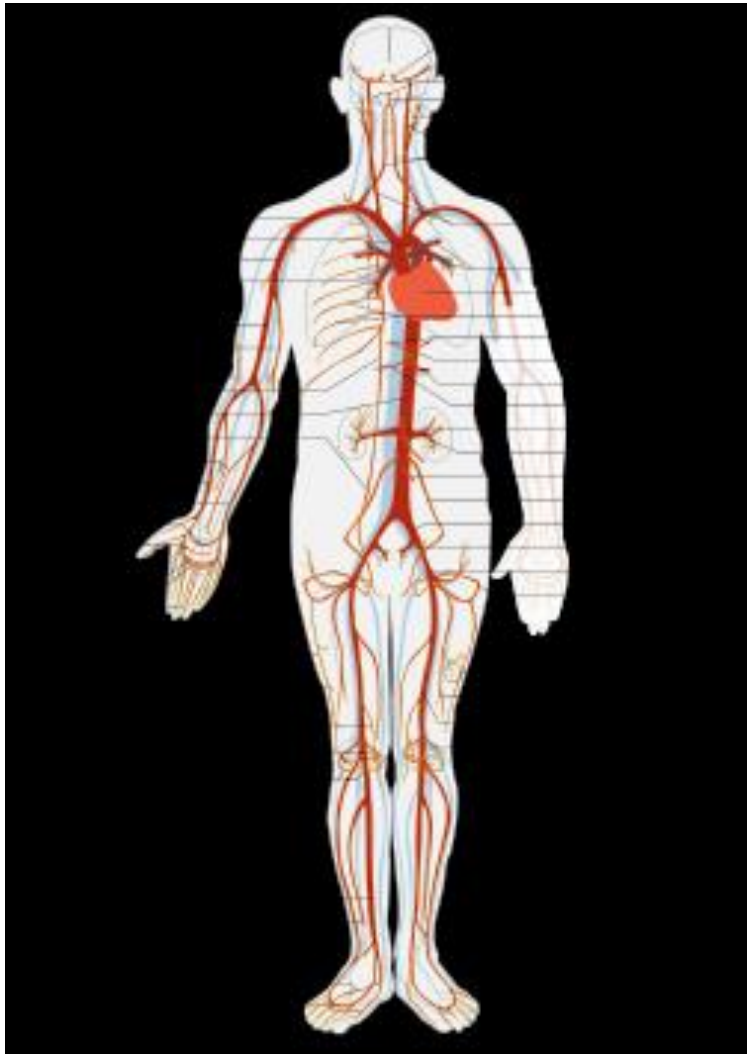
RISK FACTOR CONTROL

- Lipid control
- Blood pressure control
- Glycaemic control

VASCULAR PROTECTION

High/moderate risk of chronic coronary syndrome

Symptomatic PAD s/p revascularisation



Cortés-Beringola A *et al*, *Eur J Prevent Cardiol* 2017;24:22–28; Knuuti J *et al, Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz42

New Guidelines Recommend a Second Antithrombotic for Selected Patients with Chronic Coronary Syndromes

2019 guidelines for the management of CCS

Recommendations	Class	Evidence level
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischaemic events** and without high bleeding risk	IIa	A
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischaemic events** and without high bleeding risk	IIb	A

High ischaemic risk defined as:

- Diffuse multivessel CAD with **at least 1** of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Moderate ischaemic risk defined as:

- **At least 1** of the following:
  - Multivessel/diffuse CAD
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Knuuti J *et al, Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz42

Conclusion

- Antithrombotic therapy remains as an important strategy to tackle chronic coronary syndrome and peripheral artery disease (PAD)
- Use of NOAC for dual pathway inhibition reduces ischemic CV event but is associated with increased bleeding
- Dual antithrombotic therapy should be considered in patients with high ischemic (eg PAD) but low bleeding risk.

Queen Mary Hospital

Hong Kong College of Cardiology ASM 2020

Thank You

Dr Tam Frankie CC 譚礎璋醫生

Division of Cardiology, Medicine

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COMPASS Enrolled a Broader Population of Patients with CAD than the DAPT or PEGASUS Studies

	DAPT[1] (clopidogrel plus aspirin or prasugrel plus aspirin)	PEGASUS[2] (ticagrelor plus aspirin)	COMPASS[3] (rivaroxaban 2.5 mg bid plus aspirin)
N- numbers	9961	21,162	24,824 (CAD cohort)
Index event	PCI (for ACS, stable angina or other)	MI	Chronic CAD (MI, multivessel CAD with symptoms or history of angina, or multivessel PCI/CABG)
Time from index event to drug initiation	12 months	1–3 years	≤20 years*
Key inclusion (✓) or exclusion (✗) criteria	✗ Moderate to severe bleeding or ischaemic event on DAPT in first 12 months after PCI	✓ ≥1 ischaemic risk factor[#] ✗ Prior ICH or ischaemic stroke at any time ✗ GI bleeding ≤6 months ✗ Major surgery ≤30 days	✓ ≥1 ischaemic risk factor[‡] ✗ Stroke ≤1 month or any haemorrhagic or lacunar stroke ✗ High bleeding risk

*Time limit only for prior MI; [#]Patient must have ≥1 of: age ≥65 years; diabetes requiring medication; history of a second prior MI; history of multivessel CAD involving the main vessel, a major branch or a bypass graft; eGFR <60 ml/min (ESRD excluded); [‡]Patient must be aged ≥65 years or have atherosclerosis or revascularization involving ≥2 vascular beds or ≥2 of the following: current smoker, diabetes, eGFR 15–<60 ml/min, HF, or prior non-lacunar ischaemic stroke (≥1 month ago)

1. Mauri L *et al*, *N Engl J Med* 2014;371:2155–2166; 2. Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800; 3. Connolly SJ *et al*, *Lancet* 2018;391:205–218

Dual Anti-Thrombotic

Dual Anti-platelet		Dual Pathway	
	Aspirin + Clopidogrel	Aspirin + Clopidogrel	
	Aspirin + Ticagrelor	Aspirin + Ticagrelor	
			Aspirin + Rivaroxaban
Post PCI/ACS within one year:	Aspirin + Clopidogrel	Aspirin + Ticagrelor	
High Risk CCS or MI			
MACE reduction	Aspirin + Clopidogrel	Aspirin + Ticagrelor	Aspirin + Rivaroxaban
Increase bleeding risk	Aspirin + Clopidogrel	Aspirin + Ticagrelor	Aspirin + Rivaroxaban
All cause mortality reduction			Aspirin + Rivaroxaban
PAD: MACE reduction	Aspirin + Clopidogrel	Aspirin + Ticagrelor	Aspirin + Rivaroxaban
PAD s/p revascularisation: limb event			Aspirin + Rivaroxaban

Modified ISTH Major Bleeding Definition Applied at Regulators' Request with the Intent of Capturing all Bleeding that Required Medical Attention

ISTH major bleeding[1]	Modified ISTH major bleeding (COMPASS)
◆ Fatal bleeding, *and/or*	◆ Fatal bleeding, *and/or*
◆ Symptomatic bleeding in a critical area or organ (such as intracranial), *and/or*	◆ Symptomatic bleeding in a critical area or organ (such as intracranial), *or*
◆ ***Bleeding causing a drop in haemoglobin level of ≥20 g/l, or leading to transfusion of ≥2 units of whole blood or red cells***	◆ ***Bleeding into the surgical site requiring re-operation, and/or*** ◆ ***Bleeding leading to hospitalization***

Unlike the standard ISTH criteria, all bleeding that led to presentation to an acute care facility or hospitalization were considered as major compared with the standard ISTH major bleeding definition

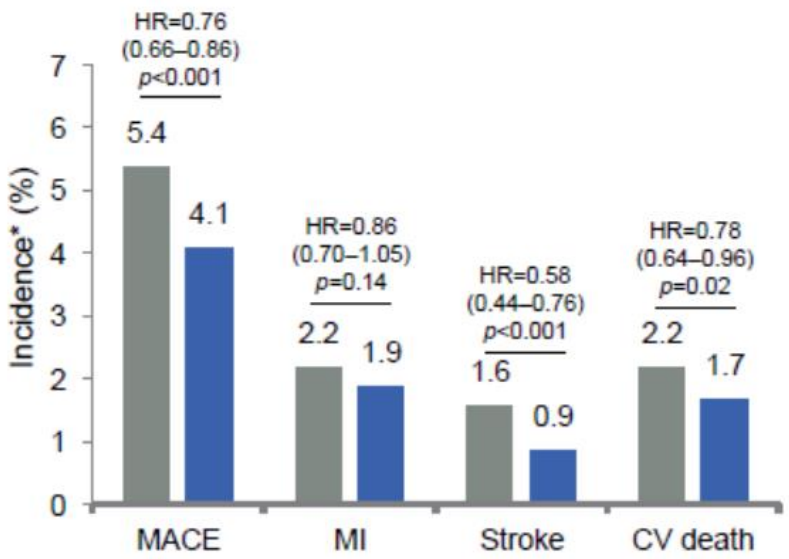
1. Schulman S *et al*, *J Thromb Haemost* 2005;3:692–694

COMPASS

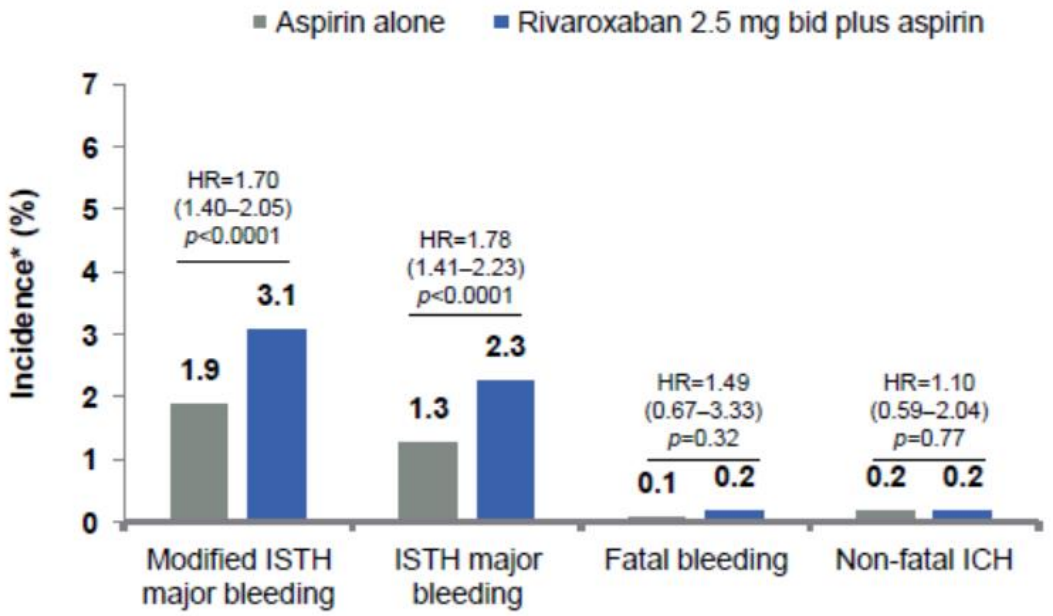
Bleeding

Efficacy and Safety Outcomes

Major adverse cardiovascular events



Major bleeding events



Major bleeding rates according to the modified ISTH definition were higher than according to the ISTH definition

Data shown above the line are hazard ratio (95% confidence interval) and p-value

*Crude incidence over mean follow-up of 23 months; ‡modified ISTH definition: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial), or bleeding into the surgical site requiring re-operation, and/or bleeding leading to hospitalization

Eikelboom JW *et al, N Engl J Med* 2017;377:1319–1330

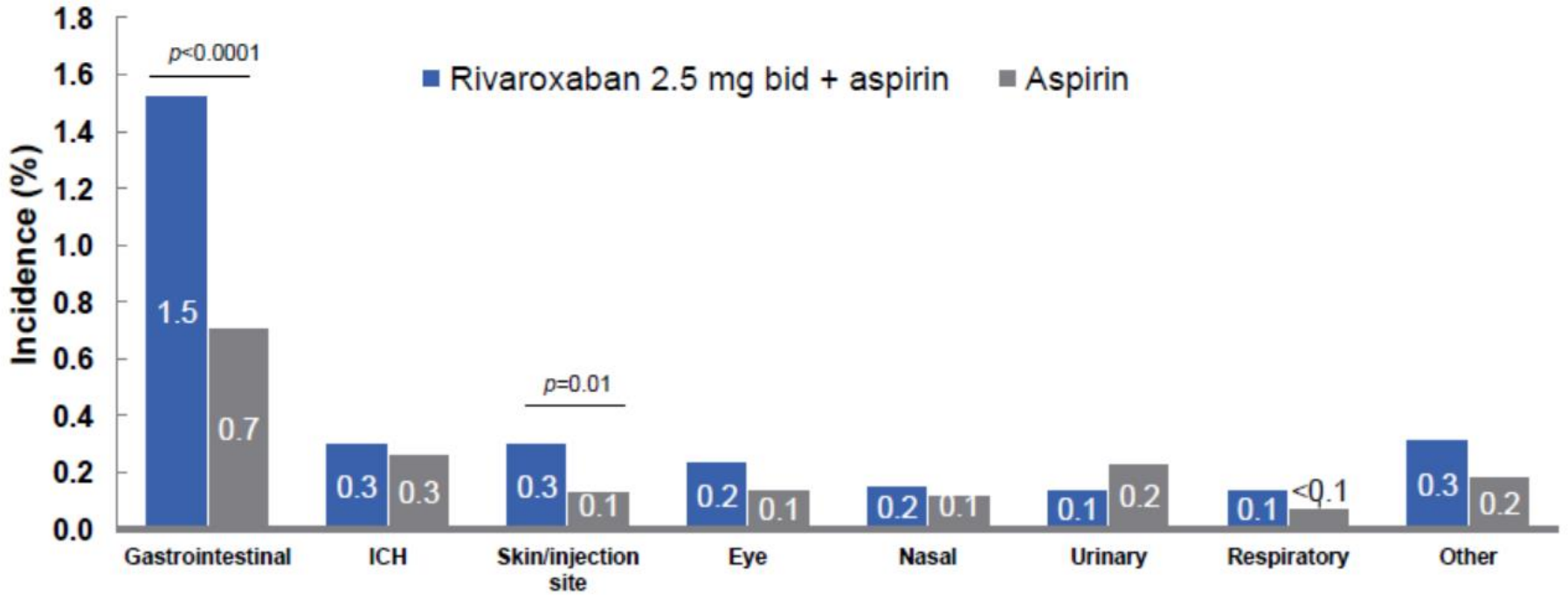
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Bleeding

The Majority of Major Bleeding Events in COMPASS Were Gastrointestinal

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Sites of major bleeding in COMPASS



All differenes are non-significant unless otherwise stated
Eikelboom JW *et al*, manuscript in preparation

Bleeding

Major Bleeding Events Are Most Common in the First Year of Treatment in the Overall COMPASS Population: Landmark Analysis

		Rivaroxaban 2.5 mg bid + aspirin, n (%) N=9152	Aspirin only, n (%) N=9126	Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI)
MACE	Year 1	195 (2.1)	244 (2.7)	0.79 (0.66–0.96)
	Year 2	123 (1.6)	179 (2.3)	0.68 (0.54–0.85)
	Year 3 or later	61 (1.6)	73 (1.9)	0.82 (0.88–1.15)
Major GI bleeding	Year 1	88 (1.0)	25 (0.3)	3.51 (2.25–5.48)
	Year 2	35 (0.6)	27 (0.4)	1.30 (0.78–2.14)
	Year 3 or later	17 (0.7)	13 (0.5)	1.32 (0.64–2.71)

Eikelboom JW *et al*, manuscript in preparation

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Bleeding

Association Between GI Bleeding and GI Cancer

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Population	Total N	New GI cancers (n=307)		HR (95% CI)	*p* value
		N	%		
GI bleeding					
After bleeding	901*	70	7.8	12.9 (9.77–17.0)	<0.0001
No prior bleeding	27,395	237	0.9		
Non-GI bleeding					
After bleeding	1898*	29	1.5	1.77 (1.20–2.61)	0.004
No prior bleeding	27,395	278	1.0		

*Excludes patients with bleeding who were diagnosed with cancer before the bleeding event
Eikelboom JW *et al*, manuscript in preparation

Bleeding

Association Between GU Bleeding and GU Cancer

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Population	Total N	New GU cancers diagnoses (n=138)		HR (95% CI)	*p* value
		N	%		
GU bleeding					
After bleeding	462*	62	13.4	83.4 (58.6–118.6)	<0.0001
No prior bleeding	27,395	76	0.3		
Non-GU bleeding					
After bleeding	2301*	14	0.6	1.70 (0.97–2.99)	0.06
No prior bleeding	27,395	124	0.5		

*Excludes patients with bleeding who were diagnosed with cancer before the bleeding event
Eikelboom JW *et al*, manuscript in preparation

Bleeding

Timing of Cancer Diagnosis in Relation to Bleeding

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Site of cancer	Timing of GI and GU cancer diagnosis		
	Within 6 months of bleeding event	Between 6 and 12 months after bleeding event	More than 12 months after bleeding event
Gastrointestinal	54 (77.1%)	6 (8.6%)	10 (14.3%)
Genitourinary	55 (88.7%)	6 (9.7%)	1 (1.6%)

Eikelboom JW *et al*, manuscript in preparation

Bleeding

Frequency of GI Cancer Diagnosis After GI Bleeding in Year 1, 2 and 3+

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Year	Rivaroxaban 2.5mg bid + ASA 100 mg od N (%)	Rivaroxaban 5 mg bid N (%)	Aspirin 100 mg od N (%)
1	22/268 (8.2%)	18/216 (8.3%)	8/114 (7.0%)
2	6/72 (8.3%)	6/81 (7.4%)	5/58 (8.6%)
3+	1/34 (2.9%)	2/29 (6.9%)	2/29 (6.9%)

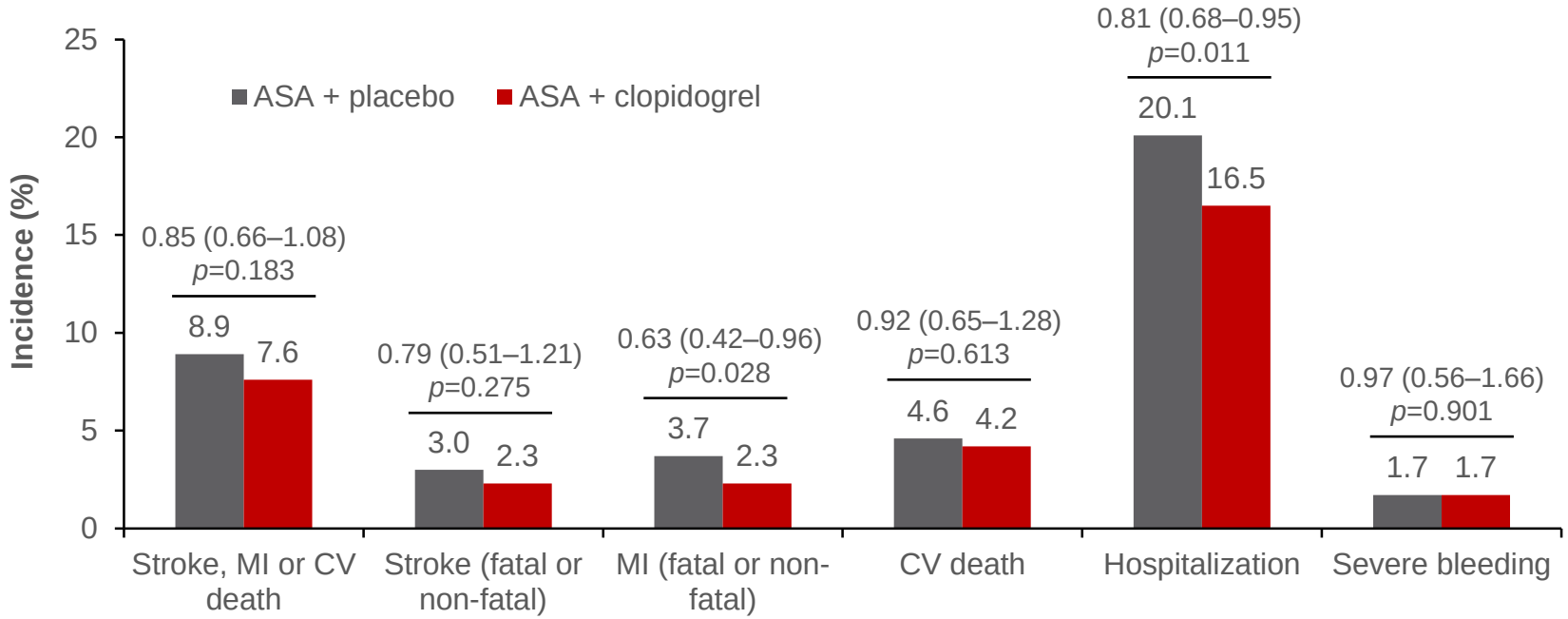
Eikelboom JW *et al*, manuscript in preparation

PAD

Lower Risk of MI or Hospitalization with Clopidogrel Versus Placebo in Patients with PAD

CHARISMA: ASA* + placebo versus ASA* + clopidogrel (75 mg od)

- Subgroup analysis in patients with PAD (n=3096)[1]
  - Compared with placebo, clopidogrel did not reduce the risk of stroke, MI or CV death, but did reduce risk of MI or hospitalization
  - Severe bleeding was similar between groups



Data shown above the line are hazard ratio (95% confidence interval) and *p*-value. *75–162 mg od

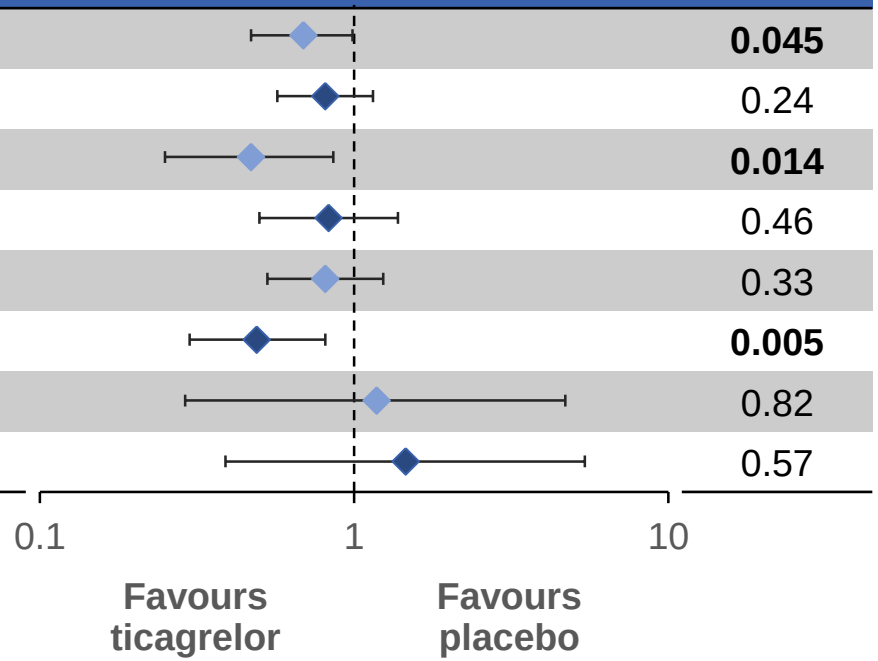
Cacoub PP *et al*, *Eur Heart J* 2009:30:192–201

Ticagrelor Reduces MACE/MALE Without Increasing Bleeding In Patient Subgroup with PAD and Prior MI

PEGASUS-TIMI 54: ticagrelor* + ASA versus placebo+ ASA

- **Subgroup analysis** in 1143 patients with PAD and MI ≥1 year previously
  - MACE higher in patients with PAD and prior MI versus prior MI alone (19.3% vs 8.4%; *p*<0.001)
  - In patients with PAD, both doses of ticagrelor were associated with efficacy benefits without increasing the risk of major bleeding

	Dose	HR	95% CI	*p*
CV death, MI or stroke	**60**	**0.69**	**0.47–0.99**	**0.045**
	90	0.81	0.57–1.15	0.24
CV death	**60**	**0.47**	**0.25–0.86**	**0.014**
	90	0.83	0.50–1.38	0.46
MALE	60	0.81	0.53–1.24	0.33
	90	**0.49**	**0.30–0.81**	**0.005**
Major bleeding	60	1.18	0.29–4.70	0.82
	90	1.46	0.39–5.43	0.57



*60 mg bid or 90 mg bid

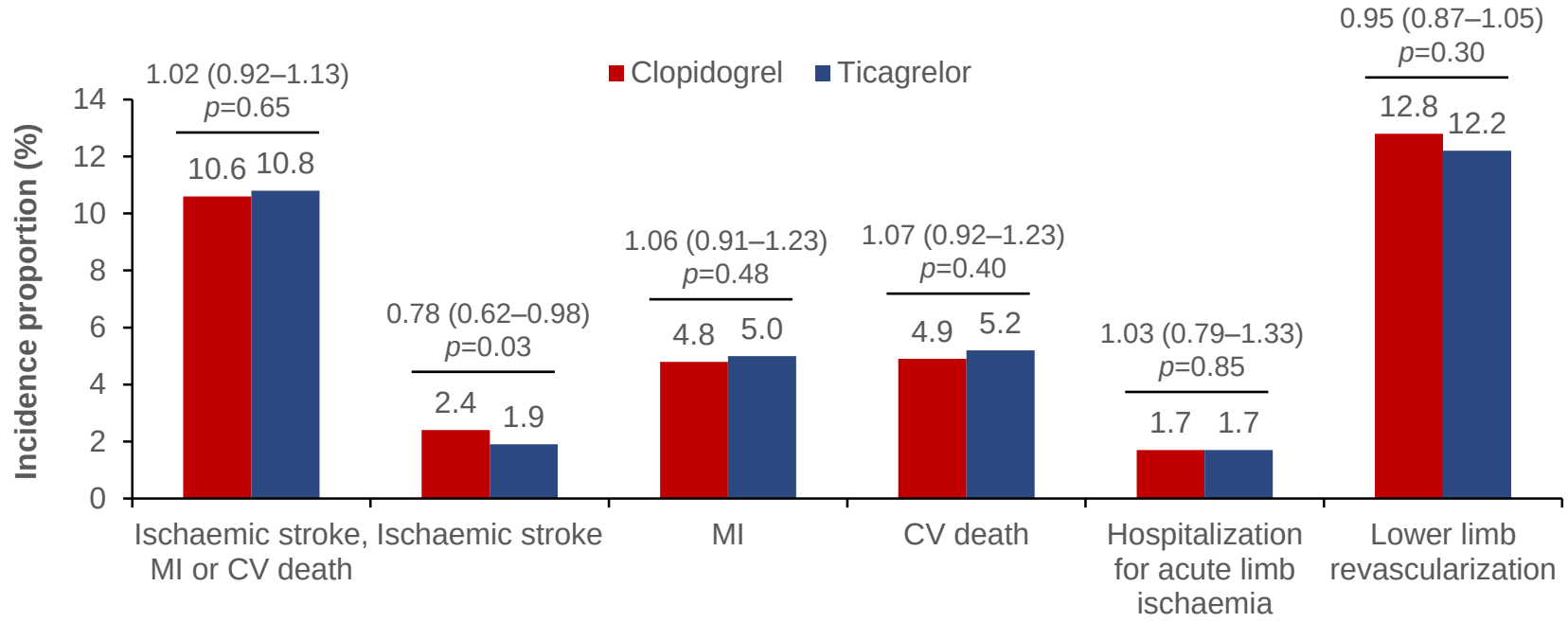
MALE; major adverse limb events (acute limb ischaemia or peripheral revascularization for ischaemia)

Bonaca MP *et al*, *J Am Coll Cardiol* 2016;67:2719–2728

Similar Risk of Non-Fatal CV or Limb Events with Ticagrelor Versus Clopidogrel in Patients with PAD

EUCLID: clopidogrel (75 mg od) versus ticagrelor (90 mg bid)

- 13,885 patients with lower extremity PAD (previous revascularization or ankle–brachial index ≤0.8 at screening)
  - Compared with clopidogrel, ticagrelor did not reduce the risk of stroke, MI or CV death, hospitalization for acute limb ischaemia or lower limb revascularization
  - Major bleeding was similar between groups



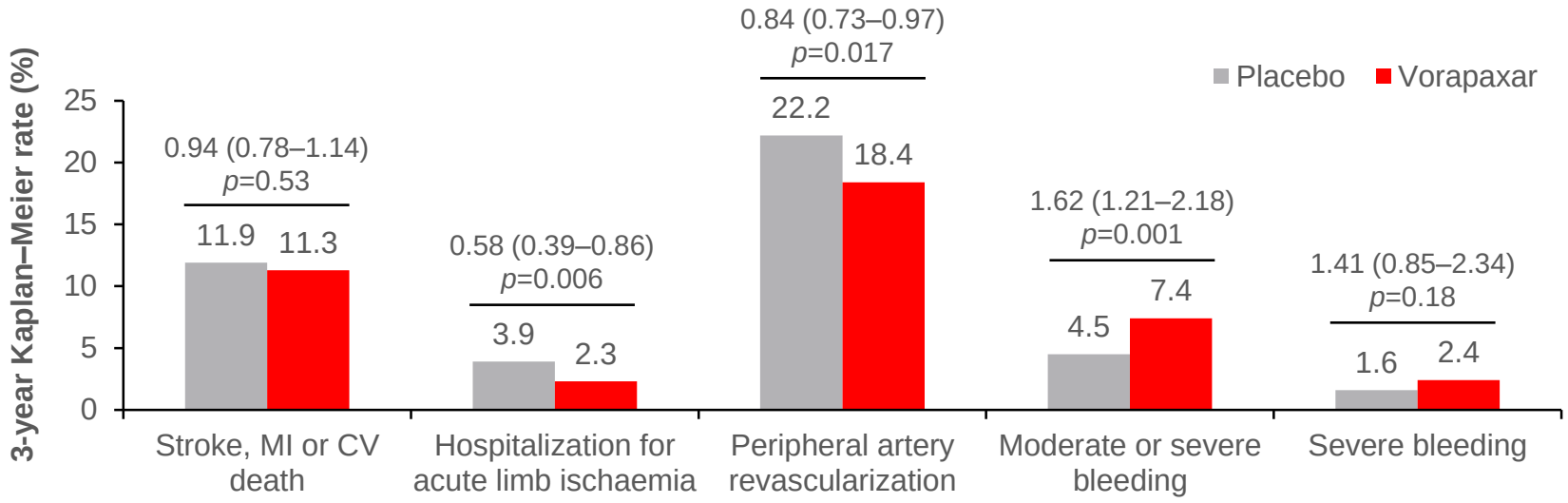
Data shown above the line are hazard ratio (95% confidence interval) and *p*-value

Hiatt WR *et al*, *N Engl J Med* 2017;376:32–40

Improved Limb Outcomes but Increased Bleeding with Vorapaxar Versus Placebo in Patients with PAD

TRA2°P-TIMI 50: vorapaxar plus standard antiplatelet therapy versus placebo plus standard antiplatelet therapy

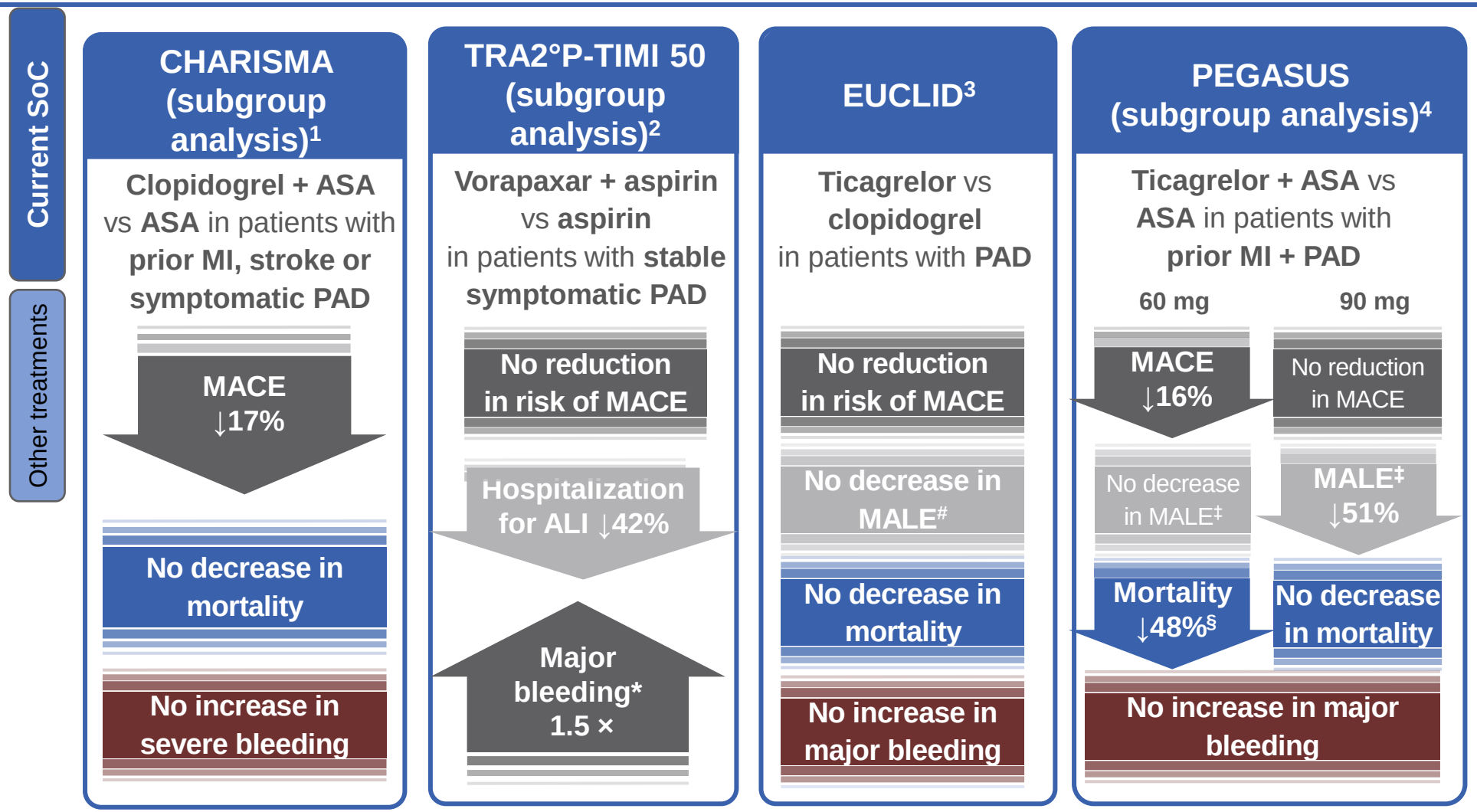
- Subgroup analysis in patients with stable symptomatic PAD* (n=3787)
  - Compared with placebo, vorapaxar did not reduce the risk of CV death, MI or stroke but did reduce acute limb ischaemia and peripheral artery revascularization
  - Increased bleeding was observed with vorapaxar versus placebo
    - Intracranial haemorrhage rates: 0.9% versus 0.4% for vorapaxar versus placebo (hazard ratio [HR]=2.03, 95% confidence interval [CI] 0.82–5.02; *p*=0.13)



Data shown above the line are HR (95% CI) and *p*-value. *Baseline antiplatelet therapy in patients with PAD included ASA (88.0%), thienopyridine (36.8%) or ASA plus a thienopyridine (28.2%). 3.4% of patients with PAD did not receive antiplatelet therapy at baseline

Bonaca MP *et al*, *Circulation* 2013;127:1522–1529

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



*Peripheral artery bypass surgery or leg amputation for CLI or other intervention for PAD (individual endpoints); #Hospitalization for ALI or lower limb revascularization (individual endpoints); ‡Composite of ALI or peripheral revascularization; §No mortality benefit in the overall trial population[4]

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

VOYAGER PAD
Study Rationale and Objective

Rationale

- Patients with PAD who undergo peripheral revascularization are at high risk of subsequent vascular complications, particularly ALI[1,2]
- There is a lack of evidence to support the selection of antithrombotic therapy following peripheral revascularization[3]
- In patients with chronic PAD, the combination of rivaroxaban vascular dose plus aspirin was associated with significant reductions in MACE and MALE compared with aspirin alone in the COMPASS trial[4]

Objective

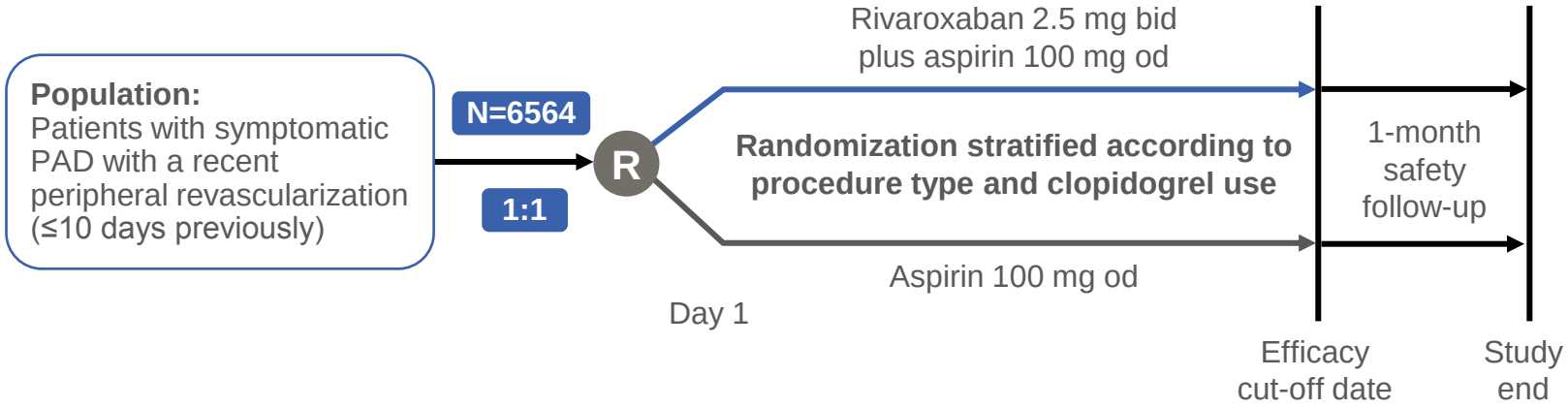
- To assess whether rivaroxaban vascular dose plus aspirin reduces the risk of ALI, vascular amputation, MI, ischaemic stroke or CV death compared with aspirin in patients with symptomatic PAD who recently underwent lower-extremity revascularization[3]
- To evaluate the safety of rivaroxaban vascular dose plus aspirin compared with aspirin[3]

1. Hess CN *et al*. *J Am Coll Cardiol* 2020;75:498–508. 2. Baumgartner I *et al*. *J Am Coll Cardiol* 2018;72:1563–1572.
3. Capell WH *et al*. *Am Heart J* 2018;199:83–91. 4. Anand SS *et al*. *Lancet* 2018;391:219–229.

VOYAGER PAD

VOYAGER PAD: Study Design

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



Short design: Randomized, double-blind, phase III, controlled trial

Indication: Symptomatic PAD

Completion date: December 2019

Mean treatment duration per patient: ~30 months.

Capell WH *et al*. *Am Heart J* 2018;199:83–91. Bayer 2019. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed Dec 2019].

VOYAGER PAD

VOYAGER PAD Enrolled Patients with Symptomatic PAD Undergoing Lower Extremity Revascularization

Key inclusion criteria	Key exclusion criteria
◆ Age ≥50 years ◆ Confirmed moderate-to-severe lower extremity occlusive PAD* ◆ Technically successful peripheral infrainguinal revascularization for symptomatic PAD within the last 10 days prior to randomization	◆ Prior revascularization on index leg within 10 days of the qualifying revascularization ◆ ALI within 2 weeks prior to the qualifying revascularization ◆ Planned post-procedural co-administration of thienopyridines along with aspirin[#] ◆ Confirmed ACS within last 30 days ◆ Medically documented history of ICH, stroke or TIA

*Based on clinical, anatomical and haemodynamic evidence; [#]except clopidogrel for up to 6 months after the qualifying revascularization.

Capell WH *et al*. *Am Heart J* 2018;199:83–91.

VOYAGER PAD

VOYAGER PAD Used a Novel Primary Efficacy Endpoint Incorporating Both Cardiovascular and Limb Events

Primary efficacy outcome
◆ Composite of ALI, major amputation of a vascular aetiology, MI, ischaemic stroke or CV death

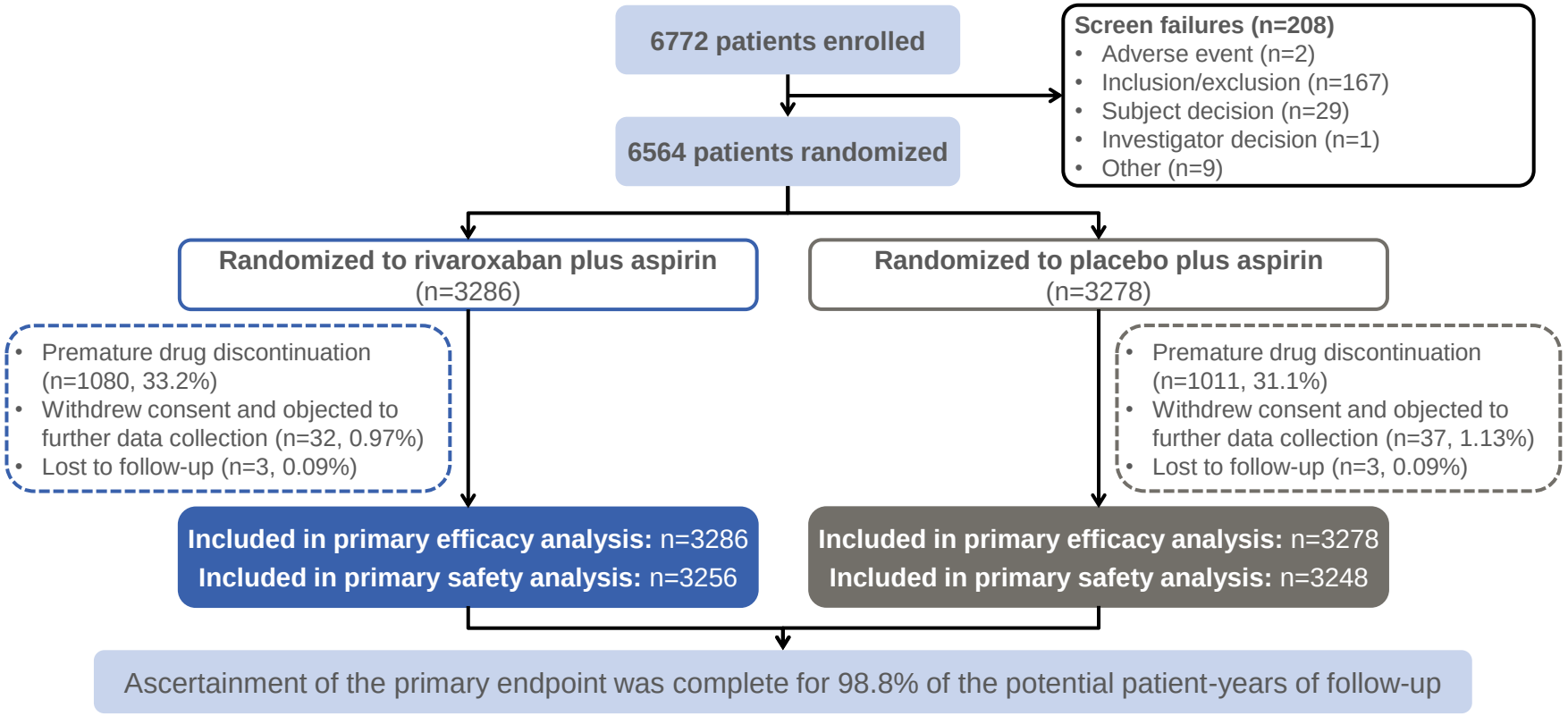
Primary safety outcome
◆ Major bleeding events (TIMI classification)

Secondary efficacy outcomes
◆ ALI, major amputation of a vascular aetiology, MI, ischaemic stroke or CHD death
◆ Unplanned index limb revascularization for recurrent limb ischaemia
◆ Vascular hospitalization for a coronary or peripheral cause (either limb) of a thrombotic nature
◆ ALI, major amputation of a vascular aetiology, MI, ischaemic stroke or all-cause mortality
◆ ALI, major amputation of a vascular aetiology, MI, all-cause stroke or CV death
◆ All-cause mortality
◆ Venous thromboembolic event

Capell WH *et al*. *Am Heart J* 2018;199:83–91.

VOYAGER PAD

Patient Disposition

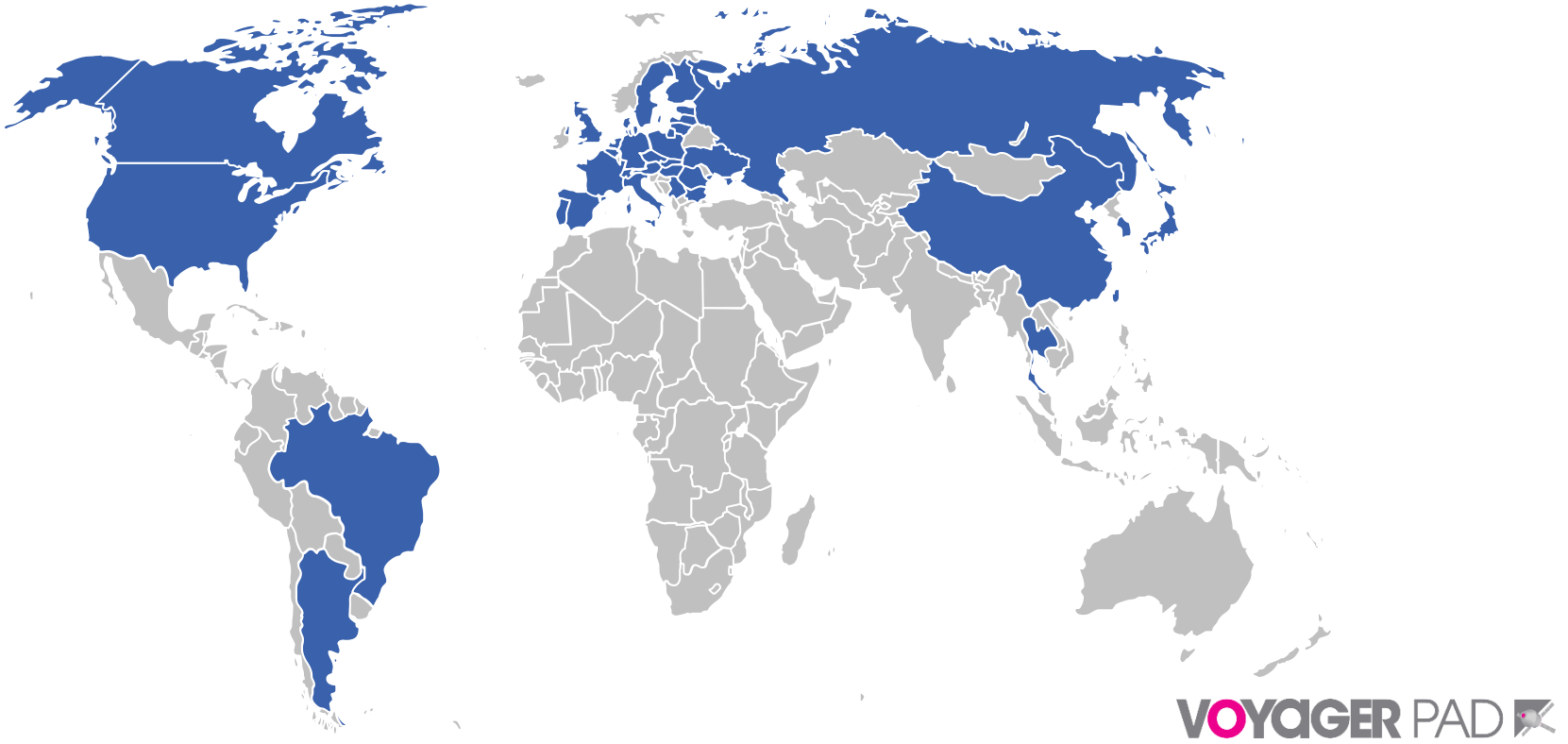


Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

VOYAGER PAD Randomized 6564 Patients Worldwide

The study was conducted at 542 sites in 34 countries



Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

Baseline Demographics Were Well Balanced Between Randomized Treatment Groups

	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
Median age (IQR), years	67.0 (61.0–73.0)	67.0 (61.0–73.0)
Female sex, n (%)	847 (25.8)	857 (26.1)
Median BMI (IQR), kg/m^2	26.0 (23.3–29.1)	26.0 (23.2–29.1)
Race, n (%)		
White	2647 (80.6)	2656 (81.0)
Asian	484 (14.7)	482 (14.7)
Black	84 (2.6)	71 (2.2)
Other	71 (2.2)	69 (2.1)

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

Risk Factors and Co-morbidities Were Similar Between Randomized Treatment Groups

	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
Hypertension	2684 (81.7)	2658 (81.1)
Hyperlipidaemia	1971 (60.0)	1968 (60.0)
Current smoker	1147 (34.9)	1132 (34.5)
Diabetes mellitus	1313 (40.0)	1316 (40.1)
eGFR <60 ml/min/1.73 m^2	661 (20.1)	666 (20.3)
Symptomatic CAD	1052 (32.0)	1015 (31.0)
MI	365 (11.1)	349 (10.6)
Carotid artery disease	282 (8.6)	293 (8.9)

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Other Clinical Characteristics Were Well Balanced Between Randomized Treatment Groups

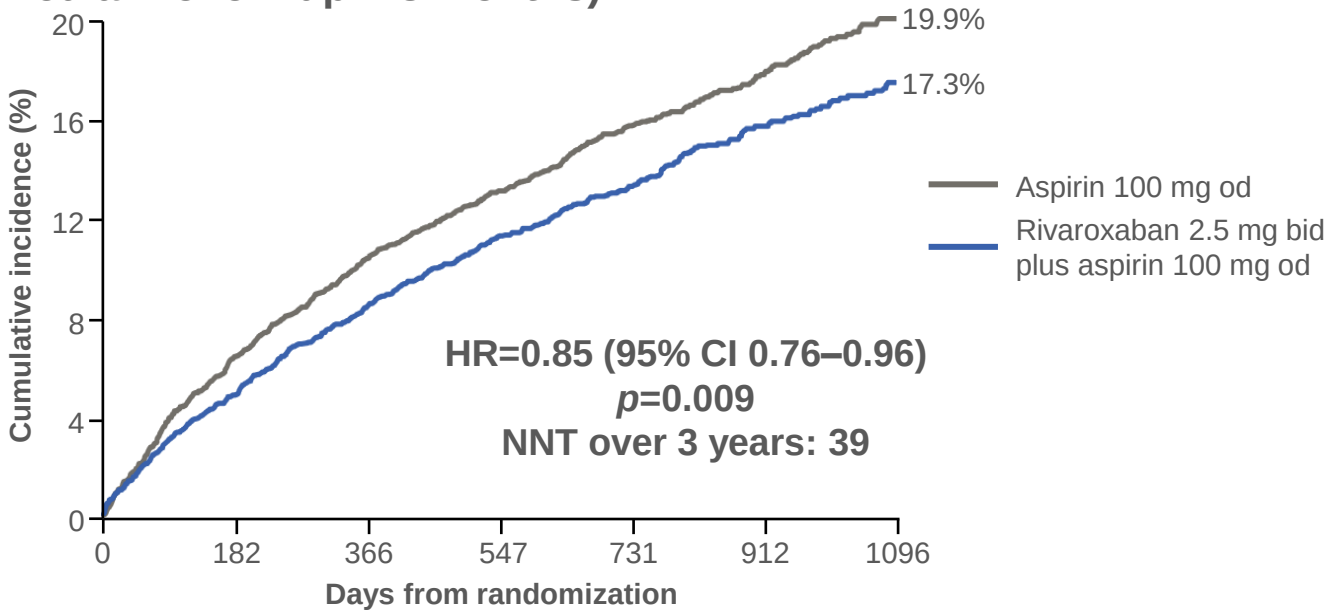
	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
PAD history		
Median ABI (IQR)	0.56 (0.42–0.67)	0.56 (0.42–0.67)
Prior amputation, n (%)	194 (5.9)	196 (6.0)
Qualifying revascularization, n (%)		
Endovascular	2153 (65.5)	2140 (65.3)
Surgical	1133 (34.5)	1138 (34.7)
Performed for CLI	762 (23.2)	771 (23.5)
Medications, n (%)		
Statin	2608 (79.4)	2641 (80.6)
ACE inhibitor or ARB	2096 (63.8)	2063 (62.9)
Clopidogrel at randomization	1658 (50.5)	1655 (50.5)

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Rivaroxaban Vascular Dose plus Aspirin Significantly Reduced Risk of the Composite Primary Endpoint by 15% Versus Aspirin

Cumulative incidence of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death (Median follow-up: 28 months)



Number at risk

Rivaroxaban plus aspirin	3286	3082	2938	2834	2219	1415	684
Aspirin	3278	3030	2881	2773	2151	1351	642

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Reduction in the Primary Endpoint Was Driven by a 33% Reduction in Risk of ALI with DPI Versus Aspirin

Endpoint	Rivaroxaban 2.5 mg bid + aspirin (N=3286)		Aspirin (N=3278)		HR (95% CI)	*p*-value
	Patients with event n (%)	K-M Estimate at 3 years	Patients with event n (%)	K-M Estimate at 3 years		
ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
ALI	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation of vascular aetiology	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
MI	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischaemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
CV death	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	

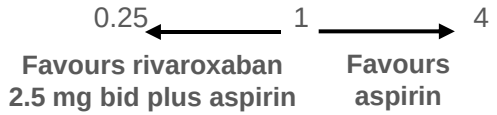
The study was not powered to test for significance in the individual components of the primary endpoint.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

The First Five Secondary Efficacy Outcomes in the Testing Hierarchy Were All Significantly Reduced with DPI vs Aspirin

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)		Aspirin (n=3278)		HR (95% CI)	HR (95% CI)	*p*-value
	Patients with event n (%)	K-M estimate at 3 years	Patients with event n (%)	K-M estimate at 3 years			
ALI, major amputation of a vascular aetiology, MI, ischaemic stroke, CHD death	433 (13.2)	14.7	528 (16.1)	18.2		0.80 (0.71–0.91)	**<0.001**
Unplanned index limb revascularization for recurrent limb ischaemia	584 (17.8)	20.0	655 (20.0)	22.5		0.88 (0.79–0.99)	**0.03**
Hospitalization for coronary or peripheral event of a thrombotic nature	262 (8.0)	8.7	356 (10.9)	12.1		0.72 (0.62–0.85)	**<0.001**
ALI, major amputation of a vascular aetiology, MI, ischaemic stroke, all-cause mortality	614 (18.7)	20.6	679 (20.7)	23.2		0.89 (0.79–0.99)	**0.03**
ALI, major amputation of a vascular aetiology, MI, all-cause stroke, all-cause mortality	514 (15.6)	17.5	588 (17.9)	20.1		0.86 (0.76–0.96)	**0.01**
All-cause mortality	321 (9.8)	11.1	297 (9.1)	10.9		1.08 (0.92–1.27)	0.34
Venous thromboembolism	25 (0.8)	0.8	41 (1.3)	1.7		0.61 (0.37–1.00)	–



*Exploratory only.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052

VOYAGER PAD

No Significant Excess in the Primary Safety Outcome of TIMI Major Bleeding with DPI Versus Aspirin

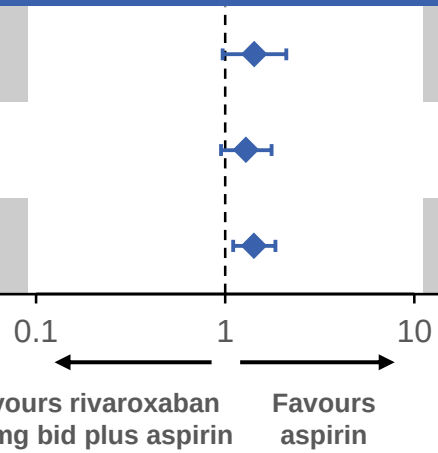
Endpoint	Rivaroxaban 2.5 mg bid + aspirin (N=3256)		Aspirin n/N (%) (N=3248)		HR (95% CI)	*p*-value
	Patients with event, n (%)	K-M Estimate at 3 years	Patients with event, n (%)	K-M Estimate at 3 years		
TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
ICH	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
ICH or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Rates of TIMI Major and BARC Major Bleeding Were Not Significantly Increased with DPI Versus Aspirin

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (n=3256)		Aspirin (n=3248)		HR (95% CI)	HR (95% CI)	*p*-value
	Patients with event n (%)	K-M estimate at 3 years	Patients with event n (%)	K-M estimate at 3 years			
TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87		1.43 (0.97–2.10)	0.07
BARC major bleeding*	93 (2.86)	3.86	73 (2.25)	2.92		1.29 (0.95–1.76)	0.10
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06		1.42 (1.10–1.84)	0.007



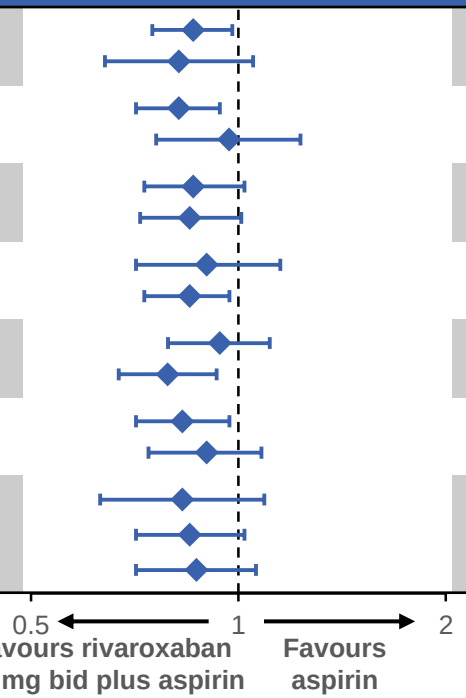
*Grade 3b or higher.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Primary Efficacy Outcomes Were Consistent Across Subgroups

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
Age (years)	<75	391/2613 (14.96)	446/2621 (17.02)		0.86 (0.75–0.98)
	≥75	117/673 (17.38)	138/657 (21.00)		0.82 (0.64–1.05)
Sex	Male	375/2439 (15.38)	445/2421 (18.38)		0.82 (0.71–0.94)
	Female	133/847 (15.70)	139/857 (16.22)		0.97 (0.76–1.23)
BMI group	< Median	262/1610 (16.27)	301/1631 (18.45)		0.86 (0.73–1.02)
	≥ Median	241/1637 (14.72)	276/1613 (17.11)		0.85 (0.72–1.01)
eGFR (ml/min/1.73 m^2)	<60	130/661 (19.67)	146/666 (21.92)		0.90 (0.71–1.15)
	≥60	360/2499 (14.41)	413/2493 (16.57)		0.85 (0.73–0.97)
Diabetes	Yes	248/1313 (18.89)	261/1316 (19.83)		0.94 (0.79–1.11)
	No	260/1972 (13.18)	323/1961 (16.47)		0.79 (0.67–0.93)
Hyperlipidaemia	Yes	294/1971 (14.92)	348/1968 (17.68)		0.83 (0.71–0.97)
	No	214/1313 (16.30)	236/1310 (18.02)		0.90 (0.74–1.08)
Smoking status	Never	95/662 (14.35)	119/689 (17.27)		0.83 (0.63–1.09)
	Former	229/1475 (15.53)	263/1456 (18.06)		0.85 (0.71–1.02)
	Current	184/1147 (16.04)	202/1132 (17.84)		0.87 (0.71–1.06)



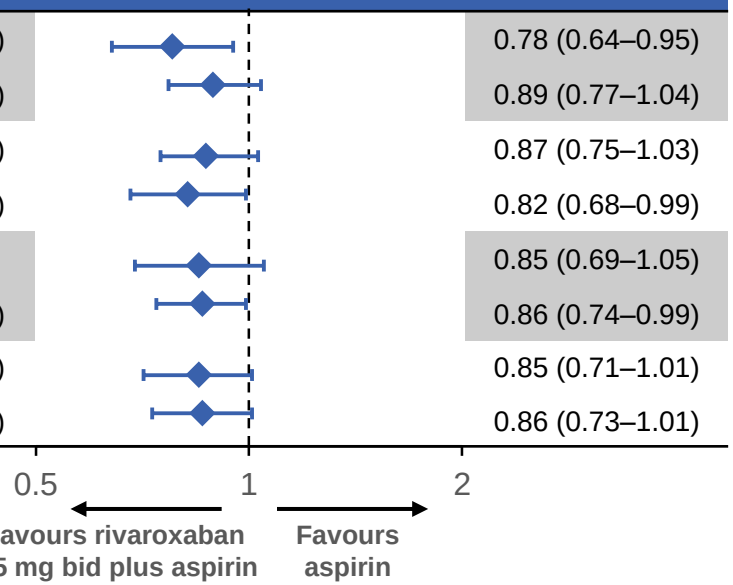
Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary efficacy outcome of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052

VOYAGER PAD

Primary Efficacy Outcomes Were Consistent Irrespective of PAD Characteristics

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
CAD	Yes	183/1052 (17.40)	220/1015 (21.67)		0.78 (0.64–0.95)
	No	325/2233 (14.55)	364/2263 (16.08)		0.89 (0.77–1.04)
Index ABI	< Median	284/1588 (17.88)	321/1582 (20.29)		0.87 (0.75–1.03)
	≥ Median	201/1588 (12.66)	239/1594 (14.99)		0.82 (0.68–0.99)
Critical limb ischaemia	Yes	159/762 (20.87)	188/771 (24.38)		0.85 (0.69–1.05)
	No	349/2524 (13.83)	396/2507 (15.80)		0.86 (0.74–0.99)
Concomitant clopidogrel use	Yes	235/1658 (14.17)	272/1655 (16.44)		0.85 (0.71–1.01)
	No	272/1621 (16.78)	310/1613 (19.22)		0.86 (0.73–1.01)



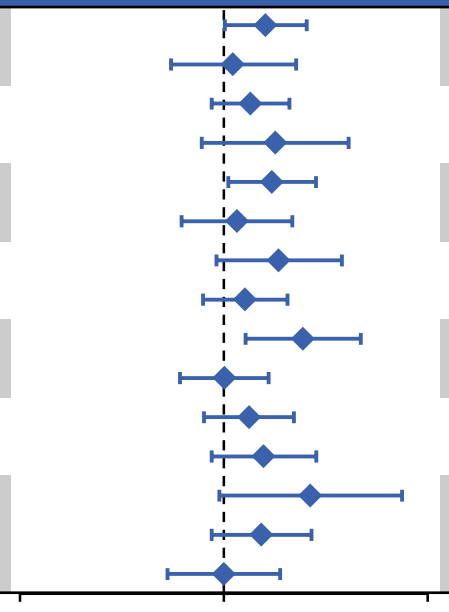
Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary efficacy outcome of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Primary Safety Outcomes Were Consistent Across Subgroups

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
Age (years)	<75	46/2595 (1.77)	29/2598 (1.12)		1.60 (1.01–2.55)
	≥75	16/661 (2.42)	15/650 (2.31)		1.11 (0.55–2.26)
Sex	Male	47/2417 (1.94)	35/2400 (1.46)		1.35 (0.87–2.10)
	Female	15/839 (1.79)	9/848 (1.06)		1.79 (0.78–4.09)
BMI group	< Median	41/1593 (2.57)	25/1615 (1.55)		1.72 (1.05–2.83)
	≥ Median	21/1626 (1.29)	18/1601 (1.12)		1.16 (0.62–2.17)
eGFR (ml/min/1.73 m^2)	<60	21/649 (3.24)	12/657 (1.83)		1.86 (0.92–3.79)
	≥60	38/2483 (1.53)	30/2474 (1.21)		1.27 (0.79–2.05)
Diabetes	Yes	31/1298 (2.39)	13/1305 (1.00)		2.45 (1.28–4.69)
	No	31/1958 (1.58)	31/1942 (1.60)		1.01 (0.61–1.66)
Hyperlipidaemia	Yes	34/1950 (1.74)	26/1953 (1.33)		1.33 (0.80–2.21)
	No	28/1305 (2.15)	18/1295 (1.39)		1.57 (0.87–2.84)
Smoking status	Never	13/653 (1.99)	5/686 (0.73)		2.66 (0.95–7.48)
	Former	30/1466 (2.05)	20/1440 (1.39)		1.53 (0.87–2.69)
	Current	19/1136 (1.67)	19/1122 (1.69)		1.00 (0.53–1.89)



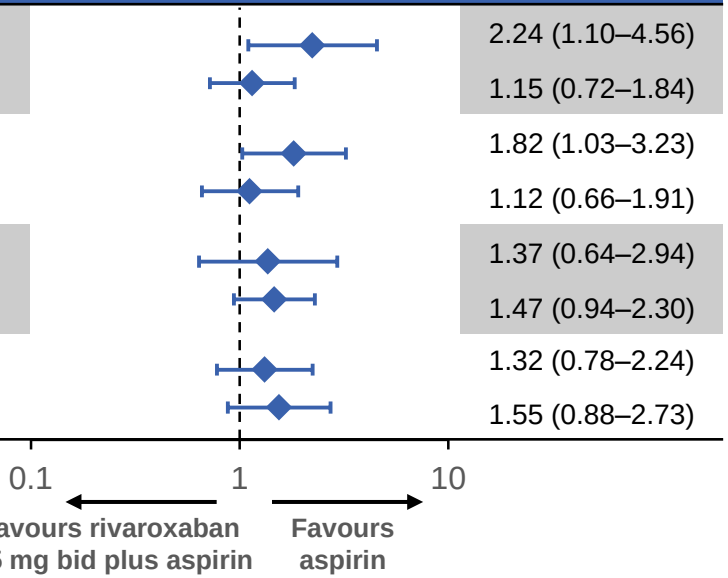
Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary safety outcome of TIMI major bleeding

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Primary Safety Outcomes Were Consistent Irrespective of PAD Characteristics

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
CAD	Yes	25/1041 (2.40)	11/1006 (1.09)		2.24 (1.10–4.56)
	No	37/2215 (1.67)	33/2242 (1.47)		1.15 (0.72–1.84)
Index ABI	< Median	33/1575 (2.10)	18/1569 (1.15)		1.82 (1.03–3.23)
	≥ Median	28/1573 (1.78)	26/1578 (1.65)		1.12 (0.66–1.91)
Critical limb ischaemia	Yes	15/754 (1.99)	12/767 (1.56)		1.37 (0.64–2.94)
	No	47/2502 (1.88)	32/2481 (1.29)		1.47 (0.94–2.30)
Concomitant clopidogrel use	Yes	32/1646 (1.94)	24/1637 (1.47)		1.32 (0.78–2.24)
	No	30/1603 (1.87)	20/1601 (1.25)		1.55 (0.88–2.73)



Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary safety outcome of TIMI major bleeding

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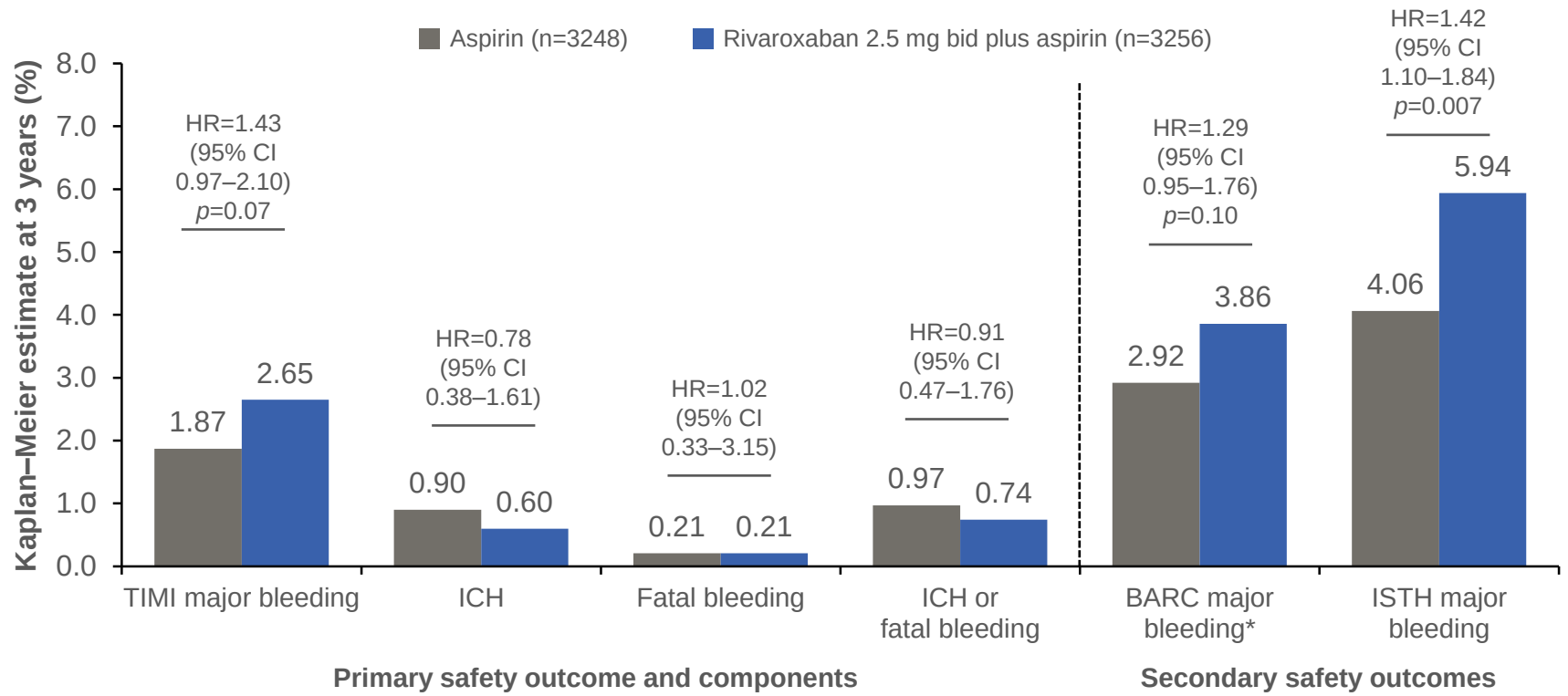
VOYAGER PAD

No Significant Excess in the Primary Safety Outcome of TIMI Major Bleeding with DPI Versus Aspirin



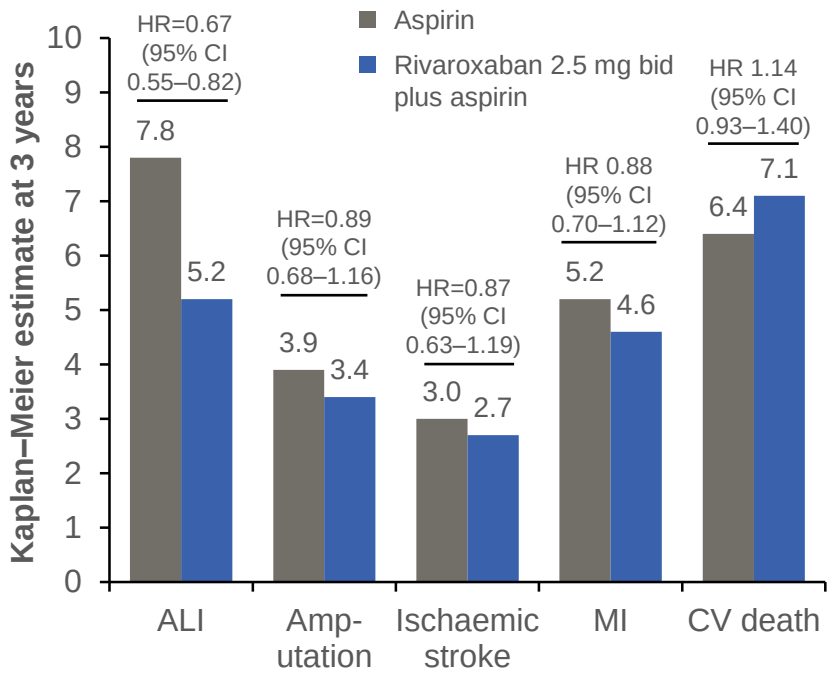
*Grade 3b or higher.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

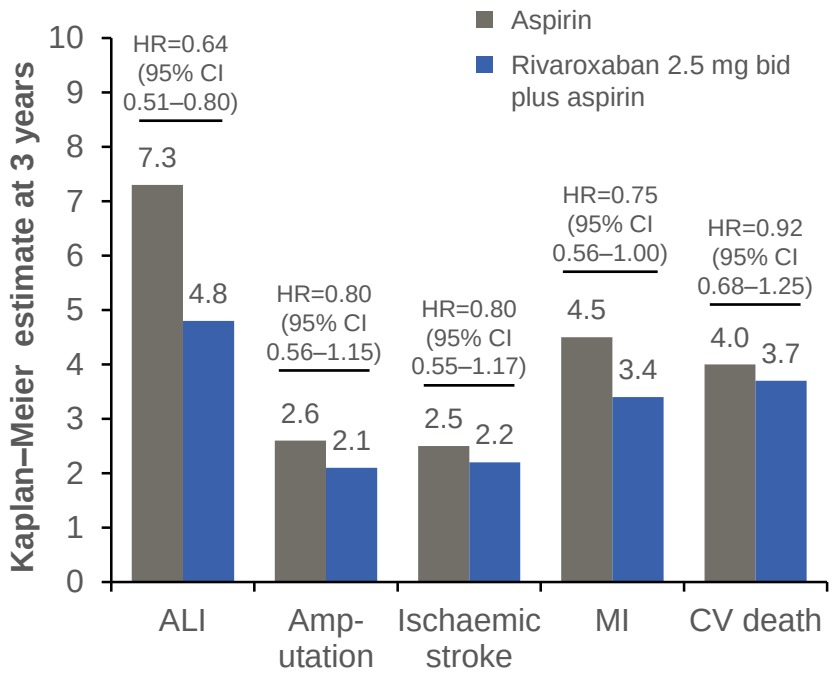
VOYAGER PAD

Efficacy Results Were Mostly Consistent Between Intention-to-Treat and On-Treatment Analyses

Intention-to-treat



On-treatment*



*Includes events from randomization until 2 days following permanent drug discontinuation.

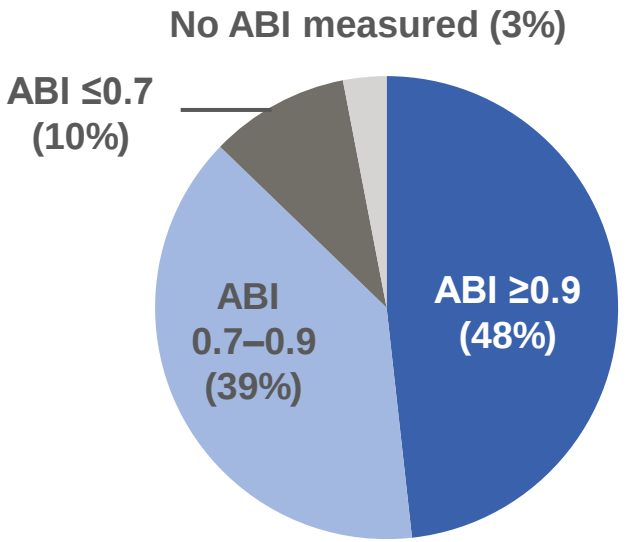
Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Rivaroxaban Vascular Dose plus Aspirin Was Investigated in Patients with Chronic PAD in COMPASS

Patients with an indication for DAPT or at high risk of bleeding were excluded from COMPASS[1]

Many patients who had recently undergone revascularization for MALE would have been excluded



~90% of patients with PAD had normal or moderately reduced ABI[2]

1. Bosch J *et al*. *Can J Cardiol* 2017;33:1027–1035. 2. Anand SS *et al*. *Lancet* 2018;391:219–229.

VOYAGER PAD and COMPASS Studied Complementary Patient Populations

	VOYAGER[1,2]	COMPASS[3,4]
PAD patient characteristics	◆ Symptomatic PAD only ◆ Undergoing peripheral revascularization ◆ Carotid disease not included	◆ Symptomatic or asymptomatic ◆ Chronic ◆ Carotid disease included as PAD
Allowance for clopidogrel	Allowed up to 6 months after qualifying revascularization	Not allowed at randomization
Primary endpoint	MACE*, ALI or major amputation of a vascular cause	MACE#
Efficacy results in patients with PAD	◆ 15% reduction in primary endpoint ◆ 33% reduction in ALI	◆ 28% reduction in primary endpoint ◆ 44% reduction in ALI‡
Safety results in patients with PAD	◆ No significant increase in TIMI major bleeding ◆ No increase in ICH or fatal bleeding	◆ 61% increase in modified ISTH major bleeding ◆ No increase in ICH or fatal bleeding

*MI, ischaemic stroke or CV death; #MI, stroke or CV death; ‡ALI was a prespecified outcome for patients with PAD.

1. Capell WH *et al*. *Am Heart J* 2018;199:83–91. 2. Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052. 3. Bosch J *et al*. *Can J Cardiol* 2017;33:1027–1035. 4. Anand SS *et al*. *Lancet* 2018;391:219–229.

Conclusions