4° CONVEGNO anticoagulazione.it

Attualità cliniche e di laboratorio. Aspetti sociali

7-8 FEBBRAIO 2019

BOLOGNA Hotel Savoia Regency

L'acido acetilsalicilico (ASA) per la prevenzione e terapia delle malattie vascolari: alti e bassi nella ricerca clinica

Associazione di acido acetilsalicilico (ASA) e rivaroxaban nei pazienti con cardio-vasculopatie: lo studio COMPASS

Francesco Dentali

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Università dell'Insubria

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

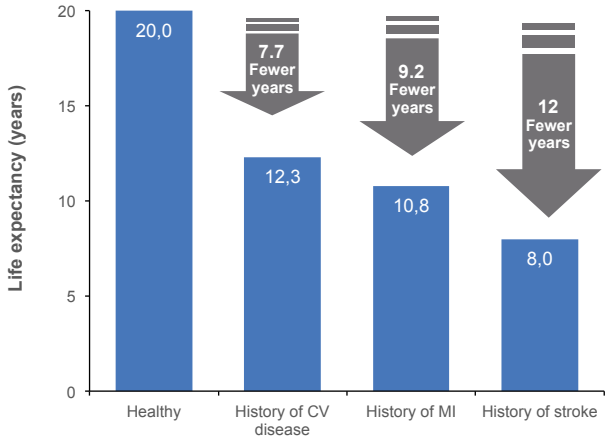
- Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
  - *Bayer*
  - *Sanofi*
  - *BMS/Pfizer*
  - *Boehringer*
  - *Daiichi*
  - *Alfa Wassermann*
  - *IL*

Cardiovascular Deaths

- >17.7 million people worldwide are estimated to have died from CV disease in 2015 and this number is projected to increase to 23.6 million/year by 2030[1]

1. WHO Factsheet. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/ [accessed August 2017] ;

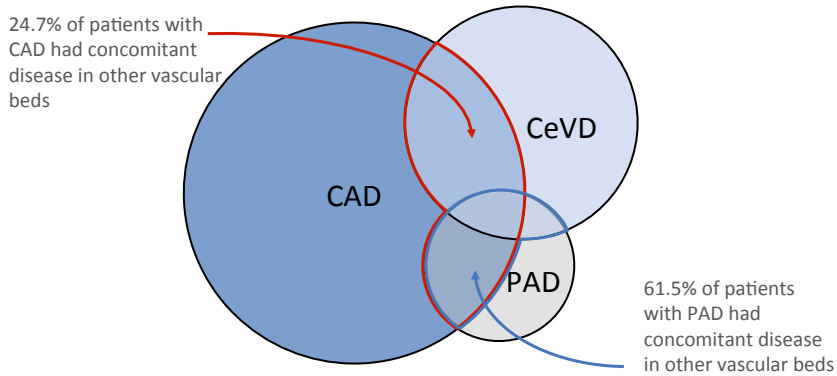
Life expectancy in patients aged 60 years ± atherosclerosis



Peeters et al. Eur Heart J 2002;23

Atherosclerosis Is a Polyvascular Disease

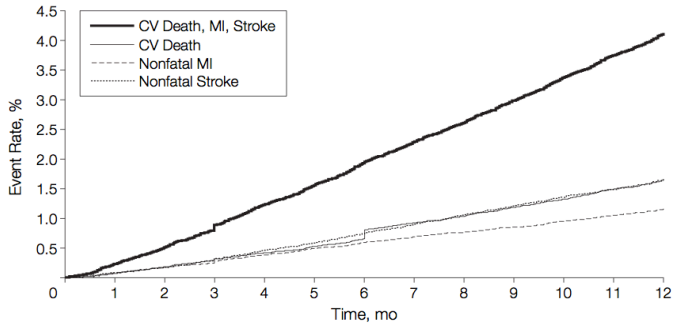
REACH: More than 3 in 5 patients with PAD have atherothrombotic disease also in other arterial territories



Percentages are calculated from the total population included in the REACH Registry. N=67,888
Bhatt DL *et al*, *JAMA* 2006;295:180–189

One-Year Cardiovascular Event Rates in Outpatients With Atherothrombosis

Event Curves for CV Death, Nonfatal Myocardial Infarction, and Stroke From Enrollment to 1 Year

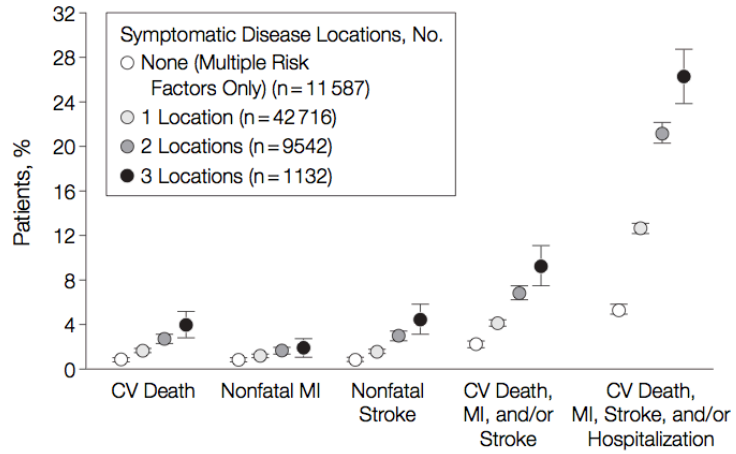


No. at Risk

CV Death, MI, Stroke	64 692	64 296	63 642	62 196	60 265	50 706	23 538
CV Death	64 749	64 555	64 194	63 029	61 339	51 798	24 099
Nonfatal MI	64 723	64 471	64 045	62 702	61 122	51 577	23 983
Nonfatal Stroke	64 718	64 466	63 979	62 576	60 910	51 360	23 889

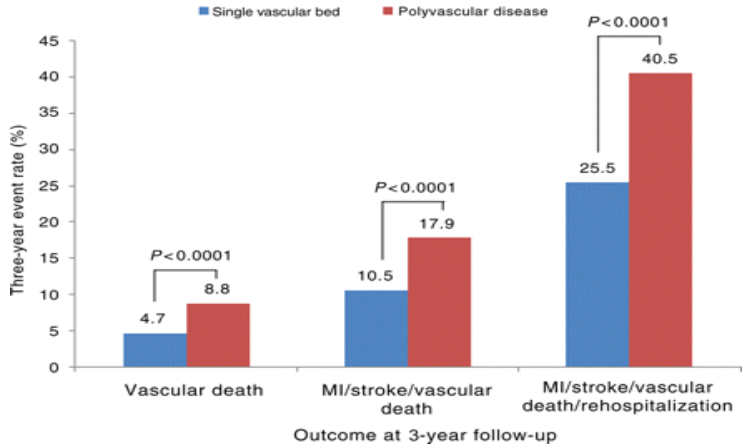
Steg et al; JAMA 2006

One-Year Cardiovascular Event Rates in Outpatients With Atherothrombosis



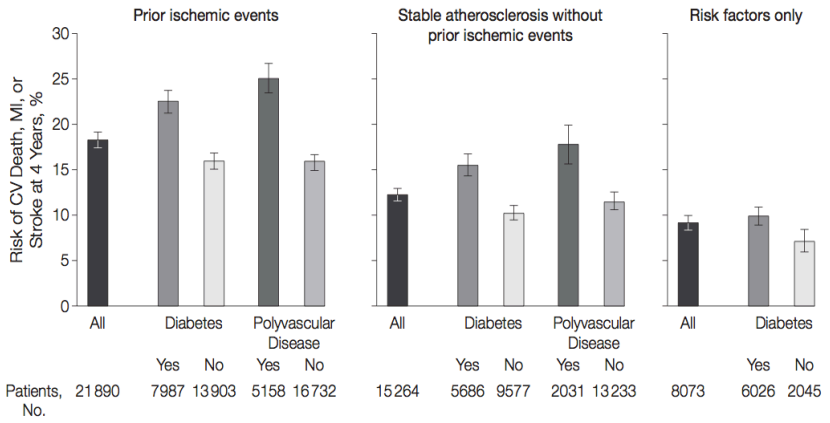
Steg et al; JAMA 2006

Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry



Alberts et al; EHJ 2009

Comparative Determinants of 4-Year Cardiovascular Event Rates in Stable Outpatients at Risk of or With Atherothrombosis



Bhatt et al; JAMA 2010

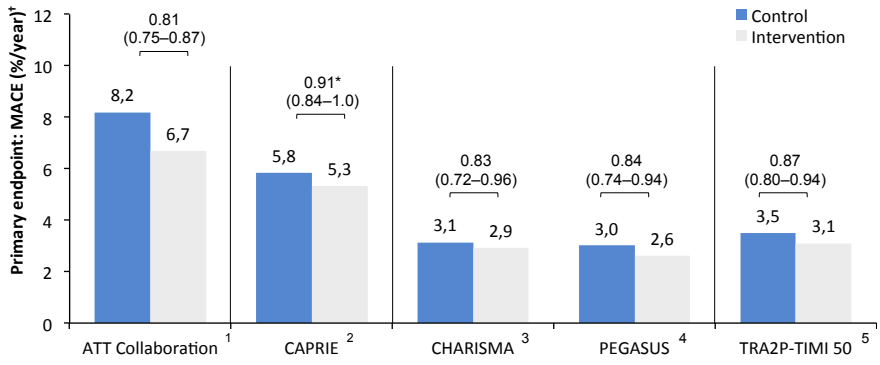
Proven effective secondary prevention therapies

Outcome	Lipid lowering (1 mmol/L)	BP lowering (10 mm Hg)	ACE (HOPE)	Aspirin
MACE	21%	20%	22%	19%
Mortality	9%	13%	16%	9%*
Stroke	15%	27%	32%	19%
MI	24%	17%	20%	20%

* CV death

Yusuf et al. N Engl j Med 2000 5; ATT Collaboration Lancet 2009
Etteha et al. lancet 2016 CTT Collaboration Lancet 2015
Collins et al. Lancet 2016

Risk of Vascular Events Despite Optimal Medical Therapy

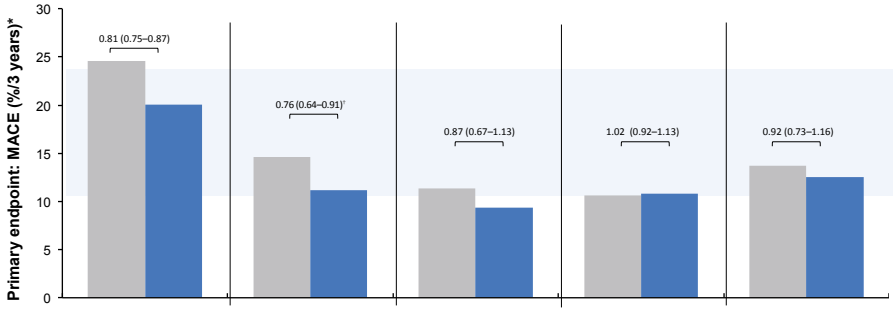


% Use of key therapies in intervention arm	Control ‖ Aspirin	Aspirin ‖ Clopidogrel	Placebo + Aspirin ‖ Clopidogrel + Aspirin	Placebo + Aspirin ‖ Ticagrelor + Aspirin	Vorapaxar ‖ Placebo + Aspirin ± Thienopyridine
ACEI/ARB	*Meta-analysis of 16 trials*	*NR*	*up to 85.3*	*80.4*	*73.5*
Statin/ lipid-lowering		*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

1. ATT Collaboration. *Lancet* 2009; 2. CAPRIE Steering Committee. *Lancet* 1996; 3. Bhatt *et al. J Am Coll Cardiol* 200; 4. Bonaca *et al. N Engl J Med* 2015; 5. Morrow *et al. N Engl J Med* 2012

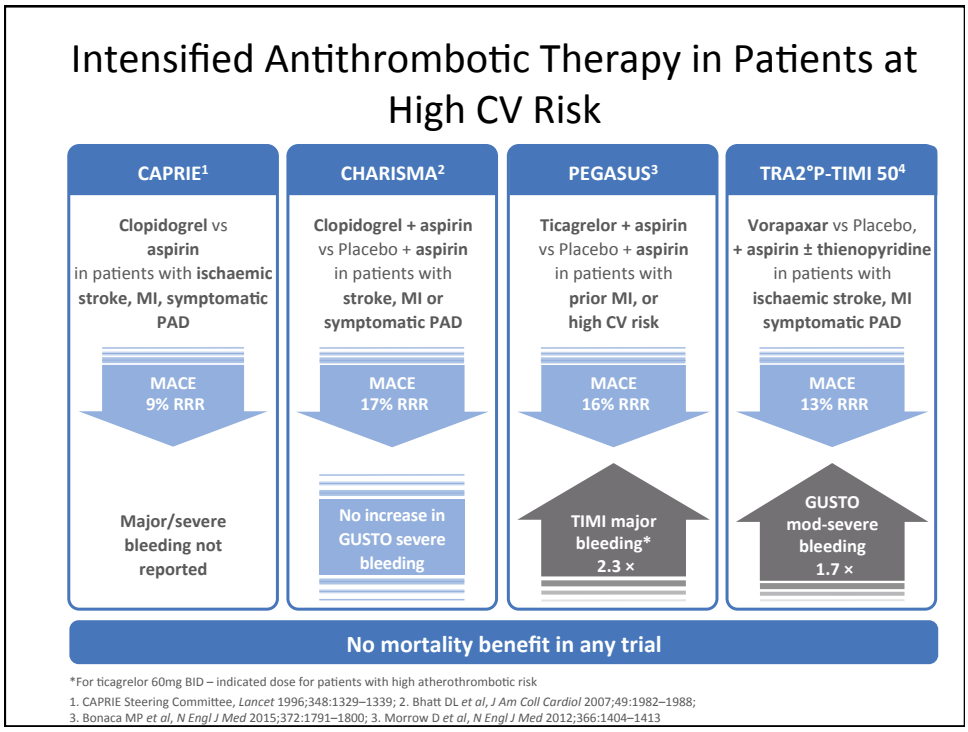
Risk of Vascular Events Despite Optimal Medical Therapy in PAD patients

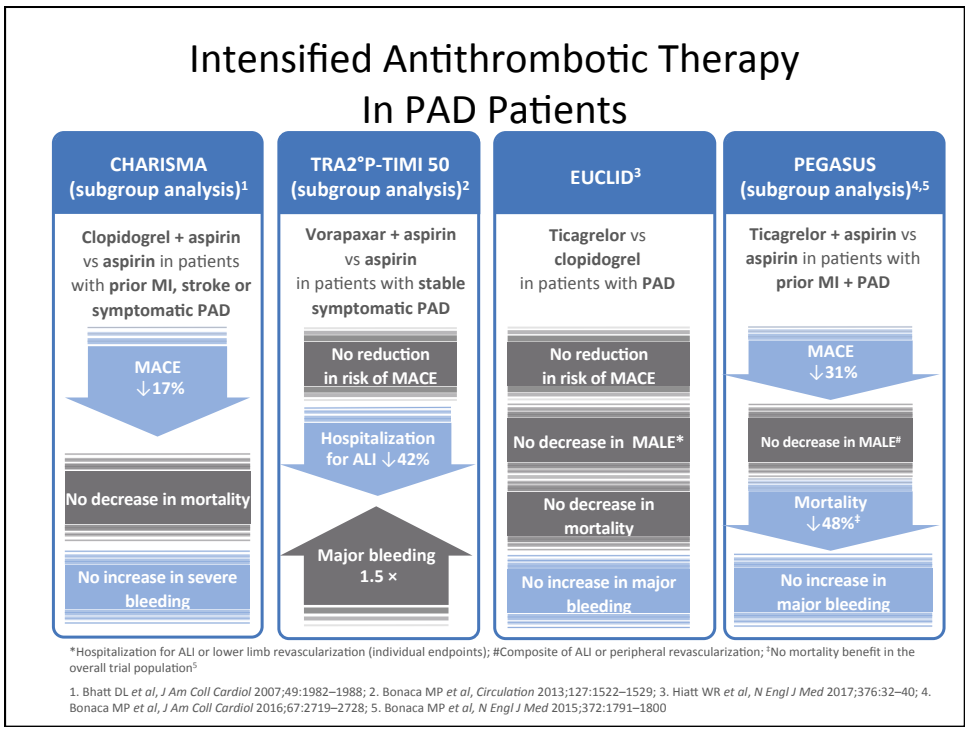


% Use of key therapies in intervention arm	ATTC[1] *Meta-analysis: secondary prevention*	CAPRIE[2] *Subgroup: symptomatic PAD*	CHARISMA[3] *Subgroup: Prior MI, stroke or symptomatic PAD*	EUCLID[4] *PAD*	WAVE[5] *PAD*
ACEi/ARB	Meta-analysis of 16 trials	Not reported	up to 85.3	up to 65.5	50.4
statin/ lipid-lowering			77.1–89.3	73.7	55.1

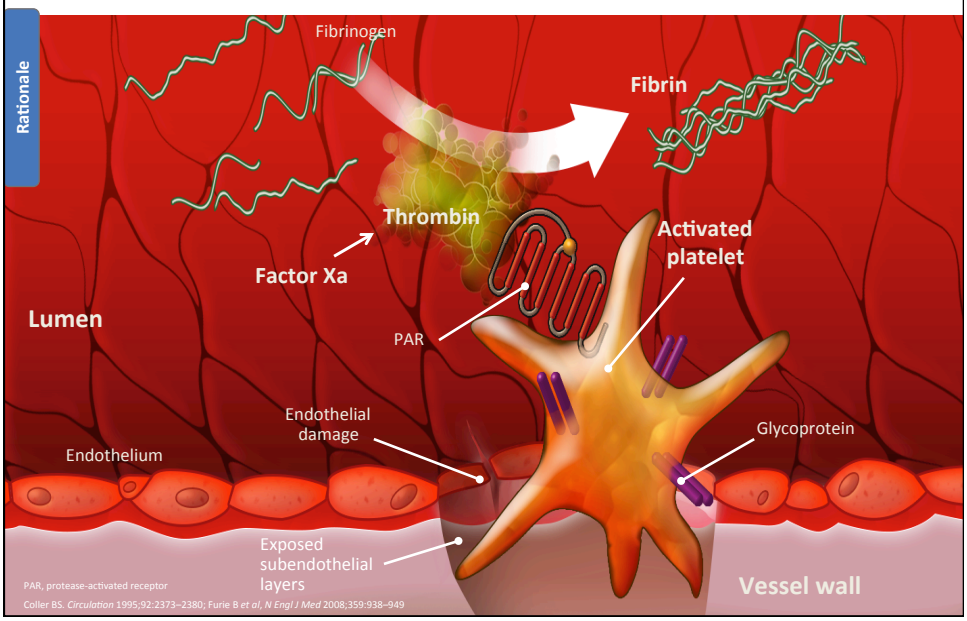
*Estimates calculated from: annual rates (ATTC & CAPRIE), % across 28 months of median follow-up (CHARISMA), 3-year Kaplan-Meier event rates (EUCLID), and % across 35 months of mean follow up (WAVE); †Calculated from relative risk reductions

1. ATT Collaboration. *Lancet* 2009;; 2. CAPRIE Steering Committee. *Lancet* 1996; 3. Bhatt et al. *J Am Coll Cardiol* 2007; 4. Hiatt et al. *N Engl J Med* 201; 5. The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. *N Engl J Med* 2007..





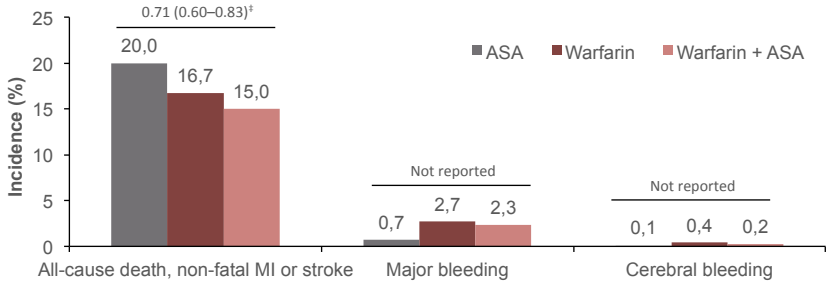
Thrombin Effect on Fibrin Generation and Platelet Activation



Warfarin Reduced CV Events in Patients with Prior MI but with Increased Bleeding

WARIS II trial: warfarin* versus ASA#

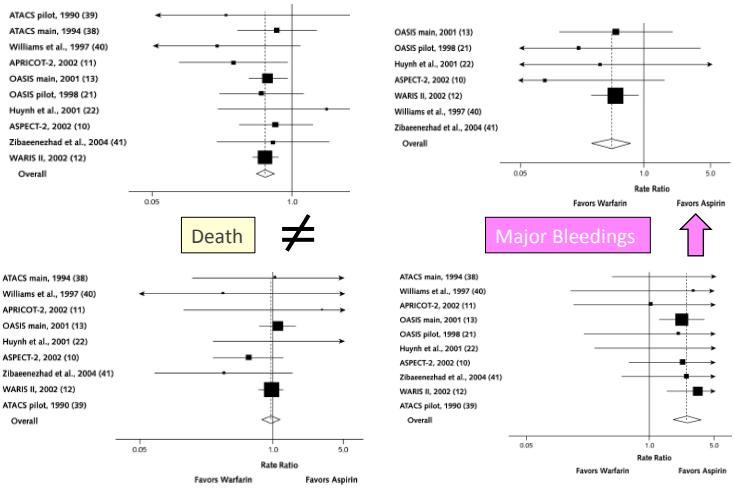
- 3630 patients who had survived acute MI
  - Compared with ASA monotherapy, warfarin, in combination with ASA or as monotherapy, reduced risk of composite of all-cause death, non-fatal MI or thromboembolic cerebral stroke, but with increased risk of bleeding



Data shown above the lines are hazard ratio (95% confidence interval) and *p*-value. *INR 2.8–4.2 in monotherapy and 2.0–2.5 in combination with ASA; #ASA: 160 mg od in monotherapy and 75 mg od in combination with warfarin; ‡warfarin + ASA vs ASA
Hurlen M *et al*, *N Engl J Med* 2002;347:969–974

Warfarin plus Aspirin after ACS

Myocardial Infarction ↓ Ischaemic Stroke ↓



Death ≠

Major Bleedings ↑

n=5938

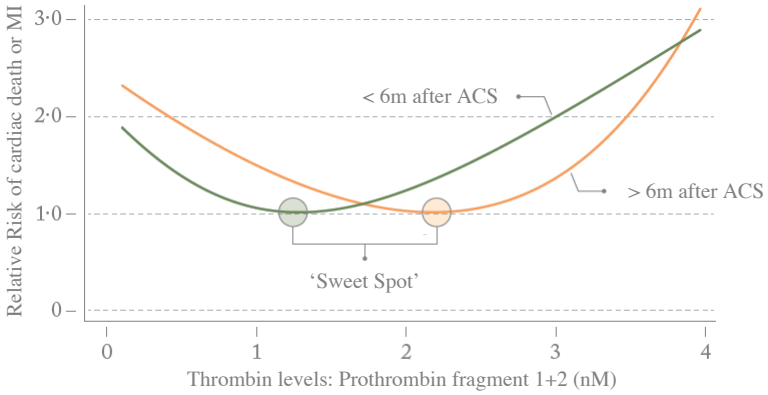
Rothberg et al. Ann Intern Med 2005

Phase II Trials of Direct Oral Anticoagulants in ACS

	Ximelagatran	Dabigatran Etexilate	Apixaban	Rivaroxaban	Darexaban
Acronym	**ESTEEM**	**REDEEM**	**APPRAISE-1**	**ATLAS TIMI-46**	**RUBY-1**
n	1900	1861	1715	3491	1279
Publication	Lancet 2003	Eur Heart J 2011	Circulation 2009	Lancet 2009	Eur Heart J 2011
STEMI/NSTE-ACS, %	66/34	60/40	61-67/33-39	52/48	71/29
Duration of therapy, months	6	6	6	6	6
Dasage	24-60 mg bid	50-150 mg bid	10-20 mg QD/ 2.5-10 mg bid	5-20 mg qd	10-60 mg QD/ 5-30 mg bid
Safety outcome, HR (95% CI)	24 mg: 2.07 (0.67–6.41) 36 mg: 0.70 (0.14–3.48) 48 mg: 3.42 (1.24–9.42) 60 mg: 1.67 (0.51–5.46)	50 mg: 1.82 (0.77–4.29) 75 mg: 2.44 (1.05–5.65) 110 mg: 3.36 (1.60–7.91) 150 mg: 3.88 (1.73–8.74)	2.5 mg bid.: 1.78 (0.91–3.48) 10 mg bid: 2.45 (1.31–4.61) 10-mg bid and 20-mg Q.D. arms terminated because of a high bleeding* risk	Stratum 1: 5 mg: 0.81 (0.09–7.23) 10 mg: 3.40 (0.91–12.65) 20 mg: 6.43 (1.94–21.37) Stratum 2: 5 mg: 2.17 (0.91–5.18) 10 mg: 3.34 (2.15–5.19) 15 mg: 3.41 (1.97–5.89) 20 mg: 4.56 (2.83–7.33)	10 mg Q.D.: 1.78 (0.68–4.60) 30 mg Q.D.: 1.83 (0.71–4.75) 60 mg Q.D.: 2.43 (0.98–5.97) 5 mg bid: 2.05 (0.81–5.15) 15 mg bid: 2.27 (0.92–5.59) 30 mg bid: 3.80 (1.66–8.68)

*Bleeding definition: International Society on Thrombosis and Haemostasis major and clinically relevant nonmajor bleeding for dabigatran etexilate, apixaban, and darexaban; Thrombolysis In Myocardial Infarction major, Thrombolysis In Myocardial Infarction minor, or bleeding requiring medical attention for rivaroxaban.

Both Low & High Thrombin levels Increase Risk of CV Events



**A U-shaped curve exists in which higher rates of cardiac death or MI were seen at both very low and very high thrombin levels –
possibly due to thrombin being both a promotor and inhibitor of coagulation, depending on its concentration**

1. Ardissino D, *et al. Blood* 2003;102:2731–5; 2. Gibbs CS *et al. Nature* 1995;378:413–6; 3. Griffin JH *et al. Nature* 1995;378:337–8

CAD

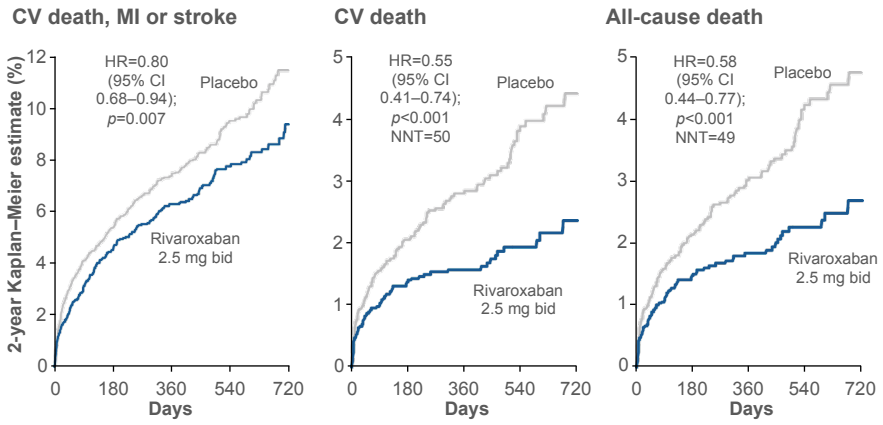
Rivaroxaban in Acute Coronary Syndrome

- The oral anticoagulant warfarin plus aspirin had previously been shown to reduce major CV events in patients with prior MI, although at the cost of increased major and severe (cerebral) bleeding[1]
- Rivaroxaban vascular dose has been shown to reduce the risk of atherothrombotic events, including death, in patients with ACS (ATLAS ACS 2 TIMI 51)[2]
- Rivaroxaban vascular dose 2.5 mg bid with single antiplatelet has an acceptable safety profile in patients with CAD (ATLAS ACS TIMI 48, ATLAS ACS 2 TIMI 51 and GEMINI ACS 1)[2-4]

1. Hurlen M *et al, N Engl J Med* 2002;347:969–974; 2. Mega JL *et al, N Engl J Med* 2012;366:9–19; 3. Mega JL *et al, Lancet* 2009;374:29–38;
4. Ohman EM *et al, Lancet* 2017;389:1799–1808

ATLAS ACS 2 TIMI 51

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

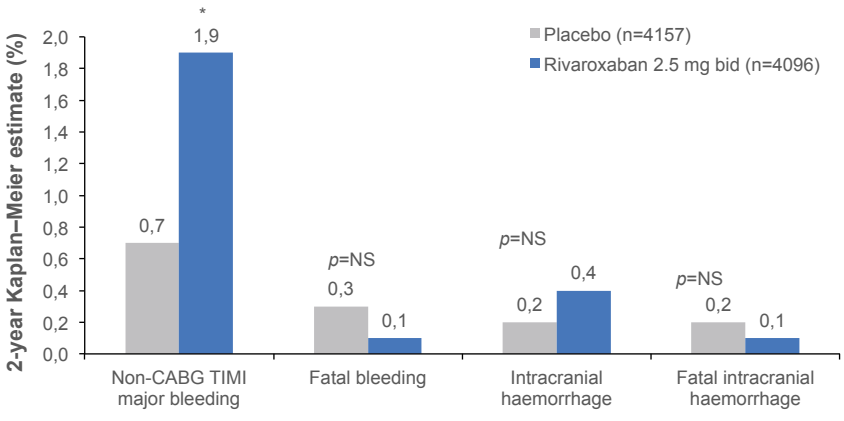


CI, confidence interval; HR, hazard ratio; NNT, number needed to treat
Patients also received antiplatelet standard of care: ASA + thienopyridine (~93%) or ASA alone (~7%)

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

Bleeding Events

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



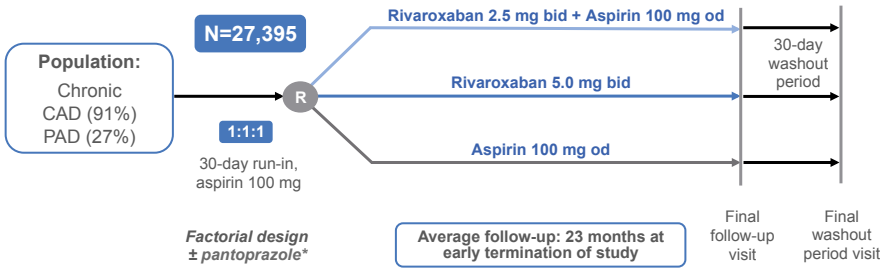
CABG, coronary artery bypass grafting; NS, not significant; TIMI, Thrombolysis In Myocardial Infarction
*$p<0.001$ vs placebo

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

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

COMPASS

CAD PAD

Inclusion and Exclusion Criteria

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

COMPASS

CAD PAD

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

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

COMPASS

CAD PAD

Modified ISTH Major Bleeding Definition

ISTH major bleeding[1]

- Fatal bleeding, *and/or*
- Symptomatic bleeding in a critical area or organ (such as intracranial), *and/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***

Modified ISTH major bleeding (COMPASS)

- 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***

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

COMPASS

Key Baseline Characteristics

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

COMPASS

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)

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

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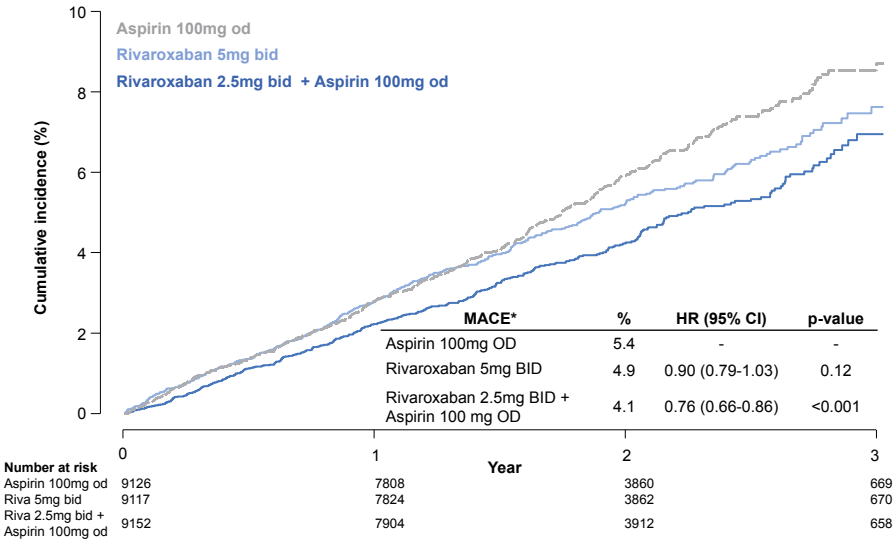
CV Death, Stroke and MI



*Rates as at mean follow up of 23 months

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

COMPASS

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

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	Aspirin 100 mg N=9126
Modified major ISTH bleeding	288 (3.1%)	170 (1.9%)
Fatal	15 (0.2%)	10 (0.1%)
Non-fatal ICH*	21 (0.2%)	19 (0.2%)
Non-fatal other critical organ*	42 (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	
	HR (95% CI)	*p*-value
Modified ISTH major bleeding	1.70 (1.40–2.05)	<0.001
Fatal	1.49 (0.67–3.33)	0.32
Non-fatal ICH*	1.10 (0.59–2.04)	0.77
Non-fatal other critical organ*	1.43 (0.89–2.29)	0.14

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

- **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

COMPASS

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

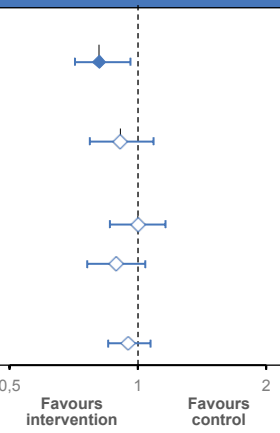
*pre-specified threshold p=0.0025

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

COMPASS

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



†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

CAD

COMPASS Enrolled over 24,000 Patients with Advanced, Chronic CAD

CAD definition	Number of patients (% of CAD population)[1]
All patients with CAD	24,824
Prior MI	17,028 (69%)
<1 year	1238 (5%)
1–<2 years	2341 (9%)
2–<5 years	4893 (20%)
≥5 years	8520 (34%)
Multivessel coronary disease*	15,469 (62%)
Prior PCI	14,862 (60%)
Prior CABG	7845 (32%)
Patients randomized immediately post-CABG	1448 (6%)

Half of all previous MIs occurred ≥5 years prior to enrolment in COMPASS[1]

*Refers to stenosis of ≥50% in 2 or more coronary arteries, confirmed using invasive coronary angiography, or non-invasive imaging or stress studies suggestive of significant ischaemia in ≥2 coronary territories; or in 1 coronary territory if at least 1 other territory has been revascularized[2]

1. Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7;
2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

COMPASS

CAD

Baseline Characteristics and Use of Guideline-Recommended Therapies

Characteristic	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261
Age, years (median and IQR)	69 (65–73)	69 (65–73)	69 (65–73)
Cardiovascular risk factors			
Current smoker, %	1679 (20)	1680 (20)	1687 (20)
Former smoker,%	3944 (47)	3889 (47)	3908 (47)
Diabetes, %	3043 (37)	3015 (37)	3040 (37)
Hypertension, %	6280 (76)	6214 (75)	6218 (75)
PAD, %	1656 (20)	1609 (20)	1641 (20)
Heart failure, %	1909 (23)	1893 (23)	1912 (23)
Prior stroke, %	279 (3)	250 (3)	268 (3)
Concomitant medications			
Lipid lowering therapy, %	7667 (92)	7604 (92)	7573 (92)
ACE inhibitor/ARB, %	5970 (72)	6059 (73)	5939 (72)
Calcium channel blocker, %	2177 (26)	2136 (26)	2224 (27)
Beta blocker, %	6124 (74)	6143 (75)	6154 (75)

Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

COMPASS

CAD

MACE

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261	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	347 (4)	411 (5)	460 (6)	0.74 (0.65–0.86)	<0.0001	0.89 (0.78–1.02)	0.094
CV death	139 (2)	175 (2)	184 (2)	0.75 (0.60–0.93)	0.010	0.95 (0.77–1.17)	0.63
Stroke	74 (1)	105 (1)	130 (2)	0.56 (0.42–0.75)	<0.0001	0.81 (0.62–1.05)	0.10
Ischaemic/ unspecified	60 (1)	79 (1)	120 (2)	0.50 (0.36–0.67)	<0.0001	0.66 (0.50–0.87)	0.0037
Haemorrhagic	14 (<1)	27 (<1)	10 (<1)	1.39 (0.62–3.32)	0.43	2.70 (1.31–5.59)	0.0051
MI	169 (2)	176 (2)	195 (2)	0.86 (0.71–1.05)	0.15	0.90 (0.74–1.11)	0.33

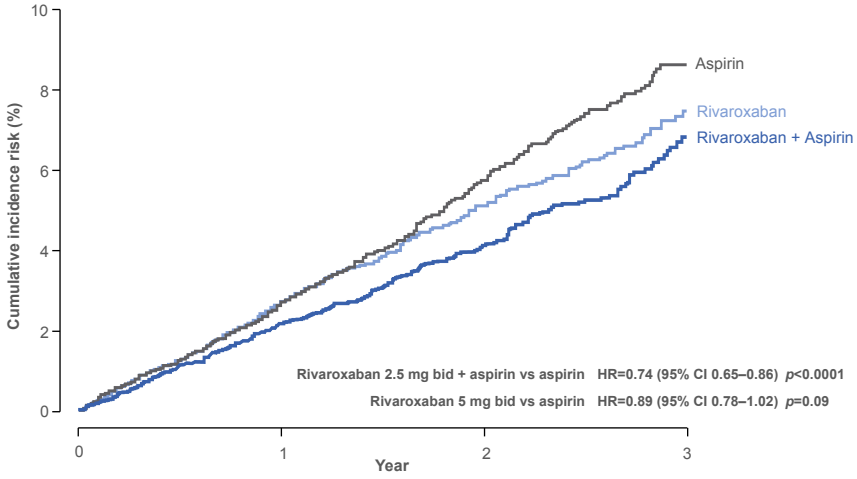
Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

COMPASS

CAD

MACE

Stroke/MI/Cardiovascular death



Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

COMPASS

CAD

Bleeding Rates

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Major bleeding	263 (3)	236 (3)	158 (2)	1.66 (1.37–2.03)	<0.0001	1.51 (1.23–1.84)	<0.0001
Fatal	14 (<1)	12 (<1)	9 (<1)	1.55 (0.67–3.58)	0.30	1.33 (0.56–3.16)	0.51
ICH	19 (<1)	32 (<1)	19 (<1)	0.99 (0.52–1.87)	0.98	1.69 (0.96–2.99)	0.065
Critical organ	36 (<1)	42 (1)	25 (<1)	1.42 (0.85–2.36)	0.18	1.70 (1.04–2.79)	0.033
Other	194 (2)	150 (2)	105 (1)	1.85 (1.46–2.34)	<0.0001	1.44 (1.12–1.84)	0.0041

No significant increase in critical organ bleeding including intracranial or fatal bleeding

Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

COMPASS

Inclusion and Exclusion Criteria in Patients with Chronic PAD

Key inclusion criteria

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

Key exclusion criteria

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

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

COMPASS

PAD

PAD-Specific Limb Outcomes

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

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

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PAD

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

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

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

COMPASS

Patients with Symptomatic PAD or Concomitant CAD and PAD

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

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

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

COMPASS

Baseline Characteristics

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

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

COMPASS

MACE

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%)	Rivaroxaban 5 mg bid N=2474 N (%)	Aspirin N=2504 N (%)	Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI)	*p*-value	Rivaroxaban 5 mg bid vs aspirin HR (95% CI)	*p*-value
MACE	126 (5)	149 (6)	174 (7)	0.72 (0.57–0.90)	0.0047	0.86 (0.69–1.08)	0.19
CV death	64 (3)	66 (3)	78 (3)	0.82 (0.59–1.14)	–	0.86 (0.62–1.19)	–
Stroke	25 (1)	43 (2)	47 (2)	0.54 (0.33–0.87)	–	0.93 (0.61–1.40)	–
MI	51 (2)	56 (2)	67 (3)	0.76 (0.53–1.09)	–	0.84 (0.59–1.20)	–

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

COMPASS

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

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

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

COMPASS

Net Clinical Benefit

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

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

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

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

COMPASS

Conclusions

- Rivaroxaban vascular dose 2.5 mg bid plus aspirin reduced the composite endpoint of stroke, MI or CV death
- Significant reduction of MALE and Major amputations
- Despite an expected increase in major bleeding events with rivaroxaban 2.5 mg bid plus aspirin, no significant increase was observed in fatal or critical organ bleeding
- This dual pathway inhibition of rivaroxaban vascular dose and aspirin may represent a major advance in the management of these patients