Primary Prevention with Anticoagulation: The COMPASS Trial

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Disclosures

Speaker has no relevant financial relationships with commercial interests.

Case Study

55 year old male with a history of peripheral and coronary artery disease, DM, HTN and current smoking presents to the office for routine evaluation regarding the management of his cardiovascular and peripheral arterial disease. He is currently not having any symptoms of claudication and no evidence of non-healing wounds or ulcerations. He states he walks daily.

- Home medications include: clopidogrel 75 mg daily, atorvastatin 40 mg po daily, lisinopril 20 mg po daily and metoprolol 50 mg po BID.

- In addition to counseling the patient on the importance of smoking cessation, what additional medication could be added or changed to his current regimen that may provide him the most benefit in reducing further cardiovascular events?

Case Study

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- A. Discontinue clopidogrel and add rivaroxaban 2.5 mg BID and asa 81 mg daily
- B. Add Rivaroxaban 2.5 mg BID and aspirin 81 mg daily to clopidogrel
- C. Discontinue clopidogrel and add rivaroxaban 2.5 mg BID
- D. Discontinue clopidogrel and add cilostazol 100 mg BID
- E. None of the above

Case Study

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- E. None of the above

COMPASS

Rivaroxaban with or without aspirin in stable cardiovascular disease

•John W. Eikelboom, M.B., B.S., , Stuart J. Connolly, M.D., Jackie Bosch, Ph.D., Gilles R. Dagenais, M.D., Robert G. Hart, M.D.,, Olga Shestakovska, M.Sc., ,Rafael Diaz, M.D.,, Marco Alings, Ph.D., Eva M. Lonn, M.D., Sonia S. Anand, M.D., Petr Widimsky, M.D., Masatsugu Hori, M.D., for the COMPASS Investigators NEJM **October 19, 2017**

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

Clinical Question

- In patients with established stable atherosclerotic disease, is rivaroxaban plus aspirin more effective than aspirin alone in reducing cardiovascular death, stroke, or nonfatal MI?

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

COMPASS Background

- An estimated 17.3 million people worldwide died from cardiovascular disease in 2012 and this number is projected to increase to 23.6 million per year by 20301

  Known coronary artery disease (CAD) and peripheral artery disease (PAD) are strong predictors of risk of future cardiovascular events [1,2]

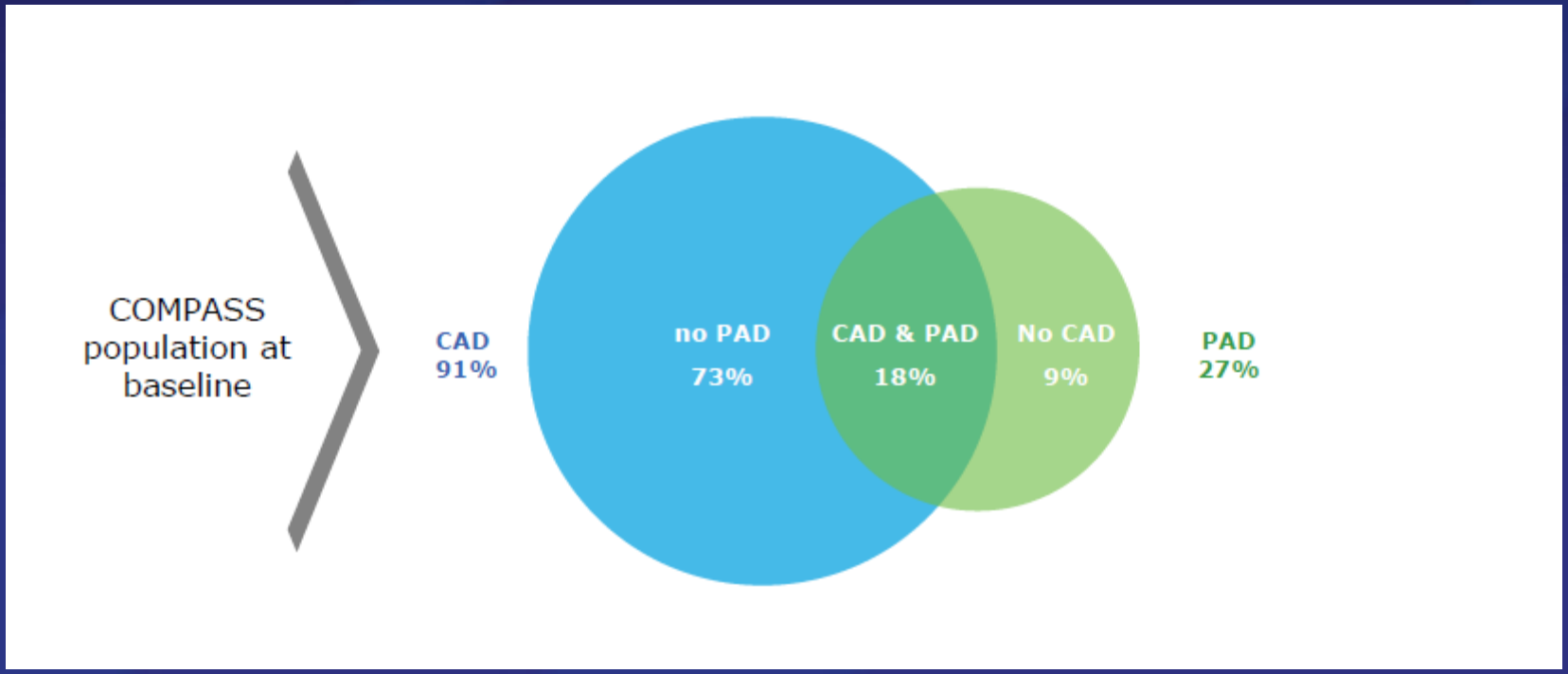
- 5-10% of patients with cardiovascular disease have recurrent events each year [3]

- When used for secondary prevention, aspirin compared to placebo reduced the risk of major adverse cardiovascular events by 19% and resulted in a 9% lower risk of cardiovascular death.[4]

•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence 1. Mozaffarian D, et al; AHA Circulation 2016;133:e38-360. 2. Hankey GJ, Norman PE, Eikelboom JW. JAMA 2006;295:547-53. 3. Bhatt DL, et al. NEJM 2010;304:1350-7. 4. Antithrombotic Trialists' (ATT) Collaboration, et al. Lancet 2009;373:1849-60.

COMPASS Background

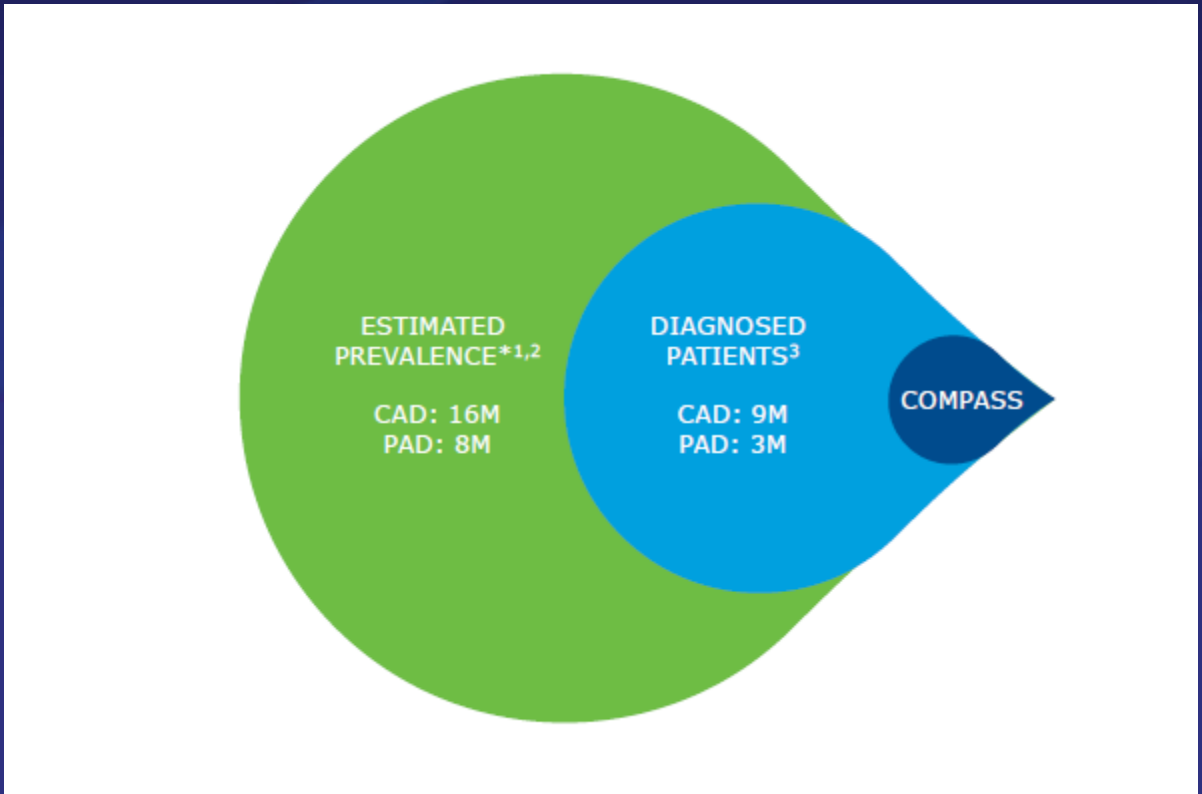
COMPASS Patient Demographics: Polyvascular Population



•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Adapted from 1. Eikelboom JW et al. Doi 10.1056 NEJMoa1709118 2. Bosch J *et al. Can J Cardiol.* 2017;33:1027-1035 3. Connolly SJ et al CAD COMPASS submitted

COMPASS Background

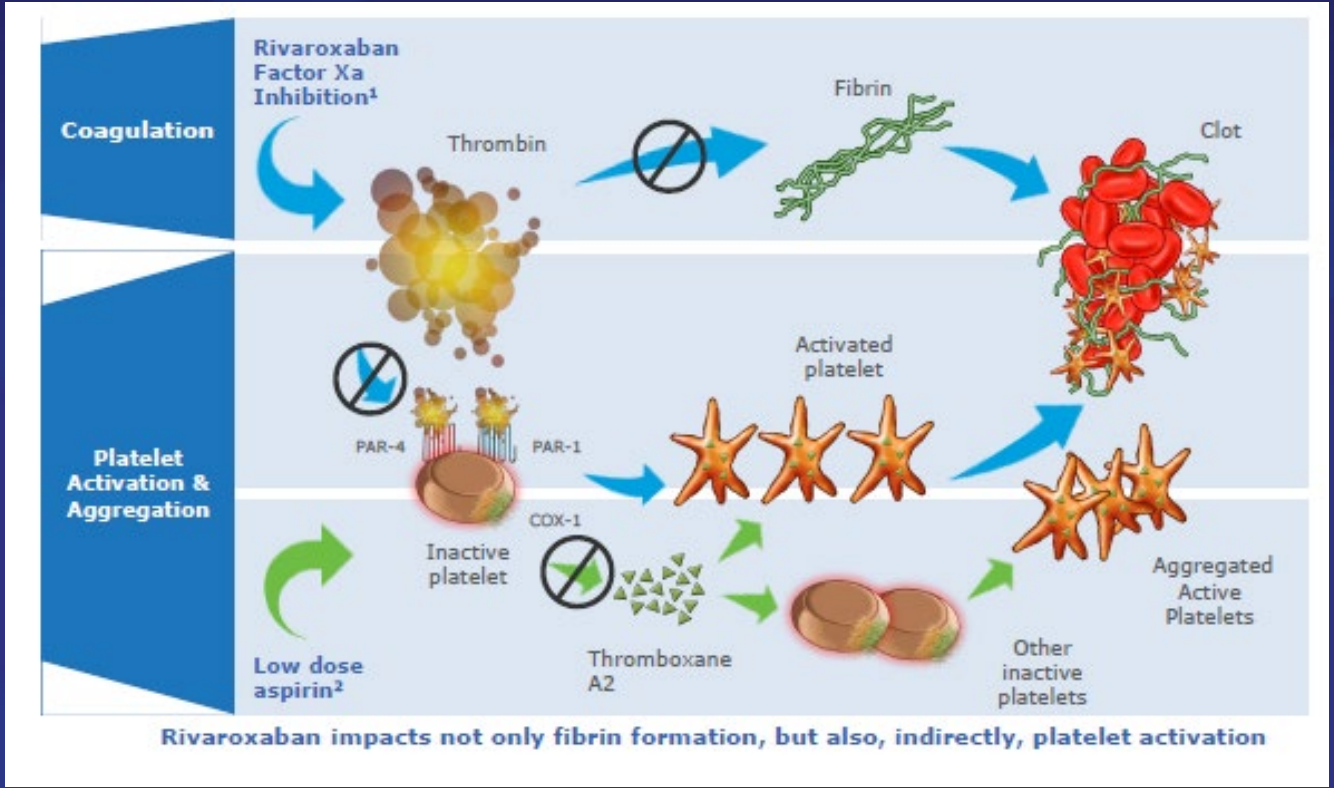
Targeted Patient Population Under Evaluation



•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Adapted from **1.** Benjamin EJ et al. *Circulation*. 2017;135:e146-e603. **2.** Gerhard-Herman MD et al. *J Am Coll Cardiol*. 2017;69(11):1465-1508. **3.** Data on file. Janssen Pharmaceuticals, Inc.

COMPASS Background

Working hypothesis: Rivaroxaban & Aspirin SynergisticallyTarget Essential Components of Atherothrombosis



•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Adapted from1. Adapted from Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28 2. Adapted from Mitchell JRA. *Br Med J*. 1981;282:590-4. Perzborn, E et al, J Cardiovasc Pharmacol Ther 2015; 20 (6): 554-562

COMPASS Background

COMPASS Peripheral Arterial Disease (PAD) Rationale

- Peripheral Arterial Disease (PAD) patients have widespread atherosclerosis and increased risk of CV & limb adverse outcomes. [1]
- Vascular events are high despite effective interventions. [2]
- Few therapies have clearly reduced both Major Adverse CV Events (MACE) and Major Adverse Limb Events (MALE). [3]

1.Bhatt DL, et al. *JAMA* 2010; **304:** 1350–57. 2.Gerhard-Herman MD, et al. *Circulation* 2017; **135:** e726–79. 3. European Stroke Organisation, et al. *Eur Heart J* 2011; **32:** 2851–906.

COMPASS Background

Patients with Chronic CAD or PAD Remain At Risk of Vascular Events

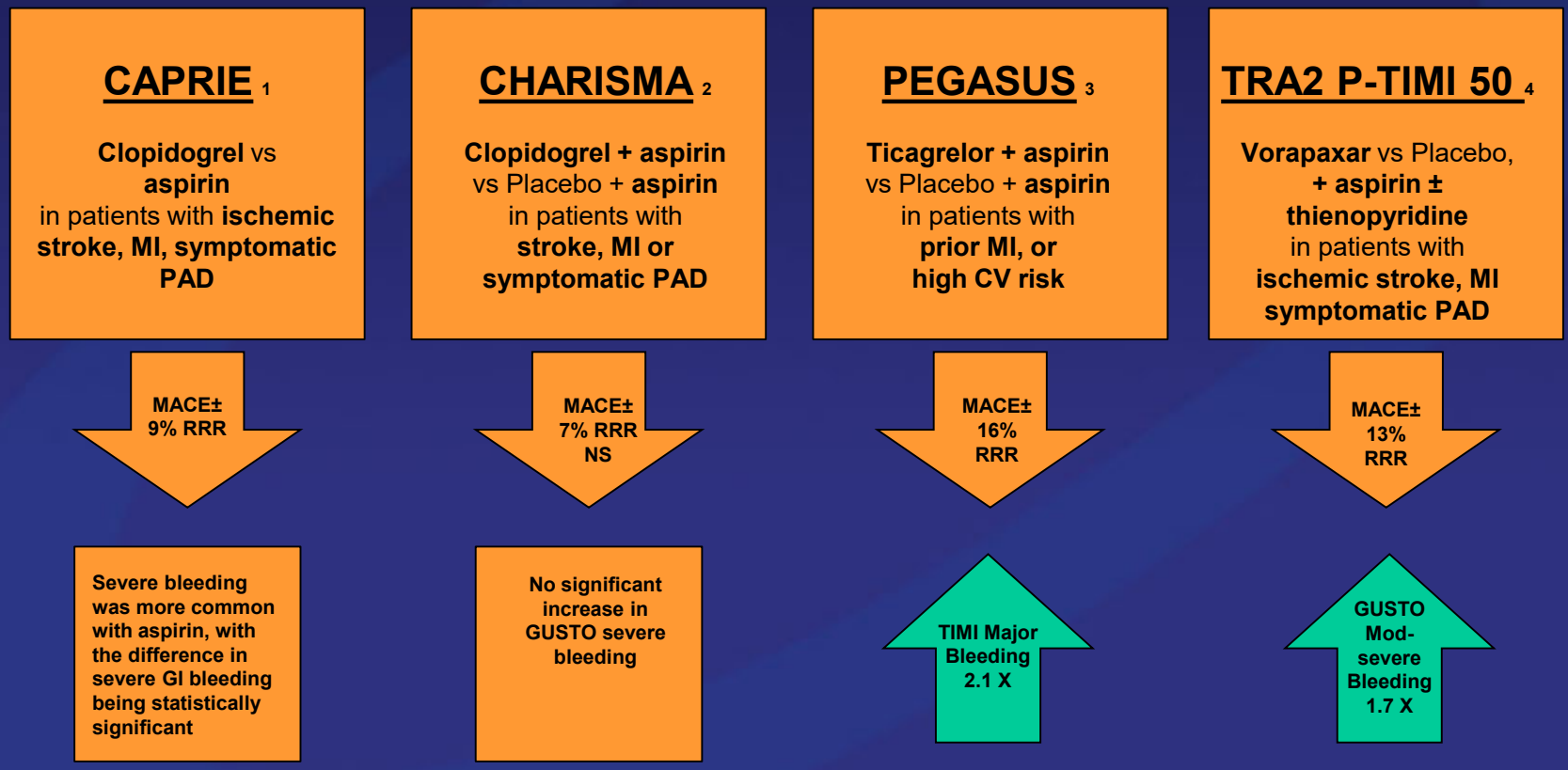
Results for primary endpoint MACE: CV death, MI & stroke

Study Title/ Population	Treatment Arms	Control %/year	Intervention %/year	HR (95%CI)	*p*-value
ATT Collaboration1 ***Meta-analysis*** **Prior MI, stroke/TIA**	Aspirin // Control	8.19	6.69	0.81 (0.75-0.87)	<0.00001
CAPRIE2 **Ischemic stroke, MI (>35d), symptomatic PAD**	Clopidogrel // Aspirin	5.83	5.32	NR	0.043
CHARISMA3 ***Sub-analysis*** **Prior MI, ischemic stroke or symptomatic PAD**	Clopidogrel + Aspirin // Placebo + Aspirin	8.8	7.3	0.83 (0.74-0.95)	0.01
PEGASUS4 **Prior MI (1-3y), high CV risk**	60 mg Ticagrelor + Aspirin // Placebo + Aspirin 90 mg Ticagrelor + Aspirin // Placebo + Aspirin	9.04 9.04	7.77 7.85	0.84 (0.74-0.95) 0.85 (0.75-0.96)	0.008 0.004
TRA2P-TIMI505 **Prior MI (2w-12m), ischemic stroke,** **symptomatic PAD**	Vorapaxar // Placebo, on top of SoC including Aspirin □ Thienopyridine	10.5	9.3	0.87 (0.80-0.94)	<0.001

- DATA DEPICTED ON THIS SLIDE ARE NOT HEAD-TO-HEAD COMPARISONS and originate from separate trials for respective agents. Due to differences in trial design, this table should not be used for direct comparison between agents
- With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence 1. ATT Collaboration. *Lancet* 2009; 373:1849–60 2. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–39; 3. Bhatt DL, et al. *J Am CollCardiol* 2007;49 (19): 1982-8; 4 Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404-13

COMPASS Background

Previous Trials Investigating Intensified Antithrombotic Therapy in Patients At High CV Risk Showed Mixed Results



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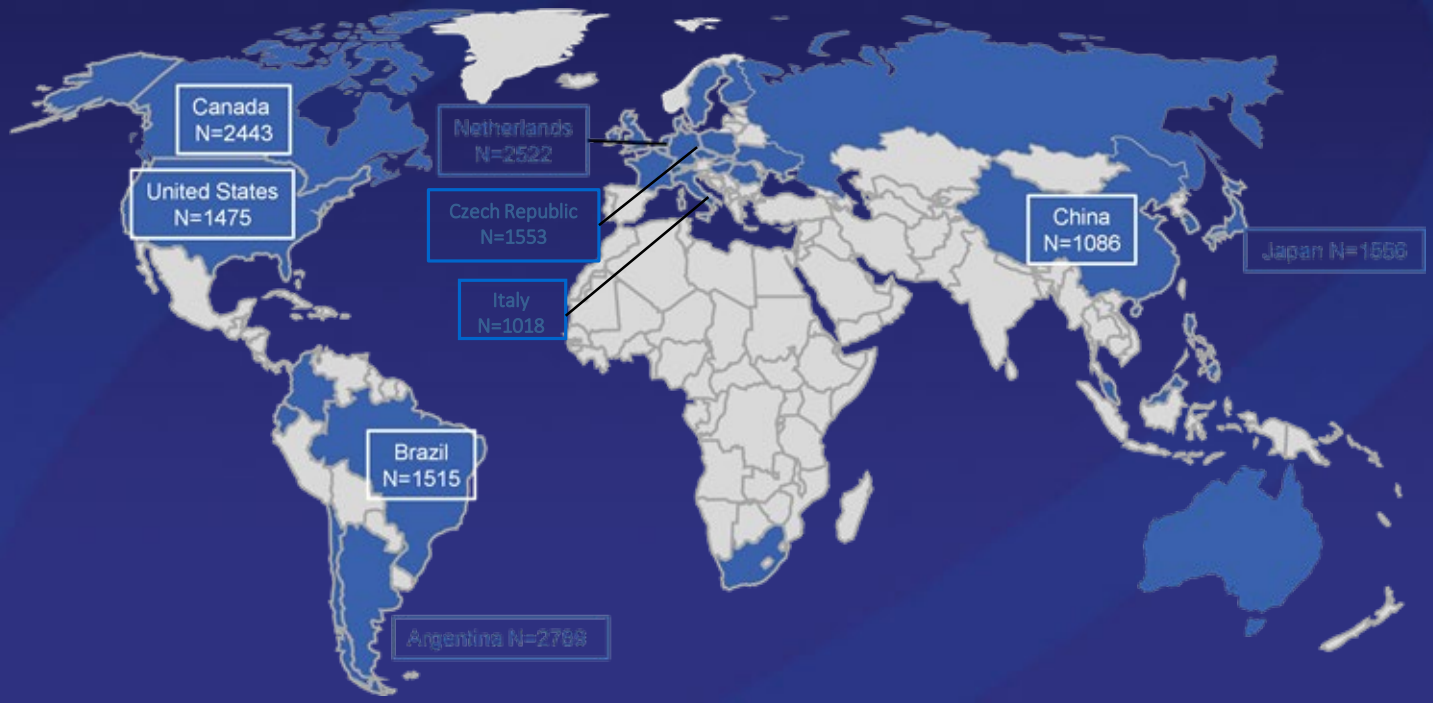
Design

- Prospective, multi-center, double-blind, randomized controlled trial
- N=27,395
- Enrollment: March 2013 to May 2016
- Mean follow-up: 23 months
- Analysis: Intention-to-treat
- Primary outcome: Cardiovascular death, stroke, or nonfatal MI
- Secondary outcome: CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia, All-cause mortality.
- On February 6, 2017 the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy (combination: Z= -4.59, P<0.00001; rivaroxaban: Z= -2.44, P=0.01)

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

602 sites, 33 countries



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COMPASS Background
Overall Primary Objectives

To determine in chronic CAD or PAD whether:

- Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily, or
- Rivaroxaban 5 mg twice daily compared with
- Aspirin 100 mg daily

Will reduce the risk of MACE and secondary outcomes:

- MACE: Composite of CV death, Stroke, or MI
- Secondary outcomes: Composite of ischemic stroke, MI, acute limb ischemia, or death from coronary heart disease*, the composite of ischemic stroke, myocardial infarction, acute limb ischemia, or cardiovascular death; and death from any cause.

 Eikelboom JW et al. *N Engl J Med* 2017;337:1319-30

COMPASS Background
PAD Primary Objectives

To determine in PAD whether:

- Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily, or
- Rivaroxaban 5 mg twice daily compared with
- Aspirin 100 mg daily

Will reduce the risk of MACE and secondary outcomes:

- MACE: Composite of CV death, Stroke, or MI
- MALE: ALI, CLI or major amputation

 Eikelboom JW et al. *N Engl J Med* 2017;337:1319-30

COMPASS Background
Eligibility: PAD

- Peripheral artery revascularization OR,

- Limb or foot amputation for arterial vascular disease OR,
- Intermittent claudication and one or more of either:
  - an ankle brachial index (ABI) of <0.90 OR,
  - a peripheral artery stenosis (≥50%)

- OR, Previous carotid revascularization, asymptomatic carotid artery stenosis ≥50%

- OR, Patients enrolled with CAD* + low ankle brachial index (ABI) (<0.90)

•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

Exclusion Criteria

- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known LVEF < 30% or NYHA III or IV
- Estimated GFR < 15mL/min
- Need for dual antiplatelet therapy or oral anticoagulant therapy
- Known non-cardiovascular disease associated with poor prognosis or increases risk of adverse effect from study medications
- Any known hepatic disease with coagulopathy.
- Subject who are pregnant, breastfeeding, or are of childbearing potential and sexually active without contraception

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

Baseline Characteristics

Characteristic	Rivaroxaban + asa	Rivaroxaban	Aspirin
	N=9,152	N=9,117	N=9,126
Age, yr	68	68	68
Blood pressure, mmHg	136/77	136/78	136/78
CAD	91%	90%	90%
PAD	27%	27%	27%
Diabetes	38%	38%	38%
Lipid-lowering	90%	90%	89%
ACE-I or ARB	71%	72%	71%

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

COMPASS Background

Efficacy and Safety Outcomes and Net Clinical Benefit

Key Efficacy Outcomes for PAD

- Primary Cardiovascular Outcome (MACE): Composite of CV death, Stroke, or MI
- Key composite outcomes: Key composite outcomes were major adverse limb events (MALE) (defined as the development of acute or chronic limb ischemia, including any additional major amputations due to a vascular event that was not included in acute or chronic limb ischemia), the composite of MACE and MALE, and the composite of MACE and MALE including major amputations

Primary Safety Outcome

- ISTH Modified Major bleeding defined as the composite of bleeding that was fatal, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalization (including presentation to an acute care facility without an overnight stay). Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1 29

Net Clinical Benefit

- Overall Net Clinical Benefit: Cardiovascular death, myocardial infarction, stroke, or fatal or critical bleeding
- For PAD, the Net Clinical Benefit of major adverse cardiovascular events (MACE) or major adverse limb events (MALE) including

 Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Background
Major Adverse Limb Event (MALE)

Acute Limb Ischemia:

- limb-threatening ischemia confirmed by limb hemodynamics or imaging and leads to a vascular intervention within 30 days of symptom onset

Chronic Limb Ischemia:

- Continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine 3/4 who has a peripheral intervention in the course of the trial

Major Amputation:

- Amputation above the forefoot due to a vascular cause.

 Eikelboom JW et al. *N Engl J Med* 2017;337:1319-30

COMPASS Results

PAD Patients in COMPASS

PAD Groups	Number of Patients
All PAD patients	7,470
Symptomatic PAD Lower Extremities	4,129
Carotid Artery Disease	1,919
CAD + Low ABI (<0.9) only *	1,422

- *These patients were considered to have asymptomatic PAD §Previous carotid artery revascularization or asymptomatic carotid artery stenosis greater than or equal to 50% diagnosed by duplex ultrasound or angiography

- With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Results

Baseline Characteristics of PAD

	Rivaroxaban 2.5mg twice daily + Aspirin 100mg daily	Rivaroxaban 5mg twice daily	Aspirin 100mg daily
	N=2492 (years or %)	N=2474 (years or %)	N=2504 (years or %)
Mean Age, years	67.9	67.8	67.8
Current Smoker	27.4	27.7	27.4
Former Smoker	46.0	46.6	45.6
Diabetes	44.1	43.8	44.1
Hypertension	78.9	78.4	80.6
History of CAD	66.5	65.0	65.5
History of Stroke	6.9	7.2	6.2
Lipid Lowering Medication	83.8	83.8	82.8
ACE-I/ARB	68.8	71.0	70.5

*The specific type of lipid lowering agent/statin use was not recorded at baseline

•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Results

Baseline Characteristics of PAD (Continued)

	Rivaroxaban 2.5mg twice daily + Aspirin 100mg daily	Rivaroxaban 5mg twice daily	Aspirin 100mg daily
	N=2492 (years or %)	N=2474 (years or %)	N=2504 (years or %)
Symptomatic PAD of LE	56.5	55.0	54.3
Carotid Artery Disease	24.8	25.1	27.2
Symptomatic PAD	81.3	80.1	81.4
CAD and ABI <0.9	18.7	19.8	18.6
ABI > 0.90	49.2	48.0	47.6
ABI 0.70-0.90	39.3	38.4	39.3
ABI < 0.70	8.5	10.8	9.9

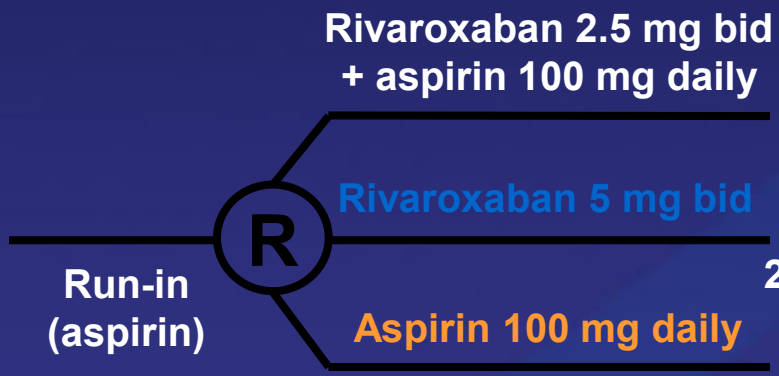
*Defined as intermittent claudication with ABI <0·90 or stenosis of ≥50%; or previous aorta-femoral or lower extremity bypass surgery, percutaneous transluminal angioplasty of iliac or infrainguinal arteries, or limb or foot amputation for arterial vascular disease. †Defined as previous carotid endarterectomy or stent or asymptomatic carotid artery stenosis of ≥50%. ‡Symptomatic PAD is the sum of symptomatic PAD of lower extremities and carotid artery disease. §Asymptomatic PAD of lower extremities. ABI, ankle brachial index; PTA, percutaneous transluminal angioplasty

 Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Design

C*ardiovascular *O*utcom*e*s for *P*eople Using *A*nticoagulation *S*trategie*s

- **Randomized, placebo controlled, double blinded trial**



***Median Follow Up*:**
23 months (1.9 years)

- **Ongoing arm testing proton pump inhibitor pantoprazole versus placebo (PPI arm)**

27,325 patients with stable CAD or PAD
1,323 with a primary outcome event

COMPASS

COMPASS: **Rationale of 100mg Aspirin**

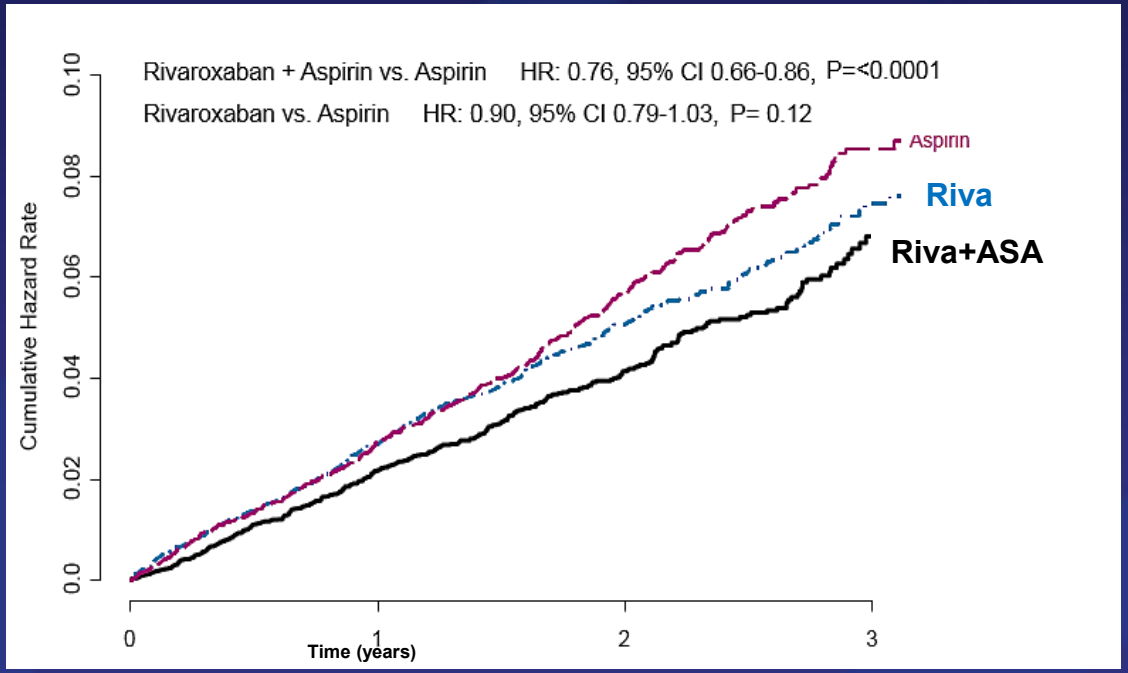
- The COMPASS trial evaluated aspirin 100 mg once daily as the standard of care for secondary prevention of major CV events in patients with chronic CAD and PAD. [1-3]

- In the United States, low-dose aspirin is available in an 81mg dose strength. Clinical evidence supports the choice of low dose aspirin. [2]

 1. Bosch J, et al. *Can J Cardiol*.2017;33(8):1027-1035 2. Fihn SD, et al. *J Am Coll Cardiol*.2012;60(24):2564-2603. 3. Gerhard-herman MD, et al. *Circulation*. 2017;135(12):e726-e779.

COMPASS Main Trial Outcomes

Primary Outcome: MACE (CV death, stroke or MI) Median 23 month follow up



Cumulative Hazard

Riva+ASA vs ASA:

- ↓ MACE 24%
- ↑ Net benefit 20%
- ↓ Mortality 18%

➢ **No benefit for Rivaroxaban alone**

ASA = aspirin; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; Riva = rivaroxaban.

Primary: CV death, stroke, MI

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
CV death, stroke, MI	379 (4.1%)	448 (4.9%)	496 (5.4%)	0.76 (0.66-0.86)	<0.0001	0.90 (0.79-1.03)	0.12

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

Primary Components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
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)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

https://www.nejm.org/doi/full/10.1056/NEJMoa1709118

COMPASS Results

Rivaroxaban 2.5mg Twice Daily Combined with Aspirin 100mg Daily Reduced Stroke, CV Death, All Cause Mortality vs Aspirin 100mg Daily

	Aspirin 100mg daily (%) N= 9126	Rivaroxaban 2.5mg BID + Aspirin (%) N=9152	HR	HR (95%CI)	*p*-value
Primary Efficacy EP CV Death, Stroke, MI (MACE)	5.4	4.1	0.76	X	<0.001
Secondary Efficacy EP All cause mortality	4.1	3.4	0.82	X	0.01
Ischemic stroke, myocardial infarction, ALI, or death from CHD	4.9	3.6	0.72	X	<0.001
Ischemic stroke, myocardial infarction, ALI, or CV death	5.7	4.3	0.74	X	<0.001
Stroke† **CV death†** **MI†**	1.6 2.2 2.2	0.9 1.7 1.9	0.58 0.78 0.86		

Favors Rivaroxaban 2.5 mg BID + Aspirin

Favors Aspirin Alone

•The threshold P value used for statistical significance of secondary efficacy outcomes was 0.0025 per the COMPASS study statistical analysis plan. For outcomes that did not meet
•this threshold, statistical significance cannot be claimed. †Not adjusted for multiplicity

COMPASS Results

Total and Major Amputation in Patients with PAD

Outcome	Rivaroxaban + Aspirin	Rivaroxaban	Aspirin	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N=2492 (%)	N=2474 (%)	N=2504 (%)	HR (95% CI)	p	HR (95% CI)	p
Total Amputation	11 (<1%)	17 (1%)	28 (1%)	0.40 (0.20-0.79)	0.0069	0.61 (0.33-1.11)	0.10
Major Amputations	5 (<1%)	8 (<1%)	17 (1%)	0.30 (0.11-0.80)	0.011	0.46 (0.20-1.08)	0.068

•Provisions to address multiple testing for subgroups were not specified and therefore, any HRs, corresponding CIs, and P
•values reported for subgroup analyses cannot be interpreted as statistically significant.

COMPASS Results

Key Composite Outcomes

Outcome	Rivaroxaban + Aspirin	Rivaroxaban	Aspirin	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N=2492 (%)	N=2474 (%)	N=2504 (%)	HR (95% CI)	p	HR (95% CI)	p
MACE or MALE	155 (6%)	184 (7%)	222 (9%)	0.69 (0.56-0.85)	0.0004	0.84 (0.68-1.01)	0.065
MACE or MALE plus Major Amputation	157 (6%)	188 (8%)	225 (9%)	0.69 (0.56-0.85)	0.0003	0.84 (0.69-1.02)	0.077

•Provisions to address multiple testing for subgroups were not specified and therefore, any HRs, corresponding CIs, and P
•values reported for subgroup analyses cannot be interpreted as statistically significant.

COMPASS Results

Significant Increase in Modified ISTH Major Bleeding; No Significant Increase in Fatal, Intracranial, or Critical Organ Bleeding and Significant Increase in Other Major Bleeding Leading to Hospitalization

Crude incidence over mean follow-up of 23 months	Aspirin n (%)	Rivaroxaban 2.5mg BID + Aspirinn (%)	HR (95%CI)	*P*-value
Primary Safety: Major bleeding	170 (1.9)	288 (3.1)	1.70 (1.40-2.05)	<0.001
Fatal bleeding†	10 (0.1)	15 (0.2)	1.49 (0.67-3.33)	0.32
Non-fatal symptomatic ICH	19 (0.2)	21 (0.2)	1.10 (0.59-2.04)	0.77
Nonfatal, non-ICH, symptomatic bleeding into a critical organ	29 (0.3)	42 (0.5)	1.43 (0.89-2.29)	0.14
Other major bleeding leading to hospitalization	112 (1.2)	210 (2.3)	1.88 (1.49-2.36)	<0.001
Pre-specified net clinical benefit (CV Death, Stroke, MI, Fatal Bleeding, or Symptomatic Bleeding into a Critical Organ)	534 (5.9)	431 (4.7)	0.80 (0.70-0.91)	<0.001

•**Modified ISTH Major Bleeding**: International Society on Thrombosis and Haemostasis: major bleeding and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay).

•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence 1. Eikelboom JW *et al. New Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
•2. Bosch J *et al. Can J Cardiol.* 2017 Aug;33(8):1027-1035

COMPASS Results

Net Clinical Benefit

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

COMPASS Results

Net Clinical Benefit in PAD

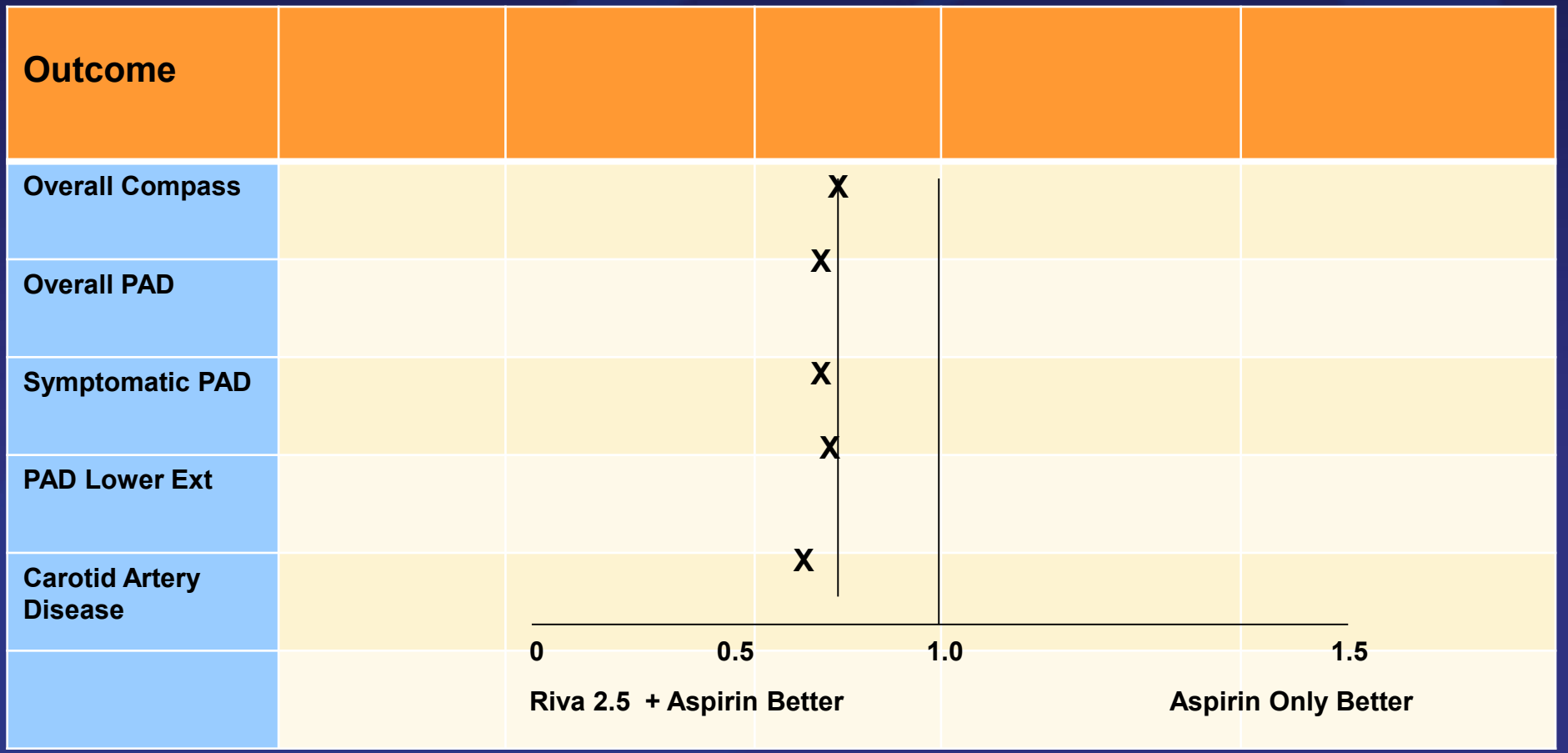
Outcome	Rivaroxaban + Aspirin	Rivaroxaban	Aspirin	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N=2492 (%)	N=2474 (%)	N=2504 (%)	HR (95% CI)	p	HR (95% CI)	p
NET Clinical Benefit	169 (7%)	207 (8%)	234 (9%)	0.72 (0.59-0.87)	0.0008	0.89 (0.74-1.07)	0.23

*Net Clinical Benefit: CV death, MI, stroke or MALE, major amputation, or fatal or critical organ bleeding

•With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Results

MACE or MALE, including Major Amputation



*Net Clinical Benefit: CV death, MI, stroke or MALE, major amputation, or fatal or critical organ bleeding

COMPASS: **Conclusions**

- Rivaroxaban 2.5mg twice daily and aspirin 100mg daily, versus aspirin alone:
  - -24% significant reduction in the combined risk of stroke, CV death and MI
    - 42% reduction in stroke and 22% reduction in CV death
  - -70% statistical increase in major bleeding rates
    - No significant increase in intracranial, critical organ or fatal bleeding
    - Increase in other major bleeding leading to hospitalization
  - -20% improvement in net clinical benefit.
  - -18% reduction in all-cause mortality

 1. Bosch J, et al. *Can J Cardiol*.2017;33(8):1027-1035 2. Fihn SD, et al. *J Am Coll Cardiol*.2012;60(24):2564-2603. 3. Gerhard-herman MD, et al. *Circulation*. 2017;135(12):e726-e779.

COMPASS: **Conclusions for PAD**

- **Rivaroxaban 2.5 mg twice daily plus aspirin 100mg daily compared to aspirin 100mg daily:**

  - Reduced MACE (28% RRR)

  - Reduced MALE including major amputation (46% RRR)

  - Reduced MACE or MALE including major amputation (31% RRR)

  - Increased ISTH major modified bleeding and bleeding leading to hospitalization but did not increase fatal or critical organ bleeding

  - Net clinical benefit was favorable with a 28% RRR

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COMPASS Background

COMPASS Coronary Arterial Disease (CAD) Rationale

- Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins.[1-3]
- Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination, or against each other, in patients with stable coronary artery disease. [3-4]

 1. Benjamin EJ, et al. *Comp Physiol* 2015; **5:** 1841–75 3. Antithrombotic Trialists' Collaboration. *Lancet* 2009; **373:** 1849–60. 4. Connolly SJ, et al. Lancet 2017;DOI:10.1016/S0140-6736(17)32458-3

COMPASS Background
Eligibility: CAD

- Key Inclusion Criteria

  To be enrolled with a diagnosis of CAD, patients had to have either MI within 20 years, multivessel CAD, history of stable or unstable angina, previous multi-vessel PCI, or previous multivessel CABG

Patients with CAD must also meet ≥1 of the following:

- Age ≥65 years, or Age <65 years with disease in ≥2 vascular beds, or ≥2 additional CV risk factors (see below)

- Included Risk Factors

  Current smoking, diabetes mellitus, renal dysfunction with eGFR <60 ml/min, heart failure, non-lacunar ischaemic stroke ≥1 month ago

 Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Results

Primary Efficacy Outcome and Components for Patients with CAD

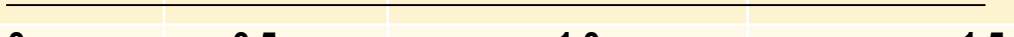
Outcome	Rivaroxaban + Aspirin	Rivaroxaban	Aspirin	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N=8313 (%)	N=8250 (%)	N=8261 (%)	HR (95% CI)	p	HR (95% CI)	p
MACE	347 (4%)	411 (5%)	460 (6%)	0.74 (0.65-0.86)	<0.0001	0.89 (0.78-1.02)	0.094
MI	169 (2%)	176 (2%)	195 (2%)	0.86 (0.70-1.05)	0.15	0.90 (0.74-1.11)	0.33
Stroke	74 (1%)	105 (1%)	130 (2%)	0.56 (0.42-0.75)	<0.0001	0.81 (0.62-1.05)	0.10
CV Death	139 (2%)	175 (2%)	184 (2%)	0.75 (0.60-0.93)	0.01	0.85 (0.77-1.17)	0.63

- Provisions to address multiple testing for subgroups were not specified and therefore, any HRs, corresponding CIs, and P values reported for subgroup analyses cannot be interpreted as statistically significant. Patients with atrial fibrillation requiring anticoagulation were excluded from entering the trial. Atrial fibrillation was documented to have occurred during the trial in 1% of patient in each arm. Only five of 74 strokes that occurred in the 2.5 mg rivaroxaban twice daily plus aspirin 100mg daily group occurred in patients who developed atrial fibrillation during the trial, compared with nine of 130 strokes that occurred in patients in the aspirin alone group.
- With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS Results

MACE or MALE, including Major Amputation

Efficacy Outcomes	Rivaroxaban 2.5mg twice daily + Aspirin 100mg daily (%)	Aspirin 100mg daily (%)	HR	HR (95% CI)	*p*-value
CV Death, Stroke, MI (MACE)	347 (4)	460 (6)	0.74	X	<0.0001
Stroke	74 (1)	130 (2)	0.56	X	<0.0001
CV Death	139 (2)	184 (2)	0.75	X	0.01
MI	169 (2)	195 (2)	0.86	X	0.15
All Cause Mortality	262 (3)	339 (4)	0.77	X	0.0012



•Provisions to address multiple testing for subgroups were not specified and therefore, any HRs, corresponding CIs, and P values reported for subgroup analyses cannot be interpreted as statistically significant With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence, Adapted from Connolly SJ, et al. Lancet 2017;DOI:10.1016/S0140-6736(17)32458-3

COMPASS Results

Net Clinical Benefit in CAD

Outcome	Rivaroxaban + Aspirin	Aspirin	Rivaroxaban + Aspirin vs. Aspirin	
	N=8313 (%)	N=8261 (%)	HR (95% CI)	p
NET Clinical Benefit	392 (5%)	494 (6%)	0.78 (0.69-0.90)	0.0003

Net Clinical Benefit is defined as a composite outcome consisting of stroke, myocardial infarction, cardiovascular death, fatal bleeding, and symptomatic bleeding into a critical organ or area.

Provisions to address multiple testing for subgroups were not specified and therefore, any HRs, corresponding CIs, and P values reported for

- subgroup analyses cannot be interpreted as statistically significant.

- With Permission. The COMPASS Program, Janssen Scientific Affairs, LLC/ Value and Evidence Anand SS, et al. *Lancet*. 2017 Nov 10. pii: S0140-6736(17)32409-1

COMPASS: **Conclusions for CAD**

In patients with stable coronary artery disease, the addition of rivaroxaban 2.5 mg BID to aspirin:

- Reduced the primary endpoint of MACE
- Reduced major vascular events by 26%, stroke by 44% and mortality by 23%
- Significantly increased major modified ISTH bleeding by 66% and increased bleeding leading to hospitalization, but no significant increase in fatal or critical organ bleeding

Vs. aspirin alone;

- the NNT to prevent occurrence of one of the primary outcomes was 72
- the NNH for fatal or symptomatic bleeding into a critical organ was 471
- the number needed to prevent one death was 105

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COMPASS: **Discussion**

Exclusion of 2320 participants after run-in period raises possibility of selection bias and decreased generalizability.

Study terminated early due to efficacy of rivaroxaban plus aspirin versus aspirin alone. As a result, the study may overestimate the degree of benefit of rivaroxaban plus aspirin and potentially underestimate the degree of increased bleeding with this therapy

When efficacy and safety endpoints are considered separately, the combination of rivaroxaban plus ASA reduced the primary efficacy endpoint by 1.3% at the cost of a 1.2% absolute increase in major bleeding. These differences represent a number needed to treat (NNT) of 77 and a number needed to harm (NNH) of 83.

COMPASS: **Discussion**

So, why aren't clinicians using these agents in combination with antiplatelet therapy more often?

– Major Bleeding

COMPASS: **Discussion**

Addition of rivaroxaban to background aspirin in patients with established stable atherosclerotic disease is now a legitimate consideration that will need to be made on a case-by-case basis particularly in patients whose high thrombotic risk is felt to substantially outweigh bleeding risk.

Despite these limitations, the combination of low-dose rivaroxaban plus ASA likely will be of benefit to select, high-risk patients.

Questions