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HEALTH THROUGH KNOWLEDGE

Dual Pathway Inhibition Anti-thrombotic Therapy: COMPASS, COMPASS Sub-studies and Secondary Analyses

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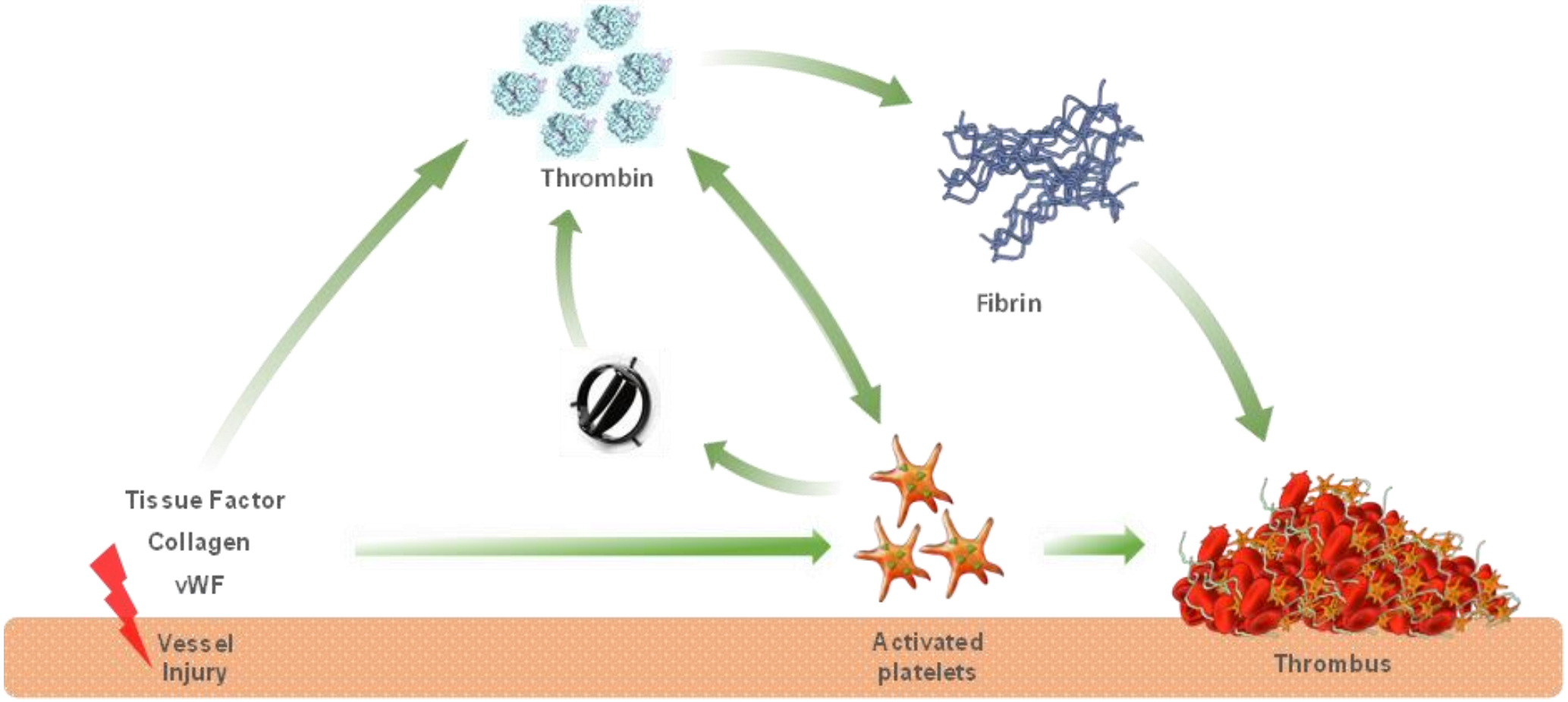
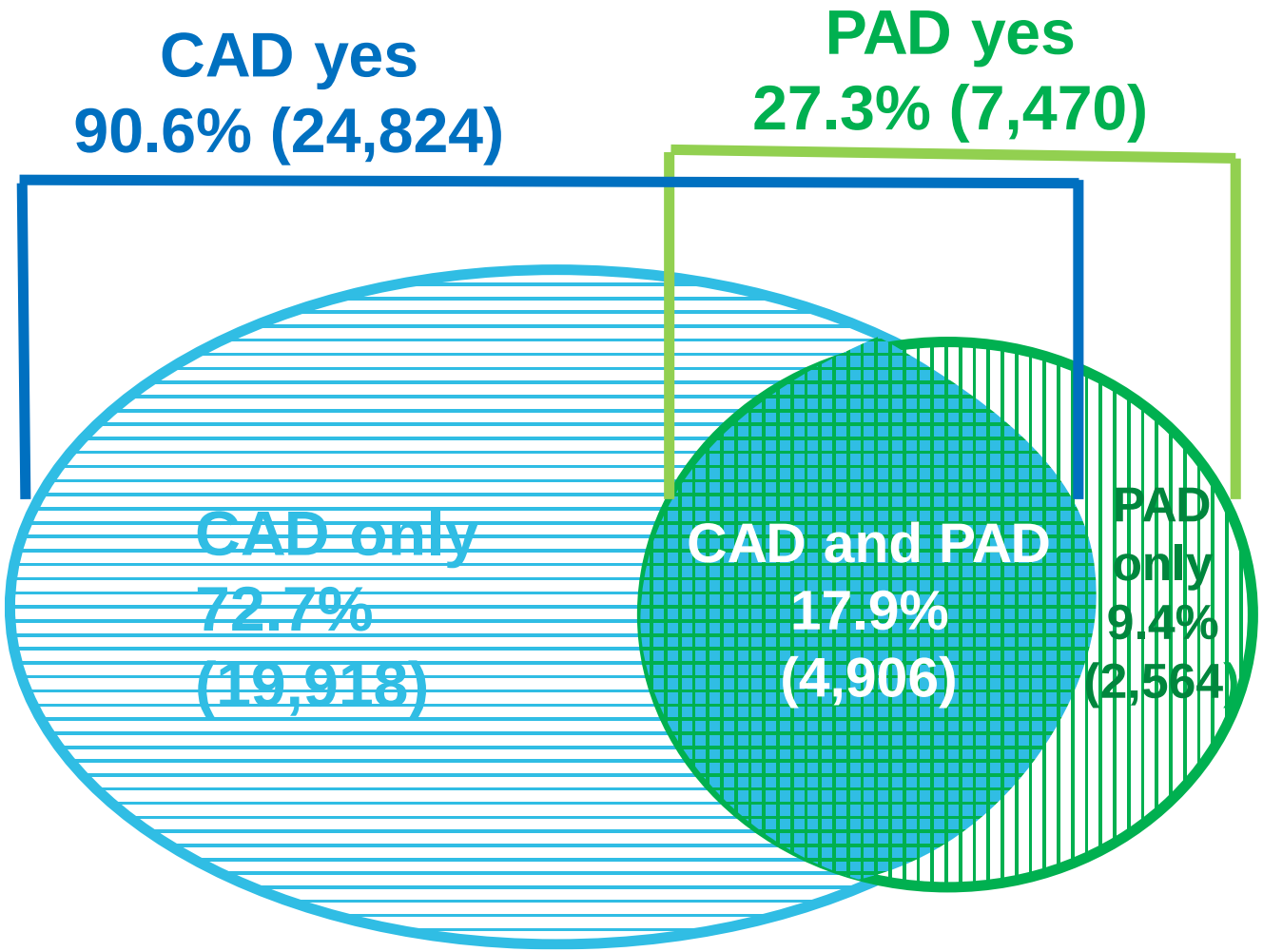
Disclosures

- Relationships with commercial interests:
  - Grants/Research Support: Bayer, BI, BMS, Daiichi-Sankyo, Janssen, Pfizer
  - Speakers Bureau/Honoraria: Bayer, BI, BMS, Daiichi-Sankyo, Janssen, Pfizer
- Employment:
  - Hamilton Health Sciences and McMaster University; I work at an anticoagulation clinic
- Government grants:
  - CIHR, HSF, NIF, NHMRC

Rationale for using a dual pathway approach



CAD and PAD populations

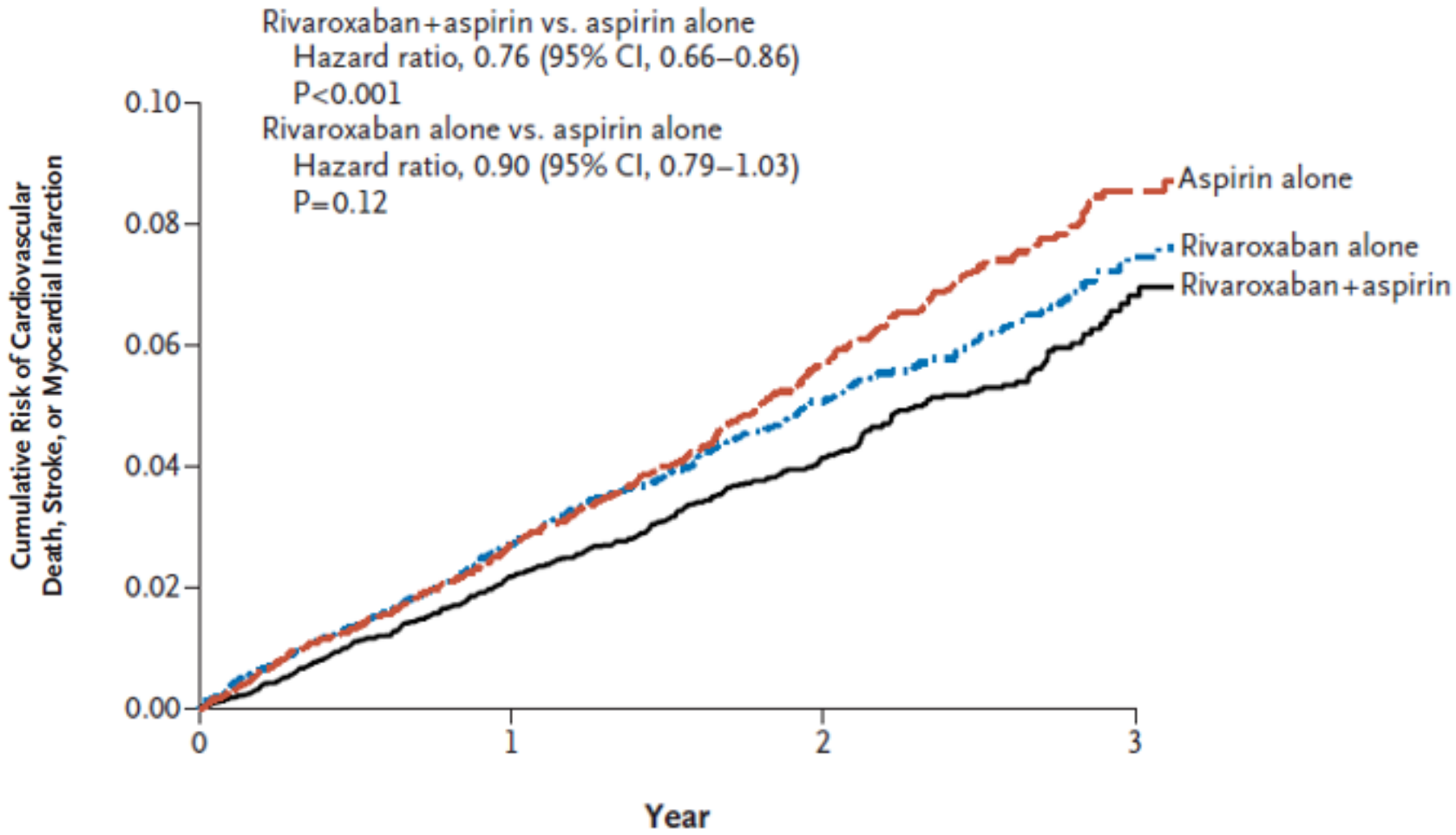


MRI lesions at baseline

	Patients N	Patients with lesions	
		N	%
Infarcts	1,760	612	34.8%
Non-lacunar		409	23.2%
Lacunar		315	17.9%
Microbleeds	1,696	497	29.3%
Cortical		307	18.1%
Subcortical		321	18.9%

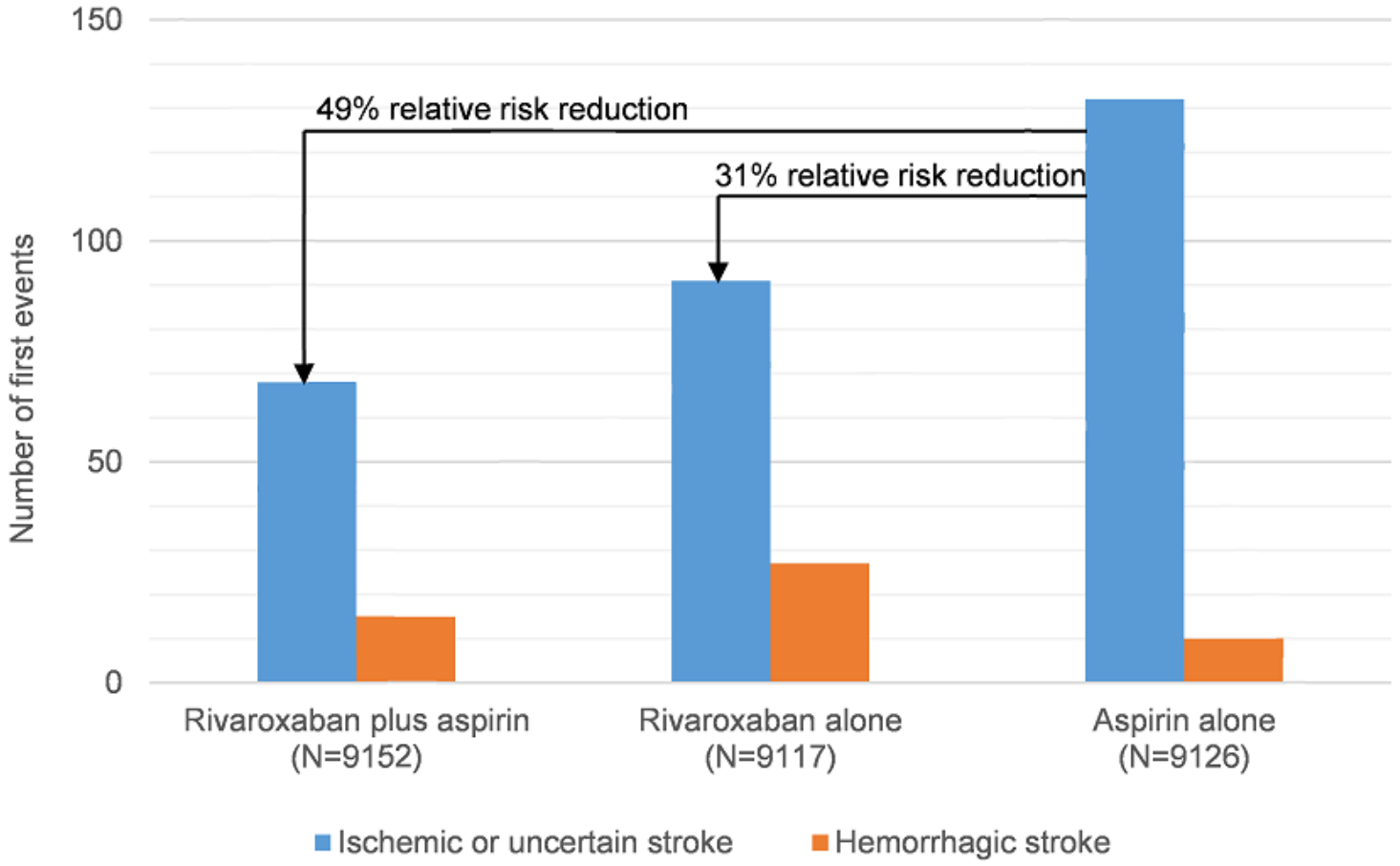
Sharma M, et al. Manuscript in preparation

COMPASS trial in patients with CAD or PAD: Primary outcome



Eikelboom JW, et al. N Engl J Med 2017; 377: 1319-30.

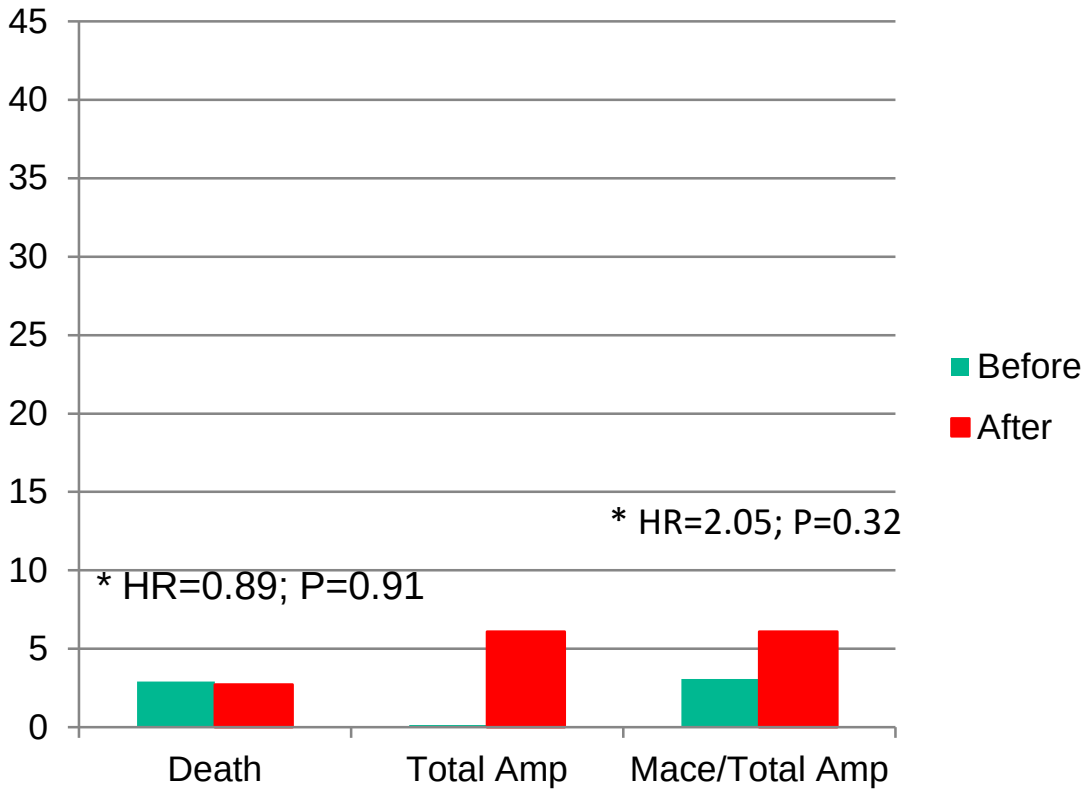
Stroke: Ischemic and hemorrhagic



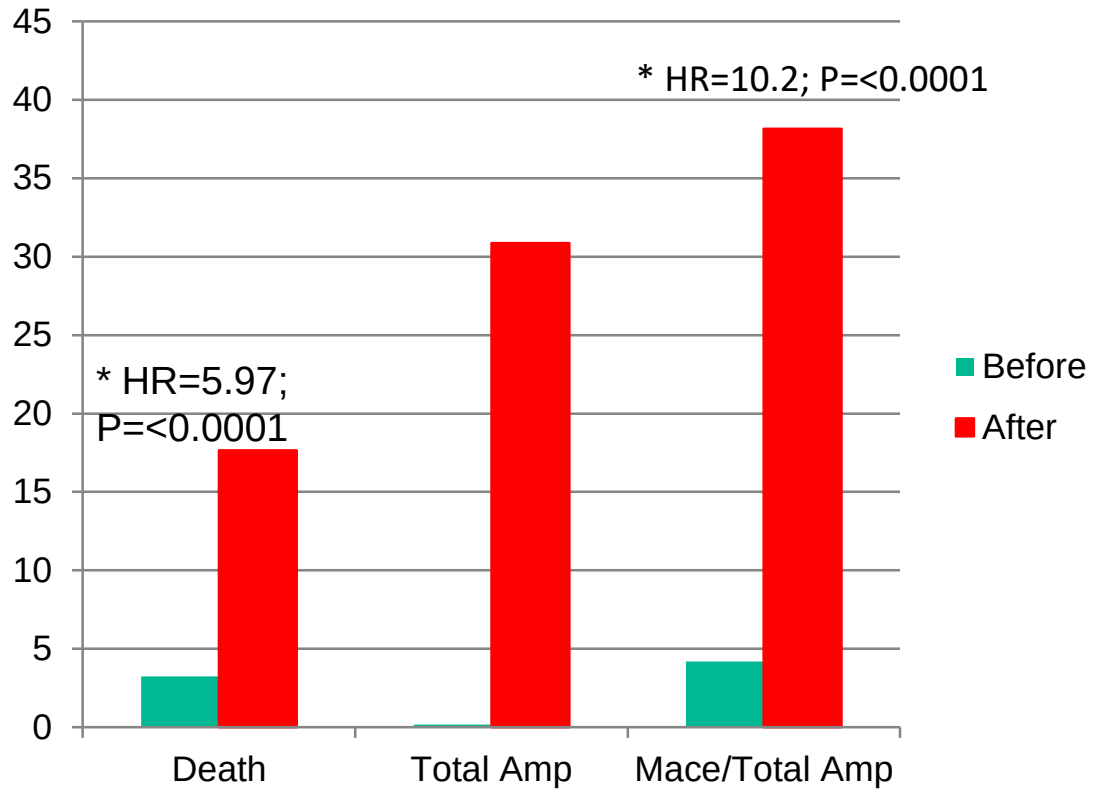
Sharma M, et al. Circulation 2019 available on-line

Prognosis of MALE by randomized treatment

- Rivaroxaban plus aspirin



- Aspirin only



Anand SS, et al. J Am Coll Cardiol 2018; 71: 2206-15.

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COMPASS in context of other proven secondary prevention therapies

	Rivaroxaban + aspirin	Lipid-lowering (1mmol/L)	BP-lowering (10mm Hg)	ACE	SGLT2 inhibitor (Empagliflozin)	PCSK9 inhibitor (Alirocumab)
Triple outcome	**-24%**	-21%	-20%	-18%	-14%	-14%
Death	**-18%**	-9%	-13%	-14%	-32%	-15%
Stroke	**-42%**	-15%	-27%	-23%	+18%	-27%
MI	-14%*	-24%	-17%	-18%	-13%	-12%

*Not significant

Eikelboom J, et al. N Engl J Med 2017; 377: 1319-1330. Ettehad D, et al. Lancet 2016;387:957-67. CTT Collaboration. Lancet 2015;385:1397-1405; Collins R, et al. Lancet 2016;388:2532-61. Dagenais GR, et al. Lancet. 2006; 368:581-8. Schwartz GG, et al. N Engl J Med 2018;379:2097-2107. Zinman B, et al. N Engl J Med 2015; 373: 2117-2128.

Health Canada
September 14, 2018

Rivaroxaban 2.5mg BID in combination with 75-100mg acetylsalicylic acid (ASA) for the prevention of stroke, myocardial infarction, cardiovascular death, and for the prevention of **acute limb ischemia** and **mortality** in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD)

Learning Objectives

Following their participation in this activity, physicians will be in a position to address the following questions:

1. **Which patients should I treat with the COMPASS regimen?**
2. Should I be concerned about the risk of bleeding?
3. Is the COMPASS treatment regimen cost-effective?

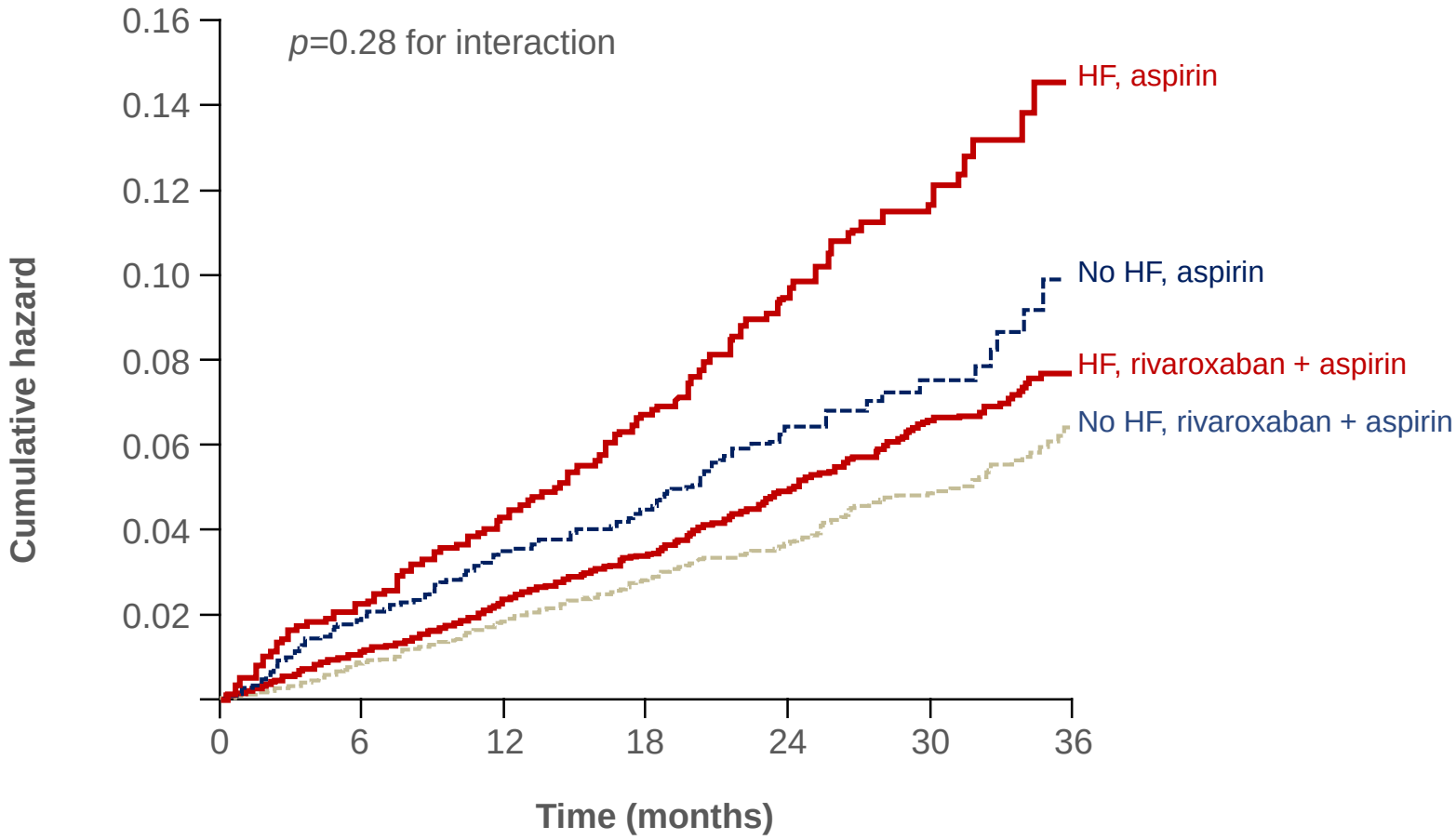
Possible approaches to identifying the high risk patient

1. Effects in subgroups are consistent therefore simply identify subgroups with the highest control event rates
2. Risk scoring system (REACH) to identify those at highest risk
3. Regression analyses (CART) to identify those at highest risk

Cardiovascular disease: who derives the greatest benefit from the COMPASS regimen?

- Polyvascular (includes PAD)
- CAD plus heart failure
- CAD plus renal impairment
- CAD plus diabetes
- Multiple risk factors

Heart Failure: Mild or moderate



Branch K, *et al.* Presented at ESC-HF. clinicaltrialresults.org [accessed Aug 2018]

Heart failure: Commander and COMPASS

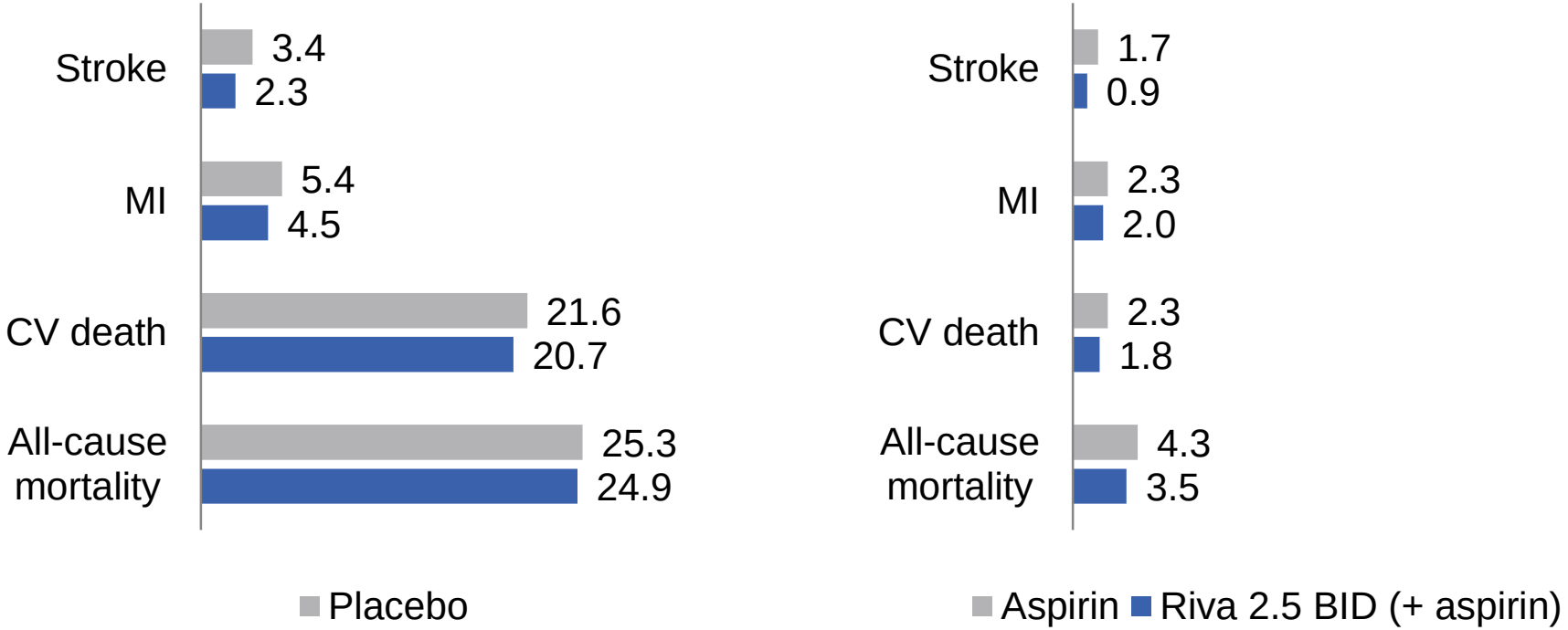
COMMANDER HF [1]

Acute Decompensated HF

COMPASS [2]

Chronic Stable HF†

2 Year Event Rates*



Zannad F et al. *N Engl J Med* 2018; 379: 1332-1342; Eikelboom JW et al. *N Engl J Med* 2017;377:1319–1330.

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Chronic Kidney Disease

	R + A (N=9152) %	Aspirin alone (N=9126) %	R + A vs. Aspirin alone		
			RRR	P (int.)	ARR
CV death, stroke, MI					
eGFR <60 ml/min	6.4	8.4	25%	0.95	2%
eGFR ≥60 ml/min	3.5	4.5	24%		1%
Major bleeding					
eGFR <60 ml/min	3.9	2.7	-47%	0.30	-1.2%
eGFR ≥60 ml/min	2.9	1.6	-81%		-1.3%
Net clinical benefit					
eGFR <60 ml/min	7.2	8.9	21%	0.89	1.7%
eGFR ≥60 ml/min	4.0	4.9	19%		0.9%

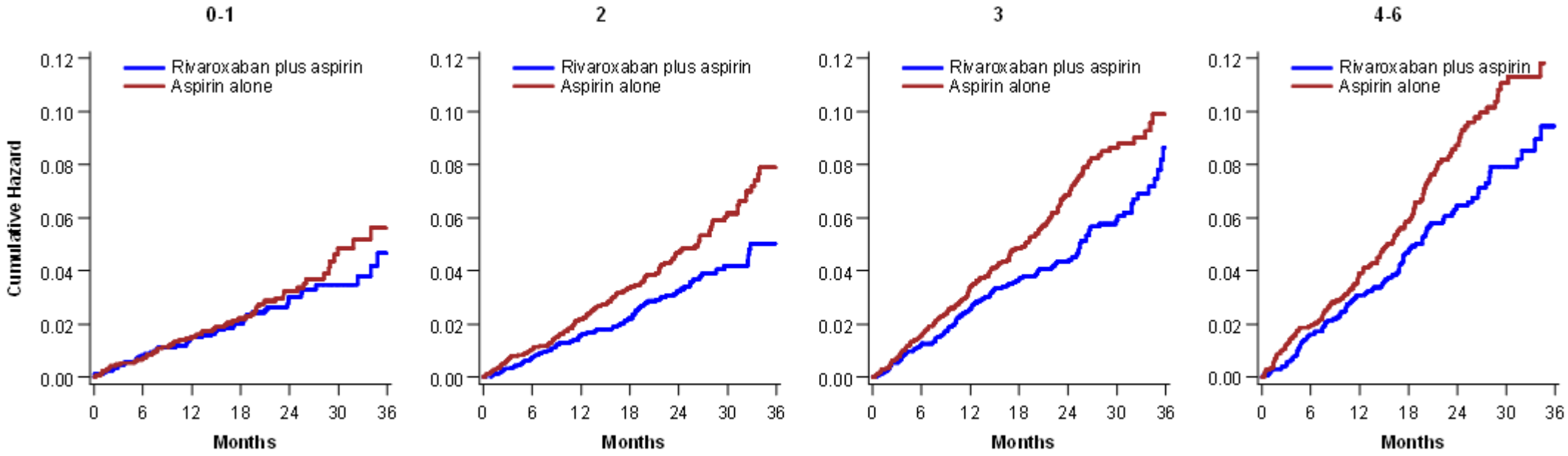
Fox KAA, et al. J Am Coll Cardiol 2019 in press

Diabetes

	R + A (N=9152) %	Aspirin alone (N=9126) %	R + A vs. Aspirin alone		
			RRR	P (int.)	ARR
CV death, stroke, MI					
Diabetes	5.2	6.9	23%	0.95	1.7%
No diabetes	3.5	4.5	26%		1.0%
Death					
Diabetes	4.3	5.2	19	0.82	0.9%
No diabetes	2.9	3.5	16		0.6%
Major bleeding					
Diabetes	3.2	1.9	-70%	0.30	-1.2%
No diabetes	3.1	1.9	-69%		-1.3%

Cardiovascular risk factors at baseline

BP control (y/n), cholesterol control (y/n), BMI elevated (y/n),
Physical Activity (y/n), Smoking (y/n), Diabetes (y/n)



Vanassche T, et al. Manuscript in preparation

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Post MI patients (n=16,992)

Outcome	Relative risk reduction
Primary endpoint	26%
CV Death	32%
MI	15%NS
Stroke	39%
Major bleeding	61%
Mortality	27%

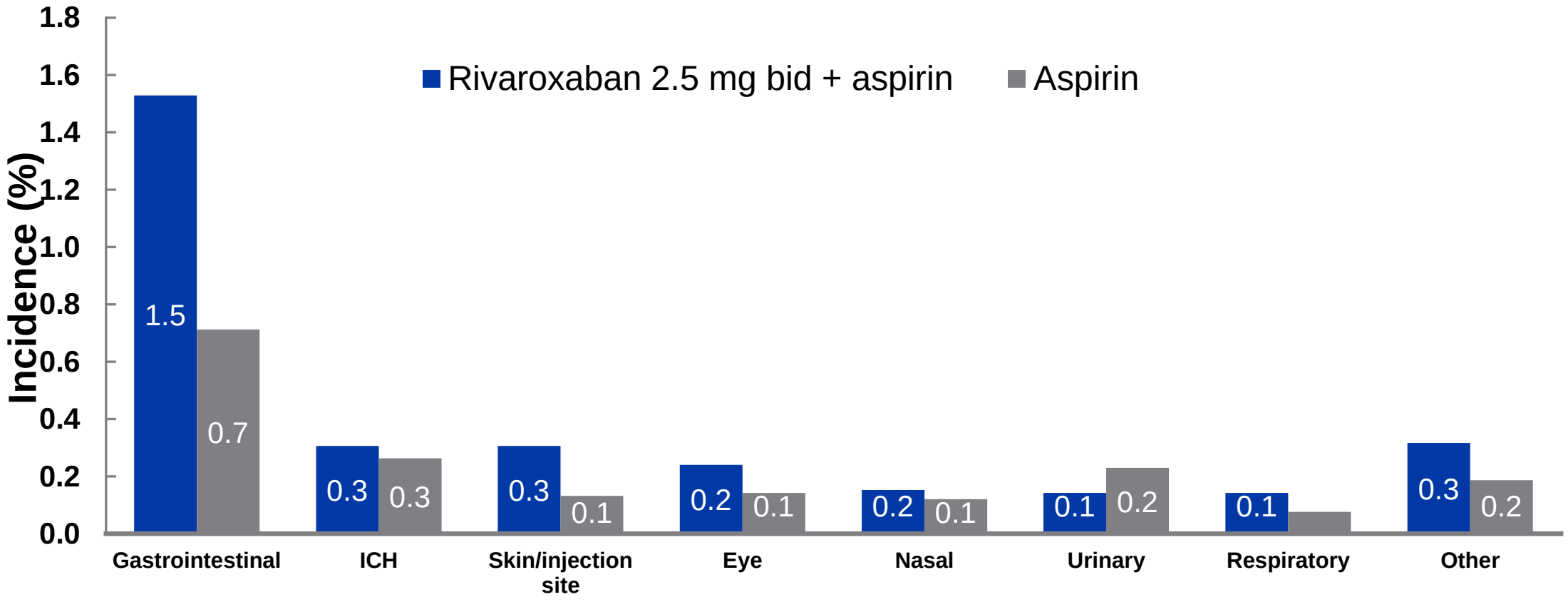
Connolly SJ, et al. Lancet 2018; 391: 205-18.

Learning Objectives

Following their participation in this activity, physicians will be in a position to address the following questions:

1. Which patients should I treat with the COMPASS regimen?
2. **Should I be concerned about the risk of bleeding?**
3. Is the COMPASS treatment regimen cost-effective?

Sites of major bleeding



Eikelboom JW, et al. Manuscript in preparation

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Association between GI bleeding and GI cancer

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	1,898*	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

Summary of bleeding

- Front loaded (mainly in the first year)
- Gastrointestinal (no increase in intracranial or fatal)
- Treated the same as bleeding on aspirin (proportion of those needing blood or platelets was no different)
- One in 13 patients with any gastrointestinal bleeding were diagnosed with a new cancer

Learning Objectives

Following their participation in this activity, physicians will be in a position to address the following questions:

1. Which patients should I treat with the COMPASS regimen?
2. Should I be concerned about the risk of bleeding?
3. **Is the COMPASS treatment regimen cost-effective?**

COMPASS economic analysis

- Includes all cardiovascular events (excludes non-cardiovascular events)
- Costs are direct medical costs consumed in hospital
  - Events and procedures (DRG approach)
  - Strokes and limb amputations incur costs beyond the event itself (1 year perspective)
- Unit costs from the following countries:
  - Canada, France, Germany
- Events and resources from all patients are applied to each country using their specific unit costs

Lamy A, et al. Presented at American Heart Association meeting. Anaheim, California, November 2017.

COMPASS economic analysis

- All costs converted to US dollars ($USD)
- Costs of rivaroxaban:
  - Canada: $2.39 USD/day
  - France: $3.18 USD/day
  - Germany $3.18 USD/day

Lamy A, et al. Presented at American Heart Association meeting. Anaheim, California, November 2017.

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Life-time cost-effectiveness: overall and subgroups

	Canada	France	Germany
COMPASS All Patients	$4,438	$8,216	$8,189
CAD only	$6,222	$9,908	$9,995
PAD Only	$2,822	$3,989	$3,551
PAD	DOMINANT	$3,108	$2,795
Previous MI & diabetes	$5,427	$9,227	$9,276
Previous MI & HF	$3,605	$7,070	$7,151

Lamy A, et al. Presented at American Heart Association meeting. Anaheim, California, November 2017.

Summary

- In patients with chronic CAD or PAD, rivaroxaban plus aspirin compared with aspirin:
  - Reduces CV death, stroke, or MI by about one-quarter
  - Reduces MALE, the most feared complication of PAD by about one-half
- Greatest benefit is patients with polyvascular disease; CAD with mild/mod heart failure, diabetes, or CKD; and those with multiple CV risk factors
- Increased bleeding is mostly GI, front-loaded, and unmasks underlying GI cancers