Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# COMPASS

A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (**COMPASS** - **C**ardiovascular **O**utco**M**es for **P**eople using **A**nticoagulation **S**trategie**S**)

# Key objectives

1. To determine in stable CAD or PAD whether:

Rivaroxaban 2.5mg bid + aspirin 100mg od, or

Rivaroxaban 5mg bid

reduces the risk of CV death, stroke or MI compared with aspirin 100 mg od

2. To determine in patients with chronic CAD or PAD whether pantoprazole 40 mg once-daily versus placebo reduces the risk of upper GI complications

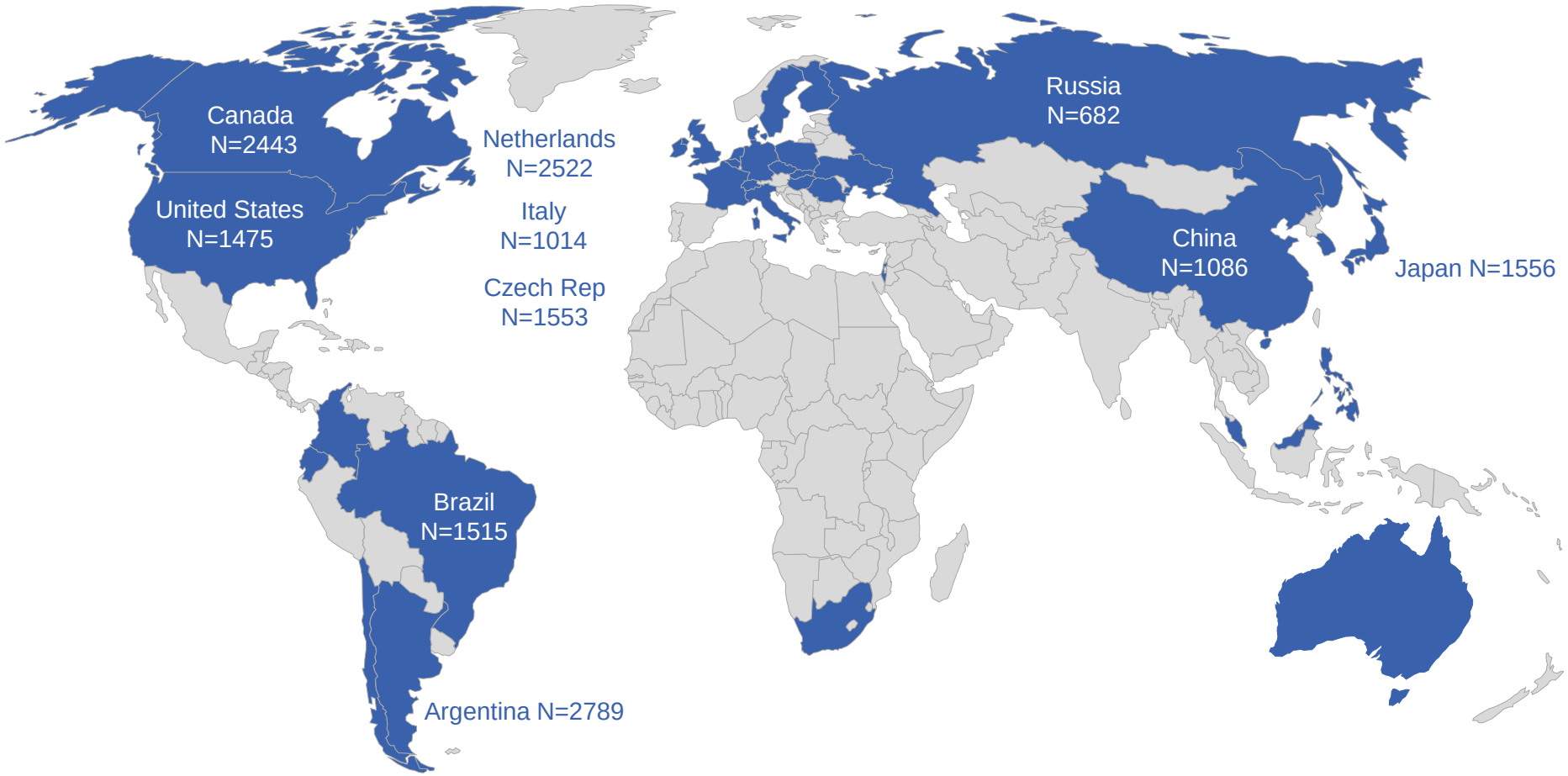
# Trial Status

- Anti-thrombotic comparison stopped early due to efficacy, and results presented at the European Society of Cardiology Congress on August 27, 2017
- Pantoprazole versus placebo comparison completed in July 2018, and results presented at the United European Gastroenterology meeting on October 23, 2018
- Long-term Open-label Extension (LTOLE) implemented to make regimen available to COMPASS trial subjects until the rivaroxaban treatment is commercially available for this indication or for approximately 3 years from regulatory approval of LTOLE in a country, whichever comes first (completion estimated early 2022)

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# COMPASS

## 33 countries, 602 centres, 27,395 patients



Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# The Vascular Dose of Rivaroxaban in the Protection of Patients with CAD or PAD

# Global burden of cardiovascular disease

- Still the single most common cause of death (17 million deaths per year, 1 in 3 deaths)
- Affects 300 million persons (4% or 1 in 25 of the world population)
- Growing burden in developing countries due to increasing risk factors and survival of persons with risk factors

Joseph P, et al. *Circ Res* 2017; 121: 677-94. World Heart Federation factsheet. Cardiovascular Diseases in Mexico 2016

# Three pillars of cardiovascular prevention

| Lifestyle | Medical | Antithrombotic |
|---|---|---|
| Smoking | Lipids | ASA |
| Nutrition | Blood pressure | Clopidogrel |
| Exercise | Glucose | Ticagrelor |
| Weight | ACE inhibition | **COMPASS** |
| Psychosocial | | |

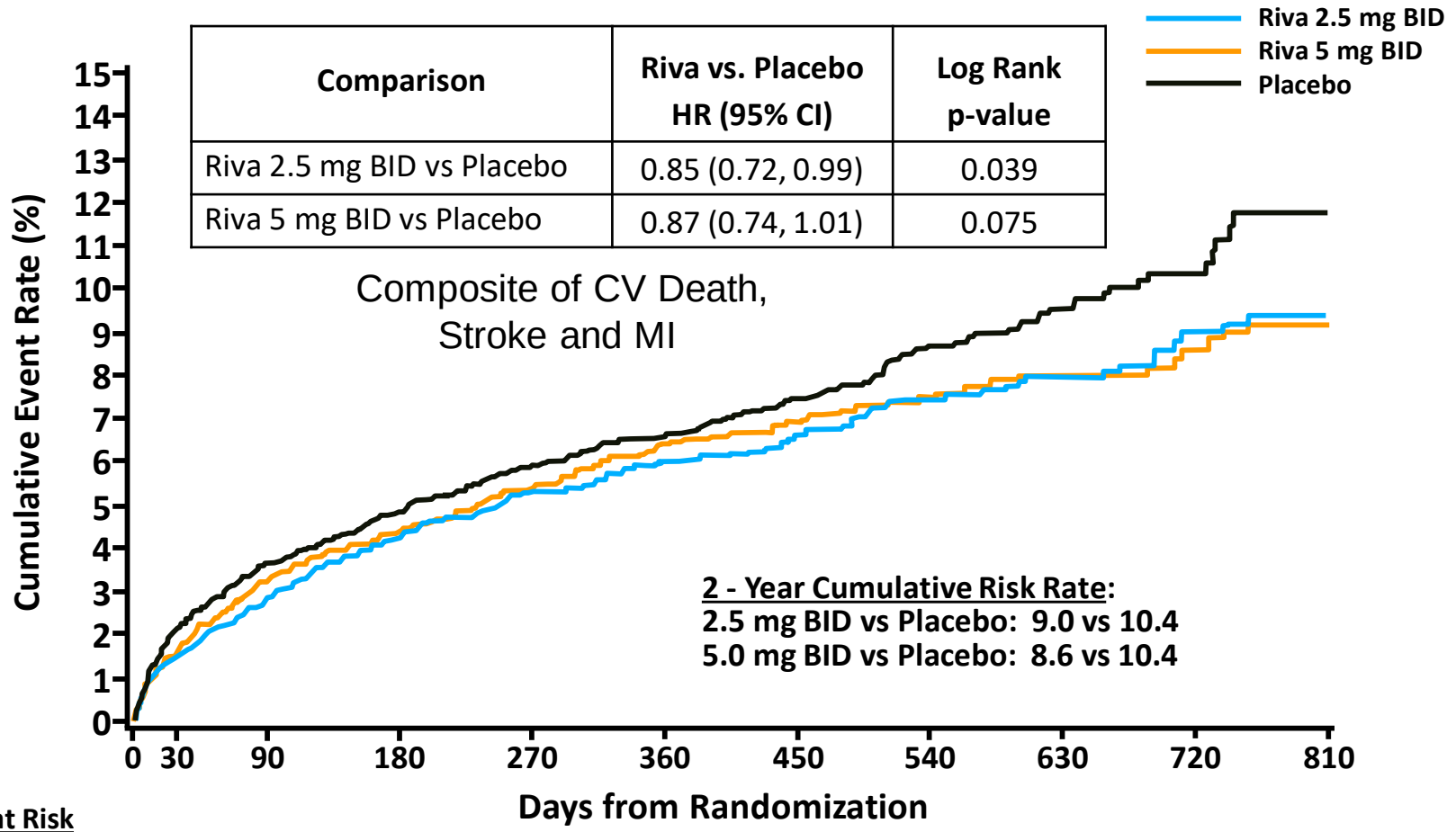
# Clinical rationale for testing dual pathway approach

- Warfarin is effective when added to aspirin in post-MI patients (meta-analysis, Andreotti et al. EHJ 2005)
- Rivaroxaban is effective when added to DAPT in post-ACS patients (ATLAS ACS 2 – TIMI 51)

Mega J, et al. *N Engl J Med* 2012; 366: 9-19.
Andreotti F, et al. *Eur Heart J* 2006; 27: 519-26. Anand S, et al. *J Am Coll Cardiol* 2003; 41: 62S-69S.

# ATLAS: clear benefit of adding rivaroxaban

| Comparison | Riva vs. Placebo HR (95% CI) | Log Rank p-value |
|---|---|---|
| Riva 2.5 mg BID vs Placebo | 0.85 (0.72, 0.99) | 0.039 |
| Riva 5 mg BID vs Placebo | 0.87 (0.74, 1.01) | 0.075 |



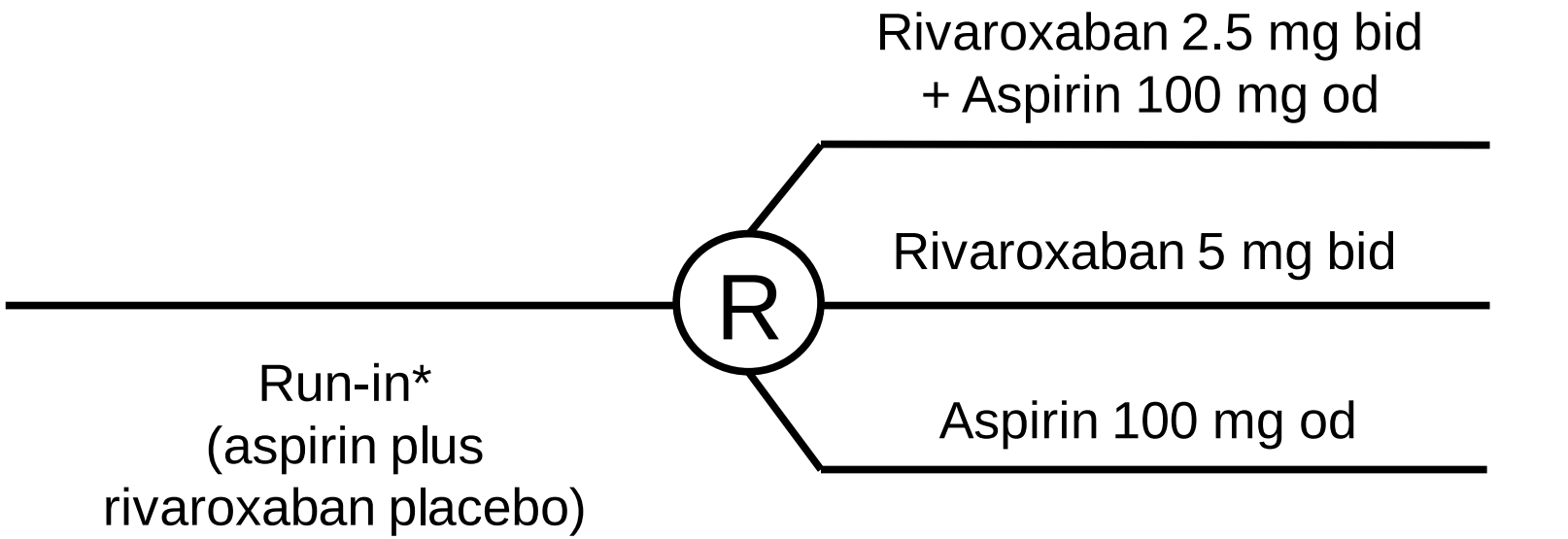

**Subjects at Risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Riva 2.5 mg BID | 4765 | 4143 | 3687 | 2995 | 2448 | 1883 | 1333 | 822 | 389 | 82 |
| Riva 5 mg BID | 4767 | 4082 | 3590 | 2920 | 2363 | 1834 | 1308 | 816 | 390 | 77 |
| Placebo | 4760 | 4152 | 3720 | 3056 | 2503 | 1935 | 1369 | 830 | 397 | 82 |

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

# Design

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




Expected mean follow up: 3-4 years

*excluding patients enrolled 4-14 days post CABG

Bosch JJ, et al. *Can J Cardiol* 2017; 33: 1027-1035.

# CAD eligibility

- Myocardial infarction within the last 20 years, or
- Multi-vessel coronary disease with symptoms or history of stable or unstable angina, or
- Multi-vessel percutaneous coronary intervention (PCI), or
- Multi-vessel CABG surgery

(If under the age of 65, patients required at least 2 additional risk factors (current smoker, diabetes mellitus, renal dysfunction with eGFR <60 mL/min, heart failure or non-lacunar stroke ≥1 month ago)

Bosch JJ, et al. *Can J Cardiol* 2017; 33: 1027-1035.

# PAD eligibility

- Previous revascularization
- Previous limb or foot amputation
- History of intermittent claudication and low ABI or significant (at least 50%) peripheral artery stenosis
- Previous carotid revascularization or asymptomatic carotid stenosis (at least 50%)

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# COMPASS: baseline characteristics
# Good baseline blood pressure & cholesterol control

| | R + A N=9,152 | Rivaroxaban N=9,117 | Aspirin N=9,126 |
|---|---|---|---|
| Age, yr* | 68 | 68 | 68 |
| Female | 23% | 22% | 22% |
| Diabetes | 38% | 38% | 38% |
| CAD | 91% | 90% | 91% |
| PAD | 27% | 27% | 27% |
| SBP/DBP, mmHg* | 136/77 | 136/78 | 136/78 |
| Cholesterol, mmol/L* | 4.2 | 4.2 | 4.2 |

*Mean

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

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

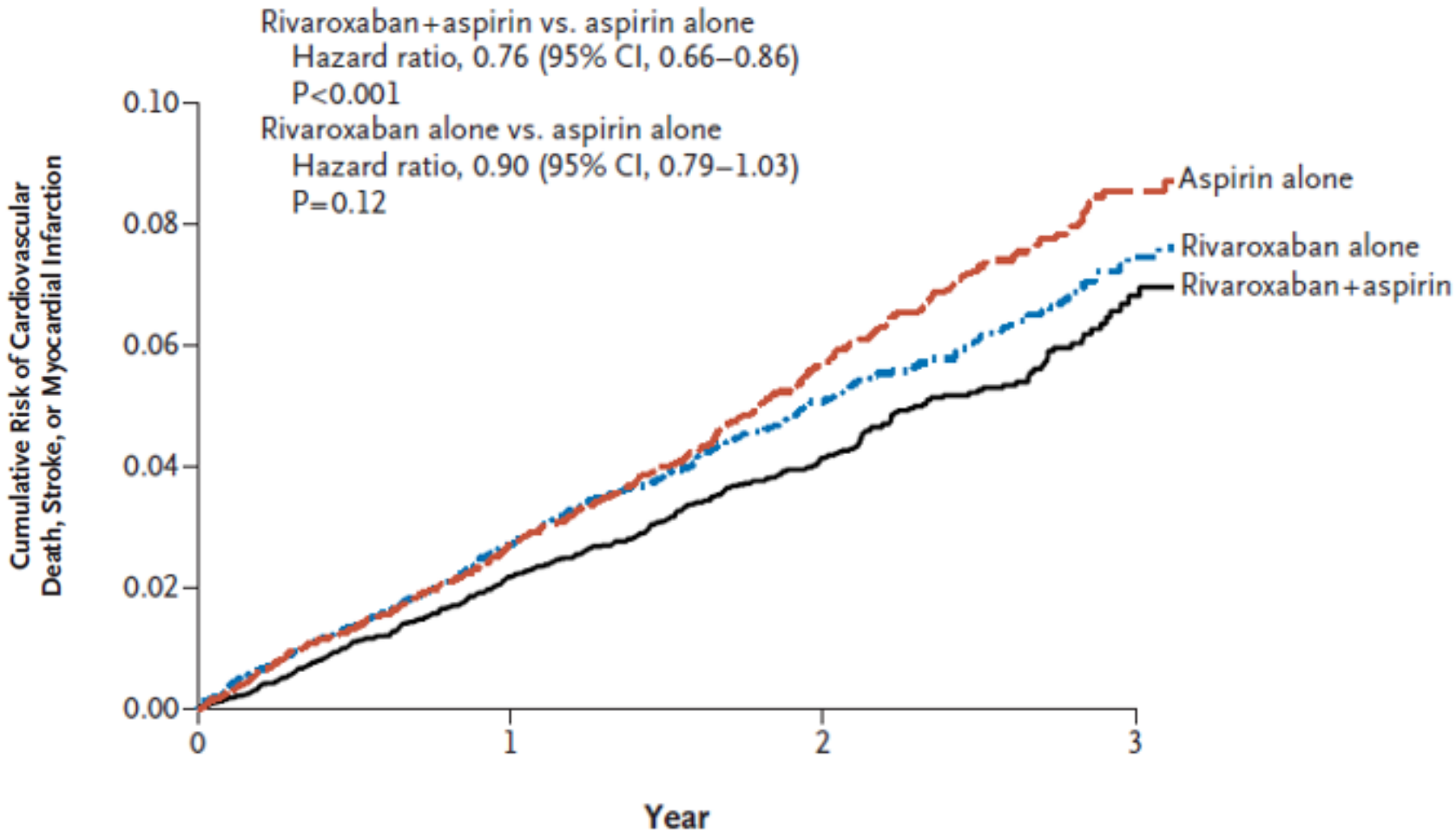
# COMPASS: a well-treated population

| | R + A N=9,152 | Rivaroxaban N=9,117 | Aspirin N=9,126 |
|---|---|---|---|
| Lipid-lowering | 90% | 90% | 89% |
| ACE-I/ARB | 71% | 72% | 71% |
| Beta blocker | 70% | 70% | 70% |
| Aspirin* | 87% | 87% | 87% |

*Excluding patients randomized 4-14 days post CABG

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

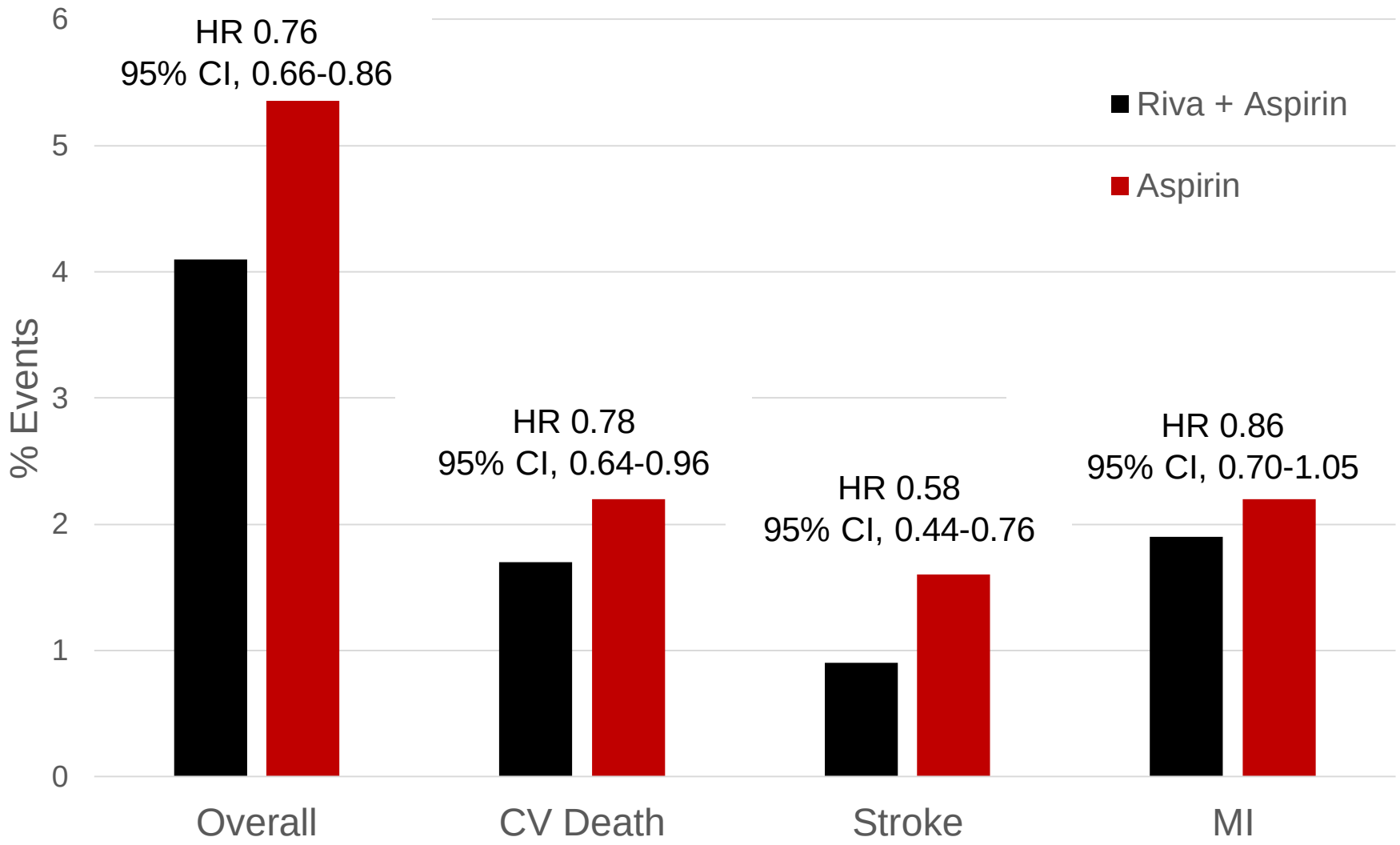
# COMPASS trial in patients with CAD or PAD: Primary outcome




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

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

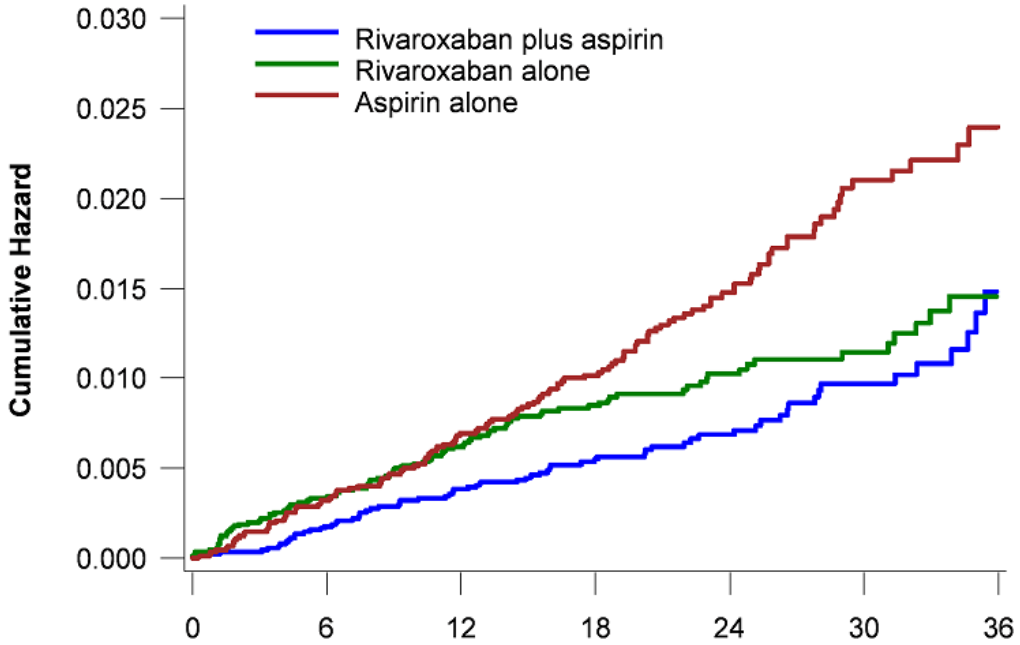
# Components of primary outcome



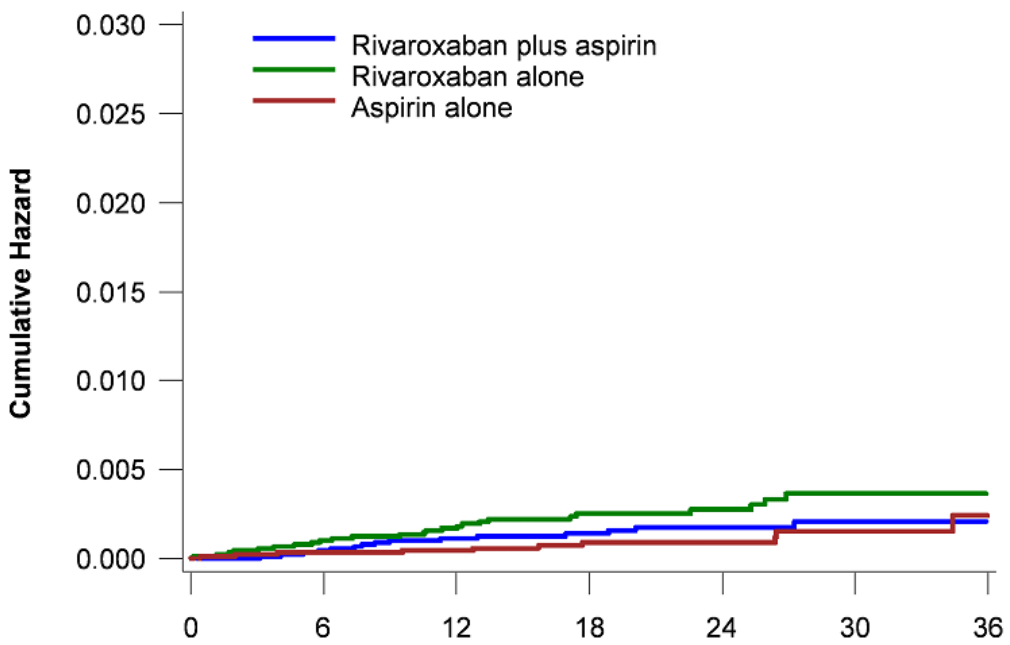

Eikelboom JW, et al. *N Engl J Med* 2017; 377: 1319-30.

# Stroke benefits

**Ischemic or uncertain stroke**




**Hemorrhagic stroke**




Sharma M, et al. *Circulation* 2019;139:1134-1145

# Peripheral limb benefits

| Outcome | R + A N=9,152 | Aspirin N=9,126 | Rivaroxaban + aspirin vs. aspirin | |
|---|---|---|---|---|
| | N (%) | N (%) | HR (95% CI) | p |
| **MALE** | 34 (0.4) | 64 (0.7) | 0.53 (0.35-0.80) | 0.002 |
| **Any amputation** | 15 (0.2) | 31 (0.3) | 0.48 (0.26-0.89) | 0.02 |

Anand SS, et al. Lancet 2018;391:219-229.

# Mortality benefits

| | **Riva + aspirin** N=9,152 | **Aspirin** N=9,126 | **Rivaroxaban + Aspirin vs. Aspirin** | |
|---|---|---|---|---|
| | **N (%)** | **N (%)** | **HR (95% CI)** | **P** |
| **Death** | 313 (3.4) | 378 (4.1) | 0.82 (0.71-0.96) | 0.01 |

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

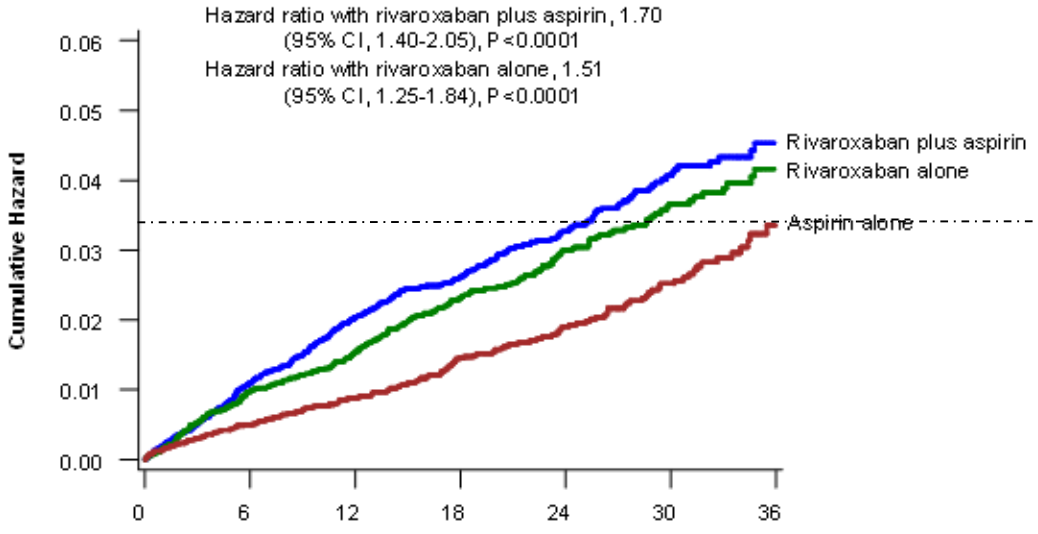
# CAD, PAD: CV death, stroke, MI

| Participant group | R + A N=2,492 | Aspirin N=2,504 | Rivaroxaban + aspirin vs. aspirin | |
|---|---|---|---|---|
| | N (%) | N (%) | HR (95% CI) | P |
| **CAD** | 347 (4.2) | 460 (5.6) | 0.74 (0.65-0.86) | <0.0001 |
| **PAD** | 126 (5.1) | 174 (6.9) | 0.72 (0.57-0.90) | 0.005 |

Anand SS, et al. *Lancet* 2018;391:219-229. Connolly SJ, et al. *Lancet* 2018; 391: 205-18.

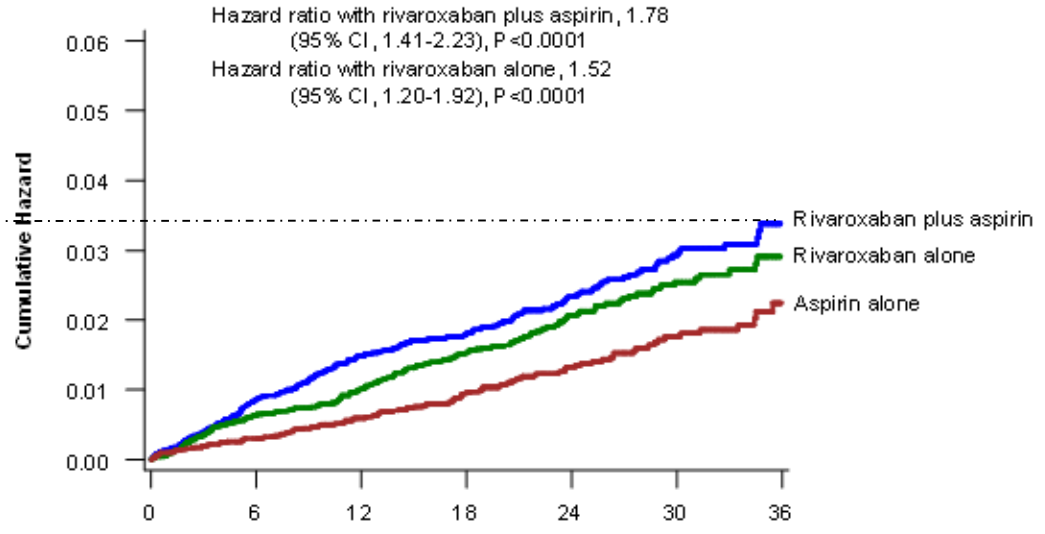
# Major bleeding: modified ISTH and conventional ISTH

A. **Modified ISTH Major Bleeding**




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rivaroxaban plus aspirin | 9152 | 8990 | 7852 | 6254 | 3879 | 2181 | 646 |
| Rivaroxaban alone | 9117 | 8961 | 7828 | 6202 | 3869 | 2172 | 661 |
| Aspirin alone | 9126 | 9006 | 7863 | 6221 | 3938 | 2225 | 680 |

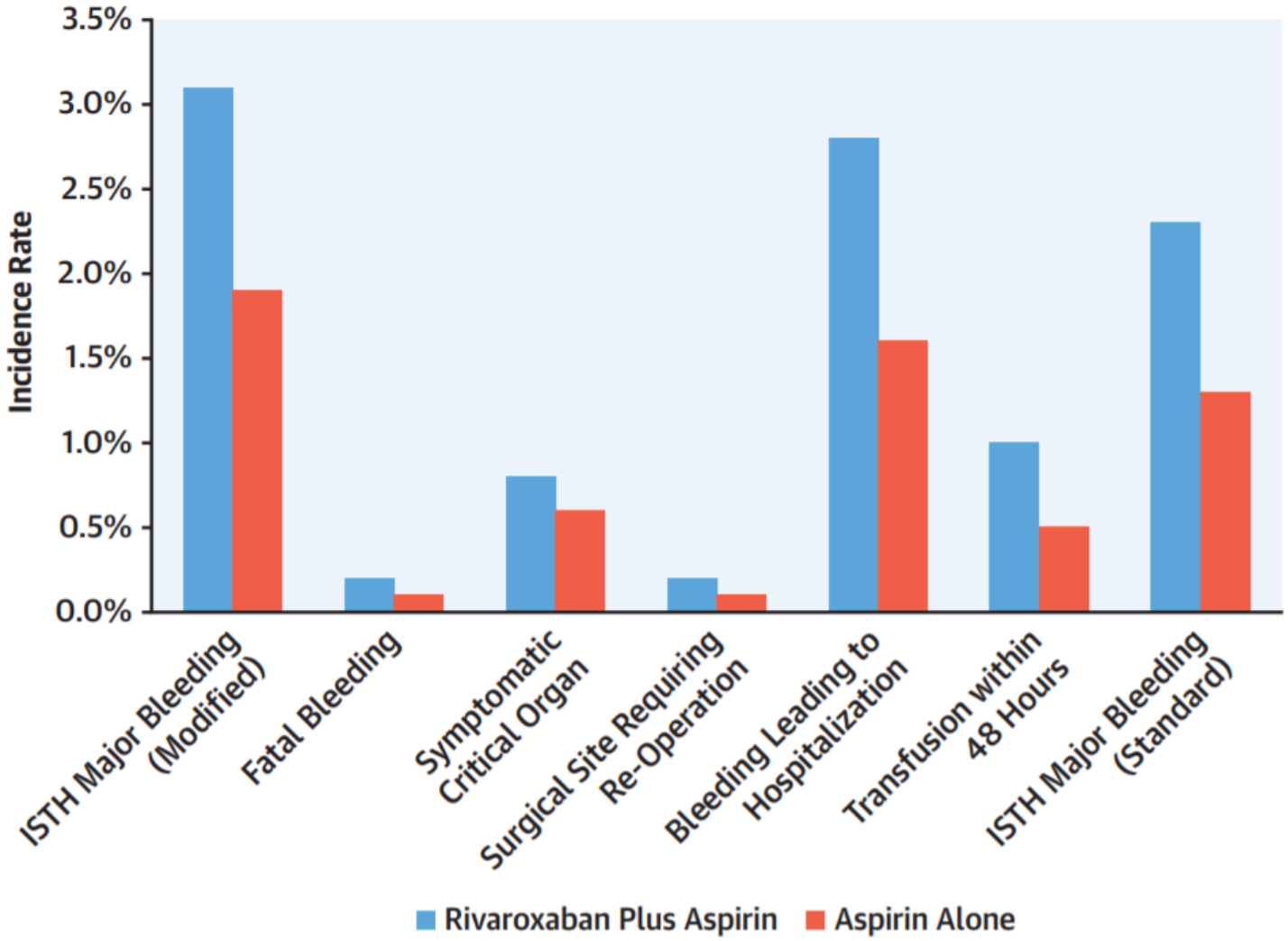
B. **ISTH Major Bleeding**




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rivaroxaban plus aspirin | 9152 | 9011 | 7892 | 6301 | 3923 | 2218 | 660 |
| Rivaroxaban alone | 9117 | 8991 | 7873 | 6241 | 3898 | 2189 | 671 |
| Aspirin alone | 9126 | 9024 | 7885 | 6250 | 3955 | 2239 | 687 |

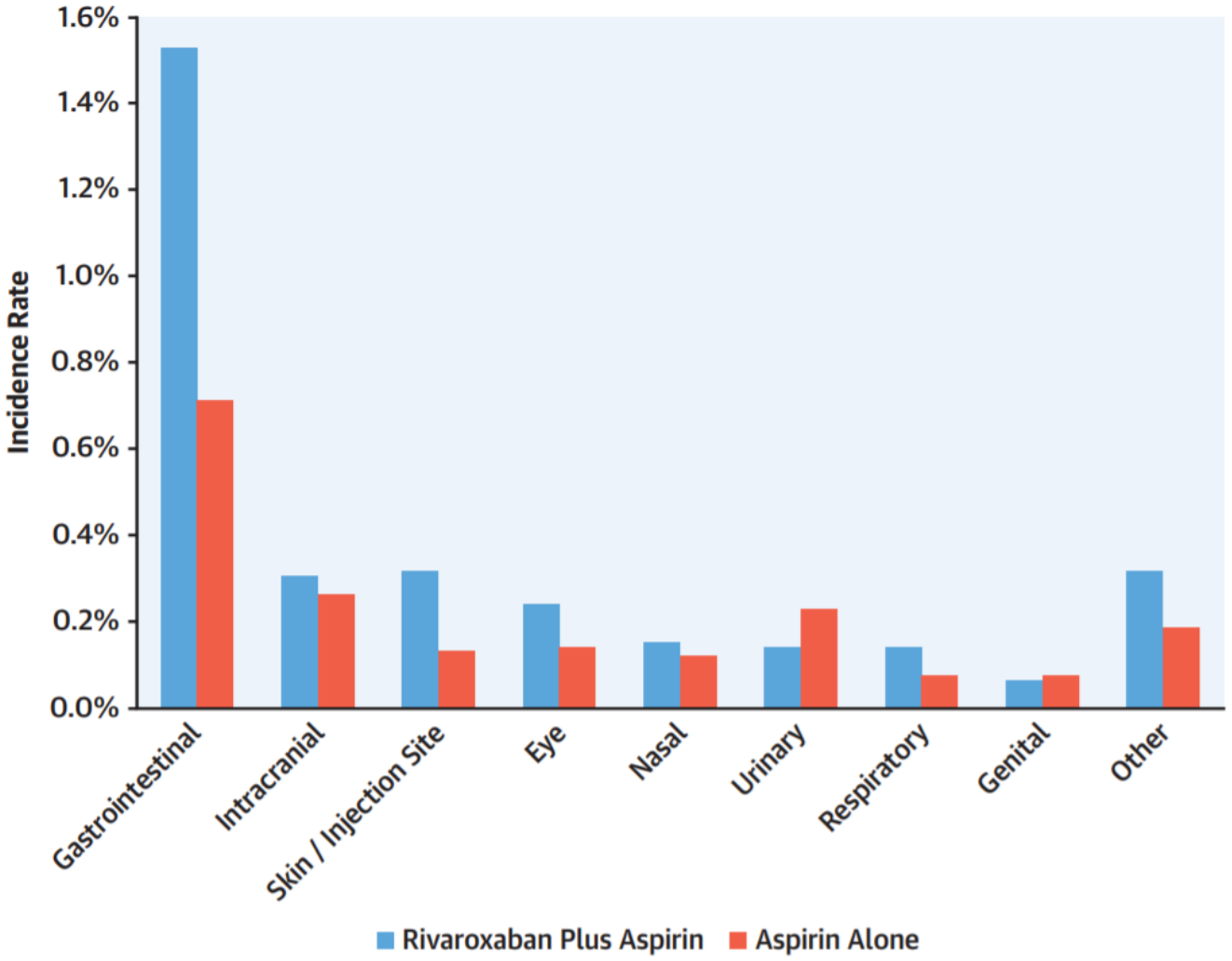
Eikelboom JW, et al. *J Am Coll Cardiol* 2019;74:1519-28.

# Major bleeding




Eikelboom JW, et al. *J Am Coll Cardiol* 2019;74:1519-28.

# Sites of major bleeding




Eikelboom JW, et al. *J Am Coll Cardiol* 2019;74:1519-28.

# Net clinical benefits

| Net clinical benefit | Riva + aspirin N=9,152 | Aspirin N=9,126 | Rivaroxaban + Aspirin vs. Aspirin | |
|---|---|---|---|---|
| | N (%) | N (%) | HR (95% CI) | P |
| **Pre-specified** | | | | |
| **Primary + critical bleeding** | 431 (4.7) | 534 (5.9) | 0.80 (0.70-0.91) | 0.0005 |
| **Death** | 313 (3.4) | 378 (4.1) | 0.82 (0.71-0.96) | 0.01 |
| **Other** | | | | |
| **Primary + MALE + severe bleeding** | 461 (5.0) | 588 (6.4) | 0.78 (0.69-0.88) | <0.0001 |

Anand S, *et al. J Am Coll Cardiol* 2019;73:3271-80.

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

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

- Polyvascular disease
- Mild or moderate heart failure
- Chronic kidney disease
- Diabetes
- Multiple risk factors

Anand S, et al. *J Am Coll Cardiol* 2019;73:3271-3280.
Vanassche T, et al. *Eur J Prevent Cardiol* 2019 Oct 15:2047487319882154. doi: 10.1177/2047487319882154. [Epub ahead of print]

# Summary

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

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

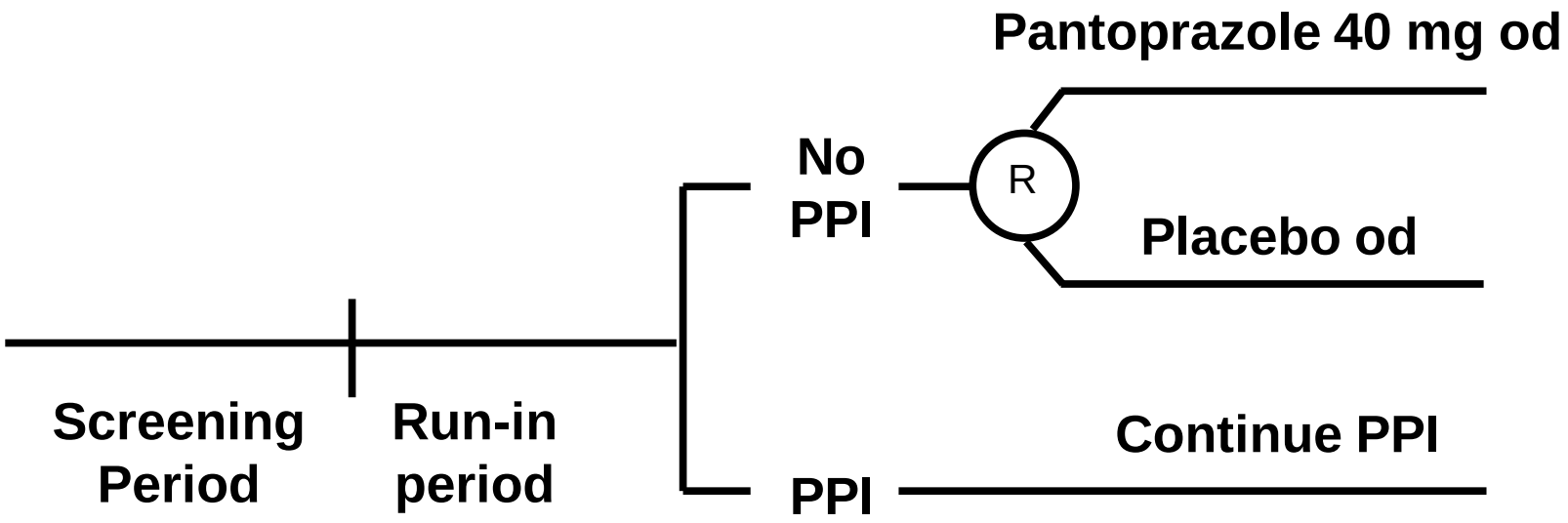
# Pantoprazole to Prevent Upper GI Events

# Background

- Antithrombotic therapies are associated with an increased risk of bleeding
- The most common site of bleeding is the gastrointestinal (GI) tract
- Proton pump inhibitors (PPIs) prevent upper GI events in patients treated with combination antiplatelet therapy or non-steroidal anti-inflammatory drugs
- It is not known whether PPIs prevent upper GI events in patients treated with anticoagulants

Bhatt DL, et al. *N Engl J Med* 2010; 363: 1909-17.

# Design




Primary outcome: upper GI complications
Expected mean follow up: 3-4 years

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

# Main Outcome

Composite of upper GI complications*

- Bleeding
  - Overt and from confirmed gastroduodenal source
  - Overt but of unknown origin
  - Occult with fall of Hb ≥2g/dL
- 5 days of upper GI pain related to peptic ulcer/erosions
- Upper GI perforation or obstruction

*Based on COGENT trial definition

Bosch J, et al. *Can J Cardiol* 2017; 33: 1027-35. Bhatt DL, et al. *N Engl J Med* 2010; 363: 1909-17.

# Baseline Characteristics

| | Pantoprazole N=8,791 | Placebo N=8,807 |
|---|---|---|
| Age, yr* | 68 | 68 |
| Female | 22% | 21% |
| Peptic ulcer disease | 3% | 3% |
| Inflammatory bowel disease | 0.4% | 0.6% |
| Diverticulitis | 1.5% | 1.4% |

*Mean

Moayyedi P, et al. *Gastroenterology* 2019; 157(2):403-412.

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

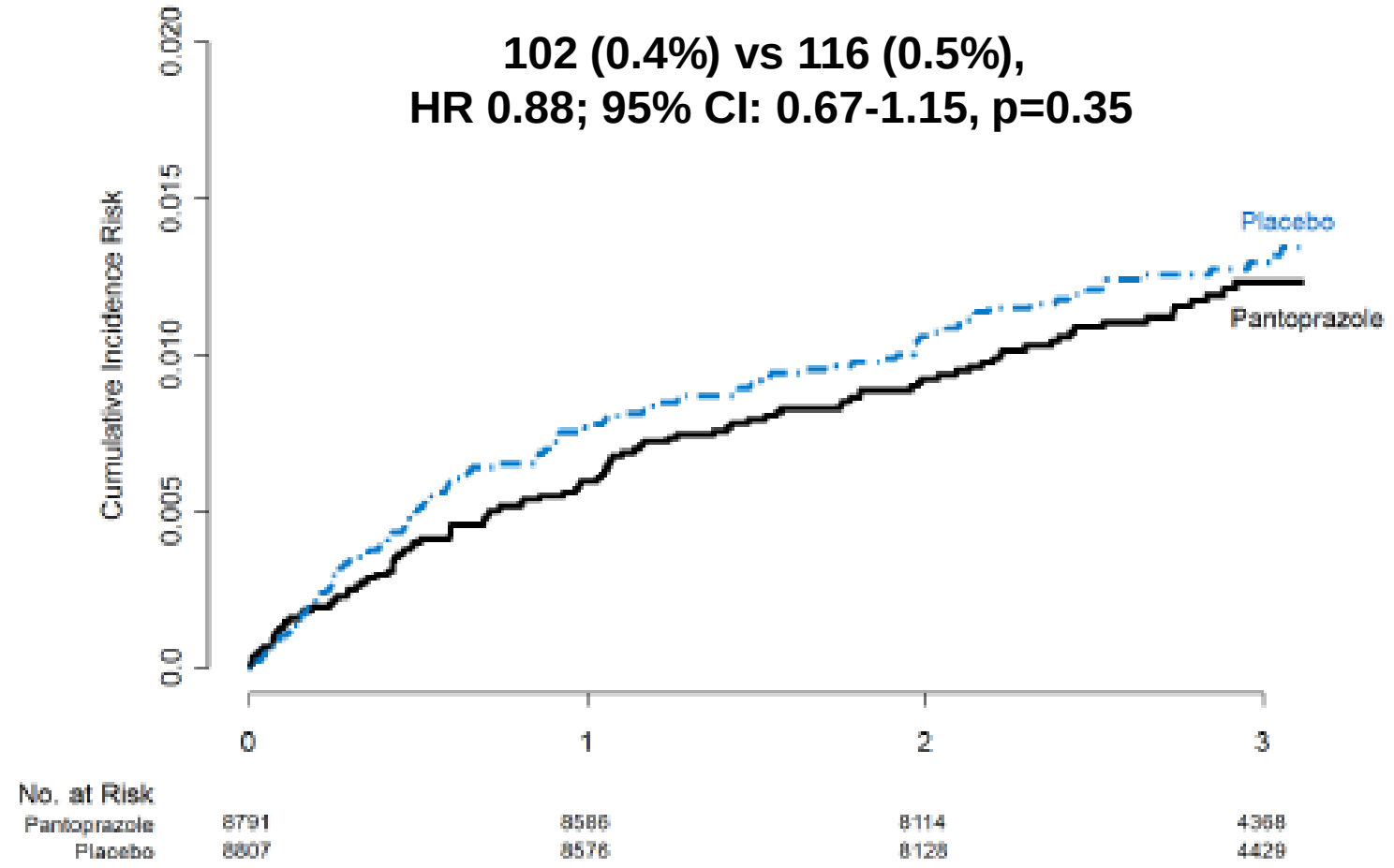
# Baseline Medications

| | Pantoprazole N=8,791 | Placebo N=8,807 |
|---|---|---|
| NSAIDs | 5% | 5% |
| SSRIs | 3% | 3% |
| ACE-I/ARB | 71% | 71% |
| Beta-blockers | 70% | 70% |
| | | |
| | | |

Moayyedi P, et al. *Gastroenterology* 2019; 157(2):403-412.

# Primary outcome

**102 (0.4%) vs 116 (0.5%),**
**HR 0.88; 95% CI: 0.67-1.15, p=0.35**




Moayyedi P, et al. *Gastroenterology* 2019; 157(2):403-412.

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# Components of Primary Outcome

| | Pantoprazole N=8,791 | Placebo N=8,807 | HR (95% CI) |
|---|---|---|---|
| **Overt bleed, gastroduodenal** | **0.2%** | **0.4%** | **0.52 (0.28-0.94)** |
| Overt bleed, source unknown | 0.6% | 0.5% | 1.09 (0.73-1.63) |
| Occult bleed, 2 g/dL Hb drop | 0.1% | 0.1% | 1.00 (0.42-2.40) |
| **Sympt. gastroduodenal ulcer** | **<0.1%** | **0.2%** | **0.47 (0.20-1.09)** |
| **GI pain and ≥5 GD erosions** | **<0.1%** | **<0.1%** | **0.57 (0.17-1.95)** |
| Upper GI obstruction / perforation | 0.2% | 0.2% | 1.32 (0.69-2.52) |

Moayyedi P, et al. *Gastroenterology* 2019; 157(2):403-412.

# Post-hoc exploratory analyses

| | Pantoprazole N=8,791 | Placebo N=8,807 | HR (95% CI) |
|---|---|---|---|
| Overt bleed, source identified (any) | 0.3% | 0.6% | 0.44 (0.27-0.73) |
| Any ulcer | 0.2% | 0.4% | 0.46 (0.25-0.83) |
| Any erosion | <0.1% | 0.2% | 0.33 (0.13-0.84) |

Moayyedi P, et al. *Gastroenterology* 2019; 157(2):403-412.

# Reported adverse effects of PPIs

- Enteric infections
- *Clostridium difficile* associated diarrhea
- Fracture
- Pneumonia
- Renal impairment
- Dementia
- Cancer
- COPD
- Diabetes mellitus
- Hospitalizations

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# Adverse effects
# Enteric infections

| Adverse effects | Pantoprazole N=8,791 | Placebo N=8,807 | OR (95% CI) |
|---|---|---|---|
| **Clostridium difficile** | 9 (0.1) | 4 (<0.1) | 2.26 (0.70 to 7.34) |
| **Other enteric infection** | 119 (1.4) | 90 (1.0) | 1.33 (1.01 to 1.75) |

Moayyedi P, et al. *Gastroenterology* 2019; 157(3):682-691.

# Summary

- In patients with chronic CAD or PAD, pantoprazole compared with placebo did not reduce upper gastrointestinal complications
- Secondary and post hoc analyses indicate that pantoprazole reduces upper GI bleeding, ulcers and erosions
- Long term pantoprazole appears to be safe expect for a possible increase in enteric infections

# Interpretation

- PPI therapy is likely to be effective for prevention of upper GI tract bleeding and ulceration / erosions in patients treated with rivaroxaban and/or aspirin but event rates are low and the results of COMPASS do not support their routine long-term use
- Long-term pantoprazole appears to be safe except that it may be associated with an increased risk of enteric infections