NOACs for stable CAD

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Background

- CV disease affects 4% of world population (300 million persons)
- Aspirin is the single most widely used secondary preventive treatment but produces only a 19% RRR during the long term
- Warfarin with or without aspirin is more effective than aspirin but increases bleeding, including intracranial hemorrhage
- Are newer anti coagulant agents safer than warfarin in reducing mortality in patients with cardiovascular disease?

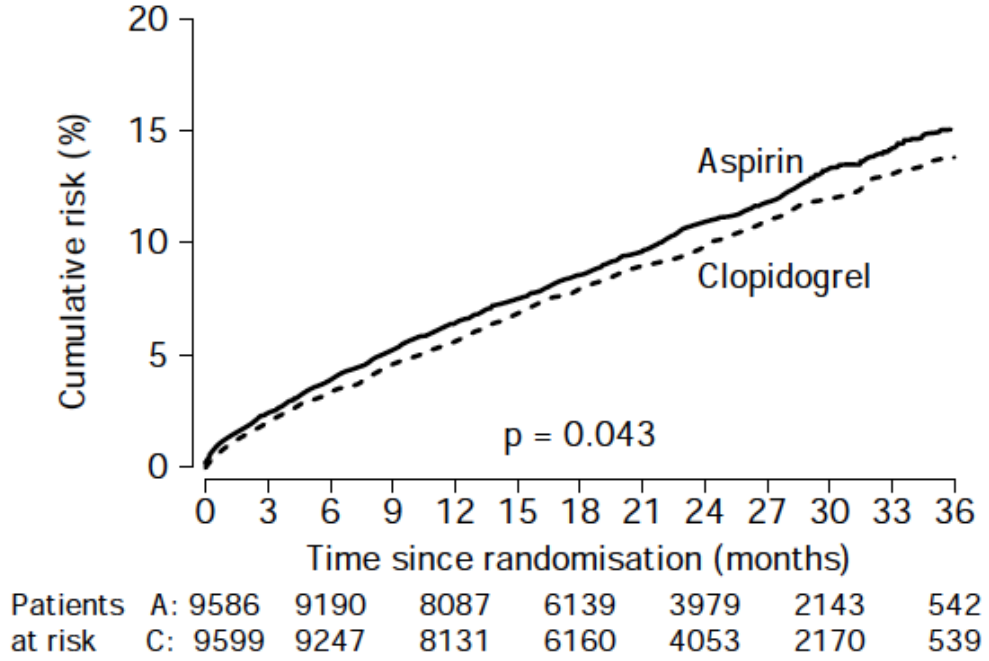
Why an anticoagulant?

The theoretical benefits of using anticoagulant therapy in patients with atherosclerotic cardiovascular disease reflect the complex orchestra of events involved in the generation of arterial thrombosis.

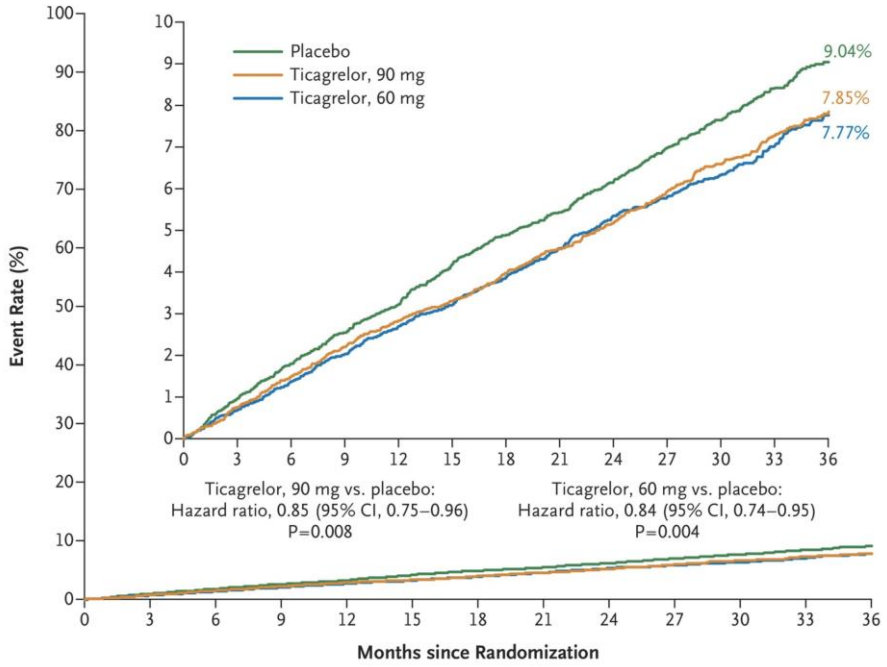
Exposure of plaque contents to circulating blood, stimulates activation of both platelets and the coagulation cascade, leading to clot formation.

Accordingly, therapeutic targeting with both antiplatelet and anticoagulant therapy has the potential to treat both of these factors more extensively than antiplatelet agents alone.

Antiplatelets



CAPRIE



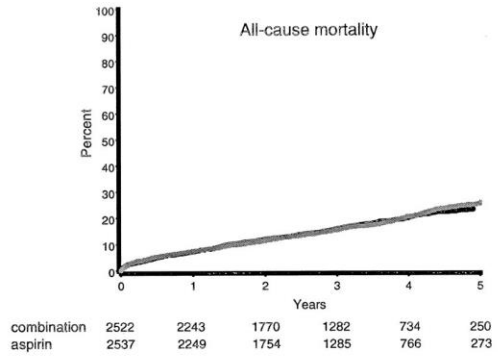
TICAGRELOR

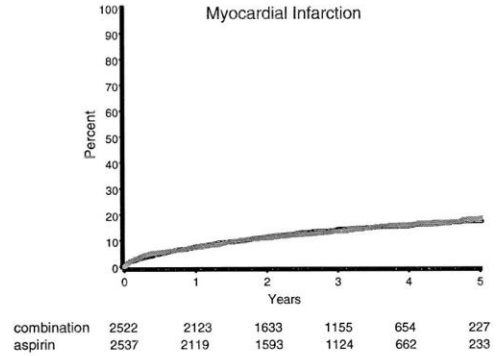
Warfarin

Department of Veterans Affairs Cooperative Studies Program Clinical Trial Comparing Combined Warfarin and Aspirin With Aspirin Alone in Survivors of Acute Myocardial Infarction

Primary Results of the CHAMP Study

Louis D. Fiore, MD; Michael D. Ezekowitz, MD, PhD; Mary T. Brophy, MD; David Lu, MD; Joseph Sacco, MD; Peter Peduzzi, PhD; for the Combination Hemotherapy and Mortality Prevention (CHAMP) Study Group*





5059 patients enrolled within 14 days of Myocardial infarction

Clinical research

Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction

the LoWASA Study

Johan Herlitz[a]*, Johan Holm[b], Magnus Peterson[c], Björn W. Karlson[a], Maria Haglid Evander[a], Leif Erhardt[b], for the LoWASA study group

4500 patients enrolled recent MI , 5 years Warfarin

Warfarin

VOLUME 347 SEPTEMBER 26, 2002 NUMBER 13

WARFARIN, ASPIRIN, OR BOTH AFTER MYOCARDIAL INFARCTION

METTE HURLEN, M.D., MICHAEL ABDELNOOR, M.P.H., PH.D., PÅL SMITH, M.D., PH.D., JAN ERIKSSEN, M.D., PH.D., AND HARALD ARNESEN, M.D., PH.D.*

3630 patients enrolled within Hx of MI

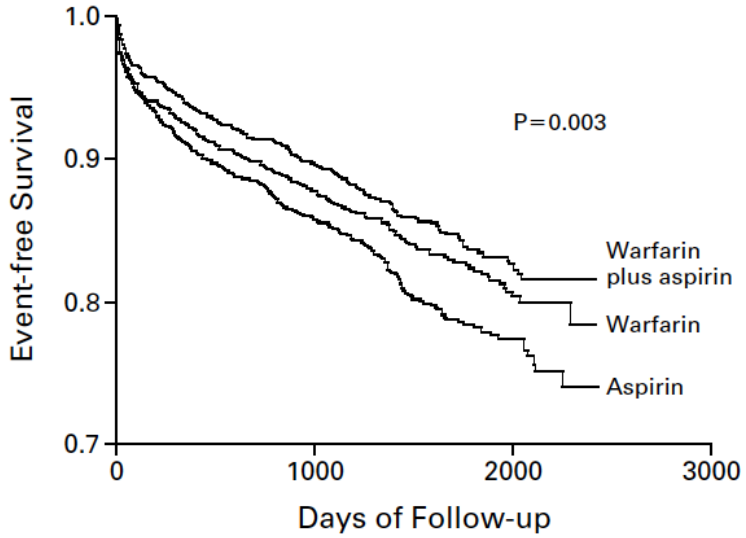


Figure 1. Event-free Survival Curves for the Composite End Point of Death, Nonfatal Reinfarction, and Thromboembolic Stroke.

The P value refers to the overall difference among the curves (Tarone–Ware method).

At a cost of 4x more bleeding

ATLAS ACS- TIMI 51

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*

15,526 pts with hx of MI.

High Dose and low dose Rivaroxiban up to 2.5 years

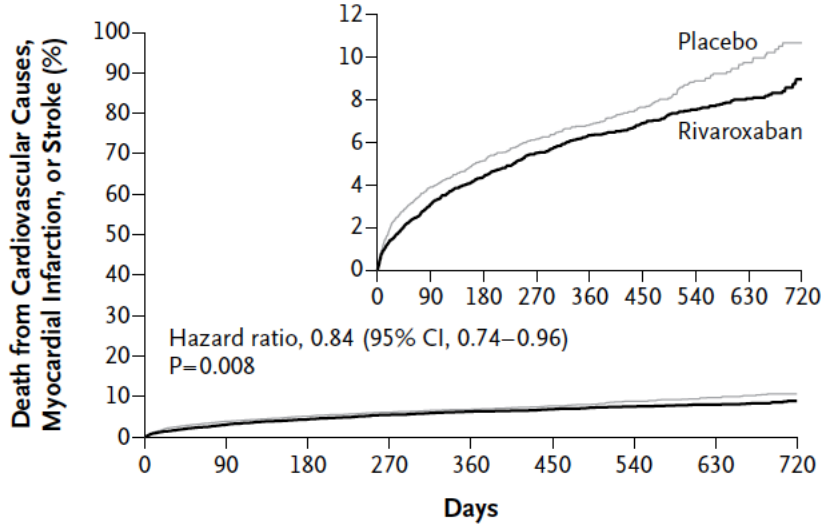


Figure 1. Cumulative Incidence of the Primary Efficacy End Point.

The primary efficacy end point consists of death from cardiovascular causes, myocardial infarction, or stroke. According to these results, the composite end point would be prevented in 1 patient if 56 patients were treated for 2 years with rivaroxaban. The P value is for the modified intention-to-treat analyses. P=0.002 for the intention-to-treat analysis.

COMPASS Trial

The NEW ENGLAND JOURNAL of MEDICINE

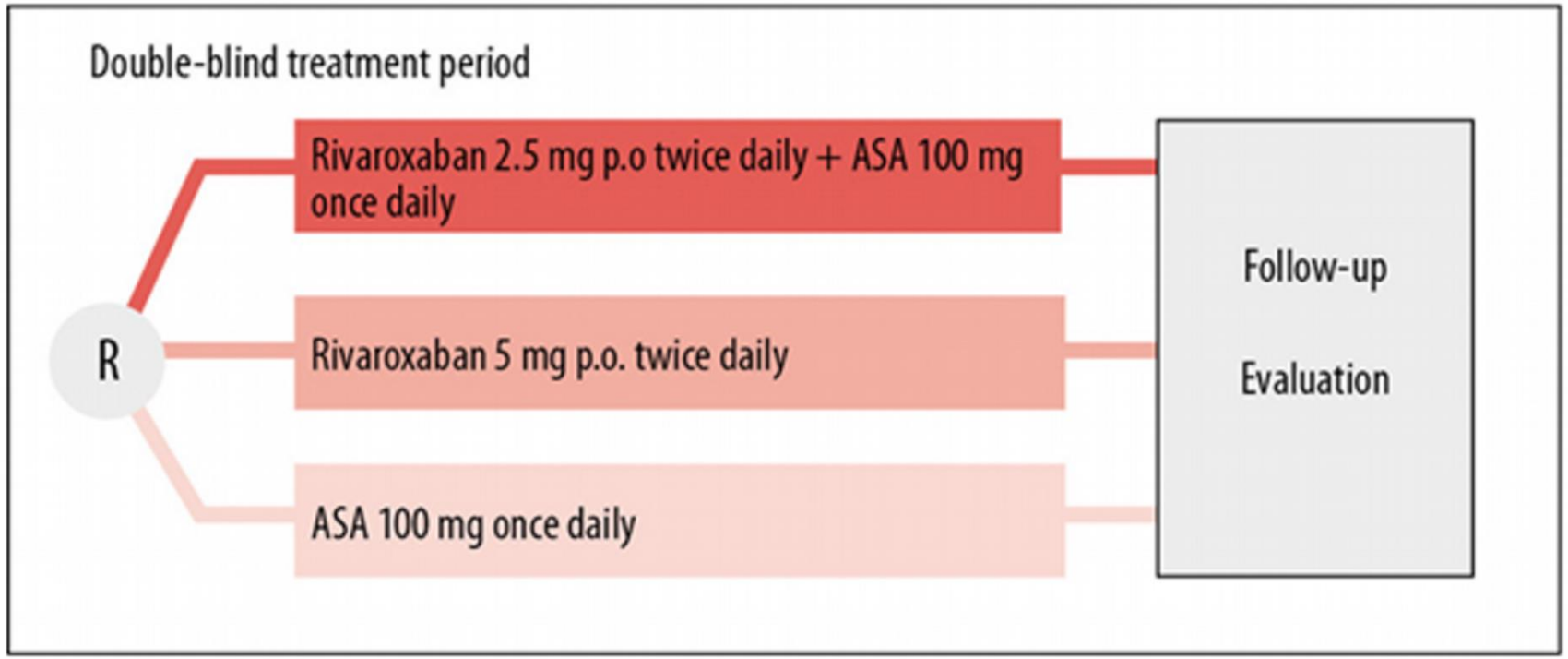
ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

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.K. 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*

Design

- Randomized placebo-controlled phase III study, event driven, expected duration 3–4 years
- 27,400 patients ≥18 years with documented atherosclerosis related to CAD or PAD plus one of the following inclusion criteria:
  - age ≥65 years
  - age <65 years plus documented atherosclerosis in at least two vascular beds or at least 2 additional risk factors



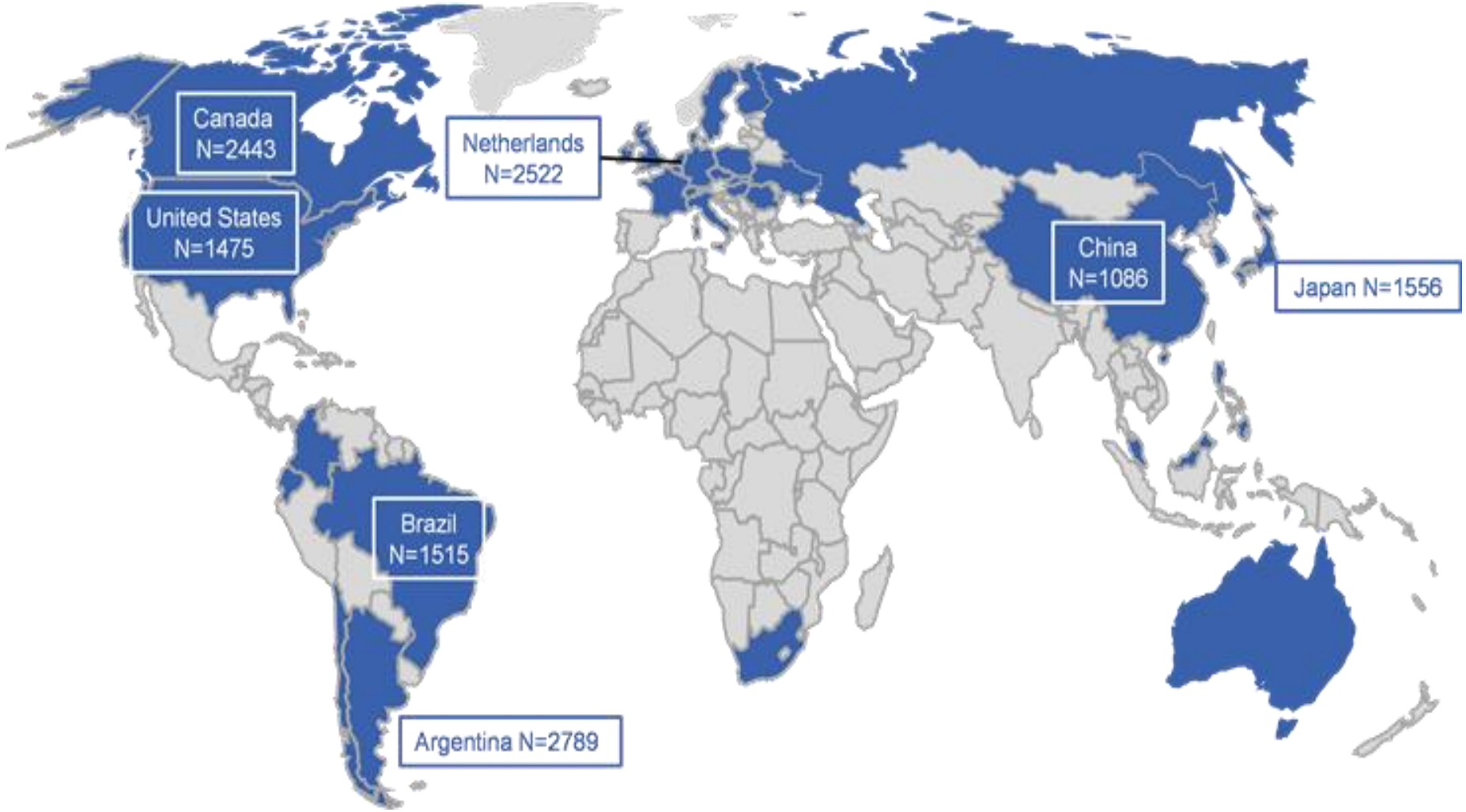
Outcomes

- Primary
  - CV death, stroke or myocardial infarction
- Secondary
  - CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - CV death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - Mortality
- Safety and net clinical benefit
  - ISTH major bleeding (modified)
    - fatal bleeding,
    - symptomatic bleeding in a critical area or organ,
    - surgical site requiring reoperation,
    - bleeding leading to hospitalization
    - presentation to an acute care facility without overnight stay;

Exclusion criteria:

- High bleeding risk
- Recent stroke or previous hemorrhagic or lacunar stroke
- Severe heart failure
- Advanced kidney disease
- Use of dual antiplatelet therapy or anticoagulation
- Limited prognosis

602 sites, 33 countries



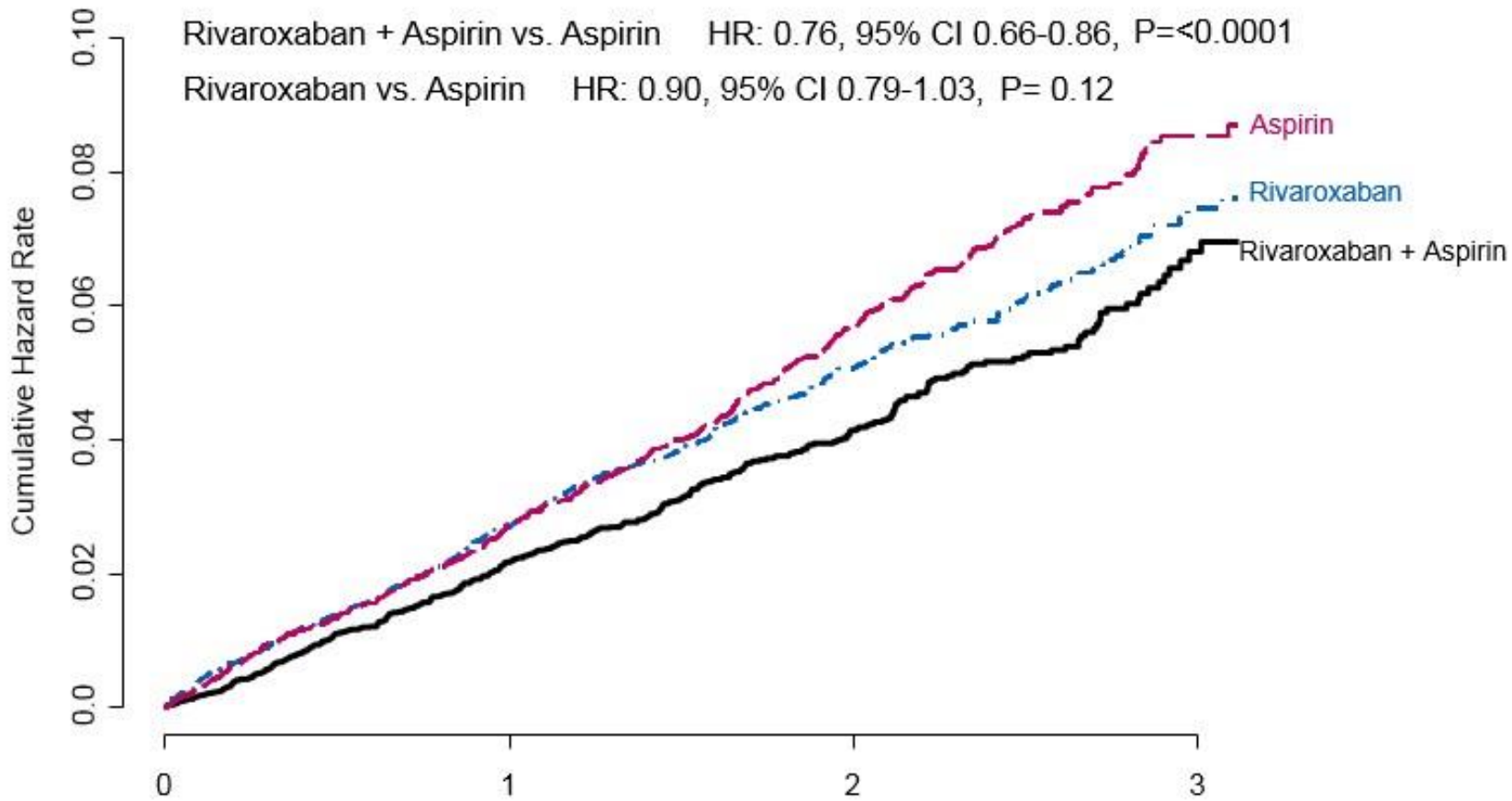
Baseline characteristics

Characteristic	Rivaroxaban + aspirin N=9,152	Rivaroxaban N=9,117	Aspirin N=9,126
Age, yr	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	90%	90%	89%
ACE-I or ARB	71%	72%	71%

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

Primary: CV death, stroke, MI



Bioactive Lipids

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
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

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

Net clinical benefit

- Primary Cardiovascular Outcome (MACE):
  - CV death, stroke, or MI

- Major Adverse Limb Events (MALE):
  - Severe limb ischemia leading to an intervention (angioplasty, bypass surgery, amputation, thrombolysis)
  - Major Amputation above forefoot due to vascular cause

Conclusion

Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- Reduces CV death, stroke, MI
- Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding
- Provides a net clinical benefit

No significant benefit of rivaroxaban alone

PAD Patients in COMPASS

PAD Groups	Number of patients
All Patients	7,470
Symptomatic PAD Limbs	4,129
Carotid Disease	1,919
CAD + Low ABI (<0.90) only	1,422

Mean Follow-up: 21 months

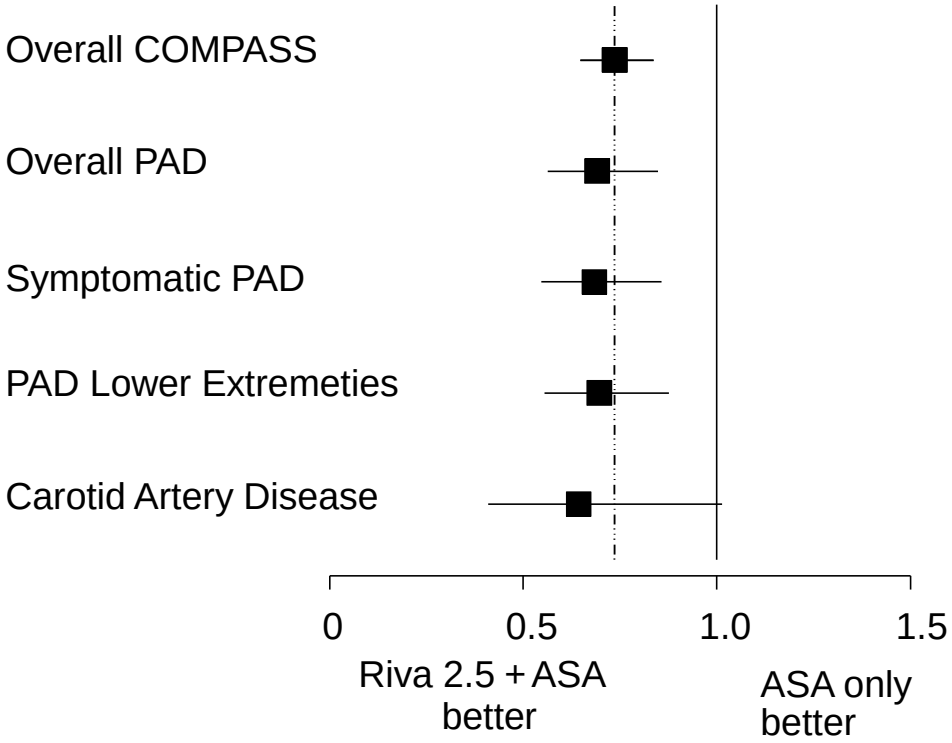
Baseline Characteristics

Characteristic	Riva + aspirin N=2,492	Rivaroxaban N=2,474	Aspirin N=2,504
Age, years (mean)	68	68	68
Current Smoker	27%	28%	27%
Former Smoker	46%	47%	46%
Diabetes	44%	44%	44%
Hypertension	79%	78%	81%
Prior CAD or Stroke	69%	69%	68%
Lipid Lowering	84%	84%	83%
ACE-I/ARB	69%	71%	70%

Limb outcomes

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
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

MACE, MALE or Major Amputation



All COMPASSING

COMPASS-PAD:

COMPASS-Lower Extremity PAD : 4,129 participants

COMPASS-CAD: 24,824 participants

COMPASS-CABG: 1,448 CABG pts. No difference in Graft failure

COMPASS-PCI: This substudy examined 9,862 pts.

COMPASS-Heart Failure: 5,902 pats

COMPASS-Diabetes

COMPASS-Sex Differences

COMPASS-Obesity

Circulation

ORIGINAL RESEARCH ARTICLE

The COMPASS Trial

Net Clinical Benefit of Low-Dose Rivaroxaban Plus Aspirin as Compared With Aspirin in Patients With Chronic Vascular Disease

The predefined NCB outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ

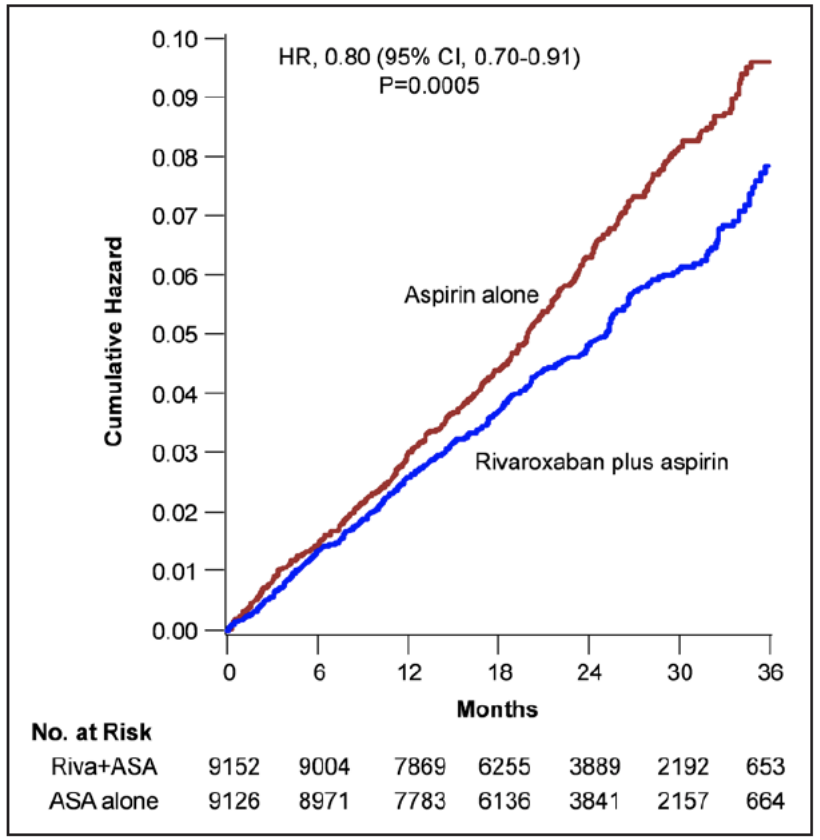
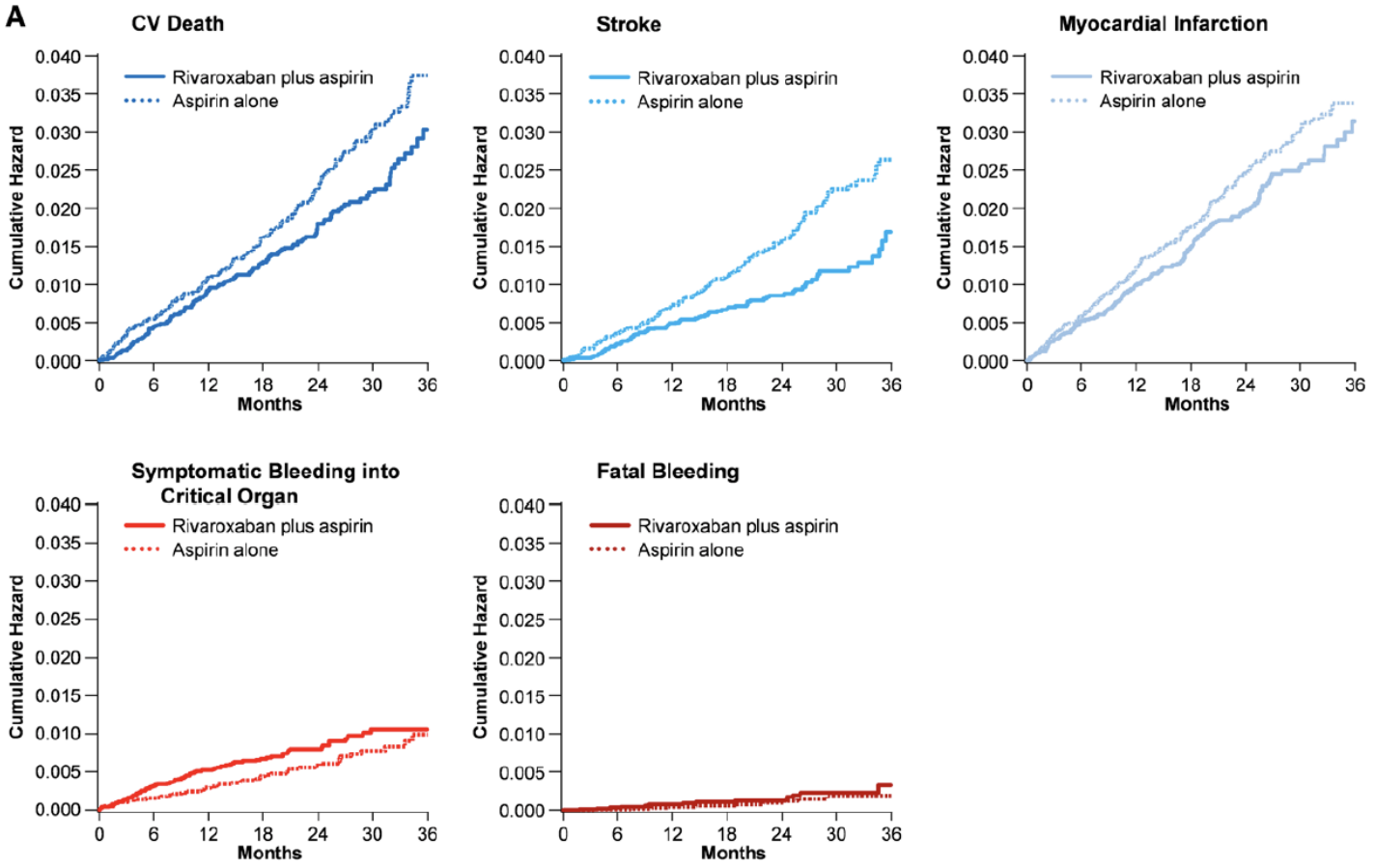
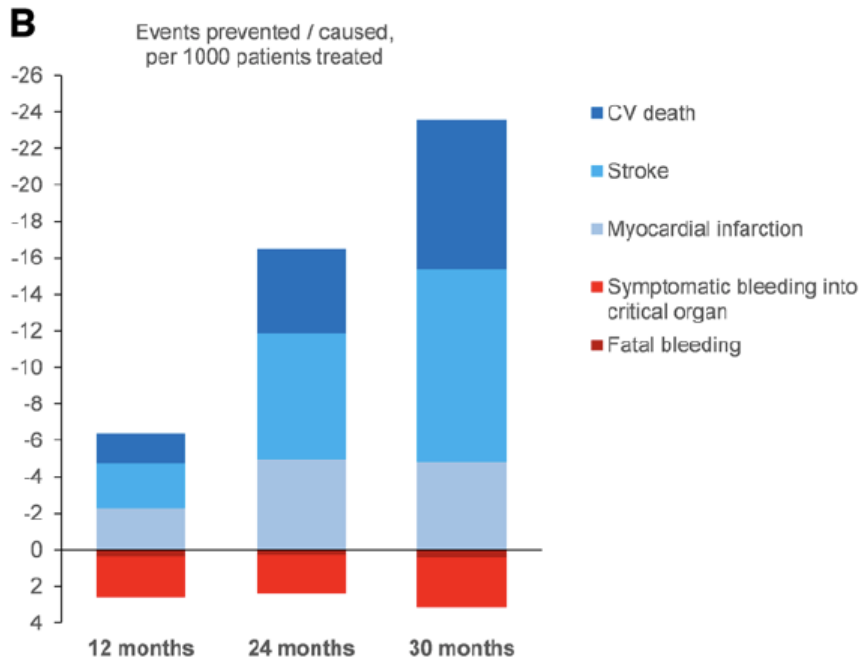


Figure 1. Cumulative incidence of the net clinical benefit outcome among participants receiving rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.
ASA indicates acetylsalicylic acid (aspirin); HR, hazard ratio; and Riva, Rivaroxaban.

Incidence of the net clinical benefit outcome components





Conclusion:

Among patients with stable atherosclerosis, rivaroxaban plus aspirin was associated with fewer adverse cardiovascular events, but more major bleeding events compared with aspirin alone.

Net clinical benefit favored the use of rivaroxaban plus aspirin, especially for high-risk groups.

Findings were the same among those with PAD, lower extremity PAD, CAD, heart failure, diabetes, women, and obesity