DOAC: future possibili indicazioni

(IMA, stroke criptogenico, TVC, TV viscerali)

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DOAC: Valve heart disease

- Mechanical heart valves:
  - Dabigatran associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin
- AF after bioprosthetic valve implantation:
  - No RCT, but post-hoc analyses demonstrate possible equivalence to VKA
- TAVI/TAVR procedures:
  - Ongoing studies

Eikelboom, et al. N Engl J Med, 2013
Anderson, et al. Clinical Medicine Insights: Therapeutics, 2018

Atypical VTE – splanchnic thrombosis

Some possible safety issues

- Mesenteric vein thrombosis may cause impaired drug absorption
- Hepatic function may change over time
- DOAC [] may be locally increased because of low flow (local bleeding)

- Screening for varices recommended
- Beta-blocker therapy and endoscopic variceal ligation before starting anticoagulation

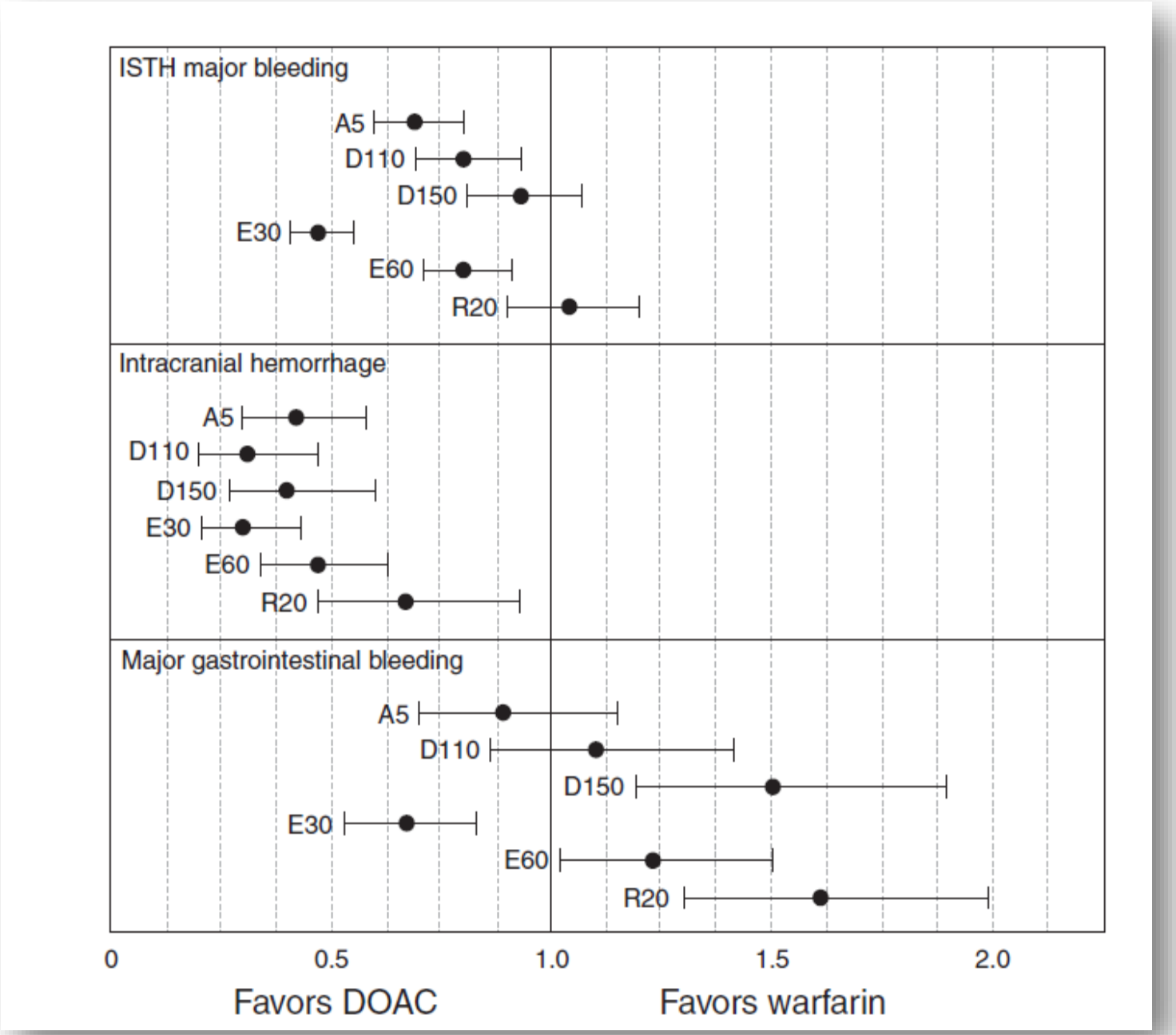
Author	Study design	Number of patients (n)	Duration	Agent	Response	Bleeding events
Janczak [19] (2018)	Prospective, non-cirrhotic, Atypical sites	Total N=36 PVT N= 16		Rivaroxaban Apixaban	Recurrence rate 7.3 % (n=2) (both had malignancy)	Minor N=1 (3.6%) Major N=2 (7.2%)
Qi [20] (2017)	Case report, cirrhotic, CPT not specified	SMV, splenic vein, N=1	11 weeks	Rivaroxaban	Recanalization	Melena and hematemesis
Nery [21] (2017)	Case report Non-cirrhotic	N=1	>6m	Rivaroxaban 20 mg daily	Complete recanalization L branch, partial recanalization right branch	None
De Gottardi [10] (2016)	Retrospective, Both cirrhotic and non-cirrhotic, Splanchnic	Total, N= 94 PVT N= 80 (Non cirrh- N=38 Cirrh- N=22)	Non-cirrhotic 13.1 m cirrhotic 9.6 m	Rivaroxaban Apixaban Dabigatran	Not studied	Cirrhosis: Minor, n=7, Major, n=2 Non-cirrh: Minor, n= 4 Major, n=1
Hum [9] (2016)	Retrospective, Cirrhotic, CPT A, B & C All indications	Total, N= 27 PVT N=4		Rivaroxaban 15 mg bid +/- 20 mg daily load, Apixaban 5mg bid +/- 10mg bid load, No bridging	Recurrence rate 4% (n=1)	Major N=1 (4%) Minor, N=7
Yang [12] (2016)	Case report, cirrhotic CPT A	N=1	6 m	Rivaroxaban 15 mg bid x 3 wks, then 20 mg/d	Complete recanalization	None
Intagliata [8] (2015)	Retrospective, cirrhotic, CPT A and B	Total N= 20 PVT, N=12	10.6 m	Apixaban Rivaroxaban	Not studied	Major, n=1
Martinez [22] (2014)	Case report, Cirrhotics, CPT A	N=1	6 m	Rivaroxaban 20 mg /d	Complete recanalization	None
Lenz [11] (2014)	Case report, Cirrhotic CPT A	N=1	5 m	Rivaroxaban 10 mg daily	Complete recanalization	None
Pannach [23] (2013)	Case report, Non-cirrhotic	N=1	>4 weeks	Rivaroxaban 20 mg daily	Complete recanalization	None

CPT: Child Pugh Turcotte; Cirrh: cirrhosis.

From *Priyanka, et al.* Newer Oral Anticoagulants in the Treatment of Acute Portal Vein Thrombosis in Patients with and without Cirrhosis *Int J Hepatol, 2018*

Gastrointestinal bleeding and DOAC use

Review of clinical trial data and 15 post-market retrospective and prospective studies



J. C. Desai, et al. The American Journal Of Gastroenterology Supplements, 2016

DOAC in cerebral vein thrombosis

Study	Design	Patient number	Treatment	Outcomes
RE-SPECT CVT	RCT	TBA	Dabigatran	TBA October 20th
Rao et al, 2017	Case report	3	Apixaban	Resolution
Hon et al, 2012	Case report	15	Dabigatran	Resolution in 12
Geisbusch, 2014	Case report	7	Rivaroxaban	Minor bleeding in 1 patient
Mendonca, 2015	Case report	15	Dabigatran	Resolution in 12
Mutgi, 2015	Case report	2	Rivaroxaban	Good resolution

Awaiting results of the RE-SPECT CVT RCT comparing Dabigatran vs warfarin

DOAC in patients with arterial disease

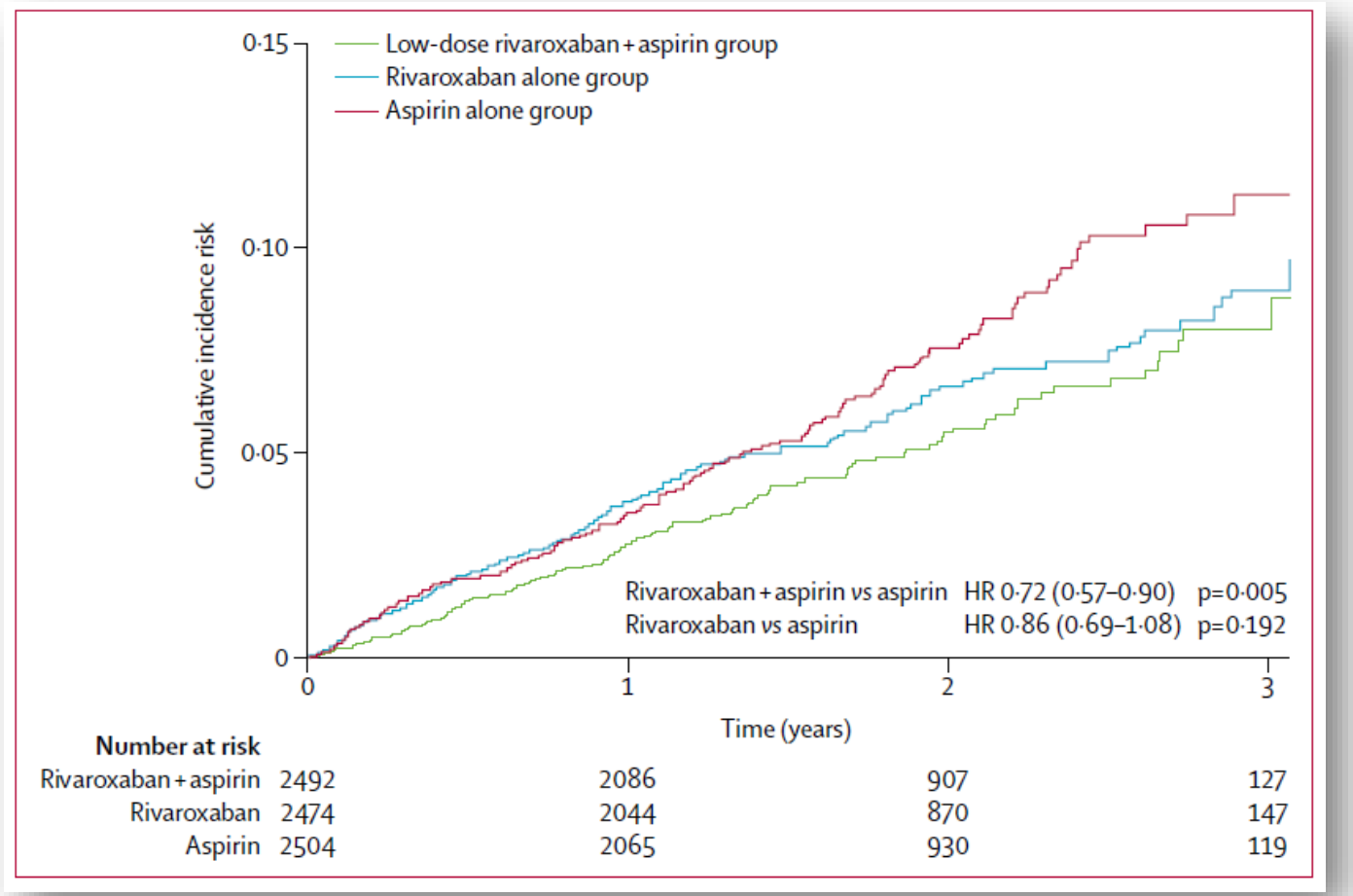
- Patients with stable peripheral or carotid artery disease
- Patients with cardiovascular disease
- Patients with embolic stroke of unknown etiology

Carotid or peripheral arterial disease

- 7470 patients with peripheral artery disease from 558 centers
- Previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication, previous carotid artery revascularization or asymptomatic carotid artery stenosis of at least 50%, or coronary artery disease with an ankle–brachial index of less than 0·90
- Assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day, or to aspirin once a day
- Primary outcome was cardiovascular death, myocardial infarction or stroke (COMPASS trial)

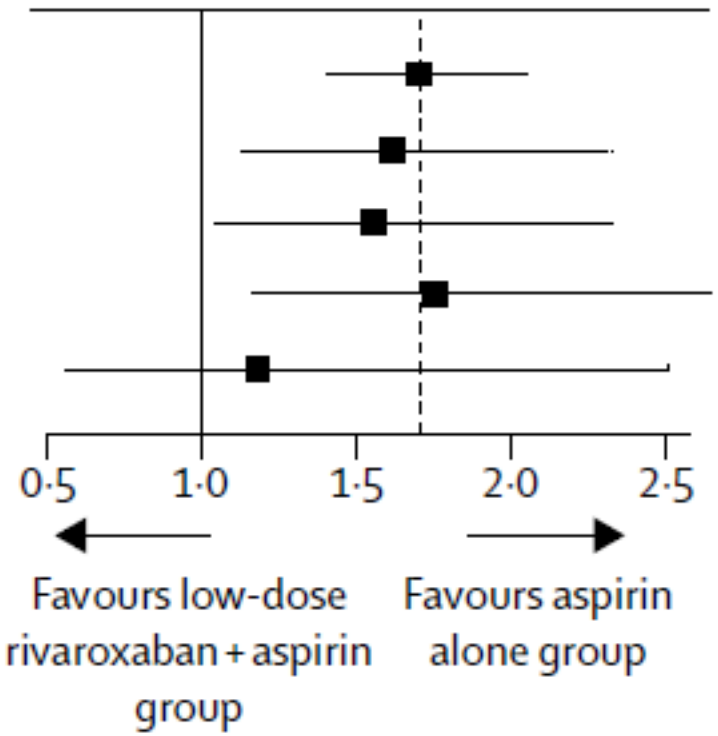
Anand, et al. Lancet, 2018

Carotid or peripheral arterial disease: efficacy



Anand, et al. Lancet, 2018

Carotid or peripheral arterial disease: safety



Overall COMPASS

Overall peripheral artery disease

Symptomatic peripheral artery disease

Peripheral artery disease lower extremities

Carotid artery disease

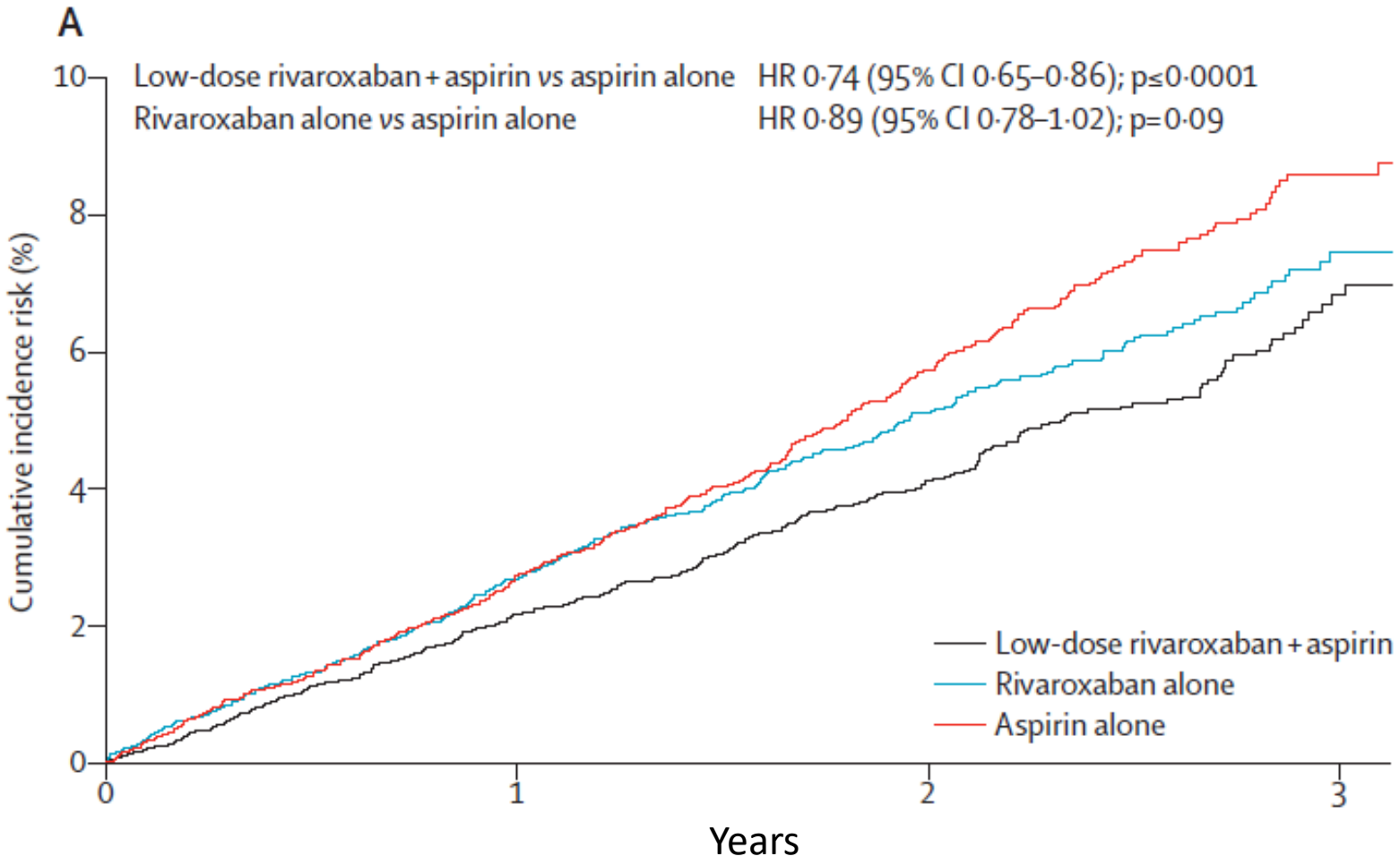
Anand, et al. Lancet, 2018

Cardiovascular disease

- 24 824 patients with stable coronary artery disease from 558 centers
- Previous MI, multi-vessel coronary artery disease, stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel BP surgery
- Assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day, or to aspirin once a day
- Primary outcome was cardiovascular death, myocardial infarction or stroke (COMPASS trial)

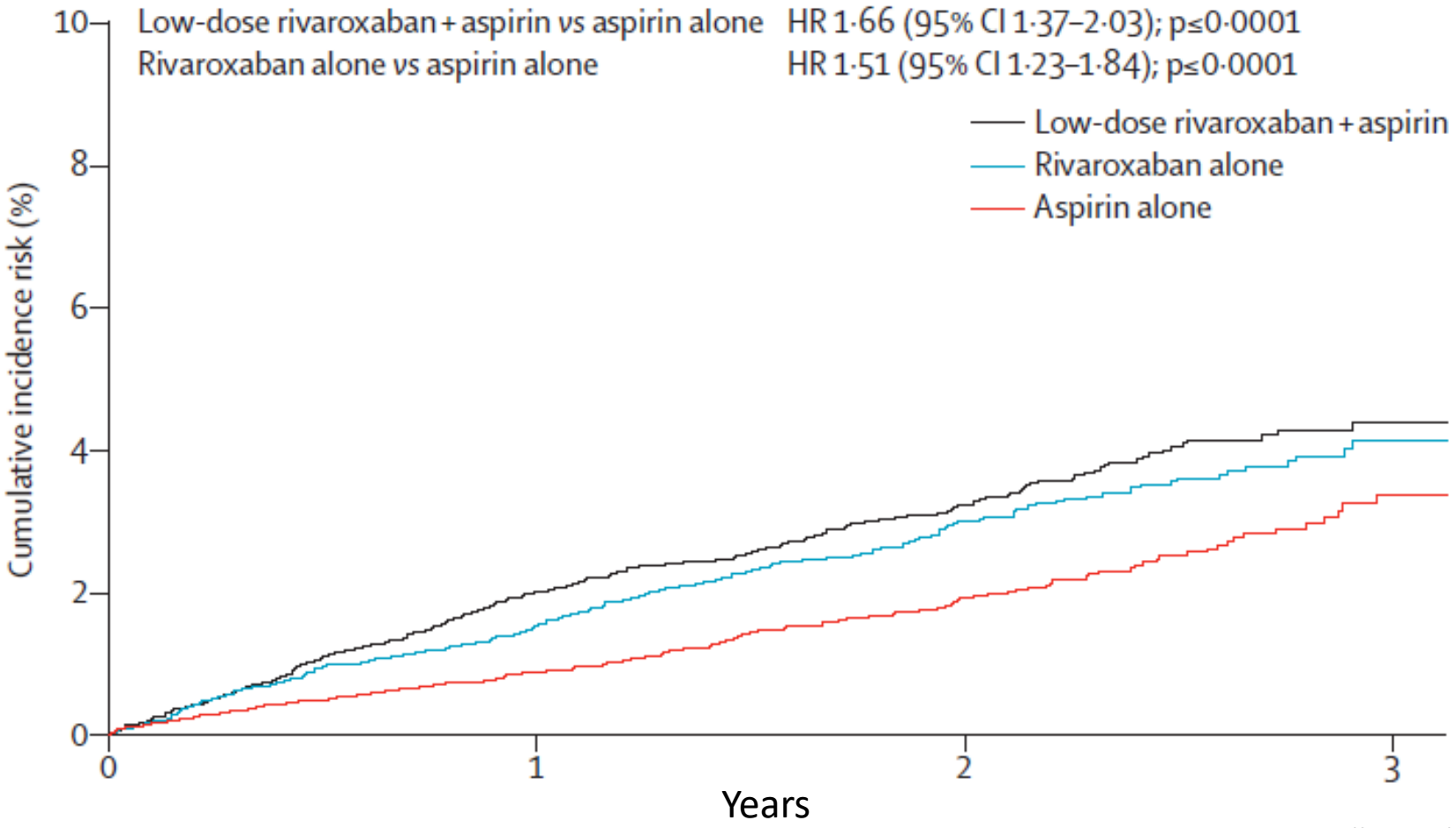
Connolly, et al. Lancet, 2018

Cardiovascular disease: efficacy



Connolly, et al. Lancet, 2018

Cardiovascular disease: safety



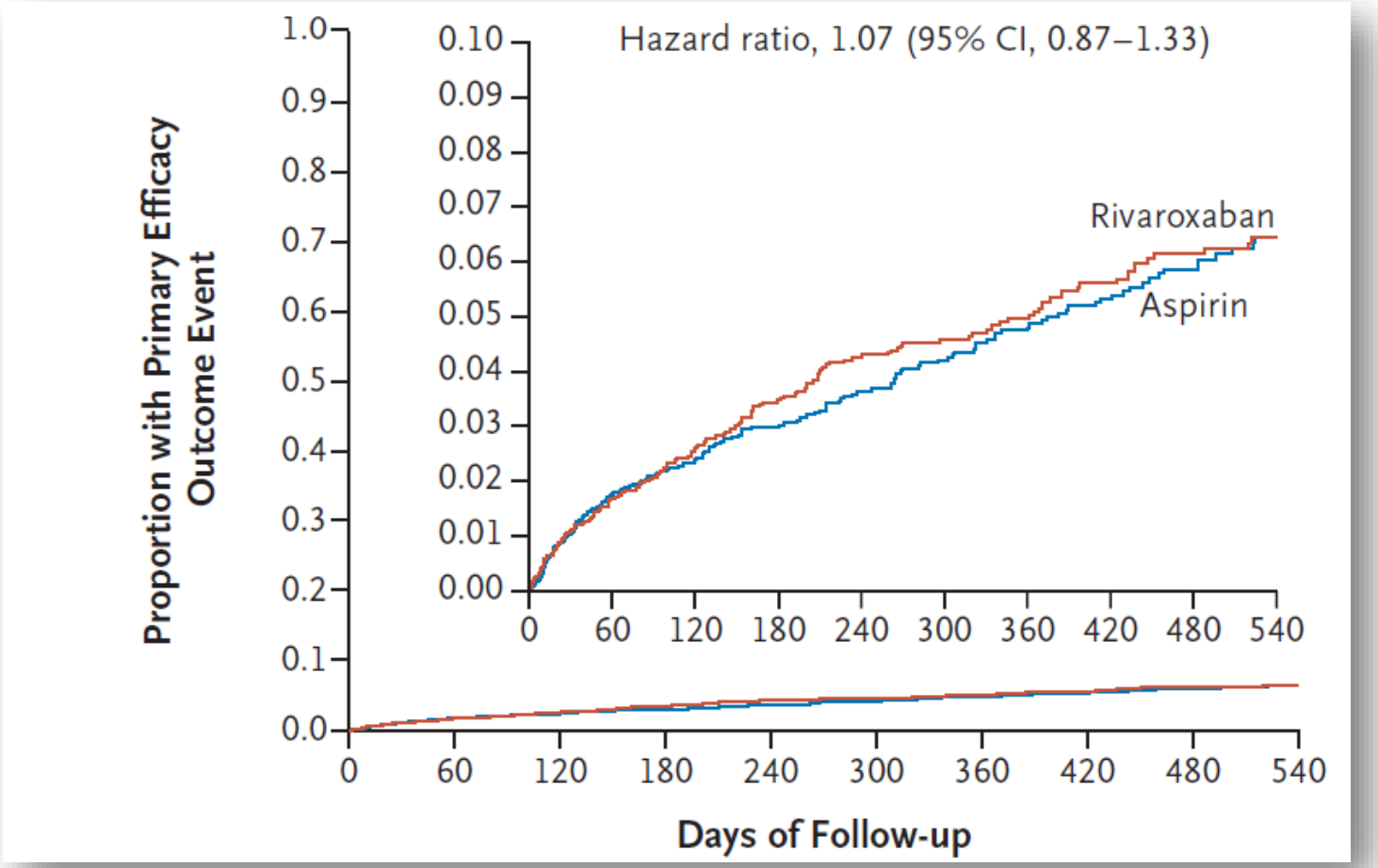
Connolly, et al. Lancet, 2018

Embolic stroke of unknown etiology

- 7213 patients with stroke from 459 centers
- Stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source
- Assigned (1:1) to receive oral rivaroxaban (15 mg), or to aspirin (100 mg) once a day
- Primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism (NAVIGATE ESUS trial)

Hart et al. NEJM, 2018

Embolic stroke of unknown etiology

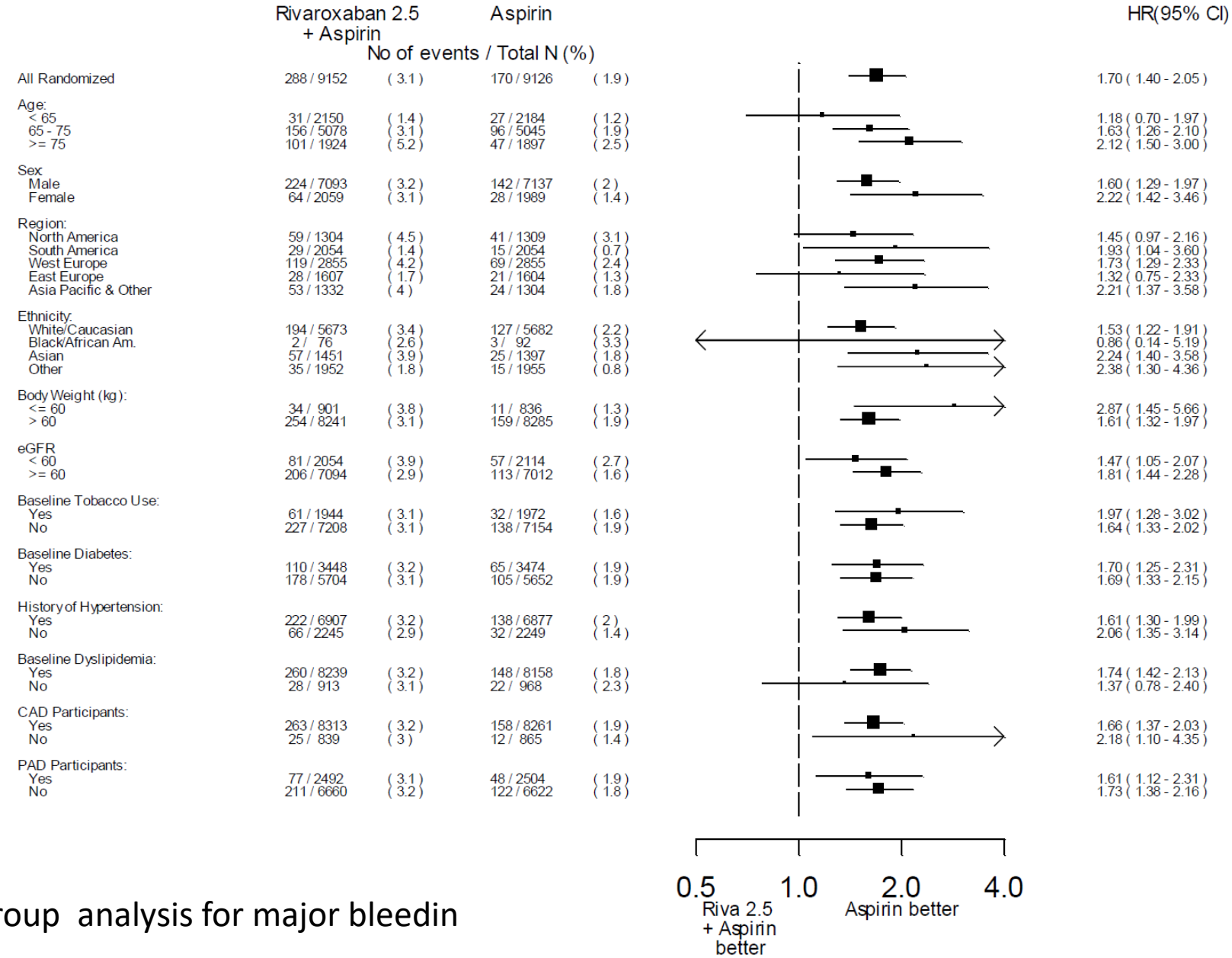


Hart et al. NEJM, 2018

Summary of low-dose rivaroxaban in arterial disease

Study	Patient, n	Intervention	NNT	NNH
Anand, 2018	PAD, 7 470	ASA vs ASA+R 2.5 mg bid	50	48
Hart, 2018	Embolic stroke, 7213	ASA vs R 15 mg oid	306	92
Connolly, 2018	CAD, 24 824	ASA vs ASA+R 2.5 mg bid	50	80
Eikelboom, 2017	PAD+CAD, 27 395	ASA vs ASA+R 2.5 mg bid	77	83

NNT: Primary composite endpoint; NNH; Major bleeding



Subgroup analysis for major bleedin

Eikelboom et al. NEJM, 2017

Conclusions

- Preliminary data suggest that DOAC may have a favorable risk/benefit profile in splanchnic and cerebral vein thromboses
- RCT support the use of rivaroxaban in patients with stable coronary or peripheral arterial disease
  - Bleeding risk should be considered
  - No comparison for efficacy/safety with DAPT
  - Surveillance?