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24-26 Maggio 2019

DOAC 4.0:
il paziente al centro e nuovi paradigmi

Studio COMPASS : un nuovo paradigma nella gestione della cardiopatia ischemica

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Pavia

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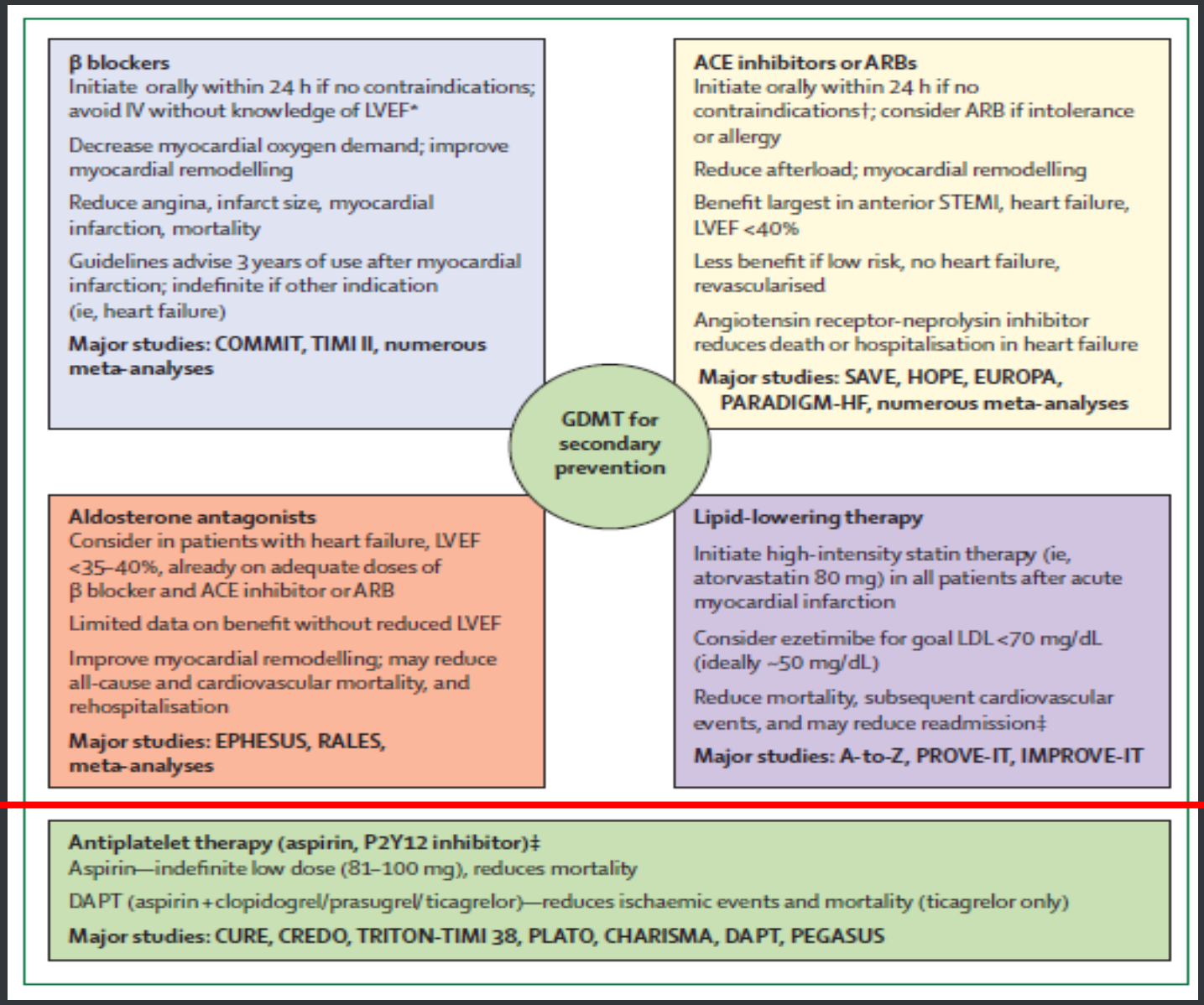
Studio COMPASS :

un nuovo paradigma nella gestione della CAD

Come fronteggiamo il rischio ischemico residuo a lungo termine in un paziente con cardiopatia ischemica cronica ?



Reed GW et al. Lancet 2017; 389:197-210

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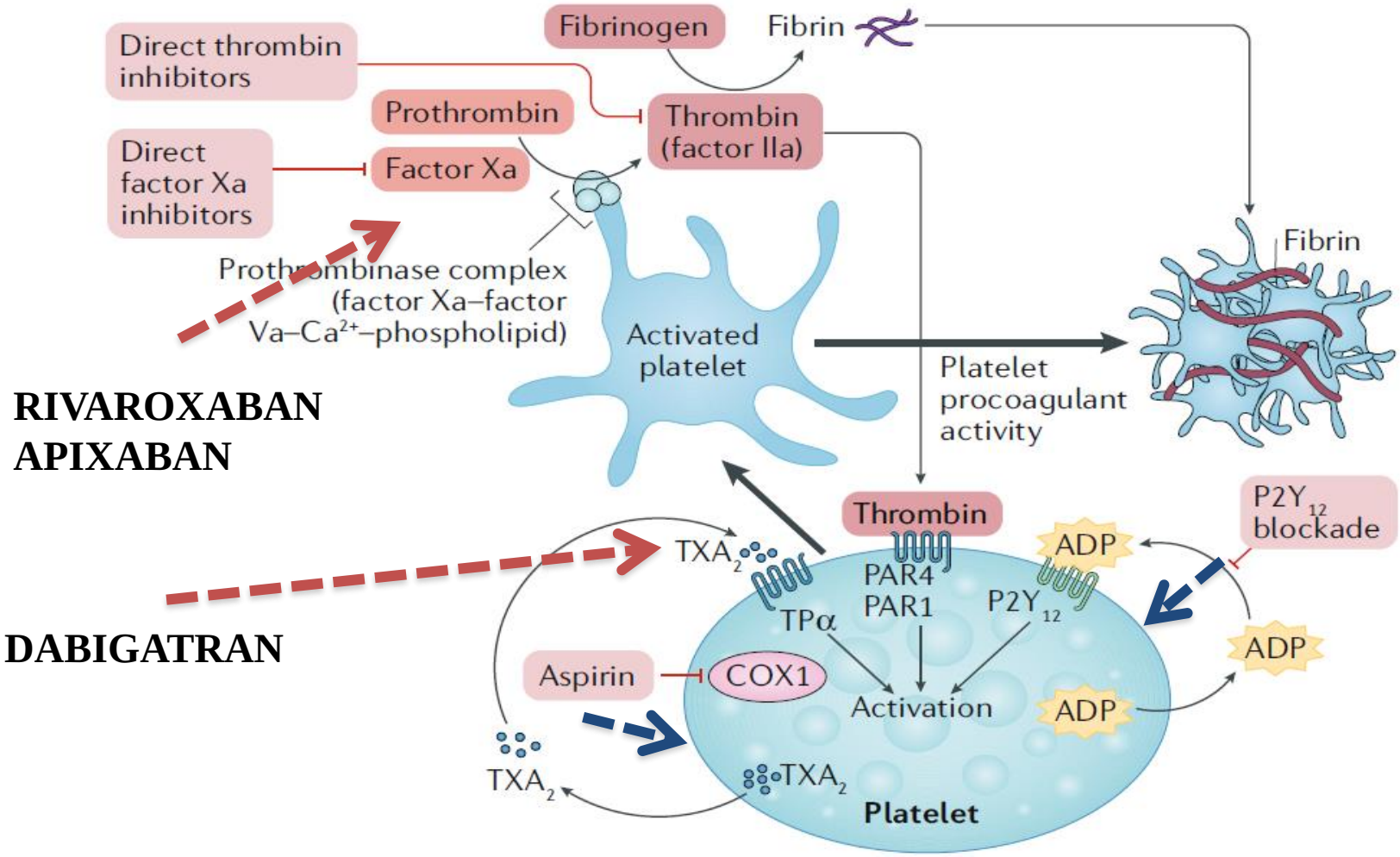
un nuovo **paradigma** nella gestione della CAD

Qual' è il ruolo dei farmaci antitrombotici in prevenzione secondaria ?

Synergy between anti-Xa and APT



Nat Rev Cardiol. 2018 Aug;15(8):480-496.

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L' inibizione della cascata emocogulativa (fattore Xa, trombina), non solo dell' aggregazione piastrinica, è un meccanismo chiave nel prevenire la trombosi coronarica

(…. dalla fisiopatologia alla clinica….)

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un nuovo **paradigma** nella gestione della CAD

Il trial COMPASS

LOV 2019

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Studio COMPASS :

un nuovo **paradigma** nella gestione della CAD

Nuova opzione terapeutica (nuova indicazione) : *rivaroxaban nella cardiopatia ischemica*

a. evidenze cliniche chiare e solide ?
b. per quali pazienti ?
c. quale sicurezza ?
d. quando iniziare la terapia ?
e. il dosaggio (“vascolare”)
f. in associazione ad aspirina ?
g. per quanto tempo ?

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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*

Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial

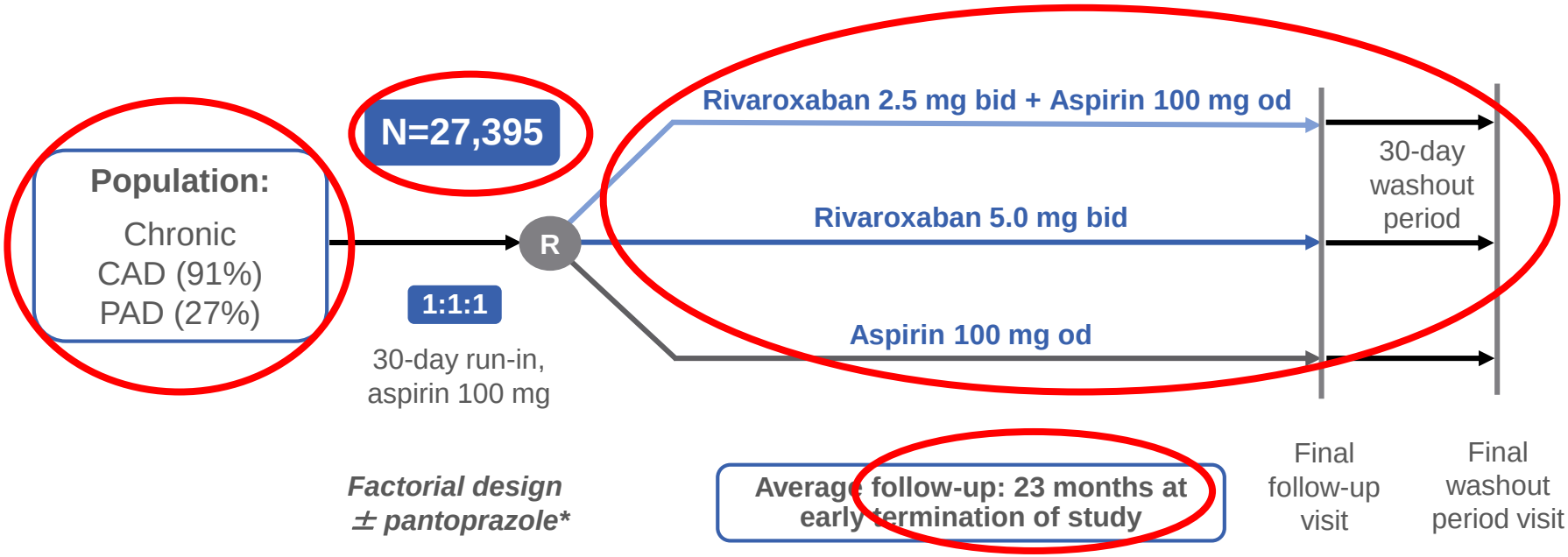
*Stuart J Connolly, John W Eikelboom, Jackie Bosch, Gilles Dagenais, Leanne Dyal, Fernando Lanas, Kaj Metsarinne, Martin O'Donnell, Anthony L Dans, Jong-Won Ha, Alexandr N Parkhomenko, Alvaro A Avezum, Eva Lonn, Liu Lisheng, Christian Torp-Pedersen, Petr Widimsky, Aldo P Maggioni, Camilo Felix, Katalin Keltai, Masatsugu Hori, Khalid Yusoff, Tomasz J Guzik, Deepak L Bhatt, Kelley R H Branch, Nancy Cook Bruns, Scott D Berkowitz, Sonia S Anand, John D Varigos, Keith A A Fox, Salim Yusuf, on behalf of the COMPASS investigators**

Lancet 2018; 391: 205–18

CAD PAD

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

Main Study Outcomes

Primary efficacy outcome

- Composite of MI, stroke or CV death

Secondary efficacy outcomes

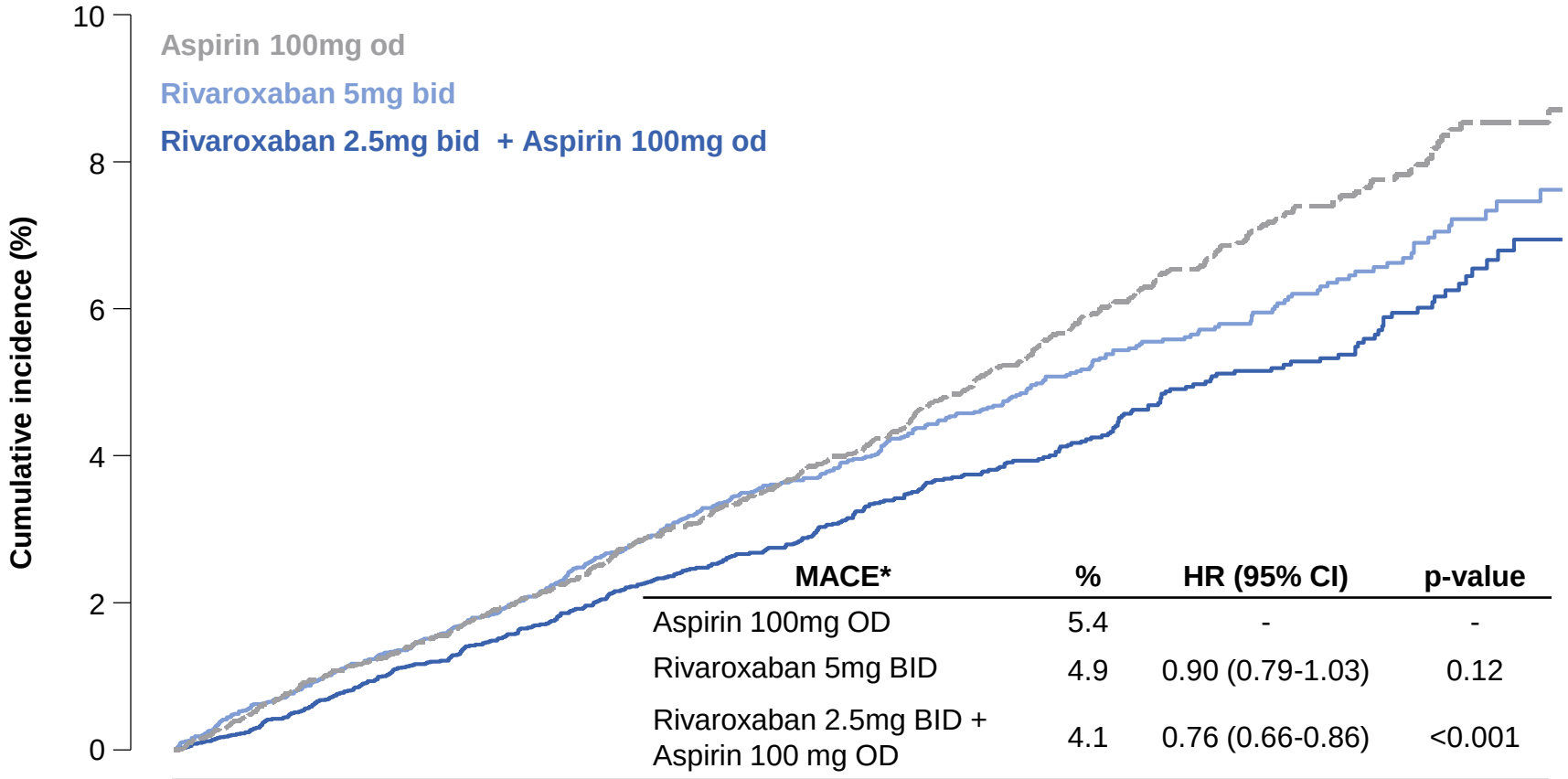
- Composite of major thrombotic events
  - Coronary heart disease death, MI, ischaemic stroke, acute limb ischaemia
  - Cardiovascular death, MI, ischaemic stroke, acute limb ischaemia
- Mortality (all cause)

Primary safety outcome

- Modified ISTH major bleeding
  - Fatal bleeding, *and/or*
  - Symptomatic bleeding in a critical area or organ, such as intracranial, *or*
  - Bleeding into the surgical site requiring re-operation, *and/or*
  - Bleeding leading to hospitalization

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

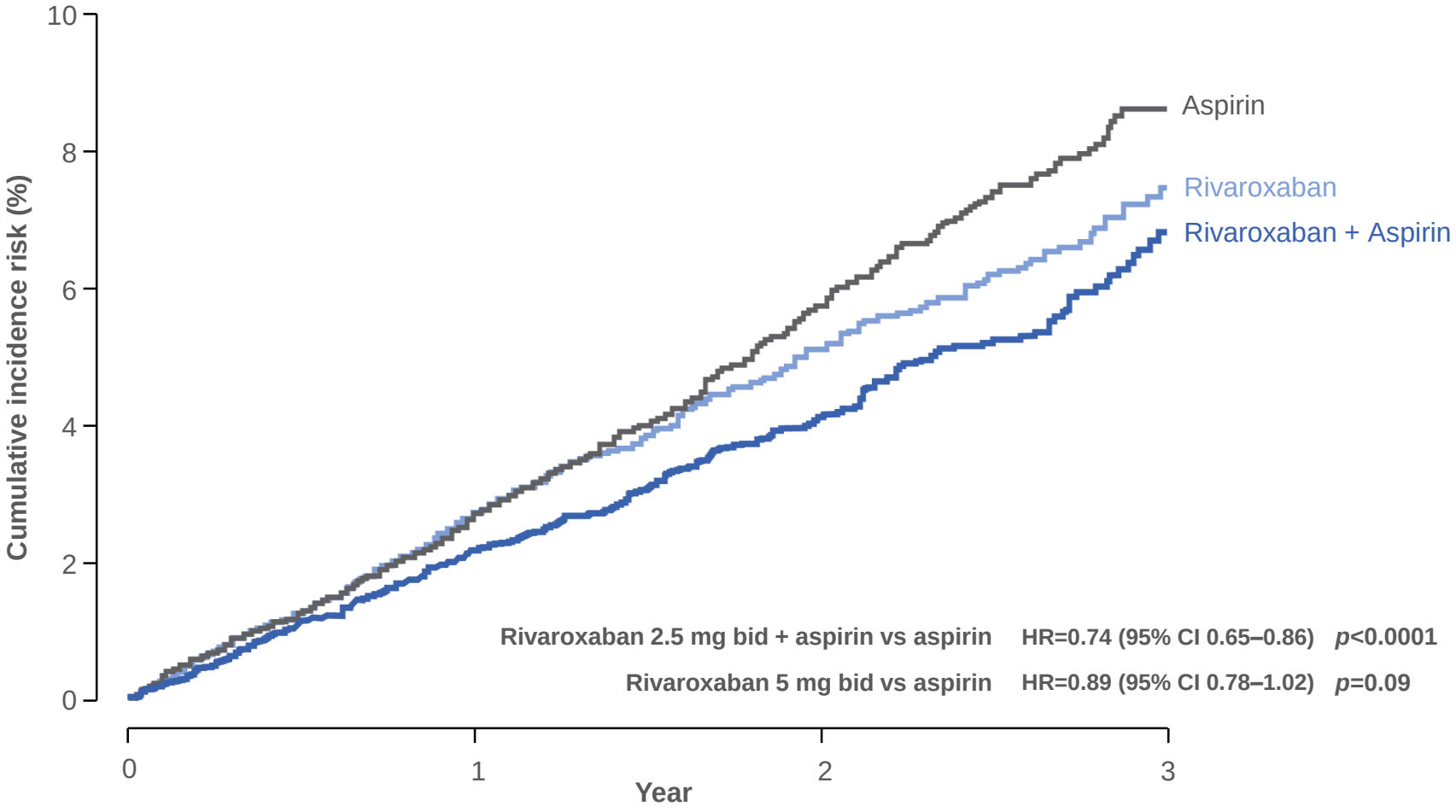
Number at risk				
Aspirin 100mg od	9126	7808	3860	669
Riva 5mg bid	9117	7824	3862	670
Riva 2.5mg bid + Aspirin 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Significantly Reduced MACE by 26% Versus Aspirin

Stroke/MI/Cardiovascular death



Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

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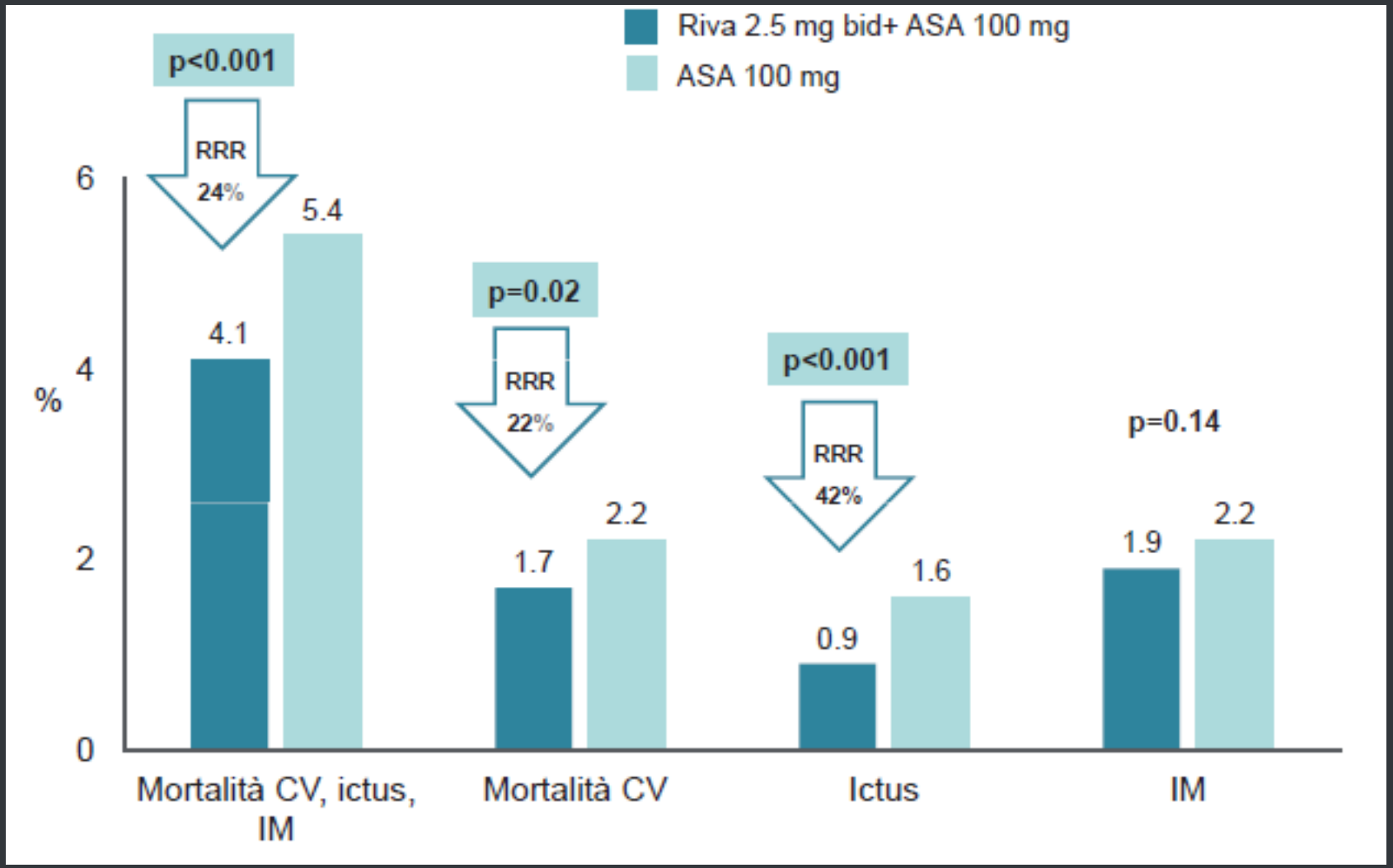

De Luca L et al. GIC 2019; 20 (1):1-7

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Nuova opzione terapeutica (nuova indicazione) : *rivaroxaban nella cardiopatia ischemica*

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e. il dosaggio (“vascolare”)

f. in associazione ad aspirina ?

g. per quanto tempo ?

COMPASS Enrolled over 24,000 Patients with Advanced, Chronic CAD

CAD definition	Number of patients (% of CAD population)[1]
All patients with CAD	24,824
Prior MI	17,028 (69%)
<1 year	1238 (5%)
1–<2 years	2341 (9%)
2–<5 years	4893 (20%)
≥5 years	8520 (34%)
Multivessel coronary disease*	15,469 (62%)
Prior PCI	14,862 (60%)
Prior CABG	7845 (32%)
Patients randomized immediately post-CABG	1448 (6%)

Half of all previous MIs occurred ≥5 years prior to enrolment in COMPASS[1]

*Refers to stenosis of ≥50% in 2 or more coronary arteries, confirmed using invasive coronary angiography, or non-invasive imaging or stress studies suggestive of significant ischaemia in ≥2 coronary territories; or in 1 coronary territory if at least 1 other territory has been revascularized[2]

1. Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7;
2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

Inclusion and Exclusion Criteria Ensure That Patients Are Chronic CAD and PAD Patients

Key inclusion criteria*

- PAD
- CAD with ≥1 of:
  - Age ≥65 years
  - Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR<60 ml/min)
    - Heart failure
    - Non-lacunar ischemic stroke ≥1 month ago

Key exclusion criteria‡

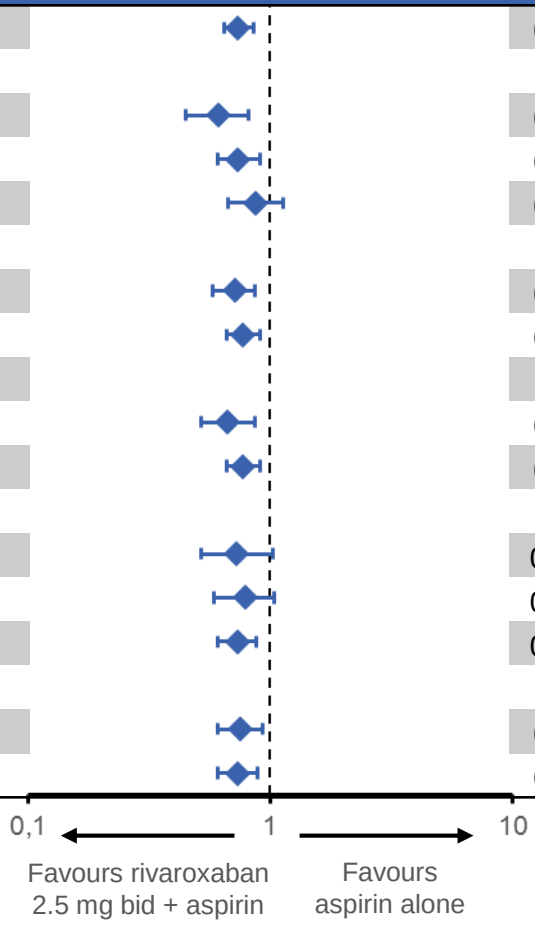
- Stroke ≤1 month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
- **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy**
- eGFR <15 ml/min

[#]Including but not limited to; ‡any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

www.clinicaltrials.gov/ct2/show/NCT01776424 [accessed 21 Mar 2017];
Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

Efficacy of Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Was Consistent Across Subgroups

Subgroup	Rivaroxaban 2.5 mg bid + aspirin n/N (%)		Aspirin alone n/N (%)		HR (95% CI)	*p*-value
All participants	347/8313	(4)	460/8261	(6)	0.74 (0.65–0.86)	
Age						0.20
<65 years	69/1864	(4)	115/1890	(6)	0.61 (0.45–0.82)	
65–75 years	168/4707	(9)	223/4661	(5)	0.74 (0.61–0.91)	
≥75 years	110/1742	(6)	122/1710	(7)	0.87 (0.67–1.13)	
Baseline diabetes						0.62
Yes	155/3043	(5)	212/3040	(7)	0.72 (0.58–0.88)	
No	192/5270	(4)	248/5221	(5)	0.77 (0.64–0.93)	
Concomitant PAD						0.37
Yes	94/1656	(6)	138/1641	(8)	0.67 (0.52–0.87)	
No	253/6657	(4)	322/6620	(5)	0.77 (0.66–0.91)	
TIMI risk score*						0.92
0–1	57/2611	(2)	77/2582	(3)	0.73 (0.52–1.03)	
2	88/2399	(4)	108/2316	(5)	0.79 (0.59–1.04)	
3–8	202/3303	(6)	275/3363	(8)	0.74 (0.61–0.88)	
Guideline-recommended therapy#						0.89
Yes	150/3431	(4)	194/3406	(6)	0.75 (0.61–0.93)	
No	197/4882	(4)	266/4855	(5)	0.74 (0.61–0.89)	



*TIMI risk score gives one point each to the following criteria: current smoker, heart failure, diabetes, CABG surgery, stroke, hypertension, age >75 years, estimated glomerular filtration rate <60 mL/min; #Non-smokers receiving lipid-lowing drugs, β-blockers and an ACEI/ARB

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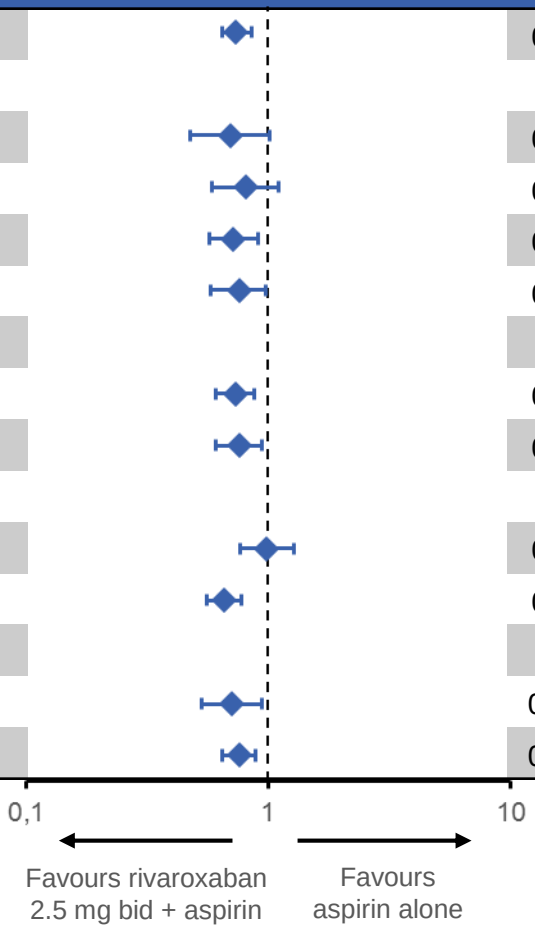
All participants	347/8313	(4)	460/8261	(6)		0.74 (0.65–0.86)	
History of MI							0.93
<2 years prior	49/1218	(4)	67/1205	(6)		0.70 (0.48–1.01)	
2–5 years prior	71/1612	(4)	91/1665	(5)		0.81 (0.59–1.10)	
≥5 years prior	127/2824	(4)	174/2849	(6)		0.72 (0.57–0.91)	
No MI prior	100/2661	(3.8)	128/2540	(5)		0.76 (0.58–0.98)	
History of PCI/PTCA							0.85
Yes	201/4971	(4)	270/4905	(6)		0.74 (0.61–0.88)	
No	146/3342	(4)	190/3356	(6)		0.76 (0.61–0.94)	
History of CABG							0.01
Yes	121/2232	(5)	117/2143	(5)		0.99 (0.77–1.28)	
No	226/6081	(4)	343/6119	(6)		0.66 (0.56–0.78)	
MI or PCI or CABG >2 years							0.71
Yes	78/2269	(3)	102/2141	(5)		0.71 (0.53–0.95)	
No	269/6044	(4)	358/6120	(6)		0.76 (0.65–0.89)	



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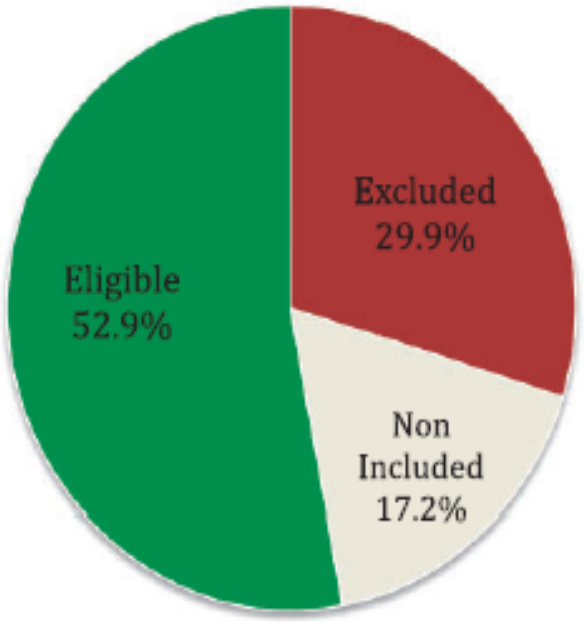

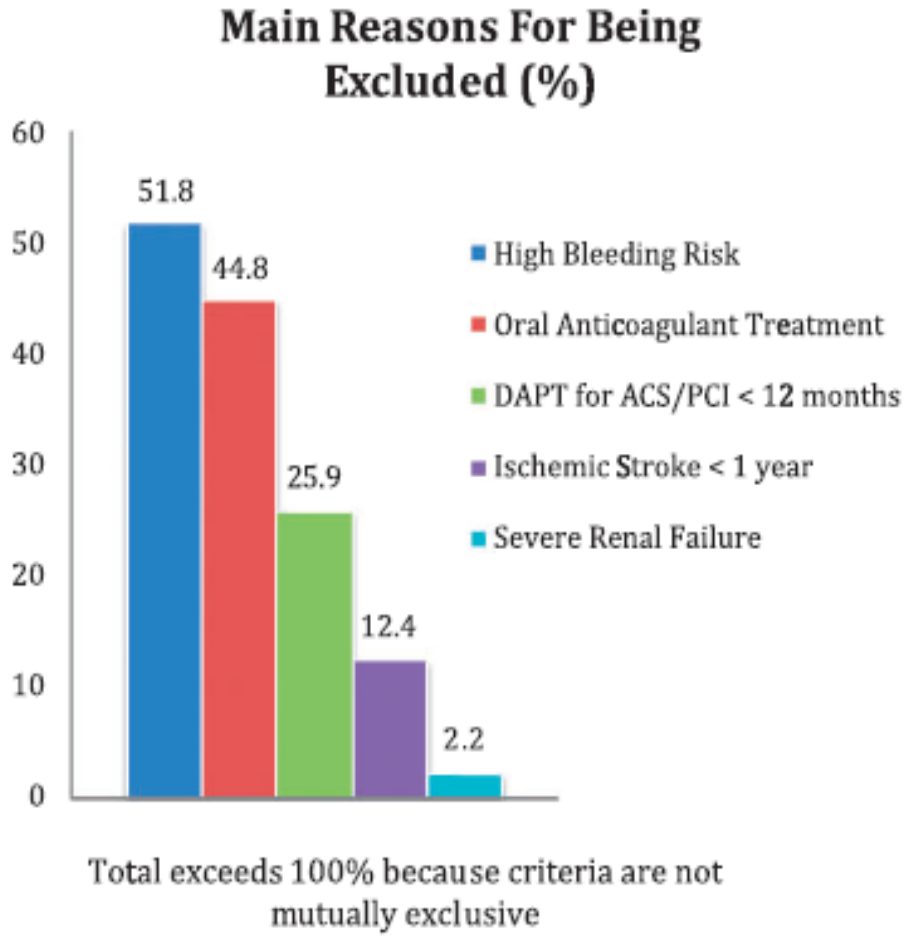

Darmon A et al. EurHJ 2018; 39:750-757

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c. quale sicurezza ?

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Modified ISTH Major Bleeding Definition Applied at Regulators' Request with the Intent of Capturing all Bleeding that Required Medical Attention

ISTH major bleeding[1]

- Fatal bleeding, *and/or*
- Symptomatic bleeding in a critical area or organ (such as intracranial), *and/or*
- ***Bleeding causing a drop in haemoglobin level of ≥20 g/l, or leading to transfusion of ≥2 units of whole blood or red cells***

Modified ISTH major bleeding (COMPASS)

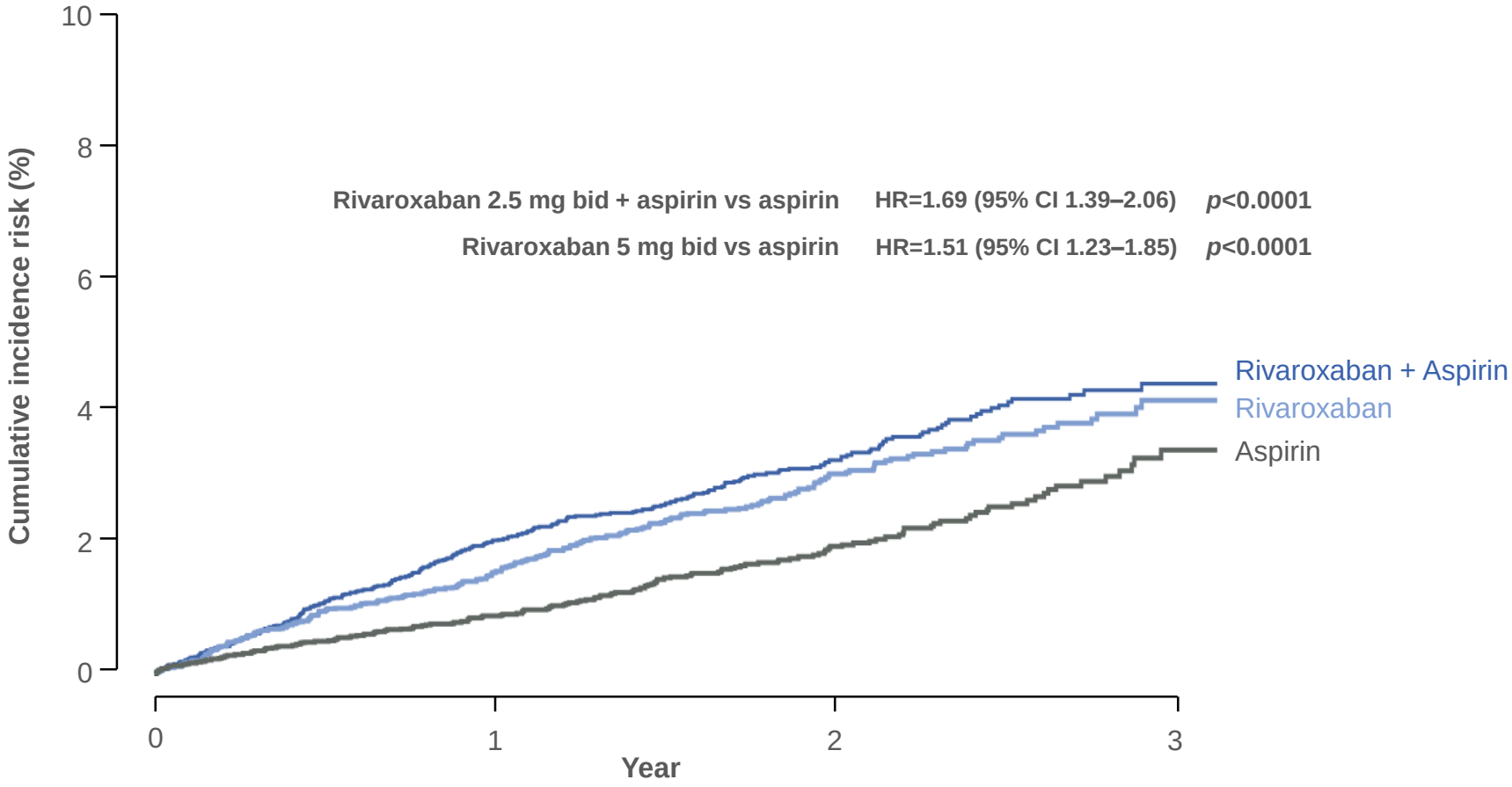
- Fatal bleeding, *and/or*
- Symptomatic bleeding in a critical area or organ (such as intracranial), *or*
- ***Bleeding into the surgical site requiring re-operation, and/or***
- ***Bleeding leading to hospitalization***

Unlike the standard ISTH criteria, all bleeding that led to presentation to an acute care facility or hospitalization were considered as major compared with the standard ISTH major bleeding definition

1. Schulman S *et al*, *J Thromb Haemost* 2005;3:692–694

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone

Major bleeding



Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

Bleeding Rates Increased but Low with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Major bleeding	263 (3)	236 (3)	158 (2)	1.66 (1.37–2.03)	<0.0001	1.51 (1.23–1.84)	<0.0001
Fatal	14 (<1)	12 (<1)	9 (<1)	1.55 (0.67–3.58)	0.30	1.33 (0.56–3.16)	0.51
ICH	19 (<1)	32 (<1)	19 (<1)	0.99 (0.52–1.87)	0.98	1.69 (0.96–2.99)	0.065
Critical organ	36 (<1)	42 (1)	25 (<1)	1.42 (0.85–2.36)	0.18	1.70 (1.04–2.79)	0.033
Other	194 (2)	150 (2)	105 (1)	1.85 (1.46–2.34)	<0.0001	1.44 (1.12–1.84)	0.0041

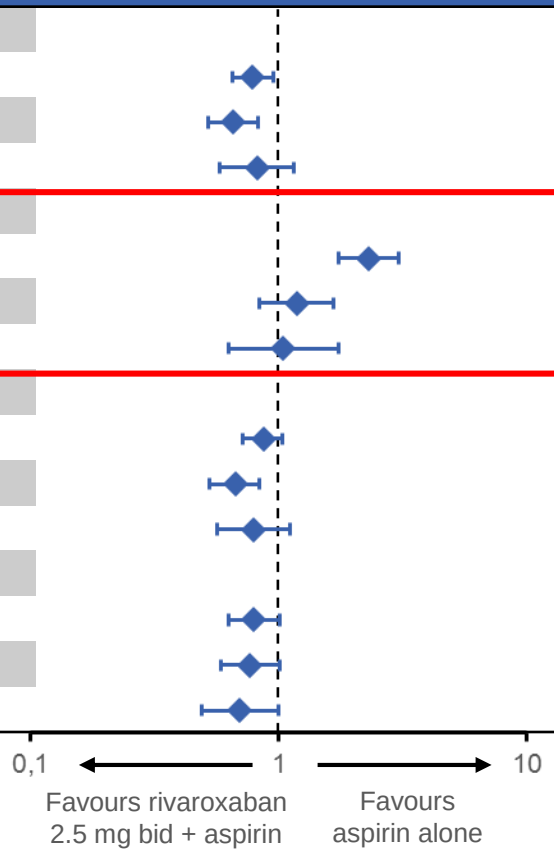
No significant increase in critical organ bleeding including intracranial or fatal bleeding

Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

Persistent Reduction in MACE with Dual Pathway Inhibition; Increased Bleeding only in the First Year

Landmark analysis for key efficacy and safety outcomes

	Rivaroxaban 2.5 mg bid + aspirin n/N (%)		Aspirin alone n/N (%)		HR (95% CI)	HR (95% CI)
MACE						
<1 year	176/8313	(2)	221/8261	(3)		0.79 (0.65–0.96)
1–<2 years	113/7228	(2)	169/7125	(2)		0.66 (0.52–0.83)
>2 years	58/3655	(2)	70/3621	(2)		0.82 (0.58–1.16)
Major bleeding						
<1 year	163/8313	(2)	70/8261	(1)		2.32 (1.75–3.07)
1–<2 years	70/7189	(1)	59/7183	(1)		1.19 (0.84–1.68)
>2 years	30/3626	(1)	30/3628	(1)		1.05 (0.63–1.75)
Net clinical benefit						
<1 year	207/8313	(2)	237/8261	(3)		0.87 (0.72–1.04)
1–<2 years	124/7201	(2)	182/7112	(3)		0.67 (0.53–0.84)
>2 years	61/3637	(2)	75/3604	(2)		0.80 (0.57–1.12)
All death						
<1 year	117/8313	(1)	145/8261	(2)		0.80 (0.63–1.02)
1–<2 years	93/7323	(1)	120/7242	(2)		0.77 (0.59–1.01)
>2 years	52/3743	(1)	74/3762	(2)		0.70 (0.49–1.00)



Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

22% Reduction in Risk of the Composite Net Clinical Benefit Outcome with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin vs Aspirin

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Net clinical benefit (CV death, stroke, MI, fatal or critical organ bleeding)	392 (5)	462 (6)	494 (6)	0.78 (0.69–0.90)	0.0003	0.94 (0.82–1.06)	0.31
All-cause mortality	262 (3)	316 (4)	339 (4)	0.77 (0.65–0.90)	0.0012	0.93 (0.80–1.09)	0.37
CV death	139 (2)	175 (2)	184 (2)	0.75 (0.60–0.93)	0.010	0.95 (0.77–1.17)	0.63
Non-CV death	123 (2)	141 (2)	155 (2)	0.79 (0.62–1.00)	0.048	0.91 (0.73–1.15)	0.43

- For every 1000 patients with CAD treated with rivaroxaban plus aspirin, 13 MACE events would be prevented and 2 fatal or critical organ bleeds would be caused over a mean 23-month period

Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

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b. per quali pazienti ? R : c. ischemica in senso ampio

c. quale sicurezza ? R : rischio emorragico accettabile

d. quando iniziare la terapia ?

e. il dosaggio (“vascolare”)

f. in associazione ad aspirina ?

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Patients randomized immediately post-CABG	1448 (6%)

Half of all previous MIs occurred ≥5 years prior to enrolment in COMPASS[1]

*Refers to stenosis of ≥50% in 2 or more coronary arteries, confirmed using invasive coronary angiography, or non-invasive imaging or stress studies suggestive of significant ischaemia in ≥2 coronary territories; or in 1 coronary territory if at least 1 other territory has been revascularized[2]

1. Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7;
2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

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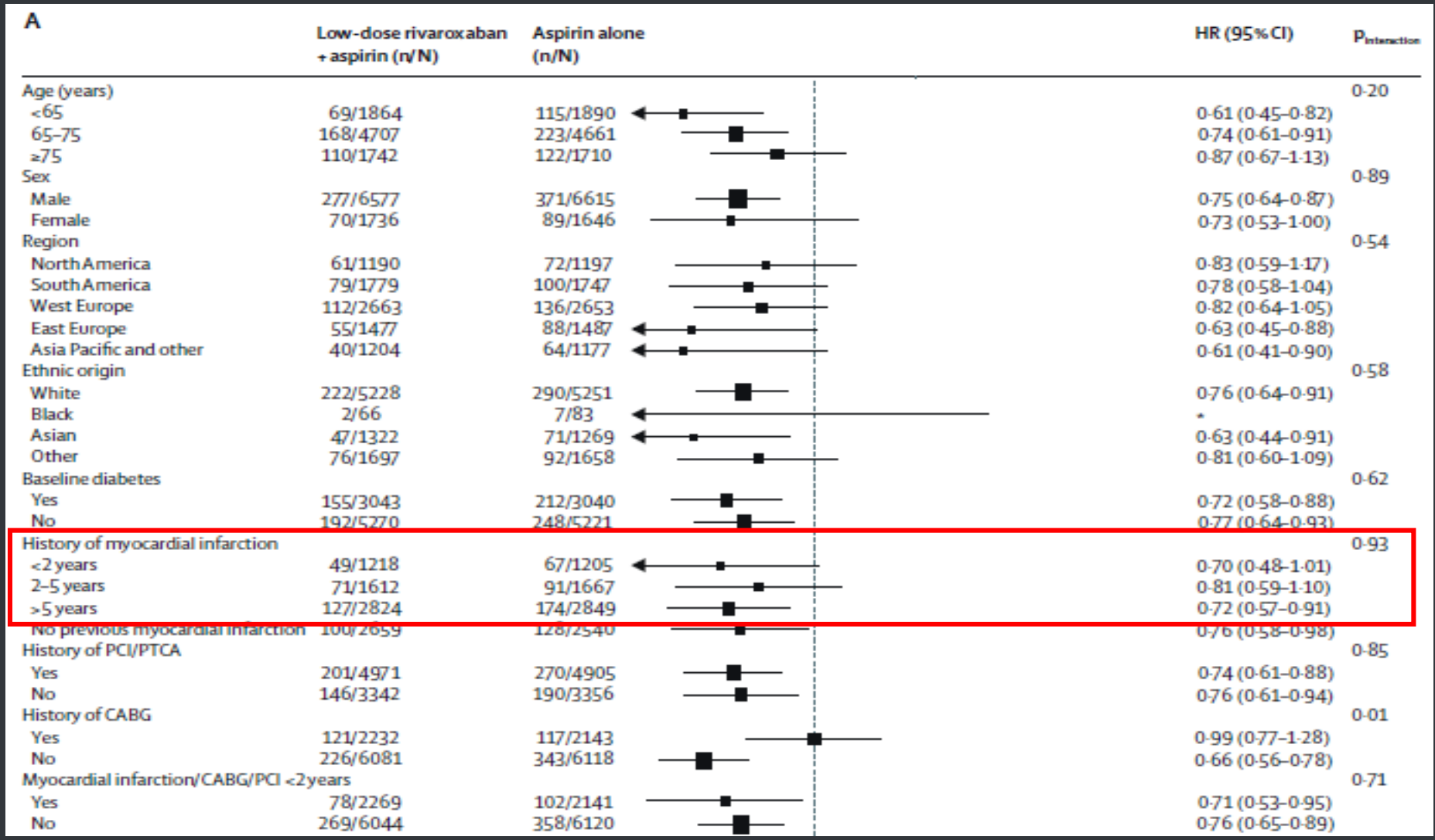

A

	Low-dose rivaroxaban + aspirin (n/N)	Aspirin alone (n/N)	HR (95% CI)	$p_{interaction}$
Age (years)				0·20
<65	69/1864	115/1890	0·61 (0·45–0·82)	
65–75	168/4707	223/4661	0·74 (0·61–0·91)	
≥75	110/1742	122/1710	0·87 (0·67–1·13)	
Sex				0·89
Male	277/6577	371/6615	0·75 (0·64–0·87)	
Female	70/1736	89/1646	0·73 (0·53–1·00)	
Region				0·54
North America	61/1190	72/1197	0·83 (0·59–1·17)	
South America	79/1779	100/1747	0·78 (0·58–1·04)	
West Europe	112/2663	136/2653	0·82 (0·64–1·05)	
East Europe	55/1477	88/1487	0·63 (0·45–0·88)	
Asia Pacific and other	40/1204	64/1177	0·61 (0·41–0·90)	
Ethnic origin				0·58
White	222/5228	290/5251	0·76 (0·64–0·91)	
Black	2/66	7/83	*	
Asian	47/1322	71/1269	0·63 (0·44–0·91)	
Other	76/1697	92/1658	0·81 (0·60–1·09)	
Baseline diabetes				0·62
Yes	155/3043	212/3040	0·72 (0·58–0·88)	
No	192/5270	248/5221	0·77 (0·64–0·93)	
History of myocardial infarction				0·93
<2 years	49/1218	67/1205	0·70 (0·48–1·01)	
2–5 years	71/1612	91/1667	0·81 (0·59–1·10)	
>5 years	127/2824	174/2849	0·72 (0·57–0·91)	
No previous myocardial infarction	100/2659	128/2540	0·76 (0·58–0·98)	
History of PCI/PTCA				0·85
Yes	201/4971	270/4905	0·74 (0·61–0·88)	
No	146/3342	190/3356	0·76 (0·61–0·94)	
History of CABG				0·01
Yes	121/2232	117/2143	0·99 (0·77–1·28)	
No	226/6081	343/6118	0·66 (0·56–0·78)	
Myocardial infarction/CABG/PCI <2 years				0·71
Yes	78/2269	102/2141	0·71 (0·53–0·95)	
No	269/6044	358/6120	0·76 (0·65–0·89)	

Connolly SG et al. Lancet 2018; 391:205-218

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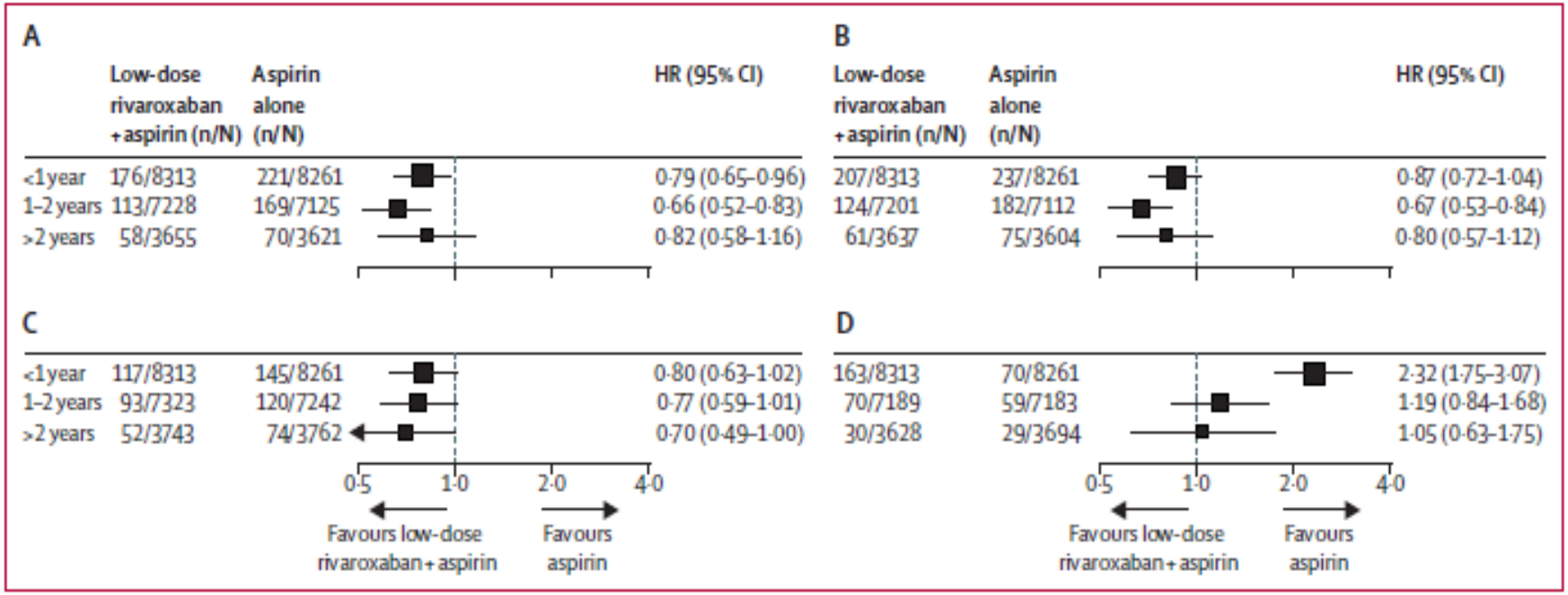

Figure 3: Landmark analysis

Analysis of (A) primary efficacy outcome, (B) net clinical benefit, (C) all-cause death, and (D) major bleeding. HR=hazard ratio.

Connolly SG et al. Lancet 2018; 391:205-218

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Nuova opzione terapeutica (nuova indicazione) : *rivaroxaban nella cardiopatia ischemica*

a. evidenze cliniche chiare e solide ? R : si

b. per quali pazienti ? R : c. ischemica in senso ampio

c. quale sicurezza ? R : rischio emorragico accettabile

d. quando iniziare la terapia ? R : no limiti di tempo

e. il dosaggio (“vascolare”)

f. in associazione ad aspirina ?

g. per quanto tempo ?

BLOOD COAGULATION

The thrombin paradox

John H. Griffin

THE thrombin paradox is like the so-called French red wine paradox[1]: too much thrombin or red wine is harmful to blood vessels, but a little bit of either is much better than none at all. On page 413 of this issue[2], Gibbs *et al.* deconstruct the thrombin paradox by showing that the mutation of glutamic acid to alanine at position 229 of the protein's sequence creating Ala-229 thrombin, alters its specificity, both *in vitro* and *in vivo*. Thrombin can both promote and prevent blood clotting, and the result of the mutation is that thrombin procoagulant activities almost disappear whereas its anticoagulant activity is conserved.

Normal blood clotting is essential to minimize bleeding and achieve haemostasis; excessive clotting contributes to thrombosis, which can have severe consequences (stroke or heart attack, for instance). Maintaining normal blood flow requires keeping a system in imbalance between the anticoagulant and procoagulant pathways, with the former prevailing. Thrombin is central to both processes (see Fig. 1, and ref. 3 for review). Low levels[4] generate marked increased levels of the endogenous circulating anticoagulant serine protease, activated protein C (aPC)[5]. In contrast, high levels of thrombin cause blood to clot by generating procoagulators Va and VIIIa, by converting fibrinogen to fibrin and by activating that then unveil concealed receptors and provide vascular thrombotic agents. Accordingly, describes the relationship between thrombotic potential of blood and thrombin concentration (Fig. 2). (The affinity of wild-type Glu-229 for thrombomodulin is very high; there is an abundance of thrombomodulin in the microcirculation, low levels of thrombin have an antithrombotic effect. At higher levels, however, free thrombin exerts its various prothrombotic effects. As Fig. 2 shows, the thrombotic profile of the Ala-229 mutant is different.)

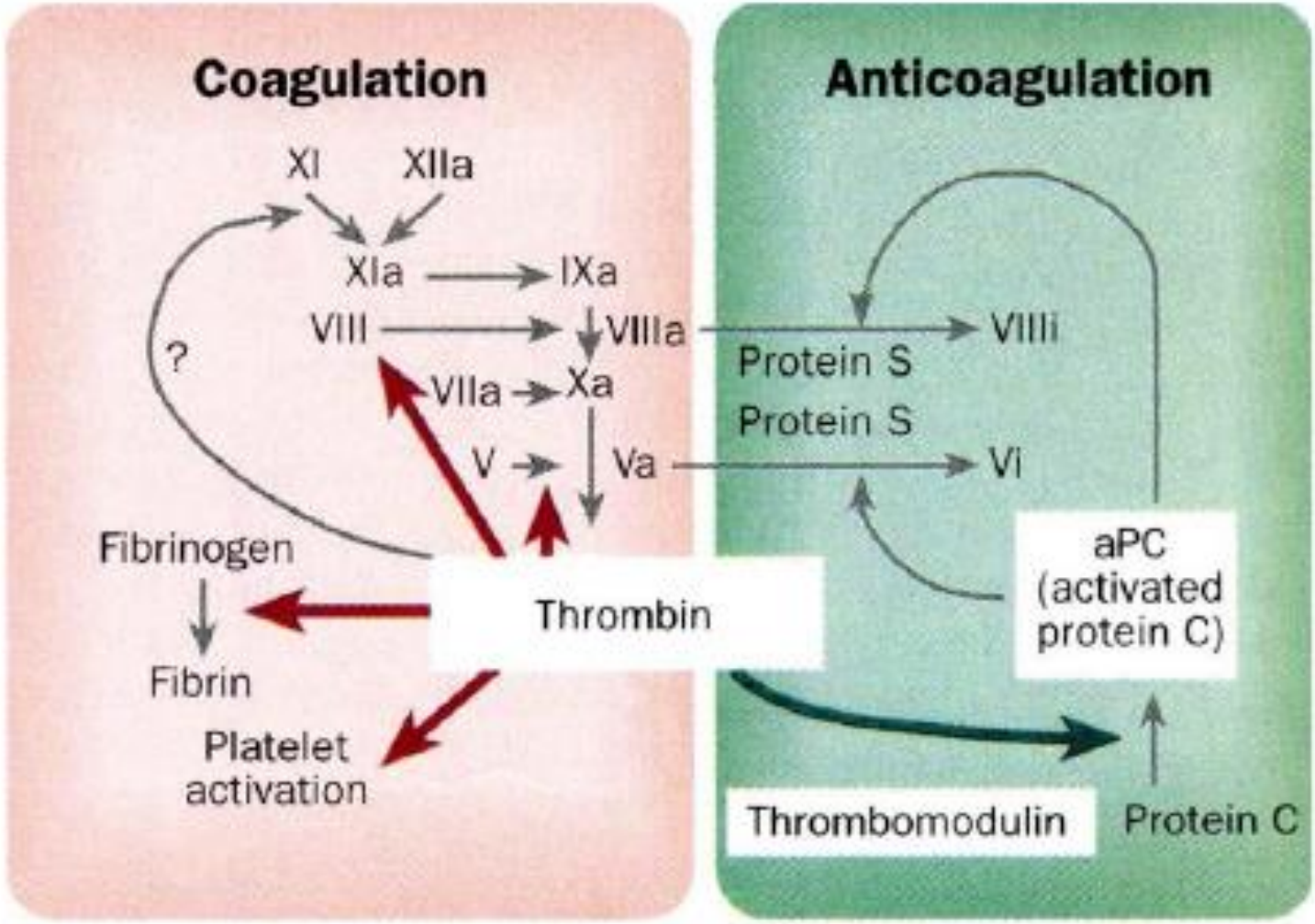
A natural 'protein C knockout experiment' tells us a great deal about the physiological importance of this system: newborn infants totally deficient in protein C suffer from extensive thrombosis and inflammation in the microvasculature. The condition is lethal unless

aggressively, and most infants suffer irreversible loss of vision and brain damage. Activated protein C circulates at 40 picomolar concentration in human blood and has a remarkably long half-life of 0.3 hours[6], suggesting that it is part of a systemic anticoagulant and anti-inflammatory surveillance system.

Animal experiments have helped to

that dissected thrombin's procoagulant and anticoagulant activities by site-directed mutagenesis and inspired an alanine-scanning study of 62 thrombin mutants[10]. Whether the new work[2] should be considered an affirmation of industrial-strength alanine scanning is left to the reader's judgement.

In any case, Gibbs *et al.* provide an appealing *post factum* rationale for the altered selectivity of Ala-229 thrombin. It seems that fibrinopeptide A, one of the two pairs of peptides in fibrinogen cleaved by thrombin (see Fig. 1), is in a conforma-



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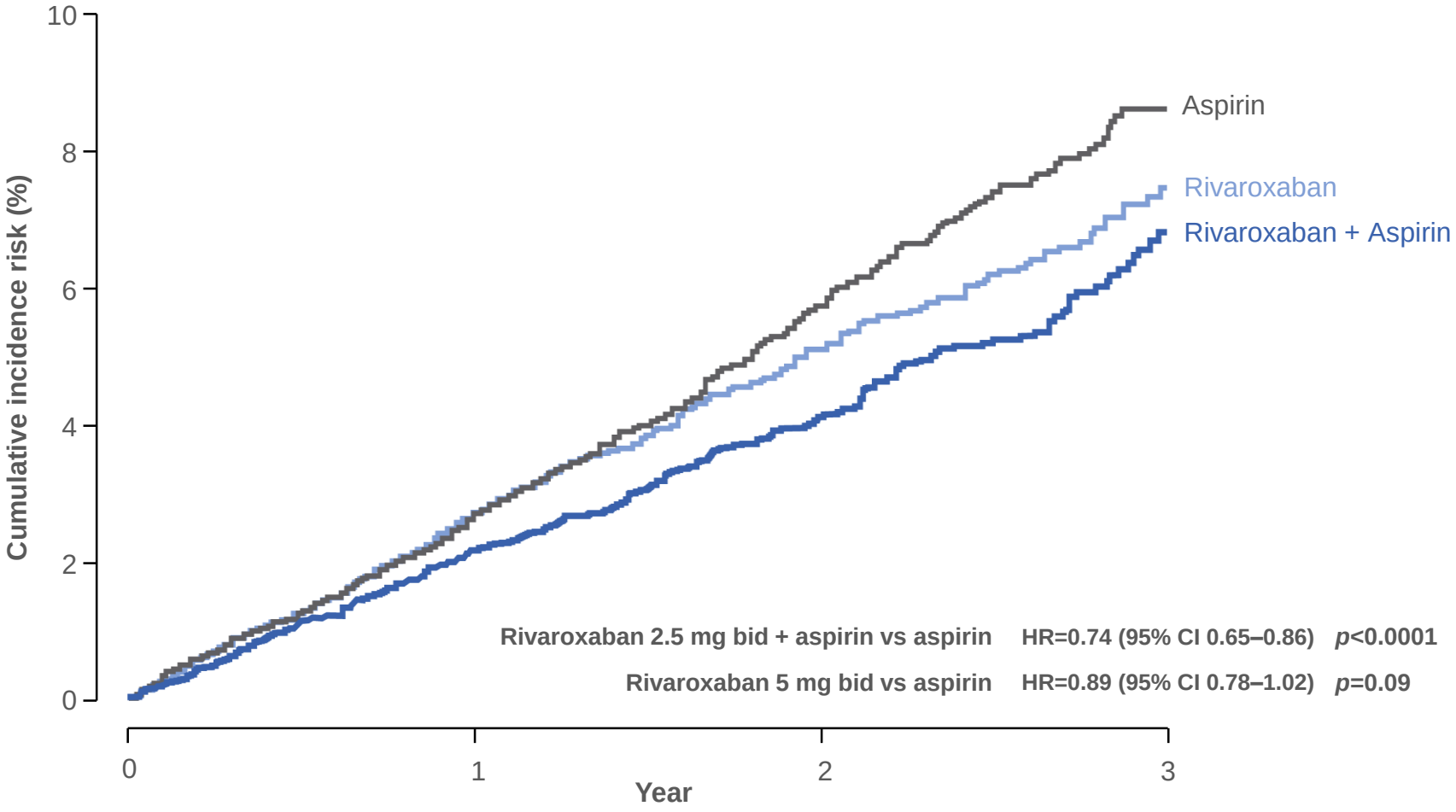
Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Significantly Reduced MACE by 26% Versus Aspirin

Stroke/MI/Cardiovascular death



Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone

Major bleeding

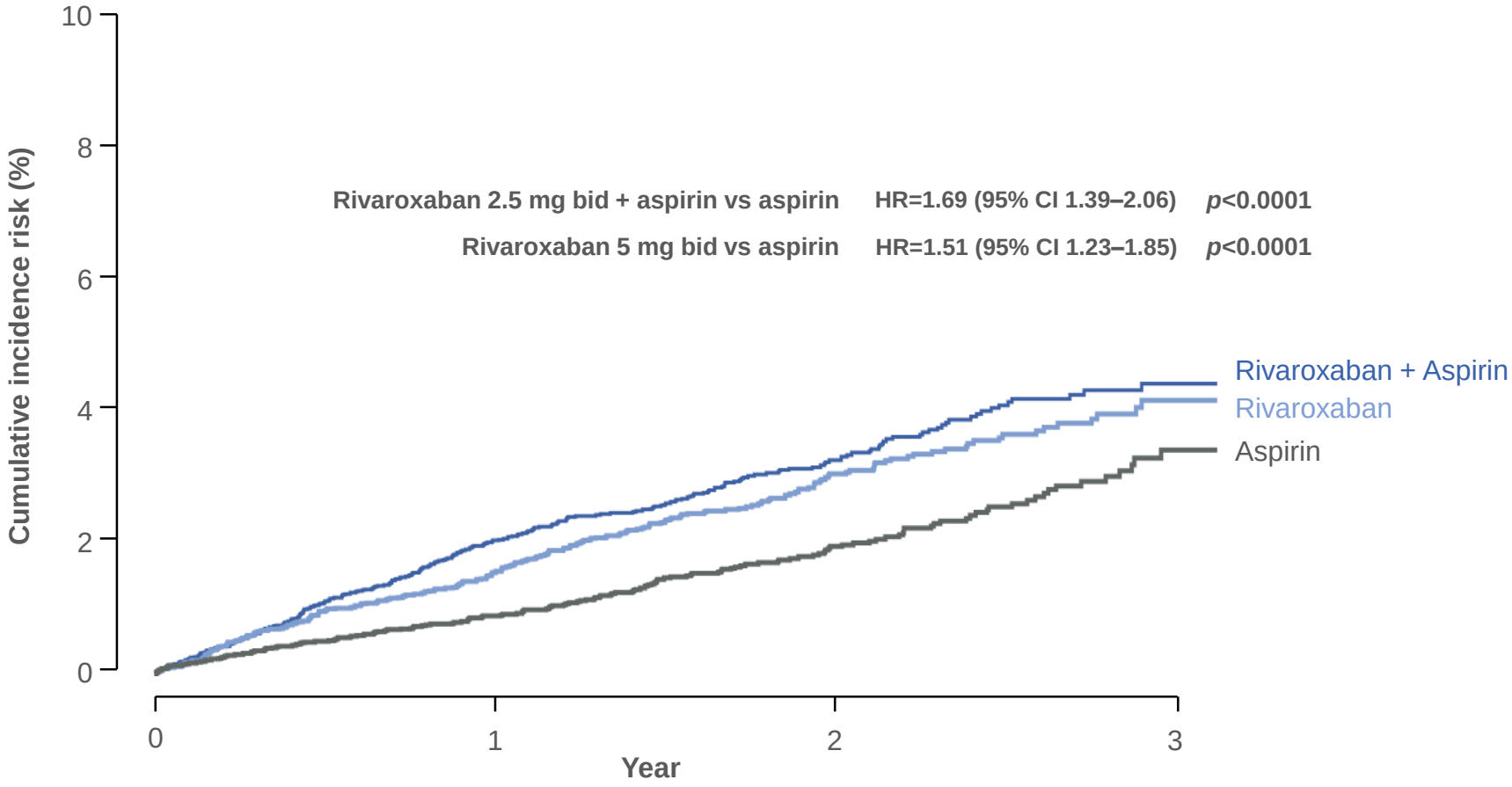


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Table 3 Comparison of the effects of guideline indicated secondary prevention pharmacological therapies for patients with vascular disease

Outcomes	Lipid lowering[41,42] (1 mmol/L reduction in LDL)	BP lowering[43] (10 mmHg reduction in systolic BP)	ACE inhibitors[44]	Aspirin[40]	COMPASS[1–3] rivaroxaban + aspirin
MACE[a]	-21%	-20%	-18%	-19%	-24%
Mortality	-9%	-13%	-14%	-9% (NS)	-18%
Stroke	-15%	-27%	-23%	-19%	-42%
MI	-24%	-17%	-18%[b]	-20%	-14% (NS)

Fox KAA et al. EurHJ 2019; 40:1466-1471

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g. per quanto tempo ? R : per sempre ?

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Rivaroxaban in prevenzione secondaria

a. evidenze cliniche chiare e solide ? R : si

b. per quali pazienti ? R : c. ischemica in senso ampio

c. quale sicurezza ? R : rischio emorragico accettabile

d. quando iniziare la terapia ? R : no limiti di tempo

e. il dosaggio (“vascolare”) R : ok rapporto benefit/risk

f. in associazione ad aspirina ? R : si

g. per quanto tempo ? R : per sempre ?

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Rivaroxaban in prevenzione secondaria

a. Un passo avanti fondamentale
b. Il primo anticoagulante (anti-FXa) efficace e tollerato
c. "On top" ad aspirina (sinergia antitrombotica)
d. Unico antitrombotico che riduce mortalità
e. Ampie indicazioni (PCI e non-PCI trattati); può essere iniziato senza condizionamenti temporali : utile nella fase di transizione "post-PCI" e "post-SCA" (= in pazienti avviati a sola aspirina)
a. Effetto su molteplici distretti vascolari (PAD e CV)

Table 1 Stable coronary artery disease - new advances in secondary prevention, overview

Variable	COMPASS	CANTOS	FOURIER	ODYSSEY	PEGASUS-TIMI 54
n	27,395	10,061	27,564	18,924	21,162
Population	Stable CAD	h/o MI, hs-CRP level ≥2 mg/L	established CV disease	ACS 1–12 months prior to randomization and on high-intensive statin therapy	h/o MI 1–3 years prior + additional risk feature
FU-time	23 months (mean)	3.7 years (median)	2.2 years (median)	2.8 years (median)	33 months (median)
Concept	Anti-thrombotic	Anti-inflammatory	lipid-lowering	lipid-lowering	anti-thrombotic/anti-platelet
Substance/dosage	Rivaroxaban 5 mg bid mono *vs.* rivaroxaban 2.5 mg bid + ASA *vs.* ASA mono	Canakinumab 50, 150 and 300 mg *vs.* placebo	Evolocumab 140 mg Q2W or 420 mg QM *vs.* placebo	Alirocumab 75 or 150 mg Q2W s.c. *vs.* placebo	Ticagrelor 60 or 90 mg bid *vs.* placebo
Adverse effects	Increased bleeding defined by ISTH (HR 1.70; 95% CI: 1.40–2.05; P<0.001)	Neutropenia, thrombocytopenia, infection	no significant side effects *vs.* placebo	local injection side reaction	increase of TIMI major bleeding (HR 2.32, 95% CI: 1.68–3.21, P<0.001)
Mortality (from any cause)	Rivaroxaban + ASA: 3.42%; placebo: 4.14%	Canakinumab 150 mg: 2.73%; placebo: 2.97%	Evolocumab (all dosages): 3.2%; placebo: 3.1%	Alirocumab: 3.5%; placebo: 4.1%	Ticagrelor 60 mg bid: 4.7%; placebo: 5.2%
RRR (mortality)	17.4%[#]	n.s.	n.s.	15%	n.s.
NNT (mortality)	139[#]	n.s.	n.s.	164	n.s.
RRR (primary endpoint)	23.8%[#]	12,4%[§]	14.0%[$] (25% for 12-month landmark analysis)	15%	15.5%*
NNT (primary endpoint)	77[#]	50[§]	63[$]	74[&]	79*
Treatment costs per year[¶]	1,298 EUR	54,160 EUR	8,535 EUR (for 140 mg)	8,359 EUR (for both dosages)	943 EUR
Treatment costs per avoidance of primary endpoint[¶]	99,8734 EUR	2,708,004 EUR	537,649 EUR (for 140 mg)	618,557 EUR	74,480 EUR
Treatment costs per avoidance of 1 death[¶]	180,291 EUR	n.s.	n.s.	1,370,855 EUR	n.s.

[#], rivaroxaban + ASA *vs.* ASA alone; [§], canakinumab 150 mg *vs.* placebo; [$], evolocumab all dosages *vs.* placebo; [&], alirocumab both dosages *vs.* placebo; *, ticagrelor 60 mg bid *vs.* placebo; [¶], prices for Germany, calculated in optimal/cheapest dosages available from www.medipreis.de, last checked 15.03.2018. ASA, acetylsalicylic acid; bid, bis in die, twice a day; CAD, coronary artery disease; CV, cardiovascular; h/o, history of; n, number; NNT, number needed to treat; n.s. not significant; RRR, relative risk reduction.

Kalbacher D, et al. Ann Transl Med 2018; 6(16):323