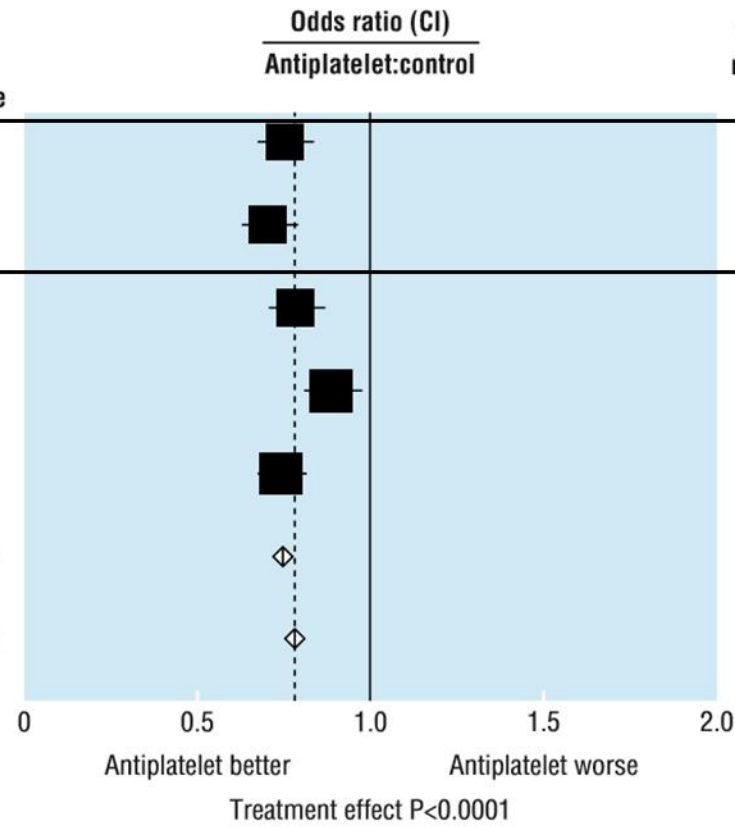
הטיפול האנטי-תרומבוטי במחלה כלילית כרונית
(Chronic Coronary Syndrome)

הכנס השנתי של החוג לשיקום הלב
אוקטובר 2019

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**	**22 (2)**



Heterogeneity of odds reductions between:

5 categories of trial: χ^2=21.4, df=4; P=0.0003

Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002

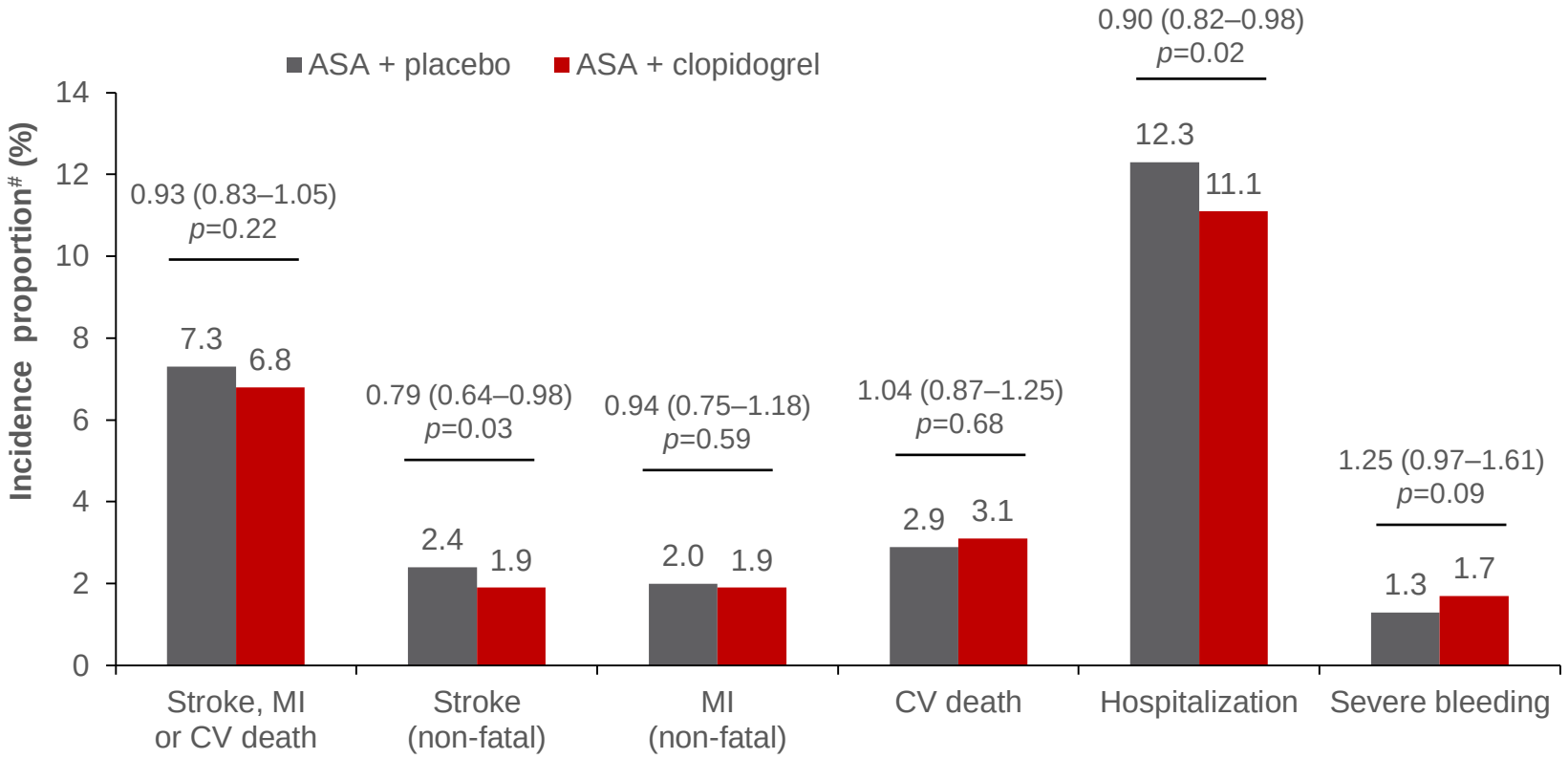
Antithrombotic Trialists' Secretariat, BMJ 2002;324:71–8

Similar Risk of Non-Fatal CV Events with Clopidogrel Versus Placebo in Patients at High Atherothrombotic Risk

CHARISMA: ASA* + placebo versus ASA* + clopidogrel (75 mg od)

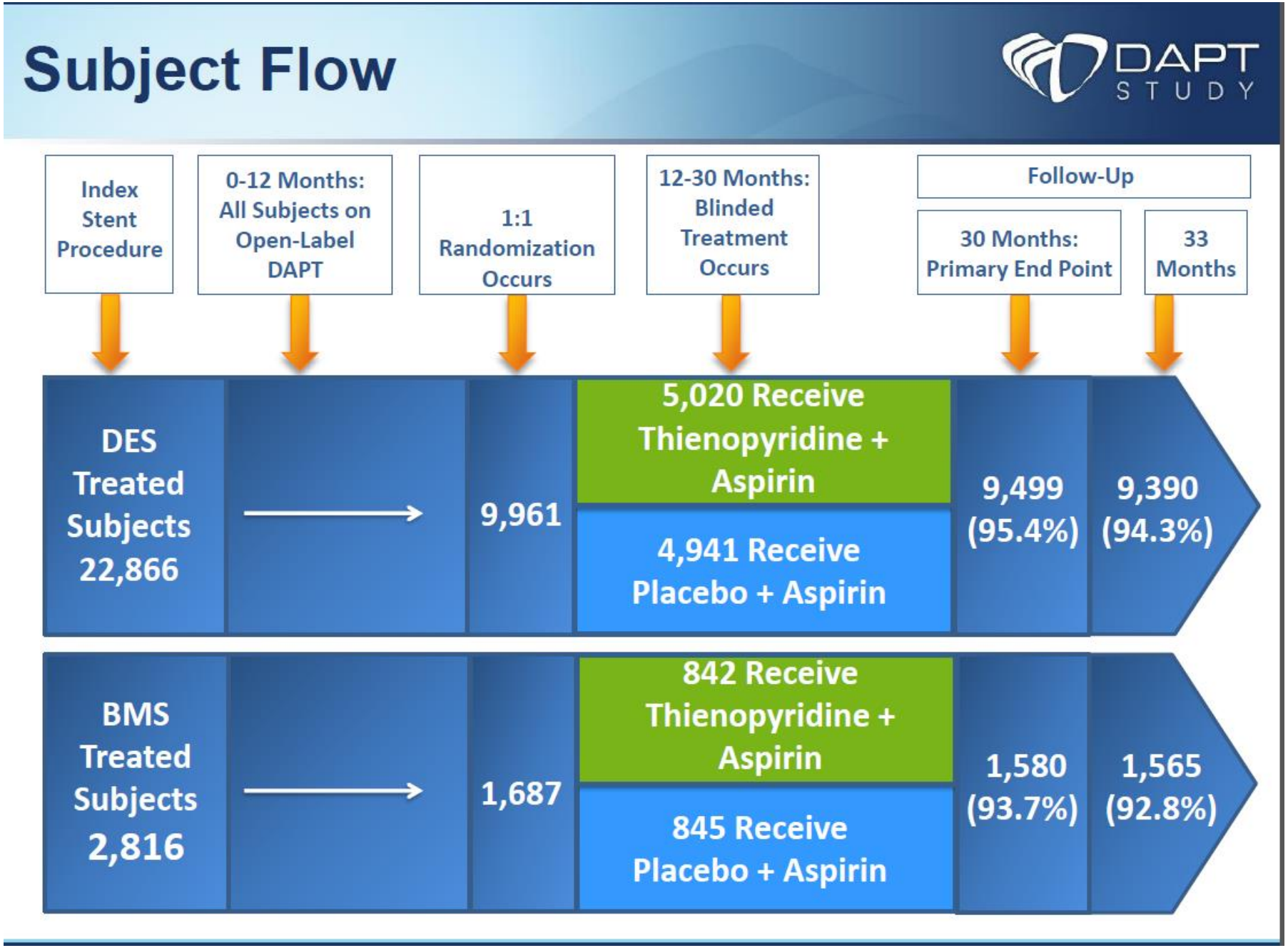
15,603 patients with clinically evident CV disease or at high risk of atherothrombotic events

A median of 28 months of follow-up



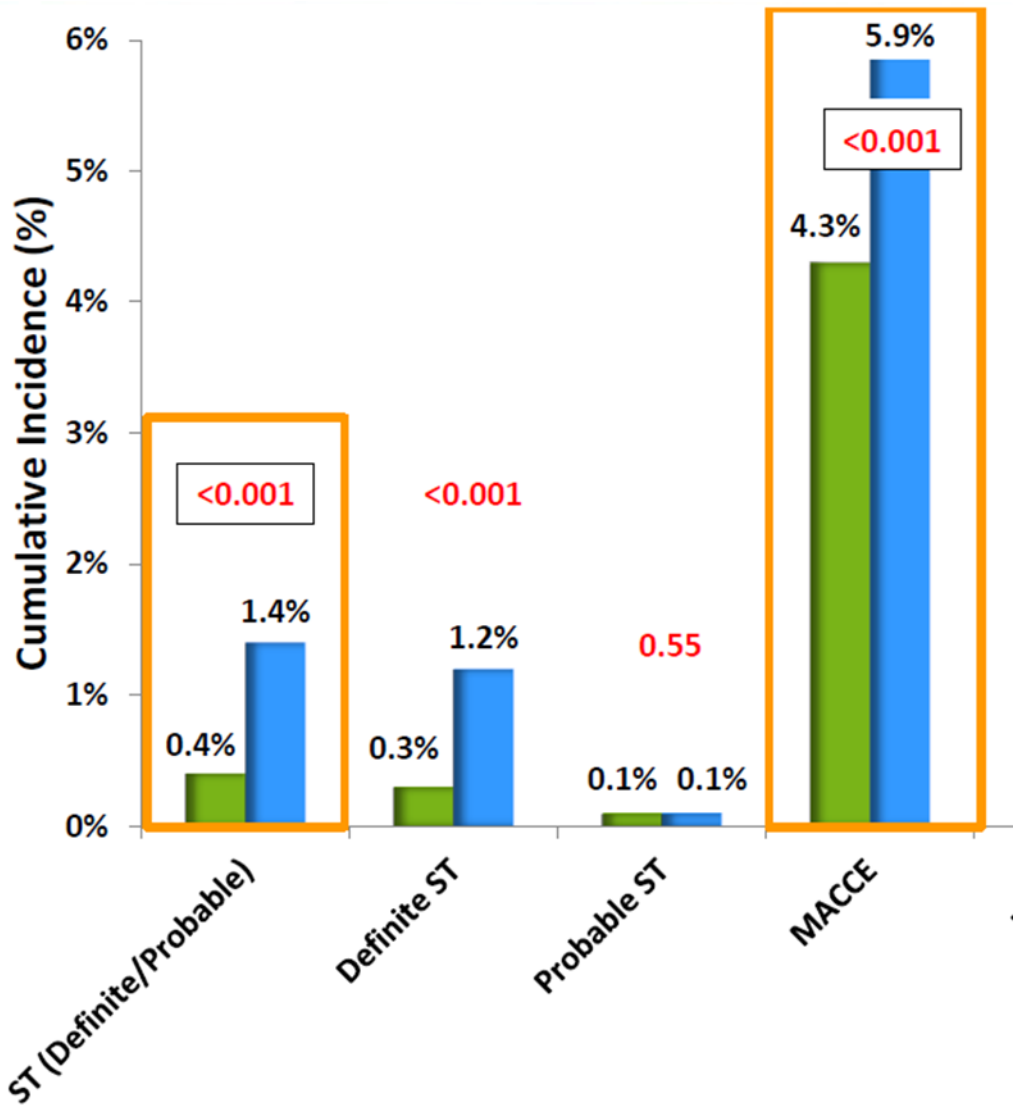
Bhatt DP *et al*, *N Engl J Med* 2006:354:1706–1717

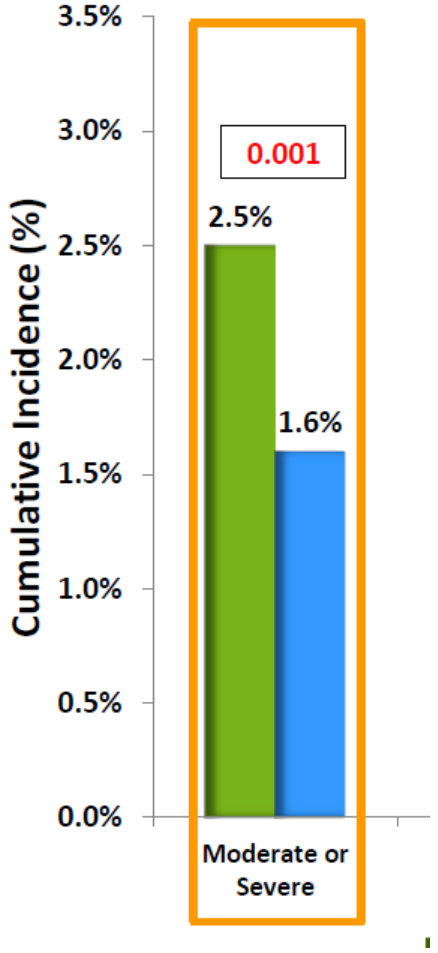
Subject Flow



N Engl J Med 2014; 371:2155-2166

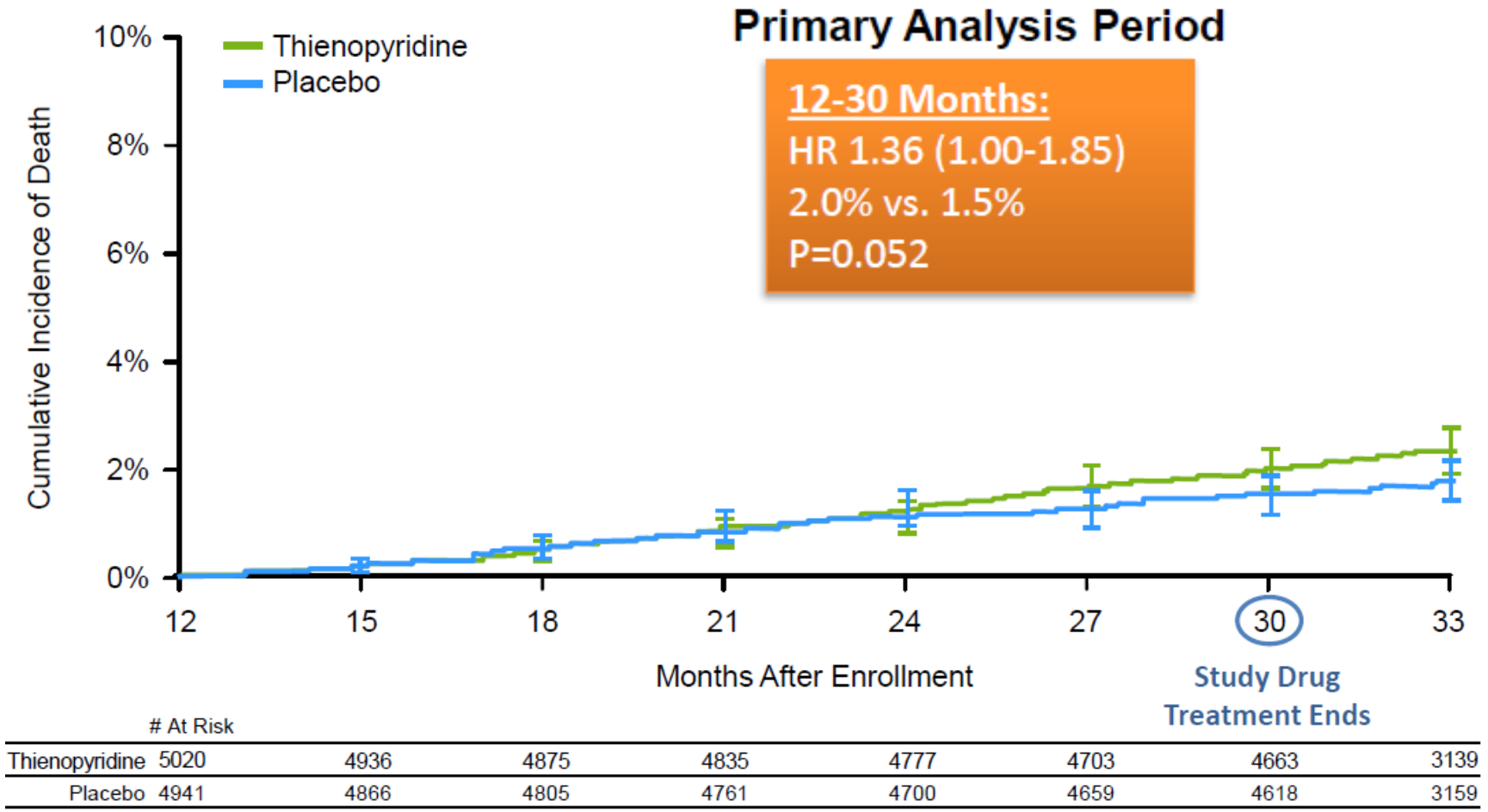
Primary Effectiveness and Safety End Points





N Engl J Med 2014; 371:2155-2166

All-Cause Mortality



# At Risk								
Thienopyridine	5020	4936	4875	4835	4777	4703	4663	3139
Placebo	4941	4866	4805	4761	4700	4659	4618	3159

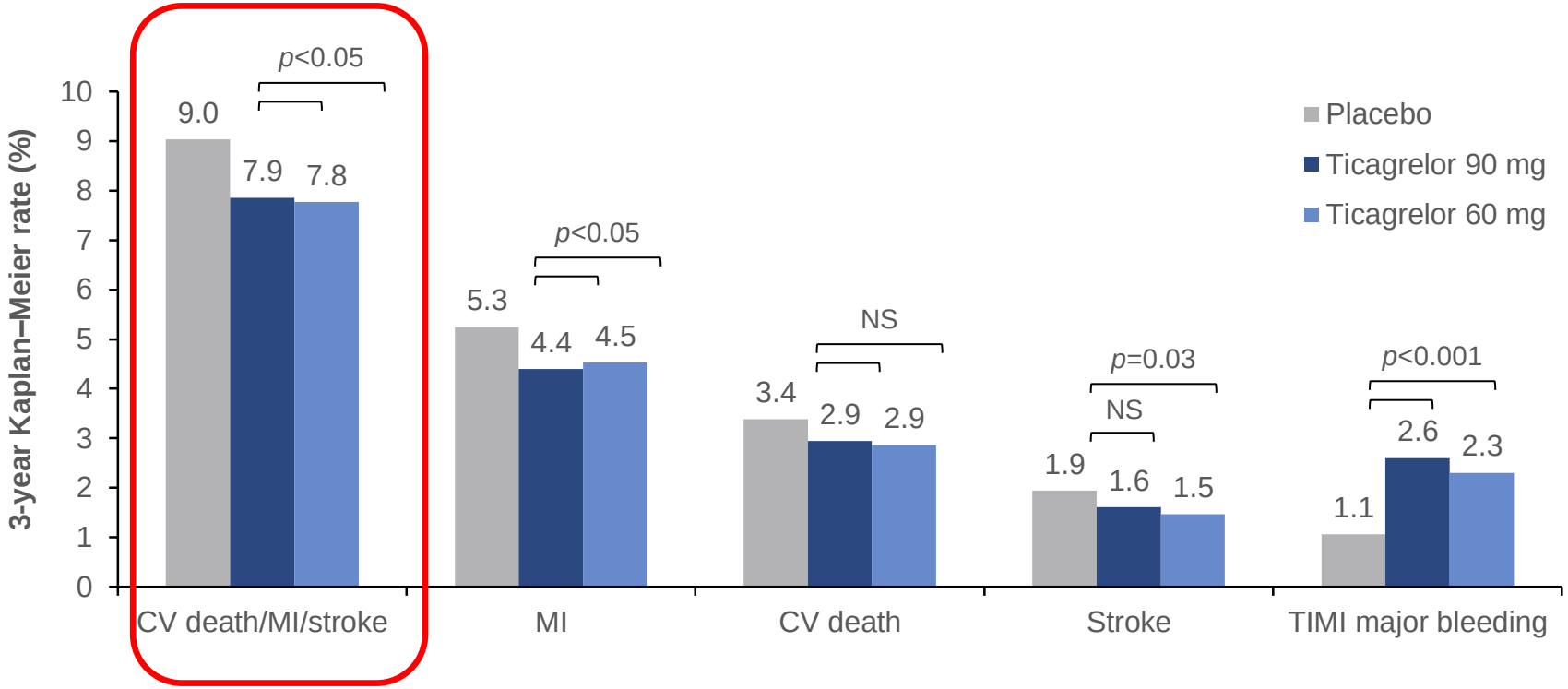
N Engl J Med 2014; 371:2155-2166

Ticagrelor Reduces Non-Fatal CV Events but Increases Major Bleeding in Patients with Prior MI

PEGASUS: ticagrelor (90 mg bid or 60 mg bid) + ASA* versus placebo + ASA*

21,162 patients who had an MI 1–3 years previously

- Compared with placebo, both doses of ticagrelor decreased the risk of CV death, MI or stroke but increased the risk of major bleeding (but not fatal bleeding)



Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800

Ticagrelor Reduces Non-Fatal CV Events but Increases Major Bleeding in Patients with Prior MI

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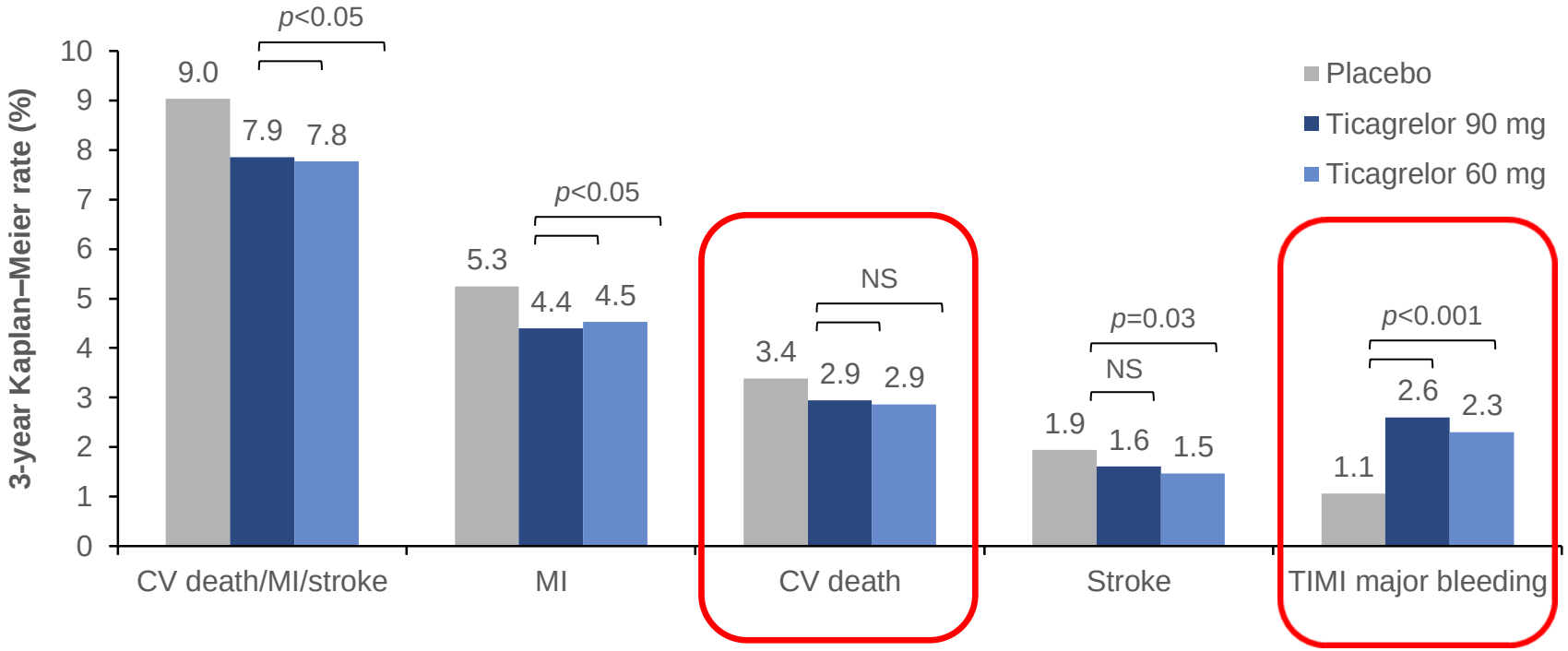
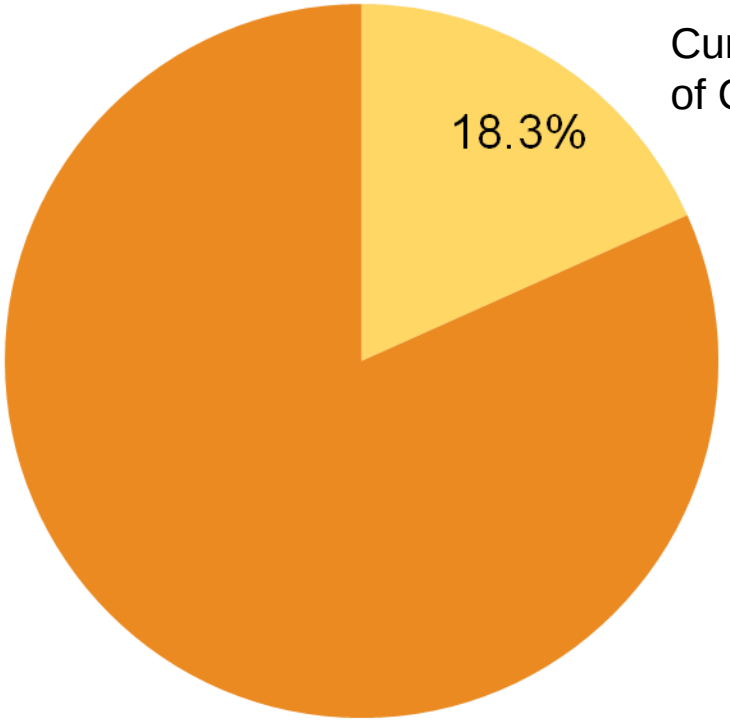


Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800

APOLLO: Global Real World Registry
5 individual studies (>150,000 patients)

1 in 5 patients will suffer an MI, stroke or CV death within the first year after an MI

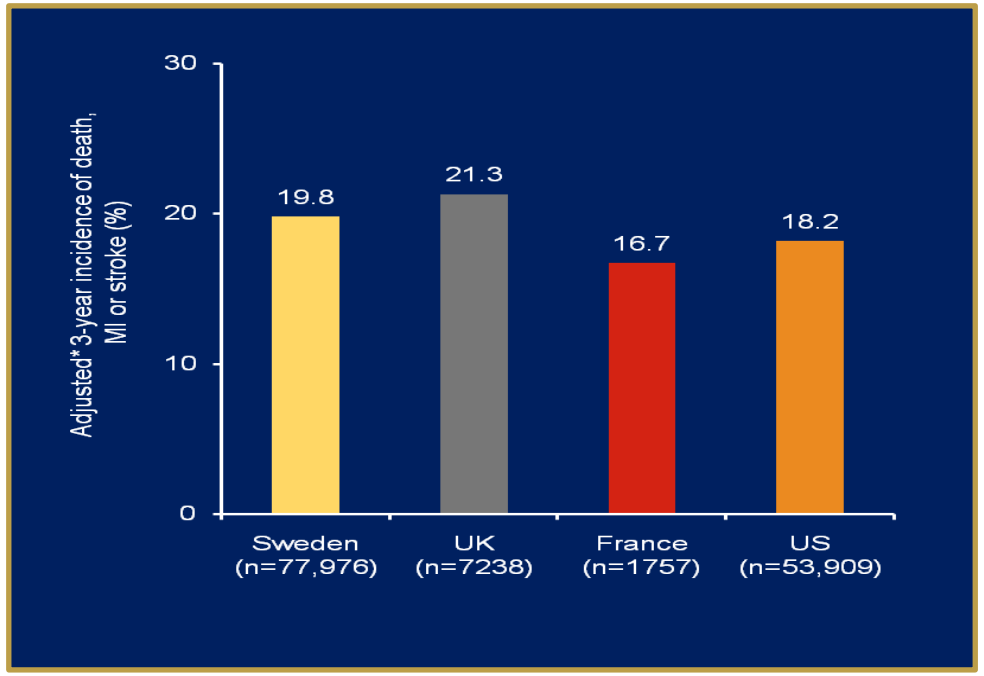


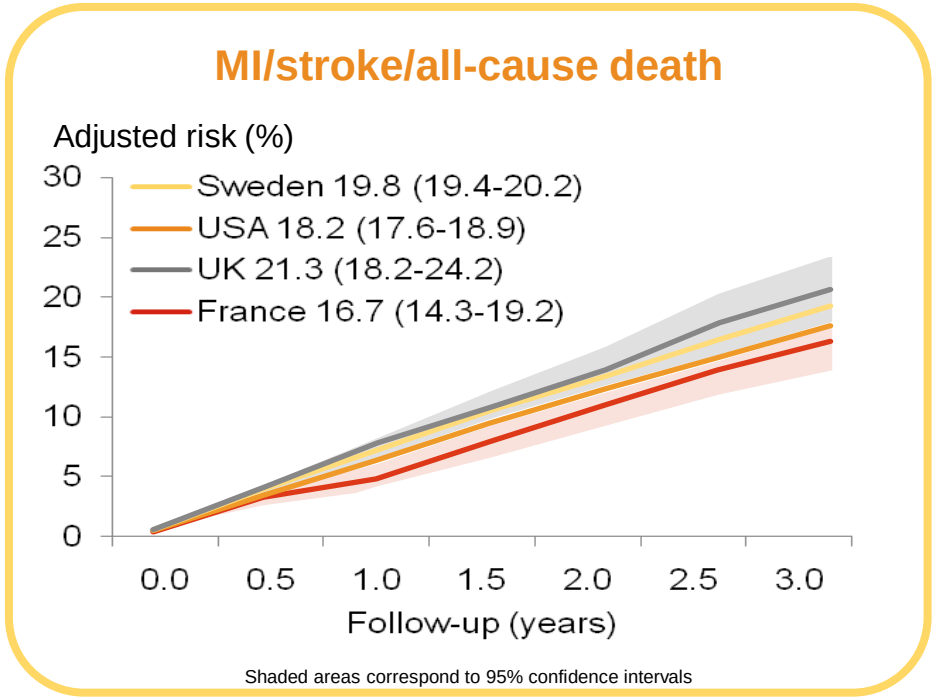
Cumulative 1 year incidence
of CV death, MI or stroke (%)

Jernberg, T. et al. Eur Heart J 2015

Patients who are event free for the first year post-MI, will suffer an MI, stroke or death within 3 years

APOLLO 4-country analysis: adjusted incidence





Rapsomaniki E *et al*. ESC Late Breaking Registry presentation 2014.

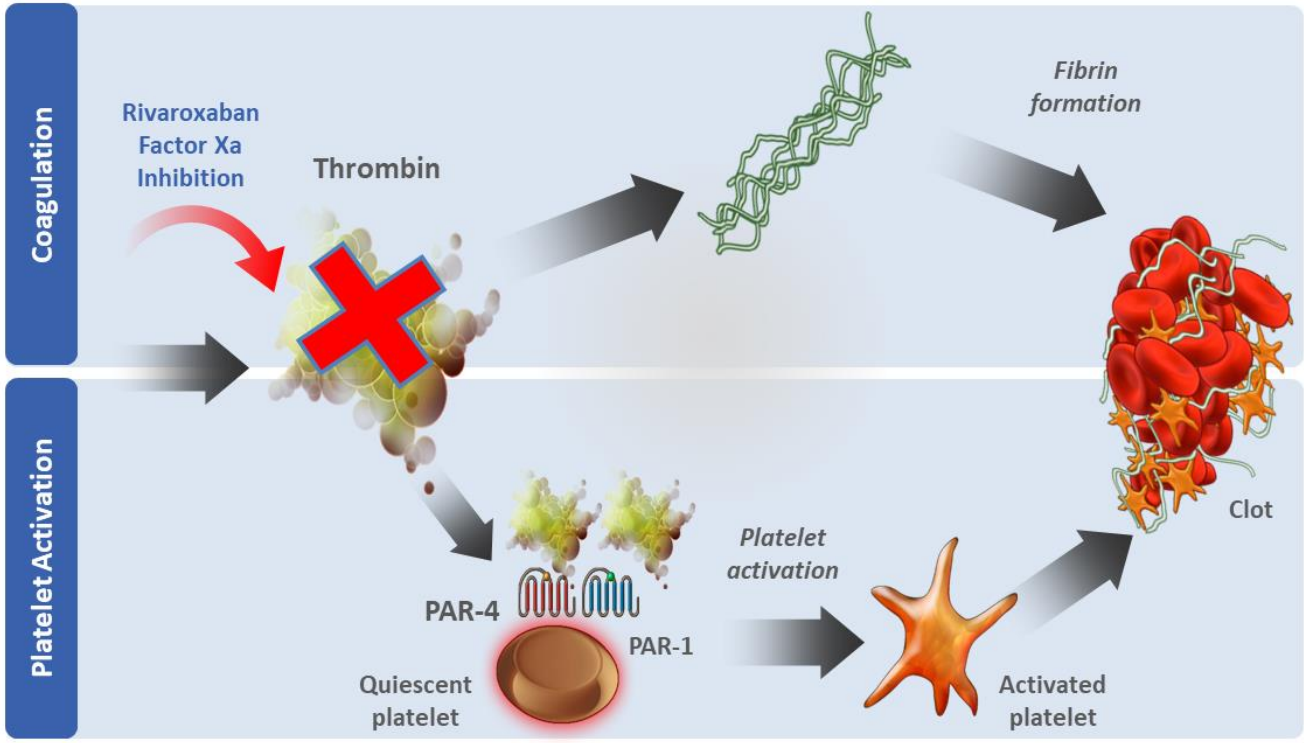
Unmet Need in Patients Post ACS and Rationale for a Combined Antithrombotic Regimen

- Despite optimization of DAPT ~10% of ACS pts will experience MACE within 1st year following ACS and another ≥20 % in the following (3-4) years.
- Although platelet activation is essential in atherothrombosis, thrombin remains a pivotal factor in thrombus formation.
- Excess thrombin generation persists in patients with atherothrombotic event for at least 6–12 months beyond the acute presentation.

1.Yusuf S *et al*, *N Engl J Med* 2001;345:494–502; 2. Roe MT *et al*, *N Engl J Med* 2012;367:1297–1309;
3. Wallentin L *et al*, *N Engl J Med* 2009;361:1045–1057; 4. Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28;
5. De Caterina R *et al*, *Thromb Haemost* 2013;109:569–579; 6. Merlini PA *et al*, *Circulation* 1994;90:61–68;
7. Ardissino D *et al*, *Blood* 2003;102:2731–2735

”Dual-Pathway” Strategy

An antithrombotic regimen consisting of anti-coagulant plus antiplatelet therapy targets complementary mechanisms associated with thrombus formation



Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.
M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Prol
Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Don
A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryde
F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J.
D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C.
K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Che
for the COMPASS Investigator

ABSTRACT

BACKGROUND

We evaluated whether rivaroxaban alone or in combina
more effective than aspirin alone for secondary cardio

METHODS

In this double-blind trial, we randomly assigned 27,3
atherosclerotic vascular disease to receive rivaroxaban
aspirin (100 mg once daily), rivaroxaban (5 mg twice dai
daily). The primary outcome was a composite of cardiova
cardial infarction. The study was stopped for superiori
aspirin group after a mean follow-up of 23 months.

RESULTS

The primary outcome occurred in fewer patients in t
group than in the aspirin-alone group (379 patients [4.
hazard ratio, 0.76; 95% confidence interval [CI], 0.66 t
but major bleeding events occurred in more patients in
rin group (288 patients [3.1%] vs. 170 patients [1.9%];
1.40 to 2.05; P<0.001). There was no significant differe
bleeding between these two groups. There were 313 d
aban-plus-aspirin group as compared with 378 (4.1%)
(hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; thr
cance, 0.0025). The primary outcome did not occur in
in the rivaroxaban-alone group than in the aspirin-alon
events occurred in more patients in the rivaroxaban-al

CONCLUSIONS

Articles

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*

Summary

Background Coronary artery disease is a major cause of morb
acute thrombotic events involving activation of platelets and
each reduce thrombotic events but have not yet been tested
stable coronary artery disease.

Methods In this multicentre, double-blind, randomised, pl
coronary artery disease or peripheral artery disease were re
in 33 countries. This paper reports on patients with corona
disease had to have had a myocardial infarction in the past
of stable or unstable angina, previous multi-vessel percuta
coronary artery bypass graft surgery. After a 30-day run
receive rivaroxaban (2·5 mg orally twice a day) plus aspiri
twice a day), or aspirin alone (100 mg orally once a day). Ra
group was double dummy, and the patients, investigator
allocation. The primary outcome of the COMPASS trial
or cardiovascular death. This trial is registered with
closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, 27 395
24 824 patients had stable coronary artery disease from 558
reduced the primary outcome more than aspirin alone (347
95% CI 0·65–0·86, p<0·0001). By comparison, treatment w
primary outcome when compared with treatment with aspir
95% CI 0·78–1·02, p=0·094). Combined rivaroxaban plus
treatment with aspirin alone (263 [3%] of 8313 vs 158 [2%]
similarly, more bleeds were seen in the rivaroxaban alone gr
158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, p<0·00
gastrointestinal, occurring in 130 [2%] patients who received
who received rivaroxaban alone, and in 61 [1%] patients who
mortality when compared with aspirin alone (262 [3%] of 8
p=0·0012).

Articles

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

Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators*

Summary

Background Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications.

Methods This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index of less than 0·90. After a 30-day run-in period, patients were randomly 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 (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, we enrolled 7470 patients with peripheral artery disease from

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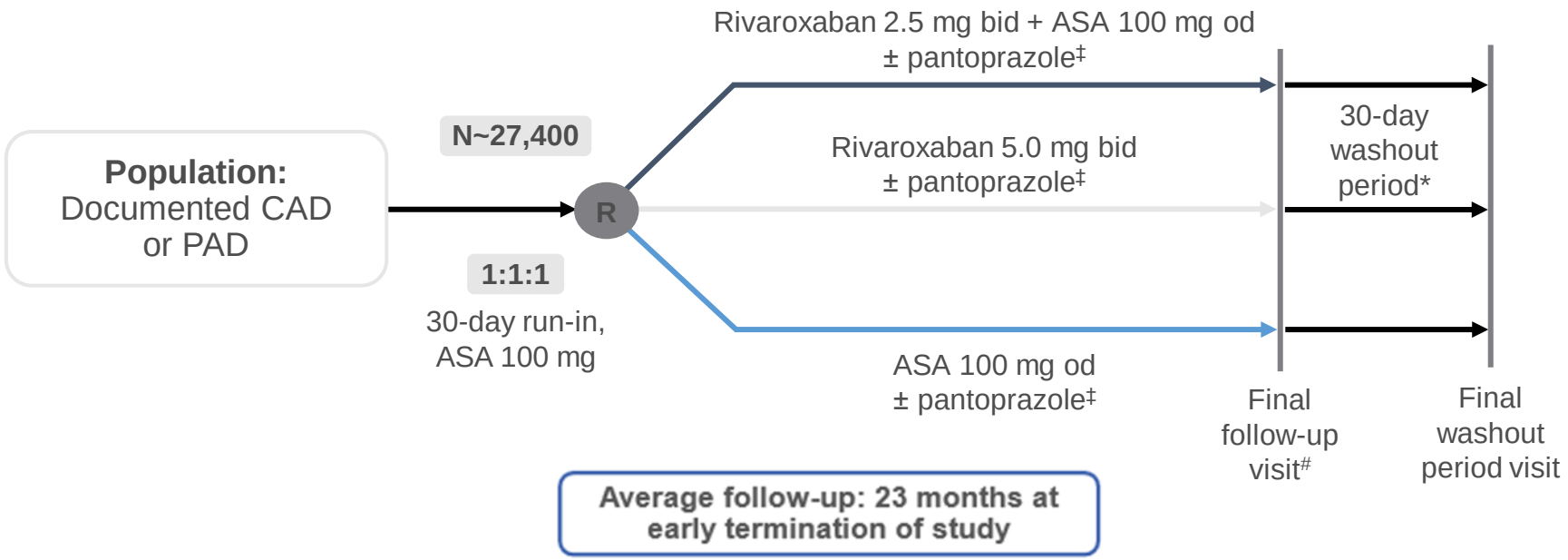
See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(17)32847-7
*Members listed in the appendix
Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (Prof S S Anand MD, J Bosch PhD, J W Eikelboom MBBS, Prof S J Connolly MD, D P Leong MBBS, Prof S I Bangdiwala PhD, Prof R G Hart MD, Prof S Yusuf MBBS); Department of Medicine (Prof S S Anand, J W Eikelboom,

PLOT TWIST AHEAD

Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330
Connolly SJ, et al. Lancet. 2018 Jan 20;391(10117):205-218
Anand SS et al. Lancet. 2018 Jan 20;391(10117):219-229.

COMPASS Trial Design

Objective: To determine the efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA 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

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%

Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

Primary EP: 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

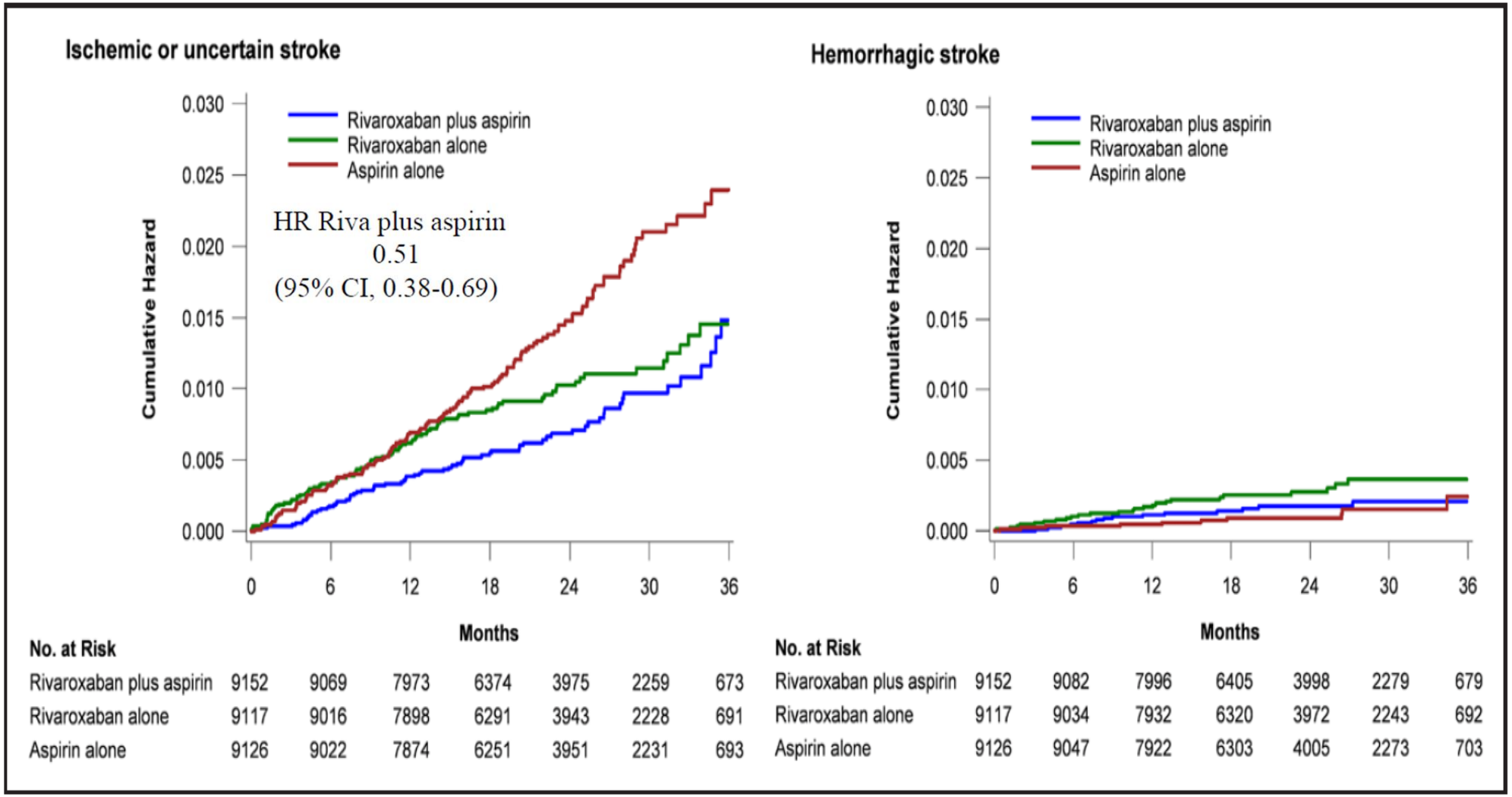
Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

Primary End Point: CV death, stroke, MI

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

Incidence rates of stroke according to treatment group



Mukul Sharma et al Circulation. 2019;139:1134–1145.

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MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

`Vascular Dose` Rivaroxaban Reduces Cardiac Events

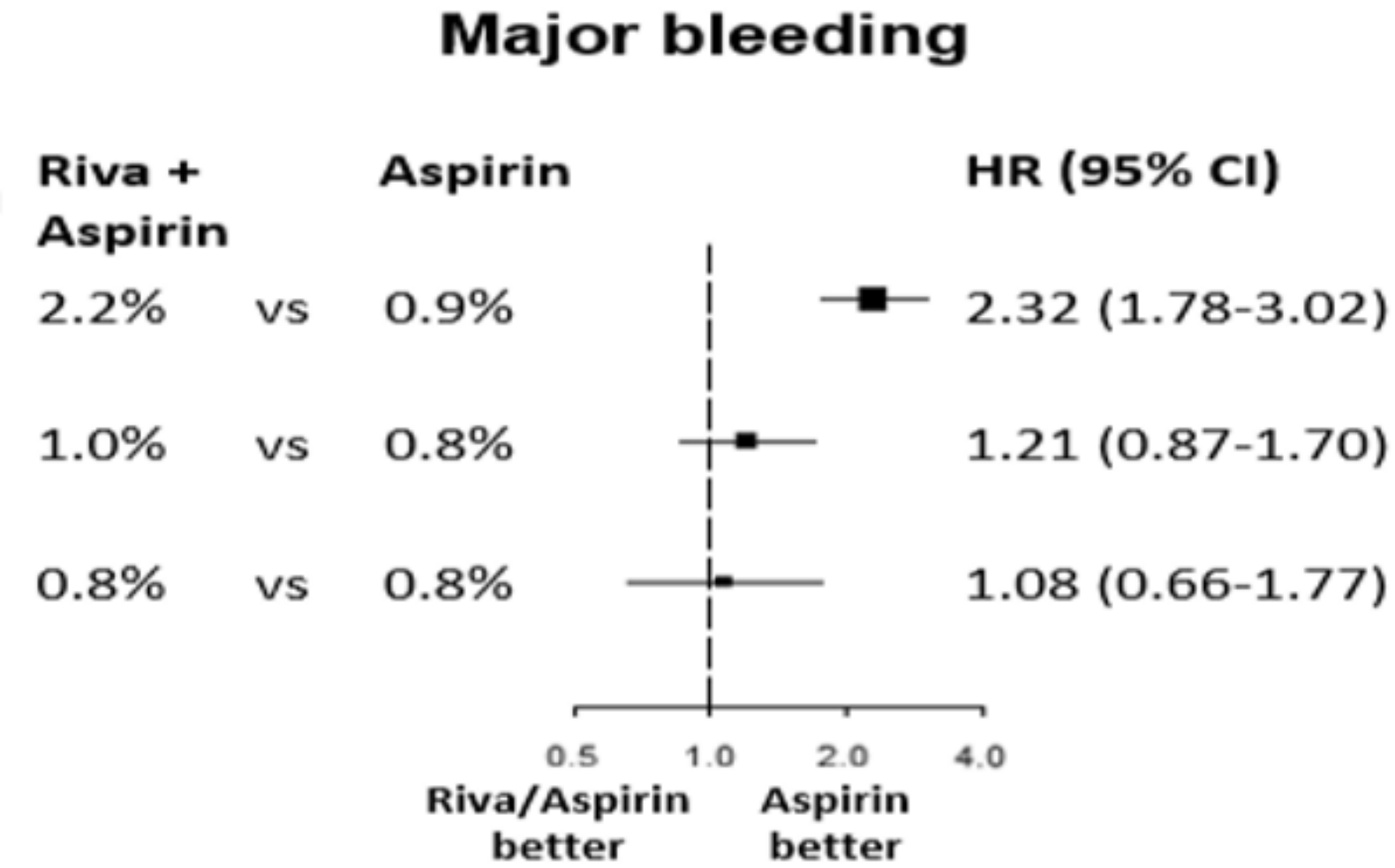
Event	R + A N=9,152	Aspirin N=9,126	Riva + aspirin vs. aspirin	
	N (%)	N (%)	HR (95% CI)	p
MI or SCD	247 (2.7%)	289 (3.2%)	0.85 (0.72-1.00)	0.06
MI, SCD, or cardiac arrest	273 (3.0%)	333 (3.6%)	0.81 (0.69-0.95)	0.01
MI, SCD, resus. Cardiac arrest, or unstable angina	277 (3.0%)	331 (3.6%)	0.83 (0.71-0.97)	0.02

Major bleeding

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

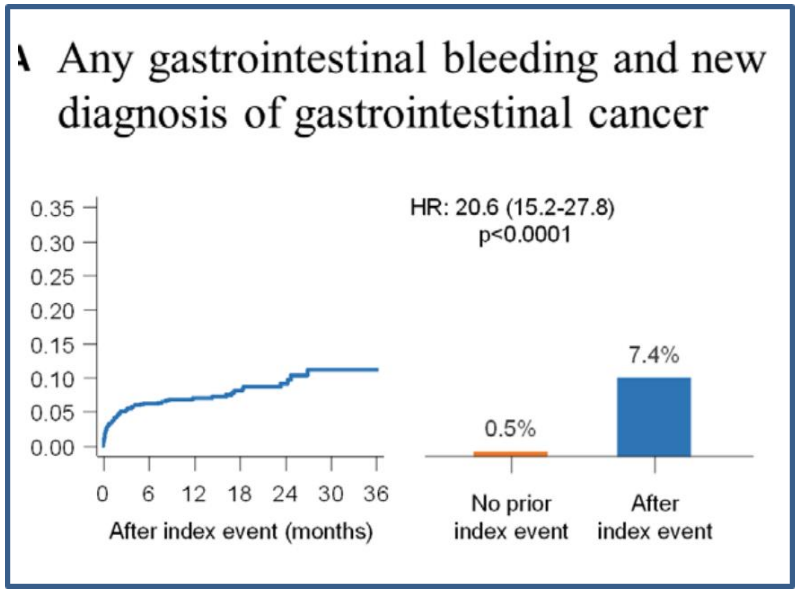
Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

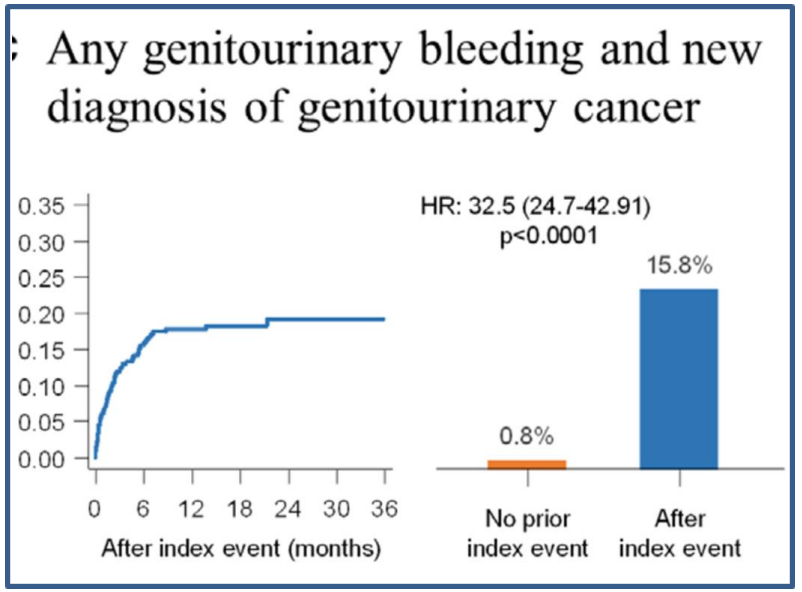
Major Bleeding Landmark Analysis

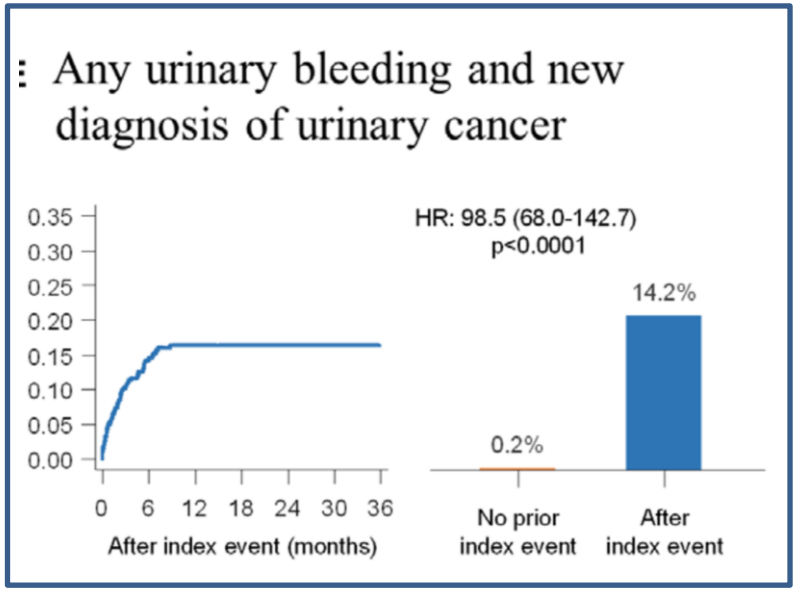


Stuart J Connolly et al. Lancet. 2018 Jan 20;391(10117):205-218

Frequency and timing of new cancer diagnosis in relation to bleeding







Eikelboom JW et al. Circulation. Oct 2019;140:1451–1459.

“Vascular Dose” Rivaroxaban - Reduced Mortality

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95%)	P*
CHD death, IS, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63-0.83)	<0.0001
CV death, IS, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65-0.85)	<0.0001
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

Eikelboom JW et al. N Engl J Med. 2017 Oct 5;377(14):1319-1330

ESC
European Society of Cardiology

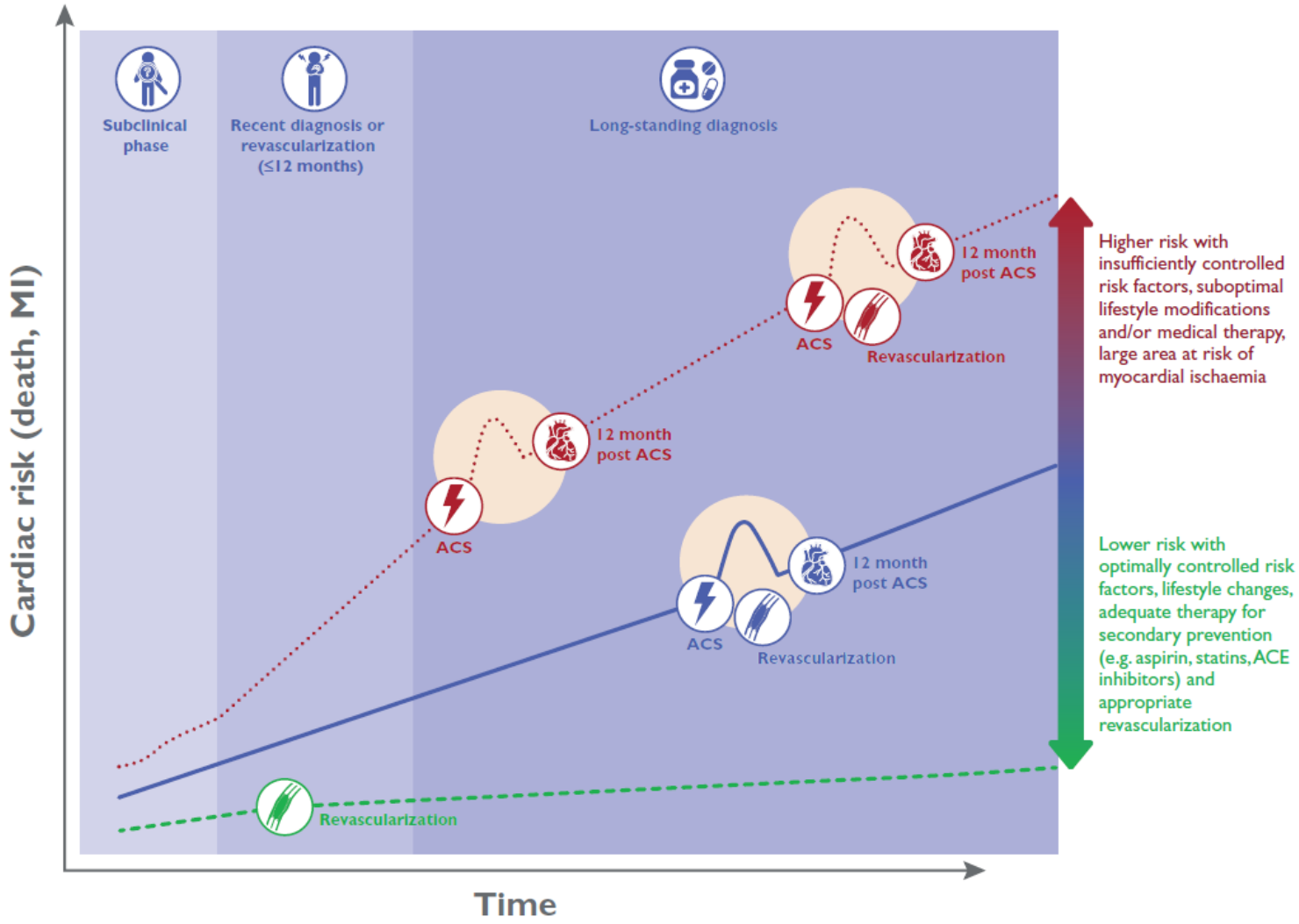
European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

The Natural History of Chronic Coronary Syndromes



New Major Recommendations in 2019

Antithrombotic therapy in patients with CCS and sinus rhythm	
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIa**
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIb**

Diffuse multivessel CAD with at least one of the following:

- Diabetes mellitus requiring medication
- Recurrent MI
- PAD
- CKD with eGFR <59 mL/min/1.73 m

Treatment options for dual antithrombotic therapy in combination with aspirin in patients who have a high or moderate risk of ischemic events, and do not have a high bleeding risk

Treatment options are presented in alphabetical order……

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

Treatment options for dual antithrombotic therapy in combination with aspirin in patients who have a high or moderate risk of ischemic events, and do not have a high bleeding risk

Treatment options are presented in alphabetical order……

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The NEW ENGLAND JOURNAL of MEDICINE

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Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver and Joseph M. Massaro, Ph.D., for the DAPT Study I

ABSTRACT

BACKGROUND

Dual antiplatelet therapy is recommended after coronary stenting to prevent th botic complications, yet the benefits and risks of treatment beyond 1 year are uncer

METHODS

Patients were enrolled after they had undergone a coronary stent procedure in w a drug-eluting stent was placed. After 12 months of treatment with a thienopyr drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to tinue receiving thienopyridine treatment or to receive placebo for another 18 mo all patients continued receiving aspirin. The coprimary efficacy end points were thrombosis and major adverse cardiovascular and cerebrovascular events (a con ite of death, myocardial infarction, or stroke) during the period from 12 to 30 mo The primary safety end point was moderate or severe bleeding.

RESULTS

A total of 9961 patients were randomly assigned to continue thienopyridine t ment or to receive placebo. Continued treatment with thienopyridine, as comp with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; hazard r 0.29 [95% confidence interval {CI}, 0.17 to 0.48]; P<0.001) and major adverse diovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio, 0.71 [95 0.59 to 0.85]; P<0.001). The rate of myocardial infarction was lower with th pyridine treatment than with placebo (2.1% vs. 4.1%; hazard ratio, 0.47; P<0. The rate of death from any cause was 2.0% in the group that continued thieno dine therapy and 1.5% in the placebo group (hazard ratio, 1.36 [95% CI, 1.00 to 1 P=0.05). The rate of moderate or severe bleeding was increased with continuec enopyridine treatment (2.5% vs. 1.6%, P=0.001). An elevated risk of stent throı sis and myocardial infarction was observed in both groups during the 3 mc after discontinuation of thienopyridine treatment.

CONCLUSIONS

Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting sten compared with aspirin therapy alone, significantly reduced the risks of stent th bosis and major adverse cardiovascular and cerebrovascular events but was assoc with an increased risk of bleeding. (Funded by a consortium of eight device and manufacturers and others; DAPT ClinicalTrials.gov number, NCT00977938.)

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Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction

Robert W. Yeh, MD, MSc,*†‡ Dean J. Kereiakes, MD,§ Philippe Gabriel Steg, MI Michael J. Rinaldi, MD,†‡ Anthony H. Gershlick, MBBS,‡‡ Donald E. Cutlip, MI Jean-Francois Tanguay, MD,¶¶ Alice Jacobs, MD,## Stephen D. Wiviott, MD,‡* Adrian C. Iancu, MD,‡‡‡ Laura Mauri, MD, MSc,‡‡*** on behalf of the DAPT Stu

ABSTRACT

BACKGROUND The benefits and risks of prolonged dual antiplatelet therapy may myocardial infarction (MI) compared with more stable presentations.

OBJECTIVES This study sought to assess the benefits and risks of 30 versus 12 m among patients undergoing coronary stent implantation with and without MI.

METHODS The Dual Antiplatelet Therapy Study, a randomized double-blind, place versus 12 months of dual antiplatelet therapy after coronary stenting. The effect of c and bleeding events among patients initially presenting with versus without MI was were definite or probable stent thrombosis and major adverse cardiovascular and c primary safety endpoint was GUSTO (Global Utilization of Streptokinase and Tissue Arteries) moderate or severe bleeding.

RESULTS Of 11,648 randomized patients (9,961 treated with drug-eluting stents, 1, presented with MI. Between 12 and 30 months, continued thienopyridine reduced stent

Interventional Cardiology

Prasugrel Plus Aspirin Beyond 12 Months Is Associated With Improved Outcomes After Taxus Liberté Paclitaxel-Eluting Coronary Stent Placement

Kirk N. Garratt, MD, MSc; W. Douglas Weaver, MD; Ronald G. Jenkins, MD; Thomas K. Pow, MD; Laura Mauri, MD, MSc; Dean J. Kereiakes, MD; Kenneth J. Winters, MD; Thomas Christen, MD, PhD; Dominic J. Allocco, MD, MSc; David P. Lee, MD

Background—The TAXUS Liberté Post Approval Study (TL-PAS) contributed patients treated with TAXUS Liberté paclitaxel-eluting stent and prasugrel to the Dual Antiplatelet Therapy Study (DAPT) that compared 12 and 30 months thienopyridine plus aspirin therapy after drug-eluting stents.

Methods and Results—Outcomes for 2191 TL-PAS patients enrolled into DAPT were assessed. The DAPT coprimary composite end point (death, myocardial infarction [MI], or stroke) was lower with 30 compared with 12 months prasugrel treatment (3.7% versus 8.8%; hazard ratio [HR], 0.407; $P<0.001$). Rates of death and stroke were similar between groups, but MI was significantly reduced with prolonged prasugrel treatment (1.9% versus 7.1%; HR, 0.255; $P<0.001$). The DAPT coprimary end point, stent thrombosis, was also lower with longer therapy (0.2% versus 2.9%; HR, 0.063; $P<0.001$). MI related to stent thrombosis (0% versus 2.6%; $P<0.001$) and occurring spontaneously (1.9% versus 4.5%; HR, 0.407; $P=0.007$) were both reduced with prolonged prasugrel. MI rates increased within 90 days of prasugrel cessation after both 12 and 30 months treatment. Composite Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate or severe bleeds were modestly increased (2.4% versus 1.7%; HR, 1.438; $P=0.234$) but severe bleeds were not more frequent (0.3% versus 0.5%; HR, 0.549; $P=0.471$) in the prolonged treatment group.

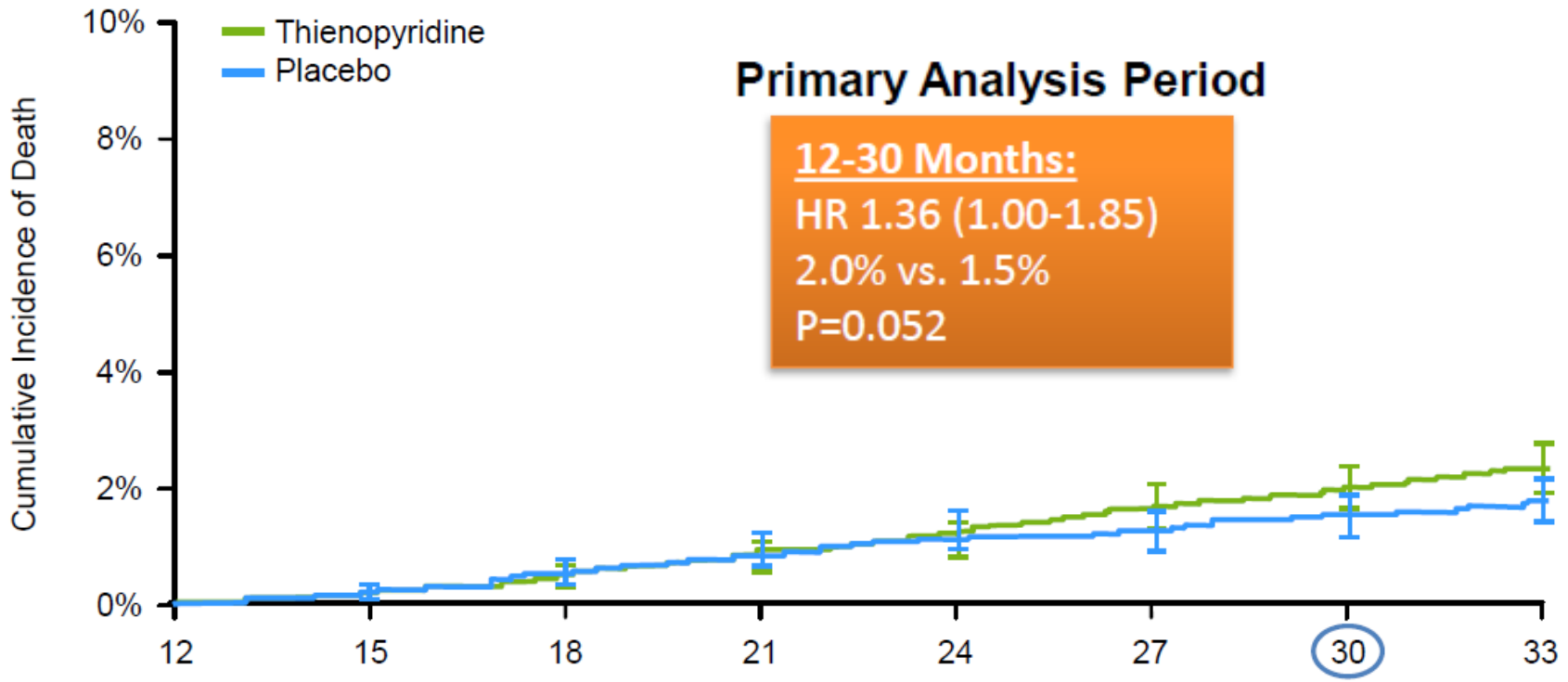
Conclusions—Prasugrel and aspirin continued for 30 months reduced ischemic events for the TAXUS Liberté paclitaxel-eluting stent patient subset from DAPT through reductions in MI and stent thrombosis. Withdrawal of prasugrel was followed by an increase in MI after both 12 and 30 months therapy. The optimal duration of dual antiplatelet therapy with prasugrel after TAXUS Liberté paclitaxel-eluting stent remains unknown, but appears to be >30 months.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00997503.

(***Circulation***. **2015;131:62-73. DOI: 10.1161/CIRCULATIONAHA.114.013570.)**

All-Cause Mortality

DAPT STUDY



Primary Analysis Period

12-30 Months:
HR 1.36 (1.00-1.85)
2.0% vs. 1.5%
P=0.052

# At Risk								
Thienopyridine	5020	4936	4875	4835	4777	4703	4663	3139
Placebo	4941	4866	4805	4761	4700	4659	4618	3159

N Engl J Med 2014; 371:2155-2166

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Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction

Robert W. Yeh, MD, MSc,*†‡ Dean J. Kereiakes, MD,§ Philippe Gabriel Steg, Michael J. Rinaldi, MD,†‖ Anthony H. Gershlick, MBBS,‡‡ Donald E. Cutlip, Jean-Francois Tanguay, MD,¶¶ Alice Jacobs, MD,## Stephen D. Wiviott, MI Adrian C. Iancu, MD,‡‡‡ Laura Mauri, MD, MSc,†‡*** on behalf of the DAPT

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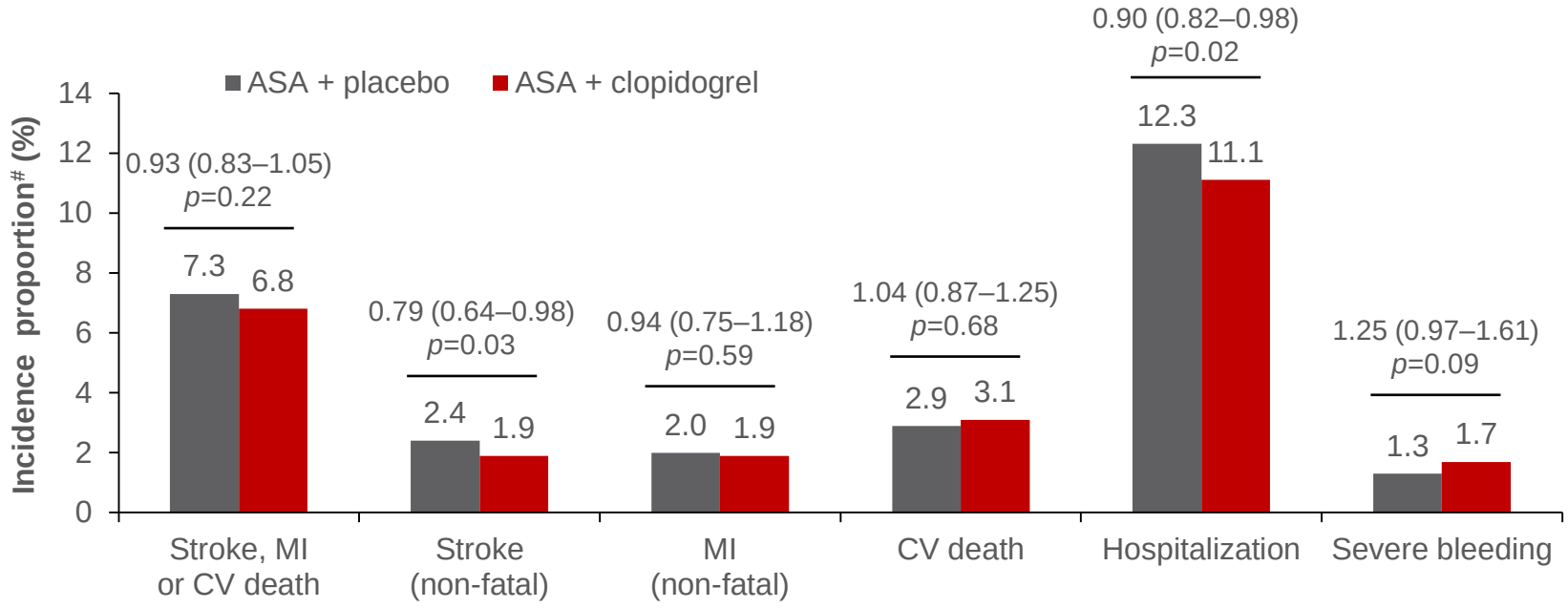
(***Circulation***. 2015;131:62-73. DOI: 10.1161/CIRCULATIONAHA.114.013570.)

Similar Risk of Non-Fatal CV Events with Clopidogrel Versus Placebo in Patients at High Atherothrombotic Risk

CHARISMA: ASA* + placebo versus ASA* + clopidogrel (75 mg od)

- 15,603 patients with clinically evident CV disease or at high risk of atherothrombotic events
- Adding clopidogrel to ASA did not reduce the risk of stroke, MI or CV death

A median of 28 months of follow-up



Bhatt DP *et al*, *N Engl J Med* 2006:354:1706–1717

Treatment options for dual antithrombotic therapy in combination with aspirin in patients who have a high or moderate risk of ischemic events, and do not have a high bleeding risk

Treatment options are presented in alphabetical order……

Drug option	Dose	Indication	Additional cautions
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Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

The NEW ENGLAND JOURNAL of MEDICINE

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Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philipp
Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer B
M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis,
Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D
Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A
Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sa
for the PEGASUS-TIMI 54 Steering Committee and Investigators*

ABSTRACT

BACKGROUND

The potential benefit of dual antiplatelet therapy beyond 1 year after a myocardial infarction has not been established. We investigated the efficacy and safety of ticagrelor, a $P2Y_{12}$ receptor antagonist with established efficacy after an acute coronary syndrome, in this context.

METHODS

We randomly assigned, in a double-blind 1:1:1 fashion, 21,162 patients who had had a myocardial infarction 1 to 3 years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. All the patients were to receive low-dose aspirin and were followed for a median of 33 months. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding.

RESULTS

The two ticagrelor doses each reduced, as compared with placebo, the rate of the primary efficacy end point, with Kaplan–Meier rates at 3 years of 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ticagrelor twice daily, and 9.04% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 0.85; 95% confidence interval [CI], 0.75 to 0.96; P=0.008; hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004). Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) (P<0.001 for each dose vs. placebo); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively.

European Heart Journal (2016) **37**, 1133–1142
doi:10.1093/eurheartj/ehv531

FASTTRACK
ESC Clinical Trial Update

Thrombosis and antithrombotic therapy

Ischaemic risk and efficacy of ticagrelor in relation to time from $P2Y_{12}$ inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54

Marc P. Bonaca[1]*, Deepak L. Bhatt[1], P. Gabriel Steg[2], Robert F. Storey[3], Marc Cohen[4], Kyungah Im[1], Ton Oude Ophuis[5], Andrej Budaj[6], Shinya Goto[7], José López-Sendón[8], Rafael Diaz[9], Anthony Dalby[10], Frans Van de Werf[11], Diego Ardissino[12], Gilles Montalescot[13], Philip Aylward[14], Giulia Magnani[1], Eva C. Jensen[15], Peter Held[15], Eugene Braunwald[1], and Marc S. Sabatine[1]

[1]TIMI Study Group, Brigham and Women's Hospital, Heart & Vascular Center, 75 Francis Street, Boston, MA 02115, USA; [2]Département de Cardiologie, Hôpital Bichat, Assistance Publique, Paris, France; [3]University of Sheffield, Sheffield, UK; [4]Cardiovascular Division, Newark Beth Israel Medical Center, Mount Sinai School of Medicine, New York, USA; [5]CWZ Hospital, Nijmegen, The Netherlands; [6]Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland; [7]Tokai University School of Medicine, Institute of Medical Science, Tokyo, Japan; [8]Hospital Universitario La Paz, Instituto de Investigación La PAZ, Madrid, Spain; [9]ECLA (Estudios Clínicos Latino América), Rosario, Argentina; [10]Milpark Hospital, Johannesburg, South Africa; [11]Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [12]Cardiovascular Division, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [13]Institut de Cardiologie, Pitié-Salpêtrière Hospital, 47 boul de l'Hôpital, Paris, France; [14]Division of Medicine, Cardiac & Critical Care Services, Flinders Medical Centre, Adelaide, South Australia, Australia; and [15]AstraZenecaAZ R&D, Molndal, Sweden

Received 31 July 2015; revised 13 September 2015; accepted 18 September 2015; online publish-ahead-of-print 21 October 2015

See page 1143 for the editorial comment on this article (doi:10.1093/eurheartj/ehv573)

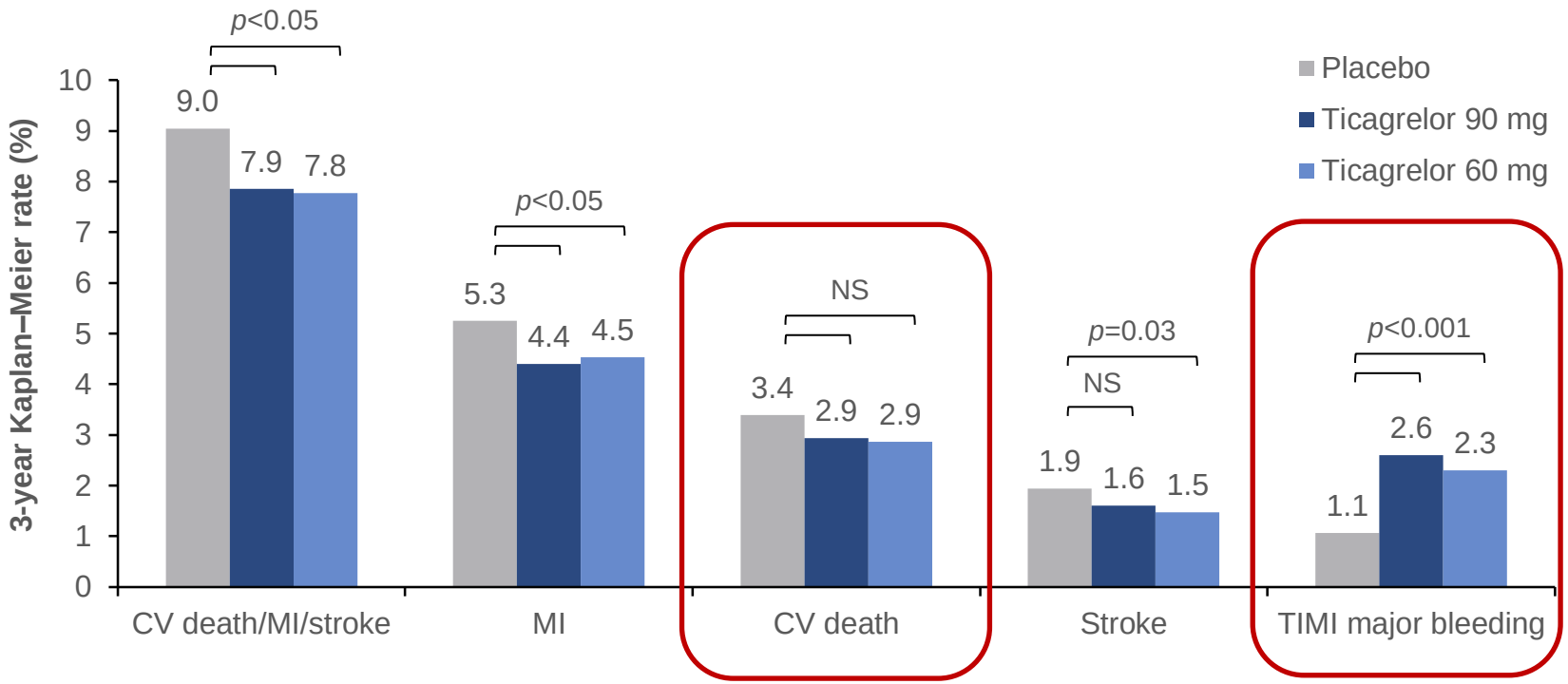
Aims Ticagrelor reduced major adverse cardiovascular event (MACE) by 15–16% in patients with prior myocardial infarction (MI) in PEGASUS-TIMI 54. We hypothesized that patients who recently discontinued $P2Y_{12}$ inhibition, even years after MI, may be at particular risk of MACE and may derive particular benefit from continuation or reinitiation of therapy.

Methods and results Patients in PEGASUS-TIMI 54 were categorized by time from last $P2Y_{12}$ inhibitor (days: ≤30, >30–360, >360). The risk of MACE and the efficacy of ticagrelor were compared across categories. In the placebo arm, patients who more recently stopped $P2Y_{12}$ inhibitor therapy had a greater number of risk factors but still had a higher risk of MACE after multivariable adjustment [≤30 days, hazard ratio $(HR)_{adj}$ 1.47, 95% confidence interval (CI) 1.12–1.93, $P = 0.0051$; 30 days–1 year, HR_{adj} 1.28, 95% CI 0.98–1.67, $P = 0.073$] compared with those who stopped >1 year prior

Ticagrelor Reduces Non-Fatal CV Events but Increases Major Bleeding in Patients with Prior MI

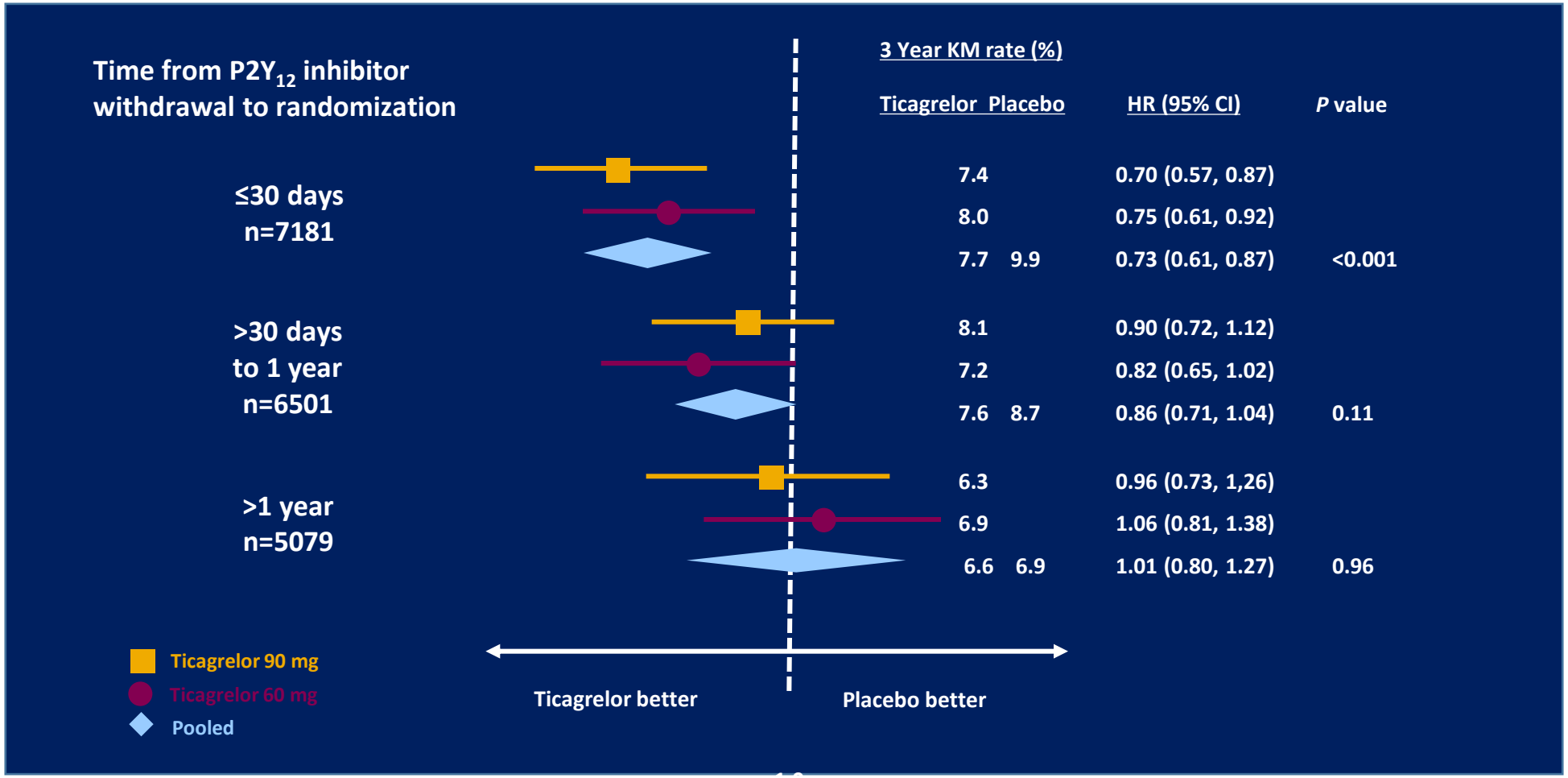
PEGASUS: ticagrelor (90 mg bid or 60 mg bid) + ASA* versus placebo + ASA*

- 21,162 patients who had an MI 1–3 years previously
  - Compared with placebo, both doses of ticagrelor decreased the risk of CV death, MI or stroke but increased the risk of major bleeding (but not fatal bleeding)



Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800

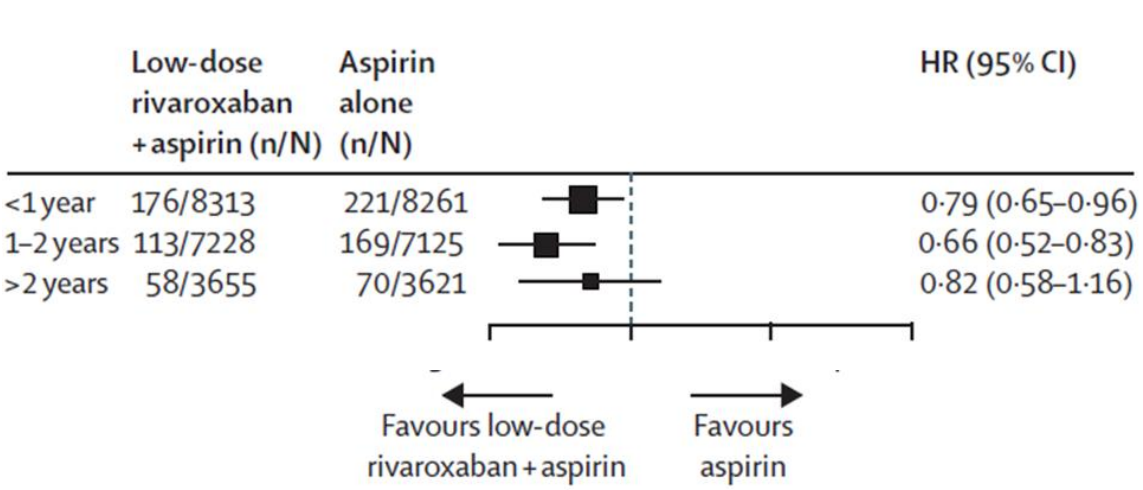
Efficacy of ticagrelor in reducing risk of atherothrombotic events declines with increasing duration of $P2Y_{12}$ inhibitor withdrawal



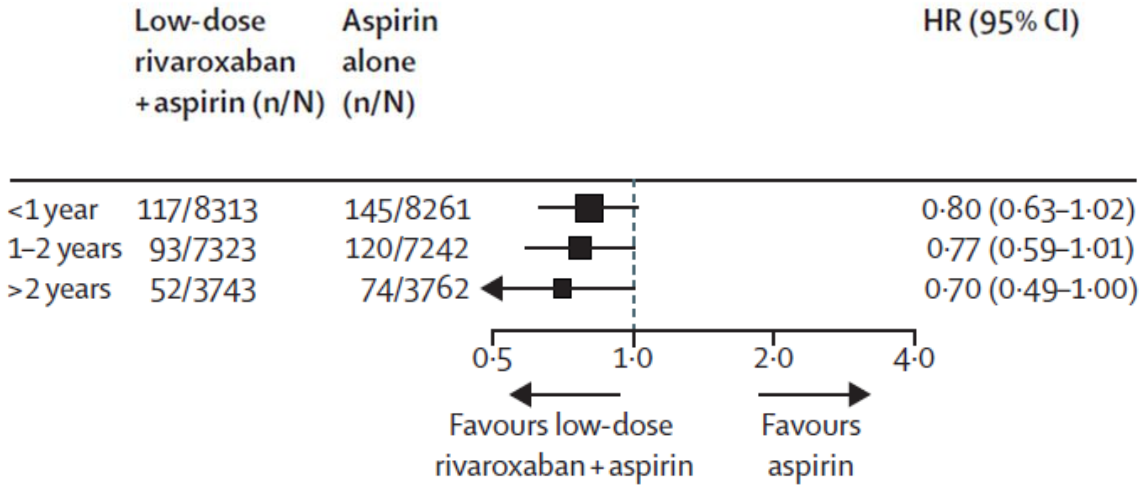
Bonaca MP et al. Eur Heart J, 2015

Landmark Analysis of the Primary Efficacy Outcome and all-Cause Death

primary efficacy outcome



all-cause death

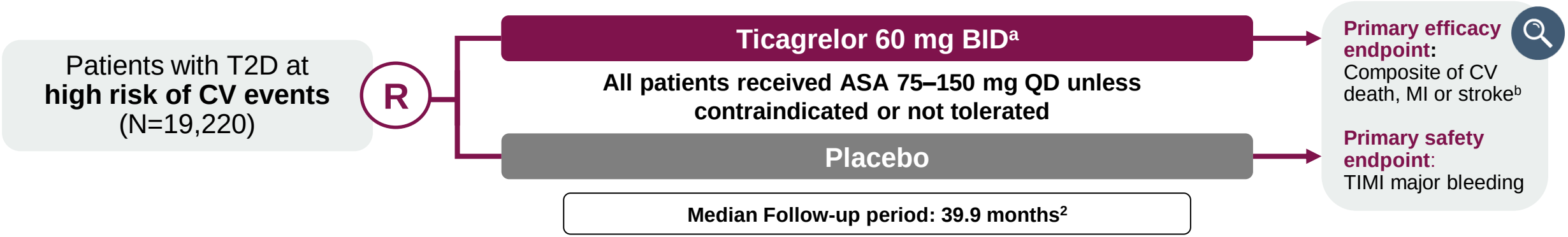


Stuart J Connolly et al. Lancet. 2018 Jan 20;391(10117):205-218

THEMIS

Study Design Overview and Key Baseline Characteristics

- **Phase 3b placebo-controlled event-driven RCT** looking to collect 1385 primary efficacy events for an annual event rate of 2.5% in placebo group to provide a power of 90%
- **Primary objective:** compare ticagrelor vs. placebo for the prevention of CV events in patients with T2D at high risk of CV events



Key inclusion criteria:

- Age ≥50 with T2D (glucose lowering medication for ≥6 months)
- History of PCI or CABG or ≥50% lumen stenosis confirmed by angiography

Key exclusion criteria:

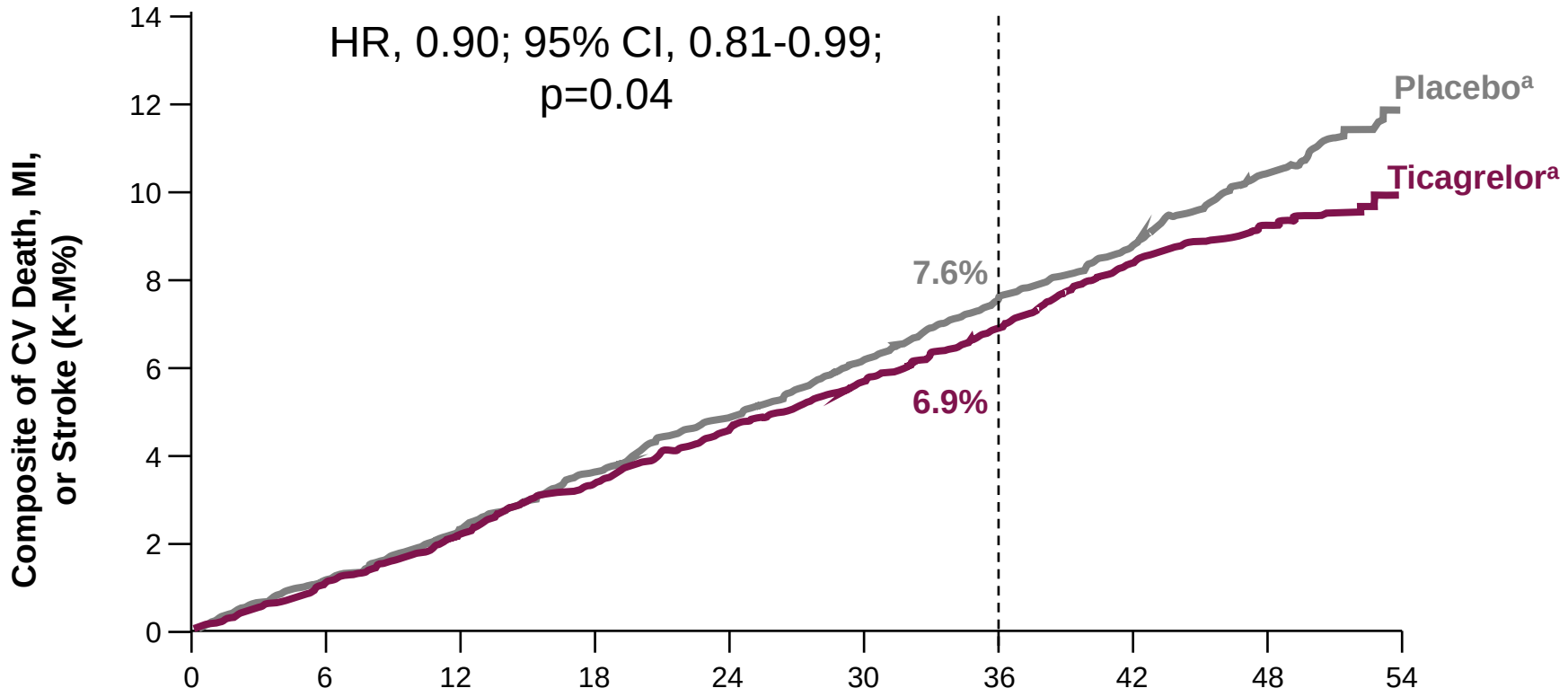
- History of previous MI or stroke
- Planned revascularization

Baseline characteristics:

- Median age: 66 years; 31.4% female
- Characteristics balanced between groups
  - Medical/surgical history: hypertension 92.5%, dyslipidemia 87.2%, coronary artery revascularization 79.8%; duration of T2D-median 10 years
  - Concomitant Medications: ASA 99.4% (median dose- 100 mg), statin 89.9%, ACE inhibitor or ARB 78.7%, insulin 28.7%, SGLT2 inhibitor 1.9%, GLP-1 receptor agonist 2.2%

Steg PG et al. NEJM. 2019 Oct 3;381(14):1309-1320

THEMIS Overall: *Primary Efficacy Endpoint (Composite of CV Death, MI or Stroke)*



Number at Risk

Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

Steg PG et al. NEJM. 2019 Oct 3;381(14):1309-1320

THEMIS Overall: Safety Outcomes

Outcome	Ticagrelor[a] (n=9562) n (%)	Ticagrelor[a] (n=9562) Event rate per 100 patient years	Placebo[a] (n=9531) n (%)	Placebo[a] (n=9531) Event rate per 100 patient years	HR (95% CI)	p-value
Primary safety endpoint						
TIMI major bleeding	206 (2.2)	0.89	100 (1.0)	0.38	2.32 (1.82-2.94)	<0.001
Other safety endpoints						
TIMI major or minor bleeding	285 (3.0)	1.23	129 (1.4)	0.49	2.49 (2.02-3.07)	<0.001
TIMI major, minor or requiring medical attention bleeding	1072 (11.2)	4.61	485 (5.1)	1.85	2.51 (2.26-2.80)	<0.001
ICH[2]	70 (0.7)	0.30	46 (0.5)	0.18	1.71 (1.18-2.48)	0.005
Procedural	1 (0.0)	0.00	3 (0.0)	0.01	---	---
Spontaneous	28 (0.3)	0.12	27 (0.3)	0.10	1.71 (0.69-1.98)	0.57
Traumatic[b]	41 (0.4)	0.18	16 (0.2)	0.06	2.87 (1.61-5.12)	<0.001
Fatal bleeding[c]	17 (0.2)	0.07	10 (0.1)	0.04	1.90 (0.87-4.15)	0.11

Steg PG et al. NEJM. 2019 Oct 3;381(14):1309-1320

THEMIS Overall

Primary and Pre-Specified Secondary Efficacy Outcomes

Outcome	Ticagrelor[a] (n=9619)		Placebo[a] (n=9601)		HR (95% CI)[b]	p-value
	Patients with events, n (%)	K-M% at 36 months	Patients with events, n (%)	K-M% at 36 months		
Primary composite endpoint						
CV death, MI or stroke	736 (7.7)	6.9	818 (8.5)	7.6	0.90 (0.81-0.99)	0.04
Hierarchical secondary efficacy endpoints						
CV death	364 (3.8)	3.3	357 (3.7)	3.0	1.02 (0.88-1.18)	0.79
MI	274 (2.8)	2.6	328 (3.4)	3.3	0.84 (0.71-0.98)	---
Ischemic stroke	152 (1.6)	1.5	191 (2.0)	1.8	0.80 (0.64-0.99)	---
All-cause death[c]	579 (6.0)	5.1	592 (6.2)	4.9	0.98 (0.87-1.10)	---
Exploratory endpoints						
All-cause death, MI or stroke	919 (9.6)	8.5	1018 (10.6)	9.2	0.90 (0.83-0.99)	---
All stroke	180 (1.9)	1.7	221 (2.3)	2.1	0.82 (0.67-0.99)	---
ALI or major amputation for vascular cause	13 (0.1)	0.1	29 (0.3)	0.3	0.45 (0.23-0.86)	---
All-cause death, MI, stroke, ALI or major amputation for vascular cause	927 (9.6)	8.5	1039 (10.8)	9.4	0.89 (0.82-0.97)	---
Coronary artery revascularization	828 (8.6)	8.2	879 (9.2)	8.9	0.94 (0.86-1.04)	---

Steg PG et al. NEJM. 2019 Oct 3;381(14):1309-1320

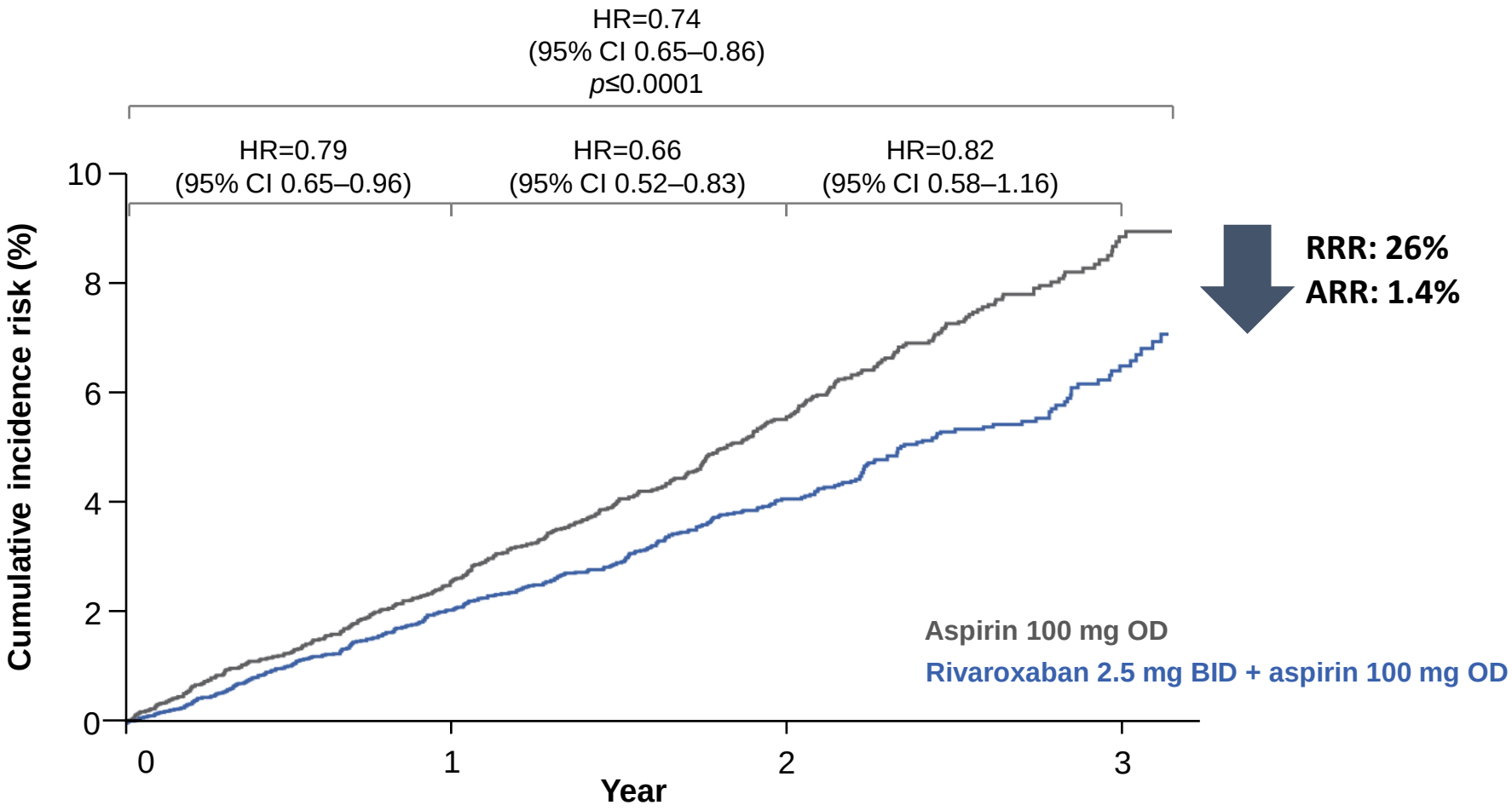
Treatment options for dual antithrombotic therapy in combination with aspirin in patients who have a high or moderate risk of ischemic events, and do not have a high bleeding risk

Treatment options are presented in alphabetical order……

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

COMPASS Demonstrated a Significant Reduction in MACE with Dual Pathway Inhibition in Patients with Chronic CAD

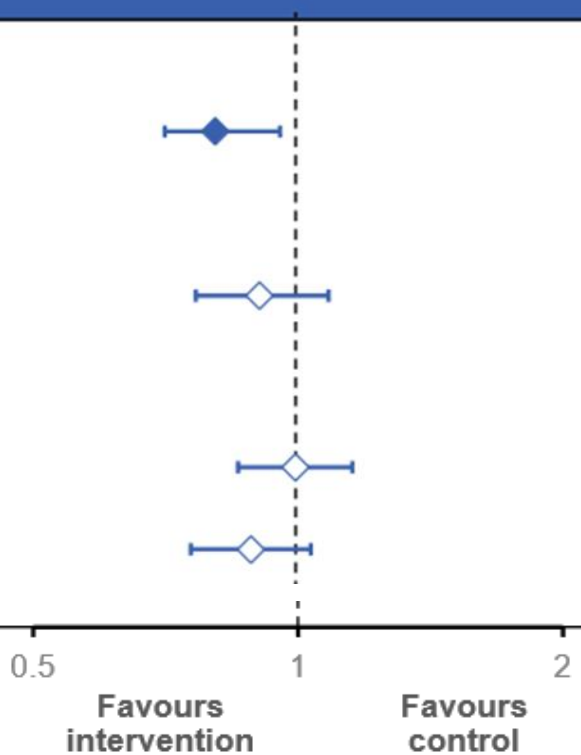
Stroke, MI or CV death



Connolly SJ et al. *Lancet* 2018;391:205–218.

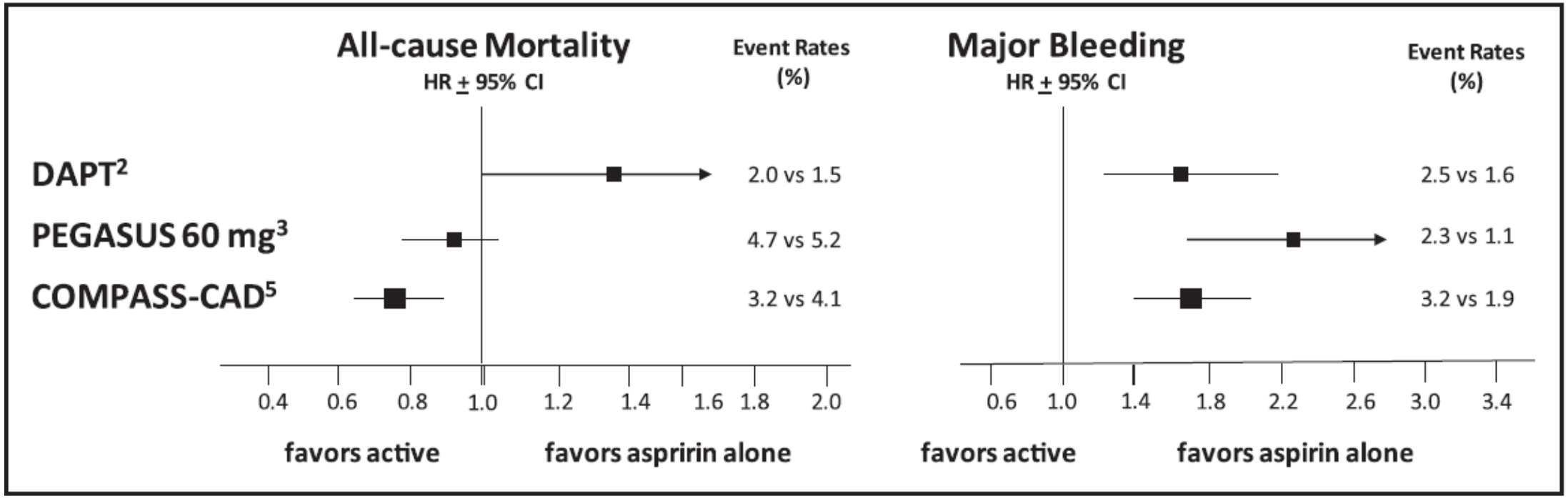
Rivaroxaban 2.5 mg bid + Aspirin Improved Overall Survival in Patients with CAD or PAD

Study / Treatment arm	Control %/year	Intervention %/year	HR	HR (95% CI)	*p*-value
COMPASS[1]					
Rivaroxaban 2.5 mg bid	2.1†	1.8†	0.82		0.01
CHARISMA[2]					
Clopidogrel 75 mg od	2.3‡	2.1‡	0.91		0.32
PEGASUS[3]					
Ticagrelor 90 mg bid	1.7¶	1.7¶	1.00		0.99
Ticagrelor 60 mg bid	1.7¶	1.6¶	0.89		0.14



1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118; 2. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988;
3. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 4. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

Forest plot of all-cause death and major bleeding in recent large aspirin-controlled trials in chronic stable coronary artery disease.



doi:10.1093/eurheartj/ehz687

The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

New features and the 'Ten Commandments' of the 2019 Guidelines are discussed by Professor Peter J. Grant and Professor Francesco Cosentino, the Task Force chairmen

EHJ 14 October 2019 Volume 40, Issue 39

Ten Commandments of the 2019 ESC Guidelines for Diabetes and CVDs

(1) Diabetes is associated with a two to three-fold increase in CV disease, a figure which increases markedly in young-onset, long-duration diabetes, and in the presence of comorbidities (previous vascular events, CKD, and risk factor clustering).

(2) Whatever treatment modalities are employed (drug therapies, PCI with stents, CABG) diabetes patients have generally worse outcomes than non-diabetes patients, a difference referred to as residual risk.

(3) In individuals who present with CV events, fasting blood glucose and HBA1C should be measured to exclude the presence of diabetes and an OGTT is added if the others are inconclusive.

(4) In diabetes, intensive management of CV risk factors (glycaemic control, BP, lipids, and antiplatelet agents) should be pursued as appropriate for the individual patient.

(5) A new CV risk stratification is presented to aid in making management decisions and to acknowledge the complexity of disease management in diabetes.

(6) In the 2019 guidelines, new targets for BP in diabetes patients are included.

(7) New guidelines for LDL-C management include <1.4 mmol/L (55 mg/dL) in very high-risk patients, with the use of PCSK9 inhibitors if unachievable with intensive statin therapy plus ezetimibe.

(8) High- and very high-risk patients may be considered for aspirin therapy and low-dose rivaroxaban with aspirin post-ACS and in the presence of peripheral artery disease.

(9) The new glucose lowering agents, SGLT2i and GLP-1 agonists are recommended as first-line therapy in T2DM with established CVD or high/very high CV risk.

(10) Think diabetes!

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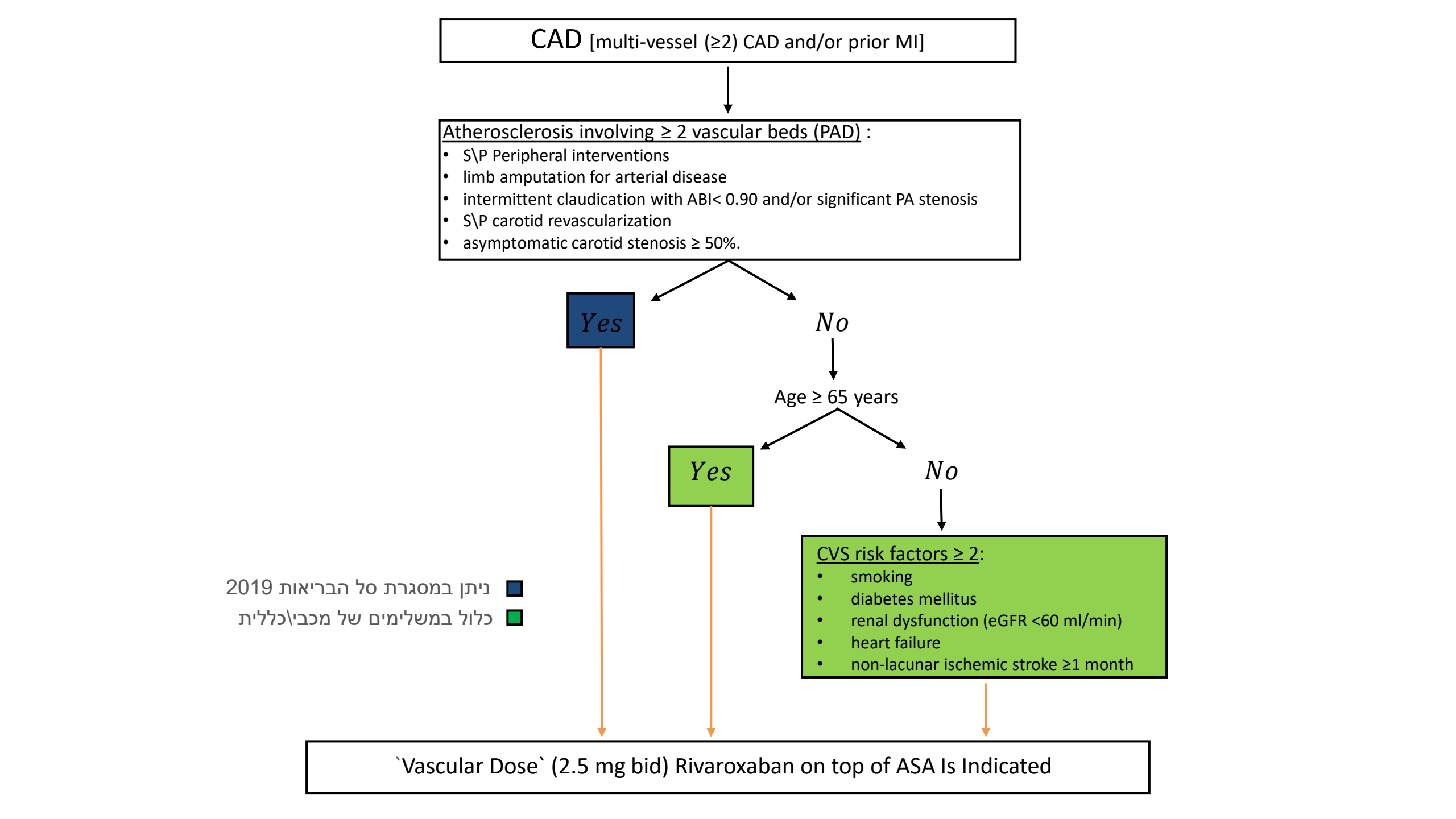
Thank You


CAD [multi-vessel (≥2) CAD and/or prior MI]
Atherosclerosis involving ≥ 2 vascular beds (PAD) :
• S\P Peripheral interventions
• limb amputation for arterial disease
• intermittent claudication with ABI< 0.90 and/or significant PA stenosis
• S\P carotid revascularization
• asymptomatic carotid stenosis ≥ 50%.
Yes
No
Age ≥ 65 years
Yes
No
CVS risk factors ≥ 2:
• smoking
• diabetes mellitus
• renal dysfunction (eGFR <60 ml/min)
• heart failure
• non-lacunar ischemic stroke ≥1 month
ניתן במסגרת סל הבריאות 2019
כלול במשלימים של מכבי\כללית
`Vascular Dose` (2.5 mg bid) Rivaroxaban on top of ASA Is Indicated

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

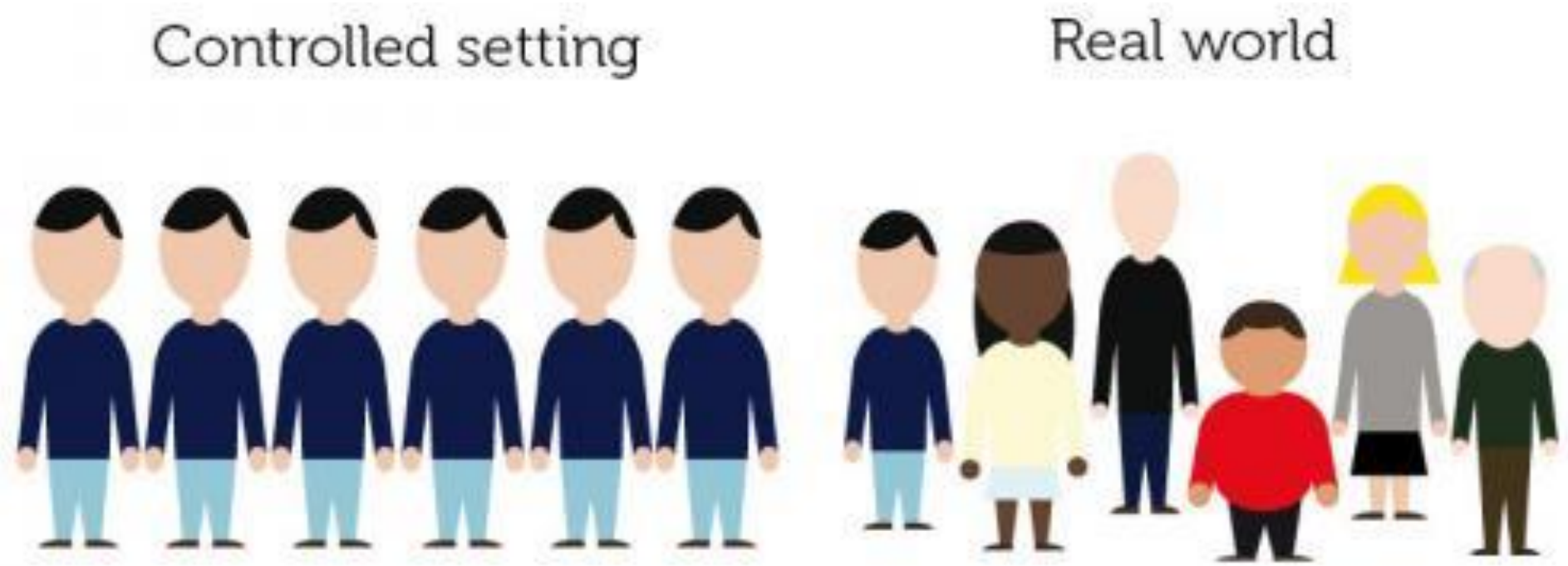
Major exclusion criteria included:

- high bleeding risk as defined by the investigator
- severe heart failure
- advanced kidney disease (eGFR<15 mL/min),
- requirement for DAPT or other AC therapy
- ischemic stroke within 1 month,
- prior hemorrhagic stroke, or symptomatic lacunar stroke (risk of ICH).

Patients with asymptomatic lacunar infarcts detected by brain imaging were otherwise eligible.

Should `Vascular Dose` Rivaroxaban Be Given to All CAD Patients According to the Compass Inclusion\Exclusion Criteria?

As Opposed to RCT`s In the Real World Not All Patients Are the Same: Who Might Benefit the Most?



COMPASS: Rivaroxaban Success in Secondary CV Prevention

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"It is not up to us to select the patients who will get this drug—that is up to guideline committees and regulatory agencies—but **to use the drug most efficiently I would start with those who stand to gain the most, and those are the patients at the highest baseline absolute risk…….“**

New Major Recommendations in 2019

Antithrombotic therapy in patients with CCS and sinus rhythm	
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIa**
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIb**

Diffuse multivessel CAD with at least one of the following:

- Diabetes mellitus requiring medication
- Recurrent MI
- PAD
- CKD with eGFR 1559 mL/min/1.73 m

High and Moderate Risk of Ischemic Events

High risk of ischemic events

Diffuse multi-vessel CAD with at least one of the following:

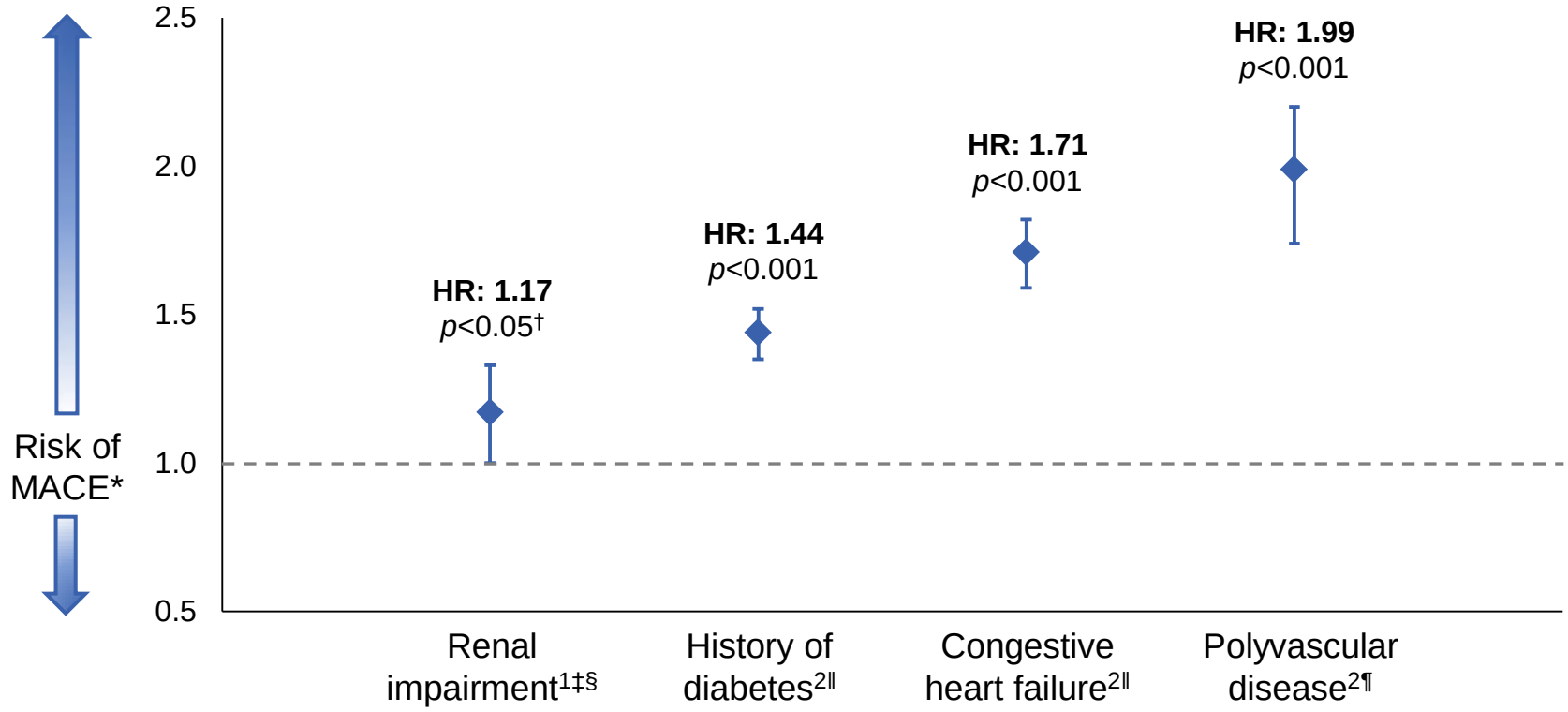
- diabetes mellitus requiring medication
- recurrent MI
- PAD
- CKD with eGFR 15 - 59 mL/min/1.73 m2

Moderately increased risk of ischaemic events

- Multi-vessel/diffuse CAD,
- diabetes mellitus requiring medication
- recurrent MI
- PAD
- HF
- CKD with eGFR 15 - 59 mL/min/1.73 m2.

Who are the high-risk patients?

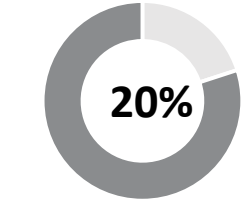
4-year analysis of the REACH registry (45,227 patients)

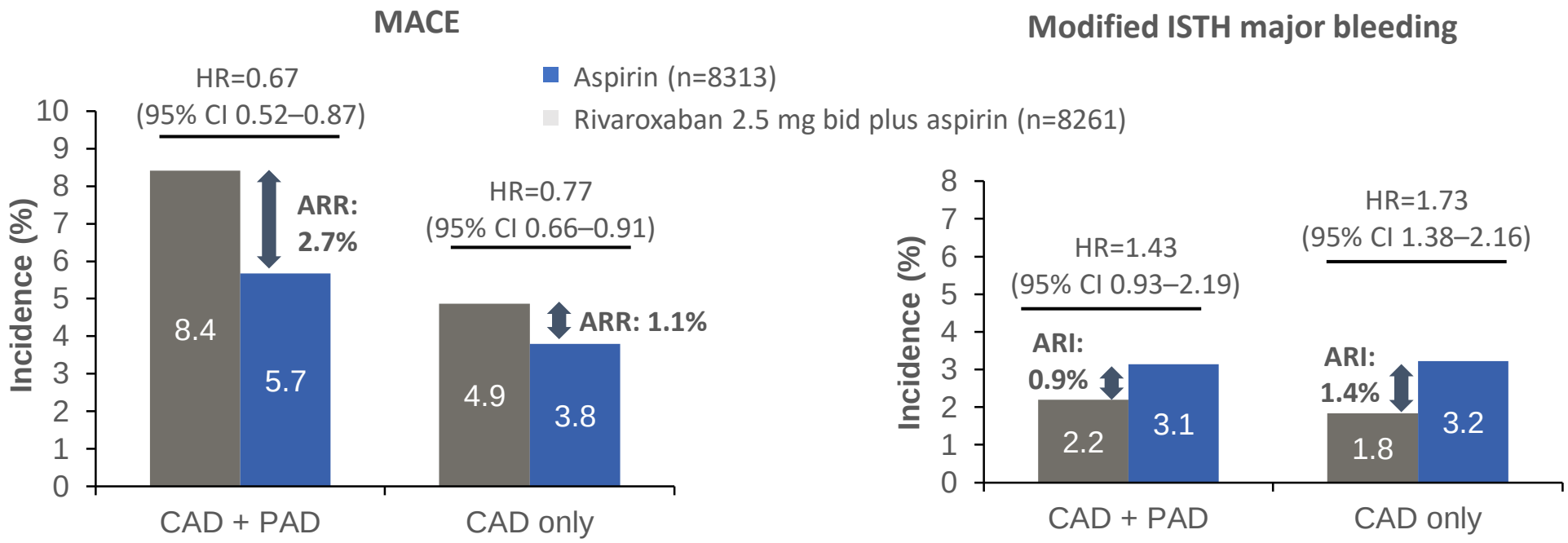


Bhatt DL et al. *JAMA* 2010;304:1350–1357.

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with Polyvascular Disease

Among COMPASS patients with concomitant PAD, whike the ARR with vascular dose rivaroxaban was more than two times greater, the increase in major bleedings was numerically smaller

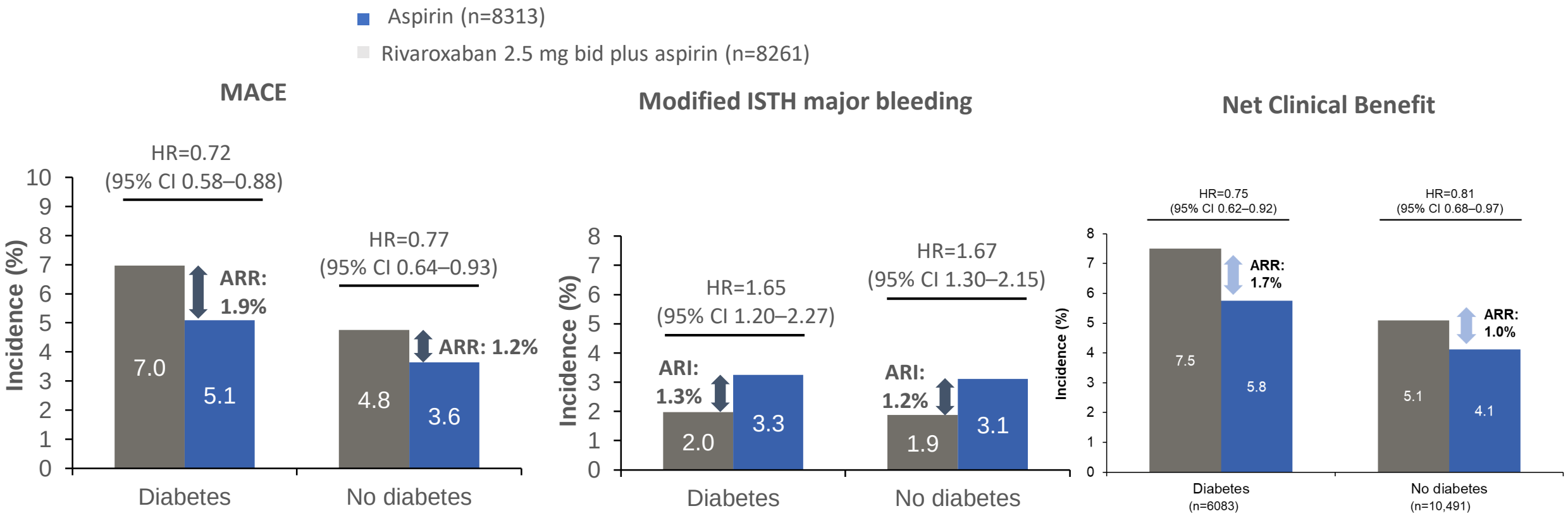




Connolly SJ *et al*, *Lancet* 2018;391:205–218

COMPASS Showed a Consistent MACE Reduction in CAD Patients With Diabetes With a Similar Major Bleeding Risk

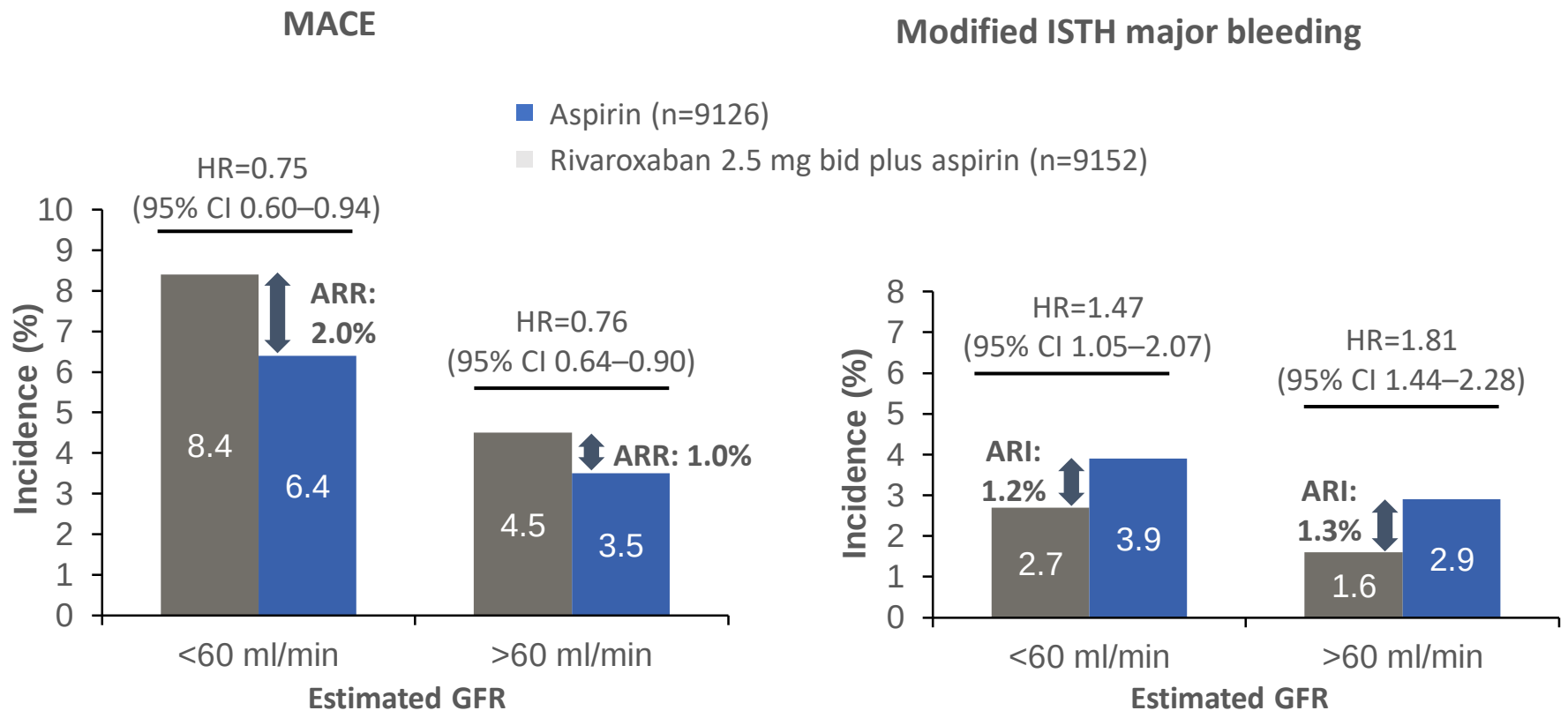
In the COMPASS population, DM patients showed numerically higher ARR, similar increase in bleedings and eventually higher net clinical benefit.



Connolly SJ *et al*, *Lancet* 2018;391:205–218

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with CAD and Renal Impairment

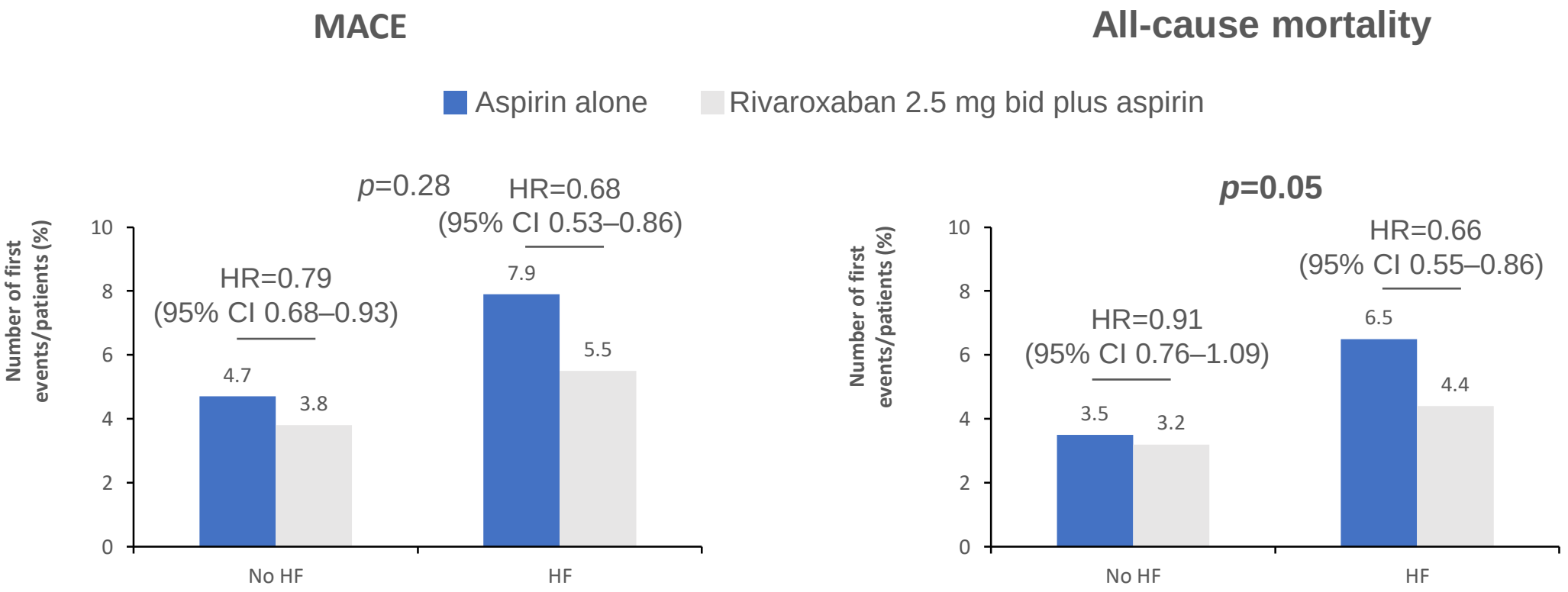
In patients with moderate renal dysfunction, absolute treatment effects were numerically greater Absolute difference in major bleeding was similar



Fox KAA *et al*, *JACC* 2019;73:2243–2250

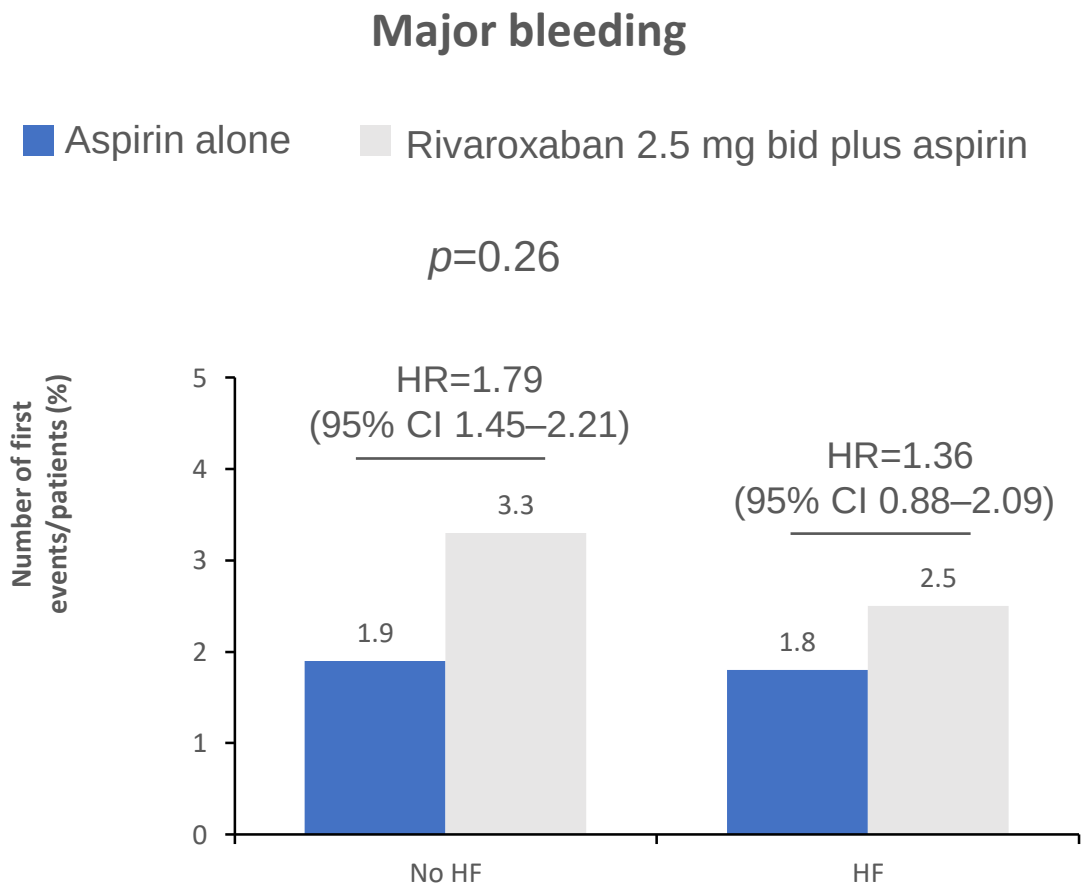
Rivaroxaban vascular dose resulted in a higher absolute risk reduction in MACE and all-cause mortality in patients with HF

In patients with mild-to-moderate HF rivaroxaban in vascular dose resulted in numerically higher ARR in MACE **(2.4% vs 0.9%)** and significantly **(p for int. = 0.05)** higher reduction in all-cause mortality compared with those without HF



Branch KR et al, Circulation 2019;

Major Bleeding Was Similar Between Patients with and Without HF



- Rivaroxaban 2.5 mg bid plus aspirin compared with aspirin alone resulted in similar rates of major bleeding, symptomatic bleeding and intracranial bleeding in patients with and without HF

Branch KR et al, Circulation 2019;

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial

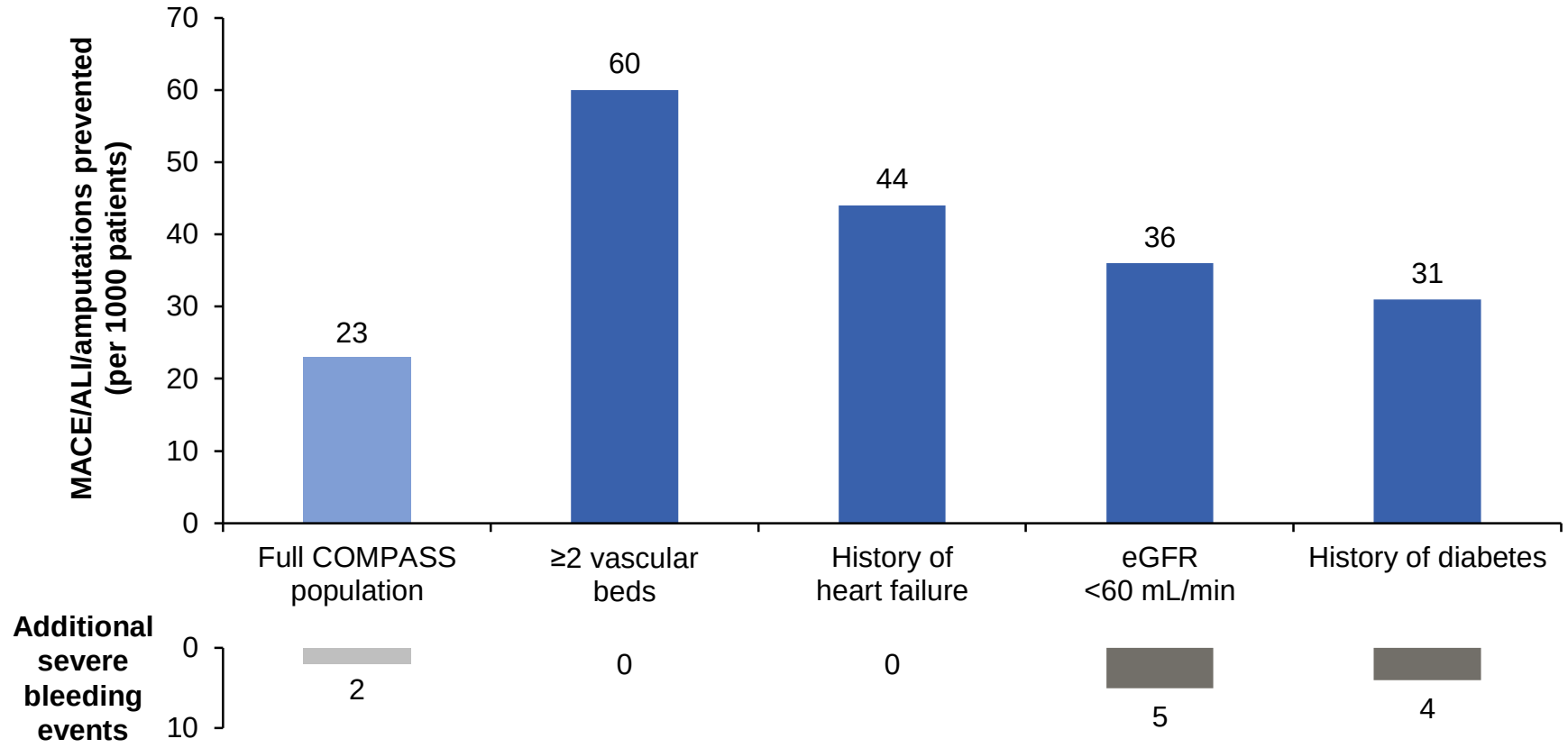
- To find whether in the already high-risk cohort of COMPASS, further risk stratification can identify subsets of the highest-risk patients with the greatest net clinical benefit

- Based on two independent methods for risk stratification (REACH and CART), the patients at highest risk of ischemic events in the COMPASS population were those with ≥1 of:
  - Poly-vascular disease
  - Chronic HF (EF ≥30% and NYHA class I or II)
  - Renal insufficiency (eGFR <60 ml/min)
  - History of diabetes

Anand SS et al. JACC Jul 2019;73:3271−3280.

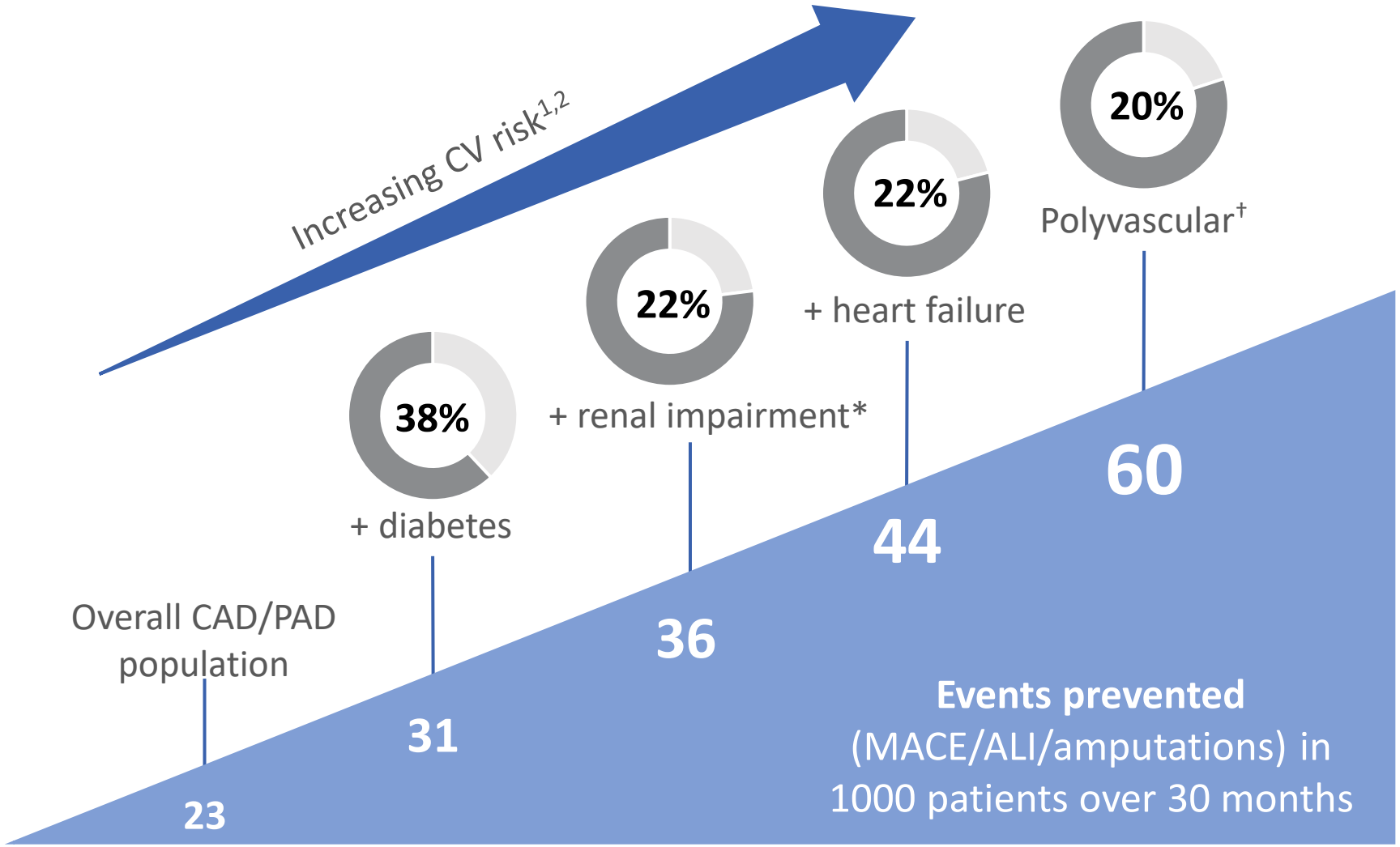
Absolute Benefit of Rivaroxaban Vascular Dose Plus Aspirin in High-risk Patient Groups

Ischaemic events prevented and bleeding events caused over 30 months with rivaroxaban vascular dose plus aspirin in high-risk groups



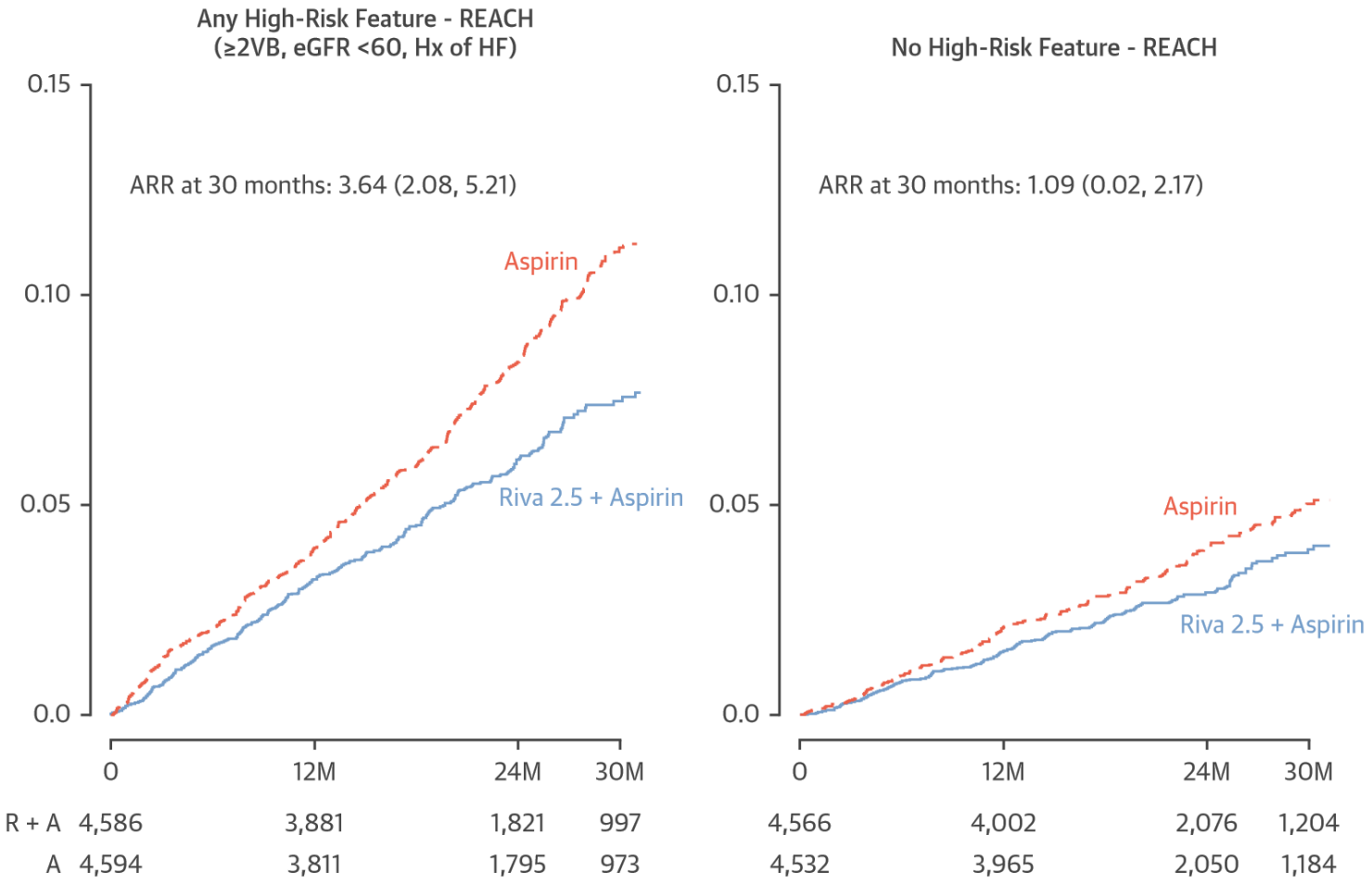
Anand SS et al. *J Am Coll Cardiol* 2019;73:3271−3280.

Patients at Higher CV Risk Benefit More from Rivaroxaban Vascular Dose Plus Aspirin



Anand SS et al. *J Am Coll Cardiol* 2019;73:3271−3280.

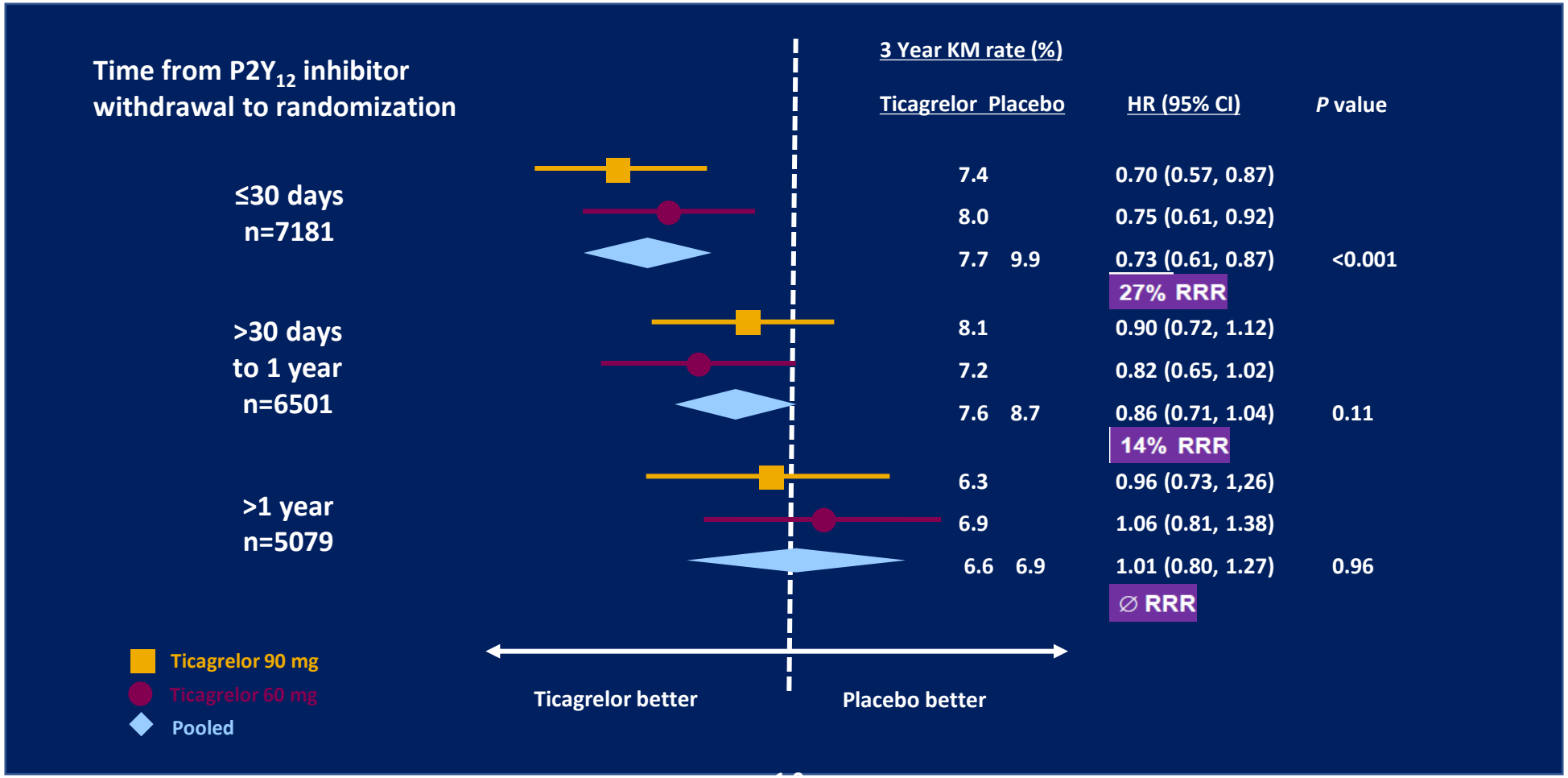
Incidence Vascular Events in Patients With Any High-Risk Feature to Those With No High-Risk Features by REACH Score Classification



In the Compass cohort the proportions of Pts with ≥1 high-risk feature score accounted for > 50% of patients, who experienced almost 70% of the vascular events.

Anand SS et al. *J Am Coll Cardiol* 2019;73:3271−3280.

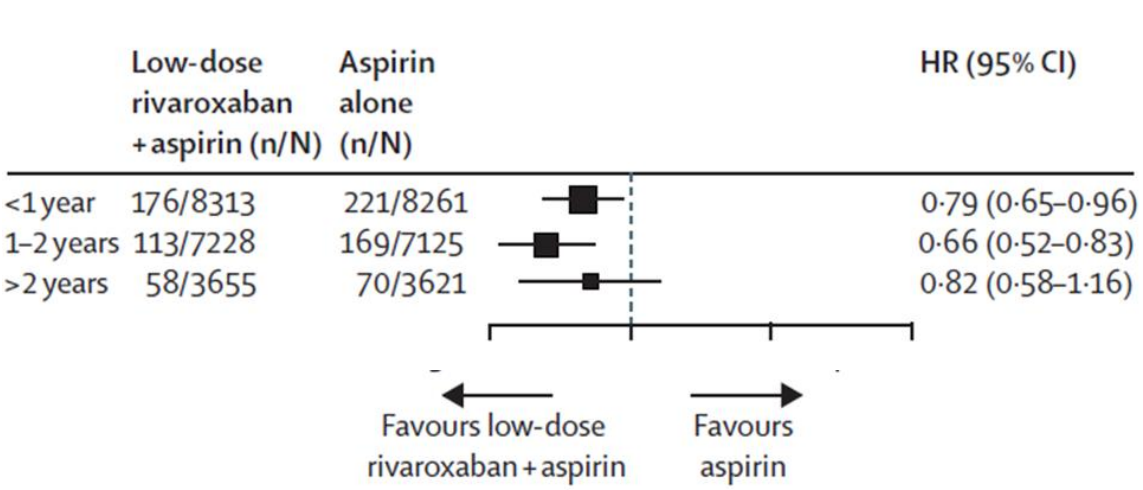
Efficacy of ticagrelor in reducing risk of atherothrombotic events declines with increasing duration of $P2Y_{12}$ inhibitor withdrawal



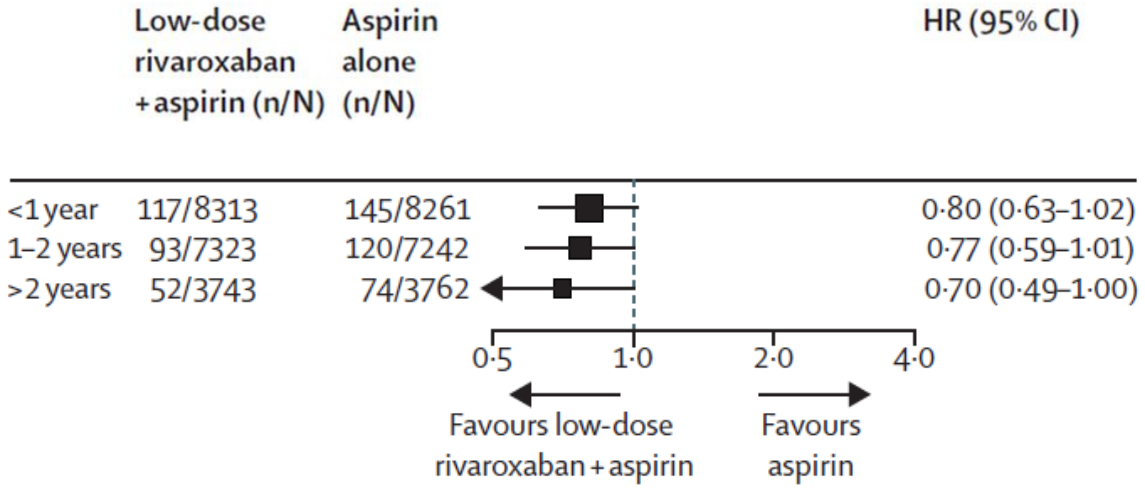
Bonaca MP et al. Eur Heart J, 2015

Landmark Analysis of the Primary Efficacy Outcome and all-Cause Death

primary efficacy outcome



all-cause death



Stuart J Connolly et al. Lancet. 2018 Jan 20;391(10117):205-218

טיפ נהיגה 4X4: מה שלא הולך בכוח

מה שלא הולך בכוח, יילך בעוד יותר כוח? זה עלול להיגמר בקריעת צמיגים, פיצוץ בולמי זעזועים, עיקום מוט הגה ועוד

יואב קווה, 09/05/2016

הסלוגן השכיח והמקובל הוא "מה שלא הולך בכוח, הולך בעוד יותר כוח". והמהדרין מוסיפים "ומה שלא הולך בכוח, הולך באלימות".

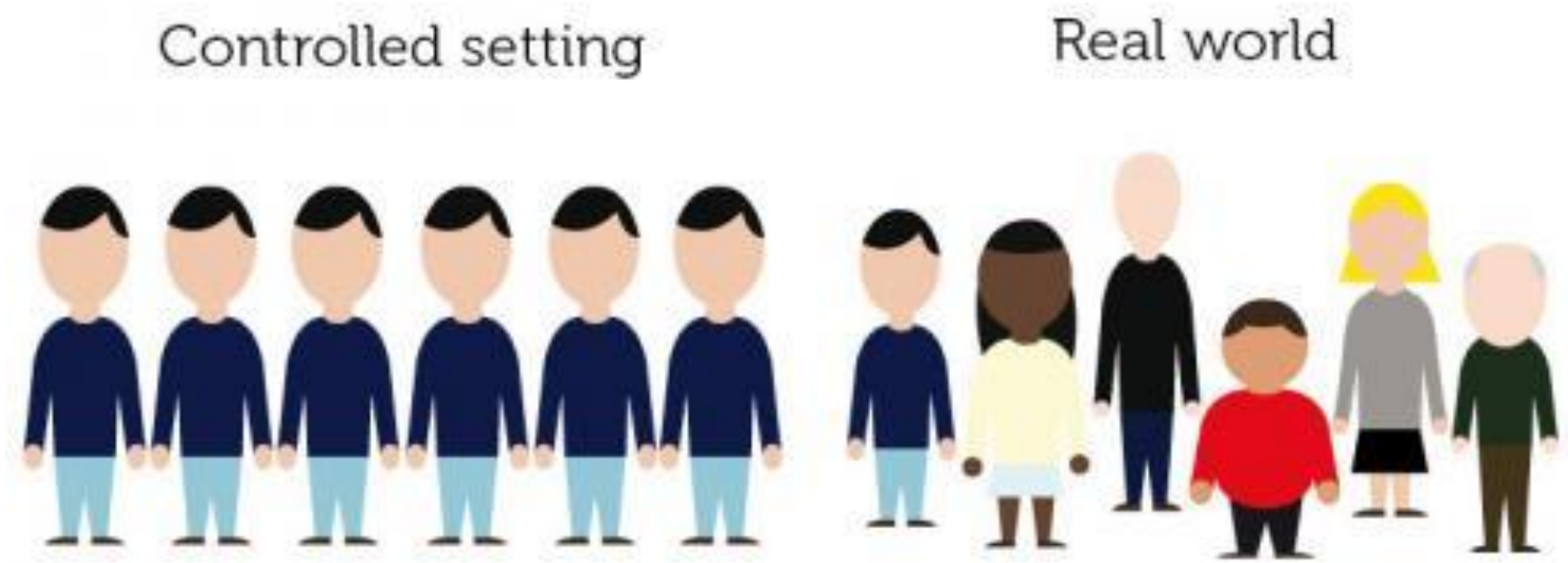
הסלוגן הזה נשמע טוב אבל מתאים אולי לחיילים בסדיר, מקסימום למילואימניקים צעירים. הוא מתאים אולי לג'יפ סופה והאמר צה"לי. הוא פחות מתאים למיצובישי פאג'רו / טויוטה לנדקרוזר אזרחי ובטח לא לסובארו פורסטר / XV.

כי בפועל, מה שלא הולך בכוח, יישבר ביותר כוח.

בחר מסלול לניווט עצמי

Should `Vascular Dose` Rivaroxaban Be Given to All CAD Patients According to the Compass Inclusion\Exclusion Criteria?

As Opposed to RCT`s In the Real World Not All Patients Are the Same: Who Might Benefit the Most?



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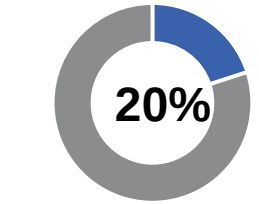
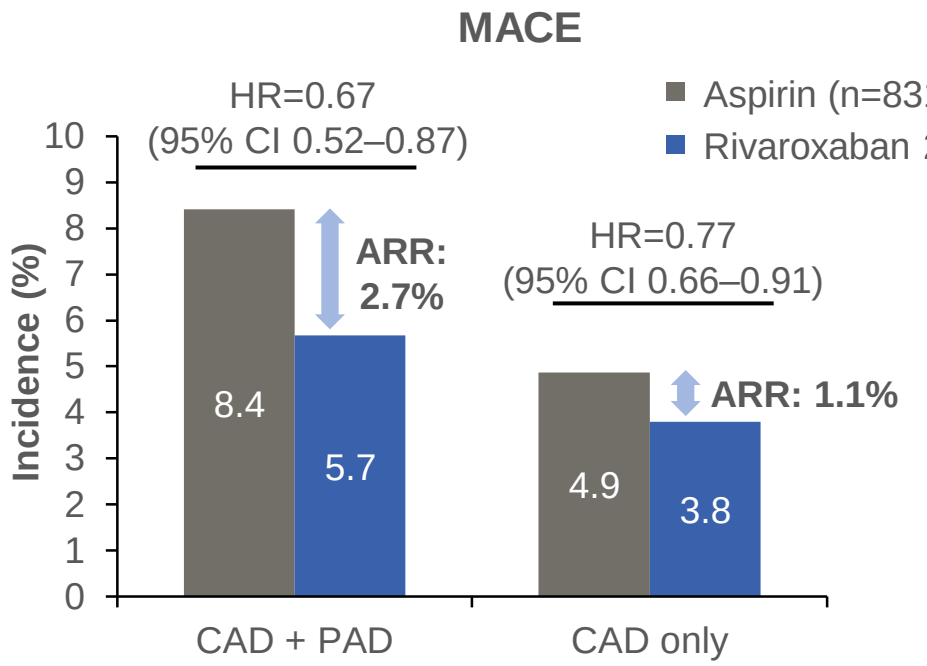
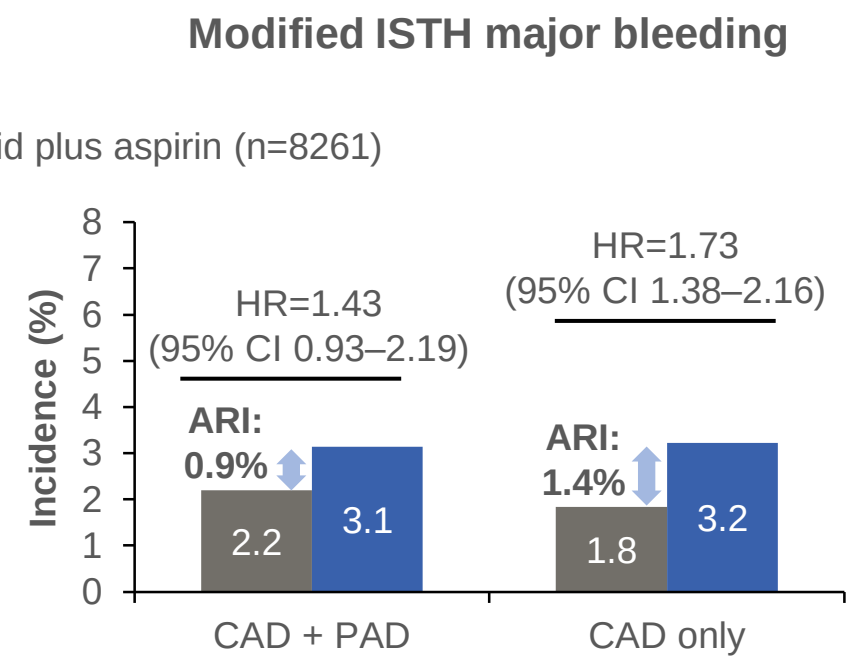
How Do these Enrichment Factors Affect the Benefit of Vascular Dose Rivaroxaban in the COMPASS Cohort ?

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with Polyvascular Disease

Among COMPASS patients with concomitant PAD, whike the ARR with vascular dose rivaroxaban was more than two times greater, the increase in major bleedings was numerically smaller







Connolly SJ *et al*, *Lancet* 2018;391:205–218

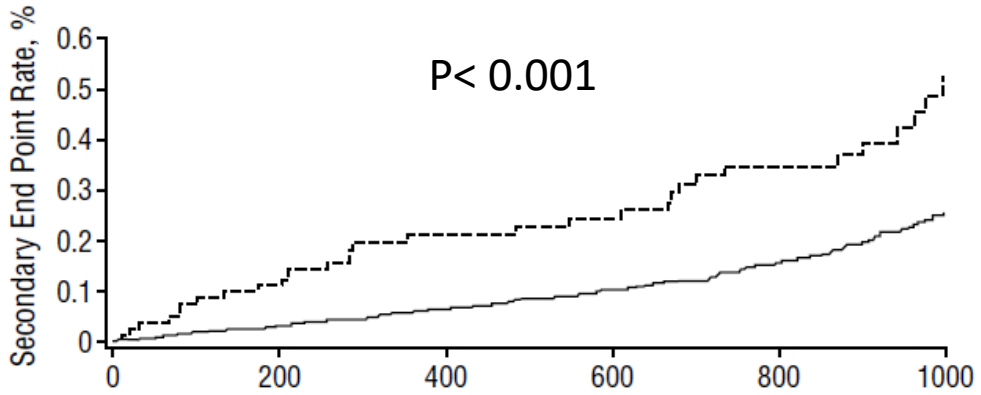
Is it only playing with the numbers (higher risk = greater ARR) ?

Or there is biologic plausibility for the greater benefit in patients with poly-vascular disease?

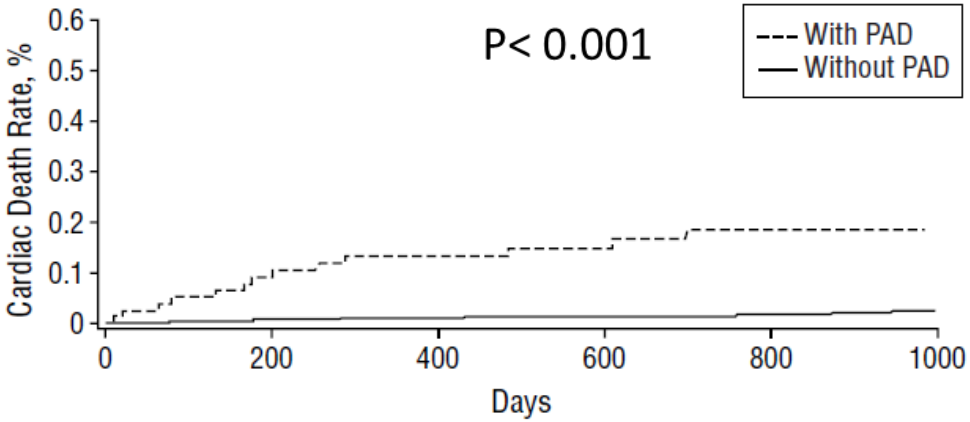
Cardiac Events in Postin-Ifarction Patients with and without PAD During the follow-up of 26 months

Stable survivors of a recent myocardial infarction (n=1,045) were prospectively followed up for a mean of 26 months

unstable angina or nonfatal myocardial infarction or cardiac death.



cardiac death



Study End Point	No. (%) No Claudication (n = 966)	No. (%) Claudication (n = 78)	*P* Value	Hazard Ratio (95% Confidence Interval)*	*P* Value*
Cardiac death	35 (3.6)	15 (19.2)	.001	6.57 (2.89-14.87)	<.001
Cardiac death or nonfatal reinfarction	62 (6.4)	19 (24.4)	.001	3.04 (1.76-5.26)	<.001
Cardiac death or nonfatal reinfarction or unstable angina	172 (17.8)	30 (38.5)	.001	2.05 (1.36-3.06)	<.001

Craig R. Narins et al. Arch Intern Med. 2004;164:440-446

In CAD Patients PAD is Associated with Markers of Increased Thrombosis

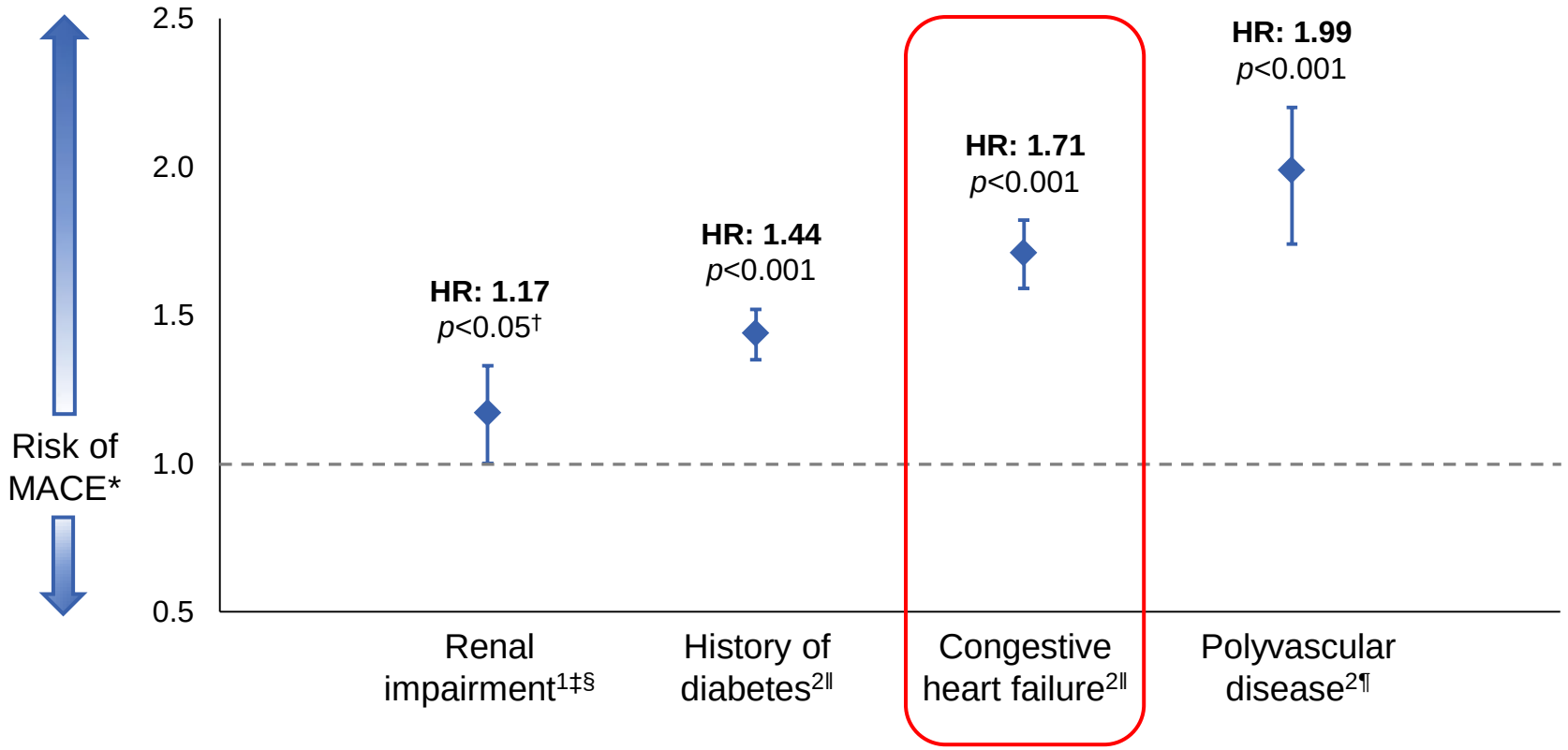
Variable	No Claudication (n = 966)	Claudication (n = 78)	*P* Value†
Hemostatic factors			
D-dimer, ng/mL	365 (232; 563)	528 (376; 933)	<.001
Fibrinogen, mg/dL	334 (290; 393)	394 (335; 460)	<.001
von Willebrand factor, U/dL	133 (100; 181)	143 (102; 212)	

Among patients not receiving warfarin, levels of factor VII were significantly higher in patients with vs without PAD (P=0.02).

Craig R. Narins et al. Arch Intern Med. 2004;164:440-446

Patients with CAD Who Also Have HF Have Almost Twofold Higher Risk of Subsequent CV Events Than Those without HF

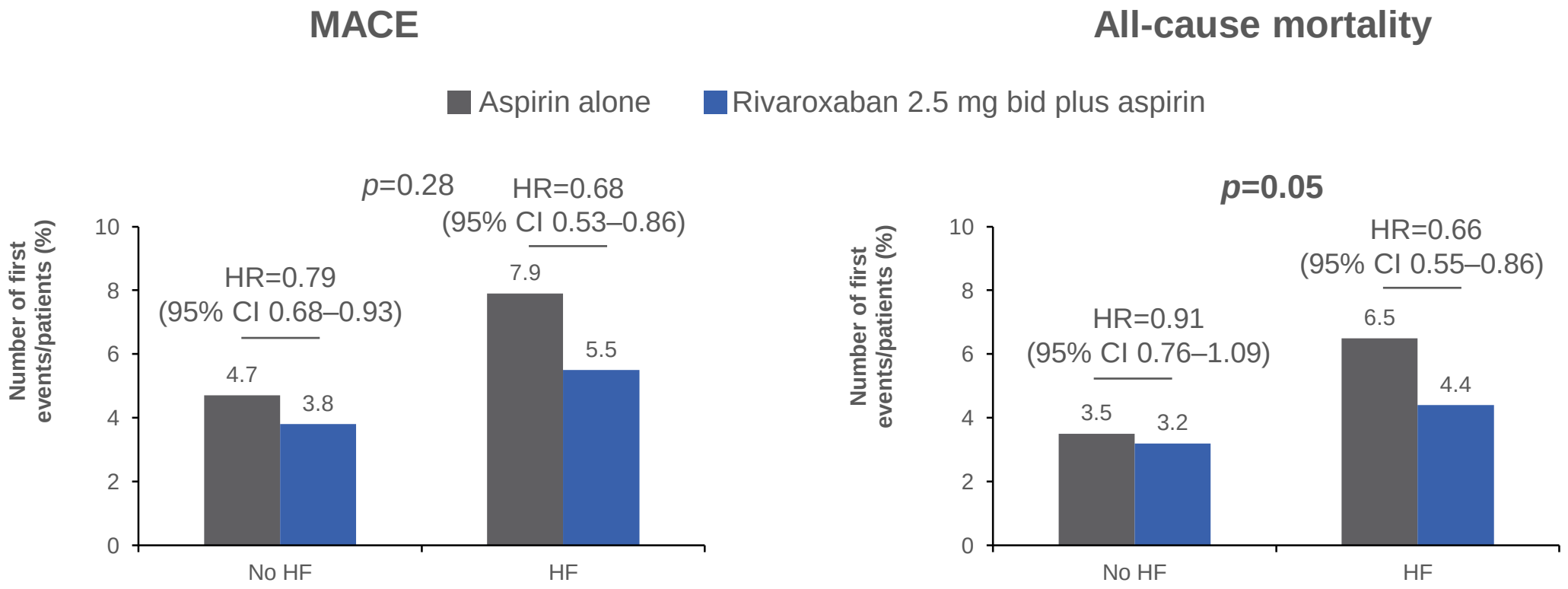
4-year analysis of the REACH registry (45,227 patients)



Bhatt DL et al. *JAMA* 2010;304:1350–1357.

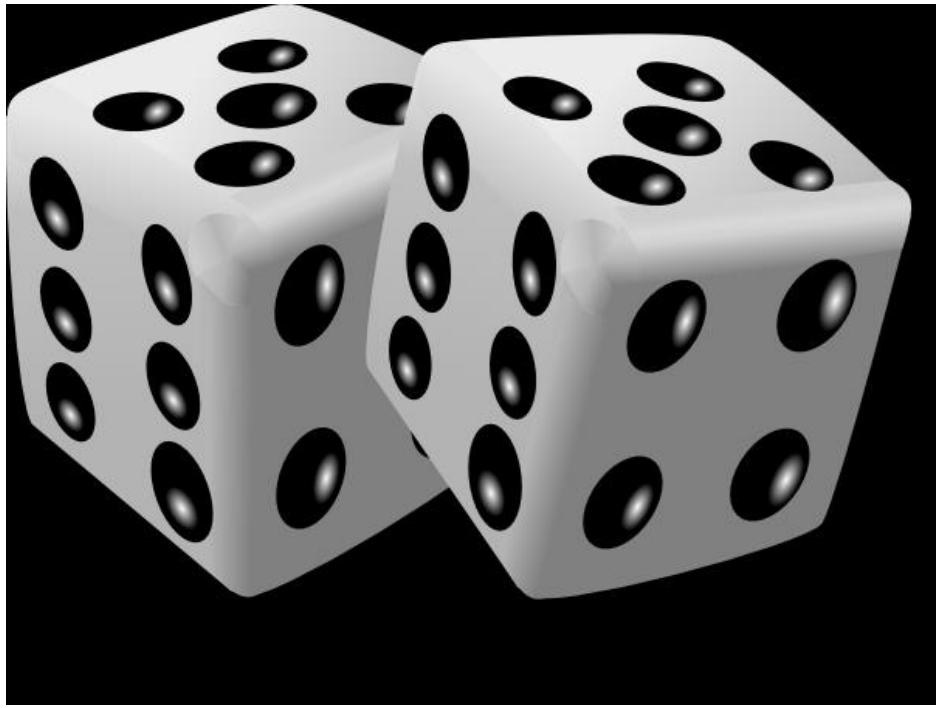
Rivaroxaban vascular dose resulted in a higher absolute risk reduction in MACE and all-cause mortality in patients with HF

In patients with mild-to-moderate HF rivaroxaban in vascular dose resulted in numerically higher ARR in MACE **(2.4% vs 0.9%)** and significantly **(p for int. = 0.05)** higher reduction in all-cause mortality compared with those without HF



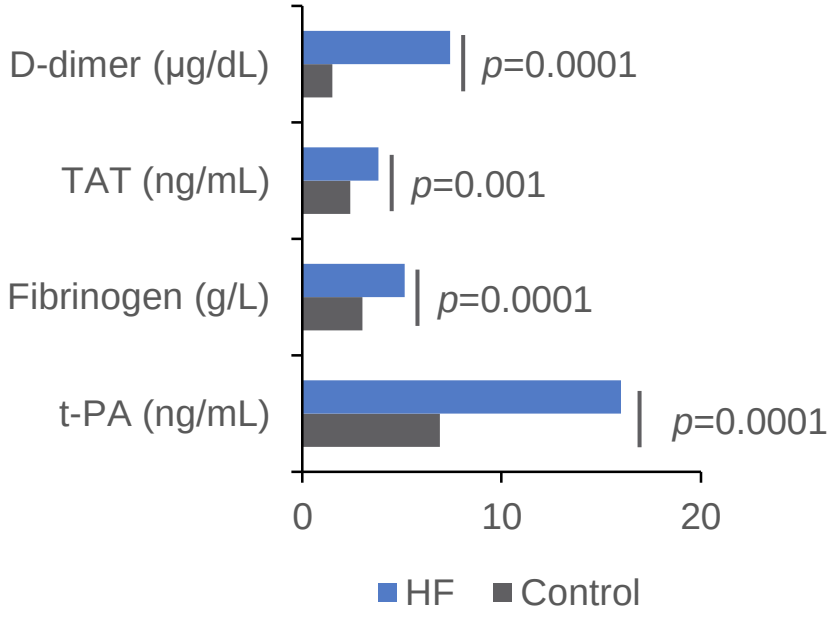
Branch KR et al, Circulation 2019;

Is it only playing with numbers (higher risk= greater benefit) ?
Or there is biologic plausibility for the greater benefit in patients with CHF?



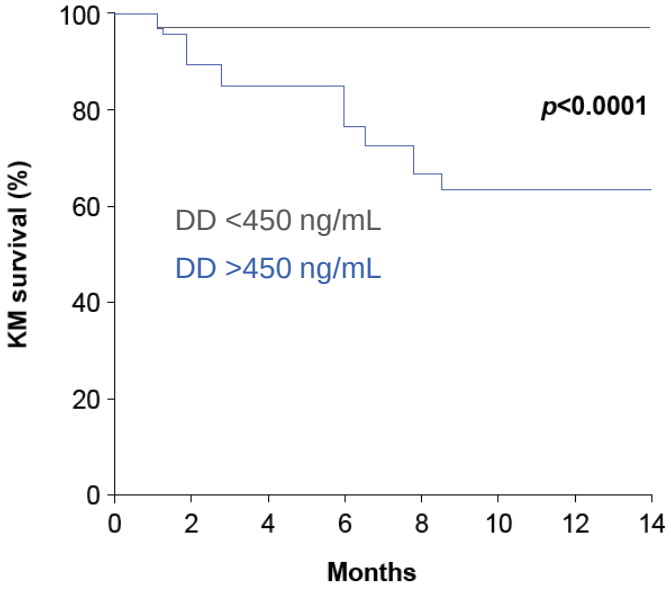
Thrombin Activity is Increased in Patients with Heart Failure

- The coagulation system is activated in patients with HF[1]



Activation of coagulation parameters in patients with HF and healthy controls[1]

- Elevated thrombin activity predicts mortality in patients with HF[2]



KM mortality-free rates according to D-dimer levels[2]

Cugno M et al. *Brit J Haematol* 2004;126:85–92;
Marcucci R et al. *J Thromb Haemost* 2006;4:1017–1022.

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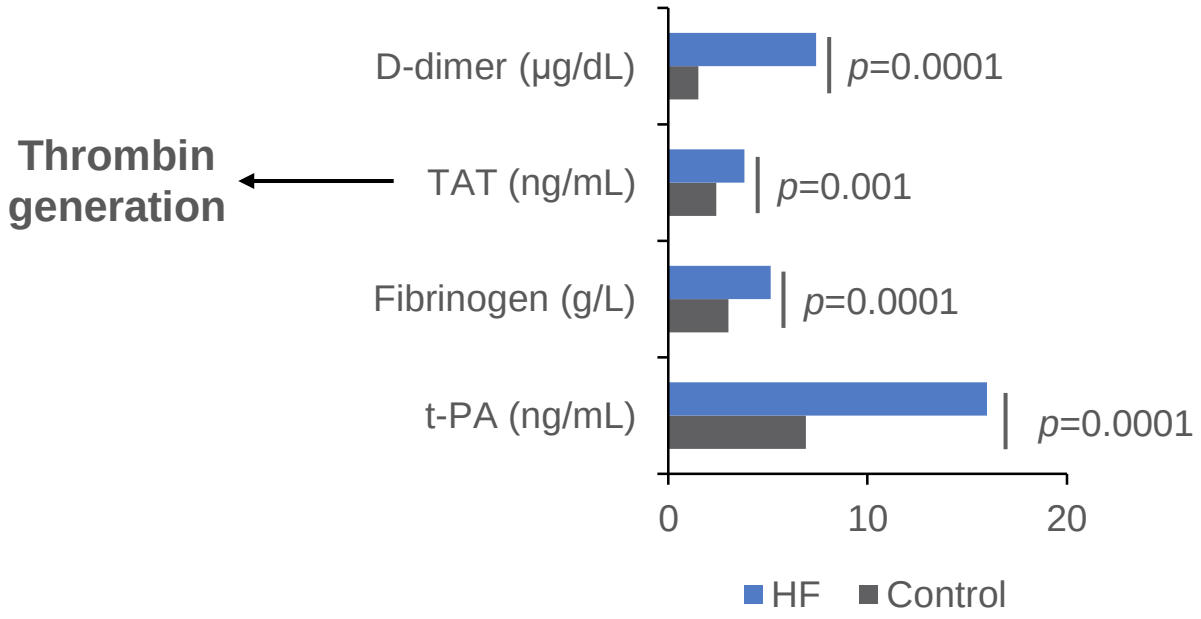

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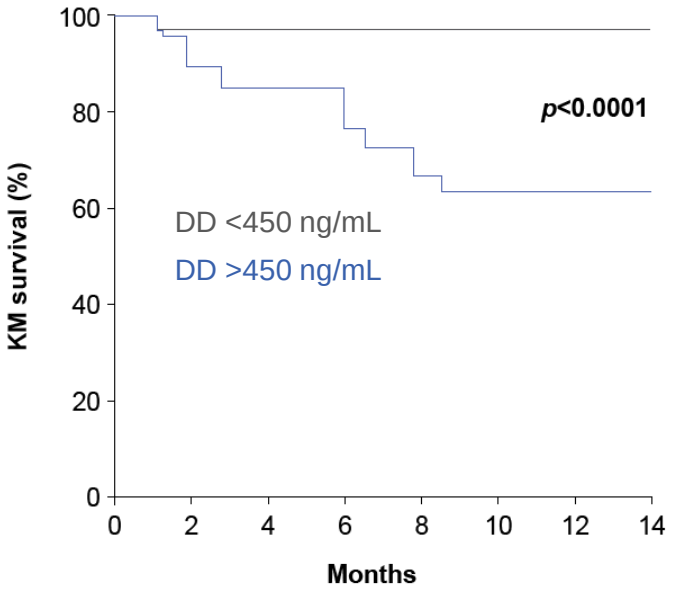

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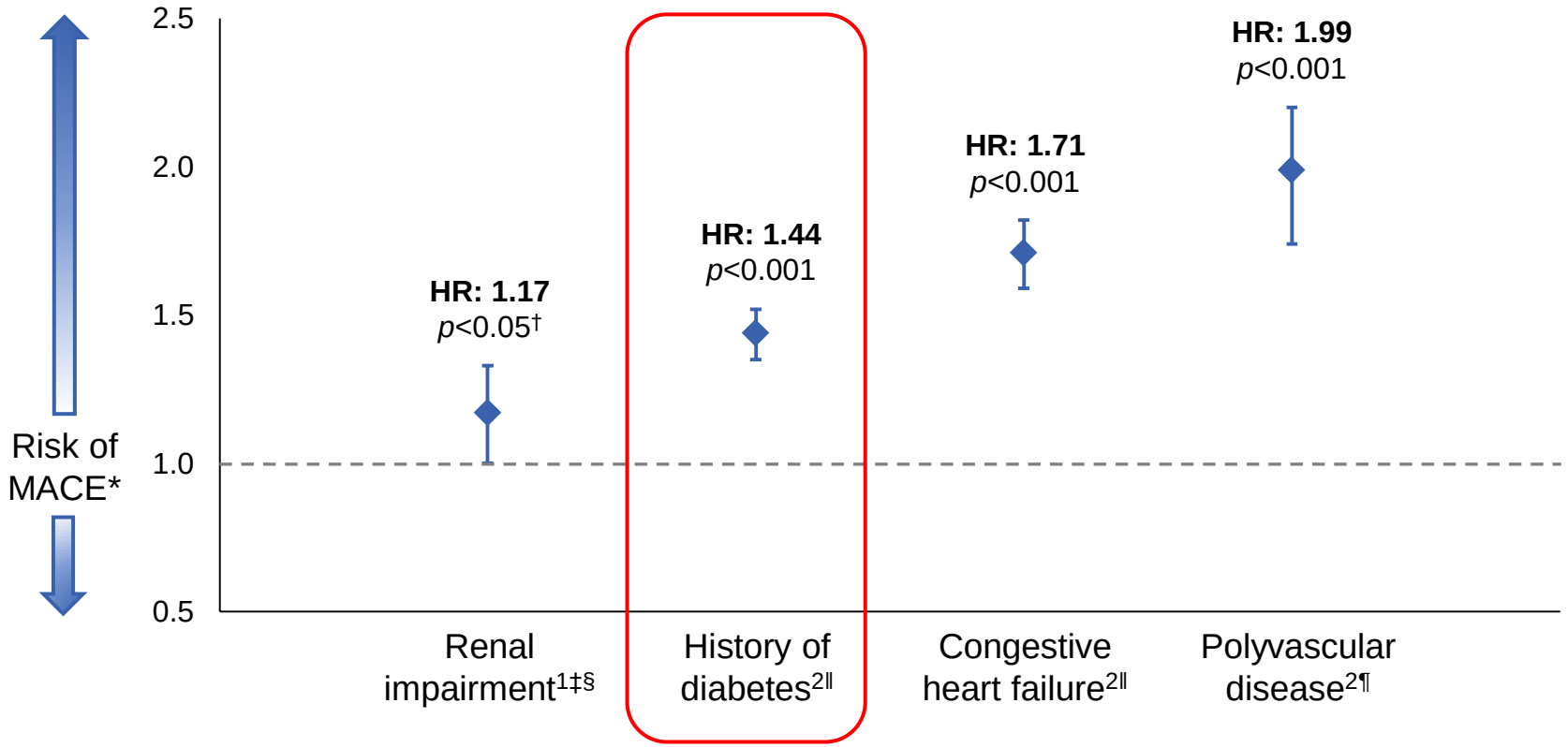
Cugno M et al. *Brit J Haematol* 2004;126:85–92;
Marcucci R et al. *J Thromb Haemost* 2006;4:1017–1022.

Patients with CAD with DM are another high-risk group

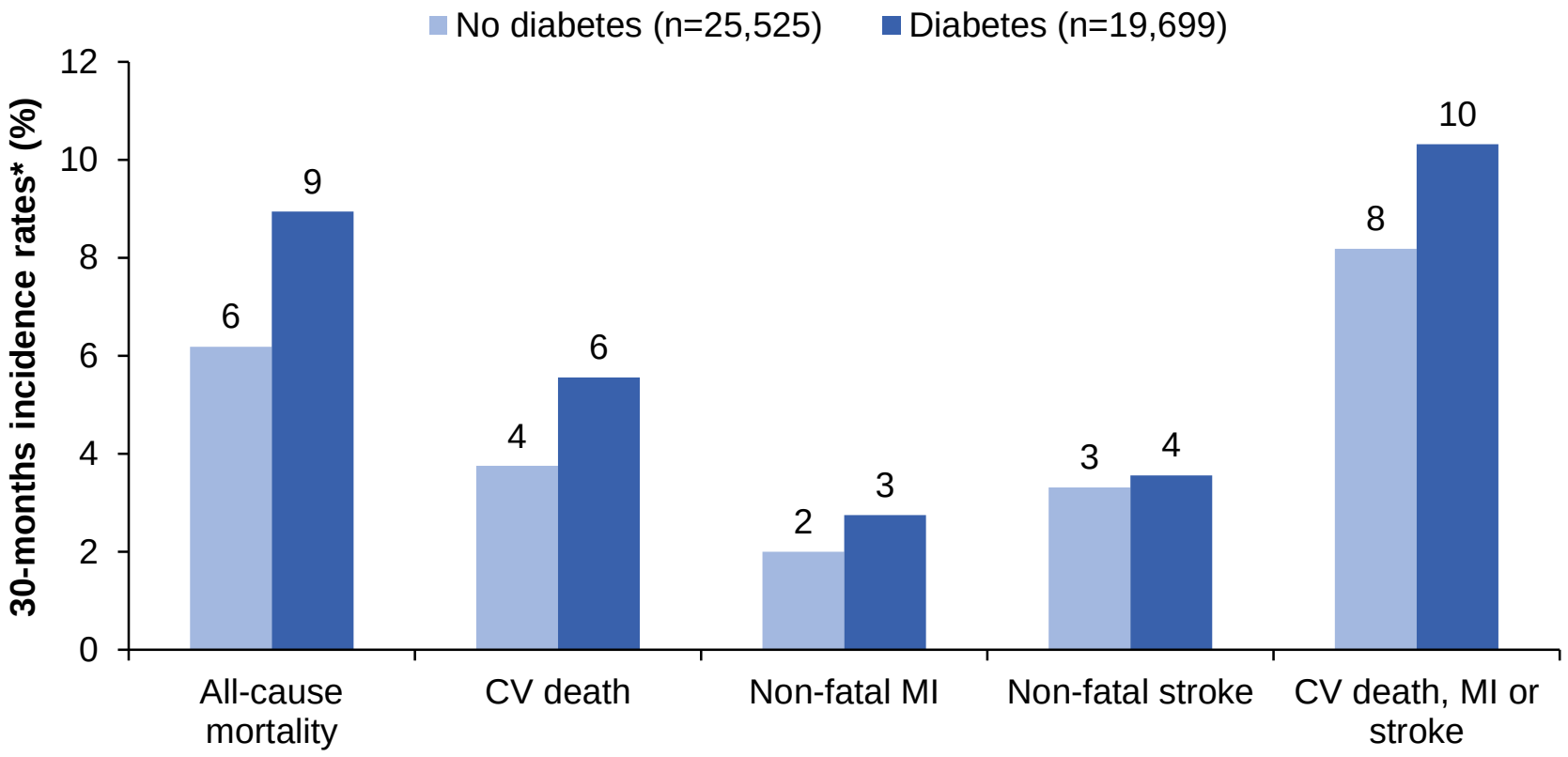
4-year analysis of the REACH registry (45,227 patients)



Bhatt DL et al. *JAMA* 2010;304:1350–1357.

Diabetes Is Associated with Increased Thrombotic Risk in Patients with Cardiovascular Disease

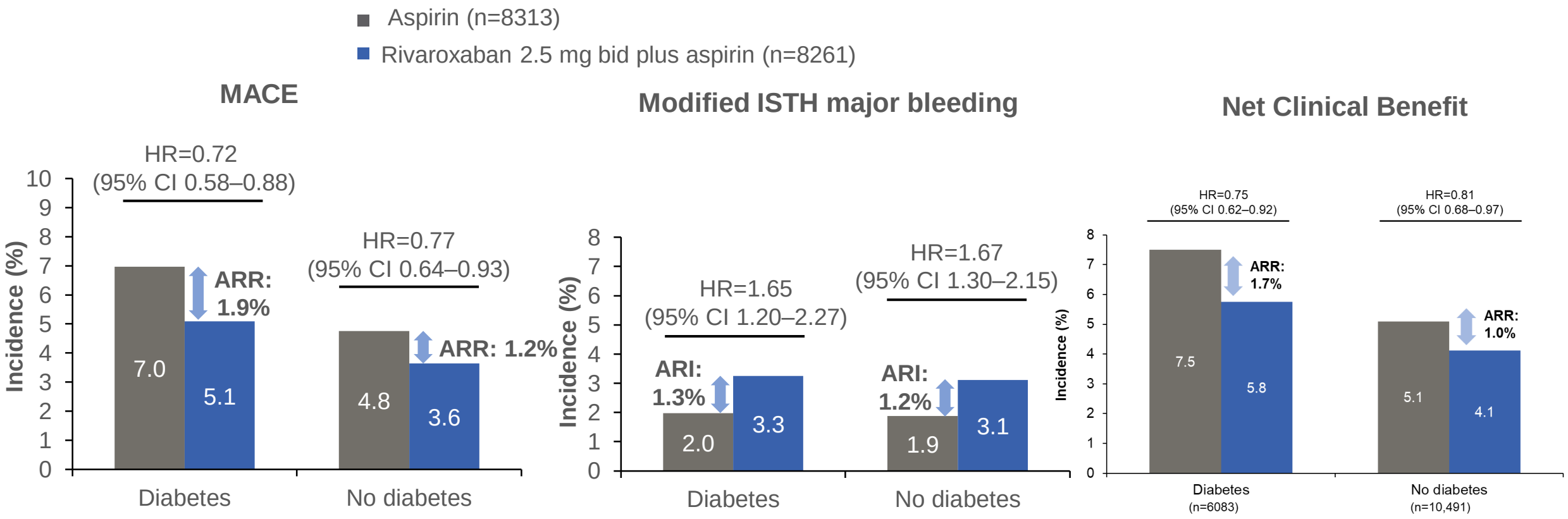
Outcomes in patients with or without diabetes in the REACH registry



Cavender MA et al. *Circulation* 2015;132:923–931.

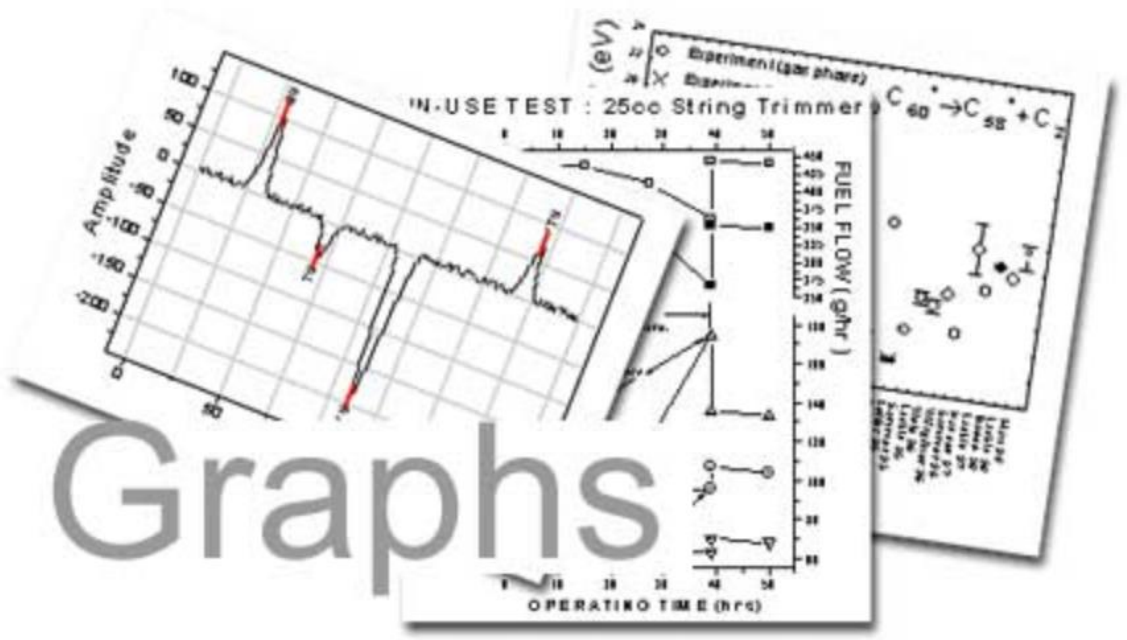
COMPASS Showed a Consistent MACE Reduction in CAD Patients With Diabetes With a Similar Major Bleeding Risk

In the COMPASS population, DM patients showed numerically higher ARR, similar increase in bleedings and eventually higher net clinical benefit.



Connolly SJ *et al*, *Lancet* 2018;391:205–218

Is it only playing with the numbers (higher risk= greater benefit) ?



Symposium | Journal of INTERNAL MEDICINE

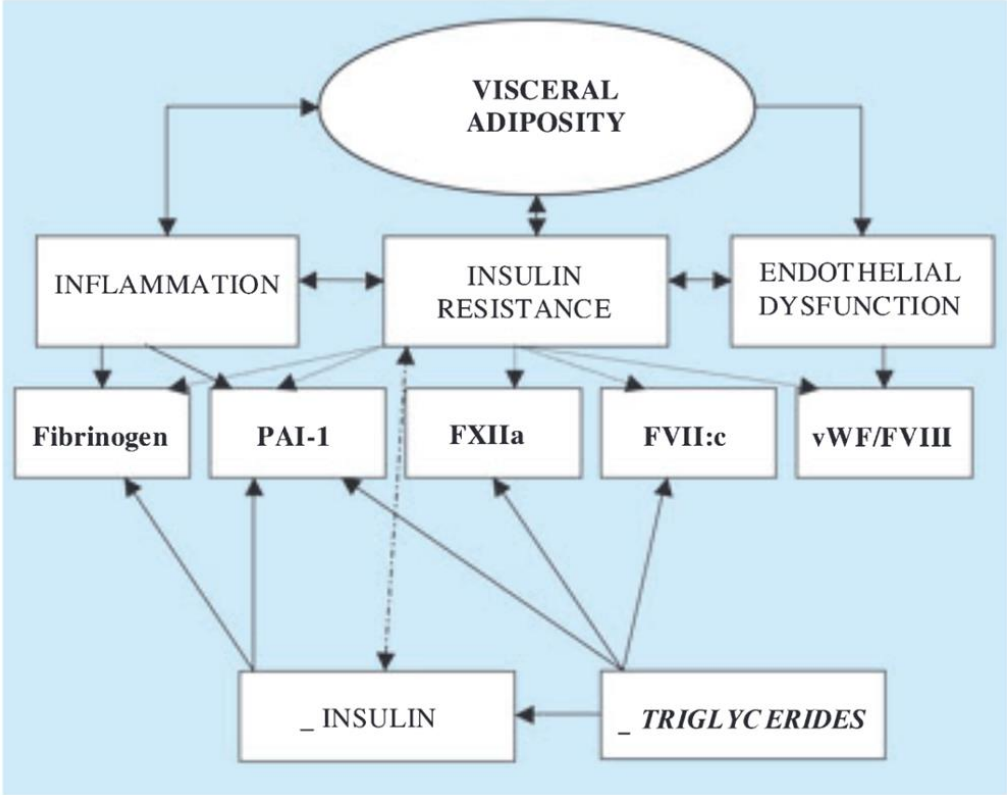
doi: 10.1111/j.1365-2796.2007.01824.x

Diabetes mellitus as a prothrombotic condition

P. J. Grant

DM is Associated with:

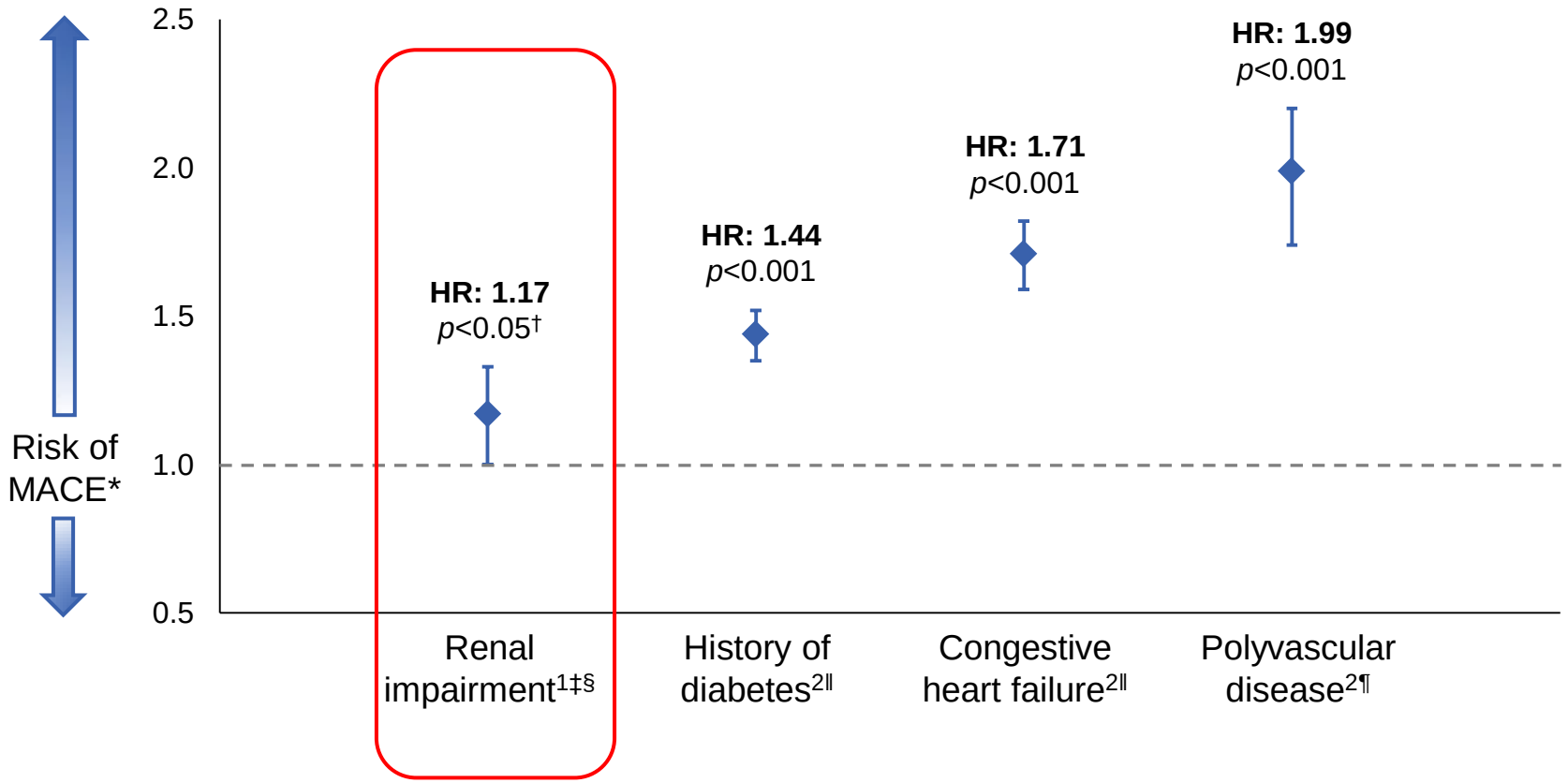
- Suppression of fibrinolysis (elevated PAI-1)
- Increased thrombotic risk through its effect on coagulation factors VII, XII and fibrinogen
- Endothelial cell dysfunction
- Increased platelet reactivity and turn-over
- Modified fibrin structure & function, generating a clot which has a denser structure, resistant to fibrinolysis



Rrant et al. J Intern Med 2007;262:157–172.

Chronic CAD Puts Patients at Risk of MACE, Particularly Those with Key Comorbidities

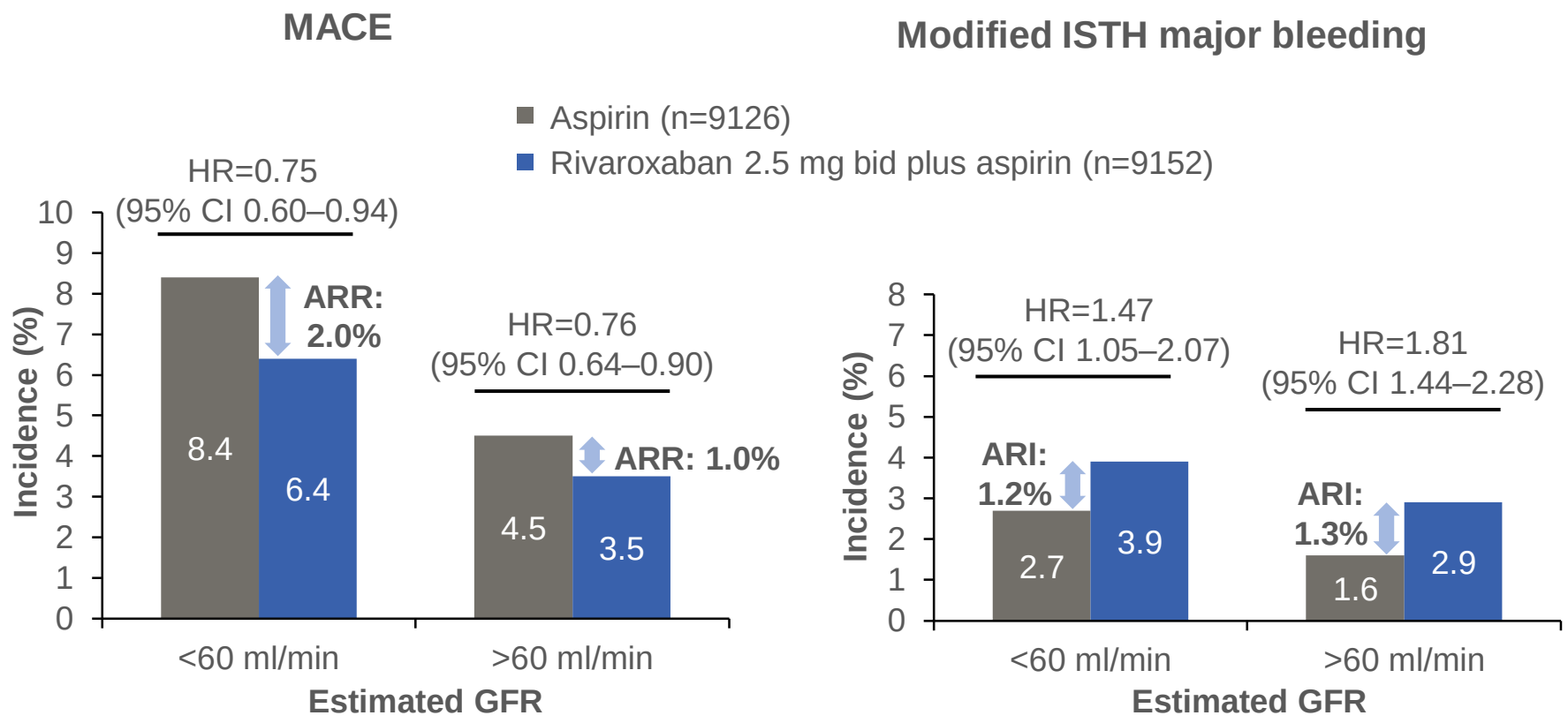
4-year analysis of the REACH registry (45,227 patients)



Bhatt DL et al. *JAMA* 2010;304:1350–1357.

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with CAD and Renal Impairment

In patients with moderate renal dysfunction, absolute treatment effects were numerically greater
Absolute difference in major bleeding was similar



Fox KAA *et al*, *JACC* 2019;73:2243–2250

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial

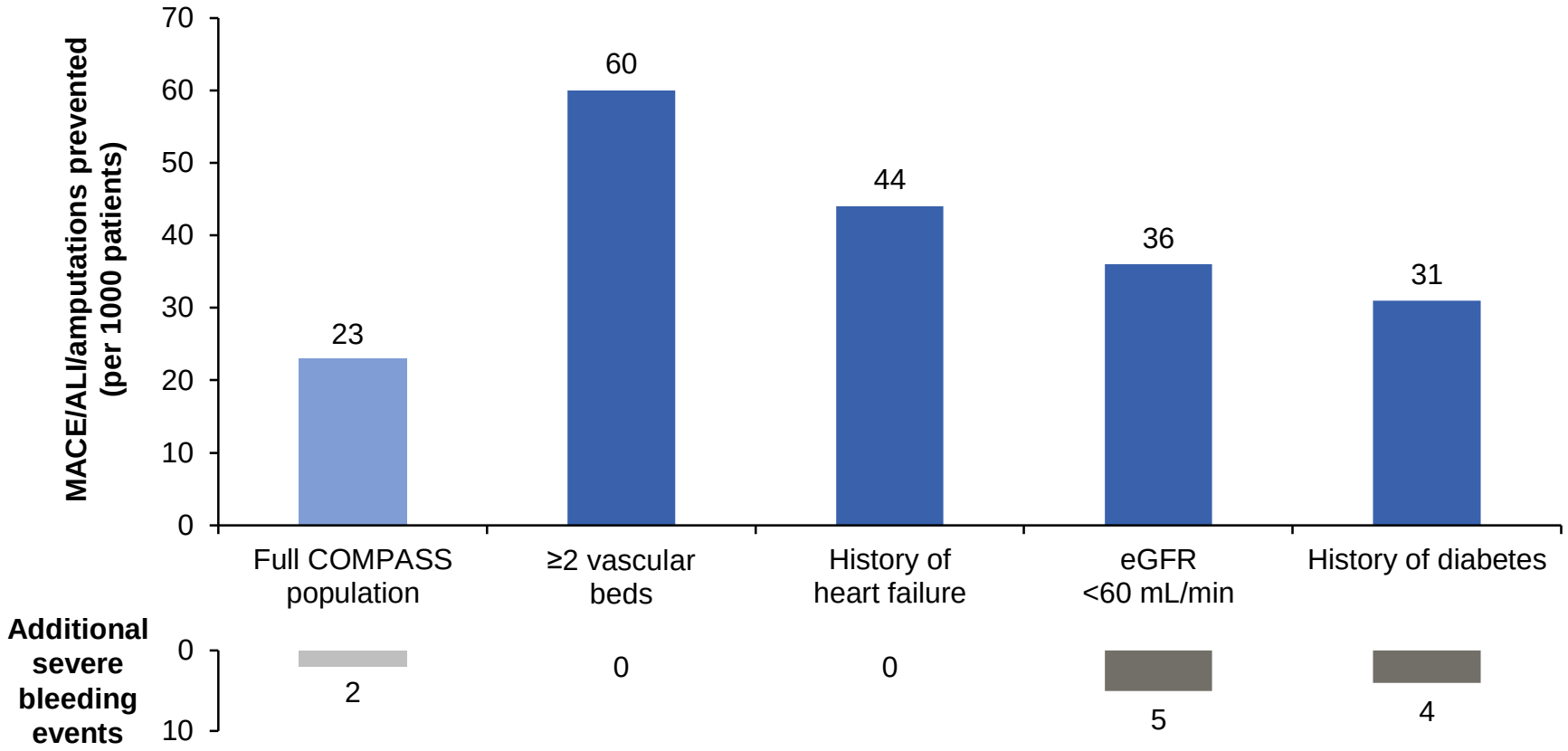
- To find whether in the already high-risk cohort of COMPASS, further risk stratification can identify subsets of the highest-risk patients with the greatest net clinical benefit

- Based on two independent methods for risk stratification (REACH and CART), the patients at highest risk of ischemic events in the COMPASS population were those with ≥1 of:
  - Poly-vascular disease
  - Chronic HF (EF ≥30% and NYHA class I or II)
  - Renal insufficiency (eGFR <60 ml/min)
  - History of diabetes

Anand SS et al. JACC Jul 2019;73:3271−3280.

Absolute Benefit of Rivaroxaban Vascular Dose Plus Aspirin in High-risk Patient Groups

Ischaemic events prevented and bleeding events caused over 30 months with rivaroxaban vascular dose plus aspirin in high-risk groups



Anand SS et al. *J Am Coll Cardiol* 2019;73:3271−3280.

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Antithrombotic therapy in patients with CCS and sinus rhythm	
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIa**
Addition of a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events and without high bleeding risk (see options in *section 3.3.2*).	**IIb**

Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 1559 mL/min/1.73 m

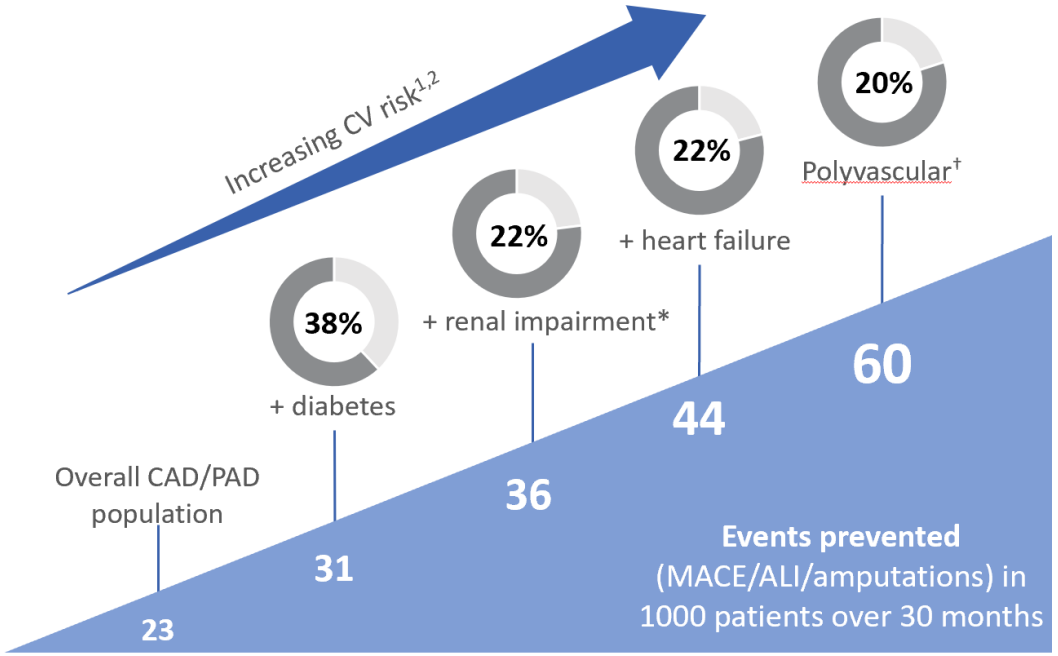
Conclusions

- The COMPASS trial enrolled patients with chronic CAD at high risk of ischemic events
- The overall treatment effect of vascular dose rivaroxaban (2.5 mg bid) plus aspirin vs. aspirin was robust in the overall COMPASS trial and the treatment effect of rivaroxaban was consistent across many subgroups
- The absolute benefit of vascular dose rivaroxaban plus aspirin was highest in the highest-risk subgroups who had ≥1 of:
  - Poly-vascular disease (≥2 vascular beds affected)
  - chronic HF (EF ≥30% and NYHA class I or II)
  - renal insufficiency (eGFR <60 ml/min)
  - history of diabetes

Conclusions

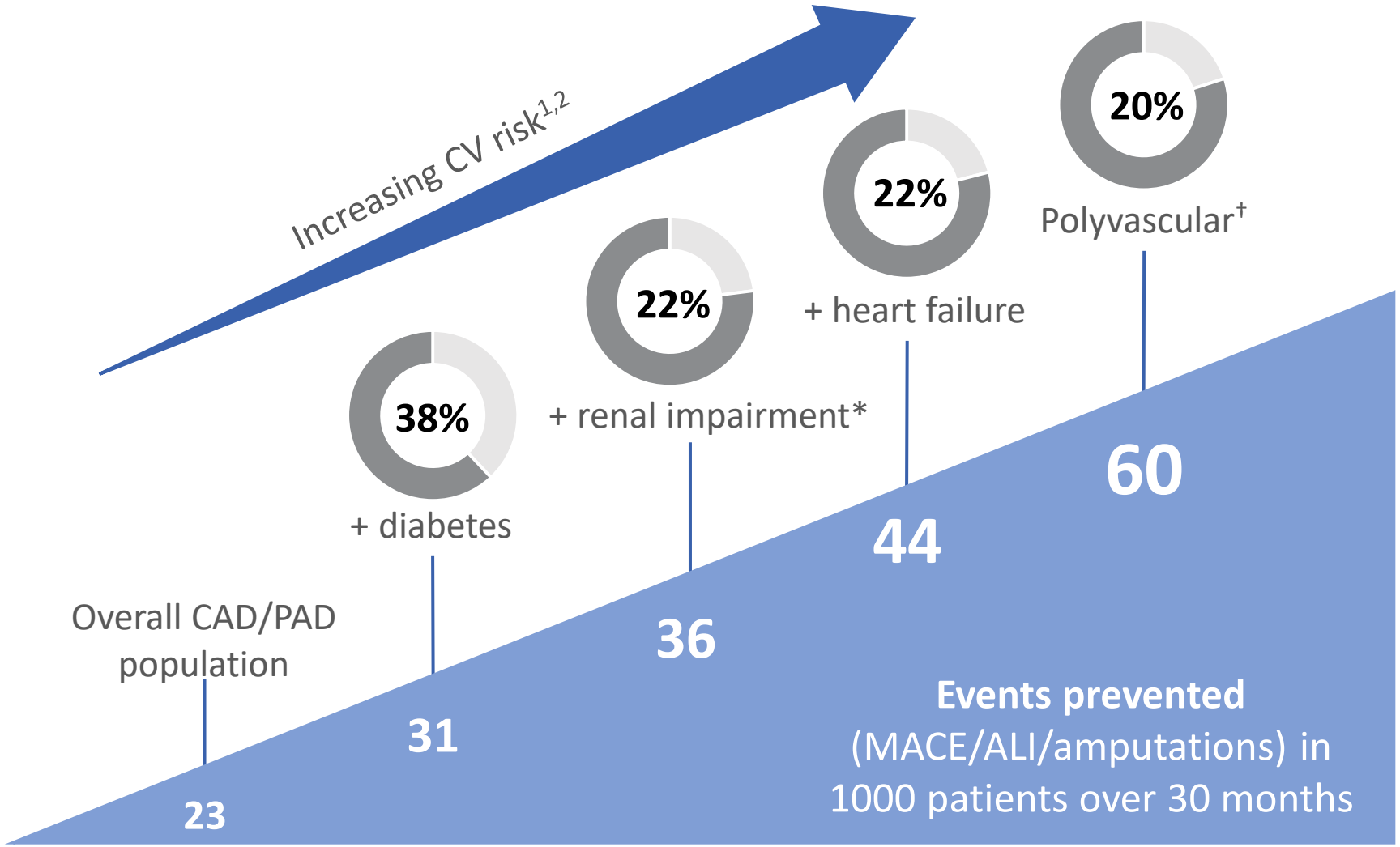
- The absolute increase in the risk of severe bleeding was not greater in higher-risk patients than in lower-risk patients, and the net benefit increased over time

- Even the lower-risk patient groups had appreciable residual risk and benefited from the more intensive treatment



Thank You

Patients at Higher CV Risk Benefit More from Rivaroxaban Vascular Dose Plus Aspirin



Summary

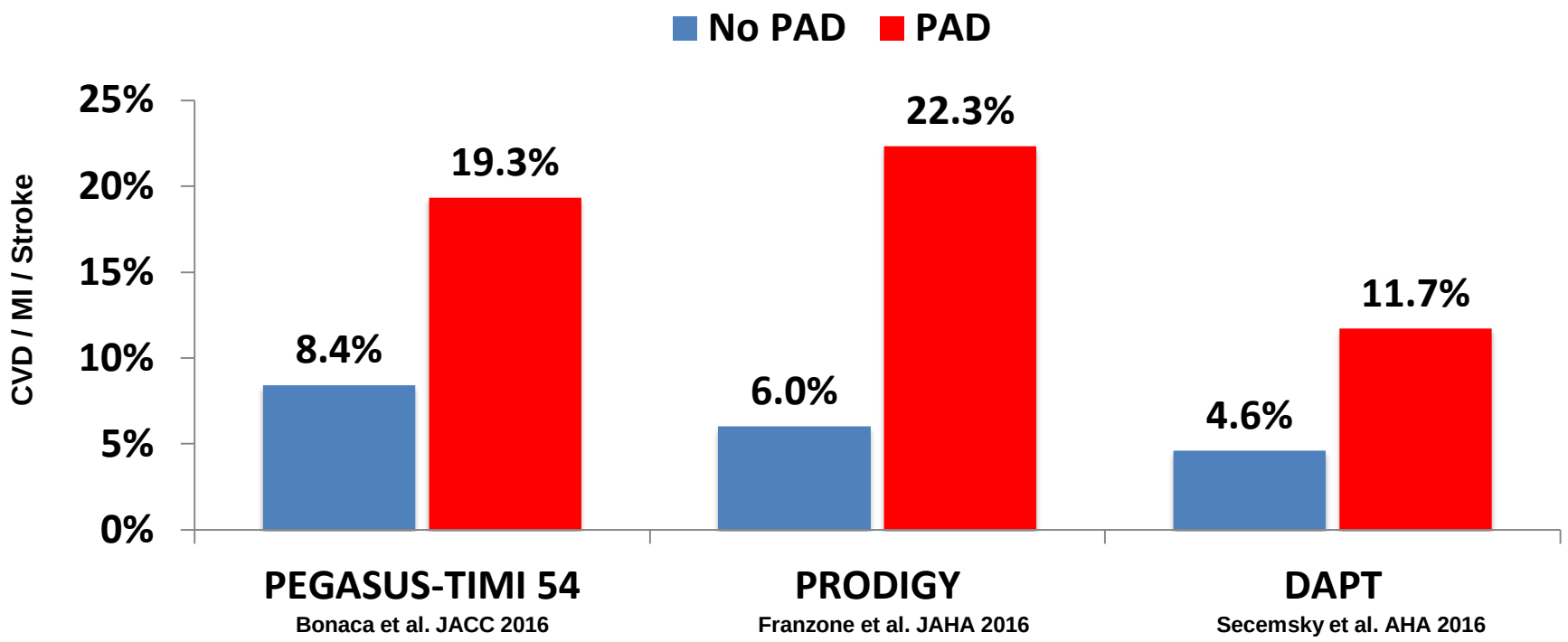
- The need to improve long-term outcomes in pts sustaining atherotrombotic event prompted a re-evaluation of the **“dual pathway” concept** : combining long-term antiplatelet and anticoagulant therapy.

- When added to antiplatelet, low doses of rivaroxaban (“vascular dose”) appear to improve outcomes while maintaining an acceptable bleeding risk.

- It is likely that the benefit of thrombin inhibition reflects not only attenuation of coagulation but also suppression of thrombin-mediated platelet activation and might reflect pleiotropic plaque stabilizing effects.

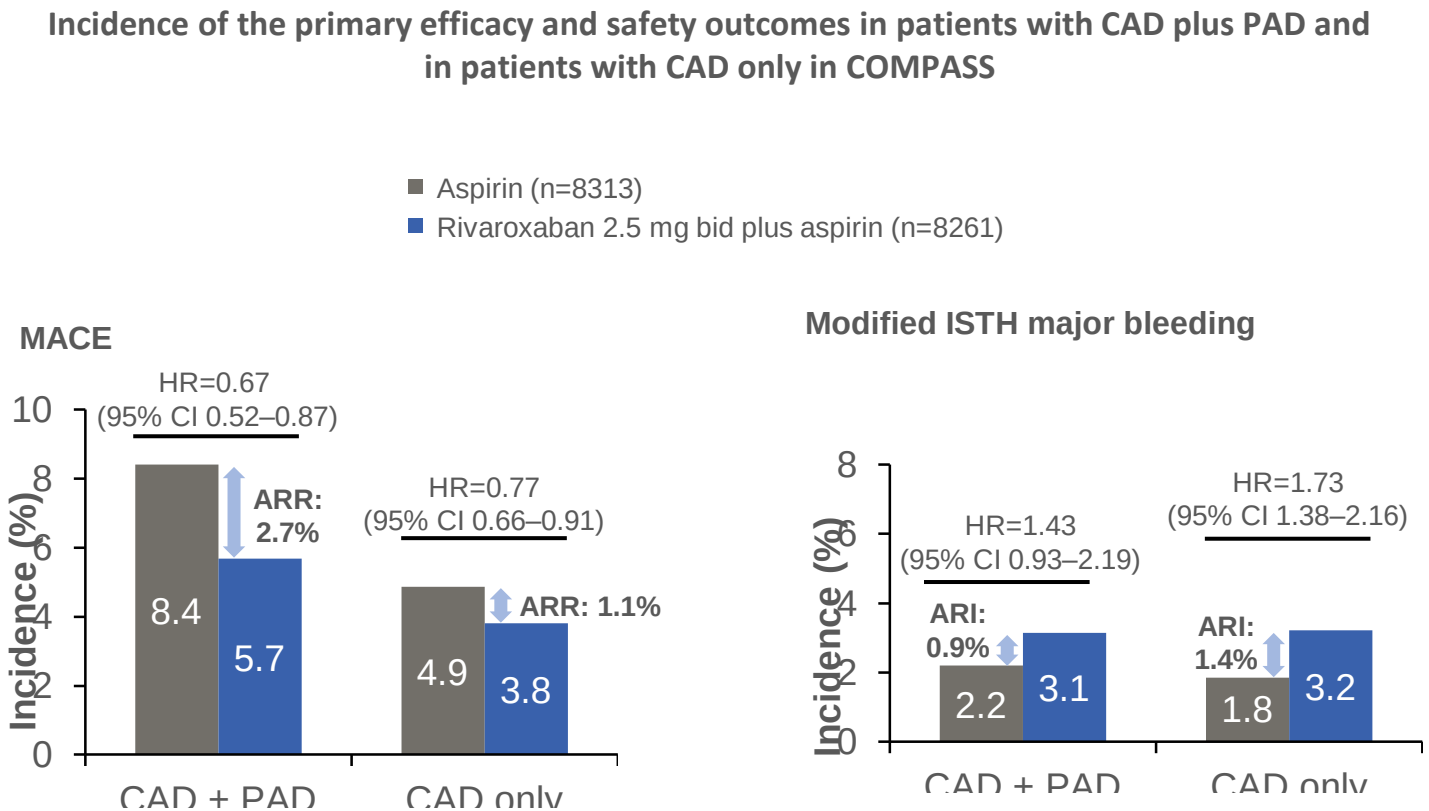
Thank You

PAD is Associated in 60% increased risk of MACE after adjusting for risk factors

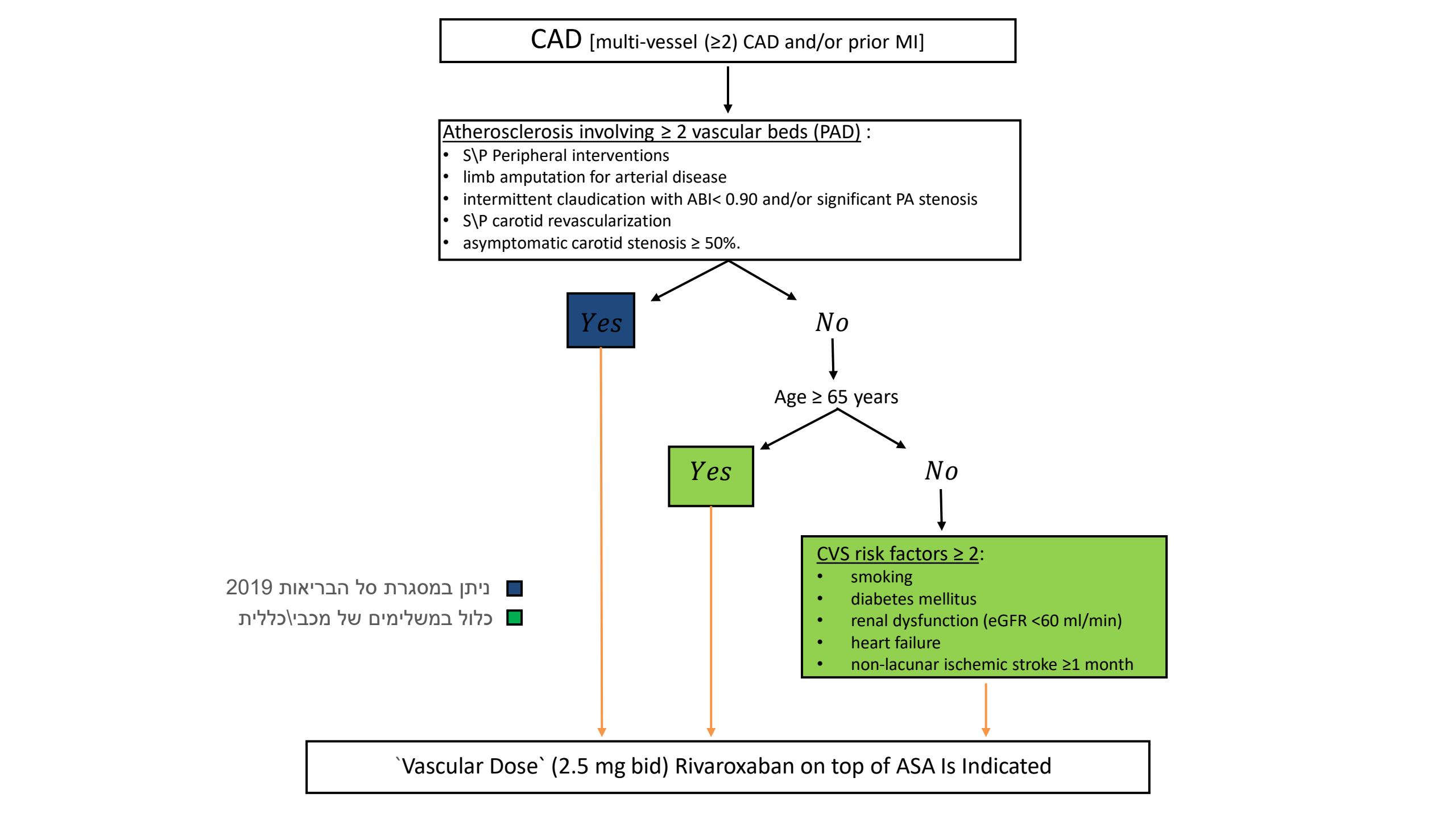


	MACE			Bleeding		
Subgroup name	Aspirin	X+A	RRR	Aspirin	X+A	RRI
Full COMPASS population	5.4%	4.1%	24%	1.9%	3.1%	70%
CAD and PAD	8.4%	5.7%	33%	2.1%	3.0%	43%
Documented PAD	7.1%	4.9%	31%	1.3%	2.6%	42%
CAD + Heart Failure	7,9%	5,5%	22%	1.9%	2.6%	76%
CAD – Heart Failure	4.9%	3.8%	22%	1.9%	3.3%	76%
CAD + Moderate Renal Impairment	8.8%	6.5%	27%	2.9%	4.1%	41%
Prior MI + Moderate Renal Impairment	9.8%	6.6%	33%	2.6%	4.0%	54%
CAD - Moderate Renal Impairment	4.6%	3.5%	24%	1.6%	2.9%	80%
CAD + Diabetes	7.0%	5.1%	28%	2.0%	3.3%	65%
CAD - Diabetes	4.8%	3.6%	23%	1.9%	3.1%	67%
CAD + Prior Stroke	11.9%	6.8%	42%	1.1%	3.6%	224%

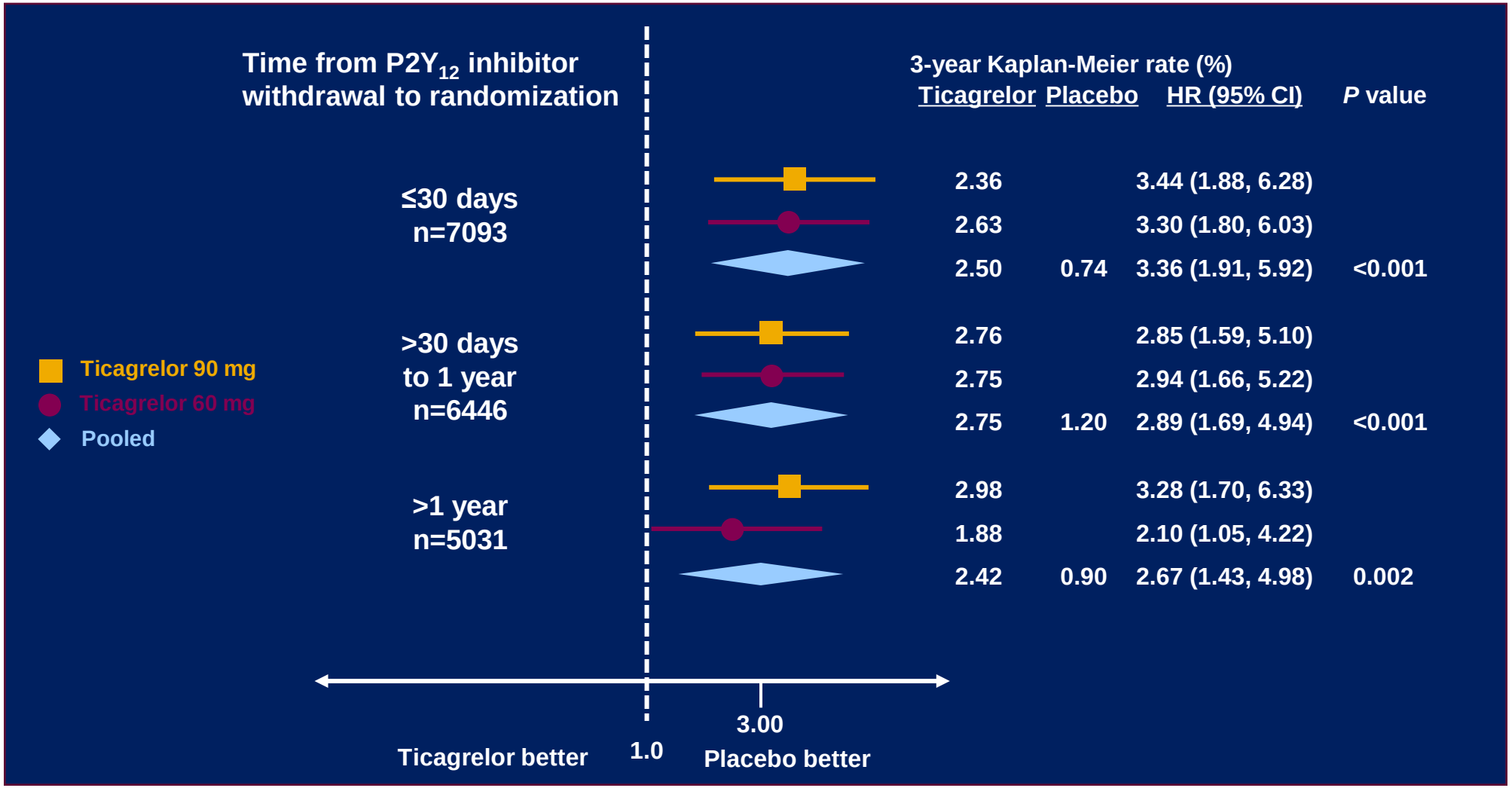
Rivaroxaban 2.5 mg bid plus Aspirin Reduced the Risk of MACE in Patients with Polyvascular Disease



Connolly SJ *et al*, *Lancet* 2018;391:205–218

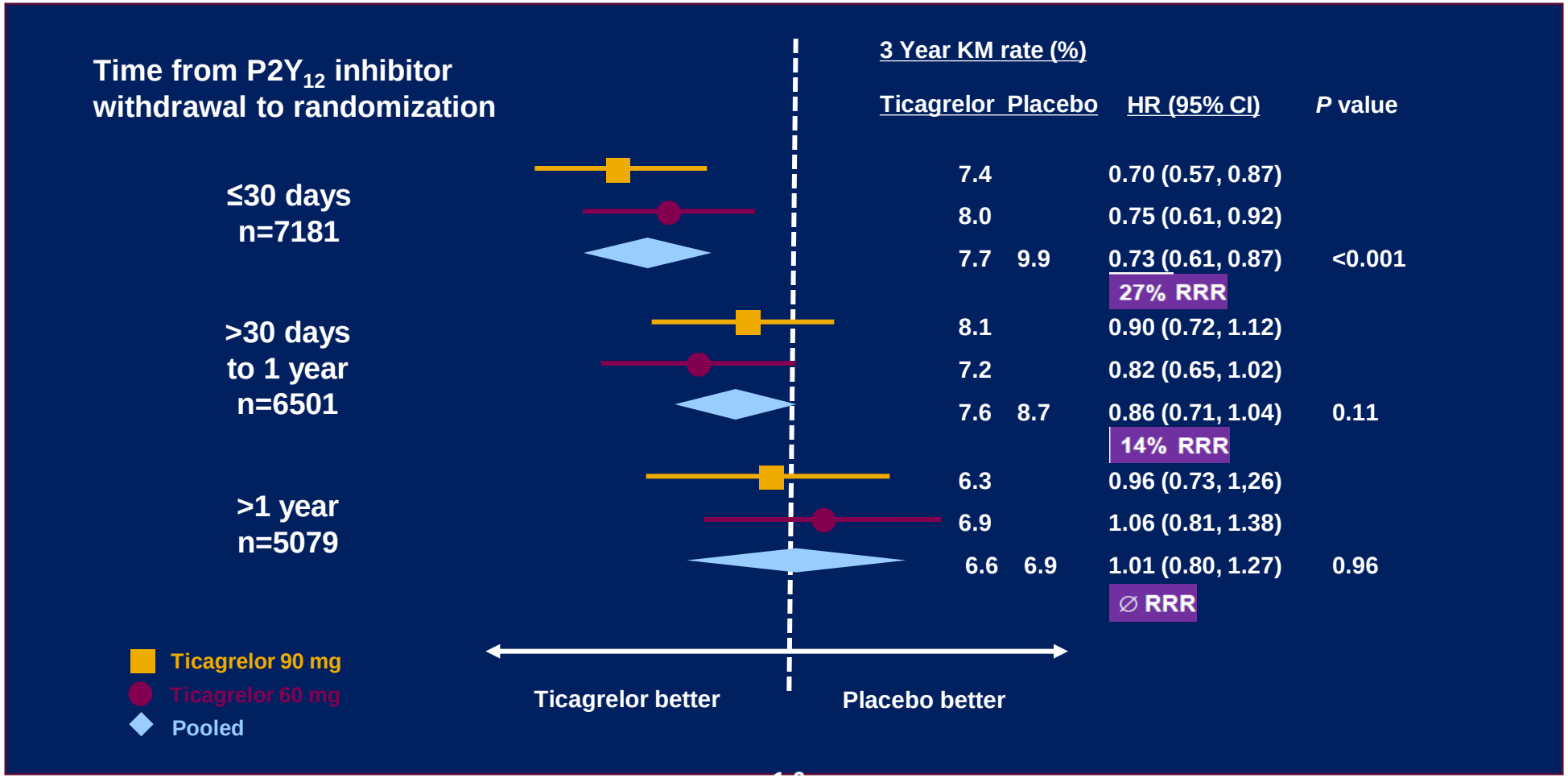

CAD [multi-vessel (≥2) CAD and/or prior MI]
Atherosclerosis involving ≥ 2 vascular beds (PAD) :
• S\P Peripheral interventions
• limb amputation for arterial disease
• intermittent claudication with ABI< 0.90 and/or significant PA stenosis
• S\P carotid revascularization
• asymptomatic carotid stenosis ≥ 50%.
Yes
No
Age ≥ 65 years
Yes
No
CVS risk factors ≥ 2:
• smoking
• diabetes mellitus
• renal dysfunction (eGFR <60 ml/min)
• heart failure
• non-lacunar ischemic stroke ≥1 month
ניתן במסגרת סל הבריאות 2019
כלול במשלימים של מכבי\כללית
`Vascular Dose` (2.5 mg bid) Rivaroxaban on top of ASA Is Indicated

The increases (versus placebo) in TIMI major bleeding were similar for the two ticagrelor dose levels



Bonaca MP et al. Eur Heart J, 2015

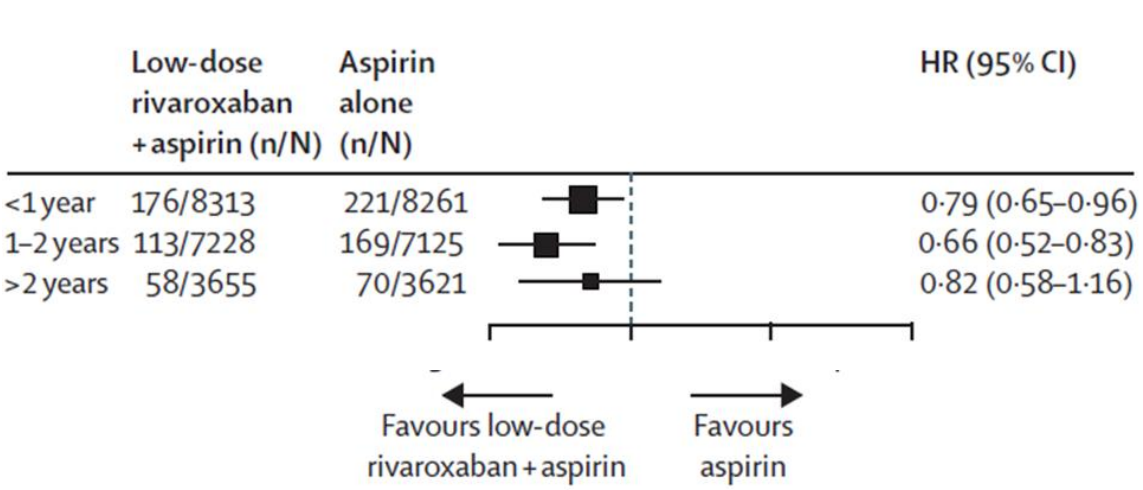
Efficacy of ticagrelor in reducing risk of atherothrombotic events declines with increasing duration of $P2Y_{12}$ inhibitor withdrawal



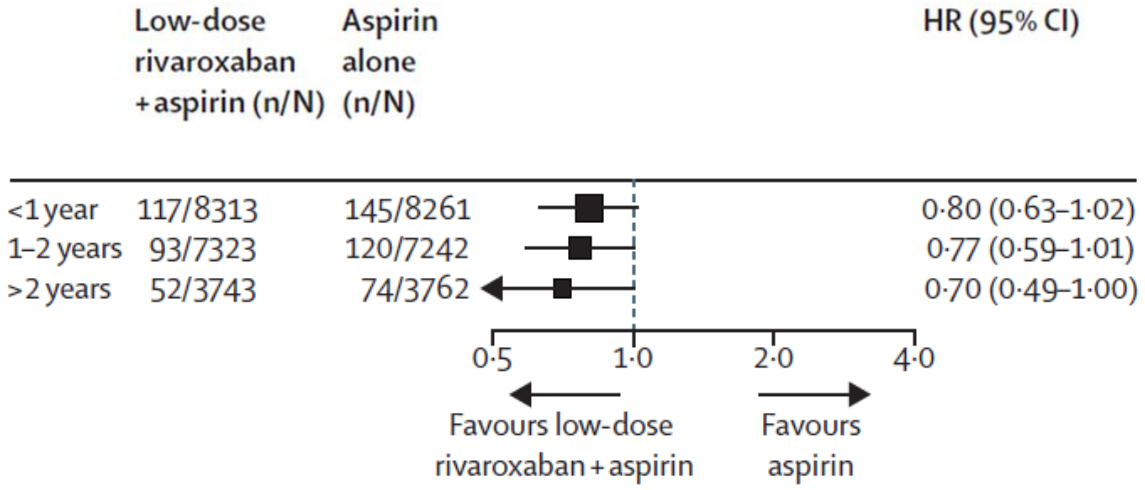
Bonaca MP et al. Eur Heart J, 2015

Landmark Analysis of the Primary Efficacy Outcome and all-Cause Death

primary efficacy outcome



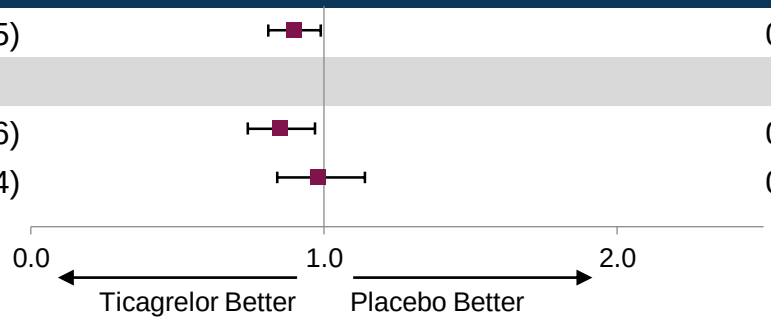
all-cause death



Stuart J Connolly et al. Lancet. 2018 Jan 20;391(10117):205-218

THEMIS-PCI
Primary and Secondary Efficacy Outcomes

CV Death, MI or stroke	Ticagrelor[a] n/N (%)	Placebo[a] n/N (%)	HR (95% CI)	p-value	$p_{interaction}$
THEMIS Overall[1]	736/9619 (7.7)	818/9601 (8.5)	0.90 (0.81-0.99)	0.04	
THEMIS-PCI[2]					
History of PCI	404/5558 (7.3)	480/5596 (8.6)	0.85 (0.74-0.97)	0.013	0.16
No history of PCI	332/4061 (8.2)	338/4005 (8.4)	0.98 (0.84-1.14)	0.76	



THEMIS-PCI Secondary Efficacy Outcomes[2]

Outcome	Ticagrelor[a] (n=5558) n (%)	Placebo[a] (n=5596) n (%)	HR (95% CI)	p-value
CV death	174 (3.1)	183 (3.3)	0.96 (0.78-1.18)	0.68
All-cause death[b]	282 (5.1)	323 (5.8)	0.88 (0.75-1.03)	0.11
MI	171 (3.1)	216 (3.9)	0.80 (0.65-0.97)	0.027
Stroke	96 (1.7)	131 (2.3)	0.74 (0.57-0.96)	0.024
ALI and major amputation of vascular cause	7 (0.1)	15 (0.3)	0.47 (0.19-1.15)	0.099
Composite of all-cause death, MI, or stroke	494 (8.9)	603 (10.8)	0.82 (0.73-0.93)	0.0014
Composite of all-cause death, MI, stroke, ALI, or major amputation of vascular cause	500 (9.0)	616 (11.0)	0.82 (0.72-0.92)	0.00068

Other Ischemic Outcomes

[a]All patients received ASA 75–150 mg QD unless contraindicated or not tolerated;
[b]Includes deaths based on publicly available vital status data in patients who have withdrawn consent.
ALI = acute limb ischemia; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

1. Steg PG et al. Online ahead of print. *N Engl J Med*. 2019; 2. Bhatt DL et al. Online ahead of print. *Lancet.* 2019.

THEMIS-PCI
Other Ischemic Outcomes

Outcome	Ticagrelor[a] (n=5558) n (%)	Placebo[a] (n=5596) n (%)	HR (95% CI)	p-value
STEMI	16 (0.3)	51 (0.9)	0.32 (0.18-0.55)	<0.0001
Ischemic stroke	88 (1.6)	113 (2.0)	0.79 (0.59-1.04)	0.089
Coronary artery revascularization[b]	599 (10.8)	645 (11.5)	0.93 (0.84-1.04)	0.22
Definite stent thrombosis	8 (0.1)	14 (0.3)	0.58 (0.24-1.37)	0.21
Definite or probable stent thrombosis	9 (0.2)	18 (0.3)	0.50 (0.23-1.12)	0.094

[a]All patients received ASA 75–150 mg QD unless contraindicated or not tolerated; [b]Defined as PCI or CABG documented by the investigator in the electronic case report form and not adjudicated.

HR = hazard ratio; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Bhatt DL et al. Online ahead of print. *Lancet.* 2019.

THEMIS-PCI
Bleeding Outcomes

Outcome	Ticagrelor[a] n/N (%)	Placebo[a] n/N (%)	HR (95% CI)	p-value
TIMI major bleeding				
THEMIS Overall[1]	206/9562 (2.2)	100/9531 (1.0)	2.32 (1.82-2.94)	<0.001
THEMIS-PCI[2]	111/5536 (2.0)	62/5564 (1.1)	2.03 (1.48-2.76)	<0.0001
THEMIS-PCI Other safety endpoints[2]				
TIMI major or minor bleeding	157/5536 (2.8)	80/5564 (1.4)	2.23 (1.70-2.92)	<0.0001
ICH	33/5536 (0.6)	31/5564 (0.6)	1.21 (0.74-1.97)	0.45
Fatal bleeding[b]	6/5536 (0.1)	6/5564 (0.1)	1.13 (0.36-3.50)	0.83

Pre-specified Safety Analyses by Subgroup

[a]All patients received ASA 75–150 mg QD unless contraindicated or not tolerated; [b]Fatal bleeding was characterized as BARC 5 bleeding in the trial.[1]
HR = hazard ratio; ICH = intracranial hemorrhage; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

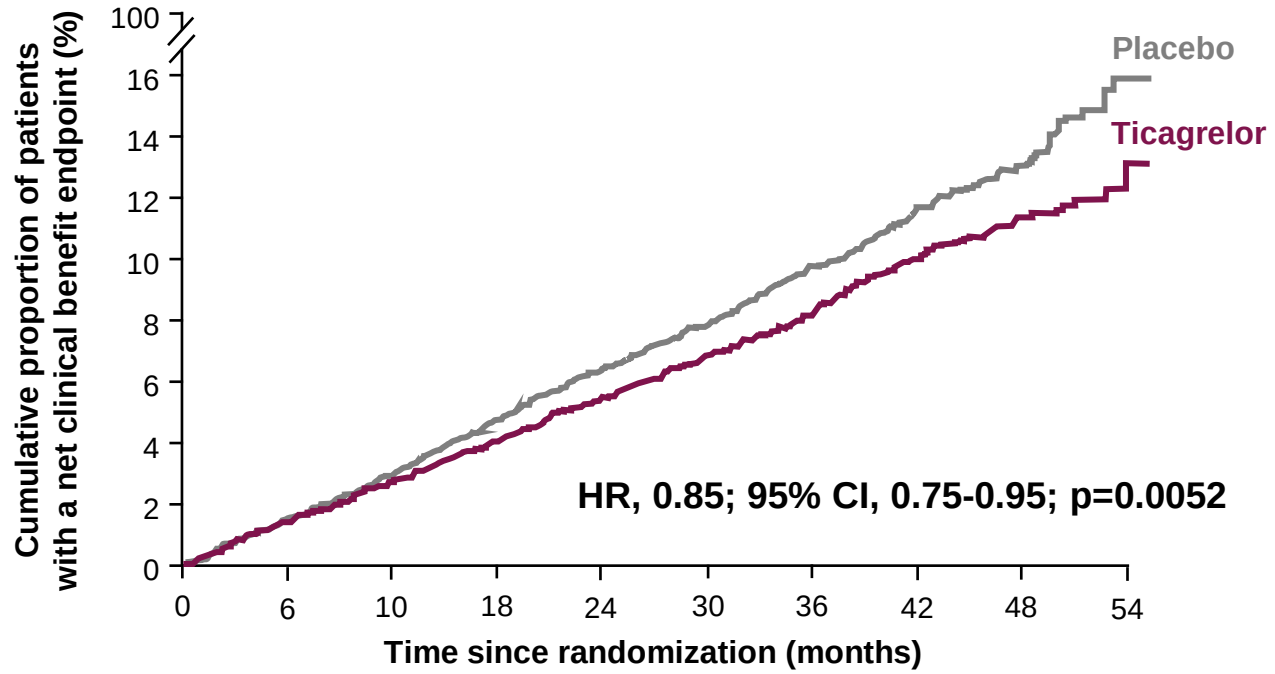
1. Steg PG et al. Online ahead of print. *N Engl J Med*. 2019; 2. Bhatt DL et al. Online ahead of print. *Lancet.* 2019.

THEMIS
Net Clinical Benefit[a]

- In **THEMIS overall**, net clinical benefit was 10.1% vs. 10.8% in the ticagrelor[b] and placebo[b] groups, respectively (HR, 0.93; 95% CI, 0.86-1.02)[1]
- In **THEMIS-PCI**, there was a more favorable net clinical benefit in the ticagrelor group vs. placebo (9.3% vs. 11%, respectively)[2]

THEMIS-PCI
Estimates of Events Prevented and Caused

THEMIS-PCI[2]
Composite of all-cause death, MI, stroke, fatal bleed, or ICH



Number at Risk

Ticagrelor	5558	5433	5339	5240	5153	5037	3484	2127	981	100
Placebo	5596	5480	5390	5274	5166	5060	3470	2128	993	102

[a]Also defined as irreversible harm;[1,2] [b]All patients received ASA 75–150 mg QD unless contraindicated or not tolerated.
HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; PCI = percutaneous coronary intervention.
1. Steg PG et al. Online ahead of print. *N Engl J Med*. 2019; 2. Bhatt DL et al. Online ahead of print. *Lancet.* 2019.

European Heart Journal

ESC European Society of Cardiology

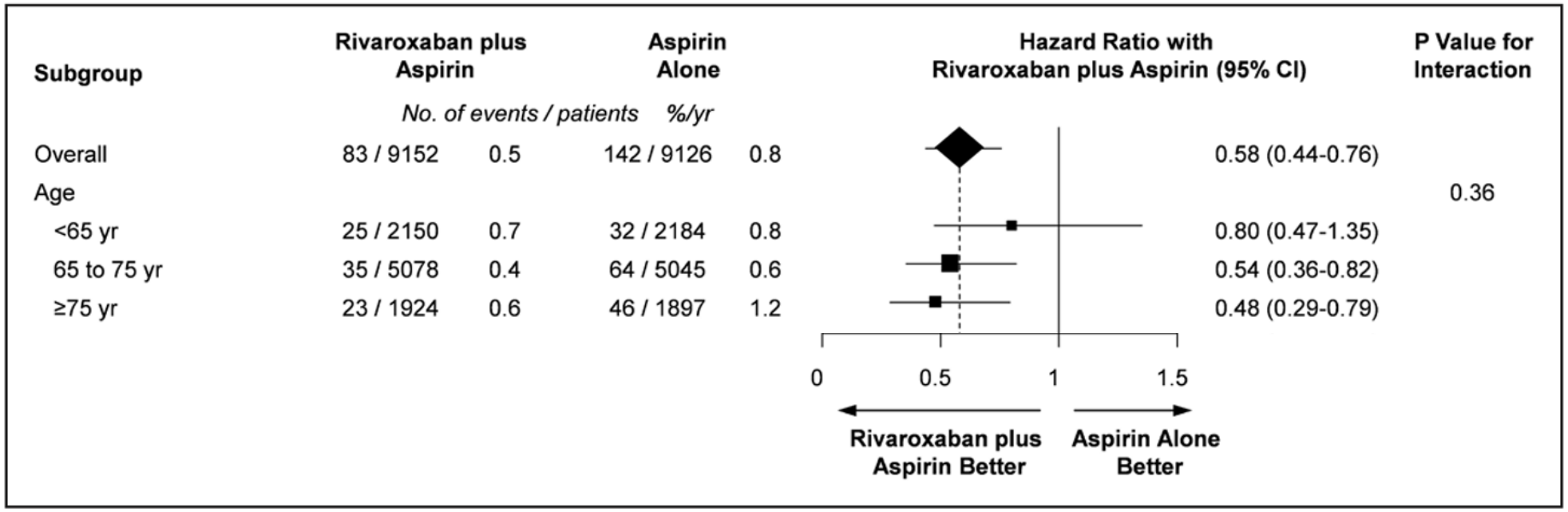
Article Contents

GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) FREE

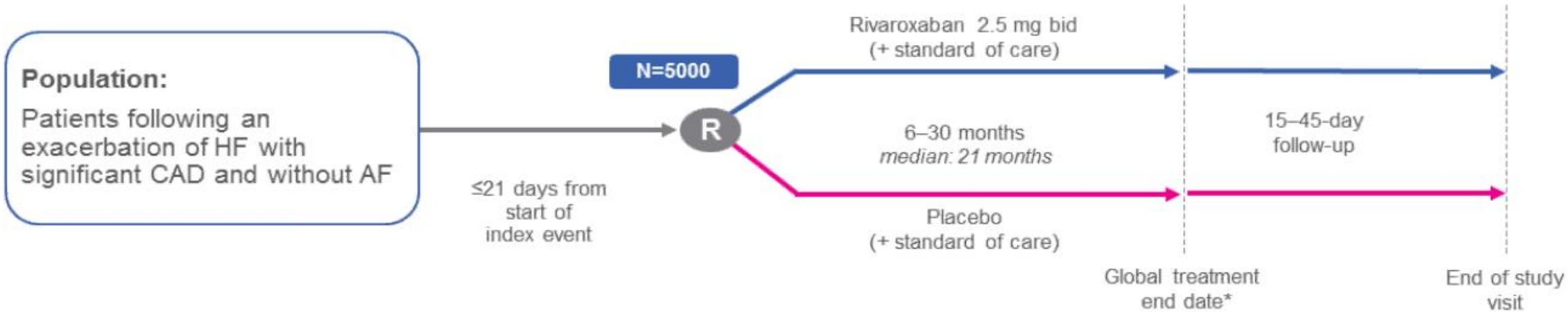
Is low-dose rivaroxaban plus aspirin an important new option for prevention of stroke in patients with atherosclerosisIs?

Comparison of Rivaroxaban Plus Aspirin Versus Aspirin Alone in Subgroups of Selected Baseline Characteristics.



Mukul Sharma, MD, MSc et al Circulation Feb. 2019;139:1134–1145.

COMMANDER HF Examines the Potential Clinical Benefit of Rivaroxaban Following Acute Decompensation of HF



Short design:
- Randomised
- Double-blind
- Placebo-controlled, parallel-group
- Multicentre
- Event-driven superiority study

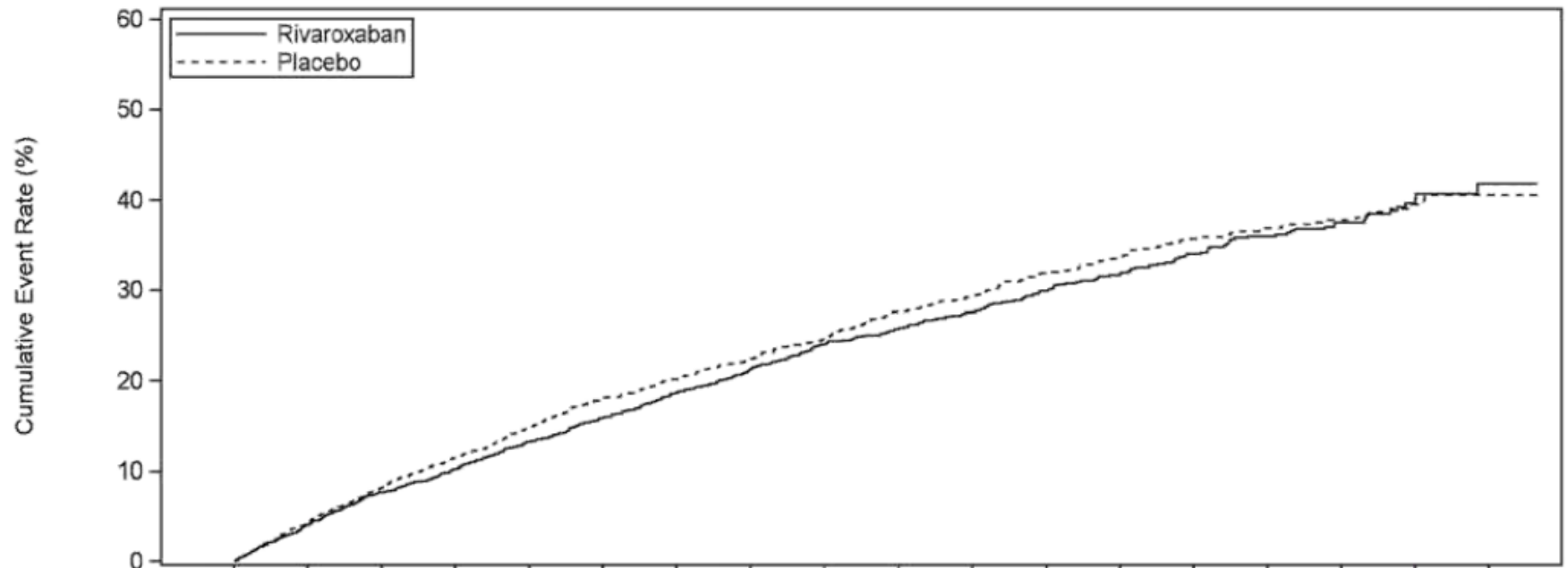
Primary Efficacy: Composite of all-cause mortality, MI, or stroke

Primary Safety: Composite of fatal bleeding or bleeding into a critical space with potential for permanent disability

Zannad F et al. N Engl J Med. 2018 Oct 4;379(14):1332-1342.

COMMANDER HF Primary Efficacy Outcome

Composite Endpoint of all-cause mortality, MI or stroke

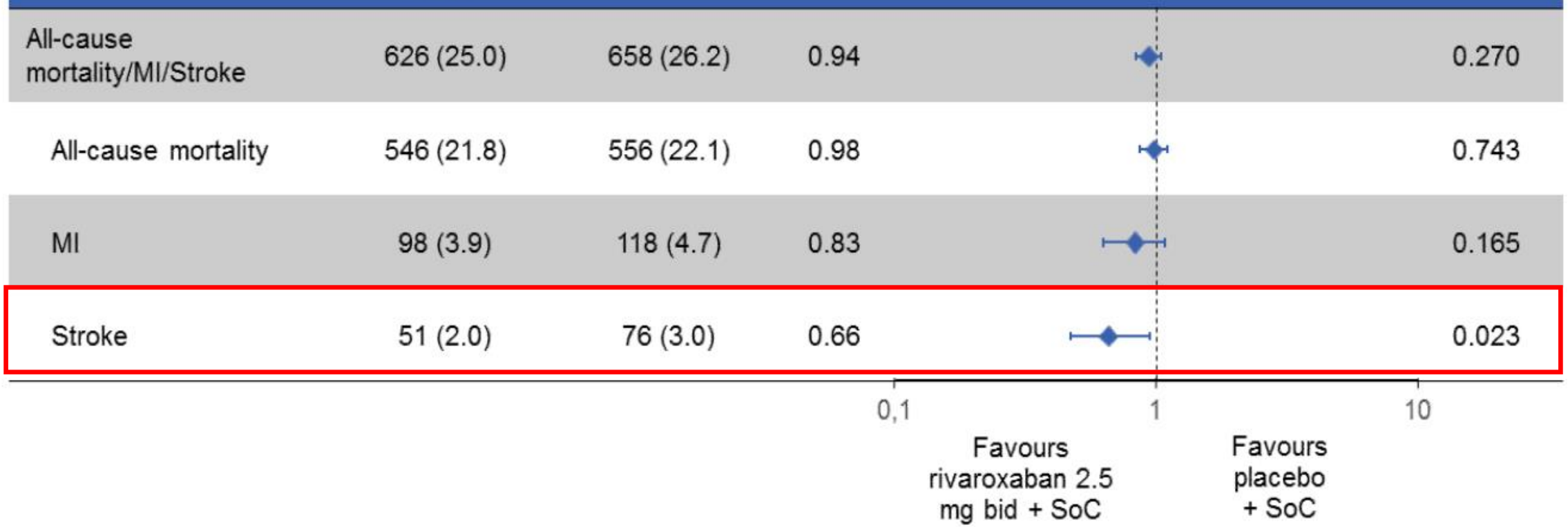


Subjects at risk																		
Rivaroxaban	2507	2404	2308	2159	1883	1637	1384	1189	974	817	668	588	505	423	327	239	121	46
Placebo	2515	2407	2303	2145	1851	1589	1353	1169	960	804	661	582	502	426	330	236	127	43

Zannad F et al. N Engl J Med. 2018 Oct 4;379(14):1332-1342.

In Acute Decompensated HF, Rivaroxaban 2.5 mg bid (+ SoC) Shows Consistent Reductions in Ischaemic Events

Outcome*	Rivaroxaban 2.5 mg bid + SoC n (%)	Placebo + SoC n (%)	HR	HR (95% CI)	*p*-value
All-cause mortality/MI/Stroke	626 (25.0)	658 (26.2)	0.94		0.270
All-cause mortality	546 (21.8)	556 (22.1)	0.98		0.743
MI	98 (3.9)	118 (4.7)	0.83		0.165
Stroke	51 (2.0)	76 (3.0)	0.66		0.023



Zannad F et al. N Engl J Med. 2018 Oct 4;379(14):1332-1342.

Stroke or TIA Incidence per 100 Patient-Years by CHA_2DS_2VASc Stratum

End Point	Placebo, Rate	Rivaroxaban, Rate	NNT
Overall	1.9	1.29	164
$CHA_2DS_2VASc \leq 4$	1.44	1.13	316
$CHA_2DS_2VASc > 4$	2.56	1.52	96

Zannad F et al. N Engl J Med. 2018 Oct 4;379(14):1332-1342.

JAMA Neurology | Original Investigation

Association Between Low-Dose Rivaroxaban With or Without Aspirin and Ischemic Stroke Subtypes

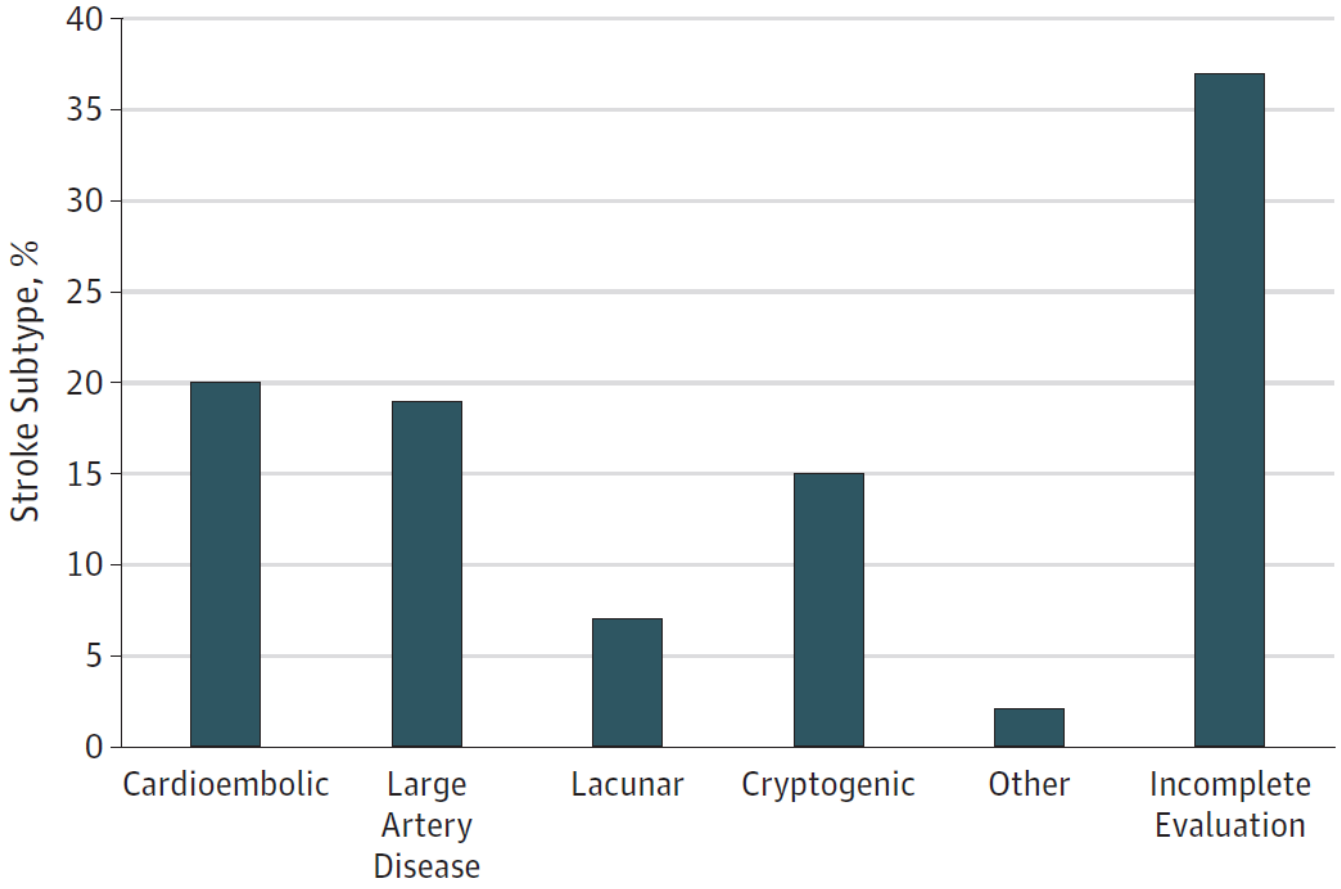
A Secondary Analysis of the COMPASS Trial

- To analyze the association between low-dose rivaroxaban with or without aspirin and different ischemic stroke subtypes.
- All ischemic strokes (confirmed neuroimaging or autopsy) and uncertain strokes (presumed likely to be ischemic based on clinical features) were adjudicated
- A total of 291 patients experienced strokes (272 ischemic and 19 uncertain) during the mean follow-up period of 23months
- TOAST criteria were used to classify the cause of the ischemic stroke

Kanjana S. Perera et al. JAMA Neurol. 2019 Sep 16.

Stroke Subtype According to TOAST Criteria Among Participants With Ischemic or Unknown Stroke

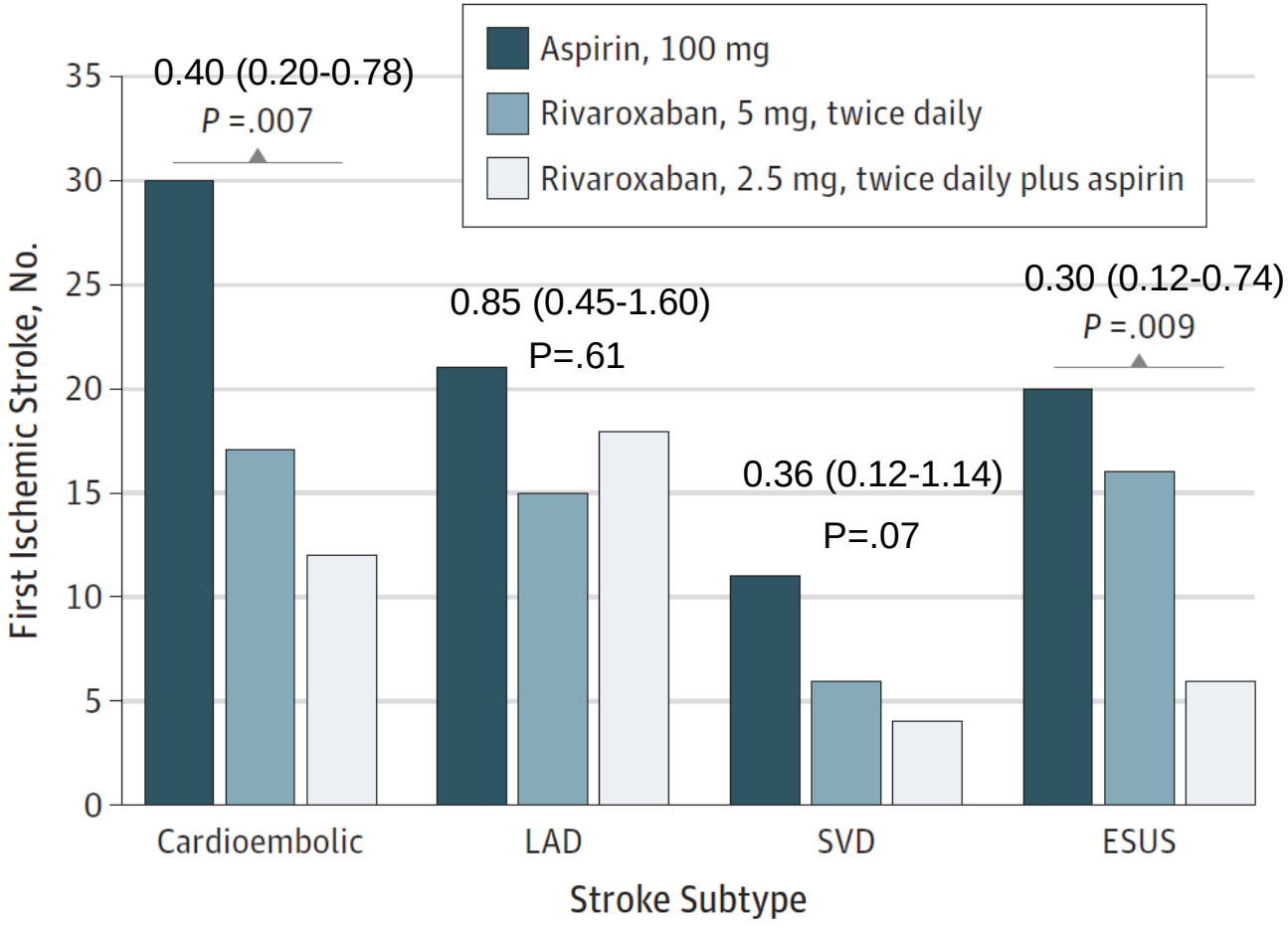
- Large Artery Disease - carotid stenosis > 50%
- Lacunar - secondary to small vessel disease
- Cryptogenic - had a negative evaluation (cortical with no ipsilateral carotid stenosis > 50% and no cardioembolic source), met the criteria for ESUS
- Other - 2 or more potential causes



Kanjana S. Perera et al. JAMA Neurol. 2019 Sep 16.

Treatment Effect on Stroke Subtypes According to TOAST Criteria Among Participants With Ischemic or Unknown Stroke

LAD-large artery disease
SVD - small vessel disease
ESUS-embolic stroke of undetermined source



Kanjana S. Perera et al. JAMA Neurol. 2019 Sep 16.

Treatment Effect on Stroke Subtypes Classification Among Participants With Ischemic or Unknown Stroke

Characteristic	Participants, No. (%)			2.5 mg of Riva + Aspirin vs Aspirin	
	Overall (N = 27 395)	2.5 mg of Riva + Aspirin (n = 9152)	Aspirin (n = 9 126)	HR (95% CI)	*P* Value
Ischemic or uncertain stroke	291 (1.1)	68 (0.7)	132 (1.4)	0.51 (0.38-0.68)	<.001
Cardioembolic	59 (0.2)	12 (0.1)	30 (0.3)	0.40 (0.20-0.78)	.005
Large artery atherosclerosis[a]	54 (0.2)	18 (0.2)	21 (0.2)	0.85 (0.45-1.60)	.61
Small vessel occlusion (lacunar)	21 (0.1)	4 (0.04)	11 (0.1)	0.36 (0.12-1.14)	.07
Stroke-other determined	2 (0.01)	0	1 (0.01)	NA	NA
Stroke of undetermined cause	155 (0.6)	34 (0.4)	69 (0.8)	0.49 (0.32-0.74)	>.001
≥2 Causes	5 (0.02)	1 (0.01)	4 (0.04)	NA	NA
Negative evaluation (ESUS)	42 (0.2)	6 (0.1)	20 (0.2)	0.30 (0.12-0.74)	.006
Incomplete evaluation	108 (0.4)	27 (0.3)	45 (0.5)	0.60 (0.37-0.96)	.03

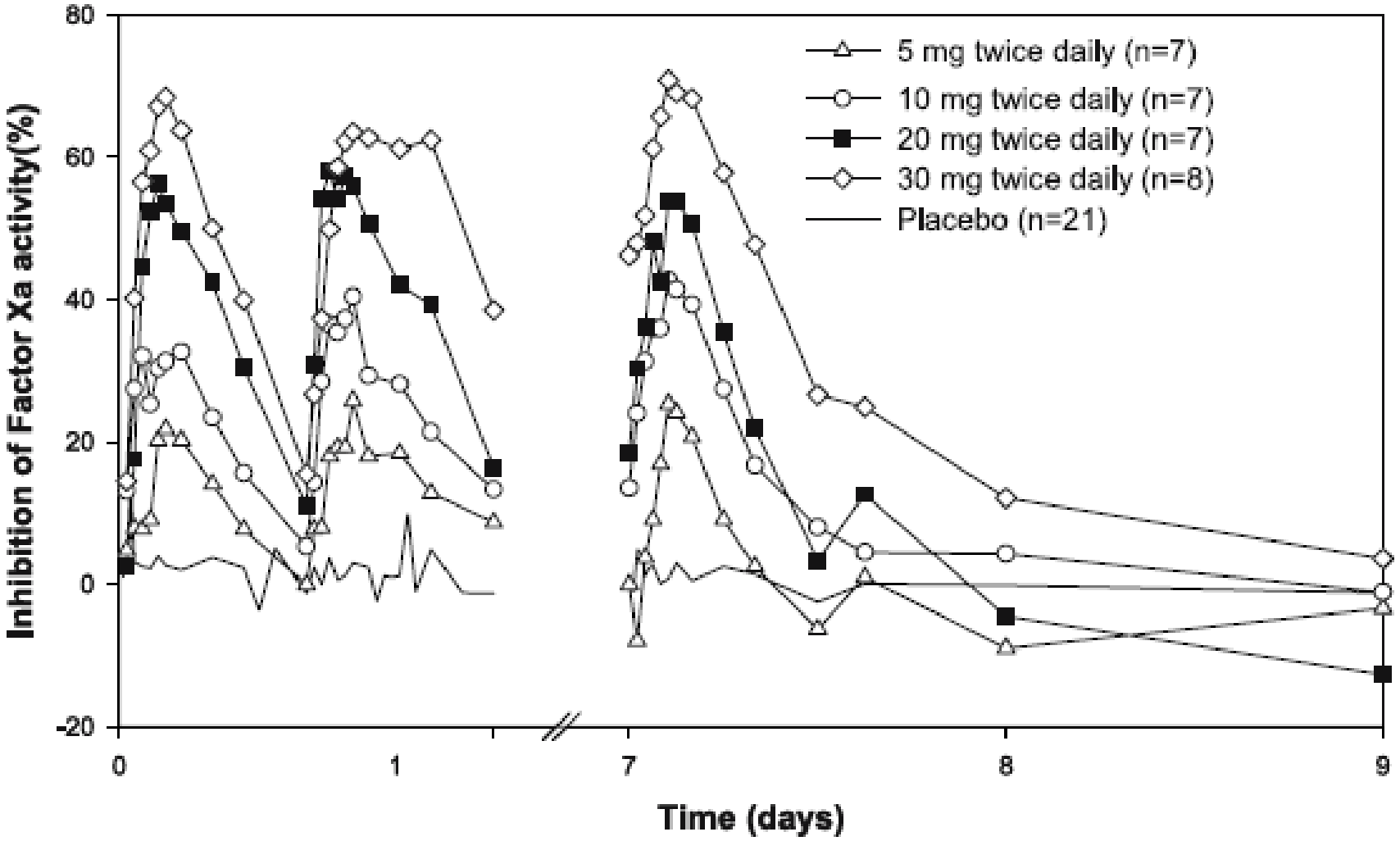
Kanjana S. Perera et al. JAMA Neurol. 2019 Sep 16.

Combination Therapy Had a Significant Effect on Cardioembolic Stroke (RRR - 60%)

- Rivaroxaban at doses of 5 to 80 mg result in dose-dependent inhibition of factor Xa activity from 20% to 60%
- Cardioembolic strokes might be associated with incident AF that occurred during the COMPASS trial
- The robust (60% reduction) raises the possibility that even at low doses rivaroxaban may have sufficient anticoagulant effect to prevent generation of AF associated thrombi and other cardiac sources in some patients

Dagmar Kubitza et alo. Eur J Clin Pharmacol (2005) 61: 873–880

Percentage Inhibition Compared With Baseline of FXa activity after administration of Rivaroxaban



Dagmar Kubitza et alo. Eur J Clin Pharmacol (2005) 61: 873–880

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Dagmar Kubitza et alo. Eur J Clin Pharmacol (2005) 61: 873–880

Combination Therapy Had a Significant Effect on ESUS (RRR - 70%)

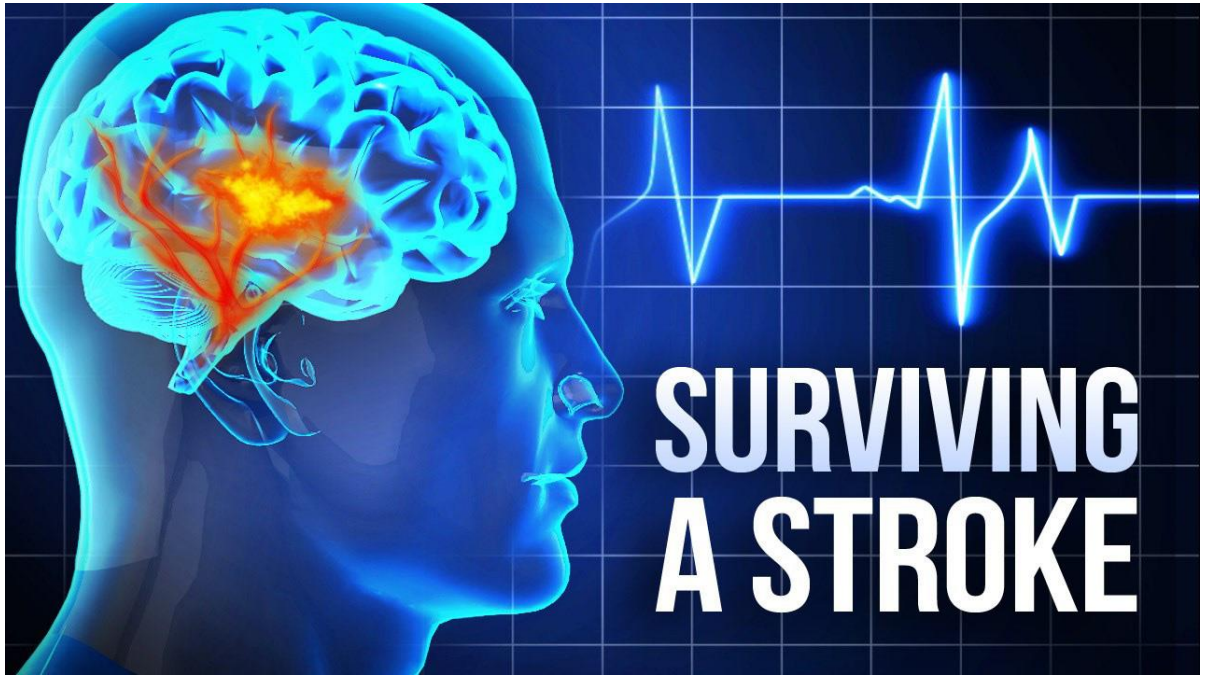
- In patients with ESUS non-stenotic (<50%stenosis) carotid plaques and aortic arch atheroma play a significant role as the underlying source of emboli.
- Emboli arising from nons-tenotic plaques in arteries are likely to be composed of both red and white thrombi, and while the red thrombus is likely to respond to anticoagulation, the white thrombus component may respond better to antiplatelet agents.
- The effect rivaroxaban on thrombin generation and the anti-cyclooxygenase effect of aspirin may better reduce arteriogenic embolism in individuals with systemic atherosclerosis with nons-tenotic plaques.

Perera KS et al. Eur Stroke J. 2018;3(2):110-116
Hart RG et al. Lancet Neurol. 2014;13(4):429-438

Patient with Prior Stroke and Carotid Disease Among COMPASS Population

1032 (4%) had prior stroke >1 month before randomization

The average time between prior stroke and trial entry was 5.3 years



Selected Predictors of Stroke:

The most important predictor of the occurrence of stroke was a history of prior stroke

Characteristic	N Pts (% of cohort)	Stroke			Ischemic/Uncertain			Hemorrhagic		
		%/yr	HR (95%CI)	P	%/yr	HR (95%CI)	P	%/yr	HR (95%CI)	P
Prev stroke	1,032 (3.8)	2.6	4.43 (3.25-6.02)	0.0001	2.4	4.82 (3.48-6.66)	0.0001	0.3	2.88 (1.14-7.23)	0.02
Prev MI	17,028 (62.2)	0.7	1.00 (0.81-1.25)	0.98	0.6	1.02 (0.80-1.23)	0.87	0.09	0.87 (0.50-1.51)	0.62
Asymptomatic Carotid stenosis ≥ 50% or revascularization	1919 (7.0)	0.9	1.40 (0.97-2.03)	0.07	0.9	1.68 (1.16-2.44)	0.006	0.03	0.28 (0.04-1.99)	0.20
Race										
White	17027	0.6	Ref		0.5	Ref		0.08	Ref	
Black	262	0.2	0.36 (0.05-2.55)	0.001	0.2	0.41 (0.06-2.96)	0.02	0	n/a	0.01
Asian	4269	1.0	1.66 (1.28-2.15)		0.8	1.55 (1.16-2.06)		0.2	2.47 (1.34-4.53)	
Other	5837	0.6	1.18 (0.89-1.55)		0.6	1.21 (0.9-1.62)		0.08	0.98 (0.44-2.16)	

Selected Predictors of Stroke:

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Characteristic	N Pts (% of cohort)	Stroke			Ischemic/Uncertain			Hemorrhagic		
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Other	5837	0.6	1.18 (0.89-1.55)		0.6	1.21 (0.9-1.62)		0.08	0.98 (0.44-2.16)	

Previous Stroke Status and Outcomes

The average time between prior stroke and trial entry was 5.3 years, and hence, the occurrence of prior stroke identifies individuals with a sustained high risk of vascular events.

Outcome	Rivaroxaban plus Aspirin (N=9152)		Aspirin (N=9126)		Rivaroxaban plus Aspirin vs. Aspirin		
	N Pts	%/yr	N Pts	%/yr	HR (95% CI)	P	P inter
Stroke							0.40
No Previous Stroke	8801	0.4	8791	0.7	0.60 (0.45-0.80)	0.0006	
Previous Stroke	351	0.7	335	3.4	0.42 (0.19-0.92)	0.03	
Ischemic or uncertain stroke							0.28
No Previous Stroke	8801	0.4	8791	0.7	0.54 (0.40-0.74)	0.0001	
Previous Stroke	351	1.1	335	3.4	0.33 (0.14-0.77)	0.01	

Previous stroke ARR = 2.7%
NNT = 37

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%

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

Carotid Disease - Previous carotid revascularization, asymptomatic carotid artery stenosis ≥50%

Primary EP: CV death, stroke, MI

Subgroup	R + A N=2,492	Aspirin N=2,504	Rivaroxaban + aspirin vs. aspirin	
	N (%)	N (%)	HR (95% CI)	P (interaction)
CAD alone	253 (3.8)	322 (4.9)	0.78 (0.68-0.91)	0.61
PAD	126 (5.1)	174 (6.9)	0.72 (0.57-0.90)	

Net Clinical Benefit with Vascular Dose Rivaroxaban & ASA Versus ASA

Definition: composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ

All Patients

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

PAD Patients

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value
Net clinical benefit	169 (6.8)	207 (8.4)	234 (9.3)	0.72 (0.59–0.87)	0.0008

Absolute Risk Reduction

1.2%

2.5%

Primary outcome & components

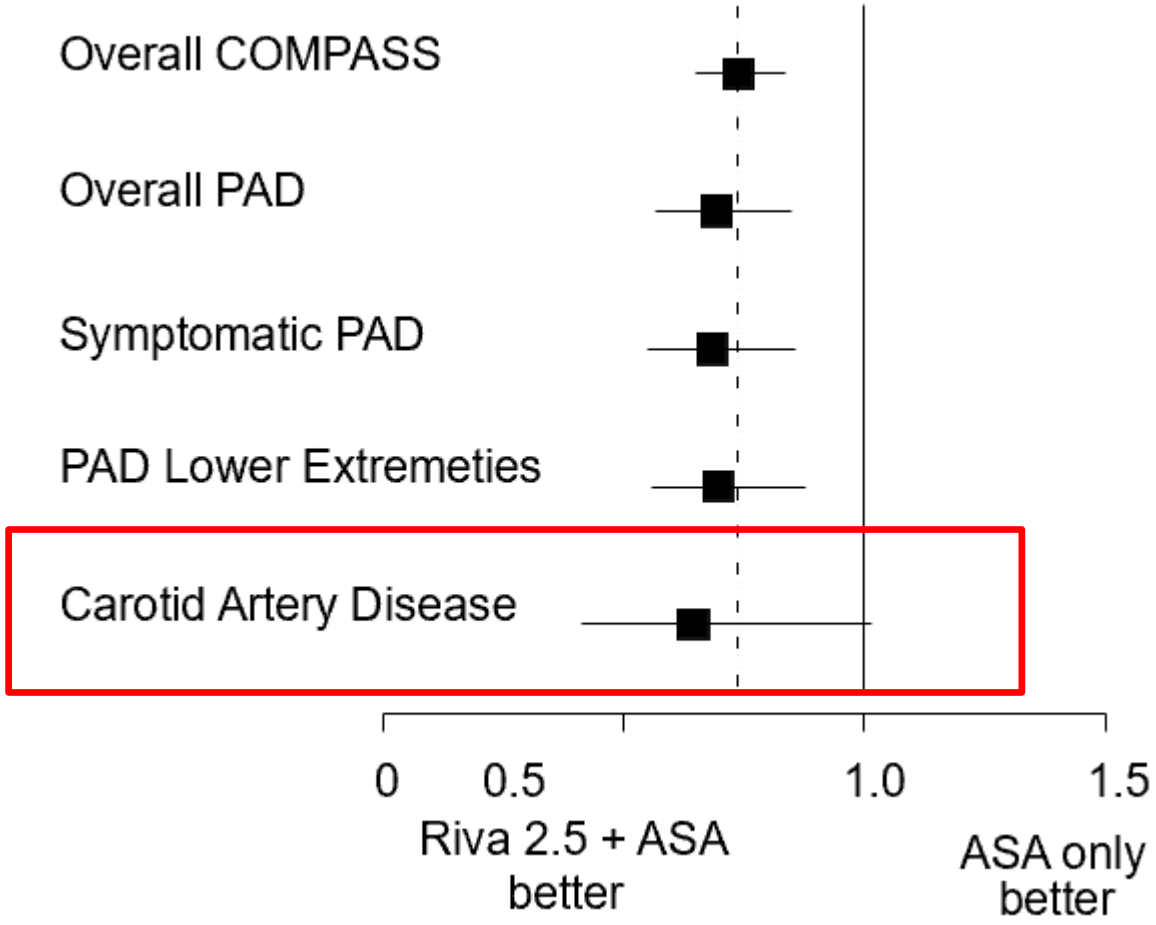
Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57-0.90)	0.005
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53-1.09)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33-0.87)	-
CV Death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59-1.14)	-

Net clinical benefit in PAD

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P
Net Clinical Benefit	169 (6.8)	207 (8.4)	234 (9.3)	0.72 (0.59-0.87)	0.0008

2017, 14August

MACE, MALE or Major Amputation



Summary

- The need to improve long-term outcomes in pts with atherosclerotic vascular disease prompted a re-evaluation of the **“dual pathway” concept** : combining long-term antiplatelet and anticoagulant therapy.

- When added to antiplatelet, low doses (2.5mg twice daily) of rivaroxaban (“vascular dose”) appear to improve outcomes (25% reduction in MACE and 20% reduction in mortality) while maintaining an acceptable bleeding risk.

- The major driver was the large and consistent reductions in ischemic strokes with the combination of low-dose rivaroxaban plus aspirin compared with aspirin (HR, 0.51 [95% CI, 0.38-0.68]; P < .001).

Summary

- A history of prior stroke identifies patients with atherosclerosis who have large absolute stroke reductions if treated with rivaroxaban added to aspirin.

- Patient with PAD including those with asymptomatic carotid artery stenosis ≥50% or post carotid revascularization derived similar benefit from adding vascular dose rivaroxaban to aspirin

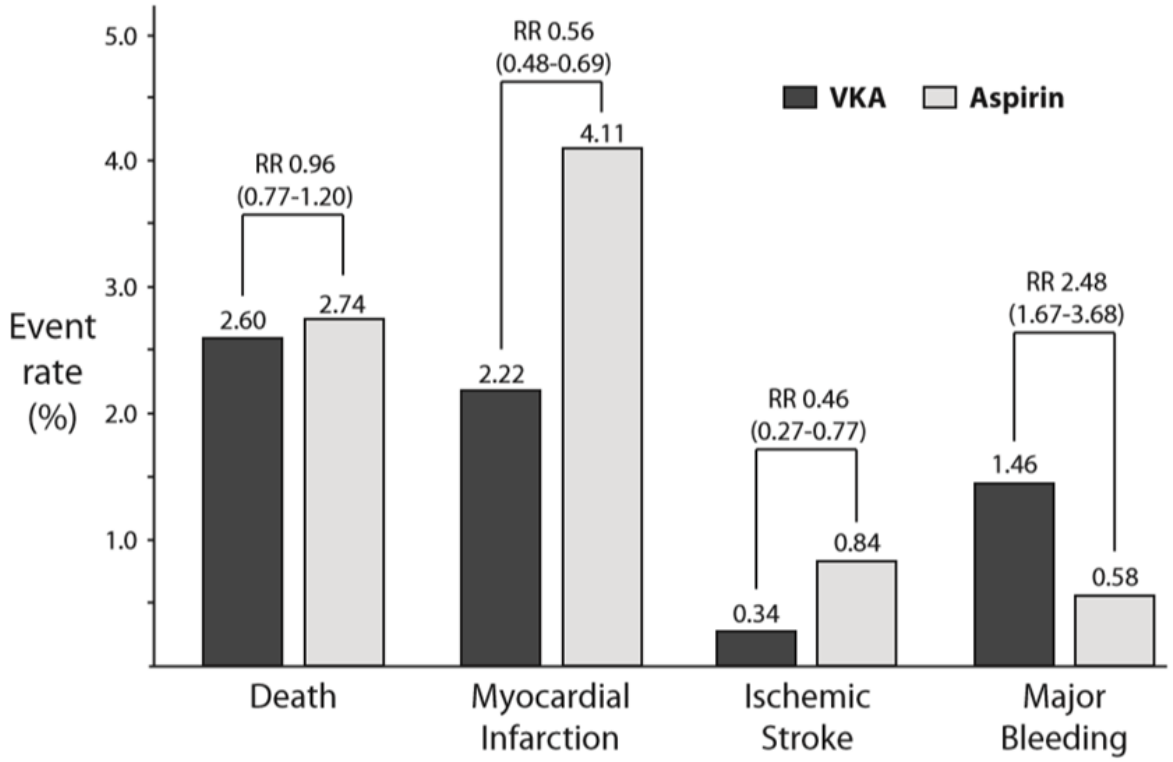
Thank You

	MACE			Bleeding		
Subgroup name	Aspirin	X+A	RRR	Aspirin	X+A	RRI
Full COMPASS population	5.4%	4.1%	24%	1.9%	3.1%	70%
CAD and PAD	8.4%	5.7%	33%	2.1%	3.0%	43%
Documented PAD	7.1%	4.9%	31%	1.3%	2.6%	42%
CAD + Heart Failure	7,9%	5,5%	22%	1.9%	2.6%	76%
CAD – Heart Failure	4.9%	3.8%	22%	1.9%	3.3%	76%
CAD + Moderate Renal Impairment	8.8%	6.5%	27%	2.9%	4.1%	41%
Prior MI + Moderate Renal Impairment	9.8%	6.6%	33%	2.6%	4.0%	54%
CAD - Moderate Renal Impairment	4.6%	3.5%	24%	1.6%	2.9%	80%
CAD + Diabetes	7.0%	5.1%	28%	2.0%	3.3%	65%
CAD - Diabetes	4.8%	3.6%	23%	1.9%	3.1%	67%
CAD + Prior Stroke	11.9%	6.8%	42%	1.1%	3.6%	224%

Which CAD Patient Should Prioritize for Anti-Thrombotic Therapy?

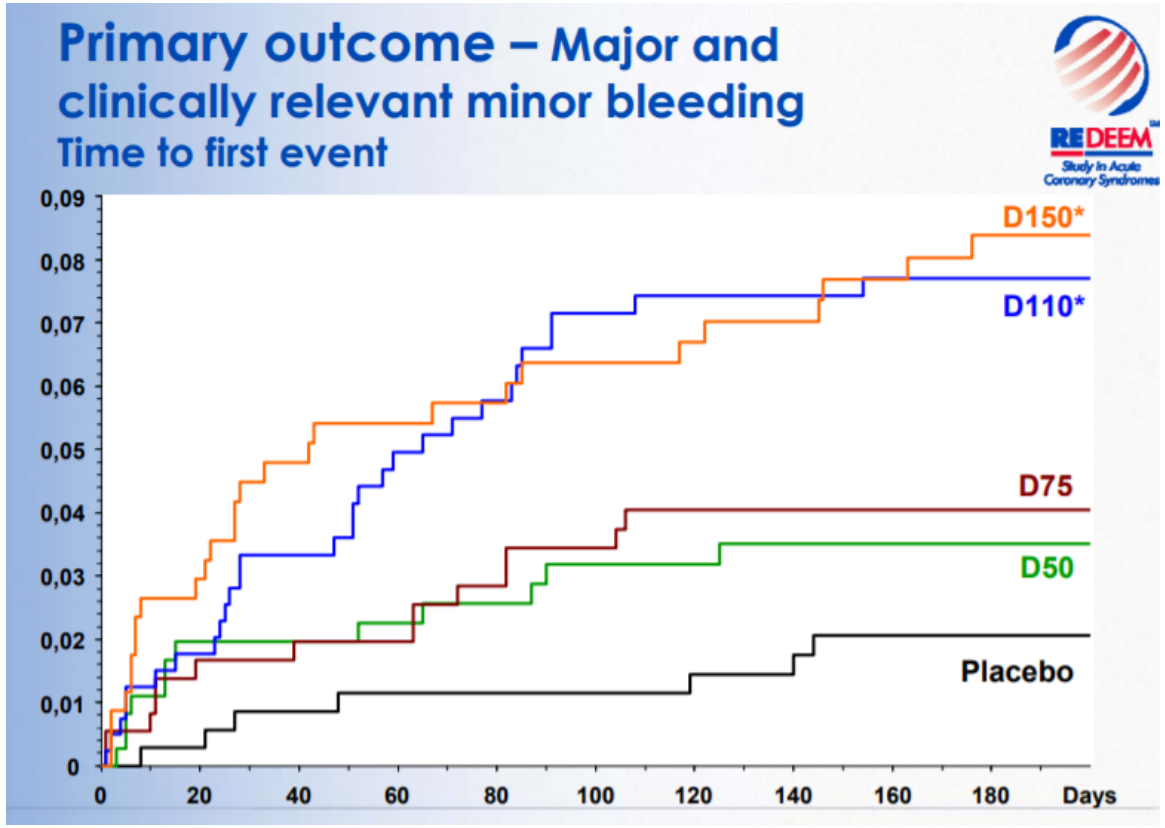
The Dual-Pathway Strategy

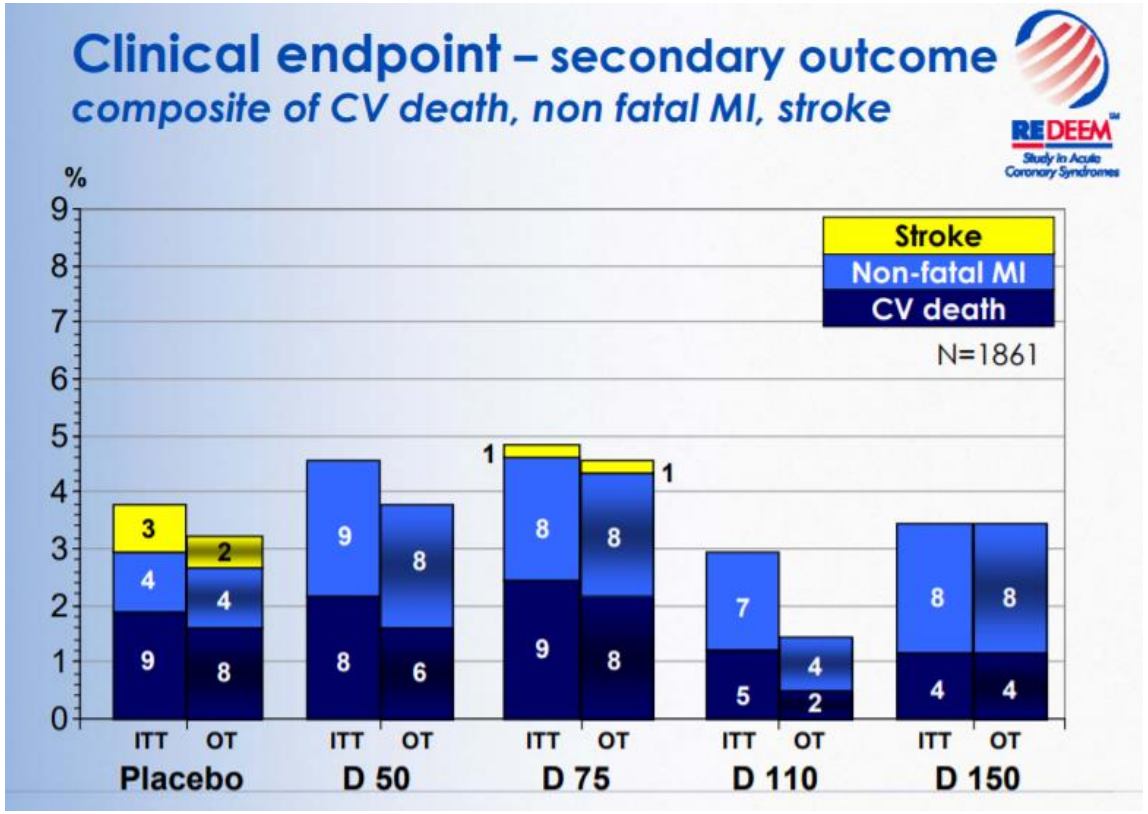
A meta-analysis of 10 trials including 5,938 ACS pts assessed the risk vs. benefit of warfarin (INR > 2) plus aspirin vs. aspirin alone



Rothberg MB et al Ann Intern Med 2005; 143: 241–250

The Dual-Pathway Strategy: Reinventing the Wheel





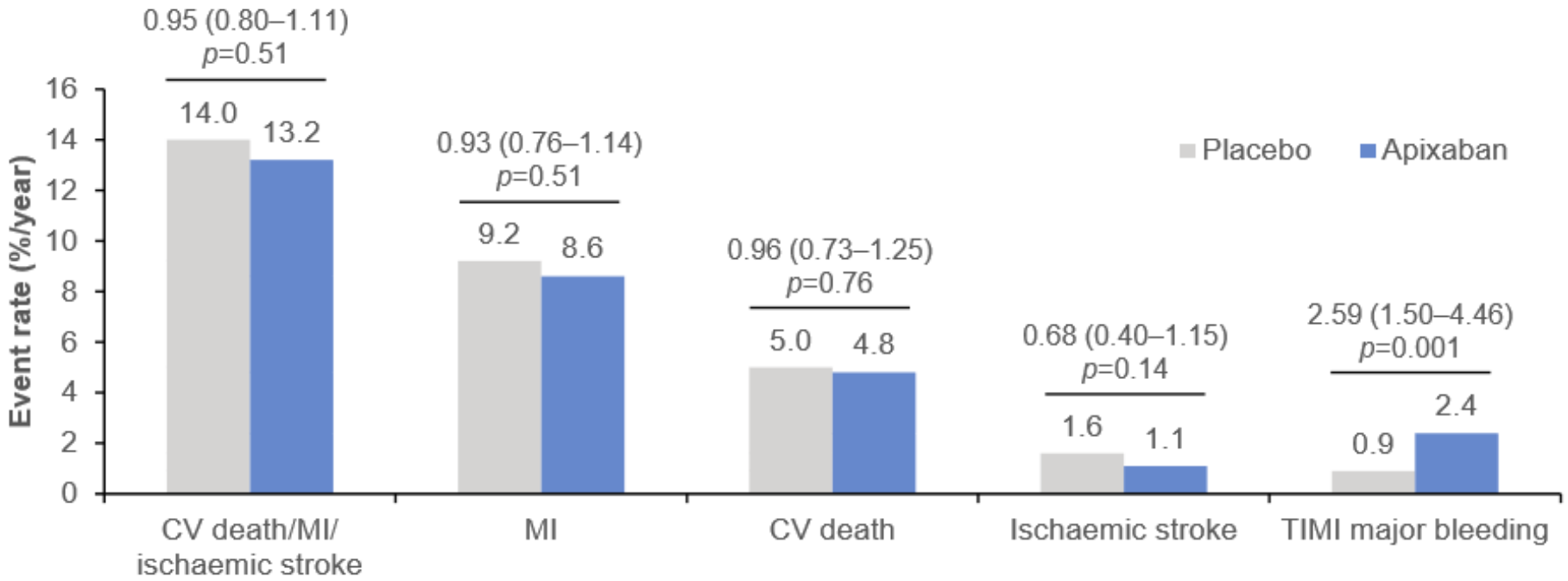
* The study was underpowered to assess efficacy !!!!

Oldgren J. Et al. Eur Heart J 2011; 32: 2781–2789.

Addition of Apixaban to Standard Therapy after ACS Increases Bleeding Without Reducing CV Events in High-Risk Patients

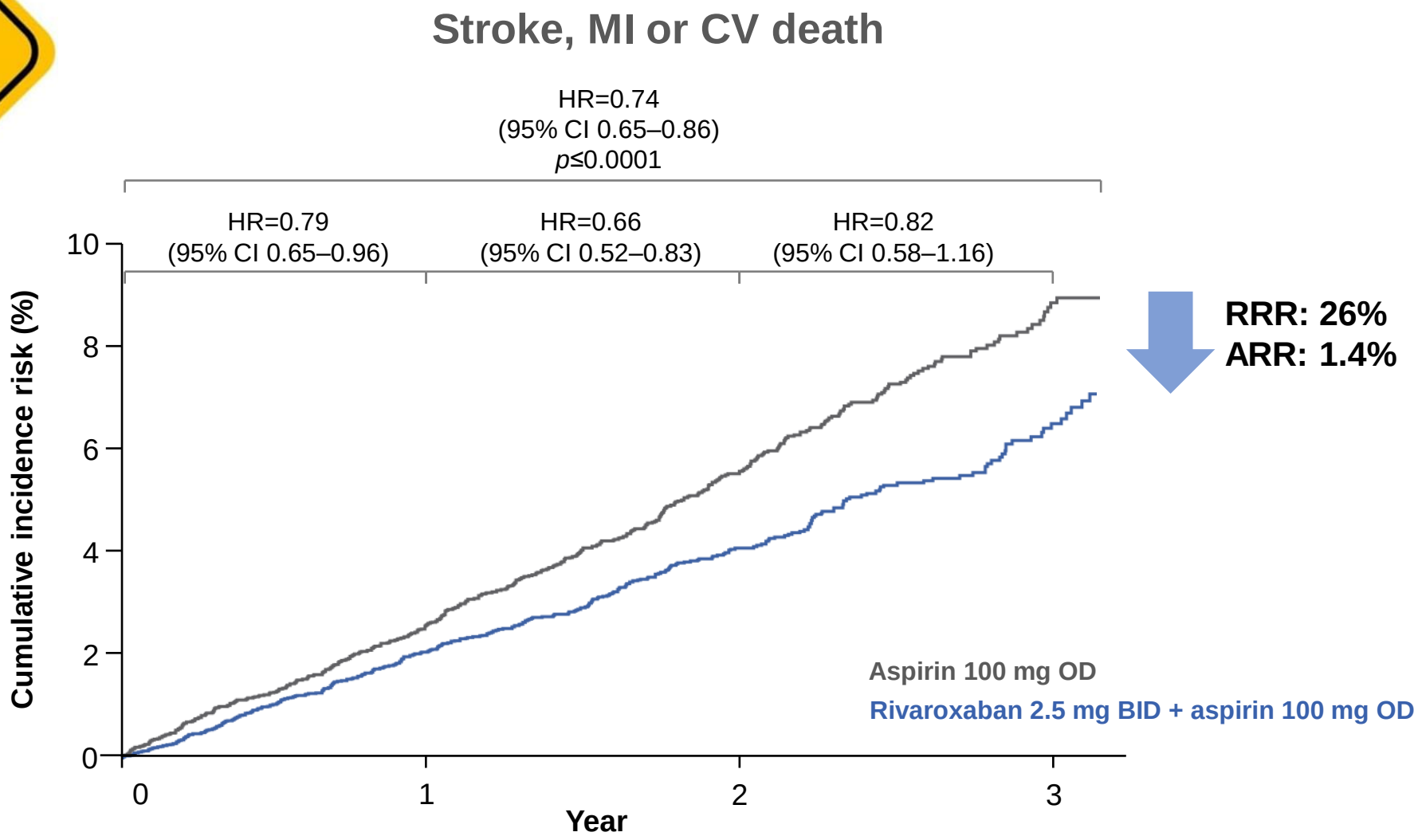
APPRAISE 2: apixaban (5 mg bid) + SoC* versus placebo + SoC*

- 7392 patients with recent ACS and ≥2 risk factors for ischaemic events#
  - Trial terminated prematurely (median follow-up 241 days) because of an increase in major bleeding events with apixaban, without a reduction in ischaemic events



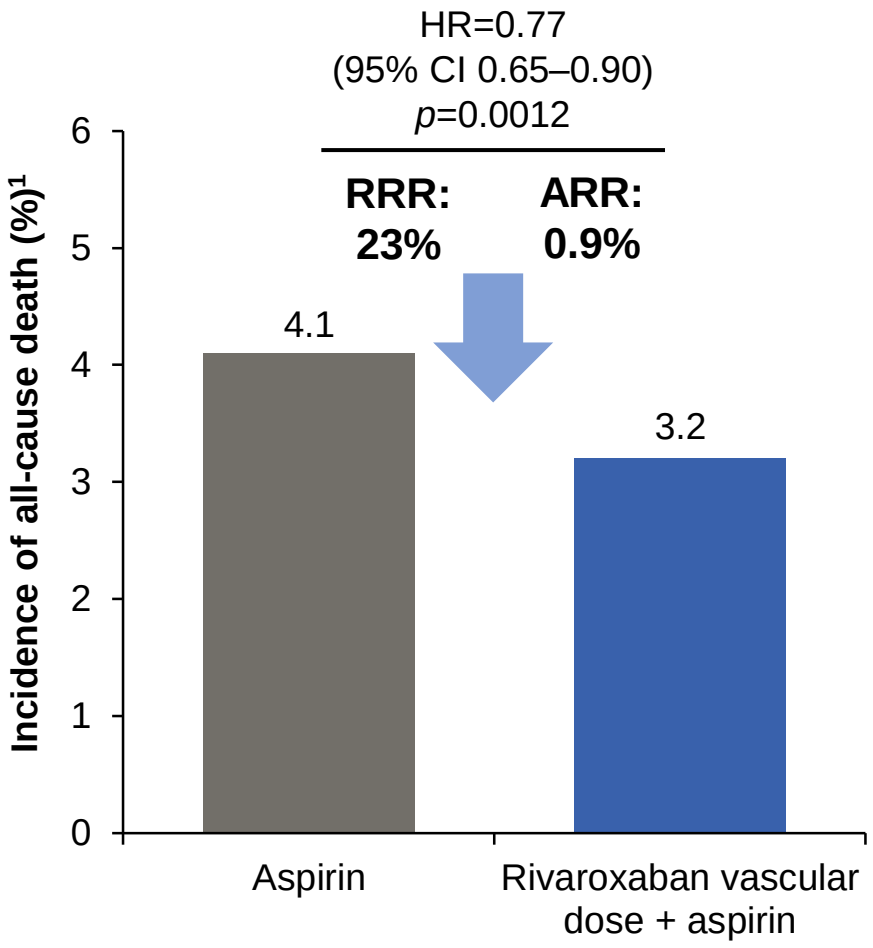
Alexander et al N Engl J Med 2011; 365(8): 699−70

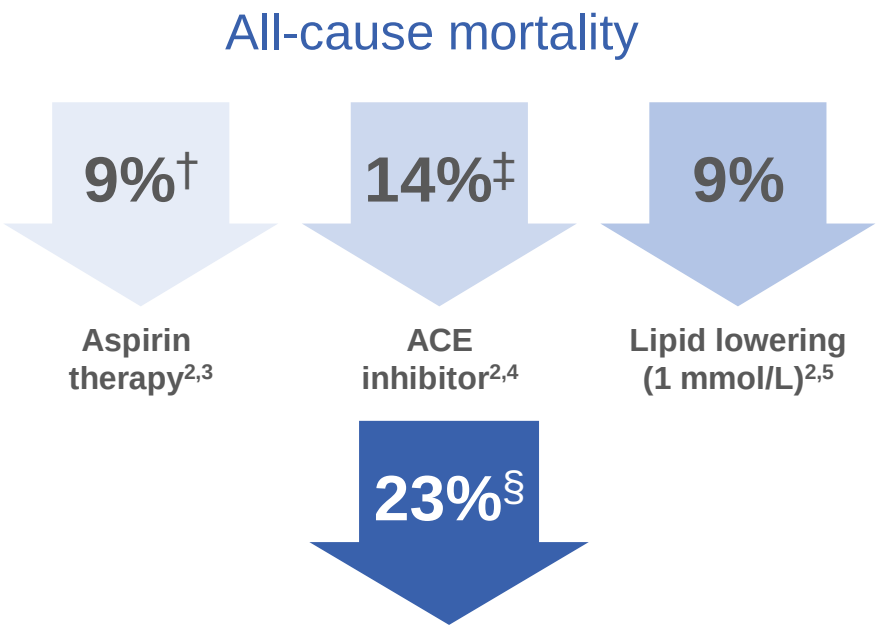
COMPASS Demonstrated a Significant Reduction in MACE with Dual Pathway Inhibition in Patients with Chronic CAD



Connolly SJ et al. *Lancet* 2018;391:205–218.

COMPASS Is the First Antithrombotic in a Chronic CAD Population to Show a Mortality Benefit





1. Connolly SJ et al. *Lancet* 2018;391:205–218; 2. Fox KAA et al. *Eur Heart J* 2018; doi:10.1093/eurheartj/ehy347; 3. ATT Collaboration. *Lancet* 2009; 373:1849–1860; 4. Dagenais GR et al. *Lancet* 2006;368:581–588; 5. CTT Collaboration. *Lancet* 2015;385:1397–1405.

COMPASS Study Included Only Non-low Risk CAD Patients