APPROCCIO ANTITROMBOTICO SINERGICO NEL PAZIENTE CON SINDROME CORONARICA CRONICA

Le soluzioni

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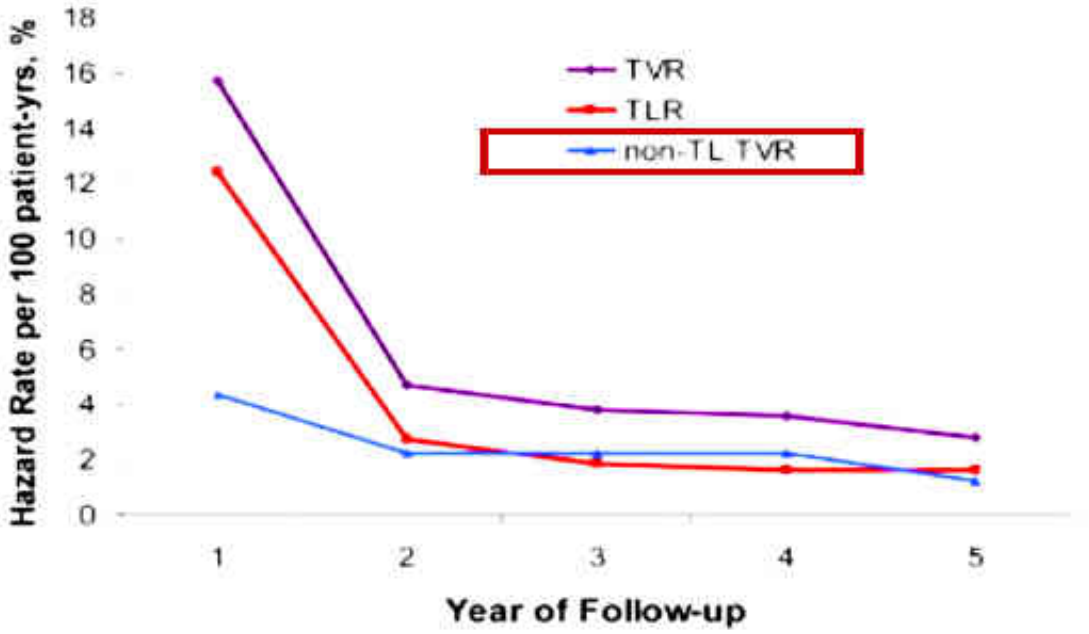
Conflicts of interest

Payment as an individual for consulting fee or honorarium from:

- Astra Zeneca
- Bayer
- Boehringer-Ingelheim
- Chiesi
- Daiichi Sankyo
- Novartis
- Pfizer

Late clinical events after DES:
The interplay between stent-related and natural history-driven events



Late events are similarly related to disease progression as to stent-related factors

2019 CCS ESC GLs strongly recommend long term DAPT

Recommendations foe event prevention I

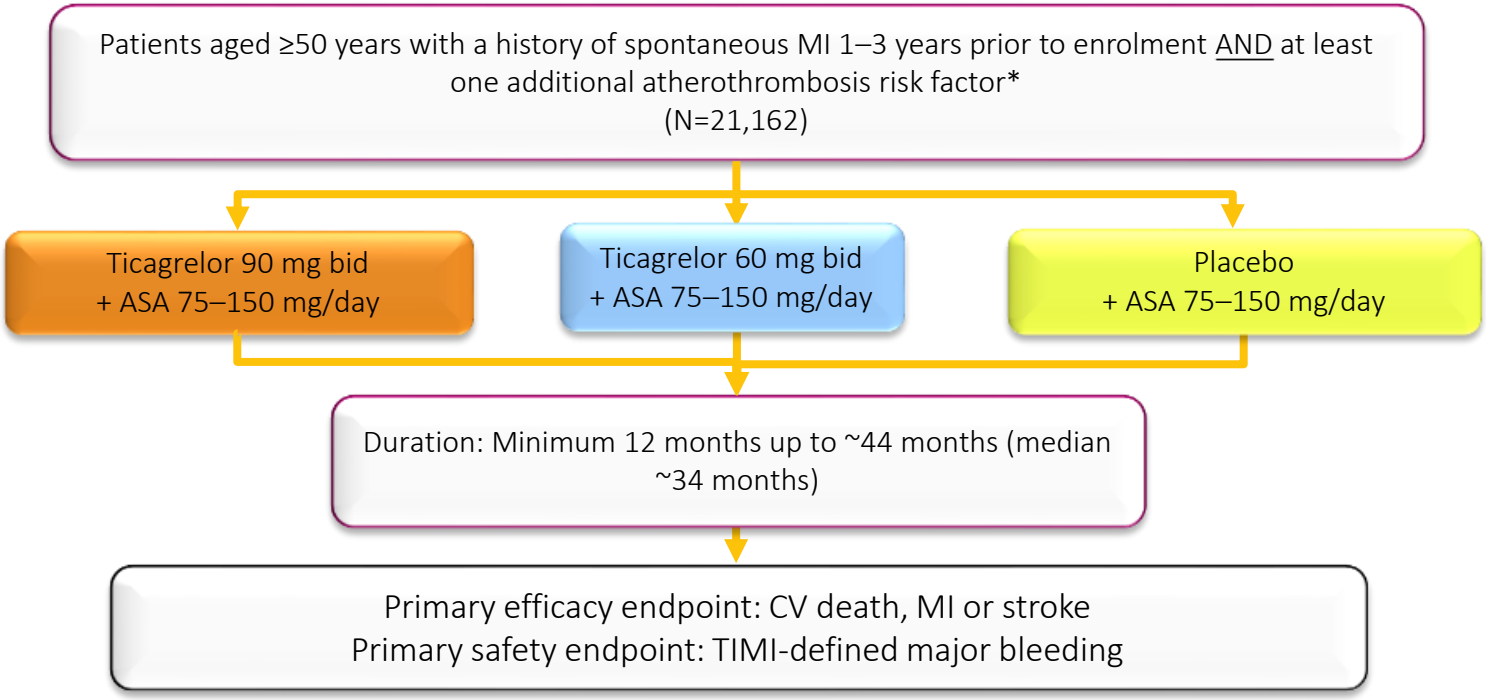
Recommendations	Class[a]	Level[b]
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.[270]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.[273]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack.[273]	IIb	B
Aspirin 75–100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIa	A
Adding 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[e] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIb	A

[c]Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15–59 mL/min/1.73 m^2.
[d]Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.
[e]At least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15–59 mL/min/1.73 m^2.

Juhani Knuuti et al. Eur Heart J European Heart Journal (2019) 00, doi:10.1093/eurheartj/ehz425

LONG-TERM DAPT: PEGASUS-TIMI 54 Trial

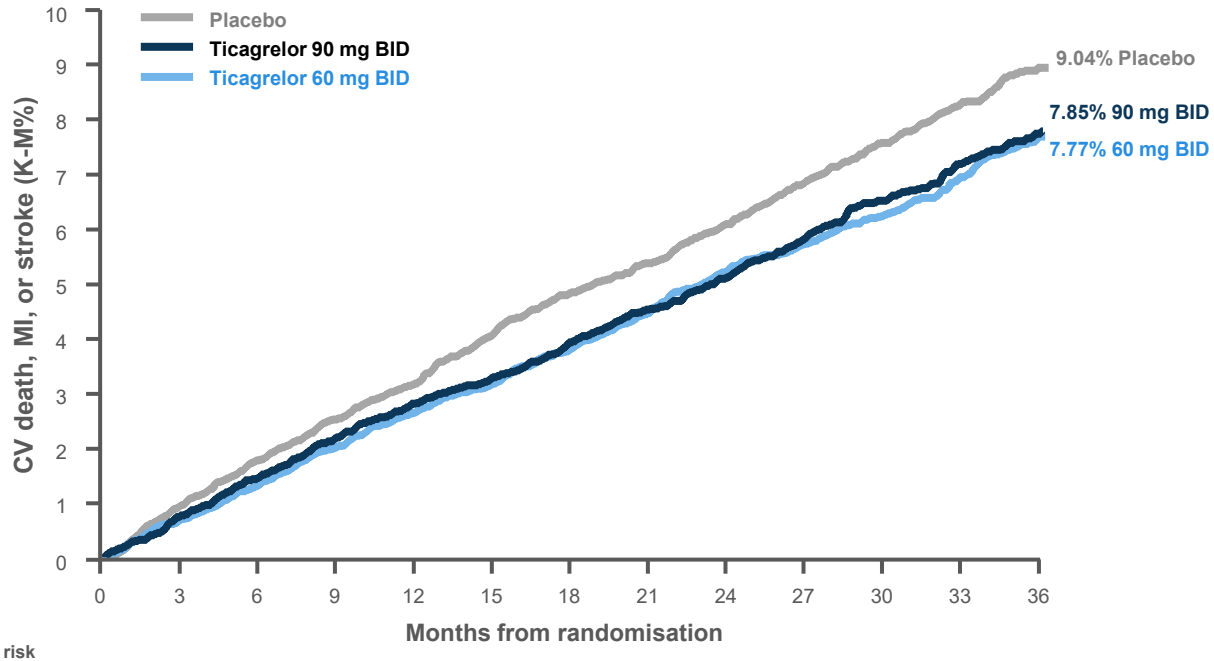
* Age ≥65
DM
CKD
Prior > 1 MI
MVD



*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease
bid, twice daily; CAD, coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction

Bonaca MP *et al. Am Heart J* 2014;167:437–444
Bonaca MP *et al. N Engl J Med* 2015 [Epub ahead of print]

PEGASUS-TIMI 54: Primary Efficacy Endpoint



Ticagrelor 90 mg BID vs placebo HR 0.85 (95% CI 0.75–0.96); p=0.008

Ticagrelor 60 mg BID vs placebo HR 0.84 (95% CI 0.74–0.95); p=0.004

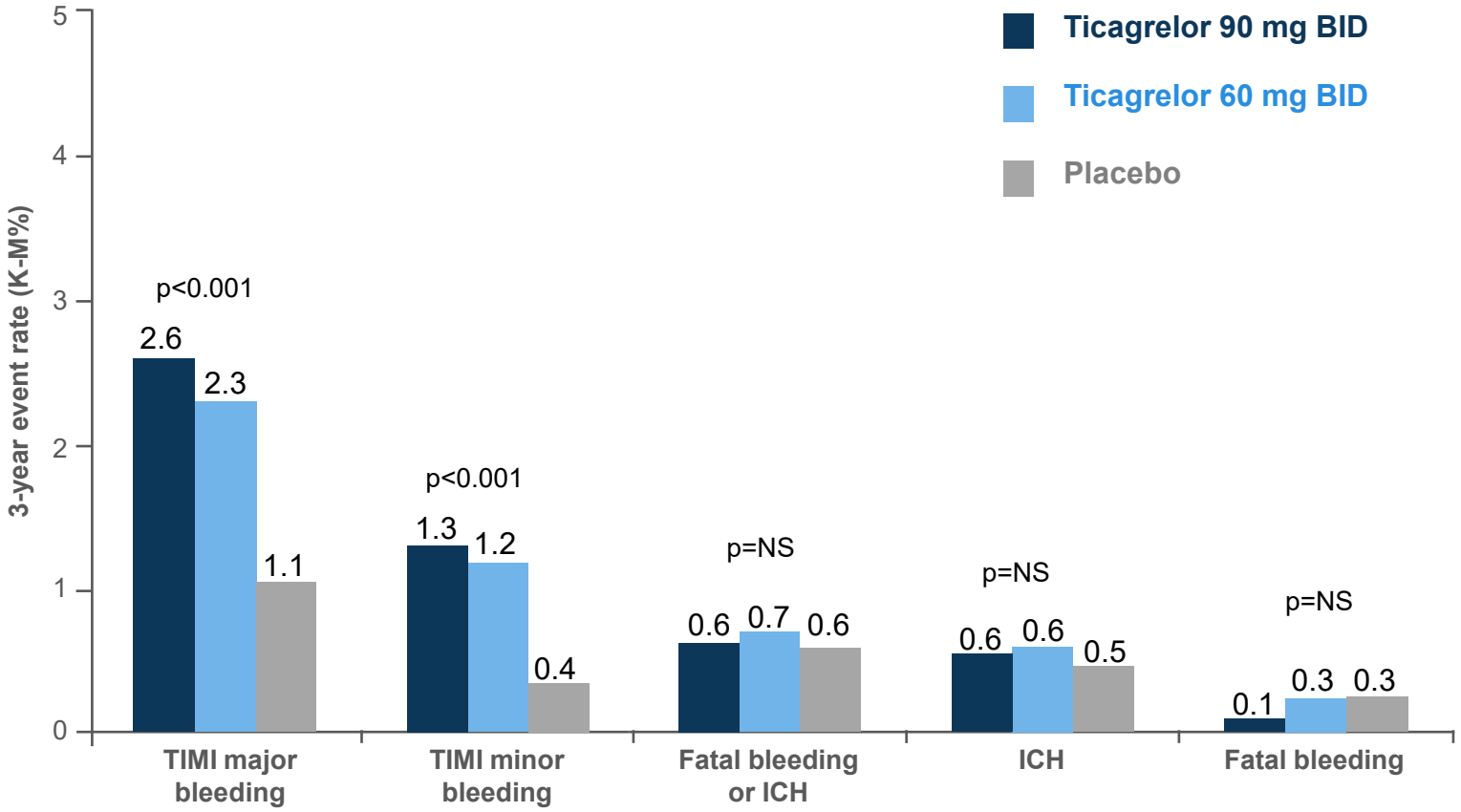
RRR 16%

P<0.026 indicates statistical significance.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

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

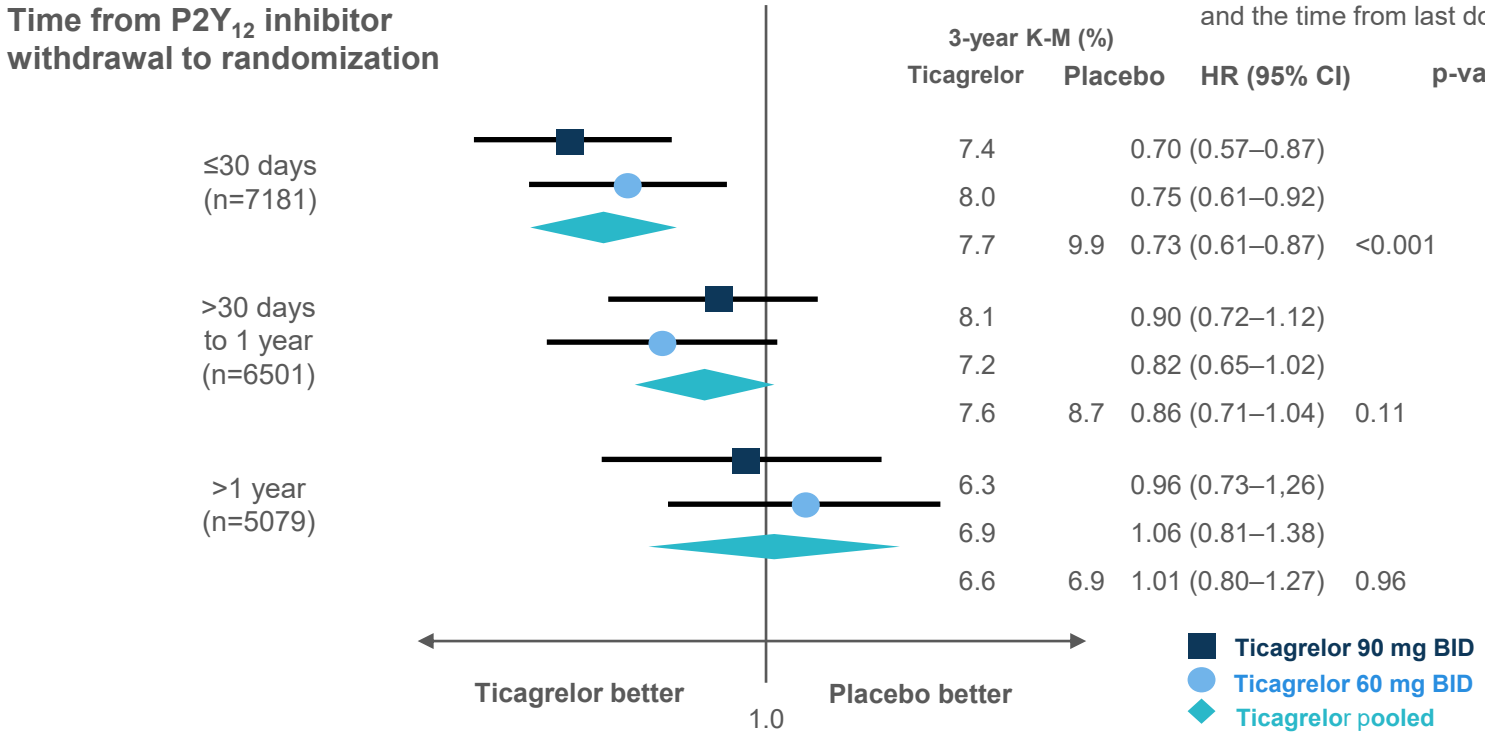
PEGASUS-TIMI 54: primary safety end point



p-values are for comparisons of each dose vs. placebo.
ICH = intracranial hemorrhage; TIMI = Thrombolysis in Myocardial Infarction.
Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54: Effect of Ticagrelor on the Composite of CV Death, MI or Stroke at 3 years by Time from $P2Y_{12}$ Withdrawal

p-trend for interaction <0.001 between the the effect of ticagrelor on the primary endpoint and the time from last dose of $P2Y_{12}$ inhibitor

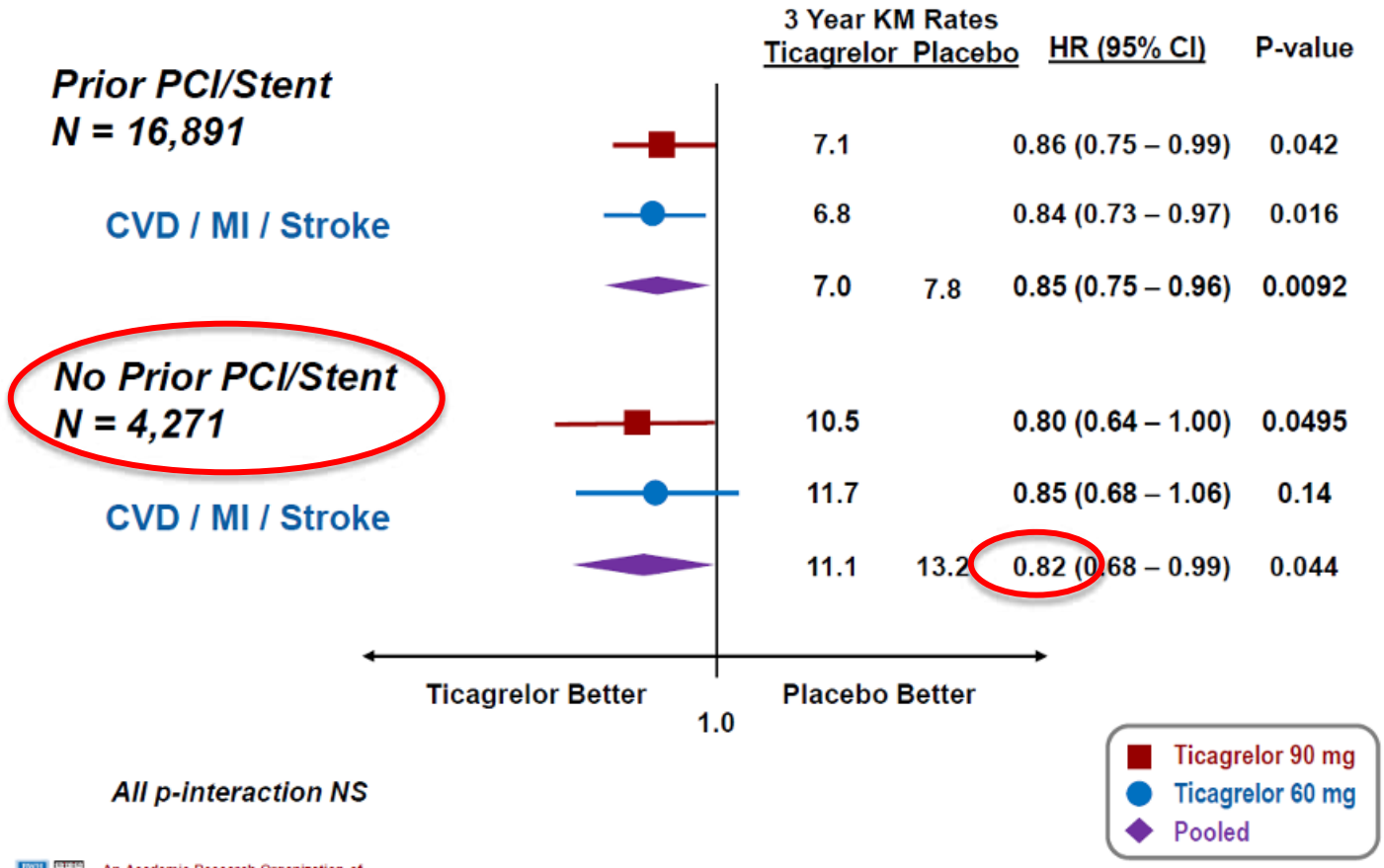


*Pre-specified exploratory subgroup analysis. Findings should be considered hypothesis generating.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

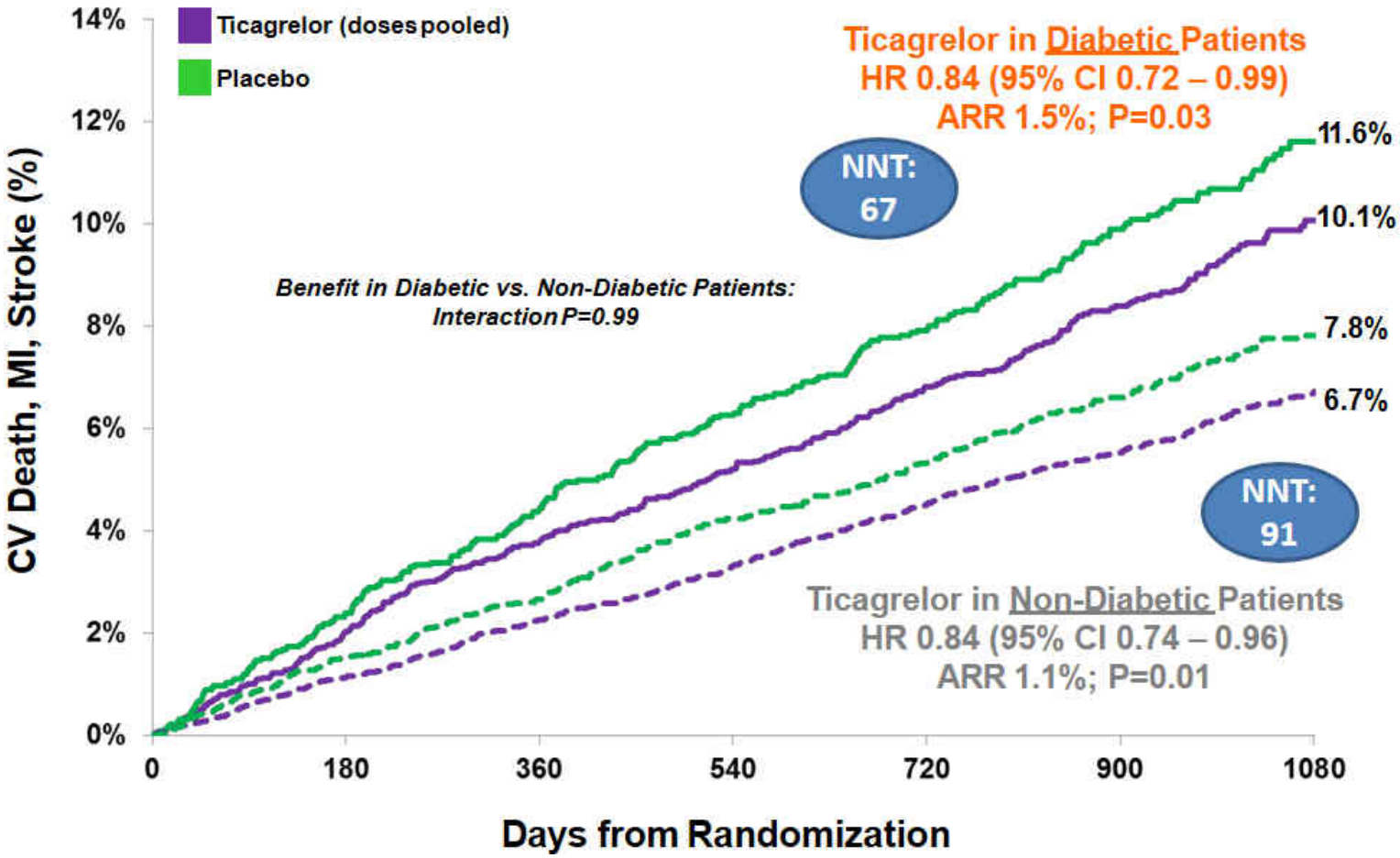
Bonaca MP et al. *Eur Heart J.* 2016;37:1133–1142.

MACE in Patients with & without Prior PCI/Stent



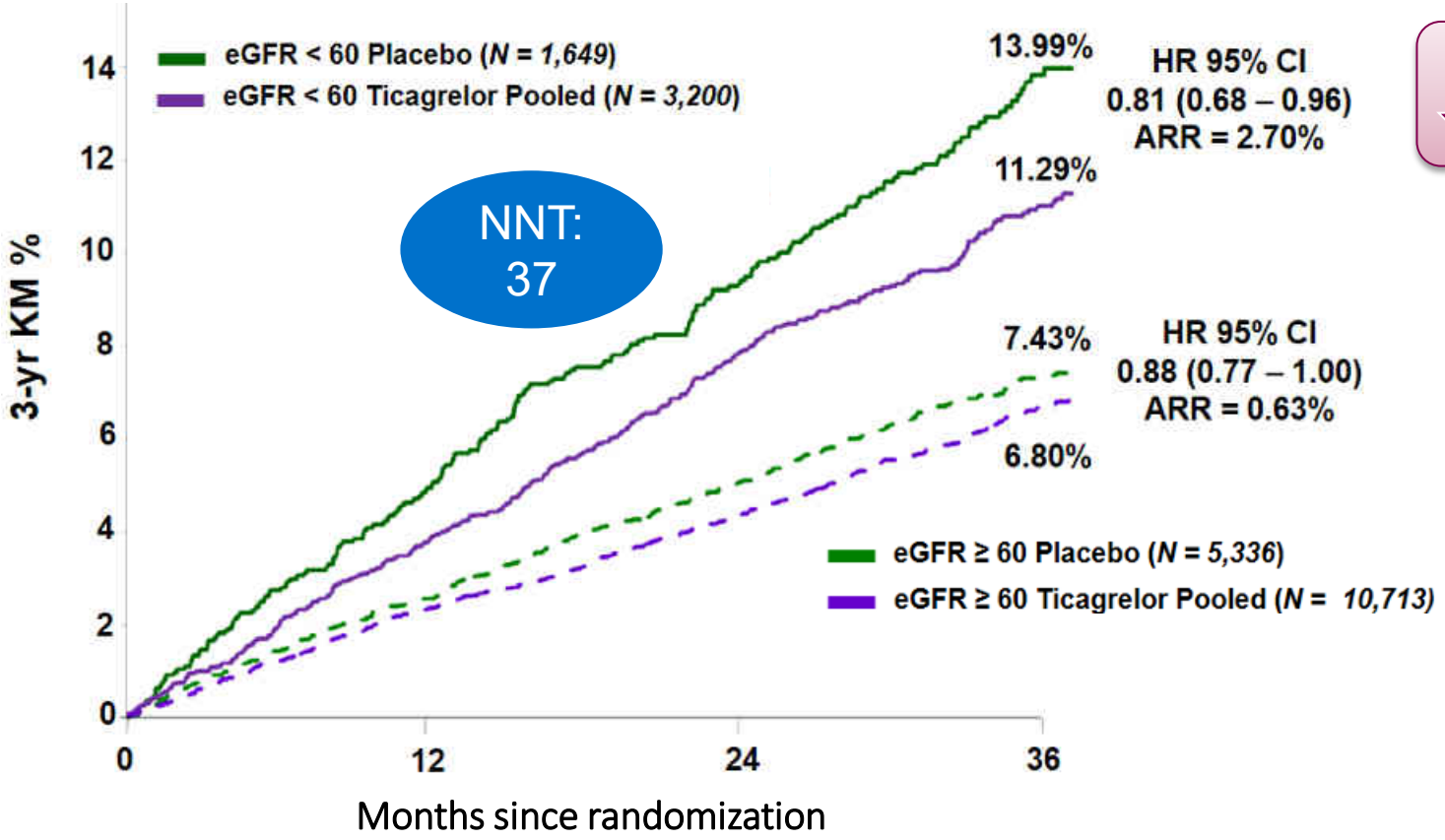
All p-interaction NS

MACE in DM patients



Bonaca MP,Bhatt DL, Cohen M, et al. Sabatine MS. NEJM.2015.

MACE in CKD patients

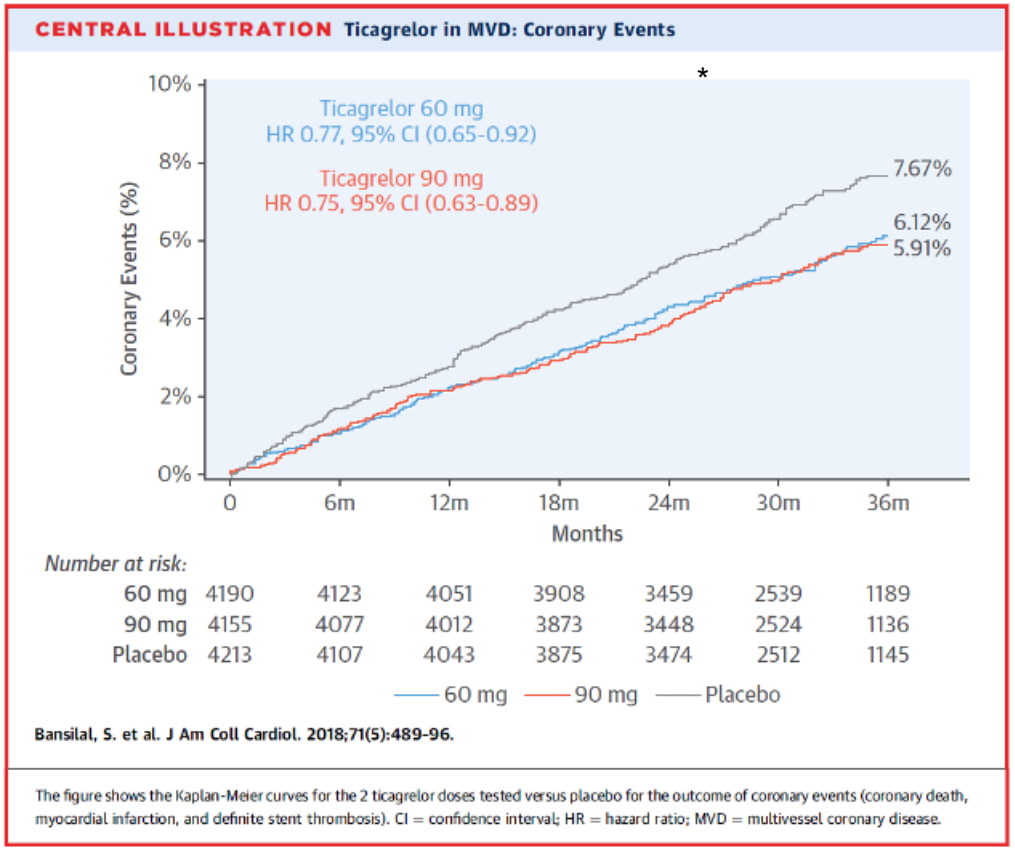


RRR 19%

Magnani et al, Eur. Heart J. 2016 Jan 21;37(4):400-8

In patients with prior MI and MVD

NNT:
58



CORONARY EVENTS

RRR 23%

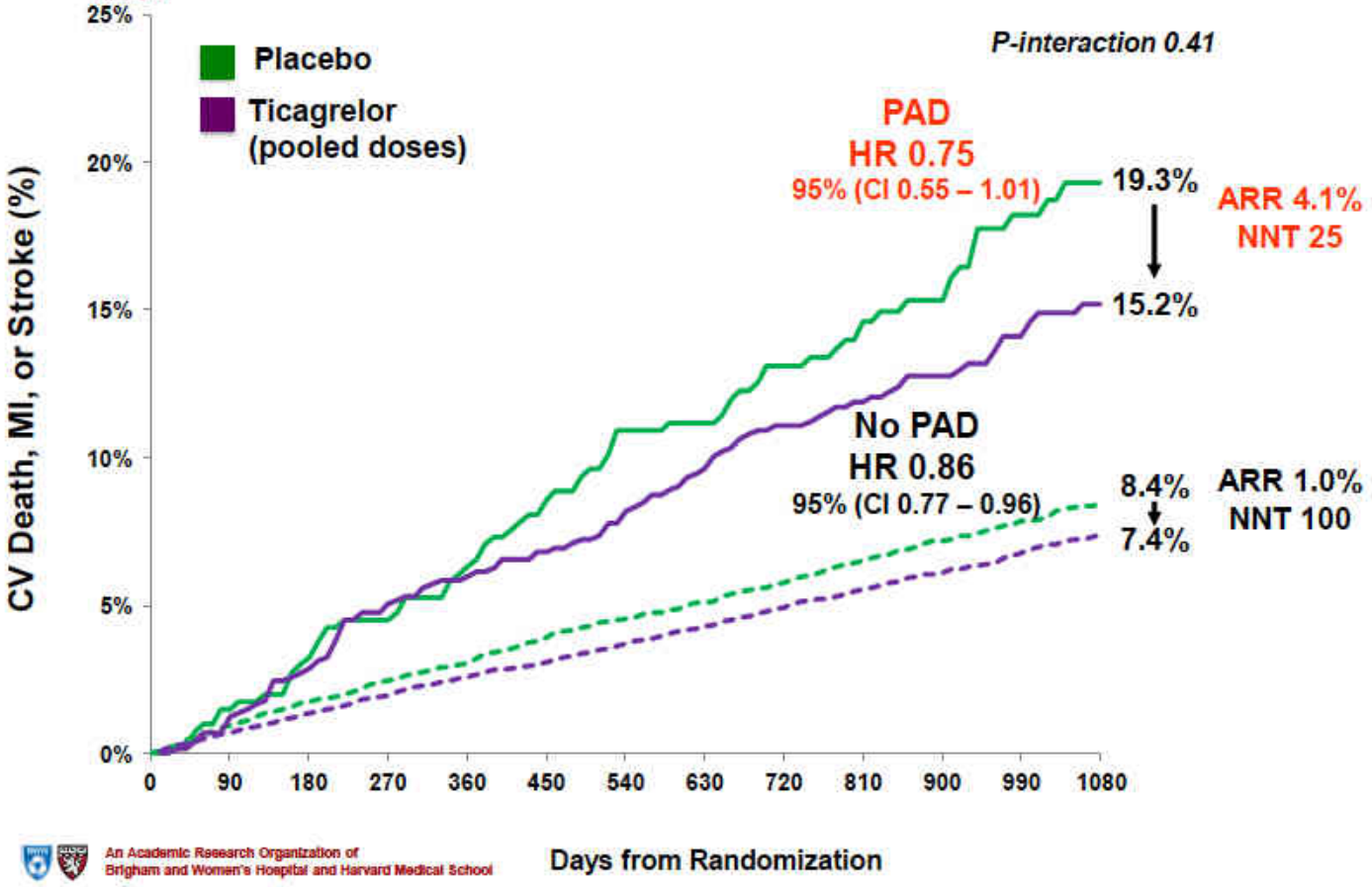
CARDIOVASCULAR MORTALITY

RRR 36%

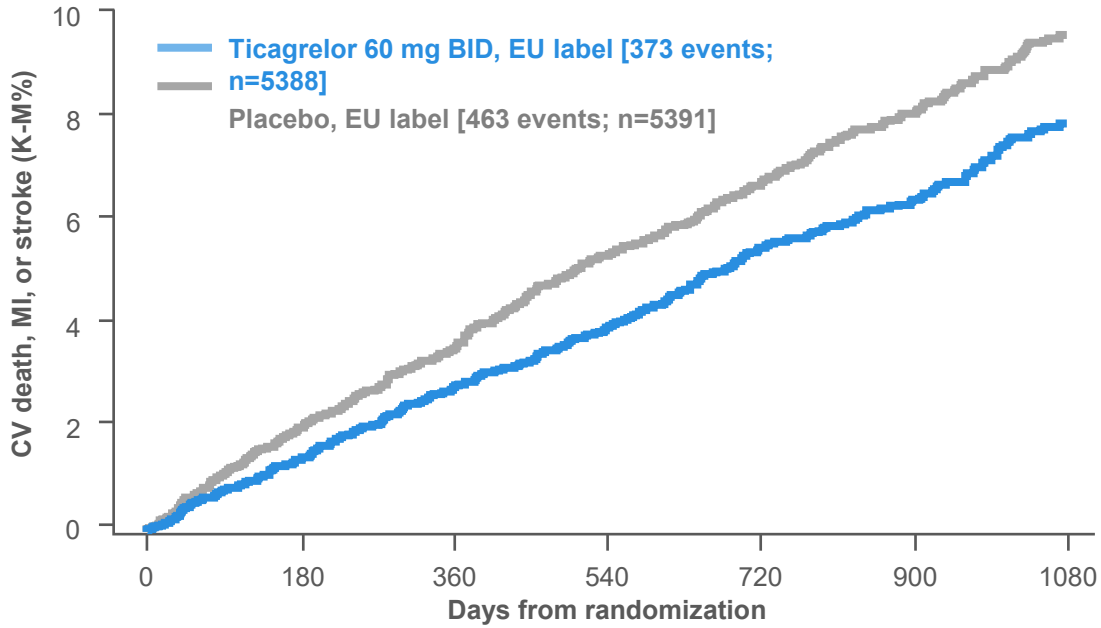
*CHD Death
MI
Def ST

Basillal S et al The American Journal of Cardiology Jan 2018

MACE with Ticagrelor by PAD at Baseline



PEGASUS-TIMI 54 EU Label Population: Primary Endpoint (CV Death, MI, Stroke) – Patients ≤2 Years from Qualifying MI or ≤1 Year from Prior ADP Receptor Inhibitor Treatment (Efficacy Cohort)



Number at risk:							
Placebo, EU	5391	5246	5138	4914	4380	3177	1485
Ticagrelor 60 mg BID, EU	5388	5280	5187	4999	4436	3253	1507

75% of PEGASUS population

The EU label subgroup includes patients with ≤2 years from qualifying MI or ≤1 year from last dose of prior ADP receptor inhibitor treatment to randomization

ADP = adenosine diphosphate; CV = cardiovascular; MI = myocardial infarction; Kaplan-Meier; TIMI = Thrombolysis in Myocardial Infarction.

Dellborg M *et al. Eur Heart J.* 2017;38(suppl):794–795. Abs P3670 (Presented at ESC 2017).

PEGASUS-TIMI 54 subanalysis EU label population:

Primary and secondary outcomes – patients with ≤2 years from qualifying MI or ≤1 year from prior ADP receptor inhibitor treatment (efficacy cohort)

Outcome	Ticagrelor 60 mg bid N=5388		Placebo N=5391		Hazard ratio (95% CI)	*P* value	RRR
	n	3 year KM%	n	3 year KM%			
Composite of CV death, MI or stroke	373	7.9	463	9.6	0.80 (0.70–0.91)	0.001	20%
CV death	119	2.6	167	3.6	0.71 (0.56–0.90)	0.0041	29%
MI	230	4.8	274	5.6	0.83 (0.70–0.99)	0.041	
Stroke	71	1.5	95	2.0	0.74 (0.55–1.01)	0.058	
All-cause mortality	206	4.4	256	5.4	0.80 (0.67–0.96)	0.018	20%

NNT: 45

PEGASUS-TIMI 54 EU label population:

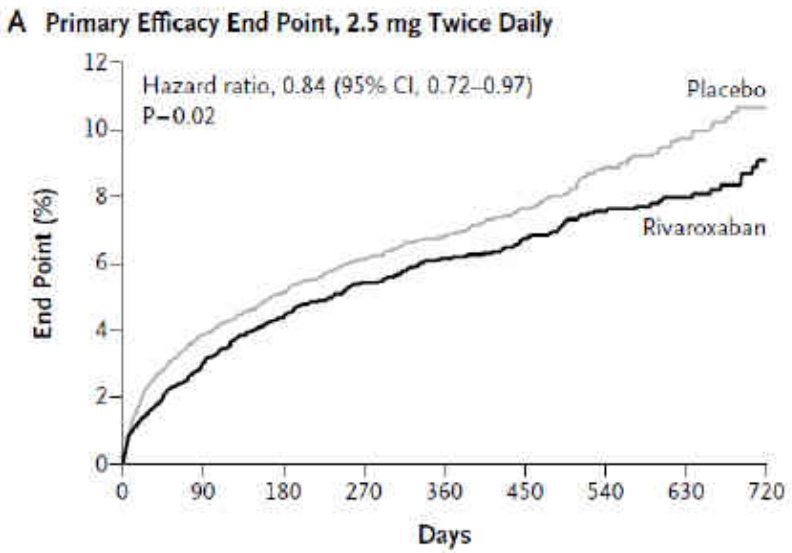
Major bleeding events – patients with ≤2 years from qualifying MI or ≤1 year from prior ADP receptor inhibitor treatment (safety cohort)

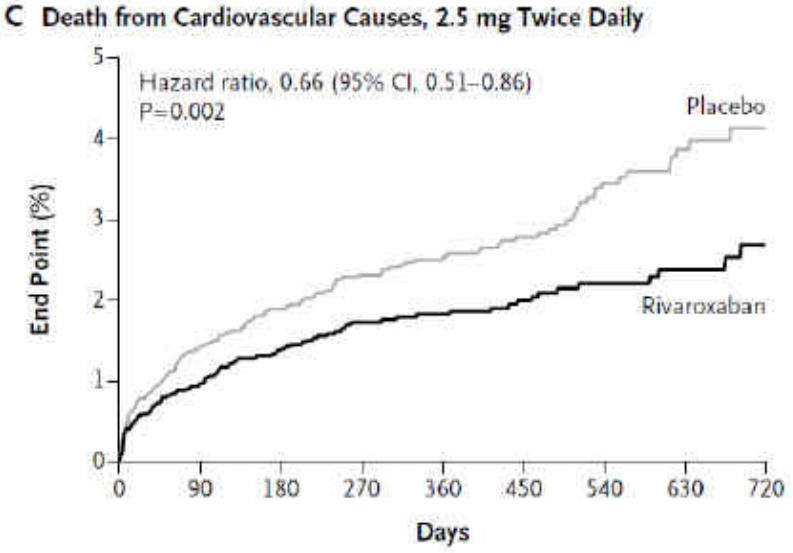
Outcome	Ticagrelor 60 mg bid N=5322		Placebo N=5331		Hazard ratio (95% CI)	*P* value
	n	3 year KM%	n	3 year KM%		
TIMI major bleeding	94	2.5	43	1.1	2.36 (1.65–3.39)	<0.0001
Fatal or intracranial bleeding	27	0.8	25	0.7	1.17 (0.68–2.01)	0.58

Rationale for evaluation of an anticoagulant

COMPASS

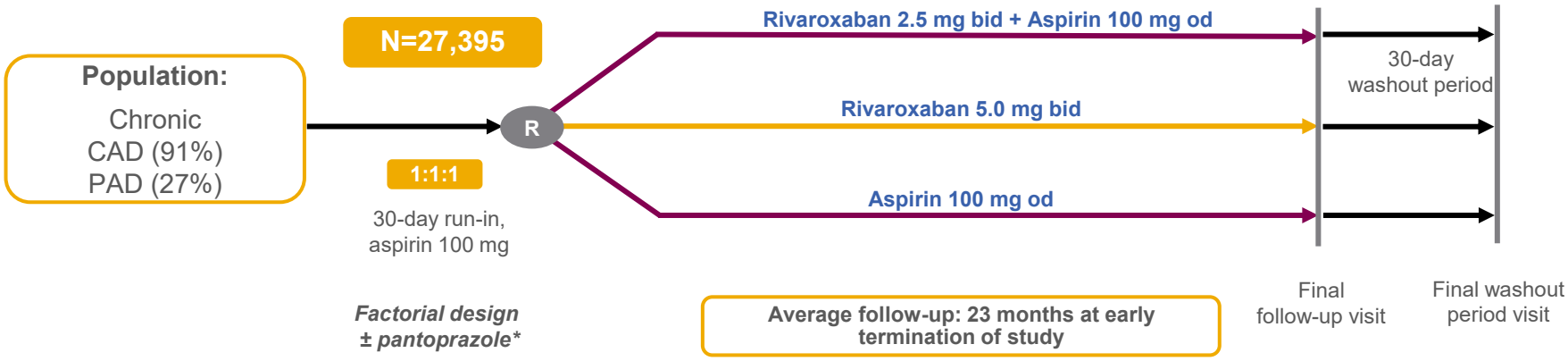
- Warfarin with or without aspirin is more effective than aspirin but increases bleeding, including intracranial hemorrhage HR 0.79 vs 2.1
- Rivaroxaban is safer than warfarin and reduces mortality in patients with recent acute coronary syndrome (ATLAS ACS-2 TIMI 51)





COMPASS Trial

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



*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design);

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

Inclusion and Exclusion Criteria

Key inclusion criteria*

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

Key exclusion criteria‡

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

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

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

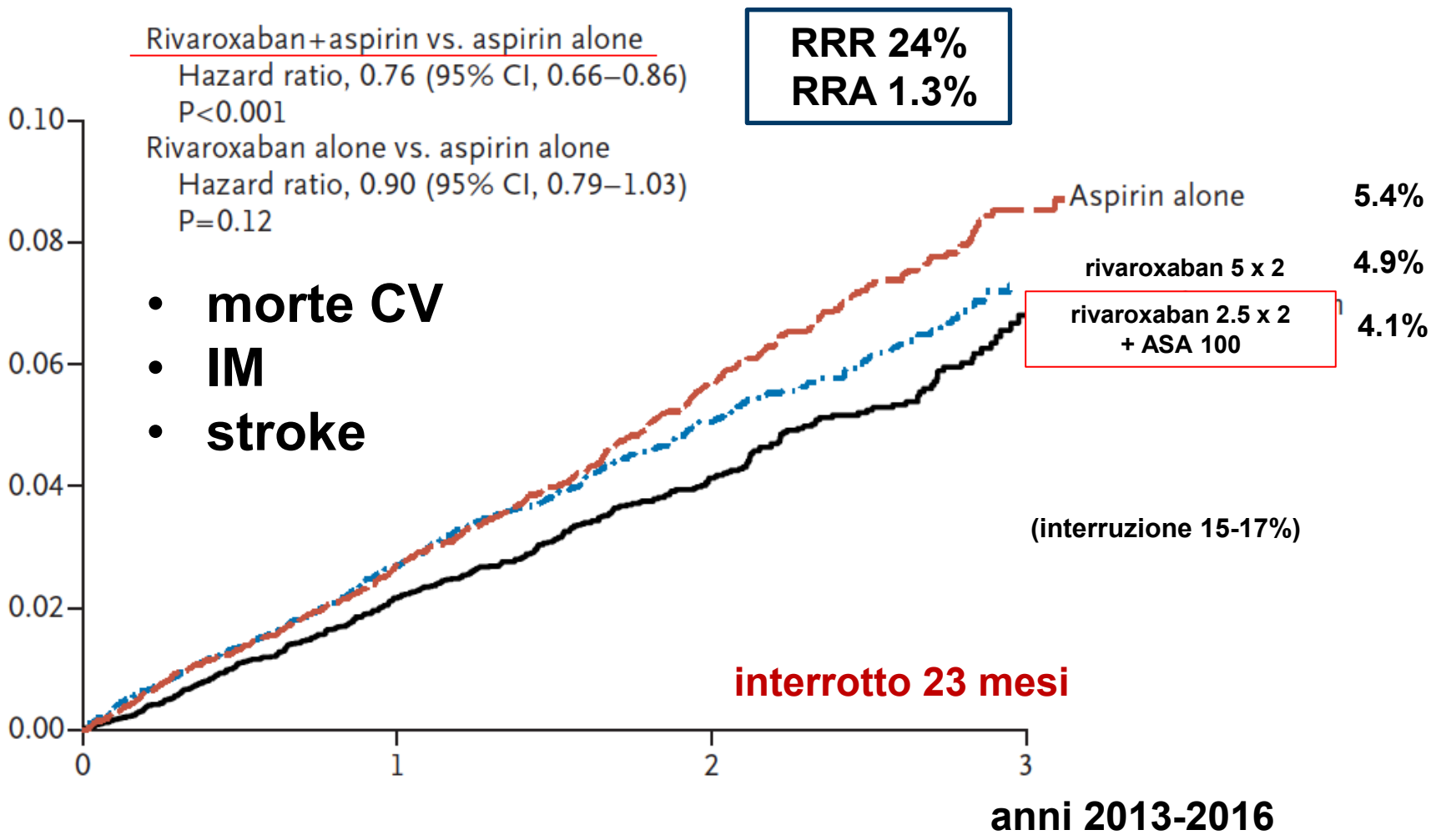
Baseline characteristics

COMPASS

	Rivaroxaban + aspirin N=9,152	Rivaroxaban N=9,117	Aspirin N=9,126
Age, yr*	68	68	68
Female	22%	22%	22%
SBP/DBP, mmHg*	136/77	136/78	136/78
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/ARB	71%	72%	71%

ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease



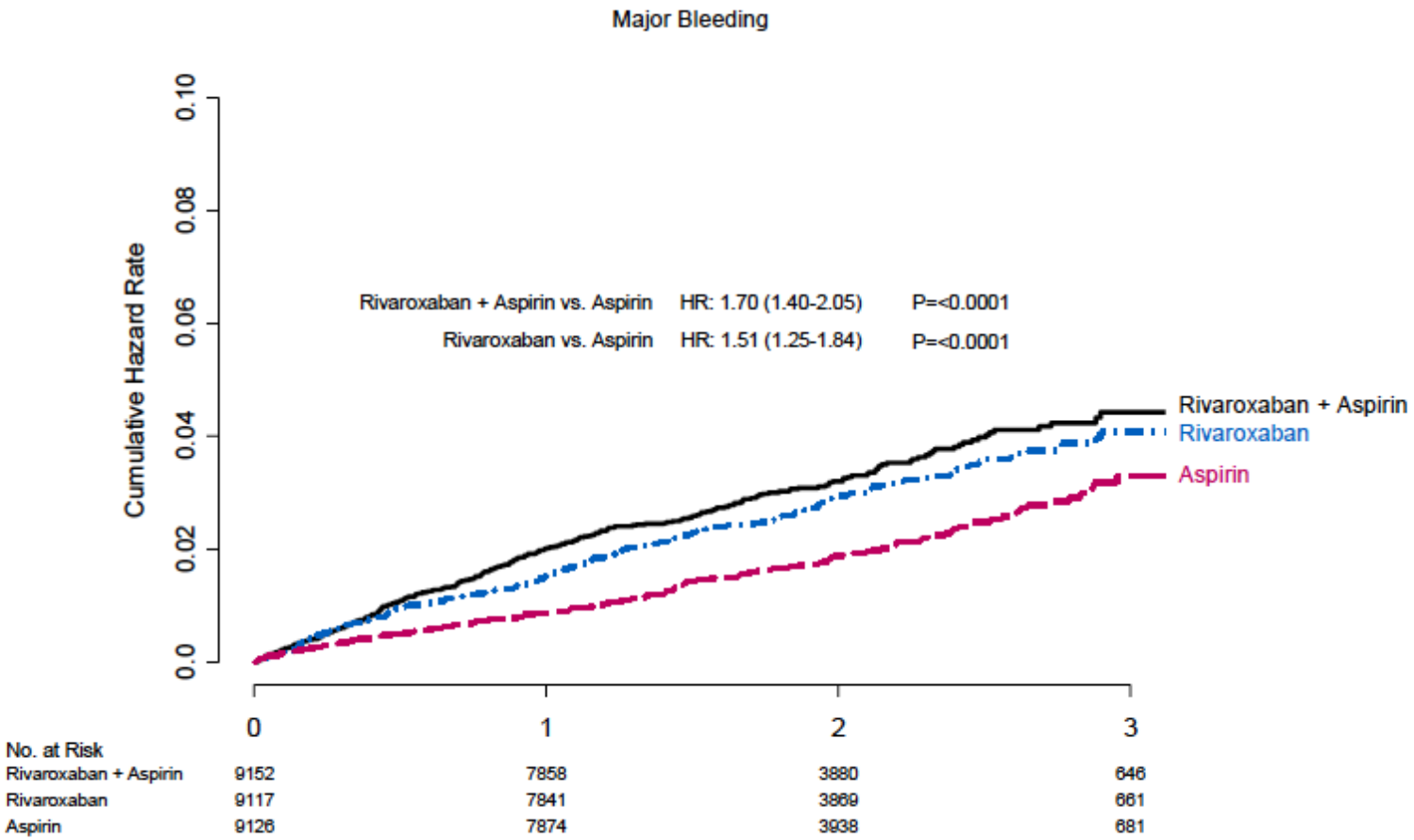
Eikelboom JW, Connolly SJ, Bosch J et al. N Engl J Med 2017

Components of primary outcome

COMPASS

	R + A N=9,152	Aspirin N=9,126	Riva + 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

Major Bleeding



Major bleeding components

Outcome	Riva + aspirin N=9,152		Aspirin N=9,126		Rivaroxaban + aspirin vs. aspirin		
	N	(%)	N	(%)	HR	(95% CI)	p
Major bleeding	288	3.1	170	1.9	1.70	1.40-2.05	<0.0001
Fatal	15	0.2	10	0.1	1.49	0.67-3.33	0.32
Non fatal ICH*	21	0.2	19	0.2	1.10	0.59-2.04	0.77
Non fatal other critical site*	42	0.5	29	0.3	1.43	0.89-2.29	0.14
Other	210	2.3	112	1.2	1.88	1.49-2.36	<0.0001

*symptomatic

Rivaroxaban + aspirin vs aspirin
Net benefit

COMPASS

Outcome	Riva + aspirin N=9,152		Aspirin N=9,126		Rivaroxaban + aspirin vs. aspirin		
	N	(%)	N	(%)	HR	(95% CI)	p
Primary + severe bleeds	426	4.7	529	5.8	0.80	0.70-0.91	0.0005

ARR -1,1%; RRR -20%

CARATTERISTICHE DEI PAZIENTI COMPASS-CAD

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

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

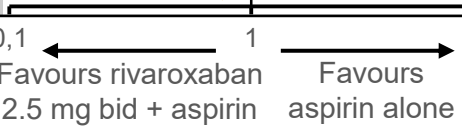
Connolly SJ, Eikelboom JW, Bosch J et al. Lancet 2018

BENEFICIO DI RIVAROXABAN ANCORA EVIDENTE IN PAZIENTI LONTANI DALLA FASE ACUTA

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

net clinical benefit (morte CV, IM, stroke, fatal bleeding o organo critico)

Subgroup	Rivaroxaban 2.5 mg bid + aspirin n/N (%)		Aspirin alone n/N (%)		HR (95% CI)	*p*-value
All participants	347/8313	(4)	460/8261	(6)	0.74 (0.65–0.86)	
History of MI						0.93
<2 years prior	49/1218	(4)	67/1205	(6)	0.70 (0.48–1.01)	
2–5 years prior	71/1612	(4)	91/1665	(5)	0.81 (0.59–1.10)	
≥5 years prior	127/2824	(4)	174/2849	(6)	0.72 (0.57–0.91)	
No MI prior	100/2661	(3.8)	128/2540	(5)	0.76 (0.58–0.98)	
History of PCI/PTCA						0.85
Yes	201/4971	(4)	270/4905	(6)	0.74 (0.61–0.88)	
No	146/3342	(4)	190/3356	(6)	0.76 (0.61–0.94)	
History of CABG						0.01
Yes	121/2232	(5)	117/2143	(5)	0.99 (0.77–1.28)	
No	226/6081	(4)	343/6119	(6)	0.66 (0.56–0.78)	
MI or PCI or CABG >2 years						0.71
Yes	78/2269	(3)	102/2141	(5)	0.71 (0.53–0.95)	
No	269/6044	(4)	358/6120	(6)	0.76 (0.65–0.89)	



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

COMPASS

COMPASS PAD

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 Chan, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators*

www.thelancet.com Published online November 10, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32409-1

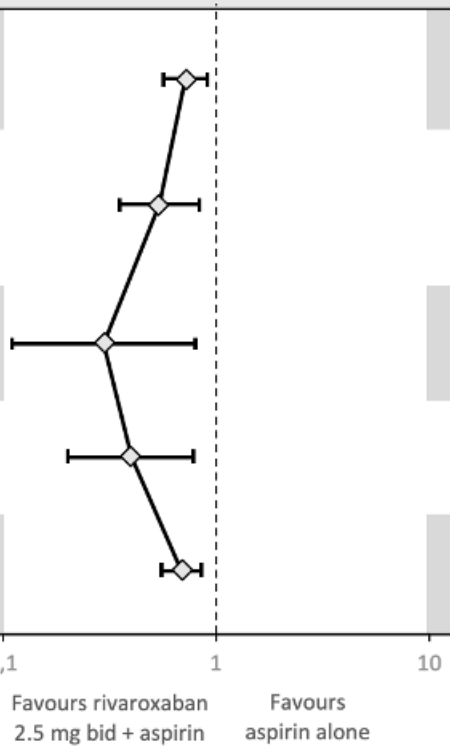
- Peripheral artery revascularization
- Limb or foot amputation for arterial vascular disease
- Intermittent claudication plus:
  - Low ABI (<0.90), or
  - Significant peripheral artery stenosis (≥50%)
- Previous carotid revascularization, asymptomatic carotid artery stenosis ≥50%
- CAD + low ABI (<0.90)

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

MENO DI UN TERZO DI AMPUTAZIONI MAGGIORI

Pre-specified PAD outcomes*	Riva 2.5 mg bid + aspirin n (%)	Aspirin n (%)	HR	p-value
CV death, stroke, MI (MACE: major adverse cardiac events)	126 (5.1)	174 (6.9)	0.72	0.0047
Acute limb ischaemia or chronic limb ischaemia (MALE: major adverse limb events)	30 (1.2)	56 (2.2)	0.54	0.0054
Major amputation	5 (0.2)	17 (0.7)	0.30	0.011
All vascular amputations	11 (0.4)	28 (1.1)	0.40	0.0069
MACE or MALE, or major amputation	157 (6.3)	225 (9.0)	0.69	0.0003

*Crude incidence over median follow-up of 21 months in 7,470 patients with PAD



RRR 28%

RRR 70%

Anand SS, Bosch J, Eikelboom JW et al. Lancet 2018

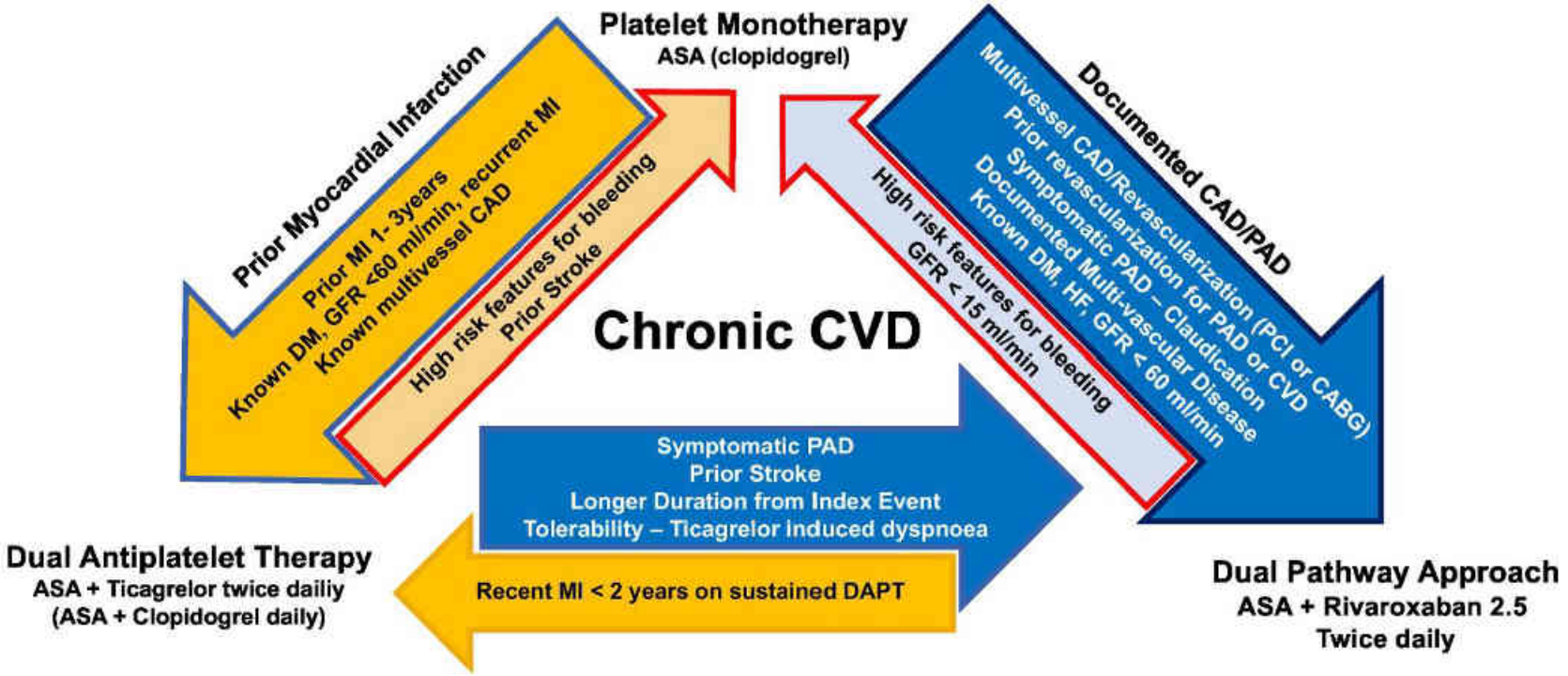
COMPASS PAD
Net clinical benefit in PAD

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
Net Clinical Benefit	169 (6.8)	207 (8.4)	234 (9.3)	0.72 (0.59-0.87)	0.0008	0.89 (0.74-1.07)	0.23

ARR -2,5%; RRR -28%

NNT 40

Different patients different pharmacological treatments



Welsh Rc et al : American Heart Journal (2019) http://doi.org/10.1016/j.ahj.2019.09.006

Conclusioni

La sindrome coronarica cronica rappresenta un continuum rispetto alla fase acuta e necessita di una costante attenzione per un rischio residuo elevato.

La terapia antitrombotica rappresenta una opportunità per ridurre il rischio ischemico residuo.

La PAD rappresenta un importante marker di rischio (anche se, per il cardiologo, non costituisce un target).

La scelta di un regime antitrombotico combinato va ponderata su ogni paziente in un’ottica di rapporto rischio-beneficio.