Prevention in Stable Post MI: Aspirin plus NOAC will be the standard of care

Roxana Mehran, MD
FACC, FAHA, MSCAI, FESC

Professor of Medicine, and Population Health Science and Policy
Icahn School of Medicine at Mount Sinai,
New York, NY, USA

Disclosure Statement of Financial Interest

- **Consulting Fees/Honoraria**: Abbot Vascular, American College of Cardiology, AstraZeneca, Medscape, Shanghai BraccoSine, Spectranetics

  Abiomed, The Medicines Company (spouse)

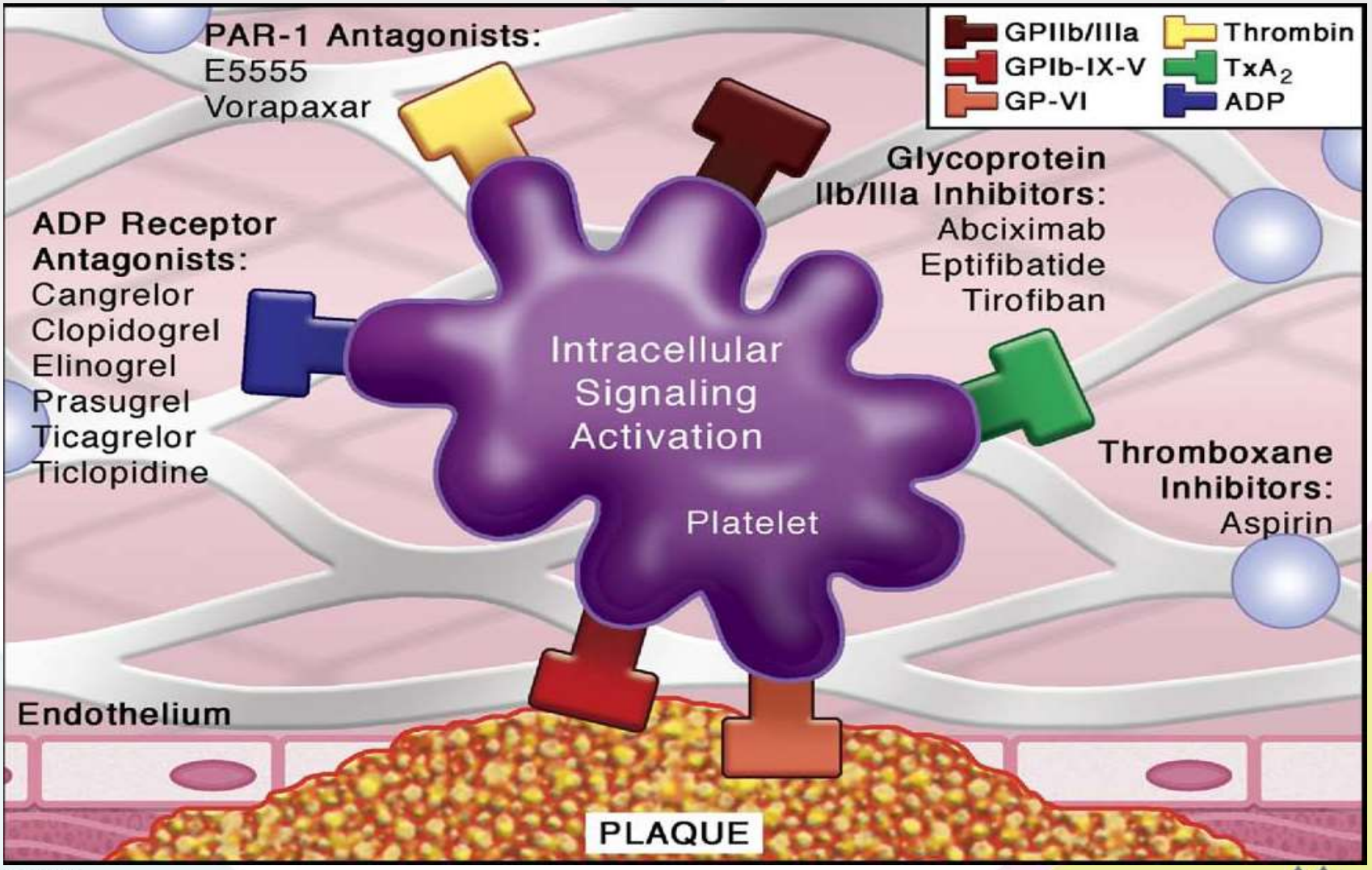
- **DSMB membership** paid to the institution: Watermark Research Partners

- **Executive Committee**: Janssen Pharmaceuticals

- **Grant/Reseach Support (Institutional):** AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers-Squibb, CSL, Behring, Diachi Sankyo, Medtronick, Novartis Pharmaceuticals, OrbusNeich

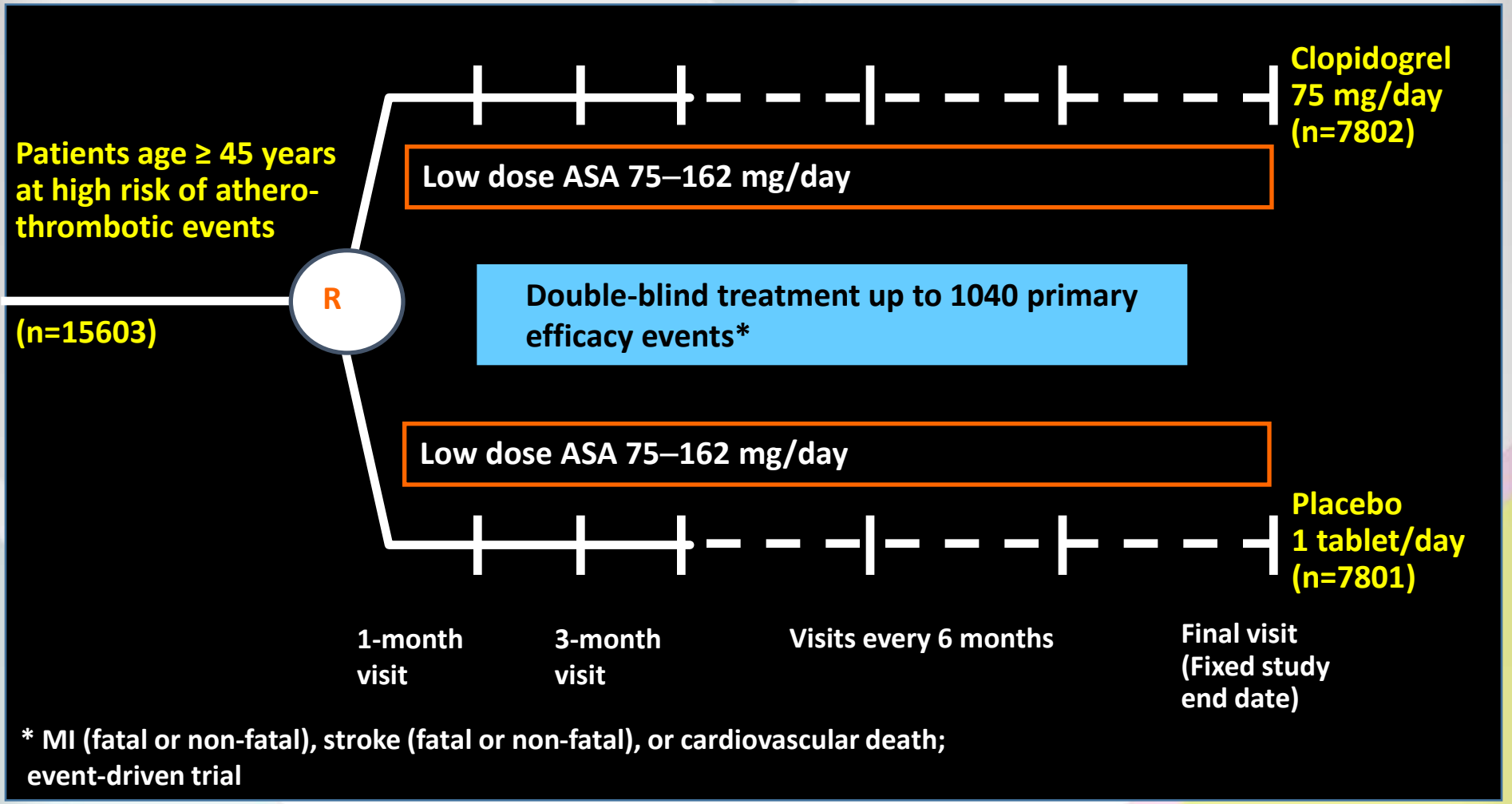
- **Speaker fees:** Lifescience Conference

Antiplatelet Agents



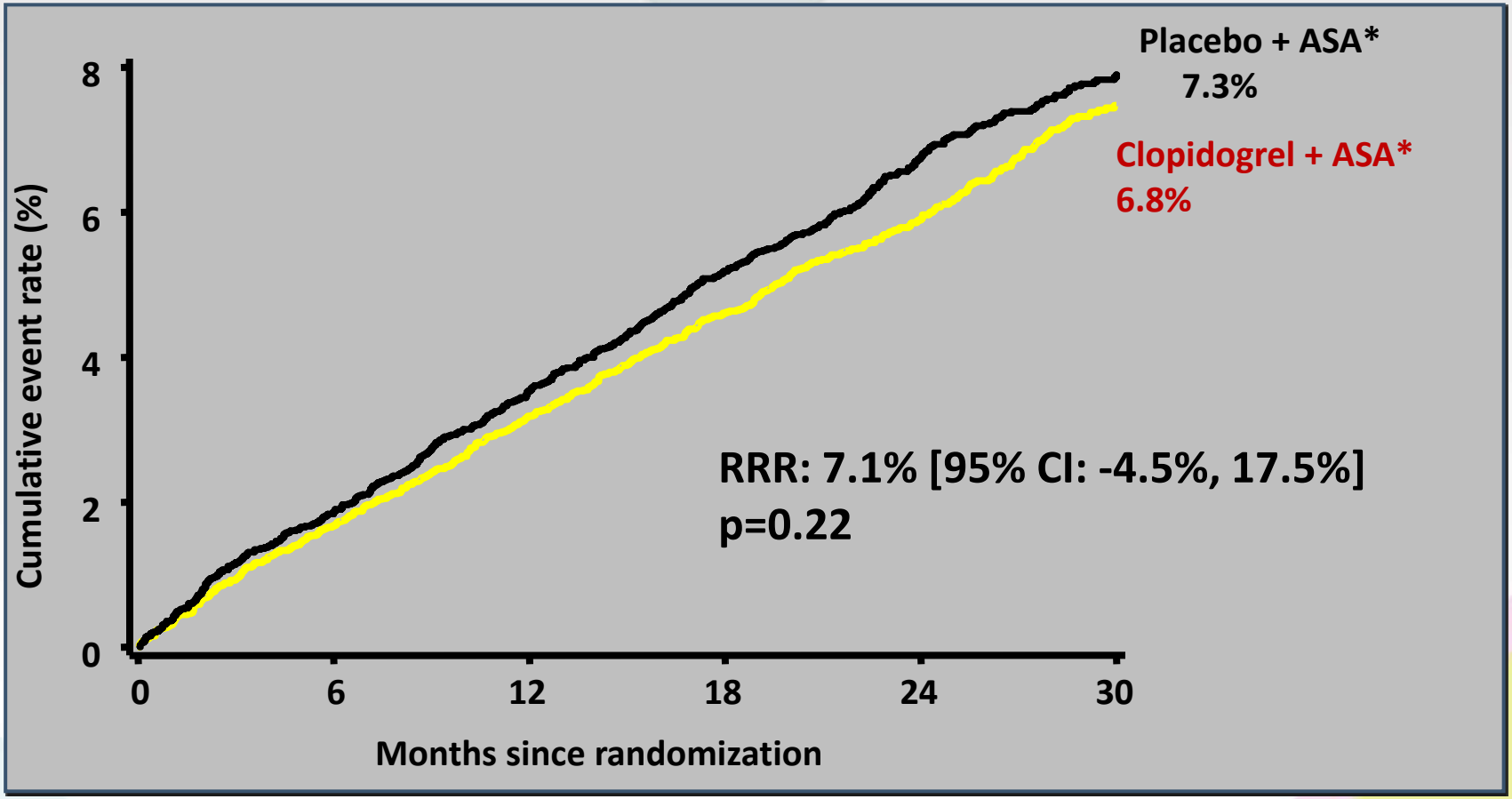
Desai NR, Bhatt DL. *JACC CV int.* 2010;3:571-83

CHARISMA Trial Design



Bhatt DL et al. Am Heart J 2004; 148: 263–268.

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

*All patients received ASA 75-162 mg/day

§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Bhatt DL, Fox KA, Hacke W, et al. NEJM 2006.

PEGASUS: Randomization

Mount Sinai Heart

Stable pts with MI
1-3 yrs prior +
≥1 high-risk factor

- Age ≥65 years
- Diabetes
- 2nd prior MI (>1 yr)
- Multivessel CAD
- CrCl <60 mL/min

Randomized 21,162 patients

at 1161 sites in 31 countries between 10/2010 – 5/2013

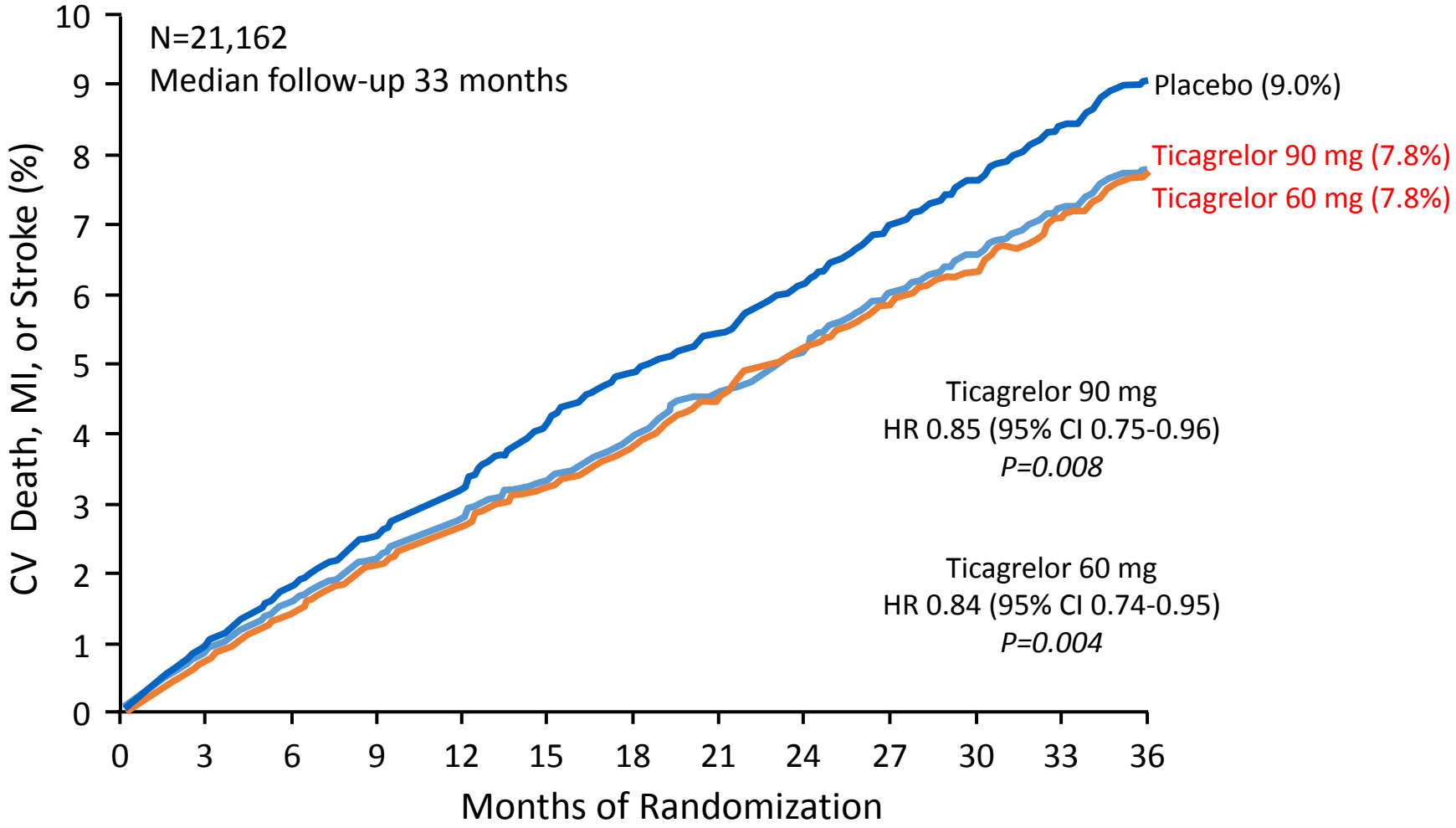
Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)

Follow-up median 33 months (IQR 28-37)
Minimum 16 months, maximum 47 months

	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)
Premature perm. drug discontinuation	12%/year	11%/year	8%/year
Withdrew consent	0.7% total	0.7% total	0.7% total
Lost to follow-up	3 patients	6 patients	1 patient

Bonaca MP et al. NEJM 2015:on-line

PEGASUS: Primary Endpoint



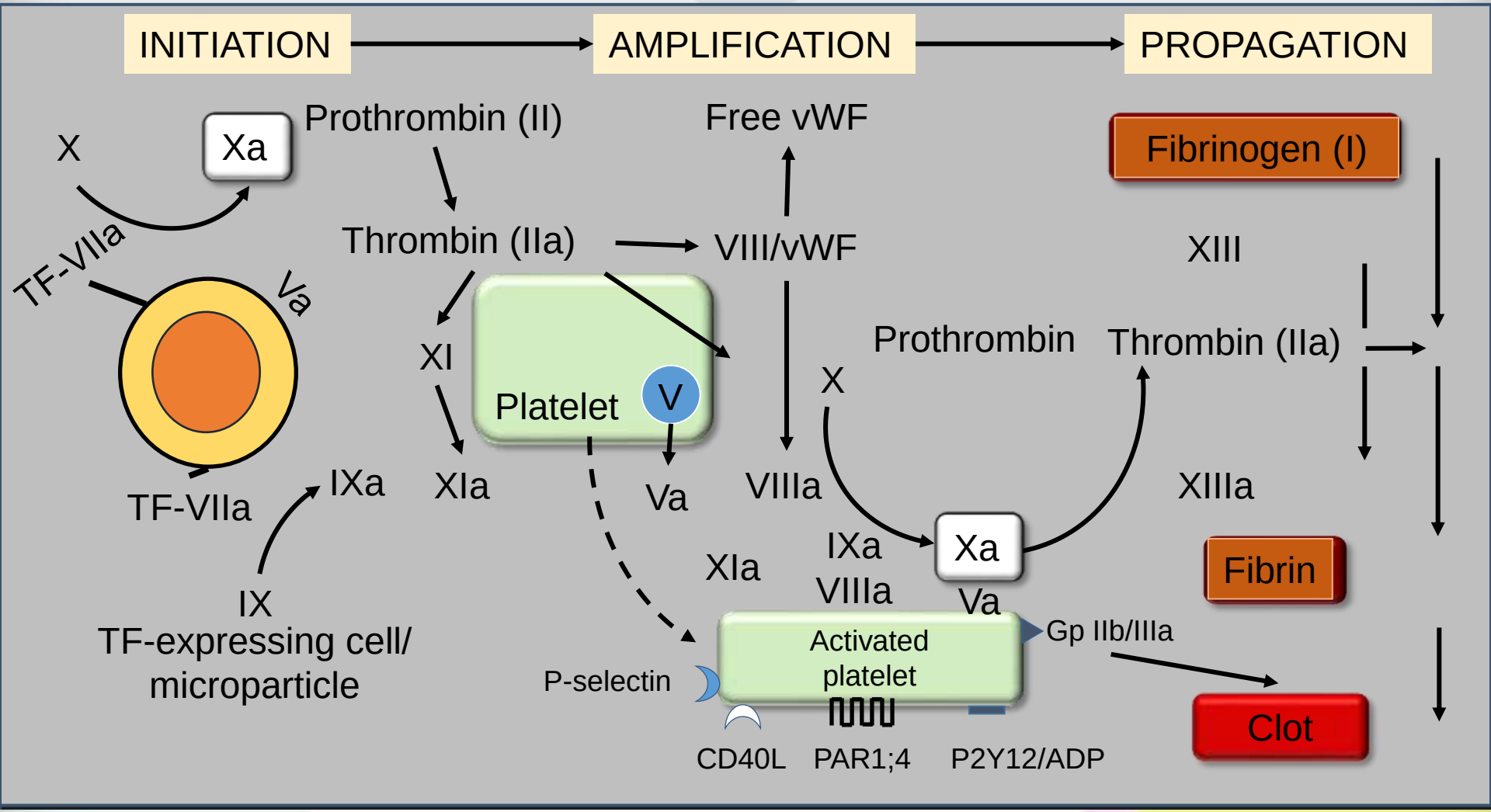
Bonaca MP et al. *NEJM* 2015:on-line

PEGASUS: Bleeding Endpoints

Mount Sinai Heart

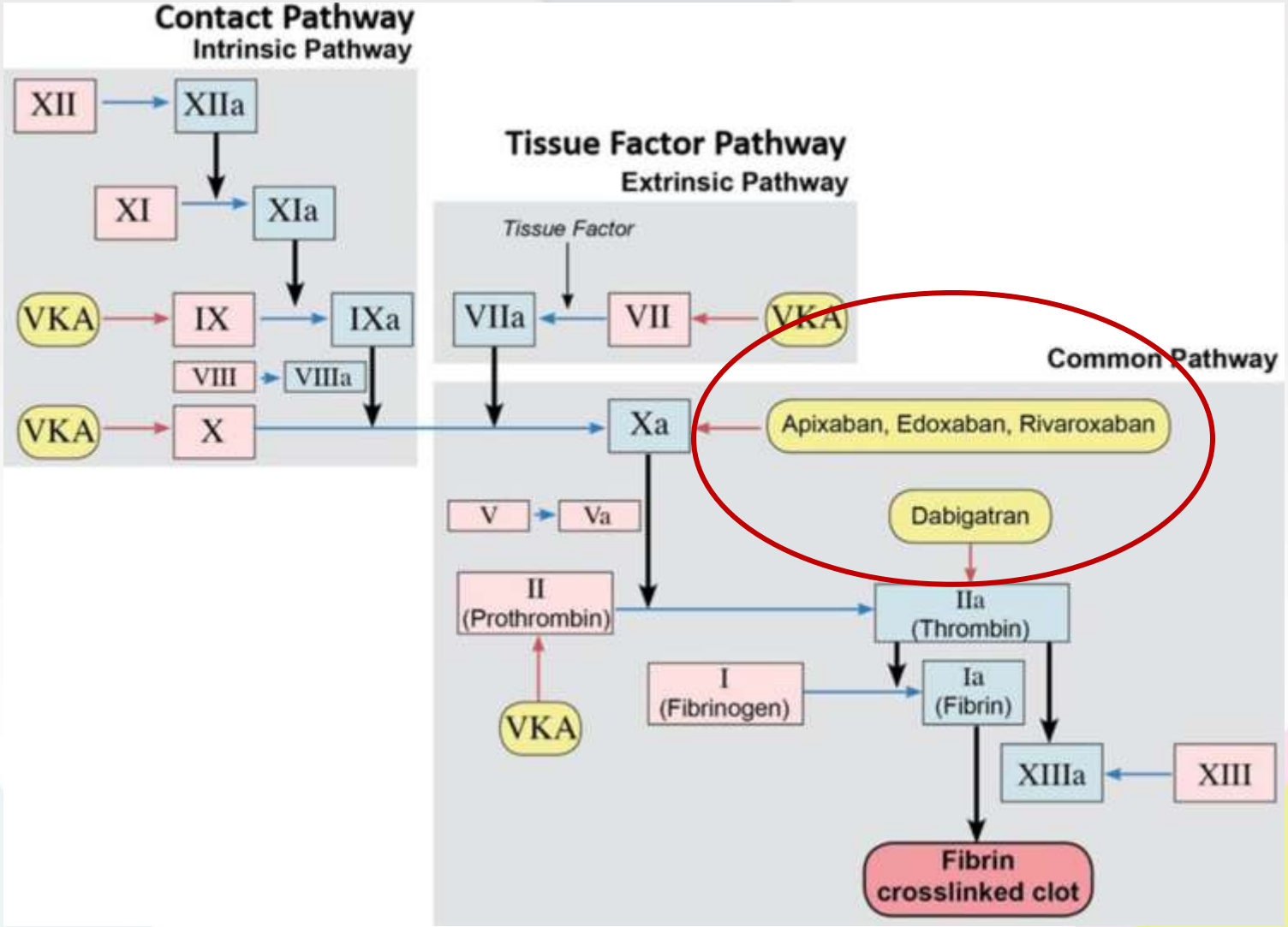
Endpoint	Ticagrelor 90 mg bid (n=6988)	Ticagrelor 60 mg bid (n=6958)	Placebo (n=6996)	Ticagrelor 90 mg vs. Placebo HR (95% CI)	Ticagrelor 90 mg vs. Placebo *P* value	Ticagrelor 60 mg vs. Placebo HR (95% CI)	Ticagrelor 60 mg vs. Placebo *P* value
TIMI major	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96-3.70)	**<0.001**	2.32 (1.68-3.21)	**<0.001**
TIMI minor	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47-7.00)	**<0.001**	3.31 (1.94-5.63)	**<0.001**
Bleeding req transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59-5.42)	**<0.001**	3.08 (2.12-4.48)	**<0.001**
Bleeding leading to study-drug d/c	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60-7.29)	**<0.001**	4.40 (3.48-5.57)	**<0.001**
Fatal bleeding or nonfatal ICH	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74-2.01)	0.43	1.20 (0.73-1.97)	0.47
- ICH	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83-2.49)	0.19	1.33 (0.77-2.31)	0.31
- Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.61-1.64)	0.26	0.97 (0.37-2.51)	0.94
- Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22-1.54)	0.27	1.00 (0.44-2.27)	1.00

Thrombus formation involves both platelet activation and blood coagulation



De Caterina R et al. *Thromb Haemost* 2013;109:569–79

Clotting cascade and anticoagulants



Raval et al Circulation. 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

ATLAS ACS 2 TIMI 51

Mount Sinai Heart

Recent ACS: STEMI, NSTEMI, UA

No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine

Stabilized 1-7 Days Post-Index Event

+ ASA 75 to 100 mg/day

Stratified by Thienopyridine use at MD Discretion

Placebo
N=5,176
ASA + Thieno, n=4,821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5,174
ASA + Thieno, n=4,825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5,176
ASA + Thieno, n=4,827
ASA, n=349

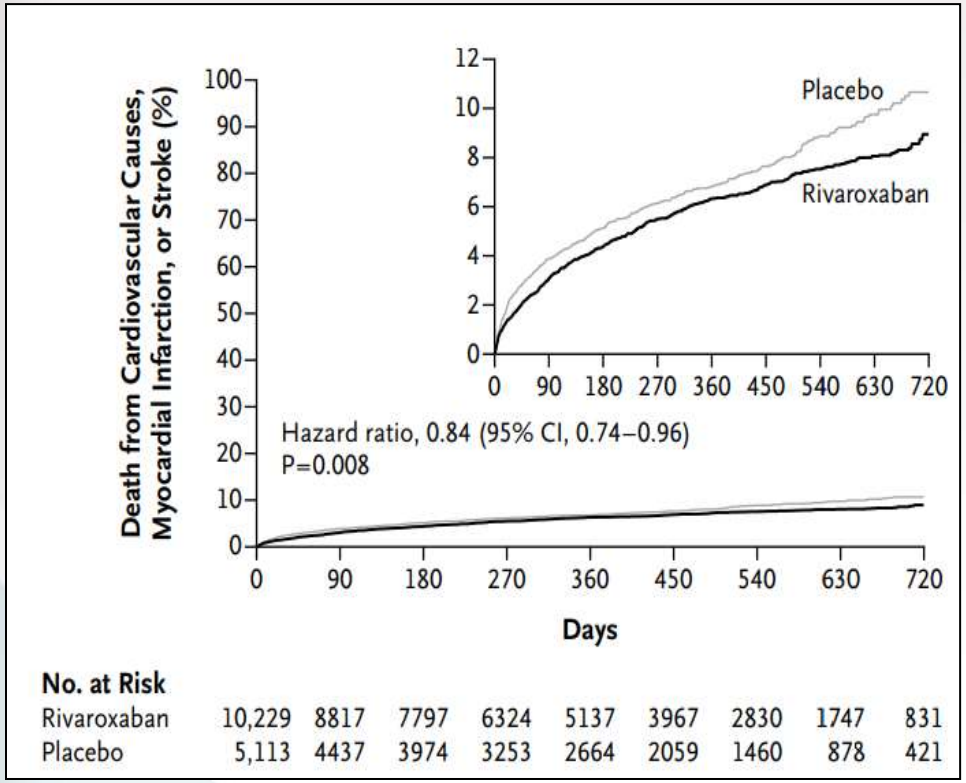
PRIMARY ENDPOINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncert ain stroke. ** 184 subjects were excluded from the efficacy analys es prior to unblinding

Mega J.L. et al N Engl J Med. 2012 Jan 5;366(1):9-19

Effect of Rivaroxaban on Primary Efficacy Endpoint

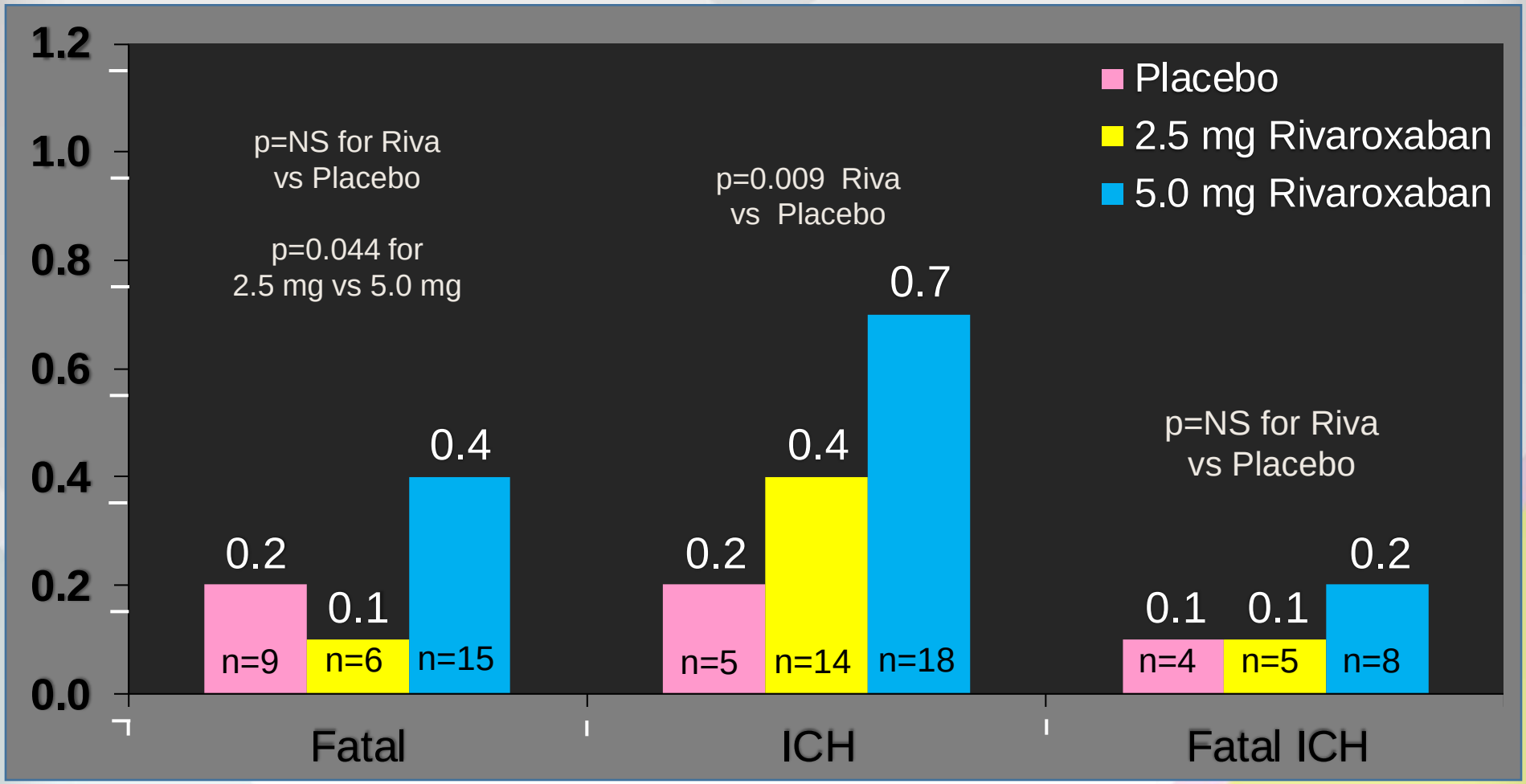
The primary efficacy end point
(Cardiovascular death, myocardial infarction, or stroke)



The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a **survival benefit that was not seen with the twice-daily 5-mg dose.**

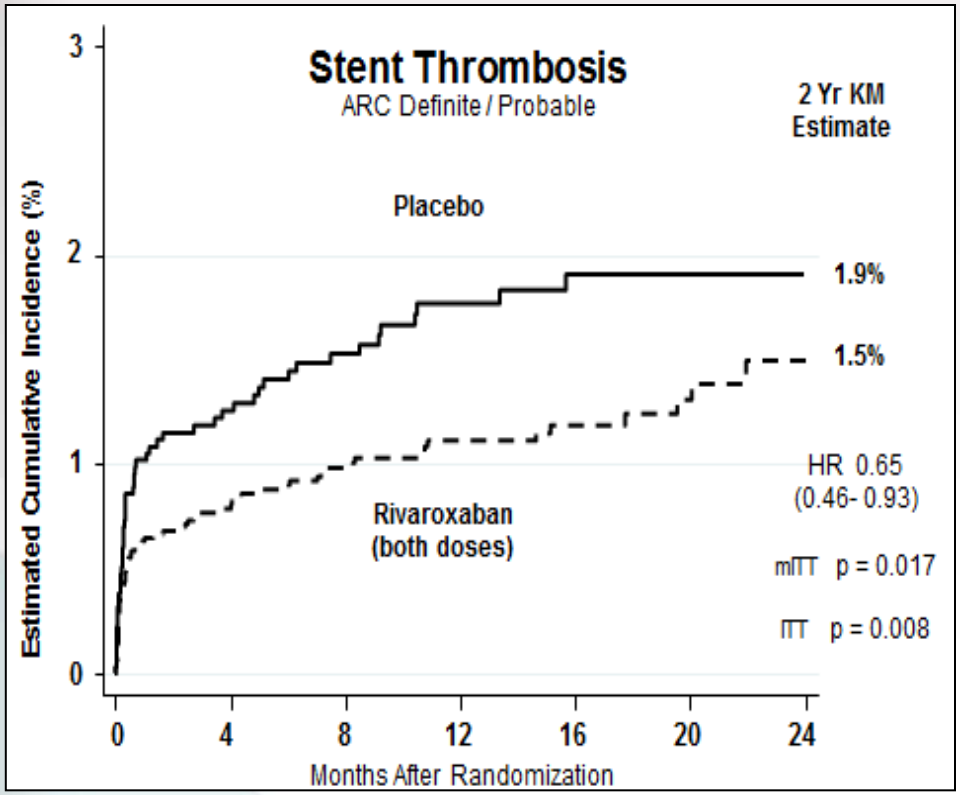
Mega J.L. et al N Engl J Med. 2012 Jan 5;366(1):9-19

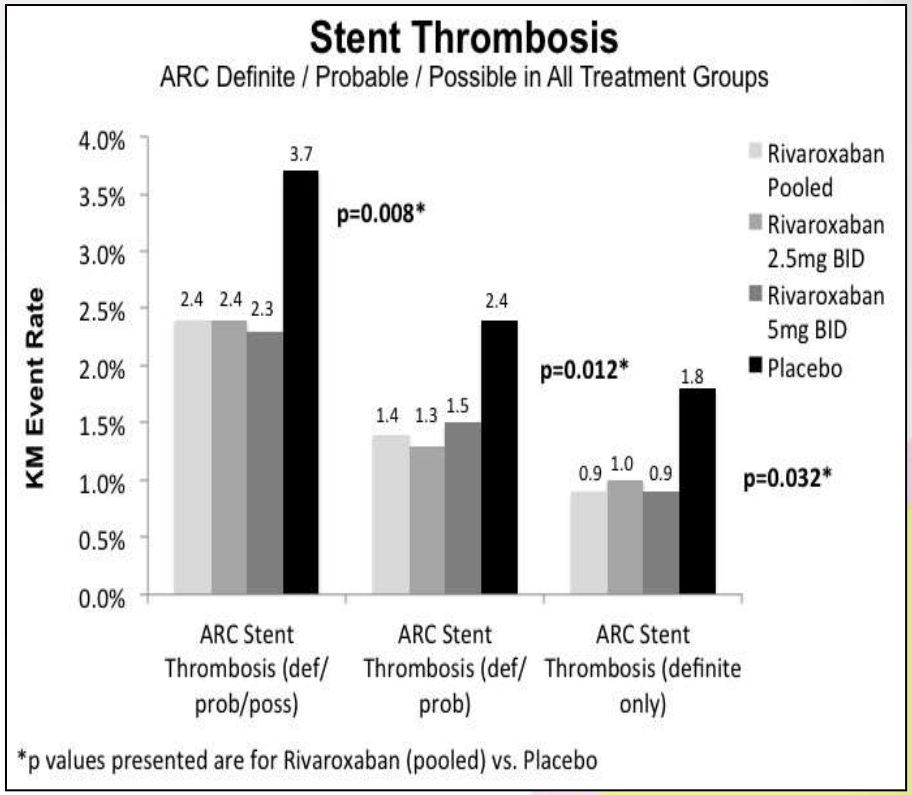
Treatment-emergent Fatal Bleeds and ICH



Mega J.L. et al N Engl J Med. 2012 Jan 5;366(1):9-19

Effect of Rivaroxaban on Stent Thrombosis ITT/All Strata/Combined Doses



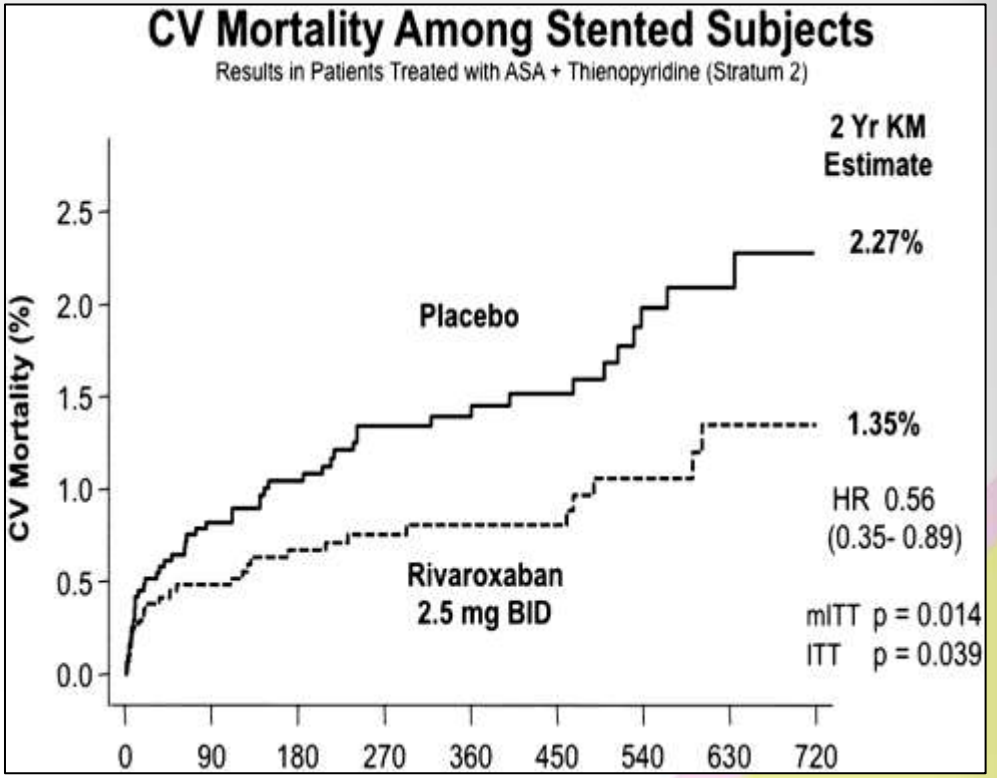


Mega J.L. et al N Engl J Med. 2012 Jan 5;366(1):9-19

Effect of Rivaroxaban on Stent thrombosis and mortality in stented patients

CONCLUSIONS:

Among stented patients with ACS treated with DAPT, the administration of twice-daily rivaroxaban 2.5 mg was associated with a reduction in stent thrombosis and mortality.



Mega J.L. et al N Engl J Med. 2012 Jan 5;366(1):9-19

Oral anticoagulants in coronary heart disease

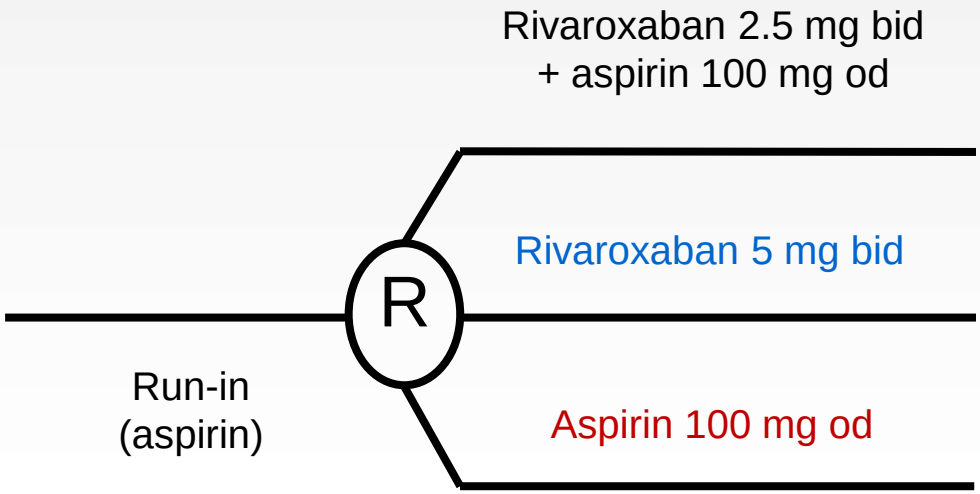
Position paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease – De Caterina et al. Thrombosis and Haemostasis 2016

".. The **ATLAS 2 study remains a cornerstone** for the entire **concept of low-dose anticoagulation long-term in addition to antiplatelet therapy**.

The availability of alternative antiplatelet and anticoagulant options, either substituting clopidogrel with a more potent P2Y12 inhibitor or adding a NOAC (low-dose rivaroxaban) or vorapaxar on top of aspirin and clopidogrel, provides opportunities for future studies."

COMPASS: Rivaroxaban in stable CAD or PAD

Stable CAD or PAD
2,200 with a primary outcome event

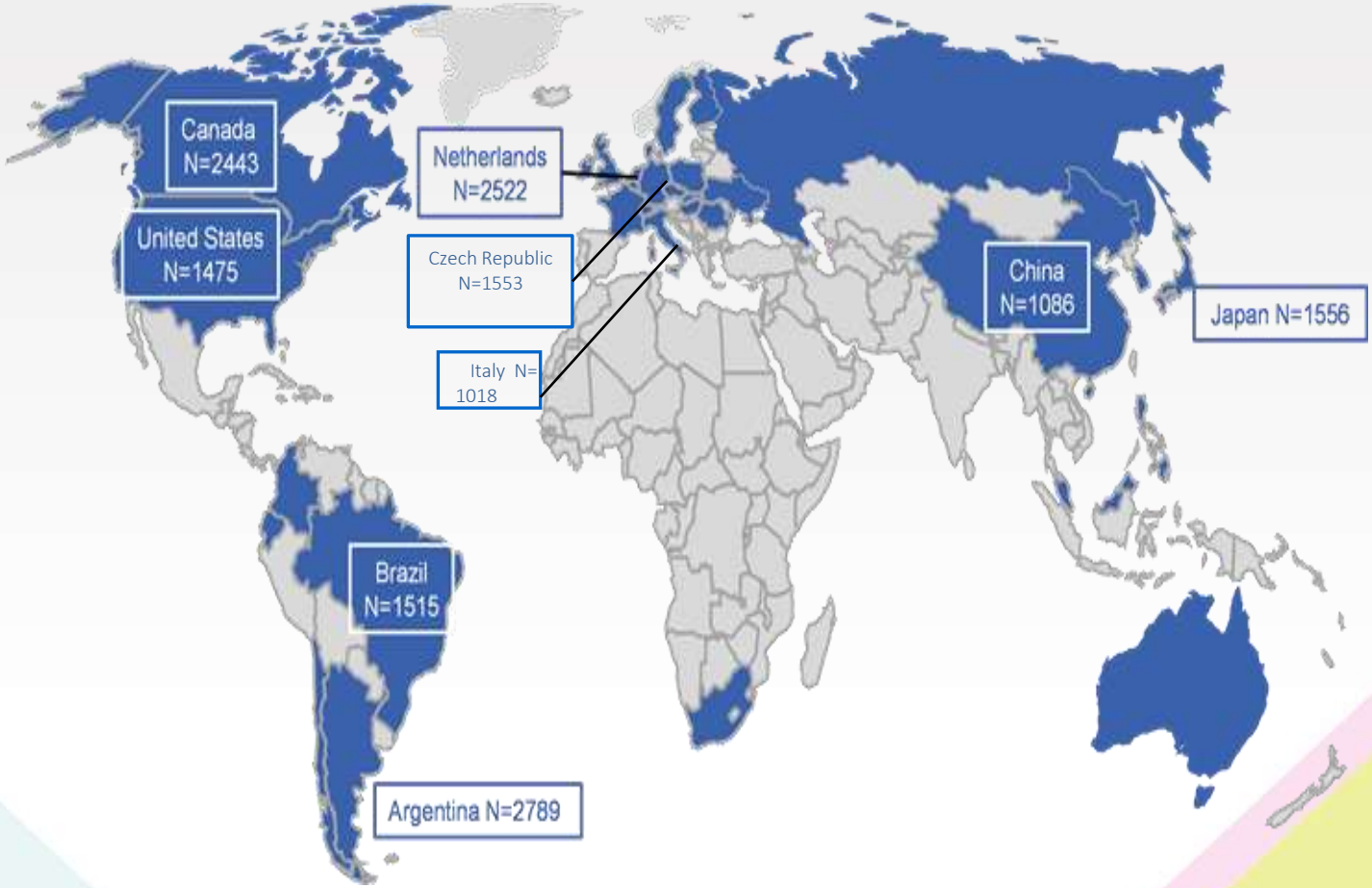


Expected follow up
3-4 years

COMPASS: Outcomes

- Primary
  - CV death, stroke or myocardial infarction
- Secondary
  - CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - CV death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - Mortality
- Safety and net clinical benefit
  - ISTH major bleeding (modified)
  - Primary plus fatal or critical organ bleeding

COMPASS: 602 sites, 33 countries



COMPASS – Follow up

- On February 6, 2017 the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy (combination: Z= -4.59, P<0.00001; rivaroxaban: Z= -2.44, P=0.01)
- Close-out between March and June 2017
- Mean follow up 23 months
- Follow up 99.8% complete

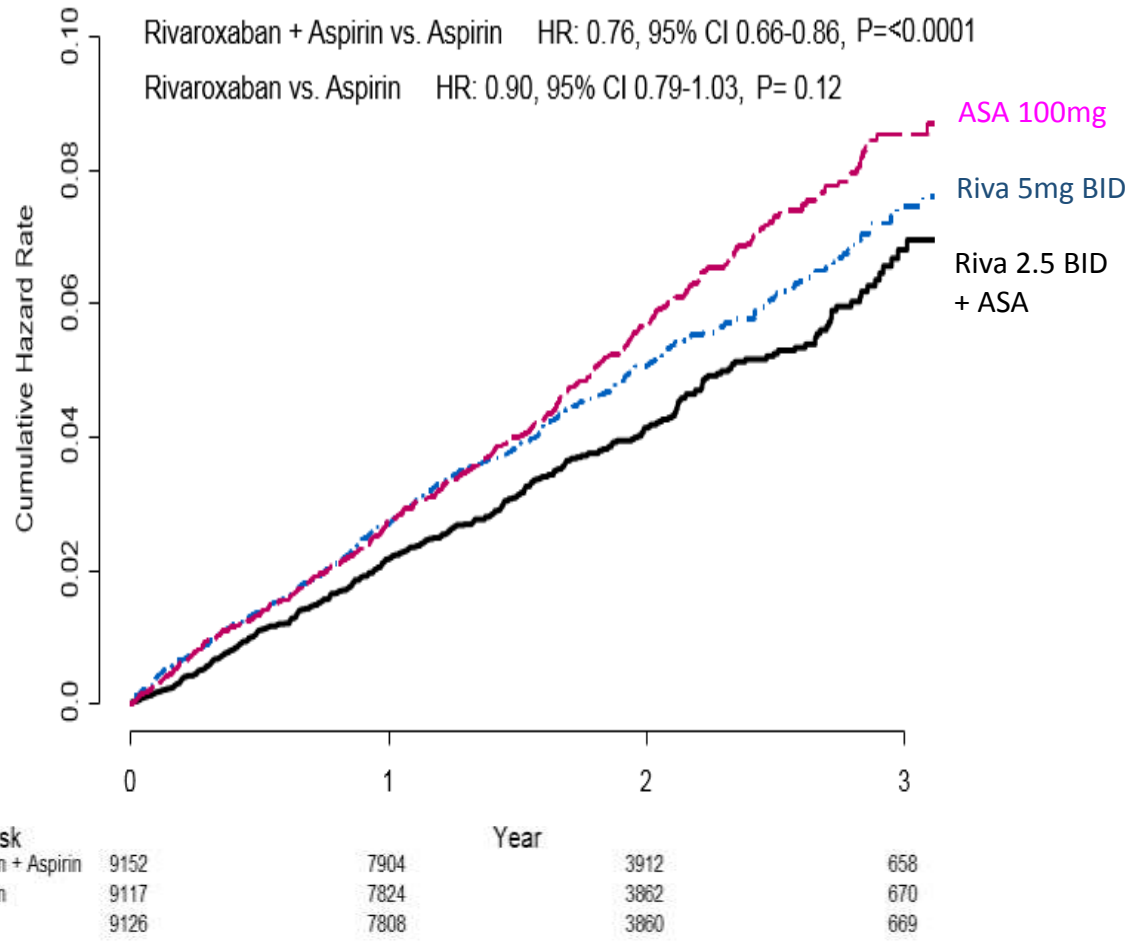
Baseline characteristics

Characteristics	Riva 2.5 BID + Aspirin N=9,152	Riva 5 BID N=9,117	Aspirin N=9,126
Age, yr	68	68	68
Blood pressure, mmHg	136/77	136/78	136/78
Total cholesterol, mmol/L	4.2	4.2	4.2
CAD	91%	90%	90%
PAD	27%	27%	27%
Diabetes	38%	38%	38%
Lipid-lowering	90%	90%	89%
ACE-I or ARB	71%	72%	71%

Primary: CV death, stroke, MI

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
CV death, stroke, MI	379 (4.1%)	448 (4.9%)	496 (5.4%)	0.76 (0.66-0.86)	<0.0001	0.90 (0.79-1.03)	0.12

COMPASS: CV Death, Stroke, MI



Eikelboom et al. for the COMPASS investigators, NEJM 2017

COMPASS: Primary components

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 et al. for the COMPASS investigators, NEJM 2017

COMPASS: Secondary Outcomes

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	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

* pre-specified threshold P=0.0025

CAD and PAD
Subgroups for primary outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

COMPASS: Major Bleeding

Outcome	R + A	R	A	Rivaroxaban 2.5 BID + Aspirin vs. Aspirin		Rivaroxaban 5 BID vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	**1.70 (1.40-2.05)**	<0.0001	**1.51 (1.25-1.84)**	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	**1.49 (0.67-3.33)**	0.32	**1.40 (0.62-3.15)**	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	**1.10 (0.59-2.04)**	0.77	**1.69 (0.96-2.98)**	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	**1.43 (0.89-2.29)**	0.14	**1.57 (0.98-2.50)**	0.06

* symptomatic

COMPASS: Net clinical benefit

	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	**N (%)**	**HR (95% CI)**	**P**
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

COMPASS: CAD and PAD Subgroups for Primary Outcome

	R + A N=9,152	**A** N=9,126	**Rivaroxaban + Aspirin vs. Aspirin**
	N (%)	**N (%)**	**HR (95% CI)**
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

Conclusions

- A low-dose regimen of rivaroxaban in addition to aspirin seems beneficial with regard to major vascular events in stable patients after myocardial infarction.

- Although the bleeding risk associated with such strategy is increased, this excess risk did not offset the benefits of adding rivaroxaban to aspirin according to the results of COMPASS.

- Further evidence for a strategy of low-dose NOACs in addition to standard antiplatelet therapy in stable patients with coronary artery disease is needed

- Evaluation of ischemic and bleeding risk seems crucial to decide for the optimal treatment strategy