ACTION Study Group
Institute of Cardiology
Pitié-Salpêtrière Hospital
Paris - France

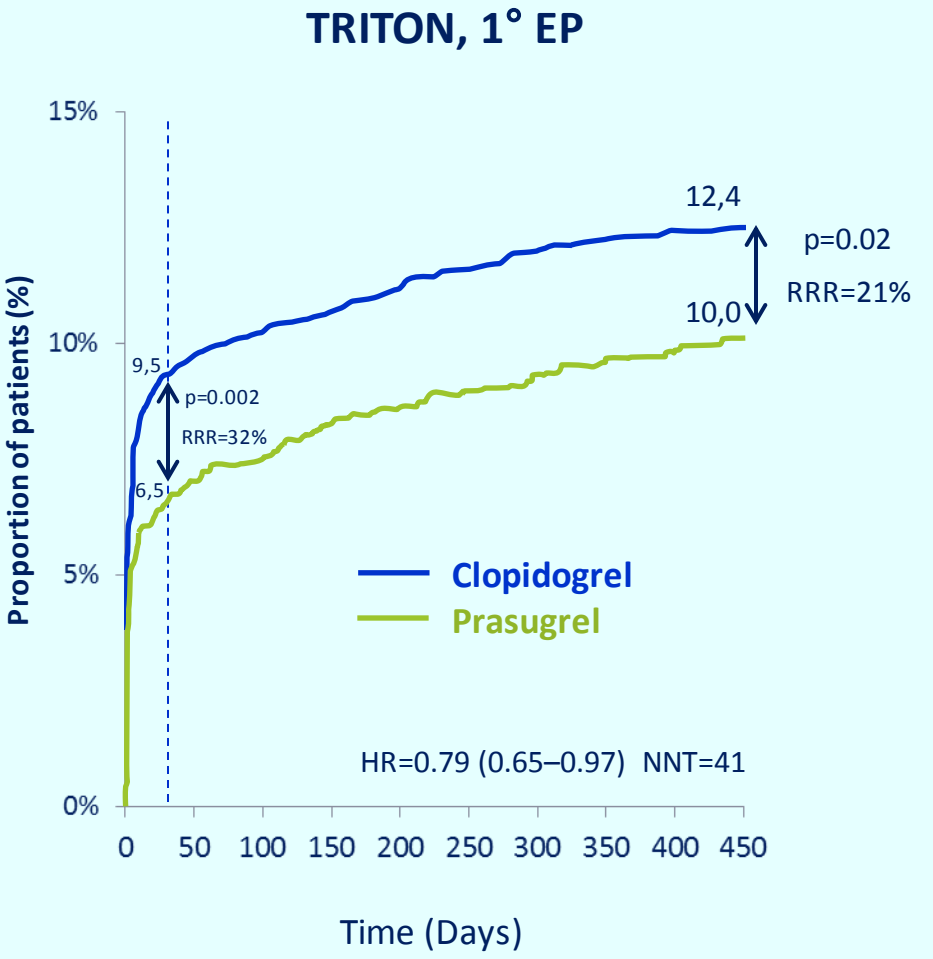
Individualisation du traitement Anti Agrégeant Plaquettaire dans la PEC des Syndromes coronaires aigus

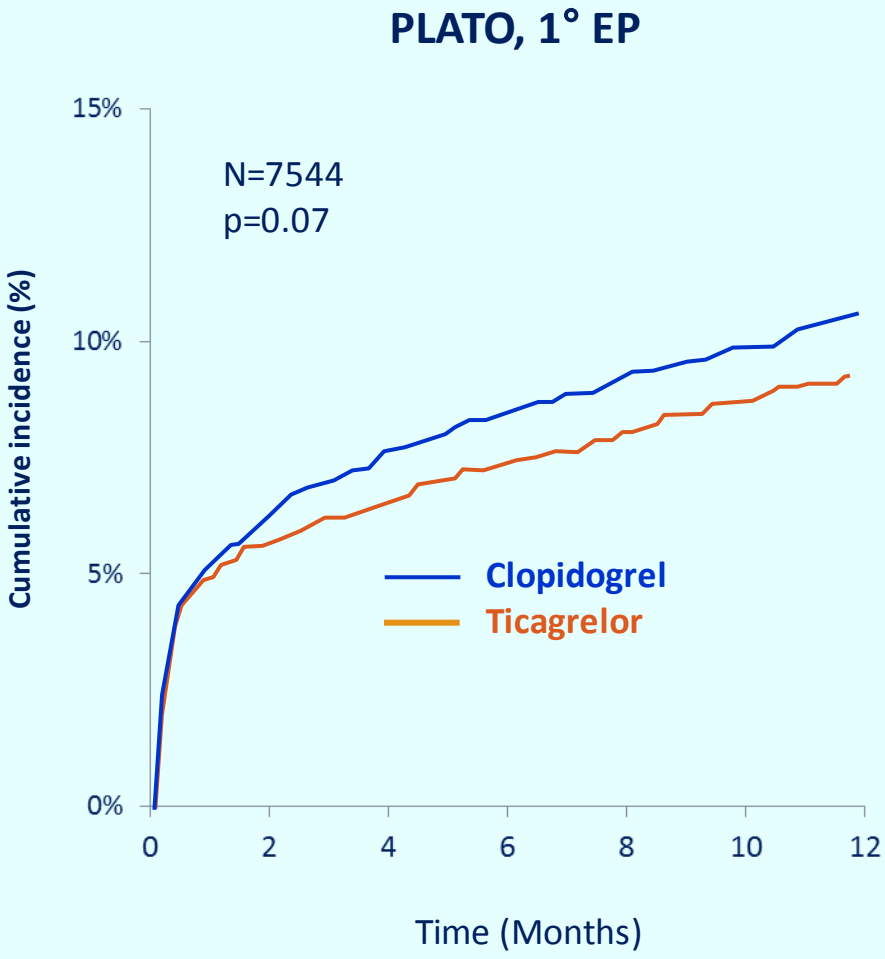
G. Montalescot

Dr. Montalescot reports research Grants to the Institution or Consulting/Lecture fees which are published at www.action-coeur.org

Giving new P2Y12 RA earlier in STEMI

New P2Y12 antagonists in STEMI



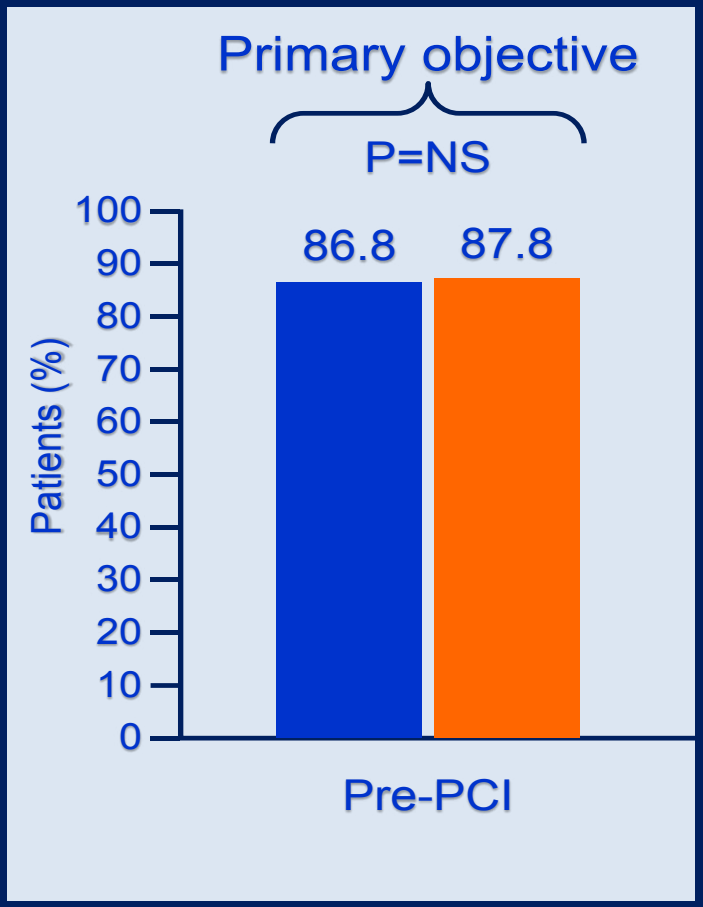


Montalescot G, et al. Lancet 2009;373:723–31

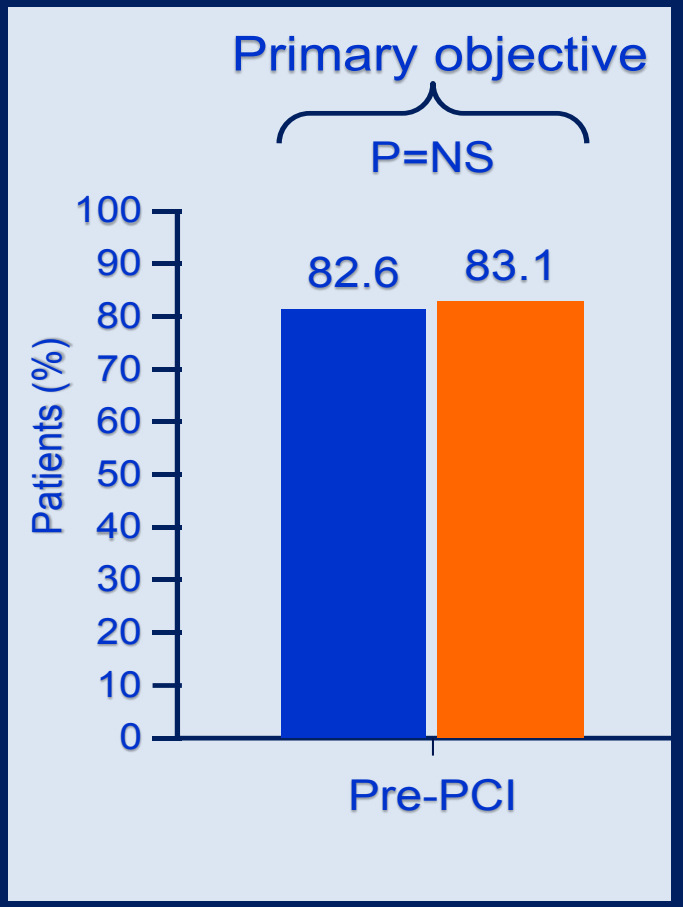
Steg PG, et al. Circulation. 2010;122:2131-41

ATLANTIC: *reperfusion criteria*

1st Co-primary endpoint
No ST-segment resolution (≥70%)



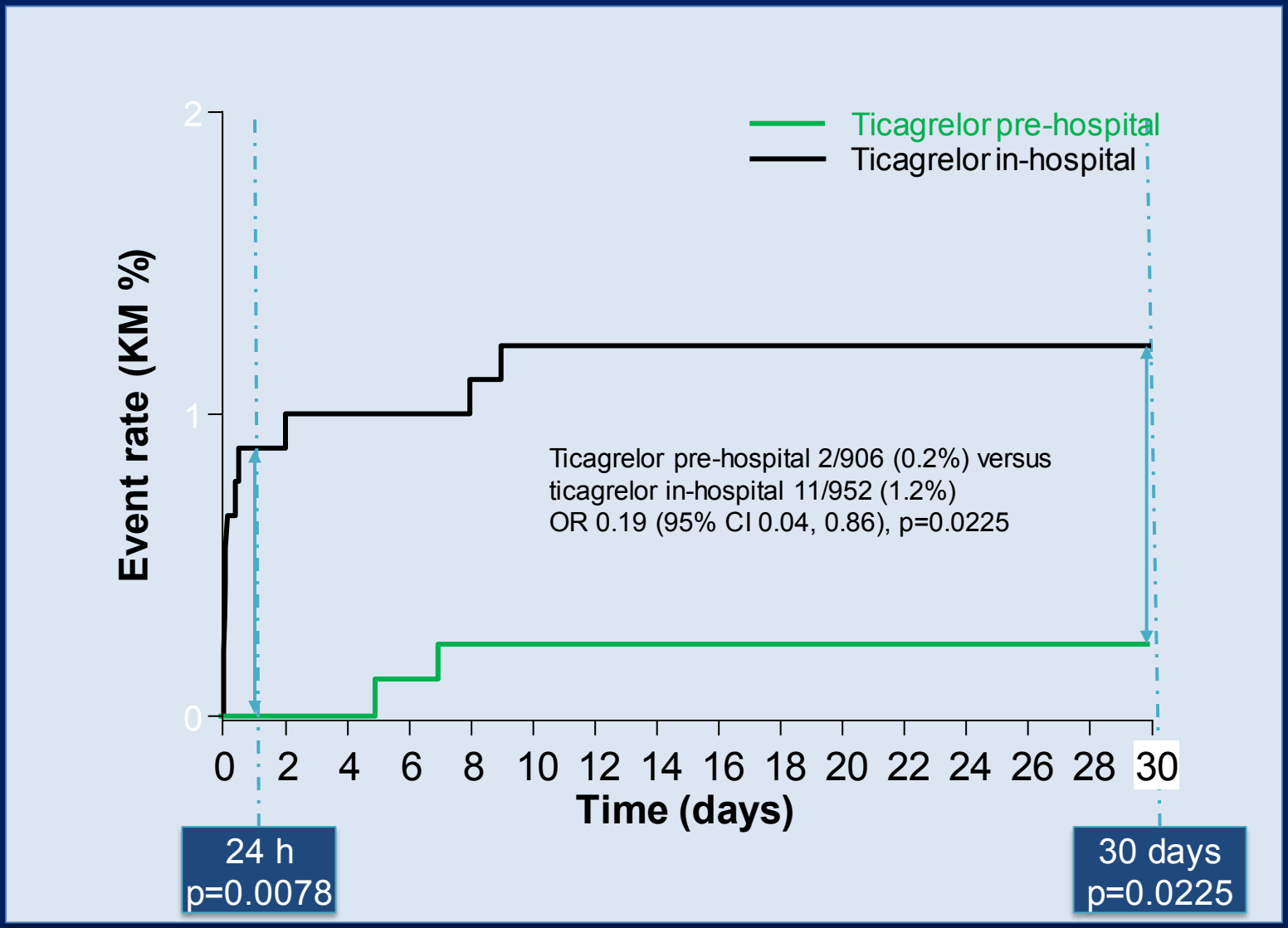
2nd Co-primary endpoint
No TIMI 3 flow in infarct-related artery



Pre-hospital In-hospital

Montalescot G, et al. NEJM 2014

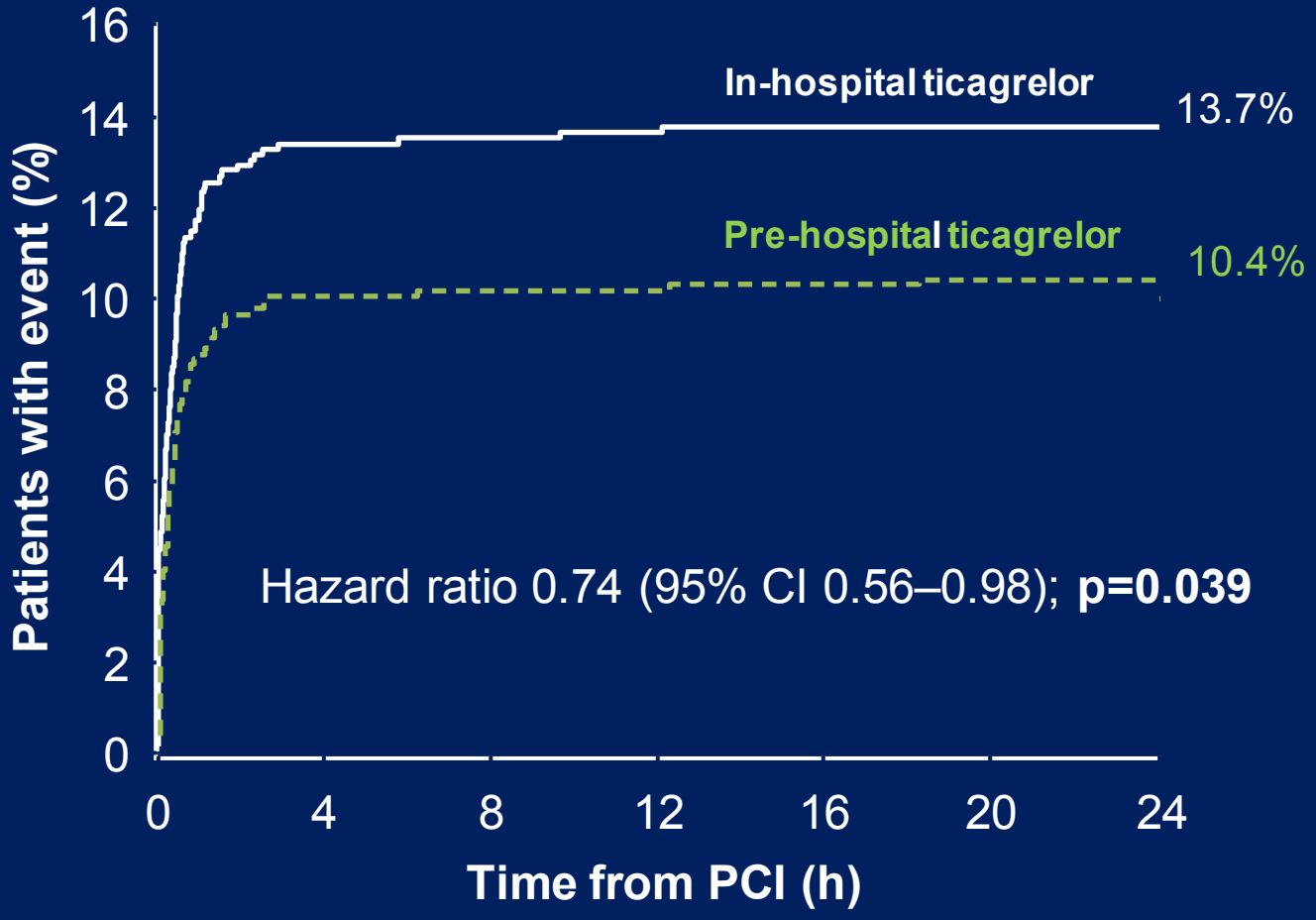
ATLANTIC *Stent thrombosis*



Montalescot G, et al. NEJM 2014

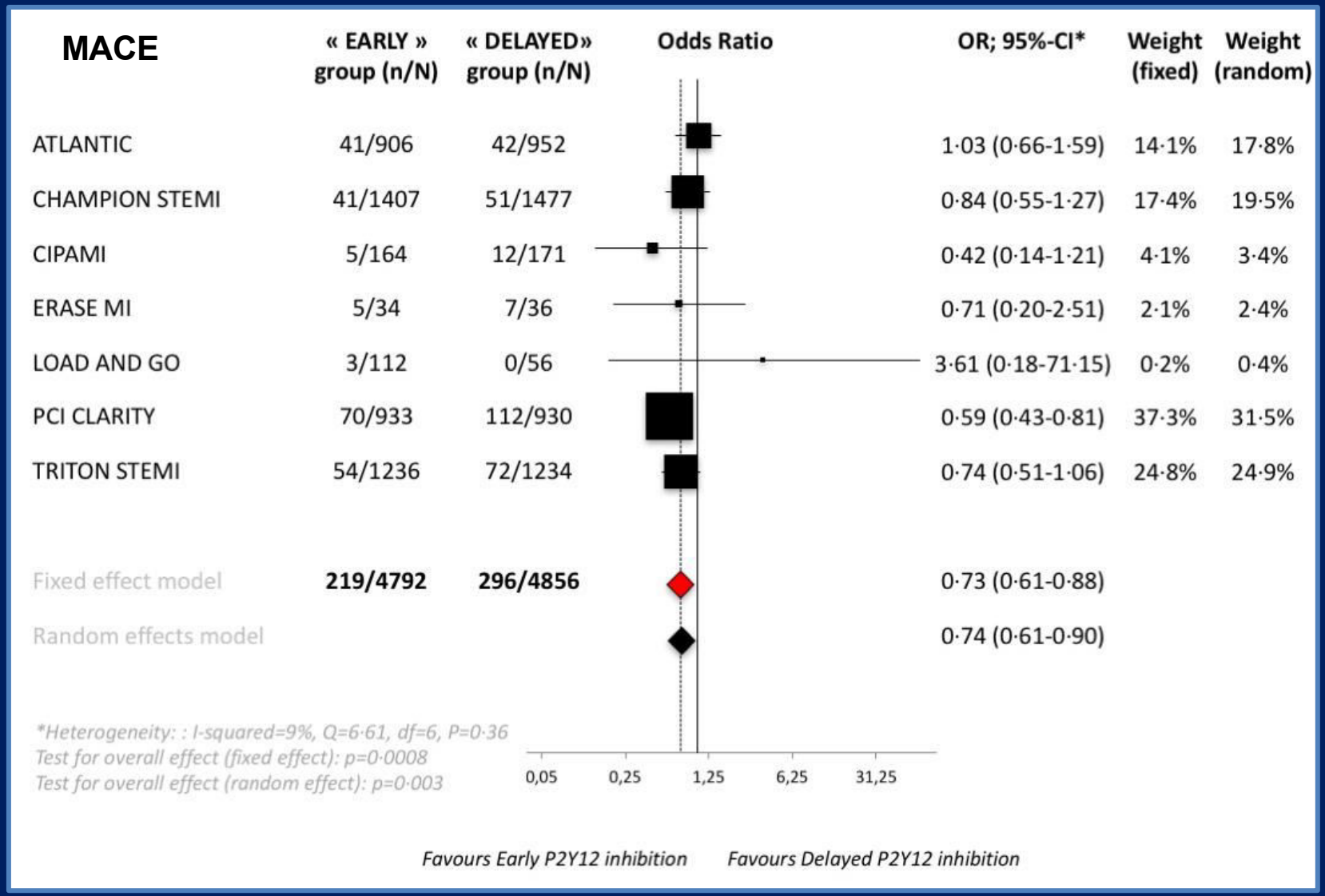
ATLANTIC-H^{24}

Composite ischaemic endpoint: death, MI, urgent revasc, definite stent thrombosis or bail-out GP IIb/IIIa inhibitor use



Montalescot G et al. JACC CVI 2016

Early administration of P2Y12 inhibitors in STEMI



Bellemain-Appaix A. et al. EuroIntervention. 2018 Feb 20. pii: EIJ-D-17-00852. doi: 10.4244/EIJ-D-17-00852

Giving new P2Y12 RA later in NSTEMI

Definition of Pre-treatment

ER-CCU

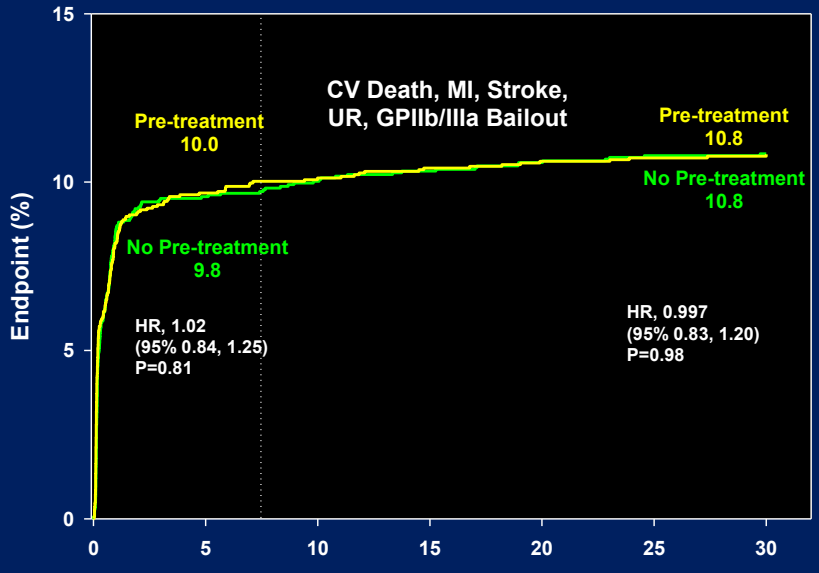
- **Working diagnosis of ACS**
- **Invasive strategy decided**
- **On aspirin + anticoagulation**

→ $P2Y_{12}$ antagonist given before coronary visualization

Cath Lab

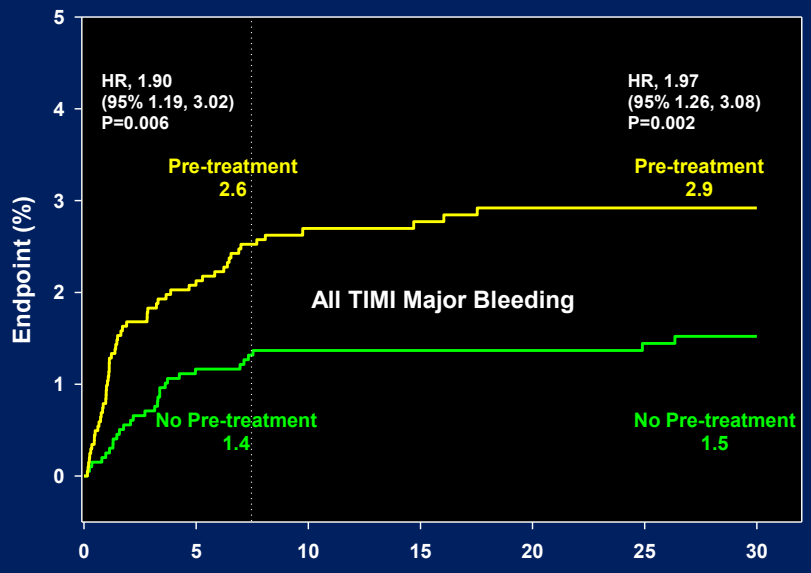
- **PCI → benefit expected**
- Medical treatment → **?**
- CABG → **no benefit expected**
- Other diagnosis (pericarditis, aortic dissection, heart failure, LVH, pulmonary embolism, GI ulcer, pancreatitis...) → **harm expected**

ACCOAST: 1° Efficacy and Safety Endpoints



No. at Risk, Primary Efficacy End Point:

No pre-treatment	1996	1788	1775	1769	1762	1752	1621
Pre-treatment	2037	1821	1809	1802	1797	1791	1616

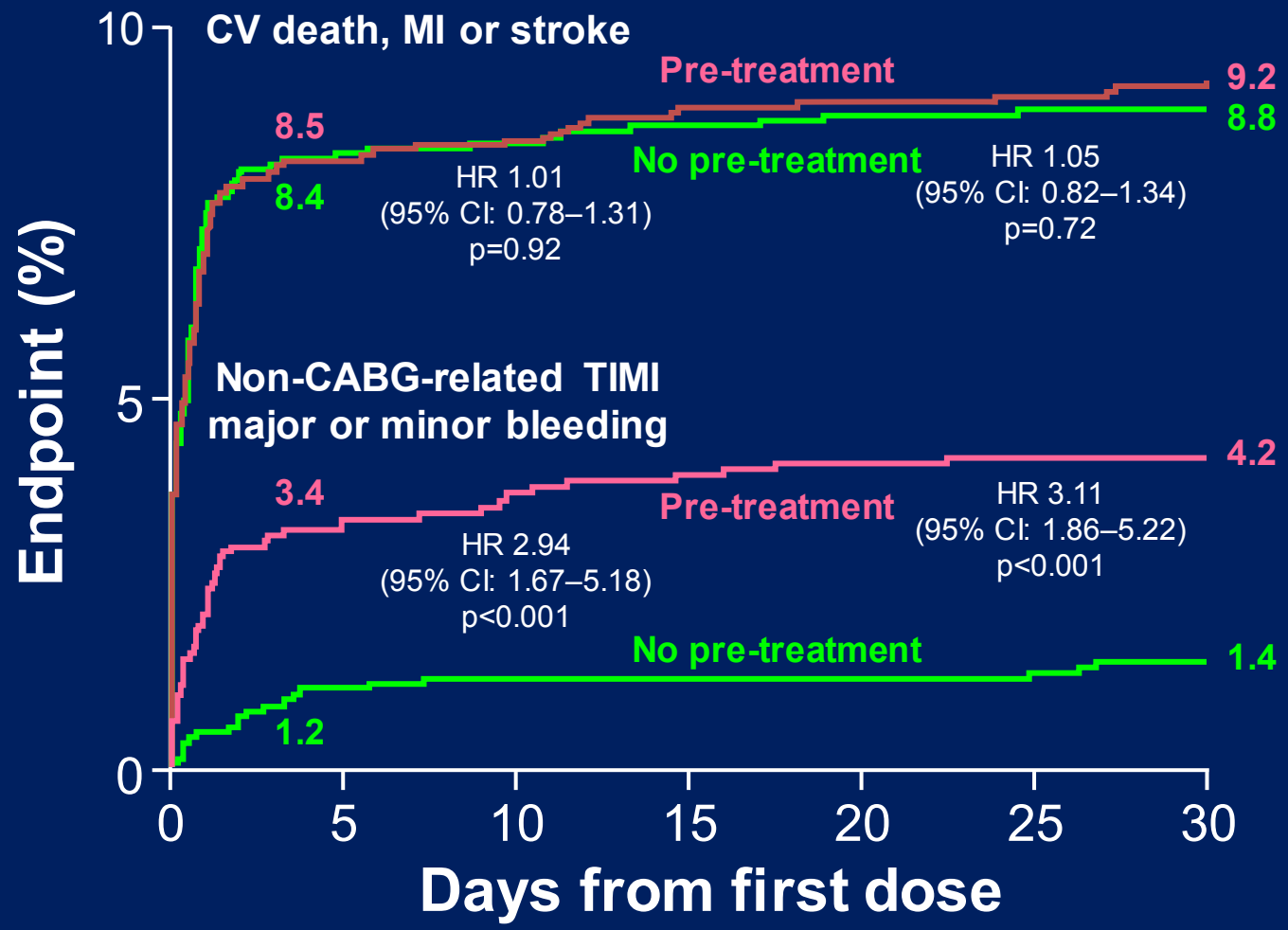


No. at Risk, All TIMI Major Bleeding:

No pre-treatment	1996	1947	1328	1297	1288	1284	1263
Pre-treatment	2037	1972	1339	1310	1299	1297	1280

Montalescot G et al. N Engl J Med.2013;369(11):999-1010

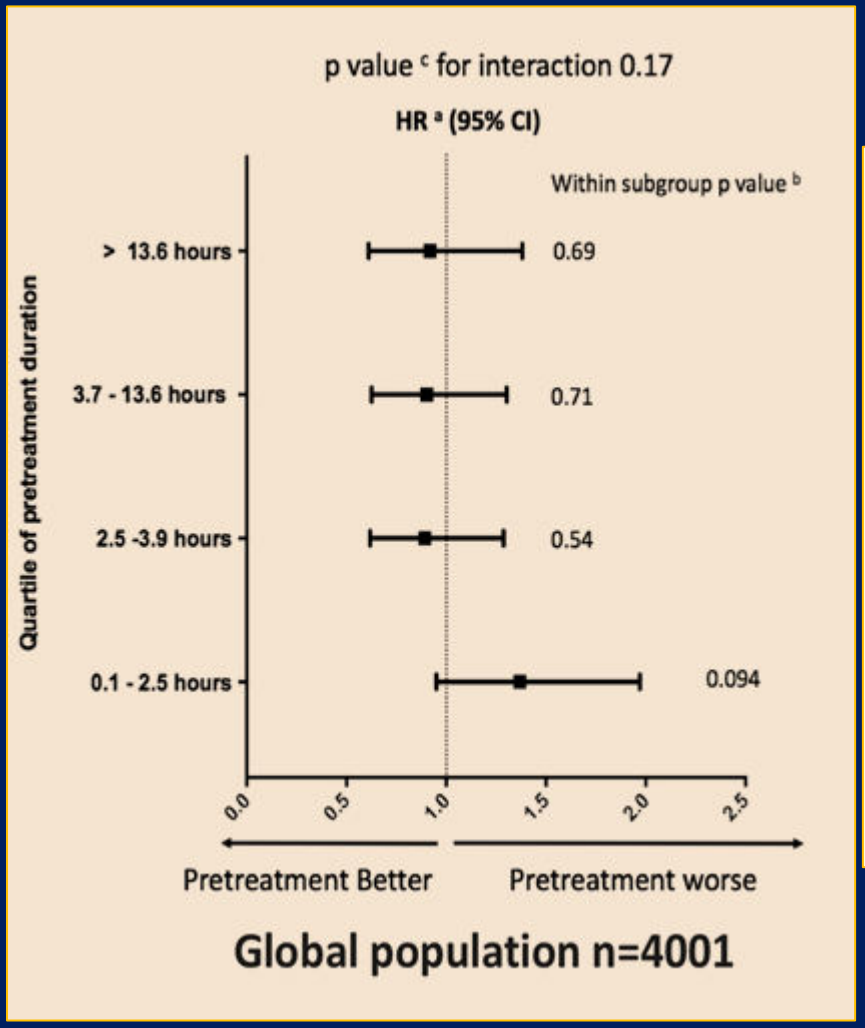
ACCOAST: PCI patients

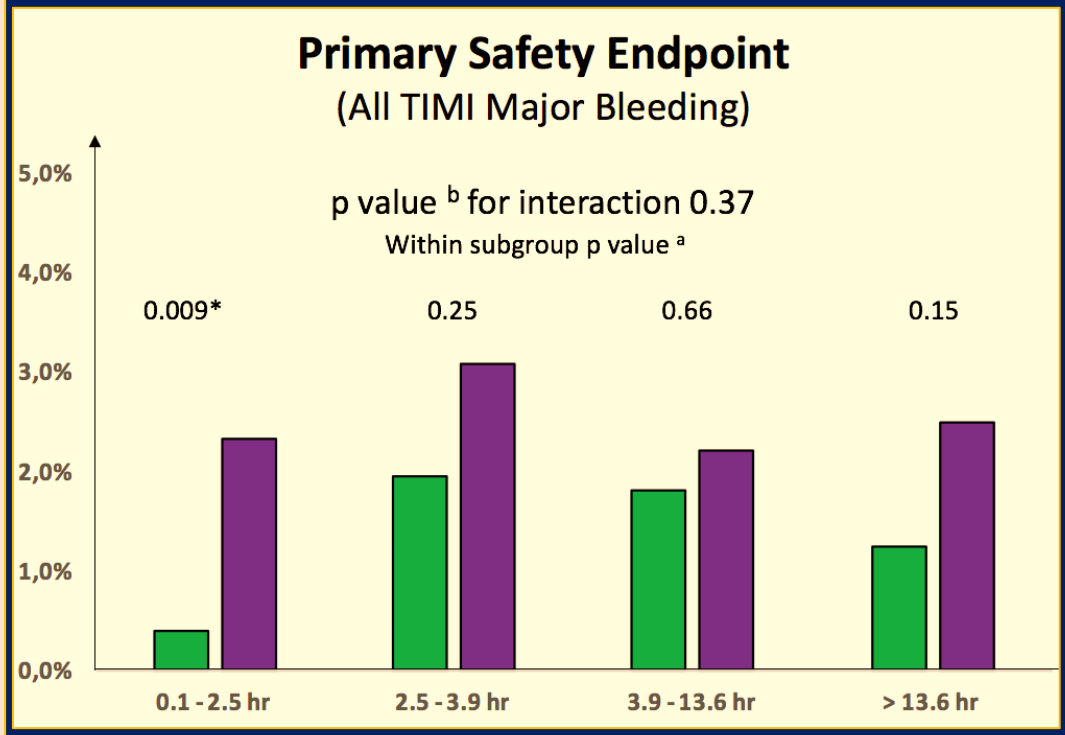


Montalescot et al. *J Am Coll Cardiol* 2014;64:2563–71

Duration of pretreatment

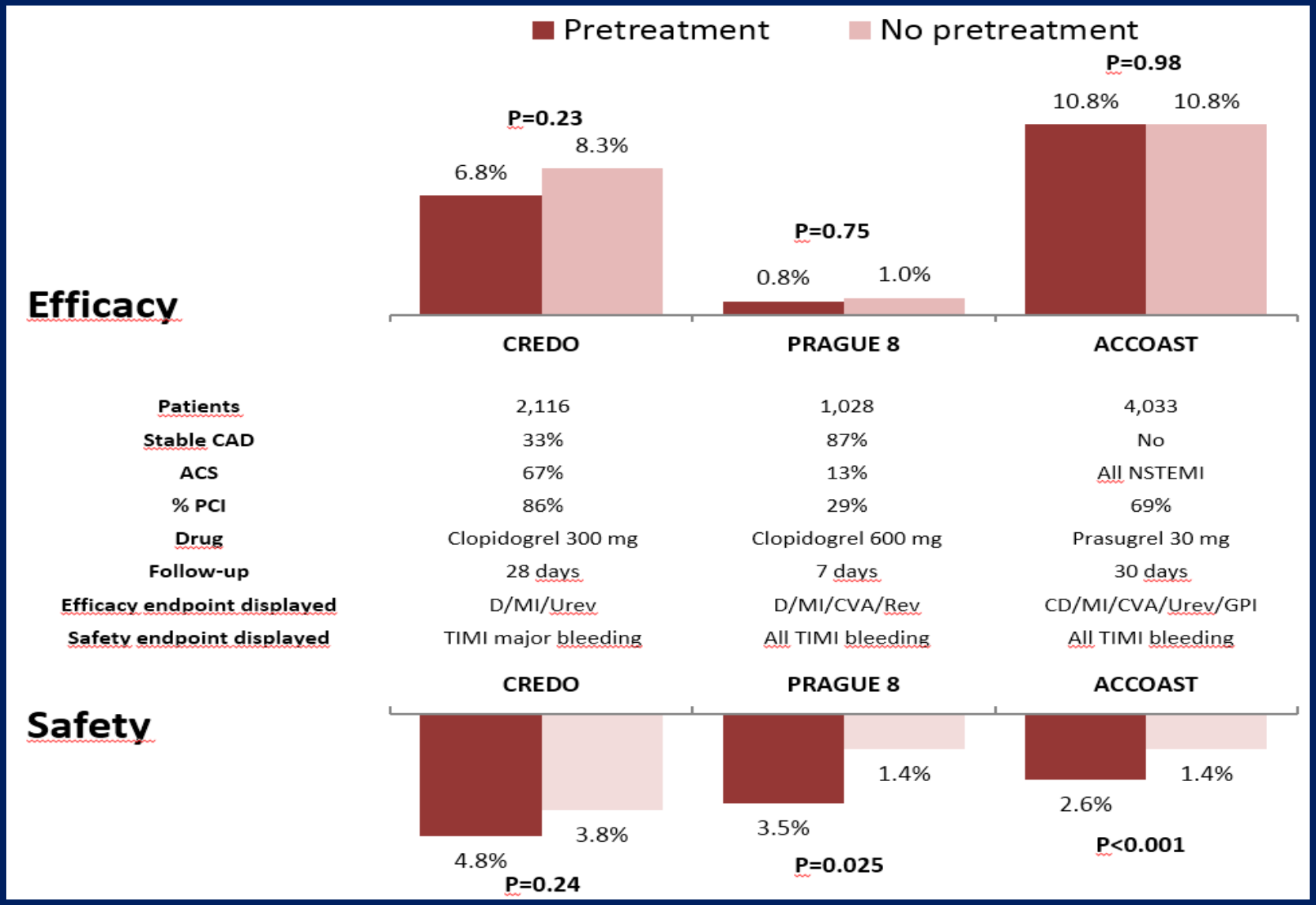
Primary efficacy EP





Silvain et al. JACC 2018 in press

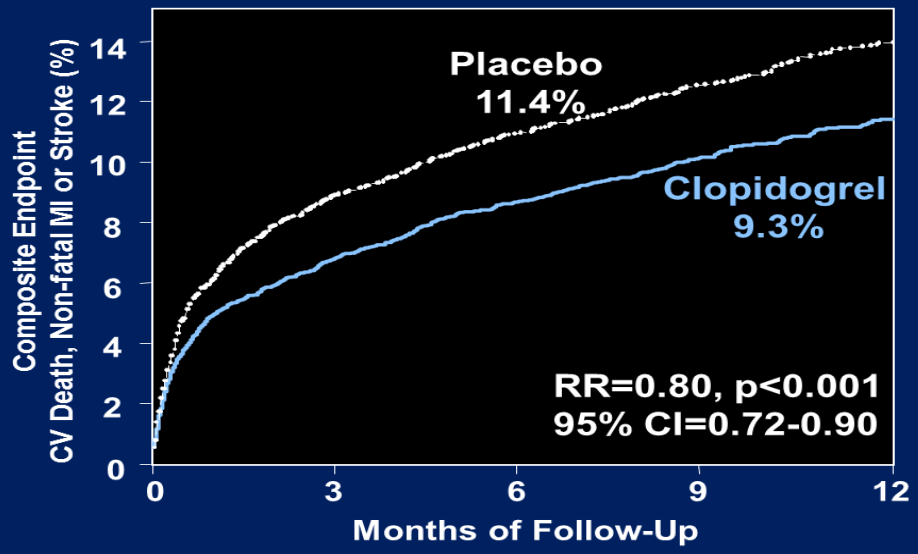
Studies of pretreatment with $P2Y_{12}$ receptor inhibitors in patients with stable CAD and NSTE-ACS



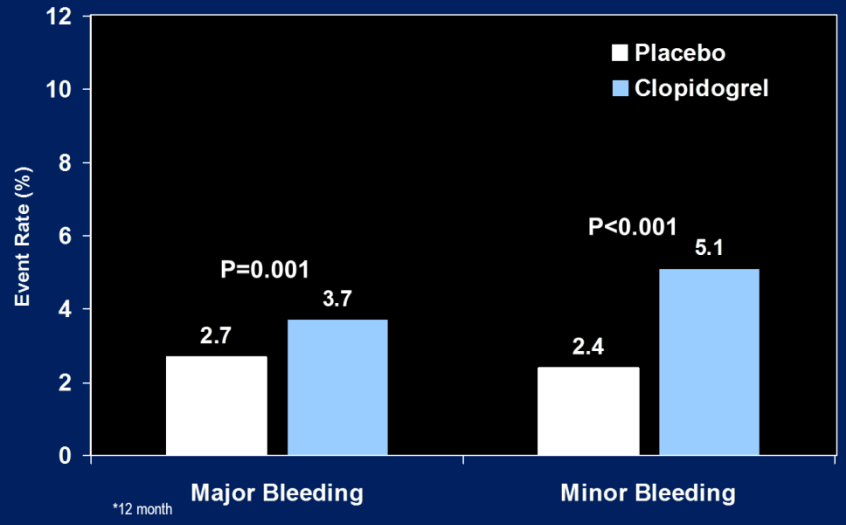
Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015

ACS

CURE Efficacy



CURE Safety*



57% no cath…

20% PCI

Yusuf S, et al. *N Engl J Med* 2001;345:494-502

DAPT Guidelines

In patients with SCAD **pre-treatment with clopidogrel** may be considered if the **probability of PCI is high.**	IIb	C
Pre-treatment with a P2Y12 inhibitor is generally recommended in patients in whom **coronary anatomy is known** and the decision to proceed to PCI is made as well as in **patients with STEMI**	I	A
In NSTE-ACS patients undergoing invasive management, ticagrelor or clopidogrel if ticagrelor is not an option, should be considered **as soon as the diagnosis is established.**	IIa	C
In NSTE-ACS patients İt is not recommended to administer **prasugrel** in patients in whom coronary anatomy is not known.	III	B

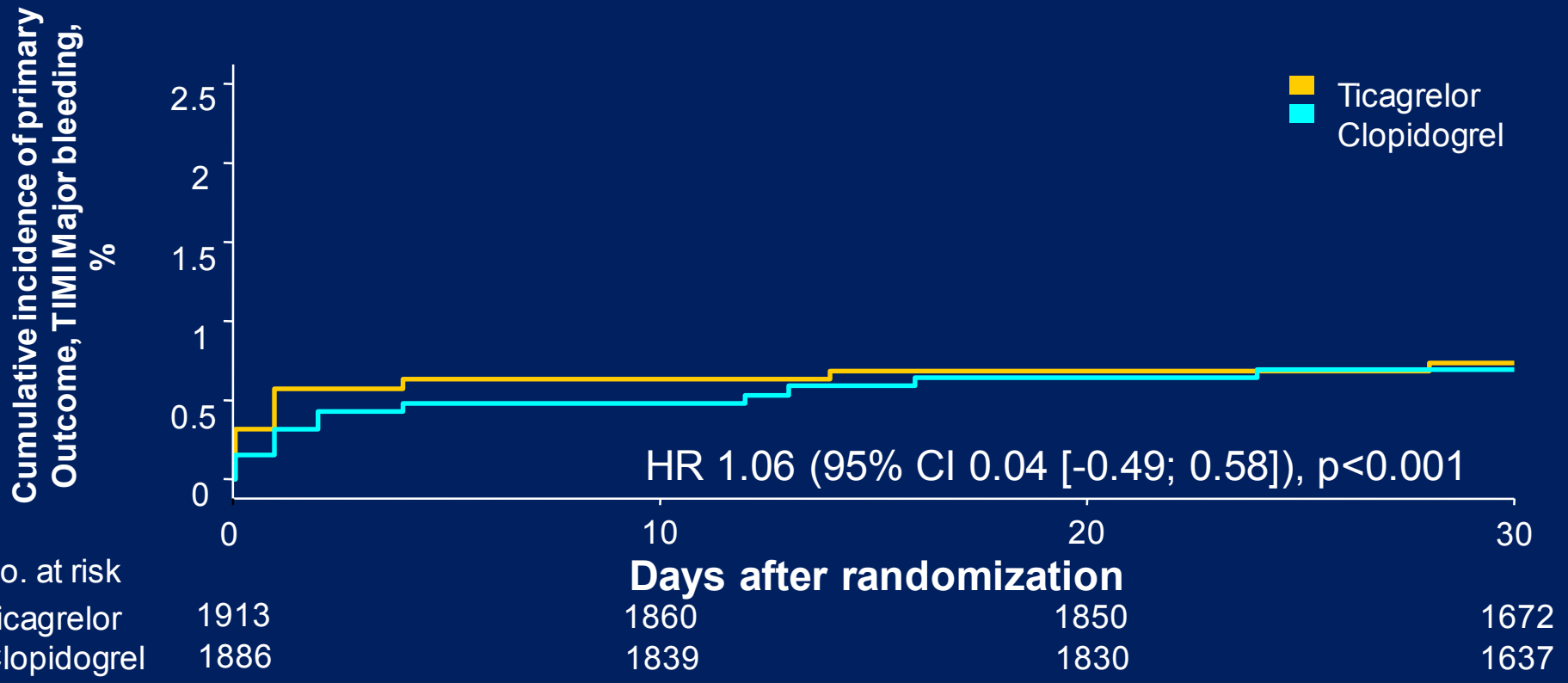
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

$P2Y_{12}$ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(291)
• $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – Clopidogrel – Ticagrelor*	300-mg or 600-mg loading dose, then 75 mg/d 180-mg loading dose, then 90 mg BID	I	B	(289,292) (293,294)
• $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B	(293,296,302, 330,331)
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B	(293,294)

P2Y12 RA with fibrinolysis

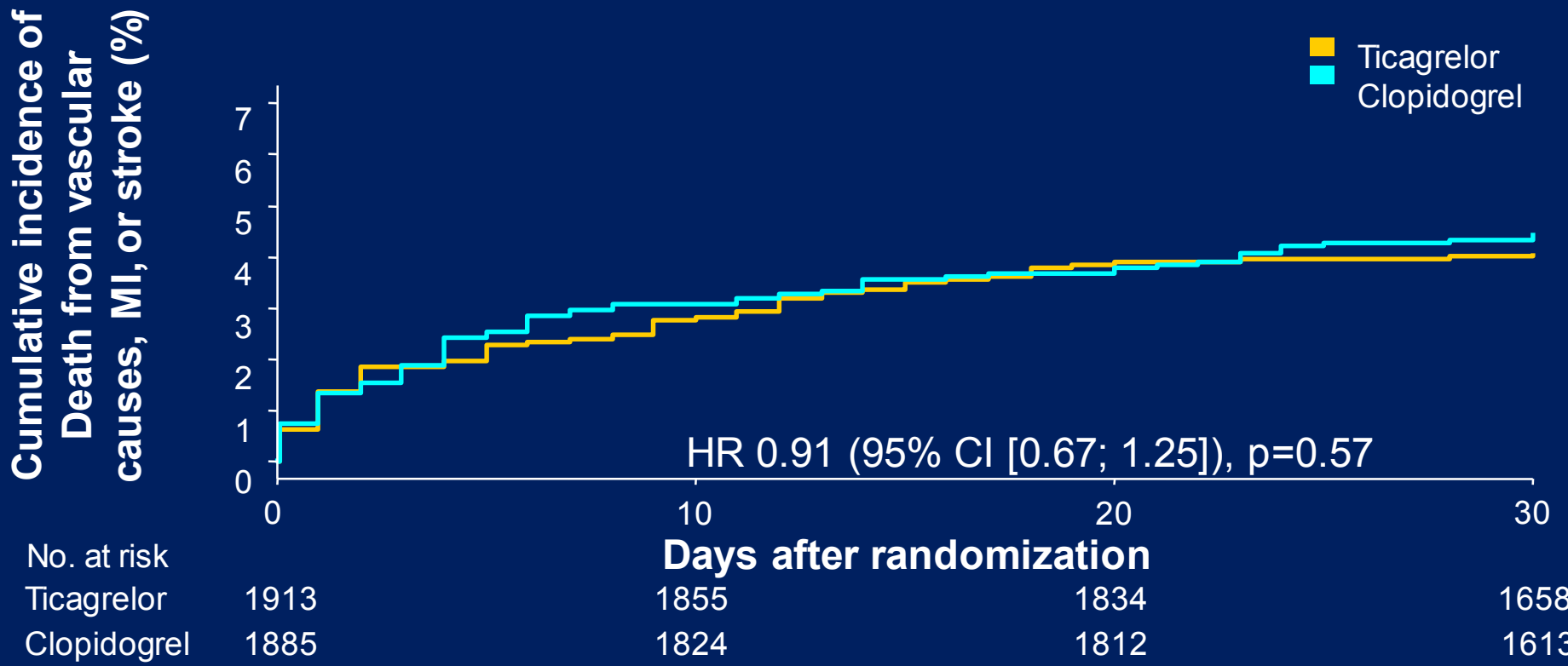
Time to major bleeding – primary safety event



Jama cardiol 2018

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Secondary efficacy – outcomes over time



No. at risk				
Ticagrelor	1913	1855	1834	1658
Clopidogrel	1885	1824	1812	1613

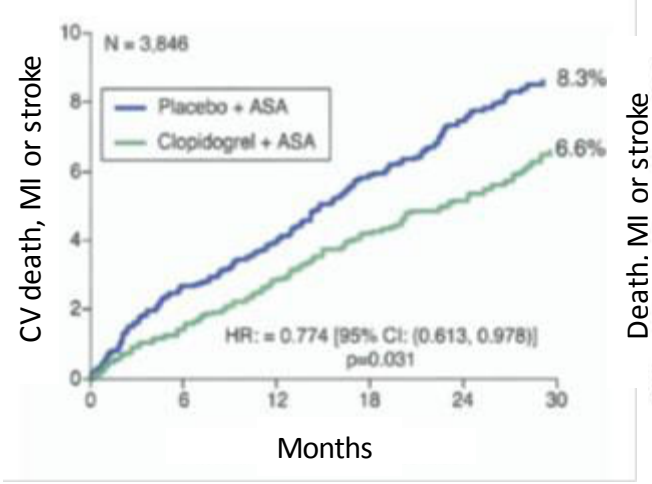
Jama cardiol 2018

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

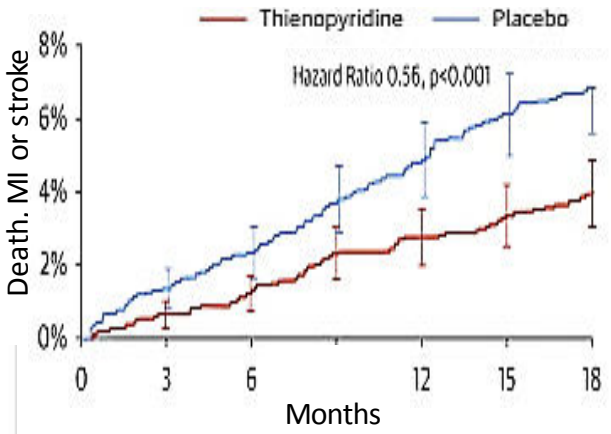
DAPT prolongation to improve post-ACS prevention

DAPT > 1year after Myocardial Infarction

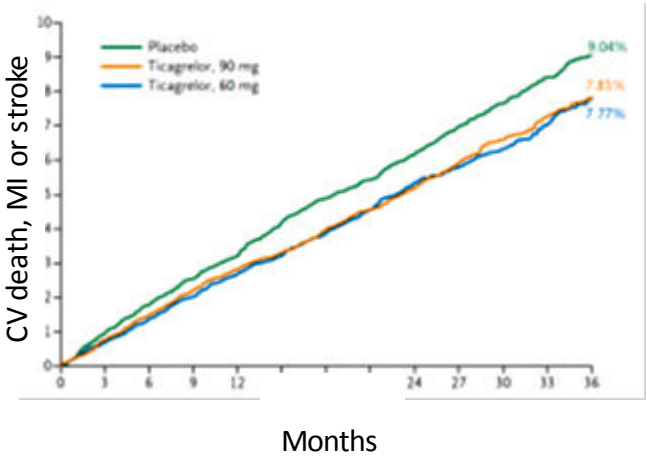
CHARISMA (prior MI subgroup)



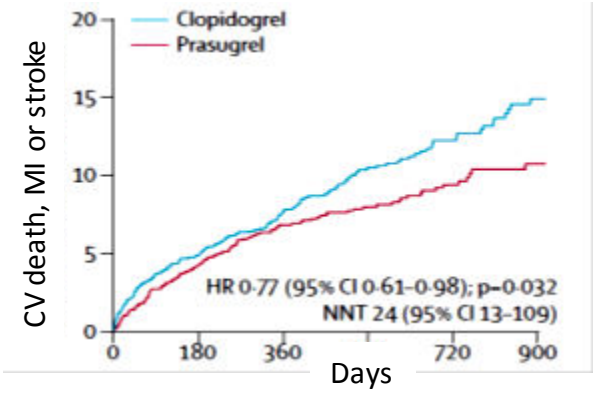
DAPT (prior MI subgroup)



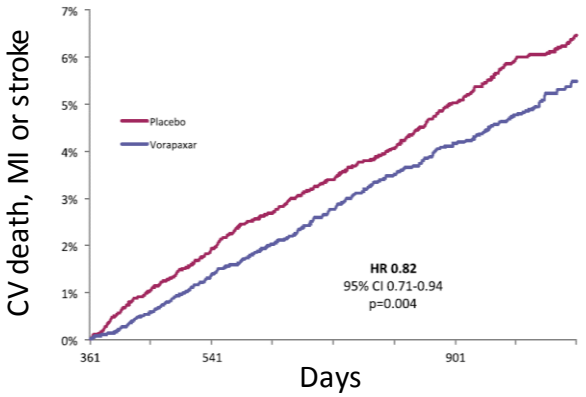
PEGASUS-TIMI 54 trial (prior MI)



TRILOGY (prior angiogram subgroup)

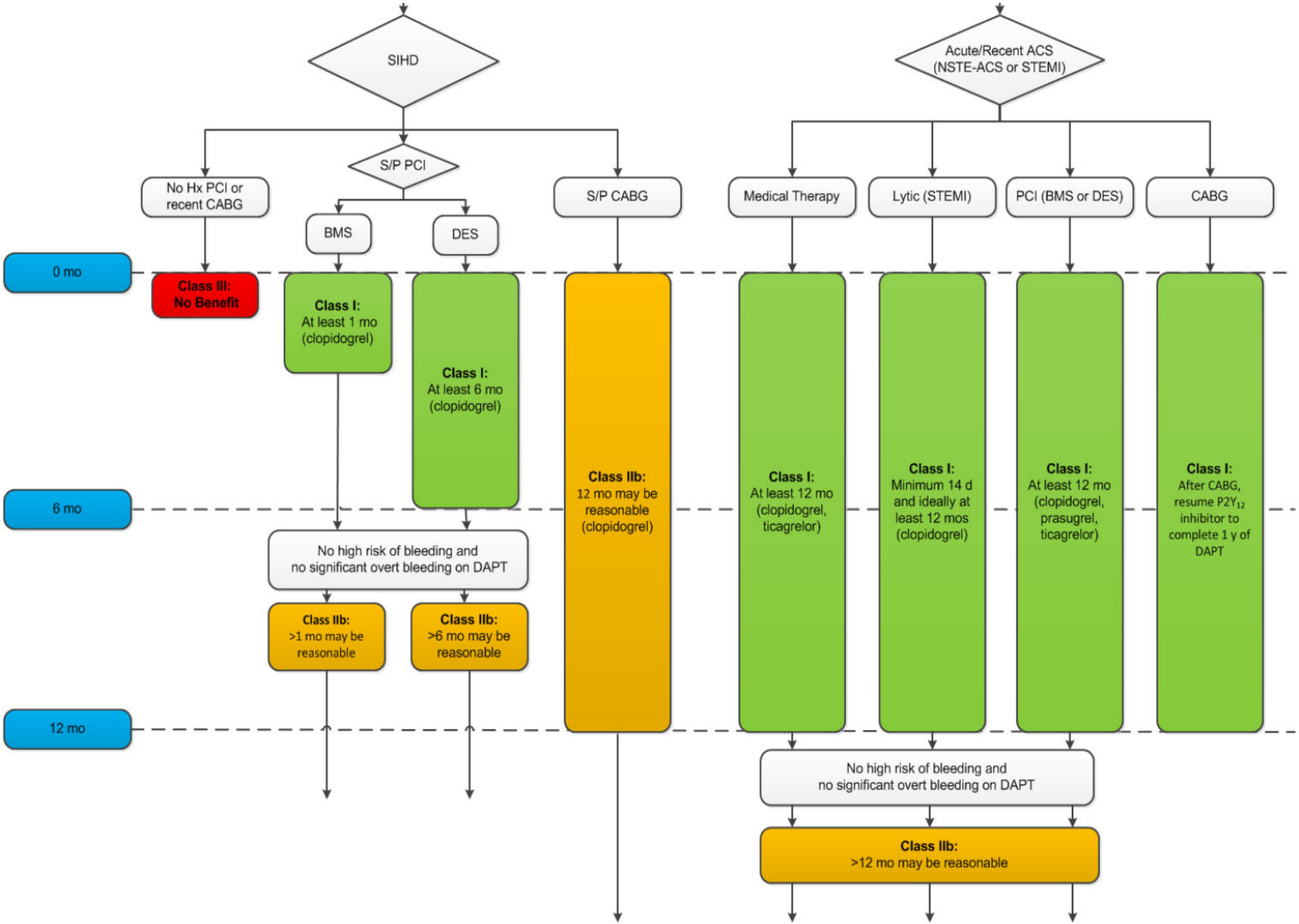


TRA-2P (prior MI subgroup)



Montalescot G and Sabatine M. EHJ 2015

Duration of DAPT in CAD



Oral dual antiplatelet therapy: what have we learnt from recent trials?

Gilles Montalescot[1]* and Marc S. Sabatine[2]

[1]ACTION Study Group, Institute of Cardiology, Pitié-Salpêtrière Hospital (AP-HP), Université Paris-6, Paris 75013, France; and [2]TIMI Study Group, Division of Cardiovascular Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

Duration of DAPT in ACS

SAPT only

- No Q-wave
- No prior stent
- No prior CABG
- No coronary angio
- No CT scan
- Negative troponin
- High bleeding risk

3-month DAPT

- Documented obstructive CAD
- Recent/prior bleeding
- Scheduled surgery
- Oral anticoagulation needed

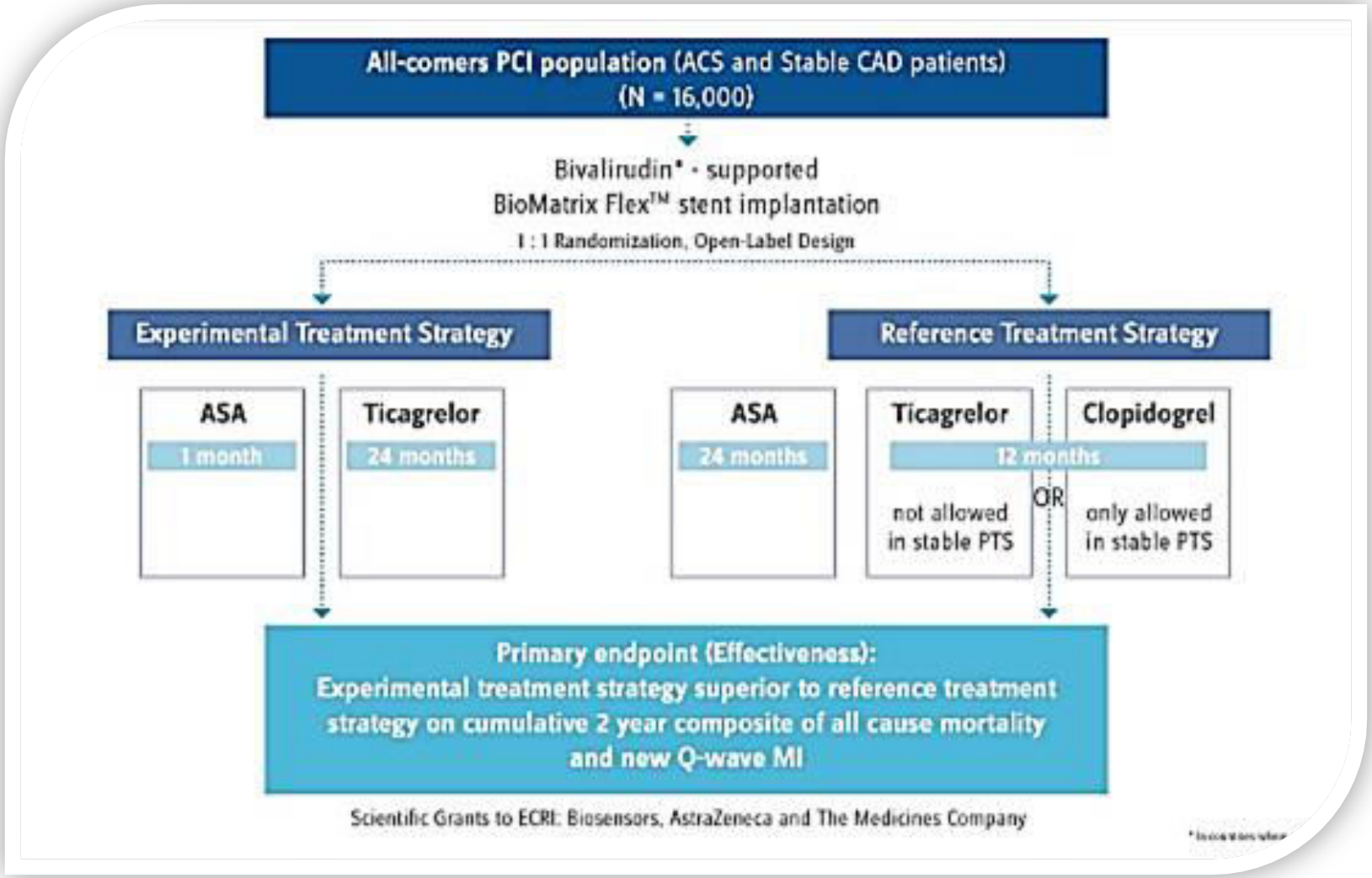
6–12 month DAPT

- Documented obstructive CAD
- Bleeding risk factors (age, gender, anaemia...)

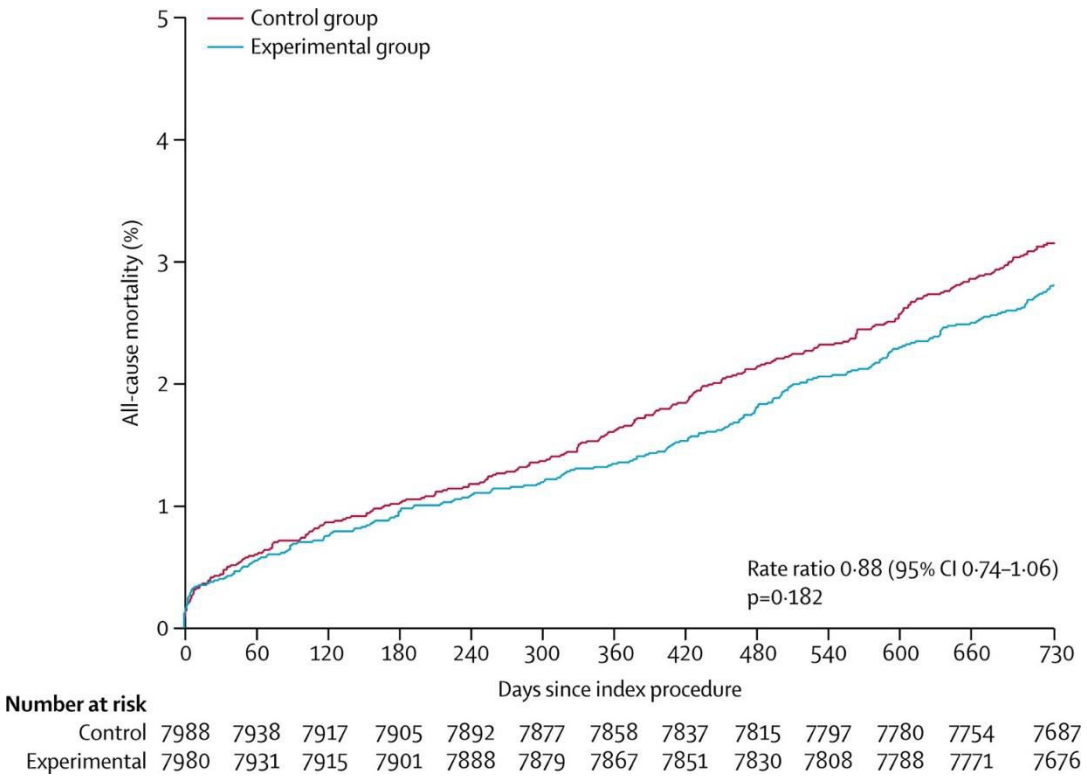
> 12-month DAPT

- Documented obstructive CAD
- No excess bleeding risk
- No bleeding event during 1st year of DAPT

Global-leaders



Global-leaders



	Experimental treatment group (N=7980)	Control group (N=7988)	Rate ratio (95% CI)	p value
All-cause mortality or new Q-wave myocardial infarction	304 (3·81%)	349 (4·37%)	0·87 (0·75–1·01)	0·073
All-cause mortality	224 (2·81%)	253 (3·17%)	0·88 (0·74–1·06)	0·182
New Q-wave myocardial infarction*	83 (1·04%)	103 (1·29%)	0·80 (0·60–1·07)	0·14
Composite of all-cause mortality, stroke, or new Q-wave myocardial infarction	362 (4·54%)	416 (5·21%)	0·87 (0·76–1·00)	0·056
Myocardial infarction	248 (3·11%)	250 (3·13%)	1·00 (0·84–1·19)	0·98
Stroke				
Overall	80 (1·00%)	82 (1·03%)	0·98 (0·72–1·33)	0·90
Ischaemic	63 (0·79%)	68 (0·85%)	0·93 (0·66–1·31)	0·68
Haemorrhagic	13 (0·16%)	9 (0·11%)	1·45 (0·62–3·39)	0·39
Undetermined	6 (0·08%)	5 (0·06%)	1·21 (0·37–3·95)	0·76
Revascularisation	739 (9·26%)	793 (9·93%)	0·93 (0·84–1·03)	0·17
Target vessel revascularisation	389 (4·87%)	442 (5·54%)	0·88 (0·77–1·01)	0·068
Definite stent thrombosis	64 (0·80%)	64 (0·80%)	1·00 (0·71–1·42)	0·98
BARC				
BARC 3 or 5 bleeding	163 (2·04%)	169 (2·12%)	0·97 (0·78–1·20)	0·77
BARC 5 bleeding				
Any	22 (0·28%)	24 (0·30%)	0·92 (0·52–1·64)	0·78
5b bleeding	15 (0·19%)	18 (0·23%)	0·84 (0·42–1·66)	0·61
5a bleeding	7 (0·09%)	6 (0·08%)	1·17 (0·39–3·49)	0·78
BARC 3 bleeding				
Any	150 (1·88%)	159 (1·99%)	0·95 (0·76–1·18)	0·63
3c bleeding	35 (0·44%)	25 (0·31%)	1·41 (0·84–2·35)	0·19
3b bleeding	53 (0·66%)	74 (0·93%)	0·72 (0·51–1·02)	0·065
3a bleeding	77 (0·96%)	70 (0·88%)	1·10 (0·80–1·53)	0·55

Shown are the first event per event type for each patient only. Multiple events of the same type within the same patient are disregarded. Data were censored 730 days after index percutaneous coronary intervention. BARC=Bleeding Academic Research Consortium.[13] *New Q-wave or equivalent left bundle branch block (n=3) as adjudicated by the core laboratory.

Table 3: Primary and prespecified secondary outcomes

Vranckx P et a. Lancet 2018

TWILIGHT

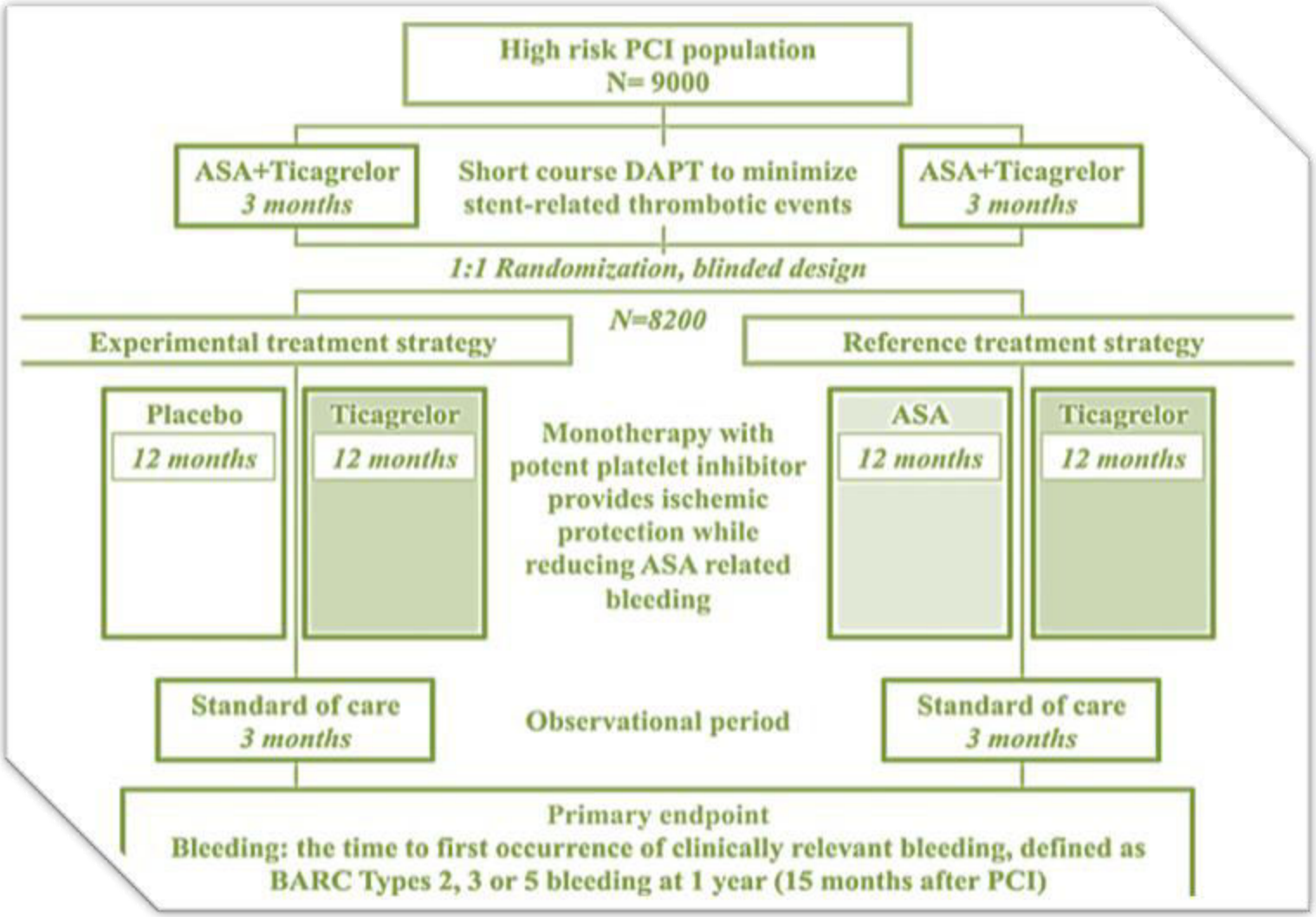
Elective

3 mths

Ticagrelor

1 year

Bleeding



Removing ASA after PCI

Study	n	Drug left	Efficacy	Safety
GLOBAL-LEADERS	16,000	ticagrelor	→	→
TWILIGHT	9,000	ticagrelor	?	?
TICO	3,056	ticagrelor	?	?
SMART-CHOICE	3,000	clopidogrel	?	?
STOPDAPT-2	3,045	clopidogrel	?	?

De-escalation if HBR

Scores (DAPT)

DAPT STUDY

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DAPT Score Calculator

Patient Characteristics

Age: Between 65 and 74

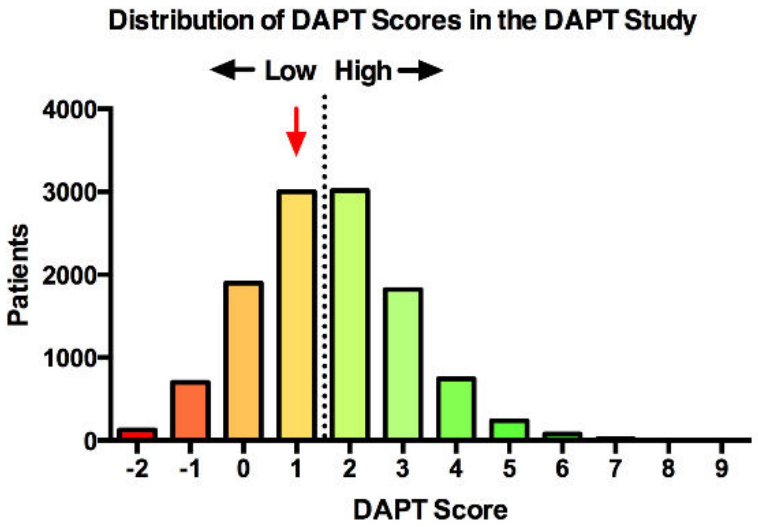
- Diabetes Mellitus ☑
- Cigarette Smoking Within Last Two Years ☐
- Prior Myocardial Infarction or Percutaneous Coronary Intervention ☑
- History of Congestive Heart Failure or Left Ventricular Ejection Fraction < 30% ☐

Index Procedure Characteristics

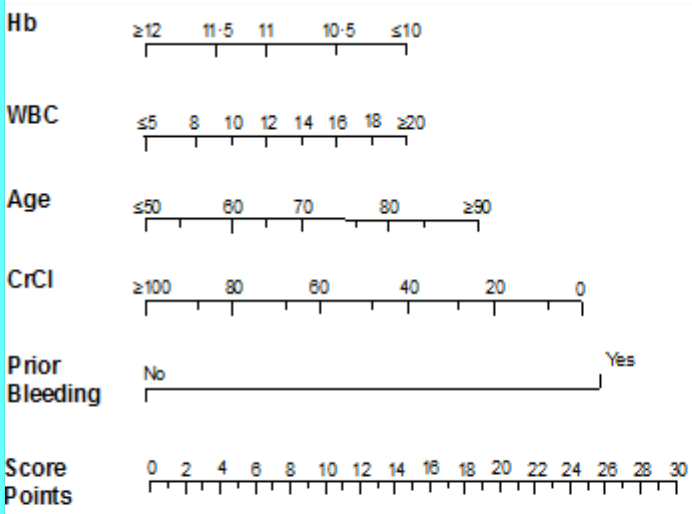
- Myocardial Infarction at Presentation ☐
- Stenting of Vein of Graft ☐
- Stent Diameter < 3mm ☐

DAPT Score = 1: LOW

Calculated DAPT Score Shown by Red Arrow



Scores to help decision

PRECISE DAPT score	DAPT score
At the time of coronary stenting	After 12 months of uneventful DAPT
Short DAPT (3-6 months) vs. Standard/Long DAPT (12-24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
	Age ≥75 –2 pt 65 to <75 –1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt
0 to 100 points	-2 to 10 points
Score ≥25	Score ≥2
www.precisedaptscore.com	www.daptstudy.org

Costa F. et al. Lancet 2017

Yeh RW et al. JAMA 2016

Scores (Paris)

Risk score for Major bleeding

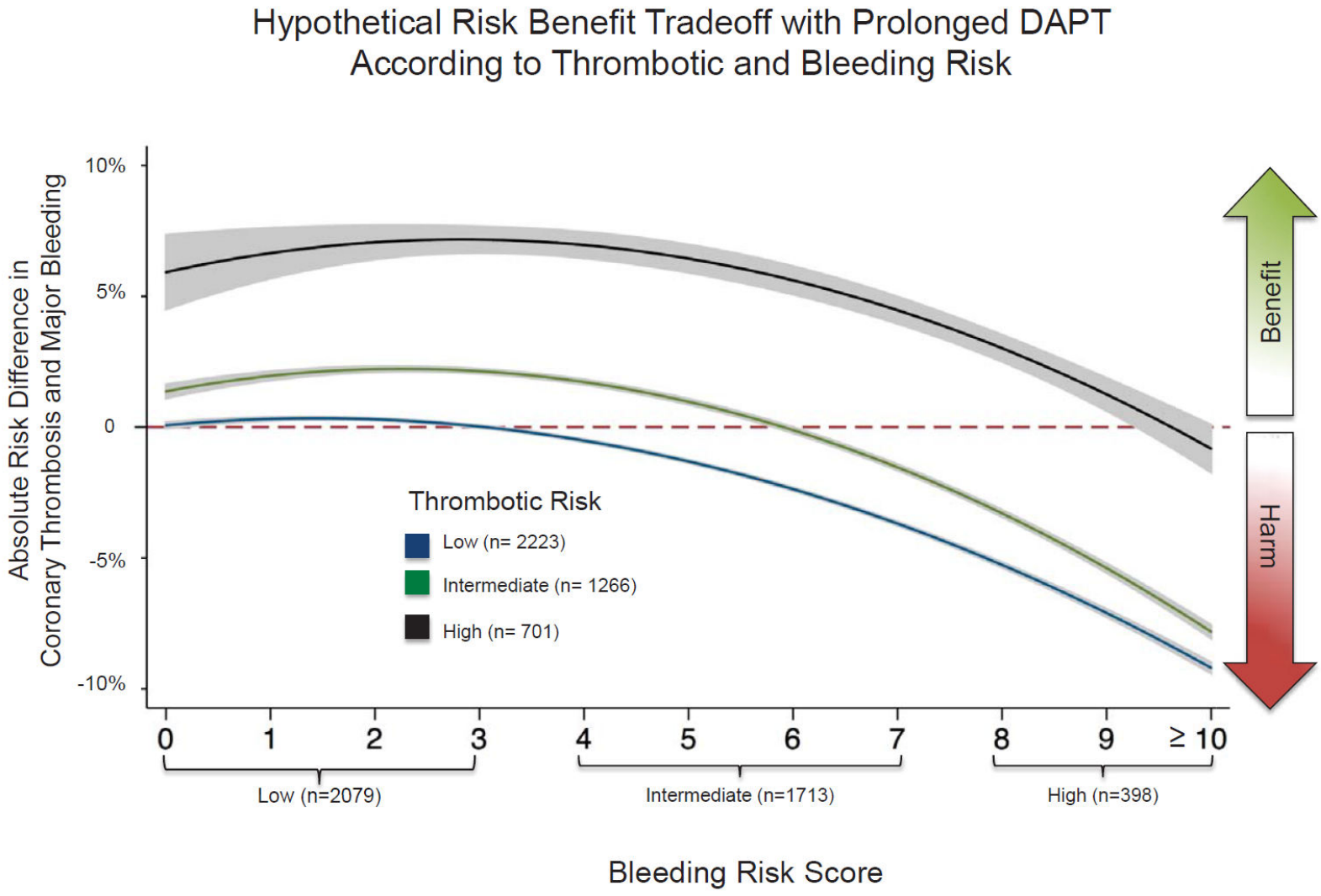
Age	0 → 4
BMI	0 → 2
Current smoking	0 → 2
Anemia	0 → 3
CrCl < 60	0 → 2
Triple therapy	0 → 2

Risk score for coronary event

Diabetes	0 → 4
ACS	0 → 2
Current smoking	0 → 2
Prior PCI	0 → 3
CrCl < 60	0 → 2
Prior CABG	0 → 2

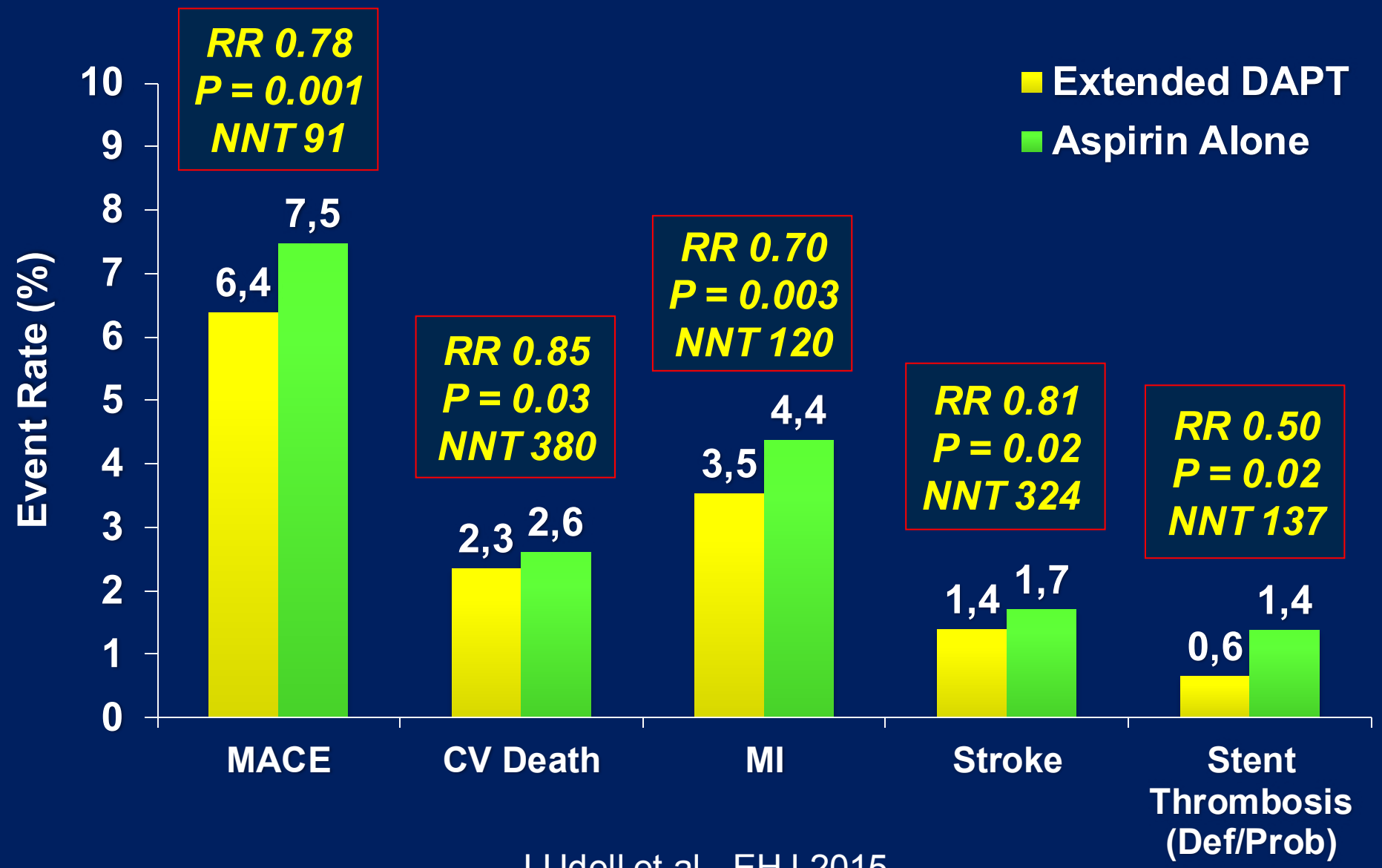
Baber U. et al. JACC 2016

Scores (Paris)



Baber U. et al. JACC 2016

Individual CV Endpoints



J Udell et al - EHJ 2015

Tradeoff between ischemic and bleeding risk

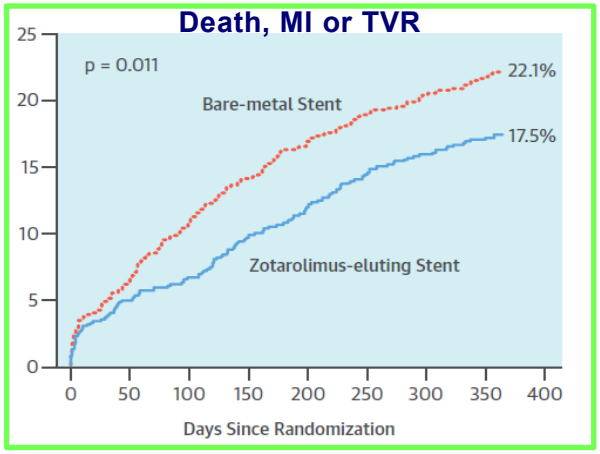
- Prolongation of DAPT for 18-36 months **in post-DES patients:**
  - –↘ ~1-2% of ST / MACE
  - –↗ ~1% of MB
  - – Neutral on death

- Prolongation of DAPT for 18-36 months **in post-MI patients:**
  - –↘ ~1% of ST / MACE
  - –↗ ~1% of MB
  - –↘ ~0.3% CV death

Duration de-escalation

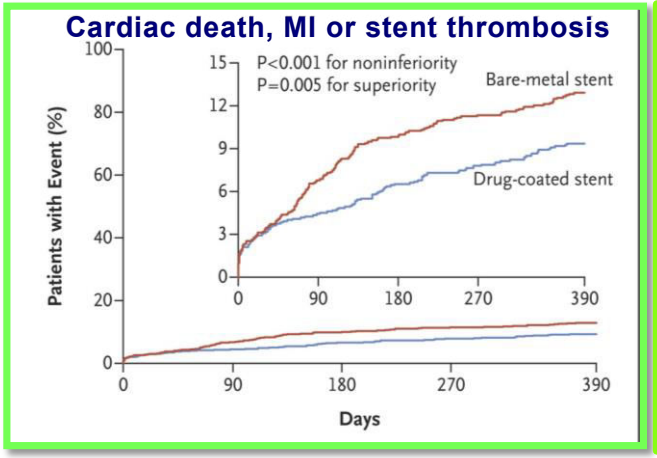
STENT in high bleeding risk

ZEUS study (n=1606)



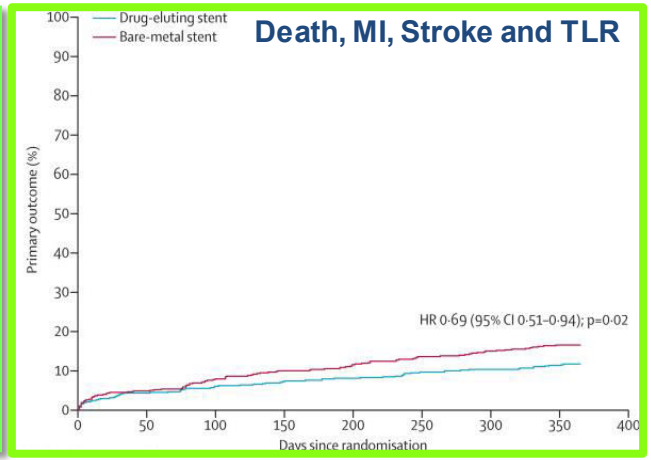
Valgimigli M et al. JACC 2015

LEADERS-FREE study (n=2466)



Urban P et al. NEJM 2015

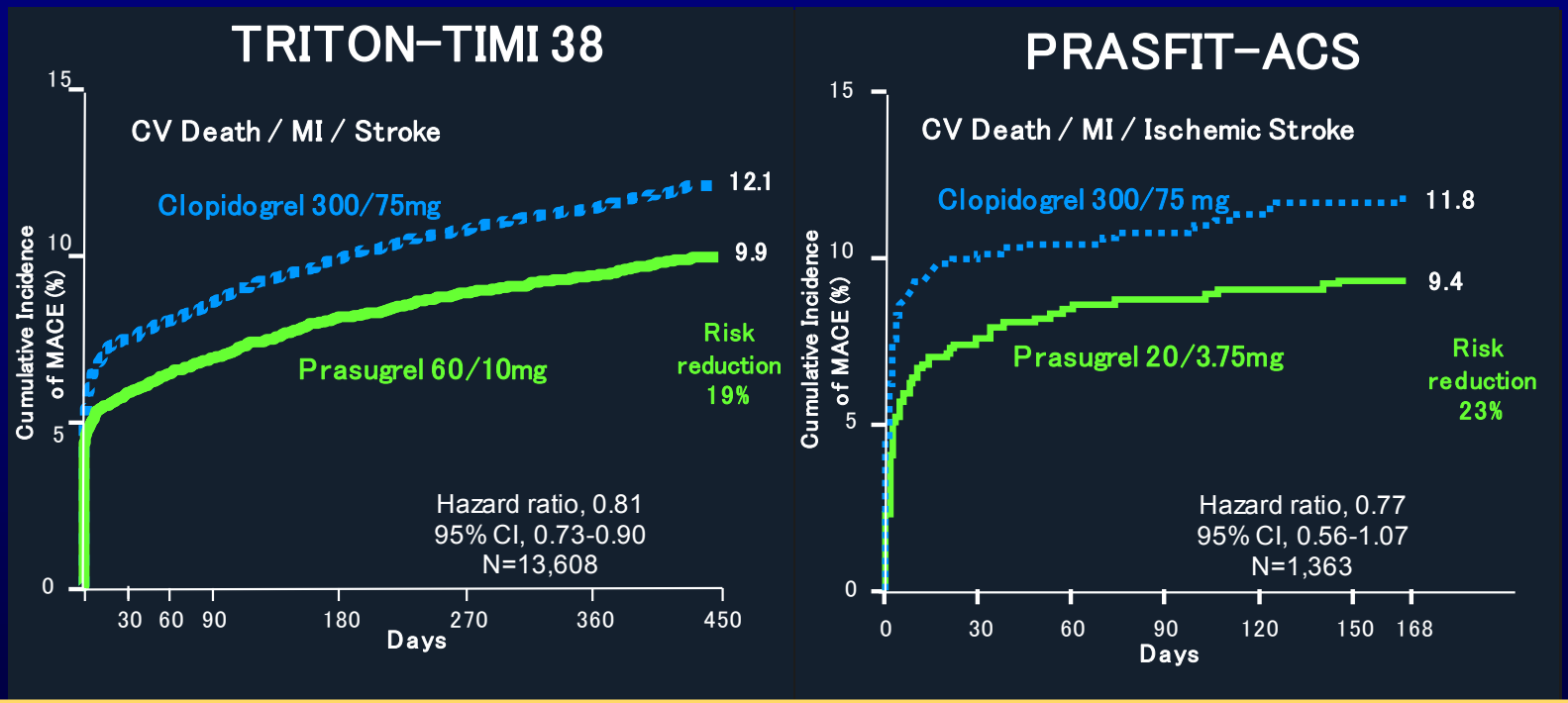
SENIOR study (n=1200)



Varenne O et al. Lancet 2017

Dose de-escalation

PRASFIT-ACS



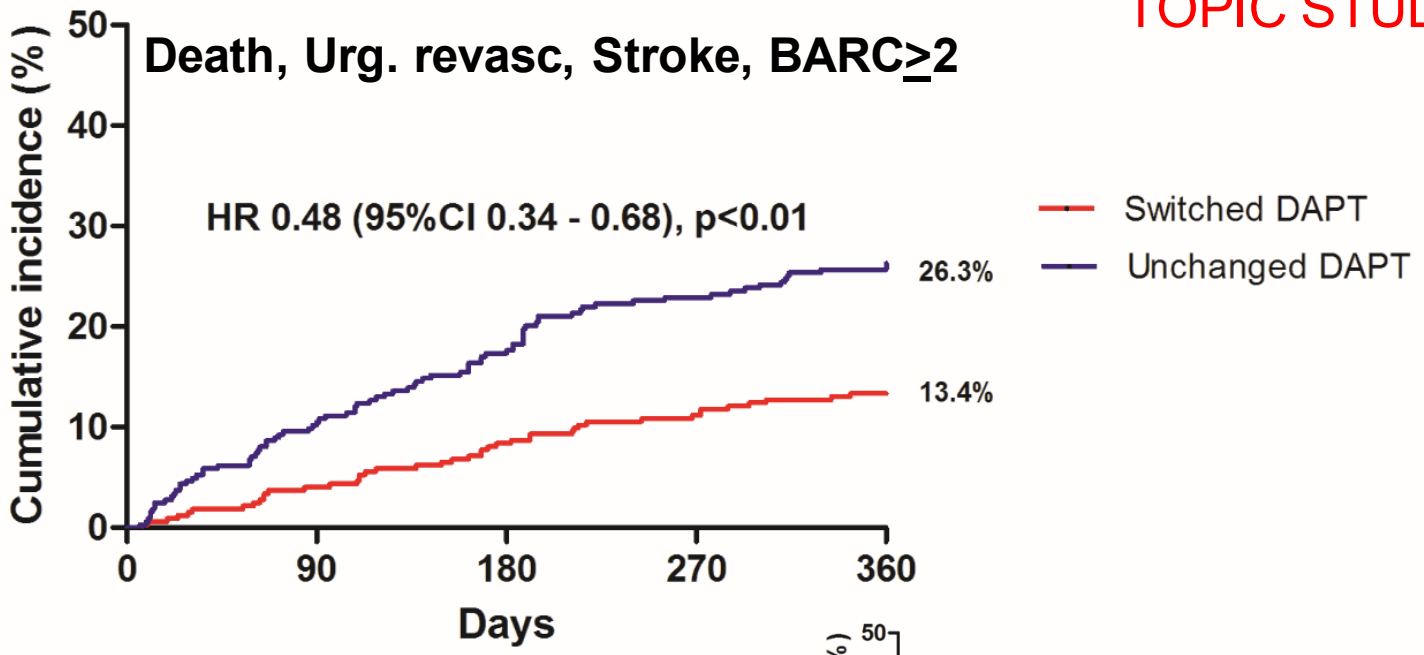
Major Bleed	2.2% prasu vs. 1.7% clopi	1.9 % prasu vs. 2.2% clopi

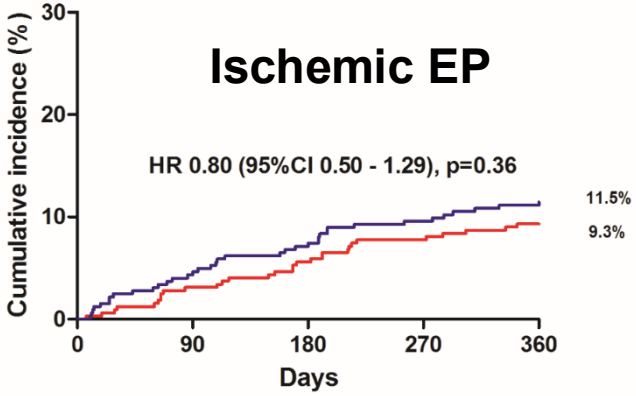
Wiviott S et al. NEJM 2007;357:2001–2015

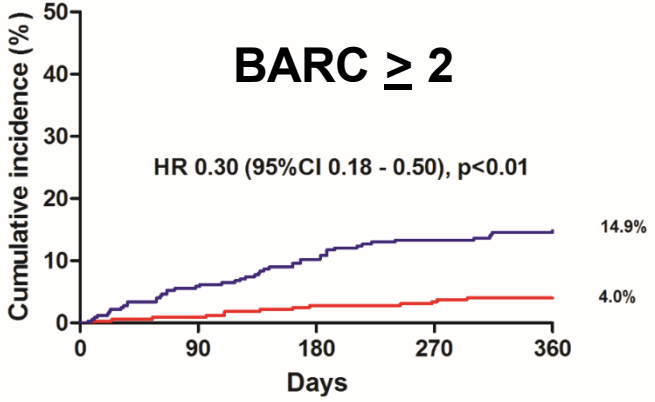
Saito S, et al. Circ J 2014; 78: 1684–92.

Time-related de-escalation

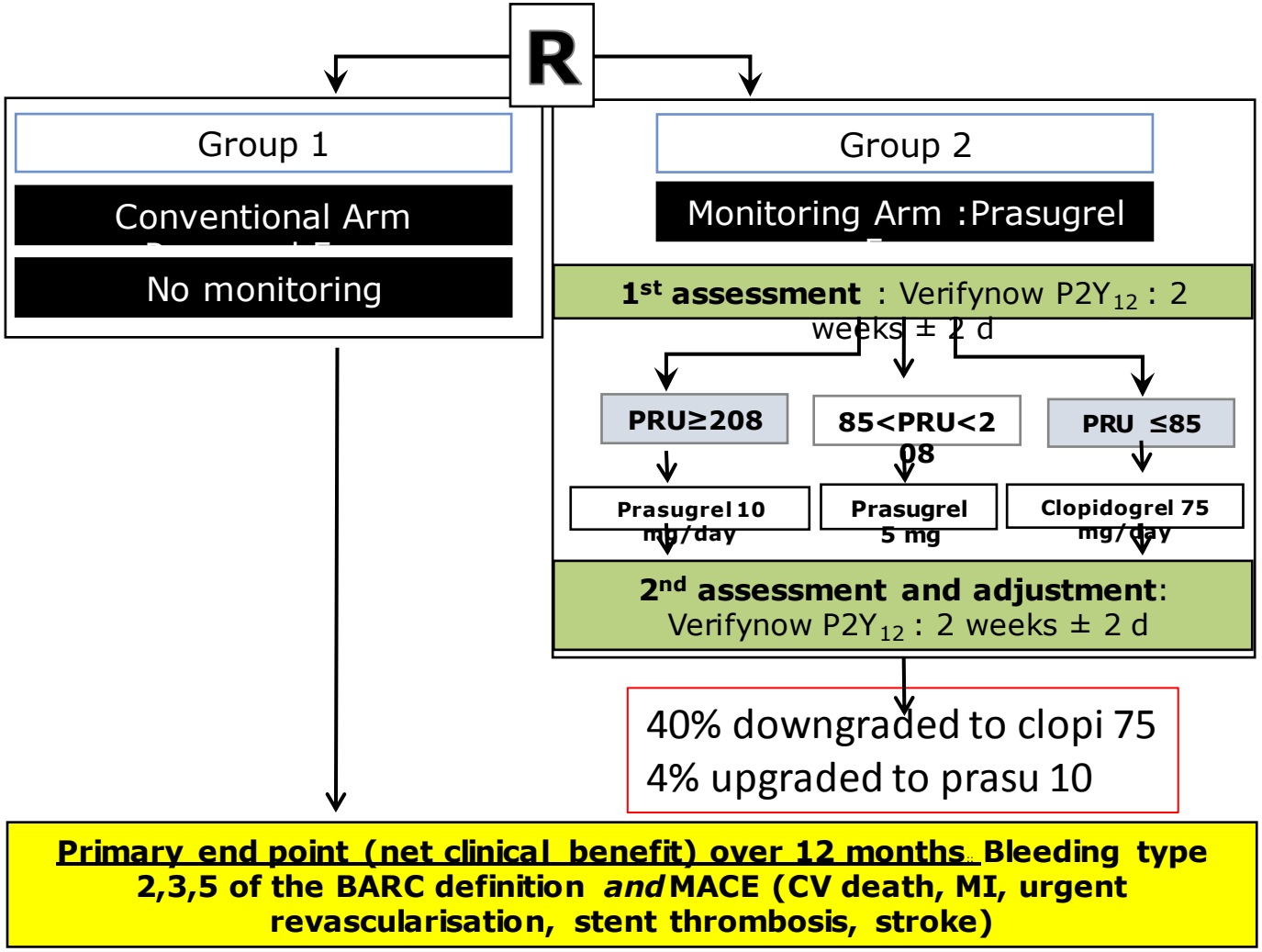
TOPIC STUDY







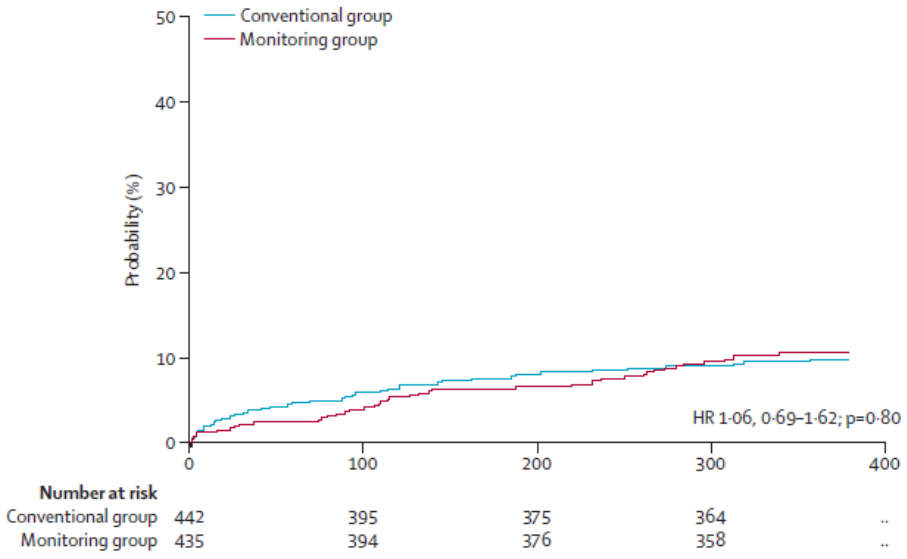
PFT-guided de-escalation: ANTARCTIC



PFT-guided de-escalation

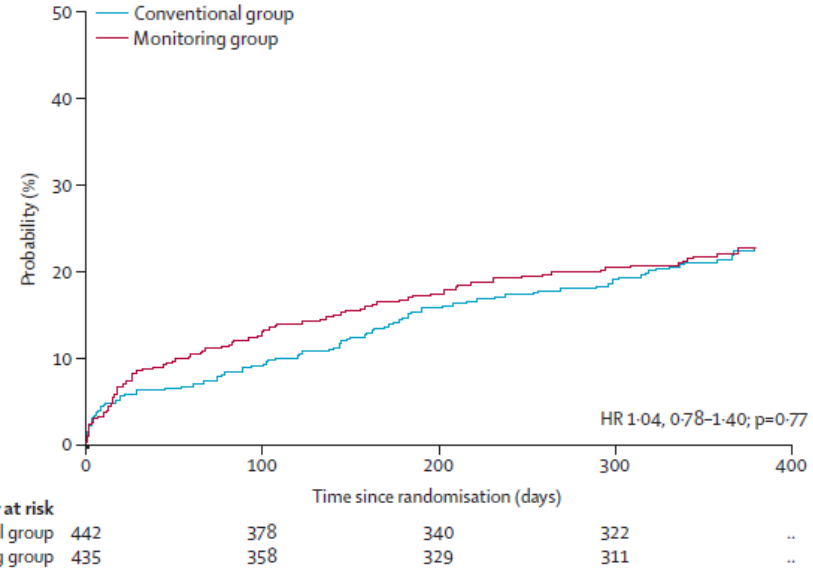
Ischemic Endpoint

CV death, MI, stent thrombosis, urgent revascularization



Bleeding Endpoint

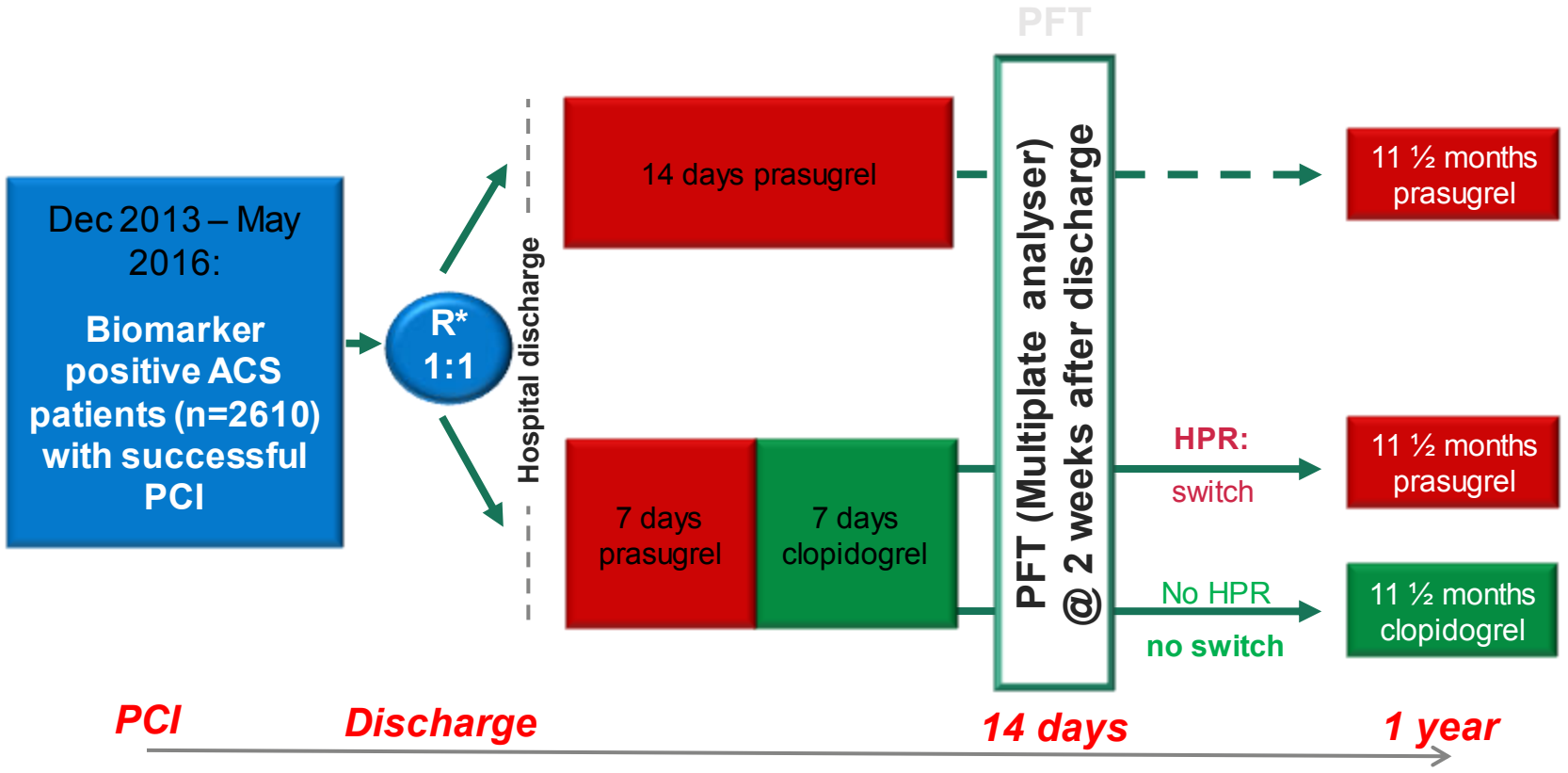
BARC 2,3,5



Cayla G. for the ANTARCTIC investigators. Lancet 2016

TROPICAL ACS

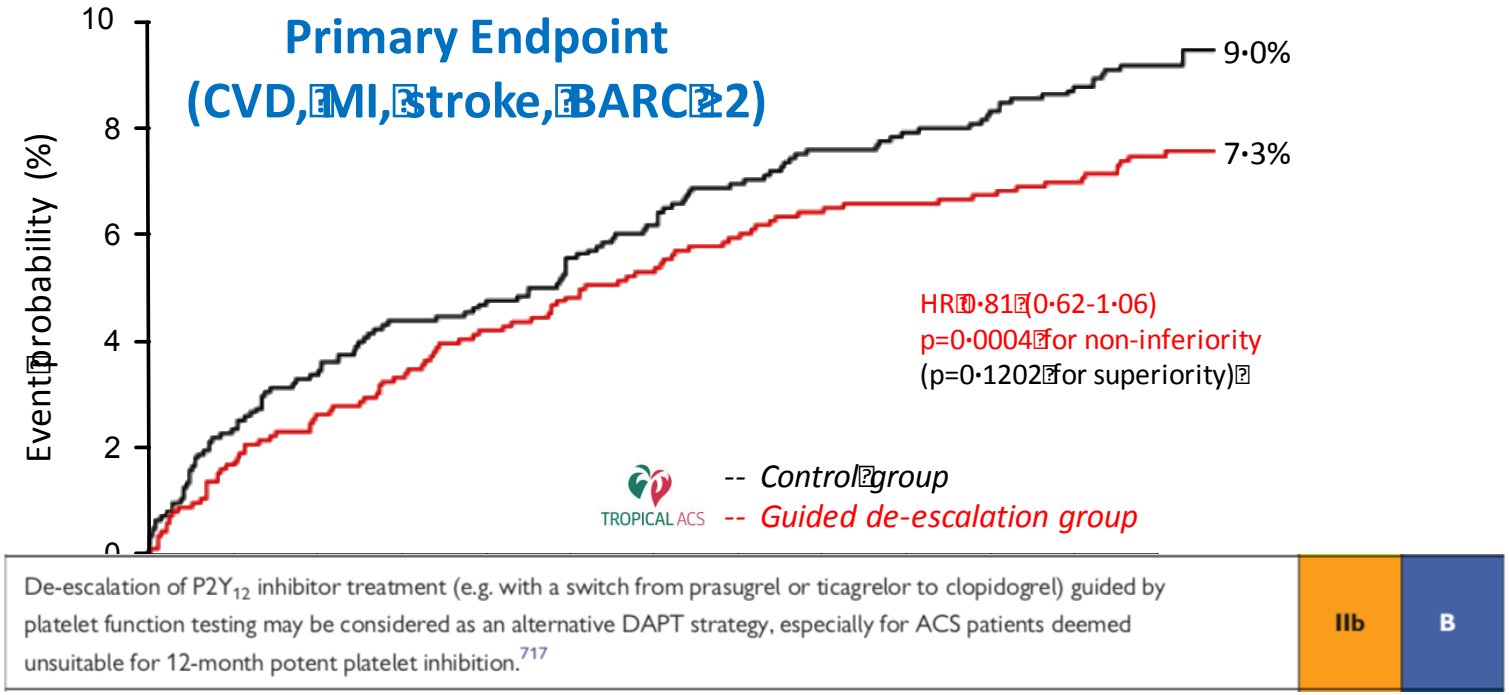
DE-ESCALATION



Sibbing, Aradi et al., Lancet 2017;390:1747-1757 .

TROPICAL ACS

DE-ESCALATION



De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition.[717]

IIb | B

Sibbing, Aradi et al., Lancet 2017;390:1747-1757 .
Neumann FJ et al. EHJ 2018;00,1–96.

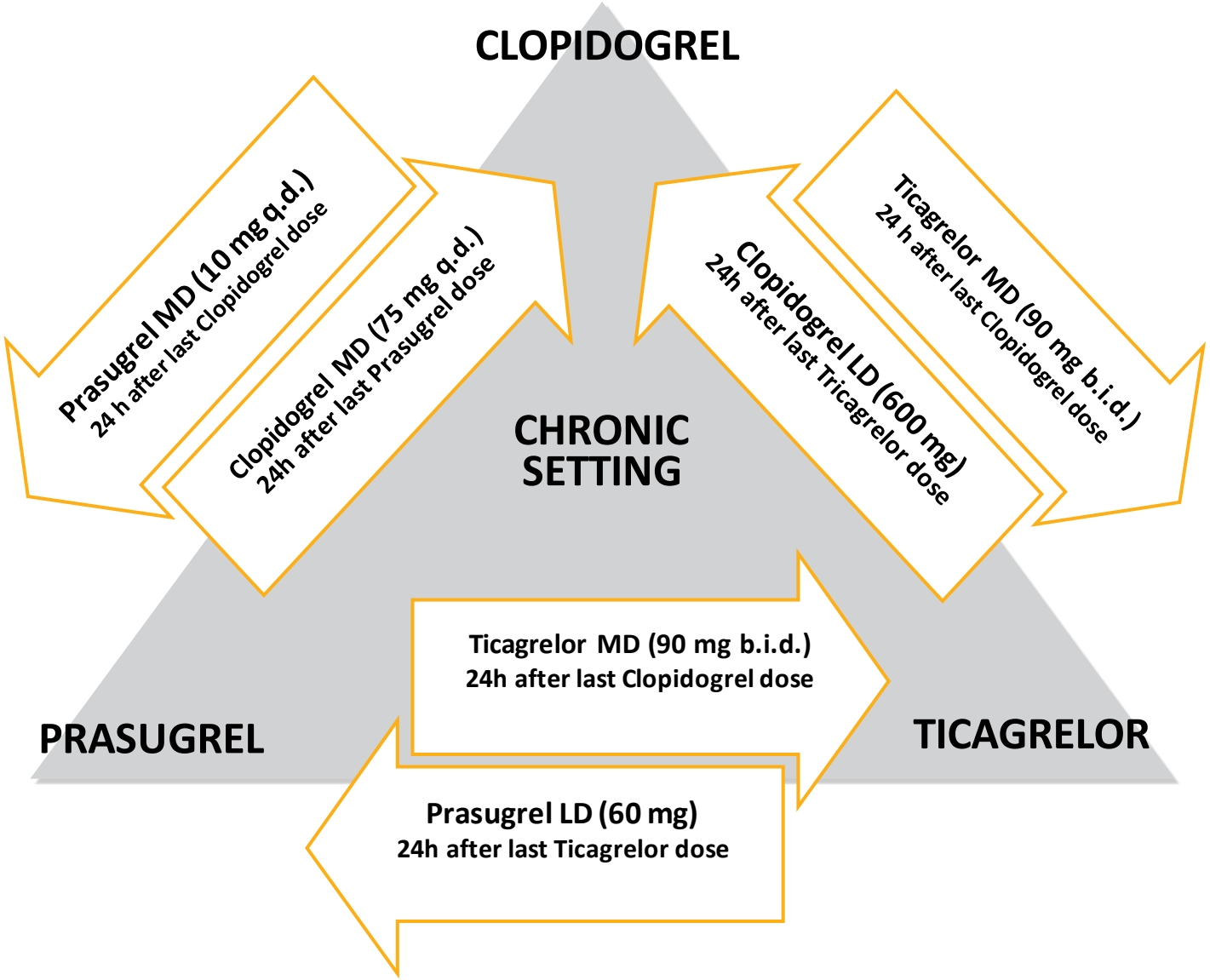
RESULTS: INDEPENDENT PREDICTORS OF BLEEDING

	Univariate analyses		Multivariate model	
	HR (95% CI)	**p**	**HR (95% CI)**	**P**
Age (years)	1.02 (1.01-1.04)	0.003	**1.02 (1.00-1.03)**	**0.04**
Female gender	1.47 (1.08-2.00)	0.015		-
BMI (kg/m^2)	0.96 (0.93-0.99)	0.014	**0.97 (0.93-0.99)**	**0.04**
STEMI vs. NSTEMI	0.69 (0.53-0.92)	0.010	**0.72 (0.54-0.95)**	**0.02**
LPR	1.71 (1.26-2.33)	0.001	**1.65 (1.21-2.26)**	**0.002**
Hemoglobin level (g/dl)	0.91 (0.85-0.97)	0.002	**0.92 (0.86-0.98)**	**0.008**
Prasugrel use **(both in control and guided groups)**	1.20 (0.88-1.65)	0.25		-
CKD 3-5	1.55 (0.95-2.51)	0.08		-

Risk factors of bleeding

- Short life expectancy
- Ongoing malignancy
- Poor expected adherence
- Poor mental status
- End stage renal failure
- Advanced age
- Prior major bleeding/prior haemorrhagic stroke
- Chronic alcohol abuse
- Anaemia
- Clinically significant bleeding on dual antithrombotic therapy

Algorithm for switching between oral $P2Y_{12}$ inhibitors in the chronic setting



Conclusions

1. STEMI: new P2Y12 tot, vite et fort
2. NSTEMI: P2Y12 qd diagnostic et PCI certains
3. CAD/PCI: clopidogrel
4. Switcher new P2Y12 vers clopidogrel quand haut risque hémorragique ou a distance de l'evenement
5. Prolonger ou interrompre P2Y12 ou ASA:

   → traitement individualisé (HBR)