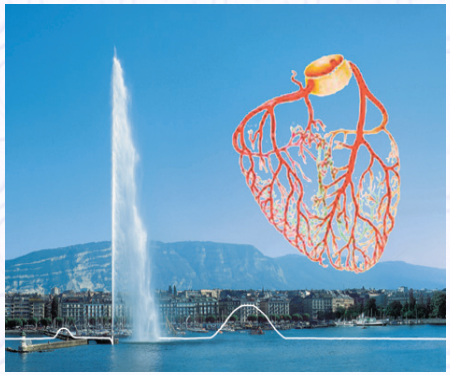
Controversies and Therapeutic Challenges : Dual Antiplatelet Therapy in ACS



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ESC GUIDELINES

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

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Conflicts of Interest

Research funding

- Abbott vascular
- Biotronik
- Biosensor
- Medtronic
- Boston Scientific

Speaker fees

- Astra Zeneca

Recommendations for platelet inhibition in NSTE-ACS

Recommendations	Class [a]	Level [b]
Oral antiplatelet therapy		
Aspirin is recommended for all patients without contra-indications at an initial oral loading dose[c] of 150–300 mg (in aspirin-naïve patients) and a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A **$P2Y_{12}$ inhibitor** is recommended, in addition to aspirin, for **12 months** unless there are contraindications such as excessive risk of bleeds.	I	A
• **Ticagrelor** (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications[d], for all patients at moderate- to high-risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• **Prasugrel** (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[d]	I	B
• **Clopidogrel** (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B

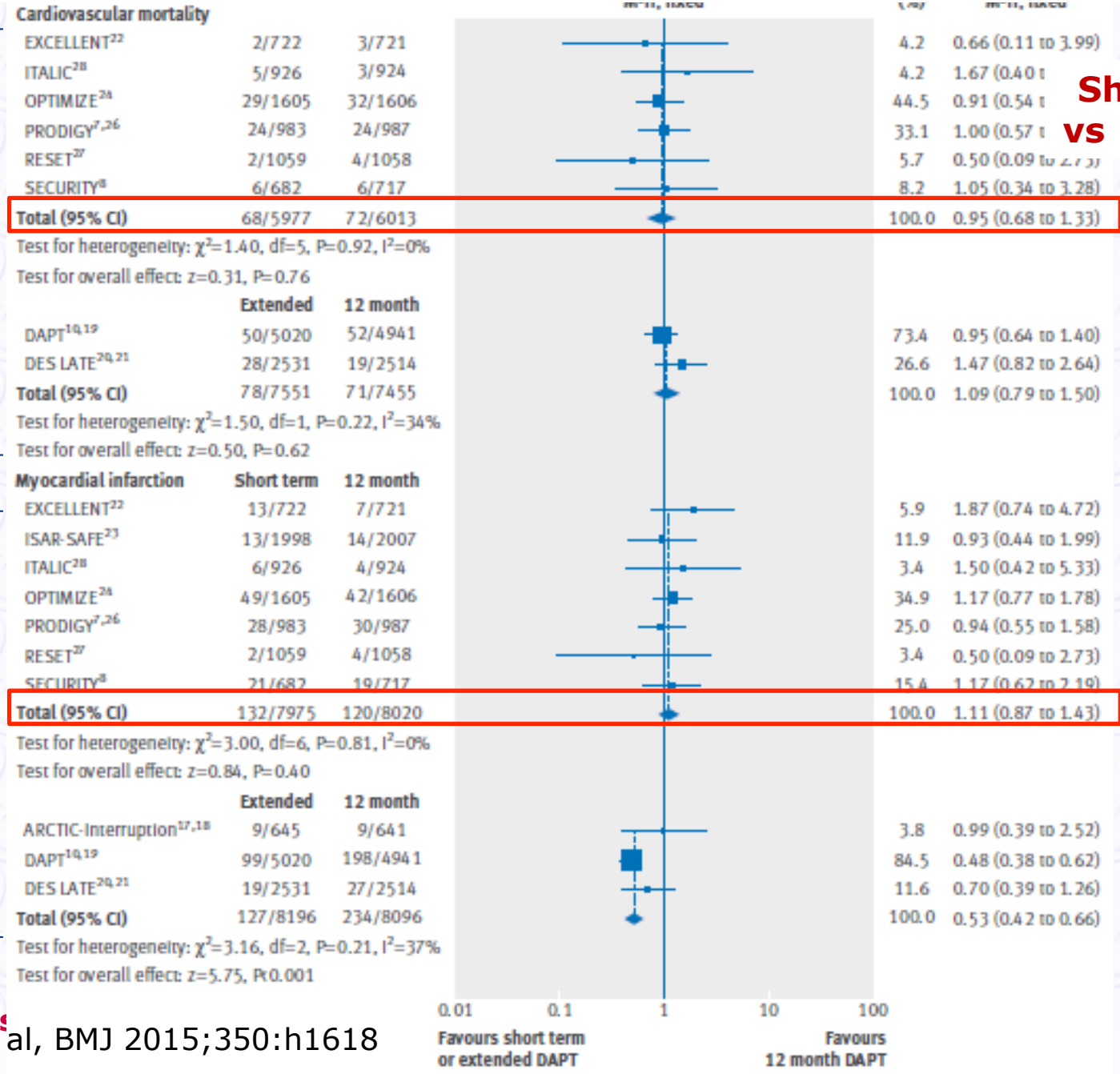
DAPT Duration after PCI with DES: Meta-analysis of RCT

CV Mortality

MI

Short term vs 12 month

Mainly stable CAD



Cardiovascular mortality				
EXCELLENT[22]	2/722	3/721	4.2	0.66 (0.11 to 3.99)
ITALIC[28]	5/926	3/924	4.2	1.67 (0.40 t
OPTIMIZE[24]	29/1605	32/1606	44.5	0.91 (0.54 t
PRODIGY[7,26]	24/983	24/987	33.1	1.00 (0.57 t
RESET[27]	2/1059	4/1058	5.7	0.50 (0.09 to 2.73)
SECURITY[8]	6/682	6/717	8.2	1.05 (0.34 to 3.28)
Total (95% CI)	68/5977	72/6013	100.0	0.95 (0.68 to 1.33)
Test for heterogeneity: χ^2=1.40, df=5, P=0.92, I^2=0%				
Test for overall effect: z=0.31, P=0.76				
	Extended	**12 month**		
DAPT[19,19]	50/5020	52/4941	73.4	0.95 (0.64 to 1.40)
DES LATE[20,21]	28/2531	19/2514	26.6	1.47 (0.82 to 2.64)
Total (95% CI)	78/7551	71/7455	100.0	1.09 (0.79 to 1.50)
Test for heterogeneity: χ^2=1.50, df=1, P=0.22, I^2=34%				
Test for overall effect: z=0.50, P=0.62				
Myocardial infarction	**Short term**	**12 month**		
EXCELLENT[22]	13/722	7/721	5.9	1.87 (0.74 to 4.72)
ISAR-SAFE[23]	13/1998	14/2007	11.9	0.93 (0.44 to 1.99)
ITALIC[28]	6/926	4/924	3.4	1.50 (0.42 to 5.33)
OPTIMIZE[24]	49/1605	42/1606	34.9	1.17 (0.77 to 1.78)
PRODIGY[7,26]	28/983	30/987	25.0	0.94 (0.55 to 1.58)
RESET[27]	2/1059	4/1058	3.4	0.50 (0.09 to 2.73)
SECURITY[8]	21/682	19/717	15.4	1.17 (0.62 to 2.19)
Total (95% CI)	132/7975	120/8020	100.0	1.11 (0.87 to 1.43)
Test for heterogeneity: χ^2=3.00, df=6, P=0.81, I^2=0%				
Test for overall effect: z=0.84, P=0.40				
	Extended	**12 month**		
ARCTIC-Interruption[17,18]	9/645	9/641	3.8	0.99 (0.39 to 2.52)
DAPT[19,19]	99/5020	198/4941	84.5	0.48 (0.38 to 0.62)
DES LATE[20,21]	19/2531	27/2514	11.6	0.70 (0.39 to 1.26)
Total (95% CI)	127/8196	234/8096	100.0	0.53 (0.42 to 0.66)
Test for heterogeneity: χ^2=3.16, df=2, P=0.21, I^2=37%				
Test for overall effect: z=5.75, P<0.001				

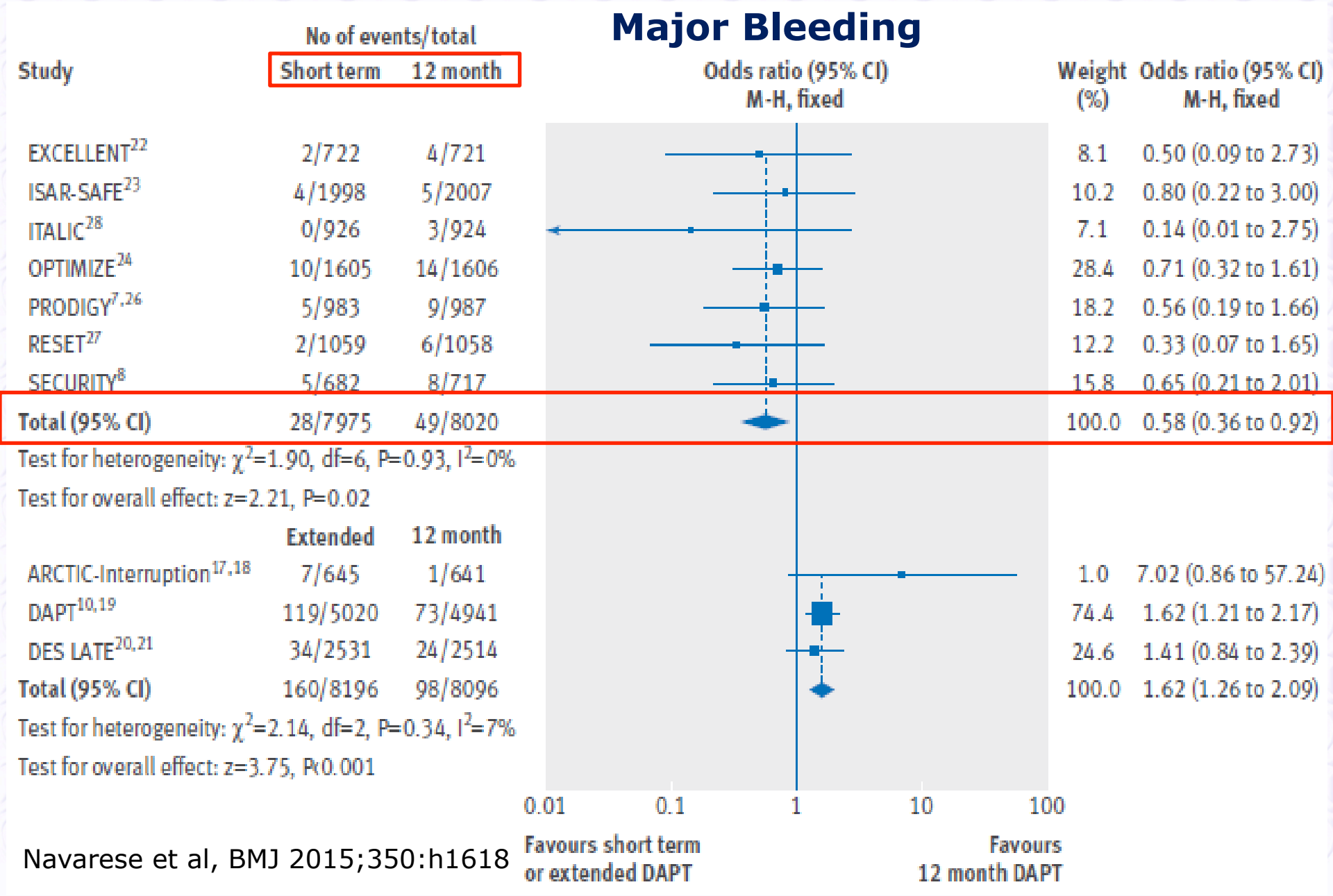
0.01 0.1 1 10 100

Favours short term or extended DAPT

Favours 12 month DAPT

Navarese et al, BMJ 2015;350:h1618

DAPT Duration after PCI with DES: Meta-analysis of RCT



Navarese et al, BMJ 2015;350:h1618

DAPT Duration and Drug-Eluting Stents

LEADERS FREE Trial

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

ACS 27%

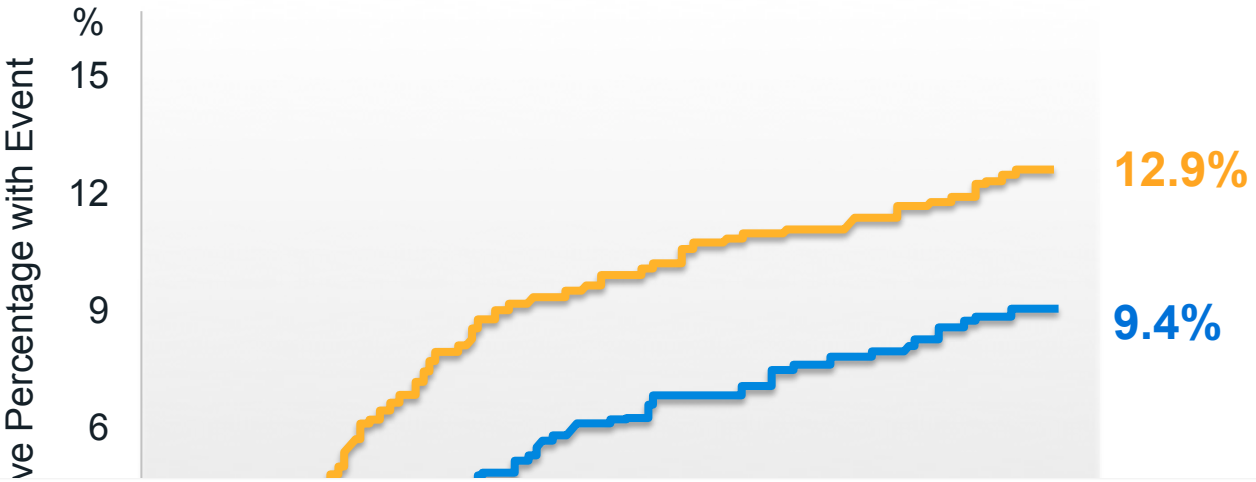
BioFreedom™ DCS **vs.** **Gazelle™ BMS**

DAPT mandated for 1 month only, followed by long-term SAPT

- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)

P. Urban, NEJM 2016

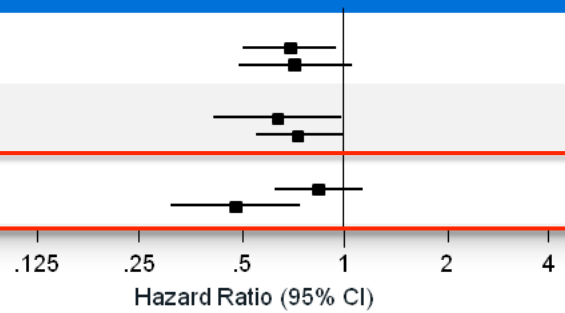
Primary Safety Endpoint (Cardiac Death, MI, ST)



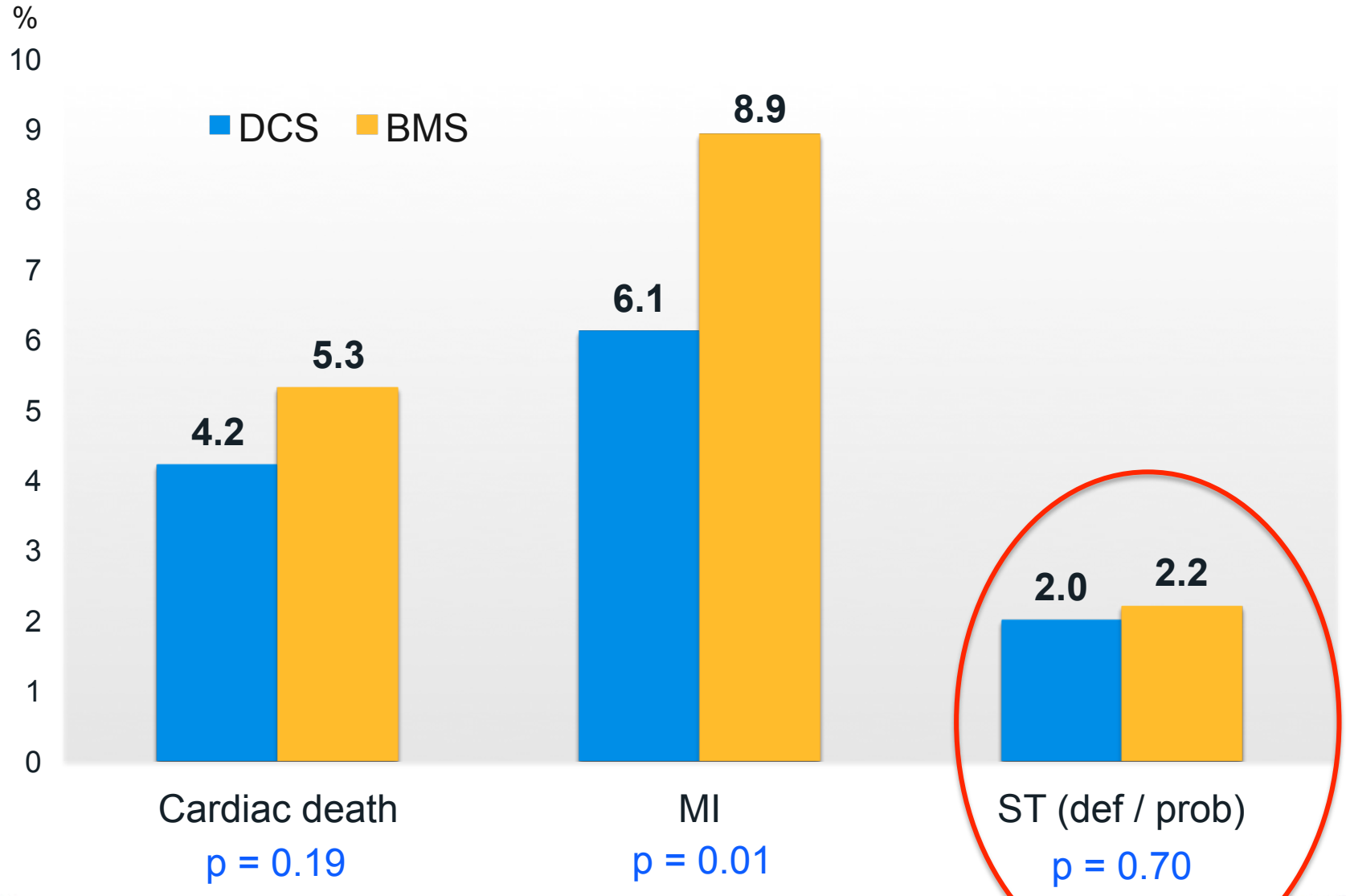
Subgroups

Composite safety endpoint (cardiac death, MI, ST)

Category		DCS: Events (%)	BMS: Events (%)	P-value for interaction
Age >80	No	65 (8.3)	92 (11.6)	0.86
	Yes	47 (11.5)	62 (15.5)	
Male	No	34 (9.6)	53 (14.4)	0.59
	Yes	78 (9.3)	101 (12.3)	
ACS at admission	No	82 (9.4)	95 (10.9)	0.04
	yes	30 (9.3)	59 (18.5)	



Components of Safety Endpoint

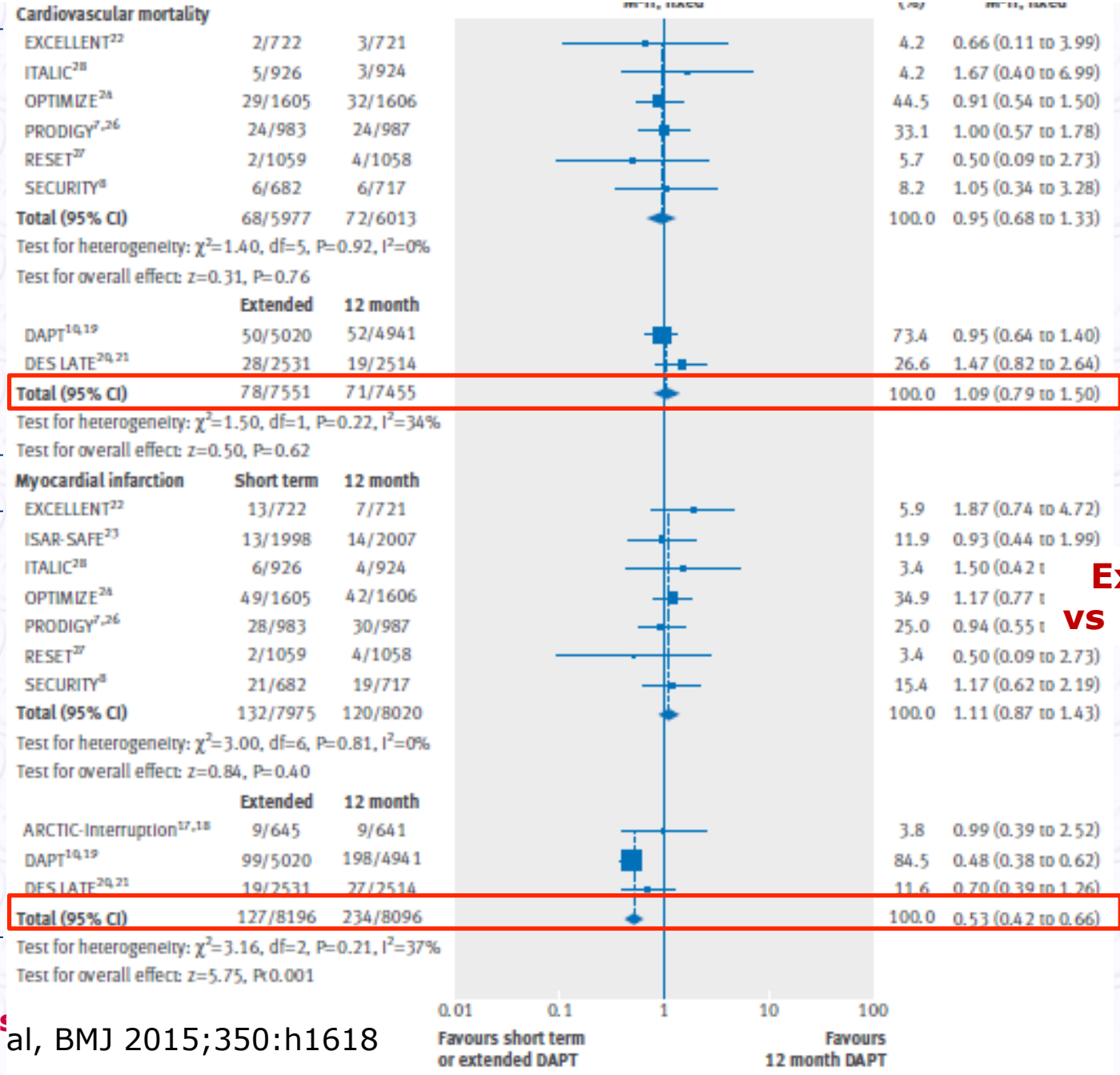


Recommendations for platelet inhibition in NSTE-ACS (continued)		
Recommendations	**Class[a]**	**Level[b]**
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	**IIb**	**A**

DAPT Duration after PCI with DES: Meta-analysis of RCT

CV Mortality

MI

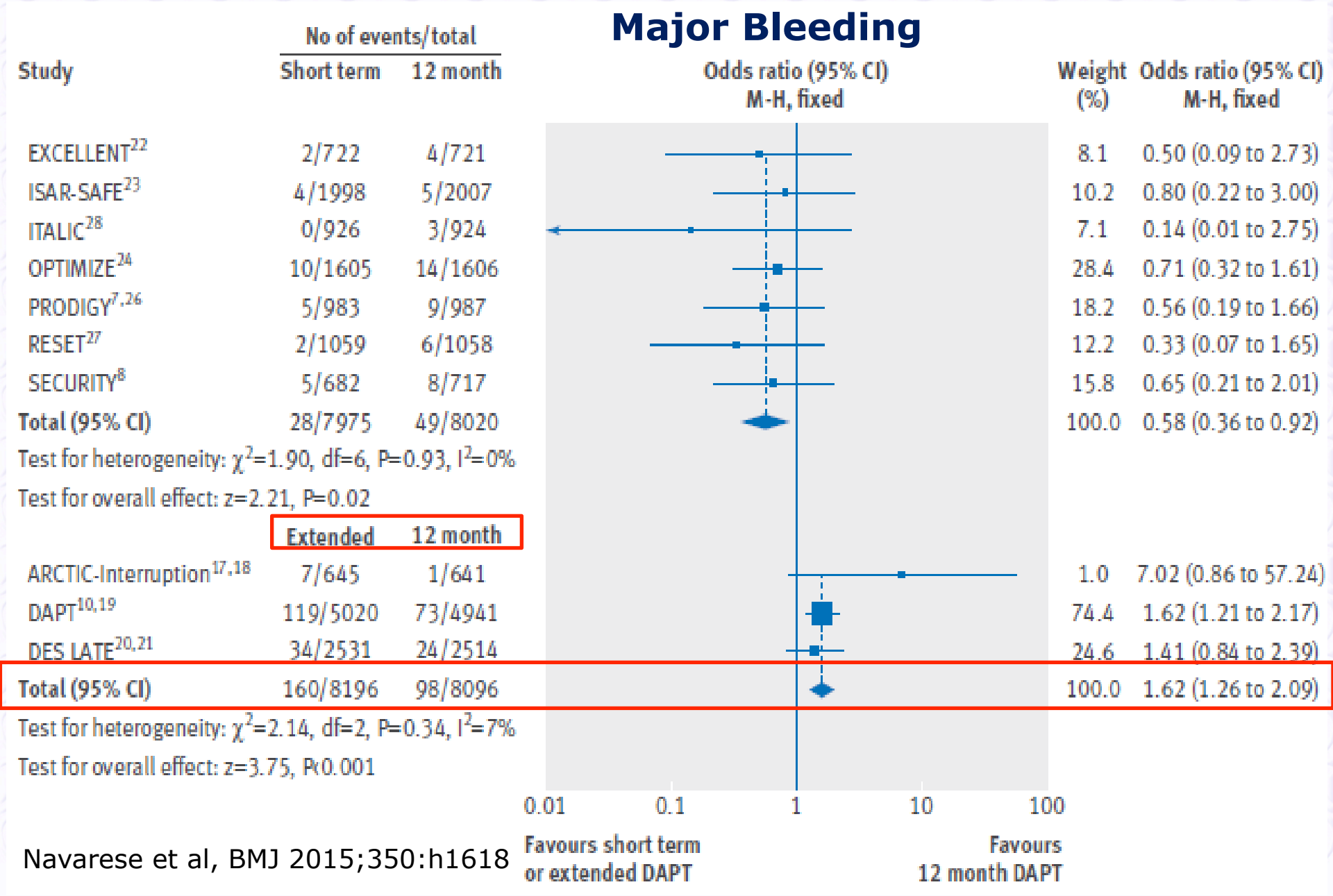


Mainly stable CAD

Extended vs 12 month

Navarese et al, BMJ 2015;350:h1618

DAPT Duration after PCI with DES: Meta-analysis of RCT



Navarese et al, BMJ 2015;350:h1618

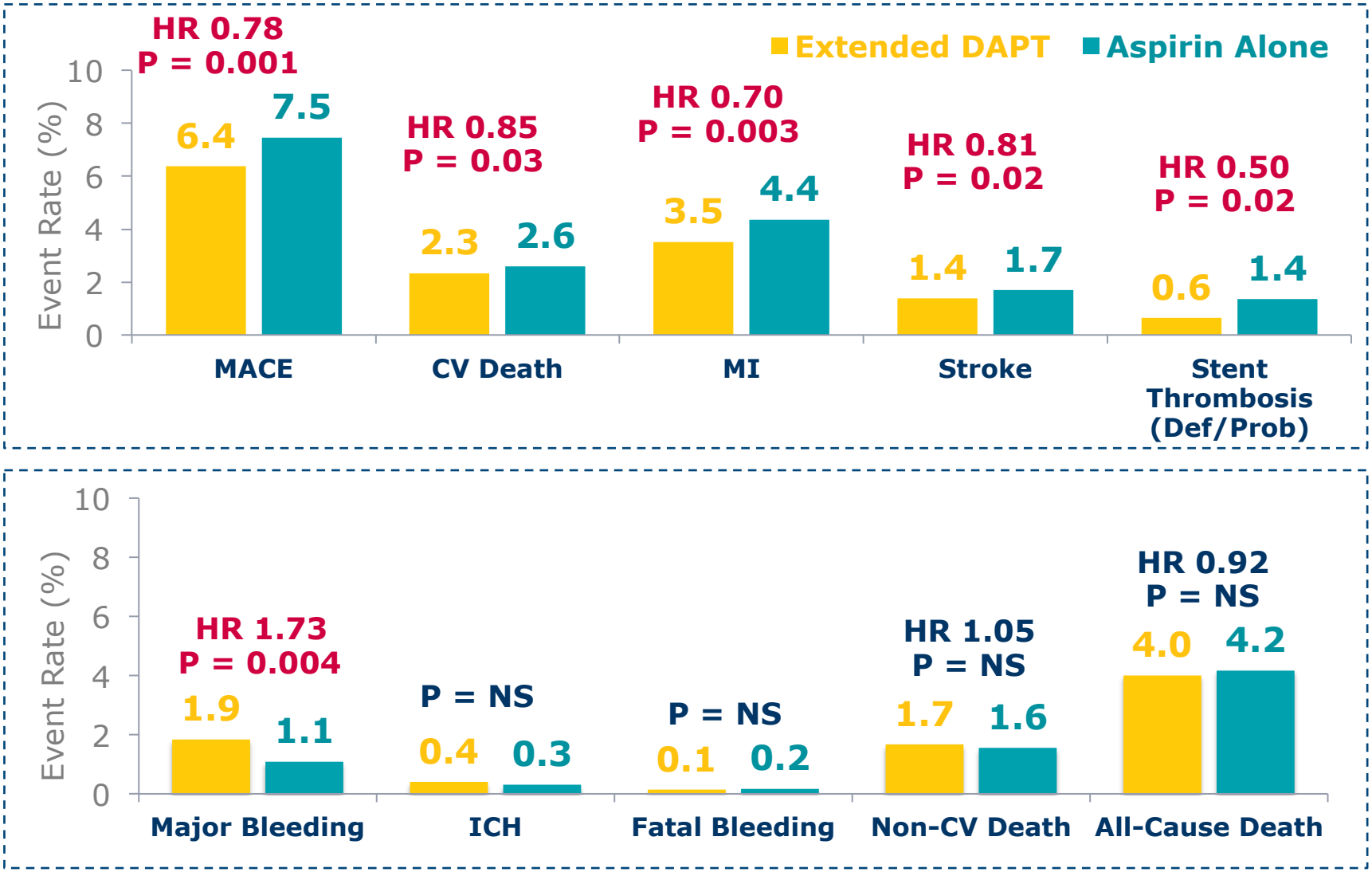
META-ANALYSIS OF TRIALS EVALUATING PROLONGED DAPT FOLLOWING MI

Trial	Subgroup / Population	N	Drug	Duration (months)	MACE Events	Bleeding EP
CHARISMA	Stable prior MI (mean 24 mo.)	3846	Clopi	28	287	GUSTO mod/ severe
PRODIGY	PCI for ACS	1465	Clopi	6 vs. 24	132	TIMI major
ARCTIC-Interruption	PCI for ACS (excluded STEMI)	323	Clopi or Pras	12 vs. 24	7	STEEPLE major
DAPT	PCI for MI	3576	Clopi or Pras	12 vs. 30	167	GUSTO mod/ severe
DES-Late	PCI for ACS	3063	Clopi	12 vs. 24	122	TIMI major
PEGASUS TIMI-54	Stable prior MI (median 20 mo.)	21162	Ticag	33	1558	TIMI major
Total		33435		30	2273	

Abbreviations: Clopi: clopidogrel; Pras: prasugrel; Ticag: ticagrelor

J. Udell (Toronto, CA) FP3913

META-ANALYSIS: INDIVIDUAL CV AND BLEEDING ENDPOINTS



J. Udell (Toronto, CA) FP 3913

Timing of $P2Y_{12}$ inhibitor initiation

As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST results, pretreatment with prasugrel is not recommended.

Purpose of P2Y12 inhibitor pre-treatment

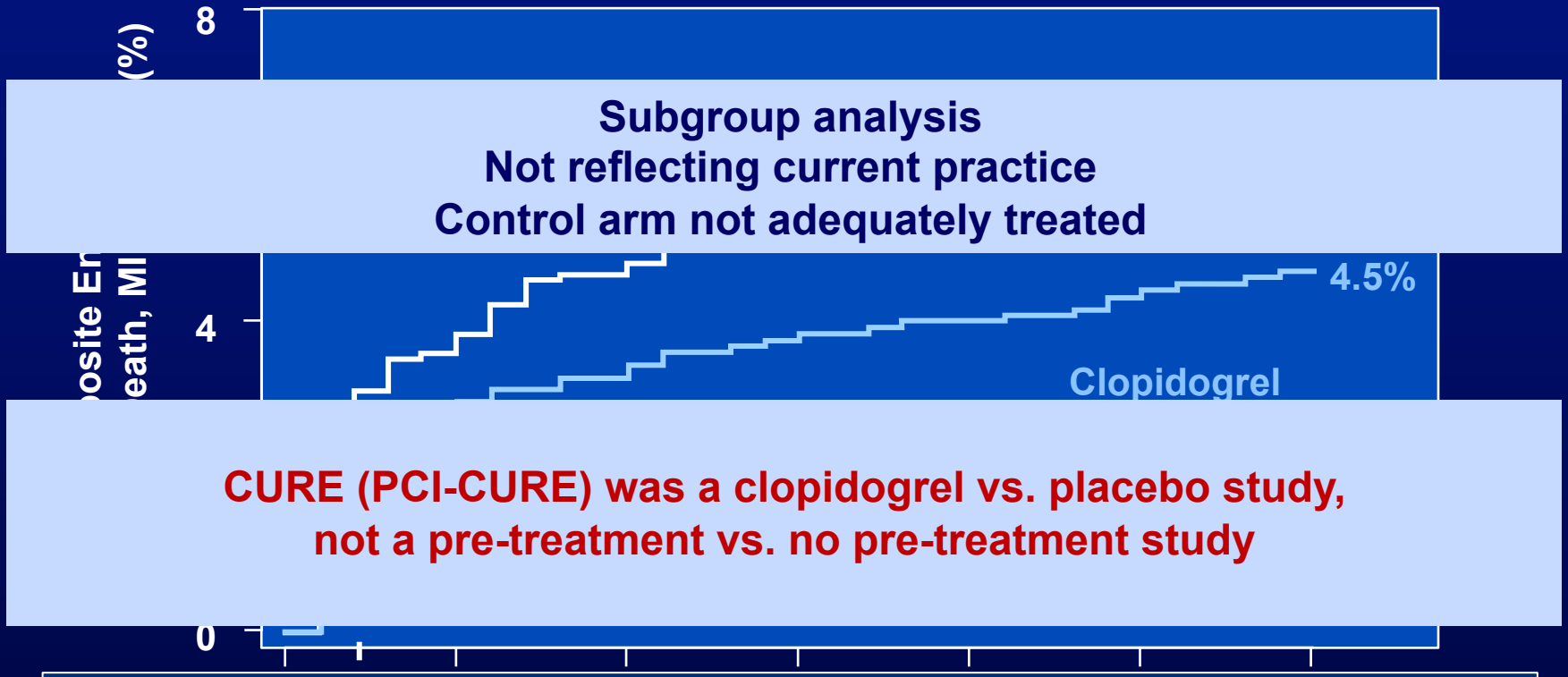
→ to avoid events related to inadequate platelet inhibition at the time of PCI (periprocedural-MI)

(and do not forget that the overall results of GP IIIb/IIIa inhibitors upstream in the P2Y12 inhibitor era were disappointing)

PCI-CURE: 30-Day CV Death, MI or UTVR

CURE performed 17 years ago, in an era of medical management of NST-ACS

2658 out of 12562 (21%) patients underwent PCI (PCI-CURE)



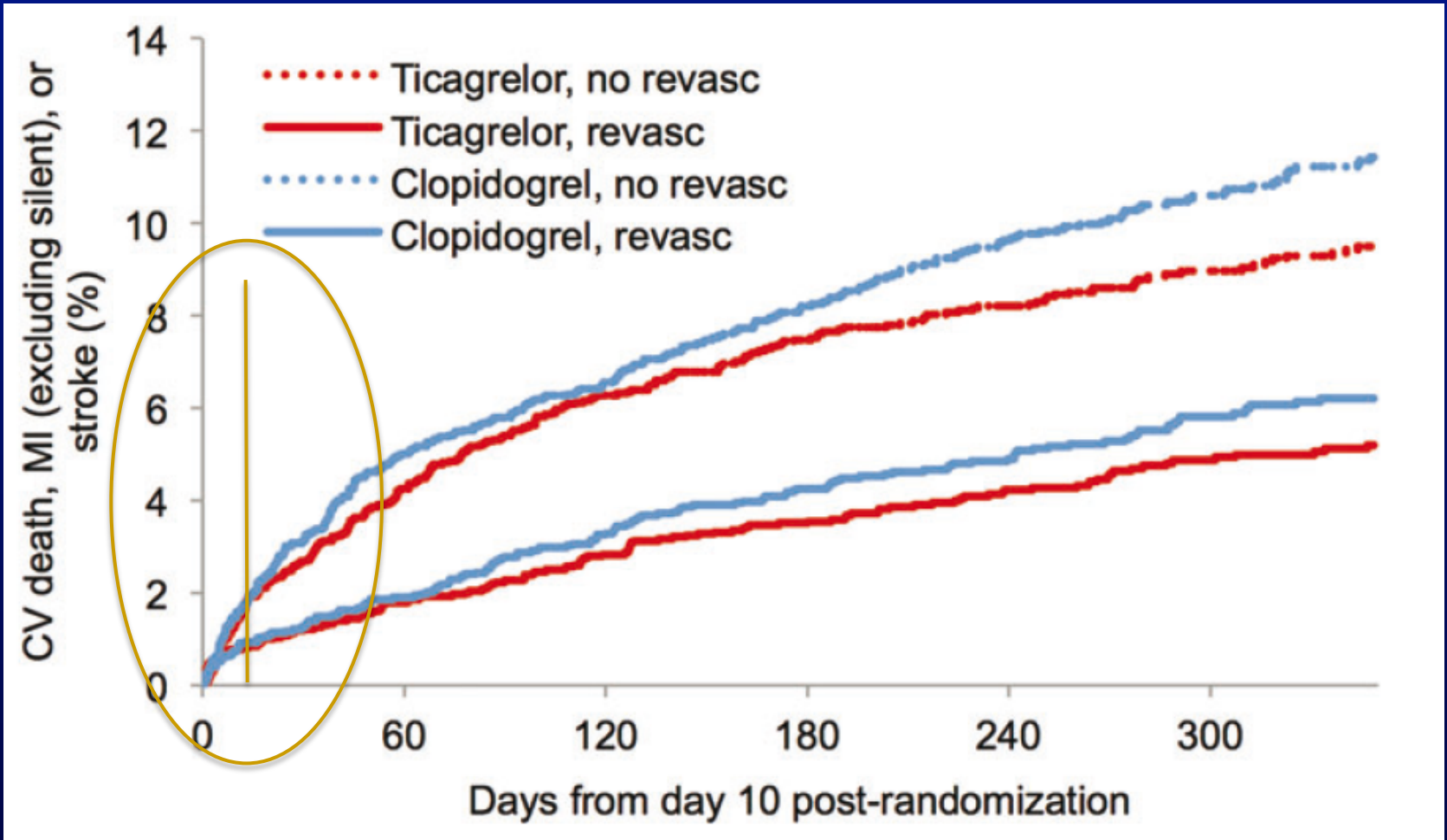
Subgroup analysis
Not reflecting current practice
Control arm not adequately treated

CURE (PCI-CURE) was a clopidogrel vs. placebo study, not a pre-treatment vs. no pre-treatment study

- **Patients on clopidogrel or placebo for a median of 10 days before PCI**
- **Treatment not randomized in the PCI population**
- **Control arm: no clopidogrel loading and 2-4 week treatment**

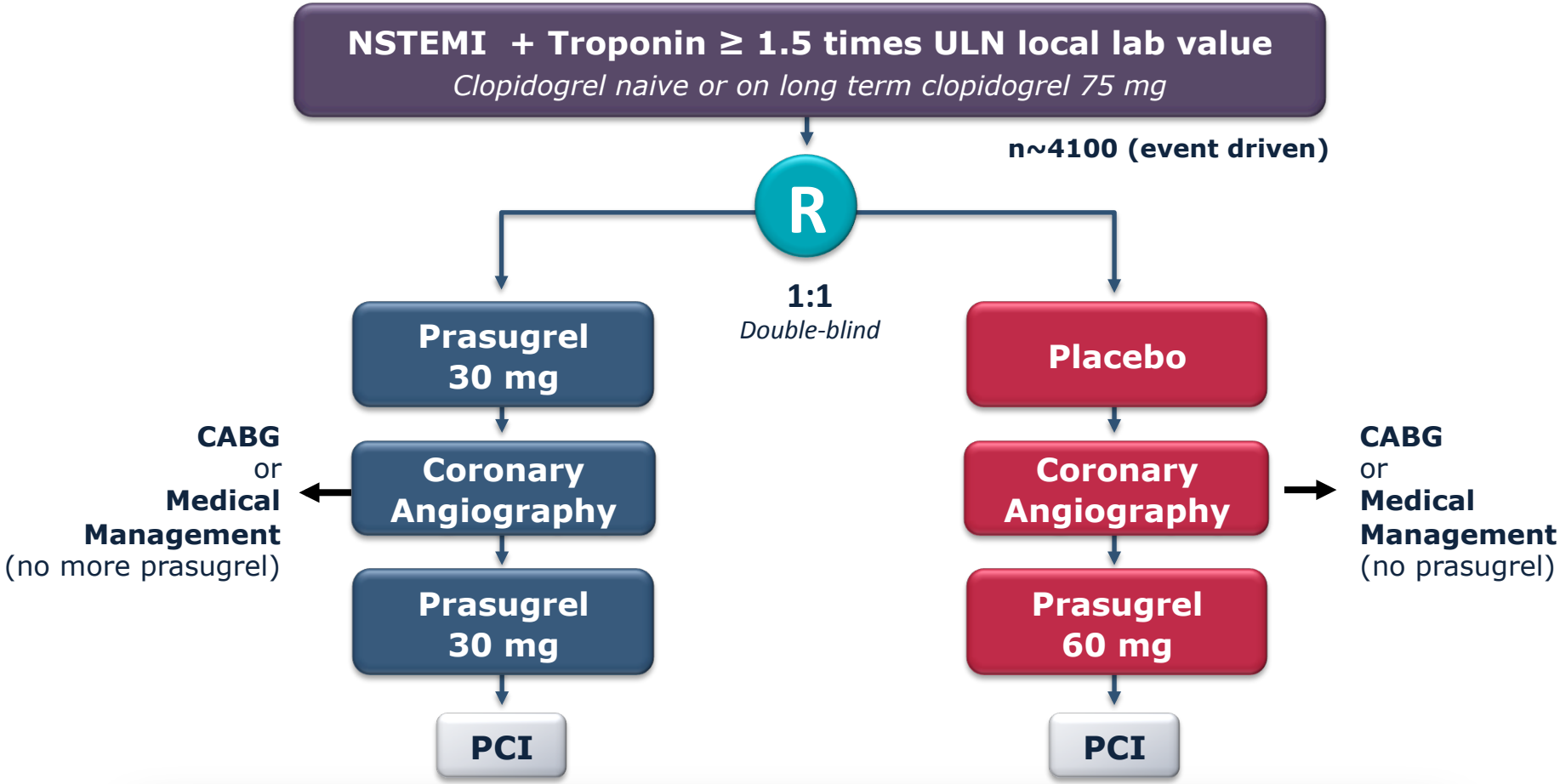
Mehta SR et al. *Lancet* 2001;358:527-533

PLATO – NSTEMI: CV Death, MI, or Stroke



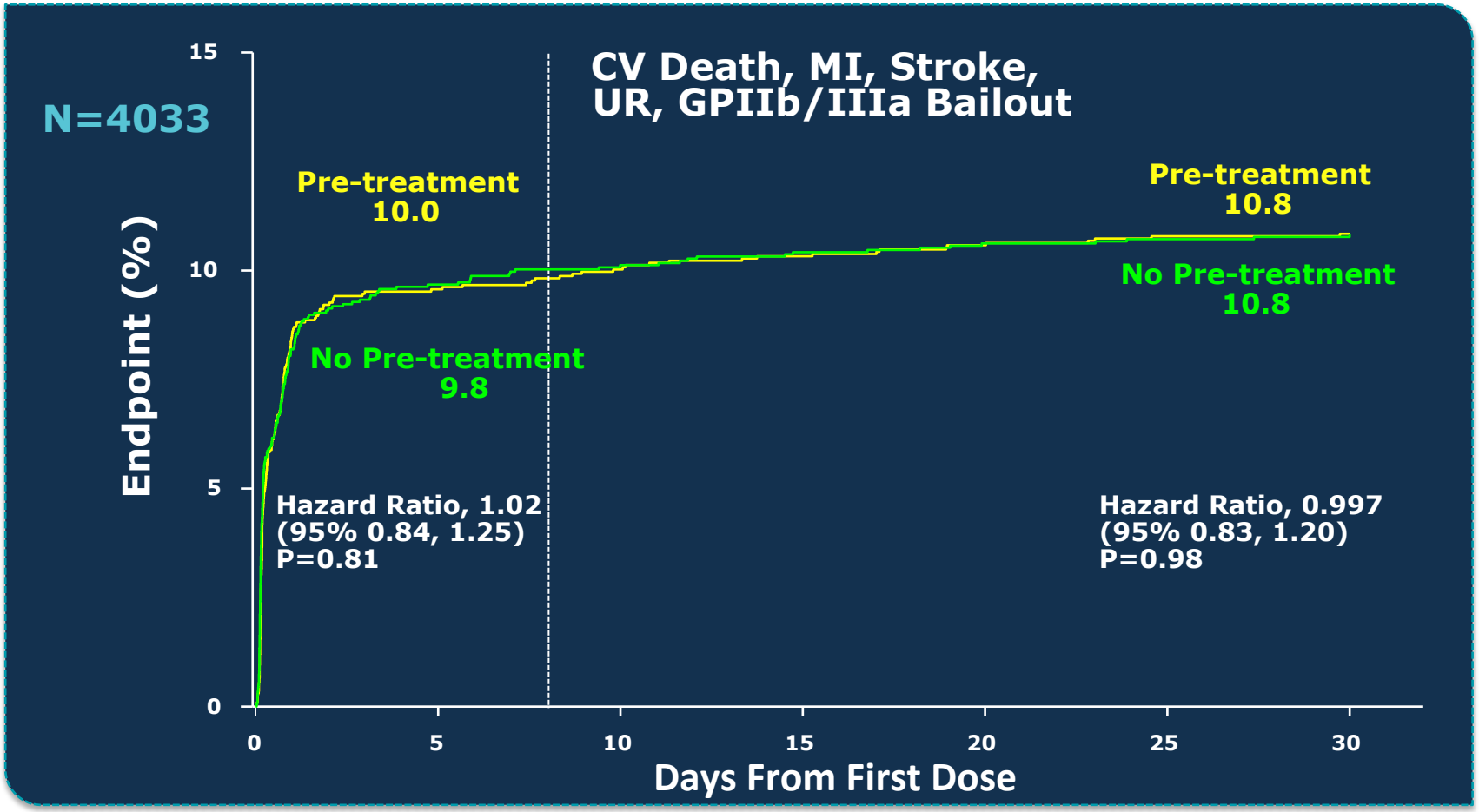
Lindholm D et al. EHJ 2014 online

ACCOAST-Trial



DSMB recommended early termination of enrollment

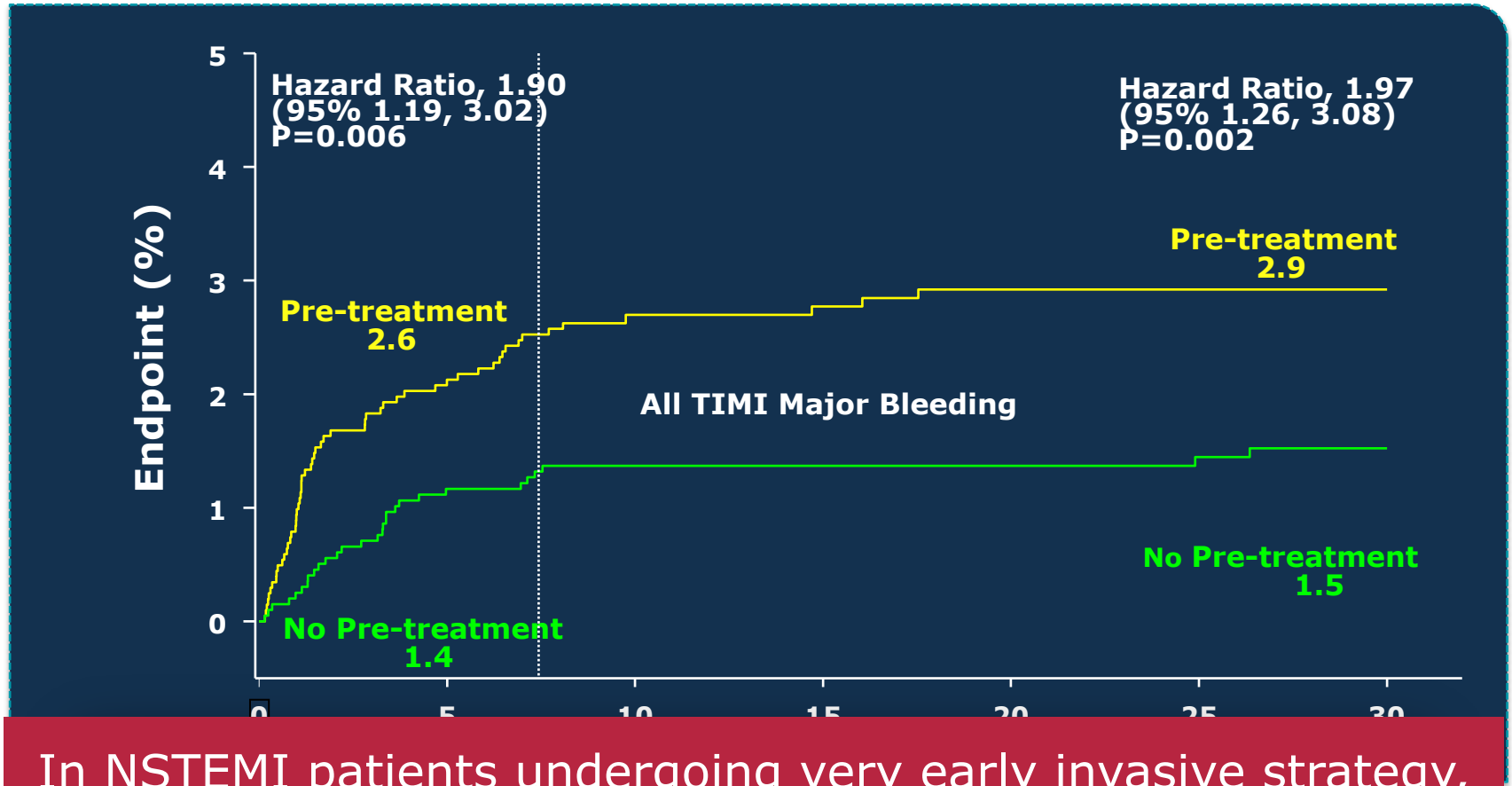
1° Efficacy End Point @ 7+30 days



- Intermediate risk population
- Median loading dose to angio <4 ½ hours
- PCI group (68% of total): curves superimposed

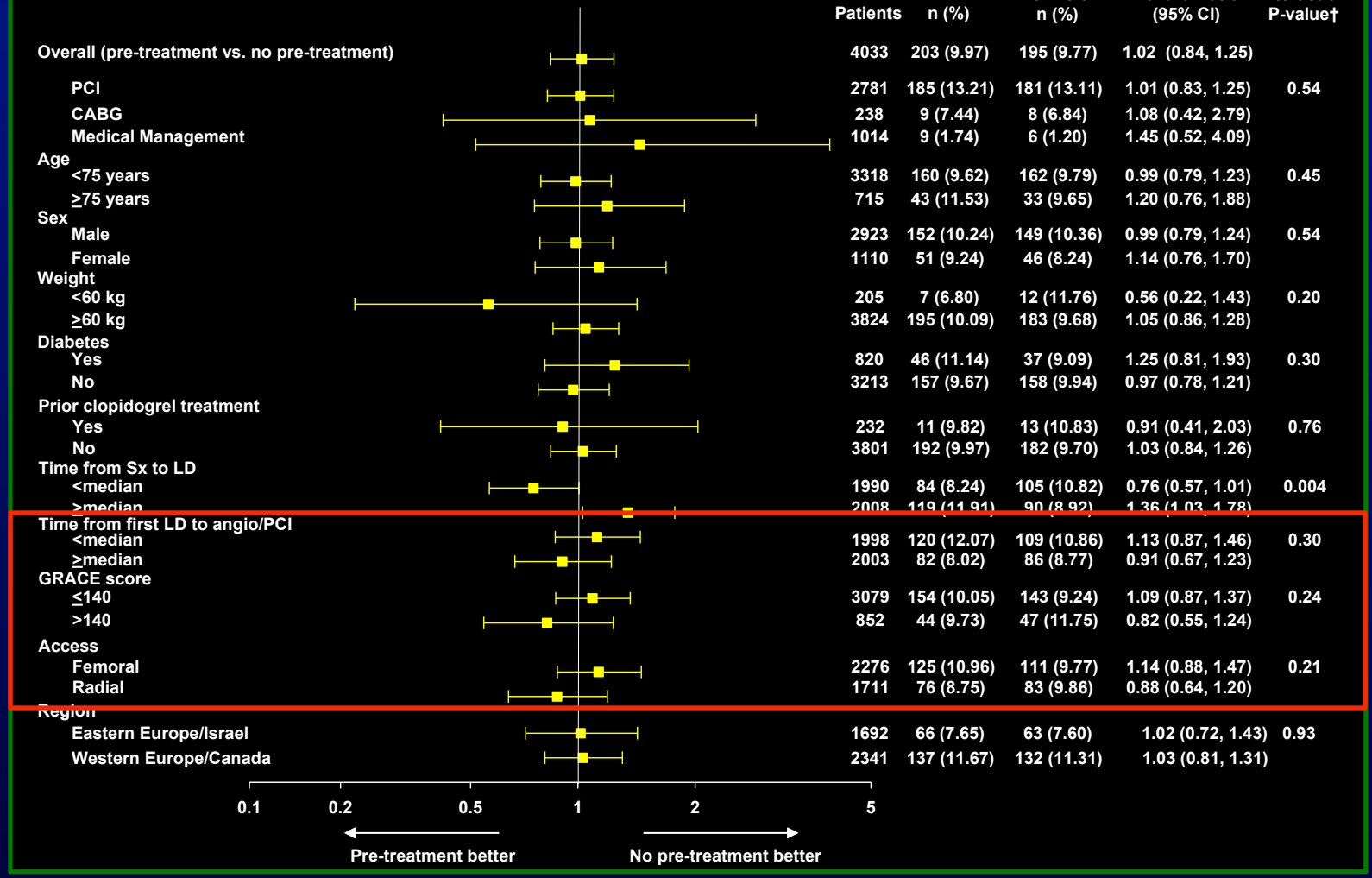
G. Montalescot / FR / 1686

All TIMI Major Bleeding



In NSTEMI patients undergoing very early invasive strategy, pre-treatment with prasugrel compared with prasugrel at the time of PCI does not reduce major ischemic events and increases major bleeding complications

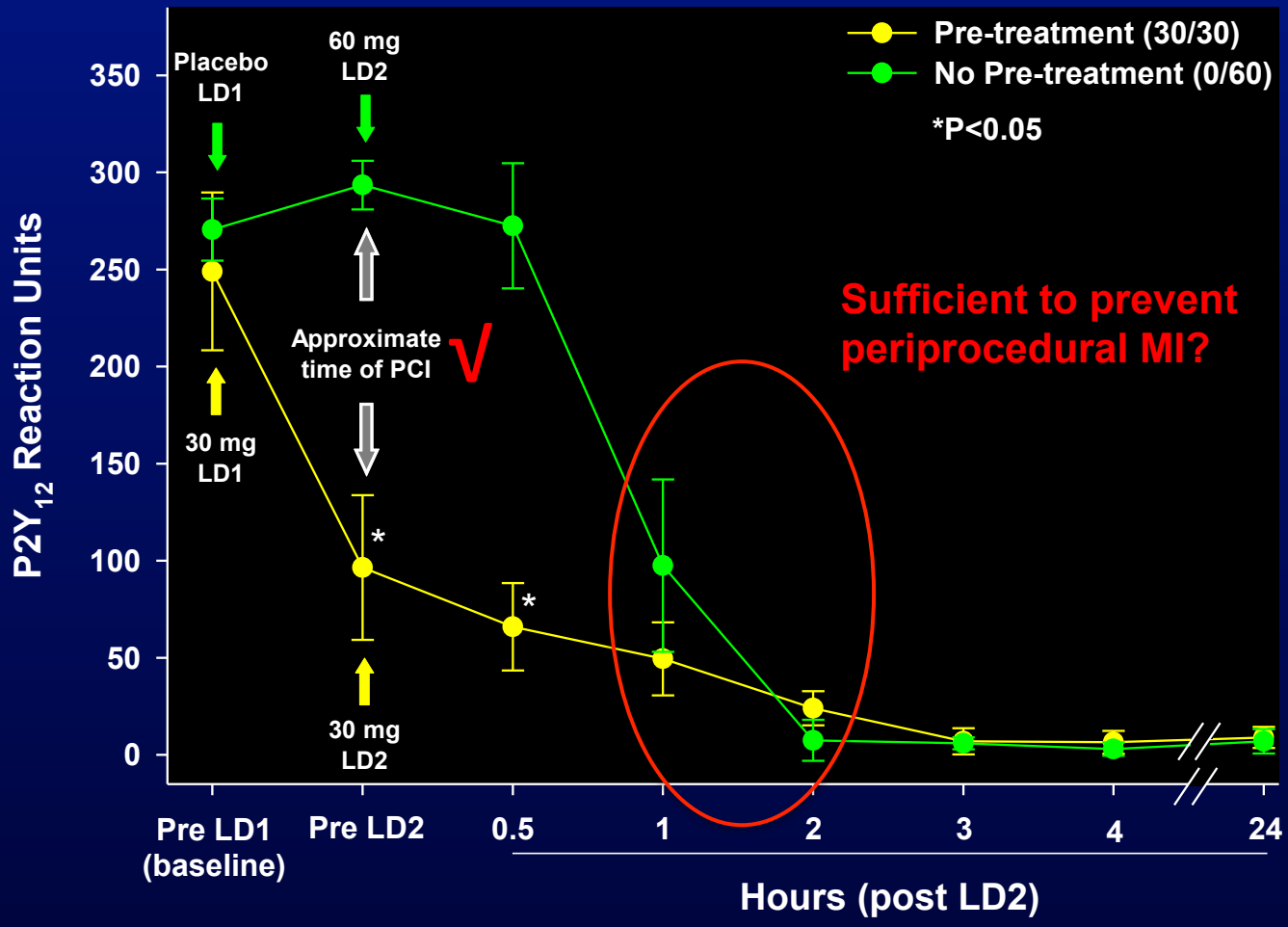
1° Efficacy Endpoint Through 7 Days



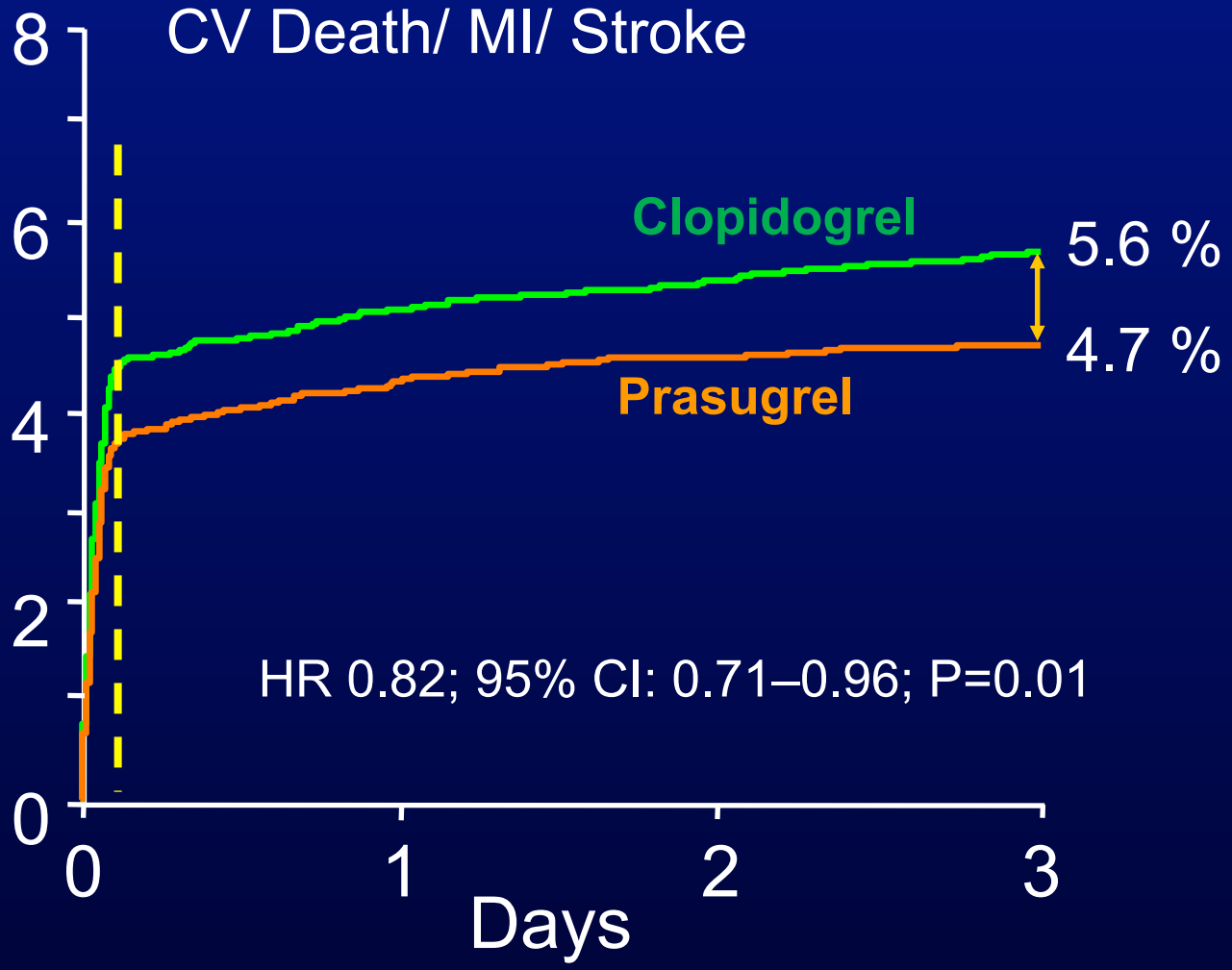
	Total Patients	Pre-tx n (%)	No Pre-tx n (%)	Hazard Ratio (95% CI)	Interaction P-value†
Overall (pre-treatment vs. no pre-treatment)	4033	203 (9.97)	195 (9.77)	1.02 (0.84, 1.25)	
PCI	2781	185 (13.21)	181 (13.11)	1.01 (0.83, 1.25)	0.54
CABG	238	9 (7.44)	8 (6.84)	1.08 (0.42, 2.79)	
Medical Management	1014	9 (1.74)	6 (1.20)	1.45 (0.52, 4.09)	
Age					
<75 years	3318	160 (9.62)	162 (9.79)	0.99 (0.79, 1.23)	0.45
≥75 years	715	43 (11.53)	33 (9.65)	1.20 (0.76, 1.88)	
Sex					
Male	2923	152 (10.24)	149 (10.36)	0.99 (0.79, 1.24)	0.54
Female	1110	51 (9.24)	46 (8.24)	1.14 (0.76, 1.70)	
Weight					
<60 kg	205	7 (6.80)	12 (11.76)	0.56 (0.22, 1.43)	0.20
≥60 kg	3824	195 (10.09)	183 (9.68)	1.05 (0.86, 1.28)	
Diabetes					
Yes	820	46 (11.14)	37 (9.09)	1.25 (0.81, 1.93)	0.30
No	3213	157 (9.67)	158 (9.94)	0.97 (0.78, 1.21)	
Prior clopidogrel treatment					
Yes	232	11 (9.82)	13 (10.83)	0.91 (0.41, 2.03)	0.76
No	3801	192 (9.97)	182 (9.70)	1.03 (0.84, 1.26)	
Time from Sx to LD					
<median	1990	84 (8.24)	105 (10.82)	0.76 (0.57, 1.01)	0.004
≥median	2008	119 (11.91)	90 (8.92)	1.36 (1.03, 1.78)	
Time from first LD to angio/PCI					
<median	1998	120 (12.07)	109 (10.86)	1.13 (0.87, 1.46)	0.30
≥median	2003	82 (8.02)	86 (8.77)	0.91 (0.67, 1.23)	
GRACE score					
≤140	3079	154 (10.05)	143 (9.24)	1.09 (0.87, 1.37)	0.24
>140	852	44 (9.73)	47 (11.75)	0.82 (0.55, 1.24)	
Access					
Femoral	2276	125 (10.96)	111 (9.77)	1.14 (0.88, 1.47)	0.21
Radial	1711	76 (8.75)	83 (9.86)	0.88 (0.64, 1.20)	
Region					
Eastern Europe/Israel	1692	66 (7.65)	63 (7.60)	1.02 (0.72, 1.43)	0.93
Western Europe/Canada	2341	137 (11.67)	132 (11.31)	1.03 (0.81, 1.31)	

*Hazard ratio not evaluated for <10 events.
†Interaction p-value is from a Cox proportional hazards model with treatment, subgroup, and the treatment-by-subgroup interaction as fixed effects; PCI includes 11 patients with PCI + CABG.

Pharmacodynamic Sub-Study

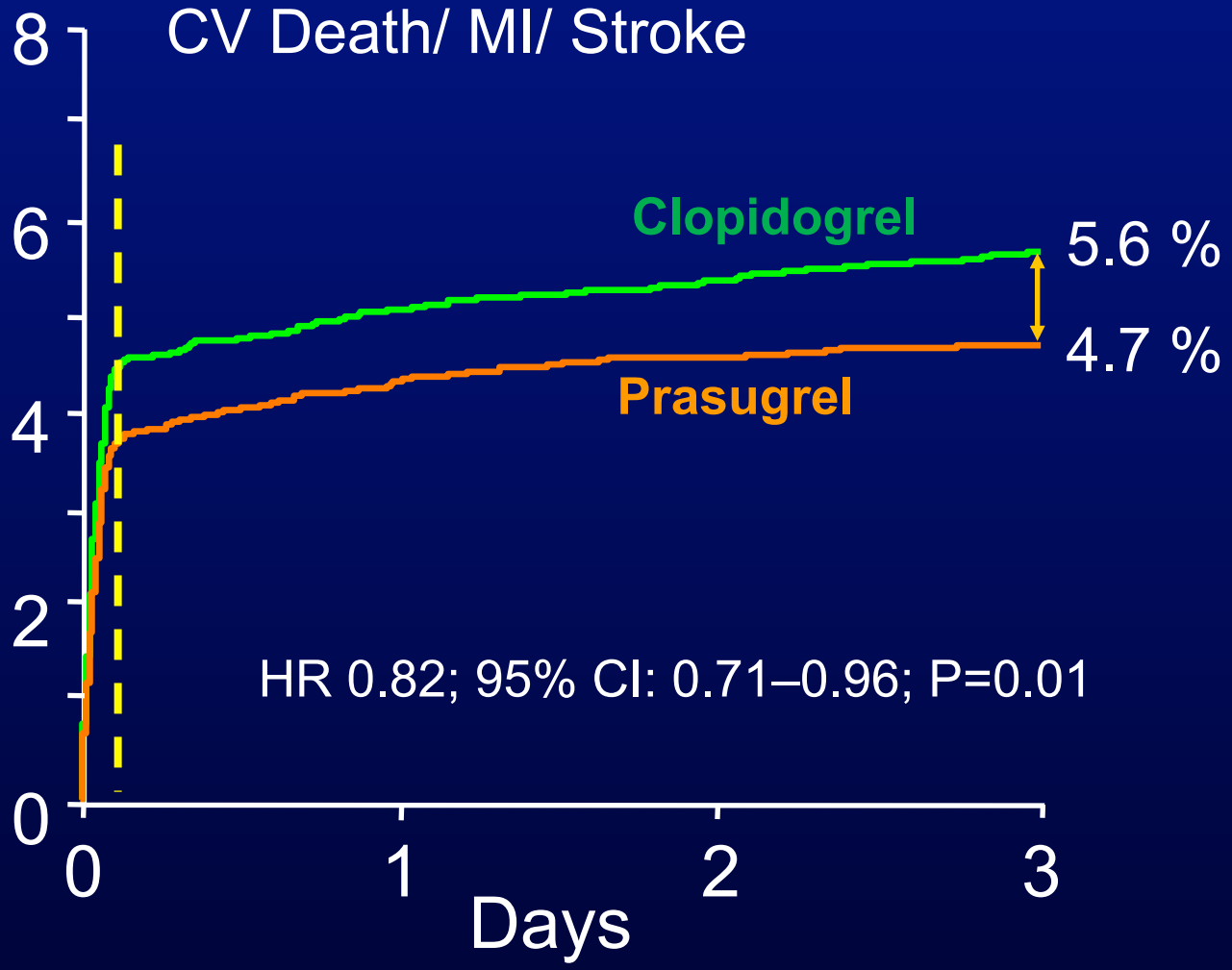


TRITON-TIMI 38: Prasugrel at the Time of PCI Sufficient to Prevent Periprocedural Ischemic Events?



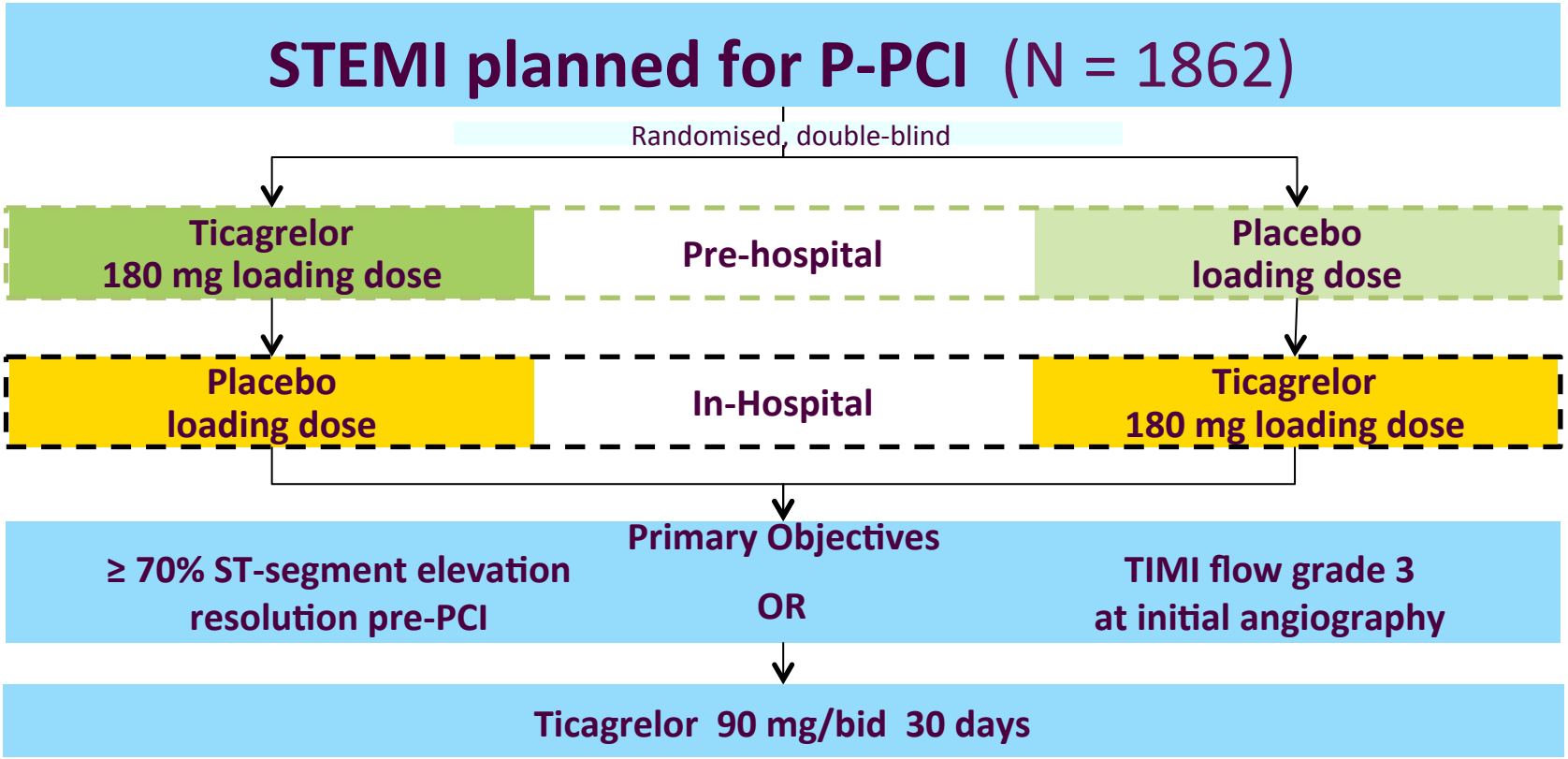
Wiviott SD et al. N Engl J Med 2007;357:2001-15

TRITON-TIMI 38: Prasugrel at the Time of PCI Sufficient to Prevent Periprocedural Ischemic Events?



Wiviott SD et al. N Engl J Med 2007;357:2001-15

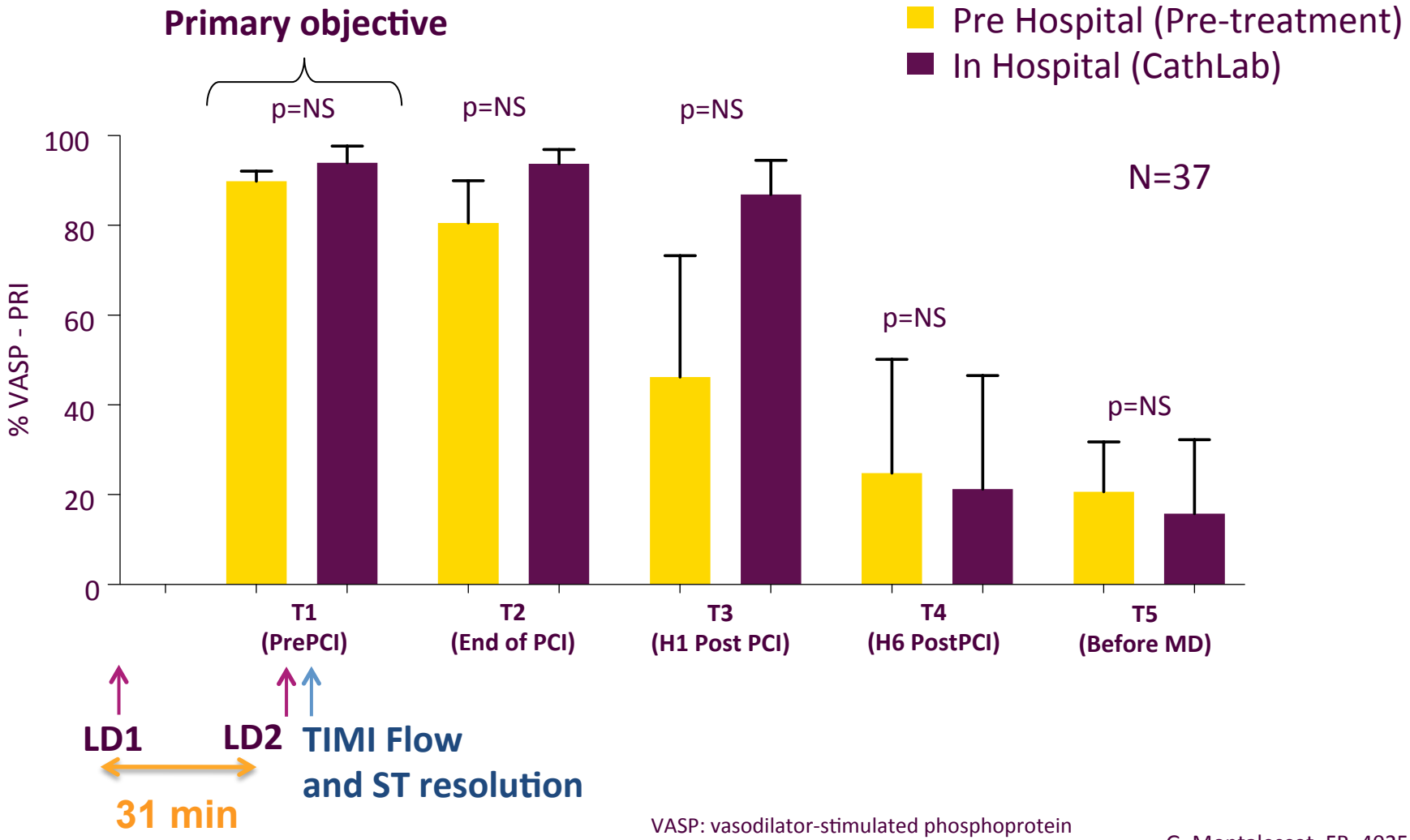
ATLANTIC: Ticagrelor in the Catheterisation Laboratory or in the Pre-Hospital Setting



Montalescot G et al. *Am Heart J*.2013;165:515–522.

G. Montalescot, FR, 4025

ATLANTIC: Pharmacodynamic Substudy

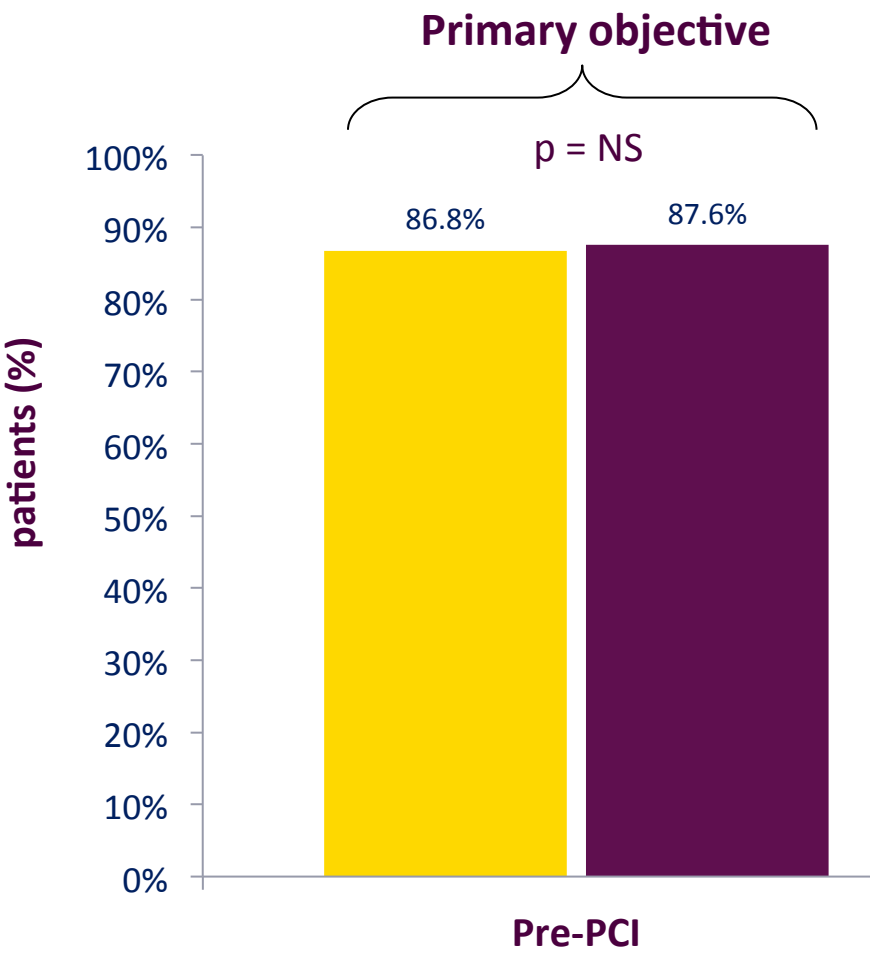


VASP: vasodilator-stimulated phosphoprotein
PRI: platelet reactivity index

G. Montalescot, FR, 4025

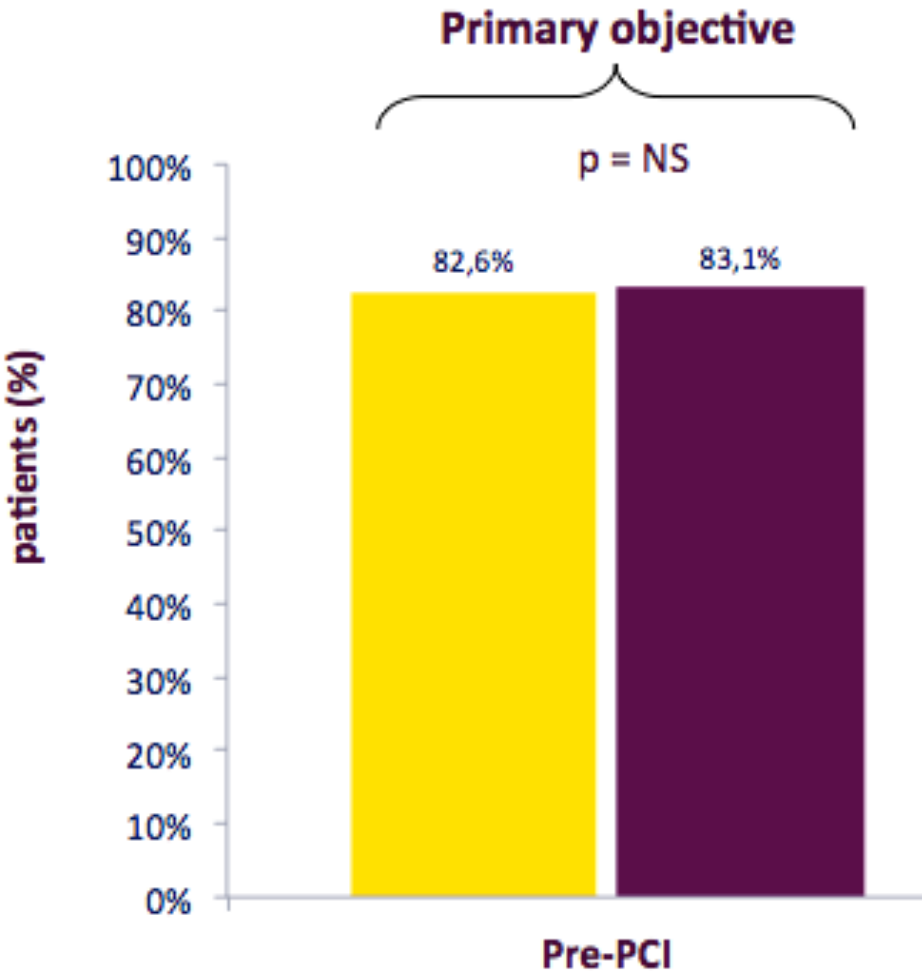
1st Co-primary endpoint

No ST-segment resolution (≥70%)



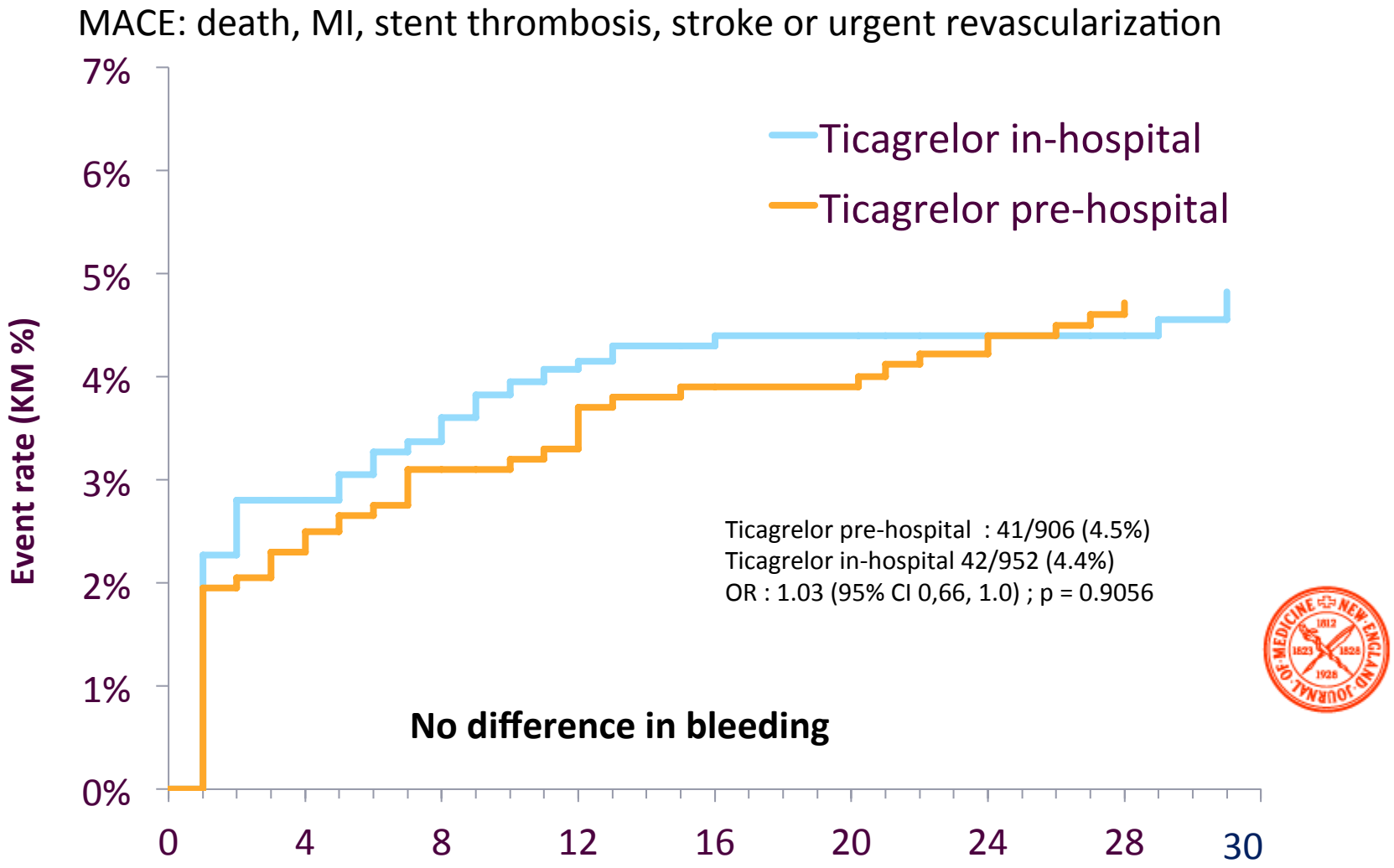
2nd Co-primary endpoint

No TIMI 3 flow in infarct-related artery



G. Montalescot, FR, 4025

Secondary Endpoint: 30-Day MACE



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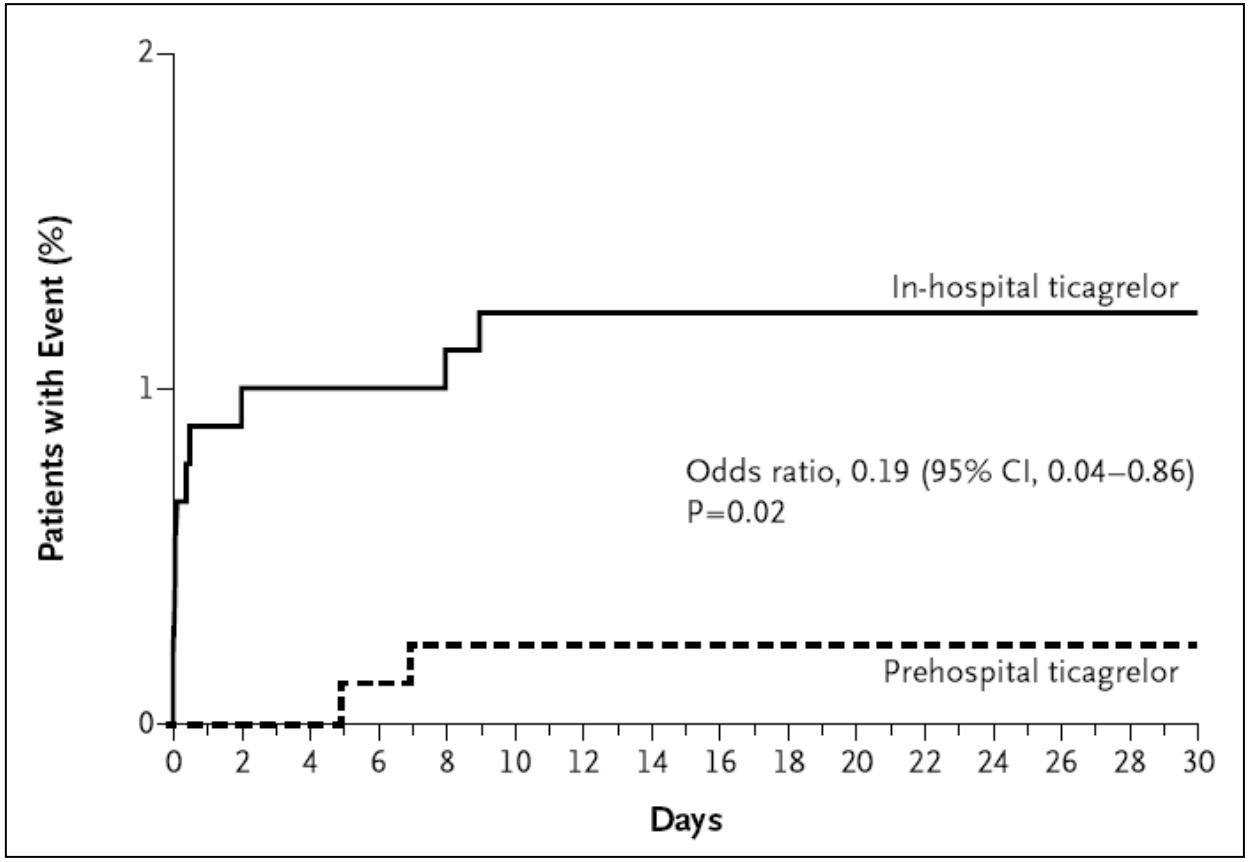
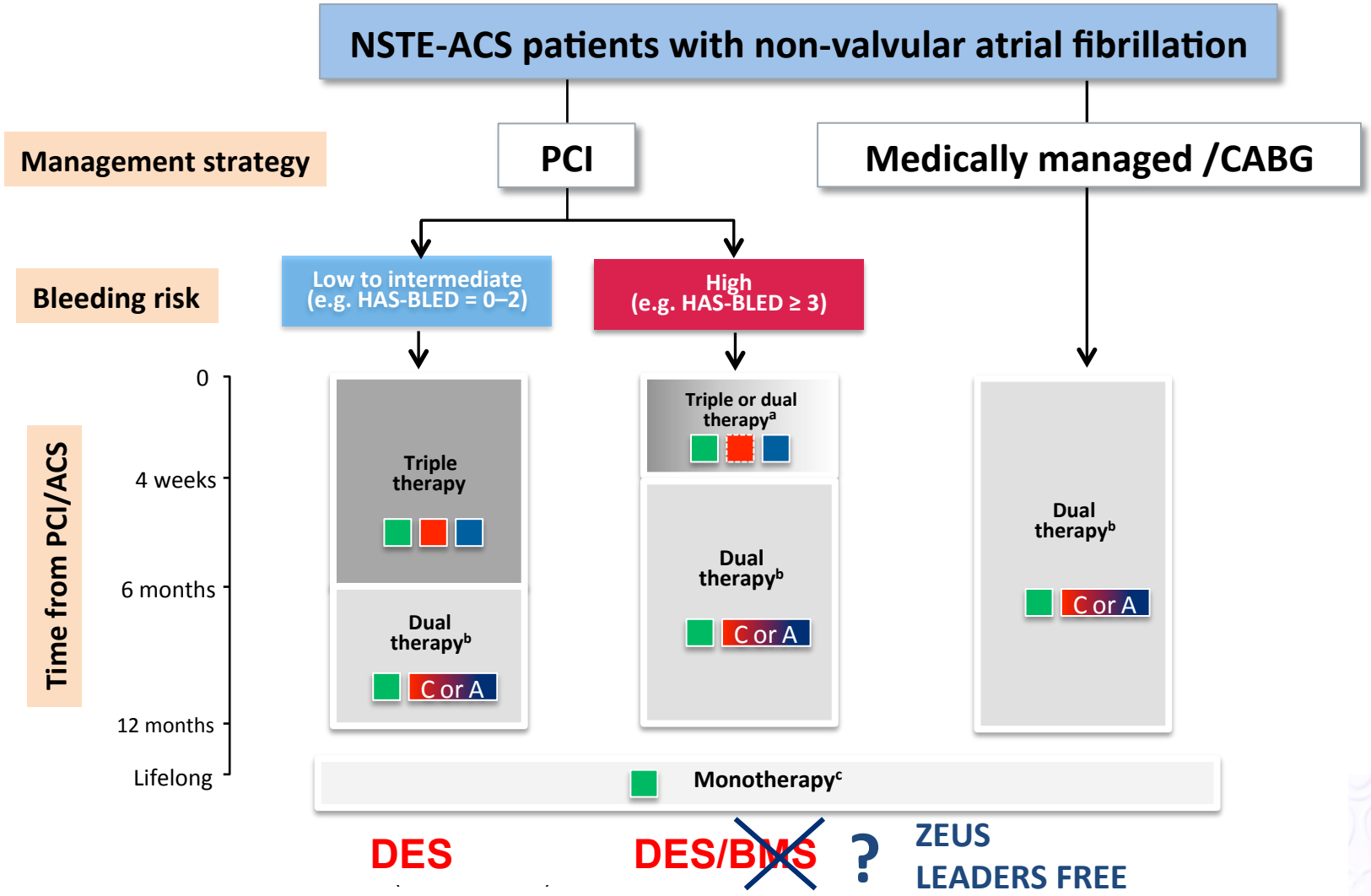
Secondary Endpoint: 30-Day Stent Thrombosis



Pre-hospital ticagrelor administration prior to P-PCI in STEMI is safe but does not improve coronary reperfusion



[a]Dual therapy with OAC and and clopidogrel may be considered in selected patients (low ischaemic risk).
[b]aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (i.e., oral anticoagulation plus single antiplatelet) Triple therapy may be considered up to 12 months in patients at very high risk for ischaemic events.
[c]Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) beyond one year may be considered in patients at very high risk of coronary events. In patients undergoing coronary stenting, dual antiplatelet therapy may be an alternative to triple or dual therapy if the CHA2DS2-VASc score is 1 (males) or 2 (females).

- **40 cases each**
- **No reference**
- **Link to the dedicated sections of the GL**

Help to implement GL in daily practice

European Heart Journal
doi:10.1093/eurheartj/ehv409

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Authors: Christian Mueller[1], Carlo Patrono[2], Marco Valgimigli[3], Jean-Philippe Collet[4], and Marco Roffi[5]*

Questions and answers on antithrombotic therapy: a companion document of the 2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation†

Authors: Jean-Philippe Collet[1], Marco Roffi[2]*, Christian Mueller[3], Marco Valgimigli[4], Carlo Patrono[5]

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