Antiplatelet therapy in patients at high risk of bleeding undergoing PCI

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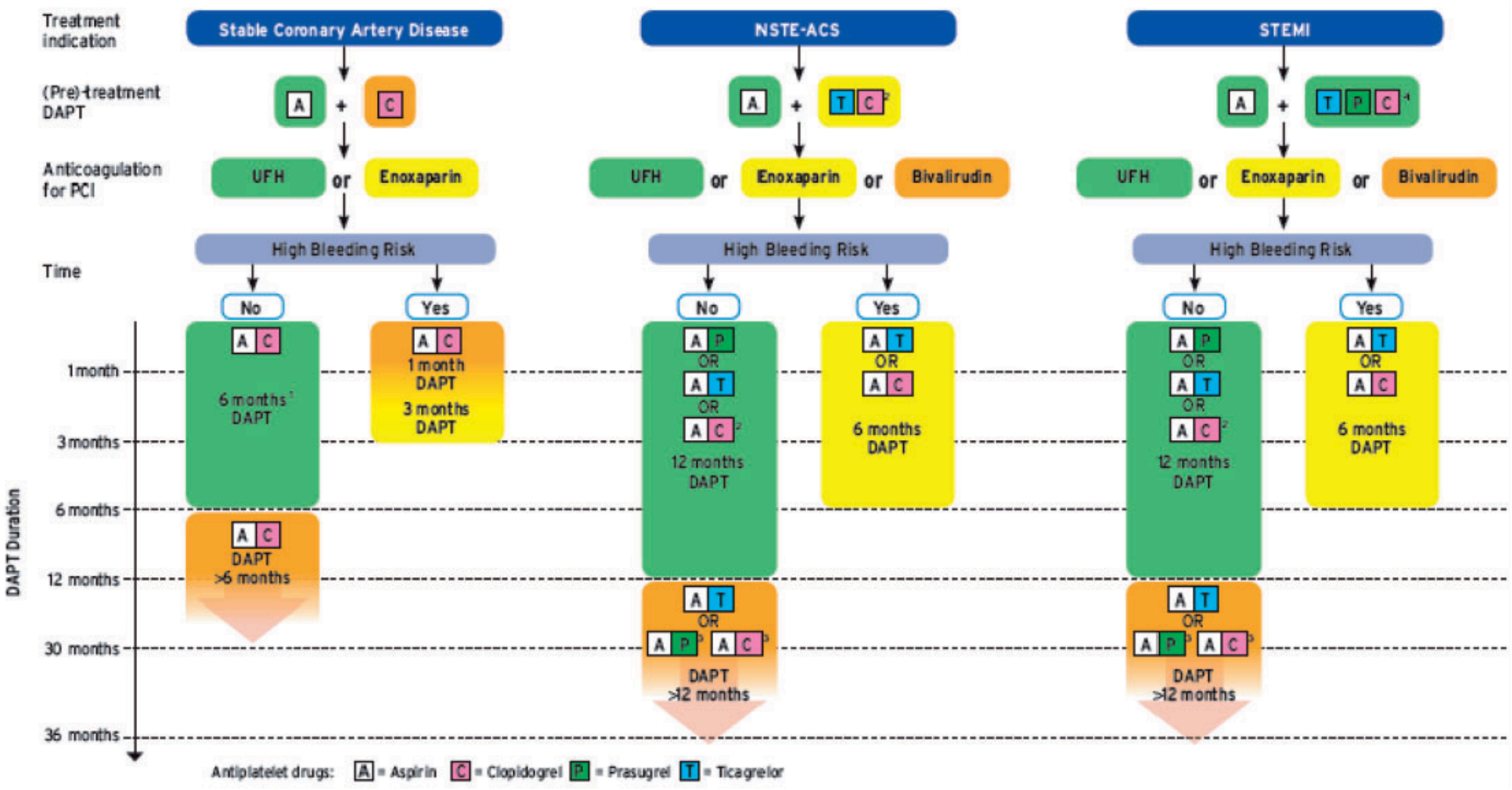
Antithrombotic treatment after PCI: ESC 2018 guidelines

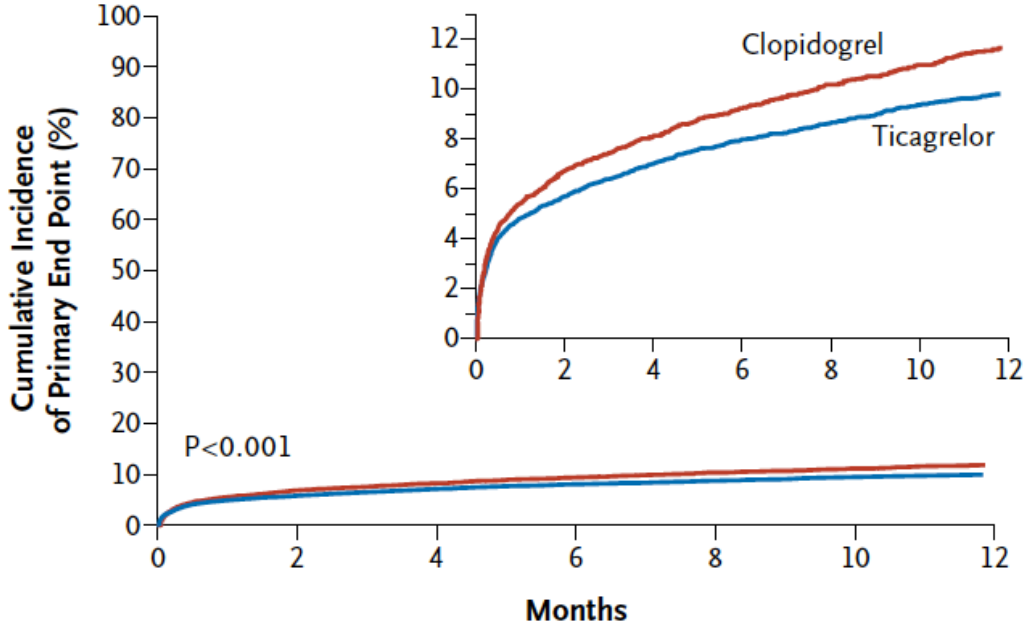


ESC 2018 guidelines: ACS.

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as an excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).[701,702,722,723]	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[729,730]	IIa	B
In patients with ACS treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
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
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.[700,731]	IIb	A
In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.[732–734]	IIb	B
In ACS patients with no prior stroke/TIA, and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.[720]	IIb	B

Clinical benefits of Ticagrelor and Prasugrel in ACS

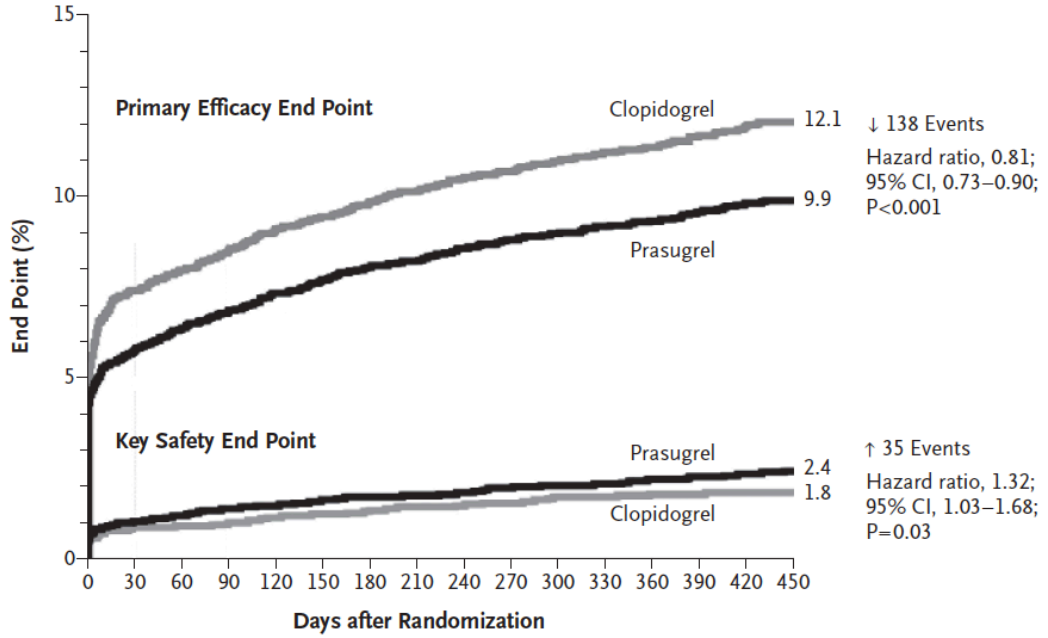
PLATO



No. at Risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

Wallentin L, et al. N Engl J Med 2009;361:1045-57.

TRITON-TIMI 28

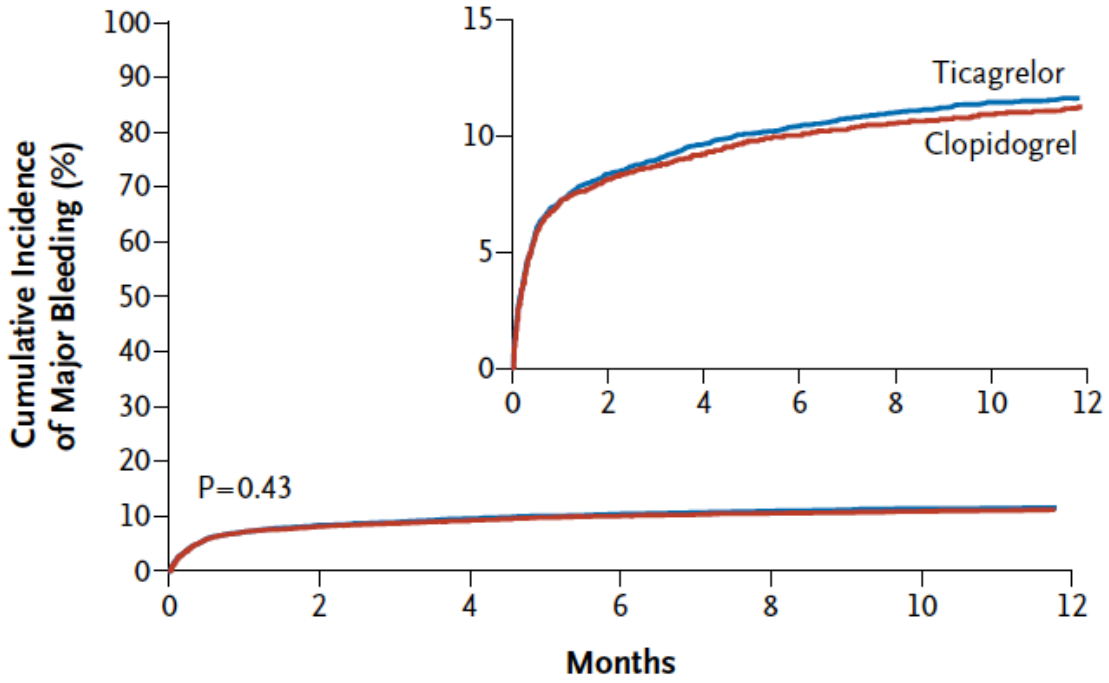


No. at Risk							
Clopidogrel	6795 6169	6036	5835	5043	4369	3017	
Prasugrel	6813 6305	6177	5951	5119	4445	3085	

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

Ticagrelor and Prasugrel & risk of bleeding

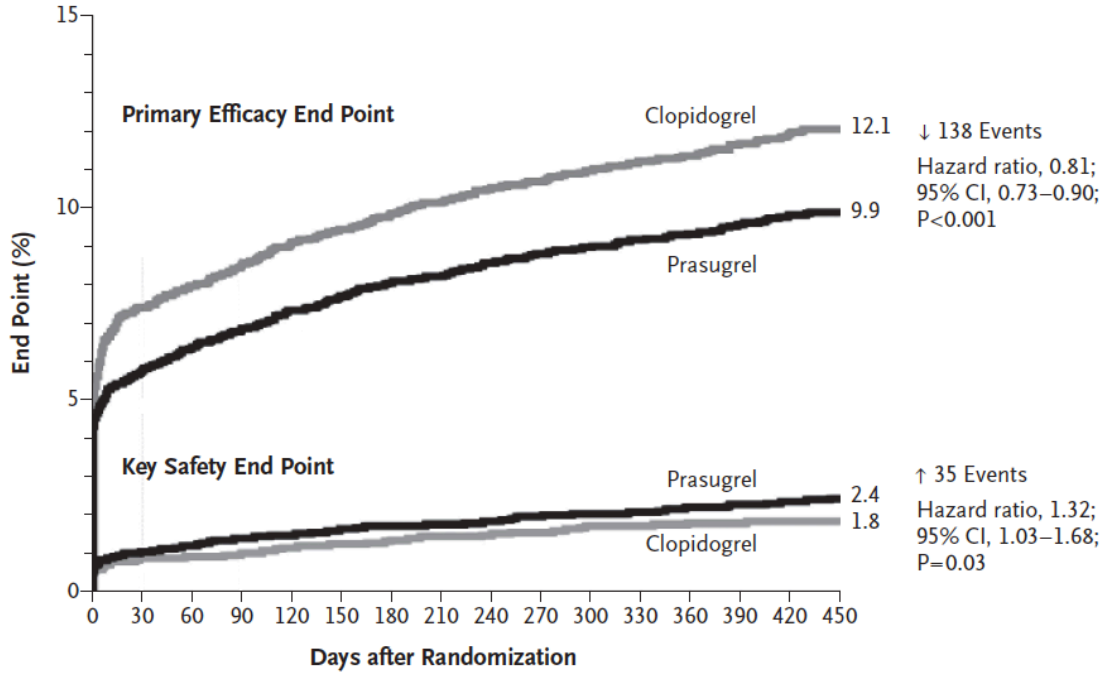
PLATO



No. at Risk							
Ticagrelor	9235	7246	6826	6545	5129	3783	3433
Clopidogrel	9186	7305	6930	6670	5209	3841	3479

Wallentin L, et al. N Engl J Med 2009;361:1045-57.

TRITON-TIMI 28



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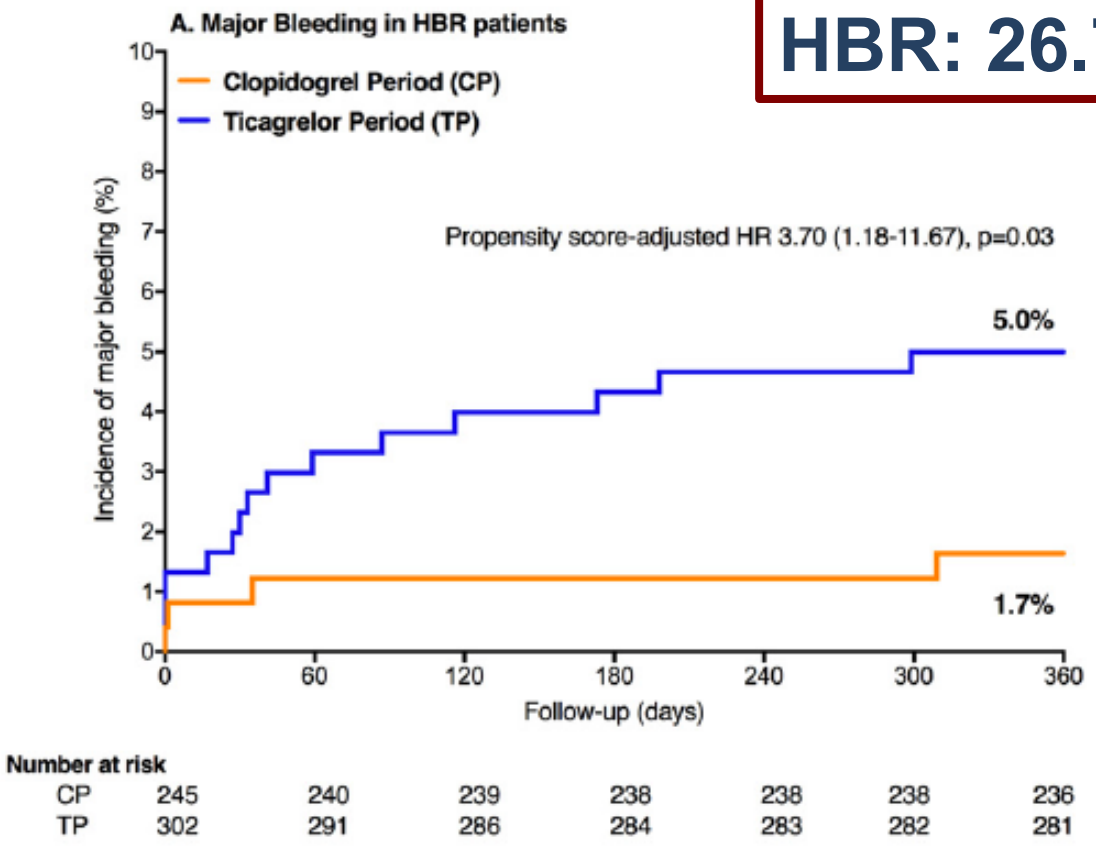
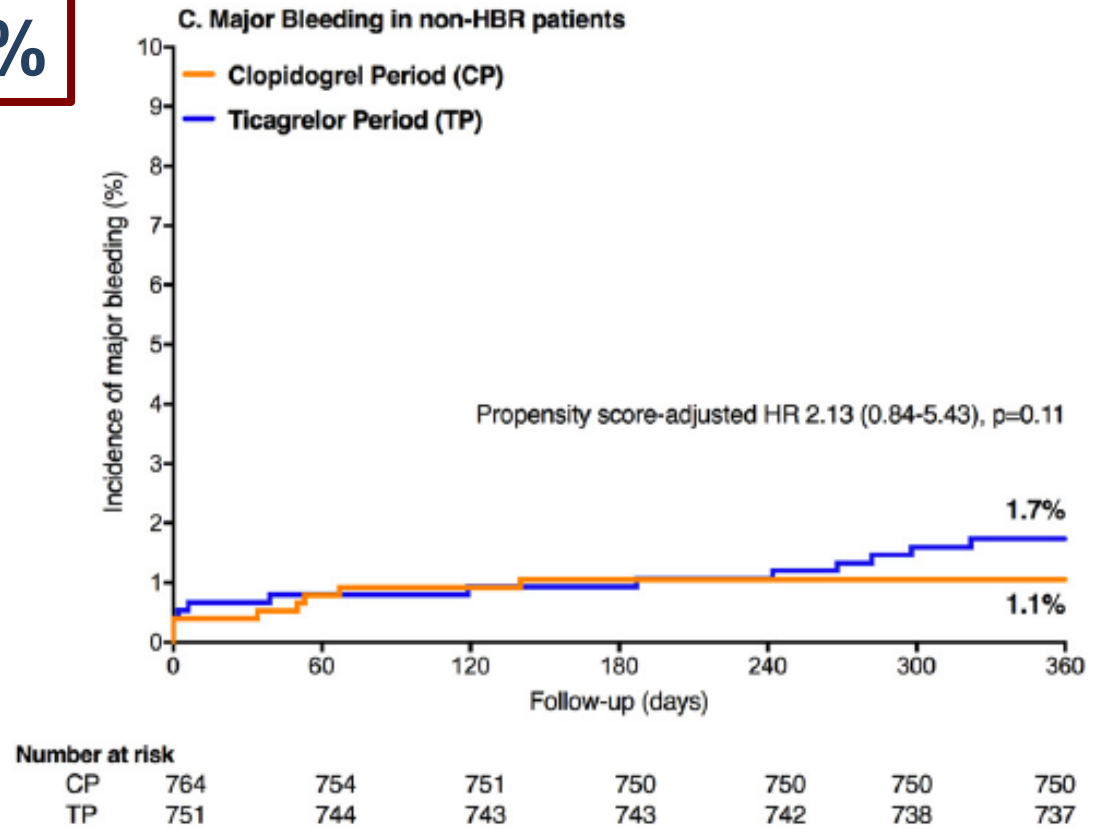
Wiviott SD, et al. N Engl J Med 2007;357:2001-15.

CHANGE-DAPT study: bleeding occurs mainly in HBR patients

2,062 real-world ACS patients treated with PCI.
Clopidogrel period (12/12-04/14, n=1,009) vs Ticagrelor period (05/14-08/16, n=1,053)

HBR: 26.7%

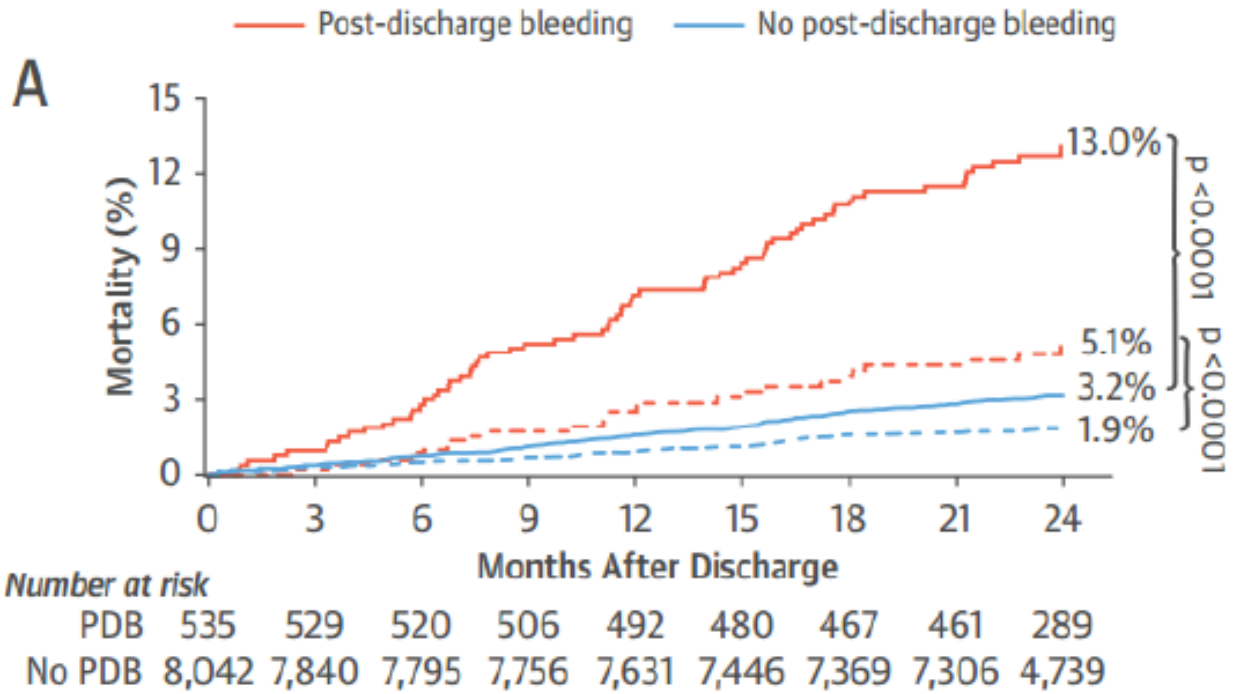




Zocca P, et al. Int J Cardiol 2018;268:11-17.

Impact of post-discharge bleeding after PCI (ADAPT-DES study)

- 8583 patients treated with ≥ 1 DES prospectively followed-up in 10-15 US and European hospitals.
- Platelet reactivity evaluated using VerifyNow showed **increased risk of events with high PRU**.

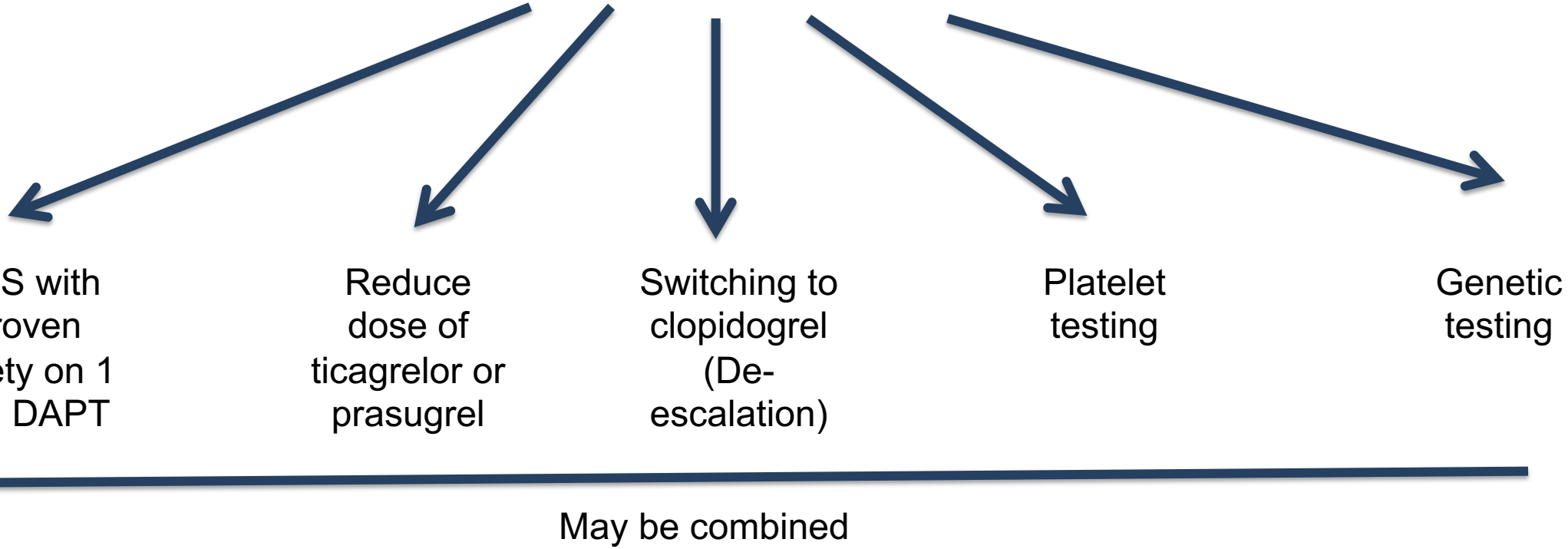


Impact of post-discharge bleeding vs MI on mortality

Variable*	Adjusted HR (95% CI)	p Value
PDB†	5.03 (3.29-7.66)	<0.0001
With transfusion	4.71 (2.76-8.03)	<0.0001
Without transfusion	5.27 (3.32-8.35)	<0.0001
Post-discharge MI†	1.92 (1.18-3.12)	0.009

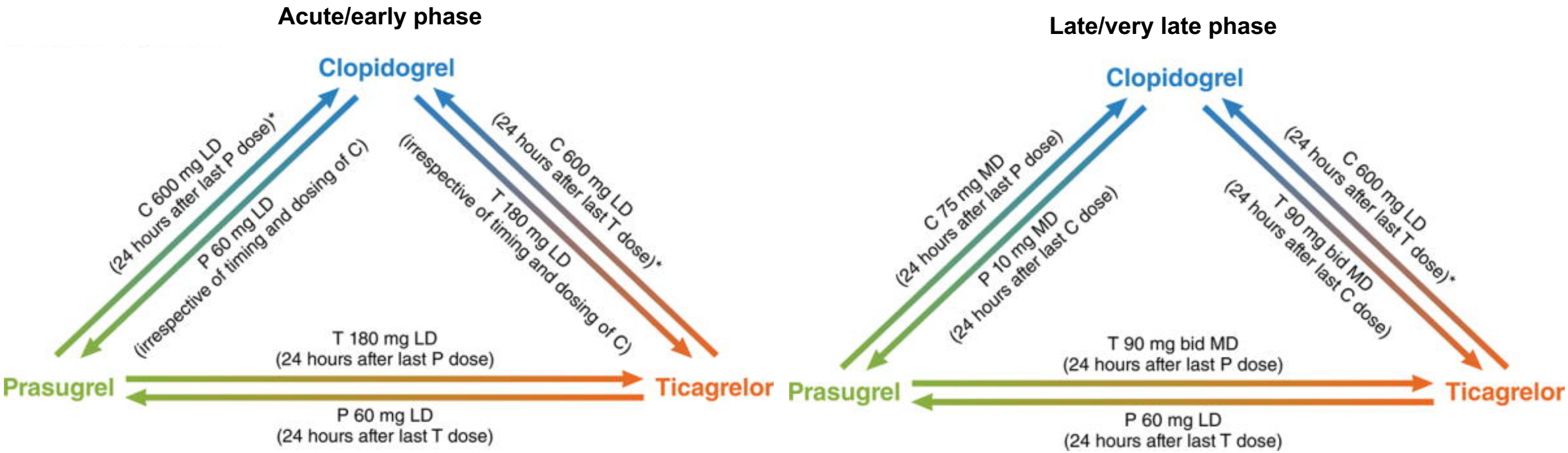
Genereux P, et al. J Am Coll Cardiol. 2015;66:1036-45.

Real-world: HBR ACS patients on DAPT with ticagrelor/prasugrel



International consensus on switching oral P2Y12 inhibitors

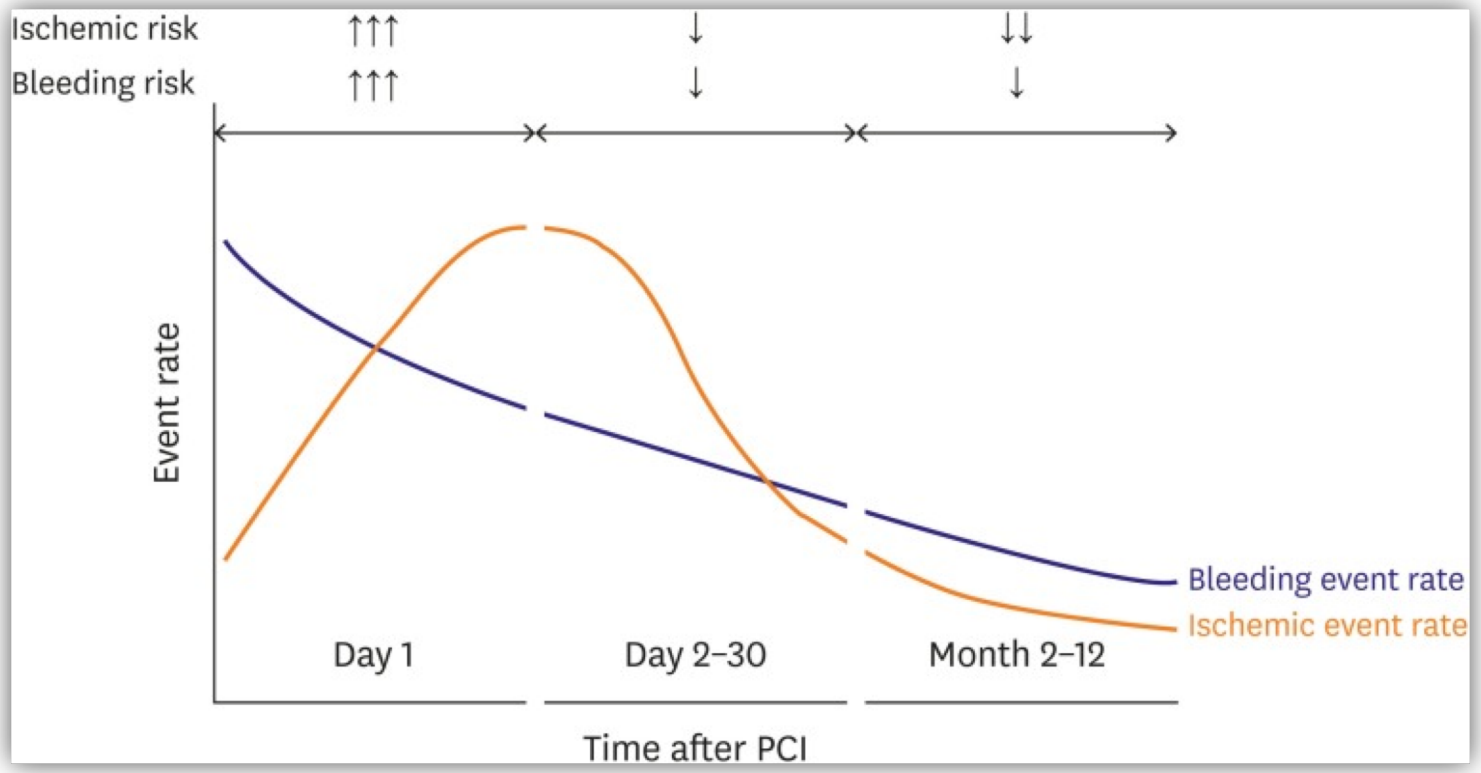
- **ESCALATION**: switching from less intensive to more intensive oral P2Y12 inhibitor.
- **DE-ESCALATION**: switching from more intensive to less intensive oral P2Y12 inhibitor.
- **CHANGE**: switching from one intensive oral P2Y12 inhibitor to another.



Angiolillo DJ, et al. Circulation. 2017;136:1955-1975.

Reasons for de-escalating to clopidogrel

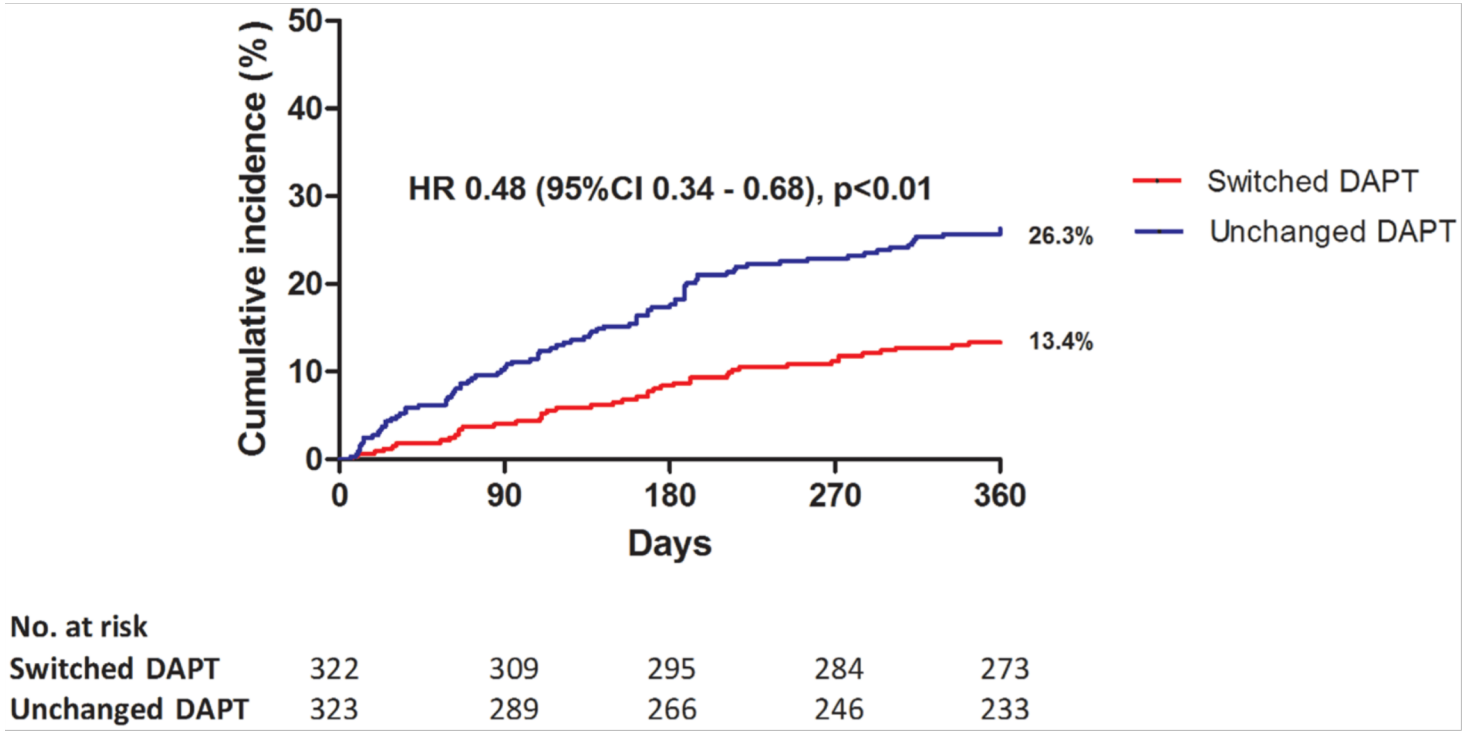
1. High bleeding risk.
2. Oral anti-coagulation (e.g. previous or new onset AF).
3. Costs.
4. Drug discontinuation (e.g. adenosine-mediated dyspnea in the case of ticagrelor).



Kupka D, et al. Korean Circ J 2018;48: 863–872

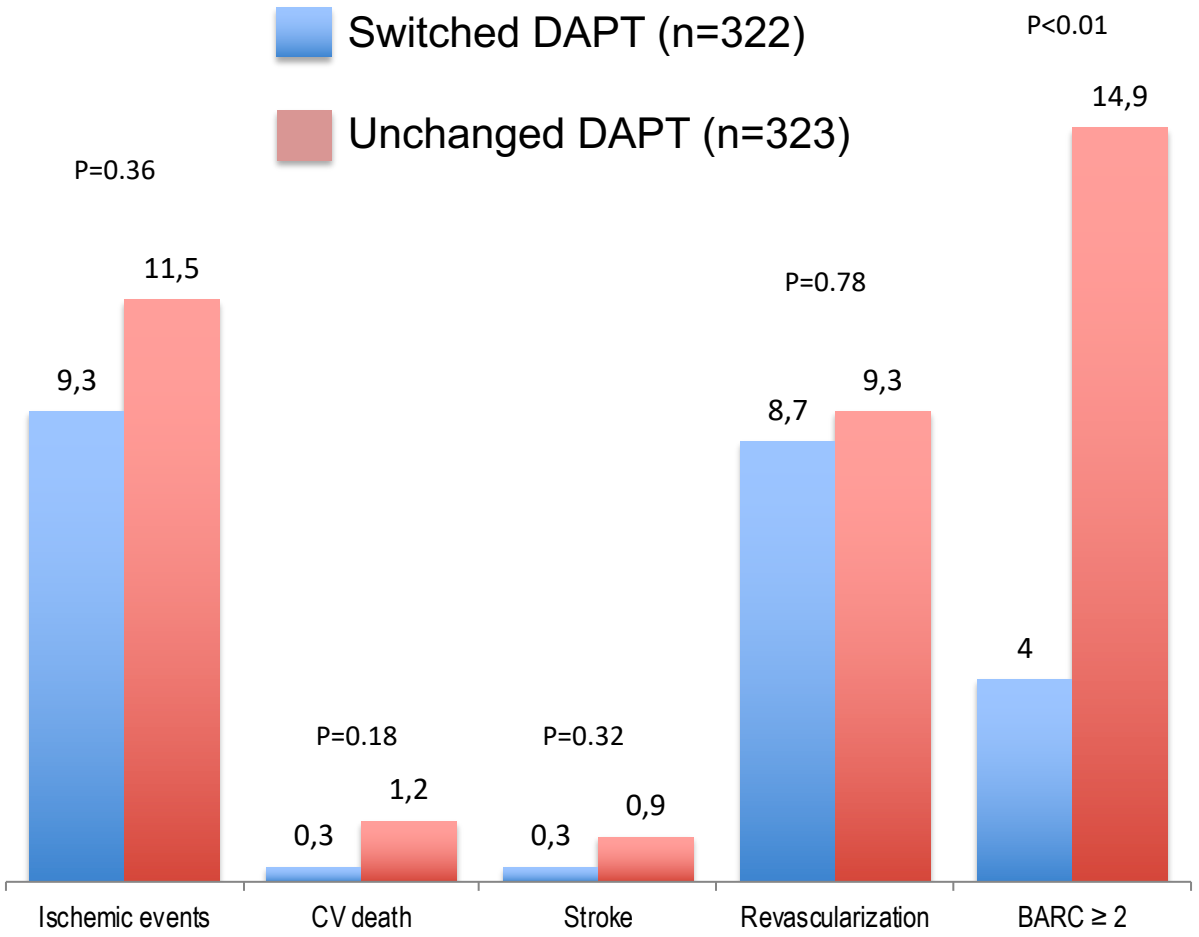
TOPIC study

- 646 patients with ACS & PCI treated with ASA and ticagrelor or prasugrel without events at 1 month.
- At 1 month, randomization to switch to ASA+clopidogrel (switched DAPT) or continuation of their drug regimen (unchanged DAPT).
- Primary outcome: CV death, urgent revascularization, stroke and bleeding (BARC ≥2) at 1 year post ACS.

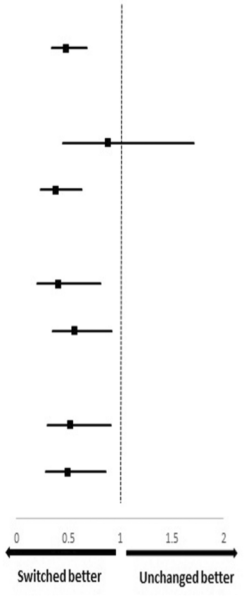


Cuisset T, et al. Eur Heart J 2017;38:3070-8.

TOPIC study



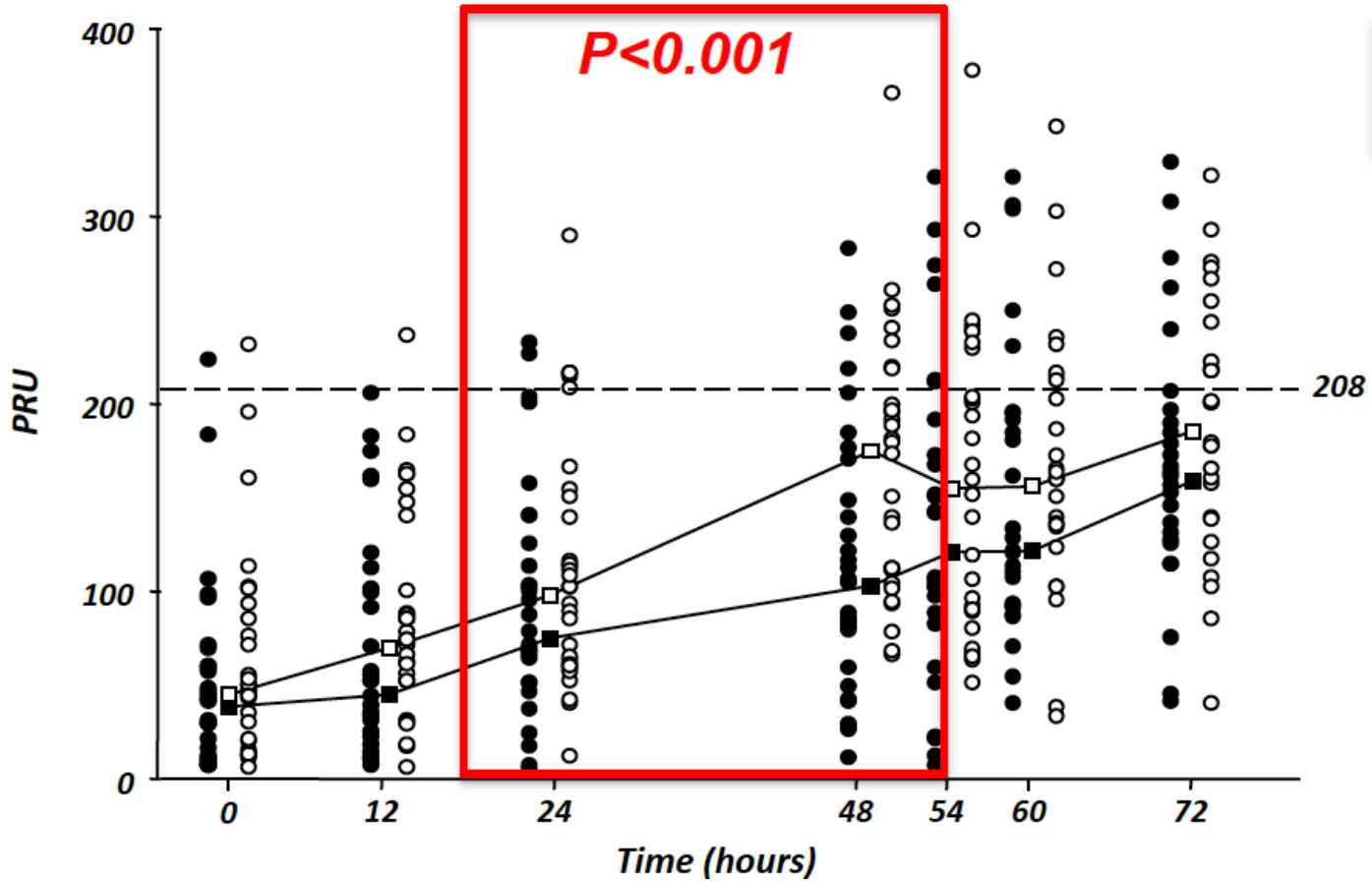
Subgroup	Switched (n=322)		Unchanged (n=323)		Odd ratio (95%CI)	p value for interaction
	Event/total patient (no)	Event rate (%)	Event/total patient (no)	Event rate (%)		
All patient	43/322	13.4	85/323	26.3	0.48 (0.34 - 0.68)	
Diabetes						0.96
Yes	19/84	22.6	24/93	25.8	0.88 (0.45 - 1.71)	
No	24/238	10.1	61/230	26.5	0.38 (0.23 - 0.63)	
ACS presentation						0.85
STEMI	12/116	10.3	36/140	25.7	0.40 (0.20 - 0.81)	
NON STEMI	31/206	15.1	49/183	26.8	0.56 (0.35 - 0.92)	
P2Y12 blocker						0.95
Ticagrelor	23/141	16.3	42/134	31.3	0.52 (0.30 - 0.91)	
Prasugrel	20/181	11.1	43/189	22.7	0.49 (0.28 - 0.86)	



Cuisset T, et al. Eur Heart J 2017;38:3070-8.

How to de-escalate: CAPITAL OPTICROSS trial

60 patients on ticagrelor whose physician had decided to switch to clopidogrel 75 mg/d.
Randomization to clopidogrel bolus dose (600 mg) vs 75 mg 12 after last dose of ticagrelor.

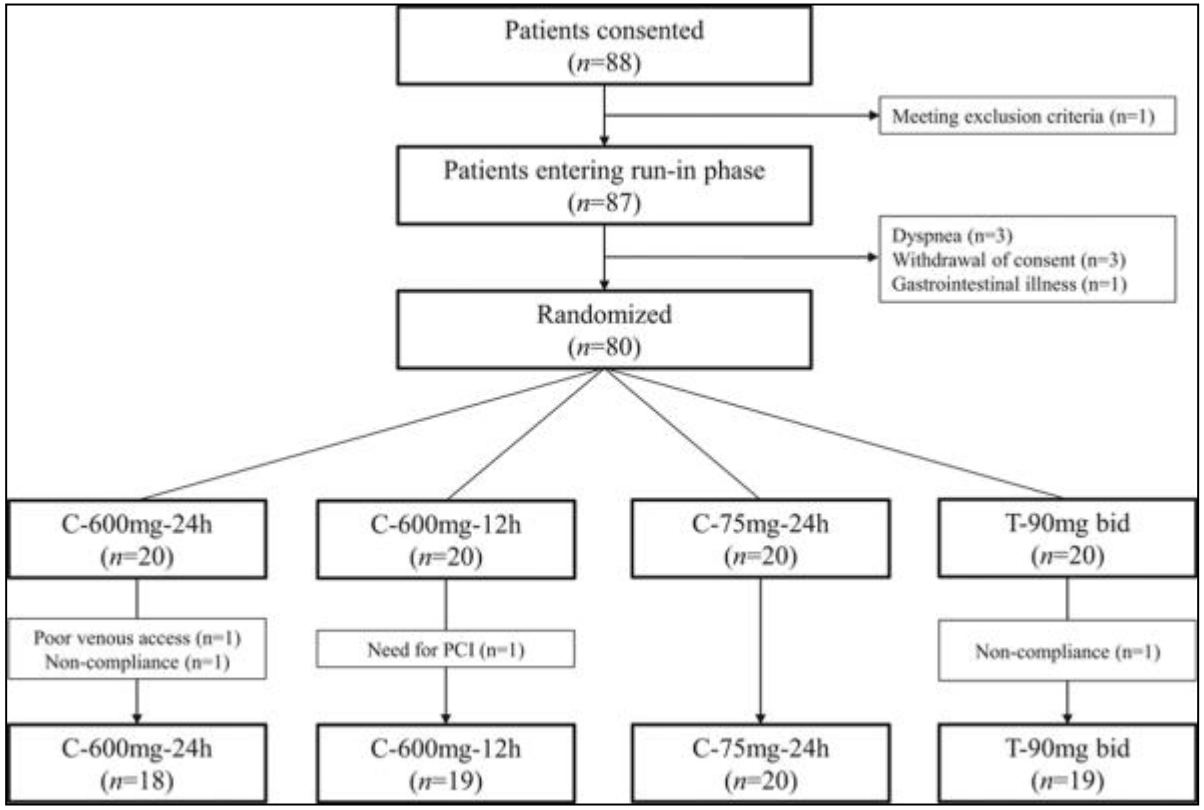


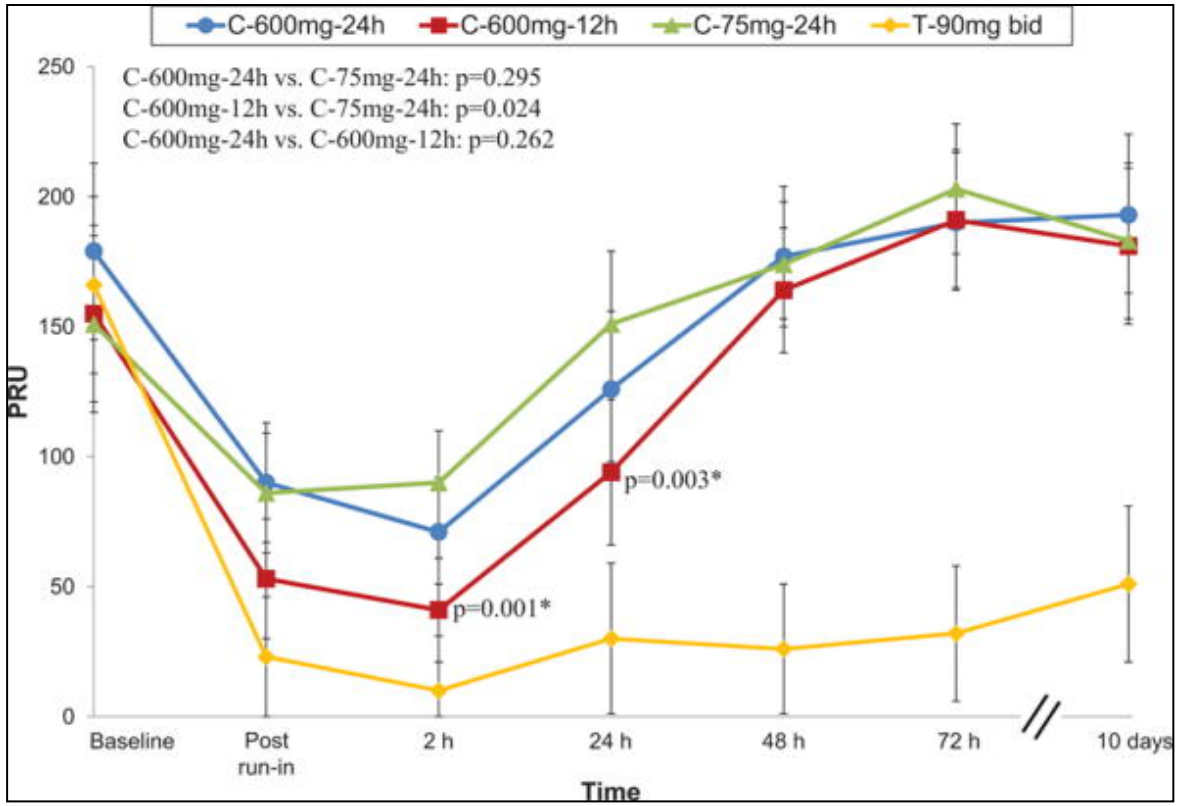
600mg Bolus
No Bolus

- Divergence in platelet reactivity observed between strategies at 24 and 48hrs

Pourdjabbar A, et al. Thromb Haemost 2017;117:303-310.

How to de-escalate: SWAP-4 study

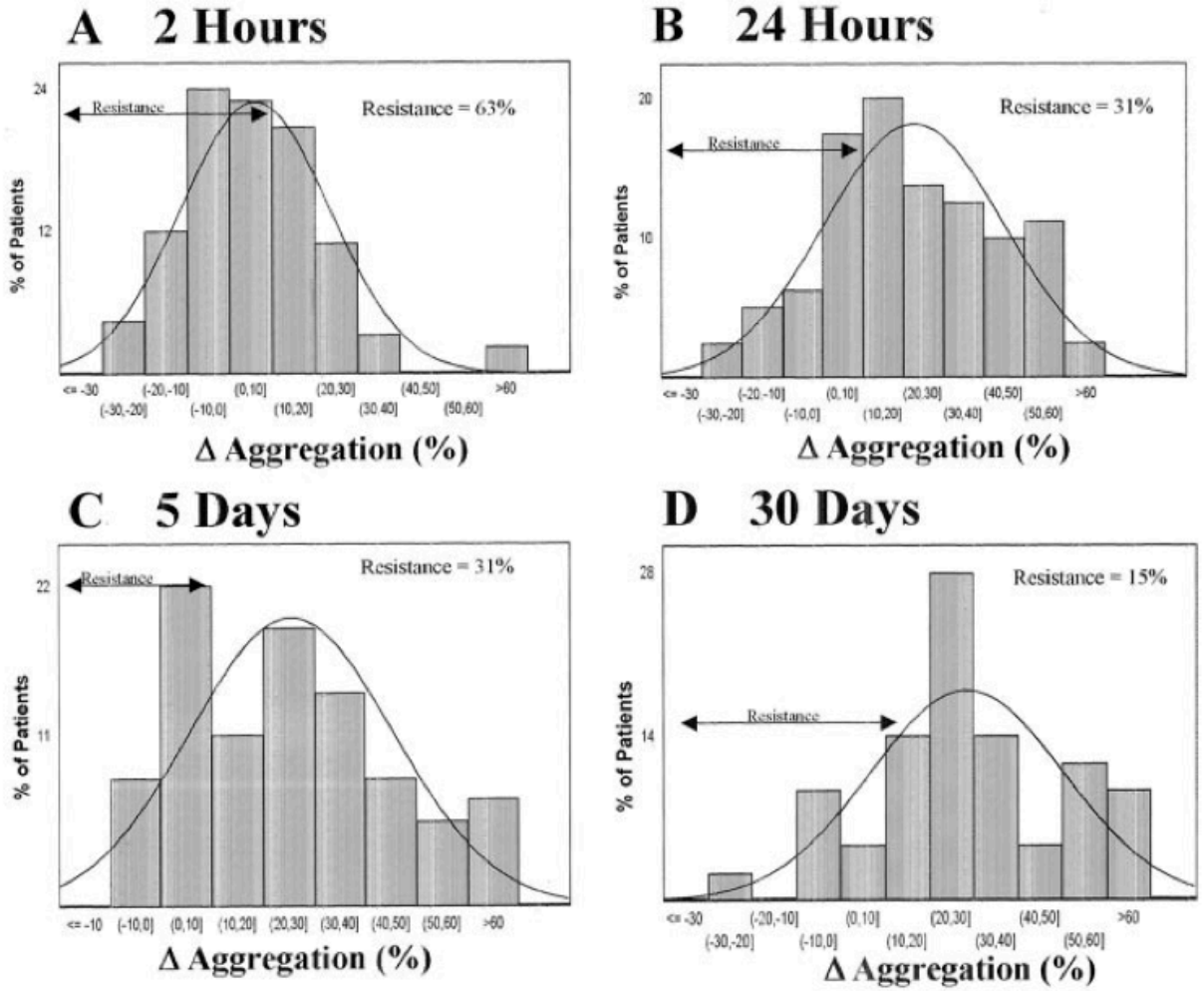




A clopidogrel loading dose avoids a gap in platelet inhibition.

Franchi F, et al. Circulation. 2018;137:2450-2462

Variable response is the main limitation of clopidogrel

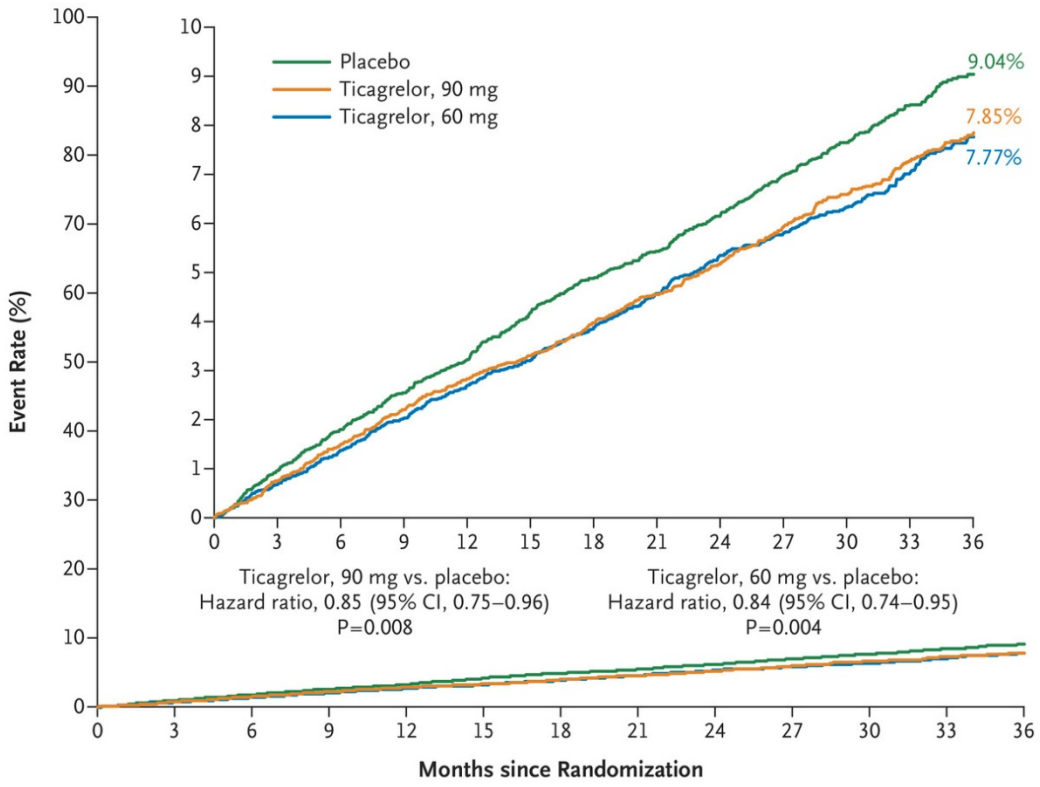


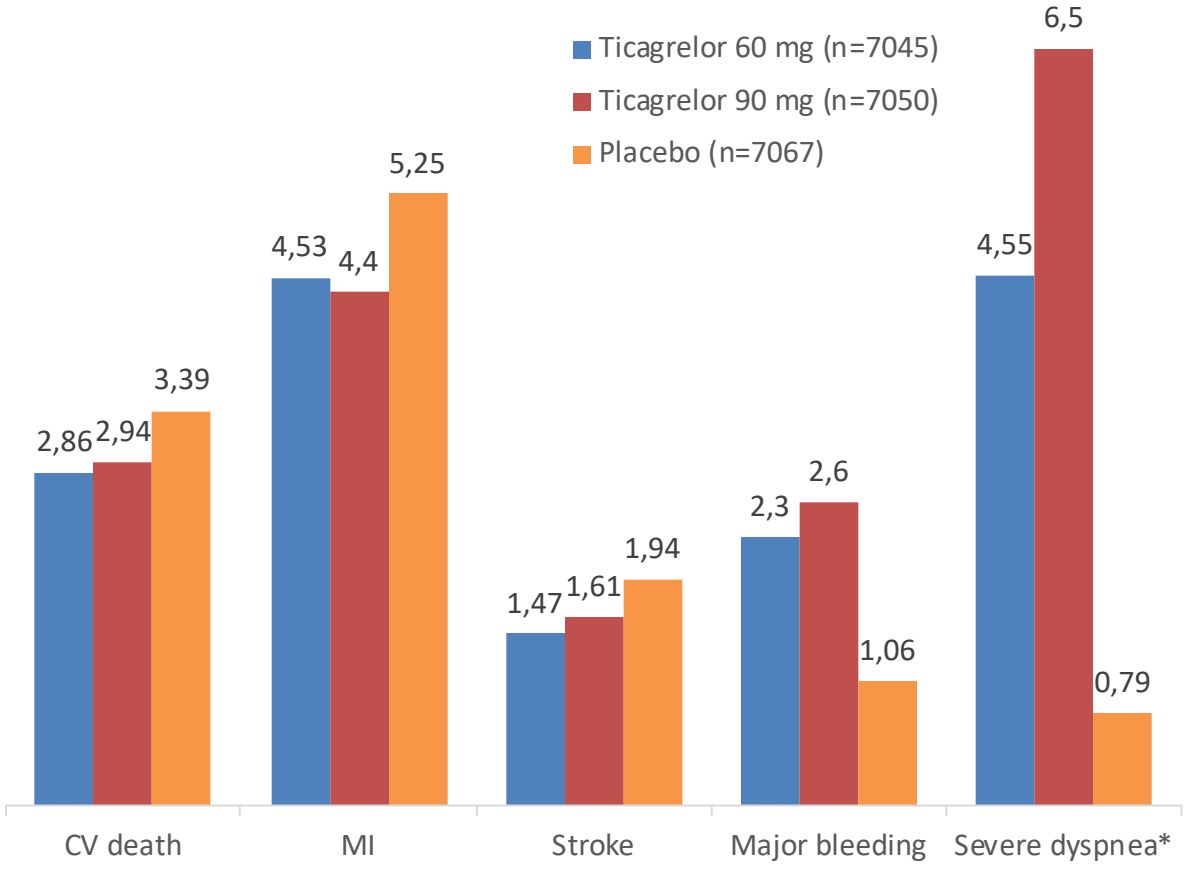
Gurbel PA, et al. Circulation 2003;107:2908-13.

PEGASUS-TIMI 54 trial

21,162 patients 1-3 yr after MI under ASA, randomized to Ticagrelor 60 mg bid / Ticagrelor 90 m bid / placebo.

CV death, MI, and Stroke through 3 Years



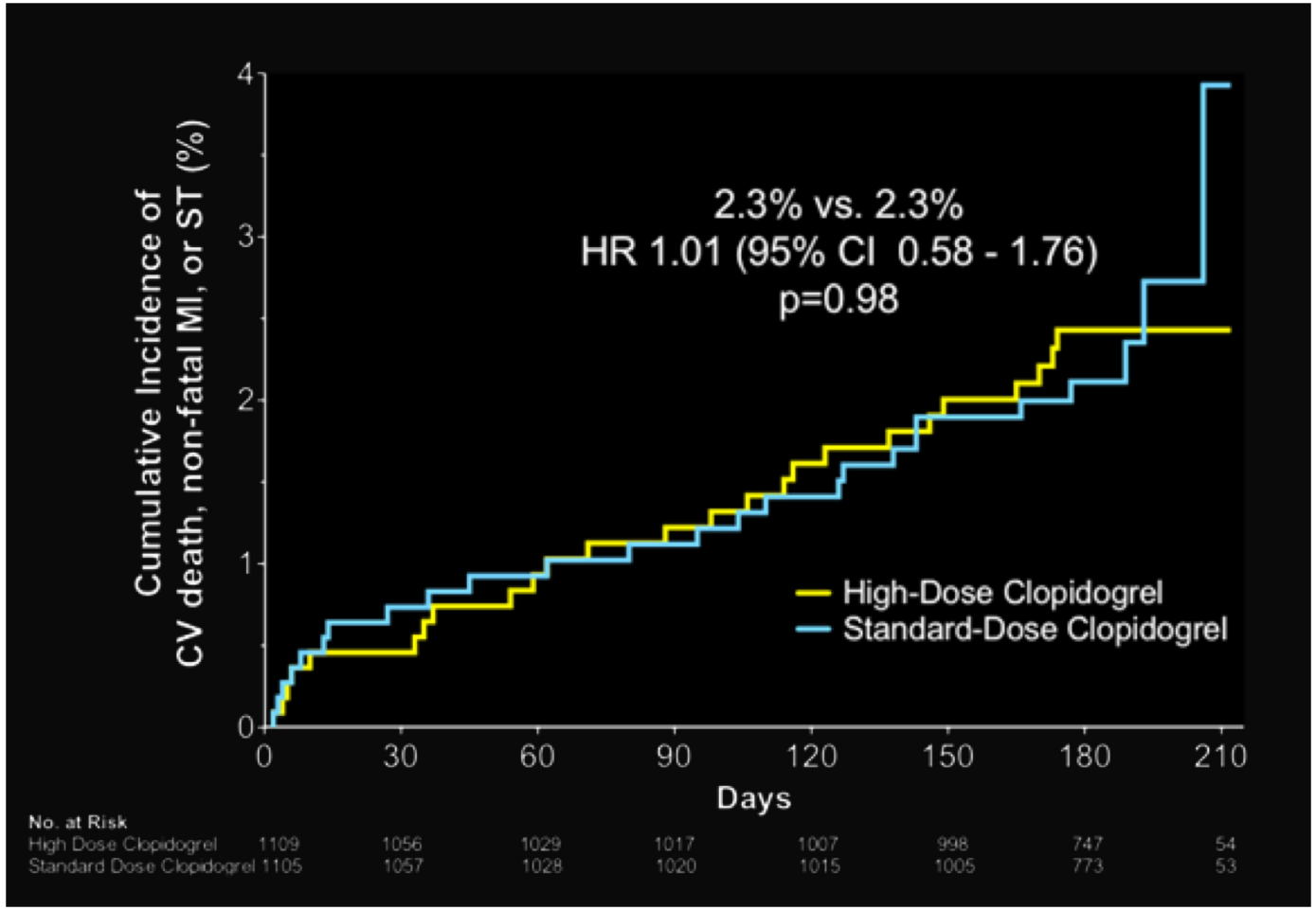


Bonaca MP et al. N Engl J Med 2015;372:1791-1800.

**leading to drug discontinuation*

GRAVITAS trial

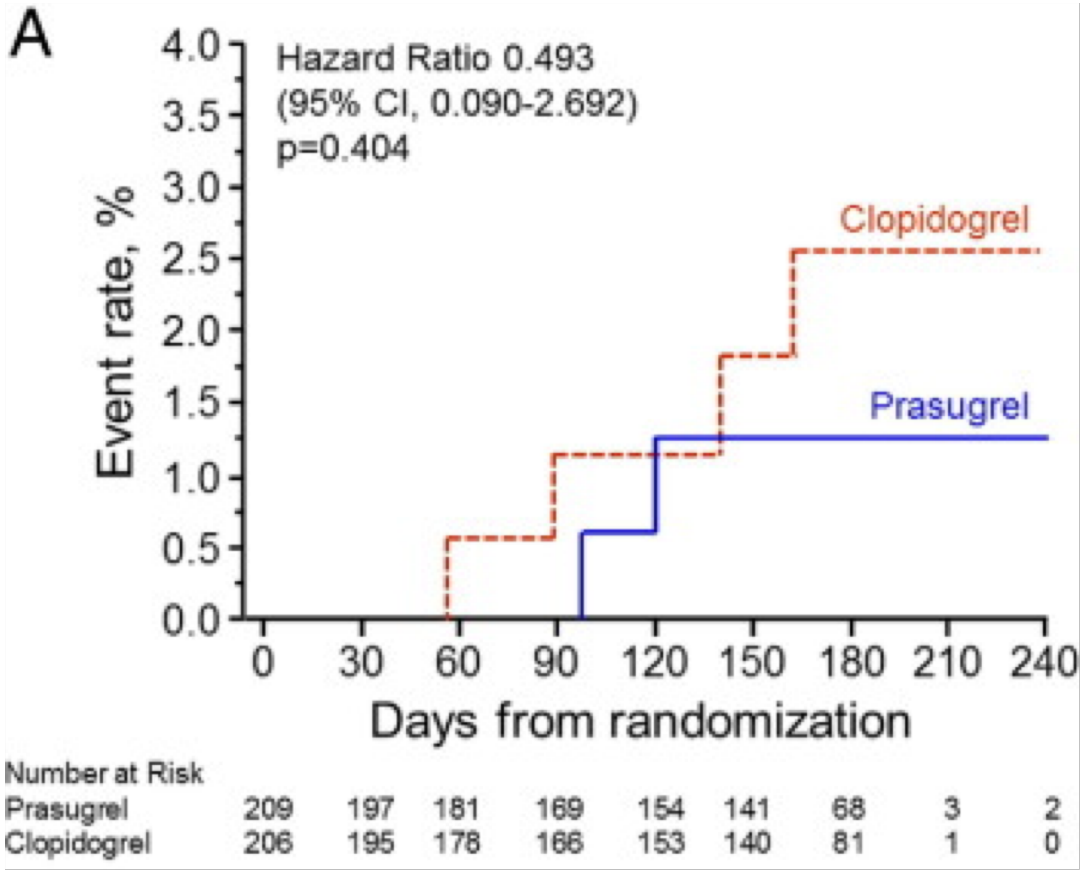
- 5,429 post-PCI patients underwent VerifyNow.
- 2,214 (≈40%) having high on-treatment reactivity (PRU ≥ 230) were randomized to high-dose clopidogrel (600-mg followed by 150 mg/d) or standard-dose clopidogrel (no additional loading dose, 75 mg/d) for 6 mo.

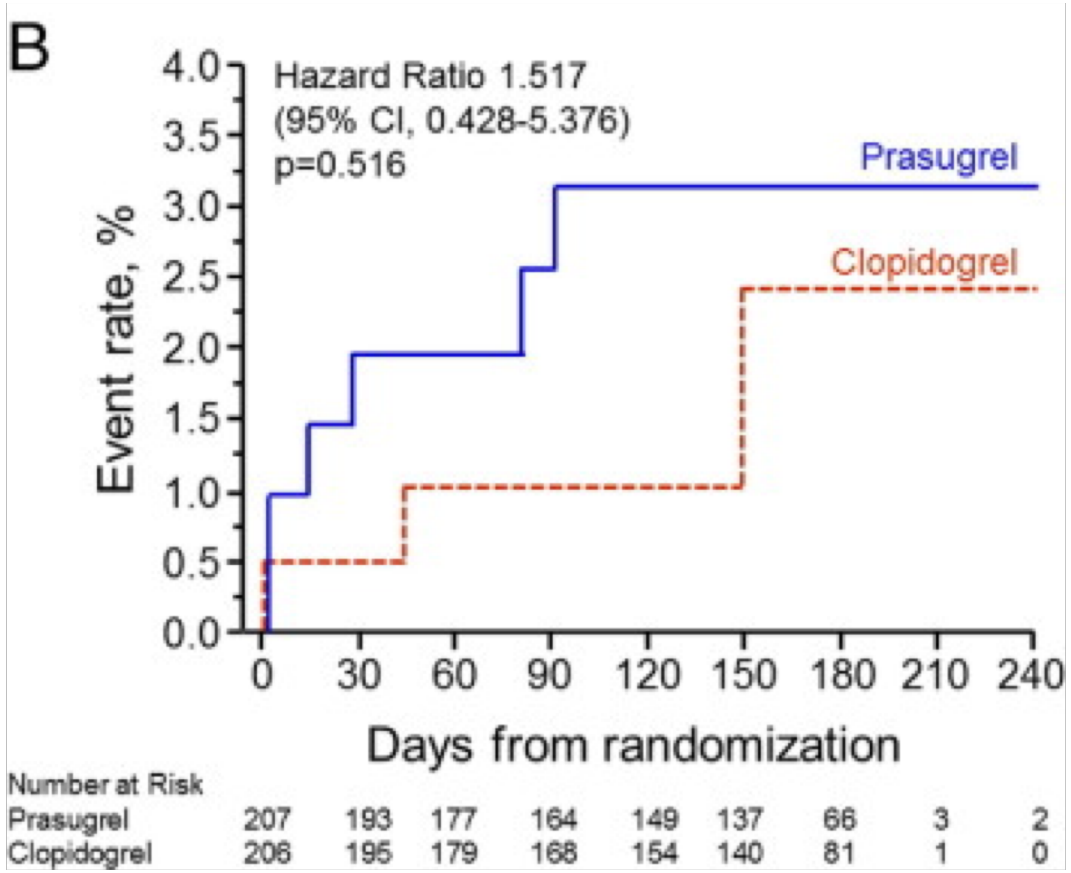


Price MJ, et al. JAMA 2011;305:1097-1105.

TRIGGER-PCI trial

- 423 patients undergoing PCI for SCAD with PRU >208.
- Randomly assigned to prasugrel 10 mg/d or clopidogrel 75 m/d.



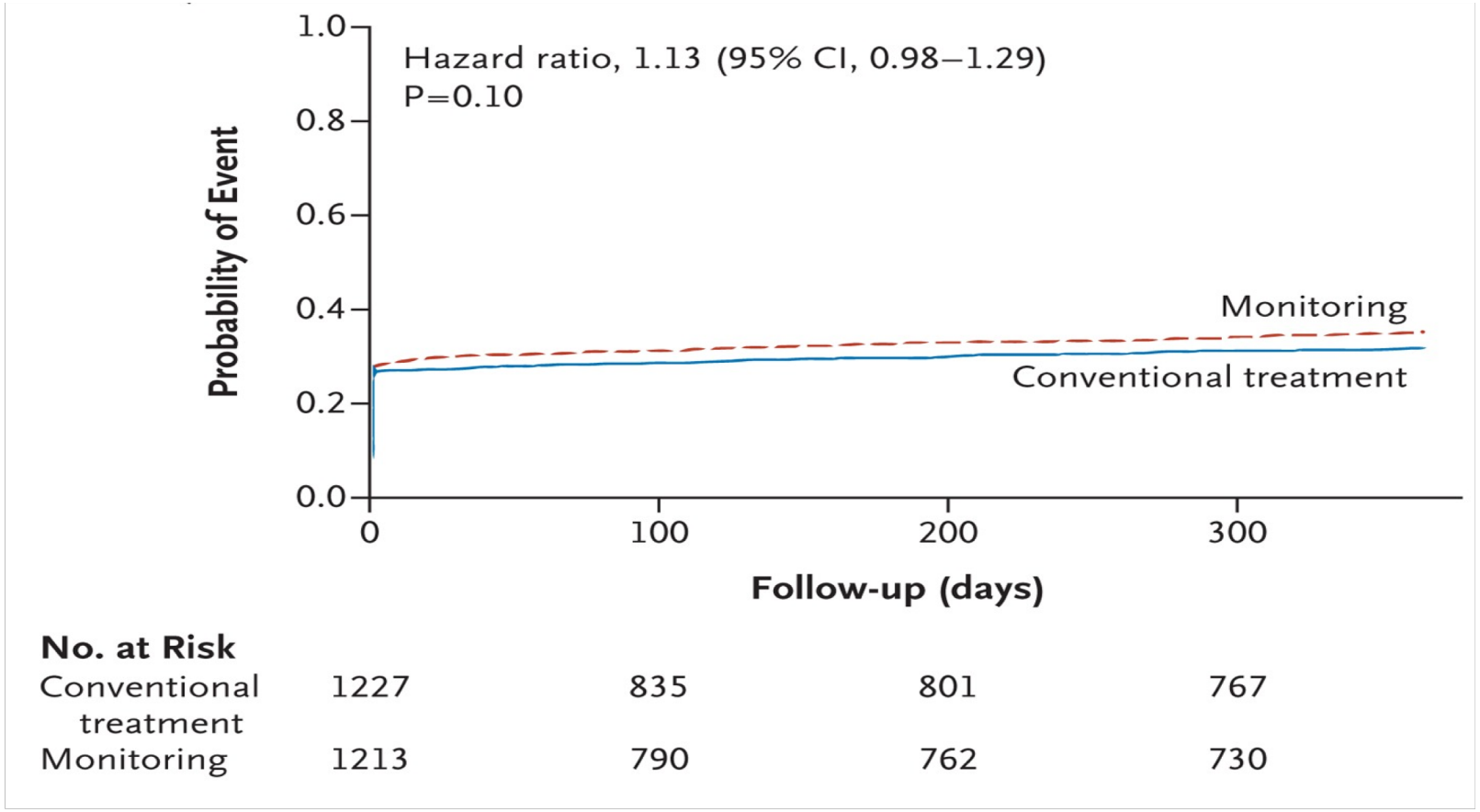


Trenk D, et al. J Am Coll Cardiol 2012;59:2159-64.

ARCTIC trial

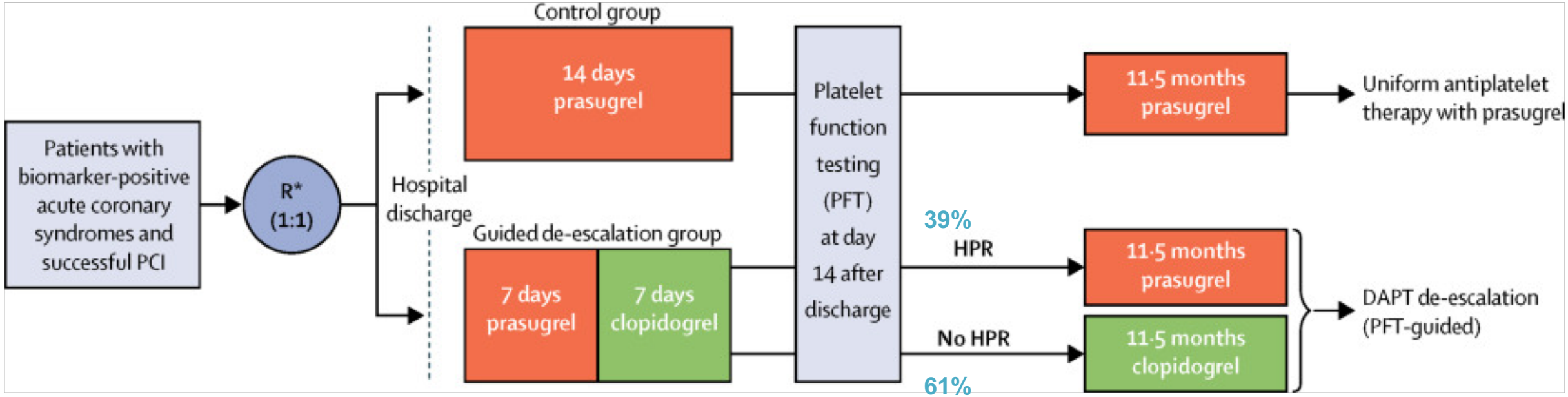
2440 patients receiving DES randomized to platelet-function monitoring (with drug adjustment if poor response to antiplatelet therapy) or to a conventional strategy without monitoring and drug adjustment.

Primary end-point: composite of death, MI, stent thrombosis, stroke, or urgent revascularization at 1 year.



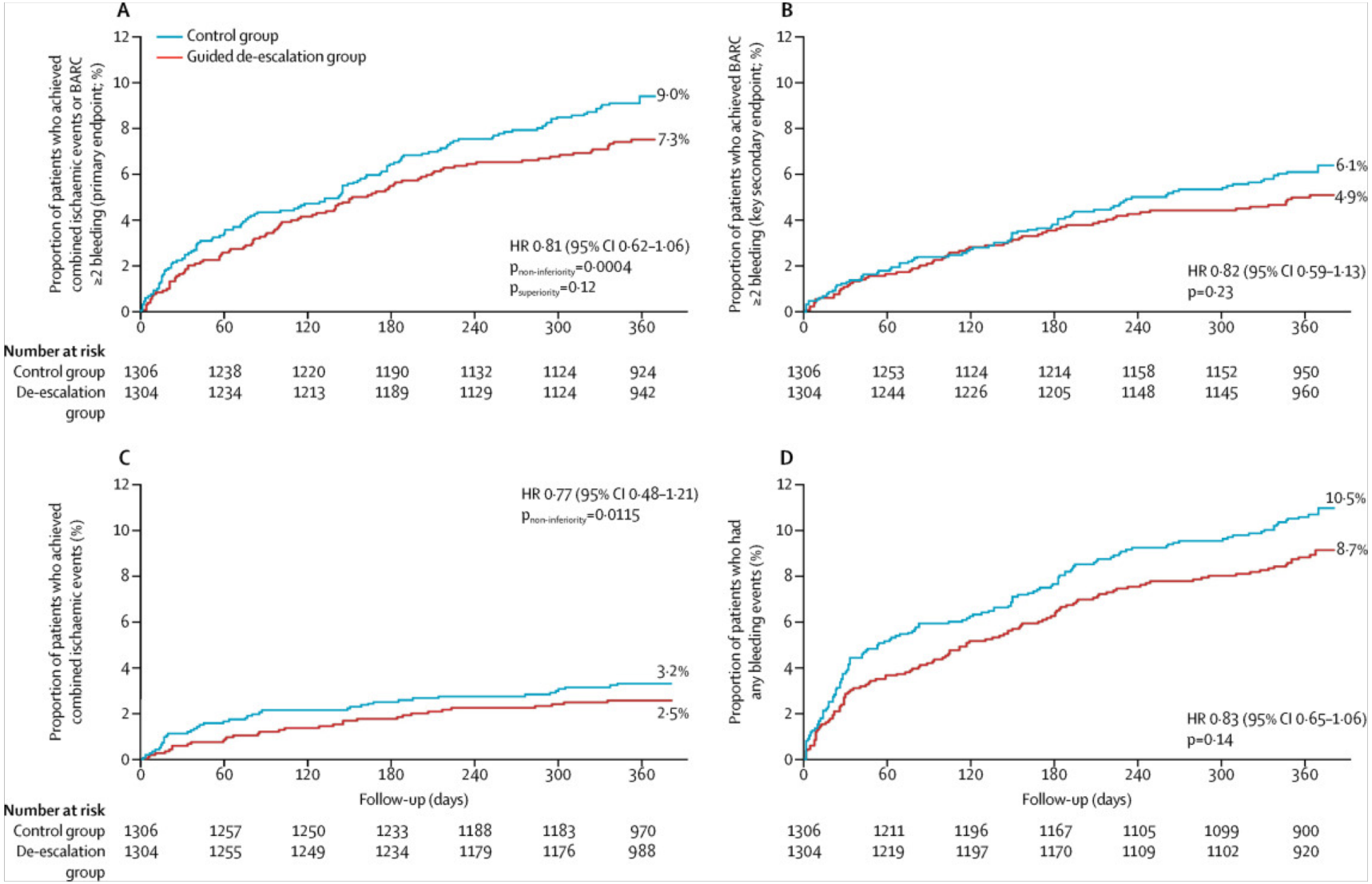
Collet JP, et al. N Engl J Med 2012;367:2100-9.

TROPICAL-ACS trial



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

TROPICAL-ACS trial



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

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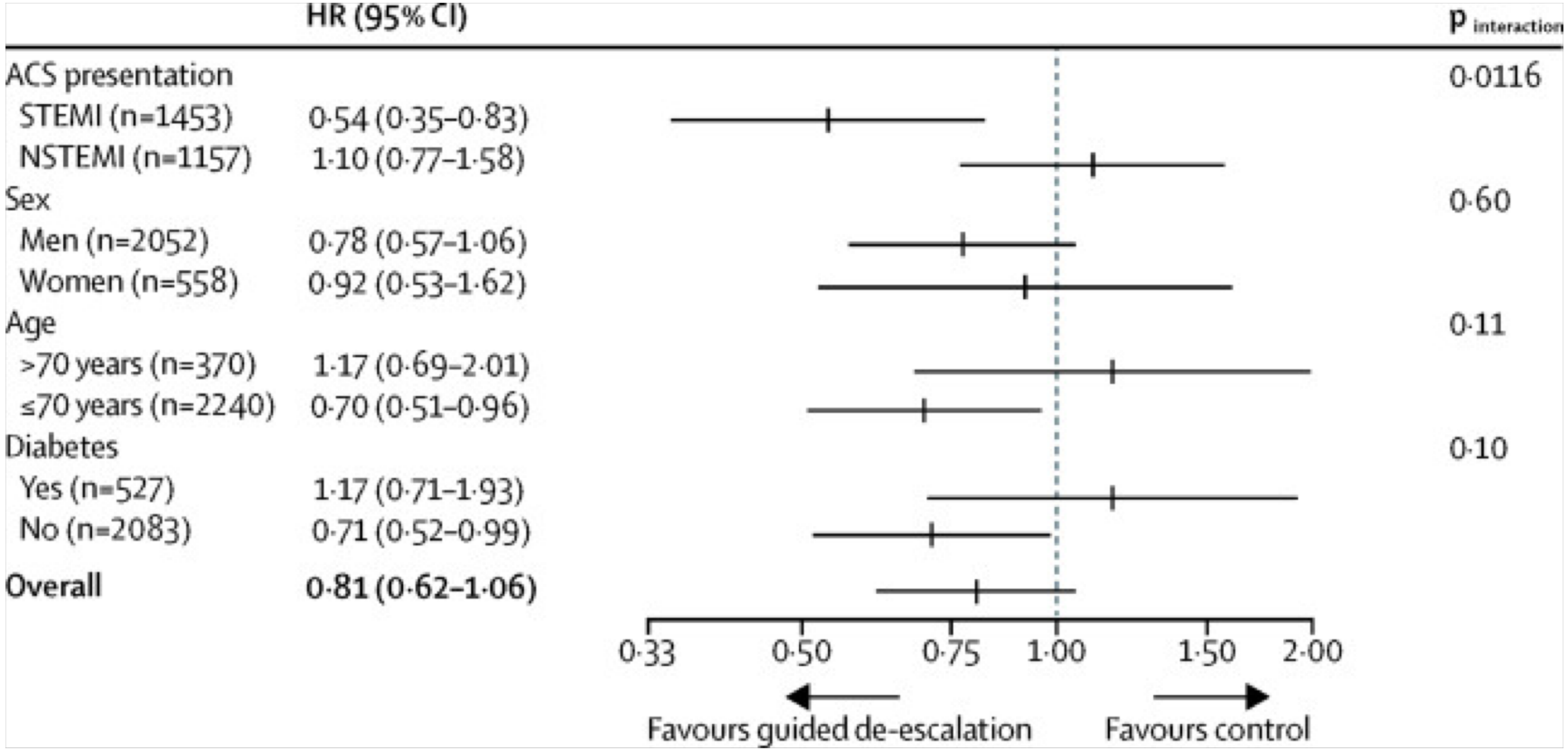
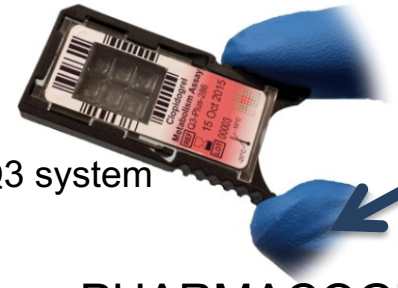


Sibbing D, et al. Lancet. 2017;390:1747-1757.

PHARMCLO study

Unselected patients admitted with ACS (STE & NSTE).
(initially planned 3,612; finally, 888 included)

Randomization



ST Q3 system

PHARMACOGENOMIC
(ABCB1, 2C19*2, 2C19*17)

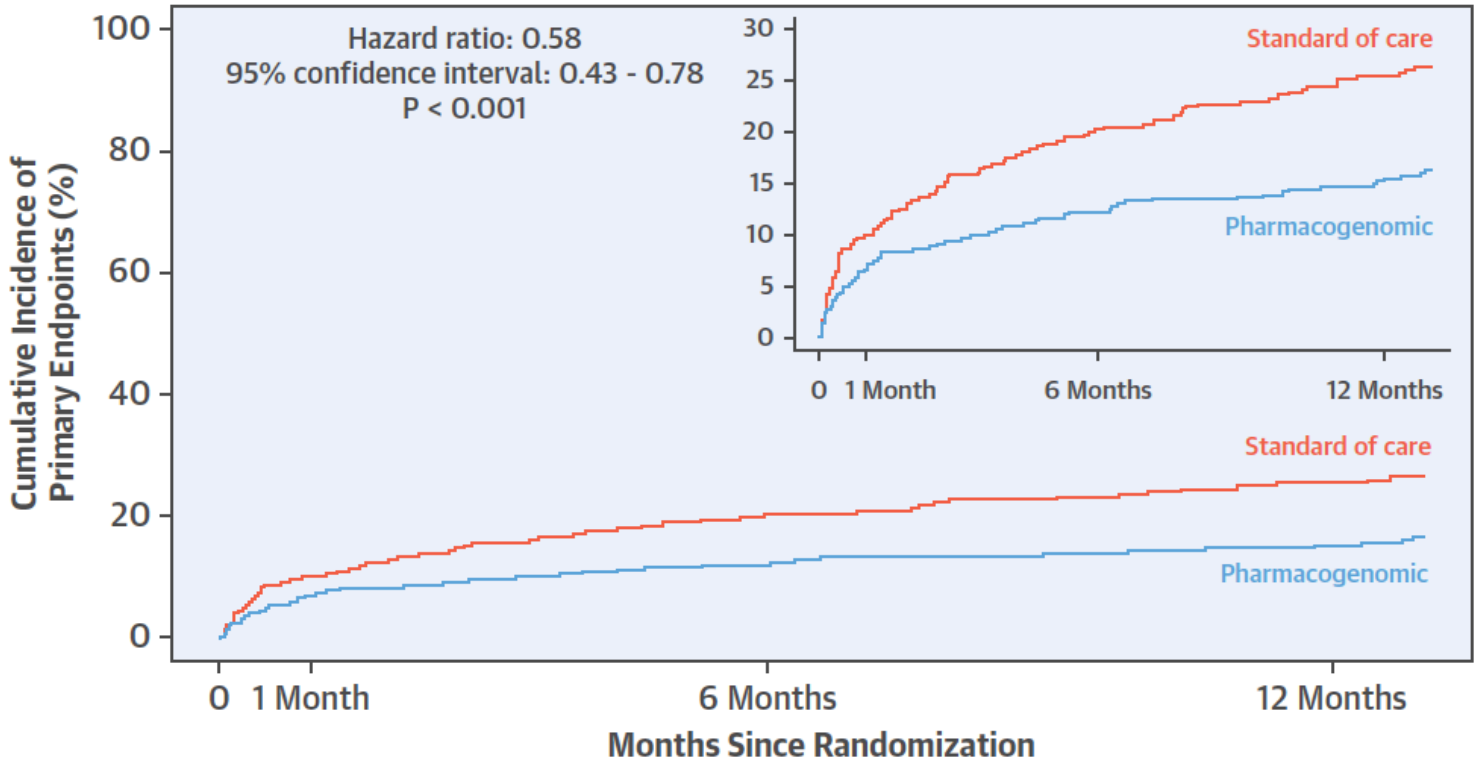
STANDARD OF CARE

1 year follow-up

Primary end-point: the composite of cardiovascular death and the first occurrence of non-fatal MI, non-fatal stroke and BARC 3 to 5-defined major bleeding

Notarangelo FM, et al. J Am Coll Cardiol 2018;71:1869-77.

PHARMCLO study

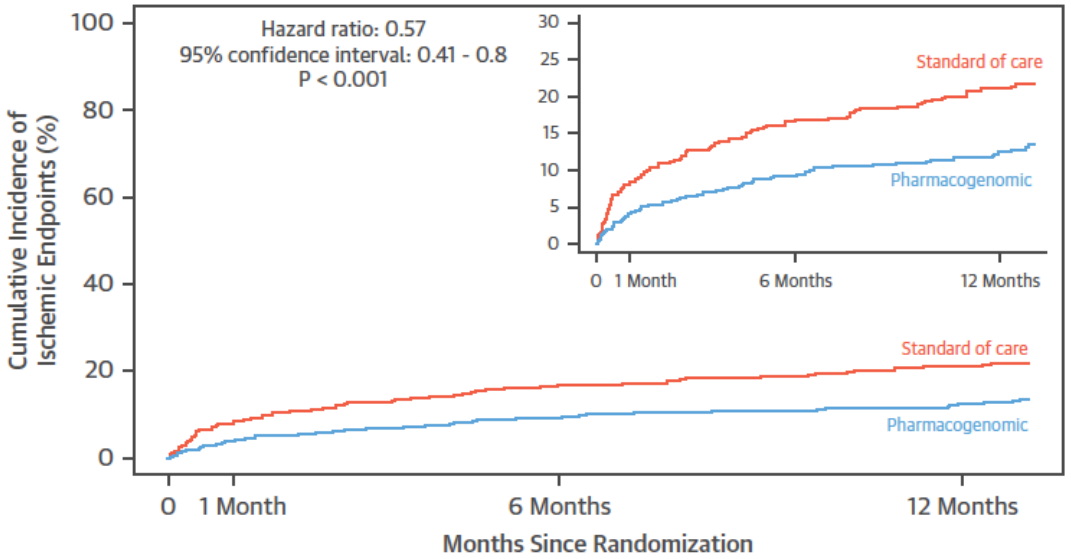


No. at risk				
Pharmacogenomic arm	448	416	390	295
Standard-of-care arm	440	397	349	280

Notarangelo FM, et al. J Am Coll Cardiol 2018;71:1869-77.

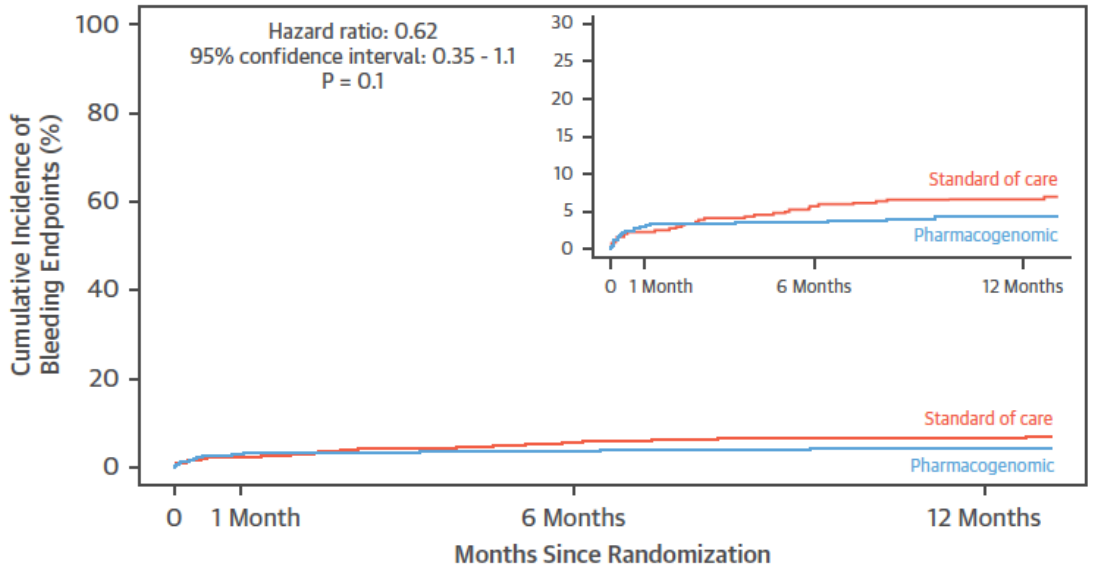
PHARMCLO study

Ischemic events



No. at risk				
Pharmacogenomic arm	448	428	402	304
Standard-of-care arm	440	404	362	294

Bleeding events



No.at risk				
Pharmacogenomic arm	448	423	406	311
Standard-of-care arm	440	420	385	319

Notarangelo FM, et al. J Am Coll Cardiol 2018;71:1869-77.

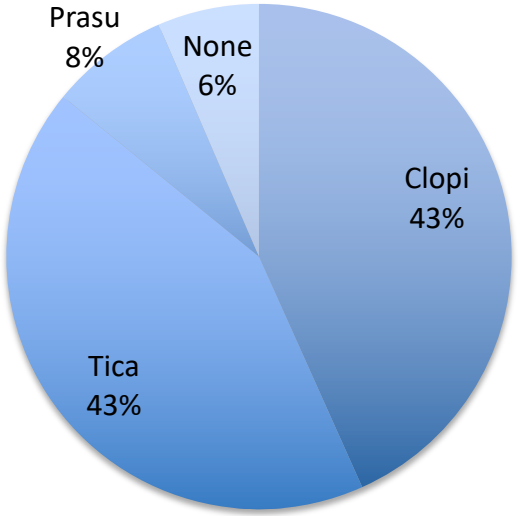
PHARMCLO study

Randomization

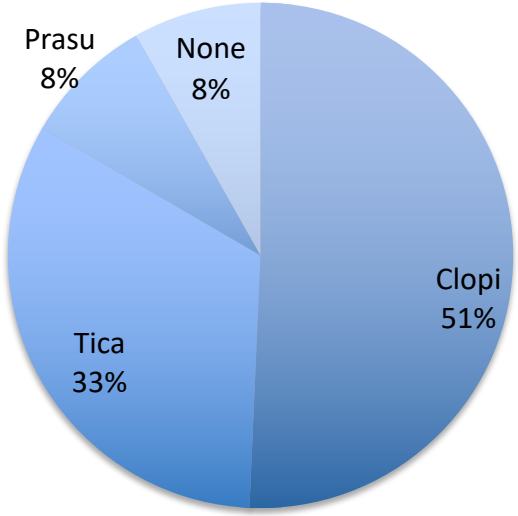
ST Q3 system

PHARMACOGENOMIC
(ABCB1, 2C19*2, 2C19*17)

STANDARD OF CARE



No clear recommendations



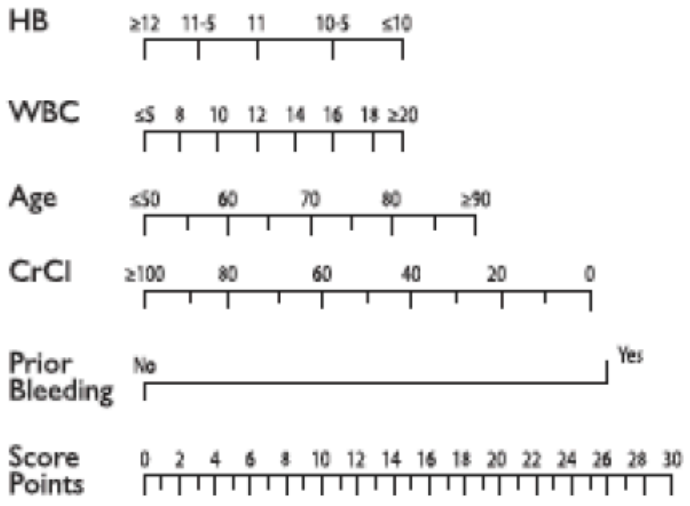
P=0.02

Notarangelo FM, et al. J Am Coll Cardiol 2018;71:1869-77.

Limitations of platelet and genetic testing

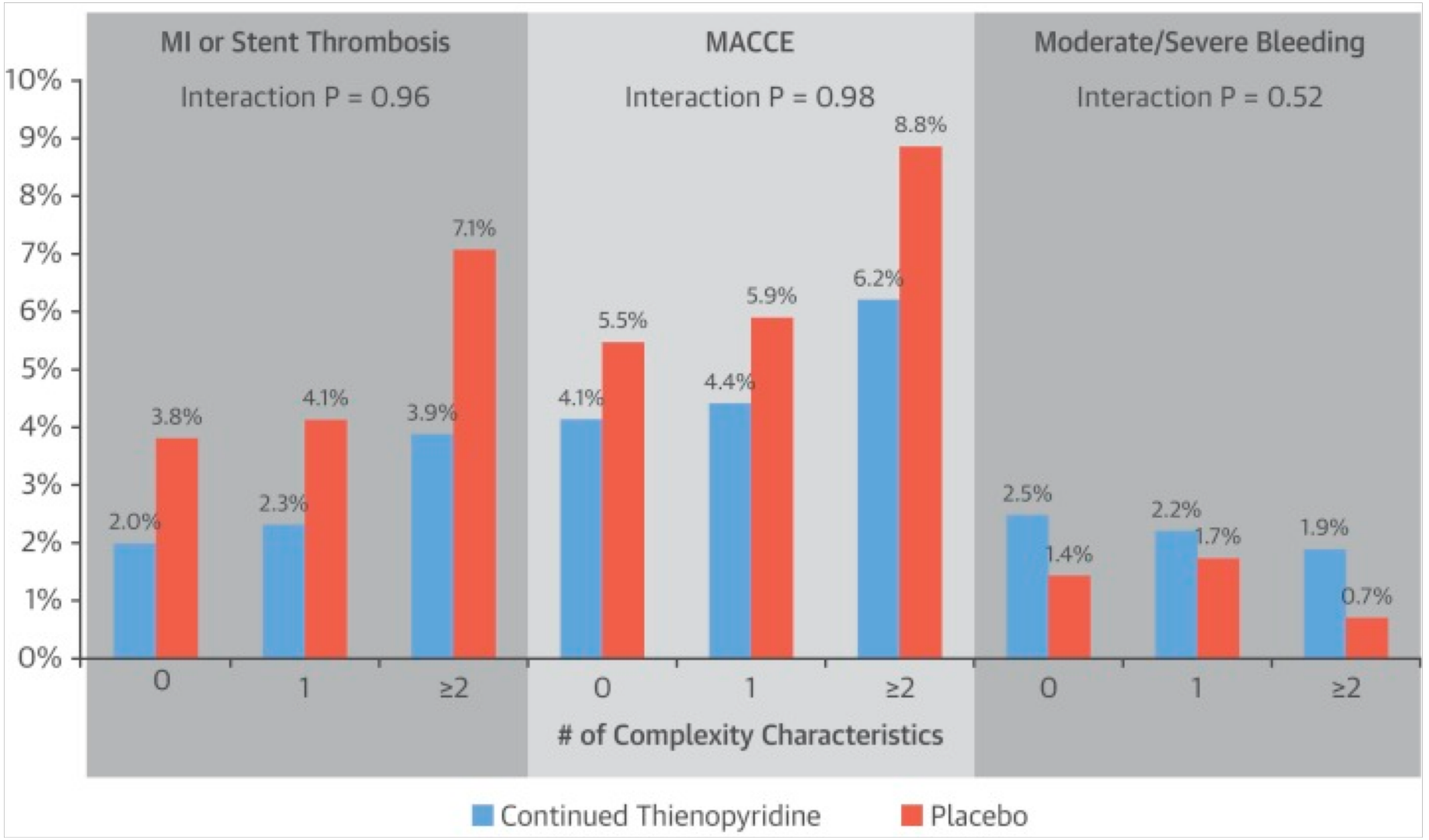
- The results of platelet testing are widely variable in the same patient.
- Tailored therapy after platelet testing have not demonstrated any benefit.
- Response to clopidogrel is not influence only by genetics, but also by clinical factors (e.g. BMI, diabetes, renal function, other drugs, etc).
- Genetic testing: insufficient data, and no clear recommendations after genetic test results.

Risk scores validated for DAPT duration decision making

	PRECISE-DAPT score[18]	DAPT score[15]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

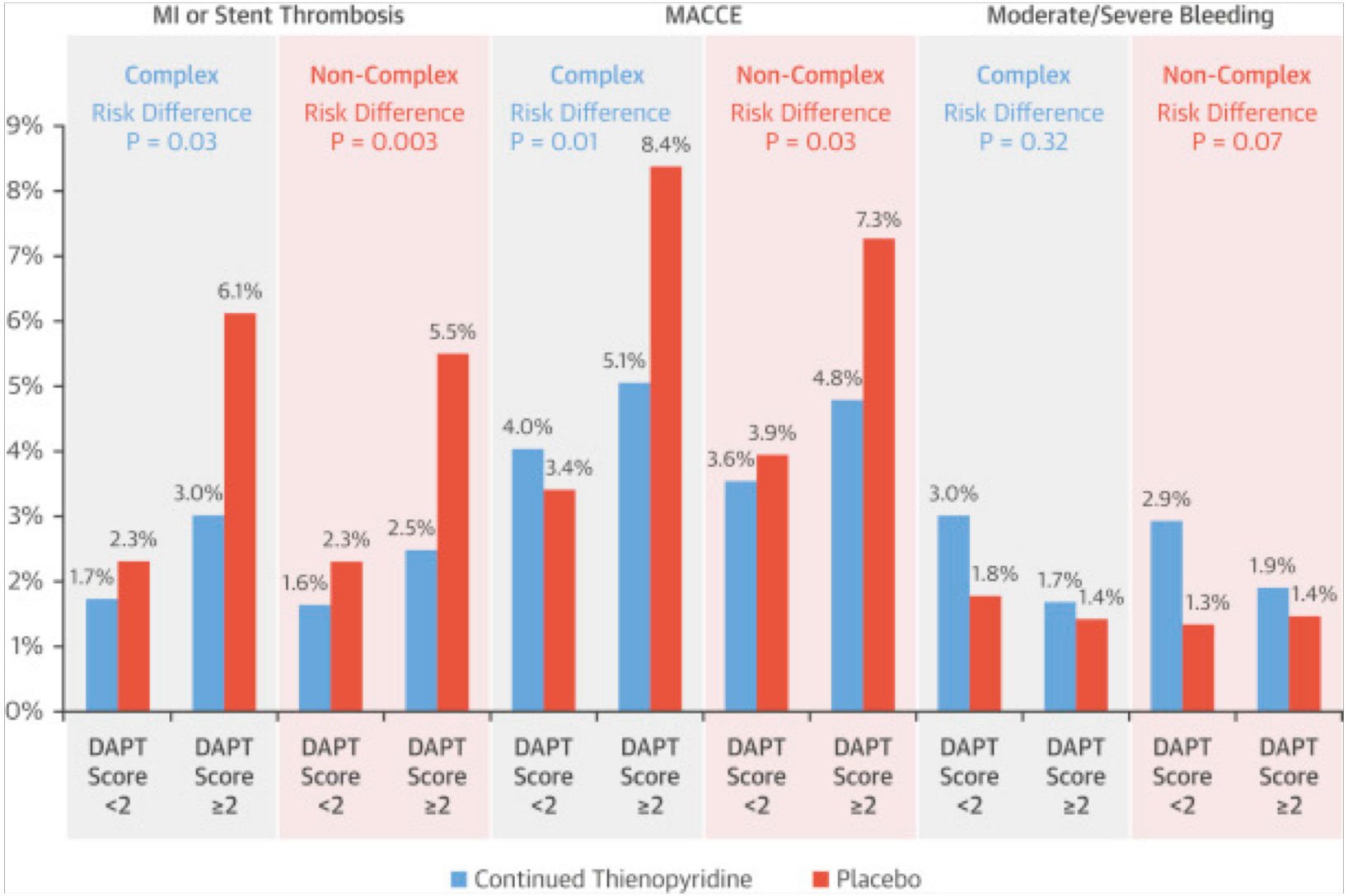
Valgimigli M, et al. Eur Heart J 2018;39:213-254-

Importance of lesion complexity. Data from the DAPT study.



Yeh RW, et al. J Am Coll Cardiol 2017;70:2213-2223

Importance of lesion complexity. Data from the DAPT study.



Yeh RW, et al. J Am Coll Cardiol 2017;70:2213-2223

CONCLUSIONS

- In HBR patients with ACS, the clinical benefit of P2Y12 may be compromised by bleeding complications.
- Several options, including de-escalation and dose reduction may be an option.
- Platelet testing has not demonstrated a clinical benefit.
- Genetic testing promising, but not ready for clinical application.
- Ischemic and bleeding scores may be useful for clinical decision making.