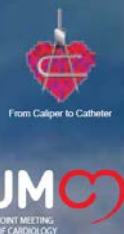


**ADVANCES IN CARDIAC
ARRHYTHMIAS**
and
**GREAT INNOVATIONS
IN CARDIOLOGY**



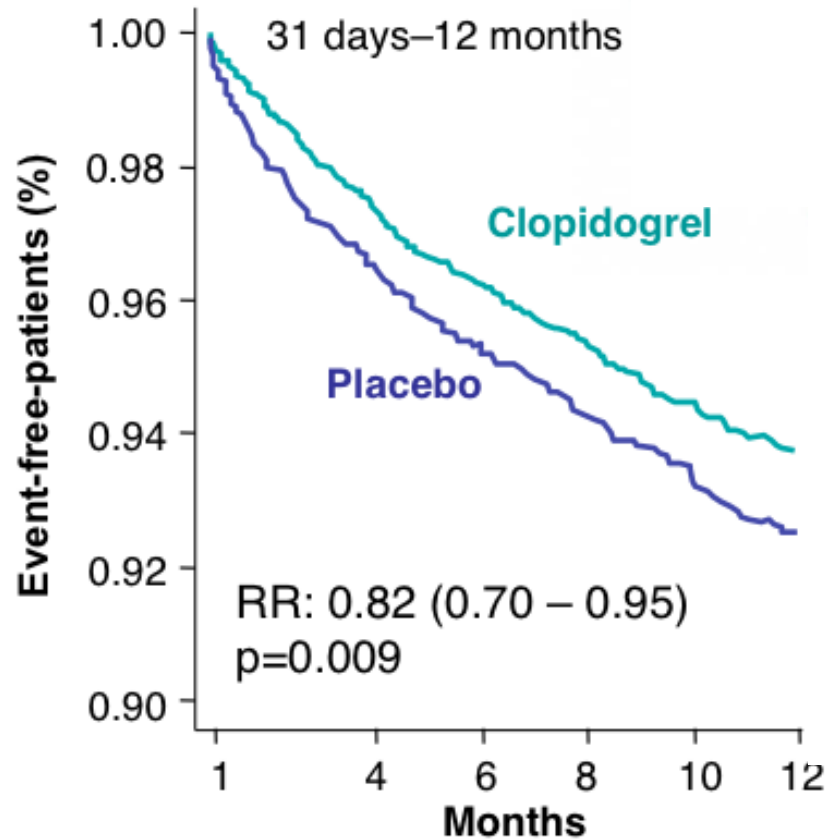
Antiplatelet therapy in acute coronary syndromes: old and new players

Marco Tubaro, MD FESC

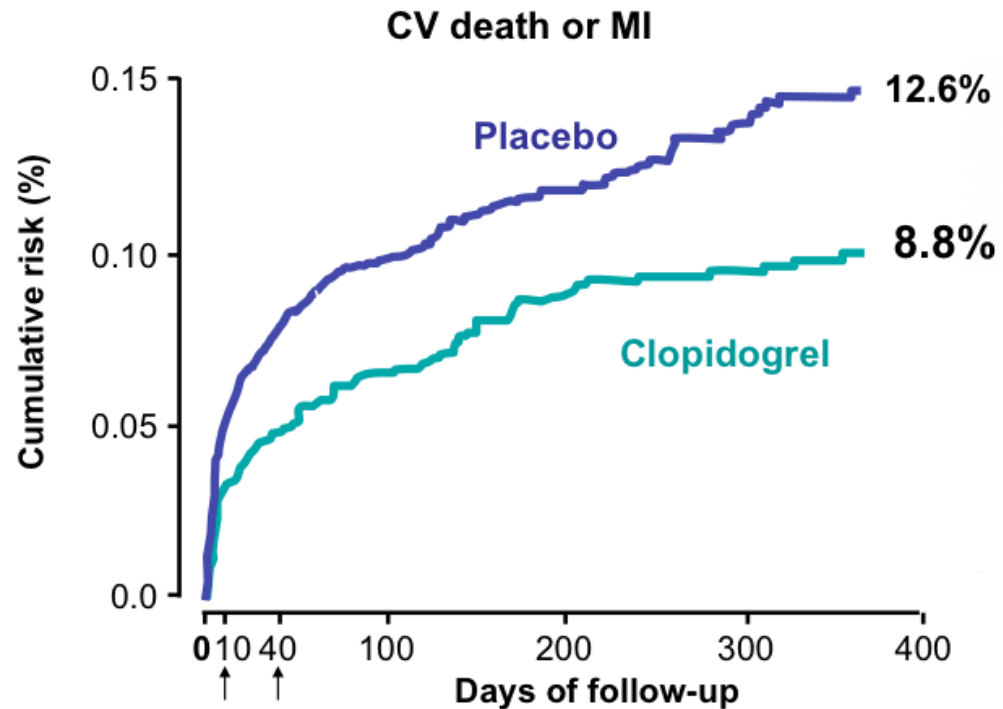
ICCU, Cardiovascular Department
San Filippo Neri Hospital, Rome (Italy)

clopidogrel in ACS

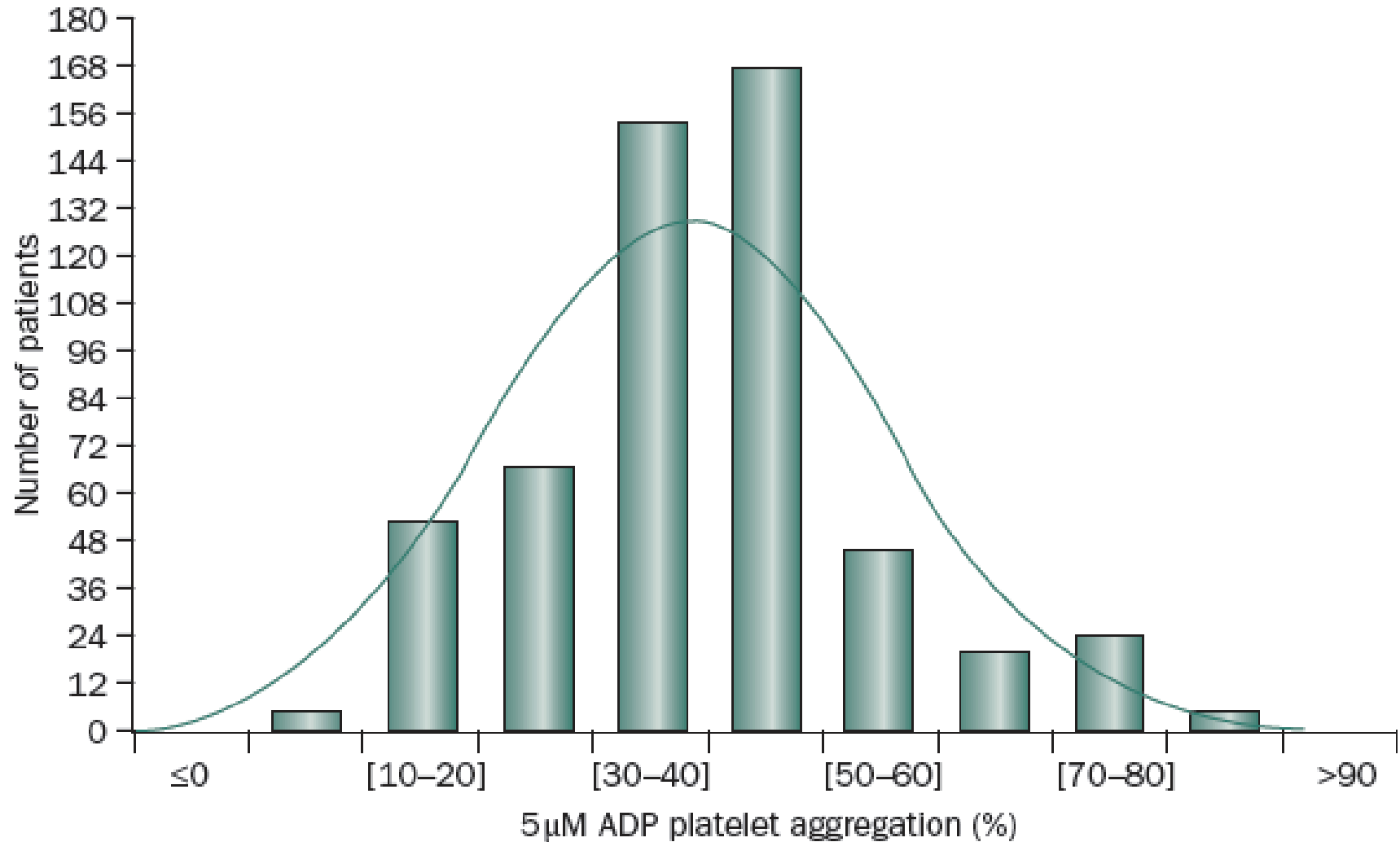
CURE



PCI-CURE

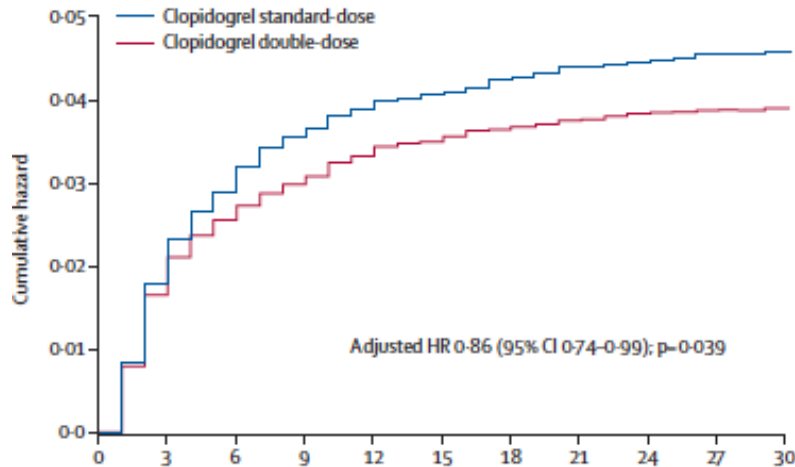


variability in platelet responsiveness to clopidogrel

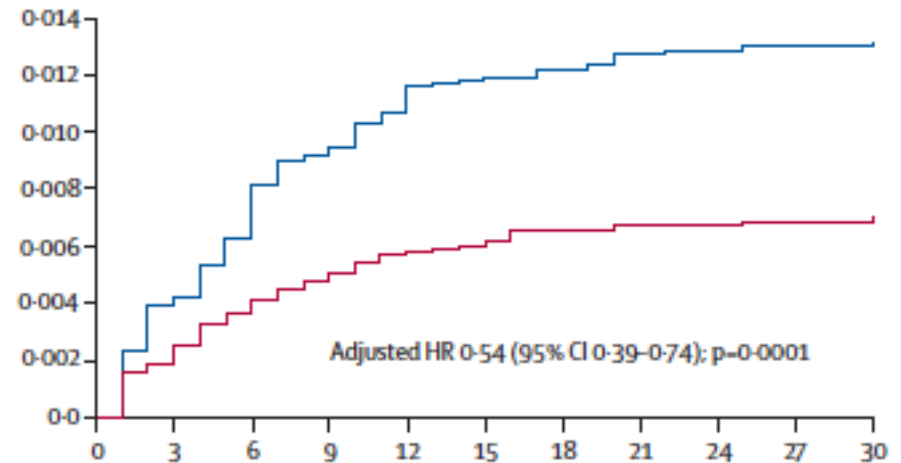


CURRENT-OASIS 7: ACS patients & PCI

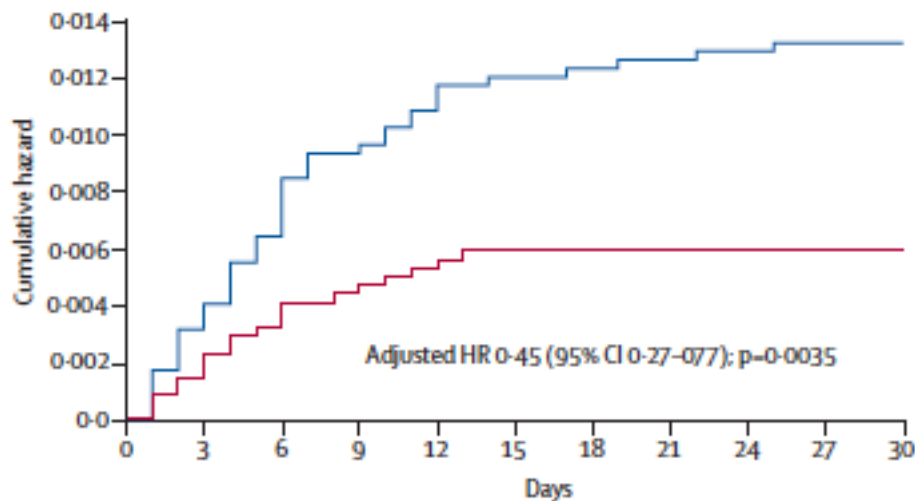
cvD/MI/stroke



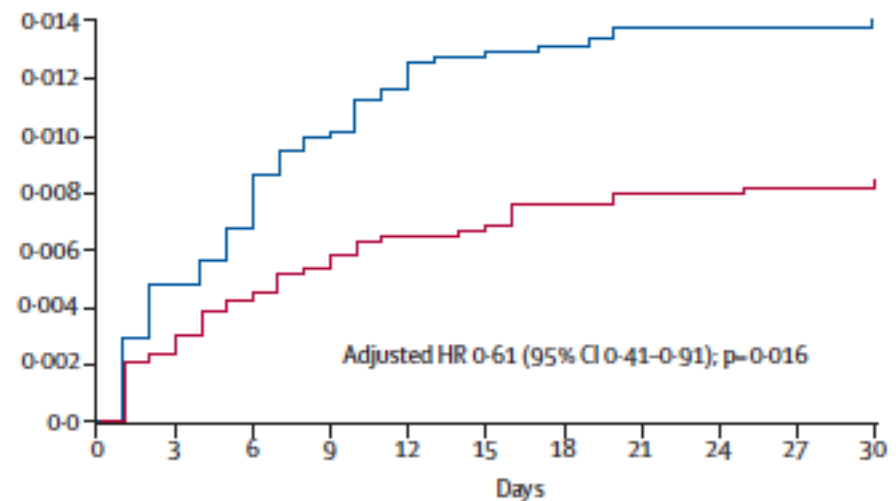
definite ST



definite ST (DES)

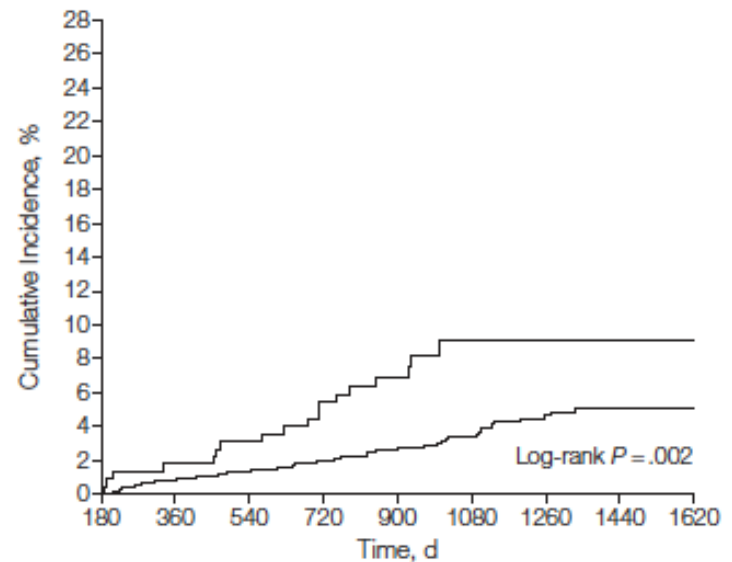
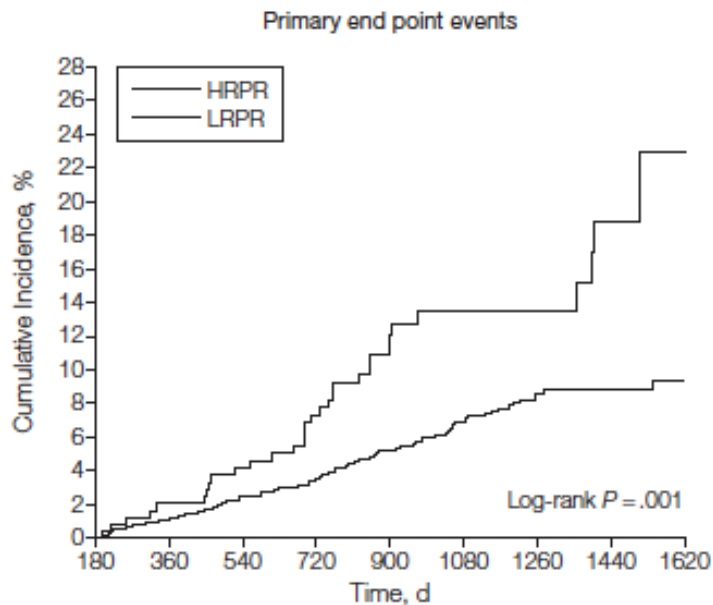
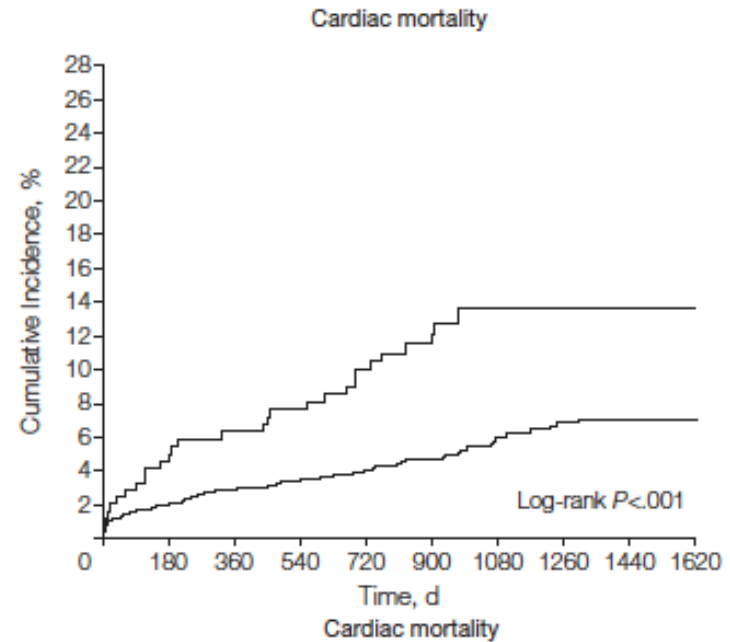
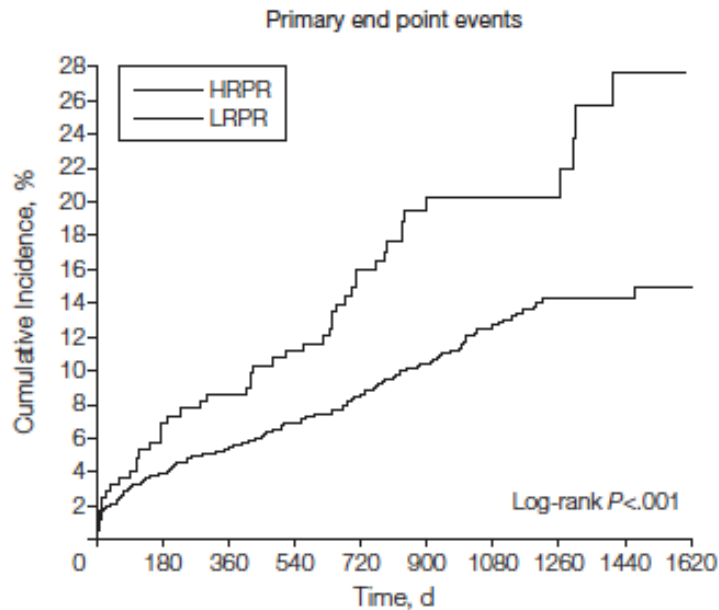


definite ST (BMS)



clopidogrel: high residual platelet reactivity and outcome

- RECLOSE 2 trial -



GRAVITAS

5429 pts (80% stable CAD) on clopidogrel
12-24 hrs after PCI: VerifyNow

↓
2114 (41%) PRU $\geq$ 230

clopi 75 mg qd

clopi 600 mg loading → 150 mg qd

	clopidogrel		HR (95% CI)	p
	high dose (%)	standard dose (%)		
cvD/MI/stent thrombosis	2.3	2.3	1.01 (0.58-6.76)	0.98
GUSTO severe/moderate bleed	1.4	2.3		0.10
any GUSTO bleed	12.0	10.2		0.18

Patient Enrollment

Patients undergoing PCI for
non ST-ACS or stable CAD
(200)

Excluded patients
After Procedure:
• 2 did not undergo PCI
• 2 withdrawn from study by
treating physician
• 1 had coronary dissection and
underwent urgent CABG

Rapid Genotyping
(102)

Standard Therapy
(98)

***CYP2C19*2* Carriers
(23)**

Non-Carriers
(74)

Prasugrel 10 mg OD

Clopidogrel 75 mg OD

Clopidogrel 75 mg OD

Excluded patients
• 1 refused to return for
Day 7 blood work
• 1 loss to follow-up

Platelet Function Testing at 1 week

***CYP2C19*2* Carriers
(23)**

Non-Carriers
(68)

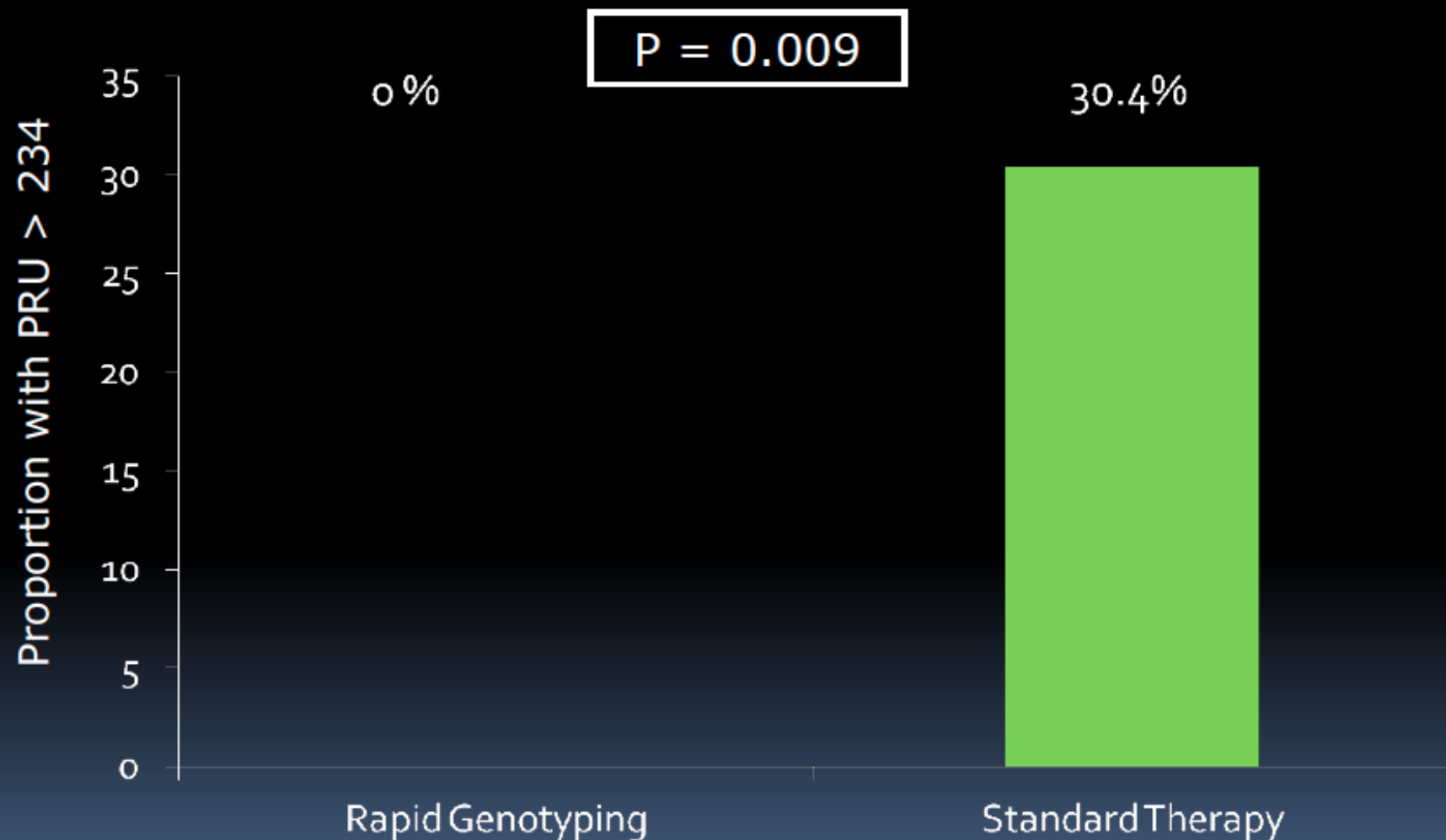
Excluded patients
• 4 refused to return for Day
7 blood work
• 2 inconclusive readings on
platelet function
measurements

Point-of-Care Genotyping

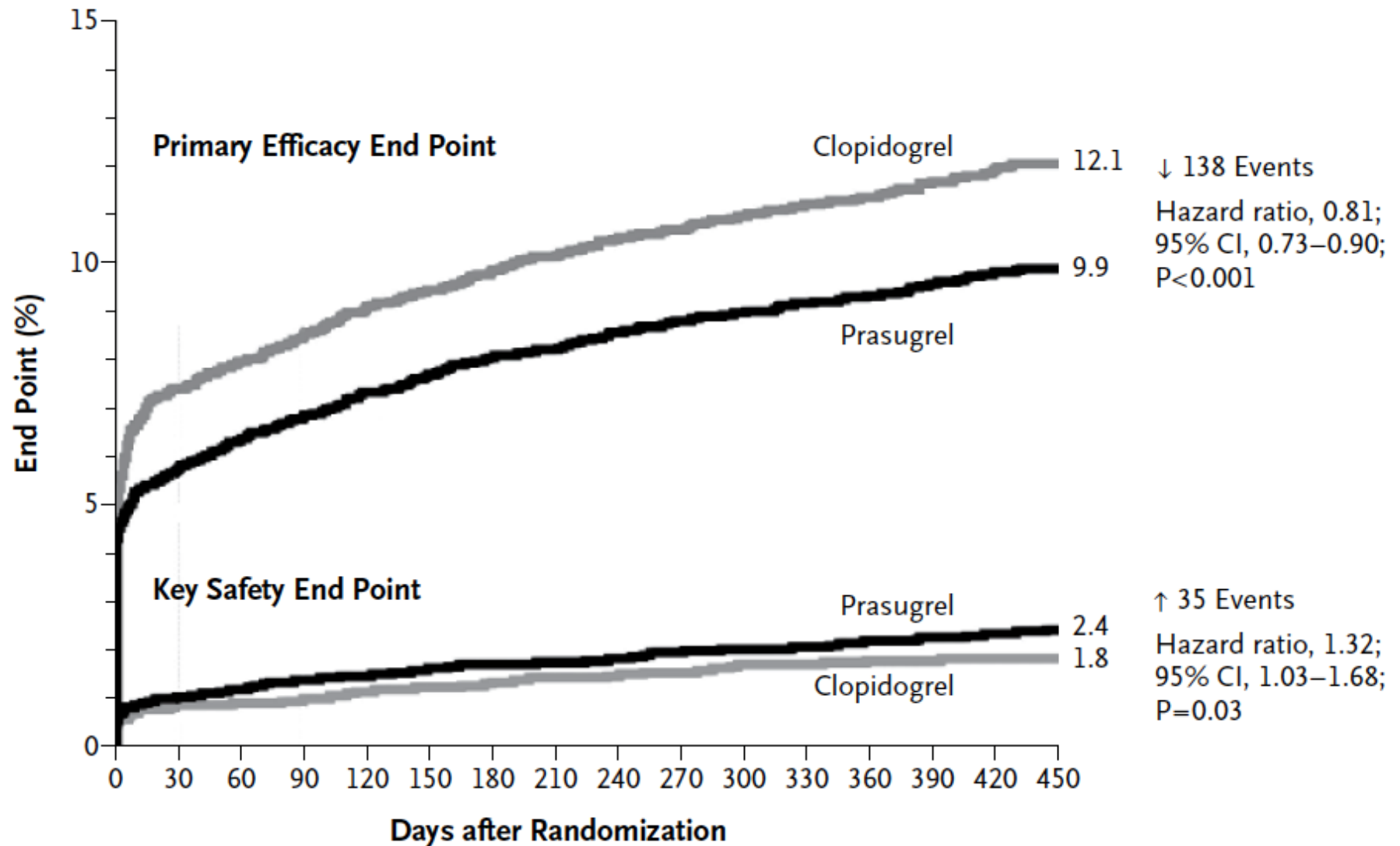
***CYP2C19*2* Carriers
(23)**

Non-Carriers
(73)

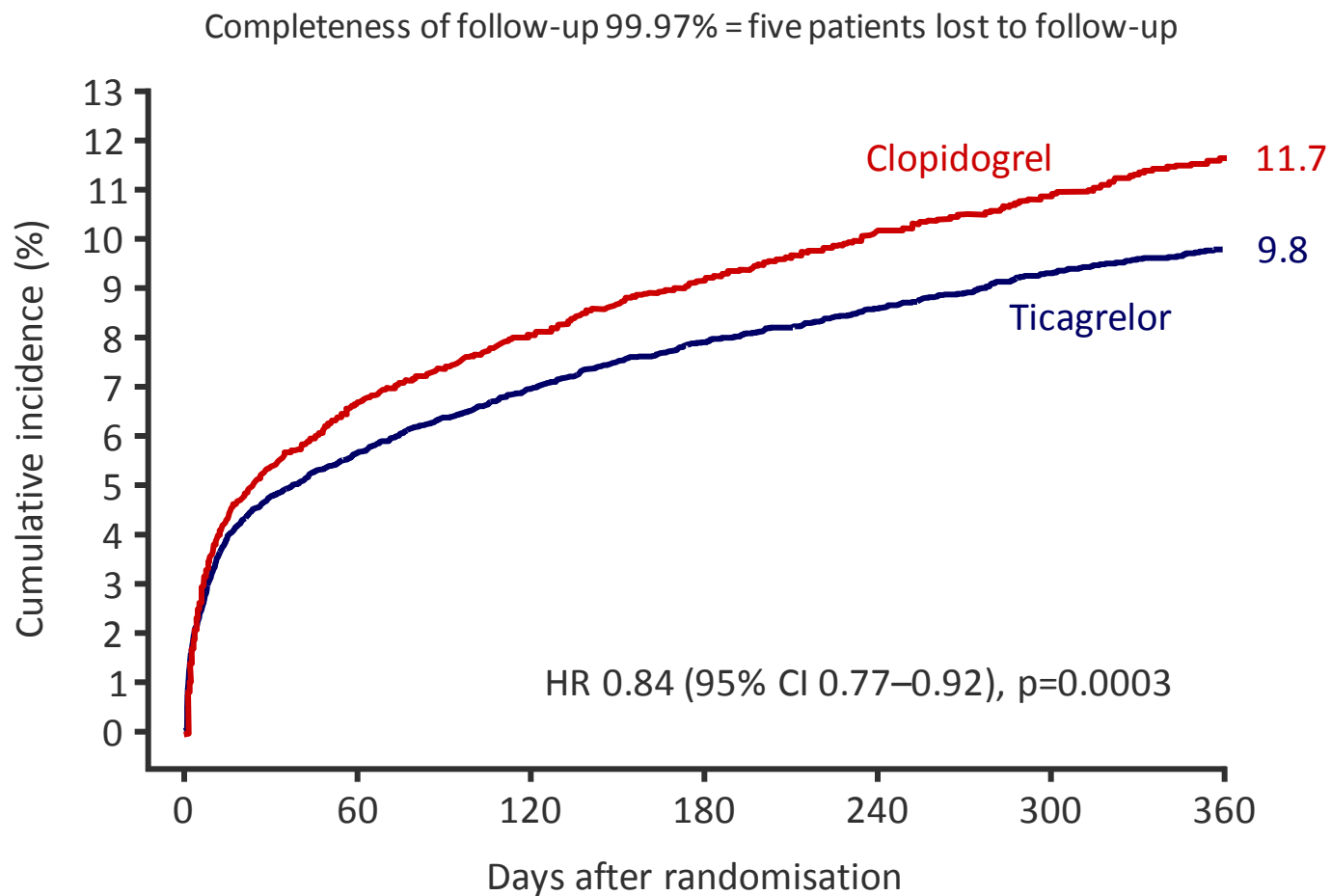
Primary Endpoint: Proportion of *CYP2C19**2 Carriers with High On-treatment Platelet Reactivity (PRU>234)



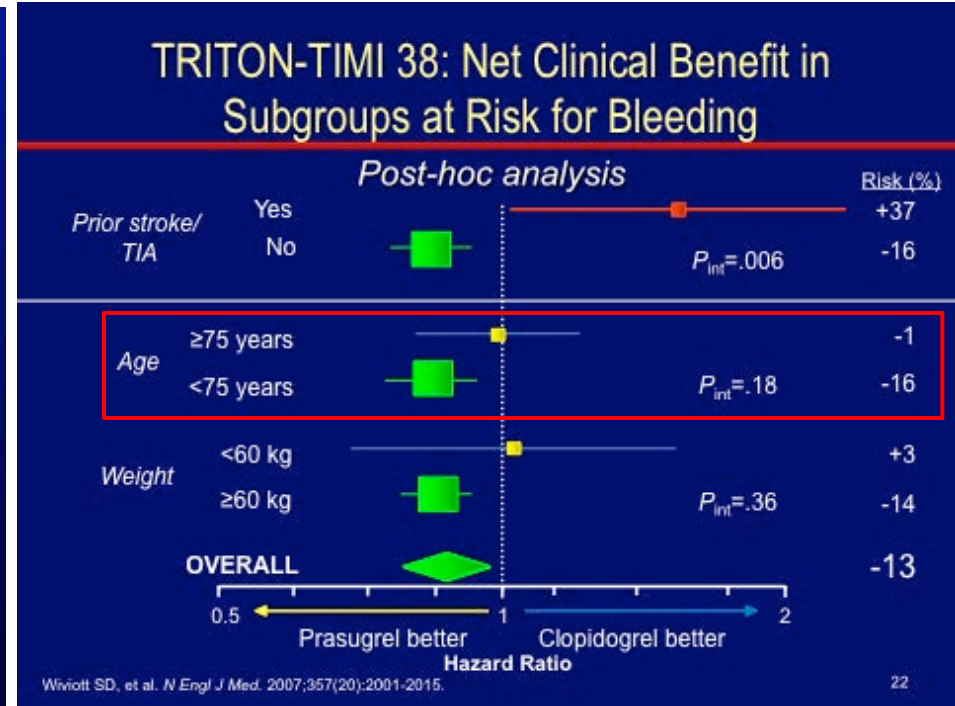
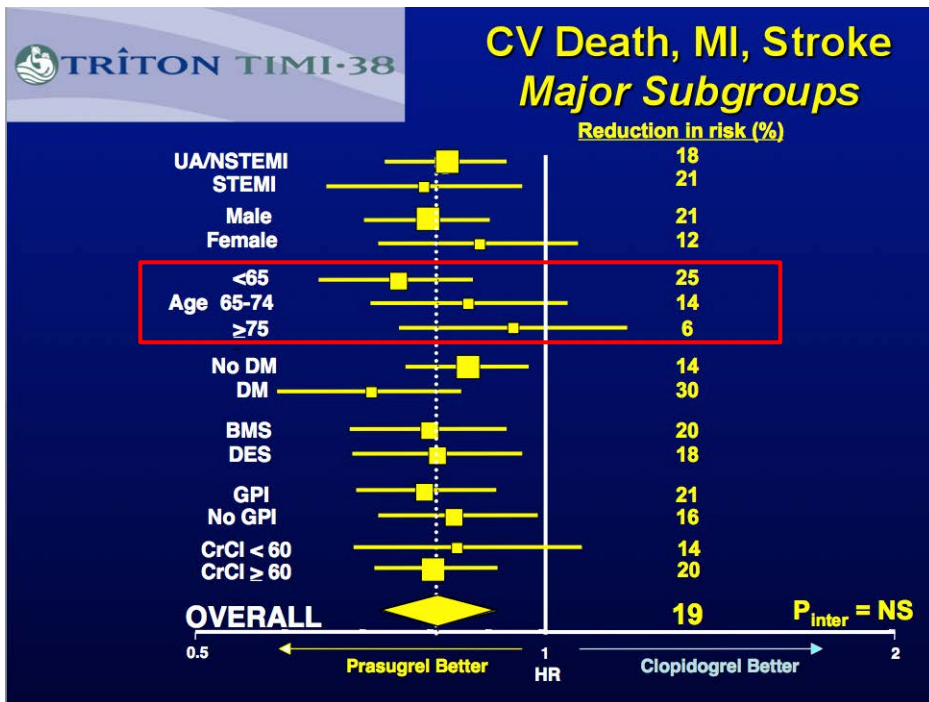
TRITON TIMI 38: main results



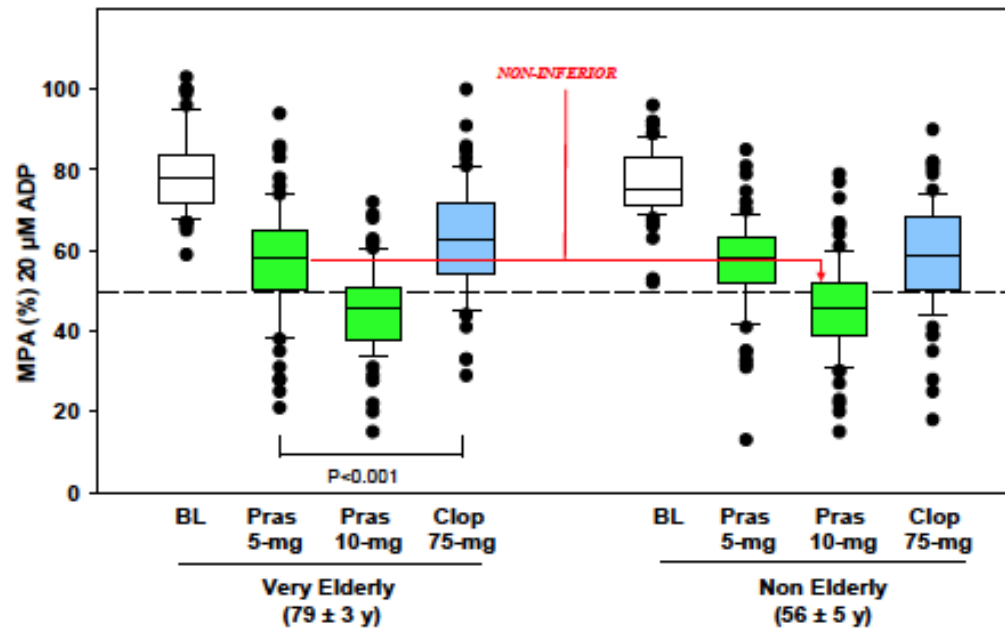
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



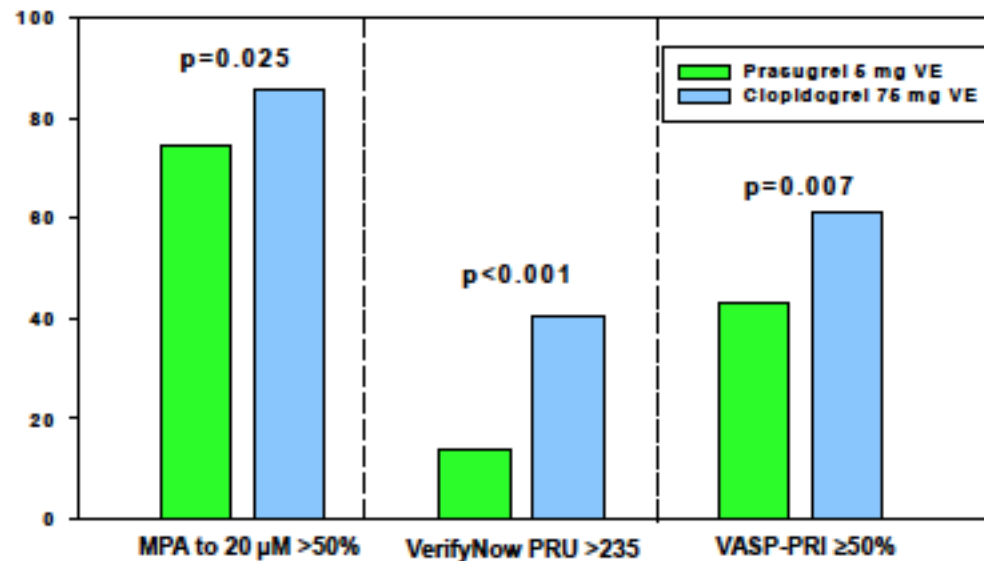
TRITON TIMI 38: prasugrel vs. clopidogrel in elderly patients



GENERATIONS: prasugrel 5 mg in the very elderly patients

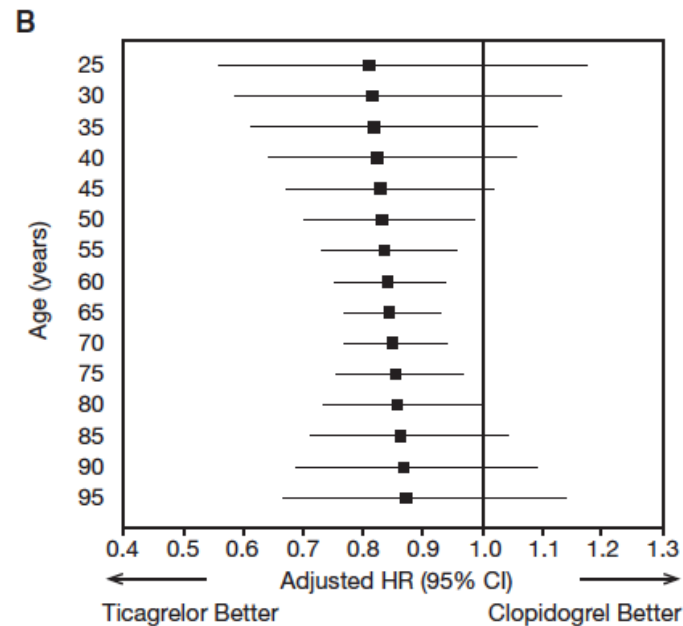
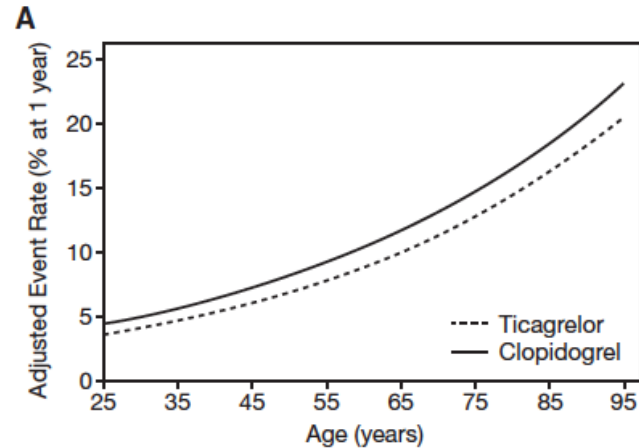


Note: Horizontal dashed line indicates HPR threshold

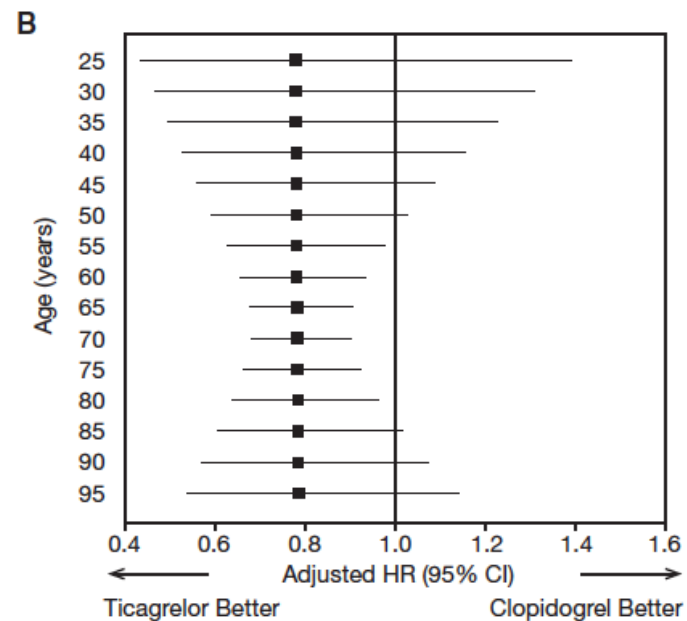
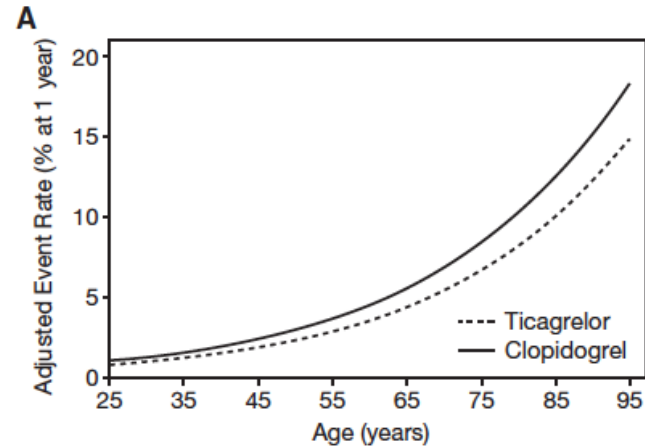


PLATO: ticagrelor, age and 12 months outcome

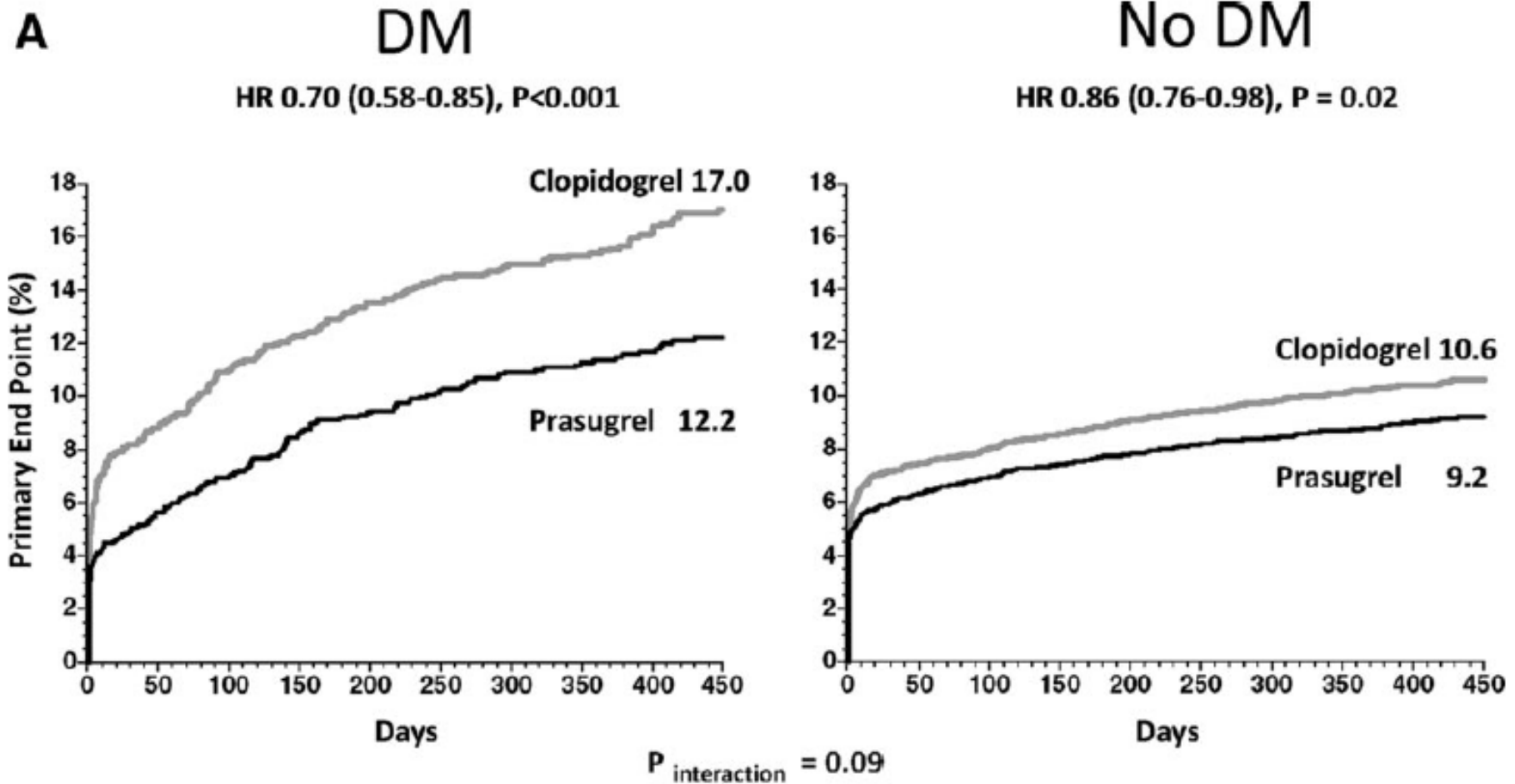
CV death/MI/stroke



all cause mortality



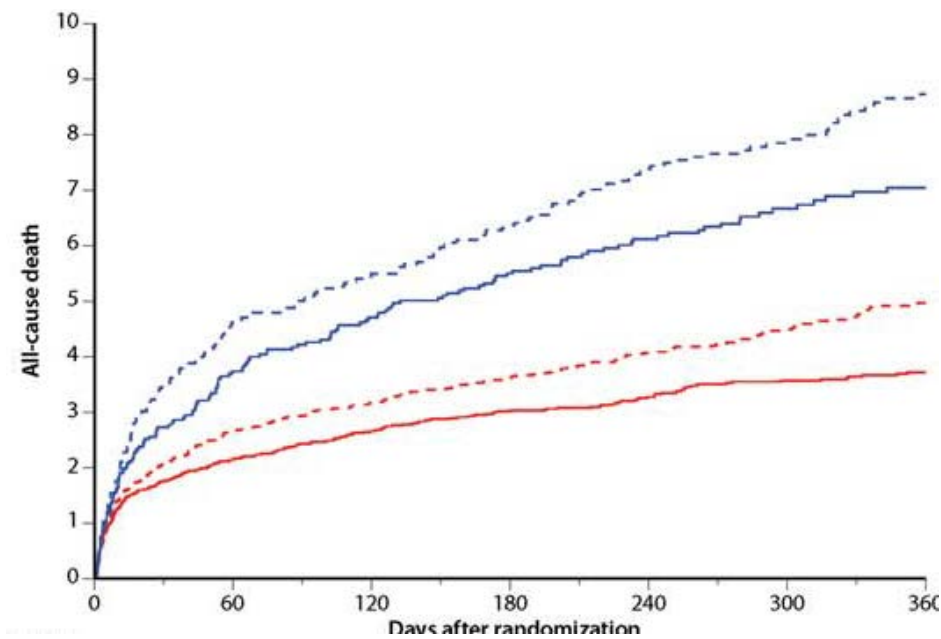
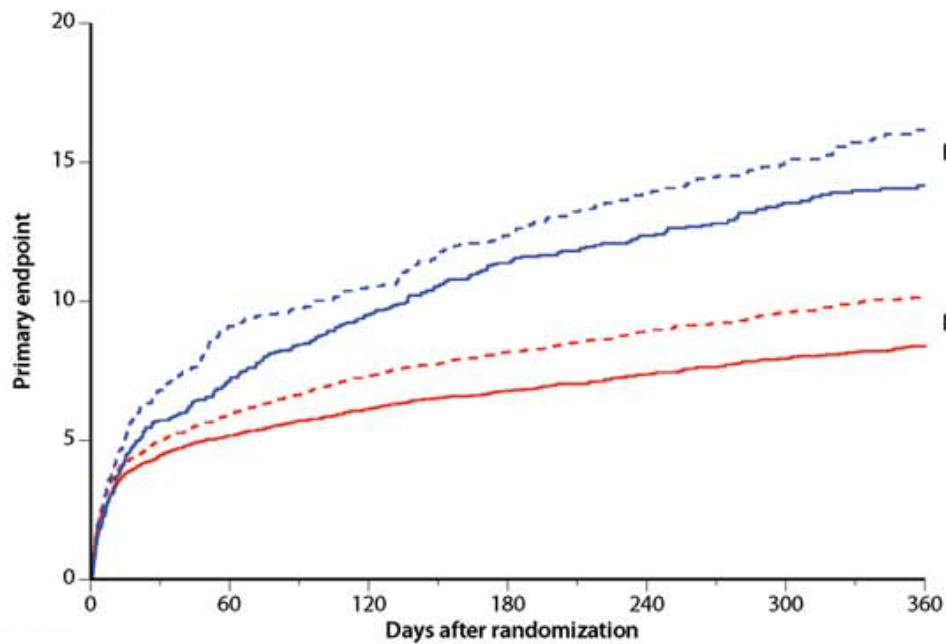
TRITON: prasugrel vs. clopidogrel in ACS + diabetics



PLATO: ticagrelor vs. clopidogrel in ACS + diabetes

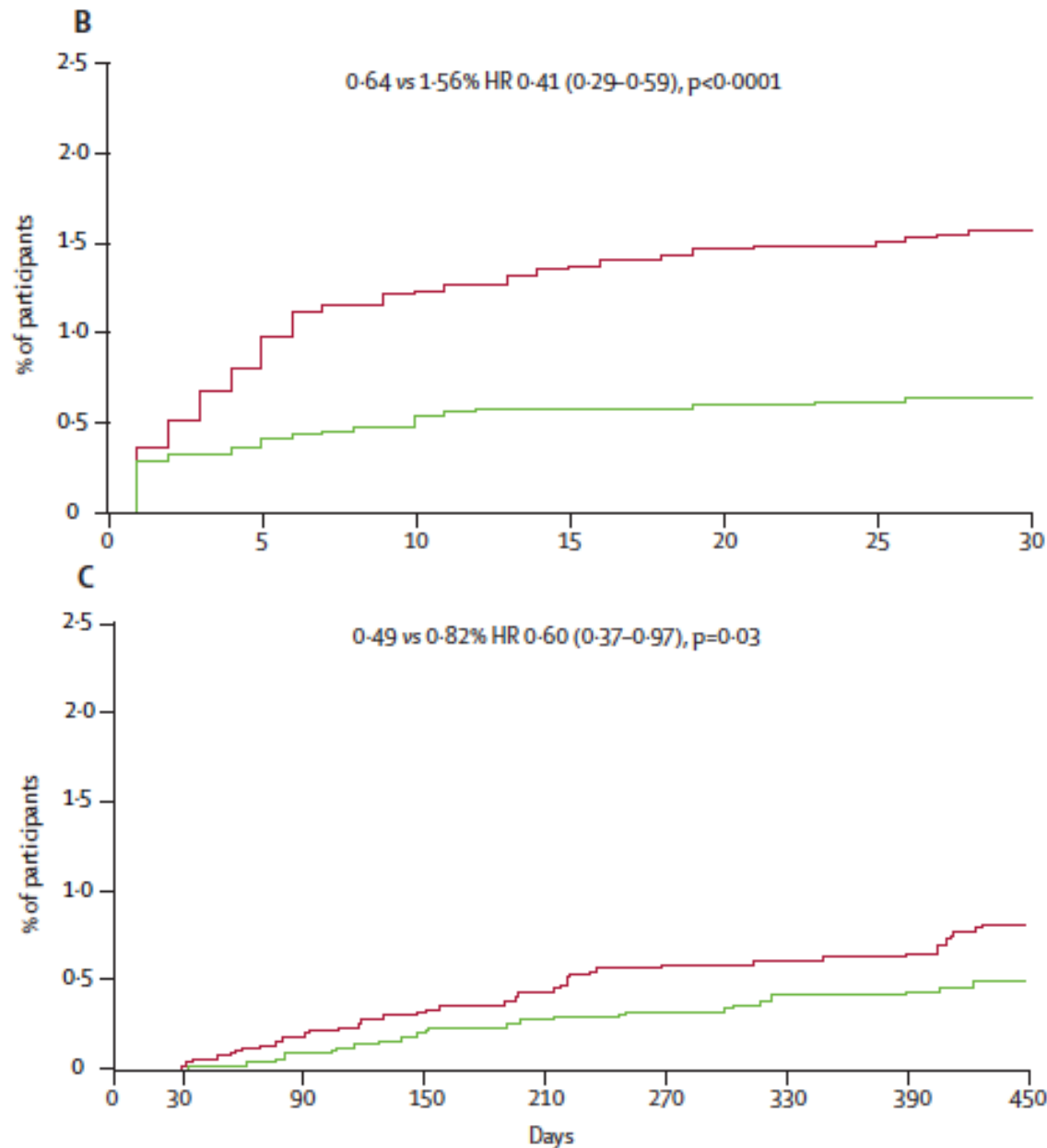
diabetes — Ticagrelor
 -- Clopidogrel

no diabetes — Ticagrelor
 -- Clopidogrel



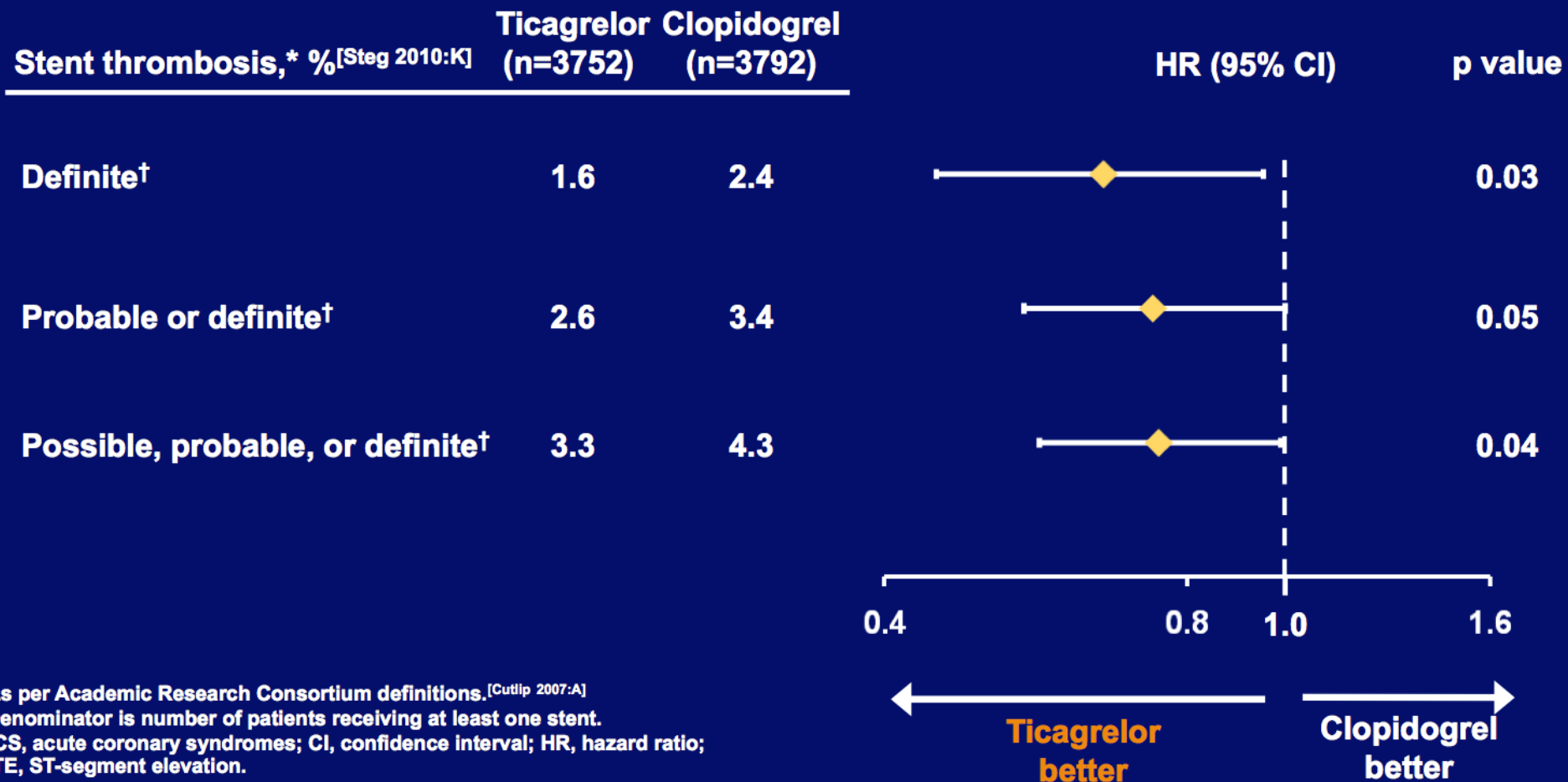
TRITON TIMI 38: stent thrombosis

ARC definite
or probable
stent thrombosis



PLATO STE-ACS: Stent thrombosis

[Steg 2010:K]



[†]As per Academic Research Consortium definitions.^[Cutlip 2007:A]

Denominator is number of patients receiving at least one stent.

ACS, acute coronary syndromes; CI, confidence interval; HR, hazard ratio;

STE, ST-segment elevation.

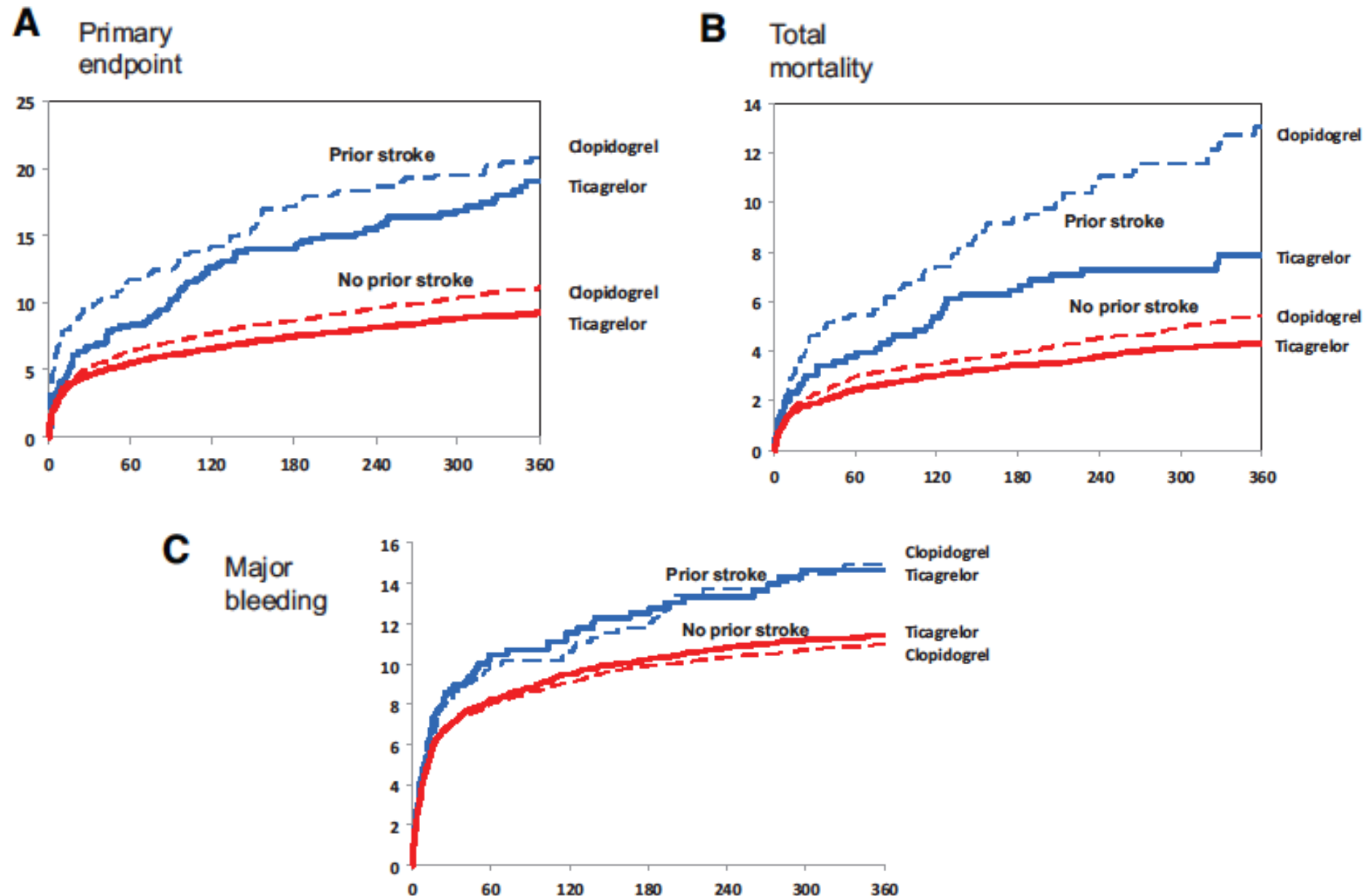
Cutlip DE, et al. *Circulation* 2007;155:2344–2351;

Steg PG, et al. *Circulation* 2010;122:2131–2141.

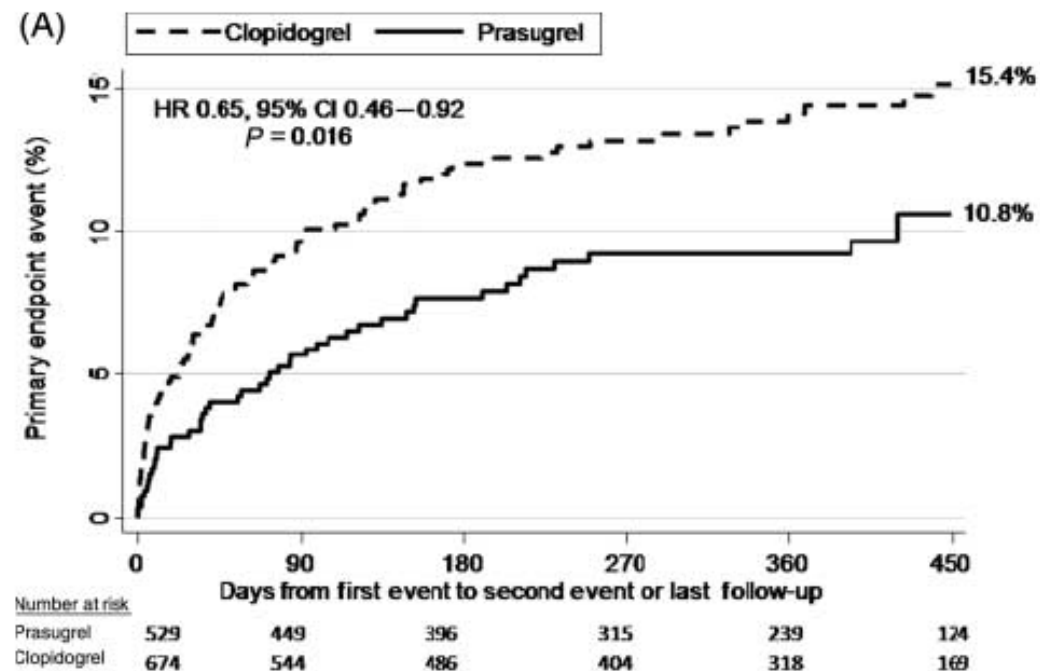
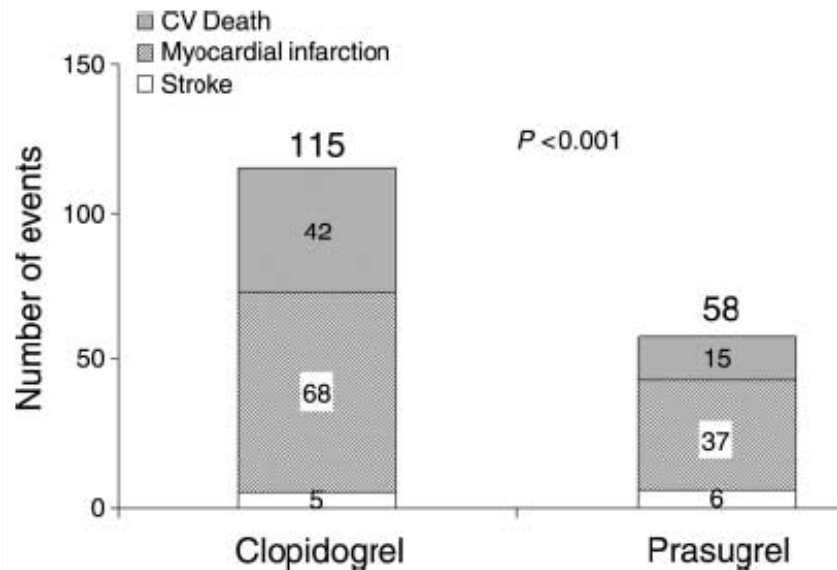
TRITON: prasugrel in pts with history of stroke/TIA

End Point	Prasugrel <i>no. of patients/total no. (%)</i>	Clopidogrel	Hazard Ratio for Prasugrel (95% CI)	P Value	P Value for Interaction†
History of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	47/262 (19.1)	35/256 (14.4)	1.37 (0.89–2.13)	0.15	
Non-CABG-related TIMI major bleeding	14/257 (5.0)	6/252 (2.9)	2.46 (0.94–6.42)	0.06	
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	57/262 (23.0)	39/256 (16.0)	1.54 (1.02–2.32)	0.04	
No history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	596/6551 (9.5)	746/6539 (12.0)	0.79 (0.71–0.88)	<0.001	0.02
Non-CABG-related TIMI major bleeding	132/6484 (2.3)	105/6464 (1.8)	1.26 (0.97–1.62)	0.08	0.22
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	727/6551 (11.8)	854/6539 (13.8)	0.84 (0.76–0.93)	<0.001	0.006

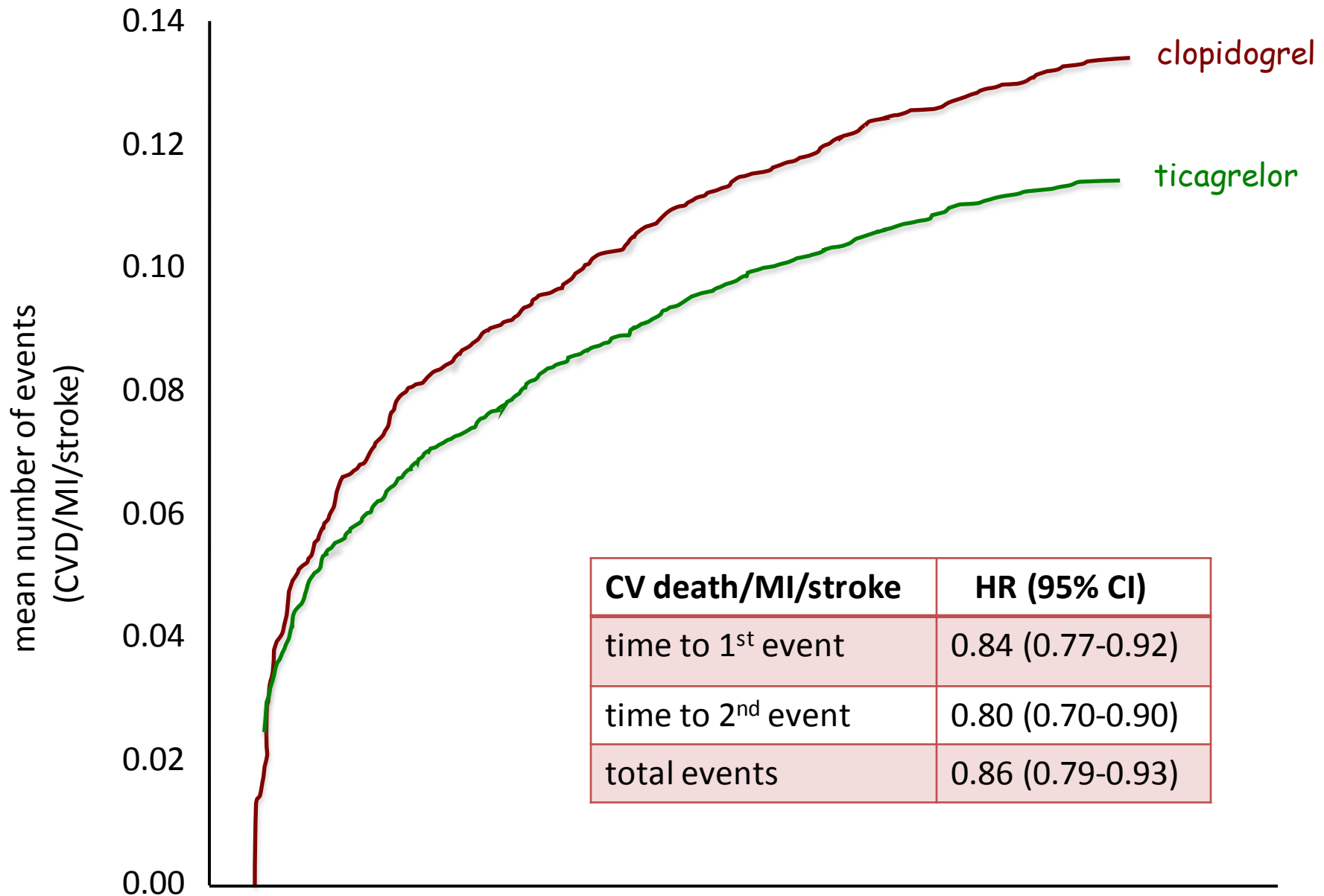
PLATO: ticagrelor vs. clopidogrel in ACS pts. with previous stroke/TIA



TRITON: recurrent cardiovascular events

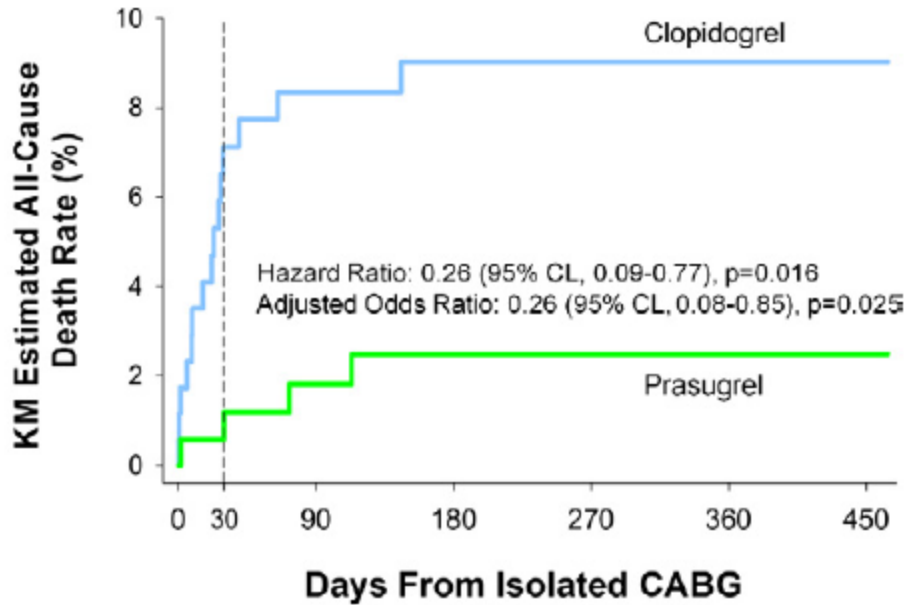


PLATO: ticagrelor vs. clopidogrel in reduction of recurrent events



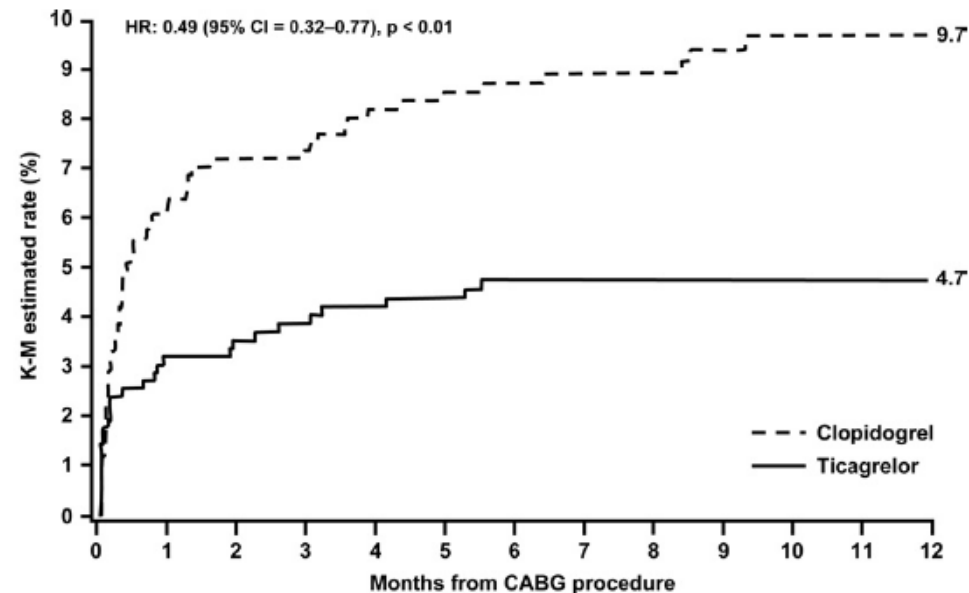
prasugrel and ticagrelor in ACS pts with CABG

TRITON TIMI 38



*increase in chest tube blood loss
and platelet transfusion*

PLATO

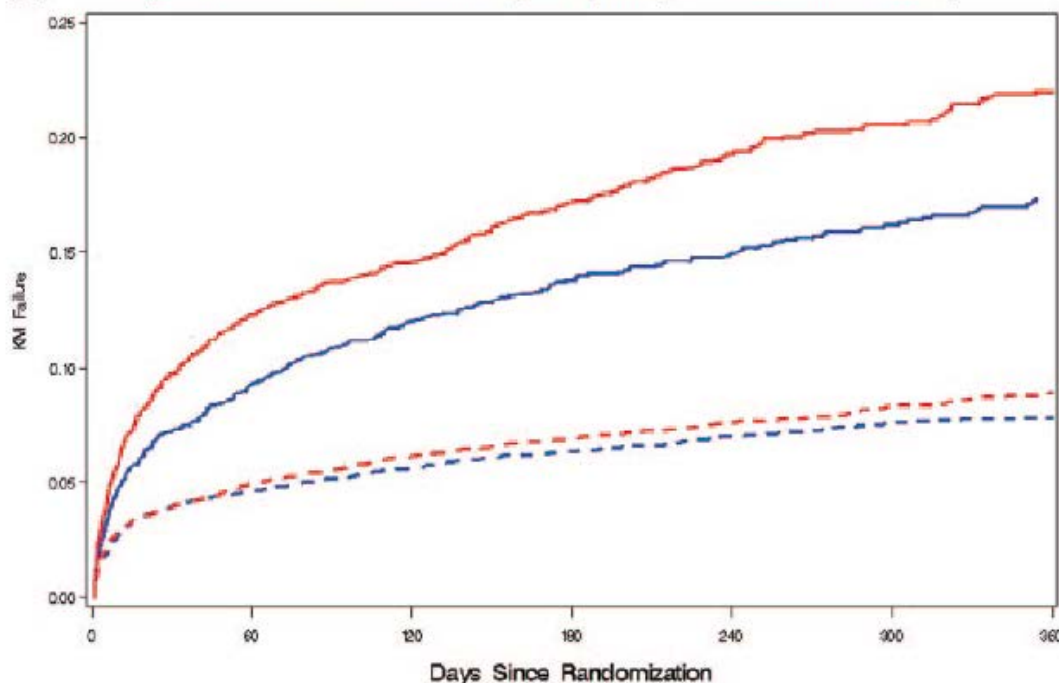


no differences in any bleeding complication

prasugrel and ticagrelor in pts with ACS & CKD

	CrCl (mL/min)	Prasugrel %	Clopidogrel %	HR (95% CI)	Interaction p-value
CVD, nonfatal MI, or nonfatal stroke	<30	21.57	38.89	0.47 (0.22-1.01)	0.279
	30 to 60	13.81	14.72	0.93 (0.70-1.23)	
	>60	8.61	10.67	0.80 (0.71-0.90)	
Non-CABG-related TIMI Major Bleeding	<30	6.00	5.56	NE	NE
	30 to 60	3.50	2.24	1.59 (0.84-3.02)	
	>60	1.95	1.53	1.27 (0.97-1.68)	

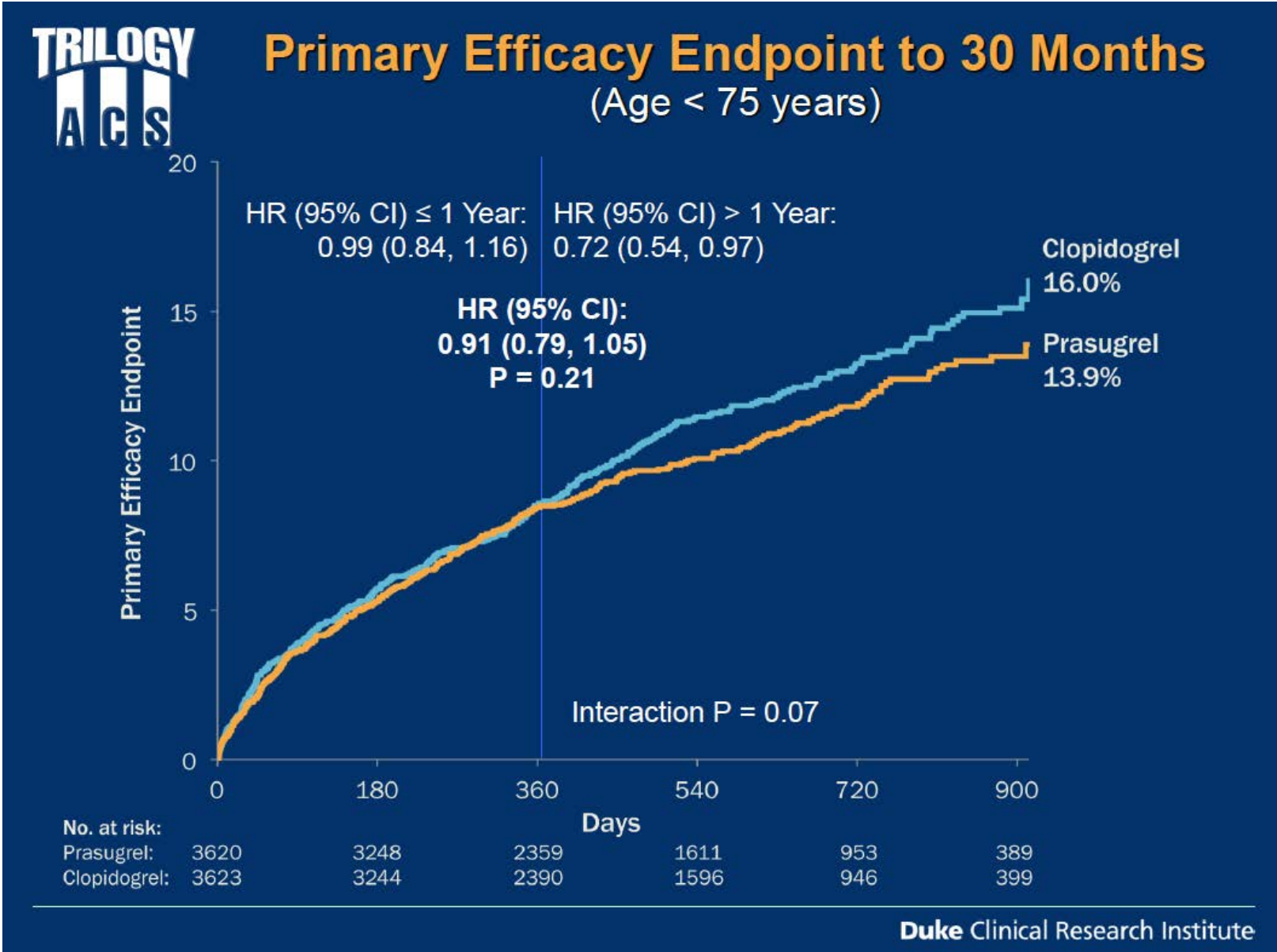
— clopidogrel
— ticagrelor



CrCl < 60

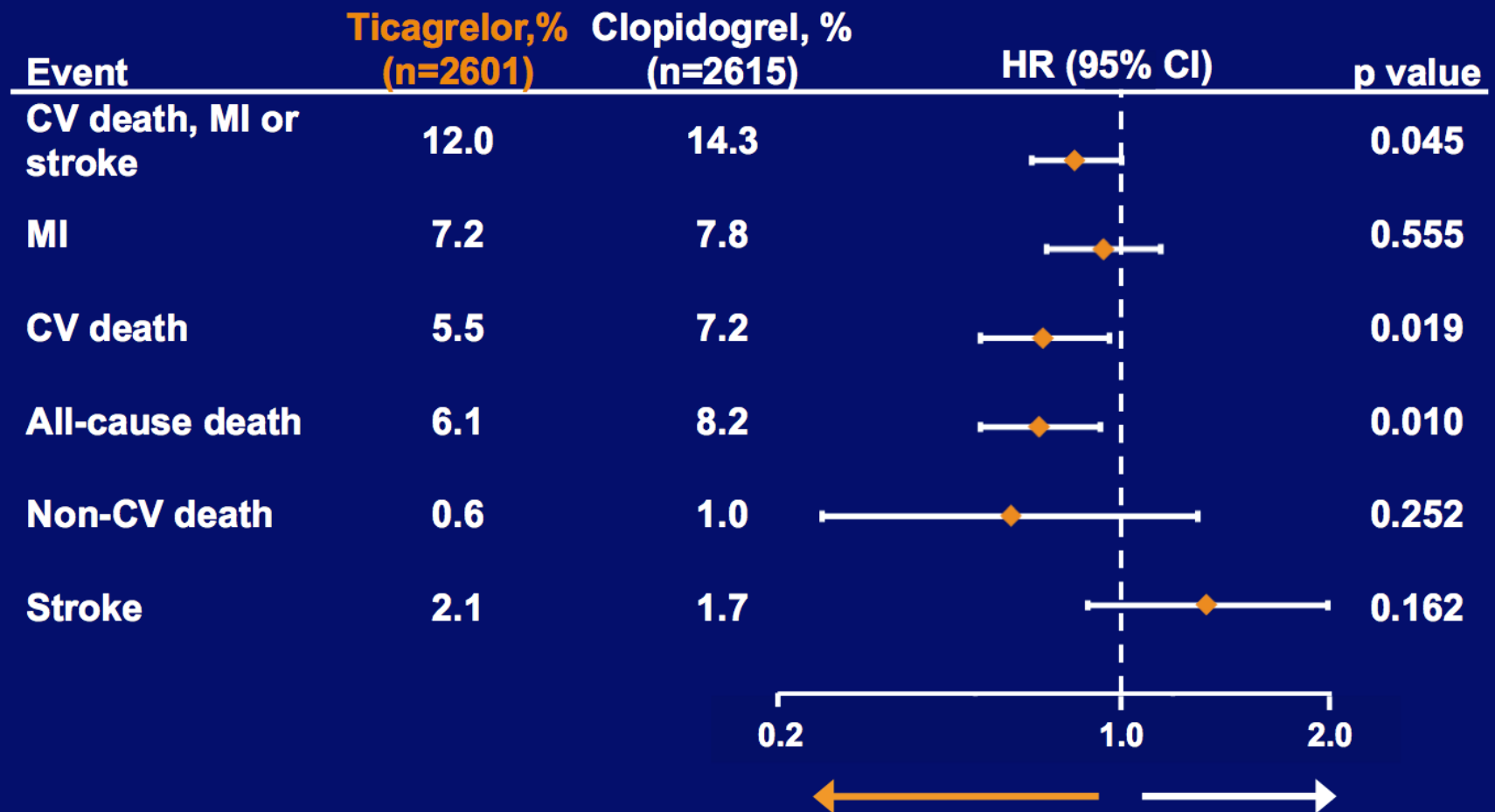
CrCl ≥ 60

TRILOGY ACS: prasugrel vs. clopidogrel for ACS without revascularization



PLATO intent for non-invasive management: Efficacy outcomes

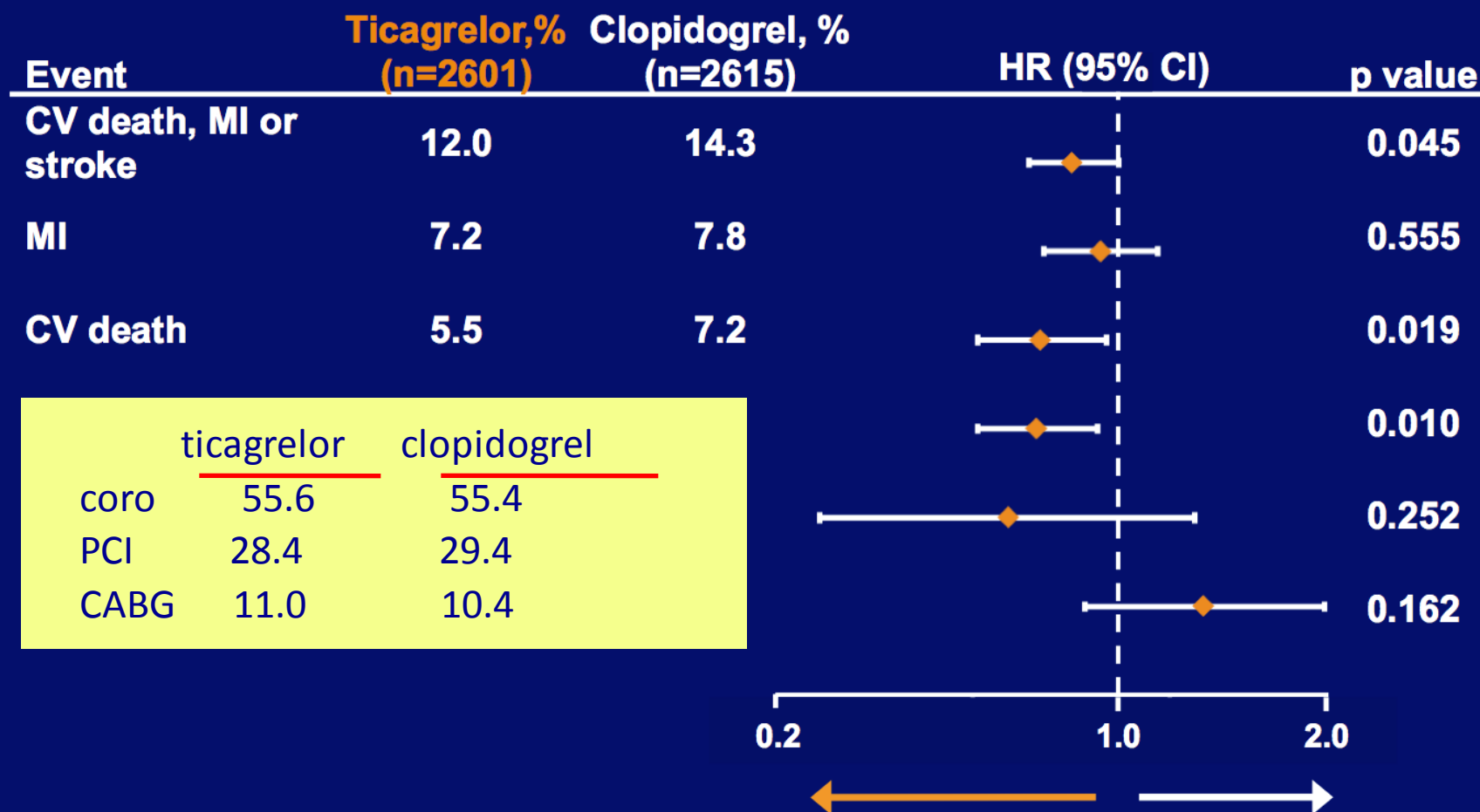
[James 2011:K]



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-segment elevated myocardial infarction; UA, unstable angina.
James S, et al. *BMJ* 2011;342:d3527.

PLATO intent for non-invasive management: Efficacy outcomes

[James 2011:K]



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-segment elevated myocardial infarction; UA, unstable angina.
James S, et al. *BMJ* 2011;342:d3527.

Conclusions

- ♥ clopidogrel maintains an indication in patients at high risk for bleeding and/or with contraindications to the new P2Y₁₂ inhibitors.
- ♥ Moreover, clopidogrel is indicated in case of use of fibrinolytic therapy and within a triple therapy strategy (patients with ACS and AF)
- ♥ the new P2Y₁₂ inhibitors, prasugrel and ticagrelor, are more effective than clopidogrel, particularly in high risk patients with ACS
- ♥ in some of the subgroups of high risk ACS patients, the two drugs share the same efficacy, while in others prasugrel and ticagrelor show different results (like elderly, diabetics, prior stroke, CKD, and medically treated) and this could drive the choice between the two
- ♥ because many risk factors for ischaemic events are also risk factors for bleeding events, clinical judgement is important in applying these new therapies to high risk ACS patients.