Platelet function testing to guide $P2Y_{12}$-inhibitor treatment in ACS patients after PCI: insights from a national program in Hungary

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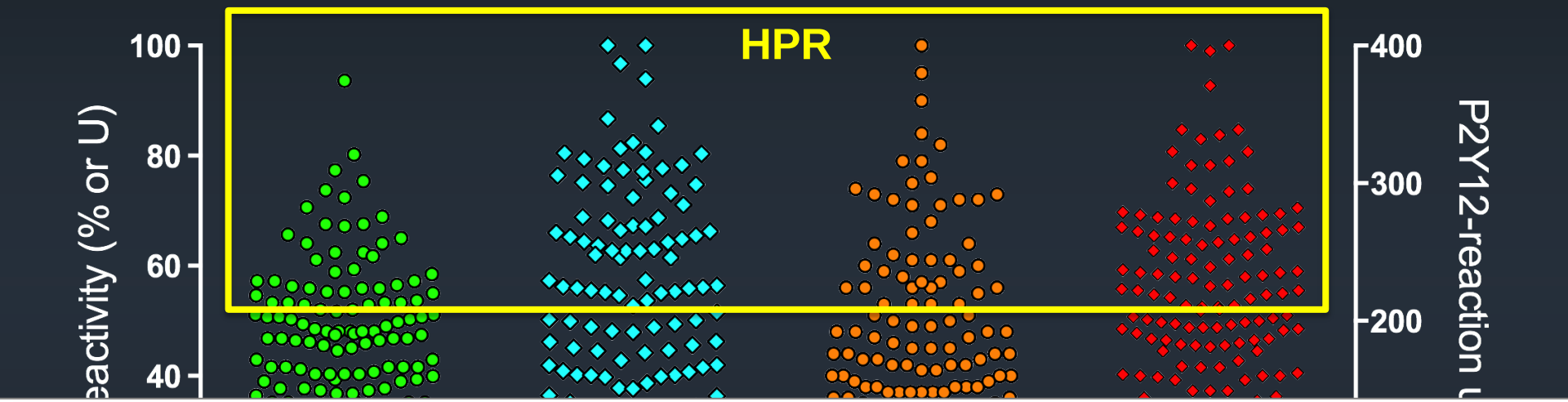
13 December I JCR 2013 I Busan, South Korea

CONFLICTS OF INTERESTS

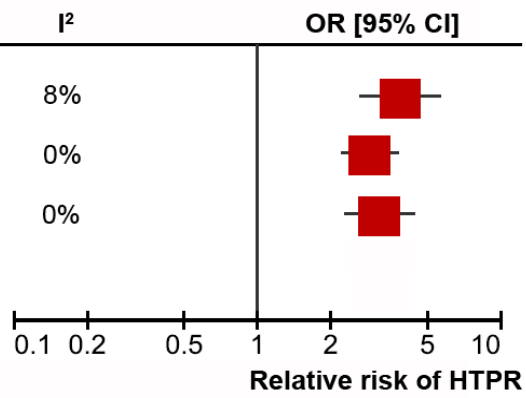
- **CONSULTING/RESEARCH GRANTS:**
  - Verum Diagnostica

- **LECTURE FEES:**
  - Roche
  - Verum Diagnostica
  - DSI/Lilly
  - AstraZeneca
  - Krka
  - Bayer
  - Pfizer

INTER-PATIENT VARIATION ON CLOPIDORGEL

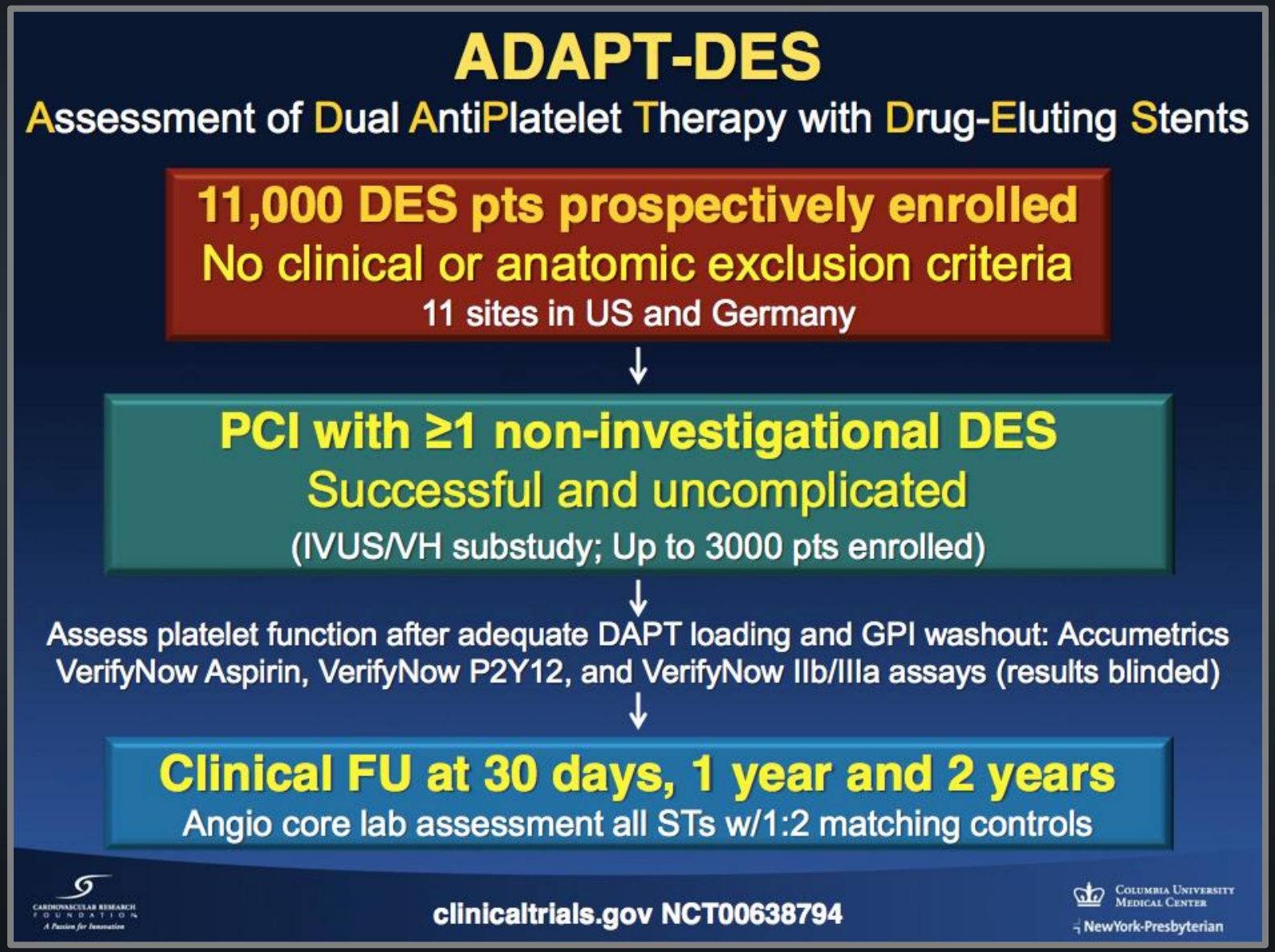


OUTCOME	HTPR	no HTPR	HTPR%	OR [95% CI]	Overall effect	I²
DEF/PROB STENT THROMBOSIS	3371	5914	36.3%	3.95 [2.68 - 5.82]	p < 0.00001	8%
NON-FATAL MI	3421	5006	40.6%	2.90 [2.21 - 3.81]	p < 0.00001	0%
CV DEATH	3616	6135	37.1%	3.18 [2.29 - 4.42]	p < 0.00001	0%

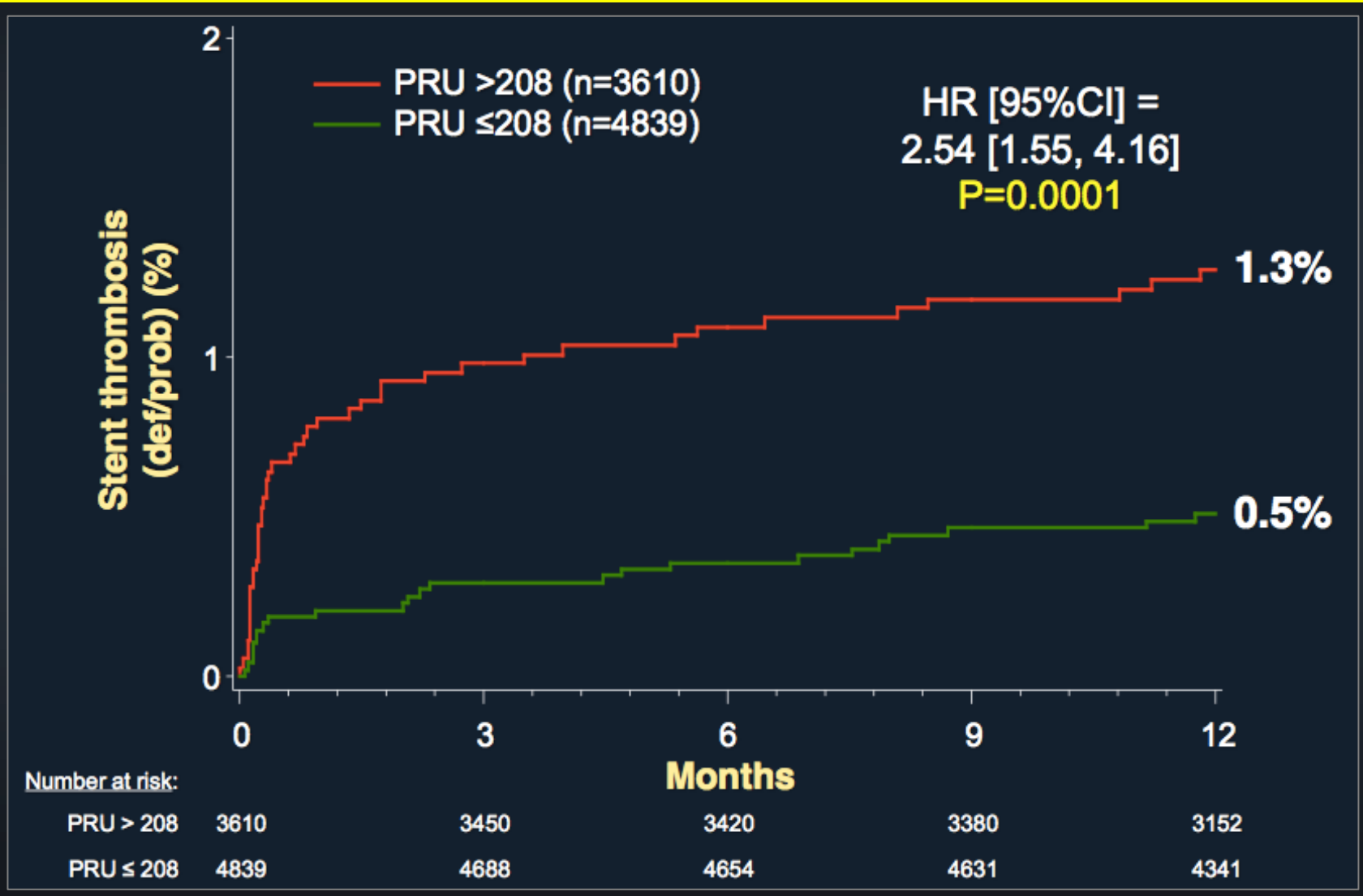


Aradi et al. Am Heart J. 2010; 160: 543-51.

ASSOCIATIONS BETWEEN HPR AND THROMBOSIS

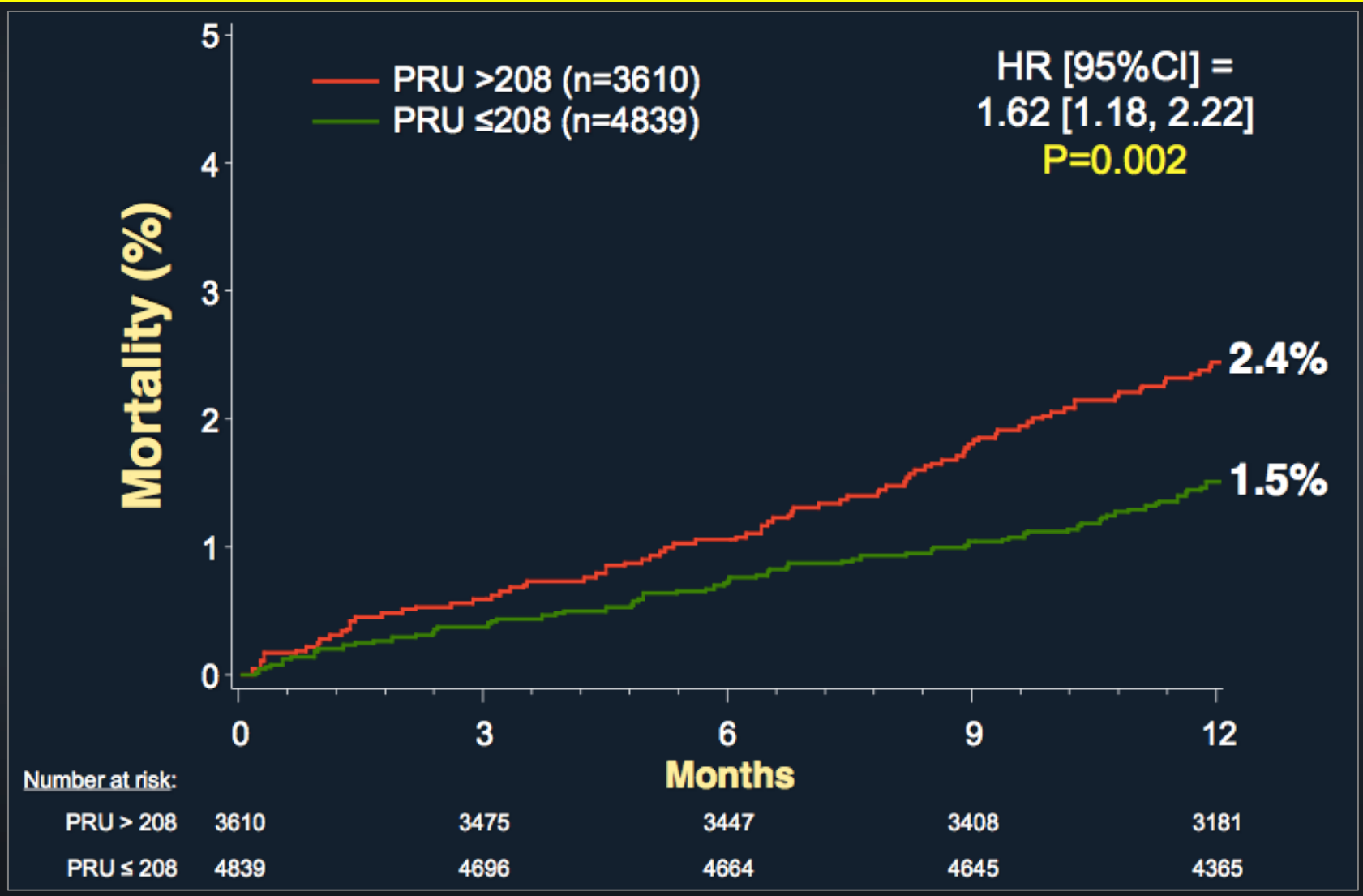


HPR AND THROMBOTIC EVENTS: ADAPT-DES (n=8,583)



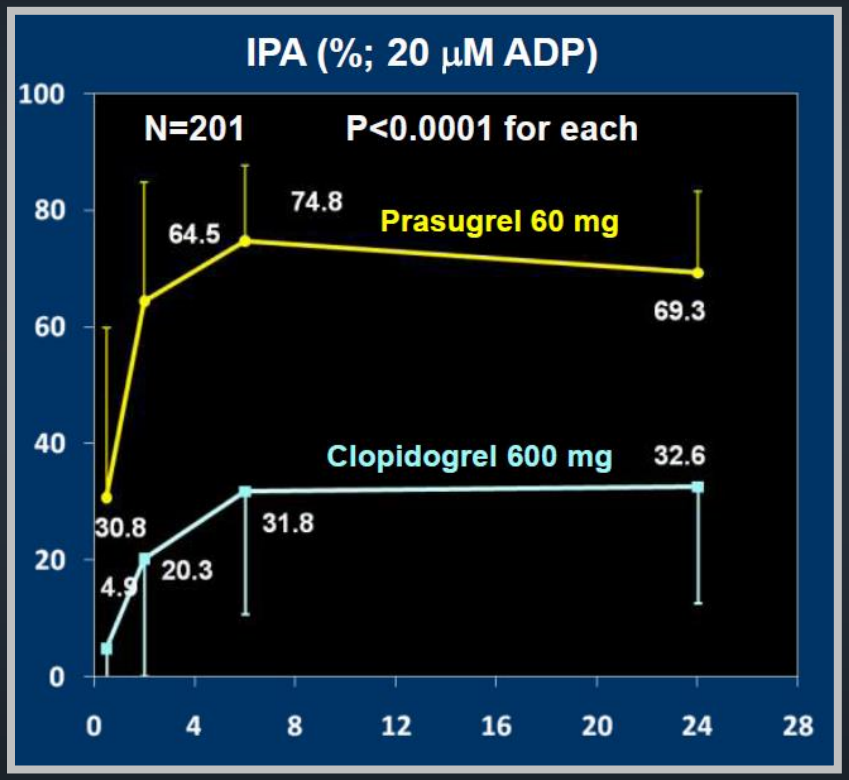
Stone et al. Lancet, 2013;382:614-23

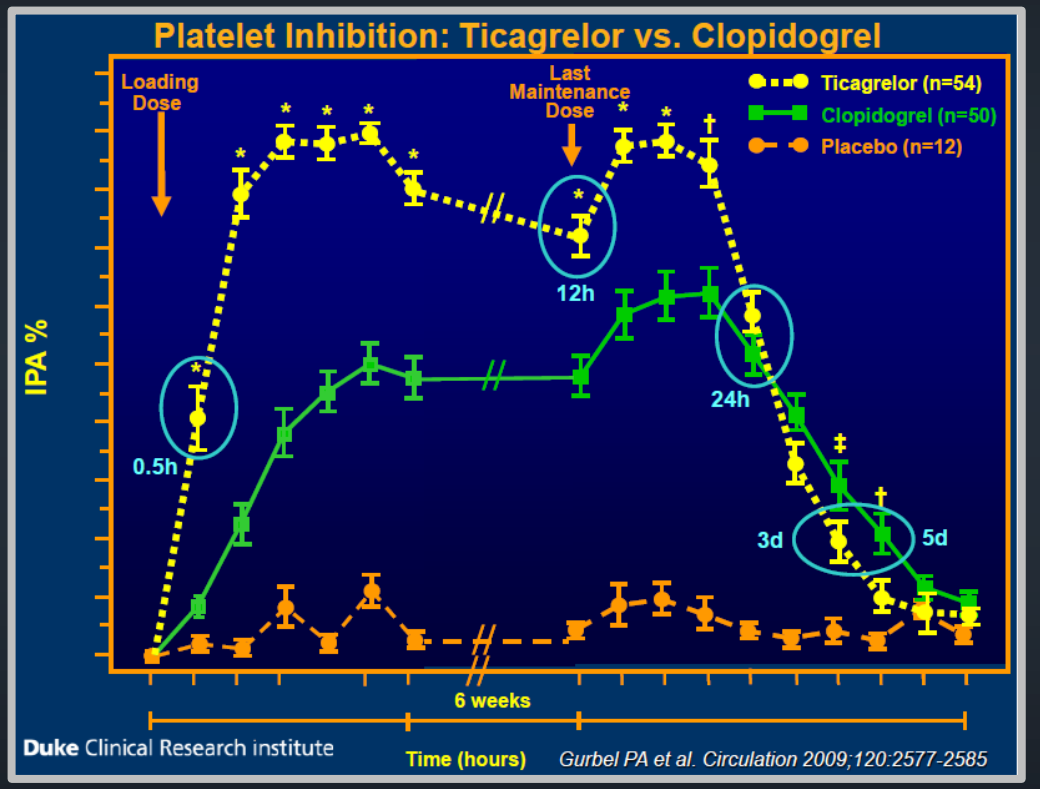
HPR AND THROMBOTIC EVENTS: ADAPT-DES (n=8,583)



Stone et al. Lancet, 2013;382:614-23

PRASUGREL / TICAGRELOR vs. CLOPIDOGREL

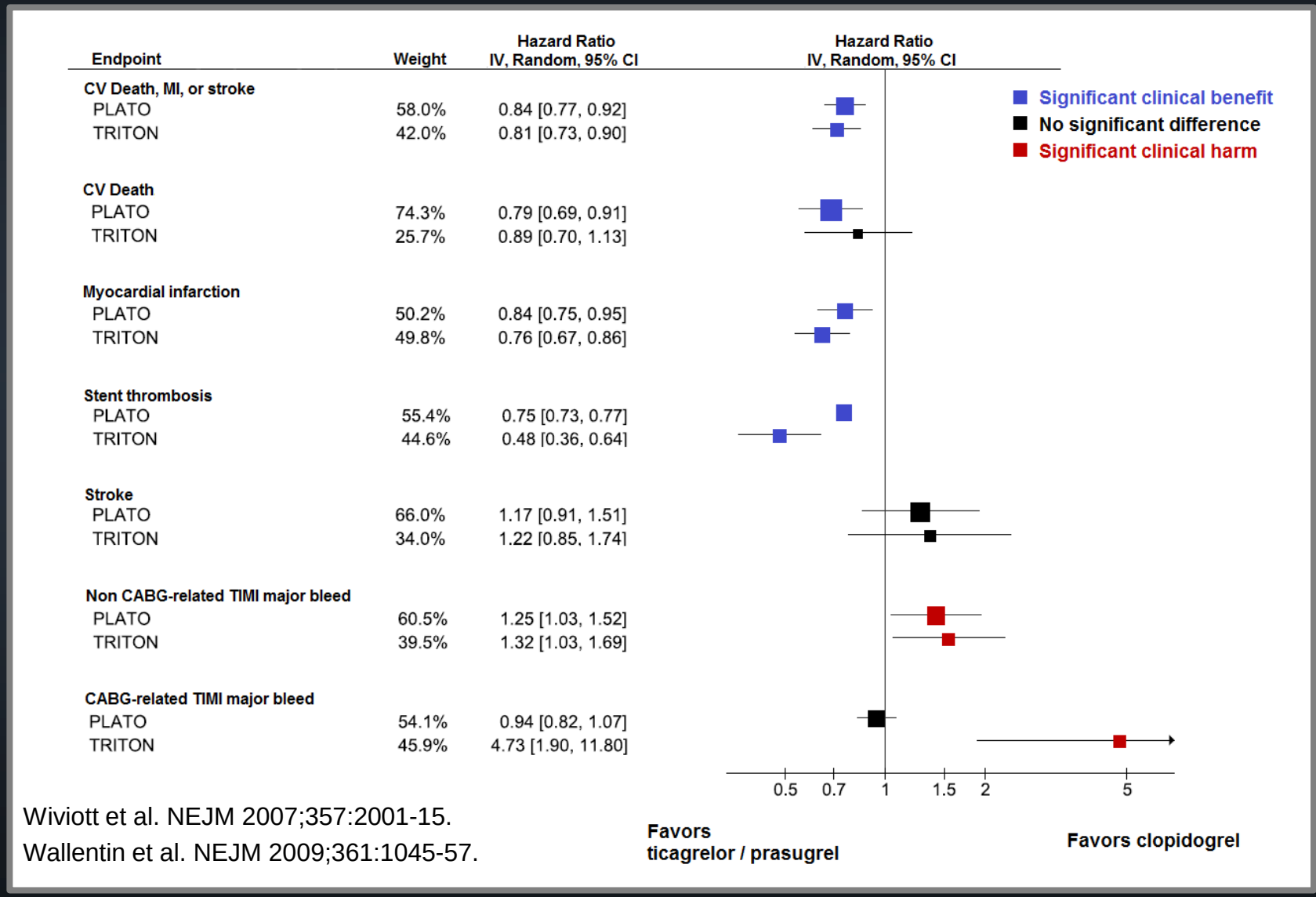




Wiviott SD et al. Circulation 2007; 116: 2923-32.

Gurbel PA et al. Circulation 2009;120:2577-85.

CLOPIDOGREL vs. NOVEL $P2Y_{12}$-INHIBITORS



Wiviott et al. NEJM 2007;357:2001-15.

Wallentin et al. NEJM 2009;361:1045-57.

ESC PRACTICE GUIDELINES

ESC guidelines on NSTE-ACS 2011.

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B	132
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B	130
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A	110, 146, 147

ESC guidelines on STEMI 2012.

An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor.	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-

Take-on of the new drugs is <20%!!!

Hamm CW et al. Eur Heart J. 2011; 2999-3054.
Steg PG et al. Eur Heart J 2012; 2569-619

HUNGARY: SELECTIVE REIMBURSEMENT FOR PRASUGREL

MAGYAR KÖZLÖNY

89. szám

A MAGYAR KÖZTÁRSASÁG HIVATALOS LAPJA

2011. július 27., szerda

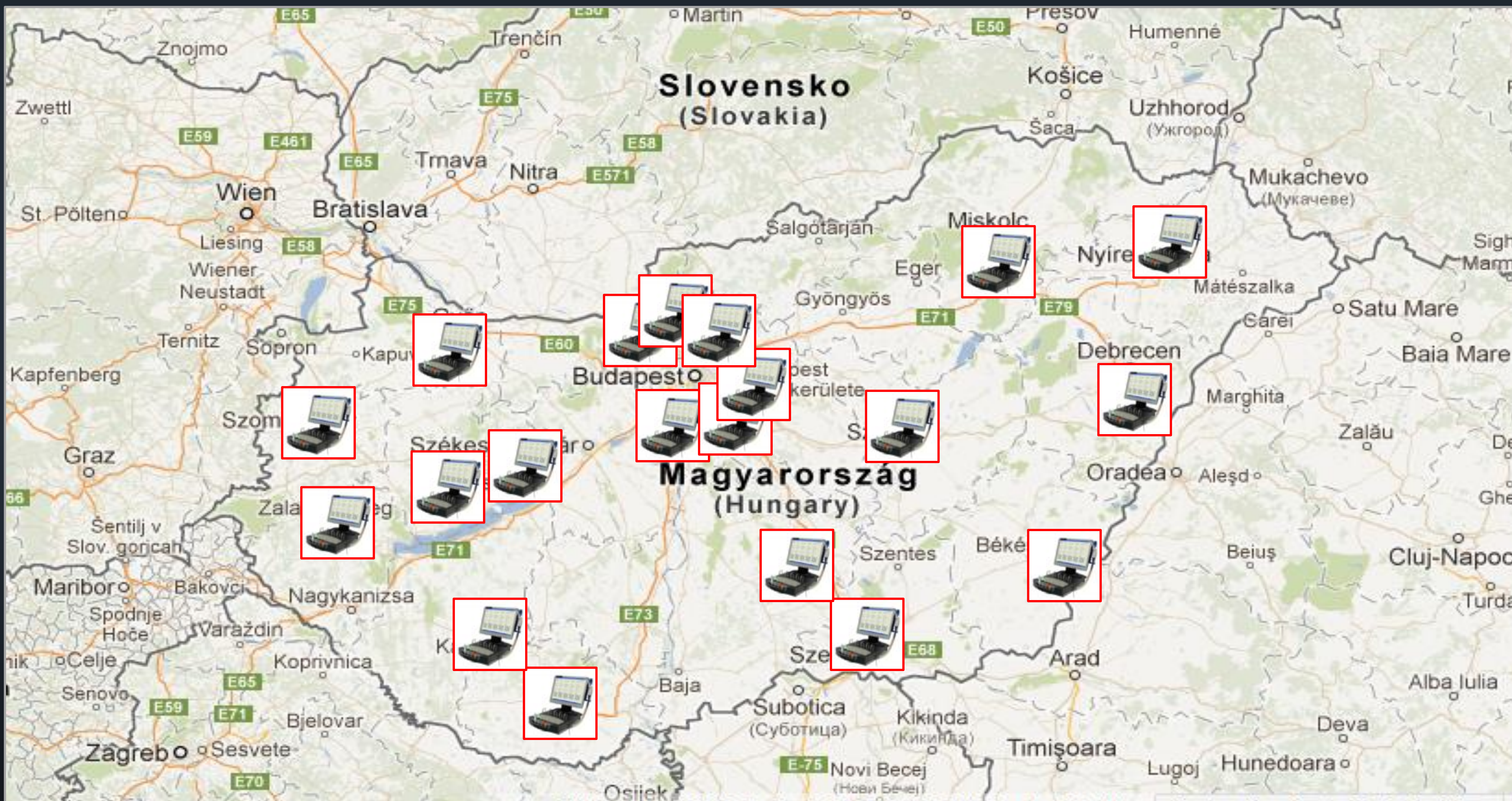
1st September 2011.:

„Acute coronary syndromes patients with either diabetes mellitus or troponin positivity who undergo PCI with stenting and have no prior TIA/stroke in history can receive 70% reimbursement for prasugrel treatment for one year *IF PLATELET FUNCTION TESTING SHOWS HIGH ON-TREATMENT PLATELET REACTIVITY AFTER CLOPIDOGREL.”*

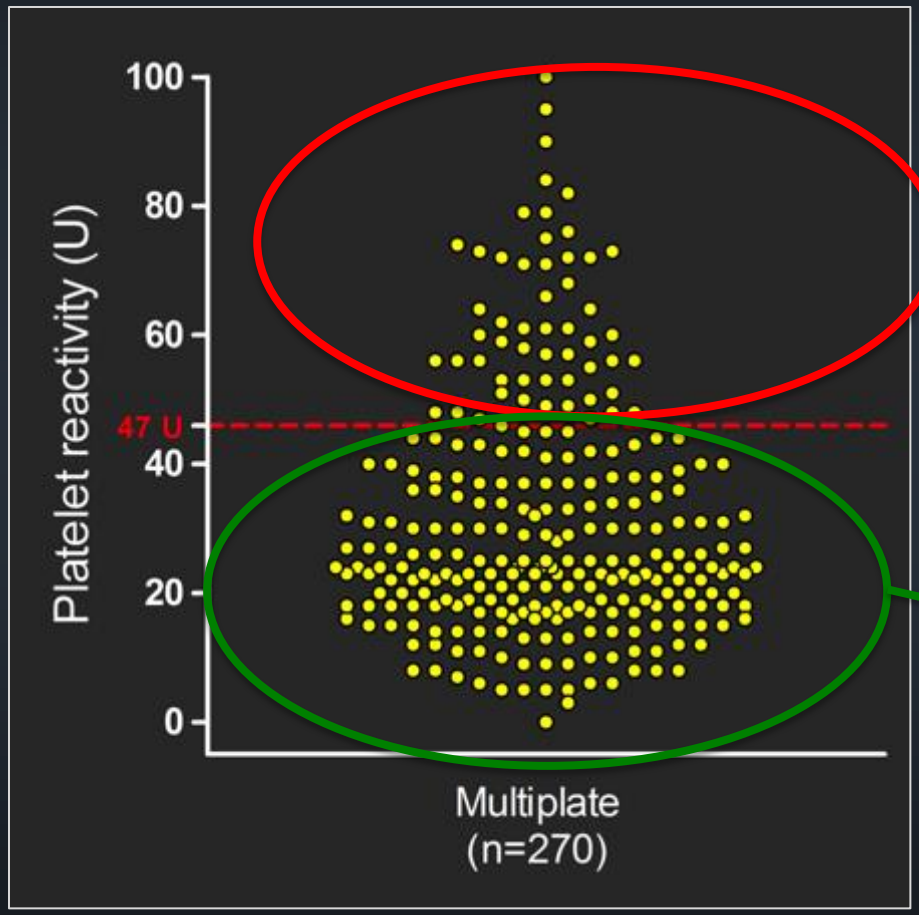
(At the time of this presentation, ticagrelor is not yet reimbursed in Hungary)

'HUNGARIAN MODEL': SELECTIVE USE OF PRASUGREL BASED ON MULTIPLATE TESTING

19 cath-labs are using Multiplate in routine to select the $P2Y_{12}$-receptor antagonist in patients after PCI



BASIC CONCEPT OF TAILORED ANTIPLATELET THERAPY



25% of patients:

Switch to prasugrel

75% of patients:

Keep generic clopidogrel

PÉCS REGISTRY: CLINICAL IMPACT OF THE SELECTIVE USE OF PRASUGREL BASED ON MULTIPLATE TESTING

AIMS:

- to evaluate the clinical and pharmacological impact of selecting $P2Y_{12}$-inhibitors based on Multiplate testing in consecutive ACS patients after PCI

- Prespecified cutoff for HPR: ADP-test ≥47 U
- Key efficacy outcomes: all-cause mortality, definite/probable ST, MI, stroke.
- Key safety outcomes: Non surgery related major bleeding (BARC 3/5)

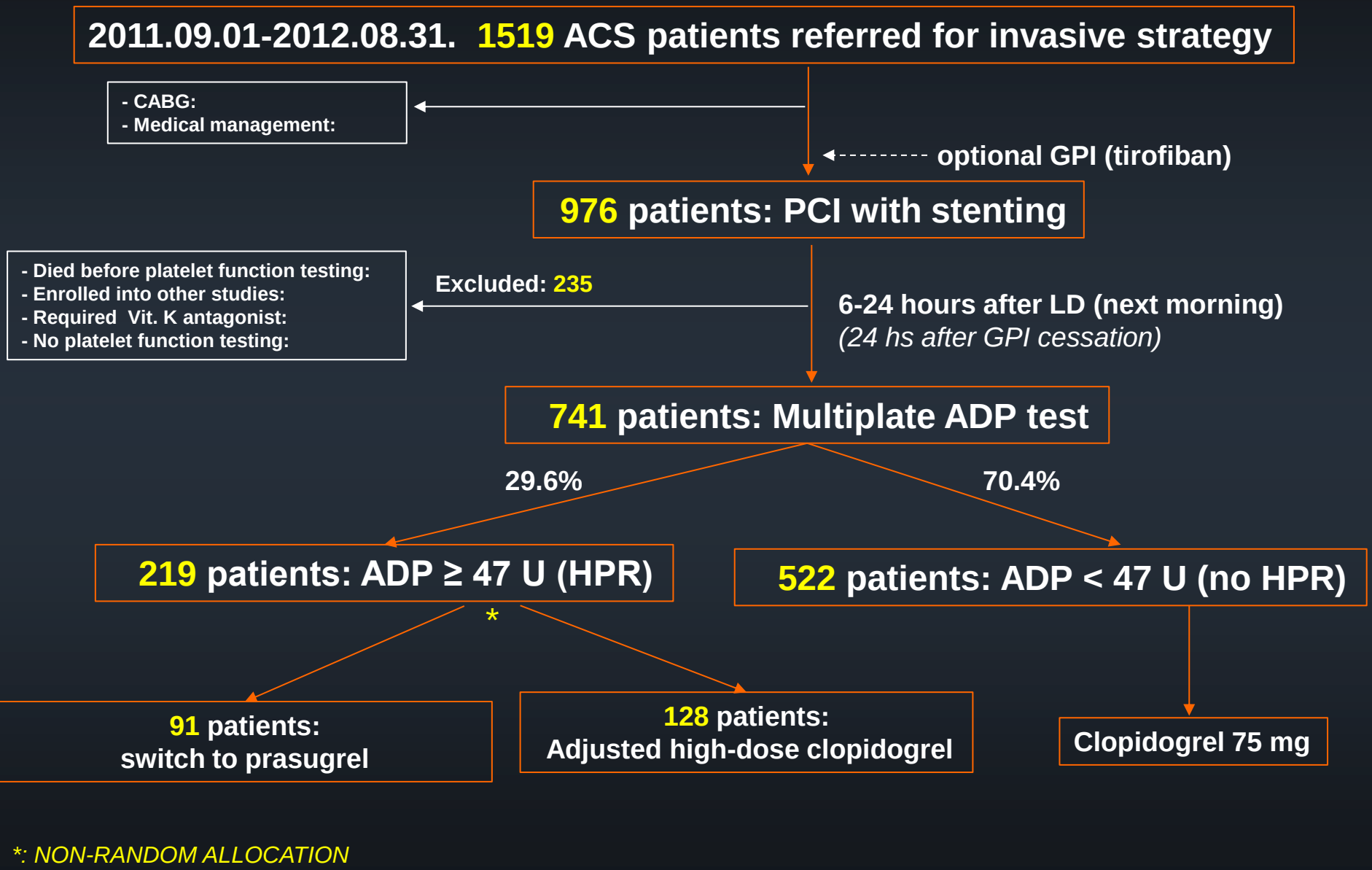
INCLUSION CRITERIA:

- Patients with ACS undergoing PCI with stent implantation
- Pretreatment with 600 mg clopidogrel or chronic treatment with clopidogrel (> 5 days)

EXCLUSION CRITERIA:

- Prior intracranial bleeding
- Indication for chronic oral anticoagulation
- Pretreated with prasugrel
- Concurrent study interfering with DAPT

PÉCS REGISTRY: 1-YEAR RESULTS



*: NON-RANDOM ALLOCATION

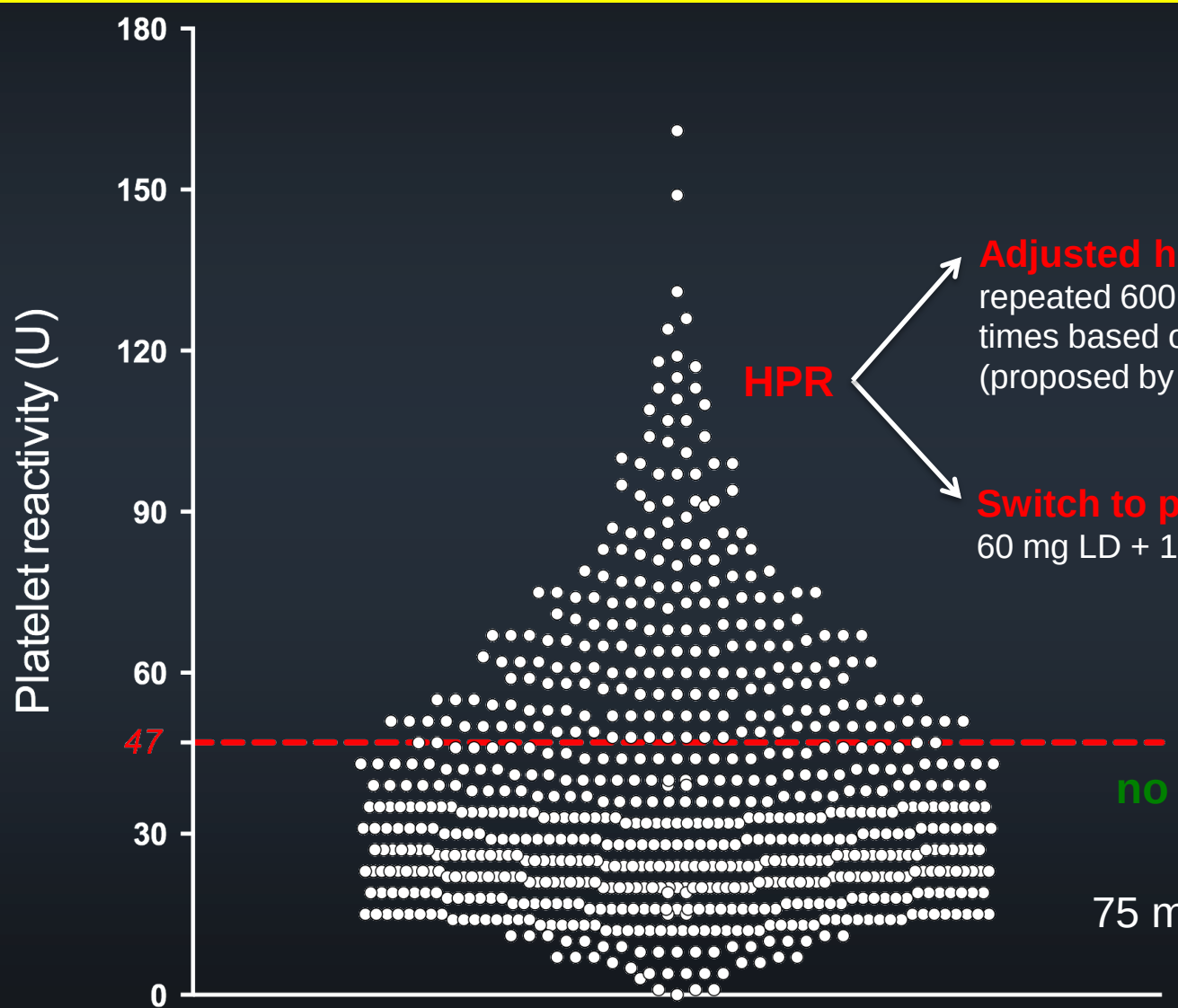
RESULTS: BASELINE CLINICAL CHARACTERISTICS

	Overall (n=741)
Age (years, ±SD)	62.3 (10.9)
Male (n, %)	483 (65.2)
Diabetes (n, %)	192 (25.9)
Hypertension (n, %)	529 (71.4)
Known dyslipidemia (n, %)	174 (23.5)
Smoking (n, %)	146 (19.7)
Prior PCI (n, %)	84 (11.3)
Prior CABG (n, %)	64 (8.6)
Prior MI (n, %)	115 (15.5)
Troponin positive (n, %)	626 (84.5)
STEMI (n, %)	358 (48.3)
NSTEMI (n, %)	268 (36.2)
UA (n, %)	114 (15.5)
Cardiogenic shock (n, %)	33 (4.5)
BMS (n, %)	549 (74.1)
Total stent length (mean, ±SD)	38.5 (22.9)

RESULTS: BASELINE CLINICAL CHARACTERISTICS

	Overall (n=741)	**HPR** (n=219)	**no HPR** (n=522)	**P** **(HPR vs. no HPR)**
Age (years, ±SD)	62.3 (10.9)	60.8 (10.7)	62,9 (10.9)	***<0.05***
Male (n, %)	483 (65.2)	136 (62.1)	347 (66.5)	0.27
Diabetes (n, %)	192 (25.9)	68 (31.1)	124 (23.8)	***<0.05***
Hypertension (n, %)	529 (71.4)	158 (72.1)	371 (71.1)	0.79
Known dyslipidemia (n, %)	174 (23.5)	46 (21.0)	128 (24.5)	0.34
Smoking (n, %)	146 (19.7)	41 (18.7)	105 (20.1)	0.69
Prior PCI (n, %)	84 (11.3)	32 (14.6)	52 (10.0)	***0.08***
Prior CABG (n, %)	64 (8.6)	15 (6.8)	49 (9.4)	0.32
Prior MI (n, %)	115 (15.5)	39 (17.8)	76 (14.6)	0.27
Troponin positive (n, %)	626 (84.5)	192 (87.7)	434 (83.1)	0.15
STEMI (n, %)	358 (48.3)	124 (56.6)	234 (44.8)	***<0.01***
NSTEMI (n, %)	268 (36.2)	68 (31.1)	200 (38.3)	***0.07***
UA (n, %)	114 (15.5)	27 (12.3)	88 (16.9)	0.15
Cardiogenic shock (n, %)	33 (4.5)	14 (6.4)	19 (3.6)	***0.12***
BMS (n, %)	549 (74.1)	160 (73.1)	389 (74.5)	0.71
Total stent length (mean, ±SD)	38.5 (22.9)	41.7 (23.9)	37.2 (22.4)	**0.01**

MULTIPLATE RESULTS:
PLATELET REACTIVITY AFTER PCI (n=741)



HPR

Adjusted high-dose clopidogrel:
repeated 600 mg clopidogrel LD up to 4 times based on PFT + 75/150 mg MD (proposed by Bonello et al.*)

Switch to prasugrel
60 mg LD + 10 mg MD

no HPR

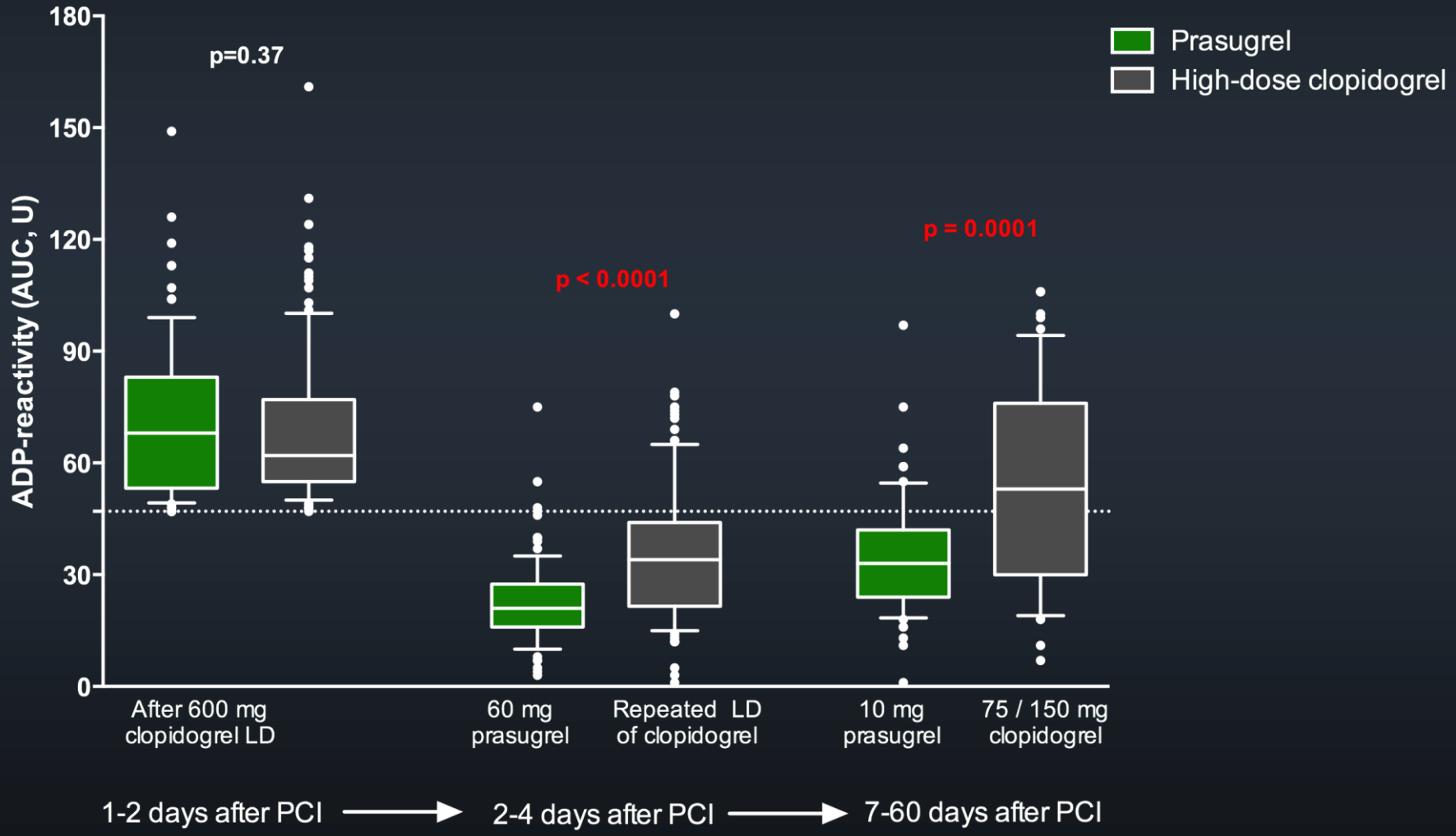
↓

75 mg generic clopidogrel

Aradi et al. JACC 2014. in press.

*: Bonello et al. JACC 2008;51:1404-11.

MULTIPLATE RESULTS:
PRASUGREL vs. HIGH-DOSE CLOPIDOGREL



Aradi et al. JACC 2014. in press.

1-YEAR CLINICAL RESULTS

	Overall population (n=741)
Efficacy outcomes	
All-cause death	**60 (8.1%)**
Definite/probable ST	**21 (2.8%)**
Myocardial infarction	**42 (5.7%)**
Stroke	**4 (0.5%)**
TVR	**137 (18.5%)**
Safety outcomes	
BARC 3 or 5 bleeding	**39 (5.3%)**

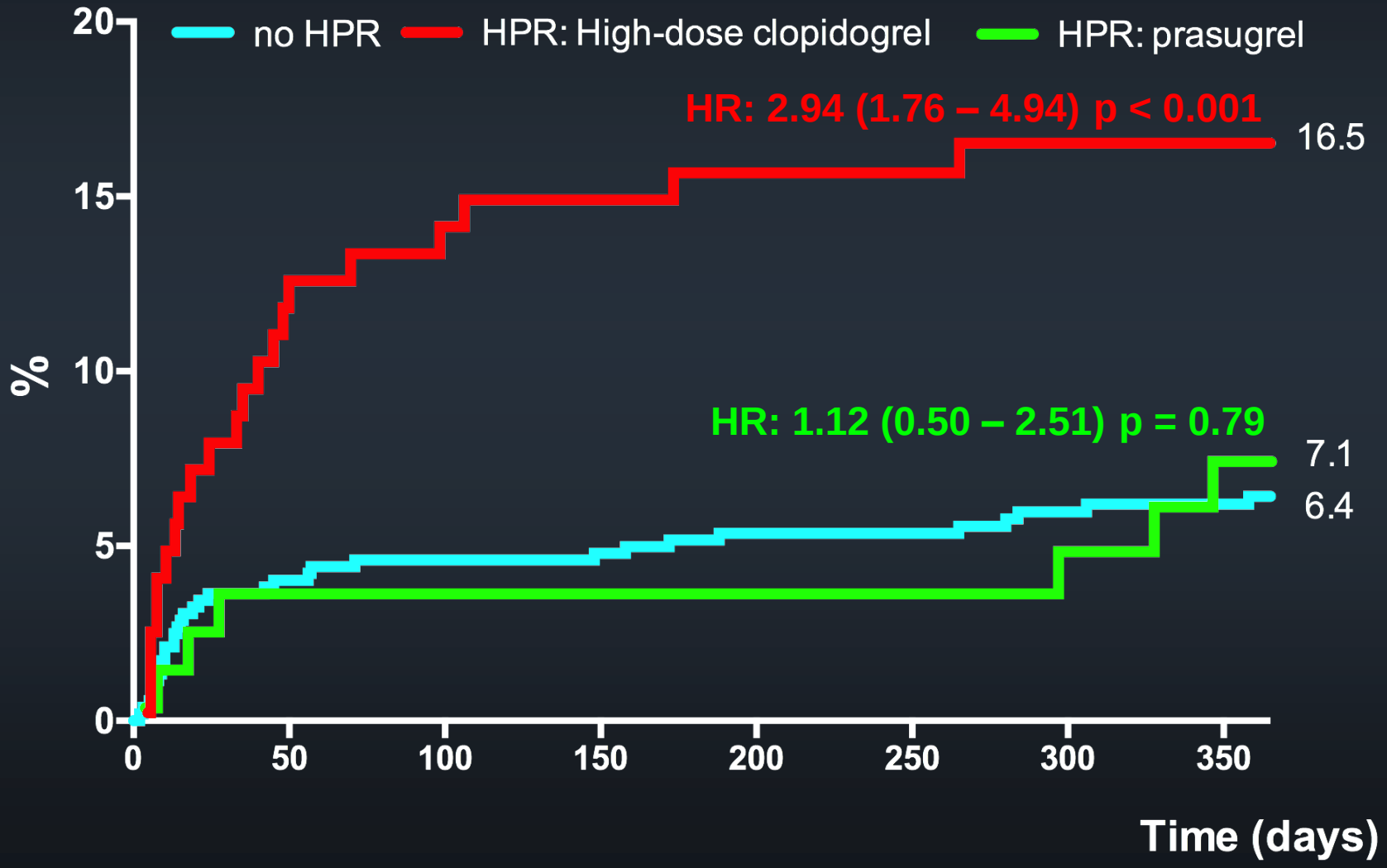
Aradi et al. JACC 2014. in press.

1-YEAR CLINICAL RESULTS

	Overall population (n=741)	no HPR (n=522)	HPR (n=219)	RR (HPR vs. no HPR)	P
Efficacy outcomes					
All-cause death	**60 (8.1%)**	33 (6.3%)	27 (12.3%)	1.95 (1.20-3.16)	*<0.01*
Definite/probable ST	**21 (2.8%)**	10 (1.9%)	11 (5.0%)	2.62 (1.13-6.09)	*<0.05*
Myocardial infarction	**42 (5.7%)**	27 (5.2%)	15 (6.9%)	1.32 (0.72-2.44)	0.39
Stroke	**4 (0.5%)**	3 (0.6%)	1 (0.5%)	0.8 (0.08-7.60)	1.00
TVR	**137 (18.5%)**	95 (18.2%)	42 (19.2%)	1.05 (0.76-1.46)	0.76
Safety outcomes					
BARC 3 or 5 bleeding	**39 (5.3%)**	25 (4.8%)	14 (6.4%)	1.34 (0.71-2.52)	0.38

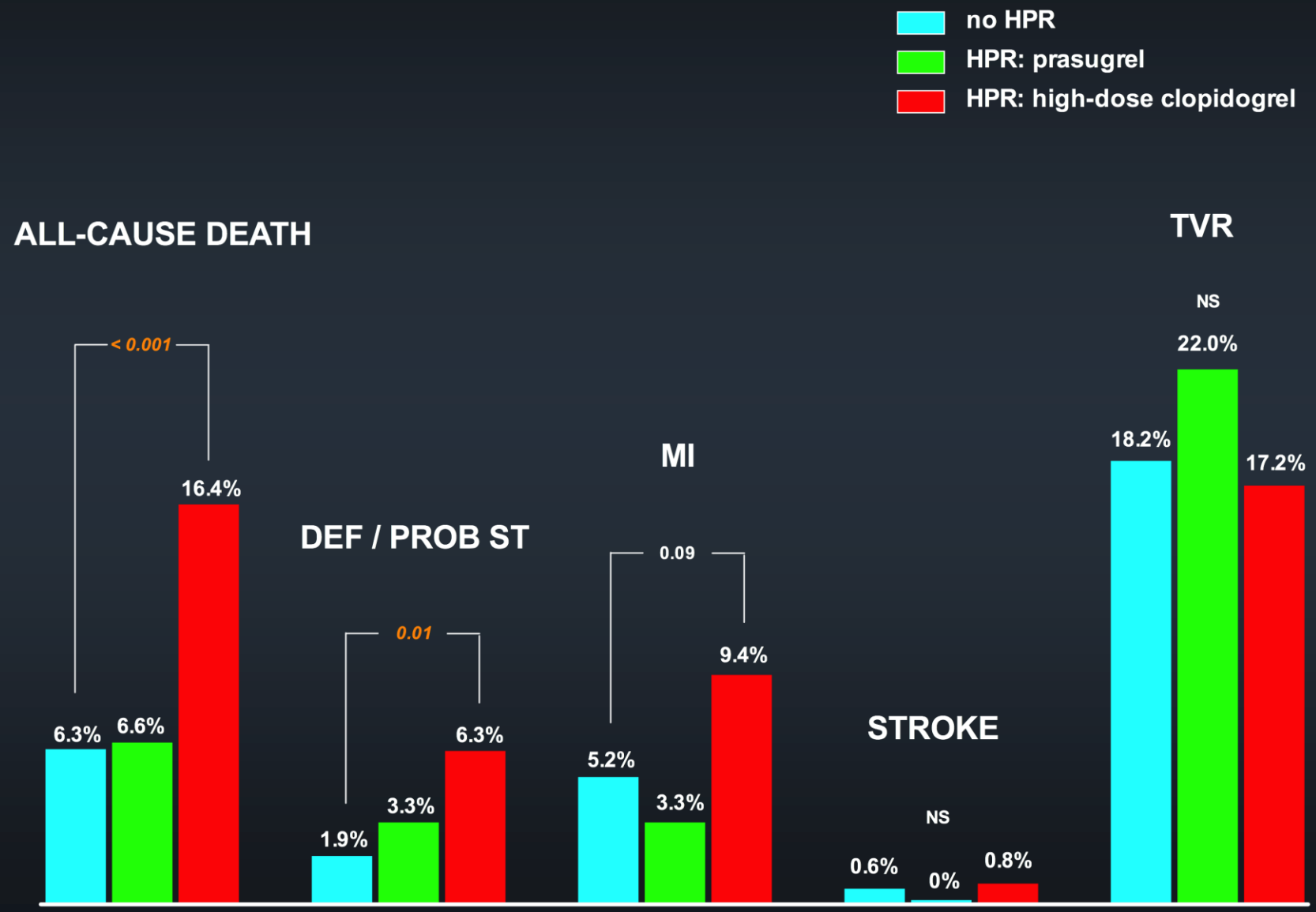
Aradi et al. JACC 2014. in press.

CLINICAL RESULTS:
MORTALITY AND STENT THROMBOSIS



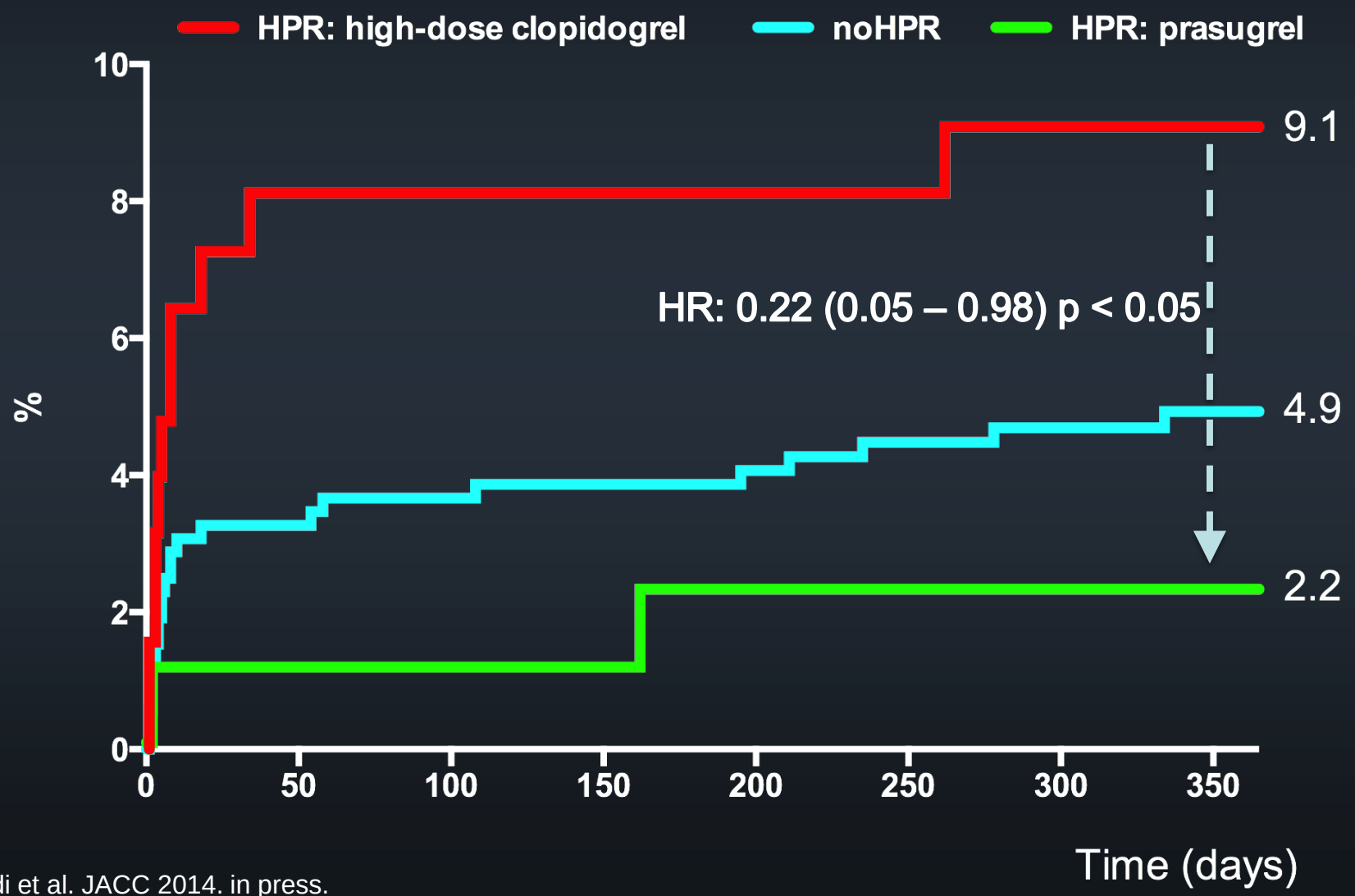
Aradi et al. JACC 2014. in press.

CLINICAL RESULTS: ISCHEMIC EVENTS



Aradi et al. JACC 2014. in press.

CLINICAL RESULTS:
MAJOR BLEEDING (BARC 3, 5)



Aradi et al. JACC 2014. in press.

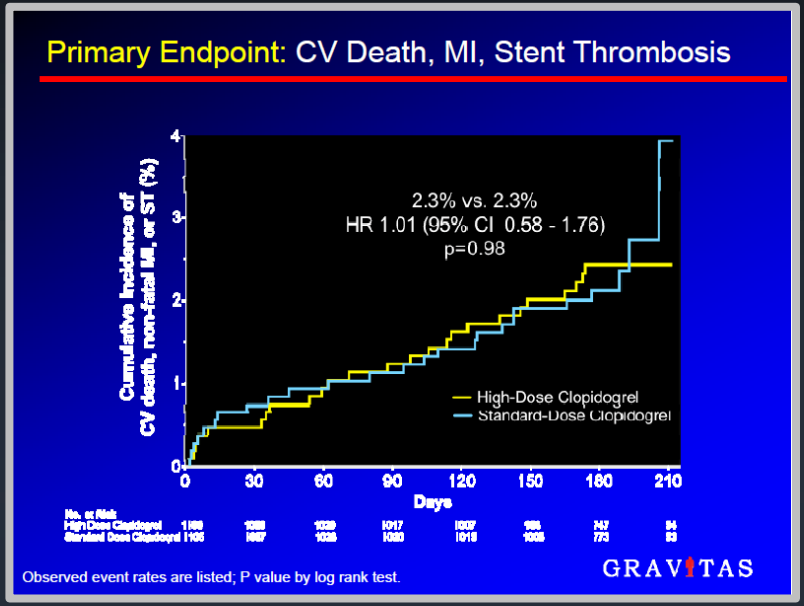
Predictors of D/MI/ST/STROKE @ 1 YEAR

Univariate model (HR 95%CI)		
1. Cardiogenic shock	15.87 (9.95-25.32)	<0.0001
2. Renal failure (stage 4/5)	7.45 (4.28-12.96)	<0.0001
3. High-dose clopidogrel, if HPR	2.27 (1.45-3.55)	<0.0001
**Prasugrel, if HPR*	*0.90 (0.44-1.81)*	*0.76**
4. Leukocyte (per 10 G/l increase)	2.39 (1.70-3.35)	<0.0001
5. Insulin-treated diabetes	2.31 (1.35-3.95)	0.002
6. Prior MI	1.92 (1.21-3.06)	0.006
7. STEMI	1.79 (1.18-2.70)	0.006
8. Age (per 10 year increase)	1.69 (1.38-2.06)	<0.0001
9. Type II. diabetes	1.57 (1.03-2.39)	0.04
10. No. of stents used (per 1 increase)	1.44 (1.22-1.70)	<0.0001
11. Stent length (per 10 mm increase)	1.16 (1.08-1.25)	<0.0001
12. CRP (per 10 ng/ml increase)	1.08 (1.05-1.11)	<0.0001
13. Creatinin (per 10 mmol/l increase)	1.04 (1.03-1.06)	<0.0001
14. Unstable angina	0.22 (0.08-0.60)	0.003
15. DES (vs. BMS)	0.35 (0.19-0.66)	0.001
16. ACEI/ARB	0.39 (0.26-0.59)	<0.0001
17. Statin	0.60 (0.33-0.96)	0.03
18. Beta-blocker	0.62 (0.41-0.96)	0.03
19. eGFR (per 10 ml/min/1.73m^2 increase)	0.82 (0.77-0.88)	<0.0001
20. Hemoglobin (per 10 g/l increase)	0.86 (0.76-0.97)	0.01

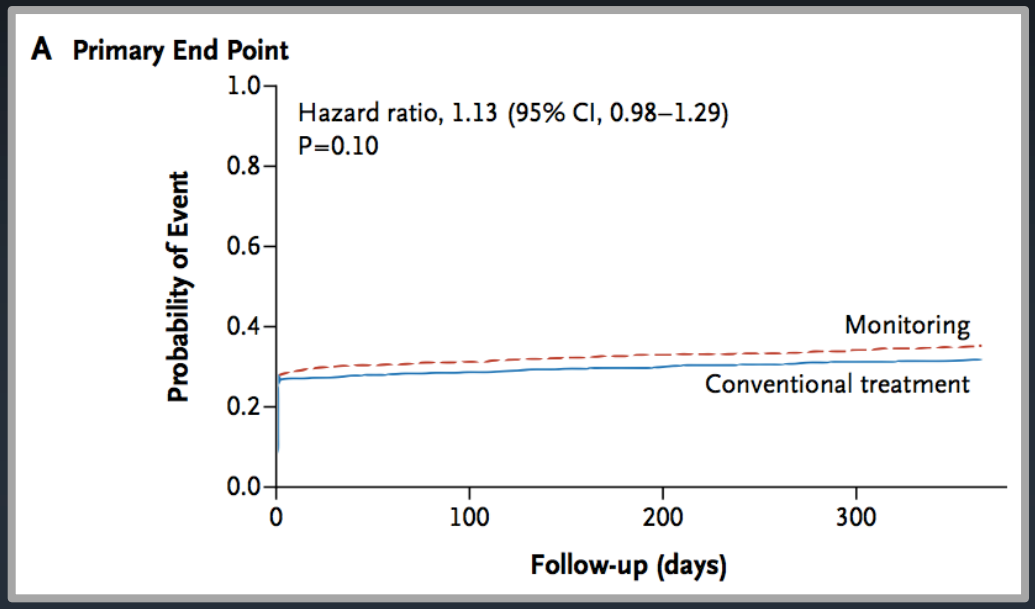
Predictors of D/MI/ST/STROKE @ 1 YEAR

	Univariate model		Multivariate model	
1. Cardiogenic shock	15.87 (9.95-25.32)	<0.0001	9.49 (5.42-16.62)	<0.0001
2. Renal failure (stage 4/5)	7.45 (4.28-12.96)	<0.0001	-	
3. High-dose clopidogrel, if HPR	2.27 (1.45-3.55)	<0.0001	1.90 (1.17-3.08)	0.01
**Prasugrel, if HPR*	*0.90 (0.44-1.81)*	*0.76**	-	
4. Leukocyte (per 10 G/l increase)	2.39 (1.70-3.35)	<0.0001		
5. Insulin-treated diabetes	2.31 (1.35-3.95)	0.002	-	
6. Prior MI	1.92 (1.21-3.06)	0.006	2.47 (1.46-4.19)	0.001
7. STEMI	1.79 (1.18-2.70)	0.006	-	
8. Age (per 10 year increase)	1.69 (1.38-2.06)	<0.0001	1.56 (1.25-1.94)	<0.0001
9. Type II. diabetes	1.57 (1.03-2.39)	0.04	-	
10. No. of stents used (per 1 increase)	1.44 (1.22-1.70)	<0.0001	-	
11. Stent length (per 10 mm increase)	1.16 (1.08-1.25)	<0.0001	1.13 (1.03-1.24)	0.01
12. CRP (per 10 ng/ml increase)	1.08 (1.05-1.11)	<0.0001	-	
13. Creatinin (per 10 mmol/l increase)	1.04 (1.03-1.06)	<0.0001	-	
14. Unstable angina	0.22 (0.08-0.60)	0.003	-	
15. DES (vs. BMS)	0.35 (0.19-0.66)	0.001	0.38 (0.16-0.89)	0.03
16. ACEI/ARB	0.39 (0.26-0.59)	<0.0001	0.45 (0.27-0.72)	0.001
17. Statin	0.60 (0.33-0.96)	0.03	-	
18. Beta-blocker	0.62 (0.41-0.96)	0.03	-	
19. eGFR (per 10 ml/min/1.73m^2 increase)	0.82 (0.77-0.88)	<0.0001	-	
20. Hemoglobin (per 10 g/l increase)	0.86 (0.76-0.97)	0.01	-	

GRAVITAS _TRIGGER _ ARCTIC



Price MJ et al. JAMA 2011; 305: 1097-105.



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

Summary of primary and secondary CEC-adjudicated efficacy endpoints

	Prasugrel N=212	Clopidogrel N=211	p HR (95% CI)
Days on study treatment(median)	174	174	-
Primary composite efficacy EP: **CV death or MI**	0	1 (0.5%)	-
Key secondary efficacy EPs:			
MI	0	1 (0.5%)	-
Rehospitalization for cardiac ischemic event	2 (0.9%)	4 (1.9%)	0.992 0.99 (0.14-7.03)
Urgent TVR	2 (0.9%)	1 (0.5%)	-
Definite ST	0	0	-
Stroke	0	1 (0.5%)	-
CV death	0	0	-
All cause death	0	1 (0.5%)	-

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

PFT-GUIDED ANTIPLATELET THERAPY

	GRAVITAS	ARCTIC	TRIGGER PCI	PÉCS REGISTRY
n (study population)	2,214	2,440	423	741
Patient risk profile				
AMI (%)	10%	27%	0%	84%
STEMI (%)	0.4%	0%	0%	48%
Shock (%)	0%	0%	0%	4.5%
All-cause mortality	0.8%	2%	0%	8.2%
Intervention				
High-dose clopidogrel	100%	80%	-	58%
High-dose ASA	-	45%	-	-
Prasugrel	-	12%	100%	42%
PFT Assay	VerifyNow	VerifyNow	VerifyNow	Multiplate
Results				
1° Endpoint	2.3% vs. 2.3%	31.1% vs. 34.6%	0.0% vs. 0.5%	***16.5% vs. 7.1%***

Price MJ et al. JAMA 2011; 305: 1097-105.
Collet et al. N Engl J Med. 2012;367:2100-9.
Trenk D et al. J Am Coll Cardiol 2012;59:2159-64.

CONCLUSIONS

- Integration of the Multiplate into routine clinical workflow to select the optimal $P2Y_{12}$-inhibitor in ACS is feasible

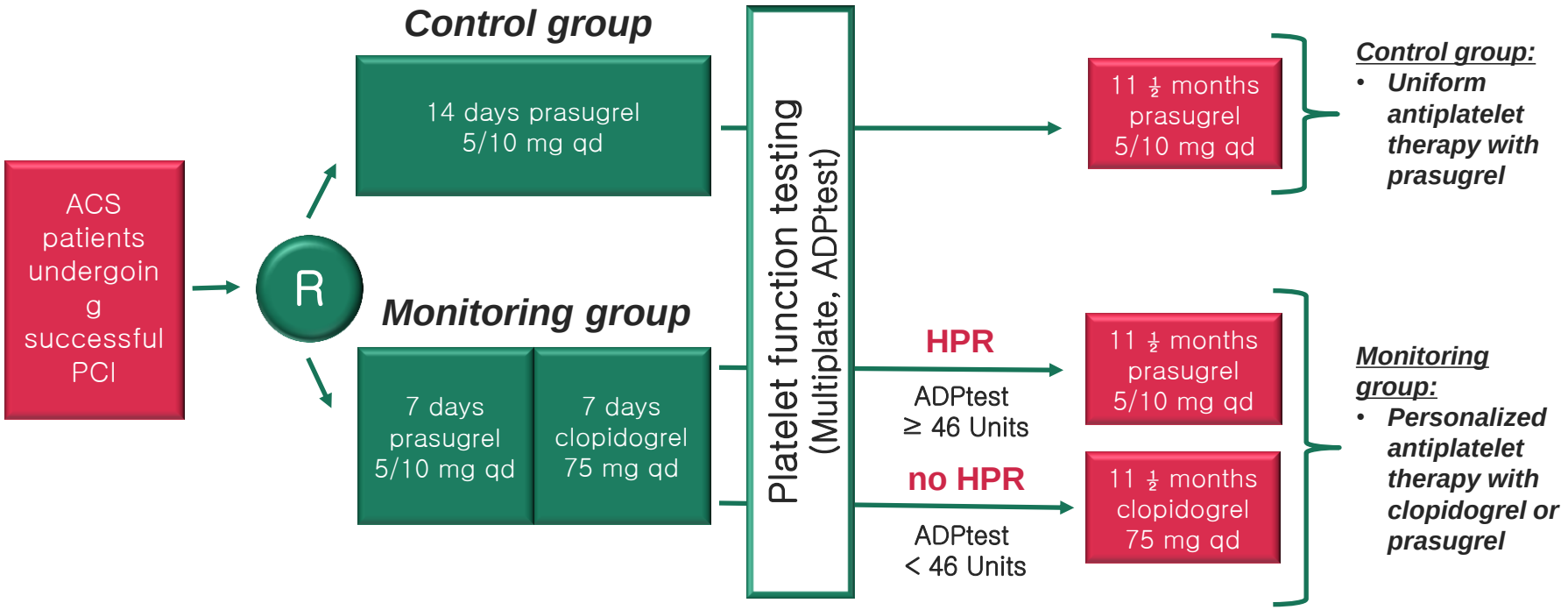
- In patients with HPR, 60 mg prasugrel LD achieves quick and potent $P2Y_{12}$-receptor inhibition that can be maintained in the majority of the patients throughout the chronic phase

- By giving repeated LDs of clopidogrel, a significant decrease in platelet inhibition can also be achieved, but:
  - It takes longer compared to prasugrel (2-3x 600 mg necessary)
  - It is less potent compared to a 60 mg LD of prasugrel
  - The achieved level of platelet inhibition cannot be maintained by using 75/150 mg MD

CONCLUSIONS

- In patients with HPR, switching over to prasugrel reduces the risk of D/MI/ST/stroke compared to adjusted high-dose clopidogrel
- In addition, the risk of severe bleeding was also lower with prasugrel compared to high-dose clopidogrel
- Further randomized studies need to confirm that tailored P2Y12-inhibitor treatment is as good/better than the unselected use of prasugrel/ticagrelor

TROPICAL ACS



THANK YOU FOR YOUR KIND ATTENTION!

Heart Center, Balatonfüred, Hungary