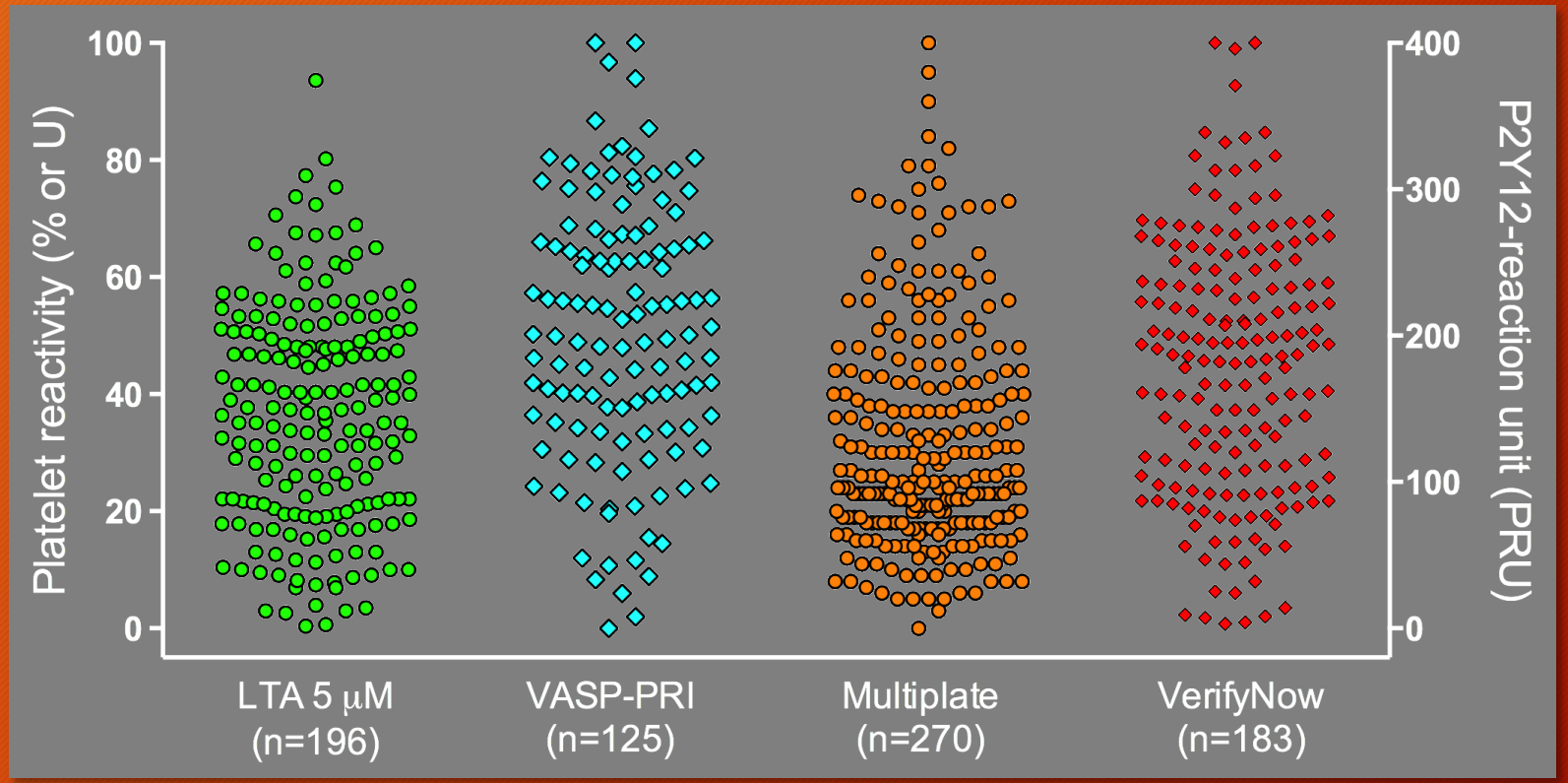
From escalation to de-escalation, role of platelet function testing in guiding P2Y12 inhibitor therapy

András Komócsi MD,DSc

Dept. of Interventional Cardiology, Heart Centre,

University of Pécs, Hungary

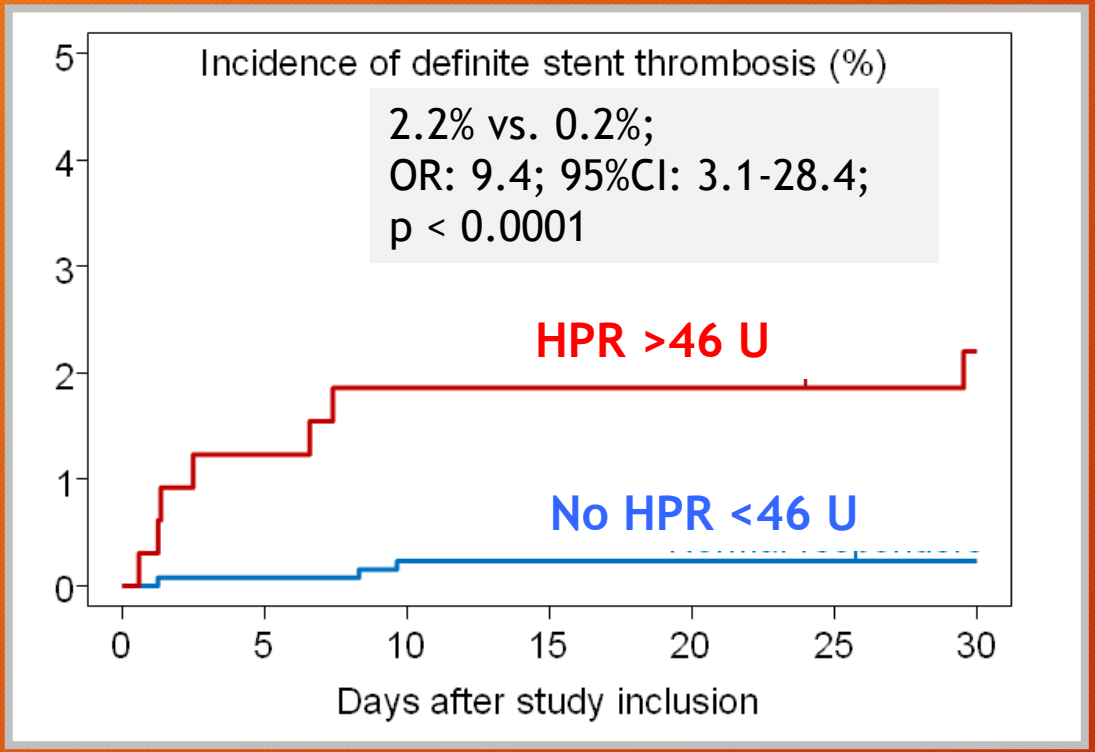
Inter-patient variability of clopidogrel



After 600 mg clopidogrel loading dose, in patients with stable angina undergoing PCI

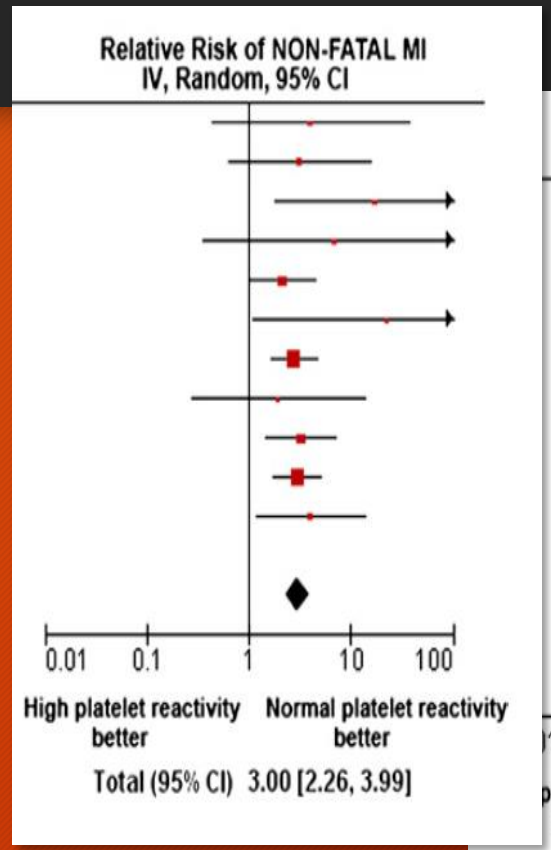
Aradi D, Storey RF, Komócsi A et al. Eur Heart J. l (2014) (35):, 209–215.

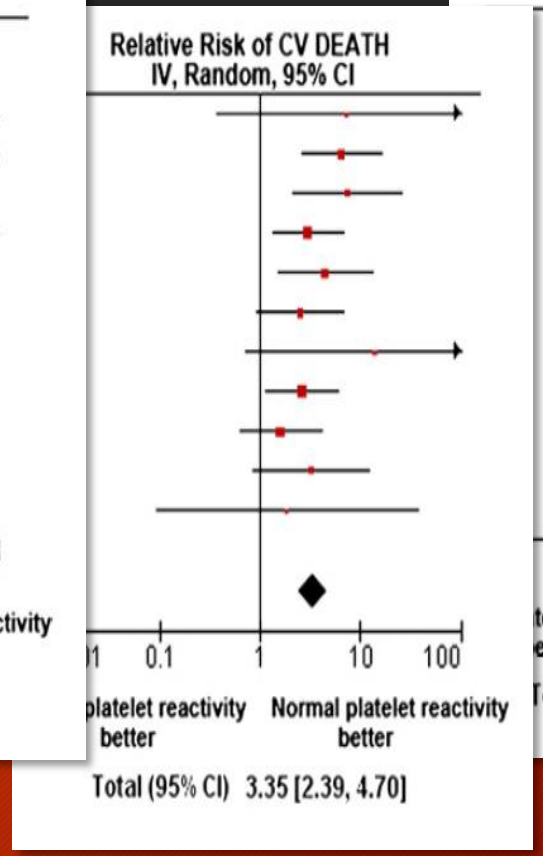
ASSOCIATION BETWEEN HPR AND CLINICAL OUTCOMES AFTER PCI

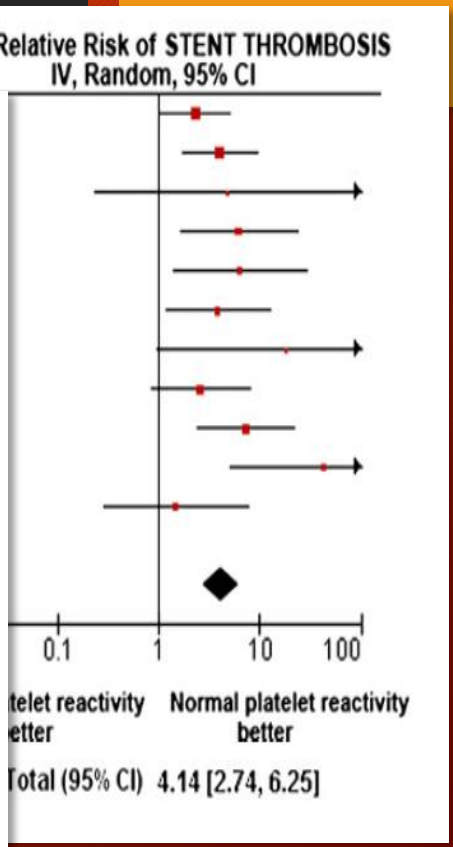


PFT with MULTIPLATE in 1608 pts after PCI

Sibbing D. J Am Coll Cardiol 2009;**53**:849-856.

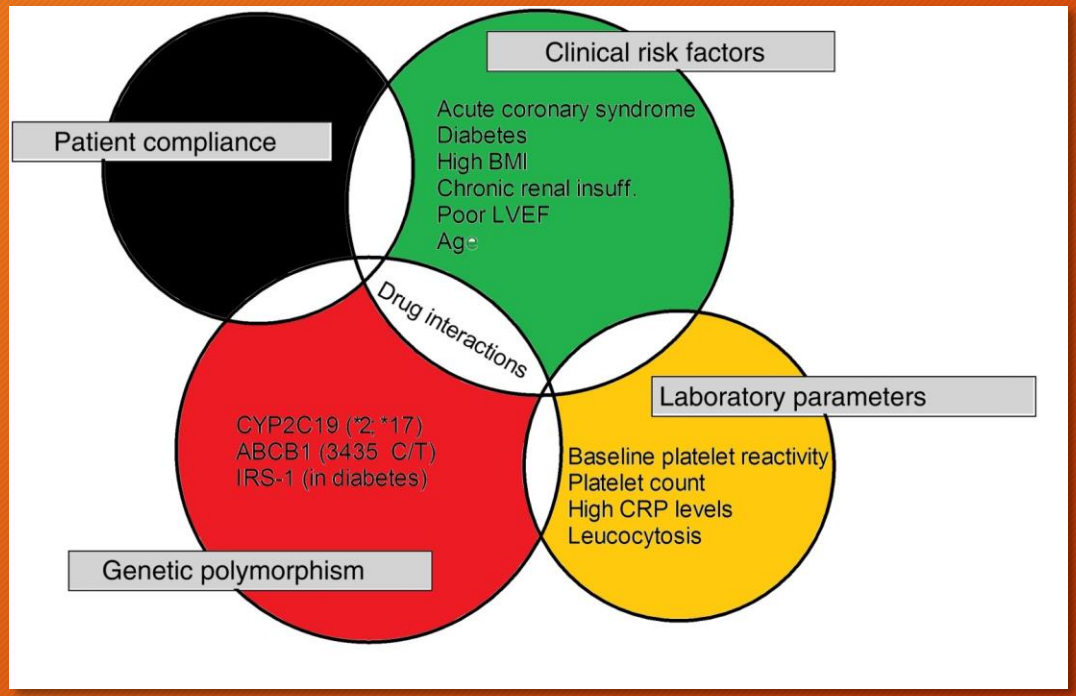


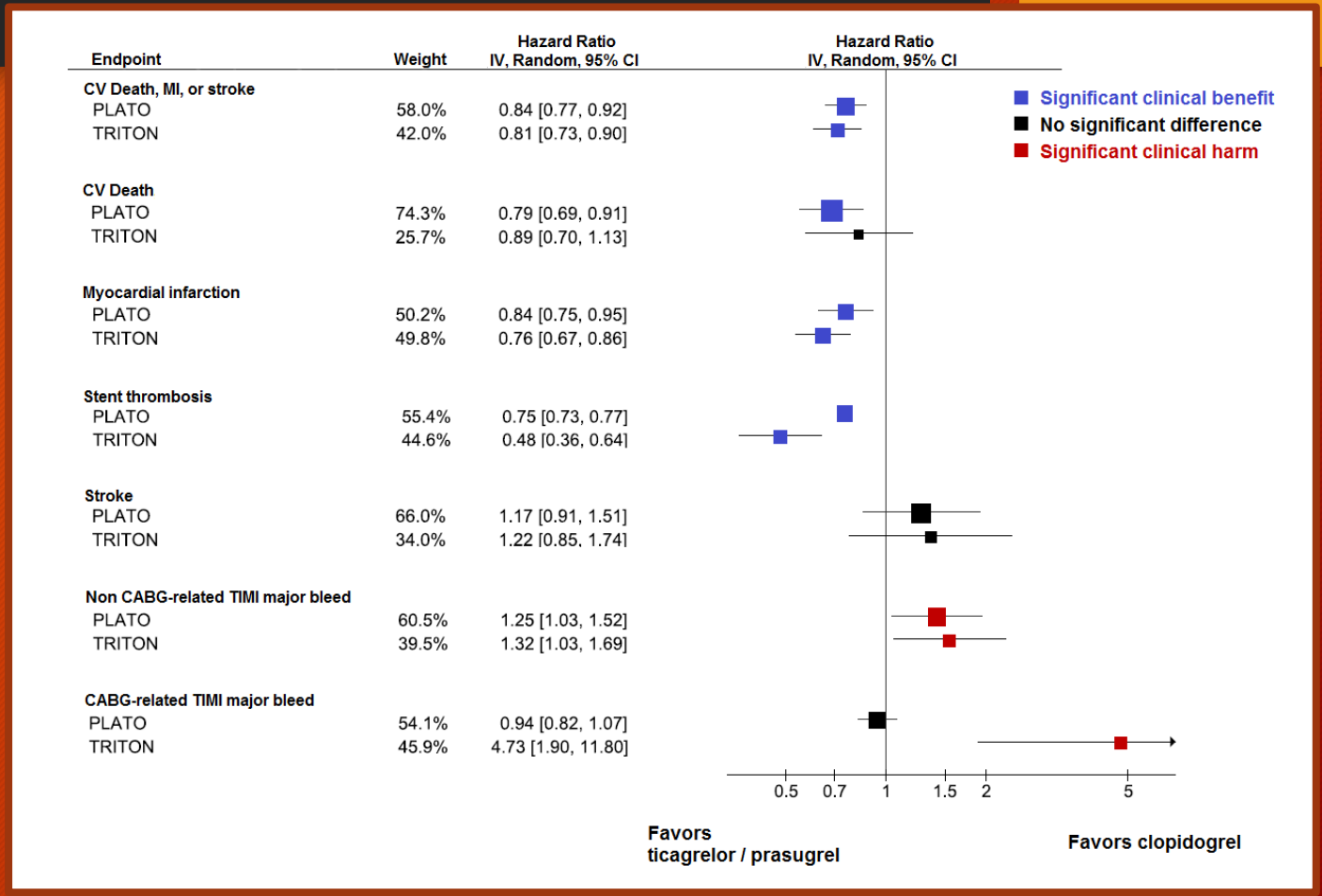




Aradi D, Komócsi A et al, *Am Heart J. 2010 Sep;160(3):543-51*

CLOPIDOGREL vs. NOVEL P2Y12-INHIBITORS





Aradi D, Komócsi A. Platelets. 2012;23(3):167-76.

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

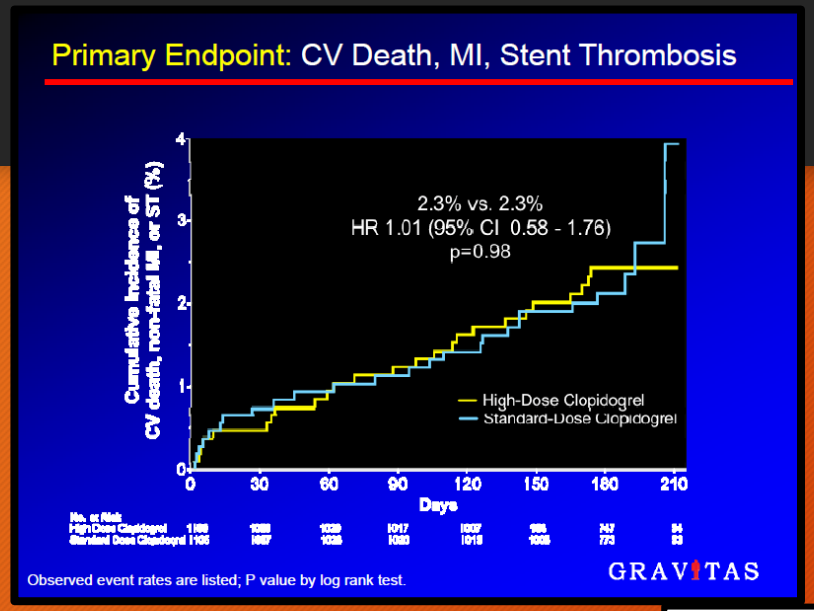
ESC guidelines on STEMI 2012.

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	-

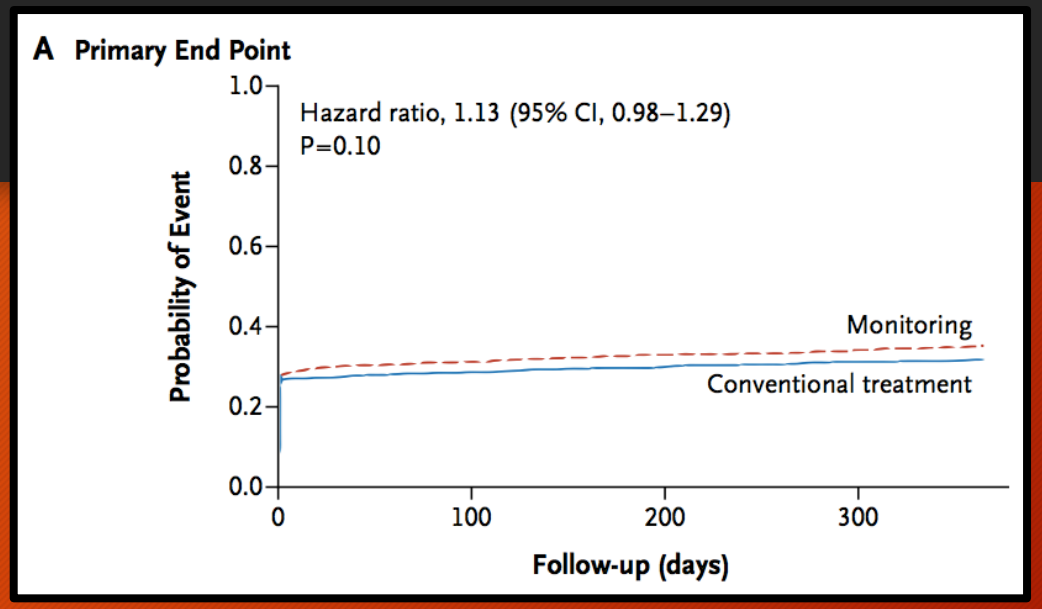
Take-on of the new drugs is <20%!!!

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

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.

HUNGARY: SELECTIVE REIMBURSEMENT FOR PRASUGREL

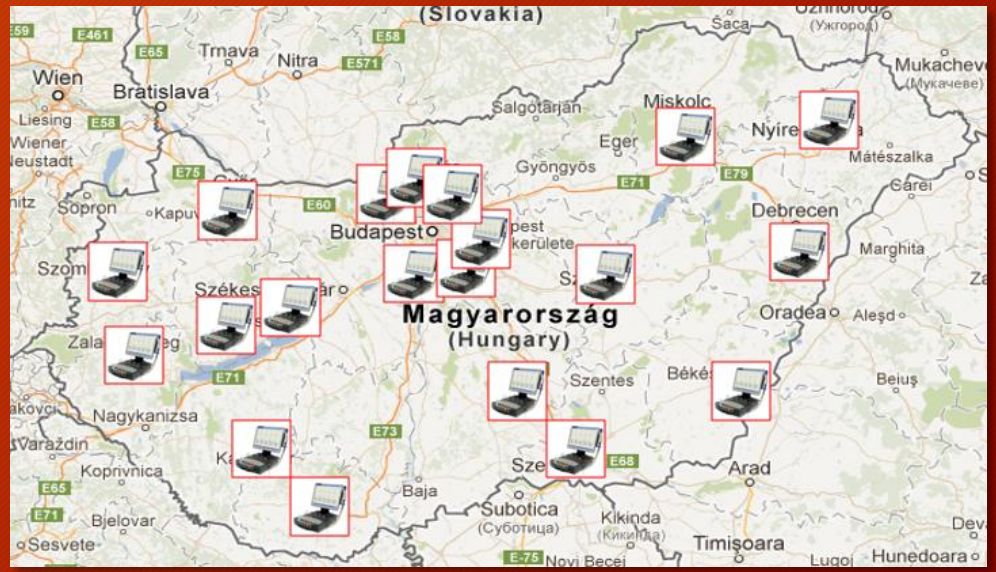
MAGYAR KÖZLÖNY 89. szám

A MAGYAR KÖZTÁRSASÁG HIVATALOS LAPJA

2011. július 27., szerda

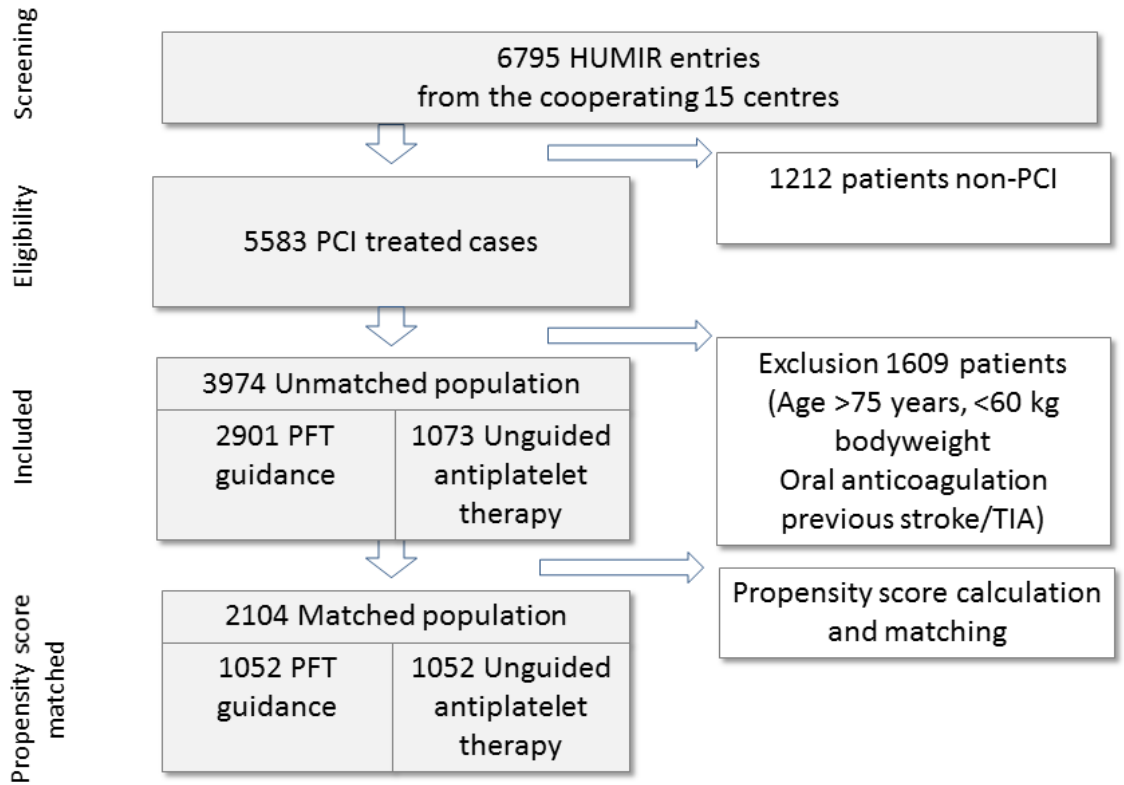
1st September 2011.:

„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 has just been reimbursed in Hungary 2018 Sep)

Flowchart of patient selection



The Hungarian Myocardial Infarction Registry is a prospective, Internet-based registry collecting clinical data on consecutive patients treated for an event of AMI in Hungary

5583 PCI treated MI cases in 15 cooperating center

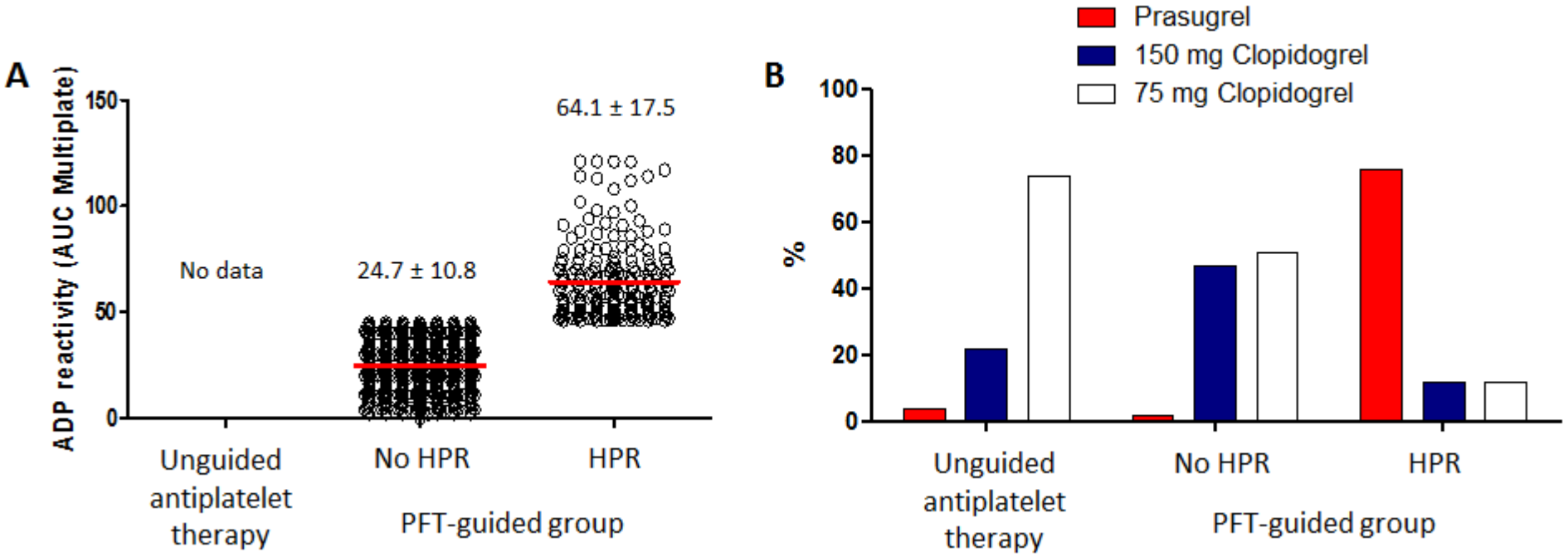
Absolute or relative contraindication to prasugrel

Propensity Score matching: 2104 patients with balanced characteristics

Komócsi et al., Am J Cardiol 2018;121:1129–1137

Clinical characteristics	Entire cohort (n=3974)			Propensity matched cohort (n=2104)		
	Aggregometry guided (n=2901)	Unguided treatment (n=1073)	P value	Aggregometry guided (n=1052)	Unguided treatment (n=1052)	P value
Age, years *	58.9 ± 9.6	60.5 ± 9.2	<0.001	60.5 ± 9.0	60.5 ± 9.1	0.926
Male *	69.3	65.7	0.035	65.3	66.1	0.748
Medical history						
Hypertension	64.6	71.2	<0.001	68.41	70.6	0.297
Diabetes	24.8	29.2	0.006	27.8	28.4	0.734
- insulin	1.6	1.6	1.000	1.0	1.5	0.324
Hyperlipidaemia *	11.1	5.1	<0.001	3.7	5.2	0.113
Smoking (current/past/never)	35.2/1.6/63.3	36.1/2.1/61.9	0.458	36.2/1.8/62.0	36.2/1.9/61.8	0.950
History of myocardial infarction	15.8	27.4	<0.001	26.6	26.0	0.771
History of CABG *	1.8	1.0	0.113	0.8	1.0	0.646
Peripheral artery disease *	5.3	11.6	<0.001	10.2	10.4	0.943
Presentation						
STEMI *	64.1	51.0	<0.001	55.1	51.7	0.126
Culprit artery (LM/LAD/Cx/RCA/VSG	2.8/46.7/23.0/35.8/1.2	3.3/44.1/25.9/35.8/1.1	0.3461	2.9/46.7/24.4/34.3/1.2	2.9/44.2/25.5/36.0/1.0	0.734
Heart rate	79.8 ± 17.1	80.6 ± 18.1	0.236	81.4 ± 18.0	80.5 ± 18.1	0.250
Systolic blood pressure *	137.9 ± 24.2	136.6 ± 25.7	0.191	138.6 ± 24.8	136.5 ± 25.7	0.054
Diastolic blood pressure *	70.0 ± 24.7	68.7 ± 25.0	0.168	67.9 ± 26.1	68.8 ± 25.1	0.440
ADP reactivity	32.5 ± 19.5	-	NA	32.5 ± 19.9	-	NA
High platelet reactivity	19.1	-	NA	18.6	-	NA
Medications						
Clopidogrel 75 mg daily	50.6	74.3	<0.001	43.6	74.2	<0.001
Clopidogrel 150 mg daily	34.4	21.6		40.2	21.8	
Prasugrel	15.0	4.1		16.2	4.0	
Aspirin	71.1	81.0	<0.001	80.9	79	0.547
ß-blocker	84.1	90.6	<0.001	88.5	90.4	0.176
Statin	81.0	91.8	<0.001	91.6	91.7	0.579

Results

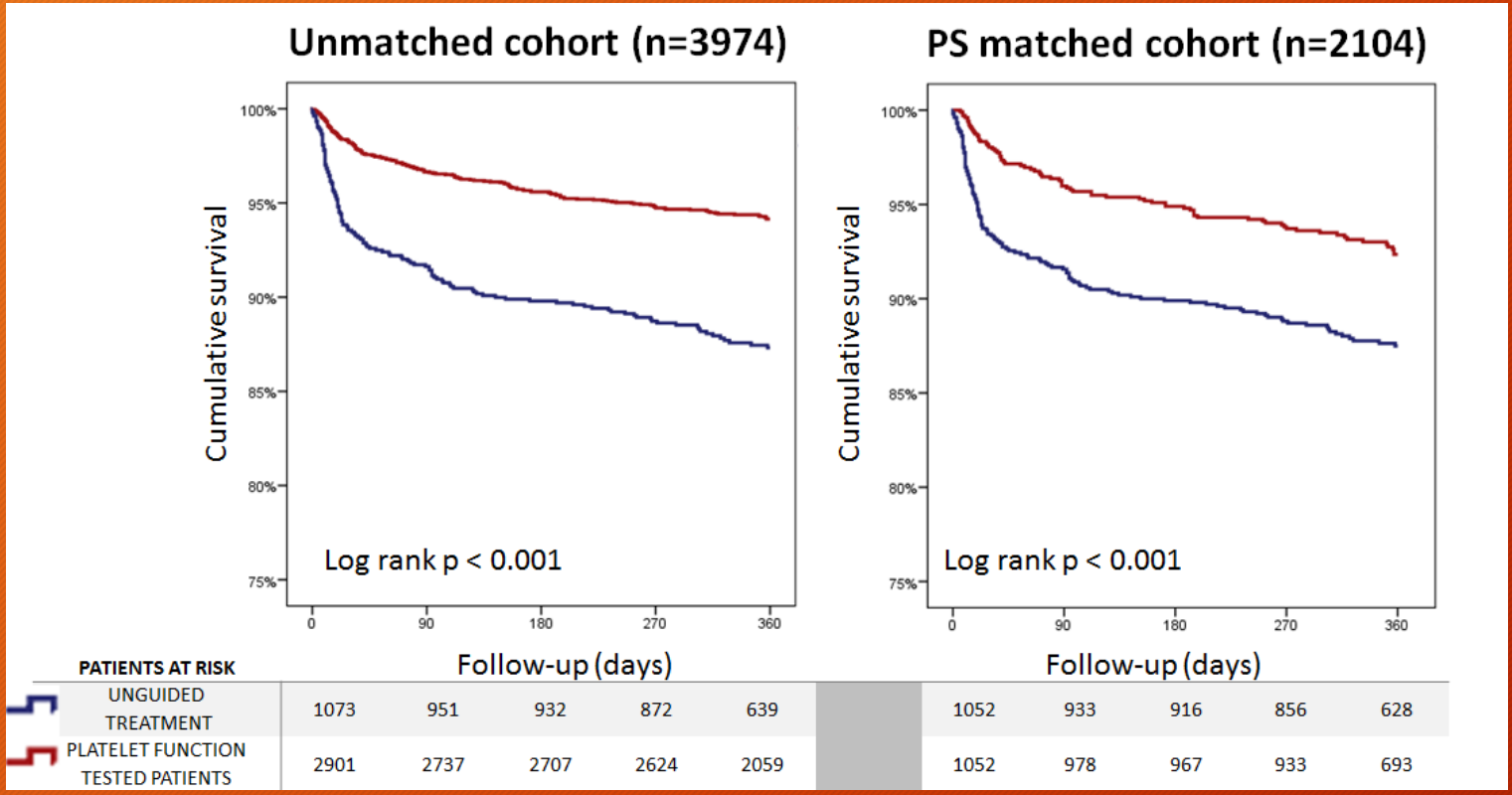


HPR treatment:
prasugrel 76%
clopidogrel 75 mg 12%
Clopidogrel 150 mg 12%

The other two groups: dominating clopidogrel treatment

Komócsi et al., Am J Cardiol 2018;121:1129–1137

Results



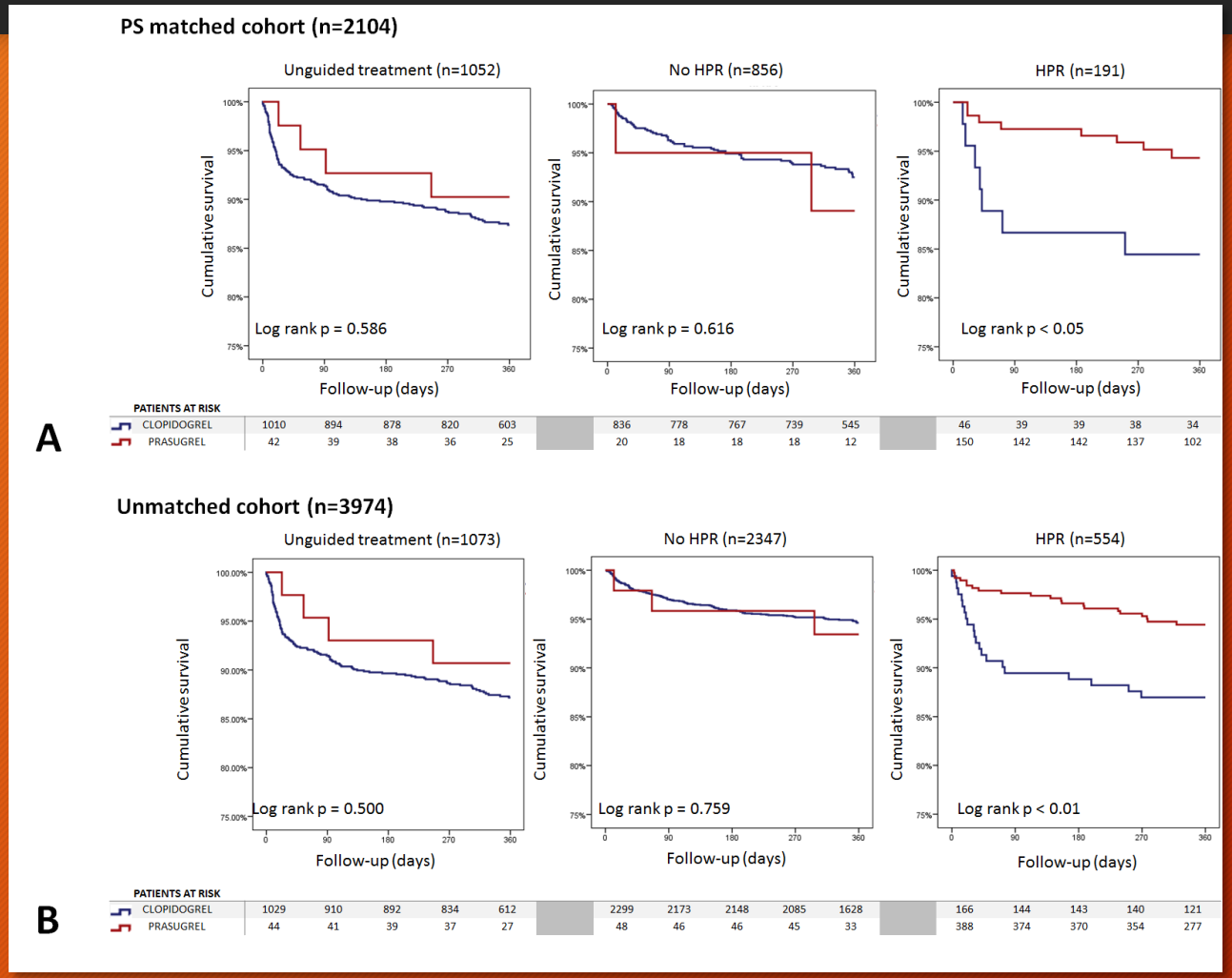
- The 1-year mortality was better in the PFT-guided group
- Hazard ratio (HR) 0.574 [0.431-0.765] in the PS matched cohort

Komócsi et al., Am J Cardiol 2018;121:1129–1137

Predictors of 1-year mortality

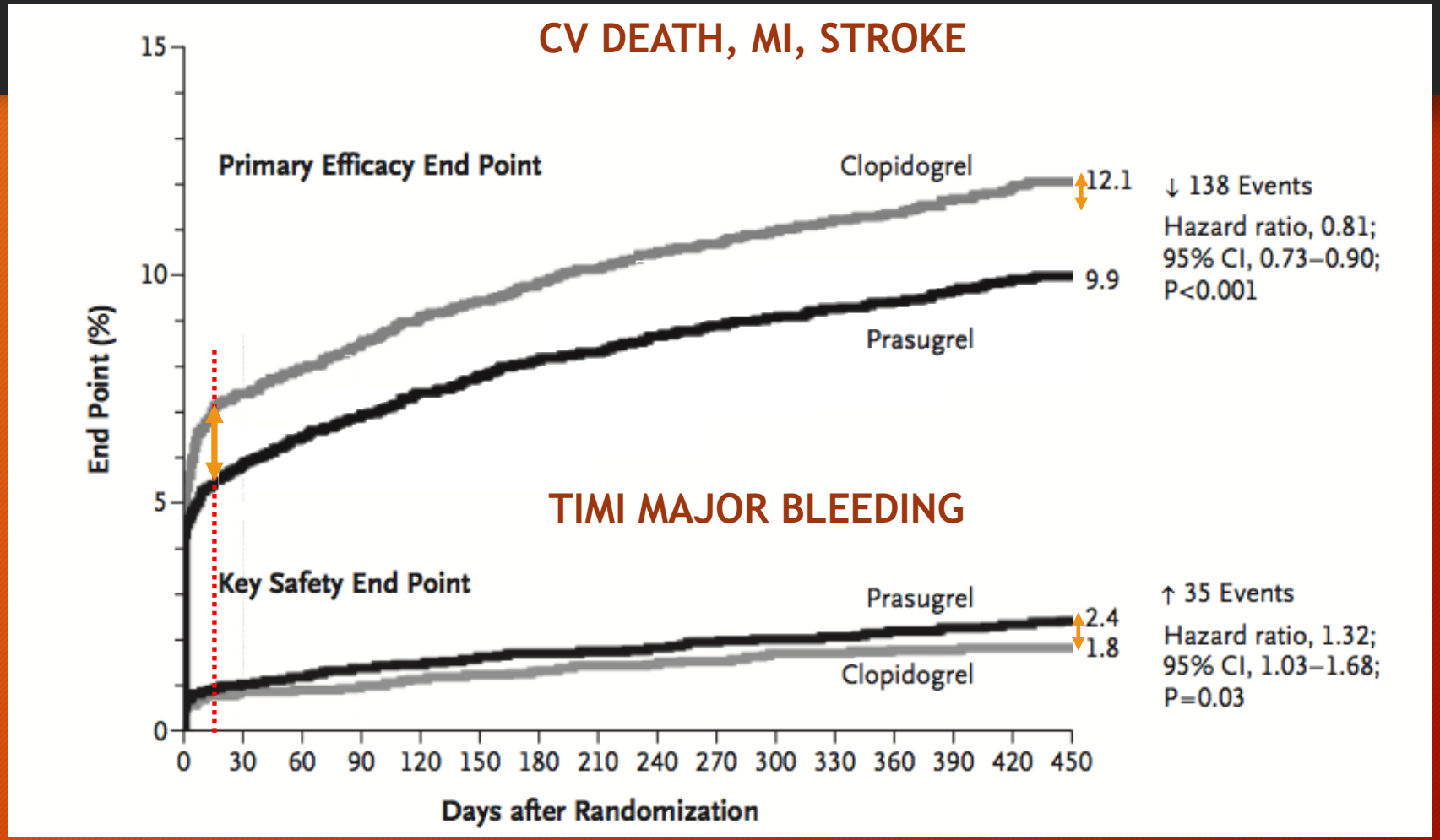
	Univariate Cox proportional hazard model		Multivariate Cox proportional hazard model	
	Hazard Ratio (HR) [95.0% CI]	p-value	Hazard Ratio (HR) [95.0% CI]	p-value
History of peripheral artery disease	2.79 [2.01-3.88]	<0.001	2.97 [2.11-4.18]	0.001
Smoking	1.59 [1.17-2.17]	0.003	1.74 [1.27-2.38]	0.001
Age (per 10 yrs increase)	1.56 [1.34-1.82]	<0.001	1.62 [1.38-1.90]	<0.001
Heart rate (per 10/min increase)	1.26 [1.18-1.34]	<0.001	1.25 [1.17-1.33]	<0.001
Systolic blood pressure (per 10 Hgmm increase)	0.85 [0.80-0.90]	<0.001	0.83 [0.78-0.88]	<0.001
PPI guidance	0.57 [0.43-0.77]	<0.001	0.52 [0.39-0.69]	<0.001
Hypertension	1.24 [0.93-1.66]	0.149	1.56 [1.14-2.10]	0.005
Diabetes	1.57 [1.18-2.08]	0.002	1.55 [1.11-2.03]	0.005
Culprit artery LM	3.01 [1.80-5.02]	<0.001	2.01 [1.18-3.39]	<0.009
Diastolic blood pressure (per 10 Hgmm increase)	0.98 [0.93-1.03]	0.422	0.94 [0.88-1.00]	0.036
Male gender	0.92 [067-1.22]	0.545		
Hyperlipidaemia	0.83 [0.39-1.76]	0.626		
History of myocardial infarction	0.98 [0.72-1.35]	0.910		
History of CABG	1.09 [0.27-4.39]	0.905		
STEMI	1.27 [0.96-1.68]	0.102		
Prasugrel treatment	0.65 [0.38-1.11]	0.116		

Results



In the PFT guided group:
Patients switched to prasugrel benefited the most
(HR: 3.00 [95% CI 1.089-8.287], p<0.05.

PRASUGREL vs. CLOPIDOGREL: TIME-DEPENDENT DIFFERENCES IN RISKS AND BENEFITS (TRITON TIMI38)



Wiviott et al., NEJM 2007

GUIDELINES vs. REAL-WORLD: DE-ESCALATION IS FREQUENT

Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: Insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study

Marjorie E. Zettler, PhD, MPH,[a] Eric D. Peterson, MD, MPH,[b] Lisa A. McCoy, MS,[b] Mark B. Effron, MD,[a] Kevin J. Anstrom, PhD,[b] Timothy D. Henry, MD,[c] Brian A. Baker, PharmD,[d] John C. Messenger, MD,[e] David J. Cohen, MD,[f] and Tracy Y. Wang, MD, MHS, MSc[b], on behalf of the TRANSLATE-ACS Investigators *Indianapolis, IN; Durham, NC; Los Angeles, CA; Parsippany, NJ; Aurora, CO; and Kansas City, MO*

Table II. Factors independently associated with postdischarge switch from prasugrel or ticagrelor to clopidogrel

Parameter	OR	95% CI	*P*
High school graduate (or beyond)	0.629	0.451-0.877	<.01
Insurance for medications: Medicare/ Medicaid (vs private)	2.383	1.863-3.049	<.01
Insurance for medications: no/non-US (vs private)	1.543	1.067-2.231	.02
Prior MI	1.371	1.047-1.794	.02
Moderate/extreme financial hardship of current monthly medications	1.401	1.042-1.884	.03
Creatinine clearance (per 10-unit decrease)	1.059	1.109-1.012	.01
In-hospital bleeding event	2.236	1.408-3.553	<.01
Any home ADPri	0.593	0.393-0.896	.01

Table I. Patient characteristics

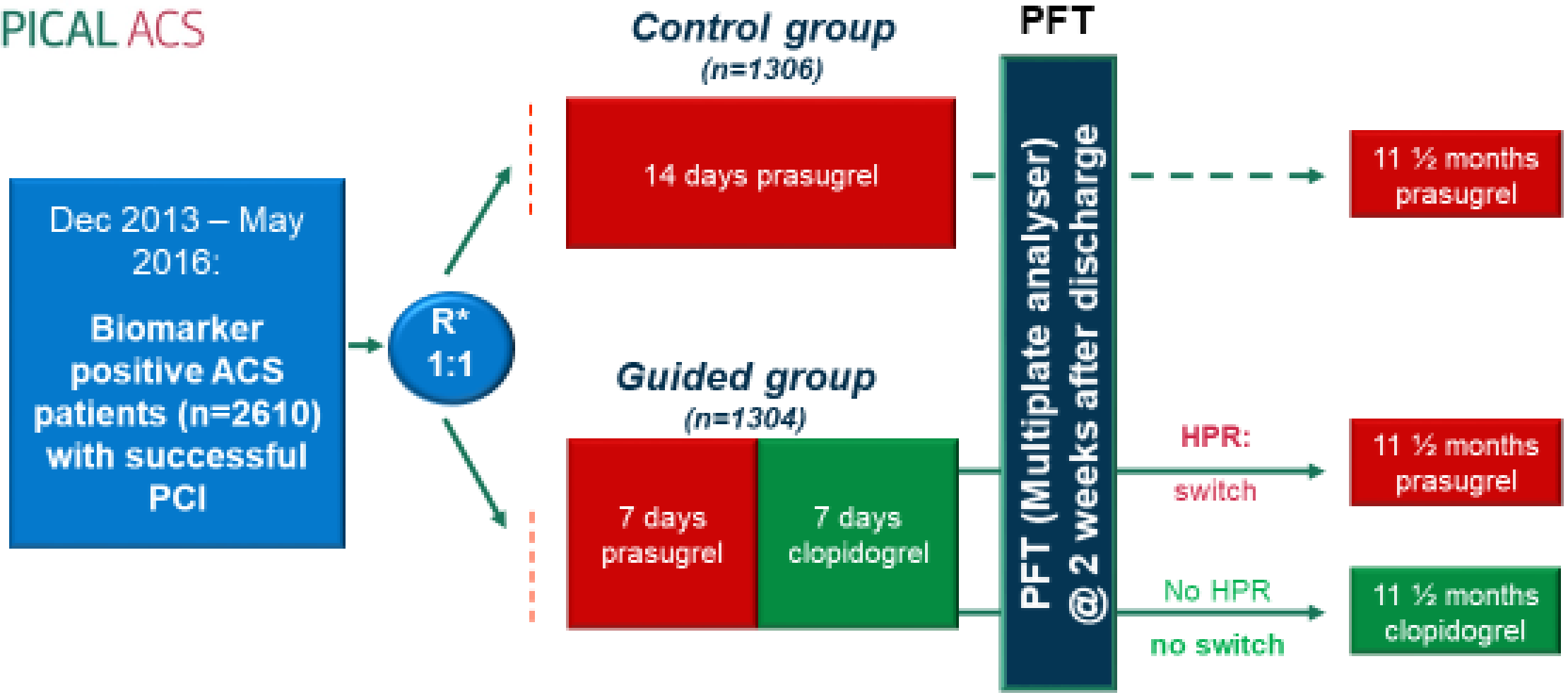
	Discharged on clopidogrel			Discharged on prasugrel			Discharged on ticagrelor		
	Switch (n = 216)	No switch (n = 5741)	*P*	Switch (n = 383)	No switch (n = 2106)	*P*	Switch (n = 64)	No switch (n = 162)	*P*

De-escalation Rate **15 %** **28 %**

Zettler et al., AHJ 2017

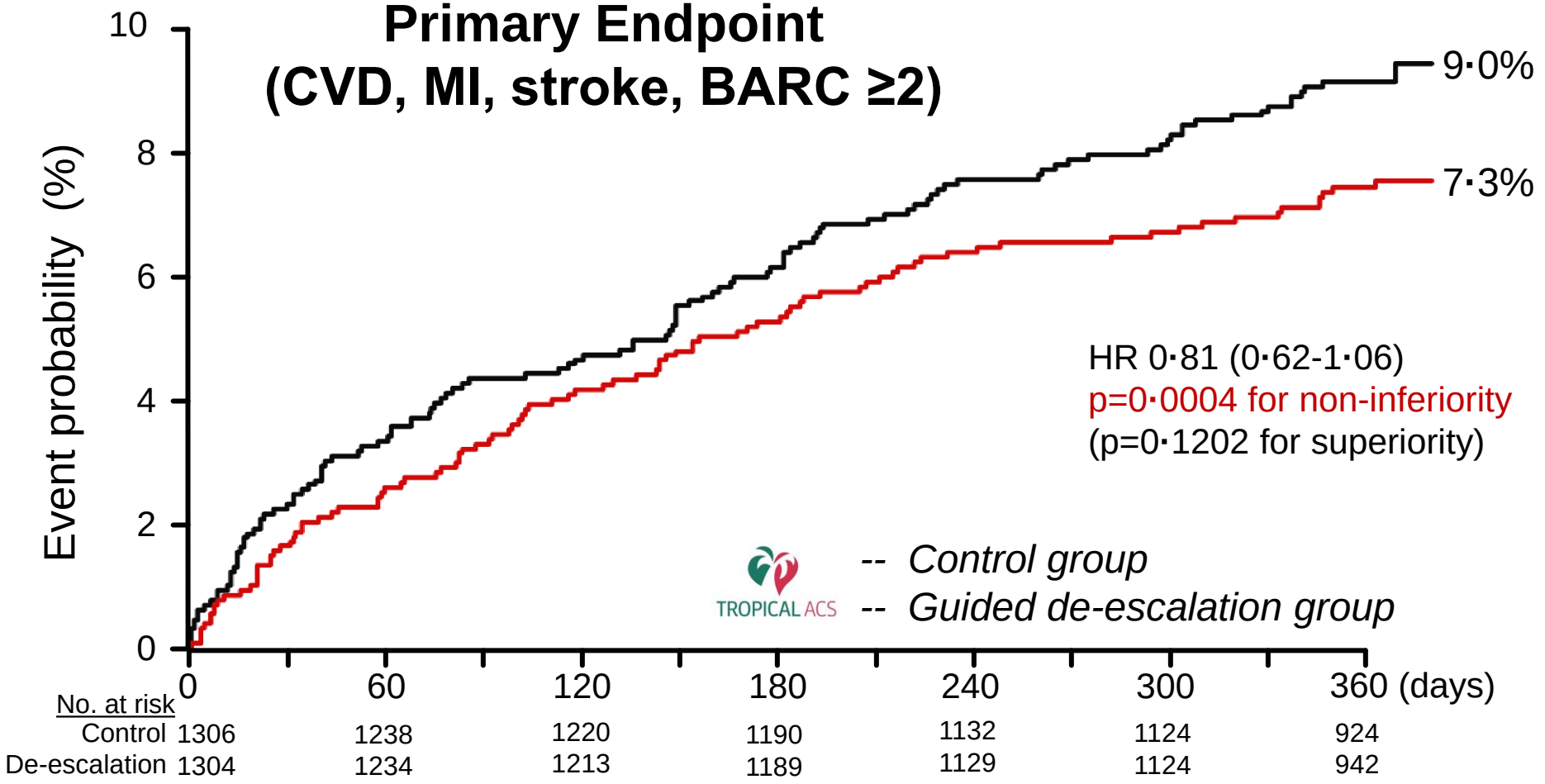
TROPICAL ACS: GUIDED DE-ESCALATION

TROPICAL ACS



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

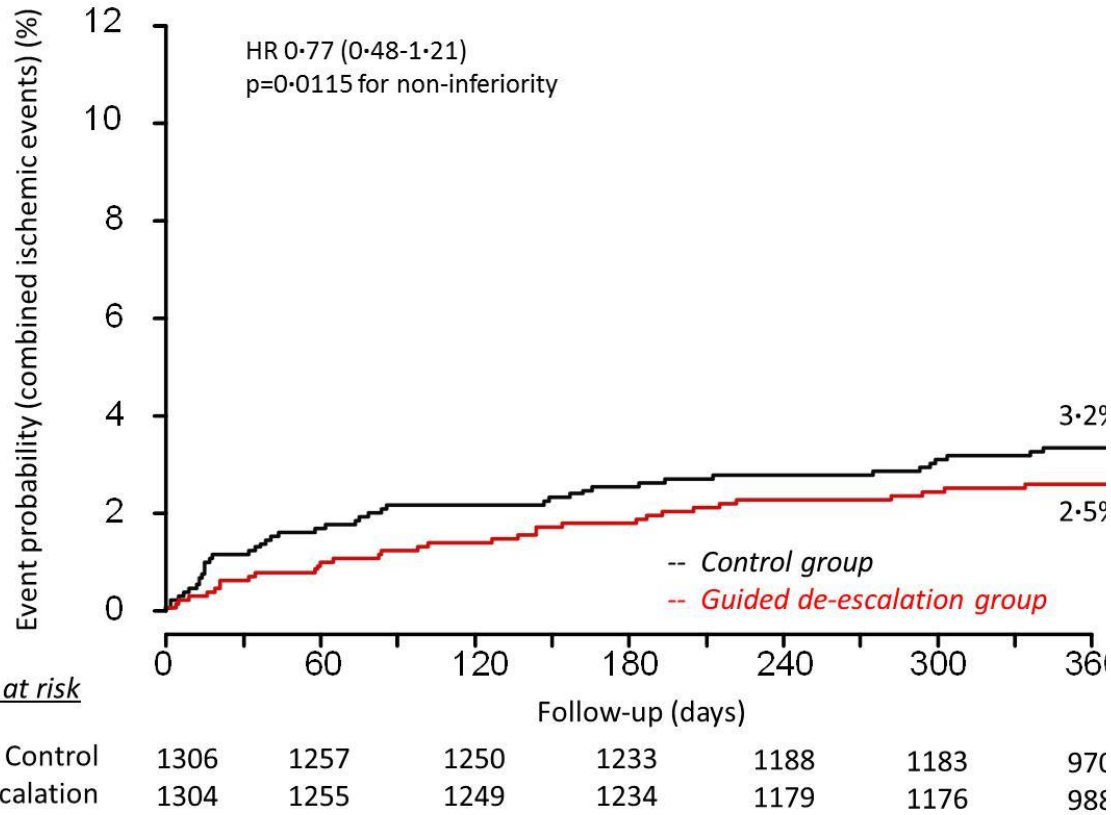
TROPICAL ACS: GUIDED DE-ESCALATION



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

TROPICAL ACS: GUIDED DE-ESCALATION

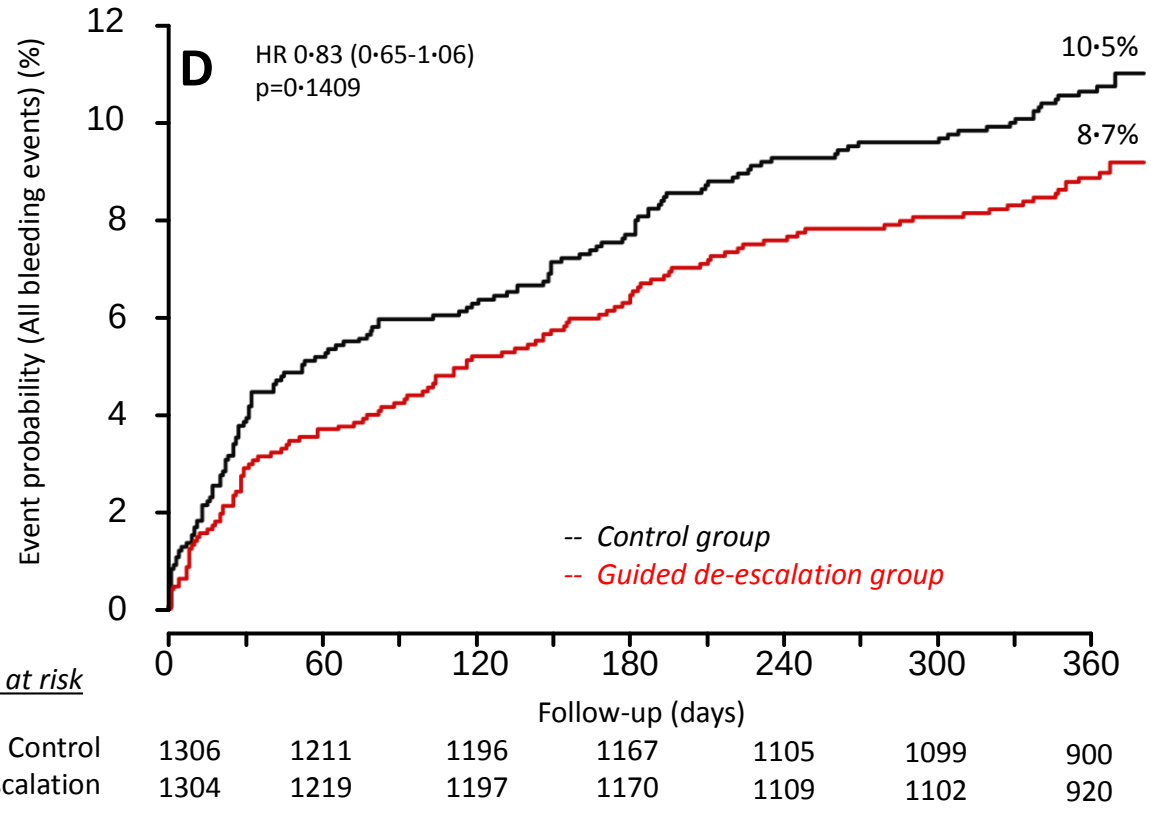
CVD, MI, stroke



No. at risk

Control	1306	1257	1250	1233	1188	1183	97(
De-escalation	1304	1255	1249	1234	1179	1176	98{

BARC 1-5 bleeding

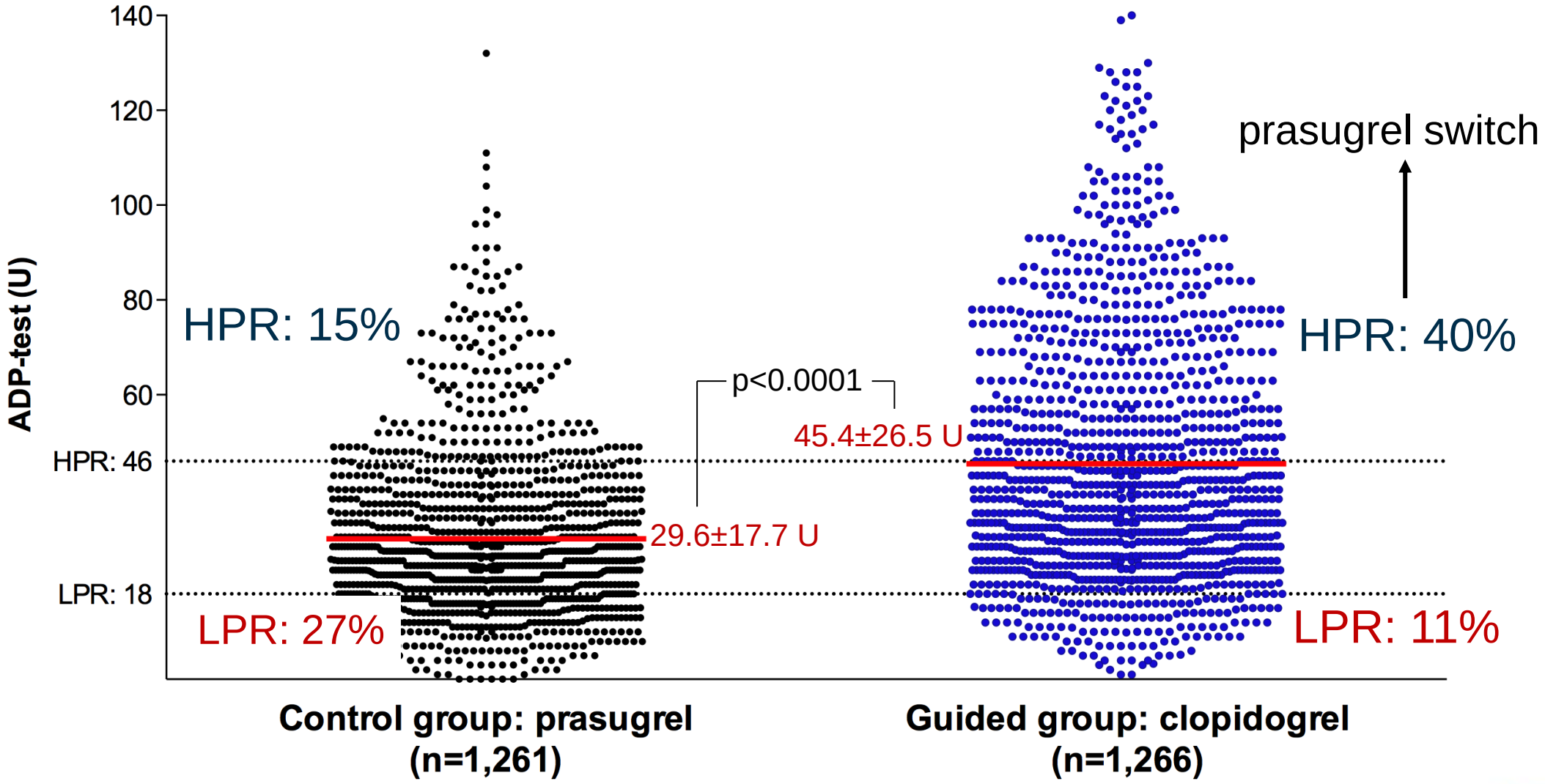


No. at risk

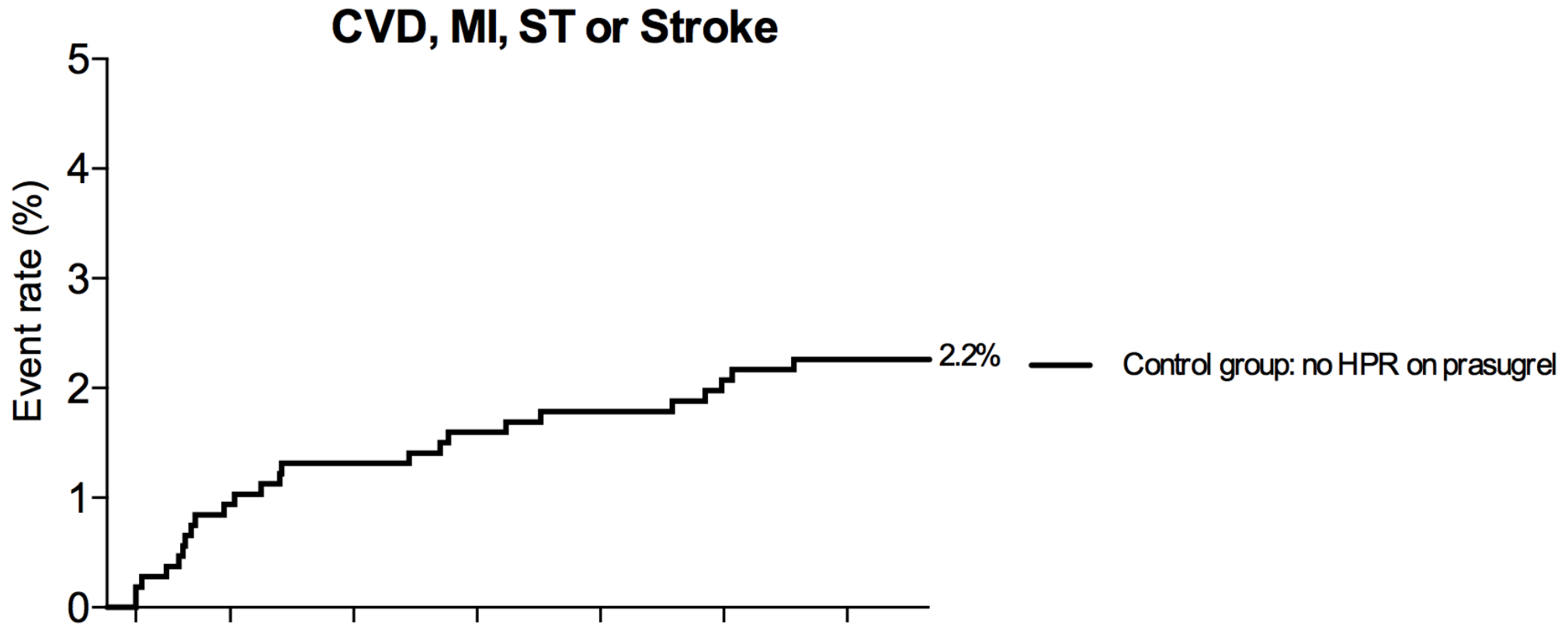
Control	1306	1211	1196	1167	1105	1099	900
De-escalation	1304	1219	1197	1170	1109	1102	920

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

RESULTS: PFT DATA

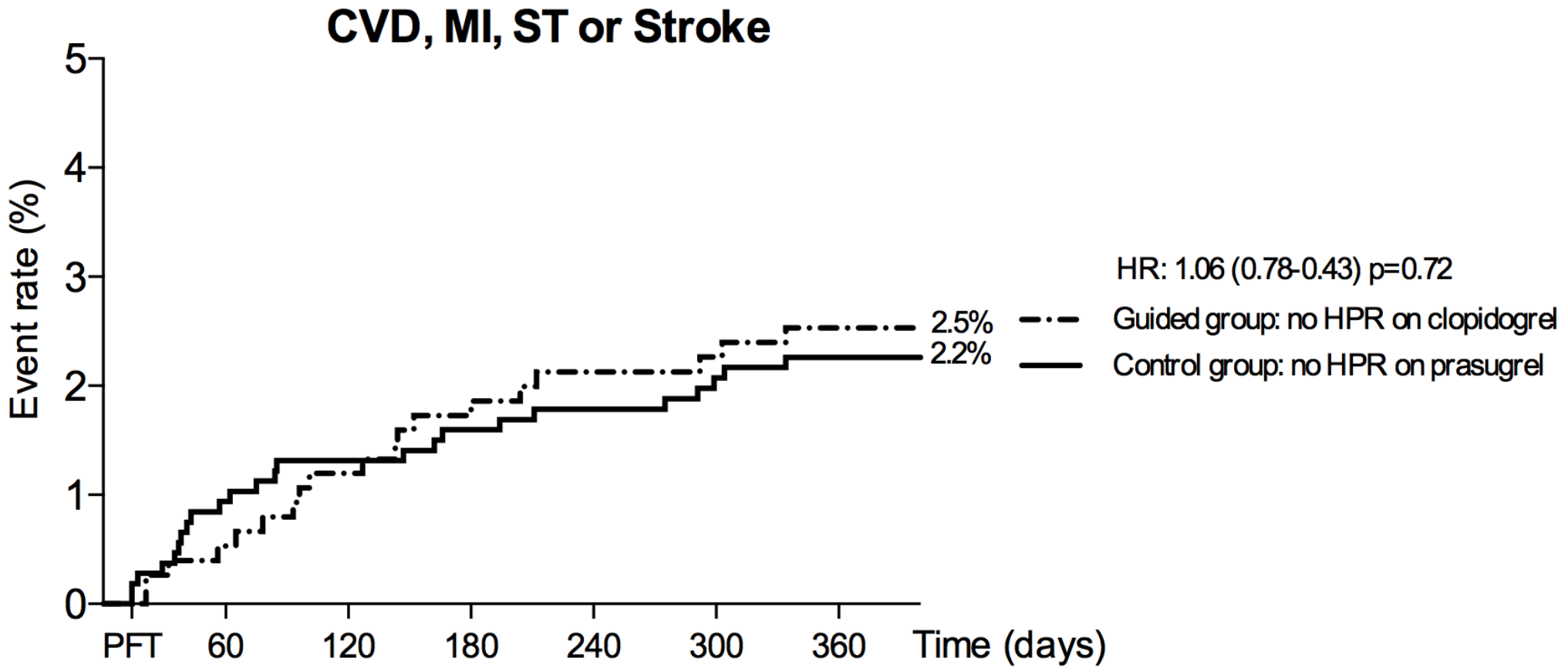


RESULTS: CLINICAL OUTCOMES & HPR



Numbers at risk:	PFT	60	120	180	240	300	360
Cotrol group, HPR:	188	186	185	182	178	176	173
Control group, no HPR:	1073	1055	1050	1043	1034	1030	1020
Guided group, HPR:	511	505	504	501	494	492	491
Guided group, no HPR:	755	749	744	737	732	730	721

RESULTS: CLINICAL OUTCOMES & HPR



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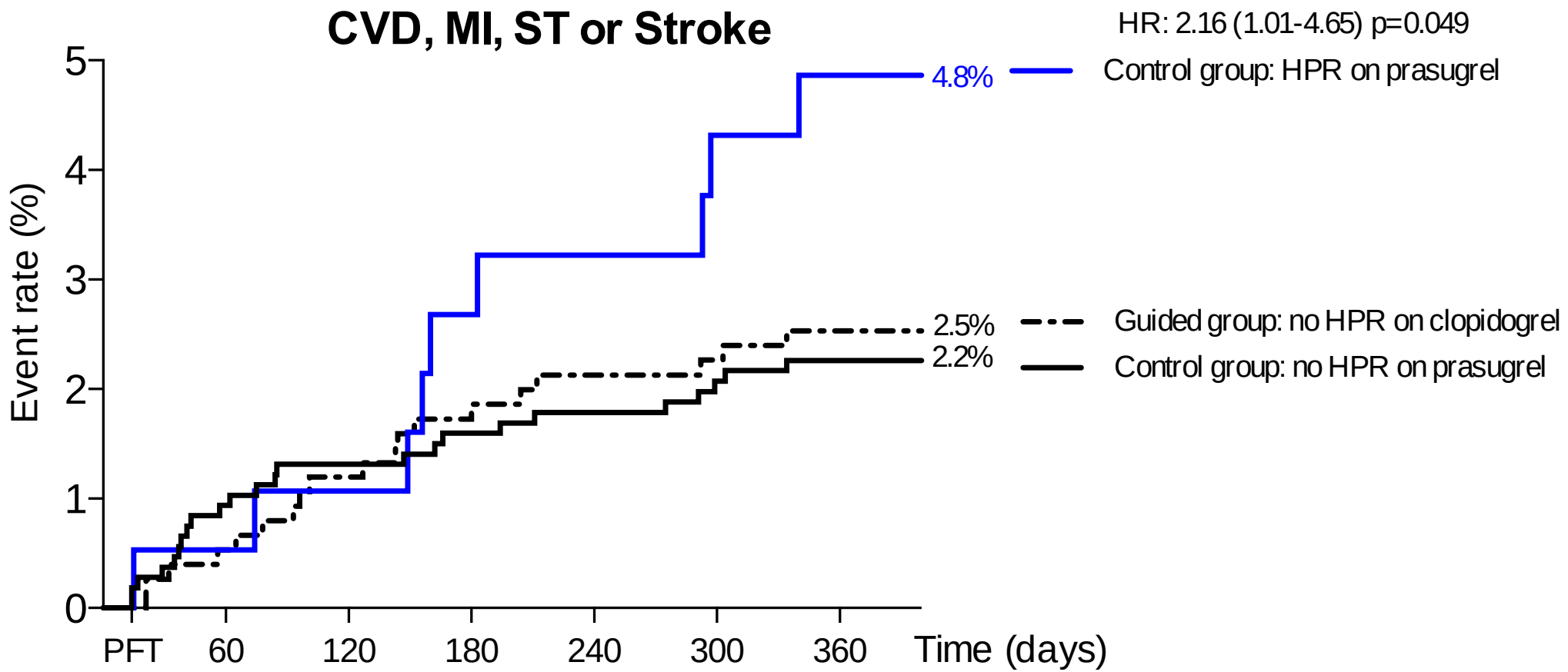

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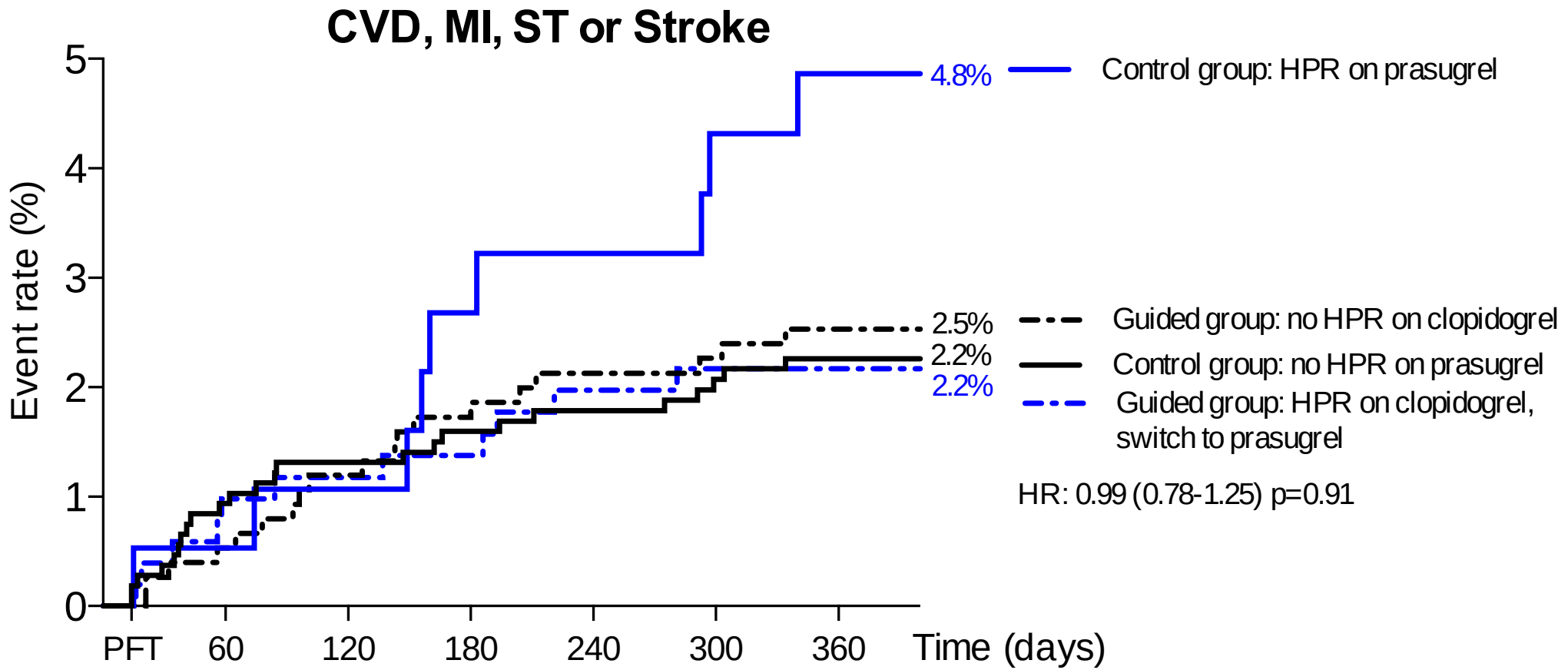

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Conclusions

- Benefit of PFT-guided treatment may be different according to the risk profile of the treated population. Recent data from high risk AMI population support benefits of platelet function based tailored antiplatelet therapy
- In a nation-wide registry of AMI patients, cases with PFT-guided selection of $P2Y_{12}$-inhibitor therapy had lower mortality.
  - prasugrel treatment improved survival in patients with HPR, compared to standard and high-dose clopidogrel.
- PFT guided 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

Thank you for your attention!

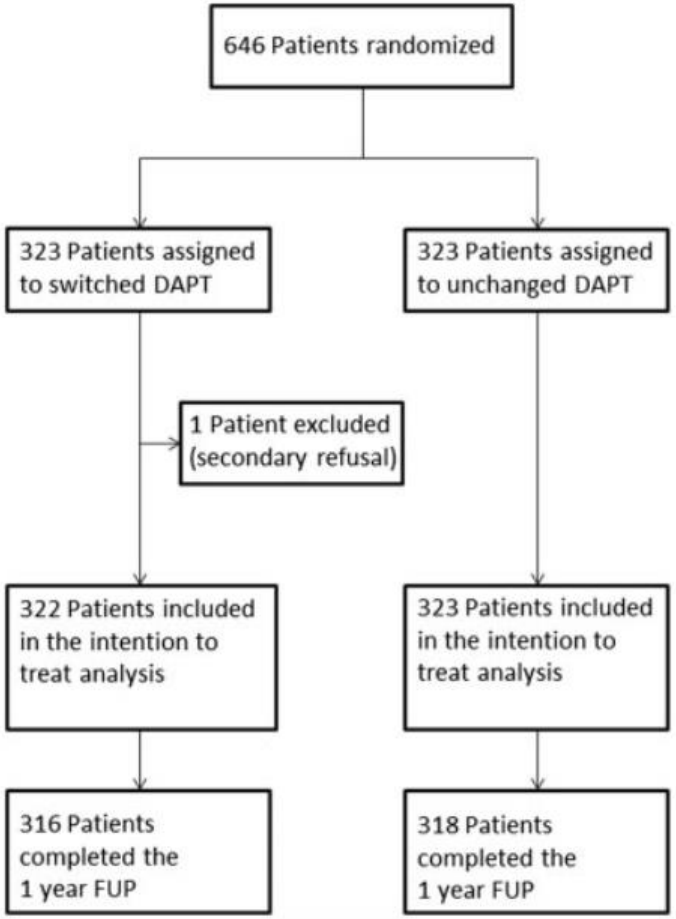
Comparison of Platelet Function Guided Versus Unguided Treatment With P2Y12 Inhibitors in Patients With Acute Myocardial Infarction (from the Hungarian Myocardial Infarction Registry)

András Komócsi, MD, DSc[a,*,1], Dániel Aradi, MD, PhD[b,c,1], Tibor Szűk, MD, PhD[d], Gergely György Nagy, MD, PhD[e], Ebrahim Noori, MD[f], Zoltán Ruzsa, MD, PhD[c,g], Róbert G. Kiss, MD, PhD[h], Péter Andrássy, MD, PhD[i], Lajos Nagy, MD, PhD[j], Ferenc Tamás Nagy, MD, PhD[k], Géza Lupkovics, MD[l], Zsolt Kőszegi, MD, PhD[m], Csaba András Dézsi, MD, PhD[n], Előd Papp, MD, PhD[o], Zsolt Molnár, MD[o], Péter Kupó, MD[a], Péter Ofner, MD[p], Béla Merkely, MD, DSc[c,1], and András Jánosi, MD, DSc[p,1]

The American Journal of Cardiology

Komócsi et al., Am J Cardiol 2018;121:1129–1137

PRO
TOPIC STUDY: SWITCH-BACK TO CLOPIDOGREL @30 DAYS



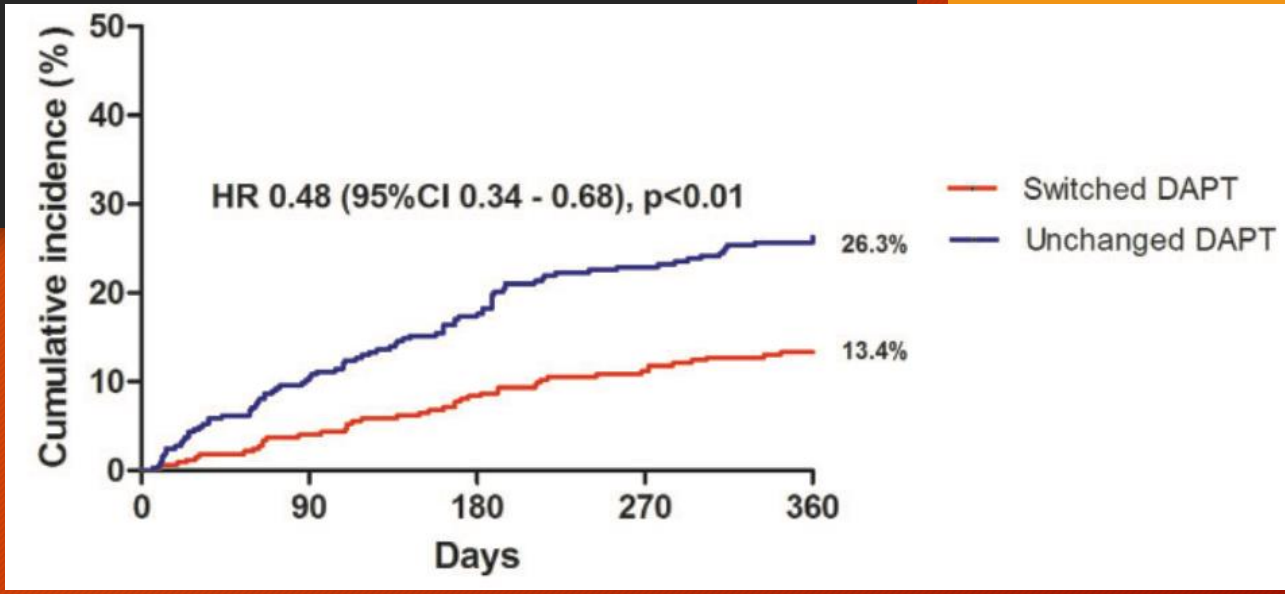
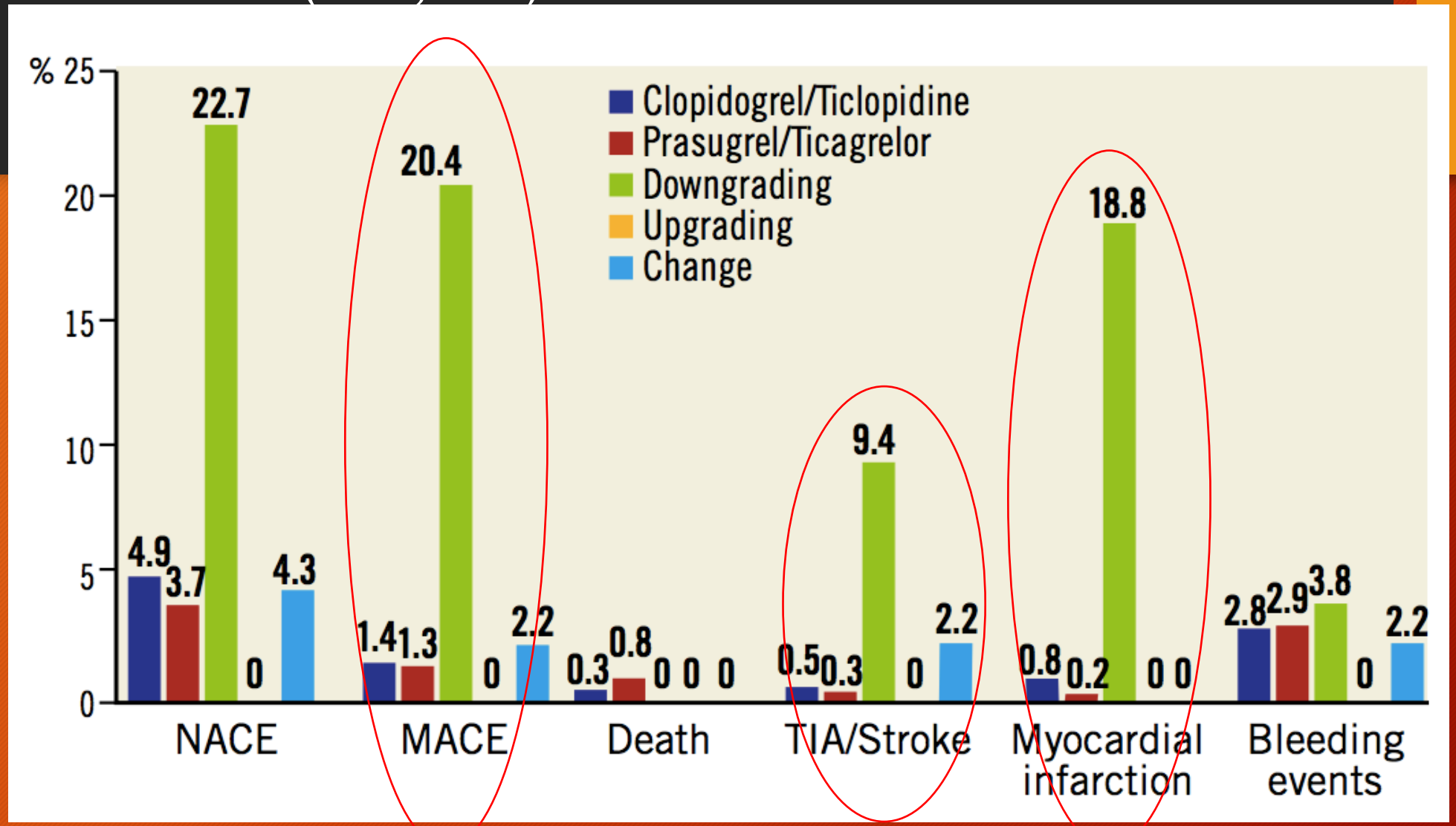


Table 3 **Endpoints at 1 year**

	Switched DAPT	Unchanged DAPT	HR (95%IC)	*P*-value
Net clinical benefit	43 (13.4%)	85 (26.3%)	0.48 (0.34–0.68)	<0.01
Any ischaemic event	30 (9.3%)	37 (11.5%)	0.48 (0.34–0.68)	0.36
Cardiovascular death	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
Unplanned revascularization	28 (8.7%)	30 (9.3%)	0.93 (0.56–1.55)	0.78
Stroke	1 (0.3%)	3 (0.9%)	0.37 (0.05–2.60)	0.32
All bleedings	30 (9.3%)	76 (23.5%)	0.39 (0.27–0.57)	<0.01
Bleeding BARC ≥ 2	13 (4.0%)	48 (14.9%)	0.30 (0.18–0.50)	<0.01
TIMI major	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
TIMI minor	9 (2.8%)	26 (8.0%)	0.37 (0.19–0.71)	<0.01
TIMI minimal	20 (6.2%)	46 (14.2%)	0.44 (0.27–0.71)	<0.01

Cuisset et al. EHJ 2017.

CONTRA
SCOPE REGISTRY (n= 1, 363)



de Luca et al. Eurointervention 2017;13:459-466.

- Régi guideline, PFT
- PFT studies
- HUMIR
- TROPICAL

NNT kalkuláció

- A PS illesztett csoport eseménygyakoriságából számítva a clopidogrel vs prasugrel döntés szempontjából érintett betegek közt végzett 34 TAG vizsgálat szükséges 1 mortalitási esemény megelőzéséhez
- A TAG mérés átlagosan 19%-os HPR gyakoriságot igazolt, így 11 HPR-es beteg prasugrelre történő átállítása szükséges 1 élet megmentéséhez

Clinical endpoints in the PS matched and in the entire cohort

A. Propensity matched cohort (n=2104)				
		Nr. of patients (%)		Hazard Ratio [95% Confidence interval]
		Platelet function guided treatment (n=1052)	Unguided treatment (n=1052)	
	Death from any cause	75 (7.1)	125 (11.9)	0.574 [0.431-0.765]***
	Death from cardiovascular causes	66 (6.3)	104 (9.9)	0.609 [0.447-0.828]**
	Repeated myocardial infarction	29 (2.8)	20 (1.9)	1.380 [0.781-2.440]
	Repeated coronary intervention	198 (18.8)	128 (12.2)	1.545 [1.237-1.930]***
	Bypass graft surgery	43 (4.1)	51 (4.8)	0.798 [0.532-1.197]
	Stroke	8 (0.8)	8 (0.8)	0.954 [0.358-2.541]
	Major adverse cardiac events (cardiovascular death, MI, or stroke)	97 (9.2)	126 (12.0)	0.736 [0.565-0.959]*
B. Unmatched cohort (n=3974)				
		Platelet function guided treatment (n=2901)	Unguided treatment (n=1073)	Hazard Ratio [95% Confidence interval]
	Death from any cause	163 (5.6)	129 (12.0)	0.441 [0.350-0.555]***
	Death from cardiovascular causes	139 (4.8)	107 (10.0)	0.454 [0.353-0.584]***
	Repeated myocardial infarction	71 (2.4)	20 (1.9)	1.223 [0.744-2.008]
	Repeated coronary intervention	490 (16.9)	128 (11.9)	1.356 [1.116-1.647]**
	Bypass graft surgery	117 (4.0)	51 (4.8)	0.781 [0.562-1.085]
	Stroke	23 (0.8)	8 (0.7)	0.987 [0.441-2.206]
	Major adverse cardiac events (cardiovascular	218 (7.5)	129 (12.0)	0.589 [0.474-0.732]***

Periprocedural and postprocedural antithrombotic therapyc in patients undergoing primary percutaneous coronary intervention

ESC European Society of Cardiology

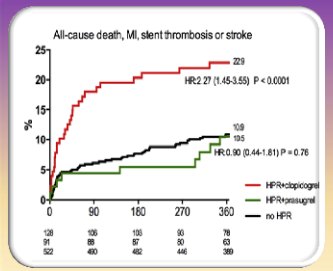
Recommendations	Class	Level
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.	IIb	A

A gyakorlati kivitelezés fő lépései

Nemzeti Szívinfarktus Regiszter

HUMIR-feltöltése
ACS miatt PCI-n átesett betegek
2013.03.01.-2014.03.01

TAG méréshez tartozó adatok felvitele



Adatok exportálása a NIR-ből
Betegek követése
forrás: OEP adatbázis
Adatfeldolgozás

Komócsi et al., Am J Cardiol 2018;121:1129–1137